REVIEW

Garner's aldehyde

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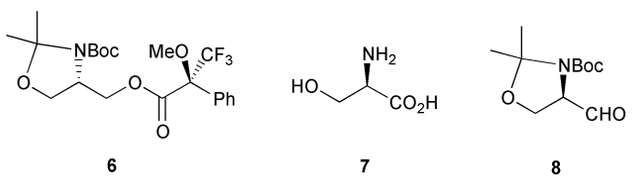
1 Introduction

In 1984 Garner published[1] a method for preparing the configurationally stable 1,1-dimethylethyl 4-formyl-2,2-dimethyloxazolidine-3-carboxylate (**1**), today called Garner's aldehyde. Since that time both enantiomers of **1** have been used extensively as chiral building blocks in asymmetric synthesis. Garner's aldehyde (**1**) is perhaps one of the most valuable chiral building blocks in recent times as it has been employed in more than 200 reported studies since its discovery.

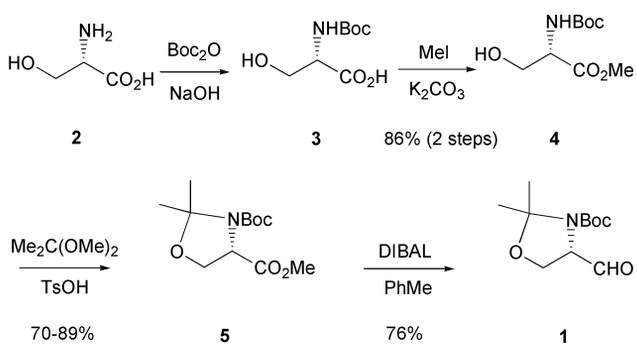
2 Synthesis of Garner's aldehyde

The first synthesis of **1** was, as the compound's name implies, reported by Philip Garner.[1] He noted that certain acetamido sugars could be protected as 2,2-dimethyloxazolidine derivatives,[2] and conceived the idea that a similar protection of the hydroxy group and the Boc-protected amino-group of serine would be desirable. His synthesis started with Boc protection of L-serine (**2**) using di-*tert*-butyl dicarbonate [$(Boc)_2O$] at pH ≥ 10 to form *N*-Boc-serine **3**, which was converted to the methyl ester **4** either by diazomethane[3] or, more conveniently, with



6 **7** **8**

Fig. 1 The Mosher ester **6**, D-serine and the (*R*)-Garner aldehyde **8**.[4]



Scheme 1 Garner's improved procedure for synthesis of **1**.[4]

MeI and K_2CO_3 (Scheme 1).[4] Compound **4** was then treated with $Me_2C(OMe)_2$ and TsOH to give the oxazolidine ester **5** in 70–89% yield. Direct reduction of ester **5** with DIBAL in toluene then afforded the title aldehyde **1** in 76% yield.[4]

As the enantiomeric purity of amino acid derivatives cannot be taken for granted, the optical purity of **1** was determined by reducing it to the corresponding alcohol and converting that into the Mosher ester **6** (Fig. 1).[3] NMR analysis of **6** revealed that **1** had an optical purity of 93–95% ee.

Garner also used his procedure to convert D-serine (**7**) into the antipode of **1**, namely **8** (Fig. 1).[3,4]

Garner's original synthesis (Scheme 1) has been subject to a number of improvements. The first two steps, Boc protection and esterification, have advantageously been reversed by McKillop *et al.*[5] Thus, treatment of **2** with HCl in MeOH gave the methyl serinate **9** in essentially quantitative yield (Scheme 2). Then **9** was reacted with $(Boc)_2O$ and Et_3N to give **4** in 90% yield from **2**. The same sequence has since been reported to proceed in 94% yield.[6]

The transformation of **4** to oxazolidine **5** has been improved by Moriwake *et al.* who used $BF_3{\cdot}OEt_2$ as catalyst in place of TsOH.[7] With this modification the yield in this step was increased to 93%; a yield that has been confirmed by others.[5]

The step that has been subjected to the most attempts at improvement is the DIBAL reduction of **5** to aldehyde **1**. Many workers noted that the reduction of **5** could be difficult to reproduce and was very dependent on the quality of the DIBAL used. A more reliable procedure was to reduce the ester to the alcohol **10** and then oxidise it back to **1** under Swern conditions (Scheme 2).[8–13] Roush and Hunt noted that not only

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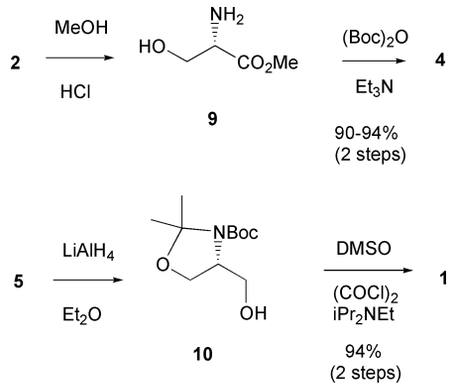


Scheme 2 Improved transformtion of **2** to **4**,[5] and two-step conversion of **5** to **1**.[12]

was the DIBAL reduction tricky, but the enantiomeric excess was also only 86–87% in their hands.[10] The reliability and yield of the synthesis was improved by replacing the DIBAL with the $LiAlH_4$–Swern protocol (Scheme 2), but not the enantiomeric purity of **1**. This was confirmed by Marshall *et al.*, who also obtained a product with 90% ee after the Swern oxidation.[9] This problem was solved by Dondoni *et al.* by changing the base used in the Swern oxidation from Et_3N to Hünig's base.[12] Hünig's base is more hindered and therefore less likely to facilitate enolisation of **1**. With this modification the enantiomeric purity of the product **1** was more than 97% ee.

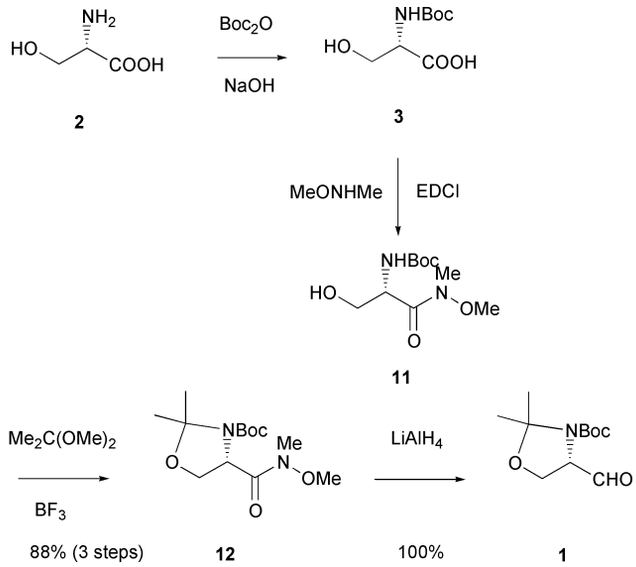
Both steps of this sequence have also been carried out with other reagents. The reduction of **5** to **10** can be performed by $NaBH_4$–LiCl and proceeds in 96% yield.[6] The oxidation of **10** to **1** can also be performed *via* a TEMPO-catalysed oxidation, which proceeds in 90% yield and with 100% ee optical purity,[14] or with DMSO–triphosgene which gives an 81% yield of a product with an optical purity similar to that reported by Garner.[15]

While Garner's original synthesis was 4 steps, circumvention of the use of DIBAL increased the synthesis to 5 steps. It appears, therefore, that there is room for improvement in the synthesis. Bold *et al.* were the first to use a Weinreb amide in place of the methyl ester to allow direct reduction to the aldehyde to occur more readily.[16] They converted Boc-protected serine **3** into the Weinreb amide by treating it with isobutyl chloroformate so as to form an anhydride and then reacted this with methoxymethylamine. This gave the Weinreb amide **11** in 65% yield. Treatment of **11** with DMP and pyridinium tosylate then gave the oxazolidine **12** in 71% yield. Finally, reduction of the *N*-methoxyamide with $LiAlH_4$ gave the aldehyde **1** in 78% yield. The yields on this route were subsequently improved by Campbell *et al.*[17] (Scheme 3). They prepared the amide **11** by direct coupling of MeONHMe with the acid **3** promoted by *N*-(3-dimethylaminopropyl)-*N*′-ethylcarbodiimide (EDCI). BF_3 was used as catalyst in the subsequent isopropylidenation, which also improved the yield there. The yield of **12** was 88% over three steps.

The above synthesis started from serine and since both D- and L-serine are available, they can be used to prepare either enantiomer of **1**. However, D-serine is somewhat more expensive and there have been some efforts to prepare **8** from a less expensive starting material. Kumar and Datta prepared **8** from L-cysteine in 6 steps,[18] while Avenoza *et al.* made it from L-serine in 7 steps.[19] The price difference between D- and L-serine is only a factor of three so it is not obvious that these more lengthy syntheses provide significant advantages.

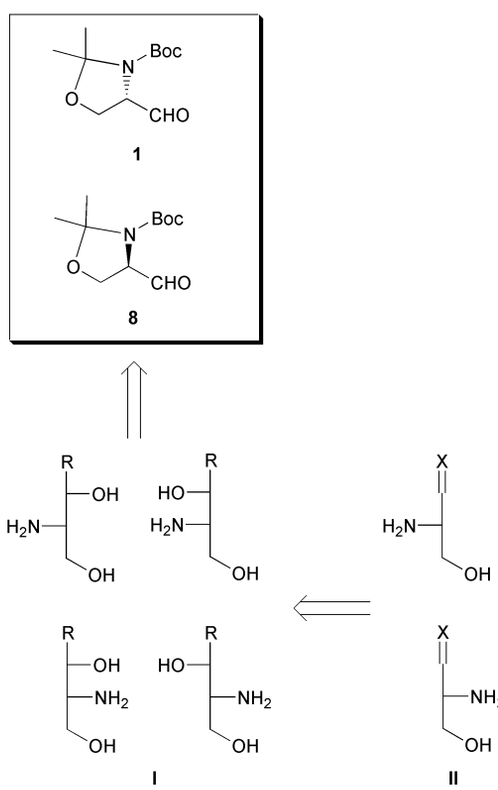
3 Nucleophilic addition reactions to Garner's aldehyde

The addition of nucleophilic compounds to Garner's aldehyde (**1**) opens access to the 2-amino-1,3-dihydroxypropyl structure motif which is widespread in natural products. The synthesis of



Scheme 3 Synthesis of **1** *via* a Weinreb amide here shown with the modifications of the Taylor group. [17]

azasugars, peptide antibiotics and sphingosines can be realised stereoselectively by this means. Nucleophilic additions to **1** lead first to the corresponding 2-amino-1,3-dihydroxypropyl derivatives **I** through the formation of a carbon–carbon or carbon–hetero atom bond (Scheme 4). Depending on the reaction conditions, subsequent elimination of water gives access to D- and L-2-amino-3-hydroxypropyl products **II**. In most cases, the constitution of **1** prevents racemisation during nucleophilic addition reactions. Therefore, starting from **1** or **8** all four possible isomers of the D-, L-*threo* and the D-, L-*erythro* series are selectively available in moderate to excellent yields.[20]

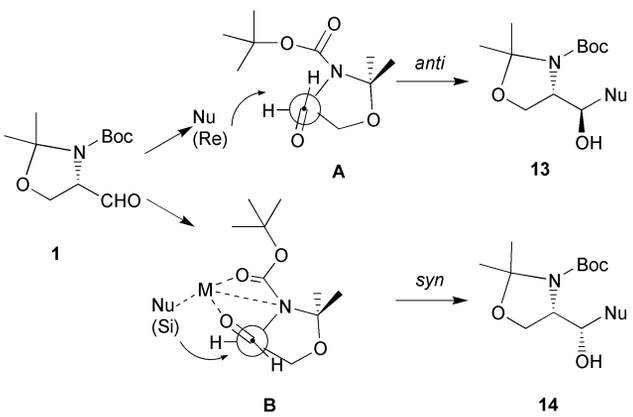


Scheme 4 **1** and **8** as precursors for the D- and L-2-amino-hydroxypropyl structural element.

In the following section, additions of nucleophiles to **1** are summarised. The influence of steric, chelation and solvent effects on the stereoselectivity of the addition reaction are discussed and natural product syntheses highlighted.

3.1 Addition of organometallic reagents

Addition of metal-activated carbon nucleophiles to **1** leads, in most cases, to mixtures of two diastereomers. *anti*-Addition gives the *erythro*-products, while *syn*-addition leads to the *threo*-products. Herold first reported that high asymmetric induction in both directions could be achieved using different solvents and additives with chelation effects.[21] The formation of the reaction products is explained either with the Felkin–Ahn model **A**, involving a non-chelating transition state and leading to the *anti*-adduct **13**, or with the Cram model **B** having a chelation-controlled transition state and leading to the *syn*-adduct **14** (Scheme 5).[22] Without chelation the formation of *syn*-products is believed to be disfavoured because of repulsion between the electronegative O- and N-atoms.



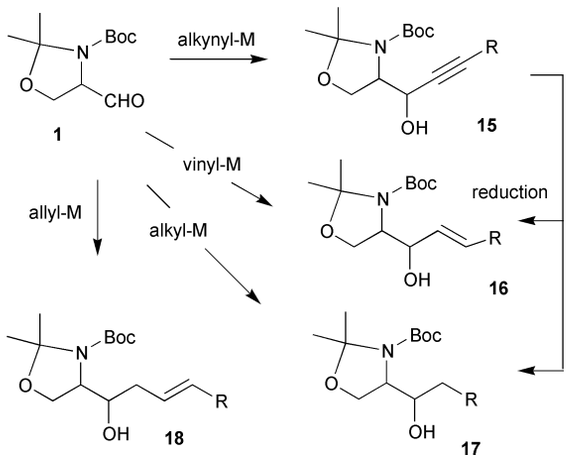
Scheme 5 L-*erythro* (*anti*) or L-*threo* (*syn*) product formation by nucleophilic additions to **1**; **A** *Felkin–Ahn* model, **B** *Cram* model.

Efficient formation of *syn*-products can also be achieved by simple oxidation of the diastereoisomeric *anti–syn* mixture to the corresponding ketone followed by metallohydride-type reduction (with $NaBH_4$,[23–32] $LiBH_4$,[33] $Zn(BH_4)_2$,[34,35] K-Selectride, DIBAL[36–38] or Bu_3BHK[39]), which is highly biased towards formation of the *syn*-product **14**.

It is possible to make almost equal mixtures of **13** and **14**, which might be useful in combinatorial syntheses, since all four isomers of the D-, L-*threo* and the D-, L-*erythro* 2-amino-1,3-dihydroxypropyl structure element would be obtained by this means. However, it is also possible to obtain enantiomerically pure compounds even on a solid phase. For instance, ω-aminosphingosine derivatives have been synthesised on a solid phase and used to purify sphingosine kinase, an enzyme involved in a variety of mammalian processes.[40,41] Depending on the carbon nucleophile and the metal counterion differing stereoselectivities are observed. One of the most important addition reactions is the alkynylation, which gives selective access to all possible stereoisomers of alkynyl, vinyl and alkyl products **15**–**18** (Scheme 6).

3.1.1 Lithium-activated nucleophiles

Herold described the first efficient and completely diastereo-



Scheme 6 Addition of metal alkynyl, -vinyl,-alkyl and allyl reagents to **1**.

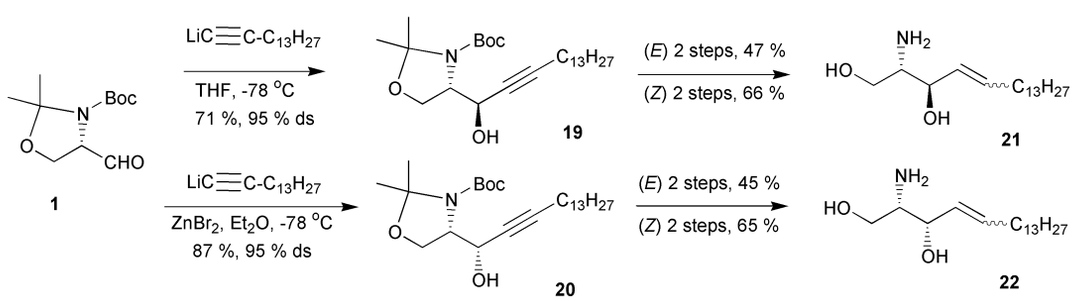
selective routes to enantiomerically pure sphingosines **21**–**22** by the addition of pentadec-1-ynyllithium to **1** (Scheme 7).[21] When the reaction was carried out without additives, the *anti*-product **19** was obtained. When $ZnBr_2$ was used as chelating agent then epimer **20** was obtained. The products **19**–**20** were shown to be enantiomerically pure by conversion to their respective Mosher esters. Similar stereodivergent syntheses of D-*erythro*- and D-*threo*-sphingosine were achieved from **1** in two steps by Garner *et al* (Scheme 8).[42] Thus, addition of pentadec-1-ynyllithium afforded the *anti*-product **23** in 74% yield (8 : 1 *syn* : *anti* ratio). On the other hand, addition of a *trans*-vinylalane reagent gave rise to mainly the *syn*-product **24** (>80%, 1 : 2 *anti* : *syn* ratio). The procedure has been reported to afford D-*erythro*-sphingosine in 40% overall yield from L-serine representing one of the most efficient syntheses of this substance.

Similar approaches to these sphingosines have been reported by others.[43,37] Such work has also included the synthesis of (2*S*,3*S*,4*R*)-phytosphingosine by addition of dithianide to **1** (*anti* : *syn* 99 : 1) followed by hydrolysis of the dithiane moiety and addition of dodecylacetylide.[44] Furthermore, lithium acetylide addition has been applied, as a key step, in a novel method for the preparation of (2*R*)-2-amino-5-phosphonopentanoic acid **25** (Scheme 9), a potent *N*-methyl-D-aspartate antagonist.[45]

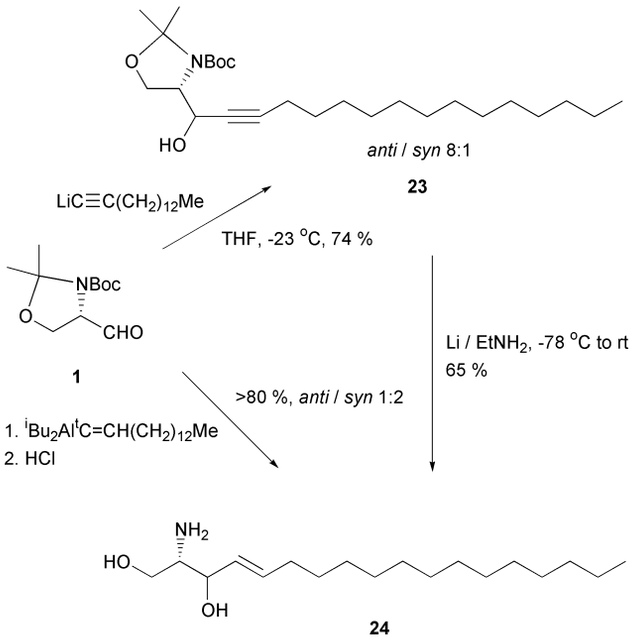
Enantiomerically pure β-branched α-amino acids such as **30**–**31** have been made by 1,3-diastereocontrol with bromoallenes **28**–**29** obtained from acetylide addition to **8** with and without chelation control (Scheme 10).[46]

The addition of indole derivatives to Garner's aldehyde has been used to obtain chiral 2-alkyl-substituted indoles.[47,48]

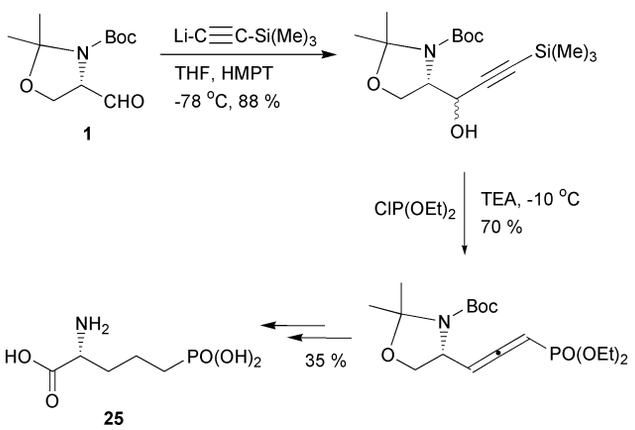
A practical and stereoselective synthesis of inhibitors of the sphingolipid biosynthesis pathway, namely L-*threo*- and D-*erythro*-1-phenyl-2-palmitoylamino-3-morpholinopropan-1-ol (PPMP), has been reported by M. Nakagawa *et al*. The *erythro*-precursor has been obtained by *anti*-selective addition of PhLi to **1** or **8** respectively (50% yield, *anti* : *syn* 3.9 : 1), while oxidation of an *anti–syn* mixture derived from PhMgBr addition



Scheme 7



Scheme 8 D-*erythro*-Sphingosine in 40% overall yield from L-serine.



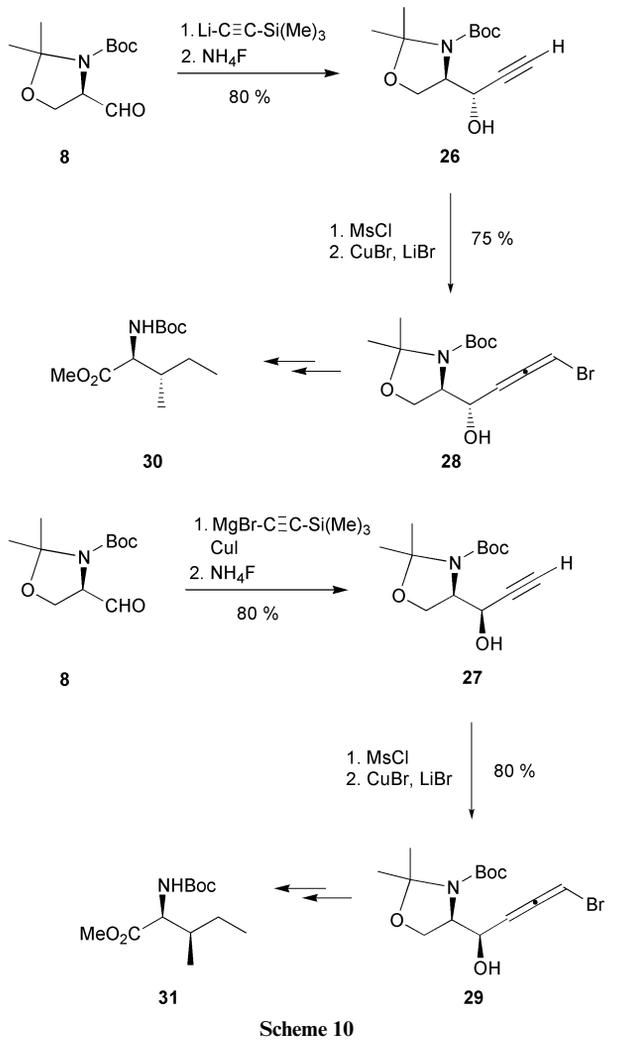
Scheme 9 Synthesis of (2*R*)-2-amino-5-phosphonopentanoic acid.

(76% yield, 1 : 1.8 *anti* : *syn*) and subsequent diastereoselective reduction with n-Bu_4NBH_4 gave rise to the *threo* compound (99% yield, 1 : 11 *anti* : *syn*).[49]

The *anti*-selective addition of lithiated methoxyallene to **1** and subsequent ozonolytic cleavage gives α-hydroxy-β-amino acid derivative **32**. The enantiomeric purity of the product (>90%) has been determined using the Mosher ester method (Scheme 11).[50]

Finally, the addition of lithium acetylides to **1** has been investigated in connection with a new method for the synthesis of pyrroles.[51]

Because of the good *anti*-stereoselectivity observed in the addition of lithium nucleophiles to **1** such reactions have often been applied in natural product syntheses where a vicinal aminohydroxy functionality with an *erythro*-configuration is required. In this connection, Garner has described a method for the synthesis of various glycosyl α-amino acids. The synthesis provides a novel approach to thymine polyoxine C, the nucleosidic portion of peptidyl antibiotic polyoxine J (Fig. 2). Polyoxines are important phytopathogenic fungal antibiotics from *Streptomyces cacaoi*.[52] Access to the 5-amino-5-deoxyallofuranose system was achieved by the *anti*-addition of lithiated propionaldehyde dimethyl acetal to **8** (78% *anti* : *syn* 13 : 1)[53] as well as by addition of ethyl lithiopropiolate (87%, *anti* : *syn* 8 : 1).[54] The 5-*O*-carbamoylpolyoxamic part has been synthesised from **8** *via anti*-addition of vinylmagnesium bromide.[55]



Scheme 10

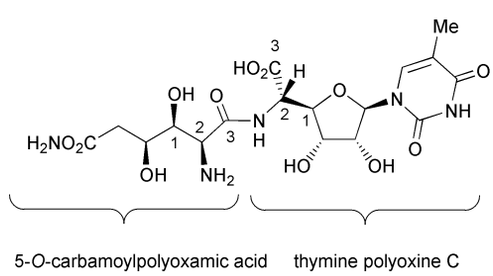
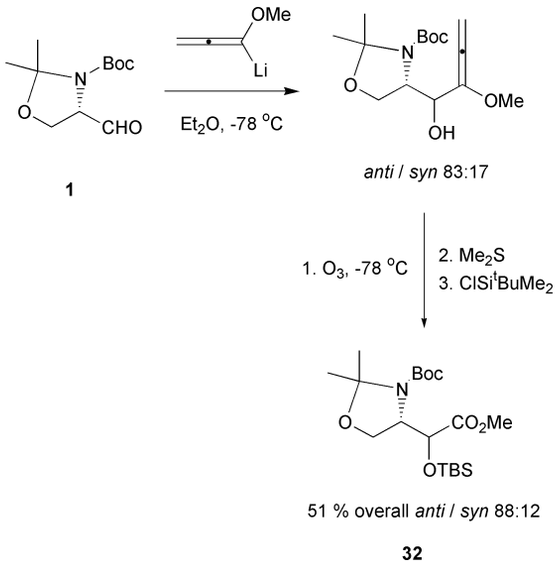


Fig. 2 Peptidyl antibiotic polyoxin J.

(+)-Deoxybiotin (Fig. 3)—a precursor of biotin (vitamin H)—was diastereoselectively synthesised from L-cysteine in 12 steps.[56] Aldehyde **1** was used as a model compound for the evaluation of the required *anti*-selective nucleophilic addition reaction. However, a remarkable *syn*-selectivity was observed, even under non-chelation conditions, when **33**, the benzyl imine corresponding to **1**, reacted with metal acetylides (THF, −78 °C, 15 h, 44% yield, >99% de; Et_2O, ZnBr, −78 °C, 15 h, 81% yield, >99% de). The required vicinal *anti*-diamino compound was finally obtained from a corresponding *syn*-aminohydroxy compound, derived *via* Herold's procedure,[21] by S_N2 type displacement of the hydroxy functionality.

Dondoni *et al.* observed the same effect when they reacted the (*Z*)-configured *N*-benzyl nitrone derived from **1** and 2-lithiothiazole. The *threo*-configuration was unequivocally established by X-ray analysis of product **35** (89% yield, >95% de).[57] The scope of that reaction has been expanded to highly *syn*-selective *Grignard* reactions.[58] Even MeMgBr, known to always give *anti*-selectivity in *Grignard* reactions with **1**, gave almost



Scheme 11 Synthesis of α-hydroxy-β-amino acid derivatives.

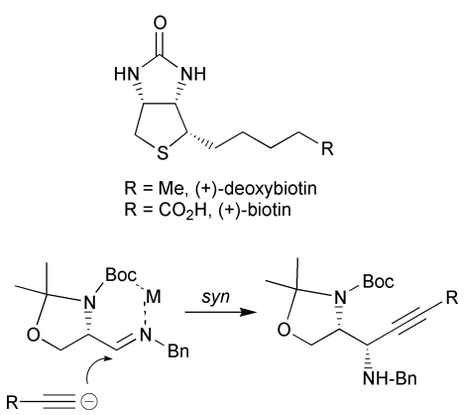
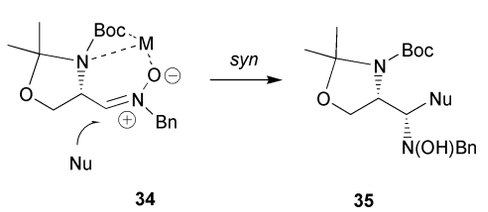


Fig. 3 Deoxybiotin and biotin.

exclusively the *syn*-product (88% yield, >95% de). No reduction in selectivity was observed on changing the reaction conditions, additives or solvent (Scheme 12).



Scheme 12

Merino *et al.*[58] suggested achieving stereodivergency by varying the *N*-protecting groups. Reactions of organometallic reagents with vicinal diamines of 2-(*N*,*N*-dibenzylamino)-benzylimine type are known to lead to the *threo*-products (>98% ee) under chelation control, while less basic 2-(*N*,*N*-dibenzylamino)tosylimines lead to *erythro*-products (>98% ee) under non-chelation conditions.[59–61] Because of the *trans*-configuration of the benzyl group relative to the CH-*N*-Boc group only a cyclic transition state or intermediate favours nucleophilic attack from the *Si*-side leading to the exclusive formation of the *syn*-product (Scheme 12). However, the precise nature of the transition state warrants further investigation. The fixed structure of **1** or other *N*-protected serinal derivatives are ideal substrates for that purpose. On the other hand, a Mukaiyama-type aldol reaction with the *N*-*p*-anisyl imine of **8** has been reported to give 86% de of *erythro* products.[62,63] The structure has been assumed to be similar to the corresponding products derived from **8**.

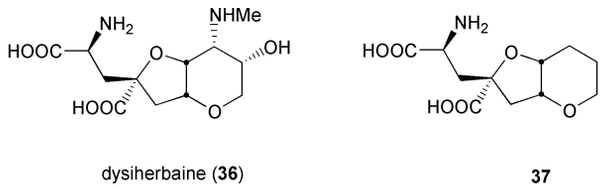


Fig. 4

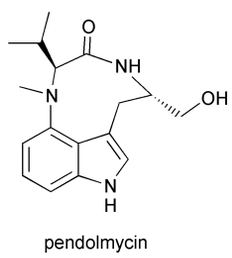


Fig. 5

The neuroexitoxin dysiherbaine **36** was isolated from the marine sponge *Dysidea herbacea*.[64] The dysiherbaine skeleton **37** has been synthesised by lithium nucleophile addition to **1** (Fig. 4).[65]

The synthesis of rare natural compounds not only gives access to suitable amounts of them, but very often the synthesis is also a proof of their structure. The absolute configuration of L-*erythro*-*N*-lauroyldocosasphinga-4,8-dienine isolated from *Anemonia sulcata* has been determined through its synthesis by M. Nakagawa *et al*. An *anti*-selective lithium acetylide addition to **1** was the key step of the reaction sequence.[66]

Starting from **1** and lithium nucleophiles the enantioselective syntheses of protein kinase C inhibitory penaresidin alkaloids isolated from the Okinawan marine sponge *Penares* sp.[67] and a related alkaloid, penazetidine A, isolated from the Indo-Pacific marine sponge *Penares sollasi*[68] and the first sphingosines possessing an azetidine ring, have been achieved.[69–72] Similarly **8** has been used as precursor for the synthesis of tumor promoter pendolmycin, an indole alkaloid from *Nocardiopsis* strain SA 1715 (Fig. 5).[73]

The synthesis of an esterified cerebroside isolated from human and pig epidermis has been reported.[74]

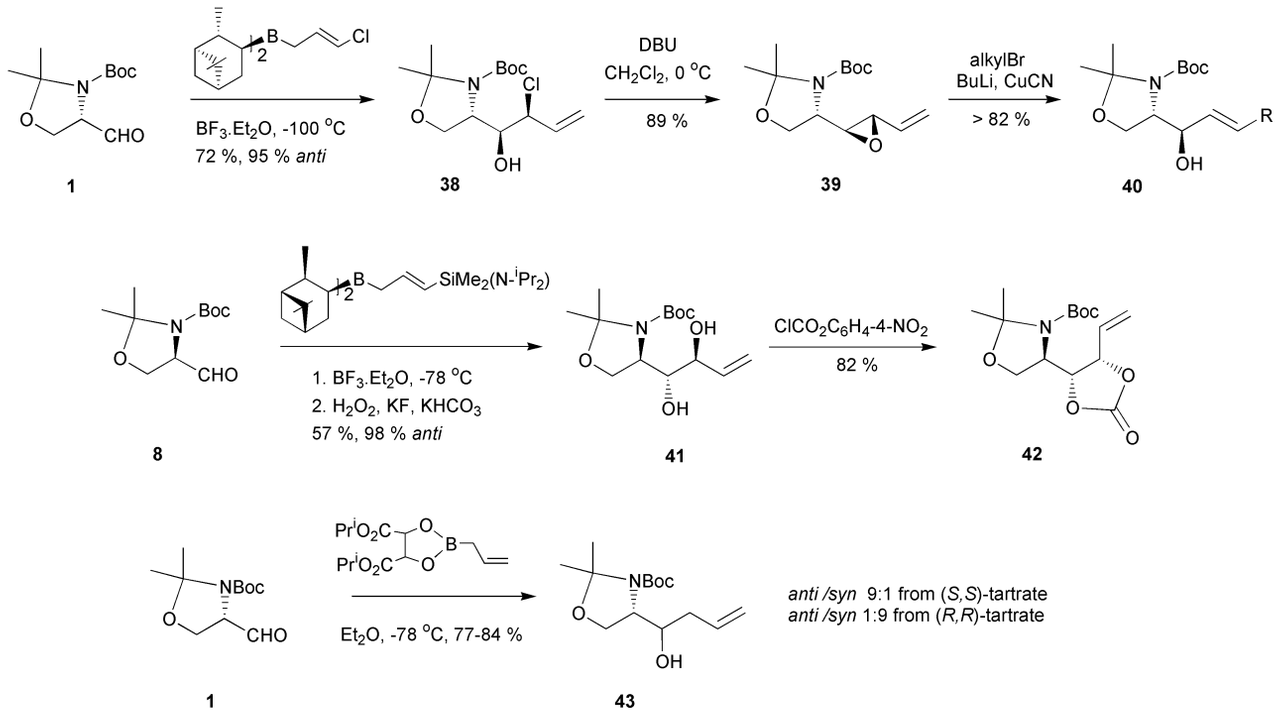
Following Herold's method, the synthesis of morpholino- and pyrrolidinosphingolipids as glucosylceramide synthase inhibitors,[75] and silica-immobilised ceramide analogues as skin models[76] has been reported.

Phosphoserine mimetics were synthesised starting with addition of LDA activated difluoromethylphosphonate to **1** in THF at −78 °C (*anti* : *syn*, 4.5 : 1).[77]

3.1.2 Allylboration

Stereodiscrimination has been observed when *in situ* formed γ-(*Z*)-chloroallyl-(+)-diisopinocampheylborane reacts with **1** and thereby providing chlorohydrin **38** in 72% yield and essentially complete *anti*-selectivity (95% de). The mismatched pathway with the corresponding (−)-reagent leads to a dramatic decrease of yield and selectivity (37%, *anti* : *syn* 62 : 38). Subsequent treatment of the resulting *anti*-chlorohydrin, **38**, with DBU provided vinyl oxirane **39** as an enantiopure and versatile building block (Scheme 13).[78,79] Enantiomer **8** has been reported to give analogous results in its conversion to **41** and, subsequently, **42** (Scheme 13).[80]

Similar results in stereoselectivity and yields were observed with a (+)-diisopinocampheylborane of benzophenone protected allylamine which gave access to aminoallyl substituted **1**



Scheme 13 Allylborations.

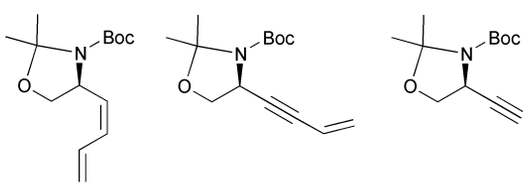
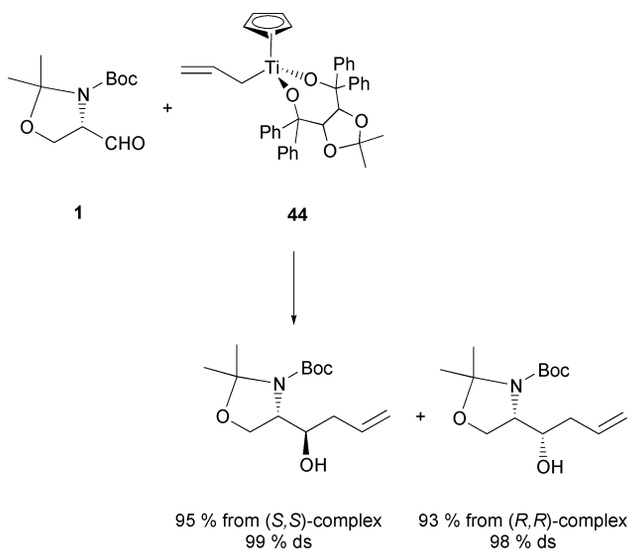


Fig. 6



Scheme 14 Double stereodiscriminated allyltitanation.

(40% yield, *anti* : *syn* 95 : 5). However, the reaction with the corresponding (−)-borane derivative *via* a mismatched pathway[81] led only to an isomeric mixture in 38% yield and an *anti* : *syn* selectivity of 1 : 1.2.[82]

Double stereodiscriminated allylboration of **1** in Et_2O at −78 °C with allylboronates of isopropyl (*S*,*S*)-tartrate or its (*R*,*R*)-isomer gave 77–84% yield of addition product **43**. The ratios of *anti*- and *syn*-addition products have been reported to be 9 : 1 in the matched case derived from the (*S*,*S*)-tartrate and 1 : 9 from the "mismatched" case involving the (*R*,*R*)-tartrate.[10]

Several useful unsaturated building blocks have been derived from **1** in one or two simple steps by nucleophilic addition of pinacol (*E*)-1-trimethylsilylprop-1-ene-3-boronate or CBr_4 and subsequent elimination (Fig. 6).[83]

3.1.3 Allyltitanation

Enantioselective allyltitanation of aldehydes with cyclopentadienyldialkoxyallyltitanium complexes have been reported.[84] The reaction of (*S*,*S*)- or (*R*,*R*)-complex **44** with **1** was reported to lead to the formation of 95% *anti*-product (99% de) or to 93% *syn*-product (98% de), respectively (Scheme 14).

3.1.4 Allylindium reagents

Indium-mediated allylation of α-amino aldehydes was intensively studied by Paquette *et al.*[85] The not yet predictable *anti*/*syn* selectivity of the reaction was found to depend on the *N*-protecting group, β-substituents, chelation effects and very likely on hydrogen bonding depending on the pH of the solution and/or the pK_a value of the substrate. Compound **1** was found to react relatively rapidly (within 0.5–2 h) at room temperature in water, THF or mixtures of these solvents and thereby giving a 1 : 3 *anti* selectivity (77–90% yield). Other *N*-protected or *N*,*N*-diprotected α-amino aldehydes needed 6–72 h reaction time. For instance, *N*-Boc L-leucinal gave a very low *syn* selectivity (*anti* : *syn* 1 : 1.2). However, refluxing a solution of *N*-Boc L-leucinal in THF with allyl bromide and indium for 24 h gave the opposite result (*anti* : *syn* 1.2 : 1, 81% yield). On the other hand, *N*,*N*-dimethyl-L-aminopropionaldehyde gave almost exclusively the *syn*-product (50% yield) in contrast to the *N*,*N*-dibenzyl derivative which gave a 3.3 : 1 mixture of *anti* : *syn* products (50% yield).[85]

3.1.5 Chromium reagents

Chromium(II) chloride-mediated coupling reactions of **1** with allyl bromides have been investigated by Ohta *et al.*[86] The isolated yields have been reported to be 80–98% when the reactions were performed in THF at room temperature. However, the highest obtained stereoselectivity was moderate (*anti* : *syn* 63 : 37).[86]

3.1.6 Allylstannation

Allylstannation of **1** with tributylallylstannane has been reported to be moderately stereoselective in both directions. However, use of optically active or racemic γ-oxygenated allylic stannanes in the presence of $MgBr_2 \cdot Et_2O$ led to *syn*-products in CH_2Cl_2 at −20 °C (70–93% yield, 85–92% de).[87]

3.1.7 Grignard reagents

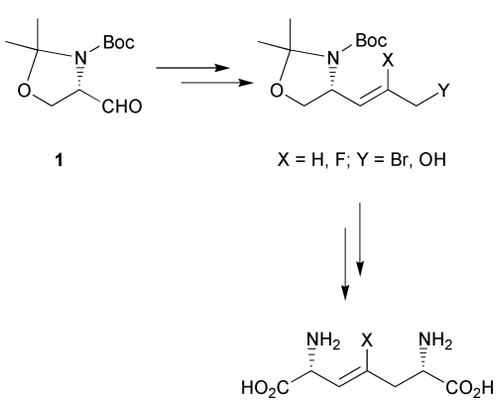
The reactivity and stereoselectivity of Grignard reagents with **1** have been extensively studied.[88] The reaction was found to depend on the steric bulk of the alkylmagnesium halides as well as on the steric bulk of the oxazolidine ring. Exchange of the isopropylidene-protecting group of **1** with cyclohexylidene gave, under the same reaction conditions (THF, −78 to 0 °C), about 5% greater diastereoselectivity. Et, ^{i}Pr, ^{t}Bu or C_6H_{11} magnesium halides led to the *syn*-products in ratios of *ca.* 9 : 1 to 15 : 1. In contrast, the more reactive CH_3 (1 : 2) and Ph (1 : 8) halides provided mainly the *anti*-derivative because addition from the *Re*-side of **1** is faster than chelation. Changing the solvent from THF to Et_2O (a solvent favouring increased chelation) or addition of metal salts like $CeCl_3$[89] increased the yields of the *syn*-products dramatically.

Addition of vinylmagnesium bromide in THF at −78 °C gave a precursor of 5-*O*-carbamoylpolyoxamic acid in 80% yield (*anti* : *syn* 6 : 1).[90] A decreased yield of 67% and diastereoselectivity (5.3 : 1) has been observed using vinylmagnesium chloride.[91] Vinylmagnesium bromide in the presence of one equivalent of $ZnCl_2$ gave no selectivity in THF–Et_2O (1 : 1) at −78 °C and only moderate *anti*-selectivity (3 : 1) in THF was observed without a Lewis acid present.[92]

Unnatural α-amino acids have been synthesised by Grignard reaction of **1** with phenylmagnesium bromide and subsequent oxidation of the primary alcohol at C-3. The addition was reported to be quantitative and leading, within 1 h, to a 2 : 3 *anti* : *syn* mixture in Et_2O at 0 °C.[93]

The total synthesis of sanjoinine-G1, a 14-membered cyclopeptide, has been achieved. The precursor (*S*,*S*)-β-phenoxyleucine was generated by a highly *syn*-selective Grignard reaction of **8** (see Fig. 1) with ^{i}PrMgCl (*anti* : *syn* 1 : 14).[94]

The enantioselective synthesis of the natural amino acid L,L-diaminopimelate and derivatives as possible antibiotics or herbicides has been reported.[96] Vinylation of **1** with Grignard and Reformatsky reagents has been used as an approach to fluorinated and unsaturated DL-diaminopimelates (Scheme 15).[95]



Scheme 15

A series of piperidine alkaloids has been made by addition of Grignard reagents to Garner's aldehyde. Thus, the piperidine alkaloid micropine from leaves of *Microcos philippinensis* has been synthesised from **1**.[96] Congener **8** was used for the synthesis of the related piperidine alkaloids pseudodistomin C from the tunicate *Pseudodistoma kanoko*[97] and for the

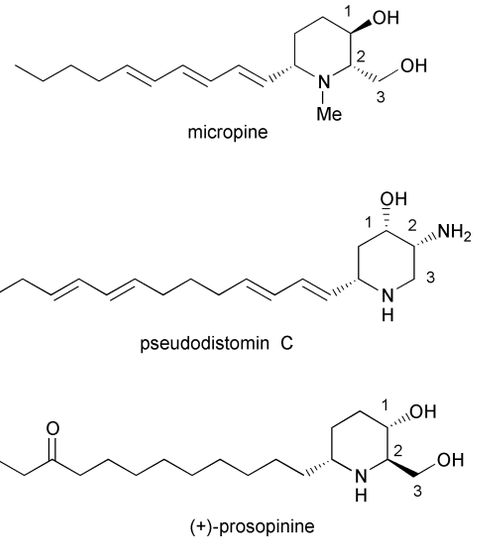


Fig. 7

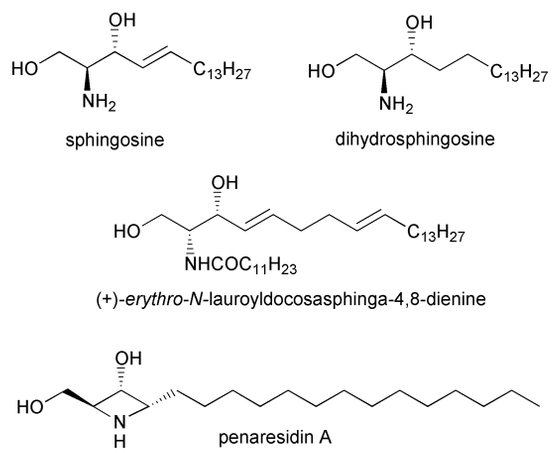


Fig. 8 Sphingosine type compounds.

antibiotic (+)-prosopinine from *Prosopis africana* Taub leaves (Fig. 7).[98]

In conclusion, the nucleophilic addition of alkylmagnesium halides to compounds **1** or **8** proceeds with high *syn*-selectivity in Et_2O and thereby provides a very effective means for preparing the relevant adducts.

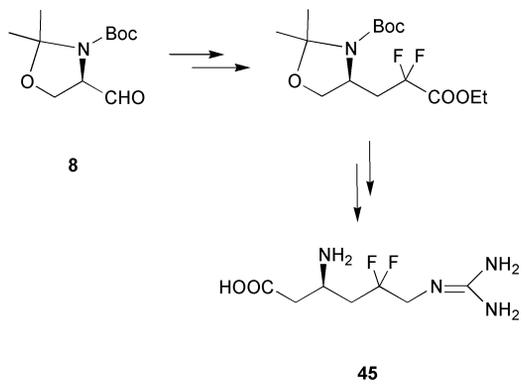
3.1.8 Zinc-mediated reactions

The highly diastereoselective addition of dihexylzinc, prepared *in situ* from $ZnCl_2$ and the appropriate Grignard reagent, to **1** provided dihydrosphingosine analogues (Fig. 8). Depending on additives, the ratio of products could switch between *anti* and *syn* (toluene, rt, 67%, *anti* : *syn*, 91 : 9; toluene, 0 °C, 79%, $ZnCl_2$, *N*,*N*-dibuthylethanolamine, *anti* : *syn*, 17 : 83). However, the highest yield of *syn*-product (90%, *anti* : *syn* 5 : 95) was obtained by Grignard reaction with hexylmagnesium bromide in Et_2O.[99]

The addition of vinyl organometallic reagents to **1** has been investigated by Coleman *et al.*[92] The highest *syn*-selectivity was observed with vinylzinc chloride (70–90% yield, *anti* : *syn*, 1 : 6) in Et_2O at −78 °C, while vinyllithium addition in THF at −78 C gave rise to the *anti*-product (*anti* : *syn*, 6 : 1). It had earlier been reported that addition of pentadec-1-enyl(ethyl)-zinc to **1** gave protected sphingosines in 52% yield at 0 °C in toluene. It has also been reported that the addition favours *anti*-product formation and that the reaction is influenced by the presence of an amino alcohol [*R*- and *S*-diphenyl(1-methylpyrrolidin-2-yl)methanol : *anti* : *syn* 4 : 1 and 2 : 1 respectively]. However, the product ratio without amino alcohol has

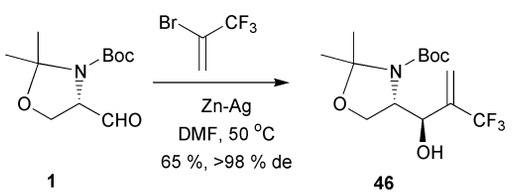
not been reported and achiral 2-(dibutylamino)ethanol gave the best *anti*-selectivity (*anti* : *syn*, 7.3 : 1).[100]

The Reformatsky reaction of zinc and α-halogen carboxylic esters with carbonyl compounds is closely related to the Grignard reaction. The reaction of ethyl 2-bromo-2,2-difluoroacetate with **8**, subsequent deoxygenation and functionalisation provided the amino acid 4,4-difluoro-L-arginine **45** (Scheme 16).[101] This amino acid has been used for the preparation of thrombin inhibitors to argatroban analogues wherein the guanidine moiety is of reduced basicity.[102] Other fluorinated amino acid derivatives have also been reported.[103] A CF_3-substituted amino acid precursor **46** was obtained in high diastereoselectivity from the Zn–Ag promoted Barbier-type reaction of 2-bromo-3,3,3-trifluoropropene with **1** (Scheme 17).[104]



8 **45**

Scheme 16

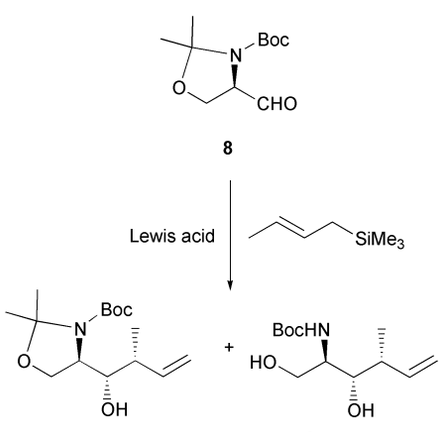


1 **46**

Scheme 17

3.1.9 Silylated nucleophiles

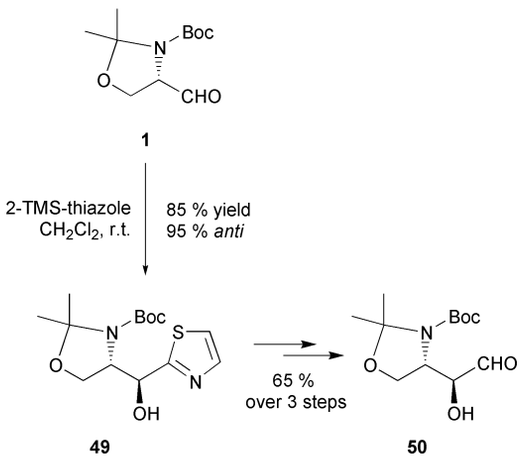
γ-Branched amino acids were synthesised by *anti*-selective addition of crotylsilane to **8** in the presence of one equivalent of a Lewis acid. Best results were obtained with $TiCl_4$ in CH_2Cl_2 at −78 °C to give 66% of **47** (90% de). Prolongation of the reaction time or use of excess Lewis acid gave rise to the corresponding deisopropylidene derivative **48** (Scheme 18).[105]



8 **47** **48**

Scheme 18

2-(Trimethylsilyl)thiazole has been reported to give *anti*-addition to **1** in CH_2Cl_2 at room temperature with 85% yield (*anti* : *syn* 92 : 8).[11,23,106] The optical purity of the product **49** has been demonstrated by ^{1}H NMR spectroscopy using a chiral shift reagent.[24] Subsequent unmasking by a standard procedure gives access to chiral aldehyde **50**, which was subsequently converted to D-*erythro*-C_{20}-sphingosine (Scheme 19).[107]



1 **49** **50**

Scheme 19

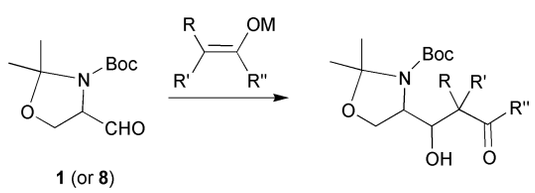
The synthesis of (2*R*)-*N*-Boc-2-amino-4,4,4-trifluorobutanoic acid has been synthesised by the initial addition of TMS-CF_3 to **1**.[108]

3.1.10 Other alkylmetals

The addition of alkyl-Cu or -Mn reagents to *N*-Boc protected α-amino aldehydes in THF at −78 °C led to the selective formation of *syn*-products (60–80% yield, 89–98% de).[109] Addition of a vinylalane obtained by hydroalumination of pentadec-1-yne with $(^iBu)_2AlH$ has been reported to react with **1** and proceeds with modest *syn*-selectivity.[110] Alkylzirconocene chlorides are less reactive. (*E*)-Hex-1-enylzirconocene chloride has been reported to react with **1** although no diastereoselection was observed.[111]

3.2 Aldol condensation and related reactions

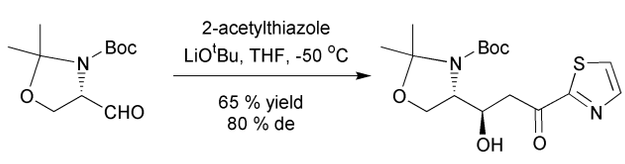
The aldol-type addition to Garner's aldehyde can provide access to important classes of D- and L-4-amino-2-deoxypentoses, ketoses or even higher order carbohydrates (Scheme 20). The aldol reaction of 2-acetylthiazole with several aldehydes was investigated by Dondoni *et al.*[106,107]



1 (or **8**)

Scheme 20

The reaction with **1** in THF and LiO^tBu at −50 °C led to the formation of the *anti* product **51** (80% de) in 65% yield (Scheme 21). Conversion of related glycerine aldehyde derivatives gave rise to 3-deoxyaldo-2-uloses and 3-deoxy-2-ulosonates, which are important natural products.

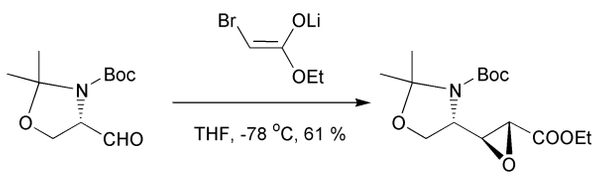


1 **51**

Scheme 21 Aldol condensation of 2-acetylthiazole with **1**.

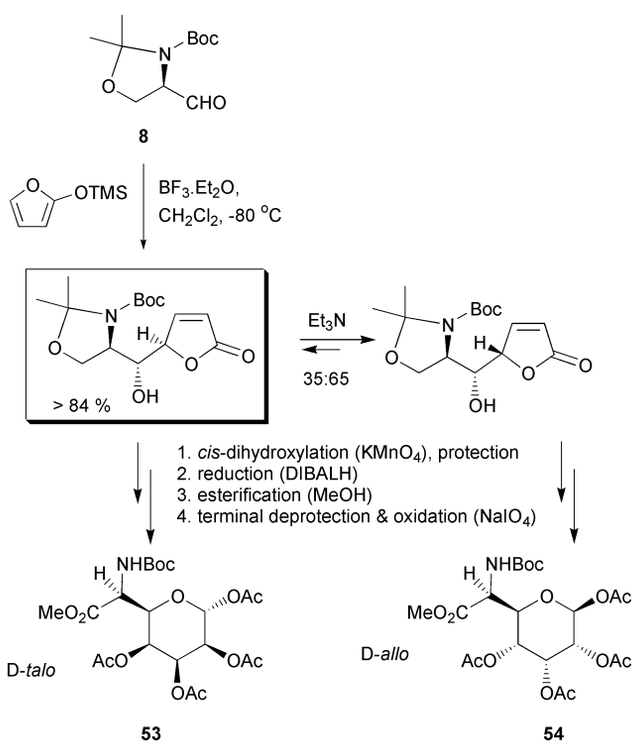
Selective access to amino-hydroxy oxiranes by an *anti*-aldol selective Darzén reaction of **1** with ethyl bromoacetate so as to give (*E*)-epoxy derivative **52** has been reported (Scheme 22).[112]

The condensation of dimethyl 3-methylglutaconate with several amino aldehydes to form 5,6-dihydro-(2*H*)-pyran-2-ones has been studied. Compound **8** gave the corresponding product in 60% yield with less diastereoselectivity (*anti* : *syn*, 57 : 43).[113] Chiral, cyclic amino aldehydes have been reacted with methyl acrylate and DABCO, in a process known as the Baylis–Hillman reaction, as a means for preparing sphingosine analogues.[114] An efficient synthesis of chiral dihydropyridinone derivatives was reported using an aldol-type coupling reaction between *N*-alkylpiperidin-2-one and **1** followed by a silane–Rh-mediated olefin isomerisation.[115] A lithium-activated difluoro-acyl equivalent, prepared from trifluoroethanol, has been applied.[116] Lithium-activated dithioacetate enethiols followed by alkylation of the intermediate aldolates gave hydroxyketene-dithioacetals with moderate *anti*-selectivity.[117] Acyclic stereo-selection in the tertiary amine-catalysed addition of activated vinyl systems (Baylis–Hillman reaction) to protected chiral α-hydroxy and α-amino aldehydes has been investigated.[118] 6-Deoxy-6-aminoheptopyranouronic acid derivatives have been prepared by Casiraghi *et al.*[119,120] Thus. the addition of commercially available 2-(trimethylsiloxy)furan to **1** or **8** and subsequent *cis*-dihydroxylation with $KMnO_4$ provided D- or L-pairs of the *glycero-talo* and *glycero-allo* pyranosyl glycine derivatives, **53** and **54** (Scheme 23).



1 **52**

Scheme 22 *anti*-Aldol selective tandem aldol–substitution to (*E*)-epoxy derivatives.



53 **54**

Scheme 23 Use of **8** for the synthesis of D-*talo*- and D-*allo*-pyranose derivatives.

The corresponding L-*talo*- and L-*allo*-pyranoses were obtained in the same manner from **1**.[120] The iminosugars 2,4-diamino-2,4-deoxy-L-arabinose and 2,4-diamino-2,4-deoxy-L-ribose have been synthesised from **1** by a $BF_3{\cdot}Et_2O$-assisted Mukaiyama-aldol reaction. However, even while starting from 93–95% ee enriched **1**, the final enantiomeric purity of the products has not been reported.[121]

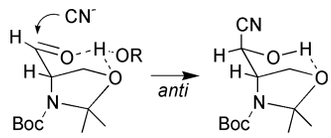
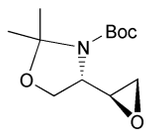
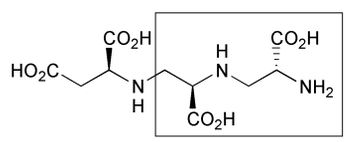


Fig. 9



55

Fig. 10



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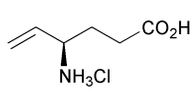

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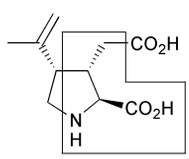


58

Fig. 11

The diastereoselective addition of HCN[121a] to Garner's aldehyde was investigated by Marcus *et al.* when the reaction performed in an aqueous buffer system of pH 5.4 at room temperature led to a *ca.* 9 : 1 mixture of *anti* : *syn* cyanohydrins. Best results were observed at room temperature with isopropanol as solvent (>99% de). The use of less polar aprotic solvents like ethyl acetate, Et_2O or toluene decreased the selectivity dramatically, except at lower temperature (toluene, −78 °C, 84% de) or if $BF_3{\cdot}Et_2O$ was added (toluene, rt, 84% de). Therefore, the authors proposed a model involving hydrogen bonds (Fig. 9).

Epoxidation of **1** with dimethylsulfonium methylide led to the epoxy building block **55** in 55% yield (Fig. 10).[122]

The preparation of polyhydroxylated compounds has been investigated by coupling of 5,6-dihydro-1,4-dithiines with chiral aldehydes and, in sequence, stereoselective removal of the dithiodimethylene dithiine bridge and stereospecific dihydroxylation of the resulting polyhydroxy alkenes. The addition to **1** favours the *syn*-product (80% yield, *anti* : *syn* 2 : 3).[123]

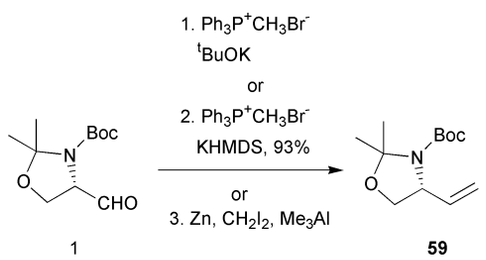
3.3 Wittig reactions

3.3.1 Simple Wittig reactions

The simplest Wittig reaction of Garner's aldehyde is the preparation of vinylglycinol **59**. The importance of enantiopure **59** as a building block has stimulated much synthetic effort.[124] Many biologically active targets may be prepared from it, such as metal-chelating polyamino acid aspergillomarrasamine A (**56**),[125] the selective enzyme-activated inhibitor of GABA-T vigabatrin (**57**)[126] and a neuroexcitor (−)-α-kainic acid (**58**) (Fig. 11).[127]

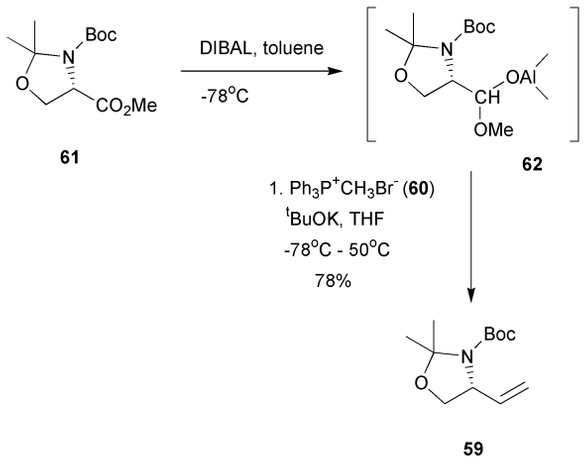
A straightforward route to **59** is the Wittig methylenation of **1** (Scheme 24). The first reported procedure has been shown to be problematic. Moriwake *et al.* obtained N,O-protected vinylglycinol **59** using methyltriphenylphosphonium bromide **60** and

KH as base in 66% yield with complete racemisation.[7] Later publications have demonstrated that the results depend strongly on the bases used to generate phosphonium ylide. Beaulieu *et al.* obtained **59** in very low yield (27%) with poor optical purity (69% ee) when *n*-BuLi was used.[128] The conditions using potassium *tert*-butoxide or potassium bis(trimethysilyl)amide (KHMDS) as base have subsequently been investigated by Boyd and Paton[129] and McKillop *et al.*[5] and provided **59** with no loss of optical purity (Scheme 24). A different system, $AlMe_3$–Zn–CH_2I_2, turns out to be a good alternative. Under such conditions a 75% yield of material with high enantiopurity was achieved.[7]



Scheme 24

Knaus *et al.*[129a] reported a one-pot procedure for preparation of vinylglycinol. This involved performing consecutive reactions that include a reduction of the α-amino acid ester **61** with DIBAL, followed by directed treatment of the intermediate aluminoxy acetal **62** with phosphonium ylide which was generated by deprotonation of **60** using potassium *tert*-butoxide as base. Good yields (78%) without racemization were achieved in this one-step tandem reduction–Wittig olefination process (Scheme 25).



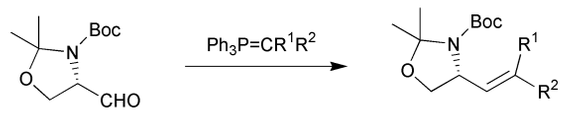
Scheme 25

3.3.2 Wittig reactions of 1 with non-stabilised ylides

The Wittig reaction of **1** with non-stabilised ylides favours the formation of the corresponding *Z*-olefin. Beaulieu *et al.*[128] investigated such processes in detail. Thus, treatment of **1** with a variety of phosphorus ylides generated from the corresponding phosphonium salts provides alkenes (Table 1). In most instances, *Z*-olefins are formed exclusively.

Glycosphingolipids and sphingomyelins that are biomembrane components play physiologically important roles in bioorganisms. As a consequence, sphingosines, dihydrosphingosines and phytosphingosines have been independently synthesised by many groups. Very recently, three different types of sphingosine derivative were prepared using **1** as starting material.[130] Wittig olefination of **1** using *n*-BuLi and pentadecyltriphenylphosphonium bromide **63** ($C_{15}H_{31}PPh_3Br$) only resulted in low yields of the desired olefin. In contrast, by using

Table 1



1

Entry	Compd.	R^1	R^2	Yield (%)	*Z*
1	**a**	Me	H	62[a]	93
2	**b**	n-C_5H_{11}	H	78[a]	>98
3	**c**	CH_2CH_2Ph	H	96[a]	>98
4	**d**	$(CH_2)_2COOH$	H	73[b]	>98
5	**e**	Et	Me	50	70

[a] Ylide generated from phosphonium salt using *n*-BuLi. [b] Ylide generated from phosphonium salt using LiHMDS.

$C_{15}H_{31}PPh_3Br$–LHMDS–**1** in combination, a 9 : 1 mixture of (*Z*)- and (*E*)-isomers was obtained in 83% total yield. Use of sodium hexamethyldisilazide (NaHMDS) as a base gave a similar result. Column chromatographic purification then provided pure (*Z*)-**64**. Further functional group manipulation then afforded dihydrosphingosines **65**–**66**, phytosphingosines **67**–**68** and sphingosines and **69**–**70** (Scheme 26). A similar approach to phytosphingosines has been described by Horikawa *et al.*[131] Reagent-controlled *cis*-dihydroxylation using AD-mix was investigated in detail.

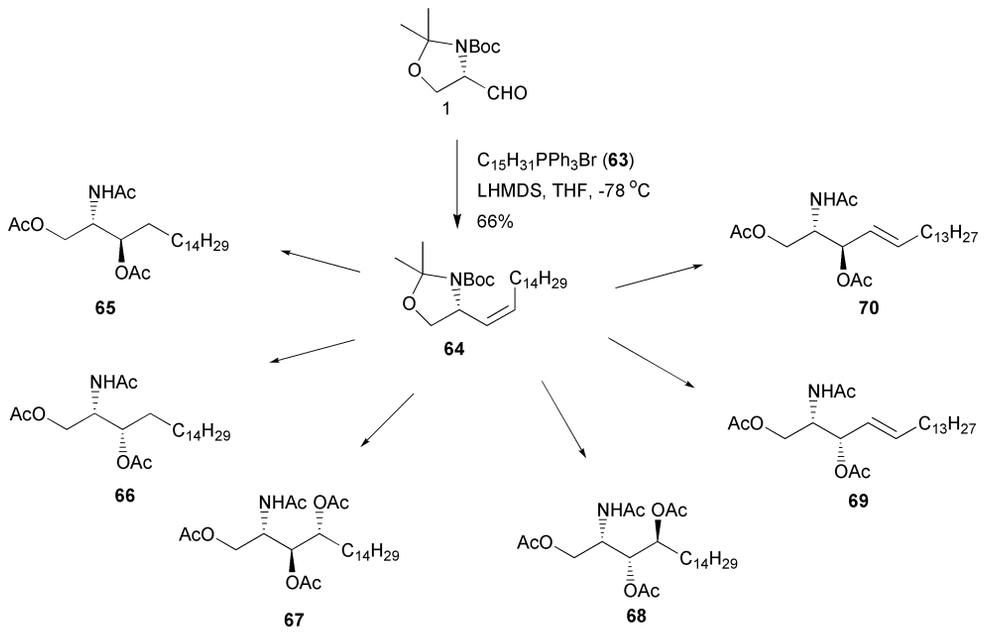
Compound **1** was also used by Boger *et al.* as a starting material in the synthesis of endogenous sleep-inducing lipids.[132] The key step was the Wittig olefination of **1** with the *in situ* generated phosphorane derived from the phosphonium salt **71** (THF, −78 to 25 °C, 30 min, 68–82%) providing the protected 3*Z*-alkene **72** ($Z : E \geq 10 : 1$) containing small amounts of the readily separable 3*E*-alkenes. Acid-catalysed deprotection then gave desired product (3*Z*,12*Z*)-**73** (Scheme 27). Related olefination reactions were also carried out during this study.

In the preparation of the immunosuppressive agent **76**, Wittig reaction of **1** with alkyltriphenylphosphonium bromide in the presence of KHMDS afforded the condensation product **74**, which was exposed to acid-catalysed hydrolysis to **75** and Pd/C catalysed hydrogenation to give **76** (Scheme 28). The activity of **76** on the mouse allogenic mixed lymphocyte reaction (MLR) was examined: **76a** showed very potent activity (IC_{50} 68.8 nM).[133]

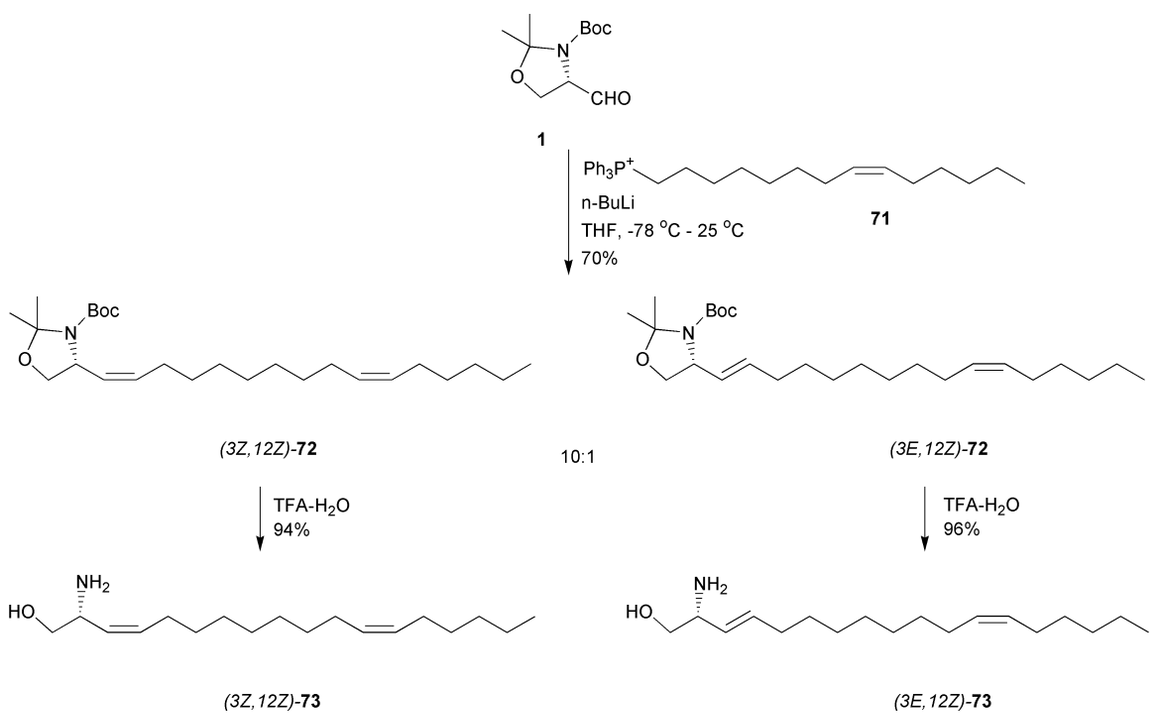
Two papers on the synthesis of NMDA receptor agonists have been published by Bernabe *et al.*[134,135] Compound **1** was repeatedly used as starting material. The reactions with non-stabilised ylides, generated from propyltriphenylphosphonium bromides by treatment with *n*-BuLi, produced 25 : 75 mixtures of (*E* : *Z*)-**77**. These mixtures were readily separated by flash chromatography. Isomer (*E*)-**77** was converted, by reaction with dibromocarbene into the corresponding cyclopropyl dibromides, and then into the dehalogenated analogue by reduction using 2 equivalents of tributyltin hydride. Acid-catalysed cleavage of the oxazolidine moiety produced the corresponding alcohols which were treated with Jones reagent to deliver the desired product **78**. The sequence has also been carried out with 2-(1,3-dioxan-2-yl)ethylidenetriphenylphosphonium bromide (Scheme 29).

In a synthesis of azocine derivatives (azacyclooctane), **1** was selected as a starting material. Wittig reaction of **1** with the ylide generated from carboxybutyltriphenylphosphonium bromide **79** using potassium bis(trimethylsilyl)amide afforded the unsaturated acid **80** in 80% yield. Further steps then provided the desired products **81**–**83** (Scheme 30).[136]

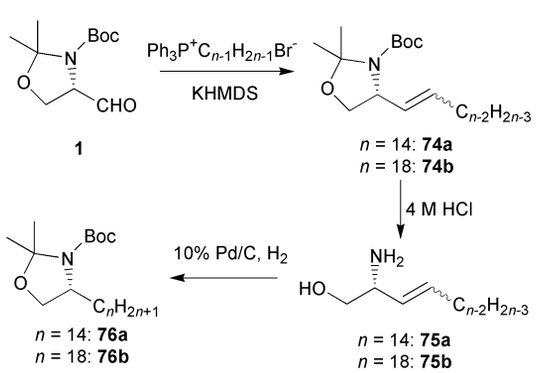
Three different groups have independently synthesised (+)-curacin A (**84**), an antiproliferative agent from the cyanobacterium *Lyngbya majuscula*. Even though the strategies are



Scheme 26



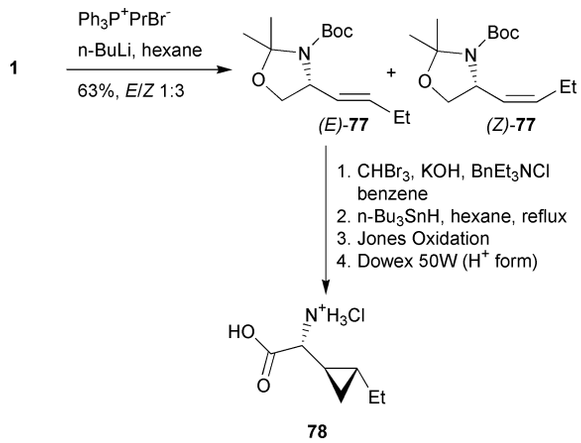
Scheme 27



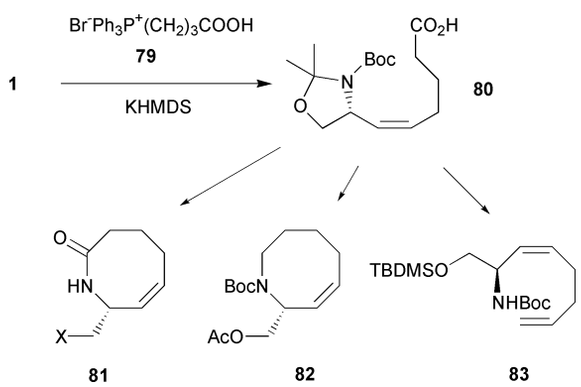
Scheme 28

different, the same intermediate **86**, which is obtained from Wittig olefination of **1** with the ylides generated from the corresponding phosphonium salt, is used. In all three cases, the *Z*-isomers are obtained in a selective manner (Scheme 31).[137–139]

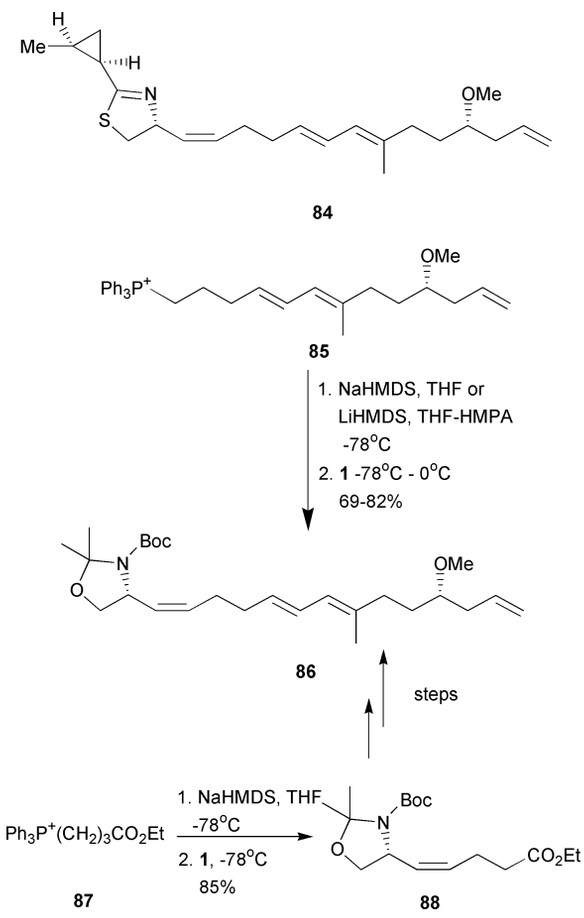
Compound **8** has also served as a key building block in the synthesis of *C*-glycopeptides. Usually, *N*- or *O*-linked glycopeptides occur in nature, but they lack *in vivo* stability under acidic and basic conditions. Consequently, more stable isosteric *C*-glycosylated peptides have become of interest. Therefore, during the last decade several different synthetic pathways for the synthesis of *C*-glycosylamino acids have been described. In Dondoni's synthesis[139a] of β-D-galactosyl ceramide methylene isostere, the key step again was a Wittig olefination reaction. Thus, the sugar phosphorane, generated from the sugar phosphonium salt **89** by treatment with *n*-BuLi in THF–HMPA was reacted with a solution of **8** to give **90**. The removal of the acetonide protecting group and Swern oxidation of the corresponding alcohol provided the aldehyde **91**. Reaction of this aldehyde with lithium pentadec-1-yne then afforded the expected alcohol **92**. Further transformations give the desired product **93** (Scheme 32).



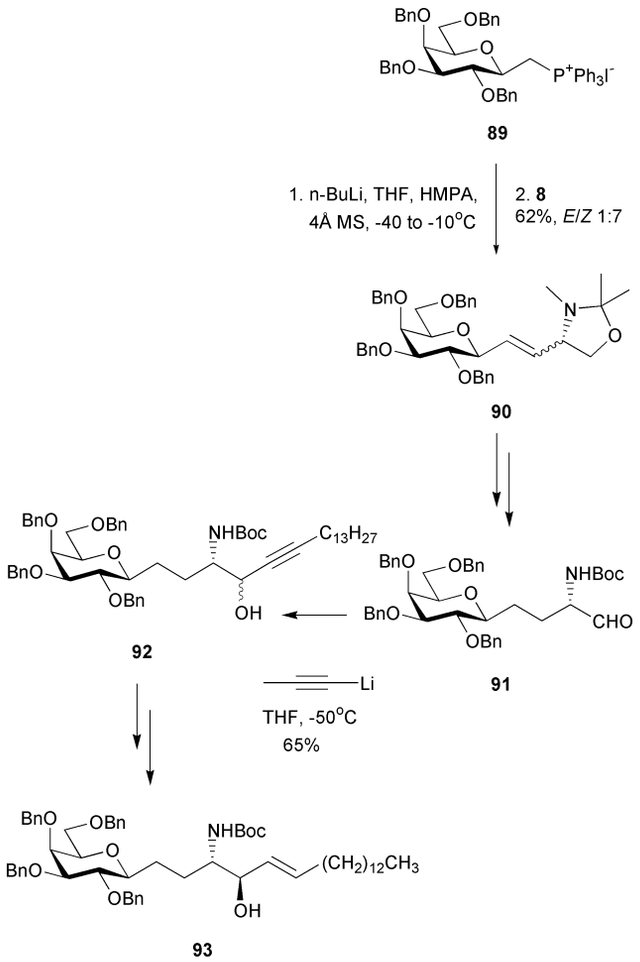
Scheme 29



Scheme 30

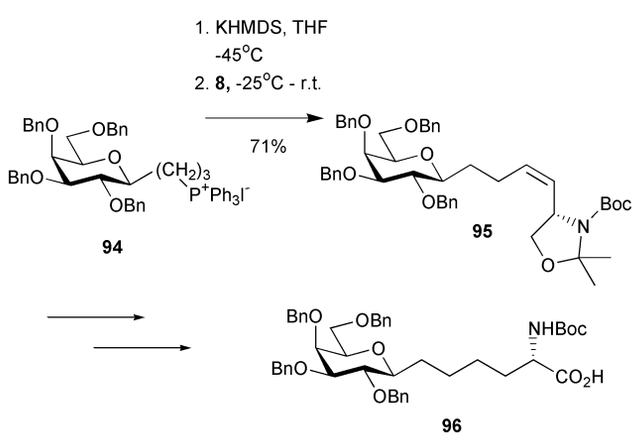


Scheme 31



Scheme 32

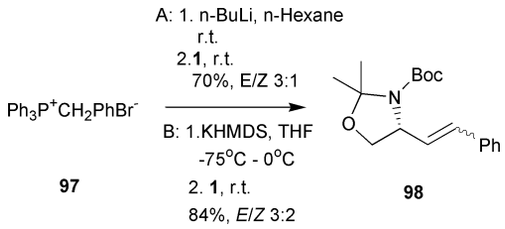
A similar strategy was pursued in the synthesis of a *C*-glycoside analogue of β-D-galactosyl hydroxynorvaline. The ylide of **94** was coupled with the aldehyde **8** to give *Z*-alkene **95** together with a small amount of the corresponding *E*-isomer (71%; *Z*/*E* > 14.1). After several steps, the desired protected β-D-galactosyl-CH_2-hydroxynorvalin building block **96** was obtained (Scheme 33).[139b]



Scheme 33

3.3.3 Wittig reactions of 1 with semi-stabilised ylides

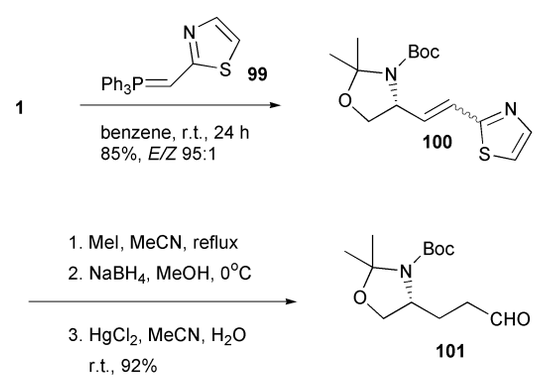
The reaction of aldehydes with semi-stabilised ylides normally produces mixtures of *Z*/*Z*-isomers. This was also true for the olefination of **1**. Bernabe *et al.* and Beaulieu *et al.* have independently prepared the olefin **98**, through Wittig reaction of **1** with the corresponding ylide, in a good yield but with poor *E*/*Z* selectivity (Scheme 34)[134,128] although the isomers (*Z*)-**98** and



Scheme 34

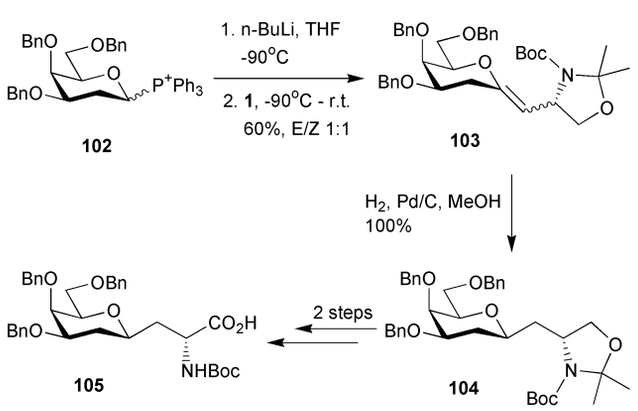
(*E*)-**98** were separable by chromatography. The enantiopurities of both were determined to be of ~99% ee.[131]

In the synthesis of γ-functionalised aldehydes, olefination of **1** with a semistabilised ylide **99** led to the alkenylthiazole **100** in high yield and excellent stereoselectivity, although the selectivity was variable with other aldehydes (Scheme 35). This is a convenient method to prepare γ-functionalised aldehydes such as **101**.[140] **100** has also been used to synthesise (−)-mannonojirimycin.[141]



Scheme 35

The last example of the use of this type of ylide is 2-deoxygalactopyranosylphosphorane **102** (Scheme 36). Wittig reaction of the α,β-mixture of phosphonium salt **102** and **1** using *n*-BuLi as base in THF afforded, as expected, a mixture of the exocyclic enol ethers **103** (60%, *E* : *Z* 1 : 1). Hydrogenation to **104**, deprotection and Jones oxidation gave **105** as the final product.[142]

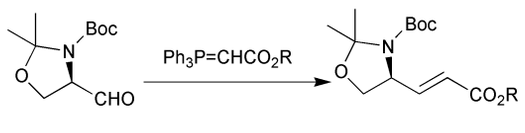


Scheme 36

3.3.4 Wittig reactions of 1 with stabilised ylides

Garner's aldehyde (**1**) has been used often in the synthesis of another important building block, compound **106**, which also offers many possibilities for chemical transformation. This α,β-unsaturated ester can undergo Michael type addition, cyclopropanation, [2+3]cycloaddition, Diels–Alder reaction, epoxidation, dihydroxylation *etc*. Further functional group interconversions will pave the way to many other useful building blocks. Here, the preparation of **106** using the Wittig reagent is described and later some uses of this building block will be discussed.

Table 2



Entry	R	Solvent	Yield (%)	*E* : *Z*	Ref.
1	Me	MeOH	93	3 : 2	143
2	Me	MeOH	78	3 : 1	144
3	Et	THF	72	1 : 0	145
4	Et	benzene	82	1 : 0	141, 146
5	Me	benzene	86	94 : 6	147
6	Et	benzene	100	1 : 0	148
7	Me	benzene	95	1 : 0	149

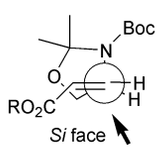
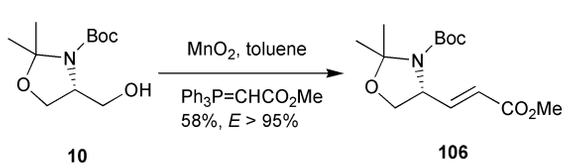


Fig. 12 Felkin–Ahn model for the 1,4 nucleophilic addition of metal dialkylcuprates to enoate (*S*)-**52**.

Wittig reaction of **1** with commercially available ylides proved to be a very convenient procedure for preparation of **106**. Both reactants can be simply mixed in a solvent and stirred at room temperature, though the work up does involve chromatography. The stereochemical outcome of this reaction strongly depended on solvents. When the reaction was performed in methanol, poor *E*/*Z* ratios were observed, while in THF or benzene, high stereoselectivity was observed (Table 2).[141,143–149]

Taylor and coworkers have developed a one pot procedure for the preparation of **106**. The corresponding alcohol **10** was oxidised using manganese dioxide in the presence of the ylide and the aldehyde (**1**) so formed was trapped as formed to produce the α,β-unsaturated ester **106** directly. Even though this *in situ* oxidation–Wittig methodology proceeded in moderate yield, the stereoselectivity was very high (>95% *E*) (Scheme 37).[150]

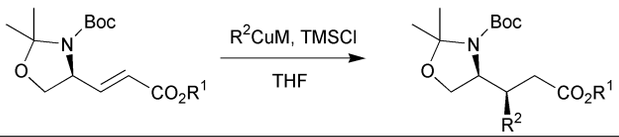


Scheme 37

Due to the presence of the chiral oxazolidine moiety, Michael addition of organometallic reagents to compound **106** was expected to be diastereoselective. Yoda *et al.*, C. Wermuth *et al.* and Hanessian *et al.* have systematically investigated the reactivity and stereochemical outcome of this reaction (Table 3). The reaction conditions are similar in all three cases. Conjungate addition of organocuprates to **106** esters in the presence of trimethylsilyl chloride led to faster reaction and higher yield. The diastereoselectivities observed ranged from good to excellent (Table 3).[151–154] The formation of the favoured *syn*-isomer was rationalised by the Felkin–Ahn model wherein nucleophilic addition takes place preferentially from the *Si*-face (Fig. 12).[154] Other possible explanations for the observed stereoselectivity have also been discussed.[152]

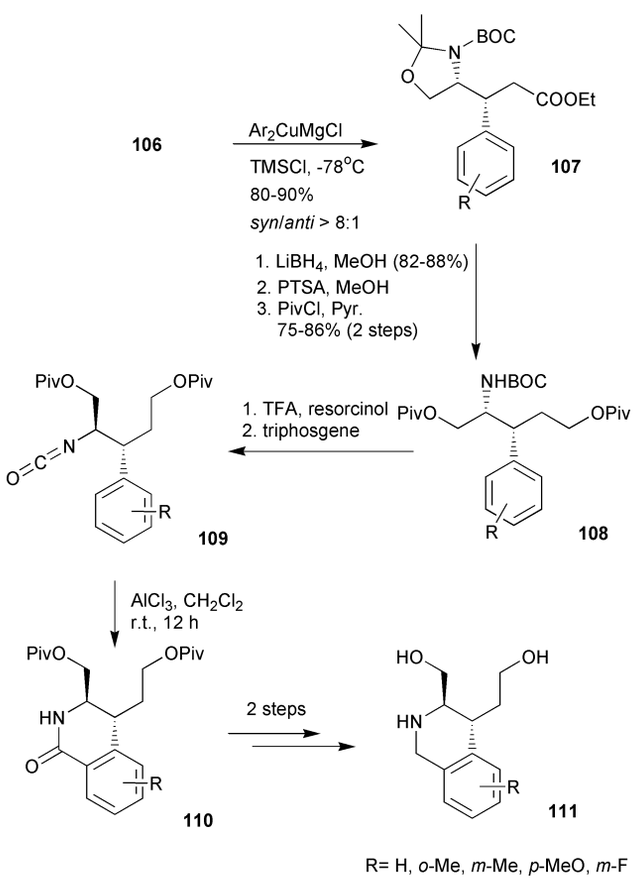
In Hanessian's synthesis of various functionalised and enantiopure tetrahydroisoquinolines, the key step was the Michael addition of **106**. Application of this reaction to a variety of

Table 3 Michael additions to **106**. (Differently configured examples of **106** have been employed).



Entry	R^1	R^2	M	Yield (%)	*syn* : *anti*	Ref.
1	Me or Et	Methyl	Li	70–97	>50 : 1	151, 152, 153
2	Et	Methyl	MgBr	57	>99 : 1	151
3	Me	Ethyl	MgBr	70	>50 : 1	152, 153
4	Et	Propyl	MgBr	62	>99 : 1	151
5	Me	Propyl	Li	71	95 : 1	154
6	Et	Butyl	MgBr	55	>99 : 1	151
7	Me, Et	Butyl	Li	85–90	>50 : 1	151, 152, 153
8	Me	Vinyl	MgBr	80	>50 : 1	152, 153
9	Me	Prop-2-enyl	Li	75	>14 : 1	152, 153
10	Me	Phenyl	MgBr	80	>8 : 1	152, 153
11	Et	Octyl	MgBr	52	87 : 13	151
12	Me	Methallyl	Li	78	9 : 1	154
13	Me	Benzyl	Li	86	8 : 2	154
14	Me	Allyl	Li	74	9 : 1	154

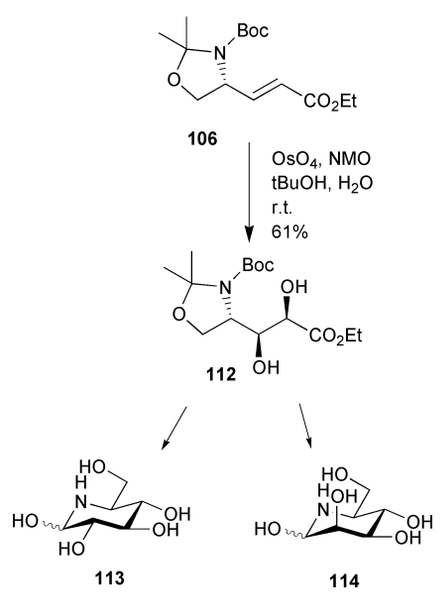
monosubstituted diarylmagnesiocuprates led to the corresponding β-aryl adducts **107** in excellent yields. These adducts were then transformed into the bis-pivaloyl esters **108** over three steps. Removal of the *N*-Boc group with TFA in the presence of resorcinol, followed by treatment with triphosgene led to the corresponding isocyanates **109** which underwent Friedel–Crafts reaction to provide the desired products **110**. These last compounds could then be reduced to the corresponding tetrahydroisoquinolines **111** (Scheme 38).[155]



Scheme 38

Another example of Michael type reaction was also reported. Conjungate addition of benzylhydroxylamine to **106** gave a mixture of two diastereomers with poor stereoselectivity.[156]

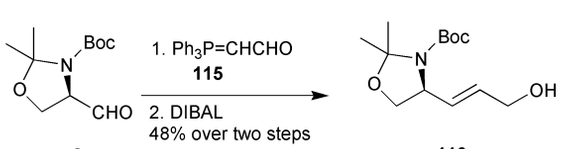
Dondoni and his coworkers have used **106** in their synthesis of (−)-nojirimycin **113** and (−)-mannonojirimycin **114**. The *cis*-dihydroxylation of unsaturated ester **106** using the Upjohn procedure afforded a 75 : 25 mixture of expected *anti*- and *syn*-diols in 82% yield. The major isomer, **112**, was isolated by chromatography (Scheme 39).[141]



Scheme 39

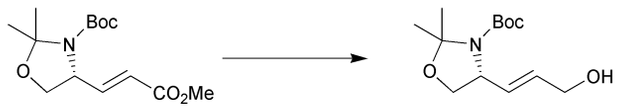
The allylic alcohol **116** can also be prepared from **106** using DIBAL. This reaction is not as simple as it seems to be, because quantities of corresponding fully saturated alcohol can be produced during the reduction of the ester, and the yield varies from 40 to 70%. The best result was achieved by using the DIBAL–*n*-BuLi system (87%) (Table 4).[143,146,147,149,157]

An alternative approach was to carry out a Wittig reaction of **1** with (triphenylphosphoranylidene)acetaldehyde **115** to provide the α,β-unsaturated aldehyde, which was reduced to the corresponding alcohol **116** in 48% yield over two steps and with only trace quantities of the saturated alcohol now being observed (Scheme 40).[157]



Scheme 40

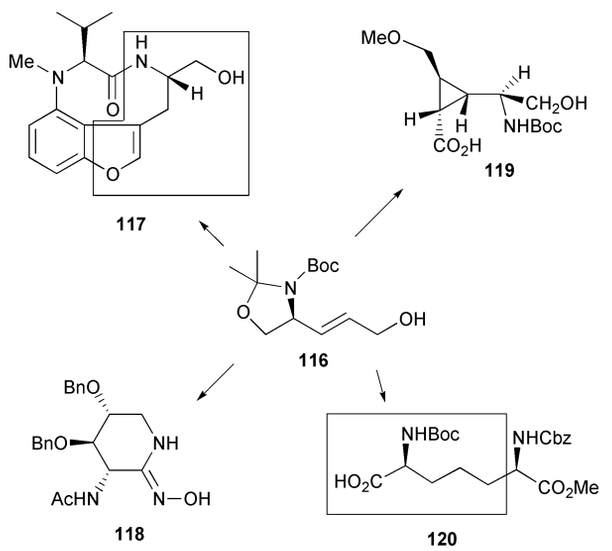
Table 4



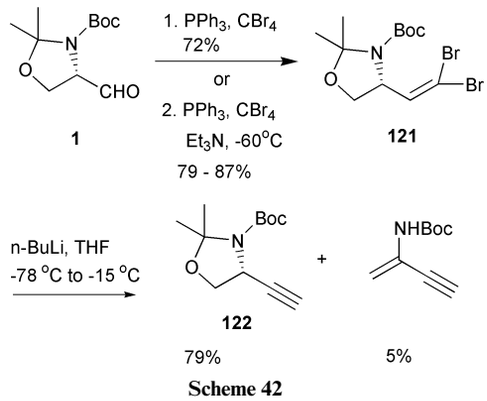
106

Entry	R	Solvent	Reagent	Yield (%)	Ref.
1	Me	CH_2Cl_2	DIBAL	72	143,146
2	Me	THF	DIBAL	40	157
3	Me	Toluene	DIBAL	61	148
4	Me	Toluene	DIBAL–*n*-BuLi	87	160

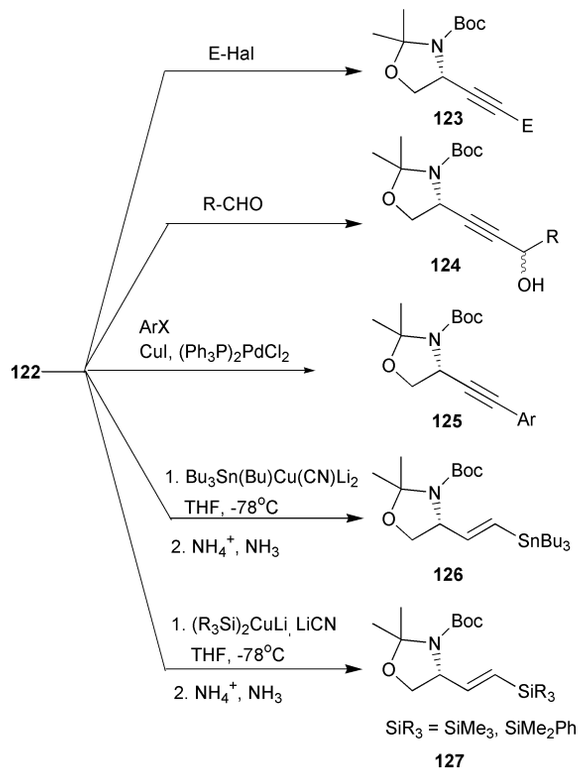
The allyl alcohol **116** has been used in the preparations of different compounds, such as PKC (protein kinase C) activator **117**,[147] the protected glycosyltransferase inhibitor **118**,[148] conformationally constrained analogues of L-glutamate, glycinol derivative **119**[158] and differentially protected *meso*-2,6-diaminopimelic acid **120** (Scheme 41).[157]



Scheme 41



Scheme 42



Scheme 43

3.3.5 Corey–Fuchs olefination

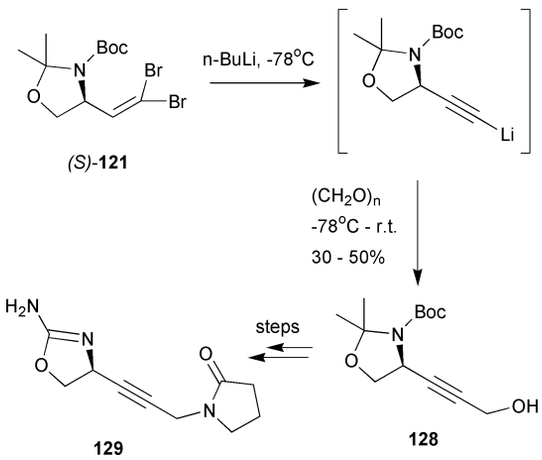
Terminal alkynes play an important role in organic synthesis because they can undergo, either directly or indirectly, many different C–C bond forming reactions. Corey and Fuchs developed one of the easiest methods for preparation of terminal alkyne derivatives from aldehydes in 1972.[159] This methodology has also demonstrated its utility in Garner's aldehyde chemistry. The Corey–Fuchs procedure involves a two-step sequence. The first step, one carbon homologation of **1** to form dibromoalkene **121**, was accomplished by reaction of **1** with CBr_4–Ph_3P[160] or CBr_4–Ph_3P–Et_3N.[161–163] Reaction of **121** with *n*-BuLi or NaHDMS in THF then results in formation of the lithioalkyne which on protic work-up affords the terminal alkyne **122**. According to Reginato *et al.*, careful control of the reaction conditions was necessary in order to avoid the formation of undesired by-products. For example, prolonged reaction times or use of a large excess of base induced the formation of an enamine as predominant product (Scheme 42).

Compound **122** has been used in many different types of reaction. Thus, deprotonation of this material using *n*-BuLi and subsequent reaction with electrophiles, such as TMSCl, RCH_2I, acetyl chloride, methoxycarbonyl chloride, or MOMCl was investigated in order to generate a series of new chiral 4-ethynyloxazolidine derivatives **123**–**127** (Scheme 43).[161–164]

The reactions proceeded in moderate to excellent yields. In some cases the formation of enamines and other by-products were observed. The possibility of condensation of the desired lithium acetylide with various aldehydes has also been tried. Formation of the corresponding lithium acetylide by reaction of **122** with *n*-BuLi in THF at −100 °C and condensation with a number of different aromatic and aliphatic aldehydes afforded the propargylic alcohol derivatives **124** in 62–96% yield, generally as a 5 : 1 mixture of diastereoisomers. Under such conditions, not even traces of the enamine by-product could be detected.[165] The use of **122** has been extended to Sonogoshira copper–palladium-catalysed C–C coupling to give **125**, stannylcupration for Stille coupling to **126** and silylcupration to obtain **127** (Scheme 43).[162,166,167]

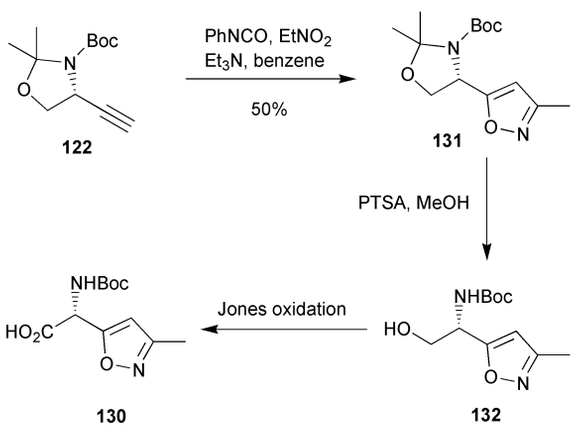
If the corresponding lithium acetylide of **122** is quenched with $(CH_2O)_n$, propargylic alcohol **128** can be produced and has been used in the synthesis of compound **129**, an analogue of the muscarinic agent oxotremorine (Scheme 44).[160]

A further example of the utility of compound **122** is its application in a synthesis of new α-amino acid derivatives, **130**, containing isoxazol-5-yl groups. Thus, compound **122** underwent 1,3-dipolar cycloaddition with a nitrile oxide, generated *in situ* from nitroethane, to afford adduct **131** in 50% yield.



Scheme 44

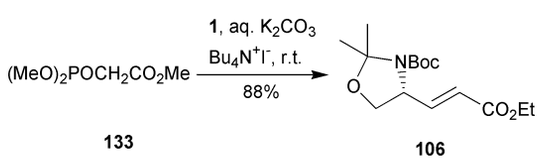
Subsequent deprotection and oxidation provided (*R*)-2-(*N*-*tert*-butoxycarbonylamino)-2-(3-methylisoxazol-5-yl)acetic acid (**130**, Scheme 45).[163]



Scheme 45

3.3.6 Horner–Wadsworth–Emmons reactions

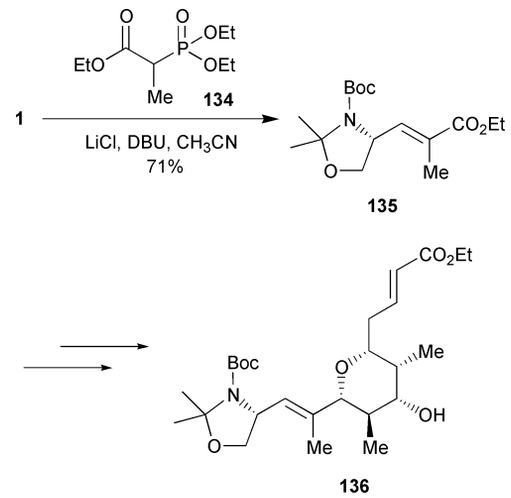
Building block **106** can also be prepared by Horner–Wadsworth–Emmons reaction of **1** with alkyl dialkoxyphosphorylacetate **133** under standard conditions. Normally, this reaction proceeds in high yield (>80%) and with excellent stereoselectivity (>95 : 5, Scheme 46). Its advantage over the Wittig reaction is that the water soluble **133** makes the work up easier.[154,157,168]



Scheme 46

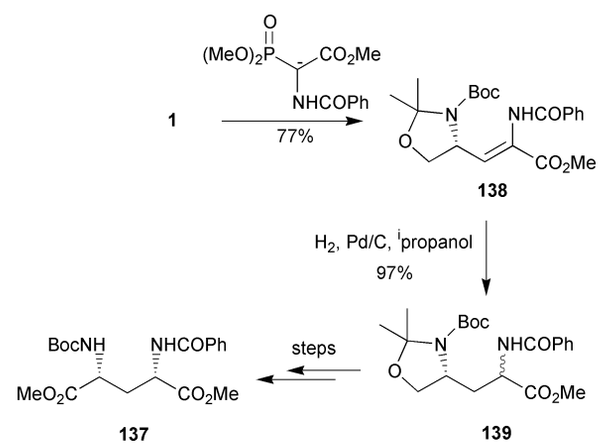
In an approach to the central C18–C30 core of the phorboxazole natural products, compound **1** was condensed with ethyl diethoxyphosphorylpropionate **134** under Masamune–Roush conditions thereby giving (*E*)-acrylate **135** in 71% yield. After multiple steps, the desired segment, **136**, was obtained (Scheme 47).[169]

The 2,4-diaminoglutaric acid derivative **137** has been synthesised from **1** by Avenoza *et al*. Firstly, olefin **138** was prepared by condensation of **1** with the potassium salt of methyl 2-benzamido-2-(dimethoxyphosphoryl)acetate. The crude **138** was contaminated with 13% of the *Z*-isomer as judged by ^{1}H NMR spectroscopic analysis and was purified by crystallisation from diethyl ether to give *E*-isomer in 77% yield. Hydrogen-



Scheme 47

ation of the olefin proceeded in the presence of Pd/C in isopropanol to provide the dihydro compound **139** in 100% yield and with 94 : 6 stereoselectivity. After several standard steps the desired differentially protected *meso*-2,4-diaminoglutaric acid **137** was obtained (Scheme 48).[170]

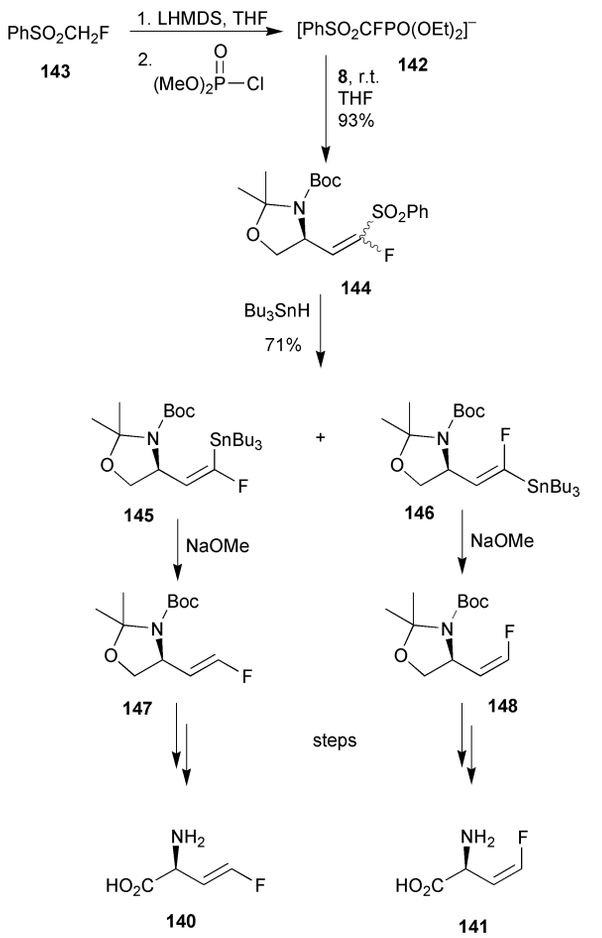


Scheme 48

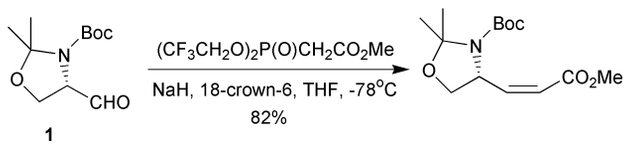
Because of their potential antibacterial activity as alanine racemase inhibitors, amino acids **140** and **141** have been prepared (Scheme 49). Thus, treatment of **8** with the anion **142**, generated *in situ* from fluoromethyl phenyl sulfone **143**, diethyl chlorophosphate and LHMDS, provided **144** in 93% yield. Reaction of **144** with tributyltin hydride gave an 11 : 2 mixture of stannanes **145** and **146**, which were separated by chromatography. Products **145** and **146** were treated with NaOMe in MeOH to give **147** and **148**, respectively. After several additional but standard steps, targets **140** and **141** were then obtained.[171]

The Horner–Wadsworth–Emmons reaction normally affords α,β-unsaturated ketones with high *E*-selectivity. The same applies to formation of α,β-unsaturated esters. However, Still and Gennari have demonstrated that replacement of alkyl dialkoxyphosphorylacetate with bis(trifluoroethyl) phosphonate esters can switch such selectivity so that the *Z*-isomer[172] is now favoured and obtained in high yield (Scheme 50).

The utility of this method has been demonstrated by the stereoselective synthesis of different synthetic targets, *e.g.*, a peptide antibiotic, galantin I,[173,174] conformationally constrained analogues of L-glutamate, 3′-methoxy-L-2-(carboxycyclopropyl)glycines,[149,175] a potential building block for the synthesis of kainoids,[144] acyclic analogues of kainoids,[176,177] a potent inhibitor of protein phosphatases, calyculin,[178] and a segment of a lincomycin type antibiotic (Fig. 13).[179]



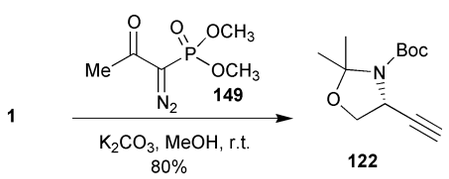
Scheme 49



Scheme 50

3.3.7 Miscellaneous Wittig procedures

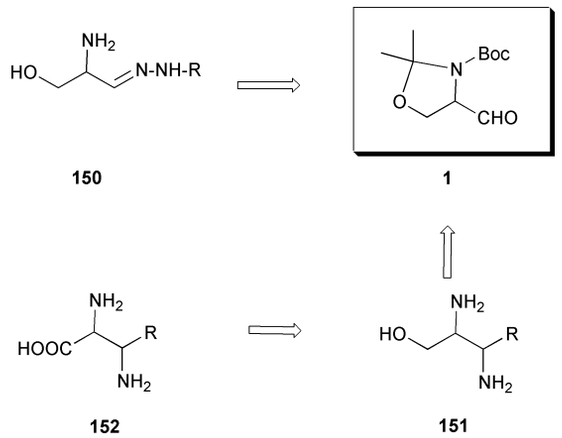
Ohira has developed a one-step procedure to prepare terminal alkynes from aldehydes and dimethyl 1-diazo-2-oxopropylphosphonate **149** (Scheme 51).[180] This method has also been used in the preparation of **122**.[181] Phosphonate **149** reacted with **1** smoothly at room temperature in the presence of K_2CO_3 in MeOH to give **122** in ~80% yield. The only disadvantage is that the reagent is not commercially available, but even then it is a good alternative to the Corey–Fuchs procedure.



Scheme 51

3.4 Other nucleophilic additions; formation of hydrazones, nitrones, amines, oximes and acetals

The easy formation of hydrazones of the general type **150** (Scheme 52) from **1** has been exploited in the solid phase synthesis of 1-aminohydantoin libraries. Compound **1** has also been used as substrate for the preparation of a variety of potentially biologically active 2-amino-3-hydroxypropyl derivatives.[182]



Scheme 52 Addition of *N*-nucleophiles to **1**.

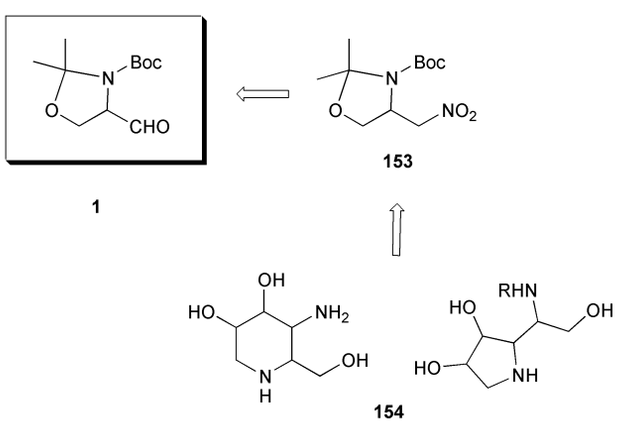
Thus, reductive amination of **1** and subsequent oxidation of the 3-hydroxy group of **151** (R = H) to 2,3-diaminopropionic acid derivative **152** has been used in solid phase peptide synthesis.[183]

Reductive amination to form *N*-5 substituted 1-(1-adamantylmethyl)-3-arylureido-2,4-dioxo-1,5-benzodiazepines, which proved to be potent CCK-B receptor antagonists, has been reported.[184]

Exclusively *syn* products **151** (R = H) were obtained if imine derivatives of **1** were reacted with carbon nucleophiles (Scheme 52).[185–187]

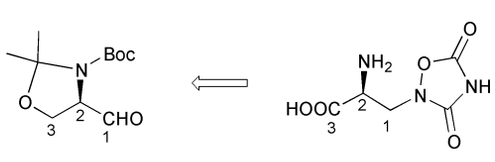
Another approach to 2,3-diaminopropionic acids **152** was achieved by nitrone formation with *N*-benzylhydroxylamine and subsequent diastereoselective chain elongation by Grignard reaction and C-3 oxidation.[188]

Oximes of **1** have been used as a protecting group for the aldehyde moiety. Cleavage of the oxime occurred under mild conditions with IBX 1-hydroxy-1λ^3-1,2-benziodoxol-3(1*H*)-one 1-oxide in 91% yield.[189] On the other hand the oxime can be oxidised with H_2O_2 to nitroalkyl derivatives **153**, which have been used as precursors for several azasugars **154** (Scheme 53).[190]

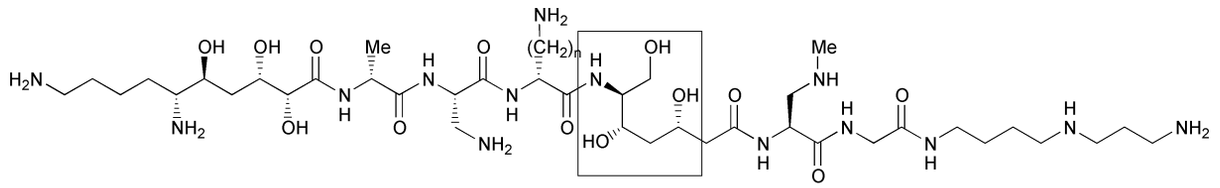


Scheme 53 Azasugars derived from oximes of **1**.

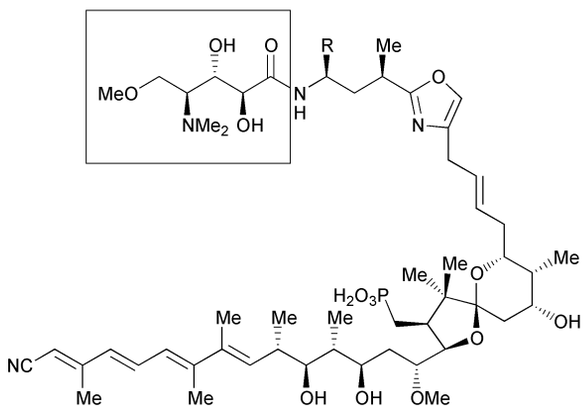
The natural amino acid L-quisqualic acid, as well as its D-isomer, was synthesised from **8** *via* an oxime. A 17% overall yield was reported starting from *N*-Boc-L-serine (Scheme 54).[191]



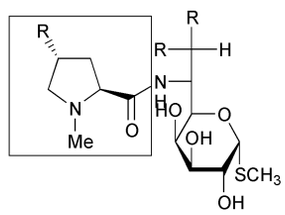
Scheme 54 Natural α-amino acid L-quisqualic acid derived from **8**.



galantin I



calyculin

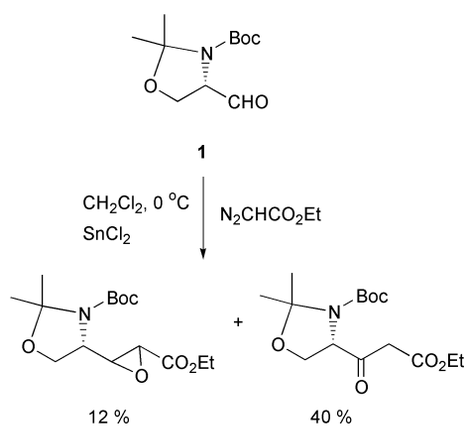


lincomycin

Fig. 13

A methodology for preparing a series of α-amino acids containing an isoxazol-5-yl moiety by cyclisation of the oxime of **1** has been reported.[192]

β-Keto-γ-amino acid derivatives have been synthesized by treating **1** with ethyl diazoacetate in the presence of catalytic amounts of $SnCl_2$ (Scheme 55).[193]



Scheme 55

Furthermore, the synthesis of *N*,*Se*-acetals of **1** as precursors for radical reactions has been reported.[194]

A 5-step synthesis of *N*-Boc-D-albizziine from Garner's aldehyde, *via* a protected derivative of (*R*)-2,3-diaminopropanol, has been reported. The overall yield was 30%.[195]

A summary of the stereoselectivities associated with nucleophilic additions to Garner's aldehyde is provided in Table 5.

Table 5 General conditions for diastereoselective addition of nucleophiles to **1**. In general *anti* addition occurs with very reactive organometallic reagents in nonpolar aprotic solvents while *syn* addition occurs in polar solvents with chelating additives

Reaction	*anti*	*syn*
Allylboration with isopropyl (*R*,*R*)-tartrate	+	
Allylboration with isopropyl (*S*,*S*)-tartrate		+
ZnR_2, rt	+	
ZnR_2, 0 °C, $ZnCl_2$, $Bu_2NCH_2CH_2OH$		+
Alkyl-Grignard reagents in Et_2O		+
Lithium acetylides, vinyllithium in THF	+	
Alkyl-Cu or -Mn reagents in THF at −78 °C		+
Silanes in CH_2Cl_2	+	
HCN in ^{i}PrOH or H_2O, rt	+	
Reformatsky reaction		+
Zn acetylides in Et_2O		+
Vinylzinc chloride in THF at −78 °C		+

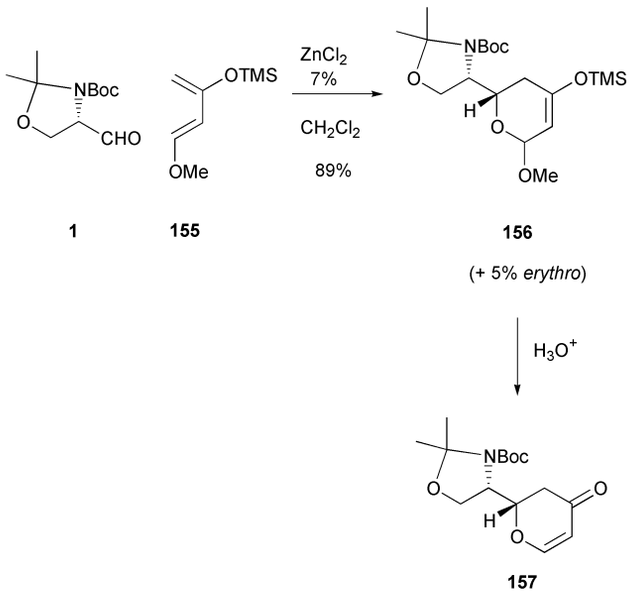
4 Cycloaddition reactions with Garner's aldehyde

4.1 Diels–Alder reactions

One of the first reactions carried out on **1** was a hetero Diels–Alder reaction.[1] The electron rich diene **155** was added to **1** in the presence of a catalytic amount of $ZnCl_2$, which gave the Diels–Alder adduct as a mixture of diastereomers.[196] However, with 5 or more mol% of $ZnCl_2$ present the *threo*-isomer **156** could be made to dominate by a factor of at least 16 : 1 over its *erythro*-counterpart. Adduct **156** was not isolated, but immediately treated with hydrochloric acid to give the pyrone **157**, which could be recrystallised and thereby be obtained in diastereomerically pure form and good yield. The related diene **158** also reacted with **1** with similar selectivity to yield the adduct **159** and the *threo*-pyrone **160**.[196] The diastereoselectivity was believed to be caused by chelation control as it was observed that *threo*-selectivity was lost in polar solvents (Scheme 56).

The *erythro*-isomer could be obtained by nucleophilic addition of the lithium enolate **161** to the aldehyde **1** (Fig. 14). After treatment with acid the *erythro*-pyrone **162** was obtained in 53% yield and with a diastereoselectivity (over **157**) of 7 : 1.[196] This procedure could not be used to obtain the *erythro*-isomer of **160**, because the lithium enolate of 3-acetoxy-4-methoxybut-3-en-2-one could not be formed. Recently, this problem was solved by employing a BF_3-catalysed Mukaiyama aldol reaction between **8** and **158**, which gave the *erythro*-pyrone **163** in 50% yield and with a diastereoselectivity of 49 : 1.[197]

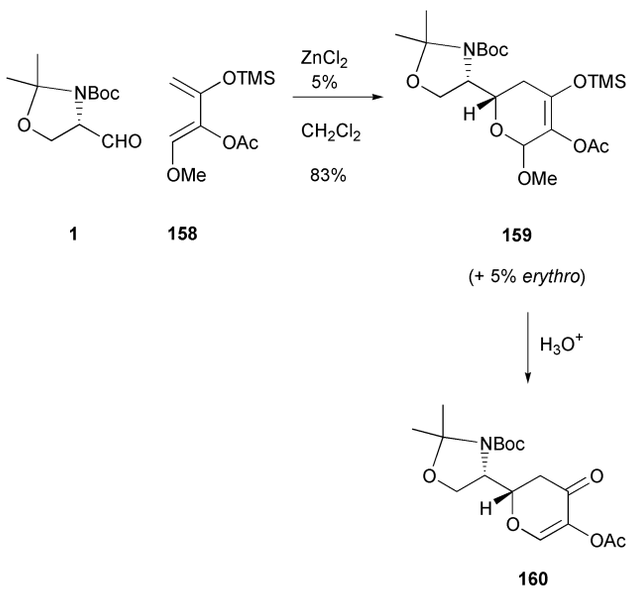
The Diels–Alder reaction between **1** and **155** to form pyrone **157** was subsequently used in the synthesis of methyl 2,4-dideoxy-4-*N*-ethyl-3-*O*-methyl-L-*erythro*-pentose, a constituent



1 155 156

(+ 5% *erythro*)

157

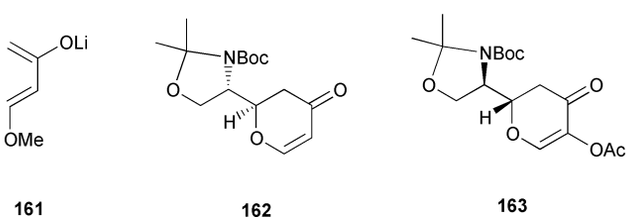


1 158 159

(+ 5% *erythro*)

160

Scheme 56

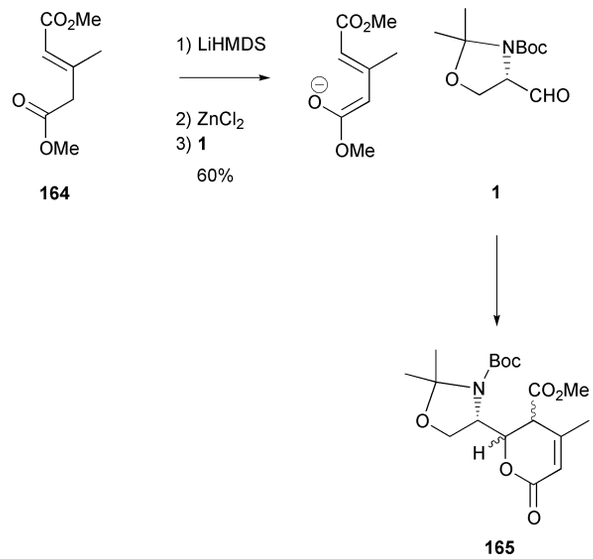


161 162 163

Fig. 14

of the antitumour antibiotic Calicheamycin γ^1.[198] It has also been found that $LiClO_4$ can be used as Lewis acid to catalyse the Diels–Alder reaction, but this gives slightly inferior yields and diastereoselectivities.[199]

A *de facto* [4 + 2] cycloaddition was observed when **1** was reacted with the zinc enolate of dimethyl 3-methylglutaconate (**164**). Thus, when compound **164** was treated with lithium bis(trimethylsilyl)amide (LiHMDS) and $ZnCl_2$ and the resulting enolate allowed to react with **1**, the lactone **165** was obtained in 60% yield, but without any diastereoselectivity (Scheme 57).[200,201]

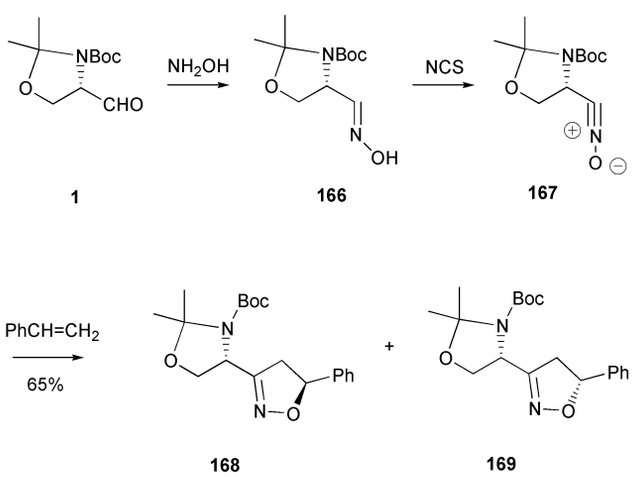


164 1 165

Scheme 57

4.2 Other cycloadditions

In a number of cases **1** has been converted to a 1,3-dipole, which has been used in cycloaddition reactions. Thus, reaction of **1** with hydroxylamine to form oxime **166** followed by treatment with *N*-chlorosuccinimide (NCS) and Et_3N gave a nitrile oxide **167** which was then added to three different alkenes to form the relevant cycloadducts (Scheme 58).[202] When styrene was used, a roughly 1 : 1 mixture of diastereomers **168** and **169** was obtained in 65% yield. With oct-1-ene or diethyl fumarate the corresponding cycloadducts were obtained in 36–70% yield and similar diastereomeric ratio.



1 166 167

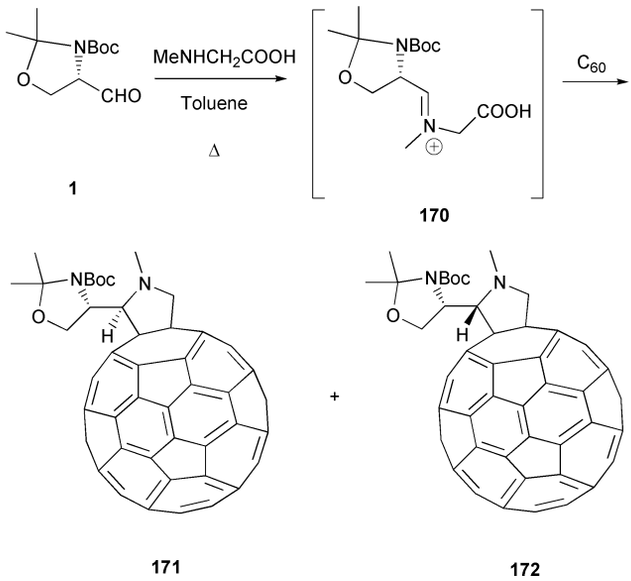
168 169

Scheme 58

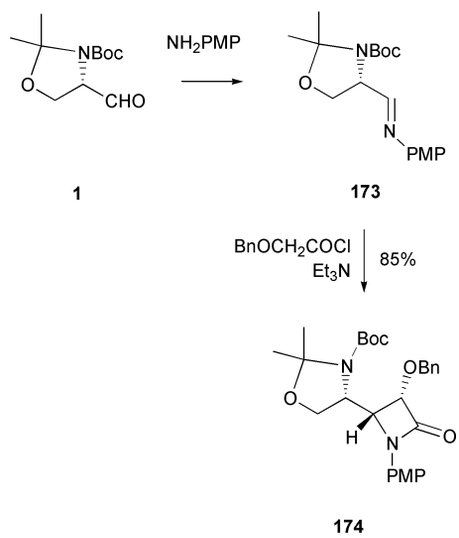
The *N*-Cbz analogue of the nitrite oxide **167** has also been engaged in cycloaddition reactions.[203] By adding this compound to a chiral acroleyl amide it was possible to obtain approximately 9 : 1 diastereoselectivity and isolate the main diastereomer which had a stereochemistry corresponding to **169** in 66% yield.

A different type of 1,3-dipolar cycloaddition was carried out by condensing **1** with *N*-methylaminoacetic acid in toluene and reacting the ensuing product **170** with C_{60}.[204] This gave a 22% combined yield of the two diastereomeric pyrrolidines, **171** and **172**, and in an 86 : 14 ratio (Scheme 59).

Imines of **1** have been used in [2 + 2] addition reactions to synthesise β-lactams.[205] Thus, **1** was reacted with *p*-methoxyphenylamine ($PMPNH_2$) to give the imine **173**, which then was subjected to Staudinger reaction with a ketene formed *in situ* from benzyloxyacetyl chloride and triethylamine (Scheme 60). The resulting β-lactam, **174**, was thereby obtained in



Scheme 59



Scheme 60

85% yield and as a single diastereomer. The reaction was carried out with a number of different ketenes and was generally diastereoselective.[205]

5 Summary and outlook

Garner's aldehyde has, in a very short time, proven an extremely useful chiral building block in organic synthesis. Its value is due to its simple structure that allows it to be used for many targets and because good methods exist for diastereoselective elaboration of aldehydes. It may be anticipated that similar simple chiral building blocks for alternative purposes are in demand and will developed in the future.

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