NOVEL APPLICATIONS of MORITA-BAYLIS-HILLMAN METHODOLOGY IN ORGANIC SYNTHESIS

THESIS

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ABSTRACT

The overall approach in the present investigation has been to explore applications of the Morita-Baylis-Hillman (MBH) reaction in asymmetric synthesis and in the continuation of systems with medicinal potential. To this end, a series of varied camphor-derived acrylate esters was prepared to serve as chiral substrates in asymmetric Morita-Baylis-Hillman reactions. Reduction of *N*-substituted camphor-10-sulfonamides afforded the 3-*exo*-hydroxy derivatives as the major products. Acylation of the corresponding sodium alkoxides gave the desired 3-*exo*-acrylate esters, isolation of which was complicated by concomitant formation of hydrochlorinated and diastereomeric competition products. Bulky camphorsulfonamides containing alkyl, dialkyl, aromatic and adamantyl groups were selected as *N*-substituents with the view of achieving stereoselective outcome in subsequent MBH reactions. The synthesis of novel camphor-derived Morita-Baylis-Hillman adducts using various pyridine-carboxaldehydes proceeded with exceptionally high yields with diastereoselectivities ranging from 7-33% d.e. Both 1D and 2D NMR and HRMS techniques were employed to confirm the structures and an extensive study of the electropositive fragmentation patterns of a number of camphor-derived chiral acrylate esters was conducted.

Attention has also been given to the application of MBH methodology in the construction of heterocyclic ‘cinnamate-like’ AZT conjugates which were designed to serve as dual-action HIV-1 integrase-reverse transcriptase (IN-RT) inhibitors. A number of pyridine carboxaldehyde-derived MBH adducts were synthesized using methyl, ethyl and *t*-butyl acrylates in the presence of 3-hydroxyquinuclidine (3-HQ) as catalyst. The yields for these reactions were excellent. The resulting MBH adducts were acetylated and subjected to aza-Michael addition using propargylamine. The resulting alkylamino compounds were then used in ‘Click reactions’ to form the targeted AZT-conjugates in moderate to excellent yield. *In silico* docking of computer modelled AZT-conjugates into the HIV-1 integrase and reverse transcriptase enzyme-active sites and potential hydrogen-bonding interaction with active-site amino acid residues were identified. The electrospray MS fragmentations of the AZT and the novel AZT-conjugates were also investigated and common fragmentation pathways were identified.

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Above all I thank God for the gift of life.

1. INTRODUCTION

The major thrusts in this research project have involved the application of Morita-Baylis-Hillman chemistry in:-

i) the construction of compounds with medicinal potential; and

ii) the investigation of asymmetric synthesis methodologies.

Consequently, the introduction will focus broadly on developments in these areas, with a particular emphasis on the use of D-(+)-camphor as a source of chirality in asymmetric synthesis.

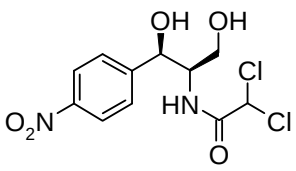
1.1. ASYMMETRIC SYNTHESIS

For those whose interests penetrate deep into the magical world of organic permutations, no compelling evidence is needed to spotlight the importance of enantioselective synthesis.[1] Asymmetric synthesis has undergone tremendous developments during the past few decades[2] and, in fact, three scientists, William S. Knowles, Ryojl Noyori and K. Barry Sharpless,[3] shared the Nobel Prize in Chemistry in 2001 for their work in this area. Asymmetric synthesis is supremely evidenced by the regular, exclusive biosynthesis of single enantiomeric compounds in nature, the mother of all asymmetric synthetic processes.

1.1.1. Importance of Asymmetric Synthesis

The heart of asymmetric synthesis lies in the selective creation of new asymmetric (or stereogenic) centres. The presence of one such centre results in a pair of non-superimposable mirror-image molecules, termed enantiomers. New asymmetric centres are typically generated stereoselectively in prochiral molecules through the use of chiral reagents or catalysts or by asymmetric induction in molecules already possessing asymmetric centres.[4,5,6]

The majority of commercially available chemical compounds, which are manufactured as pharmaceuticals, food additives and fragrances possess one or more stereogenic centres and can therefore exist in more than one stereoisomeric form. The biological receptors with which these molecules interact are also often chiral and thus provide asymmetric environments in which these molecules may be distinguishable. This results in situations in which only one particular stereoisomer exhibits beneficial biological properties. Other stereoisomers may be pharmacologically inactive or even hazardous. Examples include:- chloramphenicol **1** [the (*R*,*R*)-stereoisomer alone exhibits anti-bacterial activity];[6] the stereoisomeric triazole derivatives, one of which, paclobutrazol **2**, is a fungicide and the other a plant-growth regulator;[7] and thalidomide, now used in the treatment of leprosy but previously marketed as a racemic sedative-hypnotic drug which, due to the presence of the teratogenic (*S*)-enantiomer **3**, resulted in the birth of tragically deformed babies when used by pregnant women.[8]



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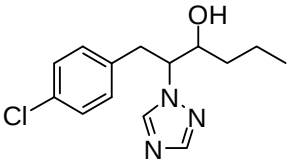

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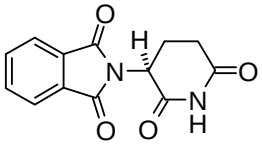


3

Thus, the need for single enantiomeric or diastereomeric drugs is of critical importance, and stereocontrol in the synthesis of such compounds constitutes a great challenge for organic chemists.[9]

1.1.2. The Design Challenge

Asymmetric synthesis may be achieved in many ways. These include exploiting intrinsic chirality in chiral substrates or the use of chiral auxiliaries, reagents or catalysts, which function as extrinsic sources of asymmetry.[1] These methods can be grouped into four broad categories.

(i) *First generation: Substrate-controlled methods*

These methods make use of naturally occurring, enantiomerically pure substrates, such as, amino acids, carbohydrates and alkaloids (components of the "chiral pool"), to make final products that retain the initially inherent chirality.[9,10] The overall stereochemistry of these products is directly informed by the pre-existing chiral centre(s) in the starting material.[5]

(ii) *Second generation: Auxiliary-controlled methods*

In this approach a chiral auxiliary is covalently attached to a prochiral substrate, thereby creating an enabling asymmetric environment around the prochiral centre. The resulting molecule is then able to undergo a reaction in which the attached chiral auxiliary induces some degree of stereocontrol in the formation of the products.[5] Removal (and, ideally, re-cycling) of the auxiliary then affords a single enantiomer as the major, if not the sole, product. There are, of course, certain requirements for the successful use of a chiral auxiliary: it should:- be readily available as a homochiral moiety that can be easily attached to the prochiral substrate; induce a high measure of stereoselectivity; be easily detached from the product; be recoverable in high yield; and, ideally, the derivatives should be crystalline to facilitate separation of the diastereomeric products prior to removal of the chiral auxiliary.[5]

(iii) *Third generation: Reagent-controlled methods*

To achieve stereocontrol, this approach involves conversion of a prochiral substrate into a chiral product using at least stoichiometric amounts of a chiral reagent which directly influences the stereochemical outcome of the reaction. In this method, there is no introduction or removal of the auxiliary and thus two of the steps required in the use of chiral auxiliaries are eliminated. Chiral reagents are often complexes of metals, such as Ti[11], Li, Mg, Al[12] and Fe,[13] with chiral ligands.

(iv) *Fourth generation*: *Catalyst-controlled methods*

Chiral catalysts typically comprise asymmetric ligands co-ordinated to a suitable metal. The chiral catalysts may be temporarily attached to the substrate or they may act in an intermolecular fashion inducing stereocontrol in the overall transformation. Catalytic methods have perhaps the greatest potential as only catalytic quantities of the asymmetric agent may be required, thus alleviating waste (monetary as well as material). These are critical factors in a world that is placing increasing emphases on sustainability.[14]

1.1.3. Camphor In Asymmetric Synthesis

Camphor **10** (Scheme 1.1) has been found to exhibit multiple therapeutic properties, and has been widely used for many years as an analgesic, antidepressant, anti-inflammatory and antiseptic. It has also been used as a rubefacient, as an ointment or liniment to treat sprains, joint and muscle pain, as a balm for chapped lips and cold sores, and as an inhalant to relieve nasal, bronchial or upper respiratory congestion. The Chinese have also used camphor as an inhalant to revive people from faints and other unconscious states, for various skin diseases and to treat wounds.[15-17]

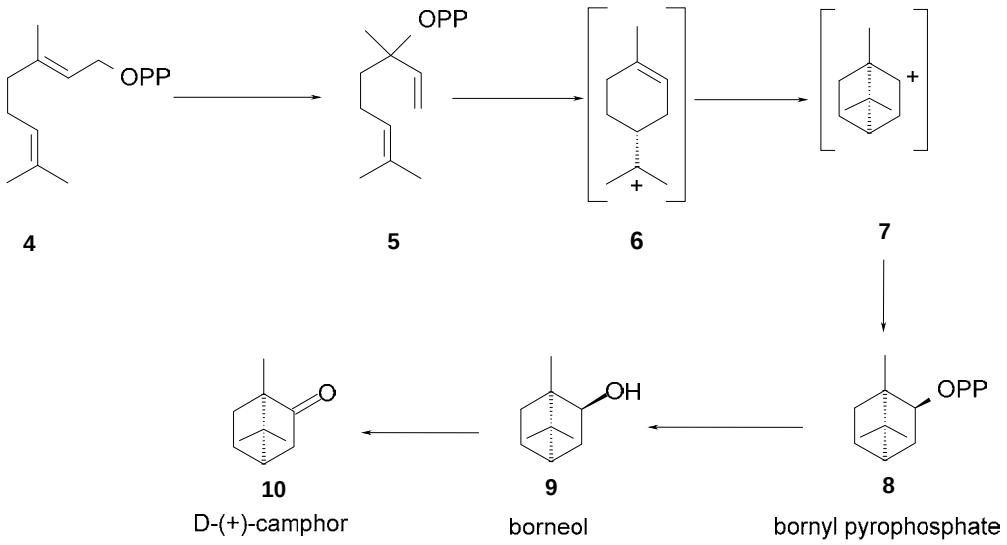
1.1.3.1. Occurrence of camphor

The camphor tree, also known by names such as camphorwood or camphor laurel, is taxonomically classified as *Cinnamomum camphora* and is an evergreen whose height can reach 20-30 metres. The leaves are characterized by a glossy, waxy appearance and scent of camphor when crushed. During the flowering season, the tree prides itself with bright green leaves, a spectacle of white flowers and bunches of berry-like fruit *ca*. 1 cm in diameter. *Cinnamomum camphora* is native to Taiwan, Southern Japan, Southeast China and Indo-china, where it yields economic benefit as the tree provides camphor and timber. There is a rich history associated with the camphor tree. For example, wherever the tree was conspicuous, stills would be set-up in the mountainous areas to isolate the camphor. The wood is chipped and heated in a retort, allowing the volatile oil, with its characteristic pungent odour, to crystallize on the inside of a cooling chamber. Trees that

produce camphor are slow-growing and, in fact, the Chinese believe that it cannot be extracted from trees under fifty years old.[18]

1.1.3.2. Biosynthesis of camphor

Camphor **10** is biosynthesized enantioselectively from geranyl pyrophosphate **4** *via* cyclisation of linayl pyrophosphate **5**, followed by hydration to borneol **9** and subsequent oxidation[18] as illustrated in Scheme 1.1.

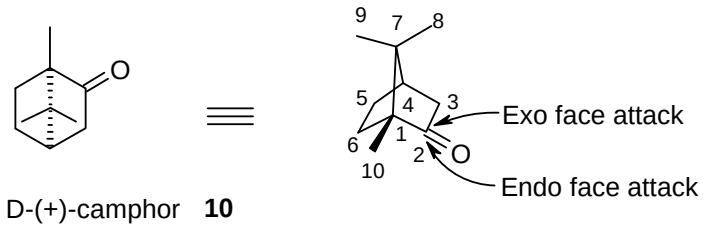


Scheme 1.1. The biosynthesis of camphor **7** from geranyl pyrophosphate.[17,19]

1.1.3.3. Structure and reactivity of camphor

Due to the availability of both (+)- and (-)-enantiomeric forms, camphor has enjoyed wide interest as a source of chirality. Its versatility in the formation of specific derivatives and its rigid bicyclic skeleton, with steric bulk being provided by the 8-, 9- and 10-methyl groups make camphor a compound of choice in the synthesis of chiral auxiliaries. The use of enantiopure camphor as a chiral precursor in asymmetric synthesis stems primarily from the availability of methods for functional modification at C(3), C(5), C(8), C(9) and C(10).[20] Moreover, there are numerous ways of splitting the C(1)-C(2), C(2)-C(3) and C(1)-C(7) connectivities in camphor and related derivatives to furnish valuable synthetic intermediates.[21,22] Thus, nucleophilic attack on the carbonyl group in camphor is

generally expected to be favoured at the less sterically hindered *endo*-face (Figure 1.1). The resulting derivatives may be used, in turn, to induce stereocontrol in subsequent steps by either blocking or reinforcing attack at one face or the other - a phenomenon known as secondary interaction.[23,24]



D-(+)-camphor **10**

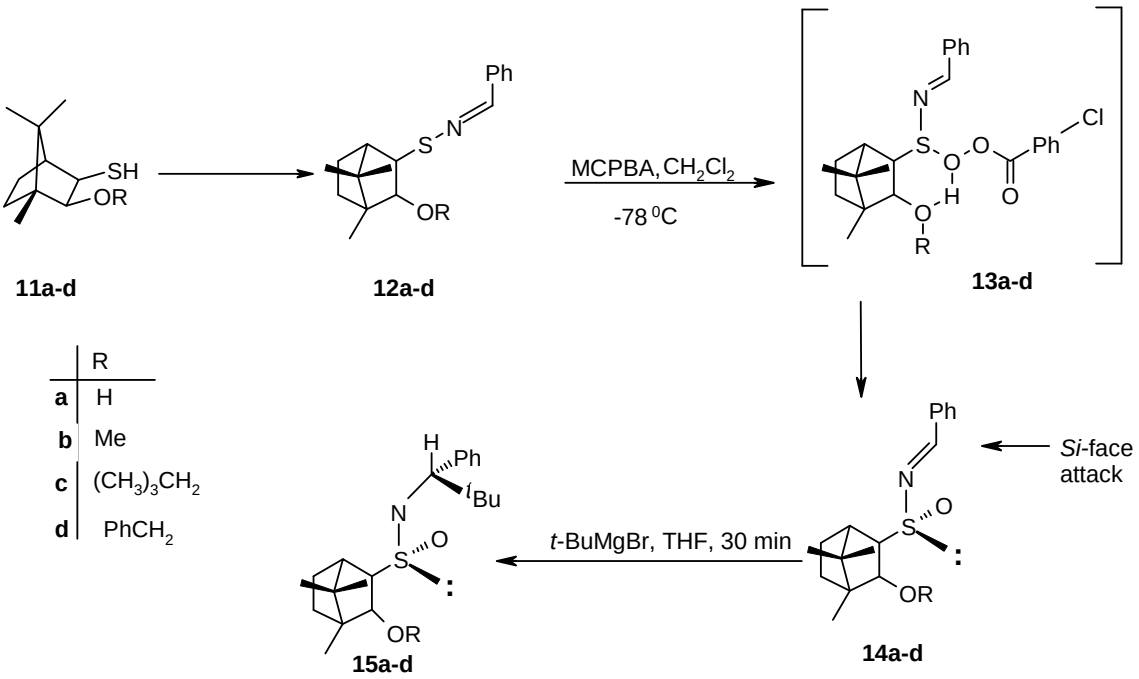
Figure 1.1. Stereochemical options for nucleophilic attack on D-(+)-camphor **10**.

This phenomenon may play a crucial role in effecting stereocontrol in various transformations. Modifications of camphor at different positions will be dealt with in the following section and specific examples will be used to illustrate the usefulness of such modifications.

1.1.4. Functionalization of Camphor

1.1.4.1. C(2)-Modification

The carbonyl group at C(2) is highly reactive and can be transformed into a wide spectrum of functionalities. Hung and co-workers[25] synthesized the camphor-derived thiols **11a-d**, which they employed as chiral auxiliaries in order to achieve high asymmetric induction in Solladie-type reductions of sulfides or sulfoxide intermediates. It is noteworthy that the level of asymmetric induction varies depending on the catalyst used. Yang and co-workers[26] used the same series of compounds **11a-d** as chiral auxiliaries to prepare the corresponding sulfenimines **12a-d**, which were oxidized, in turn, to the sulfinimines, **14a-d** in moderate to excellent diastereomeric excess (40-98% d.e.). The stereocontrol was attributed to the chelation shown in structures **13a-d**. Finally, attack of the Grignard reagent occurred at the *si*-face due to chelation and/or shielding of the *re*-face by the bicyclic skeleton to afford **15a-d**.



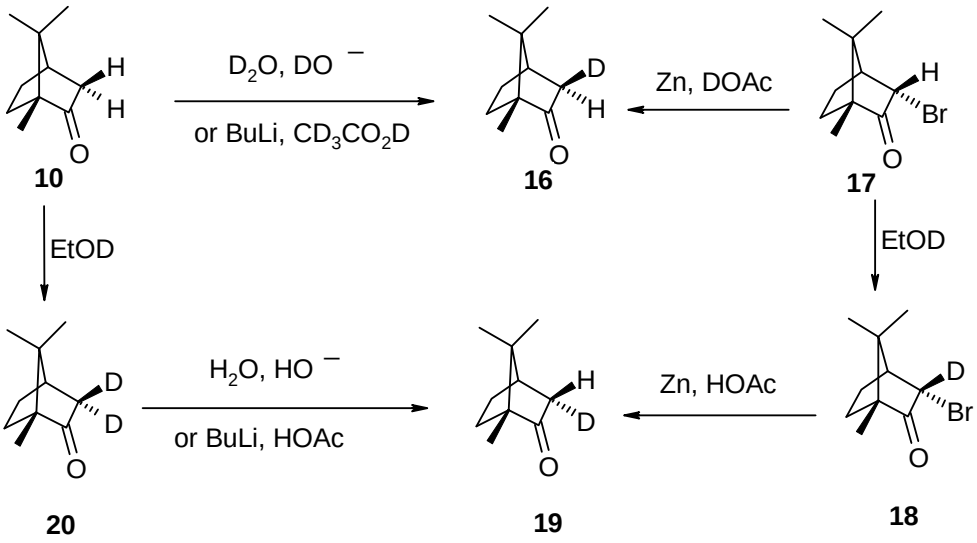
Scheme 1.2. Diastereoselectivity in the formation of C(2)/C(3) modified camphor derivatives.[25,26]

1.1.4.2. C(3)-Modification

The reactivity of the 3-methylene group has generated a sizeable number of camphor derivatives which are functionalized at C(3). Nevertheless, the stereoselectivity patterns that involve monosubstitution at this position remain a puzzle; while knowledge of camphor system is significant, the observed stereoselectivity patterns have not been satisfactorily elucidated.[20]

1.1.4.2.1. ***C(3)-Hydrogen exchange***

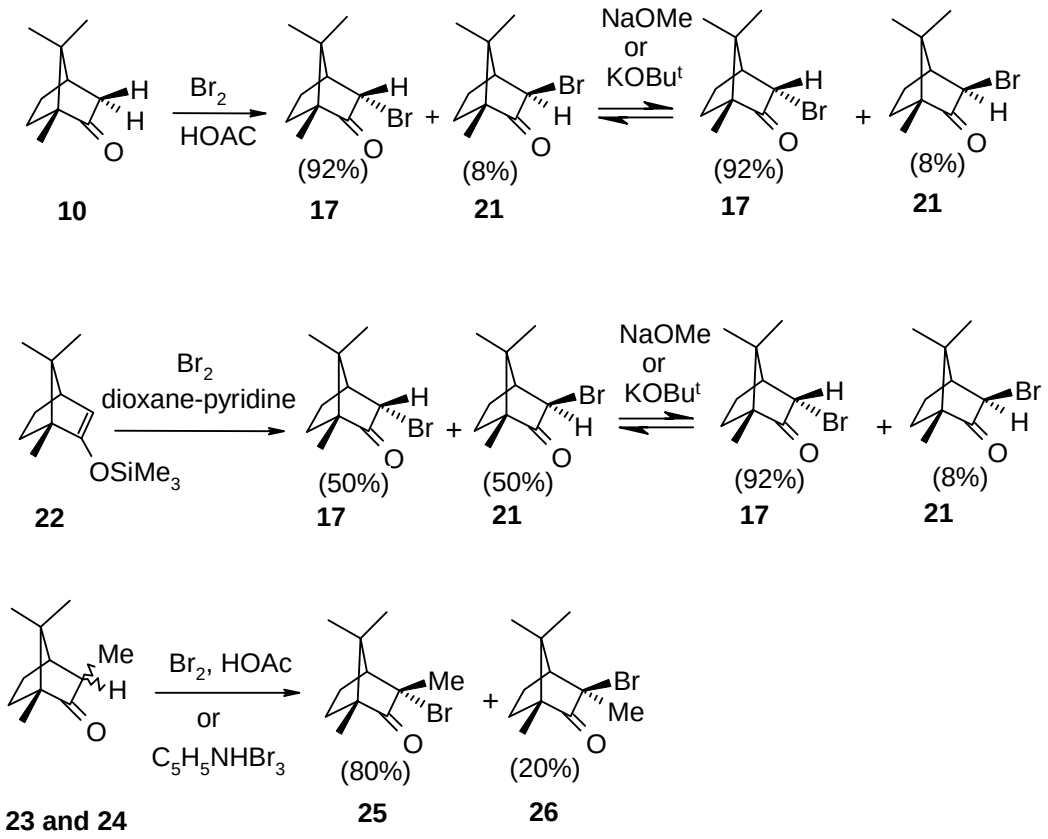
The base-promoted interchange between hydrogen and deuterium in camphor and similar systems appears to involve abstraction of the *exo*-hydrogen followed by *exo*-protonation or deuteration of the resulting enolate ion (Scheme 1.3).[20] Similarly, removal of a bromine atom from 3-*endo*-bromocamphor also appears to involve exclusive *exo*-protonation of the resulting enolate system.[20] Although steric and torsional effects have been thought to account for the observed stereoselectivity of enolization and enolate protonation, experimental data are not always in line with the proposed explanations.[20]



Scheme 1.3. Stereoselectivity of enolization and enolate protonation of camphor and 2-bromocamphor.[20]

1.1.4.2.2. ***C(3)-Monobromination***

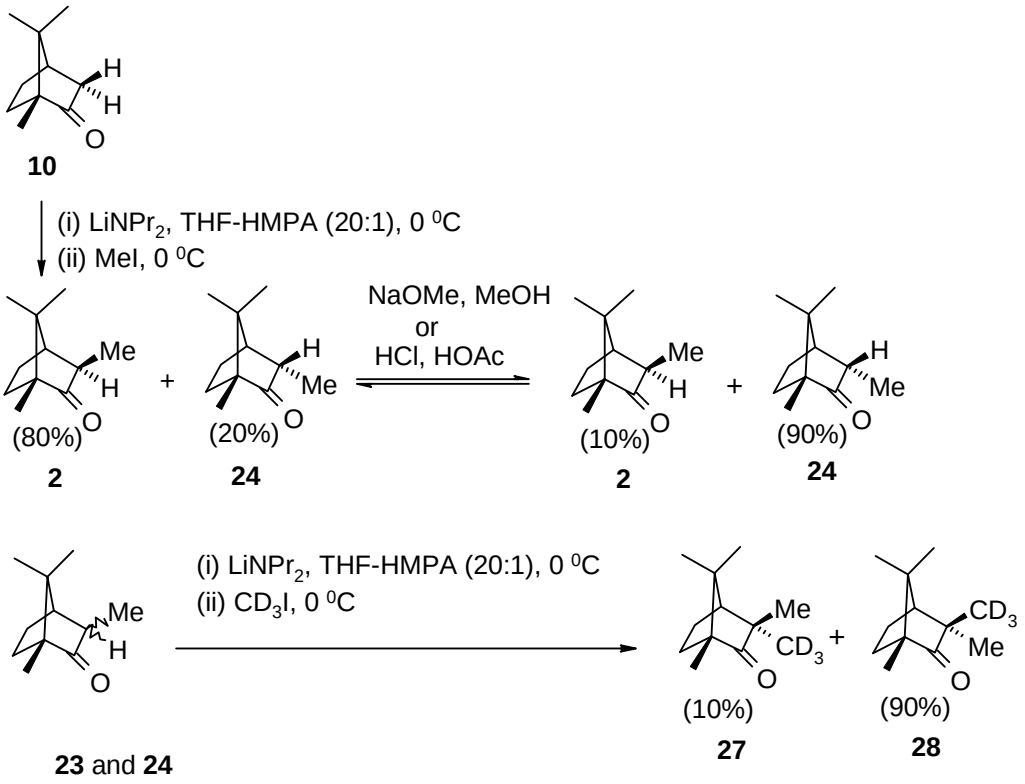
Bromination of camphor in the presence of acetic acid, ethanol or chloroform results in the formation of the 3-*endo*-epimer **17** as the most favoured product (~92%) (Scheme 1.4). Subsequent addition of base (NaOMe or KOBu^t) yields the same result with respect to the ratio of the C(3)-epimers (*endo*:*exo*::92:8).[20] On the other hand, treatment of camphor **10** with pyridinium tribromide, or bromination of the camphor-based silyl enol ether **22** with 1,4-dioxane-pyridine provides more or less equal proportions of the 3-*exo*-epimer **21** and the 3-*endo*-epimer **17**.[20] However, equilibration of this mixture with base again favours the thermodynamically controlled product mixture (*endo*:*exo*::92:8). In an opposing scenario, when 3-*exo*-methylcamphor **23** or its 3-*endo*-epimer **24** reacts with bromine in acetic acid, *endo*-stereoselectivity is observed with an 80:20 mixture of the 3-*exo*-methylcamphor **25** and its epimer **26**.[20]



Scheme 1.4. C(3)-Bromination of camphor and camphor derivatives.[20]

1.1.4.2.3. ***C(3)-Methylation***

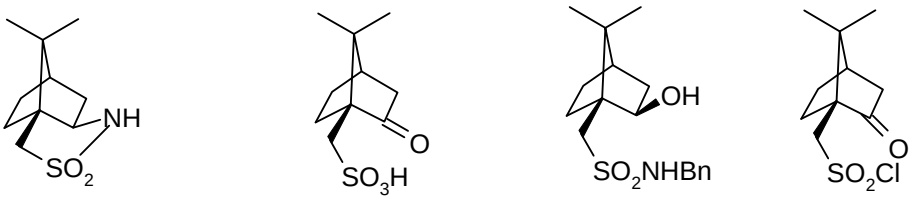
Although C(3)-monomethylation may be readily achieved, the stereochemistry of the incoming methyl group has yet to be fully understood.[20] Treatment of camphor **10** with one equivalent of lithium diisopropylamide and excess methyl iodide at 0ºC yields, in *ca.* 75% yield, a *ca.* 4:1 mixture of 3-*exo*-methylcamphor **23** and 3-*endo*-methylcamphor **24** (Scheme 1.5).[20] Treatment of this mixture either with base (NaOMe in MeOH) or with acid (HCl and HOAc) gives rise to a *ca.* 9:1 mixture in which the major product is the 3-*endo*-methylcamphor **24**.[20] Protonation of 3-methylcamphor enolate also leads to the formation of 3-*endo*-methylcamphor **24** as the major product together with the epimer **23**.In contrast to the reaction of camphor with methyl iodide, C-3-deuteromethylation (using CD_3I) of the diastereomeric 3-methylcamphors **23** and **24** proceeds with *endo*-stereoselectivity.[20]



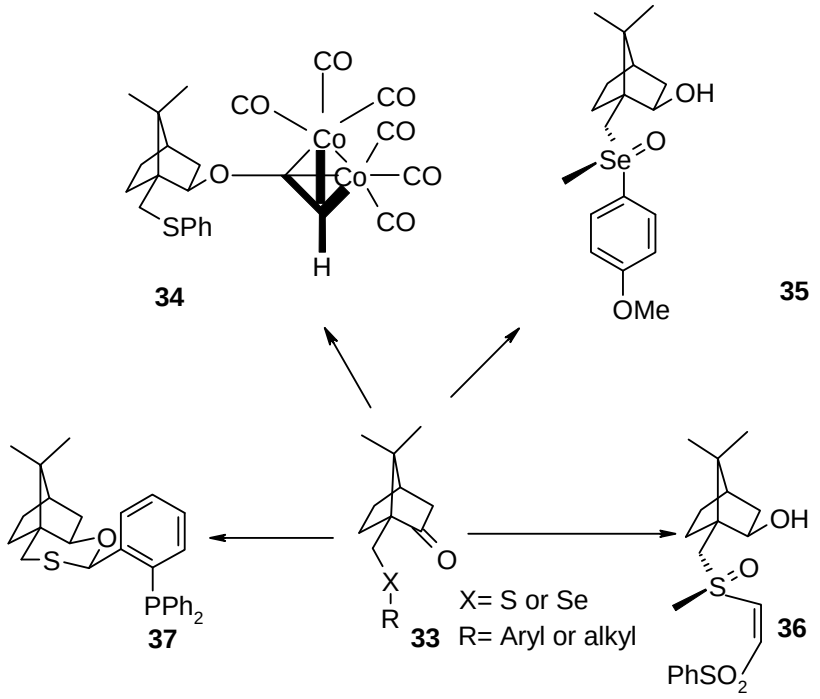
Scheme 1.5. C(3)-methylation of the diastereomeric 3-methylcamphors **23** or **24**.[20]

1.1.4.2.4. ***C(10)-Modification***

Chiral C(10)-modified camphor analogues have been employed in a large number of asymmetric reactions as:- chiral auxiliaries (*e.g.* Oppolzer's sultam **29**); chiral resolving agents (*e.g.*, camphor-10-sulfonic acid **30**) or chiral catalysts (*e.g.*, Yus' sulfonamide **31**).[27] They have also found use as fascinating chiral synthons in the total synthesis of natural products. Many of the synthetic routes involve the transfunctionalization of commercially available camphor-10-sulfonic acid **30** or camphor-10-sulfonyl chloride **32**.[27,28]



Regiospecific C(10)-sulfonation is often achieved by treating camphor with a mixture of sulphuric acid and acetic anhydride, the mechanism involving a Wagner-Meerwein rearrangement.[20] Martinez *et al.* have reported the use of various C(10)-substituted camphor derivatives as chirality transfer agents; these include compounds **29**-**32**.[27]



Scheme 1.6. C(10)-S- and C(10)-Se-camphor derivatives.[27]

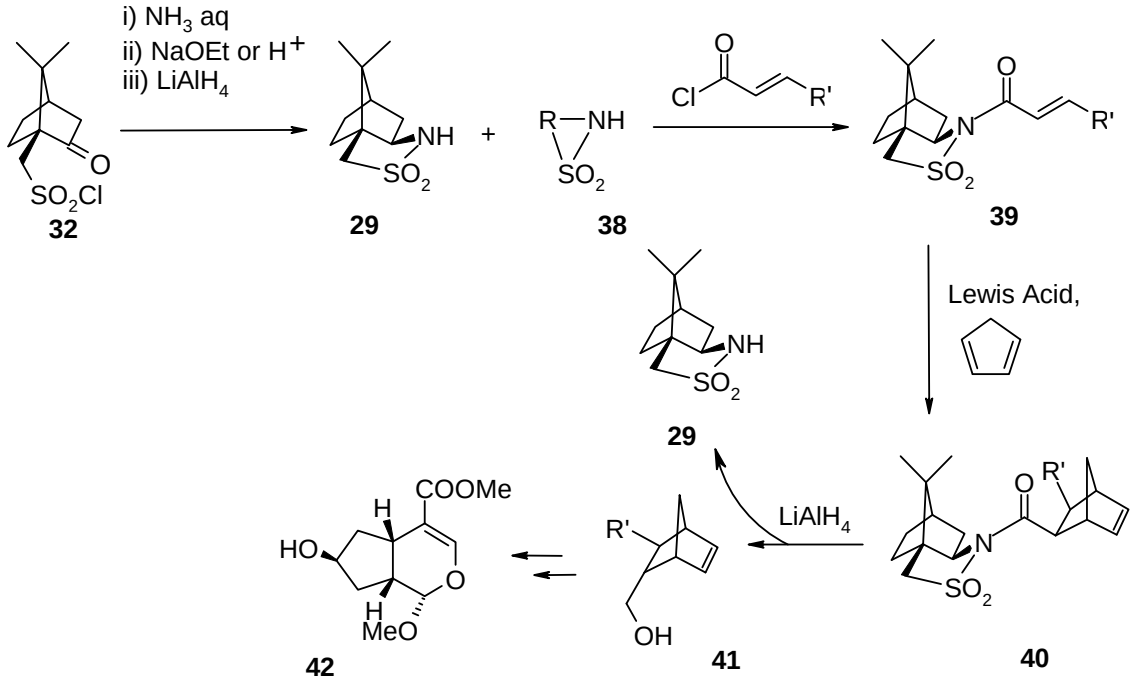
The camphor derivatives **33** and the readily available 10-sulfanylisoborneol provide convenient access to the C(10)-S(II)-, C(10)-Se(IV)- and C(10)-S(IV)-camphor derivatives **34**-**37** (Scheme 1.6). Due to apparent difficulties and poor yields this approach remains an avenue to be effectively exploited.

1.1.5. Camphor-Derived Chiral Auxiliaries

1.1.5.1.Oppolzer's sultam

Oppolzer's camphorsultam **29** is, apparently, the most studied and widely employed chiral auxiliary in asymmetric synthesis.[29,30] The sultam **29** is synthesized with ease from

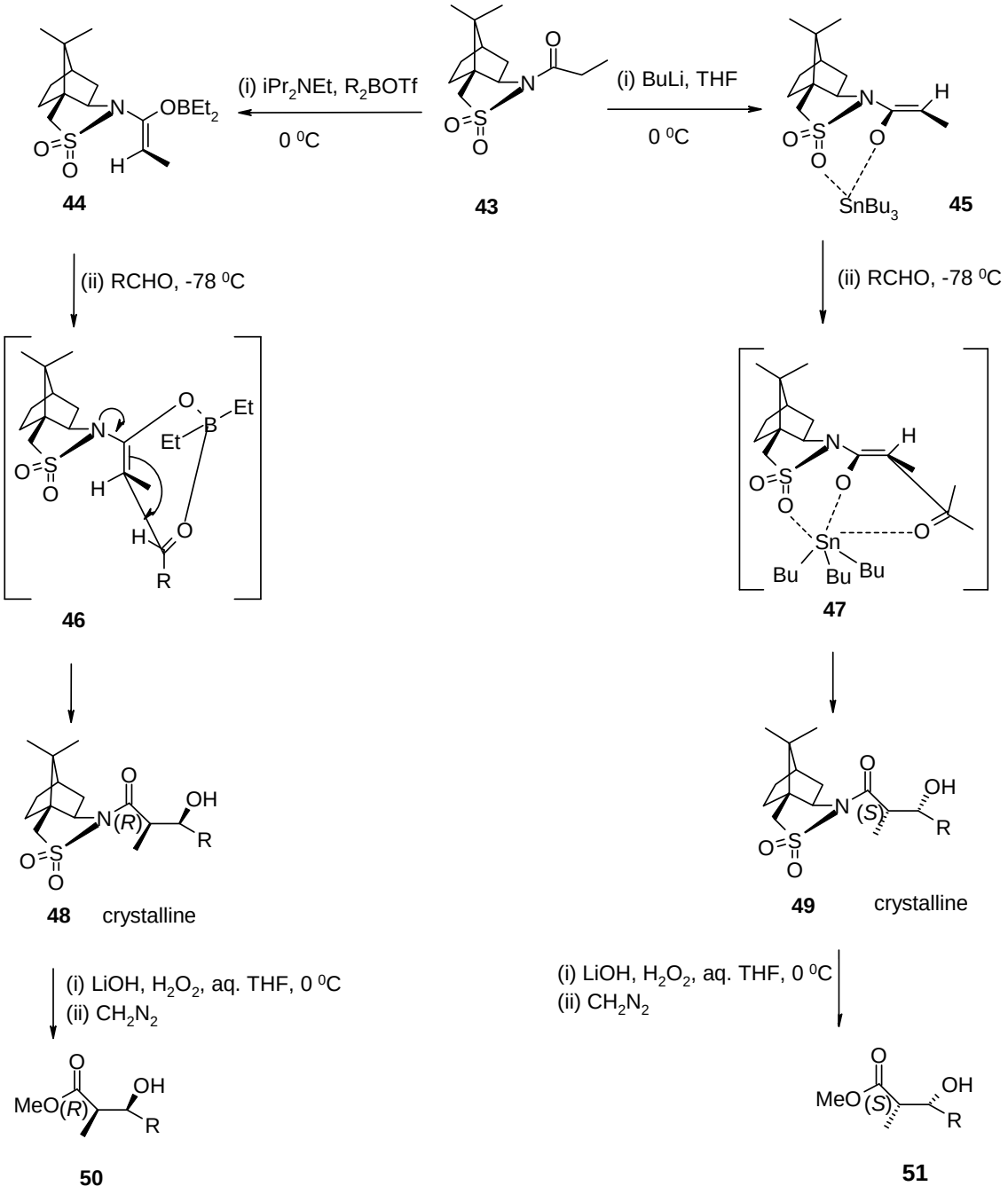
camphor-10-sulfonyl chloride **32**[30,31] and has been employed to induce asymmetry in many transformations, including Diels Alder reactions,[30] aldol condensations,[32] alkylations[33] and aminations.[34] The Oppolzer sultam **29** (Scheme 1.7) was originally created to stereoelectronically enhance the dienophilicity of the *N*-enoyl moiety and, in so doing, broaden the scope of Diels-Alder chemistry.[30] Addition of cyclopentadiene to the *N*-enoyl derivative **39** afforded the corresponding *N*-acyl product **40** in high yield. The *N*-acyl product **40** was found to be stable, readily purified by crystallization, and the auxiliary to be readily cleaved by $LiAlH_4$ under mild conditions with retention of the induced chirality. The chiral auxiliary was recovered quantitatively, while the *N*-acyl product **40** was isolated with superb *endo*- and π-face selectivities and eventually transformed in a number of steps to the pure loganin **42**.[31,35-36]



Scheme 1.7. Synthesis and use of the Oppolzer camphorsultam **29** as a chiral auxiliary in a Diels-Alder reaction.[30,31,35,36]

The high stereoselectivity observed in the Lewis acid-catalyzed reaction is attributed to the fact that both the carbonyl and the upper sulfonyl oxygen atoms complex with the di-coordinating Lewis acid ML_n, thereby directing attack by cyclopentadiene to the π-face directly opposite the C(3)-methylene hydrogens. When the same reaction was carried out

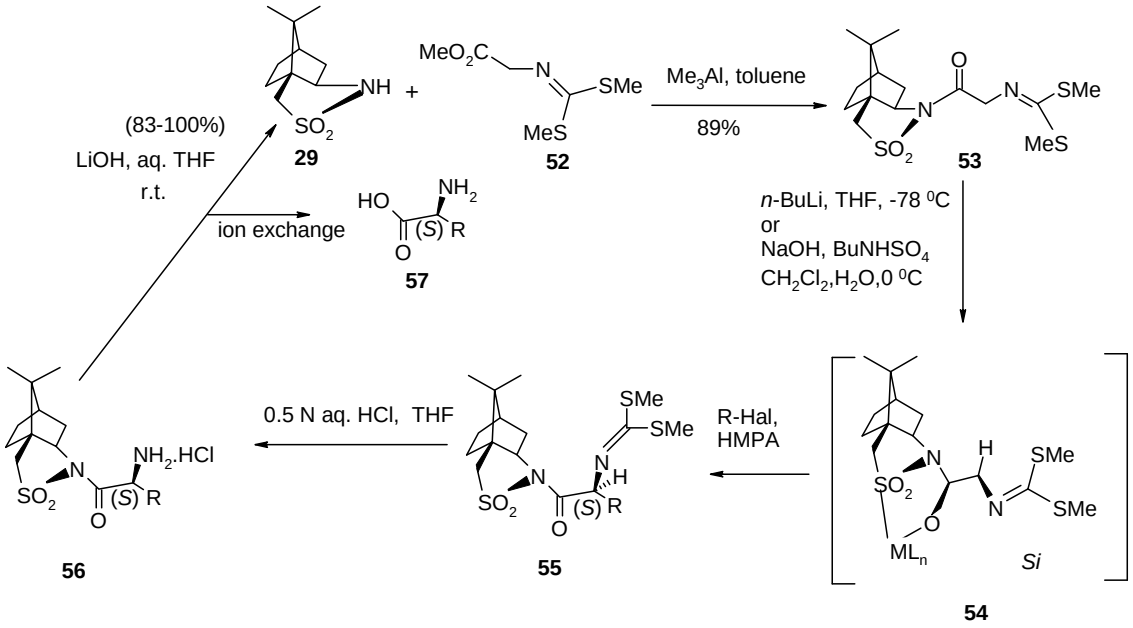
in the absence of a Lewis catalyst, unexpectedly high stereoselectivity was observed and this is attributed to transmission of chiral information from the rigid bornane moiety to the prochiral centres C_α and C_β *via* the pyramidal nitrogen atom leading to *exo* C_α-*Re* face attack.



Scheme 1.8. Use of the Oppolzer camphorsultam derivative in Aldol reactions.[32]

Oppolzer camphorsultam enolates have also found application in asymmetric aldol condensation reactions. The diastereomeric aldols **50** and **51**, for example, may be obtained selectively from the *N*-acyl camphorsultam derivative 4**3** as illustrated in Scheme 1.8. The choice of enolate counterion determines the absolute configuration of end-product. Use of boron or tin enolates involves coordination of the aldehyde (RCHO) with the (*Z*)-enolate in both cases, the former favouring C_α-*Re*-face attack, the latter C_α-*Si*-face.[32]

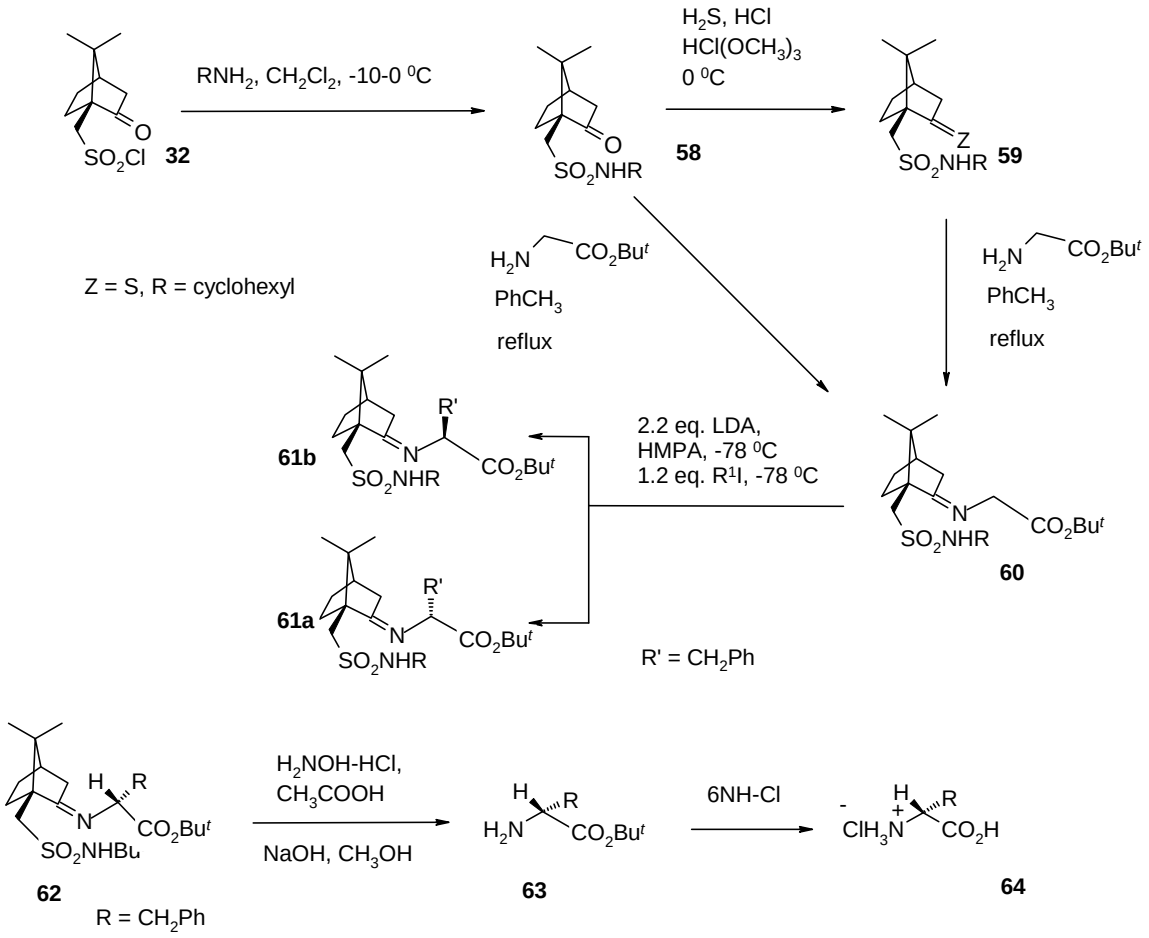
Use of the Oppolzer camphorsultam **29** has also proved to be particularly advantageous in alkylation reactions. Thus, treatment of the sultam **29** with methyl *N*-[bis(methylthio)methylene]glycinate **52** in the presence of Me_3Al afforded the glycinate **53**, which serves as a substrate for the preparation of a variety of α-amino acids **57** (Scheme 1.9). The Oppolzer camphorsultam **29** permits alkylation with non-activated and even with secondary alkyl iodides to afford alkylation products with excellent diastereomeric excess ratios. The formation of chelated (*Z*)-enolate derivatives leads to alkylation at the C_α-*Si*-face, opposite to the nitrogen lone pair of the sultam.[33]



Scheme 1.9. Preparation of enantiomerically pure α-amino acid **47** *via* *N*-alkylation.[33]

1.1.5.2. Camphor-10-sulfonamides as chiral auxiliaries in the asymmetric synthesis of α-aminoacids

α-Amino acids are crucial components in biological systems and the synthesis of optically active α-amino acids has been widely investigated. Yeh and co-workers[37] reported an asymmetric synthesis of α-amino acids **64** from glycine *t*-butyl ester, using (+)-*N*-cyclohexyl-10-camphorsulfonamide **58** as a chiral auxiliary and benzyl bromide as an alkylating agent, and observed 98% induction (Scheme 1.10).[37] Alkylation of Schiff base **60** gave rise to diastereoselectivity of 1: 1.5.

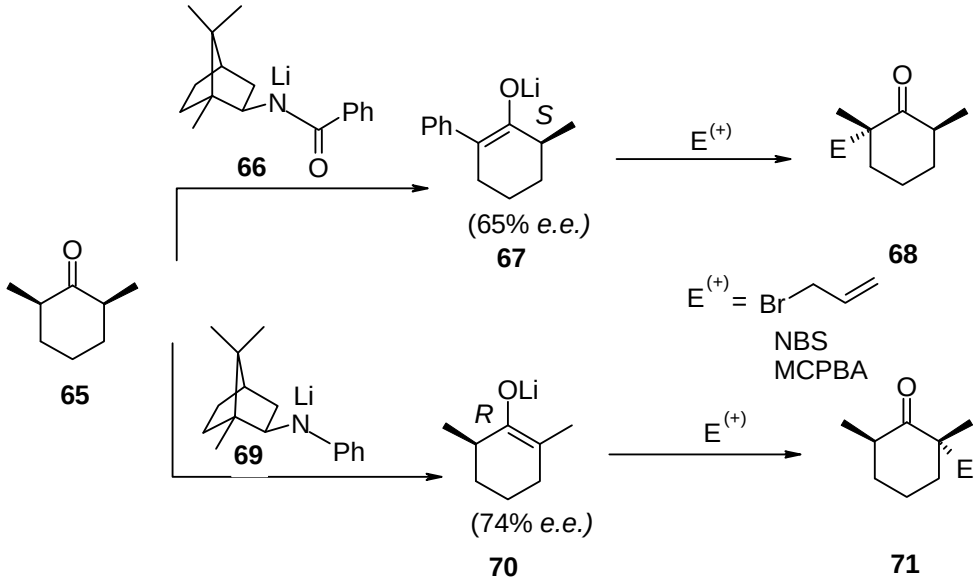


Scheme 1.10. Synthesis of α-amino acids from glycine *t*-butyl ester.[37]

1.1.5.3. Camphor-derived chiral reagents

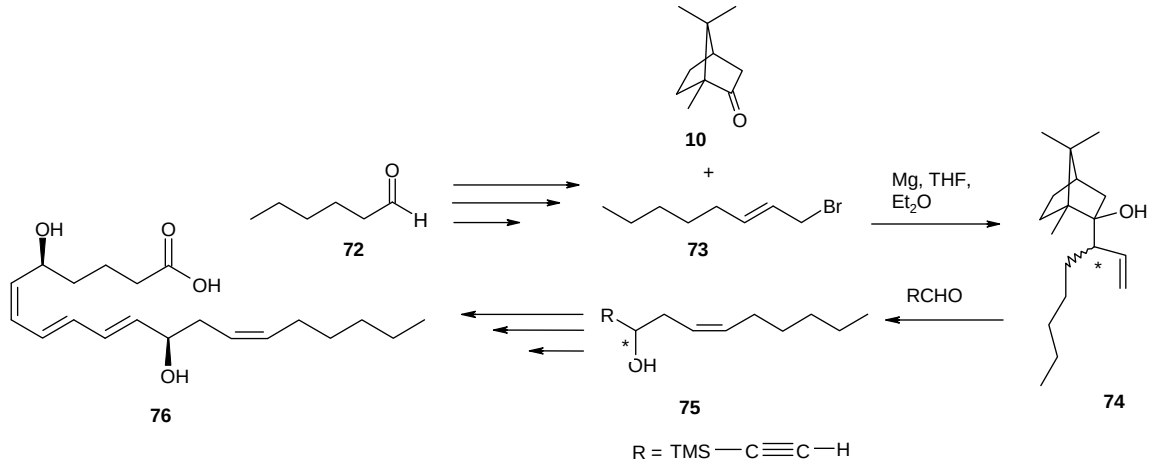
Breath-taking advancements in the development and application of camphor-derived chiral reagents have been witnessed in recent years. Despite their pivotal practical role,

progress has been hampered somewhat by the apparently confusing enantioselectivities which have been observed. Examples of camphor-derived reagents include compounds **66** and **69** (Scheme 1.11). The enantioselective removal of a proton from the prochiral ketone by **66** or **69** in THF resulted in the chiral lithium enolates **67** (65% *e.e.*) and **70** (74% *e.e.*) respectively. This was followed by the reaction of the chiral lithium enolates with allyl bromide to afford the enantiomeric ketones **68** or **71** in *ca* 65% overall yield.[30]



Scheme 1.11. Enantioselective abstraction of proton of prochiral ketone.[30]

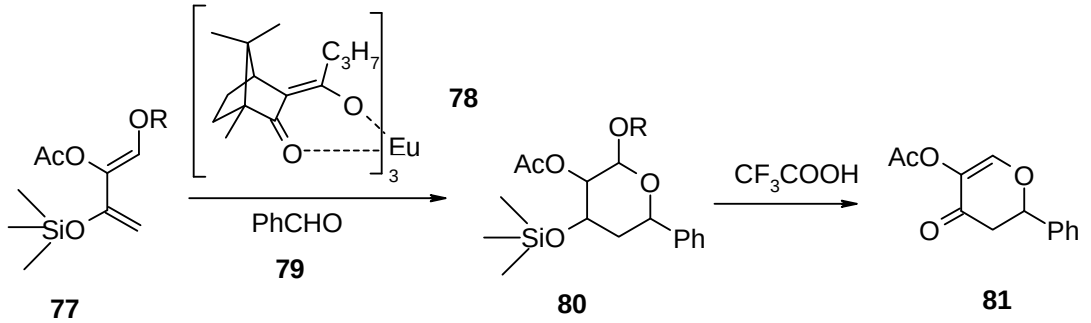
Another example which illustrates the usefulness of camphor-derived chiral reagents is an allyl transfer reaction which involves the 2-oxonia Cope rearrangement – a reaction that has recently gained attention due to the variety of linear homoallylic alcohols it produces with stereocontrolled chirality transfer. Using the chiral camphor reagent **74**, Loh and co-workers synthesized the (*Z*)-*α*-homoallylic alcohol **75** in high regio- and enantioselectivity. They also employed this camphor reagent **74** as a precursor to generate the C_{12}-C_{20} fragment of leukotriene B4 **76** which shows antiviral properties against retroviruses, including HIV-1 and HIV-2. Loh and co-workers inherently believe that the chiral camphor reagent **74** exists as a mixture of two diastereomers, one of which transfers chirality to the aldehyde.[38]



Scheme 1.12. Allyl transfer of chiral camphor reagent **74**.[38]

1.1.5.4. Camphor-derived chiral catalysts

The past few decades have seen the introduction of the chiral europium complex $Eu(hfc)_3$ **78**, which has not only been used as a chiral NMR shift reagent but has also been shown to catalyze hetero-Diels-Alder reactions of silyloxydienes **77** with arylaldehyde **79** as shown in Scheme 1.13. Thus, in the presence of this catalyst, reaction of dienes **77** with benzaldehyde **79** at room temperature proceeds in a stereoselective fashion to furnish the *cis*-substituted dihydropyrans **80**, which undergo elimination to afford the dihydropyrones **81** in relatively good yield (Table 1). Compound (*R*)-**81** was generated from the prochiral substrate **77a** in 42% *e.e*, whereas use of the chiral menthyloxy-substituted diene **77b** afforded the same product in 86% *e.e* (Table 1). The intriguing aspect in these reactions is that the interactivity of the (3*R*)-menthyl diene auxiliary group with catalyst **78** yields an enantiomeric excess of 86% (*entry 2*); (Table 1).[31]

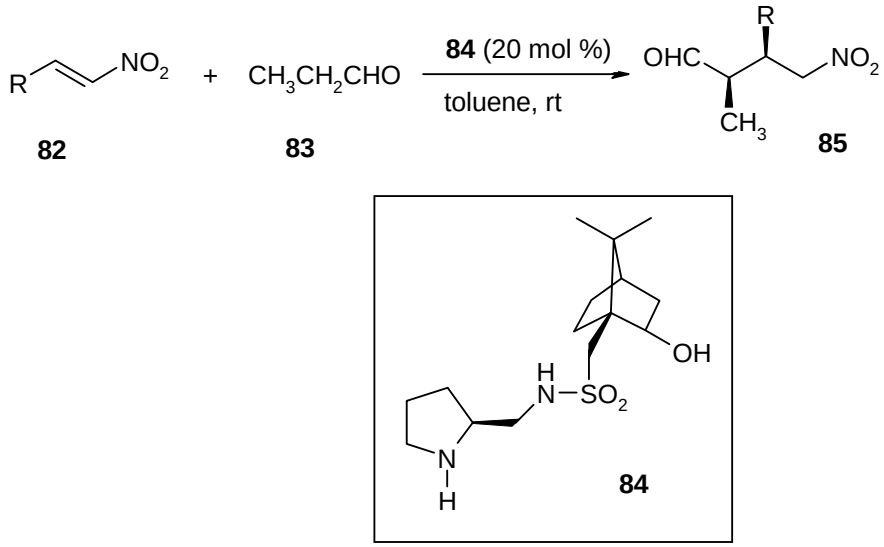


Scheme 1.13. Catalysis of Diels-Alder adduct with europium complex.[30]

Table 1. Diels-Alder reaction with europium-complex[30]

Entry	Series	R	Eu complex	Configuration	% e.e.
1	a	*t*-Bu	**78**	*R*	42
2	b	(3*R*)-menthyl	**78**	*R*	86
3	c	(3*S*)-menthyl	**78**	*R*	18
4	d	(3*R*)-menthyl	$Eu(fod)_3$	*S*	10

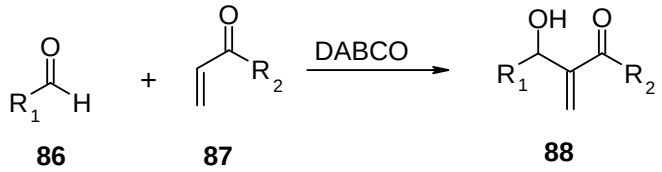
The puckered and rigid bicyclic framework of camphor became a driving force for Weng and co-workers to exploit its stereo-directing and discriminating ability. Weng and co-workers[39] synthesized pyrrolidine-camphor derivative **84** which they employed as an organocatalyst in the asymmetric version of Michael reaction of *n*-propanal **83** with β-nitroalkene **82** to generate the corresponding chiral nitrocarbonyl adduct **85** as shown in Scheme 1.14. The reaction furnished a good yield (91%) with 94% e.e. and a *syn*:*anti* ratio of 88:12. This is attributable to the key role played by the free hydroxyl group which is thought to interact with the nitroalkene moiety by hydrogen bonding bonding.



Scheme 1.14. Michael reaction catalyzed by pyrrolidine-camphor derivative.[39]

1.2. THE MORITA-BAYLIS-HILLMAN REACTION

The Morita-Baylis-Hillman (MBH) reaction (Scheme 1.15) involves reaction between an sp^2-hybridized carbon electrophile, such as an aldehyde, and an α,β-unsaturated electron-withdrawing group catalyzed by a nucleophilic amine, such as 1,4-diazabicyclo[2.2.2]octane (DABCO), 4-(dimethylamino)pyridine (DMAP), 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) or 3-hydroxyquinuclidine (3-HQ).[40-43] The reaction affords product capable of further synthetic elaboration. The reaction is referred to as an atom-efficient and inherently green process, since all the reactants' atoms are incorporated in the final product.[42,44-47] The reaction is named after Anthony B. Baylis and Melville E.D. Hillman who patented the transformation, and Ken-ichi Morita whose use of tertiary phosphine catalysts in similar transformations was published first.[41-43]



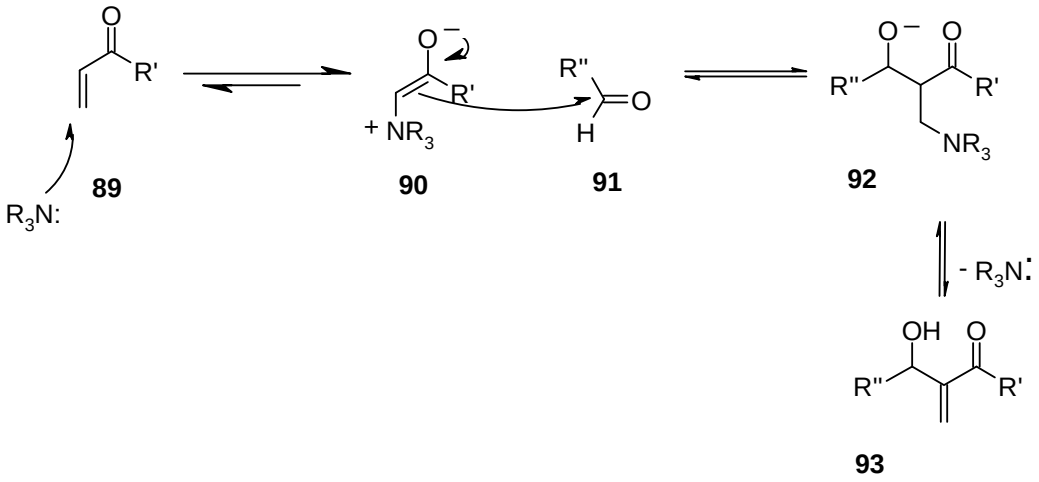
86 **87** **88**

Scheme 1.15. Morita-Baylis-Hillman reaction.[44]

1.2.1. Mechanism of the MBH Reaction

The reaction is initiated by nucleophilic attack of a tertiary amine catalyst on an activated alkene, affording a zwitterionic intermediate which can then attack the electrophilic aldehyde to give a second zwitterionic adduct.[48] Various views have been held about the details of the final elimination step, *viz*., E_2 , $E1_{cb}$ and, more recently, the involvement of a further molecule of aldehyde to facilitate elimination of the proton.[48-51] The essential details of the mechanism are outlined in Scheme 1.16. Bode and Kaye[52] explored the mechanism of the reaction by treating acrylates with electrophilic pyridinecarbaldehydes, in the presence of 3-HQ or DABCO, and observed that the rate of the reaction was accelerated when using 3-HQ instead of DABCO. They conducted ^{1}H NMR kinetic studies which led them to conclude that the experimental data was in line with third-order

kinetics overall, or pseudo-second-order kinetics if the concentration of tertiary amine was assumed to remain unchanged. It is apparent that the reaction rate is dependent on both the concentration of the aldehyde and the activated alkene.



Scheme 1.16. Essential aspects of the mechanism of Morita-Baylis-Hillman reaction.[52]

1.2.1.1. Reaction Parameters

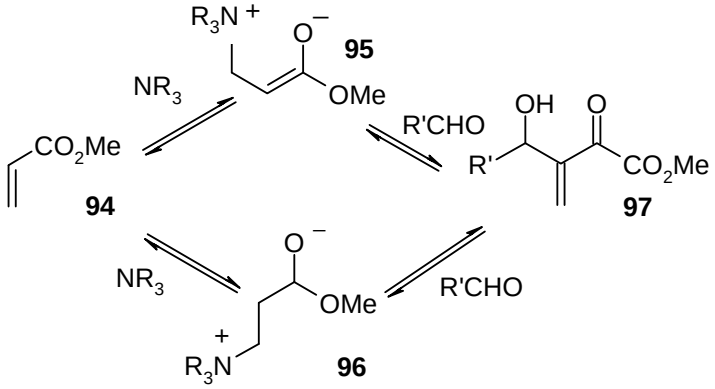
1.2.1.1.1. Solvents

Morita-Baylis-Hillman reactions can often be carried out in the absence of a solvent,[53] and these reactions usually result in good yields.[54] However, there are instances in which the use of solvents is inevitable (where starting materials are poorly soluble) or even beneficial.[43] Under such conditions, dilution adversely affects not only the reaction rate but also results in low to moderate yields.[53,55]

1.2.1.1.2. Temperature and Microwave Irradiation

Morita-Baylis-Hillman reactions are usually carried out at room temperature to avoid possible polymerization side reactions which are known to result at higher temperatures, especially over prolonged periods of time.[56,57] Microwave (MW)-mediated methodology, coupled with the addition of a radical inhibitor to protect the activated alkene from

potential polymerization, has been shown to accelerate the rate of reaction significantly, often with increased yields.[58] Leahy and co-workers[45,46] revealed that the rate of reaction is enhanced upon raising the temperature above room temperature, but found that this leads to poor yields compared to those obtained at room temperature. Surprisingly, they also observed that the reaction proceeded well with enhanced reaction rate upon lowering the temperature to 0°C. This temperature effect is quite astonishing given that the reaction rate can be enhanced both by heating and by cooling relative to room temperature. In order to rationalize the increase in reaction rate under such divergent conditions it has been suggested that formation of the product involves the zwitterionic intermediates **95** and **96** (Scheme 1.17), which are in equilibrium with each other and the starting materials. The relative concentrations of these intermediates would be different at different temperatures and the changes in the rate of reactions would mirror this difference.

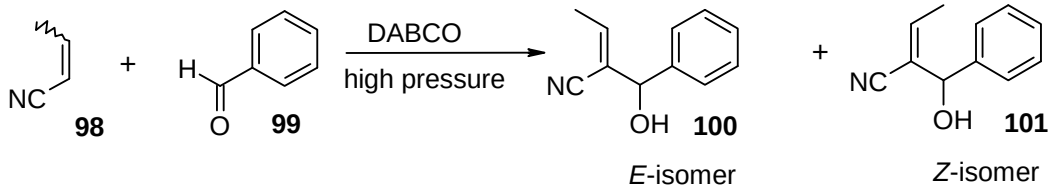


Scheme 1.17. Equilibration of intermediates considered to account for the effect of temperature on the rate of the MBH reaction.[46]

1.2.1.1.3. Pressure and Ultrasound

Studies concerned with pressure effects on the rate of the Morita-Baylis-Hillman reaction have shown the significance of employing high pressure.[59] The scope of the Morita-Baylis-Hillman reaction at atmospheric pressure can be greatly widened by exploiting the very high negative volume of activation associated with the reaction. Rozendaal and co-workers,[48] have shown that, in the reaction of 1-propenyl cyanide with benzaldehyde in

the aprotic solvent, chloroform, at 15 kbar pressure, the *E*-isomer can be formed in 96% excess (Scheme 1.18).

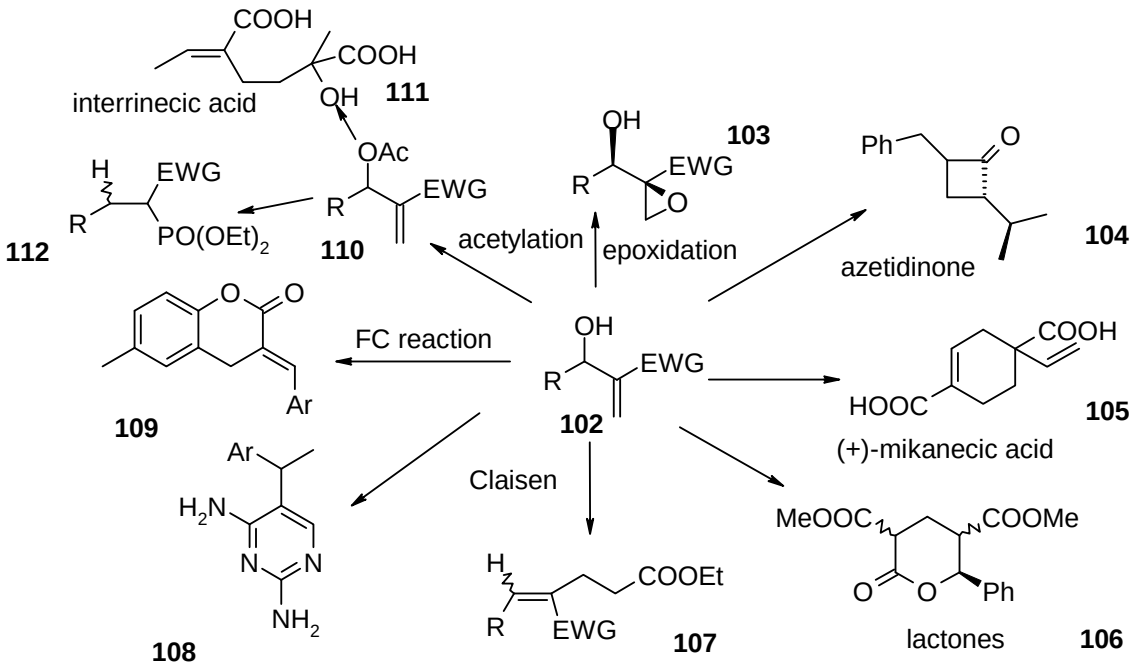


Scheme 1.18. The significance of pressure on the reaction of crotononitrile and benzaldehyde.[48]

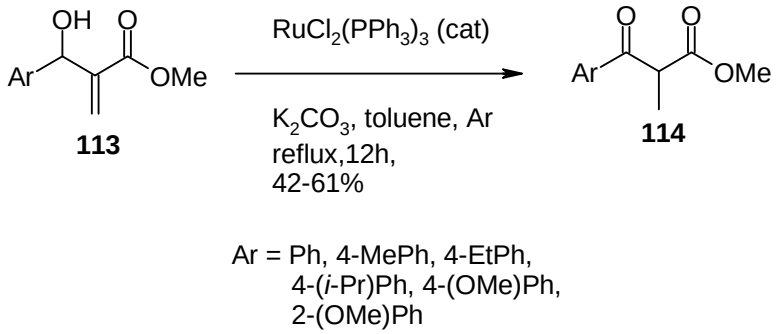
The use of ultrasound has also been used to dramatically accelerate the rate and improve the chemical yield of the Morita-Baylis-Hillman reaction.[60] Coelho and co-workers[47] have shown that the utilization of ultrasound not only shortens reaction times and enhances chemical yields but also that DABCO is a much more efficient catalyst than tributylphosphine.

1.2.2. Applications of the Morita-Baylis-Hillman Reaction in Synthesis

The variety of functional groups present in Morita-Baylis-Hillman adducts provides opportunities for building a range of intriguing chemical systems. The strategic positioning of these functional groups is often the driving force to participate in an array of synthetic transformations leading to the useful products.[43] The past 25 years has witnessed an explosive growth in applications of the Morita-Baylis-Hillman reaction and the various transformations shown in Scheme 1.19 illustrate this claim.[40,41,43,61,62] Basavaiah and co-workers,[43,77] have made a significant contribution to the application of MBH methodology, using $RuCl_2(PPh_3)_3$ they isomerized the Morita-Baylis-Hillman adducts **113** derived from methyl acrylate and aryl aldehydes into the corresponding 3-oxopropanoates **114** as shown in Scheme 1.20.

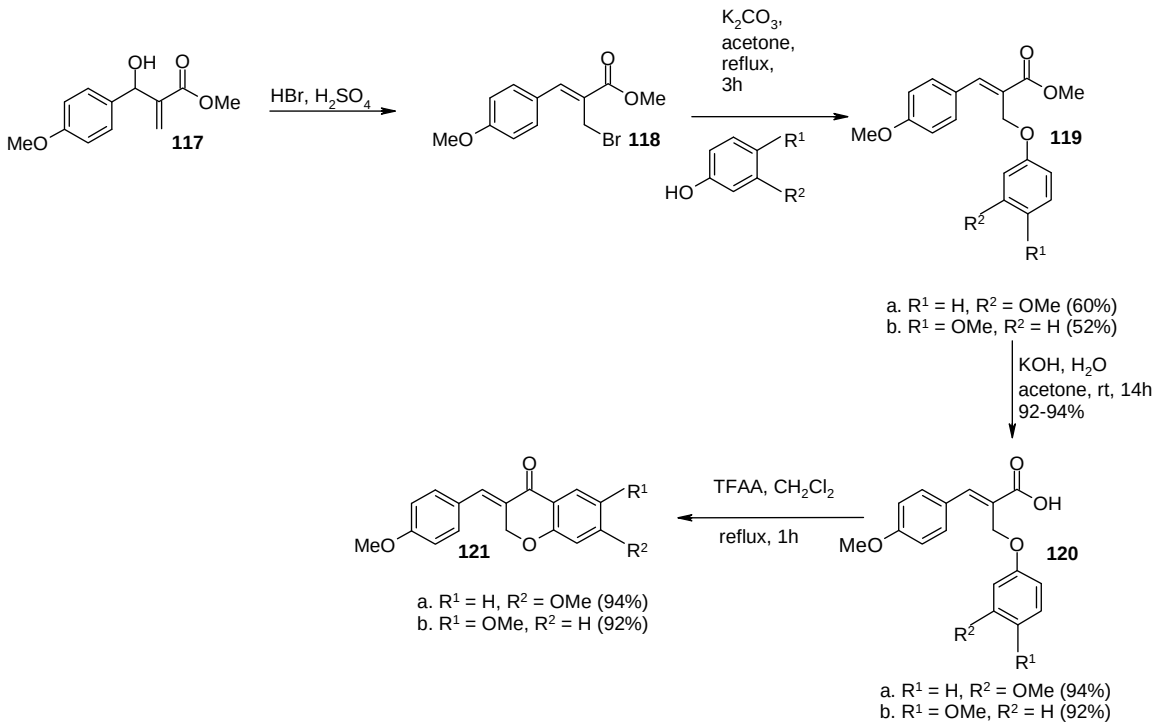


Scheme 1.19. Various applications of MBH adducts.[43,63-76]



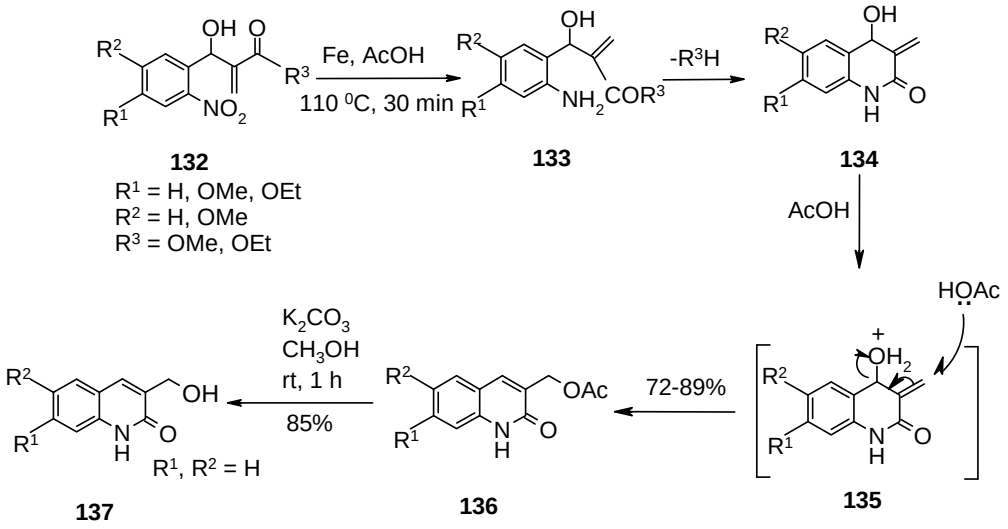
Scheme 1.20. Isomerization reaction of Morita-Baylis-Hillman adducts.[43,77]

They also demonstrated the use of the Morita-Baylis-Hillman adduct **116** (Scheme 1.21) in the synthesis of natural products **121a** (bonducellin ether) and **121b** (antifungal agent). The transformation involves an intramolecular Friedel-Crafts rearrangement.[43,78]



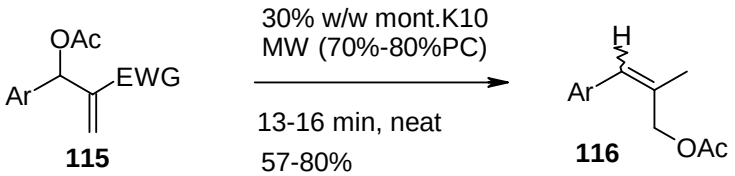
Scheme 1.21. Morita-Baylis-Hillman adducts showing Friedel-Crafts cyclization.[43,78]

Basavaiah and co-workers[79] have also described a convenient approach to quinolones when the Morita-Baylis-Hillman adducts prepared from *o*-nitrobenzaldehydes and alkyl acrylates were transformed to the corresponding quinolones **137** with the use of Fe/AcOH as shown in Scheme 1.22.



Scheme 1.22. A convenient route to functionalized quionolones.[79]

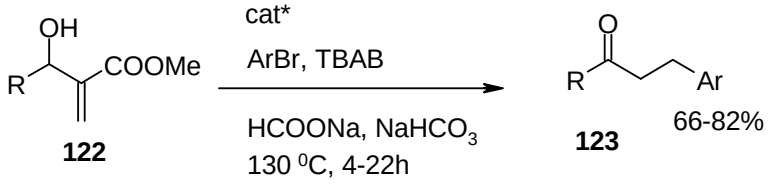
Shanmugam and Singh,[80] on the other hand, achieved the isomerization of the Morita-Baylis-Hillman adducts **116** to the non-terminal alkenes (Scheme 1.23).



EWG = COOEt, CN, COMe
Ar = Ph, 4-ClPh, 4-MePh,
2,4-$(Cl)_2$Ph, 4-(OMe)Ph,
naphth-1-yl, naphth-2-yl

Scheme 1.23. Isomerization of Morita-Baylis-Hillman acetate adducts.[80]

Morita-Baylis-Hillman adducts have also been used as precursors for the Heck reaction by Calo and co-workers, who reacted aryl bromides with methyl 3-hydroxy-2-methylenealkanoates and methyl 3-hydroxy-3-phenylpropanoate (Scheme 1.24) in the presence of Pd-catalyst **124** in which benzothiozole carbene was used as a ligand in TBAB to furnish the β-aryl ketones **123**.[81]



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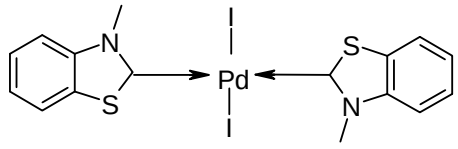
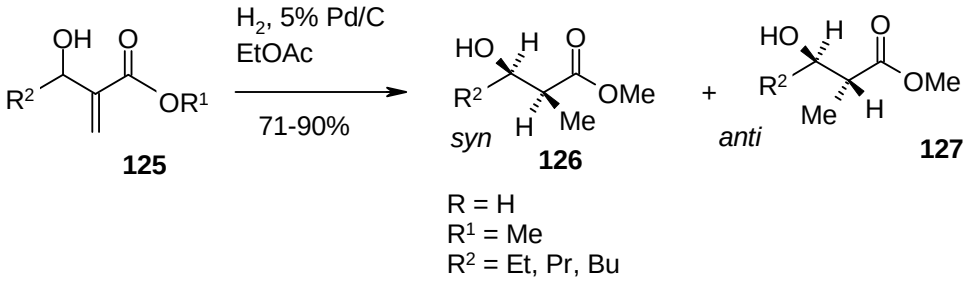


124

Ar = Ph, 4-MePh, 4-(OMe)Ph, 4-(COMe)Ph, naphth-1-yl
R = Ph,Me, Pr, Pr^i, Oct

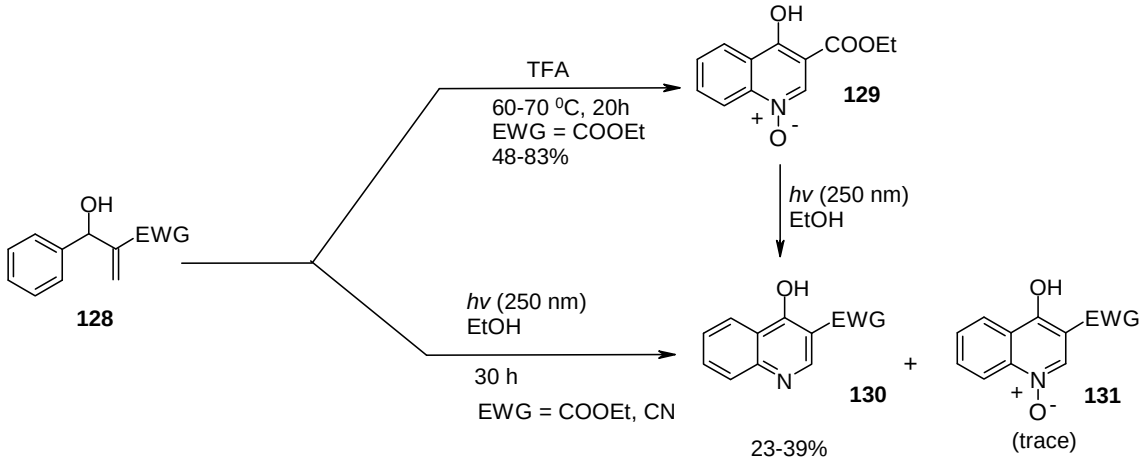
Scheme 1.24. The involvement of Morita-Baylis-Hillman adducts in the Heck reaction.[81]

Coelho and co-workers, further explored the transformation of Morita-Baylis-Hillman products using hydrogen in the presence of a heterogenous palladium catalyst to give rise to the corresponding *syn*/*anti* isomers as illustrated in Scheme 1.24.[82]



Scheme 1.25. Hydrogenation of Morita-Baylis-Hillman adducts.[82]

Kim and co-workers,[83,84] achieved successful conversion of the ethyl acrylate-derived Morita-Baylis-Hillman adduct **128** into the quinoline-*N*-oxide **129** in the presence of TFA at 60-70°C, but when acrylonitrile-derived analogue was reacted under the same conditions no positive result was obtained. The use of the acrylonitrile-derived adduct only reacted under photochemical conditions as shown in Scheme 1.26 to afford the quinoline and quinoline-*N*-oxides.



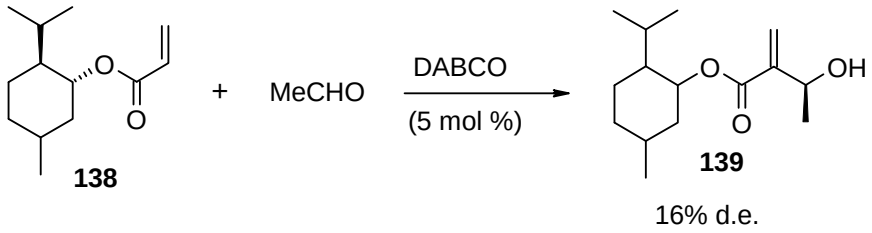
Scheme 1.26. The use of photochemical energy in Morita-Baylis-Hillman reaction.[83,84]

1.2.3. The Asymmetric Morita-Baylis-Hillman Reaction

The Morita-Baylis-Hillman reaction which involves sp^2-hybridized carbon electrophiles such as aldehydes, prochiral ketones or aldimines and suitably activated alkenes under the influence of a tertiary nucleophilic amine leads to the generation of a new stereogenic centre.[86] The asymmetric potential of this reaction did not go unnoticed, but has led to a flurry of activity in promoting the asymmetric version of the Morita-Baylis-Hillman reaction. In order to carry out such a transformation, any of the reaction components, *i.e.* activated alkene, the electrophile, the tertiary amine, the catalyst, the solvent or even an additive can be used as a chirality transfer agent.[85-90]

1.2.3.1. Chiral Activated Alkenes

Acrylate esters of chiral alcohols have, thus far, been most widely employed as the chirality transfer agent as they are easily accessible in optically pure form. The chiral auxiliary approach has, of course, been a highly effective method of generating stereochemistry in a molecule in a recoverable fashion, and hydrolysis of the ester product may generally be expected to release the chiral alcohol for re-cycling.[84] The first study of an asymmetric Morita-Baylis-Hillman reaction, which involved the use of chiral acrylates, was carried out by Brown and co-workers,[91] who treated menthyl acrylate with acetaldehyde in the presence of DABCO as a catalyst to yield the Morita-Baylis-Hillman adduct with low (16%) diastereoselectivity (Scheme 1.27).

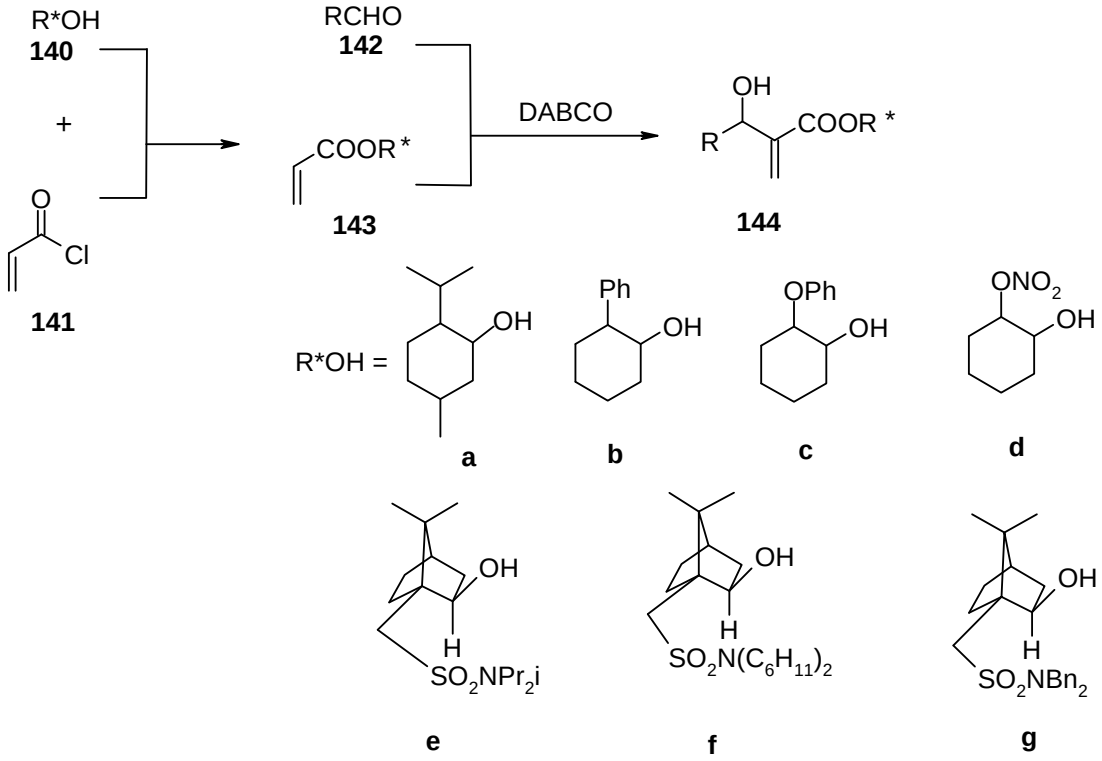


138 **139**

16% d.e.

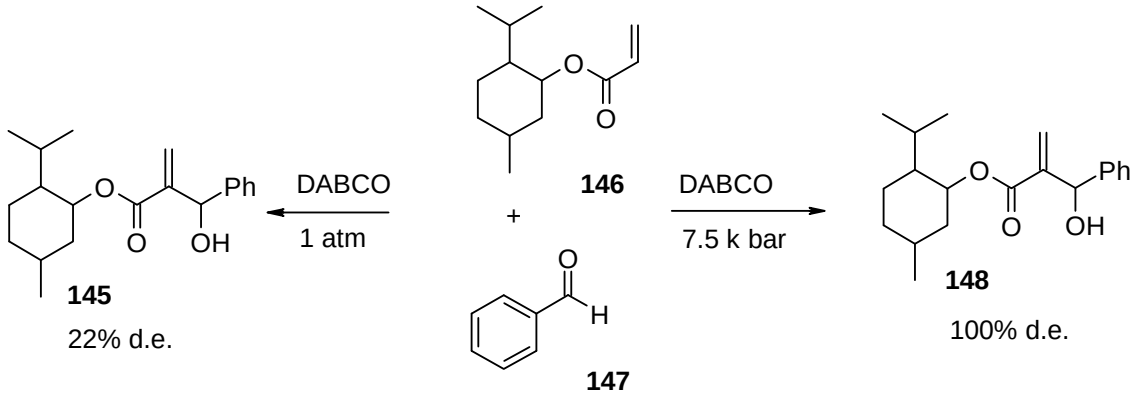
Scheme 1.27. The first diastereoselective Morita-Baylis-Hillman reaction.[91]

Basavaiah and co-workers[85] studied asymmetric induction in the Morita-Baylis-Hillman reactions of a series of chiral acrylates, (including menthyl acrylate) with a variety of aldehydes (Scheme 1.28). A maximum diastereomeric excess of 70%, was achieved in the reaction of propionaldehyde with the acrylate ester derived from Oppolzer's chiral auxiliary **140e**.



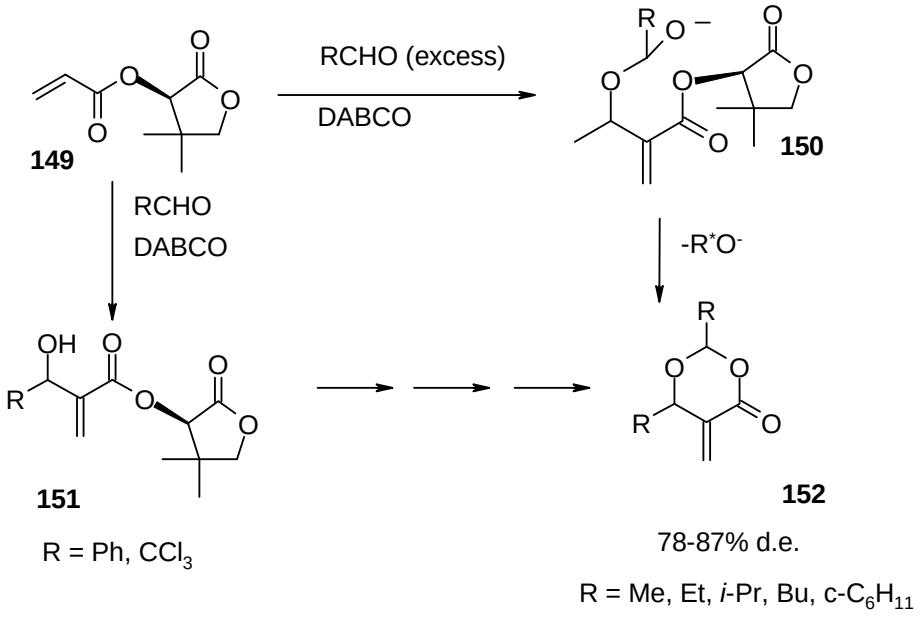
Scheme 1.28. The study of asymmetric induction involving chiral acrylates.[85]

Carrying out the reaction of 1-menthyl acrylate with a variety of aldehydes, Gilbert and co-workers[85,92] obtained more or less the same results. However, when the reactions were conducted at elevated pressures (up to 8.5 kbar), these workers observed remarkable improvements in yields, and the stereoselectivities were in the range 87-100% d.e. (Scheme 1.29).



Scheme 1.29. Asymmetric Morita-Baylis-Hillman reaction at different pressures.[85,91]

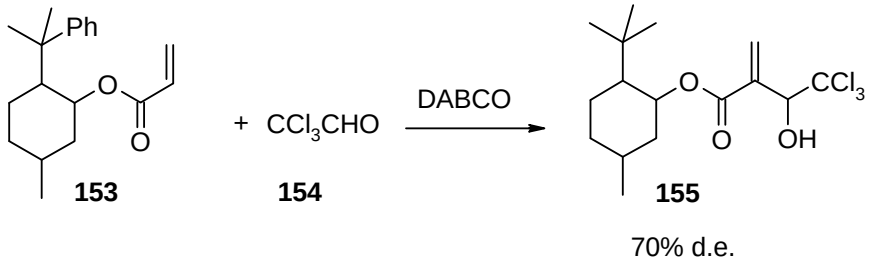
The acrylate ester **149** derived from (*R*)-(+)-pantolactone was treated with various aldehydes in the presence of DABCO to study asymmetric induction. With the exception of benzaldehyde and chloral, the reactions with selected aldehydes gave very encouraging (78-87%) diastereomeric excesses (Scheme 1.30).[85,92-94]



Scheme 1.30. Treatment of acrylate ester **149** with various aldehydes.[85]

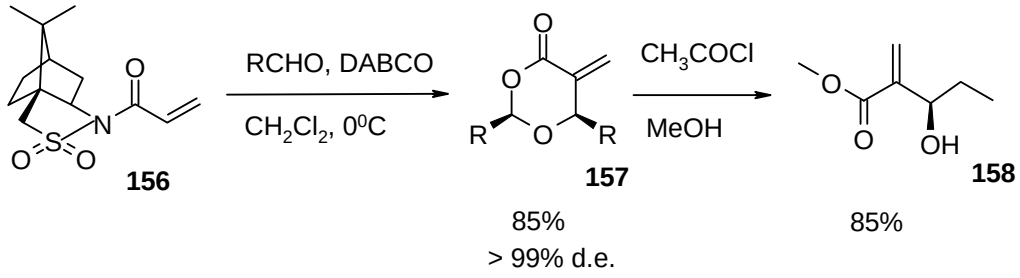
Drewes and co-workers[95] studied the levels of asymmetric induction exhibited by 8-phenylmenthyl acrylate **153** when treated with a variety of aldehydes in the presence of

DABCO at atmospheric pressure. These workers obtained the best result (70% d.e.) when using chloral (Scheme 1.31).



Scheme 1.31. Reaction of acrylate ester **153** with chloral at atmospheric pressure.[85,95]

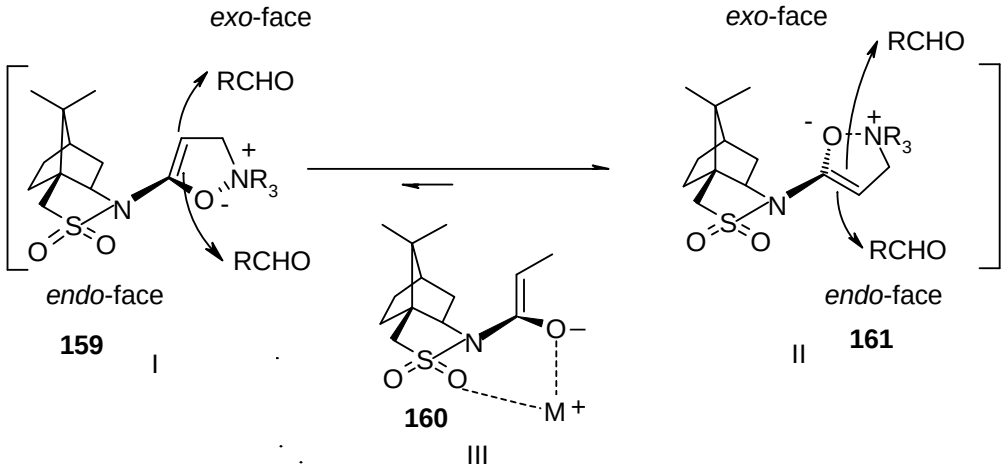
Leahy and co-workers,[46,97] who have, to date, been amongst the most successful with asymmetric Morita-Baylis-Hillman reactions,[45] made use of the commercially accessible Oppolzer camphorsultam **156** to generate the corresponding acrylamide. The resulting acrylamide derivative was then treated with a variety of prochiral aldehydes under the influence of DABCO as catalyst. Use of the Oppolzer camphorsultam **156**[30] in this way gave rise to 1,3-dioxan-4-ones **151** in good to excellent yields and diastereomeric excesses of greater than 99%. The reaction was, however, also shown to be sluggish with sterically hindered aldehydes. The versatile nature of the 1,3-dioxan-4-ones allowed them to be readily cleaved to the corresponding Morita-Baylis-Hillman adducts as shown in the Scheme 1.32.



Scheme 1.32. Employing camphorsultam **156** in the Morita-Baylis-Hillman reaction.[45,97]

The asymmetric induction that takes place with the Oppolzer sultam-derived acrylamides has been demonstrated to be heavily influenced by two principal factors: (i) the well-

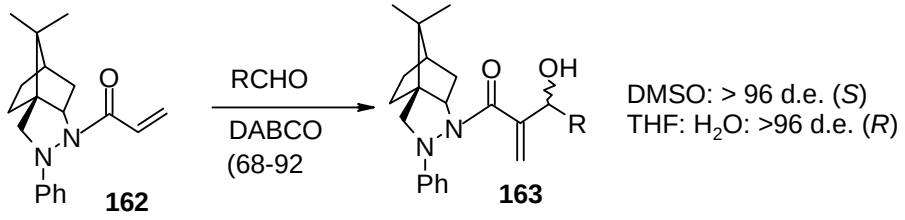
accepted notion of preferential addition to the C(α)-*re* face of the acrylamide; and (ii) the need for an "open" transition state. The *Z*-enolate intermediate, formed upon the addition of the tertiary amine catalyst to the acrylamide, could assume either of the two rotameric conformations (I) or (II), as shown in Scheme 1.33. In rotamer (II), which is favoured in the absence of a Lewis acid co-catalyst, the carbonyl and sulfonyl groups assume an *anti* arrangement so as to minimize van der Waals' interactions of the corresponding oxygen lone pairs (or comparable intramolecular dipolar interactions). In the presence of a Lewis acid, however, chelation of the carbonyl and sulfonyl groups stabilizes the *syn* geometry of the carbonyl group and sulfonyl groups as in structure (III). Overwhelming experimental evidence indicates that, in all reactions that involve acrylamides, attack at the *exo*-face is favoured, due to the steric effect of the axial oxygen of the sulfonyl group, which effectively inhibits attack from the *endo*-face.



Scheme 1.33. Rotamers I and II in the absence of chelation. Rotamer III showing chelation.[46,97]

An impressive approach, in which either individual diastereoisomers can be synthesized with high optical purity from a single enantiomeric source, was developed by Yang and Chen (Scheme 1.34).[98] The Morita-Baylis-Hillman products were obtained in good yield with exceptionally high diastereoselectivities (97-100 % d.e.) using the acryloylhydrazide **162** and, intriguingly, a complete reversal was observed when the solvent was altered

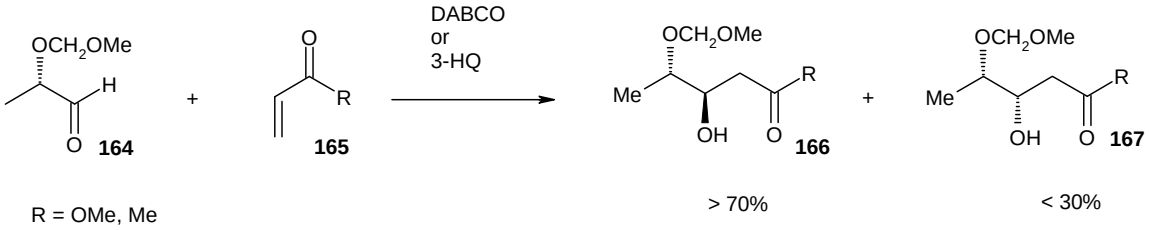
from DMSO to THF-H_2O. It has been suggested that in THF-H_2O the zwitterionic intermediate is stabilized by hydrogen-bonding with solvent molecules, whereas such stabilization is absent in DMSO.



Scheme 1.34. Stereoselective synthesis of Morita-Baylis-Hillman adducts using the aryloylhydrazide **162**.[98]

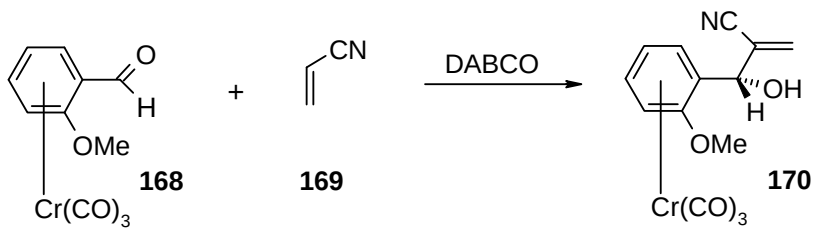
1.2.3.2. Chiral Electrophiles

Much of the work done pertaining to the use of chiral electrophiles in the asymmetric Morita-Baylis-Hillman has involved reactions of either single aldehyde enantiomers or racemic aldehydes with acrylate esters and vinyl ketones in the presence of DABCO as catalyst.[92] Drewes and co-workers[99] treated (*S*)-*O*-(methoxymethyl)acetaldehyde with methyl acrylate and methyl vinyl ketone (MVK) under the influence of DABCO or 3-hydroxyquinuclidine (3-HQ) to furnish diastereomeric mixtures with the *anti*-isomer dominating (Scheme 1.35).



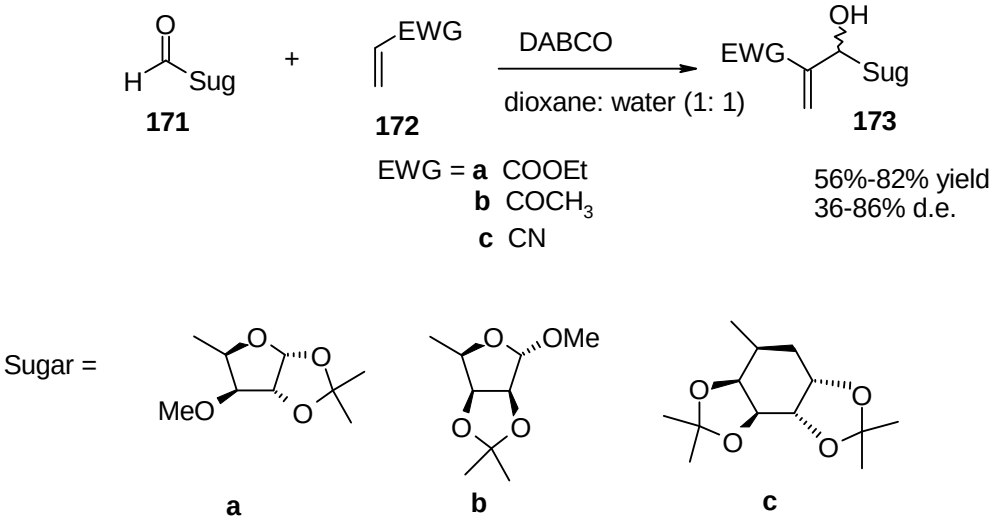
Scheme 1.35. Chiral aldehydes as electrophiles in the Morita-Baylis-Hillman reaction.[99]

Kundig and co-workers[100,101] achieved great success with excellent diastereoselectivity (> 95% d.e.) with *o*-substituted aromatic tricarbonylchromium complexes as electrophiles as shown in Scheme 1.36.



Scheme 1.36. Use of *o*-substituted tricarbonylchromium complexes.[100,101]

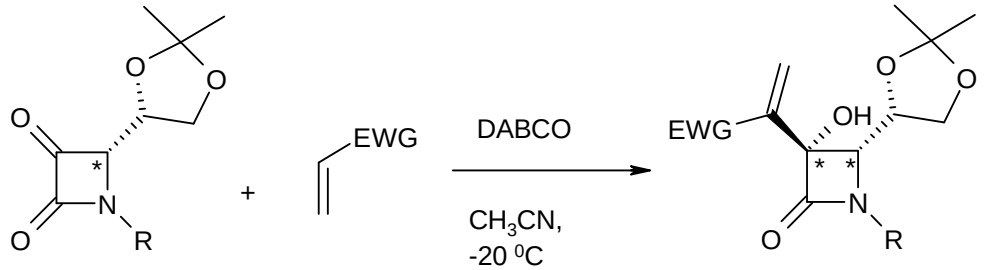
Using structurally fascinating sugar-derived aldehydes, Krishna and co-workers[90,102] pursued a study to elucidate the factors which determine the stereochemistry of the resulting asymmetric Morita-Baylis-Hillman products. The sugar-derived aldehydes were reacted as chiral electrophiles with *α,β*-unsaturated ketones in dioxane-water (1:1) with DABCO as catalyst. The reaction furnished good yields (56-82%) with low to high diastereoselectivity (36-86%) (Scheme 1.37). The stereoselectivity that leads to the *S*-isomer as major adduct, can be explained by preferred attack of the intermediate zwitterions on the *si*-face of the aldehyde in line with the Felkin-Ahn model.[103]



Scheme 1.37. Using sugar-derived aldehydes **171a-c** as electrophiles in Morita-Baylis-Hillman reaction.[90,102]

Alcaide and co-workers[89] reported a highly efficient asymmetric Morita-Baylis-Hillman reaction in which they employed 3-oxo-2-azetidinones **174** as electrophilic chiral precursors. Upon coupling of the 3-oxo-2-azetidinones **174** with various activated alkenes

in DABCO-catalyzed reactions, the Morita-Baylis-Hillman products were obtained within a short span of time, exclusively, as single diasteromers. The 3-oxo-2-azetidinones **174** were easily derived in efficient yield by Swern oxidation of 3-hydroxy-*β*-lactams.



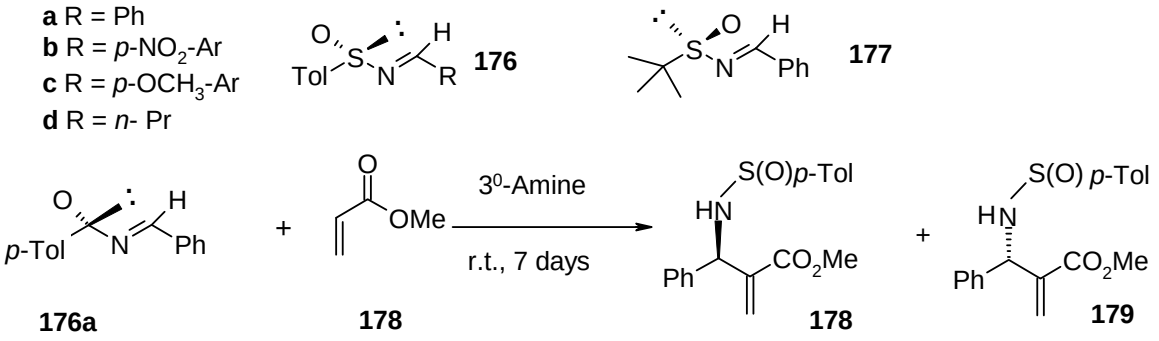
174 **172** **175**

R = 4-MeOC$_6$H$_4$, allyl or propargyl
EWG CO_2CH_3, $COCH_3$ or CN

68-90% yield
94-100% d.e.

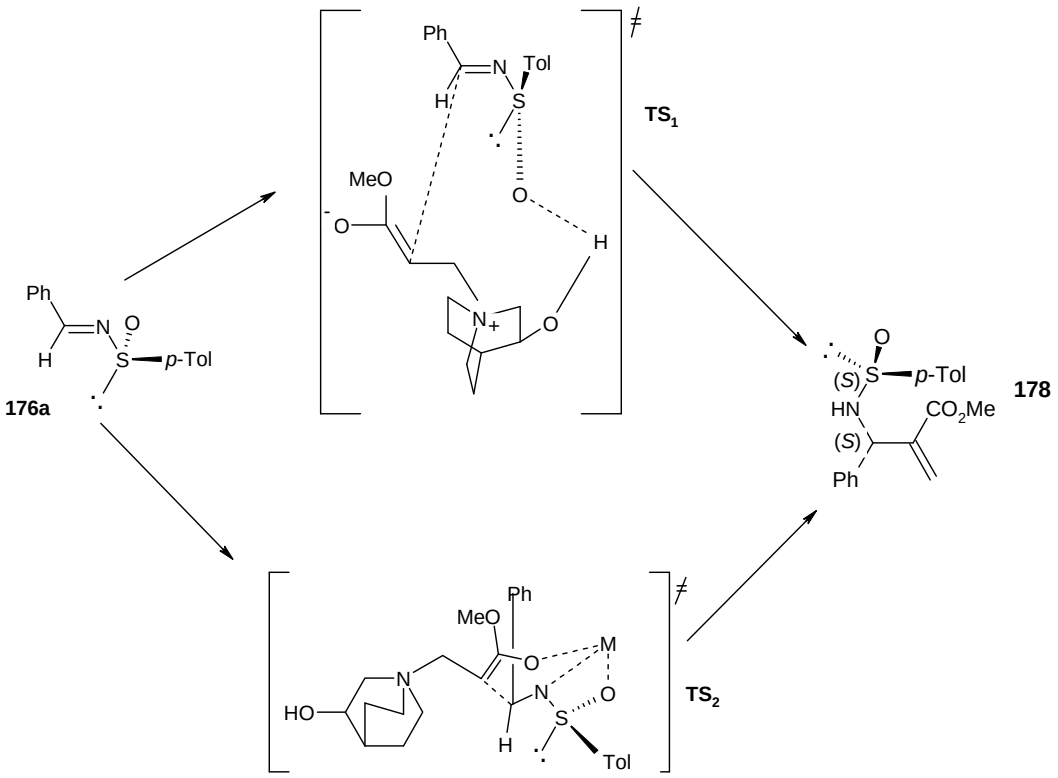
Scheme 1.38. 3-oxo-2-azetidinones as chiral electrophiles in Morita-Baylis-Hillman reactions.[89]

Cases in which imines are substituted for aldehydes in Morita-Baylis-Hillman reactions to furnish the corresponding β-amino alcohols are relatively rare.[104,105] Moreover, there appear to be even fewer initiatives to explore this route in an asymmetric way. Aggarwal and co-workers[106] saw an opportunity to advance the short-comings encountered when aromatic imine chromium tricarbonyl complexes were used as chiral electrophiles. They initially confined the Morita-Baylis-Hillman approach to *o*-substituted aryl imines, shifting the chiral unit to the imine nitrogen atom. This strategy enabled both arylimines and aliphatic imines to be used as chiral electrophiles. The study involved the reaction of *N*-*p*-toluenesulfinimines **176a-d** (Scheme 1.38) and *N*-*tert*-butylsulfinimines **177** with methyl acrylate under the influence of enantiomerically pure 3-hydroxyquinuclidine in the absence or presence of Lewis acids. The reactions were carried out over a wide spectrum of reaction conditions. However, a combination of 3-hydroxyquinuclidine as catalyst coupled with In(OTf)$_3$ gave the best yield (89% yield) while the best stereoselectivity (82%) was achieved using (*S*)-3-hydroxyquinuclidine alone.



Scheme 1.38. Sulfinimines employed as chiral electrophiles in the Morita-Baylis-Hillman reaction.[106]

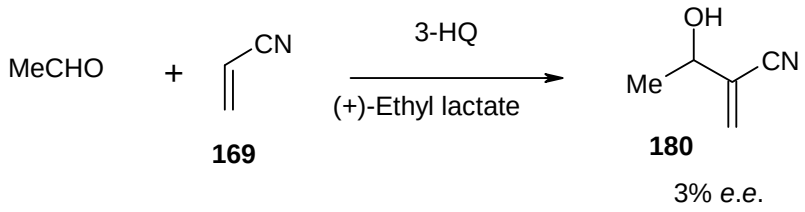
The preferred conformation of the imine allows the bulky groups around the sulfur atom to project out of the plane of the double bond thus reducing the steric strain. As a result, the incoming nucleophile prefers to approach *anti* to the large tolyl group, resulting in the stereochemistry shown in Scheme 1.39. This approach also permits electrostatic interaction between the sulfinyl oxygen and the quaternary ammonium moiety and hydrogen bonding to the 3-hydroxyl group serves to stabilize the transition state **TS_1**. Coordination of a Lewis acid with the imine, the sulfinyl oxygen and the acrylate oxygen atom in the transition state **TS_2** also channels the formation of the new C-C bond within a rigid coordinated space.



Scheme 1.39. Transition state geometries of the imine.[106]

1.2.3.3. Chiral Solvents

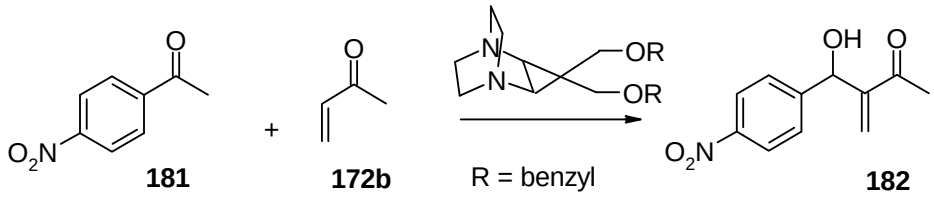
Although, as mentioned above, Yang and Chen[98] obtained remarkable solvent-induced changes in stereocontrol on replacing DMSO, as solvent, with THF-H_2O in the reaction of camphor-derived acryloylhydrazide with various aldehydes in DABCO-catalyzed reactions, the use of chiral solvents *per se* does not appear to have been useful. Gilbert and co-workers[59,92] carried out the 3-hydroxyquinuclidine-catalysed reaction of acrylonitrile **169** with acetaldehyde in the presence of (+)-ethyl lactate and obtained the product **180** in very low enantiomeric excess (3%) (Scheme 1.40).



Scheme 1.40. Using a chiral solvent in the Morita-Baylis-Hillman reaction.[58,85]

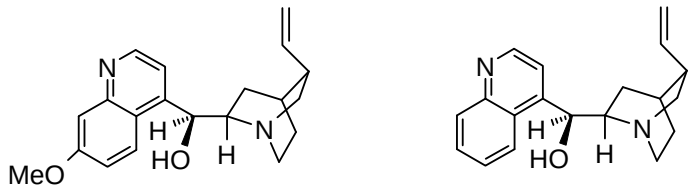
1.2.3.4. Chiral catalysts

Tertiary amines are the catalysts of choice in the Morita-Baylis-Hillman reaction. The catalyst may be expected to effect chiral discrimination as it is heavily involved in the entire path of the reaction, including the stage in which the stereogenic centre is generated. The structure of the chiral catalyst can dictate the fate and geometry of the transition state. Although a significant number of chiral catalysts have been employed in the Morita-Baylis-Hillman reaction, success in this regard has not been encouraging, resulting in disappointingly low enantioselectivities. Hirama and co-workers[87] carried out asymmetric Morita-Baylis-Hillman reactions of 4-nitrobenzaldehyde and methyl vinyl ketone in the presence of chiral DABCO derivatives (C_2-symmetric 2,3-disubstituted derivatives) under high pressure conditions (5 kbar), and observed a remarkable improvement in the rate of reaction and in the enantioselectivity (up to 47% e.e.) (Scheme 1.41).

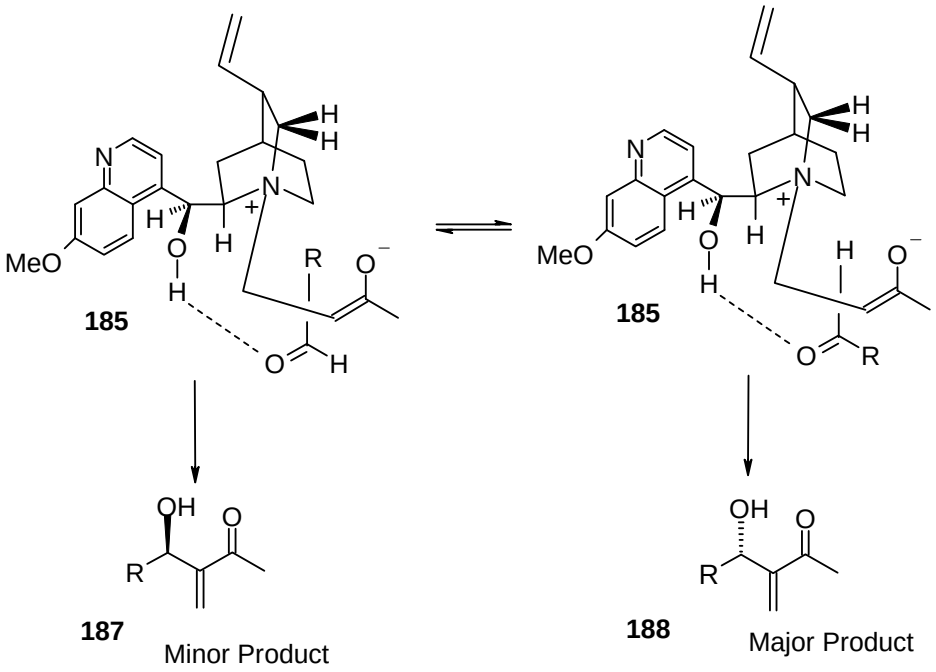


Scheme 1.41. Use of chiral DABCO in the Morita-Baylis-Hillman reaction.[87]

In an attempt to exploit hydrogen bonding effects, Marco and co-workers[88] employed a variety of chiral β-hydroxy amines as catalysts in the Morita-Baylis-Hillman reaction between methyl vinyl ketone and cyclohexylcarboxaldehyde to study how these amines might influence enantioselectivities. The results, however, revealed low enantiomeric excesses (0-25% e.e.). Quinidine **183** and cinchonine **184** gave the best enantioselectivities and hence, were selected as lead chiral catalysts to optimize reaction conditions to achieve even better enantioselectivities.



Marco and co-workers established that addition of the aliphatic nitrogen atom in these catalysts to methyl vinyl ketone gives rise to the expected zwitterion. The approaching aldehyde then leads to two transition states of different energies (Scheme 1.42). This energy difference is attributed to the unfavourable steric interactions between the R-group of the aldehyde and the two hydrogen atoms located at C(α) of the catalyst in transition state **185** compared to **186**. Thus, the larger the R-group, the higher the enantio-selectivities. This model suggests that the role played by the hydroxyl group is to lock the conformation of the ternary complex by hydrogen-bonding with one of the lone pairs of the aldehyde carbonyl oxygen and to lower the energy of the transition state by stabilizing the incipient negative charge developing on the oxygen atom during the aldol phase.

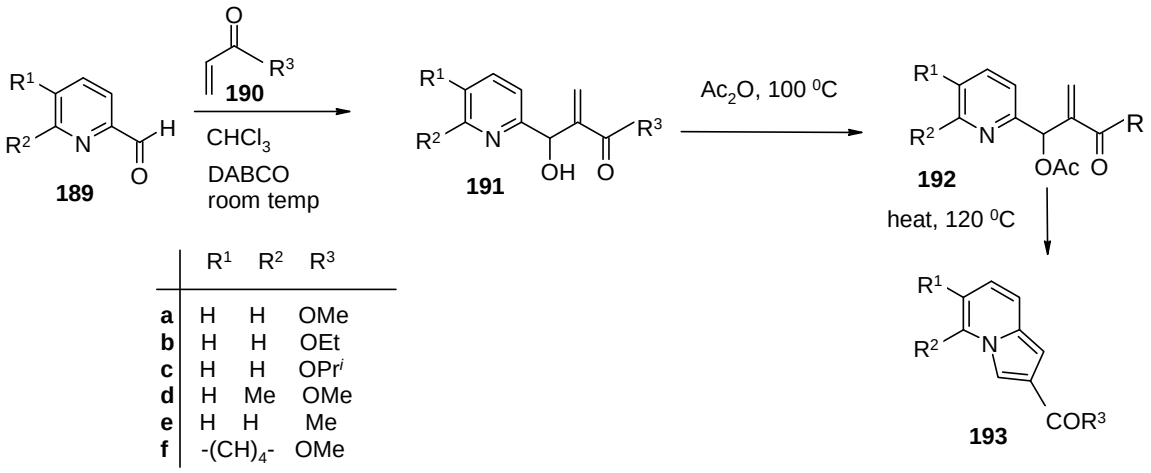


Scheme 1.42. Hydrogen-bonding in quinidine intermediate **186**.[88]

1.3. PREVIOUS WORK BY THE RHODES RESEARCH GROUP

1.3.1. Baylis-Hillman-Derived Heterocyclic Systems

Our research team at Rhodes has for the past two decades been fascinated by the Morita-Baylis-Hillman reaction, particularly with regards to its mechanistic pathway and its varied applications both of which have been investigated. The Morita-Baylis-Hillman reaction is, in fact, quite an easy reaction to set up but its sluggishness is a major drawback, with some reactions taking several weeks to reach completion and furnish acceptable yields.[87] The rate-enhancing abilities of pyridinecarbaldehydes **189** as precursors, as observed by Ameer *et al*.,[86] have, however, dramatically reduced the time it takes to acquire kinetic data to just a matter of hours permitting the first cited NMR-based kinetic-mechanistic study of this reaction. Not only that, the serendipitous discovery of colourless crystals of an indolizine **193** during distillation of a Morita-Baylis-Hillman adduct **192** enabled our group to be the first to apply the Morita-Baylis-Hillman technique in synthesizing indolizine and its derivatives as shown in Scheme 1.43.[107-109]

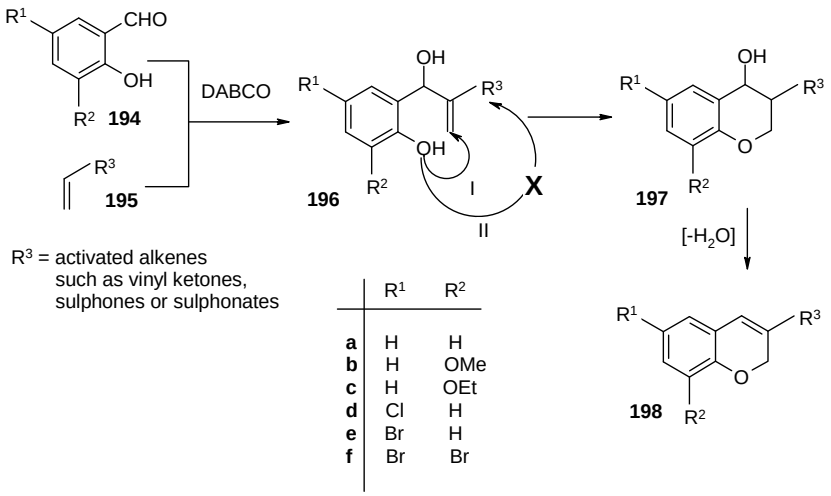


	R1	R2	R3
a	H	H	OMe
b	H	H	OEt
c	H	H	OPr*i*
d	H	Me	OMe
e	H	H	Me
f	-(CH)4-		OMe

Scheme 1.43. The formation of indolizines **193** from heating of Morita-Baylis-Hillman adducts**192**.[107-109]

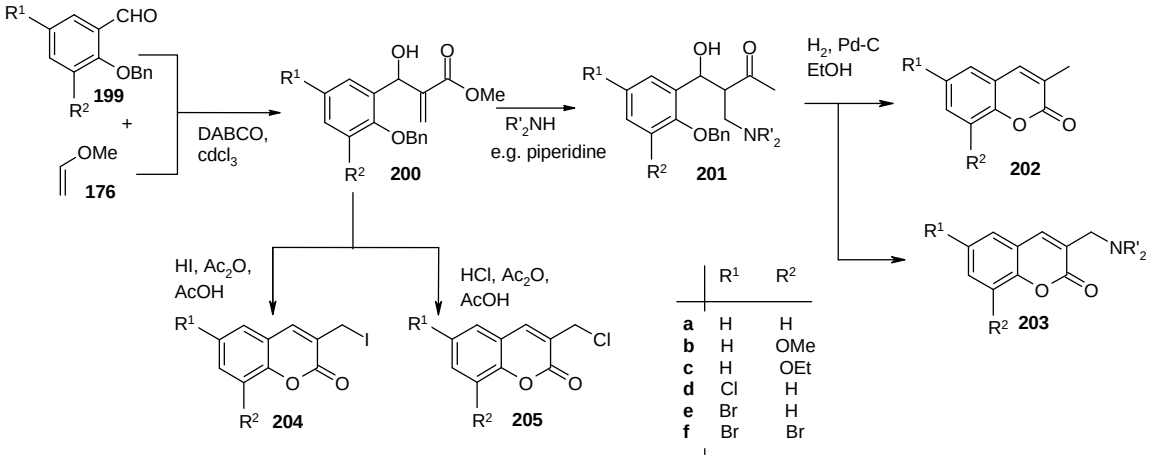
The discovery of this approach to indolizine derivatives raised a number of questions which led to the exploration of equivalent oxygen-, sulfur- and other nitrogen-containing

heterocyclic systems. The appropriate choice of activated alkenes such as vinyl ketones, sulphones or sulphonates enabled Nocanda to selectively synthesize chromene derivatives **198** as shown in Scheme 1.44.[107,110-111]



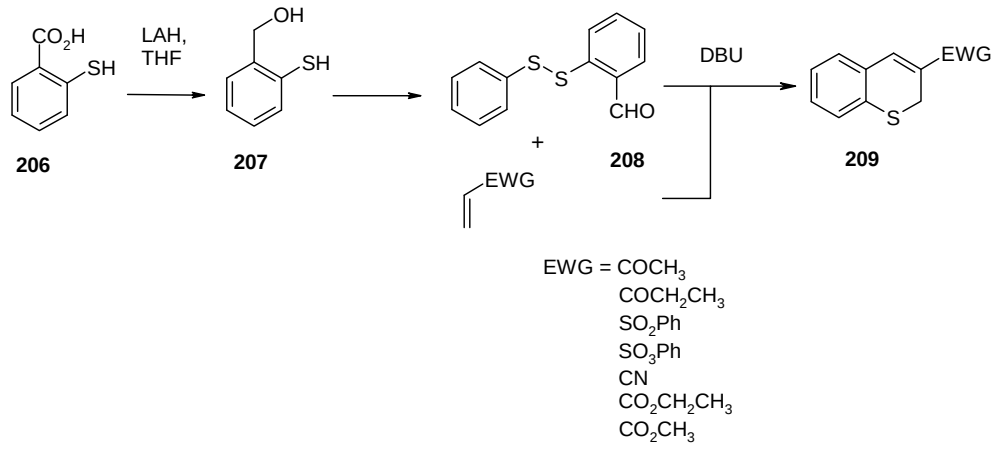
Scheme 1.44. Chemoselective synthesis of chromene derivatives **198**.

Protection of the phenolic oxygen group by *O*-benzylation accompanied by nucleophilic interception by, for example, piperidine or benzylamine (to mask the electrophilic character of the C-C double bond) allowed Musa to prepare coumarin derivatives **202** and **203** as shown in Scheme 1.44. Another approach to by-pass the need for using piperidine or benzylamine to mask the electrophilicity of the double bond is to use HI or HCl to promote cyclisation as shown in Scheme 1.45.[87,111-112]



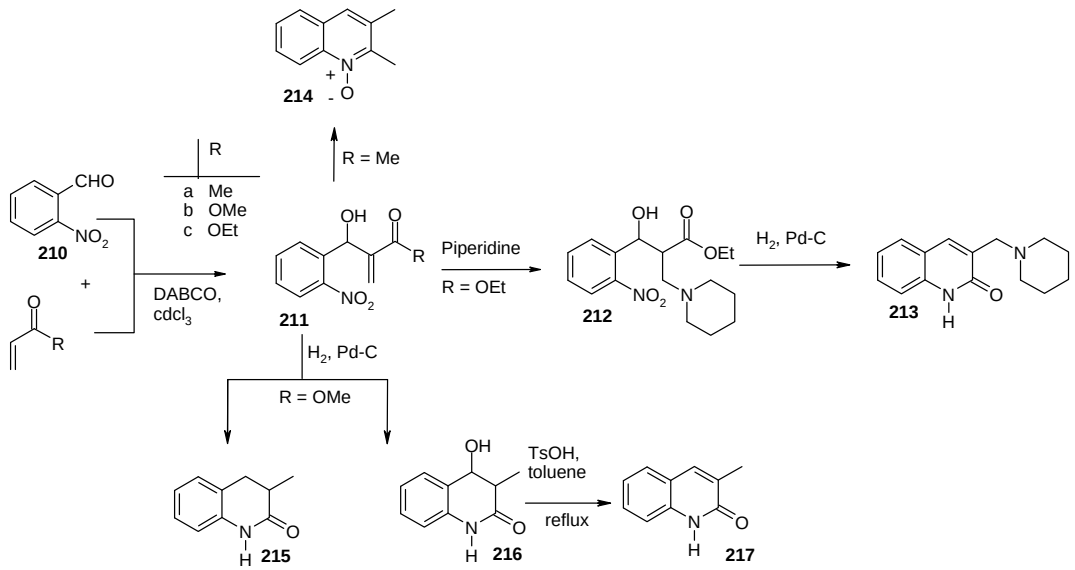
Scheme 1.45. Coumarin derivatives *via o*-benzylation.[108,113-114]

Nocanda took this chemistry even further to include thiochromene derivatives as shown in Scheme 1.46.[107,114] In these reactions, DBU serves both as an MBH catalyst and as a reducing agent to cleave the disulfide linkage as shown recently by Nyoni.[115]



Scheme 1.46. Synthesis of thiochromene derivatives **209**.[107,114-115]

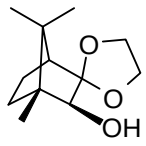
Familoni applied the Morita-Baylis-Hillman adducts in the synthesis of nitrogen-containing heterocyclic analogues **212-217** as illustrated in Scheme 1.47.[116] In fact, this work preceeded later contributions by Kim and co-workers[83,84] to the synthesis of quinoline and quinolone derivatives using MBH methodology.



Scheme 1.47. Preparation of other nitrogen-containing analogues.[116]

1.3.2. Asymmetric Synthesis

The availability of D-(+)-camphor in optically pure form, its relatively affordable price, its conformational rigidity, its versatility and capability in undergoing countless transformations has made it an attractive research focus within our group for some time. The use of camphor by our group has largely involved development of camphor derivatives as chiral auxiliaries.[117,118,117-121] In an attempt to maximize diastereofacial discrimination, Ravindran[117] and Evans[118] introduced the use of sterically demanding groups on the camphor skeleton in compounds such as **219**, **220**, **221** and **222**. Klein,[119] using the alcohol **220** to carry out the α-benzylation of the corresponding ester derivatives, obtained commendable diastereoselectivities of (60-83% d.e.).



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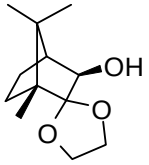

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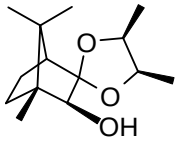

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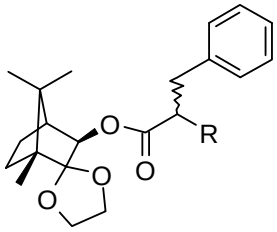
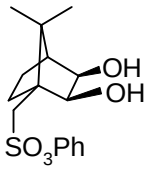


222

In an effort to improve diastereofacial selectivity, Molema[120] developed an extremely efficient chiral auxiliary **223** for the cyclopropanation of α,β-unsaturated acetal derivatives **224**. Condensation of the diol with each of the aldehydes furnished the corresponding acetals in relatively good yields (64-74%). Cyclopropanation of the acetals gave the cyclopropyl derivatives **225** in good yield (76-95%) and with complete diastereoselectivity (>99% d.e.). The chiral auxiliary was recovered by *trans*-thioacetalisation and the corresponding dithiones were isolated in 87-92% yield.



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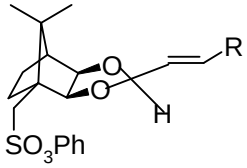

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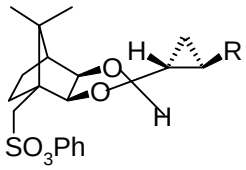
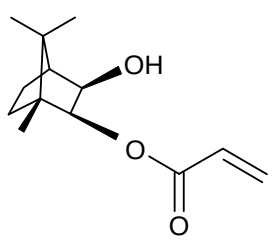


225

Duggan[121] synthesized acrylate devatives **226**, **227** and **228** to discern their stereofacial capability when applied to the Morita-Baylis-Hillman reaction. The results were variable but compound **228** appeared to be the most promising. Compound **226** undergoes ready acid-catalysed transesterification making its use more problematic.



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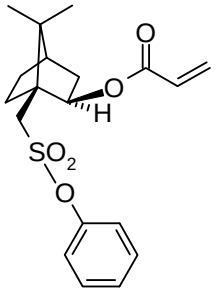

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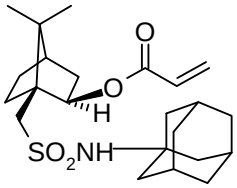


228

1.4. AIMS OF THE PRESENT INVESTIGATION

Morita-Baylis-Hillman chemistry continues to remain a research niche in our research programme. The present study explores the use of MBH methodology in asymmetric synthesis using camphor-derived acrylate esters, while also revealing its usefulness in the synthesis of pyridine-based drug compounds with medicinal potential. The present study focuses on the following outcomes.

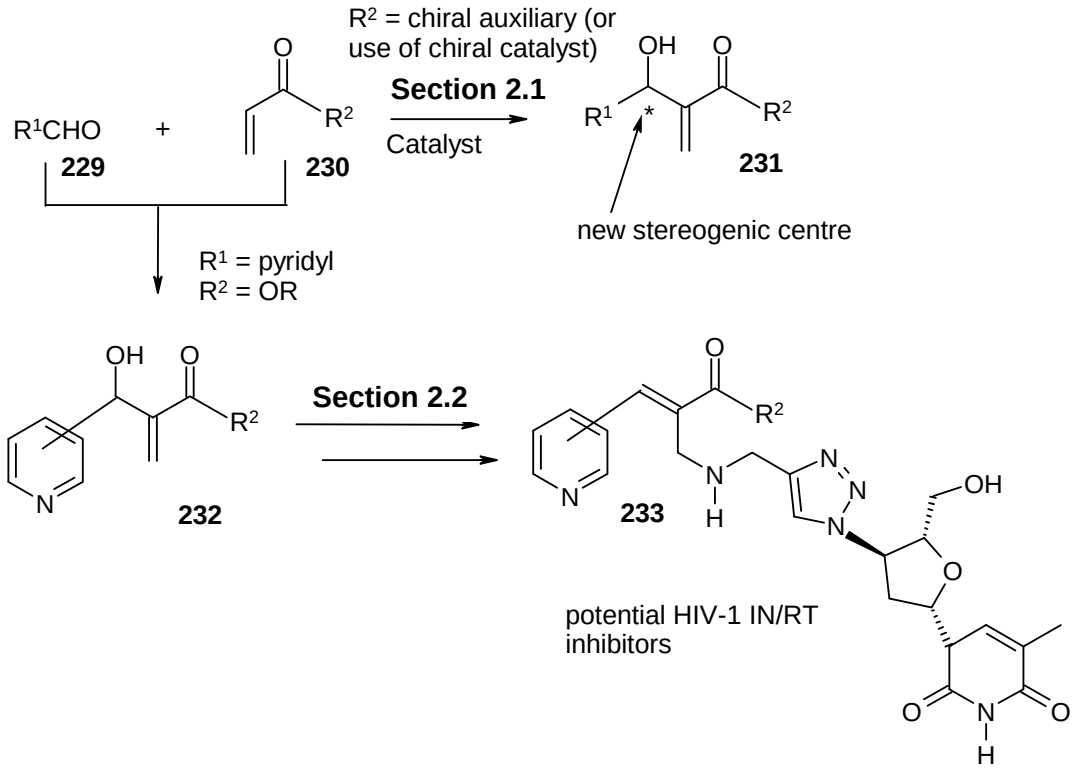
i) The preparation, use and evaluation of camphor-10-sulfonamide-derived alcohols as chiral auxiliaries in asymmetric MBH reactions.

ii) Construction of a series of heterocyclic-AZT conjugates as potential dual-action HIV-1 IN/RT inhibitors.

iii) Elucidation of the MS fragmentation patterns exhibited by camphor-derived acrylate esters and AZT-conjugates.

2. DISCUSSION

The research reported here has been concerned with applications of Morita-Baylis Hillman (MBH) methodology in Asymmetric Synthesis (Section 2.1) and the construction of Designed Multiple Ligands (DMLs) as potential dual-action HIV-1 integrase/reverse transcriptase inhibitors (Section 2.2), as outlined in Scheme 2.1.



Scheme 2.1. An overview of synthetic plan.

2.1. ASYMMETRIC SYNTHESIS

As indicated in the introduction, camphor derivatives have been used in our group as chiral auxiliaries in asymmetric synthesis. In this investigation attention has been focused on:- camphor-derived acrylate esters in a ***chiral auxiliary approach***.

2.1.1. Chiral Auxiliary Approach

2.1.1.1. Camphor-derived acrylate esters

Chiral monoacrylates, such as, compound **234**, may be expected to serve as interesting MBH precursors, with the free hydroxyl group acting as an intramolecular catalyst enhancing the electrophilicity of the acrylate moiety to attack by the tertiary amine catalyst and stabilizing the resulting enolate **235** by hydrogen-bonding as shown in Figure 2.1. Such an enolate complex could then favour stereoselective approach of the aldehyde from the less hindered *endo* face.

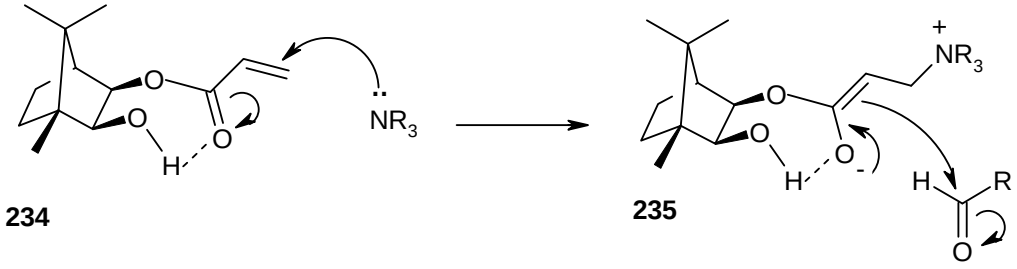
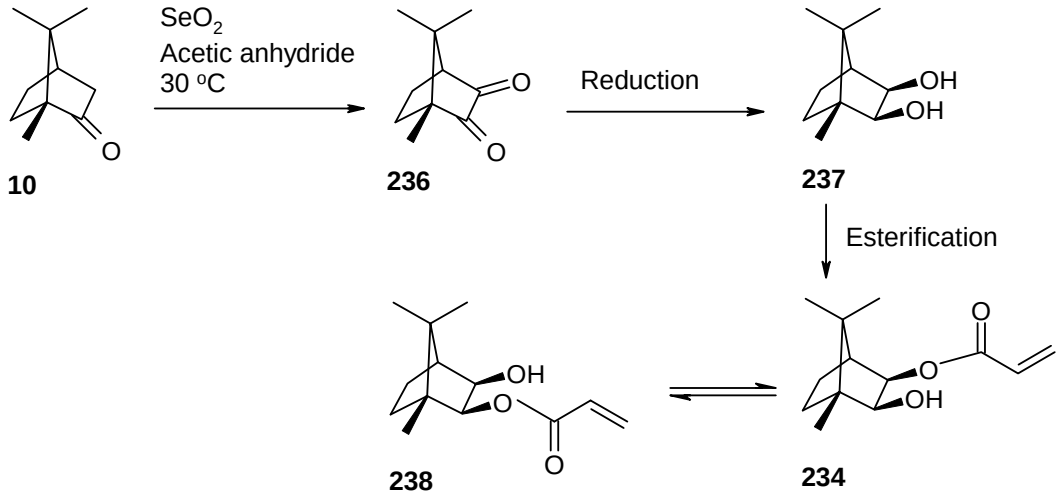


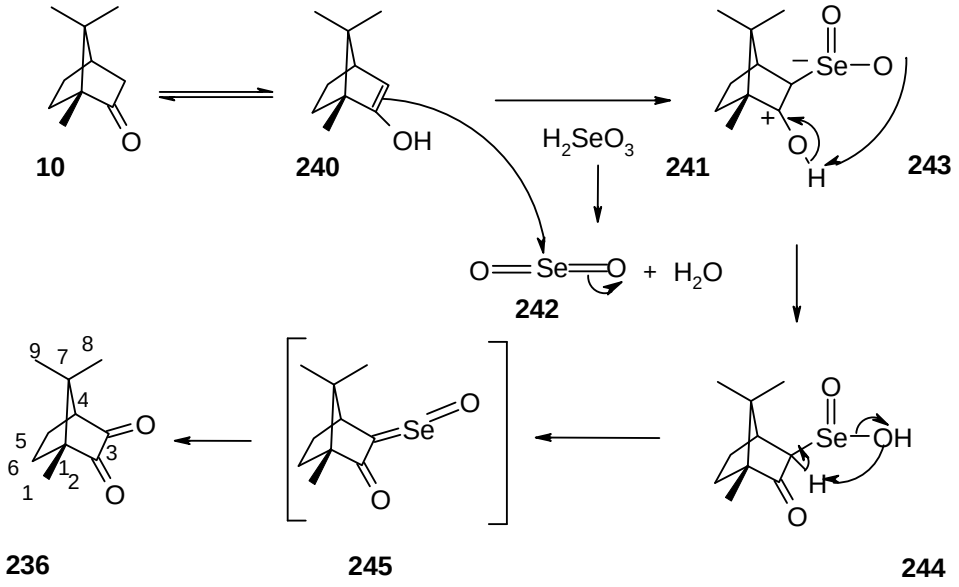
Figure 2.1. The anticipated Morita-Baylis-Hillman reaction of chiral monoacrylate **234**.

The regioisomeric monoacrylates **234** and **238** (Scheme 2.2) were also required in order to explore the kinetics of their interconversion *via* acid-catalysed trans-esterification – a phenomenon which had been observed in a previous study.[121] The proposed access to these compounds is outlined in Scheme 2.2.

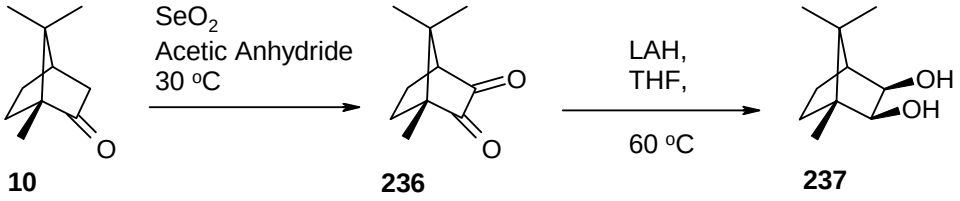


Scheme 2.2. Proposed synthetic access to the monoacrylate ester **234**.

The initial step in the synthesis of the monoacrylate esters **234** and **238** was to prepare camphorquinone **236** by selective oxidation of the 3-methylene group in camphor **10**. This transformation is feasible as the 3-methylene group is adjacent to the carbonyl group, and camphor **10** is readily converted to an α-diketone employing selenium dioxide as the oxidizing agent *via* the mechanism outlined in Scheme 2.3. A yield of 57% was obtained after repeated recrystallization of the bright-yellow camphorquinone **236**. The mechanism of this reaction has been the subject of controversy for a number of years, but Sharpless and Gordon[122] have given a precise and plausible explanation. This involves formation of the intermediate β-ketoselenic acid **244**, generated by electrophilic attack of selenium dioxide on enol **240**; the subsequently formed selenine **245** then decomposes as shown in Scheme 2.3. Formation of camphorquinone **236** was confirmed by ^{1}H NMR, ^{13}C NMR and DEPT-135 experiments, while the melting point (190-192°C) was comparable to the literature value (198-201°C). *Exo* access by nucleophiles to both C-2 and C-3 in camphorquinone **236** is hindered by the 8-methyl group and, consequently, LAH reduction was expected to afford the 2-*exo*,3-*exo*-diol **237**. Morever, access to the 2-hydroxy group is hindered relative to 3-hydroxy group by the 10-methyl group and esterification of the bornane-2-*exo*,3-*exo*-diol **237** was expected to proceed selectively as shown in Scheme 2.4.



Scheme 2.3. Mechanism showing selective oxidation of camphor **10** to camphorquinone **236**.[122]



Scheme 2.4. Synthesis of 2-*exo*-3-*exo*-bornanediol **237**.

Reduction of camphorquinone **236** to the diol **237** required careful consideration of appropriate reducing agent. The use of $NaBH_4$ in ethanol has been shown to yield *trans*-bornane-2,3-diols,[123] whereas catalytic hydrogenation may lead to 2-*endo*,3-*endo* diols.[123] However, LAH proved to to be an excellent reducing agent, furnishing the bornane-2-*exo*,3-*exo*-diol in excellent yield of 99% (Scheme 2.4). LAH is a much stronger reducing agent than $NaBH_4$ and reduces even sterically hindered ketones or α-diketones with relative ease.[118,123,124] Examination of the ^{13}C NMR spectrum (Figure 2.2) showed the presence of the requisite 10 carbons, while the DEPT-135 spectrum confirmed the presence of three methyl and three methine carbons.

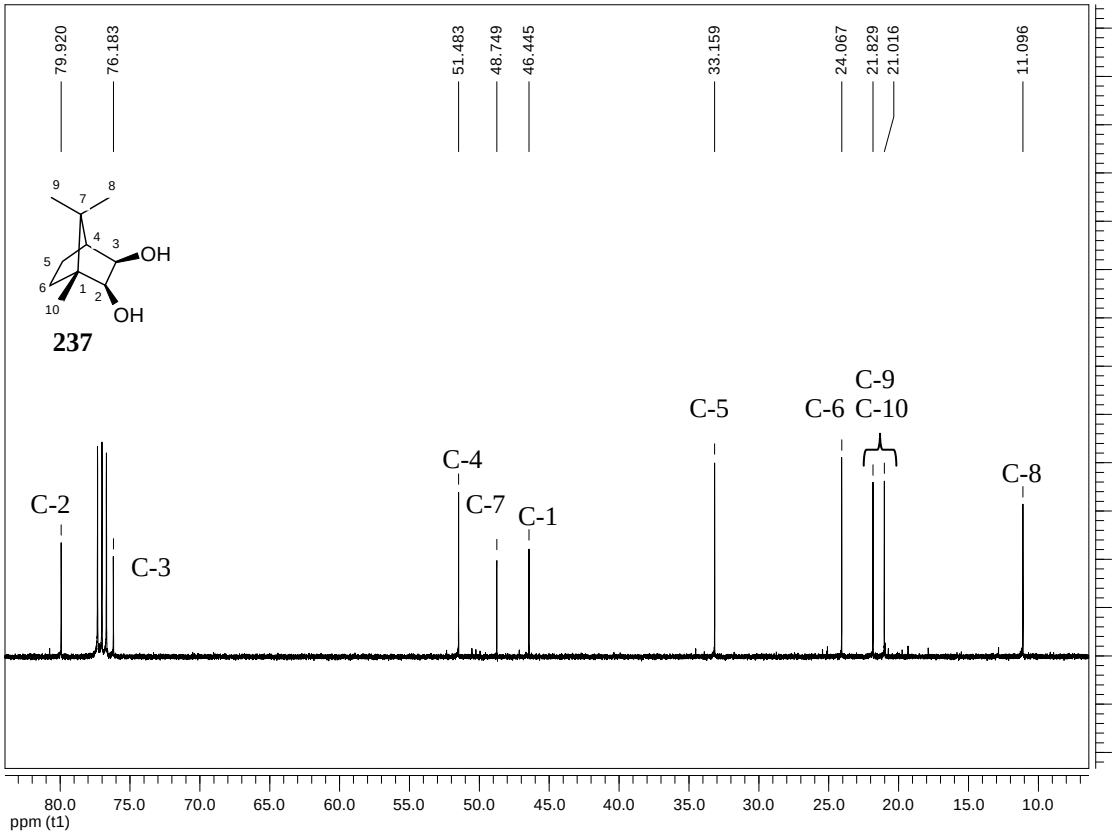


Figure 2.2. ^{13}C NMR spectrum of compound **237** (100 MHz, $CDCl_3$).

The ^{1}H NMR spectrum on the other hand permitted assignment of stereochemistry at the new stereogenic centres (Figure 2.3). Two triplets result from coupling of the 2-H (3.6 ppm) and 3-H (3.8 ppm) nuclei with each other and with their respective hydroxy protons. The proximity of the 10-methyl group to the 2-H proton leads to shielding of the 2-H proton compared to the 3-H proton. The *endo*-orientation of the 3-H nucleus is supported by the apparent absence of vicinal coupling between the 3-H and the 4-H nuclei – an observation attributed to a torsion angle of *ca* 80° between these nuclei.[2.3] The relative stereochemistry is supported by the NOESY correlations between both the 2-H and 3-H nuclei and one of the *endo* 5-H or 6-H nuclei. Given that the 2-H and 3-H protons are both *endo*-orientated, the 2- and 3-hydroxy groups must be *exo*. This stereochemistry is attributed to the preferential delivery of the hydride ion by LAH at the less hindered *endo*-face; in fact, this was the only stereoisomer isolated.

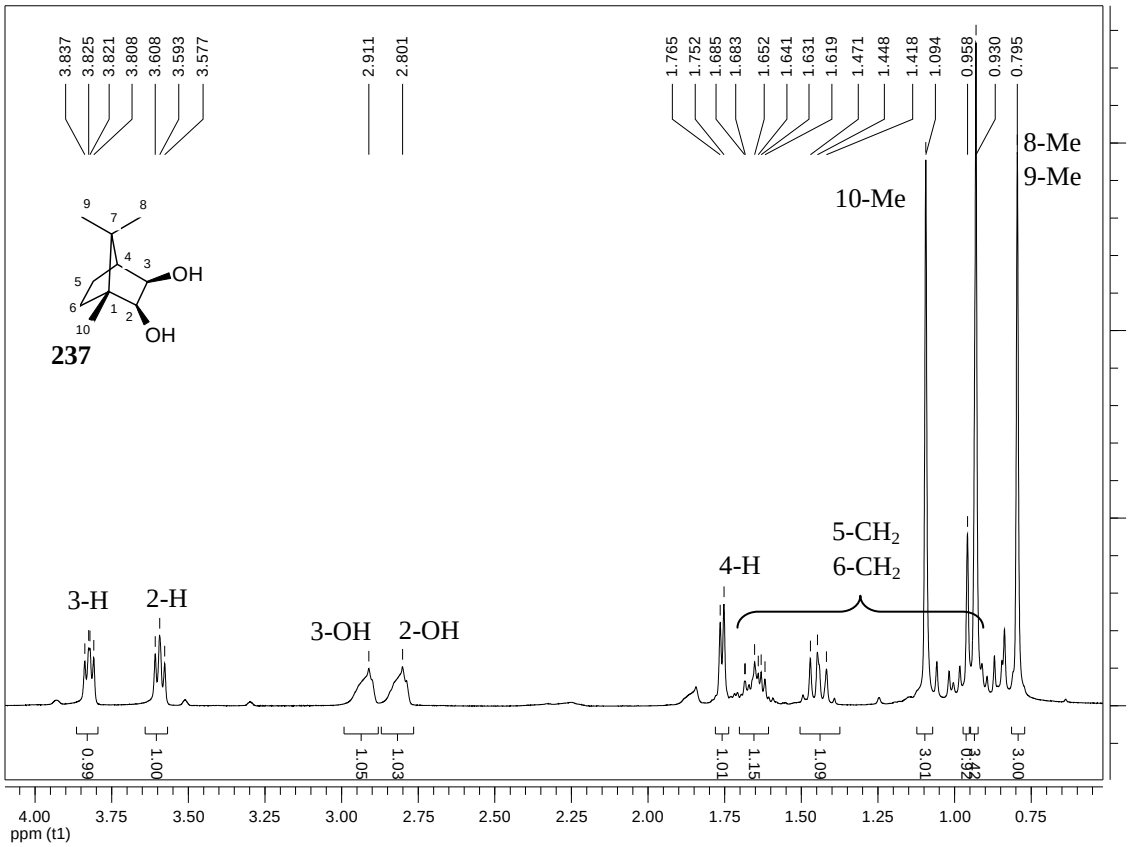
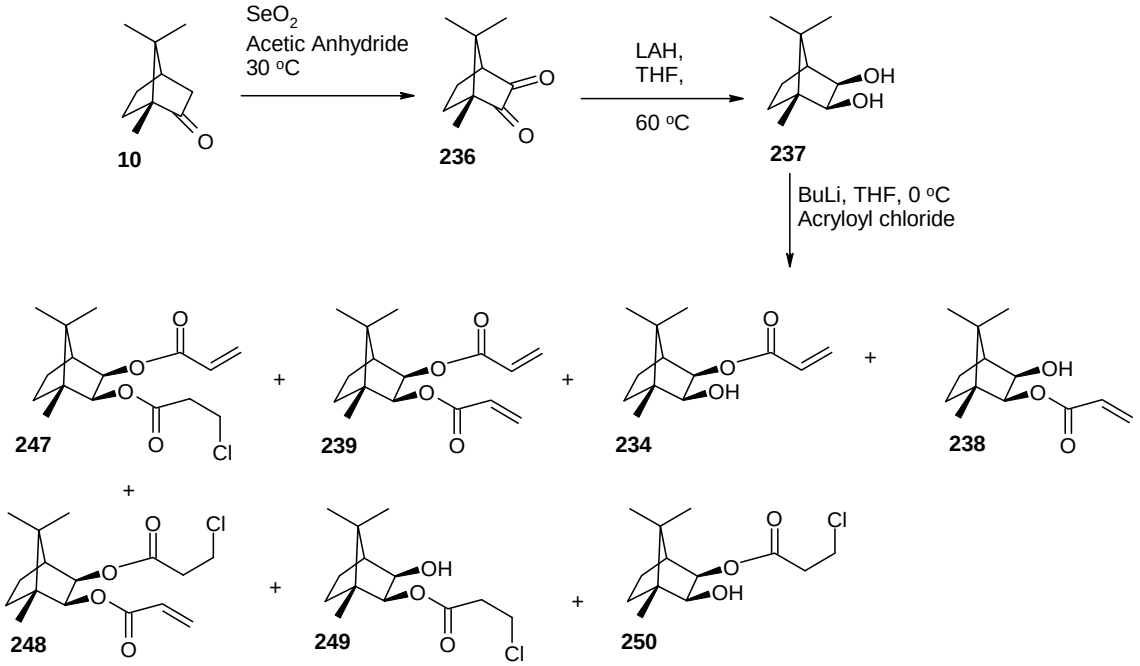


Figure 2.3. ^{1}H NMRspectrumof compound **237** (400 MHz, $CDCl_3$).

The Fischer esterification is a classic method that converts carboxylic acids and alcohols directly to esters in the presence, typically, of conc. H_2SO_4. The reactions are often very slow and reversible, thus greatly affecting the yields. Use of the alcohol in large excess or of sulfuric acid which not only catalyzes the reaction but removes water are two remedies employed to ensure that the reaction goes to completion. A variety of other methods exist that activate the carboxylic acid to further reaction.In previous studies in our laboratories, the use of the strong base BuLi to generate the nucleophilic alkoxide, followed by treatment with acryloyl chloride has shown remarkable success. Hence it was decided to pursue this appraoch. BuLi was added to 2,3-dihydroxybornane **237** over 20 min at 0°C, followed by the addition of acryloyl chloride also at 0°C. The reaction mixture was stirred for 2h and then warmed to room temperature overnight to afford mono-esters **234** and **238** (Scheme 2.5). Unfortunately, five other products were also formed, *viz*., the diester **239** and the hydrochlorinated derivatives **247**-**250**. The overall yield was 89% and separation using HPLC afforded **234** (20%), **238** (36%), **239** (trace amounts), **247** (20%), **248** (13%), **249** (trace amounts) and **250** (trace amounts).



Scheme 2.5. Synthesis of mono-esters **234** and **238**, diester **239** and hydrochlorinated derivatives **247**-**250**.

Structural elucidation of the seven products was achieved using 1-D and 2-D NMR spectroscopic data. Due to the striking similarities exhibited by the ^{1}H NMR data of the isomeric compounds **234** and **238**, careful examination of the ^{1}H NMR spectra was vital in their structural assignment. The 2-H, 2-OH and 3-H signals of the mono-esters **234** and **238** were key in assigning their structures. This assignment is possible by paying close attention to the multiplicities and coupling constants. Thus, the 2-*endo* proton in the 3-mono-ester **234** resonates as a triplet at 3.79 ppm due to coupling with the hydroxyl and the 3-H protons. The 3-H nucleus, in turn, resonates as a doublet at 4.65 ppm due to its coupling with the 2-H proton. The lack of vicinal coupling between the 3-*endo* proton and the 4-methine proton at 1.86 ppm confirms, as indicated earlier, the 3-*endo*,2-*endo* geometry of the 3-mono-ester **234**.

Similarly, the ^{1}H NMR data for the monoester **238** permits the stereochemistry to be established. The two monoesters **234** and **238** only differ in the position of their acrylate and hydroxyl groups. The differences in their ^{1}H NMR spectra can be attributed to the shielding effect of the 10-methyl group to nuclei that are in close proximity. That is, the protons closer to the 10-methyl group will be shielded and resonate upfield and *vice versa*. This is evident on comparison of the relative chemical shifts for the 3-*endo*, 2-*endo* and 2-hydroxyl protons in monoester **234** (Figure 2.4) with the 2-*endo*,3-*endo* and 3-hydroxyl protons in monoester **238** (Figure 2.5).

The structure of the diester **247** was unambiguously confirmed using 1-D and 2-D NMR analysis that included HMQC, HMBC and COSY spectra. The ^{13}C spectrum confirms the presence of 16 carbon nuclei (Figure 2.6).

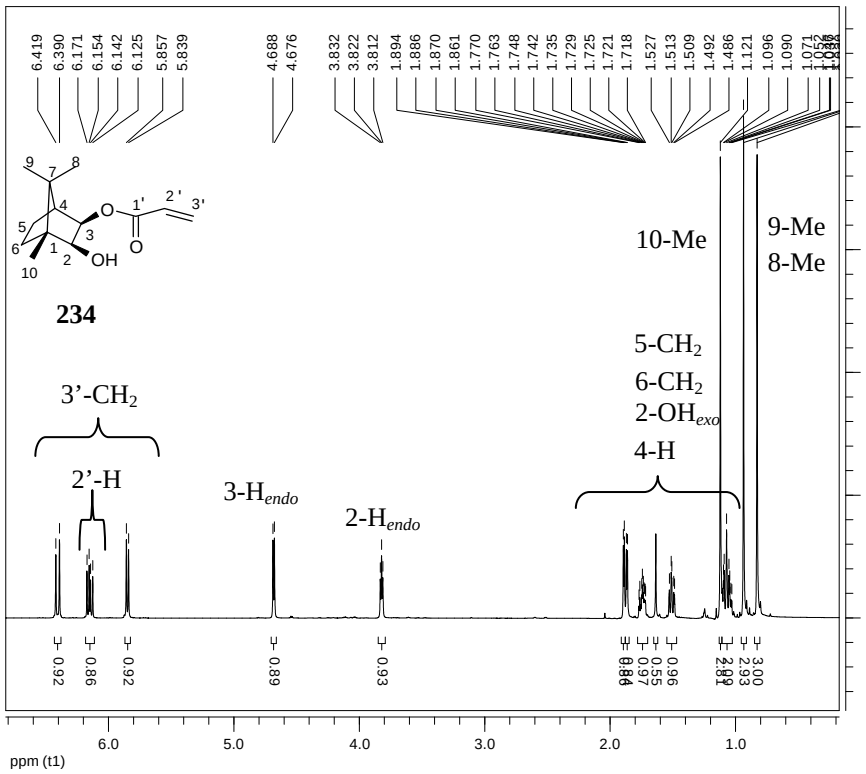


Figure 2.4 ^{1}H NMR spectrum of compound **234** (600 MHz, $CDCl_3$).

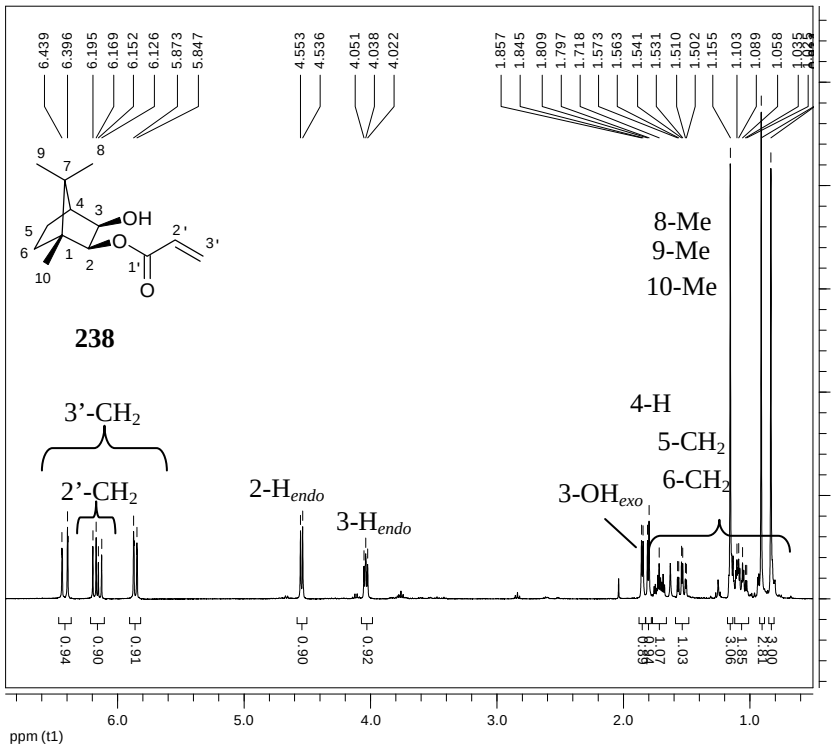


Figure 2.5: ^{1}H NMR of compound **238** (600 MHz, $CDCl_3$).

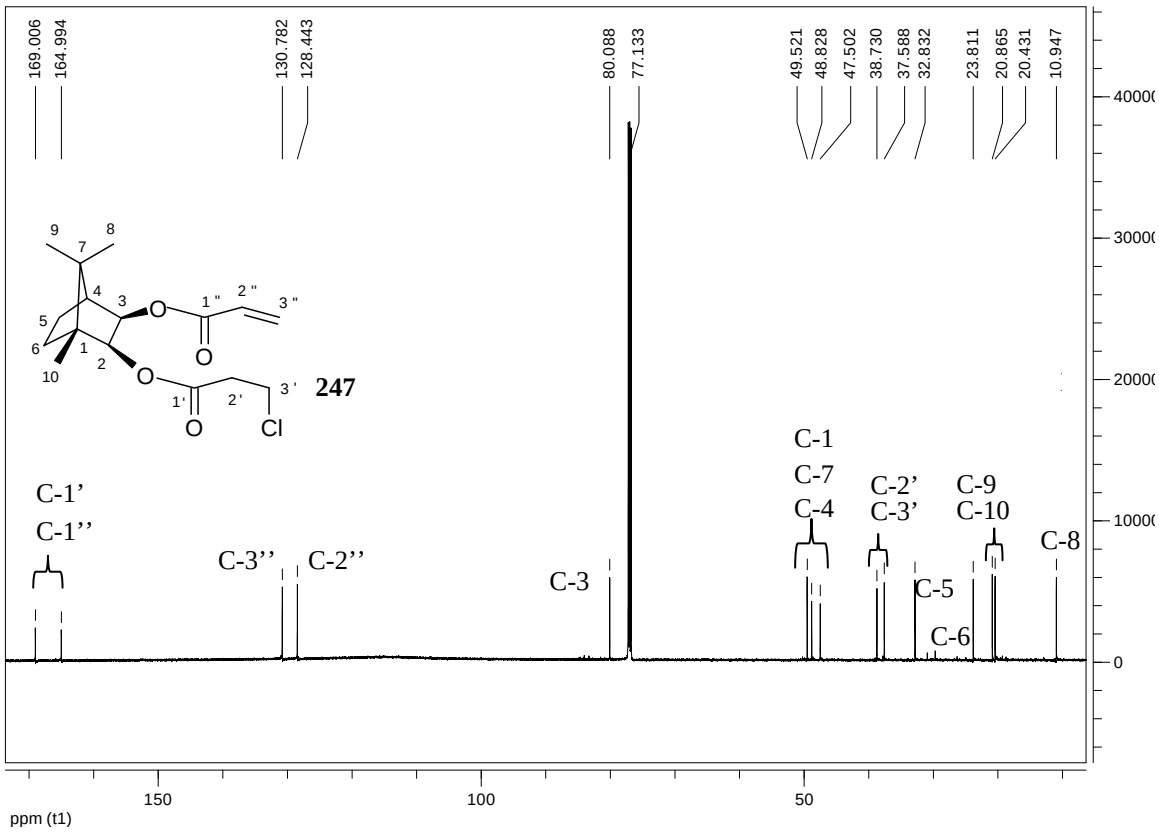


Figure 2.6. ^{13}C NMR spectrum of compound **247** (100 MHz, $CDCl_3$).

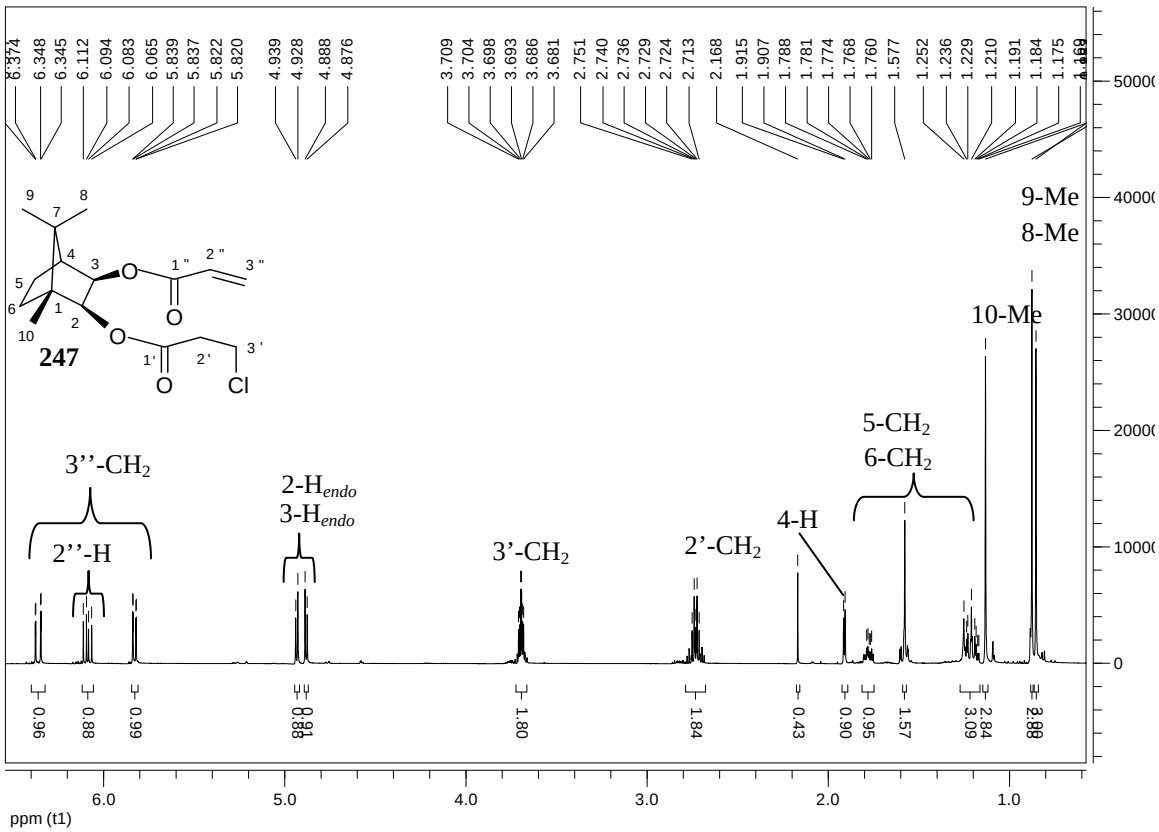


Figure 2.7. ^{1}H NMR spectrum of **247** (600 MHz, $CDCl_3$).

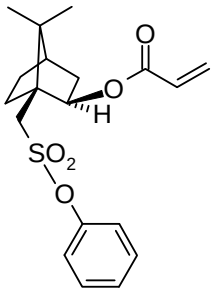
The ^{1}H NMR spectrum (Figure 2.7) on the other hand, showed signals corresponding to:

(i) the bornane moiety with the 2-*endo* and 2-*exo* protons resonating as deshielded doublets at 4.9 ppm;
(ii) the 2'- and 3'-methylene groups of the 3-chloropropanoyl group; and
(iii) the vinylic protons characteristic of the acrylate system.

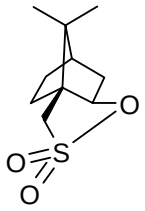
2.1.1.2. Camphor-derived acrylate esters with 10-sulfonamide groups

2.1.1.2.1. ***Synthetic Rationale***

In the continued search for a general camphor scaffold that could be utilized as a chiral auxiliary in Morita-Baylis-Hillman reactions, the bornanediol monoacrylates **234** and **238** appeared less attractive due to transesterification problems. Attention has been given to the use of the phenyl 10-sulfonate system **227**, as it was believed that the steric character of the 8-methyl group together with the phenyl sulfonate group at C-10 would direct the approaching electrophile preferentially to a single face, leading to the predominance of one diastereomeric Morita-Baylis-Hillman adduct. However, this system proved to be unsuitable as it also underwent intramolecular transesterification generating the sultone **251**. At this stage the focus was turned in the direction of camphor-10-sulfonamides.[121]



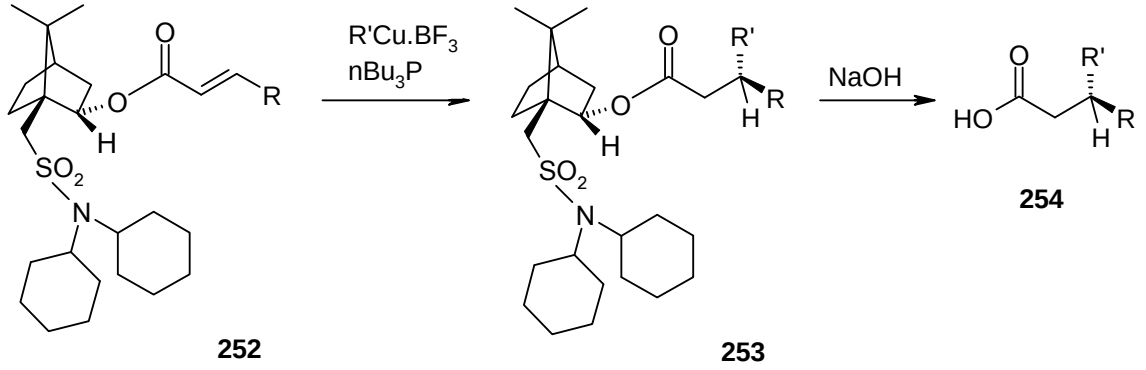
227



251

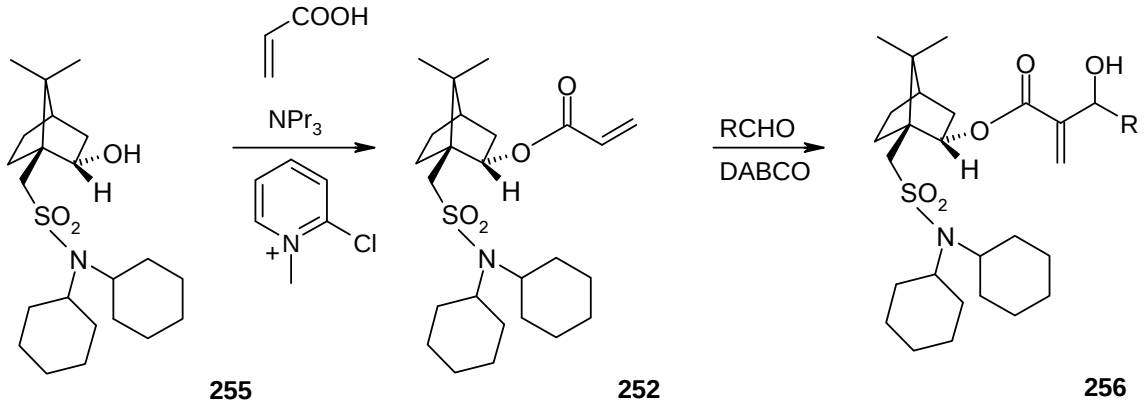
The sulfonamides have been found to be more stable than their sulfonate ester counterparts and a variety of these compounds has been studied. Various reaction models have been used by Oppolzer and co-workers[125] to demonstrate the practical utility of camphor-10-sulfonamide esters **252** as substrates in asymmetric Diels-Alder reactions with cyclopentadiene. The sulfonamide moieties act as π-face shielding discriminators in

asymmetric enolate alkylations to yield *β*-substituted carboxylic acids **254** in good yield (80-98%) and high enatiomeric excess (94-98%) (Scheme 2.6).



Scheme 2.6. Synthesis of β-carboxylic acids from camphor-10-sulfonamide **254**.[125]

However, the most notable contribution made by Oppolzer and co-workers was their use of camphor-10-sultam **29** which led to a variety of asymmetric transformations. Basavaiah and co-workers[126] employed Oppolzer's alcohol[127] to generate the chiral acrylate **252** which they used as a chiral auxiliary in the MBH reaction shown in Scheme 2.7.



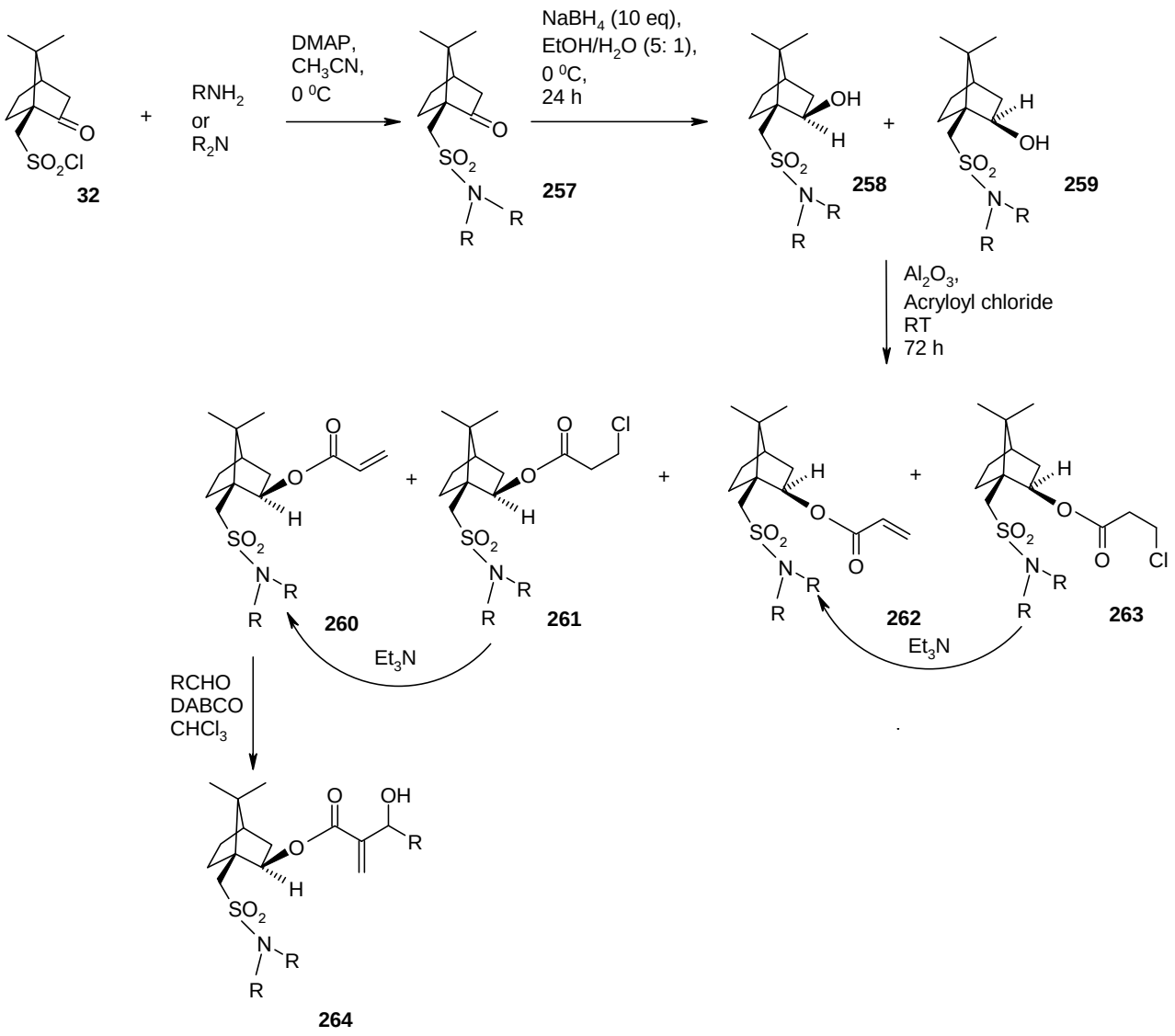
Scheme 2.7. MBH coupling reaction of compound **252**.

Additionally, adamantane and its derivatives has drawn a lot of interest in recent years. The bulky adamantyl group was expected to effectively drive the attacking electrophile to one face of an acrylate system, and it was envisaged that the delocalization of the nitrogen lone-pair would strengthen the adamantyl sulfonamide linkage and, hence, resist

the formation of the sultone **251**. Earlier success[121] with the adamantyl group led us to explore the use of other bulky alkyl and aromatic amines as shown in Scheme 2.8, the expectation being that any chloropropanoyl competition products (**261** and/or **263**) could be converted to the acrylate systems by treatment with triethylamine.

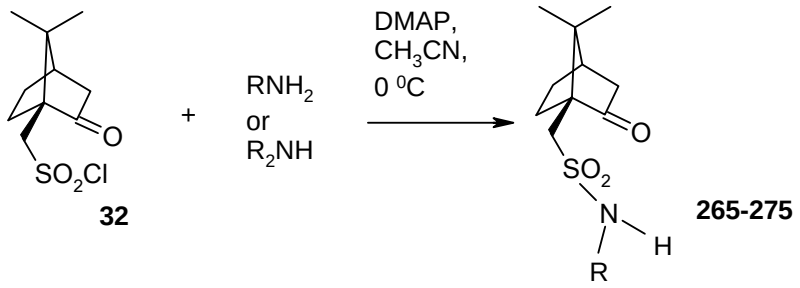
2.1.1.2.2. ***Preparation of camphor-10-sulfonamide***

Sulfonamides constitute an important class of pharmaceutical compounds which exhibit a wide range of potent biological activities. A significant number of these compounds has found application in medicine as antibacterials, diuretics, anticonvulsants, hypoglycemics and HIV protease inhibitors.[128] In recent years, sulfonamides have been shown to possess inhibitory effects towards cysteine protease, suggesting that their use could be extended to conditions such as Alzheimer's disease, arthritis and cancer. Some have, in fact, been found to be useful as herbicides and plaguicides.[129] Most sulfonamides have been prepared by the reaction of a sulfonyl chloride with ammonia, primary or secondary amines in the presence of a base. Sulfonyl chlorides are the acid chlorides of sulfonic acids and, like acyl chlorides, sulfonyl chlorides are strongly electrophilic. Given the nucleophilicity of amines, reaction of nine primary amines and a secondary amine to generate the corresponding sulfonamides **265**-**275** (Scheme 2.9) was expected to occur readily, although a catalytic amount of a tertiary amine (4-dimethylaminopyridine) was employed, in each case, as a nucleophilic catalyst and/or as a base to neutralize the released HCl.



Scheme 2.8. Proposed route to the chiral MBH adduct **264**.

In principle, primary amines could be diacylated but this was considered unlikely given the steric bulk of the camphorsulfonyl chloride. Nevertheless, sulfonyl chloride was used as the limiting reactant. Thus, sulfonyl chloride (1eq.) and a primary or secondary amine (2eq.) were allowed to react in acetonitrile at 0°C for one hour before quenching the reaction by consecutive treatment with H_2O and 2M-HCl. Separation of the product from the reaction mixture, in each case, was achieved by sequential acid and base extractions to obtain the sulfonamides **265**-**275** (Scheme 2.9) in excellent yields (Table 2.1, p58).



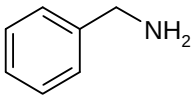
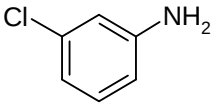
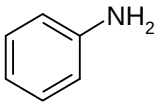
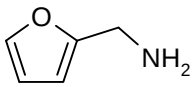
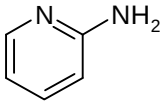
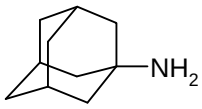
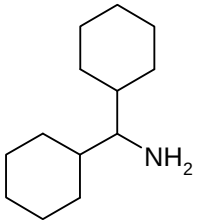
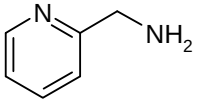
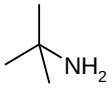
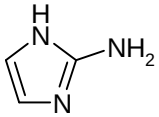
RNH_2 = Benzylamine
3-Chloroaniline
Aniline
Furfurylamine
2-Aminopyridine
Adamantylamine
Picolylamine
t-Butylamine
2-Aminoimidazole

R_2NH = Dicyclohexylamine

Scheme 2.9. Synthesis of camphor-10-sulfonamides **265**-**275**.

Analysis of the 1-D and 2-D NMR spectra for the product **265**, particularly the HSQC spectrum (Figure 2.12), permitted unambiguous characterization of the sulfonamide **265**. All the remaining products **266**-**274** of the series were characterised in a similar manner. The signals in the 600 MHz ^{1}H NMR spectrum of the sulfonamide **265** (Figure 2.8) were assigned as follows: signals in the region 7.25-7.38 ppm to the five aromatic protons; the broad singlet at 5.74 ppm to the amide proton; the multiplet at 4.34 ppm to the two benzylic protons; and the two doublets at *ca.* 3.0 ppm to the 10-methylene protons. The 3-, 5- and 6-methylene protons and the 4-methine proton resonate between 1.41-2.32 ppm, and the 8- and 9-methyl protons at 0.94 ppm and 0.73 ppm, respectively. Examination of the DEPT-135 spectrum (Figure 2.10) confirms the presence, as expected, of two methyl carbons, four methylene carbons and four methine carbons. The COSY spectrum (Figure 2.11) reflects the expected coupling due to the diastereotopic 10-methylene protons coupling with each other. The HSQC spectrum (Figure 2.12) reveals that the two intense methylene signals (43.0 and 27.0 ppm) in the ^{13}C spectrum correlate directly with the multiplets in the ^{1}H NMR spectrum between 1.41 ppm and 2.32 ppm,

Table 2.1. Yields of the camphor-10-sulfonamides **265**-**275**.

Entry	Amine	Structure	Product	Yield (%)
1	Benzylamine		**265**	99
2	3-Chloroaniline		**266**	99
3	Aniline		**267**	93
4	Furfurylamine		**268**	100
5	2-Aminopyridine		**269**	84
6	Adamantylamine		**270**	89
7	Dicyclohexylamine		**271**	88
8	Picolylamine		**272**	90
9	*t*-Butylamine		**273**	94
10	2-Aminoimidazole		**274**	83

which integrate for six protons. It is important to note that the ^{13}C spectrum (Figure 2.9) shows the presence of 14 carbon signals instead of 15 as expected and this is due to the overlapping of two methylene signals at 27.0 ppm. The 4-methine signal at 42.8 ppm in the ^{13}C NMR spectrum, was found to correlate in the HSQC directly with the signal which was almost obscured by the methylene signals in the ^{1}H NMR spectrum at 2.20 ppm. The broad singlet in the ^{1}H spectrum at 5.74 ppm was noted to have no correlations in the ^{13}C spectrum and was assigned to the amide proton. Complete characterization of *N*-benzylcamphor-10-sulfonamide **265** was thus completed.

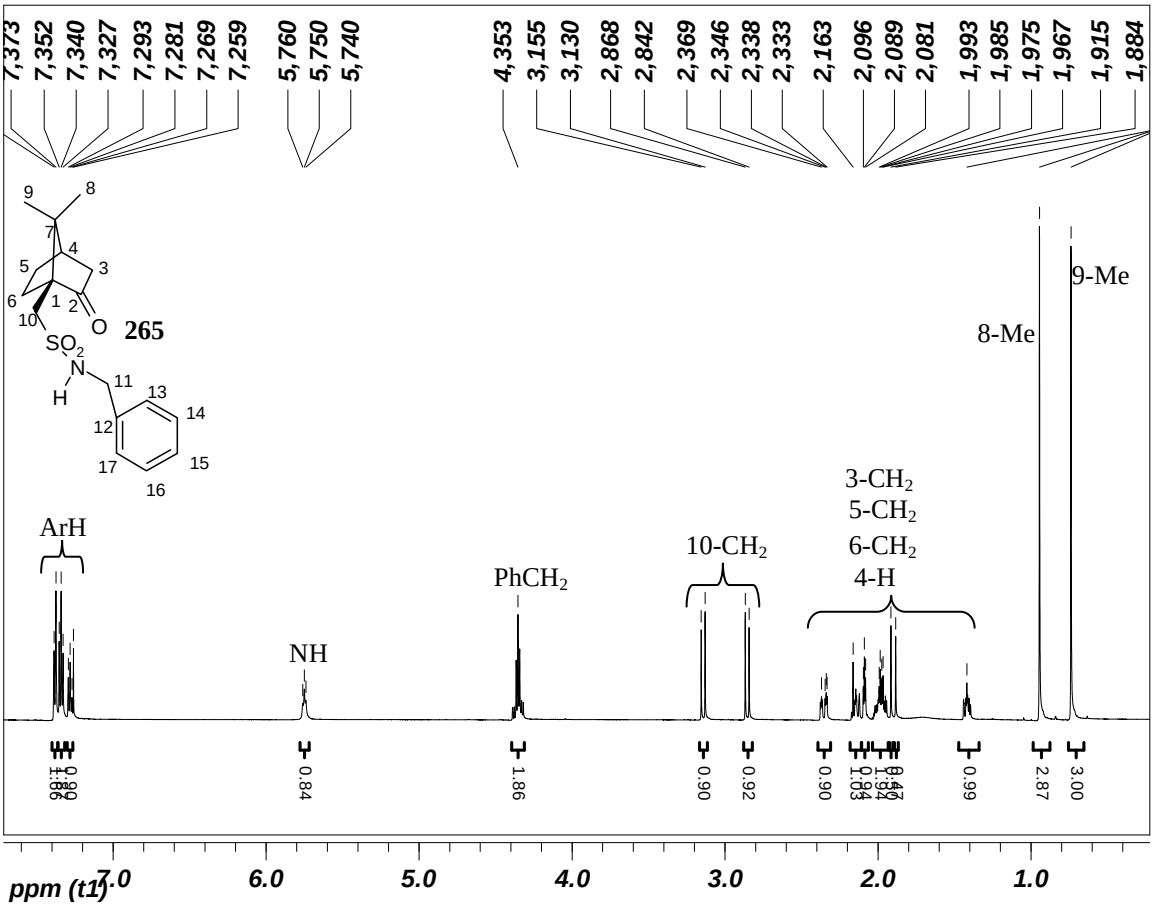


Figure 2.8. ^{1}H NMR spectrum of compound **265** (600 MHz, $CDCl_3$).

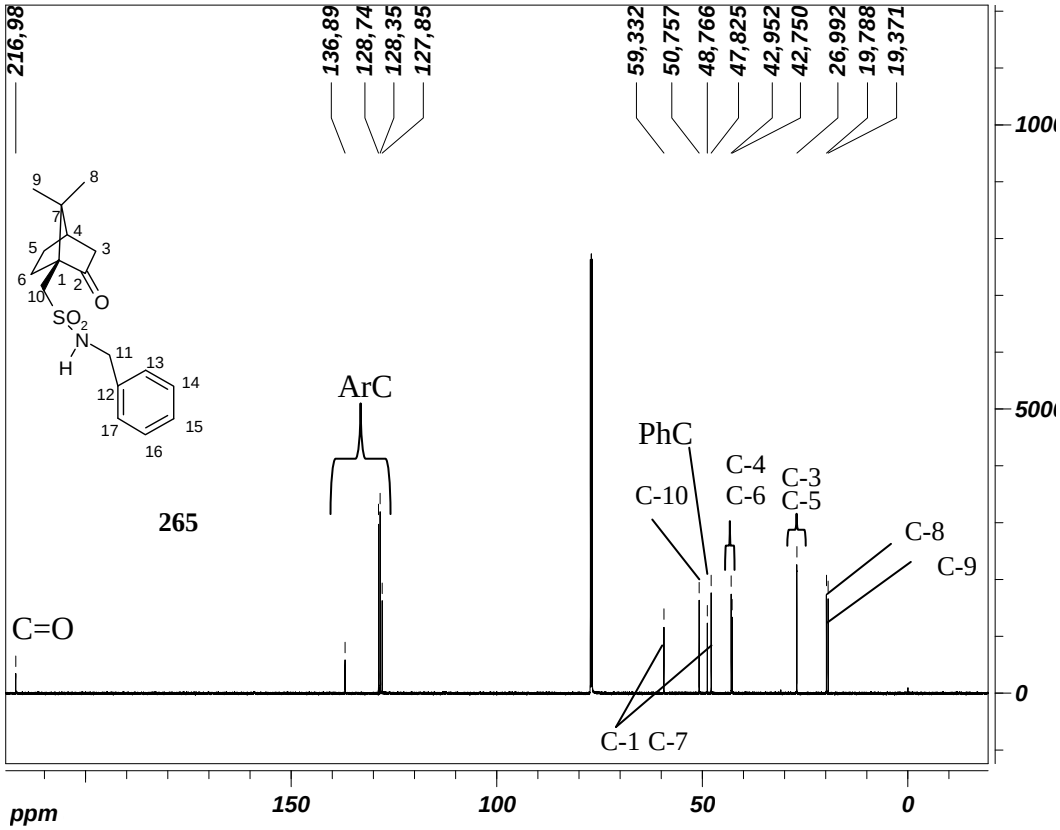


Figure 2.9. ^{13}C NMR spectrum of compound **265** (150 MHz, $CDCl_3$).

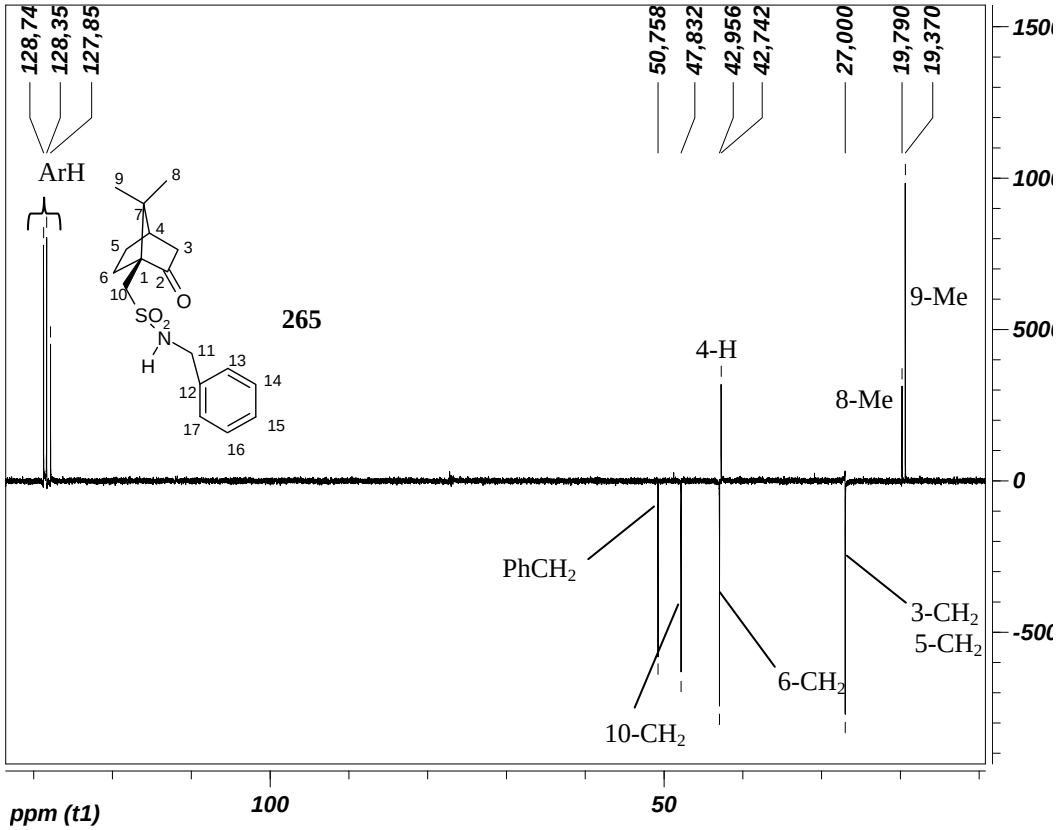


Figure 2.10. DEPT-135 spectrum of compound of **265** (150 MHz, $CDCl_3$).

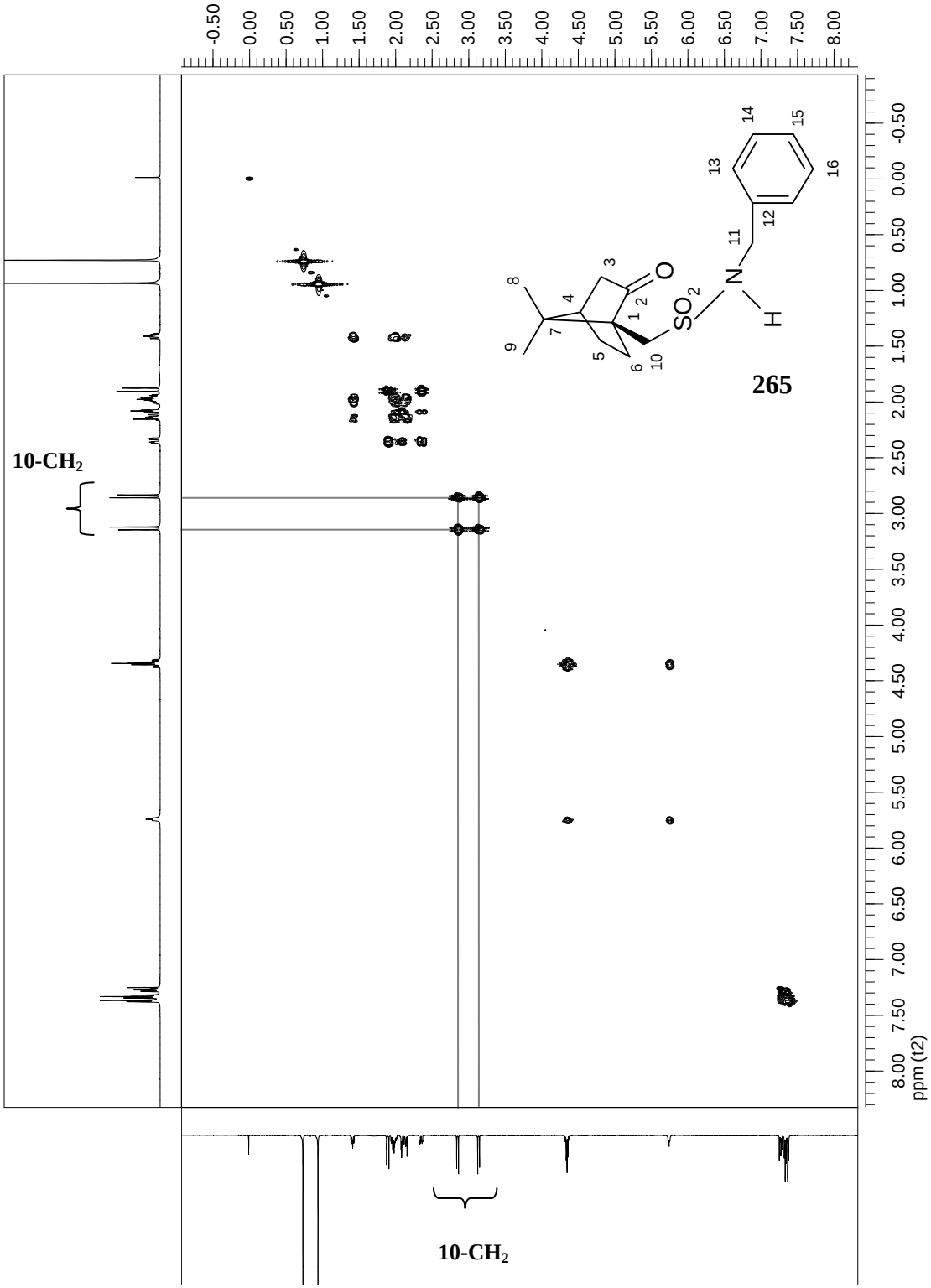


Figure 2.11. COSY spectrum of compound **265** (600 MHz, $CDCl_3$).

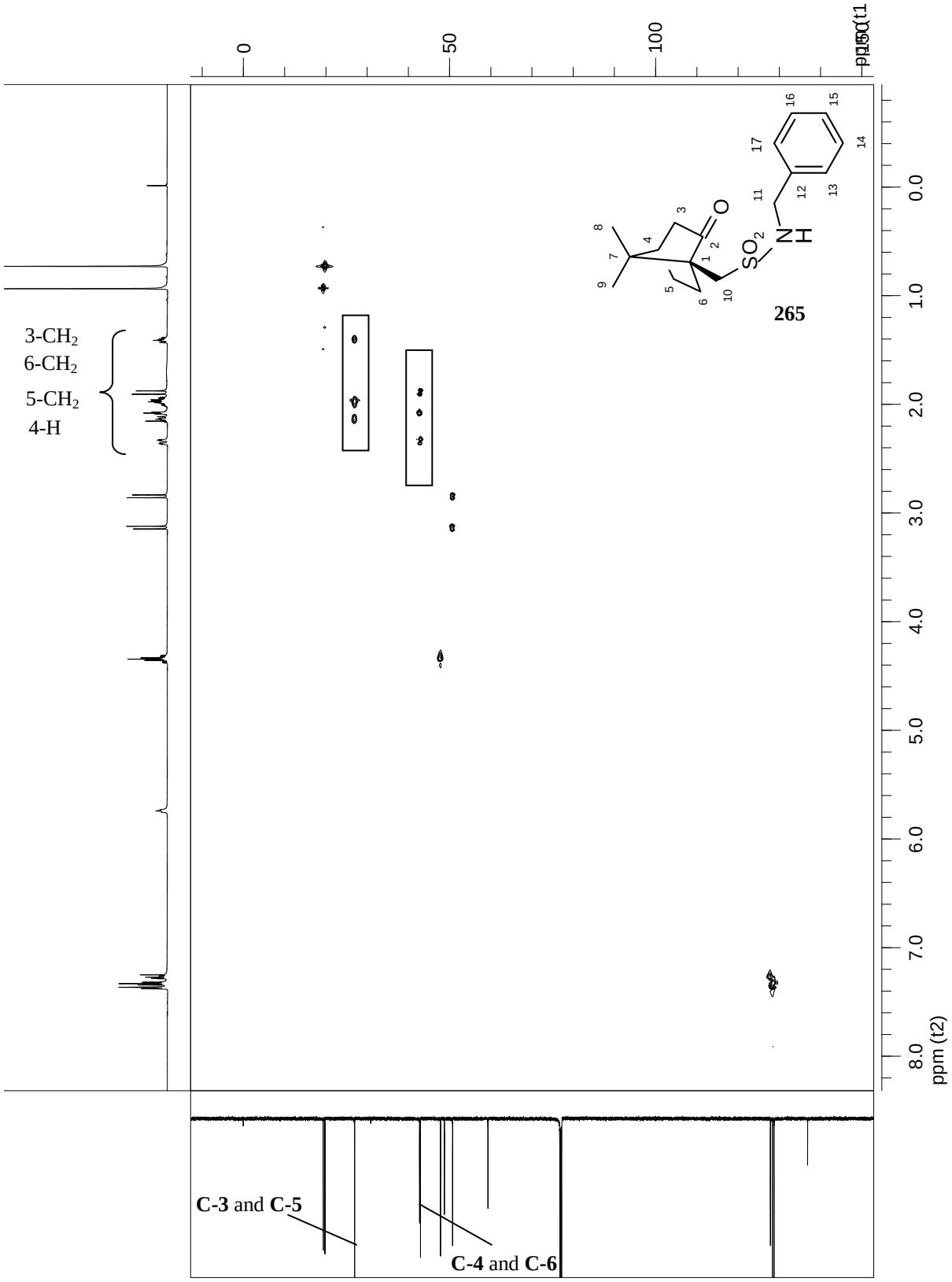
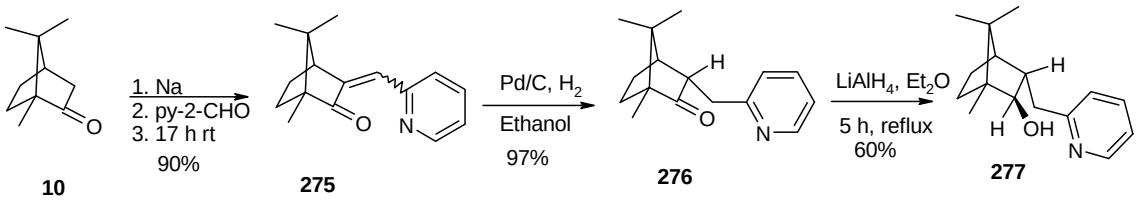


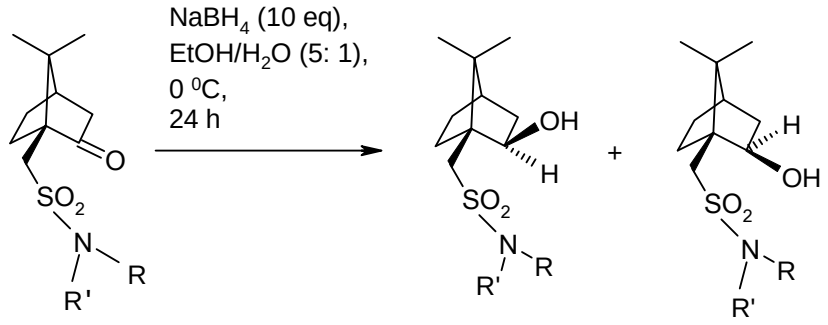
Figure 2.12. ^{13}C HSQC spectrum of compound **265** (600 MHz, $CDCl_3$).

2.1.1.2.3. ***Reduction of camphor-10-sulfonamides***

It was anticipated that reduction of the carbonyl group in the camphor-10-sulfonamides **265-274** would need to be carried out under mild conditions to ensure that the reduction of the hindered ketone functionality was not accompanied by the reduction of the susceptible sulfonamide bond. Reductions, in general, are performed using metal hydrides or through hydrogenation using a metal catalyst. However, sulfonamides are known to be susceptible to hydrogenation in the presence of a metal catalyst.[130,131] Methods that involve the use of either $LiAlH_4$ or $NaBH_4$ have an added advantage in that they contain a large number of hydrogens for a small amount of reagent. However, $LiAlH_4$ is a powerful reducing agent and its lack of selectivity made it less attractive to be used for these reactions. $NaBH_4$, on the other hand, is considered to be much milder than $LiAlH_4$ and, when dissolved in hydroxylic solvents at room temperature it rapidly reduces aldehydes and ketones whilst remaining chemically inert to other functional groups. Brown and co-workers,[132] have shown that $NaBH_4$ readily generates hydrogen when it reacts with methanol but less readily when it reacts with ethanol and not at all when combined with 2-propanol overnight. The $NaBH_4$-mediated reductions of compounds **265-274** in ethanol were expected to occur swiftly. The *endo* delivery of the hydride ion by $NaBH_4$ was expected to favour the generation of *exo* alcohols. Degni and co-workers[131] synthesized and demonstrated the use of the camphor-derived chiral alcohol **277** as a ligand for one of the most studied catalytic enantioselective addition of diethylzinc to benzaldehydes (Scheme 2.10). Weng and co-workers,[39] on the other hand, recently prepared and pointed out the organocatalytic potential displayed by the pyrrolidine-camphor derived alcohol **84** in Michael reactions of saturated carbonyl compounds with nitroalkanes (Scheme 1.14).



Scheme 2.10. Synthesis of chiral 2-amino alcohol **277**.[131]



265-274 **278-296**

R' = H, R = Benzyl
3-Chlorophenyl
Phenyl
Furfuryl
2-Aminopyridinyl
Adamantyl
Picolyl
t-Butyl
2-Aminoimidazolyl

R' = cyclohexyl and R = cyclohexyl

Scheme 2.11. Yields of the epimeric alcohols **278-296**.

We decided to use $NaBH_4$ in a mixture of ethanol and water and camphor-10-sulfonamides **265-274** shown in Scheme 2.11. Reductions proceeded with good to excellent yields and, generally, with high diastereoselectivity, as shown in Table 2.2 (p65).

The combination of very detailed 1-D and 2-D NMR experiments together with comparison with the known NMR data of the precursor **265** allowed structural assignment of the epimeric alcohols **278** and **279.** Although the ^{1}H NMR and the COSY spectra were not sufficiently resolved to analyse the complex coupling patterns exhibited by the 2-*endo*-H nucleus of the alcohol **278** and the 2-*exo*-H nucleus of the stereoisomer **279**, the 2-*endo*-H signal (4.06 ppm) appears upfield of the corresponding 2-*exo*-H signal (4.32 ppm) due to the more shielded environment of the former nucleus.

Table 2.2. Data showing epimeric alcohols **278**-**296**.

Entry	R’	R	Product (**a** + **b**)	Yield (%)	*Exo/endo* (%)
1	H	Benzyl	**278** and **279**	95	78: 22
2	H	3-Chlorophenyl	**280** and **281**	53	93: 7
3	H	Phenyl	**282** and **283**	97	90: 10
4	H	Furfuryl	**284** and **285**	83	82: 18
5	H	2-Aminopyridinyl	**286** and **287**	98	87: 13
6	H	Adamantyl	**288** and **289**	70	87: 13
7	Cyclohexyl	Cyclohexyl	**290** and **291**	100	62:38
8	H	Picolyl	**292** and **293**	93	90:10
9	H	*t*-Butyl	**294** and **295**	92	79: 21
10	H	2-Aminoimidazolyl	**296**	86	100: 0

The 2-*endo* proton of the *exo*-alcohol **278** is also responsible for shielding the 3-*endo*-H endo, 5-*endo* and 6-*endo* (1.10-1.81 ppm) protons all of which resonate further upfield than is the case with the corresponding *endo*-alcohol **279**, in which the 2-*endo*-hydroxy grants deshielding of the 3-*endo*, 5-*endo* and 6-*endo* (1.04-2.38 ppm) protons. The 10-methylene signals of the 2-*exo* alcohol **278** are widely separated from each other and appear as a pair of doublets (2.73 ppm and 3.32 ppm) with intrinsic chemical non-equivalence being increased by their relative proximity to the 2-*exo*-hydroxy group. In the spectrum of the *endo* epimer **279**, on the other hand, the diastereotopic 10-methylene protons have similar chemical shift values and resonate close to each other with the result that the pair of doublets appears to be a distorted ‘‘quartet’’. The other epimeric alcohols **280**-**296** were characterized in a similar way.

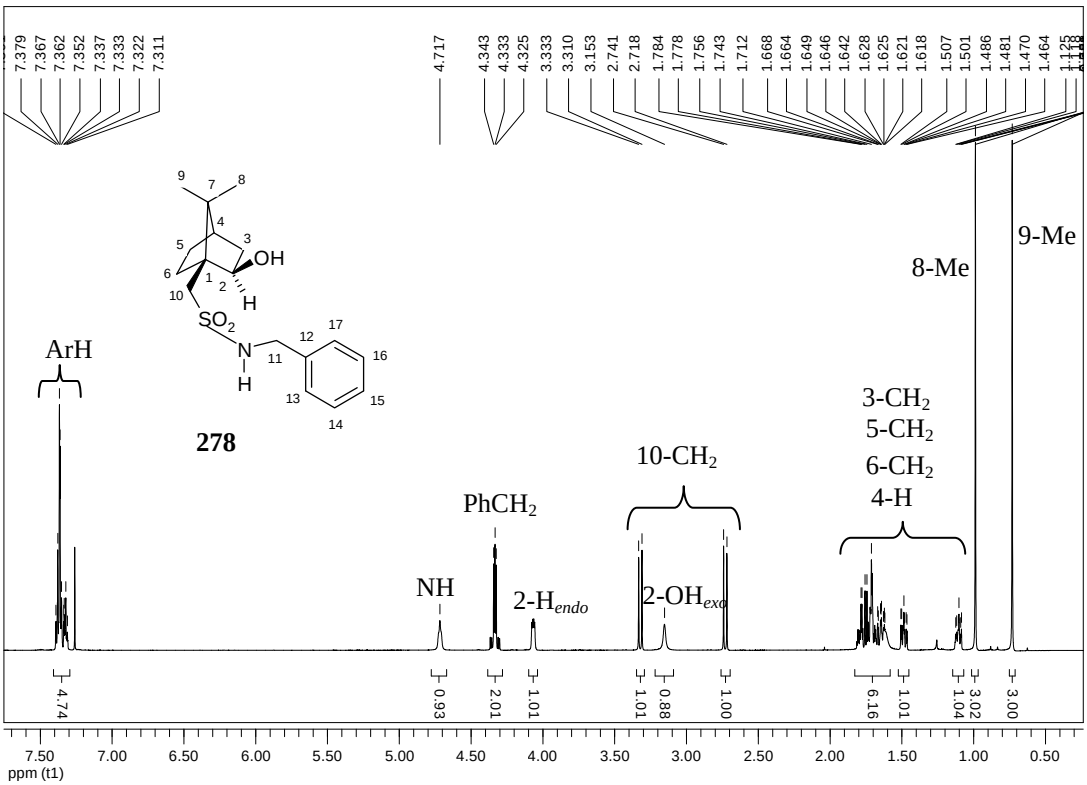


Figure 2.13. ^{1}H NMR spectrum of compound **278** (600 MHz, $CDCl_3$).

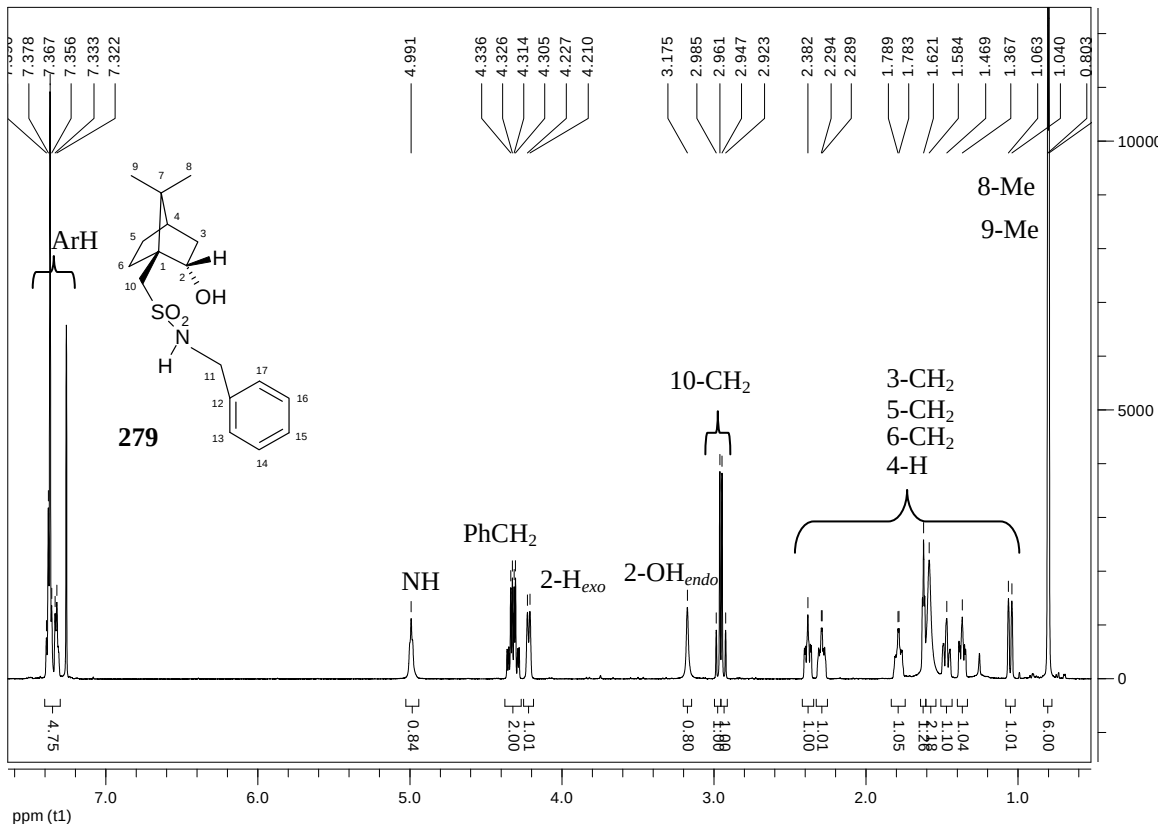
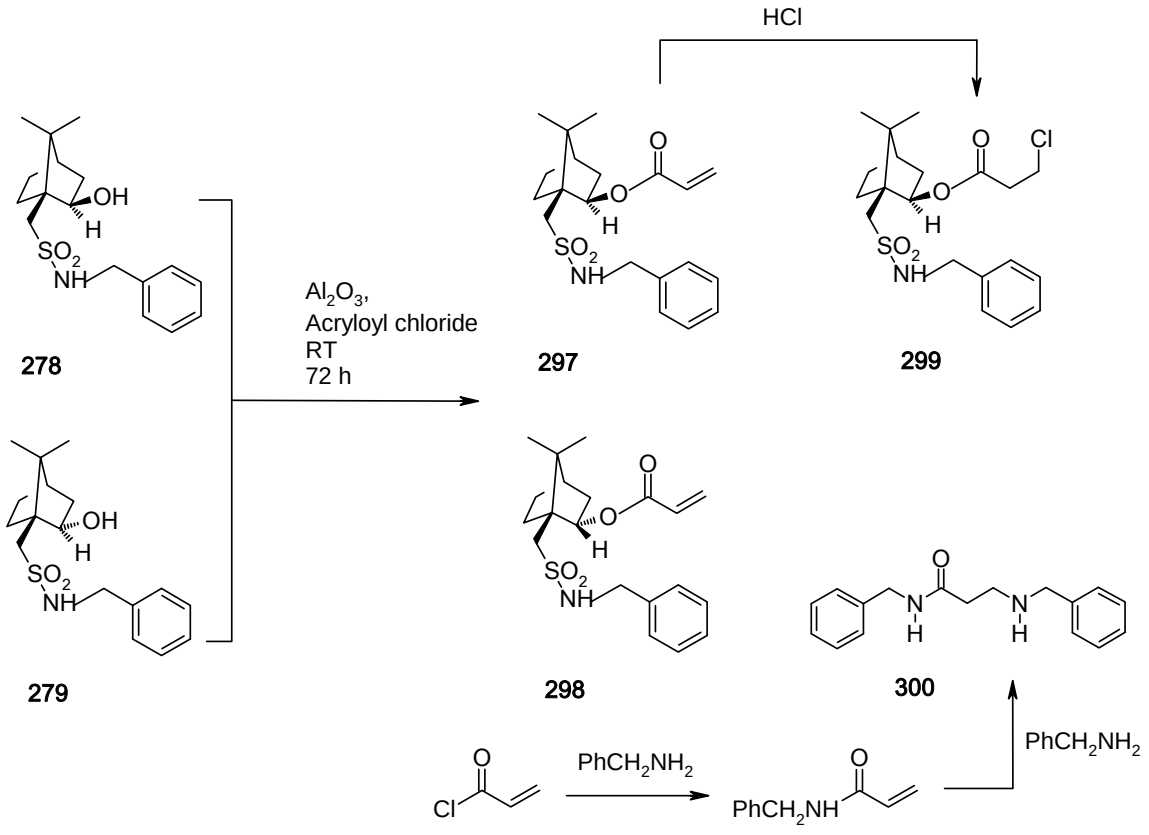


Figure 2.14. ^{1}H NMR spectrum of compound **279** (600 MHz, $CDCl_3$).

2.1.1.2.4. ***Acylation of hydroxycamphor-10-sulfonamides***

The ester functionality is commonly encountered in nature and their synthesis has received considerable attention. A variety of methods to access esters have been developed, but Yadav and co-workers[134] have reported an efficient and experimentally simple method of acylating alcohols and amines using neutral aluminium oxide (Al_2O_3) with acylating agents. In this approach, primary alcohols are readily acylated with acid chlorides, and have been shown to react five times faster than secondary alcohols; tertiary alcohols, on the other hand, were found to be completely inert. In our study, a mixture of the epimeric alcohols **278** and **279** was added to neutral Al_2O_3 (1.5 eq.), followed by the addition of acryloyl chloride (2 eq.). The resulting dispersion was allowed to stand at room temperature for 72h without stirring.



Scheme 2.12. Acylation of epimeric alcohols **278** and **279** using acryloyl chloride and Al_2O_3 as solid support.

Purification of the crude mixture by conventional chromatography proved impossible, but the use of semi-preparative HPLC permitted the isolation of the expected acrylate esters **297** and **298** as well as the 3-chloropropanoyl derivative **299** and the amide **300**. Formation of the 3-chloropropanoyl ester **299** is attributed to conjugated addition of the HCl released during the reaction with the acrylate ester **297** (Scheme 2.12). Formation of the amide **300**, on the other hand, is presumed to involve amidation of acryloyl chloride and aza-Michael addition of a second molecule of benzylamine as indicated in Scheme 2.12 – although not necessarily in that order!

Characterization of compound **297** using 1-D (Figures 2.15-2.17) and 2-D NMR experiments (Figures 2.18-2.19) confirmed the presence of the benzylic bornane-10-sulfonamide signals and the new acrylate proton signals; the complete disappearance of the 2-OH proton signal is also noticeably evident. The 2-*endo*-H signal at 5.04 ppm appears downfield in comparison to that of the precursor **278** (4.07 ppm) and this can be explained by its proximity to the deshielding effects of the acrylate and sulfonate groups. The ^{13}C NMR spectrum (Figure 2.16) showed additional carbon signals at 128.0, 130.3 and 164.8 ppm belonging to C-2', C-3' and C-1', respectively. The HSQC spectrum (Figure 2.19), on the other hand, confirmed the correlation between the new proton signals at 6.09, 5.79 and 6.33 ppm with these new carbon signals, while the DEPT-135 spectrum (Figure 2.17) indicated the presence of the vinylic methylene signal at 130.2 ppm. The COSY (Figure 2.18) experiment reveals the coupling between *inter alia* the pair of 10-CH_2 protons and between the vinylic acrylate protons, while the HSQC spectrum (Figure 2.19) confirmed correlations between the new proton signals with the new carbon signals. The ^{1}H NMR spectrum (Figure 2.20) of the 3-chloropropanoate ester **299** shared many similarities with that of the acrylate ester **297**. The only notable differences were the absence of the vinylic signals and the appearance of two new methylene signals at 2.74 and 3.71 ppm corresponding to C-2' and C-3', respectively – indicative of the loss of the double bond between C-2' and C-3'. The ^{13}C NMR and DEPT-135 spectra (Figures 2.21 and 2.24) of the 3-chloropropanoate ester **299** reveal, as expected, the absence of the vinylic methylene signal characteristic of the acrylate ester

297. From the correlations in the COSY spectrum (Figure 2.22), it is evident that the 2'-methylene proton signal overlaps with the doublet corresponding to one of the 10-methylene protons at *ca*. 2.74 ppm. These assignments are supported by the corresponding HSQC data (Figure 2.23). HRMS data confirmed the molecular composition of the acrylate ester **297** with a molecular ion peak at *m/z* 378.1747, which satisfies the expected molecular formula, $C_{20}H_{28}NO_4S$ (calculated *m/z*, 378.1747). The HRMS analysis also confirmed the molecular composition of the chlorinated derivative **299**, with the expected molecular ion peak observed at *m/z* 414.1498 corresponding to the molecular formula, $C_{20}H_{29}NO_4ClS$ (calculated *m/z*, 414.1506).

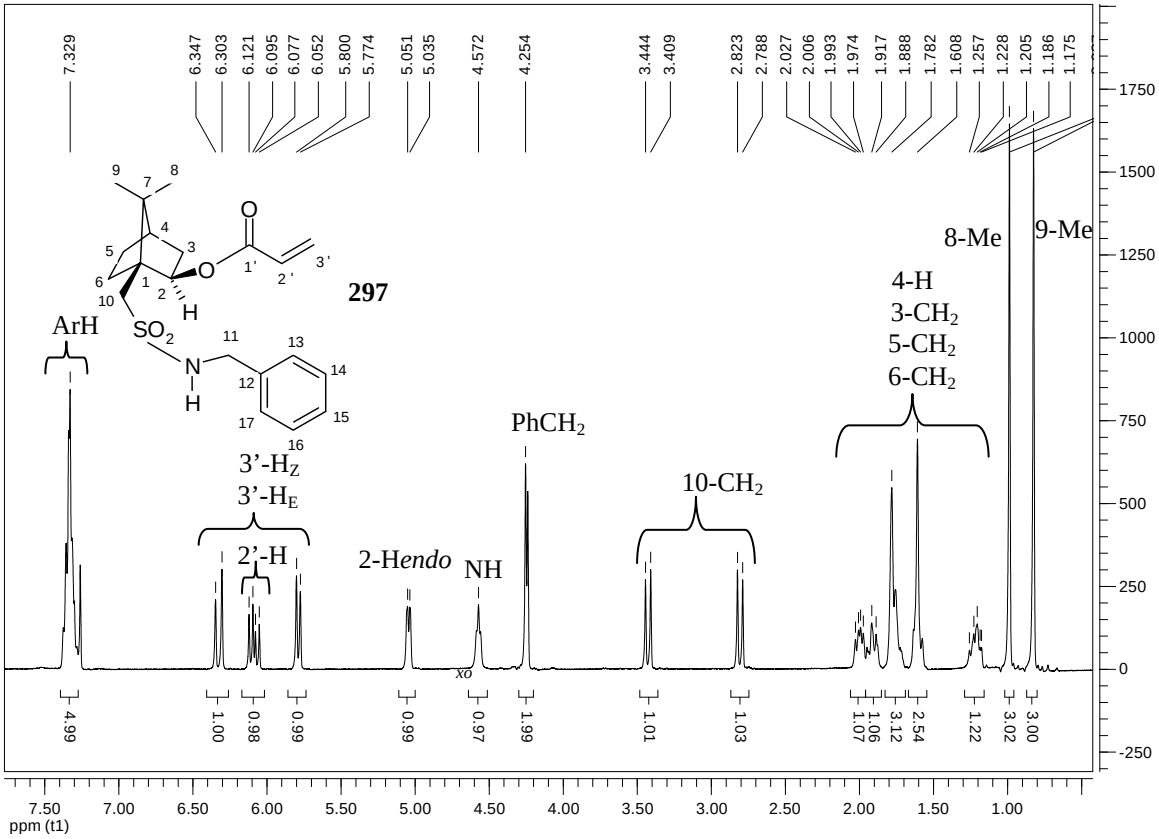


Figure 2.15. ^{1}H NMR spectrum of compound of **297** (400 MHz; $CDCl_3$).

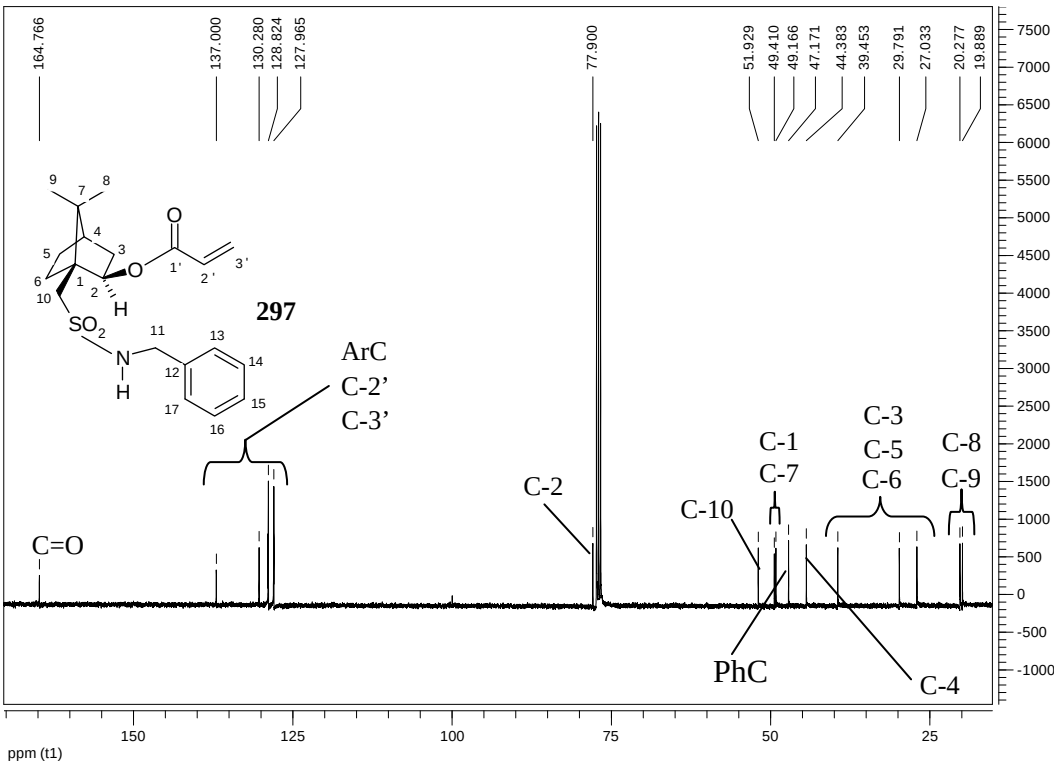


Figure 2.16. ^{13}C NMR spectrum of compound **297** (100 MHz, $CDCl_3$).

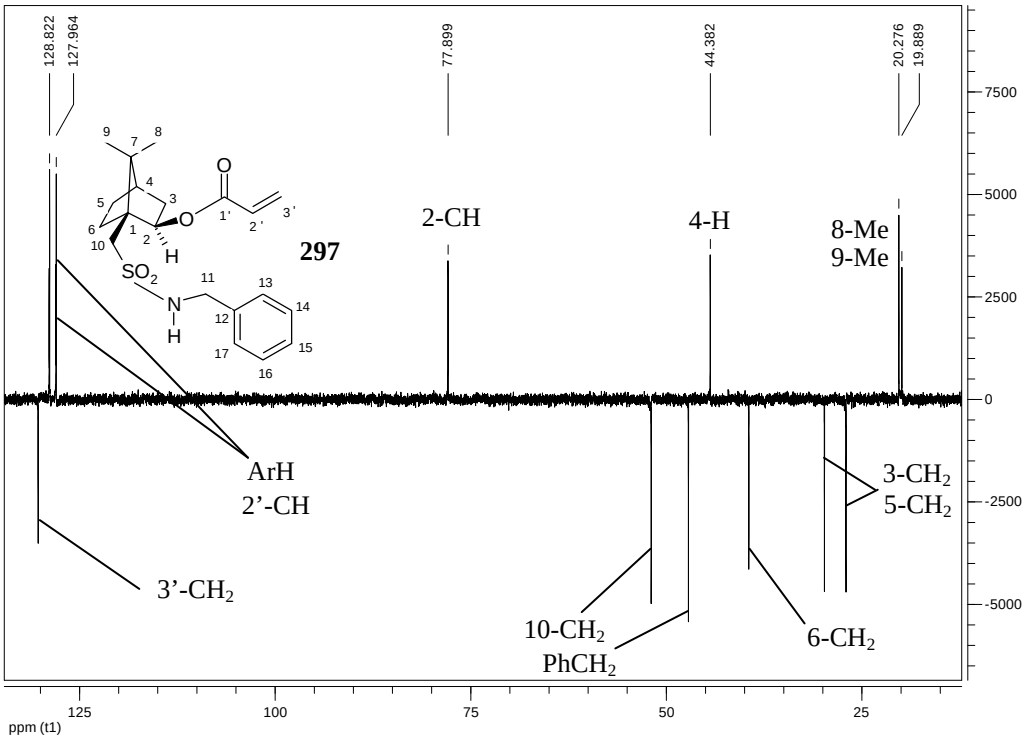


Figure 2.17. DEPT-135 spectrum of compound **297** (100 MHz, $CDCl_3$).

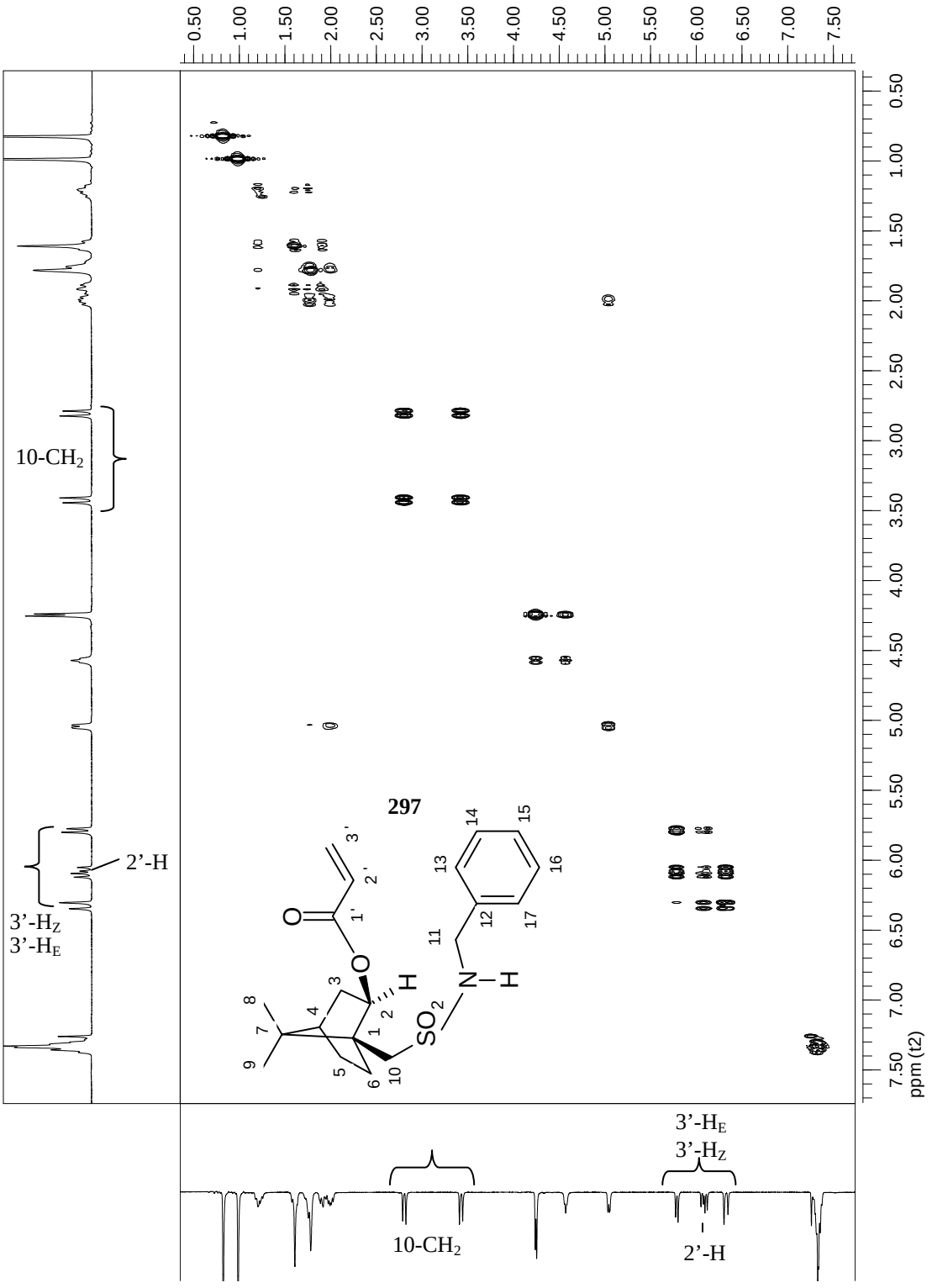


Figure 2.18. COSY spectrum of compound **297** (400 MHz, $CDCl_3$).

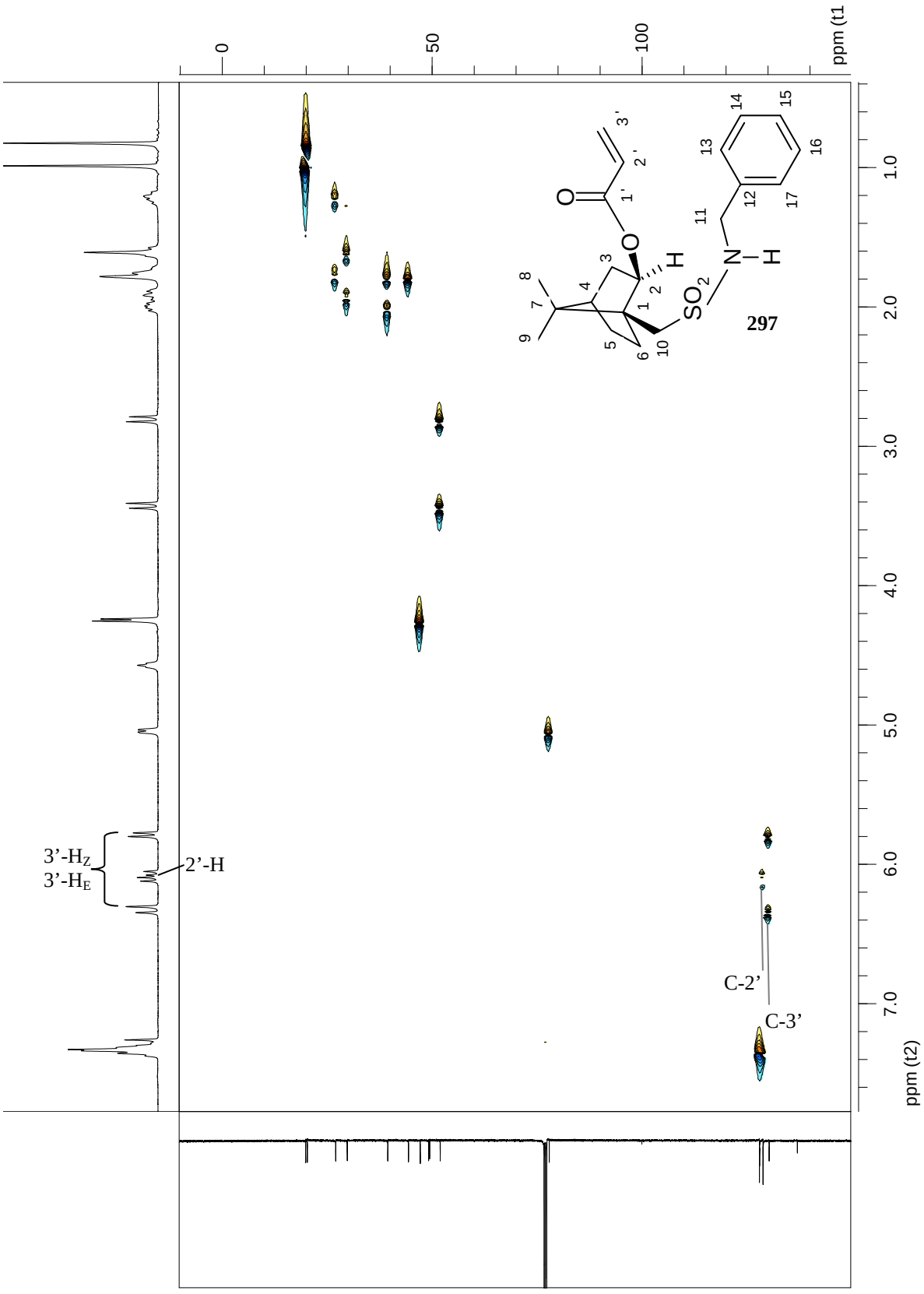


Figure 2.19. ^{13}C HSQC spectrum of compound **297** (400 MHz, $CDCl_3$).

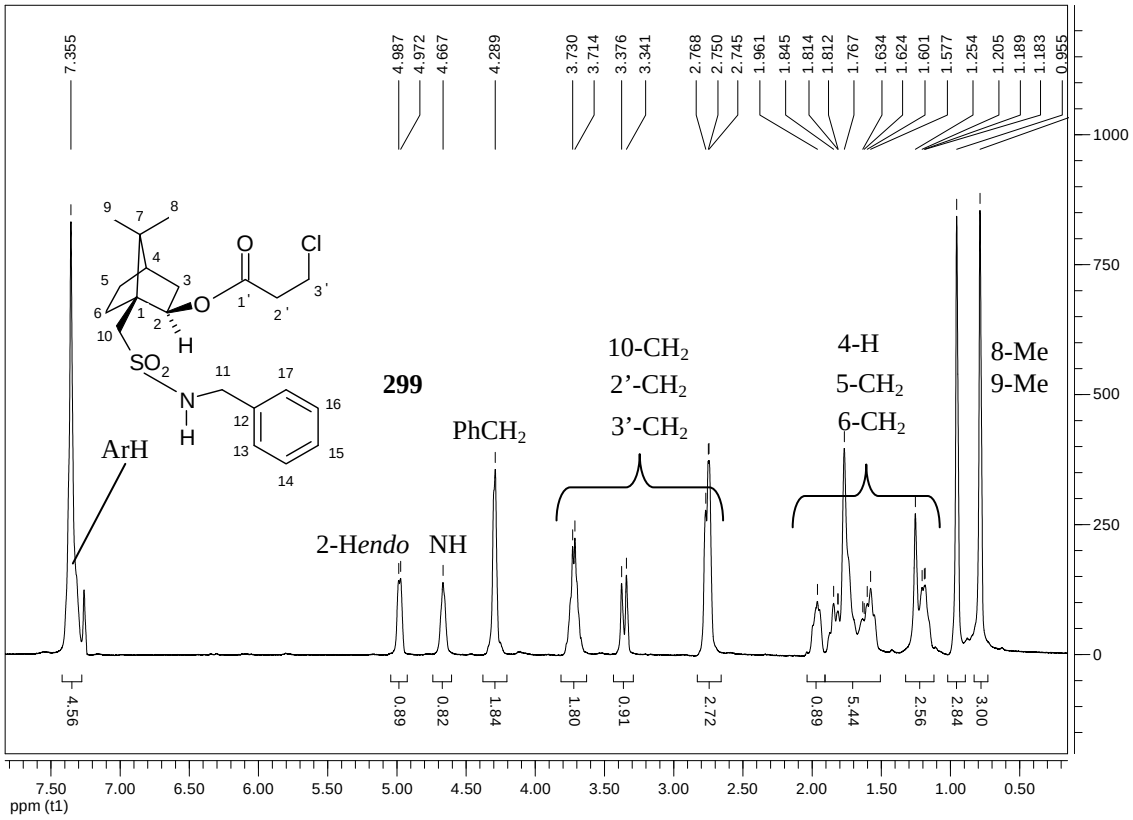


Figure 2.20. ^{1}H NMR spectrum of compound **299** (400 MHz, $CDCl_3$).

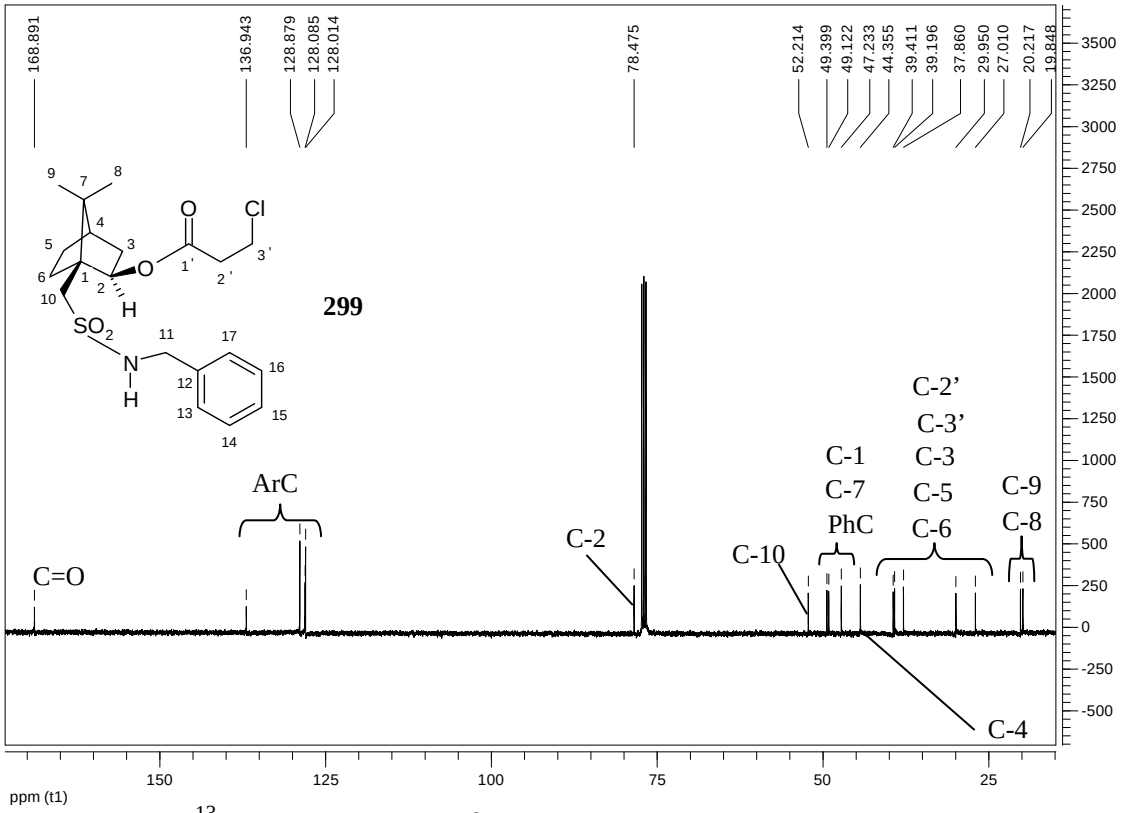


Figure 2.21. ^{13}C NMR spectrum of compound **299** (400 MHz, $CDCl_3$).

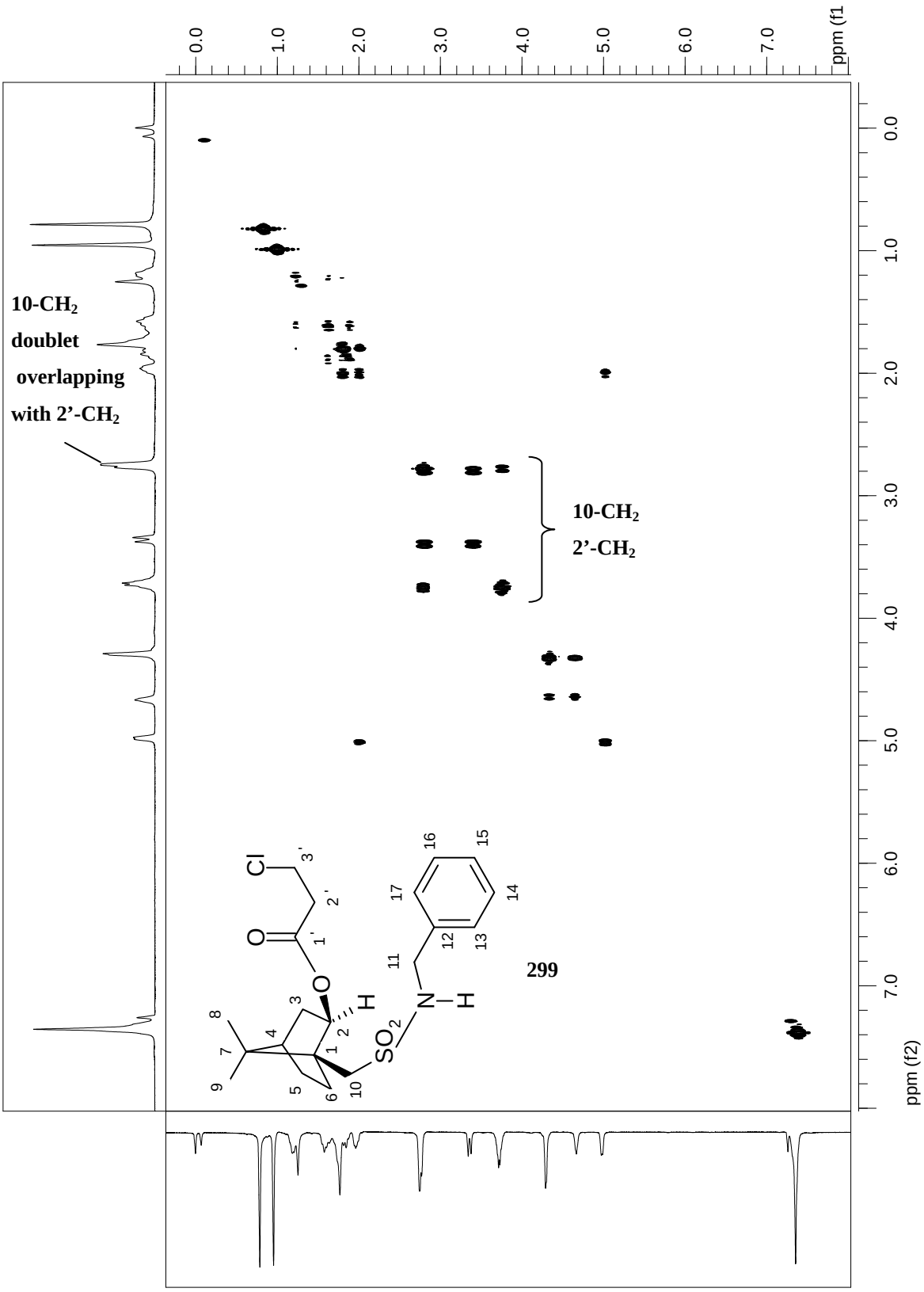


Figure 2.22. COSY spectrum of compound **299** (400 MHz, $CDCl_3$).

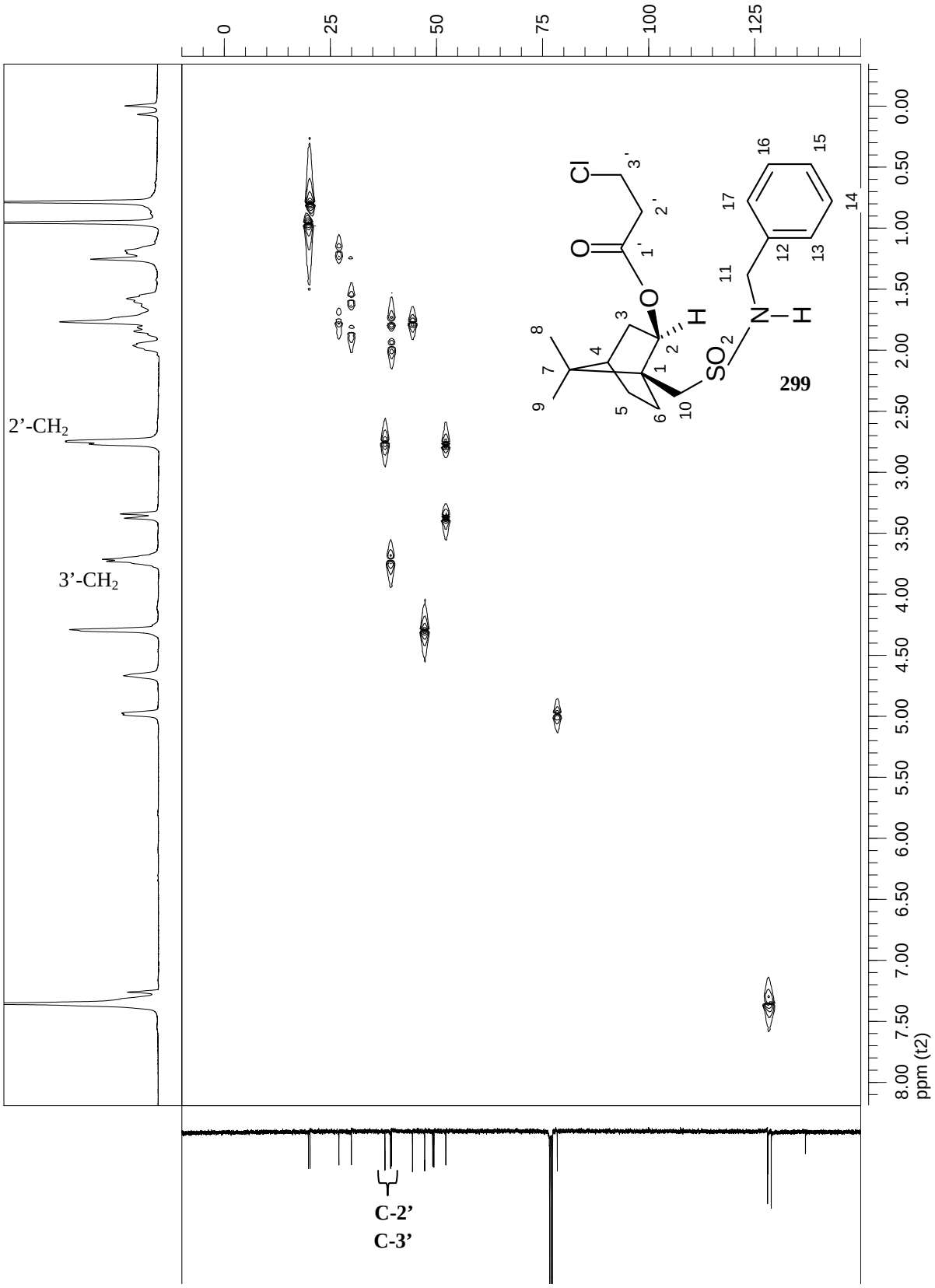


Figure 2.23. ^{13}C HSQC spectrum of compound **299** (400 MHz, $CDCl_3$).

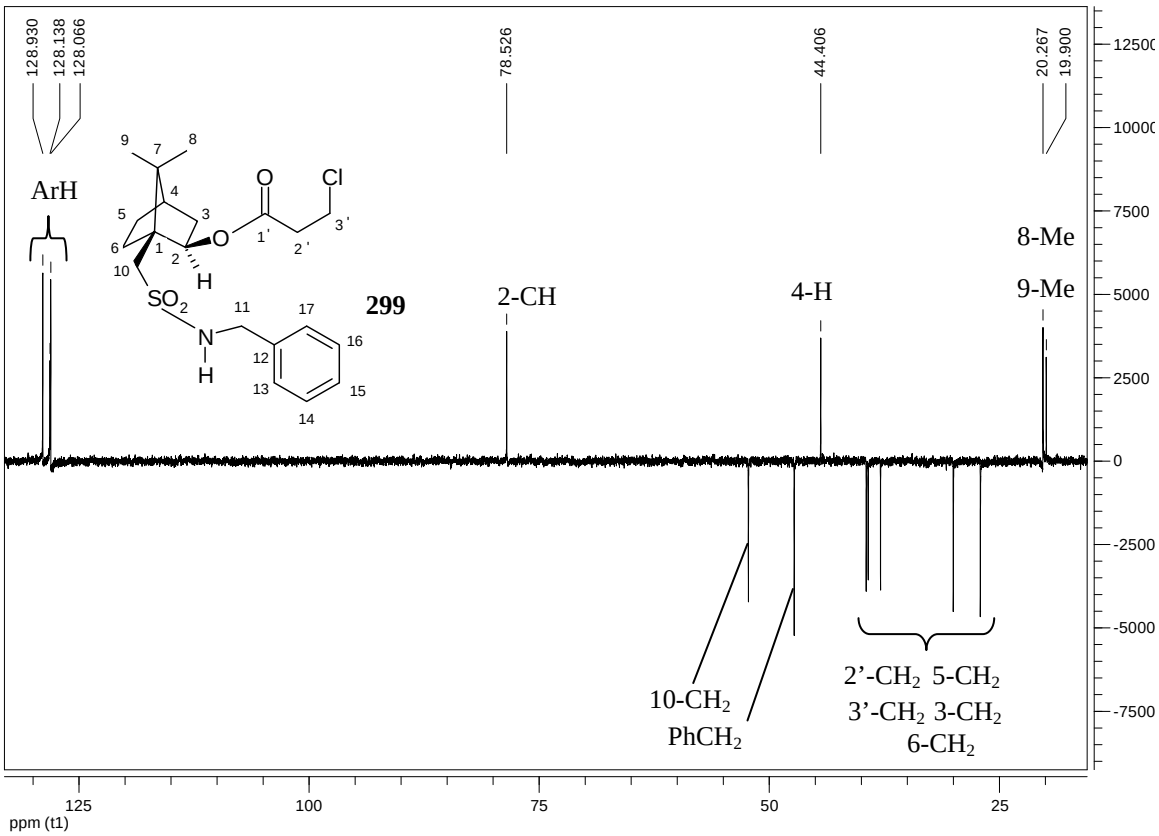
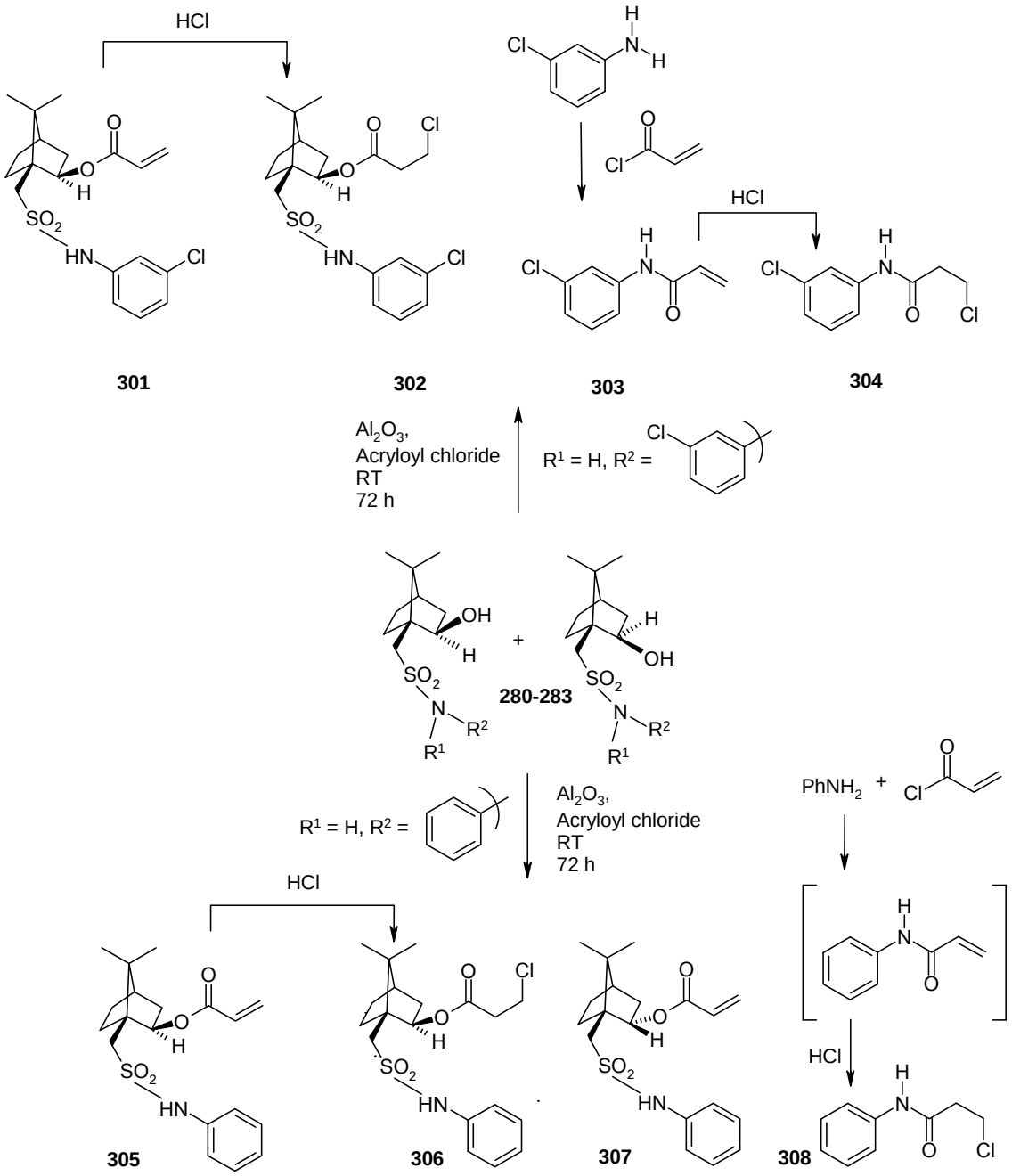
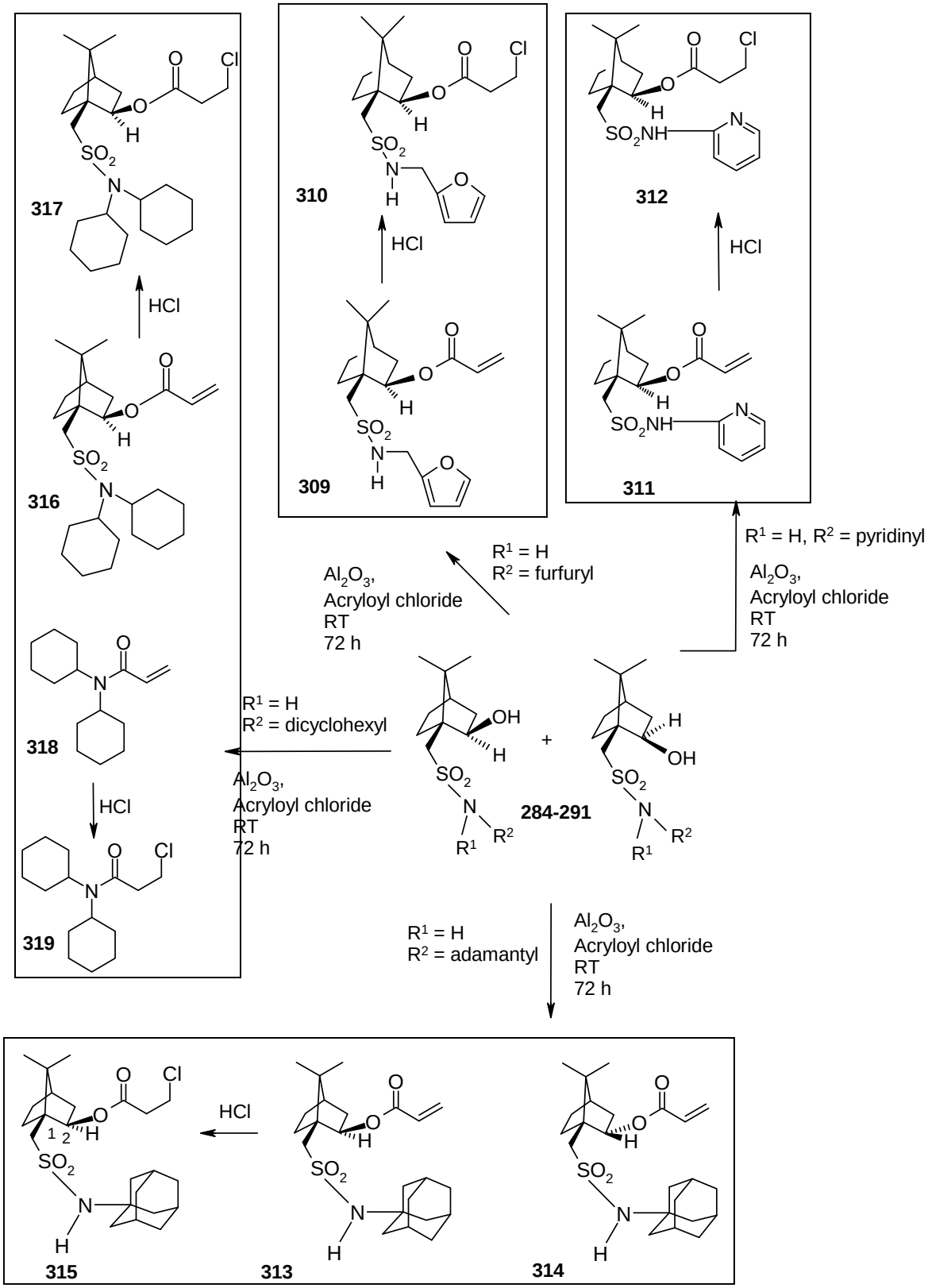


Figure 2.24. DEPT-135 spectrum of compound **299** (400 MHz, $CDCl_3$).

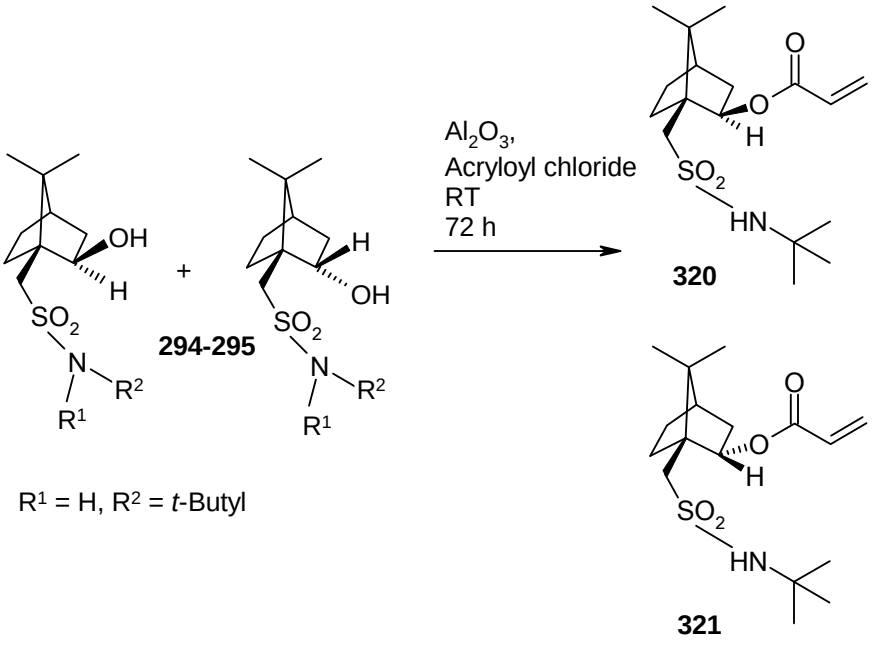
Mixtures of the analogous, diastereomeric camphorsulfonamides in which the *N*-benzyl group was replaced by *N*-(3-chlorophenyl), *N*-phenyl, *N*-furfuryl, *N*-(2-pyridinyl),*N*-(adamantyl) and *N*,*N*-dicyclohexyl groups (compounds **280** and **281**, **282** and **283**, **284** and **285**, **286** and **287**, **288** and **289**, **290** and **291** and **294** and **295**, respectively) were also treated with acryloyl chloride in the presence of Al_2O_3. Work-up and HPLC separation afforded, in each case, the products illustrated in Schemes 2.13a, 2.13b and 2.13c. Careful analysis of the NMR data, following the patterns exhibited by the *N*-benzyl derivatives discussed earlier, permitted the assignment of the structures of the various products. Not surpringly, the dominant (or sole) products in all cases are derived from the major, 2-*exo*-hydroxy precursors; in some cases derivatives of the minor, 2-*endo*-hydroxy precursors were isolated.



Scheme 2.13a. Acylation of epimeric alcohols **280**-**283**.



Scheme 2.13b. Acetylation of epimeric alcohols continued.

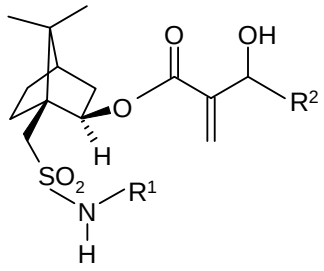


Scheme 2.13c. Acylation of epimeric alcohols continued.

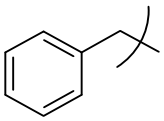
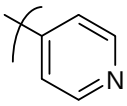
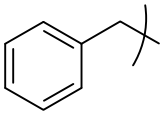
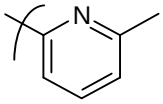
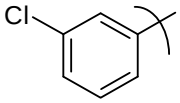
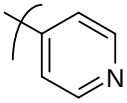
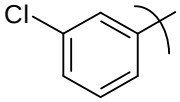
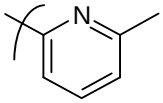
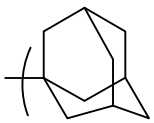
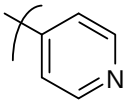
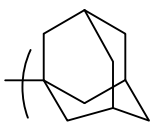
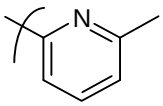
2.1.1.3. Camphor-derived acrylates as chiral auxiliaries in the Morita-Baylis-Hillman reaction

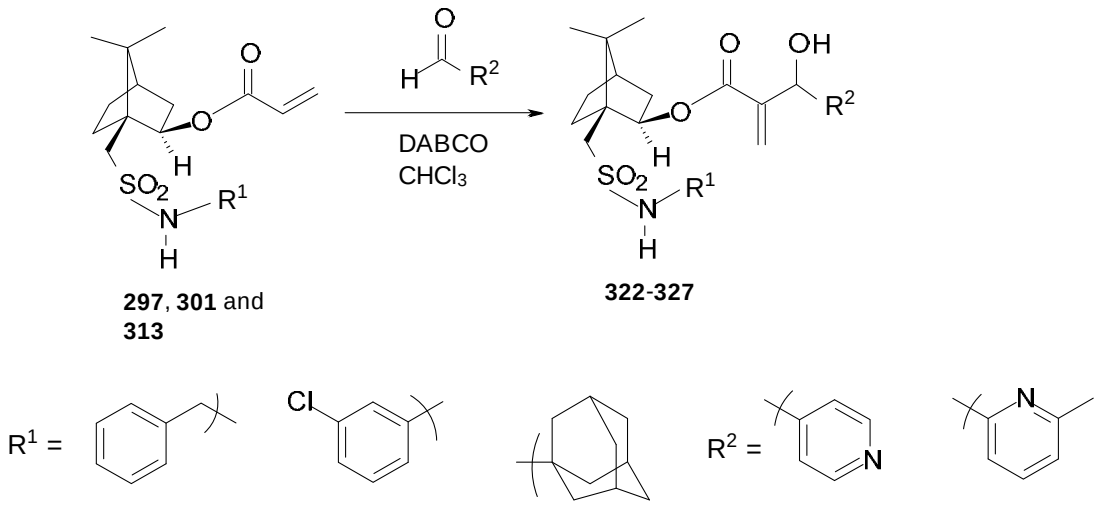
Earlier studies by Duggan[121] in our group had encouraged us to explore the use of camphor-derived *exo*-acrylates in the asymmetric Morita-Baylis-Hillman reaction. In the present study, 4-pyridinecarbaldehyde and 6-methyl-2-pyridinecarbaldehyde were selected as the aldehydes of choice and the tertiary amine, DABCO, as the catalyst. As shown in Scheme 2.13, a total of six reactions were conducted using the three *exo*-acryloyl bornane-10-sulfonamides **297**, **301** and **313**. The reactions were allowed to run for 90h and the desired MBH adducts **322-327** were obtained with excellent conversion levels (91-100%) as determined by ^{1}H NMR analysis after preliminary flash chromatography of the reaction mixtures shown in Table 2.4. The diastereoselectivities (% d.e.) were obtained by comparing the relative integrals of the MBH methylene and methine proton signals (between 5 and 6 ppm) in the ^{1}H NMR spectra of the major and the minor products signals as illustrated in Figures 2.25 and 2.26.

Table 2.4. Data for the stereoselective formation of the MBH products from the chiral acrylate esters **297**, **301** and **313**.



322-**327**

Entry	**Product**	**R[1]**	**R[2]**	**Yield (%)**	**% d.e.**
1	**322**			91	8
2	**323**			100	33
3	**324**			92	7
4	**325**			98	21
5	**326**			93	8
6	**327**			96	15



Scheme 2.13. Synthesis of camphor-10-sulfonamide-based MBH adducts **322-327**.

The disappearance of the characteristic acrylate proton signals at, for example, 5.79, 6.10 and 6.35 ppm in the precursor *N*-adamantylsulfonamide ester **313** was accompanied by the emergence of the three ‘‘fingerprint’’ Morita-Baylis-Hillman singlets, corresponding to the methine and methylene protons in the same general region; this is a clear indication of the transformations of acrylate ester substrates **297**, **301** and **313** to the corresponding diastereomeric MBH products. Analysis of ^{1}H NMR data permitted the diastereomeric ratios to be determined, as shown in Figure 2.26. The NMR spectra of the mixtures were complicated by the presence of both diastereoisomeric products and by traces of the starting materials. Nevertheless, the ^{1}H NMR spectra could be used to determine the % d.e. in each case, and the ^{13}C NMR and DEPT-135 permitted confirmation of the presence of the desired products. Thus, for example, the ^{13}C and DEPT-135 spectra of the major diastereomeric adamantyl derivatives **327**, for the major diastereomer exhibited:

(i) the three methyl signals at 20.9, 21.7 and 24.1 ppm due to C-8, C-9 and C-9’, respectively;

(ii) three intense signals at 31.1, 35.8 and 44.8 ppm typical of the adamantyl moiety;

(iii) the characteristic quaternary signals at 142.8, 155.7, 158.1 and 166.2 ppm corresponding to C-1’, C-2’, C-4’ and C-8’;

(iv) the pyridine signals at 118.1, 122.6 and 137.2 ppm due to C-5', C-6' and C-7';

(v) and lastly, a methylene signal at 127.8 ppm which is due to C-10'.

The intention was, of course, to expand significantly on the preliminary work reported by Duggan, who had focused on the *N*-adamantyl system. Unfortunately, although some diastereoselectivity was observed in all the MBH reactions of the camphor-derived acrylate esters (Table 2.4), the % d.e. values are generally low. These results, coupled with the considerable difficulties encountered in the synthesis of the chiral acrylate ester substrates, present real challenges for future development. During this aspect of the project– new compounds have been isolated and characterized. A detailed analysis of the mass spectrometric fragmentation patterns exhibited by the camphor-derived acrylate system is covered in Section 2.3.

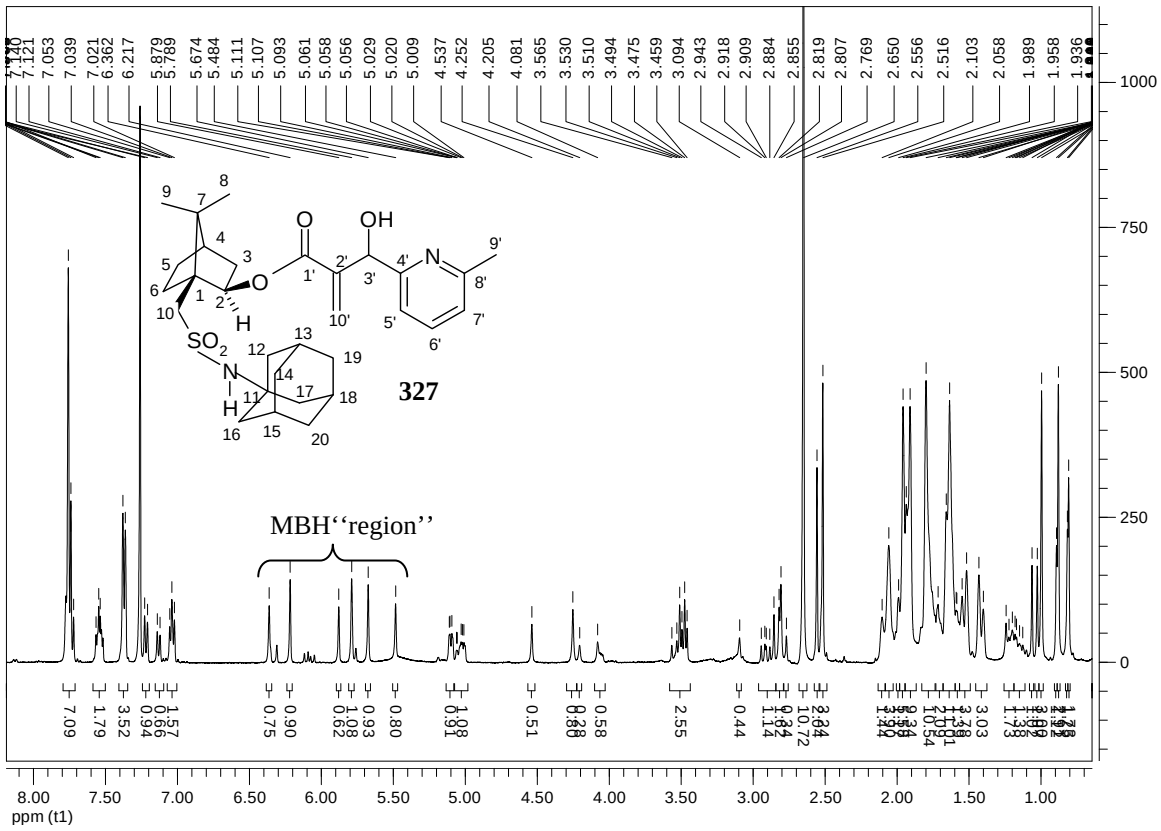


Figure 2.25. ^{1}H NMR spectrum of a mixture of the diastereomeric products **327** (400 MHz, $CDCl_3$).

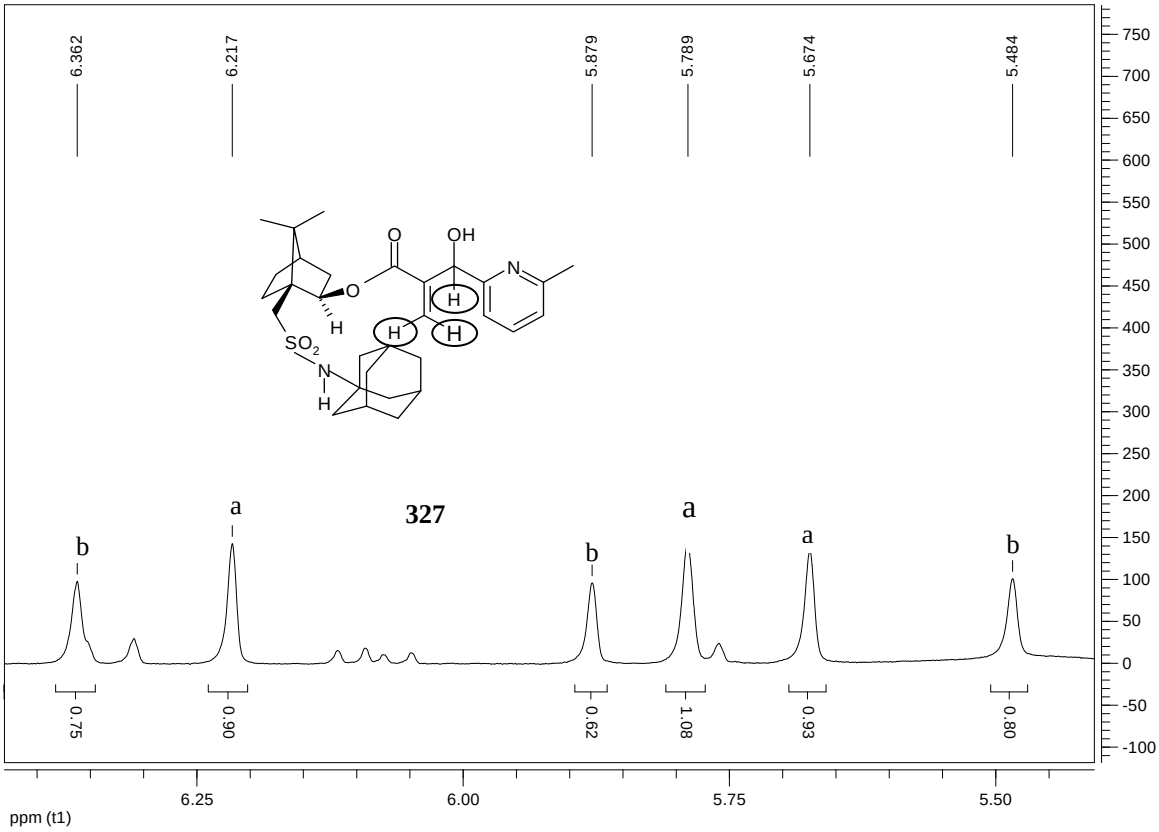
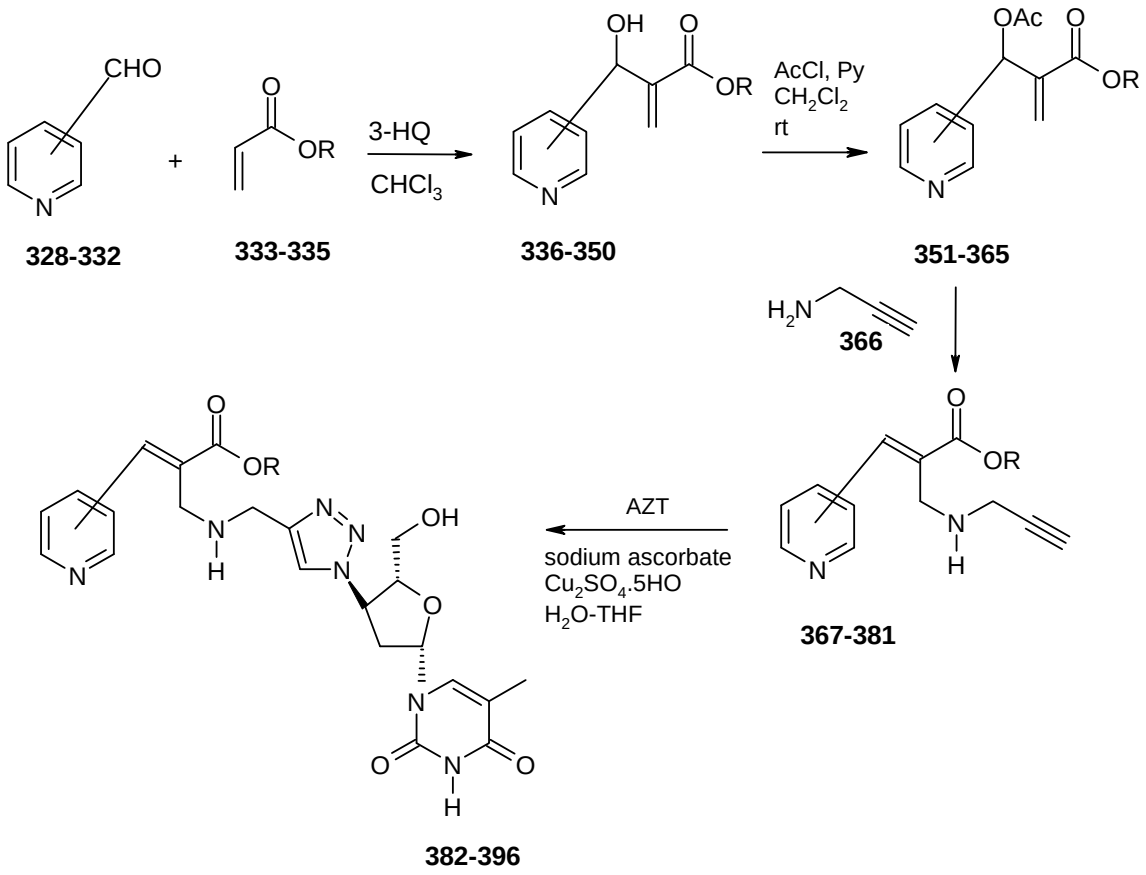


Figure 2.26. Partial ^{1}H NMR spectrum (400 MHz; $CDCl_3$) of the diastereomeric MBH adducts **327**. Signals labelled ‘a’ correspond to the circled ‘‘MBH’’ protons in the major products, those labelled ‘b’ to the minor diastereomer.

2.2. HETEROCYCLIC-AZT ANALOGUES

Acquired immune deficiency syndrome (AIDS) remains the only pandemic that has claimed more than 20 million lives since its first recognition in 1981, thus, becoming one of the most devastating and ravaging diseases known to mankind.[135] AIDS is caused by the human immune deficiency virus (HIV) which belongs to a class of retroviruses, that is, viruses that contain only one RNA strand enriched with the *pol* gene which enables it to code for reverse transcriptase, an enzyme that is commonly targeted in the battle against this dreadful disease.[136] Reverse transcriptase is key to replication of the virus, permitting the single-stranded RNA form of the virus to transcribe itself to the double stranded DNA helix form and, by so doing, allowing the double stranded DNA form to integrate itself into chromosomes belonging to the host cells.[137] Further transcription, translation and assembly results in the production of more viruses. Although highly active antiretroviral therapy (HAART), involving use of a combination of HIV enzyme inhibitors, has gained ground in reducing the number of deaths and morbidity due to HIV/AIDS, multiplication of the virus continues to grow. This is attributable to the fact that some of the antiretroviral drugs cannot cross the blood brain barrier (BBB) or access the lymph nodes, and thus the CNS and lymphatic systems serve as havens for the virus. The surfacing of the drug-resistant HIV strains due to genetic mutation exacerbates the problem.[136,137] Lastly, the unwanted side-effects of drugs, such as AZT, further compound the problem.[138] Hence, new drugs and new treatment protocols are required if the war against AIDS is to be won. Thus, as AIDS continues to pose as a serious health threat, the development of novel chemotherapeutic agents remains a challenge. Our research group has over the years showed a keen interest in the exploration of novel drug candidates that display activity against the HIV. Recently, attention has been given to the development of potential dual-action HIV-1 protease (PR)/reverse transcriptase (RT) and integrase (IN)/RT inhibitors.[139] Cinnamate esters have been identified as potential/IN inhibitors[139] and, in the present study, attention has been given to using pyridine-derived cinnamate ester analogues together with AZT in the preparation of potential, dual-action HIV-1 IN/RT inhibitors. The general approach is outlined in Scheme 2.14.

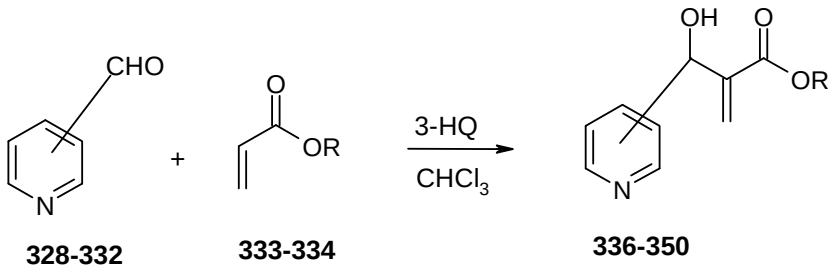


Scheme 2.14. Proposed access to heterocyclic ester-AZT conjugates.

2.2.1. Synthesis of Morita-Baylis-Hillman Adducts

This approach to novel heterocyclic-AZT conjugates was based on the application of Morita-Baylis-Hillman methodology in the synthesis of pyridine- as well as quinoline-derived adducts. Earlier work on the preparation of such adducts in our research group was initiated by Bode[107,140] and later followed by Tukulula.[141] In the present study, various pyridine- and quinoline-derived Morita-Baylis-Hillman adducts were synthesized by using different aldehydes with methyl acrylate, ethyl acrylate and *t*-butyl acrylate as the activated alkenes in the presence of catalytic amounts of 3-hydroxyquinuclidine (3-HQ) as shown in Scheme 2.15. As anticipated, the reactions proceeded readily, furnishing the desired adducts as crystals or oils within just 24 hours and in yields which ranged

from good to excellent as shown in Table 2.5. All of the adducts were satisfactorily characterized using ^{1}H and ^{13}C NMR methods.



328-332 **333-334** **336-350**

Scheme 2.15 Synthesis of MBH adducts **336**-**350**.

Table 2.5. Data showing yields of MBH adducts **336**-**350**.

Entry	**Aldehyde**	**R=OMe** **Yield (%)**	**Product**	**R=OEt** **Yield (%)**	**Product**	**R=OBu^{t}** **Yield (%)**	**Product**
1	2-Pyridinecarbaldehyde	90	**336**	93	**341**	89	**346**
2	3-Pyridinecarbaldehyde	87	**337**	92	**342**	100	**347**
3	4-Pyridinecarbaldehyde	81	**338**	95	**343**	100	**348**
4	6-Methyl-2-pyridinecarbaldehyde	52	**339**	95	**344**	100	**349**
5	2-Quinolinecarbaldehyde	100	**340**	100	**345**	34	**350**

Signals in the ^{1}H NMR spectrum of the 2-pyridinecarbaldehyde-derived adduct **336** (Figure 2.27), for example, were assigned as follows: a singlet at 3.73 ppm to the methoxy group (OMe), a broad singlet at 4.81 ppm to the hydroxyl proton (OH) and the three singlets which are characteristic of MBH products at 5.95, 5.62 and 6.35 ppm to the methine proton attached to the stereogenic centre (C-3) and the two diastereotopic methylene protons of the vinylic system, respectively. The aromatic region exhibited two triplets at 7.21 and 7.67 ppm due to the 5'- and 4'-methine protons, respectively, and two

doublets at 7.41 and 8.54 ppm due to the 3'- and 6'- methine protons, respectively. The ^{13}C NMR data (Figure 2.28) concurs with the presence of 10 carbon nuclei as expected. The methoxy carbon resonates at 52.0 ppm, the stereogenic C-3 at 70.7 ppm, the methylene carbon at 126.2 ppm, the aromatic and the vinylic (C-2) carbons in the range 123.4-148.6 ppm and the carbonyl carbon at 166.3 ppm. The other MBH adducts **337**-**345**, which are also known and the novel ones **346**-**350**, similarly, gave satisfactory ^{1}H and ^{13}C NMR spectra.

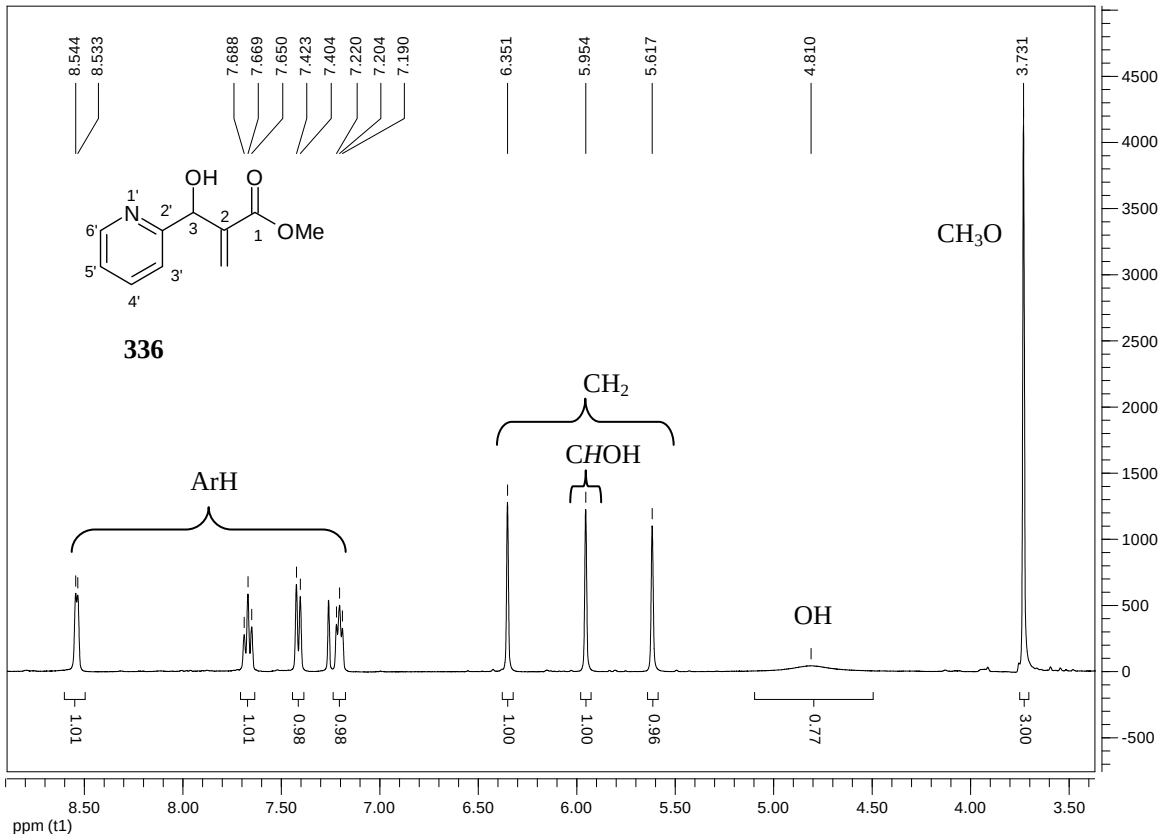


Figure 2.27. ^{1}H NMR spectrum of compound **336** (400 MHz, $CDCl_3$).

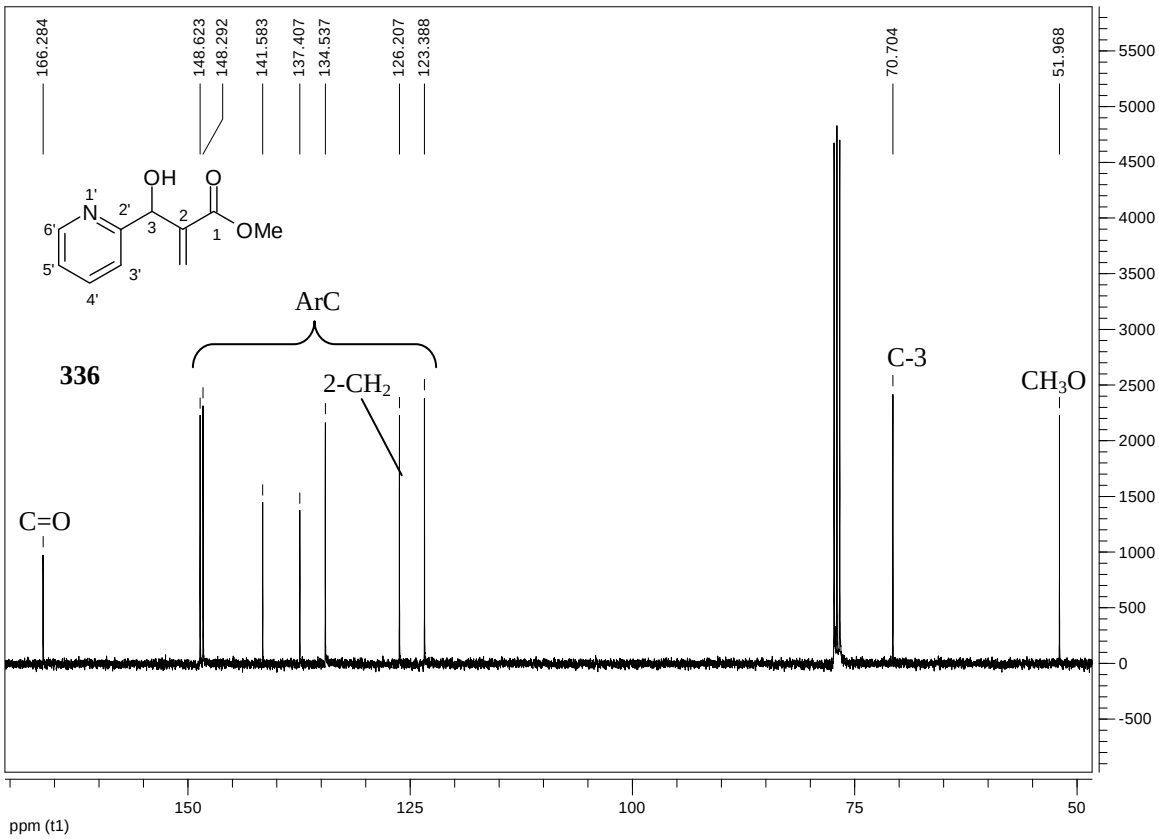
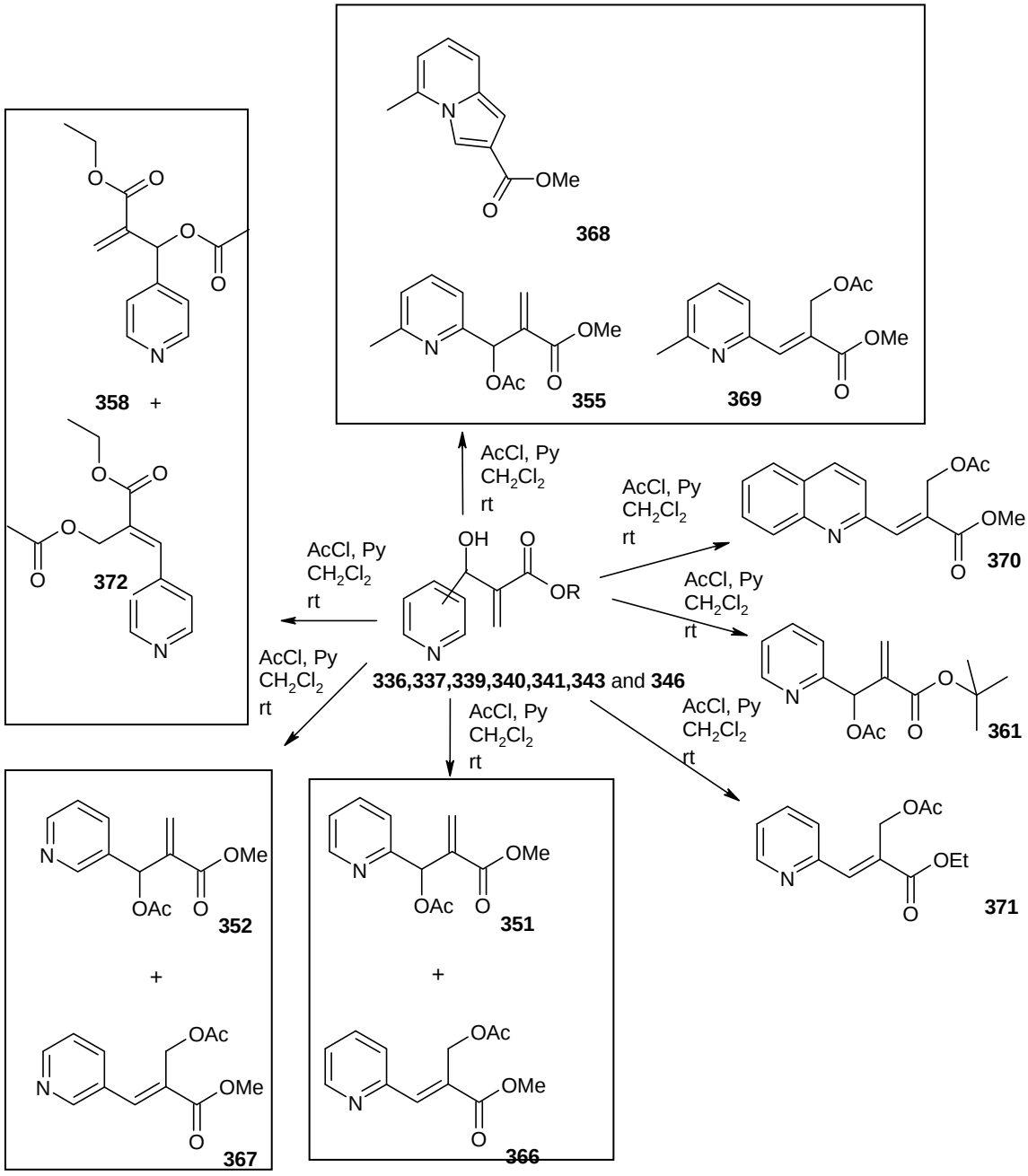


Figure 2.28. ^{13}C NMR spectrum of compound **336** (100 MHz, $CDCl_3$).

2.2.2. Acetylation of Morita-Baylis-Hillman Adducts

Conversion of alcohols to the corresponding acetoxy derivatives is a common transformation in organic synthesis. The importance of acetates is displayed in reactions that involve nucleophilic displacement by C-, N-, O- and S-nucleophiles leading to the generation of substituted and diverse products.[142] Although, environmentally friendly and economically viable methods of preparing these compounds exist, the older methods involve the use of reagents, such as acetyl chloride in dry pyridine or acetic anhydride in concentrated sulphuric acid are often more convenient. In this study, we have made use of acetyl chloride in pyridine – the reagents used in previous studies in our group in expectation of generating the acetylated products **351**-**365** (Scheme 2.14).



Scheme 2.16. Acetylation reactions of the MBH adducts **336**, **337**, **339**, **340**, **341**, **343** and **346**.

Table 2.6. Acetylated MBH adducts.

Entry	**R**	**Ring system**	**Product**	**Yield (%)**
1	OMe	6-Methyl-2-pyridinyl	**355**	47
2	OMe	Indolizine	**368**	38
3	OMe	6-Methyl-2-pyridinyl	**369**	15
4	OMe	2-Quinolinyl	**370**	60
5	OEt	2-Pyridinyl	**371**	52
6	OBu^t	2-Pyridinyl	**361**	34
7	OMe	2-Pyridinyl	**351** and **366**	59
8	OMe	3-Pyridinyl	**352** and **367**	70
9	OEt	4-Pyridinyl	**358** and **372**	42

The 400 MHz ^{1}HNMR spectrum allowed structural assignment of compound **355** (Figure 2.29). Signals were ascribed as follows: a singlet at 2.13 ppm for the acetoxy group, a singlet at 2.50 ppm for the pyridinyl methyl group, a singlet at 3.70 ppm to the methoxy group and three singlets, which are characteristic of Morita-Baylis-Hillman adducts, at 5.80, 6.43 and 6.69 ppm to the methine proton at C-3 and the two vinylic protons, respectively. The aromatic region displays two doublets at 7.04 and 7.18 ppm due to the 5'- and 3'-methine protons and a triplet at 7.54 ppm due to the 4'-methine proton, respectively. The ^{13}C NMR spectrum of compound **355** (Figure 2.30) confirms the expected presence of 13 carbon nuclei. The methyl, acetoxy and methoxy carbons resonate at 21.0, 24.4 and 51.9 ppm, respectively, the stereogenic C-3 at 74.0 ppm and the aromatic carbons at 119.1, 122.6, 136.7, 156.2 and 158.2 ppm. The methylene carbon resonates at 127.7 ppm, the vinylic (C-2) carbon at 138.4 ppm and the two carbonyl carbons at 165.6 and 169 ppm. The 400 MHz ^{1}H NMR spectrum of the regioisomeric acetate **355** (Figure 2.31) was similarly assigned and showed the absence of the

prominent Morita-Baylis-Hillman signals at 5.80, 6.43 and 6.69 ppm. A new signal emerging at 5.42 ppm accounts for the methylene protons and a new singlet at 7.79 ppm for the 3-methine proton. This is adequate confirmation that compound **355** has been transformed to the corresponding regioisomeric compound **355**. The ^{13}C NMR spectrum of compound **369** (Figure 2.32) also confirms that acetylation has occurred, effectively, *via* allylic rearrangement (S_N' mechanism), shifting the C-3 signal from 74.0 ppm in compound **355** to 136.6 ppm in compound **369**. The disappearance of the vinylic carbon at 127.7 ppm and the appearance of the methylene carbon signal at 58.9 ppm are also indicative of the new assignment. (In practice, formation of the isomeric acetate might well proceed *via* a conjugate addition-elimination sequence). The DEPT-135 spectrum of compound **369** (Figure 2.33) reinforces the fact that the reaction has occurred with rearrangement, with the appearance of four methine signals in the aromatic region and the appearance of methylene proton signals in the aliphatic region providing unambiguous evidence.

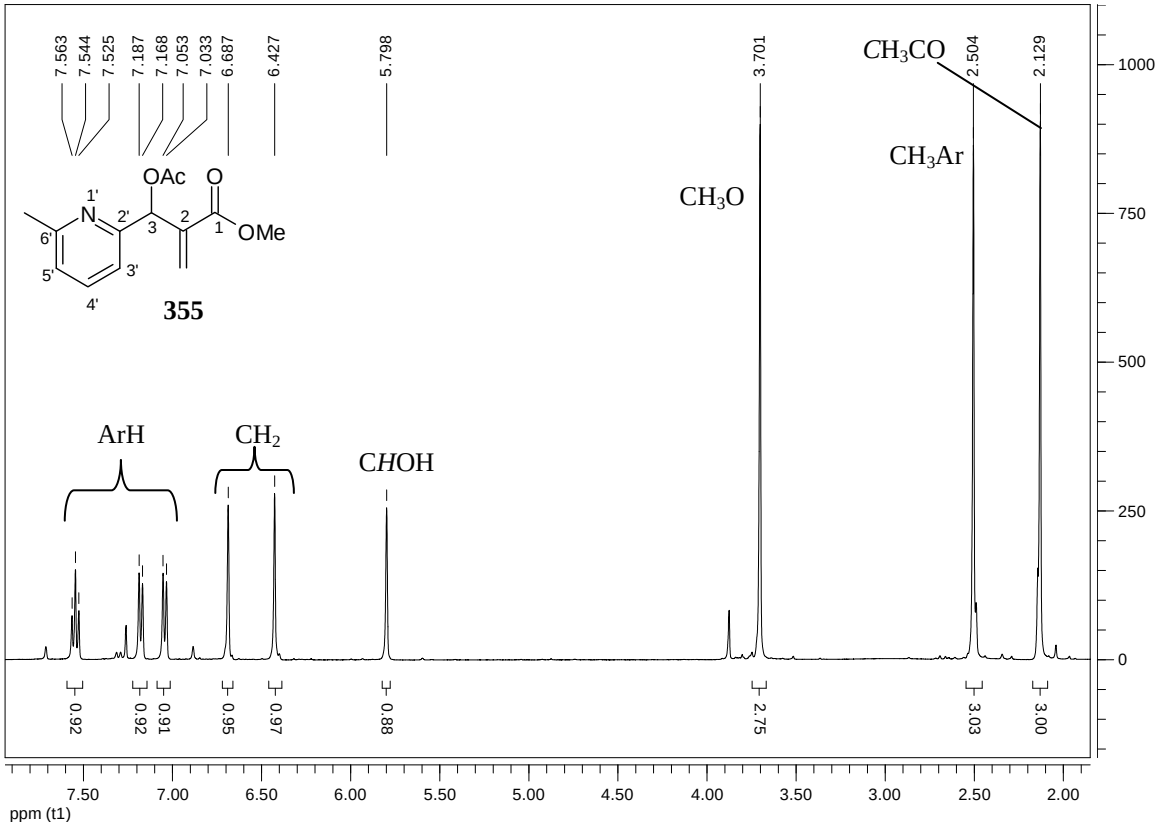


Figure 2.29. ^1H NMR spectrum of compound **355** (400 MHz; $CDCl_3$).

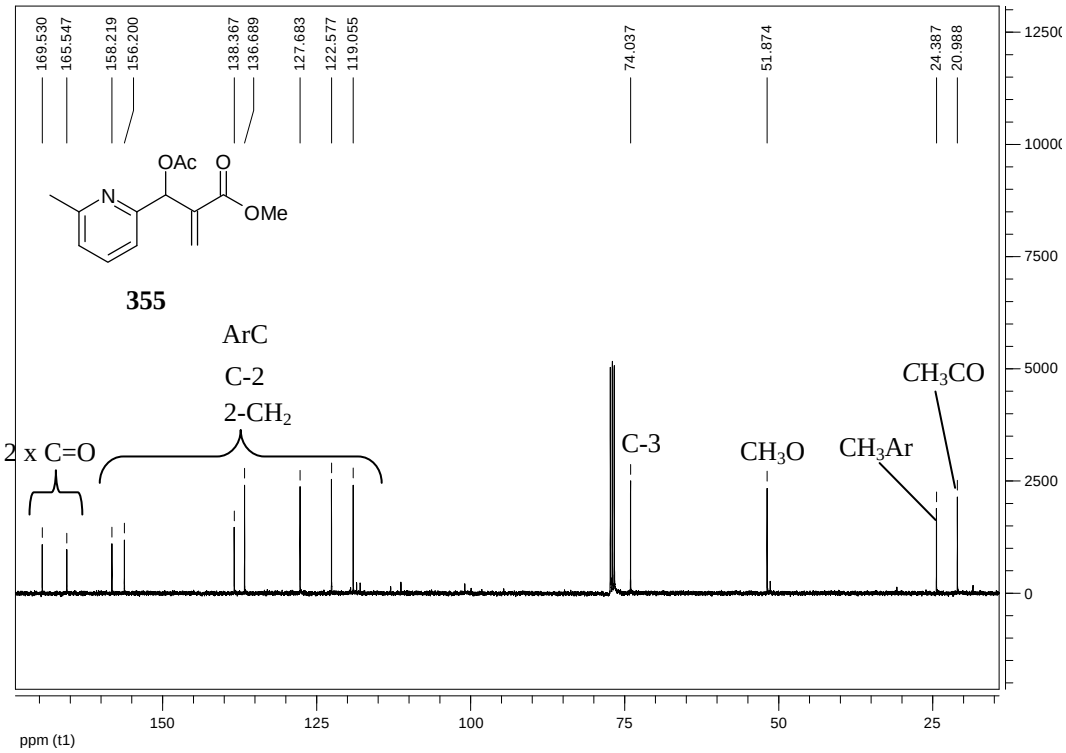


Figure 2.30. ^{13}C NMR of compound **355** (100 MHz; $CDCl_3$).

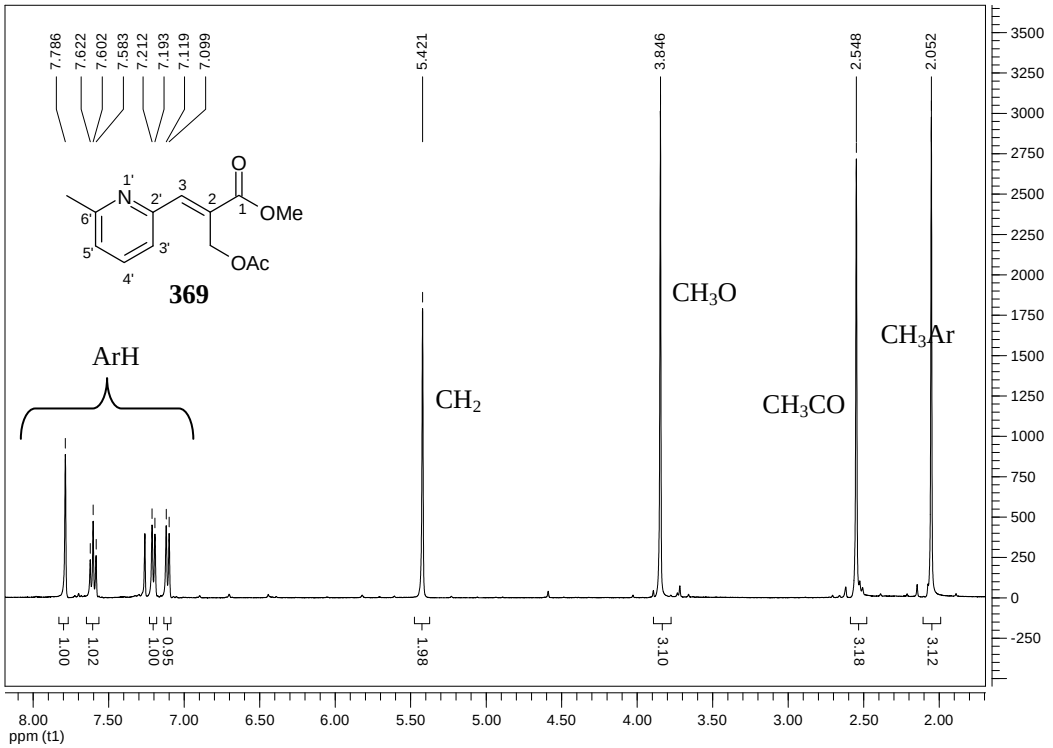


Figure 2.31. ^{1}H NMR spectrum of compound **369** (400 MHz; $CDCl_3$).

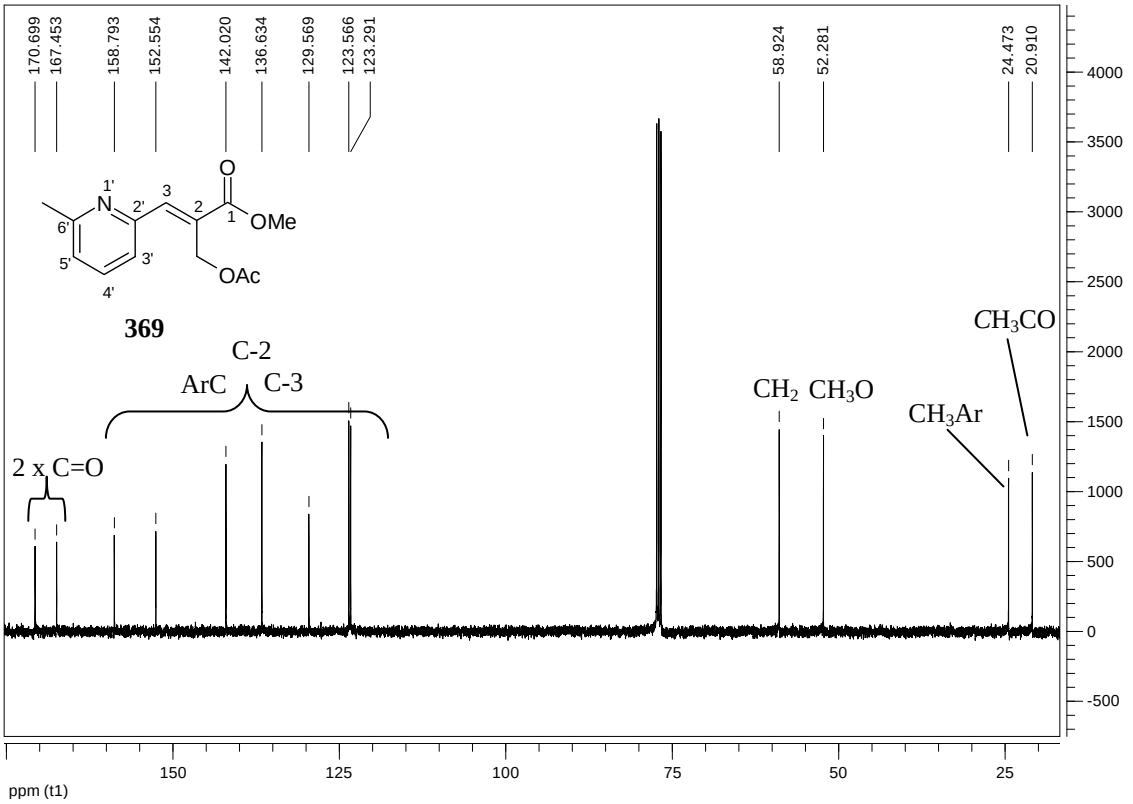


Figure 2.32. ^{13}C NMR spectrum of compound **369** (100 MHz, $CDCl_3$).

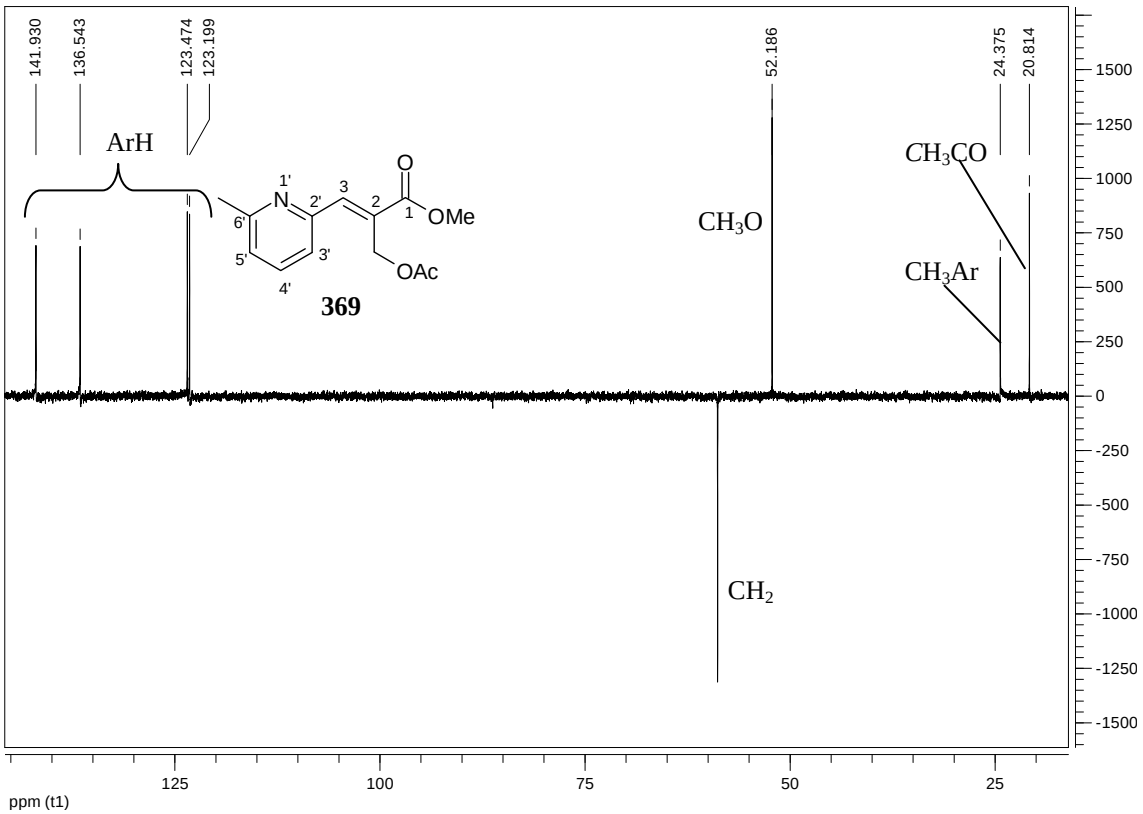


Figure 2.33. DEPT-135 spectrum of **369**. (100 MHz; $CDCl_3$).

The 400 MHz ^{1}H NMR spectrum of compound **368** (Figure 2.35), the third product isolated following acetylation of the MBH adduct **368** showed two additional signals in the aromatic region at 6.91 and 7.73 ppm, while the 100 MHz ^{13}C NMR spectrum of **368** (Figure 2.36) shows the presence of 11 carbon nuclei– 8 of them in the aromatic region and indicative of the formation of the indolizine system. The DEPT-135 spectrum of compound **368** (Figure 2.37) confirmed the presence of the methyl, methoxy and methine carbons, but the absence of any methylene carbons which provides a further indication that compound **368** is indeed an indolizine. The cyclisation of 2-pyridinecarbaldehyde derived MBH adducts to indolizines has been observed previously in our group,[107,143] and appears to be facilitated by acetylation (See Figure 2.34).

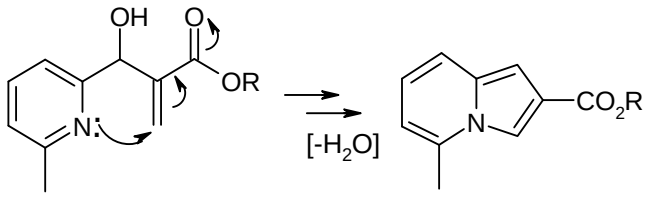


Figure 2.34. Formation of indolizines from MBH adducts.

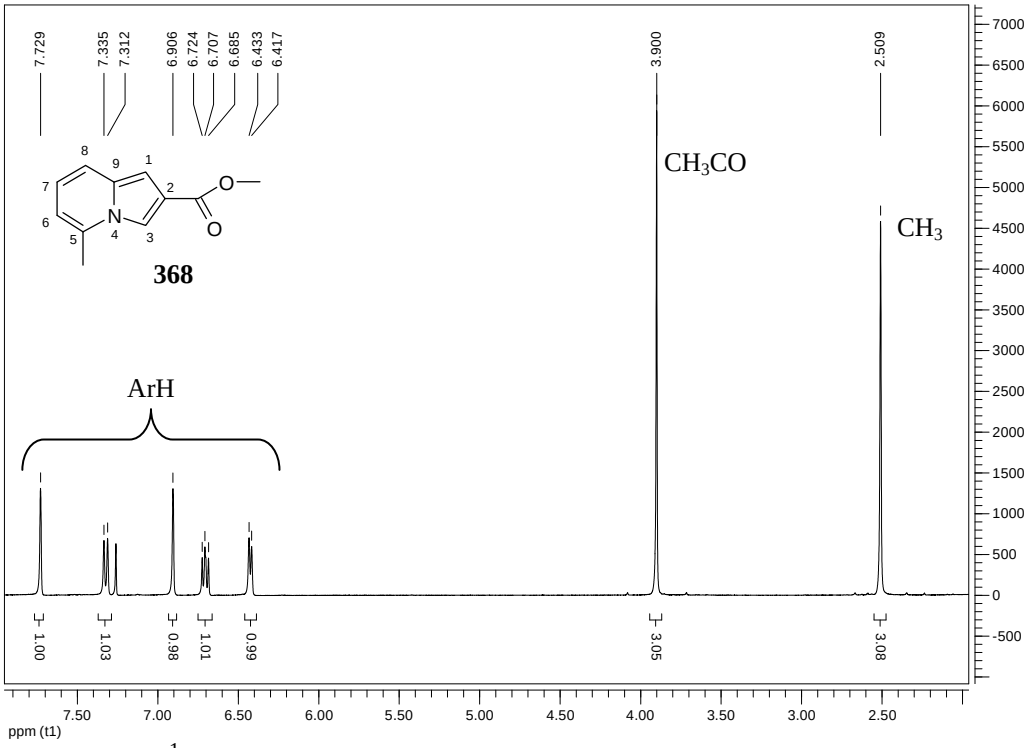


Figure 2.35. ^{1}H NMR spectrum of compound **368** (400 MHz, $CDCl_3$).

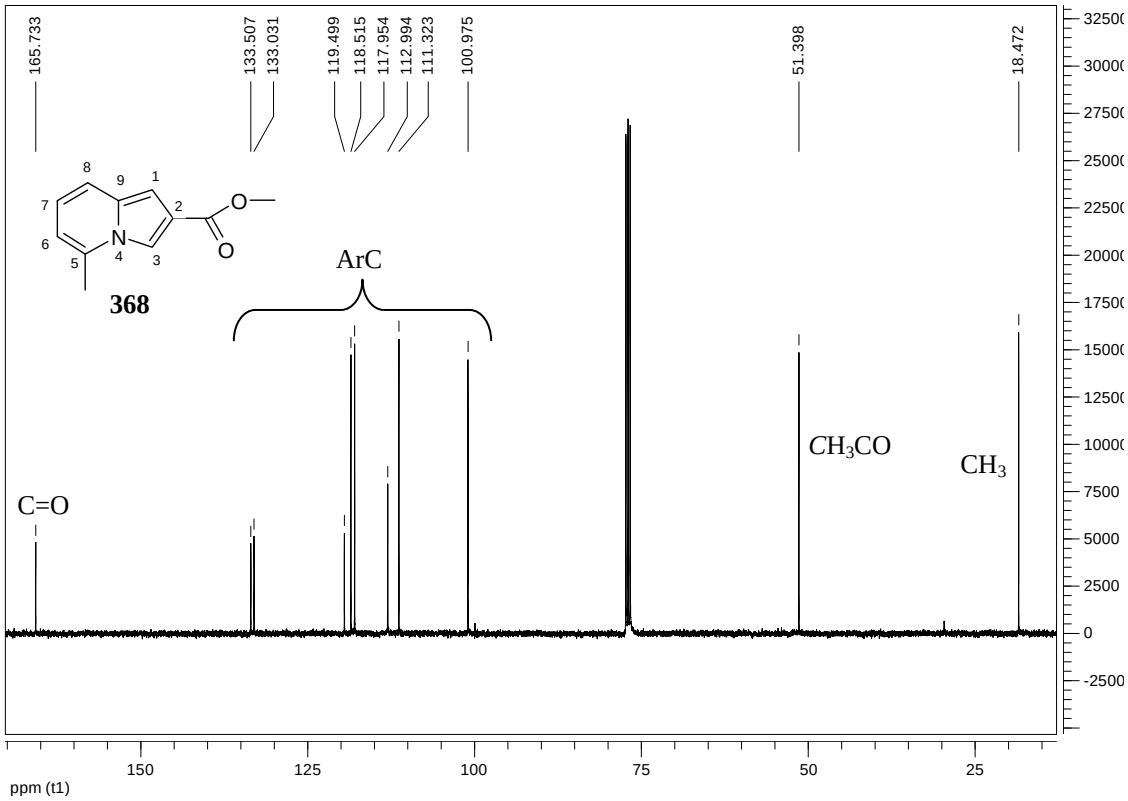


Figure 2.36. ^{13}C NMR spectrum of compound **368** (100 MHz, $CDCl_3$).

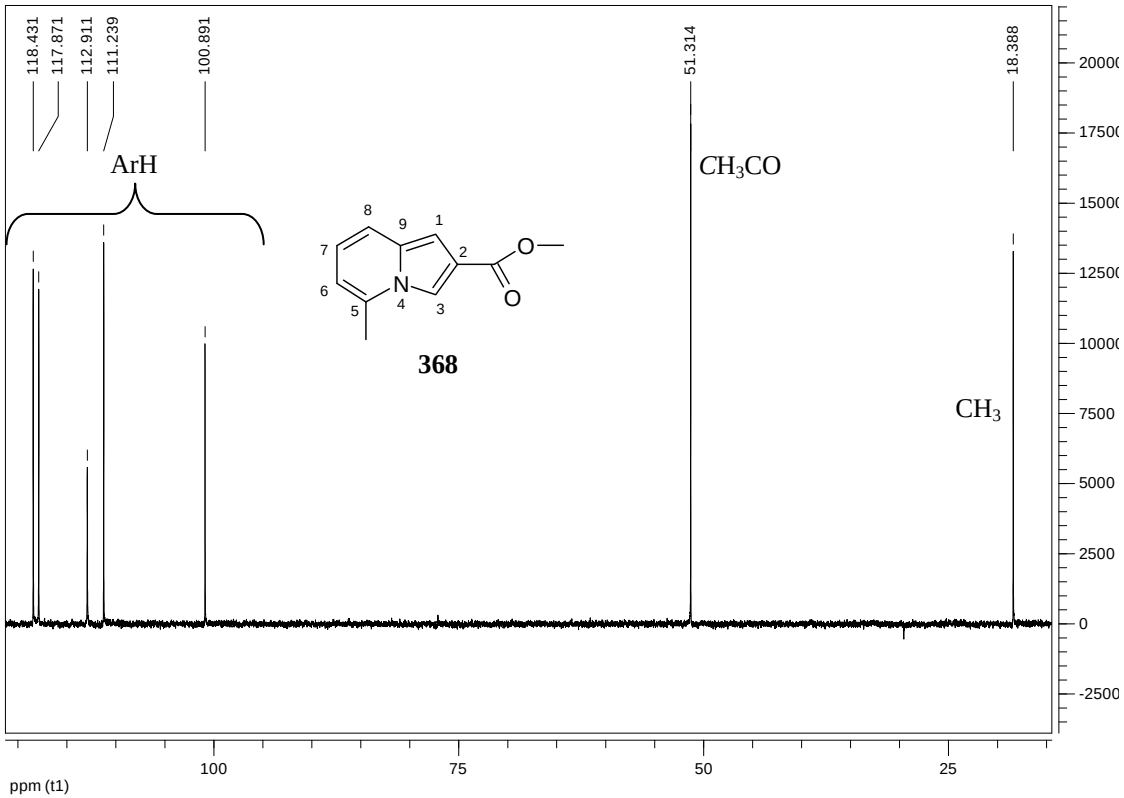
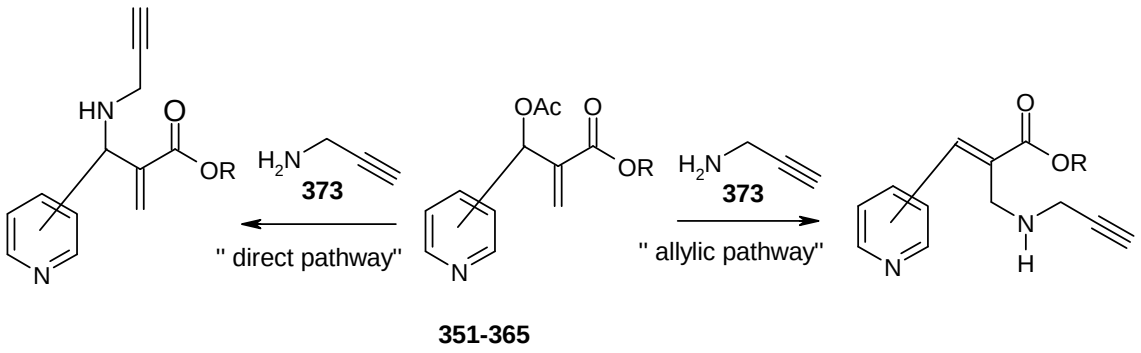


Figure 2.37. DEPT-135 spectrum of compound **368** (100 MHz; $CDCl_3$).

2.2.3. Alkynylation reactions

The next step towards the synthesis of the targeted AZT derivatives involved reaction of the acetylated MBH products with propargylamine. The acetylated MBH adducts may be expected to undergo displacement of the acetoxy groups to occur either *via* direct (S_N) or *via* allylic (S_N') substitution pathways. Given the presence of the α,β-unsaturated carbonyl moiety in the substrates **397**-**408**, the allylic pathway may well involve initial conjugate addition of the amine, followed by elimination of the acetoxy group – as suggested in a former mechanistic study of the cyclisation to indolizines conducted in the group.[107] In the present study, the allylic (conjugate addition-elimination) mechanism seemed to dominate as shown in Scheme 2.17, although one S_N product (**397**) was isolated.

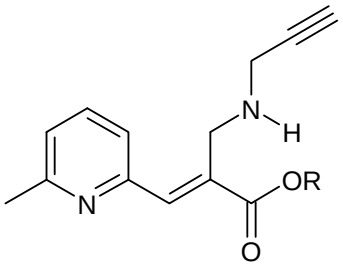


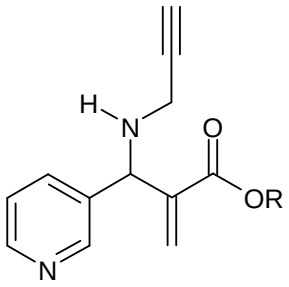
351-365

Scheme 2.17. Possible pathways for the reaction of acetylated MBH adducts **351**-**365** with propargylamine **373**.

Four of the acylated MBH adducts were treated with propargylamine **373** as a nitrogen nucleophile and to give rearranged products **374**, **376**, **385** and **387** and the S_N substituted product **389**. With the exception of compound **389**, the yields ranged from very low to excellent (See Table 2.7). Unfortunately, the products proved difficult to separate, requiring HPLC to obtain analytically pure material.

Table 2.7. Yields for the reaction of propargylamine with acetylated MBH adducts.

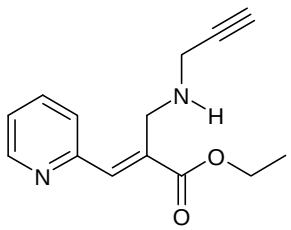




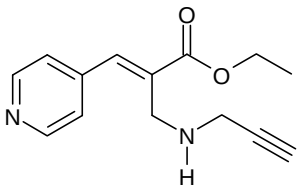
389 (Entry 4)

Entry	**Ring system**	**R**	**Product**	**Yield(%)**
1	2-Pyridinyl	Me	**374**	89
2	3-Pyridinyl	Me	**376**	58
3	3-Pyridinyl	Bu^t	**385**	54
4	3-Pyridinyl	Bu^t	**389**	trace amount
5	6-Methyl-2-pyridinyl	Bu^t	**387**	40

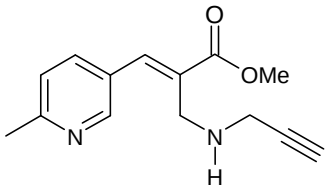
It is also important to note that considerable difficulty was encountered in attempting to purify compounds **377**, **379** and **381** below. They could only be isolated as mixtures together with their acetoxy precursors and were committed to the next step as such.



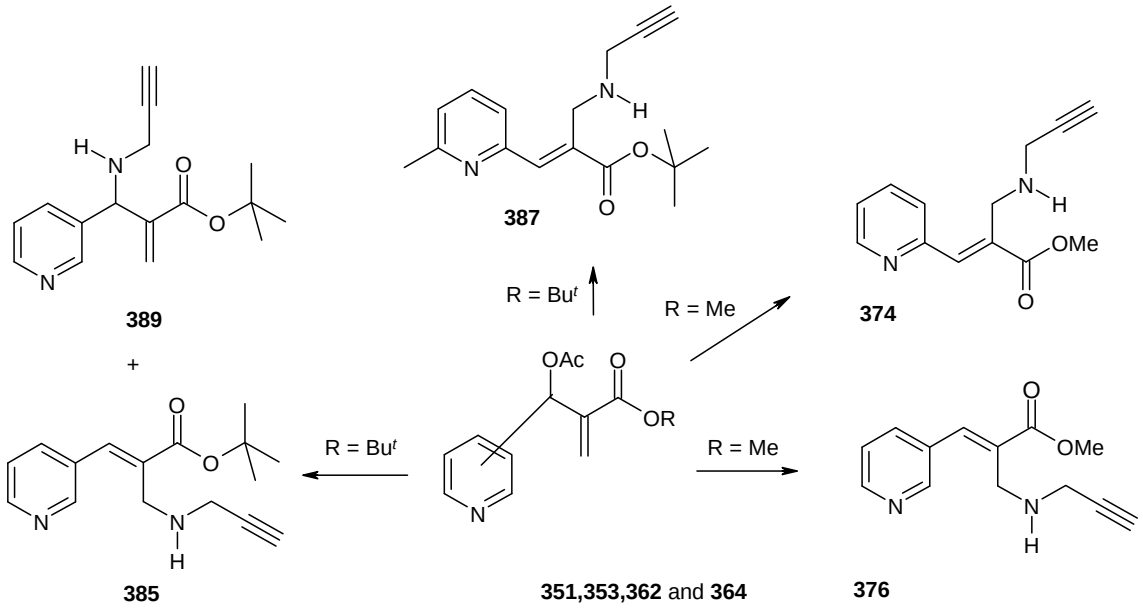
379



381



377



Scheme 2.18. Alkynylation of acetylated MBH adducts using propargylamine **373**.

The 400 MHz ^{1}H NMR spectrum of compound **374** (Figure 2.38), for example, displayed a broad singlet at 2.03 ppm due to the amine proton, a singlet at 2.23 ppm corresponding to the acetylenic proton, and signals due to methylene groups that are bound to the nitrogen atom at 3.46 and 3.63 ppm. The aromatic region showed a triplet at 7.33 ppm corresponding to the 4'-H, a singlet at 7.77 ppm due to the vinylic proton (3-H), doublets at 7.91 ppm and 8.57 ppm due to the 3'- and 5'-H protons and a singlet at 8.71 ppm due to 6'-H. Analysis of the ^{13}C NMR spectrum of compound **374** (Figure 2.39) reveals the presence of thirteen signals. The carbon signals at 38.0 and 44.8 ppm are due to carbon atoms directly linked to the nitrogen atom. The methoxy carbon signal is at 52.2 ppm and the signals at 71.7 and 81.5 ppm are due to the two acetylenic carbon nuclei. The aromatic carbon nuclei are found in the region 123.3-150.5 ppm and the carbonyl carbon resonates at 167.8 ppm. The DEPT-135 spectrum shows the presence of two methylene groups, one methyl group, five methine carbons and two signals at 71.7 and 81.5 ppm as if there were two acetylenic protons. The presence of these two signals is a very interesting phenomenon for this type of compound and is attributed to the large 2-bond coupling of the acetylenic proton with the non-terminal acetylenic carbon atom.

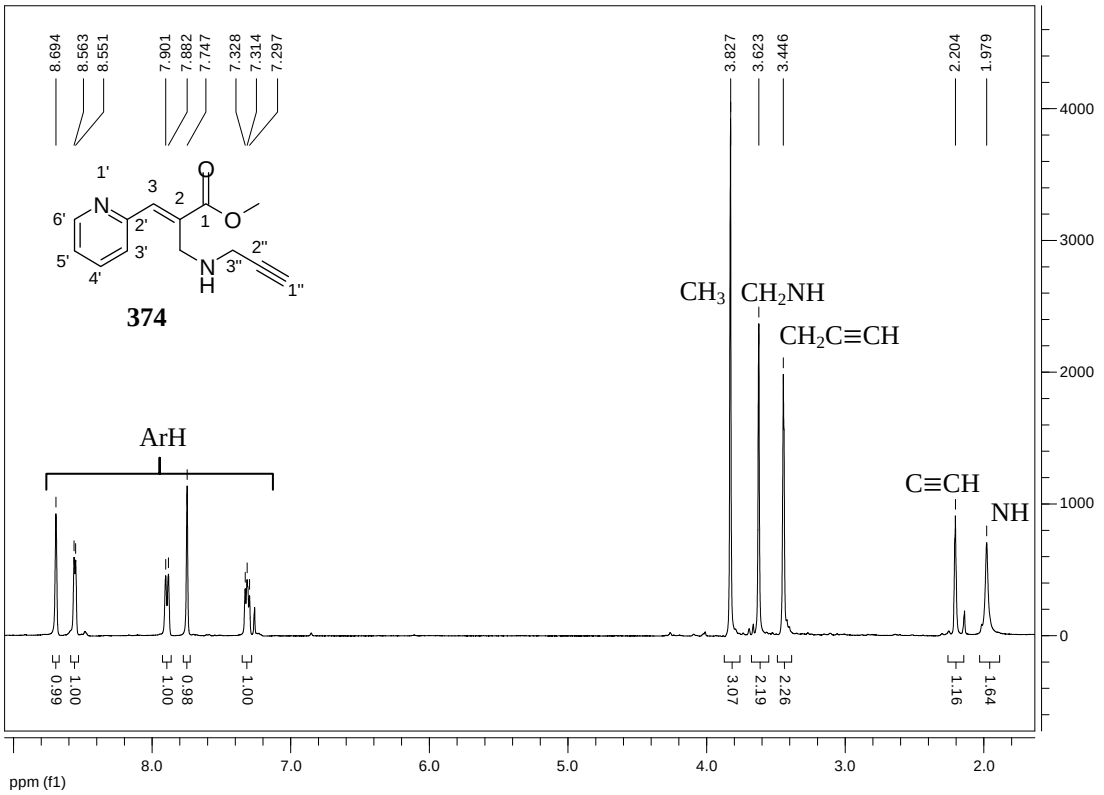


Figure 2.38. ^{1}H NMR spectrum of compound **374** (400 MHz, $CDCl_3$).

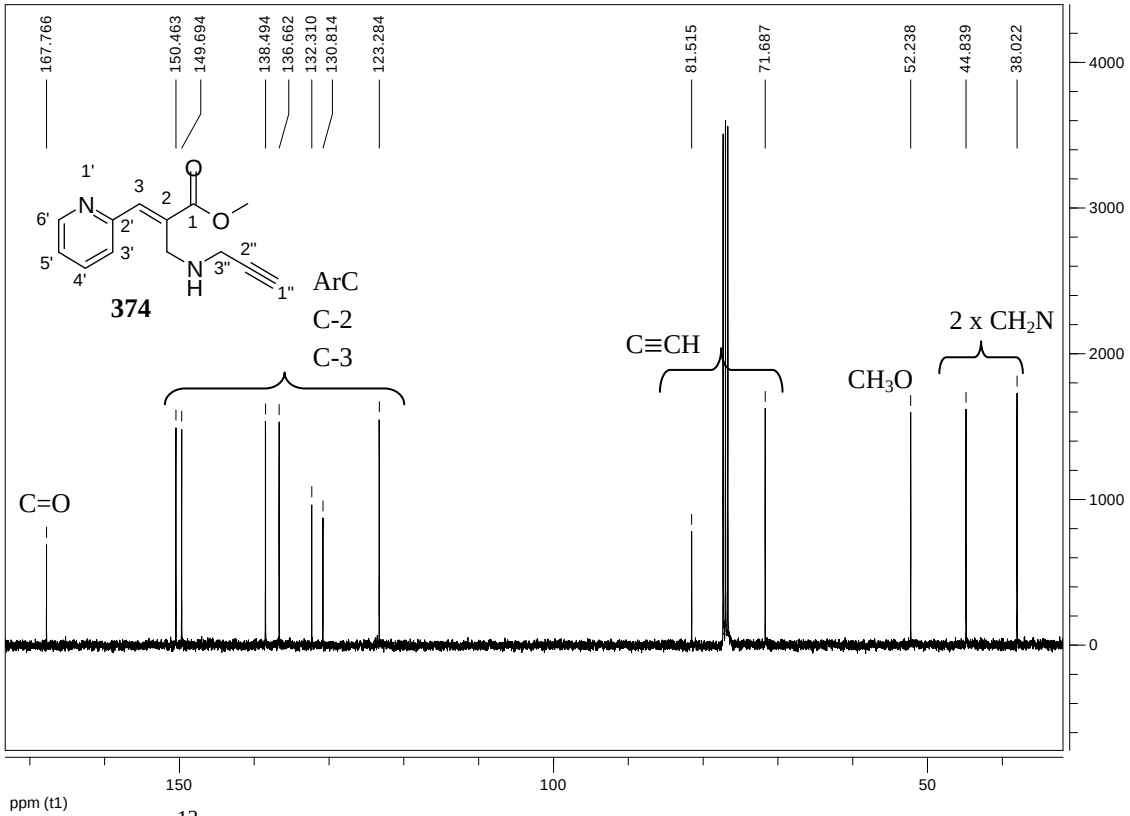
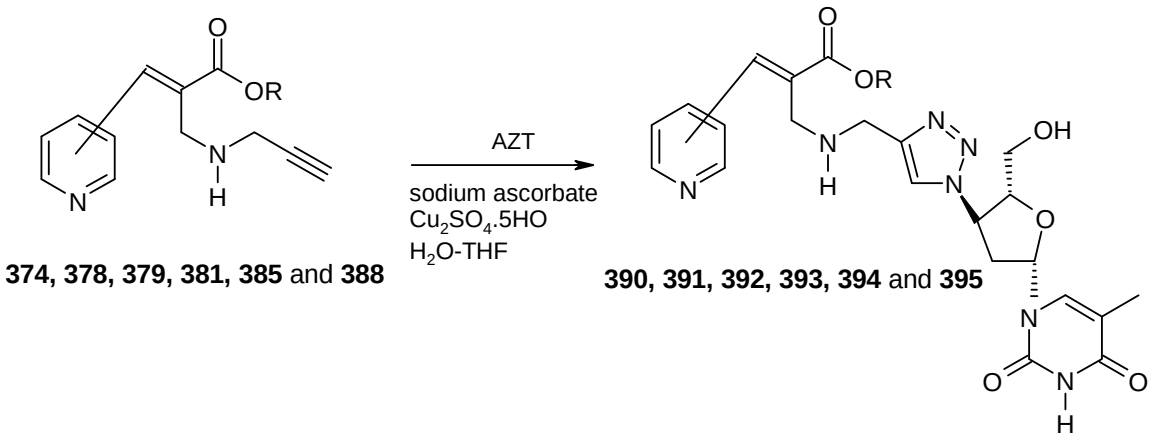


Figure 2.39. ^{13}C NMR of compound **374** (100 MHz, $CDCl_3$).

2.2.4. The 'Click Reaction'

Our group has begun to make use of 'Click Chemistry' in the construction of AZT conjugates as potential HIV-1 PR/RT and IN/RT inhibitors.[139] In this chemistry the alkynylated precursors are treated with azothymidine (AZT) in the presence of copper(II) sulfate (Cu_2SO_4) and ascorbic acid, which aid the reduction of Cu(II) to Cu(I) (Scheme 2.19). The resulting novel AZT derivatives which possess a triazole ring characteristic of this family of Click chemistry products, were isolated in moderate to excellent yield (55-91%) and the yields are shown in Table 2.8. These compounds differed from those prepared previously as they all contain the heteroaromatic pyridine nucleus rather than a benzene ring.

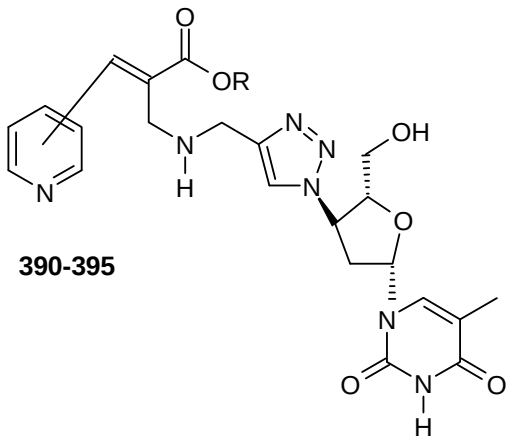


374, 378, 379, 381, 385 and **388**

390, 391, 392, 393, 394 and **395**

Scheme 2.21. The 'Click Reaction' resulting in heterocyclic AZT analogues **390**, **391**, **392**, **393**, **394** and **395**.

Table 2.8. Yields of AZT derivatives **390**, **391**, **392**, **393**, **394** and **395**.



390-395

Entry	**Ring system**	**R**	**Product**	**Yield (%)**
1	2-Pyridinyl	Et	**392**	65
2	4-Pyridinyl	Et	**393**	55
3	3-Pyridinyl	Bu^t	**394**	59
4	6-Methyl-2-pyridinyl	Bu^t	**395**	71
5	2-Pyridinyl	Me	**390**	91
6	6-Methyl-2-pyridinyl	Me	**391**	71

Analysis of the 1-D and 2D-NMR spectra of compound **392** permitted unambiguous identification. Thus, the ^{1}H NMR spectrum (Figure 2.44, p104) reveals a triplet at 1.26 ppm which is due to the ester methyl group, a singlet at 1.85 ppm corresponding to the methyl group attached to the purine ring. The aromatic region reveals signals corresponding to protons in the pyridine, triazole and purine rings and the remaining protons are assigned as indicated in Figure 2.44. Examination of the ^{13}C NMR spectrum (Figure 2.45, p105) shows, as expected, the presence of 24 carbon nuclei which have been indicated in Figure 2.45. The DEPT-135 spectrum (Figure 2.46, p105) confirmed the presence of two methyl goups, five methylene groups and ten methine carbons. The structural elucidation of the remaining Click reaction products was also accomplished in

a similar manner. These compounds, which are all new were also characterised by high resolution mass spectrometry and subjected to detailed mass fragmentation analysis. The capacity of the AZT conjugates to bind to the HIV-1 integrase and reverse transcriptase enzymes was explored by *in silico* docking of compound **392** into the respective active sites using the corresponding Protein Data Bank structures and the AUTODOCK 4 programme.[144,145] The results are illustrated in Figures 2.40-2.43. It is apparent from Figure 2.40 that the docked ligand **392** fits acceptably within the active site of the 1QS4 integrase enzyme and also shows some degree of potential hydrogen-bonding interactions with amino acid residues in the surrounding vicinity (Figure 2.41). Following our dual-action approach, the ligand **392** was also docked successfully into the active site of the 1IKW reverse transcriptase enzyme as illustrated in Figure 2.42 and also evident are the hydrogen-bonding interactions with LYS 101 and 103 and a *pi* stacking interaction with TYR 181 (Figure 2.43). The predicted inhibition for RT far exceeds that for IN (2.24 µM compared to 376 µM). It is expected that the AZT conjugate will be subjected, in due course, to bioassays involving inhibition of HIV-1 integrase and reverse transcriptase enzymes.

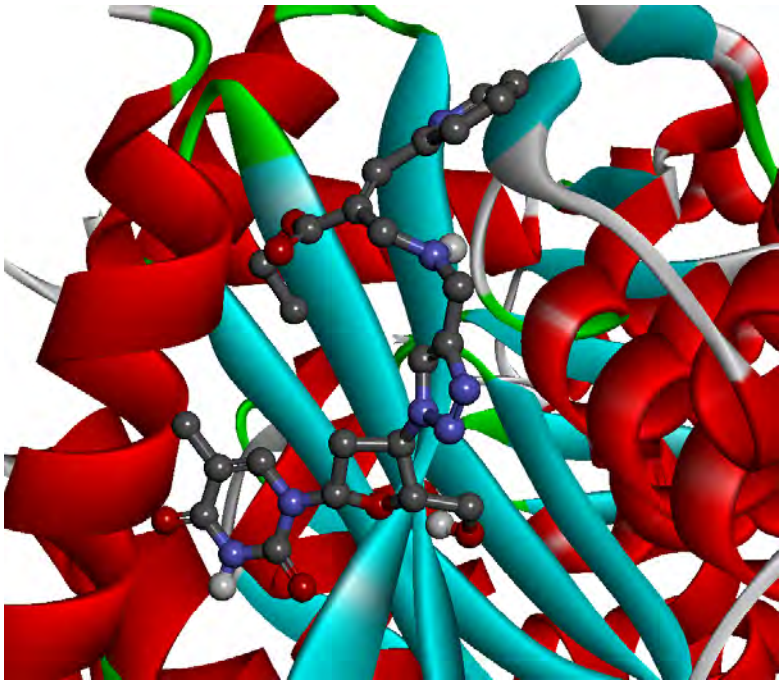


Figure 2.40. Ribbon representation of 1QS4 HIV-1 Integrase enzyme depicting ligand **392** in the active site.

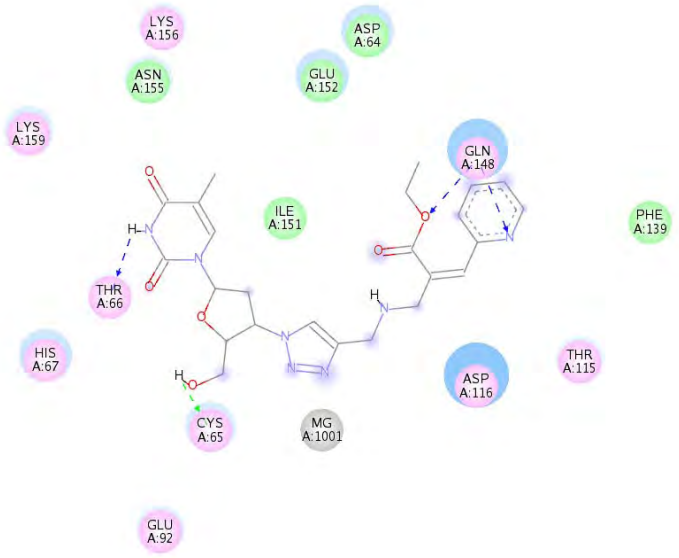


Figure 2.41. Hydrogen-bonding interactions between ligand **392** and the amino acid residues of 1QS4 HIV-1 Integrase enzyme.

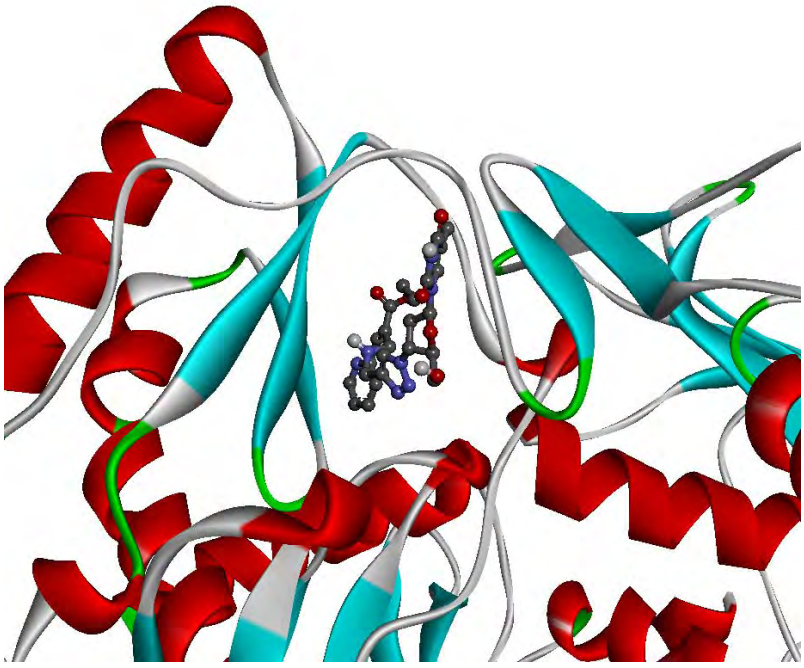


Figure 2.42. Represantation of 1IKW HIV-1 Reverse Transcriptase enzyme with ligand **392** in the active site.

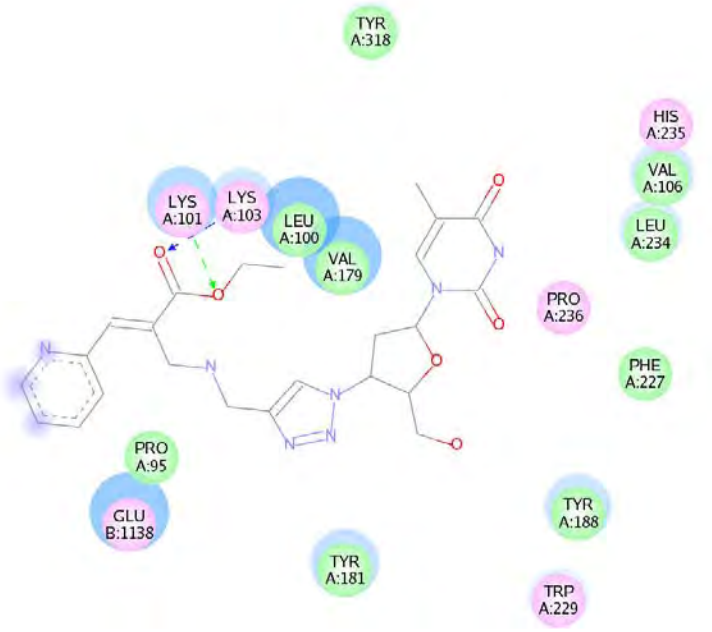


Figure 2.43. Hydrogen-bonding interactions between ligand **392** and the amino acid residues of 1IKW reverse transcriptase enzyme.

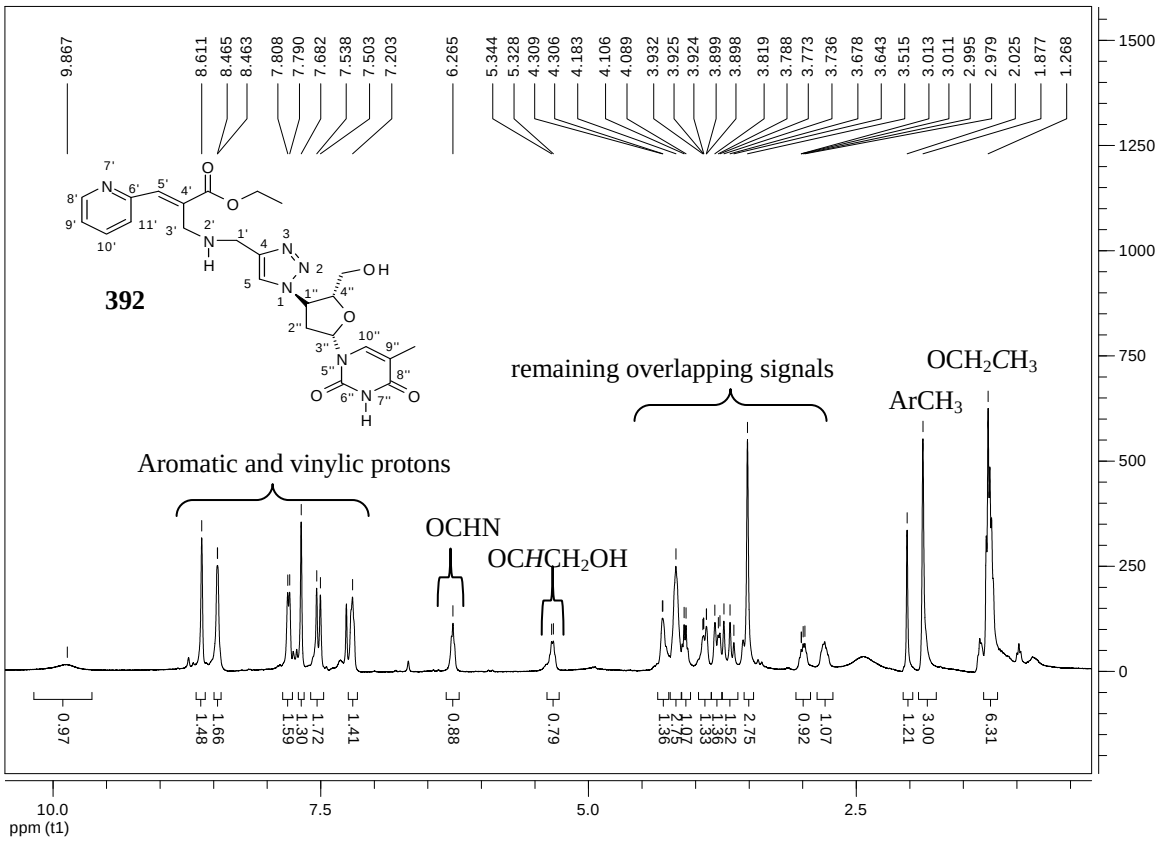


Figure 2.44. ^{1}H NMR spectrum of compound **392** (400 MHz, $CDCl_3$).

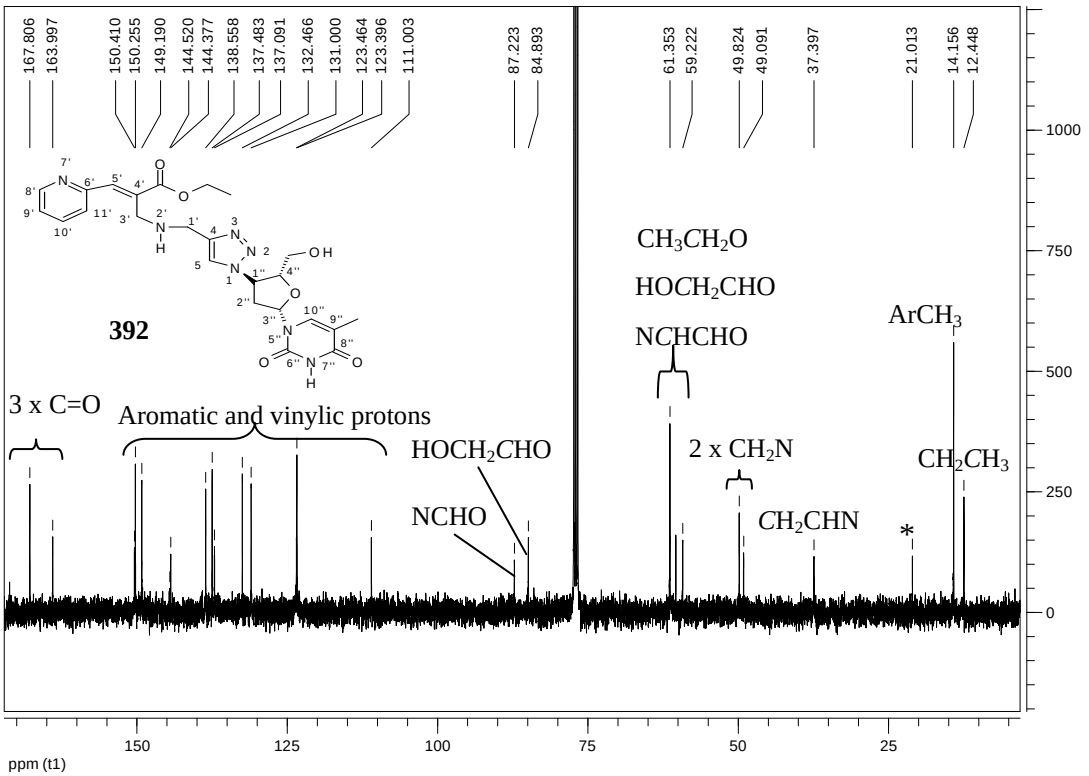


Figure 2.45. ^{13}C NMR spectrum of compound **392** (100 MHz; $CDCl_3$). * = impurity

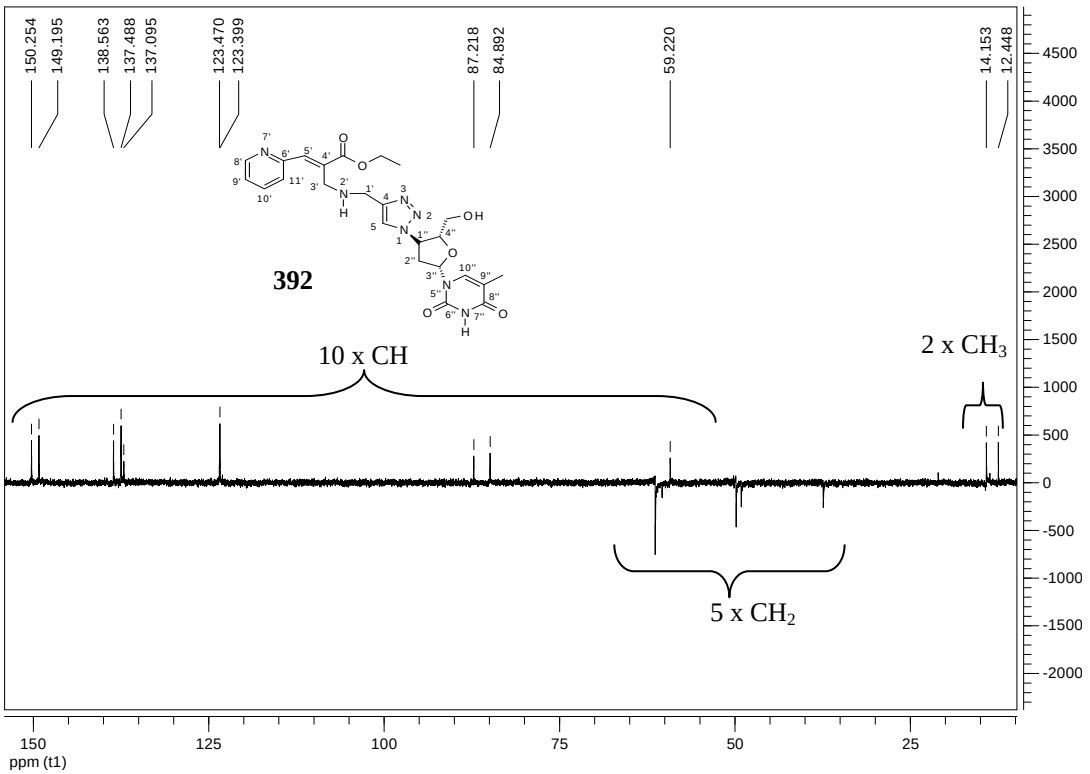


Figure 2.46. DEPT-135 spectrum of compound **392** (100 MHz; $CDCl_3$).

2.3. ELECTROSPRAY IONISATION MASS SPECTROMETRIC STUDIES

Mass spectrometric fragmentation studies of selected camphor-based acrylate ester derivatives and heterocyclic 'cinnamate-like' 3'-azido-3'-deoxythyminidine (AZT) conjugates were carried out using electrospray ionisation- mass spectrometry (ESI/MS).

2.3.1. Mass Spectrometric Studies of Camphor-derived Acrylates

2-exo-*Acryloyloxy*-N-*(benzyl)bornane-10-sulfonamide* **297**

The ESI mass spectrum of compound **297** reveals a base peak at *m/z* 306.1537 while the protonated molecular ion (MH^+) **396A** is responsible for the peak at *m/z* 378.1734. Direct fragmentation of the protonated molecular ion **396A** was explored using the ESI-MS/MS technique and revealed that the ESI positive ion mass spectral fragmentation (Figure 2.47) of compound **396A** involves the six pathways shown in Scheme 2.22.

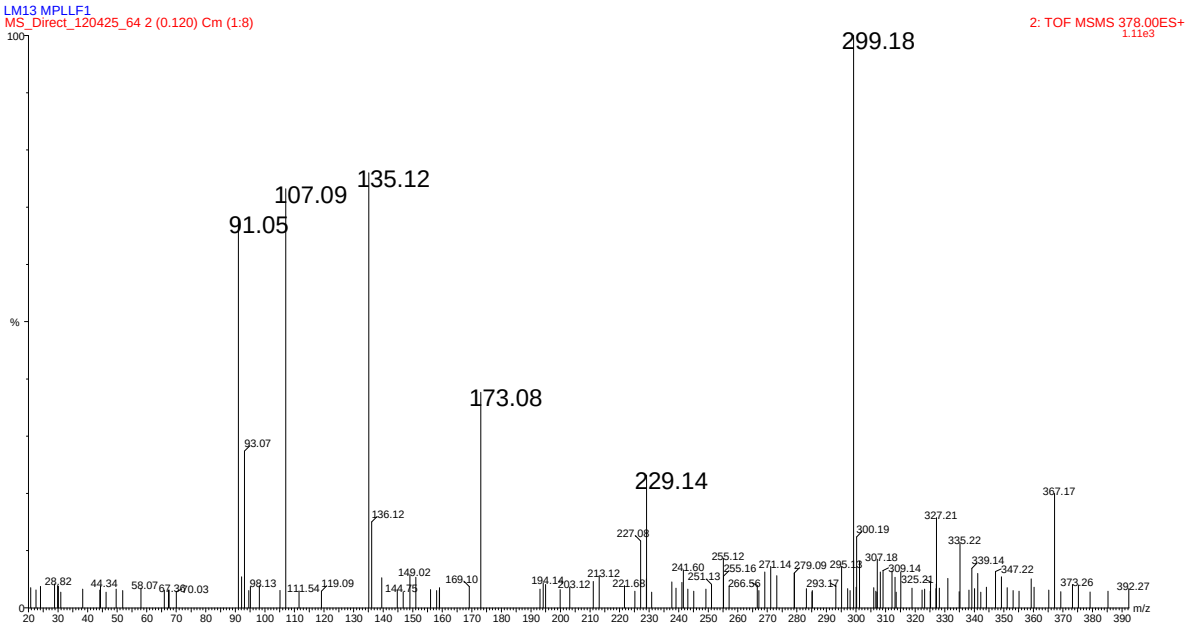
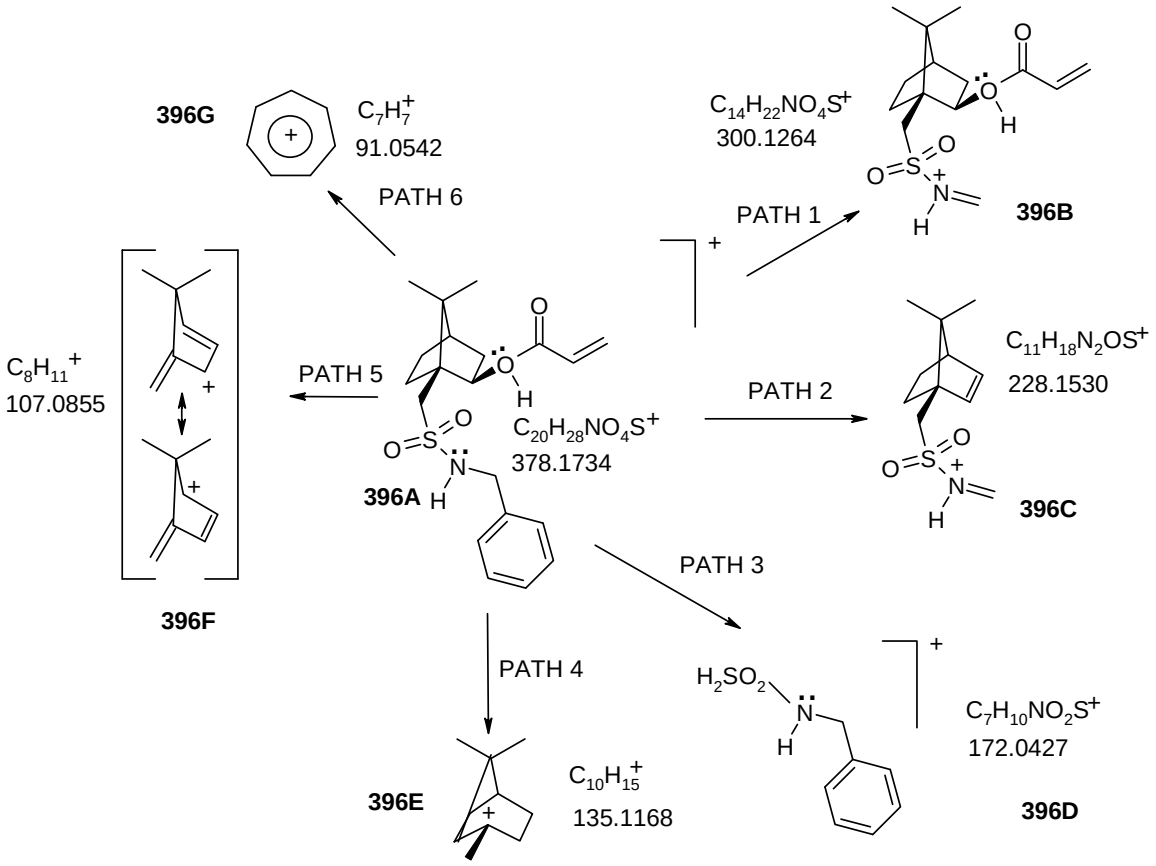
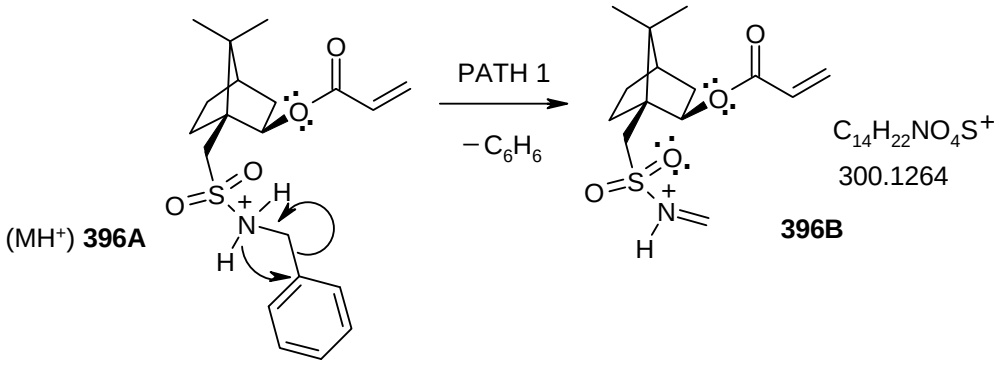


Figure 2.47. ESI-MS/MS spectrum of protonated molecular ion **396A**.



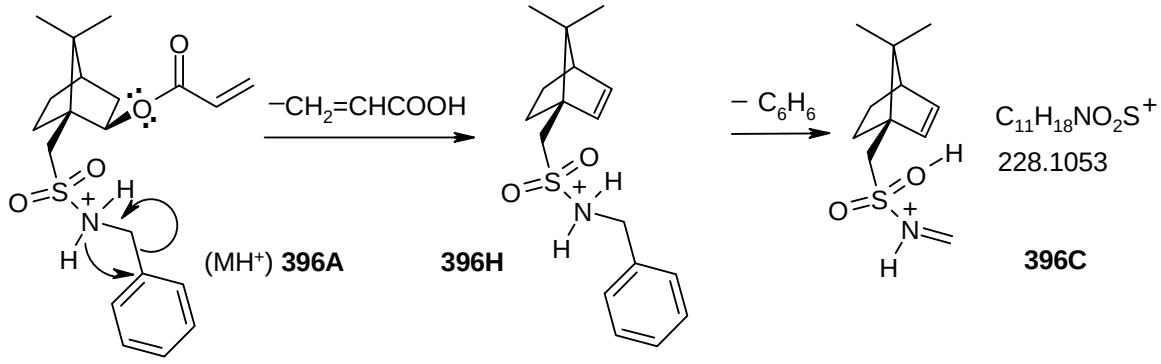
Scheme 2.22. Electrospray MS fragmentation pathways of the protonated molecular ion **396A** of compound **297**.

All six pathways appear to arise from initial protonation to afford the MH^+ cation **396A**. Thus, in Pathway 1, fission of the phenyl-methylene bond and transfer of hydrogen from the nitrogen affords benzene and the iminium cation **396B** (*m/z* = 300.1264) as illustrated in Scheme 2.23.



Scheme 2.23. Pathway 1 showing formation of the iminium cation **396B**.

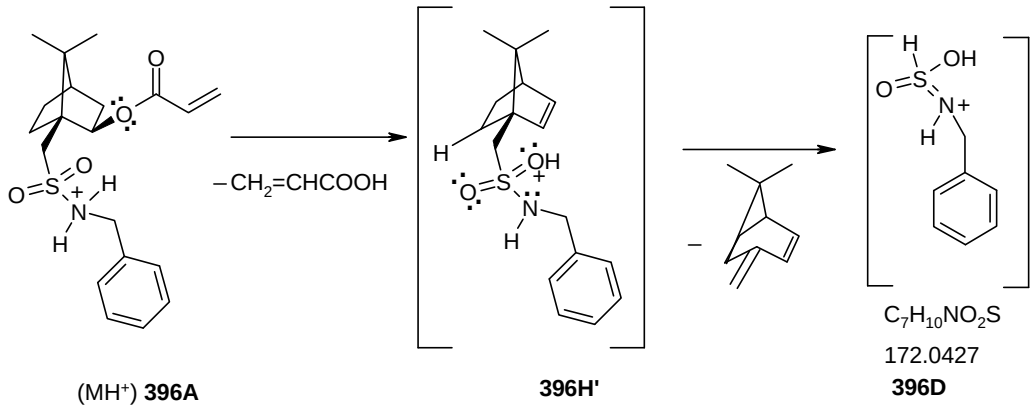
Loss of acrylic acid from the MH^+ cation **396A** is proposed to afford the cationic bornenyl species 3**96H** or **396H'** which served as common intermediates in Paths 2, 3, 4 and 5. Pathway 2 then follows the pattern observed in Pathway 1 with loss of benzene leading to the bornenyl iminium cation **396C** (*m/z* = 228.1530) (Scheme 2.24).



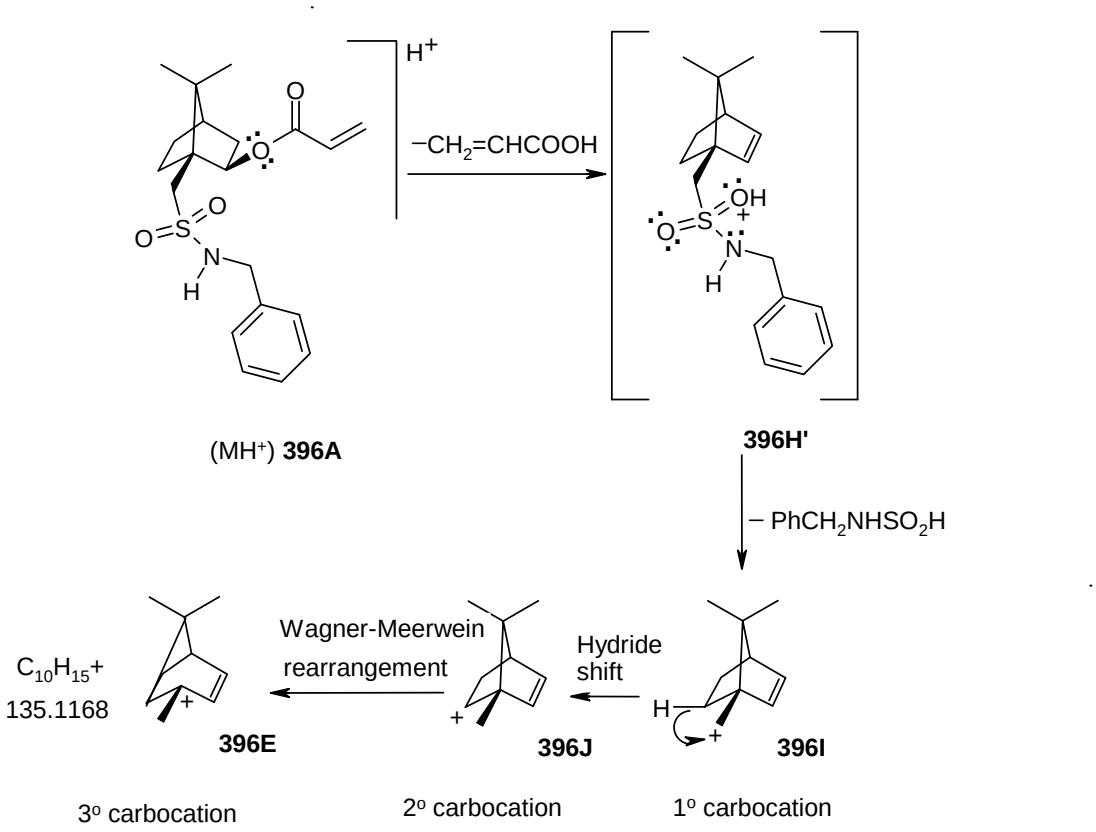
Scheme 2.24. Pathway 2 showing generation of fragment **396C**.

In Pathway 3, (Scheme 2.25), which involves the *O*-protonated analogue **396H'**, hydrogen transfer and loss of a rearranged, neutral terpenoid compound affords the resonance-stabilized cation **396D** (*m/z* = 172.0427). In Pathway 4, loss of benzylaminosulfonic acid from the same *o*-protonated cation **396H'** affords the primary carbocation **396I** which is expected to undergo sequential rearrangement to the secondary carbocation **396J** and finally to the tertiary carbocation **396E** which is presumed to be responsible for the peak at *m/z* = 135.1168. Pathway 5 similarly appears to involve the *O*-

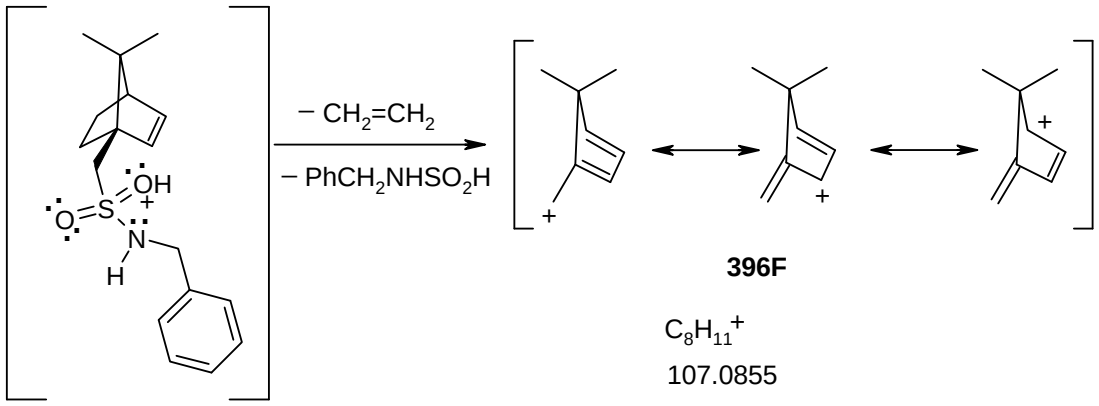
protonated species **396H**. Tandem loss of benzylaminosulfonic acid and ethylene (*via* a *retro*-Diels Alder reaction) then accounts for the formation of the resonance-stabilized allylic cationic fragment **396F** (*m/z* = 107.0855).



Scheme 2.25. Pathway 3 showing formation of fragment **396D**.

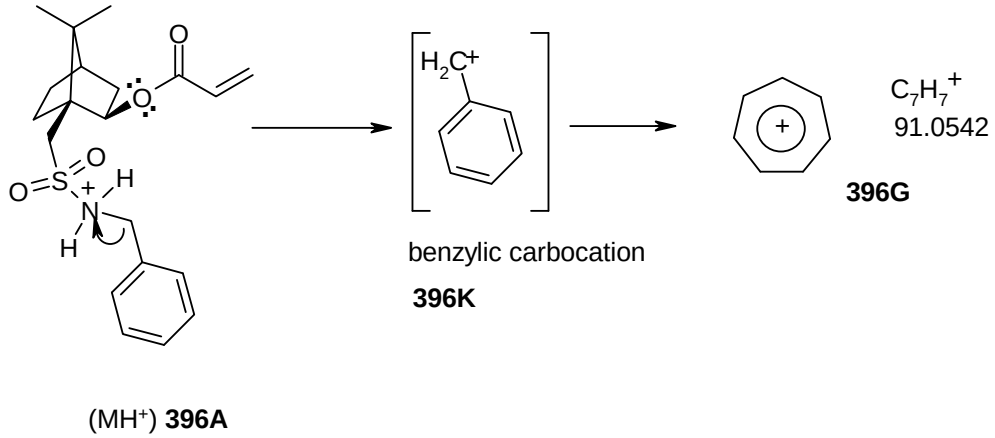


Scheme 2.26. Pathway 4 showing ESI-MS/MS fragmentation of molecular ion **396A** to fragment **396E**.



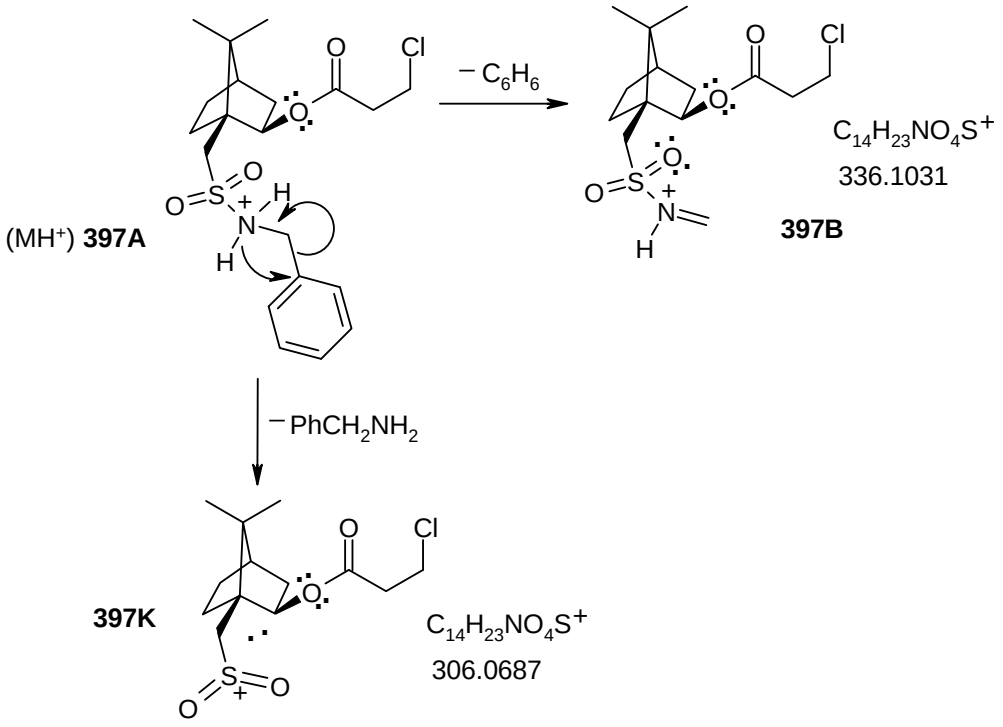
Scheme 2.27. Pathway 5 showing resonance-stabilized allylic cation **396F**.

Pathway 6 is presumed to involve heterolytic fission of the MH^+ cation **396A** to afford the aromatic tropylium cation **396F** (*m/z* = 91.0542).



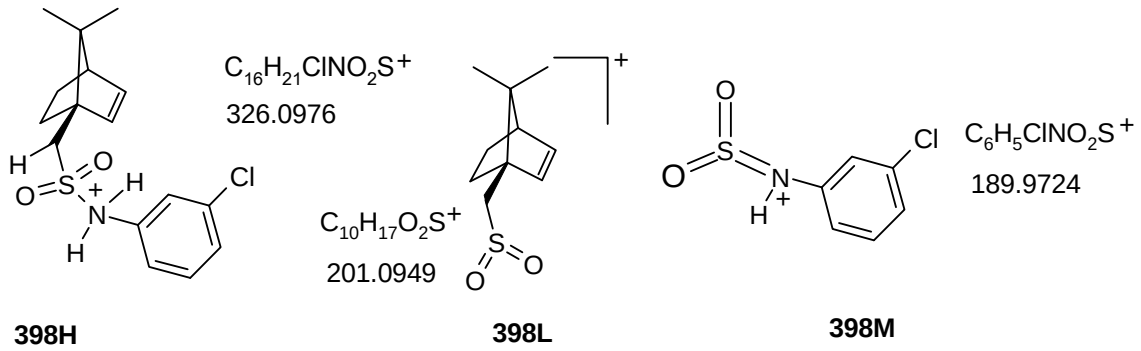
Scheme 2.28. Pathway 6 showing formation of the tropylium ion **396G**.

The hydrochlorinated analogue **299** of compound **297** displayed similar fragmentation patterns as those of compound **297** and gave rise to the fragments **396C**, **396D**, **396E**, **396F** and **396G** as seen in Scheme 2.22 above. The only significant fragments that are different are the iminium cation **397B** (Scheme 2.29), which contains the chloropropanoyl moiety and corresponds to fragment ion **396B** (Scheme 2.22) and the base peak at *m/z* = 306 (**397K**) which arises from loss of benzylamine from the protonated molecular ion as shown in Scheme 2.29.

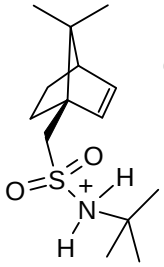


Scheme 2.29. Significant fragment ions **397B** and **397K** from the hydrochlorinated analogue of **299**.

The mass spectrum of 2-*exo*-acryloyloxy-N-3-(chlorophenyl)bornane-10-sulfonamide **301** displays a base peak at *m/z* 326.0982 and a protonated molecular ion peak **396A** at *m/z* 398.1195. Fragment ions **396C**, **396E** and **396F** were also encountered here. The only additional peaks to note in the fragmentation of compound **301** are the base peak at *m/z* 326.0982 **398H** and the cations **398L** and **398M** shown below.

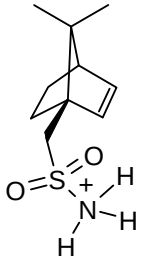


The mass spectrum of 2-*exo*-[(acryloyl)oxy]-N-(t-butyl)bornane-10-sulfonamide **320** showed a base peak at *m/z* 216.1059 and the protonated molecular ion peak **399** at *m/z* 344.1904. The mass spectral fragmentation patterns of compound **320** were similar to those described in the above cases, but peaks at *m/z* 272.1684, 216.1059, 288.1270 and 136.0432 corresponding to fragments **400H**, **400N**, **400O** and **401** at were the only additions.



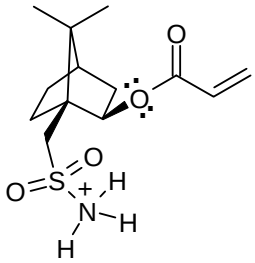
$C_{14}H_{26}NO_2S^+$
272.1684

400H



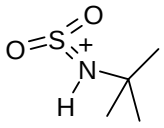
$C_{10}H_{18}NO_2S^+$
216.1058

400N



$C_{13}H_{22}NO_4S^+$
288.1270

400O



$C_4H_{10}NO_2S^+$
136.0432

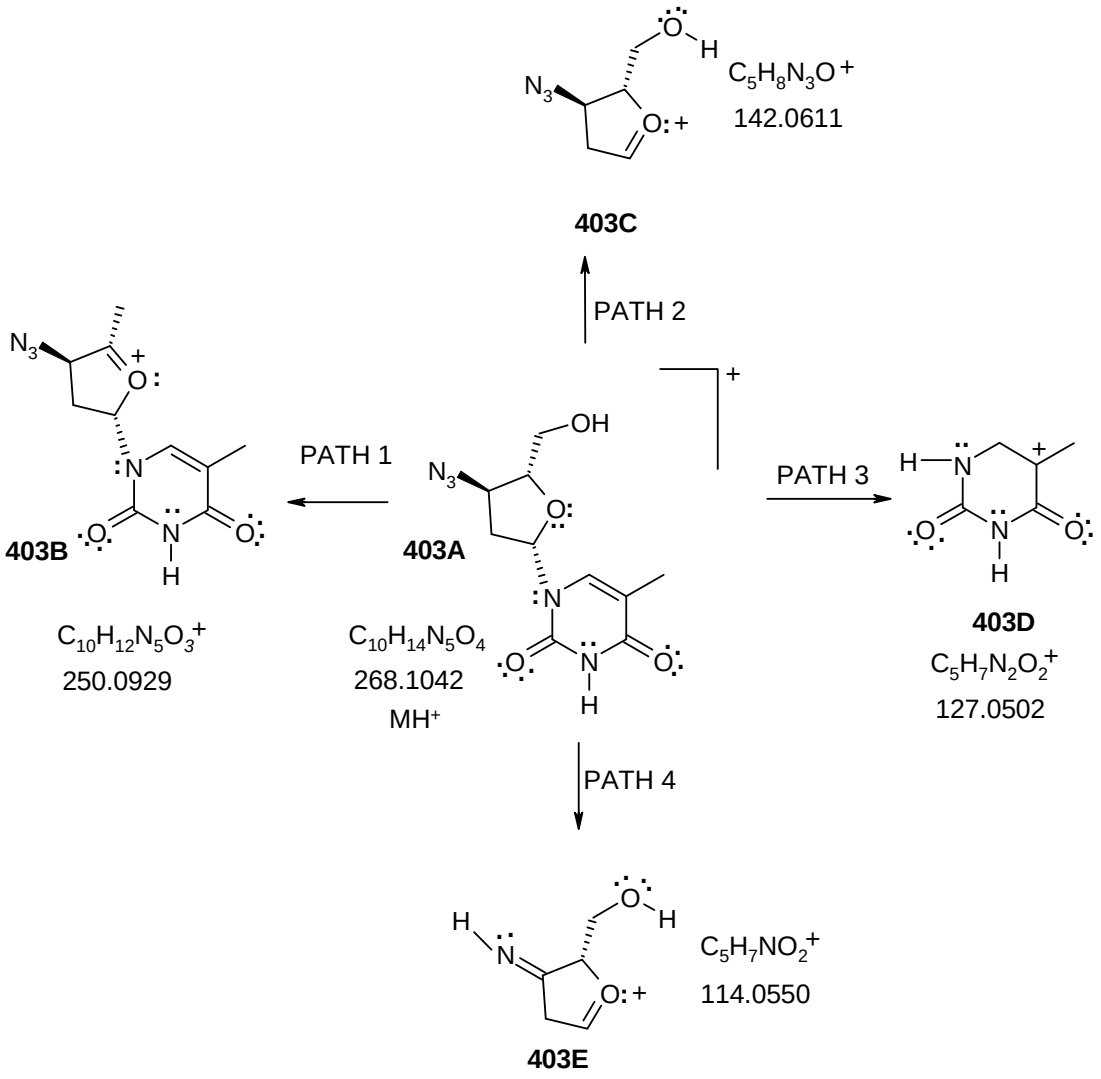
401

2.3.2. Electrospray Mass Spectrometric Studies of AZT 402 and its Derivatives

Having prepared the pyridinyl-AZT conjugates it was decided to undertake a detailed study of their positive ion electrospray fragmentation. It was also thought that similar analysis of AZT **402** itself might be informative in interpreting the fragmentation patterns of the conjugates.

The positive ion electrospray spectrum of AZT **402** in Figure 2.46 shows a base peak at *m/z* at 268.1042, which also happens to be the protonated molecular ion peak **403A**. The

observed fragmentation pattern (Figure 2.48) appears to comprise the four major pathways shown in Scheme 2.30.



Scheme 2.30. AZT **402** MS fragmentation pathways.

In pathway 1, the protonated molecular ion **403A** loses water to generate a primary carbocation which undergoes a 1,2-hydride shift to form the more stable 3^0 carbocation/oxonium ion **403B** responsible for the peak at *m/z* 250.0929 as shown in Scheme 2.31.

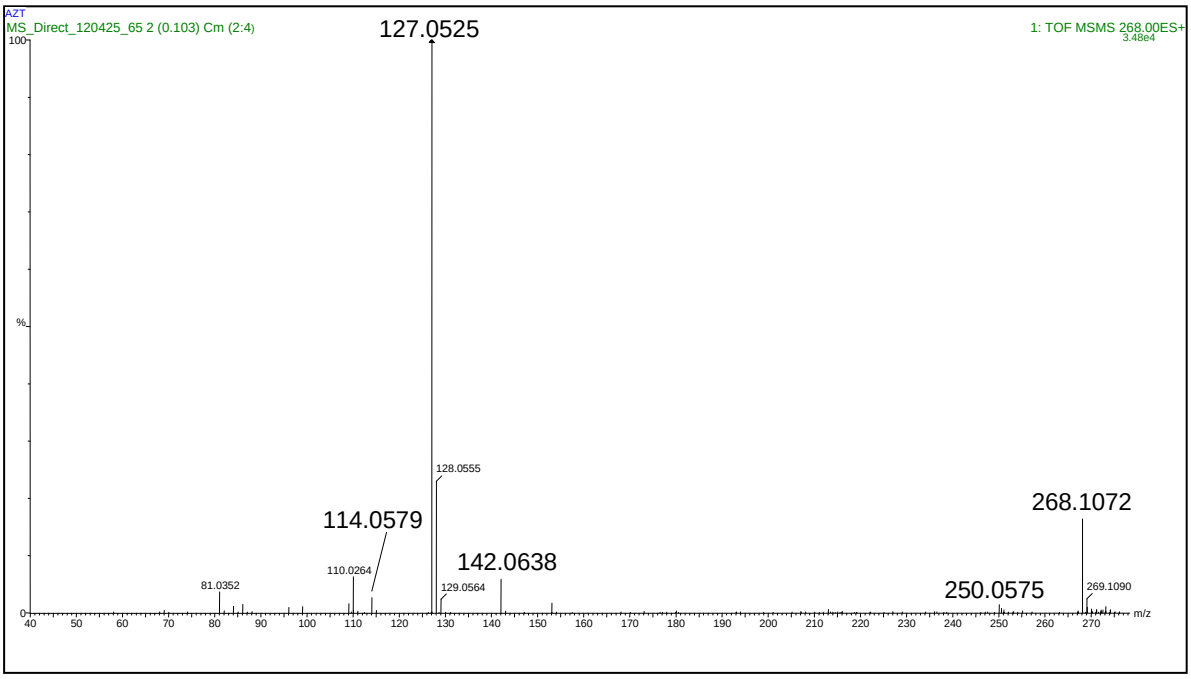
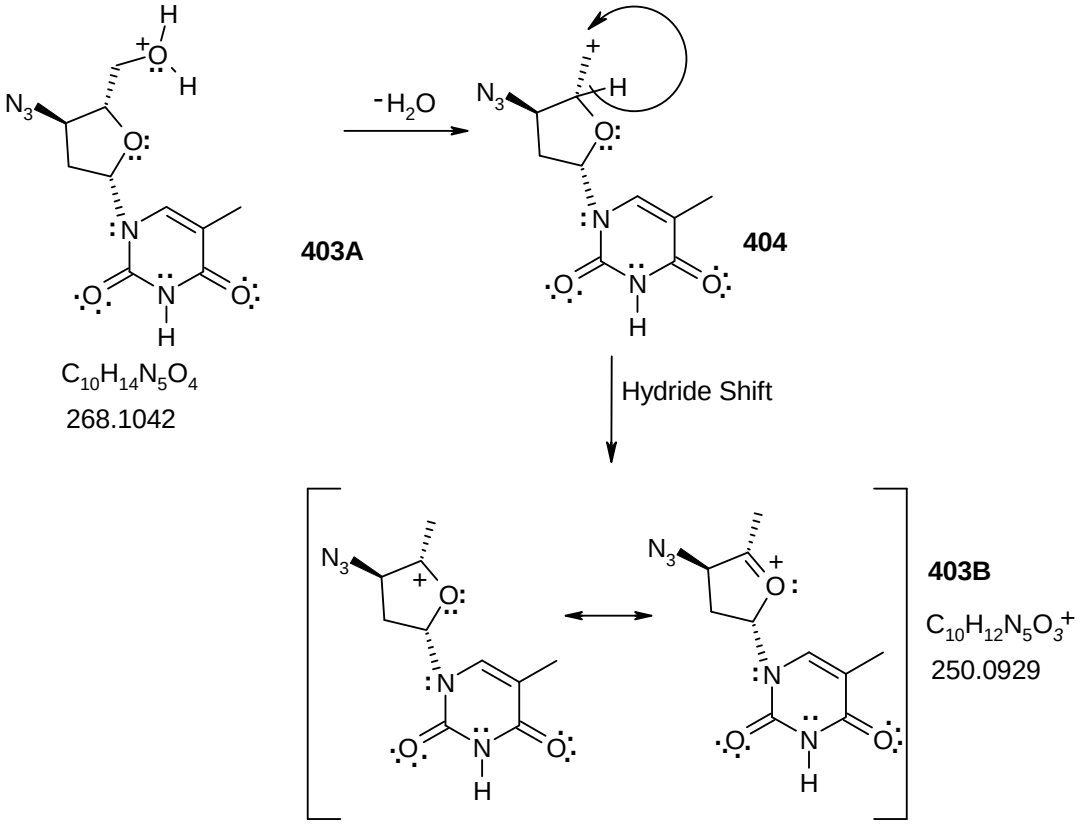
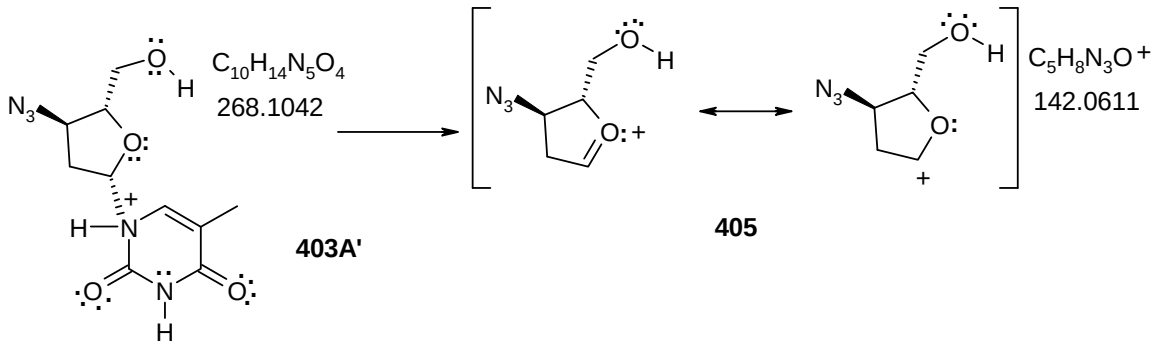


Figure 2.48. ESI-MS/MS spectrum of protonated molecular ion **403A**.



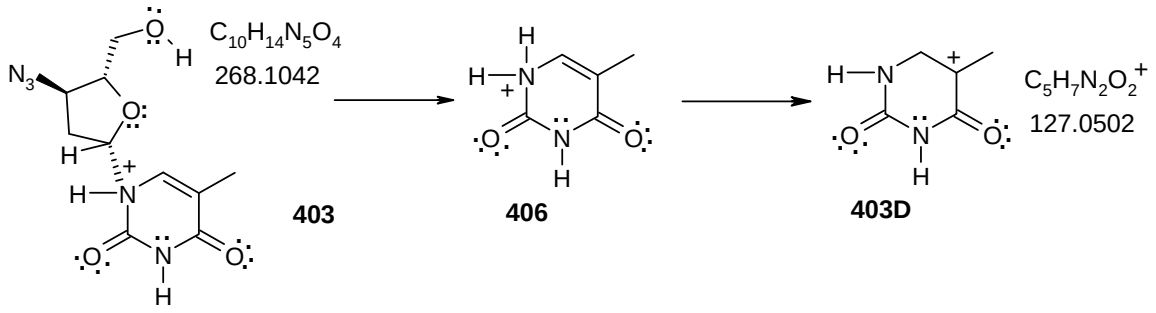
Scheme 2.31. Pathway 1 showing the formation of the resonance-stabilized oxonium ion **403B**.

In pathway 2, loss of the purine ring from the protonated molecular ion **403A'** *via* heterolytic fission affords the resonance-stabilized oxonium ion **403C** (*m/z* =142.0611; Scheme 2.32).



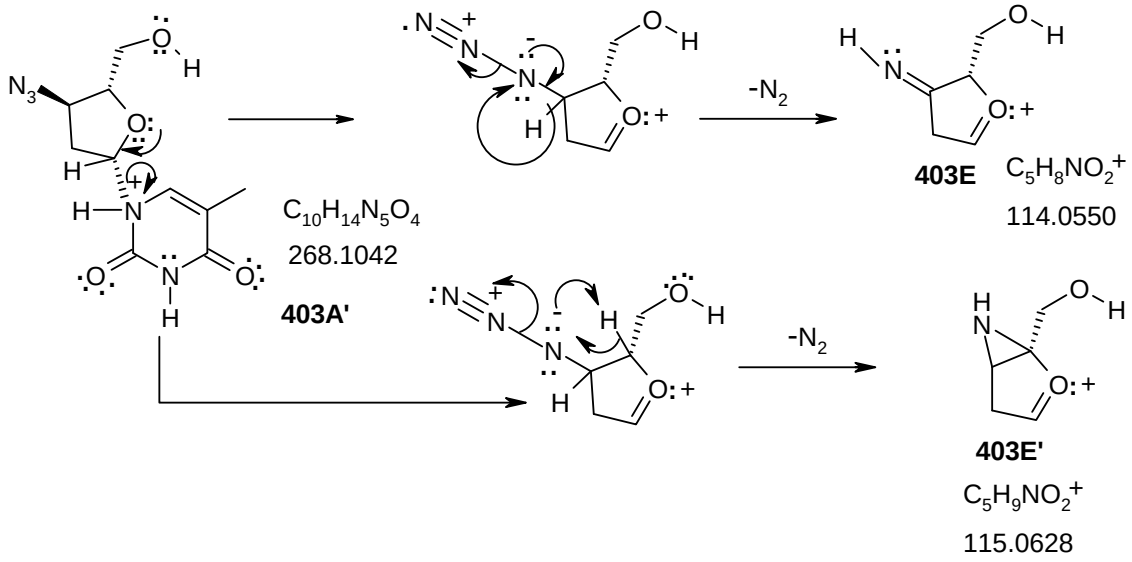
Scheme 2.32. Pathway 2 showing formation of the resonance-stabilized oxonium ion **403C**.

In pathway 3, transfer of a proton from the ether ring with concomitant fission of the two ring systems, as shown in Scheme 2.33, leads to the 3^{o} carbocation **403D** (*m/z* = 127.0502).



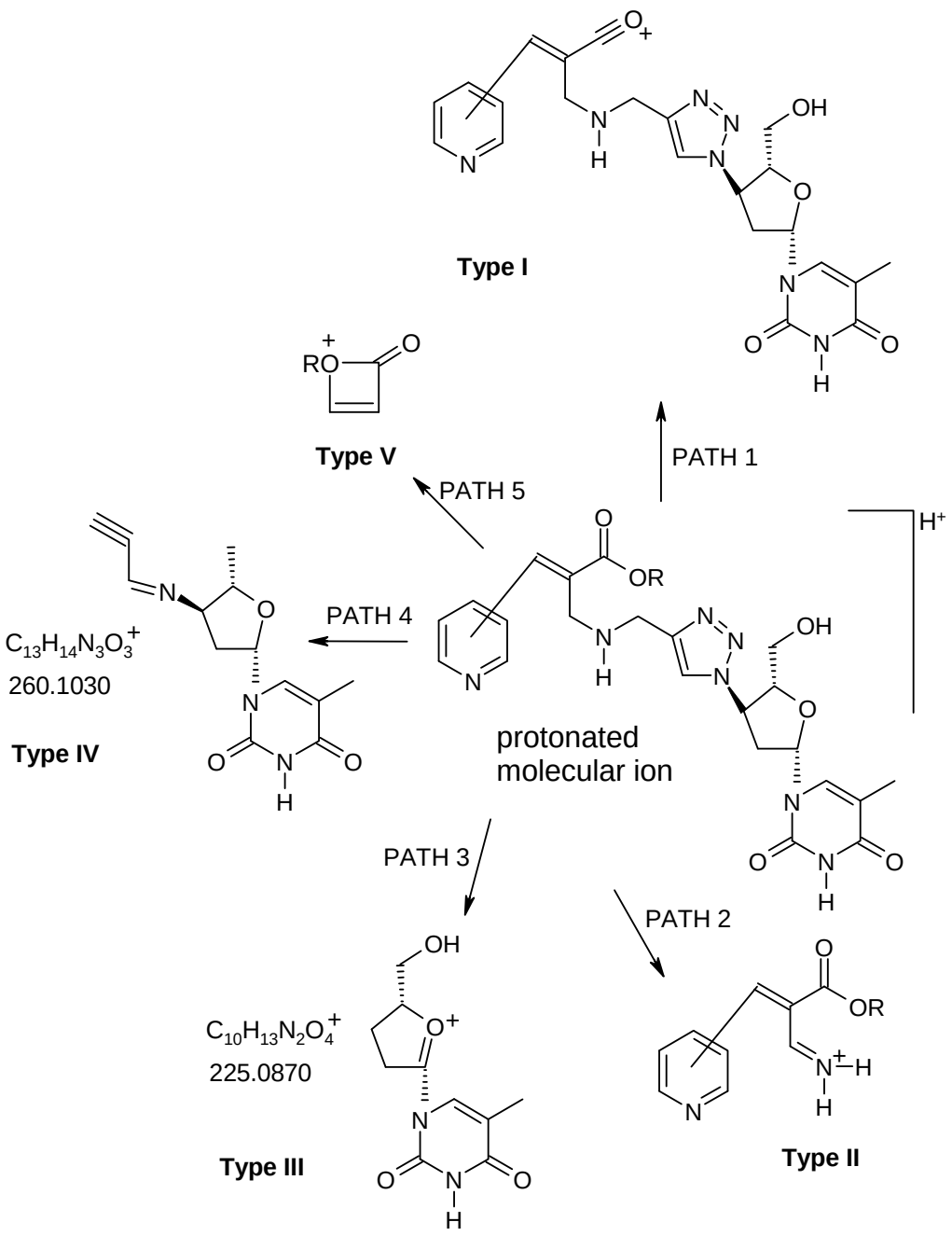
Scheme 2.33. Pathway 3 showing formation of the 3^{o} carbocation **403D**.

Pathway 4 seems to involve a tandem fragmentation of the protonated molecular ion **403A'** with loss of the purine ring and a nitrogen molecule to generate another oxonium ion fragment **403E** (*m/z* = 114.0550) as shown in Scheme 2.34. An alternative structure for the oxonium ion is also possible. In their study of electrospray positive ion mass spectrum of an AZT phosphonate ester, Xiao *et al.*[138] have suggested formation of an aziridine species, corresponding to the oxonium ion **403E'**, on loss of N_2.



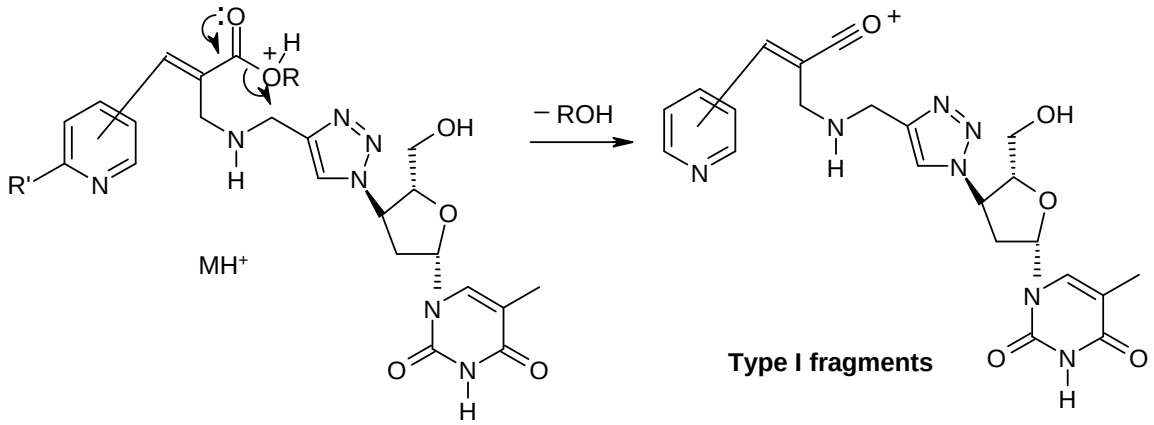
Scheme 2.34. Tandem fragmentations of molecular ion **403A'** leading to the formation of fragments **403E** and/or **403E'**.

The common mass fragmentation patterns exhibited by the AZT conjugates **390**-**395** comprise the five significant pathways shown in the generalised Scheme 2.35.

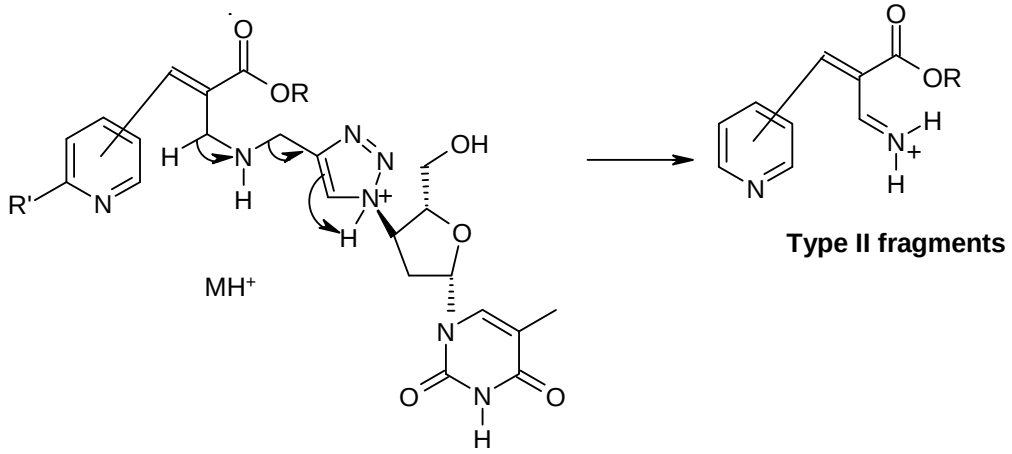


Scheme 2.35. Common fragmentation pathways of the AZT-conjugates **390-395**.

In pathway 1, the corresponding protonated molecular ions lose an alcohol molecule (ROH) to afford an acylium cation as the general Type I fragment as shown in Scheme 2.36. In pathway 2, the loss of the the triazole ring bearing the AZT group leads to the formation of Type II ion fragments as shown in Scheme 2.37.

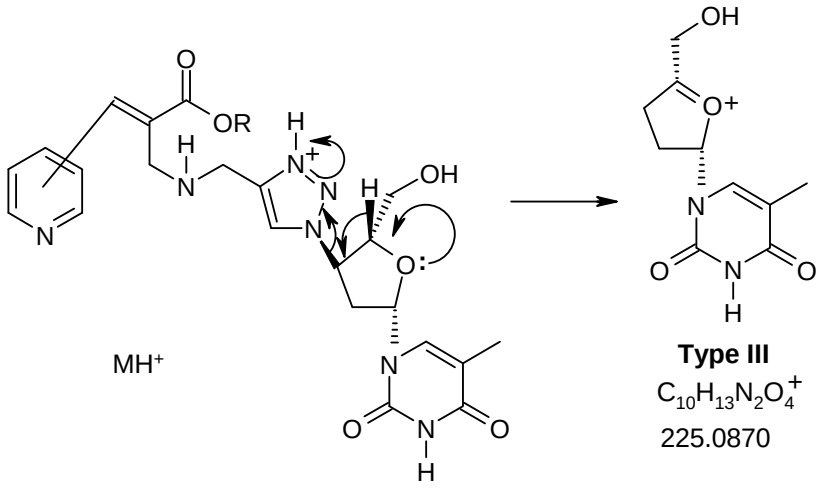


Scheme 2.36. Pathway 1 showing formation of Type I ion fragment.



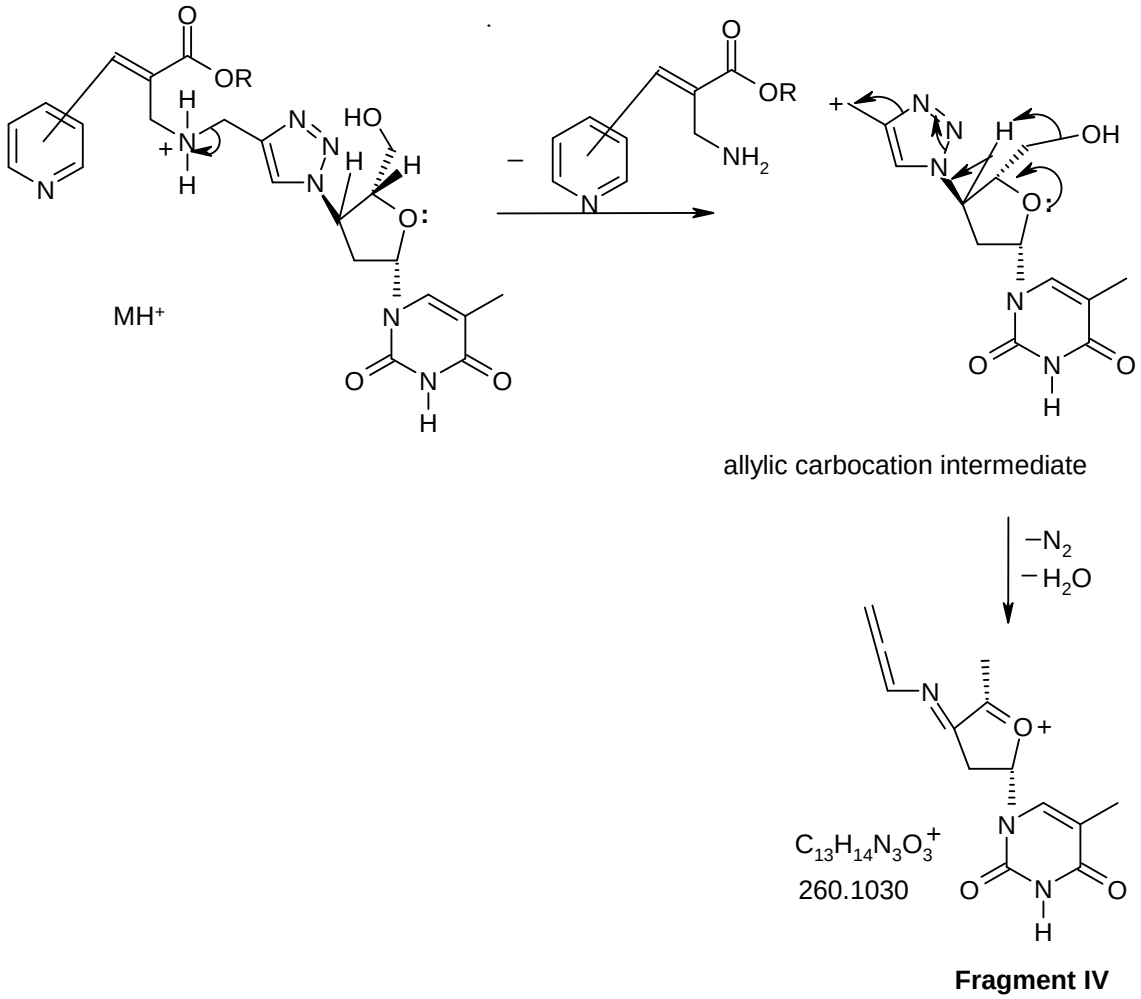
Scheme 2.37. Pathway 2 showing formation of the type II fragments.

The Type III fragment, which is common to all 6 compounds examined is formed as a result of the loss of the pyridinyl moiety as shown in Scheme 2.38. Thus, protonation of a triazole nitrogen leads to fission of the triazole-tetrahydrofuran bond and formation of the common, resonance-stabilized oxonium ion (Type III fragment).

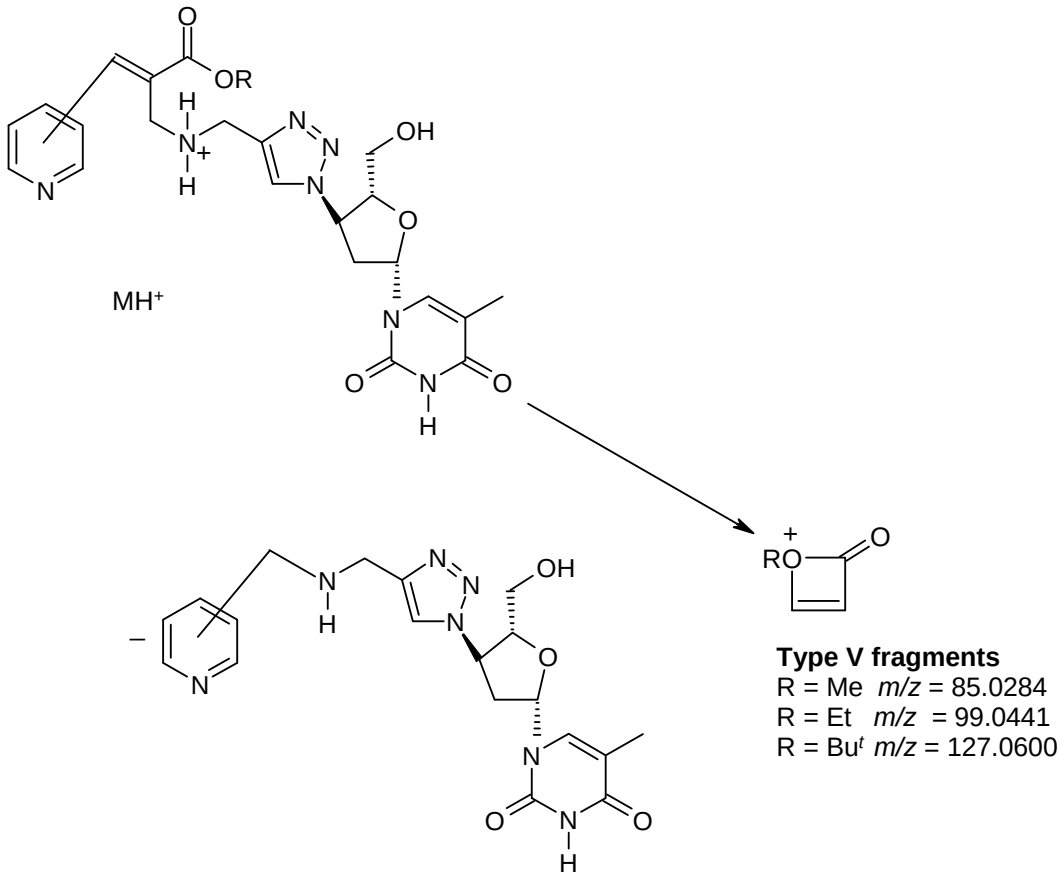


Scheme 2.38. Pathway 3 showing formation of Type III oxonium ion fragment.

The generation of fragment of the common IV is proposed to include loss of the neutral amine (which differentiates each of the AZT-conjugates) to afford an intermediate, resonance-stabilized allylic-type carbocation. Subsequent extrusion of N_2 and dehydration would then afford the *N*-alleynyl oxonium ion ion (Fragment IV *m/z* = 260.1030) (Scheme 2.39) observed in the spectra of all six compounds examined. Type V ion fragments involve the loss of both the AZT moiety as well as the pyridine system to afford cationic fragments which clearly correspond to the different acrylic esters (R = Me, Et, Bu^t). Formation of these cations formulated as oxonium ions is attributed to the unusual rearrangement outlined in Scheme 2.40. This effectively involves extrusion of the cyclic oxonium ion.



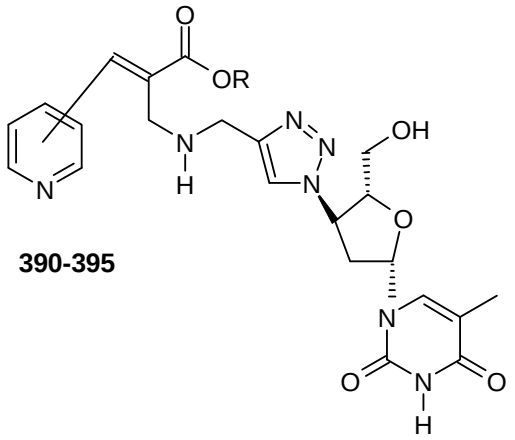
Scheme 2.39. Pathway 4 leading to ion fragment IV.



Scheme 2.40. Rearrangement involved in the formation of the Type V oxonium ion fragments.

Table 2.9 summarizes ion fragments corresponding to the AZT conjugates examined in the present study and illustrates the common patterns observed.

Table 2.23. Data for the Electrospray M fragmentation shows the *m/z* values corresponding to fragment types I-V.



390-395

Compd	R	Pyridinyl	I	II	III	IV	V
390	Me	2-pyridinyl	466.1833	205.0972	225.1	260.1030	85.0284
391	Me	6-methyl-2-pyridinyl	480.1990	219.1128	225.1	260.1030	85.0282
392	Et	2-pyridinyl	466.1833	219.1128	225.1	260.1030	99.0441
393	Et	4-pyridinyl	466.1833	219.1128	225.1	260.1030	99.0441
394	Bu^t	3-pyridinyl	466.1733	247.1441	225.1	260.1030	127.0600
395	Bu^t	6-methyl-2-pyridinyl	480.1990	261.1598	225.1	260.1030	127.0600

2.4. CONCLUSIONS

The stated objectives of exploring applications of MBH methodology in asymmetric synthesis and in constructing novel pyridinyl-AZT conjugates have been achieved. Suitable chiral, *N*-substituted camphor-derived sulfonamides were successfully prepared for use as chiral auxiliaries in asymmetric Morita-Baylis-Hillman reactions. While difficulties encountered in the purification of these chiral auxiliaries hampered progress, a range of 2-hydroxybornane-10-sulfonamides were obtained for use as chiral auxiliaries and were reacted with acryloyl chloride in the presence of Al_2O_3. These acrylate esters were used as ‘‘activated alkenes’’ in MBH reactions with selected pyridine carbaldehydes. These reactions proceeded with excellent yields (91-100%) but poor diastereoselectivity (7-33%). A major difficulty in the preparation of the acrylate ester was the concomitant formation of hydrochlorinated competition products. Although the results indicate a measure of diastereocontrol in the final MBH reactions, the % d.e. values and the difficulties in purifying the chiral auxiliaries and linking them with acryloyl chloride raise questions about their viability in asymmetric MBH reactions. Nevertheless, important insights have been obtained and a significant number of novel compounds have been isolated and fully characterized. Moreover, electrospray MS studies have permitted elucidation of the fragmentation patterns of selected products.

The application of MBH methodology in the synthesis of heterocyclic ‘cinnamate-like’ pyridine derivatives linked to the AZT sytem has led to the development of AZT conjugates as potential dual-action HIV-1 (IN/RT) inhibitors. This involved reaction of various pyridine carboxaldehydes with methyl acrylate, ethyl acrylate and *t*-butyl acrylate under MBH conditions using 3-hydroxyquinuclidine (3-HQ) as catalyst. The reactions proceeded in yields ranging from low to excellent (34-100%) over a 24 h period. The resulting MBH adducts were subsequently acylated using acetyl chloride in the presence of pyridine, with the expected acetates being isolated together, in some cases, with the isomeric products arising from allylic displacement of the acetate moiety. Yields were low to moderate (15-60%) due again to difficulties in separation. The MBH esters

generated were then treated with propargylamine to give the aminated derivatives, containing the terminal triple bond needed for the copper(I)-catalysed 1,3-dipolar Huisgen cycloaddition 'Click reaction' with AZT. These reactions furnished novel pyridine 'cinnamate-like' ester-AZT conjugates, as dual-action HIV-1 IN/RT inhibitors.The ester-AZT conjugate **392** was modelled *in silico*, and subjected to a conformational search using the Vega ZZ programme to obtain the most stable conformation, which was docked into the HIV-1 IN and RT active-sites using the Autodock 4.2 programme. The RCBS Protein Data Bank (PDB) provided access to the actual integrase (IQS4) and the reverse transcriptase (1IKW) enzymes in which the ligand **392** was independently docked. Van der Waals and hydrogen-bonding interactions were observed between the ligand **392** and the respective receptor-site substrate amino acid residues.

Electrospray MS analysis of AZT and the series of AZT-conjugates has permitted a detailed study of the fragmentation patterns exhibited by these compounds.

Future work is expected to involve:-

(i) Exploring the design of alternative chiral auxiliaries with improved synthetic accessibility and diastereoselectivity profiles.

(ii) Bioassays to evaluate the potential of the AZT-conjugates to inhibit the HIV-1 IN and RT enzymes *in vitro*.

3. EXPERIMENTAL

3.1. GENERAL

A Kofler hot-stage melting point apparatus was employed to determine melting points which were uncorrected. The IR data was obtained with the aid of a Perkin-Elmer FT-IR 2000 spectrophotometer which employed KBr discs or liquid films. The ^{1}H NMR and ^{13}C NMR data, on the other hand, were obtained using Bruker AMX 400 MHz and Avance 600 MHz spectrometers using deuterated $CDCl_3$ with reference signals for the ^{1}H and ^{13}C spectra at 7.25 ppm and 77.0 ppm respectively. Coupling constants (*J*) are given in hertz (Hz) while chemical shifts are expressed in parts per million (ppm). High resolution mass spectra were recorded at Stellenbosch University (Central Analytical Facilities).

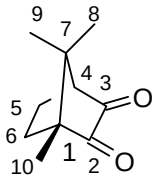
Semi-preparative HPLC was achieved using a Spectra-Physics P100 isocratic pump with chromatography on a 250 x 10 mm Spherisorb 55 W normal phase column and a differential refractometer detector. Flash chromatography was carried out using silica gel 60. Thin-layer chromatography (TLC) was conducted on precoated Merck silica gel 60 F_{254} and UV light (254 nm) and/or iodine vapour helped visualize the plates.

Vogel *et al.*[124] described standard conventional means to purify solvents. Acetonitrile was pre-dried with CaH_2, distilled and dried over 4Å molecular sieves. THF was also pre-dried over CaH_2 and then distilled in an inert atmosphere using Na and benzophenone indicator. Dichloromethane was also distilled from CaH_2.

3.2. SYNTHETIC PROCEDURES

3.2.1. Acrylate esters from 2,3-camphor diol

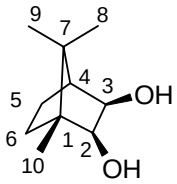
***Camphorquinone* 236**



236

Selenium dioxide (14.4 g, 130 mmol) was added to a stirred solution of (1*R*)-(+)-camphor **10** (12.17 g, 80 mmol) in acetic anhydride (12 mL). The resulting suspension was boiled under reflux for 5h and, thereafter, stirred vigorously at room temperature overnight. The black selenium powder was filtered off and washed with a minimal volume of glacial acetic acid. The filtrate and washings were then neutralized with 10% aqueous NaOH at 0°C, and the resulting yellow precipitate was filtered off and washed with a minimal volume of water and suction-dried. The yellow solid was then dissolved in petroleum ether (80-100°C) and the residual aqueous layer removed. The organic layer was concentrated *in vacuo* until crystallization began, and then heated to boiling to redissolve the crystals. Slow crystallization occurred on cooling to room temperature and further crystallization was induced by storing overnight at 10°C. Filtration afforded bright-yellow crystals of camphorquinone **236** (9.00 g, 57%), m.p. 190-192 °C (lit.,[143,144] 198-201 °C); δ_H (400 MHz; $CDCl_3$) 0.90, 1.03 and 1.07 (9H, 3 x s, 8-, 9- and 10-Me), 1.61-2.13 (4H, series of multiplets, 5- and 6-CH_2) and 2.59 (1H, d, *J* 4.80 Hz, 4-H); δ_C (100 MHz; $CDCl_3$) 8.8, 17.4 and 21.1 (C-8, C-9 and C-10), 22.3 and 29.9 (C-5 and C-6), 42.6 and 58.0 (C-1 and C-7), 58.7 (C-4), 202.8 and 204.8 (C-2 and C-3).

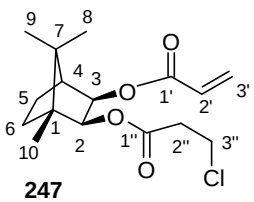
***2*-exo,*3*-exo-*Dihydroxybornane* 237**



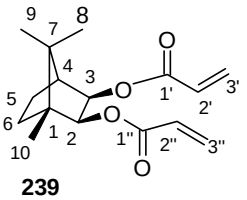
237

$LiAlH_4$ (2.5 g, 64 mmol) was added to dry THF (43 mL) under N_2 and the resulting mixture stirred for 2 hours at 0 °C. Camphorquinone **236** (4.00 g, 26 mmol) in dry THF (4 mL) was then added drop-wise under N_2 and the mixture allowed to warm to room temperature overnight. The reaction mixture was then heated to, and maintained at, 60 °C for 2 h. The reaction was then quenched under N_2 by the successive addition of 3M NaOH (2 mL) and water (1.1 mL). The resulting precipitate was filtered off, collected and extracted with boiling Et_2O (4 x 21 mL). The filtrate and extracts were combined, washed with saturated aqueous $NaHCO_3$ (3 x 8.5 mL) and dried over anhydrous $MgSO_4$. Concentration of the mixture *in vacuo* furnished, without need for further purification, 2-*exo*,3-*exo*-dihydroxybornane **237** as a white crystalline solid (4.1 g, 99%), m.p. 240-242 °C (lit.,[120] 230-231 °C); δ_H (400 MHz; $CDCl_3$) 0.81 (3H, s, 9-Me), 0.94 (3H, s, 8-Me), 1.11 (3H, s, 10-Me), 0.97-1.68 (4H, series of multiplets, 5- and 6-CH_2), 1.77 (1H, d, 4-H), 2.61-2.70 (2H, 2 x d, *J* 4.0 Hz, 2 x OH), 3.61 (1H, t, *J* 6.2 Hz, 2-H) and 3.85 (1H, t, *J* 4.0 Hz, 3-H); δ_C (100 MHz; $CDCl_3$) 11.1, 21.0 and 21.8 (C-8, C-9 and C-10), 24.1 (C-6), 33.2 (C-5), 46.5 and 48.8 (C-1 and C-7), 51.6 (C-4), 76.3 (C-2) and 80.0 (C-3).

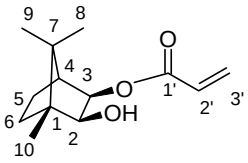
***Reaction of 2-exo,3-exo-dihydroxybornane* 237 *with acryloyl chloride to afford the acrylate esters*239, 234 *and* 238 *and the hydroclorinated analogues* 247, 248,250 *and* 249**



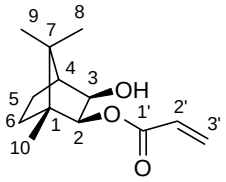
247



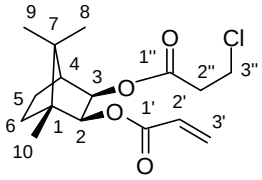
239



234



238



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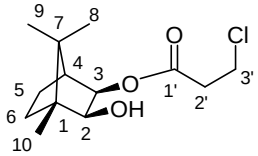
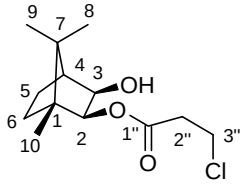


250



249

Butyllithium (1.6M solution in hexane; 7.7 mL, 12 mmol) was added drop-wise over 20 min, under N_2, to a stirred solution of 2-*exo*,3-*exo*-dihydroxybornane **237** (1.6 g, 9.4 mmol) in dry THF (20 mL) at -5 °C. After 1.5 h acryloyl chloride (1.12 g, 12.4 mmol) was added drop-wise, the mixture was stirred at 0 °C for 1 h and then allowed to warm to room temperature. The THF was removed *in vacuo* and the residue was treated with saturated aqueous $NaHCO_3$ (8.0 mL), extracted with Et_2O (3 x 10 mL) and the combined extracts were dried over anhydrous $MgSO_4$. Concentration under reduced pressure gave an oil (1.9 g), which was chromatographed [HPLC; elution with hexane-EtOAc (19: 1)] to afford seven fractions.

Fraction 1. *2*-exo-*(3-Chloropropanoyloxy)-3*-exo-*bornanyl acrylate* **247**, as a colourless oil (20%); δ_H (600 MHz; $CDCl_3$) 0.85 (3H, s, 9-Me), 0.88 (3H, s, 8-Me), 1.13 (3H, s, 10-Me), 1.13.-1.79 (4H, series of multiplets, 5- and 6-CH_2), 1.91 (1H, d, *J* 6.6 Hz 4-H), 2.73 (2H, m, 2''-CH_2), 3.70 (2H, m, 3''-CH_2), 4.88 (1H, d, *J* 7.2 Hz, 2-H), 4.93 (1H, d, *J* 6.6 Hz, 3-H), 5.83 and 6.36 (2H, 2 x dd, *J* 1.2 and 10.2 Hz, 1.8 and 17.4 Hz, 3'-CH_2) and 6.09 (1H, dd, *J* 10.8 and 17.4 Hz, 2'-H); δ_C (150 MHz; $CDCl_3$) 11.0, 20.4 and 20.9 (C-8, C-9 and C-10), 23.8 (C-6), 32.8 (C-5), 37.2 (C-2''), 38.7 (C-3''), 47.5 and 48.8 (C-1 and C-7), 49.5 (C-4), 77.1 (C-2), 80.1 (C-3), 128.4 (C-2'), 130.9 (C-3'), 165.0 and 169.0 (2 x C=O).

Fraction 2. 2-*exo*-3-*exo*-Bornanyl diacrylate **239**, as an oil (trace amounts); δ_H (400 MHz; $CDCl_3$) 0.86 (3H, s, 9-Me), 0.89 (3H, s, 8-Me), 1.16 (3H, s, 10-Me), 0.91-1.70 (4H, series of multiplets, 5- and 6-CH_2), 1.91 (1H, d, *J* 7.35 Hz, 4-H), 4.92 (2H, s, 2-H and 3-H), 5.78 and 6.03 (4H, 2 x m, 3'- and 3''-CH_2) and 6.31 (2H, m, 2'- and 2''-H).

Fraction 3. 2-*exo*-Hydroxy-3-*exo*-bornanyl acrylate **234**, as a colourless oil (20%); δ_H (400 MHz; $CDCl_3$) 0.83 (3H, s, 9-Me), 0.94 (3H, s, 8-Me), 1.12 (3H, s, 10-Me), 1.03-1.78 (4H, series of multiplets, 5- and 6-CH_2), 1.87 (1H, d, *J* 7.8 Hz, OH), 1.89 (1H, d, *J* 7.2 Hz 4-H), 3.82 (1H, t, *J* 9.0 Hz, 2-H), 4.68 (1H, d, *J* 10.2 Hz, 3-H), 5.85 and 6.40 (2H, 2 x dd, *J* 1.8 and 15.6 Hz and 1.8 and 26.1 Hz, 3'-CH_2) and 6.15 (1H, dd, *J* 10.2 and 17.4 Hz, 2'-H); δ_C (100 MHz; $CDCl_3$) 11.1, 20.7 and 21.2 (C-8, C-9 and C-10), 24.0 (C-6), 33.2 (C-5), 47.0 and 49.2 (C-1 and C-7), 49.2 (C-4), 79.7 (C-3), 80.2 (C-2), 128.4 (C-2'), 130.9 (C-3') and 166.0 (C=O).

Fraction 4. 3-*exo*-Hydroxy-2-*exo*-bornanyl acrylate **238**, as a colourless oil (36%); δ_H (600 MHz; $CDCl_3$) 0.83 (3H, s, 9-Me), 0.91 (3H, s, 8-Me), 1.51 (3H, s, 10-Me), 1.03-1.71 (4H, series of multiplets, 5- and 6-CH_2), 1.80 (1H, d, *J* 7.2 Hz 4-H), 1.88 (1H, d, *J* 7.8 Hz, 3-OH *exo*), 4.04 (1H, t, *J* 9.0 Hz, 3-H), 4.54 (1H, d, *J* 10.2 Hz, 2-H), 5.86 and 6.42 (2H, 2 x dd, *J* 1.8 and 15.6; 1.8 and 26.1 Hz, 3'-CH_2) and 6.17 (1H, dd, *J* 15.6 and 25.8 Hz, 2'-H); δ_C (150 MHz; $CDCl_3$) 11.3, 20.7 and 21.1 (C-8, C-9 and C-10), 24.1 (C-6), 33.2 (C-5), 47.1 and 48.4 (C-1 and C-7), 51.6 (C-4), 76.7 (C-3), 83.0 (C-2), 128.4 (C-2'), 131.0 (C-3') and 166.5 (C=O).

Fraction 5. *3*-exo-*(3-Chloropropanoyloxy)-2*-exo-*bornanyl acrylate* **248**, as a colourless oil (13%); δ_H (400 MHz; $CDCl_3$) 0.86 (3H, s, 9-Me), 0.89 (3H, s, 8-Me), 1.14 (3H, s, 10-Me), 1.14.-1.78 (4H, series of multiplets, 5- and 6-CH_2), 1.89 (1H, d, *J* 7.8 Hz, 4-H), 2.70 (2H, m, 2''-CH_2), 3.66 (2H, m, 3''-CH_2), 4.87 (1H, d, *J* 10.8 Hz, 2-H), 4.91 (1H, d, *J* 10.8 Hz, 3-H), 5.85 and 6.39 (2H, 2 x dd, *J* 2.4 and 15.6 Hz and 1.8 and 26.1 Hz, 3'-CH_2) and 6.12 (1H, dd, *J* 15.6 and 25.8 Hz, 2'-H); δ_C (100 MHz; $CDCl_3$) 10.9, 20.4 and 20.9 (C-8, C-9 and C-10), 23.8 (C-6), 32.9 (C-5), 37.7 (C-2'), 38.7 (C-3'), 47.5

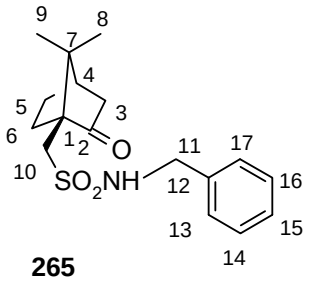
and 48.8 (C-1 and C-7), 49.7 (C-4), 77.4 (C-2), 80.0 (C-3), 128.4 (C-2''), 130.8 (C-3''), 165.1 and 169.0 (2 x C=O).

Fraction 6. *2*-exo-*Hydroxy-3*-exo-*bornanyl 3-chloropropanoate* **250**, as a colourless oil (trace amounts); δ_H (400 MHz; $CDCl_3$) 1.13 (3H, s, 9-Me), 1.22 (3H, s, 8-Me), 1.53 (3H, s, 10-Me), 1.27-1.88 (4H, series of multiplets, 5- and 6-CH_2), 2.05 (1H, br s, 2-OH), 2.17 (1H, s, 4-H), 2.77 (2H, m, 2'-CH_2), 3.73 (2H, m, 3'-CH_2), 4.82 (1H, t, *J* 2.4 Hz, 2-H) and 4.84 (1H, br s, 3-H).

Fraction 7. *3*-exo-*Hydroxy-2*-exo-*bornanyl 3-chloropropanoate* **249**, as a colourless oil (trace amounts); δ_H (400 MHz; $CDCl_3$) 0.82 (3H, s, 9-Me), 0.93 (3H, s, 8-Me), 1.10 (3H, s, 10-Me), 1.03-1.78 (4H, series of multiplets, 5- and 6-CH_2), 1.86 (1H, d, *J* 7.2 Hz, 4-H), 1.87 (1H, br s, 3-OH), 2.85 (2H, m, 2'-CH_2), 3.75 (1H, d, *J* 9.6 Hz, 2-H), 3.77 (2H, m, 3'-CH_2) and 4.66 (1H, d, *J* 10.2 Hz, 3-H).

3.2.2. Acrylate esters with sulfonamide group

N-*Benzylcamphor-10-sulfonamide* 265

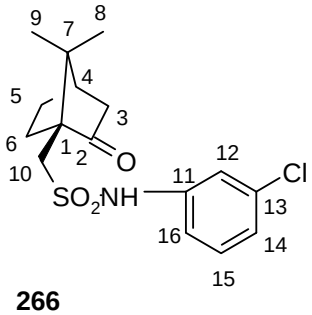


265

A solution of camphor-10-sulfonyl chloride **32** (10.0 g, 39.9 mmol) in acetonitrile (100 mL) was added drop-wise under N_2 to a stirred solution of benzylamine (8.67 mL, 79.8 mmol) and 4-(dimethylamino)pyridine (1.28 g, 10.5 mmol) in acetonitrile (50 mL) at 0 °C, and the solution was stirred for 1h. Water (50 mL) was then added followed by 10% HCl (10 mL), and the resulting mixture was extracted with EtOAc (3 × 125 mL). The organic layers were combined, washed with 5% aqueous NaOH (25 mL) and dried over

anhydrous $MgSO_4$. The solvent was removed *in vacuo* to afford *N*-benzylcamphor-10-sulfonamide **265** as colourless crystals (12.8 g, 99.0%), m.p. 56-58 °C (lit.,[145,146] 68-69 °C); δ_H (600 MHz; $CDCl_3$) 0.73 (3H, s, 9-Me), 0.94 (3H, s, 8-Me), 1.4 -2.31 (7H, series of multiplets, 3-, 5-, 6-CH_2 and 4-CH), 3.00 (2H, 2 x d, *J* 15.3 Hz, 10-CH_2), 5.74 (1H, br s, NH), 4.34 (2H, m, $PhCH_2$) and 7.25-7.38 (5H, overlapping signals, ArH); δ_C (150 MHz; $CDCl_3$) 19.4 (C-8), 19.8 (C-9), 27.0 (C-5 and C-3), 42.8 (C-4), 43.0 (C-6), 48.8 and 59.3 (C-1 and C-7), 50.8 (C-10), 47.9 ($PhCH_2$) and 127.9, 128.4, 128.7 and 136.9 (ArC) and 217.0 (C=O).

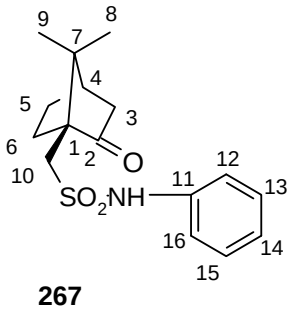
N-(***3-Chlorophenyl*)*camphor-10-sulfonamide*** **266**



266

Using the procedure described for the synthesis of *N*-benzylcamphor-10-sulfonamide **265**, a solution of camphor-10-sulfonyl chloride **32** (10.0 g, 39.9 mmol) in acetonitrile (50 mL) was added drop-wise under N_2 to a stirred solution of *m*-chloroaniline (8.38 mL, 79.8 mmol) and 4-(dimethylamino)pyridine (1.28 g, 10.5 mmol) in acetonitrile (100 mL) at 0 °C, and the solution was stirred for 1h. Work-up afforded *N*-(3-chlorophenyl) camphor-10-sulfonamide **266** as white crystals (12.4 g, 99.0%), m.p. 130-132 °C (Found: MH^+, 342.0935. $C_{16}H_{21}NO_3SCl$ requires, *M*+H: 342.0931); δ_H (600 MHz; $CDCl_3$) 0.85 (3H, s, 9-Me), 0.90 (3H, s, 8-Me), 1.41-2.40 (7H, series of multiplets, 3-, 5-, 6-CH_2 and 4-CH), 3.00 (2H, 2 x d, *J* 15.0 Hz, 10-CH_2), 7.82 (1H, s, NH) and 7.07-7.19 (4H, overlapping m,ArH); δ_C (150 MHz; $CDCl_3$) 19.3 (C-8), 19.9 (C-9), 27.1 and 27.7 (C-5 and C-3), 42.8 (C-4), 43.1 (C-6), 49.2 and 59.8 (C-1 and C-7), 49.6 (C-10) and 111.9, 121.9, 125.5, 130.4, 135.0 and 138.9 (ArC) and 217.7 (C=O).

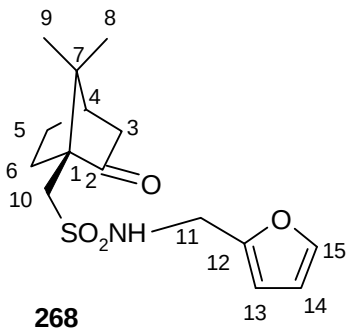
N-***Phenylcamphor-10-sulfonamide*** **267**



267

Using the procedure described for the synthesis of *N*-benzylcamphor-10-sulfonamide **265**, a solution of camphor-10-sulfonyl chloride **32** (10.0 g, 39.9 mmol) in acetonitrile (50 mL) was added drop-wise under N_2 to a stirred solution aniline (7.28 mL, 79.8 mmol) and 4-(dimethylamino)pyridine (1.28 g, 10.5 mmol) in acetonitrile (100 mL) at 0 °C, and the solution was stirred for 1h. Work-up afforded *N*-phenylcamphor-10-sulfonamide **267** as white crystals (11.4 g, 93.0%), m.p. 116-118 °C (lit.,[147] 120.5-121 °C); δ_H (400 MHz; $CDCl_3$) 0.85 (3H, s, 9-Me), 0.96 (3H, s, 8-Me), 1.45-2.44 (7H, series of multiplets, 3-, 5-, 6-CH_2 and 4-CH), 3.12 (2H, 2 x d, *J* 15.2 Hz, 10-CH_2), 7.17-7.36 (5H, overlapping signals, ArH) and 7.73 (1H, s, NH); δ_C (100 MHz; $CDCl_3$) 19.3 (C-8), 19.9 (C-9), 27.1 and 27.7 (C-5 and C-3), 42.8 (C-4), 43.1 (C-6), 49.1 and 59.7 (C-1 and C-7), 49.6 (C-10) and 122.2, 125.5, 129.4 and 137.6 (ArC) and 217.4 (C=O).

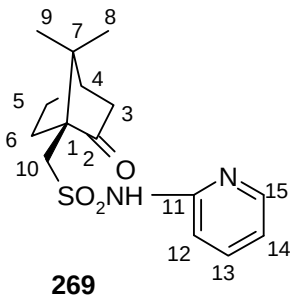
N-*(2-Furfuryl)camphor-10-sulfonamide* 268



268

Using the procedure described for the synthesis of *N*-benzylcamphor-10-sulfonamide **265**, a solution of camphor-10-sulfonyl chloride **32** (10.0 g, 39.9 mmol) in acetonitrile (50 mL) was added drop-wise under N_2 to a stirred solution of furfurylamine (7.05 mL, 79.8 mmol) and 4-(dimethylamino)pyridine (1.28 g, 10.5 mmol) in acetonitrile (100 mL) at 0 °C, and the solution was stirred for 1h. Work-up afforded *N*-(2-furfuryl)camphor-10-sulfonamide **268** as yellow crystals (11.6 g, 100%), m.p. 42-44 °C (Found: MNa^+, 334.1085. $C_{15}H_{22}NO_4SNa$ requires, *M*+Na: 334.1089); δ_H (600 MHz; $CDCl_3$) 0.78 (3H, s, 9-Me), 0.95 (3H, s, 8-Me), 1.42-2.88 (7H, series of multiplets, 3-, 5-, 6-CH_2 and 4-CH), 2.87 and 3.16 (2H, 2 x d, *J* 15.0 Hz, 10-CH_2), 4.31 and 4.42 (2H, 2 x ddd, *J* 4.8, 7.2 and 15.6 Hz, furfuryl-CH_2), 5.96 (1H, m, NH), 6.32 (2H, br s, ArH) and 7.35 (1H, s, ArH); δ_C (150 MHz; $CDCl_3$) 19.4 (C-9), 19.9 (C-8), 27.0 and 27.2 (C-5 and C-3), 40.4 (C-N), 42.8 (C-4), 42.9 (C-6), 48.8 (C-1), 51.3 (C-10), 59.4 (C-7), 108.6, 110.5, 142.6 and 150.4 (ArC) and 216.8 (C=O).

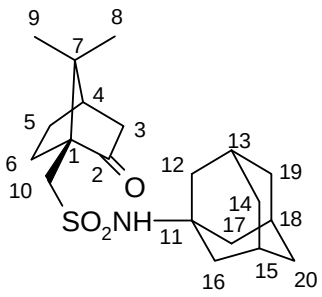
N-*(2-Pyridinyl)camphor-10-sulfonamide* 269



269

Using the procedure described for the synthesis of *N*-benzylcamphor-10-sulfonamide **265**, a solution of camphor-10-sulfonyl chloride **32** (10.0 g, 39.9 mmol) in acetonitrile (50 mL) was added drop-wise under N_2 to a stirred solution of 2-aminopyridine (7.5 g, 85.0 mmol) and 4-(dimethylamino)pyridine (1.28 g, 10.5 mmol) in acetonitrile (100 mL) at 0 °C, and the solution was stirred for 1h. Work-up afforded : *N*-(2-pyridinyl)camphor-10-sulfonamide **269** as white crystals (10.3 g, 84%), m.p. 200-202 °C (lit.,[148] 208-210 °C); δ_H (400 MHz; $CDCl_3$) 0.84 (3H, s, 9-Me), 1.07 (3H, s, 8-Me), 1.51-2.87 (7H, series of multiplets, 3-, 5- and 6-CH_2 and 4-H), 3.16 and 3.65 (2H, 2 x d, *J* 14.4 Hz, 10-CH_2) and 6.69 (1H, br s, NH) and 7.14 (1H, t, *J* 6.6 Hz, Ar-H), 7.87 (1H, d, *J* 9.0 Hz, Ar-H), 8.01 (1H, t, *J* 7.4 Hz, Ar-H) and 8.22 (1H, d, *J* 6.0 Hz, Ar-H); δ_C (100 MHz; $CDCl_3$) 19.6 (C-8), 19.7 (C-9), 22.8 and 27.0 (C-5 and C-6), 42.5 (C-3), 42.7 (C-4), 48.6 (C-1), 50.6 (C-10), 58.4 (C-7), 115.4, 115.7, 140.9, 142.5 and 153.4 (ArC) and 215.3 (C=O).

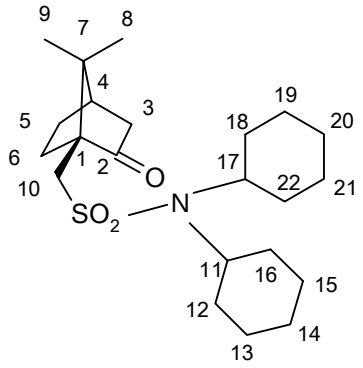
N-*(1-Adamantyl)camphor-10-sulfonamide* 270



270

Using the procedure described for the synthesis of *N*-benzylcamphor-10-sulfonamide **265**, a solution of camphor-10-sulfonyl chloride **32** (10.0 g, 39.9 mmol) in acetonitrile (50 mL) was added drop-wise under N_2 to a stirred solution of adamantylamine (12.9 g, 85.0 mmol) and 4-(dimethylamino)pyridine (1.02 g, 8.38 mmol) in acetonitrile (100 mL) at 0 °C, and the solution was stirred for 1h. Work-up afforded *N*-(1-adamantyl)camphor-10-sulfonamide **270** as white crystals (12.9 g, 89%), m.p. 196-198 °C (lit.,[149] 193-195 °C); δ_H (600 MHz; $CDCl_3$) 0.90 (3H, s, 9-Me), 1.04 (3H, s, 8-Me), 1.41, 1.86, 1.95 and 2.32 (4H, series of multiplets, 5- and 6-CH_2), 1.66 (6H, m, 14-, 19- and 20-CH_2), 1.92 and 2.38 (2H, 2 x m, 3-CH_2), 2.01 (6H, m, 12-, 16- and 17-CH_2), 2.04 (1H, s, 4-H), 2.10 (3H, m, 13-, 15- and 18-CH), 3.00 and 3.49 (2H, 2 x d, *J* 15.0 Hz, 10-CH_2) and 4.99 (1H, s, NH); δ_C (150 MHz; $CDCl_3$) 19.7 (C-8), 19.9 (C-9), 26.3 and 27.0 (C-5 and C-6), 29.7 (C-13, C-15 and C-18), 36.0 (C-14, C-19 and C-20), 42.8 (C-4), 42.9 (C-3), 43.2 (C-12, C-16 and C-17), 48.5 (C-1), 54.5 (C-10), 55.4 (C-7), 59.4 (C-11) and 216.7 (C=O).

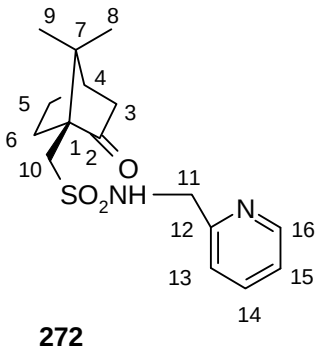
N,N-(*Dicyclohexyl)camphor-10-sulfonamide* 271



271

Using the procedure described for the synthesis of *N*-benzylcamphor-10-sulfonamide **265**, a solution of camphor-10-sulfonyl chloride **32** (7.50 g, 29.9 mmol) in acetonitrile (100 mL) was added drop-wise under N_2 to a stirred solution of dicyclohexylamine (10.8 g, 59.8 mmol) and 4-(dimethylamino)pyridine (0.96 g, 7.85 mmol) in acetonitrile (50 mL) at 0 °C, and the solution was stirred for 1h. Work-up afforded *N*, *N*-(dicyclohexlyl)camphor-10-sulfonamide **271** as white crystals (10.4 g, 88%), m.p. 108-110 °C (lit.,[147] 110-112 °C); δ_H (400 MHz; $CDCl_3$) 0.84 (3H, s, 9-Me), 1.12 (3H, s, 8-Me), 1.24-3.06 (9H, series of multiplets, cyclohexyl and camphor CH_2 ,4-H and 2 x NCH), 2.77 and 3.33 (2H, 2 x d, *J* 14.4 Hz, 10-CH_2); δ_C (100 MHz; $CDCl_3$) 19.8 (C-8), 20.2 (C-9), 24.8, 24.9 and 28.9 (cyclohexyl CH_2), 24.6, 27.0, 42.7, 42.9, 47.6, 47.8 and 58.5 (camphor CH_2 , CH and 2 x 4^0 C), 53.3 (2 x CH-N) and 216.7 (C=O).

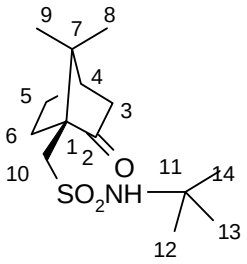
N-*(Picolyl)camphor-10-sulfonamide* 272



272

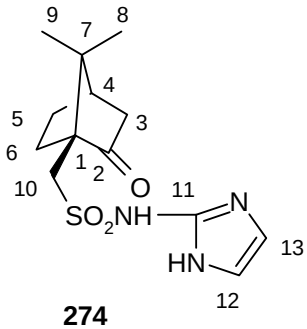
Using the procedure described for the synthesis of *N*-benzylcamphor-10-sulfonamide **265**, a solution of camphor-10-sulfonyl chloride **32** (5.00 g, 19.9 mmol) in acetonitrile (100 mL) was added drop-wise under N_2 to a stirred solution of picolylamine (4.54 g, 42.4 mmol) and 4-(dimethylamino)pyridine (0.51 g, 4.18 mmol) in acetonitrile (50 mL) at 0 °C, and the solution was stirred for 1h. Work-up afforded *N*-(picolyl)camphor-10-sulfonamide **272** as a yellow oil (5.54 g, 90%); δ_H (400 MHz; $CDCl_3$) 0.85 (3H, s, 9-Me), 1.02 (3H, s, 8-Me), 1.44-2.37 (7H, series of multiplets, 3-, 5- and 6-CH_2 and 4-H), 2.95 and 3.48 (2H, 2 x d, *J* 14.8 Hz, 10-CH_2), 4.50 (2H, m, NCH_2), 6.19 (1H,br s, NH) and 7.20 (1H, t, *J* 6.0 Hz, ArH), 7.37 (1H, d, *J* 7.6 Hz, ArH), 7.68 (1H, t, *J* 7.6 Hz, ArH) and 8.53 (1H, d, *J* 4.4 Hz, ArH); δ_C (100 MHz; $CDCl_3$) 19.5 (C-8), 19.9 (C-9), 26.3 and 27.0 (C-5 and C-6), 42.7 (C-4), 42.8 (C-3), 48.3 (NCH_2), 48.6 (C-1), 50.1 (C-10), 59.1 (C-7), 122.0, 122.6, 136.9, 149.2 and 156.1 (ArC) and 216.4 (C=O).

N-*(t-Butyl)camphor-10-sulfonamide* 273



Using the procedure described for the synthesis of *N*-benzylcamphor-10-sulfonamide **265**, a solution of camphor-10-sulfonyl chloride **32** (5.00 g, 19.9 mmol) in acetonitrile (100 mL) was added drop-wise under N_2 to a stirred solution of *t*-butylamine (3.07 g, 42.4 mmol) and 4-(dimethylamino)pyridine (0.51 g, 4.18 mmol) in acetonitrile (50 mL) at 0 °C, and the solution was stirred for 1h. Work-up afforded *N*-(*t*-butyl)camphor-10-sulfonamide **273** as white crystals (4.46 g, 94%), m.p. 96-98 °C (lit.,[145,150] 103 °C); δ_H (400 MHz; $CDCl_3$) 0.90 (3H, s, 9-Me), 1.04 (3H, s, 8-Me), 1.40 (9H, s, 12-, 13- and 14-CH_3), 1.71-2.39 (7H, series of multiplets, 3-, 5- and 6-CH_2 and 4-H), 2.98 and 3.48 (2H, 2 x d, *J* 15.0 Hz, 10-CH_2), and 5.12 (1H, s, NH); δ_C (100 MHz; $CDCl_3$) 19.7 (C-8), 19.9 (C-9), 26.3 and 27.0 (C-5 and C-6), 30.3 (C-12, C-13 and C-14), 42.7 (C-4), 42.9 (C-3), 48.5 (C-1), 53.8 (C-10), 54.9 (C-11), 59.3 (C-7) and 216.9 (C=O).

N-*(2-Imidazolyl)camphor-10-sulfonamide* 274

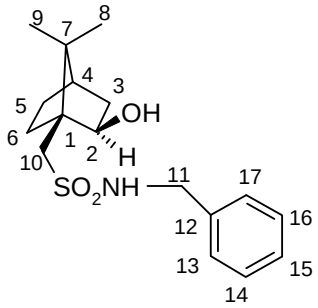


274

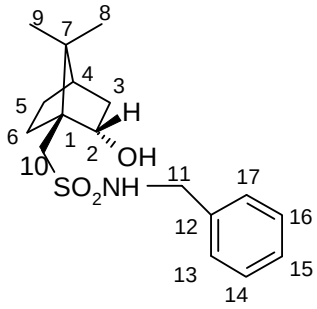
Using the procedure described for the synthesis of *N*-benzylcamphor-10-sulfonamide **265**, a solution of camphor-10-sulfonyl chloride **32** (2.01 g, 8.00 mmol) in acetonitrile (100 mL) was added drop-wise under N_2 to a stirred solution of 2-aminoimidazole (4.23

g, 16.0 mmol) and 4-(dimethylamino)pyridine (0.26 g, 0.0 mmol) in acetonitrile (50 mL) at 0 °C, and the solution was stirred for 1h. Work-up afforded: N-*(2-imidazolyl)camphor-10-sulfonamide* **274** as brown oily crystals (4.0 g, 83%), m.p. 218-220 °C (Found: MH^+, 298.1225. $C_{13}H_{20}N_3O_3S$ requires, *M*+H: 298.1225); ν_{max} (ATR)/cm^{-1} 1675 (C=O); δ_H (400 MHz; $CDCl_3$) 0.86 (3H, s, 9-Me), 1.08 (3H, s, 8-Me), 1.44-2.55 (7H, series of multiplets, 3-, 5- and 6-CH_2 and 4-H), 2.90 and 3.40 (2H, 2 x d, *J* 12.4 Hz, 10-CH_2), 6.56 and 7.23 (2H, 2 x s, 12- and 13-H) and 11.6 (2H, s, NH); δ_C (100 MHz; $CDCl_3$) 19.8 (C-8), 19.9 (C-9), 24.7 and 27.1 (C-5 and C-6), 42.7 (C-4), 43.0 (C-3), 48.2 (C-10), 48.5 (C-1), 59.3 (C-7), 112.6 (C-12 and C-13), 148.3 (C-11) and 216.5 (C=O).

N-*Benzyl-2*-exo-*hydroxybornane-10-sulfonamide* 278 *and* N-*benzyl-2*-endo-*hydroxy-bornane-10-sulfonamide* 279



278



279

A solution of *N*-benzylcamphor-10-sulfonamide **265** (12.0 g, 37.3 mmol) in EtOH-H_2O (5:1; 104 mL) was added drop-wise to a stirred solution of $NaBH_4$ (10 eq.; 14.1 g, 373 mmol) in EtOH-H_2O (5:1; 121 mL) at room temperature. The mixture was stirred overnight; the reaction was then quenched with 5% HCl (10 mL) and the resulting mixture extracted with EtOAc (3 x 25 mL). The organic layers were combined, washed with 5% brine (25 mL) and dried over anhydrous $MgSO_4$. Solvent was removed *in vacuo* to give light-yellow crystalline material (11.5 g), which was chromatographed [HPLC; elution with hexane-EtOAc (8: 2)] to afford two products.

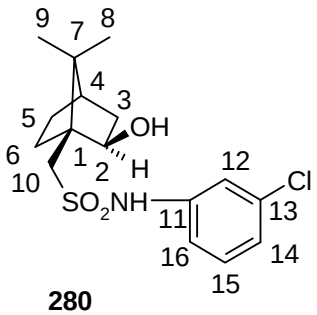
Fraction 1. *N*-Benzyl-2-*exo*-hydroxybornane-10-sulfonamide **278,** as white crystals (78%), m.p. 102-104 ºC (lit.,[145,150] 98-101 ºC); δ_H (600 MHz; $CDCl_3$) 0.77 (3H, s, 9-Me),

1.03 (3H, s, 8-Me), 1.10-1.81 (7H, series of multiplets, 3-, 5- and 6-CH_2 and 4-CH), 2.73 and 3.32 (2H, 2 x d, *J* 13.8 Hz, 10-CH_2), 3.15 (1H, br s, OH), 4.06 (1H, m, 2-H), 4.33 (2H, m,

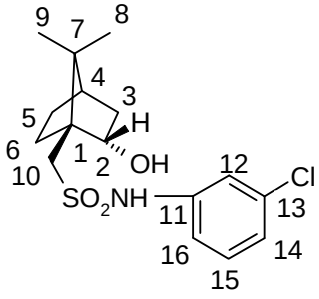
$PhCH_2$), 4.72 (1H, m, NH) and 7.31-7.39 (5H, overlapping signals, ArH); δ_C (150 MHz; $CDCl_3$) 19.8 (C-9), 20.5 (C-8), 27.3, 30.5 and 39.0 (C-3, C-5 and C-6), 44.3 (C-4), 47.4 and 48.7 (C-1 and C-7), 50.4 (C-10), 53.2 (C-11), 76.4 (C-2) and 128.1 (2 x ArC), 128.2 (ArC), 128.9 (2 x ArC) and 136.6 (ArC).

Fraction 2. *N*-Benzyl-*2-endo*-hydroxybornane-10-sulfonamide **279,** as white crystals (22.0%), m.p. 96-98 ºC (lit.,[145,150] 124-126 ºC); δ_H (150 MHz; $CDCl_3$) 0.796 (3H, s, 9-Me), 0.803 (3H, s, 8-Me), 1.05-2.38 (7H, series of multiplets, 3-, 5- and 6-CH_2 and 4-CH), 2.94 and 2.97 (2H, 2 x d, *J* 14.4 Hz, 10-CH_2), 3.18 (1H, s, OH), 4.32 (1H, d, *J* 10.2 Hz, 2-H), 4.32 (2H, m, $PhCH_2$), 4.99 (1H, m, NH) and 7.32-7.39 (5H, overlapping signals, ArH); δ_C (150 MHz; $CDCl_3$) 18.8 (C-9), 20.3 (C-8), 23.7, 28.2 and 38.5 (C-3, C-5 and C-6), 43.9 (C-4), 47.6 and 51.0 (C-1 and C-7), 51.5 (C-10), 56.7 (C-11), 75.0 (C-2), 128.1 (2 x ArC), 128.2 (ArC), 128.9 (2 x ArC) and 136.7 (ArC).

N-*(3-Chlorophenyl)-2*-exo-*hydroxybornane-10-sulfonamide* 280 *and* N-*(3-chloro-phenyl)-2*-endo-*hydroxybornane-10-sulfonamide* 281



280



281

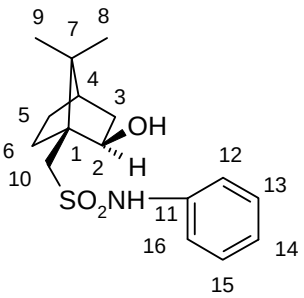
The experimental procedure employed for the synthesis of *N*-benzyl-*2-exo*-hydroxybornane-10-sulfonamide **278** and *N*-benzyl-*2-endo*-hydroxybornane-10-sulfonamide **279** was followed, using a solution of *N*-(3-chlorophenyl)camphor-10-

sulfonamide **266** (12.0 g, 38.1 mmol) in EtOH-H_2O (5:1; 104 mL) which was added drop-wise to a stirred solution of $NaBH_4$ (14.4 g, 381 mmol) in EtOH-H_2O (5:1; 121 mL) at room temperature. Work-up afforded a brown crystalline material (7.00 g), which was chromatographed [HPLC; elution with hexane-EtOAc (8: 2)] to afford two products.

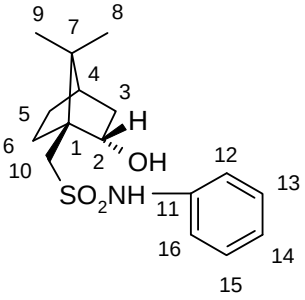
Fraction 1. N-*(3-Chlorophenyl)-2*-exo-*hydroxybornane-10-sulfonamide* **280,** as white crystals (93%), m.p. 108-110 ºC (Found: MH^-, 342.0916. $C_{16}H_{21}NO_3SCl$ requires, *M*-H: 342.0931); ν_{max}(ATR)/cm^{-1} 3441 (OH); δ_H (600 MHz; $CDCl_3$) 0.78 (3H, s, 9-Me), 1.03 (3H, s, 8-Me), 1.14- 1.83 (7H, series of multiplets, 3-, 5- and 6-CH_2 and 4-CH), 2.98 and 3.55 (2H, 2 x d, *J* 13.8 Hz, 10-CH_2), 3.05 (1H, s, OH), 4.14 (1H, m, 2-H), 6.79 (1H, br s, NH) and 7.12 (1H, ddd, *J* 0.7, 2.3 and 8.3 Hz, ArH), 7.16 (1H, ddd, *J* 1.1, 2.0 and 8.0 Hz, ArH), 7.23 (1H, t, *J* 2.1 Hz, ArH) and 7.29 (1H, t, *J* Hz, ArH); δ_C (150 MHz; $CDCl_3$) 19.9 (C-9), 20.5 (C-8), 27.3, 30.5 and 39.3 (C-3, C-5 and C-6), 44.4 (C-4), 49.0 and 50.5 (C-1 and C-7), 52.0 (C-10), 76.4 (C-2) and 118.0, 120.1, 125.3, 130.8, 135.4 and 138.0 (ArC).

Fraction 2. N-*3-Chlorophenyl-2*-endo-*hydroxybornane-10-sulfonamide* **281,** as white crystals (7%) (Found: MH^-, 342.0946. $C_{16}H_{21}NO_3SCl$ requires, *M*-H: 342.0931); δ_H (600 MHz; $CDCl_3$) 0.85 (6H, s, 9-Me and 8-Me), 1.06-2.44 (7H, series of multiplets, 3-, 5- and 6-CH_2 and 4-CH), 3.13 and 3.19 (2H, 2 x d, *J* 14.6 Hz, 10-CH_2), 4.32 (1H, dt, *J* 3.9 and 15.0 Hz, 2-H), and 7.12-7.28 (5H, series of multiplets, ArH).

***2*-exo-*Hydroxy*-N-*phenylbornane-10-sulfonamide* 282 *and 2*-endo-*hydroxy*-N-*phenyl-bornane-10-sulfonamide* 283**



282



283

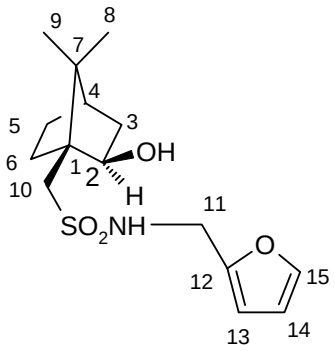
The experimental procedure employed for the synthesis of *N*-benzyl-2-*exo*-hydroxybornane-10-sulfonamide **278** and *N*-benzyl-2-*endo*-hydroxybornane-10-sulfonamide **279** was followed, using a solution of *N*-phenylcamphor-10-sulfonamide **267** (11.4 g, 36.9 mmol) in EtOH-H_2O (5:1; 99 mL) which was added drop-wise to a stirred solution of $NaBH_4$ (14.0 g, 369 mmol) in EtOH-H_2O (5:1; 120 mL) at room temperature. Work-up afforded a dark green crystalline material (11.0 g), which was chromatographed [HPLC; elution with hexane-EtOAc (8: 2)] to afford two products.

Fraction 1. 2-*exo*-Hydroxy-*N*-phenylbornane-10-sulfonamide **282,** as white crystals, (90%), m.p. 92-94 ºC (lit.,[147] 100-102 ºC); δ_H (600 MHz; $CDCl_3$) 0.76 (3H, s, 9-Me), 1.01 (3H, s, 8-Me), 1.13-1.82 (7H, series of multiplets, 3-, 5- and 6-CH_2 and 4-CH), 2.98 and 3.53 (2H, 2 x d, *J* 13.8 Hz, 10-CH_2), 3.14 (1H, s, OH), 4.14 (1H, m, 2-H), 6.72 (1H, t, *J* 22.5 Hz, NH) and 7.19 (1H, t, *J* 7.2 Hz, ArH), 7.22 (2H, t, *J* 8.1 Hz, ArH) and 7.36 (2H, d, *J* 8.4 Hz, ArH); δ_C (150 MHz; $CDCl_3$) 19.8 (C-9), 20.5 (C-8), 27.3, 30.5 and 39.1 (C-3, C-5 and C-6), 44.4 (C-4), 48.9 and 50.4 (C-1 and C-7), 51.6 (C-10), 76.4 (C-2) and 120.4 (2 x ArC), 125.3 (ArC), 129.8 (2 x ArC) and 136.7 (ArC).

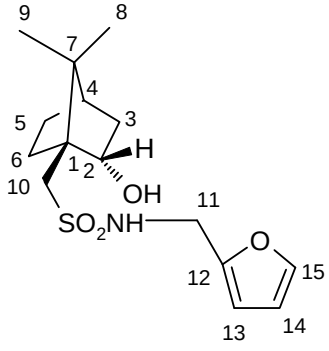
Fraction 2. 2-*endo*-Hydroxy-*N*-phenylbornane-10-sulfonamide **283,** as white crystals (10%), m.p. 86-88 ºC (lit.,[150] 124-126 ºC); δ_H (600 MHz; $CDCl_3$) 0.82 (3H, s, 9-Me), 0.83 (3H, s, 8-Me), 1.07-1.81 (7H, series of multiplets, 3-, 5- and 6-CH_2 and 4-CH), 3.13 and 3.19 (2H, 2 x d, *J* 14.4 Hz, 10-CH_2), 3.18 (1H, br s, OH), 4.33 (1H, d, *J* 2-H), 7.16 (1H,

NH) and 7.15-7.36 (5H, series of multiplets, ArH); δ_C (150 MHz; $CDCl_3$) 18.8 (C-9), 20.3 (C-8), 24.0, 28.3 and 38.8 (C-3, C-5 and C-6), 43.9 (C-4), 51.0 and 51.6 (C-1 and C-7), 54.6 (C-10), 75.3 (C-2) and 119.9 (2 x ArC), 125.0 (ArC), 129.7 (2 x ArC) and 137.1 (ArC).

N-*(2-Furfuryl)-2*-exo-*hydroxycamphor-10-sulfonamide* 284 *and* N-*(2-furfuryl)-2*-endo-*hydroxycamphor-10-sulfonamide* 285



284



285

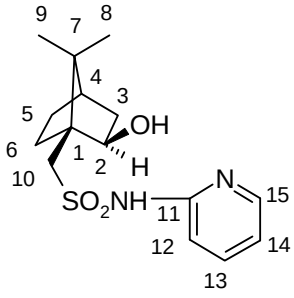
The experimental procedure employed for the synthesis of *N*-benzyl-2-*exo*-hydroxybornane-10-sulfonamide **278** and *N*-benzyl-2-*endo*-hydroxy-bornane-10-sulfonamide **279** was followed, using a solution of *N*-2-furfuryl-camphor-10-sulfonamide **268** (12.2 g, 39.0 mmol) in EtOH-H_2O (5:1; 106 mL) which was added drop-wise to a stirred solution of $NaBH_4$ (14.8 g, 390.0 mmol) in EtOH-H_2O (5:1; 127 mL) at room temperature. Work-up afforded a brown oil (10.1 g), which was chromatographed [HPLC; elution with hexane-EtOAc (8: 2)] to afford two products.

Fraction 1. *N*-Furfuryl-2-*exo*-hydroxycamphor-10-sulfonamide **284**, as yellow crystals (82%), m.p. 60-62 °C; ν_{max}(ATR)/cm^{-1} 3493 (OH); δ_H (400 MHz; $CDCl_3$) 0.72 (3H, s, 9-Me), 0.97 (3H, s, 8-Me), 1.408-1.75 (7H, series of multiplets, 3-, 5-, 6-CH_2 and 4-CH), 2.97 and 3.26 (2H, 2 x d, *J* 15.0 Hz, 10-CH_2), 3.16 (1H, br s, 2-OH), 4.04 (1H, 2-CH), 4.33 (2H, s, furfuryl CH_2), 4.87 (1H, br s, NH), 6.33 (2H, m, 13-H and 14-H) and 7.40 (1H, br s, 15-H); δ_C (100 MHz; $CDCl_3$) 19.8 (C-9), 20.5 (C-8), 27.3 (C-3), 30.3 (C-5),

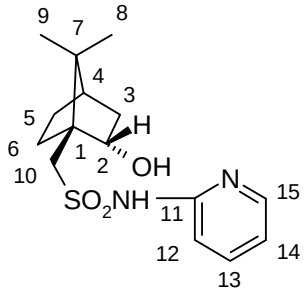
38.9 (C-11), 40.0 (C-6), 44.3 (C-4), 48.6 and 50.3 (C-1 and C-7), 53.1 (C-10), 76.4 (C-2), 108.9 (C-14), 110.7 (C-13), 142.8 (C-15) and 150.0 (C-12).

Fraction 2. N-*Furfuryl-2*-endo-*hydroxycamphor-10-sulfonamide* **285**, as a brown oil (trace amounts) (Found: MH^-, 312.1281. $C_{15}H_{22}NO_4S$ requires, *M*-H: 312.1270); δ_H (400 MHz; $CDCl_3$) 0.81 (6H, br s, 8-Me and 9-Me), 1.41-1.75 (7H, series of multiplets, 3-, 5-, 6-CH_2 and 4-CH), 2.92 and 2.97 (2H, 2 x d, *J* 14.0 Hz, 10-CH_2), 3.10 (1H, br s, 2-OH), 4.16 (1H, d, *J* 10.0 Hz, 2-CH), 4.34 (2H, m, furfuryl CH_2), 5.17 (1H, br s, NH), 6.34 and 6.36 (2H, m, 13-H and 14-H) and 7.41 (1H, m, 15-H).

N-*(2-Pyridinyl)-2*-exo-*hydroxycamphor-10-sulfonamide* 286 *and* N-*(2-pyridinyl)-2*-endo-*hydroxycamphor-10-sulfonamide* 287



286



287

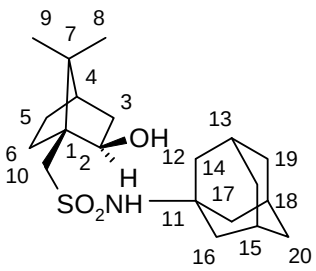
The experimental procedure employed for the synthesis of *N*-benzyl-2-*exo*-hydroxybornane-10-sulfonamide **278** and *N*-benzyl-2-*endo-hydroxybornane-10-sulfonamide* **279** was followed, using a solution of *N*-2-aminopyridinyl-camphor-10-sulfonamide **269** (5.78 g, 18.8 mmol) in EtOH-H_2O (5:1; 52 mL) which was added drop-wise to a stirred solution of $NaBH_4$ (7.10 g, 188 mmol) in EtOH-H_2O (5:1; 61 mL) at room temperature. Work-up afforded a yellow crystalline material (5.70 g), which was chromatographed [HPLC; elution with hexane-EtOAc (8: 2)] to afford two products.

Fraction 1. *2*-exo-*Hydroxy*-N-(*2-pyridinyl)camphor-10-sulfonamide* **286**, as white crystals (87%), m.p. 230-232 °C (Found: MH^+, 311.1423. $C_{15}H_{23}N_2O_3S$ requires, *M*+H:

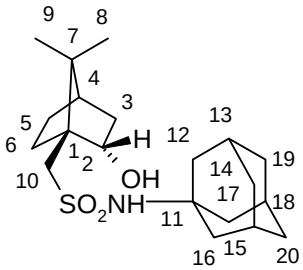
311.1429); ν_{max}(ATR)/cm^{-1} 3413 (OH); δ_H (400 MHz; $CDCl_3$) 0.81 (3H, s, 9-Me), 1.06 (3H, s, 8-Me), 1.60-1.85 (6H, series of multiplets, 3-, 5- and 6-CH_2), 2.09 (4-CH), 3.12 and 3.74 (2H, 2 x d, *J* 9.2 Hz, 10-CH_2), 4.17 (1H, dd, *J* 2.4 Hz, 2-CH), 6.84 (2H, br s, NH and OH), 7.05 (1H, s, 14-H), 7.61 (1H, d, *J* 5.6 Hz, 12-H), 7.91 (1H, t, *J* 5.0 Hz, 13-H) and 8.18 (1H, s, 15-H); δ_C (150 MHz; $CDCl_3$) 20.0 (C-9), 20.5 (C-8), 27.3, 30.5 and 39.4 (C-3, C-5 and C-6), 44.5 (C-4), 49.1 and 50.7 (C-1 and C-7), 53.5 (C-10), 75.9 (C-2) and 115.1 (C-14), 116.3 (C-12), 140.1 (C-13), 143.4 (C-15) and 152.1 (C-11).

Fraction 2. *2*-endo-*Hydroxy*-N-(*2-pyridinyl)camphor-10-sulfonamide* **287**, as a yellow oil (13%) (Found: MH^+, 311.1430. $C_{15}H_{23}N_2O_3S$ requires, *M*+H: 311.1429); ν_{max}(ATR)/cm^{-1} 3413 (OH); δ_H (400 MHz; $CDCl_3$) 0.89 (3H, s, 9-Me), 0.89 (3H, s, 8-Me), 1.60-1.85 (6H, series of multiplets, 3-, 5- and 6-CH_2), 2.04 (1H, br s, 4-CH), 3.30 (2H, 2 x d, *J* 9.2 Hz, 10-CH_2), 4.44 (1H, d, *J* 6.4 Hz, 2-CH), 6.84 (2H, br s, NH and OH) and 7.05-8.18 (5H, overlapping signals, ArH); δ_C (150 MHz; $CDCl_3$) 20.7 (C-9 and C-8), 23.6, 28.2 and 38.4 (C-3, C-5 and C-6), 44.2 (C-4), 48.2 and 51.6 (C-1 and C-7), 54.5 (C-10), 75.1 (C-2) and 115.1 (C-14), 116.3 (C-12), 140.1 (C-13), 143.4 (C-15) and 152.1 (C-11).

_N_-(1-adamantyl)-2-exo-hydroxybornane-10-sulfonamide 288 and _N_-(1-adamantyl)-2-endo-hydroxybornane-10-sulfonamide 289



288



289

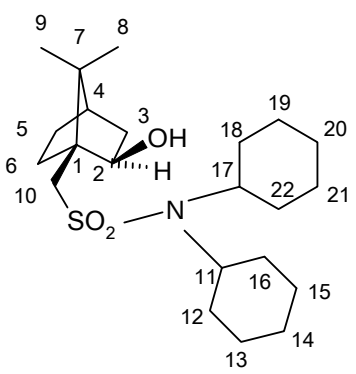
The experimental procedure employed for the synthesis of *N*-benzyl-2-*exo*-hydroxybornane-10-sulfonamide **278** and *N*-benzyl-2-*endo*-hydroxy-bornane-10-sulfonamide **279** was followed, using a solution of *N*-(1-adamantyl)camphor-10-sulfonamide **270** (9.30 g, 25.4 mmol) in EtOH-H_2O (5:1; 83 mL) which was added

dropwise to a stirred solution of $NaBH_4$ (9.59 g, 369 mmol) in EtOH-H_2O (5:1; 82 mL) at room temperature. Work-up afforded a brown crystalline material (6.8 g), which was chromatographed [HPLC; elution with hexane-EtOAc (8: 2)] to afford two products.

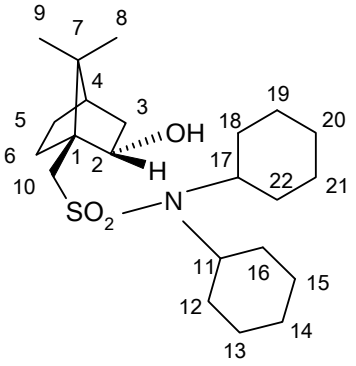
Fraction 1. *N*-(1-Adamantyl)-2-*exo*-hydroxybornane-10-sulfonamide **288,** as white crystals (87%), m.p. 184-186 °C (lit.,[149] 191-194 °C); δ_H (400 MHz; $CDCl_3$) 0.83 (3H, s, 9-Me), 1.07 (3H, s, 8-Me), 1.10-1.83 (6H, series of multiplets, 3-, 5- and 6-CH_2), 1.67 and 1.96 (12H, 2 x m, AdCH_2), 1.73 (1H, m, 4-H), 2.12 (3H, m, AdCH), 2.93 and 3.50 (2H, 2 x d, *J* 13.8 Hz, 10-CH_2), 3.33 (1H, d, *J* 4.2 Hz, OH), 4.07 (1H, m, 2-H) and 4.17 (1H, br s, NH); δ_C (100 MHz; $CDCl_3$) 19.9 (C-9), 20.6 (C-8), 27.4, 30.7 and 38.9 (C-3, C-5 and C-6), 29.6 (AdCH), 35.9 and 43.4 (AdCH_2), 44.4 (C-4), 48.6 and 50.8 (C-1 and C-7), 55.3 (AdC), 57.0 (C-10) and 76.2 (C-2).

Fraction 2. *N*-(1-Adamantyl)-2-*endo*-hydroxybornane-10-sulfonamide **289,** as white crystals (13%), m.p. 156-158 °C (lit.,[149] 156-158 °C); δ_H (400 MHz; $CDCl_3$) 0.90 (3H, s, 9-Me), 0.91 (3H, s, 8-Me), 1.10-2.45 (6H, series of multiplets, 3-, 5- and 6-CH_2), 1.64 (1H, partially overlapped t, *J* 4.8 Hz, 4-H), 1.67 and 1.97 (12H, 2 x m, *J* 1.6 Hz, AdCH_2), 2.12 (3H, m, AdCH), 3.09 and 3.17 (2H, 2 x d, *J* 14.2 Hz, 10-CH_2), 3.48 (1H, d, *J* 2.8 Hz, OH), 4.23 (1H, br s, NH) and 4.34 (1H, ddd, *J* 10.0, 7.2 and 2.8 Hz, 2-H); δ_C (100 MHz; $CDCl_3$) 18.9 (C-9), 20.5 (C-8), 23.8, 28.2 and 38.3 (C-3, C-5 and C-6), 29.6 (AdCH), 35.9 and 43.3 (AdCH_2), 43.9 (C-4), 51.3 and 51.5 (C-1 and C-7), 55.5 (AdC), 60.6 (C-10) and 75.2 (C-2).

N,N-(*Dicyclohexyl)-2*-exo-*hydroxycamphor-10-sulfonamide* 290 *and* N,N-(*dicyclohexyl)-2*-endo-*hydroxycamphor-10-sulfonamide* 291



290



291

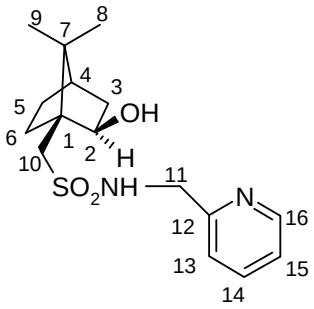
The experimental procedure employed for the synthesis of *N*-benzyl-2-*exo*-hydroxybornane-10-sulfonamide 2**78** and *N*-benzyl-2-*endo*-hydroxy-bornane-10-sulfonamide **279** was followed, using a solution of *N*-(dicyclohexyl)camphor-10-sulfonamide **271** (8.69 g, 22.0 mmol) in EtOH-H_2O (5:1; 78 mL) which was added dropwise to a stirred solution of $NaBH_4$ (8.32 g, 220 mmol) in EtOH-H_2O (5:1; 71 mL) at room temperature. Work-up afforded white crystals (8.7 g), which were chromatographed [HPLC; elution with hexane-EtOAc (8: 2)] to afford two products.

Fraction 1. *N,N*-(Dicyclohexyl)-2-*exo*-hydroxycamphor-10-sulfonamide **290** as white crystals (62%), m.p. 158-160 °C (lit.,[151] 163-164 °C); δ_H (400 MHz; $CDCl_3$) 0.80 and 1.05 (6H, 2 x s, 8- and 9-Me), 1.11-3.27 (31H, m, 14 x CH_2 and 3 x CH), 3.51 (1H, d, *J* 4.0 Hz, 2-H) and 4.08 (1H, m, 2-OH); δ_C (100 MHz; $CDCl_3$) 20.0 and 20.6 (C-8 and C-9), 44.6 (C-4), 57.9 (2 x CHN), 76.6 (C-2), 25.2, 26.5, 32.8 and 33.0 (cyclohexyl CH_2), 27.4, 31.0, 39.0 and 55.3 (camphor CH_2), 48.5 and 50.9 (C-1 and C-7).

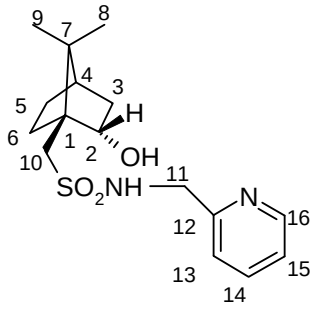
Fraction 2. N,N-*(Dicyclohexyl)-2*-endo-*hydroxycamphor-10-sulfonamide* **291**, as white crystals (38%), m.p. 162-164 °C (Found: MH^+, 398.2725. $C_{22}H_{40}NO_3S$ requires, *M*+H: 398.2729); ν_{max}(ATR)/cm^{-1} 3503 (OH); δ_H (400 MHz; $CDCl_3$) 0.87 and 0.88 (6H, 2 x s, 8- and 9-Me), 1.11-3.27 (31H, m, 14 x CH_2 and 3 x CH), 3.82 (1H, m, 2-OH) and

4.29 (1H, d, *J* 8.8 Hz, 2-H); δ_C (100 M Hz; $CDCl_3$) 20.0 and 20.6 (C-8 and C-9), 44.0 (C-4), 57.8 (2 x CH-N), 75.5 (C-2), 25.1, 26.4, 32.7 and 32.8 (cyclohexyl CH_2), 27.4, 33.5, 38.1 and 59.2 (camphor CH_2), 49.7 and 51.6 (C-1 and C-7).

N-*2*-exo-*hydroxy-(2-picolyl)camphor-10-sulfonamide* 292 *and* N-*2*-endo-*hydroxy- (2-picolyl)camphor-10-sulfonamide* 293



292



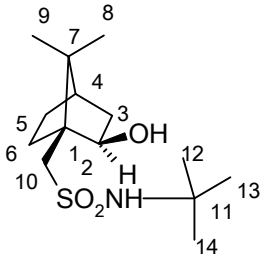
293

The experimental procedure employed for the synthesis of *N*-benzyl-2-*exo*-hydroxybornane-10-sulfonamide **278** and *N*-benzyl-2-*endo*-hydroxy-bornane-10-sulfonamide **279** was followed, using a solution of *N*-(2-picolyl)camphor-10-sulfonamide **272** (1.00 g, 3.10 mmol) in EtOH-H_2O (5:1; 9 mL) which was added drop-wise to a stirred solution of $NaBH_4$ (0.94 g, 24.8 mmol) in EtOH-H_2O (5:1; 8 mL) at room temperature. Work-up and HPLC chromatography [elution with hexane-EtOAc (8:2)] furnished two products.

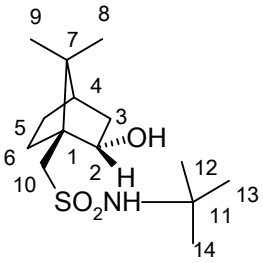
Fraction 1. *N*-2-*exo*-Hydroxy-(2-picolyl)camphor-10-sulfonamide **292**, as a colourless oil (90%); δ_H (400 MHz; $CDCl_3$) 0.76 (3H, s, 9-Me), 1.01 (3H, s, 8-Me), 1.08-1.78 (7H, series of multiplets, 3-, 5- and 6-CH_2 and 4-H), 2.83 and 3.43 (2H, 2 x d, *J* 14.0 Hz, 10-CH_2), and 4.09 (1H, dd, *J* 4.0 and 8.0 Hz, 2-H), 4.46 (2H, br s, NCH_2), 5.46 (1H, br s, NH), 7.24 (1H, m, ArH), 7.31 (1H, d, *J* 8.0 Hz, ArH), 7.71 (1H, t, *J* 7.6 Hz, ArH) and 8.53 (1H, d, *J* 4.0 Hz, ArH); δ_C (100 MHz; $CDCl_3$) 19.9 (C-8), 20.5 (C-9), 27.4, 30.4 and 39.3 (C-5, C-6 and C-3), 44.4 (C-4), 47.7 (C-1), 48.7 (C-7), 50.4 (C-11), 52.5 (C-10), 76.1 (C-2), 122.2, 122.9, 137.2, 149.3 and 155.3 (ArC).

Fraction 2. N-*2*-endo-*Hydroxy-(2-picolyl)camphor-10-sulfonamide* **293**, as a colourless oil (10%) (Found: MH^+, 325.1592. $C_{16}H_{25}N_2O_3S$ requires, *M*+H: 325.1586); ν_{max}(ATR)/cm^{-1} 3524 (OH); δ_H (400 MHz; $CDCl_3$) 0.76 (3H, s, 9-Me), 1.01 (3H, s, 8-Me), 1.08-1.78 (7H, series of multiplets, 3-, 5- and 6-CH_2 and 4-H), 2.83 and 3.43 (2H, 2 x d, *J* 14.0 Hz, 10-CH_2), and 4.09 (1H, dd, *J* 4.0 and 7.8 Hz, 2-H), 4.46 (2H, br s, NCH_2), 5.46 (1H, br s, NH), 7.24 (1H, m, ArH), 7.31 (1H, d, *J* 8.0 Hz, ArH), 7.71 (1H, t, *J* 7.6 Hz, ArH) and 8.53 (1H, d, J 4.0 Hz, ArH); δ_C (100 MHz; $CDCl_3$) 18.9 (C-8), 20.4 (C-9), 26.7, 30.2 and 38.5 (C-5, C-6 and C-3), 44.0 (C-4), 47.6 (C-1), 47.9 (C-7), 51.1 (C-11), 51.5 (C-10), 75.1 (C-2), 122.9, 122.9, 137.1, 149.2 and 154.9 (ArC).

N-*(t-Butyl)-2-exo-hydroxycamphor-10-sulfonamide* 294 *and* N-*(t-butyl)-2-endo-hydroxycamphor-10-sulfonamide* 295



294



295

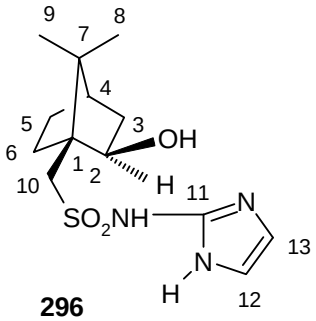
The experimental procedure employed for the synthesis of *N*-benzyl-2-*exo*-hydroxybornane-10-sulfonamide **278** and *N*-benzyl-2-*endo*-hydroxy-bornane-10-sulfonamide **279** was followed, using a solution of *N*-(*t*-butyl)camphor-10-sulfonamide **273** (1.00 g, 3.48 mmol) in EtOH-H_2O (5:1; 9 mL) which was added drop-wise to a stirred solution of $NaBH_4$ (1.05 g, 34.8 mmol) in EtOH-H_2O (5:1; 9 mL) at room temperature. Work-up and HPLC chromatography [elution with hexane-EtOAc (8:2)] furnished two fractions.

Fraction 1. *N*-(*t*-Butyl)-2-*exo*-hydroxycamphor-10-sulfonamide **294**, as white crystals (79%), m.p. 206-208 °C (lit.,[150] 94-96 °C); δ_H (400 MHz; $CDCl_3$) 0.82 (3H, s, 9-Me), 1.07 (3H, s, 8-Me), 1.40 (9H, s, 12-, 13- and 14-CH_3), 1.13-1.76 (6H, series of multiplets,

3-, 5- and 6-CH_2), 2.16 (1H, s, 4-H), 2.93 and 3.49 (2H, 2 x d, *J* 13.8 Hz, 10-CH_2), 3.30 (1H, d, *J* 3.6 Hz, 2-OH), 4.07 (1H, m, 2-H) and 4.22 (1H, s, NH); δ_C (100 MHz; $CDCl_3$) 19.9 (C-8), 20.6 (C-9), 27.4 (C-5), 30.4 (C-12, C-13 and C-14), 30.7 (C-6), 38.9 (C-3), 44.5 (C-4), 48.7 (C-11), 50.8 (C-7), 54.9 (C-1), 56.3 (C-10) and 76.5 (C-2).

Fraction 2. *N*-(*t*-Butyl)-2-*endo*-hydroxycamphor-10-sulfonamide **295** as mixture of white crystals; δ_H (400 MHz; $CDCl_3$) 0.89 (3H, s, 9-Me), 0.91 (3H, s, 8-Me), 1.40 (9H, s, 12-, 13- and 14-CH_3), 1.13-1.76 (6H, series of multiplets, 3-, 5- and 6-CH_2), 2.37 (1H, m, 4-H), 3.12 (2H, 2 x d, *J* 14.0 Hz, 10-CH_2), 3.48 (1H, m, 2-OH), 4.33 (1H, d, *J* 10.0 Hz, 2-H) and 4.37 (1H, br s, NH); δ_C (100 MHz; $CDCl_3$) 18.9 (C-8), 20.4 (C-9), 28.3 (C-5), 30.4 (C-12, C-13 and C-14), 29.7 (C-6), 38.3 (C-3), 44.0 (C-4), 48.7 (C-11), 50.8 (C-7), 54.8 (C-1), 59.9 (C-10) and 76.3 (C-2).

***2*-exo-*Hydroxy*-N-*(2-imidazolyl)camphor-10-sulfonamide* 296**

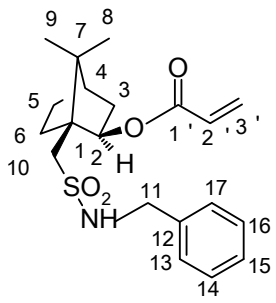


296

The experimental procedure employed for the synthesis of *N*-benzyl-2-*exo*-hydroxybornane-10-sulfonamide **278** and *N*-benzyl-2-*endo*-hydroxy-bornane-10-sulfonamide **279** was followed, using a solution of *N*-(1-imidazolyl)camphor-10-sulfonamide **274** (2.00 g, 6.73 mmol) in EtOH-H_2O (5:1; 18 mL) which was added drop-wise to a stirred solution of $NaBH_4$ (2.04 g, 53.8 mmol) in EtOH-H_2O (5:1; 18 mL) at room temperature. Work-up and HPLC chromatography [elution with hexane-EtOAc (8:2)] furnished *2*-exo-*hydroxy*-N-*(2-imidazolyl)camphor-10-sulfonamide* **296**, as a black oil (1.73 g, 86%) (Found: MH^+, 300.1395. $C_{13}H_{22}N_3O_3S$ requires, *M*+H: 299.1304); ν_{max} (ATR)/cm^{-1} 3378 (OH); δ_H (400 MHz; $CDCl_3$) 0.83 (3H, s, 9-Me), 1.09 (3H, s, 8-Me),

1.22-1.80 (6H, series of multiplets, 3-, 5- and 6-CH_2), 2.17 (1H, s, 4-CH), 2.87 and 3.42 (2H, 2 x d, *J* 13.6 Hz, 10-CH_2), 3.25 (1H, s, 2-OH), 3.93 (1H, m, 2-H), 6.53 (2H, br s, 12- and 13-CH) and 11.6 (2H, s, NH); δ_C (100 MHz; $CDCl_3$) 19.8 (C-8), 20.4 (C-9), 27.1, 30.7 and 30.9 (C-5, C-6 and C-3), 44.1 (C-4), 47.3 (C-7), 50.1 (C-1), 50.6 (C-10), 75.8 (C-2), 106.7 (C-12), 113.5 (C-13) and 147.6 (C11).

2*-exo-*Acryloyloxy*-N-*(benzyl)bornane-10-sulfonamide* 297, N-*benzyl-2*-exo-*[(3-chloro-propanoyl)oxy]bornane-10-sulfonamide* 298, *2*-endo-*acryloyloxy*-N-*(benzyl)bornane-10-sulfonamide 299 and* N-*(phenylmethyl)-3-[(phenylmethyl)amino]propanamide 300



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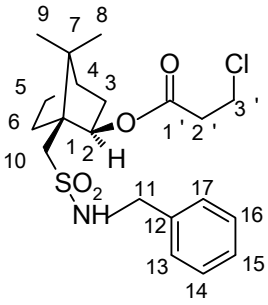

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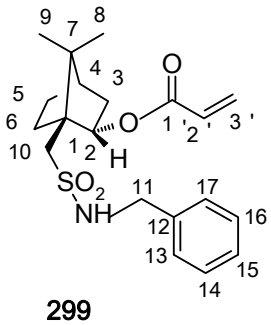
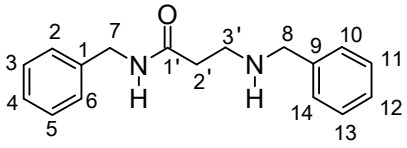


299



300

Neutral Al_2O_3 (0.244 g, 2.4 mmol) was added to the mixture of the diastereomeric alcohols **278** and **279** (0.50 g, 1.6 mmol), followed by acryloyl chloride (0.3 g, 3 mmol). The resulting dispersion was shaken, sealed and kept unstirred at r.t. for 72h. The mixture was then taken up in $CHCl_3$ (3 x 1 mL), filtered and the filtrate dried over anhydrous $MgSO_4$. The solvent was removed *in vacuo* to givean oil which was then treated with triethylamine (0.46 g, 3.1 mmol). The resulting mixture was stored under N_2 and stirred at 25 °C for 1 h and the taken up in EtOAc (5 mL); the organic solution was washed with brine and dried over anhydrous $MgSO_4$. Solvent was removed *in vacuo* to give an oil which was chromatographed [HPLC; elution with hexane-EtOAc (8: 2)] to afford four fractions.

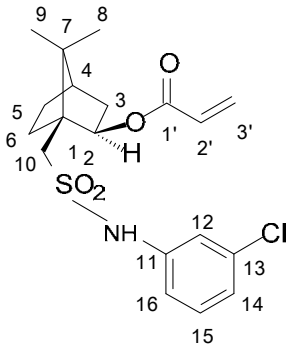
Fraction 1. *2*-exo-*Acryloyloxy*-N-*(benzyl)bornane-10-sulfonamide* **297** as white crystals (0.39 g, 65 %), m.p. 82-84 °C (Found: MH^+, 378.1747. $C_{20}H_{28}NO_4S$ requires, *M*+H: 378.1747); ν_{max}(ATR)/cm^{-1} 1706 (C=O); δ_H (400 MHz; $CDCl_3$) 0.82 and 0.99 (6H, 2 x s, 8- and 9-Me), 1.18-2.03 (7H, series of multiplets, 3-, 5- and 6-CH_2 and 4-H), 2.81 and 3.43 (2H, 2 x d, *J* 14.0 Hz, 10-CH_2), 4.25 (2H, d, *J* 6.0 Hz, PhCH_2), 4.57 (1H, br s, NH), 5.04 (1H, d, *J* 6.4 Hz, 2-H) and 5.79 (1H, d, *J* 10.4 Hz, 3'-H_E), 6.09 (1H, dd, *J* 10.2 and 17.4 Hz, 2'-H) and 6.33 (1H, d, *J* 17.6 Hz, 3'-H_Z) and 7.33 (5H, overlapping signals, Ar-H); δ_C (100 MHz; $CDCl_3$) 19.9 and 20.3 (C-8 and C-9), 27.0, 29.8 and 39.5 (C-3, C-5 and C-6), 44.4 (C-4), 47.2 (C-11), 49.2 and 49.4 (C-1 and C-7), 51.9 (C-10), 77.9 (C-2), 128.9 (C-2'), 130.3 (C-3'), 127.97, 128.0, 128.8 and 137.0 (ArC) and 164.8 (C=O).

Fraction 2. N-*Benzyl*-*2*-exo-*[(3-chloropropanoyl)oxy]bornane-10-sulfonamide* **298**, as white crystals (0.13 g, 22 %), m.p. 92-94 °C (Found: MH^+, 414.1498. $C_{20}H_{29}NO_4ClS$ requires, *M*+H: 414.1506); ν_{max}(ATR)/cm^{-1}1728 (C=O); δ_H (400 MHz; $CDCl_3$) 0.79 and 0.96 (6H, 2 x s, 8- and 9-Me), 1.18 - 1.96 (7H, series of multiplets, 3-, 5- and 6-CH_2 and 4-H), 2.74 (2H, m, 2'-CH_2), 2.76 and 3.55 (2H, 2 x d, *J* 14.0 Hz, 10-CH_2), 3.71 (2H, d, *J* 6.4 Hz, 3'-CH_2), 4.29 (2H, 1 x d, *J* 6.0 Hz, PhCH_2), 4.66 (1H, s, NH), 4.98 (1H, d, *J* 6.0 Hz, 2-H) and 7.36 (5H, overlapping signals, ArH); δ_C (100 MHz; $CDCl_3$) 19.9 and 20.2 (C-8 and C-9), 27.0, 30.0 and 39.4 (C-3, C-5 and C-6), 37.9 (C-2'), 39.2 (C-3'), 44.4 (C-4), 47.2 (C-11), 49.1 and 49.4 (C-1 and C-7), 52.2 (C-10), 78.5 (C-2), 128.0, 128.1, 128.9 and 137.0 (ArC) and 169.0 (C=O).

Fraction 3. *2*-endo-*Acryloyloxy*-N-*(benzyl)bornane-10-sulfonamide* **299**, a solid isolated as a mixture with **298** (trace amounts); δ_H (400 MHz; $CDCl_3$) 0.85 and 0.86 (6H, 2 x s, 8- and 9-Me), 1.19-1.98 (7H, series of multiplets, 3-, 5- and 6-CH_2 and 4-H), 2.92 (2H, 2 x d, *J* 14.4 Hz, 10-CH_2), 4.27 (2H, 1 x d, *J* 6.0 Hz, PhCH_2), 5.16 (1H, d, *J* 6.0 Hz, NH), 5.16 (1H, d, *J* 10.4 Hz, 3-H_E), 5.79 (1H, d, *J* 1.2 Hz, 2-H), 6.10 (1H, dd, *J* 10.4 and 17.2 Hz, 2'-H), 6.42 (1H, d, *J* 17.2 Hz, 3'-H_Z), and 7.31-7.37 (5H, overlapping signals, Ar-H).

Fraction 4. *N*-(Phenylmethyl)-3-[(phenylmethyl)amino]propanamide **300** (trace amounts); δ_H (400 MHz; $CDCl_3$) 2.17 (2H, s, 2 x NH), 2.89 (2H, t, *J* 6.8 Hz, 2'-CH_2), 3.91 (2H, t, *J* 6.8 Hz, 3'-CH_2), 4.47 (2H, s, 8-CH_2), 4.64 (2H, s, 7-CH_2) and 7.16-7.38 (10H, overlapping signals, ArH).

***2*-exo-*Acryloyloxy*-N-*3-(chlorophenyl)bornane-10-sulfonamide* 301, N-*3-chlorophenyl-2*-exo-*[(3-chloropropanoyl)oxy]bornane-10-sulfonamide* 302, N-*(3-chloro-phenyl)-2-propenamide* 303 *and 3-chloro*-N-*(3-chlorophenyl)propanamide* 304**



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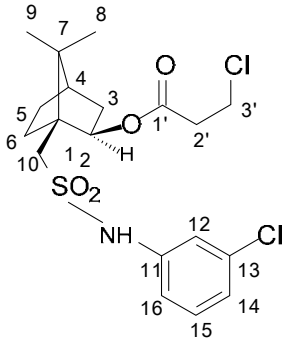
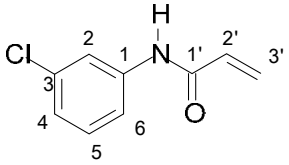


302



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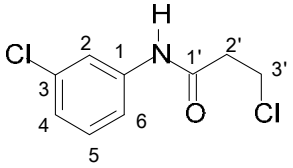


304

The experimental procedure described for the synthesis of compounds **297**-**300** was employed, using neutral Al_2O_3 (0.28 g, 3.1 mmol), which was added to the mixture of alcohols 2**80** and **281** (0.50 g, 1.5 mmol), followed by addition of acryloyl chloride (0.28 g, 3.1 mmol). Likewise work-up and purification by HPLC [elution with hexane-EtOAc (8: 2)] afforded four fractions.

Fraction 1. *2*-exo-*Acryloyloxy*-N-*3-(chlorophenyl)bornane-10-sulfonamide* **301**, as white crystals (0.42 g, 70 %), m.p. 150-152 °C (Found: MH^+, 398.1195. $C_{19}H_{25}NO_4ClS$ requires, *M*+H: 398.1193); ν_{max}(ATR)/cm^{-1} 1710 (C=O); δ_H (400 MHz; $CDCl_3$) 0.86 and

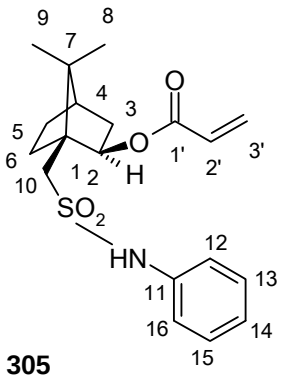
1.00 (6H, 2 x s, 8- and 9-Me), 1.26 -2.02 (7H, series of multiplets, 3-, 5- and 6-CH_2 and 4-H), 3.03 and 3.62 (2H, 2 x d, *J* 14.0 Hz, 10-CH_2), 5.07 (1H, d, *J* 8.4 Hz, 2-H), 5.75 (1H, d, *J* 10.4 Hz, 3'-H_E), 5.98 (1H, dd, *J* 10.4 and 17.2 Hz, 2'-H), 6.24 (1H, d, *J* 17.2 Hz, 3'-H_Z), 7.05-7.21 (5H, overlapping signals, ArH and NH); δ_C (400 MHz; $CDCl_3$) 19.9 and 20.3 (C-8 and C-9), 27.1, 30.1 and 39.5 (C-5, C-6 and C-3), 44.4 (C-4), 49.2 and 49.7 (C-7 and C-1), 50.7 (C-10), 77.7 (C-2), 117.0, 119.1 and 124.5 (C-16, C-12 and C-14), 128.5 and 130.4 (C-2' and C-3'), 130.6, 135.3 and 138.5 (ArC) and 164.8 (C=O).

Fraction 2. N-*3-Chlorophenyl-2*-exo-*[(3-chloropropanoyl)oxy]bornane-10-sulfonamide* **302** as white crystals (0.10 g, 17 %), m.p. 120-122 °C; ν_{max}(ATR)/cm^{-1} 1698 (C=O); δ_H (400 MHz; $CDCl_3$) 0.84 and 0.99 (6H, 2 x s, 8- and 9-Me), 1.67-1.99 (7H, series of multiplets, 3-, 5- and 6-CH_2 and 4-H), 2.68 (2H, t, *J* 6.6 Hz, 2'-CH_2), 3.01 and 3.55 (2H, 2 x d, *J* 14.0 Hz, 10-CH_2), 3.66 (2H, m, and 3'-CH_2), 5.02 (1H, d, *J* 6.8 Hz, 2-H), 6.69 (1H, br s, NH) and 7.06 (1H, ddd, *J* 0.9, 2.1 and 8.1 Hz, ArH), 7.14 (1H, ddd, J 0.8, 2.0 and 8.0 Hz, ArH), 7.23 (1H, t, 2.0 Hz, ArH) and 7.28 (1H, t, *J* 8.0 Hz, ArH);); δ_C (100 MHz; $CDCl_3$) 19.9 and 20.3 (C-8 and C-9), 27.0, 30.2 and 39.5 (C-5, C-6 and C-3), 37.7 (C-2'), 39.1 (C-3'), 44.4 (C-4), 49.1 and 49.7 (C-7 and C-1), 50.9 (C-10), 78.4 (C-2), 117.7, 119.6, 125.0, 130.7, 135.4, 138.3 (ArC) and 168.9 (C=O).

Fraction 3. *N*-(3-Chlorophenyl)-2-propenamide **303**, as (trace amounts); δ_H (400 MHz; $CDCl_3$) 5.79 (1H, d, *J* 10.0 Hz, 3'-H_Z), 6.25 (1H, dd, *J* 10.4 and 16.8 Hz, 2'-H), 6.44 (1H, d, *J* 16.8 Hz, 3'-H_Z), 7.10 (1H, d, *J* 7.6 Hz, 4-H), 7.24 (1H, t, *J* 8.0 Hz, 5-H), 7.42 (1H, d, *J* 7.2 Hz, 6-H), 7.54 (1H, s, NH) and 7.70 (1H, s, 2-H); δ_C (100 MHz; $CDCl_3$) 128.4 (C-3'), 130.8 (C-2'), 117.9, 120.1, 124.6, 130.0, 134.7 and 138.8 (ArC) and 163.6 (C=O).

Fraction 4. 3-Chloro-N-(3-chlorophenyl)propanamide **304** as off-white crystals (0.03 g, 5 %), m.p. 68-70 °C (lit.,[147] 81-83 °C); δ_H (400 MHz; $CDCl_3$) 2.85 (2H, t, *J* 6.0 Hz, 2'-CH_2), 3.90 (2H, t, *J* 6.4 Hz, 3'-CH_2), 7.13 (1H, d, *J* 8.0 Hz, 4-H), 7.27 (1H, m, 5-H), 7.38 (1H, d, *J* 8.4 Hz, 6-H), 7.68 (1H, s, 2-H) and 7.73 (1H, s, NH).

***2*-exo-*Acryloyloxy*-N-*(phenyl)bornane-10-sulfonamide* 305, *2*-exo-*[(3-chloropropanoyl)oxy]*-N-*(phenyl)bornane-10-sulfonamide* 306, *2*-endo-*acryloyloxy*-N-*(phenyl)bornane-10-sulfonamide* 307 *and* N-*(3-chlorophenyl)propanamide* 308**



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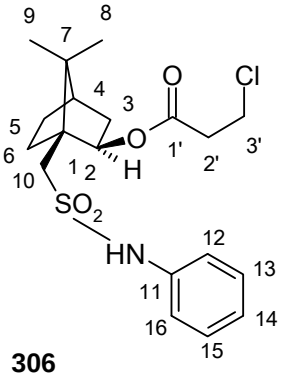

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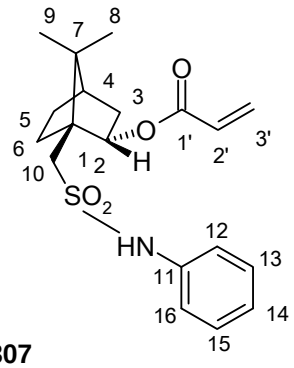

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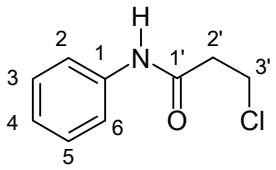


308

The experimental procedure described for the synthesis of compound **297**-**300** was employed, using neutral Al_2O_3 (0.26 g, 2.3 mmol), which was added to the mixture of alcohols **282** and **293** (0.51 g, 1.7 mmol), followed by addition of acryloyl chloride (0.32 g, 3.6 mmol). Work-up and purification by HPLC [elution with hexane-EtOAc (8: 2)] afforded four fractions.

Fraction 1. *2*-exo-*Acryloyloxy*-N-*(phenyl)bornane-10-sulfonamide* **305** (36% - contaminated with compound **15b**); δ_H (400 MHz; $CDCl_3$) 0.82 and 0.96 (6H, 2 x s, 8- and 9-Me), 1.20-2.03 (7H, series of multiplets, 3-, 5- and 6-CH_2 and 4-H), 3.01 and 3.54 (2H, 2 x d, *J* 14.0 Hz, 10-CH_2), 5.04 (1H, d, *J* 6.4 Hz, 2-H), 5.73 (1H, d, *J* 12.0 Hz, 3'-H_E), 5.97 (1H, dd, *J* 10.4 and 17.2 Hz, 2'-H), 6.22 (1H, d, *J* 17.2 Hz, 3'-H_Z) and 7.10-7.34 (5H, m, Ar-H); δ_C (100 MHz; $CDCl_3$) 19.8 and 20.2 (C-8 and C-9), 27.0, 30.0 and 39.4 (C-5, C-6 and C-3), 44.3 (C-4), 49.0 and 49.6 (C-7 and C-1), 50.1 (C-10), 78.3 (C-

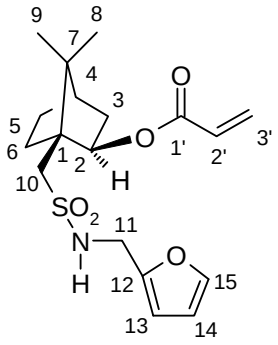
2), 128.6 and 130.3 (C-2' and C-3') 119.1, 119.2, 120.1, 124.9, 129.6, 137.1 (ArC) and 169.0 (C=O).

Fraction 2. *2*-exo-*[(3-Chloropropanoyl)oxy]*-N-*phenylbornane-10-sulfonamide* **306** (64% -contaminated with compound **305**); δ_H (400 MHz; $CDCl_3$) 0.83 and 1.00 (6H, 2 x s, 8- and 9-Me), 1.20-2.03 (7H, series of multiplets, 3-, 5- and 6-CH_2 and 4-H), 2.58 and 3.00 (2H, t, *J* 6.8 Hz, 2'-CH_2), 3.12 (2H, d, *J* 14.0 Hz), 3.61 (2H, d, *J* 7.0 Hz, 3'-CH_2), and 7.10-7.34 (5H, m, Ar-H); δ_C (100 MHz; $CDCl_3$) 19.9 and 20.2 (C-8 and C-9), 27.0, 29.9 and 39.5 (C-5, C-6 and C-3), 37.6 and 39.0 (C-2' and C-3'), 44.4 (C-4), 49.1 and 49.6 (C-7 and C-1), 50.1 (C-10), 77.8 (C-2), 119.2 (2 x C, ArC), 120.1 (ArC), 129.6 (2 x ArC), 137.2 (ArC) and 164.8 (C=O).

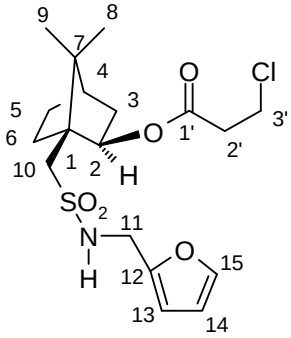
Fraction 3. *2*-endo-*Acryloyloxy*-N-*(phenyl)bornane-10-sulfonamide* **307** as (trace amounts and contaminated); δ_H (400 MHz; $CDCl_3$) 0.85 and 0.86 (6H, 2 x s, 8- and 9-Me), 1.96-1.98 (7H, series of multiplets, 3-, 5- and 6-CH_2 and 4-H), 2.87 and 2.97 (2H, 2 x d, *J* 14.4 Hz, 10-CH_2), 4.58 (1H, br s, NH), 5.16 (1H, d, *J* 9.6 Hz, 2-H), 5.80 (1H, d, *J* 10.4 Hz, 3'-H_E), 6.10 (1H, dd, *J* 10.4 and 17.2 Hz, 2'-H), 6.42 (1H, d, *J* 17.2 Hz, 3'-H_Z) and 7.30-7.37 (5H, m, Ar-H).

Fraction 4. *N*-(3-Chlorophenyl)propanamide **308** as (trace amounts and contaminated); δ_H (400 MHz; $CDCl_3$) 2.82 (2H, t, *J* 6.0 Hz, 2'-CH_2), 3.89 (2H, t, *J* 6.4 Hz, 3'-CH_2), 7.13 (1H, t, *J* 7.2 Hz, ArH), 7.34 (2H, t, *J* 7.6 Hz, ArH) and 7.52 (2H, d, *J* 7.6 Hz) (ArH) and 7.25 (1H, s, NH); δ_C (100 MHz; $CDCl_3$) 29.7 (C-2'), 39.9 (C-3'), 120.0, 125.0, 129.1 and 136.6 (ArC) and 175.8 (C=O).

***2*-exo-*Acryloyloxy*-N-*(furfuryl)bornane-10-sulfonamide* 309 *and 2*-exo-*[(3-chloroprop-ano-yl)oxy]*-N-*(furfuryl)bornane-10-sulfonamide* 310**



309



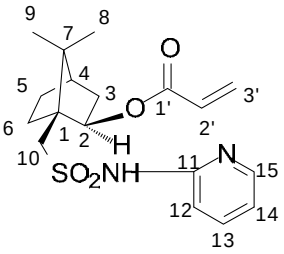
310

The experimental procedure described for the synthesis of compounds **297**-**300** was employed, using neutral Al_2O_3 (0.44 g, 4.3 mmol), which was added to the mixture of alcohols **284** and **285** (0.91 g, 3.0 mmol), followed by addition of acryloyl chloride (0.59 g, 6.5 mmol). Work-up and purification by HPLC [elution with hexane-EtOAc (8: 2)] afforded two compounds as a mixture.

Fraction 1. *2*-exo-*Acryloyloxy*-N-*(furfuryl)bornane-10-sulfonamide* **309** (31%) as a yellow oil contaminated with compound **310**; δ_H (400 MHz; $CDCl_3$) 0.84 (3H, s, 9-Me), 0.96 (3H, s, 8-Me), 1.23-1.77 (6H, series of multiplets, 3-, 5- and 6-CH_2), 2.05 (1H, s, 4-CH), 2.99 and 3.54 (2H, 2 x d, *J* 13.8 Hz, 10-CH_2), 3.89 (2H, t, *J* 6.4 Hz, furfural-CH_2), 5.01 (1H, d, *J* 6.8 Hz, 2-H), 5.76 (1H, d, *J* 10.4 Hz, 3'-H_E), 5.98 (1H, dd, *J* 10.4 and 17.4 Hz, 2'-H), 6.25 (1H, d, *J* 17.2 Hz, 3'-H_Z), 6.81 (1H, br s, NH) and 6.83-7.86 (3H, series of multiplets, ArH).

Fraction 2. *2*-exo-*[(3-Chloropropanoyl)oxy]*-N-*(furfuryl)bornane-10-sulfonamide* **310** (69%) as a yellow oil contaminated with compound **309**; δ_H (400 MHz; $CDCl_3$) 0.85 (3H, s, 9-Me), 0.98 (3H, s, 8-Me), 1.23-1.77 (6H, series of multiplets, 3-, 5-, 6-CH_2), 2.14 (1H, s, 4-CH), 2.82 (2H, t, *J* 6.4 Hz, 2'-CH_2), 2.98 and 3.63 (2H, 2 x d, *J* 13.8 Hz, 10-CH_2), 3.89 (4H, overlapping signals, 3'-CH_2 and furfural-CH_2), 5.08 (1H, d, J 6.4 Hz, 2-H), 6.69 (1H, br s, NH) and 6.81-7.86 (3H, series of m, ArH).

***2*-exo-*Acryloyloxy*-N-*(pyridinyl)bornane-10-sulfonamide* 311 *and* *2*-exo-*[(3-chloro-propanoyl)oxy]*-N-*(pyridinyl)bornane-10-sulfonamide* 312**



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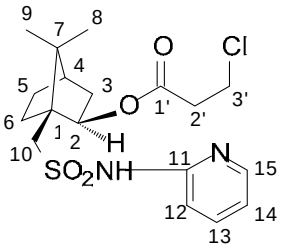


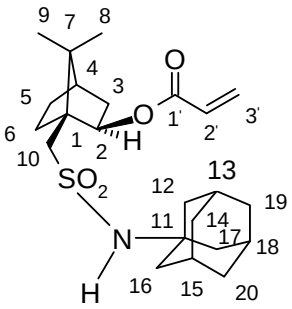
312

The experimental procedure described for the synthesis of **297**-**300** was employed, using neutral Al_2O_3 (0.71 g, 7.0 mmol), which was added to the mixture of alcohols **286** and **287** (1.39 g, 4.5 mmol), followed by addition of acryloyl chloride (0.09 g, 0.98 mmol). Work-up and purification by HPLC [elution with hexane-EtOAc (8: 2)] afforded two compounds as a mixture.

Fraction 1. *2*-exo-*Acryloyloxy*-N-*(pyridinyl)bornane-10-sulfonamide* **311** (37%) as a yellow solid mixture with compound **312**; δ_H (400 MHz; $CDCl_3$) 0.82 (3H, s, 9-Me), 0.85 (3H, s, 8-Me), 1.24-2.17 (7H, series of multiplets, 3-, 5-, 6-CH_2 and 4-CH), 3.06 and 3.57 (2H, 2 x d, *J* 14.4 Hz, 10-CH_2), 5.07 (1H, d, *J* 5.2 Hz, 2-H), 5.73 (1H, d, *J* 10.4 Hz, 3'-H_E), 5.98 (1H, dd, *J* 10.4 and 17.6 Hz, 2'-H), 6.26 (1H, d, *J* 17.6 Hz, 3'-H_Z), 6.55 (1H,br s, NH) and 7.43-7.75 (3H, series of multiplets, ArH).

Fraction 2. N-*Pyridinyl*-*2*-exo-*(3-chloropropanoyloxy)bornane-10-sulfonamide* **312** (63%) as a yellow solid mixture with compound **311**; δ_H (400 MHz; $CDCl_3$) 0.91 (3H, s, 9-Me), 1.01 (3H, s, 8-Me), 1.24-2.17 (7H, series of multiplets, 3-, 5-, 6-CH_2 and 4-CH), 3.04 and 3.57 (2H, 2 x d, *J* 14.4 Hz, 10-CH_2), 2.93 (2H, m, 2'-CH_2), 4.33 (2H, m, 3'-CH_2), 5.07 (1H, d, *J* 5.2 Hz, 2-H), 6.48 (1H, br s, NH) and 7.43-7.75 (3H, series of multiplets, ArH).

***2*-exo-*Acryloyloxy*-N-*(adamantyl)bornane-10-sulfonamide* 313, *2*-endo-*acryloyloxy*-N-*(adamantyl)bornane-10-sulfonamide* 314 *and* *2*-exo-*[(3-chloropropanoyl)oxy]*-N-*(adamantyl)bornane-10-sulfonamide* 315**



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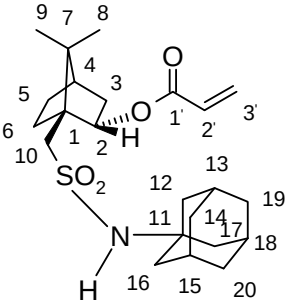
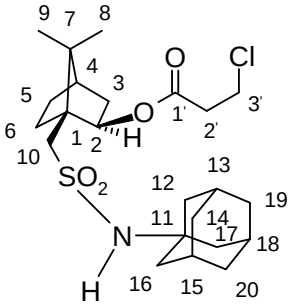


314



315

The experimental procedure described for the synthesis of compounds **297**-**300** was employed, using neutral Al_2O_3 (0.38 g, 3.7 mmol), which was added to a mixture of alcohols **288** and **289** (0.88 g, 2.4 mmol), followed by addition of acryloyl chloride (0.47 g, 5.1 mmol). Work-up and purification by HPLC [elution with hexane-EtOAc (8: 2)] afforded three fractions.

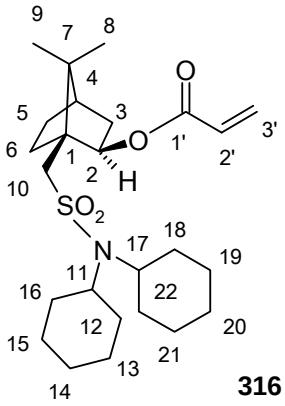
Fraction 1. 2-*exo*-Acryloyloxy-*N*-(adamantyl)bornane-10-sulfonamide **313** as white crystals (0.61 g, 60 %), m.p. 142-144 °C (lit.,[149] 173-176 °C); δ_H (400 MHz; $CDCl_3$) 0.90 and 1.03 (6H, 2 x s, 8- and 9-Me), 1.18-2.01 (6H, series of multiplets, 3-, 5- and 6-CH_2), 1.60 and 1.92 (12H, 2 x m, 12-, 14-, 16-, 17-, 19- and 20-CH_2), 1.79 (1H, m, 4-H), 2.07 (3H, m, 13-, 15- and 18-CH), 2.91 and 3.56 (2H, 2 x d, *J* 14.0 Hz, 10-CH_2), 4.06 (1H, s, NH), 5.06 (1H, m, 2-CH), 5.79 (1H, d, *J* 10.4 Hz, 3-H_E), 6.10 (1H, dd, *J* 10.4 and 17.2 Hz, 2'-H) and 6.35 (1H, d, *J* 17.2 Hz, 3'-H_Z); δ_C (100 MHz; $CDCl_3$) 20.0 and 20.4 (C-8 and C-9), 27.1, 29.9 and 39.5 (C-3, C-5 and C-6), 29.6 (C-13, C-15 and C-18), 35.9 (C-14, C-19 and C-20), 43.4 (C-12, C-16 and C-17), 44.4 (C-4), 49.3 and 49.5 (C-1 and C-7), 55.1 (C-10), 78.1 (C-2), 129.0 (C-2'), 130.0 (C-3') and 164.7 (C=O).

Fraction 2. 2-*endo*-Acryloyloxy-*N*-(adamantyl)bornane-10-sulfonamide **314** contaminated with compound **315**; δ_H (400 MHz; $CDCl_3$) 0.90 and 1.03 (6H, 2 x s, 8- and 9-Me), 1.18-2.01 (6H, series of multiplets, 3-, 5- and 6-CH_2), 1.60 and 1.92 (12H, 2 x m,

12-, 14-, 16-, 17-, 19- and 20-CH_2), 1.79 (1H, m, 4-H), 2.07 (3H, m, 13-, 15- and 18-CH), 2.91 and 3.56 (2H, 2 x d, *J* 14.0 Hz, 10-CH_2), 4.06 (1H, s, NH), 5.06 (1H, m, 2-CH), 5.79 (1H, d, *J* 10.4 Hz, 3-H_E), 6.10 (1H, dd, *J* 10.4 and 17.2 Hz, 2'-H) and 6.35 (1H, d, *J* 17.2 Hz, 3'-H_Z); δ_C (100 MHz; $CDCl_3$) 20.0 and 20.4 (C-8 and C-9), 27.1, 29.9 and 39.5 (C-3, C-5 and C-6), 29.6 (C-13, C-15 and C-18), 35.9 (C-14, C-19 and C-20), 43.4 (C-12, C-16 and C-17), 44.4 (C-4), 49.3 and 49.5 (C-1 and C-7), 55.1 (C-10), 78.1 (C-2), 129.0 (C-2'), 130.0 (C-3') and 164.7 (C=O).

Fraction 3. 2-exo-[(3-Chloropropanoyl)oxy]-N-(adamantyl)bornane-10-sulfonamide **315** as white crystals (0.33 g, 34 %), m.p. 146-148 °C; δ_H (400 MHz; $CDCl_3$) 0.90 and 1.03 (6H, 2 x s, 8- and 9-Me), 1.26 - 2.02 (6H, series of multiplets, 3-, 5- and 6-CH_2), 1.67 and 1.95 (12-H, 2 x m, 12-, 14-, 16-, 17-, 19- and 20-CH_2), 1.79 (1H, m, 4-H), 2.11 (3H, m, 13-, 15- and 18-CH), 2.78 (2H, t, *J* 6.4 and 6.8 Hz, 2'-CH_2), 3.21 (2H, 2 x d, *J* 14.0 Hz, 10-CH_2), 3.75 (2H, m, 3'-CH_2), 4.02 (1H, s, NH) and 5.00 (1H, d, *J* 5.6 Hz, 2-CH); δ_C (100 MHz; $CDCl_3$) 20.0 and 20.4 (C-8 and C-9), 27.1, 30.1 and 39.5 (C-3, C-5 and C-6), 29.6 (C-13, C-15 and C-18), 36.0 (C-14, C-19 and C-20), 43.4 (C-12, C-16 and C-17), 38.0 (C-2'), 39.2 (C-3'), 44.5 (C-4), 49.4 and 49.5 (C-1 and C-7), 55.1 (C-11), 55.6 (C-10), 78.1 (C-2) and 168.8 (C=O).

***2*-exo-*(Acryloyloxy)*-N,N-*(dicyclohexyl)bornane-10-sulfonamide* 316, *2*-exo-*[(3-chloro-propanoyl)oxy]*-N,N-*dicyclohexyl-bornane-10-sulfonamide* 317, N,N-*dicyclohexylpro-penamide* 318 *and 3-chloro*-N,N-*dicyclohexylpropanamide* 319**



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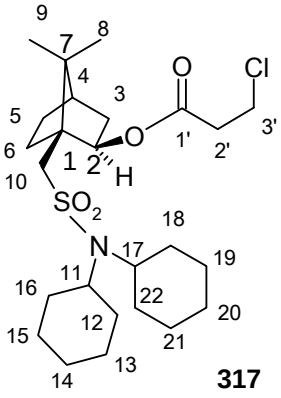
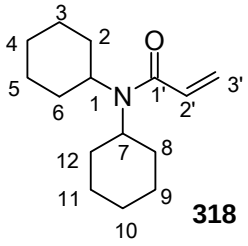


317



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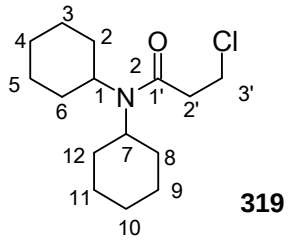


319

The experimental procedure described for the synthesis of compound **297**-**300** was employed, using neutral Al_2O_3 (0.23 g, 2.25 mmol), which was added to the mixture of alcohols **290** and **291** (0.59 g, 1.5 mmol), followed by addition of acryloyl chloride (0.28 g, 3.09 mmol). Work-up and purification by HPLC [elution with hexane-EtOAc (8: 2)] afforded four fractions.

Fraction 1. 2-*exo*-(Acryloyloxy)-*N*,*N*-(dicyclohexyl)bornane-10-sulfonamide **316** (42 %) as a white solid mixture contaminated with compound **317**; δ_H (400 MHz; $CDCl_3$) 0.89 and 1.01 (6H, 2 x s, 8- and 9-Me), 1.05-3.22 (31H, series of multiplets, 13 x CH_2 and 3 x CH), 5.09 (1H, d, *J* 7.6 Hz, 2-CH), 5.79 (1H, d, *J* 10.4 Hz, 3'-H_E), 6.10 (1H, dd, *J* 10.8 and 13.6 Hz, 2'-H) and 6.35 (1H, d, *J* 17.2 Hz, 3'-H_Z); δ_C (100 MHz; $CDCl_3$) 20.0 and 20.5 (C-8 and C-9), 44.6 (C-4), 57.4 (2 x CHN), 78.4 (C-2), 129.2 (C-2'), 129.8 (C-

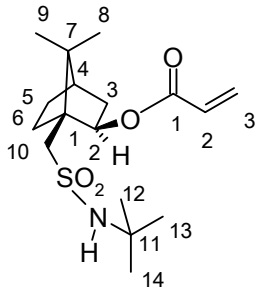
3'), 25.2, 26.4, 32.8 (cyclohexyl CH_2), 27.0, 29.9, 39.1 and 49.1 (camphor CH_2), 49.5 and 53.7 (C-1 and C-7) and 164.5 (C=O).

Fraction 2. *2*-exo-*[(3-Chloropropanoyl)oxy]*-N,N-*dicyclohexyl-bornane-10-sulfonamide* **317** (58%) as solid white crystals contaminated with **316**; δ_H (400 MHz; $CDCl_3$) 0.88 and 0.99 (6H, 2 x s, 8- and 9-Me), 1.05-3.22 (31H, series of m, 13 x CH_2 and 3 x CH), 4.99 (1H, d, *J* 7.6 Hz, 2-CH), 2.77 (2H, t, *J* 7.0 Hz, 2'-CH_2) and 3.76 (2H, m, 3'-CH_2); δ_C (100 MHz; $CDCl_3$) 20.0 and 20.4 (C-8 and C-9), 57.4 (2 x CHN of cyclohexyl), 37.8 (C-2'), 39.1 (C-3'), 44.5 (C-4), 79.2 (C-2), 25.1, 26.5 and 32.8 (cyclohexyl CH_2) , 27.0, 30.3, and 49.2 (camphor CH_2), 49.5 and 53.9 7 (C-1 and C-7) and 168.7 (C=O).

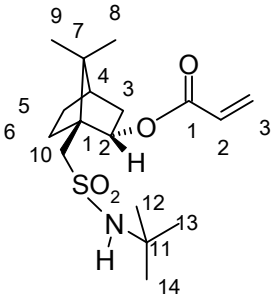
Fraction 3. *N,N*-dicyclohexylpropenamide **318** (trace amount) as a white solid mixture with compound **319**; δ_H (400 MHz; $CDCl_3$) 1.25-3.49 (22H, series of multiplets, 10 x CH_2 and 2 xCH), 5.55 (1H, d, *J* 10.4 Hz, 3'-H_Z), 6.16 (1H, d, *J* 16.8 Hz, 3'-H_E) and 6.54 (1H, dd, *J* 10.4 and 16.6 Hz, 2'-H).

Fraction 4. 3-chloro-*N,N*-dicyclohexylpropanamide **319** (trace amount) as white solid mixture with compound **318**; δ_H (400 MHz; $CDCl_3$) 0.89-1.24 (22H, series of multiplets, 10 x CH_2 and 2 x CH), 2.87 (2H, t, *J* 6.6 Hz, 2'-CH_2) and 3.76 (2H, t, *J* 6.6 Hz, 3'-CH_2).

***2*-exo-*(Acryloyloxy)*-N-*t*-butylbornane-*10*-sulfonamide 320 and *2*-endo-*(acryloyloxy)*-N-*t*-butylbornane-*10*-sulfonamide 321**



320



321

The experimental procedure described for the synthesis of compound **297**-**300** was employed, using neutral Al_2O_3 (0.16 g, 1.56 mmol), which was added to the mixture of alcohols **294** and **295** (0.30 g, 1.04 mmol), followed by addition of acryloyl chloride (0.19 g, 2.15 mmol). Work-up and purification by HPLC [elution with hexane-EtOAc (8: 2)] afforded two fractions.

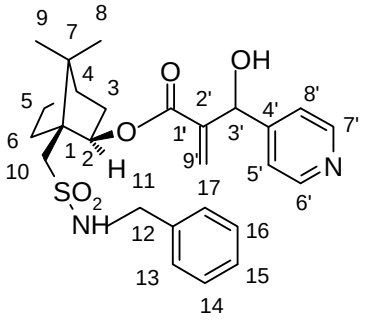
Fraction 1. *2-**exo**-(Acryloyloxy)-N-t-butylbornane-10-sulfonamide* **320** as a colourless oil (0.86 g, 86%) (Found: MH^+, 344.1897. $C_{17}H_{30}NO_4S$ requires, *M*+H: 344.1896); δ_H (400 MHz; $CDCl_3$) 0.90 and 1.03 (6H, 2 x s, 8- and 9-Me), 1.34 [9H, s, $C(CH_3)_3$], 1.21-1.99 (7H, series of multiplets, 3-, 5- and 6-CH_2 and 4-H), 2.91 and 3.54 (2H, 2 x d, *J* 14.0 Hz, 10-CH_2), 4.12 (1H, s, NH), 5.05 (1H, d, *J* 7.2 Hz, 2-H), 5.79 (1H, d, *J* 10.4 Hz, 3'-H_E), 6.09 (1H, dd, *J* 10.4 and 17.2 Hz, 2'-H) and 6.34 (1H, d, *J* 17.2 Hz, 3'-H_Z); δ_C (400 MHz; $CDCl_3$) 20.0 and 20.4 (C-8 and C-9), 27.1, 29.9 and 39.5 (C-3, C-5 and C-6), 30.3 [C (*C*H_3)], 44.4 (C-4), 49.4 and 54.7 (C-7 and C-1), 54.8 [*C*$(CH_3)_3$] 58.9 (C-10), 78.0 (C-2), 129.0 (C-2'), 130.1 (C-3') and 164.7 (C=O).

Fraction 2. *2-endo-(Acryloyloxy)-N-t-butylbornane-10-sulfonamide* **321** as a colourless oil (0.14, 14%) (Found: MH^+, 344.1892. $C_{17}H_{30}NO_4S$ requires, *M*+H: 344.1896); δ_H (400 MHz; $CDCl_3$) 0.94 and 0.98 (6H, 2 x s, 8- and 9-Me), 1.33 [9H, s, $C(CH_3)_3$], 1.07-1.78 (7H, series of multiplets, 3-, 5- and 6-CH_2 and 4-H), 3.06 and 3.16

(2H, 2 x d, *J* 14.0 Hz, 10-CH_2), 4.01 (1H, s, NH), 5.05 (1H, d, *J* 9.6 Hz, 2-H), 5.86 (1H, d, *J* 10.8 Hz, 3'-H_E), 6.15 (1H, dd, *J* 10.8 and 17.2 Hz, 2'-H) and 6.47 (1H, d, *J* 17.2 Hz, 3'-H_Z); δ_C (400 MHz; $CDCl_3$) 19.7 and 19.9 (C-8 and C-9), 25.5, 28.0 and 29.7 (C-5, C-6 and C-3), 30.3 [C(*C*H_3)], 44.0 (C-4), 50.1 and 50.7 (C-7 and C-1), 54.5 [*C*$(CH_3)_3$] 58.9 (C-10), 78.0 (C-2), 128.9 (C-2'), 130.9 (C-3') and 165.9 (C=O).

3.2.3. Morita-Baylis-Hillman Adducts from camphor-derived acrylates

Morita-Baylis-Hillman products **322**

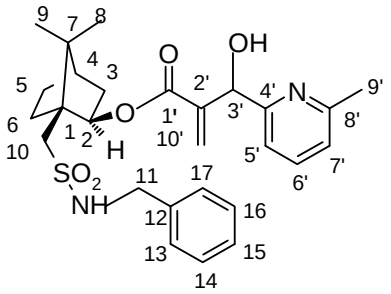


322

To a solution of 2-*exo*-acryloyloxy-*N*-1-benzylbornane -10-sulfonamide **297** (0.03 g, 0.07 mmol) in $CDCl_3$ (0.1 mL) was added pyridine-4-carbaldehyde (0.01 g, 0.07 mmol), and DABCO (0.001 g, 0.01 mmol). The solution was stirred at room temperature for 90 h then concentrated *in vacuo*. The residue was purified by flash chromatography and HPLC [elution with hexane-EtOAc (8: 2)] to afford a mixture of the diastereomeric *Morita-Baylis-Hillman products* **322** as yellow crystals (0.03 g, 91%; 8% d.e), m.p. 98-100 °C (Found: MH^+, 485.2111. $C_{26}H_{33}N_2O_5S$ requires, *M*+H: 485.2110); ν_{max}(ATR)/cm^{-1} 3274 (OH); δ_H (400 MHz; $CDCl_3$) 0.67 (3H, s, 9-Me), 0.68 (3H, s, 8-Me), 0.92-1.87 (7H, series of multiplets, 3-CH_2, 5-CH_2, 6-CH_2 and 4-H), 2.64 and 3.19 (2H, 2 x d, 14.0 Hz, 10-CH_2), 4.90 (2H, s, PhCH_2), 4.93 (2H, br s, 2-H and NH), 5.49 (1H, s, C*H*OH), 6.12 (1H, br s, OH), 5.72 and 6.17 (2H, 2 x s, 9'-CH_2), 7.40 (2H, d, *J* 4.5 Hz, ArH), 8.38 (5H, overlapping signals, ArH) and 8.56 (2H, d, *J* 4.5 Hz, ArH).); δ_C (400 MHz; $CDCl_3$) 19.3 and 19.9 (C-8 and C-9), 26.7, 29.7 and 39.1 (C-3, C-5 and C-6), 44.0 (C-4), 46.7 PhCH_2),

49.0 and 49.1 (C-7 and C-1), 51.8. (C-10), 71.2 (CHOH), 78.6 (C-2), 121.2 (2 x ArC), 126.4 (*C*=CH_2), 127.6 (2 x ArC), 128.5 (2 x ArC), 142.2 and 142.4 (C-1 and C-7), 149.3 (2 x ArC) and 164.6 (C=O).

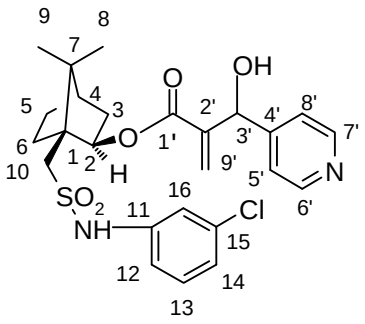
Morita-Baylis-Hillman products **323**



323

The procedure employed for the synthesis of the Morita-Baylis-Hillman products **322** was followed, using 2-*exo*-acryloyloxy-*N*-1-benzylbornane -10-sulfonamide **297** (0.03 g, 0.07 mmol) in $CDCl_3$ (0.1 mL), 6-methylpyridine-2-carbaldehyde (0.01 g, 0.07 mmol) and DABCO (0.001 g, 0.01 mmol). Work-up and purification afforded a mixture of the diastereomeric *Morita-Baylis-Hillman products* **323** as a brown oil (0.03 g, 100%; 33% d.e.) (Found: MH^+, 499.2252. $C_{27}H_{35}N_2O_5S$ requires, *M*+H: 499.2267); ν_{max}(ATR)/cm^{-1} 3266 (OH); δ_H (400 MHz; $CDCl_3$) 0.78 (3H, s, 9-Me), 0.93 (3H, s, 8-Me), 1.14-1.97 (6H, series of multiplets, 3-CH_2, 5-CH_2 and 6-CH_2), 2.17 (1H, s, 4-H), 2.65 and 3.27 (2H, 2 x d, 14.0 Hz, 10-CH_2), 4.18 (2H, d, *J* 5.6 Hz, PhCH_2), 4.27 (1H, t, 4.8 Hz, NH), 5.00 (1H, d, *J* 5.6 Hz, 2-H), 5.46 (1H, s, OH), 5.64 (1H, s, C*H*OH), 5.95 and 6.29 (2H, 2 x s, 9'-CH_2), 7.14 (2H, m, ArH), 7.33 (5H, overlapping signals, ArH) and 7.70 (1H, m, ArH). δ_C (100 MHz; $CDCl_3$) 19.8 and 20.1 (C-8, C-9 and ArCH_3), 27.0, 29.8 and 39.0 (C-3, C-5 and C-6), 44.4 (C-4), 47.0 (PhCH_2), 49.2 and 49.5 (C-7 and C-1), 52.1 (C-10), 70.8 (CHOH), 78.6 (C-2), 126.7 (C=*C*H_2), 127.8 (2 x ArC), 128.1 (2 x ArC), 128.2 (ArC), 128.7 (2 x ArC), 137.7 (*C*=CH_2), 148.7 (ArC), 155.8 (ArC) and 164.8 (C=O).

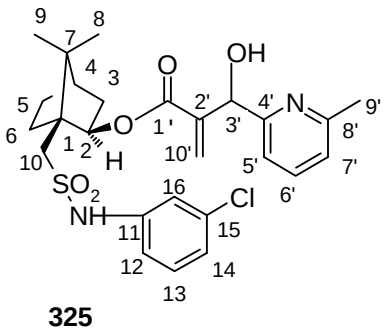
Morita-Baylis-Hillman products **324**



324

The procedure employed for the synthesis of the Morita-Baylis-Hillman products **322** was followed, using 2-*exo*-acryloyloxy-*N*-(3-chlorophenyl)bornane-10-sulfonamide **313** (0.03 g, 0.06 mmol) in $CDCl_3$ (0.1 mL), pyridine-4-carbaldehyde (0.01 g, 0.06 mmol) and DABCO (0.001 g, 0.01 mmol). Work-up and purification afforded a mixture of the diastereomeric *Morita-Baylis-Hillman products* **324** as a yellow oil (0.03 g, 92%; 7% d.e.) (Found: MH^+, 505.1542. $C_{25}H_{30}N_2O_5SCl$ requires, *M*+H: 505.1564); ν_{max}(ATR)/cm^{-1} 3374 (OH); δ_H (400 MHz; $CDCl_3$) 0.76 (3H, s, 9-Me), 0.81 (3H, s, 8-Me), 0.97-1.90 (7H, series of multiplets, 3-CH_2, 5-CH_2, 6-CH_2 and 4-H), 3.05 and 3.44 (2H, 2 x d, *J* 14.4 Hz, 10-CH_2), 5.00 (2H, m, 2-H and NH), .93 (2H, br s, 2-H and NH), 5.53 (1H, s, C*H*OH), 5.67 and 6.16 (2H, 2 x s, 9'-CH_2), 6.43 (1H, br s, OH) and 6.99-7.31 (8H, overlapping signals, ArH). δ_C (100 MHz; $CDCl_3$) 19.8 and 20.1 (C-8, C-9 and $ArCH_3$), 27.0, 29.8 and 39.0 (C-3, C-5 and C-6), 44.4 (C-4), 47.0 ($PhCH_2$), 49.2 and 49.5 (C-7 and C-1), 52.1 (C-10), 70.8 (CHOH), 78.6 (C-2), 126.7 (C=*C*H_2), 127.8 (2 x ArC), 128.1 (2 x ArC), 128.2 (ArC), 128.7 (2 x ArC), 137.7 (*C*=CH_2), 148.7 (ArC), 155.8 (ArC) and 164.8 (C=O).

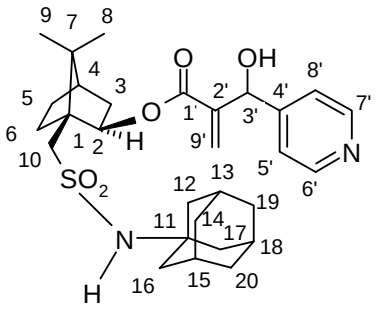
Morita-Baylis-Hillman products **325**



325

The procedure employed for the synthesis of the Morita-Baylis-Hillman products **322** was followed, using 2-*exo*-acryloyloxy-*N*-(3-chlorophenyl)bornane-10-sulfonamide **301** (0.03 g, 0.06 mmol) in $CDCl_3$ (0.1 mL), 6-methylpyridine-2-carbaldehyde (0.01 g, 0.07 mmol) and DABCO (0.001 g, 0.01 mmol). Work-up and purification afforded a mixture of the diastereomeric *Morita-Baylis-Hillman products* **325** as a yellow oil (0.03 g, 98%; % d.e.) (Found: MH^+, 520.3279. $C_{25}H_{30}N_2O_5SCl$ requires, *M*+H: 519.1720); ν_{max}(ATR)/cm^{-1} 3510 (OH); δ_H (400 MHz; $CDCl_3$) 0.69 (3H, s, 9-Me), 0.82 (3H, s, 8-Me), 0.99-1.95 (7H, series of multiplets, 3-CH_2, 5-CH_2, 6-CH_2 and 4-H), 2.63 (3H, s, ArCH_3), 2.91 and 3.30 (2H, 2 x d, 14.4 Hz, 10-CH_2), 5.05 (2H, m, 2-H and NH), 5.52 (1H, s, C*H*OH), 5.64 and 6.15 (2H, 2 x s, 9'-CH_2), 5.71 (1H, br s, OH) and 6.97-7.75 (7H, overlapping signals, ArH).

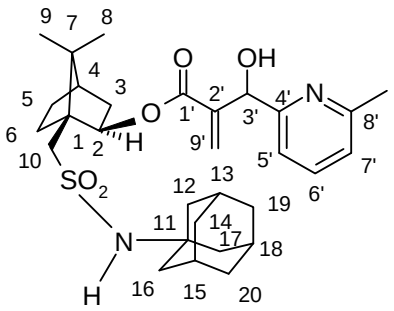
Morita-Baylis-Hillman products **326**



326

The procedure employed for the synthesis of the Morita-Baylis-Hillman products **322** was followed, using 2-*exo*-acryloyloxy-*N*-(1-adamantyl)bornane-10-sulfonamide **313** (0.03 g, 0.06 mmol) in $CDCl_3$ (0.1 mL), pyridine-4-carbaldehyde (0.01 g, 0.06 mmol) and DABCO (0.001 g, 0.01 mmol). Work-up and purification afforded a mixture of diastereomeric *Morita-Baylis-Hillman products* **326** as yellow crystals (0.03 g, 93%; 8% d.e.), m.p. 138-140 °C; δ_H (400 MHz; $CDCl_3$) 0.71 (3H, s, 9-Me), 0.78 (3H, s, 8-Me), 1.05-1.96 (7H, series of multiplets, 3-CH_2, 5-CH_2, 6-CH_2 and 4-H), 1.53 and 1.84 (12H, 2 x m, 12-, 14-, 16-, 17-, 19- and 20-CH_2), 1.94 (3H, m, 13-, 15- and 18-CH), 2.78 and 3.32 (2H, 2 x d, *J* 14.4 Hz, 10-CH_2), 4.79 (1H, m, 2-H), 4.85 (1H, br s, NH), 4.93 (1H, br s, OH), 5.51 (1H, s, C*H*OH), 5.72 and 6.20 (2H, 2 x s, 10'-CH_2), and 8.43 (4H, m,ArH). δ_C (100 MHz; $CDCl_3$) 20.9 and 21.7 (C-8, C-9), 24.1 (C-9'), 31.1 (C-13, C-15 and C-18), 31.1 (C-6), 35.8 (C-14, C-19 and C-20), 40.8 (C-3), 44.7 (C-4), 44.8 (C-12, C-16 and C-17), 50.5 and 50.9 (C-7 and C-1), 56.3 (C-11), 56.9 (C-10), 70.8 (CHOH), 79.8 (C-2), 118.1 (ArC), 122.6 (ArC), 127.8, (C-10'), 137.2 (ArC), 142.8 (C-2'), 155.7 (C-4'), 158.1 (ArC) and 166.2 (C=O).

Morita-Baylis-Hillman products **327**

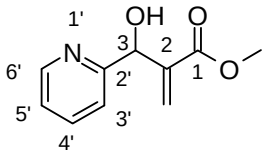


327

The procedure employed for the synthesis of the Morita-Baylis-Hillman products **322** was followed, using 2-*exo*-acryloyloxy-*N*-(1-adamantyl)bornane-10-sulfonamide **313** (0.03 g, 0.06 mmol) in $CDCl_3$ (0.1 mL), 6-methylpyridine-2-carbaldehyde (0.01 g, 0.06 mmol) and DABCO (0.001 g, 0.01 mmol). Work-up and purification afforded a mixture of diastereomeric *Morita-Baylis-Hillman products* **327** as a brown oil (0.03 g, 96%; 15% d.e.); δ_H (400 MHz; $CDCl_3$) 0.63 (3H, s, 9-Me), 0.83 (3H, s, 8-Me), 1.14-2.04 (7H, series of multiplets, 3-CH_2, 5-CH_2, 6-CH_2 and 4-H), 1.65 and 1.96 (12H, 2 x m, 12-, 14-, 16-, 17-, 19- and 20-CH_2), 2.08 and 2.57 (3H, m, 13-, 15- and 18-CH), 2.61 (3H, s, 9'-Me), 2.81 and 3.48 (2H, 2 x d, *J* 14.4 Hz, 10-CH_2), 4.64 (1H, br s, NH), 5.26 (1H, m, 2-H), 5.36 (1H, br s, OH), 5.54 (1H, s, C*H*OH), 5.94 and 6.39 (2H, 2 x s, 10'-CH_2), 7.12 (1H, d, *J* 8.0 Hz, ArH), 7.23 (1H, d, *J* 8.4 Hz, ArH) and 7.62 (1H, t, *J* 8.0 Hz, ArH). δ_C (100 MHz; $CDCl_3$) 20.9 and 21.7 (C-8, C-9), 24.1 (C-9'), 31.1 (C-13, C-15 and C-18), 31.1 (C-6), 35.8 (C-14, C-19 and C-20), 40.8 (C-3), 44.7 (C-4), 44.8 (C-12, C-16 and C-17), 50.5 and 50.9 (C-7 and C-1), 56.3 (C-11), 56.9 (C-10), 70.8 (CHOH), 79.8 (C-2), 118.1 (ArC), 122.6 (ArC), 127.8, (C-10'), 137.2 (ArC), 142.8 (C-2'), 155.7 (C-4'), 158.1 (ArC) and 166.2 (C=O).

3.2.4. Synthesis of heterocyclic MBH derivatives

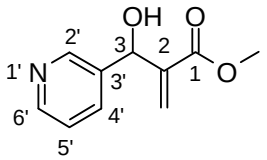
Methyl 3-hydroxy-2-methylene-3-(2-pyridinyl)propanoate **336**



336

A solution of methyl acrylate (2.50 g, 29 mmol), pyridine-2-carboxaldehyde (3.00 g, 28 mmol) and 3-hydroxyquinuclidine (0.17 g, 1.3 mmol) in $CHCl_3$ (2 mL) was stirred at room temperature. After 1 d, crystals appeared and a number of crops were collected and dried to afford methyl 3-hydroxy-2-methylene-3-(2-pyridinyl)propanoate **336** as white crystals (4.84 g, 90%), m.p. 96-98 °C (lit.,[147] 50-51 °C); δ_H (400 MHz; $CDCl_3$) 3.73 (3H, s, CH_3O), 4.81 (1H, br s, OH), 5.62 (1H, s, C*H*OH), 5.95 and 6.35 (2H, 2 x s, CH_2), 7.21 (1H, t, *J* 6.0 Hz, ArH), 7.41 (1H, d, *J* 7.6 Hz, ArH), 7.67 (1H, t, *J* 7.6 Hz, ArH) and 8.54 (1H, d, *J* 4.4 Hz, ArH); δ_C (100 MHz; $CDCl_3$) 52.0 (CH_3O), 70.7 (C-3), 126.2 (2-CH_2), 137.4 (C-2), 123.4, 134.5, 141.6, 148.3 and 148.6 (ArC) and 166.3 (C=O).

Methyl 3-hydroxy-2-methylene-3-(3-pyridinyl)propanoate **337**

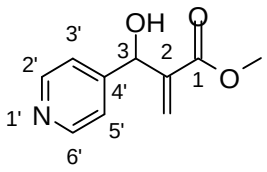


337

The procedure employed in the synthesis of methyl 3-hydroxy-2-methylene-3-(2-pyridinyl)propanoate **336** was followed, using methyl acrylate (2.50 g, 29 mmol), pyridine-3-carboxaldehyde (3.00 g, 28 mmol) and 3-hydroxyquinuclidine (0.17 g, 1.3 mmol) in $CHCl_3$ (2 mL). The solvent was removed *in vacuo* yielding methyl 3-hydroxy-

2-methylene-3-(3-pyridinyl)propanoate **337**, as a black oil (4.71 g, 87%); δ_H (400 MHz; $CDCl_3$) 3.73 (3H, s, CH_3O), 4.81 (1H, br s, OH), 5.62 (1H, s, C*H*OH), 5.96 and 6.35 (2H, 2 x s, CH_2), 7.21 (1H, t, *J* 6.0 Hz, ArH), 7.41 (1H, d, *J* 8.0 Hz, ArH), 7.67 (1H, t, *J* 7.6 Hz, ArH) and 8.54 (1H, d, *J* 4.4 Hz, ArH); δ_C (100 MHz; $CDCl_3$) 51.8 (CH_3O), 72.1 (C-3), 126.8 (CH_2), 141.7 (C-2), 121.2, 122.6, 136.8, 148.2 and 159.5 (ArC) and 166.5 (C=O).

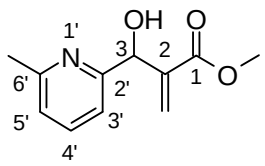
***Methyl 3-hydroxy-2-methylene-3-(4-pyridinyl)propanoate* 338**



338

The procedure employed in the synthesis of methyl 3-hydroxy-2-meth-ylene-3-(2-pyridinyl)propanoate **337** was followed, using methyl acrylate (2.50 g, 29 mmol), pyridine-4-carboxaldehyde (3.00 g, 28 mmol) and 3-hydroxyquinuclidine (0.17 g, 1.3 mmol) in $CHCl_3$ (2 mL). The crystals formed were filtered off and dried yielding methyl 3-hydroxy-2-methylene-3-(4-pyridinyl)propanoate **338** as orange crystals (4.37 g, 81%), m.p. 132-134°C (lit.[147] 129.5°C); δ_H (400 MHz; $CDCl_3$) 1.71 (1H, s, OH), 3.73 (3H, s, CH_3O), 5.52 (1H, s, C*H*OH), 5.86 and 6.38 (2H, 2 x s, CH_2), 7.32 (2H, d, *J* 5.2 Hz, ArH) and 8.56 (2H, d, *J* 4.8 Hz, ArH); δ_C (100 MHz; $CDCl_3$) 52.1 (CH_3O), 72.1 (C-3), 127.1 (CH_2), 141.0 (C-2), 121.3, 149.6 and 150.7 (ArC) and 166.5 (C=O).

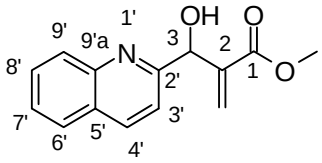
***Methyl 3-hydroxy-2-methylene-3-(6-methyl-2-pyridinyl)propanoate* 339**



339

The procedure employed in the synthesis of methyl 3-hydroxy-2-meth-ylene-3-(2-pyridinyl)propanoate **336** was followed, using methyl acrylate (2.50 g, 29 mmol), 6-methylpyridine-2-carboxaldehyde (3.39 g, 28 mmol) and 3-hydroxyquinuclidine (0.17 g, 1.34 mmol) in $CHCl_3$ (2 mL). The crystals formed were filtered off and dried yielding methyl 3-hydroxy-2-methyl-ene-3-(6-methyl-2-pyridinyl)propanoate **339** as colourless crystals (2.82 g, 52%), m.p. 78-80°C (lit.,[109] 84-85°C); δ_H (400 MHz; $CDCl_3$) 2.53 (3H, s, CH_3), 3.73 (3H, s, CH_3O), 5.21 (1H, br s, OH), 5.59 (1H, s, C*H*OH), 5.92 and 6.32 (2H, 2 x s, CH_2), 7.04 (1H, d, *J* 7.2 Hz, ArH), 7.08 (H, d, *J* 7.6 Hz, ArH) and 7.53 (1H, t, *J* 8.0 Hz, ArH); δ_C (100 MHz; $CDCl_3$) 24.2 (CH_3), 51.8 (CH_3O), 71.2 (C-3), 126.6 (CH_2), 142.1 (C-2), 118.0, 122.1, 137.0, 157.0 and 158.3 (ArC) and 166.5 (C=O).

***Methyl 3-hydroxy-2-methylene-3-(2-quinolinyl)propanoate* 340**

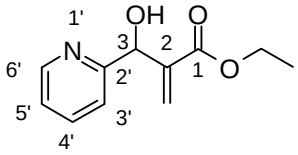


340

The procedure employed in the synthesis of methyl 3-hydroxy-2-methylene-3-(2-pyridinyl)propanoate **336** was followed, using methyl acrylate (1.25 g, 14.5 mmol), quinoline-2-carboxaldehyde (2.20 g, 14 mmol) and 3-hydroxyquinuclidine (0.09 g, 0.67 mmol) in $CHCl_3$ (2 mL). Work-up and flash chromatography afforded methyl 3-hydroxy-2-methylene-3-(2-quinolinyl)propanoate **340** as a brown oil (3.41 g, 100%); δ_H (400 MHz; $CDCl_3$) 3.73 (3H, s, CH_3O), 5.63 (1H, br s, OH), 5.82 (1H, s, C*H*OH), 6.02 and

6.42 (2H, 2 x s, C*H*$_2$), 7.49 (1H, d, *J* 8.8 Hz, ArH), 7.57 (1H, t, *J* 7.6 Hz, ArH), 7.75 (1H, t, *J* 8.0 Hz, ArH), 7.84 (1H, d, *J* 8.0 Hz, ArH) and 8.13 (2H, m, ArH); δ_C (400 MHz; $CDCl_3$) 51.9 (CH_3O), 71.8 (C-3), 127.6 (CH_2), 128.8 (C-2), 118.8, 126.6, 128.8, 129.8, 130.1, 137.1, 141.8, 146.4, 159.3 (ArC) and 166.6 (C=O).

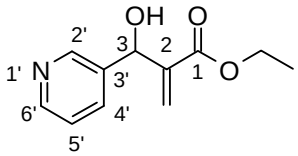
***Ethyl 3-hydroxy-2-methylene-3-(2-pyridinyl)propanoate* 341**



341

The procedure employed in the synthesis of methyl 3-hydroxy-2-methylene-3-(2-pyridinyl)propanoate **336** was followed, using ethyl acrylate (2.90 g, 29 mmol), pyridine-2-carboxaldehyde (3.00 g, 28 mmol) and 3-hydroxyquinuclidine (0.17 g, 1.3 mmol) in $CHCl_3$ (2 mL). Work-up afforded ethyl 3-hydroxy-2-methylene-3-(2-pyridinyl)propanoate **341** as a brown oil (5.36 g, 92%); δ_H (400 MHz; $CDCl_3$) 1.22 (3H, m, CH_3), 4.16 (2H, m, CH_2O), 4.80 (1H, br s, OH), 5.61 (1H, s, C*H*OH), 5.95 and 6.36 (2H, 2 x s, 2-CH_2), 7.20 (1H, m, ArH), 7.41 (1H, 1 x d, *J* 7.6 Hz, ArH), 7.67 (1H, m,ArH) and 8.53 (1H, s, ArH); δ_C (100 MHz; $CDCl_3$) 14.0 (CH_3), 60.7 (CH_2O), 72.2 (C-3), 126.6 (CH_2), 142.0 (C-2), 121.6, 122.6, 136.7, 148.2, 159.6 (ArC), and 166.1 (C=O).

***Ethyl 3-hydroxy-2-methylene-3-(3-pyridinyl)propanoate* 342**

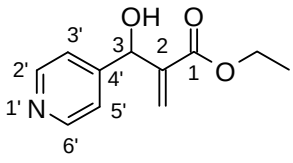


342

The procedure employed in the synthesis of methyl 3-hydroxy-2-methylene-3-(2-pyridinyl)propanoate **336** was followed, using ethyl acrylate (2.90 g, 29 mmol), pyridine-

3-carboxaldehyde (3.00 g, 28 mmol) and 3-hydroxyquinuclidine (0.17 g, 1.3 mmol) in $CHCl_3$ (2 mL). The crystals formed were filtered off, yielding ethyl 3-hydroxy-2-methylene-3-(3-pyridinyl)propanoate **342** as off-white crystals (5.51 g, 95%), m.p. 58-60 °C; δ_H (400 MHz; $CDCl_3$) 1.23 (3H, t, *J* 6.8 Hz, CH_3), 4.16 (3H, m, OH and CH_2O), 5.59 (1H, s, C*H*OH), 5.91 and 6.38 (2H, 2 x s, CH_2), 7.26 (1H, s, ArH), 7.72 (1H, d, *J* 7.6 Hz, ArH), 8.46 (1H, s, ArH) and 8.54 (1H, s, ArH); δ_C (100 MHz; $CDCl_3$) 14.0 (CH_3), 61.0 (CH_2O), 70.7 (C-3), 125.9 (CH_2), 137.6 (C-2), 123.3, 134.6, 141.9, 148.3 and 148.5 (ArC) and 165.8 (C=O).

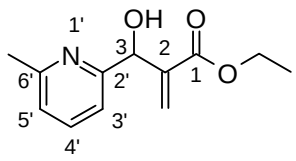
Ethyl 3-hydroxy-2-methylene-3-(4-pyridinyl)propanoate **343**



343

The procedure employed in the synthesis of methyl 3-hydroxy-2-methylene-3-(2-pyridinyl)propanoate **336** was followed, using ethyl acrylate (2.90 g, 29 mmol), pyridine-4-carboxaldehyde (3.00 g, 28 mmol) and 3-hydroxyquinuclidine (0.17 g, 1.3 mmol) in $CHCl_3$ (2 mL). The crystals formed were filtered off, yielding ethyl 3-hydroxy-2-methylene-3-(4-pyridinyl)propanoate **343** as orange crystals (5.51 g, 95%), m.p. 90-92 °C; δ_H (400 MHz; $CDCl_3$) 1.24 (3H, t, *J* 7.2 Hz, CH_3), 3.71 (1H, br s, OH), 4.17 (2H, dd, *J* 2.0 and 14.2 Hz, CH_2O), 5.52 (1H, s, C*H*OH), 5.88 and 6.38 (2H, 2 x s, CH_2), 7.31 (2H, s, ArH) and 8.50 (2H, d, *J* 4.0 Hz, ArH); δ_C (100 MHz; $CDCl_3$) 14.0 (CH_3), 61.2 (CH_2O), 72.0 (C-3), 126.8 (CH_2), 141.3 (C-2), 121.5, 149.5 and 151.0 (ArC) and 165.9 (C=O).

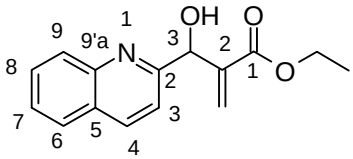
***Ethyl 3-hydroxy-2-methylene-3-(6-methyl-2-pyridinyl)propanoate* 344**



344

The procedure employed in the synthesis of methyl 3-hydroxy-2-methylene-3-(2-pyridinyl)propanoate **336** was followed, using ethyl acrylate (2.9 g, 29 mmol), 6-methylpyridine-2-carboxaldehyde (3.39 g, 28 mmol) and 3-hydroxyquinuclidine (0.17 g, 1.34 mmol) in $CHCl_3$ (2 mL). The crystals formed were filtered off, yielding ethyl *3-hydroxy-2-methylene-3-(6-methyl-2-pyridinyl)propanoate* **344** as off-white crystals (5.9 g, 95%), m.p. 70-72 °C (Found: MH^+, 222.1136. $C_{12}H_{16}NO_3$ requires, *M*+H: 222.1130); ν_{max}(ATR)/cm^{-1} 3106 (OH), 1716 (C=O) and 1643 (C=C); δ_H (400 MHz; $CDCl_3$) 1.24 (3H, t, *J* 7.2 Hz, CH_3), 2.54 (3H, s, $ArCH_3$), 4.19 (2H, m, CH_2O), 5.19 (1H, br s, OH), 5.59 (1H, s, C*H*OH), 5.91 and 6.33 (2H, 2 x s, CH_2), 7.05 (1H, d, *J* 7.6 Hz), 7.15 (1H, d, *J* 7.6 Hz) and 7.54 (1H, t, *J* 7.6 Hz) (ArH); δ_C (100 MHz; $CDCl_3$) 14.0 ($ArCH_3$), 24.2 (CH_3CH_2), 60.7 (CH_2O), 71.4 (C-3), 126.4 (CH_2), 142.4 (C-2), 118.0, 122.0, 137.0, 156.9 and 158.4 (ArC) and 166.1 (C=O).

***Ethyl 3-hydroxy-2-methylene-3-(2-quinolinyl)propanoate* 345**

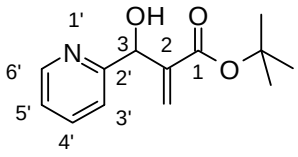


345

The procedure employed in the synthesis of methyl 3-hydroxy-2-methylene-3-(2-pyridinyl)propanoate **336** was followed, using ethyl acrylate (1.25 g, 14.5 mmol), quinoline-2-carboxaldehyde (2.20 g, 14 mmol) and 3-hydroxyquinuclidine (0.17 g, 1.3 mmol) in $CHCl_3$ (2 mL). The reaction yielded *ethyl 3-hydroxy-2-methylene-3-(2-quinolinyl)propanoate* **345** as a black oil (3.41 g, 100%) (Found: MH^+, 258.1128.

$C_{15}H_{16}NO_3$ requires, *M*+H: 258.1130); ν_{max}(ATR)/cm^{-1} 3043 (OH), 1723 (C=O) and 1617 (C=C); δ_H (400 MHz; $CDCl_3$) 3.73 (3H, s, CH_3O), 5.63 (1H, br s, OH), 5.82 (1H, s, C*H*OH), 6.02 and 6.42 (2H, 2 x s, CH_2), 7.49 (1H, d, *J* 8.8 Hz, ArH), 7.57 (H, t, *J* 7.4 Hz, ArH), 7.75 (1H, t, *J* 7.6 Hz, ArH), 7.84 (1H, d, *J* 8.0 Hz, ArH) and 8.13 (2H, m, ArH); δ_C (100 MHz; $CDCl_3$) 51.9 (CH_3O), 71.8 (C-3), 118.8 (CH_2), 126.6 (C-4'), 137.0 (C-4'), 142.1 (C-2), 157.0 (C-6'), 158.3 (C-2') and 166.5 (C=O).

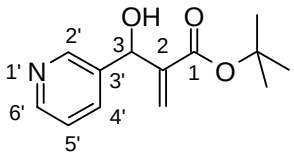
t-*Butyl 3-hydroxy-2-methylene-3-(2-pyridinyl)propanoate* 346



346

The procedure employed in the synthesis of methyl 3-hydroxy-2-methylene-3-(2-pyridinyl)propanoate **336** was followed, using *t*-butyl acrylate (3.72 g, 29 mmol), pyridine-2-carboxaldehyde (3.00 g, 28 mmol) and 3-hydroxyquinuclidine (0.17 g, 1.3 mmol) in $CHCl_3$ (2 mL). Wash-up yielded *t-butyl 3-hydroxy-2-methylene-3-(2-pyridinyl)propanoate* **346** as a colourless oil (5.90 g, 89%) (Found: MH^+, 236.1298. $C_{13}H_{18}NO_3$ requires, *M*+H: 236.1287); ν_{max}(ATR)/cm^{-1} 3345 (OH), 1708 (C=O) and 1630 (C=C); δ_H (400 MHz; $CDCl_3$) 1.38 [9H, s, $(CH_3)_3$], 3.19 (1H, br s, OH), 5.55 (1H, s, C*H*OH), 5.84 and 6.26 (2H, 2 x s, CH_2), 7.19 (1H, t, *J* 6.2 Hz, ArH), 7.39 (1H, d, *J* 8.0 Hz, ArH), 7.66 (1H, t, *J* 7.6 Hz, ArH) and 8.52 (1H, t, *J* 4.4 Hz, ArH); δ_C (100 MHz; $CDCl_3$) 27.9[C(CH_3)$_3$] 72.5 (C-3), 81.3 [*C*(CH_3)$_3$], 126.0 (CH_2), 143.2 (C-2), 121.0, 122.4, 136.7, 148.1 and 159.9 (ArC) and 165.4 (C=O).

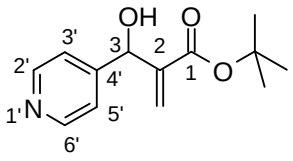
t-*Butyl 3-hydroxy-2-methylene-3-(2-pyridinyl)propanoate* 347



347

The procedure employed in the synthesis of methyl 3-hydroxy-2-methylene-3-(2-pyridinyl)propanoate **336** was followed, using *t*-butyl acrylate (3.72 g, 29 mmol), pyridine-3-carboxaldehyde (3.00 g, 28 mmol) and 3-hydroxyquinuclidine (0.17 g, 1.3 mmol) in $CHCl_3$ (2 mL). Wash-up yielded *t-butyl 3-hydroxy-2-methylene-3-(3-pyridinyl)propanoate* **347** as a colourless oil (6.60 g, 100%) (Found: MH^+, 236.1297. $C_{13}H_{18}NO_3$ requires, *M*+H: 236.1287); ν_{max}(ATR)/cm^{-1} 3144 (OH), 1696 (C=O) and 1628 (C=C); δ_H (400 MHz; $CDCl_3$) 1.38 [9H, s, $(CH_3)_3$], 3.90 (1H, br s, OH), 5.51 (1H, s, C*H*OH), 5.79 and 6.27 (2H, 2 x s, CH_2), 7.24 (1H, d, *J* 5.6 Hz), 7.69 (1H, d, *J* 7.6 Hz), 8.45 (1H, d, *J* 3.2 Hz) and 8.52 (1H, s) (ArH); δ_C (100 MHz; $CDCl_3$) 27.9 [$(CH_3)_3$], 71.1 (C-3), 81.8 [$C(CH_3)_3$], 125.4 (CH_2), 137.6 (C-2), 123.3, 134.4, 142.9, 148.4 and 148.6 (ArC) and 165.2 (C=O).

t-*Butyl 3-hydroxy-2-methylene-3-(4-pyridinyl)propanoate* 348

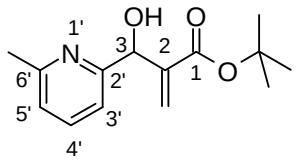


348

The procedure employed in the synthesis of methyl 3-hydroxy-2-methylene-3-(2-pyridinyl)propanoate **336** was followed, using *t*-butyl acrylate (3.72 g, 29 mmol), pyridine-4-carboxaldehyde (3.00 g, 28 mmol) and 3-hydroxyquinuclidine (0.17 g, 1.3 mmol) in $CHCl_3$ (2 mL). Wash-up yielded *t-butyl 3-hydroxy-2-methylene-3-(4-pyridinyl)propanoate* **348** as off-white crystals (6.6 g, 100%), m.p. 96-98 °C; δ_H (400

MHz; $CDCl_3$)1.41 [9H, s, $(CH_3)_3$], 3.73 (1H, br s, OH), 5.45 (1H, s, C*H*OH), 5.76 and 6.29 (2H, 2 x s, CH_2), 7.31 (2H, 2 x d, *J* 4.8 Hz, ArH) and 8.55 (2H, 2 x d, *J* 4.8 Hz, ArH); δ_C (100 MHz; $CDCl_3$) 27.9 [*C*$(CH_3)_3$], 71.8 (C-3), 81.1[C(*C*$H_3)_3$], 125.9 (CH_2), 143.6 (C-2), 121.9, 136.9 and 156.8 (ArC) and 165.4 (C=O).

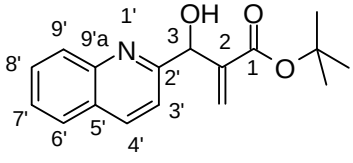
t-*Butyl 3-hydroxy-2-methylene-3-(6-methyl-2-pyridinyl)propanoate* 349



349

The procedure employed in the synthesis of methyl 3-hydroxy-2-methylene-3-(2-pyridinyl)propanoate **336** was followed, using *t*-butyl acrylate (3.72 g, 29 mmol), 6-methylpyridine-2-carboxaldehyde (3.39 g, 28 mmol) and 3-hydroxyquinuclidine (0.17 g, 1.3 mmol) in $CHCl_3$ (2 mL). Wash-up yielded *t-butyl 3-hydroxy-2-methylene-3-(6-methyl-2-pyridinyl)propanoate* **349** as off-white crystals (7.00 g, 100%), m.p. 96-98 °C (Found: MH^+, 273.1440. $C_{14}H_{20}NO_3$ requires, *M*+H: 250.1443); ν_{max}(ATR)/cm^{-1} 3085 (OH), 1722 (C=O) and 1645 (C=C); δ_H (400 MHz; $CDCl_3$) 1.40 [9H, s, C(*C*$H_3)_3$], 2.54 (CH_3), 5.17 (1H, br s, OH), 5.54 (1H, s, C*H*OH), 5.83 and 6.25 (2H, 2 x s, CH_2), 7.05 (1H, d, *J* 7.6 Hz, ArH), 7.14 (1H, d, *J* 7.6 Hz, ArH) and 7.54 (1H, t, *J* 7.6 Hz, ArH).

t-*Butyl3-hydroxy-2-methylene-3-(2-quinolinyl)propanoate* 350

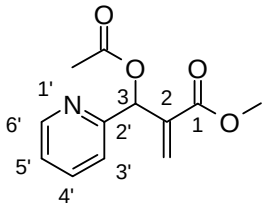


350

The procedure employed in the synthesis of methyl 3-hydroxy-2-methylene-3-(2-pyridinyl)propanoate **336** was followed, using *t*-butyl acrylate (3.72 g, 29 mmol), quinoline-2-carboxaldehyde (4.40 g, 28 mmol) and 3-hydroxyquinuclidine (0.17 g, 1.3

mmol) in $CHCl_3$ (2 mL). Wash-up yielded *t-butyl 3-hydroxy-2-methylene-3-(4-pyridinyl)propanoate* **350** as maroon crystals (2.7 g, 34%), m.p. 78-80 °C; ν_{max}(ATR)/cm^{-1} 2978 (OH), 1723 (C=O) and 1601 (C=C); δ_H (400 MHz; $CDCl_3$) 1.37 [9H, s, C(*C*H_3)$_3$], 4.49 (1H, br s, OH), 5.73 (1H, s, C*H*OH), 5.90 and 6.31 (2H, 2 x s, CH_2), 7.45 (1H, d, *J* 8.4 Hz, ArH), 7.54 (1H, t, *J* 6.8 Hz, ArH), 7.72 (1H, t, *J* 6.8 Hz, ArH), 7.82 (1H, d, *J* 8.0 Hz, ArH), 8.06 (1H, *J* 8.4 Hz, ArH) and 8.13 (1H, t, *J* 8.4 Hz, ArH.); δ_C (100 MHz; $CDCl_3$) 28.7 [C(*C*H_3)$_3$], 73.2 (CHOH), 82.0 [*C*(CH$_3$)$_3$], 119.5 (ArC), 127.1 (ArC), 127.6 (C=*C*H_2), 128.3 (2 x ArC), 129.6 (ArC), 130.5 (ArC), 137.6 (ArC), 144.1 (*C*=CH_2), 147.2 (ArC), 160.6 (ArC) and 166.2 (C=O).

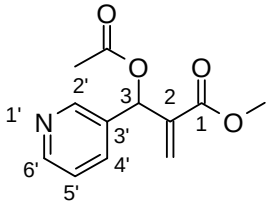
***Methyl 3-acetoxy-2-methylene-3-(2-pyridinyl)propanoate* 351**



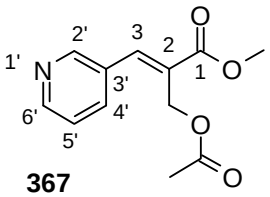
351

To a solution of the alcohol **336** (2.00 g, 10.4 mmol) in dry CH_2Cl_2 (31.2 mL), acetyl chloride (3.10 mL, 43.7 mmol) and pyridine (0.62 mL) were added and the solution stirred at room temperature for 4 h. Aqueous $NaHCO_3$ was then added to the solution to neutralize the HCl. The resulting mixture was extracted with EtOAc (3 x 25 mL). The organic layers were combined and dried over anhydrous $MgSO_4$. The solvent was then removed *in vacuo* and the residue was purified by PLC on silica gel; elution with acetone-hexane, 1:3) to afford a crude mixture (1.35 g, 59%) comprised mainly of methyl 3-acetoxy-2-methylene-3-(2-pyridinyl)propanoate **351**; δ_H (400 MHz; $CDCl_3$) 2.17 (3H, s, OAc), 3.72 (3H, s, CH_3O), 6.23 (1H, s, C*H*OAc), 6.55 and 6.69 (2H, 2 x s, CH_2), 7.99 (2H, m, ArH), 8.48 (1H, m, ArH) and 8.93 (1H, d, *J* 5.6 Hz, ArH); δ_C (100 MHz; $CDCl_3$) 20.8 (*C*H_3C=O), 52.3 (CH_3O), 70.0 (C-3), 128.1 (CH_2), 136.6 (C-2), 126.5, 139.3, 140.3, 140.6 and 144.8 (ArC), 164.4 and 168.9 (2 x C=O).

***Methyl 3-acetoxy-2-methylene-3-(3-pyridinyl)propanoate* 352 *and methyl 2-(acetoxymethyl)-3-(pyridiny-3-yl)propenoate* 367**



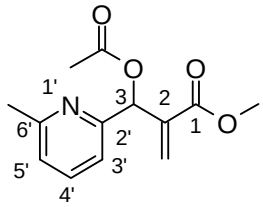
352



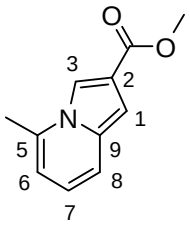
367

The procedure employed in the synthesis of methyl 3-acetoxy-2-methylene-3-(2-pyridinyl)propanoate **351** was followed, using a solution of the alcohol **337** (2.00 g, 10.4 mmol) in dry CH_2Cl_2 (31.2 mL) to which acetyl chloride (3.10 mL, 43.7 mmol) and pyridine (0.62 mL) were added, and the solution was stirred at room temperature for 4 h.Work-up and purification afforded a crude mixture (1.6 g, 70%) which contained methyl 3-acetoxy-2-methylene-3-(3-pyridinyl)propanoate **352** [δ_H (400 MHz; $CDCl_3$) 2.17 (3H, s, OAc), 3.72 (3H, s, CH_3O), 6.23 (1H, s, C*H*OAc), 6.55 and 6.69 (2H, 2 x s, CH_2), 7.99-8.93 (4H, a series of multiplets, ArH)] and **367** [δ_H (400 MHz; $CDCl_3$) 2.31 (3H, s, OAc), 3.73 (3H, s, CH_3O), 5.29 (2H, s, CH_2) and 7.98-8.93 (5H, series of multiplets, CH=C and ArH)].

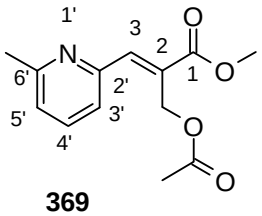
***Methyl 3-acetoxy-2-methylene-3-(6-methyl-2-pyridinyl)propanoate* 355, *methyl 5-methylindolizine-2-carboxylate* 368 *and methyl 2-(acetoxymethyl)-3-(6-methylpyridiny-2-yl)propenoate* 369**.



355



368



369

The procedure employed in the synthesis of methyl 3-acetoxy-2-methylene-3-(2-pyridinyl)propanoate **351** was followed, using a solution of the alcohol **339** (2.00 g, 9.6

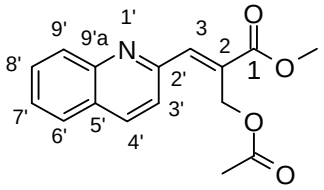
mmol) in dry CH_2Cl_2 (31.2.0 mL) to which acetyl chloride (2.86 mL, 40.3 mmol) and pyridine (0.58 mL) were added, and the solution was stirred at room temperature for 4 h. Work-up and chromatography afforded three fractions.

Fraction 1. Methyl 3-acetoxy-2-methylene-3-(6-methyl-2-pyridinyl)propanoate **355** as a black oil (1.0 g, 47%); δ_H (400 MHz; $CDCl_3$) 2.13 (3H, s, CH_3Ar), 2.50 (3H, s, CH_3CO), 3.70 (3H, s, CH_3O), 5.80 (1H, s, C*H*OAc), 6.43 and 6.69 (2H, 2 x s, CH_2), 7.04 (1H, d, *J* 8.0 Hz, ArH), 7.18 (1H, d, *J* 7.6 Hz, ArH) and 7.54 (1H, t, *J* 7.6 Hz, ArH); δ_C (100 MHz; $CDCl_3$) 21.0 (CH_3CO), 24.4 (CH_3Ar), 51.9 (CH_3O), 74.0 (C-3), 127.7 (CH_2), 138.4 (C2), 119.1, 122.6, 136.7, 156.2 and 158.2 (ArC) and 165.6 and 169.5 (2 x C=O).

Fraction 2. Methyl 5-methylindolizine-2-carboxylate **368** as green crystals (0.8 g, 38%), m.p. 34-36 °C; δ_H (400 MHz; $CDCl_3$) 2.51 (3H, s, CH_3), 3.90 (3H, s, CH_3O), 6.43 (1H, d, *J* 6.4 Hz, ArH), 6.71 (1H, t, *J* 7.8 Hz, ArH), 6.91 (1H, s, ArH), 7.32 (1H, d, *J* 9.2 Hz, ArH) and 7.73 (1H, s, ArH); δ_C (100 MHz; $CDCl_3$) 18.5 (CH_3), 51.4 (CH_3O), 101.0, 111.3, 113.0, 118.0, 118.5, 119.5, 133.0 and 133.5 (ArC) and 165.7 (C=O).

Fraction 3. *Methyl 2-(acetoxymethyl)-3-(6-methylpyridiny-2-yl)propenoate* **369** as a colourless oil (0.4 g, 15%) (Found: MH^+, 250.1082. $C_{13}H_{16}NO_4$ requires, *M*+H: 250.1079); ν_{max}(ATR)/cm^{-1} 1713 (C=O) and 1640 (C=C); δ_H (400 MHz; $CDCl_3$) 2.05 (3H, s, CH_3Ar), 2.55 (3H, s, CH_3CO), 3.85 (3H, s, CH_3O), 5.42 (2H, s, CH_2), 7.11 (1H, d, *J* 8.0 Hz, ArH), 7.20 (H, d, *J* 7.6 Hz, ArH), 7.60 (1H, t, *J* 7.8 Hz, ArH) and 7.79 (1H, s, ArH); δ_C (100 MHz; $CDCl_3$) 20.9 (CH_3CO), 24.5 (CH_3Ar), 52.3 (CH_3O), 58.9 (CH_2), 129.6 (C-2), 136.6 (C-3), 123.3, 123.6, 142.0, 152.6 and 158.8 (ArC), 167.5. and 170.7 (2 x C=O).

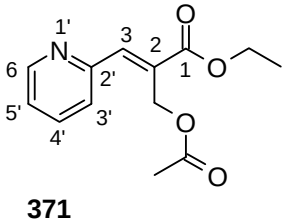
***Methyl 2-(acetoxymethyl)-3-(quiolin-2-yl)propenoate* 370**



370

The procedure employed in the synthesis of methyl 3-acetoxy-2-methylene-3-(2-pyridinyl)propanoate **351** was followed, using a solution of B-H alcohol **340** (2.00 g, 8.22 mmol) in dry CH_2Cl_2 (31.2 mL) to which acetyl chloride (2.50 mL, 35.0 mmol) and pyridine (0.49 mL) were added, and the solution was stirred at room temperature for 4 h. Work-up and chromatography afforded *methyl 2-(acetoxymethyl)-3-(quiolin-2-yl)propenoate* **370** as a black oil (1.2 g, 60%) (Found: MH^+, 286.1087. $C_{16}H_{21}N_2O_2$ requires, *M*+H: 286.1079); ν_{max}(ATR)/cm^{-1} 1719 (C=O) and 1640 (C=C); δ_H (400 MHz; $CDCl_3$) 2.02 (3H, s, OAc), 3.88 (3H, s, OMe), 5.55 (2H, s, CH_2), 7.49 (1H, d, *J* 8.4 Hz, ArH), 7.56 (1H, t, *J* 7.3 Hz, ArH), 7.73 (1H, t, *J* 7.6 Hz, ArH) 7.80 (1H, d, *J* 8.8 Hz, ArH), 7.98 (1H, s, CH=C), 8.08 (1H, d, *J* 8.8 Hz, ArH) and 8.18 (1H, d, *J* 8.0 Hz, ArH); δ_C (100 MHz; $CDCl_3$) 21.1 (OAc), 52.5 (OMe), 58.9 (CH_2), 131.1 (C-3), 148.0 (C-2), 123.4, 127.3, 127.4, 127.5, 130.0, 130.1, 136.5, 141.8 and 153.1 (ArC), 167.3 and 170.8 (2 x C=O).

***Ethyl 2-(acetoxymethyl)-3-(pyridiny-2-yl)propenoate* 371**

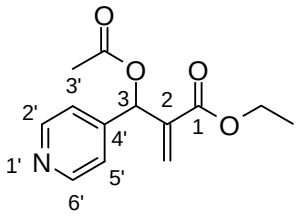


371

The procedure employed in the synthesis of methyl 3-acetoxy-2-methylene-3-(2-pyridinyl)propanoate **351** was followed, using a solution of B-H alcohol **341** (2.00 g, 9.70

mmol) in dry CH_2Cl_2 (29.1 mL) to which acetyl chloride (2.90 mL, 40.7 mmol) and pyridine (0.58 mL) were added, and the solution was stirred at room temperature for 4 h. Work-up and chromatography afforded, as a brown oil ethyl 2-(acetoxymethyl)-3-(pyridiny-2-yl)propenoate **371** (1.2 g, 52%); δ_H (400 MHz; $CDCl_3$) 1.35 (3H, t, *J* 7.2 Hz, CH_3), 2.08 (3H, s, OAc), 4.32 (2H, m, CH_2O), 4.92 (2H, s, $AcOCH_2$), 7.35 (1H, t, *J* 5.6 Hz, *J* 6.0 Hz, ArH), 7.71 (1H, d, *J* 8.0 Hz, ArH), 7.91 (1H, s, 3-H), 8.61 (1H, d, *J* 3.6 Hz, ArH) and 8.64 (1H, s, ArH); δ_C (100 MHz; $CDCl_3$) 14.2 (CH_3), 20.8 (CH_3CO), 58.8 (CH_2OAc), 61.4 (CH_3CH_2), 123.4 (C-3' and C-5'), 129.3 (C-2), 130.2 (C-2'), 136.2 (C-3), 141.0 (C-4'), 150.1 (C-6'), 166.1 and 170.4 (2 x C=O).

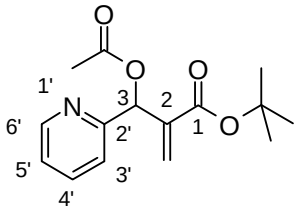
***Ethyl 2-(acetoxymethyl)-3-(pyridiny-4-yl)propanoate* 405**



358

The procedure employed in the synthesis of methyl 3-acetoxy-2-methylene-3-(2-pyridinyl)propanoate **351** was followed, using a solution of the alcohol **343** (2.00 g, 9.70 mmol) in dry CH_2Cl_2 (29.1 mL) to which acetyl chloride (2.90 mL, 40.7 mmol) and pyridine (0.58 mL) were added, and the solution was stirred at room temperature for 4 h. Work-up and chromatography afforded ethyl 2-(acetoxymethyl)-3-(pyridiny-4-yl)propenoate **358** as a black oil (1.1 g, 42%); δ_H (400 MHz; $CDCl_3$) 1.20 (3H, t, *J* 7.0 Hz, CH_3), 2.15 (3H, s, CH_3CO), 4.15 (2H, m, CH_2O), 5.93 (1H,s, AcOCH), 6.48 and 6.73 (2H, 2 x s, CH_2), 7.21 (1H, t, *J* 6.2 Hz, ArH), 7.44 (1H, d, *J* 7.6 Hz, ArH), 7.69 (1H, t, *J* 7.8 Hz, ArH) and 8.58 (1H, d, *J* 4.0 Hz, ArH); δ_C (100 MHz; $CDCl_3$) 14.0 (CH_3), 21.0 (CH_3CO), 60.9 (CH_2OAc), 73.9 (C-3), 127.3 (CH_2), 138.2 (C-2), 122.7, 123.0, 136.6, 149.4 and 157.0 (ArC), 164.9 and 169.6 (2 x C=O).

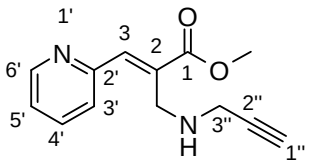
t-*Butyl 2-(acetoxymethyl)-3-(pyridiny-4-yl)propanoate* 361



361

The procedure employed in the synthesis of methyl 3-acetoxy-2-methylene-3-(2-pyridinyl)propanoate **351** was followed, using a solution of the alcohol **346** (2.00 g, 8.50 mmol) in dry CH_2Cl_2 (25.5 mL) to which acetyl chloride (2.50 mL, 35.7 mmol) and pyridine (0.51 mL) were added, and the solution was stirred at room temperature for 4 h. Work-up and chromatography afforded *t*-butyl 2-(acetoxymethyl)-3-(pyridiny-4-yl)propanoate **361** as a black oil (0.75 g, 34%); δ_H (400 MHz; $CDCl_3$) 1.35 (9H, s, [C(*C*H_3)$_3$], 2.13 (CH_3CO), 5.78 (1H, s, C*H*OAc), 6.38 and 6.69 (2H, 2 x s, CH_2), 7.20 (1H, t, *J* 3.6 Hz, ArH), 7.40 (1H, d, *J* 7.6 Hz, ArH), 7.68 (1H, t, *J* 7.8 Hz, ArH) and 8.58 (1H, d, *J* 4.0 Hz, ArH); δ_C (400 MHz; $CDCl_3$) 21.0 (CH_3CO), 27.9 [C(*C*H_3)$_3$], 74.1 (C-3), 81.3 [*C*(CH_3)$_3$], 126.3 (CH_2), 139.6 (C-2), 122.7, 122.9, 136.5, 149.4 and 157.3 (ArC), 164.1 and 169.5 (2 x C=O).

***Methyl 2-[(2-propynylamino)methyl]-3-(pyridin-2-yl)acrylate* 376**

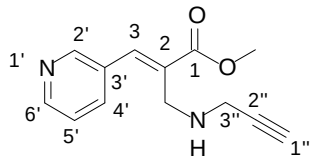


374

A mixture of the Baylis-Hillman acetate **351** (0.50 g, 2.3 mmol) and propargylamine (0.25 g, 4.6 mmol) in EtOH (15.1 mL) was stirred at room temperature for 48 h. After the reaction was complete (monitored by TLC eluting with a mixture of ethyl acetate and hexane), the reaction mixture was concentrated under reduced pressure, and the

concentrate was eluted through a short silica-gel pad using a solution of ethyl acetate and hexane (1: 10) to give the corresponding *methyl 2-[(2-propynylamino)methyl]-3-(pyridin-2-yl)acrylate* **374** as a yellow oil (0.47 g, 89%); δ_H (400 MHz;$CDCl_3$) 1.87 (1H, br s, NH), 2.19 (1H, s, C≡CH), 3.49 (2H, s, $CH_2C{\equiv}CH$), 3.89 (3H, s, CH_3O), 3.96 (2H, s, CH_2NH), 7.23 (1H, t, *J* 1.2 Hz, *J* 5.2 Hz, ArH), 7.43 (1H, d, *J* 7.6 Hz, ArH), 7.72 (2H, s, 2'-H and 3-H) and 8.69 (1H, d, *J* 4.4 Hz, ArH); δ_C (400 MHz; $CDCl_3$) 38.0 and 44.6 (2 x CH_2N), 52.3 (CH_3O), 71.7 and 82.5 (C≡CH), 123.3 (ArC), 126.4 (C-3), 134.5 (C-2), 136.5, 139.5, 149.8 and 154.0 (ArC) and 168.5 (C=O).

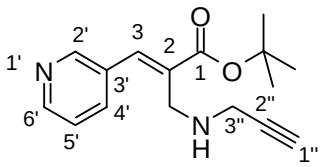
***Methyl 2-[(2-propynylamino)methyl]-3-(pyridin-3-yl)acrylate* 376**



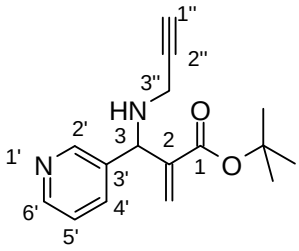
376

The procedure employed in the synthesis of compound **374** was employed using a mixture of Baylis-Hillman acetates **353** (0.50 g, 2.3 mmol). Work-up and elution with a mixture of ethyl acetate and hexane through a short silica gel afforded *methyl 2-[(2-propynylamino)methyl]-3-(pyridin-3-yl)acrylate* **376** as a yellow oil (0.31 g, 58%); (Found: MH^+, 231.1140. $C_{13}H_{15}N_2O_2$ requires, *M*+H: 231.1134); ν_{max}(ATR)/cm^{-1} 3272 (C≡CH), 1707 (C=O) and 1600 (C=C); δ_H (400 MHz;$CDCl_3$) 1.98 (1H, br s, NH), 2.20 (1H, s, C≡CH), 3.45 (2H, s, $CH_2C{\equiv}CH$), 3.63 (2H, s, CH_2NH), 3.83 (3H, s, CH_3), 7.31 (1H, t, *J* 6.2 Hz, ArH), 7.75 (1H, s, 3-H), 7.89 (1H, d, *J* 7.6 Hz, ArH), 8.56 (1H, d, *J* 4.8 Hz, ArH) and 8.69 (1H, s, ArH); δ_C (100 MHz; $CDCl_3$) 38.0 and 44.8 (2 x CH_2-N), 52.2 (CH_3O), 71.7 and 81.5 (C≡CH), 123.3 (C-5'), 130.8 (C-2), 132.3 (C-2'), 136.7 (C-3'), 138.5 (C-3), 149.7 (C-4'), 150.5 (C-6') and 167.8 (C=O).

(E)-tert-*Butyl 2-(prop-2-ynylamino)methyl-3-(pyridinyl-3-yl)acrylate* 385 *and tert*-butyl 2-(prop-2-ynylamino)methyl-3-(pyridinyl-3-yl)acrylate 389



385



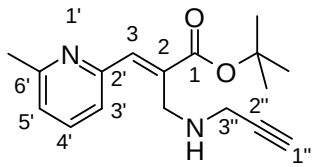
389

The procedure employed in the synthesis of methyl 3-acetoxy-2-methylene-3-(2-pyridinyl)propanoate **351** was employed using *t-butyl 3-hydroxy-2-methylene-3-(3-pyridinyl)propanoate* **347** but without purification. The resulting residue **362** was further treated with amine **373** as in the synthesis of **374**. Work-up and purification afforded.

***Fraction* 1**. (E)-tert-*butyl 2-(prop-2-ynylamino)methyl-3-(pyridinyl-3-yl)acrylate* **385** as yellow oil (54 mg) (Found: MH^+, 273.1601. $C_{16}H_{21}N_2O_2$ requires, *M*+H: 273.1603); ν_{max}(ATR)/cm^{-1} 2977 (C≡CH), 1706 (C=O) and 1635 (C=C); δ_H (400 MHz; $CDCl_3$) 1.34 (1H, s, C≡CH), 1.53 (9H, s, 3 x CH_3), 2.20 (1H, br s, NH), 3.44 (2H, s, C*H*$_2$C≡CH), 3.55 (2H, s, CH_2NH), 7.31 (1H, d, *J* 5.2 Hz, 4'-H), 7.65 (1H, s, 2'-H), 7.88 (1H, d, *J* 7.2 Hz, 5'-H), 8.54 (1H, d, *J* 4.4 Hz, 6'-H) and 8.68 (1H, s, 3-H); δ_C (100 MHz; $CDCl_3$) 28.1 (3 x CH_3), 38.1 and 45.1 (2 x CH_2N), 71.7 and 81.6 (C≡CH), 81.5[*C*$(CH_3)_3$], 123.3 (C-2'), 131.1 (C-2), 133.9 (C-3'), 136.6 (C-4'), 137.4 (C-3), 149.4 (C-5'), 150.4 (C-6') and 165.2 (C=O).

***Fraction* 2**. *tert*-butyl 2-(prop-2-ynylamino)methyl-3-(pyridinyl-3-yl)acrylate **389** as a brown oil (trace amounts); δ_H (400 MHz; $CDCl_3$) 1.36 (1H, s, C≡CH), 1.42 (9H, s, 3 x CH_3), 2.09 (1H, br s, NH), 3.59 (CH_2N), 4.88 (1H, s, *C*HN), 5.44 and 6.19 (2H, 2 x s, CH_2), 7.22 (1H, t, *J* 5.2 and 6.8 Hz, 5'-H), 7.52 (1H, d, *J* 7.2 Hz, 4'-H), 8.47 (1H, s, 3'-H) and 8.63 (1H, d, *J* 7.6 HZ, 6'-H); δ_C (100 MHz; $CDCl_3$) 28.1 (3 x CH_3), 35.5 (CH_2N), 77.2 and 86.4 (C≡CH), 81.1 [($C(CH_3)_3$], 123.4 (C-2'), 125.9 (CH_2), 134.7 (C-2), 136.4 (C-4'), 140.2 (C-3'), 140.6 (C-3), 147.7 (C-5'), 150.3 (C-6') and 165.5 (C=O).

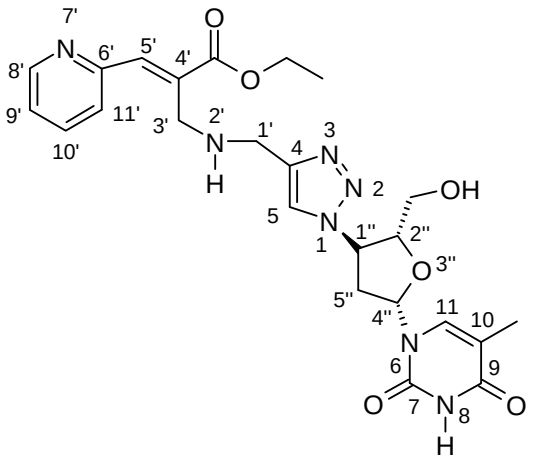
tert-*Butyl 2-(prop-2-ynylamino)methyl-3-(6-methylpyridinyl-2-yl)acrylate* 387



387

The procedure employed in the synthesis of compounds **385** and **389** was employed, affording tert-*butyl 2-(prop-2-ynylamino)methyl-3-(6-methylpyridinyl-2-yl)acrylate* **387** as a brown oil (0.13 g, 40%) (Found: MH^+, 287.1761. $C_{17}H_{23}N_2O_2$ requires, *M*+H: 287.1760); ν_{max}(ATR)/cm^{-1} 2975 (C≡CH), 1721 (C=O) and 1646 (C=C); δ_H (400 MHz; $CDCl_3$) 1.53 (9H, s, 3 x CH_3), 2.16 (1H, br s, NH), 2.50 (1H, s, C≡CH), 2.56 (3H, s, CH_3), 3.47 (2H, s, $CH_2C{\equiv}CH$), 3.85 (2H, CH_2NH), 7.06 (1H, d, *J* 7.6 Hz, 5'-H), 7.22 (1H, d, *J* 7.6 Hz, 3'-H), 7.56 (1H, d, *J* 7.6 Hz, 4'-H) and 7.59 (1H, s, 3-H); δ_C (100 MHz; $CDCl_3$) 24.6 (CH_3), 28.1 (3 x CH_3), 37.8 and 44.7 (2 x CH_2N), 71.7 and 82.5 (C≡CH), 81.2 [$C(CH_3)_3$], 122.6 (C-3'), 123.3 (C-5'), 135.6 (C-2), 136.6 (C-4'), 138.8 (C-3), 153.5 (C-6'), 158.5 (C-2') and 167.2 (C=O).

***4-[(*E*)-5-(2-Pyridinyl)-4-(ethoxycarbonyl)-2-aza-4-pentenyl]-1-[(2*R*,3*R*,5*S*)-4-(5-methyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-1-yl)-2-(hydroxymethyl)tetrahydrofuran-3-yl]-1H-1,2,3-triazole* 392**

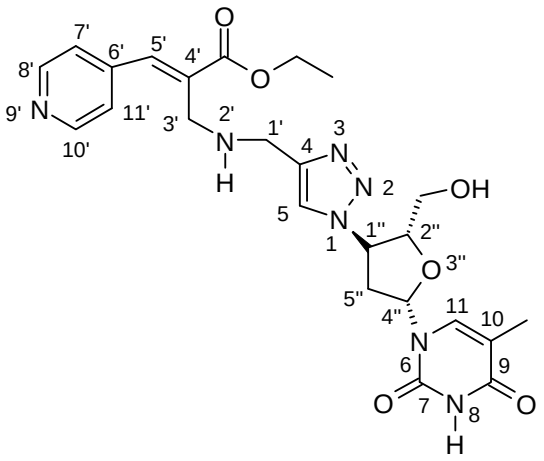


392

3'-Azido-3'-deoxythymidine (0.16 g, 0.61 mmol) was dissolved in H_2O/THF (1:1: 6.0 mL) and compound **379** (0.15 g, 0.61 mmol), sodium ascorbate (25.9 mg, 0.13 mmol) and $CuSO_4.5H_2O$ (4.54 mg, 18.2 µmol) were added to the solution. After stirring for 24 h at room temperature, the mixture was extracted with CH_2Cl_2 (2 x 50 mL) and washed sequentially with H_2O (25 mL) and brine (15 mL). The organic layers were combined, dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*.The crude material was purified by flash chromatography [on silica; elution with EtOAc and then MeOH/EtOAc (2:3)] to afford *4-[(*E*)-5-(2-pyridinyl)-4-(ethoxycarbonyl)-2-aza-4-pentenyl]-1-[(2*R*,3*R*,5*S*)-4-(5-methyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-1-yl)-2-(hydroxymethyl)tetrahydrofuran-3-yl]-1H-1,2,3-triazole* **392** as a yellow oil (0.20 g, 65%) (Found: MH^+, 540.2235. $C_{24}H_{30}N_7O_6$ requires, *M*+H: 512.2258); ν_{max}(ATR)/cm^{-1} 3330 (OH); δ_H (400 MHz; $CDCl_3$) 1.27 (3H, t, *J* 6.8 and 7.2 Hz, C*H*$_3$CH$_2$O), 1.88 (3H, s, C*H*$_3$CCHN), 2.45-3.01 (3H, overlapping br s and m, NH and C*H*$_2$CHN), 3.51-3.92 (6H, overlapping s and m, NCH$_2$CN, NCH$_2$CC=O and CH$_3$C*H*$_2$O), 4.17 (3H, m, C*H*$_2$OH and OH), 4.31 (1H, m, OCHC*H*N), 5.35 (1H, m, OC*H*CH$_2$OH), 6.27 (1H, t, *J* 6.0 Hz, OCHN), 7.19 (1H, m, ArH), 7.53 (1H, d, *J* 6.4 Hz, overlapping sArH), 7.67 (1H, s, *J* 7.6 Hz, CCHN), 7.80 (1H, d, *J* 7.6 Hz, ArH), 8.45 (2H, d, *J* 4.4 Hz, overlapping s, ArH and *H*CCCH$_3$), 8.61 (1H, s, 5'-H) and 10.1 (1H, br s, NHC=O); δ_C (100 MHz; $CDCl_3$) 12.5 (*C*H$_3$CH$_2$), 14.2

(*C*H_3C=C), 37.4 (*C*H_2CHN), 49.1 and 49.8 (2 x CH_2N), 59.2 (CH_3*C*H_2O), 61.3 (HO*C*H_2CHO), 61.2 (N*C*HCHO), 84.9 (HOCH_2*C*HO), 87.2 (NCHO), 111.0, 123.4, 131.0, 132.5, 137.0, 137.5, 138.5, 144.3, 149.2, 150.2, 150.5 (ArC and C=C), 164.0 and 167.8 (3 x C=O).

4-[(E)-5-(4-Pyridinyl)-4-(ethoxycarbonyl)-2-aza-4-pentenyl]-1-[(2R,3R,5S)-4-(5-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrimidin-1-yl)-2-(hydroxymethyl)tetrahydrofuran-3-yl]-1H-1,2,3-triazole **393**

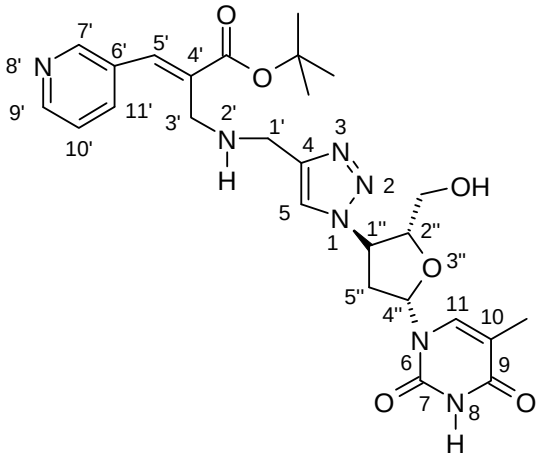


393

The procedure employed in the synthesis of the AZT-conjugate **392** was followed using 3'-azido-3'-deoxythymidine (0.16 g, 0.61 mmol) which was dissolved in H_2O/THF (1:1: 6.0 mL) and followed by addition of compound **376** (0.15 g, 0.61 mmol), sodium ascorbate (25.9 mg, 0.13 mmol) and $CuSO_4.5H_2O$ (4.54 mg, 18.2 µmol). Work-up and purification afforded *4-[(*E*)-5-(4-pyridinyl)-4-(ethoxycarbonyl)-2-aza-4-pen-ten--yl]-1-[(2*R,*3*R,*5*S*)-4-(5-methyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-1-yl)-2-(hydr-oxy-methyl)tetra-hydrofuran-3-yl]-1*H-*1,2,3-triazole* **393** as a yellow oil (0.17 g, 55%) (Found: MH^+, 540.2259. $C_{24}H_{30}N_7O_6$ requires, *M*+H: 512.2250); ν_{max}(ATR)/cm^{-1} 3399 (OH); δ_H (400 MHz; $CDCl_3$) 1.29 (3H, t, *J* 7.0 Hz, C*H*$_3$CH$_2$O), 1.87 (3H, s, C*H*$_3$CCHN), 2.81-3.00 (3H, overlapping br s and m, NH and C*H*$_2$CHN), 3.55-3.97 (6H, overlapping s and m, NCH$_2$CN, NCH$_2$CC=O and CH$_3$C*H*$_2$O), 4.20 (2H, dd, 7.0 Hz, C*H*$_2$OH), 4.30 (1H, d, *J* 6.4 Hz, OH), 4.36 (1H, s, OCHC*H*N), 5.41 (1H, s, OC*H*CH$_2$OH), 6.29 (1H, br s, OCHN), 7.19 (1H, t, *J* 5.6 and 6.8 Hz, ArH), 7.50 (1H, d, *J* 8.0 Hz, ArH), 7.60 (2H, d, *J*

6.8 Hz, ArH), 7.66 (1H, t, *J* 7.8 Hz, CCHN), 7.73 (1H, m, *H*CCCH$_3$), 8.55 (1H, d, *J* 4.0 Hz, 5'-H) and 8.65 (1H, br s, NHC=O) ; δ_C (100 MHz; $CDCl_3$) 14.2 (*C*H$_3$CH$_2$), 18.4 (*C*H$_3$C=C), 37.6 (*C*H$_2$CHN), 49.7 and 49.8 (2 x CH$_2$N), 58.3 (CH$_3$*C*H$_2$O), 61.2 (HO*C*H$_2$CHO), 61.4 (N*C*HCHO), 85.3 (HOCH$_2$*C*HO), 87.1 (NCHO), 111.0, 123.6, 132.4, 137.3, 138.0, 146.6, 149.4, 150.5 (ArC and C=C), 164.0, 167.3 and 168.1 (3 x C=O).

***4-[(*E*)-5-(3-Pyridinyl)-4-(*t*-butoxycarbonyl)-2-aza-4-pentenyl]-1-[(2*R*,3*R*,5*S*)-4-(5-meth-yl-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-1-yl)-2-(hydroxymethyl)tetrahydrofuran-3-yl]-1*H*-1,2,3-triazole* 394**

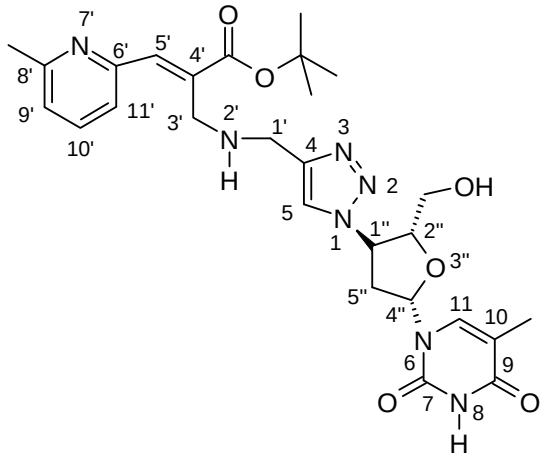


394

The procedure employed in the synthesis of AZT conjugate **392** was followed using 3'-azido-3'-deoxythymidine (0.03 g, 0.12 mmol) which was dissolved in H$_2$O/THF (1:1: 6 mL) and followed by addition of compound **385** (0.03 g, 0.12 mmol), sodium ascorbate (15.0 mg, 0.09 mmol) and $CuSO_4.5H_2O$ (0.9 mg, 3.61 µmol). Work-up and purification afforded *4-[(*E*)-5-(3-pyridinyl)-4-(t-butoxycarbonyl)-2-aza-4-pen-tenyl]-1-[(2*R*,3*R*,5*S*)-5-(5-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrimidin-1-yl)-2-(hydroxymethyl)tetrahydrofuran-3-yl]-1*H*-1,2,3-triazole* **394** as yellow oil (0.04 g, 59%) (Found: MH$^+$, 540.2578. $C_{26}H_{34}N_7O_6$ requires, *M*+H: 540.2571); ν_{max}(ATR)/cm^{-1} 3330 (OH); δ_H (400 MHz; $CDCl_3$) 1.53 [9H, s, C(CH$_3$)$_3$], 1.85 (3H, s, C*H*$_3$CCHN), 2.82-2.96 (2H, m, C*H*$_2$CHN), 3.39-3.78 (5H, overlapping s and m, NH, NHC*H*$_2$CN and NCH$_2$CC=O), 3.94 (3H, s, C*H*$_2$OH and OH), 4.36 (1H, br s, OCHC*H*N), 5.40 (1H, d, *J*

6.0 Hz, OC*H*CH_2OH), 6.27 (1H, br s, OCHN), 7.31 (1H, m, ArH), 7.52 (1H, s, HCCCH_3), 7.59, 7.61 (1H, s, CCHN), 7.72 (1H, d, *J* 8.0 Hz, ArH), 7.76 (1H, s, 5'-H), 8.49 (1H, br s, ArH) and 8.63 (1H, s, ArH); δ_C (100 MHz; $CDCl_3$) 12.5 (*C*CH_3C=C), 28.1 (3 x CH_3), 37.5 (*C*H_2CHN), 44.5 and 45.5 (2 x CH_2N), 50.6 (HO*C*H_2CHO), 59.0 (NCHCHO), 61.0 (CCHC=O), 81.7 [C$(CH_3)_3$], 85.1 (HOCH_2*C*HO), 111.1, 122.3, 123.6, 131.4, 133.9, 137.1, 137.2, 146.7, 148.9, 149.4 and (ArC, C=C) and 166.4 (3 x C=O).

***4-[(*E*)-5-(6-Methyl-2-pyridinyl)-4-(*t*-butoxycarbonyl)-2-aza-4-pentenyl]-1-[(2*R*,3*R*,5*S*)-4-(5-methyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-1-yl)-2-(hydroxymethyl)tetrahydrofu-ran-3-yl]-1*H*-1,2,3-triazole* 395**

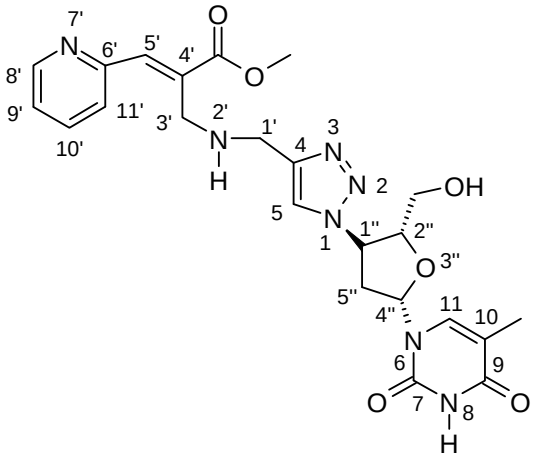


395

The procedure employed in the synthesis of the AZT conjugate **392** was followed using 3'-azido-3'-deoxythymidine (0.05 g, 0.17 mmol) which was dissolved in H_2O/THF (1:1: 6 mL) and followed by addition of **388** (0.05 g, 0.17 mmol), sodium ascorbate (7.2 mg, 0.007 mmol) and $CuSO_4.5H_2O$ (1.3 mg, 5.03 µmol). Work-up and purification afforded *4-[(*E*)-5-(6-Methyl-2-(pyridinyl)-4-(*t*-butoxycarbonyl)-2-aza-4-pentenyl]-1-[(2*R*,3*R*,5*S*)-(5-methyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-1-yl)-2-(hydroxymethyl)tetrahydrofuran-3-yl]-1*H*-1,2,3-triazole* **395** as yellow oil (0.09 g, 71%) (Found: MH^+, 554.2722. $C_{27}H_{36}N_7O_6$ requires, *M*+H: 554.2727); ν_{max}(ATR)/cm^{-1} 3330 (OH); δ_H (100 MHz; $CDCl_3$) 1.53 [9H, s, C$(CH_3)_3$], 1.90 (3H, s, CH_3CCHN), 2.55 (3H, s, pyr-CH_3), 2.87-2.96 (2H, m, C*H*$_2$CHN), 3.41-3.94 (5H, overlapping s and m, NH, NCH_2CC=O and CH_3C*H*$_2$O), 3.98 (3H, s, C*H*$_2$OH and OH), 4.37 (1H, br s, OCHC*H*N), 5.41 (1H, m,

OC*H*CH_2OH), 6.24 (1H, t, *J* 6.0 Hz, OCHN), 7.09 (1H, d, *J* 7.6 Hz, ArH), 7.22 (1H, d, *J* 6.4 Hz, ArH), 7.54 (1H, s, HCCCH_3), 7.59 (1H, d, *J* 7.6 Hz, ArH), 7.62 (1H, s, CCHN) and 7.81 (1H, s, 5'-H); δ_C (100 MHz; $CDCl_3$) 12.5 (*C*H_3C=C), 24.7 (pyr-CH_3), 28.1 (3 x CH_3), 37.6 (*C*H_2CHN), 43.8 and 44.8 (2 x CH_2N), 58.9 (CH_3*C*H_2O), 61.2 (HO*C*H_2CHO), 81.3 [C(CH_3)$_3$], 85.4 (HOCH_2*C*HO), 88.1 (NCHO), 111.1, 122.1, 123.6, 135.1, 136.8, 137.5, 139.0, 147.3, 150.4, 153.3 (ArC and C=C), 158.5, 163.7 and 167.1 (3 x CO).

***4-[(*E*)-5-(2-Pyridinyl)-4-(methoxycarbonyl)-2-aza-4-pentenyl]-1-[(2*R*,3*R*,5*S*)-4-(5-meth-yl-2,4-dioxo-1,2,3,4-tetrahydro-pyrimidin-1-yl)-2-(hydroxymethyl)tetrahydrofuran-3-yl]-1*H*-1,2,3-triazole* 390**

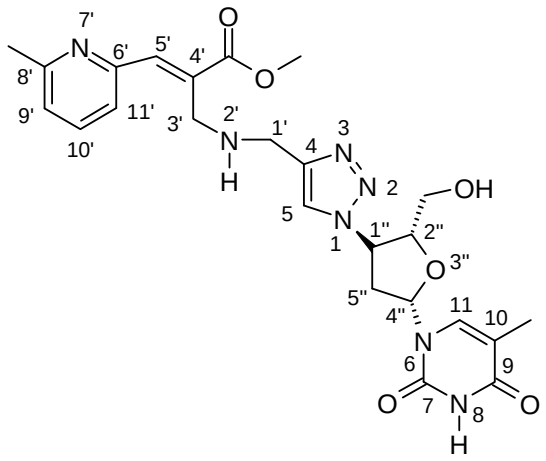


390

The procedure employed in the synthesis of AZT-conjugate **392** was followed using 3'-azido-3'-deoxythymidine (0.11 g, 0.40 mmol) which was dissolved in H_2O/THF (1:1: 6 mL) and followed by addition of **374** (0.09 g, 0.40 mmol), sodium ascorbate (17.1 mg, 0.086 mmol) and $CuSO_4.5H_2O$ (3.00 mg, 12.0 µmol) to the solution. Work-up and purification afforded *4-[(*E*)-5-(2-pyridinyl)-4-(methoxycarbonyl)-2-aza-4-pentenyl]-1-[(2*R*,3*R*,5*S*)-4-(5-methyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-1-yl)-2-(hydroxymethyl)tetrahydrofuran-3-yl]-1*H*-1,2,3-triazole* **390** as a yellow oil (0.07 g, 91%) (Found: MH^+, 498.2091. $C_{23}H_{28}N_7O_6$ requires, *M*+H: 498.2101); ν_{max}(ATR)/cm^{-1} 3337 (OH), δ_H (400 MHz; $CDCl_3$) 1.90 (3H, s, CH_3CCHN), 2.17 (3H, s, OCH_3), 2.37-2.57 (2H, overlapping m, NH and C*H*$_2$CHN), 3.74-3.86 (4H, overlapping s and m, NCH_2CN and NCH_2CC=O), 3.98 (2H, s, C*H*$_2$OH), 4.01 (1H, br s, OH), 4.27 (1H, m,

OCHC*H*N), 4.41 (1H, m, OC*H*CH_2OH), 6.06 (1H, t, *J* 6.4 Hz, OCHN), 7.40 (2H, br s signal, ArH and $HCCHH_3$), 7.48 (1H, m, ArH), 7.70 (1H, s, CCHN), 7.79 (1H, d, *J* 8.4 Hz, ArH), 8.50 (1H, d, *J* 4.8 Hz, ArH), 8.62 (1H, s, 5'-H) and 10.1 (1H, s, NH).

***4-[(E)-5-(6-Methyl-2-pyridinyl)-4-(methoxycarbonyl)-2-aza-4-pentenyl]-1-[(2R,3R,5S)-4-(5-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrimidin-1-yl)-2-(hydroxymethyl)tetrahydro-furan-3-yl]-1H-1,2,3-triazole* 391**



391

The procedure employed in the synthesis of AZT conjugate **392** was followed using 3'-azido-3'-deoxythymidine (0.28 g, 1.1 mmol) which was dissolved in H_2O/THF (1:1: 6 mL) and followed by addition of compound **377** (0.30 g, 1.1 mmol), sodium ascorbate (44 mg, 0.22 mmol) and $CuSO_4.5H_2O$ (7.7 mg, 31 µmol). Work-up and purification afforded *4-[(*E*)-5-(6-Methyl-2-(pyridinyl)-4-(methoxycarbonyl)-2-aza-4-pentenyl]-1-[(2*R,*3*R,*5*S)-*4-*(5-methyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-1-yl)-2-(hydroxymethyl)tetrahydrofuran-3-yl]-1*H-*1,2,3-triazole* **391** as a yellow oil (0.40 g, 71%); δ_H (400 MHz; $CDCl_3$) 1.90 (3H, s, CH_3CCHN), 2.51 (3H, s, pyr-CH_3), 2.94 (3H, m, NH and CH_2CHN), 3.64-4.07 (10H, overlapping signals, NCH_2CN, $NCH_2CC{=}O$, CH_2OH, OH and CH_3O), 4.40 (1H, m, OCHC*H*N), 5.38 (1H, m, OC*H*CH_2OH), 6.06 (1H, t, *J* 6.4 Hz, OCHN), 7.01-7.67 (10H, overlapping signals, ArH, 5'-H and NHC=O).

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