UNIWERSYTET JAGIELLOŃSKI
W KRAKOWIE

Cumulative Doctorate

Biomimetic carbon-carbon bond formation: synthesis of ulosonic acids

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Supervisor

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Krakow, 2014

UNIWERSYTET JAGIELLOŃSKI
W KRAKOWIE

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Przygotowany w oparciu o stosowną ustawę (Dz.U. 2011 nr 84 poz. 455) materiał składa się z dwóch monotematycznych publikacji w których wkład doktoranta jest kluczowy. W jednej występuję tylko z promotorem, w przygotowaniu drugiej udział brali studenci kierowani przez doktoranta (Piotr Oskwarek i Darius Schwarzer – student programu ERASMUS z Niemiec). W uznaniu dokonań naukowych doktoranta zdecydowałem, że jest on obok mnie, autorem korespondencyjnym w publikacji o wysokim współczynniku oddziaływania. W przygotowaniu publikacji nie brali udziału inni doktoranci, ani pracownicy naukowi.

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Mimo iż Ustawa nie nakazuje dołączania komentarza do ocenianych publikacji niniejsze zestawienie zostało opatrzone krótkim wstępem pokazującym tło literaturowe szerzej niż było to możliwe w publikacjach.

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Osama El-Sepelgy

Contents

1. Introduction

Living organisms are the most complex of all chemical systems, thus, nature is the wealthiest source of chemist's inspiration who want to construct complex targets in the most atom economy fashion. As the biologists take the information from chemistry to understand how the biological systems work, the bio-information can flow into chemistry providing insight for developing similar transformation by synthetic chemistry. In 1917 Robert Robinson has synthesized phenolics (orcinol) and alkaloids (tropinone) providing the concept of the biomimetic chemistry. Since then, the area of biomimetic synthesis has rapidly grown, especially in the last two decades proving the significance of these tools in the modern organic chemistry. The high efficiency of biotransformations inspire chemists to create small molecules, to mimic the reactivity and selectivity of the enzymes, but also to develop catalytic systems for a wide range of substrates, which enzymes will not tolerate.

The search for sustainable transformations which takes the cost and environmental impact into account is a current challenge for organic chemists. In this direction, development of catalytic methods that avoid the pre-modifications of the substrates, using less hazardous chemicals, reducing dangerous side-products, should be considered as a parallel channel of efforts.

Among the variants of asymmetric aldol reactions, pyruvate dependent aldol reaction are of particular interest as these processes are vital steps of the *in vivo* synthesis of 3-deoxy-ulosonic acids which are essential sugar units in many biological processes. Facile biomimetic synthesis of these targets will be presented and discussed.

Furthermore, mild generation of *o*-quinonmethides, which are proposed to be reactive intermediates in the biosynthesis of a number of natural products, will be presented. Importantly, starting from unmodified alcohols, a variety of highly enantiomerically enriched chromenes will be synthesized *via* these reactive intermediates.

1. Short Literature Overview

2.1. The chemistry of the bioactive 3-deoxy-ulosonic acids

The confrontation of emerging infectious diseases, which are resistant to antibiotics, is the crucial challenge in the post-genomic era. The necessity to develop new weapons against pathogenic bacteria has promoted much effort to understanding the role of carbohydrates in physiological processes and to enable the carbohydrate-based drug discovery process.

Naturally occurring 3-deoxy-2-ulosonic acids[1,2] are an important family of complex monosaccharides which are essential sugar units for many biological processes and transformations. The phosphorylated form of the 2-keto-3-deoxy-D-glucosonic acid (KDG, **1**), is part of the Entner–Doudoroff pathway[3] and the 7-phosphate of the 3-deoxy-α-D-*arabino*-2-heptulosonic acid (DAH, **2**) is a key intermediate in the biosynthesis of aromatic amino acids *via* the shikimate pathway.[4] The 2-keto-3-deoxy-D-*manno*-octulosonic acid (KDO, **3**) has been found in Gram-negative bacteria lipopolysaccharides (LPS).[5,6] 2-Keto-3-deoxy-D-*glycero*-D-*galacto*-nonulosonic acid (KDN, **4**) and N-acetylneuraminic acid (Neu5Ac, **5**) are significantly involved in the pathogenesis of microorganisms and various disease states.[7-10] The nine carbon 3-deoxy ulosonic acids, generally known as sialic acids, are widely used as precursors in the synthesis of important targets, such as: the industrial production of the anti-influenza drug (*Zannamivir*),[11] the anti-fungal amphotericin B[12,13] and the castanospermine-analogues.[14]

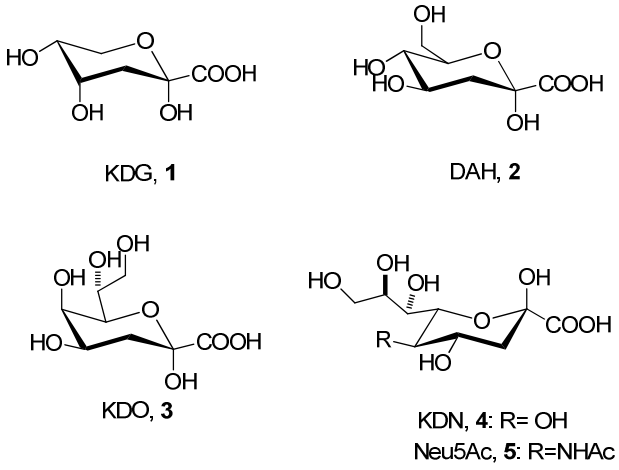


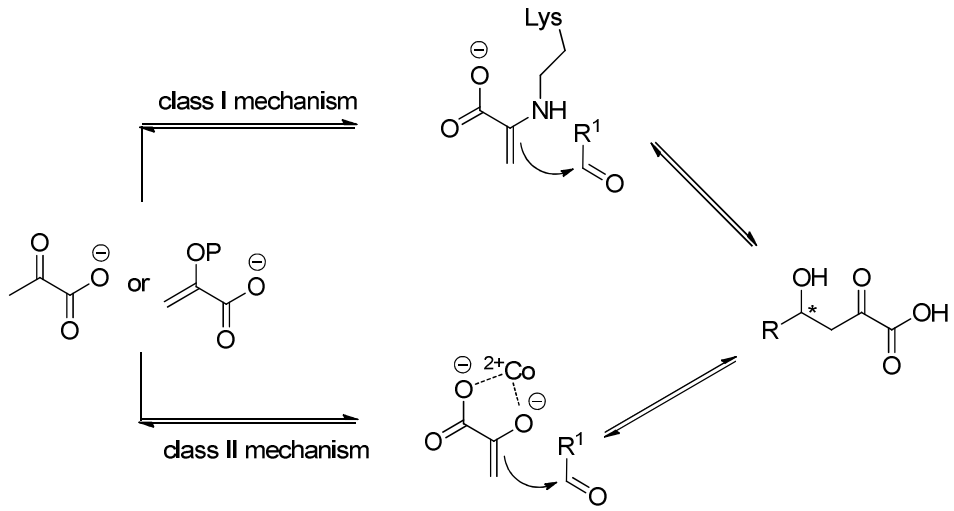
Fig.1. Sialic and ulosonic acids

2.1.1. Biosynthesis of ulosonic acids

The aldol reaction is one of the most important methods for the C-C bond formation.[15] Natural aldolases catalyze different seteroselective aldol and retro-aldol pathways *in vivo*. They mediate the biosynthesis of carbohydrates, ketoacids and amino acids, as well as in the carbohydrate catabolism.[16,17] More than forty known aldolases have been identified and isolated so far, most of them catalyze the reversible stereoselective addition of carbon nucleophiles to aldehydes.[18,19]

Mechanistically, aldolases, can be divided into two major classes. Class I aldolases activate the donor by forming a Schiff base as an intermediate in the active site. The enamine is stereoselectively formed by the abstraction of a proton and then the activated donor is added to the acceptor aldehyde.[20]

In the class II aldolases, a metal co-factor (mostly Zn^{II} but also Co^{II} or Fe^{II}) is bound to the enzyme active site *via* coordination and is capable of acting as a Lewis acid. These coordinated metal cations promote the activation of the donor ketone by chelation. This facilitates the removal of a proton and the generation of the reactive enolate, which is able to trap the acceptor aldehyde (Scheme 1).[21-23] The presented mechanisms involve pyruvate and phosphoenol pyruvate as the donor substrate.



Scheme 1. Class I and II aldolase-catalyzed aldol reactions of pyruvate donors

On the basis of functionality, aldolases can be divided into four groups; pyruvate, dihydroxyacetone phosphate, dihydroxyacetone, glycine/alanine and acetaldehyde dependent aldolases. Despite the fact that aldolases exhibit high specificity and generally

and don't accept any other donors, some interesting examples of their applications are recorded in recent literature. Pyruvate dependent aldolases have catabolic functions *in vivo*, whereas their counterparts, employing phosphoenolpyruvate as a donor play roles in the biosynthesis of those ketoacids.[24,25] These enzymes can be utilized in organic synthesis, by shifting the equilibrium towards the condensation product. The shifting is achieved by using an excess of pyruvate in the reactions catalyzed by pyruvate-dependent aldolases and through the irreversible releasing of the inorganic phosphate in phosphoenolpyruvate aldol reactions (Table 1).

Neu5Ac aldolase, which has been isolated from bacteria and mammals, catalyzes the aldol reaction between N-acetylneuraminic acid and the pyruvate donor. This enzyme works *via* a type I mechanism, which forms an enamine intermediate of pyruvate, and thus enables a *Si-face* attack to the aldehyde, leading to the formation of 4*S* stereocentre.[26, 27]

KDO aldolase is the enzyme responsible for the degradation of KDO *in vivo*. The *E.coli* KDO commercially avialble enzyme can promote the reversible condensation of pyruvate with D-arabinose to deliver KDO. The pyruvate donor is generally attacked from the *Re-face* of the acceptor aldehyde, so the newly formed stereocenter has a *R* configuration.[28-30]

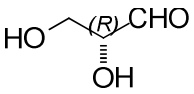
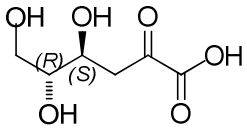
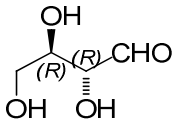
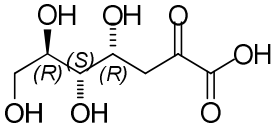
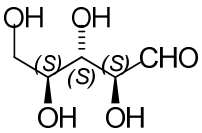
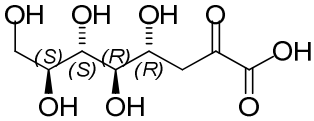
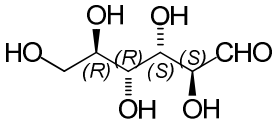
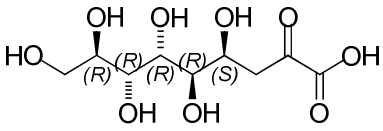
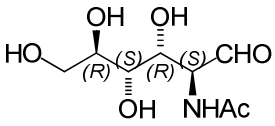
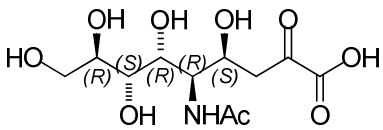
Moreover, KDPG aldolase catalyze the reversible condensation of pyruvate with D-glyceraldehyde-3-phosphate to produce KDPG. The type I pyruvate aldolase (KDPG) mediates the Entner–Doudoroff glycolytic pathway.[3] Unlike other pyruvate-dependent aldolases, KDPG aldolase work under kinetic control, giving aldol adducts with *S*-configuration at C4.[31-32]

Table 1. Pyruvate- and phoshoenolpyruvate-dependent aldolases

Natural acceptor	Natural donor	Enzyme	Product
N-acetyl mannosamine	Phosphenolpyruvate	EC 2.5.1.56	Neu5Ac
D-arbinose-5-phosphate	Phosphenolpyruvate	EC 2.5.1.55	KDOP
D-erythrose-4-phosphate	Phosphenolpyruvate	EC 2.5.1.54	DAHP
N-acetyl mannosamine	pyruvate	EC 4.1.3.3	Neu5Ac
D-arbinose	pyruvate	EC 4.1.2.23	KDO
D-Glyceraldehyde-3-phosphate	pyruvate	EC 4.1.2.14	KDPG

The examination of the stereochemistry of the natural aldehyde acceptors and the target six-carbon to nine-carbon ulosonic acids shows that; D-glyceraldehyde and D-erythrose have *R* configurations on the α-carbon, whereas the newly formed stereogenic centre in KDG is *S* (*anti* product) and in DAH is *R* (*syn* product). Furthermore, the eight carbon ulosonic acid exhibits C4-C5 *anti* configuration by starting from (*S*)-arabinose and forming a new chiral centre with a *R* configuration. Moreover, the C(4)-*S*-sialic acids are prepared from *S* acceptors. These examples show the need for the construction of the four possible C4-C5 absolute configurations, which cannot be easily achieved by the application of the enzymes due to its non-relaxed stereochemical induction (Table 2).

Table 2. Stereochemistry of C_6-C_9 natural ulosonic acids

C_n	**Substrate**	**Product**	**Attack**	**C4**	**C4-C5**
C_6	 **D-Glyceraldehyde**	 **KDG**	*Si*	4*S*	*Anti*
C_7	 **D-Erythrose**	 **DAH**	*Re*	4*R*	*Syn*
C_8	 **D-Arabinose**	 **KDO**	*Re*	4*R*	*Anti*
C_9	 **D-Mannose**	 **KDN**	*Si*	4*S*	*Syn*
C_9	 **D-Mannoseamine**	 **Neu5Ac**	*Si*	4*S*	*Syn*

2.1.2. Selected synthesis of ulosonic acids

The chemical synthesis of 3-deoxy-2-ulosonic acids has fascinated chemists over the last years.[1,2] It can be performed by the installation of a C_3 or C_2 building block into the proper sugar aldehyde in addition to different miscellaneous methods. Herein, the efficient [3+X] strategies that mimics the biosynthesis of KDG, DAH, KDN, KDO and Neu5Ac will be highlighted. Getting a simple and versatile equivalent of phosphoenolpyruvate to act as C_3 reactive nucleclophile, which in turn can be smoothly demasked to the pyruvate function, is the most important aspect in such chemistry. In this context, several C_3 building blocks have been explored like; oxaloacetic acid (**6**), α-(bromomethyl)acrylates **7**, thiazole derivatives **8**, **9** and propagayl bromide (**10**) are shown in Fig.2.

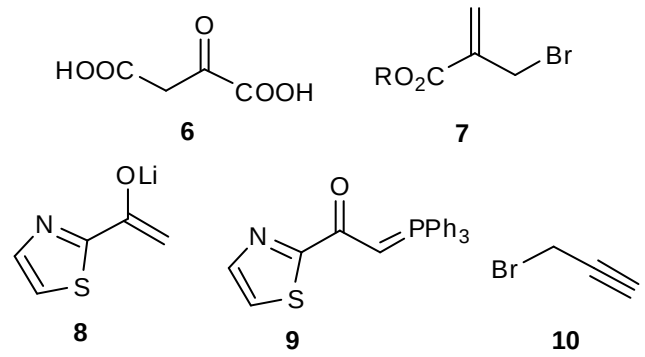


Fig.2. C_3 masked pyruvates

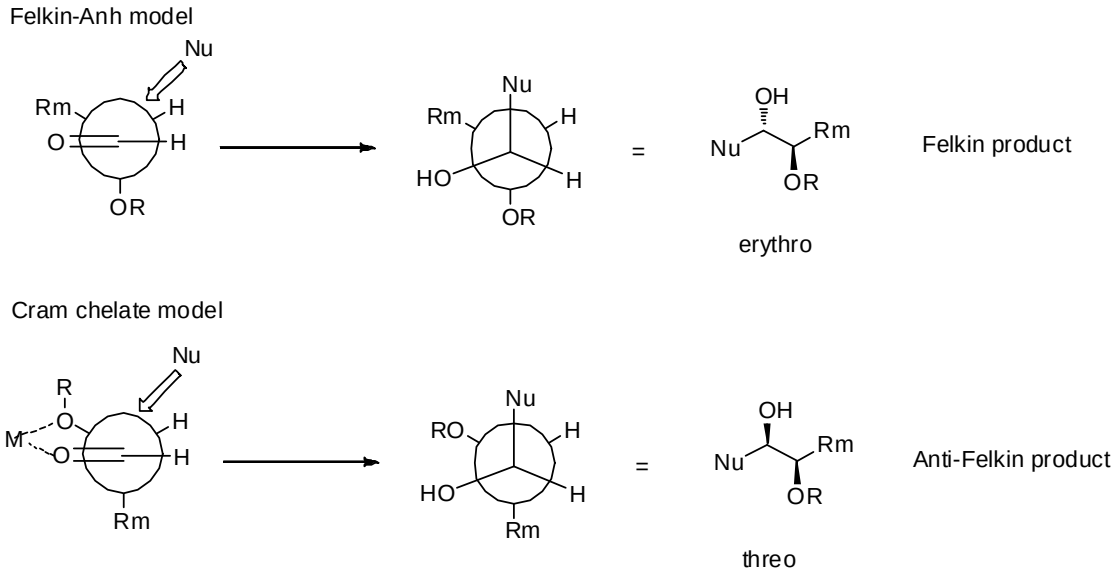
The second challenge of these protocols is how to control the stereochemical outcome of the newly formed stereogenic centre at C4. In some natural ulosonic acids, like KDO and KDG the relative configuration between hydroxyl group at C4 and C5 is *anti*, whereas, in DAH, KDN and sialic acids is *syn*.

Transition state models that predict the stereochemical course of the nucleophilic addition to acyclic aldehydes containing an adjacent stereogenic centre is one of the fundamental issues in synthetic chemistry. Several models have been developed to explain the influence of this centre on the diastereoface selection, such as Cram and Felkin models.

Taking only steric factors into consideration, Cram has designed a “product-like” transition-state-model in 1952 to predict the stereochemical direction of different acyclic systems.[33] Then, Felkin modified the Cram model by taking into account stabilizing transition state geometries and interactions based on both steric and electronic effects.

The electron withdrawing substituent is treated as the largest group due to the overlapping of the low-laying C-X σ* antibonding orbital with the π* orbital of the carbonyl, which causes a new, lower energy LUMO, allowing for a more stable transition state. Since Felkin's "reactant like" model has received the theoretical support from the work of the Anh group, the Felkin-Anh model has become the most acceptable model for the 1,2-asymmetric induction.[34-36]

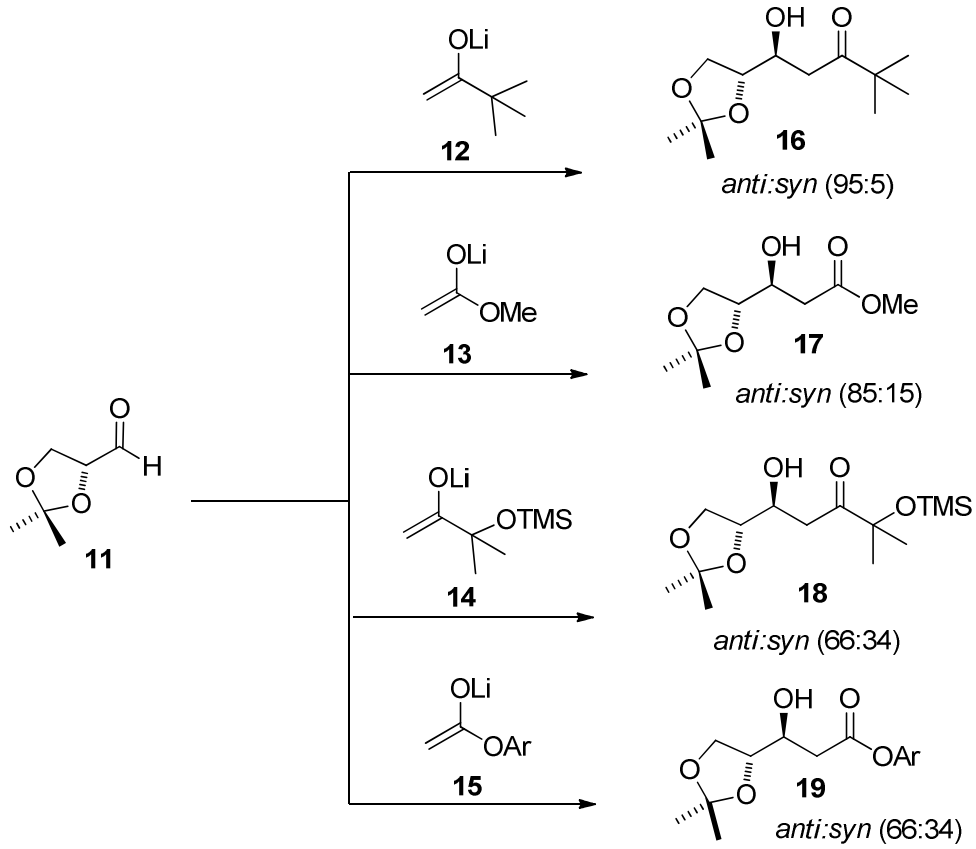
When viewing the Newman projection that places the carbonyl in a vertical position with the oxygen pointing left and the large group pointing down, the best position is the one that places the smallest group H closer to the aldehyde H. When the aldehyde is in the correct conformation the nucleophile will predominantly attack the carbonyl from the opposite side at an angle approximately 109^{o} to the carbonyl group, forming a Felkin product (Scheme 2).



Scheme 2. Felkin-Anh and Cram-chelate models

If the substituted α-heteroatom (*i.e.* O, N, S, P substituent) of the aldehyde acceptors possesses a Lewis base character the pathway of the reaction can be changed in the presence of chelation atom. In this situation, if a Lewis acid is introduced, a bidentate chelation can be observed between the carbonyl and the X group. This locks the carbonyl and the Lewis base substituent in an eclipsed conformation, and the nucleophile will then attack from the side with the smallest free α-carbon substituent affording the anti-Felkin product (Scheme 2).[33,37]

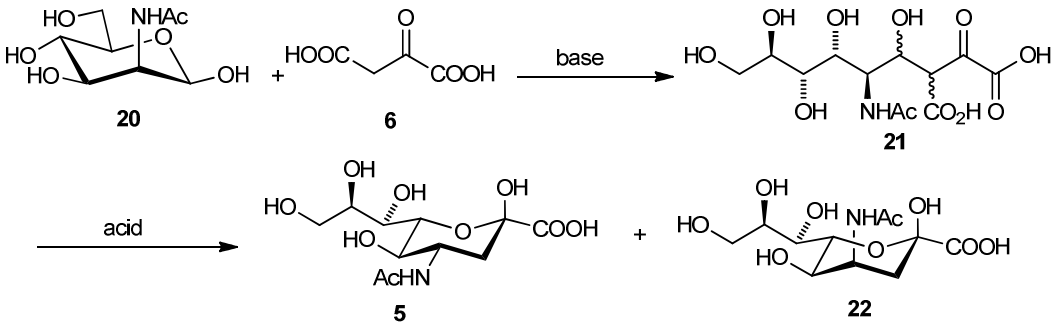
Heathcock has experimentally investigated the stereochemistry of the addition of various lithium enolates derived from esters and ketones to a (*R*)-glyceraldehyde derivative **11**. In all cases, the major products **16**-**19** are those expected by the application of the Felkin-Anh model of asymmetric induction and by assuming the alkoxy group to be the large group. The author has observed a high diastereoselectivity (90% *de*) by adding the lithiated pinacolone **12**, and a slightly lower selectivity in the case of the methyl acetate enolate **13**. Whereas, the α-heteroatom substituted ketone **14** and the bulky ester **15** condensation with the aldehyde **11** gave aldol adducts in a low asymmetric induction, showing the difficulty of such aldolizations (Scheme 3).[38]



Scheme 3. Addition of enolates to chiral aldehyde

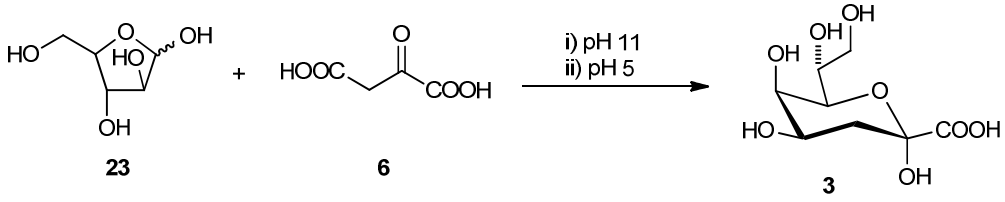
2.1.2.1. Cornforth synthesis of ulosonic acids

The first chemical synthesis of N-acetylnuraminic acid was demonstrated by Cornforth in 1958. The aldol decarboxylation reaction of oxaloacetic acid (**6**), used as a C_3 building block, and cyclic acetylhexosamine **20** afforded a mixture of (Neu5Ac, **5**) and its 4-*epi* isomer **22** in 8.5% yield *via* the intermediate **21** (Scheme 4).[39] Ghalambor and Heath in 1963 have disclosed the first chemical synthesis of KDO by following the Cornforth protocol.[40] Although, McNicholas and co-workers have further improved the procedure for the KDO synthesis by adding sodium carbonate to optomize the pH for aldol condensation to be exactly 11, the KDO was produced only in 35% yield (Scheme 5).[41]



Scheme 4. Cornforth's synthesis of Neu5Ac

Furthermore, Ogura and Shirai have claimed that the low yields and non reproducible protocols based on oxaoloacetic acid is attributed to the non-optimized conditions of the decarboxylation step. By adding a catalytic amount of $NiCl_2$ during the decarboxylation step, the KDO yield has been increased to 66% yield and a high diastereoselectivity (*anti:syn*, 10:1).[42] It was reported that under the same condition, KDN and its 4-*epi* epiemer (4.3:1) can be obtained in 69% yield. Without providing an explanation, the reaction between cyclic arabinose and oxaloacetic acid forms mainly *anti* aldols. Whereas under the same conditions the D-mannose gave mainly a *syn* configuration adduct.[42]

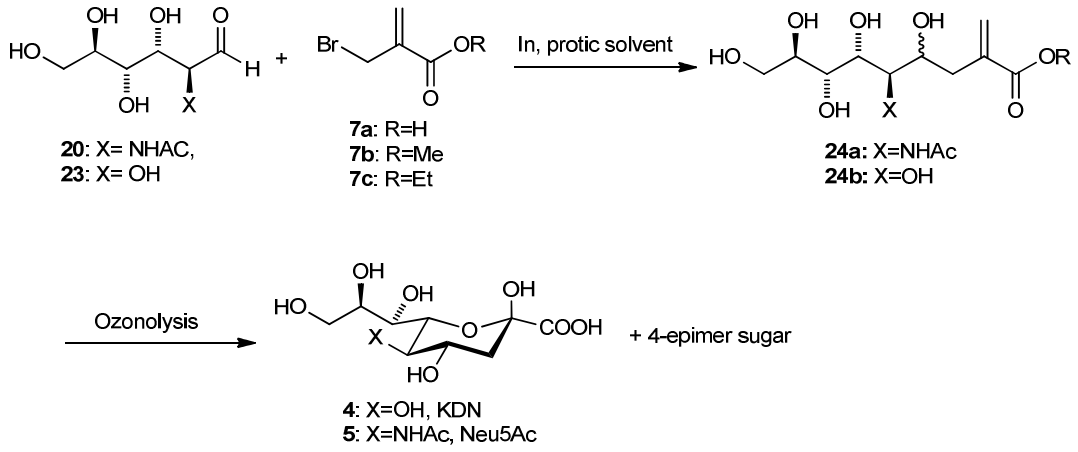


Scheme 5. Cornforth's method for synthesis of KDO

Recently, Kiefel attempts to repeat the Ogura methodology with the same yield and selectivity was not successful as he obtained only 60% yield of a (5:1) ratio of KDO and its 4-epmier. Kiefel and co-workers have modified the aldol condensation by using an excess of oxaloacetic acid to obtain 65% yield with the same selectivity. Authors have also outlined the use of different C_5 modified arabinose derivatives for the synthesis of a variety of KDO modifications.[43]

2.1.2.2. Chan-Whitesides synthesis of ulosonic acids

Indium mediated C_3 chain extension of aldehydes and ketones in an aqueous medium has been developed by Chan's group in 1991.[44,45] The reaction was extended to the synthesis of various ulosonic acids utilizing Vasella's pyruvate equivalents **7a-c** as C_3 building blocks.[46]



Scheme 6. Chan-Whitesides's synthesis of sialic acids

In 1993 Whitesides reported a short synthesis of the protected (Neu5Ac, **5**) by indium mediated allylation of unprotected aldehydes in acidic ethanol. The ethyl α-(bromomethyl)acrylate (**7c**, 6 folds) was used as a coupling reagent in the presence of four equivalents of indium powder. The inseparable mixture of enoates (*syn*:*anti*, 4:1) **24a** was formed in 90% yield. Ozonolysis and acetylation of the stereoisomeric mixture **24a** produce the protected (Neu5Ac, **5**) along with its 4-epimer (scheme 6).[47]

In order to facilitate the separation of the diastereoisomers of the key intermediates **24**, Chan employed the α-(bromomethyl)acrylic acid (**7a**) as a nucleophile instead of its corresponding esters. The coupling reaction between D-mannose (**23**) and a combination of four equivalents of indium powder and the acid **7a** in water afforded the key

intermediate **24b** in 64% yield and *syn:anti* ratio (5:1). The pure *syn* diastereoisomer was easily isolated and ozonoied in methanol at -78 ^{o}C to give the natural (KDN, **4**) in 95% yield.[48]

A modified protocol was applied to the coupling with N-acetyl-D-mannosamine (**20**) by allylation in an acidic ethanol medium and by increasing the indium loading to 6 times the amount of the aldehyde. The key intermediate **24a** was formed in 77 % yield of an inseparable (3:1) mixture of the *threo*:*erthreo* diastereoisomers. Ozonolysis of the adducts **24a** in aqueous THF at -60 ^{o}C afforded a mixture of the natural Neu5Ac and its 4-epimer in 74% yield. The disastereomerically pure (Neu5Ac, **5**) was separated by recrystallisation from ether/wet ethanol.[48]

Fessner's improvements of Chan and Whitesides methodologies allow the allylation of D-mannose (**23**) with ethyl 2-(bromomethyl)acrylate (**7c**) under acidic an medium to give exclusively *syn* products in high yields. A simple precipitation of the indium by using phosphate buffers was also outlined.[49]

The *threo* diastereoselectivity observed on the formation of enoate adducts **24a**, **24b** was attributed to the formation of a Cram chelate under the reaction conditions. Then the nucleophilic allylindium reagent attacks the activated carbonyl group to furnish the *syn* diastereoisomer (Fig 3).

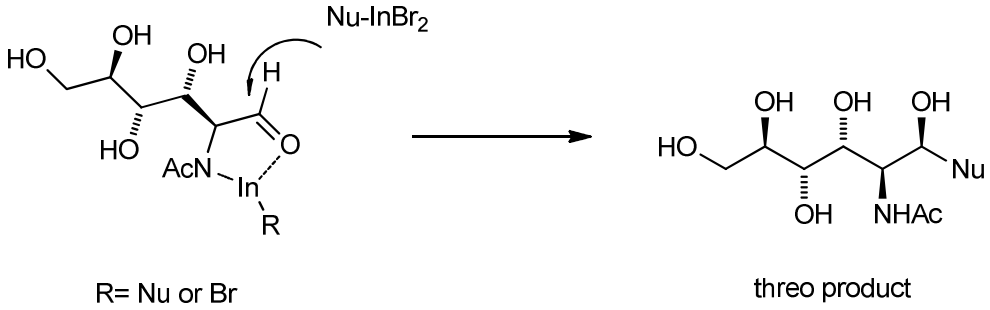
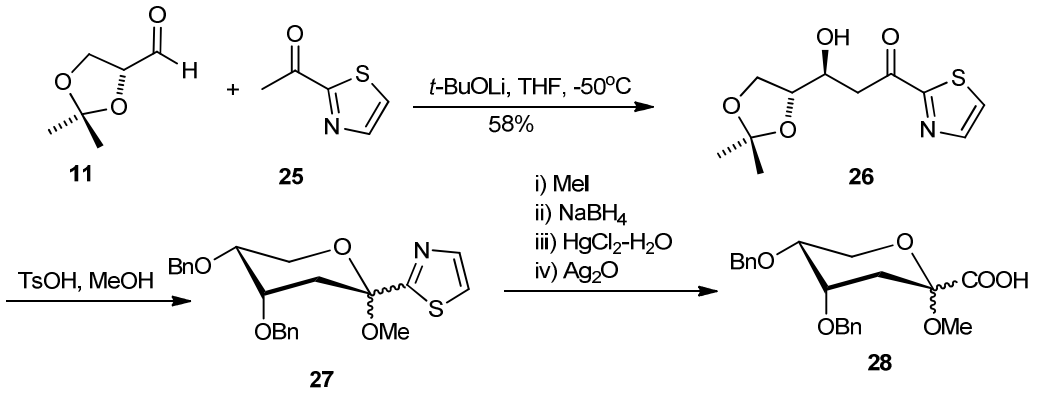


Fig. 3. Cram chelate proposed transition state

In summary, Chan and Whitesides protocols, along with Fessner's modifications of the *syn* selective extension of chiral aldehydes, leading to a short synthesis of KDN and Neu5Ac have been demonstrated. Although, these methodologies avoid the conventional carbohydrate chemistry protection deprotection steps, they suffer from the high loading of the costly indium metal and the harmful allylation by-products.

2.1.2.3. Dondoni synthesis of ulosonic acids

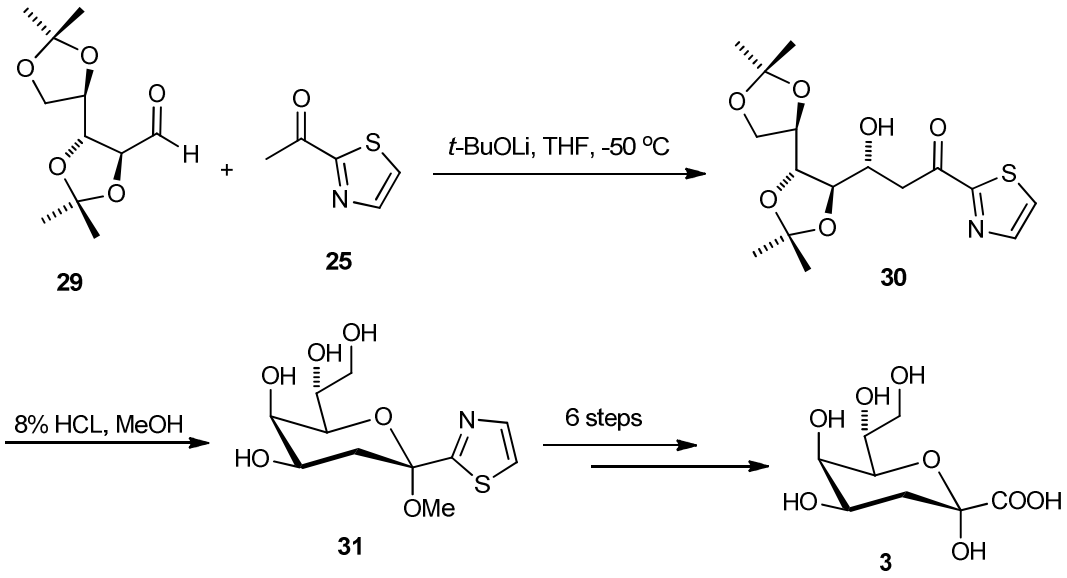
Dondoni and co-workers have outlined two methods for the installation of the (2-thiazole carbonyl) group as a masked pyruvate unit to sugar aldehydes. First, he used the lithium enol ether formed by the treatment of 2-acetylthiazole (**25**) with lithium *tert*-butoxide under kinetic control. The aldol condensation between the lithium enolate of the thiazole **25** and D-glyceraldehyde acetonide (**11**) afforded an anti-aldol product **26** in 58% yield and 90% *de*. The isopyroldine residue was easily removed under mild acidic conditions followed by benzylation to give a mixture of pyranose anomers **27**. The unmasking of the thiazole ring to a carboxyl group *via* a formyl intermediate involves a further four steps; N-methylation, reduction, hydrolysis and oxidation to furnish the protected KDG **28** (Scheme 7).[50,51]



Scheme 7. Dondoni's synthesis of KDG

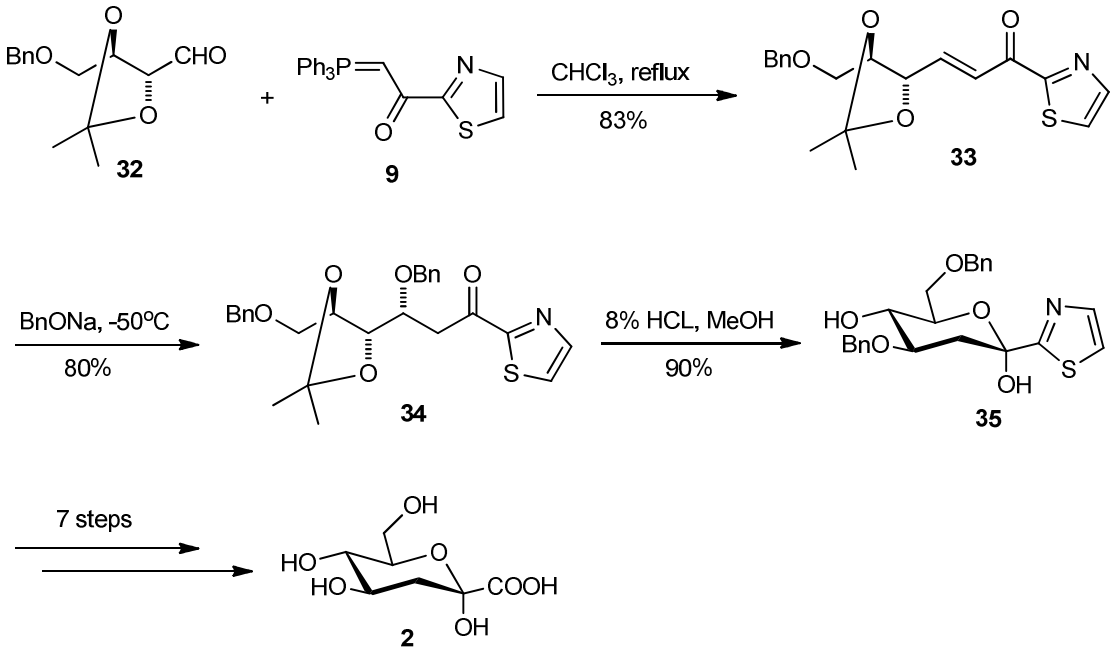
Following the above methodology to synthesize the natural KDO, the lithiuated acetylthiazole **25** was treated with arabinose diaceonoide **29**. The anti-aldol adduct **30** was formed in 54 % yield and 90 % *de*. The key intermediate **30** was further deprotected using 8 % methanolic HCL and to give the thiazole derived KDO **31** in 30% yield as an alpha pyranose anomer. Then, the thiazole moiety was converted to carboxylic group and the final deprotection of all hydroxyl groups was achieved by treatment with acetic acid, furnishing the natural KDO (Scheme 8).[50,51]

Dondoni has explained the stereochemical outcome based on the Felkin-Anh model of asymmetric induction. However, the high levels of the *anti* selectivity were not in agreement with the results of Heathcock[38] and our experiments. The aldol adducts **26** and **30** were formed in *anti:syn* ratios (3.6:1) and (2.8:1) respectively, which were determined by ^{1}HNMR of the crude reaction mixture in C_6D_6.



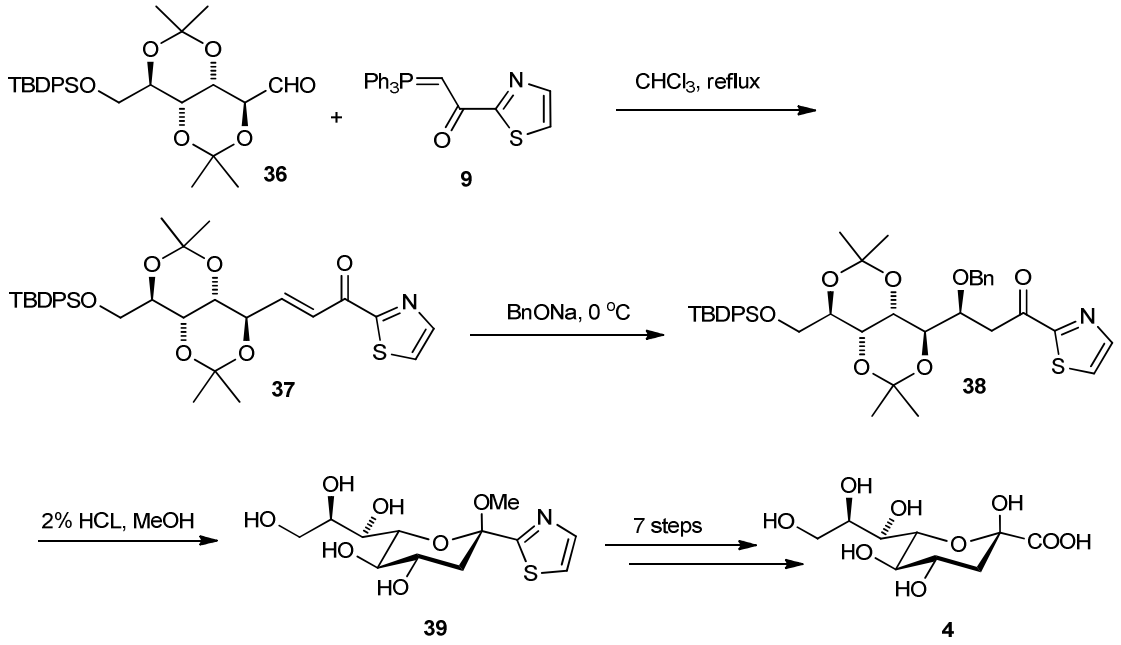
Scheme 8. Dondoni's synthesis of KDO

In order to reverse the diastereoselectivity to *syn* aldols, the same group has reported another two steps route involving a Witting olefination-Michael addition sequence by using thiazole-armed carbonyl ylid **9**.The Witting olefination of protected D-erythrose **32** proceeds smoothly and exclusively to the corresponding (*E*)-α,β-enone **33**. The stereoselective *syn* addition of sodium benzoxide to the enone **33** gave the precursor **34** in 62% *de*. Acid catalyzed methanolysis of the intermediate **34** gave pyranose **35**, which can be further converted to the natural (DAH, **2**) after seven steps (Scheme 9).[52]



Scheme 9. Dondoni's synthesis of DAH

The synthesis of KDN can also be performed by applying a witting-Michael route, the D-mannose derived aldehyde **36** was converted to the enone **37** by a Witting reaction. The subsequent addition of BnONa to the olefin **37** afforded the key precursor **38** with poor selectivity of 40% *de*. Further treatment of the major *syn* isomer with acid gave the thiazole derived sugar **39**. The natural (KDN, **4**) can be produced from the sugar intermediate **39** after multiple steps (Scheme 10).[52]

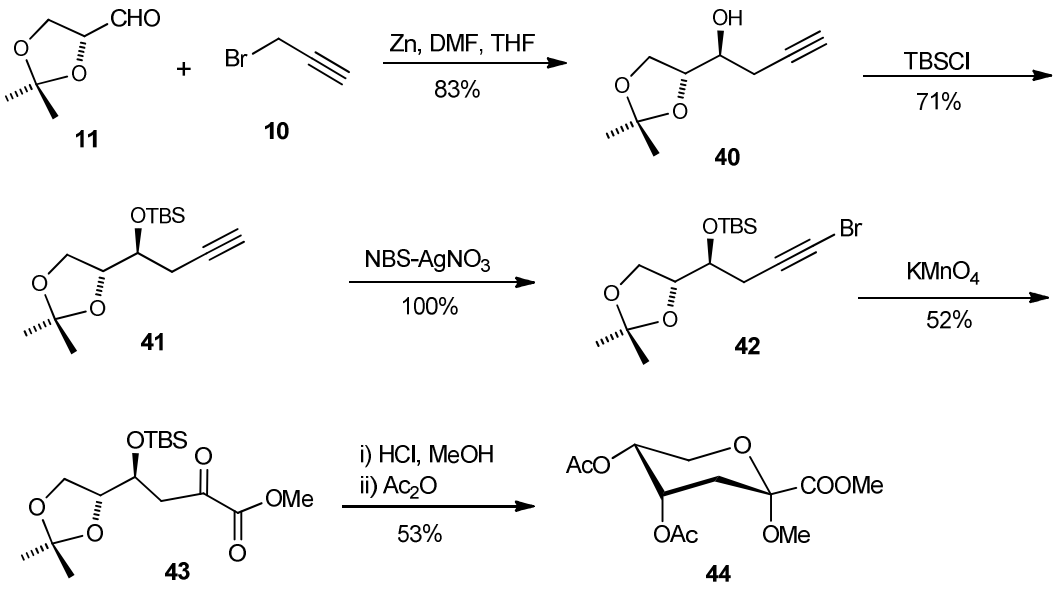


Scheme 10. Dondoni's synthesis of KDN

2.1.2.4. Wu synthesis of ulosonic acids

Another C_3-synthetic building block equivalent to phoshpoenolpyruvate has been introduced by the Wu group in 2002. He has developed an efficient protocol for the C_3 extension of the sugar aldehydes by propargylation. The terminal alkynes were subsequently converted into the corresponding α-keto ester *via* a two steps sequence (bromination and permanganate oxidation).[53]

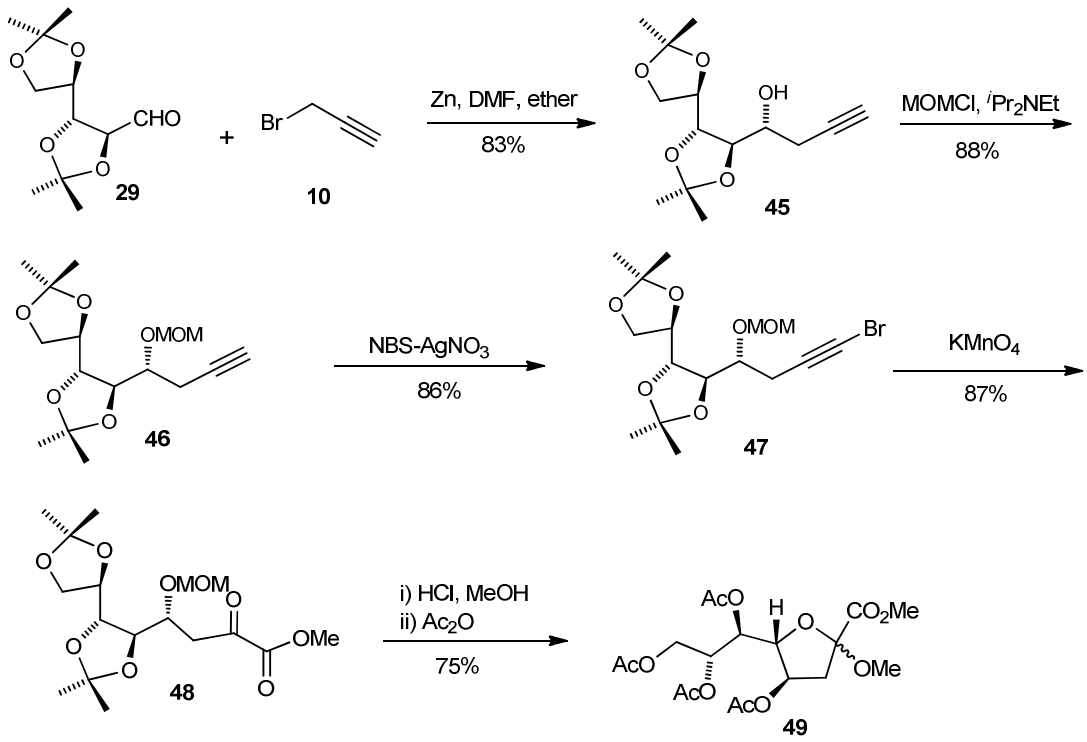
The addition of the organozinc reagent to the protected D-glyceraldehyde **11** afforded the corresponding alcohol **40** in a high yield and a moderate diastereoselectivity of 36% *de* favoring the *anti* isomer. The bromination of the terminal alkyne **41** afforded the compound **42**, which was oxidized by potassium permanganate, giving the desired α-ketocarboxylate **43** in high yields. The *anti* adduct **43** was easily deprotected by methanolic hydrochloric acid treatment followed by acetylation to deliver the protected KDG **44** in the pyranose form (Scheme 11).[54]



Scheme 11. Wu's synthesis of KDG

Further exploration the Wu strategy, the eight carbon ulosonic acid was also prepared. The coupling of the D-arabinose derived aldehyde **29** with 3-bromopropyne (**10**)/zinc combination gave the desired *anti* product **45** in 83% yield. After MOM protection of the newly formed hydroxyl group, the compound **46** was brominated by NBS in the presence of silver nitrite to give the corresponding terminal bromo alkyne **47**. Permanganate oxidation afforded the key intermediate **48** in a very good yield. Subsequent cyclization

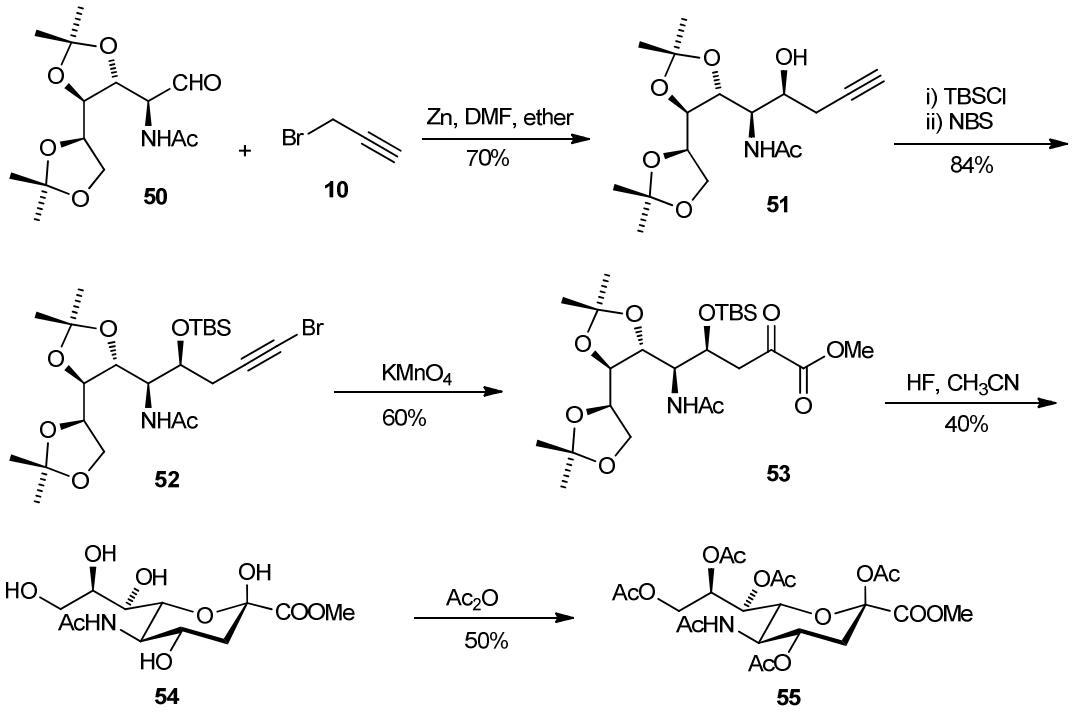
by acidic deprotection of the isopyroldine groups then protection of the formed sugar with acetic anhydride produced the protected KDO **49** in a (4:1) mixture of furanose anomers (Scheme 12).[55]



Scheme 12. Wu's synthesis of KDO

Wu propargylation of sugar aldehydes was accomplished with *anti* selectivity which fit the Felkin-Anh model, allowing the access to the correct C4 configuration in KDO and KDG. They also outlined that this protocol cannot be applied to the synthesis of the natural DAH and KDN due to their C4-C5 *syn* configuration.

In construct with previous protected sugars, the propargylation of the protected aminosugar **50** with 3-bromopropyne (**10**) and zinc combination gave predominantly *syn* product **51** in 70% yield and 63% *de*. The key intermediate **51** was converted by same way to the protected KDN, **55** through the compounds **52**, **53** and **54** (Scheme 13).[56] The author did not explain the reason of the stereochemical outcome which shows the aminosugar tendency to form the Cram chelate transition state rather than that of the Felkin model.

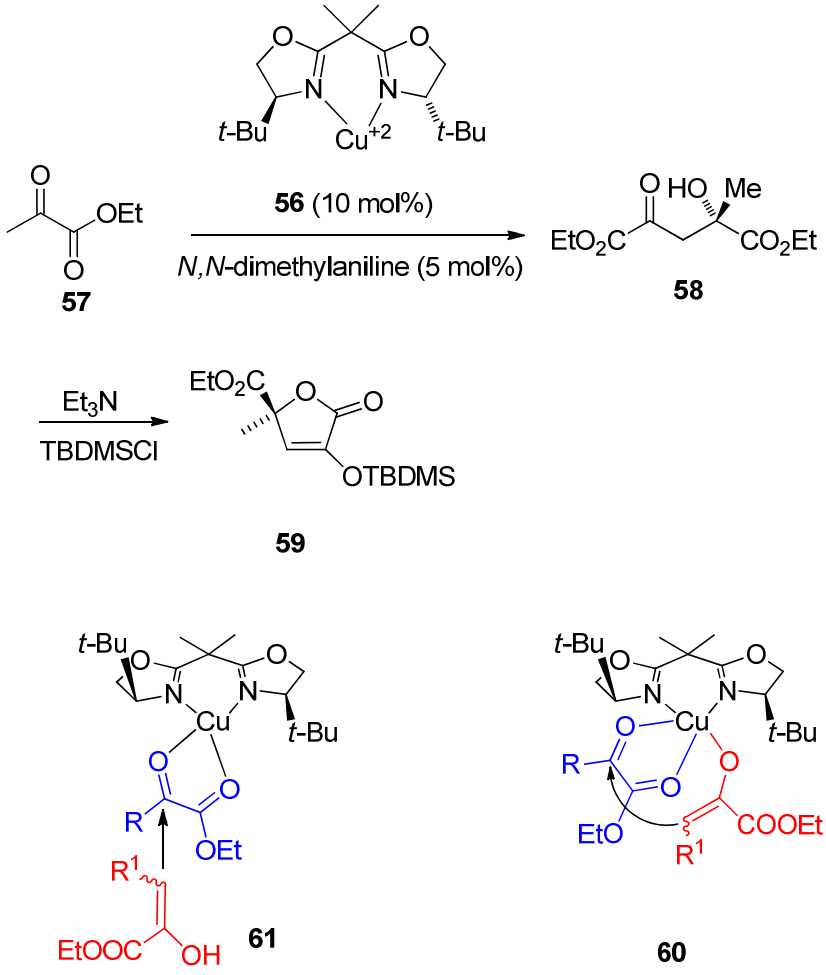


Scheme 13. Wu's synthesis of N-acetylnuraminic acid

2.1.3. The direct catalytic asymmetric aldol reaction of pyruvic derivatives

An exciting challenge in the enhancement of the efficiency of the aldol reaction is to find a method that will asymmetrically catalyze a wide range of direct aldol addition examples without the pre-formation of the nucleophile. Since the early discoveries by Shibasaki,[57] Trost[58] and List,[59] plenty of small chiral organic molecules with or without metal cofactors, have been developed to be capable of simultaneously activating the donor and the acceptor carbonyls,[60] even in water.[61-63]

The aldol reaction of pyruvate donors is an interesting and fundamental C-C bond forming reaction in both chemistry and biology.[64,65] In 2000 Jørgensen presented the first significant lewis acid complex able to mimic pyruvate- and phosphoenol-pyruvate dependent aldolases, yet limited to the self-condensation of pyruvate esters.[66]



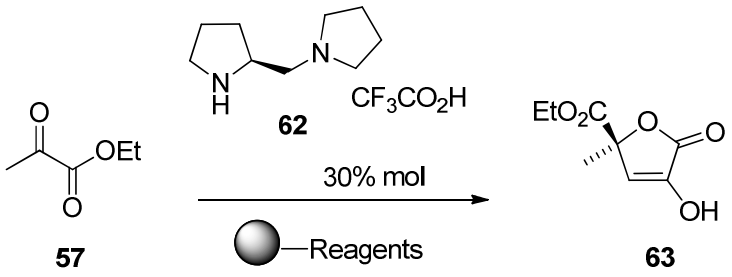
Scheme 14. Chiral Lewis acid catalyzed homoaldolization of ethyl pyruvate

They have developed a chiral bisoxazoline-Cu (II) complex **56** to catalyze homo-aldol reaction of ethyl pyruvate (**57**) *via* a type II aldolase mechanism, providing diethyl-2-

hydroxy-2-methyl-4-oxoglutarate **58**. The intermediate **58** was further converted to the more stable isotetronic acid derivative **59** in high yields and with excellent enantioselectivity up to 96% *ee*. This chiral catalyst can efficiently catalyzed the homo- and cross- aldol reaction of pyruvates with only pyruvate-type acceptors (Scheme 14).[67]

The authors have observed a dramatic change in enantiomeric excess from (*S*)-96% *ee* to (*R*)-77% *ee* by only changing the solvent and the counter ion. To demonstrate that, they have postulated that there are two possible transition states (**60** and **61**) present under the reaction conditions. The transition state **60** shows the homo-aldol reaction of ethyl pyruvate, which depends on the enol concentration in the solution, with the attack occurring from the *Si*-face. The second hypothesis, explaining the change of the reaction pathway to the *Re*-face attack, is the presence of the solvent or the counterion hidering the binding of the enol-form. Thus, the uncoordination of the enolate from the metal center is required before the addition to the acceptor as shown in the transition state **61**.[67]

Dondoni and co-workers have found that the homoaldolization of etheyl pyruvate (**57**) can also be performed under organocatlytic control mimicking class I aldolases. Proline proved to be a poor catalyst for this reaction but the application of a pyrrolidine based diamine-acid combination **62** resulted in the formation of a isoteronic acid derivative **63**. The authors were able to perform the lactonization and separation of the isotertronic acid in the hydroxyl-free form by using polymer supporting reagents as shown in scheme 15.[68]

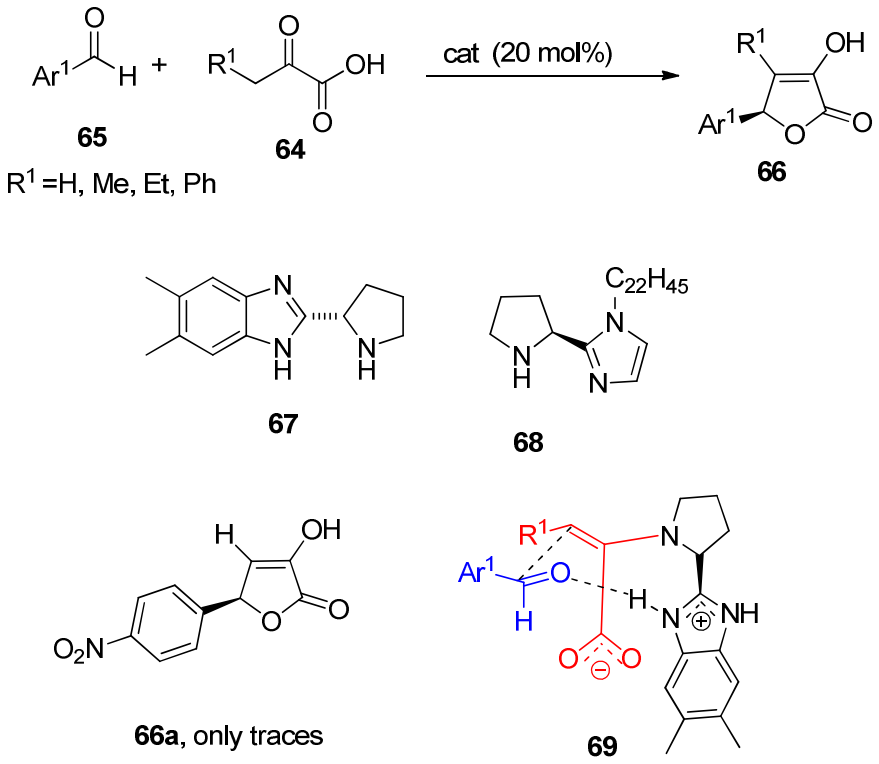


Scheme 15. Organocatalytic homoaldolization of ethyl pyruvate

Shortly thereafter, the aldol–lactonization domino process of β-substituted 2-oxocarboxylic acids **64**; (oxobutyric, phenylpyruvic and 2-oxovaleric) and a series of aldehydes **65** was described by Landais and co-workers.[69] The benzoimidazole proline-driven catalyst **67** was employed to synthesize various isoteronic acid derivatives **66**. Importantly, under the same conditions, the pyruvic acid afforded the corresponding isotetronic acid **66a** in only trace amounts. The authors postulated that the acid protonates the benzoimidazole ring to give a chair-like transition state **69** behaving as a stable

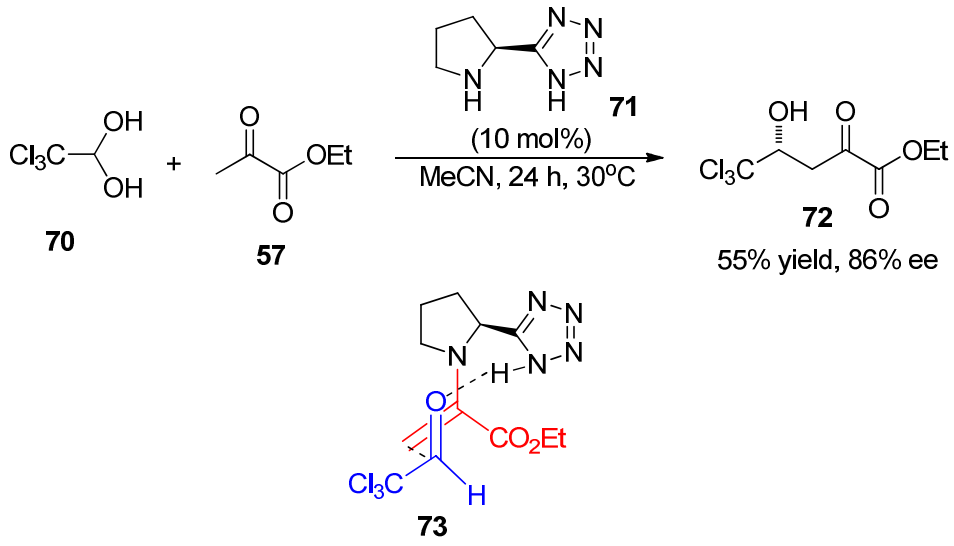
zwitterion species with the bulky groups located in the equatorial positions. The aldehyde is typically activated by the hydrogen bonding with the catalyst's N-H bond (Scheme 16).

Very recently, Li showed another proline-imidazole organocatalyst **68**, which has long alkyl chain and is able to catalyze the reaction of the same keto acids **64** with aromatic and aliphatic aldehydes **65** in water. This amphiphilic organocatalyst **68** is efficient during the reaction leading to various isotetronic acids **66** with high yields (up to 94%) with high enantioselectvities (89 - 99%).[70]



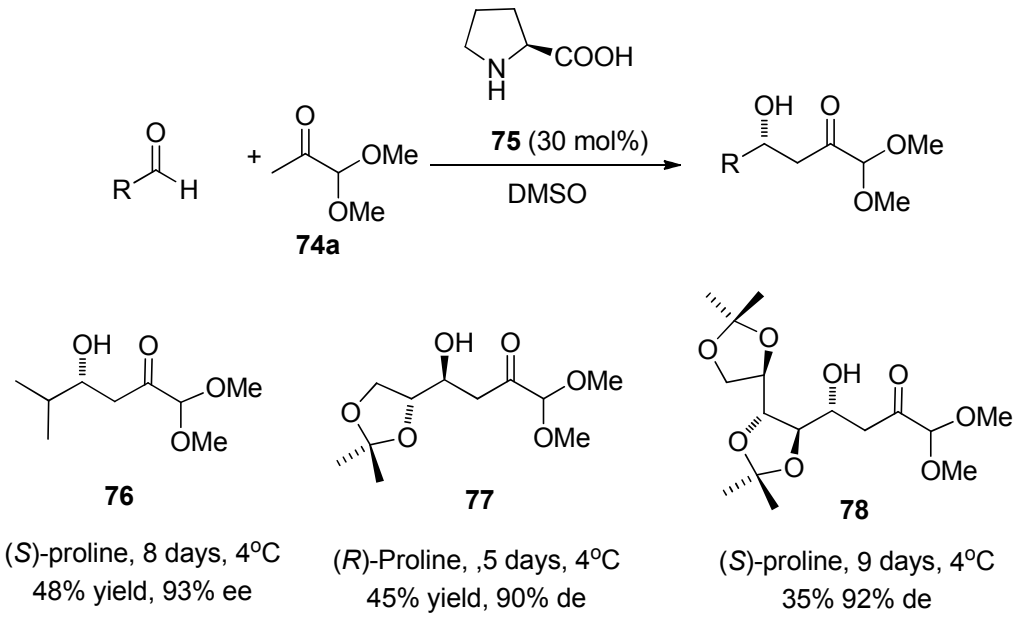
Scheme 16. Organocatlytic synthesis of isotetronic acids

In 2004, Yamamoto *et al.* reported the sole example of a catalytic asymmetric cross-aldol reaction of ethyl pyruvate (**57**) *via* enamine activation using a proline-tetrazole catalyst **71** assisted by water. The secondary amine activated the pyruvate by forming the corresponding more nucleophilic enamine **73**, while the tetrazole moiety enhanced the acceptors reactivity by hydrogen bond formation, delivering the aldol adduct **72** in 55% yield and 86% *ee* (Scheme 17).[71]



Scheme 17. Aldol condensation of ethyl pyruvate with chloral hydrate

Due to the competitive reactivity of simple pyruvate esters as electrophiles, most of the catalytic processes direct the reaction to the useless products of self condensation. Hence, masked pyruvates have been used instead of the simple acid or esters. Enders was the first to employ the pyruvic aldehyde dimethyl acetal (**74a**) as a phosphenolpyruvate equivalent.[72]



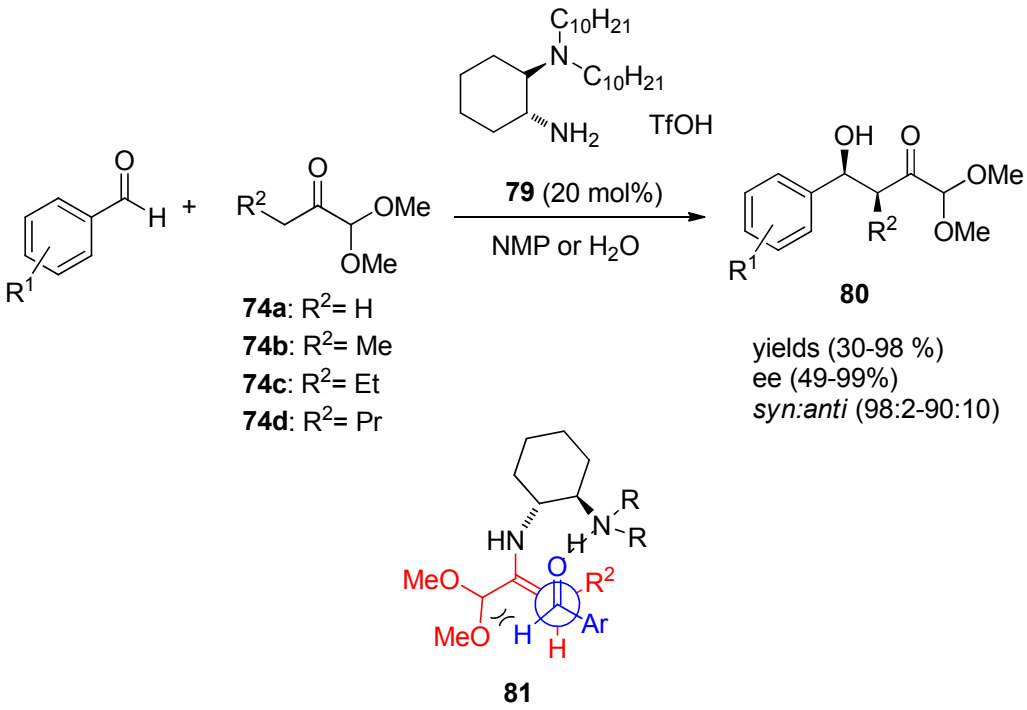
Scheme 18. Organocatlytic synthesis of ulosonic acid precursors

Surprisingly, the initial examination of several proline based catalysts in a model reaction of isobutyraldehyde and the pyruvate equivalent **74a**, proved that proline (**75**) is the best

catalyst. The authors claim that the elaborate enamine based protocol can be used to synthesize the aldol **76**, in addition to several ulosonic acid precursors in moderate yields and high selectivity (Scheme 18).[72]

Unfortunately, our efforts to reproduce the same results to get the adducts **77** and **78** were unsuccessful and the best yields observed by us was 8% of the desired product **77** when a fivefold excess amount of the ketone was used. The major product was the corresponding dehydrated compound, which might be produced due to Mannich-elimination sequence and not by dehydration of the aldols.[73]

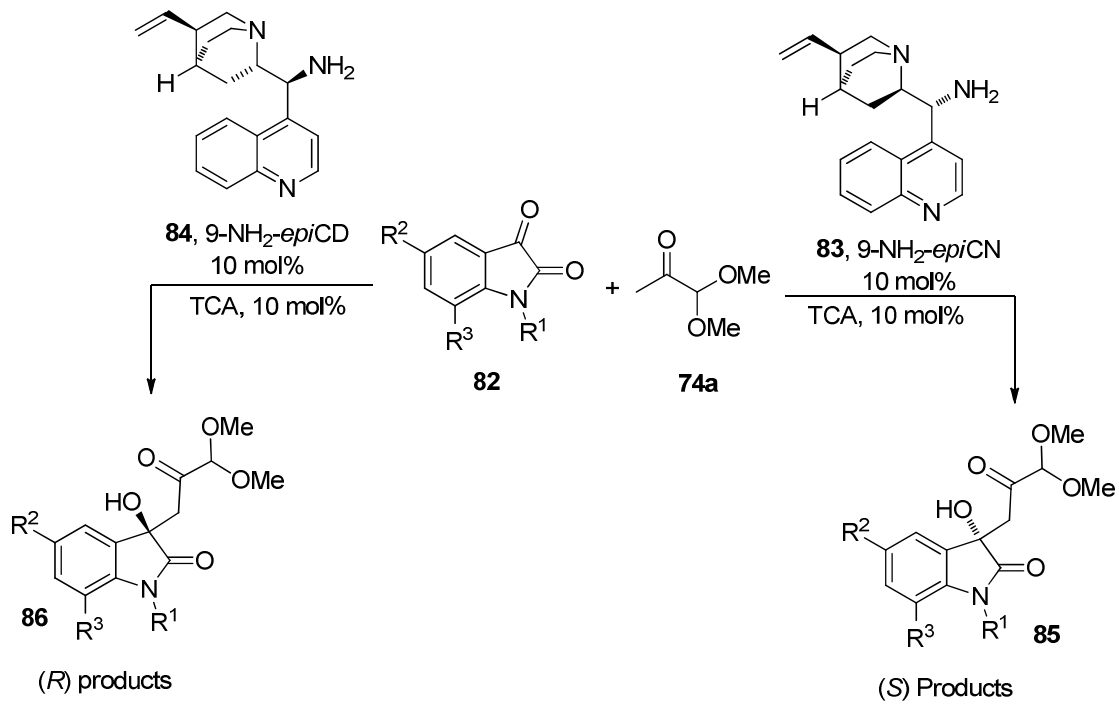
A year later, a primary amine derived catalyst **79** was employed to form the nucleophilic enamine of the pyruvic, oxobutyric, and 2-oxovaleric aldehyde dimethyl acetals **74a**-**74d**. This in turn, was used in a reaction with aromatic aldehydes to give aldol adducts **80** in moderate to very good yields and high enantio- and *syn* diastereoselectivities (up to 99% *ee* and 98:2 *syn*:*anti* ratio). To explain the stereochemical outcome, the authors postulated a Z-enamine transition state **81** where the aldehyde is activated through the hydrogen-bonding with the ammonium salt moiety of the catalyst (Scheme 19).[74]



Scheme 19. Direct aldol reaction of masked pyruvates with aromatic aldehydes

The same concept was very recently used by Chimni to achieve the 1,2-nucelophilic addition of the pyruvic aldehyde dimethyl acetal (**74a**) to a series of unmodified isatins

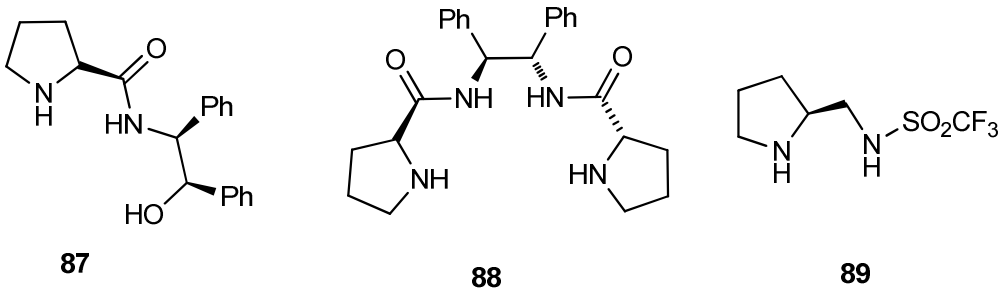
82. Cinchona-derived primary amines **83** and **84** were used in combination with trichloroacetic acid to synthesize the enantiomerically enriched 3-substituted 3-hydroxy-2-oxindoles **85** and **86** (91-95% *ee*) in high yields under mild conditions. Interestingly, the cinchona alkaloid **83** can be used to lead to (*S*) alcohols whereas, the primary amine derivative **84** gave the mirror aldols **86** (Scheme 20).[75]



Scheme 20. Direct aldol reaction of masked pyruvates with isatin

2.1.4. Comments on attempts to explore the literature protocols

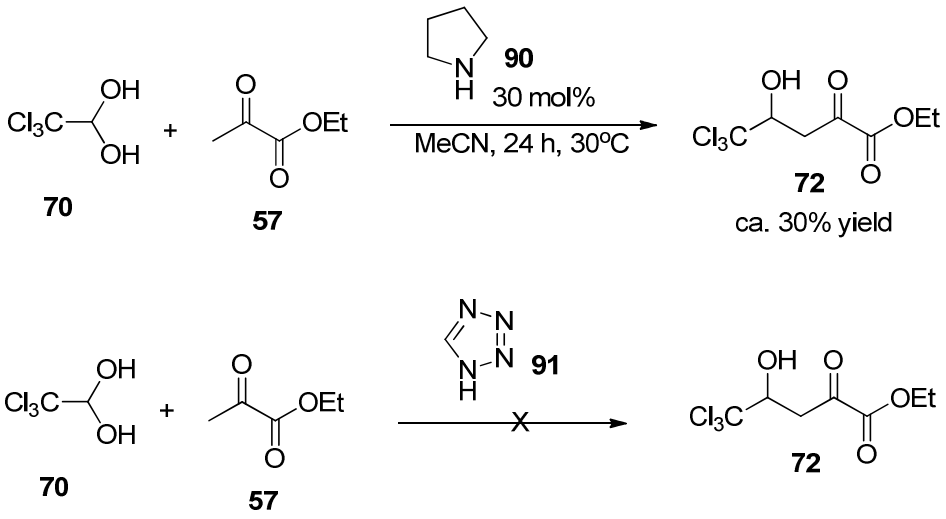
The initial research was initiated by the work of Yamamoto presented in scheme 17.[71] The attempts were directed to use different pyrroldine based organocatalysts with hydrogen bond moieties **87**, **88** and **89** shown in Fig 4, aiming to mediate the reaction of **57** with aromatic and aliphatic aldehydes. Unfortunately, the powerful enamine-hydrogen bond bifunctional catalysts were only able to catalyze the addition of the donor **57** to the highly reactive chloral hydrate **70**.



87 **88** **89**

Fig 4. Pyrrolidine- hydrogen bond bifunctional organoacatalysts

Trying to understand the reaction, we have repeatedly tested the reaction in the presence of pyrroline (**90**) or tetrazole (**91**). The reaction can be mediated by using a 0.3 equivalent of **90** leading to the formation of the desired product **72** in 30% yield, whereas the tetrazole itself (**91**) cannot catalyze the reaction (Scheme 21). This suggests that the formation of a stable enamine is the essential step for promoting the reaction and the tetrazole moiety enhances the reaction by hydrogen bonding with the aldehyde.



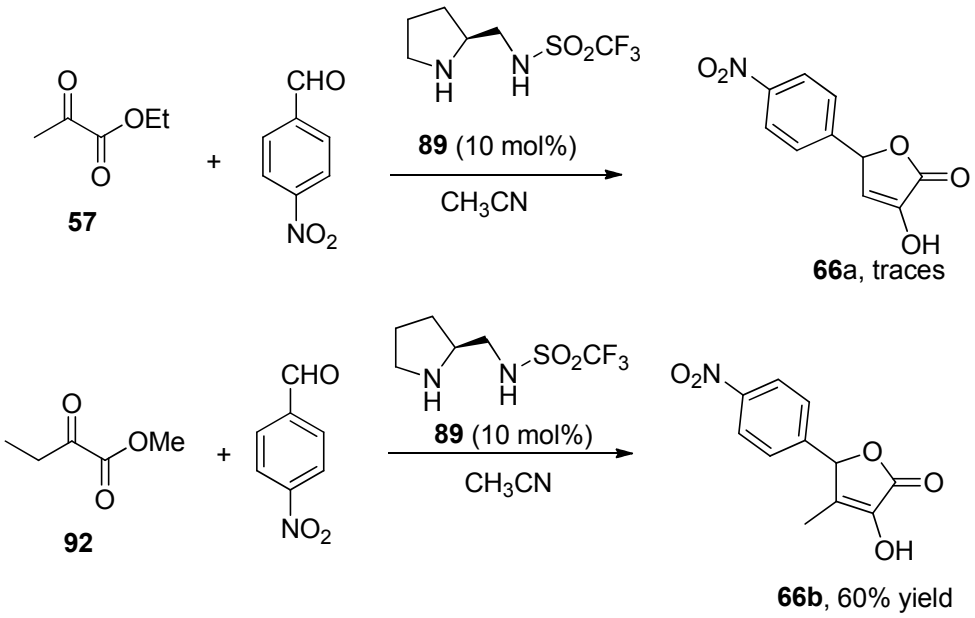
70 **57** **72**

ca. 30% yield

70 **57** **72**

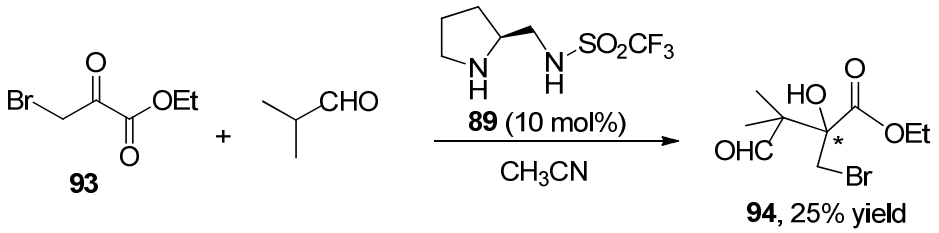
Scheme 21. Aldol condensation of ethyl pyruvate with chloral hydrate

The β-substituted pyruvate aldol reaction with aldehydes has been further investigated by using the pyrrolidine catalyst **89** in acetonitrile. The oxobutrate **92** shows a very high reactivity towards the aldol reaction with *p*-nitrobenzaldehyde compared to the ethyl pyruvate (**57**), which gave only traces of the cyclized isotetronic acids **66a**. The formation of **66b** in a reasonable yield can be illustrated by the effect of the extra methyl group on the stabilization of the key enamine intermediate (Scheme 22).



Scheme 22. Cross-aldol reaction of ethyl pyruvate vs methyl oxobutrate

When the pyruvate **93**, which has a bromo group in the β-position was used, the reactivity of the pyruvate was reversed and became more electrophilic. The isobutraldehyde was acted as the donor partner, affording the quaternary alcohol **94**, in a low yield (Scheme 23).

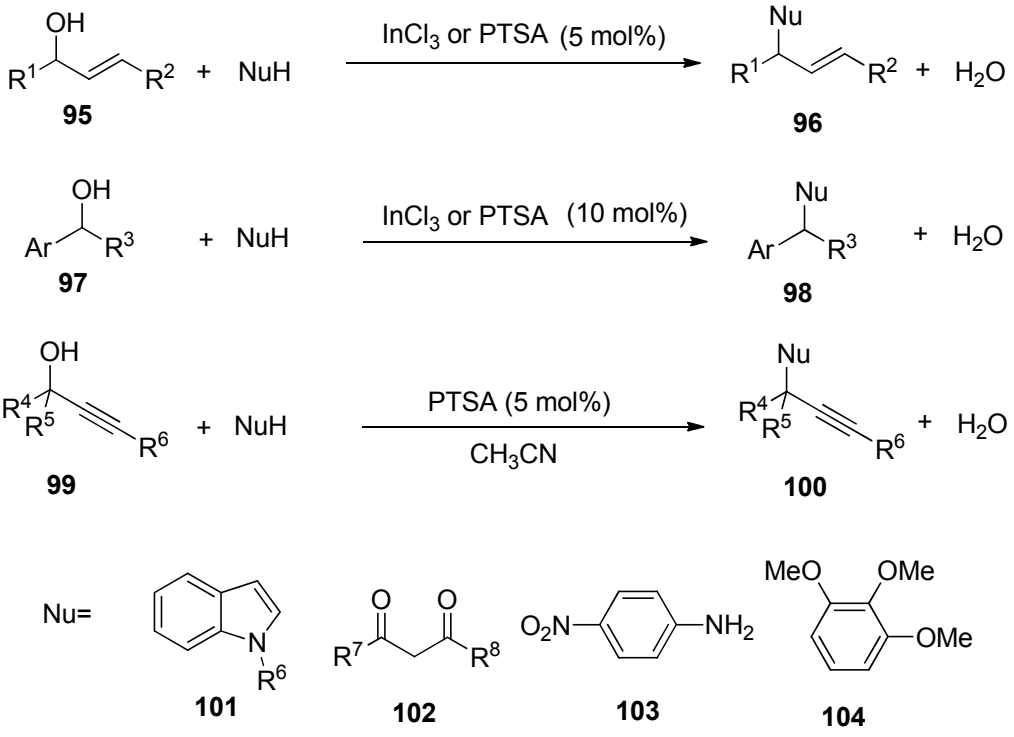


Scheme 23. Direct aldol reaction of ethyl bromopyruvate

2.2. Catalytic asymmetric alkylation with benzylic alcohols

The catalytic asymmetric alkylation is a very important carbon-carbon, carbon-oxygen and carbon-nitrogen bond formation process. Redeveloping these chemical transformations to be more atom economy and environmentally friendly is becoming a key focus of many research groups. Currently, the activation of substrates through additional steps is a quite wasteful operation. In this context, direct nucleophilic substitution *via* OH activation can be considered as an attractive approach, as water is the only produced by-product.

In 2002, Poli has reported the ability of carbocations generated from the benzylic alcohols **97** to react with active methylene compounds **102** by using stoichiometric amounts of BF_3.[76] Then, the conceptually more attractive approach of direct substitution of alcohols, by using only catalytic amounts of Lewis or Brønsted acids, has emerged.

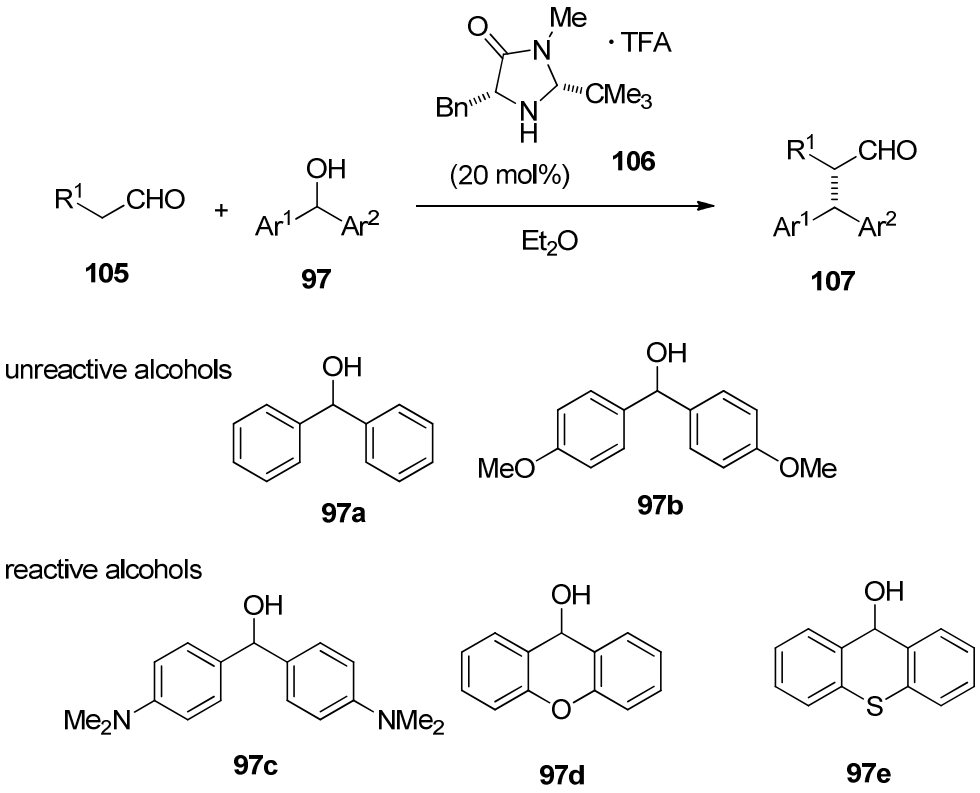


Scheme 24. Catalytic alkyation with different alcohols

The first example the catalytic allylic substitution with alcohols was achieved by using palladium type complexes.[77] Interestingly, Baba has shown the ability of the simple Indium salts for alkylation of a number of nucleophiles with alcohols **95** and **97**.[78] Whereas, Sanz and co-workers have demonstrated the alkylation of the nucleophiles **101**-

104 with a series of alcohols to deliver the compounds **96**, **98** and **100** in the presence of only 5-10 mol % of *p*-toluenesulfonic acid (Scheme 24).[79-82]

A number of synthetic methods for enantioselective alkylation with allylic alcohols are known,[83,84] however the asymmetric alkylation with benzylic alcohols is still a challenging operation. Cossi has first reported an efficient protocol for the asymmetric α-alkylation of aldehydes with benzylic alcohols. McMillan organocatalyst **106** was employed to convert the aldehydes **105** to the corresponding chiral enamine intermediates, which in turn react with the carbenium ions generated in the presence of an acid co-catalyst. The diphenylmethanol **97a** and a more reactive alcohol **97b** showed no reactivity under these conditions. On the other hand, the Michler's hydrol **97c**, xanthydrol **97d** and 9*H*-thioxanthen-9-ol **97e**, which can form long life carbenium ions, can smoothly alkylate a series of alphatic aldehydes. The obtained yields of **107** range from 56 to 95% with an enantiomeric excess between 69 to 80% *ee* (Scheme 25).



Scheme 25. Asymmetric alkyation with benzylic alcohols catalyzed by McMillan catalyst

The reaction mechanism can be explained by the formation of a chiral enamine intermediate owing the reaction between the aldehyde and the imidazolidinone-based catalyst **106**. In the catalytic cycle shown in Fig.5, the carbocation is generated by the

action of the acid co-catalyst. The *in situ* formed *E*-enamine and the carbocation can asymmetrically interact *via* a S_N1 type mechanism.

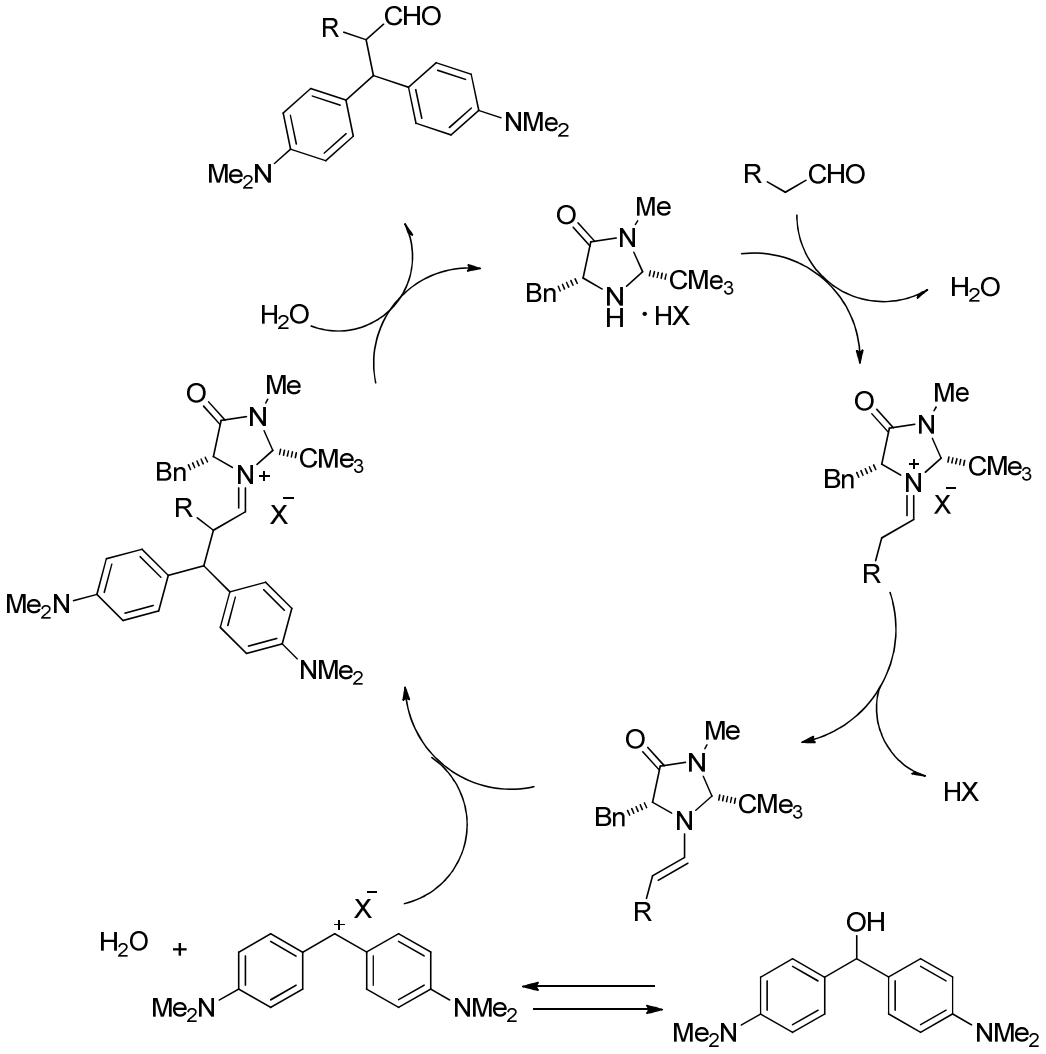
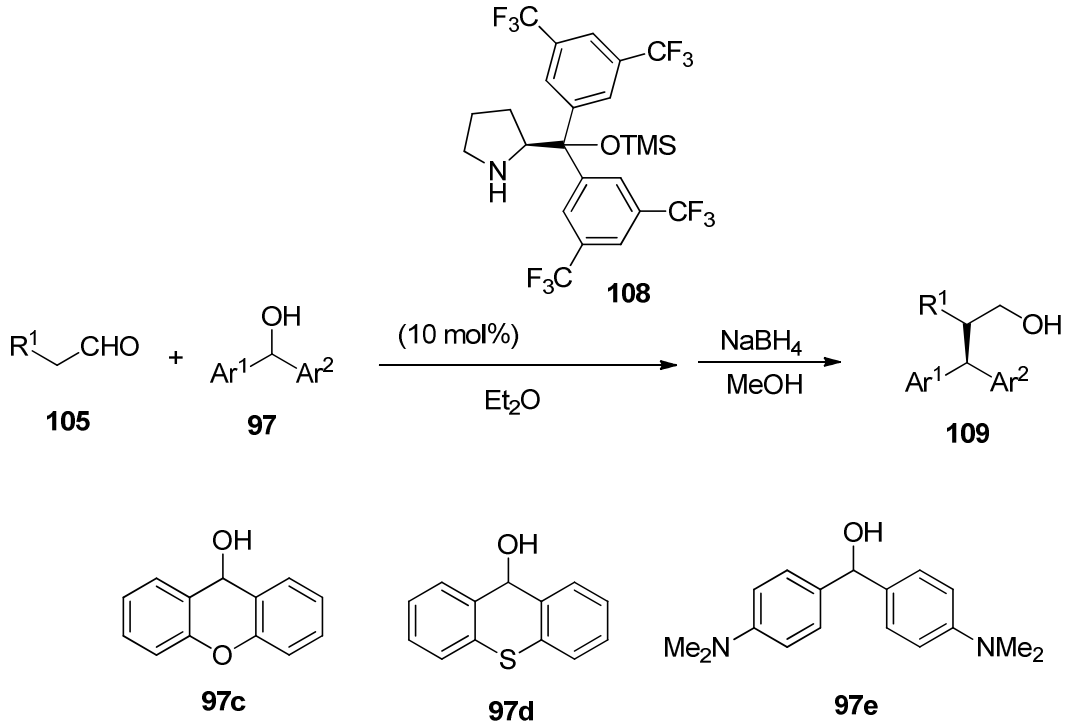


Fig 5. The proposed catalytic cycle of asymmetric S_N1-type reaction of alcohols

In order to increase the enantiomeric excess, Xiao and co-workers have modified Cossi's protocol by employing Jørgensen's diarylprolinol silyl ether **108** for leading to the formation of the chiral enamine intermediate. Instead of the Brønsted acid, transition metal salts ($IrCl_3$, CuCl or $InBr_3$) or trifluroethanol were used to promote the formation of the carbenium ion species. Even though, the improved protocol works very well to afford the corresponding products **109** in better yields and higher levels of stereochemical chemical control, it was only able to tolerate the same alcohols used by Cossi (Scheme 26).



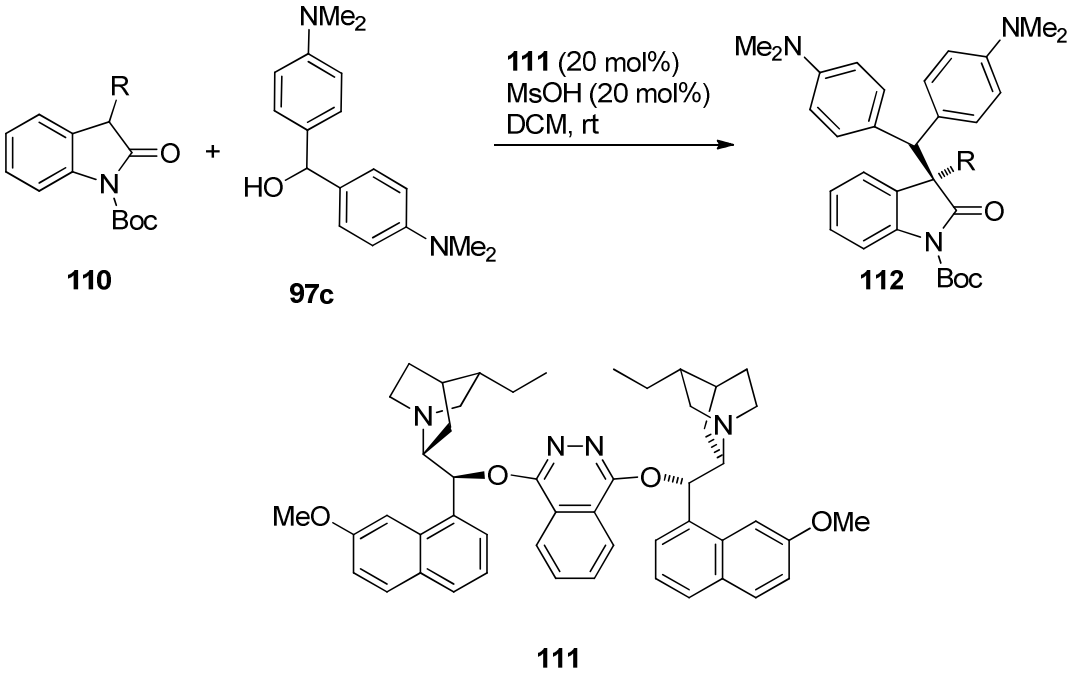
Scheme 26. Asymmetric alkyation with benzylic alcohols catalyzed by Jørgensen catalyst

Recently, Liu and co-workers have accomplished a successful example of the enantioselective α-alkylation of 2-oxindoles **110** with Michler's hydrol **97c** catalyzed by bis-tertiary amine **111** and an achiral acid in a non-covalent mechanism.

The combined di-tertiary amine catalyst and methansulfonic acid induce simultaneous activation of both reaction partners, the protonated tertiary amine moiety interact with the alcohol to give the carbocation and the second tertiary amine deprotonate the amides **110** to generate reactive enolate-anion intermediates. The alkylated products **112** were formed in good yields of up to 85%. The good asymmetric induction (70-82% *ee*) support the hypothesis that biscinchona alkaloids provide a stronger interaction with the substrates than monocinchona alkaloids. The authors proposed that the biscichona alkaloid catalyst constructs a chiral pocket firmly fixed both of the carbocation and the enolate in the S_N1-type alkylation reaction (Scheme 27).

In conclusion, the asymmetric alkylation with benzylic alcohols became a powerful and attractive tool in synthetic chemistry. Even so, the emerged protocols are, so far, very limited to the highly reactive alcohols. The catalytic mode involves the activation of the nucleophile by asymmetric fashion *via* the formation of an enamine or enolate. The electrophilic alcohols are activated by an achiral acid to form the corresponding

carbocation. Therefore, developing catalytic systems with different concepts and activation modes are a significant goal in order to further expand the substrate scope of this important reaction.



Scheme 27. Asymmetric alkyation of 2-oxindoles

3. Aim of the work

I) Direct aldol reaction of pyruvic acid derivatives

Although, there is a huge number of articles for asymmetric aldol reaction, the direct activation of pyruvates is long standing challenge for the synthetic community. The state of the known methodologies is narrow and strictly limited to self-condensation of pyruvate-type acceptors. We sought to select the appropriate substrates and design a catalytic system able to solve the problem in the biomimetic fashion. We also put in our mind to search for a catalytic protocol, which would have no match-dismatch effects between the substrates and the catalysis. This elusive target methodology can be extended to the synthesis of the valuable class of natural monosaccharides.

II) Brønsted acid catalyzed asymmetric alkylation with benzylic alcohols

Asymmetric benzylic alkylation with alcohols is a very interesting carbon-carbon bond forming process. Even so, the known protocols are very few and limited only to highly reactive alcohols. We postulates that *o*-quinomethide reactive species, which are proposed to be a reactive intermediates in different natural product synthesis, can be generated in situ from corresponding *o*-hydroxybenzylic alcohols. These intermediate can be used for the alkylation of different nucleophiles through the asymmetric 1,4-conjugate by the application of chiral Brønsted acids. The presence of *o*-hydroxy group ultimately allows access to a variety of biologically important enantiomerically enriched 4*H*-chromene.

4. Conclusions

I) Direct aldol reaction of pyruvic acid derivatives

First, the catalytic asymmetric aldol reaction of pyruvic aldehyde dimethyl acetal and 2-acetylthiazole with sugar aldehydes is demonstrated to be the key step in the synthesis of 3-deoxy-2-ulosonic acids. Efficient and stereoselective pyruvate aldol reactions are catalyzed by chiral Lewis acid-Brønsted base bifuctional metal-based catalyses. The elaborated synthetic methodology mimics aldolase-catalyzed reactions by direct activation of C_3 pyruvate equivalents with the use of metal-based chiral catalysts *en route* to the synthesis of KDO and KDG precursors.

Also the to-date problematic aldol reaction of pyruvate ester donors was solved by the application of sterically hindered aryl esters. Direct aldol reaction of pyruvate esters with sugar aldehydes is efficiently promoted by dinuclear metal complexes or chiral *Cinchona* alkaloid organocatalysts with *syn*- or *anti*-selectivity *en route* to the short and efficient synthesis of different 3-deoxy-2-ulosonic acids.

Notably, the presented elegant organocatalytic protocol allows the first carbon-carbon bond forming process, where the absolute configuration of the newly formed stereo center, created adjacent to chiral centre, can be switched by only changing the stereoisomer of the catalyst, leading to diastereodivergent selectivity. The chiral catalyst independently control the stereochemical course, diminishing match-mismatch effect between the chiral catalyst and the chiral substrate.

II) Brønsted acid catalyzed asymmetric alkylation with benzylic alcohols

The chiral phosphoric acids have been discovered to catalyze the asymmetric intermolecular benzylic alkylation of 1,3-dicarbonyl compounds *via* the formation of highly reactive *o*-quinomethide intermediates. The presented methodology has a broad scope, providing the corresponding 4*H*-chromenes in excellent yields and enantioselectivities (up to 98% yield, 96% *ee*). The presented approach which avoids the use of often toxic metals and substrates, is particularly attractive and we are confident that the concept of mild *o*-quinomethide generation and subsequent asymmetric 1,4-conjugate addition by means of a chiral phosphoric will find a broader application.

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6. Scientific contributions – Publications and additional materials

The presented achievements are divided into four parts; two articles based on direct aldol reaction of pyruvic derivatives, the results of the research on asymmetric alkylation with benzylic alcohols and the best methods of aldol reaction in water published in SoS reference library.

The results have been also presented in few international conferences

I) International conference "Catalysis in Organic Synthesis", 15-20 September 2012, Moscow, Russia, poster.
II) 4th Microsymposium on asymmetric synthesis, 7 September 2011, Warsaw, Poland, poster.
III) 17th European symposium on organic chemistry, 10-15 July 2011, Crete, Greece, poster.
IV) Flavors& Fragrances conference, 11-13 September 2013, Leipzig, Germany, without presentation.

6.1 Direct Aldol Reaction of Pyruvic Derivatives: Catalytic Attempt to Synthesize Ulosonic Acids

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SHORT COMMUNICATION

EurJOC European Journal of Organic Chemistry

DOI: 10.1002/ejoc.201200325

Direct Aldol Reaction of Pyruvic Derivatives: Catalytic Attempt To Synthesize Ulosonic Acids

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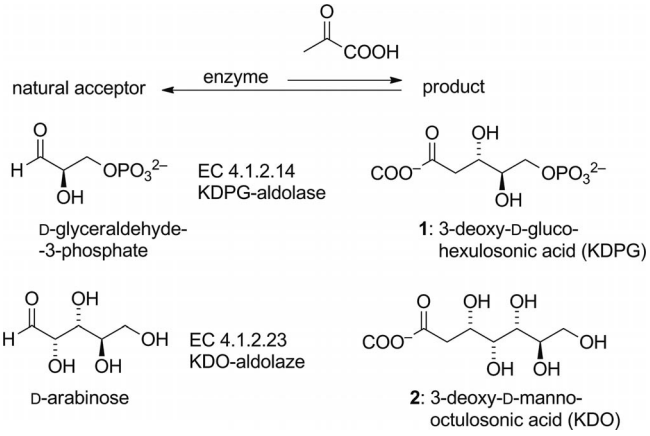
Keywords: Aldol reactions / Asymmetric catalysis / Carbohydrates / Enzymes

The catalytic asymmetric aldol reaction of pyruvic aldehyde dimethyl acetal and 2-acetylthiazole with sugar aldehydes is demonstrated to be the key step in the synthesis of 3-deoxy-2-ulosonic acids. Efficient and stereoselective pyruvate aldol reactions are catalyzed by metal-based chiral Trost and Shibasaki catalysts. The presented synthetic methodology mimics aldolase-catalyzed reactions by direct activation of C_3 pyruvate equivalents with the use of metal-based chiral catalysts en route to the synthesis of 2-keto-3-deoxy-D-glucosonic acid and 3-deoxy-D-manno-2-octulosonic acid derivatives.

Introduction

The direct asymmetric aldol reaction of unmodified carbonyl compounds represents one of the most powerful carbon–carbon bond-forming reactions in both nature[1] and synthetic organic chemistry.[2] Although enzymes are increasingly recognized as useful catalysts for asymmetric organic preparations, their application is mostly limited to a narrow scope of substrates similar to that used by nature. Nevertheless, observation of enzymatic modes of substrate activation provides insight for achieving similar transformations by chemical synthesis. As a result, the efficient and direct aldol reactions of important biological donors such as hydroxyacetone and dihydroxyacetone have been successfully realized by using biomimetic pathways.[3]

Among the variants of asymmetric aldol reactions, pyruvate-dependent aldol reactions are of particular interest, as these processes are vital in the formation of 3-deoxy-2-ulosonic acids (3-deoxy-2-keto acids), which are essential sugar units for many biological processes and transformations.[4] The phosphorylated form of 2-keto-3-deoxy-D-glucosonic acid (KDG), that is, KDPG (**1**), is part of the Entner–Doudoroff pathway, whereas 3-deoxy-D-manno-2-octulosonic acid [KDO (**2**)] has been found in Gram-negative bacteria lipopolysaccharides (LPS).[5] Pyruvate-dependent aldolase enzymes have catabolic function in vivo in the degradation of 3-deoxy-2-ulosonic acids, whereas their counterparts employ phosphoenolpyruvate as a donor in the synthesis of target biomolecules (Scheme 1).[6]



Scheme 1. Biosynthesis of 3-deoxy-2-ketoacids by phosphoenolpyruvate-dependent aldolases.

In recent years, a number of chemical and enzymatic methodologies have been reported for the synthesis of higher sialic and ulosonic acids.[6,7] However, in spite of the many published attempts, non-enzymatic syntheses based on chain extension with the use of an appropriate sugar unit as the electrophile and a C_3 pyruvate as the nucleophile under asymmetric control (see Scheme 1 for the biosynthetic pathway) is still troublesome, if simply not possible.[8] In a broader context, the direct catalytic aldol reaction of pyruvate and pyruvate derivatives still remains an elusive goal despite the breakthroughs in many other direct asymmetric aldol methodologies.[2] In spite of the tremendous effort, the scope of the known methodologies are narrow and are strictly limited to highly active and non-enolizable aldehydes[9] or the self-condensation of pyruvate donors with pyruvate-type acceptors.[10] Even so, we assumed that the direct activation of the donor could be possible in an asymmetric manner by using biomimetic metal-based catalysts.

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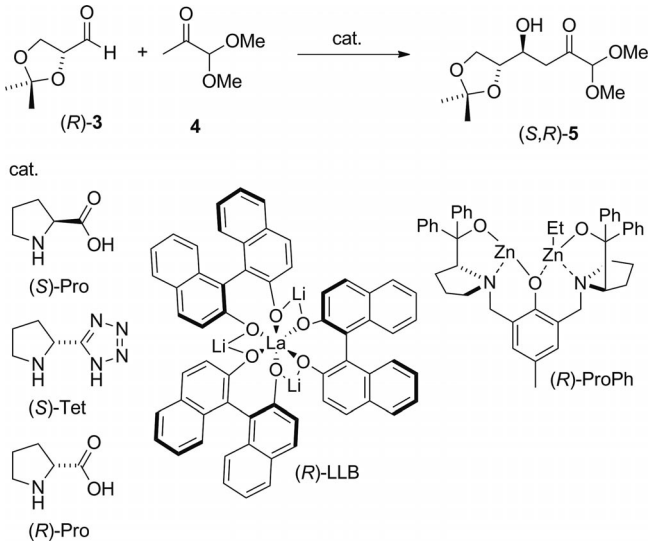
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/ejoc.201200325.

Results and Discussion

In this paper, we report that chiral metal complexes can act as a pyruvate-dependent aldolase, that is, a type II aldolase, to catalyze the direct asymmetric aldol reaction of pyruvate derivatives and their equivalents with aliphatic aldehyde electrophiles. The products obtained from this reaction can be further successfully transformed into 3-deoxy-2-ulosonic acids by using previously elaborated and reliable methodologies.

First, we focused on the troublesome aldol reaction between (*R*)-glyceraldehyde and dimethyl acetal **4** leading to *anti*-configured 3-deoxy-2-keto-D-glucosonic acid precursor **5** (Scheme 2). For our initial trials and to have a general overview, we simultaneously used organocatalysts mimicking type I aldolases and metal complexes acting as type II aldolases.



Scheme 2. Direct aldol reaction of pyruvic aldehyde dimethyl acetal with glyceraldehyde.

Initial investigations of the direct aldol reaction between selected acceptor **3** and donor **4** were conducted by employing (*R*)-proline as the enamine-formed organocatalyst (Table 1, Entry 1).

According to previous reports, "natural" (*S*)-proline proved to be a better catalyst when the (*S*)-configured protected glyceraldehyde was used, whereas with (*R*)-configured 2,3-*O*-isopropylidene-D-glyceraldehyde (**3**), (*R*)-proline afforded the best results in terms of yield.[3] Keeping this in mind, we tested both enantiomeric proline organocatalysts, but the observed catalytic activity of both mirror molecules was simply disappointing. The reactions were unsuccessful, which was quite surprising, as a similar reaction performed under asymmetric control was described previously by Enders.[11] The best results were observed by us in the reaction with (*R*)-proline (30 mol-%) to afford aldol **5** in 8% yield when a fivefold excess amount of the ketone was used (Table 1, Entry 1). Thus, the reaction cannot be seen as a catalytic process when 30 mol-% of the catalyst resulted in the formation of 8% of the desired product. Moreover, for

Table 1. Direct aldol reaction of pyruvic aldehyde dimethyl acetal with glyceraldehyde.

Entry	Catalyst (mol-%)	Time	Yield [%][b]	*anti*/*syn*[a]
1	(*R*)-Pro (30)[c]	5 d	8	4:1
2	(*S*)-Pro (30)[c]	5 d	4	1:4
3	(*S*)-Tet (30)[c]	5 d	8	4:1
4	LDA (110)[d]	20 min	35	2.2:1
5	(*R*)-ProPh (10)[e]	36 h	56	3:1
6	(*S*)-ProPh (10)[e]	36 h	49	2.5:1
7	(*R*)-LLB (10)[f]	8 h	45	2:1
8	(*S*)-LLB (10)[f]	8 h	45	7:1
9	(*S*)-LLB (10)[g]	24 h	40	13:1

[a] Determined by ^{1}H NMR spectroscopy. [b] Yield of isolated product. [c] Reactions were performed with **3** (5 mmol), **4** (25 mmol), catalyst (1.5 mmol, 30 mol-%) in DMSO at 4 °C for 5 d. [d] Reaction was performed with **3** (1 mmol), **4** (1 mmol), LDA (1.1 mmol, 110 mol-%) in THF at –78 °C for 20 min. [e] Reactions were performed with **3** (1 mmol), **4** (1.5 mmol), catalyst (10 mol-%) in DMF at r.t. for 36 h. [f] Reactions were performed with **3** (1 mmol), **4** (1 mmol), catalyst (10 mol-%) and KHMDS additive (10 mol-%) in THF at r.t. for 8 h. [g] Reactions were performed with **3** (1 mmol), **4** (1 mmol), catalyst (10 mol-%) and KHMDS additive (10 mol-%) in THF at 0 °C for 24 h.

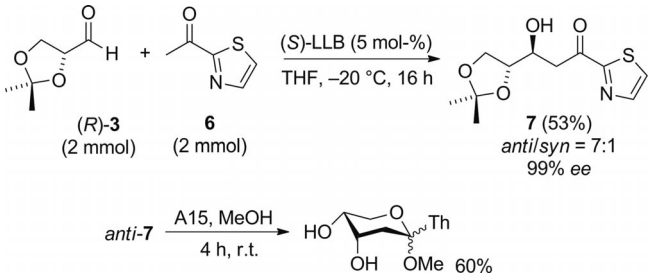
all reactions performed under organocatalytic control, we observed predominant formation of the corresponding dehydration product, which greatly affected the yield of the desired aldol. We believe that the elimination step is not an aldol reaction step but rather results from the competitive Mannich reaction/elimination pathway, so further optimization of the proline-catalyzed reaction may not be possible.[12]

Our efforts in the application of various organocatalysts to the reaction were also unsuccessful. After this initial trial, we decided to focus on metal-assisted activation of pyruvic aldehyde dimethyl acetal, which constitutes a white area in the map of the asymmetric aldol reaction. This can be compared mechanistically to type II aldolases, which employ a zinc ion to acidify the α proton of the donor component to form an enolate. As a reference example, we performed the aldol reaction of the stoichiometrically generated lithium enolate of **4** with glyceraldehyde.[13] The reaction was quite inspiring, and desired aldol **5** was obtained in 35% yield with a moderate *anti*/*syn* (ca. 2:1) ratio (Table 1, Entry 4). Encouraged by these results, we decided to test an asymmetric dinuclear zinc catalyst with the ProPh ligand presented in 2000 by Trost for the reaction of aryl methyl ketones.[14] Pleasingly, both enantiomeric catalysts exhibited good catalytic activity, and more importantly, good stereoselectivity was observed for a catalyst loading of only 10 mol-% (Table 1, Entries 5 and 6). For the reaction performed at room temperature, (*R*)-ProPh proved to be a slightly better catalyst, as reflected in both the yield and the diastereomeric ratio (3:1). Further progress in the reaction was observed for the Shibasaki lanthanium-based catalyst with (*S*)-BINOL ligands.[15] The (*S*)-LLB catalyst proved to be the most suitable catalyst when (*R*)-configured aldehyde **3** was used, as the best results in terms of the *anti*/*syn* ratio (7:1) were obtained, even at room temperature (Table 1, En-

try 8). The reaction stereoselectivity could be further improved by performing the reaction for 24 h at 0 °C. *anti*-Configured KDG precursor **5** was formed predominantly with a *syn*/*aldol* ratio of 13:1 (Table 1, Entry 9). For all tested catalysts, a slight excess of the ketone donor was sufficient to achieve a good yield of the aldol product.

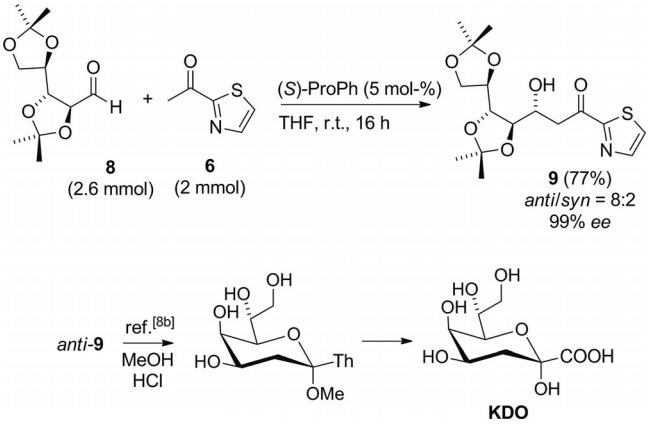
Both epimeric aldols of (*S*,*R*)- and (*R*,*R*)-configuration were easily deprotected with an acidic ion-exchange resin (Amberlyst 15) to give the cyclic forms of the desired sugars. It is important to stress that we did not observe racemization of glyceraldehyde under the elaborated reaction conditions. Application of both types of chiral catalyst did not affect the enantiomeric excess values of the product, which depends only on the enantiomeric excess value of the starting material. This was proved by using HPLC analysis on a chiral stationary phase.

Subsequently, en route to the ulosonic acid derivatives, we decided to test also the use of 2-acetylthiazole (**6**), successfully introduced by Dondoni, to the chemistry of ulosonic acids.[16] This was also an interesting challenge in the field of the catalytic asymmetric aldol reaction, as application of heterocyclic methyl ketone could possibly expand the still-narrow scope of the Shibasaki and Trost catalysts.[2] Application of (*R*)-ProPh resulted in the formation of aldol **7** in 50% yield with ca. 5:1 *anti*/*syn* ratio. To our gratification, only 5 mol-% of the chiral (*S*)-LLB catalyst was necessary to afford a promising yield and stereoselectivity in the aldol reaction of **6** with (*R*)-glyceraldehyde (**3**, Scheme 3). Desired aldol **7** was formed in 53% yield with 75%*de* for equimolar amounts of both substrates on a 2-mmol scale. Efficient transformation of this KDG-precursor to the ulosonic acid was described previously by Dondoni.[8b]



Scheme 3. Synthesis of the KDG precursor.

Next, we carried out a more demanding synthesis of a higher 2-ulosonic acid – KDO precursor, starting from D-arabinose diacetonide (**8**, Scheme 4). The synthesis of desired *anti*-configured aldol **9** was performed by (*S*)-ProPh-controlled addition of 2-acetylthiazole to protected sugar aldehyde **8**. A low catalyst loading (5 mol-%) and the option of performing the reaction at room temperature proved to be additional practical advantages of the described methodology. By using only a 1.3-fold excess of the aldehyde to ketone, the isolated yield increased to 77%. From this key intermediate, the synthesis proceeded over three previously described steps, namely, intramolecular hemiketalization, thiazole-to-formyl conversion, and oxidation of the aldosulose to the target KDO.[8b]



Scheme 4. Synthesis of KDO precursor.

Conclusions

In conclusion, we have successfully developed efficient and stereoselective pyruvate aldol reactions catalyzed by metal-based chiral catalysts. This methodology allowed the first catalytic synthesis of 3-deoxy-2-keto acid precursors through direct aldol reaction of sugar aldehydes with pyruvic derivatives. An elaborated direct aldol reaction promoted by chiral metal complexes acting as type II aldolases can be seen as resembling the natural pathway of substrate activation. The presented protocol, which utilizes C_3 pyruvic aldehyde dimethyl acetal, provides an attractive and biomimetic approach to ulosonic acids and constitutes another interesting field of application for the powerful Trost and Shibasaki catalysts. A variety of pyruvate derivatives were efficiently activated under the elaborated protocol, including 2-acetylthiazole, which is a fundamental achievement when compared to previously published methodologies for the synthesis of ulosonic acids. We believe that this work can be seen as the intermingling of two fundamental streams of chemical research: biomimetic direct aldol methodology and the synthesis of defined sugar structures.

Experimental Section

Supporting Information (see footnote on the first page of this article): Detailed experimental procedures and copies of the ^{1}H NMR and ^{13}C NMR spectra of all key intermediates and products.

Acknowledgments

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[9] a) For the reaction with chloral monohydrate, see: H. Torii, M. Nakadai, K. Ishihara, S. Saito, H. Yamamoto, *Angew. Chem.* **2004**, *116*, 2017; *Angew. Chem. Int. Ed.* **2004**, *43*, 1983–1986; b) for the reaction with activated aromatic aldehydes, see: S. Luo, H. Xu, L. Chen, J.-P. Cheng, *Org. Lett.* **2008**, *10*, 1775–1778.
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SUPPORTING INFORMATION

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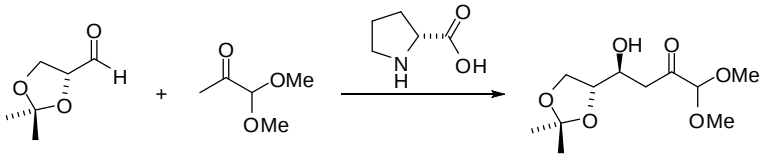
Title: Direct Aldol Reaction of Pyruvic Derivatives: Catalytic Attempt To Synthesize Ulosonic Acids
Author(s): Osama El-Sepelgy, Darius Schwarzer, Piotr Oskwarek, Jacek Mlynarski*

Direct aldol reaction of pyruvic aldehyde dimethyl acetal and glyceraldehyde with proline catalyst

based on literature protocol D. Enders, T. Gasperi, *Chem. Commun*. **2007**, 88-90

Table 1, entries 1-3



Dimethyl acetal **4** (2.95 g, 25 mmol) was added to a suspension of (*R*)-proline (172.5 mg, 1.5 mmol, 30 mol%) in DMSO (2.0 mL). The reaction mixture was stirred at 4 ^{o}C for 2 h after which freshly distilled aldehyde **3** (650 mg, 5 mmol) was slowly added. After 5 days at 4 ^{o}C, the reaction was quenched by saturated solution of ammonium chloride and extracted with ethyl acetate (3×15 mL). The organic layers were washed with brine, dried with ($MgSO_4$), concentrated and purified on silica gel (hexane:ethyl acetate, 3:2) to give aldol adduct **5** (*syn*/*anti*, 98 mg, overall 8%).

NMR data of isolated aldols have been in good agreements with previously published data:
D. Enders, T. Gasperi, *Chem. Commun*. **2007**, 88-90

anti-aldol

^{1}H NMR (300 MHz, **C_6D_6**) δ 1.28 (s, 3H), 1.37 (s, 3H), 2.80 (dd, J=9.1Hz, J=17.9Hz, 1H), 3.03 (dd, *J*=2.9Hz, *J*=17.9Hz, 1H), 2.86 (bs, 1H), 3.07 (s, 6H), 3.58–3.98 (m, 4H), 4.17 (s, 1H); ^{13}C NMR (75 MHz, C_6D_6) δ 25.8, 27.29, 42.08, 54.93, 54.98, 67.56, 69.54, 78.71, 105.08, 109.85, 205.82.

^{1}H NMR (300 MHz, **$CDCl_3$**) δ 1.28 (s, 3H), 1.34 (s, 3H), 2.67 (dd, *J*=8.8Hz, *J*=18Hz, 1H), 2.86 (dd, *J*=2.9Hz, *J*=18Hz, 1H), 2.87 (*bs*, 1H), 3.37 (s, 6H), 3.74-4.00 (m, 4H), 4.42 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 25.81, 27.27, 41.74, 55.54, 67.19, 69.13, 78.32, 104.59, 110.111, 206.38.

syn-aldol

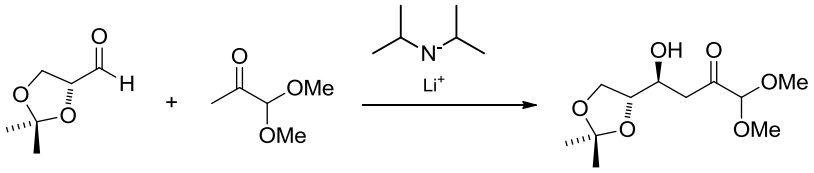
^{1}H NMR (300 MHz, **C_6D_6**) δ 1.30 (s, 3H), 1.39 (s, 3H), 2.63 (dd, J=3.8Hz, J=17.3Hz, 1H), 3.98 (dd, J=8.8Hz, J=17.4Hz, 1H), 2.87 (bs, 1H), 3.07 (s, 6H), 3.58–3.98 (m, 4H), 4.24 (s, 1H); ^{13}C NMR (75 MHz, C_6D_6) δ 25.8, 27.29, 42.08, 54.93, 54.98, 67.56, 69.54, 78.71, 105.08, 109.85, 205.82.

^{1}H NMR (300 MHz, **$CDCl_3$**) δ 1.30 (s, 3H), 1.38 (s, 3H), 2.60 (dd, *J*=3.5Hz, *J*=17.4Hz, 1H), 2.79 (dd, *J*=8.1Hz, *J*=17.1Hz, 1H), 2.87 (*bs*, 1H), 3.37 (s, 6H), 3.74-4.00(m, 4H), 4.43 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 25.82, 27.04, 41.67, 55.54, 66.25, 68.20, 78.54, 104.72, 110.24, 205.14.

Direct aldol reaction of pyruvic aldehyde dimethyl acetal and glyceraldehyde with stoichiometric amount of lithium diisoprobylamide (LDA)

based on K. Narasaka, F.-C. Pai, *Tetrahedron* **1984**, *40*, 2233-2238

Table 1, entry 4

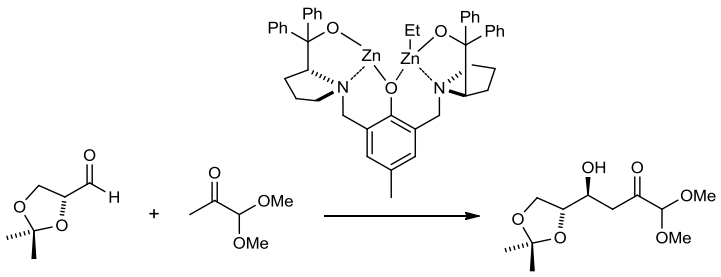


Lithium diisopropylamide (1.1 mmole, 10 wt% in hexane) was added to 2 mL of dry THF at -78 ^{o}C. A solution of methyglyoxal dimethoxyacetal **4** (118 µl, 1 mmole) in THF (1mL) was added and the mixture was stirred for 10 min. Then a solution of freshly distilled protected glyceraldehde **3** (130 mg, 1 mmole) was added dropwise and stirred at the same temperature for 20 min. The mixture was quenched by saturated ammonium chloride and extracted with dichloromethane. The organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified on silica gel by flash chromatography (hexane:acetone, 3:1) to give the aldol adduct **5** (*syn*/*anti*, 87 mg, 35%).

Direct aldol reaction of pyruvic aldehyde dimethyl acetal and glyceraldehyde with Trost's catalyst

catalyst: B. M. Trost, H. Ito, *J. Am. Chem. Soc*. **2000**, *122*, 12003-12004

Table 1 entry 5-6

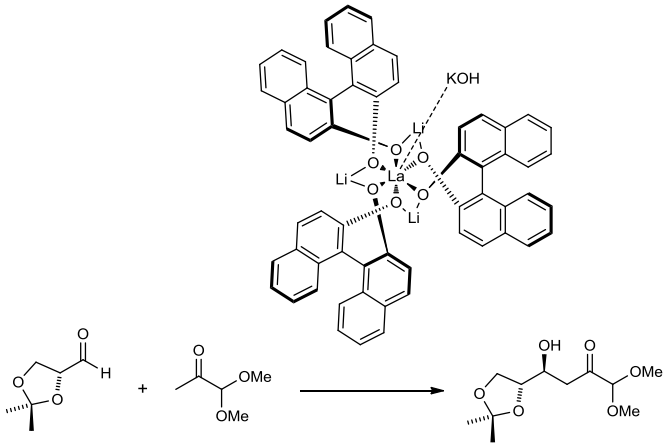


Under an argon atmosphere, a solution of diethylzinc (1M in hexane, 0.2 mL, 0.2 mmole) was added to a solution of Trost's ligand (64 mg, 0.1 mmole) in DMF (1 mL) at room temperature. After stirring for 30 min with evolution of ethane gas, triphenylphosphine sulfide (22.1 mg, 0.075 mol) and dry powdered molecular sieves 4A (100 mg) were added. A solution of pyruvic aldehyde dimethoxy acetal **4** (177 mg, 1.5 mmole) in 0.5 mL of DMF was added at room temperature and stirred for 30 min at room temperature. The resulting solution was cooled to 0 ^{o}C and a solution of freshly distilled aldehyde **3** (130 mg, 1 mmole) in 0.5 mL of DMF was added dropwise. The stirring was continued for at room temperature for 36 h. The reaction mixture was quenched by ammonium chloride, extracted with diethylether, dried with magnesium sulphate and purified on silica gel using hexane:acetone (3:1) as eluent to give aldol adduct **5** (139 mg, 56%).

Direct aldol reaction of pyruvic aldehyde dimethyl acetal and glyceraldehyde with Shibasaki's catalyst

catalyst: N.Yoshikawa, N. Kumagai, S. Matsunaga, G. Moll, T. Ohshima T. Suzuki, M. Shibasaki, *J. Am. Chem. Soc.* **2001**, *123*, 2466-2467

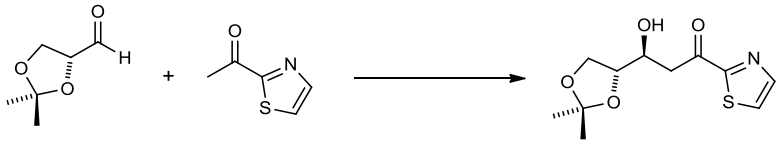
Table 1 entry 7-8



To a solution of potassium bis(trimethylsilyl)amide (KHMDS) in toluene (0.09 mmol, 180 μL, 0.5 M) at 0 ^{o}C, water in THF (0.2 mmole, 200 μL, 1M) was added. After stirring for 15 min a solution of $LaLi_3$tris((*S*)-binaphthoxide)((*S*)-LLB) in THF (0.1 mmole, 1 mL, 0.1M) was added and the stirring was continued at 0^{o}C for 30 min. A mixture of aldehyde **3** (260 mg, 1 mmole), ketone (1 mmole) were successfully added to the solution. The reaction mixture was stirred for 8 h at room temperature quenched by ammonium chloride, extracted with diethylether, dried with magnesium sulphate and purified on silica gel using ethyl acetate: hexane (3:2) as eluent to give aldol adduct **5** (112 mg, 45%).

Direct aldol reaction of acetylthiazole and glyceraldehyde with Shibasaki's catalyst

Scheme 3



To a solution of potassium bis(trimethylsilyl)amide (KHMDS) in toluene (0.09 mmol, 180 µL, 0.5 M) at 0 °C, was added water in THF (0.2 mmole, 200 µL, 1M). After stirring for 15 min a solution of $LaLi_3$tris((*S*)-binaphthoxide)((*S*)-LLB) in THF (0.1 mmole, 1 mL, 0.1M) was added and the stirring was continued at 0 °C for 30 min. The catalyst solution was cooled down to -20 °C and the solution of aldehyde **3** (260 mg, 2 mmole), acetylthiazole **6** (254 mg, 2 mmole) in 5 mL of THF were successfully added to the previous mixture. The reaction mixture was stirred for 16 h at the same temperature then quenched by ammonium chloride, extracted with ethyl acetate, dried with magnesium sulphate and purified on silica gel using hexane:diethylether (1:1) as eluent to give aldol adduct **7** (273 mg, 53%).

NMR data of isolated aldols have been in good agreements with previously published data: A. Dondoni, P. Merino, *J. Org. Chem*. **1991**, *56*, 5294-5301

anti-aldol

^{1}H NMR (300 MHz, **C_6D_6**) δ 1.27 (s, 3H), 1.37 (s, 3H), 3.33 (dd, J=8.86Hz, *J*=16.81Hz, 1H), 3.53 (dd, *J*=3.06Hz, *J*=16.81Hz, 1H), 3.24 (*bs*, 1H), 3.70–4.00 (m, 4H), 6.63 (d, *J*= 3Hz, 1H), 7.46 (d, *J*= 3Hz, 1H) ; ^{13}C NMR (75 MHz, C_6D_6) δ 25.81, 27.25, 43.71, 67.48, 70.03, 78.91, 109.95, 126.60, 145.04, 167.83, 193.37.

^{1}H NMR (300 MHz, **$CDCl_3$**) δ 1.29 (s, 3H), 1.35 (s, 3H), 3.26 (dd, *J*=8.8Hz, *J*=17.1Hz, 1H), 3.45 (dd, *J*=2.9Hz, *J*=17.1Hz, 1H), 3.36 (*bs*, 1H), 3.48–3.56 (m, 4H), 7.65 (d, *J*= 3Hz, 1H), 7.96 (d, *J*= 3Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 25.84, 27.28, 43.27, 67.23, 69.64, 78.50, 110.20, 127.30, 145.48, 167.46, 193.72.

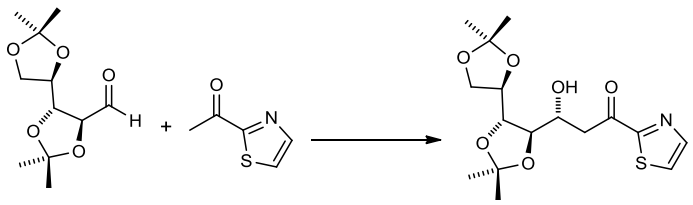
syn-aldol

^{1}H NMR (300 MHz, **C_6D_6**) δ 1.26 (s, 3H), 1.36 (s, 3H), 3.11 (dd, *J*=3.67Hz, *J*=16.06Hz, 1H), 3.51 (dd, J=9Hz, *J*=15.9Hz, 1H), 3.24 (*bs*, 1H), 3.70–3.00 (m, 4H), 6.64 (d, *J*= 3Hz, 1H), 7.49 (d, *J*= 3Hz, 1H); ^{13}C NMR (75 MHz, C_6D_6) δ 25.76, 26.85, 43.52, 66.14, 68.60, 78.83, 109.95, 126.60, 145.04, 167.83, 193.37.

^{1}H NMR (300 MHz, **$CDCl_3$**) δ 1.31 (s, 3H), 1.38 (s, 3H), 3.21 (dd, *J*=3.6Hz, *J*=16.3Hz, 1H), 3.38 (dd, *J*=8.4Hz, *J*=16.2Hz, 1H), 3.36 (*bs*, 1H), 3.48–3.56 (m, 4H), 7.64 (d, *J*= 3Hz, 1H), 7.95 (d, *J*= 3Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 25.80, 27.02, 43.45, 66.35, 68.86, 78.65, 110.31, 127.30, 145.41, 167.46, 193.72.

Direct aldol reaction of acetylthiazole and arabinose with Trost's catalyst

Scheme 4



Under an argon atmosphere, a solution of diethylzinc (1M in hexane, 0.2 mL, 0.2 mmole) was added to a solution of Trost's ligand (64 mg, 0.1 mmole) in THF (1 mL) at room temperature. After stirring for 30 min with evolution of ethane gas, triphenylphosphine sulfide (44.2 mg, 0.15 mol) and dry powdered molecular sieves 4A (200 mg) were added. The catalyst solution was cooled to -20^{o}C. A solution of acetylthiazole **6** (254 mg, 2 mmole) and arbinose **8** (600 mg, 2.6 mmole) in 4 mL THF was added. Then the temperature was raised to room temperature and stirring was continued for 16 h. The reaction mixture was quenched by ammonium chloride, extracted with ethyl acetate, dried with magnesium sulphate and purified on silica gel using hexane:diethylether (1:1) as eluent to give aldol adduct **5** (448 mg, 77%).

NMR data of isolated aldols have been in good agreements with previously published data: A. Dondoni, P. Merino, *J. Org. Chem*. **1991**, *56*, 5294-5301

^{1}H NMR (300 MHz, **C_6D_6**) δ 1.17 (*s*, 3H), 1.25 (*s*, 3H), 1.28 (*s*, 3H), 1.33 (*s*, 3H), 3.66 (*bs*, 1H), 3.70 (m, 1H), 3.73–4.05 (m, 6H), 4.65 (*m*,1H), 6.63 (d, *J*= 3Hz, 1H), 7.51 (d, *J*= 3Hz, 1H). ^{13}C NMR (75 MHz, C_6D_6) δ25.64, 26.85, 27.40, 27.50, 43.66, 68.26, 70.03, 77.39, 81.28, 83.76, 109.95, 110.53, 126.26, 144.95, 168.47, 192.66.

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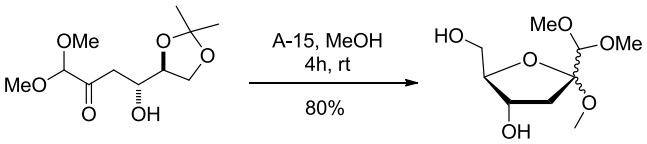
^{1}H NMR (300 MHz, **$CDCl_3$**) δ 1.27 (*s*, 3H), 1.30 (*s*, 6H), 1.33 (*s*, 3H), 3.70 (*bs*, 1H), 3.77 (*m*, 1H), 3.85–4.15 (m, 6H), 4.33 (m,1H), 7.62 (d, *J*= 3Hz, 1H), 7.96 (d, *J*= 3Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 25.81, 27.04, 27.46, 27.52, 43.27, 68.46, 69.69, 81.25, 83.39, 110.26, 110.79, 126.90, 127.02, 145.35, 168.03, 193.05.

Deprotection of aldol 5



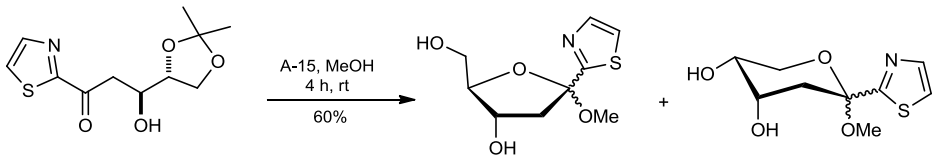
D-KDG precursor

To a stirred solution of aldol product (100 mg) in dry methanol Amberlyst 15 (200 mg) was added. After stirring for 4 h the ion exchange resin was removed by filtration and the solvent was evaporated under vaccum. The hemiacetal was purified on silica gel using a mixture of 5% methanol in ethyl acetate to give (71 mg, 80%).

NMR data of isolated aldols have been previously published: D. Enders, T. Gasperi, *Chem. Commun*. **2007**, 88-90

^{1}H-NMR (300 MHz) 1.73 (dd, J=5.3, J=13.84, 1H), 2.07 (dd, J=7.78, J=13.61, 1H), 2.16 (dd, J=8.31, J=13.6, 1H), 2.41 (dd, J=8.05, J=13.85, 1H), 3.32 (s, 3H), 3.33 (s, 3H), 3.34 (s, 3H), 3.35 (s, 3H), 3.40 (s, 3H), 3.42 (s, 3H), 3.5-3.88 (m, 5H), 3.90 (dt, J=3.63, J=5.83, 1H), 4.13 (dt, J=5.4, J=8, 1H) 4.18 (q, J=8, 1H), 4.23 (s, 1H), 4.24 (s,1H). *m/z* (ESI): 244.7 (M^{+}+Na, 100).

Deprotection of aldol 7



D-KDG precursors

To a stirred solution of aldol product (100 mg) in dry methanol Amberlyst 15 (200 mg) was added. After stirring for 4h the ion exchange resin was removed by filtration and the solvent was evaporated under vacuum. The hemiacetal was purified on silica gel using a mixture of 5% methanol: ethyl acetate to give a mixture of *β and* α-pyranose and furanose (53 mg, 60 %). The previous mixture was reseparated by column chromatography using methanolic dichloromethane as eluent. *β*-Pyranose and *β*-furanose were successively separated but *α*-furanose and *α*-pyranose have been characterized as a mixture.

NMR data of isolated aldols have been in good agreements with previously published data: A. Dondoni, P. Merino, *J. Org. Chem*. **1991**, *56*, 5294-5301 and R. Plantier-Royon, F. Cardona, D. Anker, *J. Carbohydr. Chem.* **1991**, *10*, 787-811

β-pyranose-form

^{1}H-NMR (300 MHz, CD_3OD) δ 1.92 (dd, *J*=12.0Hz, *J*=12.5Hz, 1H), 2.25 (dd, *J*=4.9Hz, *J*=12.7Hz, 1H), 3.00 (s, 3H), 3.87 (dd, 2H, *J*=1.8Hz, *J*=4.3Hz), 3.76 (m, 1H), 4.07 (m, 1H), 7.56 (d, *J*=3.2Hz, 1H), 7.77 (d, *J*=3.3Hz, 1H). *m/z* (ESI): 253.8 (M^++Na, 100).

α-furanose-form

^{1}H-NMR (300 MHz, CD_3OD) δ 2.55 (dd, *J*=5.0Hz, *J*=13.2Hz, 1H), 2.70 (dd, *J*=6.8Hz, *J*=13.2Hz, 1H), 3.11 (s, 3H), 3.63 (dd, *J*=6.6Hz, *J*=11.8Hz, 1H), 3.72 (dd, *J*=4.4Hz, *J*=11.8Hz, 1H), 4 (m,1H), 4.36 (dt, *J*=5.4Hz, *J*=7.0Hz, 1H), 7.56 (d, *J*=3.2Hz, 1H), 7.77 (d, *J*=3.3Hz, 1H).

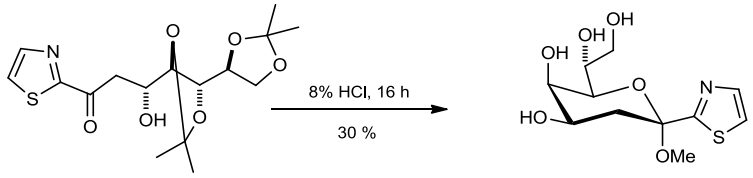
α-pyranose-form

^{1}H-NMR (300 MHz, CD_3OD) δ 1.52 (dd, *J*=11.4Hz, *J*=13.2Hz, 1H), 2.15 (dd, *J*=7.2Hz, *J*=13.2Hz, 1H), 3.00 (s, 3H), 3.44-3.47 (m, 2H), 3.82-3.87 (m, 2H), 7.56 (d, *J*=3.2Hz, 1H), 7.77 (d, *J*=3.3Hz, 1H)..

β-furanose-form

^{1}H-NMR (300 MHz, CD_3OD) δ 2.39 (m, 2H), 3.16 (s,3H), 3.66 (dd, 1H, J=5.0Hz, *J*=12.1Hz), 3.75 (dd, 1H, *J*=3.6Hz, *J*=12.1Hz), 4.08 (dt, 1H, *J*=3.6Hz, *J*=4.8Hz), 4.22 (td, *J*=4.9Hz, *J*=6.4Hz, 1H), 7.55 (d, *J*=3.3Hz, 1H), 7.77 (d, *J*=3.3Hz, 1H).

Deprotection of aldol 9



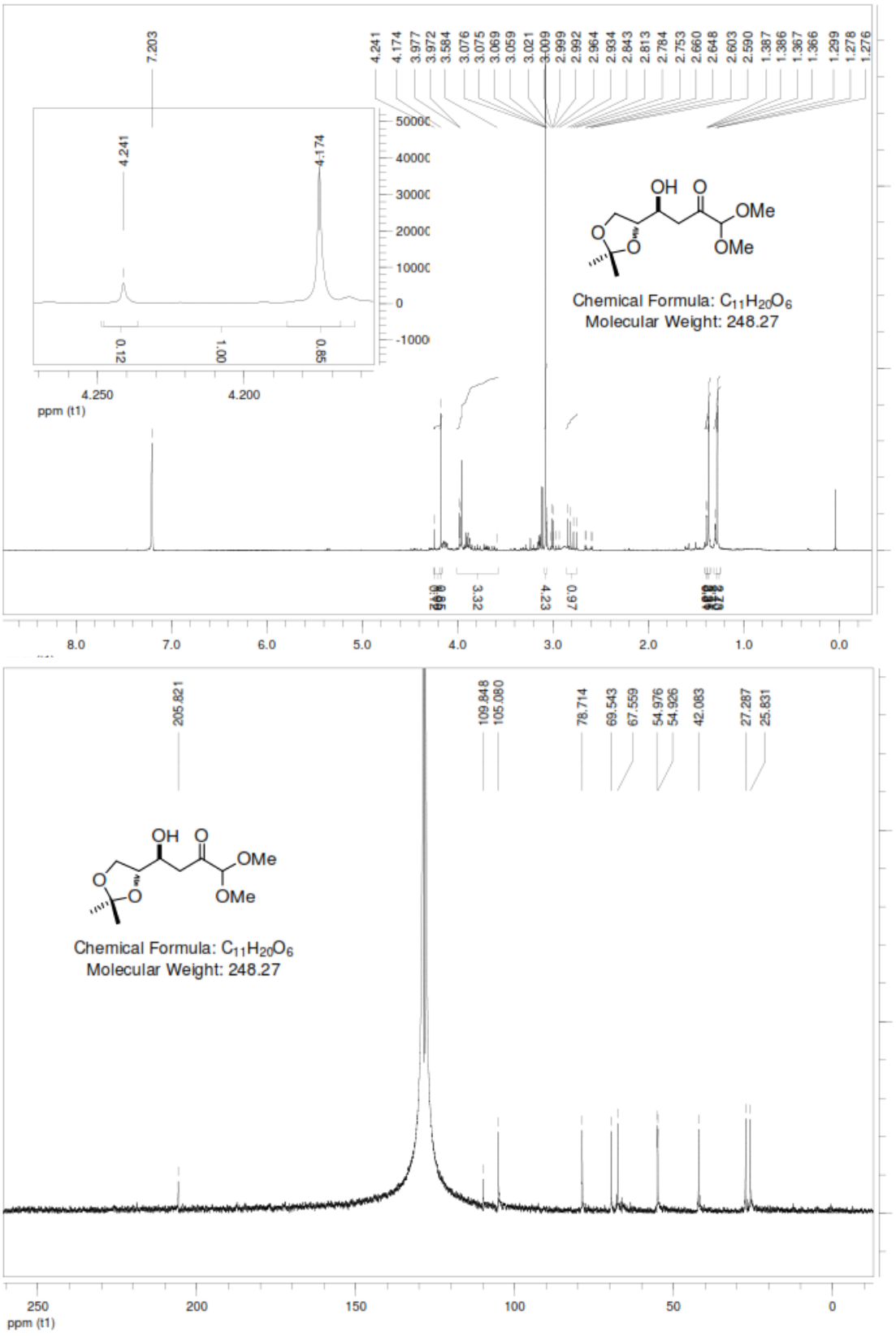
Aldol **9** (46 mg, 0.13 mmole) was treated with 8 % methanolic HCl (4 mL). The mixture was stirred for 16h. The reaction mixture was neutralized by aqueous sodium bicarbonate. The solvent was evaporated under reduced pressure and purified using column chromatography using 10 % methanol:ethyl acetate to give (11 mg, 30 %).

NMR data of isolated aldols have been in good agreements with previously published data: A. Dondoni, P. Merino, *J. Org. Chem*. **1991**, *56*, 5294-5301

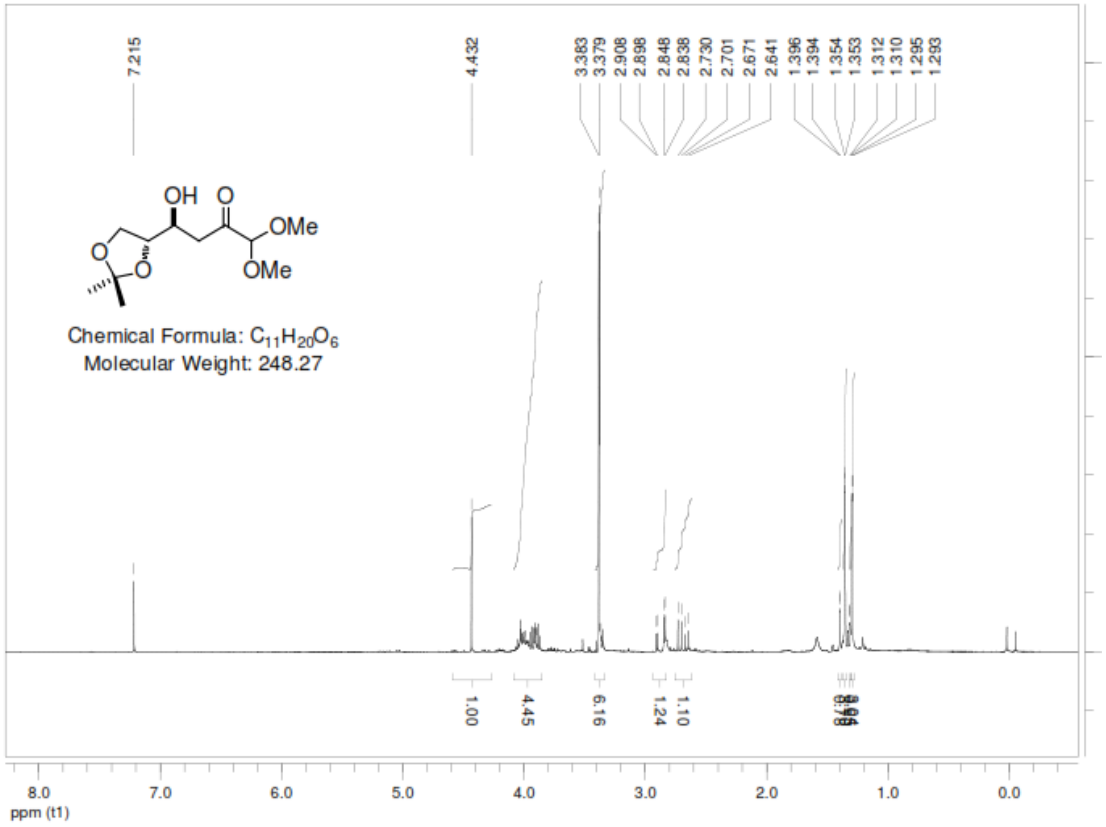
α -pyranose-form

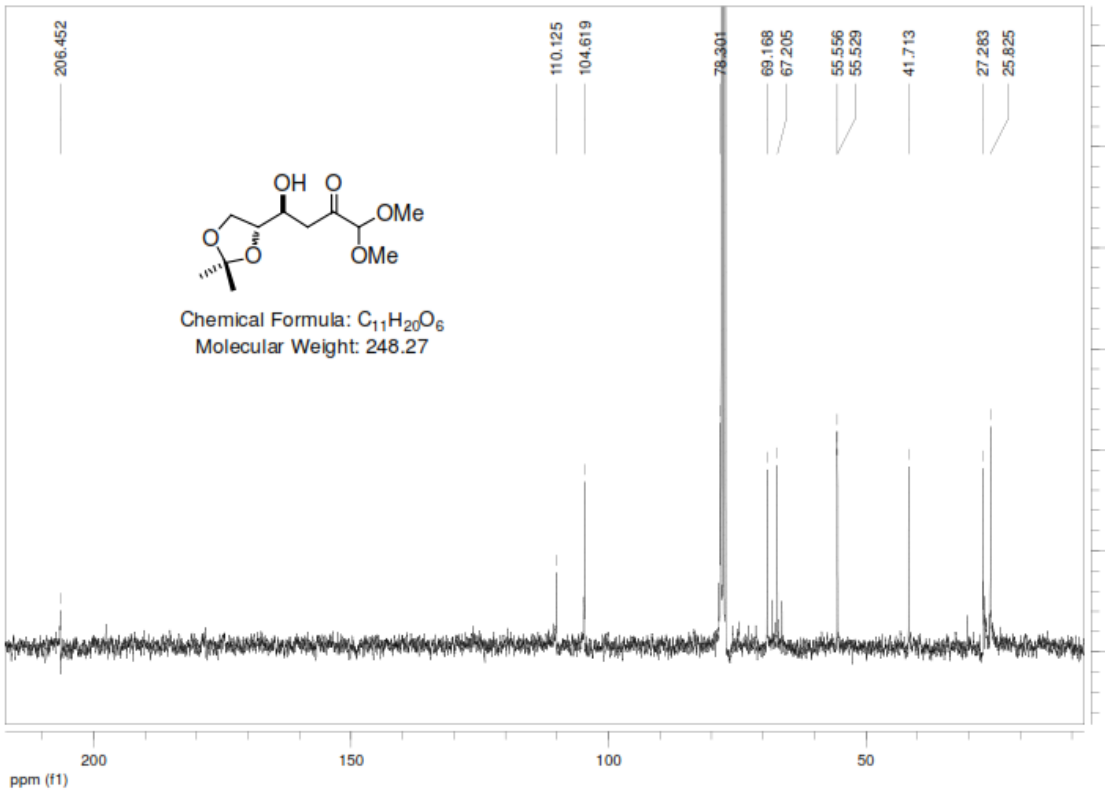
^{1}H-NMR (300 MHz, D_2O) δ 1.85 (dd, *J*=12.1Hz, *J*=13.1Hz, 1H,), 2.26 (dd, J=5.0Hz, *J*=13.1Hz, 1H,), 2.95 (s, 3H), 3.63-4.1 (m, 6H), 7.76 (d, *J*=3.3Hz, 1H), 7.54 (d, *J*=3.3Hz, 1H).

aldol **5**: Table 1, entry 8 (*syn*/*anti*, 1:7, in C_6D_6)

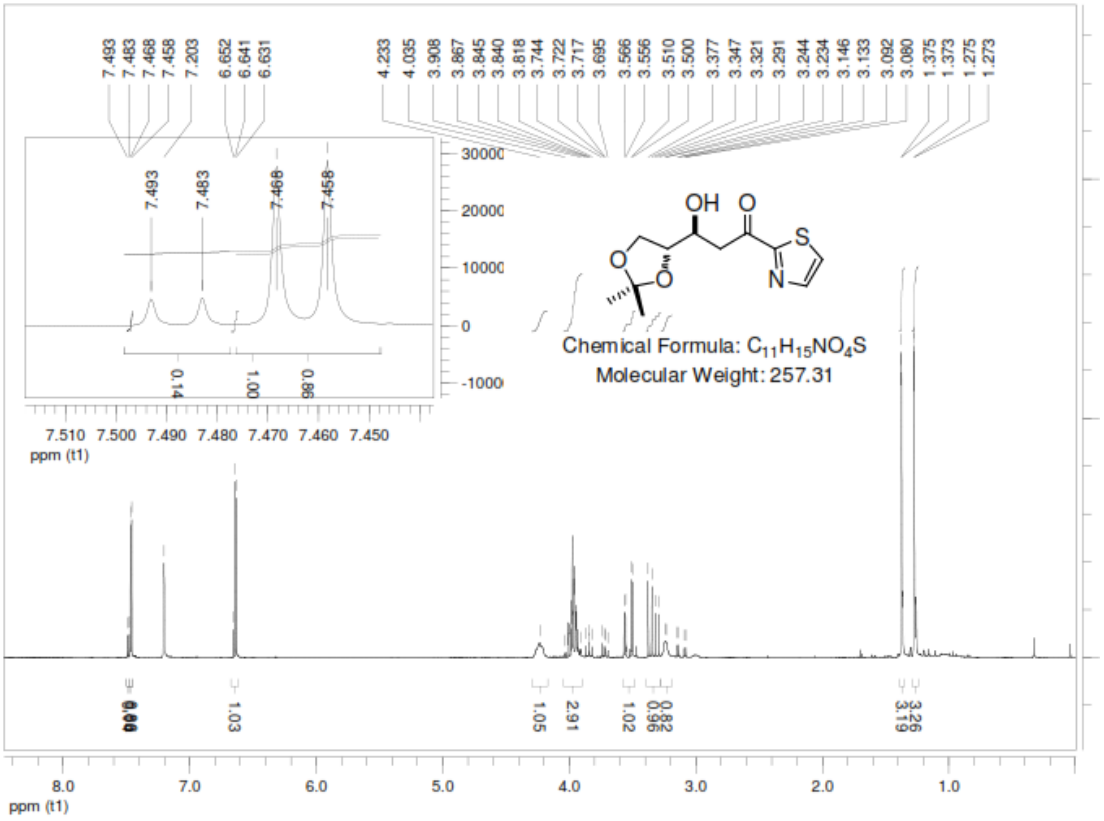


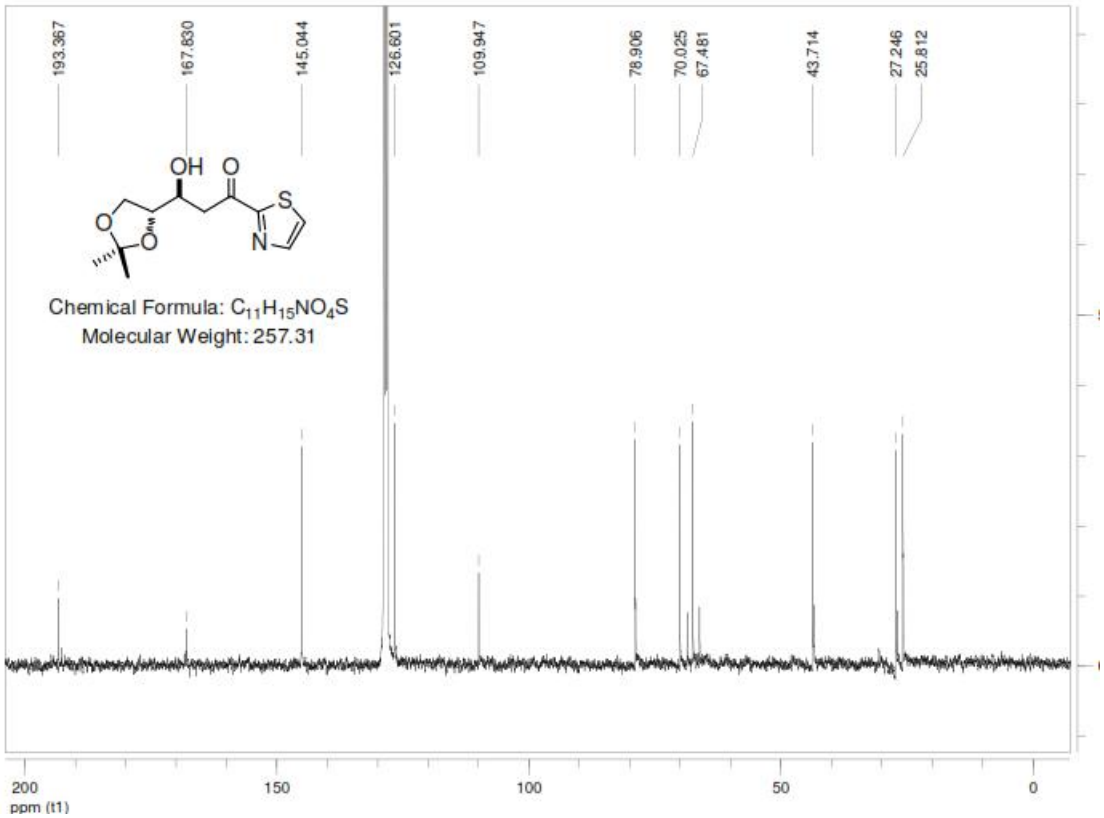
aldol **5**: Table 1, entry 8 (*syn*/*anti*, 1:7, in $CDCl_3$)



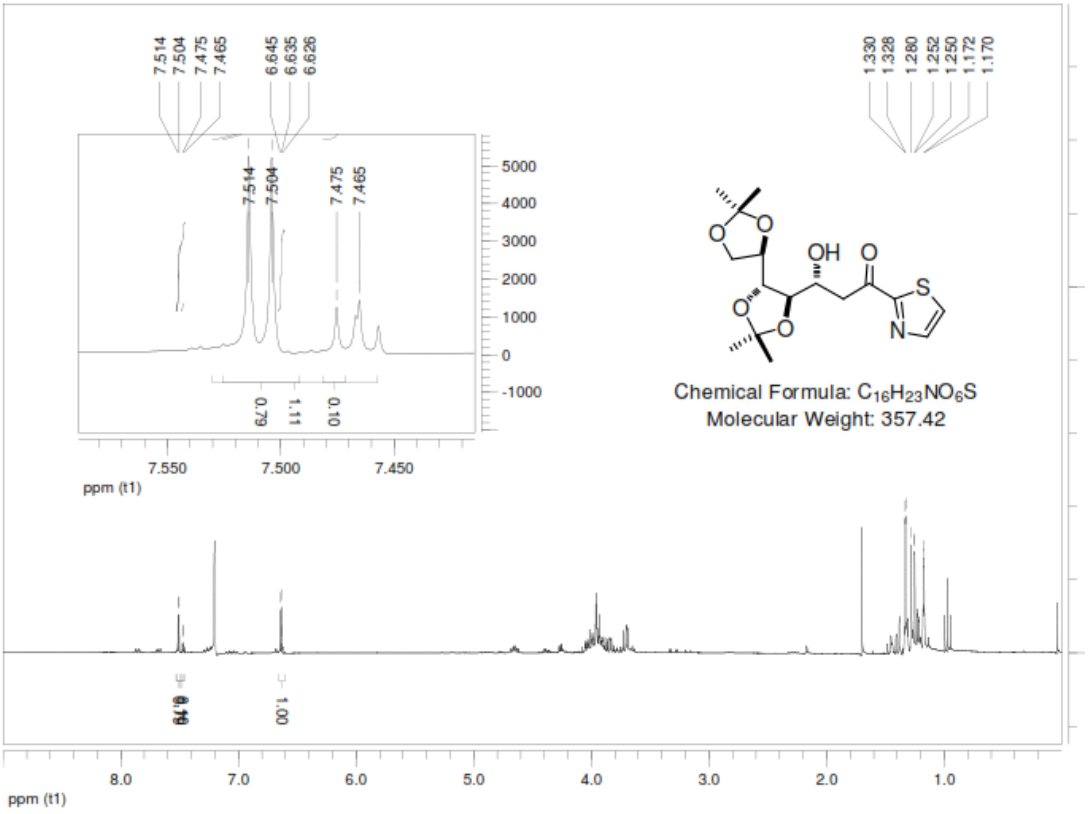


aldol **7**: Scheme 3 (*syn*/*anti*, 1:7, in $CDCl_3$)

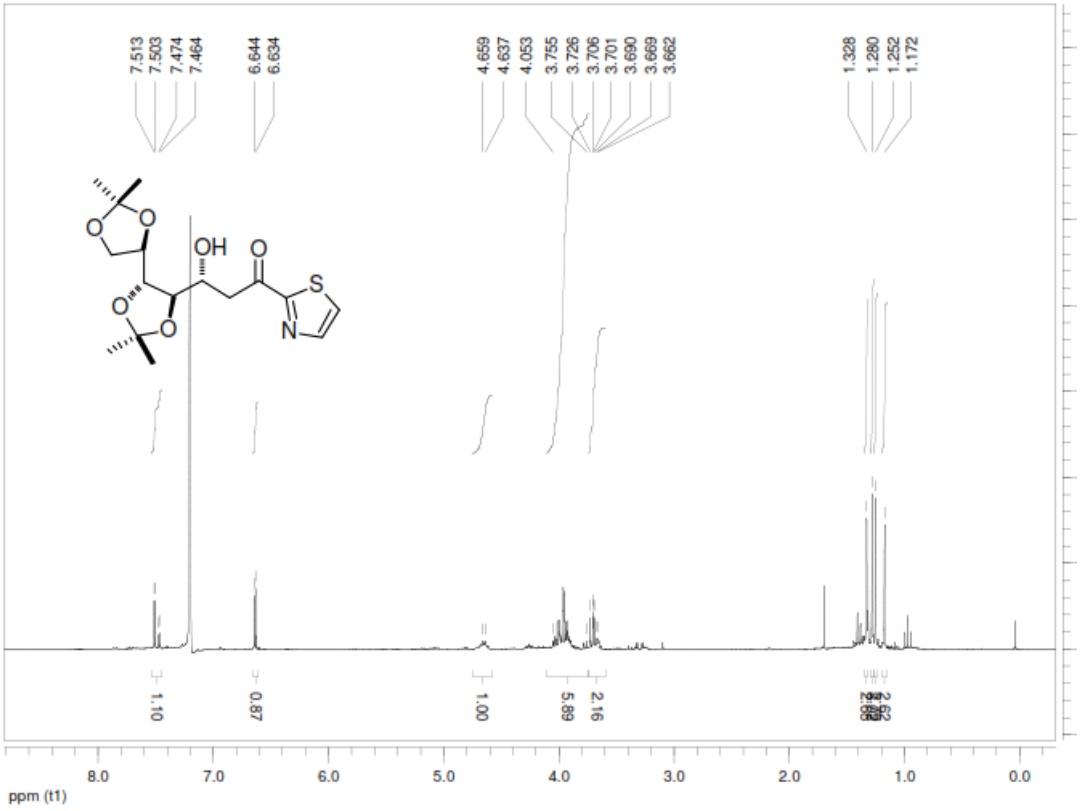


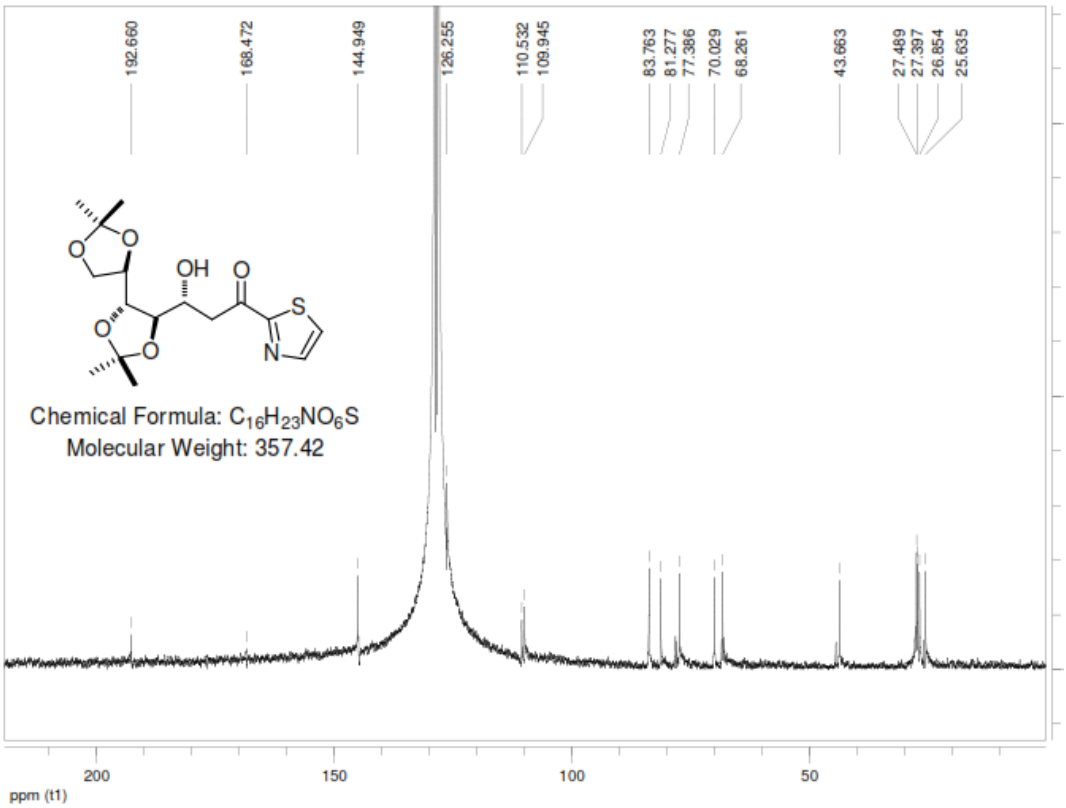


aldol **9**: reaction mixture in C_6D_6

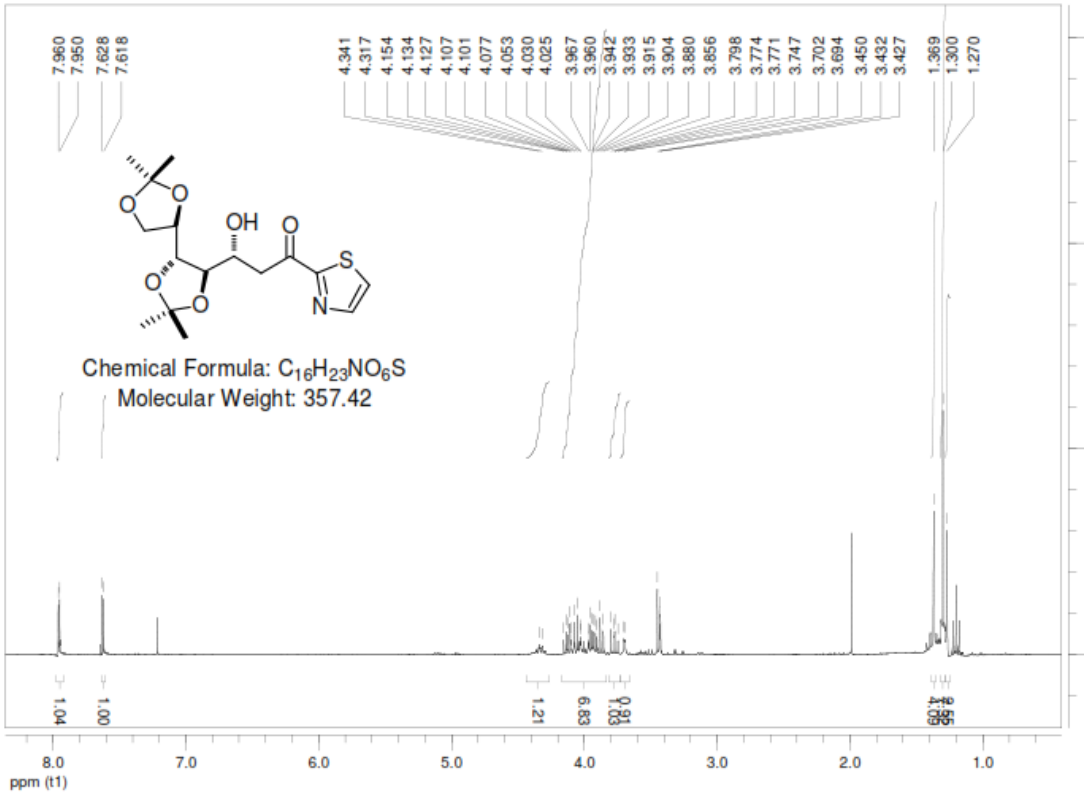


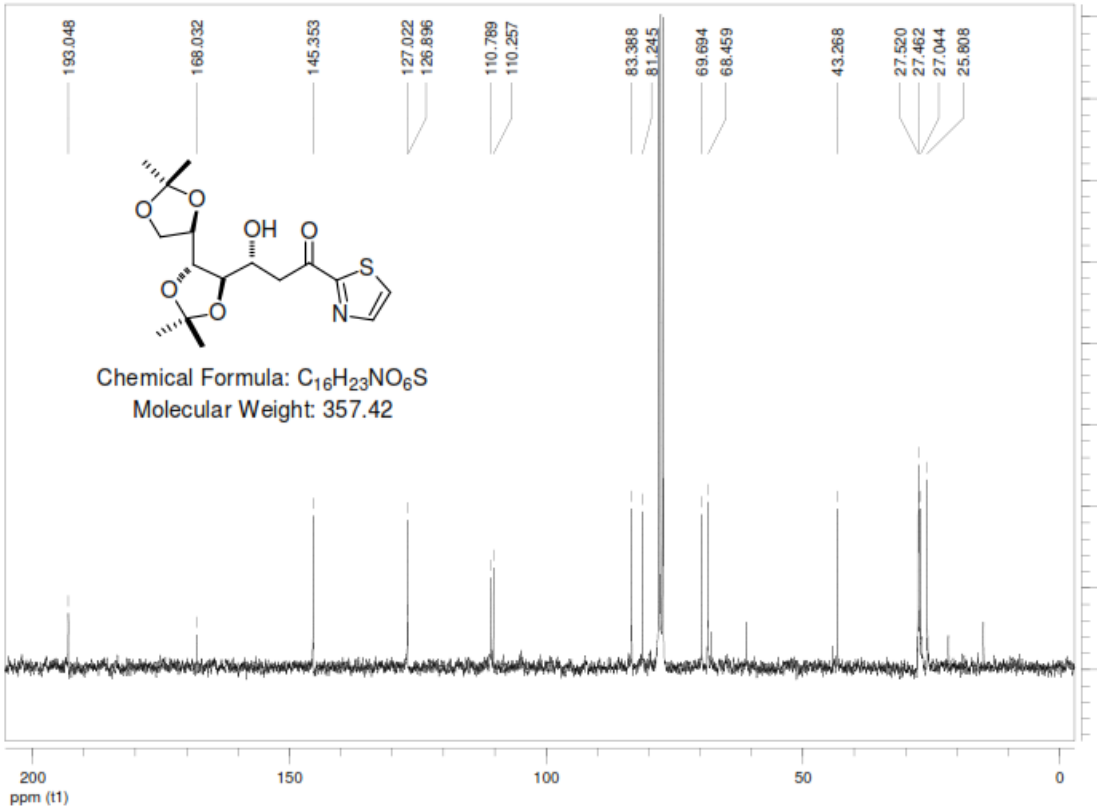
aldol **9**: Scheme 4 (*syn*/*anti*, 1:4, in C_6D_6)



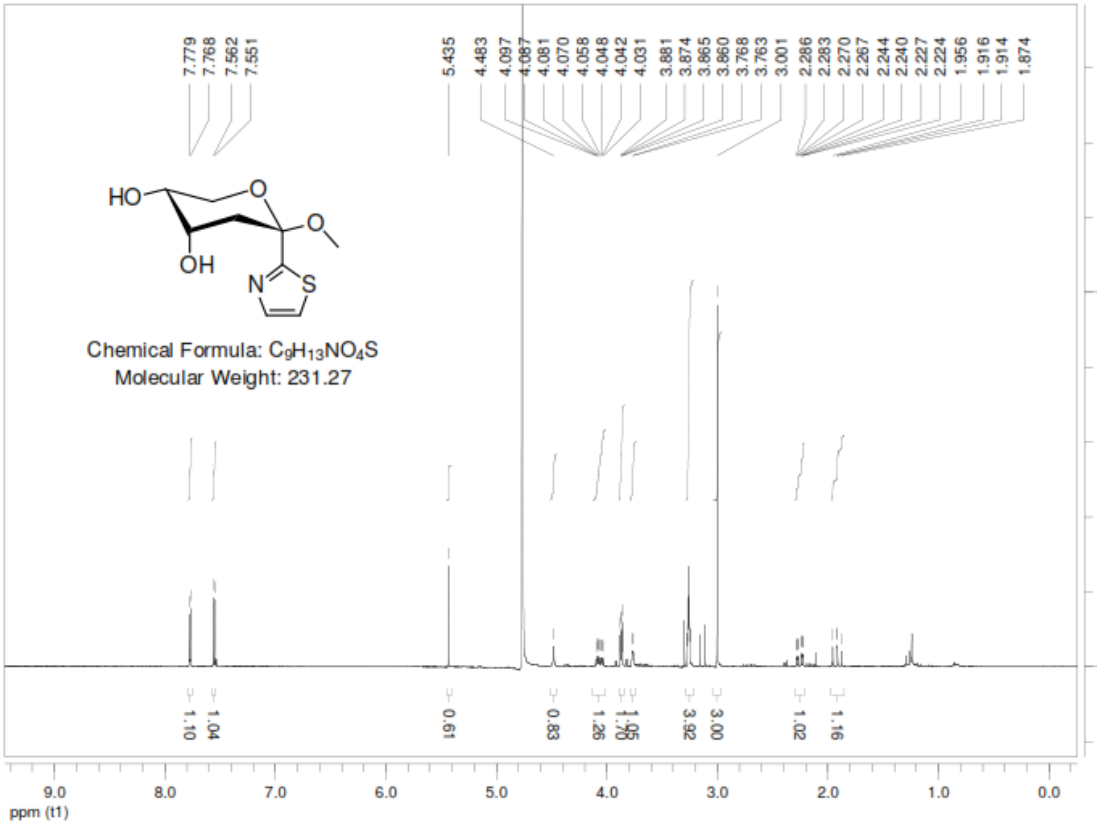


aldol **9**: Scheme 4 (*syn*/*anti*, 1:4, in $CDCl_3$)

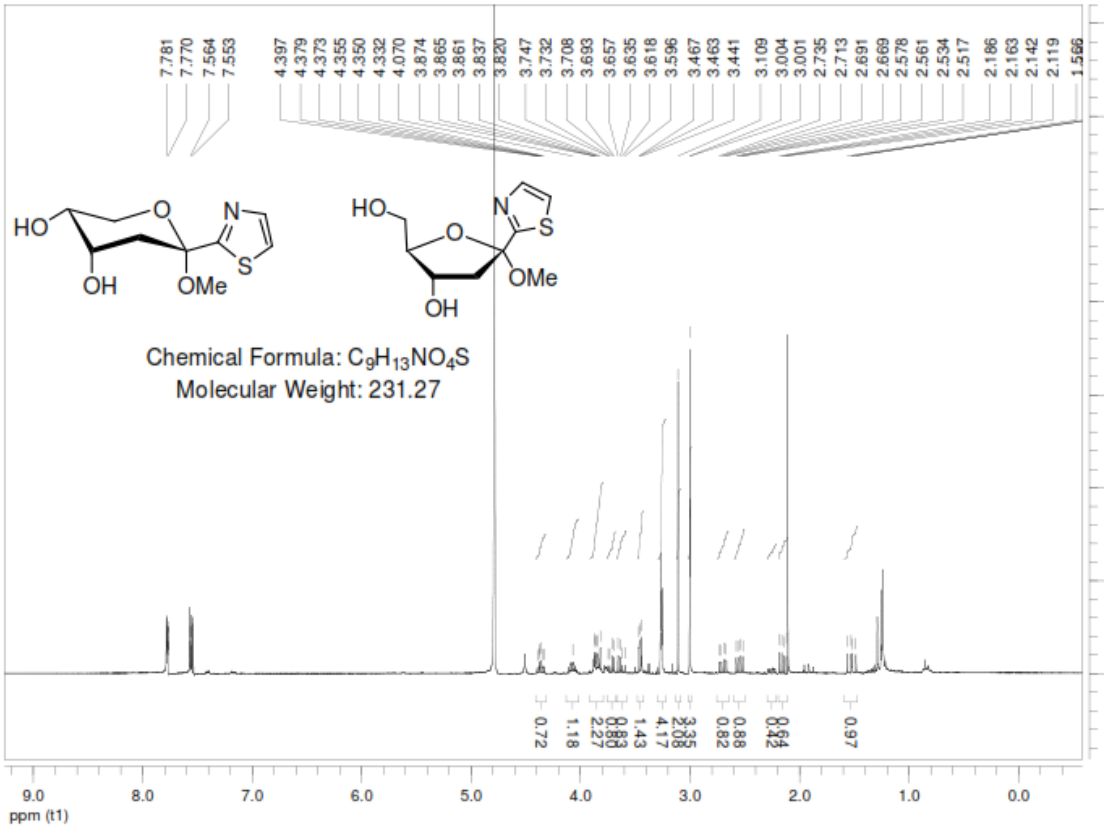




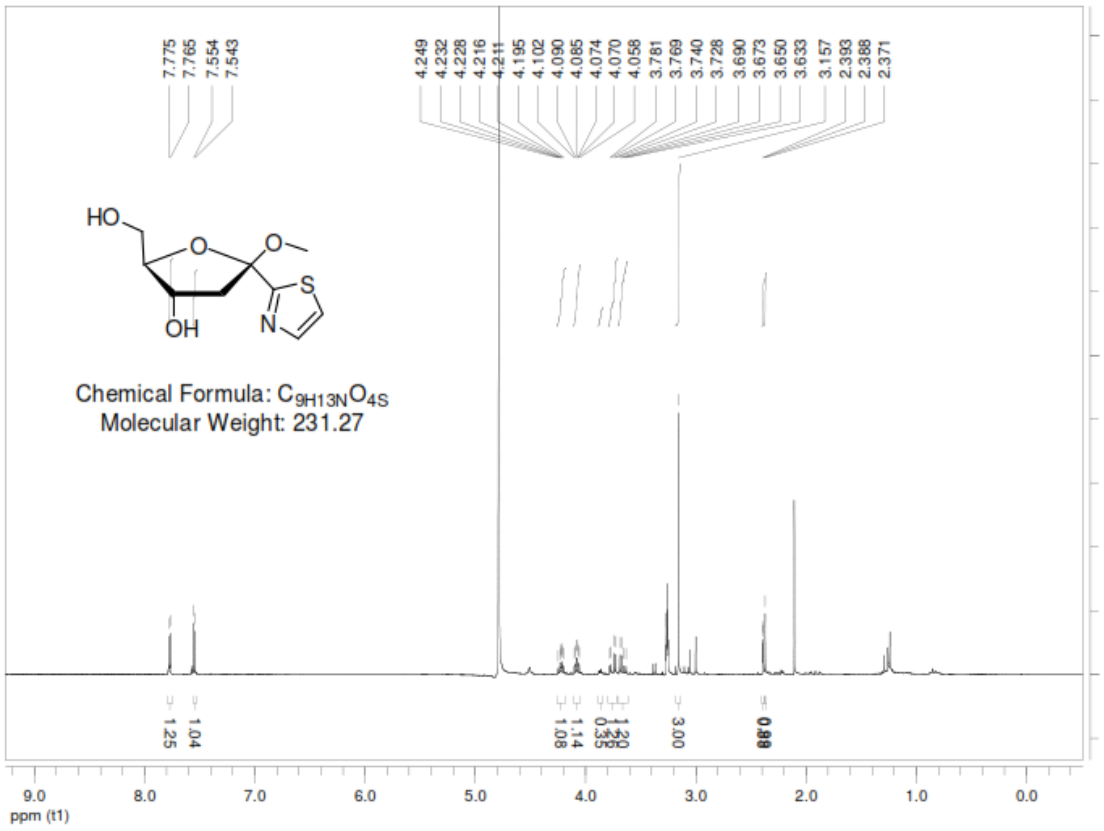
Deprotection of **7**, **KDG** precursor, S-8 (α-pyranose)



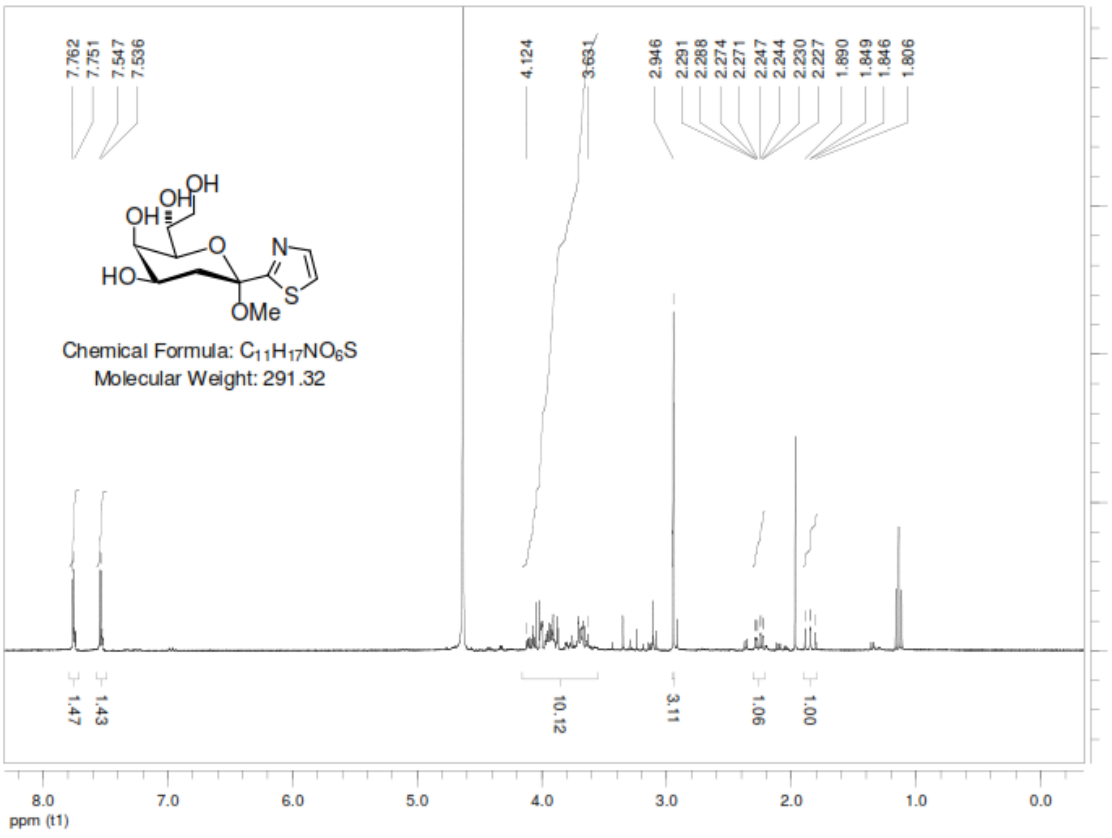
Deprotection of **7**, **KDG** precursor, S-8 (unseparated β-pyranose , β-furanose)



Deprotection of **7**, **KDG** precursor, S-8 (α-furanose)



Deprotection of **9**, **KDO** precursor, page S-9



6.2. Biomimetic Direct Aldol Reaction of Pyruvate Esters with Chiral Aldehydes.

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DOI: 10.1002/adsc.201200914

Biomimetic Direct Aldol Reaction of Pyruvate Esters with Chiral Aldehydes

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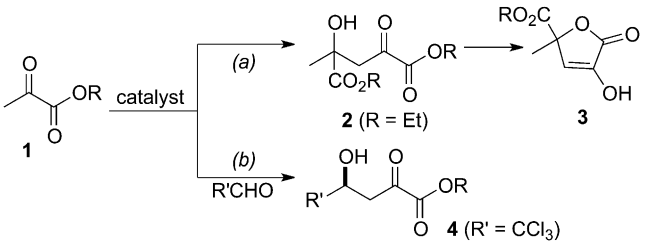
Abstract: Direct aldol reactions of pyruvate esters with sugar aldehydes is efficiently promoted by dinuclear metal complexes or chiral *Cinchona* alkaloid organocatalysts. Application of sterically hindered aryl esters enables the to-date problematic aldol reaction of pyruvate donors with *syn*- or *anti*-selectivity *en route* to the short and efficient synthesis of 3-deoxy-2-ulosonic acids.

Keywords: aldol reaction; asymmetric synthesis; carbohydrates; organocatalysis; pyruvates

The aldol reaction, in addition to being an effective method for the formation of carbon-carbon bonds, is also an outstanding example of the inspiration transferred from a biochemical processes to chemical synthesis. While initially the aldol reaction was used for the synthesis of relatively simple organic compounds,[1] now it constitutes an intensively explored tool for the synthesis of complex natural products including monosaccharides.[2] An important way to improve the efficiency of chemical methods for the aldol reaction is the development of a catalytic system where both donor and acceptor substrates are activated simultaneously to perform the direct aldol reaction with high efficiency and stereoselectivity similar to aldolase enzymes.[3]

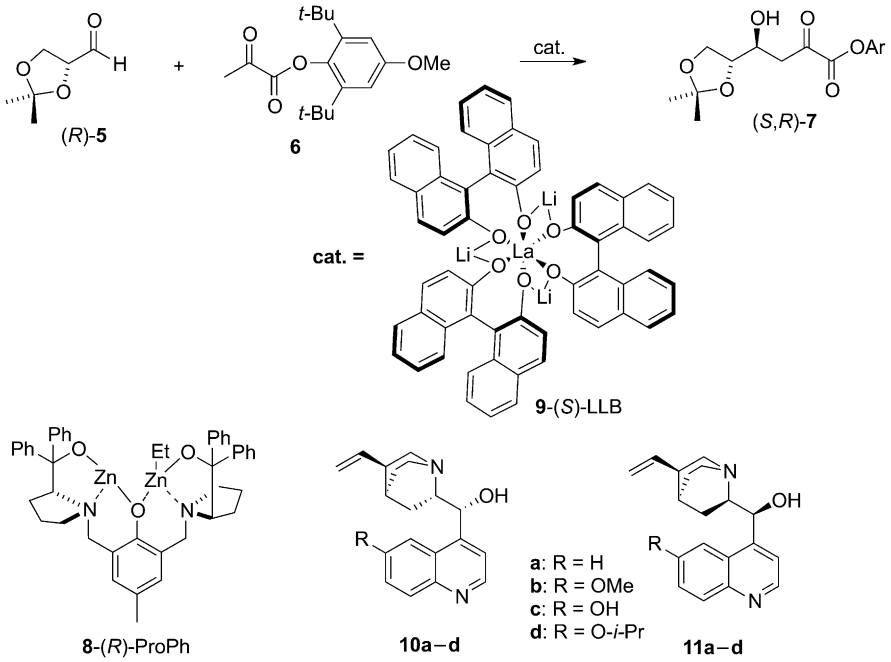
While such a methodology is known for many other asymmetric aldol syntheses, the direct activation of pyruvate esters **1** still remains an elusive goal if not simply a white spot on the aldol reaction map. The state-of-the-art of known methodologies is narrow and strictly limited to the self-condensation of pyruvate donors with pyruvate-type acceptors (Scheme 1, path a) or the cross aldol reaction of active and non-enolizable aldehydes (Scheme 1, path b).



Scheme 1. Homo (a) and cross (b) aldol reactions of pyruvate esters.

Trying to solve the problem, Jørgensen developed a chiral copper-based catalyst for asymmetric homoaldol reaction of ethyl pyruvate leading to diethyl 2-hydroxy-2-methyl-4-oxoglutarate (**2**). This, in turn, was isolated as the more stable isotetronic acid (**3**).[4] A direct catalytic homoaldol reaction of ethyl pyruvate leading to **3** was also performed by Dondoni under pyrrolidine-based organocatalytic control.[5] On the other hand, an organocatalytic cross aldol reaction of pyruvate ester was demonstrated only for highly active chloral hydrate.[6] In spite of many trials, a direct activation of pyruvate donors towards reaction with aliphatic aldehydes was long thought to be confined to the realm of enzymes.[7] Solving this problem is not only important from the conceptual point of view, but also because pyruvate- and phosphoenol pyruvate-dependent aldol reactions are vital in the formation of 3-deoxy-2-ulosonic acids and sialic acids, which are essential sugar units for many biological processes and transformations.[8] As a C_3 building block phosphoenol pyruvate participates also in the biosynthesis of the aromatic core of aryl amino acids in the shikimate pathway.

Now, we postulate that the stability of simple aliphatic pyruvate ester is sufficient for the reaction with fast-reactive electrophiles, while addition to other aldehydes needs the more stable enol form and a disciplined reaction course. In this article we show that the better stability of the pyruvate ester enol



Scheme 2. Direct aldol reaction of the pyruvic ester **6** with glyceraldehyde.

form may result from the bulky ester group attached to the keto ester which allows one to perform the elusive reaction with aliphatic aldehydes eventually following the biomimetic synthesis of ulosonic acids.

Previously Enders[9] and our group[10] had shown that pyruvic derivatives such as those with dimethyl acetal or thiazole ring moieties can be used as chemical equivalents of pyruvic esters in the catalytic reaction with chiral glyceraldehyde. Unfortunately, despite the enormous effort which we put in the activation of pyruvate methyl and ethyl esters by using a broad range of metal catalysts and organic molecules, we could not observe their reactions with aliphatic aldehydes.

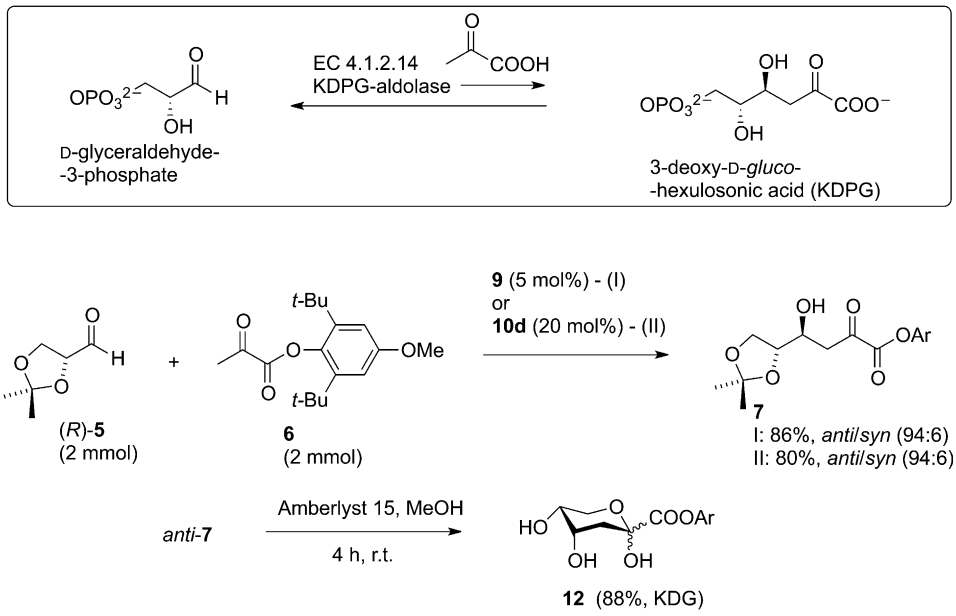
Now, we began our thorough study by considering the catalytic aldol reaction of various pyruvate esters with (*R*)-glyceraldehyde (**5**) promoted by the asymmetric dinuclear zinc catalyst with the ProPh ligand (**8**)[11] and the lanthanium-lithium-BINOL complex (**9**)[12] (Scheme 2). To test our presumption that sterically hindered esters might support enol formation, we tested *tert*-butyl, phenyl, and 4-methoxyphenyl esters. Our initial attempts were, however, unsuccessful and did not result in the formation of desired aldols.

Therefore, we investigated enolization of the more bulky 2,6-di-*tert*-butyl-4-methoxyphenyl ester (**6**) by using (*S*)- and (*R*)-ProPh catalysts (Table 1).[13] To our delight the reaction of ester **6** with (*R*)-glyceraldehyde acetonide promoted by (*R*)-ProPh catalysts resulted in the clean and efficient formation of desired cross aldol product **7** with a very good level of *syn*/*anti* diastereoselectivity favouring *anti* isomer (Table 1, entry 2). The stereoselectivity of the reaction was further improved by using the La-Li-(*S*)-BINOL catalyst and performing the reaction at −20 °C (Table 1, entry 4). The *anti*-configured aldol ester was formed predominantly with high yield (81%) and an excellent *anti/syn* ratio of 16:1. The here elaborated efficient reaction conditions need only a (1:1) ratio of the two substrates. Application of either (*R*)-configured catalyst (entry 3) and (*S*)-glyceraldehyde with (*S*)-config-

Table 1. Direct aldol reaction of the pyruvic ester **6** with glyceraldehyde.[a]

Entry	Catalyst	Solvent	Yield[c] [%]	*anti/syn*[d]
1	(*S*)-**8** (5 mol%)	THF	62	3/1
2	(*R*)-**8** (5 mol%)	THF	62	8/1
3	(*R*)-**9** (5 mol%)	THF	81[b]	4/1
4	**(*S*)-9 (5 mol%)**	**THF**	**81[b]**	**16/1**
5	(*S*)-**9** (5 mol%)	THF	81[b]	2/1[e]
6	**10a** (20 mol%)	$CHCl_3$	31	5/1
7	**11a** (20 mol%)	$CHCl_3$	31	2/1
8	**10b** (20 mol%)	$CHCl_3$	75	7/1
9	**11b** (20 mol%)	$CHCl_3$	61	1/1
10	**10c** (20 mol%)	$CHCl_3$	51	1.5/1
11	**11c** (20 mol%)	$CHCl_3$	62	6/1
12	**10d (20 mol%)**	**$CHCl_3$**	**80**	**16/1**
13	**11d** (20 mol%)	$CHCl_3$	59	1/1.5

[a] Reactions were performed with **5** (0.1 mmol), **6** (0.1 mmol), catalyst (see Table) in THF (12 h) or $CHCl_3$ (48 h) at room temperature.
[b] Reaction was performed at −20 °C.
[c] Yield of isolated product.
[d] Determined by ^{1}H NMR analysis.
[e] The (*S*)-aldehyde was used.



Scheme 3. Efficient diastereoselective synthesis of KDG ester.

ured catalyst (entry 5) resulted in the loss of stereoselectivity as a consequence of the formation of mismatched substrate-catalyst pairs.

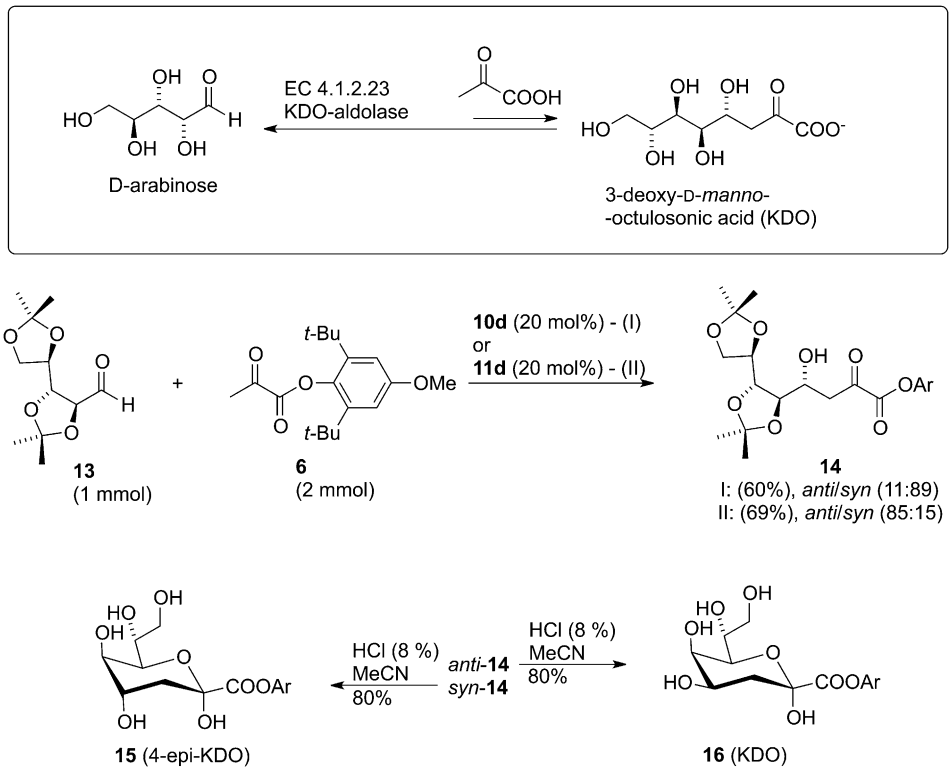
Our results suggest that the remarkable stability of the pyruvate enol esters was attributed to the steric hindrance present in the aryl moiety. This particular feature of the 2,6-di-*tert*-butyl-4-methoxyphenyl derivative was previously observed during the Grignard addition to 1,2-esters.[14]

To explore further this concept of stable hindered enol formation, we tested also the possibility of a parallel organocatalytic protocol for pyruvate ester deprotonation. This was an exciting challenge in the light of unknown protocol for such a substrate activation. After many trials including various organocatalyst structures and modes of activation, we selected tertiary amines of *Cinchona* alkaloids as the most promising candidates for further research.[15] The tertiary amine-based catalysts could act through formation of a tight ion pair followed by aldehyde addition giving an additional evidence for the easy deprotonation and stable enol formation from **6**.

The results collected in Table 1, entries 6–13 highly support our concept. Initial application of cinchonidine (**10a**, **CD**) and cinchonine (**11a**, **CN**) to the elaborated reaction showed promising results while yield and stereoselectivity remained poor (Table 1, entries 6 and 7). The most efficient means turned out to be variation of the *Cinchona* alkaloid scaffold at the C-6′ position of the quinoline core of quinine (**10b**, **QN**) and quinidine (**11b**, **QD**). Further alkylation of the quinine by the bulky isopropyl group delivered an efficient and selective catalyst. To our delight the aldol reaction from Scheme 2 promoted by 20 mol% of **10d** afforded high *anti*-diastereoselectivity (16:1) and high yield (80%) of aldol **7**. It is interesting to mention that application of a quinidine-based catalyst favoured formation of the oposite *syn*-configured aldol albeit with lower diastereoselectivity (entry 13).

This newly elaborated methodology could easily be applied for the synthesis of sugar 3-deoxy-2-keto acids (ulosonic acids), and to prove this concept we scaled up the synthesis and compared results obtained by using both enolization ways (Scheme 3). In recent years, several chemical and enzymatic methodologies have been reported for the synthesis of sialic and ulosonic acids[16] but our attempt seems to be the simplest and more closely related to enzymatic pathway. The *anti*-configured aldol product **7** possesses the configuration of natural 3-deoxy-D-*gluco*-hexulosonic acid (KDG, Scheme 3) and can be easily transformed into this biomolecule. By using the biomimetic concept and following the KDPG-aldolase function the synthesis of **7** can be performed by using metal catalyst (**9**) or organocatalyst (**10d**) in high yield and high stereoselectivity. Thus, the obtained *anti*-aldol **7** was easily deprotected with an acidic ion-exchange resin (Amberlyst 15) in methanol to give the cyclic forms of the desired KDG ester **12** (Scheme 3).[17]

Next, we tested the flexibility of our methodology for the synthesis of a higher, eight-carbon ulosonic acid – KDO ester, starting from arabinose diacetonide **13** and the same pyruvate ester **6** (Scheme 4). Because of the different structure of the chiral aldehyde, application of the metal-based catalyst resulted in a less selective formation of the desired aldol **14**. The most promising catalyst was (*R*)-ProPh yet the unexpected formation of *syn*-configured aldol (*anti/syn*, 1:6, 70%



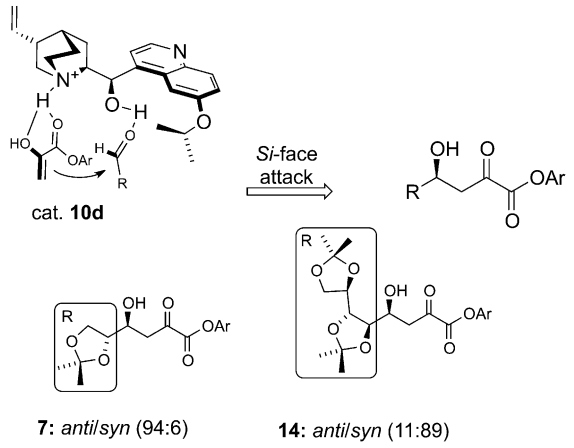
Scheme 4. Synthesis of KDO and 4-epi-KDO esters.

yield) closed this entry to natural 3-deoxy-D-*manno*-octulosonic acid (KDO).

However, the biomimetic synthesis of the desired *anti*-configured aldol **14** was successfully performed by using organocatalyst **11d** (*anti/syn*, 85:15, 69% yield). Interestingly, a parallel synthesis of the *syn*-configured aldol by using organocatalyst **10d** proved to have additional practical advantages of the newly described methodology (*anti/syn*, 11:89, 60% yield). It is also a highly important observation as previously published methodologies based on addition of lithium enolates to chiral aldehydes led to *anti*-configured products only.[18] Now, from both *syn*- and *anti*-configured key intermediates, the syntheses of KDO ester **16** and pharmaceutically important 4-epi-KDO ester **15** were flexibly accomplished by simple deprotection of isopropylidene residues (Scheme 4).

The diastereomeric excesses of the aldols **7** and **14** were determined by high resolution NMR of the reaction mixtures. For both aldol products separation of the diastereomers was easily possible by simple flash chromatography making the elaborated methodology useful for a practical synthesis of natural keto acids and their isomers.

Although the number of possible conformations of *Cinchona* alkaloids in the solution makes it difficult to analyse,[19] the transition state structure of the substrate-catalyst complex can be rationalised by using the model depicted at Scheme 5. While the reaction



Scheme 5. Proposed approximate structure of the substrate-catalyst **10d** complex for the *S*-selective formation of aldols.

of pyruvate ester involves initial deprotonation by the *Cinchona* catalyst **10d** (**CD**, **QN** native configuration) and subsequent attack to the aldehyde, the role of catalyst is also to provide an asymmetric environment to the reaction center through a network of hydrogen bonds. The large substituent in the aldehyde molecule is placed away from the bulky catalyst substituent. The *Re* face of the aldehyde is covered so effectively by the quinolone ring that the pyruvate enol approaches the *Si* face to produce the *S*-configured alcohol **7** or **14**. By using catalyst **11d** (**CN**, **QD** native

configuration) the diastereoisomeric (*R*)-alcohols are formed predominantly.

In conclusion, we showed that both metal-based complexes and chiral tertiary amines can initiate stable enol formation from hindered pyruvate esters which can be further trapped by electrophilic aldehydes. This is the first example of an efficient *catalytic stereoselective* aldol reaction of pyruvate esters with aliphatic aldehydes closely resembling the biomimetic synthesis of ulosonic acids. The elaborated methodology allowed the first catalytic synthesis of 3-deoxy-2-keto esters through a direct aldol reaction of sugar aldehydes with pyruvate esters. The presented protocol provides an attractive and biomimetic approach to ulosonic acids and constitutes another interesting field of application for the powerful Trost and Shibasaki catalysts.

Moreover, we have presented new concept of direct aldol reaction of keto esters promoted by chiral tertiary amines. The described methodology delivers a flexible entry to both *syn*- and *anti*-configured aldols while *syn*-selectivity was not achievable previously by using stoichiometrically generated lithium enolates. Although obtaining better diastereoselectivity in the aldol reaction of hindered keto esters is troublesome and constitutes a general problem,[20] our further efforts will be direct to designing even more efficient and stereoselective catalysts for the elaborated direct aldol reaction of pyruvate esters.

Experimental Section

Direct Aldol Reaction of Aryl Pyruvate with Glyceraldehyde

(1) Using catalyst 9: A solution of water in THF (0.01 mmol, 10 μL, 1 M) was added to a solution of potassium bis(trimethylsilyl)amide (KHMDS) in toluene (0.0045 mmol, 9 μL, 0.5 M) at 0 °C. After stirring for 15 min a solution of LLB in THF (0.005 mmol, 0.1 mL, 0.05 M) was added and the stirring was continued at 0 °C for 30 min. The catalyst solution was cooled to −20 °C and a mixture of aldehyde **5** (13 mg, 0.1 mmol) and aryl pyruvate **6** (31 mg, 0.1 mmol) in 0.5 mL THF was added to the solution. The reaction mixture was stirred for 12 h at −20 °C, then quenched with ammonium chloride, extracted with ethyl acetate, dried with magnesium sulfate and purified on silica gel using 0–2% methanolic dichloromethane as eluent to give aldol adduct **7**; yield: 35.5 mg (81%).

(2) Using Cinchona catalyst 10d: A mixture of aldehyde **5** (260 mg, 2 mmole), aryl pyruvate **6** (613 mg, 2 mmol) and catalyst **10d**[21] (141 mg, 0.4 mmol) in 10 mL of chloroform was stirred for 48 h at room temperature. The reaction mixture was purified on silica gel using 0–2% methanolic dichloromethane as eluent to give aldol adduct **7**; yield: 698 mg (80%).

Acknowledgements

This project was operated within the Foundation for Polish Science TEAM and MPD Programmes co-financed by the EU European Regional Development Fund. The research was carried out with the equipment purchased thanks to the financial support of the European Regional Development Fund in the framework of the Polish Innovation Economy Operational Program (contract no. POIG.02.01.00-12-023/08).

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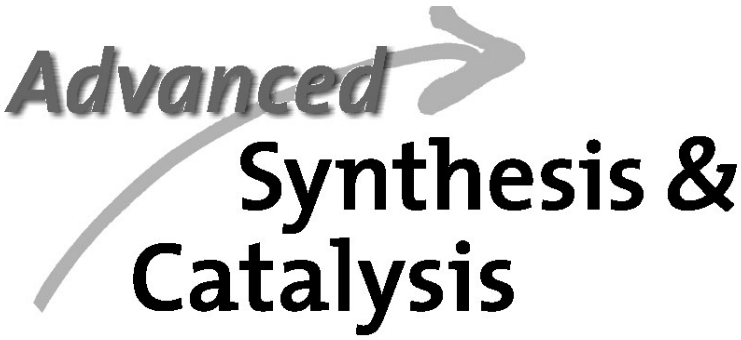

Supporting Information

Biomimetic Direct Aldol Reaction of Pyruvate Esters with Chiral Aldehydes

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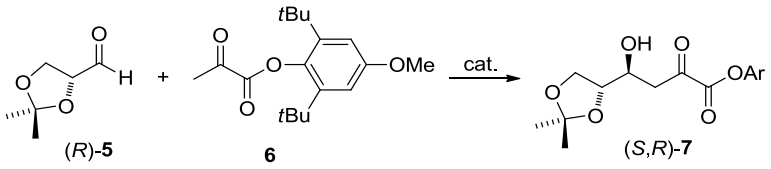
Direct Aldol Reaction of Aryl Pyruvate with Glyceraldehyde
(Scheme 2)



by using Trost's Catalyst

catalyst: B. M. Trost, H. Ito, *J. Am. Chem. Soc*. **2000**, *122*, 12003-12004

(Table 1, entry 1-2)

A solution of diethylzinc (1M in hexane, 11 µL, 0.011 mmol) was added to a solution of Trost's ligand (3.55 mg, 0.0055 mmol) in THF (0.1 mL) at room temperature under argon atmosphere. The reaction mixture was stirred for 30 min with evolution of ethane gas to give 0.005 mmol of the catalyst. The prepared catalyst was added to a suspension of freshly distilled aldehyde **5** (13 mg, 0.1 mmol), aryl pyruvate **6** (31 mg, 0.1 mmol), triphenylphosphine sulfide (2.2 mg, 0.0075 mol) and dry powdered molecular sieves 4A (20 mg) in 0.5 mL of THF at -20 ºC. The temperature was raised to room temperature and the stirring was continued for 12 h. The reaction mixture was quenched by ammonium chloride, extracted with ethyl acetate, dried with magnesium sulphate and purified on silica gel using 0-2% methanolic dichloromethane as eluent to give aldol adduct **7** (27 mg, 62%).

^{1}H-NMR (600 MHz, $CDCl_3$); 1.30 (s, 9H), 1.31 (s, 9H), 1.35 (s, 3H), 1.42 (s, 3H), 2.69 (s,1H), 3.12 (dd, 1H, *J*=8.9, 18.3 Hz), 3.30 (dd, 1H, *J*=2.9, 18.3 Hz), 3.80 (s, 3H), 3.97 (dd, 1H, *J*=5.3, 8.3 Hz), 4.04 (dd, 1H, *J*=6.5, 11.9 Hz), 4.11 (dd, 1H, *J*=6.3, 8.3 Hz), 4.18 (m, 1H), 6.88 (s, 2H).

^{13}C-NMR (150 MHz, $CDCl_3$); 25.1, 26.7, 31.4, 31.5, 35.7, 43.1, 55.3, 66.5, 68.5, 77.5, 109.7, 111.9, 140.9, 143.2, 156.9, 161.7, 193.3.

MS *m/z* (ESI): 437.7 (M^++H).

IR (neat) 3441, 2961, 2931, 2873, 1739 and 1590 cm^{-1}.

$[\alpha]_D$ = -3.6 (*c* 1.0, $CHCl_3$).

For similar aldols see, Dondoni, P. Merino, *J. Org. Chem*. **1991**, *56*, 5294-5301; El-Sepelgy, O., Schwarzer, D., Oskwarek, P. and Mlynarski, J. *Eur. J. Org. Chem.*, 2012, 2724–2727.

by using Shibasaki's catalyst

catalyst: N.Yoshikawa, N. Kumagai, S. Matsunaga, G. Moll, T. Ohshima T. Suzuki, M. Shibasaki, *J. Am. Chem. Soc.* **2001**, *123*, 2466-2467

(Table 1 entry 3-5)

To a solution of potassium bis(trimethylsilyl)amide (KHMDS) in toluene (0.0045 mmol, 9 µL, 0.5 M) at 0 ^{o}C, water in THF (0.01 mmol, 10 µL, 1M) was added. After stirring for 15 min a solution of (LLB) in THF (0.005 mmol, 0.1 mL, 0.05M) was added and the stirring was continued at 0 ^{o}C for 30 min. The catalyst was cooled to -20 ^{o}C and a mixture of aldehyde **5** (13 mg, 0.1 mmol) and Aryl pyruvate **6** (31

mg, 0.1 mmol) in 0.5 mL THF as successfully added to the solution. The reaction mixture was stirred for 12 h at -20 ^{o}C quenched by ammonium chloride, extracted with ethyl acetate, dried with magnesium sulphate and purified on silica gel using 0-2% methanolic dichloromethane as eluent to give aldol adduct **7** (35.5 mg, 81%).

by using Cinchona alkaloids

(Table 1 entry 6-13)

A mixture of aldehyde **5** (13 mg, 0.1 mmol), Aryl pyruvate **6** (31 mg, 0.1 mmol) and cinchona-alkaloid (0.02 mmol) in 0.5 mL chloroform was stirred for 48 h. The reaction mixture was purified on silica gel using 0-2% methanolic dichloromethane as eluent to give aldol adduct **7**.

Synthesis in 2 mmol scale

(Scheme 3)

under organometallic control

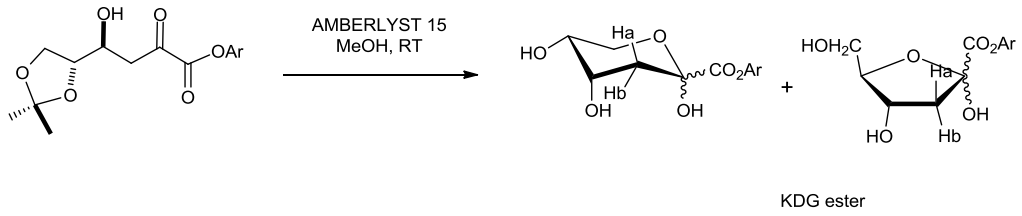
To a solution of potassium bis(trimethylsilyl)amide (KHMDS) in toluene (0.09 mmol, 180 μL, 0.5 M) at 0 ^{o}C, was added water in THF (0.2 mmol, 200 μL, 1M). After stirring for 15 min a solution of ((*S*)-LLB) in THF (0.1 mmol, 1 mL, 0.1M) was added and the stirring was continued at 0 ^{o}C for 30 min. The catalyst solution was cooled down to -20 ^{o}C and the solution of glyceraldehyde **5** (260 mg, 2 mmol) and aryl pyruvate **6** (613 mg, 2 mmol) in 7 mL of THF was successfully added to the previous mixture. The reaction mixture was stirred for 12 h at the same temperature then quenched by ammonium chloride, extracted with ethyl acetate, dried with magnesium sulphate and purified on silica gel using 0-2% methanolic dichloromethane as eluent to give aldol adduct **7** (707 mg, 81 %).

using cinchona-alkaloid 10d

A mixture of aldehyde **5** (260 mg, 2 mmol), Aryl pyruvate **6** (613 mg, 2 mmol) and cinchona-alkaloid **10d** (141 mg, 0.4 mmol) in 10 mL of chloroform was stirred for 48h. The reaction mixture was purified on silica gel using 0-2% methanolic dichloromethane as eluent to give aldol adduct **7** (698 mg, 80 %).

Synthesis of KDG Ester 12

(Scheme 3)



To a stirred solution of aldol *anti*-**7** (437 mg, 1 mmol) in 8 mL of dry methanol Amberlyst 15 (1 g) was added. After stirring for 4 h the ion exchange resin was removed by filtration and the solvent was evaporated under vaccum. The product was purified on silica gel using a mixture of hexane:ethyl acetate (1:2) to give KDG ester **12** as a mixture of pyranose and furanose forms (349 mg, 88 %).

MS *m/z* (ESI): 397.4 (M^++H).

IR (neat) 3403, 2957, 2924, 2873, 1754 and 1590 cm^{-1}.

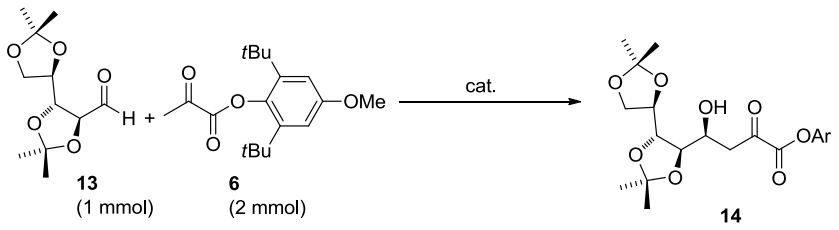
The assignment of the C-3 protons for the different stereoisomers are:

	δ_{3a}	δ_{3b}	$J_{3a,3b}$	$J_{3a,4}$	$J_{3b,4}$	%
β-pyranose	2.09	2.51	12.5	4.8	12.5	31
α-pyranose	2.32	2.27	14.4	3.1	4.4	15
β-furanose	2.72	2.45	12.7	8.8	7.1	22
α-furanose	2.93	2.17	13.7	7.2	3.9	32

The NMR of both pyranose and furanose forms are similar to those published for the corresponding methyl ester, see and R. Plantier-Royon, F. Cardona, D. Anker, *J. Carbohydr. Chem.* **1991**, *10*, 787-811.

Synthesis of *syn*-Aldol 14

(Scheme 4)



under organometallic control

Under an argon atmosphere, a solution of diethylzinc (1M in hexane, 0.22 mL, 0.22 mmol) was added to a solution of Trost's prophenol (R) (71 mg, 0.11 mmol) in THF (1 mL) at room temperature. The mixture was stirring for 30 min with evolution of ethane gas to get 0.1 mmol of the catalyst. Triphenylphosphine sulfide (88 mg, 0.3 mol) and dry powdered molecular sieves 4A (400 mg) were added. The catalyst solution was cooled to -20^{o}C. A solution of aryl pyruvate **6** (613 mg, 2 mmol) and arbinose **13** (460 mg, 2 mmol) in 7 mL THF was added. Then the temperature was raised to room temperature and stirring was continued for 16 h. The reaction mixture was quenched by ammonium chloride, extracted with ethyl acetate, dried with magnesium sulphate and purified on silica gel using 0-2% methanolic dichloromethane as eluent to give aldol adduct **14** (751 mg, 70 %).

using cinchona-alkaloid 10d

A mixture of arabinose **13** (230 mg, 1 mmol), aryl pyruvate **6** (613 mg, 2 mmol) and cinchona-alkaloid **10d** (70.5 mg, 0.2 mmol) in 5 mL of chloroform was stirred for 48h. The reaction mixture was purified on silica gel using 0-2% methanolic dichloromethane as eluent to give aldol adduct **14** (322 mg, 60 %).

^{1}H-NMR (600 MHz, $CDCl_3$); 1.31 (s, 18H), 1.34 (s, 3H), 1.38 (s, 3H), 1.41 (s, 3H), 1.42 (s, 3H), 3.16 (dd, 1H, *J*=3.4, 17.2 Hz), 3.33 (dd, 1H, *J*=9.2, 17.2 Hz), 3.80 (s, 3H), 3.98 (dd, 1H, *J*=4.7, 8.7 Hz), 3.95 (t, 1H, *J*=7.5), 3.96 (dd, 1H, *J* =7.5, 9.3 Hz), 4.06 (m, 1H), 4.15 (dd, 1H, *J* =6.1, 8.6 Hz), 4.42 (td, 1H, *J* =3.3, 6.0 Hz), 6.87 (s, 2H).

^{13}C-NMR (150 MHz, $CDCl_3$); 25.3, 26.7, 26.9, 27.2, 31.5, 31.5, 35.7, 35.7, 43.9, 55.3, 66.5, 67.9, 82.5, 109.8, 110.0, 111.9, 141.0, 143.3, 143.3, 156.8, 161.8, 192.1.

MS *m/z* (ESI): 537.3 (M^{+}+H).

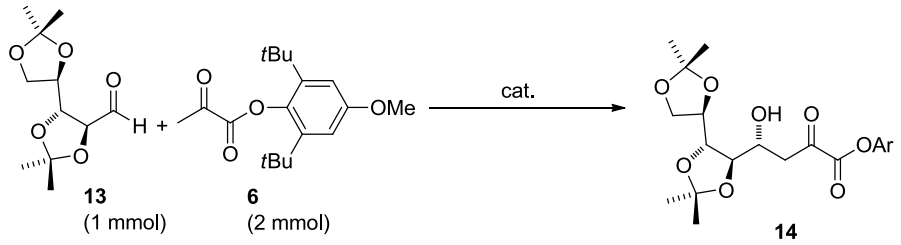
IR (neat) 3481, 2962, 2929, 2873, 1738 and 1590 cm^{-1}.

$[\alpha]_D$ = -2.8 (*c* 1.0, $CHCl_3$).

Synthesis of *anti*-Aldol 14

by using cinchona-alkaloid 11d

(Scheme 4)



A mixture of arabinose **13** (230 mg, 1 mmol), Aryl pyruvate **6** (613 mg, 2 mmol) and cinchona-alkaloid **11d** (70.5 mg, 0.2 mmol) in 5 mL of chloroform was stirred for 48h. The reaction mixture was purified on silica gel using 0-2% methanolic dichloromethane as eluent to give aldol adduct **14** (370 mg, 69 %).

^{1}H-NMR (600 MHz $CDCl_3$); 1.31 (s, 9H), 1.32 (s, 9H), 1.36 (s, 6H), 1.37 (s, 3H), 1.45 (s, 3H), 3.17 (dd, 1H, *J*=8.2, 17.5 Hz), 3.36 (dd, 1H, *J* =3.8, 17.5 Hz), 3.59 (s, 1H), 3.76 (dd, 1H, *J* =7.4, 8.6 Hz), 3.83 (t, 1H, *J* =7.4 Hz), 4.02 (dd, 1H, *J*=5.3, 8.7 Hz), 4.08 (m, 1H), 4.20 (dd, 1H, *J*=6.1, 8.7 Hz), 4.34 (m, 1H), 6.88 (s, 2H).

^{13}C-NMR (150 MHz, $CDCl_3$); 25.8, 27.1, 27.5, 30.3, 32.2, 36.3, 44.1, 55.9, 68.6, 69.0, 77.0, 81.6, 83.4, 110.3, 111.0, 112.5, 144.0, 157.4, 162.4, 192.5.

MS *m/z* (ESI): 537.3 (M^++H).

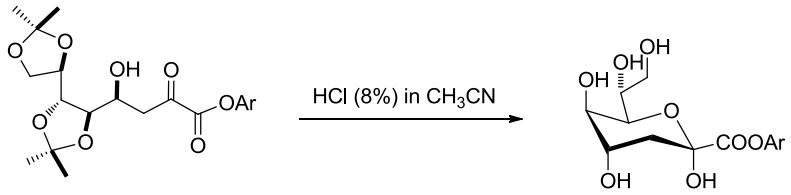
IR (neat) 3447, 2963, 2931, 2873, 1739 and 1590 cm^{-1}.

$[\alpha]_D$ = +10.2 (*c* 1.0, $CHCl_3$).

For similar aldols see, Dondoni, P. Merino, *J. Org. Chem*. **1991**, *56*, 5294-5301; El-Sepelgy, O., Schwarzer, D., Oskwarek, P. and Mlynarski, J. *Eur. J. Org. Chem.*, **2012**, 2724–2727.

Synthesis of 4-epi-KDO ester 15

(Scheme 4)



Aldol ***Syn*-14** (268 mg, 0.5 mmol) was treated with 8 % HCl in acetonitrile (20 mL). The mixture was stirred for 12h. The reaction mixture was neutralized by potassium carbonate and extracted with chloroform. The extracts was dried with magnesium sulphate and purified on silica gel using methanol: dichloromethane (1:10) as eluent to give 4-epi-KDO ester **15** (182 mg, 80 %).

^{1}H-NMR (600 MHz, CD_3OD); 1.33 (s, 18H), 1.93 (ddd, 1H, *J*= 0.8, 3.1, 14.2 Hz, H-3), 2.69 (dd, 1H, *J*=3.4, 14.2 Hz, H-3), 3.70 (dd, 1H, *J*=5.5, 11.6 Hz, H-8), 3.78 (s, 3H), 3.83 (dd, 1H, *J*=3.1, 11.6 Hz, H-8), 3.87 (m, 1H, H-5), 3.91 (ddd, 1H, *J*=3.1, 5.5, 8.6 Hz, H-7), 4.08 (dd, 1H, *J*=3.1, 3.3, 6.7 Hz, H-4), 4.24 (dd, 1H, *J*=1.5, 8.6 Hz, H-6), 6.86 (s, 2H).

^{13}C-NMR (150 MHz, CD_3OD); 34.3, 34.4, 35.3, 39.1, 39.2, 58.3, 67.2, 69.7, 71.5, 71.8, 73.7, 99.7, 115.1, 115.2, 146.0, 147.5, 147.6, 160.7, 173.8.

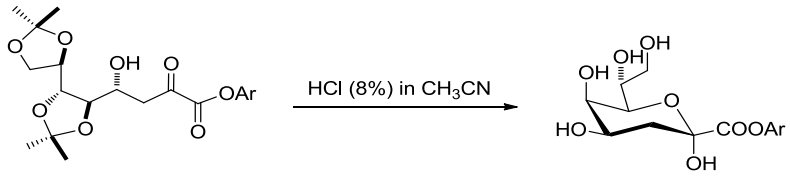
MS *m/z* (ESI): 479.2 (M^++Na).

IR (neat) 3354, 2964, 2926, 2870, 1745 and 1591 cm^{-1}.

$[\alpha]_D$ = +5.5 (*c* 1.0, CH_3OH).

Synthesis of KDO ester 16

(Scheme 4)



Aldol ***anti*-14** (268 mg, 0.5 mmol) was treated with 8 % HCl in acetonitrile (20 mL). The mixture was stirred for 12h. The reaction mixture was neutralized by potassium carbonate and extracted with chloroform. The extracts was dried with magnesium sulphate and purified on silica gel using methanol: dichloromethane (1:10) as eluent to give KDO ester **16** (182 mg, 80 %).

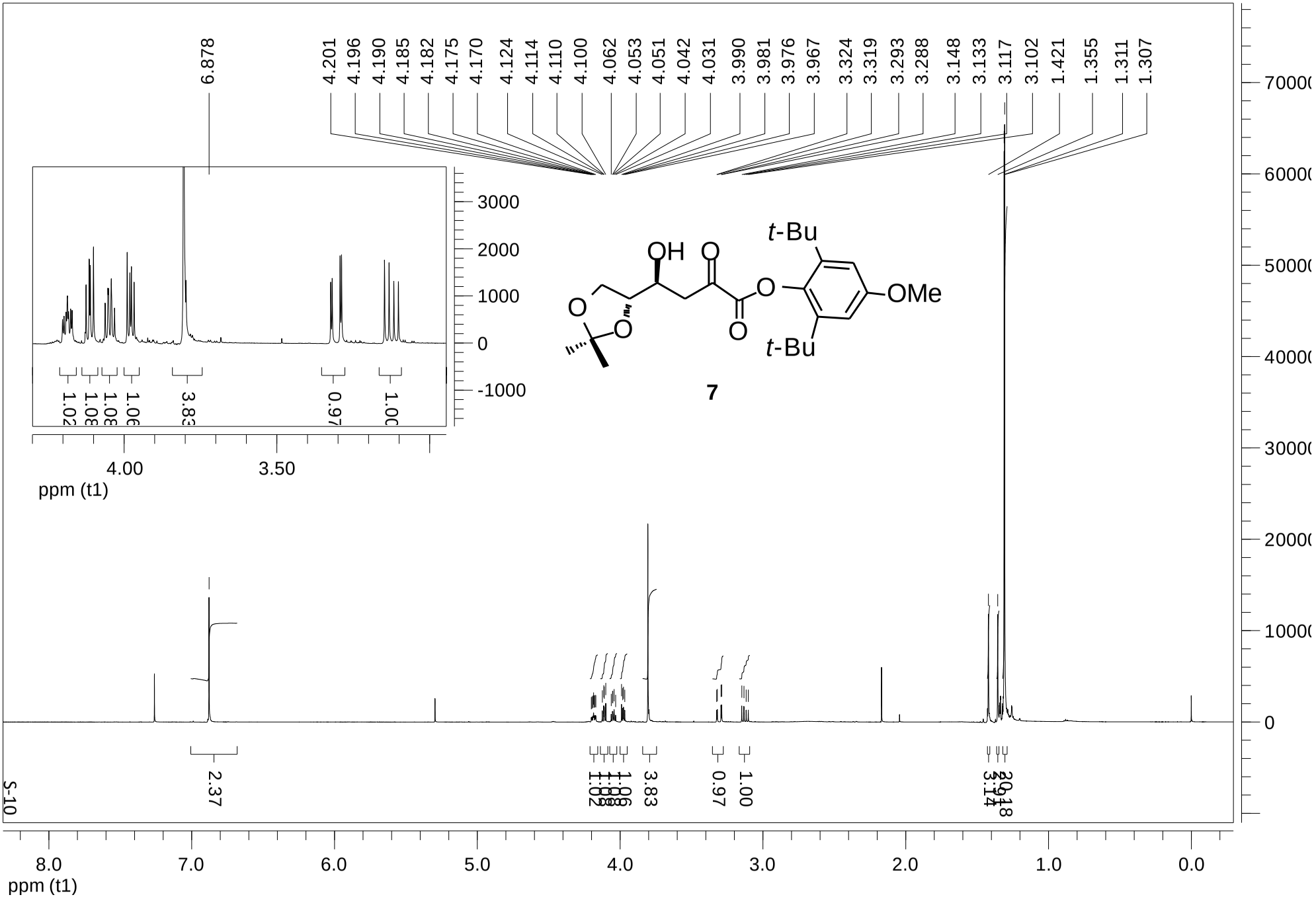
^{1}H-NMR (600 MHz CD_3OD); 1.33 (s, 9H), 1.34 (s, 9H), 1.93 (ddd, 1H, *J*=0.8, 4.8, 12.2 Hz, H-3), 2.53 (t, 1H, *J*=12.2 Hz, H-3), 3.70 (dd, 1H, *J*=4.6, 11.6 Hz, H-8), 3.78 (s, 3H), 3.79 (dd, 1H, *J*=2.8, 11.8 Hz, H-8), 3.91 (m, 1H, H-7), 3.93 (dd, 1H, *J*=1.1, 8.8 Hz, H-6), 4.03 (m, 1H, H-5), 4.08 (ddd, 1H, *J*=3.0, 4.7, 11.9 Hz, H-4), 6.96 (s, 2H).

^{13}C-NMR (150 MHz, CD_3OD); 31.8, 31.9, 35.0, 36.6, 36.7, 55.8, 64.6, 67.7, 67.8, 70.8, 73.0, 97.4, 112.5, 112.6, 143.5, 144.9, 145.1, 158.1, 171.7.

MS *m/z* (ESI): 479.3 (M^++Na).

IR (neat) 3354, 2964, 2926, 2870, 1745 and 1591 cm^{-1}.

$[\alpha]_D$ = +20.9 (*c* 1.0, CH_3OH).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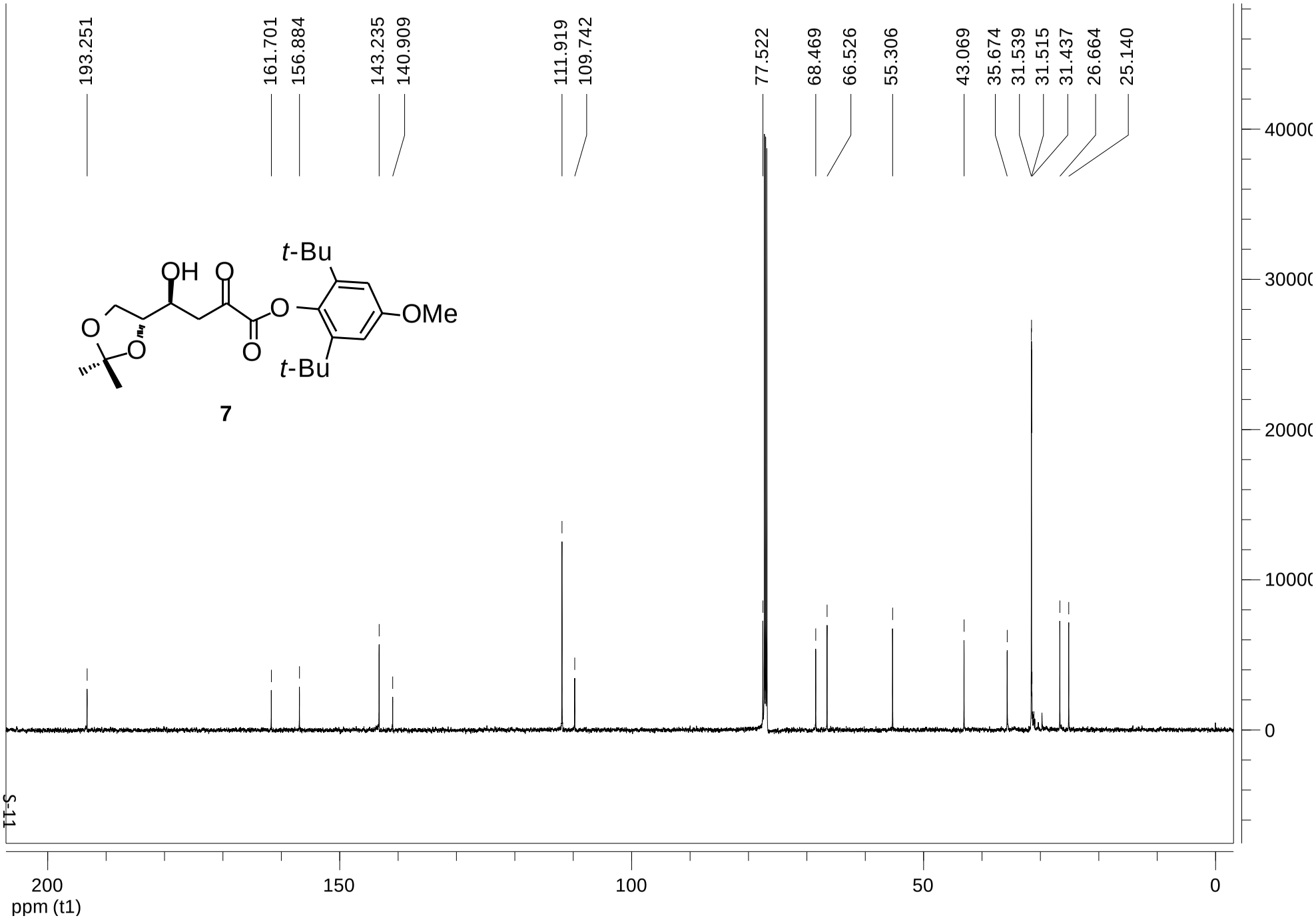
4.196
4.190
4.185
4.182
4.175
4.170
4.124
4.114
4.110
4.100
4.062
4.053
4.051
4.042
4.031
3.990
3.981
3.976
3.967
3.324
3.319
3.293
3.288
3.148
3.133
3.117
3.102
1.421
1.355
1.311
1.307
OH
O
O
O
O
O
t-Bu
t-Bu
OMe
7
1.02
1.08
1.08
1.06
3.83
0.97
1.00
4.00
3.50
ppm (t1)
2.37
1.02
3.83
0.97
1.00
3.14
20.18
S-10
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
ppm (t1)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31.539
31.515
31.437
26.664
25.140
t-Bu
OH
O
O
O
O
O
OMe
t-Bu
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30000
20000
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0
S-11
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50
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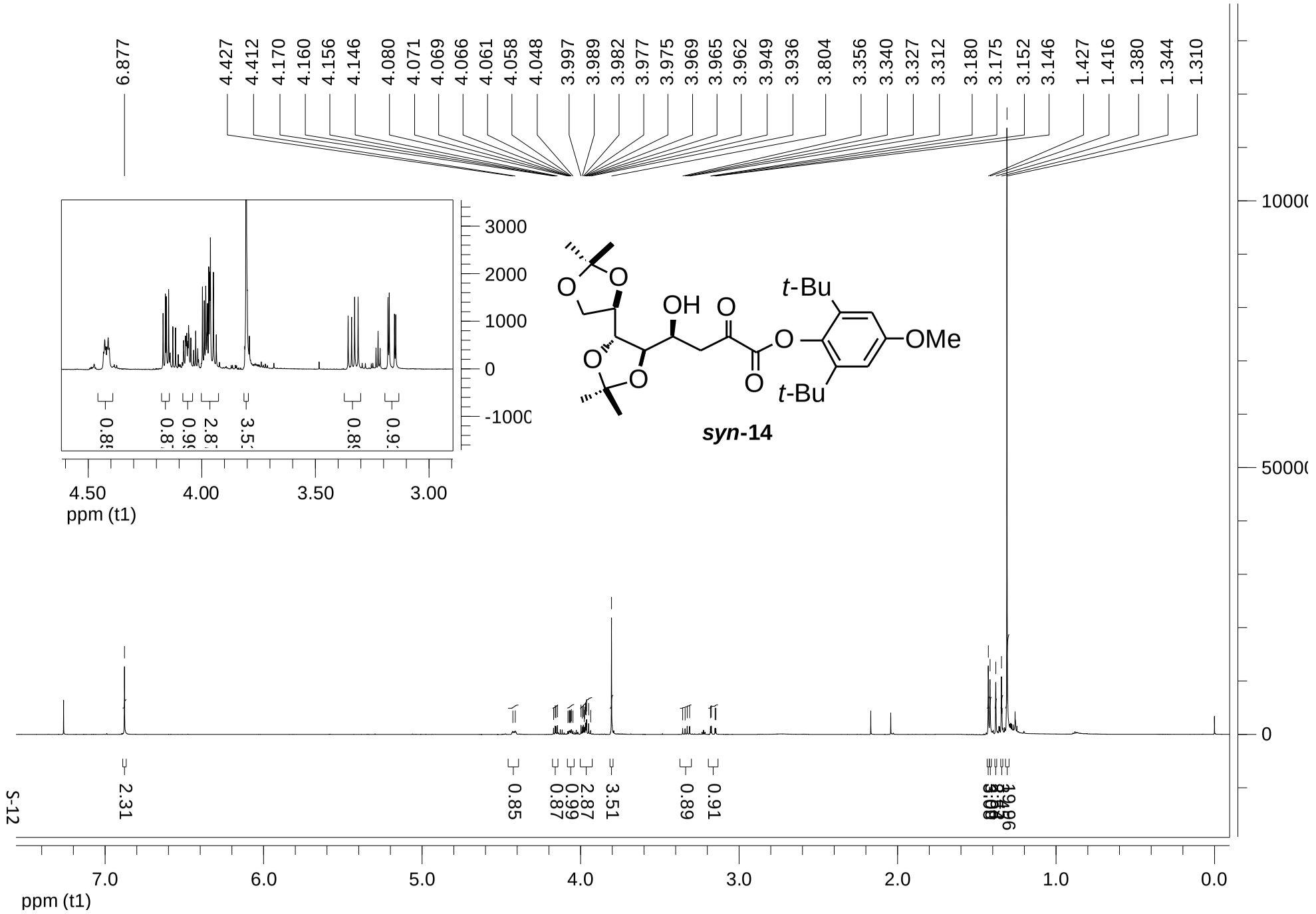
ppm (t1)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4.058
4.048
3.997
3.989
3.982
3.977
3.975
3.969
3.965
3.962
3.949
3.936
3.804
3.356
3.340
3.327
3.312
3.180
3.175
3.152
3.146
1.427
1.416
1.380
1.344
1.310
OH
O
t-Bu
OMe
t-Bu
syn-14
ppm (t1)
ppm (t1)
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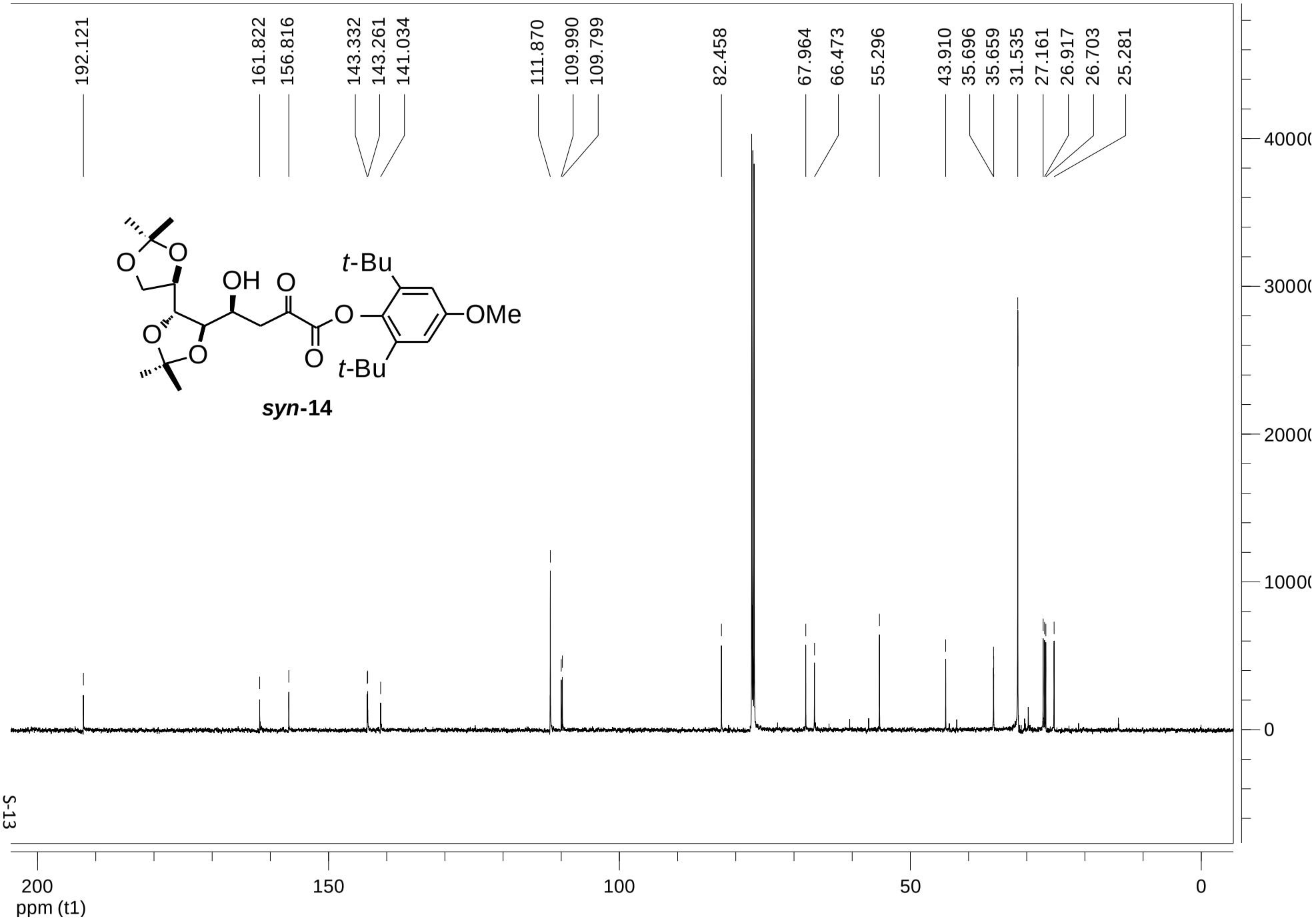
0.91
S-12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55.296
43.910
35.696
35.659
31.535
27.161
26.917
26.703
25.281
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O
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OMe
t-Bu
syn-14
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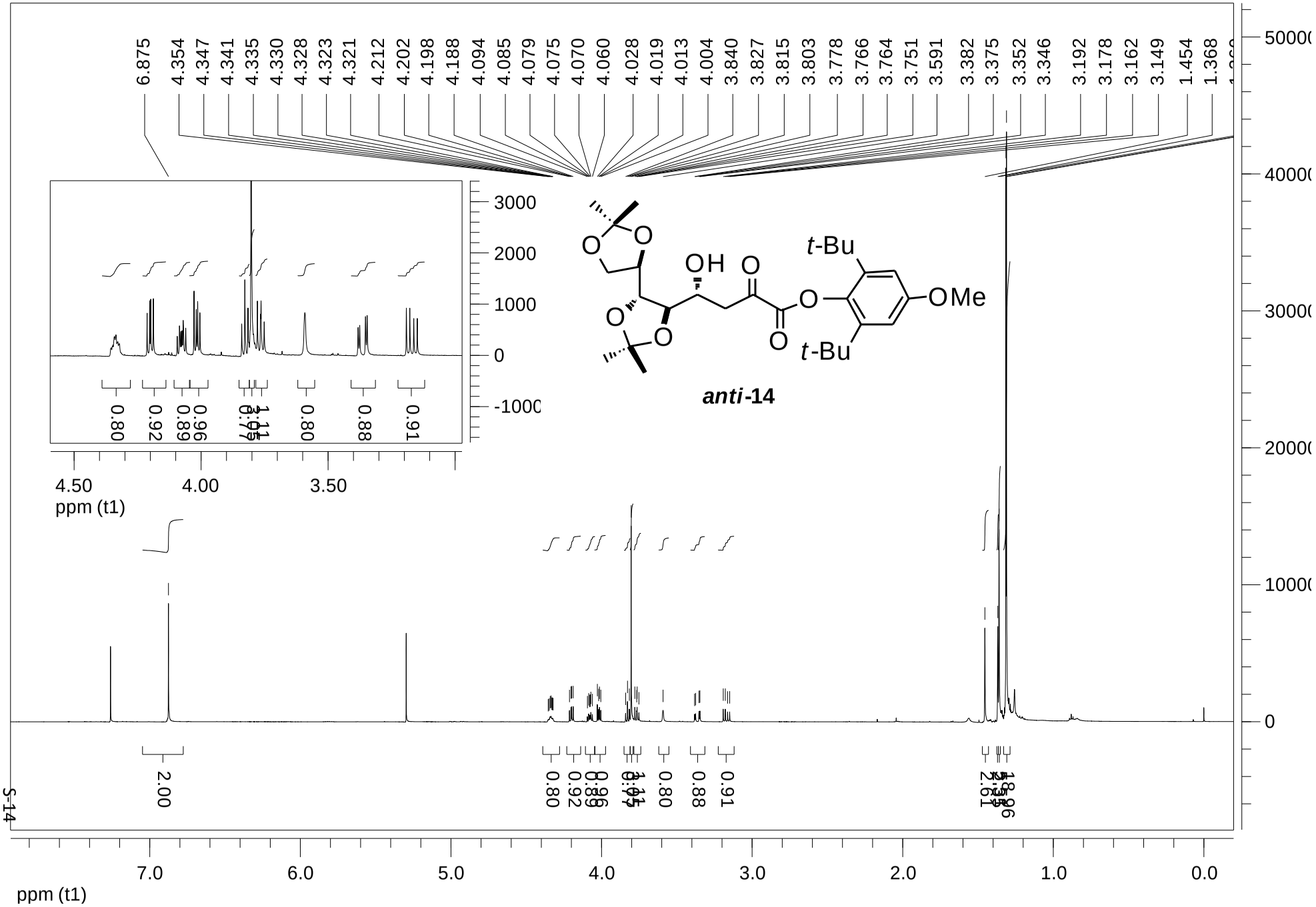
2000
1000
0
200
150
100
50
0
ppm (t1)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4.094
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4.079
4.075
4.070
4.060
4.028
4.019
4.013
4.004
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3.827
3.815
3.803
3.778
3.766
3.764
3.751
3.591
3.382
3.375
3.352
3.346
3.192
3.178
3.162
3.149
1.454
1.368
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O
t-Bu
OMe
t-Bu
anti-14
4.50
4.00
3.50
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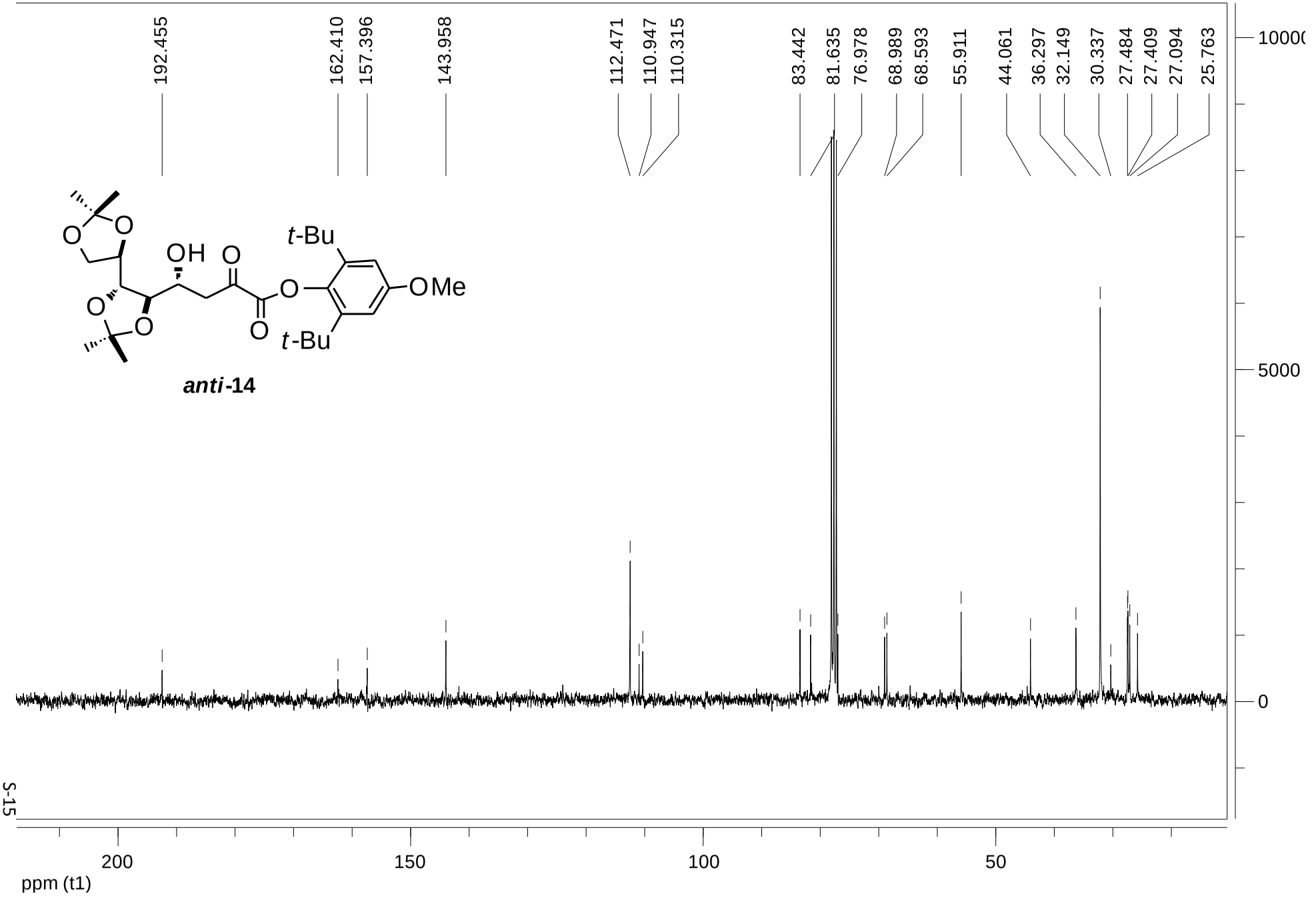
5.0
4.0
3.0
2.0
1.0
0.0
ppm (t1)
S-14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44.061
36.297
32.149
30.337
27.484
27.409
27.094
25.763
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O
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O
OMe
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O
O
O
t-Bu
anti-14
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0
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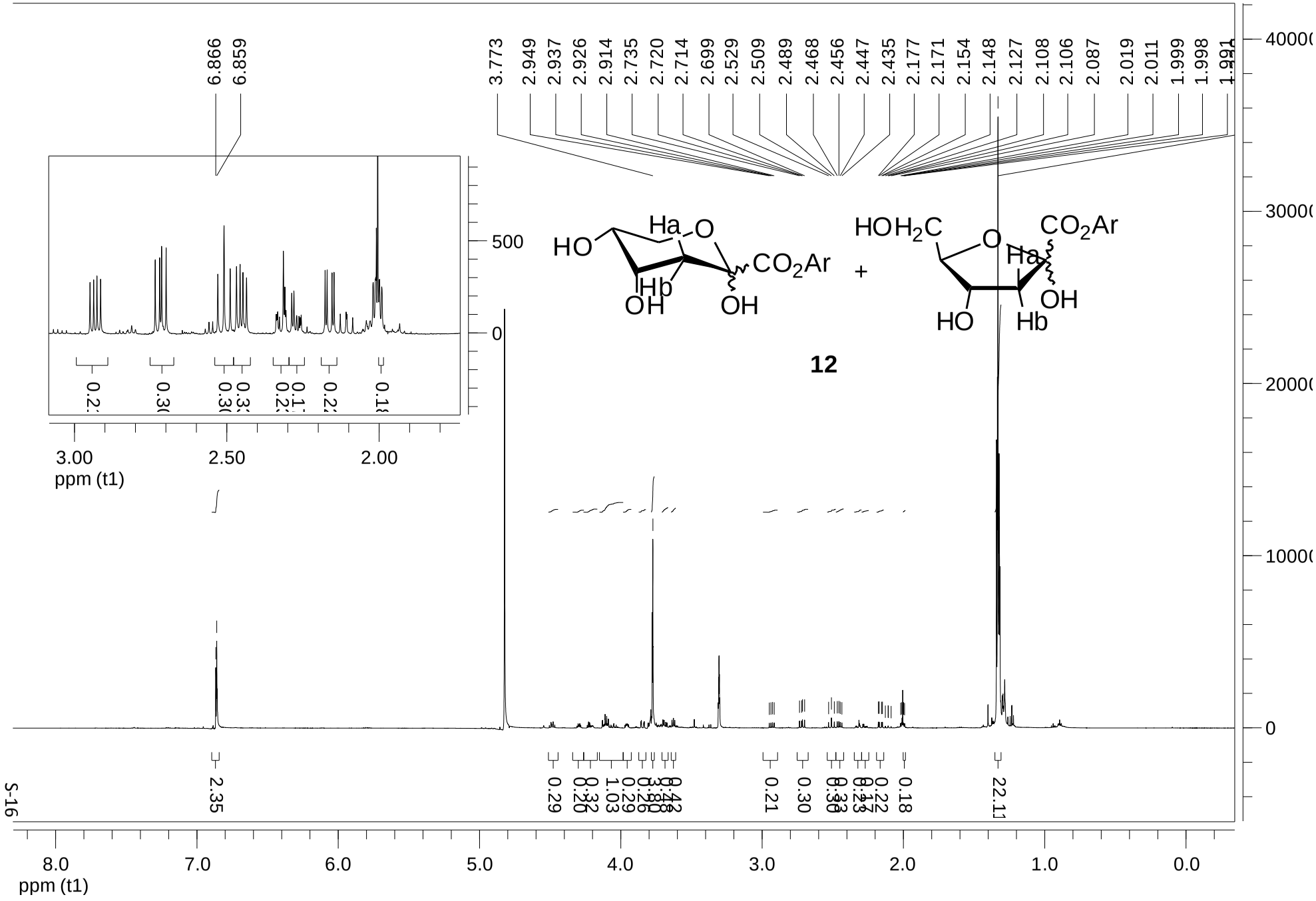
150
100
50
ppm (t1)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2.468
2.456
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2.435
2.177
2.171
2.154
2.148
2.127
2.108
2.106
2.087
2.019
2.011
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1.998
1.991
HO
Ha
O
CO2Ar
Hb
OH
OH
+
HOH2C
O
CO2Ar
Ha
OH
HO
Hb
12
500
0
3.00
2.50
2.00
ppm (t1)
2.35
0.29
1.03
0.21
0.30
0.22
0.18
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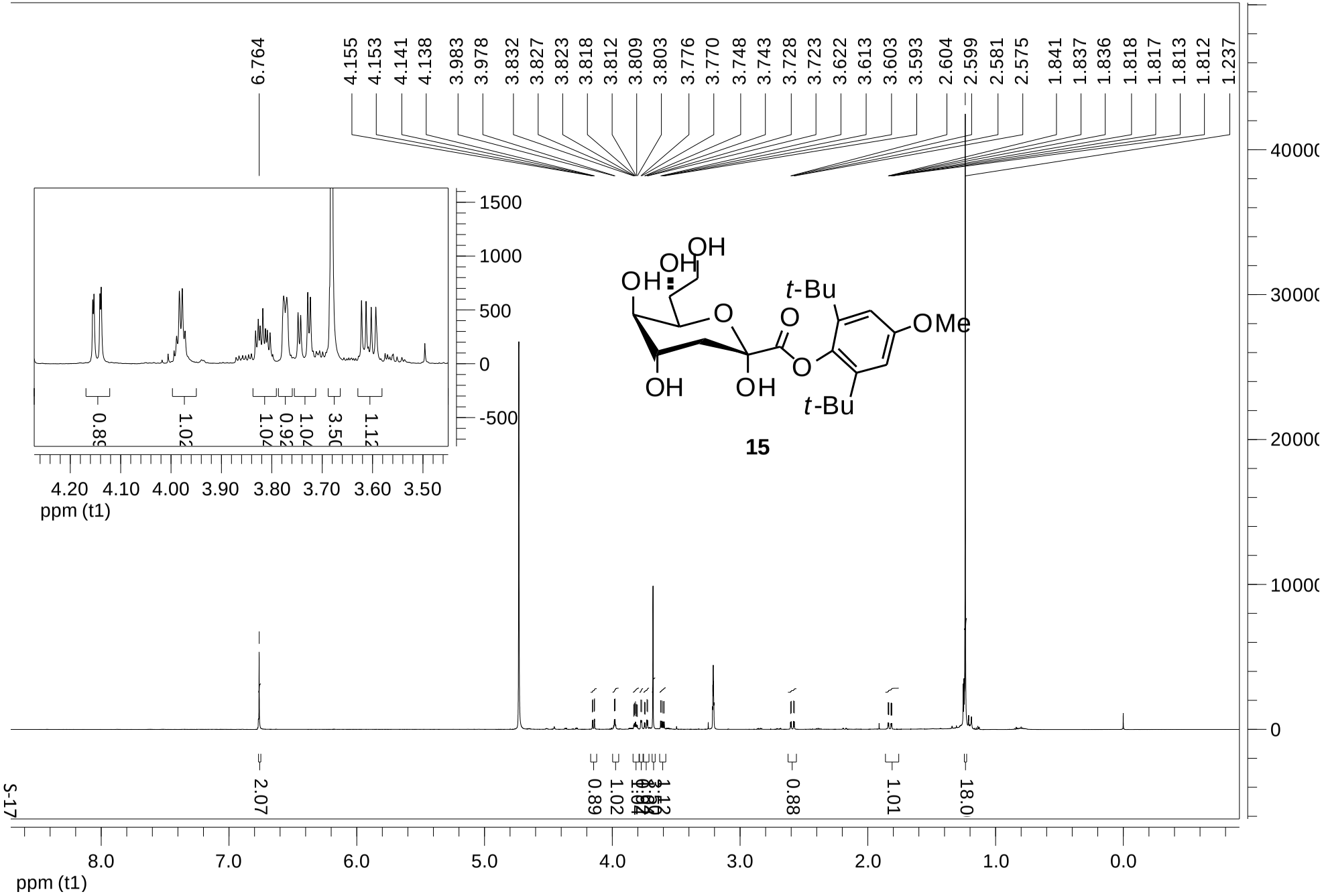
2.0
1.0
0.0
ppm (t1)
S-16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3.809
3.803
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3.770
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3.728
3.723
3.622
3.613
3.603
3.593
2.604
2.599
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1.817
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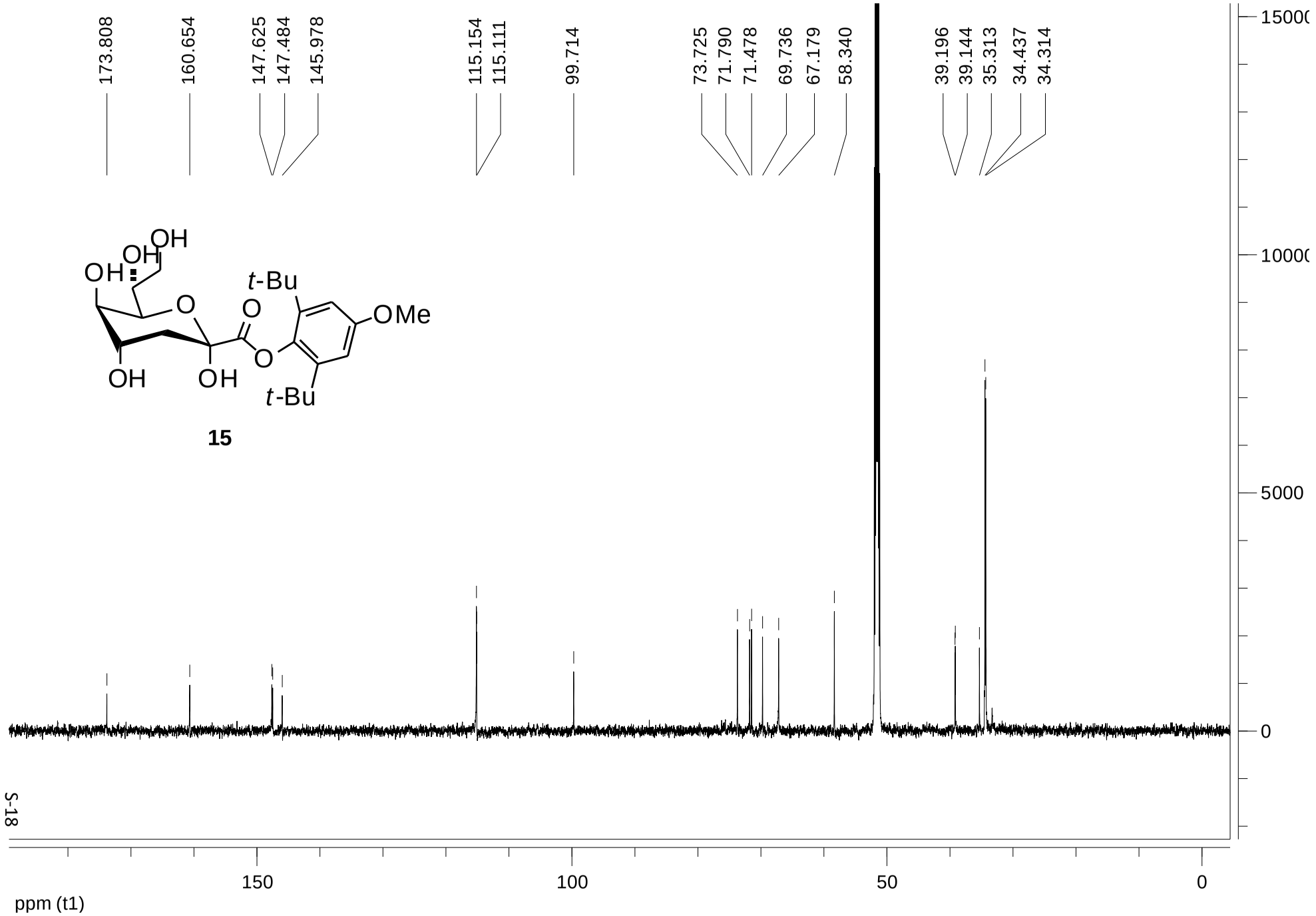
OH
O
O
O
t-Bu
OMe
OH
OH
t-Bu
15
0.89
1.02
1.04
0.92
1.04
3.50
1.12
4.20 4.10 4.00 3.90 3.80 3.70 3.60 3.50
ppm (t1)
2.07
0.89
1.02
0.88
1.01
18.0
8.0 7.0 6.0 5.0 4.0 3.0 2.0 1.0 0.0
ppm (t1)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71.790
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58.340
39.196
39.144
35.313
34.437
34.314
OH
OH
OH
O
O
t-Bu
OMe
O
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OH
t-Bu
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10000
5000
0
S-18
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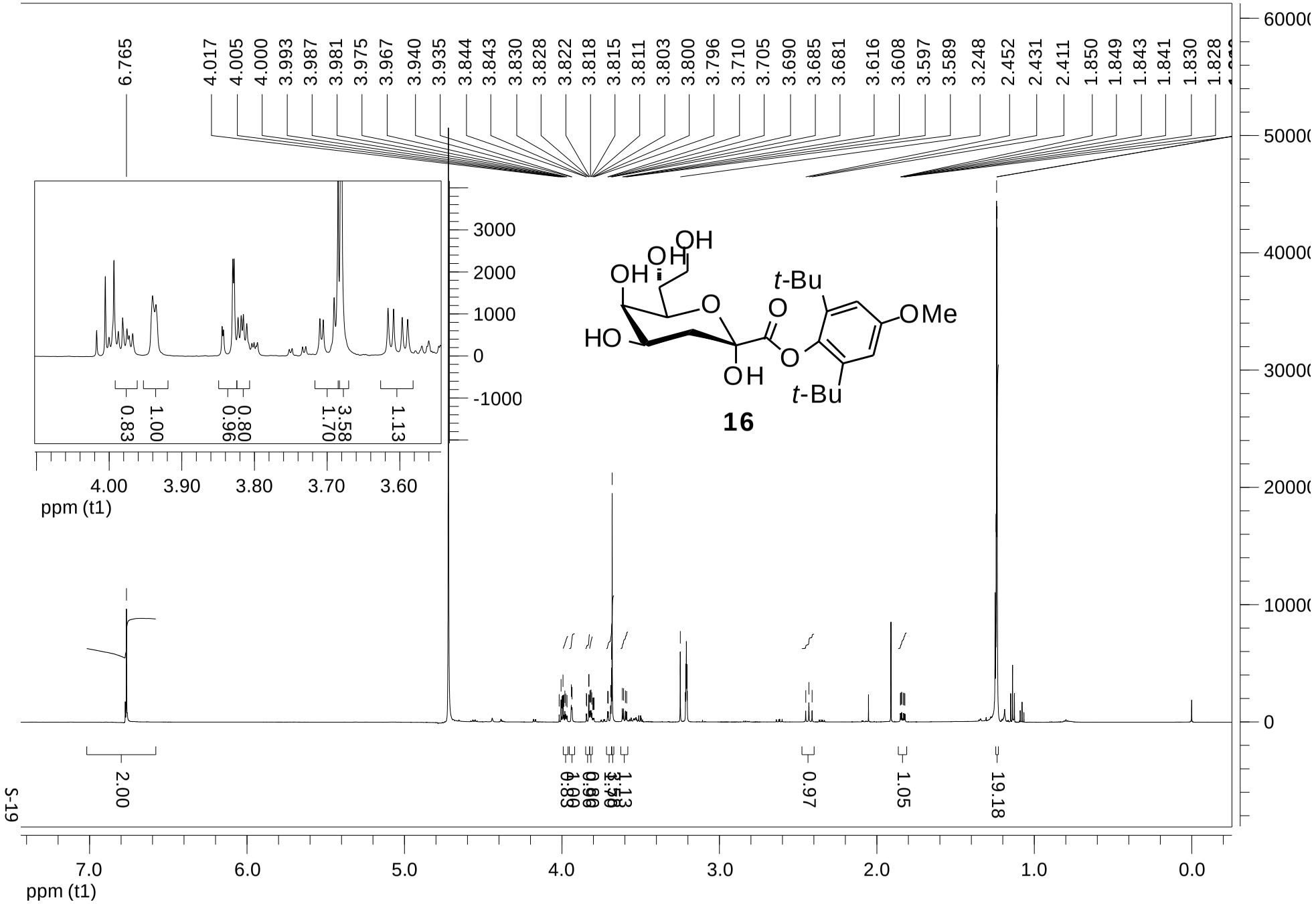
100
50
0
ppm (t1)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3.843
3.830
3.828
3.822
3.818
3.815
3.811
3.803
3.800
3.796
3.710
3.705
3.690
3.685
3.681
3.616
3.608
3.597
3.589
3.248
2.452
2.431
2.411
1.850
1.849
1.843
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1.830
1.828
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OH
HO
O
O
O
OH
t-Bu
t-Bu
OMe
16
0.83
1.00
0.96
0.80
1.70
3.58
1.13
4.00
3.90
3.80
3.70
3.60
ppm (t1)
3000
2000
1000
0
-1000
6000
5000
4000
3000
2000
1000
0
2.00
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7.0
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2.0
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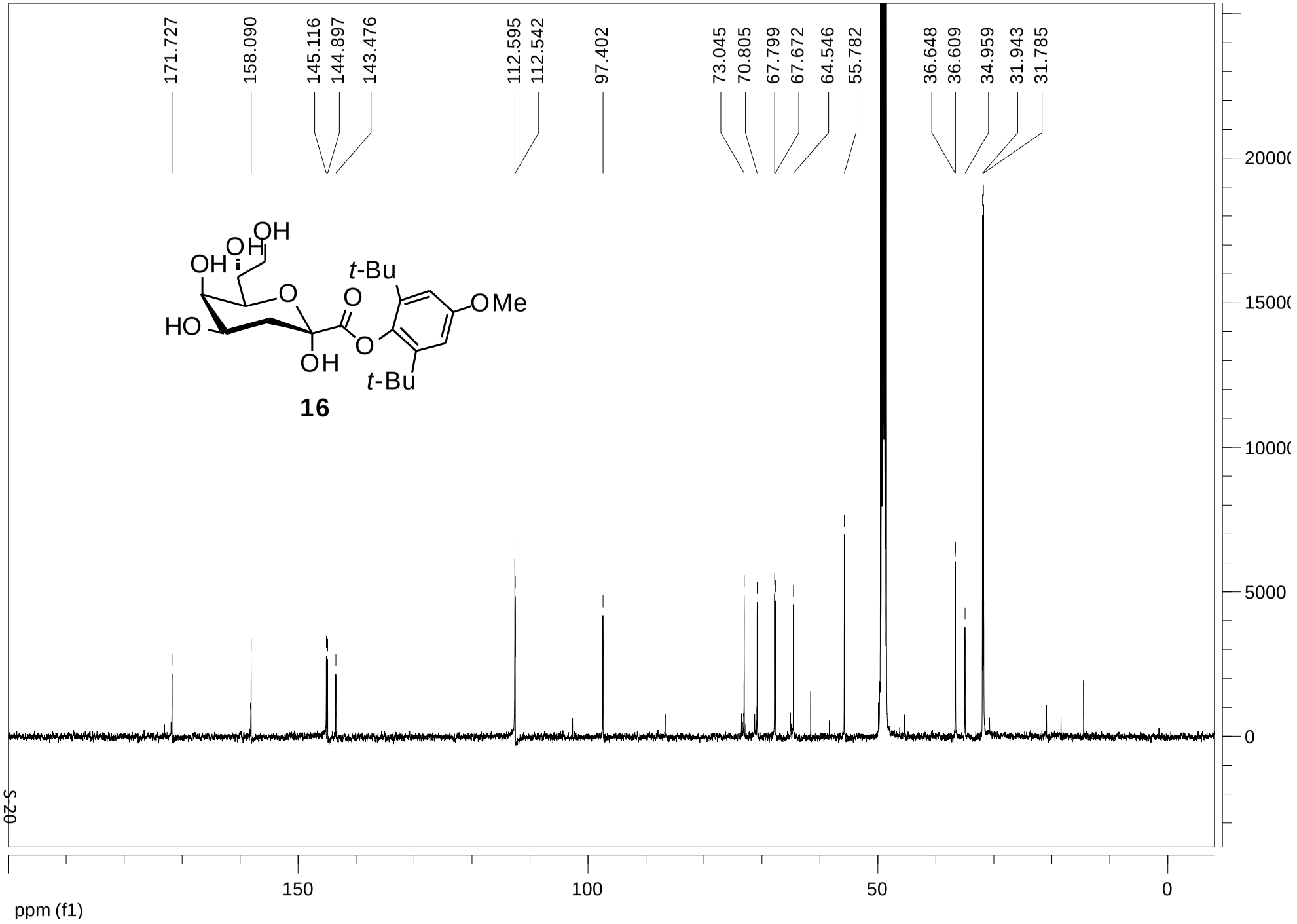
ppm (t1)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OH
HO
O
O
O
t-Bu
OMe
OH
t-Bu
16
S-20
20000
15000
10000
5000
0
150
100
50
0
ppm (f1)

6.3. Brønsted Acid-Catalyzed, Asymmetric, Conjugate Addition to *o*-quinomethides – a Highly Enantioselective Synthesis of Chromenes

In the publication process

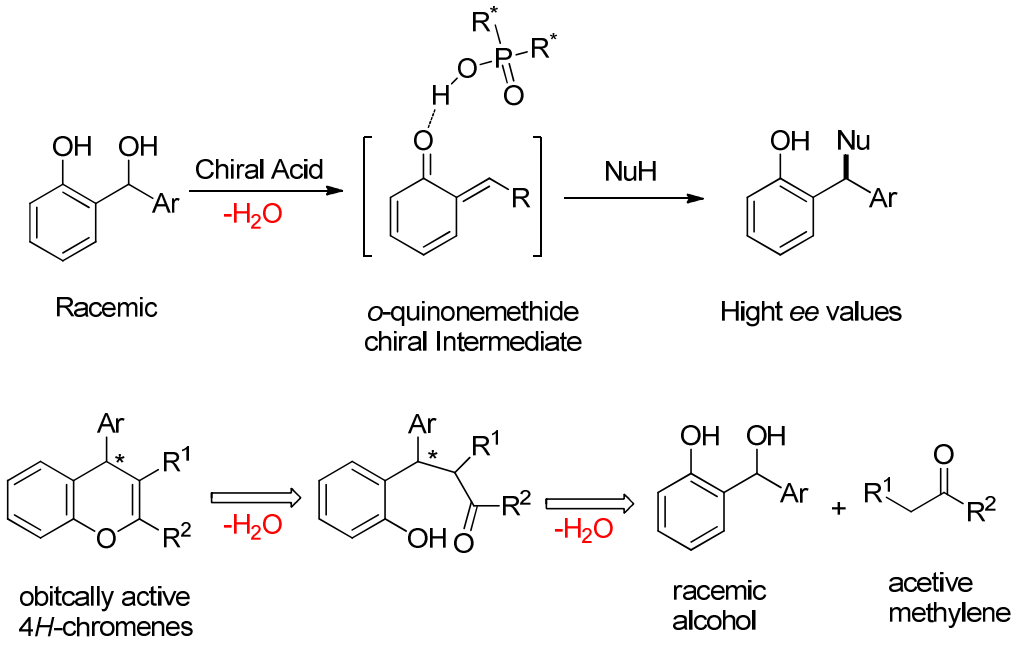
Brønsted Acid-Catalyzed, Asymmetric Conjugate Addition to *o*-quinomethides: a Highly Enantioselective Synthesis of Chromenes

Electrophilic alkylation reactions are one of the most abundant and powerful tools in synthetic chemistry. They are typically performed using activated electrophiles i.e. alkyl halides or related species which are often toxic due to their ability to alkylate DNA. Alternatively, alkylation with alcohols *via* direct substitution of its hydroxyl group can been seen as an ideal process characterized by being green, atom-economical and environmentally benign as water is the only side product of the transformation. Poli has shown the ability of carbocation generation from the benzhydylic alcohol by using stoichiometric amounts of Lewis acid in 2002, making a breakthrough in the research by replacing the traditional alkylating agents with unfunctionalized alcohols.[1] Even though, the alcohols have a poor leaving group, catalytic amounts of Brønsted or Lewis acids were found to be sufficient to catalyze the direct activation of allylic and benzylic alcohols.[2]

Despite significant advances having been made, the asymmetric α-alkylation of carbonyl compounds is still in its infancy. The asymmetric alkylation with prochiral or racemic alcohols is currently exciting the synthetic community. Most of the advances in this field are transition metal catalyzed alkylation with simple allylic alcohols.[3] Whereas Reuping has reported a metal free intramolecular alkylation with allylic alcohol *via* the formation of a chiral carbenium ion by the application of a chiral phosphoramide.[4] In contrast with asymmetric allylic alkylations, enantioselective benzylic alkylation with alcohols has remained a long standing challenge. In this context, chiral enamine catalysts have been used by Cossi to achieve the first benzylic alkylation of aldehydes with alcohols.[5] The α-alkylation of 2-oxindoles with Mischler hydrols was performed through the non-covalent activation mode of the nucleophile by using bis-cinchona alkaloids.[6] In all reports, concerning asymmetric alkylation with benzylic alcohols, the authors use highly reactive alcohols in order to form stable carbocations due to the influence of an achiral acid co-catalyst. Moreover, there is no protocol involving a chiral electrophile intermediate generated in the catalytic cycle or alcohols with electron withdrawing groups.

o-Quinomethides[7] are elusive synthetic intermediates, which are widely implicated in biological processes and subsequently in a series of biomimetic natural product synthesis.[8] They can be employed as synthetic intermediates exhibiting different modes of reactivity, mostly, cycloaddition and 1,4-conjugate addition reactions.[9] Schaus has recently disclosed the enantioselective addition of boronates to *o*-quinomethides catalyzed by chiral biphenols.[10] The chiral Brønsted acids, especially the BINOL-based phosphoric acids, have attracted much attention as powerful organocatalyst tool for many asymmetric transformations.[11,12]

Based on this basis, we sought to develop a new protocol for the *in situ* generation of *o*-quinomethides using chiral phosphoric acids, which in turn might give a chiral intermediate generated in the catalytic cycle by the means of the hydrogen-bonding with the O-H bond of the chiral phosphoric acid. We assumed that this chiral reactive dienophile system can be utilized for the asymmetric alkylation of carbonyl compounds through the 1,4-conjugate addition process. The simple rerosynthesis of the biologically important 4*H*-chromenes directed our attention to designing our roadmap with the possibility of allowing access to the biologically and optically active chromenes (Scheme 1).



Scheme1. Ideal asymmetric benzylic alkylation and 4*H*-chromene synthesis

Chromenes are attractive targets in organic synthesis due to their significance as biologically active agents. They extensively present in nature and exhibits different biological properties including antimalarial, anticoagulant, antiviral, anti-HIV, antioxidant and antifungal. For example, the antibiotics rhodomyrtone B and rhodomyrtosone, the α-glucosidase inhibitor myrtucommulone E. Our motivation to synthesize the chiral 4*H*-chromenes, has also been raised by the facts that, asymmetric methods for their construction are still extremely rare.[13]

In order to validate our proposal, we select the *o*-hydroxybenzylic alcohol **1** and acetylacetone **2a** as model substrates during the preliminary evaluation and reaction optimization. Initial application of the phosphoric acid **3a** at RT in dichloromethane for 24h gave promising results while selectivity remained poor (**4**, 70% yield, 56:44 *er*). The most efficient means turned out to be a variation of the substituents of position 3 of the chiral BINOL. Thus, a broad range of different phosphoric acids **3** that meet these criteria were investigated in the elaborated reaction. Catalyst **3b** lacking a mesityl substituent gave an *er* of 78.5:21.5 with an excellent yield (Table 1, entry 2) while replacing the methyl groups with ethyl groups slightly increase the enantioselectivity of the reaction to 84.5:15.5 *er* (cat **3c**, entry 3). Interestingly, the use of the promising TRIP catalyst **3d** with isoprobyl substituents lead to an unexpected decrease in selectivity to 81:19 *er*. However, introducing a *t*-Bu group in the para-position significantly increased the selectivity to 85.5:14.5 *er* in excellent yield (cat **3e**, entry 5), whereas replacing the methyl group by a OMe group resulted in a drop in enatioselectivity (*er* =75.5:24.5). The increase in the number of substituents to the pentamethylsubstituted catalyst **3g** did not furnish higher selectivity than the catalyst **3e** (entry 6). Importantly, the catalyst **3h** with a 2-naphthyl substituent proved to be a poor catalyst for this reaction. Finally, the phenanthryl and $SiPh_3$ species completely shut down the reaction and no product was observed.

The best catalyst in terms of yield and selectivity **(*R*)-3e** was further retested in a number of solvents shown in table 2. While chloroform was the optimal solvent for the reaction (95% yield, 88:12 *er*), no product was observed upon doing the reaction in tetrahydrofuran. Another important optimization was performed by reducing the catalyst loading to only 5 mol% while maintaining the same reactivity and selectivity of the reaction.

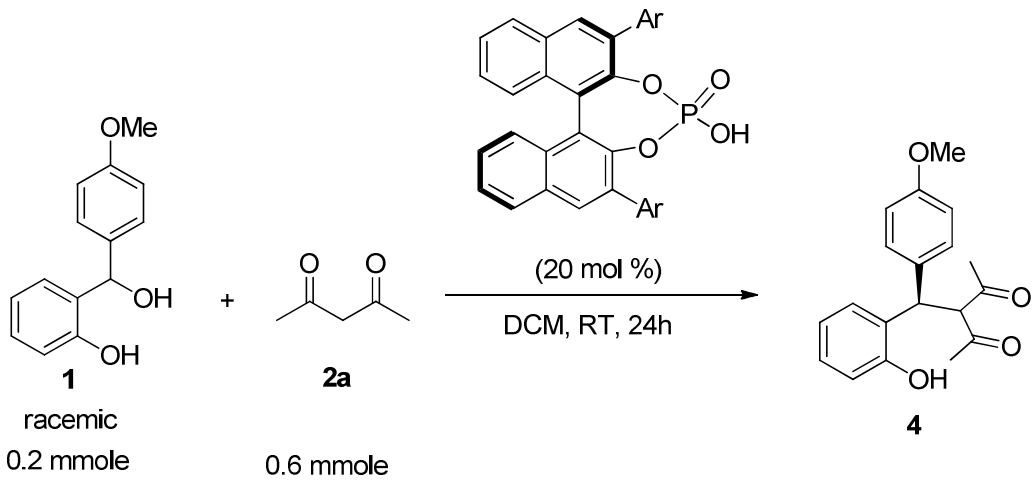
The intermediate **4** was not further dehydrated to the chromene **5a** under the influence of the chiral phosphoric acid. Whereas, the addition of *p*-tolunesulphonic acid (20 mol%) to the reaction mixture with stirring at 45 ^{o}C, nicely cyclized **4** to the valuable chromene **5a** in 82% yield over the two steps without changing the optical purity of the intermediate **4** (88:12 *er*).

Next, we tested the flexibility of our methodology with the β-keto ester **2b**, giving the desired chromene **5b** in a good yield of 70% and a good enantiomeric ratio 89:11. When the cyclic 1,3-diketone **2c** was evaluated in the reaction, the alkylation reaction was completed after only 2 hours and after the subsequent cyclization with a stronger acid, the chromene **5c** was obtained in 95% yield and 91:9 *er*. These results encouraged us to reduce the reaction temperature to 0 ^{o}C and the ketone loading to 1.2 eq of the alcohol, furnishing higher enantioselectivity (94.5:5.5 *er*).

With the optimal results in hand, we decided to investigate the generality of the *o*-hydroxybenzylic alcohols. Various alcohols with electron rich and electron poor substituents can be tolerated in the reaction have been shown in table 4. The absolute configuration of the chromenes were determined by X-ray crystal structure of the chromene **7m**, providing information that the catalyst **(*R*)-3e** deliver chromenes with *R* configuration (Fig. 1).

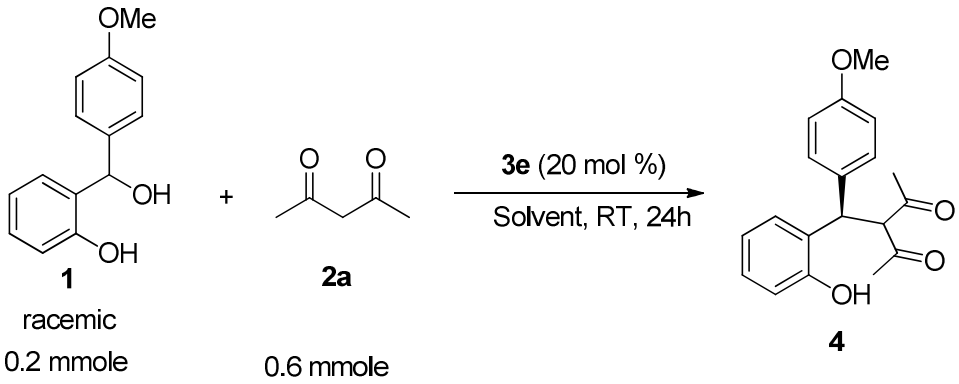
Regarding the reaction mechanism, several different pathways might be taken into account. The first possible pathway involving the formation of a chiral carbenium ion was completely eliminated because the phenolic OH was determined to be crucial for the reactivity and its absence lead to no product formation. Also no product was formed if the OH was exchanged by OCH_3, providing evidence of the formation of the *o*-quinone methide intermediate. On the other hand, the non-enolized active methylene compounds such as, ethyl cyanoacetate and malontitrile cannot be alkylated under these conditions. Therefore, the enolizable 1,3-dicarbonyl compounds are probably activated by hydrogen-bonding with the carbonyl group of the phosphoric acid. Hence, the 1,4-conjugate addition to the *o*-quinomethides *via* dual activation modes might be considered (Fig. 2).

Table 1. Catalyst optimization



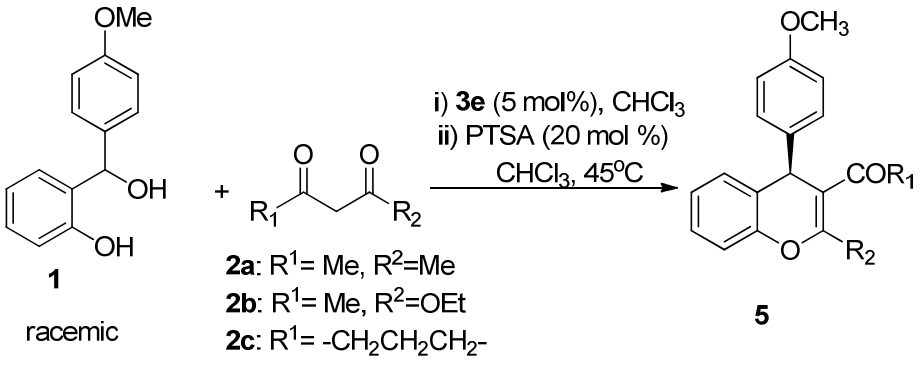
Entry	Ar	Yield (%)	*er*
1	Ph (**3a**)	70	56:44
2	Mes (**3b**)	95	78.5:21.5
3	2,4,6-$Et_3C_6H_2$ (**3c**)	97	84.5:15.5
4	TRIP (**3d**)	97	81:19
5	**2,6-diMe-4-*t*Bu-C_6H_2 (3e)**	**97**	**85.5:14.5**
6	2,6-diMe-4-OMe- C_6H_2 (**3f**)	95	75.5:24.5
7	PentaMe-C_6 (**3g**)	93	83.5:16.5
8	2-Naphthyl (**3h**)	78	54.5:45.5
9	9-Phenanthryl (**3i**)	-	NI
10	$SiPh_3$ (**3j**)	-	NI

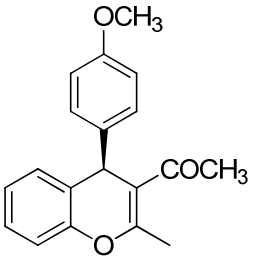
Table 2. Solvent optimization



Entry	Solvent (1 ml)	Yield (%)	*er*
1	CH_2Cl_2	97	85.5:14.5
2	**$CHCl_3$**	**95**	**88:12**
3	$ClCH_2CH_2Cl$	95	82.5:17.5
4	CH_3CN	84	72:28
5	PhMe	88	86:14
6	PhH	87	85:15
7	C_6H_5Cl	90	85:15
8	1,2- $C_6H_4Cl_2$	69	84:16
9	$PhCF_3$	82	82:18
10	THF	-	-

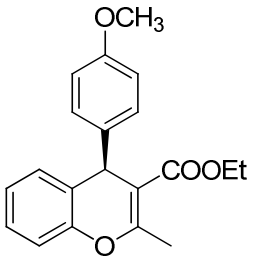
Table 3. Alkylation of 1,3-dicarbonyl compounds





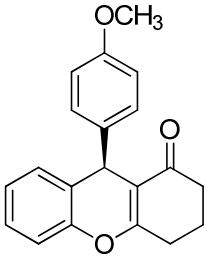
5a

24 h, RT
82% yield, 88:12 *er*



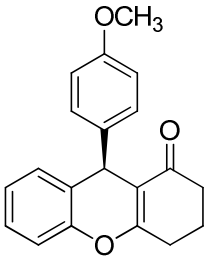
5b

24h, RT
70 % yield, 89:11 *er*



5c

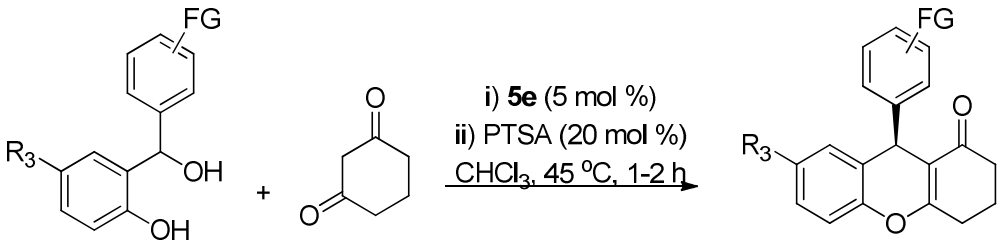
2h, RT
95% yield, 91:9 *er*



5c

1.2 eq. ketone, 24h, 0°C
95% yield, 94.5:5.5 *er*

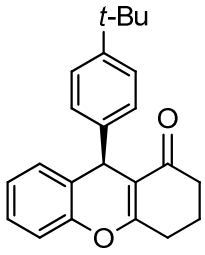
Table 4. Enatioselective synthesis of tricyclic chromenes



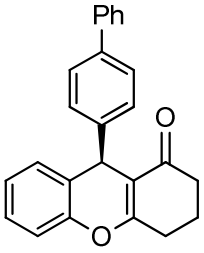
6a-p
Racemic
0.2 mmole

2c
0.24 mmole

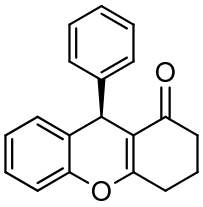
7a-p



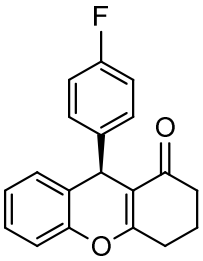
48h, 0 °C **7a**
92% yield, 95.5:4.5 *er*



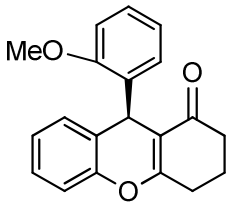
36h, RT **7b**
91% yield, 94:6 *er*



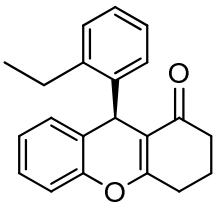
36h, RT **7c**
94% yield, 95:5 *er*



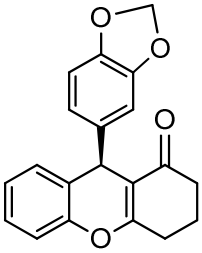
36h, RT **7d**
92% yield 98:2 *er*



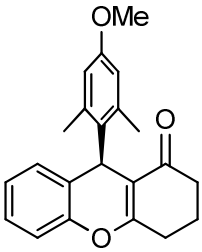
36h, RT **7e**
97% yield, 95.5:4.5 *er*



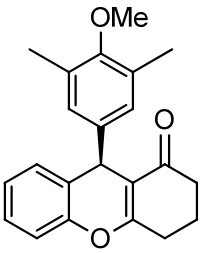
36h, RT **7f**
98% yield, 96:4 *er*



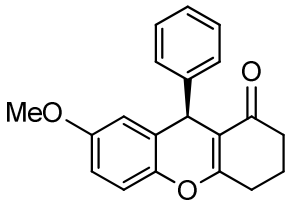
24h, 0 °C **7g**
92% yield,95:5 *er*



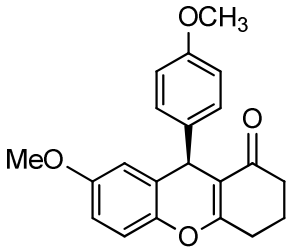
24h, 0 °C **7h**
85% yield,94.5:5.5 *er*



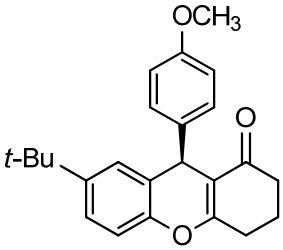
24h, 10 °C **7i**
97% yield, 95:5 *er*



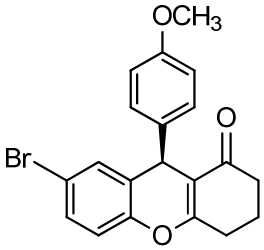
36h, RT **7j**
93% yield, 98:2 *er*



24h, 0 °C **7k**
97% yield, 95.5:4.5 *er*



24h, 0 °C **7l**
97% yield, 96:4 *er*



24h, 10 °C **7m**
97% yield, 94.5:5.5 *er*

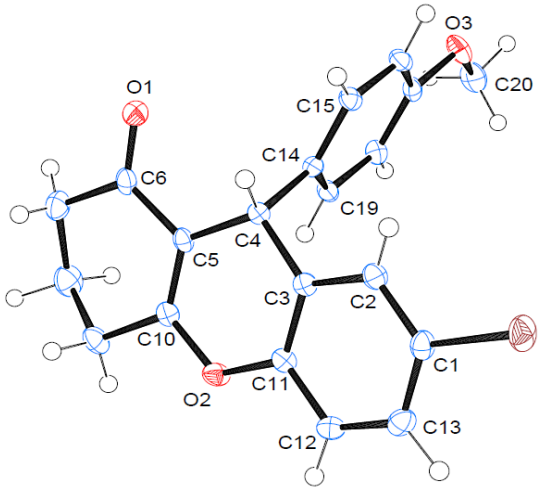


Fig. 1. The X-ray crystal structure of compound **7m**

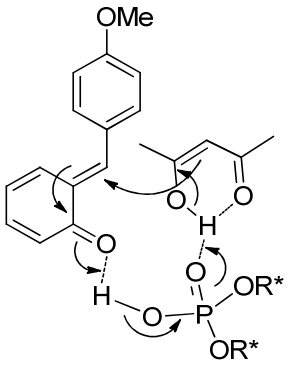


Fig. 2. The proposed dual activated transition state

In conclusion, the chiral phosphoric acids have been discovered to catalyze for the asymmetric intermolecular benzylic alkylation of 1,3-dicarbonyl compounds *via* the formation of highly reactive *o*-quinomethide intermediates. The presented methodology has a broad scope, resulting in the corresponding 4*H*-chromenes in excellent yields and enantioselectivities. The presented approach, which avoids the use of often toxic metals and substrates, is particularly attractive. We are also confident that the concept of mild *o*-quinomethide generation and subsequent asymmetric 1,4-conjugate addition by means of chiral phosphoric will find broader applications.

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Supporting Information

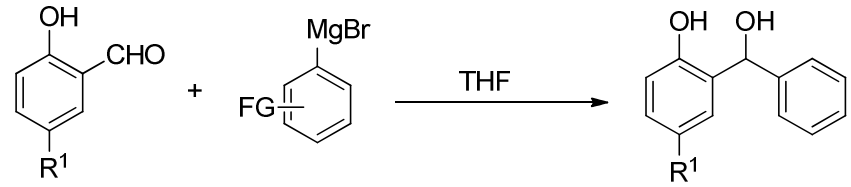
Contents

I- General Information.

^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ and solutions using a Varian Gemini 2000 spectrometer (300 MHz) and Brucker Avance DRX 400 (400 MHz). The signals were referenced to residual chloroform (7.26 ppm, ^{1}H, 77.00 ppm, ^{13}C). Chemical shifts are reported in ppm, multiplicities are indicated by s (singlet), d (doublet), t (triplet), q (quartet), quint (quintet), sext (sextet) and m (multiplet). Melting points were determined uncorrected on a Boetius heating table. IR spectra were obtained with a FTIR spectrometer (Genesis ATI Mattson/Unicam). Optical rotations were measured using a Polarotronic polarimeter (Schmidt & Haensch). All ESI mass spectra were recorded on a Brucker APEX II FT-ICR. HPLC analyses were carried out on a Jasco MD-2010 plus instrument with chiral stationary phase column (Daicel Chiralcel OD column or Daicel Chiralcel OD-H column). The solvents were distilled from indicated drying reagents: dichlormethane (CaH_2), tetrahydrofuran (Na, benzophenone), diethyl ether (Na, benzophenone). Diethyl ether, ethyl acetate and hexane were technical grade and distilled from KOH. Flash column chromatography was performed by using Merck silica gel 60 230-400 mesh (0.040-0.063 mm). All reactions were monitored by thin- layer chromatography using precoated silica gel plates. Spots were visualized by UV and were treated with a solution of vanillin in methanol (technical grade).

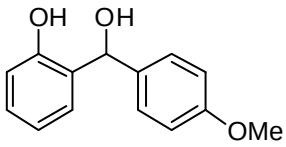
II- Experimental procedure and characterizations of the alcohols

General procedure for the synthesis of *o*-hydroxybenzylic alcohols (*Chem Commun*., 2008, 5341)



To a solution of magnesium (1.46 g, 60.0 mmol) and a granule of I_2 in anhydrous THF (30 ml) was added dropwise a solution of the aryl bromide (3eq, 60.0 mmol) in anhydrous THF (20 ml), controlling the speed to maintain THF boiling. After adding, the system was heated until the complete consumption of the magnesium. Then cooled to 0 ˚C, a solution of the aldehyde (20.0 mmol) in THF (20 ml) was added dropwise to the mixture in 15 min, and then the system was gently warmed for a subsequent 30 min. Then the reaction mixture was cooled again to 0 ˚C and quenched with saturated NH_4Cl carefully. The resulting solution was extracted with Et_2O, dried with anhydrous sodium sulphate and concentrated *in vacuo*. The residue was purified by flash chromatography (SiO_2, ethyl acetate:hexane mixtures 1:8 to 1:3) to give the alcohols in ca.90% yields.

2-(Hydroxy(4-methoxyphenyl)methyl)phenol

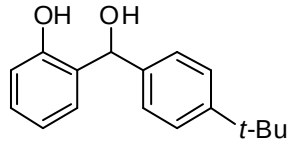


^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.01 (s, 1H), 7.54 – 7.08 (m, 4H), 7.01 – 6.46 (m, 4H), 5.97 (d, *J* = 2.8 Hz, 1H), 3.80 (s, 3H), 2.87 (d, *J* = 3.1 Hz, 1H).

^{13}C NMR (75 MHz, $CDCl_3$) δ = 159.6, 155.6, 134.3, 129.3, 128.4, 128.3, 126.9, 120.0, 117.3, 114.2, 76.85, 55.42.

HR-MS (ESI): calc. for: ([M+Na]+): 253.0841; found: 253.0835.

2-((4-(*tert*-Butyl)phenyl)(hydroxy)methyl)phenol

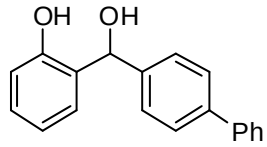


^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.48 – 7.28 (m, 4H), 7.19 (m, 1H), 7.00 – 6.75 (m, 3H), 5.99 (s, 1H), 1.32 (s, 9H).

^{13}C NMR (75 MHz, $CDCl_3$) δ = 155.7, 151.4, 139.0, 129.3, 128.4, 126.7, 126.6, 125.8, 120.0, 117.4, 77.3, 34.72, 31.43.

HR-MS (ESI): calc. for: ([M+Na]+): 279.1361; found: 279.1365.

2-([1,1'-Biphenyl]-4-yl(hydroxy)methyl)phenol

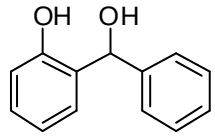


^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.87 (s, 1H), 7.64 – 7.54 (m, 4H), 7.50 – 7.40 (m, 4H), 7.37 (m 1H), 7.22 (ddd, *J* = 8.0, 7.4, 1.7 Hz, 1H), 6.98 – 6.88 (m, 2H), 6.86 (dd, *J* = 7.4, 1.2 Hz, 1H), 6.06 (s, 1H), 2.99 (s, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ = 155.7, 141.4, 141.0, 140.8, 129.6, 129.0, 128.5, 127.7, 127.7, 127.5, 127.3, 126.8, 120.2, 117.6, 77.08.

HR-MS (ESI): calc. for: ([M+Na]+): 299.1048; found: 299.1043.

2-(Hydroxy(phenyl)methyl)phenol

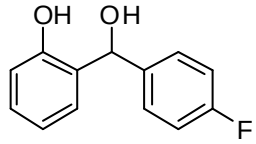


^{1}H NMR (400 MHz, CDCl3) δ = 7.93 (1H, s), 7.44 – 7.29 (m, 5H), 7.19 (ddd, *J* = 8.2, 7.2, 1.9 Hz, 1H), 6.90 (dd, *J* = 8.1, 1.1 Hz, 1H), 6.84 (dtd, *J* = 14.7, 7.6, 1.6 Hz, 2H), 6.00 (s, 1H), 3.13 (s, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ = 155.49, 141.93, 129.40, 128.82, 128.38, 128.31, 126.93, 126.76, 120.08, 117.33, 77.04.

HR-MS (ESI): calc. for: ([M+Na]+): 223.0735; found: 223.0730.

2-((4-Fluorophenyl)(hydroxy)methyl)phenol

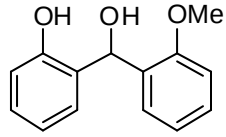


^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.70 (s, 1H), 7.44 – 7.28 (m, 2H), 7.24 – 7.16 (m, 1H), 7.11 – 6.97 (m, 2H), 6.95 – 6.78 (m, 3H), 5.99 (s, 1H), 2.99 (s, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ = 164.0, 161.5, 155.5, 137.9, 137.8, 129.7, 128.9, 128.8, 128.4, 126.7, 120.3, 117.6, 115.9, 115.7, 105.0, 76.45.

HR-MS (ESI): calc. for: ([M+Na]+): 241.0641; found: 241.0635.

2-(Hydroxy(2-methoxyphenyl)methyl)phenol

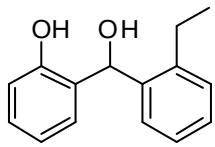


^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.29 (s, 1H), 7.33 (ddd, *J* = 8.4, 7.2, 2.0 Hz, 1H), 7.23 (ddd, *J* = 8.7, 5.6, 3.4 Hz, 1H), 7.03 – 6.90 (m, 4H), 6.84 – 6.79 (m, 2H), 6.21 (d, *J* = 4.6 Hz, 1H), 4.03 (d, *J* = 4.7 Hz, 0H), 3.91 (s, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ = 157.2, 156.7, 129.8, 129.5, 129.4, 128.7, 128.2, 125.4, 121.5, 119.9, 117.4, 111.0, 74.13, 55.77.

HR-MS (ESI): calc. for: ([M+Na]+): 253.0841; found: 253.0835.

2-((2-Ethylphenyl)(hydroxy)methyl)phenol

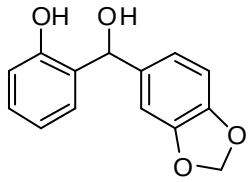


^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.10 (s, 1H), 7.42 – 7.04 (m, 5H), 6.93 (dd, *J* = 8.1, 1.1 Hz, 1H), 6.81 – 6.68 (m, 1H), 6.64 – 6.56 (m, 1H), 6.35 (s, 1H), 2.77 (s, 1H), 2.71 (q, *J* = 7.6 Hz, 4H), 1.21 (t, *J* = 7.6 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ = 156.2, 142.4, 139.1, 129.5, 129.2, 128.9, 128.4, 128.0, 126.8, 126.6, 120.1, 117.2, 73.26, 25.65, 15.83.

HR-MS (ESI): calc. for: ([M+Na]+): 251.1048; found: 251.1043.

2-(Benzo[d][1,3]dioxol-5-yl(hydroxy)methyl)phenol

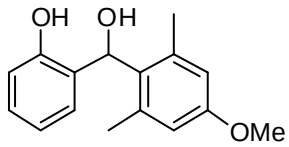


^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.91 (s, 1H), 7.23 – 7.13 (m, 1H), 6.95 – 6.72 (m, 6H), 5.94 (s, 1H), 5.95 – 5.92 (m, 4H), 2.95 (s, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ = 155.6, 148.3, 147.8, 136.2, 129.5, 128.4, 126.7, 120.6, 120.1, 117.5, 108.4, 107.7, 101.4, 77.14.

HR-MS (ESI): calc. for: ([M+Na]+): 267.0633; found: 267.0628.

2-(Hydroxy(4-methoxy-2,6-dimethylphenyl)methyl)phenol

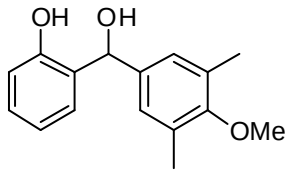


^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.85 (s, 1H), 7.21 – 7.11 (m, 1H), 6.91 (dd, *J* = 8.1, 1.1 Hz, 1H), 6.68 (td, *J* = 7.5, 1.2 Hz, 1H), 6.62 (s, 2H), 6.60 (d, *J* = 2.7 Hz, 1H), 6.45 (dt, *J* = 7.7, 1.2 Hz, 1H), 3.81 (s, 3H), 2.69 (d, *J* = 3.1 Hz, 1H), 2.29 (s, 6H).

^{13}C NMR (100 MHz, $CDCl_3$) δ = 159.7, 155.7, 134.2, 129.3, 128.4, 128.3, 126.7, 120.0, 117.4, 114.2, 104.9, 77.01, 55.44.

HR-MS (ESI): calc. for: ([M+Na]+): 281.1154; found: 281.1148.

2-(Hydroxy(4-methoxy-3,5-dimethylphenyl)methyl)phenol

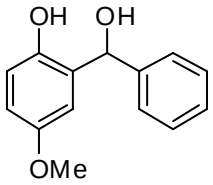


^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.12 (s, 1H), 7.18 (ddd, *J* = 8.3, 7.1, 2.0 Hz, 1H), 7.01 (m, 2H), 6.90 (dd, *J* = 8.1, 1.1 Hz, 1H), 6.82 (dtd, *J* = 14.7, 7.6, 1.6 Hz, 2H), 5.9 (s, 1H), 3.70 (s, 3H), 3.05, (s, 1H), 2.25 (s, 6H).

^{13}C NMR (100 MHz, $CDCl_3$) δ = 156.9, 155.8, 137.5, 131.4, 129.3, 128.4, 127.5, 126.7, 120.0, 117.5, 77.32, 59.87, 16.41.

HR-MS (ESI): calc. for: ([M+Na]+): 281.1154; found: 281.1148.

2-(Hydroxy(phenyl)methyl)-4-methoxyphenol

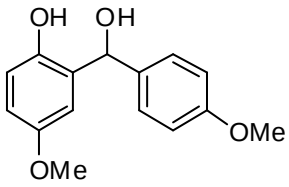


^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.53 – 7.26 (m, 6H), 6.82 (d, *J* = 8.8 Hz, 1H), 6.74 (dd, *J* = 8.8, 3.0 Hz, 1H), 6.45 (d, *J* = 3.0 Hz, 1H), 5.94 (s, 1H), 3.68 (s, 3H), 3.03 (s, 1H).

^{13}C NMR (75 MHz, $CDCl_3$) δ = 153.1, 149.3, 141.8, 128.9, 128.4, 127.6, 126.9, 117.9, 114.2, 114.1, 76.87, 55.85.

HR-MS (ESI): calc. for: ([M+Na]+): 253.0841; found: 253.0835.

2-(Hydroxy(4-methoxyphenyl)methyl)-4-methoxyphenol

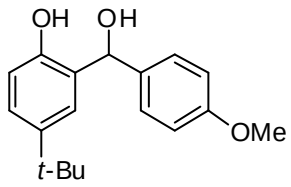


^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.54 (s, 1H), 7.36 – 7.21 (m, 2H), 6.93 – 6.85 (m, 2H), 6.82 (d, *J* = 8.8 Hz, 1H), 6.73 (dd, *J* = 8.8, 3.0 Hz, 1H), 6.42 (d, *J* = 3.0 Hz, 1H), 5.91 (s, 1H), 3.80 (s, 3H), 3.68 (s, 3H), 2.96 (d, *J* = 2.8 Hz, 1H).

^{13}C NMR (75 MHz, $CDCl_3$) δ = 159.8, 153.1, 149.5, 134.2, 128.5, 127.8, 118.0, 114.3, 114.3, 114.1, 76.78, 55.95, 55.53.

HR-MS (ESI): calc. for: ([M+Na]+): 283.0946; found: 283.0941.

4-(*tert*-Butyl)-2-(hydroxy(4-methoxyphenyl)methyl)phenol

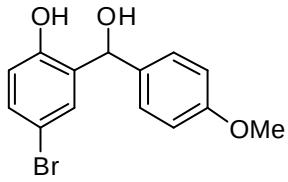


^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.71 (s, 1H), 7.35 – 7.27 (m, 2H), 7.21 (dd, *J* = 8.5, 2.5 Hz, 1H), 6.94 – 6.86 (m, 2H), 6.90 (s, 1H), 6.83 (d, *J* = 8.5 Hz, 1H), 5.95 (s, 1H), 3.80 (s, 3H), 1.23 (s, 9H).

^{13}C NMR (75 MHz, $CDCl_3$) δ = 159.5, 153.2, 142.7, 134.4, 128.3, 126.2, 126.0, 125.2, 116.9, 114.2, 77.35, 55.43, 34.14, 31.62.

HR-MS (ESI): calc. for: ([M+Na]+): 309.1467; found: 309.1461.

4-Bromo-2-(hydroxy(4-methoxyphenyl)methyl)phenol



^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.09 (s, 1H), 7.35 – 7.22 (m, 3H), 6.98 – 6.86 (m, 2H), 6.91 (d, *J* = 8.8 Hz, 1H), 6.79 (d, *J* = 8.6 Hz, 1H), 5.94 (d, *J* = 2.9 Hz, 1H), 3.82 (s, 2H), 2.72 (d, *J* = 2.9 Hz, 1H).

^{13}C NMR (75 MHz, $CDCl_3$) δ = 159.9, 154.8, 133.6, 132.0, 130.8, 128.8, 128.4, 119.2, 114.4, 111.9, 77.6, 77.1, 76.7, 76.4, 55.5.

HR-MS (ESI): calc. for: ([M+Na]+): 330.9946; found: 330.9940.

III - Experimental Procedures and Characterizations of the Chromenes

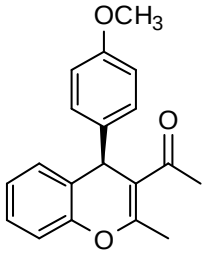
General methodology for the optimization of the reaction condition

The alcohol **1** (46 mg, 0.2 mmol, 1.0 equiv) and chiral phosphoric acid (0.04 mmol, 20 mol %) were dissolved in 1 mL of solvent at RT. Then acetylacetone **2a** (42 µl, 0.4 mmol, 2 equiv) was added in one portion, whereupon the reaction mixture was stirred for 24 h at RT. The crude reaction mixture was purified by short flash chromatography (SiO_2, ethyl acetate:hexane 1:3) to afford the substituted product **4**. The enantiomeric ratio was determined by HPLC on a chiral stationary phase (Daicel Chiralcel OD column, hexane: *i*-propanol 95:5, 1ML/min at 220 nm).

General methodology for conjugate addition of acyclic 1,3-diketones.

The alcohol **1** (0.2 mmol, 1.0 equiv) and the catalyst **(*R*)-3e** (6.7 mg, 0.01 mmol, 5 mol %) were dissolved in 1 mL of chloroform at RT. Then 1,3-dicarbonyl compound (0.4 mmol, 2 equiv) was added in one portion, whereupon the reaction mixture was stirred for 24 h at RT. Then *p*-toluenesulphonic acid monohydrate (7.6 mg, 0.04 mmol, 20 mol %) was added and the reaction mixture was further stirred for another 2 h at 45 °C. The crude reaction mixture was purified by short flash chromatography (SiO_2, ethyl acetate:hexane 1:6 to 1:3) to afford the desired chromene. The enantiomeric ratio was determined by HPLC on a chiral stationary phase.

(*R*)-1-(4-(4-Methoxyphenyl)-2-methyl-4*H*-chromen-3-yl)ethanone



Yield 82%, ***er***: 88:12, $[\alpha]^{24}$ = –10 (c= 1.0, $CHCl_3$), **mp** = 52-55 ^oC

^{1}H NMR (400 MHz, $CDCl_3$) δ = δ 7.21 – 7.14 (m, 2H), 7.14 – 7.06 (m, 2H), 7.03 – 6.95 (m, 2H), 6.84 – 6.76 (m, 2H), 4.97 (s, 1H), 3.74 (s, 3H), 2.45 (s, 3H), 2.18 (s, 3H).

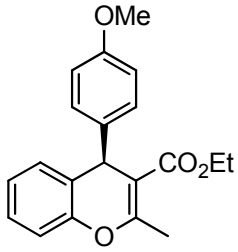
^{13}C NMR (100 MHz, $CDCl_3$) δ = 199.2, 158.9, 158.5, 149.1, 138.3, 129.0, 128.7, 127.6, 125.3, 124.6, 116.4, 114.4, 114.3, 55.3, 41.5, 30.2, 20.2.

IR (film, cm^{-1}): 3030, 2999, 2955, 2931, 2835, 1682, 1609, 1578, 1509, 1486, 1254, 1219, 1033, 938.

HR-MS (ESI): calc. for: ([M+Na]+): 317.1154; found:. 317.1148.

HPLC: ODH Column (95% hexane: 5% *i*-propanol, 1ml/min, 232 nm); minor enantiomer: t_R = 8.7 min and major enantiomer: t_R = 10.8 min.

(*R*)-Ethyl 4-(4-methoxyphenyl)-2-methyl-4*H*-chromene-3-carboxylate



Yield: 70%, ***er***: 89:11, **[α]** ^{24} = –8 (c= 1.0, $CHCl_3$), oil

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.18 – 7.09 (m, 3H), 7.06 – 6.95 (m, 3H), 6.80 – 6.73 (m, 2H), 4.97 (s, 1H), 4.21 – 3.98 (m, 2H), 3.74 (s, 3H), 2.48 (s, 3H), 1.20 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ = 167.39, 159.88, 158.24, 149.50, 139.29, 129.30, 128.93, 127.52, 125.25, 124.59, 116.30, 113.88, 106.49, 60.26, 55.33, 40.77, 40.74, 19.66, 14.31.

IR (film, cm^{-1}): 3062, 3030, 2979, 2931, 1710, 1644, 1585, 1509, 1255, 1218, 1064, 985.

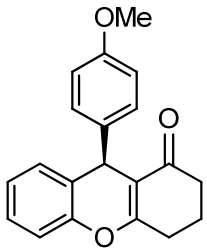
HR-MS (ESI): calc. for: ([M+Na]+): 347.1259; found: 347.1253.

HPLC: ODH Column (99% hexane: 1% *i*-propanol, 1ml/min, 270 nm); minor enantiomer: t_R = 8.1 min and major enantiomer: t_R = 9.1 min.

General methodology for conjugate addition of 1,3-cyclohexandione.

o-Hydroxybenzylic alcohol (0.2 mmol, 1.0 equiv) and catalyst **(*R*)-3e** (6.7 mg, 0.01 mmol, 5 mol %) were dissolved in 1.5 mL of chloroform at RT or 0 °C. Then 1,3-cyclohexanedione **2c** (27 mg, 0.24 mmol, 1.2 equiv) was added in one portion, whereupon the reaction mixture was stirred for 1-2 days at the same temperature. The crude reaction mixture was filtered over pad of silica gel (2 cm) using 25% of ethyl acetate in hexane to remove the water and the excess of the diketone. The solvents were removed in vacuo and the crude white solid was dissolved in 1 ml of chloroform. Then *p*-toluenesulphonic acid monohydrate (7.6 mg, 0.04 mmol, 20 mol %) was added and the reaction mixture was further stirred for 2 h at 45 °C. The crude reaction mixture was purified by short flash chromatography (SiO_2, ethyl acetate:hexane 1:6 to 1:3) to afford the desired chromene. The enantiomeric ratio was determined by HPLC on a chiral stationary phase.

(*R*)-9-(4-Methoxyphenyl)-2,3,4,9-tetrahydro-1*H*-xanthen-1-one



Yield: 95%, ***er***: 94.5:5.5, **[α]** ^{24} = –54 (c= 1.0, $CHCl_3$), **mp** = 113-116 ^{o}C.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.21 – 6.99 (m, 6H), 6.86 – 6.65 (m, 2H), 5.02 (s, 1H), 3.73 (s, 3H), 2.80 – 2.59 (m, 2H), 2.45-2.31 (m, 2H), 2.17 – 1.92 (m, 2H).

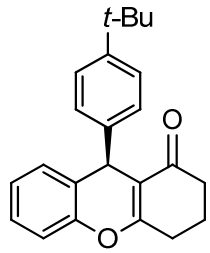
^{13}C NMR (100 MHz, $CDCl_3$) δ = 197.1, 166.1, 158.1, 149.5, 138.8, 130.1, 129.0, 127.62, 125.8, 125.1, 116.5, 115.1, 113.9, 55.27, 37.15, 37.03, 28.01, 20.53.

IR (KBr, cm^{-1}): 3031, 3013, 2953, 2899, 2835, 16.58, 1640, 1612, 1582, 1509, 1487, 1458, 1375, 1260, 1243, 1223, 1181, 1172, 1128, 1030, 996.

HR-MS (ESI): calc. for: ([M+Na]+): 329.1154; found: 329.1148.

HPLC: ODH Column (95% hexane: 5% *i*-propanol, 1ml/min, 270 nm); minor enantiomer: t_R = 15.1 min and major enantiomer: t_R = 18.6 min.

(*R*)-9-(4-(*Tert*-butyl)phenyl)-2,3,4,9-tetrahydro-1*H*-xanthen-1-one



Yield: 92%, ***er***: 95.5:4.5, **[α]** ^{24} = –42 (c= 1.0, $CHCl_3$), **mp** = 50-53 ^{o}C.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.24 – 7.20 (m, 2H), 7.20 – 7.10 (m, 4H), 7.10 – 7.00 (m, 2H), 5.05 (s, 1H), 2.82 – 2.55 (m, 2H), 2.52 – 2.24 (m, 2H), 2.16 – 1.90 (m, 2H), 1.25 (s, 9H).

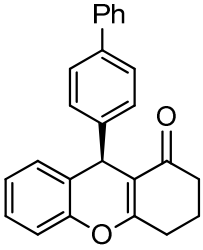
^{13}C NMR (100 MHz, $CDCl_3$) δ =197.2, 166.5, 149.8, 149.1, 143.3, 130.3, 127.69, 127.6, 125.9, 125.5, 125.2, 116.6, 115.2, 37.43, 37.25, 34.53, 31.56, 28.13, 20.60.

IR (KBr, cm^{-1}): 3044, 3026, 2960, 2901, 2868, 1663, 1646, 1639, 1613, 1581, 1485, 1456, 1375, 1236, 1177, 1132, 994.

HR-MS (ESI): calc. for: ([M+Na]+): 355.1674; found: 355,1668.

HPLC: ODH Column (95% hexane: 5% *i*-propanol, 1ml/min, 270 nm); minor enantiomer: t_R = 8.2 min and major enantiomer: t_R = 9.6 min.

(*R*)-9-([1,1'-Biphenyl]-4-yl)-2,3,4,9-tetrahydro-1*H*-xanthen-1-one.



Yield: 91%, ***er***: 94:6, **[α]** ^{24} **=** –8 (c= 1.0, $CHCl_3$). **mp** = 169-171 ^{o}C

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.51 (m, 2H), 7.48 – 7.43 (m, 2H), 7.41- 7.37 (m, 2H), 7.33 – 7.28 (m, 3H), 7.22 – 7.14 (m, 2H), 7.12 – 7.04 (m, 2H), 5.12 (s, 1H), 2.84 – 2.58 (m, 2H), 2.34 – 2.49 (m, 2H), 2.23 – 1.85 (m, 2H).

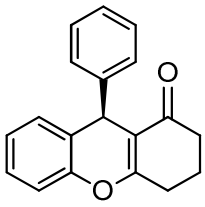
^{13}C NMR (100 MHz, CDCl3) δ = 197.2, 166.5, 149.6, 145.4, 141.1, 139.4, 130.2, 128.8, 128.4, 127.8, 127.3, 127.1, 125.4, 125.3, 116.6, 114.8, 37.61, 37.15, 28.05, 20.53.

IR (KBr, cm^{-1}): 3057, 3054, 3027, 2944, 2894, 1660, 1639, 1579, 1485, 1374, 1236, 1226, 1177, 1131, 996, 758.

HR-MS (ESI): calc. for: ([M+Na]+): 375.1361; found: 375.1356.

HPLC: ODH Column (95% hexane: 5% *i*-propanol, 1ml/min, 270 nm); minor enantiomer: t_R = 14.2 min and major enantiomer: t_R = 17.9 min.

(*R*)-9-Phenyl-2,3,4,9-tetrahydro-1*H*-xanthen-1-one



Yield: 94%, ***er***: 95:5, **[α]** ^{24} = –68 (c= 1.0, $CHCl_3$), **mp** = 130-131 ^{o}C.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25 – 6.99 (m, 9H), 5.23 (s, 1H), 2.81 – 2.58 (m, 2H), 2.51 – 2.28 (m, 2H), 2.15 – 1.88 (m, 2H).

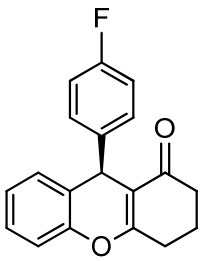
^{13}C NMR (100 MHz, $CDCl_3$) δ = 197.1, 166.3, 149.6, 146.3, 130.2, 128.5, 128.0, 127.7, 126.5, 125.5, 125.2, 116.6, 114.9, 37.93, 37.13, 28.03, 20.52.

IR (KBr, cm^{-1}): 3059, 3025, 2954, 2889, 2869, 1662, 1644, 1486, 1455, 1374, 1237, 1226, 1177, 1130, 996, 759.

HR-MS (ESI): calc. for: ([M+Na]+): 299.1048; found: 299.1043.

HPLC: ODH Column (95% hexane: 5% *i*-propanol, 1ml/min, 274 nm); minor enantiomer: t_R = 11 min and major enantiomer: t_R = 13,4 min.

(*R*)-9-(4-Fluorophenyl)-2,3,4,9-tetrahydro-1*H*-xanthen-1-one



Yield: 92%, ***er***: 98:2, **[α]** ^{24} = –73 (c= 0.41, $CHCl_3$), **mp** = 108-110 ^{o}C.

^{1}H NMR (400 MHz, $CDCl_3$) δ= 7.24 – 7.12 (m, 3H), 7.12 – 7.00 (m, 3H), 6.90 (t, *J* = 8.8 Hz, 2H), 5.05 (s, 1H), 2.86 – 2.50 (m, 2H), 2.50 – 2.22 (m, 2H), 2.21 – 1.83 (m, 2H).

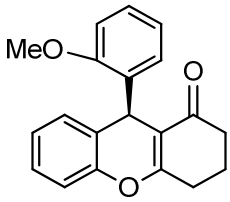
^{13}C NMR (100 MHz, $CDCl_3$) δ = 197.19, 166.45, 162.81, 160.38, 149.61, 142.26, 142.23, 130.21, 129.68, 129.60, 127.98, 125.35, 116.76, 115.48, 115.27, 114.89, 37.29, 37.20, 28.09, 20.60.

IR (KBr, cm^{-1}): 3071, 3042, 3015, 2960, 2936, 2893, 2876, 1656, 1600, 1580, 1506, 1375, 1237, 1177, 997, 845, 754.

HR-MS (ESI): calc. for: ([M+Na]+): 317.0954; found: 317.0948.

HPLC: ODH Column (95% hexane: 5% *i*-propanol, 1ml/min, 270 nm); minor enantiomer: t_R = 9.7 min and major enantiomer: t_R = 11.3 min.

(*R*)-9-(2-Methoxyphenyl)-2,3,4,9-tetrahydro-1*H*-xanthen-1-one



Yield: 97%, ***er***: 95.5:4.5, **[α]** ^{24} = –54 (c= 1.0, $CHCl_3$), **mp** = 113-116 ^{o}C.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.30 – 7.19 (m, 1H), 7.18 – 7.05 (m, 3H), 7.03 – 6.92 (m, 2H), 6.83 (m, 2H), 5.45 (s, 1H), 3.85 (s, 3H), 2.85 – 2.54 (m, 2H), 2.48 – 2.18 (m, 2H), 2.18 – 1.89 (m, 2H).

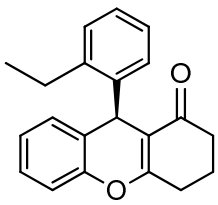
^{13}C NMR (100 MHz, $CDCl_3$) δ = 197.0, 167.1, 156.8, 149.6, 134.9, 129.9, 129.2, 127.8, 127.4, 126.0, 124.9, 121.0, 116.2, 113.9, 111.9, 56.09, 37.27, 32.04, 28.16, 20.83.

IR (KBr, cm^{-1}): 3014, 2951, 2894, 2832, 1667, 1644, 1579, 1491, 1456, 1375, 1253, 1235, 1222, 1178, 1134, 1025, 994, 769, 754.

HR-MS (ESI): calc. for: ([M+Na]+): 329.1154; found: 329.1148.

HPLC: ODH Column (95% hexane: 5% *i*-propanol, 1ml/min, 267 nm) minor enantiomer: t_R = 22.1 min and major enantiomer: t_R = 18.8 min.

(*R*)-9-(2-Ethylphenyl)-2,3,4,9-tetrahydro-1*H*-xanthen-1-one



Yield: 98%, ***er***: 96:4, **[α]** ^{24} = –78 (c= 1.0, $CHCl_3$), **mp** = 133-134 ^{o}C.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.22 – 6.90 (m, 8H), 5.33 (s, 1H), 3.16 (qd, *J* = 7.5, 4.2 Hz, 2H), 2.83 – 2.58 (m, 2H), 2.45 – 2.30 (m, 2H), 2.16 – 1.95 (m, 2H), 1.41 (t, *J* = 7.6 Hz, 3H).

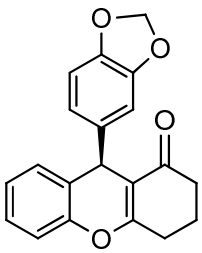
^{13}C NMR (100 MHz, $CDCl_3$) δ = 197.19, 166.34, 149.25, 144.74, 141.00, 129.95, 129.29, 128.54, 127.62, 126.53, 126.47, 126.37, 125.19, 116.74, 115.65, 37.27, 33.46, 28.19, 25.61, 20.65, 15.57.

IR (KBr, cm^{-1}): 2963, 2928, 2892, 2878, 2847, 1644, 1580, 1485, 1373, 1234, 1177, 1132, 994, 762.

HR-MS (ESI): calc. for: ([M+Na]+): 327.1361; found: 327.1356.

HPLC: ODH Column (95% hexane: 5% *i*-propanol, 1ml/min, 240 nm); minor enantiomer: t_R = 8 min and major enantiomer: t_R = 9.8 min.

(*R*)-9-(Benzo[d][1,3]dioxol-5-yl)-2,3,4,9-tetrahydro-1*H*-xanthen-1-one



Yield: 92%, ***er***: 95:5, **[α]** ^{24} = –44 (c= 1.0, $CHCl_3$), **mp** = 121-124 ^{o}C.

^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.22 – 6.98 (m, 4H), 6.75 (dd, *J* = 8.1, 1.7 Hz, 1H), 6.71 – 6.62 (m, 2H), 5.89 – 5.80 (m, 2H), 4.98 (s, 1H), 2.82 – 2.56 (m, 2H), 2.52 – 2.23 (m, 2H), 2.17 – 1.83 (m, 2H).

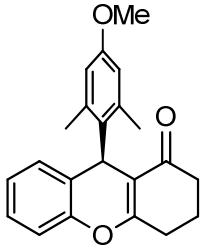
^{13}C NMR (75 MHz, $CDCl_3$) δ = 197.2, 166.3, 149.4, 147.8, 146.1, 140.5, 130.0, 127.8, 125.54, 125.18, 121.13, 116.63, 108.52, 108.18, 100.96, 37.56, 37.14, 28.01, 20.53.

IR (KBr, cm^{-1}): 2952, 2928, 2889, 1664, 1645, 1580, 1500, 1484, 1375, 1234, 1182, 1138, 1039, 996, 929, 761.

HR-MS (ESI): calc. for: ([M+Na]+): 343.0946; found: 343.0941.

HPLC (for the substituted intermediate) : ODH Column (80% hexane: 20% *i*-propanol, 1ml/min, 270 nm); minor enantiomer: t_R = 9.7 min and major enantiomer: t_R = 16.8 min.

(*R*)-9-(4-Methoxy-2,6-dimethylphenyl)-2,3,4,9-tetrahydro-1*H*-xanthen-1-one



Yield: 85%, ***er***: 94.5:5.5, **[α]** ^{24} = +12 (c= 1.0, $CHCl_3$), **mp** = 171-173 ^{o}C.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.18 – 7.05 (m, 1H), 6.95 (t, *J* = 7.8 Hz, 2H), 6.90 – 6.82 (m, 1H), 6.64 (d, *J* = 2.5 Hz, 1H), 6.38 (d, *J* = 2.5 Hz, 1H), 5.47 (s, 1H), 2.77 (s, 3H), 2.72 – 2.55 (m, 2H), 2.43 – 2.28 (m, 2H), 2.19 – 1.99 (m, 2H), 1.97 (s, 3H).

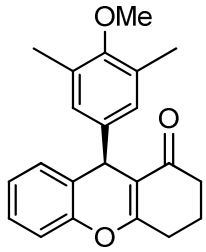
^{13}C NMR (100 MHz, $CDCl_3$) δ = 197.2, 166.0, 157.5, 149.4, 138.9, 138.1, 134.0, 129.4, 127.6, 124.9, 124.7, 115.8, 115.5, 113.5, 113.3, 54.98, 37.33, 32.26, 28.03, 22.35, 20.68, 19.70.

IR (KBr, cm^{-1}): 2938, 2869, 2832, 1660, 1644, 1603, 1580, 1485, 1455, 1370, 1230, 1186, 1063, 997, 861, 846, 757.

HR-MS (ESI): calc. for: ([M+Na]+): 357.1467; found: 357.1461.

HPLC: ODH Column (95% hexane: 5% *i*-propanol, 1ml/min, 270 nm); minor enantiomer: t_R = 10.8 min and major enantiomer: t_R = 13.1 min.

(*R*)-9-(4-Methoxy-3,5-dimethylphenyl)-2,3,4,9-tetrahydro-1*H*-xanthen-1-one



Yield: 97%, ***er***: 95:5, **[α]** ^{24} = –52 (c= 1.0, $CHCl_3$), **mp** = 61-63 ^{o}C.

^{1}H NMR (400 MHz, $CDCl_3$) δ =7.22 – 6.95 (m, 4H), 6.83 (s, 2H), 4.93 (s, 1H), 3.63 (s, 3H), 2.79 – 2.60 (m, 2H), 2.46 – 2.31 (m, 2H), 2.19 (s, 6H), 1.98 – 2.10 (m, 2H).

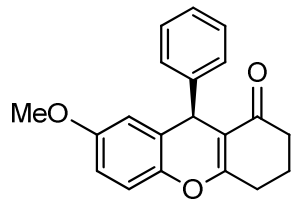
^{13}C NMR (100 MHz, $CDCl_3$) δ =197.2, 166.3, 155.5, 149.5, 141.5, 130.6, 130.1, 128.2, 127.6, 125.9, 125.1, 116.6, 115.0, 59.63, 37.32, 37.17, 28.05, 20.54, 16.35.

IR (KBr, cm^{-1}): 3028, 2948, 2897, 2870, 2824, 1662, 1644, 1581, 1485,1456, 1375, 1235, 1225, 1181, 1127, 1016, 995, 911, 757, 732.

HR-MS (ESI): calc. for: ([M+Na]+): 357.1467; found: 357.1461.

HPLC: ODH Column (95% hexane: 5% *i*-propanol, 1ml/min, 270 nm) minor enantiomer: t_R = 10.2 min and major enantiomer: t_R = 12.1 min.

(*R*)-7-Methoxy-9-phenyl-2,3,4,9-tetrahydro-1*H*-xanthen-1-one



Yield: 93%, ***er***: 98:2, **[α]** ^{24} = –132 (c= 1.0, $CHCl_3$), **mp** = 102-105 ^{o}C.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.24 – 7.17 (m, 4H), 7.16 – 7.06 (m, 1H), 7.02 (d, *J* = 8.9 Hz, 1H), 6.72 (dd, *J* = 8.9, 3.0 Hz, 1H), 6.59 (d, *J* = 2.9 Hz, 1H), 5.02 (s, 1H), 3.69 (s, 3H), 2.79 – 2.50 (m, 2H), 2.49 – 2.20 (m, 2H), 2.11 – 1.83 (m, 2H).

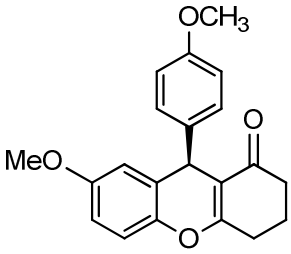
^{13}C NMR (100 MHz, $CDCl_3$) δ = 197.1, 166.5, 156.7, 146.2, 143.8, 128.5, 128.0, 126.5, 126.3, 117.4, 114.2, 114.0, 113.9, 55.68, 38.39, 37.13, 28.05, 20.53.

IR (KBr, cm^{-1}): 3061, 3032, 3013, 2956, 2945, 2926, 1659, 1639, 1587, 1491, 1374, 1216, 1197, 997, 835, 823, 702.

HR-MS (ESI): calc. for: ([M+Na]+): 329.1154; found: 329.1148.

HPLC: ODH Column (95% hexane: 5% *i*-propanol, 1ml/min, 274 nm); minor enantiomer: t_R = 13.5 min and major enantiomer: t_R = 15.1 min.

(*R*)-7-Methoxy-9-(4-methoxyphenyl)-2,3,4,9-tetrahydro-1*H*-xanthen-1-one



Yield: 97%, ***er***: 95.5:4.5, **[α]** ^{24} = +34 (c= 1.0, $CHCl_3$), **mp** = 149-147 ^{o}C.

^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.19 – 7.09 (m, 2H), 7.01 (d, *J* = 8.9 Hz, 1H), 6.71 (dd, *J* = 8.9, 2.9 Hz, 1H), 6.80 – 6.74 (m, 2H), 6.57 (d, *J* = 2.9 Hz, 1H), 4.98 (s, 1H), 3.69 (s, 3H), 3.73 (s, 3H), 2.66 (d, *J* = 4.7 Hz, 2H), 2.78 – 2.55 (m, 2H), 2.49 – 2.25 (m, 2H), 2.17 – 1.85 (m, 2H).

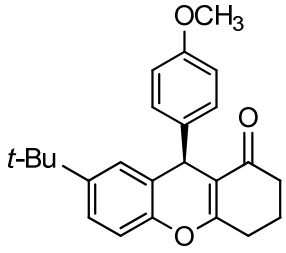
^{13}C NMR (75 MHz, $CDCl_3$) δ = 197.2, 166.3, 158.1, 156.7, 143.8, 138.6, 129.0, 126.6, 117.4, 114.4, 113.9, 113.8, 55.67, 55.28, 37.51, 37.15, 28.03, 20.54.

IR (KBr, cm^{-1}): 2954, 2946, 1659, 1639, 1511, 1496, 1377, 1256, 1222, 1197, 1028, 998, 832.

HR-MS (ESI): calc. for: ([M+Na]+): 359.1259; found: 359.1254.

HPLC: ODH Column (95% hexane: 5% *i*-propanol, 1ml/min, 274 nm)); minor enantiomer: t_R = 18 min and major enantiomer: t_R = 23.4 min.

(*R*)-7-(*t*ert-Butyl)-9-(4-methoxyphenyl)-2,3,4,9-tetrahydro-1*H*-xanthen-1-one



Yield: 97%, ***er***: 96:4, **[α]** ^{24} = +74 (c= 1.0, $CHCl_3$), **mp** = 119-122 ^{o}C.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.20 (dd, *J* = 8.6, 2.4 Hz, 1H), 7.16 – 7.11 (m, 2H), 7.09 (d, *J* = 2.3 Hz, 1H), 7.01 (d, *J* = 8.6 Hz, 1H), 6.80 – 6.70 (m, 2H), 5.02 (s, 1H), 3.74 (s, 3H), 2.78 – 2.53 (m, 2H), 2.49 – 2.23 (m, 2H), 2.13 – 1.84 (m, 2H), 1.23 (s, 9H).

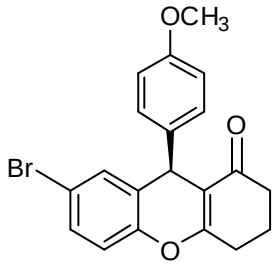
^{13}C NMR (100 MHz, $CDCl_3$) δ = 197.2, 166.5, 158.0, 148.1, 147.7, 138.8, 128.9, 126.6, 125.0, 124.8, 115.95, 115.29, 113.83, 55.27, 37.23, 37.17, 34.49, 31.48, 28.05, 20.54.

IR (KBr, cm^{-1}): 2960, 2903, 2869, 2831, 1660, 1641, 1587, 1509, 1498, 1376, 1256, 1175, 1132, 1034, 997, 828.

HR-MS (ESI): calc. for: ([M+Na]+): 385.1779; found: 385.1774.

HPLC: ODH Column (95% hexane: 5% *i*-propanol, 1ml/min, 220 nm); minor enantiomer: t_R = 8.7 min and major enantiomer: t_R = 10.5 min.

(*R*)-7-Bromo-9-(4-methoxyphenyl)-2,3,4,9-tetrahydro-1*H*-xanthen-1-one



Yield: 92%, ***er***: 95.5:4.5, **[α]** ^{24} = +82 (c= 1.0, $CHCl_3$), **mp** = 182-184 ^{o}C.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.26 (dd, *J* = 2.3, 8.8 Hz, 1H), 7.21 (d, *J* = 2.3 Hz, 1H), 7.19 – 7.05 (m, 2H), 6.95 (d, *J* = 8.7 Hz, 1H), 6.82 – 6.68 (m, 2H), 4.95 (s, 1H), 3.74 (s, 3H), 2.84 – 2.50 (m, 2H), 2.48 – 2.20 (m, 2H), 2.13 – 1.83 (m, 2H).

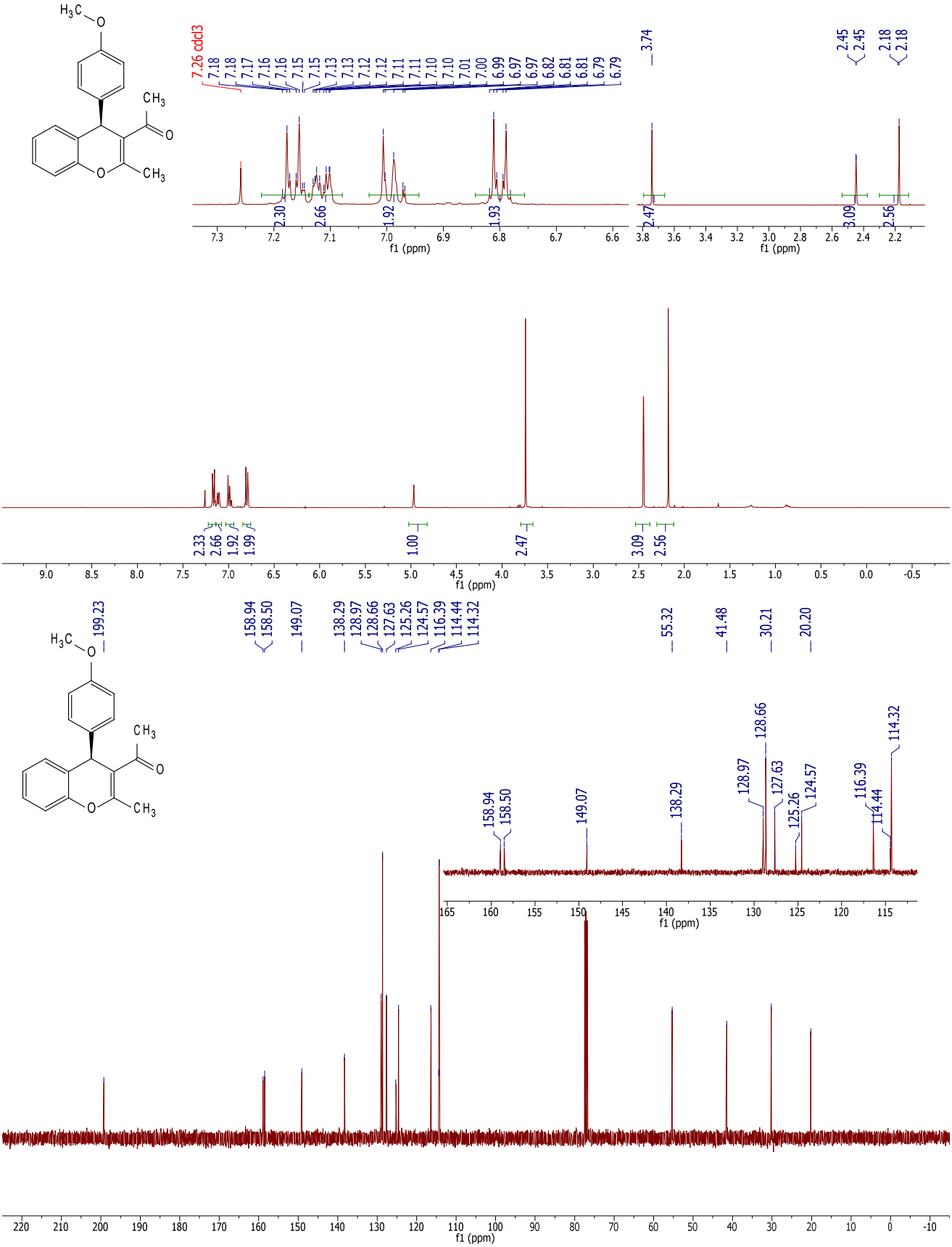
^{13}C NMR (100 MHz, $CDCl_3$) δ = 197.0, 165.9, 158.5, 148.7, 138.2, 132.9, 130.8, 129.1, 128.0, 118.5, 117.6, 114.9, 114.2, 55.41, 37.16, 37.15, 27.98, 20.56.

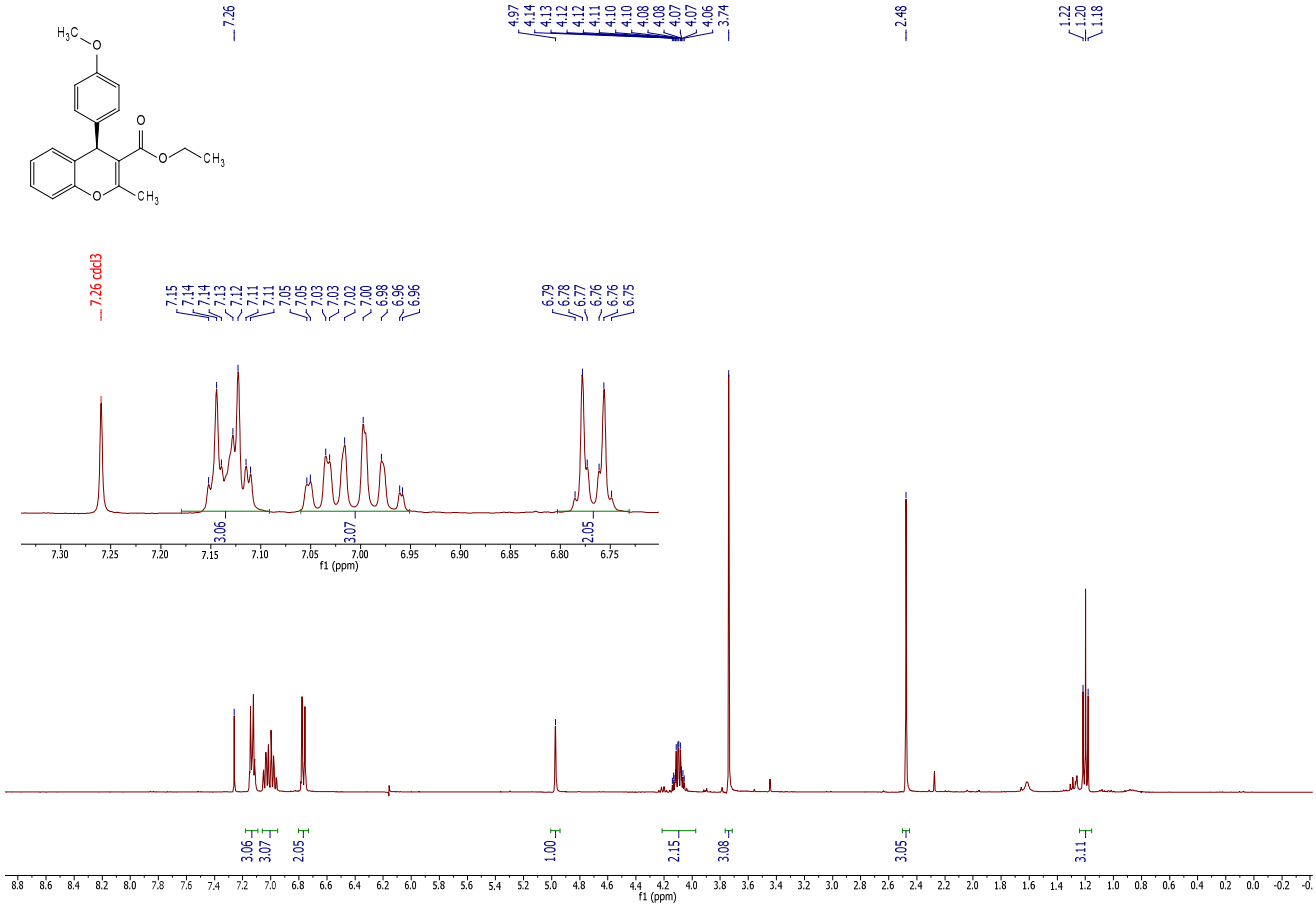
IR (KBr, cm^{-1}): 2948, 2934, 2890, 2876, 2834, 1663, 1645, 1611, 1509, 1375, 1256, 1237, 1176, 1129, 1027, 997, 831.

HR-MS (ESI): calc. for: ([M+Na]+): 407.0259; found: 407.0253.

HPLC: ODH Column (95% hexane: 5% *i*-propanol, 1ml/min, 270 nm); minor enantiomer: t_R = 14.7 min and major enantiomer: t_R = 20.6 min.

IV –NMR-Spectra

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4.12
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4.10
4.10
4.08
4.08
4.07
4.07
4.06
3.74
2.48
1.22
1.20
1.18
7.26 cdcl3
7.15
7.14
7.14
7.13
7.12
7.11
7.11
7.05
7.05
7.03
7.03
7.02
7.00
6.98
6.96
6.96
6.79
6.78
6.77
6.76
6.76
6.75
3.06
3.07
2.05
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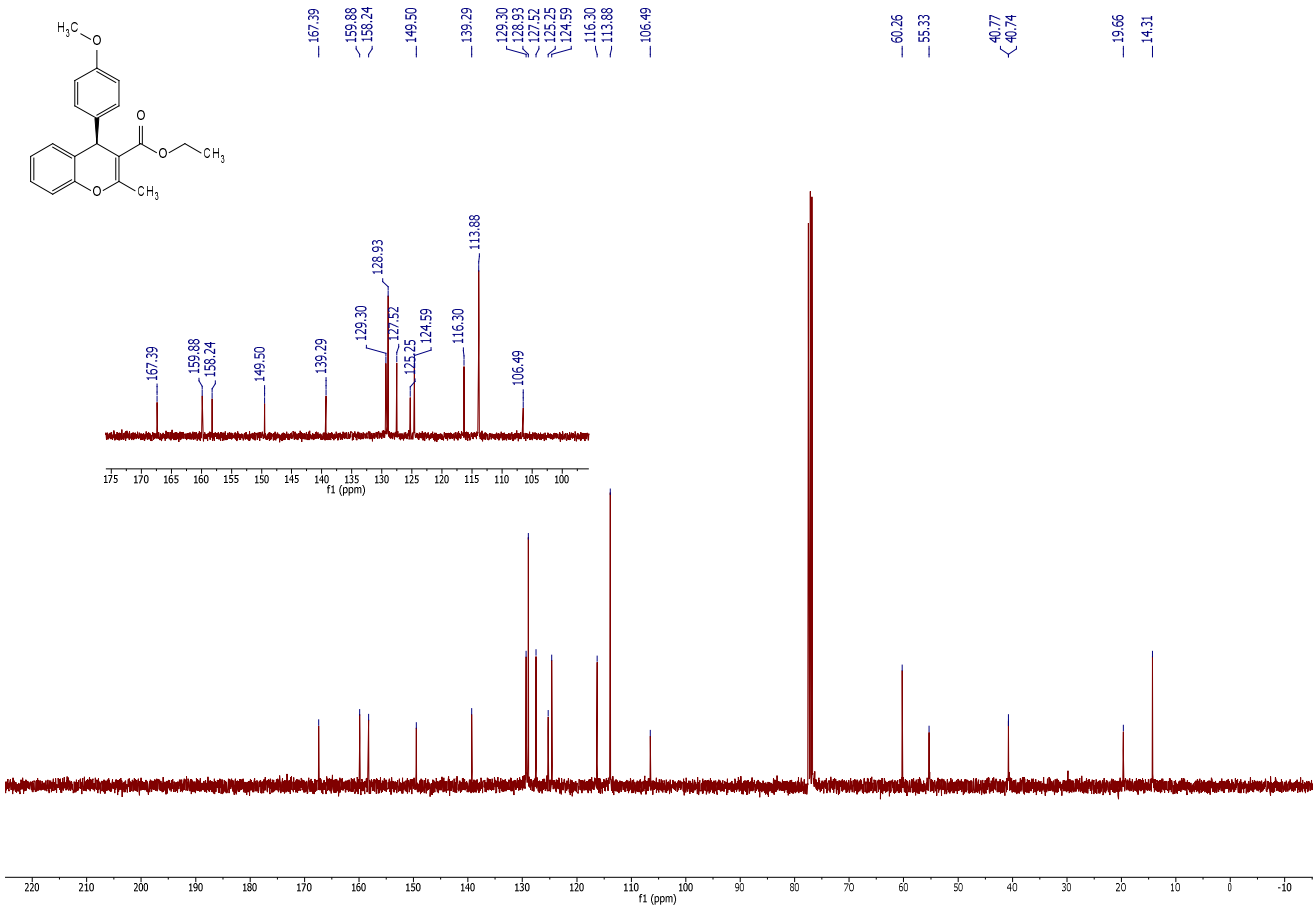
2.15
3.08
3.05
3.11
f1 (ppm)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158.24
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129.30
128.93
127.52
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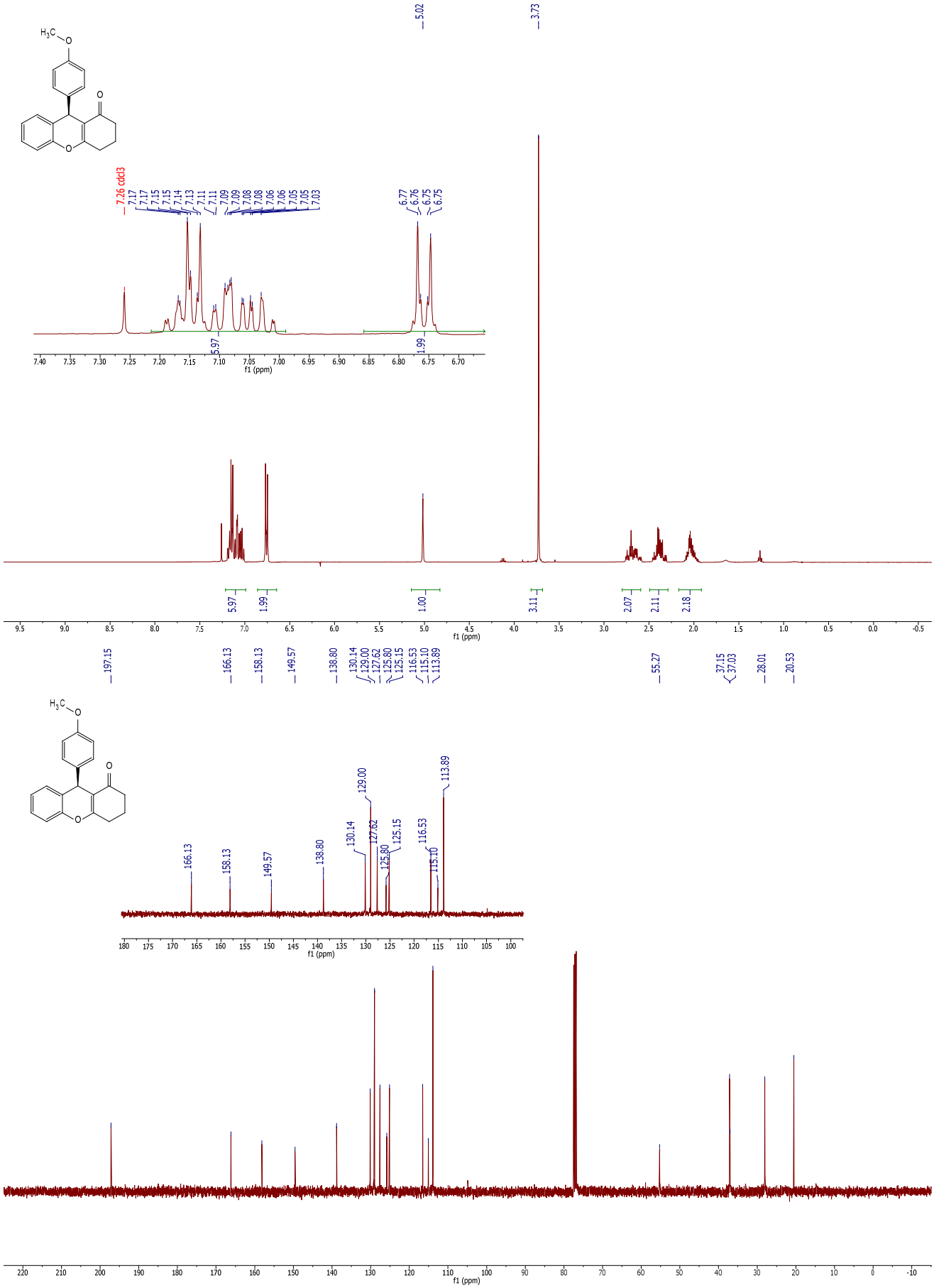
40.77
40.74
19.66
14.31
f1 (ppm)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O
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7.13
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7.06
7.06
7.05
7.05
7.03
6.77
6.76
6.75
6.75
5.97
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f1 (ppm)
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3.73
5.97
1.99
1.00
3.11
2.07
2.11
2.18
f1 (ppm)
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158.13
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129.00
127.62
125.80
125.15
116.53
115.10
113.89
55.27
37.15
37.03
28.01
20.53
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O
O
166.13
158.13
149.57
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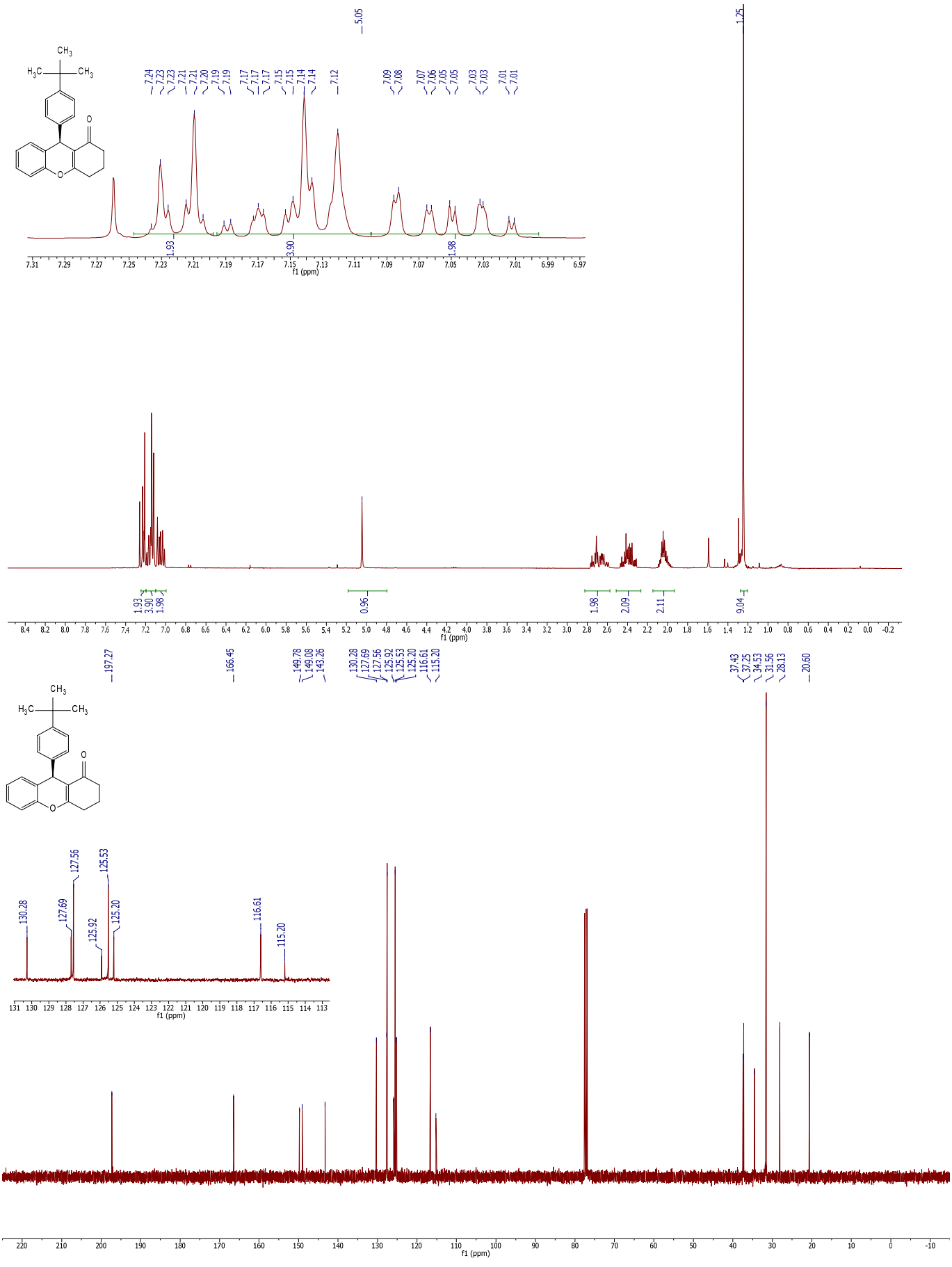
115.10
113.89
f1 (ppm)
f1 (ppm)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CH3
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7.17
7.17
7.17
7.15
7.15
7.14
7.14
7.12
7.09
7.08
7.07
7.06
7.05
7.05
7.03
7.03
7.01
7.01
5.05
1.25
1.93
3.90
1.98
f1 (ppm)
0.96
1.98
2.09
2.11
9.04
f1 (ppm)
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166.45
149.78
149.08
143.26
130.28
127.69
127.56
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125.53
125.20
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115.20
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37.25
34.53
31.56
28.13
20.60
CH3
H3C
CH3
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127.56
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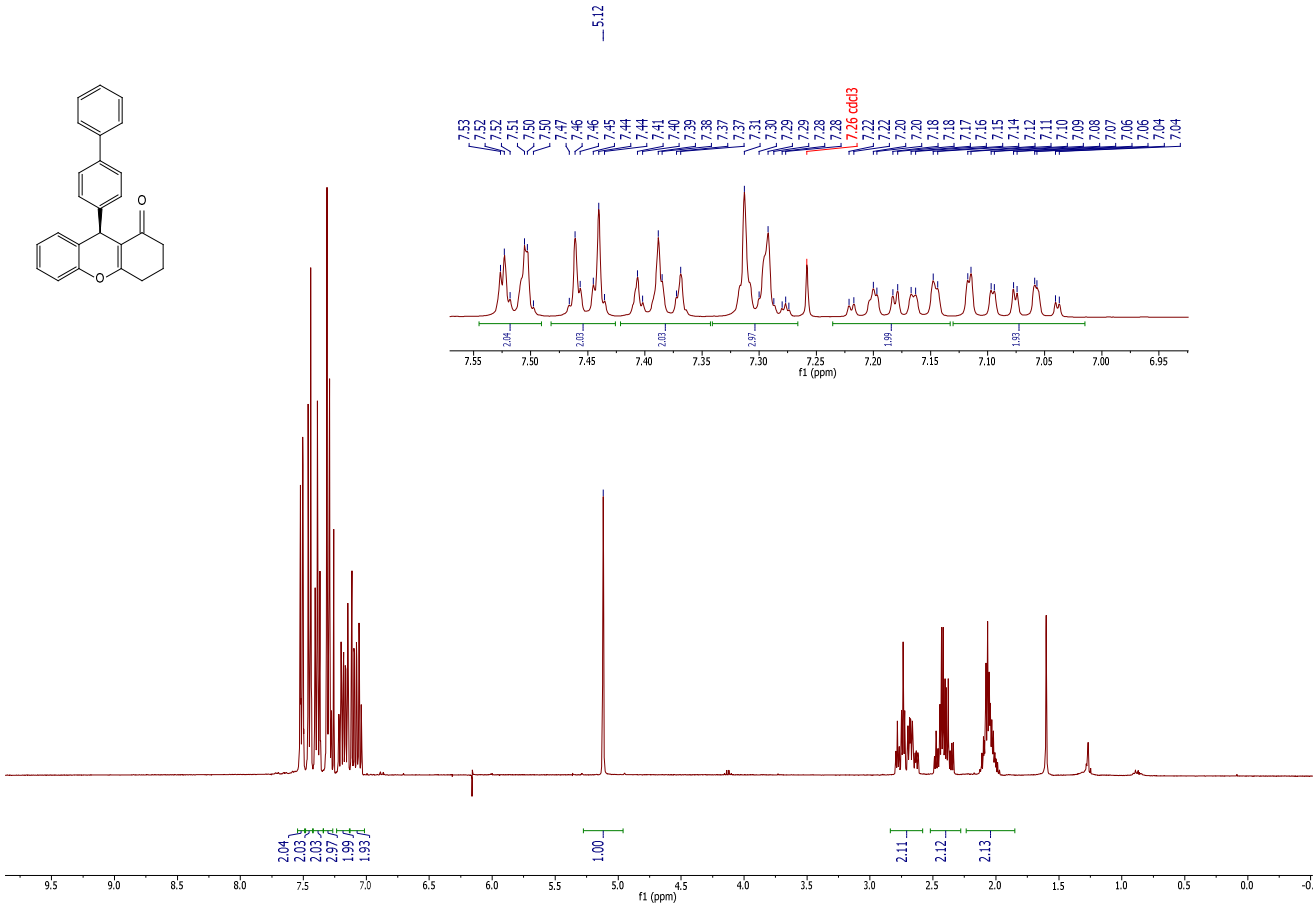
116.61
115.20
f1 (ppm)
f1 (ppm)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7.37
7.31
7.30
7.29
7.29
7.28
7.28
7.26 cdcl3
7.22
7.22
7.20
7.20
7.18
7.18
7.17
7.16
7.15
7.14
7.12
7.11
7.10
7.09
7.08
7.07
7.06
7.06
7.04
7.04
f1 (ppm)
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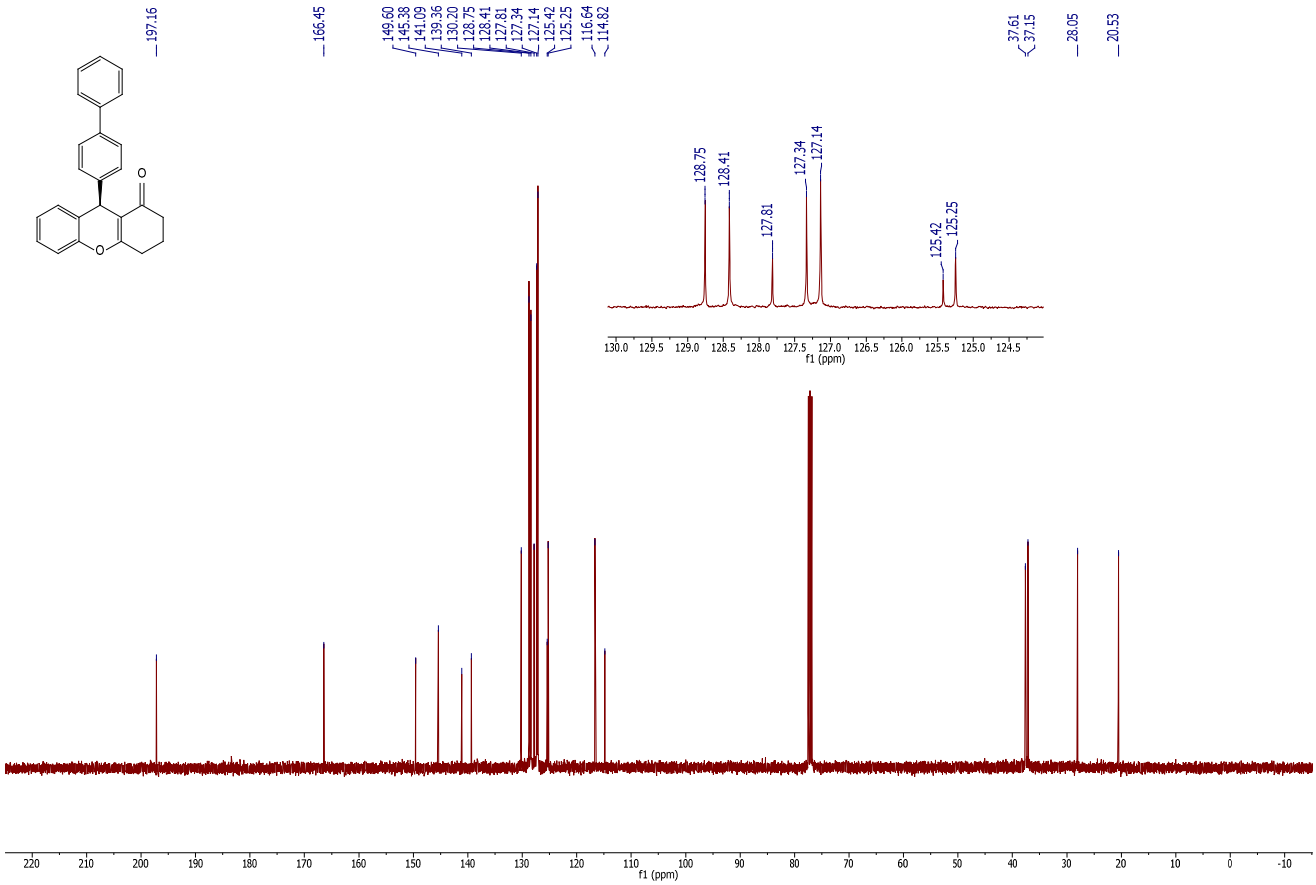
2.11
2.12
2.13
f1 (ppm)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125.42
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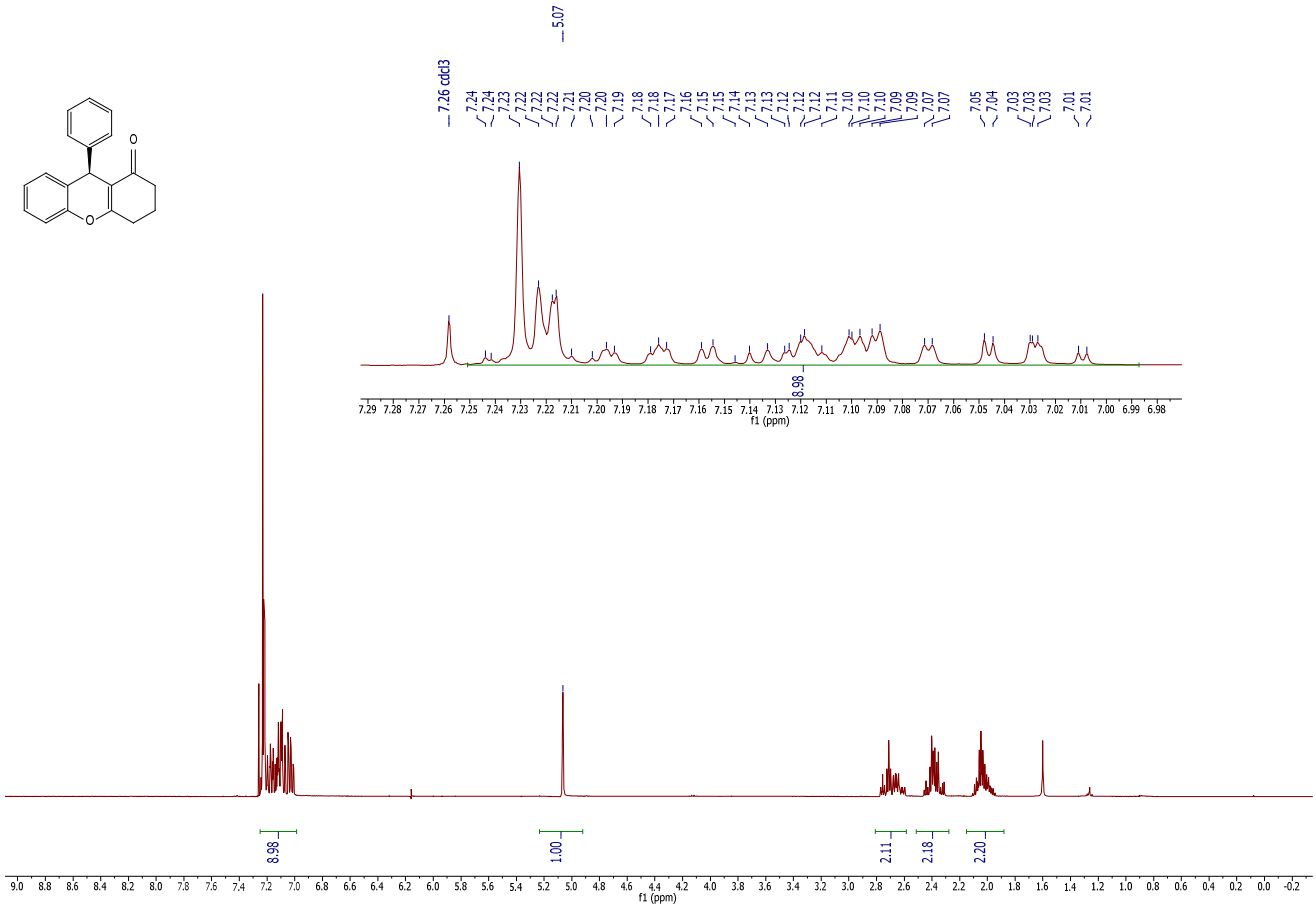
f1 (ppm)
f1 (ppm)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O
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7.24
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7.20
7.19
7.18
7.18
7.17
7.16
7.15
7.15
7.14
7.13
7.13
7.12
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7.12
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7.09
7.07
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7.03
7.03
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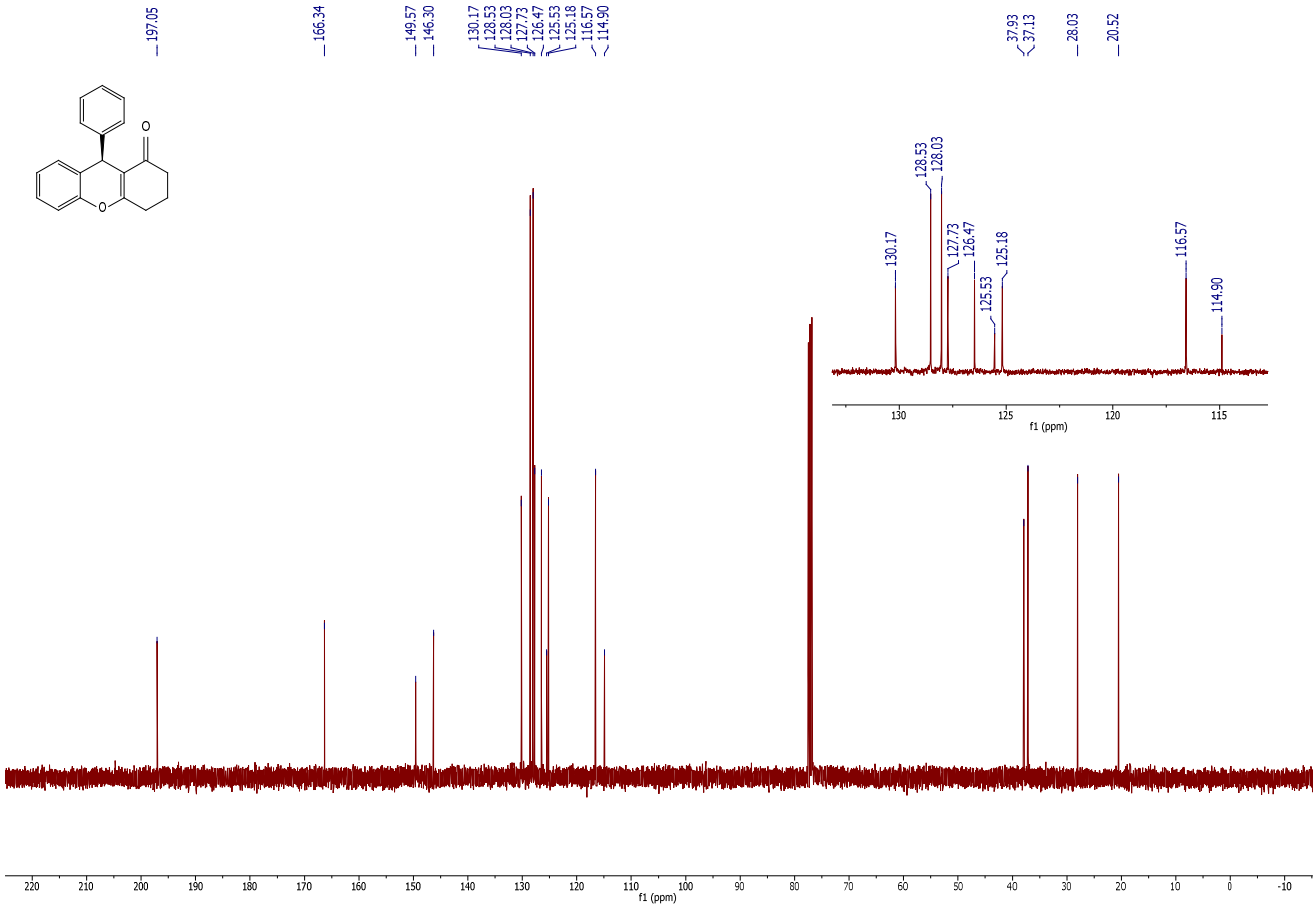
2.20
f1 (ppm)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128.03
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126.47
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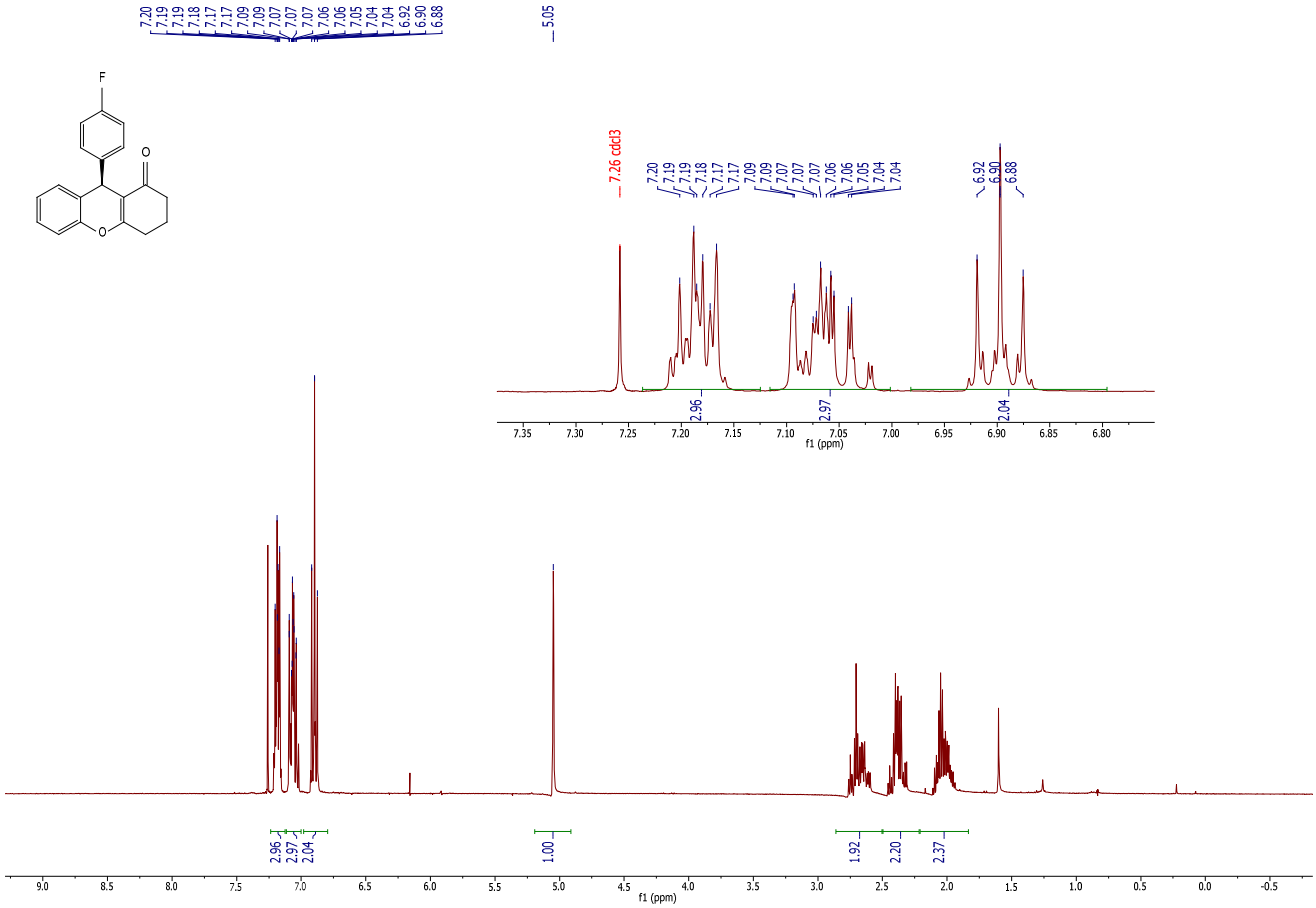
125.18
116.57
114.90
f1 (ppm)
f1 (ppm)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7.18
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7.17
7.09
7.09
7.07
7.07
7.07
7.06
7.06
7.05
7.04
7.04
6.92
6.90
6.88
5.05
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O
O
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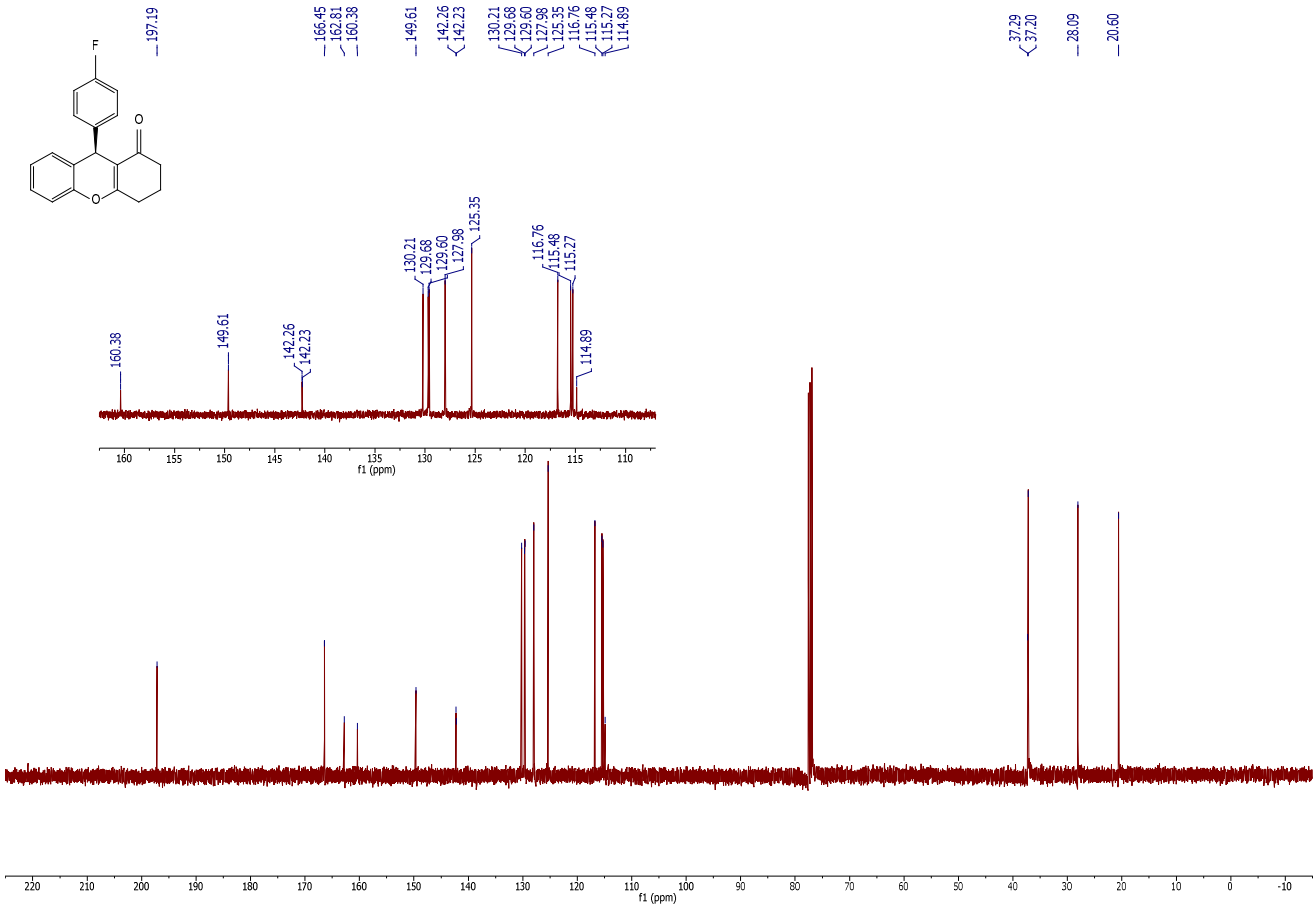
2.04
1.00
1.92
2.20
2.37
f1 (ppm)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129.60
127.98
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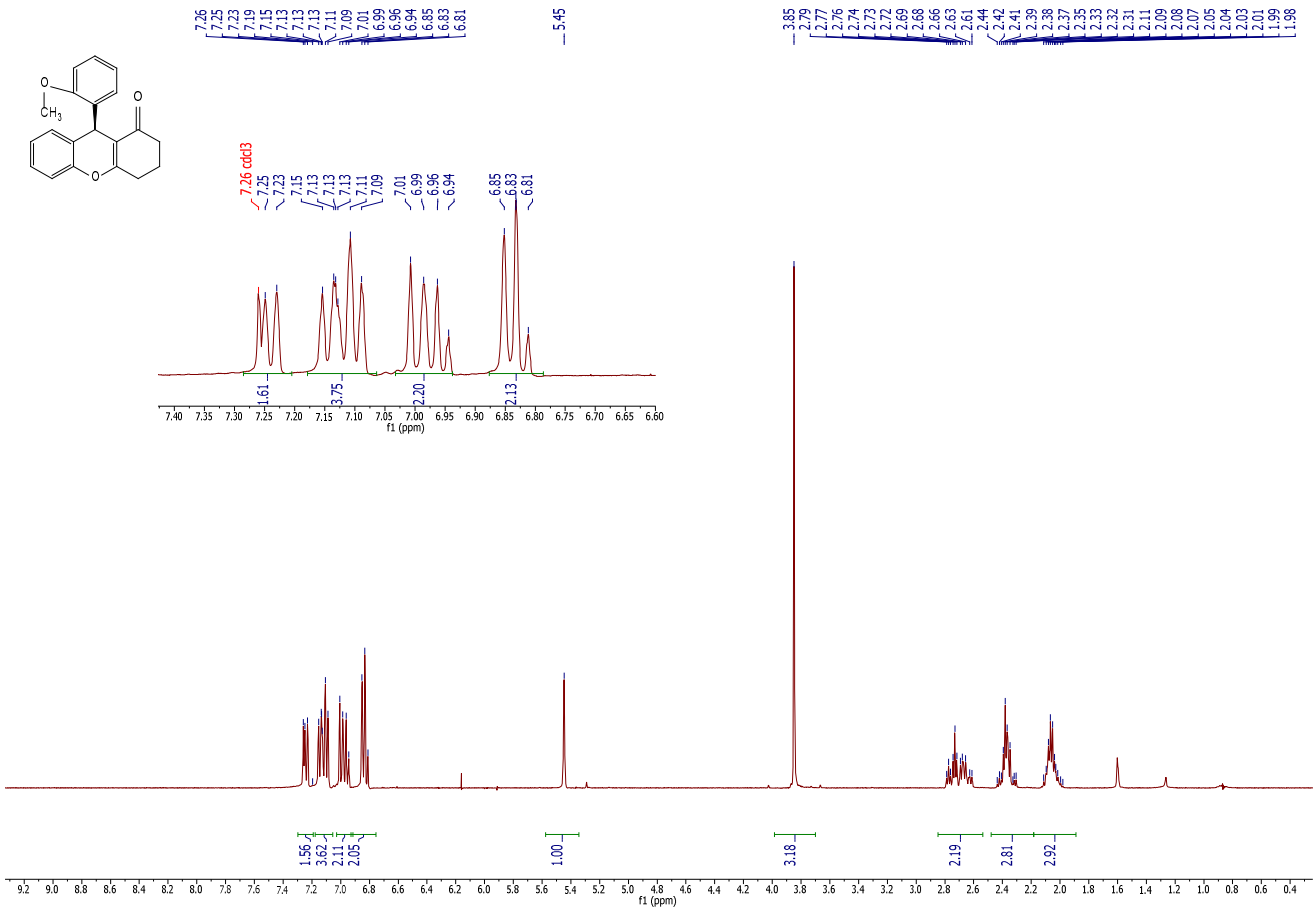
28.09
20.60
F
O
O
f1 (ppm)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5.45
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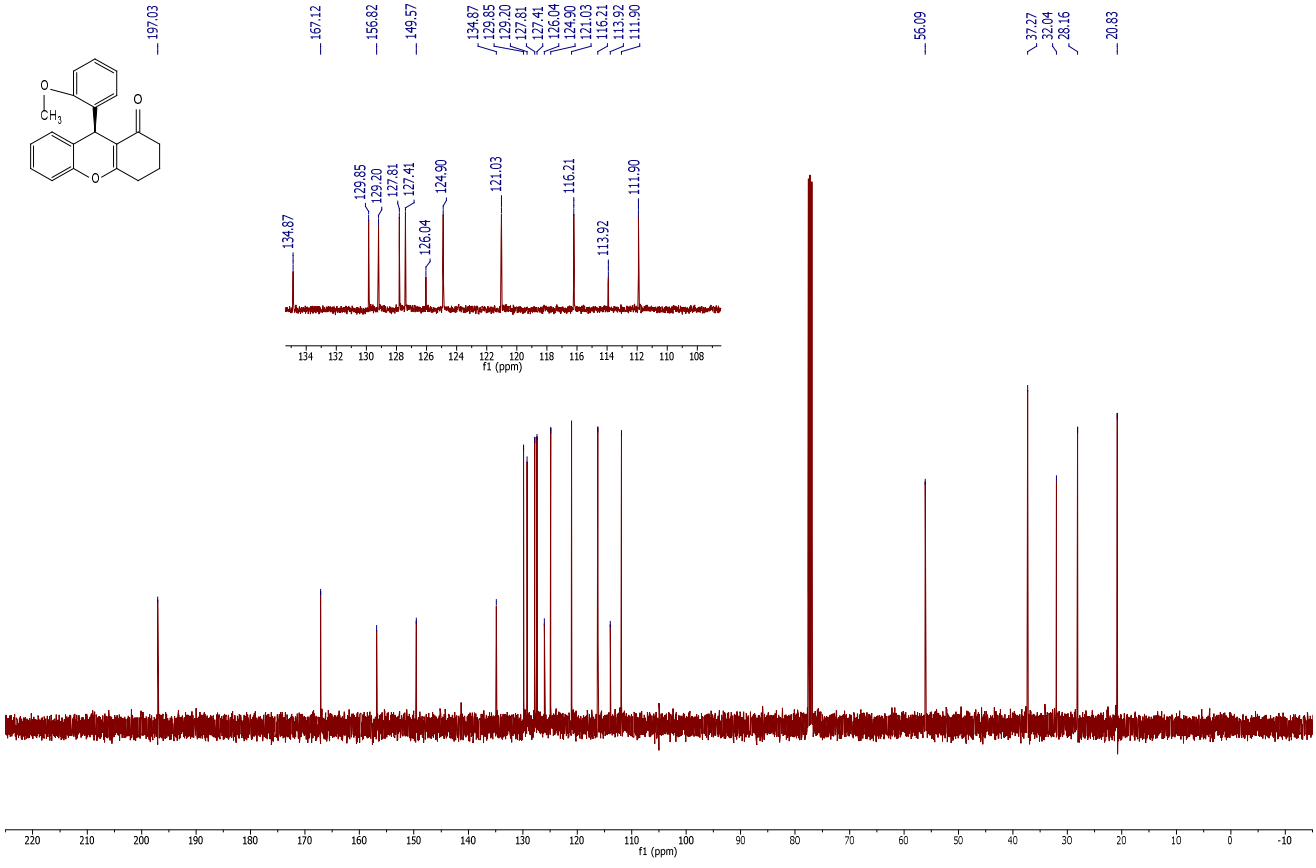
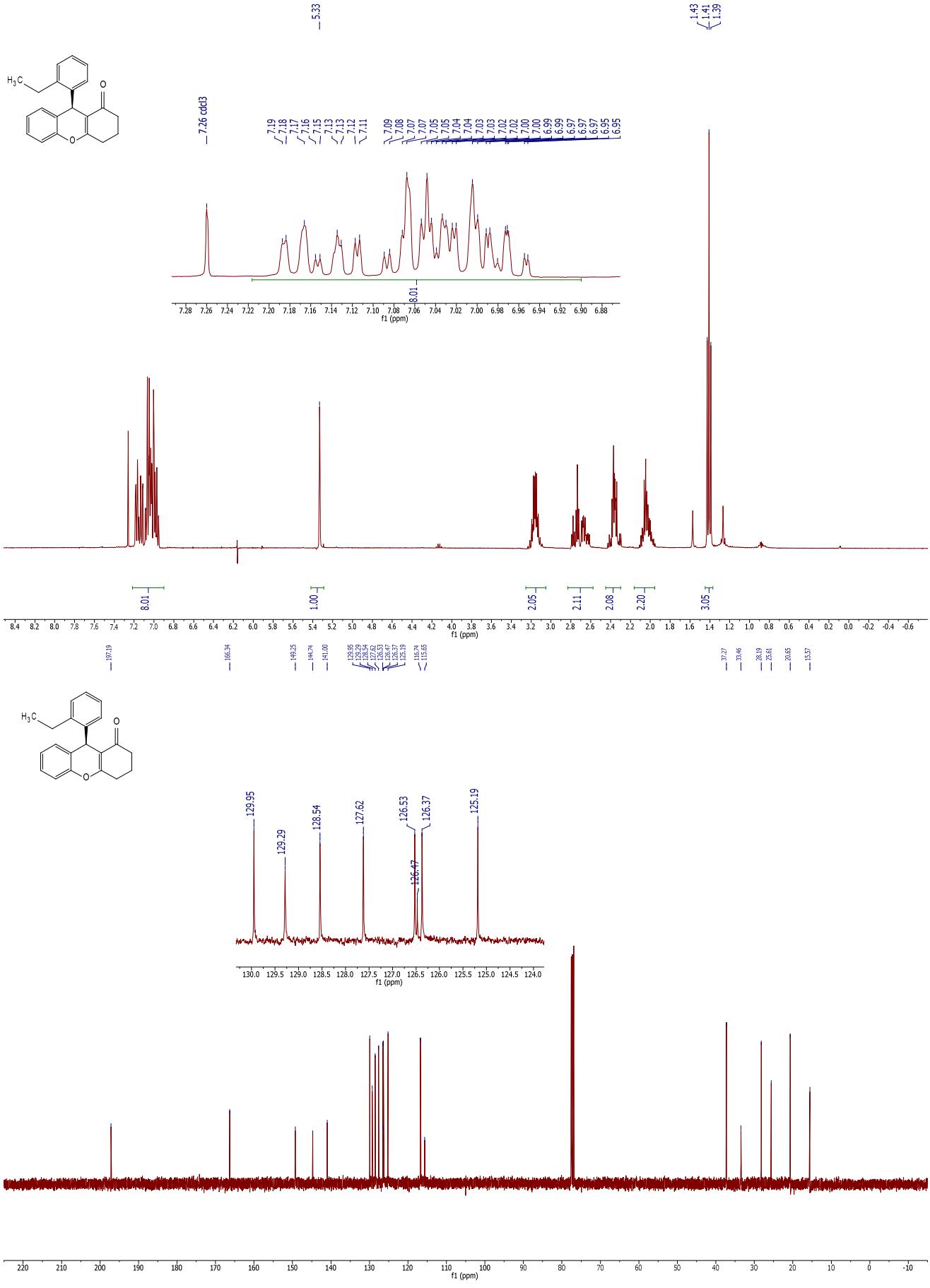
O
CH3
O
O
7.26 ddd3
7.25 7.23 7.15 7.13 7.13 7.13 7.11 7.09 7.01 6.99 6.96 6.94 6.85 6.83 6.81
1.61 3.75 2.20 2.13
f1 (ppm)
1.56 3.62 2.11 2.05 1.00 3.18 2.19 2.81 2.92
f1 (ppm)


197.03 167.12 156.82 149.57 134.87 129.85 129.20 127.81 127.41 126.04 124.90 121.03 116.21 113.92 111.90 56.09 37.27 32.04 28.16 20.83
O
CH3
O
O
134.87 129.85 129.20 127.81 127.41 126.04 124.90 121.03 116.21 113.92 111.90
f1 (ppm)
f1 (ppm)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O
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7.17
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7.15
7.13
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7.12
7.11
7.09
7.08
7.07
7.07
7.05
7.05
7.04
7.04
7.03
7.03
7.02
7.02
7.00
7.00
6.99
6.99
6.97
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6.95
6.95
5.33
1.43
1.41
1.39
8.01
f1 (ppm)
8.01
1.00
2.05
2.11
2.08
2.20
3.05
f1 (ppm)
197.19
166.34
149.25
144.74
141.00
129.95
129.29
128.54
127.62
126.53
126.37
125.19
116.74
115.65
37.27
33.46
28.19
25.61
20.85
15.57
H3C
O
O
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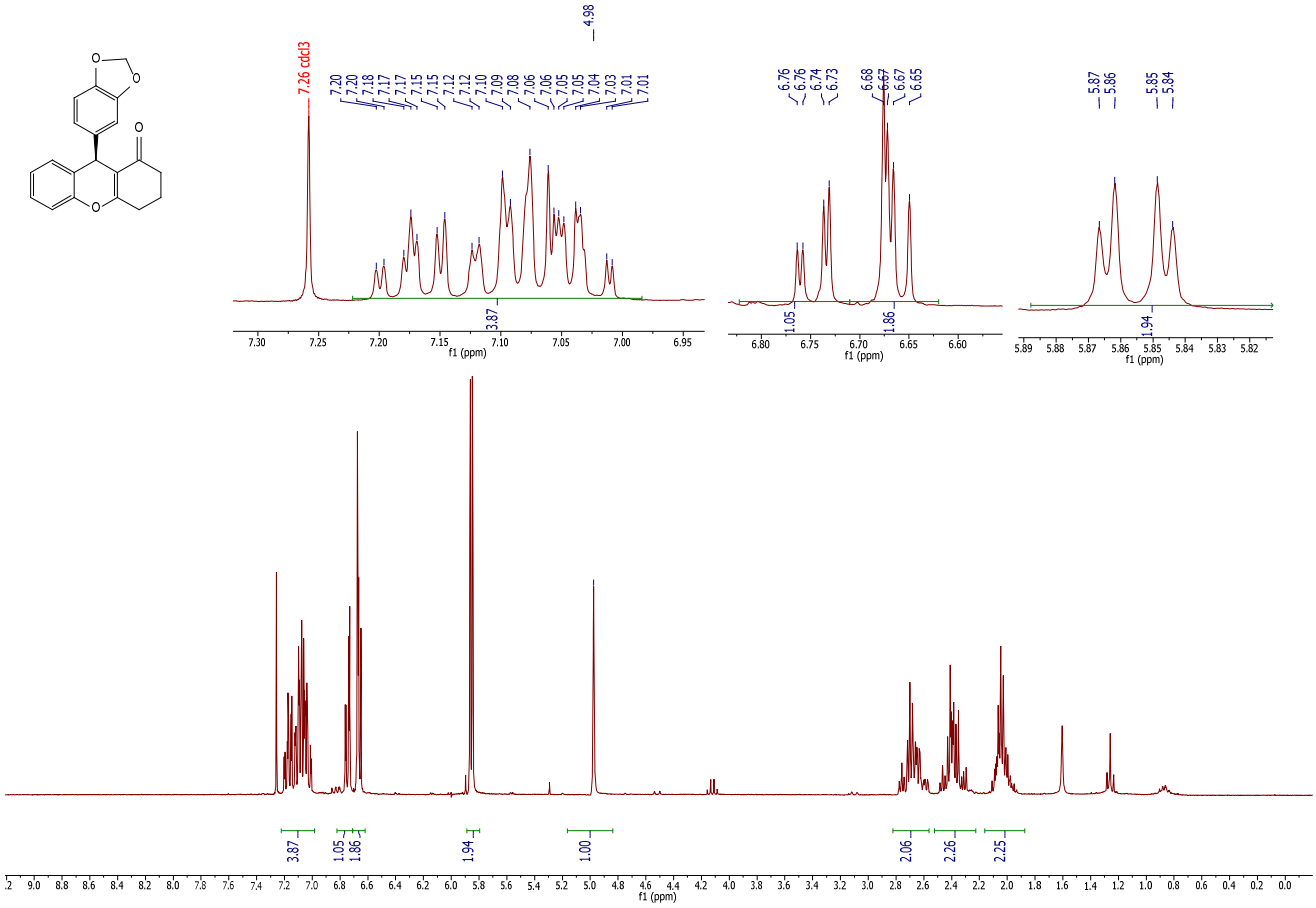
128.54
127.62
126.53
126.47
126.37
125.19
f1 (ppm)
f1 (ppm)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4.98
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1.86
1.94
f1 (ppm)
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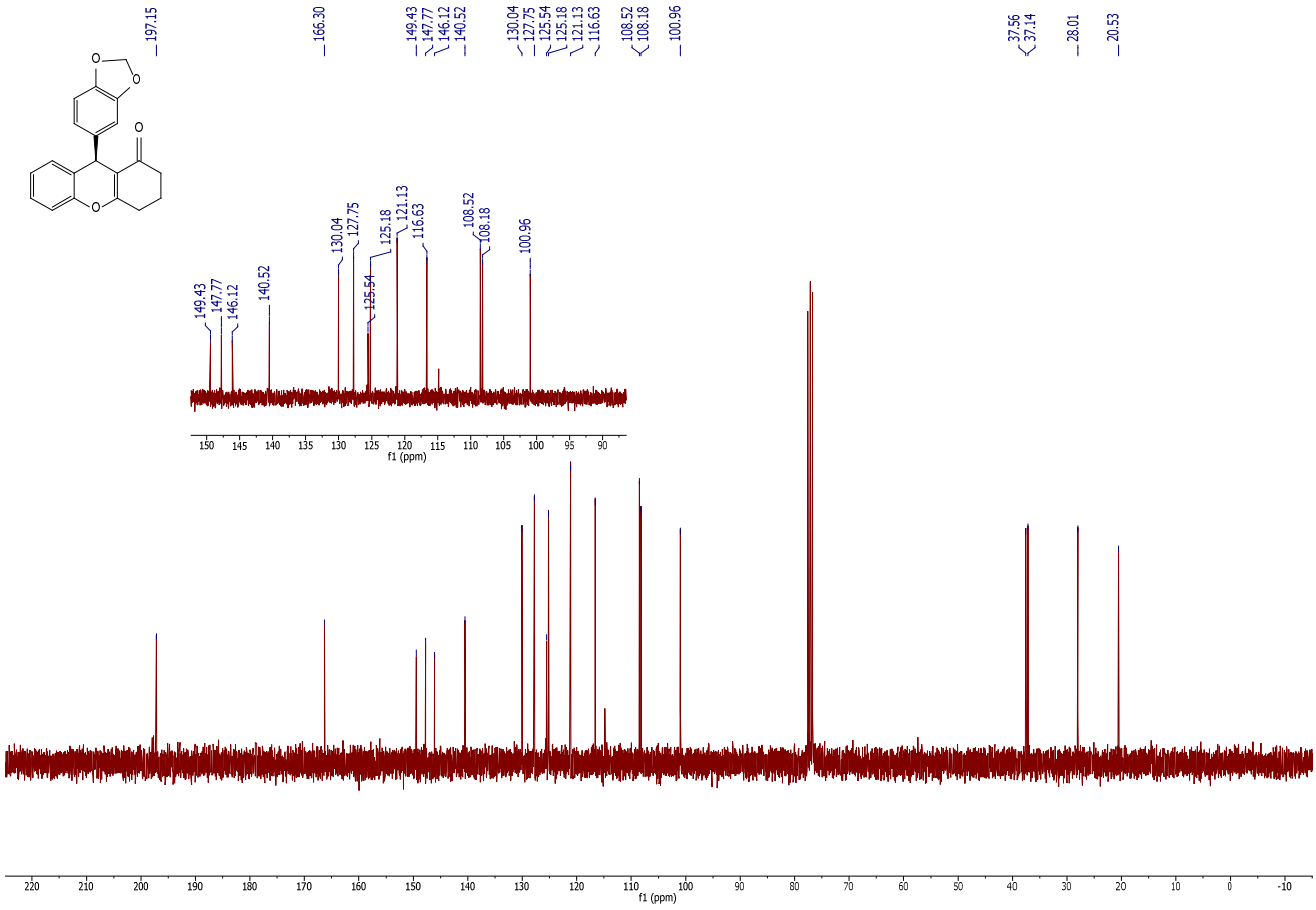
1.86
1.94
1.00
2.06
2.26
2.25
f1 (ppm)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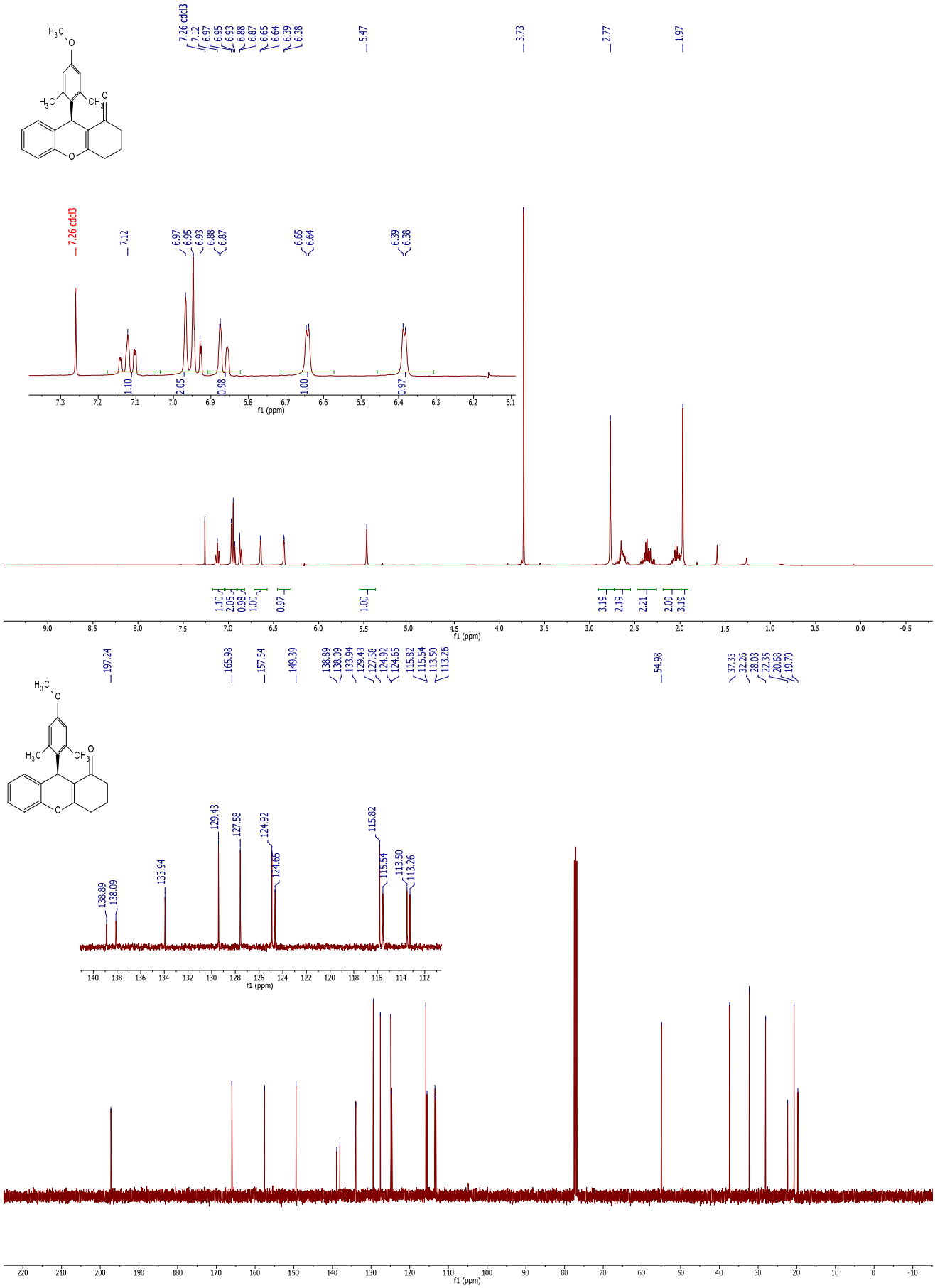
108.52
108.18
100.96
37.56
37.14
28.01
20.53
f1 (ppm)
f1 (ppm)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6.93
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6.87
6.65
6.64
6.39
6.38
5.47
3.73
2.77
1.97
f1 (ppm)

197.24
165.98
157.54
149.39
138.89
138.09
133.94
129.43
127.58
124.92
124.65
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115.54
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113.26
54.98
37.33
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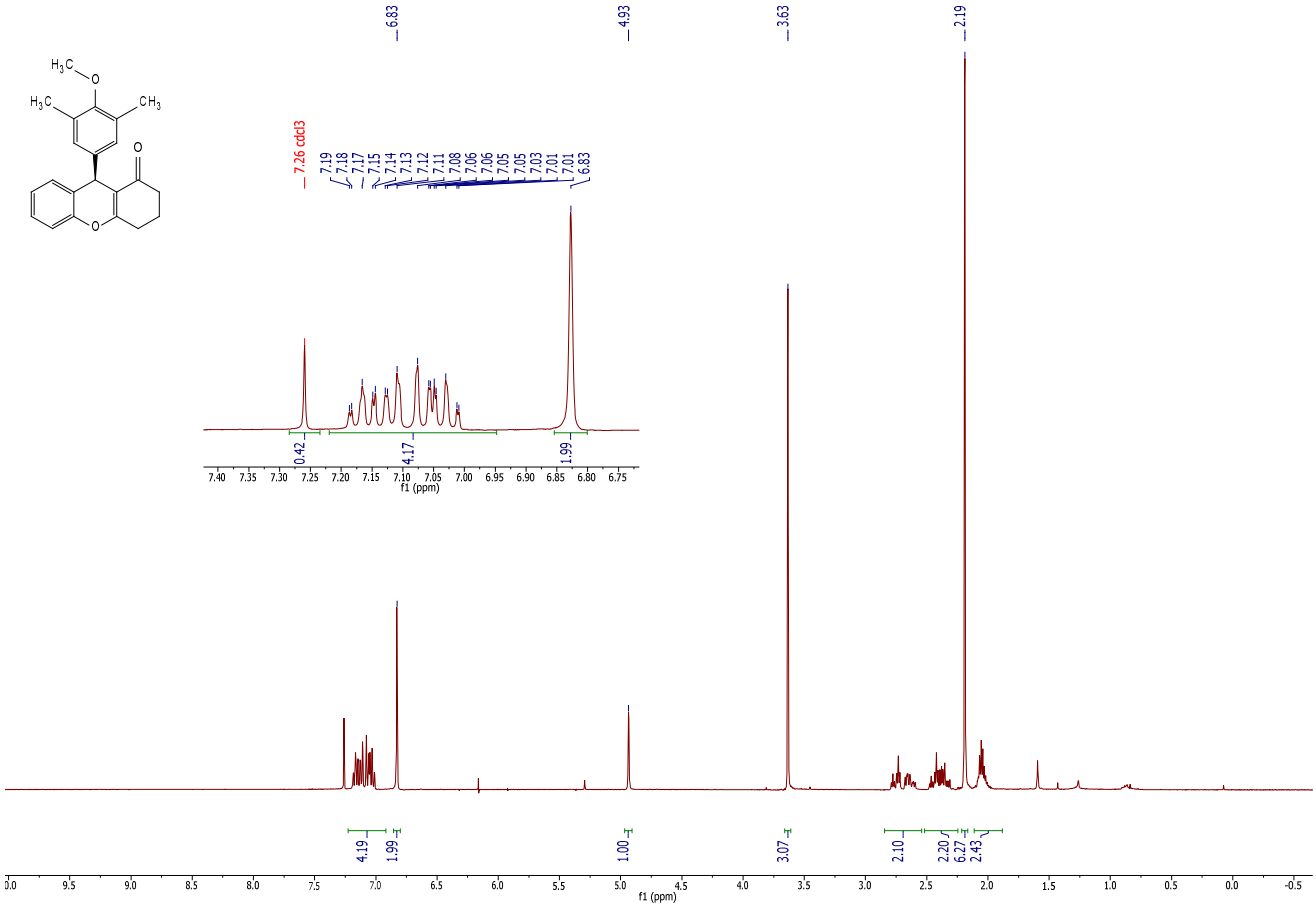
28.03
22.35
20.68
19.70
f1 (ppm)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7.17
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7.13
7.12
7.11
7.08
7.06
7.06
7.05
7.05
7.03
7.01
7.01
6.83
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4.17
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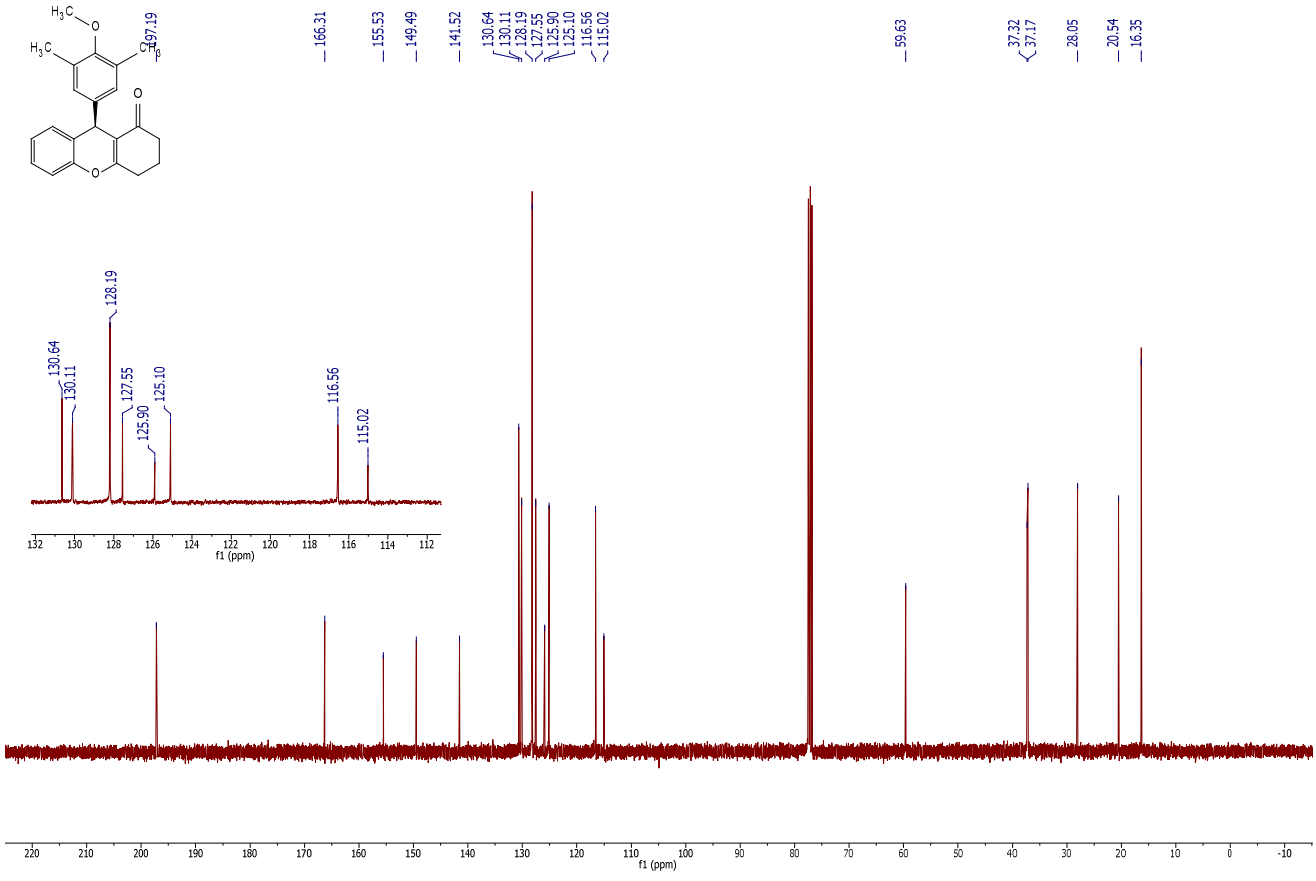
2.10
2.20
6.27
2.43
f1 (ppm)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125.10
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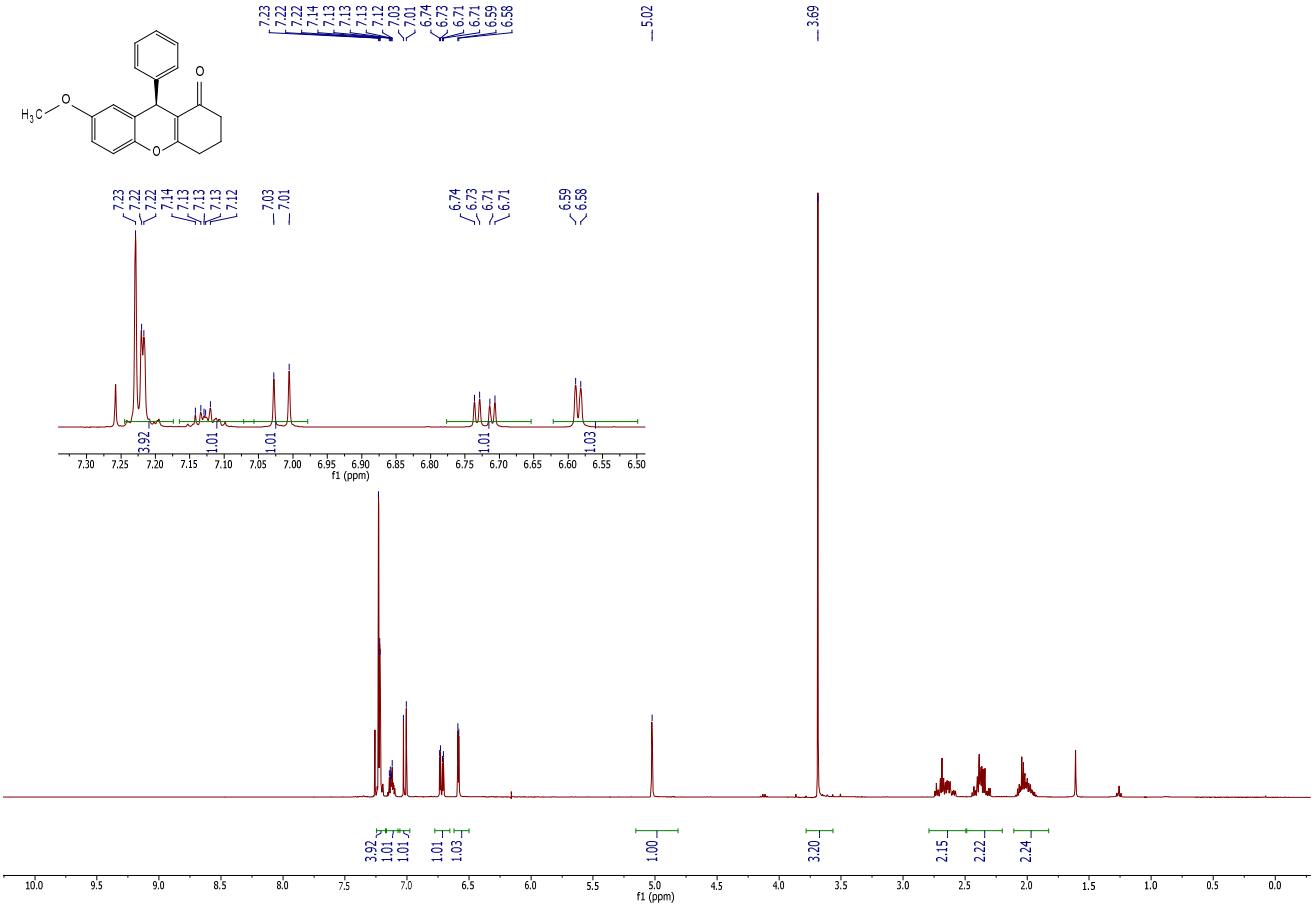
37.17
28.05
20.54
16.35
f1 (ppm)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7.13
7.13
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7.01
6.74
6.73
6.71
6.71
6.59
6.58
5.02
3.69
O
H3C
O
O
3.92
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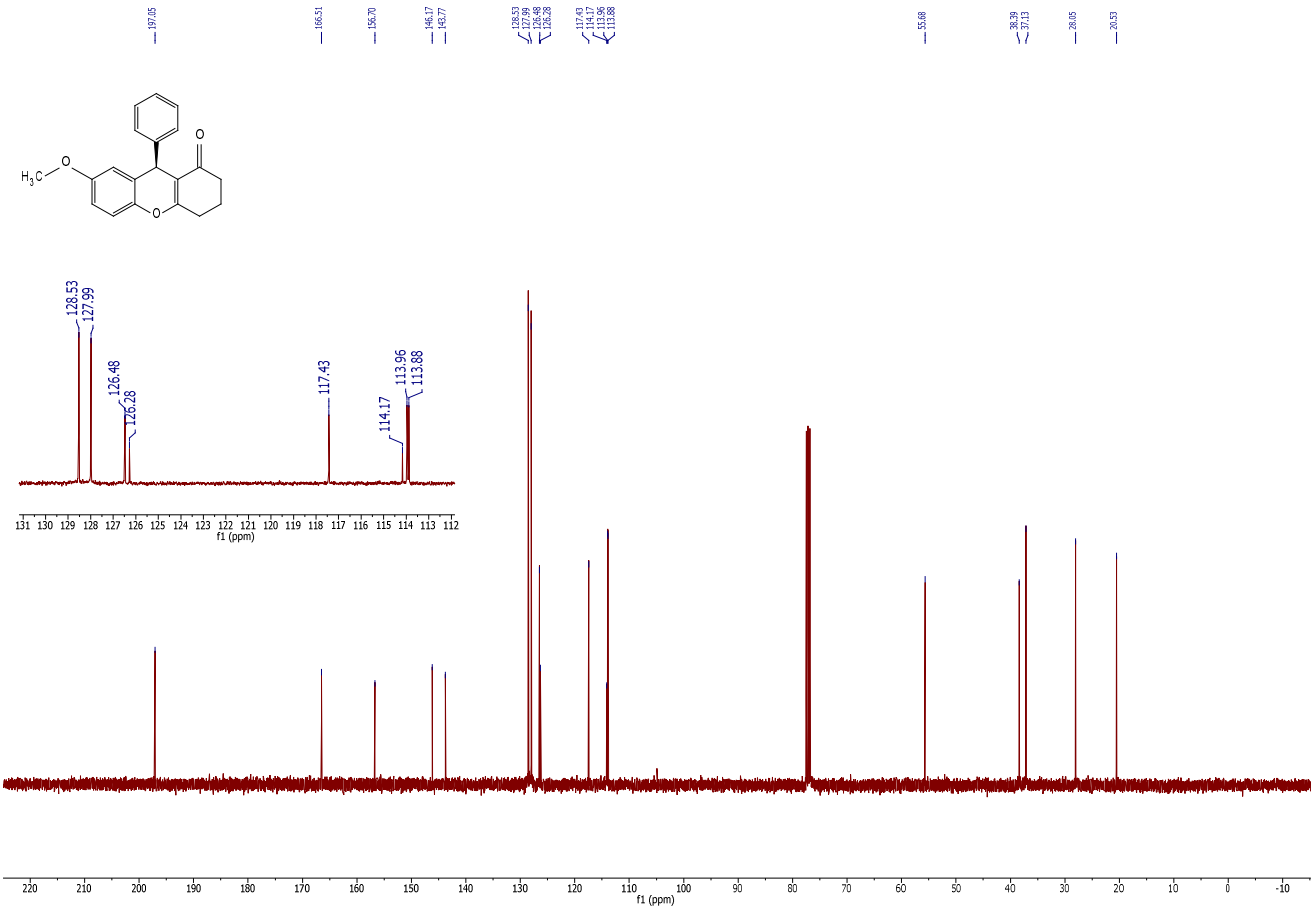
1.01
1.01
1.03
1.00
3.20
2.15
2.22
2.24
f1 (ppm)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127.99
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126.28
117.43
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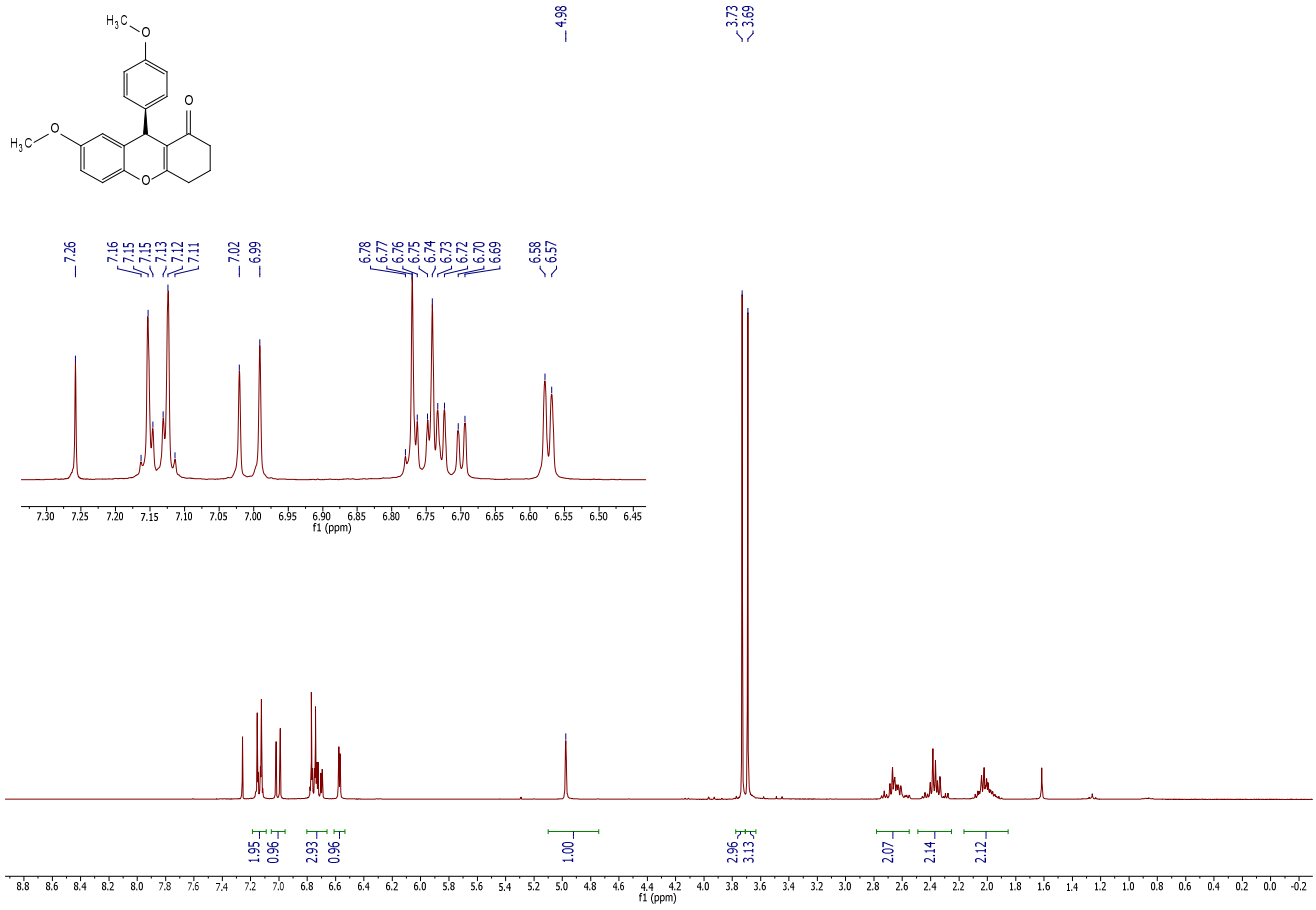
113.96
113.88
55.68
38.39
37.13
28.05
20.53
O
H3C
O
O
f1 (ppm)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7.26
7.16
7.15
7.15
7.13
7.12
7.11
7.02
6.99
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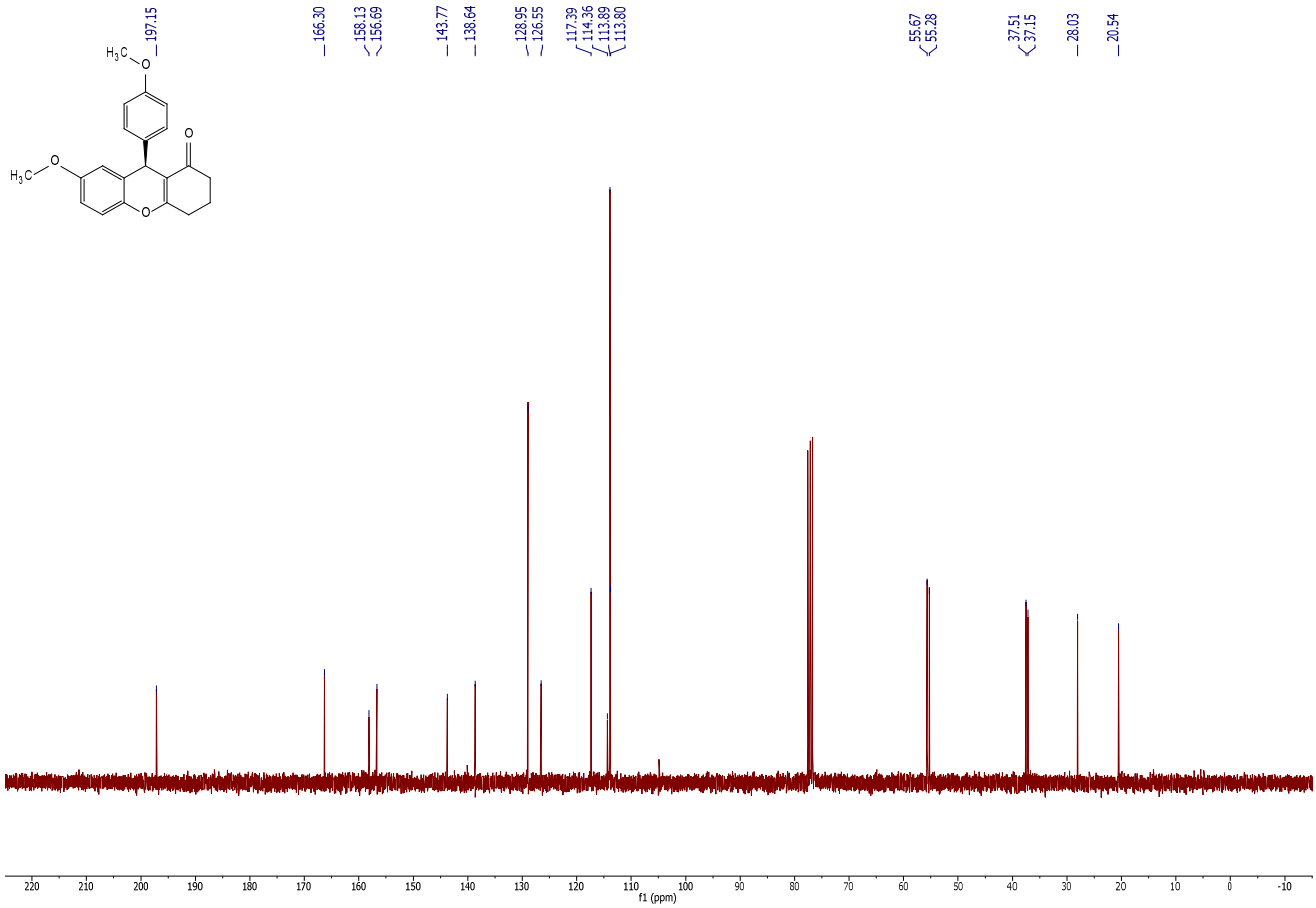
6.75
6.74
6.73
6.72
6.70
6.69
6.58
6.57
f1 (ppm)
1.95
0.96
2.93
0.96
1.00
2.96
3.13
2.07
2.14
2.12
f1 (ppm)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143.77
138.64
128.95
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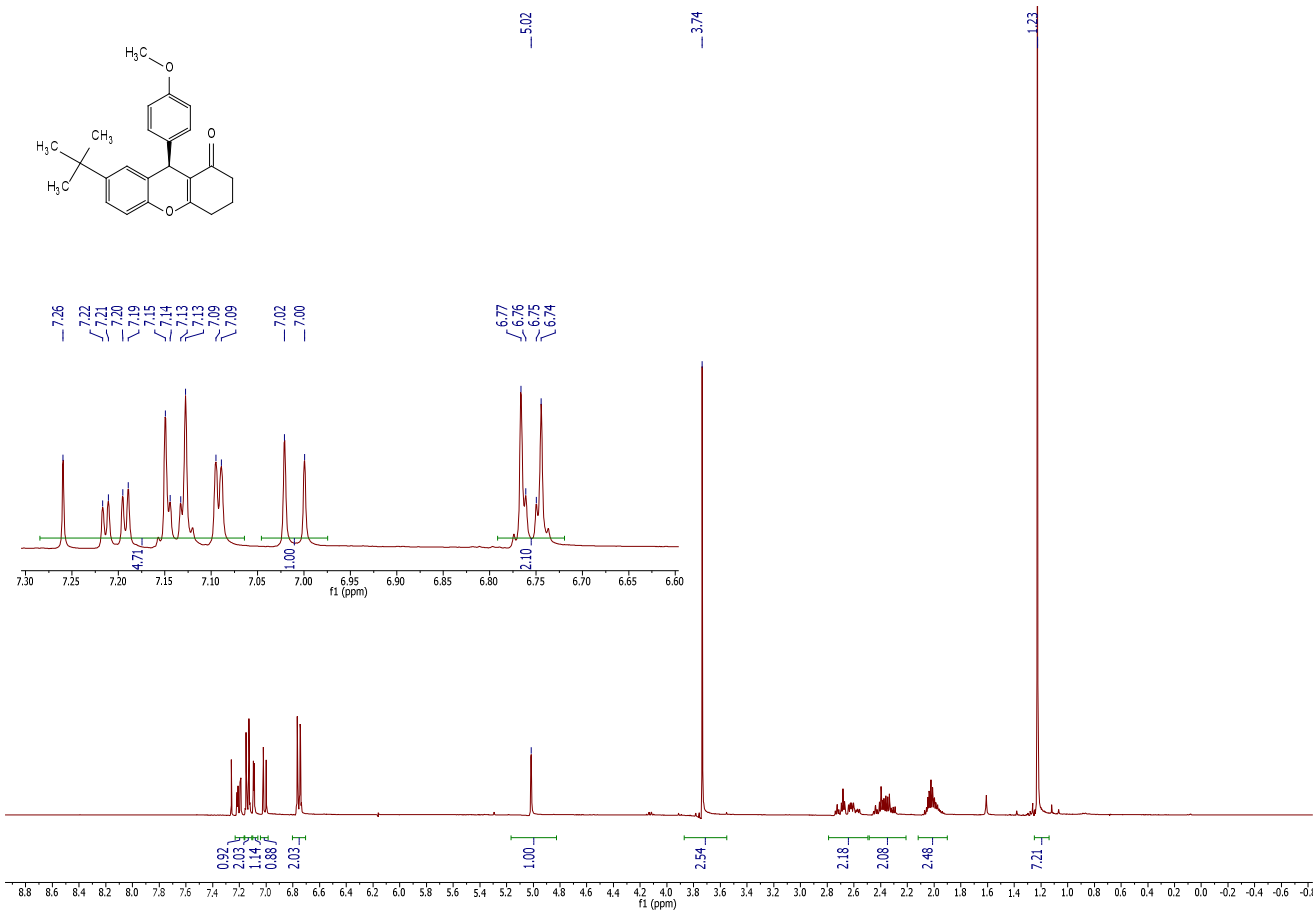
37.51
37.15
28.03
20.54
f1 (ppm)


5.02
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7.21
7.20
7.19
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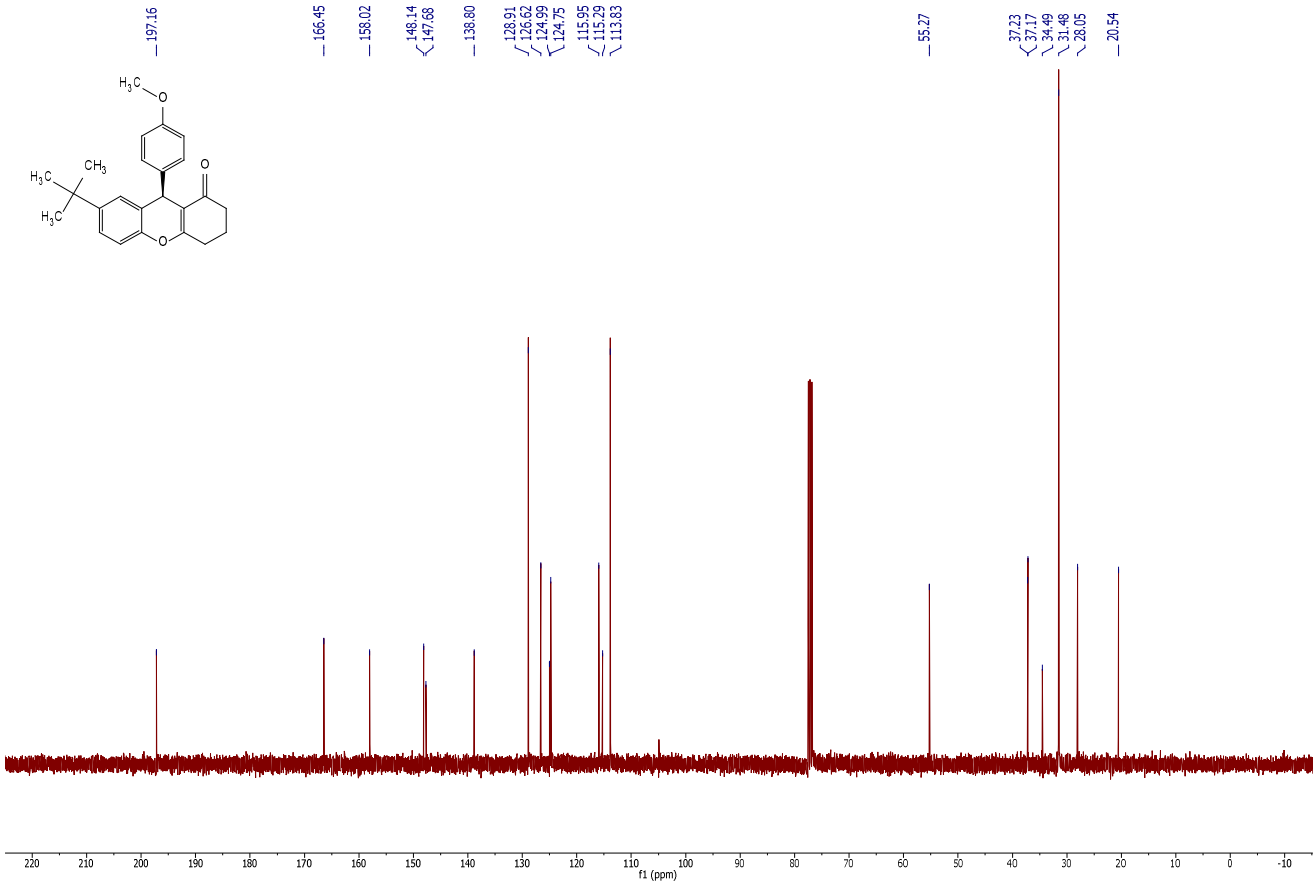
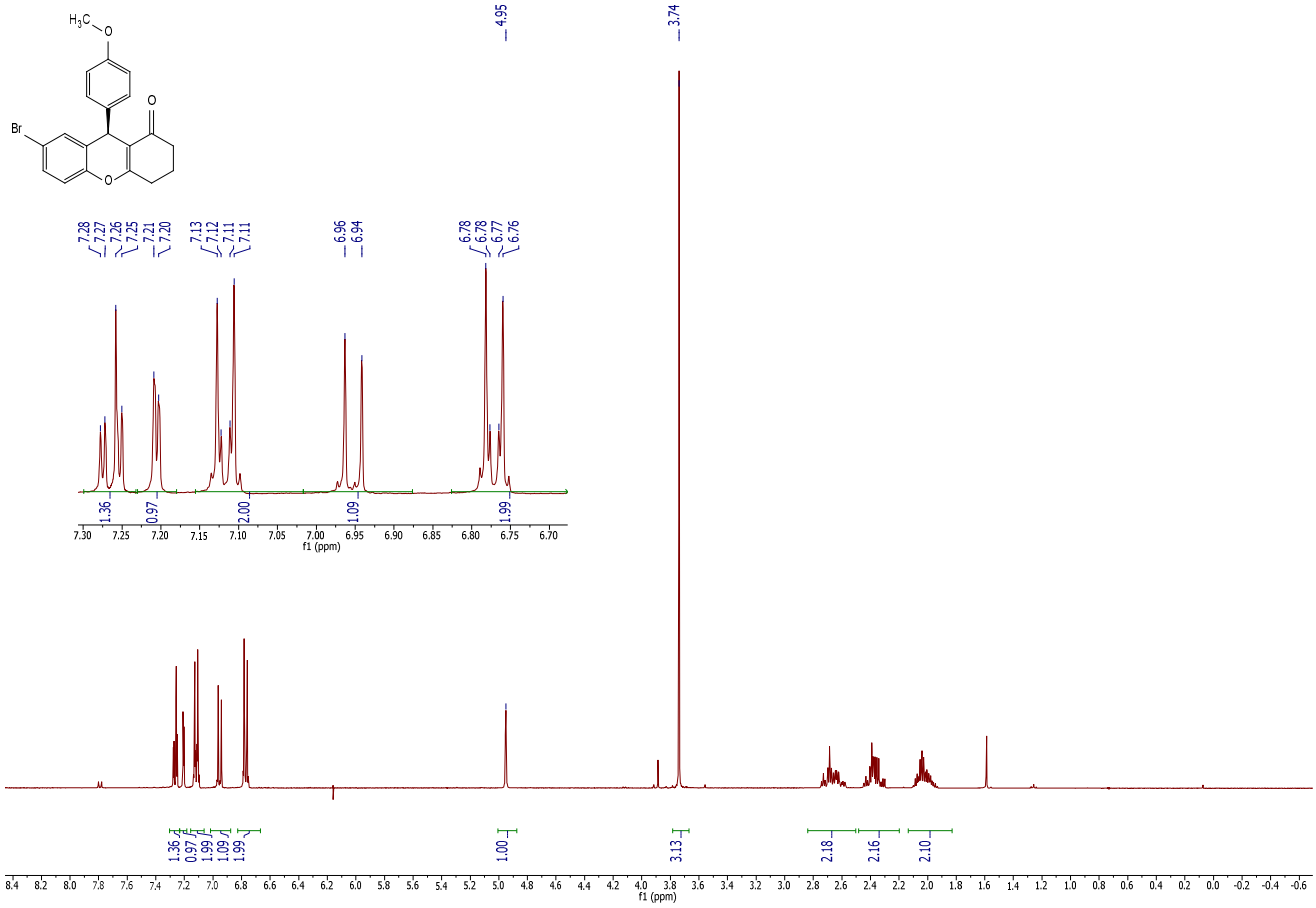
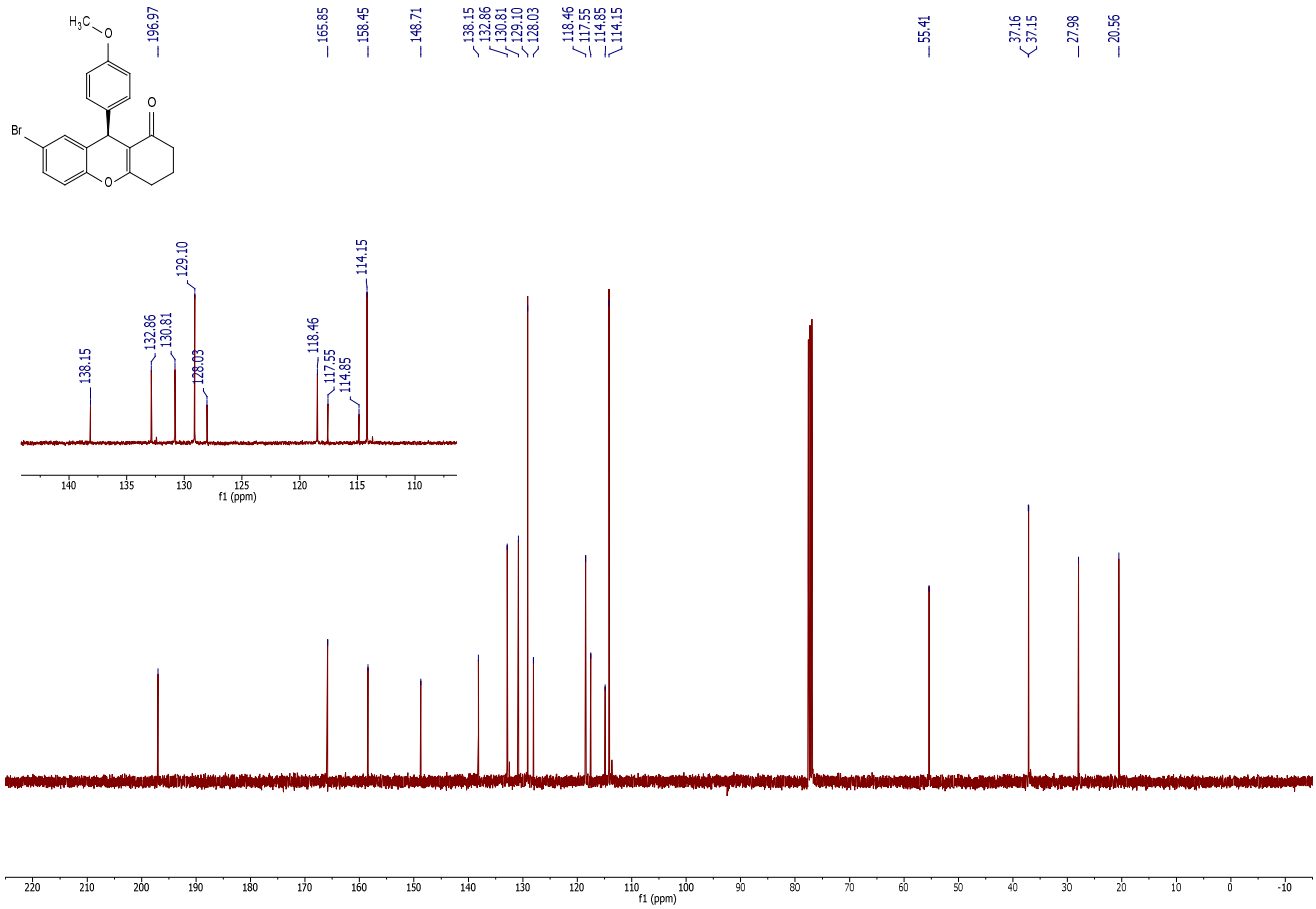
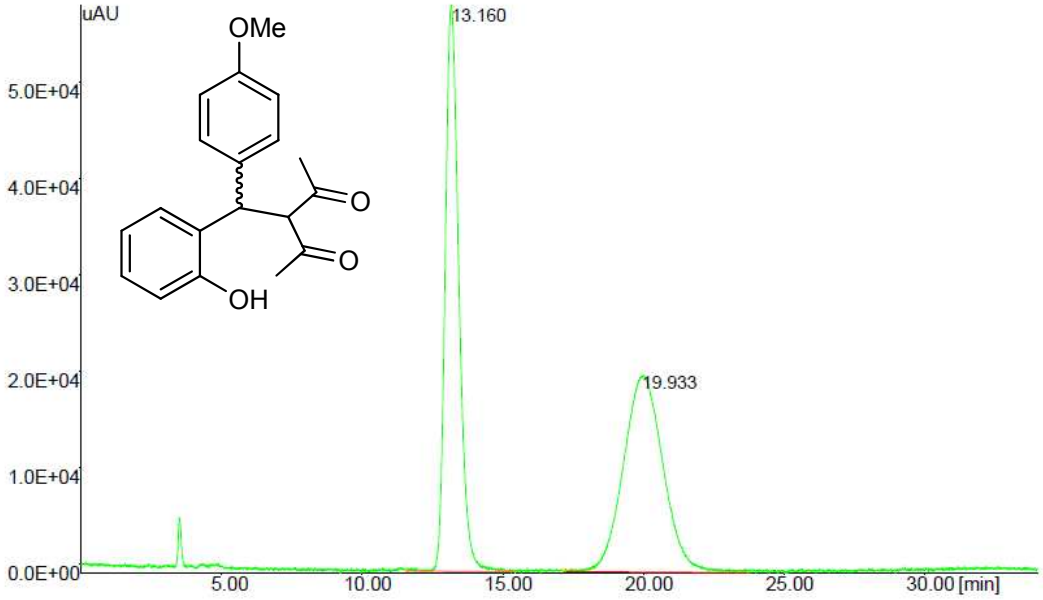
7.14
7.13
7.13
7.09
7.09
7.02
7.00
6.77
6.76
6.75
6.74
4.71
1.00
2.10
f1 (ppm)
0.92
2.03
1.14
0.88
2.03
1.00
2.54
2.18
2.08
2.48
7.21
f1 (ppm)


197.16
166.45
158.02
148.14
147.68
138.80
128.91
126.62
124.99
124.75
115.95
115.29
113.83
55.27
37.23
37.17
34.49
31.48
28.05
20.54
f1 (ppm)


H3C
O
Br
O
O
4.95
3.74
7.28
7.27
7.26
7.25
7.21
7.20
7.13
7.12
7.11
7.11
6.96
6.94
6.78
6.78
6.77
6.76
1.36
0.97
2.00
1.09
1.99
f1 (ppm)
1.36
0.97
1.99
1.09
1.99
1.00
3.13
2.18
2.16
2.10
f1 (ppm)

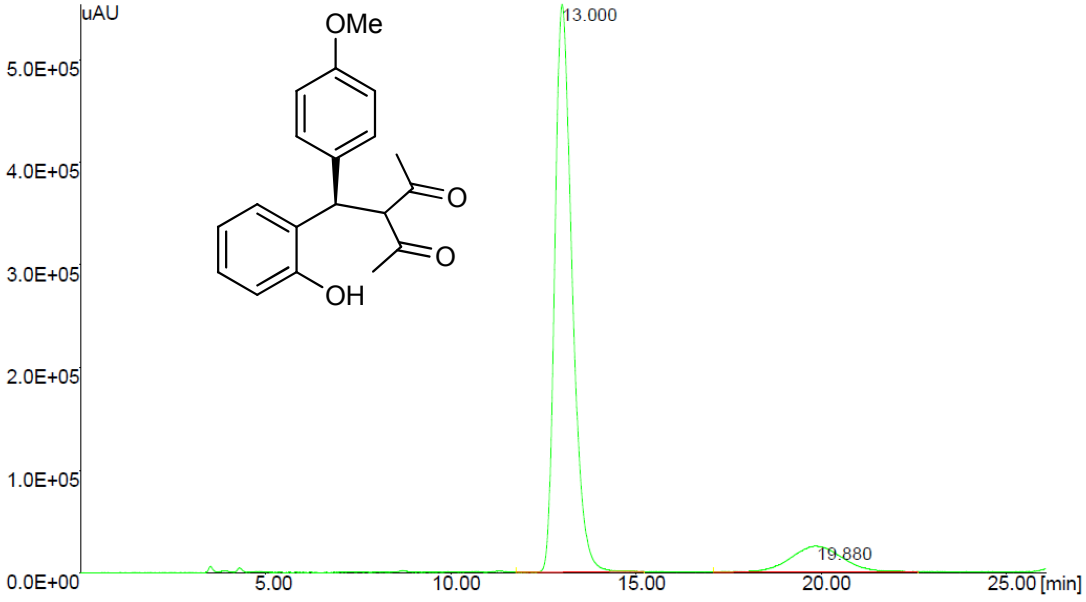

H3C
O
Br
O
O
196.97
165.85
158.45
148.71
138.15
132.86
130.81
129.10
128.03
118.46
117.55
114.85
114.15
55.41
37.16
37.15
27.98
20.56
138.15
132.86
130.81
129.10
128.03
118.46
117.55
114.85
114.15
f1 (ppm)
f1 (ppm)

V –HPLC-Chromatograms



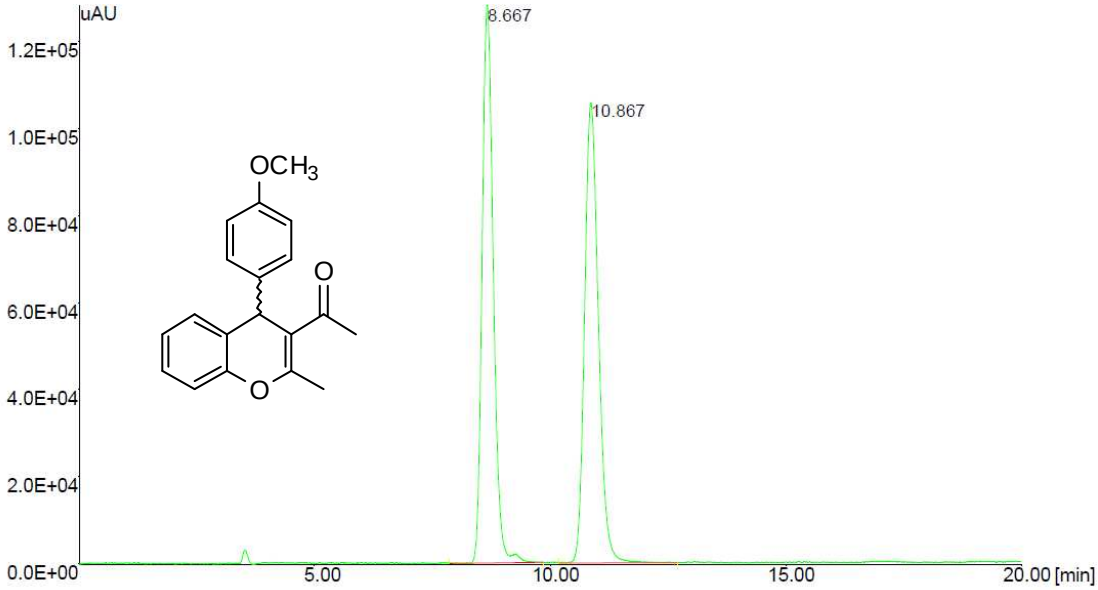
OD, 95:5, 1ml/min, 220 nm

#	Name	RT	Height [uAU]	Area [uAU.Sec]	%Area
1		13.160	58707	1981467.354	49.68
2		19.933	20396	2006911.378	50.32



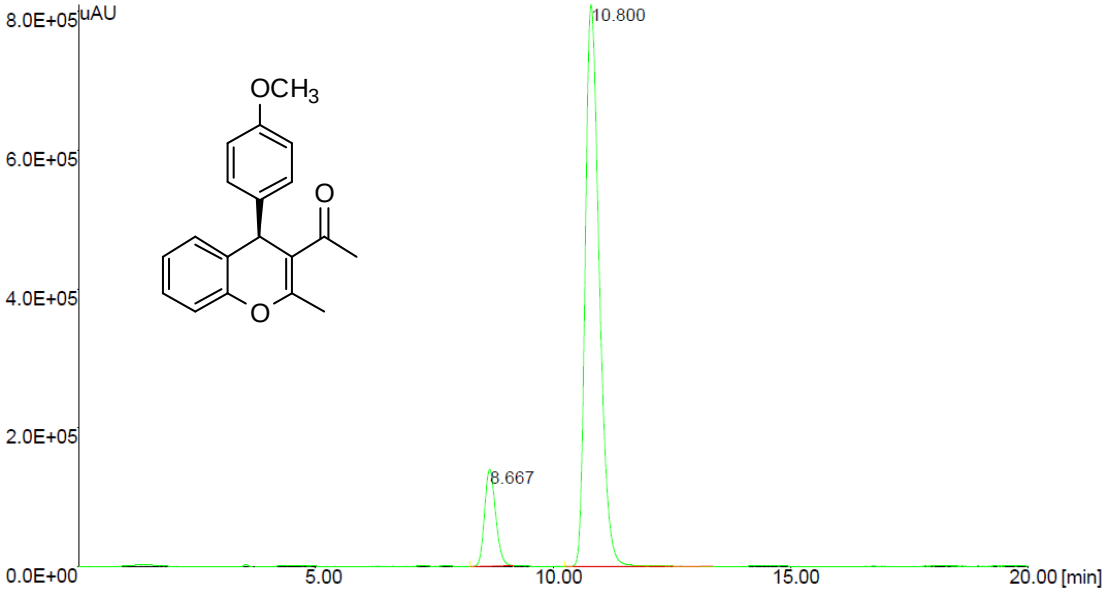
OD, 95:5, 1ml/min, 220 nm

#	Name	RT	Height [uAU]	Area [uAU.Sec]	%Area
1		13.000	552765	17972154.853	88.09
2		19.880	24953	2429511.636	11.91



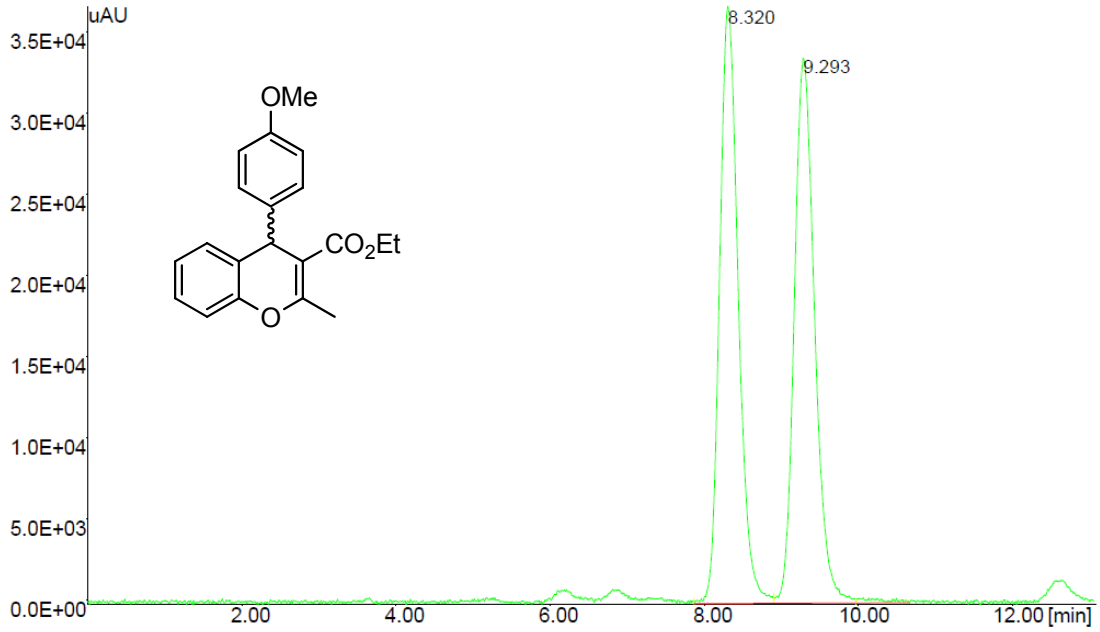
ODH, 95:5, 1ml/min, 232 nm

#	Name	RT	Height [uAU]	Area [uAU.Sec]	%Area
1		8.667	128086	2121010.206	49.60
2		10.867	105643	2155266.824	50.40



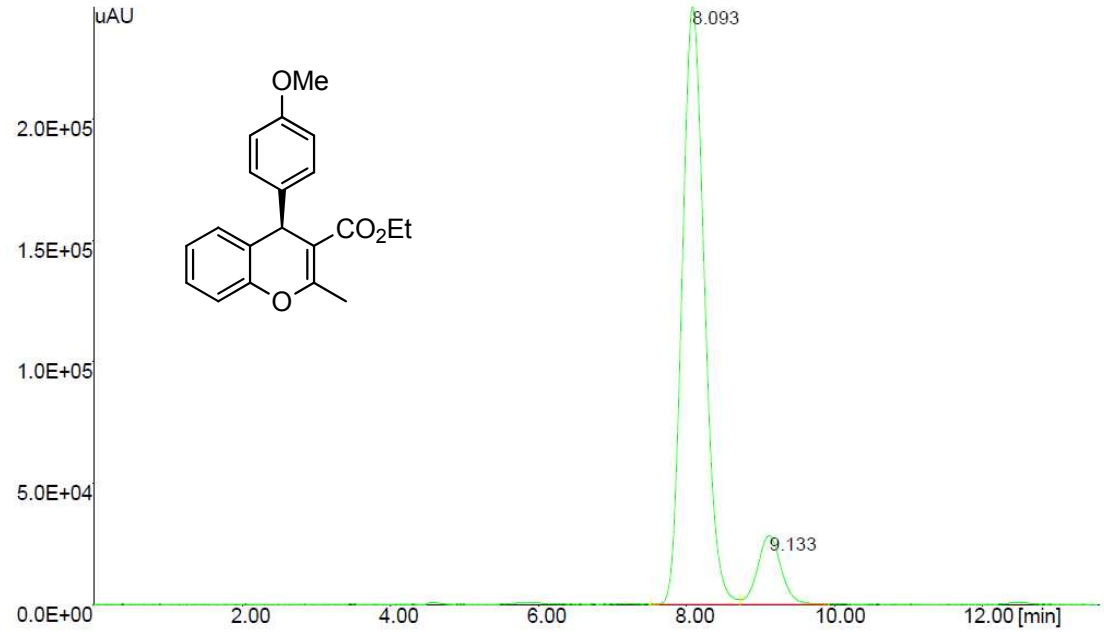
ODH, 95:5, 1ml/min, 232 nm

#	Name	RT	Height [uAU]	Area [uAU.Sec]	%Area
1		8.667	139302	2256128.834	11.92
2		10.800	809458	16669285.448	88.08



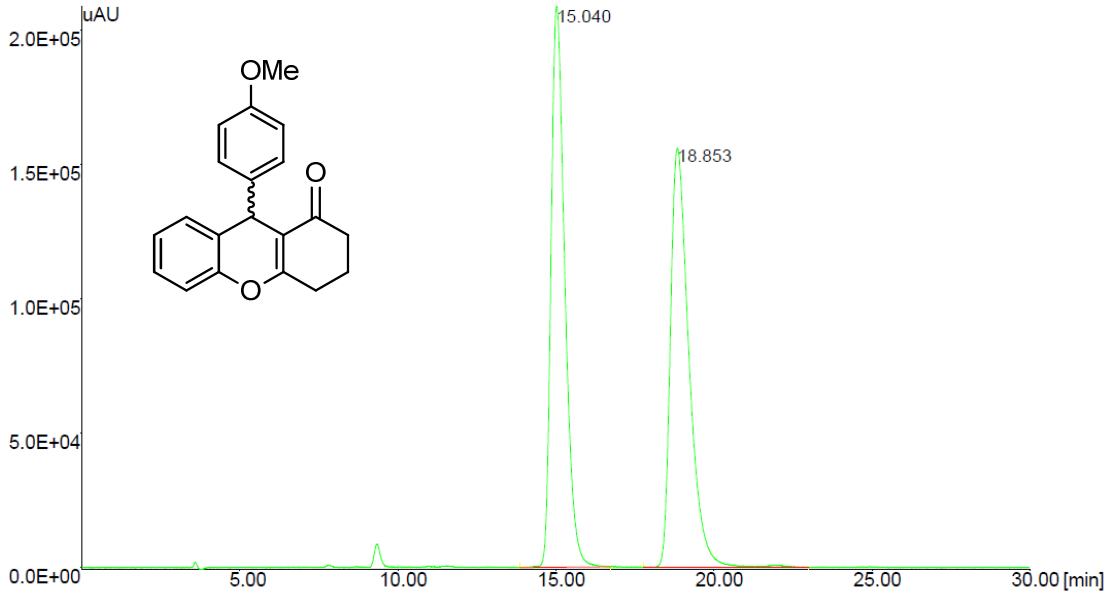
ODH, 99:1, 1ml/min, 270 nm

#	Name	RT	Height [uAU]	Area [uAU.Sec]	%Area
1		8.320	36727	619583.506	50.22
2		9.293	33511	614087.842	49.78



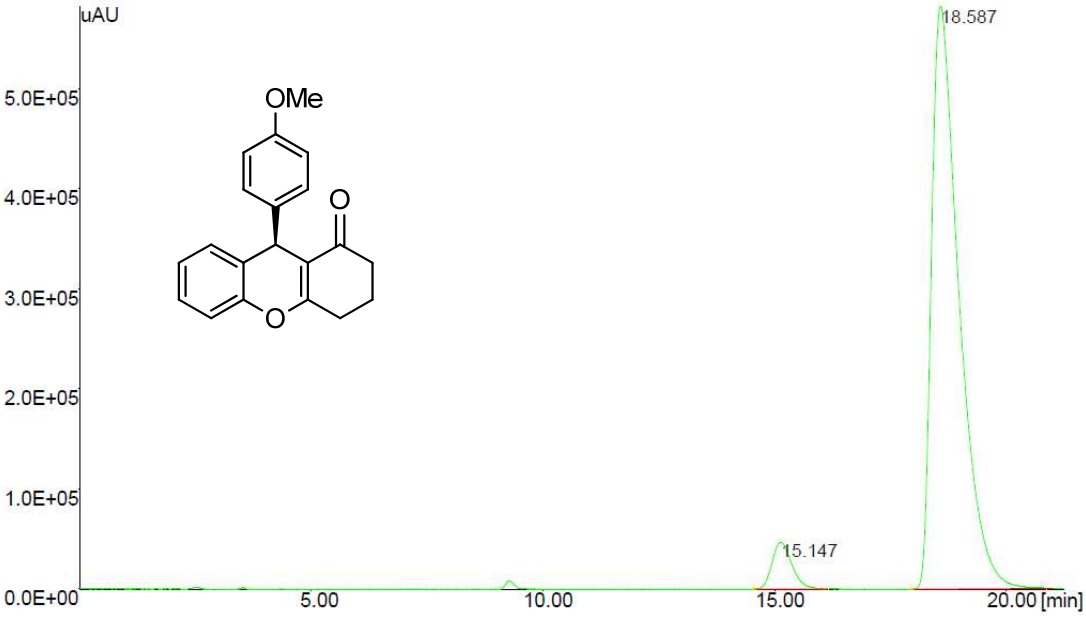
ODH, 99:1, 1ml/min, 270 nm

#	Name	RT	Height [uAU]	Area [uAU.Sec]	%Area
1		8.093	246237	5133711.477	89.15
2		9.133	28194	624608.209	10.85



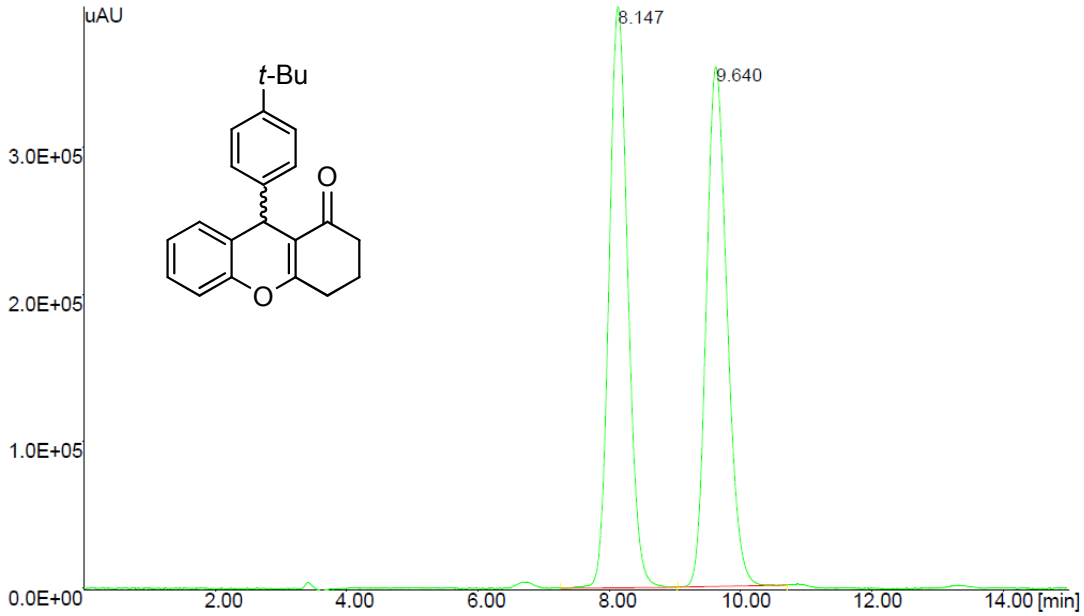
ODH, 95:5, 1ml/min, 270 nm

#	Name	RT	Height [uAU]	Area [uAU.Sec]	%Area
1		15.040	208798	6315332.191	49.72
2		18.853	155982	6385665.347	50.28



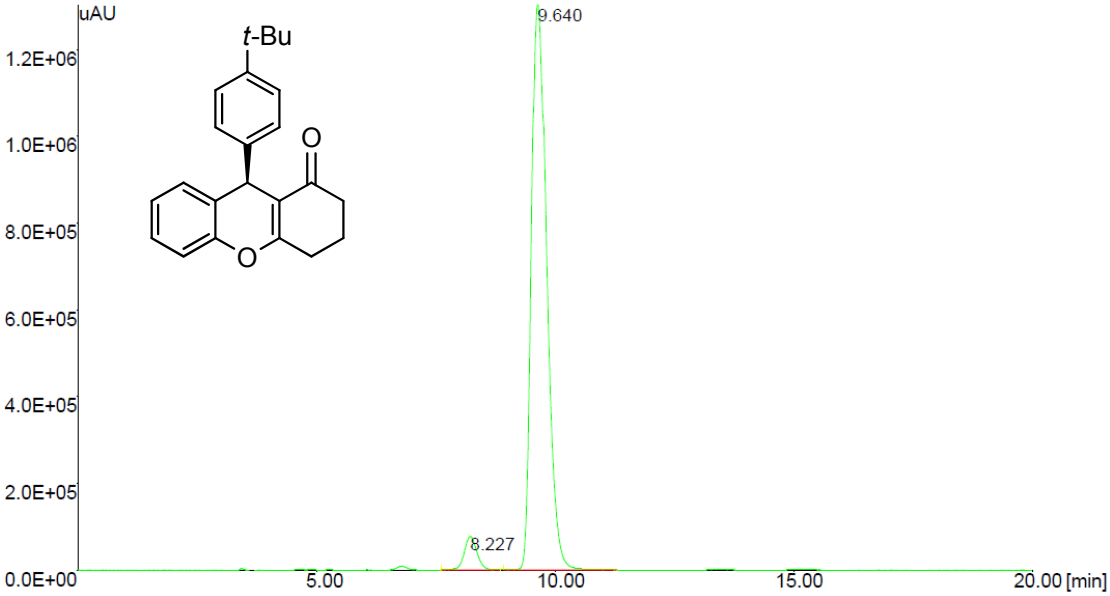
ODH, 95:5, 1ml/min, 270 nm

#	Name	RT	Height [uAU]	Area [uAU.Sec]	%Area
1		15.147	46736	1389300.021	5.48
2		18.587	582383	23971989.296	94.52



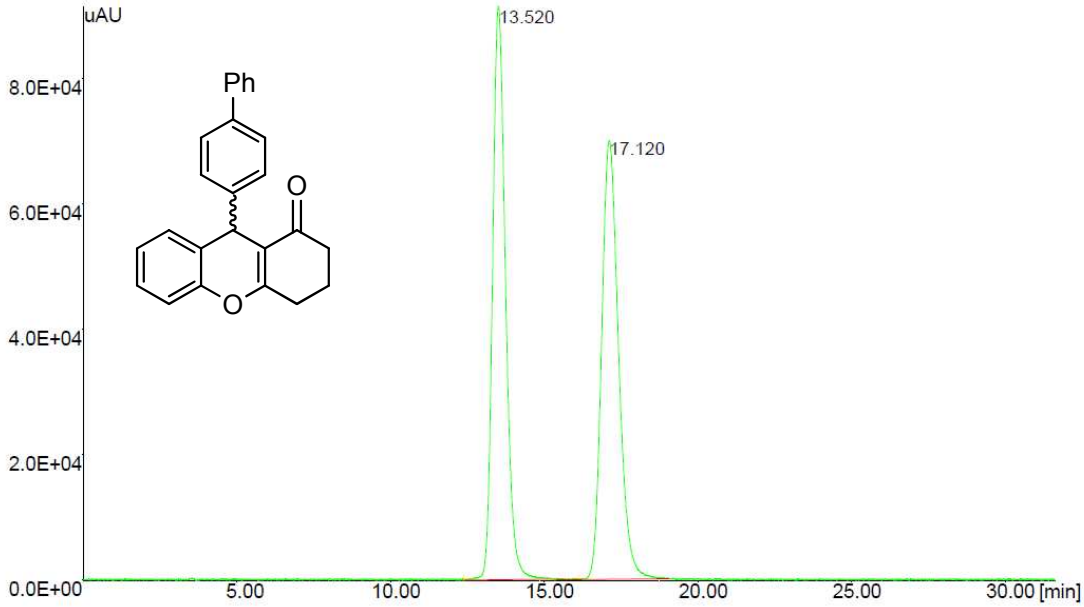
ODH, 95:5, 1ml/min, 270 nm

#	Name	RT	Height [uAU]	Area [uAU.Sec]	%Area
1		8.147	395322	7873548.117	50.33
2		9.640	353349	7768998.864	49.67



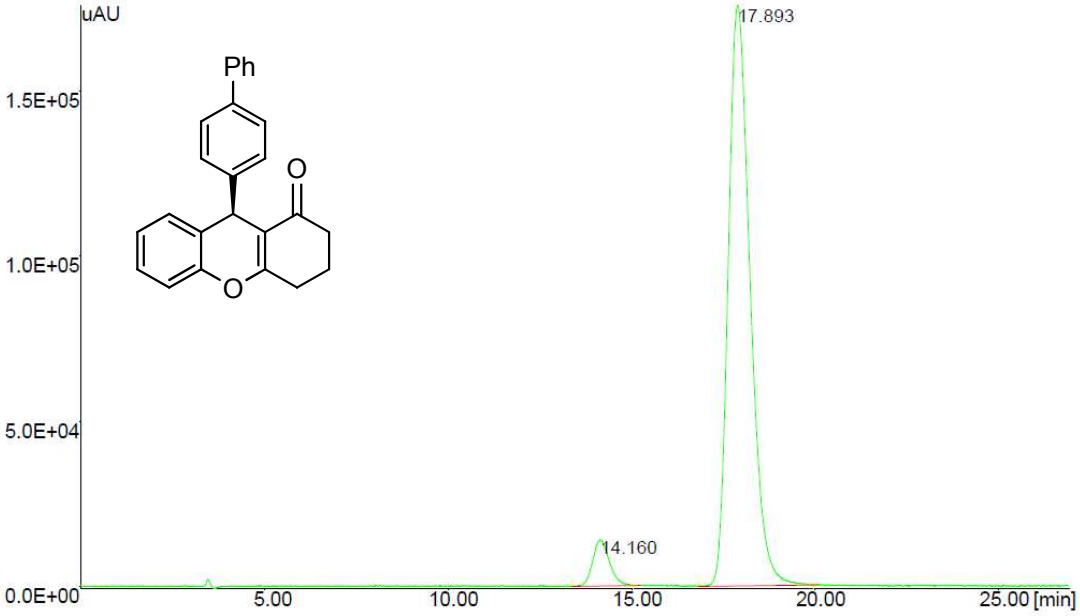
ODH, 95:5, 1ml/min, 270 nm

#	Name	RT	Height [uAU]	Area [uAU.Sec]	%Area
1		8.227	76938	1420178.421	4.61
2		9.640	1301695	29365333.638	95.39



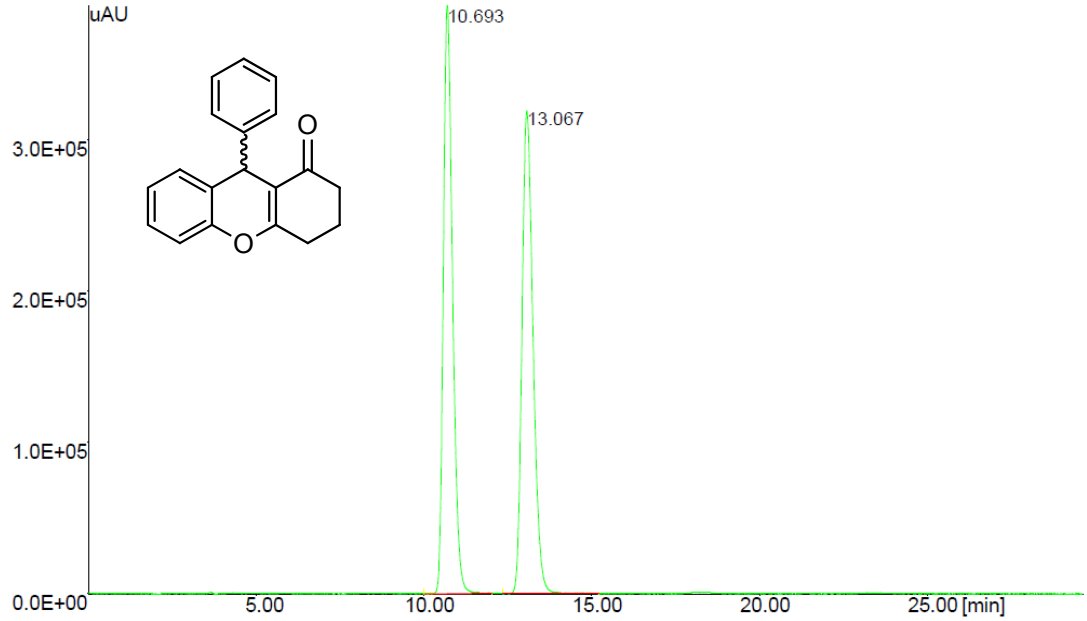
ODH, 95:5, 1ml/min, 270 nm

#	Name	RT	Height [uAU]	Area [uAU.Sec]	%Area
1		13.520	91578	2677403.162	50.00
2		17.120	70051	2677756.480	50.00



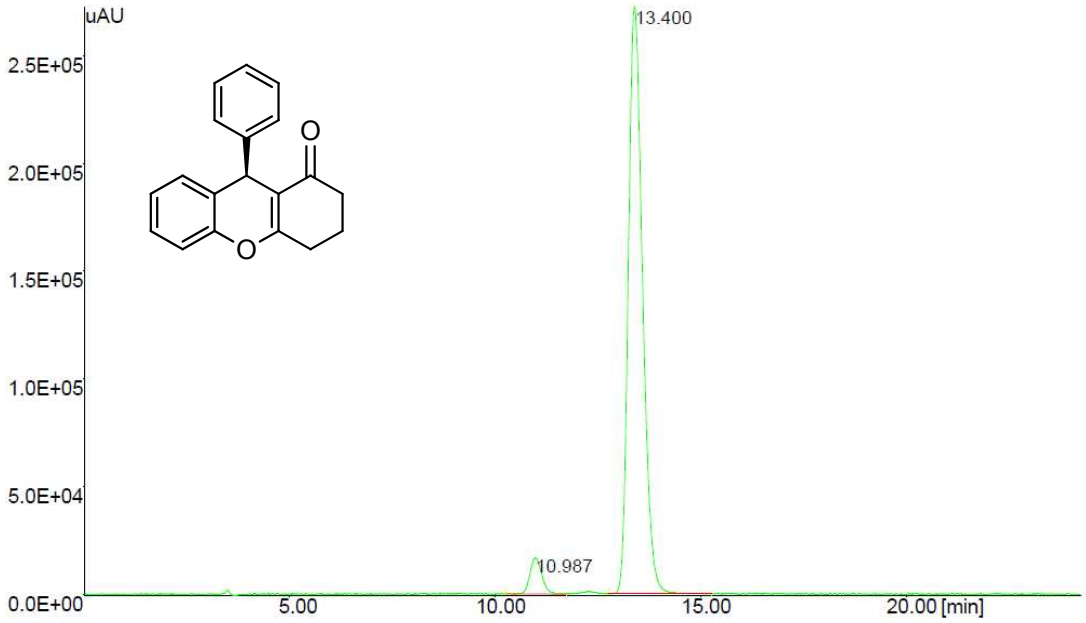
ODH, 95:5, 1ml/min, 270 nm

#	Name	RT	Height [uAU]	Area [uAU.Sec]	%Area
1		14.160	14067	448104.534	5.82
2		17.893	176005	7247985.975	94.18



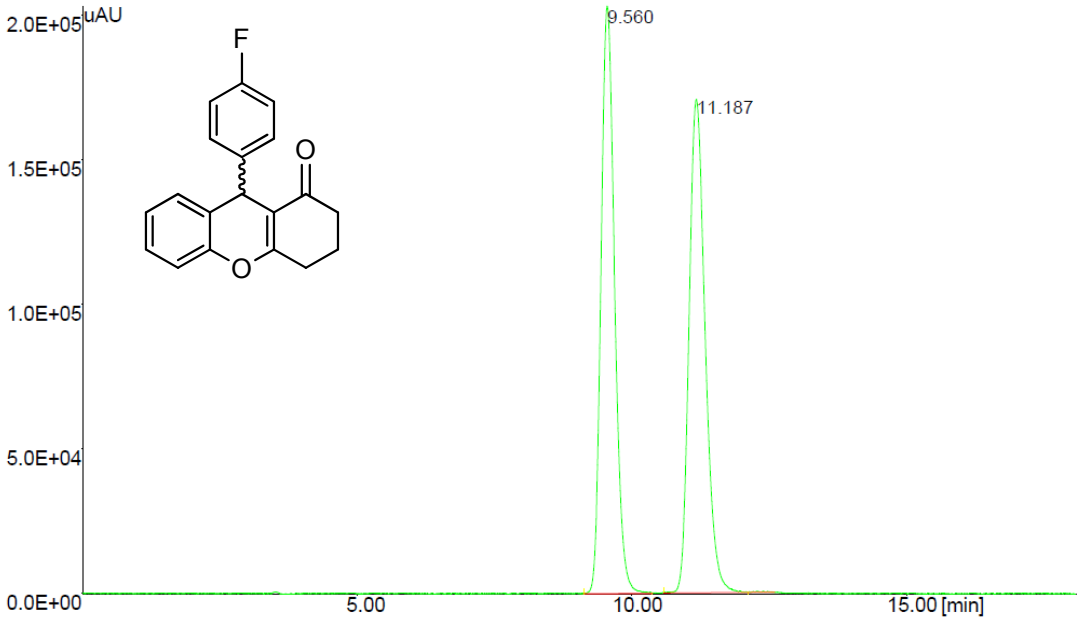
ODH, 95:5, 1ml/min, 274 nm

#	Name	RT	Height[uAU]	Area[uAU.Sec]	%Area
1		10.693	389025	7444928.111	50.44
2		13.067	319251	7316305.963	49.56



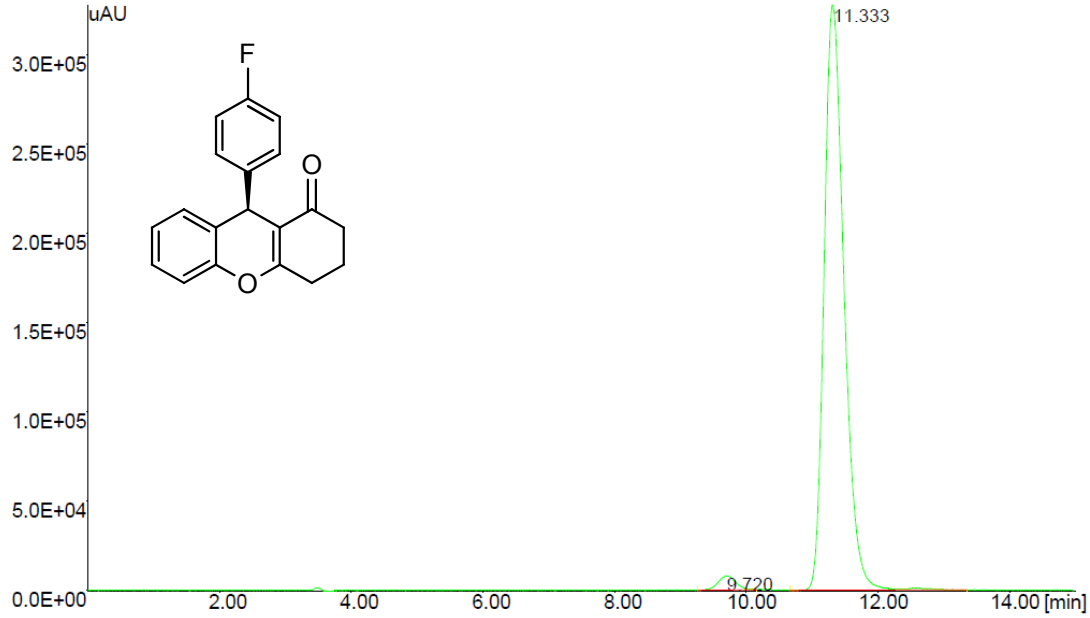
ODH, 95:5, 1ml/min, 274 nm

#	Name	RT	Height[uAU]	Area[uAU.Sec]	%Area
1		10.987	16956	338718.304	4.91
2		13.400	272374	6559518.498	95.09



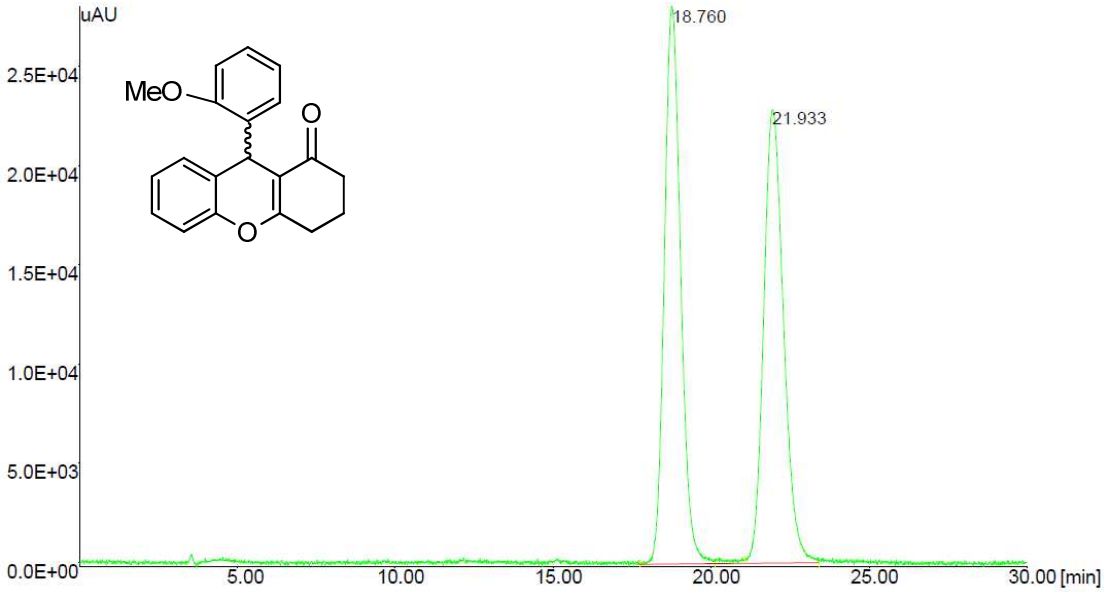
ODH, 95:5, 1ml/min, 270 nm

#	Name	RT	Height[uAU]	Area[uAU.Sec]	%Area
1		9.560	203254	3482769.652	50.06
2		11.187	170806	3474484.104	49.94



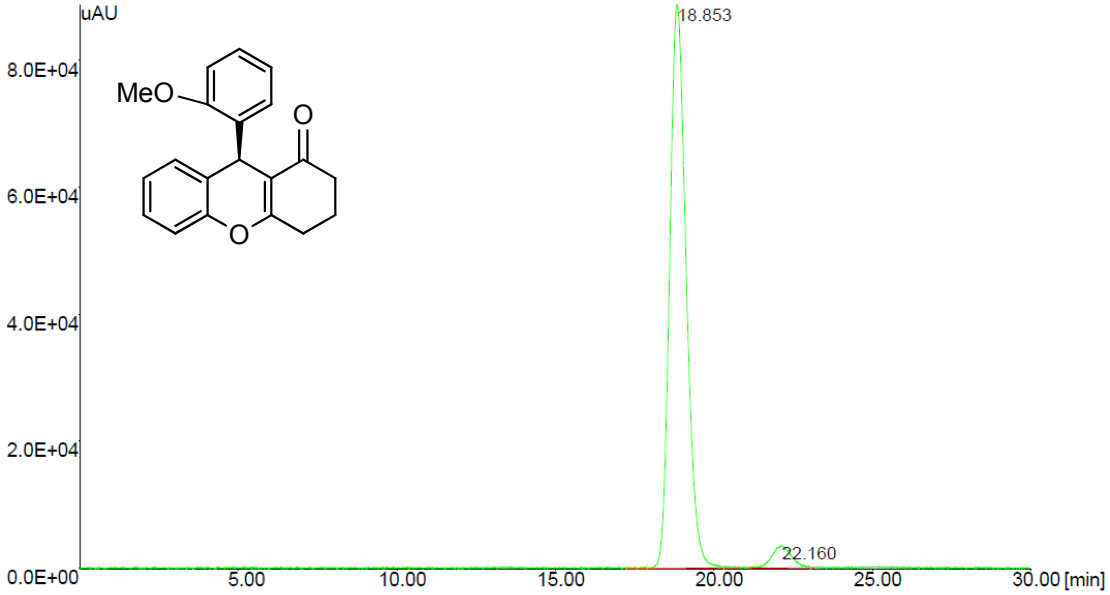
ODH, 95:5, 1ml/min, 270 nm

#	Name	RT	Height[uAU]	Area[uAU.Sec]	%Area
1		9.720	8057	149591.907	2.13
2		11.333	328080	6875365.996	97.87



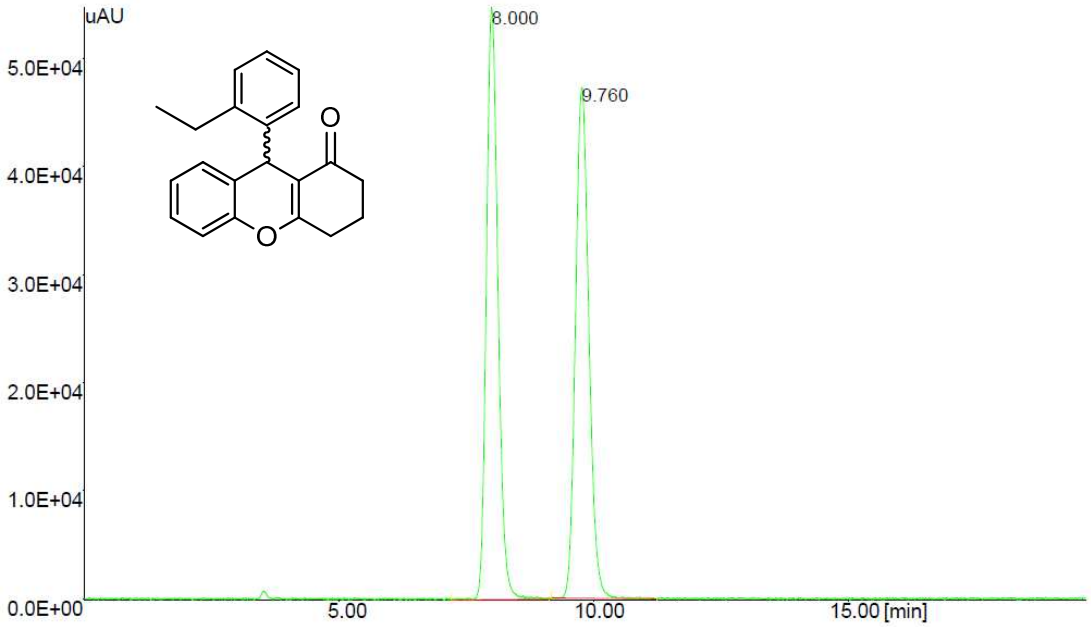
ODH, 95:5, 1ml/min, 267 nm

#	Name	RT	Height [uAU]	Area [uAU.Sec]	%Area
1		18.760	28135	1009613.203	50.28
2		21.933	22865	998524.815	49.72



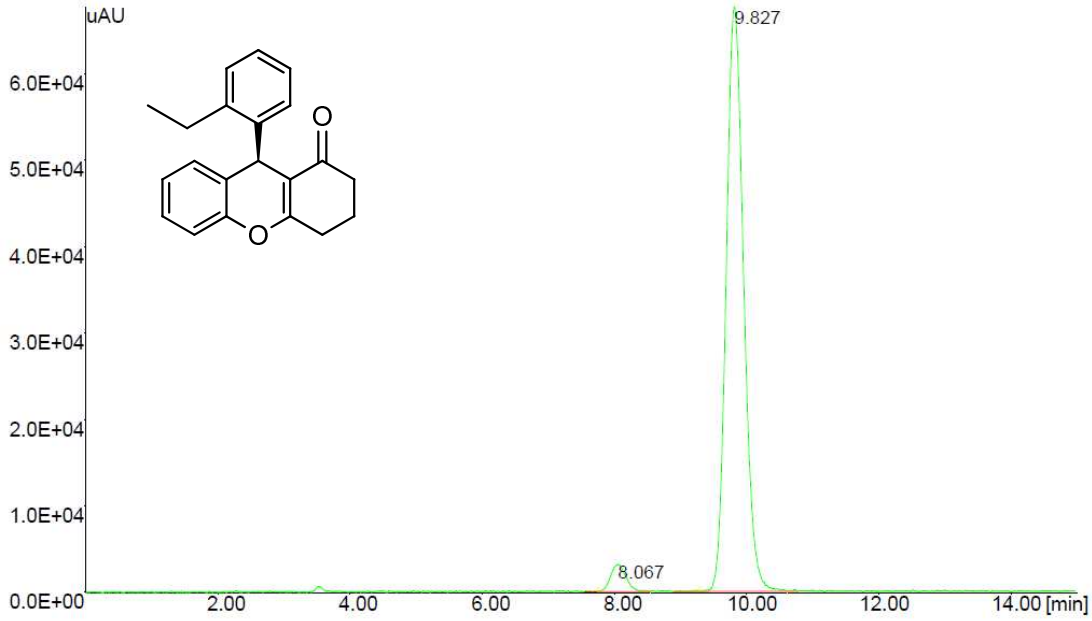
ODH, 95:5, 1ml/min, 267 nm

#	Name	RT	Height [uAU]	Area [uAU.Sec]	%Area
1		18.853	88884	3202276.910	95.52
2		22.160	3535	150026.465	4.48



ODH, 95:5, 1ml/min, 240 nm

#	Name	RT	Height [uAU]	Area [uAU.Sec]	%Area
1		8.000	54821	868080.013	50.22
2		9.760	47260	860425.686	49.78



ODH, 95:5, 1ml/min, 240 nm

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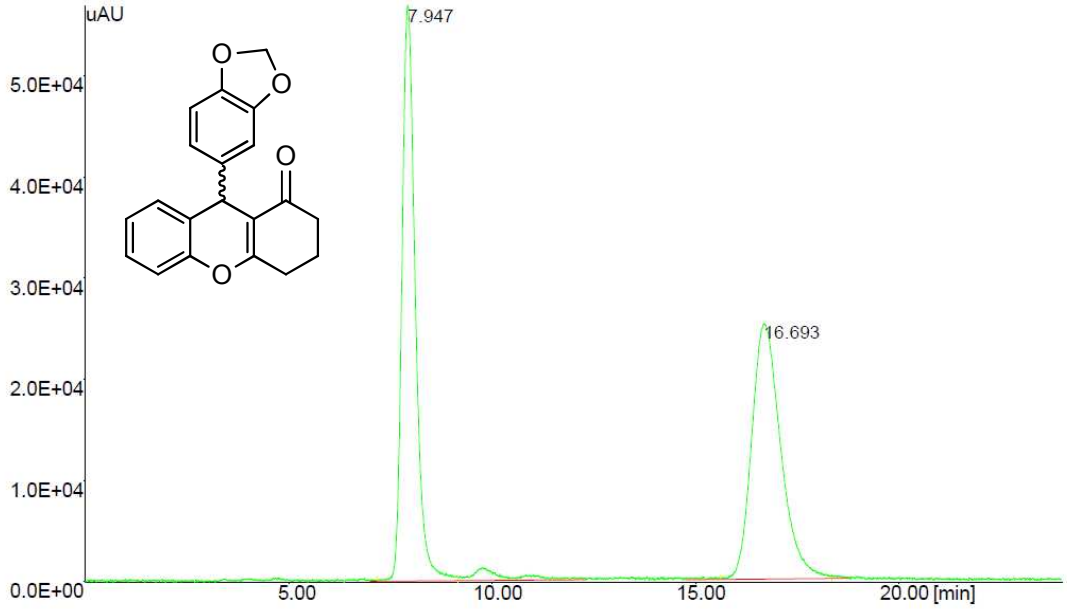
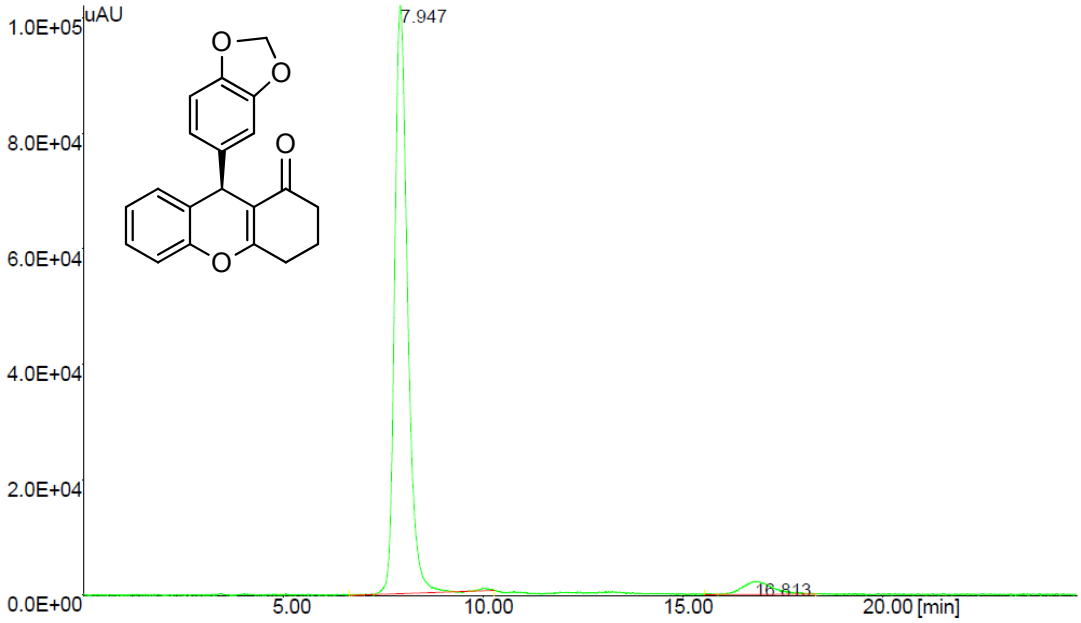
2		9.827	67597	1241194.418	96.02



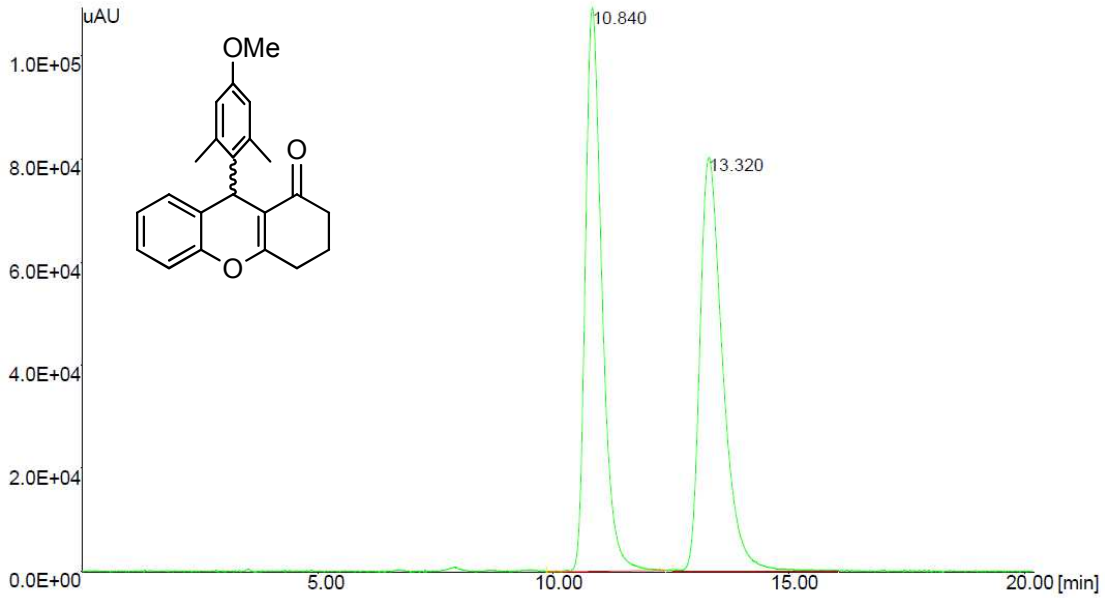
ODH, 80:20, 1ml/min, 270 nm

#	Name	RT	Height [uAU]	Area [uAU.Sec]	%Area
1		7.947	56921	1295011.402	50.79
2		16.693	25238	1254680.223	49.21



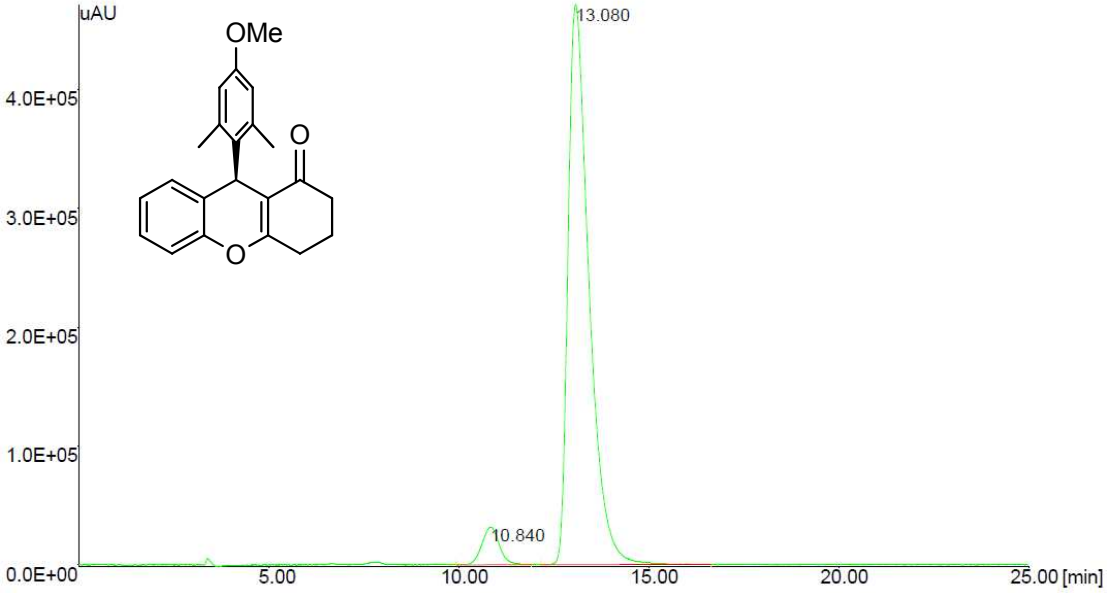
ODH, 80:20, 1ml/min, 270 nm

#	Name	RT	Height [uAU]	Area [uAU.Sec]	%Area
1		7.947	102032	2307059.240	94.95
2		16.813	2278	122677.200	5.05



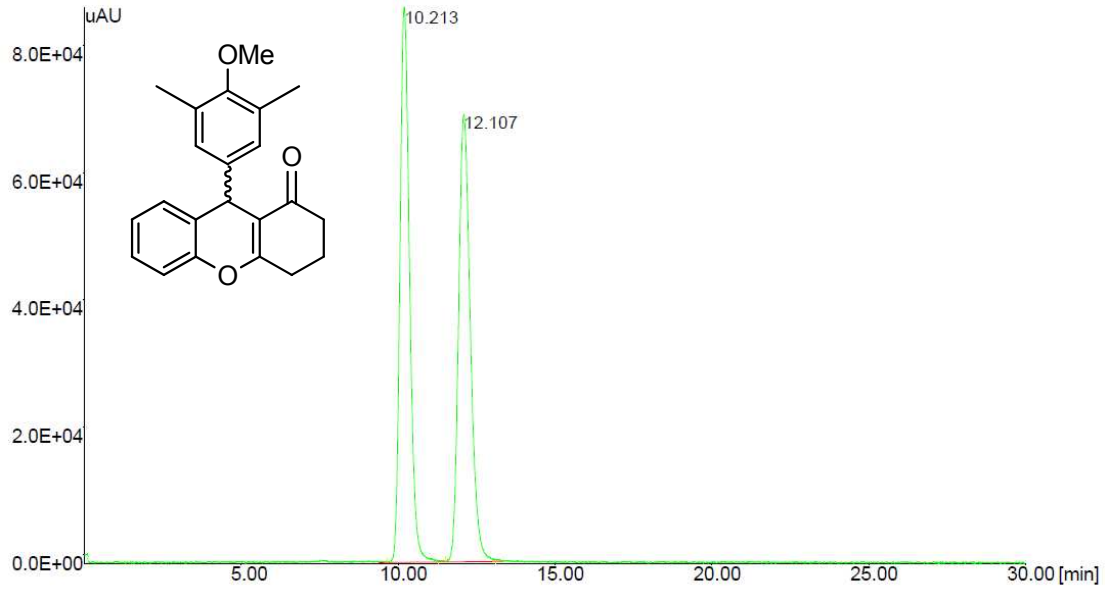
ODH, 95:5, 1ml/min, 270 nm

#	Name	RT	Height [uAU]	Area [uAU.Sec]	%Area
1		10.840	109406	2683432.840	49.95
2		13.320	80246	2689057.240	50.05



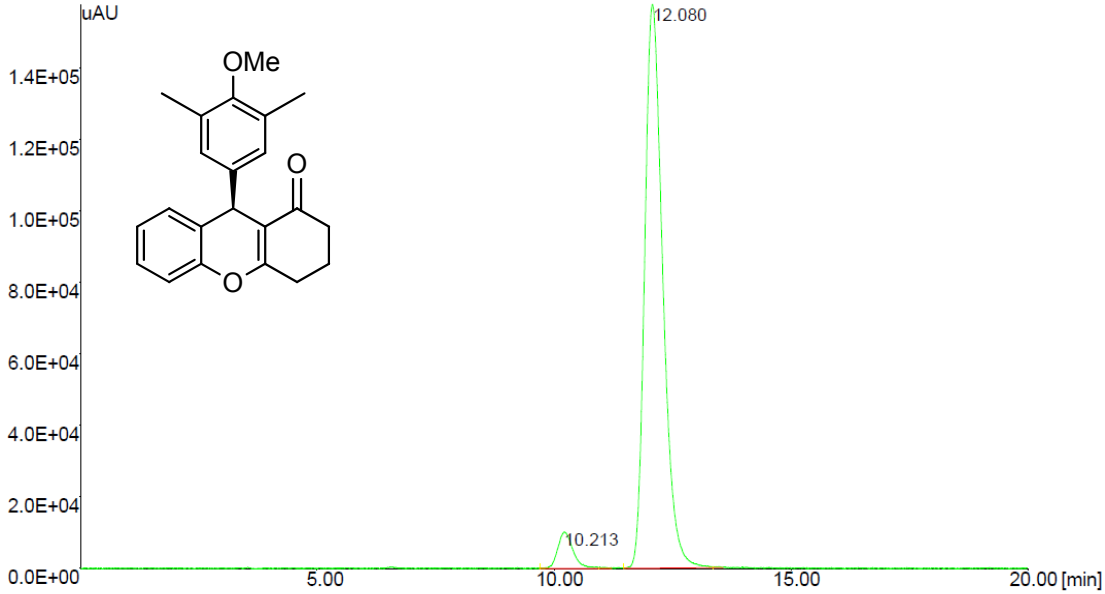
ODH, 95:5, 1ml/min, 270 nm

#	Name	RT	Height [uAU]	Area [uAU.Sec]	%Area
1		10.840	31649	1017216.815	5.32
2		13.080	471159	18086610.670	94.68



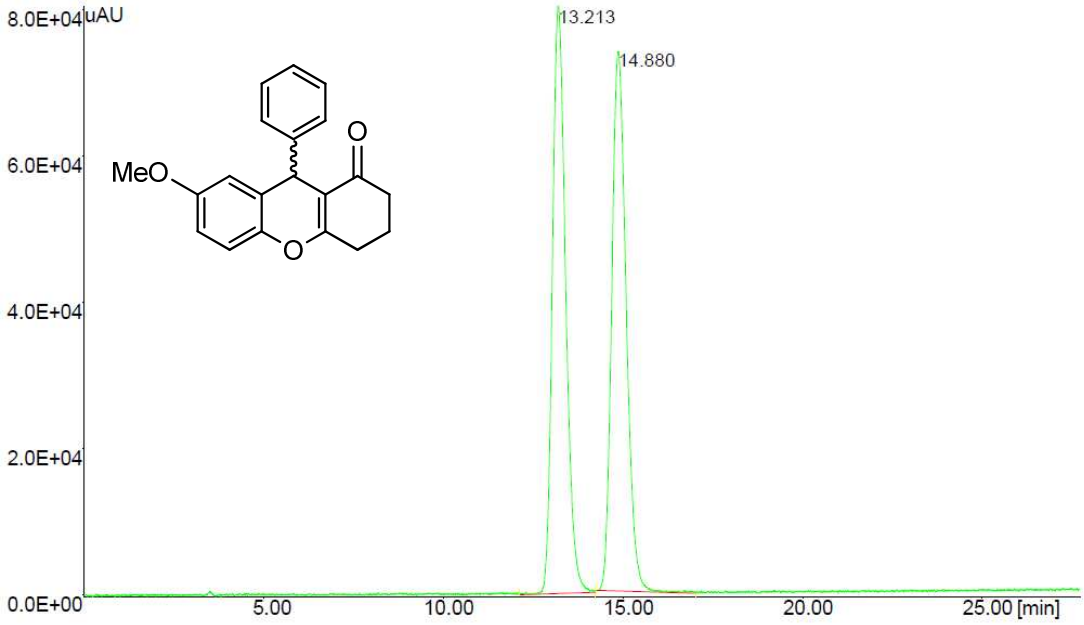
ODH, 95:5, 1ML/min, 270 nm

#	Name	RT	Height[uAU]	Area[uAU.Sec]	%Area
1		10.213	87246	1857945.078	50.32
2		12.107	70327	1834484.057	49.68



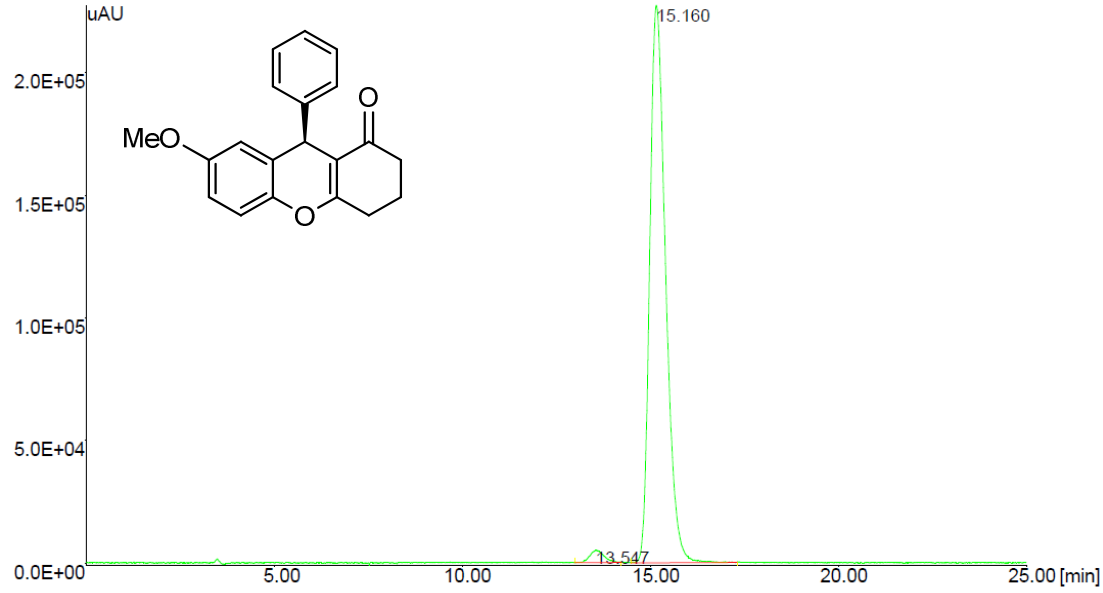
ODH, 95:5, 1ml/min, 270 nm

#	Name	RT	Height[uAU]	Area[uAU.Sec]	%Area
1		10.213	10208	229362.424	5.20
2		12.080	157717	4177279.237	94.80



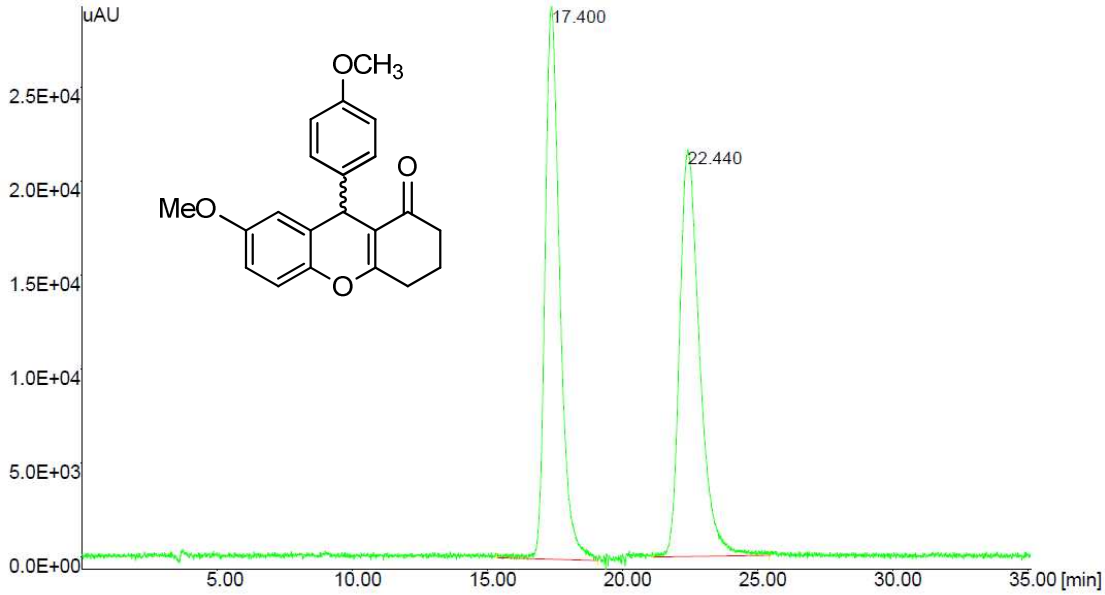
ODH, 95:5, 1ml/min, 274 nm

#	Name	RT	Height [uAU]	Area [uAU.Sec]	%Area
1		13.213	80301	2062340.163	50.09
2		14.880	73714	2054879.633	49.91



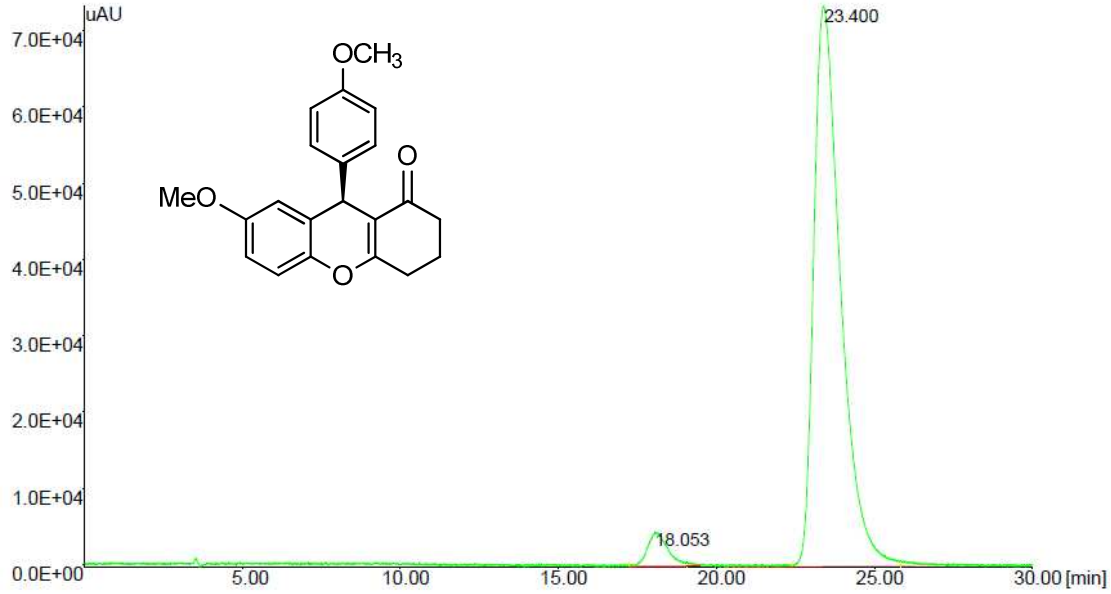
ODH, 95:5, 1ml/min, 274 nm

#	Name	RT	Height [uAU]	Area [uAU.Sec]	%Area
1		13.547	4974	130452.802	1.93
2		15.160	227259	6637195.665	98.07



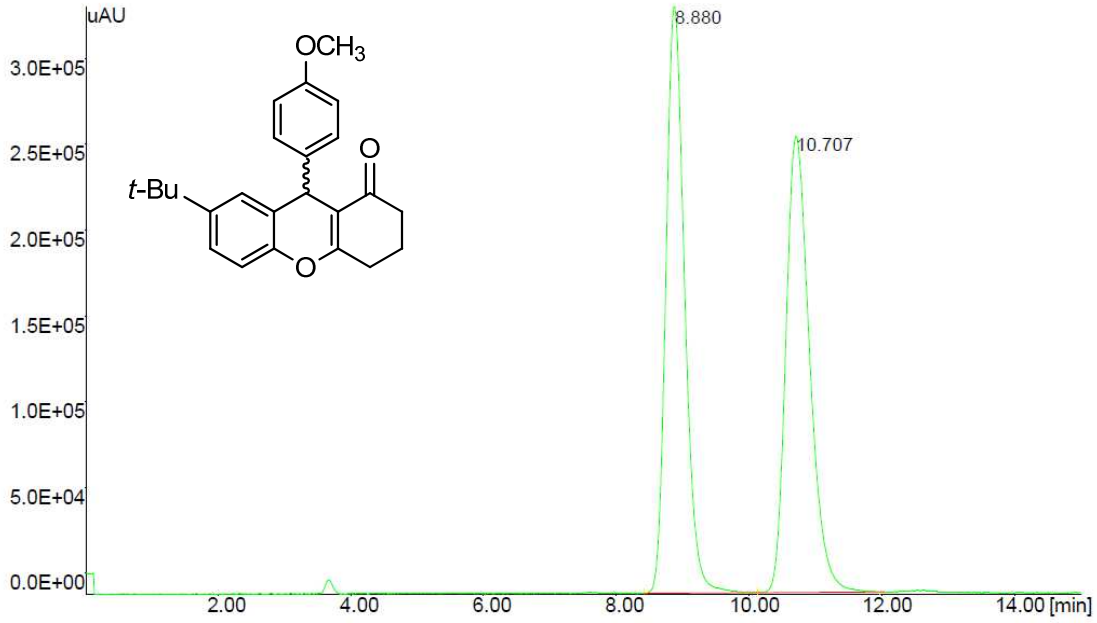
ODH, 95:5, 1ml/min, 274 nm

#	Name	RT	Height[uAU]	Area[uAU.Sec]	%Area
1		17.400	29384	1119661.674	50.02
2		22.440	21624	1118639.999	49.98



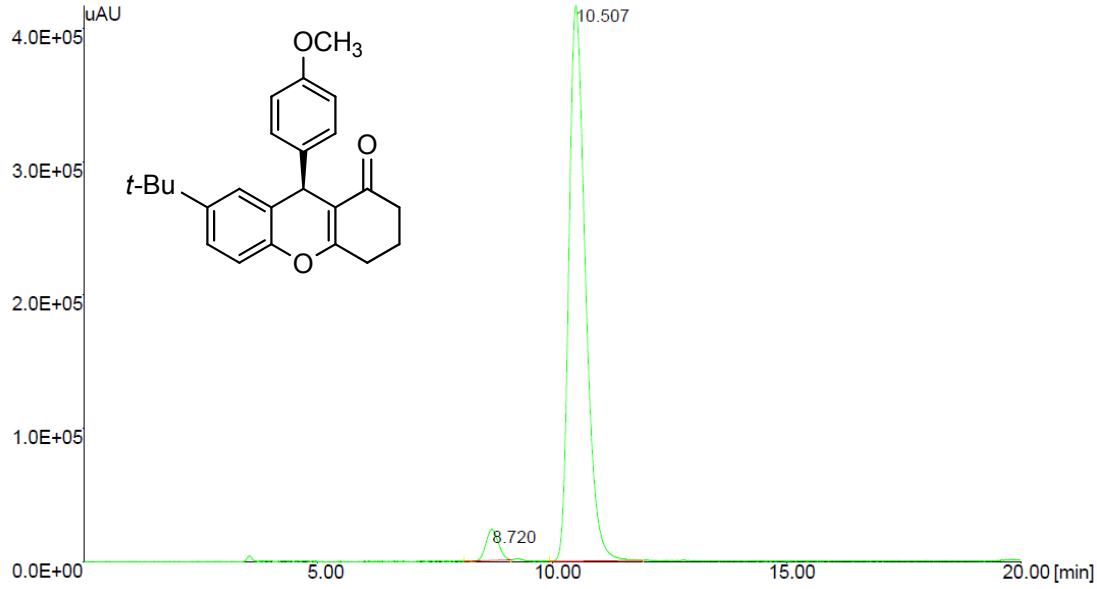
ODH, 95:5, 1ml/min, 274 nm

#	Name	RT	Height[uAU]	Area[uAU.Sec]	%Area
1		18.053	4474	198053.232	4.38
2		23.400	73565	4326362.111	95.62



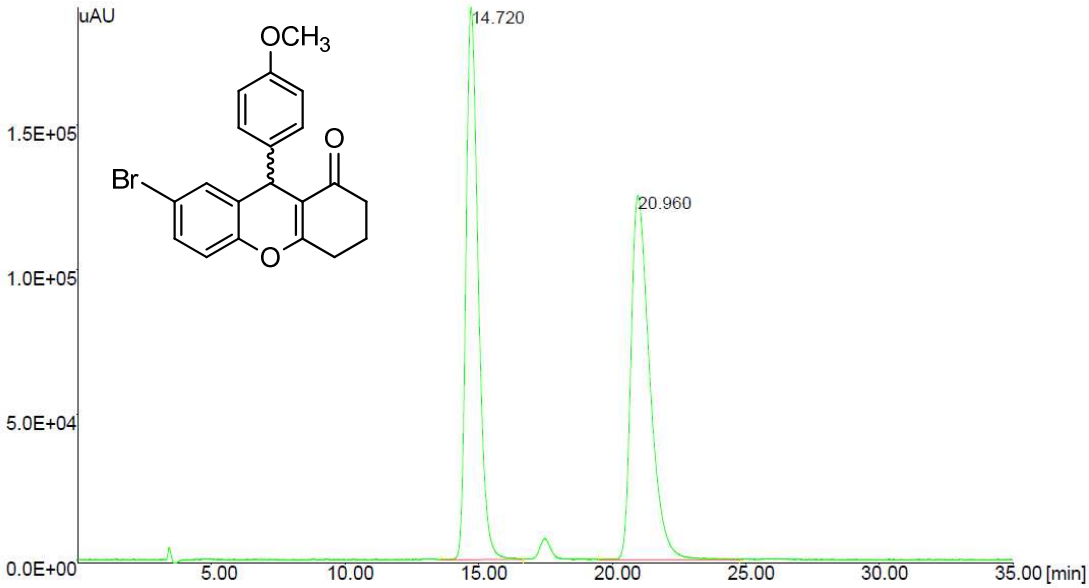
ODH, 95:5, 1ml/min, 220 nm

#	Name	RT	Height [uAU]	Area [uAU.Sec]	%Area
1		8.880	341631	6673908.099	50.25
2		10.707	265730	6607231.338	49.75



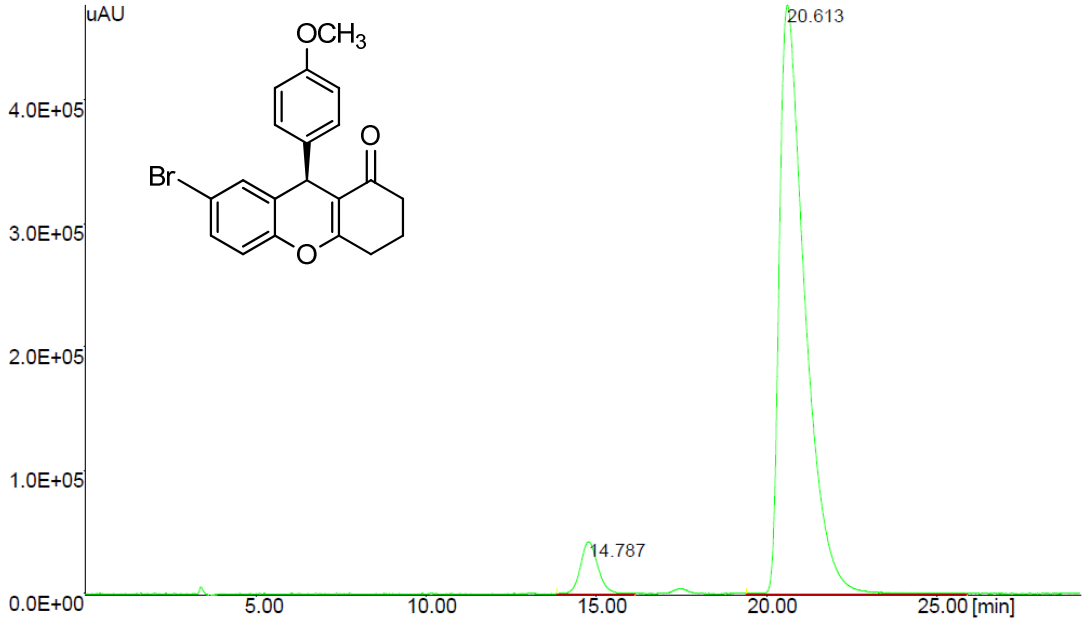
ODH, 95:5, 1ml/min, 220 nm

#	Name	RT	Height [uAU]	Area [uAU.Sec]	%Area
1		8.720	23391	432354.833	4.08
2		10.507	416453	10169720.952	95.92



ODH, 95:5, 1ml/min, 270 nm

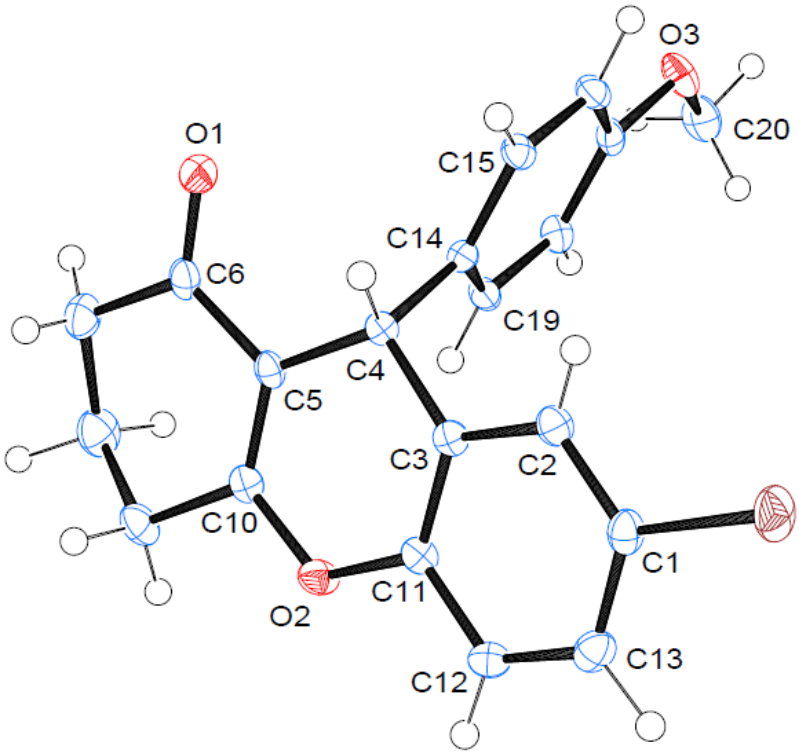
#	Name	RT	Height [uAU]	Area [uAU.Sec]	%Area
1		14.720	190618	6084034.491	49.80
2		20.960	125713	6134012.491	50.20



ODH, 95:5, 1ml/min, 270 nm

#	Name	RT	Height [uAU]	Area [uAU.Sec]	%Area
1		14.787	42293	1499387.222	5.69
2		20.613	477187	24837124.805	94.31

VI – Crystallographic data



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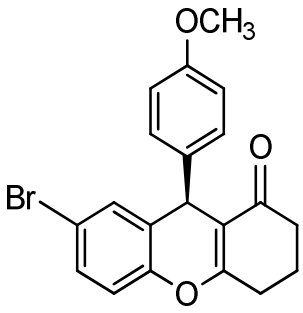

Table 1. Crystal data and structure refinement for x1881fin.

Identification code	x1881fin	
Empirical formula	C_{20} H_{17} Br O_3	
Formula weight	385.24	
Temperature	130(2) K	
Wavelength	71.073 pm	
Crystal system	Orthorhombic	
Space group	P 21 21 21	
Unit cell dimensions	a = 550.060(10) pm	α= 90°.
	b = 1720.05(2) pm	β= 90°.
	c = 1726.38(2) pm	γ = 90°.
Volume	1.63338(4) nm^3	
Z	4	
Density (calculated)	1.567 Mg/m^3	
Absorption coefficient	2.532 mm^{-1}	
F(000)	784	
Crystal size	0.35 x 0.2 x 0.2 mm^3	
Theta range for data collection	3.344 to 30.501°.	
Index ranges	-7<=h<=7, -24<=k<=23, -24<=l<=23	
Reflections collected	16305	
Independent reflections	4967 [R(int) = 0.0285]	
Completeness to theta = 25.242°	99.7 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	1 and 0.8846	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	4967 / 0 / 285	
Goodness-of-fit on F^2	1.033	
Final R indices [I>2sigma(I)]	R1 = 0.0271, wR2 = 0.0587	
R indices (all data)	R1 = 0.0337, wR2 = 0.0617	
Absolute structure parameter	-0.009(3)	
Extinction coefficient	n/a	
Largest diff. peak and hole	0.723 and -0.338 e.$Å^{-3}$	

Comments: Structure solution with SHELXS-2013. Anisotropic refinement of all non-hydrogen atoms with SHELXL-2013. All H atoms were located on difference Fourier maps calculated at the final stage of the structure refinement. The relatively high residual electron density of 0.72 e·$Å^{-3}$ may be attributed to a minor disorder of carbon atom C(8), representing the second envelope conformer of the C(5) → C(10) ring. This effect was ignored.

6.4. Water in Organic Synthesis: Aldol Reaction

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Water in Organic Synthesis

Volume Editor **S. Kobayashi**

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4.4 Aldol Reaction

M. Woyciechowska, O. El-Sepelgy, and J. Mlynarski

General Introduction

The aldol reaction is an effective method for the formation of C—C bonds in organic synthesis, but is also a critical reaction in the context of metabolism.[1,2] Aldolases operate in many biosynthetic pathways involving carbohydrates, keto acids, and some amino acids; they have evolved to catalyze the catabolism and anabolism of highly oxygenated metabolites,[3] and they catalyze both C—C bond formation and cleavage in a stereoselective fashion. The utilization of biocatalysis in synthesis has much to offer as it operates in an environmentally benign solvent, namely water, but the broad synthetic utility of enzymes is limited by their being difficult to use on a large scale and their typically narrow substrate acceptance.

Enzymatic processes in nature occur in an aqueous environment by necessity but in the laboratory water has generally been treated as a solvent to be avoided for common organic reactions. However, from a green chemistry perspective, the use of water instead of organic solvent is preferred in order to minimize environmental contamination. Moreover, water has unique physical and chemical properties, such as a high dielectric constant and a high cohesive energy density relative to most organic solvents, and as a result some reactions are accelerated by water, whereas others are inhibited. Nowadays, water is a candidate as a solvent or cosolvent for both industrial and laboratory processes, taking advantage of the varied interactions (hydrogen bonding, polarity, acidity, hydrophobicity, etc.) between it and many substrates. In addition, from practical and synthetic standpoints, the application of water brings obvious benefits; for example, it is not necessary to dry solvents and substrates for reactions in aqueous media.

In spite of the fact that several reactions with unique reactivity and selectivity have been developed in water or mixed water/organic solvents, the optimization of asymmetric aqueous aldol reactions is still ongoing. Thus, owing to the high synthetic utility of such processes,[4] there is a growing search for organic catalysts that can effectively promote asymmetric aldol reactions in water. Indeed, both chiral metal complexes and small chiral organic molecules have already been recognized that catalyze aldol reactions with relatively high chemical and stereochemical efficiency. The most interesting examples will be grouped into two categories for the purposes of this chapter: (1) indirect catalytic aldol reactions and (2) direct catalytic aldol reactions, highlighting developments in aldol-reaction-type bond-forming reactions catalyzed by metal complexes and organocatalysts in aqueous media with and without the addition of organic solvents.

4.4.1 Indirect Catalytic Aldol Addition Reactions

In nature, biochemical aldol reactions occur between substrates with unmodified carbonyl groups under catalytic control, whereas most chemical methods require the application of donor substrates in their reactive forms (e.g., silyl enol ethers).[2] The catalytic activation of the acceptor aldehyde toward the addition of a silyl enol ether, commonly referred to as the Mukaiyama reaction,[5] is one of the most successful ways of performing an asymmetric aldol reaction (Scheme 1).

for references see p 383

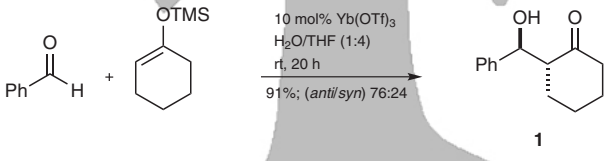
Scheme 1 The Mukaiyama Reaction

Lewis acid catalyzed aldol-type reactions of silyl enol ethers with aldehydes and ketones are very popular due to their high regio- and stereoselectivities.[6] In the reaction cycle an aldehyde is coordinated by the chiral catalyst and an asymmetric environment is created, thereby ensuring that the coordinated aldehyde is attacked by a suitable enolate derivative from the less hindered face and the aldol product is produced asymmetrically.[7]

4.4.1.1 Mukaiyama-Type Aldol Reactions

Silyl enol ethers decompose relatively quickly in protic solvents, as do traditional Lewis acid catalysts, so the application of water as a reaction medium for aldolization reactions might seem to be limited. In addition, competitive ligand exchange between a chiral catalyst and water molecules easily occurs so high enantioselectivity is difficult to achieve and, unsurprisingly, the utilization of asymmetric catalysis in aqueous solvents is still at an early stage. Nevertheless, Mukaiyama aldol reactions in water do proceed successfully thanks to the discovery of new Lewis acids that can tolerate aqueous media. Such work marks an important breakthrough in modern stereoselective synthesis because, as hinted at previously, the presence of even a small amount of water (let alone the huge excess when it is used as the solvent) stops reactions that employ traditional Lewis acids (e.g., $AlCl_3$, BF_3, $TiCl_4$, $SnCl_4$, etc.). Such Lewis acids immediately react with water, acting as the Lewis base, rather than with the substrate; however, comprehensive studies by the Kobayashi group have revealed that various lanthanide trifluoromethanesulfonates,[8] and some other metal salts,[9] do promote selected organic reactions in water. The reaction of benzaldehyde with the trimethylsilyl enol ether of cyclohexanone was initially studied and, using ytterbium(III) trifluoromethanesulfonate in water/tetrahydrofuran (1:4), the corresponding aldol **1** can be obtained in a high yield (Scheme 2).[10]

Scheme 2 Aqueous Mukaiyama Reaction Promoted by Ytterbium(III) Trifluoromethanesulfonate[10]

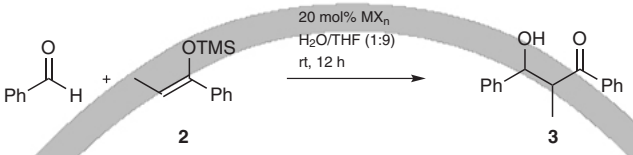


1

The same reaction carried out in dry tetrahydrofuran results in very low yield of the aldol adduct, showing that water is crucial for success and suggesting the following mechanism: After the addition of the salt to water it dissociates to give a metal cation, and hydration occurs immediately. The aldehyde already present in the system is then activated by coordination to the metal cation instead of water.

Metal salts other than those derived from rare earth elements are also water-compatible Lewis acids.[11] Indeed, other Lewis acids such as group 1–15 metal salts (chlorides, perchlorates, and trifluoromethanesulfonates) can be also applied in the aldol reaction of benzaldehyde with the silyl enol ether **2** in water/tetrahydrofuran (1:9) to give the adduct **3**. This study further reveals that iron(II), copper(II), zinc(II), cadmium(II), and lead(II) salts also work as promoters in this medium to afford the aldol **3** in good to high yields (Scheme 3).[12]

Scheme 3 The Effect of Metal Salts in a Mukaiyama Aldol Reaction in an Aqueous Solvent[12]



2 3

MX_n	Yield (%)	Ref
$ScCl_3$	70	[12]
$FeCl_2$	39	[12]
$CuCl_2$	25	[12]
$Zn(ClO_4)_2$	45	[12]
$Y(ClO_4)_3$	90	[12]
$La(OTf)_3$	80	[12]
$Pr(OTf)_3$	83	[12]
$Yb(OTf)_3$	92	[12]
$Pb(ClO_4)_2$	59	[12]

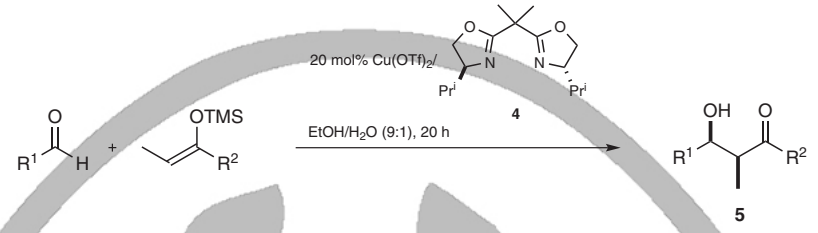
Even after the discovery of Lewis acids that are stable in aqueous media and allow catalytic stereoselective aldol-type reactions to be successfully carried out in the presence of water, two problems need to be solved before really efficient asymmetric syntheses can be undertaken. Firstly, many chiral catalysts that promote stereocontrol have low water solubility and, secondly, the metal complexes of such ligands are often unstable in water. Thus, the most important issue in the design of chiral ligands for asymmetric reactions in aqueous media is how to optimize their binding properties to the central metal cation. In spite of the aforementioned challenges, new methods have now been discovered mostly based on a multicoordination concept.

4.4.1.1.1 Application of Bis(4,5-dihydrooxazole) Ligands

The first catalytic asymmetric reactions in water were performed with copper(II) trifluoromethanesulfonate and chiral bis(4,5-dihydrooxazole) (box-type) ligands.[13,14] The combination of a copper salt and the bis(4-isopropyl-4,5-dihydrooxazole) ligand **4** is effective for aldol reactions of silyl enol ethers with aldehydes in the presence of water, affording the products **5** (Scheme 4). The results obtained in such experimentally simple procedures suggest that water accelerates the reaction and plays a crucial role in achieving good enantioselectivity.[15]

for references see p 383

Scheme 4 Mukaiyama Aldol Reactions Catalyzed by a Chiral Copper Catalyst[13]



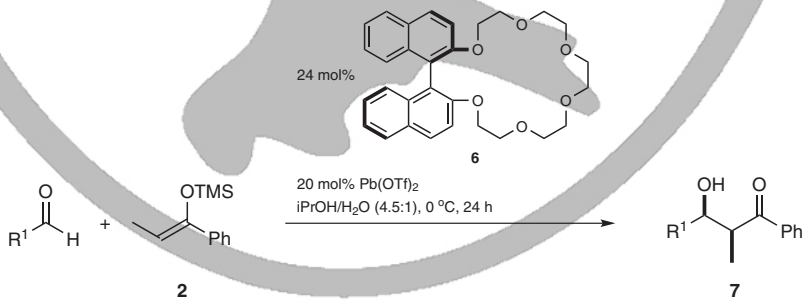
R^1	R^2	Ligand **4** (mol%)	Temp (°C)	dr (*syn*/*anti*)	ee (%)	Yield (%)	Ref
Ph	Et	20	−15	3.5:1	81	81	[13]
Ph	Et	10	−15	3.7:1	80	64	[13]
2-naphthyl	Et	20	−10	4.0:1	79	91	[13]
2-naphthyl	iPr	20	−10	4.0:1	81	97	[13]
Ph	iPr	20	5	4.0:1	77	95	[13]

β-Hydroxylated Ketones 5; General Procedure:[13]
An aldehyde (0.5 mmol), a silyl enol ether (0.75 mmol), and the ligand **4** in combination with $Cu(OTf)_2$ (5–20 mol%) were combined in $EtOH/H_2O$ (9:1; 1.5 mL) at the appropriate temperature. The mixture was stirred for 20 h at the same temperature, and brine was then added. After extraction, the crude product was purified by column chromatography (silica gel) to afford the corresponding adduct.

4.4.1.1.2 Application of Crown Ether Type Ligands

Transition metals and rare earth metals, in association with chiral crown ether type ligands, are effective Lewis acids for asymmetric Mukaiyama reaction in aqueous media. Thus, Nagayama and Kobayashi have shown that lead(II) trifluoromethanesulfonate in association with the chiral 18-crown-6 type ligand **6** catalyzes aldol reactions in aqueous alcohols affording the products **7** with enantiomeric excesses of up to 87%,[16] thereby providing the first example of a chiral crown ether based Lewis acid system that can be successfully applied to the reactions of both aryl and aliphatic aldehydes in aqueous media (Scheme 5).

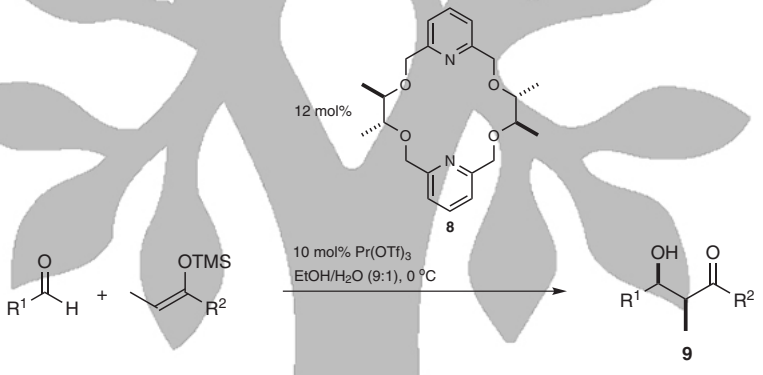
Scheme 5 Asymmetric Aldol Reactions Using a Chiral 18-Crown-6 Type Ligand[16]



R^1	dr (*syn*/*anti*)	ee (%)	Yield (%)	Ref
$(CH)_7Me$	90:10	82	79	[16]
$(CH)_5Me$	92:8	80	82	[16]
iBu	94:6	87	99	[16]
2-thienyl	82:18	62	74	[16]
iPr	90:10	75	67	[16]

The ionic diameter of the metal cation influences both diastereo- and enantioselectivity, and a good fit in size between the metal cation and the crown ligand is responsible for high stereoselectivity; this relationship is also observed for the combination of rare earth metals and the bispyridine crown ether type ligand **8**.[17] Thus, the best results are obtained when the ligand (12 mol%) and praseodymium(III) trifluoromethanesulfonate (10 mol%) are used, which promote the reaction of aromatic aldehydes with various silyl enol ethers to give the desired products **9** in high yields with good diastereoselectivities (up to 95%) and enantioselectivities (up to 85% ee) (Scheme 6). Moreover, the addition of 2,6-di-*tert*-butylpyridine (100 mol%) suppresses the hydrolysis of silyl enol ethers derived from thioesters and the use of this additive then allows access to β-hydroxylated thioesters that can be subsequently transformed into optically active alcohols.

Scheme 6 Asymmetric Aldol Reactions Using a Crown Ether Type Chiral Lewis Acid[17]



R^1	R^2	dr (*syn*/*anti*)	ee (%)	Yield (%)	Ref
2-$MeOC_6H_4$	Ph	95:5	83	96	[17]
4-ClC_6H_4	Ph	90:10	83	87	[17]
1-naphthyl	Ph	91:9	81	96	[17]
2-pyridyl	Ph	85:15	85	99	[17]
CH=CHPh	Ph	78:22	76	77	[17]
Ph	S-*t*-Bu	95:5	83	86[a]	[17]

[a] 2,6-di-*tert*-butylpyridine (100 mol%) was used as an additive.

3-Hydroxy-2-methyl-1-phenylpropan-1-ones 7; General Procedure:[16]
The aldehyde (0.5 mmol) and the silyl enol ether (0.75 mmol) in H_2O/iPrOH (1:4.5; 1.0 mL) were added to a mixture of $Pb(OTf)_2$ and the ligand **6** (0.1 mmol) in H_2O/iPrOH (1:4.5; 0.5 mL) held at 0 °C. After the mixture had been stirred for 20 h at the same temperature, H_2O (10 mL) and EtOAc (15 mL) were added. The organic layer was then separated and the aqueous layer was extracted with EtOAc. After removing the H_2O from the aqueous layer,

for references see p 383

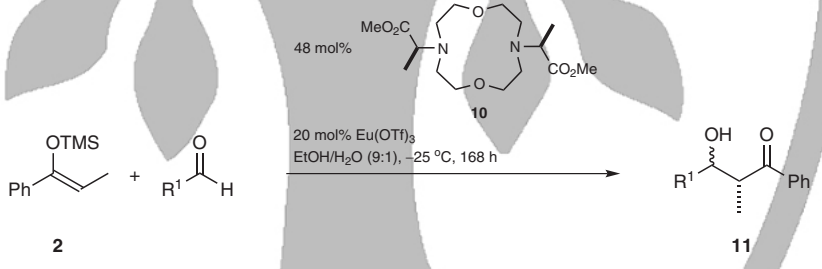
$Pb(OTf)_2$ was recovered quantitatively. The organic layer was dried (Na_2SO_4) and concentrated under reduced pressure, and the residue was purified by column chromatography (silica gel) to afford the corresponding aldol product. The chiral crown ether **6** was also recoverable during the column chromatography procedure. The diastereomers of the adduct **7** were separated, and the enantiomeric excess of each diastereomer was determined by HPLC analysis using a chiral column.

β-Hydroxylated Ketones 9; General Procedure:[17]
The chiral ligand **8** (12–24 mol%) in H_2O/EtOH (1:9; 0.4 mL) was added to a soln of $Pr(OTf)_3$ (10–20 mol%) in H_2O/EtOH (1:9; 0.1 mL) at 0 °C. The aldehyde (0.2 mmol) in H_2O/EtOH (1:9; 0.3 mL) and a soln of the silyl enol ether (0.3 mmol) in H_2O/EtOH (1:9; 0.3 mL) were then added, and the mixture was stirred for 18 h at the same temperature. The reaction was quenched by the addition of aq $NaHCO_3$ and the resulting mixture was extracted with CH_2Cl_2 (3 ×), dried (Na_2SO_4), and concentrated. The residue was purified by chromatography (silica gel, EtOAc/hexane 1:6).

4.4.1.1.3 Europium-Catalyzed Mukaiyama Aldol Reactions

The water-tolerant ligand **10**, the structure of which was inspired by that of a macrocyclic contrast agent containing gadolinium,[18] has been developed by Allen.[19] Application of this ligand in association with europium(III) trifluoromethanesulfonate in aqueous Mukaiyama aldol reactions results in the highest stereoselectivities reported to date for any Lewis acid based catalyst. Here, a wide range of aromatic aldehydes with both electron-donating and electron-withdrawing substituents, as well as aliphatic and α,β-unsaturated aldehydes, are shown to react with the silyl enol ether **2** to give the aldol products **11** (Scheme 7).

Scheme 7 Asymmetric Mukaiyama Reactions Catalyzed by a Europium(III) Complex[19]



R^1	dr (*syn*/*anti*)	ee[a] (%)	Yield (%)	Ref
Ph	32:1	93	92	[19]
4-ClC_6H_4	21:1	91	75	[19]
4-Tol	24:1	90	73	[19]
CH=CHMe	21:1	93	65	[19]
Me	1:22	97	32	[19]
$(CH_2)_5Me$	23:1	96	22	[19]
Cy	1:49	95	12	[19]

[a] Of major isomer.

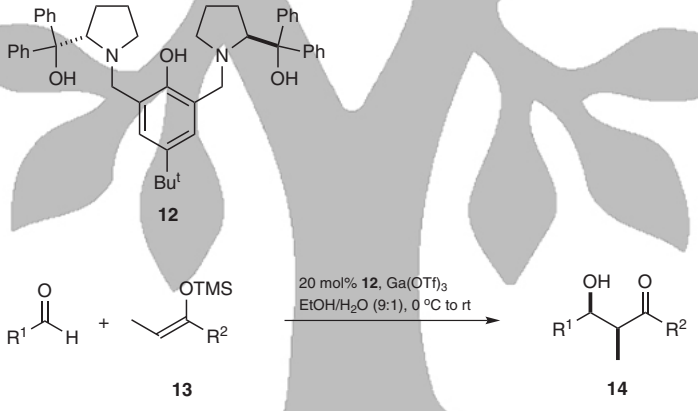
3-Hydroxy-2-methyl-1-phenylpropan-1-ones 11; General Procedure:[19]
A mixture of the chiral ligand **10** (48 mol%) and $Eu(OTf)_3$ (20 mol%) in EtOH/H_2O (9:1; 0.4 mL) was stirred at 50 °C for 2 h and then cooled to −25 °C. The aldehyde

(0.0325 mmol, 1.0 equiv) and the silyl enol ether **2** (0.0488 mmol, 1.5 equiv) were added, and the resulting mixture was stirred for 168 h at −25 °C. This mixture was then directly subjected to column chromatography (silica gel, EtOAc/hexane 1:10), and the volatiles were removed from the eluent under reduced pressure to yield a mixture of the *syn*- and *anti*-products. The diastereomeric ratio and enantiopurity were determined by HPLC analysis.

4.4.1.1.4 Application of a Trost-Type Semicrown Ligand

In 2005 Li demonstrated the use of a gallium(III) trifluoromethanesulfonate based Lewis acid incorporating the chiral semicrown ligand (Trost's ligand) **12** for catalytic asymmetric Mukaiyama aldol reactions between aldehydes and silyl enol ethers in aqueous media.[20] Gallium(III) trifluoromethanesulfonate alone cannot be used as it decomposes in aqueous solution and rapid hydrolysis of the silyl enol ether then occurs, but the strong binding of the gallium(III) cation to the semicrown ligand **12** and the ligand acceleration effect of the resultant chiral gallium catalyst are responsible for the high enantioselectivities observed in subsequent aqueous asymmetric aldolization reactions. Thus, in general, for the combination of the silyl enol ethers **13**, derived from aromatic ketones, and aromatic aldehydes the corresponding products **14** are obtained with high diastereoselectivities and enantioselectivities (Scheme 8); however, for silyl enolates derived from aliphatic ketones or aliphatic aldehydes lower yields and selectivities are observed.

Scheme 8 Mukaiyama Aldol Reactions Catalyzed by a Gallium-Based Chiral Lewis Acid[20]



R^1	R^2	dr (*syn*/*anti*)	ee[a] (%)	Yield (%)	Ref
Ph	Ph	85:15	85	85	[20]
4-Tol	Ph	90:10	88	89	[20]
4-$MeOC_6H_4$	Ph	88:12	84	80	[20]
4-ClC_6H_4	Ph	82:18	78	77	[20]
CH=CHPh	Ph	90:10	86	90	[20]
1-naphthyl	Ph	80:20	82	87	[20]
1-naphthyl	S-*t*-Bu	99:1	96	72	[20]

[a] Of *syn*-isomer.

for references see p 383

(2*S*,3*S*)-3-Hydroxy-2-methyl-1,3-diphenylpropan-1-one (14, $R^1 = R^2 = Ph$);
Typical Procedure:[20]

A soln of the chiral ligand **12** (0.12 mmol) and $Ga(OTf)_3$ (51.7 mg, 0.1 mmol) in CH_2Cl_2 (1 mL) was stirred for 6 h at rt. The solvent was then evaporated to give slightly yellow solid, which was used directly as the chiral catalyst.

PhCHO (5 mL, 0.5 mmol) and the silyl enol ether **13** ($R^2 = Ph$; 154.4 mg, 0.75 mmol) were added to a soln of the previously prepared catalyst in H_2O/EtOH (1:9) held at 0–5 °C, followed by stirring for 36 h at 0 °C to rt. The reaction was quenched by the addition of aq $NaHCO_3$ and the resultant mixture was extracted with Et_2O (3 ×). The combined extracts were dried (Na_2SO_4) and concentrated, and the residue was purified by flash chromatography (silica gel, EtOAc/petroleum ether 1:10) to give a mixture of the *syn*- and *anti*-isomers.

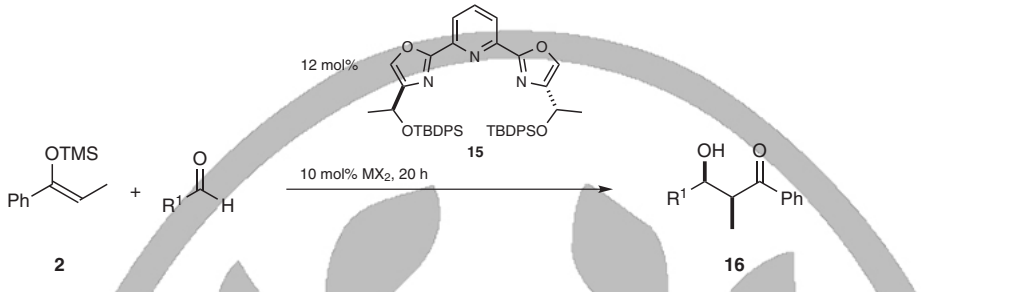
4.4.1.1.5 Application of Iron(II) and Zinc(II) Complexes

Except for the examples shown in Scheme 7 (Section 4.4.1.1.3), previously used methodologies fail when aliphatic aldehydes are the substrates and a major decrease of enantioselectivity is commonly observed. However a simple solution has been reported by Mlynarski and co-workers, who used chiral zinc[21] and iron[22] catalysts with pybox-type ligands for asymmetric aqueous Mukaiyama reactions.

Most of the other catalysts used for such reactions contain heavy or rare earth metals, which create difficulties due to their toxicity and/or high price. In contrast, iron is the most widespread metal on earth, making it inexpensive and environmentally benign, so that enantioselective reactions promoted by iron complexes are in much demand. In fact, the use of iron-based chiral Lewis acids for the Mukaiyama reaction is possible, but there are problems; for example, some iron complexes are unstable in aqueous media and the catalytic system itself is capricious and very sensitive to many other factors. In spite of these difficulties, a complex of iron(II) chloride with hindered 2,6-bis(4,5-dihydrooxazol-2-yl)pyridine ligand **15** shows very good catalytic activity and enantioselectivity in aqueous media. For example, this water-stable chiral Lewis acid promotes condensations between aromatic silyl enol ethers and a range of aldehydes affording the products **16** in good yields, with excellent *syn*-diastereoselectivity and enantiomeric excesses up to 92% (Scheme 9).[22,23]

Synthetic zinc(II) coordination complexes have been studied extensively as simplified models for various biological processes;[24,25] for example, in nature aldol reactions can be catalyzed by class II aldolases, which contain a zinc(II) cofactor in the active site.[26] This has inspired the utilization of a combination of the ligand **15** and zinc(II) trifluoromethanesulfonate [$MX_2 = Zn(OTf)_2$] to form a complex that is a remarkably efficient water-compatible chiral Lewis acid catalyst for reactions between the silyl enol ether **2** and aldehydes. Employed in this way, it affords the corresponding aldol products **16** with enantiomeric excesses up to 95% (Scheme 9). The catalyst complex is considered to have an octahedral structure where the octahedron positions are occupied by water molecules. Due to the presence of bulky substituents, attack toward the coordinated carbonyl group of the aldehyde is more effectively shielded on one face than on the other.[21,23]

Scheme 9 Examples of Iron(II)- and Zinc(II)-Catalyzed Mukaiyama Aldol Reactions[21,23]



R^1	MX_2	Conditions	dr (*syn*/*anti*)	ee[a] (%)	Yield (%)	Ref
4-$MeOC_6H_4$	$FeCl_2$	EtOH/H_2O (9:1), 0 °C	94:6	92	94	[21]
Ph	$FeCl_2$	EtOH/H_2O (9:1), 0 °C	96:4	84	84	[21]
4-Tol	$FeCl_2$	EtOH/H_2O (9:1), 0 °C	95:5	84	95	[21]
Ph	$Zn(OTf)_2$	EtOH/THF/H_2O (45:45:10), −20 °C	93:7	90	90	[21]
Ph	$Zn(OTf)_2$	EtOH/H_2O (9:1), −20 °C	95:5	91	80	[21]
4-$MeOC_6H_4$	$Zn(OTf)_2$	EtOH/H_2O (9:1), −20 °C	93:7	95	90	[21]
4-Tol	$Zn(OTf)_2$	EtOH/H_2O (9:1), −20 °C	92:8	90	92	[21]
CH=CHPh	$Zn(OTf)_2$	EtOH/THF/H_2O (45:45:10), −20 °C	9:1	86	94	[21]
CH=CHPh	$Zn(OTf)_2$	EtOH/H_2O (9:1), −20 °C	9:1	87	98	[21]

[a] Of *syn*-isomer.

3-Hydroxy-2-methyl-1-phenylpropan-1-ones 16; General Procedure Using Iron(II) Chloride:[23]

A mixture of the pybox ligand **15** (47 mg, 0.06 mmol, 12 mol%) and $FeCl_2$ (6.5 mg, 0.05 mmol, 10 mol%) in deoxygenated EtOH/H_2O (9:1; 1.5 mL) was stirred at 0 °C under argon until all the solids dissolved (15–20 min). The silyl enol ether **2** (230 μL, 1.0 mmol, 2 equiv) and the appropriate aldehyde (0.5 mmol) were added to the resulting deep-red soln, and the mixture was stirred at 0 °C for 5 h under argon. This mixture was diluted with *t*-BuOMe and washed with H_2O and brine. The organic phase was collected, dried, and concentrated to dryness, and the residue was purified by chromatography (silica gel, typically EtOAc/hexane 1:4).

3-Hydroxy-2-methyl-1-phenylpropan-1-ones 16; General Procedure Using Zinc(II) Trifluoromethanesulfonate:[23]

A mixture of the pybox ligand **15** (23 mg, 0.03 mmol, 12 mol%) and $Zn(OTf)_2$ (9 mg, 0.025 mmol, 10 mol%) in EtOH/H_2O (9:1; 1.0 mL) was stirred at −20 °C (15–20 min) to form a homogeneous soln, before the silyl enol ether **2** (115 μL, 0.5 mmol, 2 equiv) and the appropriate aldehyde (0.25 mmol) were added. The mixture was left in a refrigerator at −20 °C overnight without stirring and then poured directly onto a silica gel column, and the adduct was eluted with EtOAc/hexane (1:4).

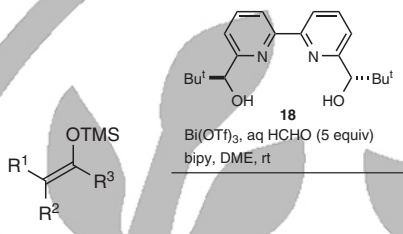
4.4.1.1.6 Hydroxymethylation of Silyl Enol Ethers

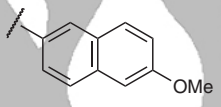
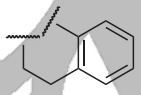
The hydrophilic compound formaldehyde is one of the most important C1 electrophiles in organic synthesis; for example, it reacts with enolates to introduce a hydroxymethyl function α to the carbonyl group in the product. Although bismuth(III) trifluoromethanesulfonate is unstable in the presence of water, it is stabilized when complexed with the chiral bipyridine **18**, and as a result it enables catalytic hydroxymethylation reactions of

for references see p 383

silylated enolates in aqueous media to be carried out. Thus, when 1 mol% of the bismuth catalyst is used in reactions between the silyl enol ethers **17** and formaldehyde it smoothly affords the hydroxymethylated products **19** in high yields, and with high enantioselectivity (Scheme 10).[27]

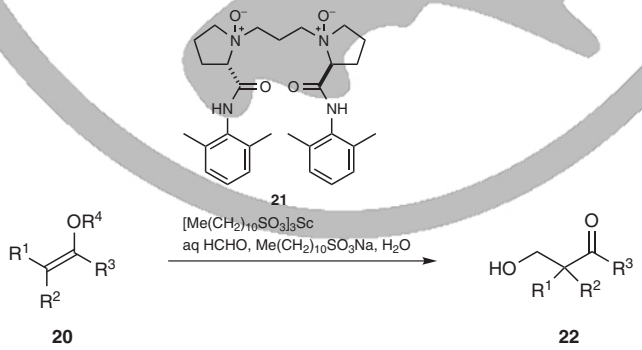
Scheme 10 Catalytic Hydroxymethylation Reactions of Silyl Enol Ethers Using Bismuth(III) Trifluoromethanesulfonate and a Chiral Bipyridine Ligand[27]

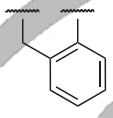


R^1	R^2	R^3	Time (h)	ee (%)	Yield (%)	Ref
Me	H	Ph	21	91	93	[27]
Et	H	Ph	70	92	79	[27]
Me	H		22	92	59	[27]
Pr			22	93	68	[27]
Bn		$(CH_2)_4$	48	92	79	[27]

Kobayashi and co workers have developed another methodology for the asymmetric hydroxymethylation of the silyl enol ethers **20**, this time utilizing an aqueous solution of formaldehyde in the absence of an organic cosolvent. In this case, the chiral ligand **21** in association with scandium(III) undecanesulfonate and sodium undecanesulfonate (or with scandium dodecyl sulfate) provides the desired products **22** in good to high yields and stereoselectivities (>90% ee) (Scheme 11).[28]

Scheme 11 Catalytic Hydroxymethylation Reactions of Silyl Enol Ethers Using Scandium(III) Undecanesulfonate and a Chiral Bis(2-carbamoylpyrrolidine oxide) Ligand[28]



R^1	R^2	R^3	R^4	Time (h)	ee (%)	Yield (%)	Ref
Me	H	4-ClC_6H_4	TMS	48	92	84	[28]
Me	H	Ph	$SiMe_2H$	48	91	91	[28]
Et	H	Ph	$SiMe_2H$	48	90	92	[28]
Me			TMS	48	94	83	[28]

β-Hydroxy Ketones 19; General Procedure Using Bismuth(III) Trifluoromethanesulfonate:[27]

CAUTION: *Formaldehyde is a probable human carcinogen, a severe eye, skin, and respiratory tract irritant, and a skin sensitizer.*

A mixture of $Bi(OTf)_3$ (14 mg, 0.020 mmol) and the chiral ligand **18** (20 mg, 0.060 mmol) in DME (1 mL) was stirred at rt for 30 min to afford a 20 mM soln of the catalyst. This soln (150 μL) was cooled at 0 °C for 10 min and 81 mM 2,2′-bipyridyl in DME (185 μL) was added, followed by 35% aq HCHO (129 mg, 1.5 mmol) and the silyl enol ether **17** (0.30 mmol). The resulting suspension was stirred until the silyl enol ether had disappeared completely (TLC), and then the reaction was quenched by the addition of sat aq $NaHCO_3$. The resultant mixture was extracted with CH_2Cl_2 (3 ×) and the combined extracts were dried (Na_2SO_4), and concentrated. The residue was purified by preparative TLC (silica gel, hexane/EtOAc 2:1) to give the appropriate adduct. The enantiomeric excess of this product was determined by chiral HPLC.

β-Hydroxy Ketones 22; General Procedure Using Scandium(III) Undecanesulfonate:[28]

CAUTION: *Formaldehyde is a probable human carcinogen, a severe eye, skin, and respiratory tract irritant, and a skin sensitizer.*

A mixture of $[Me(CH_2)_{10}SO_3]_3Sc$ (30 μmol), the chiral ligand **21** (36 μmol), and sodium undecanesulfonate (450 μmol) in H_2O (3.0 mL) was first stirred for 1 h at 20 °C, and then cooled to 5 °C as aq HCHO (125 mg, 1.5 mmol) and the silyl enol ether **20** (0.3 mmol) were introduced. The mixture was stirred at 5 °C for 48 h, before the reaction was quenched by the addition of sat. aq $NaHCO_3$ and brine, and the resulting mixture was extracted with CH_2Cl_2 (3 ×). The combined extracts were washed with brine (3 ×), dried (Na_2SO_4), and concentrated, and the residue was purified by preparative TLC (silica gel, hexane/EtOAc 3:2) to give the appropriate adduct. The enantiomeric excess of this product was determined by chiral HPLC.

4.4.2 Direct Catalytic Aldol Reactions

A variety of in vitro aldol reactions can be performed with artificial aldolase antibodies, but not without problems.[29] In nature, stereoselective C—C bond formation readily occurs assisted by enzymes (for example, by lyase enzymes) that catalyze the usually reversible additions of carbon nucleophiles to carbonyl groups. As a result, aldolases are essential for many biosynthetic pathways that involve carbohydrates, keto acids, and some amino acids.[30] Such enzymes bind their respective donor substrates (e.g., pyruvate, dihydroxyacetone phosphate, dihydroxyacetone, glycine/alanine, and acetaldehyde) with high specificity and generally do not accept any other donors. This is a major drawback in organic synthesis, as is a lack of large-scale compatibility but, despite the fact that the

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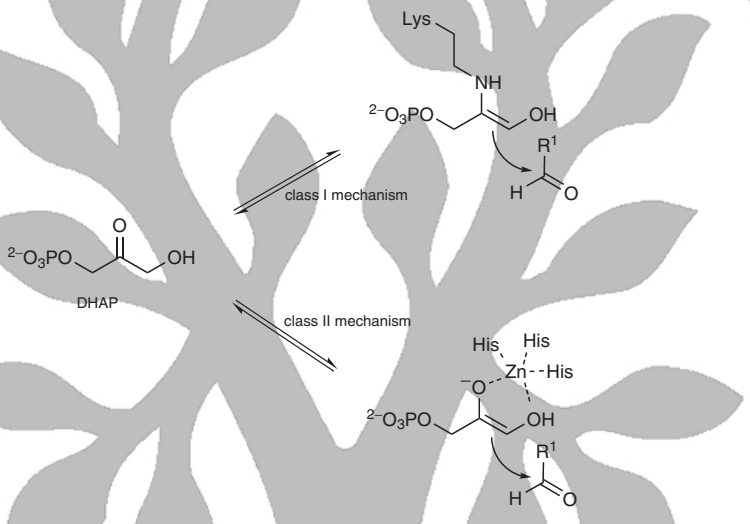
inherent specificity of aldolases limits the number of substrates that can be used and also the stereochemical outcomes of the reactions involved, some examples of successful applications are now recorded in the literature.[3]

Aldolases, in general, can be divided into two major classes based on their working mechanisms. Representative cases are depicted in Scheme 12 where dihydroxyacetone phosphate (DHAP) is the donor substrate.[3] Thus, class I aldolases activate this donor by forming a Schiff base as an intermediate in the active site, and the activated donor then adds stereoselectively to the acceptor aldehyde (R^1CHO). On the other hand, for class II aldolases a metal cofactor is bound to the enzyme active site via coordination to three histidine residues. The coordinated metal cations [mostly Zn(II) but also Co(II) or Fe(II)] then act as Lewis acids, and activate the carbonyl compound for a reaction with the aldehyde.

Scheme 12 Class I and Class II Aldolase Catalyzed Aldol Reactions[3]



A challenge in enhancing the efficiency of the aldol reaction is to find a method that will asymmetrically catalyze a wide range of direct additions without requiring the preformation of the nucleophile. Indeed, since the beginning of the current century, many small chiral organic molecules, with or without a metal cofactor, have been reported as being capable of simultaneously activating the donor and the acceptor carbonyl compound,[31,32] even in water.[33–38]

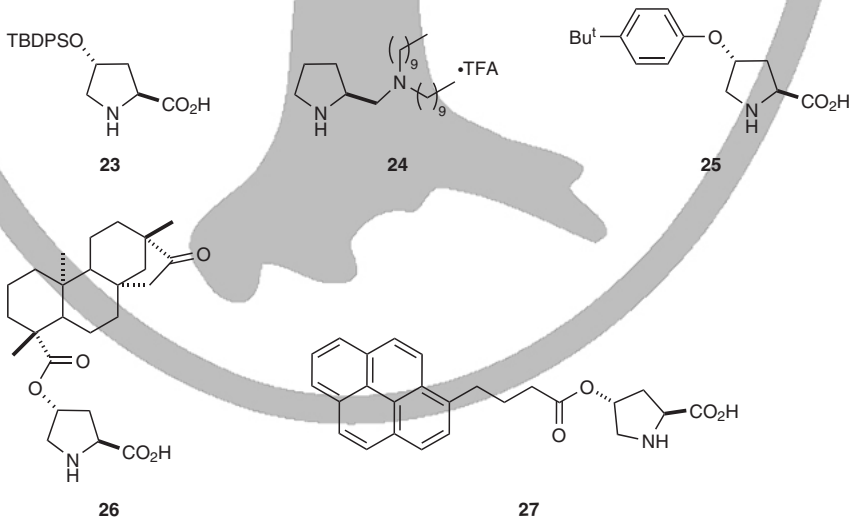
4.4.2.1 Enamine-Based Direct Aldol Reactions

Asymmetric aldol additions of unmodified ketones or aldehydes promoted by purely organic molecules have received great attention and the seminal work by List and co-workers[39] on the intermolecular application of proline-catalyzed direct asymmetric aldol reactions has stimulated further research, so that the application of small organic molecules as catalysts (organocatalysts) now gives a means of mimicking class I aldolases.[40] Such organocatalysts are most often substituted primary amino acids,[33] substituted proline amides, or prolines substituted in positions C2 or C4.[33–38] Most of the direct aldol reactions described are carried out either in water or in the presence of water and conducted in the heterogeneous phase either in a biphasic medium or in the form of an emulsion. In most cases, the presence of a hydrophobic group in the water-compatible catalyst is essential to achieve high activity and stereoselectivity.

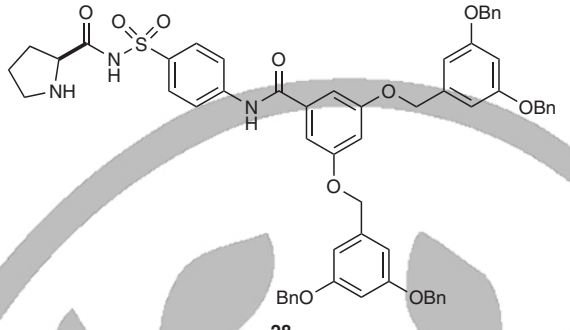
4.4.2.1.1 Synthesis of 2-[Aryl(hydroxy)methyl]cycloalkanones

The simplicity and reactivity of cyclohexanone has attracted several research groups to select its condensation reaction with activated 4-nitrobenzaldehyde to produce the aldol adduct **34** (Scheme 13) as a model for developing new water-compatible organocatalysts that work efficiently without the addition of organic solvents. The unexpected discovery of the efficiency of siloxylated prolines in direct aqueous aldol reactions enables the design of water-compatible 2-substituted proline organocatalysts from commercially available *trans*-4-hydroxyproline,[41] and ultimately to large-scale protocols for the aldol condensations of cyclic ketones and aldehydes in presence of water using only 1 mol% of the siloxylated proline **23**.[42] Similarly, the trifluoroacetate **24**, bearing a hydrophobic tertiary amino group bonded to the proline nucleus, can be used in a large excess of water.[43] Both of these catalysts demonstrate excellent reactivity and stereoselectivity without need for an organic cosolvent. Following on from these discoveries, several other proline-based organocatalysts that can work "in water", "on water" or "in the presence of water" have been reported.[38,44–46] The term "in water" is suggested to be used for reactions in which the participating substrates and the catalyst are homogeneously dissolved in water, whereas both of the phrases "in the presence of water" and "on water" refer to reactions in biphasic systems and emulsion media in which the reactions occur in an organic phase, and water has an effect on the reaction activity and selectivity. In other examples of the organocatalysts listed in Scheme 13, the phenoxylated proline **25**, in combination with sulfated β-cyclodextrin, demonstrates excellent enantioselectivity for stoichiometric direct aldol reactions between cyclohexanones and aromatic aldehydes.[47] Changing the phenoxy group to an isosteviol unit or a large acyl group as exemplified by the organocatalysts **26** and **27**, respectively, achieves similar results.[48,49] Furthermore, different amide and sulfonamide proline derivatives show high activity and stereoselectivity such as that demonstrated by the proline sulfonamide **28**, the proline amide **29**,[50,51] and the bis(proline amide) **30** in combination with trifluoroacetic acid.[52] Other amides and sulfonamides derived from proline are modified by introducing a more hydrophobic group at position C4; examples are the phenoxylated proline amide **31**,[53] the siloxylated proline amide **32**,[54] and the siloxylated proline sulfonamide **33**.[55]

Scheme 13 Synthesis of (2*S*)-2-[(*R*)-Hydroxy(4-nitrophenyl)methyl]cyclohexanone Using a Variety of Chiral Catalysts[42,43,47–55]



for references see p 383



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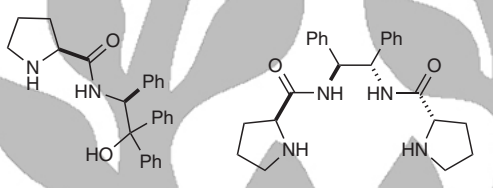
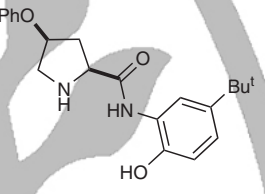
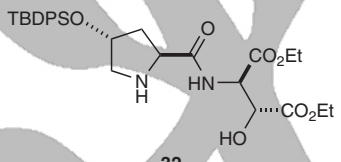


29 30



31



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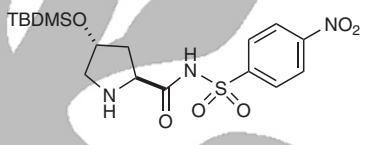
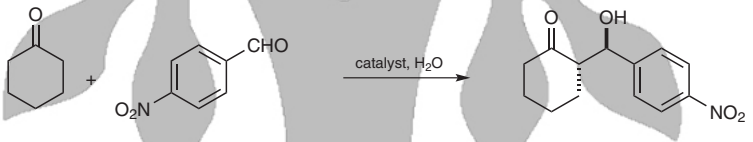


33



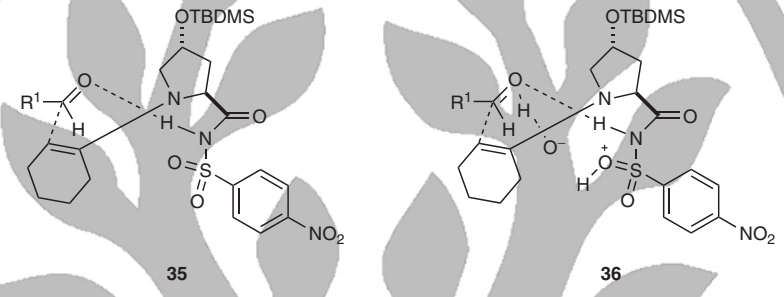
34

Catalyst (mol%)	Cyclohexanone (equiv)	Temp (°C)	Time (h)	de (%)	ee (%)	Yield (%)	Ref
23 (10)	5	rt	42	90	>99	86	[42]
24 (10)	2	25	24	78	94	99	[43]
25 (2)[a]	1	rt	48	92	>99	100	[47]
26 (5)	5	25	9	82	99	>99	[48]
27 (2)	5	rt	24	98	>99	>99	[49]
28 (10)	5	rt	24	98	>99	>99	[50]
29 (0.5)	4	−10	20–48	74	91	80	[51]
30 (10)[b]	5	0	70	92	95	89	[52]
31 (10)	2	rt	12	98	94	99	[53]
32 (1)	2	25	5	>98	94	99	[54]
33 (3)	1	rt	12	94	99	>99	[55]

[a] With sulfated β-cyclodextrin.
[b] With TFA.

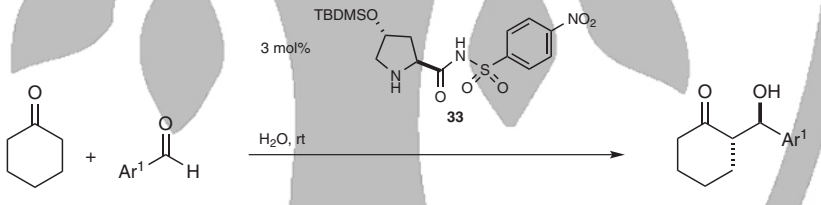
The design of the most effective catalysts takes into consideration the well-known concept that the presence of a hydrophobic moiety allows the reaction to take place within a hydrophobic pocket well away from water molecules, thus mimicking the behavior of natural aldolases. Furthermore, it is proposed that the reaction between cyclohexanone and 4-nitrobenzaldehyde using the catalyst **33** may occur via an enamine intermediate within the transition states **35** and **36**, where the aldehyde is strongly activated by N—H hydrogen bonding to the catalyst ensuring high stereochemical control (Scheme 14);[51,55] presumably, similar transition states may operate in the other aldolizations of this type.

Scheme 14 Proposed Transition States for a Crossed Aldol Reaction Between Cyclohexanone and 4-Nitrobenzaldehyde[55]



Stoichiometric aldol condensations between cyclohexanone and aromatic aldehydes in large amounts of water have also been achieved.[55] Only 3 mol% of the *N*-arylsulfonylated proline amide **33** is used at room temperature, in the absence of any Brønsted acid or surfactant, giving very good yields (up to 100%) of the aldol adducts **37** in excellent diastereoselectivities (dr up to >99:1) and enantioselectivities (98 to >99% ee) (Scheme 15).[55]

Scheme 15 Synthesis of (2*S*)-2-[(*R*)-Aryl(hydroxy)methyl]cyclohexanones[55]

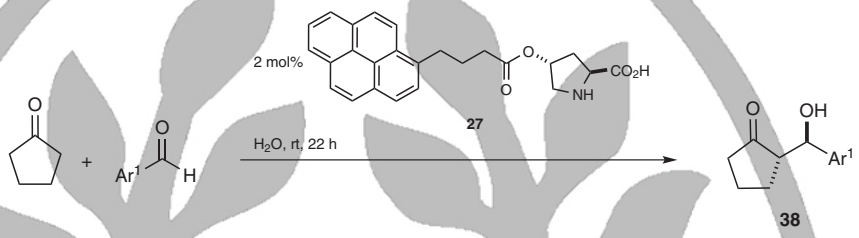


Ar^1	Time (h)	dr (*anti*/*syn*)	ee (%)	Yield (%)	Ref
Ph	96	93:7	98	75	[55]
2-$O_2NC_6H_4$	48	98:2	98	99	[55]
3-$O_2NC_6H_4$	12	96:4	98	99	[55]
4-NCC_6H_4	48	>99:1	>99	70	[55]
4-ClC_6H_4	96	>99:1	>99	86	[55]
4-$F_3CC_6H_4$	96	97:3	>99	67	[55]
4-Tol	96	95:5	>99	72	[55]
4-BrC_6H_4	96	97:3	>99	74	[55]
3-ClC_6H_4	96	96:4	99	83	[55]
2-ClC_6H_4	96	98:2	>99	80	[55]

for references see p 383

In contrast to reactions with cyclohexanone, most of the known organocatalysts exhibit low diastereoselectivity when cyclopentanone is the donor. However, the hydrophobic acyloxylated proline **27** is an exception and it reacts with aromatic aldehydes showing excellent activity and stereoselectivity. Additives are not required and when 5 equivalents of the donor are used 2 mol% of the catalyst is sufficient to achieve a high conversion into the corresponding aldol products **38** (Scheme 16).[49]

Scheme 16 Synthesis of (2*S*)-2-[(*R*)-Aryl(hydroxy)methyl]cyclopentanones[49]



Ar^1	dr (*anti*/*syn*)	ee (%)	Yield (%)	Ref
4-$O_2NC_6H_4$	88:12	>99	>99	[49]
3-$O_2NC_6H_4$	92:8	99	>99	[49]
4-$F_3CC_6H_4$	85:15	98	>99	[49]
4-NCC_6H_4	86:14	99	>99	[49]
4-ClC_6H_4	88:12	98	>99	[49]
2-ClC_6H_4	88:12	98	>99	[49]
Ph	86:14	96	97	[49]
4-BrC_6H_4	87:13	98	98	[49]
4-Tol	85:15	96	85	[49]
4-$MeOC_6H_4$	80:20	93	97	[49]

(2*S*)-2-[(*R*)-Aryl(hydroxy)methyl]cyclohexanones, e.g. 34; General Procedure:[55]
Cyclohexanone (2 mmol) was added to a mixture of the aldehyde (2 mmol), the siloxylated proline **33** (3 mol%) and H_2O (0.5 mL) at rt. After being stirred for the indicated time, the mixture was treated with sat. aq NH_4Cl and extracted with EtOAc. The organic layer was dried ($MgSO_4$) and concentrated, and the residue was purified by flash TLC (silica gel, petroleum ether/EtOAc).

(2*S*)-2-[(*R*)-Aryl(hydroxy)methyl]cyclohexanones, e.g. 34; Large-Scale General Procedure for Liquids:[42]
Catalyst **23** (259 mg, 0.74 mmol) was added to a mixture of the aldehyde (74.4 mmol) and cyclohexanone (13.7 g, 149 mmol) in H_2O (3.8 mL) at rt. After the mixture had been stirred for 48 h, silica gel (2.5 g) was added and the resulting mixture was filtered through more silica gel using EtOAc (60 mL) as the eluent. The filtrate was distilled to afford the aldol product as a colorless oil

(2*S*)-2-[(*R*)-Aryl(hydroxy)methyl]cyclohexanones, e.g. 34; Large-Scale General Procedure for Solids:[42]
Cyclohexanone (13.7 mL, 132 mmol) was added to a mixture of the aldehyde (66.2 mmol), the siloxylated proline **23** (244 mg, 0.66 mmol), and H_2O (3.6 mL) at rt. After the mixture had been stirred for 42 h at ambient temperature, a solid separated out and this was filtered off, and washed with hexane (5.0 mL). The filtrate was concentrated to dryness, and

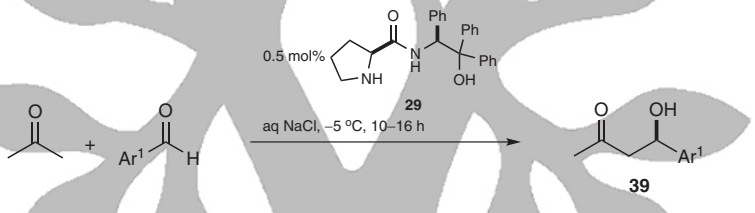
the residue was dried in vacuo and purified by recrystallization [iPrOH (21.5 mL)] to obtain colorless crystals.

(2*S*)-2-[(*R*)-Aryl(hydroxy)methyl]cyclopentanones 38**; General Procedure:**[49]
The catalyst **27** (0.01 mmol) was added to a mixture of the aldehyde (0.5 mmol) and cyclopentanone (2.5 mmol) in distilled H_2O (0.175 mL), and the mixture was stirred at rt. When the reaction was over, EtOAc was added and the organic phase was washed with H_2O. The organic layer was dried ($MgSO_4$) and concentrated under reduced pressure, and the residue was purified by chromatography (petroleum ether/EtOAc).

4.4.2.1.2 Synthesis of 4-Aryl-4-hydroxybutan-2-ones

Singh and co-workers have reported the use of the proline amide **29** as an organocatalyst capable of mediating the direct asymmetric aldol reactions of acetone with aldehyde acceptors to furnish the adducts **39** with high enantioselectivities. The medium used is brine with a low catalyst loading (0.5 mol%) (Scheme 17).[51] The authors suggest that the aldehyde is activated by double hydrogen bonding[56] utilizing the NH and OH functions of the catalyst; this enhances overall efficiency and the yields observed are up to 85%. The diphenyl groups at the terminus of the side chain of the catalyst also seem to be an important factor in achieving stereochemical control during such reactions.

Scheme 17 Synthesis of 4-Aryl-4-hydroxybutan-2-ones[51]



Ar^1	ee (%)	Yield (%)	Ref
Ph	>99	83	[51]
2-ClC_6H_4	>99	80	[51]
3-FC_6H_4	>99	85	[51]
3-ClC_6H_4	99	85	[51]
4-FC_6H_4	>99	80	[51]
3-$MeOC_6H_4$	>99	85	[51]
4-$F_3CC_6H_4$	91	84	[51]
3-BrC_6H_4	>99	75	[51]
4-$MeOC_6H_4$	>99	75	[51]
3-Tol	>99	72	[51]

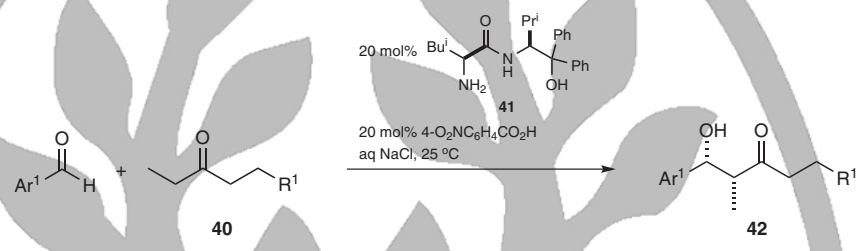
4-Aryl-4-hydroxybutan-2-ones 39**; General Procedure:**[51]
The aldehyde (0.5 mmol) was added to a mixture of acetone (2 mmol) and the organocatalyst **29** (0.5 mol%) in brine (0.5 mL) held at −5 °C. The mixture was stirred and the progress of the reaction was monitored (TLC). After the reaction was over, the mixture was diluted with EtOAc (10 mL) and the organic layer was dried (Na_2SO_4), and filtered. The filtrate was purified by column chromatography (silica gel) and the enantiomeric excess of the aldol product was determined by chiral HPLC.

for references see p 383

4.4.2.1.3 Synthesis of *syn*-α-Methyl-β-hydroxy Ketones

Long-chain aliphatic ketones that act as donors in cross-aldol reactions have been investigated by Gong who has used organocatalyst **41** with 4-nitrobenzoic acid as an additive to prepare a set of (1*R*,2*R*)-1-aryl-1-hydroxy-2-methylpentan-3-ones **42** in high yields from the ethyl ketones **40**. The modified primary amino acid catalyst **41** promotes the formation of the *syn*-diastereomers of the products with diastereomeric ratios up to 7:1 and enantioselectivities of up to 97% (Scheme 18).[57]

Scheme 18 Synthesis of (1*R*,2*R*)-1-Aryl-1-hydroxy-2-methylpentan-3-ones[57]



Ar^1	R^1	Time (h)	dr (*syn*/*anti*)	ee (%)	Yield (%)	Ref
4-O$_2$NC$_6$H$_4$	H	30	5:1	95	98	[57]
4-MeO$_2$CC$_6$H$_4$	H	48	5:1	93	95	[57]
4-F$_3$CC$_6$H$_4$	H	48	3:1	92	92	[57]
2-ClC$_6$H$_4$	H	72	4:1	95	82	[57]
3-BrC$_6$H$_4$	H	72	4:1	94	98	[57]
2,3-Cl$_2$C$_6$H$_3$	H	48	4:1	97	78	[57]
3,4,5-F$_3$C$_6$H$_2$	H	48	7:1	94	88	[57]
4-O$_2$NC$_6$H$_4$	Et	48	5:1	94	86	[57]
4-O$_2$NC$_6$H$_4$	Bu	60	5:1	94	85	[57]
3-O$_2$NC$_6$H$_4$	Me	48	5:1	92	81	[57]

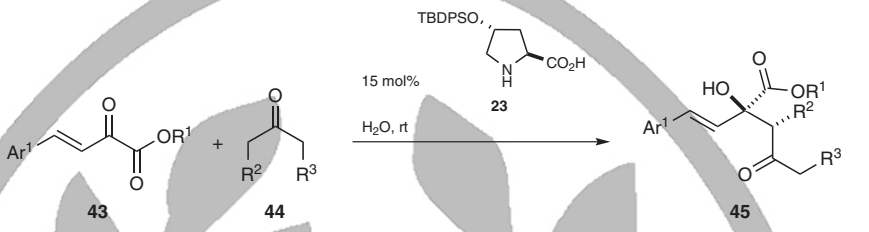
(1*R*,2*R*)-1-Aryl-1-hydroxy-2-methylpentan-3-ones 42; General Procedure:[57]
A suspension of the aldehyde (0.3 mmol), the catalyst **41** (20 mol%), 4-nitrobenzoic acid (20 mol%), and the ketone **40** (3 mmol) in brine (0.5 mL) was stirred at rt for 30–120 h. The reaction was quenched with sat. aq NH_4Cl and the resulting mixture was extracted with EtOAc (3 × 15 mL). The combined organic layers were washed with brine (1 × 10 mL) and dried (Na_2SO_4). After removal of the solvent under reduced pressure, the residue was purified by flash column chromatography (silica gel) to give the aldol product.

4.4.2.1.4 Synthesis of Alcohols Containing a Quaternary Carbon Atom

The development of the asymmetric formation of a quaternary carbon center is an instructive subject due to its great importance for the total synthesis of optically active natural products. In an example of ketone–ketone cross-aldol reactions that generate a quaternary carbon center, the siloxylated proline **23** is shown to efficiently catalyze reactions between donor ketones **44** and electrophilically activated β,γ-unsaturated keto esters **43** in water to produce tertiary stereogenic alcohols **45** in high yields. The products are almost enantiomerically pure and are obtained with high diastereoselectivity (up to 24:1) using an excess of the donor ketone (5–10 equiv). These reactions have been widely applied and can be performed in a variety of solvents, but water gives the best results; how-

ever, a decrease in yield and enantioselectivity is observed by changing from cyclohexanone to acetone or to a less reactive cyclic ketone (Scheme 19).[58]

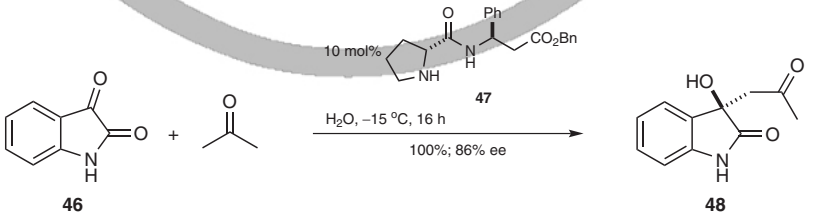
Scheme 19 Synthesis of Tertiary Stereogenic Alcohols[58]



Ar^1	R^1	R^2	R^3	Donor Ketone (equiv)	Time (h)	dr (*anti*/*syn*)	ee (%)	Yield (%)	Ref
Ph	Me	$(CH_2)_3$		5	24	>19:1	99	76	[58]
Ph	Et	$(CH_2)_3$		5	18	>19:1	>99	99	[58]
Ph	$CH_2CH{=}CH_2$	$(CH_2)_3$		5	18	>19:1	>99	99	[58]
Ph	iPr	$(CH_2)_3$		5	18	>19:1	>99	98	[58]
Ph	Bn	$(CH_2)_3$		5	24	>19:1	>99	77	[58]
Ph	*t*-Bu	$(CH_2)_3$		5	18	>19:1	>99	85	[58]
4-FC_6H_4	Me	$(CH_2)_3$		5	18	>19:1	>99	99	[58]
4-ClC_6H_4	Me	$(CH_2)_3$		5	24	>19:1	>99	74	[58]
4-BrC_6H_4	Me	$(CH_2)_3$		5	24	>19:1	>99	77	[58]
3-ClC_6H_4	Me	$(CH_2)_3$		10	24	>19:1	>99	74	[58]
2-BrC_6H_4	Me	$(CH_2)_3$		5	24	>19:1	>99	92	[58]
4-Tol	Me	$(CH_2)_3$		10	24	>19:1	>99	80	[58]
2-furyl	Me	$(CH_2)_3$		5	24	>19:1	>99	72	[58]
Ph	Et	H	H	5	48	–	45	85	[58]
Ph	Et	CH_2CH_2		10	48	19:1	93	41	[58]
Ph	Et	CH_2OCH_2		10	48	19:1	93	53	[58]
Ph	Et	CH_2SCH_2		10	48	24:1	86	50	[58]
Ph	Et	$CH_2N(Boc)CH_2$		10	48	19:1	81	56	[58]

The proline amide catalyst **47** provides (*R*)-3-hydroxy-3-(2-oxopropyl)-2,3-dihydroindol-2(1*H*)-one (**48**) in a quantitative yield via a ketone–ketone cross-aldol reaction between isatin (**46**) and acetone in the presence of small quantities of water (40 equiv). No organic solvent is required (Scheme 20).[59]

Scheme 20 Synthesis of (*R*)-3-Hydroxy-3-(2-oxopropyl)-2,3-dihydroindol-2(1*H*)-one[59]



for references see p 383

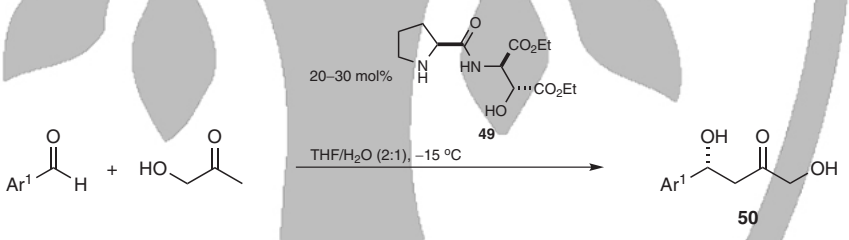
2-(Alkoxycarbonyl)-4-aryl-2-hydroxybut-3-en-1-yl Ketones 45**; General Procedure:**[58]
The siloxylated proline **23** (6.0 mg, 0.015 mmol), the β,γ-unsaturated keto ester **43** (0.1 mmol), and the ketone **44** (0.5–1.0 mmol) were mixed with H_2O (1.0 mL) at rt and vigorously stirred. When the reaction was over, the mixture was extracted with EtOAc (3 × 3 mL) and the combined extracts were dried (Na_2SO_4). After removal of the solvent, the residue was purified by flash chromatography. The enantioselectivity was determined by chiral HPLC, whereas the diastereomeric ratio of the crude product was determined by ^1H NMR spectroscopy and HPLC analysis.

(*R*)-3-Hydroxy-3-(2-oxopropyl)-2,3-dihydroindol-2(1*H*)-one (48**); Typical Procedure:**[59]
The proline amide **47** (10 mol%) was added to a soln of isatin (**46**; 44.1 mg, 0.3 mmol) in acetone (2 mL, 90 equiv) and H_2O (216 μL, 12 mmol). After the mixture had been stirred at −15 °C for 16 h, the usual workup and purification procedures were performed in order to obtain the title compound; yield: 100%; 86% ee.

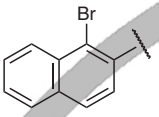
4.4.2.1.5 Synthesis of 1,4-Dihydroxylated Ketones

The novel L-proline amide **49** is prepared by the condensation of diethyl (2*R*,3*R*)-2-amino-3-hydroxysuccinate and L-proline, and in turn is used for the synthesis of the 1,4-diols **50**. The aldolization procedure is successful for the condensation of a wide range of aldehydes, including aliphatic aldehydes, with unprotected hydroxyacetone employing 20–30 mol% of the catalyst in aqueous tetrahydrofuran. The products from aromatic aldehydes are formed with excellent stereocontrol (91–99% ee) but, surprisingly, water is essential in order to achieve regioselective control; thus, in aqueous tetrahydrofuran the major product is the corresponding 1,4-diol arising from reaction of the methyl group of hydroxyacetone, whereas in dry organic solvents the major product arises from reaction of the methylene group of hydroxyacetone (Scheme 21).[60]

Scheme 21 Synthesis of 4-Aryl-1,4-dihydroxybutan-2-ones[60]



Ar^1	Catalyst (mol%)	Time (d)	ee (%)	Yield (%)	Ref
$4\text{-}O_2NC_6H_4$	20	2.5	95	95	[60]
$2\text{-}ClC_6H_4$	20	3	93	84	[60]
$4\text{-}F_3CC_6H_4$	20	3	96	90	[60]
$3,5\text{-}Br_2C_6H_3$	20	3	96	85	[60]
$4\text{-}NCC_6H_4$	20	3.5	94	90	[60]
$3,5\text{-}(F_3C)_2C_6H_3$	20	2.5	96	79	[60]
$2\text{-}BrC_6H_4$	20	3.5	93	84	[60]

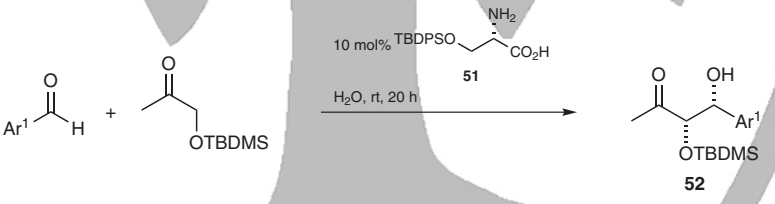
Ar^1	Catalyst (mol%)	Time (d)	ee (%)	Yield (%)	Ref
2-FC_6H_4	30	3.5	93	80	[60]
2,6-$Cl_2C_6H_3$	30	3	99	84	[60]
	30	5	99	77	[60]

4-Aryl-1,4-dihydroxybutan-2-ones 50; General Procedure:[60]
Hydroxyacetone (0.5 mL) was added to a soln of the aldehyde (0.5 mmol) and the catalyst **49** (20–30 mol%) in a mixture of H_2O (0.5 mL) and THF (1.0 mL). After the mixture had been stirred at −15 °C for 2.5–5 d, the reaction was quenched by the addition of sat. aq NH_4OH. The aqueous layer was then extracted with EtOAc (3 × 10 mL), and the combined extracts were washed with brine and dried ($MgSO_4$). After removal of the solvent, the residue was purified by flash column chromatography (silica gel, CH_2Cl_2/EtOAc 6:1) to give the pure adduct. The enantioselectivity was determined by chiral HPLC.

4.4.2.1.6 Synthesis of *syn*-3,4-Dihydroxylated Ketones

The vicinal diol unit is present in many different biologically active natural products, such as carbohydrates, polyketides, and alkaloids. As a result, the development of enantioselective methodologies for the construction of this unit has been at the forefront of modern catalytic asymmetric synthesis.[61] For example, highly enantioselective direct aldolizations between *tert*-butyldimethylsiloxy-protected hydroxyacetone and a set of aromatic aldehydes, which give the 3,4-dihydroxylated ketones **52** in good yields and *syn*-selectivity up to 92%, are promoted by 10 mol% of the siloxylated L-serine **51** in water (Scheme 22).[62]

Scheme 22 Synthesis of (3*S*,4*R*)-3-(*tert*-Butyldimethylsiloxy)-4-hydroxybutan-2-ones[62]



Ar^1	dr (*syn*/*anti*)	ee (%)	Yield (%)	Ref
4-$O_2NC_6H_4$	92:8	88	83	[62]
3-$O_2NC_6H_4$	87:13	86	84	[62]
4-NCC_6H_4	90:10	90	90	[62]
4-ClC_6H_4	84:16	92	71	[62]
4-BrC_6H_4	87:13	76	80	[62]
Ph	88:12	92	62	[62]
2-naphthyl	81:19	74	64	[62]
4-Tol	80:20	80	78	[62]

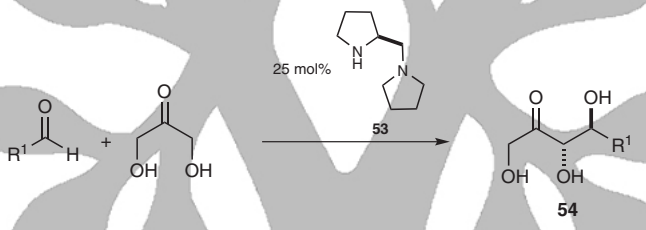
for references see p 383

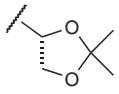
(3*S*,4*R*)-3-(*tert*-Butyldimethylsiloxy)-4-hydroxybutan-2-ones 52**; General Procedure:**[62]
A catalytic amount of the siloxylated serine **51** (0.05 mmol, 0.1 equiv) was added to a vial containing the aldehyde (0.5 mmol), (*tert*-butyldimethylsiloxy)acetone (1.0 mmol), and H_2O (0.3 mL) under air in a closed system. The mixture was stirred at rt for 20 h and then poured into an extraction funnel containing brine (5 mL) and H_2O (5 mL). The reaction vial was washed with EtOAc (5 mL) and the washings were added to the extraction funnel. After separation, the aqueous phase was extracted with EtOAc (3 × 15 mL), the combined organic extracts were dried ($MgSO_4$), and the solvent was removed under reduced pressure. The crude product was purified by column chromatography (silica gel, hexane/EtOAc 9:1) and the *anti*/*syn* ratio was determined by ^{1}H NMR analysis of the crude mixture. The enantiomeric excess of the *syn*-isomer was determined by HPLC analysis on a chiral column.

4.4.2.1.7 Synthesis of 1,3,4-Trihydroxylated Ketones

The organocatalyst **53** combining both secondary and tertiary amino groups can be used for aldol reactions between unprotected 1,3-dihydroxyacetone and a variety of aromatic and aliphatic aldehydes in phosphate-buffered saline (PBS) or a mixture of phosphate-buffered saline and dimethyl sulfoxide. Yields of the triols **54** obtained range from low to good and diastereoselectivities of up to >20:1 are observed (Scheme 23).[63]

Scheme 23 Synthesis of 4-Substituted 1,3,4-Trihydroxybutan-2-ones[63]

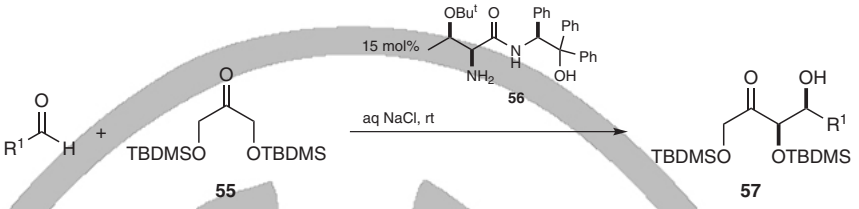


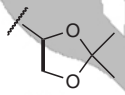
R^1	Solvent[a]	Temp (°C)	Time (h)	dr (*anti*/*syn*)	Yield (%)	Ref
4-$O_2NC_6H_4$	PBS/DMSO (1:1)	rt	72	2:1	87	[63]
CH_2OBn	PBS/DMSO (1:1)	rt	24	>20:1	50	[63]
Cy	PBS/DMSO (1:1)	rt	48	>20:1	55	[63]
Ph	PBS	37	48	1:1	35	[63]
	PBS	37	24	1:1	47	[63]

[a] PBS = phosphate-buffered saline.

The amide **56** effectively catalyzes aldol reactions between the protected dihydroxyacetone **55** and a set of aldehydes at room temperature to afford the *syn*-aldol adducts **57** in high yields (up to >99%) and good diastereo- and enantioselectivities (dr up to 11:1; 98% ee) (Scheme 24). This procedure is best carried out in brine, without the requirement for any organic solvent, and overcomes the limitations of other methodologies that employ organic solvents, and which are restricted to aromatic aldehydes.[64]

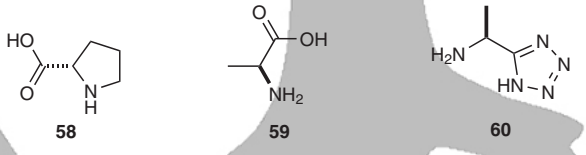
Scheme 24 Synthesis of 4-Hydroxy-1,3-bis(*tert*-butyldimethylsiloxy)alkan-2-ones[64]



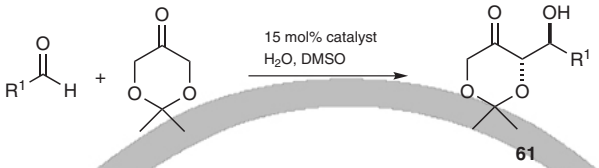
R^1	Time (h)	dr (*syn*/*anti*)	ee (%)	Yield (%)	Ref
4-$O_2NC_6H_4$	20	5:1	87	81	[64]
$(CH_2)_2Ph$	30	7:1	96	83	[64]
$(CH_2)_4Me$	20	11:1	95	77	[64]
CH_2NPhth	18	5:1	96	60	[64]
$CH(OMe)_2$	20	9:1	97	>99	[64]
	20	3:1	98	86	[64]
CO_2Et	24	3:1	96	77	[64]
CONHPh	18	3:1	94	55	[64]

Two articles published in 2006 detail the organocatalytic aldol reactions of 2,2-dimethyl-1,3-dioxan-5-one with a set of aromatic and aliphatic aldehydes in wet conditions. For example, unmodified (*S*)-proline (**58**) (30 mol%) in the presence of 5 equivalents of water in dimethyl sulfoxide gives the appropriate aldols **61** in good yields and with excellent stereochemical control in condensations with 4-nitrobenzaldehyde, 3-methylpropanal, or the isopropylidene derivative of glyceraldehyde (Scheme 25).[65] Moreover, alanine (**59**) and chiral tetrazole **60** also act as catalysts in the presence of 10 equivalents of water, affording good yields of the corresponding aldol products **61** with excellent enantioselectivities (up to 99% ee) and variable diastereoselectivities (dr 1:1 to >19:1) (Scheme 25).[66]

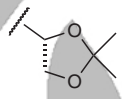
Scheme 25 Synthesis of 4-(Hydroxymethyl)-2,2-dimethyl-1,3-dioxan-5-ones[65,66]



for references see p 383



61

R^1	Catalyst	Water (equiv)	Time (d)	dr (*anti*/*syn*)	ee (%)	Yield (%)	Ref
iPr	**58**	5	1	>19:1	99	90	[65]
	**58**	5	1	>19:1	98	74	[65]
$4\text{-}O_2NC_6H_4$	**58**	5	1	18:1	93	72	[65]
$4\text{-}O_2NC_6H_4$	**59**	10	3	6:1	>99	84	[66]
$4\text{-}NCC_6H_4$	**59**	10	3–4	6:1	>99	84	[66]
$4\text{-}BrC_6H_4$	**59**	10	3–4	6:1	97	77	[66]
CH_2OBn	**59**	10	3–4	>19:1	99	41	[66]
Ph	**59**	10	3–4	1:1	94	68	[66]
$4\text{-}NCC_6H_4$	**60**	10	3–4	12:1	99	68	[66]
$4\text{-}BrC_6H_4$	**60**	10	3–4	13:1	96	55	[66]

4-Substituted 1,3,4-Trihydroxybutan-2-ones 54**; General Procedure:**[63]
The aldehyde (1.0 mmol) was added to brine (10 mL), followed in turn by 1,3-dihydroxyacetone (0.1 mol) and the catalyst **53** (25 mol%), and the mixture was stirred for 24–48 h at rt. Aqueous workup with half-sat. aq NH_4Cl and extraction with EtOAc gave an organic phase, which was dried ($MgSO_4$), filtered, and concentrated. The residue obtained was purified by column chromatography (silica gel, hexane/ EtOAc 1:10) to afford the appropriate aldol product.

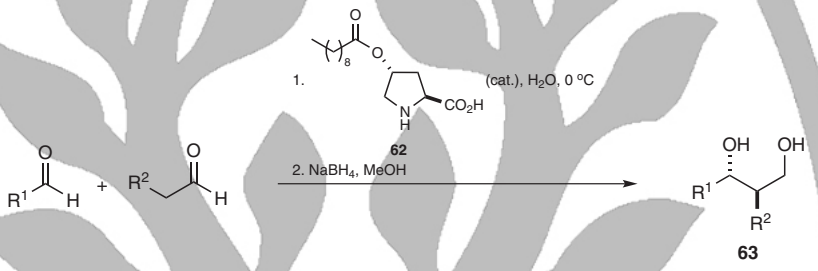
4-Hydroxy-1,3-bis(*tert*-butyldimethylsiloxy)alkan-2-ones 57**; General Procedure:**[64]
1,3-Bis(*tert*-butyldimethylsiloxy)acetone (**55**; 0.5 mmol), followed by the amide catalyst **56** (0.0375 mmol) was added to a soln of the aldehyde (0.25 mmol) in brine (0.25 mL) at rt. The mixture was stirred until the aldehyde was consumed (TLC), and then it was diluted with EtOAc (2 mL) and poured into half sat. aq NH_4Cl. The resultant mixture was extracted with EtOAc and the combined extracts were washed with brine, before being dried (Na_2SO_4) and concentrated. The residue obtained was purified by flash column chromatography (silica gel, hexane/EtOAc) to afford the desired aldol.

4-(Hydroxymethyl)-2,2-dimethyl-1,3-dioxan-5-ones 61**; General Procedure:**[65,66]
A catalytic amount of the (*S*)-amino acid **58** or either of the chiral amines **59** or **60** (0.15 mmol, 30 mol%) were added to a vial containing the acceptor aldehyde (0.5 mmol), the donor ketone (1.5 mmol), and H_2O (5–10 mmol) in DMSO (2 mL). After vigorous stirring at rt, the mixture was poured into an extraction funnel containing brine (5.0 mL) and then diluted with H_2O (5.0 mL) and EtOAc (15 mL). The vial was also washed with EtOAc (2 mL), and the solvent was poured into the extraction funnel. When the reaction was over, the aqueous phase was extracted with EtOAc (2 × 15 mL), the combined extracts were dried (Na_2SO_4), and the solvent was removed under reduced pressure. The residue was purified by column chromatography (silica gel, EtOAc/pentane or toluene/EtOAc mixtures) to furnish the desired aldol product, the enantiomeric selectivity of which was determined by either chiral-phase HPLC or chiral-phase GC analysis.

4.4.2.1.8 Synthesis of 1,3-Dihydroxylated Compounds

A highly diastereo- and enantioselective catalyst **62** for use in aqueous direct cross-aldolizations between two aldehydes to afford the diols **63** has been reported. This catalyst contains a decanoyl unit, which provides surfactant properties, bonded to C4 of commercial L-4-hydroxyproline. Optimum conditions use the proline catalyst with 18 equivalents of water, and the surfactant nature of the catalyst is assumed to ensure good mixing of the two aldehydes. This methodology needs a lower aldehyde donor loading (5 equiv), added in one portion, than a similar reaction carried out in an organic solvent, which involves the slow addition of 10 equivalents of the donor. The 1,3-diols **63** are isolated after the reduction of the corresponding aldol adducts using sodium borohydride (Scheme 26).[67]

Scheme 26 Synthesis of 1-Substituted (1*R*,2*R*)-2-Alkylpropane-1,3-diols[67]

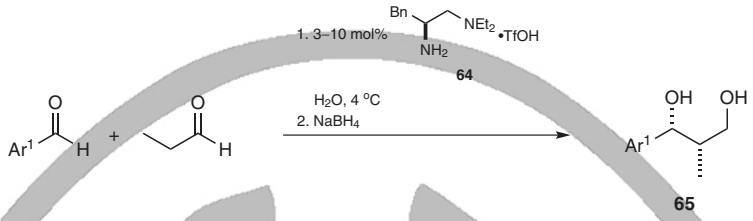


R^1	R^2	Catalyst (%)	Time (h)	dr (*anti*/*syn*)	ee (%)	Yield (%)	Ref
4-ClC_6H_4	Me	10	110	>20:1	99	90	[67]
Ph	Me	10	73	>20:1	99	88	[67]
2-naphthyl	Me	10	110	>20:1	99	54	[67]
4-Tol	Me	20	68	>20:1	99	65	[67]
2-$MeOC_6H_4$	Me	10	72	20:1	95	83	[67]
Cy	Me	10	118	10:1	92	29	[67]
2-furyl	Me	10	68	8:1	92	58	[67]
2-ClC_6H_4	Bn	20	93	14:1	92	57	[67]
$CH(OMe)_2$	Bn	10	62	4:1	93	35	[67]
Et	Me	10	96	10:1	89	35	[67]

An efficient protocol for *syn*-selective cross-aldol reactions of aldehydes has been achieved in which the chiral diamine trifluoromethanesulfonic acid salt **64** successfully catalyzes the formation of the *syn*-1,3-diols **65** with a β-substituent no larger than methyl. Screening of various vicinal diamine catalysts and other Brønsted acid additives indicates that this catalytic system, when employed with a small amount of water (2 equiv), is the best available and, in contrast to sluggish reactions that take place in an organic solvent, an ionic liquid, or larger amounts of water, good results for the syntheses of the *syn*-diols are possible (up to 97% yield, *syn*-selectivity from 13:1 to 2:1, and up to 87% ee) (Scheme 27).[68]

for references see p 383

Scheme 27 Synthesis of (1*R*,2*S*)-1-Aryl-2-methylpropane-1,3-diols[68]



Ar^1	Catalyst (mol%)	dr (*syn*/*anti*)	ee (%)	Yield (%)	Ref
$4\text{-}O_2NC_6H_4$	3	7:1	87	94	[68]
$3\text{-}O_2NC_6H_4$	3	10:1	84	94	[68]
$2\text{-}O_2NC_6H_4$	3	8:1	87	93	[68]
$4\text{-}NCC_6H_4$	3	13:1	84	97	[68]
$4\text{-}F_3CC_6H_4$	3	10:1	84	87	[68]
3-pyridyl	3	6:1	82	87	[68]
$2\text{-}ClC_6H_4$	10	6:1	87	64	[68]
$4\text{-}ClC_6H_4$	10	6:1	81	56	[68]
$2,4\text{-}Cl_2C_6H_3$	10	7:1	87	75	[68]
$4\text{-}PhC_6H_4$	10	2:1	83	75	[68]

1-Substituted (1*R*,2*R*)-2-Methylpropane-1,3-diols 63 **(R^2 = Me); General Procedure:**[67]
The acceptor aldehyde (0.4 mmol) and EtCHO (2.0 mmol, 144 mL) were added in succession to a mixture of (2*S*,4*R*)-4-(decanoyloxy)pyrrolidine-2-carboxylic acid (**62**; 0.04 or 0.08 mmol), and H_2O (130 μL) at 0 °C. After the mixture had been stirred for 72 h at this temperature, MeOH (2 mL) and $NaBH_4$ (151 mg, 4 mmol) were added. The resulting mixture was stirred for 1 h at 0 °C, before the reaction was quenched with pH 7.0 phosphate buffer soln. The suspension was extracted with $CHCl_3$ (3 ×) and the combined organic extracts were dried (Na_2SO_4) and concentrated under reduced pressure. Purification of the residue was carried out by preparative TLC. The enantiopurity of the *anti*-isomer was determined by chiral HPLC, and its diastereoselectivity was determined by ^1H NMR spectroscopy.

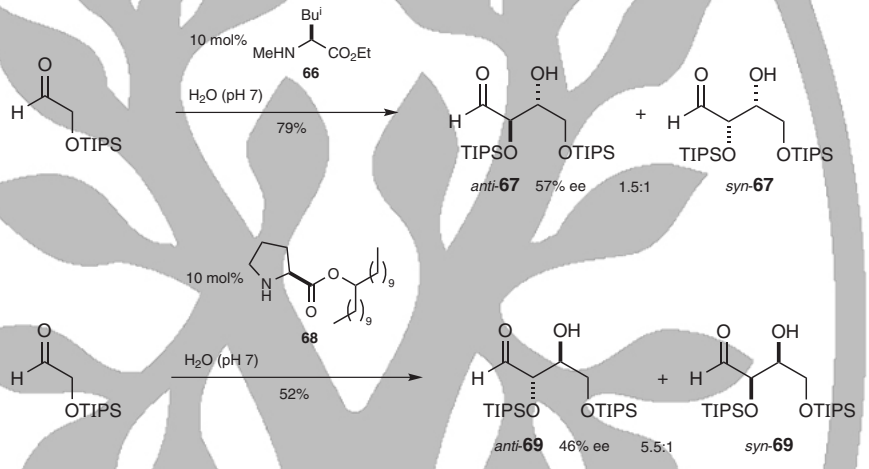
(1*R*,2*S*)-1-Aryl-2-methylpropane-1,3-diols 65**; General Procedure:**[68]
The catalyst **64** (5.4 mg, 0.015 mmol), H_2O (18 mg, 1 mmol), EtCHO (0.5 mL), and the aromatic aldehyde (0.5 mmol) were mixed together and stirred at 4 °C for 24 h. The mixture was concentrated and then diluted with CH_2Cl_2/MeOH (5:1; 20 mL). $NaBH_4$ (76 mg, 2 mmol) was added and allowed to react for 10 min, before 3% aq $NaHCO_3$ (20 mL) was added. After 15 min, the organic phase was separated and the aqueous phase was extracted with CH_2Cl_2 (10 mL). The organic phase and the extract were combined, dried (Na_2SO_4), and concentrated and, with care, the residue was directly purified by flash column chromatography to afford the aldol adduct. The enantiomeric excess of the product was determined by chiral HPLC after or before acetylation of the purified adduct.

4.4.2.1.9 Synthesis of Erythrose and Threose Derivatives

One theory postulates that in nature the first carbohydrates may have formed in aldol reactions of glycolaldehyde catalyzed by amino acids but, in the laboratory, model experiments afford low yields and the products exhibit poor enantiopurity. Thus, although the nonproteinogenic amino acid (*R*)-isovaline catalyzes the aldol dimerization of glycolalde-

hyde in water to afford L-threose, the enantiomeric excess is only 10%.[69] Similarly, it is known that the formation of simple sugars through aldolization processes in water may be catalyzed by zinc–proline complexes,[25] but again the yields obtained are very low. Despite these disappointing results, in 2010 Clarke and Hayes demonstrated that application of L-*N*-methylleucine ethyl ester (**66**) to the aldolization of the triisopropylsilyl ether of glycolaldehyde (hydroxyacetaldehyde) provides the D-erythrose derivative *anti*-**67** and the D-threose derivative *syn*-**67** in good yields, although the highest enantiomeric excess (obtained for the D-erythrose derivative *anti*-**67**) is just 57% (Scheme 28). Similarly, the application of buffered conditions and the use of the branched heneicosyl ester **68** as a catalyst give the L-erythrose derivative *anti*-**69** and the L-threose derivative *syn*-**69** in modest combined yield (52%); the enantiomeric excess for the D-erythrose derivative *anti*-**69** is 46% (Scheme 28).[70]

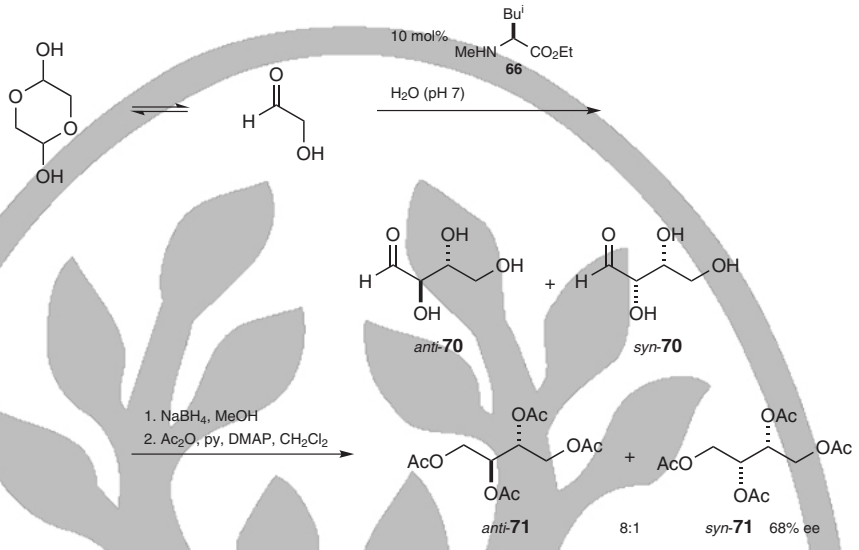
Scheme 28 Formation of Protected Tetroses in Water[70]



The aldol dimerization of unprotected glycolaldehyde in the presence of L-*N*-methylleucine ethyl ester (**66**) as the catalyst under buffered conditions has also been examined, but as the expected products, unprotected erythrose (*anti*-**70**) and threose (*syn*-**70**), are very soluble in water, the mixture obtained was reduced and acetylated prior to isolation. In this way, the tetraacetylated products *anti*-**71** and *syn*-**71** are obtained in the ratio 8:1 (Scheme 29), the latter being formed with an enantiomeric excess of 68%.[70]

for references see p 383

Scheme 29 Formation of Erythrose and Threose in Water[70]



2,4-Di-*O*-silyltetroses 67 and 69; General Procedure:[70]
2-(Triisopropylsiloxy)acetaldehyde (1.29 mmol) was added to the catalyst **66** or **68** (0.129 mmol) in pH 7 phosphate buffer (5 mL). After 5 h, the mixture was extracted with $CHCl_3$ (3 × 10 mL) and the combined extracts were dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The residue was then purified by flash column chromatography (silica gel, pentane/Et_2O (15:1) to provide the aldol products as clear, colorless oils.

***anti*- and *syn*-Butane-1,2,3,4-tetrayl Tetraacetate (*anti*- and *syn*-71); Typical Procedure:**[70]
Glycolaldehyde dimer (240 mg, 2.00 mmol) was added to a stirred mixture of L-*N*-methylleucine ethyl ester (**66**; 17.3 mg, 0.10 mmol) in a pH 7 phosphate buffer (3 mL). After 5 h, the mixture was concentrated under reduced pressure and the residue was redissolved in MeOH (3 mL) held at 0 °C. $NaBH_4$ (152 mg, 4.00 mmol) was then added carefully, and the resulting mixture was kept at 0 °C for 3 h, after which time it was allowed to warm to rt. After a further 15 h, the mixture was cooled again to 0 °C and the reaction was quenched by the addition of 2 M HCl (3 mL). The mixture obtained was concentrated under reduced pressure and the residue was redissolved in CH_2Cl_2 (5 mL), before pyridine (1 mL) was added, followed by DMAP (1.3 mg, 0.01 mmol), and then Ac_2O (3 mL). This mixture was stirred for 7 h, then washed with H_2O (10 mL), and extracted with CH_2Cl_2 (3 × 5 mL). The combined extracts were washed in turn with 1 M HCl (10 mL), brine (10 mL), and H_2O (10 mL), then dried ($MgSO_4$), and concentrated under reduced pressure to give the acylated tetroses.

4.4.2.2 Direct Aldol Reactions Assisted by Chiral Metal Complexes

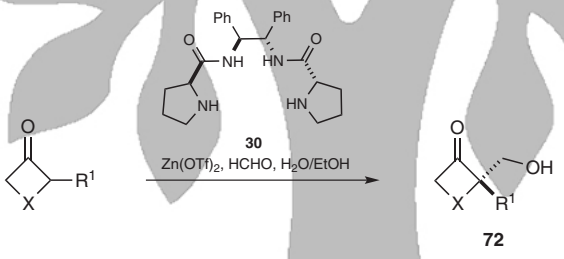
In contrast to the growing development of the direct asymmetric aldol methodology promoted by purely organic molecules, the application of methods carried out in aqueous solvents utilizing Lewis acids as catalysts that rely on metal complexes bearing chiral ligands may still prove troublesome. The first examples of aqueous asymmetric direct aldol reactions assisted by a metal were presented in 2003;[71] here, the zinc–proline complex prepared from proline and zinc acetate is shown to catalyze aldol reactions between acetone and aromatic aldehydes, giving moderate yields but low enantiomeric excesses. However, high enantioselectivities are achieved by employing a zinc(II) complex generat-

ed in situ from a combination of zinc trifluoromethanesulfonate and the chiral C_2-symmetric proline amide ligand **30**. The presence of 5 mol% of this catalyst furnishes asymmetric intermolecular aldol reactions between cyclic or acyclic ketones with aromatic aldehydes to give the *anti*-products with excellent enantioselectivities (86–98% ee).[52]

4.4.2.2.1 Synthesis of Hydroxymethyl Ketones

Hydroxymethylation reactions represent one of the cornerstone one-carbon extension methods. The direct use of commercially available aqueous formaldehyde solution gives the safest and most economically attractive reaction conditions, but the requirement for a water-compatible catalyst is a challenging issue. However, in 2010 the groups led by Mlynarski and Kobayashi independently reported successful aqueous hydroxymethylations that are assisted by chiral metal complexes. In the work by the Mlynarski group, 10 mol% of the chiral proline amide **30**, in the form of its zinc trifluoromethanesulfonate complex, is shown to catalyze efficiently the one-carbon extensions of various monocyclic ketones by aqueous formaldehyde to give the corresponding adducts **72** in good yields with high enantioselectivities (Scheme 30).[72] This methodology employs a distinct homogenous aqueous mixture compared to most other procedures of aldolizations in water that occur inside the hydrophobic pocket of a sparingly soluble catalyst. In the Kobayashi contribution, the hydroxymethylations of another set of useful ketones, i.e. fused bicyclic ketones and ethyl phenyl ketone, using the chiral *N*-oxide ligand **73** with scandium(III) trifluoromethanesulfonate are described. The authors mention that the addition of a catalytic amount of pyridine is essential to achieve high yields and enantioselectivities of the products **74** and **75** (Scheme 31).[73]

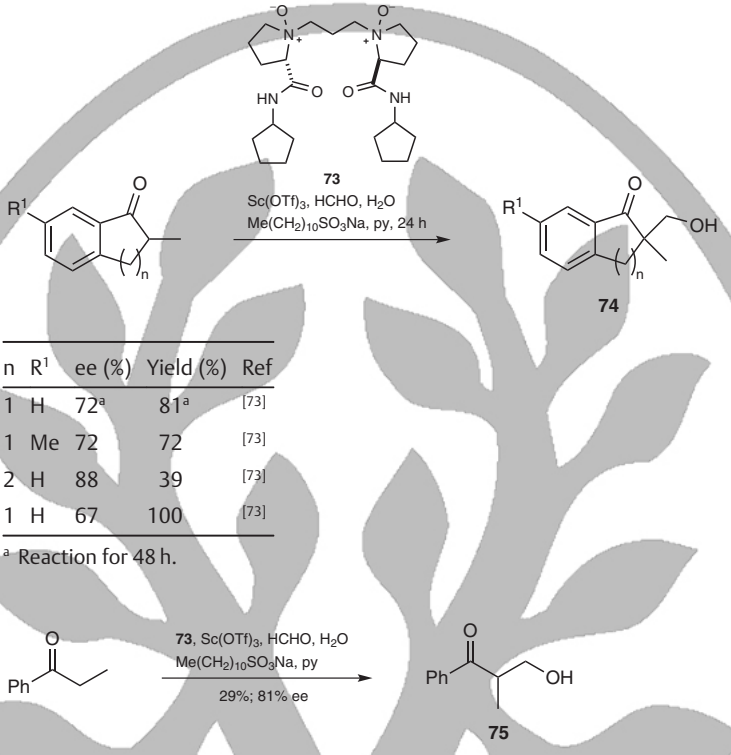
Scheme 30 Synthesis of Hydroxymethyl Ketones Using a Chiral Proline Amide–Zinc Catalyst[72]



X	R^1	ee (%)	Yield (%)	Ref
$(CH_2)_3$	H	94	60	[72]
$(CH_2)_2$	H	98	58	[72]
$(CH_2)_4$	H	93	59	[72]
$(CH_2)_3$	Me	95	<10	[72]
$CH_2CHMeCH_2$	H	94 (dr 3:2)	63	[72]

for references see p 383

Scheme 31 Synthesis of Hydroxymethyl Ketones Using a Chiral *N*-Oxide–Scandium Catalyst[73]



n	R^1	ee (%)	Yield (%)	Ref
1	H	72[a]	81[a]	[73]
1	Me	72	72	[73]
2	H	88	39	[73]
1	H	67	100	[73]

[a] Reaction for 48 h.

Hydroxymethylated Ketones 72; General Procedure Using Catalyst 30:[72]

CAUTION: *Formaldehyde is a probable human carcinogen, a severe eye, skin, and respiratory tract irritant, and a skin sensitizer.*

The proline amide **30** (30.5 mg, 0.075 mmol, 10 mol%) and $Zn(OTf)_2$ (27.3 mg, 0.075 mmol, 10 mol%) were stirred for 5 min in EtOH/H_2O (9:1; 0.5 mL). To the resulting soln the ketone (1.5 mmol) and 37% aq HCHO (0.75 mmol) were added at rt and the mixture was stirred for 20 h. The mixture was extracted with CH_2Cl_2, and the extract was dried (Mg_2SO_4). The solvents were evaporated and the residue was purified by chromatography. The enantiomeric excess of the product was determined by chiral HPLC analysis of the corresponding benzoate derivative.

Hydroxymethylated Ketones 74 or 75; General Procedure Using Catalyst 73:[73]

CAUTION: *Formaldehyde is a probable human carcinogen, a severe eye, skin, and respiratory tract irritant, and a skin sensitizer.*

The ketone (0.3 mmol), $Sc(OTf)_3$ (10 mol%), the chiral *N*-oxide **73** (12 mol%), sodium undecane-1-sulfonate (150 mol%), pyridine (20 mol%), and formalin (5 equiv) were combined in H_2O (0.5 mL) at rt. After 25 h, a mixture of sat. aq $NaHCO_3$ and brine (1:1; 5–10 mL) was added, and the aqueous layer was extracted with CH_2Cl_2 (3 ×). The combined extracts were dried (Na_2SO_4), filtered, and concentrated. The crude product was purified by preparative TLC and the enantiomeric excess was determined by chiral HPLC analysis.

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