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Par

TAN Jia-Neng

La chimie des carbohydrates en milieu aqueux et dans des solvants bio-sourcés: Utilisation du glycosyloxyméthyl furfural (GMF) et analogues dans la réaction de Baylis-Hillman

Carbohydrate chemistry in aqueous and bio-based solvents: Exploring the use of glycosyloxymethyl furfural (GMF) and analogues in the Baylis-Hillman reaction

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Key words

Morita-Baylis-Hillman (MBH) reaction

Isomaltolose

Furfural

Hydroxymethylfurfural (HMF)

Glucosyloxymethyl-furfural (GMF)

Green chemistry

Biobased solvents

Water

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Abbreviations

APGs	Alkyl polyglucosides
BINAP	2,2′-bis(diphenylphosphino)-1,1′-binaphthyl
CMG	Carboxymethyl glucopyranoside
CMGLs	Carboxymethyl glycoside lactone
$scCO_2$	Supercritical carbon dioxide
COSY	Correlation spectroscopy
DABCO	1,4-Diazabicyclo[2.2.2]octane
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DDQ	2,3-Dichloro-5,6-dicyano-benzoquinone
DFF	Diformylfuran
DIBAL	Diisobutylaluminium hydride
DMAP	4-Dimethylaminopyridine
DMSO	Dimethyl sulfoxide
DMF	Dimethylformamide
DMI	Dimethylisosorbide
DPI	6,7-Dihydro-5H-pyrrolo[1,2-a]imidazole
Et_3N	Triethylamine
FCAN	2-(Furan-2-carbonyl) acrylonitrile
GMF	Glucosyloxymethylfurfural
GGLs	Glycoglycerolipids

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GPPPs	Glycosyl phosphopolyprenols
GSLs	Glycosphingolipids
GVL	γ-Valerolactone
HDI	1,6-Hexamethylene diisocyanate
HMF	Hydroxymethylfurfural
HMBC	Heteronuclear multiple-bond correlation
3-HQD	3-hydroxyquinuclidine
HSQC	Heteronuclear single-quantum correlation spectroscopy
KIE	Kinetic isotopic effect
MBH	Morita-Baylis-Hillman
aza-MBH	aza-Morita-Baylis-Hillman
2-MeTHF	2-Methyltetrahydrofuran
MDI	4,4'-Methylene-bis(phenyl diisocyanate)
MVK	Methyl vinyl ketone
NMP	N-Methylpyrrolidinone
NMR	Nuclear magnetic resonance
p-TSA	*p*-Toluenesulfonic acid
PPh_3	Triphenylphosphine
RAFT	Reversible addition fragmentation chain-transfer
RDS	Rate-determining step
RTIL	Room temperature ionic liquid
TEMPO	(2,2,6,6-Tetramethylpiperidin-1-yl) oxidanyl

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THF	Tetrahydrofuran
TLC	Thin layer chromatography
VOC	Volatile Organic Compounds

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Résumé

Introduction

Durant les dernières décennies, des besoins de plus en plus important en ressources, en produits chimiques et en énergie nécessaires au développement de l'humanité a incité les hommes à tenter de construire une société plus durable et respectueuse de l'environnement.

Les progrès réalisés dans le domaine de la chimie verte et de celui de l'ingénierie écologique constituent désormais une opportunité pour réduire les impacts négatifs de ce développement et une opportunité pour le développement économique car apportant aussi des améliorations de rentabilité.

Dans le domaine de la chimie, douze principes ont été énoncés par P. T. Anastas et J. C. Warner pour définir la chimie verte. Le développement de l'utilisation de ressources renouvelables comme matière première pour la production de combustibles et de produits chimiques de base constitue un des ces principes.

La biomasse est certainement la source de matières premières la plus attrayante puisqu'elle est la source de carbone la plus largement disponible en dehors des énergies fossiles telles que le pétrole et le charbon. Pour plusieurs raisons qui tiennent à la pénurie de sources d'énergie fossile bon marché, et aux conséquences des émissions des gaz à effet de serre, il est nécessaire d'intégrer une part maximale de carbone renouvelable dans la conception des produits chimiques afin de réduire leur empreinte carbone. Un intérêt supplémentaire est d'offrir des opportunités d'applications de plus haute valeur ajoutée pour les produits et co-produits issus des productions agricoles. La biomasse contient des hydrates de carbone (autre nom pour les sucres ou glucides), de la lignine, des acides gras, des lipides, ou encore des protéines. Les hydrates de carbone constituent deux-tiers de la biomasse renouvelable annuelle et représentent ainsi la plus abondante de ces matières

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organiques renouvelable. Ils sont omniprésents dans la nature et représentent un intéret chimique extrêmement important, non seulement en raison de leurs multiples rôles biologiques mais également concernant leur possible utilisation en tant que matières de base pour la synthèse d'intermédiaires chimiques et de produits chimiques de spécialité.

Cette thèse est une contribution à l'utilisation de matières premières renouvelables pour la chimie, explorant en particulier l'utilisation d'aldéhydes furaniques biosourcés, tels que l'hydroxyméthyl furfural (HMF) et de ses analogues, en tant que substrat pour la réaction de Morita-Baylis-Hillman (MBH). L'étendue de la réaction a été étudiée avec une attention particulière portée sur la possibilité d'utiliser des milieux aqueux et biosourcés comme solvants pour effectuer cette transformation (**Fig. 1**).

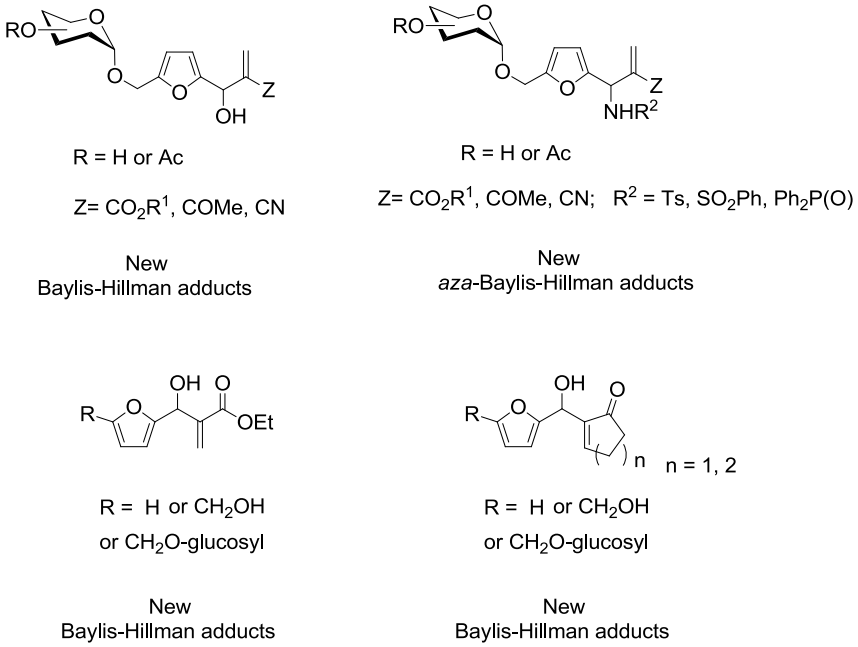

Fig. 1

Réaction de Baylis-Hillman avec le glycosyloxyméthyl furfural (GMF) en milieu aqueux.

En premier lieu, nous avons synthétisé de nouveaux glycoacrylates découlant d'une

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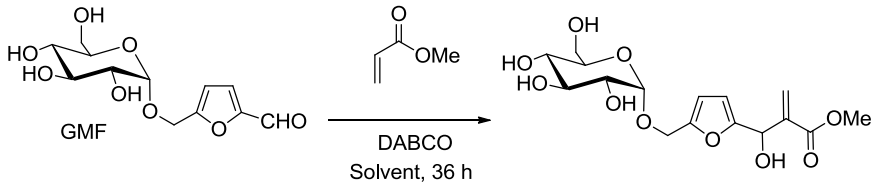
réaction de Baylis-Hillman, en milieu aqueux, avec le glycosyloxyméthyl furfural (GMF) et divers acrylates (**Fig. 2**). Différentes conditions de solvant ont été comparées et les meilleurs rendements ont été obtenus lorsqu'un mélange 1:1 (v/v) de diméthylisosorbide (DMI) et d'eau a été utilisé : cela a conduit à un rendement de 56% des produits d'addition de Baylis-Hillman. Il est important de noter que la réaction fonctionne aussi dans de l'eau pure, avec un rendement en produit isolé de 33%. La réaction du GMF et certains de ses analogues ont ensuite été étudiés et les résultats sont indiqués dans la figure **3**. Ceci constitue nouvelle approche vers des composés fonctionnels totalement biosourcés (monomères potentiels, surfactants), dans des conditions de solvant très attractives si l'on considère le fait que cette réaction peut prendre place dans l'eau ou dans d'autres solvants biosourcés.



Solvent	Yield (%)
H_2O	33
1,4-Dioxane	0
DMI	<5
CH_3CN/H_2O	31
1,4-Dioxane/H_2O	35
DMI/H_2O	56

Fig. 2

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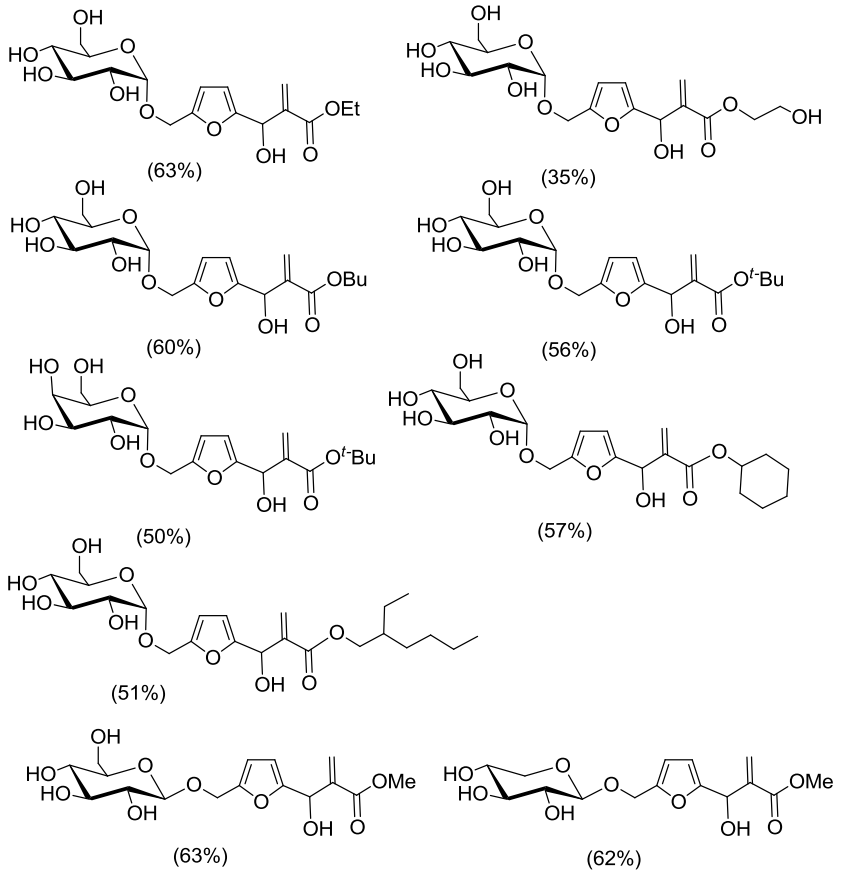

Fig. 3

La réactivité du tétraacétate de GMF a également été étudiée. L'utilisation des conditions DMI-H_2O-DABCO n'a pas permis l'obtention des produits désirés suivant un temps de réaction acceptable, mais les adduits MBH correspondants ont pu être obtenus en utilisant des conditions aqueuses (DABCO, 1,4-dioxane / eau 1:1 v/v). L'acrylate de méthyle et l'acrylonitrile ont donné les adduits Baylis-Hillman désirés avec des rendements acceptables à bons (**Fig.4**). La réaction utilisant la méthyle vinyle cétone (MVK) a été infructueuse sous ces conditions, cependant en utilisant un catalyseur tel que le DMAP et le DMI comme solvant, l'adduit Baylis-Hillman a été formé exclusivement avec un bon rendement (**Fig. 4**).

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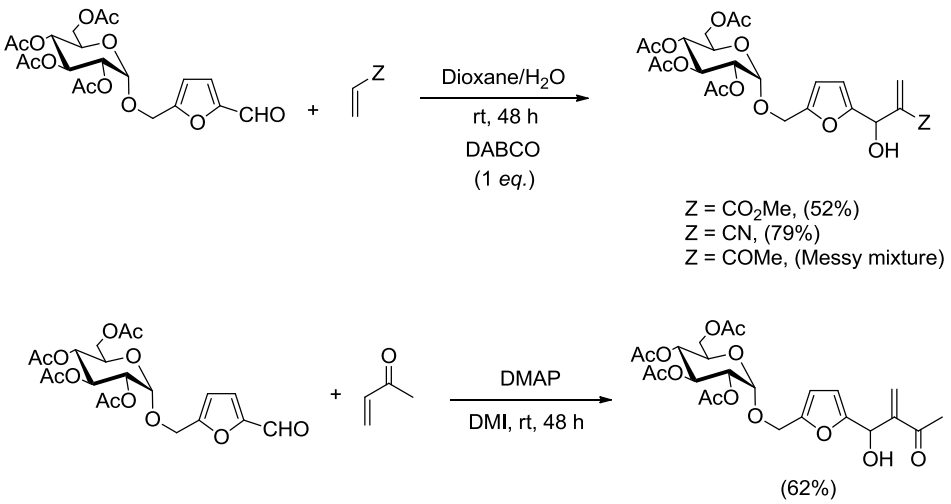
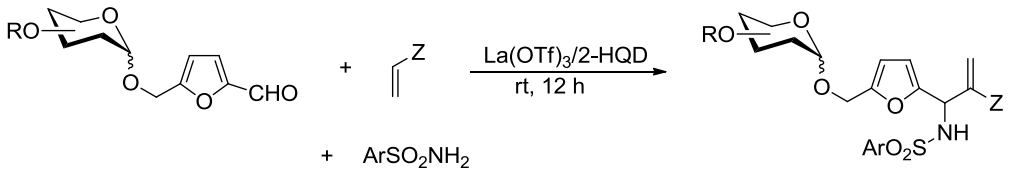


Fig. 4

Réaction d'*aza*-Baylis-Hillman avec le GMF

Ci-après (**Fig.5**), sont résumés les différents résultats obtenus dans cette réaction à trois composants qu'est la réaction d'aza-MBH à partir de GMF, sulfonylamine, et d'esters insaturés. Le meilleur résultat est obtenu en employant 3-HQD (20 mol %) avec $La(OTf)_3$ (5 mol %) en présence de tamis moléculaire, et donne les β-amino esters glucidiques désirés avec de bons rendements.



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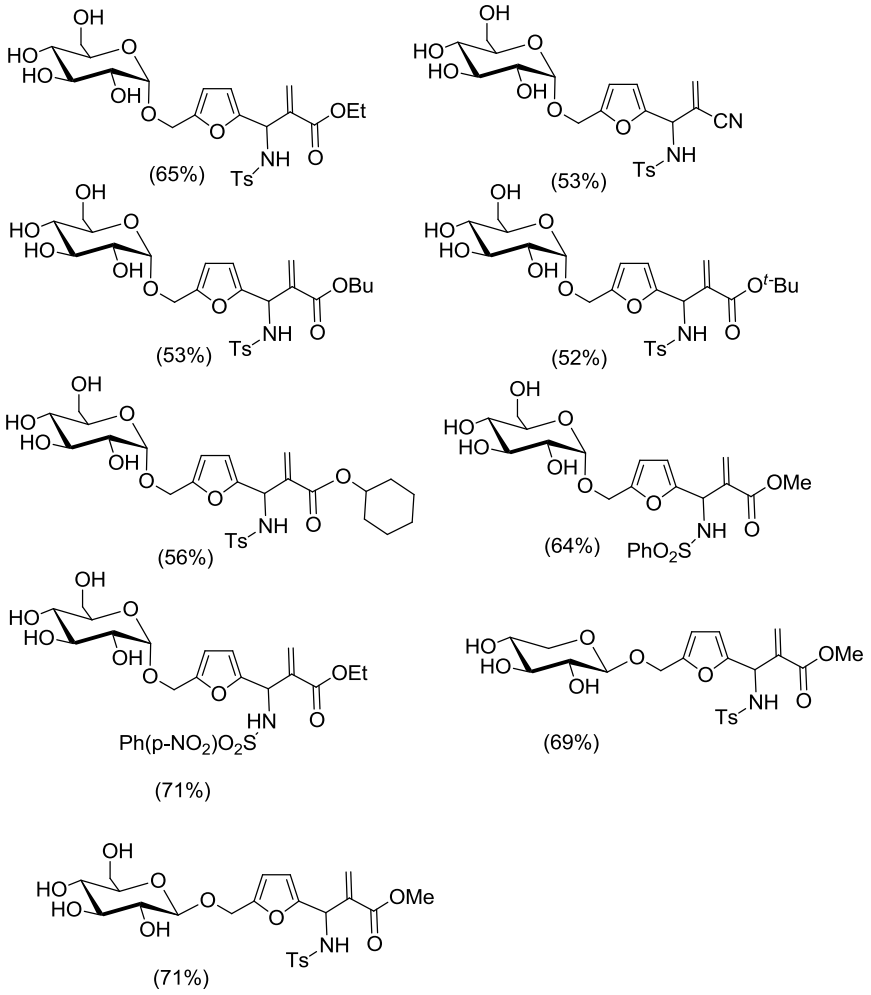

Fig. 5

Cette nouvelle approche a été étendue aux GFM-tétraacétate-diphénylphosphinamides avec la méthyle vinyl cétone (MVK), et a conduit à d'autres types de dérivés de sucres fonctionnels avec des rendements acceptables **Fig. 6**.

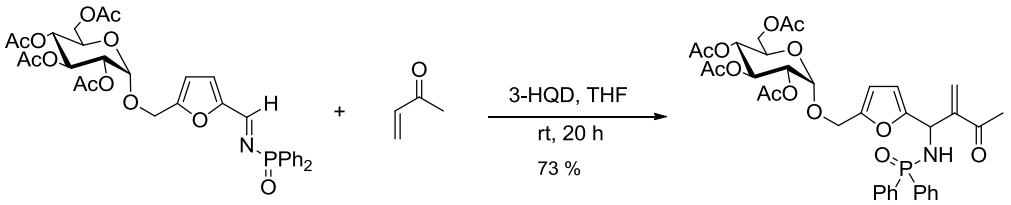

Fig. 6

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Réaction de Baylis-Hillman avec le HMF et ses analogues en milieu bio-sourcé (H_2O-solvant).

En accord avec l'étude des réactions de MBH, nous avons alors porté notre attention sur l'utilisation de divers solvants d'origine biologique pour la réaction de MBH avec HMF, furfural et GMF et les résultats sont présentés dans ce résumé. Dans ce but, la réaction de MBH avec le HMF et l'acrylate d'éthyle dans différents mélanges solvant-eau bio-sourcés avec le DABCO a été explorée (**Fig. 7**). Les systèmes de solvants utilisés étaient les suivants: éthanol, isopropanol, isopropylidéneglycérol, 2-hydroxyméthylfurane, 2-hydroxyméthyl-tétrahydrofurane, 2-méthyl-tétrahydrofurane, lactate d'éthyle et diéthyle succinate, et leurs mélanges avec de l'eau. La réaction s'est avérée efficace dans plusieurs de ces systèmes. Un effet bénéfique de la réaction dans l'eau a été montré dans le cas du HMF, alors que dans le cas de la GMF qui possède ses propres fonctions OH abondantes, de mêmes rendements ont été obtenus avec ou sans eau.

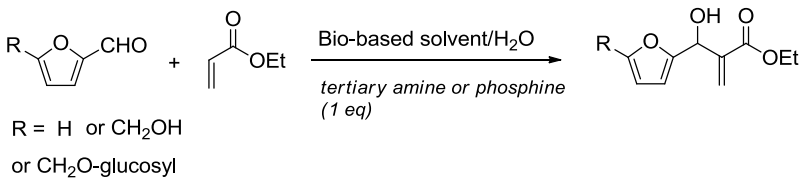

Fig. 7

Réaction Baylis-Hillman du HMF avec les énones dans de l'eau

Nous avons ensuite étudié la réaction de la cyclopenténone avec le HMF dans l'eau et prospecté les effets de différents catalyseurs aminés et phosphorés sur cette réaction et les résultats sont présentés sur la figure. **8**. La réaction de Baylis-Hillman avec la cyclopent-2-énone est très lente lorsqu'elle est effecuée dans les conditions classiques. Plusieurs catalyseurs tels que DBU, 3-HQD, DABCO, Et_3N, PPh_3 et

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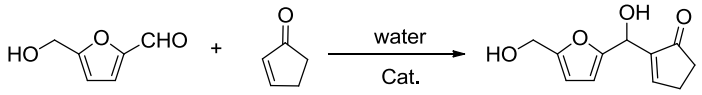
$P(m\text{-}C_6H_4\text{-}SO_3Na)_3$ ont été utilisés mais aucun produit désiré n'a été obtenu dans l'eau. L'utilisation de DMAP et de pyridine a donné des rendements faibles. Par contre, on a pu confirmer que l'imidazole agit comme un remarquable catalyseur dans l'eau, ce dernier donnant les meilleurs résultats en comparaison aux autres catalyseurs utilisés, en termes de rendement. La réaction optimisée a donné un rendement de 50% du produit désiré, après 15 h en la présence de 50% d' imidazole. De plus, un analogue bicyclique de l'imidazole encore plus réactif, le DPI, a été utilisé et a donné le meilleur rendement (71%).



Cat.	yield (%)
3-HQD	none
DBU	none
DMAP	5
DABCO	none
PPh_3	none
Py	10
Et_3N	none
Imidazole	50
DPI	71

Fig. 8

Afin de compléter cette étude, nous avons aussi examiné la réaction MBH d'analogues de HMF (furane, GMF) avec la cyclopentenone, et la réactivité de la cyclohex-2-énone avec le HMF dans les conditions optimisées précédemment. Nous avons ainsi pu constater que les adduits de MBH ont été obtenus dans tous les cas, avec des rendements modérés à bons. La réaction de MBH entre le furfural et cyclopent-2-énone a donné 88% de rendements alors qu'avec le GMF le rendement n'excède pas 55% (**Fig. 9**).

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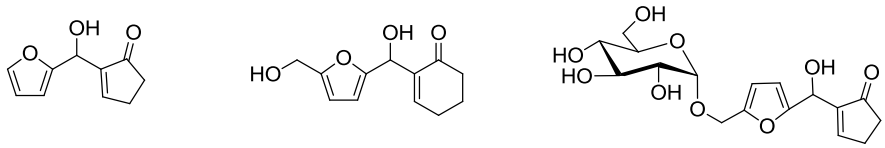

88% 70% 55%

Fig. 9

Conclusion

Dans ces travaux de thèse, nous avons étudié la réaction de Morita-Baylis-Hillman et d'aza-Morita-Baylis-Hillman (MBH/*aza*-MBH) avec divers aldehydes biosourcés, tels que le furfural, hydroxyméthyl furfural (HMF) and glucosyloxymethylfurfural (GMF) et différents accepteurs de Michael dans des conditions variables (concentration, l'influence de différents catalyseurs ou solvants). Avec des moyens analytiques, tels que la spectroscopie RMN et la spectroscopie de masse, les structures ainsi que la pureté de tous les composés ont été soigneusement établis.

En premier lieu, l'étude a montré que la réaction de MBH du glycosyloxyméthylfurfural (GMF) avec des motifs acryliques, conduisant à des rendements acceptables à de nouveaux glycodérivés porteurs de motifs α-hydroxyacrylates et α-méthylène-β-amino acrylates. Pour les réactions conduisant aux α-hydroxyacrylates, l'eau peut être utilisée comme solvant, de même que des mélanges d'eau et de diméthylisosorbide (DMI), remplaçant ainsi efficacement le dioxane ou le THF comparativement aux méthodes habituellement employées. Les esters acryliques de départ pouvant être eux-mêmes biosourcés, les glycoacrylates obtenus par la réaction MBH sont donc potentiellement 100% biosourcés. La version *aza*-MBH de la réaction a été ensuite explorée, associant 3 composants: le GMF, une sulfonamide et un accepteur de Michael, conduisant à de nouveaux dérivés α-méthylène-β-amino carbonyles construits sur un motif glucidique.

L'étude s'est ensuite focalisée sur le HMF lui-même. Plusieurs solvants biosourcés, en particulier le 2-hydroxyméthyl THF et l'isopropylidèneglycérol, se sont révélés

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efficaces pour la réaction de MBH du HMF avec l'acrylate d'éthyle. Pour le HMF et le furfural, la réaction est améliorée en présence d'eau; ce qui permet d'étendre la gamme de solvants biosourcés pouvant être utilisée dans ce processus. Il a aussi été montré que l'imidazolyl alcool bicyclique DPI est un catalyseur très efficace pour la réaction MBH du HMF, du furfural ou du GMF avec des énones cycliques, conduisant à une diversité de nouvelles structures par une voie écorespectueuse et efficacement. Les adduits de MBH peuvent être utilisés comme synthons valorisables pour la synthèse de produits naturels ou non-naturels, et des molécules bioactives. Dans la suite de ces travaux seront étudiés les potentialités de l'utilisation de ces adduits de MBH comme des plateformes polyvalentes pour la synthèse de divers polymères fonctionnalisés. Cette stratégie sera développée davantage au sein de nouveaux projets collaboratifs.

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GENERAL INTRODUCTION

Over the last century, with the growth in demand of chemicals and energy, human beings are now more and more emerged to build an eco-friendly and sustainable society. The progress of green chemistry and environmentally-friendly chemical engineering is an opportunity for reducing negative human impact on earth, and, being also related to cost efficiency, an opportunity for economic development. With regards to the 12 principles of green chemistry developed by P. T. Anastas and J. C. Warner, the development of new, sustainable sources for fuels and bulk chemicals are core interests.

Biomass definitely is the most attractive feedstock, as it is the only widely available carbon source apart from fossil ones such as oil and coal. Due to different reasons which relate to the shortage of cheap fossil resources and the excessive production of greenhouse gases, it is necessary to integrate renewable carbon in chemicals for lowering their carbon footprint, or the search for added-value products from agricultural crops or by-products. Biomass consists of carbohydrates, lignin, fatty acids, lipids, proteins, and others. Among them, carbohydrates, as the most abundant of these organic materials, which in fact, consist 75% of the annually renewable biomass produced on earth, are the major biofeedstocks. Carbohydrates are ubiquitous in nature and show extremely high chemical interest, either with respect to biological issues or to their possible use as starting materials for the synthesis of chemical intermediates and fine chemicals.

As a contribution on chemical processes involving carbohydrate-based feedstocks, this thesis explore the use of biosourced furanic aldehydes, namely hydroxymethyl furfural (HMF) and analogues, as a substrate for the Morita-Baylis-Hillman (MBH) reaction. The scope of the reaction has been explored, with a focus on the possibility to perform the reaction in aqueous or biobased medium.

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1.1 Green chemistry, a brief overview

What is green chemistry? Anastas and Warner (Green Chemistry: Theory and Practice, P. T. Anastas and J. C. Warner, Oxford University Press, Oxford, 1998) have provided a concise and comprehensive definition [1] :

Green chemistry is the utilization of a set of principles that reduces or eliminates the use or generation of hazardous substances in the design, manufacture and application of chemical products.

Those well defined principles are namely “12 Principles of Green Chemistry” and list as fellows:

1. Prevention

It is better to prevent waste than to treat or clean up waste after it has been created.

2. Atom Economy

Synthetic methods should be designed to maximize the incorporation of all materials used in the process into the final product.

3. Less Hazardous Chemical Syntheses

Wherever practicable, synthetic methods should be designed to use and generate substances that possess little or no toxicity to human health and the environment.

4. Designing Safer Chemicals

Chemical products should be designed to affect their desired function while minimizing their toxicity.

5. Safer Solvents and Auxiliaries

The use of auxiliary substances (e.g., solvents, separation agents, etc.) should be made unnecessary wherever possible and innocuous when used.

6. Design for Energy Efficiency

Energy requirements of chemical processes should be recognized for their environmental and economic impacts and should be minimized. If possible, synthetic

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methods should be conducted at ambient temperature and pressure.

7. Use of Renewable Feedstocks

A raw material or feedstock should be renewable rather than depleting whenever technically and economically practicable.

8. Reduce Derivatives

Unnecessary derivatization (use of blocking groups, protection/ deprotection, temporary modification of physical/chemical processes) should be minimized or avoided if possible, because such steps require additional reagents and can generate waste.

9. Catalysis

Catalytic reagents (as selective as possible) are superior to stoichiometric reagents.

10. Design for Degradation

Chemical products should be designed so that at the end of their function they break down into innocuous degradation products and do not persist in the environment.

11. Real-time analysis for Pollution Prevention

Analytical methodologies need to be further developed to allow for real-time, in-process monitoring and control prior to the formation of hazardous substances.

12. Inherently Safer Chemistry for Accident Prevention

Substances and the form of a substance used in a chemical process should be chosen to minimize the potential for chemical accidents, including releases, explosions, and fires.

Over the past ten years, Green Chemistry has reached all the frontiers of chemical research, and those principles are now well accepted and moreover becoming a regular thinking basis for chemist to design new chemical processes. Of course, no chemcial process will fulfill all of these twelve criteria. However, those processes which would fulfill several of these criteria would be already more favorable. In this thesis, we are not going to detail all of those principles. We will specifically focus on *Principle 2: Atom Econom, Principle 5: Safer Solvents and Auxiliaries* and *Principle 7. Use of Renewable Feedstocks.*

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1.1.1 Atom Economy

The concept of atom economy was first proposed by Trost in 1991(**Scheme 1**) [2]. At about the same time Sheldon proposed the very similar concept of atom utilisation, but it is the atom economy name that has become widespread in use [3, 4]. Atom economy is simply defined as:

$$\text{Atom economy} = \frac{\text{Molecular wt. of the desired product}}{\text{Molecular wt: of all products}} \; 100\%$$

Scheme 1: The definition of Atom economy.

An example of a reaction with perfect atom economy is the MBH reaction, shown in **Scheme 2** (further discussion will be present in the fellowing chapter). In this reaction all of the atoms from the two starting materials are incorporated into the product, there are no co-products and so the atom economy is 100%. In contrast a reaction with poor atom economy is the Wittig reaction, has an atom economy of 18.5%. While the concept of atom economy is simple and can be calculated directly from the reaction scheme, it has a number of downsides. It does not take into account reaction yield, or stoichiometry or make any allowance for the amount of solvents or other reagents used either in the reaction or the work up.

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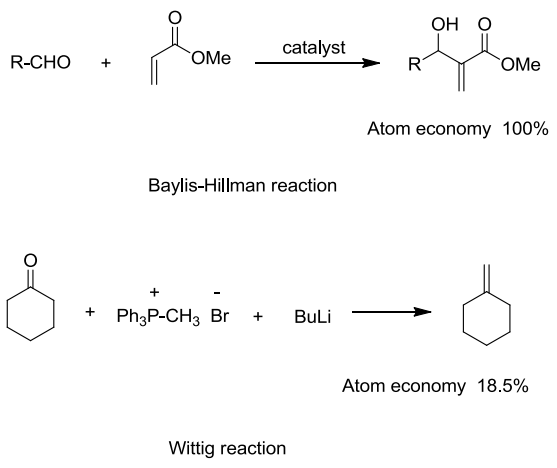

Scheme 2: Example of the Baylis-Hillman reaction and the Wittig reaction.

1.1.2 Green and sustainable solvents

Solvents are liquid substances that are able to dissolve, dilute or extract other compounds without modifying them chemically. Solvents constitute around 80% of the total volume of chemicals used in a process [5]. Up to now, the most commonly used solvents in industrial applications are the aliphatics, the aromatics, the terpenic and chlorinated hydrocarbons, the alcohols, the esters, the ketones, the glycol ethers and other miscellaneous solvents, most of them being from petrochemical origin [6]. However, over the past 20 years, environmental and health concerns have given birth to several drivers that tend to modify the panorama of industrial solvents. Regulations limiting the use or even prohibiting some classes of solvents have been adopted, as for instance European directives 1999/13/EC and 2004/42/EC for air quality limiting the emission of Volatile Organic Compounds (VOC) [7]. Being conscious of this problem for a long time, the chemical industry is continuously searching for innovative and safe media with the aim of maximizing the sustainability and safety of chemical processes.

The term “green solvent” has been used by Capello *et al.* [8] to “express the goal to

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minimize the environmental impact resulting from the use of solvents in chemical production". Alternatively, Estévez proposed that a "green solvent" has to bear a number of environment, health and safety characteristics that differentiate it from existing "hazardous solvents" [9]. Although the general idea is to minimize health and environmental risks, there is a lack of agreement concerning the exact definition of what a green solvent is. Hence, in order to well define what is a green solvent, also following the inspiration of the twelve principles of green chemistry proposed by Anastas and Warner, Gu and Jérôme [10] list below the twelve criteria that a green solvent needs to meet:

(1) Availability: a green solvent needs to be available on a large scale, and the production capacity should not greatly fluctuate in order to ensure a constant availability of the solvent on the market.

(2) Price: green solvents have to be not only competitive in terms of price but also their price should not be volatile during time in order to ensure sustainability of the chemical process.

(3) Recyclability: in all chemical processes, a green solvent has to be fully recycled, of course using eco-efficient procedures.

(4) Grade: technical grade solvents are preferred in order to avoid energy-consuming purification processes required to obtain highly pure solvents.

(5) Synthesis: green solvents should be prepared through an energy-saving process and the synthetic reactions should have high atom-economy.

(6) Toxicity: green solvents have to exhibit negligible toxicity in order to reduce all risks when manipulated by humans or released in nature when used for personal and home care, paints, etc.

(7) Biodegradability: green solvents should be biodegradable and should not produce toxic metabolites.

(8) Performance: to be eligible, a green solvent should exhibit similar and even superior performances (viscosity, polarity, density, etc.) compared to currently employed solvents.

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(9) Stability: for use in a chemical process, a green solvent has to be thermally and (electro)chemically stable.

(10) Flammability: for safety reasons during manipulation, a green solvent should not be flammable.

(11) Storage: a green solvent should be easy to store and should fulfill all legislations to be safely transported either by road, train, boat or plane.

(12) Renewability: the use of renewable raw materials for the production of green solvents should be favored with respect to the carbon footprint.

Even so, finding “green” alternatives to in-place solvents is still not an easy task. Because the “greeness” of a solvent relate to very diverse parameters and considerations, there is no general rule in the search for a green solvent. So a universal green solvent does not exist and the green aspect of a solvent is closely dependent on the reaction considered. Nowadays, the so-called: “green solvents” (**Fig. 10**) described in the current literature were *water* [11], *ionic liquids* [12], *bio-based solvents* [10], *deep eutectic solvents* [13, 14] and *supercritical fluids* [15].

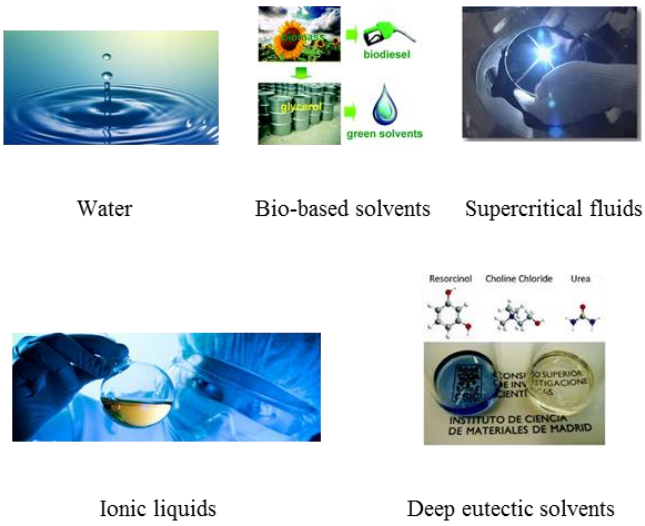

Fig. 10: “Green solvents”

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1.1.3 Use of Renewable Feedstocks

There is a growing interest for one of the key element of green chemistry, namely the substitution of non-renewable fossil resources (crude oil, coal and natural gas) by renewable biomass as a sustainable feedstock for the manufacture of chemicals. The switch to renewable biomass as a feedstock will afford an environmentally beneficial reduction in the carbon footprint of commodity chemicals and liquid fuels. The advantages of using biomass as a chemical feedstock is illustrated by Bozell [16]:

1. A huge array of diverse materials, frequently stereochemically and enantiomerically defined, is available from biomass giving the user many new structural features to exploit.
2. Biomass is already highly oxygenated, and could be used to avoid problems with oxidation.
3. Increased use of biomass would extend the lifetime of diminishing crude oil supplies.
4. The use of biomass could be a way to mitigate the buildup of CO_2 in the atmosphere because the use of biomass as a feedstock results in no net increase in atmospheric CO_2 content.
5. A chemicals industry incorporating a significant percentage of renewable materials is secure because the feedstock supplies are domestic.
6. Biomass is a more flexible feedstock than is crude oil.

The estimated global production of biomass amounts to ca. 10^{11} tonnes per annum which is divided into ca. 60% terrestrial and 40% aquatic biomass [17]. Surprisingly, only 3-4% of these compounds are used by humans for food and non-food purposes. It consists of ca. 75% carbohydrates and 20% lignin, with the remaining 5% comprising triglycerides (fats and oils), proteins and terpenes (**Fig. 11**). Biomass carbohydrates are the most abundant renewable resources available, and they are

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currently viewed as a feedstock for the Green Chemistry of the future.

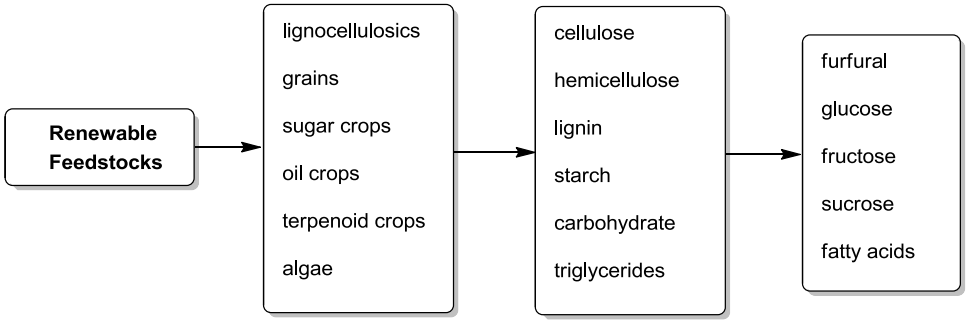

Fig. 11: Biomass refining

1.2 The use of carbohydrate as renewable resources

Carbohydrates play an important role in industrial society as they form the basis for the manufacture of sugar, starch, paper, wood pulp and heat. On another hand, carbohydrates and their derivatives are essential biomolecules that key play roles in many biological processes, such as the immune system, fertilization, preventing pathogenesis, blood clotting, and development. Polysaccharides also serve for the storage of energy (for example: starch and glycogen), and as structural components (for example: cellulose in plants and chitin in arthropods).

Nowadays, a hot spot for carbohydrate chemistry concerns their uses as a renewable resource for chemistry. Many research groups have in the past decades focused their work on finding new ways and methods for transforming carbohydrates (either small sugars or polysaccharides) into useful functional molecules of valuable chemical intermediates [18-26].

However, the chemical transformation of carbohydrate is rather complex, due to the polyfunctionnality of those moleculars. The structural complexity exhibited by carbohydrates is at the same time a gift and a challenge to chemists, allowing a wide

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range of innovation and applications, but also requiring methods showing selectivity and able to adapt to the peculiar chemical sensitivity of sugars. Therefore, in order to avoid the formation of side products, conventional processes require assistance of protective and deprotective agents, resulting in low yielding, multistep sequences. But here, because targets are of low or medium added value (sugar-based surfactants, complexing agents and polymerisable compounds), processes should include only a few steps, preferably one or two. (**Fig. 12**)

fossil resources:	*renewable resources:*
HYDRO-CARBONS	**CARBO-HYDRATES**
C_nH_{2n+2}	$C_{n(}H_2O)_n$
oxygen-free, lacking functional groups	overfunctionalized with hydroxyl groups

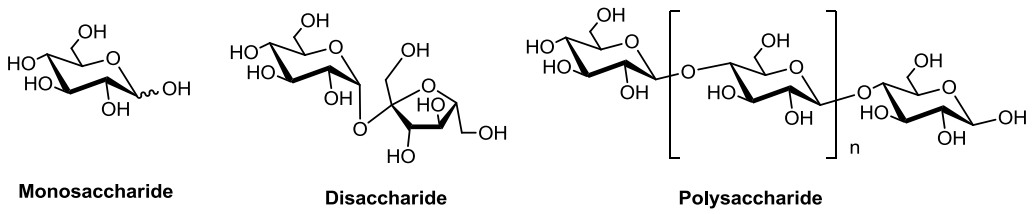

Fig. 12: Hydrocarbons vs carbohydrates

There are several types of chemcials which can take advantage of the specific polyol strcuture of carbohydrates, primarily surfactant and polymers, and those two types of compounds are briefly overviewed in the next sections (**Fig. 13**).

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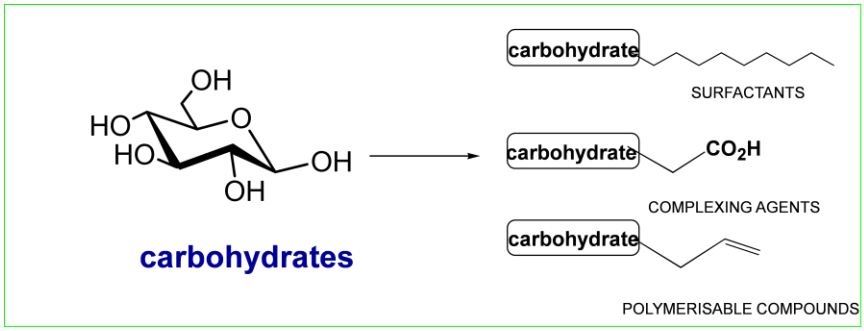

Fig. 13: Raw materials derivatized from carbohydrates.

1.2.1 Carbohydrate-based surfactants

Surfactants are used in every corner in daily life. **Fig. 14** shows surfactant market demand in the US in 2007 [27]. Among them, sugar-based amphiphiles rank high among compounds that are designed due to carbohydrates abundance in Nature and of their easy access [28].

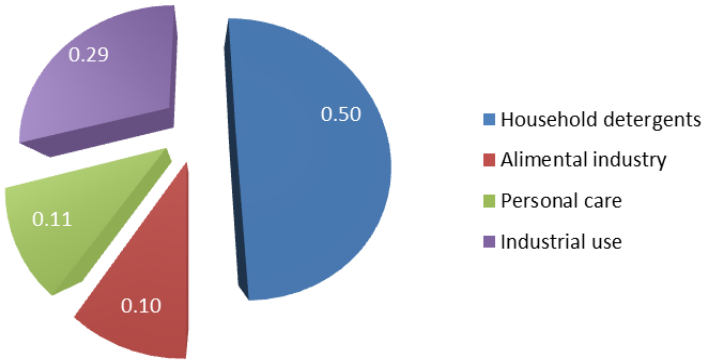

Fig. 14: US surfactants market demand in 2007

The raw materials for producing sugar-based amphiphiles, such as monosaccharides or disaccharides are abundant of easy access, like for example for sucrose which is obtained by crystallization from concentrated cane sugar or sugar beet juice. Though plenty of methods have been used to bind the carbohydrate moiety to an hydrophobic tail, on the industrial point of view (price, quality, properties), only a few carbohydrates

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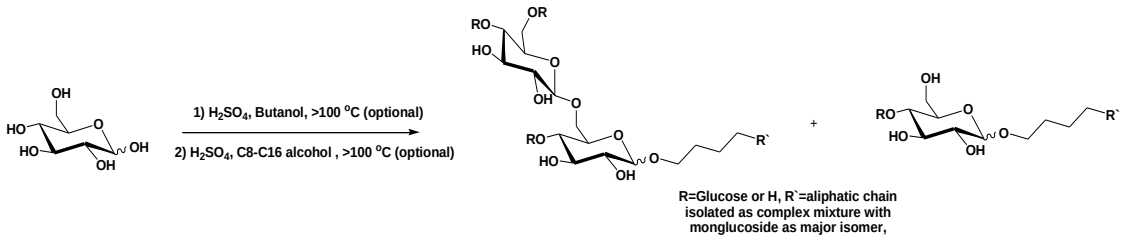
derived surfactants have reached the commercial stage. Thus, more convenient and economically acceptable manufacturing procedures in industrial scale are still under research. Nowadays, the best-known carbohydrate based surfactants are alkyl polyglycosides (APGs), sorbitan esters, and sucrose esters.

1.2.1.1 Alkyl polyglucosides (APGs)

APGs are the most extensively studied carbohydrate based surfactants [29]. As the starting materials are from fatty alcohol and glucose or starch, they are the first commercial series to offer a variety of properties based on the green chemistry concept [28]. The synthesis method is known as the Fischer glycosydation reaction. Currently, the industrial available processes are the direct glycosydation and double alcohol exchange [30]. The double alcohol exchange process employs short chain alcohol, like butanol, as reagent to convert glucose into *O*-alkylglucoside at the first step, which is the solvent in the following transglycosidation with long chain fatty alcohol (C8~C16), as shown in **Scheme 3**. This process is not as popular as direct glycosydation since the latter process could save time and control the selectivity. An alternative is enzymatic synthesis, using β-glucosidase as catalyst which yields only the β-anomer though such processes are less easy to be used in large scale syntheses. APGs are widely used as the liquid dishwashing agents and personal care products for C12/14 series, cleaners for hard surface and industrial cleaning for C8/10 series.



Scheme 3: Industrial manufacturing procedure for obtaining alkyl polyglucosides

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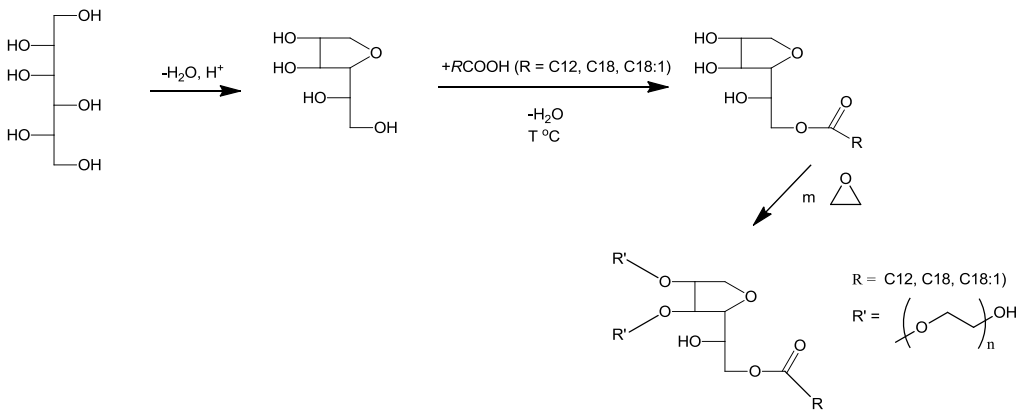
1.2.1.2 Sorbitan esters

Known under the trade name of Span™ (sorbitan alkanoates) and Tween™ (ethoxylated sorbitan alkanoates) [31], the sorbitan esters find main applications in pharmaceuticals [32], cosmetic products [33], latex polymerization [34]. **Scheme 4** shows the general synthetic procedure for obtaining sorbitan esters [35].



Scheme 4: Synthetic procedure for obtaining sorbitan esters

1.2.1.3 Sucrose esters

The only commercially available surfactants using sucrose as the polar head are the sucrose esters, which are found in the food emulsification, personal care and pharmaceutical domains. Because of multifunctionalities as three primary alcohols, five secondary alcohols, and two anomeric carbons on the sucrose matrix [28, 36], it is difficult to control the degrees of substitution: 255 distinct possible isomers with varying degrees of substitution can be obtained from acylation with a single fatty acid. However, due to rapid acyl group migration towards primary positions [37], fatty chains are essentially found at the primary position in the final products.

Early condensed process was performed in DMSO or DMF [28, 30, 36], in which the

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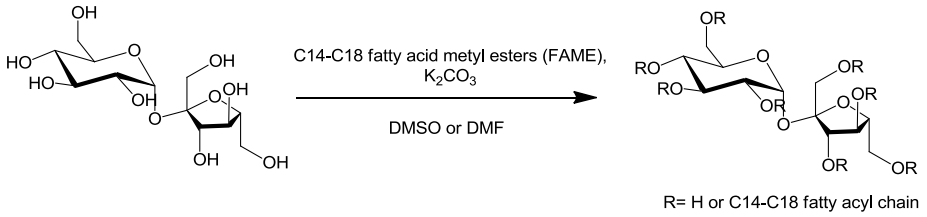
sucrose could be dissolved, with K_2CO_3 as the basic catalyst, shown in **Scheme 5**. But the problematic removal of solvent made it not easy to conduct, so an important know-how has been developed to have this reaction optimized for industrial production, for example, transesterification and solvent-free process. These methods have been proved to have a good yield and facile workup.



Scheme 5: Industrial manufacturing procedure for obtaining sucrose esters.

1.2.1.4 Glycolipids and glycolipid biosurfactants

Another rich resource of carbohydrate amphiphiles is found in the natural organisms [38-40], these glycolipids, the biological name of carbohydrate amphiphiles, are known to play key roles in immune and endocrine systems, fertilization, brain development, prevation of pathogenesis and blood clotting [41, 42]. The glycolipid biosurfactants discovered as the metabolic compounds from fermentation of microorganisms are also found very important in some specific domains. Owing to their biocompatibility and some ecological advantages, they were firstly considered as the alternatives to chemical surfactants, but as their unique properties explored recently and optimized conditions for large scale manufacturing, they will be seen in great growth in the cosmetic, medical domains [40]. Glycolipids are widely found in the cell membranes [42]. The most common seen glycolipids in the organisms are glycosphingolipids (GSLs), glycoglycerolipids (GGLs) and glycosyl phosphopolyprenols (GPPPs) [29]. Among them, GSLs and GGLs are those which

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are the most studied. GSLs are widely distributed in the eukaryotes, some prokaryotes and viruses [43], containing a hydrophobic ceramide anchor *N*-acylsphingosine and a hydrophilic head group composed of sugars, which could be sorted into three subgroups: cerebrosides, globosides, and gangliosides. Since many important biological behaviors like cell-cell recognition, membrane transport, are related to the activity of this species, thousands of studies have been dedicated to this type of glycolipids. It was found that absence or a too low level of GSLs may cause some physiological problems. GM1 (**Fig. 15**), a kind of GSLs, is found to one of important components forming a microdomain, “lipid raft”, in the membranes for selective membrane transport [44].

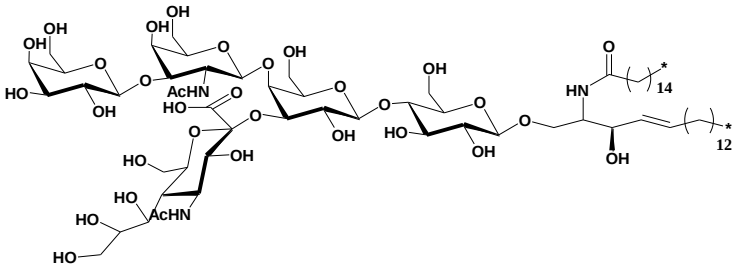

Fig. 15: Chemical structure of GM1 ganglioside.

Glycoglycerolipids are found in chloroplasts of plants and eukaryotic algae and in cyanobacteria [45]. Monogalactosyl- and digalactosyl-diacylglycerol (MGDG and DGDG) are two major glycoglycerolipids found. The DGDGs are found to play a crucial role in plant growth, thylakoid function and protein import into chloropalsts [46]. One of this kind of compound digalactosyldiacylglycerol mono-estolides, isolated from oat seeds, is shown in **Fig. 16** [47].

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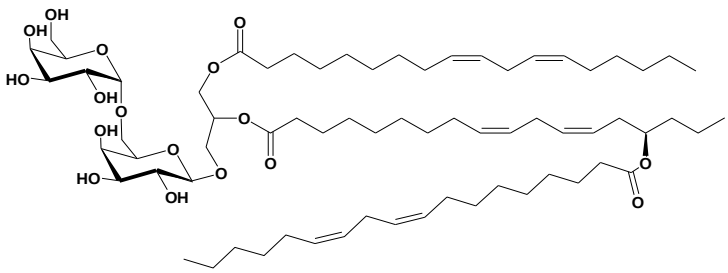

Fig. 16: Digalactosyldiacylglycerol mono-estolides were reported in oat kernels.

1.2.2 Carbohydrate-based polymers and glycopolymers

As biomimetic counterparts of natural polysaccharides, carbohydrate-based polymers and glycopolymers have received much attention lately. Such synthetic polymers displaying saccharide moieties play a central role at the interface between polymer science and biology due to potential biocompatibility and also enhanced carbohydrate-protein interactions benefitting from multivalency [48]. Applications of glycopolymers include among others, therapeutics [49], cell sensing [50], tools for glycobiology as selectin antagonists [51], model biomembranes [52], targeted drug/gene delivery [53], or synthetic biology [54].

Some reviews have been published on the synthetic carbohydrate-based polymers and glycopolymers [55]. They refer mainly to two types of structures: i) polymers having the sugar units incorporated into the main chain (**Fig. 17**); ii) polymers having the sugar as a groups pendant from the main chain (**Fig. 18**).

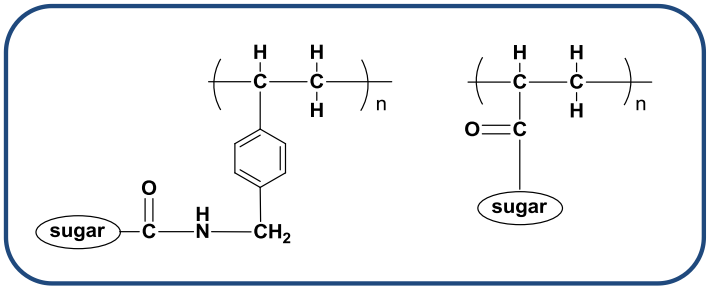

Fig. 17: Structure of polymers having the sugar units incorporated into the main chain

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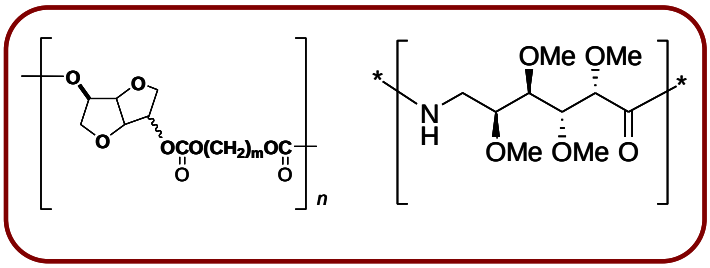
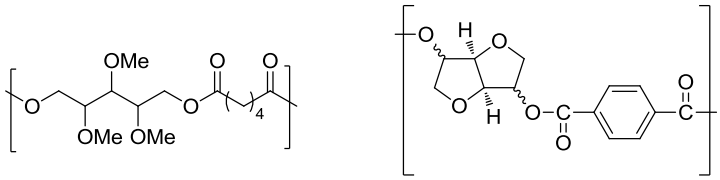


Fig. 18: Structure of polymers having the sugar as a groups pendant from the main chain

It is feasible to prepare sugar-based monomers, by introduction of an polymerizable functional group like amino group, carboxylic acid group, urethane group and urea group, etc…which led to a series of enhanced hydrophilicity and degradable carbohydrate-based polymers.

1.2.2.1 Polyesters

Polyesters can be divided into two different kinds of catalogues: aliphatic polyestes and aromatic polyesters. Sugar-based aliphatic polyestes was synthesized by polycondensation reaction of carbohydrate-based diols with hydroxy acids or dicarboxylic acids [56]. Also these polyesters are biodegradable, they often lack of good thermal and mechanical properties. On the other hand, aromatic polyesters, have excellent mechanical properties, but are resistant to degradation by chemical or biological agents (**Fig. 19**).



aliphatic polyestes aromatic polyesters

Fig. 19

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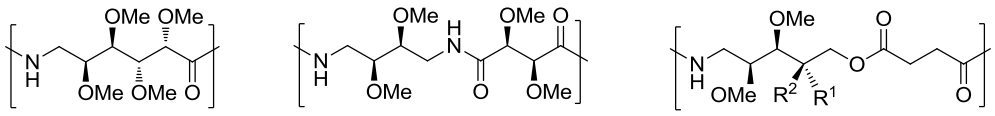
1.2.2.2 Polyamides

Polyamides has been the carbohydrate-based polymers most widely studied. The polymerizable sugar monomer required for the synthesis of polyamides should be diamino-sugar, aldaric acides or aminoaldonic acides. The multifunctionality of sugars required several protection and deprotection steps. The introduction of amino froup is generally accomplished by preparation of sulfonyl ester, nucleophilic displacement by azide and subsequent hydrogenation reaction. A groups of AB-Type and AABB-Type polyamides were synthesized from the corresponding carbohydrate-based monomers [57]. In some cases, ployesteramides were also prepared by active ester polycondensation methold (**Fig. 20**) [58].



AB-Type polyamide AABB-Type polyamide ployesteramide

Fig. 20

1.2.2.3 Polyurethanes and Polyureas

Galbis et al used the secondary *O*-protected L-threitol, L-arabinitol and xylitol as monomers for the preparation of a series of linear [*m.n*]-type polyurethane by polycondensation in solution with 1,6-hexamethylene diisocyanate (HDI) and 4,4'-methylene-bis(phenyl diisocyanate) (MDI) [59a]. They found that the alditol size, that is the number of methoxy side froups present in the repeating unit, seems to be of prime important in the determining the hydrodegradability of these polyurethanes (**Fig. 21**). Galbis and co-workers also obtained a polyurea by polyaddition reaction of the

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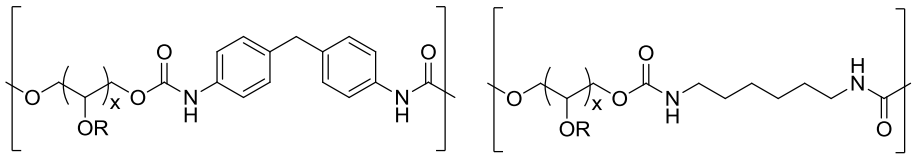
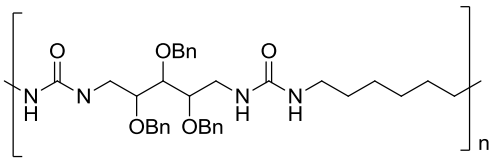
diaminopentitol with 1,6-hexamethylene diisocyanate (HDI) [59b]. This polymer was also a semicrystalline material that showed high melting temperature and thermal stability up to 250 °C (**Fig. 21**).



R = Me, Bn

x = 2,3 (L-threitol, L-arabinitol, xylitol)

Polyurethanes



Polyurea

Fig. 21

As reported recently by Moebs-Sanchez and Cramail in a work arising in part from our laboratory [60], two novel sugar-based fatty ester polyols were used as polyurethane precursors in the polyaddition with isophorone diisocyanate (IPDI) in the presence of dibutyl tin dilaurate as a catalyst (**Fig. 22)**. Interestingly, the reactivity of the hydroxyl functions attached to the sugar and to the fatty ester chain moieties respectively could be discriminated with respect to the solvent used, enabling the synthesis of either linear or cross-linked sugar based polyurethanes.

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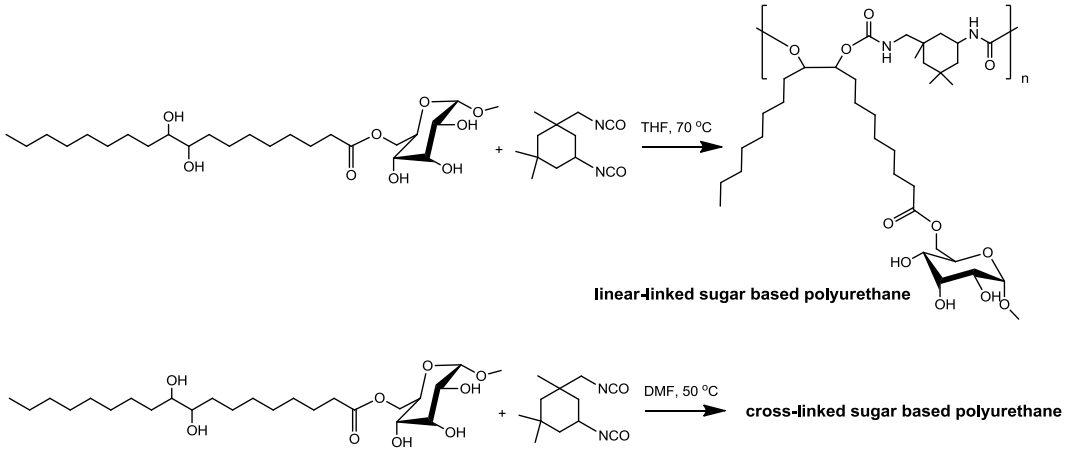

Fig. 22

1.3 Isomaltulose and its chemistry

Among sugars which are widely available, isomaltulose **1** is an interesting disaccharide. Isomaltulose (6-*O*-α-D-glucopyranosyl-D-fructofuranose, also referred to as Palatinose®), is synthesized from sucrose by bioconvesion on the industrial scale [61]. It has been used as a food in Japan since 1985 [62].

Depending on the microorganism used for the biochemical isomerisation different glucose-fructose disaccharides can be obtained [63-65]. Analogous fructose-containing disaccharides can also be produced either by degradation of naturally occurring oligosaccharides [66, 67] or by chemical isomerisation using sodium aluminate (**Scheme 6**) [68].

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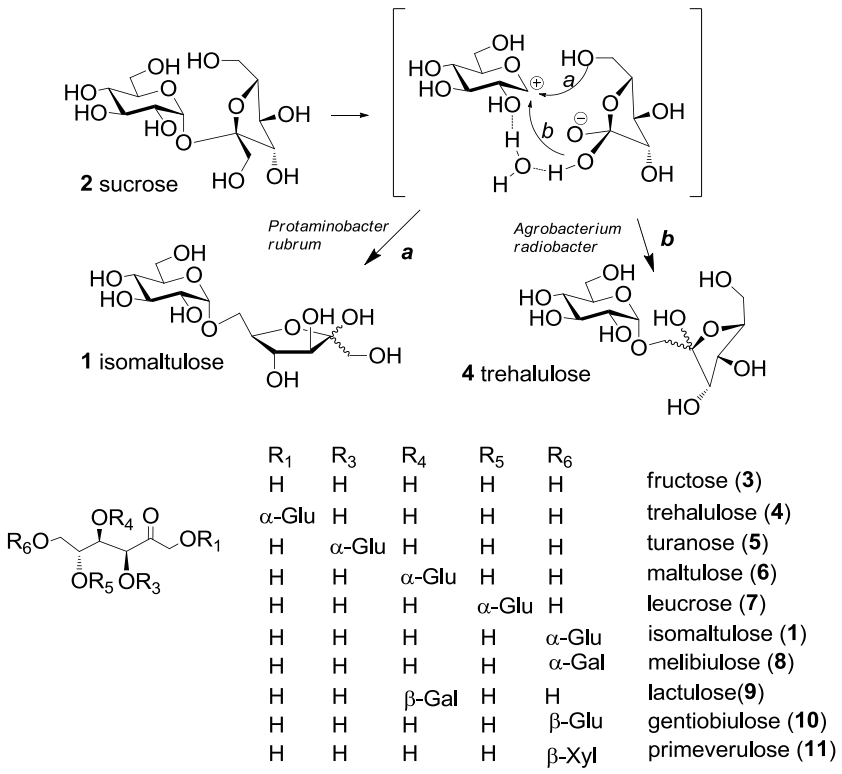

Scheme 6

In solution (DMSO, water, pyridine), isomaltulose is mainly present in the form of its fructofuranose, with the β anomer as the major one [68]. In this β form, an intramolecular H-bond with OH-2 of the glucose moiety is evidenced in the crystalline state [68, 69]. In DMSO, the open chain form was also identified by NMR in a 3 to 5 % ratio. A recent review covers the main biological routes to sucrose analogs, in particular using enzymatic processes [70].

The chemistry of isomaltulose, in part schematized in **Scheme 7**, has been intensely studied since late 1980's notably by the groups of Lichtenthaler and Kunz who reported very sensible routes towards various kinds of derivatives [36, 71, 72]. Main strategies are those based on the hydrogenation (to **12**) or reductive amination of the ketone function (to **13** or **14**), on the oxidative degradation to glucosylated carboxylic acids such as **15** or **16**, in which the fructosyl moiety has been partly cleaved, and on the triple dehydration product of the fructosyl moiety, glucosyloxymethylfurfural **17**.

After a brief overview of some aspects of isomaltulose chemistry, we will focus on two

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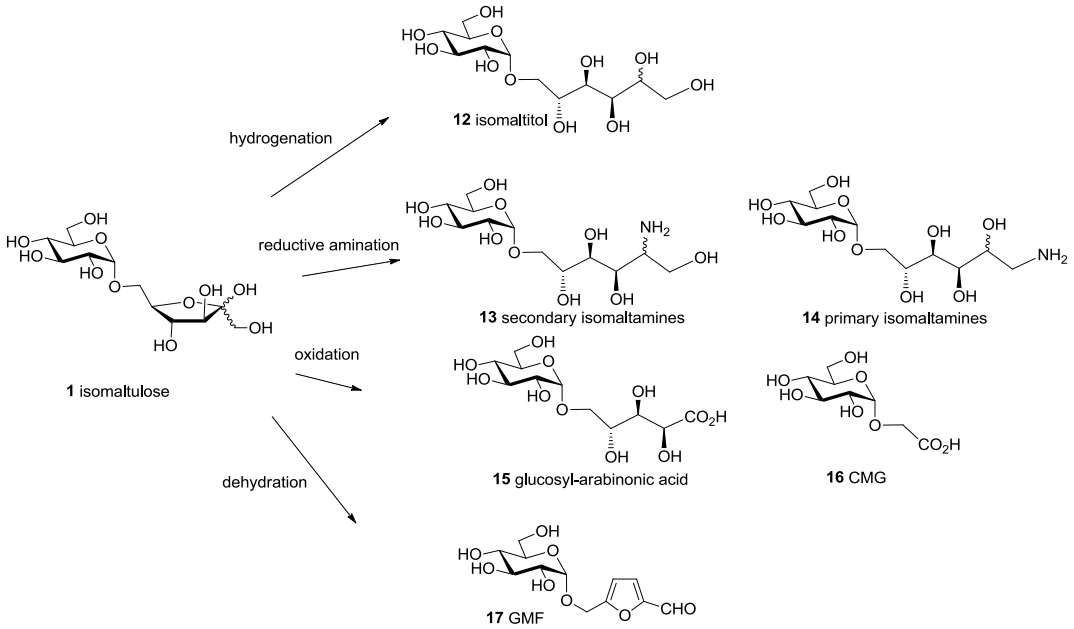
types of reactions and products, those derived from carboxylic derivatives such as those obtained by different oxidation methods, and those which concern glucosyloxymethylfurfural (GMF), obtained by the triple dehydration under methods similar to those used for the synthesis of hydroxymethyl furfural (HMF) from fructose. After highlighting the work by other groups, we will notably overview our recent results related to these two types of approaches from isomaltulose, achieved in the context of our work dedicated to application of carbohydrates as organic raw materials [22, 23, 36, 73, 74].



Scheme 7: The main chemical transformations of isomaltulose.

1.3.1 Background on isomaltulose chemistry

Isomaltulose, like sucrose, is a disaccharide made of glucose and fructose, however having its glycosidic bond connecting C-1 of the glucosyl moiety and O-6 of the fructosyl one. Therefore, isomaltulose possesses a hemiketalic function (the masked ketone function of the fructose moiety) which can be discriminated from the other hydroxyl groups, whereas the chemistry of sucrose mostly relies on selective OH

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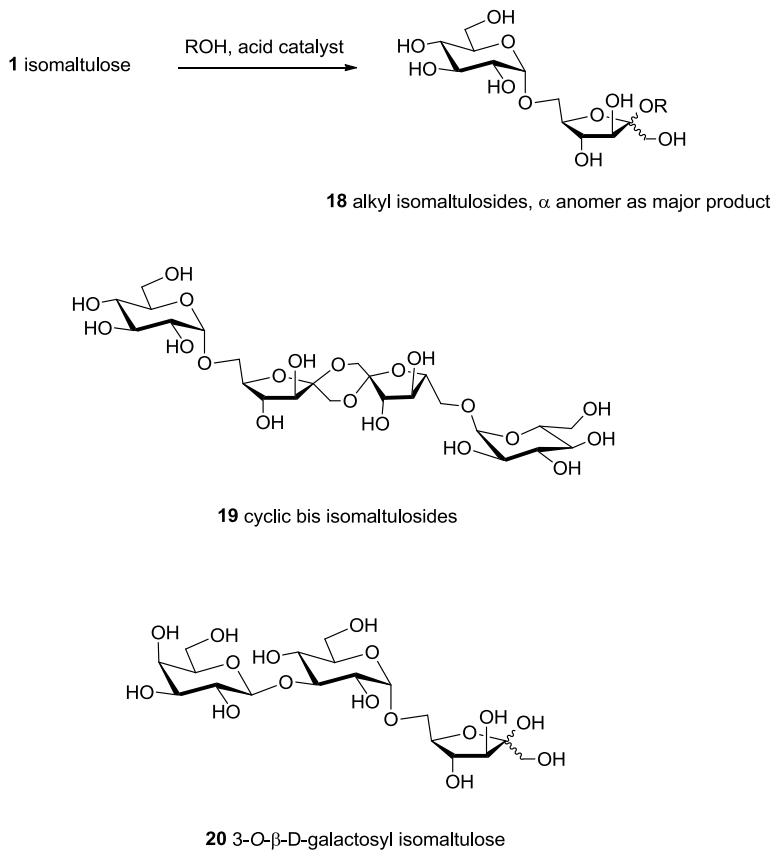
group transformations because both anomeric carbons are connected together [36, 74].

Of course, like any other reducing sugar, isomaltulose can also undergo glucosidation reactions. Either simple alkyl glycosides can be obtained by treatment with alcohols in the presence of acidic catalysts [75], or dimeric spirodioxanyl tetrasaccharides such as those found in mixtures of oligosaccharides obtained by treatment with citric acid [76] or more selectively synthesized by activation with hydrogen fluoride (**Scheme 8**) [77, 78].



Scheme 8

As any other sugar, isomaltulose can be functionalized by reaction of its non anomeric hydroxyl groups. For example, enzymatic galactosylation at the OH-3' can be achieved by treatment of isomaltulose with β-galactosidase [79].

Enzymatic esterification of isomaltulose leads to amphiphilic esters. In a comprehensive study on acylation of various disaccharides using the protease

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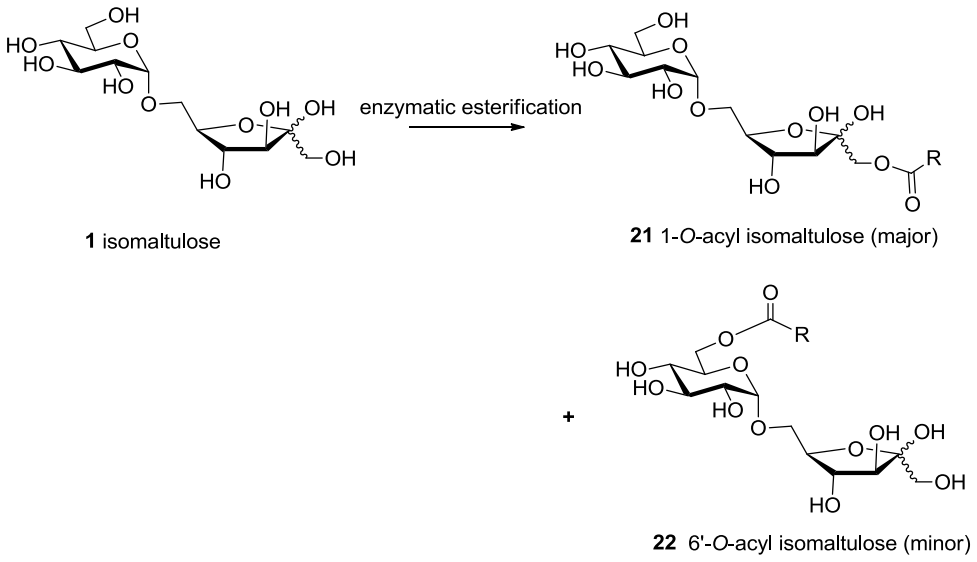
subtilisin as catalyst, the OH-1 of isomaltulose was found to be more reactive than the other primary hydroxyl, OH-6' [80]. More recently, the lipase from *Candida antarctica* was used to form different disaccharidic esters including isomaltulose myristate (**Scheme 9**) [81].



Scheme 9: Enzymatic esterification of isomaltulose.

By reaction with amines, isomaltulose can be transformed to several types of nitrogen containing heterocycles (**Scheme 10**). For example, the synthesis of imidazoles such as **23** by reaction of formamidine acetate with isomaltulose in the presence of hydrazine was reported by Lichtenthaler and co-workers [71]; it was recently revisited using a melt of ammonium carbonate as ammonia source and medium [82]. Pyrazoles were also synthesized from isomaltulose by reaction with phenylhydrazine. An intermediate bis phenylhydrazone **24** evolves to the pyrazole **25** upon acetylation, which then can lead to variously functionalized glucosylated pyrazoles **26** and **27** (**Scheme 5**) [83]. Another reaction involving the ketone group of isomaltulose with an amine is the Heyns rearrangement which leads to N-acetyl-(6-*O*-α-D-glucopyranosyl) glucosamine **28** in 40% yield (**Scheme 11**) [84].

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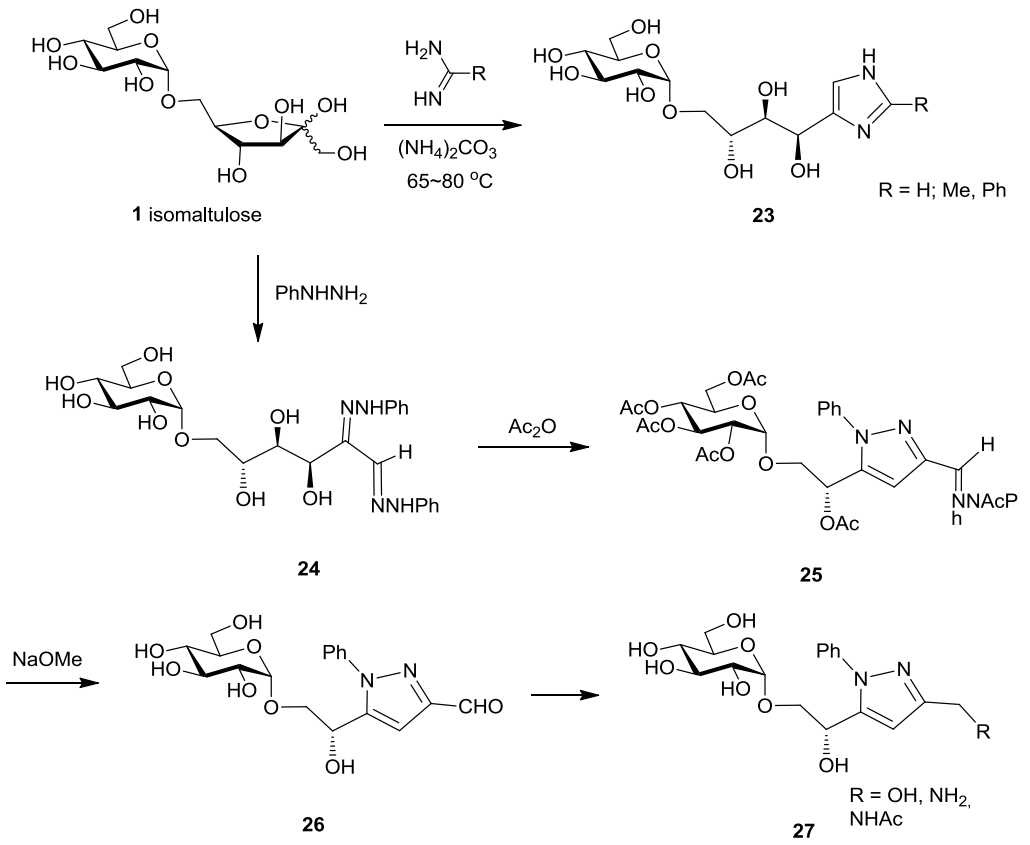
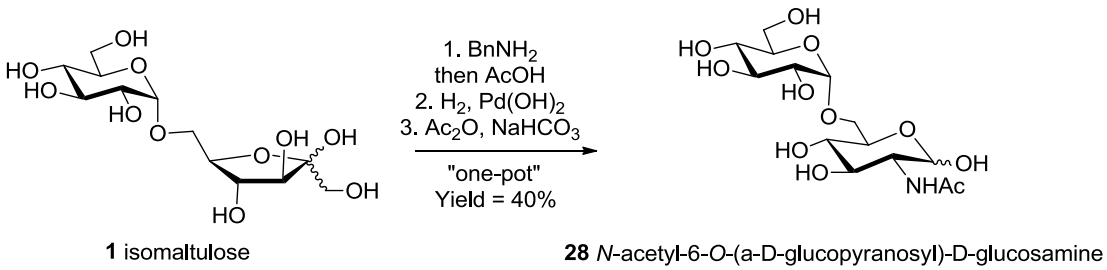


Scheme 10



Scheme 11. Heyns rearrangement of isomaltulose.

Preparation of isomaltitol **12** (also referred to as isomalt or palatinit), obtained by hydrogenation of the carbonyl group, and used as a food additive and in many applications is the main industrial application of isomaltulose [25, 85]. Isomaltulose or isomaltitol can be used as polyols for preparing amphiphilic derivatives such as **29** via ester or ether linkages by reaction with esters, acylhalides or alkylhalides [86]. Other amphiphilic isomalt ethers **30** and **31** were prepared by palladium catalyzed

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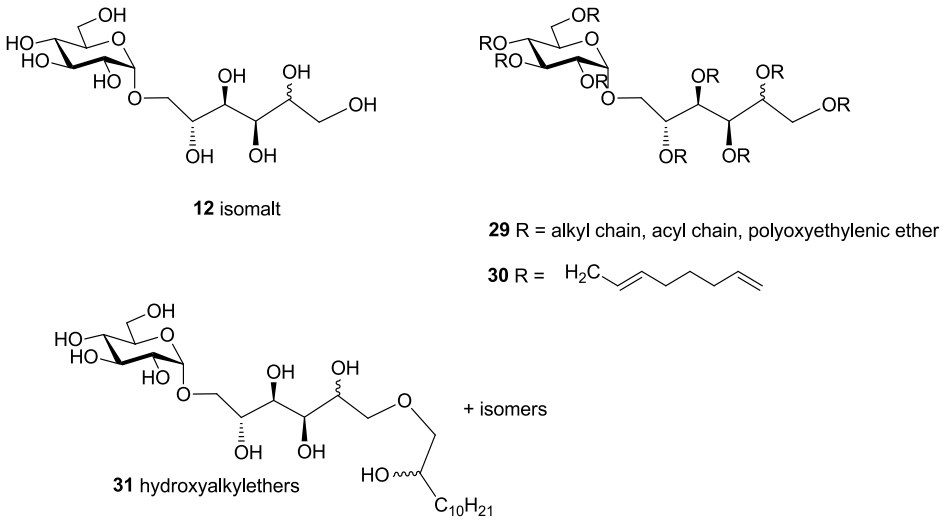
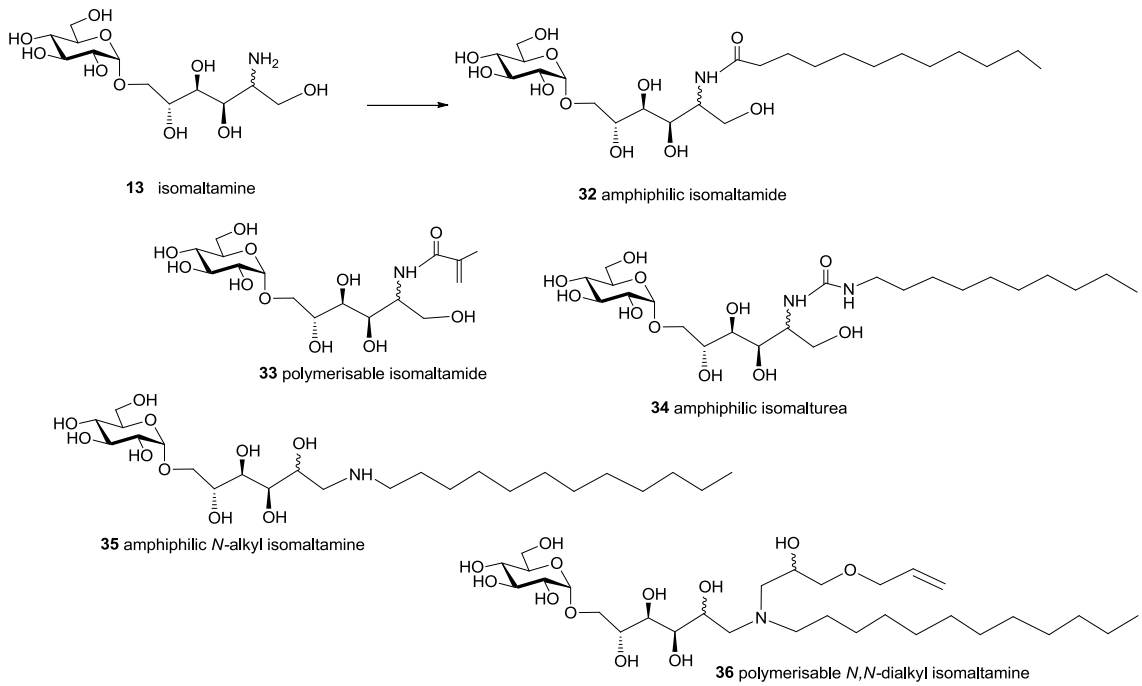
telomerisation of butadiene [87] or base catalyzed fatty epoxide ring-opening (**Scheme 12**) [88]. Reductive amination of Palatinose® offers also various routes from **13** towards surfactants or monomers such as compounds **32** to **36**, following classical strategies applied to glucose or other available reducing sugars (**Scheme 13**) [89-91].



Scheme 12: isomalt and isomalt derivatives.



Scheme 13

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1.3.2 Oxidation of isomaltulose

Oxidation products of carbohydrates are useful in the context of the design of biobased chemical intermediates and products, since polyhydroxycarboxylates have potential industrial applications due to their cation sequestering properties [92, 93]. They have received considerable interest in recent years, with methodological studies in all fields of chemical [94, 95] and biochemical oxidation [96, 97]. This applies to polysaccharides (starch, cellulose, chitin…) and also to smaller sugars, and in particular sucrose and isomaltulose which are available on the industrial scale. In this section, several oxidation methods will be discussed especially in the context of isomaltulose chemistry: i) oxidation of primary alcohols to carboxylic acids using oxygen in the presence of platinum or using the TEMPO hypochlorite oxidizing system, 2) biochemical oxidation to 3'-oxo isomaltulose and their derivatives, 3) oxidative degradation of the fructosyl moiety of isomaltulose to glucosyl arabinonic or 4) glycolic acids, leading also to lactones which serve as synthons towards various types of neoglycoconjugates.

1.3.2.1 Oxidation with the Pt/O_2 and TEMPO systems

The Pt/O_2 and the TEMPO oxidizing systems are normally used for selective oxidation of primary alcohols to carboxylic acids. For example, this method has been applied to sucrose, leading to derivatives with carboxyl groups at the primary positions [98-102]. In the case of the Pt/O_2 method, the issue is to get defined products among the mono-, di-, and tricarboxy-derivatives, with difficulties related with catalyst poisoning which prevent to reach polycarboxylated products. Continuous extraction of the monocarboxylated derivatives from the medium by electrodialysis was reported [103, 104]. Heyns [105, 106] and van Bekkum [107] have thoroughly investigated the field of catalytic oxidation of carbohydrates and established some general rules which are: i) aldehyde function of aldoses is readily oxidized; ii) the alcohol functions require

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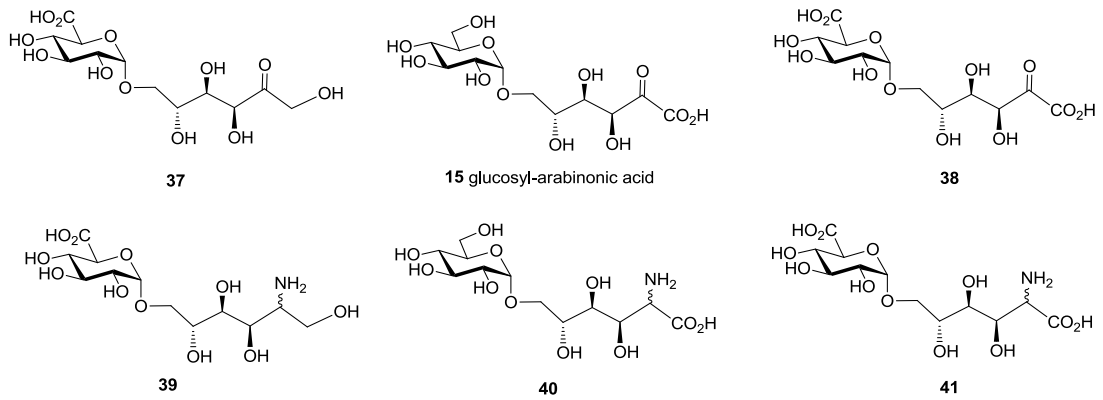
more aggressive reaction conditions, with primary ones reacting faster than secondary ones; iii) primary alcohols adjacent to the carbonyl group in ketoses react faster, nearly as fast as an aldose. Therefore, it was expected that OH-1 of isomaltulose would be oxidized more rapidly (to provide **15**) than OH-6' (leading to **37**), but it was found by Kunz and coworkers that both positions actually underwent oxidation in similar rates, forming compound **38**. The carboxylated derivatives of isomaltulose can undergo reductive amination providing aminoacids **39, 40, 41** (**Scheme 14**) [108, 109]. Such products were further used for the synthesis of monomers by reaction with isocyanatoethyl methacrylate [110] or by simple methacryloylation leading to monomers which were used in various polymerisation conditions [111].



Scheme 14

The hypochlorite-TEMPO system has found successful applications in the oxidation of polysaccharides [111, 112] and unprotected small carbohydrates [113-117]. Oxidation of isomaltulose [118] however, is not selective and leads to a mixture of four methyl esters (characterized as their peracetylated derivatives: **42**, **43**, **44**, and **45**) differing by the length of the chain arising from the fructose moiety, associated with a glucose moiety which is either unchanged or oxidized at the C-6. The presence of products **42** and **44**, not oxidized at C-6, and the absence of any product with the unchanged fructose part and oxidized at C-6, confirm that the oxidative cleavage occurring on the

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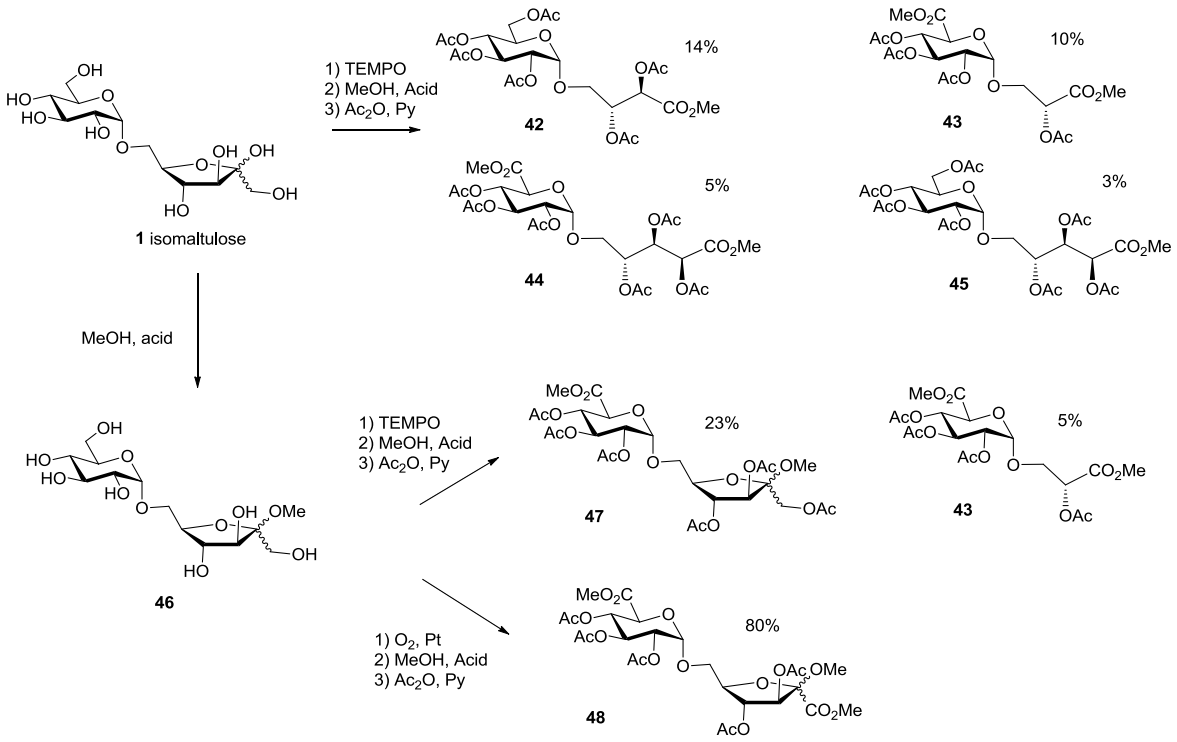
fructose ring is always faster compared to the primary alcohol oxidation, as already observed in the case of inulin. Applied to methyl isomaltuloside **46**, a mixture of products is also obtained in which the major ones were characterized as their peracetylated methyl ester derivatives **43** and **47**. Alternatively, the Pt/O_2 oxidation of methyl isomaltuloside proved to be much more efficient and led selectively to 6'-monocarboxylated methyl isomaltuloside **48** in good yield (**Scheme 15**).



Scheme 15

1.3.2.2 Microbial oxidation to 3-keto isomaltulose

Microbial oxidation of disaccharides to 3-keto products was originally reported by De Ley et al. [119]. The active catalyst of the reaction was found to be the D-glucoside 3-dehydrogenase of *Agrobacterium tumefaciens*. Being very selective and rather efficient, this bioconversion was further investigated by the groups of De Ley and Buchholz. It was in particular applied in the synthesis of 3-keto-sucrose, from which

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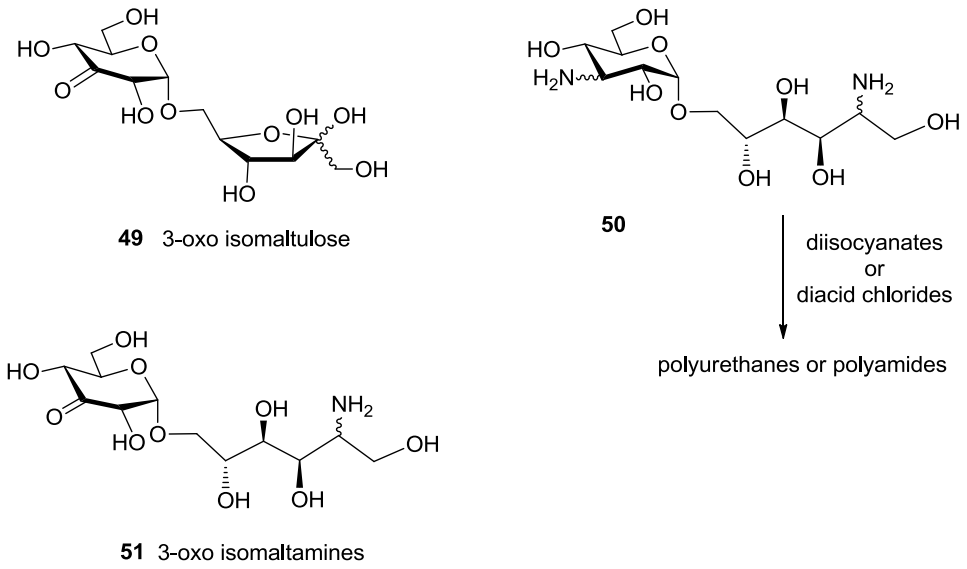
several interesting new sucrose derivatives, such as sucrose 3-epimer or amino derivatives could be obtained [120-123]. The reaction was found to be even more efficient when applied to isomaltulose, which led to 3-ketoisomaltulose (**49**) in good yield. Careful kinetic investigations of the reaction conditions with respect to oxygen concentration and pH were performed [124]. 3-Ketoisomaltulose could be further transformed to aminated derivatives **50** by reductive amination, after careful optimization of the reaction conditions for preventing base-catalyzed retro aldol degradation of the starting 3-keto compound. The resulting diamino product **50** was used in poly-addition reactions with diisocyantes leading to carbohydrate containing polyurethanes or in polycondensation reactions with dicarboxylic acid dichlorides [108, 111, 125]. The oxidation reaction catalyzed with D-glucoside 3-dehydrogenase is thus rather general and highly selective in terms of regiochemistry with respect to OH-3 of the glucose moiety. However, important variations in the structure of the substrate are acceptable, as illustrated by the ability to oxidize also 6-*O*-(α-D-glucopyranosyl)-D-2-amino-2-deoxy-mannitol **13**, obtained by reductive amination from isomaltulose, which led the corresponding 3-keto analogue, or glucopyranosylmannitol **51** (**Scheme 16**) [126].



Scheme 16

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1.3.2.3 5-Glucosyl arabinonic acid and derivatives

Under strongly alkaline conditions, the reaction of isomaltulose with oxygen provides glucosyl arabinonic acid **15**, isolated by crystallization of its potassium salt in 80-90% yield. This reaction is particularly efficient as compared to other substrates such as fructose itself or other fructosyl disaccharides. It results probably from easier formation of the enediolate precursor when the substrate is predominantly in the furanosyl form [108, 127]. Several studies by Lichtenthaler and Kunz groups have demonstrated the usefulness of glucosyl arabibonic acid. Notably, it could be transformed to the methyl ester **52** then reduced to the arabinitol analog **53** or isomaltitol **12**. By reaction with amines, the amides **54** and **55** are formed, and when fatty amine is used, the products exhibit surfactant properties. The liquid crystalline properties of a series of fatty amides such as **55** were investigated, showing smectic A mesophases (**Scheme 17**) [128].

Glucosyl arabinonic acid is transformed to its lactone **56** by simple treatment with strongly acidic resin. While DIBAL reduction of this lactone afforded the 5-*O*-glucosyl arabinose disaccharide (characterized as its peracetate **57**); many other interesting synthons could be also prepared. Notably, once the lactone was perbenzoylated to give **58**, base catalyzed elimination led to compound **59**, in which the carbon-carbon double bond could be specifically hydrogenated to 3-deoxy-D-threo-pentonic acid lactone **60** in high yield. Alternatively, SmI_2 reduction of lactone led to the furanone **61** which could also be further hydrogenated to its saturated counterpart **62** [129]. Such carbohydrate based lactones are extremely useful synthons for grafting sugars on other chemical architectures (**Scheme 17**) [130, 131].

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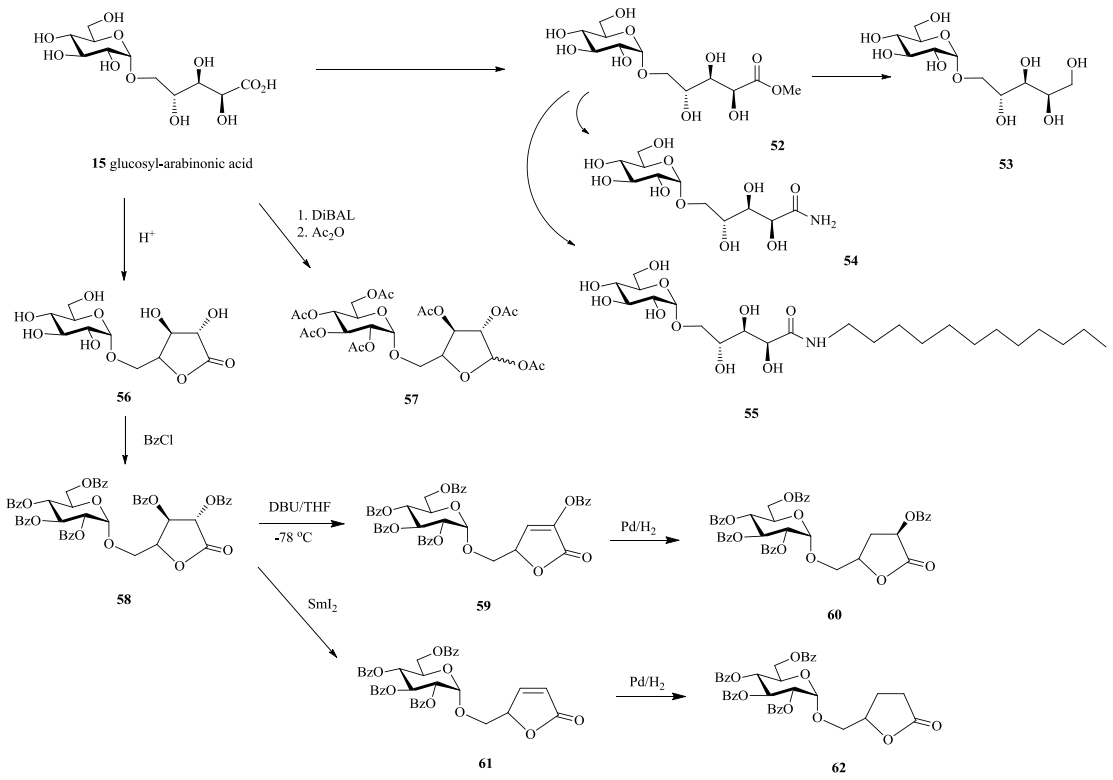

Scheme 17

1.3.2.4 Carboxymethyl glycoside (CMG) and carboxymethyl glycoside lactones (CMGLs)

Carboxymethyl α-D-glucopyranoside (CMG, **16**) can be obtained by simple oxidation of isomaltulose by hydrogen peroxide in acidic media. This one-step process, using cheap reagents and simple reaction conditions, is an attractive alternative to previous syntheses despite rather low yield (ca. 35%) [132]. Another alternative is simple Fischer glycosylation of glycolic acid with glucose in the presence of hydrochloric acid, described by Petersson *et al.*, but the yield is even lower 6% yield, and it leads to a 70:30 α/β mixture [133]. CMG was also obtained from trehalulose or from isomalt. The addition of sodium tungstate, known to promote the oxidative cleavage of glycols *via* peroxotungstate species [134-137], was indispensable in the case of isomaltulose [138] whereas for isomaltulose and trehalulose led only to slightly higher yields. CMG could be obtained on a 5-10 g scale. The product obtained by acetylation of CMG is its

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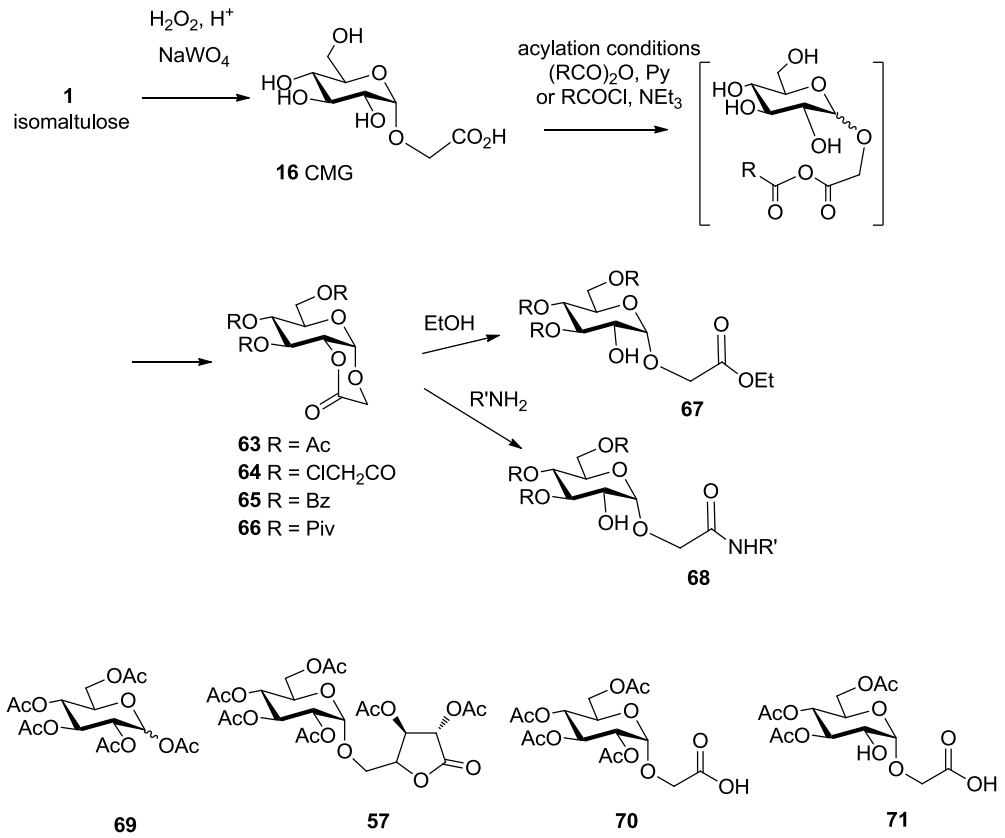
2-*O*-lactone (CMGluL, **63**) which was found to be easily opened with alcohols or amines leading to esters or amides **67** and **68** [130-141].

Among side products after acetylation, were found: lactone **57** (**Scheme 18**), resulting from incomplete oxidation to glycosyl arabinonic acid, glucose pentaacetate **69** arising from CMG hydrolysis, tetraacetyl carboxymethyl glucoside **70** or its analog having free OH-2 **71** reflecting the opening of the lactone during the reaction or at the work-up stages. Other acylating reagents (chloroacetyl chloride, pivaloyl anhydride or benzoyl chloride) can be used in order to tune the stability of the protecting groups in **64-66**. Similar lactones with variations in the sugar type, the anomeric configuration, mono- or disaccharides were also prepared by the oxidation of allyl glycosides or anomeric alkylation with *tert*-butylbromoacetate [138, 142, 143].



Scheme 18

The reactivity of these lactones, and in particular of gluco-CMGL arising from isomaltulose, was studied in different conditions. Reaction with alcohols in either basic or acidic media led to the corresponding esters having a free 2-OH while all three other

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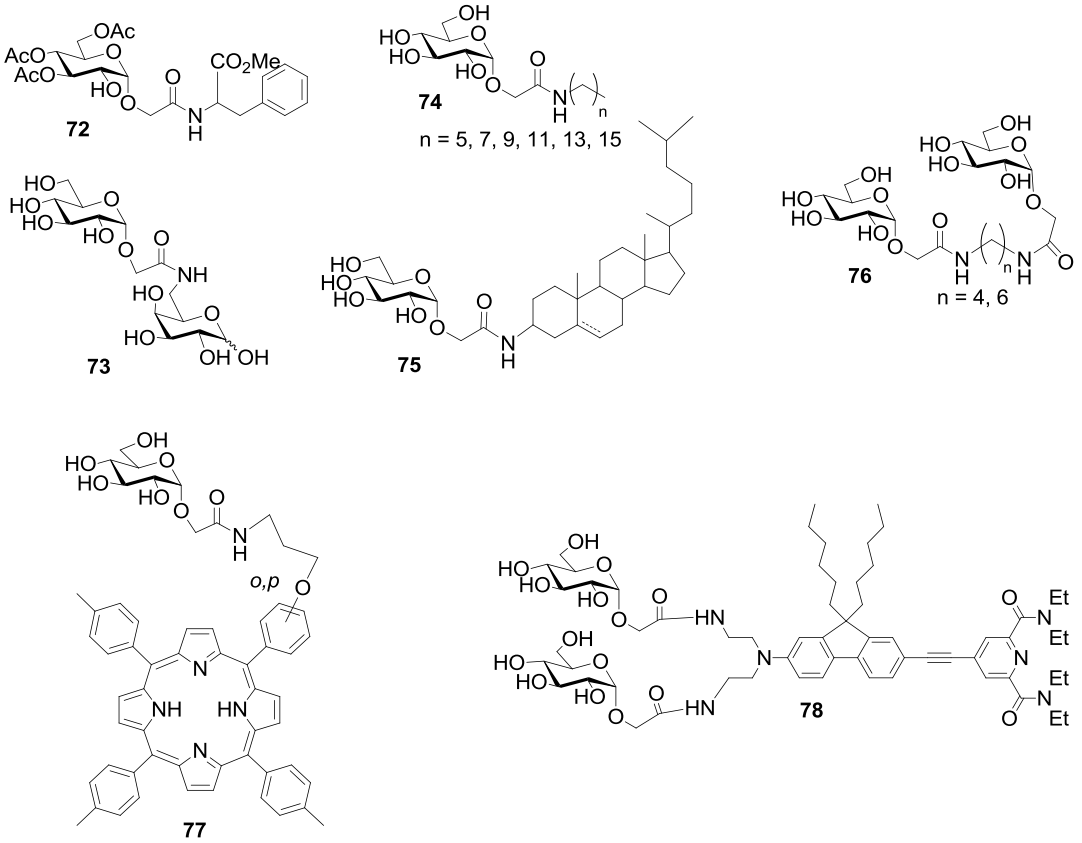
positions: 3, 4 and 6 were acetylated. As shown in **Scheme 19**, the scope of the reaction with amines is wider, because the amides formed are more stable and can be used further. The reaction with amines proved to be very general giving good to excellent yields of a wide range of pseudoglycoconjugates such as: glycoaminoacids hybrids such as **72** [139], pseudooligosaccharides such as **73** [140], amphiphilic compounds arising from fatty amines (**74**) or aminocholesterol (**75**) [142, 143]; some of them were investigated with respect to their liquid crystalline properties in the context of a more general study of liquid crystalline glycolipids [144]. Bolaamphiphiles (**76**) were obtained by reaction with diamines [139].

Glucosylated porphyrins such as **77**, potentially useful for cancer photochemotherapy, were prepared by reaction of CMGL with amino functionalized porphyrins [145, 146] and found to exhibit clearly improved photoactivity compared to the non-glycosylated ones. Original membrane imaging probes exhibiting non-linear optical properties were also prepared [147].



Scheme 19

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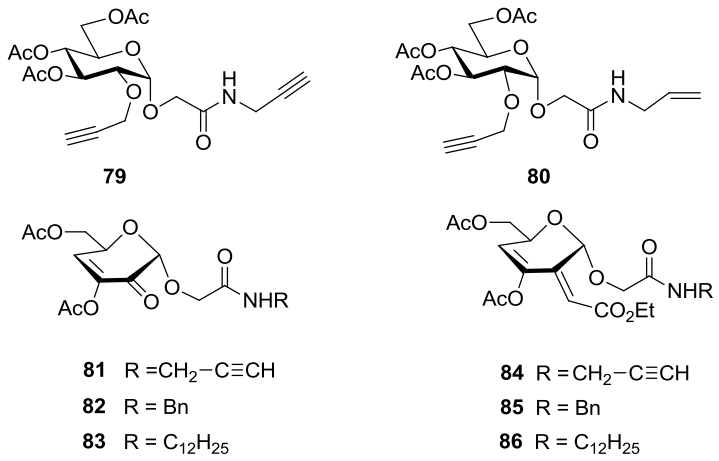
One advantage of CMGL synthons is the possible subsequent functionalisation at the position 2 which readily yields 1,2-bisfunctionalized carbohydrates derivatives. Several examples of such systems are depicted in **Scheme 20**, including diyne and enyne **79**, **80**, and unsaturated derivatives **81-83** (obtained after oxidation of the OH-2 and concomittant elimination) further elongated to compounds **84** by Wittig olefination. Interesting antifungal and antibacterial activities were found for these two last types of products [148]. This method was applied to the synthesis of two new types of carbohydrate-based monomers. The first example represents a series of azido-alkynes prepared from **87** by formation of the triflate **88** followed by sodium azide substitution to **89**, deprotected to the bifunctional 2-deoxy-2-azido manno derivative **90** which underwent copper (I)-catalyzed azide-alkyne polyaddition [149]. The second kinds of monomers are acrylamides which were used in RAFT (reversible addition fragmentation chain-transfer) polymerization reactions. Monomers were prepared by acryloylation of the intermediate aminoethylamide derivative **92**. Whereas the 2-OH gluco monomer **93** readily polymerized to **95** as expected, reaction of the 2-N_3-manno monomer **94** was more difficult, and was only able to produce **96** at a lower temperature, thus necessitating a more reactive initiator (**Scheme 21**) [150].



Scheme 20

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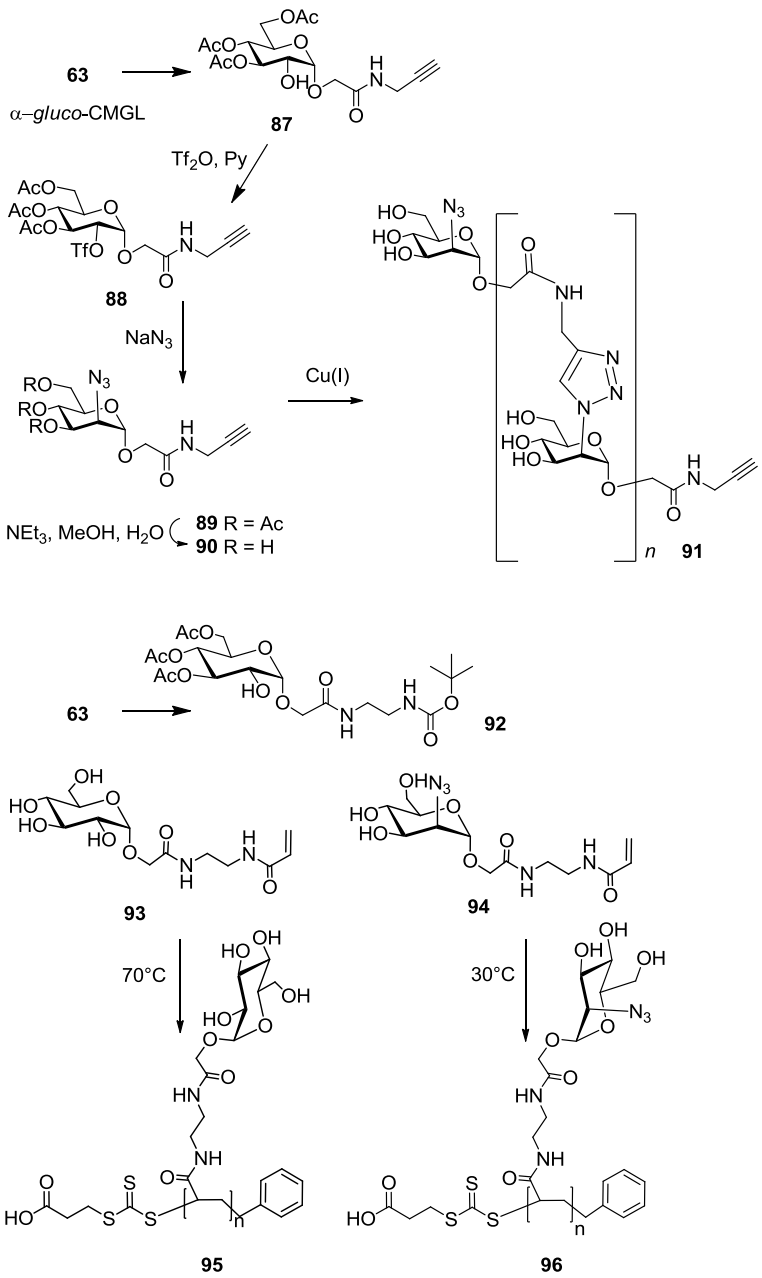

Scheme 21

Overall, a number of products can be designed by exploiting isomaltulose oxidation products. Besides carboxy-isomaltulose and glucosylarabinonic acid derivatives offering easy accesses to many different targets, the CMG 2-*O*-lactone which arises from carboxymethyl glucoside appears also as an interesting synthon, providing an original way towards 1,2-bisfunctionalized carbohydrate derivatives.

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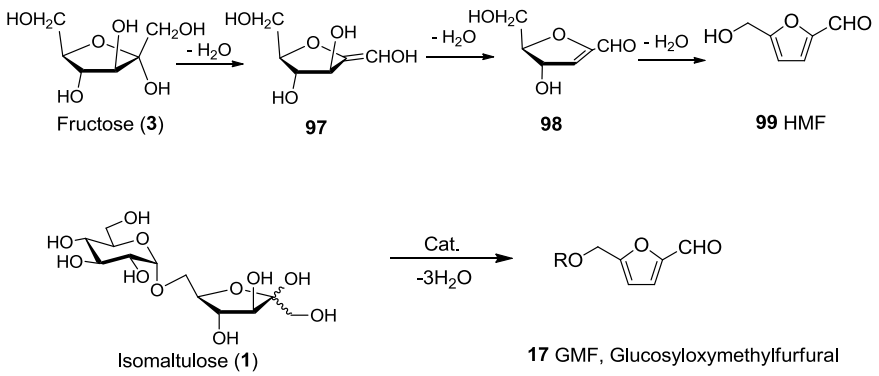
1.3.3 Dehydration of isomaltulose to GMF

Dehydration of isomaltulose to α-D-glucosyloxymethylfurfural (GMF **17**), a glycosylated hydroxymethylfurfural, is another interesting option towards biobased derivatives (**Scheme 22**). Formation of GMF broadens the scope of hydroxymethylfurfural (HMF **99**), which appears as one of the most attractive bio-based chemicals established by Bozell and Petersen in the "Top 10 + 4 chemicals" list [24, 151-153]. The higher polarity of the products might be useful in various aspects such as novel hydrophilic polymers, surfactants, liquid crystals and other functionalized materials.



Scheme 22: General dehydration route into HMF and GMF

Compared to dehydration of monosaccharides (fructose or glucose) or selected polysaccharides [152], the conditions to generate GMF from isomaltulose required to carefully prevent undesired cleavage of the intersaccharide linkage. Dehydration of isomaltulose under aqueous acidic conditions led mostly to glucose and HMF, after hydrolysis of GMF glycosidic bond, or after prior isomaltulose hydrolysis and further fructose dehydration to HMF. Therefore anhydrous systems should be used. Compared to organic solvents commonly used to convert fructose to HMF, like dimethylformamide (DMF), acetonitrile and quinoline, dimethyl sulfoxide (DMSO) shows the best results for the dehydration of isomaltulose. As reported by Lichtenthaler *et al*. [154], GMF can be obtained in up to 70% yield by heating

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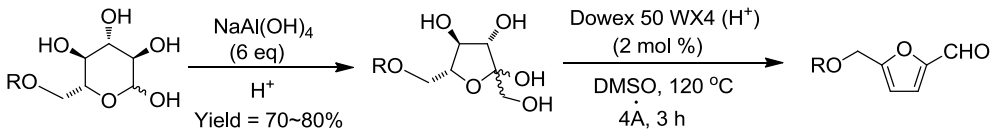
isomaltulose in DMSO in the presence of a strongly acidic ion-exchange resin (Dowex 50 WX4, H^+ form) and freshly desiccated molecular sieve, along with dimeric isomaltulose anhydrides (l0%), HMF, glucose (5-10%), and the starting material (10%). This procedure can be adapted from the batch into a continuous process using a flow reactor [155] making GMF available on possibly larger scale thus more attractive as a bio-based building block. This protocol has been further applied to access several other hydrophilic HMF analogues [68] that are: β-GalMF **100**, β-GMF **101**, and β-XylMF **102**. Their preparation from the respective disaccharides: glycosyl-(1-6)-glucoses melibiose, gentiobiose, and primeverose, involves a simple two-step process, aluminate-promoted isomerization of their reducing glucose moiety to fructose, then acid-induced dehydration of the fructose unit (**Scheme 23**).



100: R = α-Gal, Yield = 65%
101: R = β-Glc, Yield = 63%
102: R = β-Xyl, Yield = 58%

Scheme 23: Isomerization of glycosylated glucoses to their fructose analogs and their dehydration to the glycosylated HMFs.

Koenig and co-workers [156] recently developed a novel method to prepare GMF, by using isomatulose-choline chloride melts with different acidic catalysts under mild reaction conditions (**Scheme 24**). The best yield (52% yield of GMF **17** in 1 hour) was reported for $ZnCl_2$ as catalyst. Montmorillonite also showed catalytic activity in this reaction, giving 46% of GMF within 15 minutes. Due to the fact that it is nontoxic and recyclable, use of Montmorillonite as a catalyst is attractive. Although the yield are lower than in the DMSO solution protocol, such dehydration of isomaltulose in a neat melt system, without addition of any organic solvents, is a convenient and nontoxic alternative process for GMF synthesis.

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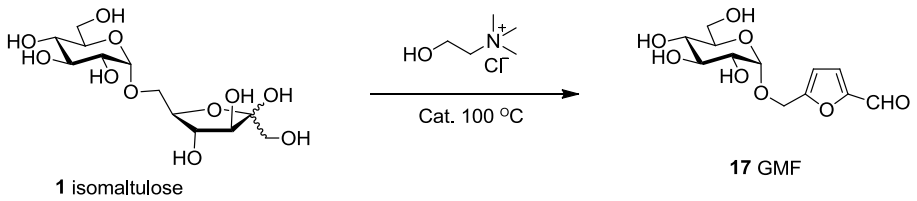

Cat.	Time (min)	Yield (%)
$ZnCl_2$	60	52
Montmorillonite	15	46
Amberlyst	15	34
p-TsOH	15	35
$FeCl_3$	15	27

Scheme 24: GMF yields for different catalysts in isomatulose-choline chloride mixture.

As described by Urashima *et al*. [157], a series of glycosylated HMF can be generated by heating HMF with galactose (**103**) in 1,4-dioxane (**Scheme 25**). Under catalyst-free conditions, four different types of HMF-galactosides were detected, namely HMF α-D-galactofuranoside **104**, HMF β-D-galactofuranoside **105**, HMF-α-D-galactopyranoside **100** and HMF β-D-galactopyranoside **106**. Heating HMF with glucose (**107**) gives HMF α-D-glucofuranoside **108**, HMF β-D-glucofuranoside **109**, HMF α-D-glucopyranoside **(GMF, 17)** and HMF β-D-glucopyranoside respectively **101**. Major products are the pyranosidic forms, as expected for glucose or galactose glycosidations. HMF D-galactopyranoside and HMF D-glucopyranoside were also detected under direct heating of galactose and glucose at 215°C in the absence of any catalysts or solvents.

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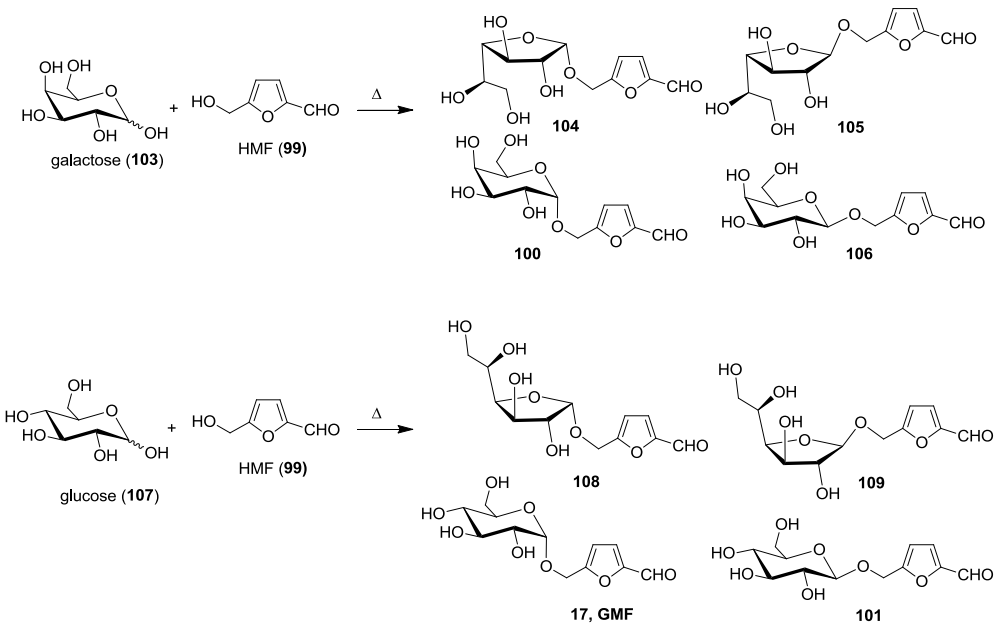
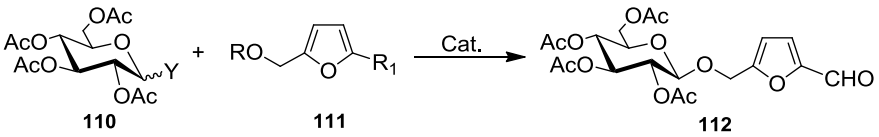


Scheme 25: The condensation of D-galactose and HMF in 1,4-dioxane.

In keeping with glycosylations of HMF, Cottier *et al*. [158] investigated preparation of peracetylated β-GMF **112** (the corresponding β anomer of GMF) by glycosylation of HMF or its silylated derivative (**Table 1**). This reaction was studied using differently activated glucosyl donors **110** and differently substituted furanoic alcohols **111**. Direct condensation of HMF with a glucosyl donor gave only moderate yield of **112** (32%).

Table 1. Condensation between glucose derivatives and the furanic alcohols.



Y	R	R_1	Condition	Yield (%)
Br (α)	H	CHO	Ag_2O, rt	11
Br (α)	H	$CH(OMe)_2$	Ag_2O, I_2, $CaSO_4$, rt	8
O-C(NH)CCl_3 (α, β)	H	CHO	$BF_3.Et_2O$, -20°C - rt	32
O-C(NH)CCl_3 (α, β)	TBDMS	CHO	$BF_3.Et_2O$, -20°C - rt	0
OAc (β)	TBDMS	CHO	$BF_3.Et_2O$, -20°C - rt	33

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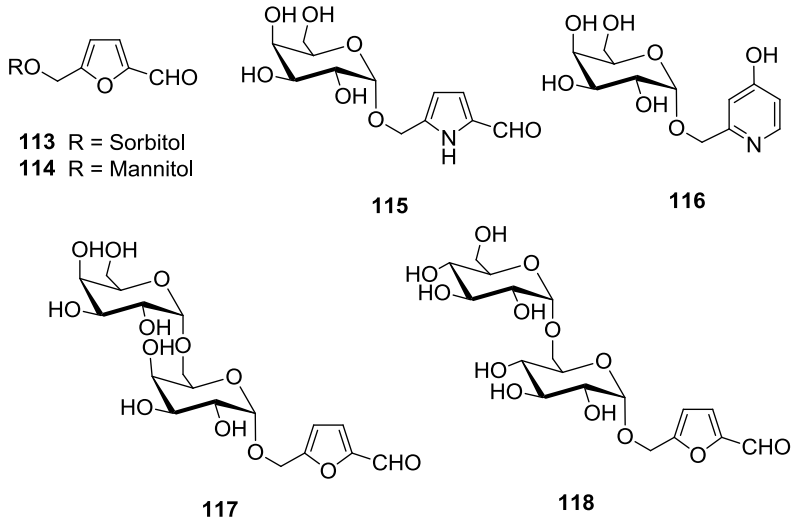
It is important to note that GMF (**17**) and some of its analogs (**100**, **101, 106**, **113**-**118**) have been also found in different natural products, plants and foods (**Scheme 26**), such as *Rehmanniae Radix* (Di Huang) [159-161], the kernel of *Prinsepia uniflora* [162], the fruit of *Amelanchier Canadensis* [163] and in commercial caramel and caramel candy [157].



Scheme 26: Chemical structures of GMF and the representative derivatives isolated as natural products.

Many reactions have been performed on GMF, involving either the aldehyde group or the furan unit [154]. A series of interesting derivatives have thus been synthesized (**Scheme 27**). Reduction of GMF by $NaBH_4$ gives the respective GMF-alcohol **122** (85%), while reductive amination provides GMF-amine **127** (97%). Selective oxidation of GMF by chlorite gives the corresponding furancarboxylic acid **119** (89%). Both GMF-amine **127** and the furancarboxylic acid **119** can be transformed to a series of non-ionic amphiphilic compounds **120**, **121**, **128-130** by esterification with long-chain alcohols or by *N*-acylation with fatty acid chlorides, respectively (Scheme **27**). Such compounds can be regarded as surfactants and also exhibit liquid crystalline properties [128]. Heating GMF with hydroxylammonium chloride provides nitrile **123** (61%), which can be further transformed to tetrazolide **124** (90%) by a [1,3]dipolar cycloaddition with sodium azide in DMF. Also GMF readily undergoes base-catalyzed

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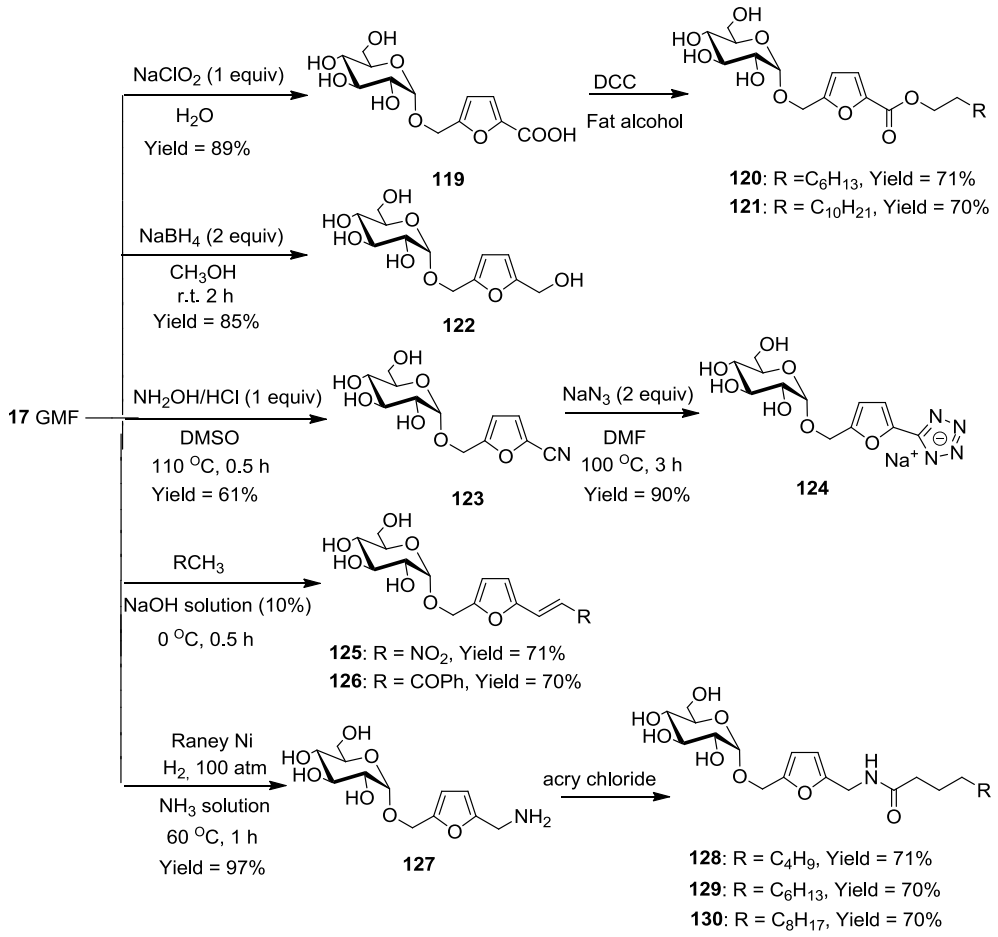
aldol-type reaction with nitromethane and acetophenone leading to the corresponding 2-nitrovinyl and 2-benzoylvinyl compounds (**125** and **126** respectively) in good yields.



Scheme 27: Reactions of the aldehyde group of GMF.

Lichtenthaler *et al.* [82, 164] reported an efficient protocol for the conversion of GMF **17**, GMF-alcohol **122,** and GMF-amine **127** into *N*-heterocycles such as: pyrrole, pyridazine, pyridinol, pyridazinone, and benzodiazepinone. Oxidation of the furan moiety of GMF or per-acetylated-GMF generated three different highly reactive γ-keto-carboxylic acid intermediates, namely **131** (85%), **132** (93%) and **133** (98%) under different reaction conditions (**Scheme 28**). The reaction between glucosylated hydroxybutenolide **131** and *o*-phenylenediamine **134** led to the formation of glucosylated benzodiazepinone **135** (65%). This product could be further dehydrogenated with 2,3-dichloro-5,6-dicyano-benzoquinone (DDQ), to glucosylated

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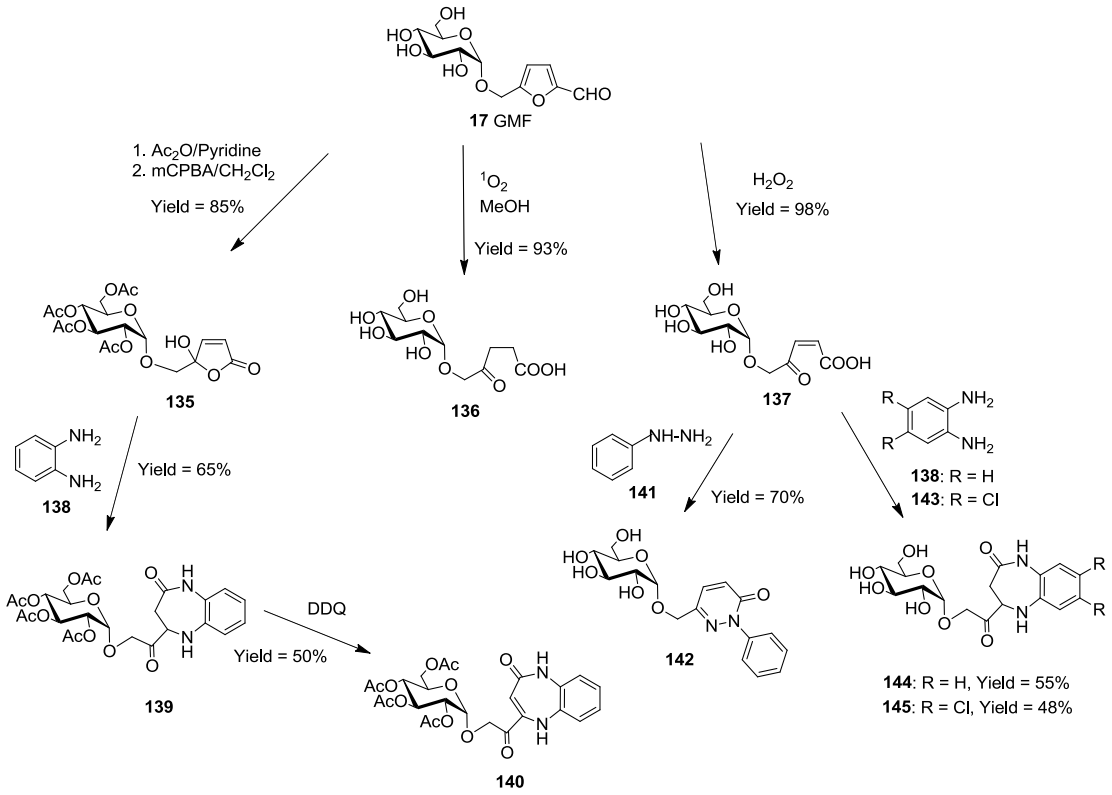
benzodiazepinone **136** (50%). Treatment of **133** with phenyl hydrazine **137** afforded pyridazinone **138** (70%), whereas with 1,2-diaminobenzene **134** or 1,2-diamino-4,5-dichloro-benzene **139** gave benzodiaze-pinones **140** (55%) and **141** (48%) respectively.



Scheme 28: Conversion of GMF into different types of ketocarboxylic acid and its futher N-heterocyclization.

Reaction between GMF-alcohol **122** and bromine in water generates glucosyloxy-*cis*-hexenedione **148**, which spontaneously cyclized to dihydropyranone **149** (95%) through Achmatowicz reaction (**Scheme 29**) [165]. Further treatment of the dihydropyranone with hydrazine gives glucosylated 3,6-dihydroxymethyl-pyridazine **150** (68%). Oxidation of perbenzylated GMF-alcohol with 3-chloroperbenzoic acid gave glucosylated *cis*-hexenediones **140** (79%). Further reduction of the olefinic double bond followed by N-cyclizations with ammonium acetate, aniline, benzylamine, and dodecylamine provided glucosylated pyrroles **144** (70%), **145** (75%), **146** (84%), **147** (83%) respectively [164].

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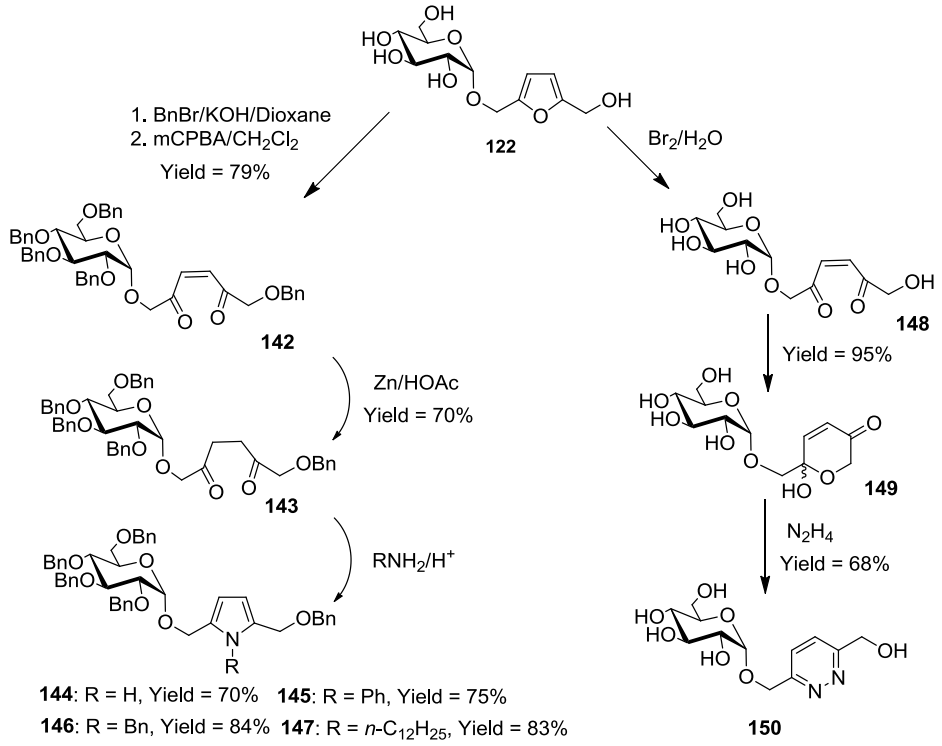
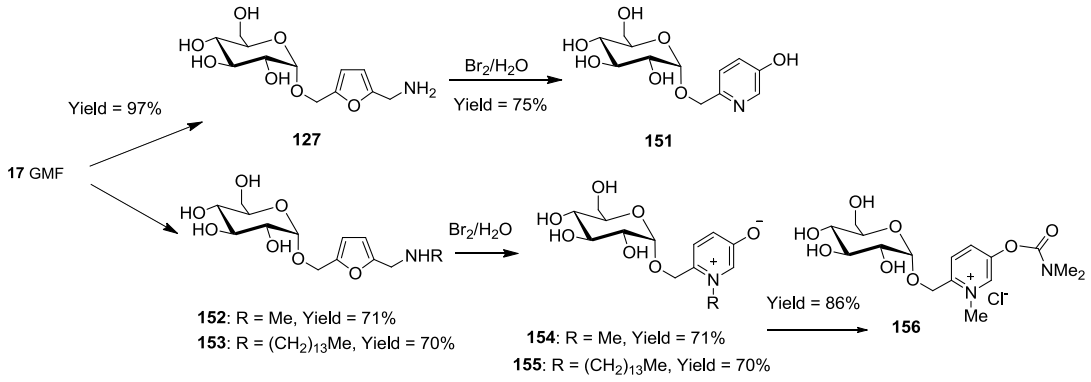


Scheme 29: Conversion of GMF-alcohol into GMF-derived pyrroles and pyridazines.

The *aza*-Achmatowicz reaction [166] of GMF-amine **127** with bromine in water gives the 6-(glucosyloxymethyl)-3-pyridinol **151** (75%) (**Scheme 30**). When the terminal group was changed to a secondary amino group, this oxidation provided *N*-alkyl pyridinium betaines **154** (71%) and **155** (70%), thus affording original cationic surface-active compounds. Through selective carbamoylation, **155** can also be converted into a hydrophilic pyridostigmine **156** (86%), exhibiting cholinesterase inhibitory activity [167].



Scheme 30: Conversion of GMF-amine into hydrophilic pyridinols, pyridinium betaines and pyfidostigmine.

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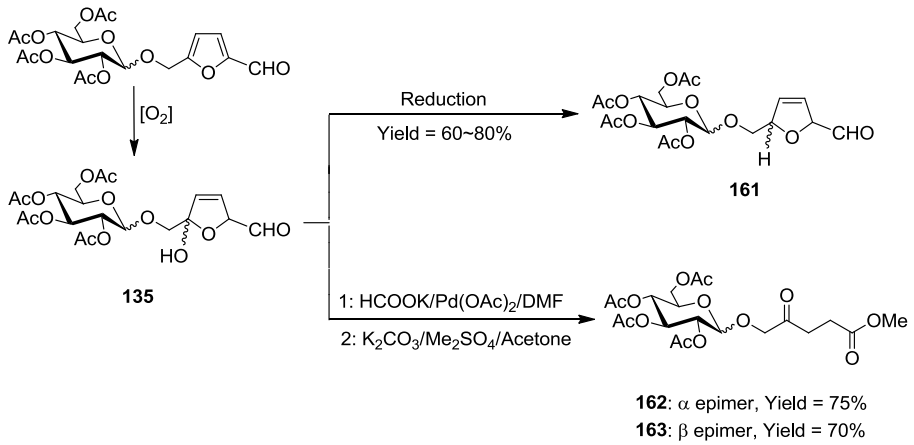
In keeping with reaction on the furanic moiety of GMF, Cottier *et al.* [158] reported that hydroxy butenolides **131α** and **131β** could be easily generated from per-acetylated GMF or β-GMF by photooxygenation (**Scheme 31**). Reduction of the same intermediate led to the acetylated diastereoisomers of acetylated diastereoisomers of ranunculin **161** (60~80%) in moderate to good yield. Alternatively, via a hydrogen transfer reaction, this intermediate gave access to γ-keto esters **162** (75%) and **163** (70%), which can be further transformed to glycosyl γ-aminobutyric acid derivatives.



Scheme 31: Conversion of α- and β-GMF into acetylated ranunculin and δ-glucosyloxy-γ-oxo esters.

Isomaltulose offers a wide range of strategies for designing new biobased chemicals. Besides its interest as precursor of the industrially relevant product isomalt, hydroxy groups transformations such as glycosidation, glycosylation, etherification, esterification, oxidation to carboxylated derivatives, and reactions of the fructose ketone with aminated reagents have demonstrated its extremely versatile interest as a starting chemical. Through the fascinating triple dehydration to GMF, the fructose structure offers additional ways towards carbohydrate-based functional compounds and materials. GMF can be further transformed in three directions, either by reaction of the OH groups, the furanic moiety or the isolated aldehyde function. Taking into account the importance of HMF in biobased chemistry nowadays, GMF finds a renewed interest as exemplified by some recent results reported above.

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1.4 Chemical transformations of carbohydrates in aqueous medium

Water, being cheap, safe, non-toxic, and environmentally benign, was recognized as the most ideal solvent for chemistry, it complies with all the current requirements on sustainable chemistry. In view of the potential reward of replacing hazardous organic solvents with water, researchers took up the academic challenge of developing new synthetic methods that were compatible with the aqueous medium. In terms of chemical characteristics, water is known for two aspects as a solvent, firstly its protic and polar character, and secondly, its high cohesive energy density which is the physicochemical origin for developing hydrophobic effects. The types of organic reactions in water are broad including pericyclic reactions, reactions of carbanion equivalent, reactions of carbocation equivalent, reactions of radicals and carbenes, transitionmetal catalysis, oxidations-reductions, which have been discussed in many revews and books:

1. Chao-Jun Li, *Organic Reactions in Aqueous Media-With a Focus on Carbon-Carbon Bond Formation, Chem. Rev.* **1993***, 93,* 2023-2035.
2. André Lubineau, Jacques Augé, Yves Queneau*, Water-promoted organic reaction, Synthesis,* ***1994****,* 741-760.
3. Chao-Jun Li, *Organic Reactions in Aqueous Media with a Focus on Carbon-Carbon Bond Formations: A Decade Update, Chem. Rev.* ***2005,*** *105,* 3095-3165;
4. Chao-Jun Li, Liang Chen, *Organic chemistry in wate, Chem. Soc. Rev.,* **2006***, 35,* 68-82.
5. U. Marcus Lindström, *Organic Reactions in Water: Principles, Strategies and Applications, Blackwell Publishing Ltd, UK,* ***2008****.*
6. Paul, T. Anastas, Chao-Jun Li; Green solvents, volume 5: Reactions *in water,* Wiley-VCH, Germany, **2008**.

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The types of organic reactions in water are broad, while, in our thesis, we only foucus on carbohydrate chemistry in aqueous media. Carbohydrates are polyols which exhibit generally good solubility in water. It was thus of interest to explore their reactivity in aqueous media, the selectivity of their transformations, and the design of specifically adapted catalysts, with the perspective of applications as several functional compounds of potential industrial interest. Many reactions can be performed on carbohydrates in aqueous media [168, 169]. This includes C-C bond formation reactions such as Knoevenagel condensations, Barbier-type reactions, Baylis-Hillman reactions, electrophilic aromatic substitution reactions. Also, C-N bond formation reactions have been well explored, including notably reductive amination. Of course, the functionalization of hydroxyl groups is itself is an important part of carbohydrate chemistry, including esterification, etherification, carbamatation, and oxidation reactions.

1.4.1 Functionalization of hydroxy groups

The esterification and carbamatation reactions have been investigated in water using sucrose. Sucrose is not soluble in many solvents, and those which are the most often used, DMF, DMSO or pyridine. Sucrose being very soluble in water, this becomes a solvent of choice.

A first study of the possibility of using water as an alternative solvent concerned the esterification of sucrose, which can lead either to polymerisable compounds or to amphiphilic derivatives, these latter being used as food and cosmetic emulsifiers. Methacryloyl esters were obtained by reaction with methacryloyl chloride in good yields in an aqueous or hydro-organic medium (**Scheme 32**) [170]. Chloroformates could also be used in aqueous media leading to alkyloxycarbonyl derivatives [171] (**Scheme 32**). Isocyanates were shown to lead to sucrose carbamates under similar conditions. Reaction with octyl isocyanate in pure water led to polysubstituted

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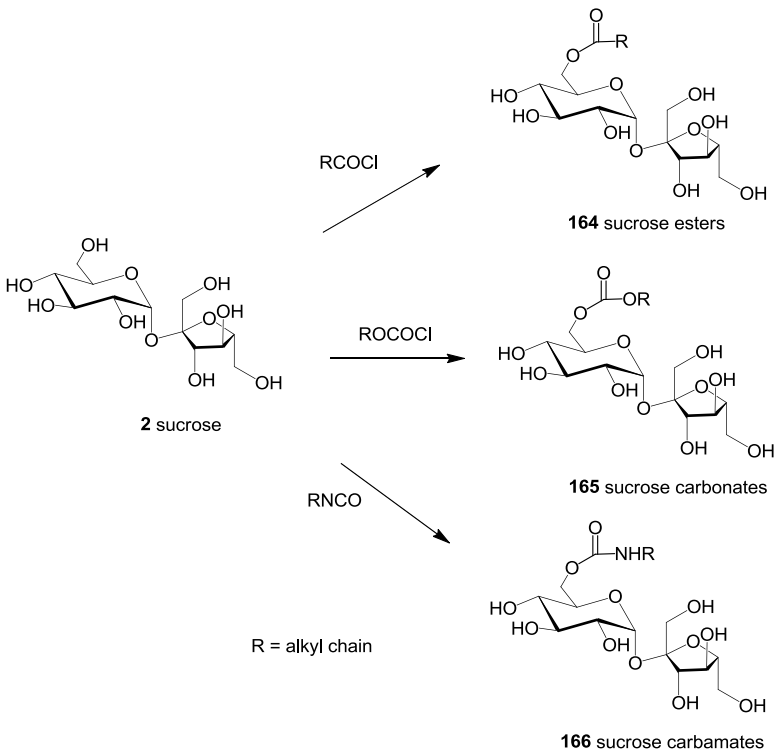
derivatives, whereas in water-THF or water-alcohol mixtures, good yields of lowsubstituted sucrose octyl carbamates are obtained [172].



Scheme 32: Preparation of sucrose esters, carbonates and carbamates in aqueous basic medium

Many routes are available for the synthesis of mono- or poly-ethers of saccharides [18-21]. Common route for the preparation of long chain substituted ethers is based on the palladocatalyzed coupling of sugars with butadiene known as the telomerization reaction. This reaction has been largely studied with different nucleophiles such as alcohols, phenol, carboxylic acids, amines and active methylene groups (**Scheme 33**) [173]. This reaction can be carried out in the presence of water as solvent. This reaction can be extended to much more complicated substrates such as polysaccharides (starch, cellulose. . .) [174].

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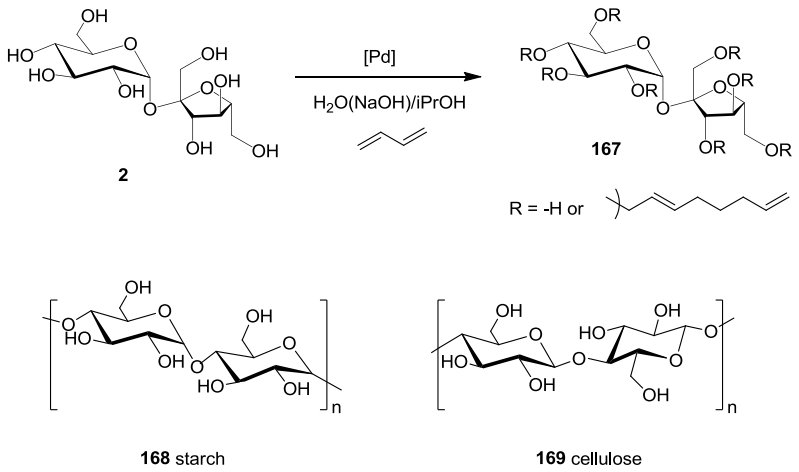
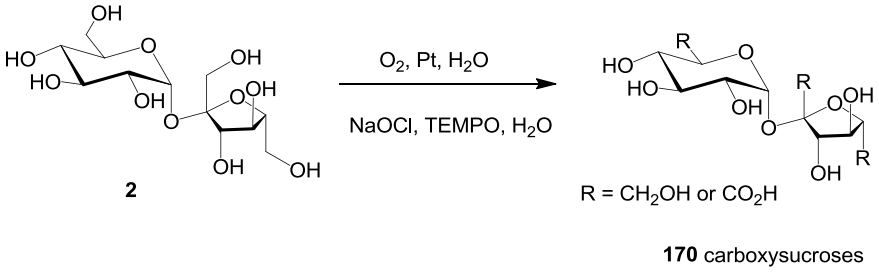


Scheme 33: Telomerization of butadiene with unprotected sugar

1.4.2 Oxidation reaction

Aqueous media are more conventional for oxidations reactions, since many oxidizing systems are stable in water [175]. Taking into account the natural good or high solubility of carbohydrates in water, it is thus obvious that many examples of oxidations reactions of carbohydrates have been reported, with important contributions in the field of metal-catalyzed processes. The oxidation of sucrose by oxygen catalyzed by platinum provides derivatives with carboxy groups at the primary positions (a mixture of mono-, di-, and tricarboxy derivatives) [100-102]. Alternatively, TEMPO-mediated oxidation using hypochlorite as stoichiometric oxidant also led to selective tricarboxysucrose in yields up to 80% [176]. This method has been applied to many carbohydrates with success. With respect to environmental concerns, many variations of the method have been reported, notably heterogeneous TEMPO analogs [177] and bromidefree methods (**Scheme 34**) [113].



Scheme 34: Example of oxidation methods in water applied to sucrose.

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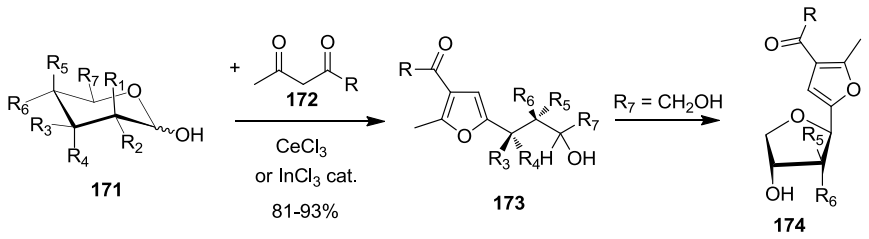
1.4.3 Knoevenagel Condensations

The Knoevenagel Condensation is a simple and easy to perform reaction for carbon-carbon formation by reacting carbonyl compounds and actived methylene [178]. Various promoters like both lewis acids and bases have been found to be efficient for this reaction [179]. The present part is focused on the Knoevenagel reaction applied to sugar. The reaction of 1,3-diketone with reducing sugars had been studied in acidic media or under mildly basic conditions. When treated with 1,3-diketones or β-keto esters in the presence of acids, unprotected aldoses gave C-glycosylfurans or polyhydroxyalkylfuran derivatives. Garcia Gonzalez presented the first report on this topic in 1956, describing the condensation of D-glucose with acetylacetone promoted by zinc chloride [180]. Using milder conditions, Misra and Agnihotri obtained an excellent yield of furyl C-glycosides from hexoses and trihydroxyalkyl-substituted furans from pentose using cerium (III) chloride as promoter in aqueous solution [181]. Later on, Yadav *et al*. [182] reported the same reaction catalyzed by indium (III) chloride; and similar yields were obtained (**Scheme 35**).



Scheme 35: Synthesis of trihydroxyalkyl-substituted furans derivatives.

The reaction between dimedone and unprotected sugars was studied by Sato's group [183]. Different products were obtained, depending on the promoter: the use of $Sc(OTf)_3$ resulted in the production of hydroxyalkyl-6,7-dihydrobenzofuran-4(5H)-one (**177**)d erivatives in 86% yield, whereas scandium cation-exchanged montmorillonite gave hydroxyalky-3,3,6,6,-tetramethyl-3,4,5,6,7,9-hexahydro-1H-xanthene-1,8 (2H)-dione (**178**) as the sole product in good yield (**Scheme 36**). Later on, it has been proved that when $Sc(OTf)_3$ employed as catalyst, the transformation fellow the the

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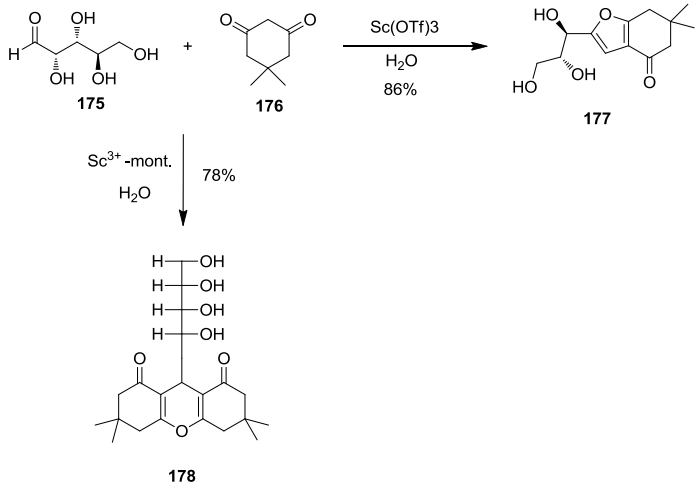
same mechanism as other lewis acids catalyzed conditions such as cerium(III) chloride or indium(III) chloride. While, Sc^{3+}-mont is used, the Sc^{3+} center was coordinate within the interlayers of montmorillonites clays, giving rise to the addition of two moleculars of dimedone.



Scheme 36: Reaction of D-ribose with dimedone catalyzed by scandium cation-exchanged mont-morillonite or scandium triflate.

The quantitative one-step synthesis of β-D-*C*-glycosidic ketones by condensation of pentane-2,4-dione with unprotected sugars in alkaline aqueous media was explored by Lubineau's group [184]. The reaction in water of pentane-2,4-dione with D-glucose, D-mannose, D-galactose, D-maltose and D-cellobiose, in the presence of sodium hydrogencarbonate gave quantitatively in one-step the β-C-glycosidic ketones (**Scheme 37**). Also in this process, the reaction started with the Knoevenagel condensation of the β-diketone with the hemiacetalic sugar. Then, the β-elimination of water was followed by cyclization to the intermediate C-glycoside **181**, which underwent a retro-Claisen aldolization under basic conditions with concomitant sodium acetate elimination to give **182**. The base used for the preparation of **185** was carefully studied in order to optimize the synthesis of **190**, an activator of glycosaminoglycans biosynthesis, launched on the market by L'Oréal on 2006 in cosmetic skincare products as Pro-Xylane™ [185]. The condensation of pentane-2,4-dione with unprotected N-acetyl-D-gluco-, manno-, in alkaline aqueousmedia was also explored [186].

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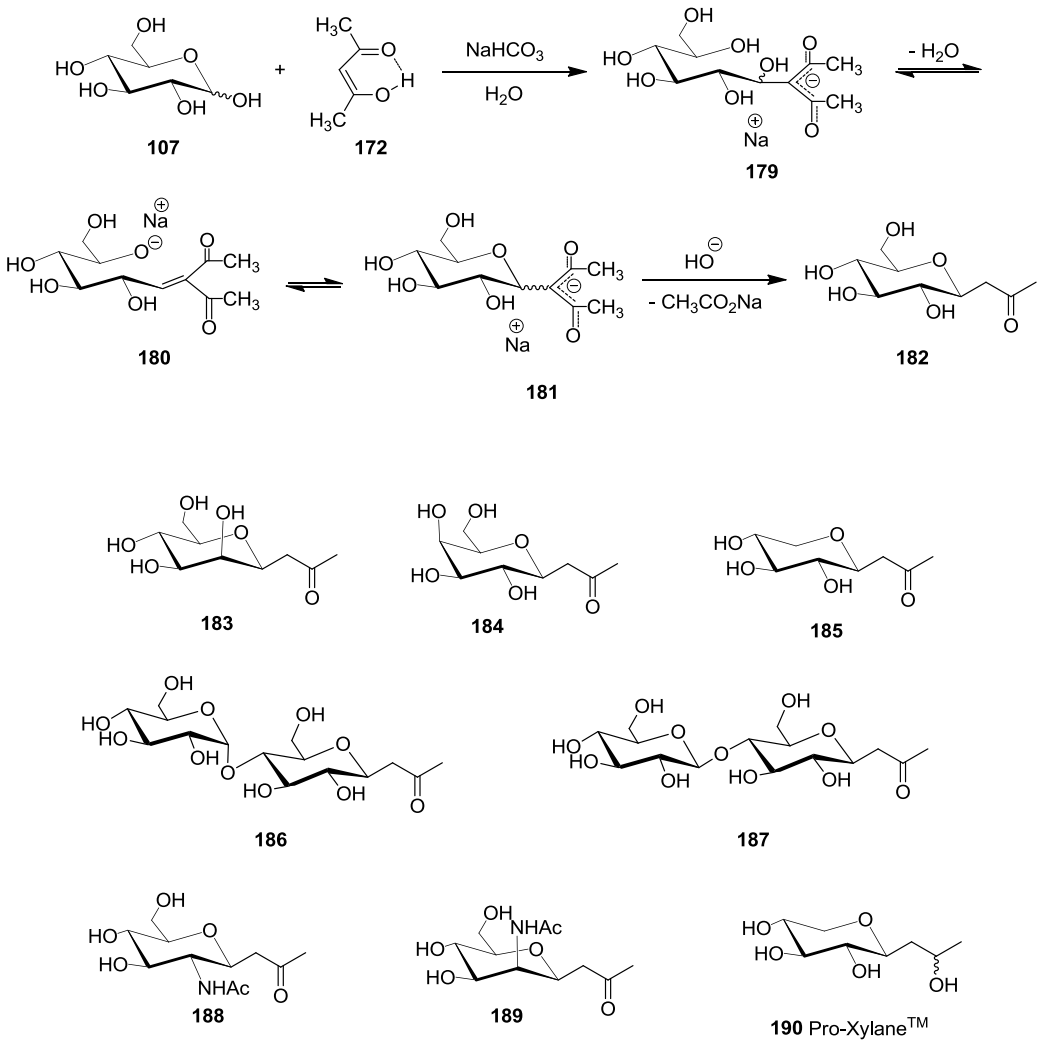

Scheme 37: One step synthesis of a β-*C*-glucosidic ketone and various β-*C*-glycosidic ketones obtained from unprotected sugar through an aqueous Knoevenagel condensation.

1.4.4 Baylis-Hillman reaction

The Baylis-Hillman reaction, the condensation between an activated alkene and a carbonyl group, was found to be greatly accelerated in water compared with usual organic solvents. Asymmetric Baylis-Hillman reaction of sugar-derived aldehydes as chiral electrophiles with an activated olefin in dioxane/water (1:1) proceeded with 36-86% *de* and in good yields of the corresponding glycosides (**Scheme 38**) [187]. **Section 1.6** will provide more detailed information on MBH reaction and solvent effects.

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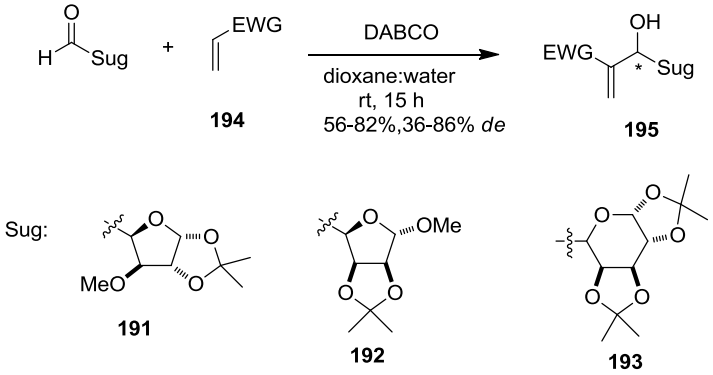
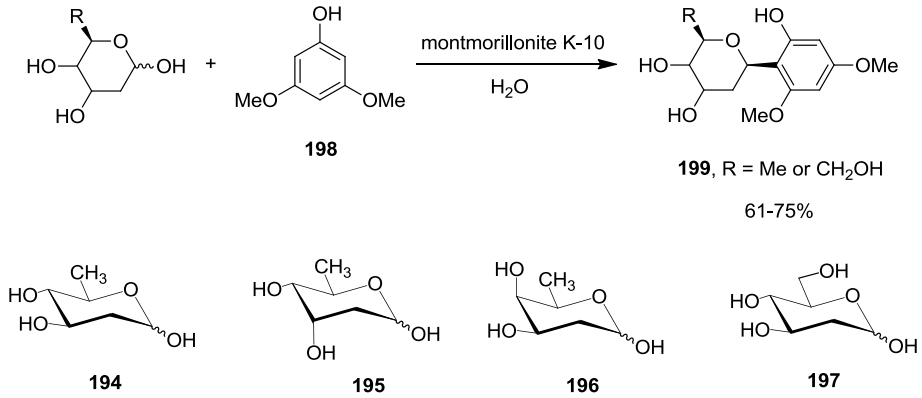


Scheme 38: Baylis-Hillman reactions of sugar aldehydes with activated olefins.

1.4.5 Electrophilic Aromatic Substitution Reactions

Electron-rich aromatics can react in water with unprotected sugars in the presence of an acid catalyst to give aryl C-glycosides (**Scheme 39**). The aqueous electrophilic aromatic substitution reactions of 3,5-dimethoxyphenol with 2-deoxy-D-aldoses were reported by Toshima *et al.* [188] using montmorillonite K-10 as catalyst. The aryl C-glycosides were obtained with high β-D stereoselectivities (>99%) and in yields varying from 61 to 75%.



Scheme 39: Montmorillonite-catalyzed C-glycosidation of electron-rich aromatics using 2-deoxy sugars.

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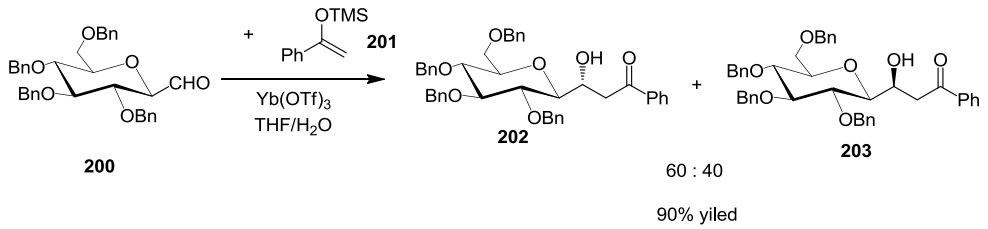
1.4.6 Mukaiyama aldol reaction

The reaction between a silyl enol ether and an aldehyde in an organic solvent requires the presence of a stoichiometric amount of titanium tetrachloride (Mukaiyama's conditions) [189], leading mainly to the anti addition product, or the use of high pressure (without acidic promoter) affording preferentially, in this case, the syn hydroxy ketone. In aqueous medium the reaction proceeds under atmospheric pressure without any catalyst, with the same *syn* selectivity as under high pressure. Kobayashi and co-workers developed water-tolerant Lewis acids in order to improve the yields and therefore the scope of this aqueous aldolization [190-191]. The use of Lewis acid-surfactant combined catalysts promotes the reaction only in water and avoids the need for an organic cosolvent. Therefore, Lubineau's group developed a synthesis of C-glycosides and C-disaccharides based on this aqueous condensation as the key step [192]. The reaction with of the protected C-glycoside and the trimethylsilyl enol ether derived from acetophenone was found to give the best results when the reaction carried out in aqueous media (THF-H_2O) in the presence of $Yb(OTf)_3$. The two C-glycosides were isolated in a 60 : 40 ratio and 90% total yield (**Scheme 40**).



Scheme 40: Mukaiyama aldol reaction involving a formyl C-glucoside.

1.4.7 C-N bond formation reactions

The reaction of aldoses with ammonia or primary amines gives glycosylamines. These compounds are generally not stable in neutral or slightly acidic aqueous media but can be efficiently prepared in aqueous ammonia in the presence of 1 equiv. of ammonium hydrogencarbonate [193]. This method was also applied to other sugars such as D-galactose, D-lactose, D-cellobiose, and D-maltose, giving quantitatively the

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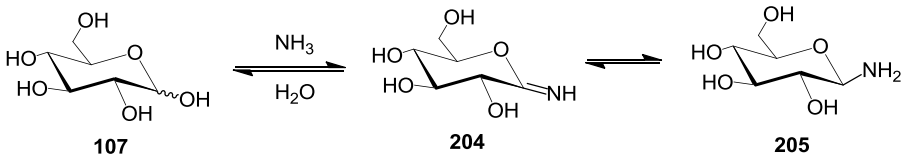
corresponding β-D-glycosamines (**Scheme 41**).



Scheme 41: Reaction of glucose with aqueous ammonia in the presence of ammonium hydrogencarbonate.

1.5 General aspects on bio-based solvent

Apart from water, biobased solvents, as an emerging generation of fluids for the design of eco-efficient processes in catalysis and organic chemistry, have drawn many attentions in recent years. The search for alternative reaction media to replace petroleum-based solvents commonly used in chemical processes is an important objective of significant environmental consequence. Biobased derivatives have been used entirely as green solvents for the production of innovative solvents potentially less toxic and more bio-compatible. Plenty of reviews and books present the background and classification of these new media and highlights recent advances in their use in various areas including organic synthesis, catalysis, biotransformation and separation [10].

Reaction solvents are used in huge amounts and are one of the most important constituents in any chemical process. Synthetic organic chemistry is traditionally carried out in solution to facilitate the intimate contact of reactants and catalysts. Although any liquid may be potentially used as a solvent, the most widely employed in both academia and industries are the hydrocarbons (including halogenated and aromatic ones), ethers and alcohols derived from fossil fuels. However, despite the obvious usefulness of these organic solvents, problems associated with their volatility, flammability and toxicity, as well as their increasing prices, advises against their utilization.

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Bio-based solvents are now considered as emerging media for the design of eco-efficient processes. With respect to sustainable chemistry, the implementation of solvent-free chemical processes would be ideal. However, in many cases solvents are essential to improve mass and heat transfer, and they may also significantly improve reaction rates, selectivities, or the position of chemical equilibria. So, if a solvent is crucial to a process, solvents with no or limited impact on health and the environment should be selected. Compared to volatile organic solvents (VOC) commonly used for chemical transformations, bio-based solvents, in terms of low toxicity, low vapour pressure, good biodegradability or non-environmentally damaging, are regarded as alternative “green solvent” in organic synthesis [10, 194].

Up to now, several biobased solvents have been commercialized, including protic compounds such as bio-ethanol and glycerol [195, 196], and 2-methyltetrahydrofuran as a medium polarity solvent [197]. Also dihydrolevoglucosenone (Cyrene) has been established as replacements for highly dipolar aprotic solvents like N-Methylpyrrolidinone (NMP) [198]. From the current literature, it appears that bio-based solvents sometimes provide improved reaction performance in terms of selectivity, catalyst activity, stability and reusability, and also with respect to isolation of the reaction products which is a prerequisite for the emergence of a new solvent [199]. The use of a renewably sourced solvent goes a long way towards satisfying the growing consumer and legislative demands with regard to sustainability.

1.5.1 Glycerol and its derivatives

Glycerol is a viscous liquid produced on a large scale from vegetable oils. Glycerol is the main co-product of the biodiesel industry and its utilization in chemical processes is highly desirable in order to favor the industrial emergence of the vegetable oil industry. Because it is a cheap, renewable, non-flammable and biocompatible liquid, glycerol appears to be a promising candidate for a green solvent [200]. Through a related condensation reaction with acetone, solketal(2,2-dimethyl-4-hydroxymethyl-1-

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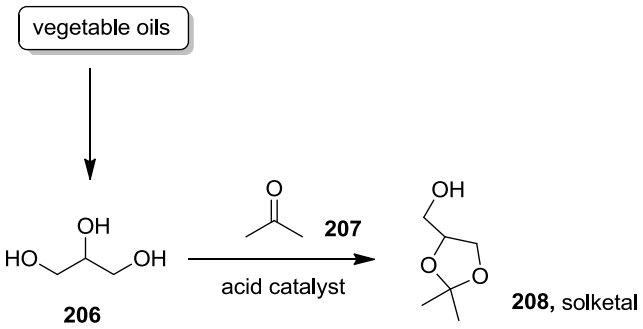
-3-dioxolane, **208**) is also accessible. As in the precedent case, the low toxicity of solketal has allowed its use as a solvent in several large-scale applications. Like glycerol, solketal is a viscous colorless liquid of high boiling point, which finds applications as a low-toxic solvent in different areas (injectable preparations, paints, plastifying agents, insecticide delivery systems, etc.). Note that, unlike glycerol, solketal is completely miscible with ethers and acetone. Moreover, its polarity and hydrophobicity parameters have been determined, pointing out that its polarity lies between those of acetonitrile and ethanol, whereas its hydrophobicity is halfway between those of ethanol and 2-propanol (**Scheme 42**) [195].



Scheme 42: Synthesis of glycerol and further transformation to solketal.

Estévez et al reported improved processes for the preparation of the antidiarrhetic and antipsychotic drugs loperamide, respectively, have been patented using solketal (**Scheme 43**) [201]. This inert solvent conveniently replaces the methyl isobutyl ketone employed in the most classical preparations. In addition, solketal exhibits a superior technical performance than methyl isobutyl ketone as evidenced by the lower equivalents of base required, the reduced temperature regime, the shorter reaction times, and the possibility of carrying out an aqueous work-up, thus simplifying the isolation and purification of the products.

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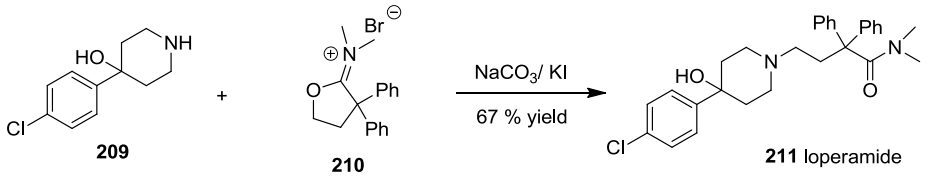
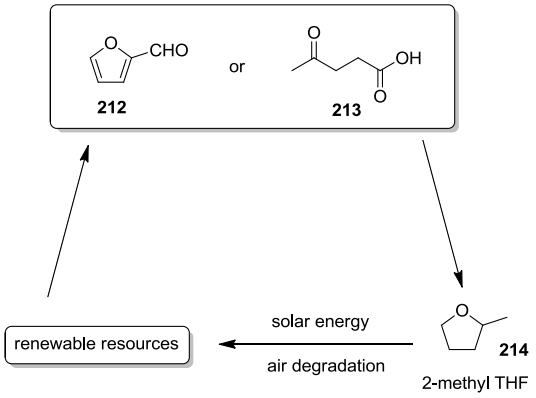


solvent	base (equiv.)	temp. (°C)	time (h)
methyl isobutyl ketone	1.6-2.6	120	15-65
solketal	1.1	60-90	2-7

Scheme 43: Synthesis of loperamide in solketal

1.5.2 2-Methyltetrahydrofuran (2-methyl THF)

2-Methyl THF is a commercially available solvent produced from renewable resources. 2-Methyl THF is generally obtained from furfural or levulinic acid, which are produced from lignocellulosic biomass. 2-Methyl THF possesses noticeable advantages, such as a biobased origin, abiotical degradability and a better stability towards acid and base than other ether solvents [10]. All these aspects have strongly boosted the application of 2-methyl THF as a bio-based solvent (**Scheme 44**).



Scheme 44: Bio-based production of 2-methyl THF.

In 2-methyl THF, the use of CaO as an innocuous acid scavenger which allows the stoichiometric acylation of primary alcohols (**Scheme 45**) [202]. Interestingly, no competitive ketene formation was observed with acylating agents **215** bearing acidic α-hydrogens. In this system, the use of 2-methyl THF as a reaction solvent is crucial as it leads to maximized yields. Furthermore, 2-methyl THF can also avoid the need

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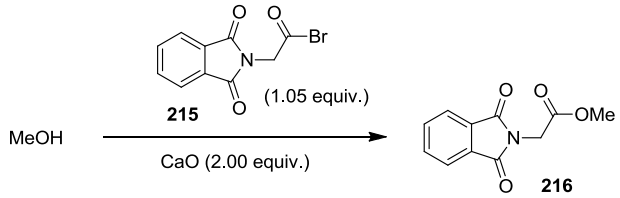
for chromatographic purifications, which endowed this system a salient feature of green organic synthesis.

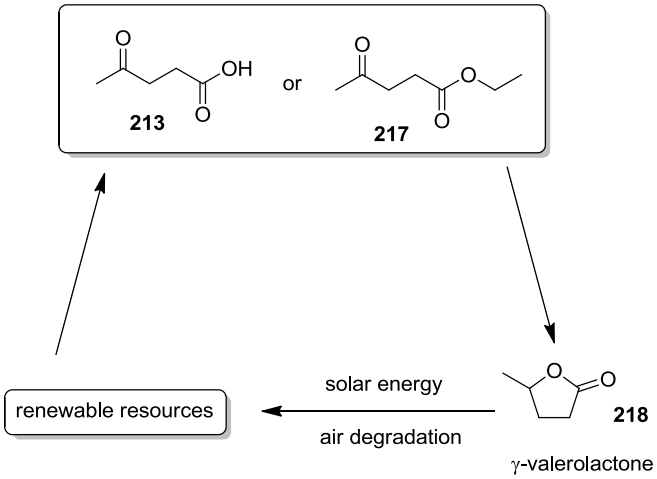


solvent	time (h)	yields (%)
Et_2O	8	82
2-methyl THF	6	97
DCM	10	65
CH_3CN	8	81
toluene	8	72
THF	8	85

Scheme 45: Acylation of methanol in 2-methyl THF

1.5.3 γ-valerolactone (GVL)

γ-Valerolactone (GVL) produced from lignocellulosic biomass to various chemicals and fuels, such as polymers, fuel additives, and jet fuel. Furthermore the use of GVL as a solvent for biomass processing are leading to significant improvements in product yields and a more simplified process for producing biomass-derived chemicals such as levulinic acid, furfural, and hydroxymethylfurfural [203]. Generally, GVL is obtained from hydrogenation of the ethyl levulinate and levulinic acid (**Scheme 46**).



Scheme 46: Bio-based production of GVL.

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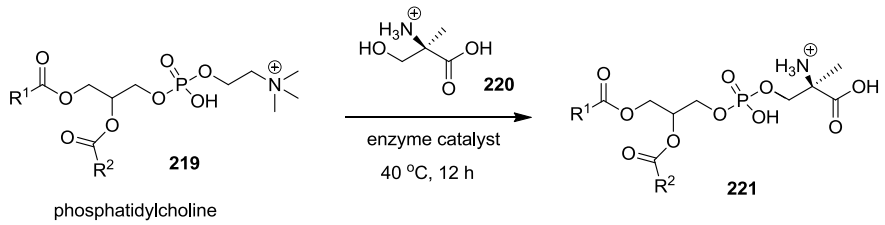
Duan and Hu have studied phospholipase D (*Streptomyces chromofuscus*)-mediated transphosphatidylation of phosphatidylcholine (**219**) with L-serine (**220**) in GVL [204]. Phosphatidylserine (**221**), one of the most important phospholipids, can be produced in up to 95% yield in this system (**Scheme 47**). Under similar conditions but replacing GVL by ethyl acetate, **221** was obtained in a lower yield (74%). Additionally, in the ethyl acetate system, 10% of phosphatidic acid was also formed, decreasing thus the selectivity of the reaction. The reaction in neat water gave only 23% yield of **221** with an extensive generation of phosphatidic acid. This work is therefore a very nice proof-of-concept that may open up new horizon in the use of GVL in biotransformation.



solvent	yield (%)
ethyl acetate/water	74
pure water	23
GVL	95

Scheme 47: Enzymatic transphosphatidylation of phosphatidylcholine with L-serine in GVL.

1.5.4 Lactic acid and its derivatives

Lactic acid is a α-hydroxy acid containing a hydroxyl group adjacent to a carboxylic acid group. Generally, it can be produced through chemical synthesis or through the fermentation of carbohydrates, such as glucose, maltose, sucrose, or lactose. With the increasing demand for sustainable materials, lactic acid has become an important chemical platform [25]. Lactic acid is also a building block for the synthesis of chemicals such as acrylic acid, pyruvic acid, 2,3-pentanedione, 1,2-propanediol and lactic acid esters. In spite of this increasing interest, less attention was given to the use of lactic acid and its derivatives as green solvents. Considering the fact that ethyl lactate is often obtained as an aqueous solution in industry, and because its

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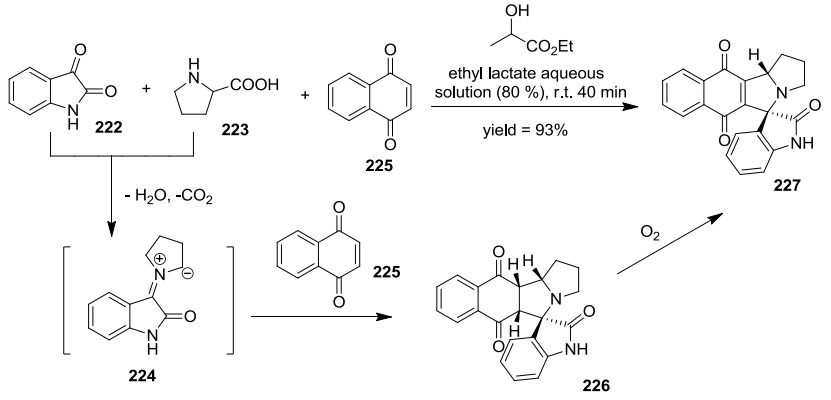
purification is also a cost-intensive procedure, the strategy to directly use aqueous solution of ethyl lactate definitely deserves further investigations from the viewpoint of green chemistry.

An aqueous solution of ethyl lactate was used to promote the 1,3-dipolar cycloaddition reaction of azomethine ylide generated in situ by the decarboxylative condensation of substituted isatin and proline with naphthoquinone as a dipolarophile, which generated various spiro[benzo[f]pyrrolo[2,1-a]isoindole-5,30-indoline]-20,6,11-trione derivatives **227** in excellent yields at room temperature (**Scheme 48**) [205]. The use of aqueous solution of ethyl lactate as a reaction medium not only avoided the dimerization of the reactive azomethine ylide, the main drawback often encountered with previous systems, but also simplified the isolation of the product, the product being not soluble in the reaction solvent.



Scheme 48: Three-component reaction of isatin, proline and naphthoquinone in ethyl lactate.

1.6 General aspects of the Baylis-Hillman reaction

1.6.1 Introduction

The carbon-carbon bond forming reaction is one of the most important reactions in organic synthesis. Many such carbon-carbon bond formations have been well discovered, which apparently led to a group of multi-functionalized synthons. Recently, synthetic organic chemistry has clearly focused on the development of a reaction with two main criteria: atom economy and selectivity (chemo-, regio-, stereo-) (**Fig. 23**) [2, 206].

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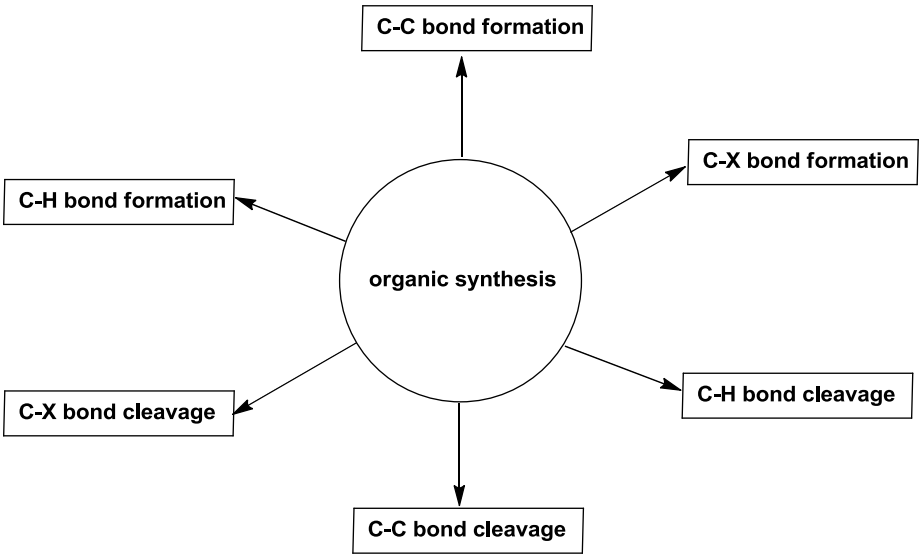
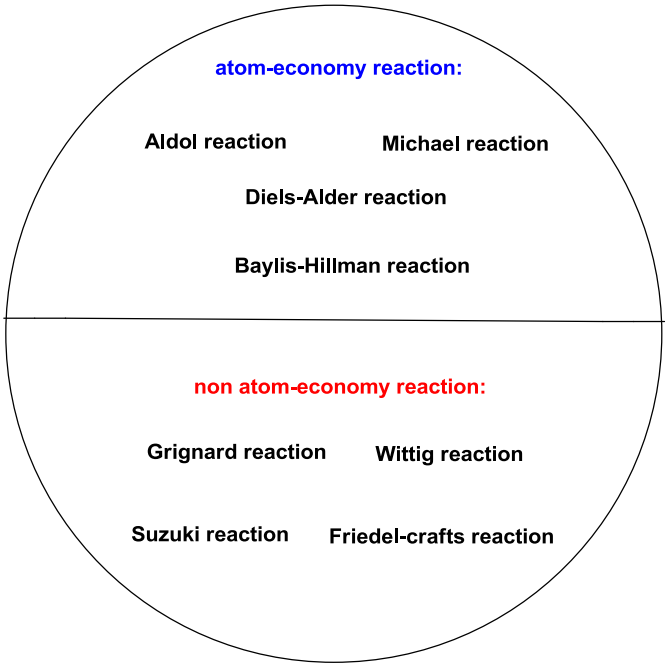


X = N, O, S, P, *etc*



C-C bond formation reactions

Fig. 23

Among those carbon-carbon bond forming reactions, the Morita-Baylis-Hillman (MBH) reaction has drawn many attentions **Scheme 49** [207-209], due to the facts that (i) it uses commercially available starting materials and the reaction is adapted to large-scale; (ii) a very favorable atom economy character; (iii) densely functionalized

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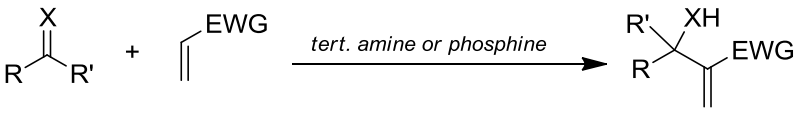
Baylis-Hillman adducts with the creation of a new chiral center; (iv) organic catalytic processes avoiding utilization of any heavy metals; (v) mild reaction conditions. Generally, the MBH reaction is a tertiary amine or alkylphosphine catalyzed reaction of α-position of an activated double bond with a sp^2 electrophilic carbon (normally being an aldehyde), if the aldehyde replaced by an activated imine, this process is named corresponding as aza-Morita-Baylis-Hillman (aza-MBH) reaction. Despite those advantages, there are still a number of problems associated with this reaction, especially the mechanistic studies and the low reaction rate. Many researchers have tried to overcome these problems, in particular, by attempting to increase the reaction rate employing high-pressure conditions, microwave irradiation, the addition of a Lewis acid, or by the use of other catalysts such as 1,8-diazabicyclo[5.4.0] undec-7-ene (DBU) or 2,2′-bis(diphenylphosphino)-1,1′-binaphthyl (BINAP) [207].



R = aryl, alkyl, heteraoaryl, *etc*. R' = H, CO_2R, alkyl, *etc*.
X = O, NCO_2R, NSO_2Ar, *etc*.
EWG = COR, CHO, CN, CO_2R, $PO(OEt)_2$, SO_3Ph, SO_2Ph, SOPh, $CONR_2$, *etc.*

Scheme 49: The Morita-Baylis-Hillman (MBH) reaction.

Numerous of activated alkenes and alkynes such as acrylic esters, acrylonitrile, vinyl ketones, phenyl vinyl sulphone, vinyl phosphonate, allenic acid ester, acrolein and also some β-substituted acrylic esters, vinyl aldehydes, ketones, nitriles, and sulfones have been employed in the Baylis-Hillman reaction (**Fig. 24**). The common used electrophiles in this reaction are aldehydes, ketones, simple alkyl/allyl halides, tosylates, triflates, aziridines, epoxides, imines and indole (**Fig. 25**). A large number of tertiary amines, phosphines, and polymer-supported amine and phosphines catalyze a variety of Baylis-Hillman reactions. Numerous Lewis acids also promoted the Baylis–Hillman reaction (**Fig. 26**) [208-211].

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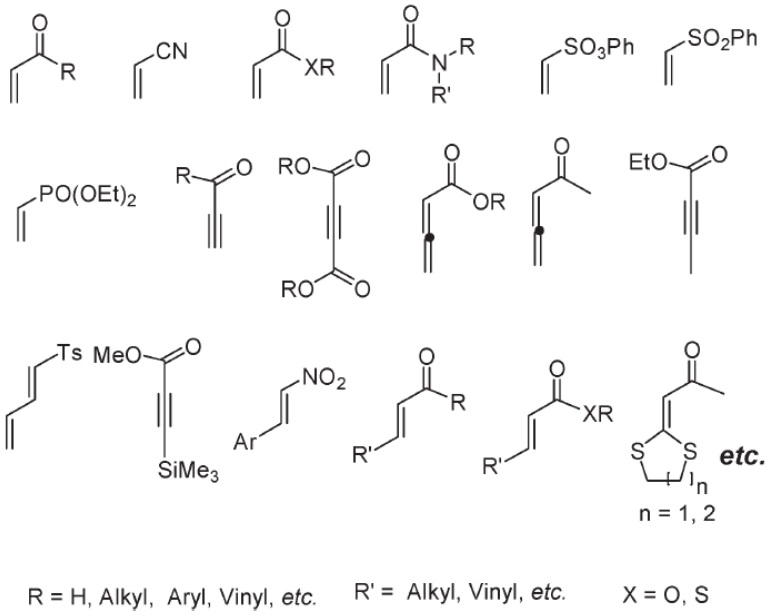

Fig. 24: Acyclic activated alkenes, alkynes and allenes.

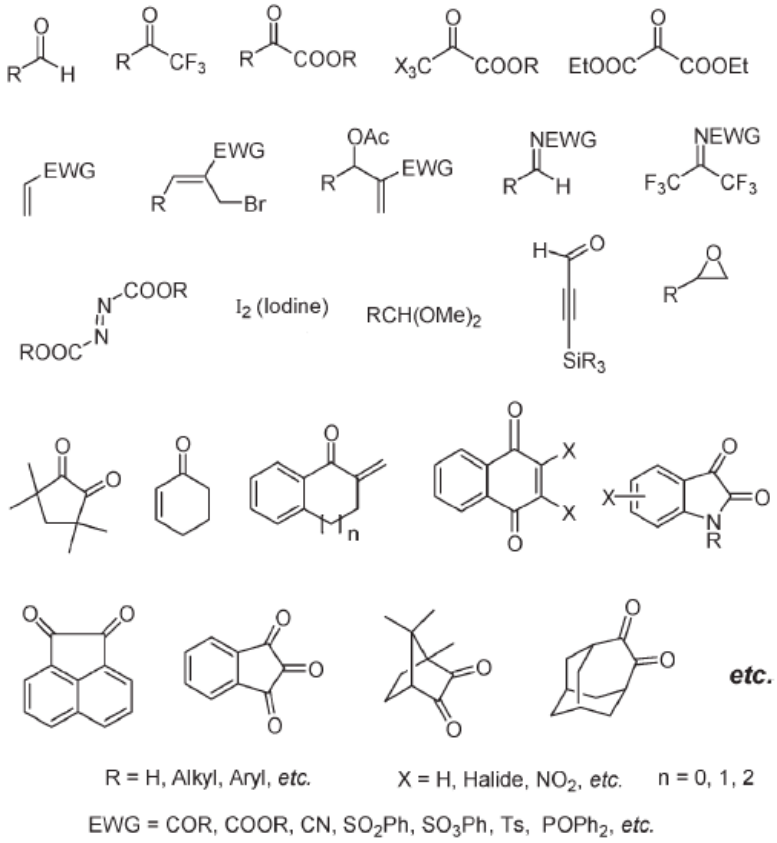

Fig. 25: Electrophiles.

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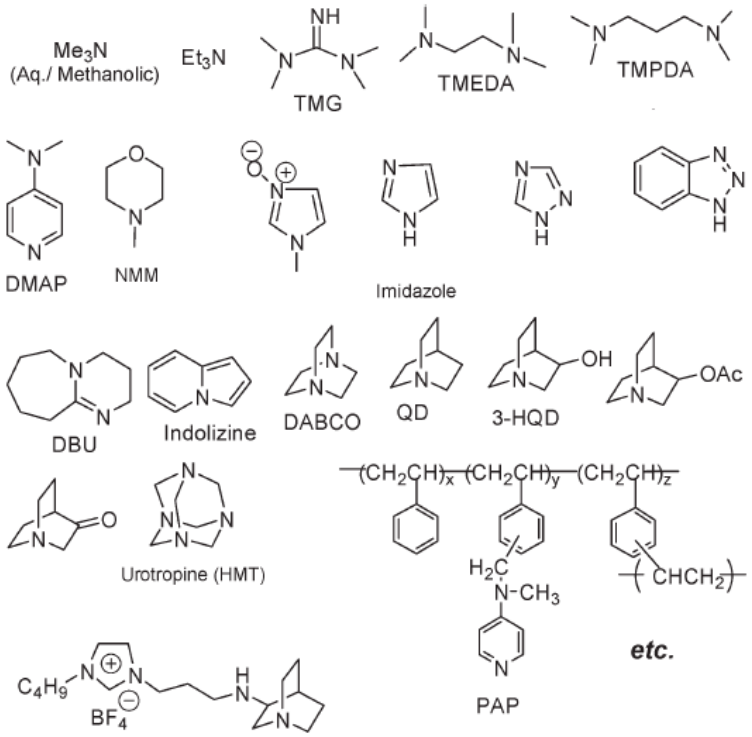

Fig. 26: Catalysts.

1.6.2 Mechanistic aspects

1.6.2.1 Amine-Catalyzed Mechanism

The commonly accepted mechanism for the MBH transformation involves a reversible conjugated addition of the nucleophilic catalyst to the activated alkene to generate an enolate (step I), which is followed by nucleophilic attack of this in situ formed enolate on the aldehyde, affording a second zwitterionic intermediate (steps II and III). Then an elimination reaction (step IV) releases the amine catalyst and forms the final MBH product (**Scheme 50**). This commonly accepted mechanism for the MBH reaction was first proposed by Hoffmann [211] and supported by kinetic data studied by Hill and Isaacs in the late 1980s [212] and others [213]. The ongoing debate on the MBH mechanism has been fuelled by recent experimental and theoretical contributions. The general catalytic cycle depicted in **Scheme 50** seems to be now well accepted, and debates are now centered on the rate-determining step, that is, the dynamics of the hydrogen shift as well as the source of this hydrogen.

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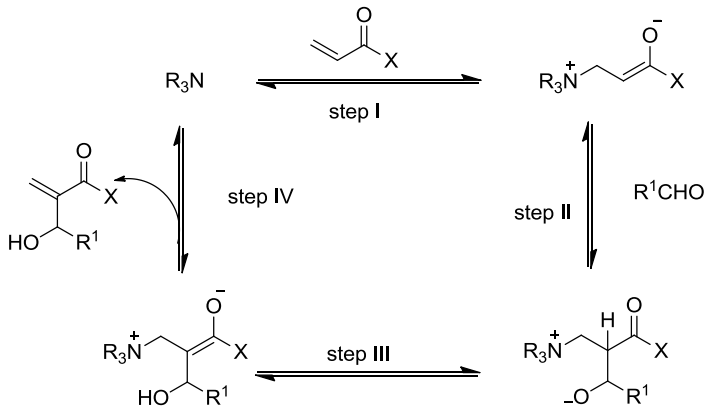
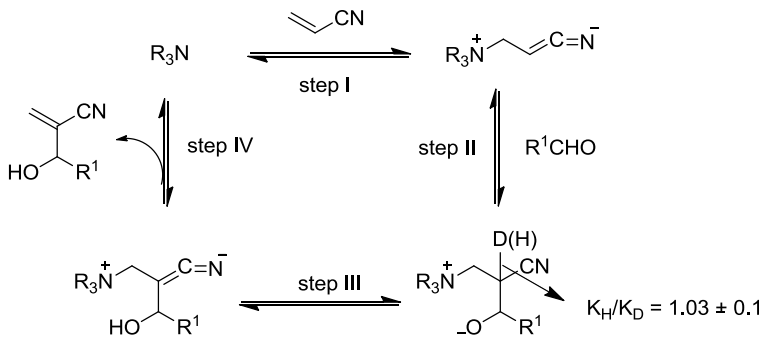


Scheme 50: A plausible mechanistic pathway.

Through the kinetic studies by Hill and Isaacs [212], using acrylonitrile as an electron-deficient alkene and acetaldehyde as a carbon nucleophile for the MBH reaction, step II was initially suggested as the MBH rate-determining step (RDS), due to the low kinetic isotopic effect (KIE = 1.03 ± 0.1) **Scheme 51**.



Scheme 51: Hill and Isaacs proposed mechanism

However, McQuade *et al.* [214, 215] and Aggarwal *et al*. [216] re-evaluated the MBH mechanism through kinetic study, focusing on the proton-transfer step and proposed the protontransfer step as RDS. McQuade observed that the MBH reaction was second order relative to the aldehyde and showed a significant kinetic isotopic effect (KIE: k_H/k_D = 5.2 ± 0.6) in DMSO, and primary KIE (>2) was found in other tested

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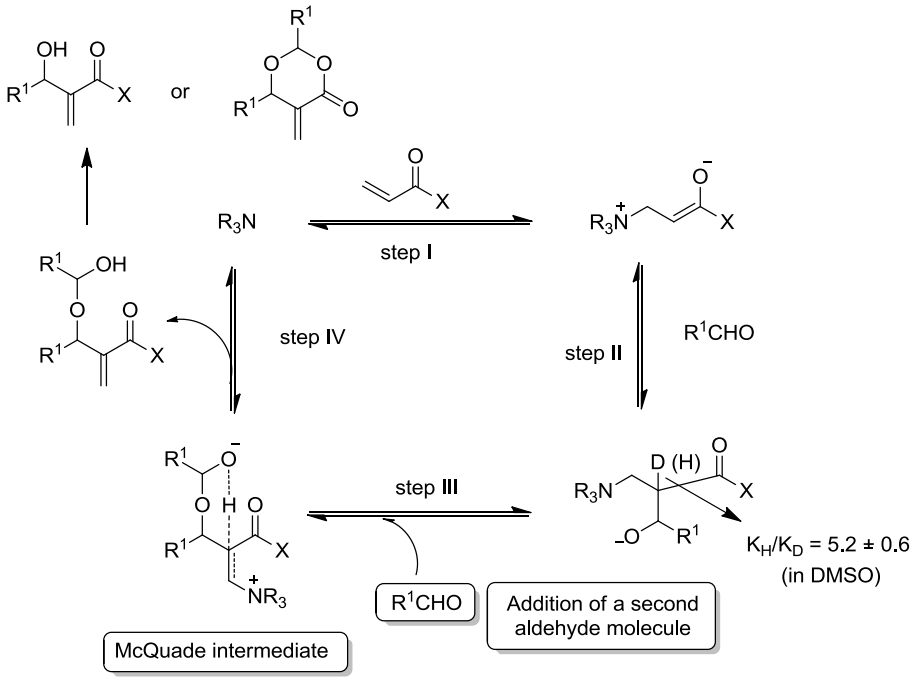
solvents (DMF, MeCN, THF, $CHCl_3$), indicating the relevance of proton abstraction on the RDS. On the basis of these kinetic data, McQuade proposed a new mechanism view for the proton transfer step (**Scheme 52**), suggesting the proton transfer step as the RDS.



Scheme 52: Mechanism involving a hemiacetal intermediate as proposed by McQuade.

Aggarwal [216] also proposed that the proton transfer step was the rate-determining step based on their kinetic studies, but only at its beginning (⩽20% of conversion), and then step II was the RDS when the product concentration built and proton transfer became increasingly efficient. They suggested that the MBH adducts may act as a proton donor and therefore can assist the proton-transfer step via a six-membered intermediate (**Scheme 53**). This model also explained the autocatalytic effect of the product.

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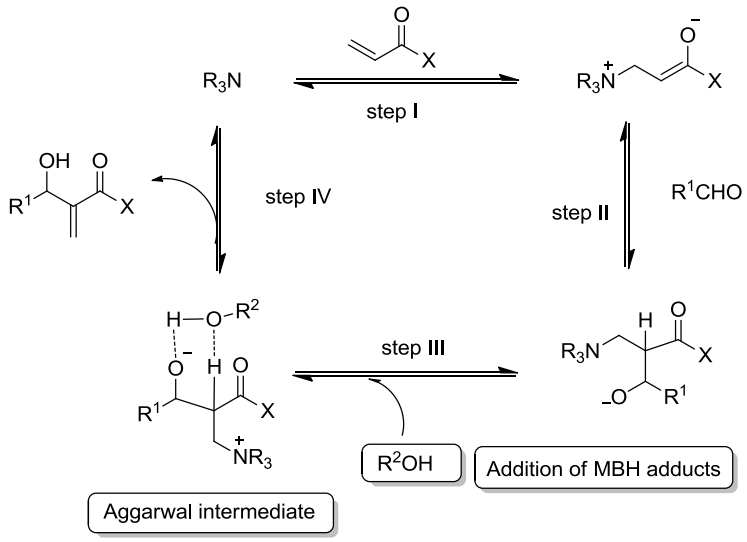

Scheme 53: Proposed mechanism involving a six-membered intermediate by Aggarwal.

Besides kinetic studies, theoretical studies on the MBH mechanism were conducted initially by Sunoj [217]. Subsequently, Aggarwal and co-workers [218] performed an extensive theoretical study, which supported their own kinetic observations and those of McQuade about the proton transfer step. Two distinct pathways leading to the products were proposed: (i) a second molecule of aldehyde participates the reaction to form a hemiacetal alkoxide followed by rate-limiting proton transfer as proposed by McQuade (non-alcohol-catalyzed pathway) and (ii) an alcohol acts as a shuttle to transfer a proton from the α-position to the alkoxide (**Scheme 54**). In addition, a few computational studies recently appeared in the literature attempting to address mechanistic questions in the MBH reaction, including the addition of explicit water or methanol molecules. However, some limitations exist in all these studies. The popular B3LYP functional which may not be appropriate for this system was always used, and only potential electronic energies were employed to describe the energetics. It should be mentioned that Sunoj *et al.* [217, 219] have employed interesting CBS-4 M and mPW1K methods to compute the free energies for the reaction pathways. However, they just compared the energetics of the direct proton transfer pathways (via a four membered transition structure) and the 1,3-proton transfer assisted by water and did not consider the possibility of the influences by a second molecule of aldehyde or

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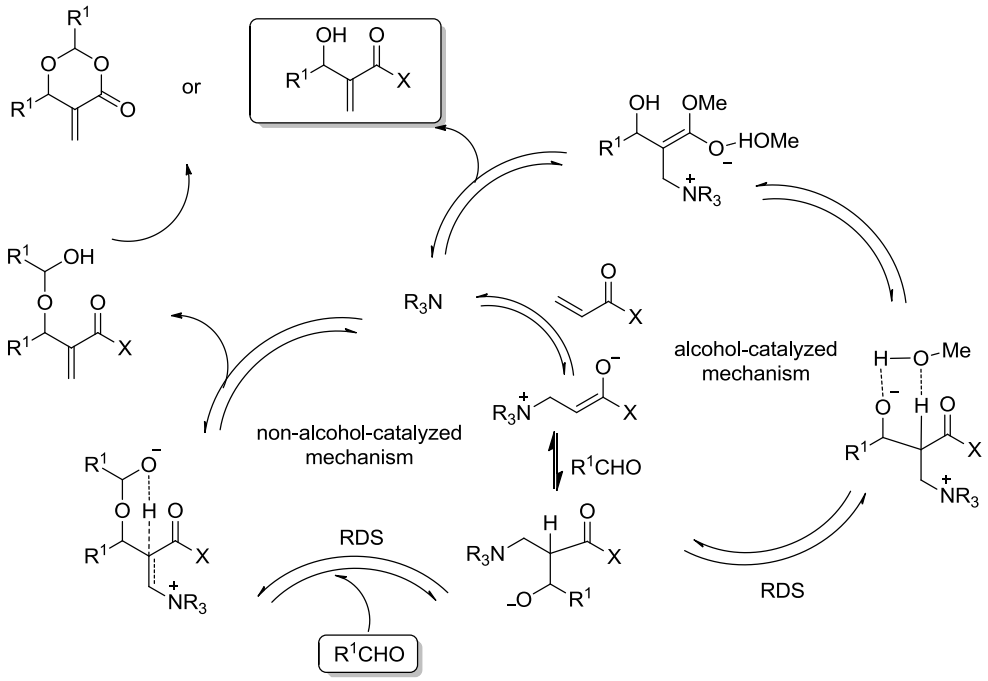
other protic species. More recently, Cantillo and Kappe [220] presented a detailed computational and experimental reinvestigation on the aminecatalyzed MBH reaction of benzaldehyde with methyl acrylate. They have proven that it was impossible to accelerate the reactions through variable-temperature experiments and MP2 theoretical calculations of the reaction thermodynamics. The complex reaction mechanism for the MBH reaction has been revisited using the M06-2X computational method. The results provided by this theoretical approach are in agreement with all the experimental/kinetic evidence such as reaction order, acceleration by protic species (methanol, phenol), and autocatalysis. They also pointed out that the suggested pathways (Aggarwal and McQuade pathways) are competing mechanisms, and either of two mechanisms is more favored depending on the specific reaction conditions (**Scheme 54**).



Scheme 54：New proposed mechanistic pathway.

Elberlin and Coelho [221, 222] performed complementary investigations on the MBH reaction mechanism via electrospray ionization mass spectrometry (ESI-MS) (/MS). New key intermediates for the RDS of the MBH reaction have been successfully

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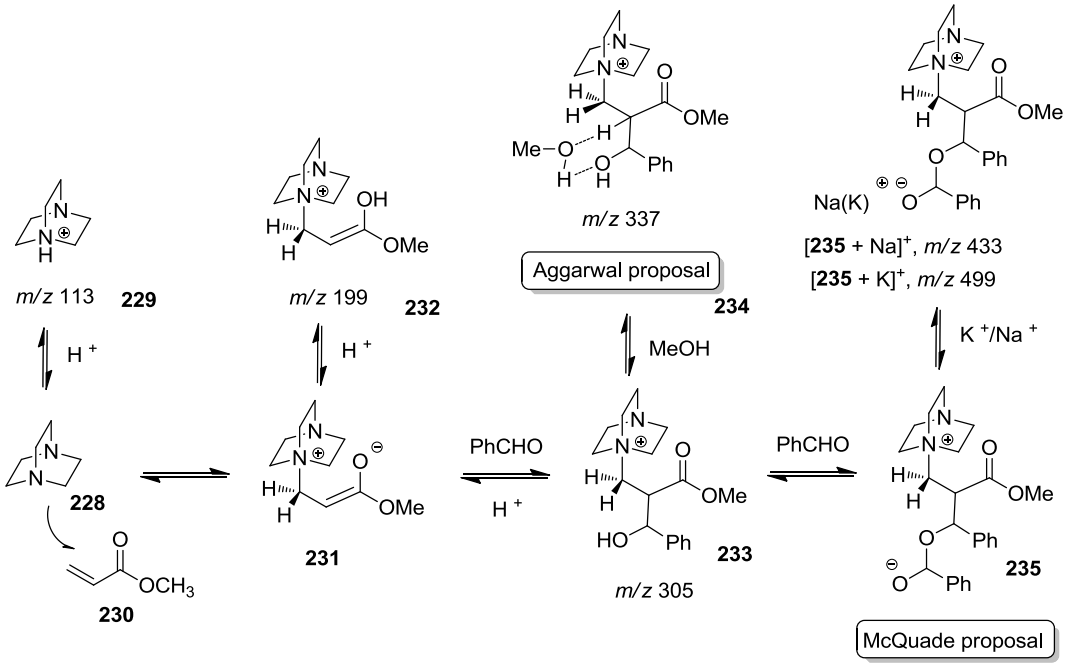
intercepted and structurally characterized, which provide strong experimental evidence that both mechanisms proposed by McQuade et al. and Aggarwal et al. are possible (**Scheme 55)**. For example, after 10 min of reaction, an aliquot of a MBH reaction solution was diluted in acetonitrile and its ESI-MS collected. Intermediate **235** (R = Ph) proposed by McQuade from the nucleophilic attack of the MBH alkoxyde to the aldehyde (**Scheme 55)** was intercepted as [**235** + Na]$^+$ of *m/z* 433 and [**235** + K]$^+$ of m/z 499. Also a new ion of *m/z* of 337 [**233** + H]$^+$ was intercepted and characterized via ESI-MS(/MS), provide the structural evidence supporting the mechanistic propositions made by Aggarwal (**Scheme 55)** [218].



Scheme 55. Species characterized by off-line ESI–MS(/MS) monitoring for a MBH after 10 min of reaction.

1.6.2.2 Phosphine-Catalyzed Mechanism

The most likely mechanism of the MBH/aza-MBH reaction catalyzed by tertiary phosphines is identical to that of the aminecatalyzed reaction via path a shown in **Scheme 56** [223], giving the normal MBH/aza-MBH adducts. In principle, the initially formed zwitterionic intermediate **237** during the phosphinecatalyzed MBH/aza-MBH reaction can isomerize to phosphorus ylide **240**, which can then undergo a Wittig

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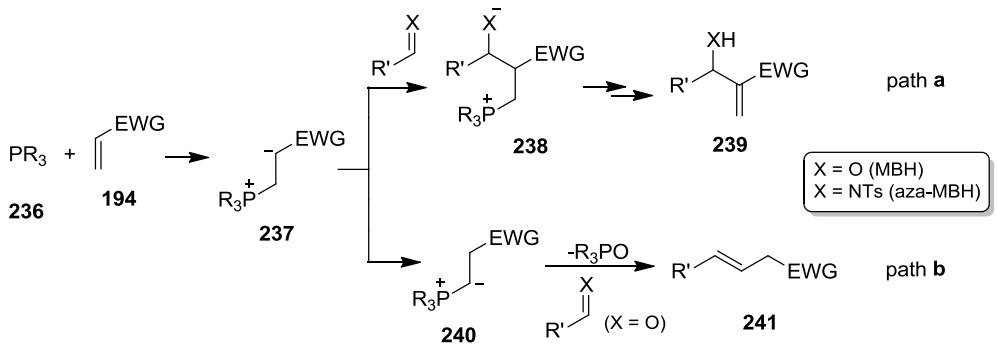
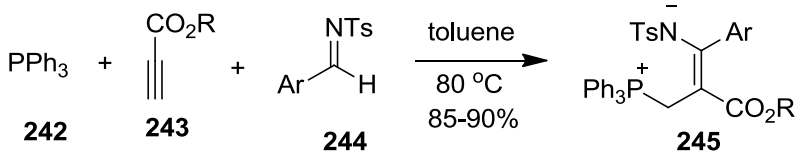
reaction to give olefins **241** (**Scheme 56**, path b). The latter process may require elevated temperatures, since it is not observed in reactions such as the MBH reaction involving the more reactive α,β-unsaturated ketones under mild conditions.



Scheme 56

Sunoj and co-workers [219] have also done theoretical studies on the mechanism of the trimethylphosphine catalyzed aza-MBH reaction between acrolein and mesyl imine. They found that the relative energies of the crucial transition states for the PMe_3-catalyzed reaction are lower than those of the corresponding NMe_3-catalyzed reaction. The kinetic advantage of the PMe_3-catalyzed reaction is also evident in the proton transfer step, where the energies of the transition states are much lower than those of the corresponding NMe_3-catalyzed reaction.

Most recently, Tong *et al*. [224a] isolated a stable phosphonium-enamine zwitterion **245**, which has long been postulated as one of the key intermediates in the aza-MBH reaction, from the PPh_3-catalyzed reaction between propiolate **243** and *N*-tosylimine **244** (**Scheme 57**), which provides some experimental evidence to support the postulated reaction mechanism of the phosphine catalyzed MBH reaction.



Scheme: 57

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1.6.3 Solvent issues

Generally, the Baylis-Hillman coupling of activated alkenes with electrophiles catalyzed by DABCO [α-hydroxyalkylation of acrylate esters can take several weeks to evolve fully] is a very slow process when carried out at room temperature and atmospheric pressure under neat conditions [207]. As it is desirable for any synthetic process, from both a practical and economic point of view, to be accomplished rapidly and with high yields, efforts have been made to circumvent this undesirable nature of the Baylis-Hillman reaction. The first and obvious option of using higher proportions of catalyst has been tried on many an occasion. In addition, the effect of factors such as solvents, substrate structure, pressure, temperature, ultrasound and microwave irradiation on the rate of the reaction were studied. Although the dilution slowed down the Baylis-Hillman reaction, numerous solvents were used for this reaction. The solvent is mainly used to solubilize nonhomogeneous reaction mixtures and to promote the formation of zwitterionic species. For this reason, polar and/or aprotic solvents are the most appropriate ones (alcohols, acetonitrile, THF, 1,4-dioxane, DMSO, and DMF). Recently, the use of sulpholane as a new aprotic polar solvent for the Baylis-Hillman reactions is demonstrated by Krishna *et al.* [224b]

Nowadays, the search for environmentally benign media media to replace petroleum-based solvents commonly used in chemical processes is an important objective of significant environmental consequence. In view of the emerging importance of this area, in this thesis, we will focus on the rate enhancement of MBH reaction in unconventional solvents. Because water and ionic liquids are the main contenders in the area of green solvents, the majority of this section will cover MBH reaction in these two solvents. Recent attempts at using bio-based solvents and supercritical carbon dioxide ($scCO_2$) as reaction media for MBH reaction also will be described in the present section.

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1.6.3.1 Rate enhancement in aqueous solution

Auge [225], Aggarwal [226], and Hu [227] report large rate enhancements caused by water and other polar protic additives. To extend the mechanism, McQuade [214] found the order in the additive was one for each protic additive tested-formamide, water, and methanol-using THF as the cosolvent. Each additive also showed saturation behavior, indicating that the protic additive may form a hemiacetal ground state at high protic concentrations. The solvent-induced acceleration roughly follows the dielectric constant of the solvent or mixture. The first-order dependence on solvent could be interpreted as a medium effect or as a molecular interaction. Because the rate correlates with solvent polarity, suggests that the rate increase is a medium effect in which the ionic transition states are stabilized in the presence of polar solvents.

Sunoj and co-workers [219] have identified the role of protic cocatalysts such as water, methanol, and formic acid in the MBH/aza-MBH reaction by theoretical studies. They found that the protic cocatalysts had a profound influence in decreasing the activation barriers associated with the key elementary steps due to the improved stabilization of the proton transfer transition state through a relay mechanism.

DFT calculations carry out by Cantillo and Kappe [220] show that the aprotic pathway is always faster than the reaction assisted by water, the energy barriers for the proton transfer assisted by the second molecule of aldehyde and water are 22.4 and 24.1 kcal mol^{-1}, respectively, and this explains also why the transformation is second order for the aldehyde even after the addition of water. However, taking into account that the difference is not high, as the reaction advances, the protic mechanism will become more important and the reaction will not be second order for the aldehyde anymore. When adding water (ε=78.4) to THF (ε=7.4) in sufficient amount, the dielectric constant of the bulk medium will become intermediate between both solvents and therefore similar to methanol (ε=32.6). In this way the protic and aprotic pathways will become faster. Therefore, the theoretical study can well explain the previously observed acceleration of the MBH reaction when altering the solvent, as a

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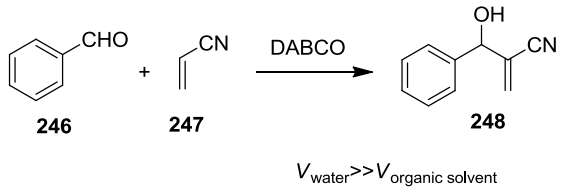
result of the change in the dielectric constant of the medium. The choice of reaction pathway will depend on the amount of protic species and the progress (early or late stage) of the reaction.

Augé *et al.* [225] studied the DABCO catalyzed MBH reaction of benzaldehyde with acrylonitrile in an aqueous medium. A significant increase in reactivity has been observed when the reaction is carried out in water compared to usual solvents, such as THF, toluene or DMF (**Scheme 58**).



Scheme 58: The MBH reaction of benzaldehyde with acrylonitrile in an aqueous medium.

Trimethylamine-mediated Baylis-Hillman coupling of alkyl acrylates with aldehydes also proceeds in aqueous media [228]. Later on, a practical and efficient set of conditions were developed using stoichiometric base catalyst DABCO and an aqueous medium to overcome problems commonly associated with the MBH reaction, such as low reaction yields and long reaction time (**Scheme 59**) [224]. Water was proved to be critical for achieving the high yield of Baylis-Hillman adducts, suggesting that water might help stabilize the transition states or intermediates in the coupling reaction. During the kinetic studies, their deuterium-exchange experiments indicated that the Michael addition adduct formed between DABCO and methyl acrylate is the active intermediate for the Baylis-Hillman reaction in aqueous conditions, because of its hydrolysis, leading to the formation of a stable betaine product, consumes both the catalyst and methyl acrylate, making it necessary to add more base catalyst and acrylate. It is also well explained why stoichiometric base catalyst should be added in aqueous conditions. Acrylamides were also employed as Michael acceptors, gave the corresponding 3-hydroxy-2-methylenepropionamides **253** in moderate yields (**Scheme 59**) [229].

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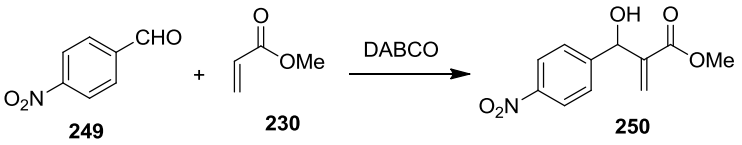
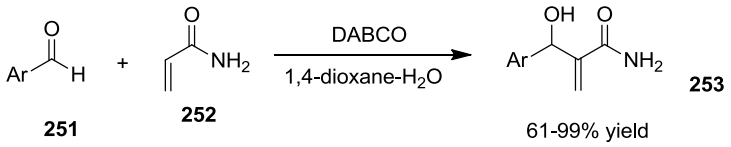


solvent	yield (%)
H_2O	0
1,4-dioxane	0
1,4-dioxane-H_2O	68
THF-H_2O	21
CH_3CN-H_2O	56



Scheme 59: Baylis-Hillman reactions of aldehyde with methyl acrylate or acrylamide

Through re-examination by Tang and co-workers [230] of the reaction conditions used by Basaviah and co-workers, they found that the homogeneity of the reaction medium was also very important. An obvious rate acceleration was observed when low-carbon alcohols or other polar solvents, such as THF, 1,4-dioxane, acetonitrile, etc., was added, which transform the heterogeneous mixture of aqueous trimethylamine and the substrate into a clear homogeneous liquid. Hence, compared with the literature reported results, in the homogeneous H_2O/solvent medium, the reaction rate of aromatic aldehydes and acrylonitrile or acrylate was greatly accelerated, which led to shorter reaction time, lower reaction temperature, and higher yield.

Asymmetric Baylis-Hillman reaction of sugar-derived aldehydes as chiral electrophiles with an activated olefin in dioxane/water (1:1) proceeded with 36-86% *de* and in good yields of the corresponding glycosides (see in Section **1.4**, Scheme **38**).

Other catalysts have also been used. As described by Tomkinson *et al*. [231], in the proline/imidazole catalysed Baylis-Hillman reaction between methyl vinyl ketone and aldehydes, the nature of the solvent is crucial for effective catalyst activity (**Scheme 60)**. Addition of small amounts of water brings about more effective reaction with a solvent mixture of DMF/H_2O (9:1) being optimal. This solvent mixture is effective with

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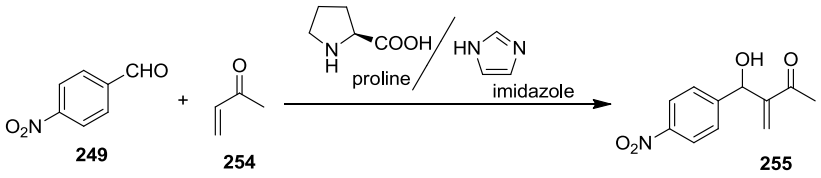
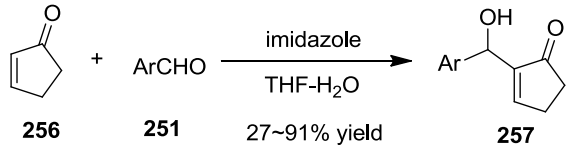
a variety of substrates within the reaction. Increasing or decreasing the amount of water present is detrimental to the observed yield, indicated that water was an important factor in optimizing catalyst activity in the MBH reaction.



solvent	yield (%)
DMF	54
DMF/H_2O 19:1	63
DMF/H_2O 9:1	80
DMF/H_2O 1:1	30
H_2O	16
THF	27

Scheme 60: The Baylis-Hillman reaction catalysed by imidazole and proline.

In aqueous media, imidazole and azoles were found to be efficient catalyze the Baylis-Hillman reaction of cyclopent-2-enone **256** with various aldehydes to afford the desired adducts **257** in high yields. In 2002, El Gaïed's group [232] and Cheng's group [233] separately reported the use of imidazole as a promoter for the MBH reaction of cyclic enones with aldehydes. Both research groups found that in 1:1 THF/water mixtures at room temperature, good yields of the MBH adducts between 2-cyclopentenone or 2-cyclohexenone and formaldehyde or aromatic aldehydes could be obtained in reasonable reaction times, however, only trace or poor yield was obtained in organic solvent along like THF, dioxane, DMF and acetonitrile (**Scheme 61**).



Scheme 61: Aqueous MBH reaction between aldehydes and cycloalkenones.

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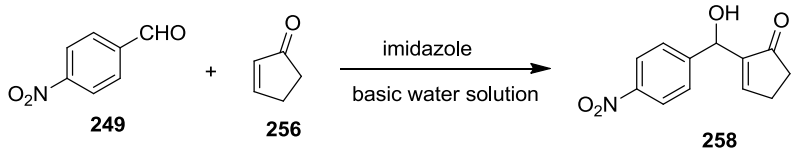
Subsequently, Cheng and co-workers [234] found that the Baylis-Hillman reaction of cyclic enones was greatly accelerated in basic water solution with imidazoles as catalysts, which resulted in short reaction time, high yields, and border substrate scopes. They results indicated that in basic water solution, the protonation of imidazole is depressed, thus increasing the active molarity of imidazole in catalysis (**Scheme 62**).



basic water solution	time (h)	yield (%)
1 M $NaCO_3$	10 min	53
1 M $NaHCO_3$	1.5	88
H_2O	20	48

Scheme 62: Aqueous MBH reaction between nitrobenzaldehyde and cycloalkenones.

Thorough re-examination by Williams and co-workers [235] of the reaction conditions used by El Gaïed and co-workers [232] concluded that the use of aqueous sodium hydrogen carbonate in the absence of an organic co-solvent is a necessary but not sufficient condition for imidazole catalysis, thus a surfactant must be added to the aqueous mixture to achieve useful reaction rates.

Recently, Coelho *et al.* [236] developed a bicyclic imidazolyl alcohol (namel imidazole 6,7-dihydro-5H-pyrrolo[1,2-a]imidazole **259**, abbreviated as DPI) catalyse the MBH reaction of 2-cyclopentenone and 2-cyclohexanone with aromatic aldehydes, afford the corresponding adducts **257** in good average yields and reasonable reaction times in aqueous medium (**Scheme 63**). Their results indicated that due to the conjugate bicyclic structure along with the additional hydrogen-bond donor group, this new catalyst shown a better efficiency compared to imidazole. It should be noted that this reaction works in aqueous medium, but no reaction occurred in pure water, so a catalytic amount of sufactant, such as assodium dodecyl sulphate, was added in order to furnish the MBH reaction in water. This strategy also applied in the aqueous MBH

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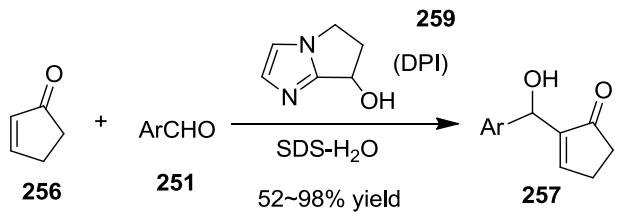
reaction between unprotected isatins and cyclic enones to afford the corresponding 3-substituted 3-hydroxy-2-oxindoles [237].



Scheme 63: Aqueous MBH reaction between aldehydes and cycloalkenones catalyzed by DPI.

A substantial acceleration of the Baylis-Hillman reaction between cyclohexenone and benzaldehyde has been observed when the reaction is conducted in water [226]. Further studies on the use of polar solvents revealed that formamide also provided significant acceleration and the use of 5 equiv of formamide (optimum amount) gave faster rates than reactions conducted in water. Using formamide, further acceleration was achieved in the presence of $Yb(OTf)_3$ (5 mol %), rate enhancements of up to 120-fold have been achieved in the coupling of methyl acrylate with benzaldehyde over standard DABCO-catalyzed reaction.

Moreover, high pressure (ca. 200 MPa), generated by freezing H_2O in a sealed autoclave, was successfully applied to the MBH reaction, in which an efficient rate enhancement was observed [238].

1.6.3.2 Other MBH-type reactions in aqueous medium

There are few reactions that a not formally MBH reactions, however which go through comparable pathways. A convenient and efficient synthesis of 2-methylenealkanoates **262** is accomplished via the regioselective nucleophilic addition of hydride ion from $NaBH_4$ to (2*Z*)-2-(bromomethyl)alk-2-enoates **260** respectively in the presence of DABCO in aqueous media (**Scheme 64**) [239].

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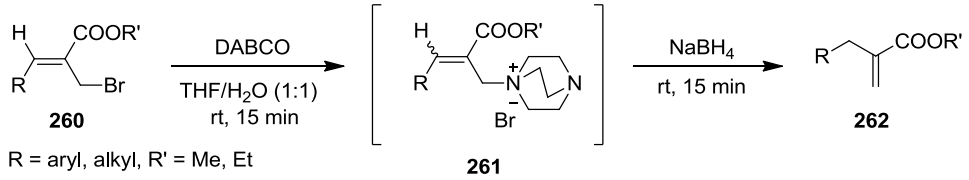
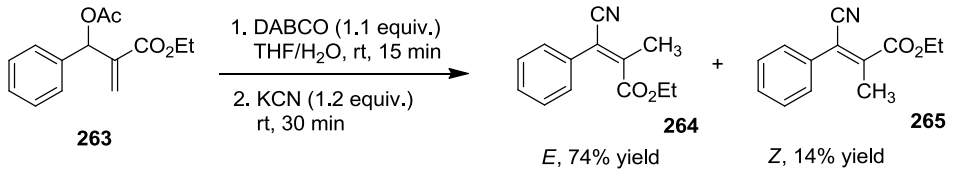


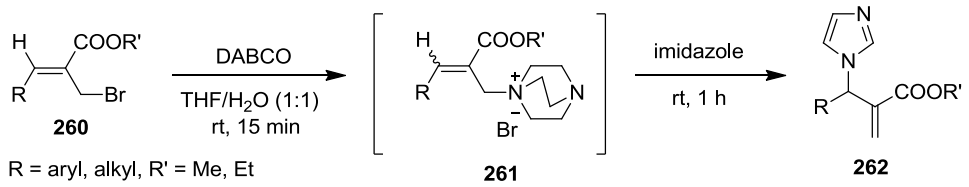
Scheme 64: Synthesis of 2-methylenealkanoates

As reported by Kim *et al.* [240], ethyl 3-cyano-2-methylcinnamates **264** and 3-cyano-2-methylcinnamonitriles **265** could be obtained by using the successive S_N2-S_N2-isomerization strategy with DABCO and KCN from the easily available Baylis-Hillman acetates in aqueous THF (**Scheme 65**).



Scheme 65: Synthesis of ethyl 3-cyano-2-methylcinnamates

A remarkable rate acceleration of water-promoted nucleophilic substitution of Baylis-Hillman acetate was described by Zhang's group [241], which led to a serious of *N*-substituted imidazole **262** (**Scheme 66)**. Without additional reagents, the Baylis-Hillman acetates underwent nucleophilic substitution reaction with imidazole readily in aqueous THF solution to afford the corresponding S_N2 type *N*-substituted imidazole derivatives in good to excellent yields in the presence of DABCO. Mechanic experiment shows that the DABCO salt **261** was a key intermediate. Also, the presence of water as a co-solvent was crucial: all runs were finished in 1.5 h in aqueous medium, compared with the sluggish process (5 days) in dry methanol.



Scheme 66: Synthesis of *N*-substituted imidazole with MBH acetate.

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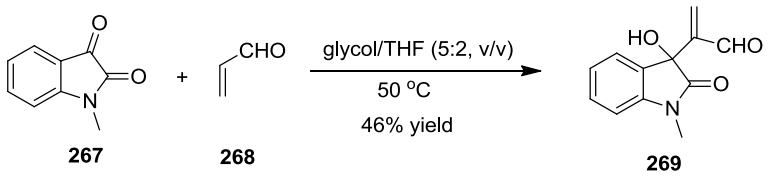
1.6.3.3 MBH reaction in other unconventional solvents

1.6.3.3.1 MBH reaction in ethylene glycol/THF

Zhou *et al.* [242] reported the first example of catalyst-free MBH reaction between isatin **267** and acrolein **268**, the reaction take place in a mixed solvent of ethylene glycol/THF (5:2, v/v) at 50 ^{o}C, leading to 46% yield of Baylis-Hillman adducts **269** (**Scheme 67**). Ethylene glycol play a key role during this process, no reaction took place when pure THF used as the solvent. The existence of ethylene glycol promotes the reactivity of both electrophilic and nucleophilic reaction partners through H-bonding interactions that facilitate this reaction without association of any catalysts. Furthermore, a variety of different substituted isatins could react with acrolein to give their corresponding products in moderate yield.



Scheme 67: The MBH reaction of istain with acrolein.

1.6.3.3.2 MBH reaction in supercritical carbon dioxide ($scCO_2$)

The use of supercritical carbon dioxide ($scCO_2$) as a green reaction medium for the MBH reaction was reported by Rayner's group [243]. Under similar reaction conditions, the MBH reaction of 4-Nitrobenzaldehyde **249** with methyl acrylate in $scCO_2$ leading to 48% yield of Baylis-Hillman adducts **250**, while in toluene or acetonitrile, less than 5% of conversions were detected, which indeed demonstrate the unusual nature of this reaction medium and the dramatically rate acceleration effect when it's appointed as solvent for the MBH reaction compare to in conventional solvents (**Scheme 68)**. The reaction can be extended further to a range of electron deficient aromatic aldehydes. However, due to the unique properties of $scCO_2$, when the reaction pressures decrease around 11.0 MPa or below, the unprecedented etherification reaction of MBH adducts occur, led to the formation of a significant

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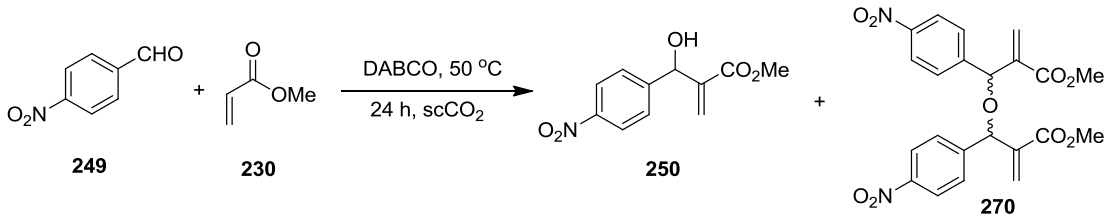
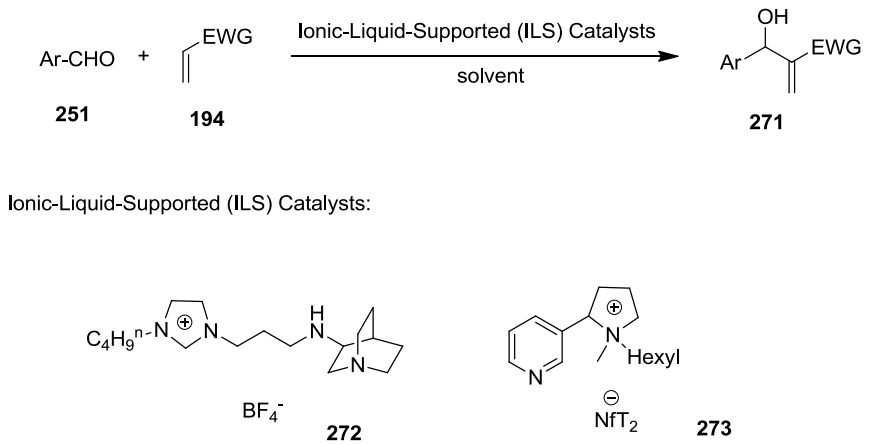
dimerisation product **270**.



Scheme 68: The Baylis-Hillman reaction in $scCO_2$.

1.6.3.3.3 MBH reaction in ionic liquids (Ils)

Room temperature ionic liquids (RTILs), being regarded as an environmentally benign reaction media, have gained great attention during the past decades [244]. Compared to volatile organic solvents (VOC) commonly used for chemical transformations, ILs, in terms of thermal stability, low vapor pressure, excellent ability to dissolve polar and non-polar organic and inorganic compounds, are regarded as alternative “green solvent” in organic synthesis. One of the concerns about using ILs as promising solvents for the MBH reaction is the formation of zwitterionic intermediates during the process could probably be stabilized in the ILs environment through charge-dipole interaction, which might be significantly accelerated the reaction rate. A lot of ionic liquid-immobilized tertiary amine or alkylphosphine-based catalysts have been applied in the MBH reaction (**Scheme 69**) [245, 246]. However, in this review, we only highlight the ILs as a medium for the MBH reaction.



Scheme 69: Ionic liquid-immobilized catalysts applied in MBH reaction.

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Early studies were reported by Afonso and Santos [247], shown that the MBH reaction can be efficiently performed in 1-butyl-3-methylimidazolium (bmim)-based ionic liquids, [bmim][PF_6] (33.6 times faster than in acetonitrile which regard as the best reported solvent for the MBH reaction). The reaction show a good substrate generality for several aldehydes, especially when aromatic aldehydes were used. Nevertheless, the ionic liquid medium [bmim][PF_6] can be recycled after the reaction and reused without reduction of reaction yields, which bringing even more attractiveness to this reaction with regards to the field of green chemistry.

Furthermore, results were observed by Ko [248] and Kumar [249] shown the acceleration effect was quite dependent of the anion in the series [bmim][X] ionic liquids, the following reactivity orders were observed: BF_4> PF_6 > Cl > [bmim][NTf_2] > CH_3CN. Interestingly, in contrast to Afonso's studies, Aggarwal *et al.* [250] reported that in case of [bmim]Cl a reversible adduct [bmim-PhCHOH]Cl **276** was formed in 49% between the imidazolium cation and the benzaldehyde (**Scheme 70**). Probably due to the nature of the C(2)-H hydrogen bond presence in imidazolium salts, plays an important role in facilitating the formation of [bmim-PhCHOH]Cl **276** induced by the base DABCO or 3-HQD. Later on, Zhang and co-workers [251] release their results of a detailed theoretical study of the reaction between imidazolium cation and benzaldehyde in the absence and presence of DABCO. The results show that in the absence of DABCO, the barrier of the reaction is as high as 54.53 kcal mol^{-1}, indicating that [bmim] cation is very stable. However, with the assistance of DABCO, the overall energy barrier for the base-catalyzed reaction is remarkably reduced to 24.81 kcal mol^{-1}, this significantly decreases the positive charge on C(2) and hence enhances its nucleophilic ability. Moreover, those results are in line with some reported examples in several reactions and affinity studies in ILs, like palladium catalysed Heck reactions and it has been suggested that using imidazolium salts, the transformations could occur via Pd-carbene complexes; the carbene being derived from deprotonation of the imidazolium salt by a weak base [252].

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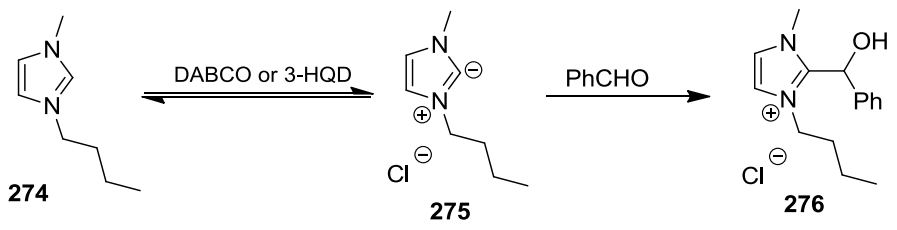

Scheme 70: Reaction of ionic liquid with benzaldehyde.

While in case of [bmim][X] ionic liquids, the formation of the undesired adduct [bmim-PhCHOH]X limits their reuse for different substrates, ether C2 substituted or non-imidazolium-based ionic liquids were then explored. Chu *et al.* [252] applied a new ionic liquid, 1-*n*-butyl-2,3-dimethylimidazolium hexafluorophosphate ([bdmim][PF_6]) as solvent for MBH reaction. Contrast to [bdmim][PF_6], after methylation, [bdmim][PF_6] ionic liquid is inert in C-2 carbon, which led to better yield for MBH reaction. However, the C-2 methyl group also undergoes slow proton exchange in the presence of triethylamine. Therefore, Ryu and co-works [254] synthesized a novel inert ionic liquids, 1,3-dialkyl-1,2,3-triazolium ionic liquids, which has been a suitable ILs for the MBH reaction under strong bases conditions (**Scheme 71**). A typical Baylis-Hillman reaction of *p*-chlorobenzaldehyde, methyl acrylate, and DABCO in the presence of 1,2,3-triazolium ionic liquids as solvent was explored. All 1,2,3-triazolium ionic liquids were good reaction media for the MBH reaction. Moreover, they found that the MBH reaction can be greatly accelerated in triazolium-based ionic liquids. In particular, the 1,2,3-triazolium ionic liquids with the same anion like PF_6 and NTf_2 afforded better yields than in [bmim][PF_6] and [bmim][NTf_2] (96% and 83% vs 67% and 63%).

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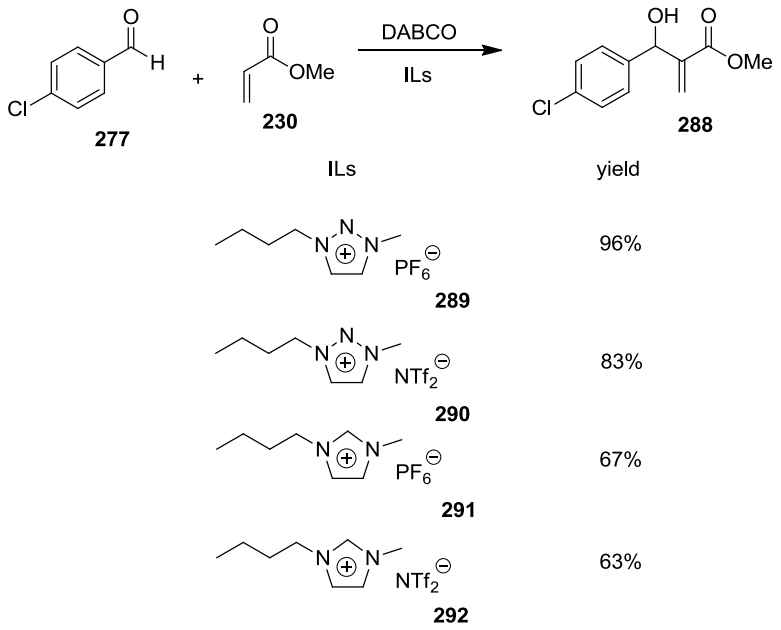

Scheme 71: Baylis-Hillman Reactions of *p*-Chlorobenzaldehyde and Methyl Acrylate in Various 1,2,3-Triazolium Ionic Liquids.

Meanwhile, other researchers focused on exploring non-imidazolium-based ionic liquids and its utilization as solvent for MBH reaction. The application of pyridinium ionic liquid [EtPy][BF_4] (N-1-ethylpyridinium tetrafluoraborate) as recyclable solvent for the Baylis-Hillman reactions was presented by Gong *et al.* [255] Compared with the commonly used imidazolium-based ionic liquid [bmim][PF_6] and [bdmim][PF_6] that evidently reacts with aldehydes under basic conditions, ionic liquid [EtPy][BF_4] is inert and the Baylis-Hillman reactions in [EtPy][BF_4] proceed quickly with good yields.

Eberlin and Coelho [256] have investigated the role of ionic liquids in Baylis-Hillman reaction via the ESI-MS(/MS) technique. They performed on-line monitoring of the DABCO-catalyzed MBH reaction of methyl acrylate with 2- thiazolecarboxaldehyde in the presence of imidazolium ionic liquids. Results show that several supramolecular species were formed by coordination of reagents and products as well as protonated MBH zwitterionic intermediates with both the cations and anions of the ionic liquids. On the basis of those results, they proposed that imidazolium ionic liquids function as efficient co-catalysts for the MBH reaction through coordination effect:

(i) by activating the aldehyde through nucleophilic addition;

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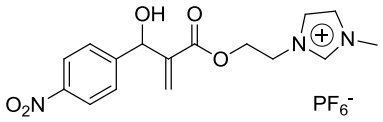
(ii) by stabilizing the zwitterionic intermediates through supramolecular coordination. An interesting charge-tagged acrylate derivative bearing an imidazolium tag **293** was formed to study the MBH reaction via ESI-MS(/MS) monitoring the effect of such tag (imidazolium cations and ion pairs) over transition state (**Fig. 27**) [257]. DFT calculations predicted the formation of electrostatic intermediate complexes with both the cation and anion when charge-tagged reagents are used. In this sense, the ILs effect and its origin have been explained on the basis of the formation of those unique electrostatic intermediate complexes take place during a specific chemical transformation. Those results are plausible explanation why ionic liquids have the positive effect on the MBH reaction.



293

Fig. 27: Charge-tagged MBH adducts.

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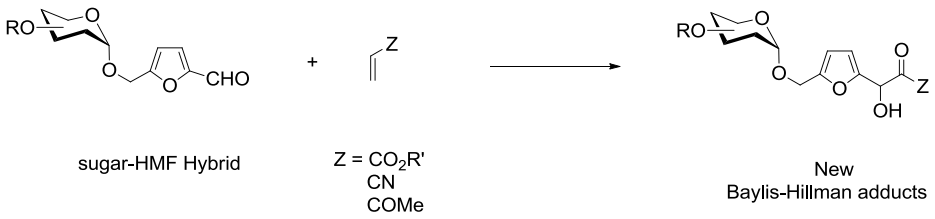
Chapter II Baylis-Hillman reaction of glucosyloxymethyl-furfural (GMF)

2.1 Introduction

Carbohydrates acrylates and methacrylates are, among vinylsaccharides, very attractive functional molecules, notably as building blocks for the synthesis of carbohydrates-based polymers. A lot of effort has thus been devoted to the synthesis of carbohydrate based acrylates and methacrylates, the common strategy consisting of anchoring a sugar to a polymerizable acrylate or methacrylate derivatives through esterification, etherification or C-C bond forming reactions, including chemical or enzymatic transformations. However due to the structural complexity of carbohydrates, the control of selectivity, in terms of degree of substitution and in terms of regioselectivity, remains challenging. With regards to properties of the sugar derivatives, monofunctional or multifunctional compounds exhibit very different properties, either in the surfactant of the polymer fields.

In order to get purely monofunctional carbohydrate-based acrylates, it is therefore necessary to isolate one specific functional group on the starting material for elaborating the sugar backbone only once. With this aim, we have investigated how the aldehyde group present in α-D-glucosyloxymethylfurfural (GMF) could be used in the MBH reaction to lead new monosubstituted sugar acrylates (**Scheme 2.1**).



Scheme 2.1: New route for the synthesis of carbohydrates acrylates.

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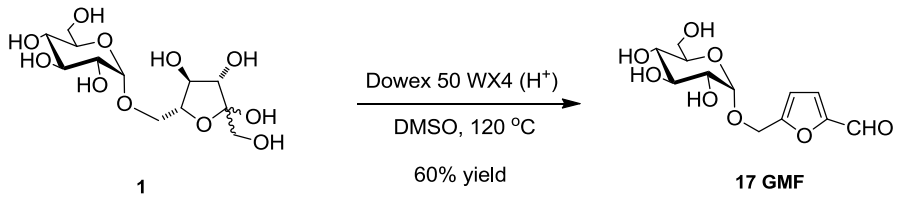
In a first series of experiments, we investigated the Baylis-Hillman reaction of the isomaltulose-derived aldehyde GMF and analogous compounds with α,β-unsaturated ketones and esters. This investigation aimed at providing some preliminary insights on this reaction with respect to the nature of the alkene and the possibility to use aqueous media and one biobased solvent.

2.2 Preparation of GMF and its use in Baylis-Hillman reaction

The protocol for the preparation of the substrate GMF is depicted in **Scheme 2.3**. It is available in one step from the selective dehydration of isomaltulose [68]. Conditions: after heating in an anhydrous DMSO solution in the presence of a dry, strongly acidic ion exchange resin for 3 h at 120 ^{o}C, the desired product was obtained in 60% yield.



Scheme 2.3: The synthesis of GMF.

The structure of the obtained product was in accordance with the literature and also confirmed by analyzing the ^{1}H NMR, HSQC and HMBC spectrum, as shown in the **Fig. 2.1**. The proton of the aldehyde group appears in the ^{1}H NMR spectrum at δ 9.57 ppm, the anomeric H is at δ 4.93 ppm with a doublet, with interactions with the C-6 and C-3' at δ 60.8, 73.4 ppm, respectively, observed in the HMBC spectrum. And the corresponding carbon was found at δ 95.4 ppm in the HSQC spectrum.

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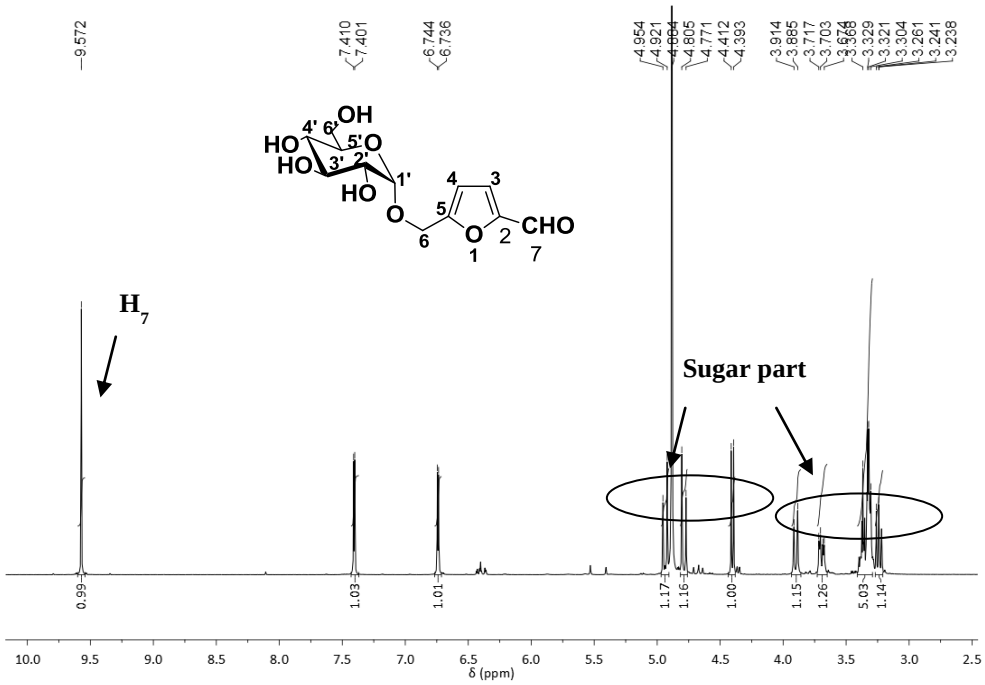

Fig. 2.1a: ^{1}HNMR spectrum of compound GMF(**17**).

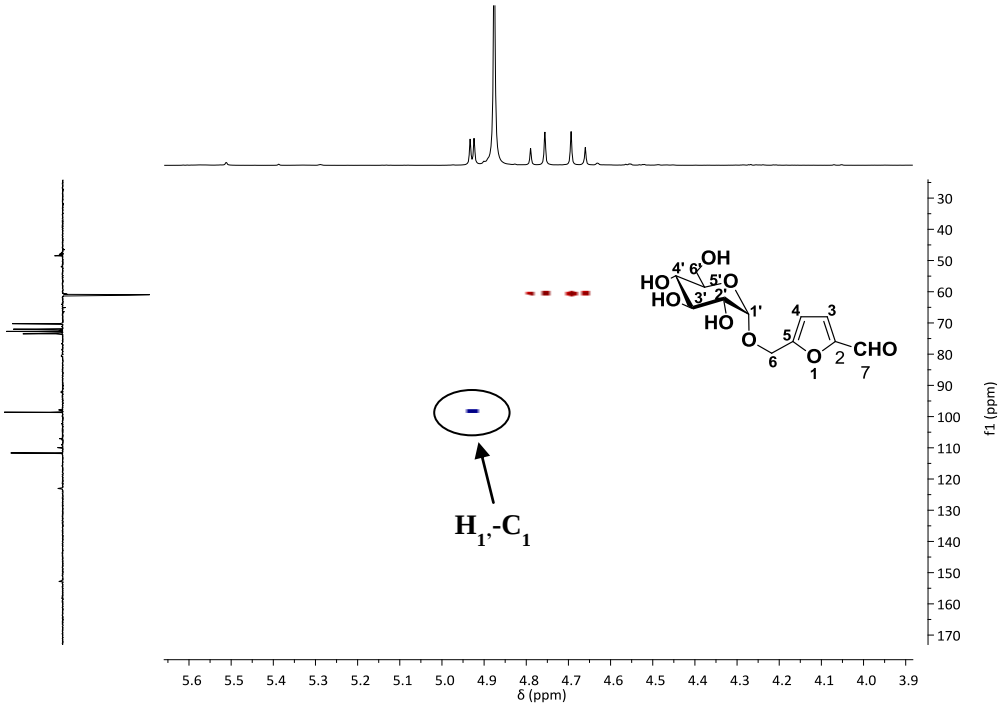

Fig. 2.1b: ^{1}H-^{13}C HSQC spectrum GMF(**17**).

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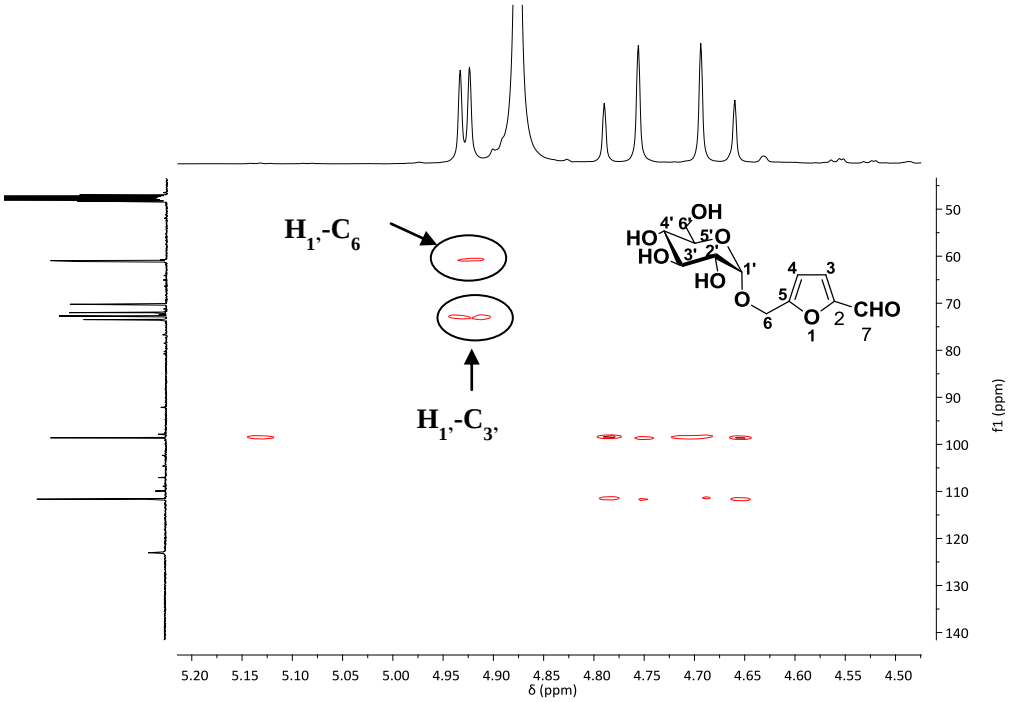

Fig. 2.1c: ^{1}H-^{13}C HMBC spectrum GMF(**17**).

The reaction of GMF with methyl acrylate was studied in different conditions of temperature, solvent, time and basic catalyst and the results are reported in **Table 2.1**. The MBH adduct methyl 2-[hydroxy-(5-(α-D-glucopyranosyloxymethyl) -furan-2-yl)-methyl]-acrylate (**298a**) was obtained and clearly identified by NMR and mass spectroscopy (**Fig. 2.2**). Notably, the proton of the newly formed CHOH appears in the ^{1}HNMR spectrum at δ 5.43 ppm, with interactions with the acrylic methylene and the ester carbonyl group at δ 125.4, 165.8 ppm, respectively, observed in the HMBC spectrum. The newly formed carbon-carbon bond was thus demontrated unambiguously. Though the aldehyde is chiral, no diasteroselectivity of the reaction was observed, all products were being found to be 1:1 mixtures of the two possible diatereoisomers (as seen when the signals of the two epimers differ slightly for some of the H or C atoms and show equivalent integration).

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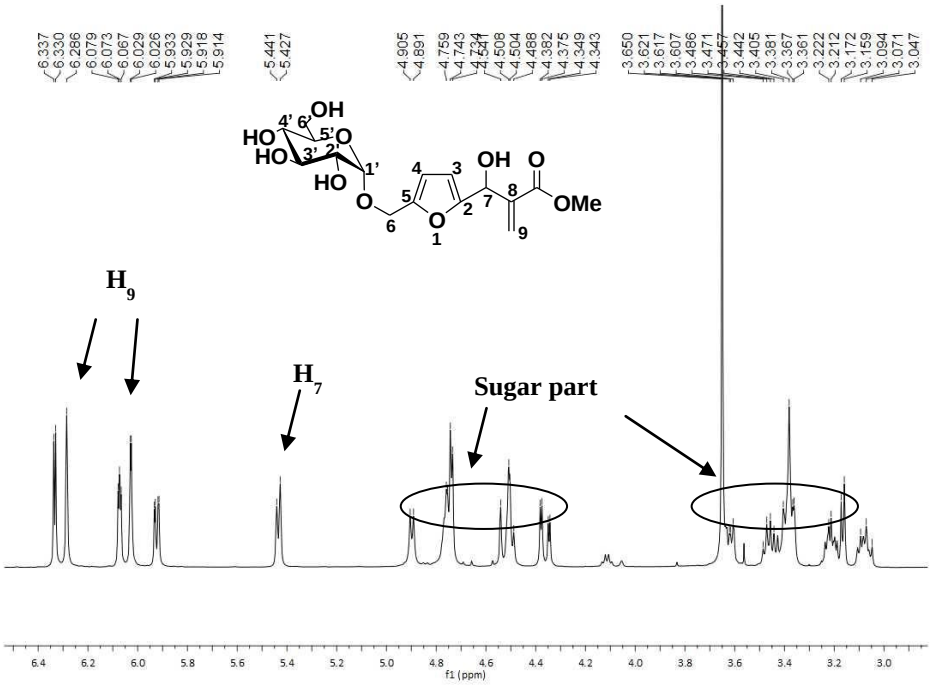

Fig. 2.2a: ^{1}HNMR spectrum of compound **298a**.

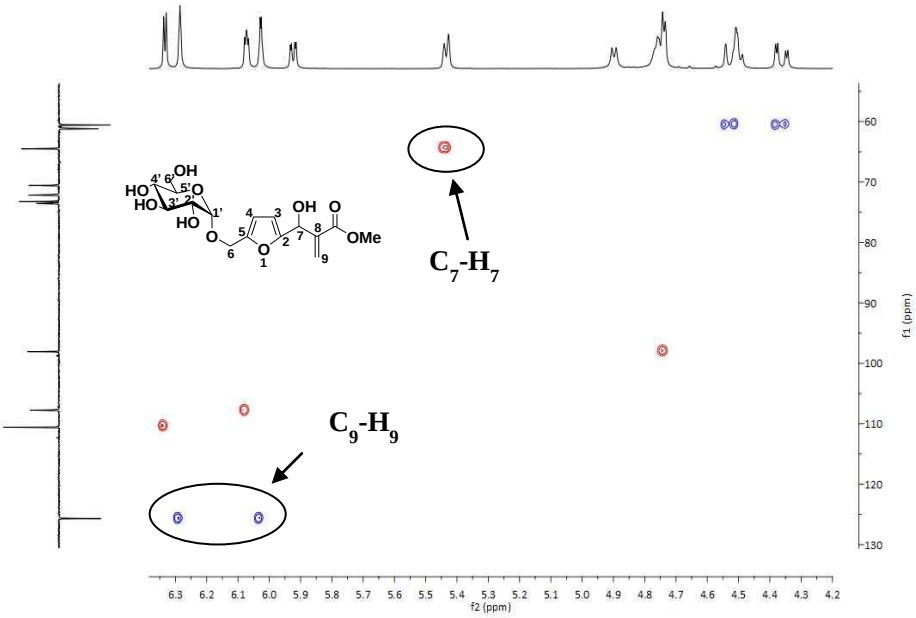

Fig. 2.2b: ^{1}H-^{13}C HSQC spectrum of compound **298a**.

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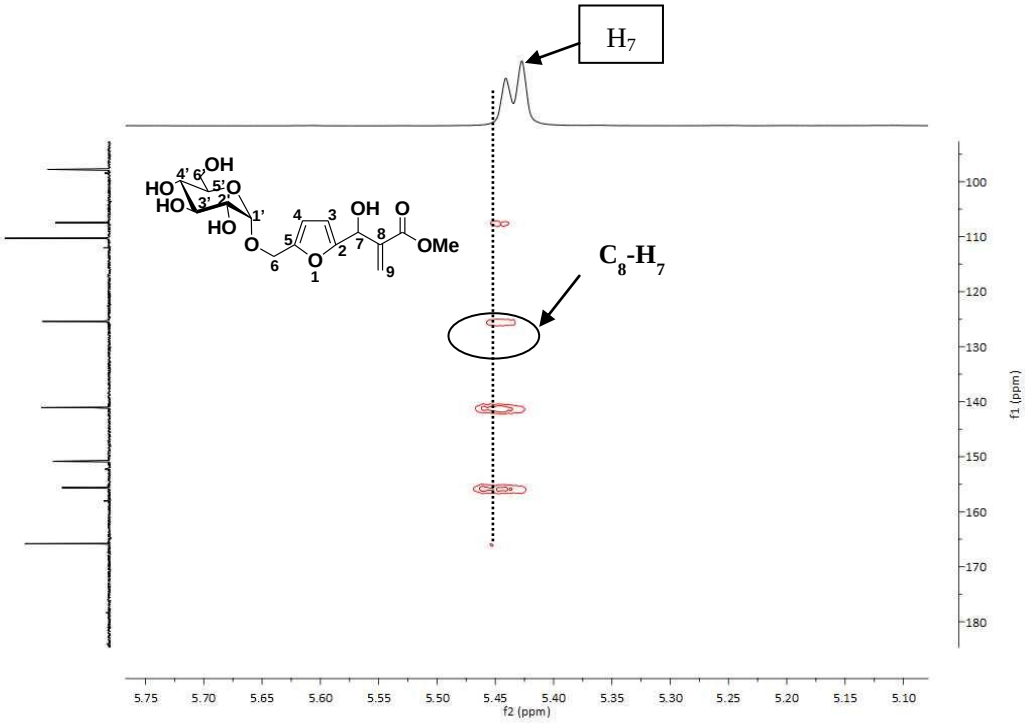

Fig. 2.2c: ^{1}H-^{13}C HMBC spectrum of compound **298a**.

The reaction was found to proceed quite slowly, as it is often observed for MBH reactions. At this stage of our investigations, the best yields were found when a 1:1 (v/v) ratio of dimethylisosorbide (DMI) and water was used (**Table 2.1**, entry 7) leading to a 56% yield of the desired MBH adducts. DMI is an isosorbide ether. It finds application in pharmaceutical and cosmetic industries. As its high boiling point, it was used as a substitute for DMSO and DMF in some reactions (**Scheme 2.2**) [24].

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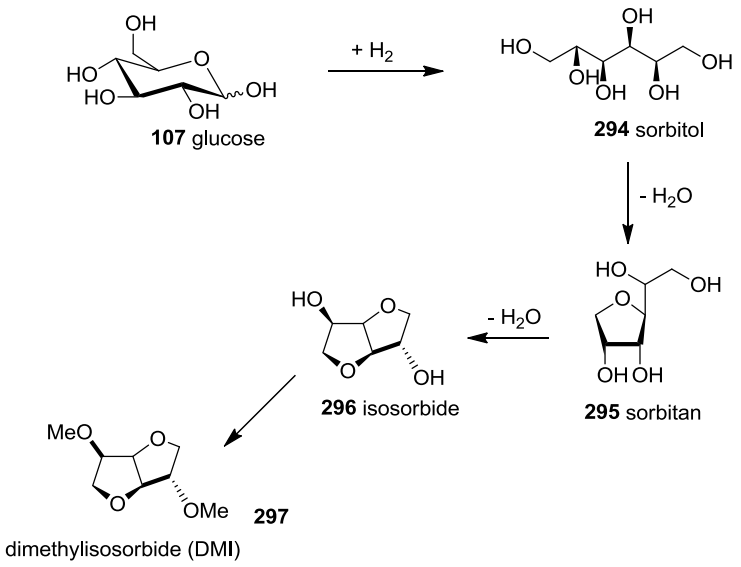

Scheme 2.2: Sorbitol and derivatives.

In pure water in the presence of 1,4-diazabicyclo[2.2.2]octane (DABCO), a 33% isolated yield of adduct **298a** was obtained (**Table 2.1**, entry 1), along with of 30% of starting aldehyde **17** thus giving a 47% yield based on starting material recovery. The binary medium DMI/H_2O proved to be preferable compared to other tested solvents, such as dioxane or DMI alone, or other binary media such as dioxane/H_2O or CH_3CN/H_2O, all of them leading to lower yields (**Table 2.1**, entries 3 to 6). DMI is thus shown to substitute efficiently dioxane or THF which are often used for the reaction.

In these solvent conditions, we found that an equimolar amount of DABCO was essential to the reaction, as when the amount of base was reduced to half, the yield dropped to 17% (**Table 2.1**, entry 8). Other tertiary amines like DMAP or aryl phosphines PPh_3 did not allow to obtain the desired adducts even when a water soluble aryl phosphine such as $P(m\text{-}C_6H_4\text{-}SO_3Na)_3$ was used (**Table 2.1**, entries 2, 13 to 15). The reaction was not much affected by temperature (**Table 2.1**, entries 11, 12).

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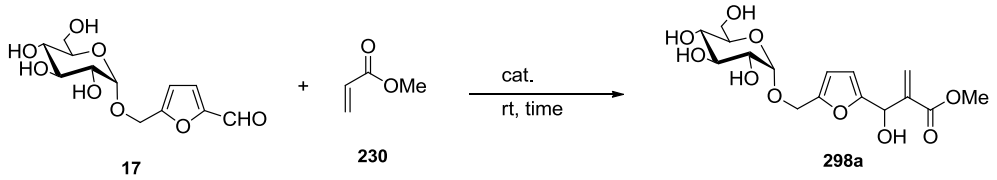
Table 2.1: Baylis-Hillman reaction of GMF with methyl acrylate[a]



Entry	Cat. (mol %)	Solvent	Time (h)	Yield (%)[b]
1[c]	DABCO	water	120	33
2	P(*m*-C_6H_4-$SO_3Na)_3$	H_2O	120	0
3	DABCO	Dioxane	36	0
4	DABCO	DMI	36	<5
5	DABCO	CH_3CN/H_2O	36	31
6	DABCO	Dioxane/ H_2O	36	35
7	DABCO	DMI/H_2O	36	56
8[d]	DABCO	DMI/H_2O	36	17
9[e]	DABCO	DMI/H_2O	36	42
10	DABCO	DMI/H_2O	18	40
11[f]	DABCO	DMI/H_2O	36	47
12[g]	DABCO	DMI/H_2O	36	28
13	PPh_3	DMI/H_2O	36	0
14	P(*m*-C_6H_4-$SO_3Na)_3$	DMI/H_2O	36	0
15	DMAP	DMI/H_2O	36	0

[a]: all reactions were conducted using 3:1 molar ratio of methyl acrylate and **2a,** 25 ^oC, with one equimolar amount of catalyst;

[b]: yield of isolated product;

[c]: 47% yield based on starting material recovery;

[d]: 50 mol % of DABCO has been used;

[e]: the ratio of **2a/3a** was 1:1.

[f]: 0~4 ^oC

[g]: 45 ^oC

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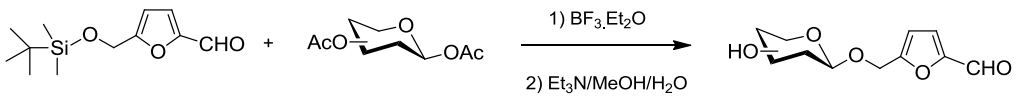
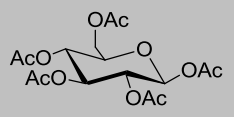
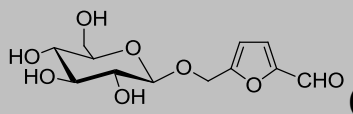
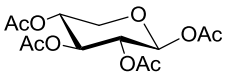
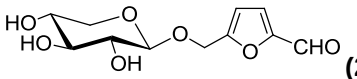
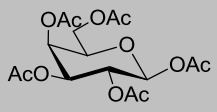
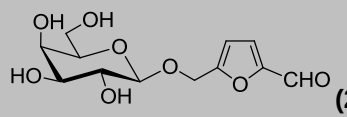
Having these results in hand, we then investigated the substrate scope of the DABCO-promoted Baylis-Hillman reactions of other hydroxymethyl furfural (HMF) glycosides derivatives with methyl acrylate in binary medium of (DMI/H_2O). Glycosylation of hydroxymethylfurfural was performed following a reported method in order to obtain the new β-gluco, β-xylo and β-galacto glycosides [158]. First, HMF was converted into the silylated HMF, and then submitted to glycosylation reaction with the corresponding peracylated monosaccharide under the presence of $BF_3.Et_2O$. Subsequent deprotection of the acyl groups, afforded the desired product in moderate yield (**Table 2.2**).

Table 2.2. Condensation reaction between the acylated monosaccharide and silylated HMF.



Substrates	Products	Isolated yield (%)
	 **(299a)**	25
	 **(299b)**	32
	 **(299c)**	20

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The structure of the obtained product was confirmed by analyzing the ^{1}H NMR, ^{13}C NMR and HMBC spectrum, for example the spectrum of the newly formed β-xylo glycosides as shown in the **Fig. 2.3**. The proton of the aldehyde group appears in the ^{1}H NMR spectrum at δ 9.56 ppm, the corresponding anomeric H moved from δ 4.93 ppm to δ 4.39 ppm compared to GMF, with interactions with the C-6 and C-3' at δ 63.7, 77.7 ppm, respectively, observed in the HMBC spectrum. And the corresponding anomeric carbon was found at δ 103.5 ppm in the HSQC spectrum compared to GMF at at δ 95.4 ppm. All those datas proved that the configuration of the anomeric position is β.

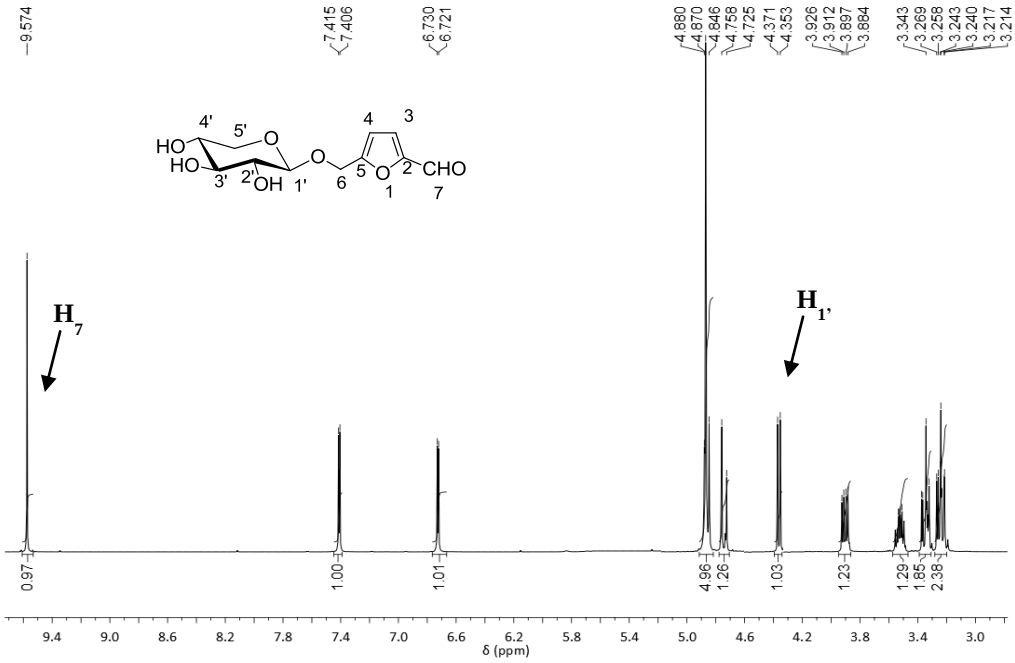

Fig. 2.3a: ^{1}HNMR spectrum of compound **299b.**

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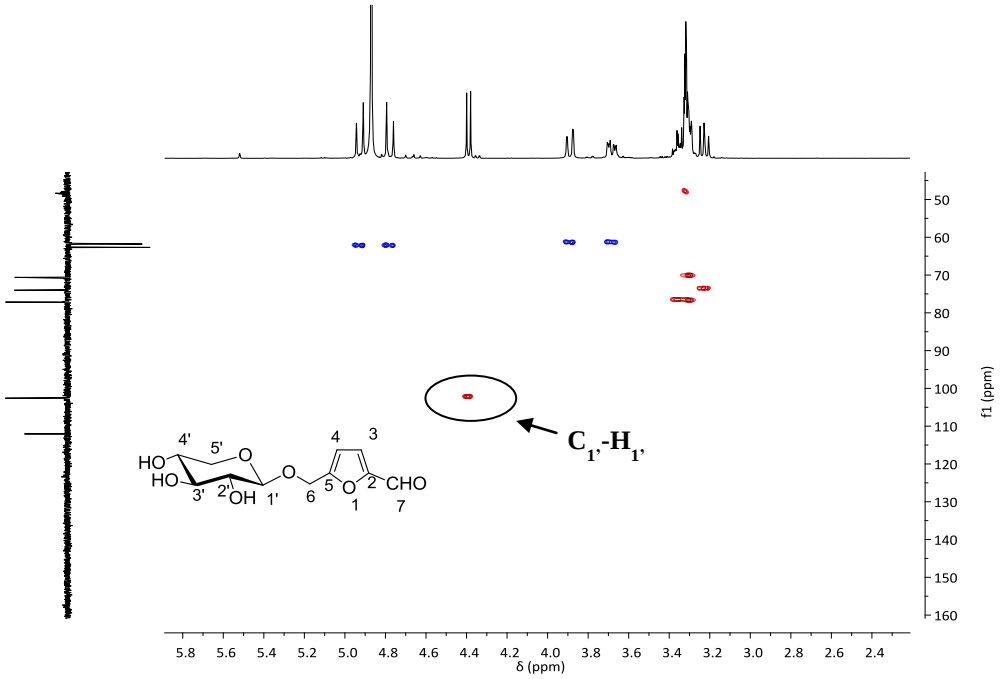

Fig. 2.3b: HSQC spectrum of compound **299b.**

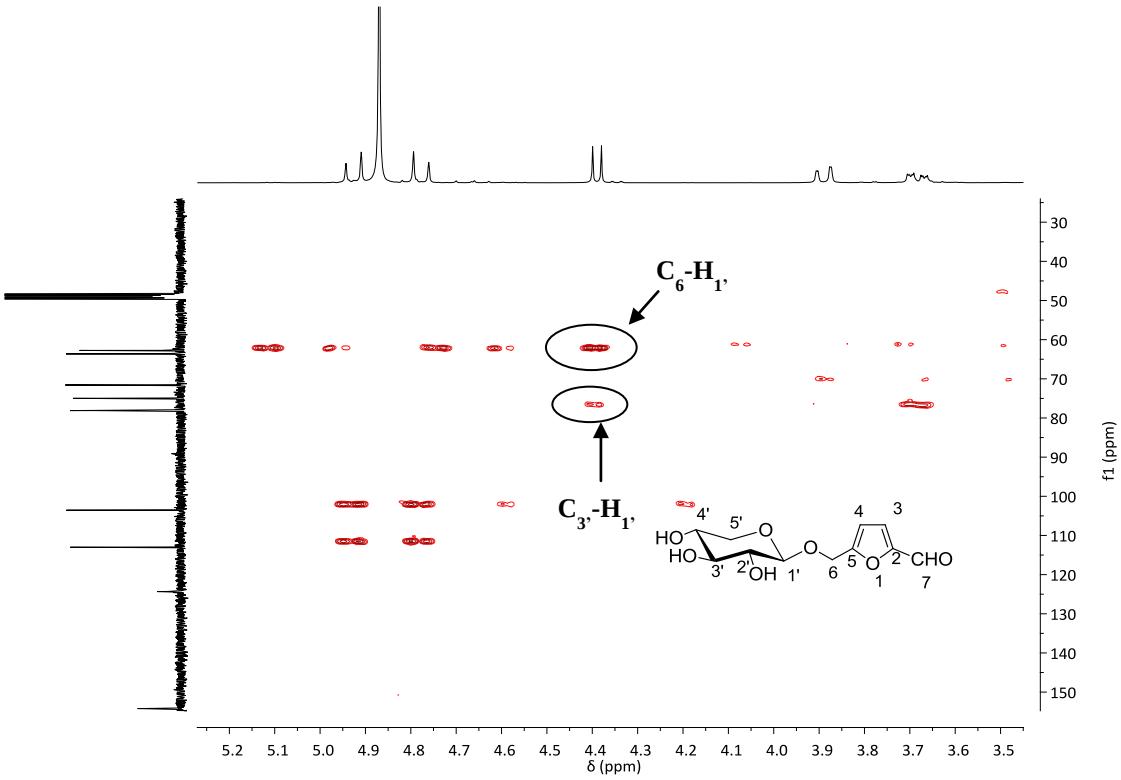

Fig. 2.3c: HMBC spectrum of compound **299b.**

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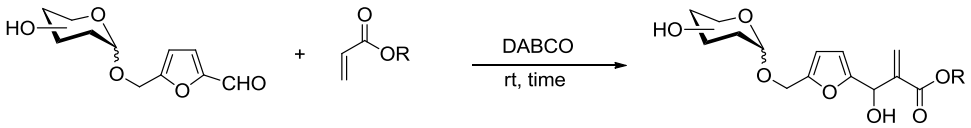
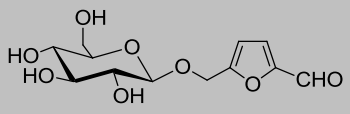
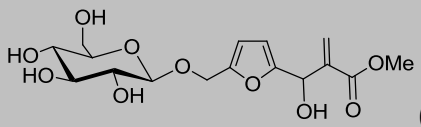
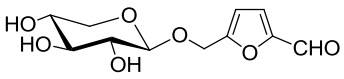
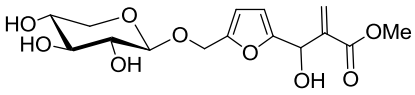
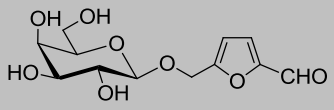
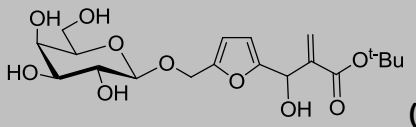
The three new HMF glucosides (**299a-c**) were submitted to the MBH reaction. As shown in **Table 2.3**, in all cases, MBH adducts (**298b-d**) were obtained with similar yields as observed for GMF.

Table 2.3. Baylis-Hillman reaction of acrylate with different sugar-based aldehyde



Substrates	Products	Isolated yield (%)
	 **(298b)**	63
	 **(298c)**	62
	 **(298d)**	50

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The reaction of GMF was then investigated with various acrylates differing in their ester group and the results are listed in **Table 2.4**, with yields in the same range. Hydroxymethyl acrylate was also applicable in this reaction. A series of non-ionic amphiphilic compounds has also been synthesized by using long-chain (C_6-C_{12}) acrylic esters. Comparation the MBH adducts arising from GMF with methyl acrylate, the aliphatic part was clearly identified in ^{1}H NMR spectra (**Fig. 2.4**). Such compounds can be regarded as surfactants and may also exhibit liquid crystalline properties.

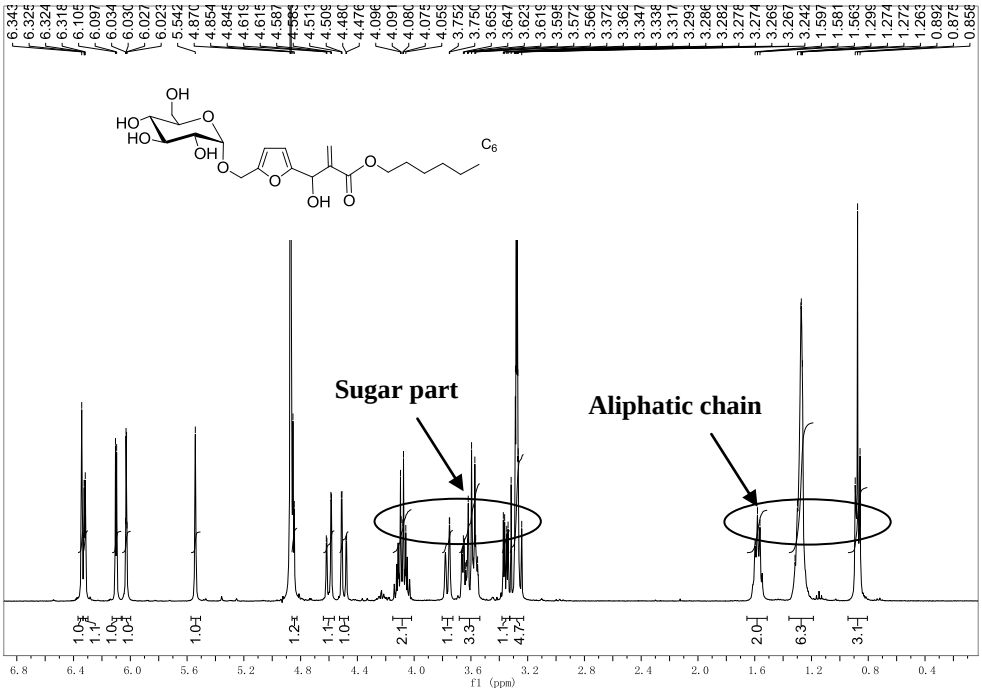

Fig. 2.4: ^{1}HNMR spectrum of compound **298j**.

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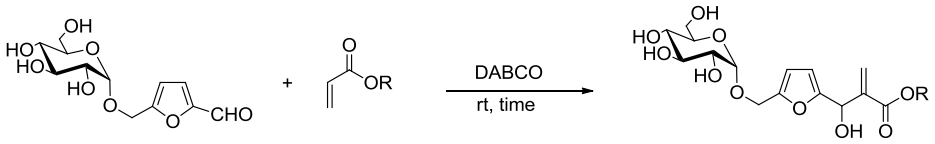
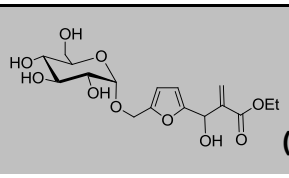
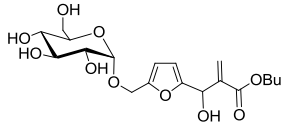
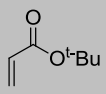
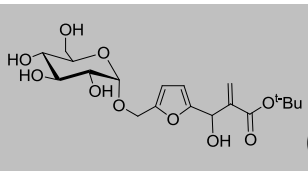
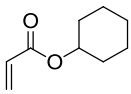
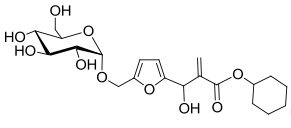
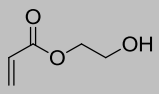
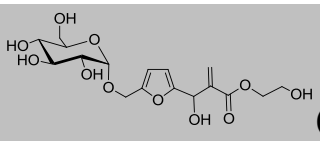
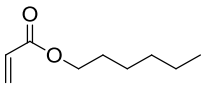
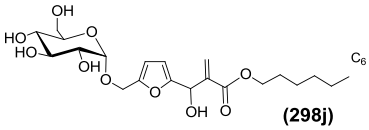
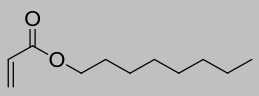
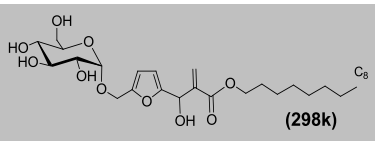
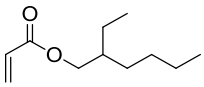
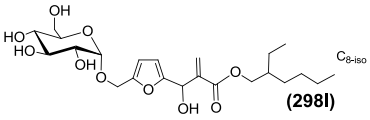
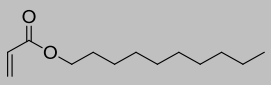
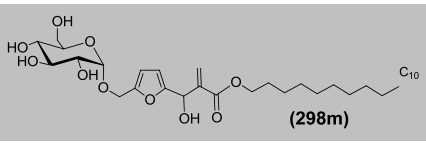
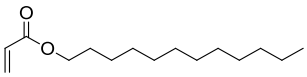
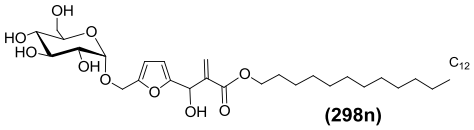
Table 2.4. Baylis-Hillman reaction of GMF with different acrylates.



Acrylates	Products	Isolated yield (%)
	 **(298e)**	64
	 **(298f)**	60
	 **(298g)**	56
	 **(298h)**	57
	 **(298i)**	35
	 **(298j)**	58
	 **(298k)**	56
	 **(298l)**	57
	 **(298m)**	53
	 **(298n)**	48

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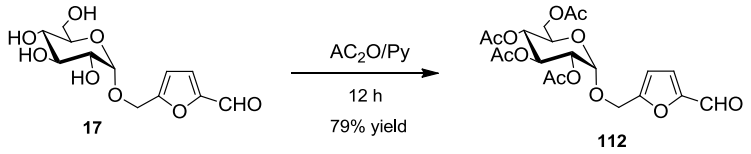
2.3 Baylis-Hillman reaction of GMF tetraacetate

The reactivity of GMF tetraacetate (Ac_4-GMF, **112**) was also investigated. GMF tetraacetate was synthesized as already by acylation of GMF with acetic anhydride in pyridine solution [71]. The reaction gave the desired product in 79% yield (**Scheme 2.4**).



Scheme 2.4: The synthesis of GMF tetraacetate

The structure of the obtained product was confirmed by analyzing the ^{1}H NMR, HSQC and HMBC spectrum, as shown in the **Fig 2.6**. The proton of the aldehyde group appears in the ^{1}H NMR spectrum at δ 9.63 ppm, the anomeric H is at δ 5.18 ppm, with interactions with the C-6 and C-3' at δ 62.0, 69.8 ppm, respectively, observed in the HMBC spectrum. And the corresponding carbon was found at δ 95.4 ppm in the HSQC spectrum.

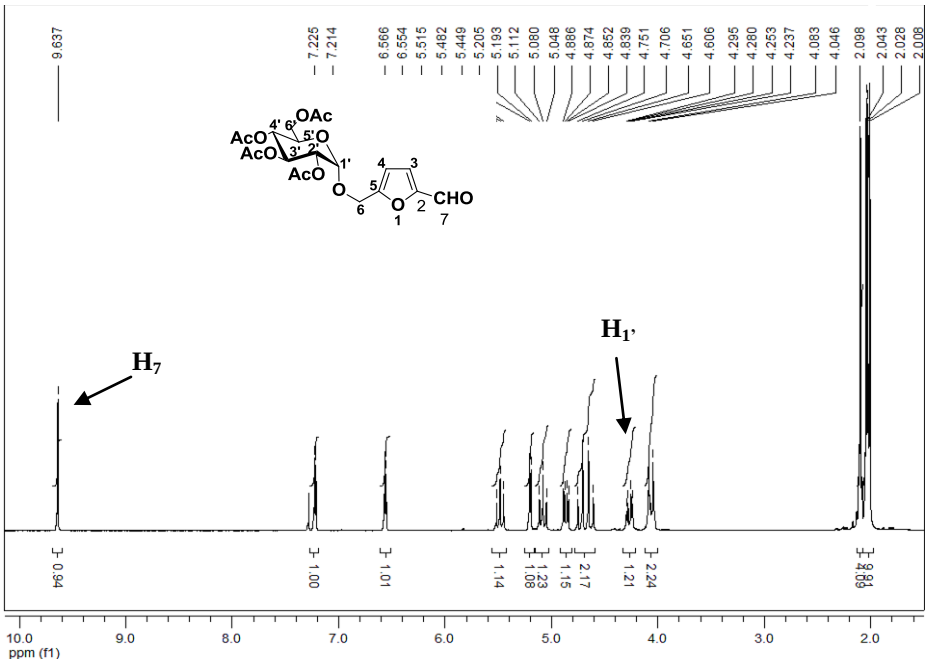


Fig 2.6a: ^{1}HNMR spectrum of compound **112**.

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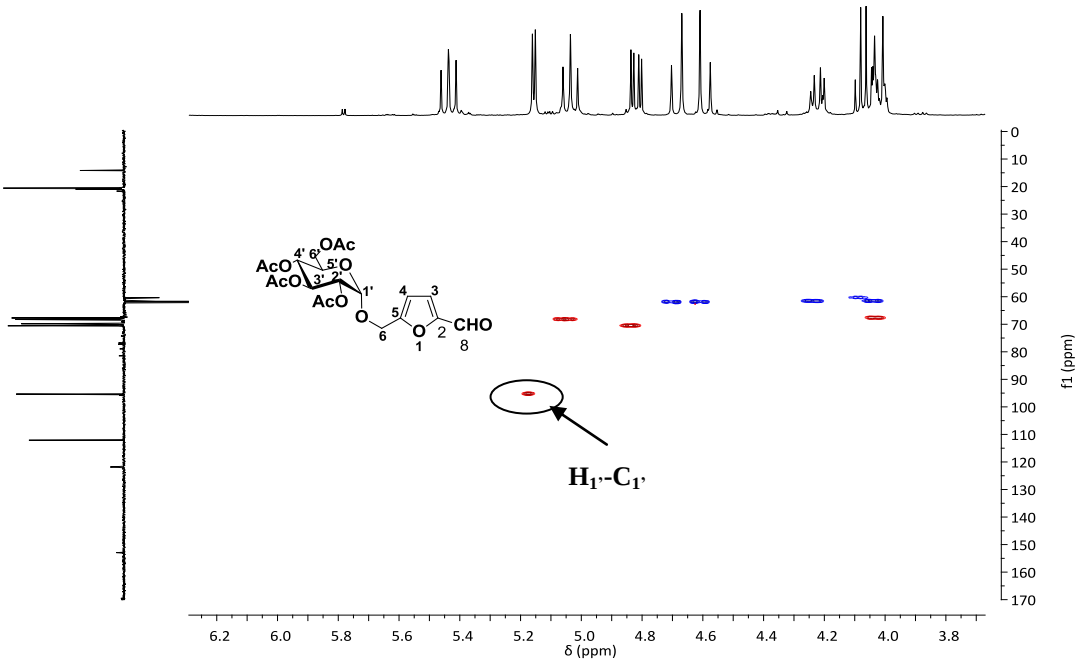

Fig 2.6b: HSQC spectrum of compound **112**.

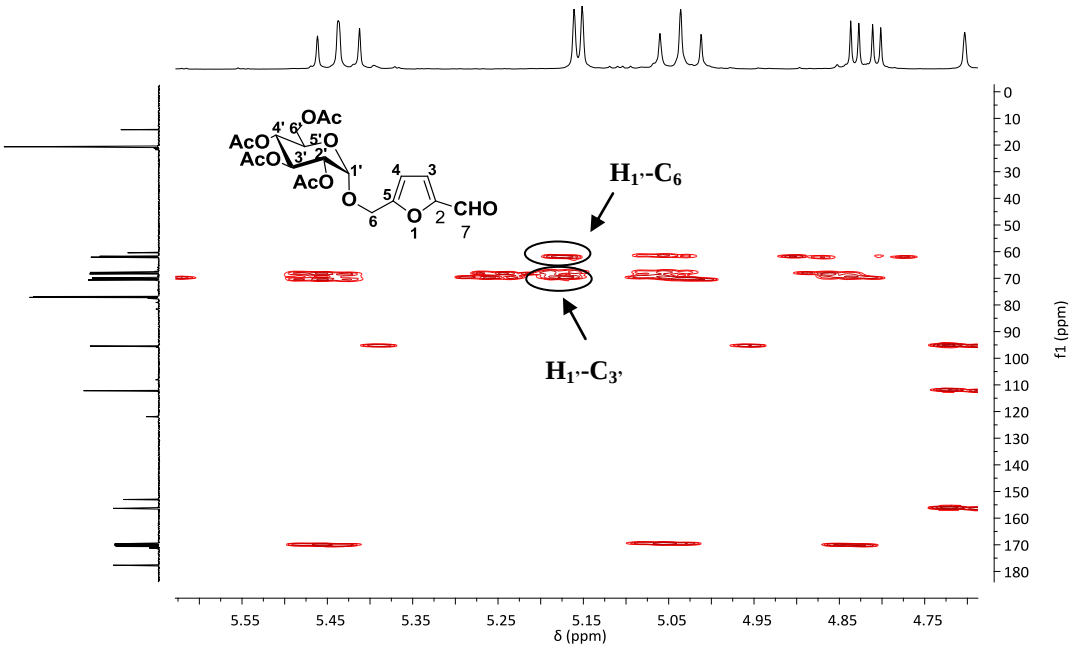

Fig 2.6c: HMBC spectrum of compound **112**.

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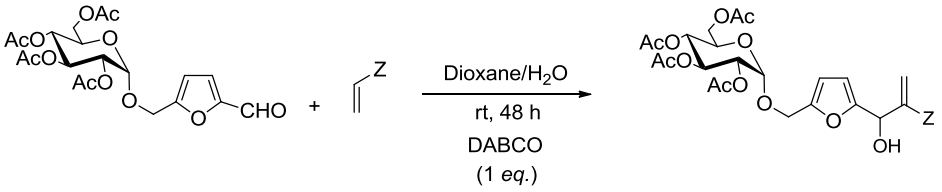
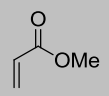
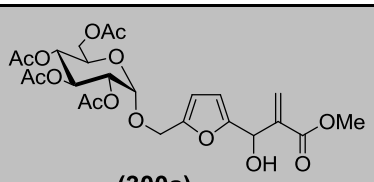
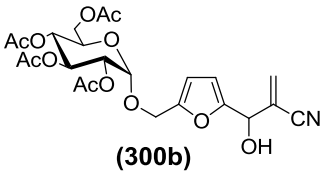
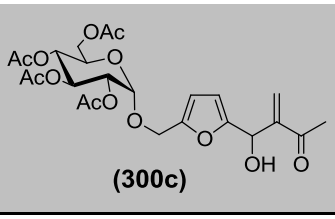
Using the DMI-water-DABCO conditions did not allow to observe the desired products within acceptable time, but the corresponding BH adducts could be obtained by using Hu's aqueous conditions (DABCO, 1,4-dioxane and water 1:1 v/v) [227]. Both methyl acrylate and acrylonitrile gave the desired Baylis-Hillman adducts in fair to good yields (**Table 2.5**).

Table 2.5. Reaction of GMF tetraacetate with different micheal acceptors.



Michael acceptor	Products	Isolated yield (%)
	 **(300a)**	52
	 **(300b)**	62
	 **(300c)**	Messy mixture

The reaction using methyl vinyl ketone (MVK) was unsuccessful under these conditions: either in dioxane/H_2O, DMI or DMF. As reported by Shi *et al.* [258], the Baylis-Hillman reaction of *p*-nitrobenzaldehyde with MVK under the presence of DABCO, they found that besides the normal Baylis-Hillman adduct **255**, the diadduct **301** can also be formed at the same time and the yield of **301** can reach to 55% if increasing the amount of methyl vinyl ketone (**Scheme 2.5)**. When DMAP as a Lewis base in DMSO or DMF was used, **255** was exclusively obtained in high yields under

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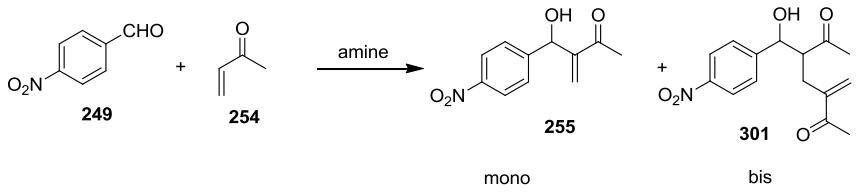
the same reaction conditions, indicated DMAP could prevent the formation of the the diadduct and get a better selectivity.

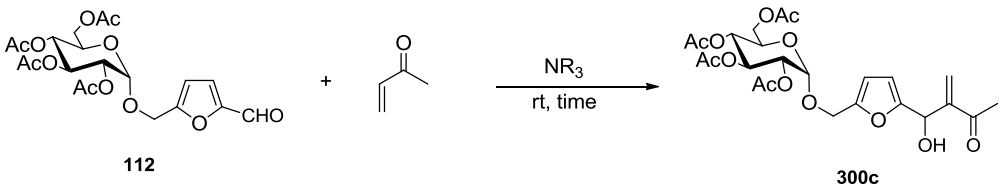


Lewis base	solvent	yield	
		1	2 (syn/anti)
DABCO	DMSO	60	20 (1:1)
DABCO	DMF	63	23 (1:1)
DMAP	DMSO	83	0
DMAP	DMF	85	0

Scheme 2.5: Baylis–Hillman reactions of *p*-nitrobenzaldehyde with MVK in the presence of different Lewis base.

So the less reactive DMAP was used as catalyst for the reaction of GMF tetraacetate **112** with MVK, and it was found that the Baylis-Hillman adduct **300c** was exclusively formed in good yield (**Table 2.6**, entry 4). All MBH reactions conducted on GMF **17** and GMF tetraacetate **112** could easily be performed on a 10 mmol scale making the method applicable for practical synthesis of these new sugar-based acrylates.

Table 2.6. Reaction of GMF tetraacetate with MVK.



Entry	Cat. (mol %)	Solvent	Yield (%)
1	DABCO (100)	Dioxane/H_2O	-
2	DABCO (100)	DMF	-
3	DABCO (100)	DMI	-
4	DMAP (40)	DMI	62

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The structure of the obtained product was confirmed by analyzing the ^{1}H NMR, ^{13}C NMR and HMBC spectrum, as shown in the **Fig 2.7**. In proton NMR spectrum, the realization of coupling is identified by the disappearance of the singlet peak of the aldehyde group of HMF at δ 9.53 ppm to the benefit of the newly formed CHOH which appears at δ 5.60 ppm, combining with the data on the HSQC spectrum, and the corresponding carbon signals found at δ 66.9, 67.0 ppm. The newly formed carbon-carbon bond was thus demontrated unambiguously. The singlet of methyl group appears at δ 2.37 ppm. The methylene group of the adducts appears at δ 6.21, 6.27 ppm, combining with the data on the HSQC spectrum, and the carbon signals are found at δ 127.6 ppm. Like for GMF MBH adduct **298a**, though the aldehyde is chiral, no diasteroselectivity of the reaction was observed, in the case of Ac_4-GMF **112**, all products were being found to be 1:1 mixtures of the two possible diatereoisomers (as seen when the signals of the two epimers differ slightly for some of the C atoms and show equivalent integration, as seen in **Fig 2.7b**).

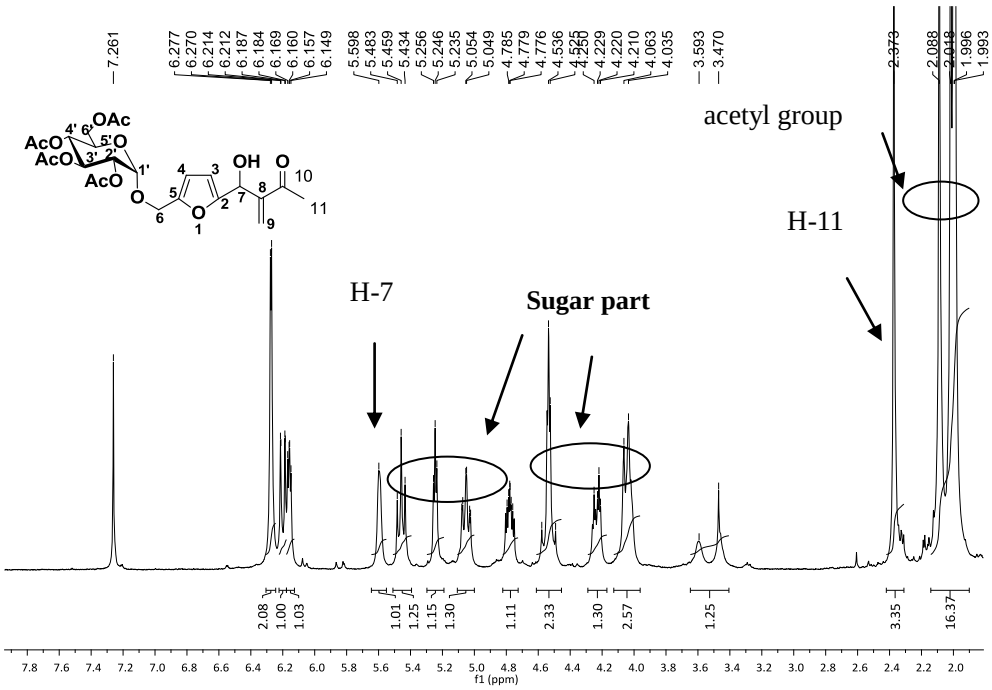

Fig 2.7a: ^{1}H NMR spectrum of compound **300c**.

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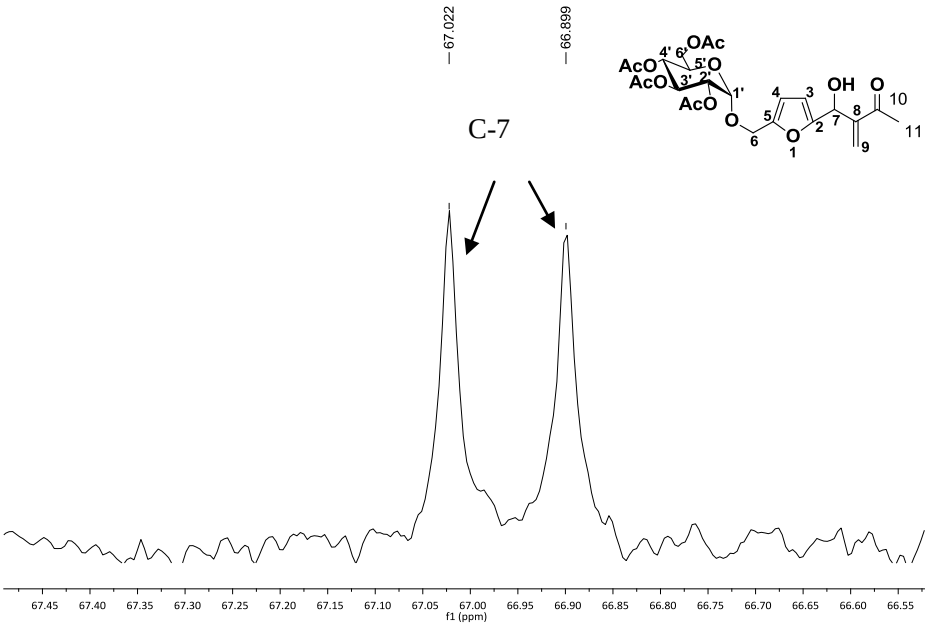

Fig 2.7b: ^{13}C NMR spectrum of compound **300c**.

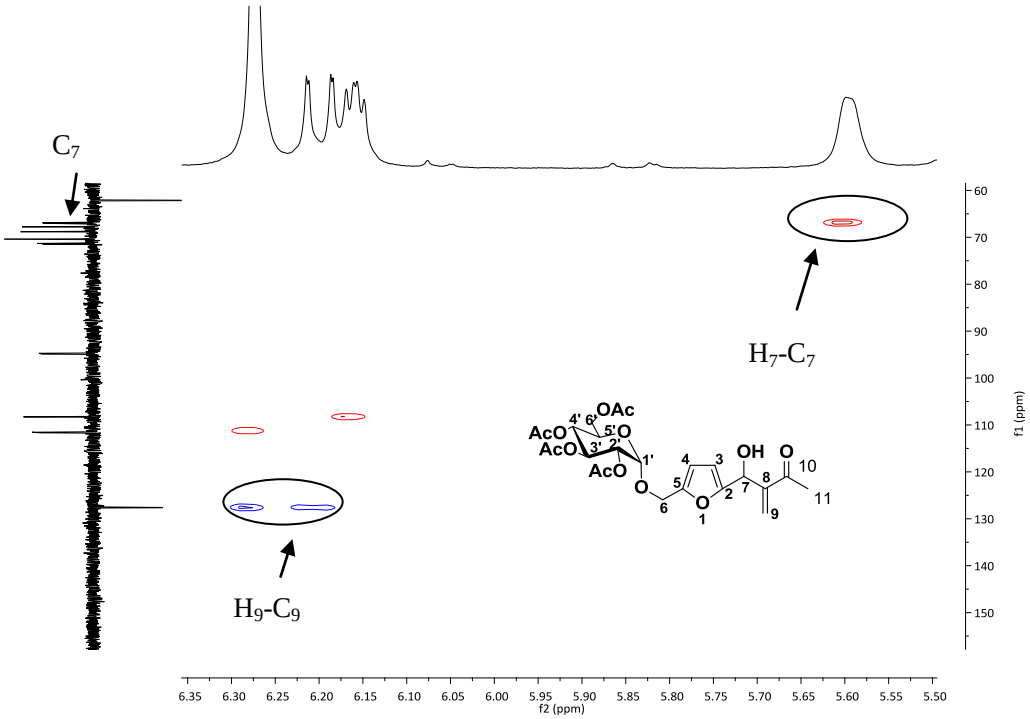

Fig 2.7c: ^{1}H - ^{13}C HSQC spectrum of compound **300c**.

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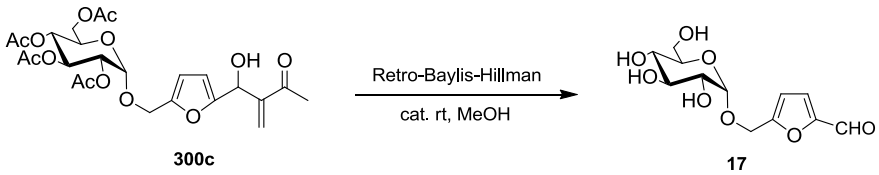
2.4 *Retro* Baylis-Hillman reaction

For the specific case of GMF tetraacetate **112**, the late deacetylation reaction was studied in order to reach fully deprotected MBH adducts. During the removal of the acetyl group, we found that MBH adducts underwent a *retro* Baylis-Hillman reaction to afford the substrate (GMF) in moderate yield. The reaction was carried out in aqueous medium, in the presence of 0.5 *equiv* of trimethyl amine or sodium methylate at room temperature. After 12 h, none of the desired product was found while GMF was isolated in 37% and 30 % yield respectively. Even after the reaction, an acidic resin was added to neutralize the base before the purification, there was still 40% yield of GMF generated (**Scheme 2.6**).



cat.(%)	Time	2a
CH_3ONa (50)	12 h	37%
CH_3ONa (50)[a]	12 h	40%
Et_3N (50)	12 h	30%

a: after reaction, 100 g of Dowex 50 WX4 (H^+ form) was added.

Scheme 2.6: *retro* Baylis-Hillman

In order to understand why such large quantities of starting GMF are present in the final reaction mixture, the stability of GMF and the deprotected Baylis-Hillman adduct was studied in the presence of base. DABCO (1 mmol) and GMF (1 mmol) or the Baylis-Hillman adduct (1 mmol) were dissolved in a mixture of 1,4-dioxane-d_8 (5 mL) and D_2O (5 mL) and the evolution of the mixture was monitored using ^{1}H NMR. The results showed that GMF was stable after 30 h with no detectable hydrolysis. However, the integration of the proton of the CHOH (at δ 5.43 ppm in the ^{1}HNMR) in the Baylis-Hillman adduct decreased along with the appearance of a new sharp

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singlet at δ 9.65 ppm in ^{1}H NMR which represent for the aldehyde group of the GMF. After 30 h, almost half of the Baylis-Hillman adduct hydrolyzed while the amount of GMF increased to 40%, suggesting that the Baylis-Hillman reaction is reversible and also the *retro*-Baylis-Hillman reaction occur under the presence of base (**Figure 2.8**). This results explain why in all of our cases the reaction yield is low or moderate: i) the Baylis-Hillman reaction is a slow and reversible reaction; ii) under the presence of a base like DABCO, hydrolysis of Baylis-Hillman adducts always happened, those two processes are in competition.

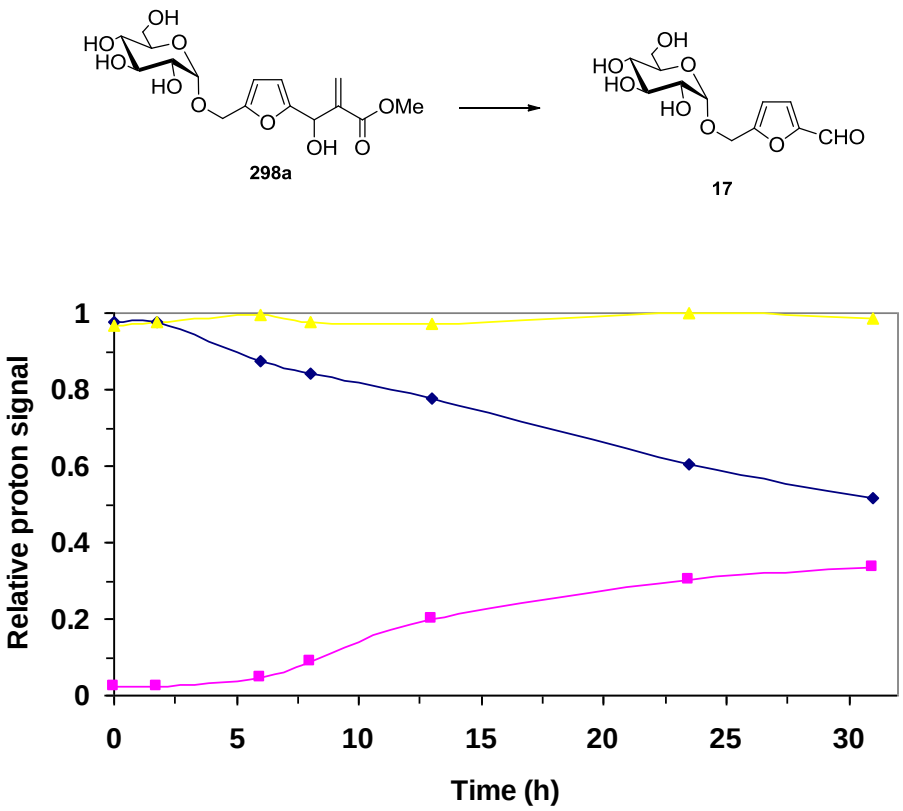

Figure 2.8. Effect of base, DABCO, on the time-dependent stability of MBH product **298a** and GMF as monitored by ^{1}H NMR:

1) Time-dependent deuterium exchange of MBH adduct (◆) and appearance of GMF (■). MBH adduct and DABCO were incubated in a 1:1 (v/v) mixture of 1,4-dioxane-d_8 and D_2O;

2) Time-dependent deuterium exchange of GMF (▲), GMF and DABCO were incubated in a 1:1 (v/v) mixture of 1,4-dioxane-d_8 and D_2O.

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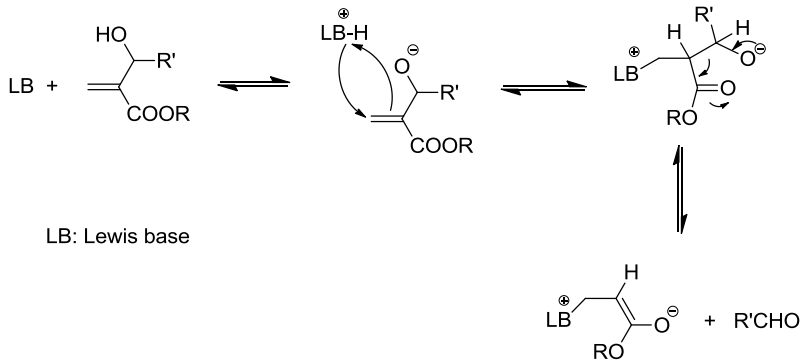
The proposed mechanism showed in **Scheme 2.7**. As we know the MBH adduct itself is also a very good Michael acceptor, so after the conjugated addition of the nucleophilic catalyst to the MBH adduct, a second zwitterionic intermediate is thus obtained. Then fellow by a retro-aldol reaction, the aldehyde is forms along with an enolate.



Scheme 2.7: Proposed mechanism for the retro MBH transformation.

2.5 *aza* Baylis-Hillman reaction

The MBH reaction is a reaction occurring at the α-position of an activated double bond with a sp^2 electrophilic carbon (normally being an aldehyde), catalyzed by tertiary amine or alkylphosphine. If the aldehyde is replaced by an activated imine, this process is referred to as the *aza* Morita-Baylis-Hillman (aza-MBH) reaction (**Scheme 2.8**) [259]. This reaction leads to α-methylene-β-amino derivatives and, in particular, to β-amino esters when an acrylate is used as a Michael acceptor. The reaction is flexible toward the choice of starting materials. As electrophiles, various activated aldimines like tosylimines and phosphinoylimines can be used. The spectrum of Michael acceptors that can be used for this reaction is even broader. Vinyl ketones, acrolein, acrylates, and cyclic enones as well as other α,β-substituted activated alkenes were reported as suitable Michael acceptors. Also, activated allenes and alkynes are appropriate substrates. Moreover, aza-MBH products are multifunctional synthons that have been used to synthesize various compounds, especially peptidomimetics and a wide variety of heterocyclic structures.

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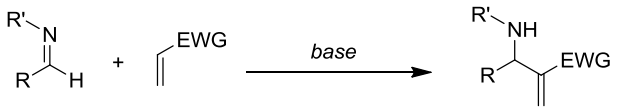


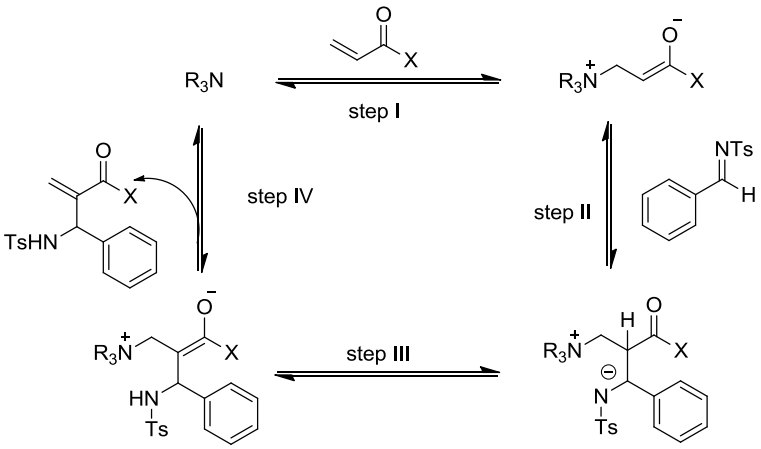
R = Ar

X = Ts, SO_2Ph, PPh_2, CO_2Me, *etc.*

EWG = COR, CHO, CN, CO_2R, $PO(OEt)_2$, SO_3Ph, SO_2Ph, SOPh, $CONR_2$, *etc.*

Scheme 2.8: The *aza* Baylis-Hillman reaction.

In a similar manner to the MBH reaction, the aza-MBH reaction consists of a sequence of addition-elimination. In the case of the reaction of a tosylimine with a Michael acceptor, catalyzed by a tertiary amine or phosphine, the commonly adopted mechanism is presented in **Scheme 2.9** [260]. The first step consists of a nucleophilic addition of the catalyst on the activated double bond. The enolate thus formed is responsible for a nucleophilic attack on the imine. Finally, a proton transfer followed by an elimination of the catalyst furnishes the aza-Baylis-Hillman adduct. Addition of the catalyst to the Michael acceptor and attack of the resulting enolate to the imine are reversible, and the proton transfer constitutes the rate-determining step.



Scheme 2.9: A plausible mechanistic pathway.

Very recently, Eberlin and Coelho [261] have investigated the mechanism of aza-MBH via the ESI-MS(/MS) technique and proposed a rational mechanism for the aza-MBH reaction. They monitored the DABCO-catalyzed aza-MBH reaction of

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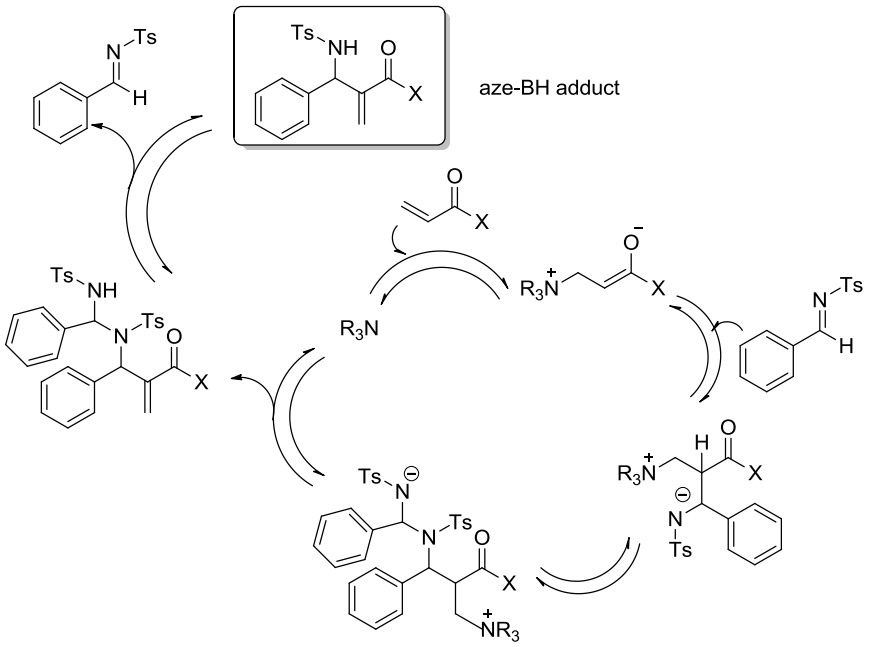
methyl acrylate with imine by ESI-MS(/MS) spectrometry and intercepted the key intermediates and a unique bissulfonamide intermediate (through the addition of second imine molecular) and the reaction exhibits an autocatalysis effect. On the basis of their results, they proposed the mechanistic cycle for the aza-MBH reaction as depicted in **Scheme 2.10**.



Scheme 2.10: Proposed Mechanism

Hereafter, we wish to report our investigations on the three component aza-MBH reaction of GMF, sulfonylimine, and unsaturated ketones and esters. This investigation aimed at providing a new synthetic route towards carbohydrate-based β-amino esters.

As a model for the optimization we chose to study the reaction between *p*-toluenesulfonamide, GMF and methyl acrylate, in the presence of a base catalyst (**Table 2.7**). In an initial experiment, mixing all three components in stoichiometric amounts and using a catalytic amount of 3-HQD (20 mol %) as base and molecular sieves (to increase the rate of aldimine formation, and thus push the equilibrium toward the aldimine, molecular sieves (4 Å) were added to trap the water formed in the reaction. We obtained after 36 h a low yield of the tosylamido adduct **302a** (27%). Recent developments of the Baylis-Hillman reaction involve the use of bifunctional

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catalyst systems, such as Lewis acids in combination with nucleophilic bases, which significantly increased the rate of the adduct formation. Several lanthanide triflates, e.g., $La(OTf)_3$, $Sm(OTf)_3$, used in catalytic amounts were shown to accelerate the reaction. Adding 5 mol % of $La(OTf)_3$ combined with 20 mol % 3-HQD to the three-component reaction resulted in good yields reached 60% at short time (**Table 2.7**, entry 6).

The product was clearly identified by NMR and mass spectroscopy. Notably, the proton of the newly formed CHN(H)Ts appears in the ^{1}HNMR spectrum at δ 5.46 ppm, with interactions with the acrylic methylene and the ester carbonyl group at δ 125.4, 165.0 ppm, respectively, observed in the HMBC spectrum. And the corresponding carbon was found at δ 51.2 ppm in the HSQC spectrum. Once again here, no diasteroselectivity of the reaction was observed, all products were being found to be 1:1 mixtures of the two possible diatereoisomers (as seen when the signals of the two epimers differ slightly for some of the C atoms and show equivalent integration (**Fig. 2.9**).

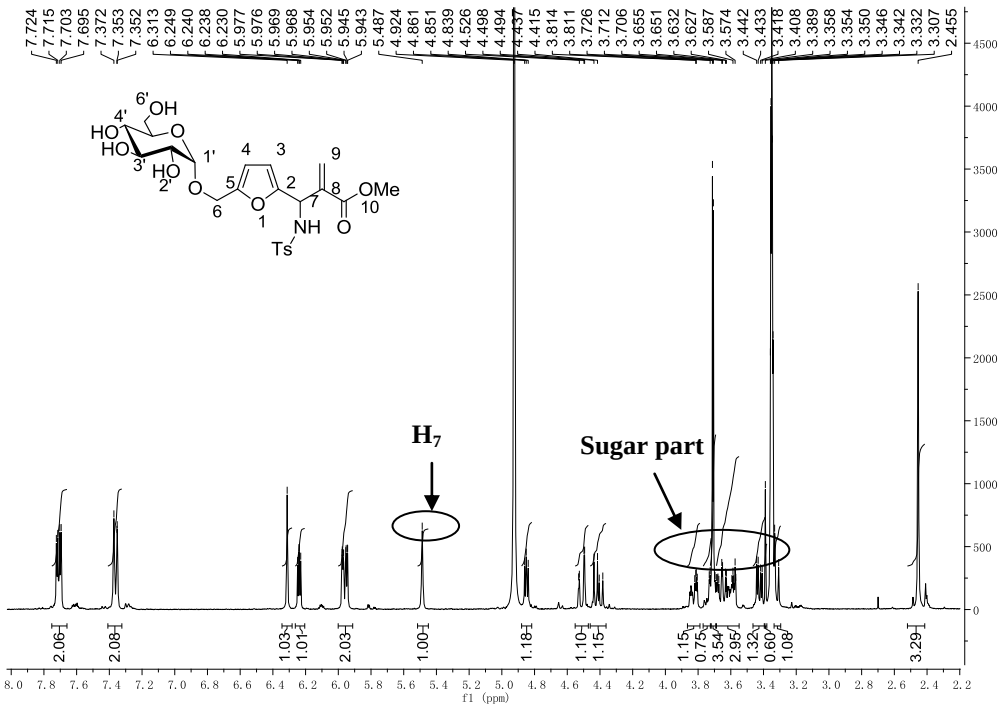

Fig. 2.9a: ^{1}HNMR spectrum of compound **302a**.

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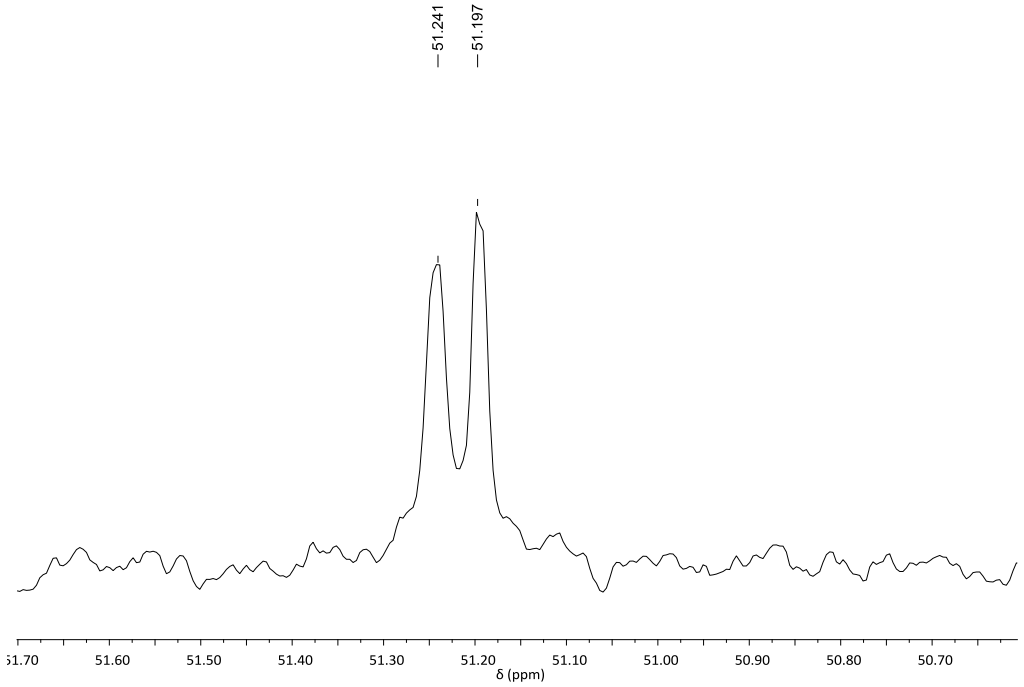

Fig. 2.9b: ^{13}C NMR spectrum of compound **302a.**

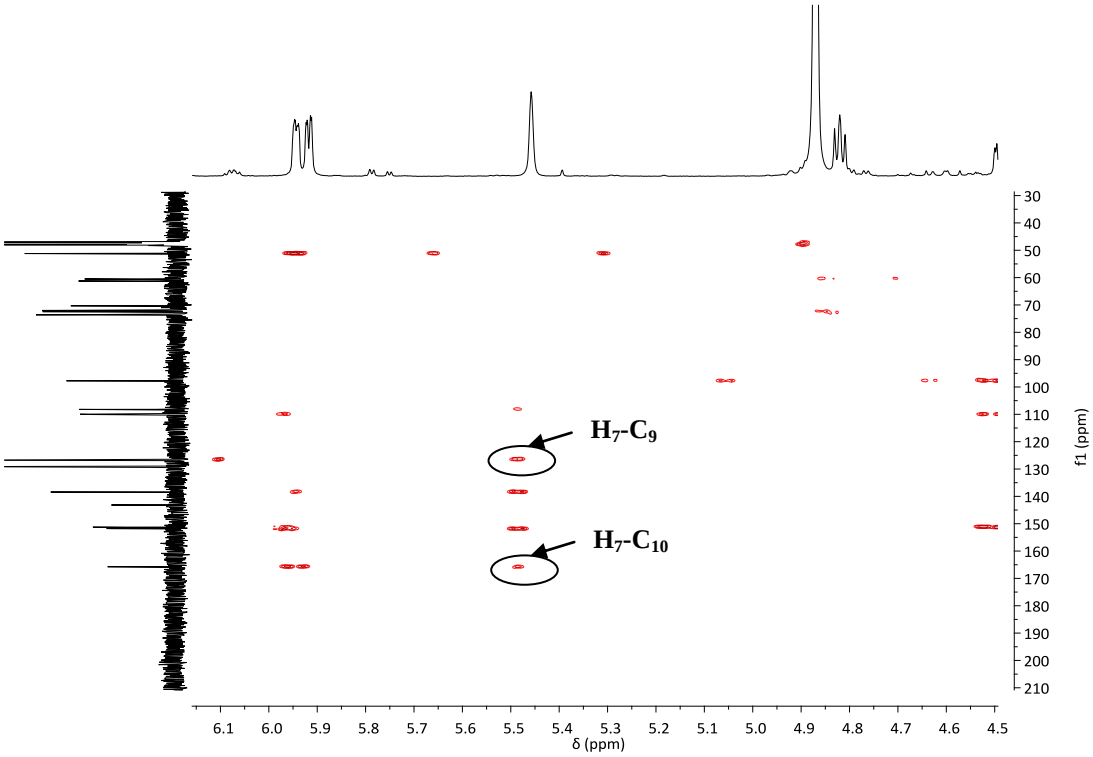

Fig. 2.9c: HMBC spectrum of compound **302a.**

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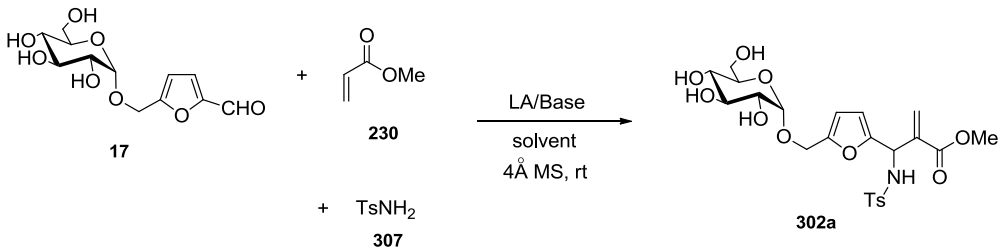
Recently, Kobayashi et al [262] made a classification of Lewis acid activity and selectivity in enolate additions to aldehydes and aldimines. The results show that group 3-15 metal triflates (Lewis acids) were classified to be more aldimine-selective in an addition reaction of a silyl enol ether. Adding 5 mol % of other metal triflate salts such as $Zn(OTf)_2$, $Y(OTf)_3$, $Cu(OTf)_2$ $Sc(OTf)_3$, $Yb(OTf)_3$ and $Er(OTf)_3$ resulted in yields in the same range as obtained for $La(OTf)_3$ (**Table 2.7**, entries 8-13). While, some other acids either weak or strong, such as PTSA, $BF_3{\cdot}Et_2O$, $Ti(OPr)_4$, $FeCl_3$ were used, the product, **302a**, was formed, but the yields obtained are rather poor (**Table 2.7**, entries 2-5). A solid acid, Dowex 50 WX_4, was also used, and in this case, a 32% yield was obtained (**Table 2.7**, entry 14). The ratio between the base and the Lewis acid turned out to be crucial; at low loadings of 3-HQD (10 mol %), no reaction occurred possibly because all the 3-HQD was associated with the Lewis acid (**Table 2.7**, entry 7).

Table 2.7: *aza*-Baylis-Hillman reaction of GMF, tosylamide and methyl acrylate under different conditions.[a]



Entry	LA (mol%)	Base (mol%)	Solvent	Yield (%)[b]
1[c]	No catalyst	3-HQD (20)	MeOH	27
2	PTSA (5)	3-HQD (20)	MeOH	38
3	$BF_3{\cdot}Et_2O$ (5)	3-HQD (20)	MeOH	35
4	$Ti(OPr)_4$ (5)	3-HQD (20)	MeOH	40
5	$FeCl_3$ (5)	3-HQD (20)	MeOH	40
6	$La(OTf)_3$ (5)	3-HQD (20)	MeOH	60

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7	$La(OTf)_3$ (5)	3-HQD (10)	MeOH	0
8	$Zn(OTf)_2$ (5)	3-HQD (20)	MeOH	54
9	$Y(OTf)_3$ (5)	3-HQD (20)	MeOH	58
10	$Cu(OTf)_2$ (5)	3-HQD (20)	MeOH	57
11	$Sc(OTf)_3$ (5)	3-HQD (20)	MeOH	55
12	$Yb(OTf)_3$ (5)	3-HQD (20)	MeOH	58
13	$Er(OTf)_3$ (5)	3-HQD (20)	MeOH	65
14	Dowex 50 WX_4 (5)	3-HQD (20)	MeOH	32
15	$La(OTf)_3$ (5)	DABCO (20)	MeOH	55
16	$La(OTf)_3$ (5)	DBU (20)	MeOH	0
17	$La(OTf)_3$ (5)	PPh_3 (20)	MeOH	25
18	$La(OTf)_3$ (5)	DMAP (20)	MeOH	0
19	$La(OTf)_3$ (5)	3-HQD (20)	Glycerol	0
20	$La(OTf)_3$ (5)	3-HQD (20)	H_2O	0
21	$La(OTf)_3$ (5)	3-HQD (20)	CH_3CN	45
22	$La(OTf)_3$ (5)	3-HQD (20)	MeOH/H_2O	10
23	$La(OTf)_3$ (5)	3-HQD (20)	THF	54
24[d]	$La(OTf)_3$ (5)	3-HQD (20)	MeOH	70

[a] Reaction conditions: GMF, tosylamide, and methyl acrylate (1:1:1.2), base (0.20 equiv), acid (0.05 equiv), and molecular sieves (4 Å, 100 mg/mmol substrate) in solvent (substrate concentration 2 M) at room temperature in 12 h.
[b] yield of isolated product
[c] reaction time: 36 h
[d] tosylamide (1.5 equiv.)

This is consistent with the formation of $La(OTf)_n(DABCO)_2$ complex **305** which performs its role as a Lewis acid and at concentrations above 10 mol % the DABCO

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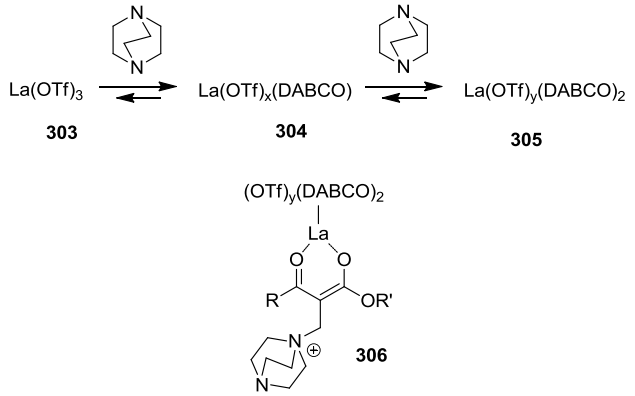
can perform its role as a nucleophilic catalyst. The reaction is believed to occur via the metallic complex **306**. It was thought that the binding of DABCO to the Lewis acid to give **305** have moderated the Lewis acidity of the metal due to the powerful nitrogen donor ligands (**Scheme 2.11**) [263].



Scheme 2.11: The formation of $La(OTf)_n(DABCO)_2$ complex.

We then examined the influence of the solvent on the reaction. It was believed alcohol had a positive influence on the reaction rate of the Baylis-Hillman reaction, which arise from a beneficial hydrogen bond formation between the alcohol moiety and the enolate formed by the Michael addition of the tertiary amine on the acrylate. With this in mind, we evaluated three solvent systems, namely glycerol, water and methanol. We found that the methanol was the solvent of choice. The use of glycerol or water as the solvent failed to produce any desired product, while only a poor yield was obtained in the binary medium consisting of methanol and water as the solvent. The reaction also works in the classical solvent system like THF or acetonitrile, but resulted in a lower yield compared to methanol. For the catalyst part, the use of 3-HQD resulted in a higher reaction yield, a minor decrease of yiled was observed when using DABCO as catalyst. Some of the other catalysts previously employed in the Baylis-Hillman reaction, e.g. PPh_3 gave poor results when applied in the aza-Baylis-Hillman protocol (**Table 2.7**, entry 17), while the use of DBU or DMAP as amine catalyst failed to produce any desired product. To our satisfaction when the amount of tosylamide was increased to 1.5 equivalents, **302a** was finally obtained in 70% yield (**Table 2.7**, entry 24). So the best conditions found were employing 3-HQD (20 mol %) together with

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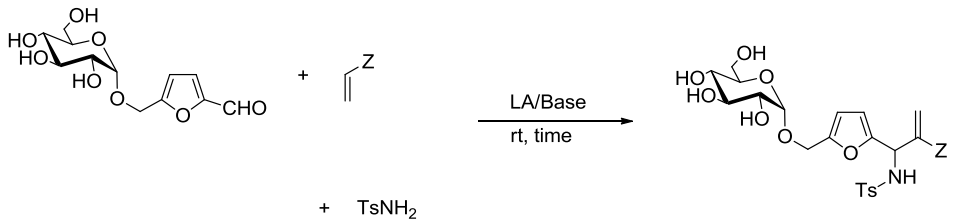
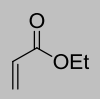
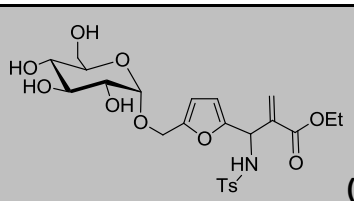
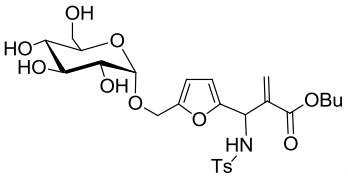
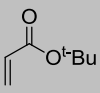
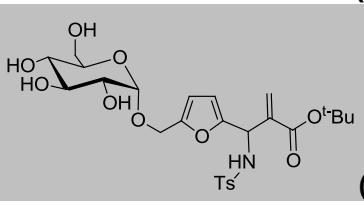
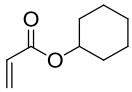
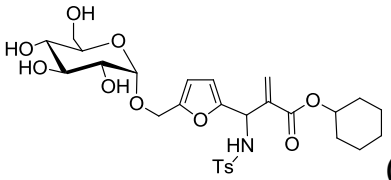
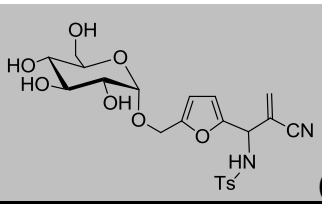
$La(OTf)_3$ (5 mol %) and molecular sieves.

We then investigated the range of possible Michael acceptors working in this three-component reaction under optimized conditions (**Table 2.8**). All acrylic esters gave good results even some bulky esters being employed such as tert-butyl acrylate or cyclohexyl acrylate, which give **302d** (52%) and **302e** (56%) of yield respectively. Acrylonitrile was also applicable in this reaction, giving 53% yield of the corresponding *aza* MBH adducts **302f** with a cyano group.

Table 2.8 : *aza*-Baylis-Hillman of GMF, tosylamide with different Micheal acceptors.



Acrylates	Products	Isolated yield (%)
	 **(302b)**	65
	 **(302c)**	53
	 **(302d)**	52
	 **(302e)**	56
	 **(302f)**	53

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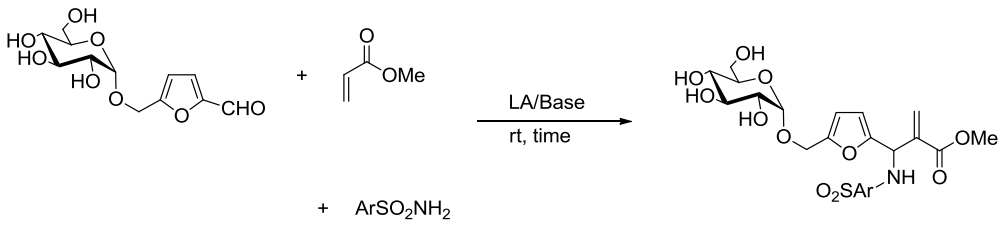
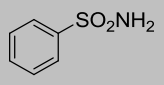
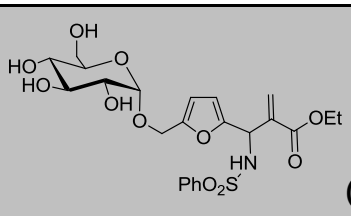
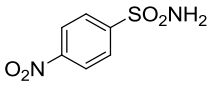
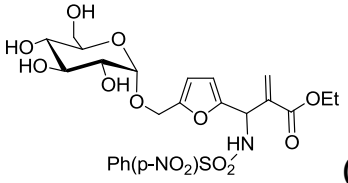
Furthermore, we investigated the scope of using different amines in the reaction. As observed above for tosylamide, benzenesulfonamide performed well under the optimized conditions and gave aza adducts in 64% of yield (**Table 2.9**). The electron-poor sulfonamide, 4-nitrobenzenesulfonamide, was efficiently used as amine-source in this *aza*-Baylis-Hillman reaction. The mild cleavage protocol available for this particular sulfonamide suggests a straightforward approach toward non-protected α-methylene-β-amino acid derivatives.

Table 2.9 : *aza*-Baylis-Hillman of tosylamide, methyl acrylate with sugar-based aldehyde.



$ArSO_2NH_2$	Products	Isolated yield (%)
	 **(302g)**	64
	 **(302h)**	51

Finally, we then investigated the substrate scope of the $La(OTf)_3$/3-HQD-promoted aza-Baylis-Hillman reactions of other hydroxymethyl furfural (HMF) glycosides derivatives with methyl acrylate and tosylamide under optimized conditions. As shown in **Table 2.10**, in all cases, aza Baylis-Hillman adducts were obtained with similar yields as observed for GMF.

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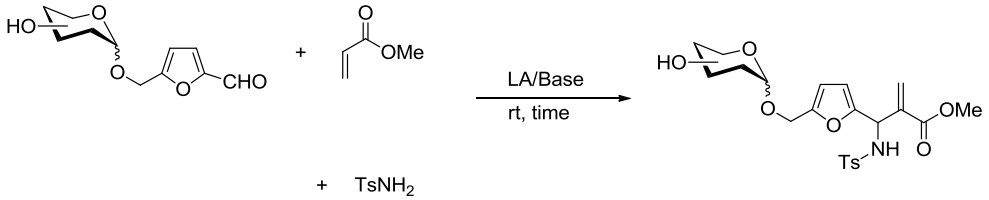
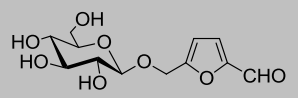
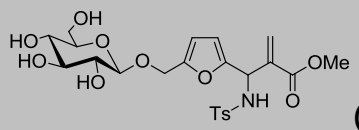
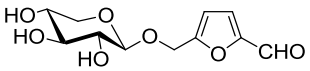
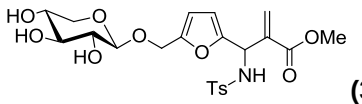
Table 2.10 : *aza* Baylis-Hillman reaction of methyl acrylate with different sulfonylimines.



Substrates	Products	Isolated yield (%)
	 **(302i)**	71
	 **(302j)**	69

Apart from sulfonylimine, diphenylphosphinamides are another well-known class of electron-deficient imines [264]. They are prepared starting from a phosphonic amide and an aldehyde. Shi *et al.* [265] have comprehensively examined the *aza* Baylis-Hillman reactions of diphenylphosphinamides with various activated olefins. The results obtained were quite good, in particular for methyl vinyl ketone, with conditions close to those used for tosylimines. Hereafter, we report our investigations on the *aza*-Baylis-Hillman reaction of the diphenylphosphinamides derived from GMF and analogous compounds with methyl vinyl ketone (MVK). This investigation aimed at providing some preliminary insights on alternative route to carbohydrate-based β-amino compounds with a phosphinoyl group, which might be easily removed and used for further transformation.

Generally, the imine was prepared starting from a diphenylphosphonic amide and an aldehyde under the presence of titanium tetrachloride ($TiCl_4$). While in our case, because GMF is unstable under this acid condition (the reaction between GMF and diphenylphosphonic amide only gave a messy mixture after 12 h when monitor by

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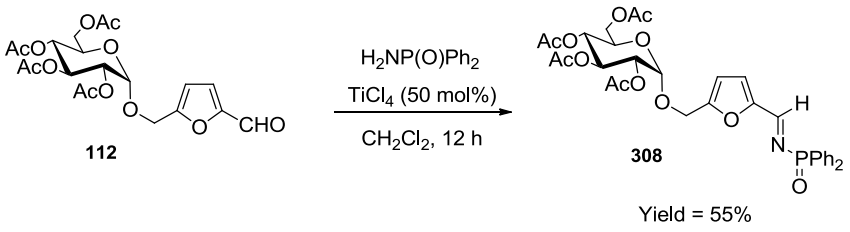
TLC). So GMF tetraacetate **112** was employed. The condensation reaction between GMF tetraacetate and diphenylphosphonic amide gave 55% yield of imine **308** after 12 h in CH_2Cl_2 (**Scheme 2.12**).



Scheme 2.12: The synthesis of GMF-based imine **308**.

In proton NMR spectrum, the coupling was confirmed by the disappearance of singlet peak of the aldehyde group of GMF which disappears at δ 9.53 ppm to the benefit of the newly formed H_7 which appears in the ^{1}HNMR spectrum at δ 9.00 ppm, combining with the data on the HSQC spectrum. The anomeric H is a doublet at δ 4.93 ppm, with interactions with the C-6 and C-3' at δ 62.0, 70.6 ppm, respectively, observed in the HMBC spectrum, and the corresponding carbon was found at δ 95.0 ppm in the HSQC spectrum (**Fig 2.10**).

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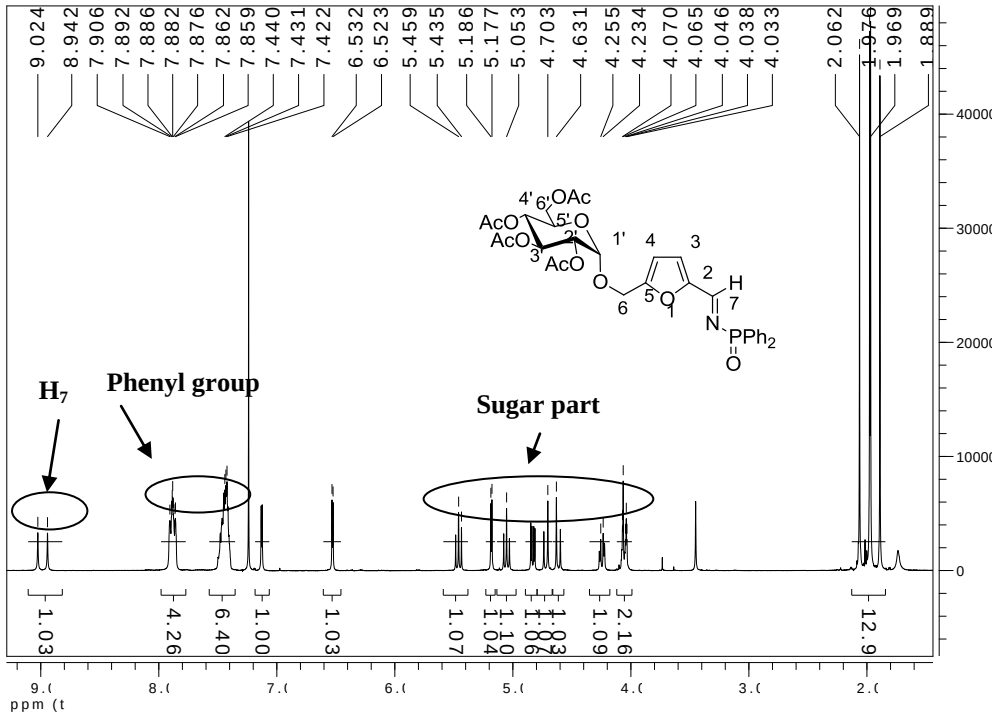

Fig 2.10a: ^{1}HNMR spectrum of compound **308**.

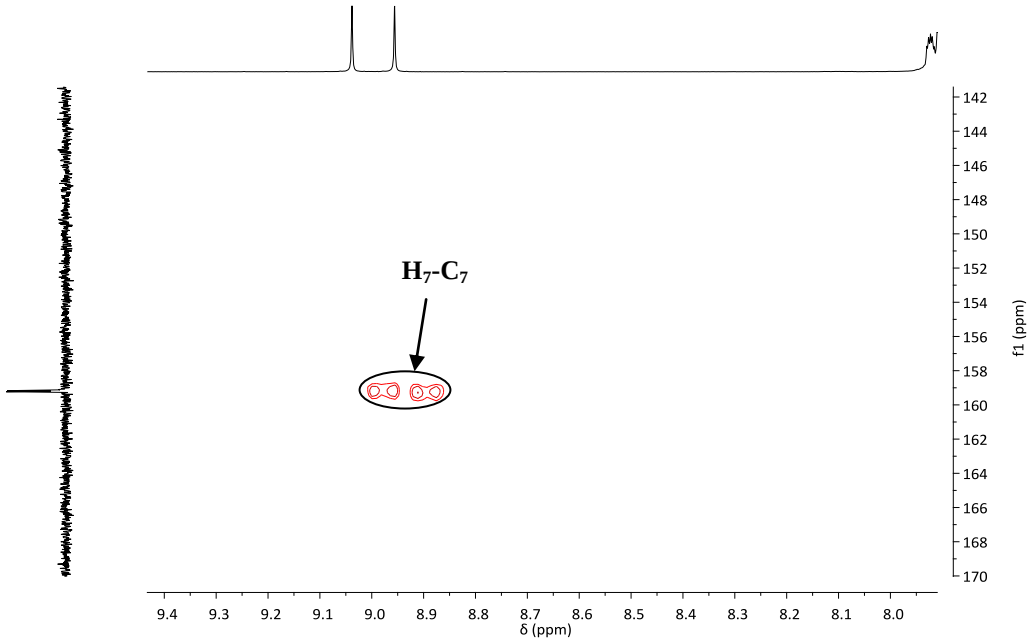

Fig 2.10b: HSQC spectrum of compound **308**.

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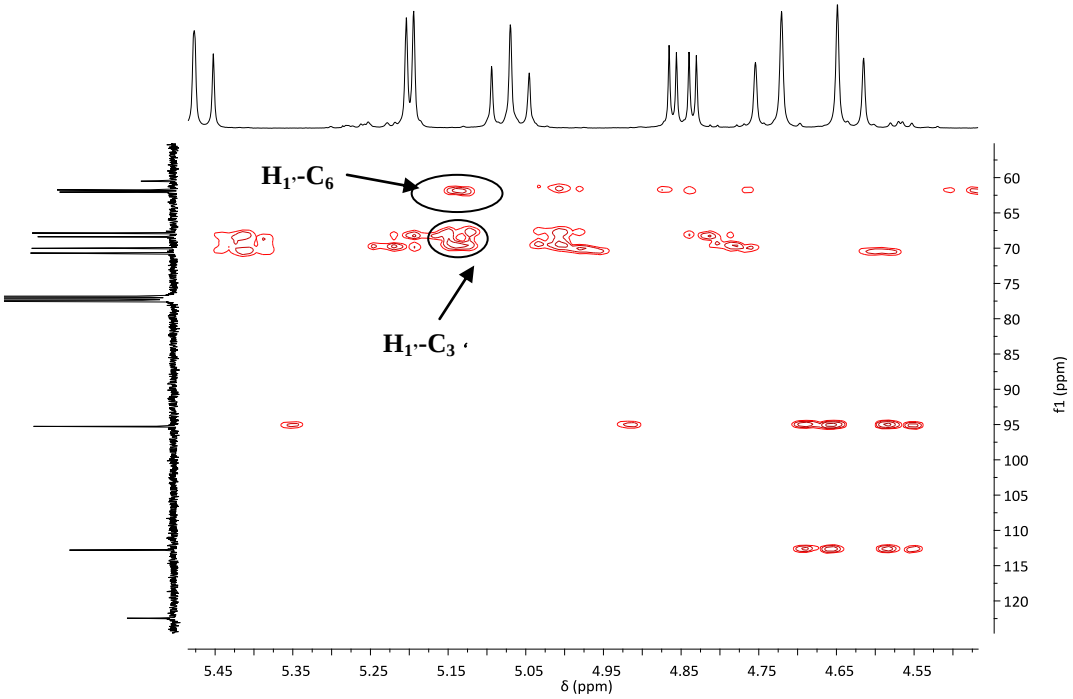

Fig 2.10c: HMBC spectrum of compound **308**.

Hereafter, we investigated the *aze* Baylis-Hillman reaction of this intermediate with MVK. As shown in **Table 2.11**, we found that this type of *aza*-Baylis-Hillman reaction is extremely sensitive to solvents and Lewis base catalysts. We examined the reaction of imine (0.5 equiv.) with MVK (1.0 equiv.) under various reaction conditions. A variety of Lewis base catalysts (20 mol %) were examined. The use of tertiary phosphines such as Ph_3P, PPh_2Me and $PPhMe_2$ as a Lewis base gave the corresponding *aza*-Baylis-Hillman adduct **309** in 35%, 20% and 15% yield in acetonitrile, respectively (**Table 2.11,** entries 3-5). While DABCO and 3-HQD can more efficiently catalyze this reaction, for example, Lewis base DABCO gave the aza-Baylis-Hillman adduct **309** in 60% yield after 12 h (**Table 2.11,** entry 1), the best yeild was observed when 3-HQD was employed as a Lewis base, which give 68 % yield of desired product. We then studied the effects of solvent, no reaction occurred when using methanol as solvent (**Table 2.11,** entry 7), later, we found that the THF is the best solvent for this version of aza-Baylis-Hillman reaction (**Table 2.11,** entry 6).

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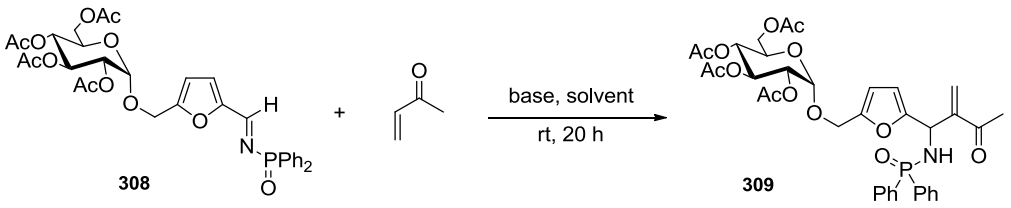
Table 2.11: *aza* Baylis-Hillman reaction of MVK with different diphenylphosphinamides.[a]



Entry	Base (20 mol%)	Solvent	Yield (%)[b]
1	DABCO	CH_3CN	60
2	3-HQD	CH_3CN	68
3	PPh_3	CH_3CN	35
4	PPh_2Me	CH_3CN	20
5	$PPhMe_2$	CH_3CN	15
6	3-HQD	THF	73
7	3-HQD	MeOH	trace

[a] all reaction were conducted using 1:1.22 molar ratio of and MVK, with 20% amount of catalyst;

[b] yield of isolated product.

The structure of the obtained product **309** was confirmed by analyzing the ^{1}H NMR, ^{13}C NMR and HMBC spectrum, as shown in the **Fig. 2.11**. The coupling was confirmed by the disappearance of the doublet peak of the imine group of **308** at δ 9.00 ppm to the benefit of the newly formed H_7 which appears in the ^{1}HNMR spectrum at δ 5.45 ppm, combining with the data on the HSQC spectrum, and the corresponding carbon signals found at δ 66.9, 67.0 ppm. The singlet of methyl group appears at δ 2.37 ppm. Like for the regular MBH reaction of Ac_4-GMF, though the

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aldehyde is chiral, no diasteroselectivity of the reaction was observed, **309** were being found to be 1:1 mixtures of the two possible diatereoisomers (as seen when the signals of the two epimers differ slightly for some of the C atoms and show equivalent integration, as seen in **Fig. 2.11b**).

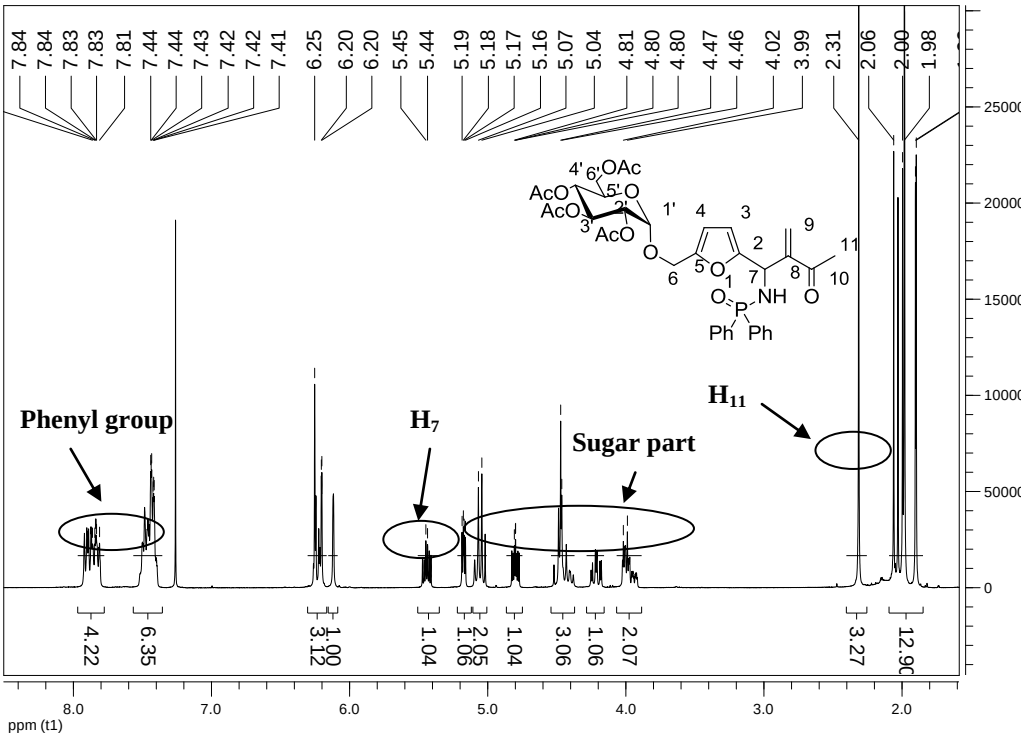

Fig 2.11a: ^{1}HNMR spectrum of compound **309**.

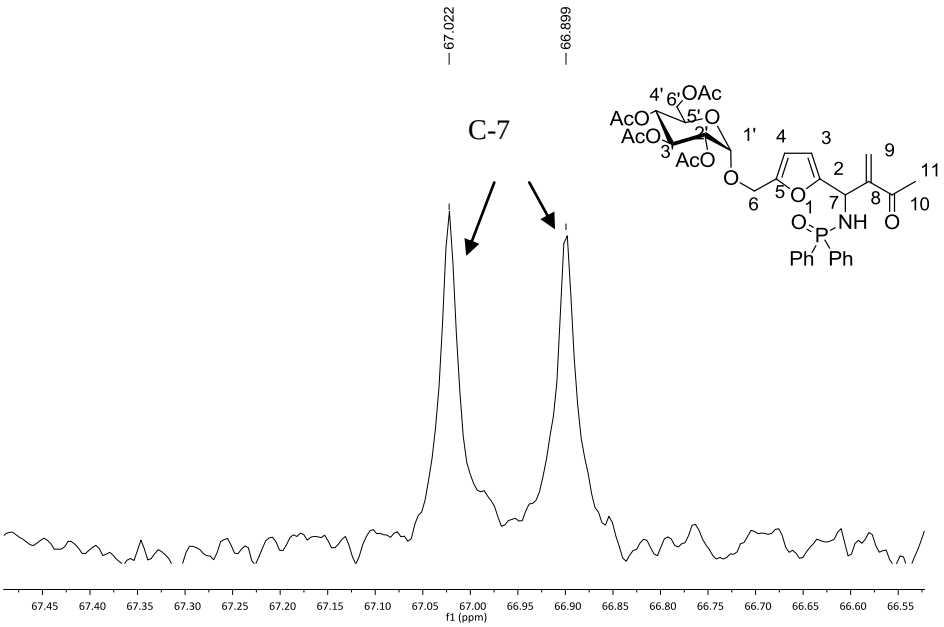

Fig 2.11b: ^{13}C NMR spectrum of compound **309**.

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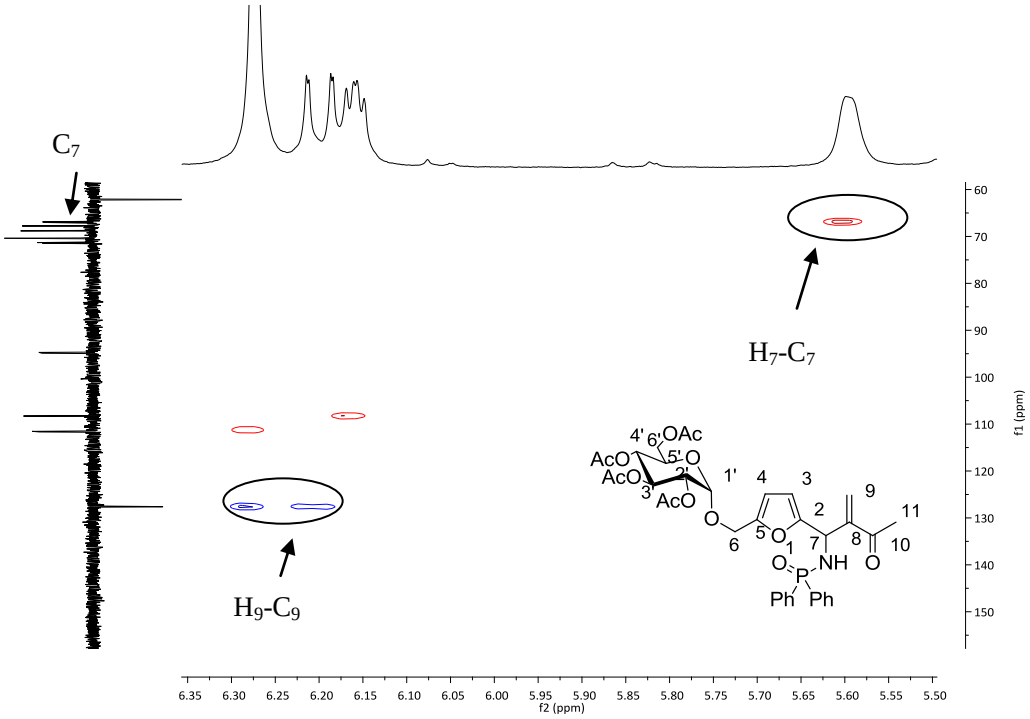

Fig 2.11c: ^{1}H - ^{13}C HSQC spectrum of compound **309**.

2.6 Conclusion

The use of GMF and analogues in MBH reaction has been explored.

The aqueous Baylis-Hillman reaction of GMF with acrylic building blocks led to new carbohydrate containing α-hydroxyacrylates in fair yields. It has been found that pure water can be used for this reaction, yet leading to rather slow reactions. Mixtures of water and DMI, or pure DMI in some cases, have also been shown to be possibly used, allowing replacement of dioxane or DMF compared to previous methods. The acrylic esters being also available from biomass (from glycerol or lactic acid) [25], such new acrylates appear as possibly 100% bio-based, and obtained via a reaction

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that offers favorable atom economy and solvent conditions.

Peracetylated GMF could also be used with different Michael acceptors. Attempts for final deprotection of the adducts pointed out that the reversibility of the reaction should be considered.

The *aza*-MBH version of the reaction was also explored, studying the reaction involving the three components (GMF, sulfonamides and a Micheal acceptor), leading to carbohydrate-based α-methylene-β-amino carbonyl derivatives in moderate to good yield. The results show that the choice of a Lewis acid combined with the base was crucial for improving the efficiency of the reaction.

These explorations show that GMF can be transformed in very short sequences to rather elaborated new compounds using the MBH strategy.

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Chapter III Baylis-Hillman reaction of HMF and derivatives in water or bio-based solvent-water mixtures

3.1 Introduction

Carbohydrates are by far, the most abundant and cheap carbon renewable resources and show high chemical interest. Lot of research has been achieved in the past decades on the use of carbohydrates as a feedstock towards added-value chemicals and functional products. A list of platform molecules has been been established notably by Bozell and Petersen in the “Top 10 + 4 chemicals” list [151], with respect to their wide range of potential applications, such as 5-hydroxymethyl furfural (HMF), furfural, γ-valerolactone, glycerol, succinic acid, 2-methyl THF, lactic acid, etc... Among them, HMF and its ensuing substituted furan derivatives appears as one of the most attractive bio-based chemicals and a key building block for transforming biomass-derived oxygenated hydrocarbons to fuels and chemicals (**Fig. 3.1**).

Succinic, fumaric and malic acids
2,5-Furan dicarboxylic acid
3-Hydroxypropionic acid
Aspartic acid
Glucaric acid
Glutamic acid
Itaconic acid
Levulinic acid
3-Hydroxybutyrolactone
Glycerol
Sorbitol
Xylitol/arabinitol

Fig. 3.1: The DOE top chemical opportunities from carbohydrates, 2004 (taken from J. J. Bozell and G. R. Petersen, *Green Chem.*, **2010**, 12, 539-554).

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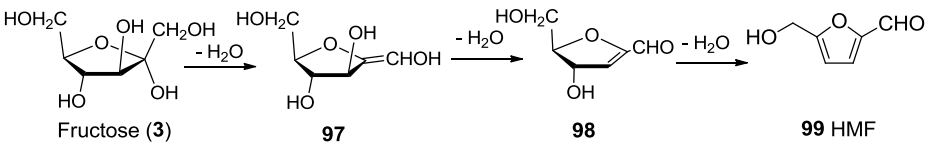
3.2 HMF: overview on its formation and uses

HMF was identified early as very promising chemical intermediates obtained by the catalytic conversion of carbohydrates based on C6 units. It stands out among the platform chemicals for it has retained all six carbon atoms that were present in the hexoses and high selectivities have been reported for its preparation, in particular from fructose. 5-HMF was obtained by dehydration of fructose in the presence of soluble or solid acid catalysts or from glucose or even polysaccharides by more complex catalytic systems and reaction media (**Scheme 3.1**) [152, 266, 267]. The difficulty of achieving a highly selective process with a high isolated yield has thus far resulted in a relatively high cost price of HMF, restricting its potential as a key platform chemical. So The key issue was to prepare 5-HMF with economically acceptable processes that could be scaled up at the industrial level. From the viewpoint of organic chemistry, the synthesis of HMF seems rather simple. However this reaction is not as easy as it looks since numerous side reactions may occur. Cottier *et al*. [268] shown that at least 37 products can be produced, thus showing the complexity of this reaction .



Scheme 3.1: General dehydration route into HMF.

This section will focus on the manufacture of HMF. Several catalysts have been reported for the dehydration of carbohydrates, and Cottier *et al*. [269] organize them into five groups: organic acids, inorganic acids, salts, Lewis acids, and others. In recent years, carbohydrate dehydration catalysts have undergone a remarkable

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process of evolution, and several new catalysts have been reported. Here, dehydration reactions can be grouped by the catalysis type: acid catalysis (homogeneous liquid, heterogeneous liquid-liquid, solid-liquid and gas-liquid) and metal catalysis (**Fig. 3.2**).

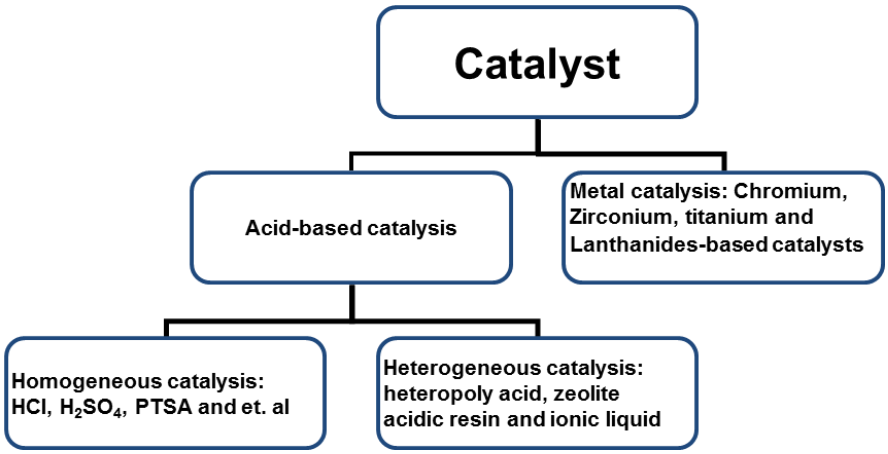

Fig. 3.2: Catalysts used for the dehydration of carbohydrates.

On the basis of the solvent system used, HMF synthesis from carbohydrates can roughly be divided into three types of processes: traditional single-phase systems, biphasic systems, and ionic liquid-based systems.

3.2.1 HMF Formation in Single-Phase Systems

Research on carbohydrate dehydration to HMF in traditional single-phase liquid systems will be discussed in this part. Going back as far as the early 20th century, most research on the formation of HMF was performed in aqueous systems with mineral acids as catalysts (mainly sulfuric and hydrochloric acid). Water is an obvious choice of solvent because it dissolves the majority of the sugars in high concentrations unlike most organic solvents [152]. Because of the relatively low HMF yields in aqueous systems, the use of organic solvents has grown since the 1980s.

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Solvents like DMSO, DMF, DMA, acetone, acetic acid, and methanol have been reported in the literature.

In general, the dehydration of aqueous solutions of carbohydrate in the presence of liquid or solid acid catalysts resulted in modest yields to 5-HMF because of the formation of levulinic acid, formic acid and humins. Also high yield of 5-HMF can be obtained by conducting carbohydrate dehydration in DMSO to avoid the formation of side products, but there is a risk of formation of sulfur-containing, toxic compounds at the temperature required for DMSO distillation.

3.2.2 HMF Formation in Biphasic Solvent Systems

The low HMF yields sometimes observed simultaneously with high levulinic acid yields point to the importance of repressing the HMF rehydration. In addition, HMF is assumed to react with sugars and sugar intermediates to form so-called humins (humins are poly disperse insoluble by-products formed during carbohydrate conversion). A number of groups have combined the sugar dehydration under aqueous conditions with an in situ extraction of the HMF in an organic phase. By continuously removing HMF, these undesired side reactions can be suppressed to a large extent. Fructose, glucose, oligo- and polysaccharides dehydration reactions could be performed in biphasic solvent systems [152, 267].

In general, HMF is not easy to extract from aqueous phase, since the distribution coefficient between the organic and the aqueous phase is not favourable. However, this problem has been overcome by the use of organic solvents such as MIBK (methyl isobutyl ketone), DCM, ethyl acetate, THF, diethyl ether, and acetone, which have been reported to be efficient extraction solvents. Those biphasic solvent systems could improve the synthesis of HMF, since they may avoid the formation of by-products, such as soluble polymers or humins, or others. While, in-situ extraction somehow also improved the formation of HMF in different processes. However, most

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of the data on carbohydrate dehydration in aqueous mixtures are difficult to compare with the presented data on carbohydrate dehydration under in situ extraction because of the small amount of experiments that were performed under exactly comparable conditions.

3.2.3 HMF Formation in Ionic Liquids

Recently, there has been a strong growth in interest toward the use of ionic liquids in biomass conversion. This started with a publication on fructose dehydration by Moreau's group in 2003 [270]. Since then a variety of imidazolium-based ionic liquids has been used in the dehydration of especially fructose [271]. Zakrzewska *et al.* [272] wrote an elaborate review on the solubility of a number of carbohydrates in a wide range of ionic liquids, divided in six categories. Ionic liquids based on imidazolium, pyridinium, benzotriazonium, pyrrolidinium, alkylammonium and alkyphosphonium cations were reviewed.

In general the selectivities and yields of HMF synthesis in ionic liquids from different types of biomass are high compared to the other systems discussed, with the exception of aprotic polar organic solvents like DMSO. Because of their unique dissolution properties, some ionic liquids could dissolve over 10 wt % cellulose, which is notoriously difficult to solubilize. In general, there was no levulinic acid formation has been reported in ionic liquid systems, even under the presence water. Thus the ionic liquids apparently stabilize the formed HMF, preventing its rehydration. This apparent stabilizing effect also has a disadvantage, as it is difficult to separate the HMF from the ionic liquid, requiring large amounts of extracting solvent. Since ionic liquids have essentially no vapor pressure and HMF is heat sensitive, solvent evaporation and HMF distillation are off the table, leaving extraction as the only method for HMF purification.

To apply ionic liquids as reaction media for HMF production from biomass, highly efficient recycling is required because of their high cost price. This will present

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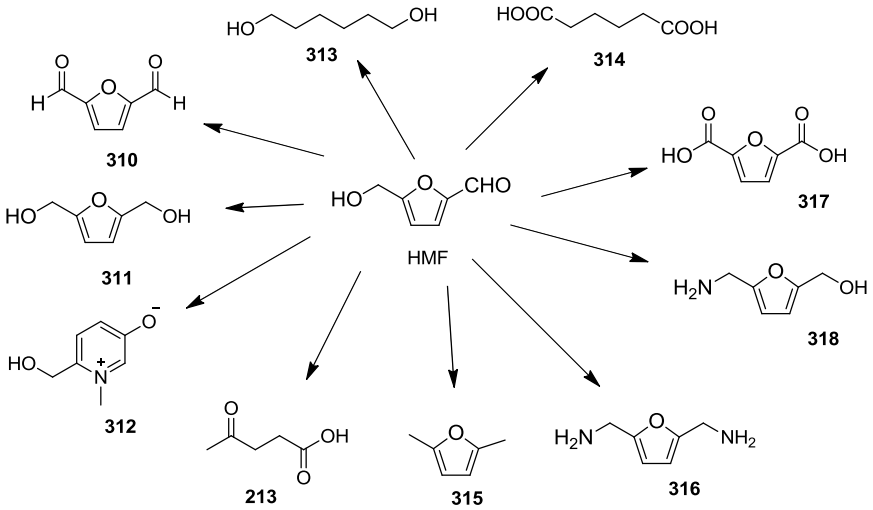
challenges when using untreated biomass feedstock, because these contain many inorganic (ash) and organic impurities that will have to be removed form the ionic liquid at some point [152].

3.2.4 Synthetic applications of HMF to fine chemicals

Many reactions have been performed on HMF, involving either the primary hydroxyl , aldehyde group, or the furan unit. They include selective oxidation and reduction of the formyl, hydroxyl groups and furan ring; carbonyl and hydroxyl homologation; and whole-skeleton transformations [71, 152, 266].

As can be seen in **Scheme 3.3** a number of important C-6 compounds can be formed through one common intermediate molecule, HMF. 2,5-Furandicarboxylic acid (**317**), bishydroxymethylfuran (**311**), and 2,5-dimethylfuran (**315**) are furan derivatives. Some important nonfuranic compounds can also be produced from HMF, namely, levulinic acid (**213**), adipic acid (**314**), 1,6-hexanediol (**313**).



Scheme 3.3: HMF as a platform chemical.

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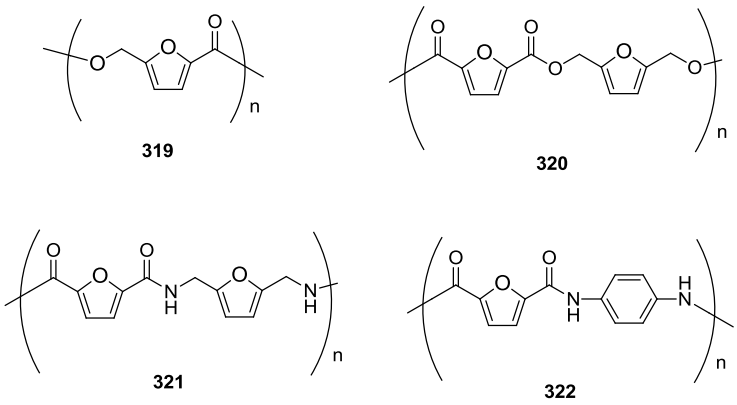
3.2.5 Synthetic applications of HMF to furanoic polyesters

Among these products, 2,5-bis(hydroxymethyl)furan (**311**), and 2,5-dicarboxylic furan (**317**) acid have extensively been exploited for the preparation of furanoic polyesters [71]. The diol has been reacted with various aliphatic and aromatic diacids; the ethyl ester, upon polycondensation, gave a mixture of linear and cyclic products, while the furan-diacid has been polyesterified with a series of aliphatic diols or bisphenols. Even the all-furanic polyester has been successfully prepared from its respective monomeric components. Another obvious outgrowth from diamine and dicarboxylic acid was the preparation of furanic polyamides, as they could potentially replace the present, petroleum-based diamines and diacids in the industrially produced polyamides. Of the series of furanic polyamides prepared by utilizing and aliphatic or aromatic diamines, polyamide has particularly promising decomposition and glass temperature parameters, distinctly better than those found for the all-furanic polyamide (**Scheme 3.4**).



Scheme 3.4: Synthetic applications of HMF to furanoic polyesters

With respect to the solvent issue, it has been reported MBH reaction could proceed in the presence of water, with possible action of the hydrophobic effect, or by stabilization the zwitterionic intermediate. This latter also acts as proton donnor during the proton-transfer step of the reaction which has been proposed as the

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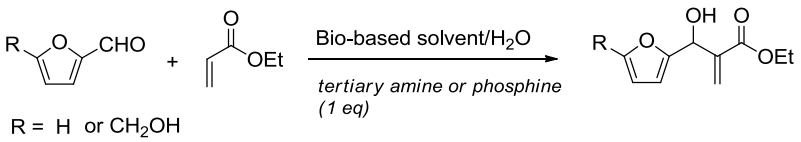
rate-determining step for MBH reaction based on kinetic and theoretical studies. Hence, aqueous (especially homogeneous H_2O/solvent medium) have been widely used for this reaction to overcome problems commonly associated with the reaction like low reaction yields and long reaction time [227, 230]. However, apart from simple alcohols, no bio-based solvent were included in former studies, either for HMF or any other MBH substrate. In the light of our explorations on GMF reported the preceding chapter, we thus widened our study to the reaction of HMF and furfural in various biobased solvents and their mixtures with water (**Scheme 3.5**).



Scheme 3.5: Baylis-Hillman reaction of HMF and furfural in bio-based solvent-water mixtures

3.3 Results and Discussion

As a model reaction, the DABCO promoted Baylis-Hillman reaction of HMF with ethyl acrylate in different bio-based medium was explored. Bio-based solvents used in this study are those which are commercially available such as: 2-methyl THF, isopropylidene glycerol, 2-hydroxymethyl furan, 2-hydroxymethyl THF, ethyl lactate, γ-valerolactone, diethyl succinate and their relative derivatives. A stoichiometric amount of DABCO as the promoter (known to be necessary for aqueous MBH reactions, was used in all cases to make consistent comparisons. Previous studies show that in aqueous MBH reactions, larger quantities of the promotor and acrylate were necessary, due to hydrolysis of the enolate formed by Michael addition of DABCO and the acrylate, which consumes both the catalyst and the acrylate.

The structure of the obtained MBH product was confirmed by analyzing the ^{1}H NMR, ^{13}C NMR and HMBC spectrum, as shown in the **Fig. 3.2**. In proton NMR spectrum, the

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coupling is identified by the disappearance of singlet peak of aldehyde group of HMF at δ 9.51 ppm to the benefit of the newly formed CHOH which appears in the ^{1}HNMR spectrum at δ 5.58 ppm, with interactions with the methylene and the carbonyl group of acrylate at δ 125.7, 167.2 ppm, respectively, observed in the HMBC spectrum. And the corresponding carbon signals are found at δ 66.4 ppm. The newly formed carbon-carbon bond was thus demonstrated unambiguously.

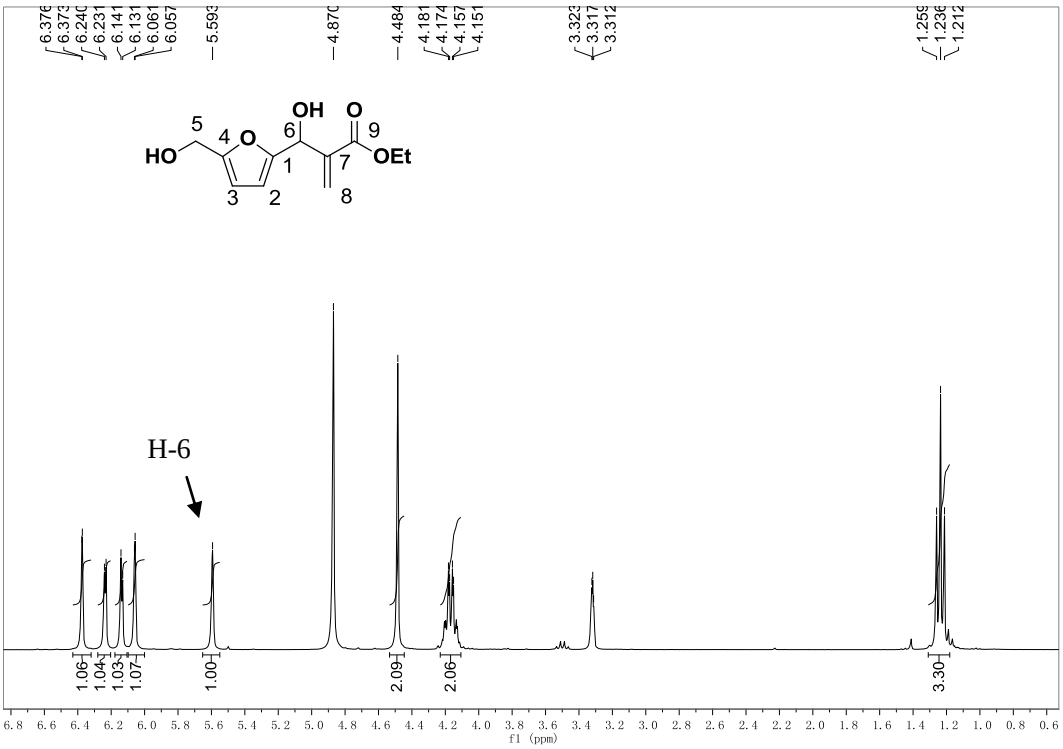

Fig. 3.2a: ^{1}H NMR spectrum of compound **323**.

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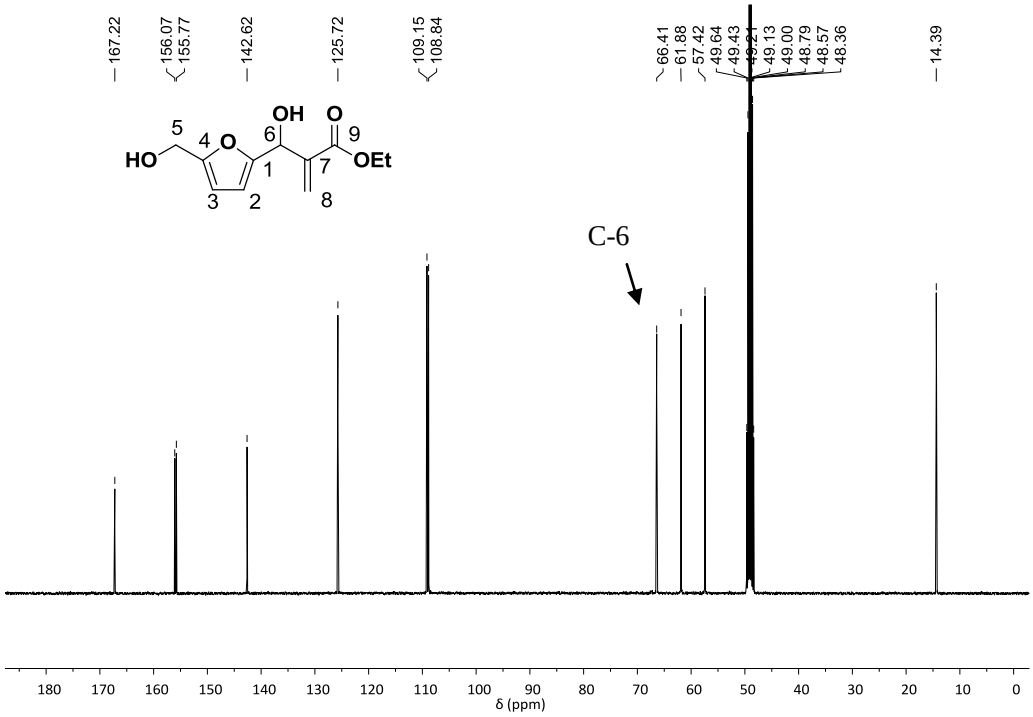

Fig. 3.2b: ^{13}C NMR spectrum of compound **323**.

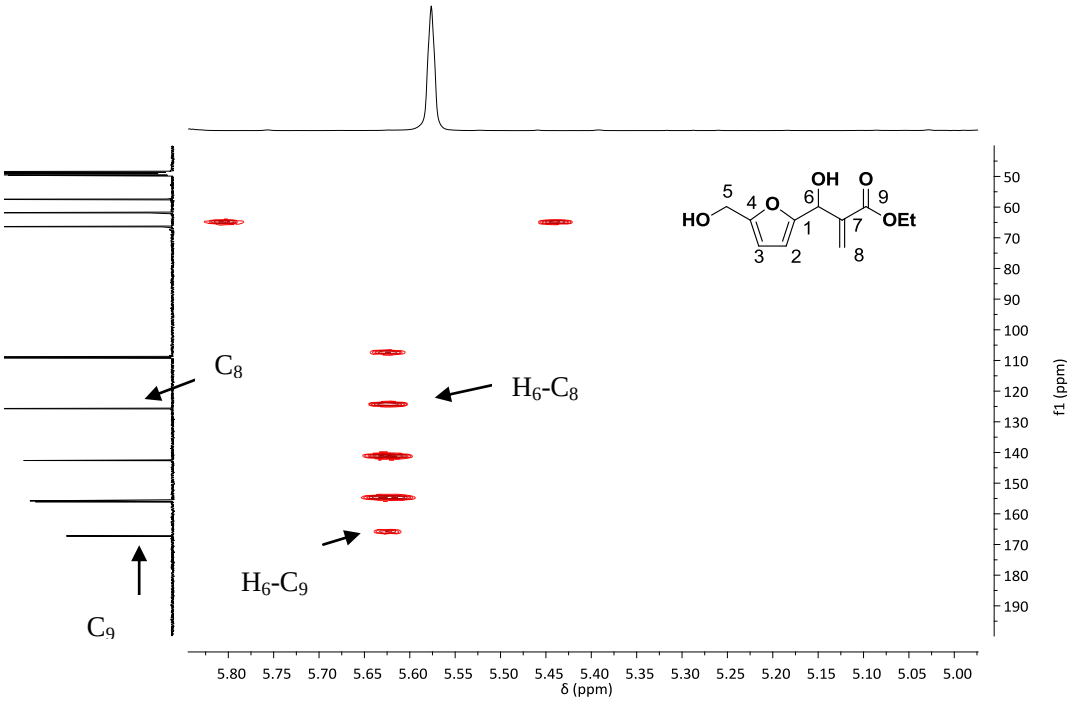

Fig. 3.2c: HMBC spectrum of compound **323**.

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The efficiency of these solvents and their mixture with water in the model reaction was compared by measuring conversion and yields after 24 h at room temperature. The reaction mixture was analyzed with ^{1}H NMR to estimate the conversion of HMF and the formation the desired MBH adduct. The validity of these measurements and comparisons were checked carefully by isolating the products for entries showing best conversions.

The conversions were estimated by measuring the integrations of specific peaks in the ^{1}HNMR spectra, specifically on the aldehyde group at δ 9.51 ppm for HMF, while the MBH adducts are measured on the peak of the newly formed CHOH at δ 5.58 ppm. In **Fig 3.3** is shown the ^{1}HNMR spectra of the mixture of some molar ratio of HMF and the MBH adducts which allowed to verify the accuracy and validity of this method.

$$\text{Conversion} = \frac{\text{peak area (MBH adducts)}}{\text{peak area (MBH adducts + HMF)}} 100\%$$

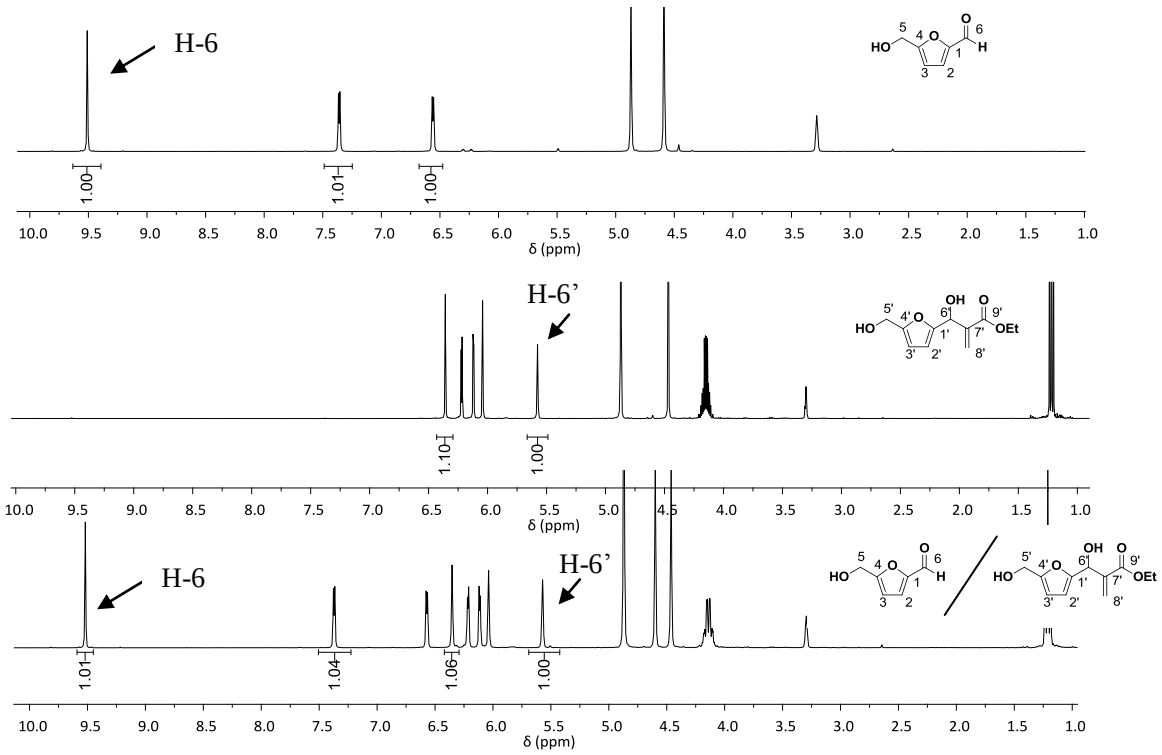

Fig. 3.3: ^{1}H NMR spectra of HMF, MBH adducts, and HMF/ MBH adducts (1/1) in MeOD.

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For example, when the reaction carried out in ethyl lactate/water, the ^{1}H NMR of the crude product shown that the conversation is 50% after 24 h (**Fig. 3.4**).

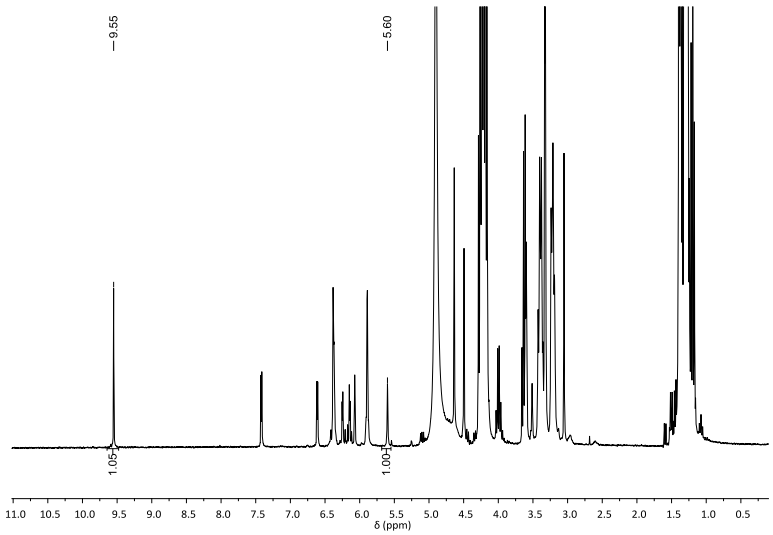

Fig. 3.4: ^{1}H NMR spectrum of the MBH reaction of HMF in ethyl lactate/water.

The results shown in **Table 3.1** show that the MBH reaction of HMF can proceed in several biobased solvents, in particular in 2-hydroxymethyl THF and 2-hydroxymethyl furan, and with lower conversions in isopropylidene glycerol, ethyl lactate and γ-valerolactone. No reaction reaction was observed in diethyl succinate or 2-methyl THF. However, for the few cases for which there was no reaction when the pure solvent was used (diethyl succinate, 2-methyl THF), the reaction was found to proceed slowly once water was added, despite the loss of medium homogeneity. All other systems led to homogeneous reaction mixtures.

The results also confirm that addition of water is beneficial to the MBH reaction in all cases. Water as a co-solvent is indeed known to improve reaction rates and yields of product, suggesting that water might act by stabilizing the transition state or the intermediates (enolate, zwitterionic adduct) through intermolecular charge-dipole and/or hydrogen-bonding interactions. Subsequent studies also showed that the role of the hydrogen donor additives (water, alcohols...) could act as a shuttle for rate-determining proton transfer step [218]. In addition, results provided by computational studies and the ESI-MS (/MS) spectrometry are also in agreement with

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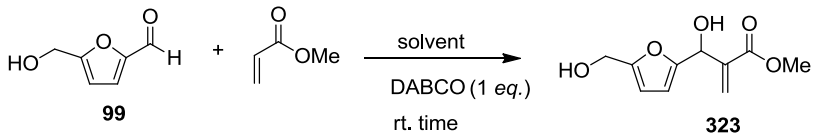
the experimental/kinetic evidence that that MBH reaction could be accelerated by protic species like water [221].

Table 3.1: Solvent issue for B-H reaction of HMF with ethyl acrylate[a]



Entry	Solvent	Ratio (mL/mL)	Conversion(%)[b]
1	EtOH	2	53
2	H_2O	2	82
3	isopropanol	2	38
4	ethyl lactate	2	30
5	diethyl succinate	2	0
6	2-methyl THF	2	0
7	2-hydroxymethyl THF	2	60
8	2-hydroxymethyl furan	2	62
9	γ-valerolactone	2	14
10	isopropylideneglycerol	2	47
11	isopropanol/H_2O[c]	1/1	90
12	EtOH/H_2O[c]	1/1	91
13	ethyl lactate/H_2O	1/1	35
14	diethyl succinate/H_2O	1/1	50
15	2-methyl THF/H_2O	1/1	50
16	2-hydroxymethyl THF/H_2O[c]	1/1	90
17	2-hydroxymethyl furan/H_2O	1/1	71
18	γ-valerolactone/H_2O	1/1	37
19	isopropylideneglycerol/H_2O[c]	1/1	89

[a] all reaction were conducted using 1:2 molar ratio of HMF and ethyl acrylate, with one equimolar amount of DABCO; [b] conversion ratio based on ^{1}H NMR;
[c] yield of isolated product for entry 11, 12, 16 and 19 were 72%, 75%, 70% and 73% respectively.

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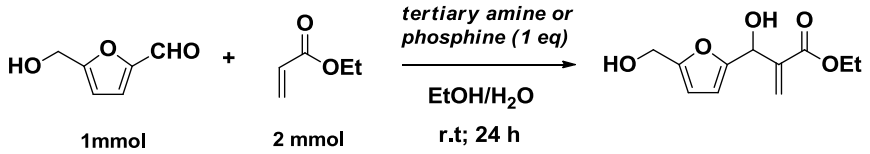
Having those results in hand, we then evaluated the influence of the nature of the catalyst by using the reaction between HMF and ethyl acrylate as a model reaction. Based on the previous results, we choose to carry out these reactions in two systems, EtOH/H_2O and 2-hydroxymethyl THF/H_2O. When aqueous trimethylamine was used as catalyst, the reaction process well and gave good results (**Table 3.2,** entry 3). However, when triphenylphosphine, 3-HQD or DMAP was used, the reaction gave unsatisfactory lower yields (**Table 3.2,** entries 4 and 5) while DBU did not allow obtain the desired adducts (**Table 3.2,** entry 6).

Table 3.2. Influence of the nucleophilic promoter on Baylis-Hillman reaction [a]



Entry	Cat.	Yield (%)[b]
1	PPh_3	10
2	$P(m\text{-}C_6H_4\text{-}SO_3Na)_3$	15
3	$Me_3N_{(aq)}$	70
4	3-HQD	50
5	DMAP	20
6	DBU	0

[a] all reaction were conducted using 1:2 molar ratio of HMF and ethyl acrylate, with one equimolar amount of catalyst;

[b] yield of isolated product.

In the previous chapter, we reported our investigation on the MBH reaction of GMF and methyl acrylate in the binary medium of DMI and water. But more detailed information like the use of other biobased solvents and the role of water should be re-evaluated in the light of the results on HMF shown above. Compared to HMF, the presence of OH groups in GMF and consequently in all the newly formed intermediates and products, make it behave differently in the MBH reaction with

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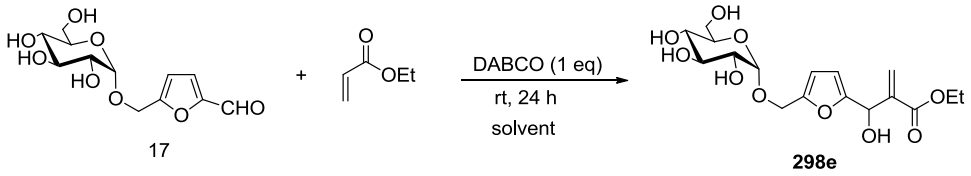
respect to the necessity of adding water. As show in table **3.3**, after 24 h at room temperature in the presence of 100 mol % DABCO, we found that the reaction proceeded well in EtOH, 2-hydroxymethyl THF, and isopropylideneglycerol, which give good isolated yield like 65%, 68% and 61% respectively (**Table 3.3**, entries 1, 6 and 9). The addition of water did not result in any changes, supporting the hypothesis that the free sugar OH groups act similarly as water.

Table 3.3. Solvent issue for the MBH reaction of GMF and ethyl acrylate[a]



Entry	Solvent	Yield (%)[b]
1	EtOH	65
2	H_2O	35
3	ethyl lactate	35
4	diethyl succinate	0
5	2-methyl THF	0
6	2-hydroxymethyl THF	61
7	2-hydroxymethyl furan	40
8	γ-valerolactone	41
9	isopropylideneglycerol	68
10	EtOH/H_2O	50
11	isopropanol/H_2O	72
12	2-hydroxymethyl THF/H_2O	60
13	isopropylideneglycerol/H_2O	63

[a] all reaction were conducted using 1:2 molar ratio of GMF and ethyl acrylate, with one equimolar amount of DABCO;
[b] yield of isolated product.

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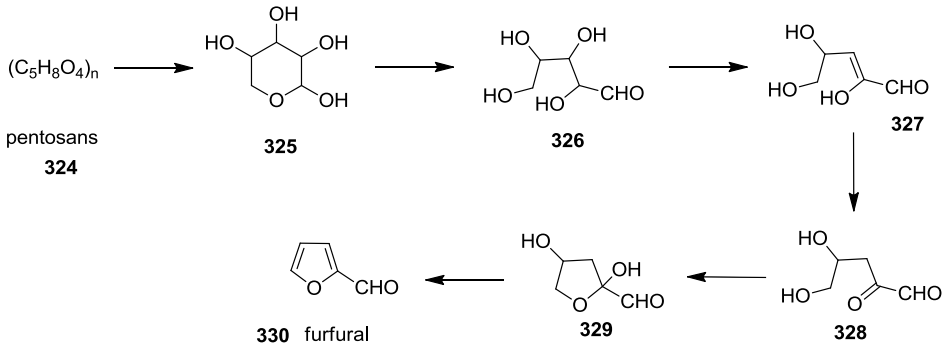
Furfural is another important furanic derivative produced from the dehydration of carbohydrates (from pentoses). Various acidic conditions have been used for this propose. A plausible mechanism is shown in **Scheme 3.6**.



Scheme 3.6: Plausible mechanism of the acid-catalyzed formation of furfural.

The chemistry of furfural is well-developed, providing a host of versatile industrial chemicals (**Scheme 3.7**) [273]: furfuryl alcohol (hydrogenation), furfurylamine (reductive amination), furoic acid (oxidation), furfural is also the key chemical for the commercial production of furan (through catalytic decarbonylation) and THF (hydrogenation). THF is not only an extensive solvent used for chemistry, also it providing a biomass-based alternative to its petrochemical production via dehydration of 1,4-butanediol [71]. 2-Methyltetrahydrofuran (2-Methyl THF) produced from furfural by hydrogenation associate with reduction. It possesses interesting solvent properties [10, 70]. The further importance of these furanic chemicals stems from their ring-cleavage chemistry, which has led to a variety of other established chemicals, e.g., levulinic acid and maleic anhydride.

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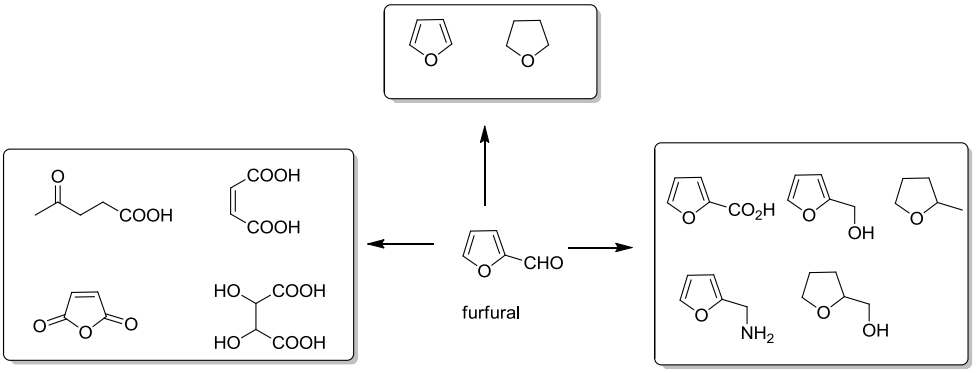
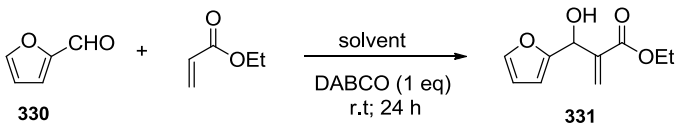


Scheme 3.7: Bulk products obtained from furfural

Furfural was therefore also considered as substrate in our study, and found to efficiently produce MBH adducts in several solvent systems, notably using ethanol and 2-hydroxymethyl tetrahydrofurane or their mixtures with water (**Table 3.4**, entries 4 and 5).

Table 3.4. Solvent issue for the MBH reaction of furfural with ethyl acrylate [a]



Entry[a]	Solvent	Yield (%)[b]
1	EtOH	35
2	H_2O	45
3	2-hydroxymethyl THF	33
4	EtOH/H_2O	90
5	2-hydroxymethyl THF/H_2O	80

[a] all reaction were conducted using 1:2 molar ratio of furfural and ethyl acrylate, with one equimolar amount of DABCO;

[b] yield of isolated product.

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The structure of the obtained product was confirmed by analyzing the ^{1}H NMR, ^{13}C NMR and HMBC spectrum, as shown in the **Fig 3.4**. In proton NMR spectrum, the coupling is identified by the disappearance of singlet peak of aldehyde group of HMF at δ 9.53 ppm to the benefit of the newly formed CHOH which appears in the ^{1}HNMR spectrum at δ 5.60 ppm, with interactions with the methylene and the carbonyl group of acrylate at δ 111.2, 167.2 ppm, respectively, observed in the HMBC spectrum. The corresponding carbon signals are found at δ 66.4 ppm. The newly formed carbon-carbon bond was thus demontrated unambiguously.

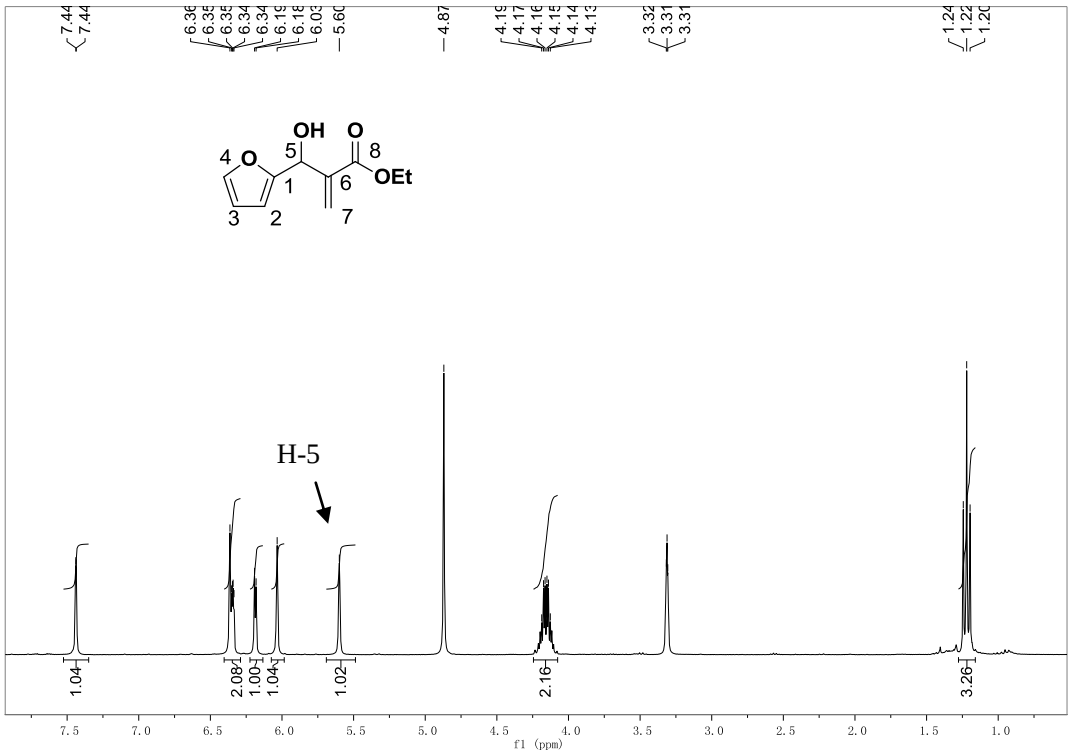

Fig. 3.4a: ^{1}H NMR spectrum of compound **331**.

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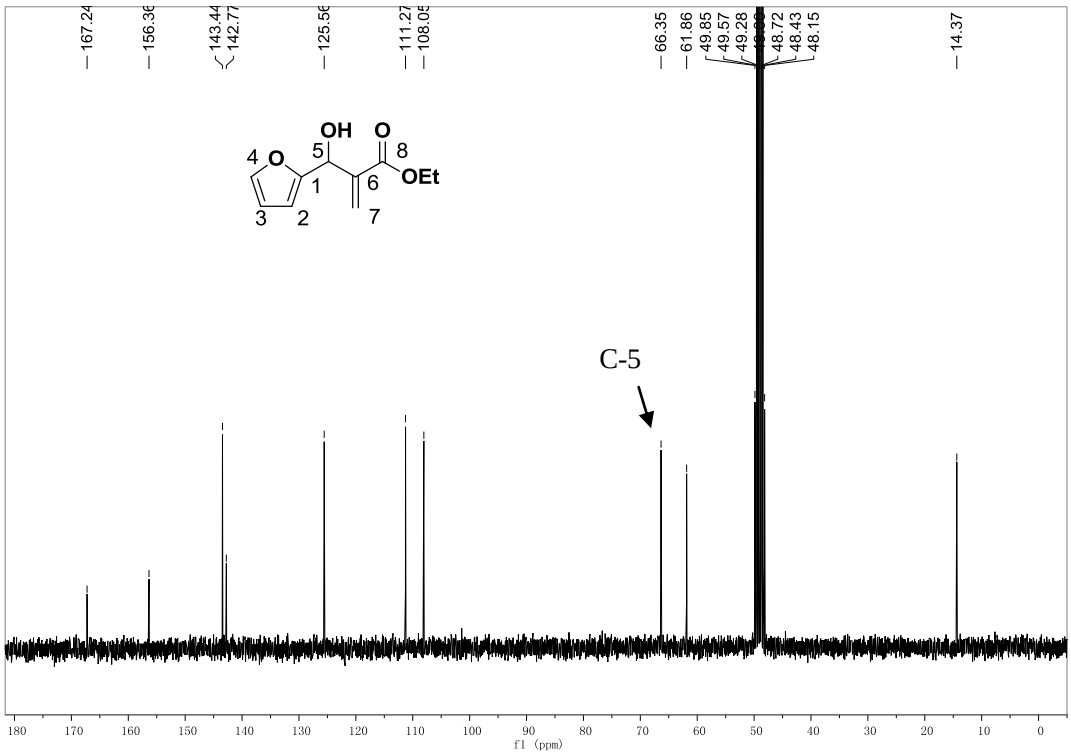

Fig. 3.4b: ^{13}C NMR spectrum of compound **331**.

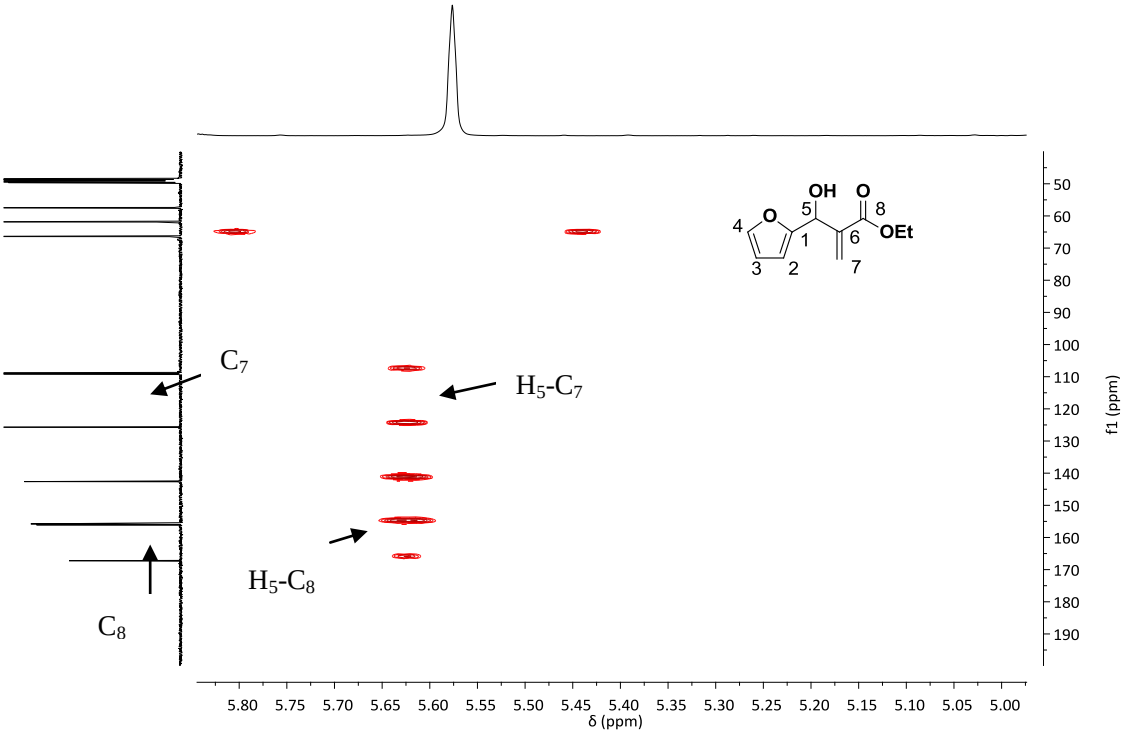

Fig. 3.4c: HMBC spectrum of compound **331**.

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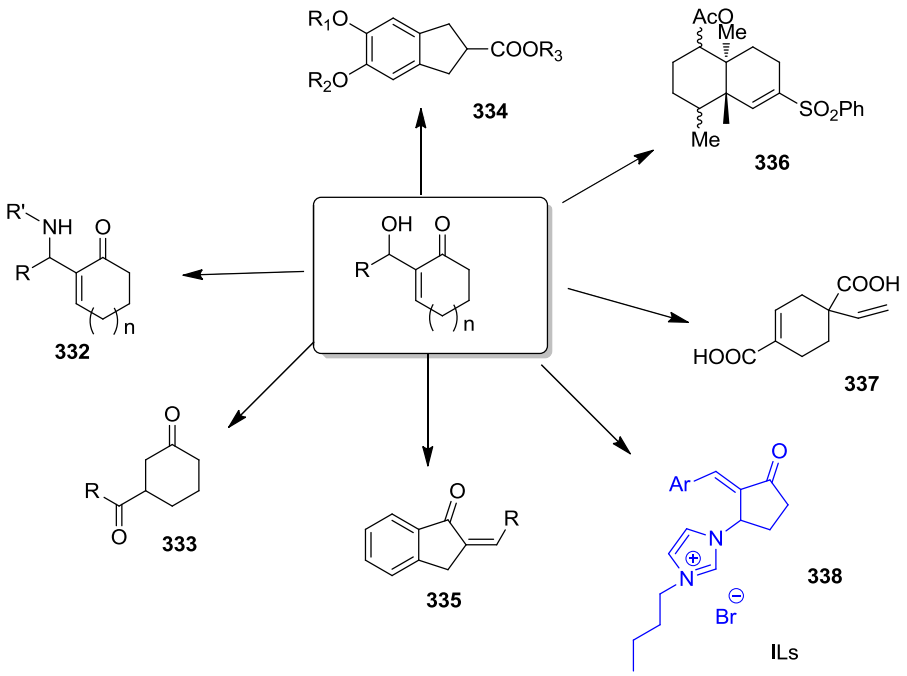
3.4 Baylis-Hillman reaction of HMF with enone in water

Cyclopentenones and cyclohexenones are interesting nucleophilic components for the MBH reaction because they provide adducts that can be readily transformed into polycyclic or other functional compounds as shown in **Scheme 3.8**. And in fact, some of these strategies methodologies were also successfully employed in the synthesis of various biologically active molecules and natural products [208, 209]. Resently, Coelho *et al.* [274] describe new synthesis of novel ionic liquids **338** from the MBH adducts between 2-cyclopentenone and aromatic aldehydes.



Scheme 3.8: Products obtained from the MBH intermediate.

However, cyclic enones being relatively poor Michael acceptors compare to acyclic enone such as MVK, they show a lower reactivity in the experimental procedures usually employed for the MBH process. To circumvent this drawback, several strategies have been developed, most of which involve the use of either strong Lewis acids ($TiCl_4$, Et_2Al), strong bases (NaOMe) as co-catalysts [236]. On the other hand,

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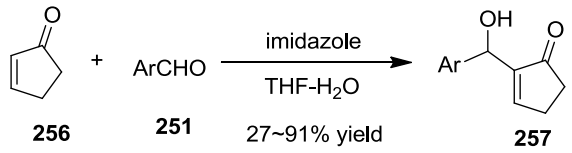
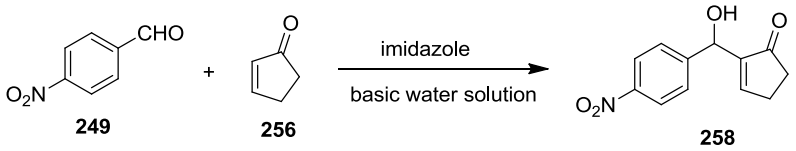
Yamada and Ikegami [275] found that the MBH reaction of cyclic enones can be promoted by mild cooperative catalysis of trialkylphosphanes with hydrogen-bond donors such as phenols in anhydrous THF.

In 2002, El Gaïed's group [232] and Cheng's group [233] separately reported the use of imidazole as a promoter for the MBH reaction of cyclic enones with aldehydes (**Scheme 3.9**). Both research groups found that in 1:1 THF/water mixtures at room temperature, good yields of the MBH adducts between 2-cyclopentenone or 2-cyclohexenone and formaldehyde or aromatic aldehydes could be obtained in reasonable reaction times, however, one equimolar amounts of imidazole were used.



Scheme 3.9: Aqueous MBH reaction between aldehydes and cycloalkenones.

Later on, Cheng and co-workers [234] found The Baylis-Hillman reaction of cyclic enones was greatly accelerated in basic water solution with imidazoles as catalysts, which resulted in short reaction time, high yields, and border substrate scopes (**Scheme 3.10**). They results indicated that in basic water solution, the protonation of imidazole is depressed, thus increasing the active molarity of imidazole in catalysis.



basic water solution	time (h)	yield (%)
1 M $NaCO_3$	10 min	53
1 M $NaHCO_3$	1.5	88
H_2O	20	48

Scheme 3.10: Aqueous MBH reaction between nitrobenzaldehyde and cycloalkenones.

A thorough re-examination by Williams and co-workers [235] of the reaction conditions used by El Gaïed and co-workers [232] concluded that the use of aqueous sodium hydrogen carbonate in the absence of an organic co-solvent is a necessary

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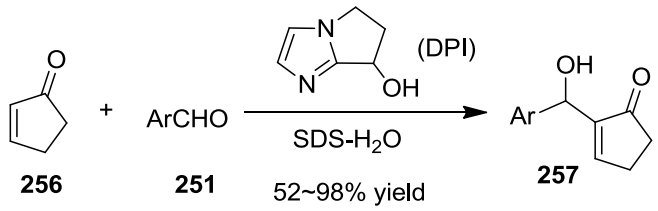
but not sufficient condition for imidazole catalysis, thus a surfactant must be added to the aqueous mixture to achieve useful reaction rates.

Recently, Coelho *et al.* [236] developed a bicyclic imidazolyl alcohol (namel imidazole 6,7-dihydro-5H-pyrrolo[1,2-a]imidazole, abbreviated as DPI) which catalyses the MBH reaction of 2-cyclopentenone and 2-cyclohexanone with aromatic aldehydes, affording the corresponding adducts in good average yields and reasonable reaction times. Their results indicated that due to the conjugate bicyclic structure along with the additional hydrogen-bond donor group, this new catalyst shown a better efficiency compared to imidazole. It should be noted that this reaction works in aqueous medium, but no reaction occurred in pure water, so a catalytic amount of sufactant, such as assodium dodecyl sulphate, was added in order to furnish the MBH reaction in water. This strategy also applied in the aqueous MBH reaction between unprotected isatins and cyclic enones to afford the corresponding 3-substituted 3-hydroxy-2-oxindoles (**Scheme 3.11**) [237].



Scheme 3.11: Aqueous MBH reaction of aldehydes with cycloalkenones catalyzed by DPI.

We began our studies with the reaction between cyclopentenone and HMF in water and investigated the effect of different amine and phosphorus catalysts on this reaction and the results are reported in **Table 3.5**. The Baylis-Hillman reaction of cyclopent-2-enone is sluggish under traditional conditions. Various catalysts such as DBU, 3-HQD, DABCO, Et_3N, PPh_3 and $P(m\text{-}C_6H_4\text{-}SO_3Na)_3$ have been used but no desired products were obtained in water. While the use of DMAP and pyridine gave low somewhat diminished yields (**Table 3.5**, entries 3, 7). While, it is interesting to note that imidazole act as remarkable catalysts in water with the former giving the best results compared to other commonly used catalysts in terms of yield. The model

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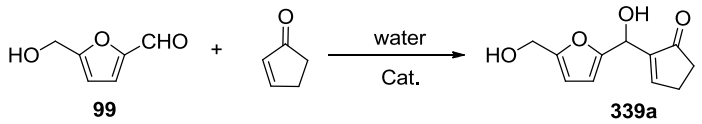
reaction gave 50% yield of desired products, 2-[hydroxy-(5-hydroxymethyl-furan-2-yl) methyl] cyclopent-2-en-1-one after 15 h in the presence of 60% of imidazole (**Table 3.5**, entry 11).

Table 3.5: The MBH reaction of HMF with cyclopent-2-enone.[a]



Entry	Cat.	Time/h	Yield (%)[b]
1	3-HQD	15	none
2	DBU	15	none
3	DMAP	15	5
4	DABCO	15	none
5	PPh_3	15	none
6	$P(m\text{-}C_6H_4\text{-}SO_3Na)_3$	15	none
7	Py	15	10
8	Et_3N	15	none
9	Imidazole	15	50
10	DPI	15	71
11	DPI	15	60
12[b]	DPI	15	54
13	DPI	30	83

[a] General conditions: HMF (1 mmol), cyclopent-2-enone (2 mmol), catalyst (60%), H_2O (1 ml), rt.;

[b] yield of isolated product.

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The structure of the obtained product was confirmed by analyzing the ^{1}H NMR, ^{13}C NMR and HMBC spectrum, as shown in the **Fig. 3.5**. In proton NMR spectrum, the coupling is identified by the disappearance of singlet peak of aldehyde group of HMF at δ 9.53 ppm to the benefit of the newly formed CHOH at δ 5.50 ppm, with interactions with the methylene and the carbonyl group of cyclopent-2-enone at δ 108, 209 ppm, respectively, observed in the HMBC spectrum. The corresponding carbon signals are found at δ 62.9 ppm. Again in this case, the newly formed carbon-carbon bond was thus demontrated unambiguously.

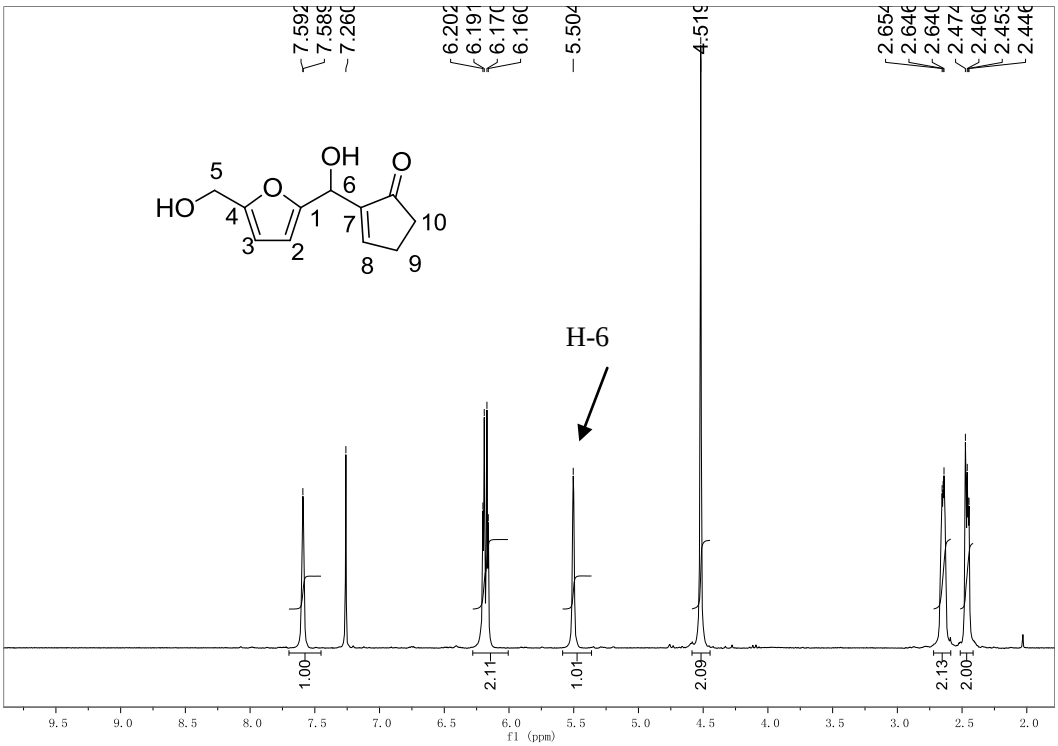

Fig. 3.5a: ^{1}H NMR spectrum of compound **339a**.

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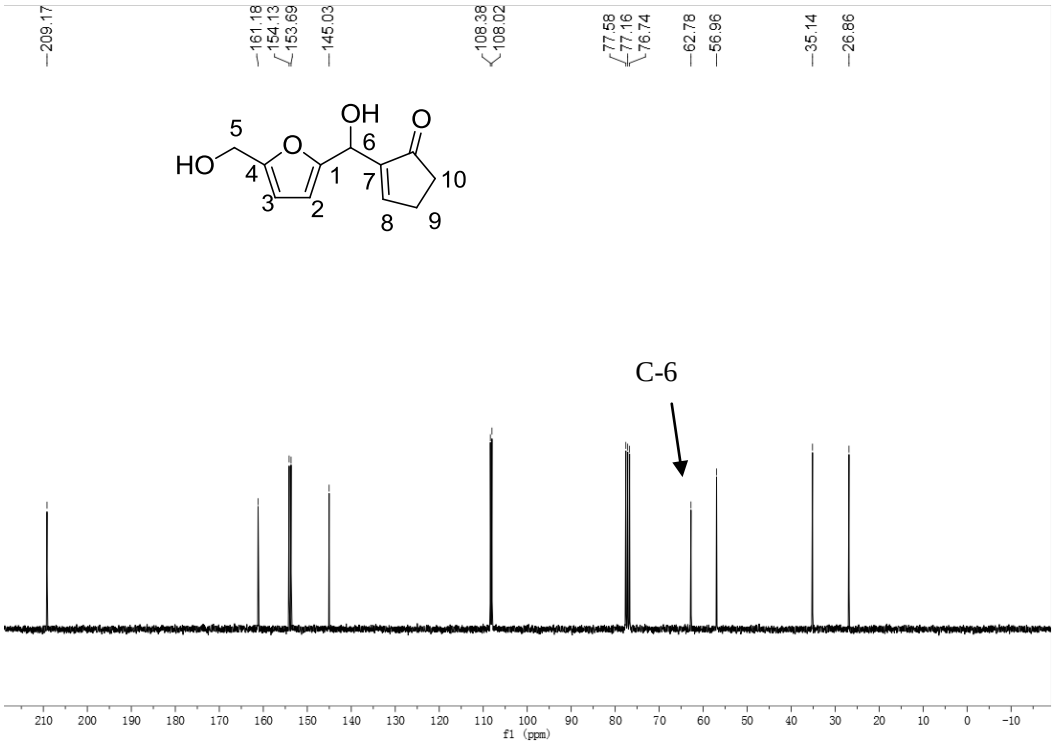

Fig. 3.5b: ^{13}C NMR spectrum of compound **339a**.

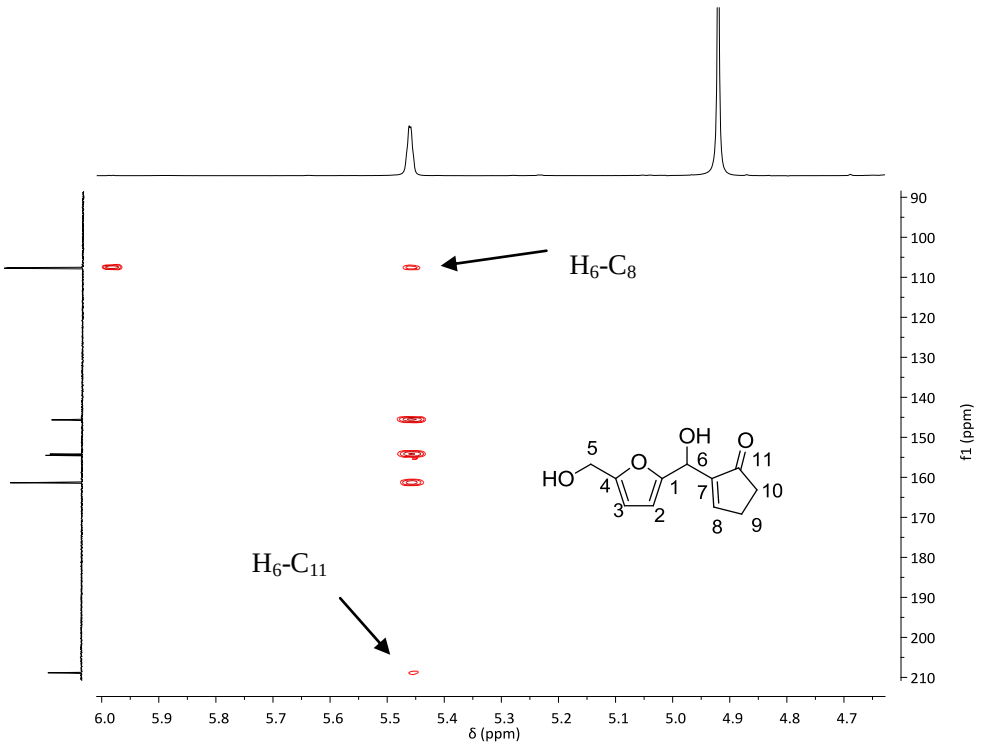

Fig. 3.5c: ^{1}H - ^{13}C HMBC spectrum of compound **339a**.

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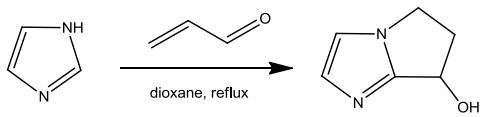
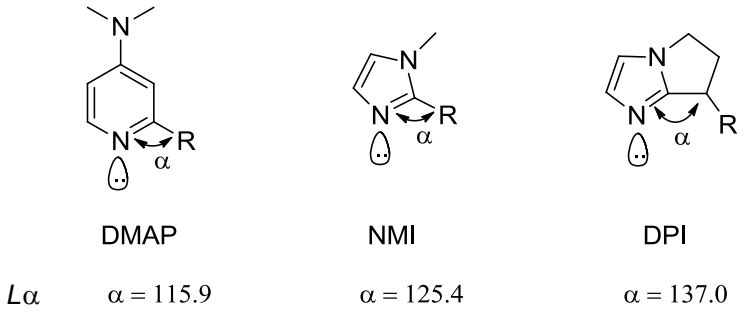
When the bicyclic imidazole DPI was used, the reaction gave a better yield (**Table 3.5**, entry 9). DPI is prepared by using the method described by Zhang *et al.* [276]. A mixture of imidazole and acrolein was heated to reflux in dioxane with a catalytic amount of acetic acid for 24 h to provide 87% yield of DPI (**Scheme 3.12**).



Scheme 3.12: Preparation of DPI.

Application of this catalyst in asymmetric Steglich rearrangement has shown that this rigid bicyclic DPI has a much larger angle $\widehat{NCC}$ compared to DMAP and *N*-Methylimidazole (NMI) [276]. Therefore, good stereocontrol would be expected since the stereocontrol group R designed at the 7-position of DPI is nearby to the catalytic active site and allowed to be efficiently adjustable which effectively enhanced the nucleophilicity (**Scheme 3.13**).



Scheme 3.13: Design of Catalyst DPI.

Further studies were explored by Coelho *et al*. [236] shown that the hydroxyl group in DPI may assist in the stabilization of the betaine intermediate resulting from the initial Michael addition of the nucleophilic catalyst to the activated alkene (**Fig. 3.6**). Both of those advantages benefit the MBH reaction between the cyclopentenone and HMF.

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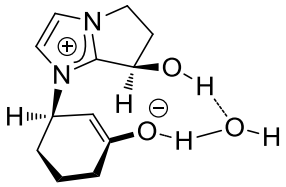
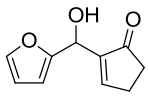


Fig. 3.6: Possible role of the hydroxyl group of DPI in the stabilization of the initial betaine intermediate of the MBH reaction in aqueous solution.

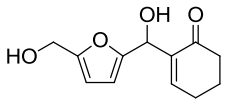
As shown in **Table 3.5**, DPI is efficient for the MBH reaction of HMF with cyclopet-2-enone gave yield up to 71% (**Table 3.5**, entry 10), are even 83% when the reaction time further extende to 30 h. (**Table 3.5**, entry 13).

Finally, the scope of this reaction was explored, using furfural and GMF as aldehyde, and cyclohex-2-enone as Michael acceptor. These reactions were carried out in the optimized condition: DPI (0.6 equiv), 30 h, rt, water. The MBH adducts were obtained with moderate to good yield (**Scheme 3.14**).



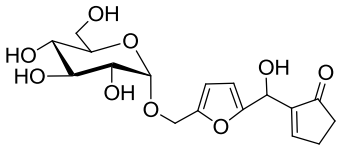
339b

88%



339c

70%



339d

55%

Scheme 3.14: Substrate scope for MBH reaction in water.

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3.5 Conclusion

This chapter has focused on the use of HMF in MBH reactions, focusing on solvent issues.

The results show that several biobased solvents, in particular 2-hydroxymethyl THF and isopropylideneglycerol, can be used for the MBH reaction of HMF and ethyl acrylate. For HMF and furfural, the reaction was improved when water was added allowing to widen the range of biobased solvent systems for the MBH reaction.

We have also found that the bicyclic imidazolyl alcohol DPI is an efficient catalyst for the aqueous MBH reaction between HMF, furfural or GMF, with cyclic enones which gives access to a variety of potentially useful molecules in an efficient and environmentally friendly sequence.

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General conclusion

In this thesis, we have studied the Morita-Baylis-Hillman (MBH) reaction of three biosourced furanic aldehydes, namely furfural, hydroxymethyl furfural (HMF) and glucosyloxymethylfurfural (GMF) with various Michael acceptors under different conditions.

New carbohydrate containing α-hydroxyacrylates were obtained in fair yields by Baylis-Hillman reaction of GMF with acrylic building blocks. The reaction could be performed in aqueous medium. Acrylic esters being also available from biomass (from glycerol or lactic acid) [25], such new compounds appear as possibly 100% bio-based. This exploration show that GMF can be transformed in very short sequences to rather elaborated new compounds using the MBH strategy.

The study was extended to HMF and furfural, notably with respect to the solvent issue. The results show that several biobased solvents, in particular 2-hydroxymethyl THF and isopropylideneglycerol, can be used for the MBH reaction of HMF and ethyl acrylate. For HMF and furfural, the reaction was improved when water was added allowing to widen the range of biobased solvent systems used in the MBH reaction.

When cyclic enones were used as Michael acceptors, it was found that the bicyclic imidazolyl alcohol DPI was an efficient catalyst to produce MBH adducts from HMF, GMF or furfural in water.

The *aza*-MBH reaction of GMF was also explored. The three components GMF, sulfonamides and a Micheal acceptor, underwent the aza-MBH reaction leading to carbohydrate-based α-methylene-β-amino carbonyl derivatives in moderate to good yield, under combined catalysis by a Lewis acid and a base.

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Considering the wide range of applications of MBH adducts, either as synthons or starting materials towards the synthesis of natural products, bioactive molecules, and specialty chemicals, it is foreseen that the results provided in this thesis will serve for widening the scope of this strategy which offers excellent atom economy and short synthetic sequences towards elaborated architectures.

The MBH reaction is known to provide several classes of functionalized polymers, as in the work reported by Joy *et al.* [277] or Sagheer *et al*. or Goodby *et al*. [279]. Thus, perspectives of our work will include the exploration of the reactivity of carbohydrate based MBH adducts in polymerization reactions to produce new, functional, carbohydrate containing polymers and innovative biosourced materials. Also, taking into account the amphiphilic character of some of the GMF-derived MBH adducts, the self-assembling properties of such compounds will be interesting to investigate in the context of our work on glycolipidic liquid crystals [114].

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Experimental section

A. General aspect

The solvents used for reactions and chromatography were bought from SDS, Carlo Erba, and Sigma-Aldrich. Most of the solvents used in the syntheses were distilled before use, dichloromethane over the P_2O_5, THF over Na and benzophenone, DMF and DMSO over CaH_2.

The reagents used in this thesis were bought from Aldrich and used directly without purification.

The TLC plates are from Merck 60F, coated with silica gel GF_{254} (0.25 mm).

The purification using the chromatographies is by column of silica gel flash Merck (60, 40-63 µm).

NMR spectroscopy: Bruker AC or DRX spectrometers at 75.47 MHz (100.61 MHz, or 125.77 MHz) for ^{13}C NMR and 300.13 MHz (or 400.13 MHz, or 500.13 MHz) for ^{1}H NMR. Chemical shifts (δ) are given in parts per million (ppm) and were measured relative to the signal of tetramethylsilane ($\delta = 0$).

The abreviations used in the list of NMR characterization are: s (singulet); ls (large singulet); d (doublet); t (triplet); dt (doublet and triplet); dd (doublet of doublet); q (quadruplet); m (multiplet).

Mass spectroscopy: The spectra were recorded by “Centre de Spectrométrie de Masse” of the “Université Claude Bernard (Villeurbanne)” using electrospray (ESI) technique.

Optical rotation: Perkin Elmer 241 polarimeter at 589 nm (sodium D line). The measurements were carried out at 20 ^{o}C and the concentrations are reported in g/100 mL.

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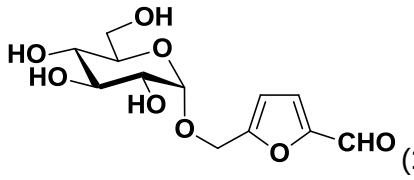
B. Synthetic procedures and characterizations of all the products studied

B. 1 Synthesis of suger-derived hydroxymethylfurfural

B. 1.1 5-α-D-glucosyloxymethylfurfural (17):



(**17**)

A solution of 10.0 g (30.0 mmol) isomaltulose in anhydrous DMSO (70 mL) was heated to 120 ^{o}C, 1.2 g of Dowex 50 WX4 (H^+ form) and freshly desiccated molecular sieve (4A, 6.0 g) were added, and stirring was continued for 3 h at 120 ^{o}C, where after TLC indicated absence of educts in favor of GMF and some HMF. Filtration, removal of the solvent under vacuum provided syrup, which was purified by elution from a silica gel column with acetone give the desired product **17** (5.5 g, 63% yield) as a yellow liquid;

^{1}H NMR (300 MHz, DMSO): 3.08 (m, 1H, O<u>H</u>), 3.23 (m, 1H, O<u>H</u>), 3.40 (m, 2H, 2O<u>H</u>), 3.43~3.50 (dd, 1H, J_a = 5.7 Hz, J_b = 11.7 Hz, H-6'), 3.60 (dd, 1H, J_a = 4.8 Hz, J_b = 10.5 Hz, H-5'), 4.49 (t, 1H, J_a = 6.0 Hz, J_b = 12.0 Hz, H-6'), 4.65 (part A, AB system, 1H, J = 13.5 Hz, H-6), 4.75 (part B, AB system, 1H, J = 13.5 Hz, H-6), 4.78 (t, 2H, J_a = 3.6 Hz, J_b = 8.7 Hz, H-2', H-4'), 4.83 (d, 1H, J = 6.3 Hz, H-1'), 4.91 (d, 1H, J = 5.7 Hz, H-3'), 6.71 (d, 1H, J = 3.3 Hz, H-3), 7.37 (d, 1H, J = 3.6 Hz, H-4), 9.54 (s, 1H, C<u>H</u>O);

^{13}C NMR (75 MHz, DMSO): 60.8 (C-6), 61.2 (C-6'), 70.5 (C-5'), 72.1 (C-4'), 73.4 (C-3'), 73.5 (C-2'), 98.7 (C-1'), 112.3 (C-3), 124.5 (C-4), 152.5 (C-5), 158.3 (C-2), 178.6 (<u>C</u>HO);

$[\alpha]_D$ = + 96 (c = 1.0, CH_3OH);

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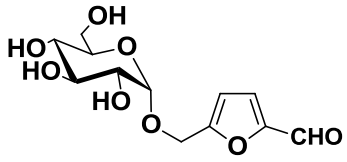
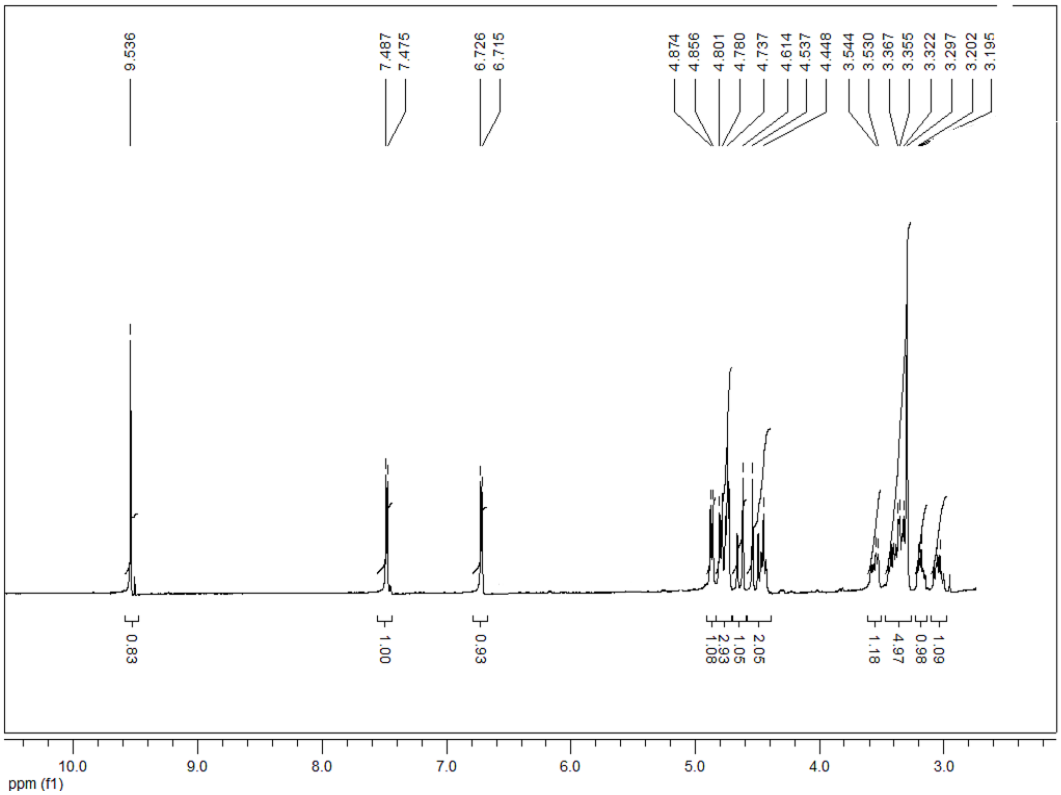
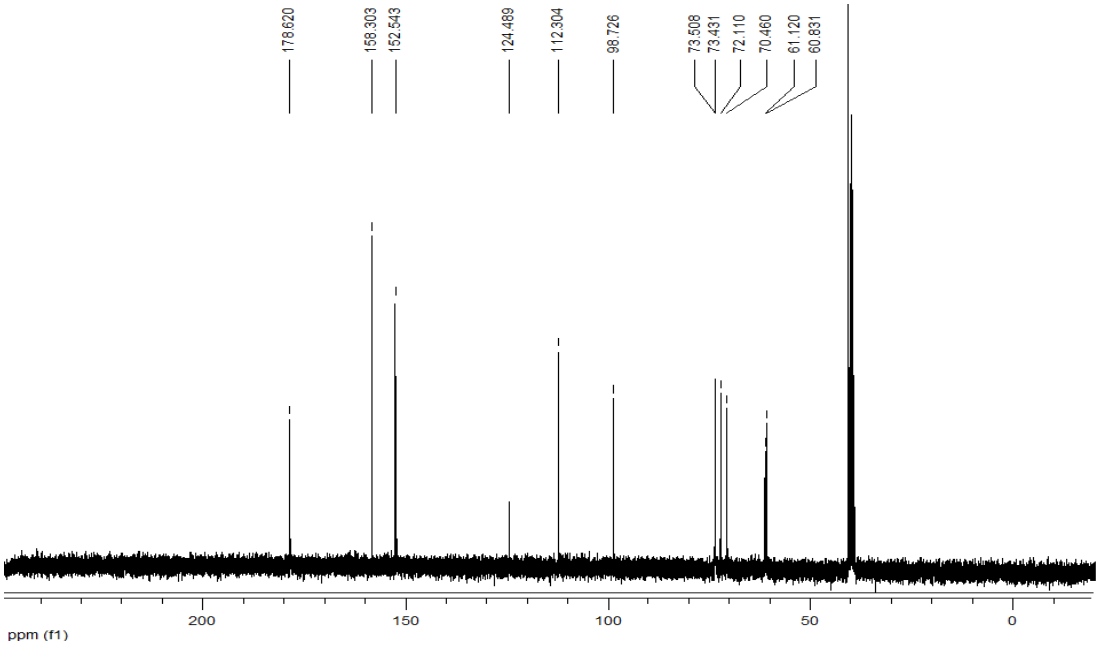


(17)





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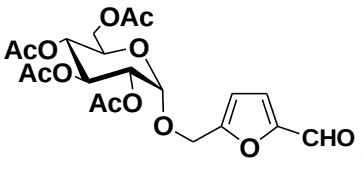
B.1.2 2,3,4,6-tetra-*O*-acetyl-5-α-D-glucosyloxymethylfurfural (112):



(112)

A solution of 5.5 g (19.2 mmol) GMF (**17**) in 75 mL of acetic anhydride-pyridine (35/40, v/v) was stirred for 12 h at room temperature. The reaction progress was monitored by TLC. Upon completion, removal of the solvent in vacuum provided a syrup, which was purified by elution from a silica gel column with ethyl acetate and pentane (ethyl acetate/pentane: 1/2) give the desired product **112 (**6.9 g, 79% yield) as a yellow liquid;

^{1}H NMR (300 MHz, $CDCl_3$): 1.98 , 2.01 , 2.02 , 2.08 (s, 12 H , 4 OAc, C<u>H</u>$_3$), 4.06 (m, 2H, H-5', H-6'), 4.25 (dd, 1H, J_a = 4.5 Hz, J_b = 12.6 Hz, H-6'), 4.61 (d, 1H, part A, AB system, J = 13.5 Hz, H-6), 4.70 (d, 1H, part B, AB system, J = 13.5 Hz, H-6), 4.84 (dd, 1H, J_a = 3.8 Hz, J_b = 10.2 Hz, H-2'), 5.06 (dd, 1H, J = 9.7 Hz, H-4'), 5.18 (d, 1H, J = 3.8 Hz, H-1'), 5.46 (dd, 1H, J = 9.7 Hz, H-3'), 6.54 (d, 1H, J = 3.5 Hz, H-3), 7.20 (d, 1H, J = 3.5 Hz, H-4), 9.61 (s, 1H, C<u>H</u>O);

^{13}C NMR (75 MHz, $CDCl_3$): 20.5, 20.6, 20.6, 20.7 (4 OAc, <u>C</u>H$_3$), 61.7 (C-6'), 62.0 (C-6), 67.7 (C-5'), 68.3 (C-4'), 69.8 (C-3') 70.6 (C-2'), 95.4 (C-1'), 112.1 (C-3), 121.8 (C-4), 152.9 (C-5), 156.3 (C-2), 169.5, 170.0, 170.1, 170.5 (<u>C</u>O, 4OAc), 177.6 (<u>C</u>HO);

$[\alpha]_D$ = + 129 (c = 0.6, CH_3OH);

HRMS m/z (ESI) calculated for $C_{20}H_{24}NaO_{12}$, $[M + Na]^+$ 479.1160; found 479.1136.

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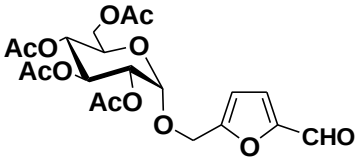
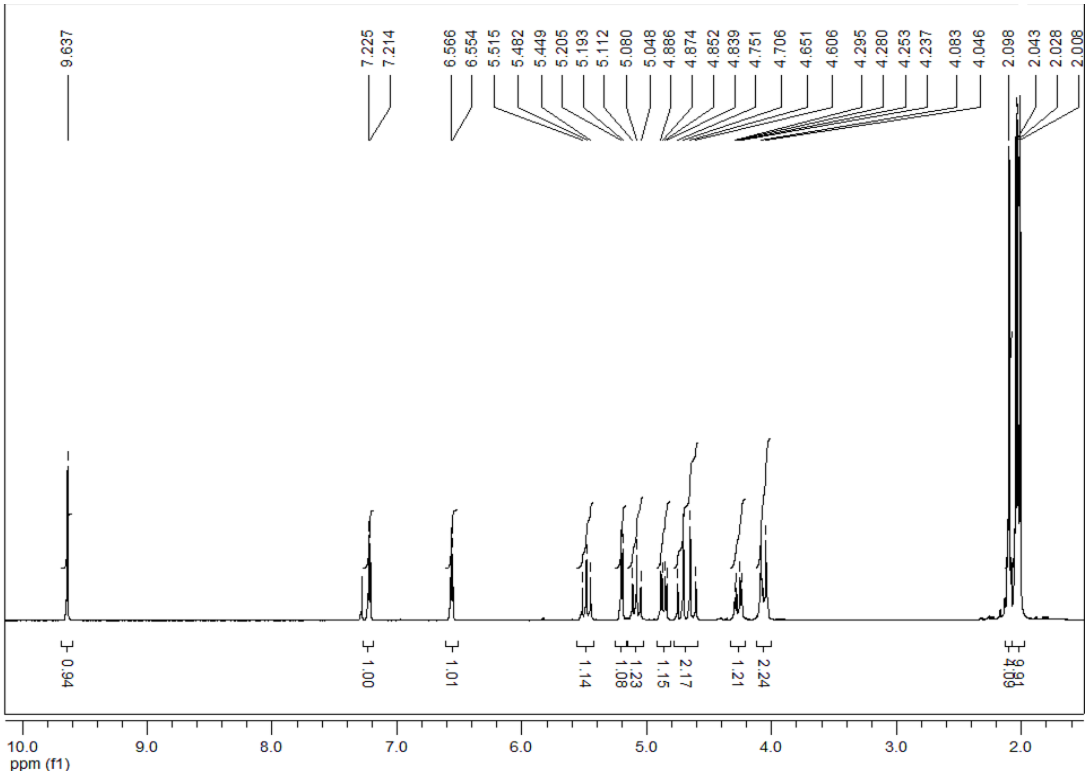
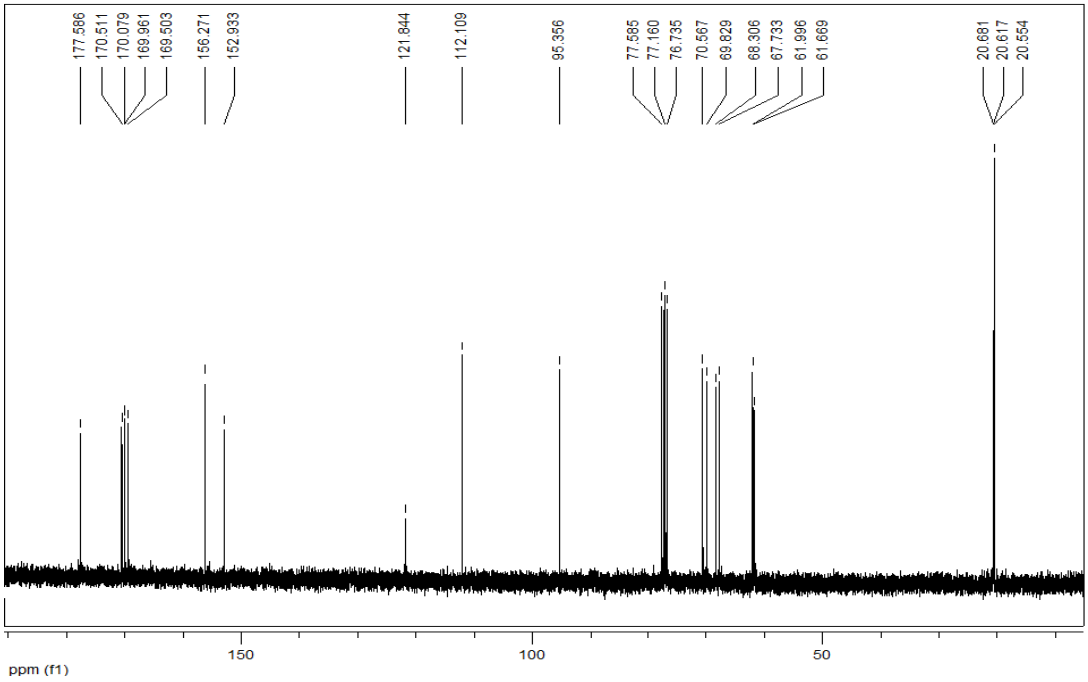


(112)





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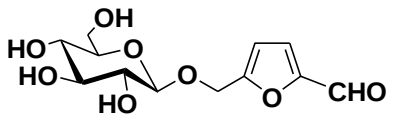
B. 1.3 5-β-D-Glucosyloxymethylfurfural (299a):



(299a)

The compound 5-(tert-butyl(dimethyl)silyl-oxy-methyl)-2-furaldehyde (0.25 g, 2 mmol) then boron trifluoride diethyl etherate (4 mL) were added at -20 ^{o}C to a solution of β-D-glucose pentaacetate (0.86 g, 2.2 mmol) in dry dichloromethane (15 mL). After stirring for 5 h at -20 ^{o}C, the mixture was neutralized with sodium hydrogenocarbonate and diluted with diethyl ether (75 mL). The organic phase was washed with water (2 x 15 mL) and then with brine (10 mL), and dried. After filtration, the solvent was evaporated. The yellow residues obtained was mixed with a solution of $CH_3OH/H_2O/Et_3N$, and stirred for one night. After evaporation the crude was purified with column by using CH_3OH/H_2O as eluting solvent (CH_3OH/H_2O: 10/90), give desired products **299a** (144 mg, 25% yield) as a yellow liquid;

^{1}H NMR (400 MHz, CD_3OD): 3.45~3.70 (t, 1H, J_a = 8.0 Hz, J_b = 16.8 Hz, H-2'), 3.28~3.40 (m, 3H, H-3', H-4', H-5'), 3.68 (m, 1H, H-6'), 3.90 (d, 1H, J = 11.6 Hz, H-6'), 4.40 (d, 1H, J = 7.6 Hz, H-1'), 4.79 (part A, AB system, 1H, J = 13.2 Hz, H-6), 4.94 (part B, AB system, 1H, J = 13.2 Hz, H-6), 6.74 (d, 1H, J = 3.6 Hz, H-3), 7.41 (d, 1H, J = 3.6 Hz, H-4), 9.57 (s, 1H, C<u>H</u>O);

^{13}C NMR (100 MHz, CD_3OD): 62.7 (C-6), 63.6 (C-6'), 71.5 (C-4'), 75.0 (C-2'), 78.0 (C-3'), 78.1 (C-5'), 103.5 (C-1'), 113.0 (C-3), 124.4 (C-4), 154.2 (C-5), 159.6 (C-2), 179.6 (<u>C</u>=O);

IR (cm^{-1}): 3885, 2981, 2936, 1722, 1637, 1620, 1480, 1468, 1403, 1394, 1369, 1300, 1294, 1267, 1221, 1161, 1051, 1038, 987, 965, 928, 850, 812, 757;

HRMS m/z (ESI) calculated for $C_{12}H_{16}NaO_8$, $[M + Na]^+$ 311.0737; found 311.0738.

$[\alpha]_D$ = - 48 (c = 1.1, CH_3OH);

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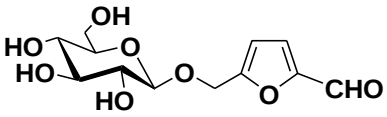
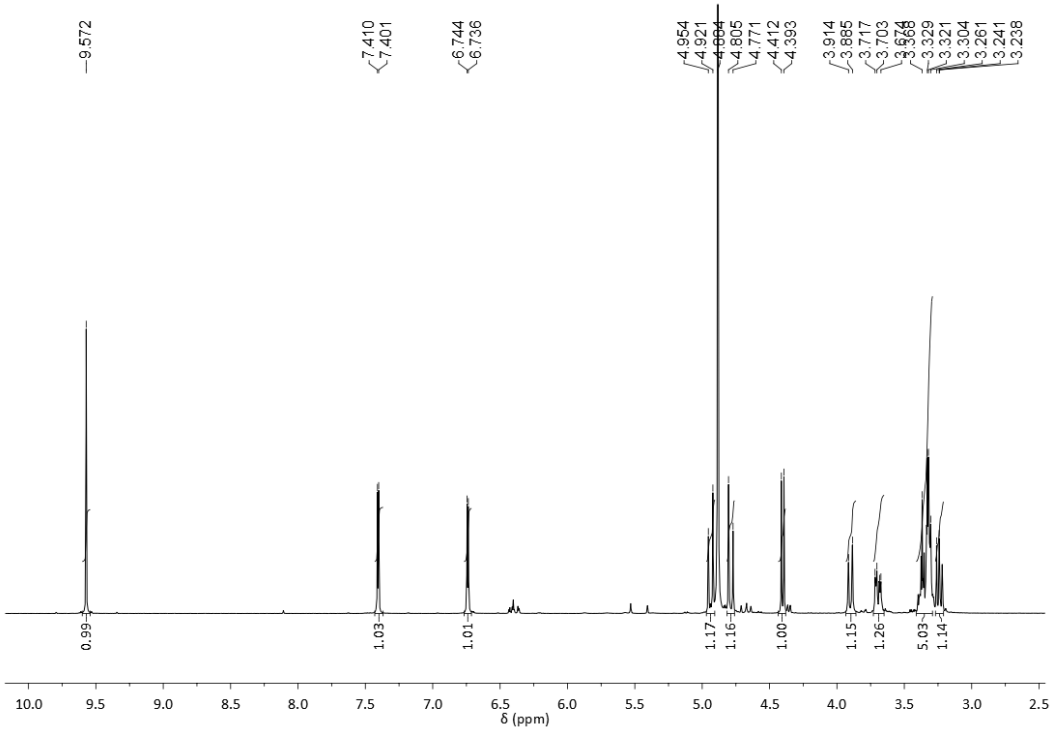
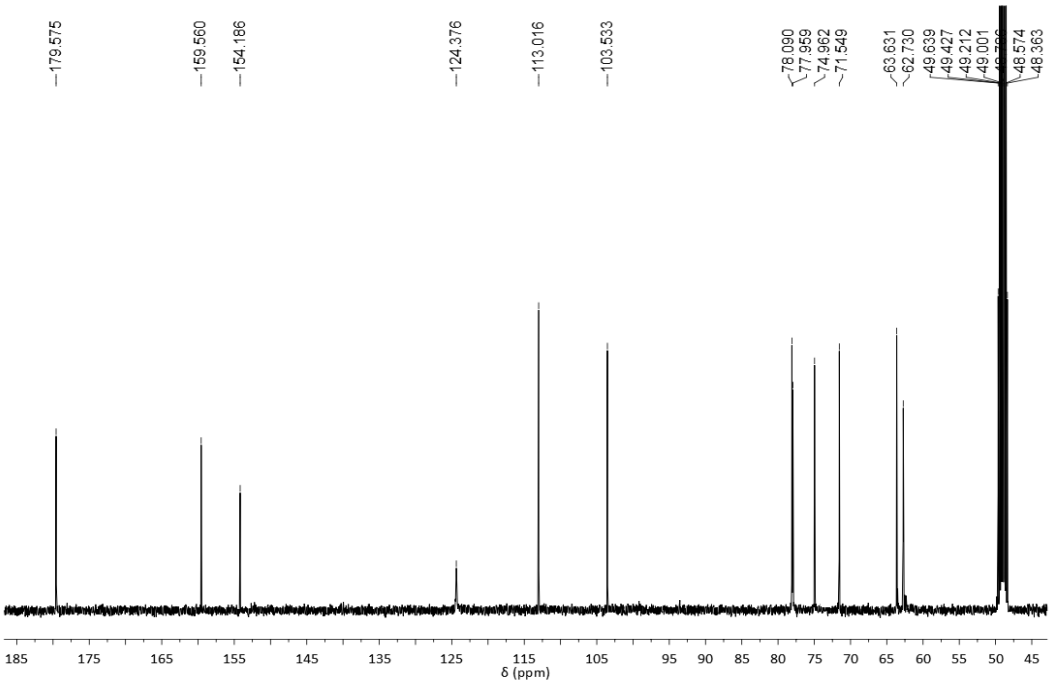


(299a)





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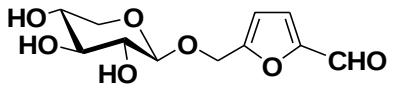
1.3 5-α-D-Xylosyloxymethylfurfural (299b):



(299b)

The compound 5-(tert-butyl(dimethyl)silyl-oxy-methyl)-2-furaldehyde (0.25 g, 2 mmol) then boron trifluoride diethyl etherate (4 mL) were added at -20 ^{o}C to a solution of β-xylose pentaacetate (0.86 g, 2.2 mmol) in dry dichloromethane (15 mL). After stirring for 5 h at -20 ^{o}C, the mixture was neutralized with sodium hydrogenocarbonate and diluted with diethyl ether (75 mL). The organic phase was washed with water (2 x 15 mL) and then brine (10 mL), and dried. After filtration, the solvent was evaporated to give a yellow residue. Then mixed with a solution of $CH_3OH/H_2O/Et_3N$, stirring for one night, upon completion, the crude was purified with column by using CH_3OH/H_2O as eluting solvent (CH_3OH/H_2O: 10/90) to give the desired product **299b** (90 mg, 32% yield) as pale-yellow liquid.

^{1}H NMR (400 MHz, CD_3OD): 3.20~3.29 (m, 2H, H-2'+ H-5'), 3.37 (d, 1H, J = 8.4 Hz, H-3'), 3.60(m, 1H, H-4'), 3.90 (dd, 1H, J_a = 5.6 Hz, J_b = 11.6 Hz, H-5'), 4.36 (d, 1H, J = 7.2 Hz, H-1'), 4.74 (part A, AB system, 1H, J = 13.6 Hz, H-6), 4.86 (part B, AB system, 1H, J = 13.6 Hz, H-6), 6.73 (d, 1H, J = 3.6 Hz, H-3), 7.41 (d, 1H, J = 3.6 Hz, H-4), 9.57 (s, 1H, C<u>H</u>O);

^{13}C NMR (100 MHz, CD_3OD): 63.7 (C-6), 67.0 (C-5'), 71.1 (C-4'), 74.7 (C-2'), 77.7 (C-3'), 104.3 (C-1'), 112.9 (C-3), 124.4 (C-4), 154.1 (C-5), 159.5 (C-2), 179.6 (<u>C</u>=O);

IR (cm^{-1}): 3885, 2985, 2930, 1722, 1637, 1620, 1480, 1468, 1407, 1394, 1369, 1308, 1290, 1263, 1221, 1161, 1059, 1030, 985, 971, 923, 852, 811, 764;

$[a]_D$ = - 58 (c = 0.9, CH_3OH);

HRMS m/z (ESI) calculated for $C_{11}H_{14}NaO_7$, $[M + Na]^+$ 281.0632; found 281.0636.

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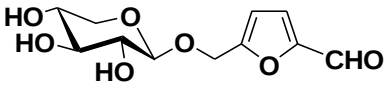

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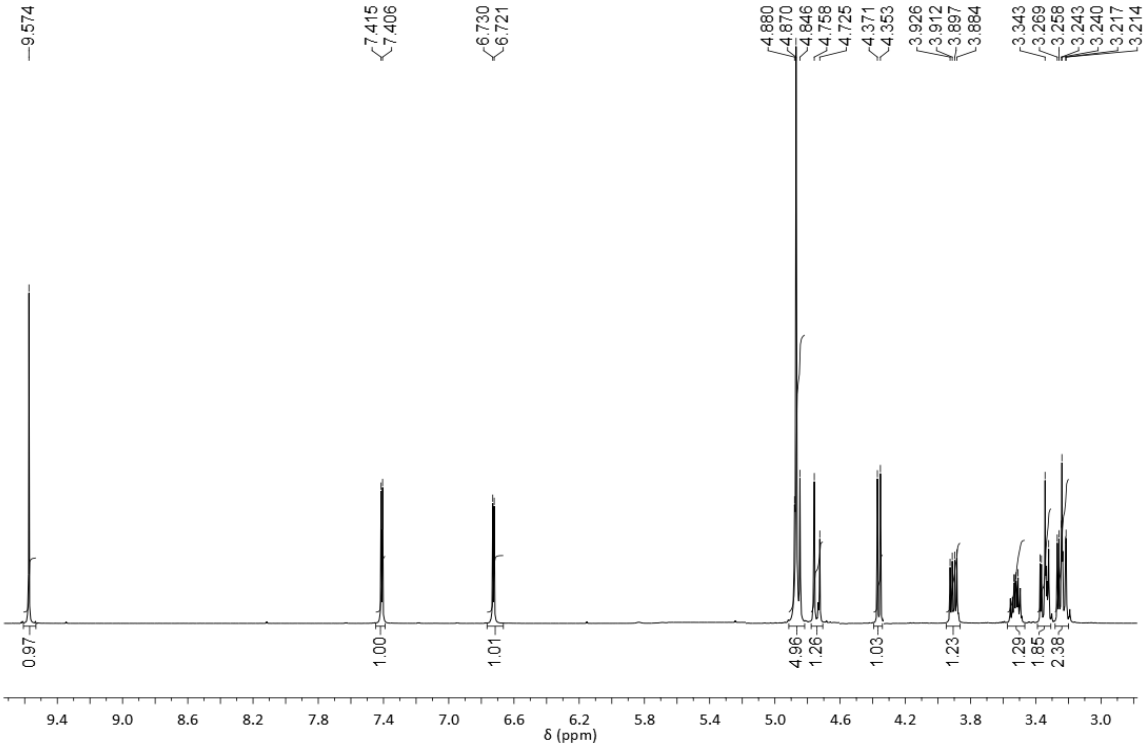

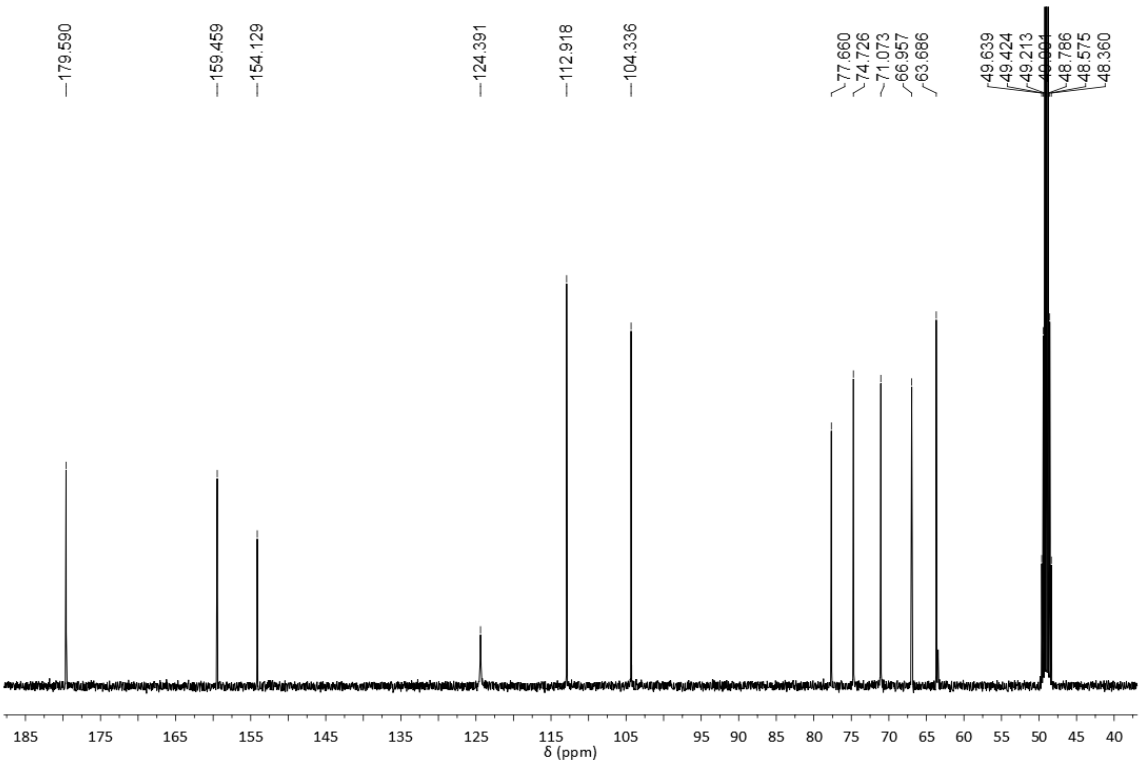

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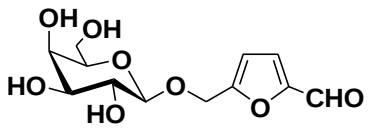
B. 1.4 5-α-D-Galactosyloxymethylfurfural (299c):



(299c)

The compound 5-(tert-butyl(dimethyl)silyl-oxy-methyl)-2-furaldehyde (0.25 g, 2 mmol) then boron trifluoride diethyl etherate (4 mL) were added at -20 ^{o}C to a solution of β-galactose pentaacetate (0.86 g, 2.2 mmol) in dry dichloromethane (15 mL). After stirring for 5 h at -20 ^{o}C, the mixture was neutralized with sodium hydrogenocarbonate and diluted with diethyl ether (75 mL). The organic phase was washed with water (2 x 15 mL) and then with brine (10 mL), and dried. After filtration, the solvent was evaporated to give a yellow residue. This later mixed with a solution of $CH_3OH/H_2O/Et_3N$ and stirred for one night. The crude was purified with column by using CH_3OH/H_2O as eluting solvent (CH_3OH/H_2O: 10/90) to give the desired products **299c** (62 mg, 20% yield) pale-yellow liquid.

^{1}H NMR (300 MHz, CD_3OD): 3.45~3.70 (m, 3H, H-2', H-3' + H-5'), 3.70~3.85 (m, 2H, H-6'), 3.88 (d, 1H, J = 2.1 Hz, H-4'), 4.38 (d, 1H, J = 7.8 Hz, H-1'), 4.79 (part A, AB system, 1H, J = 13.5 Hz, H-6), 4.93 (part B, AB system, 1H, J = 13.5 Hz, H-6), 6.74 (d, 1H, J = 3.6 Hz, H-3), 7.41 (d, 1H, J = 3.6 Hz, H-4), 9.55 (s, 1H, C<u>H</u>O);

^{13}C NMR (75 MHz, CD_3OD): 62.4 (C-6'), 63.6 (C-6), 70.3 (C-4'), 72.4 (C-2'), 74.9 (C-3'), 76.7 (C-5'), 104.0 (C-1'), 113.0 (C-3), 124.7 (C-4), 152.9 (C-5), 159.6 (C-2), 179.6 (<u>C</u>=O);

IR (cm^{-1}): 3880, 2981, 2943, 1720, 1642, 1621, 1470, 1468, 1433, 1390, 1369, 1307, 1290, 1269, 1221, 1166, 1053, 1030, 979, 965, 923, 854, 810, 759;

$[\alpha]_D$ = - 53 (c = 1.0, CH_3OH);

HRMS m/z (ESI) calculated for $C_{12}H_{16}NaO_8$, $[M + Na]^+$ 311.0737; found 311.0736.

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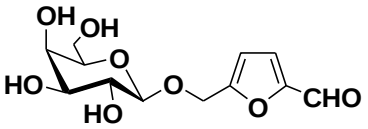
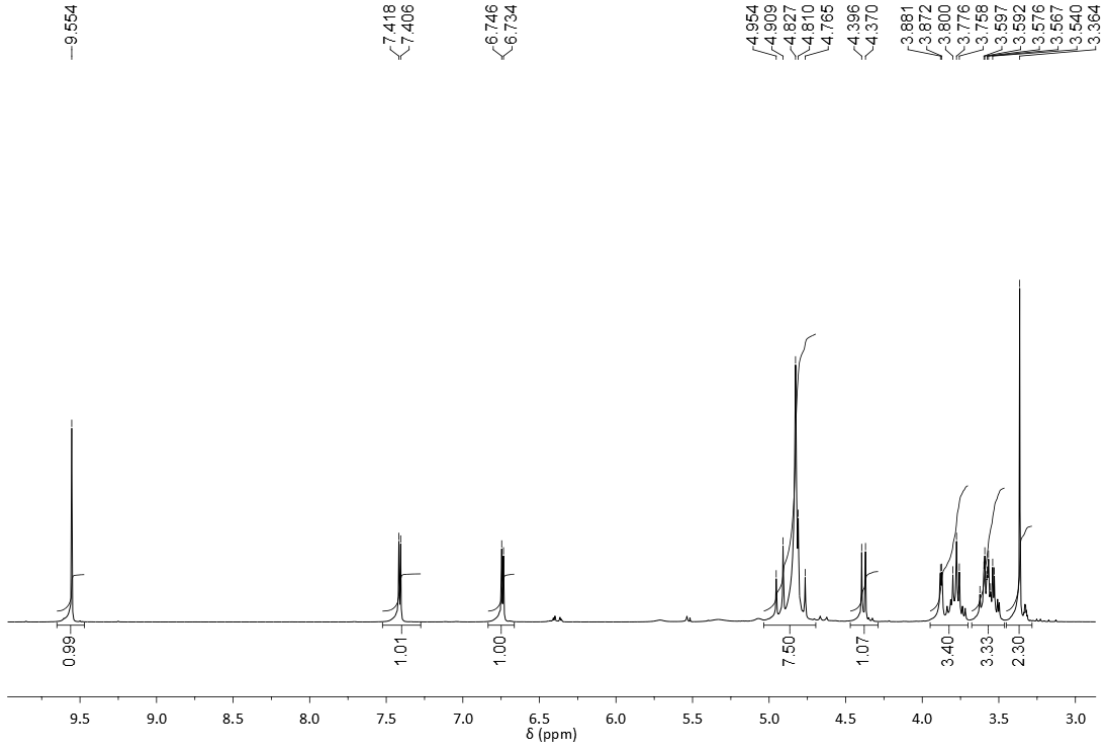
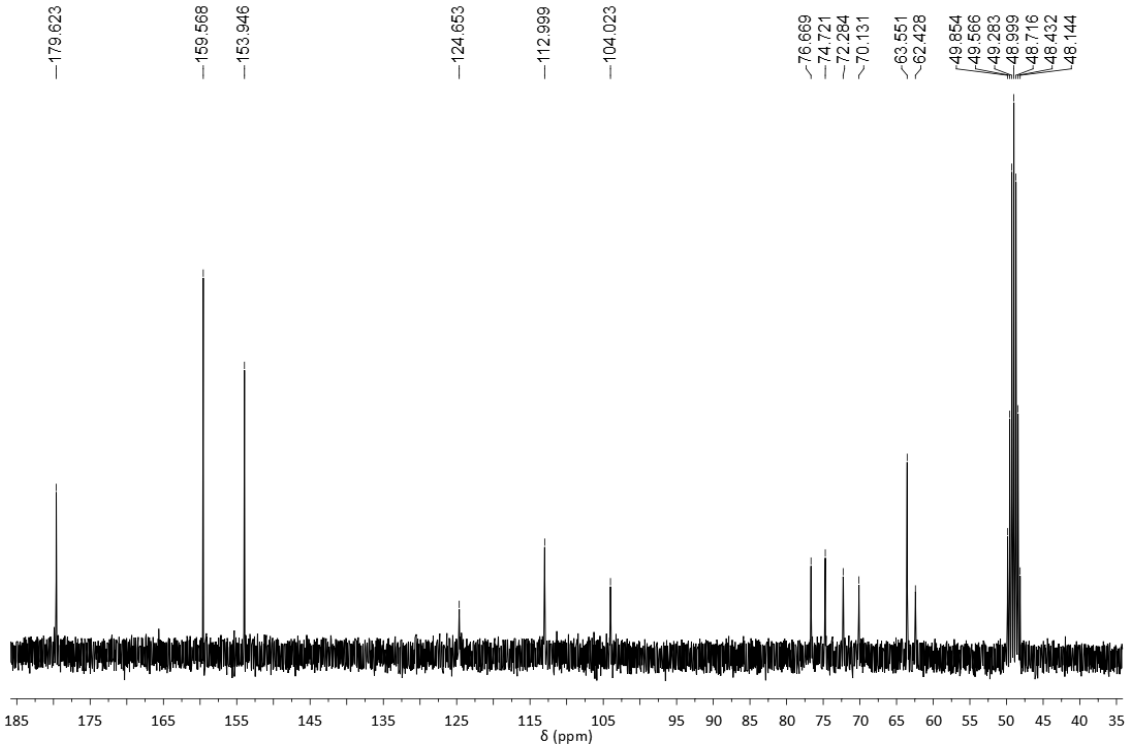


(299c)





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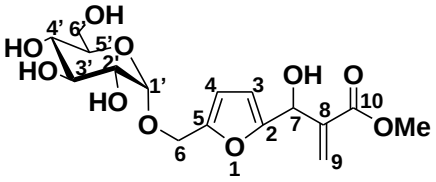
1.2.4 Typical procedure for Baylis-Hillman reaction of acrylate with GMF in DMI/H_2O:

All reactions were conducted in a 10 mL flask equipped with magnetic stirring. In a typical reaction, GMF (145 mg, 0.5 mmol) was mixed with DABCO (67 mg, 0.5 mmol) and methyl acrylate (140 µL, 1.5 mmol) in 1 mL of DMI-H_2O (1/1, v/v) under air. The reaction progress was monitored by TLC. Upon completion, remove the solvent in vacuum. The crude product was purified by flash column chromatography on silica gel, using CH_2Cl_2/CH_3OH as the eluting solvents to give the desired product **298a** (111 mg, 56% yield) as a pale-yellow gum.

Products **298b-n** were synthesized fellowing the same manner as for **298a**.

Methyl 2-[hydroxy-(5-(α-D-glucopyranosyloxymethyl)-furan-2-yl)methyl]acrylate (298a)



(298a)

^{1}H NMR (400 MHz, DMSO): 6.33 and 6.34 (2s, 1H, H-4), 6.29 (s, 1H, H-9), 6.07 (2d, 1H, *J* = 2.4 Hz, H-3), 6.03 (2s, 1H, H-9'), 5.92 and 5.93 (2d, 1H, *J* = 1.6 Hz, OH), 5.43 and 5.44 (2s, 1H, H-7), 4.90 and 4.91 (2s, 1H, O<u>H</u>), 4.70~4.80 (m, 3H, H-1' + 2OH), 4.49~4.55 (m, 2H, H-6 + O<u>H</u>), 4.35 and 4.38 (2d, 1H, *J* = 2.4 Hz, H-6), 3.60~3.70 (m, 4H, OC<u>H</u>$_3$+H-6'), 3.45 and 3.48 (2d, 1H, *J* = 6.0 Hz, H-6'), 3.35~3.41 (m, 3H, H-3', H-5', O<u>H</u>), 3.17~3.25 (m, 1H, H-2'), 3.04~3.12 (m, 1H, H-4');

^{13}C NMR (100 MHz, DMSO): 51.9 (CO_2<u>C</u>H_3), 60.3 (C-6), 60.9 (C-6'), 64.2, 64.2 (C-7, R, S), 70.3 (C-4'), 71.9 (C-2'), 72.9 (C-5'), 73.3 (C-3'), 97.8, 97.8 (C-1'), 107.5, 107.5 (C-3), 110.3 (C-4), 125.4 (C-9), 141.1 (C-8), 150.8, 150.9 (C-5), 155.6, 155.7 (C-2), 165.8 (C-10);

IR (cm^{-1}): 3885, 2918, 1716, 1654, 1636, 1438, 1406, 1340, 1274, 1199, 1147, 1105, 1010, 953, 819, 708;

$[\alpha]_D$ = + 53 (c = 1.0, CH_3OH);

HRMS m/z (ESI) calculated for $C_{16}H_{22}NaO_{10}$, $[M + Na]^+$ 397.1112; found 397.1105.

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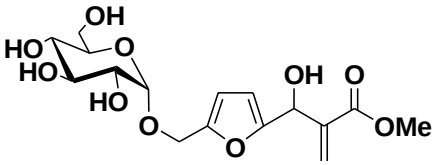
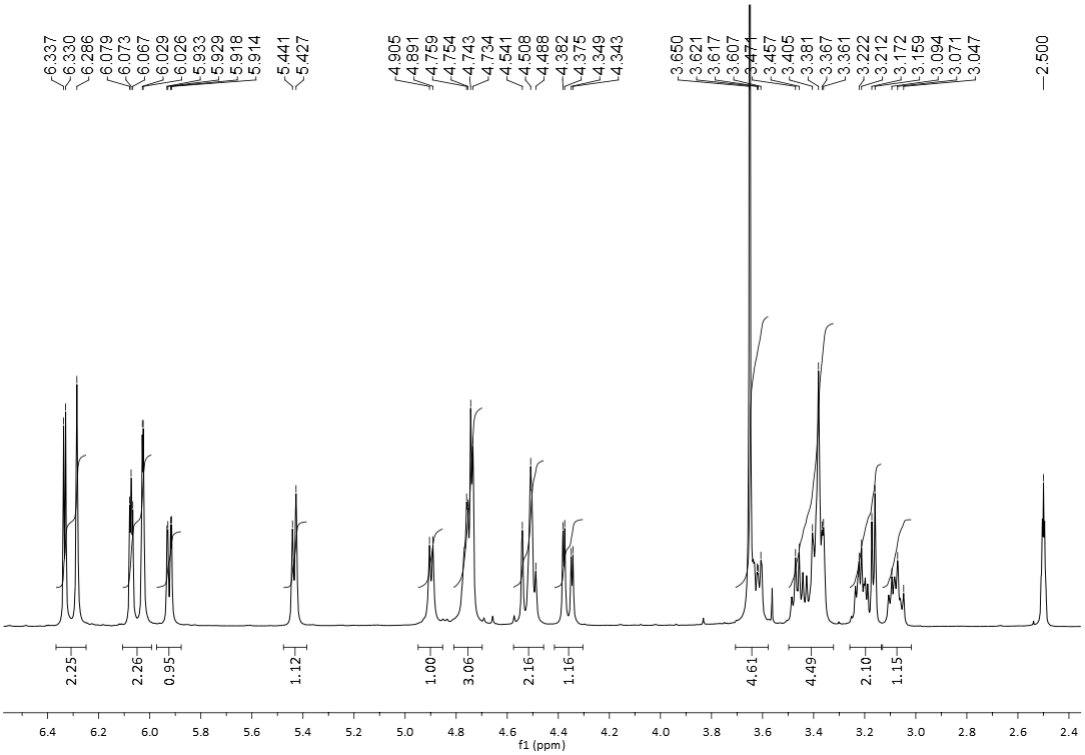
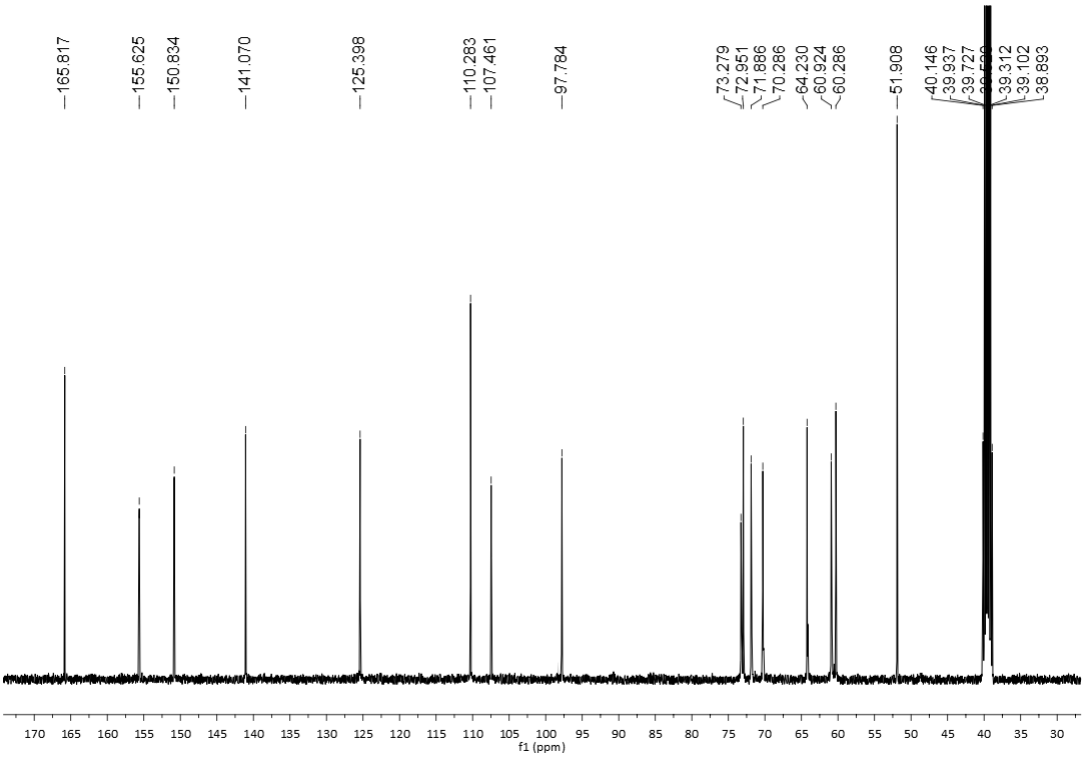


(298a)





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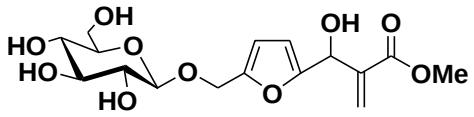
Methyl 2-[hydroxy-(5-(β-D-glucopyranosyloxymethyl)-furan-2-yl)methyl]acrylate (298b)



(298b)

Pale-yellow gum (125mg, 63% yield)

^{1}H NMR (400 MHz, CD_3OD): 3.22 (2d, 1H, J = 8.4 Hz, H-2'), 3.26~3.35 (m, 3H, H-3', H-4', H-5'), 3.68 and 3.71 (2d, 1H, J = 5.2 Hz, H-6'), 3.73 (s, 3H, $CO_2C\underline{H}_3$), 3.88 and 3.91 (2s, 1H, H-6'), 4.35 and 4.37 (2s, 1H, H-1'), 4.63 and 4.66 (2s, 1H, H-6), 4.78 and 4.82 (2d, 1H, J = 2.8 Hz, H-6), 5.60 (s, 1H, H-7), 6.09 (s, 1H, H-9), 6.17 and 6.18 (2s, 1H, H-3), 6.37 and 6.38 (2s, 1H, H-4), 6.40 (s, 1H, H-9);

^{13}C NMR (100 MHz, CD_3OD): 52.4 ($CO_2\underline{C}H_3$), 62.7 (C-6), 63.5 (C-6'), 66.3 (C-7), 71.5 (C-4'), 74.9 (C-2'), 77.9 (C-3'), 77.9 (C-5'), 102.7 and 102.8 (C-1'), 108.9 and 108.9 (C-3), 111.7 (C-4), 126.3 (C-9), 142.1 (C-8), 152.3 and 152.3 (C-5), 156.5 and 156.6 (C-2), 167.6 ($\underline{C}O_2CH_3$);

IR (cm^{-1}): 3885, 2919, 1718, 1650, 1636, 1438, 1406, 1347, 1270, 1199, 1140, 1109, 1019, 950, 814, 712;

$[\alpha]_D$ = - 40 (c = 1.0, CH_3OH);

HRMS m/z (ESI) calculated for $C_{16}H_{22}NaO_{10}$, $[M + Na]^+$ 397.1105; found 397.1110.

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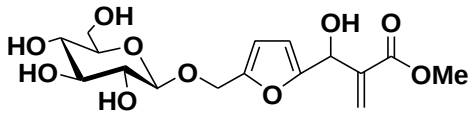
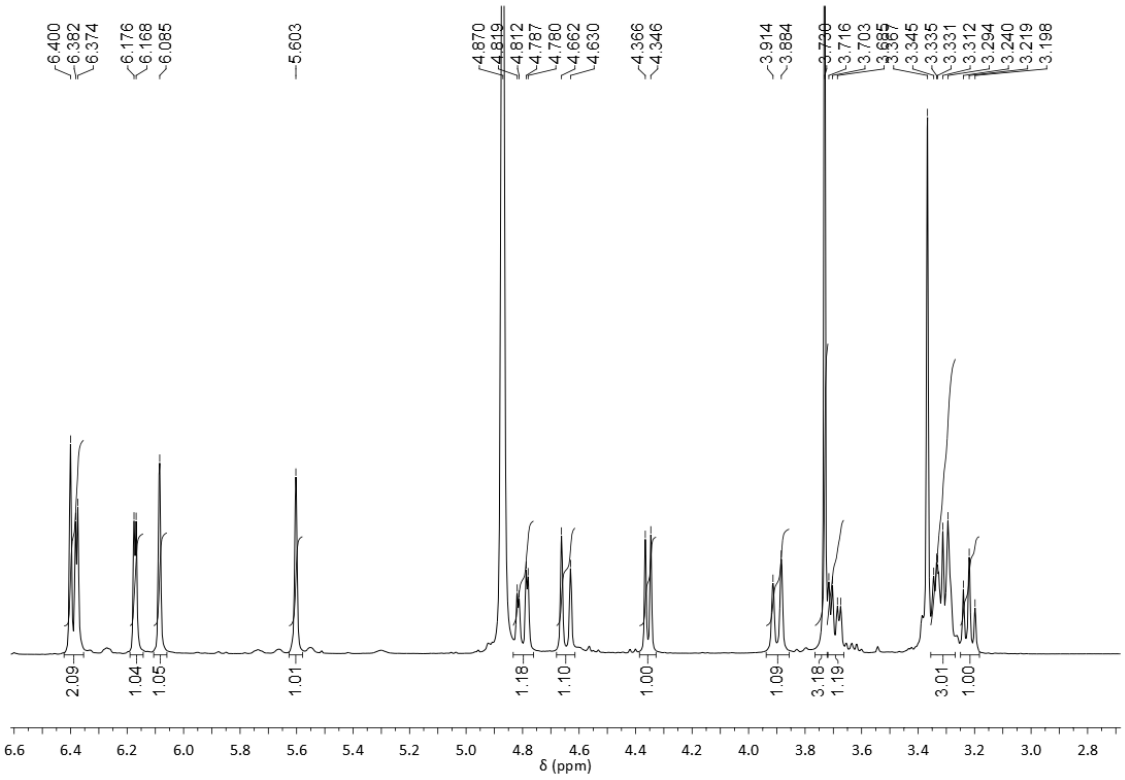
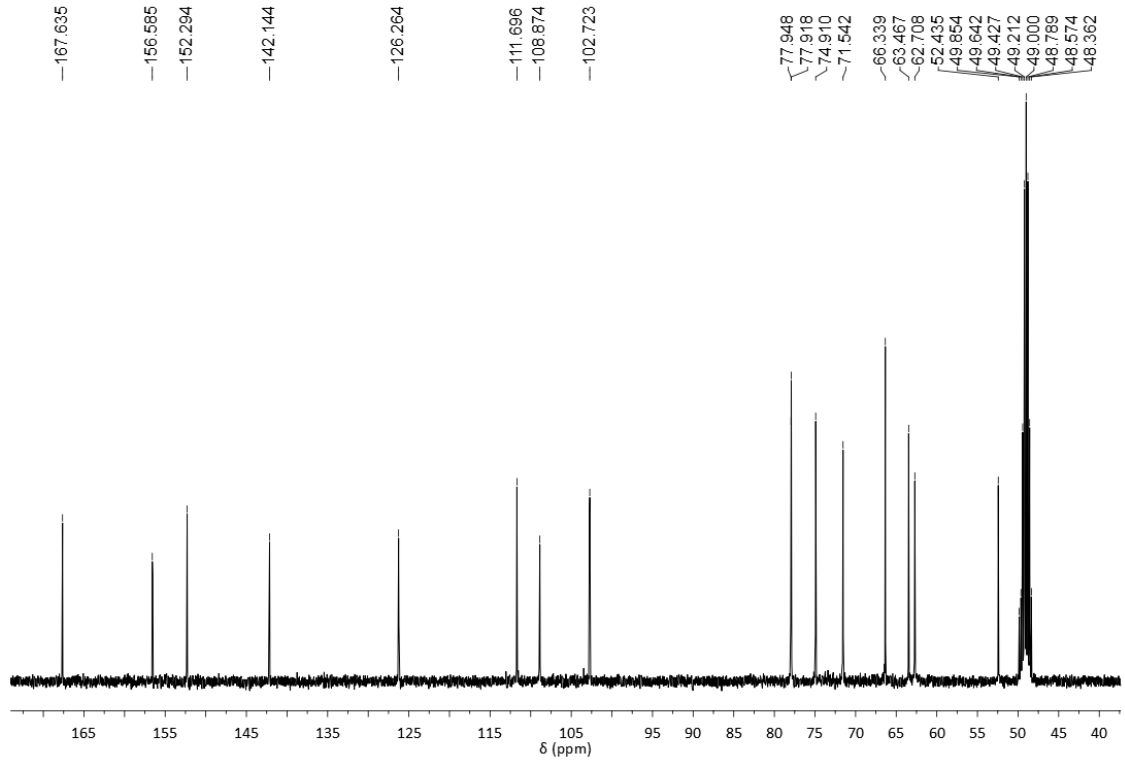


(298b)





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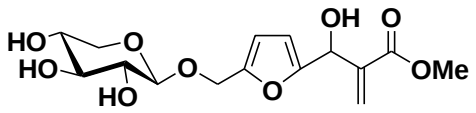
Methyl2-[hydroxy-(5-(α-D-xylopyranosyloxymethyl)-furan-2-yl)-furan-2-yl)meth--yl]acrylate (298c)



(298c)

Pale-yellow gum (113mg, 62% yield)

^{1}H NMR (400 MHz, CD_3OD): 3.20~3.30 (m, 2H, H-2'+ H-5'), 3.36 and 3.38 (2s, 1H, H-3'), 3.57(2dd, 1H, J = 10.4 Hz, H-4'), 3.78 (s, 3H, $CO_2C\underline{H}_3$), 3.92 and 3.95 (2d, 1H, J = 5.6 Hz, H-5'), 4.35 and 4.36 (2d, 1H, J = 1.2 Hz, H-1'), 4.63 (part A, AB system, 1H, J = 12.8 Hz, H-6), 4.77 (part B, AB system, 1H, J = 12.8 Hz, H-6), 5.65 (s, 1H, H-7), 6.13 (2d, 1H, J = 1.2 Hz, H-9), 6.22 and 6.23 (2s, 1H, H-3), 6.41 (2s, 1H, H-4), 6.45 (s, 1H, H-9);

^{13}C NMR (100 MHz, CD_3OD): 52.5 ($CO_2\underline{C}H_3$), 63.4, 63.4 (C-6), 66.2 (C-7), 66.7 (C-5'), 71.0 (C-4'), 74.6 (C-2'), 77.5 (C-3'), 103.4 (C-1'), 108.9, 108.9 (C-3), 111.6, 111.6 (C-4), 126.4 (C-9), 141.9, 141.9 (C-8), 152.1, 152.1 (C-5), 156.4, 156.5 (C-2), 167.6 ($\underline{C}O_2CH_3$);

IR (cm^{-1}): 3880, 2916, 1716, 1657, 1630, 1438, 1406, 1347, 1279, 1201, 1144, 1105, 1021, 953, 815, 717;

$[\alpha]_D$ = - 48 (c = 1.0, CH_3OH);

HRMS m/z (ESI) calculated for $C_{15}H_{20}NaO_9$, $[M + Na]^+$ 367.1000; found 367.1010.

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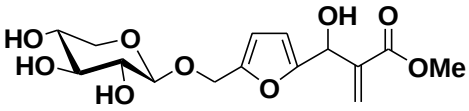
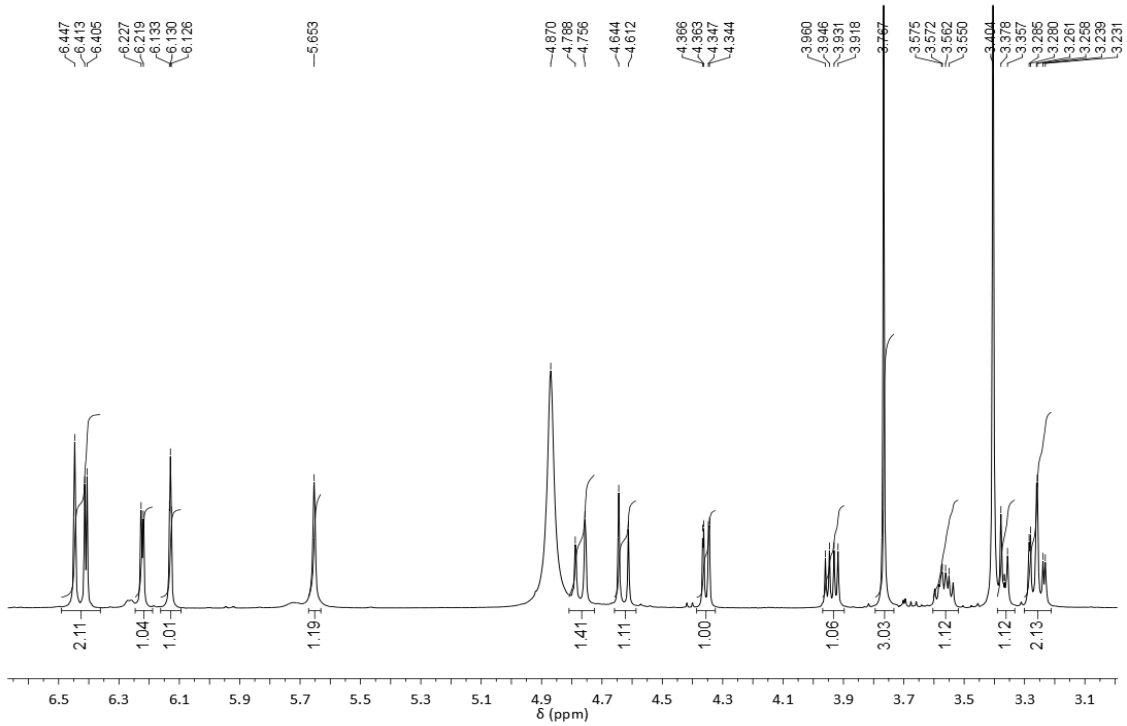
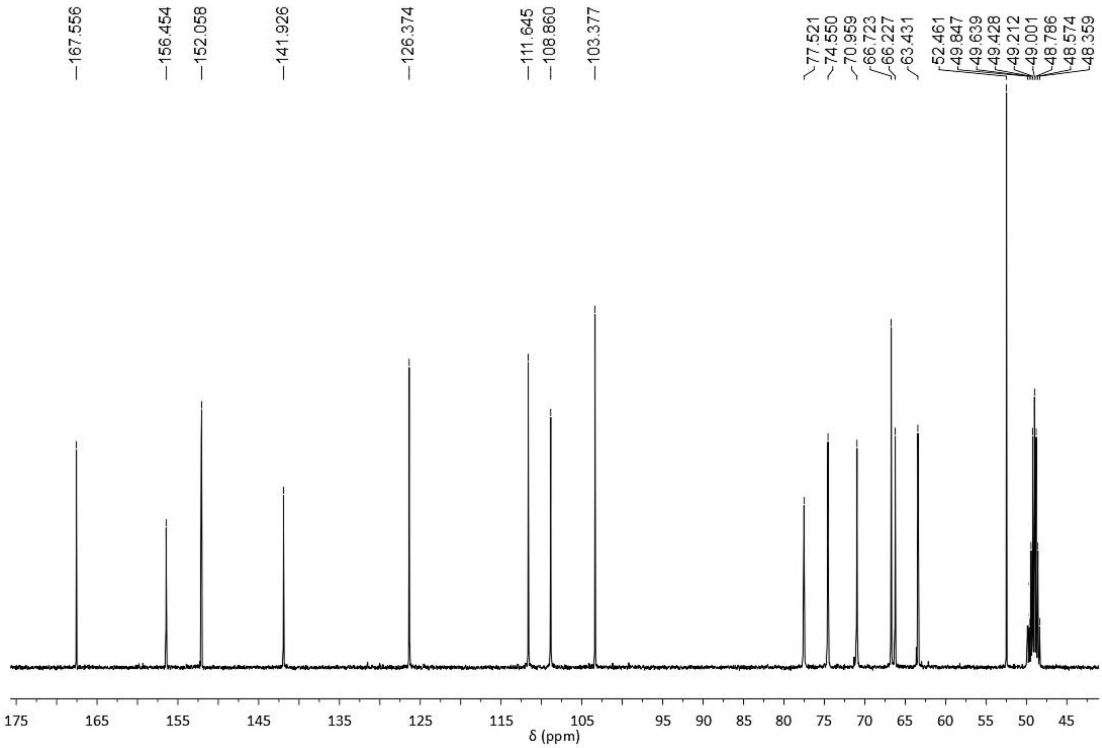


(298c)





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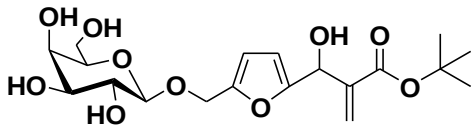
tert-Butyl 2-[hydroxy-(5-(β-D-galactopyranosyloxymethyl)-furan-2-yl)methyl]--acrylate (298d)



(298d)

Pale-yellow gum (103 mg, 47% yield)

^{1}H NMR (400 MHz, CD_3OD): 1.43 (s, 9H, OC(C<u>H</u>$_3$)$_3$), 3.33 (s, 1H, OH), 3.49 and 3.46 (2d, 1H, J = 2.8 Hz, H-3'), 3.50~3.59 (m, 2H, H-2' + H-5'), 3.71~3.84 (m, 2H, H-6'), 3.85 and 3.86 (2s, 1H, H-4'), 4.31 and 4.32 (2s, 1H, H-1'), 4.65 (part A, AB system, 1H, J = 12.8 Hz, H-6), 4.78~4.84 (part B, AB system,, 1H, J_a = 2.0 Hz, J_b = 12.8 Hz, H-6), 5.54 (s, 1H, H-7), 6.00 (2s, 1H, H-9), 6.15 (2d, 1H, J = 0.8 Hz, H-3), 6.29 (s, 1H, H-9), 6.38 and 6.39 (2s, 1H, H-4);

^{13}C NMR (100 MHz, CD_3OD): 28.2 (OC(<u>C</u>H$_3$)$_3$), 62.5 (C-6'), 63.4 (C-6), 66.5 (C-7), 70.3 (C-4'), 72.4 (C-2'), 74.9 (C-3'), 76.7 (C-5'), 82.3 (O<u>C</u>(CH$_3$)$_3$), 103.4, 103.4 (C-1'), 108.7, 108.7 (C-3), 111.6 (C-4), 124.8 (C-9), 143.8 (C-8), 152.2, 152.3 (C-5), 156.9, 156.9 (C-2), 166.5 (<u>C</u>=O);

IR (cm^{-1}): 3887, 2981, 2942, 1720, 1639, 1627, 1480, 1468, 1403, 1394, 1369, 1305, 1294, 1267, 1221, 1161, 1051, 1038, 987, 965, 928, 847, 819, 757;

$[\alpha]_D$ = - 31 (c = 1.0, CH_3OH);

HRMS m/z (ESI) calculated for $C_{19}H_{28}NaO_{10}$, $[M + Na]^+$ 439.1575; found 439.1573.

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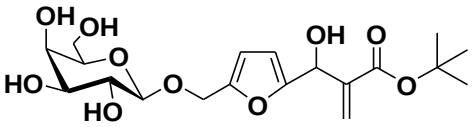
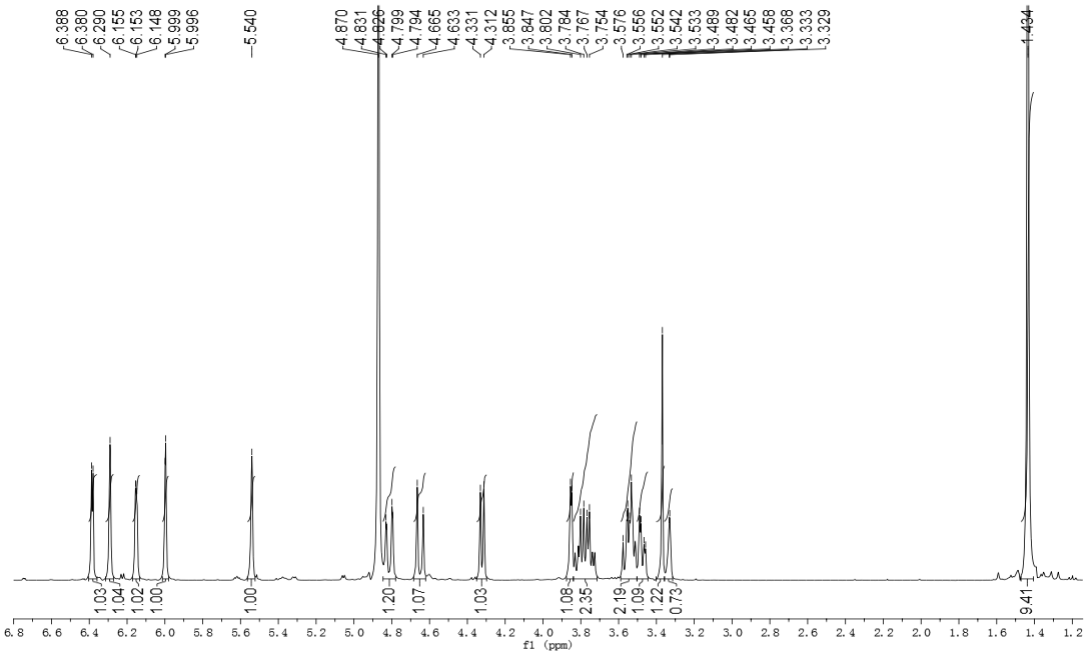
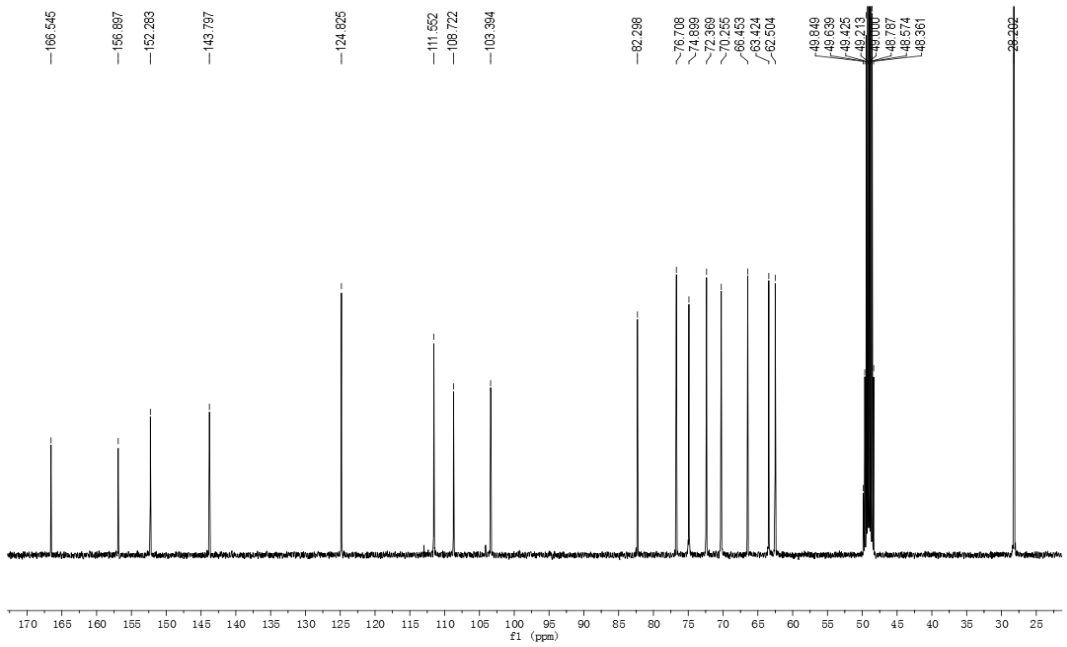


(298d)





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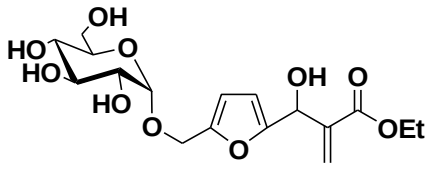
Ethyl 2-[hydroxy-(5-(α-D-glucopyranosyloxymethyl)-furan-2-yl)methyl]acrylate (298e)



(298e)

Pale-yellow gum (134 mg, 65% yield)

^{1}H NMR (400 MHz, CD_3OD): 1.26 (t, 3H, J = 7.2 Hz, $OCH_2C\underline{H}_3$), 3.32 and 3.35 (2s, 1H, H-4'), 3.42 and 3.45 (2d, 1H, J = 4.0 Hz, H-2'), 3.60~3.75 (m, 3H, H-3', H-5', H-6'), 3.81 and 3.83 (2d, 1H, J = 2.4 Hz, H-6'), 4.05~4.20 (m, 1H, $OC\underline{H}_2CH_3$), 4.55 (part A, AB system, 1H, J = 13.2 Hz, H-6), 4.67 (part B, AB system, 1H, J = 13.2 Hz, H-6), 4.92 and 4.93 (2d, 1H, H-1'), 5.61 (s, 1H, H-7), 6.09 (2s, 1H, H-9), 6.16 (2s, 1H, H-3), 6.38 and 6.39 (2s, 1H, H-4), 6.40 (s, 1H, H-9);

^{13}C NMR (100 MHz, CD_3OD): 14.4 ($CH_2\underline{C}H_3$), 61.9 ($CO_2\underline{C}H_3$), 62.1 (C-6), 62.5 (C-6'), 66.3, 66.3 (C-7), 71.6 (C-4'), 73.3 (C-2'), 73.7 (C-5'), 74.9 (C-3'), 99.0, 99.1 (C-1'), 108.8 (C-3), 111.4, 111.5 (C-4), 126.0 (C-9), 142.4 (C-8), 152.3, 152.4 (C-5), 156.6 (C-2), 167.2 ($\underline{C}O_2C_2H_5$);

IR (cm^{-1}): 3880, 2917, 1715, 1654, 1636, 1438, 1406, 1340, 1270, 1203, 1148, 1105, 1010, 953, 819, 708;

$[\alpha]_D$ = + 65 (c = 1.0, CH_3OH);

HRMS m/z (ESI) calculated for $C_{17}H_{24}NaO_{10}$, $[M + Na]^+$ 411.1262; found 411.1259.

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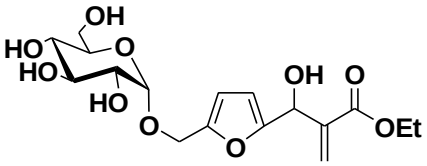
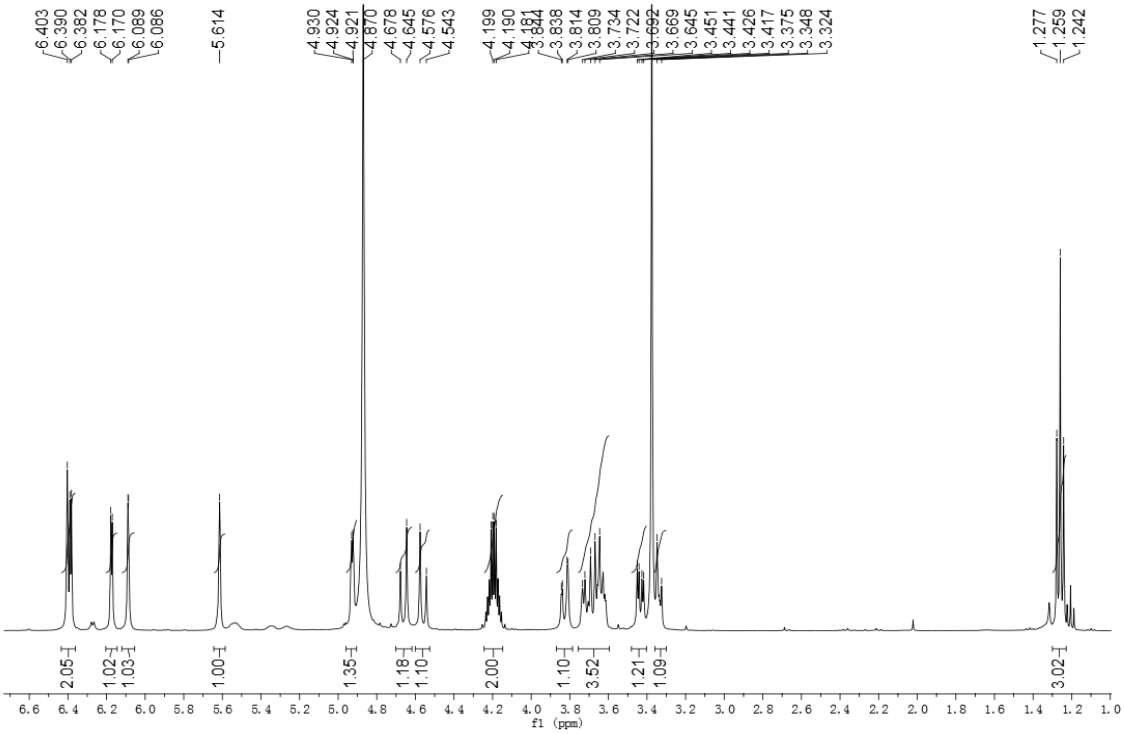
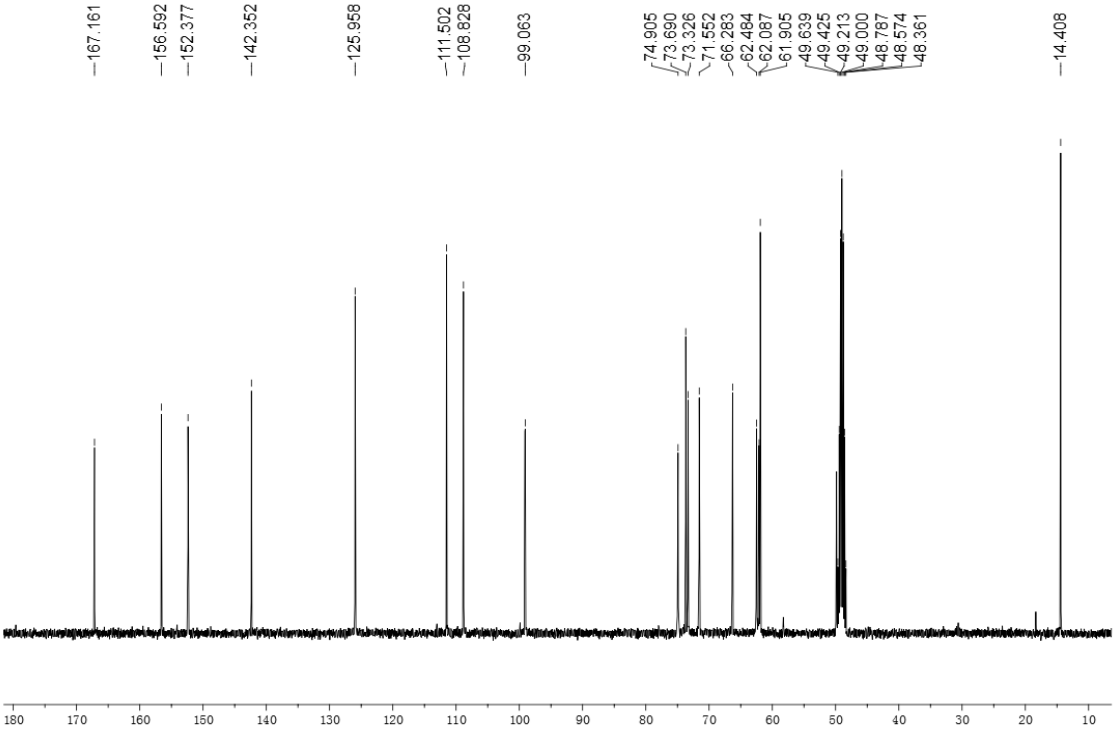


(298e)





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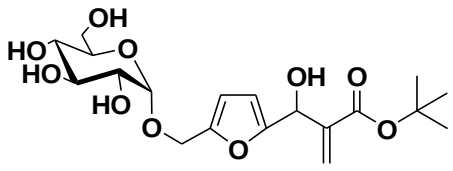
tert-Butyl 2-[hydroxy-(5-(α-D-glucopyranosyloxymethyl)-furan-2-yl)methyl] acrylate (298g)



(298g)

Pale-yellow gum (124 mg, 56% yield)

^{1}H NMR (400 MHz, DMSO): 1.35 (s, 9H, OC(C<u>H</u>$_3$)$_3$), 3.03~3.12 (m, 1H, H-4'), 3.16~3.25 (m, 1H, H-2'), 3.31~3.52 (m, 5H, H-3', H-5', H-6', O<u>H</u>), 3.64 and 3.60 (2dd, 1H, J_a = 5.6 Hz, J_b = 11.2 Hz, H-6'), 4.34 and 4.38 (2s, 1H, H-6), 4.46~4.56 (m, 2H, H-6+O<u>H</u>), 4.69~4.77 (m, 3H, H-1', 2OH), 4.88 and 4.89 (2s, 1H, O<u>H</u>), 5.36 and 5.36 (2s, 1H, H-7), 5.85 and 5.86 (2d, 1H, J = 0.8 Hz, O<u>H</u>), 5.92 (s, 1H, H-9), 6.04 and 6.05 (2d, 1H, J = 3.2 Hz, H-3), 6.16 (s, 1H, H-9), 6.34 and 6.35 (2s, 1H, H-4);

^{13}C NMR (100 MHz, DMSO): 27.6 (OC(<u>C</u>H$_3$)$_3$), 60.2 (C-6), 60.9 (C-6'), 64.3 (C-7), 70.2 (C-4'), 71.8 (C-2'), 73.0 (C-5'), 73.2 (C-3'), 80.4 (O<u>C</u>(CH$_3$)$_3$), 97.7 (C-1'), 107.1, 107.1 (C-3), 110.2 (C-4), 123.9 (C-9), 142.7 (C-8), 150.5, 150.5 (C-5), 156.0, 156.0 (C-2), 164.6 (<u>C</u>=O);

IR (cm^{-1}): 3885, 2981, 2936, 1722, 1637, 1620, 1480, 1468, 1403, 1394, 1369, 1300, 1294, 1267, 1221, 1161, 1051, 1038, 987, 965, 928, 850, 812, 757;

$[\alpha]_D$ = + 85 (c = 1.0, CH$_3$OH);

HRMS m/z (ESI) calculated for $C_{19}H_{28}NaO_{10}$, $[M + Na]^+$ 439.1575; found 439.1554.

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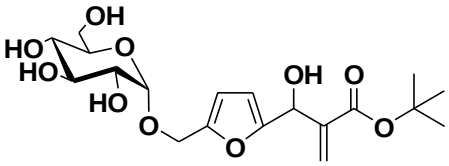
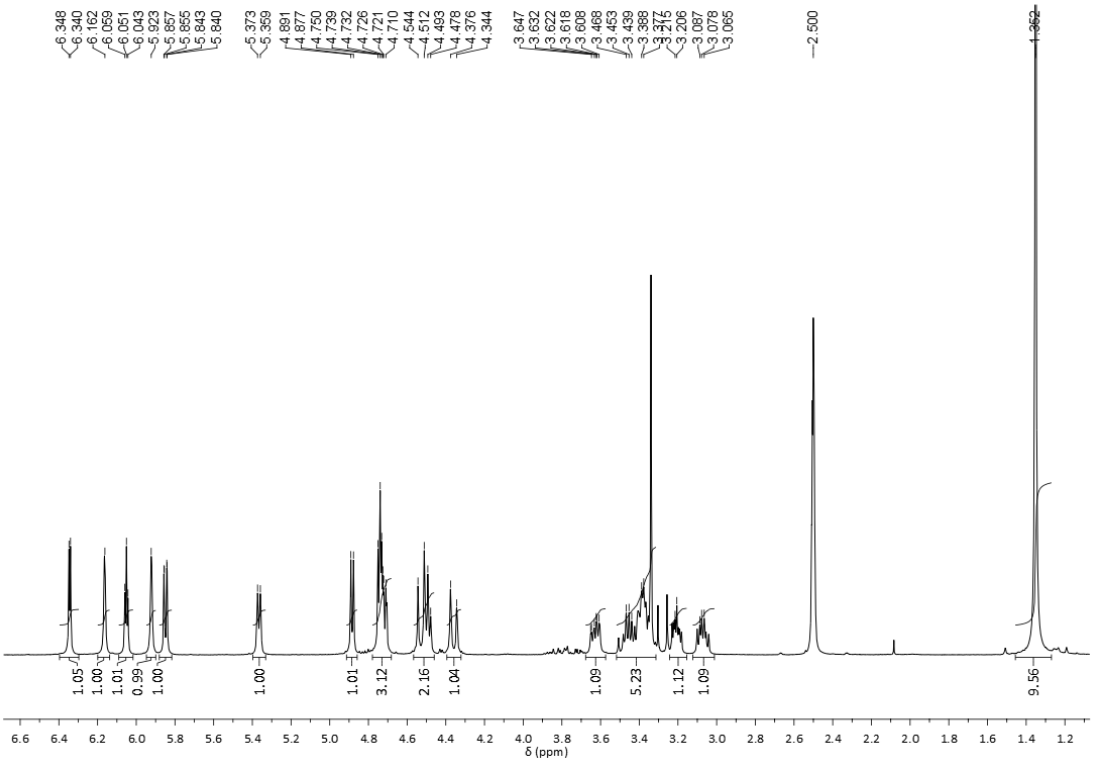
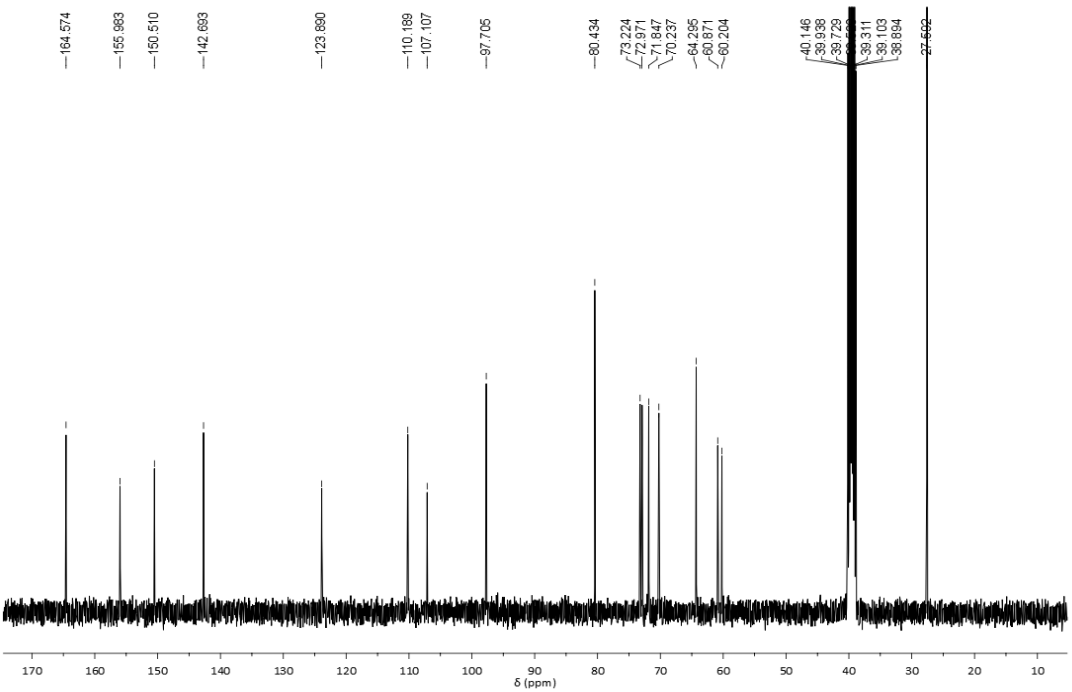


(298g)





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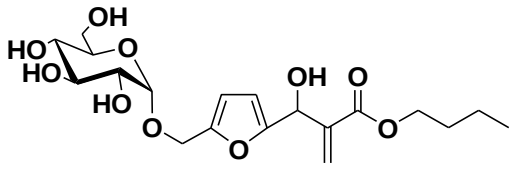
Butyl 2-[hydroxy-(5-(α-D-glucopyranosyloxymethyl)-furan-2-yl)methyl]acrylate (298f)



(298f)

Pale-yellow gum (131 mg, 60% yield)

^{1}H NMR (400 MHz, CD_3OD): 0.95 (t, 3H, J = 7.2 Hz, $OCH_2CH_2CH_2C\underline{H}_3$), 1.30~1.40 (m, 2H, $OCH_2CH_2C\underline{H}_2CH_3$), 1.56~1.66 (m, 2H, $OCH_2C\underline{H}_2CH_2CH_3$), 3.32 and 3.35 (2s, 1H, H-4'), 3.42 and 3.45 (2d, 1H, J = 3.6 Hz, H-2'), 3.60~3.75 (m, 3H, H-3', H-5', H-6'), 3.81 and 3.84 (2s, 1H, H-6'), 4.05~4.20 (m, 1H, $OC\underline{H}_2(CH_2)_2CH_3$), 4.55 (part A, AB system, 1H, J = 12.8 Hz, H-6), 4.66 (part B, AB system, 1H, J = 12.8 Hz, H-6), 4.92 and 4.93 (2d, 1H, J = 3.6 Hz, H-1'), 5.61 (s, 1H, H-7), 6.09 (2s, 1H, H-9), 6.16 (2s, 1H, H-3), 6.38 and 6.39 (2s, 1H, H-4), 6.40 (s, 1H, H-9b);

^{13}C NMR (100 MHz, CD_3OD): 14.0 ($OCH_2(CH_2)_2\underline{C}H_3$) 20.0, 31.6 ($OCH_2(\underline{C}H_2)_2CH_3$), 62.1 (C-6'), 62.5 (C-6), 65.6 ($O\underline{C}H_2(CH_2)_2CH_3$), 66.3, 66.3 (C-7), 71.5 (C-4'), 73.3 (C-2'), 73.7 (C-5'), 74.9 (C-3'), 99.0, 99.1 (C-1'), 108.8 (C-3), 111.4, 111.5 (C-4), 126.3 0(C-9), 142.3 (C-8), 152.3, 152.4 (C-5), 156.6 (C-2), 167.2 ($\underline{C}O_2$);

IR (cm^{-1}): 3885, 2987, 2940, 1722, 1638, 1620, 1480, 1468, 1413, 1394, 1369, 1299, 1294, 1267, 1221, 1161, 1051, 1038, 953, 928, 819, 757;

$[\alpha]_D$ = + 91 (c = 1.0, CH_3OH);

HRMS m/z (ESI) calculated for $C_{19}H_{28}NaO_{10}$, $[M + Na]^+$ 439.1575; found 439.1561.

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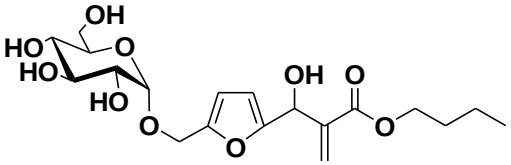
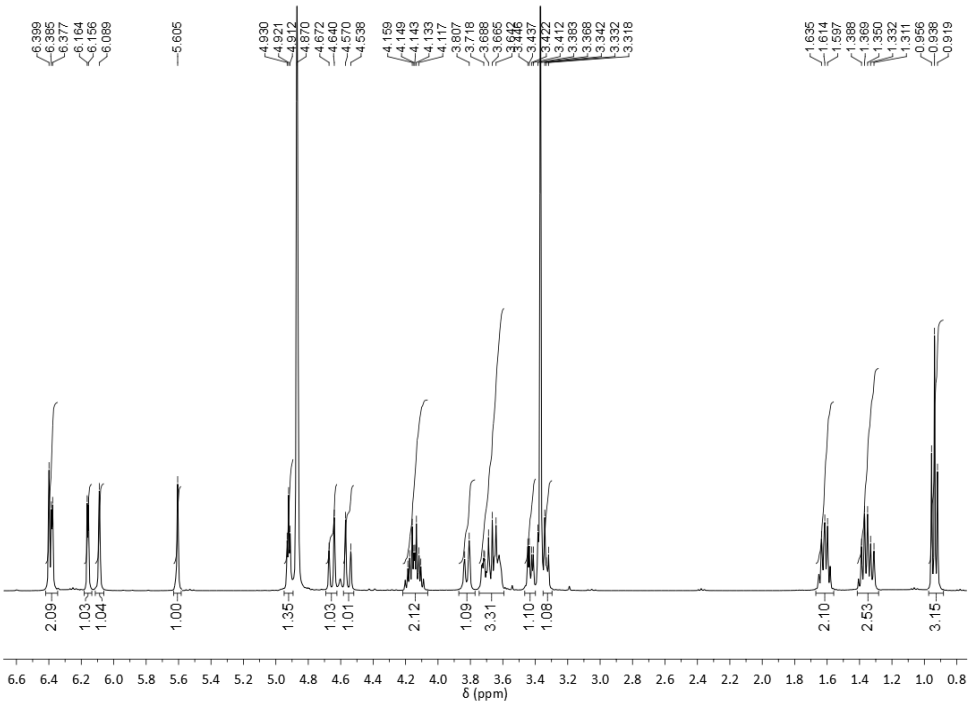
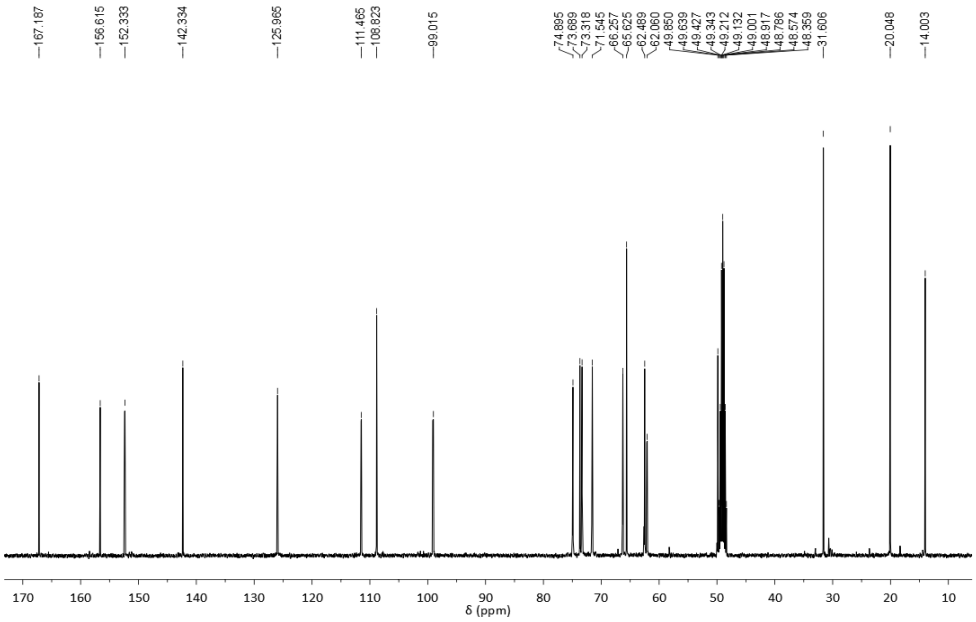


(298f)





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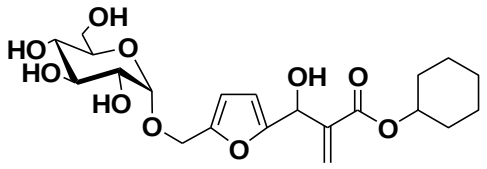
Cyclohexyl 2-[hydroxy-(5-(α-D-glucopyranosyloxymethyl)-furan-2-yl)--methyl]acrylate (298h)



(298h)

Pale-yellow gum (118 mg, 51% yield)

^{1}H NMR (400 MHz, DMSO): 1.20~1.77 (m, 10H, OCH(C<u>H</u>$_2$)$_5$), 3.03~3.12 (m, 1H, H-4'), 3.17 and 3.24 (m, 1H, H-2'), 3.33~3.43 (m, 3H, H-3', H-5', O<u>H</u>), 3.45 and 3.48 (2d, 1H, J_a = 6.0 Hz, H-6'), 3.61 and 3.65 (2d, 1H, J = 5.6 Hz, H-6'), 4.37 and 4.34 (2d, 1H, J = 1.6 Hz, H-6), 4.46~4.56 (m, 2H, H-6 + O<u>H</u>), 4.67~4.78 (m, 4H, H-1', OC<u>H</u>(CH$_2$)$_5$, 2OH), 4.88 and 4.89 (s, 1H, O<u>H</u>), 5.42 and 5.43 (2s, 1H, H-7), 5.89 and 5.90 (2d, 1H, J = 1.2 Hz, O<u>H</u>), 6.00 (2s, 1H, H-9), 6.05 (2d, 1H, J = 3.2 Hz, H-3), 6.26 (s, 1H, H-9), 6.33 and 6.34 (2s, 1H, H-4);

^{13}C NMR (100 MHz, DMSO): 22.7, 22.8, 24.9, 30.7, 30.8 (OCH(<u>C</u>H$_2$)$_5$), 60.2 (C-6), 60.9 (C-6'), 64.3 (C-7), 70.3 (C-4'), 71.9 (C-2'), 72.0 (O<u>C</u>H(CH$_2$)$_5$), 72.9 (C-5'), 73.3 (C-3'), 97.7, 97.7 (C-1'), 107.2, 107.3 (C-3), 110.2 (C-4), 124.7 (C-9), 141.7 (C-8), 150.6, 150.7 (C-5), 155.8, 155.8 (C-2), 164.6 (<u>C</u>=O);

IR (cm^{-1}): 3885, 2938, 1723, 1638, 1620, 1461, 1406, 1370, 1318, 1296, 1276, 1197, 1155, 1126, 1054, 1040, 1017, 985, 962, 811;

$[\alpha]_D$ = + 76 (c = 2.5, CH$_3$OH);

HRMS m/z (ESI) calculated for $C_{21}H_{30}NaO_{10}$, $[M + Na]^+$ 465.1731; found 465.1716.

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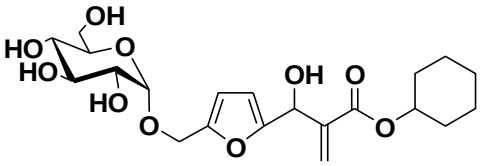
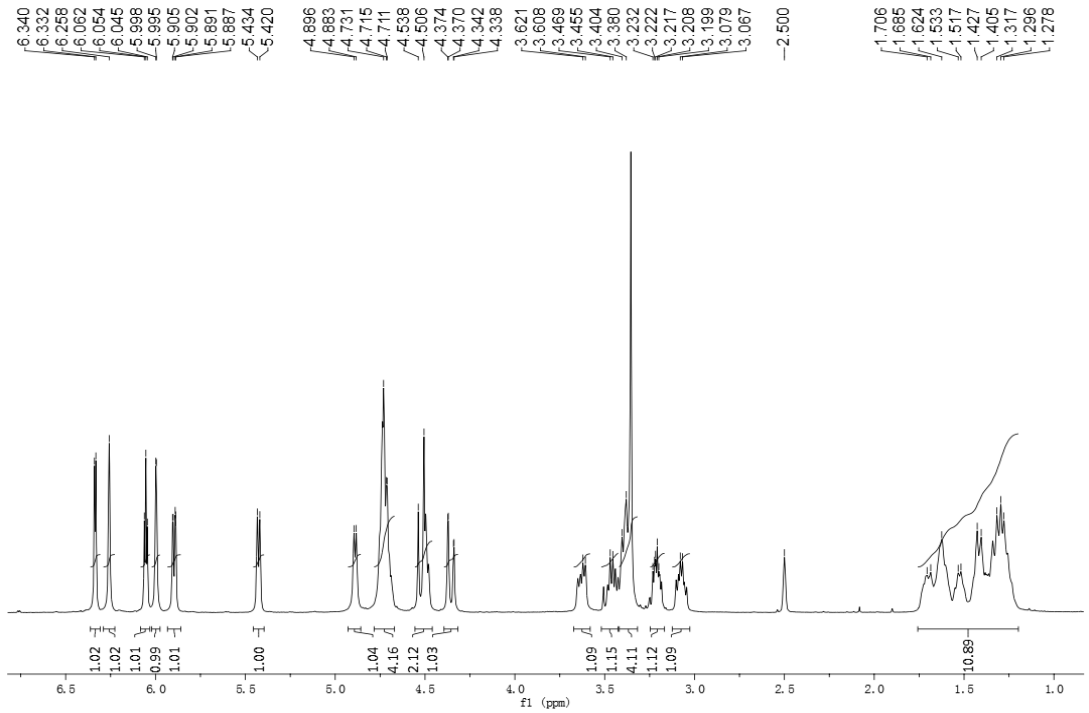
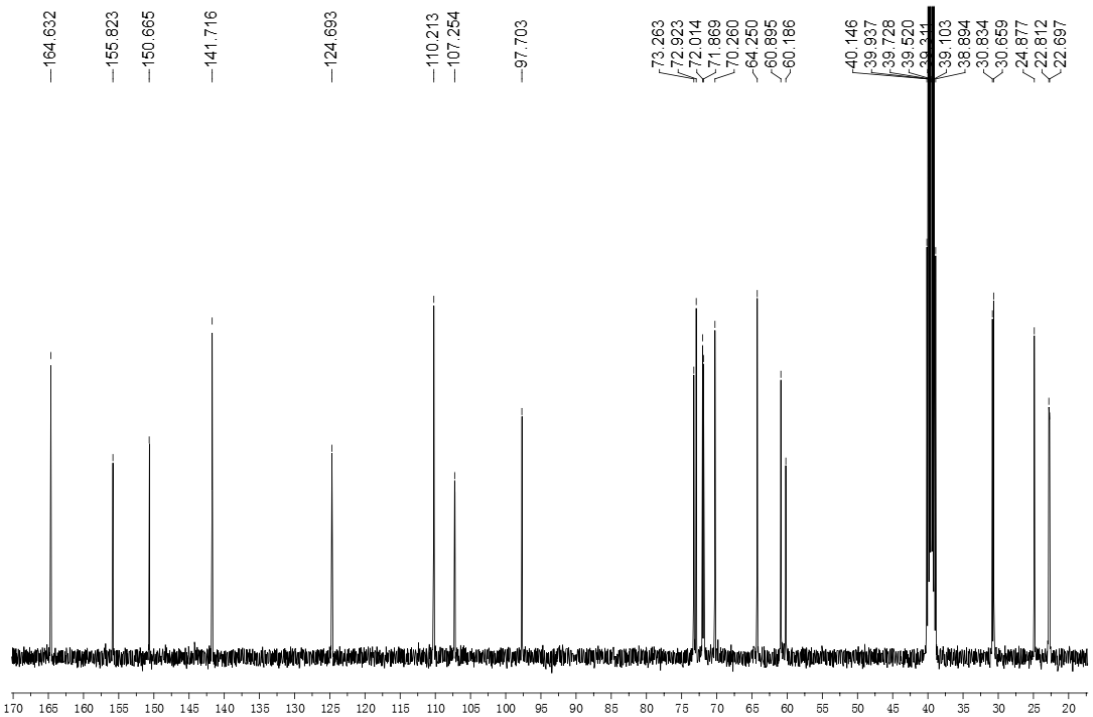


(298h)





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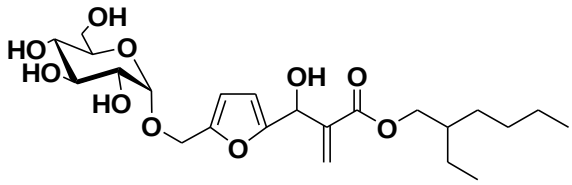
Ethylhexyl 2-[hydroxy-(5-(α-D-glucopyranosyloxymethyl)-furan-2-yl)--methyl]acrylate (298l)



(298l)

Pale-yellow gum (141 mg, 57% yield)

^{1}H NMR (400 MHz, DMSO): 0.83 (m, 6H, $CH(CH_2C\underline{H}_3)(CH_2)_3C\underline{H}_3$), 1.21 (m, 8H, $CH(C\underline{H}_2CH_3)(C\underline{H}_2)_3CH_3$), 1.50 (2s, 1H, $C\underline{H}(CH_2CH_3)(CH_2)_3CH_3$), 3.04~3.12 (m, 1H, H-4'), 3.17~3.27 (m, 1H, H-2'), 3.35~3.43 (m, 3H, H-3', H-5', O$\underline{H}$), 3.43~3.50 (m, 1H, H-6'a), 3.62 and 3.65 (2d, 1H, J = 2.4 Hz, H-6'), 3.89~4.06 (m, 1H, $CO_2C\underline{H}_2$), 4.34 and 4.37 (2s, 1H, H-6), 4.46~4.56 (m, 2H, H-6 + O$\underline{H}$), 4.70~4.78 (m, 3H, H-1', 2OH), 4.88 and 4.89 (2d, 1H, J = 2.4 Hz, O$\underline{H}$), 5.42 and 5.43 (2s, 1H, H-7), 5.90 and 5.91 (2d, 1H, J = 2.0 Hz, O$\underline{H}$), 6.00~6.06 (m, 2H, H-9+H-3), 6.28 (s, 1H, H-9), 6.33 and 6.34 (2s, 1H, H-4);

^{13}C NMR (100 MHz, DMSO): 10.9, 14.0, 22.4, 23.2, 28.3, 29.8, 38.2 ($\underline{C}H(\underline{C}H_2\underline{C}H_3)(\underline{C}H_2)_3\underline{C}H_3$), 60.2 (C-6), 60.9 (C-6'), 64.2 (C-7), 66.2 ($CO_2\underline{C}H_2$), 70.2 (C-4'), 71.9 (C-2'), 72.9 (C-5'), 73.2 (C-3'), 97.7, 97.8 (C-1'), 107.3, 107.3 (C-3), 110.1, 110.2 (C-4), 125.1 (C-9), 141.3 (C-8), 150.8, 150.8 (C-5), 155.7, 155.8 (C-2), 165.3 ($\underline{C}$=O);

IR (cm^{-1}): 3885, 2940, 1720, 1654, 1450, 1405, 1316, 1270, 1180, 1147, 1100, 1070, 1053, 1005, 927, 815;

$[\alpha]_D$ = + 75 (c = 1.1, CH_3OH);

HRMS m/z (ESI) calculated for $C_{23}H_{36}NaO_{10}$, $[M + Na]^+$ 495.2201; found 495.2184.

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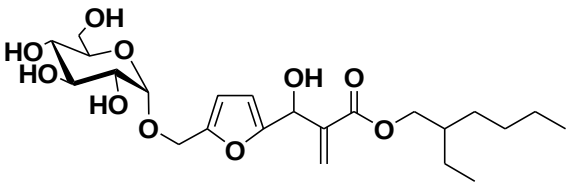
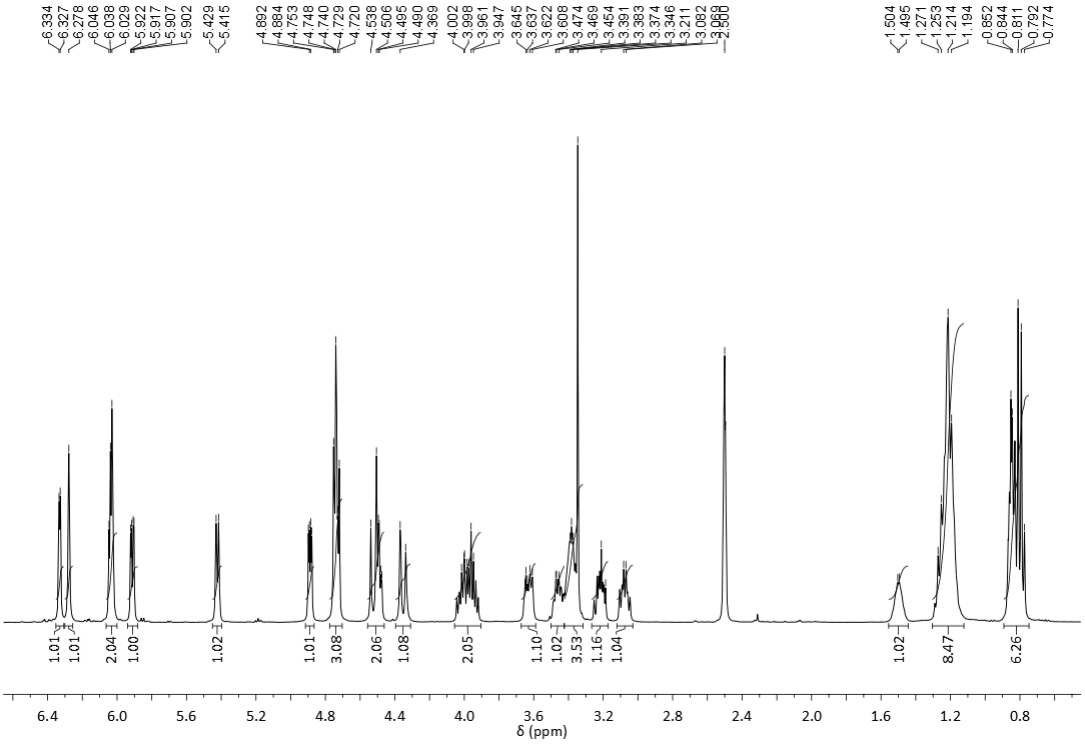
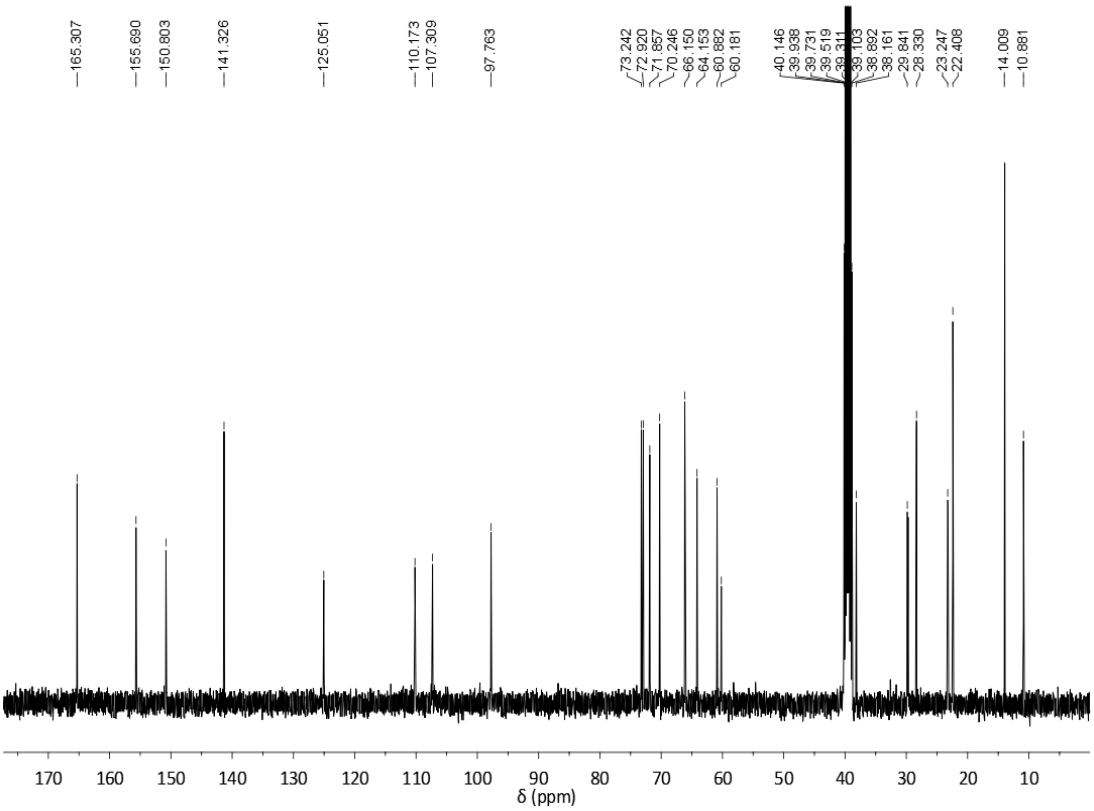


(298l)





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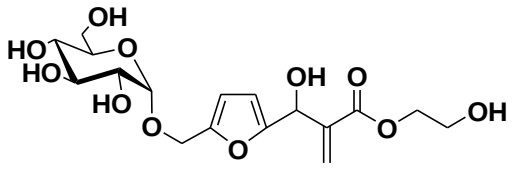
Hydroxyethyl 2-[hydroxy-(5-(α-D-glucopyranosyloxymethyl)-furan-2-yl)--methyl]acrylate (298i)



(298i)

Pale-yellow gum (149 mg, 35% yield)

^{1}H NMR (400 MHz, DMSO): 3.02~3.10 (m, 1H, H-4'), 3.15~3.25 (m, 1H, H-2'), 3.33~3.43 (m, 3H, H-3', H-5', O<u>H</u>), 3.45 (m, 1H, H-6'), 3.56 and 3.57 (2d, 2H, J = 5.2 Hz, $CH_2C\underline{H}_2OH$), 3.62 and 3.64 (2d, 1H, J = 5.6 Hz, H-6'), 4.07 (m, 2H, $CO_2C\underline{H}_2$), 4.34 and 4.37 (2d, 1H, J = 2.4 Hz, H-6), 4.46~4.57 (m, 2H, H-6 + O<u>H</u>), 4.70~4.80 (m, 3H, H-1', 2OH), 4.85 and 4.83 (2d, 1H, J = 5.6 Hz, O<u>H</u>), 4.90 and 4.91 (2s, 1H, O<u>H</u>), 5.45 and 5.45 (2s, 1H, H-7), 5.90 and 5.91 (2d, 1H, J = 1.6 Hz, O<u>H</u>), 6.03 (2s, 1H, H-9), 6.09 (2d, 1H, J = 2.8 Hz, H-3), 6.32(s, 1H, H-9), 6.33 and 6.34 (2s, 1H, H-4);

^{13}C NMR (100 MHz, DMSO): 58.9($CH_2\underline{C}H_2OH$), 60.2 (C-6), 60.9 (C-6'), 64.2 (C-7), 66.2 ($CO_2\underline{C}H_2$), 70.3 (C-4'), 71.8 (C-2'), 72.9 (C-5'), 73.2 (C-3'), 97.7, 97.7 (C-1'), 107.4, 107.4 (C-3), 110.2 (C-4), 125.3 (C-9), 141.2 (C-8), 150.7, 150.7 (C-5), 155.6, 155.6 (C-2), 165.4 (<u>C</u>=O);

IR (cm^{-1}): 3885, 2940, 1720, 1654, 1450, 1406, 1310, 1274, 1180, 1147, 1100, 1070, 1005, 920, 810;

$[\alpha]_D$ = + 105 (c = 0.8, CH_3OH);

HRMS m/z (ESI) calculated for $C_{17}H_{24}NaO_{11}$, $[M + Na]^+$ 427.1211; found 427.1199.

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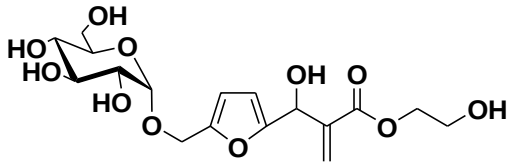
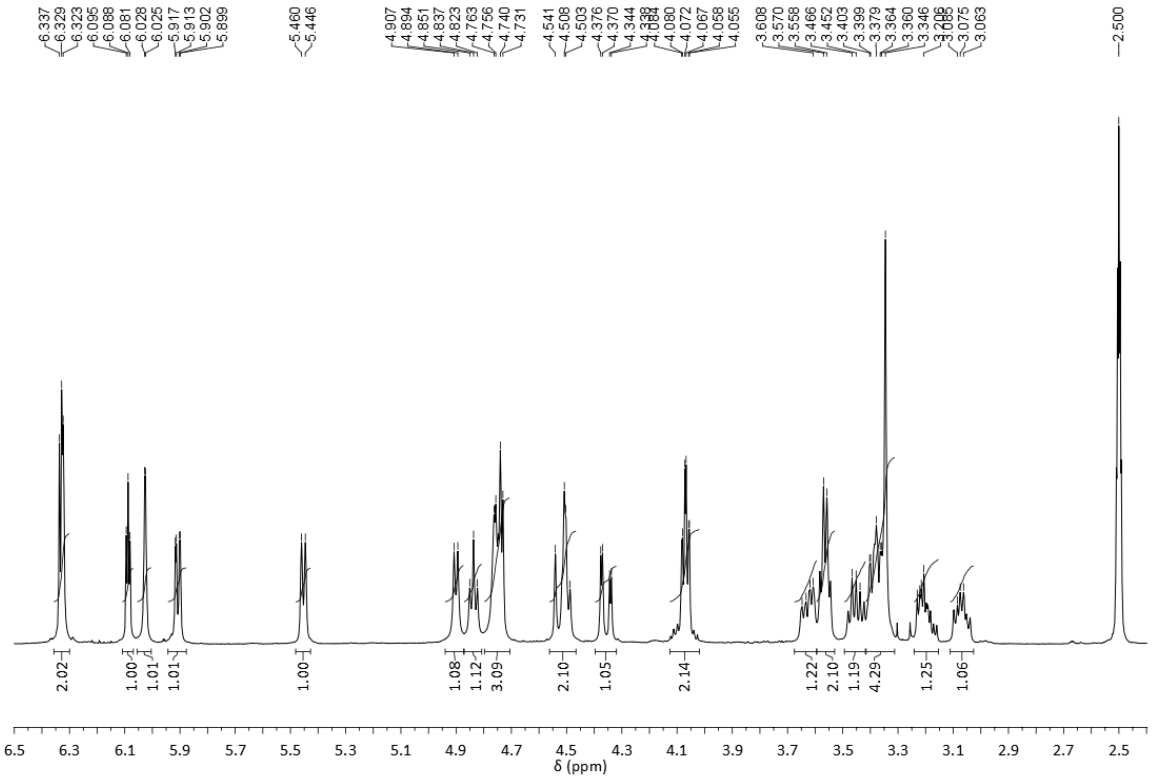
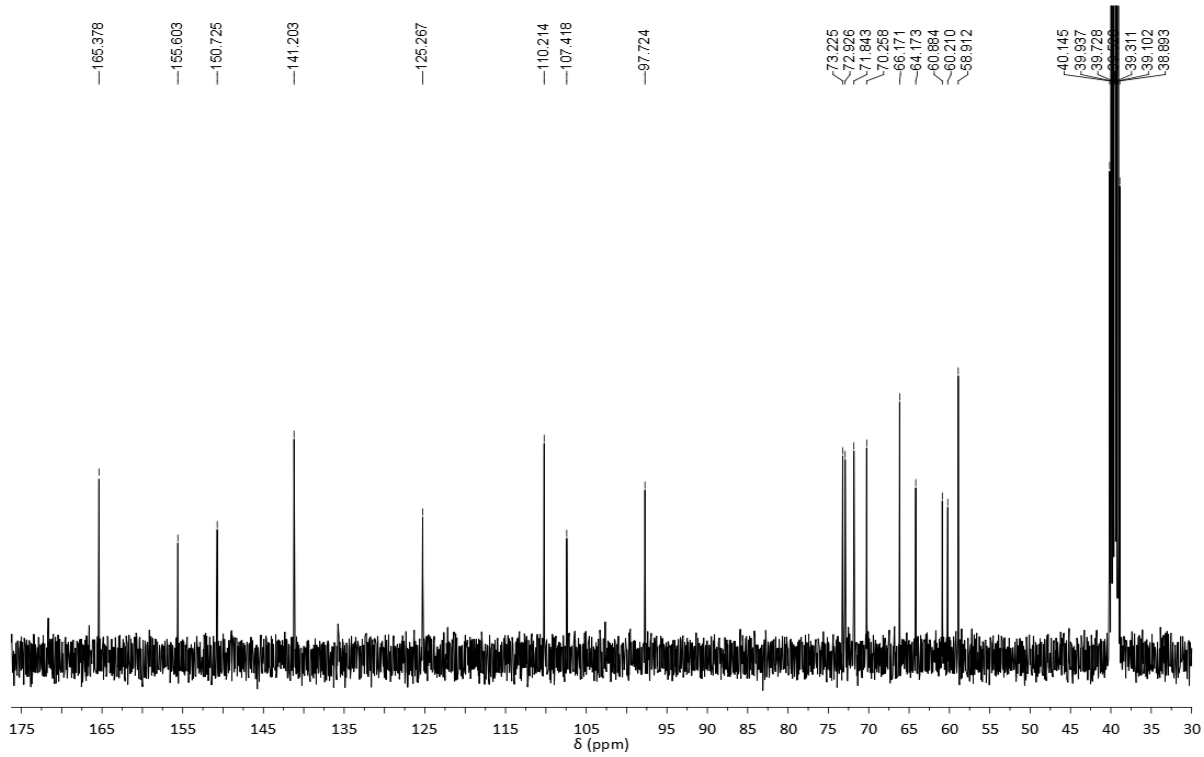


(298i)





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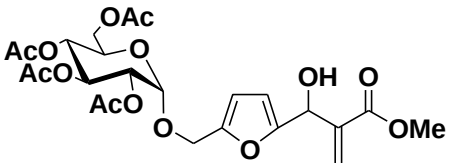
1.2.5 Typical procedure for Baylis-Hillman reaction of MVK with acetyl GMF in DMI:

All reactions were conducted in a 10 mL flask equipped with magnetic stirring. In a typical reaction, acetyl GMF (457 mg, 1.0 mmol) was mixed with DMAP (48 mg, 0.4 mmol), MVK (210 mg, 3.0 mmol) and DMI (2 mL) under air. And the reaction progress was monitored by TLC. Upon completion, the reaction mixture was extracted with CH_2Cl_2 (2 x10 mL), the organic phase was washed with brine (2 x 10 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated. The product was obtained by preparation TLC using a mixed solution of ethyl acetate and pentane (ethyl acetate/pentane: 1/2) as eluting solvent, give the desired product **300a** (273 mg, 52% yield). Products 300b-c were synthesized following the same manner as **300a.**

Methyl 2-[hydroxyl-(5-(2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyloxymethyl)--furan-2-yl) methyl] acrylate (300a)



(300a)

Pale-yellow gum (147 mg, 52% yield)

^{1}H NMR (400 MHz, $CDCl_3$): 6.40 and 6.41 (2d, 1H, *J* = 2.4 Hz, H-9); 6.28 and 6.29 (2d, 1H, *J* = 3.2 Hz, H-4); 6.19 and 6.20 (2d, 1H, *J* = 3.2 Hz, H-3); 6.03 and 6.05 (2dd, 1H, J_a = 1.2 Hz, J_b = 2.0 Hz H-9'); 5.55 and 5.57 ($2d_{br}$, 1H, *J* = 6.0 Hz, H-7); 5.46 and 5.47 (2dd, 1H, J_a = 1.2 Hz, J_b = 10.4 Hz, H-3'); 5.24 and 5.28 (2d, 1H, *J* = 3.6 Hz, H-1'); 5.06 (2dd, 1H, J_a = 2.0 Hz, J_b = 10.4 Hz, H-4'); 4.78 and 4.79 (2dd, 1H, J_a = 3.6 Hz, J_b = 10.4 Hz, H-2'); 4.53, 4.57 and 4.54, 4.58 (2d + 2d, 1H each, *J* = 13.2 Hz, H-6); 4.23 and 4.26 (2dd, 1H, J_a = 4.4 Hz, J_b = 11.6 Hz, H-6'); 4.09-4.02 (m, 2H, H-5'+ H-6'); 3.75 and 3.76 (2s, 3H, O-CH_3); 3.39 and 3.49 (2d, 1H, *J* = 6.0 Hz, OH). 2.09, 2.02, 2.01, 2.00 (s, 4 Ac-CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): 20.7, 20.7, 20.8, 20.8 (4 OAc, $\underline{C}H_3$), 52.2 and 52.2 ($CO_2\underline{C}H_3$), 61.9 (C-6), 61.9 (C-6'), 67.0 and 67.0 (C-7), 67.5 and 67.5 (C-5'), 68.5 and 68.6 (C-4'), 70.1 (C-3'), 71.1 and 71.2 (C-2'), 94.4 and 94.6 (C-1'), 108.1 and 108.1 (C-3), 111.3 and 111.5 (C-4), 126.9 and 127.0 (C-9), 139.3 and 139.3 (C-8), 150.2 and 150.4 (C-5), 155.4 (C-2), 166.4 and 166.4 (C-10), 169.8, 170.2, 170.7 and 170.8 170.9 and 170.9 (CO, 4OAc);

IR (cm^{-1}): 3471, 2960, 1751, 1676, 1434, 1369, 1228, 1136, 1043, 801, 601;

$[a]_D$ = + 100 (c 1.0, CH_3OH);

HRMS m/z (ESI) calculated for $C_{24}H_{30}NaO_{14}$, $[M + Na]^+$ 565.1533; found 565.1497.

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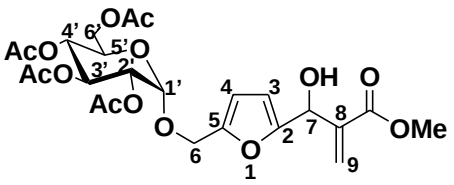
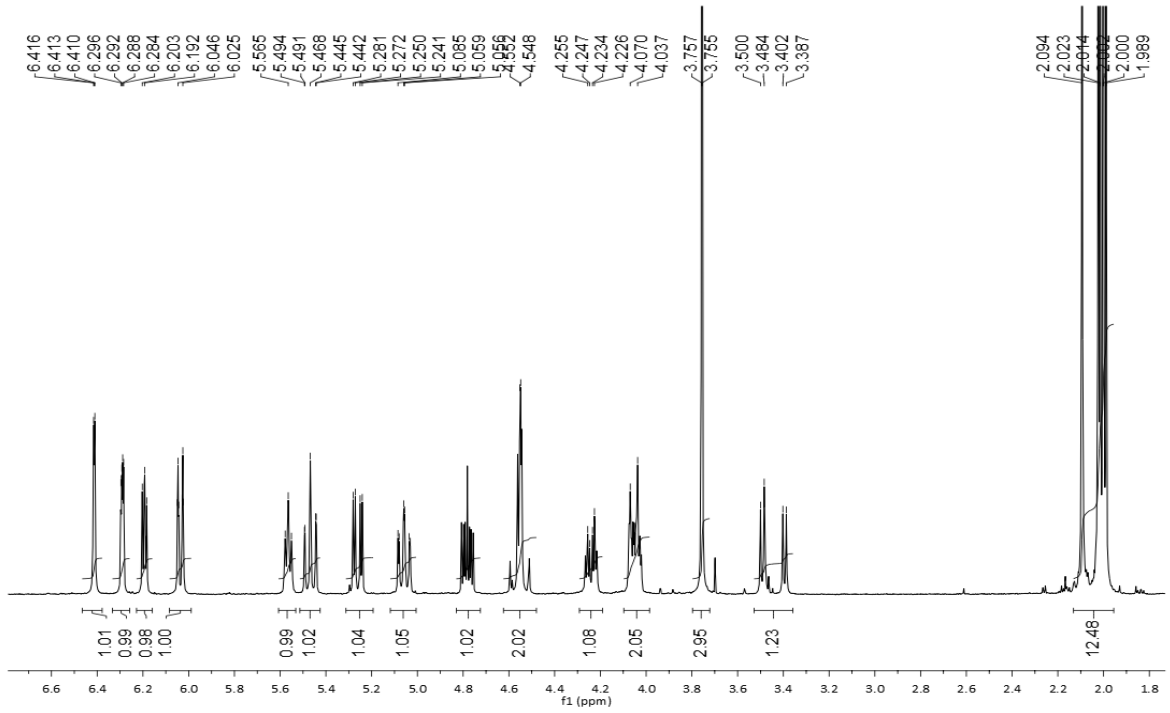
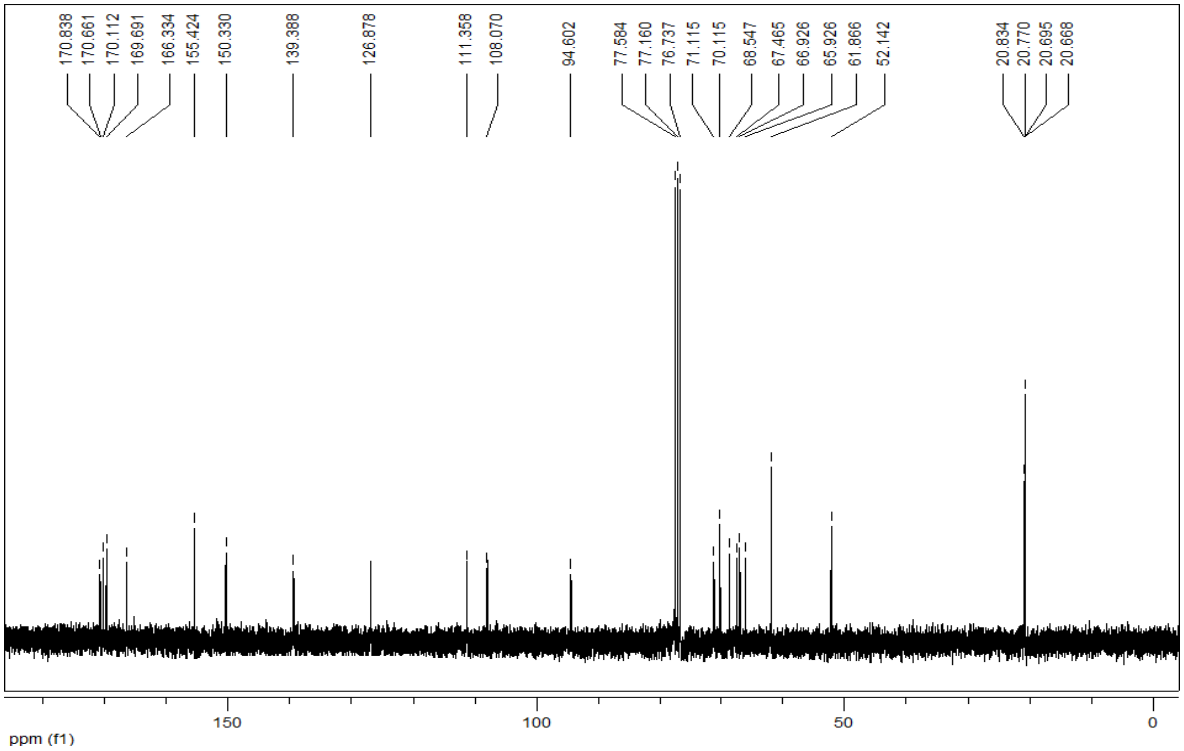


(300a)





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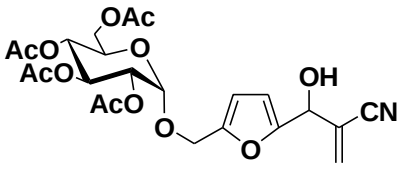
3-hydroxy-2-methylene-3-(5-(2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyloxymeth--yl)-furan-2-yl) propanenitrile (300b)



(300b)

Pale-yellow gum (210 mg, 79% yield)

^{1}H NMR (300 MHz, $CDCl_3$): 1.96 , 1.97 , 1.99 , 2.06 (s, 12 H , 4 OAc, C<u>H</u>$_3$), 3.87 and 3.95 (2d, 1H, J = 5.0 Hz, O<u>H</u>), 3.98~4.12 (m, 2H, H-5' + H-6'), 4.17 and 4.21 (2d, 1H, J = 4.2 Hz, H-6'), 4.54 (s, 2H, H-6), 4.70 and 4.74 (2dd, 1H, J_a = 1.6 Hz, J_b = 3.8 Hz, H-2'), 5.00 and 5.03 (2d, 1H, J = 9.7 Hz, H-4'), 5.25 (m, 2H, H-1', H-7), 5.41 and 5.44 (2d, 1H, J = 9.3 Hz, H-3'), 6.12 (s, 1H, H-9), 6.21 and 6.22 (2d, 1H, J = 1.6 Hz, H-3), 6.33 (s, 1H, H-9), 6.33 and 6.35 (2d, 1H, J = 2.1 Hz, H-4);

^{13}C NMR (75 MHz, $CDCl_3$): 20.6, 20.6, 20.7, 20.8 (4 OAc, <u>C</u>H$_3$), 61.6 and 61.6 (C-6'), 61.9 (C-6), 65.9 (C-7), 67.5 and 67.5 (C-5'), 68.5 and 68.5 (C-4'), 70.0 and 70.0 (C-3') 71.2 and 71.2 (C-2'), 94.4 and 94.4 (C-1'), 109.4 and 109.6 (C-3), 111.4 (C-4), 116.7 (<u>C</u>N), 123.3 and 123.3 (C-9), 131.2 and 131.4 (C-8), 151.3 (C-5), 152.8 and 152.8 (C-2), 169.7, 170.2, 170.8, 170.9 and 170.9 171.0 (CO, 4OAc);

IR (cm^{-1}): 3469, 2960, 1733, 1369, 1228, 1137, 1044, 956, 804, 602;

$[\alpha]_D$ = + 98 (c 0.8, CH_3OH);

HRMS m/z (ESI) calculated for $C_{23}H_{27}NaO_{12}$, $[M + Na]^+$ 532.1425; found 532.1410.

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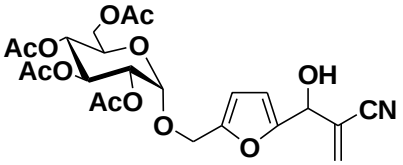
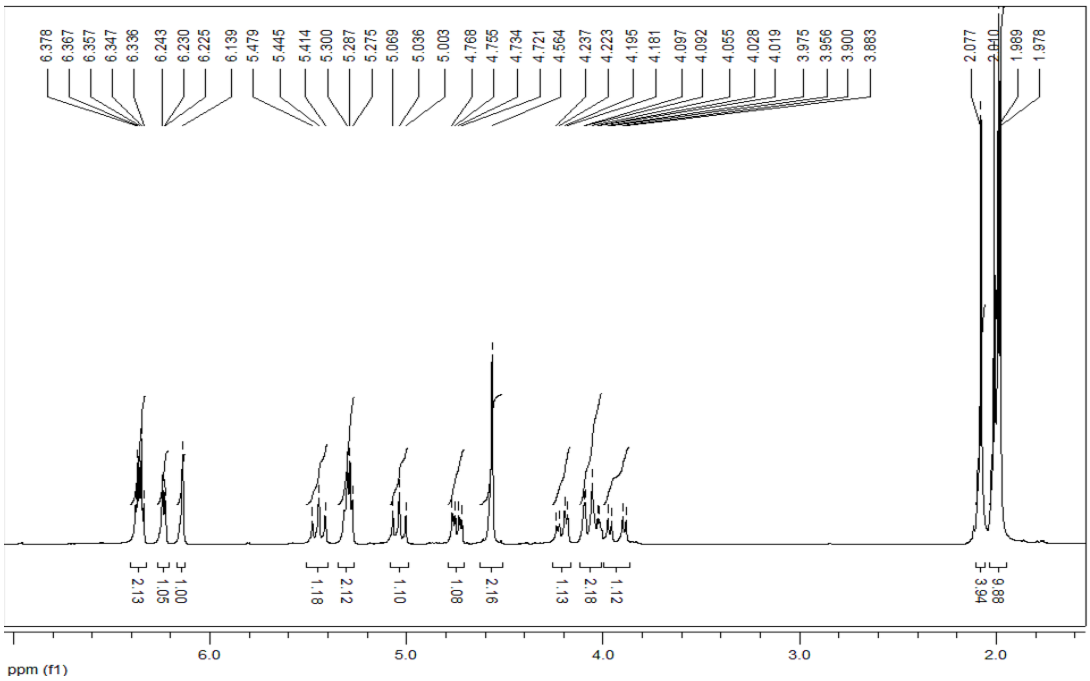
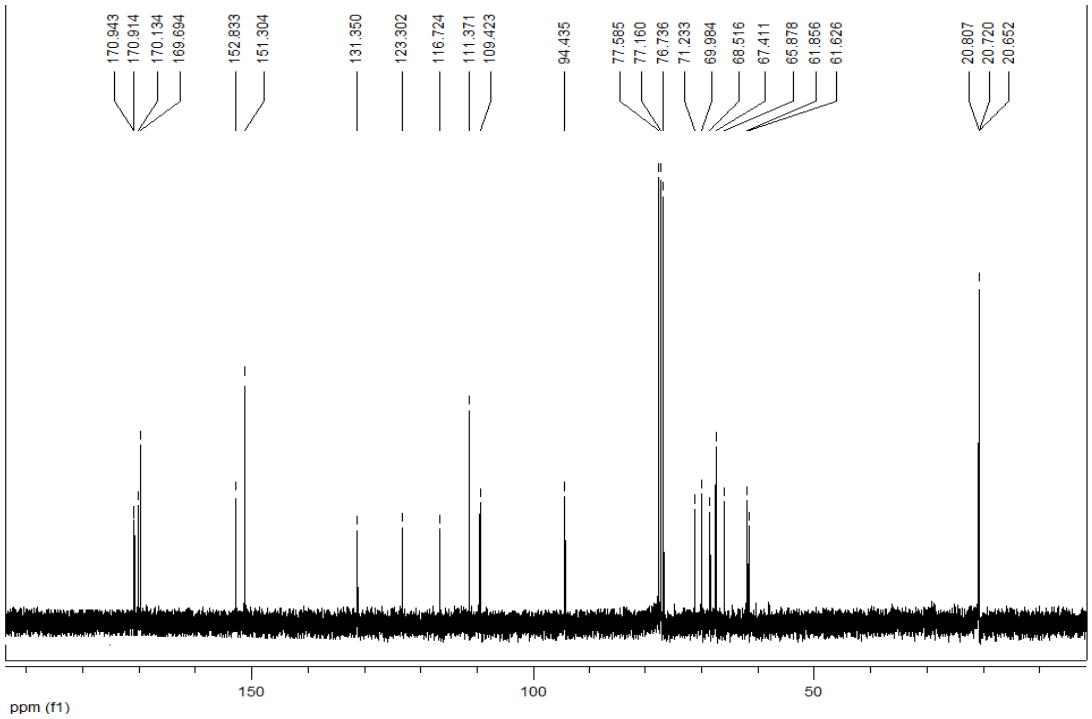


(300b)





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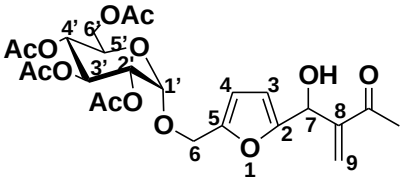
4-hydroxy-3-methylene-4-(5-(2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyloxymeth--yl)-furan-2-yl) butan-2-one (300c)



(300c)

Pale-yellow gum (170 mg, 79% yield)

^{1}H NMR (400 MHz, $CDCl_3$): 6.28 (s, 1H, H-9); 6.27 (s, 1H, H-4); 6.21and 6.18 (2d, 1H, *J* = 0.8 Hz, H-9); 6.16 and 6.15 (2d, 1H, *J* = 3.6 Hz, H-3); 5.60 (s_{br}, 1H, H-7); 5.45 (2d, 1H, *J* = 9.6 Hz, H-3'); 5.25 (2d, 1H, *J* = 4.0 Hz, H-1'); 5.05 (2dd, 1H, *J* = 10.0 Hz, H-4'); 4.76 and 4.78 (2dd, 1H, J_a = 9.6, J_b = 4.0 Hz, H-2'); 4.57, 4.51 and 4.56, 4.50 (2d, 1H each, ^{2}J = 13.6 Hz, H-6); 4.22 and 4.25 (2dd, 1H, J_a = 12.4 and J_b = 4.0 Hz, H-6'); 4.12-3.96 (m, 2H, H-5'+ H-6'); 3.59 and 3.49 (2s, 1H, OH). 2.37 (s, 3H, $COC\underline{H}_3$), 2.09, 2.02, 2.00, 2.00 (s, 4 Ac-CH_3).

^{13}C NMR (100 MHz, $CDCl_3$): 20.7, 20.8, 20.8, 20.9 (4 OAc, $\underline{C}H_3$), 26.4 ($CO\underline{C}H_3$), 61.9 (C-6'), 61.9 (C-6), 66.6 and 66.7 (C-7), 67.5 and 67.5 (C-5'), 68.5 and 68.5 (C-4'), 70.0 and 70.1 (C-3'), 71.2 (C-2'), 94.4 and 94.6 (C-1'), 108.0 and 108.0 (C-3), 111.3 and 11.4 (C-4), 127.3 and 127.4 (C-9), 147.2 and 147.3 (C-8), 150.0 and 150.2 (C-5), 155.6 and 155.6 (C-2), 169.68 170.2, 170.6, 170.8 and 170.9 (CO, 4OAc), 199.6 ($\underline{C}OCH_3$);

IR (cm^{-1}): 3470, 2965, 1750, 1676, 1434, 1369, 1228, 1136, 1043, 801, 601;

$[\alpha]_D$ = + 73 (c = 0.8, CH_3OH);

HRMS m/z (ESI) calculated for $C_{24}H_{30}NaO_{13}$, $[M + Na]^+$ 549.1581; found 549.1579.

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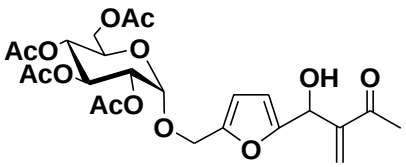

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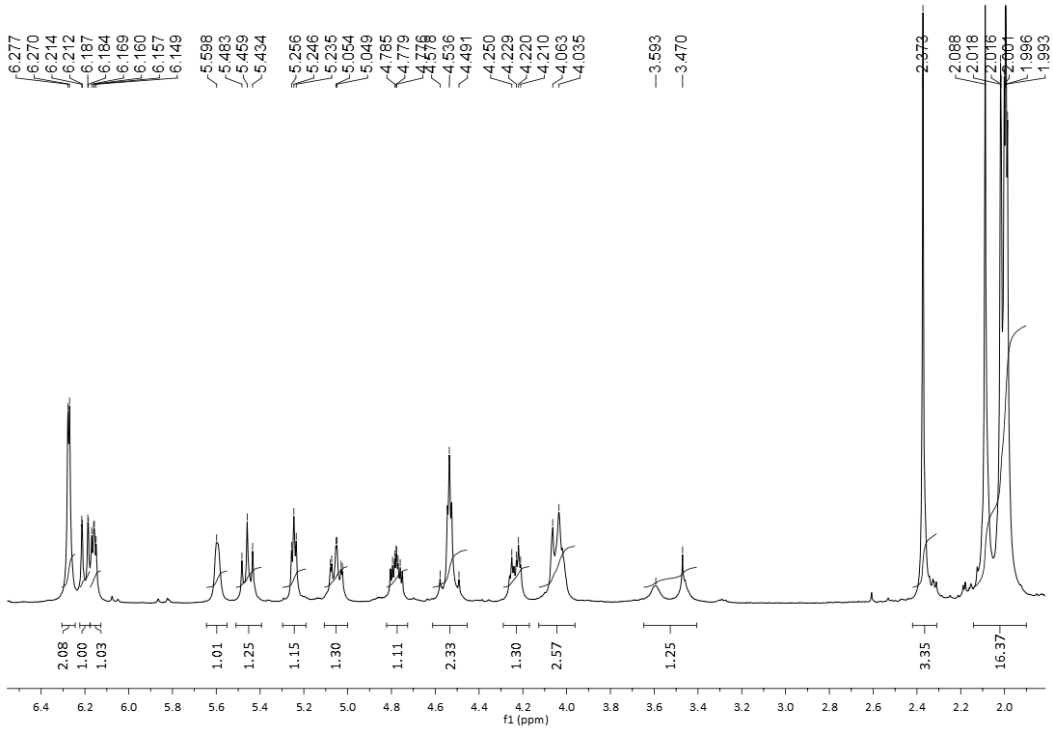

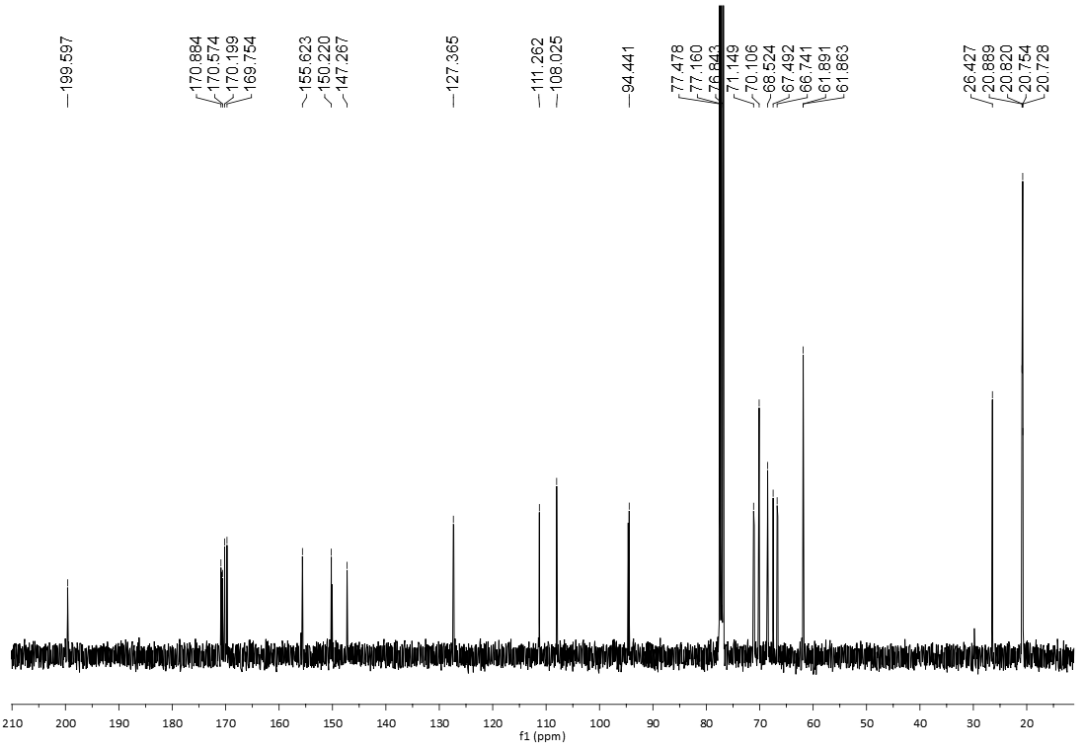

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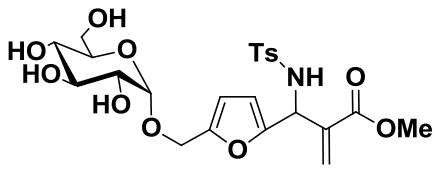
1.2.5 Typical procedure for aza-Baylis-Hillman reaction of GMF, sulfonamide and acrylate in different solvent

All reactions were conducted in a 10 mL flask equipped with magnetic stirring. To a solution of GMF (289 mg, 0.5 mmol) in MeOH (0.5 ml), added $La(OTf)_3$ (15 mg, 0.025 mmol), 2-HQD (12 mg, 0.1 mmol), $TsNH_2$ (170 mg, 1.0 mmol) and freshly desiccated molecular sieve (4A, 100 mg), after stirring for 1 min, methyl acrylate (60 µL) was added, then the mixture continue stirred for 12 h, filtrated with celite, then purified by column, gave desired product **302a** (173 mg, 63%) yield as a yellow liquid.

Products **302b-j** were synthesized following the same manner as **302a.**

Methyl α-methylene-β-[(*p*-toluenesulfonyl)amino]-3-[2-(5-(α-D-glucopyrano--syloxy methyl)-furan-2-yl] propionate (302a)



Pale-yellow gum (173 mg, 63% yield)

^{1}H NMR (400 MHz, CD_3OD): 2.44 (s, 3H, CH_3), 3.32~3.37 (m, 2H, H-4' and N-H), 3.42 and 3.44(2d, 1H, J = 4.0 Hz, H-2'), 3.57~3.62 (m, 1H, H-5'), 3.63 and 3.66 (2d, 1H, J = 2.0 Hz, H-3'), 3.69 and 3.70 (2s, 3H, CH_3), 3.72 and 3.73 (2d, 1H, J = 2.4 Hz, H-6'), 3.81 and 3.84 (2dd, 1H, J_a = 2.4 Hz, J_b = 6.0 Hz, H-6'), 4.42 (part A, AB system, 1H, J = 13.2 Hz, H-6), 4.51 (part B, AB system, 1H, J = 13.2 Hz, H-6), 4.85 (d, 1H, J = 4.4 Hz, H-1'), 5.49 (s, 1H, H-7), 5.94 and 5.95 (2d, J = 0.4 Hz, 1H, H-9), 5.97 and 5.98 (2dd, J_a = 0.8 Hz, J_b = 1.6 Hz, 1H, H-3), 6.23 and 6.24 (2d, J = 4.0 Hz, 1H, H-9), 6.30 (s, 1H, H-4), 7.34 (s, 1H), 7.36 (s, 1H), 7.70 and 7.72 (2d, 2H, J = 3.2 Hz);

^{13}C NMR (100 MHz, CD_3OD): 21.5 (CH_3), 52.6 ($CO_2\underline{C}H_3$), 52.6 (C-7), 61.9 (C-6), 62.6 (C-6'), 71.6 and 71.7 (C-4'), 73.3 (C-2'), 73.8 (C-5'), 75.0 (C-3'), 99.1 and 99.1 (C-1'), 109.6 (C-3), 111.4, 111.5 (C-4), 127.9 and 128.0 (C-9), 128.2 and 128.2, 130.5 and 130.5, 139.5 and 139.7, 144.6 and 144.6 (C-8), 152.7 and 152.7 (C-5), 153.2 and 153.2 (C-2), 167.1 ($\underline{C}O_2CH_3$);

HRMS m/z (ESI) calculated for $C_{23}H_{29}NNaO_{11}S$, $[M + Na]^+$ 550.1354; found 550.1334.

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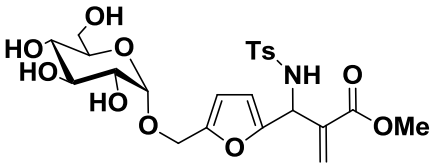
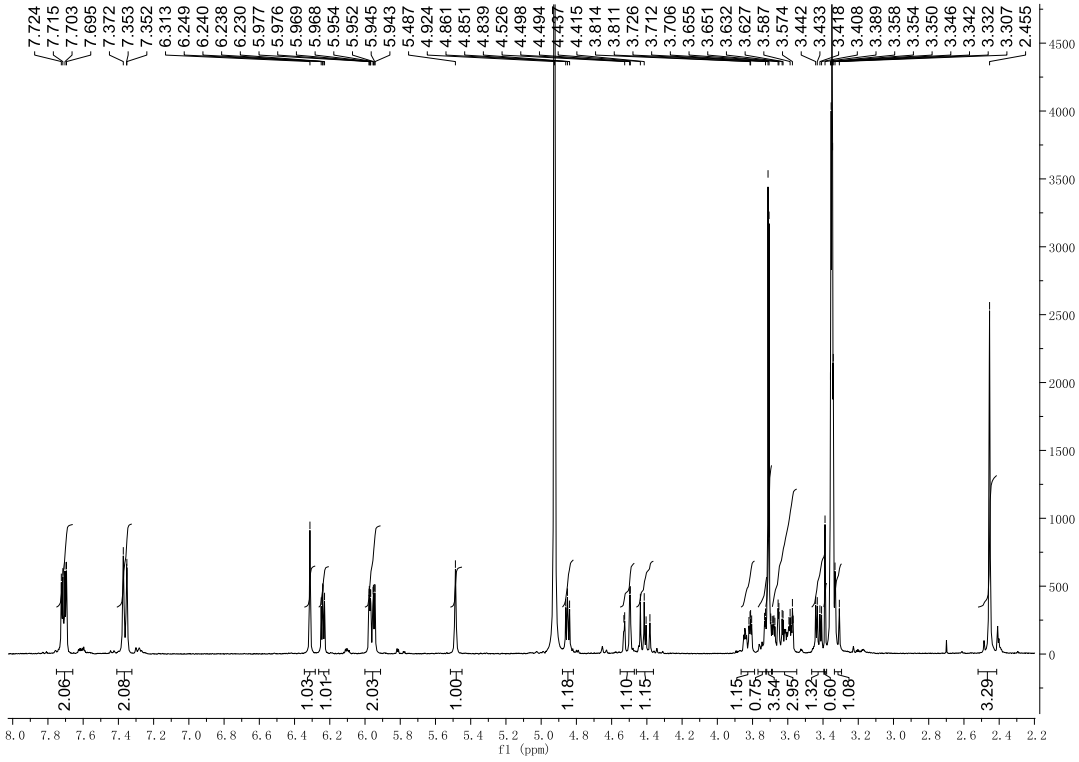
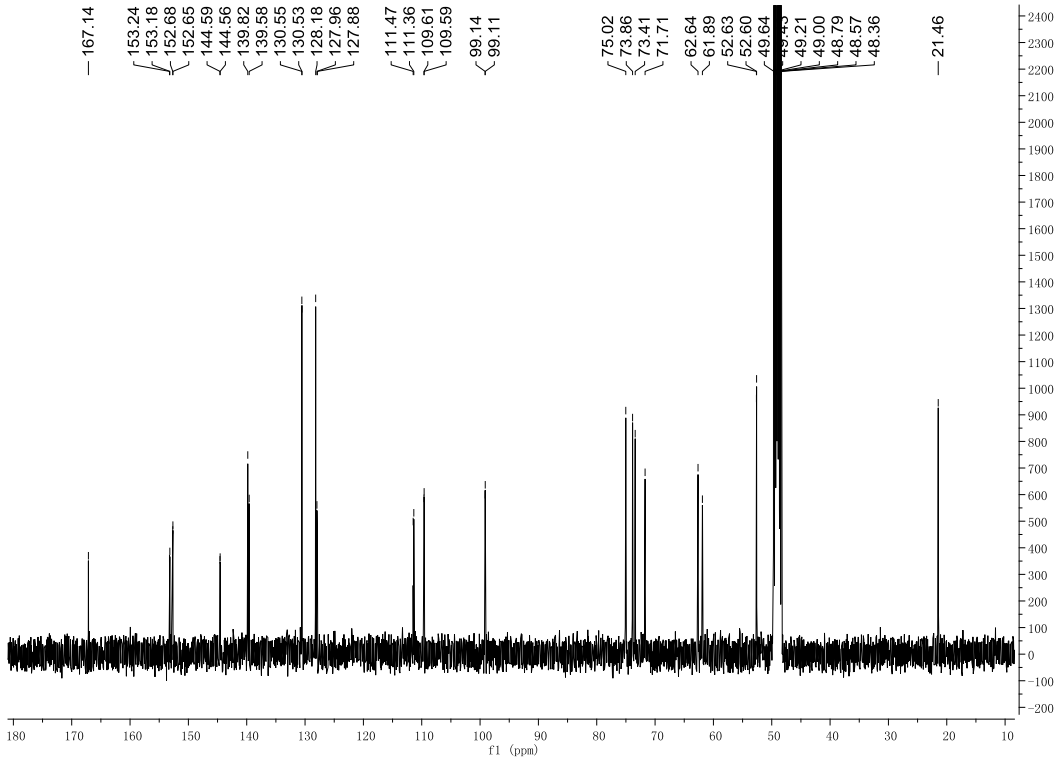


(302a)





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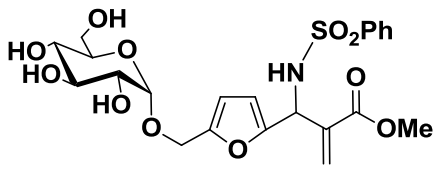
Methyl α-methylene-β-[(phenylsulfonyl)amino]-3-[2-(5-(α-D-glucopyranosyloxy--methyl)-furan-2-yl] propionate (302g)



(302g)

Pale-yellow gum (171 mg, 64% yield)

^{1}H NMR (400 MHz, CD_3OD): 3.28~3.35 (m, 2H, H-4' and N-H), 3.40 and 3.43 (2d, 1H, J = 3.6 Hz, H-2'), 3.53~3.60 (m, 1H, H-5'), 3.61 and 3.64 (2s, 1H, H-3'), 3.68 (2s, 3H, CH_3), 3.70 and 3.71 (2d, 1H, J = 1.2 Hz, H-6'), 3.80 and 3.82 (2dd, 1H, J_a = 2.6 Hz, J_b = 4.4 Hz, H-6'), 4.39 (part A, AB system, 1H, J = 13.2 Hz, H-6), 4.48 (part B, AB system, 1H, J = 13.2 Hz, H-6), 4.83 (2d, 1H, J = 3.6 Hz, H-1'), 5.49 and 5.50 (2s, 1H, H-7), 5.92 and 5.93 (2d, J = 0.8 Hz, 1H, H-9), 5.95 and 5.96 (2s, 1H, H-3), 6.20 and 6.21 (2d, J = 3.4 Hz, 1H, H-9), 6.29 (s, 1H, H-4), 7.50~7.60 (m, 3H), 7.78~7.84 (m, 2H);

^{13}C NMR (100 MHz, CD_3OD): 52.6 ($CO_2\underline{C}H_3$), 52.6 (C-7), 61.9 (C-6), 62.6 (C-6'), 71.7 (C-4'), 73.3 (C-2'), 73.8 (C-5'), 75.0 (C-3'), 99.1 (C-1'), 109.6 and 109.6 (C-3), 111.4 and 111.5 (C-4), 128.0 and 128.0 (C-9), 128.0 and 128.1, 130.0 and 130.0, 133.5 and 133.6, 139.7, 142.4 and 142.4 (C-8), 152.6 and 152.6 (C-5), 153.0 and 153.1(C-2), 167.1 ($\underline{C}O_2CH_3$);

HRMS m/z (ESI) calculated for $C_{22}H_{27}NNaO_{11}S$, $[M + Na]^+$ 536.1203; found 536.1217.

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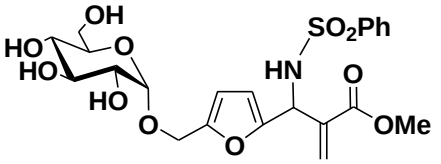
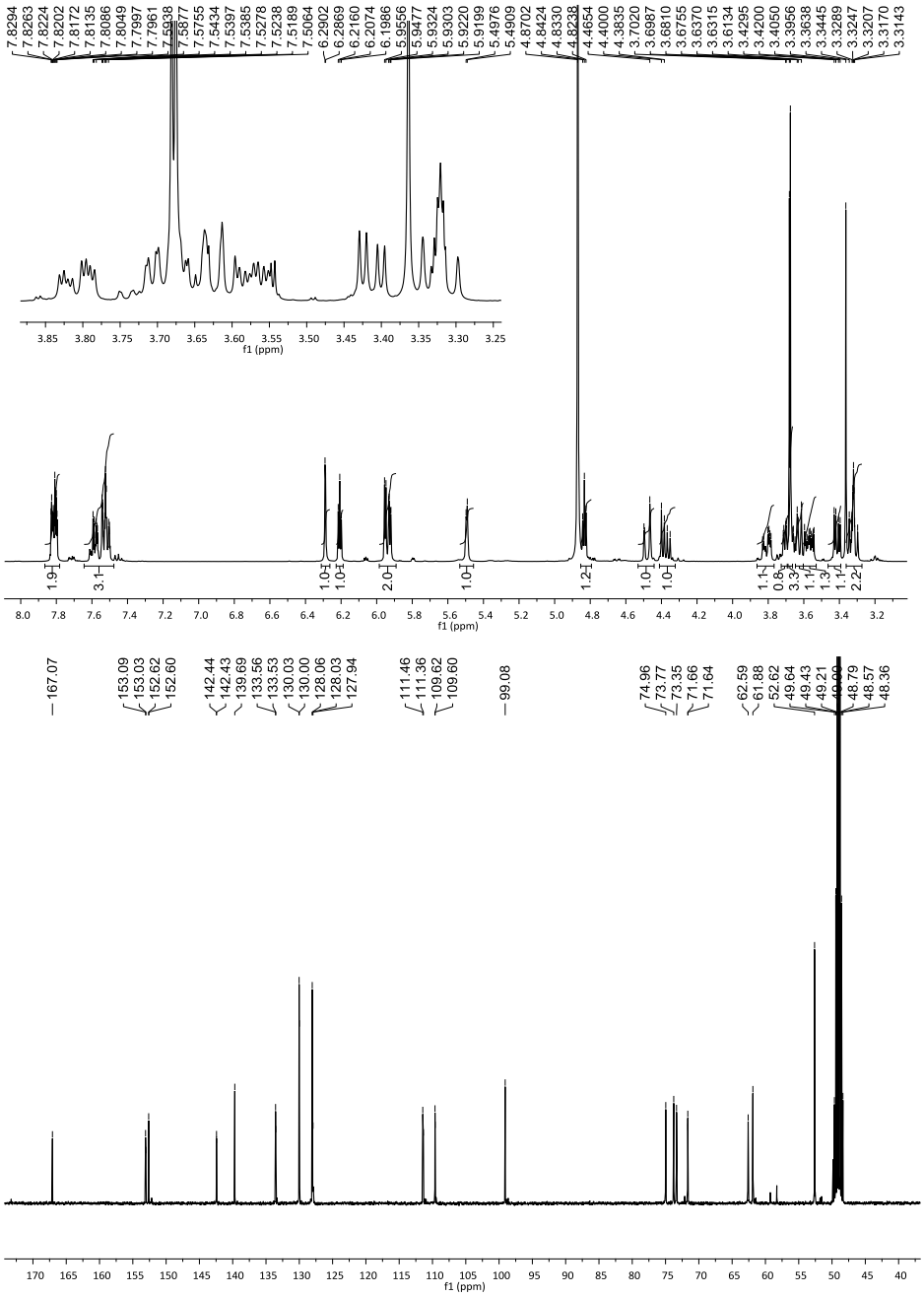


(302g)



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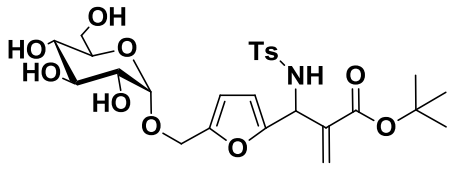
***tert*-Buthyl α-methylene-β-[(*p*-toluenesulfonyl)amino]-3-[2-(5-(α-D-glucopyrano syloxy-methyl)-furan-2-yl] propionate (302d)**



(302d)

Pale-yellow gum (151 mg, 51% yield)

^{1}H NMR (400 MHz, CD_3OD): 1.39 and 1.40 (2s, 9H, OC(CH3)3), 2.39 (s, 3H, CH_3), 3.25~3.30 (m, 2H, H-4' and N-H), 3.37 and 3.39 (2d, 1H, J = 3.6 Hz, H-2'), 3.52~3.70 (m, 3H, H-5', H-3', H-6'), 3.77 and 3.80 (2dd, 1H, J_a = 2.4 Hz, J_b = 4.4 Hz, H-6'), 4.35 (part A, AB system, 1H, J = 13.2 Hz, H-6), 4.46 (part B, AB system, 1H, J_a = 2.4 Hz, J_b = 13.2 Hz, H-6), 4.80 and 4.81 (2d, 1H, J = 4.4 Hz, H-1'), 5.41 (s, 1H, H-7), 5.76 and 5.78 (2s, 1H, H-9), 5.88 and 5.89 (2s, 1H, H-3), 6.14 and 6.13 (2s, 1H, H-9), 6.18 (2d, J = 3.2 Hz, 1H, H-4), 7.28 (d, 1H, J = 2.0 Hz), 7.30 (d, 1H, J = 2.0 Hz), 7.63 and 7.65 (2d, 2H, J = 4.4 Hz);

^{13}C NMR (100 MHz, CD_3OD): 21.5 (CH_3), 28.2 (OC(<u>C</u>H3)3), 52.5 (C-7), 61.8 (C-6), 62.6 (C-6'), 71.7 (C-4'), 73.3 (C-2'), 73.8 and 73.8 (C-5'), 75.0 (C-3'), 82.7 and 82.7 (O<u>C</u>$(CH_3)_3$), 99.0 and 99.0 (C-1'), 109.4 and 109.5 (C-3), 111.3, 111.4 (C-4), 126.5 and 126.6 (C-9), 128.1 and 128.1, 130.5 and 130.5, 139.6, 141.4, 141.4, 144.4 and 144.5 (C-8), 152.4 and 152.5 (C-5), 153.4 and 153.5 (C-2), 166.0 and 166.0 (<u>C</u>$O_2{}^{t}$Bu); HRMS m/z (ESI) calculated for $C_{26}H_{35}NNaO_{11}S$, $[M + Na]^+$ 592.1823; found 592.1801.

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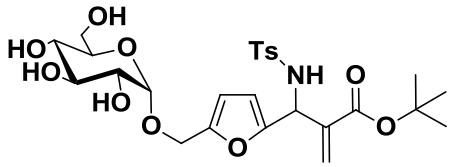
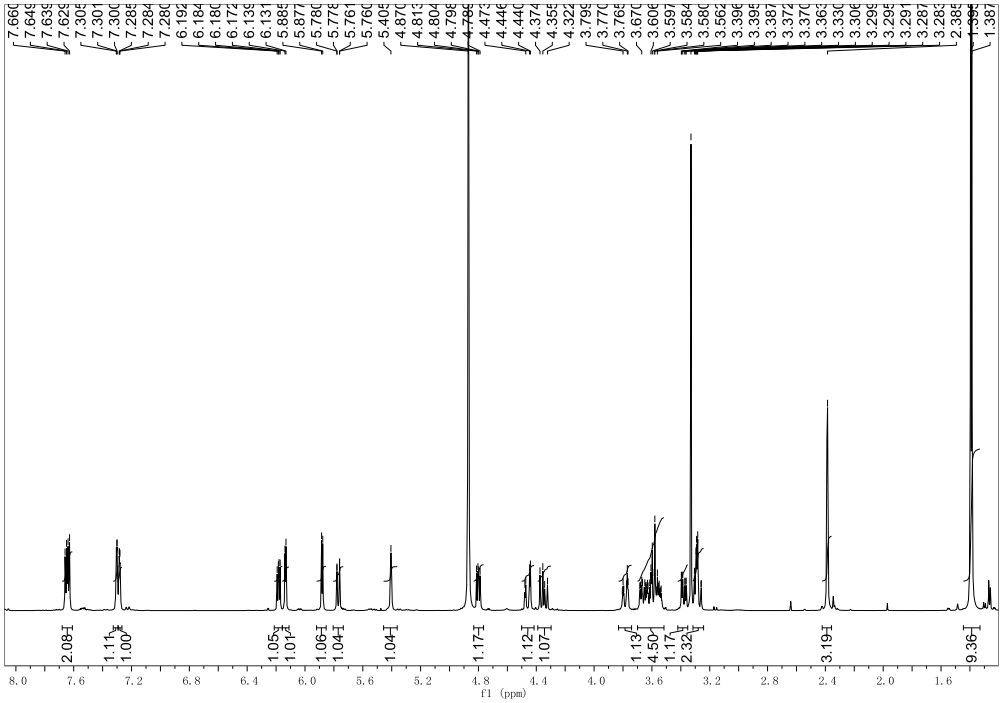
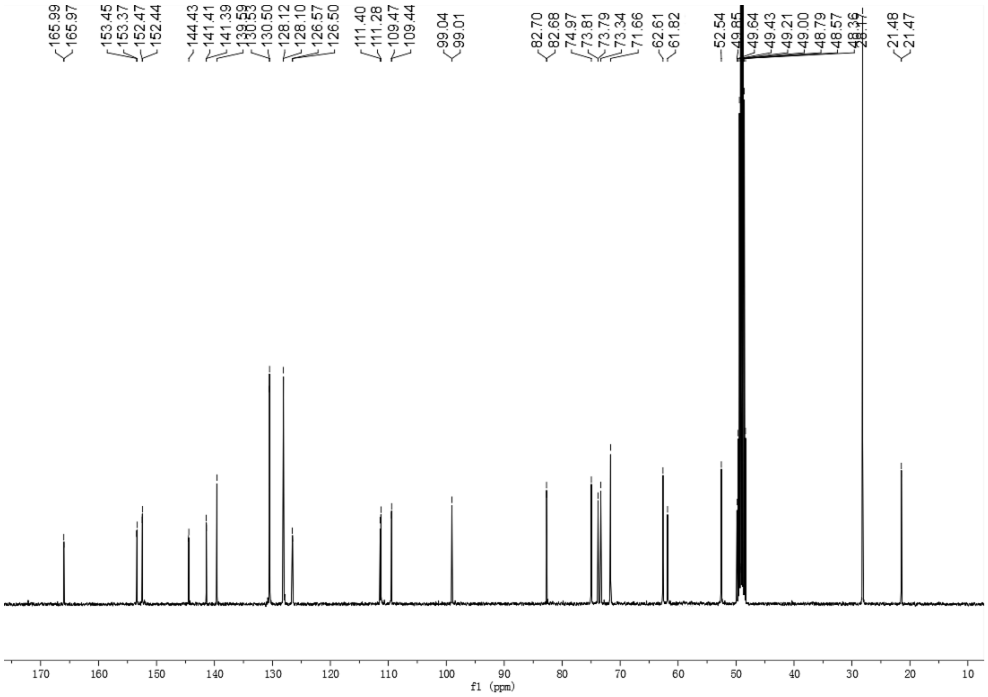


(302d)





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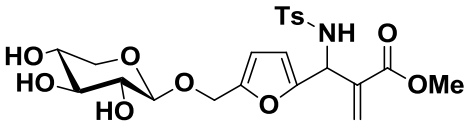
Methyl α-methylene-β-[(*p*-toluenesulfonyl)amino]-3-[2-(5-(β-D-xylopyranosylo--xy methyl)-furan-2-yl] propionate (302j)



(302j)

Pale-yellow gum (185 mg, 71% yield)

^{1}H NMR (400 MHz, CD_3OD): 2.39 (s, 3H), 3.10~3.19 (m, 2H, H-2'+ H-5'), 3.22~3.30 (m, 1H, H-3'), 3.32 (s, 1H, N-H), 3.40~3.49 (m, 1H, H-4'), 3.64 and 3.64 (2s, 3H, CH_3), 3.82 and 3.84 (2d, 1H, J = 5.2 Hz, H-5'), 4.19 (2d, 1H, J = 7.6 Hz, H-1'), 4.38 (part A, AB system, 1H, J = 13.2 Hz, H-6), 4.50 (part B, AB system, 1H, J = 13.2 Hz, H-6), 5.42 (s, 1H, H-7), 5.88 and 5.89 (2d, J = 0.8 Hz, 1H, H-9), 5.89 and 5.91 (2d, 1H, J = 3.6 Hz, H-3), 6.16 and 6.17 (2s, 1H, H-9), 6.25 and 6.25 (2s, 1H, H-4), 7.28 and 7.30 (2s, 2H), 7.63 and 7.65 (2d, 2H, J = 1.6 Hz);

^{13}C NMR (100 MHz, CD_3OD): 21.5 ($\underline{C}H_3$), 52.6 ($CO_2\underline{C}H_3$), 52.6 (C-7), 63.3 and 63.3 (C-6), 67.0 (C-5'), 71.2 (C-4'), 74.8 (C-2'), 77.8 (C-3'), 103.6 and 103.6 (C-1'), 109.6 (C-3), 111.5 (C-4), 127.9 and 128.0 (C-9), 128.2, 130.5 and 130.5, 139.6 and 139.8, 144.5 and 144.6 (C-8), 152.4 and 152.5 (C-5), 153.3 and 153.3 (C-2), 167.1 ($\underline{C}O_2CH_3$);

HRMS m/z (ESI) calculated for $C_{22}H_{27}NNaO_{10}S$, $[M + Na]^+$ 520.1253; found 520.1240.

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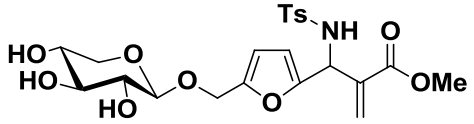
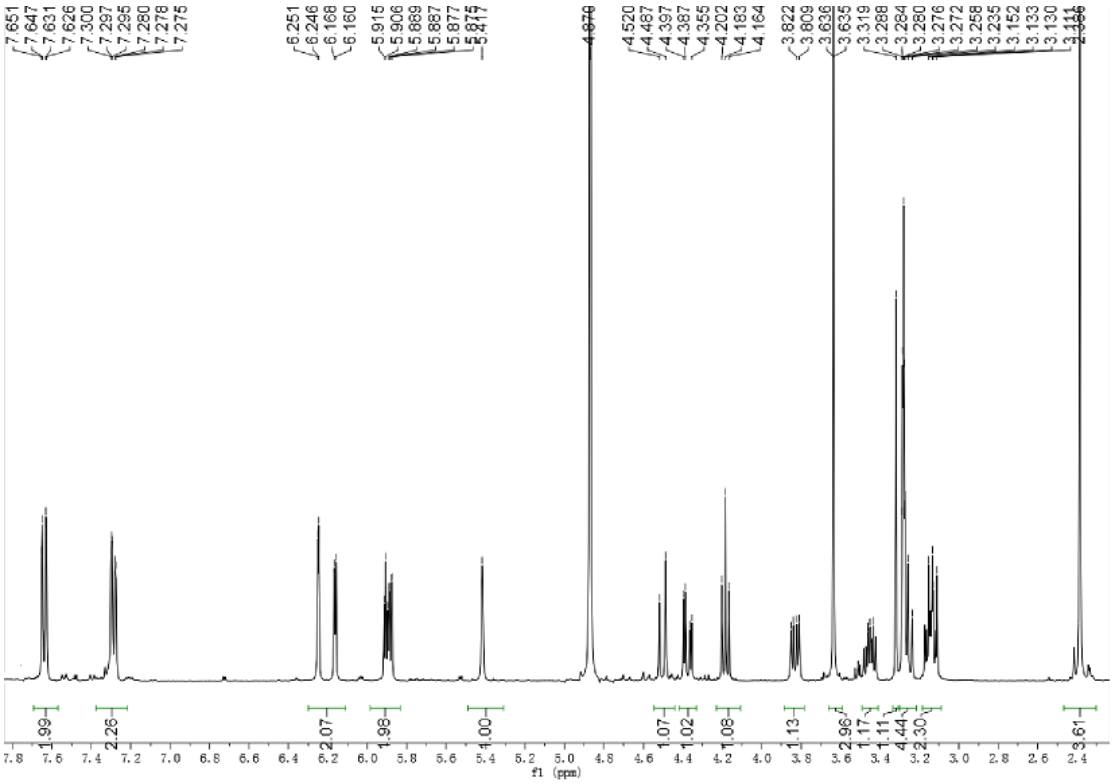
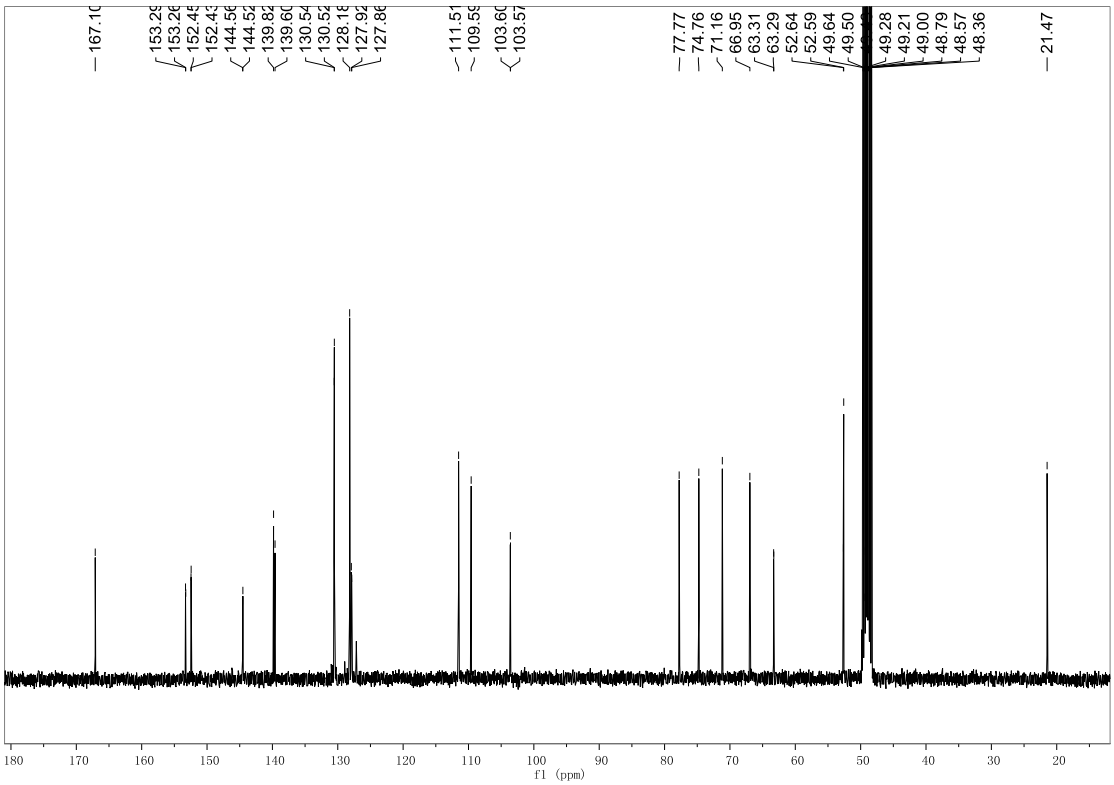


(302j)





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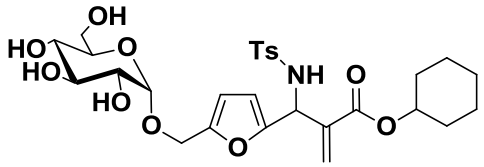
Cyclohexyl α-methylene-β-[(*p*-toluenesulfonyl)amino]-3-[2-(5-(α-D-gluco--pyranosyloxy-methyl)-furan-2-yl] propionate (302e)



(302e)

Pale-yellow gum (173 mg, 56% yield)

^{1}H NMR (400 MHz, CD_3OD): 1.25~1.95 (m, 10H, OCH(C$\underline{H}_2$)$_5$), 2.40 (s, 3H, CH_3), 3.25~3.30 (m, 2H, H-4' and N-H), 3.37 and 3.39 (2d, 1H, J = 3.6 Hz, H-2'), 3.52~3.70 (m, 3H, H-5', H-3', H-6'), 3.77 and 3.80 (2dd, 1H, J_a = 2.4 Hz, J_b = 4.4 Hz, H-6'), 4.35 (part A, AB system, 1H, J = 13.2 Hz, H-6), 4.46 (part B, AB system, 1H, J_a = 2.4 Hz, J_b = 13.2 Hz, H-6), 4.78 (s, 1H, OC$\underline{H}$(CH_2)$_5$),

4.80 and 4.81 (2d, 1H, J = 4.4 Hz, H-1'), 5.42 (s, 1H, H-7), 5.76 and 5.77 (2s, 1H, H-9), 5.88 and 5.89 (2s, 1H, H-3), 6.14 and 6.13 (2s, 1H, H-9), 6.18 (2d, J = 3.2 Hz, 1H, H-4), 7.28 (d, 1H, J = 2.0 Hz), 7.30 (d, 1H, J = 2.0 Hz), 7.63 and 7.65 (2d, 2H, J = 4.4 Hz);

^{13}C NMR (100 MHz, CD_3OD): 21.5 ($\underline{C}H_3$), 24.4 and 24.4, 26.4, 32.2 and 32.3 (OCH($\underline{C}H_2$)$_5$), 52.3 (C-7), 61.8 (C-6), 62.6 (C-6'), 71.6 (C-5'), 73.2 (C-4'), 73.8 and 73.8 (C-2'), 75.0 (C-3'), 99.0 (C-1'), 109.5 and 109.6 (C-3), 111.3 and 111.4 (C-4), 127.4 and 127.5 (C-9), 128.1 and 128.1, 130.5 and 130.5, 139.5, 140.0, 144.5 and 144.5 (C-8), 152.5 and 152.6 (C-5), 153.2 and 153.3 (C-2), 166.0 ($\underline{C}O_2CH_3$);

HRMS m/z (ESI) calculated for $C_{28}H_{37}NNaO_{11}S$, $[M + Na]^+$ 618.1980; found 618.1963.

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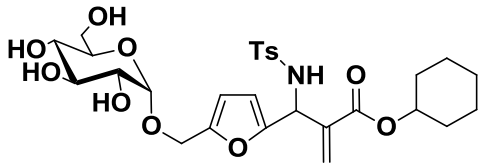

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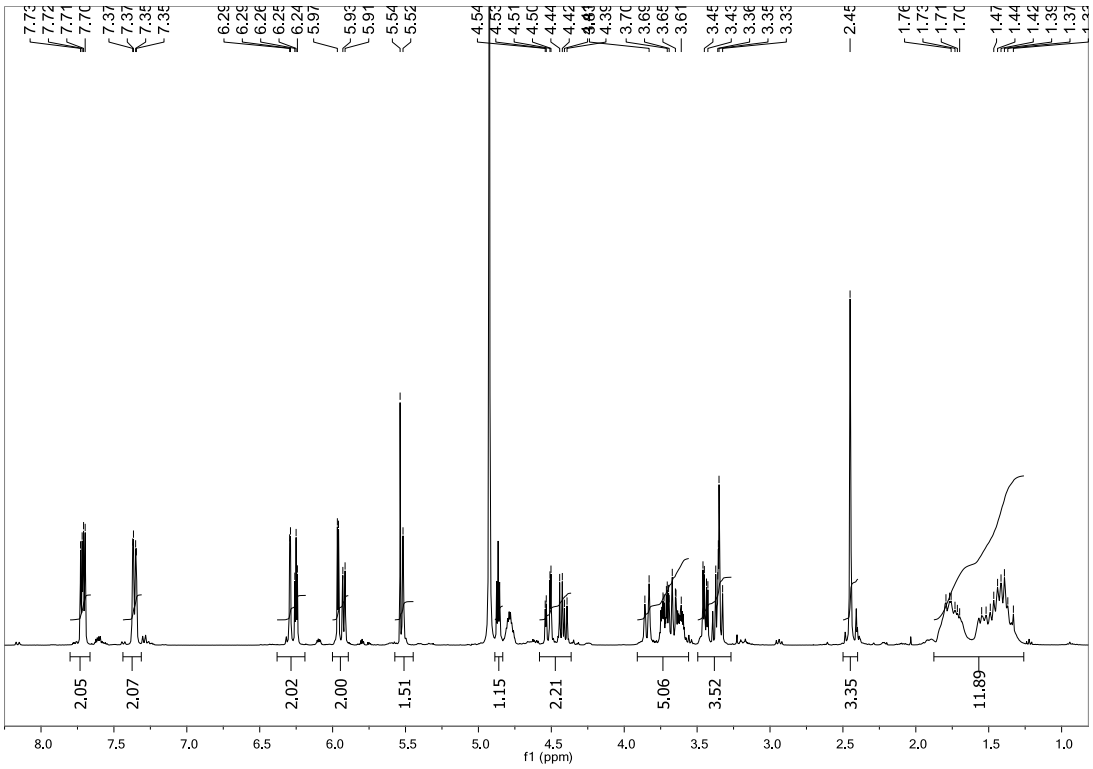

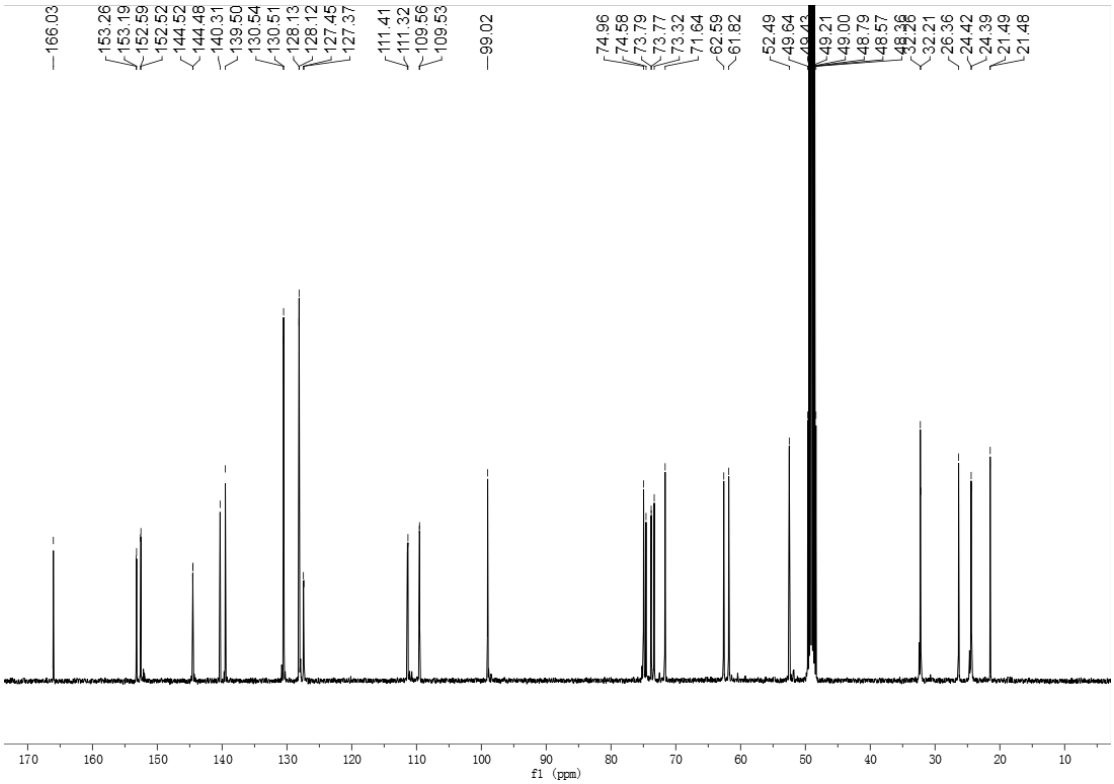

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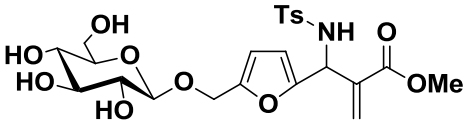
Methyl α-methylene-β-[(*p*-toluenesulfonyl)amino]-3-[2-(5-(α-D-glucopyrano--syloxymethyl)-furan-2-yl] propionate (302i)



(302i)

Pale-yellow gum (190 mg, 69% yield)

^{1}H NMR (400 MHz, CD_3OD): 2.38 (s, 3H, CH_3), 3.13 and 3.16 (2d, 1H, J = 8.0 Hz, H-2'), 3.20~3.31 (m, 3H, N-H, H-3', H-4'), 3.55 and 3.65 (m, 5H, CH_3, H-5', H-6'), 3.83 and 3.86 (2d, 1H, J = 2.0 Hz, H-6'), 4.22 and 4.24 (2d, 1H, J = 5.6 Hz, H-1'), 4.45 (part A, AB system, 1H, J = 12.8 Hz, H-6), 4.59 (part B, AB system, 1H, J = 12.8 Hz, H-6), 5.41 and 5.42 (2s, 1H, H-7), 5.86 and 5.88 (2d, J = 0.8Hz, 1H, H-9), 5.90 and 5.91 (2d, 1H, J = 3.2 Hz, H-3), 6.18 and 6.19 (2d, 1H, J = 2.8 Hz, H-9), 6.23 and 6.24 (2s, 1H, H-4), 7.28 and 7.30 (2s, 2H), 7.63 and 7.65 (2d, 2H, J = 1.2 Hz);

^{13}C NMR (100 MHz, CD_3OD): 21.5 ($\underline{C}H_3$), 52.6 and 52.7 (C-7), 62.8 (C-6), 63.2 (C-6'), 71.6 (C-4'), 75.0 (C-2'), 78.0 and 78.1 (C-3', C-5'), 102.7 (C-1'), 109.6 and 109.6 (C-3), 111.6 (C-4), 128.0 and 128.0 (C-9), 128.2 and 128.2, 130.5, 139.6 and 139.6, 139.8, 144.5 and 144.6 (C-8), 152.5 and 152.5 (C-5), 153.2 and 153.3 (C-2), 167.1 ($\underline{C}O_2CH_3$);

HRMS m/z (ESI) calculated for $C_{23}H_{29}NNaO_{11}S$, $[M + Na]^+$ 550.1354; found 550.1344.

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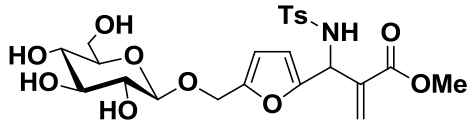
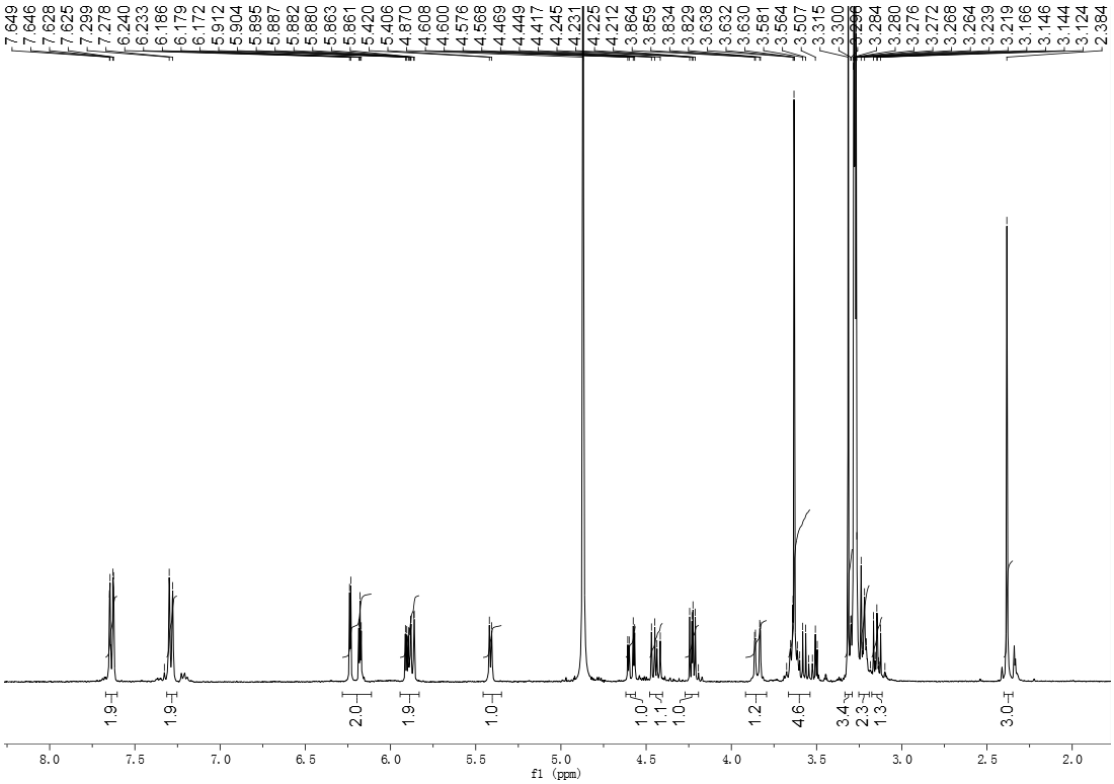
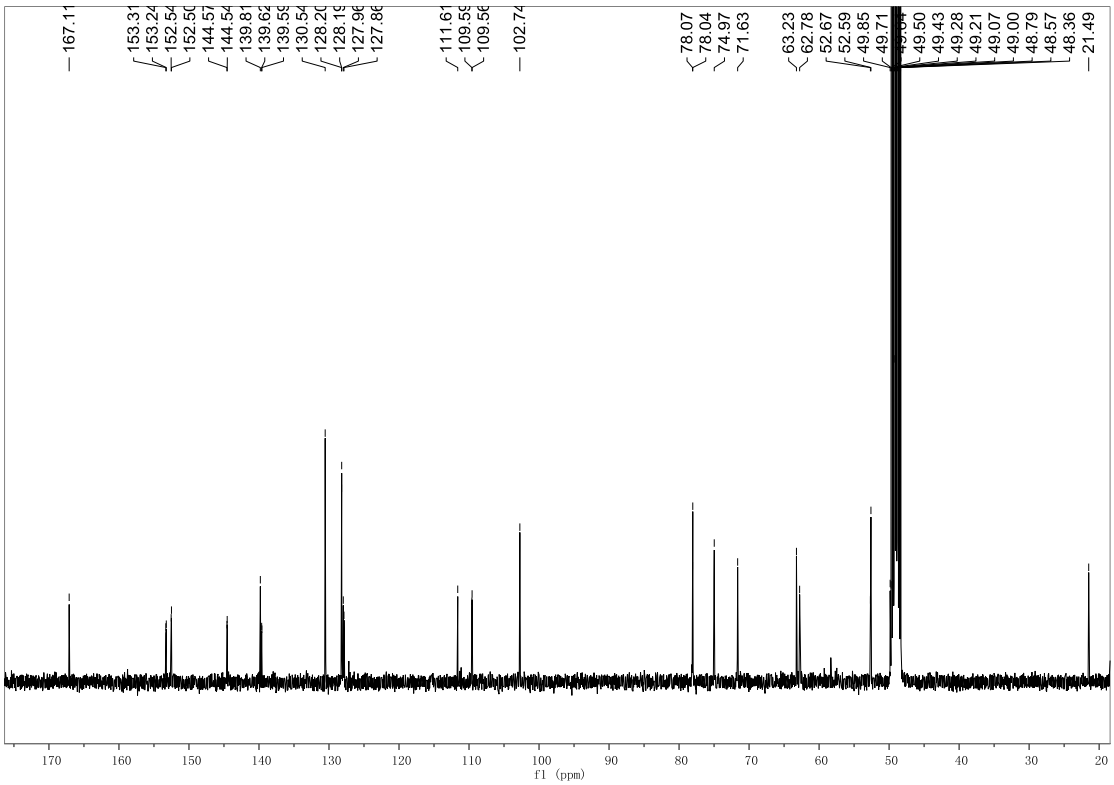


(302i)





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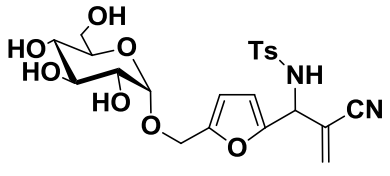
α-Methylene-β-[(*p*-toluenesulfonyl)amino]-3-[2-(5-(α-D-glucopyranosyloxymeth--yl)-furan-2-yl] propanenitrile (302f)



(302f)

Pale-yellow gum (137 mg, 53% yield)

^{1}H NMR (400 MHz, CD_3OD): 2.38 (s, 3H, CH_3), 3.22~3.30 (m, 1H, H-4'), 3.32 (s, 1H, N-H), 3.36 and 3.38 (2d, 1H, J = 4.0 Hz, H-2'), 3.50~3.70 (m, 3H, H-3', H-5' and H-6'), 3.76 and 3.78 (2dd, 1H, J_a = 3.2 Hz, J_b = 5.6 Hz, H-6'), 4.38 (part A, AB system, 1H, J = 12.8 Hz, H-6), 4.49 (part B, AB system, 1H, J = 12.8 Hz, H-6), 4.78 and 4.80 (2d, 1H, J = 3.6 Hz, H-1'), 5.18 (s, 1H, H-7), 6.01 and 6.02 (2d, J = 1.2 Hz, 1H, H-9), 6.06 and 6.06 (2s, 1H, H-3), 6.08 and 6.09 (2s, 1H, H-9), 6.22 and 6.23 (2d, 1H, J = 4.8, H-4), 7.28 and 7.30 (2s, 2H), 7.65 and 7.67 (2d, 2H, J = 4.4 Hz);

^{13}C NMR (100 MHz, CD_3OD): 21.5 ($\underline{C}H_3$), 54.8 (C-7), 61.7 and 61.7 (C-6), 62.7 (C-6'), 71.7 (C-5'), 73.4 (C-4'), 74.0 (C-2'), 75.0 (C-3'), 99.0 and 99.1 (C-1'), 110.8 (C-3), 111.4 and 111.5 (C-4), 117. 7 (CN), 123.4 and 123.4, 128.2 and 128.2, 130.6 and 130.6, 133.5 and 133.6, 139.3 (C-9), 144.8 and 144.8 (C-8), 150.5 and 150.6 (C-5), 153.5 (C-2);

HRMS m/z (ESI) calculated for $C_{22}H_{26}N_2NaO_9S$, $[M + Na]^+$ 517.1251; found 517.1235.

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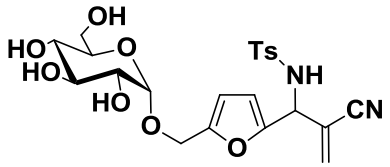

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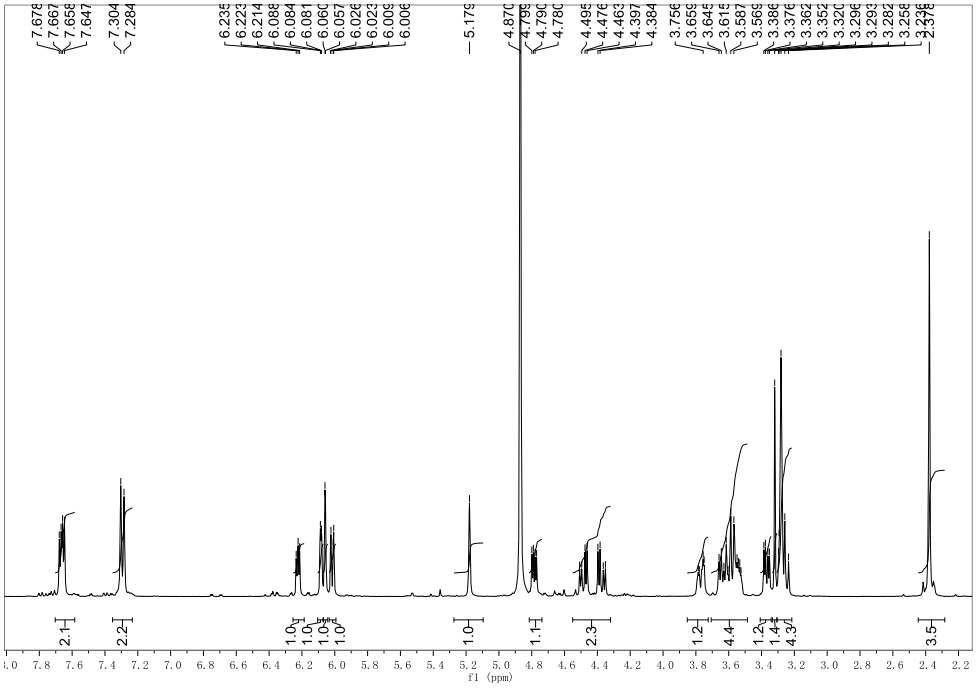

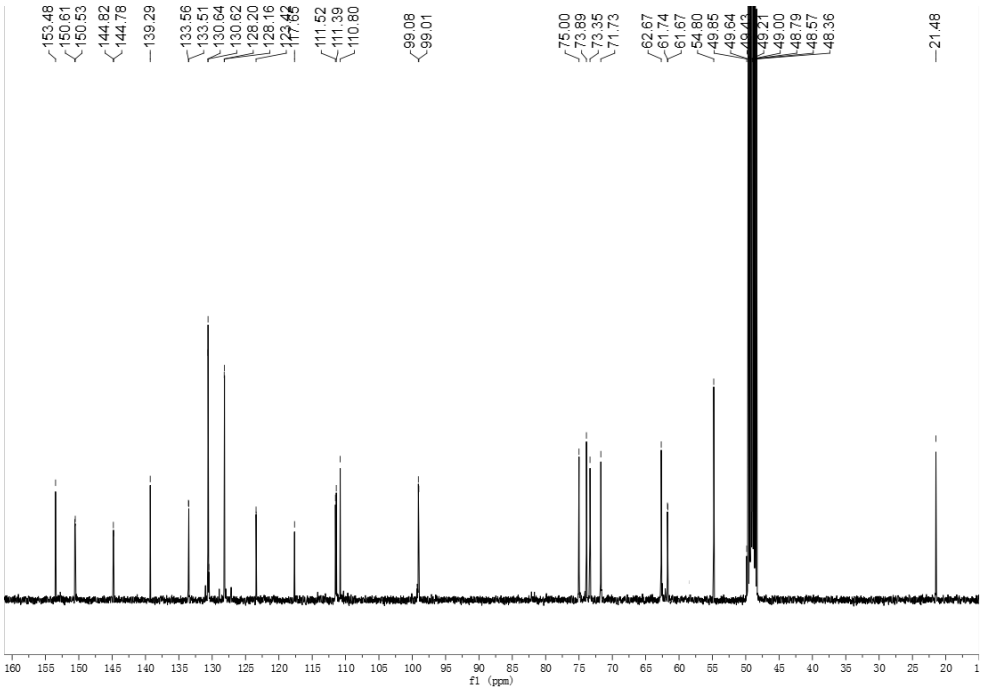

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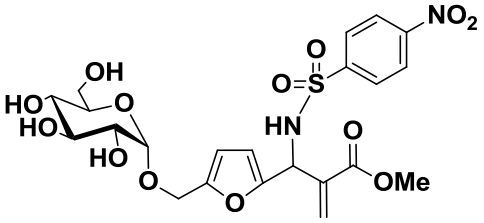
Methyl α-methylene-β-[(*p*-nitrophenylsulfonyl)amino]-3-[2-(5-(α-D-glucopyrano--syloxymeth-yl)-furan-2-yl] propionate (302h)



(302h)

Pale-yellow gum (148 mg, 51% yield)

^{1}H NMR (400 MHz, CD_3OD): 3.23~3.30 (m, 2H, H-4' and N-H), 3.35 and 3.37 (2d, 1H, J = 3.6 Hz, H-2'), 3.46~3.62 (m, 3H, H-3', H-5', H-6'), 3.65 and 3.66 (2s, 3H, OMe), 3.74 and 3.77 (2dd, 1H, J_a = 2.0 Hz, J_b = 4.4 Hz, H-6'), 4.31 (part A, AB system, 1H, J = 12.8 Hz, H-6), 4.41 (part B, AB system, 1H, J = 12.8 Hz, H-6), 4.73 and 4.75 (2d, 1H, J = 3.6 Hz, H-1'), 5.49 (s, 1H, H-7), 5.89 and 5.91 (2d, J = 1.2 Hz, 1H, H-9), 5.93 and 5.93 (2d, J = 3.2 Hz, 1H, H-3), 6.14 and 6.15 (2d, J = 3.2 Hz, 1H, H-9), 6.30 (s, 1H, H-4), 7.98 and 8.00 (2d, 2H, J = 4.4 Hz), 8.32 and 8.34 (2d, 2H, J = 4.0 Hz);

^{13}C NMR (100 MHz, CD_3OD): 52.7 (C-7), 61.6 (C-6), 62.7 (C-6'), 71.7 (C-5'), 73.4 (C-4'), 73.9 (C-2'), 75.0 (C-3'), 99.0 and 99.1 (C-1'), 109.9 and 110.0 (C-3), 111.4 and 111.5 (C-4), 125.2 and 125.3, 128.1and 128.2 (C-9), 129.6, 139.7, 144.3 (C-8), 151.3 (C-5), 152.8 and 152.9 (C-2), 167.0 ($\underline{C}O_2CH_3$);

HRMS m/z (ESI) calculated for $C_{22}H_{26}N_2NaO_{13}S$, $[M + Na]^+$ 581.1053; found 581.1060.

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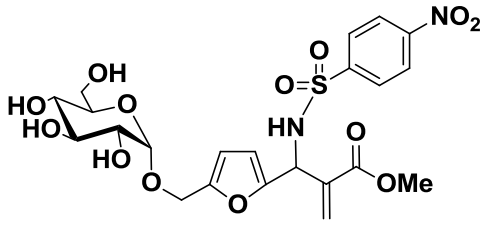
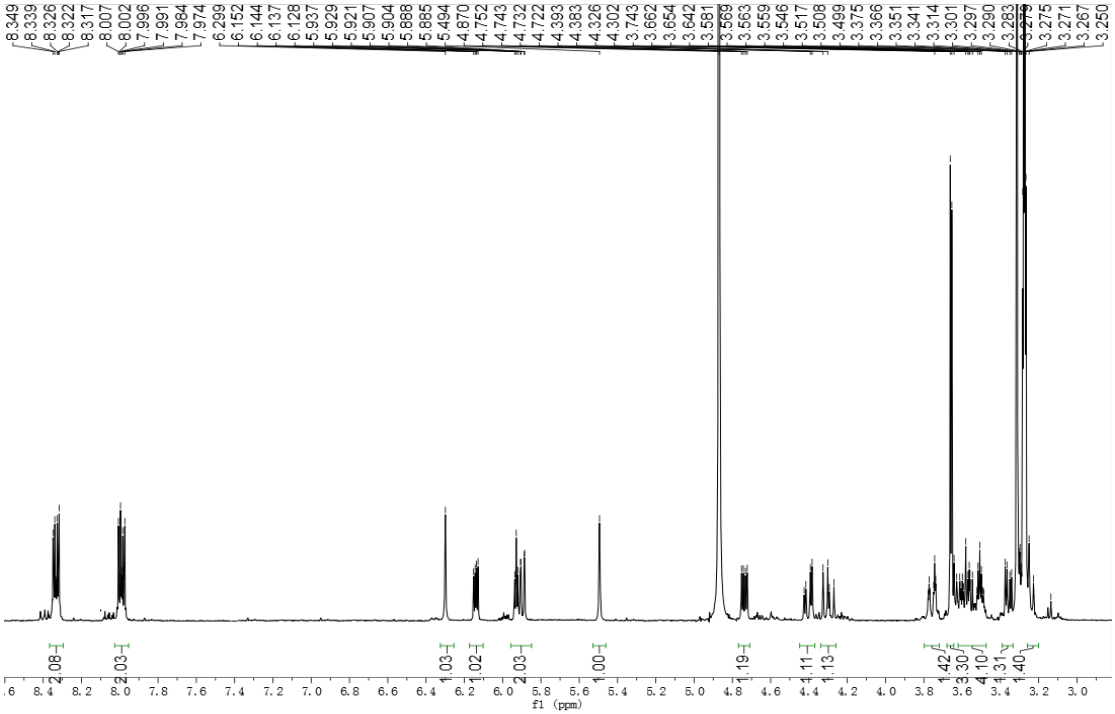
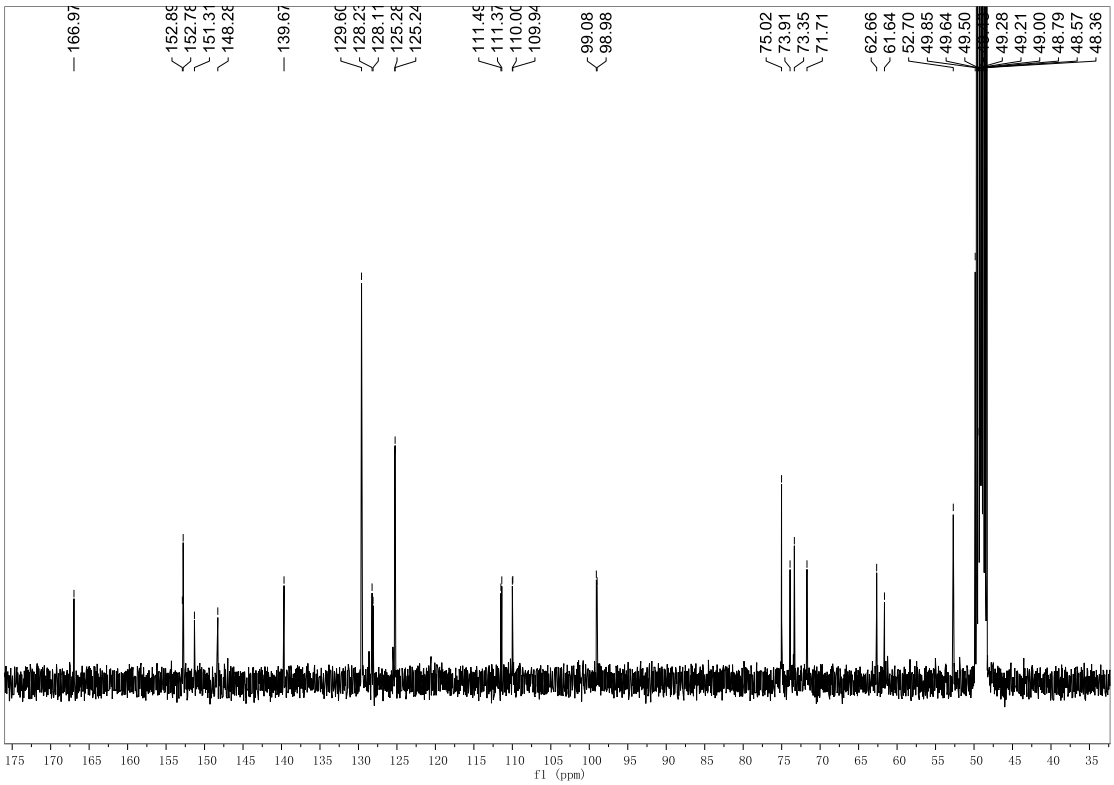


(302h)





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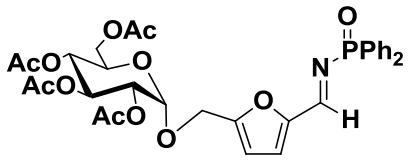
***N*-methylidene [(2,3,4,6-tetra-*O*-acetyl-5-(α-D-glucopyranosyloxymethyl)-furan--2-yl]-diphenylphosphinamide (308)**

Diphenylphosphinic amide (220 mg, 1 mmol) was place in a flam-dried 25 mL flask and dissolved in CH_2Cl_2 (4.4 mL), to the solution was added GMF tetraacetate (914 mg, 2 mmol), Et_3N (400 µL), then cooled with ice-water bath, a solution of $TiCl_4$ (550 µL) was added dropwise to the cooled mixture. After the removed of cooled bath, the mixture was continue stirred for 4 h, then filtrated through celite, evaporation of the solvent gave a brown oil, then purified by column, gave a yellow liquid (350 mg, 53% yield) of diphenylphosphinamide **308**.



(308)

^{1}H NMR (400 MHz, $CDCl_3$): 1.89, 1.97, 1.98, 2.06 (s, 12 H , 4 OAc, C<u>H</u>$_3$), 4.02~4.08 (m, 2H, H-5', H-6'), 4.26 and 4.23 (2d, 1H, J = 4.8Hz, H-6'), 4.61 (d, 1H, part A, AB system, J = 13.6 Hz, H-6), 4.72 (d, 1H, part B, AB system, J = 13.6 Hz, H-6), 4.85 and 4.82 (2d, 1H, J = 3.0 Hz, H-2'), 5.07 and 5.04 (2d, 1H, J = 12 Hz, H-4'), 5.19 (d, 1H, J = 3.0 Hz, H-1'), 5.47 and 5.45 (2d, 1H, J = 10.0 Hz, H-3'), 6.53 (d, 1H, J = 3.0 Hz), 7.13 (d, 1H, J = 3.0 Hz), 7.38~7.50 (m, 6H), 7.84~7.92 (m, 4H), 8.98 (d, J = 3.3 Hz, 1H);

^{13}C NMR (100 MHz, $CDCl_3$): 20.5, 20.6, 20.6, 20.7 (4 OAc, <u>C</u>H$_3$), 61.6 (C-6'), 61.9 (C-6), 67.7 (C-5'), 68.3 (C-4'), 69.9 (C-3') 70.6 (C-2'), 95.1 (C-1'), 112.6 (C-3), 122.3 (C-4), 128.4, 128.6, 131.6, 131.7 131.9, 152.5 and 152.8 (C-5), 156.0 (C-2), 159.2, 169.5, 170.0, 170.1, 170.5 (<u>C</u>O, 4OAc);

HRMS m/z (ESI) calculated for $C_{32}H_{35}NO_{12}P$, $[M + H]^+$ 656.1891; found 656.1871.

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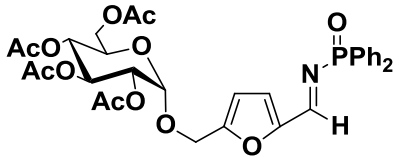

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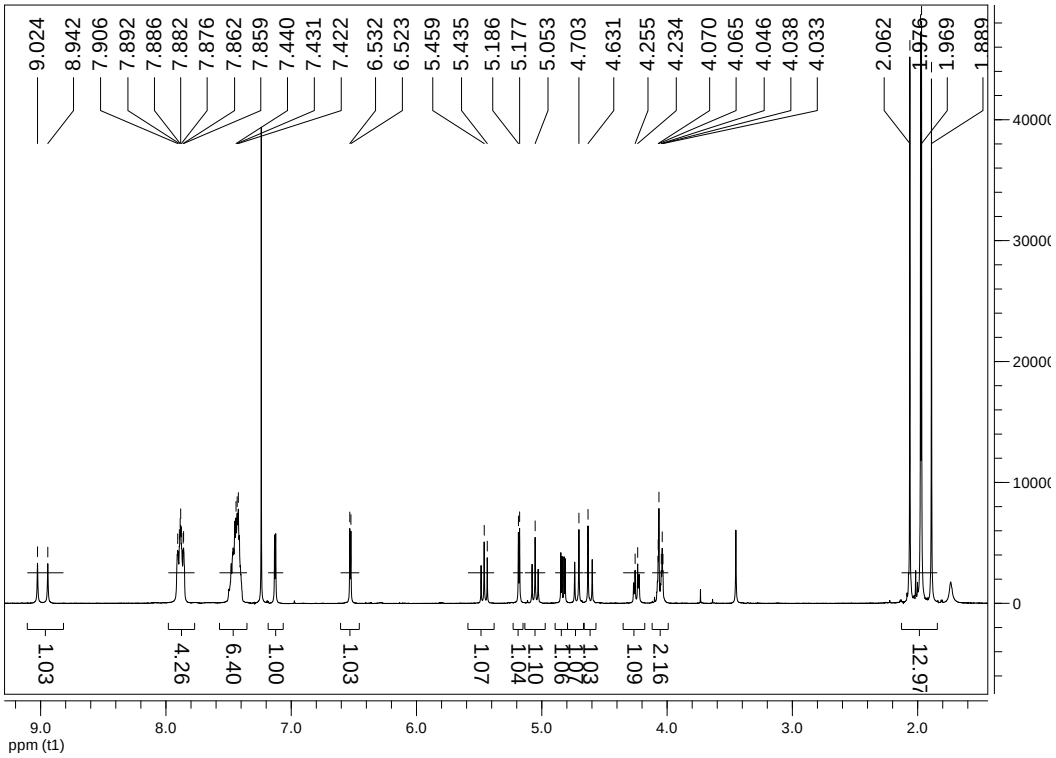

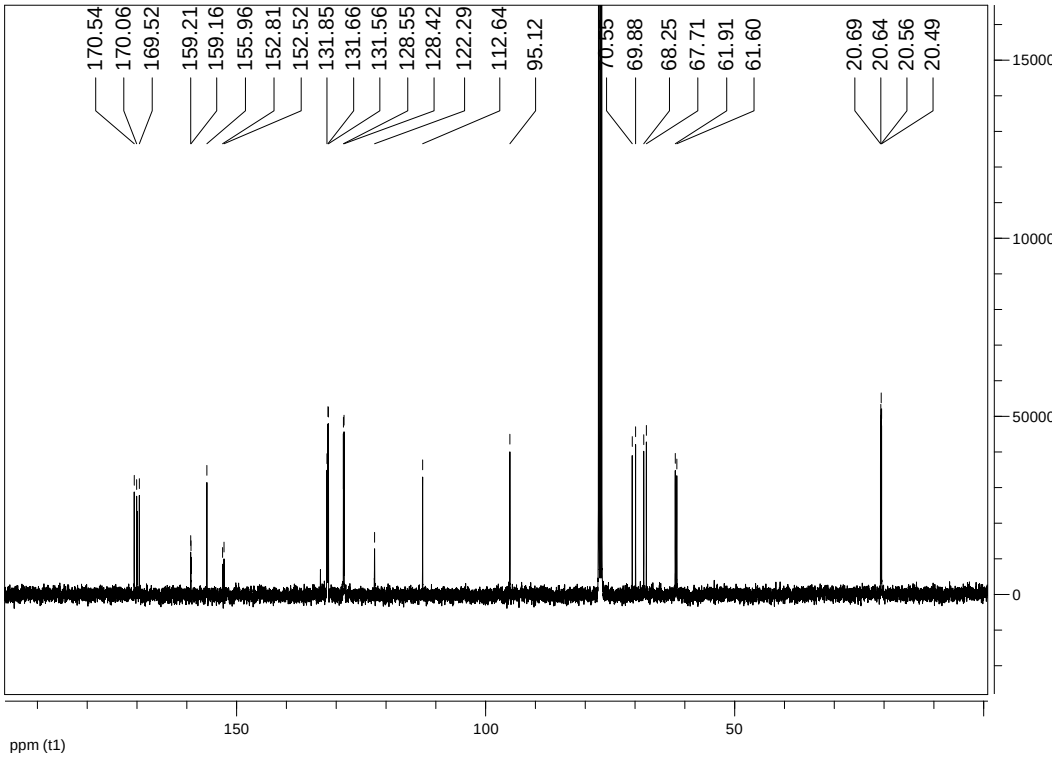

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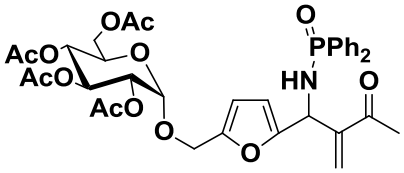
α-Methylene-β-diphenylphosphinamide-4-[(2,3,4,6-tetra-*O*-acetyl-5-(α-D-glucopyranosyloxymethyl)-furan-2-yl] butan-2-one (309)



(309)

To a mixture of 3-HQD (12.2 mg, 0.1 mmol), in THF (300 µL), 10µL MVK was added; then the reaction was stirred for 20 h, upon completition, then purified by PTLC (eluting solvent: ethyl acetate/MeOH = 96/4), gave a colorless solid (53 mg, 75% yield) of butanone **309**.

^{1}H NMR (400 MHz, $CDCl_3$): 1.90 and 1.90 (2s, 3H), 1.98 and 2.00 (2s, 3H), 1.98 (s, 3H), 2.06 and 2.03 (2s, 3H), 2.31 (s, 3H), 3.90~4.05 (m, 2H, H-5'+ H-6'), 4.21 and 4.22 (2dd, 1H, *J* = 12.0, H-6'), 4.40~4.50 (m, 2H, H-6), 4.78 and 4.82 (2dd, 1H, J_a = 3.6, J_b = 7.2 Hz, H-2'), 5.18 and 5.17 (2d, 1H, *J* = 6.4 Hz, H-1'); 5.46 and 5.44 (2d, 1H, *J* = 9.6 Hz, H-3'), 5.05 (2dd, 1H, *J* = 10.0 Hz, H-4' and H-7), 6.12 (s, 1H), 6.17~6.27 (m, 3H), 7.47~7.52 (m, 6H), 7.75~8.90 (m, 4H);

^{13}C NMR (100 MHz, $CDCl_3$): 20.5, 20,5, 20.5 20.6, 20.6, 20.7, 26.4 and 26.5, 51.5 and 51.6, 61.6, 61.6 and 61.7, 61.8, 67.3 and 67.3, 68.4 and 68.3, 67.0 and 67.0, 70.6 and 70.7, 94.6 and 94.8, 107.6, 111.2 and 111,2, 128.3, 128.4, 128.5, 128.6, 131.8, 131.9, 131.9, 132.0, 132.0, 132.3, 132.3, 132.4, 132.4, 155.1 and 155.0 (C-2), 169.5, 170.0, 170.0, 170. 6, 170.6, 199.0 and 199.0 ($\underline{C}O_2Me$).

HRMS m/z (ESI) calculated for $C_{36}H_{41}NO_{13}P$, $[M + H]^+$ 726.2310; found 726.2316.

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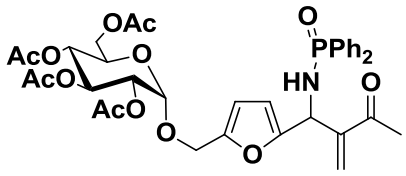

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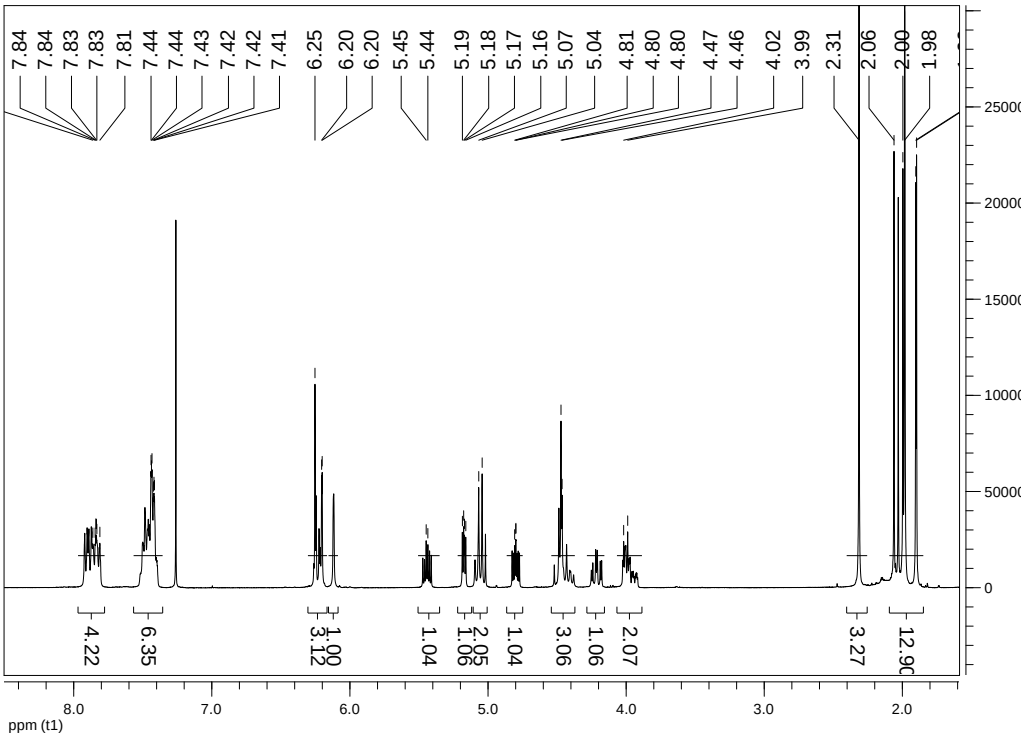

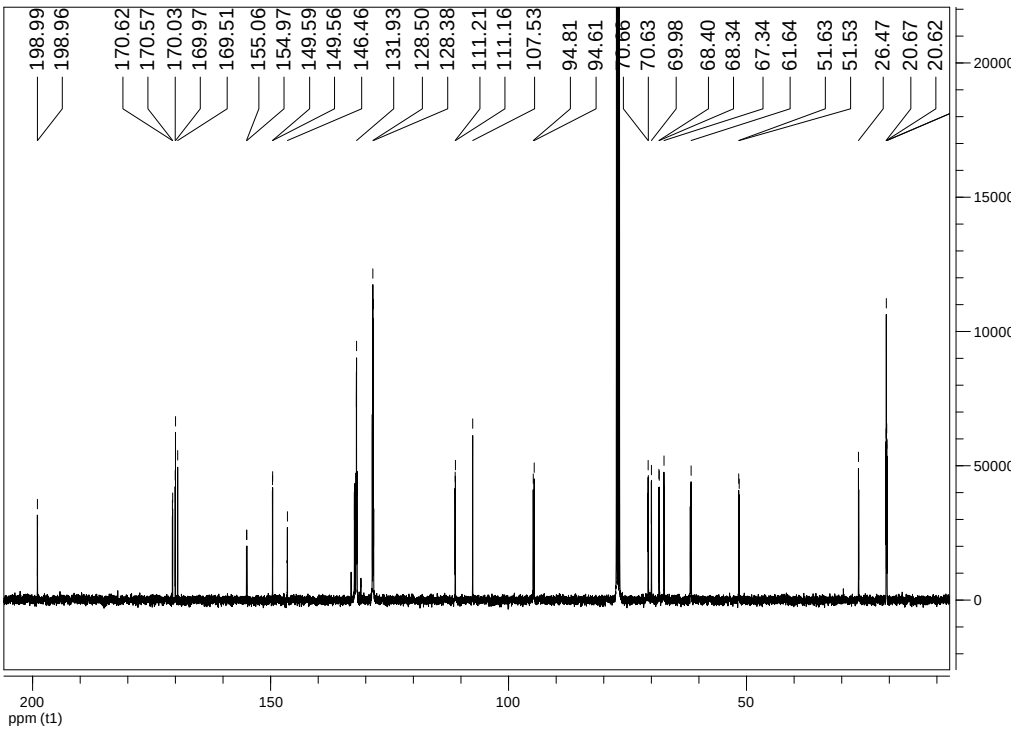

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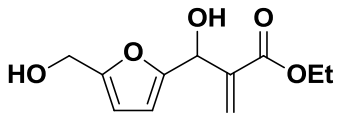
Typical procedure for Baylis-Hillman reaction of HMF with Ethyl acrylate in EtOH/H_2O:

In a typical reaction, HMF (126 mg, 1.0 mmol) was mixed with DABCO (112 mg, 1.0 mmol), and ethyl acrylate (200 mg, 2.0 mmol) in 2 mL of EtOH/H_2O (1/1, v/v) under air. The reaction was monitored by TLC, upon completion, the reaction mixture diluted with *tert*-butyl methyl ether (20 mL) and HCl (1 M, 2 mL), and then neutralized with a saturated $NaHCO_3$ solution. The resulting aqueous solution was extracted with *tert*-butyl methyl ether (2 x 20 mL). After drying over $NaSO_4$, filtration and evaporation, the crude mixture was purified by column chromatography eluting with CH_2Cl_2/Et_2O (1:1) to give the product **323** (169 mg, 75% yield) as a colorless liquid.

Ethyl 2-[hydroxy-(5-hydroxymethyl-furan-2-yl)methyl] acrylate (323)



(323)

^{1}H NMR (300 MHz, MeOD): 1.24 (t, 3H, J_a = 6.9 Hz, J_b = 14.1 Hz, $OCH_2C\underline{H}_3$), 4.10~4.25 (m, 2H, $OC\underline{H}_2CH_3$), 4.48 (s, 2H, H-6), 5.59 (s, 1H, H-7), 6.06 (d, 1H, J = 1.2 Hz, H-9a), 6.14 (d, 1H, J = 3.0 Hz, H-3), 6.24 (d, 1H, J = 2.7 Hz, H-4), 6.37 (d, 1H, J = 0.9 Hz, H-9b);

^{13}C NMR (75 MHz, MeOD): 14.4 ($OCH_2\underline{C}H_3$), 57.4 (C-6), 61.9 ($O\underline{C}H_2CH_3$), 66.4 (C-7), 108.8 (C-3), 109.1 (C-4), 125.7 (C-9), 142.6 (C-8), 155.8 (C-5), 156.1 (C-2), 167.2 ($\underline{C}O_2Et$).

MS m/z (ESI) calculated for $C_{11}H_{14}NaO_5$, $[M + Na]^+$ 249.0733; found 249.0734.

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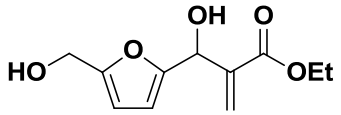

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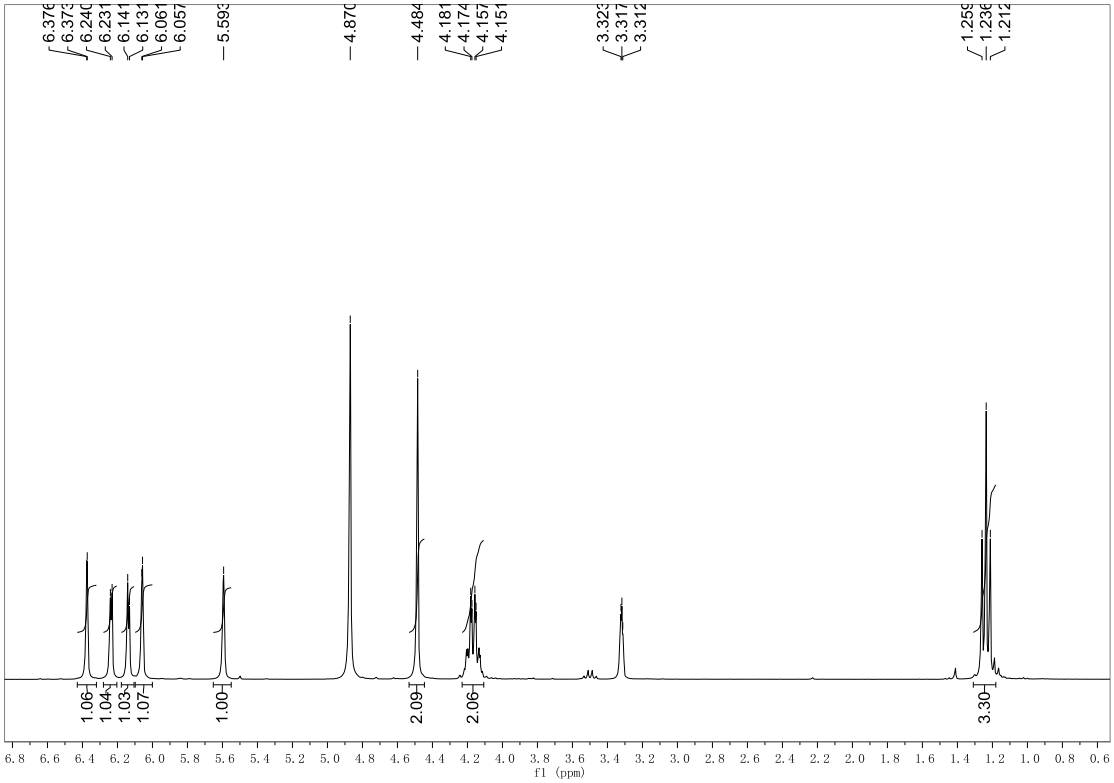

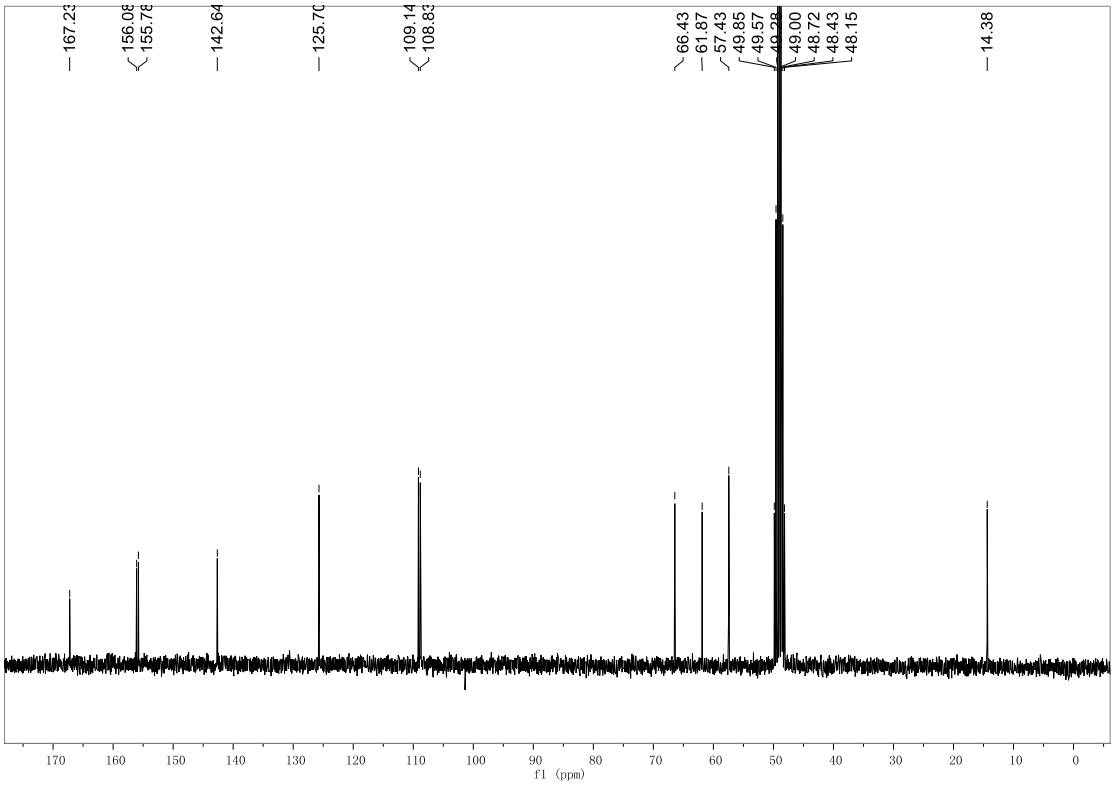

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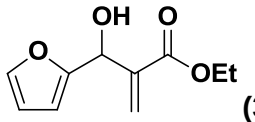
Procedure for Baylis-Hillman reaction of furfural with Ethyl acrylate in EtOH/H_2O:

In a typical reaction, furfural (96 mg, 1.0 mmol) was mixed with DABCO (112 mg, 1.0 mmol), and ethyl acrylate (200 mg, 2.0 mmol) in 2 mL of EtOH/H_2O (1/1, v/v) under air. The reaction was monitored by TLC, upon completion, the reaction mixture diluted with *tert*-butyl methyl ether (20 mL) and HCl (1 M, 2 mL) was added, and then neutralized with a saturated $NaHCO_3$ solution. The resulting aqueous solution was extracted with *tert*-butyl methyl ether (2 x 20 mL). After drying over $NaSO_4$, filtration and evaporation, the crude mixture was purified by column chromatography eluting with Et_2O to give the product **331** (180 mg, 90% yield) as a colorless liquid.

Ethyl 2-[hydroxy-(furan-2-yl)methyl] acrylate (331)



(331)

^{1}H NMR (300 MHz, MeOD): 1.22 (t, 3H, J_a = 7.2 Hz, J_b = 14.4 Hz, $OCH_2C\underline{H}_3$), 4.10~4.25 (m, 2H, $OC\underline{H}_2CH_3$), 5.60 (s, 1H, H-7), 6.03 (s, 1H, H-9a), 6.14 (dd, 1H, J_a = 1.8 Hz, J_b = 3.0 Hz, H-3), 6.19 (d, 1H, J = 3.0 Hz, H-4), 6.36 (s, 1H, H-9b); 7.44 (d, 1H, J = 0.9 Hz, H-5);

^{13}C NMR (75 MHz, MeOD): 14.4 ($OCH_2\underline{C}H_3$), 61.9 ($O\underline{C}H_2CH_3$), 66.4 (C-7), 108.1 (C-3), 111.3 (C-4), 125.6 (C-9), 142.3 (C-8), 143.4 (C-5), 156.4 (C-2), 167.2 ($\underline{C}O_2Et$).

MS m/z (ESI) calculated for $C_{11}H_{14}NaO_5$, $[M + Na]^+$ 219.0628; found 219.0638.

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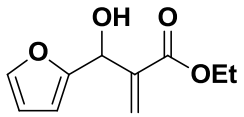

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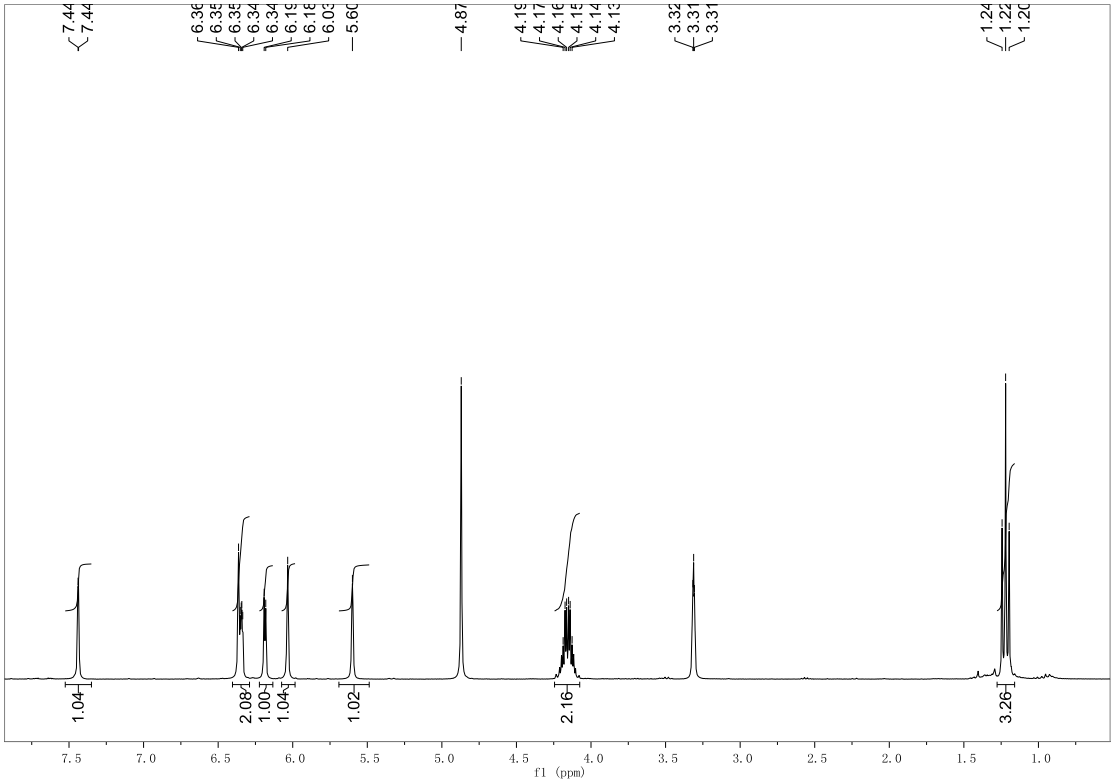

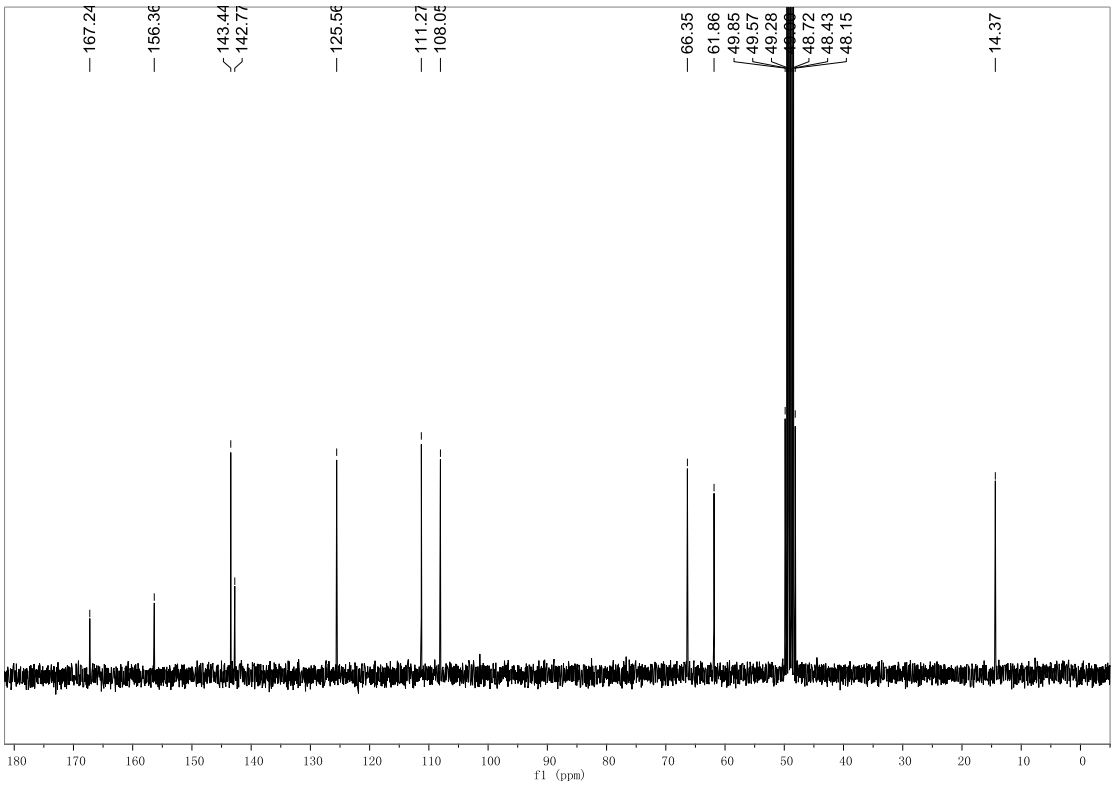

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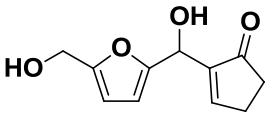
2-[hydroxy-(5-hydroxymethyl-furan-2-yl)methyl]cyclopent-2-en-1-one (339a)



(339a)

A solution of HMF (126 mg, 1.0 mmol), DPI (74 mg, 0.6 mmol), 2-cyclopenten-1-one (123 mg, 1.5 mmol) in water (1.0 mL) was stirred for 30 h, upon competition, extracted with ethyl acetate (3 x 20 mL), dried by Na_2SO_4, then concentrated under vacuum, purified by column (ethyl acetate/pentane: 70/30) to give the desired product **339a** (162 mg, 83% yield) as yellow liquid.

^{1}H NMR (300 MHz, CD_3Cl): 2.42~2.50 (m, 2H), 2.61~2.67 (m, 2H), 4.52 (s, 2H), 5.50 (s, 1H), 6.17 (d, 1H, J = 3.0 Hz), 6.20 (d, 1H, J = 3.0 Hz), 7.59 (s, 1H, J = 2.7 Hz);
^{13}C NMR (75 MHz, CD_3Cl): 26.9, 35.1, 57.0, 62.8, 108.0, 108.4, 145.0, 153.7, 154.1, 161.2, 209.2;
MS m/z (ESI) calculated for $C_{11}H_{12}NaO_4$, $[M + Na]^+$ 231.0628; found 231.0630.

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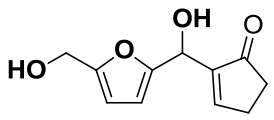
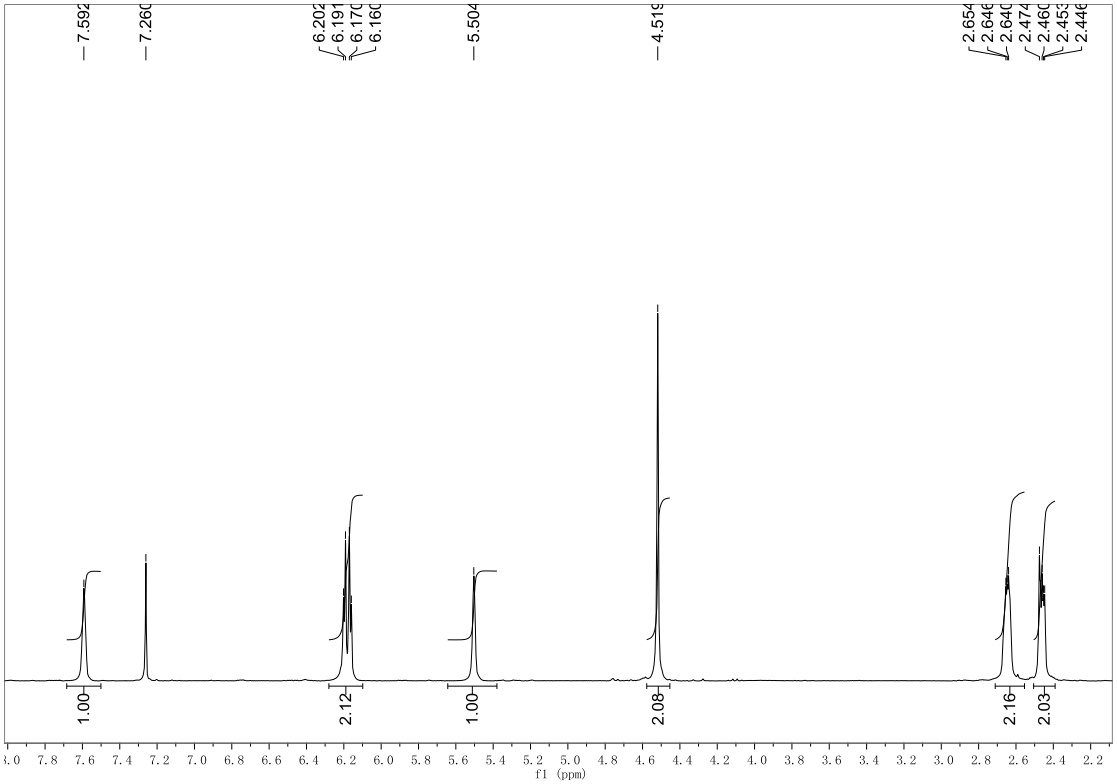
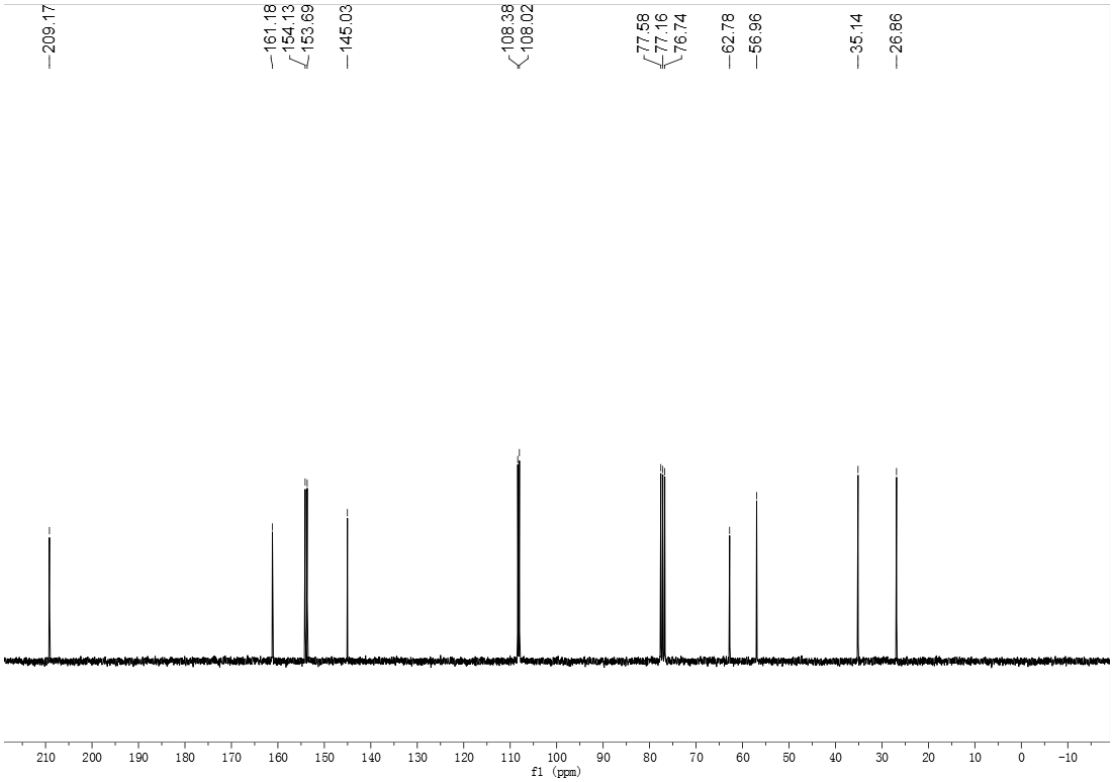


(339a)





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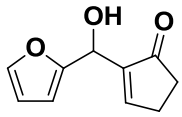
2-[hydroxy-(furan-2-yl)methyl]cyclopent-2-en-1-one (339b)



(339b)

A solution of furfural (96 mg, 1.0 mmol), DPI (74 mg, 0.6 mmol), 2-cyclopenten-1-one (123 mg, 1.5 mmol) in water (1.0 mL) was stirred for 30 h, upon competition, extracted with ethyl acetate (3 x 20 mL), dried by Na_2SO_4, then concentrated under vacuum and purified by column (ethyl acetate/pentane: 40/60) to give the desired product **339b** (156 mg, 88% yield) as a yellow liquid.

^{1}H NMR (300 MHz, CD_3Cl): 2.38~2.45 (m, 2H), 2.57~2.65 (m, 2H), 3.67 (s, 1H), 5.52 (s, 1H), 6.23 (d, 1H, J = 3.3 Hz), 6.26~ 6.30 (m, 1H), 7.33 (s, 1H), 7.51 (s, 1H);
^{13}C NMR (75 MHz, CD_3Cl): 26.8, 35.1, 63.3, 107.3, 110.3, 142.4, 144.9, 153.8, 160.5, 209.1;
MS m/z (ESI) calculated for $C_{10}H_{10}NaO_3$, $[M + Na]^+$ 201.0522; found 201.0515.

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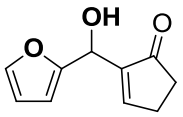
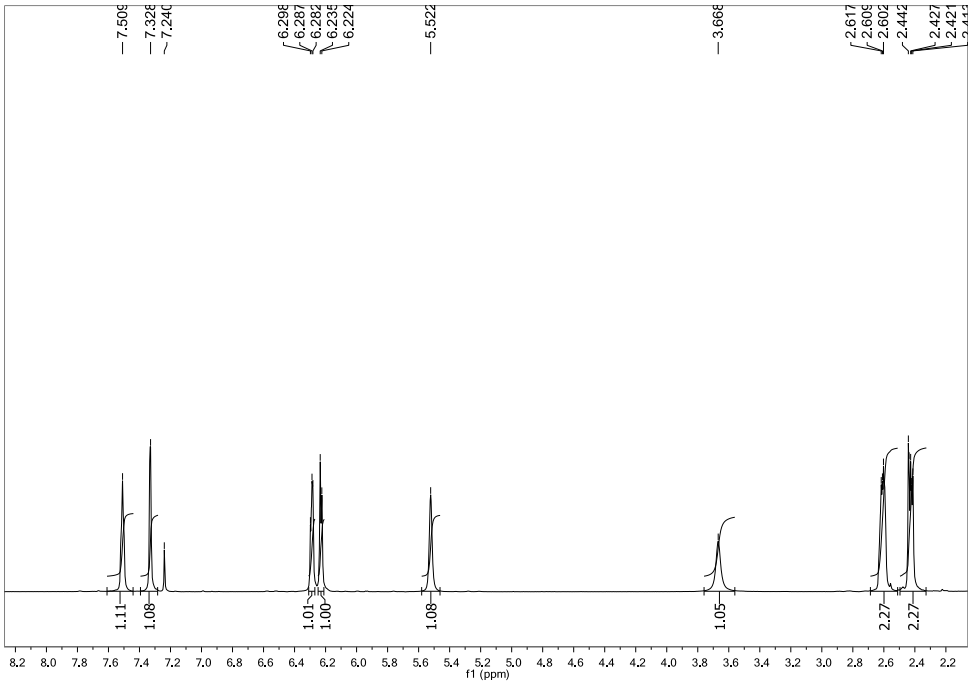
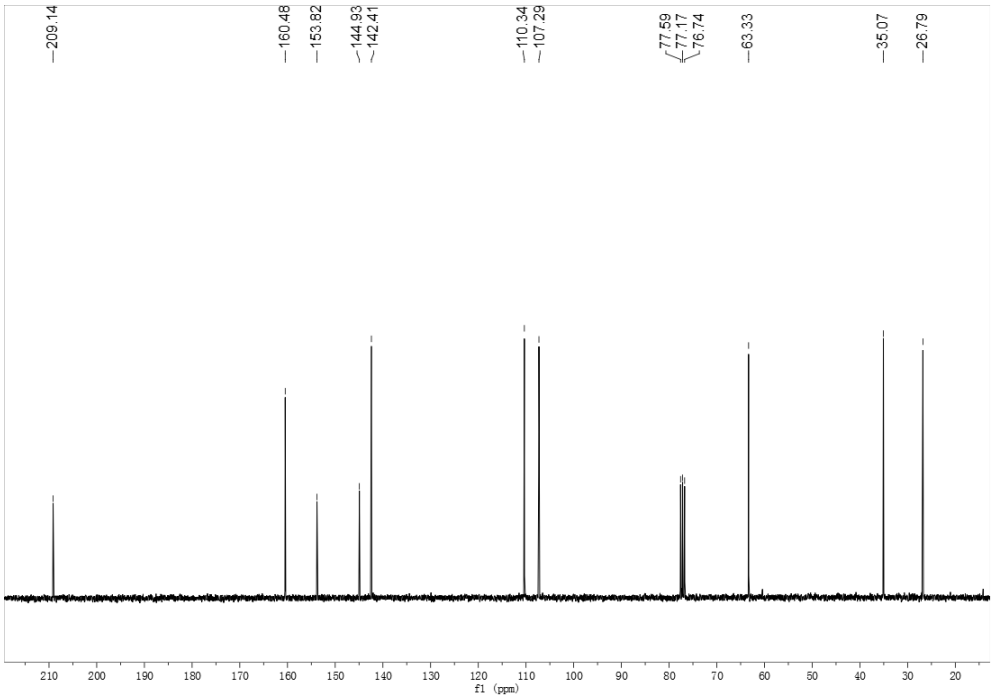


(339b)





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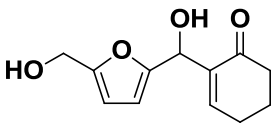
2-[hydroxy-(5-hydroxymethyl-furan-2-yl)methyl]cyclohex-2-en-1-one (339c)



(339c)

A solution of HMF (126 mg, 1.0 mmol), DPI (74 mg, 0.6 mmol), 2-cyclohexen-1-one (144 mg, 1.5 mmol) in water (1.0 mL) was stirred for 30 h, upon competition, extracted with ethyl acetate (3 x 20 mL), dried by Na_2SO_4, then concentrated under vacuum. Purification by column (ethyl acetate/pentane: 70/30) gave the desired desired product **339c** (155 mg, 70% yield) as yellow liquid.

^{1}H NMR (300 MHz, CD_3Cl): 1.75~2.00 (m, 2H), 2.25~2.5.0 (m, 4H), 4.35 (s, 2H), 5.44 (s, 1H), 5.98 (d, 1H, J = 3.0 Hz), 6.03 (d, 1H, J = 3.0 Hz), 6.97 (t, 1H, J_a = 3.9 Hz, J_b = 7.8 Hz);

^{13}C NMR (75 MHz, CD_3Cl): 22.5, 25.7, 38.3, 56.9, 65.1, 107.6, 108.3, 138.3, 148.2, 153.8, 154.6, 199.6;

MS m/z (ESI) calculated for $C_{12}H_{14}NaO_4$, $[M + Na]^+$ 245.0784; found 245.0790.

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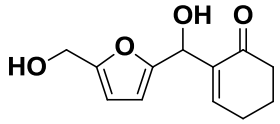

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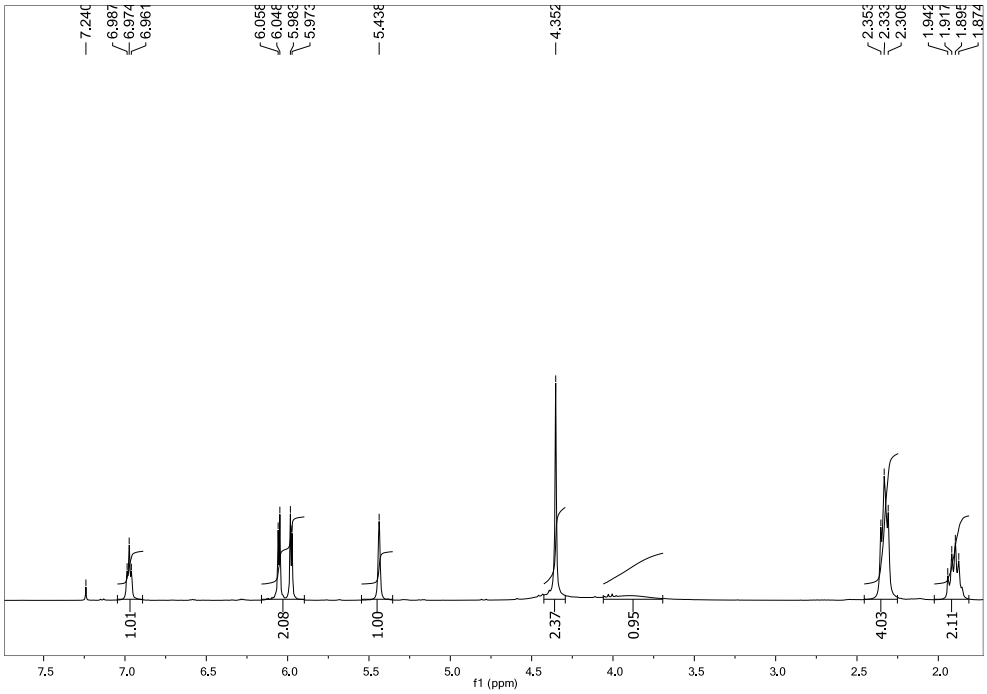

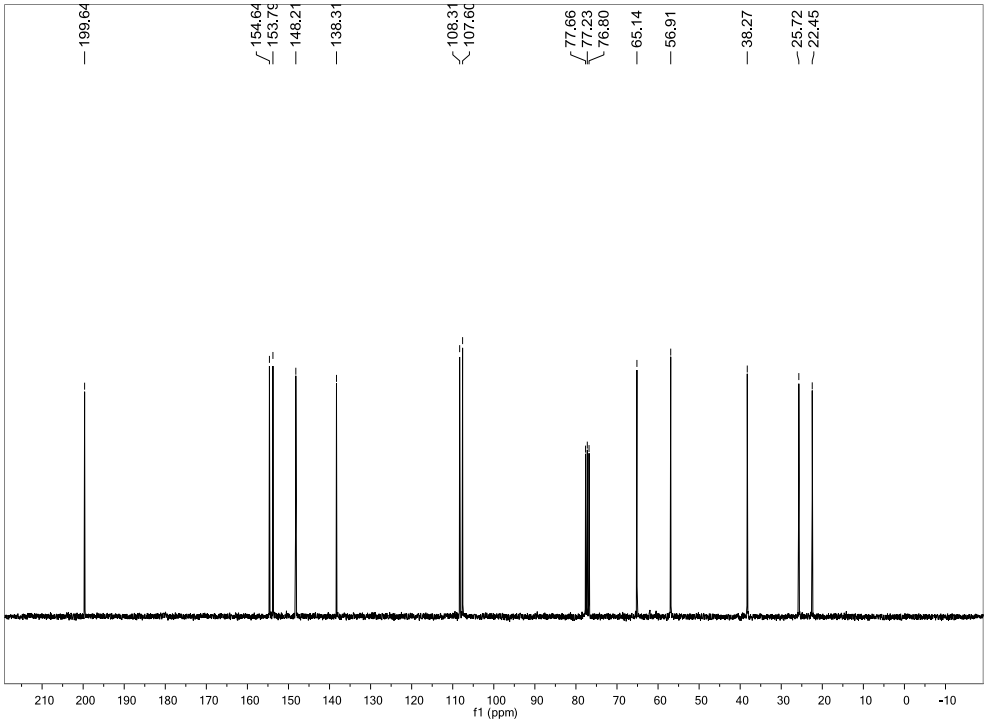

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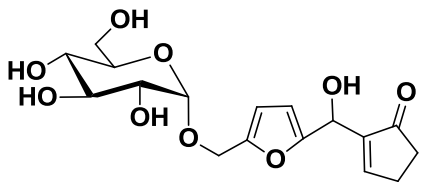
2-[hydroxy-(5-(α-D-glucopyranosyloxymethyl)-furan-2-yl)methyl]cyclopent-2-en -1-one (339d)



(339d)

A mixture of GMF (145 mg, 0.5 mmol), DPI (38 mg, 0.3 mmol), 2-cyclopenten-1-one (82 mg, 2.0 mmol) in water (0.5 mL) was stirred for 30 h, evaporation and purification by PTLC (CH_2Cl_2/MeOH = 90/10) gave the desired desired product **339d** (102 mg, 55% yield).

^{1}H NMR (300 MHz, CD_3Cl): 2.38~2.49 (m, 2H), 2.60~2.70 (m, 2H), 3.20~3.30 (m, 1H, H-4'), 3.36~3.40 (m, 1H, H-2'), 3.52~3.72 (m, 3H, H-3', H-5', H-6'), 3.72~3.80 (m, 1H, J = 2.8 Hz, H-6'), 4.50 (part A, AB system, 1H, J = 12.0 Hz), 4.61 (part B, AB system, 1H, J_a = 3.0 Hz, J_b = 12.0 Hz), 5.40 (s, 1H), 6.16 (d, 1H, J = 3.3 Hz), 6.32 (d, 1H, J = 3.3 Hz), 7.75~7.80 (m, 1H);

^{13}C NMR (75 MHz, CD_3Cl): 27.8, 36.1, 62.1 and 62.2, 62.6 and 62.6, 63.0, 71.7, 73.4, 73.8, 75.0, 99.0 and 99.2, 109.0 and 109.0, 111.5 and 111.5, 146.8 and 146.9, 152.5 and 152.6, 156.1 and 156.2, 163.1, 210.4;

MS m/z (ESI) calculated for $C_{17}H_{22}NaO_9$, $[M + Na]^+$ 393.1156; found 393.1171.

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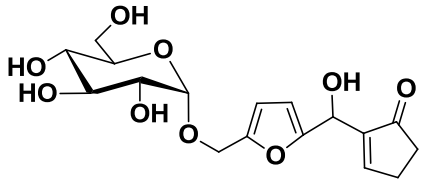
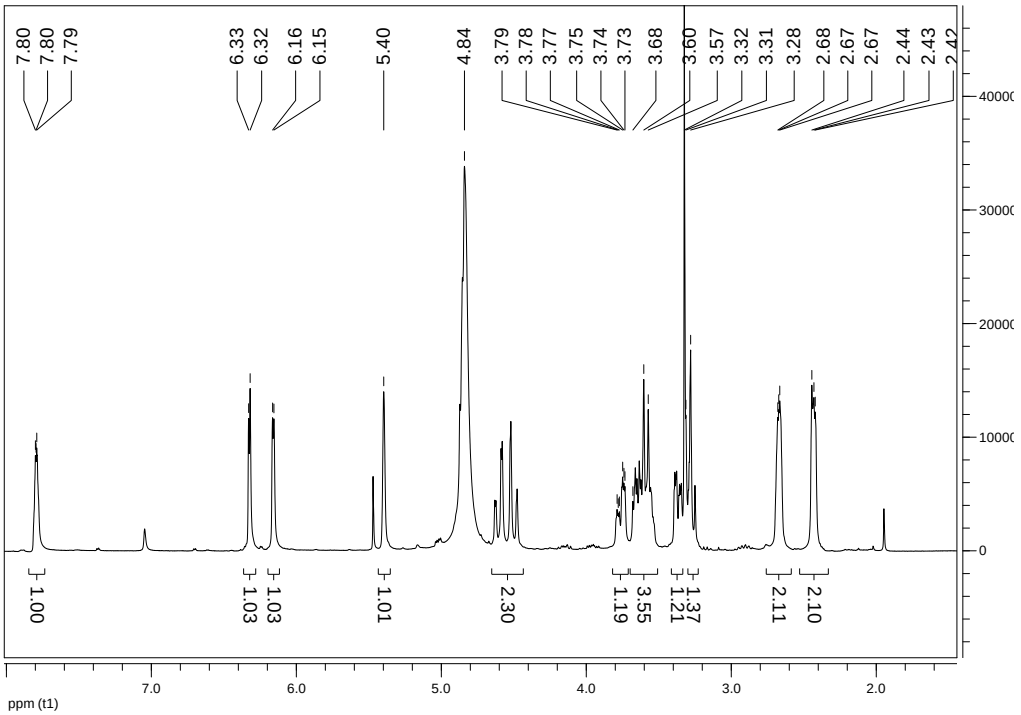
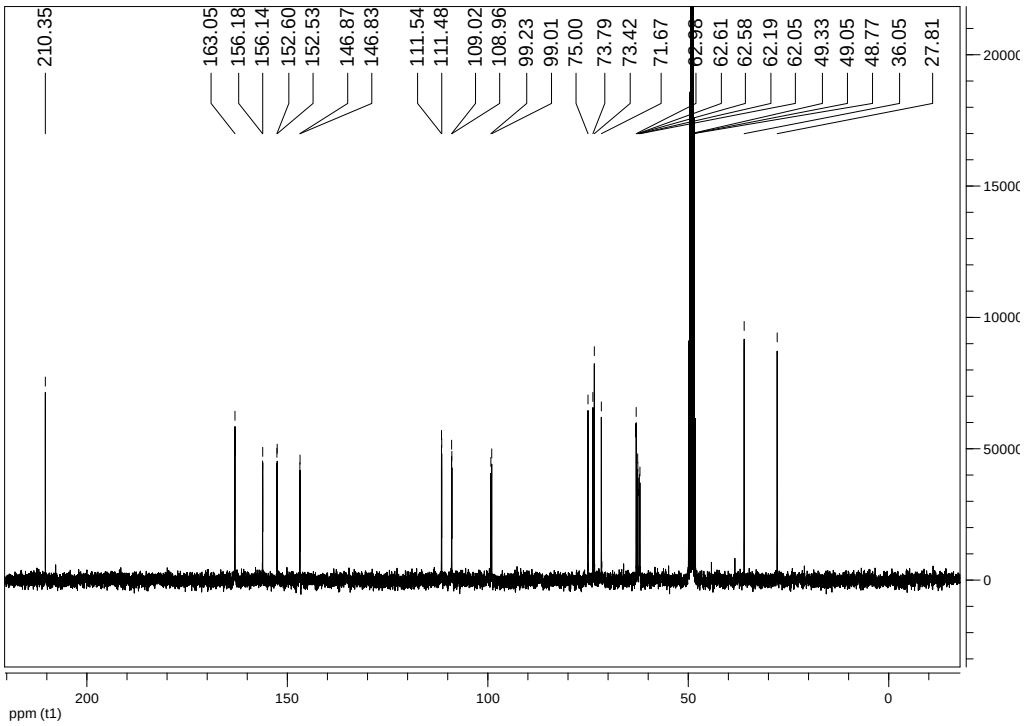


(339d)





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References

[1] Anastas, P. T.; Warner, J. C. Green Chemistry Theory and Practice. Oxford University Press, Oxford, **1998**.

[2] Trost, B. “The atom economy-a search for synthetic efficiency,” *Science*, **1991**, *254*, 1471-1477.

[3] Sheldon, R. A. Organic synthesis: past, present and future,” *Chem. Ind,* **1992**, 903–906.

[4] Sheldon, R. A. The E Factor: fifteen years on, *Green Chem*., **2007**, 9, 1273-1283.

[5] Anastas, P. T. and Kirchhoff, M. M. Origins, Current Status, and Future Challenges of Green Chemistry, *Acc. Chem. Res*., **2002**, 35, 686-694.

[6] Sullivan, D. A. Kirk-Othmer Encyclopedia of Chemical Technology. John Wiley & Sons, Inc., New York, USA, **2000**.

[7] De Caro, P. and Thiébaud-Roux, S., *Biosolvants*, **2008**.

[8] Capello, C.; Fischer, U. and Hungerbühler, K. What is a green solvent? A comprehensive framework for the environmental assessment of solvents, *Green Chem*., **2007**, 9, 927-934,.

[9] Estévez, C. Sustainable Solutions for Modern Economies, Höfer, R. Ed. RSC Publishing, Cambridge, UK, **2009**, 407-423.

[10] Gu, Y. and Jérôme, F. Bio-based solvents: an emerging generation of fluids for the design of eco-efficient processes in catalysis and organic chemistry.*Chem. Soc. Rev*., **2013**, 42, 9550-9570.

[11] Li, C. -J. Reactions in water-Green solvents. Wiley-VCH, **2010**.

[12] Stark, A. and Wasserscheid, P. Ionic liquids-Green solvents, **2010**.

[13] Zhang, Q.; De Oliveira Vigier, K.; Royer, S. and Jérôme, F. Deep eutectic solvents: syntheses, properties and applications. *Chem. Soc. Rev*., **2012**, 41, 7108-7146.

[14] Avalos, M.; Babiano, R.; Cintas, P. J.; Jiménez, L.; and Palacios, J. C. Greener media in chemical synthesis and processing., Angew. Chem. Int. Ed., **2006**, 45, 3904-3908,

[15] Philip, W. L. J. Supercritical solvents-Green solvents, Wiley-VCH, **2010**.

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[16] Bozell, J. J. Feedstocks for the Future-Biorefinery Production of Chemicals from Renewable Carbon, CLEAN-Soil, Air, Water, **2008**, 36, 641-647,

[17] Sheldon, R. A.; Arends, I. and Hanefeld, U. Green chemistry and catalysis. John Wiley & Sons, **2007**.

[18] Lichtenthaler, F. W. Carbohydrate as Organic Raw Materials. VCH Weinheim, **1991**.

[19] Descotes, G. Carbohydrate as Organic Raw Materials,Vol 2. VCH Weinheim, 1**993**.

[20] van Bekkum, H.; Röper, H.; Voragen, A. G. J. Carbohydrate as Organic Raw Materials, Vol. 3. VCH Weinheim, **1996**.

[21] Praznik, W.; Huber, H Carbohydrate as Organic Raw Materials, Vol. 4. WUV-Univ, Vienna, **1998**.

[22] Rauter, A. P.; Vogel, P.; Queneau. Y. Carbohydrates in Sustainable Development I, Topics in Current Chemistry, vol. 294. Springer, Germany, **2010**.

[23] Rauter, A. P.; Vogel, P.; Queneau. Y. Carbohydrates in Sustainable Development II, *Topics in Current Chemistry*, vol. 295. Springer, Germany, **2011**.

[24] Gallezot, P. "Conversion of biomass to selected chemical products.,"*Chem. Soc. Rev.*, **2012,** *41***,** 1538-1558.

[25] Corma, A.; Iborra, S. and Velty, A. Chemical routes for the transformation of biomass into chemicals, *Chem. Rev*. **2007**, *107*, 2411-2502.

[26] Climent, M. J.; Corma, A. and Iborra, S. Converting carbohydrates to bulk chemicals and fine chemicals over heterogeneous catalysts, *Green Chem*., **2011**, 13, 520-540.

[27] Dwight, R. Surfactants-A Market Opportunity Study Update. **1997**, Omni. Tech. International, LTD.

[28] Hill, K. Sugar-Based Surfactants for Consumer Products and Technical Applications, in Sugar-Based Surfactants: Fundamentals and Applications. *CRC Press*, **2008**.

[29] von Rybinski, W. and K. Hill, Alkyl Polyglycosides-Properties and Applications of a new Class of Surfactants, Angew. Chemie Int. Ed., **1998**, 8, 426–447.

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[30] Foley, P.; Pour, A. K.; Beach, E. S. Derivation and synthesis of renewable surfactants. Chemical Society Reviews, Chem. Soc. Rev., **2012**, 41, 1499-1518.

[31] Holmberg, K. Natural surfactants. Current Opinion in Colloid, Interface Sci., **2001**, 6, 148–159.

[32] Rees, G. D. “Microemulsion-based media as novel drug delivery systems,” Adv. Drug Deliv. Rev., **2000**, 45, 89–121.

[33] Hill, K. and Rhode,O. Sugar-based surfactants for consumer products and technical applications, Fett-Lipid, **1999**, 101, 25–33.

[34] Hunkeler, D. J. Inverse-emulsion polymerization of acrylamide using block copolymeric surfactants: Mechanism,kinetics and modelling, Polymer, **1997**, 38, 437-447,

[35] Stockburger, G. J. Process for preparing sorbitan esters. USPTO,USA, 1981.

[36] Queneau, Y.; Chambert, S.; Besset, C. and Cheaib, R. “Recent progress in the synthesis of carbohydrate-based amphiphilic materials: the examples of sucrose and isomaltulose.,” Carbohydr. Res., **2008**, 343, 1999-2009.

[37] Molinier, V.; Kouwer, P. J.; Fitremann, J.; Bouchu, A.; Mackenzie, G.; Queneau, Y.; Goodby, J. W. Self-organizing properties of monosubstituted sucrose fatty acid esters: The effects of chain length and unsaturation, Chem. Eur. J., **2006**, 12, 3547-3557.

[38] Marchant. R. and Banat, I. M. Microbial biosurfactants: challenges and opportunities for future exploitation, Trends Biotechnol., **2012**, 30, 558–565.

[39] Marchant. R. and Banat, I. M. Biosurfactants: a sustainable replacement for chemical surfactants?, Biotechnol. Lett., **2012**, 34, 1597-1605.

[40] Kitamoto, D.; Morita, T.; Fukuoka, T.; Konishi, M. Self-assembling properties of glycolipid biosurfactants and their potential applications, Curr. Opin. Colloid Interface Sci., **2009**, 14, 315–328.

[41] Hakomori, S. -I. The glycosynapse, Proc. Natl. Acad. Sci., **2002**, 99, 225–232, 2002.

[42] Yu, R. K., Suzuki, Y.; Yanagisawa, M. Membrane glycolipids in stem cells, Febs Lett., **2010**, 584, 1694-1699.

[43] Hakomori, S.-i. “Structure and function of glycosphingolipids and sphingolipids: Recollections and future trends,” Biochim. Biophys., **2008**, 1780, 325-346.

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[44] Lingwood, D,; Simons K. Lipid Rafts As a Membrane-Organizing Principle, Science, **2010**, 327, 46-50.

[45] Hölzl, G.; and Dörmann, P. Structure and function of glycoglycerolipids in plants and bacteria, Prog. Lipid Res., **2007**, 46, 225–243.

[46] Popova, A. V., Hincha, D. K. Effects of the sugar headgroup of a glycoglycerolipid on the phase behavior of phospholipid model membranes in the dry state, Glycobiology, **2005**, 15, 1150–1155.

[47] Hamberg, M.; Liepinsh, E.; Otting, G.; Griffiths, W. Isolation and structure of a new galactolipid from oat seeds, Lipids, **1998**, 33, 355–363.

[48] Lundquist, J. J. and Toone, E. J. The Cluster Glycoside Effect, Chem. Rev., **2002**, 102, 555–578.

[49] Choi, S.; Mammen, M. and Whitesides, G. M. Generation and in Situ Evaluation of Libraries of Poly (acrylic acid) Presenting Sialosides as Side Chains as Polyvalent Inhibitors of Influenza-Mediated Hemagglutination, **1997**, 7863, 4103–4111.

[50] Pasparakis, G.; Cockayne, A. and Alexander, C. Control of bacterial aggregation by thermoresponsive glycopolymers., J. Am. Chem. Soc., **2007**, 129, 11014–110145.

[51] Rele, S. M.; Cui, W.; Wang, L.; Hou, S.; Barr-Zarse, G.; Tatton, D.; Gnanou, Y.; Esko, J. D.; Chaikof, E. L. Dendrimer-like PEO glycopolymers exhibit anti-inflammatory properties., J. Am. Chem. Soc., **2005**, 127, 10132–101323.

[52] Schlaad, H.; You, L.; Sigel, R.; Smarsly, B.; Heydenreich, M.; Mantion, A. and Masić, A. Glycopolymer vesicles with an asymmetric membrane, Chem. Commun., **2009**, 1478–1480.

[53] Pearson, S. Core-shell particles with glycopolymer shell and polynucleoside core via RAFT: From micelles to rods, J. Polym. Sci. Part A Polym Chem, **2009**, 47, 1706–1723.

[54] Pasparakis G. and Alexander, C. Sweet talking double hydrophilic block copolymer vesicles, Angew. Chem. Int. Ed., **2008**, 47, 4847–4850,

[55] Ito, R. and Matsuo, Y Handbook of Carbohydrate Polymers: Development, Properties and Applications. Nova Science Publishers, Inc., **2011**.

[56] Herna E. B. and Galbis, J. A. “Linear Polyesters of the Poly [alkylene (and co-arylene) dicarboxylate] Type Derived from Carbohydrates,” Macromolecules, **2006**, 4, 7941-7949.

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[57] Bueno, M.; Galbis, J. A.; García-Martín, M. G.; De Paz, M. V.; Zamora, F. and Muñoz-Guerra, B. “Synthesis of stereoregular polygluconamides from D-glucose and D-glucosamine,” J. Polym Sci. Part A Polym. Chem., **1995**, 33, 299-305.

[58] Pinilla, I. M.; Martinez, M. B. and Perez, J. A. G. Synthesis of a Stereoregular Poly (ester amide) Derived from, Macromolecules, **1995**, 28, 3766–3770.

[59] (a) Violante de Paz S. M.-G., Marín, M. Zamora, R. Hakkou, F. Alla, K. Galbis, A. J. Muñoz-Guerra, B, Linear polyurethanes derived from alditols and diisocyanates, J. Polym Sci. Part A Polym. Chem., **2007**, 45, 4109–4117; (b) De Paz Banez, M. V. and Galbis, J. A. Versatile Sugar Derivatives for the Synthesis of Potential Degradable Hydrophilic-Hydrophobic Polyurethanes and Polyureas, J. Carbohydr. Chem, **2008**, 27, 120-140.

[60] Boyer, A.; Lingome, C. E.; Condassamy, O.; Schappacher, M., Moebs-Sanchez, S.; Queneau, Y.; Gadenne, B.; Alfos, C. and Cramail, H. Glycolipids as a source of polyols for the design of original linear and cross-linked polyurethanes. Polym. Chem., **2013**, 4, 296-306.

[61] Widenhagen, R., Lorenz, S. Ein neues bakterielles umwandlung¬sprodukt der saccharose. Angew. Chem., **1957**, 69, 641;

[62] Lina, B. A. R.; Jonker, D.; Kozianowski, G. Isomaltulose (Palatinose®): a review of biological and toxicological studies. Food. Chem. Toxicol. **2002**, 40, 1375-1381.

[63] Schiweck, H.; Munir, M.; Rapp, K.M.; Schneider, B.; Vogel, P. In: Carbohydrates as Organic Raw Materials, ED. F. W. Lichtenthaler, VCH Weinheim, **1991**, 3, 57-94.

[64] Schwengers, D. in: Carbohydrate as Organic Raw Materials, Lichtenthaler, F. W. Ed.; VCH Weinheim, **1991**, 183-195.

[65] Munir, M.; Schneider, B.; Schiweck, H. 1-O-α-D-glucopyranosyl-D-fructose: darstellung aus saccharose und ihre reduktion zu 1-O-α-D-Glucopyranosyl-D-glucitol. Carbohydr. Res., **1987**, 164, 477-485.

[66] Hicks, K. B.; Symanski, E. V.; Pfeffer. P. E. Synthesis and high-performance liquid chromatography of maltulose and cellobiulose. Carbohydr. Res., **1983**, 112, 37-50.

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[67] Hough, L.; Jones, J. K. N.; Richards, E. L. The reaction of amino-compounds with sugars. Part II. The action of ammonia on glucose, maltose, and lactose, J. Chem. Soc., **1953**, 2005-2009.

[68] Martin, D.; Lichtenthaler, F.W. Versatile building blocks from disaccharides: glycosylated 5-hydroxymethylfurfurals. Tetrahedron: Asymmetry, **2006**, 17, 756-762.

[69] Schneider, B. Lichtenthaler, F. W.; Steinle, G.; Schiweck, H. Studies on ketoses, distribution of furanoid and pyranoid tautomers of D-fructose in water, dimethyl sulfoxide, and pyridine via ^{1}H NMR intensities of anomeric hydroxy groups in [D_6]DMSO, *Liebigs Ann. Chem*, **1985**, 2443-2453.

[70] D. Daudé, M. Remaud-Siméon, I. André, Sucrose analogs: an attractive (bio)source for glycodiversification. *Nat. Prod. Rep*., **2012**, *29*, 945-960.

[71] F. W. Lichtenthaler, Unsaturated *O*- and *N*-Heterocycles from Carbohydrate Feedstocks, *Acc. Chem. Res.* **2002**, *35*, 728-737.

[72] Lichtenthaler, F. W. and Peters, S. Carbohydrates as green raw materials for the chemical industry, C. R. Chim., **2004**, 7, 65–90.

[73] Queneau, Y. Fitremann, J. and Trombotto, S. The chemistry of unprotected sucrose: the selectivity issue, C. R. Chim., **2004**, 7, 177–188.

[74] Queneau, Y. Jarosz, S. Lewandowski, B. and Fitremann, J. Sucrose chemistry and applications of sucrochemicals., **2007**, 61, 217–292.

[75] van der Heijden, A.M.; Lee, T.C.; Van Rantwijk, F.; Van Bekkum, H. Glycosidation of fructose-containing disaccharides using MCM-41 material as the catalyst. Carbohydr. Res., **2002**, 337, 1993-1998

[76] Tanaka, M.; Nakajima, Y.; Nishio, K.; Hashimoto, H. Structure of oligosaccharides prepared by acidic condensation of palatinose. J. Carbohydr. Chem., **1993**, 12, 49-61.

[77] Defaye, J.; Garcia Fernández; J. M. Selective protonic activation of isomeric glycosylfructoses with pyridinium poly(hydrogen fluoride) and synthesis of spirodioxanyl oligosaccharides. Carbohydr. Res., **1992**, 273, 223-247.

[78] Defaye, J.; Garcia Fernández; J. M. Synthesis of dispirodioxanyl pseudo-oligosaccharides by selective protonic activation of isomeric glycosylfructoses in anhydrous hydrogen fluoride. Carbohydr. Res., **1994**, 251, 1-15.

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© [J-N. Tan], [2015], INSA de Lyon, tous droits réservés

[79] Schröder, S.; Schmidt, U.; Thiem, J.; Kowalczyk, J.; Kunz, M.; Vogel, M. Synthesis of oligosaccharides as potential novel food components and upscaled enzymatic reaction employing the β-galactosidase from bovine testes. Tetrahedron, **2004**, 60, 2601-2608.

[80] Riva, S.; Nonini, M.; Ottolina, G.; Danieli, B. Subtilisin-catalyzed esterification of di- and oligosaccharides containing a D-fructose moiety. Carbohydr. Res., **1998**, 314, 259-266.

[81] Piao, J.; Takase K.; Adachi; S. Enzymatic synthesis of myristoyl disaccharides and their surface activity. J. Sci. Food Agric., **2007**, 87, 1743-1747.

[82] Brust, A.; Cuny, E. Conversion of reducing carbohydrates into hydrophilic substituted imidazoles. Green Chem., **2013**, 15, 2993-2998.

[83] Oikawaa, N.; Müller, C.; Kunz, M.; Lichtenthaler, F.W. Hydrophilically functionalized pyrazoles from Sugars. Carbohydr. Res., **1998**, 309, 269-279.

[84] Wrodnigg, T.M.; Stütz, A.E. The Heyns rearrangement revisited: an exceptionally simple two-step chemical synthesis of D-lactosamine from lactulose. Angew. Chem. Int. Ed., **1999**, 38, 827-828.

[85] Lichtenthaler, F. W. Towards improving the utility of ketoses as organic raw materials, Carbohydr. Res., **1998**, 313, 69–89.

[86] Desai, N.; Driemel, K.; Wisotzki, K.; Schneider, B. Derivatives of disaccharide alcohols, a method of preparing them, and their use, WO. Patent 9,213,866, **1991**.

[87] Pennequin, I ; Mortreux, A. ; Petit, F. ; Mentech, J. ; Thiriet, B. Procédé de télomérisation de diènes conjugués avec des polyols et notamment avec des sucres et des dérivés de sucres. F.R. Patent 2,693,188, **1994**.

[88] Villandier, N.; Adam, I.; Jérôme, F.; Barrault, J.; Pierre, R.; Bouchu, A.; Fitremann, J.; Queneau, Y. Selective synthesis of amphiphilic hydroxyalkylethers of disaccharides over solid basic catalysts influence of the superficial hydrophilic-lipophilic balance of the catalyst. J. Mol. Catal A: Chem., **2006**, 259, 67-77.

[89] Klein, J.; Kunz, M.; Guderjahn, L. New amphiphilic copolymers derived from hydrophobically modified vinyl saccharides, Can. J. Chem., **1995**, 73, 1941-1947.

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© [J-N. Tan], [2015], INSA de Lyon, tous droits réservés

[90] Cartarius, R.; Krause, T.; Vogel, H. Bioabbaubare tenside durch heterogenkatalysierte reduktive aminierung von isomaltulose, Chem. Ing. Tech., **2001**, 73, 118-123.

[91] Cartarius, R.; Krause, T.; Vogel, H. A kinetic modeling of reductive amination of isomaltulose on a palladium catalyst. Eng. Life Sci., **2002**, 2, 53-59.

[92] Besemer, A.C.; van Bekkum, H. in: Carbohydrates as organic raw materials, Vol. 3, eds. Van Bekkum, H.; Röper, A.G.J.; Voragen, VCH, Weinheim, **1996**, 273-293.

[93] de Nooy, A.E.J.; Besemer, C.; Van Bekkum, H. in: Carbohydrates as Organic raw Materials, Vol. 4, ed. W. Praznik, H. Huber, WUV-Univ, Vienna, **1998**, 88-103.

[94] van Bekkum, H. in: Carbohydrates as Organic Raw Materials, ed. Lichtenthaler, F.W. VCH Weinheim, **1991**, 289-322.

[95] Arts, S. J. H. F.; Mombarg, E. J. M.; van Bekkum, H.; Sheldon, R. A. Hydrogen Peroxide and Oxygen in Catalytic Oxidation of Carbohydrates and Related Compounds. Synthesis, **1997**, 597-613.

[96] Buchholz, K.; Stoppok, E.; Matalla, K.; Reh, K.-D.; Jördening, H.-J. in: Carbohydrates as Organic Raw Materials, Lichtenthaler, F. W. Ed. VCH Weinheim, **1991**, 155-168.

[97] Trombotto, S.; Violet-Courtens, E.; Cottier, L.; Queneau, Y. Oxidation of two major disaccharides: sucrose and isomaltulose. Top. Catal., **2004**, 27, 1-4.

[98] Fritsche-Lang, W.; Leupold, E. I. Preparation of sucrose tricarboxylic acid. DE 3555720, 1985; Chem. Abstr.. **1987**, 107, 59408v.

[99] Leupold, E. I.; Schoenwealder, K. H.; Fritsche-Lang, W.; Schlingmann, M.; Linkies, A. H.; Gohla, W.; Dany, F. G. Preparation of sucrose oxidation product containing tricarboxy derivative for use in detergents. DE 3900677, 1989; Chem. Abstr. **1990**, 113, 214316h.

[100] Edye, L. A.; Meehan, G. V.; Richards, G. N. Platinum catalysed oxidation of sucrose. J. Carbohydr. Chem. **1991**, 10, 11-23.

[101] Edye, L.A.; Meehan, G.V.; Richards, G.N. Influence of temperature and pH on the platinum catalysed oxidation of sucrose. J. Carbohydr. Chem., **1994**, 13, 273-283.

[102] Kunz, M.; Schwarz, A.; Kowalczyk, J. Verfahren zur Herstellung von di- und höheroxidierten Carbonsäuren von Kohlenhydraten, Kohlenhydratderivaten

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oder primären Alkoholen. EP. 0,775,709 A1, May 28, **1997**; Chem. Abstr. **1997**, 127, 52504.

[103] Ehrhardt, S.; Kunz, M.; Munir, M. Acides monocarboxyliques de saccharose. E.P. 0,774,469, **1997**.

[104] Kunz, M.; Puke, H.; Recker, C.; Scheiwe, L. and Kowalczyk, J. Process and apparatus for preparation of monooxidized products from carbohydrates, carbohydrate derivatives, and primary alcohols. DE 4,307,388, **1994**; Chem. Abstr. **1995**, 122, 56411q.

[105] Heyns, K.; Paulsen, H. Selective katalytische oxidation mit edelmetallkatalysatoren. Angew. Chem. **1957**, 69, 600-608.

[106] Heyns, K.; Paulsen, H.; Rudiger, G.; Weyer, J.; Configuration and conformation selectivity in catalytic oxidation with oxygen on platinum catalysts. Chem. Forsch, **1969**, 11, 285-374.

[107] van Dam, H.E.; Kieboom, A.P.G.; van Bekkum, H, Glucose-1-phoshate oxidation on platinum-on-carbon catalysts: side-reaction and effects of catalyst structure on selectivity. Recl. Trav. Chim. Pays-bas., **1989**, 108, 404-407.

[108] Kunz, M. Carbohydrate as Organic Raw Materials, F. W. Lichtenthaler, Ed. VCH Weinheim, **1991**, 127–153.

[109] Kunz, M.; Puke, H.; Recker, C. Katalytische oxidation von isomaltulose. Chem. Ing. Tech., **1995**, 67, 836-842.

[110] Klein, S. J.; Kowalczyk, J.; Engelke, S.; Kunz, M.; Puke, H. Poly(vinylsaccharide)s. 8. New anionic poly(vinylsaccharide)s. Makromol. Chem. Rapid Commun. **1990**, 11, 477-483.

[111] Kunz, M. Carbohydrate as Organic Raw Materials, Vol.2, Descotes, G. Ed. VCH Weinheim, **1993**, 135–161.

[112] de Nooy, A. E. J.; Besemer, A. C.; van Bekkum, H. Highly selective tempo mediated oxidation of primary alcohol groups in polysaccharides. Recl. Trav. Chim. Pays-Bas, **1994**, 113, 165-166.

[113] Tahiri, C.; Vignon, M. R. TEMPO-oxidation of cellulose: Synthesis and characterisation of polyglucuronans. Cellulose, **2000**, 7, 177-188.

[114] de Nooy, A.E.J.; Besemer, A.C.; van Bekkum, H. On the use of stable organic nitroxyl radicals for the oxidation of primary and secondary alcohols. Synthesis, **1996**, 1153-1176.

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[115] Brochette-Lemoine, S.; Joannard, D.; Descotes, G.; Bouchu , A.; Queneau, Y. Sonocatalysis of the TEMPO-mediated oxidation of glucosides. J. Mol. Catal. A.; **1999**, 150, 31-36.

[116] Li, K.; Helm, R.F. A practical synthesis of methyl 4-O-methyl-α-D-glucopyranosiduronic acid. Carbohydr. Res., **1995**, 273, 249-253

[117] Györgydeak, Z.; Thiem, J. Synthesis of methyl (D-glycopyranosyl azide) urinates. Carbohydr. Res., **1995**, 268, 85-92.

[118] Viollet-Courtens, E.; Cottier, L.; Descotes, G. Chemical oxidation of isomaltulose and methyl isomaltulosides. J. Carbohydr. Chem., **2001**, 20, 867-876.

[119] Bernaerts, M.J.; de Ley, J. Microbiological formation and preparation of 3-ketoglycosides from disaccharides. J. Gen. Microbial., **1960**, 22, 129-136.

[120] Hough, L.; O'Brien, E. α-D-allopyranosyl β-D-fructofuranoside (allo-sucrose) and its derivatives. Carbohydr. Res., **1980**, 84, 95-102.

[121] Stoppok, E.; Matalla, K.; Buchholz, K. Microbial modification of sugars as building blocks for chemicals. Appl. Microbiol. Biotechnol., **1992**, 36, 604-610.

[122] Pietsch, M.; Walter, M.; Buchholz, K. Regioselective synthesis of new sucrose derivatives via 3-ketosucrose. Carbohydr. Res. **1994**, 254, 183-194.

[123] Simiand, C.; Samain, E.; Martin, O.R.; Driguez, H. Sucrose analogues modified at position 3: chemoenzymatic synthesis and inhibition studies of dextransucrases. Carbohydr. Res., **1995**, 267, 1-15.

[124] Stoppok, E.; Walter, J.; Buchholz, K. The effect of pH and oxygen concentration on the formation of 3-keto disaccharides by Agrobacterium tumefaciens. Appl. Microbiol. Biotechnol., **1995**, 43, 706-712.

[125] Noll-Borchers, M.; Kunz, M. From 3'-keto-isomaltulose to polymers. J. Carbohydr. Chem., **1994**, 13, 1215-1223.

[126] Noll-Borchers, M.; Buchholz, K. Kinetics and yields of 3-keto-isomaltulose by microbial oxidation of isomaltulose. Biotechnol. Lett., **1993**, 15, 139-144.

[127] Lichtenthaler, F.W.; Rönninger, S. α-D-glucopyranosyl-D-fructoses: distribution of furanoid and pyranoid tautomers in water, dimethyl sulphoxide, and pyridine. Studies on ketoses. Part 4. J. Chem. Soc., Perkin Trans. 2, **1990**, 1489-1497.

[128] Hanemann, T.; Schumacher, E.; Haase, W.; Lichtenthaler, F.W. Some novel disaccharide-derived liquid crystals. Liq. Cryst., **1997**, 22, 47-50.

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© [J-N. Tan], [2015], INSA de Lyon, tous droits réservés

[129] Lichtenthaler, F.W.; Klimesch, R.; Müller, V.; Kunz, M. Disaccharide building blocks from isomaltulose: glucosyl-α(1-5)-D-arabinonic acid and ensuing products. Liebigs Ann. Chem., **1993**, 975-980.

[130] Queneau, Y.; Chambert, S.; Moebs-Sanchez, S.; Listkowski. A.; Cheaib. R. Glycosidic bicyclic lactones as new carbohydrate scaffolds. Carbohydr. Res. **2009**, 35, 99-126.

[131] Xavier, N.M.; Rauter, A.P.; Queneau, Y.; Carbohydrate-based lactones: synthesis and applications. Top. Curr. Chem., **2010**, 295, 19-62.

[132] Trombotto, S.; Bouchu, A.; Descotes, G.; Queneau, Y. Hydrogen peroxide oxidation of palatinose and trehalulose: direct preparation of carboxymethyl α-D-glucopyranoside. Tetrahedron Lett., **2000**, 41, 8273-8277.

[133] G. Petersson, S. Pettersson, O. Samuelson, Formation of glucopyranosylglycolic acids during the hydrolysis of cellulose. Sv. Papperstidn. **1969**, 72, 222-225; Chem. Abstr. **1969**, 71, 23035v.

[134] Venturello, C.; Ricci, M. Oxidative cleavage of 1,2-diols to carboxylic acids by hydrogen peroxide. J. Org. Chem., **1986**, 51, 1599-1602.

[135] Sato, K.; Aoki, M.; Takagi, J.; Noyori, R. Organic solvent-and halide-free oxidation of alcohols with aqueous hydrogen peroxide. J. Am. Chem. Soc., **1997**, 119, 12386-12387.

[136] Sato, K.; Aoki, M.; Noyori, R. A "Green" route to adipic acid: direct oxidation of cyclohexenes with 30 percent hydrogen peroxide. Science, **1998**, 281, 1646-1647.

[137] M. Floor, K. M. Schenk, A. P. G. Kieboom, H. Vanbekkum, Oxidation of Maltodextrins and Starch by the System Tungstate-Hydrogen Peroxide. Starch/Staerke, **1989**, 41, 303-309.

[138] Pierre, R.; Chambert, S.; Alirachedi, F.; Danel, M.; Trombotto, S.; Doutheau. A.; Queneau, Y. Carboxymethyl glucosides and carboxymethyl glucoside lactones: A detailed study of their preparation by oxidative degradation of disaccharides. C. R. Chimie, **2008**, 11, 61-66.

[139] Trombotto, S.; Danel, M.; Fitremann, J.; Bouchu, A.; Queneau, Y. Straightforward route for anchoring a glucosyl moiety onto nucleophilic species: reaction of amines and alcohols with carboxymethyl 3,4,6-Tri-O-acetyl-α-D-glucopyranoside 2-O-Lactone. J. Org. Chem., **2003**, 68, 6672-6678

Cette thèse est accessible à l'adresse : http://theses.insa-lyon.fr/publication/2015ISAL0015/these.pdf
© [J-N. Tan], [2015], INSA de Lyon, tous droits réservés

[140] Le Chevalier, A.; Pierre, R.; Kanso, R.; Chambert, S.; Doutheau, A.; Queneau, Y. Preparation of new amide-linked pseudodisaccharides by the carboxymethylglycoside lactone (CMGL) strategy. Tetrahedron Lett., **2006**, 47, 2431-2434.

[141] Chambert, S.; Doutheau, A.; Queneau, Y.; Cowling, S.J.; Goodby, J.W.; Mackenzie, G. Synthesis and thermotropic behavior of simple new glucolipid amides. J. Carbohydr. Chem., **2007**, 26, 27-39.

[142] Listkowski, A.; Ing, P.; Cheaib, R.; Chambert, S.; Doutheau, A.; Queneau,Y. Carboxymethylglycoside lactones (CMGLs): structural variations on the carbohydrate moiety. Tetrahedron: Asymmetry, **2007**, 18, 2201-2210.

[143] Cheaib, R.; Listkowski, A.; Chambert, S.; Doutheau, A.; Queneau,Y. Synthesis of new mono- and disaccharidic carboxymethylglycoside lactones (CMGLs) and their use toward 1,2-bisfunctionalized carbohydrate synthons. Tetrahedron: Asymmetry, **2008**, 19, 1919-1933.

[144] Goodby, J. W.; Görtz, V.; Cowling, S. J.; Mackenzie, G.; Martin, P.; Plusquellec, D.; Benvegnu, T.; Boullanger, P.; Lafont, D.; Queneau, Y.; Chambert, S.; Fitremann, J. Thermotropic liquid crystalline glycolipids. Chem. Soc. Rev., **2007**, 36, 1971-2032.

[145] Sol, V.; Charmot, A.; Krausz, P.; Trombotto, S.; Queneau, Y. Synthesis of new glucosylated porphyrins bearing a α-D-linkage. J. Carbohydr. Chem., **2006**, 25, 345-360.

[146] Ménard, F.; Sol, V.; Ringot, C.; Granet, R.; Alves, S.; Morvan, C.L.; Queneau, Y.; Ono, N.; Krausz, P. Synthesis of tetraglucosyl- and tetrapolyamine-tetrabenzoporphyrin conjugates for an application in PDT. Bioorg. Med. Chem., **2009**, 17, 7647-7657.

[147] Barsu, C.; Cheaib, R.; Chambert, S.; Queneau, Y.; Maury, O.; Cottet, D.; Wege, H.; Douady, J.; Bretonniere, Y.; Andraud, C. Neutral push-pull chromophores for nonlinear optical imaging of cell membranes. Org. Biomol. Chem, **2010**, 8, 142-150.

[148] Xavier, N. M.; Goulart, M.; Neves, A.; Justino, J.; Chambert, S.; Rauter, A.P.; Queneau, Y.; Synthesis of sugars embodying conjugated carbonyl systems and related triazole derivatives from carboxymethyl glycoside lactones. Evaluation of their antimicrobial activity and toxicity. Bioorg. Med. Chem.; **2011**, 19, 926-938.

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[149] Chen, J.; Miao, Y.; Chambert, S.; Bernard, J.; Fleury, E.; Queneau, Y. Carboxymethyl glycoside lactone (CMGL) synthons: Scope of the method and preliminary results on step growth polymerization of α-azide-ω-alkyne glycomonomers. Sci. China Chem., **2010**, 53, 1880-1887.

[150] Abdelkader, O.; Moebs-Sanchez, S.; Queneau, Y.; Bernard, J.; Fleury, E. Generation of well-defined clickable glycopolymers from aqueous RAFT polymerization of isomaltulose-derived acrylamides. J. Polym. Sci., Part A: Polym. Chem, **2011**, 49, 1309-1318.

[151] Bozell, J. J.; Petersen, G. R. Technology development for the production of biobased products from biorefinery carbohydrates-the US Department of Energy's "Top 10" revisited. Green Chem., **2010**, 12, 539-554.

[152] van Putten, R. -J.; van der Waal, J. C.; de Jong, Ed.; Rasrendra, C.B.; Heeres, H.J.; de Vries, J.G. Hydroxymethylfurfural, a versatile platform chemical made from renewable resources. Chem. Rev., **2013**, 113, 1499-1597.

[153] Werpy, T.; Petersen, G. Top value added chemicals from biomass volume I-results of screening for potential candidates from sugars and synthesis gas. NREL/TP-510-35523; National Renewable Energy Laboratory: Golden, CO, **2004**.

[154] Lichtenthaler, F. W.; Martin, D.; Weber, T.; Schiweck, H. 5-(α-D-Glucosyloxymethyl) furfural: preparation from isomaltulose and exploration of its ensuing chemistry. Liebigs Ann. Chem., **1993**, 967-974.

[155] Lichtenthaler, F. W.; Martin, D.; Weber, T.; Schiweck, H. 5-(R-D-Glucosyloxymethyl)-furfural: preparation from isomaltulose and exploration of its ensuing chemistry. D.E. Patent 3,936,522, **1989**.

[156] Ruβ, C.; Luff, C.; Begli, A.H.; Koenig, B. Solvent-free preparation of 5-(α-D-Glucosyloxymethyl) furfural from isomaltulose-choline chloride melts. Synth. Commun., **2012**, 42, 3112-3116.

[157] Urashima, T.; Suyama, K.; Adachi, S. The Condensation of 5-(Hydroxymethyl)-2-furfuraldehyde with some aldoses on heating. Food Chem., **1988**, 29, 7-17.

[158] Cottier, L.; Descotes, G.; Soro, Y. Synthesis of acetylated ranunculin diastereoisomers and δ-glucosyloxy-γ-oxo esters from α or β glucosylmethylfurfural. J. Carbohydr. Chem., **2005**, 24, 55-71.

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© [J-N. Tan], [2015], INSA de Lyon, tous droits réservés

[159] Won, T. H.; Liao, L.; Kang, S. S.; Shin, J. Simultaneous analysis of furfural metabolites from Rehmanniae radix preparata by HPLC-DAD-ESI-MS. Food Chem., **2014**, 142, 107-113.

[160] Lin, A. -S.; Qian, K.; Usami, Y.; Lin, L.; Itokawa, H.; Hsu, C.; Morris-Natschke, S. L.; Lee, K.-H. 5-Hydroxymethyl-2-furfural, a clinical trials agent for sickle cell anemia, and its mono/di-glucosides from classically processed steamed Rehmanniae Radix. J. Nat. Med., **2008**, 62, 164-167.

[161] Li, S.-L.; Song, J.-Z.; Qiao, C.-F.; Zhou,Y.; Qian. K.; Lee, K.-H.; Xu, H.-X. A novel strategy to rapidly explore potential chemical markers for the discrimination between raw and processed Radix Rehmanniae by UHPLC-TOFMS with multivariate statistical analysis; *J. Pharmaceut. Biomed*., **2010**, 51, 812-823.

[162] Zhou, H.; Zhao, R.; Yang, J. Two new alkaloid galactosides from the kernel of prinsepia uniflora. *Nat. Prod. Res.*, **2013**, 27, 687-690.

[163] Adhikari, D. P.; Schutzki, R.E.; DeWitt, D.L.; Nair, M.G. Effects of amelanchier fruit isolates on cyclooxygenase enzymes and lipid peroxidation. Food Chem., **2006**, 97, 56-64.

[164] Brust, A.; Liehtenthaler, F.W. Facile conversion of glycosyloxymethyl-furfural into γ-keto-carboxylic acid building blocks towards a sustainable chemical industry. Green Chem., **2013**, 15, 1368-1372.

[165] Achmatowicz, O.; Bukowski, P.; Szechner, B. and Zwierzchowska, Z.; Zamojski, A. Synthesis of methyl 2,3-dideoxy-DL-alk-2- enopyranosides from furan compounds. General approach to the total synthesis of monosaccharides. Tetrahedron, **1971**, 27, 1973-1996.

[166] Ciufolini, M. A.; Hermann, C. Y. W.; Dong, Q.; Shimizu, T. and Swaminathan, S. Xi, N. Nitrogen heterocycles from furans. The aza-Achmatowicz reaction. Synlett, **1998**, 105-114.

[167] Müller, C.; Diehl, V.; Liehtenthaler, F.W. Hydrophilic 3-pyridinols from fructose and isomaltulose. Tetrahedron, **1998**, 54, 10703-10712.

[168] Scherrmann M. -C.; Lubineau A.; Queneau, Y. Functionalization of carbohydrates in water, in *Reactions in water*, Li, C. -J. Ed. **2010**, 291-330.

[169] Queneau, Y.; Pinel, C.; Scherrmann, M. -C. Some chemical transformations of carbohydrates in aqueous medium. *C. R. Chim.*, **2011**, *14*, 688-699.

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© [J-N. Tan], [2015], INSA de Lyon, tous droits réservés

[170] Thévenet, S.; Wernicke, A; Belniak, S; Descotes, G.; Bouchu, A.; Queneau, Y. Esterification of unprotected sucrose with acid chlorides in aqueous medium: kinetic reactivity versus acyl- or alkyloxycarbonyl-group migrations. *Carbohydr. Res*, **1999**, *318*, 52-66.

[171] Wernicke, A.; Belniak, S.; Thévenet, S; Descotes, G.; Bouchu, A.; Queneau, Y. Synthesis of sucrose carbonates in aqueous medium, *J. Chem. Soc. Perkin Trans. 1*, **1998**, 1179-1181.

[172] Christian, D.; Fitremann, J.; Bouchu, A.; Queneau, Y. Preparation of amphiphilic sucrose carbamates by reaction with alkyl isocyanates in water-alcohol mixtures, *Tetrahedron Lett*, **2004**, *45*, 583-586.

[173] Behr, A.; Becker, M.; Beckmann, T.; Johnen, L.; Leschinski, J. Telomerization: Advances and Applications of a Versatile Reaction, *Angew. Chem. Int. Ed*, **2009**, *8*, 3598-3614.

[174] Donzé, C.; Pinel, C.; Gallezot, P.; Taylor, P. L. Palladium-catalyzed telomerization of butadiene with Starch, *Adv. Synth. Catal*, **2002**, *344*, 906-910.

[175] Abbadi, A. and van Bekkum, H. in *Carbohydrates as Organic Raw Materials, Vol. 3*, van Bekkum, Röper, H. Voragen, A. G. J. Eds. **1996**, 37-65, VCH Verlag GmbH, Weinheim.

[176] Davis, N. J.; Flitsch, S. Selective Oxidation of Monosaccharide Derivatives to Uranic Acids. *Tetrahedron Lett*, **1993**, 34, 1181–1184.

[177] Sheldon, R.A.; Arends, I. W. C. E. and Brink, A. G.J. and Dijksman, A. “Green, Catalytic Oxidations of Alcohols” *Acc. Chem. Res*, **2002**, 35, 774-781.

[178] Knoevenagel, E. Ueber eine Darstellungsweise der Glutarsäure, *Chem Ber*, **1894**, *27*, 2345-2346.

[179] Beifuss, U. Tietze, L. F. *Comprehensive organic synthesis*, Trost. B, Ed. **1991**, 341-394.

[180] Gonzalez, G. F. Reactions of Monosaccharides with Beta-Ketonic Esters and Related Substances, *Adv.carbohydr chem*, **1956**, 11, 97–143.

[181] Misra, A. K. and Agnihotri, G. Preparation of polyhydroxyalkyl- and *C*-glycosylfuran derivatives from free sugars catalyzed by cerium(III) chloride in aqueous solution: an improvement of the Garcia Gonzàlez reaction. *Carbohydr. Res*, **2004**, 339, 1381-1387.

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© [J-N. Tan], [2015], INSA de Lyon, tous droits réservés

[182] Yadav, J. S.; Reddy, B. V. S.; Sreenivas, M. Satheesh, G. Indium(III) Chloride/Water: A Versatile Catalytic System for the Synthesis of C-Furyl Glycosides and Trihydroxyalkyl Furan Derivatives, *Synthesis*, **2007** 1712–1716.

[183] Sato, S. Naito, Y. and Aoki, K. “Scandium cation-exchanged montmorillonite catalyzed direct C-glycosylation of a 1,3-diketone, dimedone, with unprotected sugars in aqueous solution. *Carbohydr. Res*, **2007**, 342, 913–918.

[184] Rodrigues, F., Canac, Y. and Lubineau, A. A convenient, one-step, synthesis of β-C-glycosidic ketones in aqueous media. *Chem. Commun*, **2000**, 2049-2050.

[185] Philippe, M. and Semeria, D. Nouveaux derives c-glycoside et utilisation, Patent WO 2002051803, **2002**.

[186] Bragnier, N. and Scherrmann, M. C. One-Step Synthesis of β-C-Glycosidic Ketones in Aqueous Media: The Case of 2-Acetamido Sugars. *Synthesis,* **2005**, 5, 814–818.

[187] Krishna, P. R. Kannana, V. Sharma, Gangavaram G. V. M. S. Rao, M. H. V. R. Diastereoselective Baylis-Hillman reaction: Use of Sugar Derived Aldehydes as Chiral Electrophiles. *Synlett*, **2003**, 888–890.

[188] Toshima, K., Ushiki, Y., Matsuo, G. and Matsumura, S. Environmentally Benign Aryl C-Glycosidations of Unprotected Sugars Using Montmorillonite K-10 as a Solid Acid. *Tetrahedron Lett*, **1997**, 42, 7375–7378.

[189] Mukaiyama, T., Banno, K., Narasaka, K. New cross-aldol reactions. Reactions of silyl enol ethers with carbonyl compounds activated by titanium tetrachloride, *J. Am. Chem. Soc.,* **1974**, *96*, 7503-7509.

[190] Kobayashi, S. Manabe, K. and Nagayama, S. *Modern Carbonyl Chemistry*, Otera, J. Ed. Wiley-VCH, Weinheim, **2000**.

[191] Kobayashi, S. Manabe, K. Development of Novel Lewis Acid Catalysts for Selective Organic Reactions in Aqueous Media, *Acc. Chem. Res*, **2002**, *35*, 209-217.

[192] Zeitouni, J., Norsikian, S., Merlet, D. and Lubineau, A. Synthesis of *C*-Glycosides and C-Disaccharides using Mukaiyama Aldol Reaction in Aqueous Media, *Adv. Synth. Catal*, **2006**, 348, 1662-1670.

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© [J-N. Tan], [2015], INSA de Lyon, tous droits réservés

[193] Lubineau, A., Augé, J. and Drouillat, B. Improved synthesis of glycosylamines and a straightforward preparation of N-acylglycosylamines as carbohydrate-based detergents, *Carbohydr. Res*, **1995**, 266, 211–219.

[194] Sheldon R. A. Green and sustainable manufacture of chemicals from biomass : state of the art several books on catalysis as well, **2014**, 16, 950-963.

[195] Díaz-Alvarez, A. E. Francos, J. Lastra-Barreira, B. Crochet, P. and Cadierno, V. Glycerol and derived solvents : new sustainable reaction media for organic synthesis, **2011**, 47, 6208–6227.

[196] Gu, Y. Green Chemistry Multicomponent reactions in unconventional solvents : state of the art, Green Chem., **2012**, 14, 2091–2128.

[197] Aycock, D. F. Solvent Applications of 2-Methyltetrahydrofuran in Organometallic and Biphasic Reactions, Org. Process Res. Dev., **2007**, 11, 156-159.

[198] Sherwood, J.; De bruyn, M.; Constantinou, A; Moity, L.; Mcelroy, C. R.; Farmer, T. J.; Raverty, T. W.; Hunt, A. J. and Clark, J. H. Alternative for dipolar aprotic solvents, Chem. Comm., **2014**, 9650–9652.

[199] Herná, M. J.; Alcántara, A. R.; García, J. I.; Sinisterra, J. V. Applied Biotransformations in Green Solvents, Chem. Eur. J., **2010**, 16, 9422-9437.

[200] Wolfson, A. Snezhko, A. Meyouhas, T. Tavor, D. Glycerol derivatives as green reaction mediums, *Chem. Lett. Rev*., **2012**, 5, 7-12.

[201] Estévez, C.; Bayarri, N.; Castells, J. and Echeverría, B. PCT Int. Appl., **2008**, WO 2008/080601

[202] Pace,V.; Hoyos, P.; Alcántara, A. R. and Holzer, W. Chemoselective CaO-Mediated Acylation of Alcohols and Amines in 2-Methyltetrahydrofuran, ChemSusChem, **2013**, 6, 905–910.

[203] Alonso, D. M.; Wettstein, S. G. and Dumesic, J. A. Gamma-valerolactone, a sustainable platform molecule derived from lignocellulosic biomass, Green Chem., **2013**, 15, 584-595.

[204] Duan, Z.-Q. and Hu, F. Highly efficient synthesis of phosphatidylserine in the eco-friendly solvent γ-valerolactone, Green Chem., **2012**, 14, 1581–1583.

[205] Dandia, A.; Jain, A. K. and Laxkar, A. K. Ethyl lactate as a promising bio based green solvent for the synthesis of spiro-oxindole derivatives via 1,3-dipolar cycloaddition reaction. Tetrahedron Lett. **2013**, 54, 3929–3932.

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© [J-N. Tan], [2015], INSA de Lyon, tous droits réservés

[206] Larock, R. C. Comprehensive Organic Transformations: A Guide to Functional Group Transformations. **1989**, VCH, New York.

[207] Basavaiah, D.; Rao, P. D. and Hyma, R. S. The Baylis-Hillman reaction: a novel carbon-carbon bond forming reaction, **1996**, 52, 8001–8062.

[208] Basavaiah, D.; Rao, A. J. and Satyanarayana, T. Recent advances in the Baylis-Hillman reaction and applications, Chem. Rev., **2003**, 103, 811-891.

[209] Basavaiah, D.; Reddy, B. S. and Badsara, S. S. Recent Contributions from the Baylis-Hillman Reaction to Organic Chemistry, *Chem. Rev*, **2010**, 110. 5447–5674.

[210] Basavaiah, D.; Rao, K. V.; Reddy, R. J. The Baylis-Hillman reaction: a novel source of attraction, opportunities, and challenges in synthetic chemistry. Chem. Soc. Rev., **2007**, 36, 1581-1588.

[211] Rabe, J.; Hoffmann, H. M. R. A. New, Efficient and Stereocontrolled Synthesis of Trisubstituted Alkenes via Functionalized Acrylic Esters, Angew. Chem. Int. Ed, **1983**, 22, 795-796

[212] Hill, J. S.; Isaacs, N. S. Functionalisation of the a position of acrylate systems by the addtion of carbonyl compounds; high pressure-dependent reactions Tetrahedron Lett. **1986**, 27, 5007-5010.

[213] Bode, M. L.; Kaye, P. T.; A kinetic and mechanistic study of the Baylis-Hillman reaction, Tetrahedron Lett. **1991**, 32, 5611-5614.

[214] Price, K. E.; Broadwater, S. J.; Walker, B. J. and Mcquade, D. T. A New Interpretation of the Baylis-Hillman Mechanism, J. Org. Chem. **2005**, 70, 3980–3987.

[215] Price, K. E.; Broadwater, S. J.; Jung, H. M. and Mcquade, D. T. Baylis- Hillman Mechanism : A New Interpretation in Aprotic Solvents, Org. Lett, **2005**, 7, 2713–2714.

[216] Aggarwal, V. K.; Fulford, S. Y. and Lloyd-Jones, G. C. Reevaluation of the mechanism of the Baylis-Hillman reaction: implications for asymmetric catalysis, Angew. Chem. Int. Ed., **2005**, 44, 1706–1708.

[217] Roy, D. and Sunoj, R. B. Ab initio and density functional theory evidence on the rate-limiting step in the Morita-Baylis-Hillman reaction, Org. Lett., 2007, 9, 4873–4876.

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© [J-N. Tan], [2015], INSA de Lyon, tous droits réservés

[218] Aggarwal, V. K. and Harvey, J. N. Mechanism of the Morita - Baylis - Hillman Reaction : A Computational Investigation, J. Am. Chem. Soc, **2007**, 51, 2311–2312.

[219] Roy, D.; Patel, C. and Sunoj, R. B. Mechanistic insights and the role of cocatalysts in Aza-Morita-Baylis-hillman and Morita-Baylis-Hillman reactions. J. Org. Chem., **2009**, 74, 6936–6943.

[220] Cantillo, D. and Kappe, C. O. A unified mechanistic view on the Morita-Baylis-Hillman reaction: computational and experimental investigations, J. Org. Chem., **2010**, 75, 8615-8626.

[221] Santos, L. S.; Pavam, C. H.; Almeida, W. P.; Coelho, F. and Eberlin, M. N. “Probing the mechanism of the Baylis-Hillman reaction by electrospray ionization mass and tandem mass spectrometry, Angew. Chem. Int. Ed. **2004**, 43, 4330–4333.

[222] Amarante, G. W.; Milagre, H. M. S.; Vaz, B. G.; Vilacha, B. R.; Eberlin, M. N. and Coelho, F. “Dualistic Nature of the Mechanism of the Morita-Baylis-Hillman Reaction Probed by Electrospray Ionization Mass Spectrometry, J. Org. Chem. **2009**, 74. 3031–3037.

[223] Wei, Y. and Shi, M. Recent Advances in Organocatalytic Asymmetric Morita-Baylis-Hillamn reactions, Chem. Rev, **2013**, 113, 6659-6690

[224] (a) Liu, H.; Zhang, Q.; Wang, L. and Tong, X. PPh_3-catalyzed reactions of alkyl propiolates with N-tosylimines: a facile synthesis of alkyl 2-[aryl(tosylimino)methyl]acrylate and an insight into the reaction mechanism, Chem. Eur. J. **201**0, 16,1968–1972; (b) Krishna, P. R.; Manjuvani, A.; Kannan, V.; and Sharma, G. V. M. Sulpholane-A new solvent for the Baylis–Hillman reaction, Tetrahedron Lett. **2004**, 45, 1183-1185.

[225] Augé, J.; Lubin, N.; Lubineau, A. “Acceleration in water of the Baylis-Hillman reaction, Tetrahedron Lett. **1994**, 35, 7947–7948.

[226] Aggarwal, V. K.; Dean, D. K.; Mereu, A. and Williams, R. “Rate Acceleration of the Baylis - Hillman Reaction in Polar Solvents (Water and Formamide). Dominant Role of Hydrogen Bonding , Not Hydrophobic Effects , Is Implicated” J. Org. Chem. **2002**, 67, 510–514.

[227] Yu, C.; Liu, B. and Hu, L. “Efficient Baylis - Hillman Reaction Using Stoichiometric Base Catalyst and an Aqueous Medium,” J. Org. Chem. **2001**, 66, 5413–5418.

Cette thèse est accessible à l'adresse : http://theses.insa-lyon.fr/publication/2015ISAL0015/these.pdf
© [J-N. Tan], [2015], INSA de Lyon, tous droits réservés

[228] Basavaiah, D.; Krishnamacharyulu, M. and Rao, A. J. “The Aqueous Trimethylamine Mediated Baylis-Hillman Reaction,” Synth. Commun., 2000, 30, 2061–2069.

[229] Yu, C. and Hu, L. “Successful Baylis-Hillman Reaction of Acrylamide with Aromatic,” J. Org. Chem, **2002**, 7, 219–223.

[230] Cai, J.; Zhou, Z.; Zhao, G. and Tang, C. Dramatic rate acceleration of the Baylis-Hillman reaction in homogeneous medium in the presence of water, Org. Lett., **2002**, 4, 4723–4725.

[231] Davies, H. J.; Ruda, A. M. and Tomkinson, N. C. O. Aminocatalysis of the Baylis–Hillman reaction: an important solvent effect, Tetrahedron Lett., **2007**, 48, 1461-1464.

[232] Gatri, R.; Moncef, M. and E. Gaïed, M .E, Imidazole-catalysed Baylis-Hillman reactions: a new route to allylic alcohols from aldehydes and cyclic enones, Tetrahedron Lett. **2002**, 43, 7835-7836.

[233] Luo, S.; Zhang, B.; He, J.; Janczuk, A.; Wang, P. G. and Cheng, J.-P. Aqueous Baylis–Hillman reactions of cyclopent-2-enone using imidazole as catalyst, Tetrahedron Lett., **2002**, 43, 7369–7371.

[234] Luo, S.; Wang, P. G,; Cheng, J. -P.; Remarkable Rate Acceleration of Imidazole-Promoted Baylis-Hillman Reaction Involving Cyclic Enones in Basic J. Org. Chem, **2004**, 69, 555–558.

[235] Schwartz, B.; Porzelle, D. A.; Jack, K. S.; Faber, J. M.; Gentle, I. R. and Williams, C. M. “Cyclic Enones as Substrates in the Morita-Baylis-Hillman Reaction: Surfactant Interactions, Scope and Scalability with an Emphasis on Formaldehyde,” Adv. Synth. Catal., **2009**, 351, 1148–1154.

[236] Gomes, J. C.; Rodrigues Jr. M. T., Moyano, A. and Coelho, F. Efficient Catalysis of Aqueous Morita-Baylis-Hillman Reactions of Cyclic Enones by a Bicyclic Imidazolyl Alcohol, Eur.J. Org. Chem., **2012**, 6861–6866.

[237] Gomes, J. C.; Sirvent, J.; Moyano, A.; Rodrigues Jr, M. T. and Coelho, F. Aqueous Morita-Baylis-Hillman Reaction of Unprotected Isatins with Cyclic Enones, Org. Lett, **2013**, 2391–2394.

[238] Hayashi, Y.; Okado, K.; Ashimine, I. and Shoji, M. The Baylis–Hillman reaction under high pressure induced by water-freezing, Tetrahedron Lett., **2002**, 43, 8683–8686.

Cette thèse est accessible à l'adresse : http://theses.insa-lyon.fr/publication/2015ISAL0015/these.pdf
© [J-N. Tan], [2015], INSA de Lyon, tous droits réservés

[239] Basavaiah, D. and Kumaragurubaran, N. The Baylis-Hillman chemistry in aqueous media: a convenient synthesis of 2-methylenealkanoates and alkanenitriles, Tetrahedron Lett., **2001**, 42, 477-479.

[240] Chung, Y. M.; Gong, J. H.; Kim, T. H. and Kim, J. N. Synthesis of ethyl 3-cyano-2-methylcinnamates and 3-cyano-2-methylcinnamonitriles from the Baylis–Hillman acetates, Tetrahedron Lett., **2001**, 42, 9023–9026.

[241] Li, J.; Wang, X. and Zhang, Y. Remarkable rate acceleration of water-promoted nucleophilic substitution of Baylis–Hillman acetate: a facile and highly efficient synthesis of N-substituted imidazole, Tetrahedron Lett., **2005**, 46, 5233–5237.

[242] Liu, Y. -L.; Zeng, X.-P. and Zhou, J. Ethylene glycol: a powerful catalyst-free medium for C-C bond-forming reactions, Chem. Asian J., **2012**, 7, 1759–1763.

[243] Rose, P. M.; Clifford, A. A. and Rayner, C. M. The Baylis–Hillman reaction in supercritical carbon dioxide: enhanced reaction rates, unprecedented ether formation, and a novel phase-dependent 3-component coupling, Chem. Commun., **2002**, 968–969.

[244] Rogers, R. D.; Seddon, K. R. Ionic liquids as green solvents: progress and prospects.American chemical society, Washington DC, **2003**.

[245] Hullio, A. A.; Mastoi, G. M. Nicotine-based ionic liquid as a green and recyclable catalyst for Morita Baylis-Hillman reaction, Jordan J. Chem., **2012**, 7, 125-139.

[246] Mi, X.; Luo, S. and Cheng, J. “Ionic Liquid-Immobilized Morita-Baylis-Hillman Reactions, J. Org. Chem, **2005**, 70, 2338–2341.

[247] Rosa, J. N.; Afonso, C. A. and Santos, A. G. “Ionic liquids as a recyclable reaction medium for the Baylis–Hillman reaction,” Tetrahedron, **2001**, 57, 4189-4193.

[248] Kim, J. and Ko, S. Y. “Acceleration of the Baylis-Hillman Reaction in the Presence of Ionic Liquids,” Helvetica. Chimica. Acta, **2003**, 86, 894–899.

[249] Kumar, A.; Pawar. S. S. “The DABCO-catalysed Baylis–Hillman reactions in the chloroaluminate room temperature ionic liquids: rate promoting and recyclable media,” J. Mol. Catal. A. Chem., **2004**, 211, 43–47.

[250] Aggarwal, V. K.; Emme, I. and Mereu, A. Unexpected side reactions of imidazolium-based ionic liquids in the base-catalysed Baylis-Hillman reaction Chem. Commun., **2002**, 1612–1613.

Cette thèse est accessible à l'adresse : http://theses.insa-lyon.fr/publication/2015ISAL0015/these.pdf
© [J-N. Tan], [2015], INSA de Lyon, tous droits réservés

[251] Wei, X. and Zhang, D. Theoretical study on the mechanism of the reaction of alkylmethylimidazolium cation with benzaldehyde involved in the base-catalyzed Baylis-Hillman reaction, Comput. Theor. Chem., **2013**, 1014, 24-28.

[252] Carmichael, A. J.; Earle, M. J.; Holbrey, J. D.; Mccormac, P. B. and Seddon, K. R. The Heck Reaction in Ionic Liquids : A Multiphasic Catalyst System, Org. Lett, **1999**, 1, 997-1000.

[253] Hsu, J.-C.; Yen, Y. -H. and Chu,Y. -H. "Baylis–Hillman reaction in [bdmim][PF_6] ionic liquid," Tetrahedron Lett., **2004**, 45, 4673–4676.

[254] Jeong, Y. and Ryu, J. -S. "Synthesis of 1,3-dialkyl-1,2,3-triazolium ionic liquids and their applications to the Baylis-Hillman reaction.," J. Org. Chem., **2010**, 75, 12, 4183–4191

[255] Gong, H.; Cai, C.; Yang, N.; Yang, L.; Zhang, J. and Fan, Q. "Application of non-imidazolium-based ionic liquid in the Baylis–Hillman reactions: Rate and yield promoted," J. Mol. Catal. A. Chem., **2006**, 249, 236–239.

[256] Santos, L. S.; DaSilveira Neto, B. A.; Consorti, C. S.; Pavam, C. H.; Almeida, W. P.; Coelho, F.; Dupont, J. and Eberlin, M. N."The role of ionic liquids in co-catalysis of Baylis-Hillman reaction: interception of supramolecular species via electrospray ionization mass spectrometry," *J. Phys. Org. Chem*., **2006**, 19, 731–736.

[257] Rodrigues, T. S.; Silva, V. H. C.; Lalli, P. M.; De Oliveira, H. C. B.; Silva, W. A.; Coelho, F.; Eberlin, M. N. and Neto, B. A. D. Morita−Baylis−Hillman Reaction: ESI-MS(/MS) Investigation with Charge Tags and Ionic Liquid Effect Origin Revealed by DFT Calculations, *J. Phys. Org. Chem*, **2014**, 79, 5239-5248.

[258] Shi, M.; Li, C. and Jiang, J. "Reexamination of the traditional Baylis-Hillman reaction," Tetrahedron, **2003**, 59, 1181-1189.

[259] Declerck, V. Martinez, J. and Lamaty, F. "aza-Baylis-Hillman Reaction," Chem. Rev, **2009**, 109, 1-48.

[260] Buskens, P., Klankermayer, J. and Leitner, W. Bifunctional Activation and Racemization in the Catalytic Asymmetric Aza-Baylis−Hillman Reaction, J. Am. Chem. Soc., **2005**, 127, 16762-16763.

[261] Regiani, T.; Santos, V. G.; Godoi, M. N.; Vaz, B. G.; Eberlin, M. N. and Coelho, F. "On the mechanism of the aza-Morita-Baylis-Hillman reaction:

Cette thèse est accessible à l'adresse : http://theses.insa-lyon.fr/publication/2015ISAL0015/these.pdf
© [J-N. Tan], [2015], INSA de Lyon, tous droits réservés

ESI-MS interception of a unique new intermediate.," Chem. Commun. **2011**, 6593-6595.

[262] Busujima, T. and Nagayama, S. A Novel Classification of Lewis Acids on the Basis of Activity and Selectivity, Chem, Eur. J. **2000**, 6, 3491-3494.

[263] Aggarwal, V.; Mereu, K. A.; Tarver, G. J. and Mccague, R. Metal- and Ligand-Accelerated Catalysis of the Baylis-Hillman Reaction, J. Org. Chem, **1998**, 63, 7183–7189.

[264] Yamada, K.; Harwood, S.; Gröger, H. and Shibasaki, M. The First Catalytic Asymmetric Nitro-Mannich-Type Reaction Promoted by a New Heterobimetallic Complex, Angew. Chem. Int. Ed. **1999**, 38, 3504–3506.

[265] Shi, M. and Zhao, G. Baylis-Hillman reactions of *N*-arylidenediphenyl -phosphinamides with methyl vinyl ketone , methyl acrylate , and acrylonitrile, Tetrahedron Lett. **2002**, 43, 4499–4502.

[266] Wang, T.; Nolte, M. W. and Shanks, B. H. Catalytic dehydration of C6 carbohydrates for the production of hydroxymethylfurfural (HMF) as a versatile platform chemical, Green Chem., **2014**, 16, 548-572.

[267] Saha, B. and Abu-Omar, M. M. Advances in 5-hydroxymethylfurfural production from biomass in biphasic solvents, Green Chem., **2014**, 16, 24-38.

[268] Cottier, L.; Descotes, G.; Neyret, C.; Nigay, H. Ind. Aliment. Agricol,**1989**, 567-570.

[269] Cottier, L.; Descotes, G. 5-Hydroxymethylfurfural syntheses and chemical transformations, **1991**, 2, 233-248.

[270] Lansalot-Matras, C.; Moreau, C. Dehydration of fructose into 5-hydroxymethylfurfural in the presence of ionic liquids. Catal. Commun. **2003**, 4, 517-520.

[271] Fayet, C.; Gelas, J. Nouvelle méthode de préparation du 5-hydroxyméthyl-2-furaldéhyde par action de sels d'ammonium ou d'immonium sur les mono-, oligo- et poly-saccharides. Accès direct aux 5-halogénométhyl-2-furaldéhydes. Carbohydr. Res. **1983**, 122, 59-68.

[272] Zakrzewska, R. E.; Bogel-Łukasik, M. E.; Bogel-Łukasik. R. Solubility of carbohydrates in ionic liquids, Energy Fuels, **2010**, 24, 737-745.

[273] Zeitsch, K. J. The chemistry and technology of furfural and its many by-products. Elsevier, **2000**.

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© [J-N. Tan], [2015], INSA de Lyon, tous droits réservés

[274] Rodrigues, M. T.; Santos, M. S; Santos, H. and Coelho, F. 1,1-Carbonyldiimidazole mediates the synthesis of *N*-substituted imidazole derivatives from Morita-Baylis-Hillman adducts, Tetrahedron Lett., **2014**, 55, 180-183.

[275] Yamada, Y. M. and Ikegami, S. Efficient Baylis-Hillman reactions promoted by mild cooperative catalysts and their application to catalytic asymmetric synthesis, *Tetrahedron Lett*., **2000**, 41, 2165-2169.

[276] Zhang, Z., Xie, F., Jia, J., and Zhang, W. Chiral Bicycle Imidazole Nucleophilic Catalysts: Rational Design , Facile Synthesis , and Successful Application in Asymmetric Steglich Rearrangement catalytic active site and allowed to be efficiently adjustable. *J. Am. Chem.Soc*. **2010**, *132*, 15939-15941.

[277] Peng, C., Joy, A., Baylis-Hillman Reaction as a Versatile Platform for the Synthesis of Diverse Functionalized Polymers by Chain and Step Polymerization, *Macromolecules*, **2014**, *47*, 1258-1268.

[278] Al Sagheer, F. A., Khalil, K. D., Ibrahim, E. I., Synthesis and characterization of chitosan-*g*-poly (2-(furan-2-carbonyl)-acrylonitrile): Grafting of chitosan using a novel monomer prepared by a Baylis-Hillman reaction, *European Poly. J.,* **2013**, *49*, 1662-1672.

[279] Hall, A. W.; Godber, M. J.; Blackwood, K. M.; Milneb, P. E. Y.; Goodby, J. W. The photoinitiated cyclopolymerization of dienes in the creation of novel polymeric systems and three-dimensional networks, *J. Mater. Chem.*, **2004**, *14*, 2593-2602.

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