REVIEW

Protecting groups

Krzysztof Jarowicki and Philip Kocienski

Department of Chemistry, University of Leeds, Leeds, UK LS2 9JT

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Abbreviations for reactions, reagents and protecting groups: 4 Å MS, molecular sieves, 4 Å; 9-BBN, 9-borabicyclo[3.3.1]nonane; 4-QUI, 4-quinolylmethyl; Ac, acetyl; Acm, acetamidomethyl; All, allyl; Aloc, allyloxycarbonyl; BCB, *B*-bromocatecholborane; bipy, 2,2′-bipyridyl; Bn, benzyl; BOB, 4-benzyloxybutyryl; BOBCl, bis(2-oxooxazolidin-3-yl)phosphinic chloride; BOBOH, benzyloxybutyric acid; Boc, *tert*-butoxycarbonyl; Bz, benzoyl; CAN, ceric ammonium nitrate; CBB, catechol boron bromide; Cbz, benzyloxycarbonyl; CSA, camphorsulfonic acid; ClAc, chloroacetyl; ClAzb, 4-azido-3-chlorobenzyl; CNAP, 2-naphthylmethyl carbamate; CTFB, 4-trifluoromethylbenzyl carbamate; Cy, cyclohexyl; DABCO, 1,4-diazabicyclo[2.2.1]octane; dba, dibenzylideneacetone; DBU, 1,8-diazabicyclo[5.4.0]undec-7-ene; DCC, dicyclohexylcarbodiimide; DDQ, 2,3-dichloro-5,6-dicyano-1,4-benzoquinone; DEAD, diethyl azodicarboxylate; DIAD, diisopropyl azodicarboxylate; DIB, diacetoxyiodobenzene; DIBAL-H, diisobutylaluminium hydride; Dim, 2-(hydroxymethyl)-1,3-dithiane; DIPEA, diisopropylethylamine; DMAP, 4-dimethylaminopyridine; DME, 1,2-dimethoxyethane; DMF, dimethylformamide; DMPU, 1,3-dimethyl-3,4,5,6-tetrahydropyrimidin-2(1*H*)-one; DMSO, dimethyl sulfoxide; DMTr, 4,4′-dimethoxytrityl; DOPA, 3,4-dihydroxyphenylalanine; dppe, 1,2-bis(diphenylphosphino)ethane; EDC, 1-ethyl-3-(3-dimethylaminopropyl)-carbodiimide hydrochloride; Fmoc, fluoren-9-ylmethoxycarbonyl; Fmoc-OSu, *N*-(fluoren-9-ylmethoxycarbonyloxy)-succinimide; HATU, *N*-[(dimethylamino)(3*H*-1,2,3-triazolo[4,5-*b*]pyridin-3-yloxy)methylene]-*N*-methylmethanaminium hexafluorophosphate; HMPA, hexamethylphosphoramide; HOAt, 1-hydroxy-7-azabenzotriazole; HOBT, 1-hydroxybenzotriazole; MCPBA, *m*-chloroperbenzoic acid; MEM, 2-methoxyethoxymethyl; Mes, mesityl; MMTr, *p*-methoxyphenyldiphenylmethyl; MOM, methoxymethyl; MS, molecular sieves; Ms, methylsulfonyl; MsCl, methanesulfonyl chloride; NAP, 2-naphthylmethyl; NBS, *N*-bromosuccinimide; NCE, 2-[(1-naphthyl)carbamoyloxy]-ethyl; NIS, *N*-iodosuccinimide; NMP, 1-methylpyrrolidin-2- one; Ns, 2-nitrobenzenesulfonamide; PBB, *p*-bromobenzyl; PCB, *p*-chlorobenzyl; PCC, pyridinium chlorochromate; Ph, phenyl; Pht, phthalimido; PMB, *p*-methoxybenzyl; PMBCl, *p*-methoxybenzyl chloride; PMBOTr, *p*-methoxybenzyl trityl ether; PMBOH, *p*-methoxybenzyl alcohol; PMP, *p*-methoxyphenyl; PSE, phenylsulfonylethylidene; Psoc, (2-phenyl-2-trimethylsilyl)ethoxycarbonyl; PTMSE, 2-phenyl-2-(trimethylsilyl)ethyl; Pv, pivaloyl; Pyr, pyridine; RCM, ring closing metathesis; SEM, 2-(trimethylsilyl)-ethoxymethyl; Su, succinimide; TBAF, tetrabutylammonium fluoride; TBDPS, *tert*-butyldiphenylsilyl; TBS, *tert*-butyldimethylsilyl; TBTU, *O*-(benzotriazol-1-yl)-*N*,*N*,*N*′*N*′-tetramethyluronium tetrafluoroborate; TDS, tris(2,6-diphenylbenzyl)silyl; Teoc, 2-trimethylsilylethoxycarbonyl; TES, triethylsilyl; Tf, trifluoromethylsulfonyl; TFA, trifluoroacetic acid; TfOH, trifluoromethanesulfonic acid; THF, tetrahydrofuran; THP, tetrahydropyranyl; Thr, threonine; TIPDS, 1,1,3,3-tetraisopropyldisiloxane-1,3-diyl; TIPS, triisopropylsilyl; TMEDA, *N*,*N*,*N*′*N*′-tetramethylethylenediamine; TMS, trimethylsilyl; TMSBr, bromotrimethylsilane; TMSCl, chlorotrimethylsilane; TMSE, 2-(trimethylsilyl)ethyl; TMSI, iodotrimethylsilane; TMSOTf, trimethylsilyl trifluoromethanesulfonate; Tr, trityl, (triphenylmethyl); Troc, 2,2,2-trichloroethoxycarbonyl; Ts, *p*-tolylsulfonyl; TsOH, toluene-*p*-sulfonic acid.

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1 Introduction

Our seventh review on protecting group chemistry, like its six predecessors, surveys the annual progress in protecting groups since the publication of our book on the subject in 1994. Protecting group chemistry has become a cottage industry: oftentimes papers in the area are based on infinitesimal advantages using trivial substrates. We have ignored such papers. But we may have omitted some significant work as well—especially in specialist areas such as carbohydrate, nucleic acid and peptide chemistry—because our interests and expertise occupy a different orbit. Nevertheless, we did scan all of the chemical literature using a standard menu of key words in an attempt to be as comprehensive as possible. We apologise for any serious omissions.

The bulk of our review deals with modifications in reagents and conditions for the deprotection of the standard repertoire of protecting groups. The papers that appealed most to us for their novelty or potential concerned (a) the relay deprotection of substituted benzylic ethers in carbohydrates (Schemes 27 and 28); (b) the use of (2-phenyl-2-trimethylsilyl)ethyl esters and carbamates for peptide synthesis (Schemes 63 and 87); (c) the use of benzothiazol-2-yl-sulfonamides in peptide synthesis (Scheme 92) and (d) the

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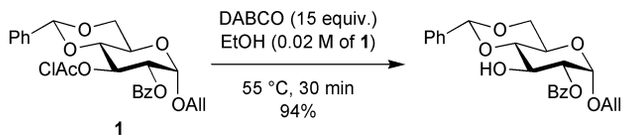
added orthogonality of naphthyl-modified protecting groups (Schemes 29, 50 and 81).

2 Hydroxy protecting groups

2.1 Esters

A large excess (15 equiv.) of 1,4-diazabicyclo[2.2.2]octane (DABCO) in ethanol gives complete and selective deprotection of chloroacetates in the presence of benzoates and acetates (Scheme 1).[1] The amount of DABCO can be reduced at the expense of a longer reaction time.



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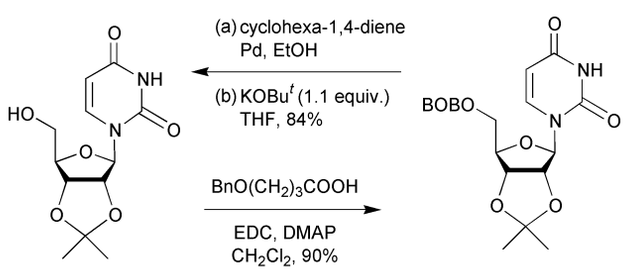
Scheme 1

A new relay deprotection of alcohols from their 4-benzyloxybutyryl (BOB) ester[2] has been reported. Deprotection of BOB esters consists of a two-step procedure. First the benzyl group is removed by hydrogenolysis (H_2, Pd/C) to give the corresponding hydroxy ester which is then treated with potassium *tert*-butoxide. The hydrogenation conditions are incompatible with double bonds and nitrile groups in which case catalytic transfer hydrogenolysis (cyclohexa-1,4-diene, Pd, EtOH) can be used. The BOB group can be introduced into a molecule by three different methods from commercial benzyloxybutyric acid (BOBOH): (a) by direct esterification of an alcohol using EDC and DMAP (Scheme 2), (b) by Mitsunobu reaction (DIAD, PPh_3) or (c) by nucleophilic opening of epoxides (Jacobsen reaction).

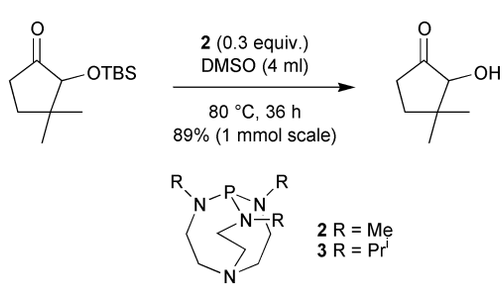


BOB = BnO(CH$_2$)$_3$CO
EDC = 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide

Scheme 2

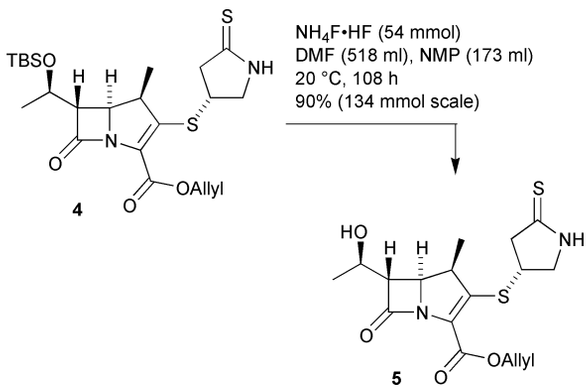
2.2 Silyl ethers

TBS ethers of primary, secondary and tertiary alcohols as well as phenols can be deprotected with a catalytic amount of proazaphosphatranes **2** and **3** by heating at 80 °C in DMSO (Scheme 3).[3] However, the reaction conditions do not tolerate 1,4-dienes, which rearrange to form the corresponding conjugated counterparts. Both catalysts are also much less effective (22–45% yield) for the desilylation of more hindered *tert*-butyldiphenylsilyl (TBDPS) ethers.



Scheme 3

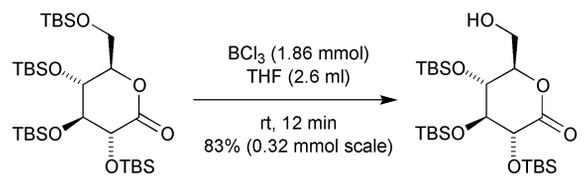
Deprotection of a sensitive TBS ether was required in a synthesis of the orally active 1-β-methylcarbapenem antibiotic TA-949 (Scheme 4).[4] A slow but efficient and mild method entailed treatment of TBS ether **4** with ammonium bifluoride in a mixture of DMF and NMP at room temperature. The desired product **5** was obtained in 90% yield.



4 5

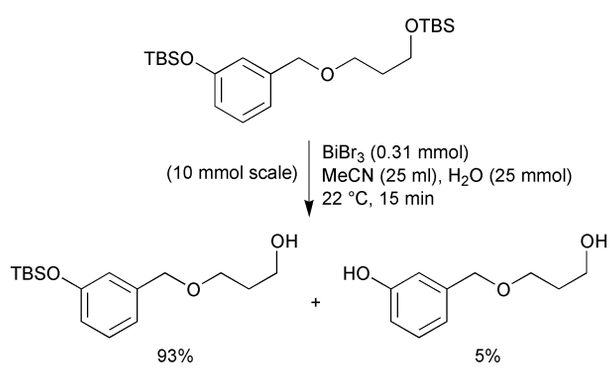
Scheme 4

Selective removal of primary TBS ethers in the presence of their secondary counterparts in carbohydrates can be achieved with boron trichloride in THF (Scheme 5).[5] The reaction conditions do not affect *O*-Bn glycosides but isopropylidene acetals appear to be incompatible.



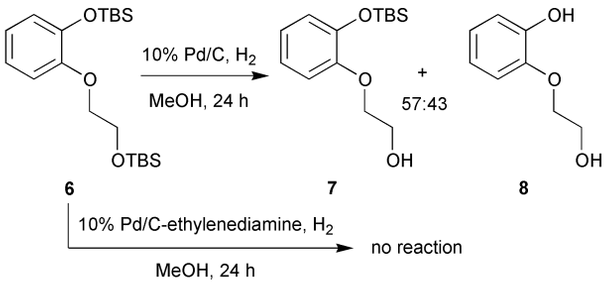
Scheme 5

Alkyl TBS ethers can be selectively cleaved in the presence of aryl ethers by brief exposure to a catalytic amount of bismuth bromide in wet acetonitrile at room temperature (Scheme 6).[6] Prolonged reaction times lead to cleavage of aryl TBS ethers as well. The hydrolysis may be catalysed by HBr generated *in situ* from the reaction of bismuth bromide with water. Bismuth bromide is a stable, yellow, commercially available solid that benefits from the low toxicity of Bi(III).



Scheme 6

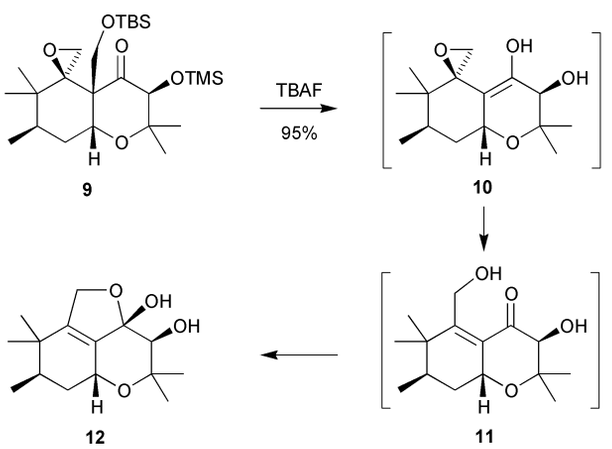
TBS ethers are labile under standard conditions used to perform catalytic hydrogenations with 10% Pd/C in methanol.[7] For example the bis-TBS ether **6** (Scheme 7) gives a mixture of **7** and **8** after 24 h. The reaction cannot be attributed to acid or base contaminants since the cleavage did not take place in the absence of hydrogen. However, the unwanted cleavage can be completely suppressed by using a carbon-supported Pd–ethylenediamine complex as the catalyst.



Scheme 7

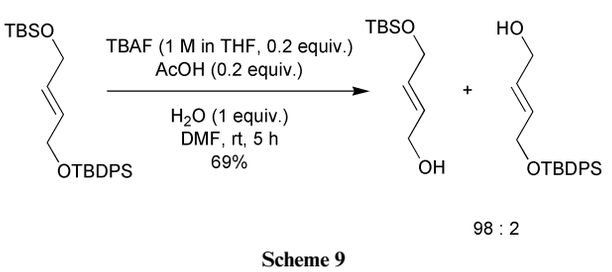
Dommisse and co-workers published a general method for the selective cleavage of phenolic TBS ethers *ortho* to a carbonyl group by sonication of a 0.1 M solution of the substrate in 1 : 1 (v/v) CH_3OH–CCl_4 at 50–55 °C.[8] Other phenolic *tert*-butyldimethylsilyl ethers are unaffected.

A synthesis of the reduced furanochromane core (**12**, Scheme 8) of the diterpene phomactin used a TBS-protected hydroxymethyl group to block the formation of an alkene at the ring junction in the steps leading up to **9**.[9] In the final step of the synthesis, treatment of **9** with TBAF led to removal of both silyl protecting groups and a retro-aldol reaction to give intermediate **10**, whereupon epoxide opening and cyclisation afforded the desired product **12** in 95% yield.



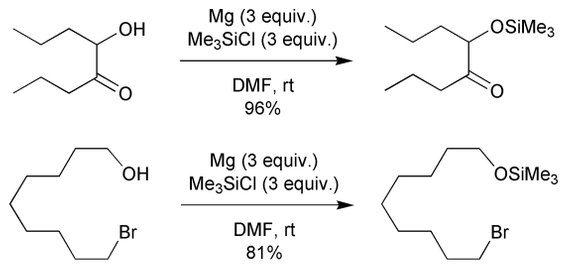
Scheme 8

tert-Butyldiphenylsilyl (TBDPS) ethers can be cleaved in the presence of *tert*-butyldimethylsilyl (TBS) ethers with excellent selectivity using a combination of a catalytic amount of TBAF, acetic acid and 1 equivalent of water in either THF or DMF (Scheme 9).[10]



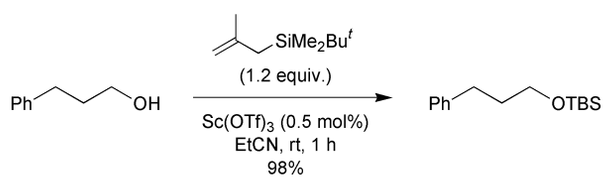
Scheme 9

An unusual and intriguing new method for forming trimethylsilyl (TMS) ethers of primary, secondary and tertiary alcohols has been described.[11] The method is simple: the alcohol is added dropwise to a solution of chlorotrimethylsilane (3 equiv.) in DMF containing Mg (3 equiv.) with water-bath cooling. After addition is complete, the mixture is stirred overnight at room temperature. The two examples shown in Scheme 10 show that carbonyl groups and bromoalkanes are inert under the reaction conditions. Chlorotriethylsilane and chlorodimethylphenylsilane can also be used but no mention is made of the use of more hindered halosilanes.



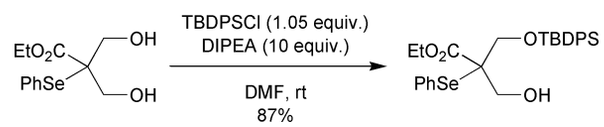
Scheme 10

Primary, secondary and tertiary alcohols as well as phenols react with various methylallylsilanes at room temperature in the presence of 0.5–5 mol% of $Sc(OTf)_3$ to give the corresponding silyl ethers in good yield (Scheme 11).[12] By using microencapsulated $Sc(OTf)_3$, the yield of silyl ether is improved, the workup is simplified (simple filtration) and the catalyst is easily recovered and reused. TBS, TES, TIPS and TBDPS ethers were prepared in this way (83–98% yield). A limited study on simple substrates indicates that ester, ether, acetal and ketone groups are compatible.



Scheme 11

Selective protection of only one hydroxy group of a 1, *n*-diol as its mono-TBDPS ether can be easily accomplished using a biphasic mixture of DIPEA (10 equiv.) and DMF as solvent (Scheme 12).[13] Under these conditions the TBDPSCl and the diol are located in the bottom DMF layer together with a constant concentration of DIPEA (16%). The reaction works equally well with 1,5-, 1,7- and 1,9-diols.

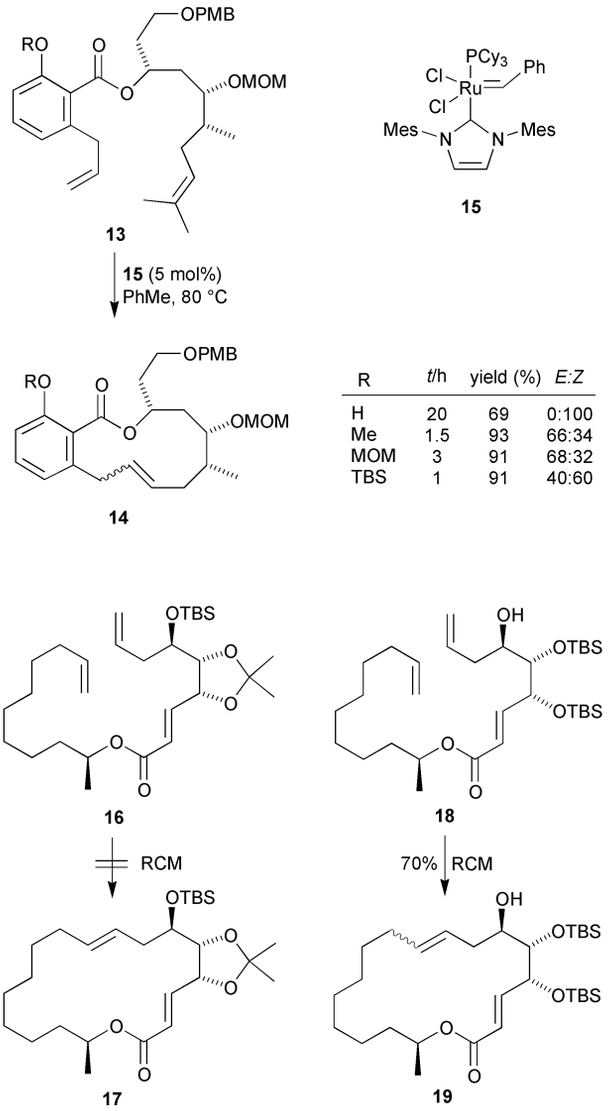


Scheme 12

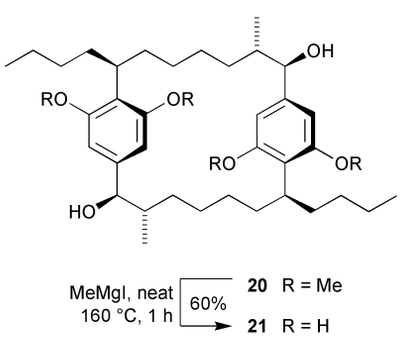
Two recent natural product syntheses unveiled effects of remote protecting groups on the course of ring closing metathesis (RCM) reactions leading to macrocycles. In a synthesis of salicylihalamide (Scheme 13), Fürstner and co-workers[14] noted that the RCM reaction of **13** to **14** (R = H) using catalyst **15** gave a 69% yield with the nascent alkene being exclusively in the (*Z*)-geometry. However, protection of the remote phenolic hydroxylic function as its Me, MOM or TBS ether gave much better yields and shorter reaction times but the stereoselectivity diminished. Similarly, a synthesis of aspicillin by Banwell and McRae[15] nearly foundered when the RCM reaction on the dioxolane derivative **16** failed to occur. Reasoning that the problem was due to a conformational effect, Banwell and McRae exchanged the rigid dioxolane ring for two TBS ethers in **18** whereupon the desired RCM reaction gave **19** in 70% yield.

2.3 Alkyl ethers

The last step in a synthesis of cylindrocyclophane A (**21**) by Hoye and co-workers required the cleavage of the four phenolic methyl groups in **20** (Scheme 14).[16] Fusion with excess methylmagnesium iodide[17] at 160 °C under vacuum afforded **21** in



Scheme 13

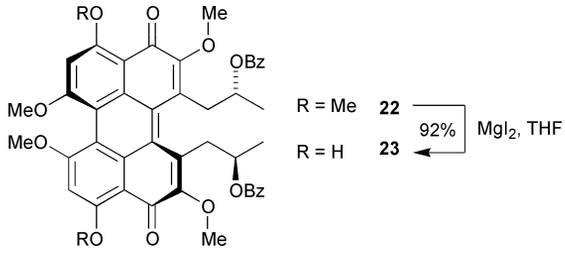


Scheme 14

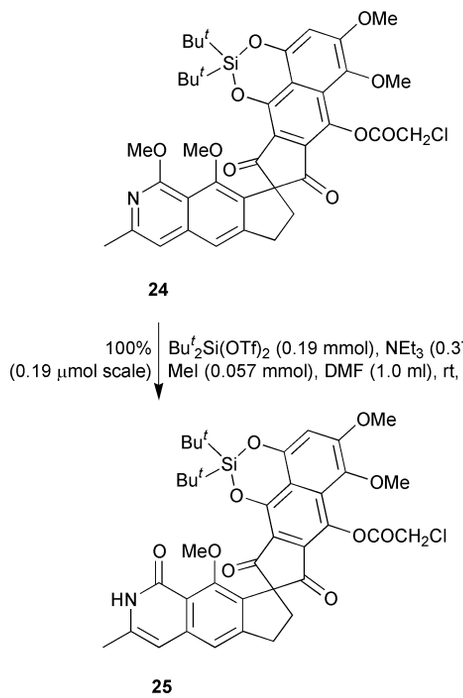
60% yield. No other by-products were observed in which both secondary benzylic alcohols survived unscathed. The same quadruple demethylation was accomplished in 60% yield by the Smith group using benzenethiol and potassium carbonate at 215 °C.[18]

The calphostins are potent inhibitors of protein kinase C. Merlic and co-workers[19] recently accomplished a short synthesis of calphostin A (**23**, Scheme 15) in which the final step entailed regioselective cleavage of the two phenolic methyl ethers in **22** using magnesium iodide in THF.[20]

In the closing stages of a synthesis of the antitumour agent fredericamycin, *O*-demethylation of the F-ring methyl ether **24** (Scheme 16) was required.[21] The task could be accomplished



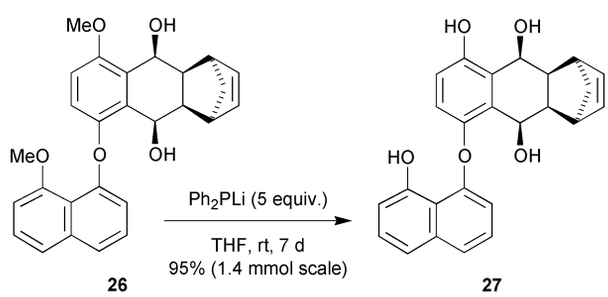
Scheme 15



Scheme 16

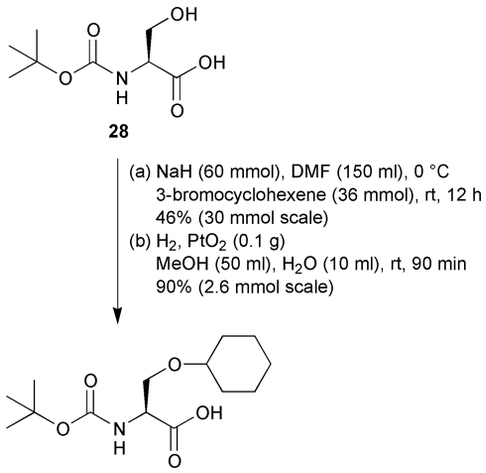
with iodotrimethylsilane but the low yield of **25** (40%) was a consequence of the lability of the bis(*tert*-butyl)silylene and chloroacetyl groups. However, by using the unusual combination of $Bu^t_2Si(OTf)_2$, NEt_3 and MeI, the desired demethylation could be accomplished in quantitative yield.

Demethylation of the two methyl ether groups in **26** (Scheme 17) was difficult because the benzylic alcohols were labile to both acid and base.[22] Protracted treatment of **26** with excess lithium diphenylphosphide at room temperature eventually gave the bis-demethylated compound **27** in 95% yield.



Scheme 17

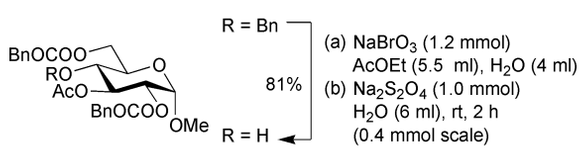
Cyclohexyl (Cy) ethers have been recommended for the protection of serine and threonine hydroxy groups.[23] The Cy group is introduced in a two-step procedure (Scheme 18). First, the protected amino acid (*e.g.* **28**) is treated with NaH followed by reaction with cyclohexen-3-yl bromide. In the second step, the double bond in the cyclohexene ring is hydrogenated in the presence of PtO_2. The *O*-Cy protecting group is stable to various acidic and basic reagents including deprotection



Scheme 18

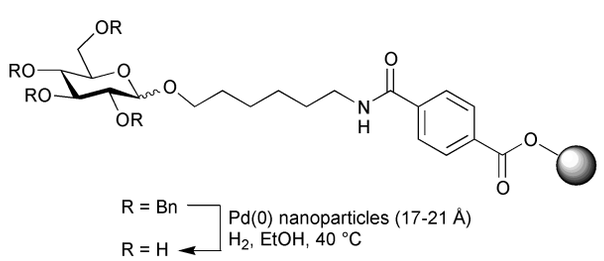
conditions for Boc, Cbz and Fmoc groups. On the other hand it is removed quantitatively with a 1 M solution of trifluoromethanesulfonic acid–thioanisole in trifluoroacetic acid. These results indicate that the Cy group is suitable for peptide synthesis based on Boc-chemistry and can also be used in combination with either N^{α}-Fmoc- or N^{α}-Cbz-protection.

Benzyl ethers and benzylidene acetals can be deprotected selectively in the presence of benzyloxycarbonyl groups with a combination of $NaBrO_3$ and $Na_2S_2O_4$ (Scheme 19).[24]



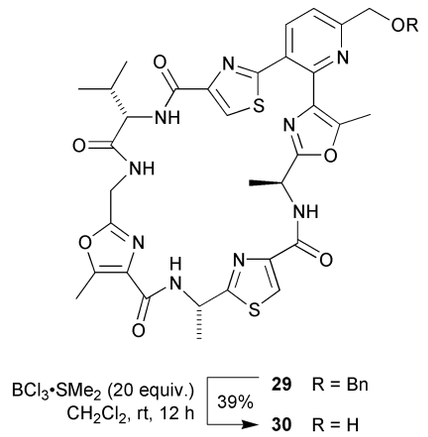
Scheme 19

Catalytic hydrogenolysis of *O*-benzyl protecting groups on solid phase is usually precluded by mass-transport problems. Although palladium acetate has been used in the hydrogenolysis of benzyl groups in peptide synthesis, the Pd(0) particles formed *in situ* immediately precipitate on the Merrifield-type resin. Recently Wong and co-workers[25] showed that monodispersed Pd nanoparticles with a mean diameter of 17 to 21 Å are effective catalysts for the hydrogenolysis of benzyl ethers on carbohydrates attached to Tentagel and PEGA supports. The catalyst is generated by refluxing H_2PdCl_4 in EtOH in the presence of poly(*N*-vinylpyrrolidin-2-one) to stabilise the nanoparticles and prevent aggregation The reaction is illustrated in Scheme 20.



Scheme 20

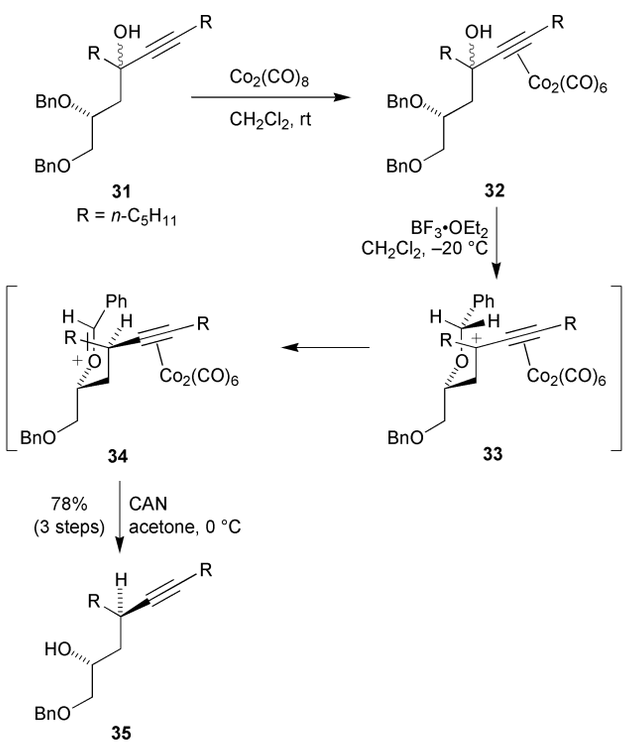
In the closing stages of a synthesis of the antibiotic promothiocin A, cleavage of the benzyl ether in the macrocycle **29** (Scheme 21) to free the hydroxy group in **30** by catalytic hydrogenolysis under a variety of conditions failed.[26] Under forcing conditions (higher temperature or pressure), the heterocyclic core was destroyed. The requisite cleavage was eventually



Scheme 21

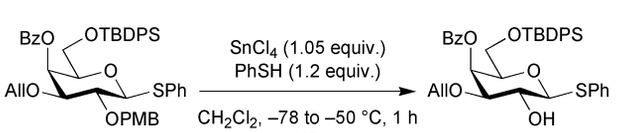
effected using a large excess of boron trichloride–dimethylsulfane complex to give **30** in a modest 39% yield.

A benzyl ether can act as an intramolecular hydride donor to a cobalt-stabilised propargylic cation.[27] In the example shown in Scheme 22, virtually complete 1,3-chirality transfer occurred to give the alcohol **35** in 78% overall yield. Note that the remote benzyl ether did not participate in the reaction in accord with a six-centre, chair transition state leading from carbocation **33** to oxonium ion intermediate **34**.



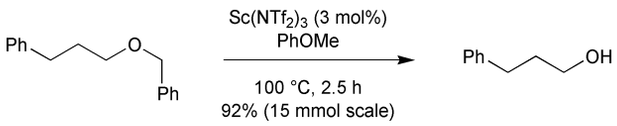
Scheme 22

Selective deprotection of carbohydrate PMB ethers can be accomplished with $SnCl_4$ but the reaction fails in the case of thioglycosides.[28] However, a combination of $SnCl_4$ and thiophenol cleaves PMB ethers in thioglycosides as well (Scheme 23).[29] The method could be useful in substrates in which PMB cleavage using the typical oxidative conditions is precluded.



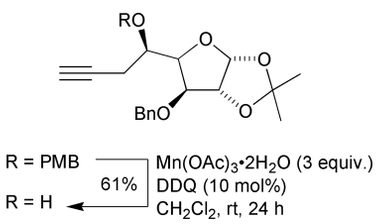
Scheme 23

A catalytic amount of scandium(III) tristriflylmethide [$Sc(CTf_3)_3$], tritriflylmethane ($HCTf_3$) or scandium(III) triflimide [$Sc(NTf_2)_3$] in an excess of anisole deprotects benzyl esters, benzyl ethers and *N*-*p*-methoxybenzylamides[30] (Scheme 24). The reaction works well with primary benzyl ethers; however, in the case of secondary alcohols, the yields are lower (43–49%). This setback can be overcome by using more reactive *p*-methoxybenzyl (PMB) ethers.



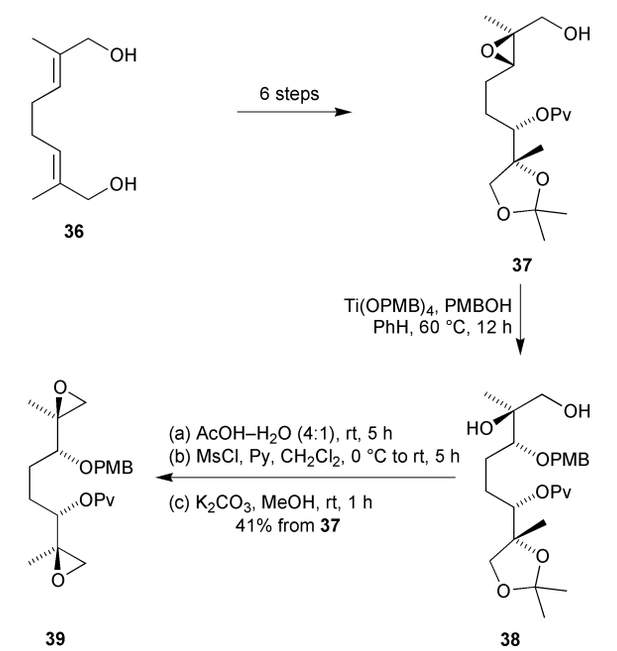
Scheme 24

$Mn(OAc)_3 \cdot 2H_2O$ (3 equiv.) in combination with a catalytic amount of DDQ has been used for the deprotection of PMB ethers (Scheme 25).[31] TBS ethers, THP acetals, benzyl esters as well as homoallylic and propargylic systems survive the reaction conditions.



Scheme 25

A synthesis of (+)-eurylene was based on a two-directional elaboration of the symmetrical bis-allylic alcohol **36** (Scheme 26).[32] Six steps, including two Sharpless asymmetric epoxidations, converted **36** to the oxirane **37**. Regioselective ring opening of the oxirane ring[33] occurred on treatment with titanium tetrakis(*p*-methoxybenzyloxide) and *p*-methoxybenzyl alcohol in benzene to give the PMB ether **38** and its regioisomeric 1,3-diol derivative in a ratio of 3 : 1 respectively. A 3-step sequence of standard transformations performed on **38** gave the desymmetrised bis-oxirane derivative **39** in 41% overall yield from **37**.



Scheme 26

Two papers have appeared that exploit the enhanced stability of benzyl ether type protecting groups bearing electron-withdrawing substituents. Sakai and co-workers[34] encountered problems with the easy autoxidation of the benzyl ether of β-hydroxytetradecanoic acid methyl ester but the corresponding *p*-trifluoromethyl-substituted benzyl ether was stable. Mehta and Whitfield[35] used the enhanced acid-stability of 3-iodo-4-methoxybenzyl ethers over their simple PMB counterparts in a trisaccharide synthesis.

Relay deprotection is the process by which a stable protecting group is first chemically converted to a labile relative which is then cleaved in a separate step. An obvious objection to the strategy is that it lengthens the protection process by a third step (protection–activation–deprotection). Nevertheless, the added measure of orthogonality relay deprotection affords can compensate for the extra step. An example of relay deprotection has recently been devised in which a fairly inert halobenzyl ether is first converted to an aminobenzyl derivative by Pd-catalysed amination.[36] The subsequent deprotection is then achieved with Lewis or protic acids. Scheme 27 illustrates the potential of the method. The *p*-iodobenzyl, *p*-bromobenzyl and finally the *p*-chlorobenzyl ether protecting groups were sequentially deprotected to reveal their hydroxy tenants in a controlled fashion.

4-Azido-3-chlorobenzyl (ClAzb) groups afforded temporary protection of hydroxy groups in the solid-phase synthesis of oligosaccharides.[37] The protection was achieved by the reaction of a sugar (*e.g.* **40**, Scheme 28) with sodium hydride followed by 4-azido-3-chlorobenzyl bromide (ClAzb-Br). The ClAzb ethers were stable during glycosylation reactions but they were removed by conversion of the azide group to the corresponding iminophosphorane followed by DDQ oxidation. The released hydroxy group in **43** was then subjected to further glycosylation and the procedure was repeated to afford the corresponding tetrasaccharide unit.

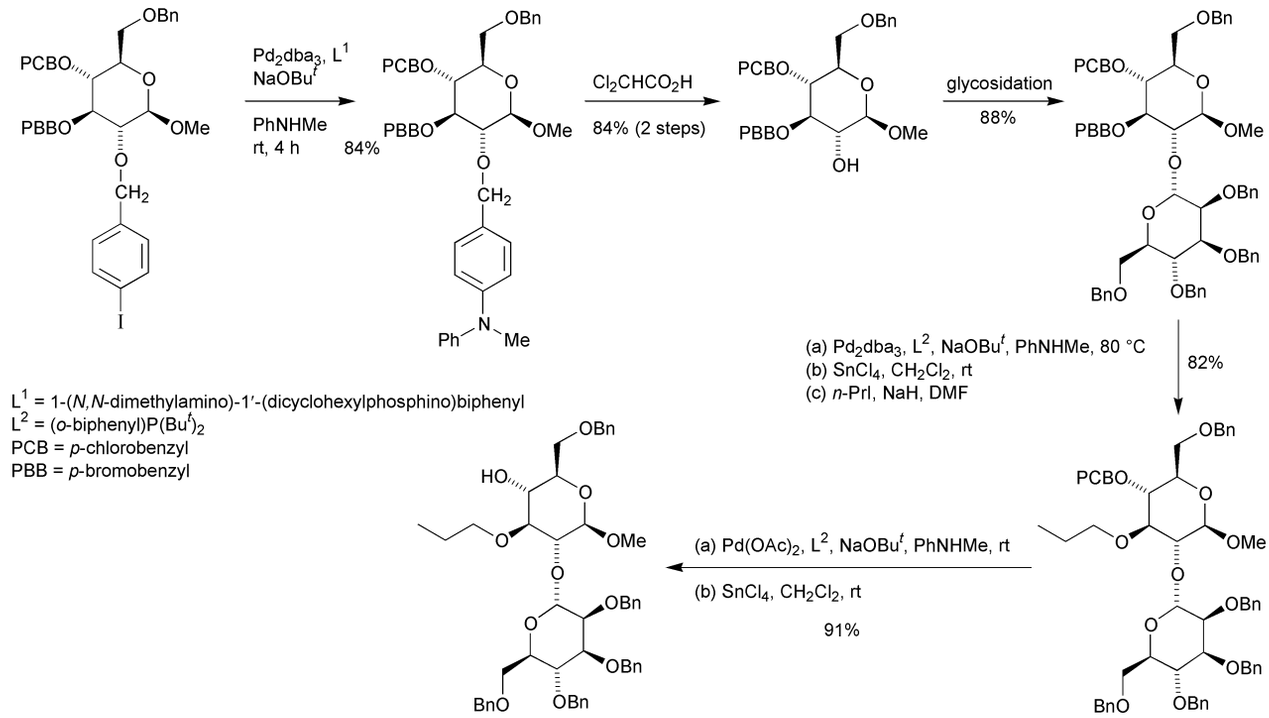
The 2-naphthylmethyl ether group[38,39] was used to protect a single primary hydroxy group in syntheses of tetra-, penta- and hexa-saccharide chains from respiratory mucins.[40] The requisite building block **45** (Scheme 29) was prepared by *O*-alkylation of the cyclic stannoxane prepared from triol **44** using 2-naphthylmethyl bromide. Deprotection was efficiently achieved under mild conditions using DDQ as exemplified by the conversion of **46** to **47**.

Triphenylmethyl (trityl, Tr) ethers can be selectively removed in the presence of other protecting groups (TES, TBS, Bn, PMB, Pv) with 0.6 equiv. of boron trichloride in dichloromethane followed by quenching with methanol[41] (Scheme 30). No epimerisation is observed under the reaction conditions.

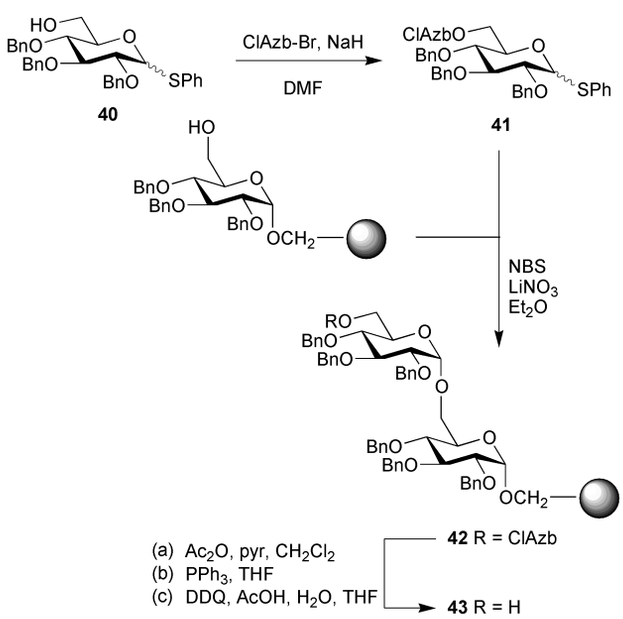
Catalytic amounts of CAN adsorbed onto silica gel suspended in CH_2Cl_2 cleave *O*- and *N*-Tr, MMTr and DMTr groups from nucleosides and nucleotides rapidly and efficiently.[42] Some acid-sensitive protecting groups such as (dimethylamino)methylene groups, isopropylidene acetals, TBS ethers and TIPS ethers survive indicating that the reaction is not an acid-catalysed process. The same catalyst deprotects primary TBS and TIPS ethers in a mixture of propan-2-ol and CCl_4 (1 : 1). The silica gel supported reagent accomplished the deprotections faster and more efficiently than CAN alone in solution. Scheme 31 illustrates the reaction and gives an electron transfer mechanism which accounts for its catalytic nature.

Alcohols can be protected as triphenylmethyl (trityl, Tr) ethers by treatment with *p*-methoxybenzyl trityl ether (PMBOTr) and DDQ under virtually neutral conditions (Scheme 32).[43] PMBOTr is prepared in one step from *p*-methoxybenzyl alcohol and trityl chloride in the presence of triethylamine.

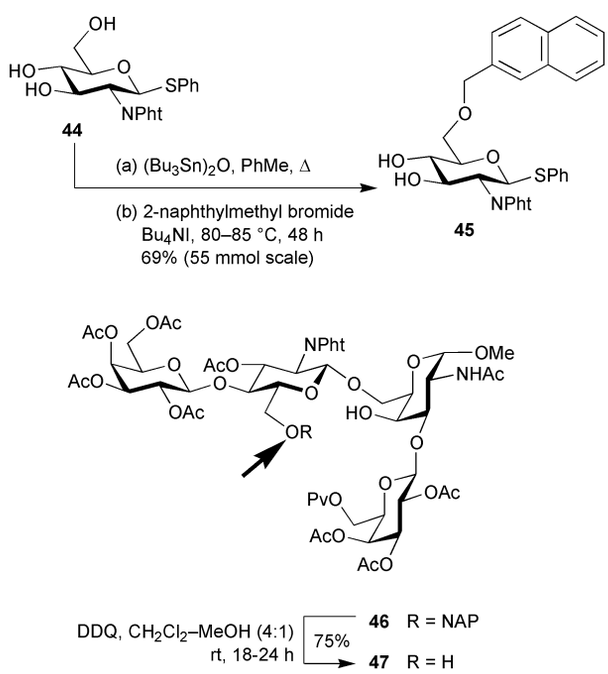
Deprotection of allyl ethers by initial transformation into prop-1-enyl ethers with base or transition metals has been known for some time.[44,45] A novel reagent—dichlorotris-(triphenylphosphine)ruthenium(II) [$(Ph_3P)_3RuCl_2$]—has been reported[46] to isomerise the double bond in *O*-allyl glycosides. The final deprotection is then achieved by treatment of the resulting prop-1-enyl ether with $HgCl_2$–HgO.



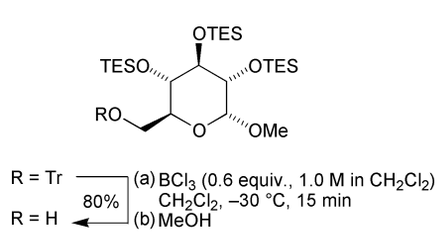
Scheme 27



Scheme 28



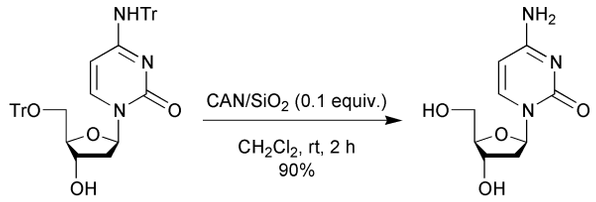
Scheme 29

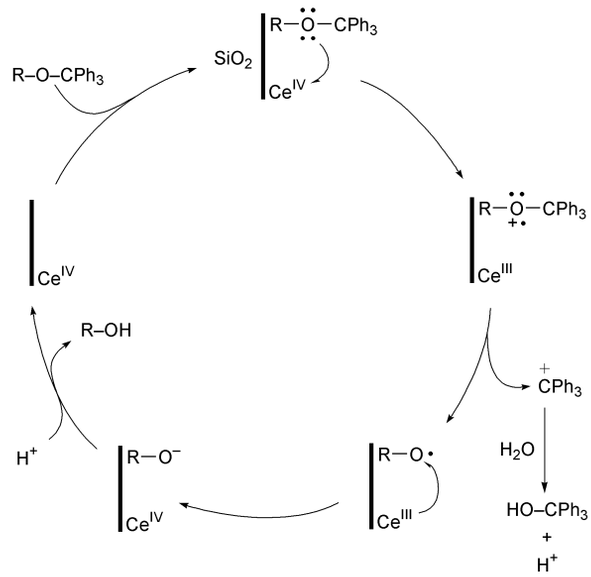


Scheme 30

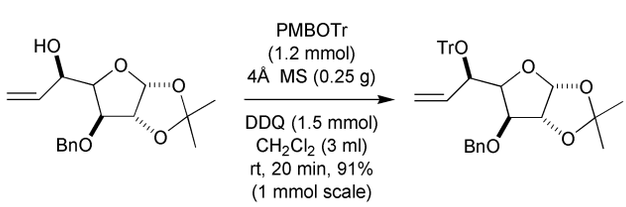
Allyl ethers can be cleaved on solid phase using 5 equiv. of toluene-*p*-sulfonic acid and a catalytic amount of $Pd(PPh_3)_4$.[47] The procedure is an adaptation of the liquid phase method described by Nagakura and co-workers.[48] The sensitive thioglycoside anchor in solid-phase bound substrates is not affected under the reaction conditions (Scheme 33), nor are esters, carbamates, amides, benzyl ethers, aryl chlorides and the TBDPS group. Allyl esters as well as Aloc groups are also removed under the conditions.

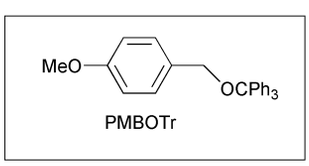
The final step in a synthesis of the antibiotic cristatic acid was frustrated by difficulty with the removal of the two SEM groups protecting the phenolic hydroxy groups in **48** (Scheme 34).[49] Attempted deprotection of **48** with TBAF in THF led to cleavage of the SEM group *para* to the carboxy but the *ortho* group remained intact even under forcing conditions.[50] A similar fate befell the use of TBAF in DMPU[51] whereas P_2I_4 in CH_2Cl_2 decomposed the starting material.[52] Good results were finally obtained using TBAF in HMPA at 50 °C. Under these conditions, cristatic acid was isolated as its methyl ester **49** in 60% yield.



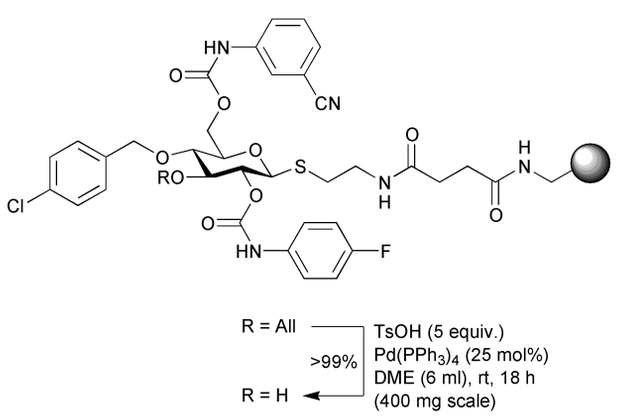


Scheme 31



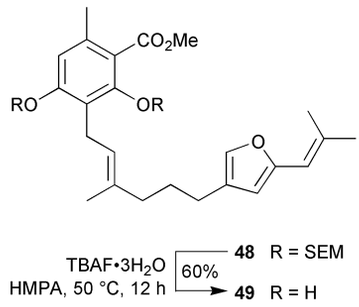


Scheme 32



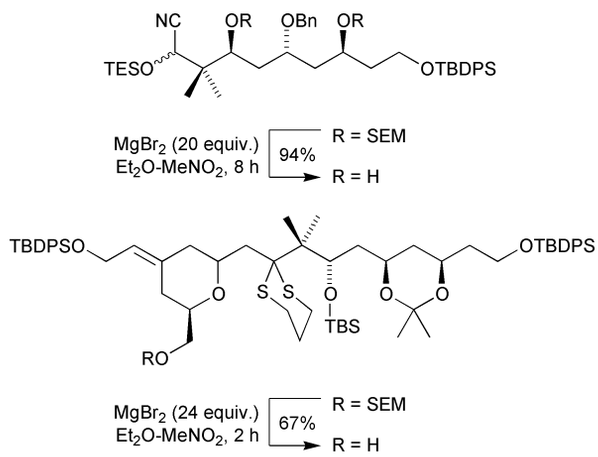
Scheme 33

A new mild and selective procedure for the deprotection of SEM ethers entails the use of excess (6–40 equiv.) magnesium bromide in Et_2O containing nitromethane (2 equiv. per equiv.



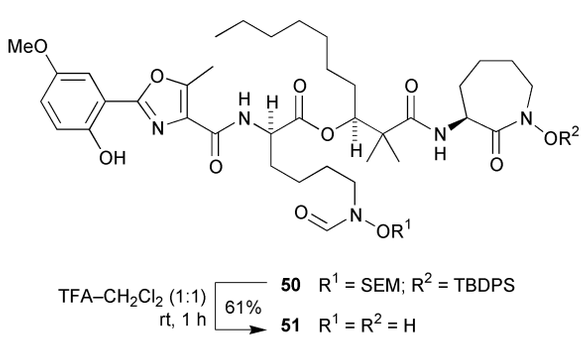
Scheme 34

of magnesium bromide) at room temperature.[53] As can be seen from the two examples shown in Scheme 35, TES, TBS, TBDPS and Bn ethers survive as do isopropylidene and dithio acetals.



Scheme 35

Amamistatin A (**51**) is an actinomycete metabolite which displays antiproliferative effects against a range of human cancer cell lines. In the final step of a synthesis of **51**, the TBDPS and SEM groups used to protect the two *N*-hydroxyamides in **50** were deprotected with TFA (Scheme 36).[54]

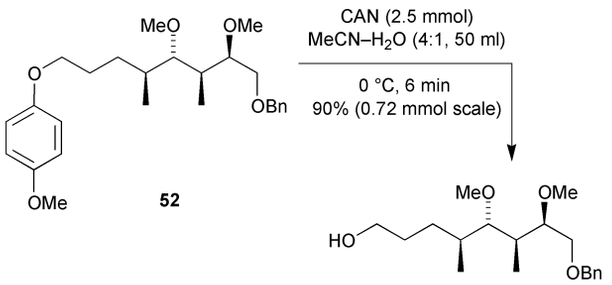


Scheme 36

During a recent synthesis of stigmastellin A, Enders and co-workers[55] accomplished the selective cleavage of the terminal *p*-methoxyphenyl ether in **52** (Scheme 37) in the presence of a terminal benzyl ether using CAN.[56]

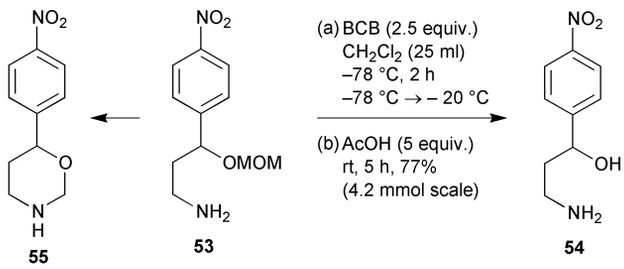
2.4 Alkoxyalkyl ethers

Hu and co-workers[57] tried to deprotect the MOM ether **53** to get the amino alcohol **54**. The typical reagents such as *B*-bromocatecholborane (BCB) in CH_2Cl_2, HCl in MeOH, $(CH_3)_3SiBr$ in CH_2Cl_2, PhSH and $BF_3{\cdot}OEt_2$ in CH_2Cl_2 and $TsOH{\cdot}2H_2O$ in toluene, gave either the corresponding formyl



Scheme 37

acetal **55** or a complex mixture of products. The task was finally achieved by treating **53** first with BCB followed by acetic acid (Scheme 38).



BCB = *B*-bromocatecholborane

Scheme 38

The MOM group played a key strategic role in a synthesis of CP-263,114, a potent squalene synthase and Ras farnesyltransferase inhibitor.[58] One of the crucial steps entailed TMSOTf-promoted ionisation of the enol carbamate **56** (Scheme 39) to liberate silylketene acetal **57** and a methoxycarbonylium ion fragment whose recombination generated the malonate derivative **58**. Both carbonyls of the nascent malonate, as their *O*-silyldioxonium ion variants, then triggered fragmentation of the two MOM groups to accomplish deprotection and bicyclisation.

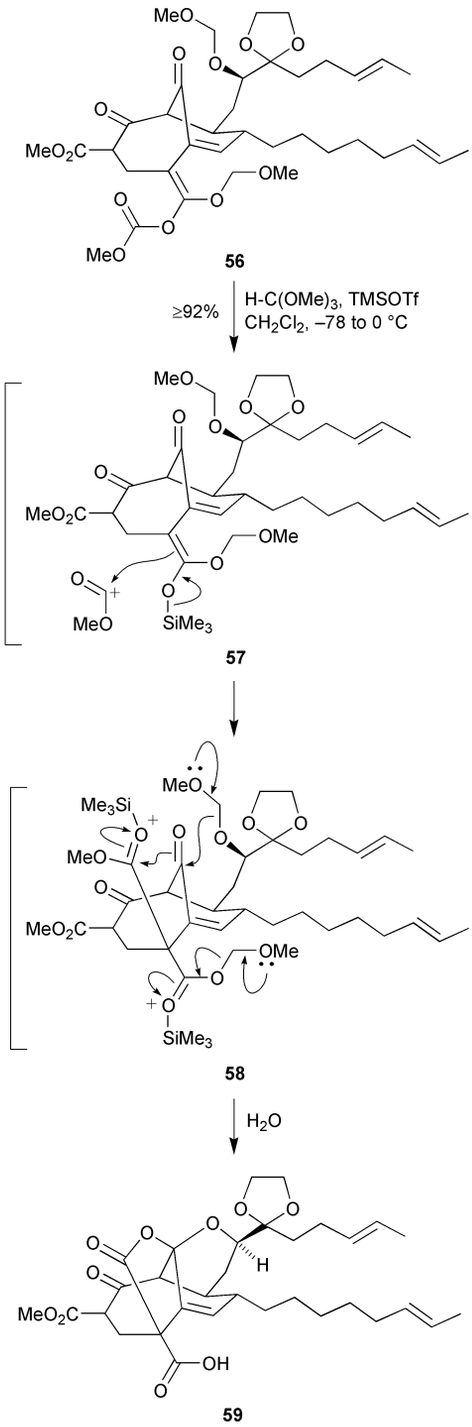
Tetrahydrofuranyl ethers are more acid-labile than their ubiquitous tetrahydropyranyl counterparts and they are more difficult to form. A new radical-based method for the synthesis of tetrahydrofuranyl ethers of primary and secondary alcohols entails reaction with $BrCCl_3$ in tetrahydrofuran at 60 °C in the presence of 2,4,6-collidine (Scheme 40).[59] Tertiary and allylic alcohols are poor substrates. The yields are generally modest (≤71%) and the method is, of course, limited to substrates devoid of unsaturation.

21-Hydroxy-12,13-desoxyepothilone B (**60**, Scheme 41) is a new synthetic analogue of the epothilones which inhibits tumour growth at concentrations well below the levels required by paclitaxel.[60] The additional hydroxy group at C21, which confers greater water solubility, and the C7 hydroxy group were both protected as their Troc derivatives. In the penultimate step, both Troc groups were removed with an excess of samarium(II) iodide and a catalytic amount of NiI_2.[61] Alternatively, the same task could be accomplished with zinc.

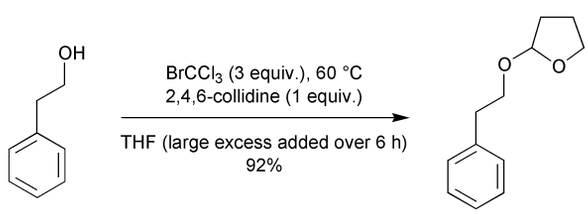
Alkoxycarbonyl groups are stable protectors of the amino function in amino acid chemistry but they are seldom used to protect hydroxy groups in carbohydrates. An Italian group[62] has disclosed that alkoxycarbonyl groups can be easily installed on carbohydrates by reaction with the appropriate chloroformate in the presence of TMEDA at low temperature (Scheme 42). The method has been used to append Cbz, Troc, Aloc and Fmoc groups.

3 Thiol protecting groups

A German group[63] showed that 2-methoxyisobutyryl thioesters are compatible with the conditions of the Suzuki coupling but



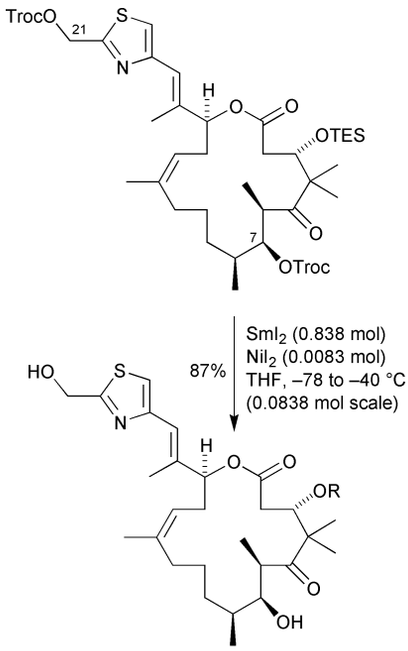
Scheme 39



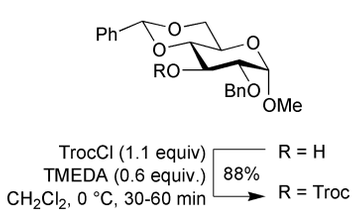
Scheme 40

they could be easily removed by basic hydrolysis (Scheme 43). Pivaloyl ester gave worse results.

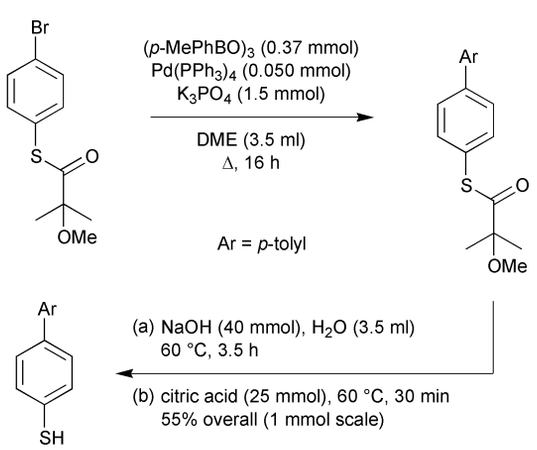
Aspirochlorine (**64**, Scheme 44) is an *Aspergillus* metabolite that is a selective and potent inhibitor of fungal protein synthesis. A synthesis of the aspirochlorine analogue **63**[64] began with the known[65,66] epidithiodiketopiperazine **61** in which the two sulfur atoms are protected as a PMP-*S,S*-acetal. In the



Scheme 41



Scheme 42

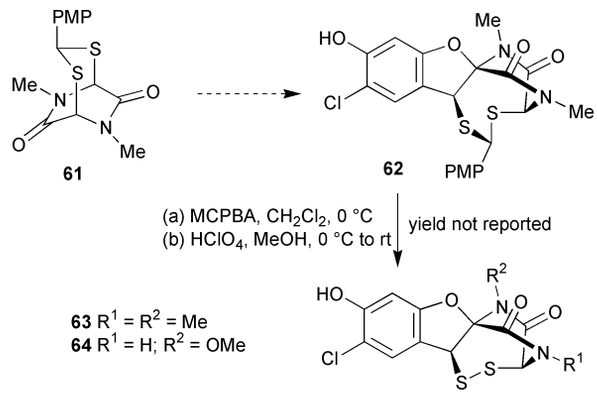


Scheme 43

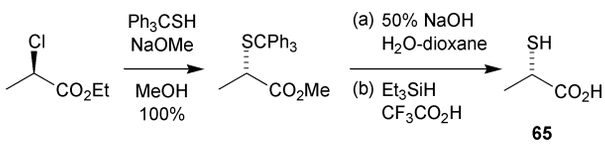
closing stages of the synthesis, the *S,S*-acetal was first oxidised to a monosulfoxide with MCPBA and thence treatment with perchloric acid generated the disulfide bridge in **63**.

Triphenylmethanethiol (mp 104–106 °C) is a stable, comparatively odourless reagent for introducing thiols into organic substrates *via* an SN_2 reaction as illustrated in Scheme 45 by the preparation of (*S*)-thiolactic acid (**65**).[67] Triphenylmethanethiol is commercially available (Aldrich) or it can be prepared in quantitative yield by the reaction of triphenylmethanol with hydrogen sulfide under acid conditions.[68]

Boger and Ichikawa reported a total synthesis of the antitumour agent thiocoraline (**72**, Scheme 46) and its relative BE-22179.[69] Thiocoraline inhibits DNA polymerase and unwinds



Scheme 44



Scheme 45

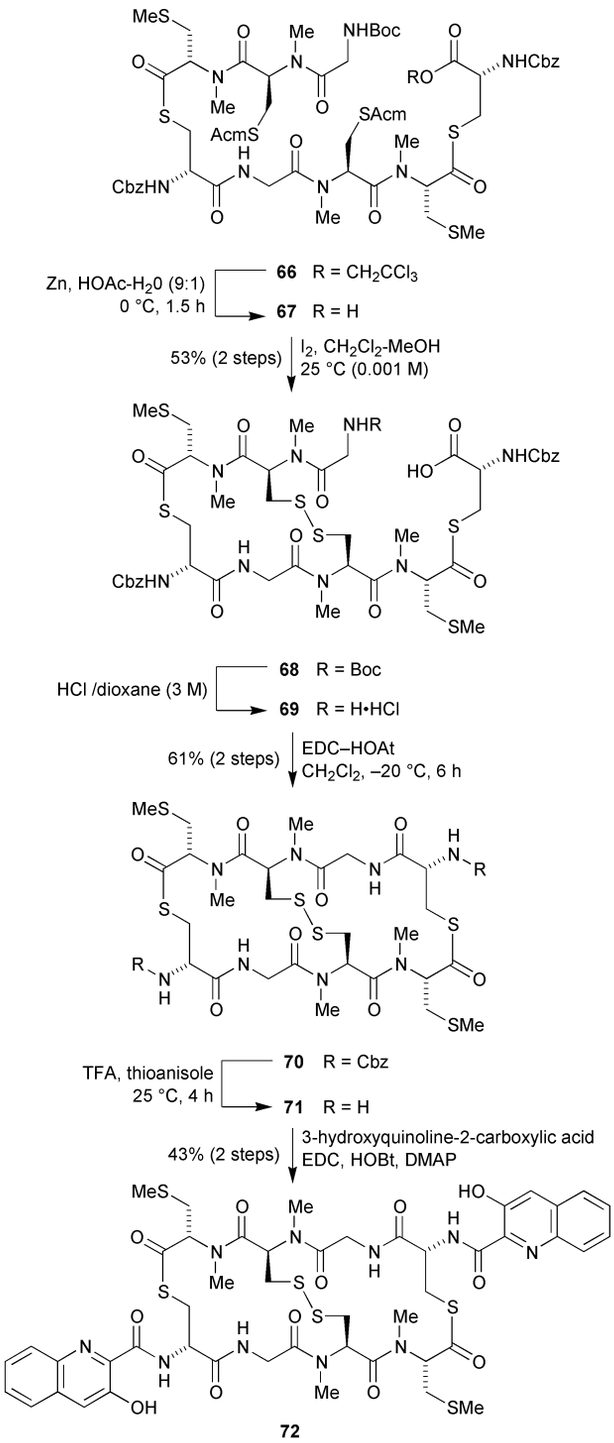
double-stranded DNA whilst BE-22179 inhibits topisomerase I and II. Completion of the synthesis required the sequential deprotection of a carboxylic acid protected as its trichloroethyl ester, two thiols protected as their acetamidomethyl (Acm) derivatives, a Boc-protected amine, and finally two Cbz-protected amines. The trichloroethyl ester in **66** was deprotected with Zn in aqueous acetic acid without affecting the two labile thiol esters. Simultaneous deprotection of the Acm-protected thiols and cyclisation to the disulfide bridge in **68** was accomplished by treatment with iodine under dilute (0.001 M) conditions. Removal of the Boc group in **68** with HCl in dioxane gave an amino acid **69** which was cyclised to generate the second macrocyclic ring in **70**. In the penultimate step, the two Cbz groups were removed with TFA to give **71** which was then converted to thiocoraline (**72**) by coupling with 3-hydroxyquinoline-2-carboxylic acid. The order in which the two rings were created deserves comment. Reversal of the *N*-Boc deprotection and disulfide bridge formation steps resulted in only 13% of a monocyclic disulfide. Moreover, all attempts to create the disulfide bridge after formation of the macrocycle failed, possibly because of competing attack of the liberated thiols on the thiol ester functions.

4 Diol protecting groups

O-4,6-Benzylidene-protected carbohydrates (*e.g.* **73**, Scheme 47) can be converted into the corresponding *O*-benzyl ethers by reduction with triethylsilane under acidic conditions.[70,71] The regioselectivity of the ring opening depends on the acid used: with TfOH and $BF_3{\cdot}OEt_2$, 6-*O*-benzyl-4-hydroxy derivative **74** is obtained whereas $PhBCl_2$ gives rise to 4-*O*-benzyl-6-hydroxy derivative **75**. Both regioisomers are obtained as exclusive products.

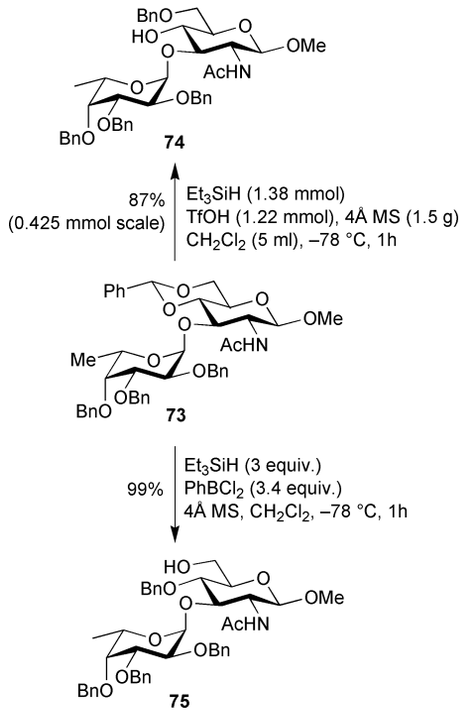
The Yonemitsu group have devised a new method for the selective mono-protection of 1,2- and 1,3-diols as their corresponding PMB ether based on chelation-controlled reductive opening of methoxybenzylidene acetals with Bu_3SnH and $MgBr_2$.[72] As can be seen from the two examples shown in Scheme 48, the proximate free hydroxy group governs the regioselectivity of the cleavage. The reaction works equally well with 5-membered methoxybenzylidene acetals. However, the regioselectivity diminishes markedly if the directing group is protected as an alkyl or silyl ether.

Reductive cleavage of unsymmetrical *p*-methoxyphenyl acetals with DIBAL-H generally liberates the less hindered hydroxy group and relegates the PMB group to the more

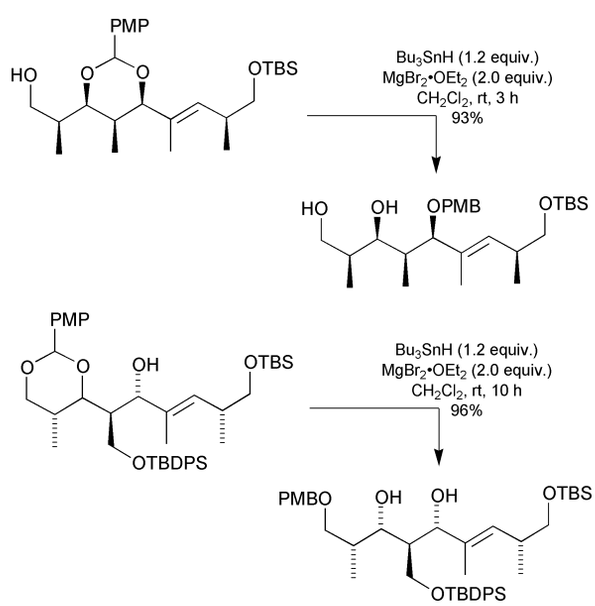


EDC = 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride
HOAt = 1-hydroxy-7-azabenzotriazole
HOBt = 1-hydroxybenzotriazole

Scheme 46



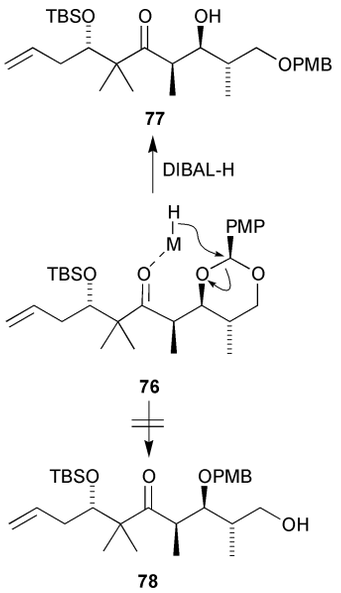
Scheme 47



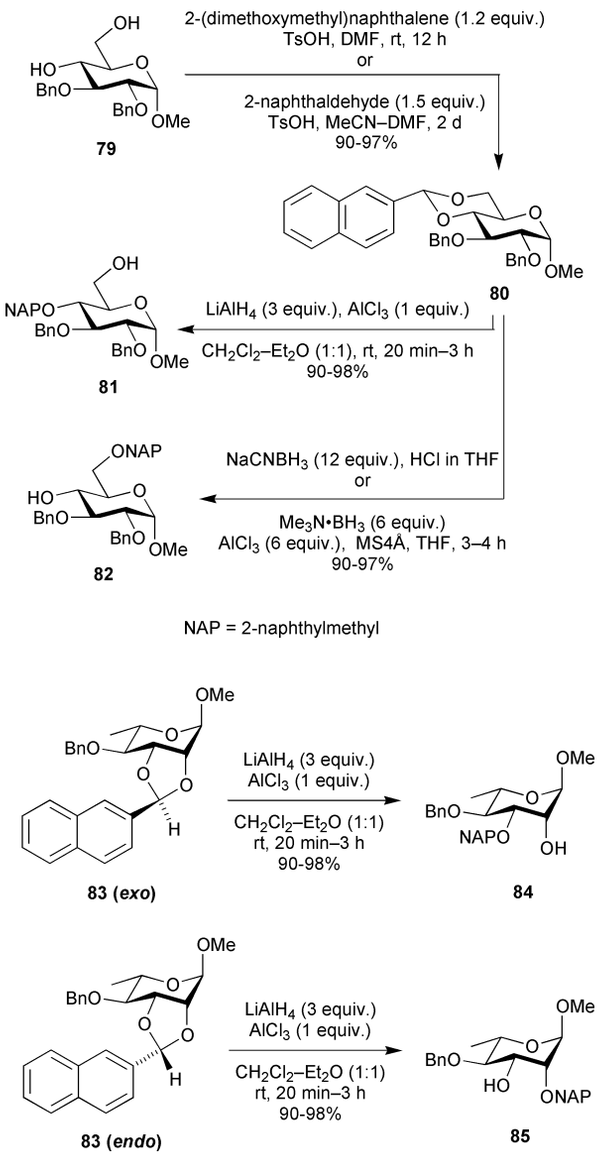
Scheme 48

hindered hydroxy group. Had the *p*-methoxyphenyl acetal **76** (Scheme 49) cleaved as expected, the secondary PMB ether **78** would have been formed; instead, the primary PMB ether **77** was generated. Mulzer and co-workers[73] suggest that the atypical regioselectivity of the cleavage is a consequence of prior coordination of the Lewis acidic reducing agent to the carbonyl group leading to internal delivery of hydride.

Dioxane- and dioxolane-type (2-naphthyl)methylene acetals of glycosides prepared by acid-catalysed transacetalisation reactions can be reductively cleaved to 2-naphthylmethyl (NAP) ethers (Scheme 50).[74] The regioselectivity of the cleavage depends on the cleavage conditions and the stereochemistry of the acetal. Three reagents are generally used for the ring-cleavage of dioxane-type acetals: (i) $LiAlH_4$–$AlCl_3$;[75,76] (ii) $NaCNBH_3$–HCl (or other strong acids);[77] and (iii) $BH_3{\cdot}NMe_3$–$AlCl_3$.[78] Reagent (i) gives the 4-*O*-NAP/6-OH product (*e.g.* **81**) predominantly (**81** : **82** = 97 : 3) whereas reagents (ii) and (iii) yield the 6-*O*-NAP/4-OH product **82** selectively (**81** : **82** = *ca.* 1 : 9). In the case of the dioxolane-type acetals **83**, the regioselectivity of the cleavage is determined by the configuration of the acetal centre. Thus, equatorial NAP ether **84** was obtained from the *exo* isomer **83** (*exo*) using all three reagent combinations, whereas the axial NAP ether **85** was obtained by reductive cleavage of the *endo* isomer **83** (*endo*). (2-Naphthyl)-methylene acetals can be deprotected using 0.4 equiv. of freshly crystallised DDQ at room temperature in 2–3 h. DDQ also removes the NAP ether group.

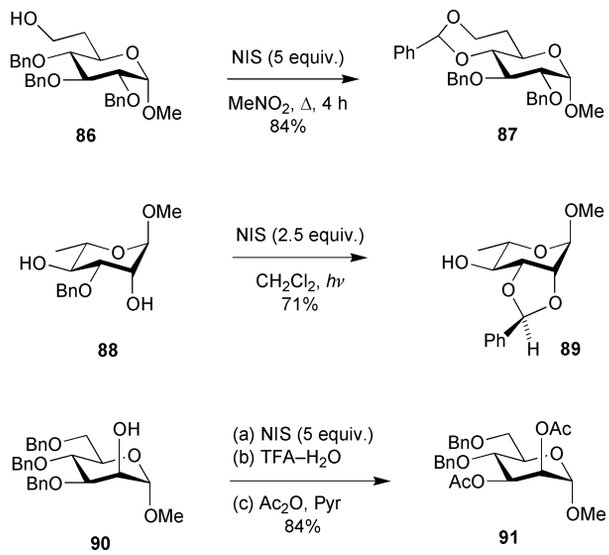


Scheme 49



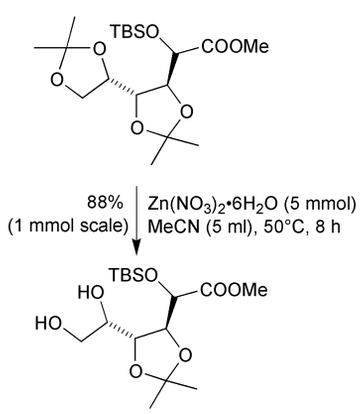
Scheme 50

A new method has been described for the formation of 5-, 6- and 7-membered benzylidene acetals from benzyl ethers with proximate hydroxy groups.[79] The reaction, which is reminiscent of the Hoffman–Löffler–Freytag reaction, entails formation of an intermediate hypoiodite that cleaves thermally or photolytically (visible light) to reactive hydroxyl radicals. The hypoiodite intermediates are generated from *N*-iodosuccinimide (NIS) or diacetoxyiodobenzene (DIB). The intermediate benzylidene acetals can be isolated (*e.g.*, **87** and **89**, Scheme 51) or selectively hydrolysed with aqueous TFA to the corresponding diol as in the transformation of **90** to **91**.



Scheme 51

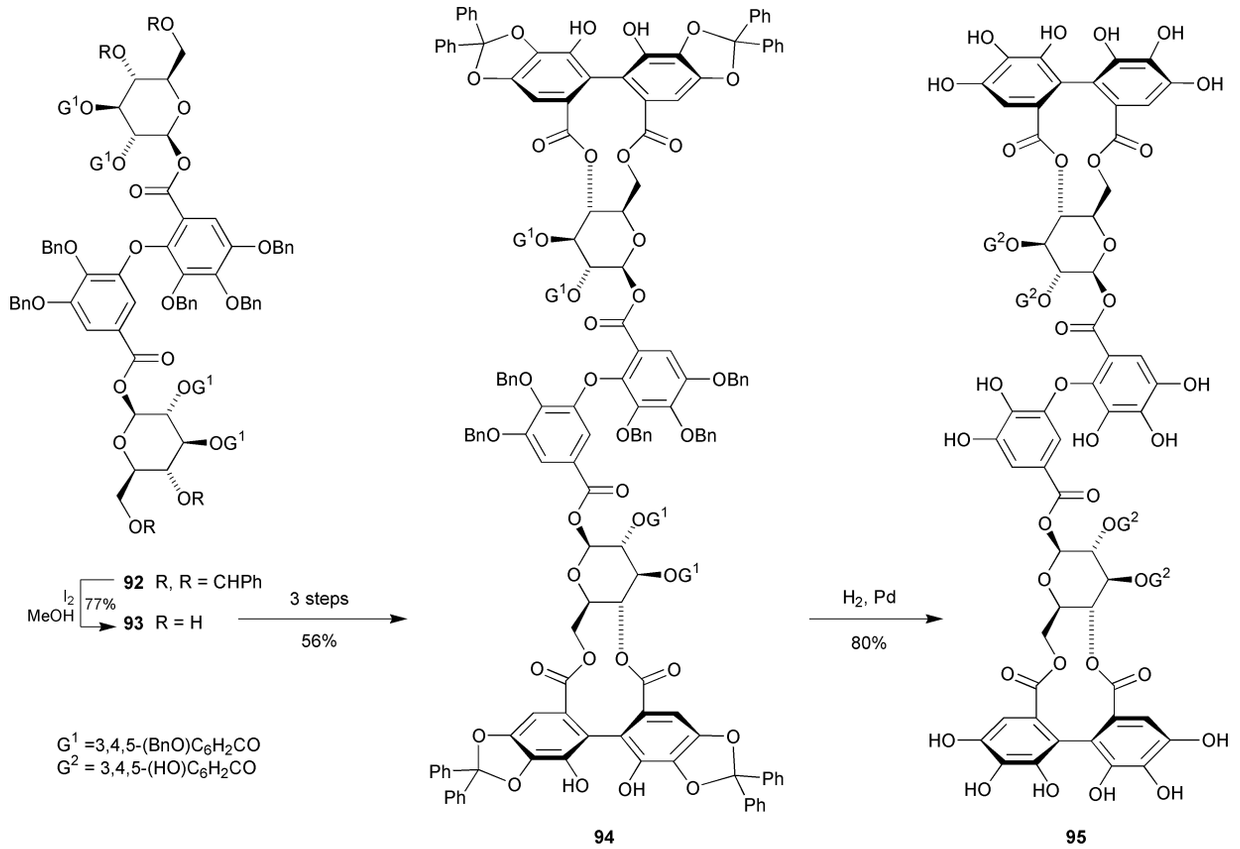
Terminal acetonide groups can be selectively hydrolysed by treatment with $Zn(NO_3)_2{\cdot}6H_2O$ (5 equiv.) in acetonitrile (Scheme 52).[80] Alternatively, a catalytic amount (0.2 equiv.) of zinc salt can be used but the solution has to be more concentrated (10 times) and the reaction time longer (18 h). Benzyl, TBS, acetate, tosyl, and benzoyl groups are compatible with the reaction conditions.



Scheme 52

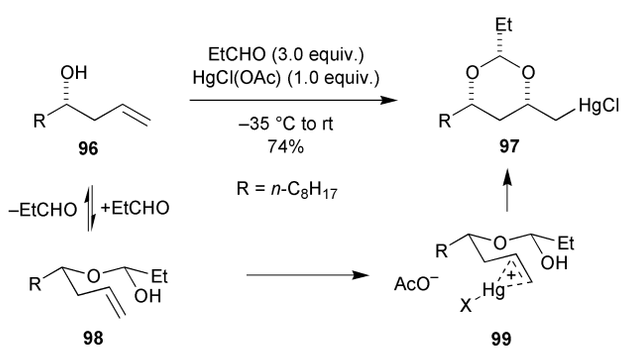
Corariin A (**95**, Scheme 53) displays tumour remissive activity owing to host-mediated immunostimulation rather than direct cytotoxicity. In the closing stages of a synthesis of corariin A,[81] the benzylidene acetals of the glucose residues in **92** were cleaved with iodine and methanol to release the 4- and 6-hydroxy groups in **93** in 77% yield. A further 3 steps achieved the construction of the two biaryl units in **94** wherein two of the three phenolic hydroxy groups of the galloyl residues were protected as their diphenyl acetals. The last step in the synthesis entailed simultaneous hydrogenolysis of 17 benzyl ethers and 4 diphenyl acetal groups in **94** to give the final target **95** in 80% yield.

Protected 1,3-diol synthons **97** are generated efficiently from homoallylic alcohols **96** and propionaldehyde by oxymercuration



Scheme 53

of intermediate hemiacetals **98** using HgCl(OAc) (Scheme 54).[82] The reactions are diastereoselective (>10 : 1) and do not require solvent. Benzaldehyde is a poor participant and acetone does not react at all. Precedent for the observation can be found in the work of Overman[83] and Kitching.[84]

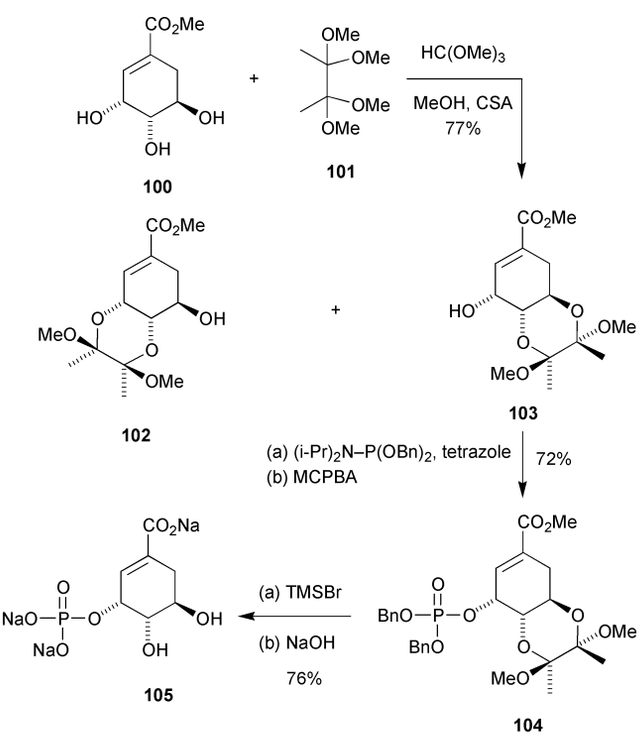


Scheme 54

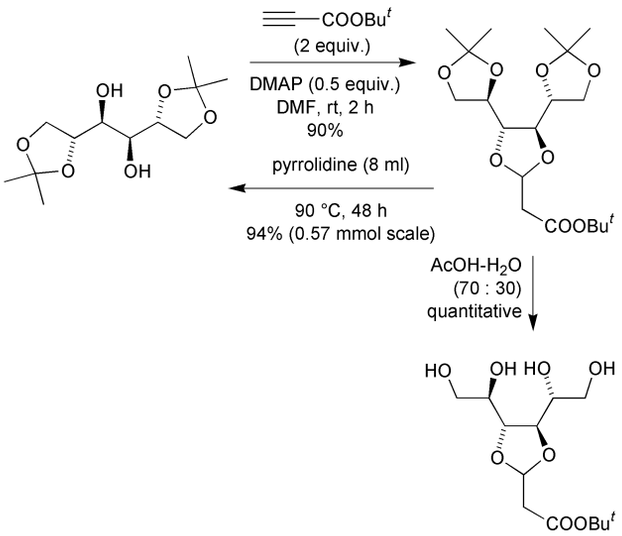
A synthesis of (−)-shikimate 3-phosphate[85] (**105**) (Scheme 55) was accomplished by protection of the vicinal *trans*-diol in (−)-methyl shikimate (**100**) using 2,2,3,3-tetramethoxybutane (**101**).[86] The product ratio in the protection step was time dependent. Thus, after 3 h at reflux, bis-acetals **102** and **103** were formed in the ratio of 1.5 : 1 but after 18 h the ratio was 1 : 1.25. However, after 48 h, the desired compound **103** was obtained as the exclusive product in 77% yield. Phosphorylation of the remaining hydroxy group in **103** (72%), followed by deprotection with bromotrimethylsilane, afforded the target **105** in 76% yield.

A detailed experimental procedure for the previously prime throughout published selective protection of diequatorial vicinal diols in carbohydrates with 6,6′-bis(3,4-dihydro-2*H*-pyran) (bis-DHP) has been reported in *Organic Syntheses*.[87]

1,2-Diols can be protected as their 2-(*tert*-butoxycarbonyl)-ethylidene (Boc-ethylidene or "Bocdene") or 2-(methoxycarbonyl)ethylidene (Moc-ethylidene or "Mocdene") derivatives in the reaction with *tert*-butyl or methyl propynoate in the presence of a catalytic amount of *N,N*-dimethylaminopyridine (DMAP).[88] The acetal-like structure of these protecting groups is misleading because they are stable under acidic conditions (AcOH–H_2O, 1 M HCl in THF and TsOH in MeOH), which allows selective deprotection of simple acetals (Scheme 56). On the other hand, unlike simple acetals, the deprotection can be accomplished under basic conditions *via* an



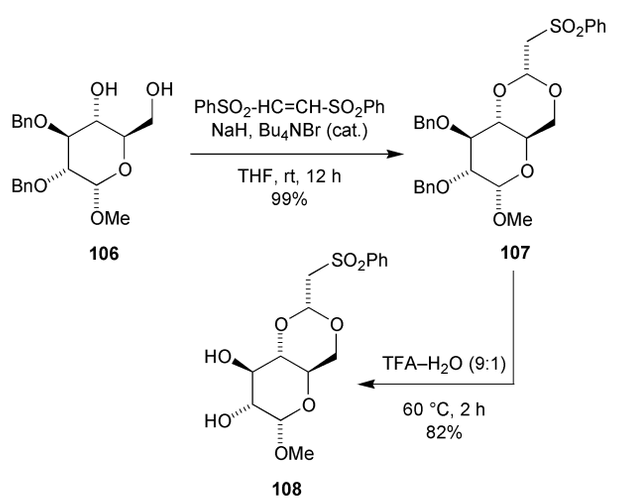
Scheme 55



Scheme 56

elimination–addition–elimination mechanism. This can be achieved with the combination of pyrrolidine and butyllithium in THF at room temperature or simply by heating the protected diol in neat pyrrolidine.

Phenylsulfonylethylidene (PSE) acetals are easily prepared[89] from carbohydrates by a double Michael addition pathway. For example, treatment of methyl glucoside **106** (Scheme 57) with (*Z*)- or (*E*)-1,2-bis(phenylsulfonyl)ethylene (1 equiv.), NaH (2 equiv.) and a few crystals of Bu_4NBr as a phase transfer catalyst in THF at room temperature gave the PSE acetal **107** in 99% yield. Alternatively *t*-BuOK in DMF can be used as the base. In either case, the initial Michael addition of an alkoxide is followed by elimination of benzenesulfinate to afford a transient β-alkoxyalkenyl sulfone which undergoes a second Michael addition to give the product.

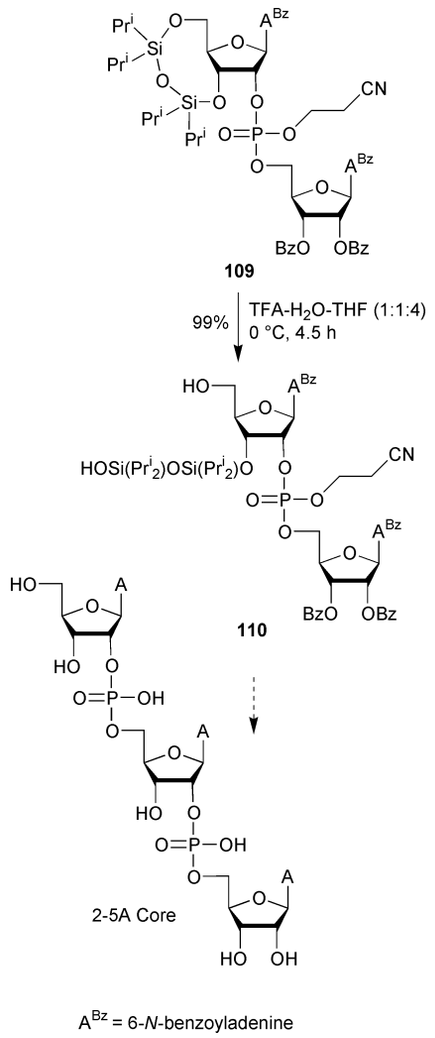


106 **107** **108**

Scheme 57

The phenylsulfonyl group renders PSE acetals remarkably stable towards acid hydrolysis or alcoholysis. For example, treatment of **107** with aqueous trifluoroacetic acid (TFA) at 60 °C results in preferential cleavage of the two benzyl ethers to give **108** in 82% yield. Similarly, PSE acetals survive 0.7 M H_2SO_4 or $BF_3{\cdot}OEt_2$ in MeOH. However, $LiAlH_4$ in Et_2O accomplishes a reductive cleavage in 75–85% yield.

The 5′ position of 3′,5′-TBS or TIPDS (1,1,3,3-tetraisopropyldisiloxane-1,3-diyl) diprotected nucleosides and nucleotides (*e.g.* **109**) can be selectively cleaved by treatment with TFA–H_2O–THF (1 : 1 : 4) (Scheme 58).[90,91] Other commonly used nucleoside protecting groups such as TBS and benzoyl groups are compatible with the reaction conditions.



109 **110**

Scheme 58

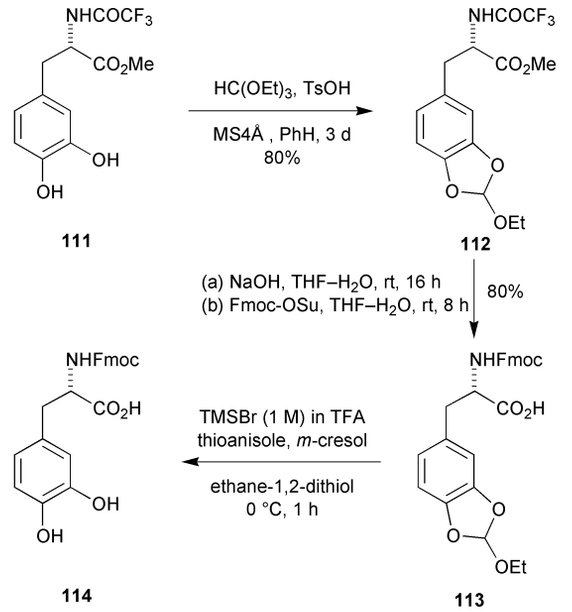
Dinucleotide **110** is a key intermediate in the synthesis of the known antiviral and anti-tumour agent 2-5A.

3,4-Dihydroxyphenylalanine (DOPA) is a natural amino acid used to treat Parkinson's disease. Although rarely present in proteins, it constitutes up to 10% of marine mussel adhesive proteins. Protection of the catechol moiety in DOPA during solid-phase peptide synthesis has been accomplished by the route shown in Scheme 59.[92] *N*-Trifluoroacetyl-L-DOPA methyl ester (**111**) was treated with triethyl orthoformate under acidic conditions to give the ethyl orthoester **112** in 80% yield. Simultaneous hydrolysis of the trifluoroacetamide and ester group, followed by reprotection of the amino group as its Fmoc derivative, gave **113**. The cyclic orthoester could be cleaved with bromotrimethylsilane in TFA containing a cocktail of three scavengers: thioanisole, *m*-cresol and ethane-1,2-dithiol.

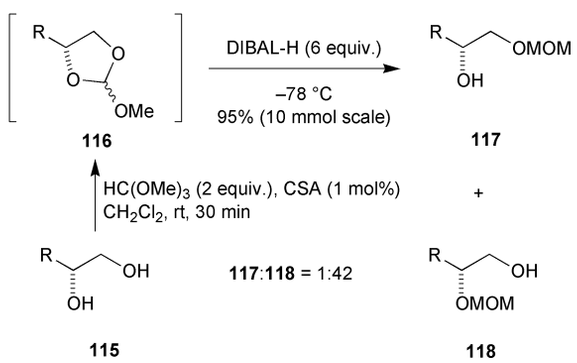
Reductive cleavage of benzylidene and *p*-methoxybenzylidene acetals to the corresponding benzyl and *p*-methoxybenzyl ethers is now a common tactic in organic synthesis but the analogous cleavage of cyclic orthoesters to give alkoxyalkyl ethers is comparatively rare.[93] In a recent synthesis of sphingolipids, the mono-MOM ether **118** (Scheme 60) of 1,2-diol **115** was prepared by regioselective cleavage of the cyclic orthoester **116** generated *in situ*.[94] Note the preponderance of the more hindered MOM ether **118**.

5 Carboxy protecting groups

The cleavage of *N*-Boc derivatives with $ZnBr_2$ has been known for more than a decade.[95] A recent study[96] has shown that $ZnBr_2$ (5 equiv.) in dichloromethane at room temperature also cleaves *tert*-butyl esters and ethers in 12–24 h. In the case of the



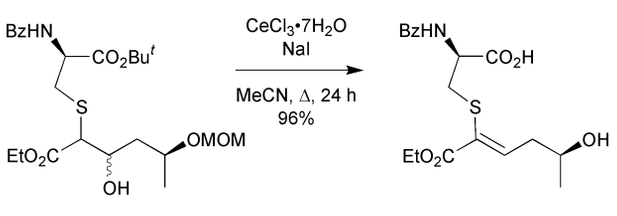
Scheme 59



Scheme 60

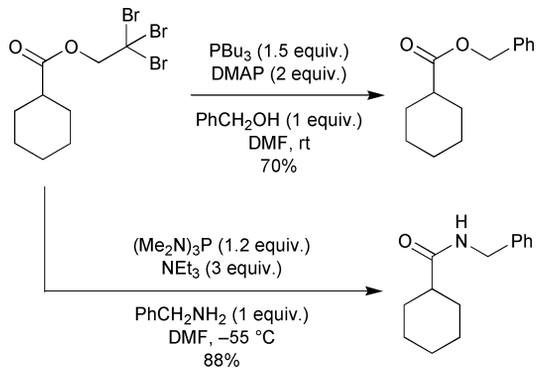
N-Boc derivative of *tert*-butyl glycinate, the *tert*-butyl ester is cleaved selectively. However, the rate differential for the deprotection of *tert*-butyl esters in the presence of *tert*-butyl ethers is insufficient to be synthetically useful.

During a synthesis of the antibiotic griseoviridin, an Italian group[97] accomplished three transformations simultaneously. Treatment of intermediate **119** (Scheme 61) with $CeCl_3 \cdot 7H_2O$ and NaI in refluxing acetonitrile effected dehydration to the vinyl sulfide, cleavage of the MOM group, as well as the unexpected cleavage of the *tert*-butyl ester, to give the hydroxy acid **120** in 96% yield.



Scheme 61

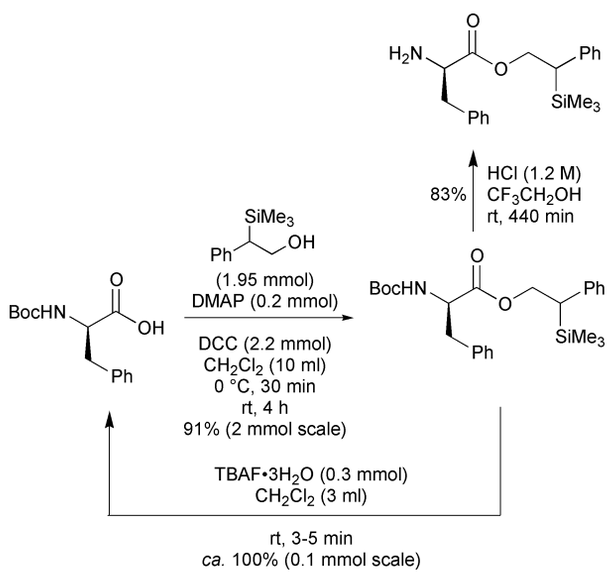
Carboxylic acids protected as their 2,2,2-trihaloethyl esters are typically deprotected under reductive conditions (*e.g.* with zinc). Transprotection can also be achieved in one pot by treatment of a 2,2,2-tribromoethyl ester with a primary or secondary alcohol (*e.g.* benzyl alcohol) using tributylphosphine and DMAP (Scheme 62).[98] The intermediate acyloxyphosphonium intermediate can also be trapped with amines to form amides.



Scheme 62

The corresponding 2,2,2-trichloroethyl esters give inferior results.

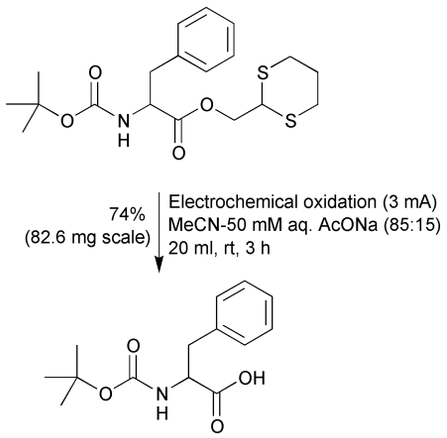
2-(Trimethylsilyl)ethyl (TMSE) esters are useful protecting groups for carboxylic acids thanks to the ease of deprotection with TBAF in THF or DMF.[99,100] However, in some cases, quite long deprotection times lead to side reactions.[99] Wagner and Kunz reported[101] that 2-phenyl-2-(trimethylsilyl)ethyl (PTMSE) esters, which incorporate a phenyl group in the α position relative to the silyl group, can be deprotected under milder conditions (TBAF in CH_2Cl_2) and shorter reaction times which gives rise to cleaner reaction. PTMSE esters are stable to the reagents that deprotect Fmoc, Cbz and Aloc groups. On the other hand, the *N*-Boc group can be cleaved selectively in the presence of a PTMSE ester (Scheme 63).



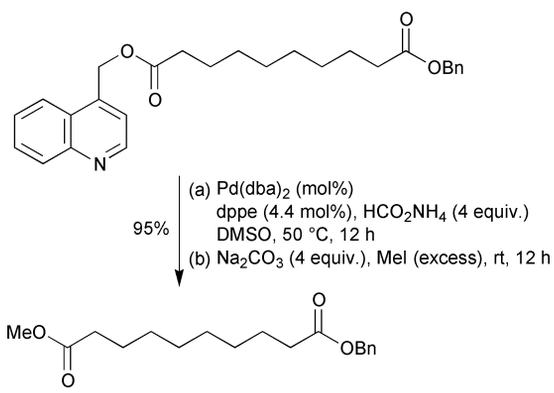
Scheme 63

Carboxylic acids can be electrochemically deprotected from their 2-(hydroxymethyl)-1,3-dithiane (Dim) esters.[102] The approach seems particularly valuable for amino acids, allowing selective protection/deprotection at the C-terminus (Scheme 64).

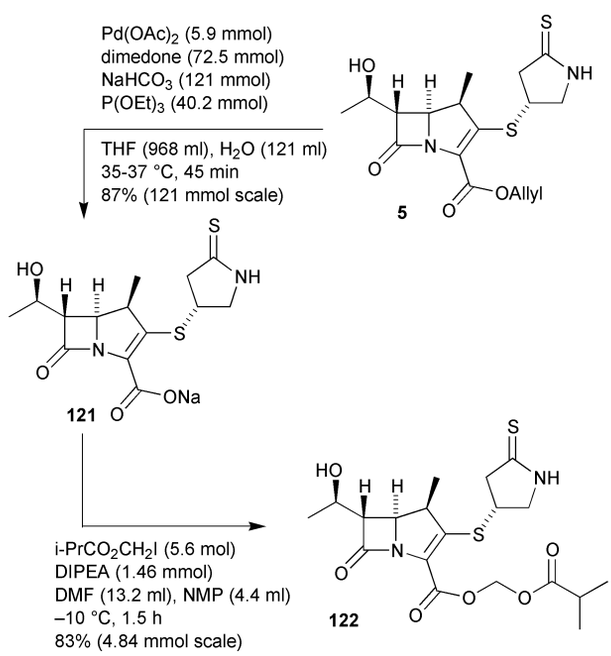
4-Quinolylmethyl esters (4-QUI) are reduced by palladium-catalysed hydrogenolysis using ammonium formate as the reductant.[103] The reaction is best conducted in DMSO at 50 °C in which case aromatic bromo compounds, aliphatic chloro compounds, alkenes, aldehydes, and nitriles are inert. However, allyl esters are cleaved selectively under these conditions leaving the 4-QUI ester intact and aromatic nitro compounds are reduced to the aniline derivative. Scheme 65 illustrates the selective cleavage of a 4-QUI ester in the presence of a benzyl ester. Some preliminary results concerning the cleavage of 1-naphthylmethyl esters of amino acid derivatives under similar conditions are also reported.



Scheme 64



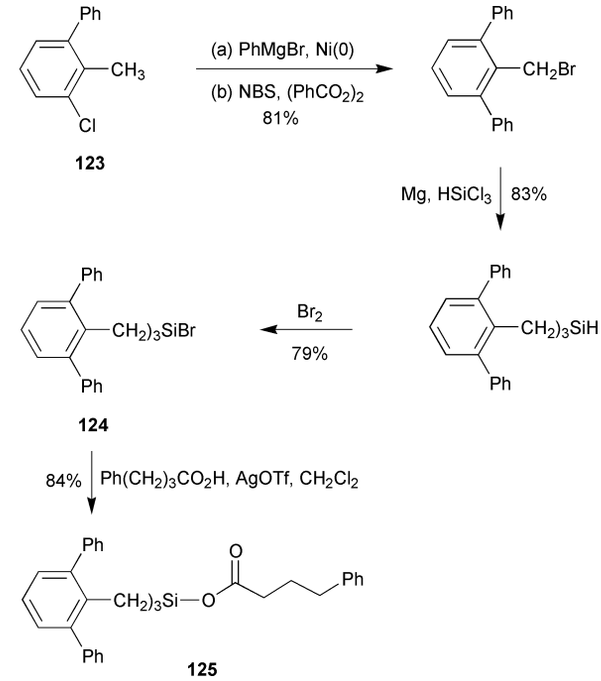
Scheme 65



Scheme 66

In the final stages of a synthesis of the orally active 1-β-methylcarbapenem antibiotic TA-949 (**122**, Scheme 66), allyl ester **5** was deprotected using dimedone and the stable and inexpensive $Pd(OAc)_2$ as catalyst.[4] By conducting the reaction in the presence of sodium hydrogen carbonate, the sodium salt **121** was obtained which was then alkylated with iodomethyl isobutyrate to give the target **122**.

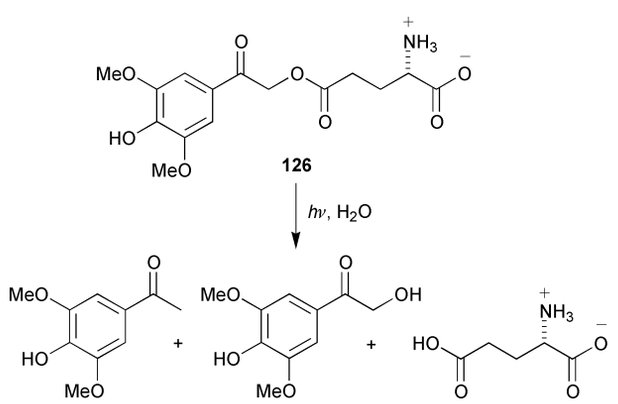
Tris(2,6-diphenylbenzyl)silyl (TDS) esters confer extraordinary steric protection upon the carboxy group.[104] For example, the TDS ester of 4-phenylbutanoic acid (**125**, Scheme 67) does not react with BuLi (2.5 equiv.) after 5 h at −78 °C or MeMgBr



Scheme 67

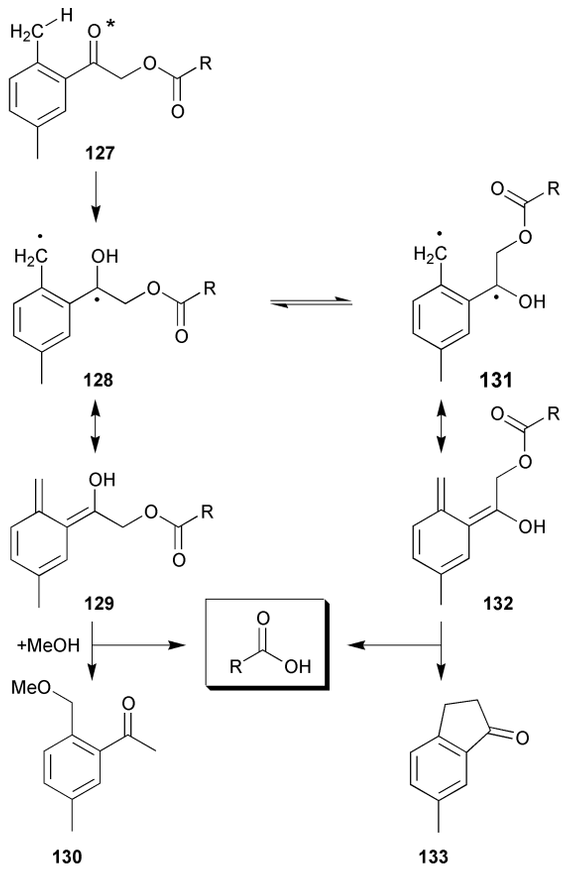
(2.5 equiv.) at room temperature. Nor did it react with $LiAlH_4$ after 30 min at 0 °C, 1 M HCl in THF at 40 °C, or aqueous NaOH at 50 °C after 5 h. Ester **125** reduced with DIBAL-H in 99% yield to give 4-phenylbutan-1-ol (99%) and Pyr·HF in THF (1 : 2) at 50 °C cleaved it back to the acid after 5 h. TDS esters are prepared from bromotris(2,6-diphenylbenzyl)silane (**124**), which is readily prepared in four steps from 2-chloro-6-phenyltoluene (**123**), and the carboxylic acid using AgOTf as the promoter. Unfortunately, the penalty for such unusual stability is high: the TDS group has a molecular formula of $C_{57}H_{46}Si$ and an FW of 758—a case of the tail wagging the dog.

3-Methoxy-4-hydroxy- and 3,5-dimethoxy-4-hydroxy-phenacyl esters have absorption maxima at 350 and 370 nm respectively, which extends the tail of the absorption bands above 400 nm, well beyond the absorptions of aromatic amino acids and nucleotides.[105] The consequent capacity for photorelease of L-glutamic acid from its 3,5-dimethoxy-4-hydroxyphenacyl ester **126** is shown in Scheme 68.



Scheme 68

2,5-Dimethylphenacyl esters undergo direct photolysis at 254–366 nm to give carboxylic acids in nearly quantitative yield.[106] The photodeprotection relies on efficient intramolecular hydrogen abstraction from within the triplet excited ester **127** to give the 1,4-diradicals **128** and **131** without the need for introducing a photosensitiser (Scheme 69). The course of the reaction is solvent dependent. In benzene, the carboxylic acid is accompanied by 6-methylindan-1-one (**133**) generated by a ring

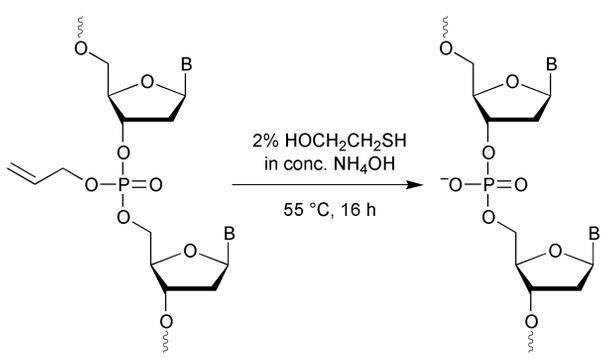


Scheme 69

closure of the dienol **132** whereas in MeOH, the isomeric dienol **129** undergoes solvolysis to give indanone **133** together with 2-(methoxymethyl)-5-methylacetophenone (**130**). Thus, the 2,5-dimethylphenacyl ester of *N*-Boc-L-phenylalanine underwent photolysis in benzene at >280 nm to give the free acid in 90% yield.

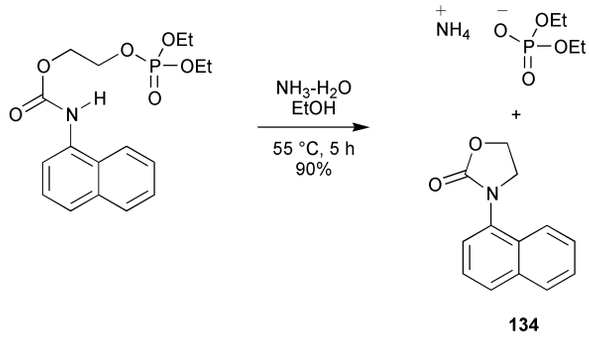
6 Phosphate protecting groups

Convenient and mild conditions for the cleavage of allyl phosphates during solid-phase DNA synthesis have been developed (Scheme 70).[107] The method simply involves heating the polymer-bound oligonucleotide with 2% mercaptoethanol in concentrated ammonia at 55 °C for 16 h. The method can also be applied to the synthesis of internucleotide thiophosphate linkages.



Scheme 70

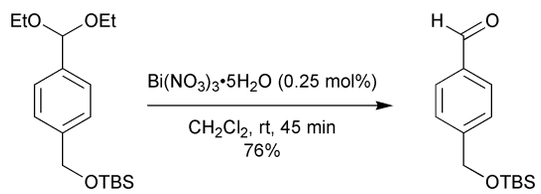
The utility of the 2-[(1-naphthyl)carbamoyloxy]ethyl (NCE) group for the protection of phosphate linkages in oligonucleotide synthesis has been examined.[108] The NCE group is stable towards standard reagents used in DNA synthesis and it is quantitatively removed under basic conditions to release the phosphate (as its ammonium salt) and the inert oxazolidinone **134** (Scheme 71).



Scheme 71

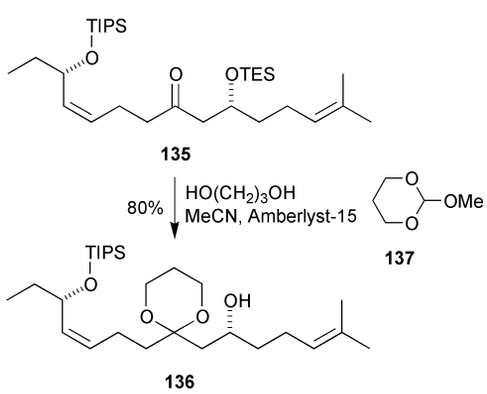
7 Carbonyl protecting groups

Acyclic acetals of ketones and α,β-unsaturated aldehydes can be deprotected with a catalytic amount of bismuth nitrate pentahydrate.[109] Acetals of nonconjugated aldehydes are resistant to the reagent; however, the presence of a methyl group α to the acetal moiety accelerates the rate of deprotection. The reaction conditions do not affect THP and TBS protecting groups (Scheme 72).



Scheme 72

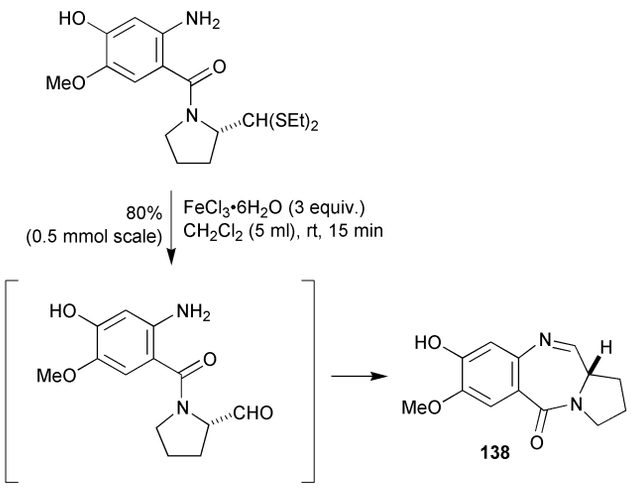
A synthesis of the crambescidin family of guanidine alkaloids was impeded by problems with ketalisation of the ketone in **135** (Scheme 73).[110] The TES group made the desired ketalisation sluggish whereas the free alcohol reacted more easily. Eventually conditions were found that accomplished the removal of the TES group, and then the desired ketalisation, without competing dehydration. Thus, reaction of **135** with the cyclic ortho ester **137** and propane-1,3-diol in the presence of Amberlyst-15 at room temperature provided hydroxy ketal **136** in 80% yield.



Scheme 73

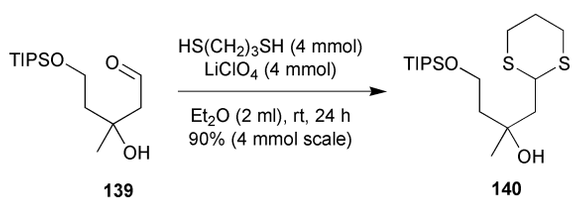
Dithioacetals can be converted to their corresponding carbonyl compounds by treatment with $FeCl_3 \cdot 6H_2O$.[111] Scheme 74 illustrates the application of the procedure in the synthesis of the DNA-binding pyrrolo[2,1-*c*][1,4]benzodiazepine ring system **138**.

Aldehydes and ketones can be transformed into the corresponding 1,3-dithianes by treatment with propane-1,3-dithiol and lithium perchlorate.[112] The method is mild enough to



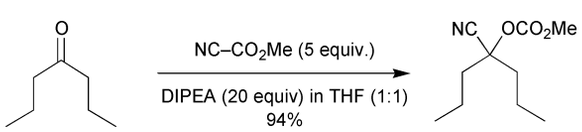
Scheme 74

tolerate even highly labile β-hydroxy aldehyde **139** without causing β-elimination (Scheme 75). The use of $BF_3 \cdot OEt_2$ instead of lithium perchlorate led to complete decomposition of **139** whereas zinc triflate gave only 10% of the desired product **140**.



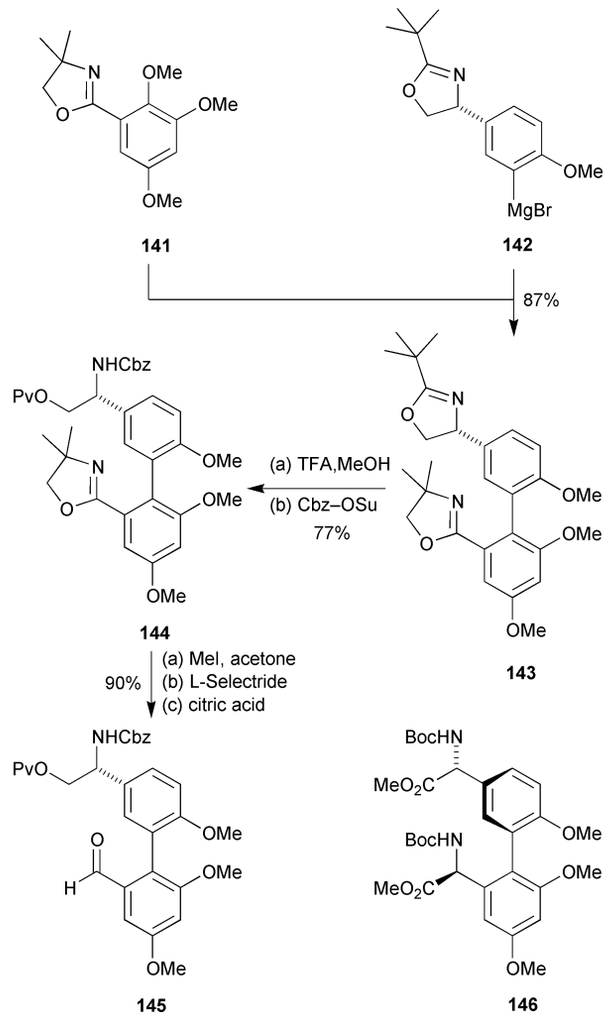
Scheme 75

A recent detailed evaluation of the *O*-methoxycarbonyl cyanohydrin protecting group for carbonyl groups was a model of clarity, depth, and breadth.[113] This new protecting group is easily introduced by reaction of a ketone or aldehyde with methyl cyanoformate and diisopropylethylamine at room temperature (Scheme 76). *O*-Methoxycarbonyl cyanohydrins are labile towards aqueous bases and nucleophiles. They are attacked by $LiAlH_4$ but they resist the ravages of DIBAL-H (2 equiv.) and $NaBH_4$ (2.5 equiv., 2.5 h). Protic acids such as aqueous HCl, AcOH, TfOH and TsOH are also tolerated as are Lewis acids ($AlCl_3$, BBr_3, $BF_3 \cdot OEt_2$). Common oxidants ($KMnO_4$, PCC, *t*-BuOOH, MCPBA) are innocuous. Deprotection is achieved under mildly basic hydrolytic conditions [1% K_2CO_3 in MeOH–H_2O (3 : 1)].



Scheme 76

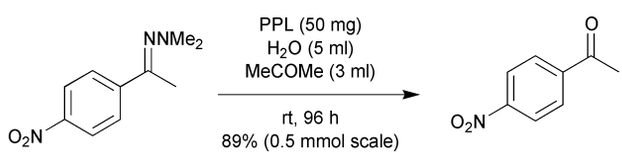
A synthesis of the fully protected derivative, **146**, of actinoidic acid (Scheme 77), a constituent of vancomycin, features the use of the oxazoline group as an activating group for an S_NAr reaction and as a protecting group for both an aldehyde and a vicinal amino alcohol.[114] The S_NAr reaction, first pioneered by Meyers and co-workers,[115,116] occurred on addition of the Grignard reagent **142** to the oxazoline **141** to give the biaryl system of **143** in 87% yield. Treatment of biaryl **143** with trifluoroacetic acid in methanol selectively cleaved the A-ring oxazoline to give an amino ester which was immediately converted to its Cbz-derivative **144** in 77% overall yield for two steps. The B-ring oxazoline was inert under these conditions. However, *N*-methylation with iodomethane followed by reduction of the oxazolinium salt with L-Selectride gave an *N,O*-



Scheme 77

acetal which was hydrolysed with aqueous citric acid to afford the aldehyde **145** in 90% yield.

The deprotection of hydrazones can be promoted using a porcine pancreatic lipase (PPL) in an acetone–H_2O system at room temp. (Scheme 78).[117] The reactivity depends on the substrate structure: in the case of the derivatives of hindered and aromatic ketones, the deprotection is quite slow.

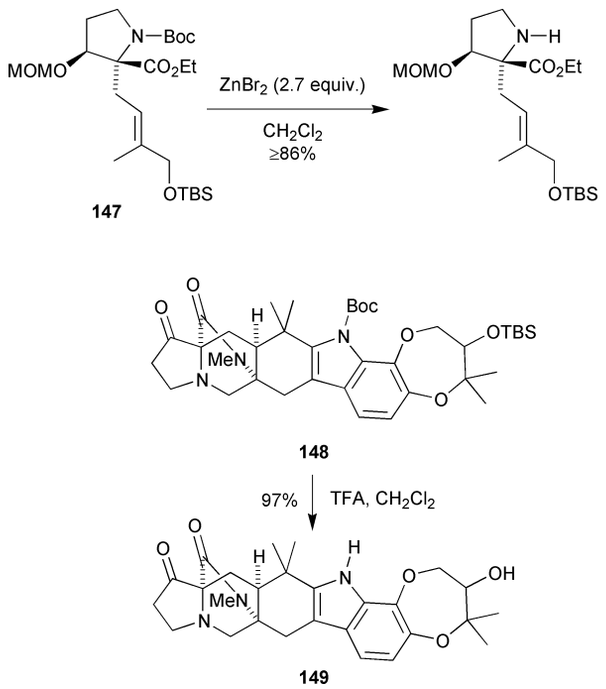


Scheme 78

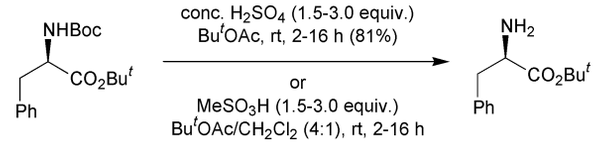
8 Amino protecting groups

During a synthesis of the antiparasitic agent paraherquamide A, Williams and co-workers accomplished the deprotection of the *N*-Boc group in **147** (Scheme 79) in the presence of a MOM ether and an allylic TBS ether with zinc bromide.[118] Later in the synthesis, a Boc group protected an indole nitrogen through 12 steps which included the DIBAL-H reduction of an amide to an amine and the deprotection of a MOM ether with *B*-bromocatecholborane. The *N*-Boc group in **148** was finally dispatched with TFA to give the free indole **149** in 97% yield.

Deprotection of *N*-Boc groups in the presence of *tert*-butyl esters can be achieved by using either concentrated H_2SO_4 (1.5–3.0 equiv.) in *t*-BuOAc or $MeSO_3H$ (1.5–3.0 equiv.) in *t*-BuOAc–CH_2Cl_2 (4 : 1 v/v) at room temperature.[119] The method is particularly suited to amino acid and peptide substrates as



Scheme 79



Scheme 80

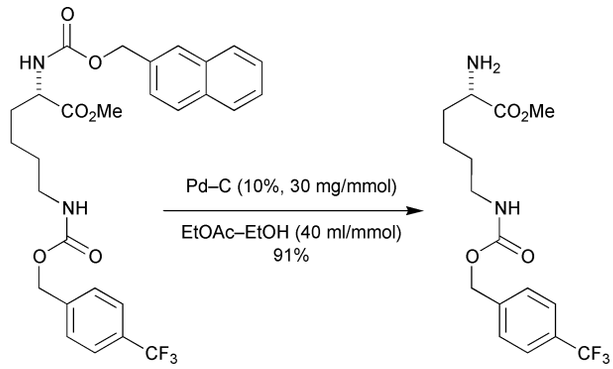
illustrated in Scheme 80. The method does not entail a selective deprotection of the *N*-Boc group; rather, it is based on reprotection of any carboxylic acid liberated under the reaction conditions.

A detailed study has been made on the protection of amines and alcohols with the Boc group using Boc_2O in the presence or absence of DMAP.[120] The study showed that conversion of aliphatic amines to their *N*-Boc derivatives occurred preferentially in the absence of DMAP but also in the presence of *N*-methylimidazole in non-protic solvents. In a polar solvent (MeCN) and in the presence of DMAP, substantial amounts of the corresponding urea and isocyanate were formed. In the case of alcohols, the high yield of the corresponding *O*-Boc derivatives resulted when less than 0.1 equiv. of DMAP was used in dioxane or with *N*-methylimidazole in toluene.

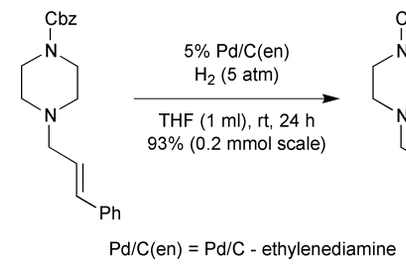
2-Naphthylmethyl carbamate (CNAP) and 4-trifluoromethylbenzyl carbamate (CTFB) groups together with the traditional Cbz group offer a wide range of conditions for selective hydrogenolysis.[121] The Cbz group is cleaved most easily followed by the CNAP group. The CTFB group is virtually inert under the conditions used to cleave the CNAP group as illustrated in Scheme 81. Similarly the CTFB group is inert under the conditions required to cleave benzyl ethers and esters or hydrogenate an aromatic nitro group to a primary amine. However, CTFB groups can be cleaved using a high loading of 10% Pd/C (60 mg $mmol^{-1}$) or, in more recalcitrant cases, by using 20% $Pd(OH)_2$ (20 mg $mmol^{-1}$).

Reducible functionalities (*e.g.* alkyne, alkene, azide, nitro and benzyl groups) can be hydrogenated chemoselectively without affecting aliphatic *N*-Cbz-protected amines with hydrogen and the combination of 5% Pd/C and ethylenediamine [Pd/C(en)] (Scheme 82).[122] In the case of aromatic amines, the reduction of Cbz groups proceeded much faster and the described selectivity could not be achieved.

Allyl carbamates can be deprotected to the corresponding amines by a Ni(II)-catalysed electrochemical procedure.[123] Electrolysis is carried out in DMF or THF in single-compartment cells in the presence of a consumable zinc anode. The method is compatible with ester, nitrile, ketone and acetal functional groups (Scheme 83).

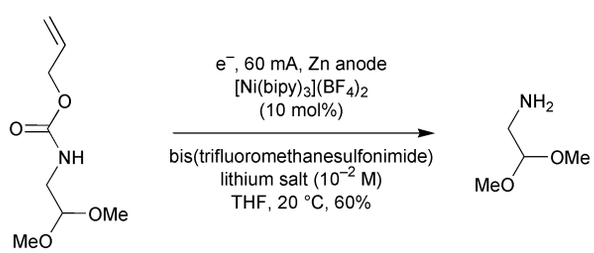


Scheme 81



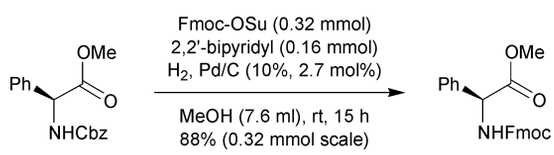
Pd/C(en) = Pd/C - ethylenediamine

Scheme 82



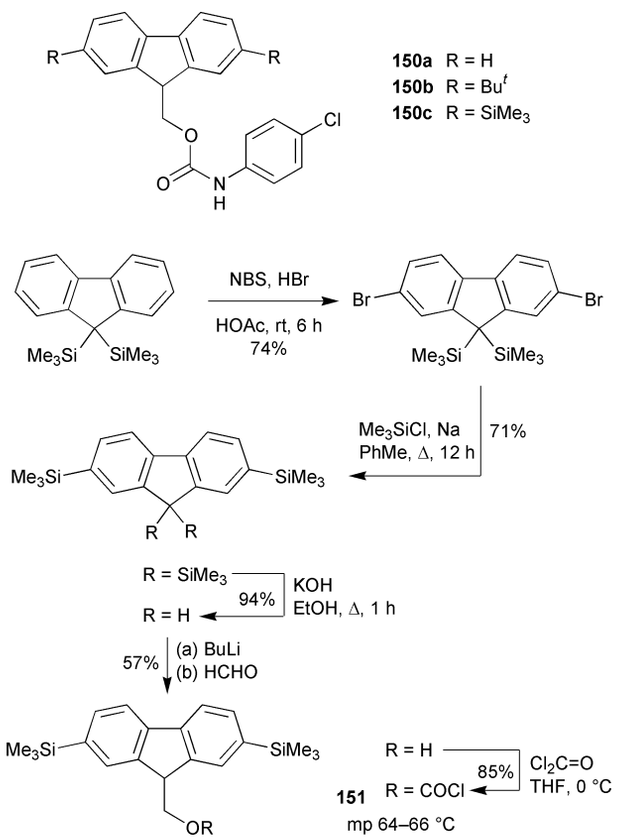
Scheme 83

The *N*-Cbz protecting group can be converted directly into the *N*-Fmoc group by hydrogenation over a palladium catalyst, poisoned with 2,2′-bipyridyl, in the presence of *N*-(fluoren-9-ylmethoxycarbonyloxy)succinimide (Fmoc-OSu) (Scheme 84).[124] *tert*-Butyl esters and ethers as well as *N*-Boc groups are stable under the reaction conditions and enantiomeric purity is preserved.



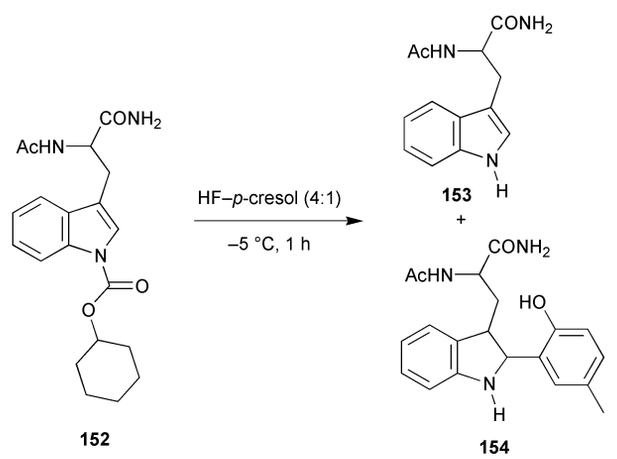
Scheme 84

2,7-Di-*tert*-butyl-[125] and 2,7-bis(trimethylsilyl)-Fmoc[126] derivatives are more soluble than their unsubstituted parent. The effect is exemplified by the three *p*-chlorocarbanilates **150a–c** whose solubilities per 100 ml of CH_2Cl_2 are 3.34, 6.74 and 22.3 g respectively. The 2,7-di-*tert*-butyl-Fmoc group is more sluggishly deprotected than the parent using piperidine, but the rate of deprotecting the 2,7-bis(trimethylsilyl)-Fmoc group is comparable to that for Fmoc. Although stable towards acetic acid, the 2,7-bis(trimethylsilyl)-Fmoc group underwent protodesilylation to the Fmoc group with TFA. Scheme 85 depicts a synthesis of the 2,7-bis(trimethylsilyl)fluoren-9-ylmethyl chloroformate **151**.



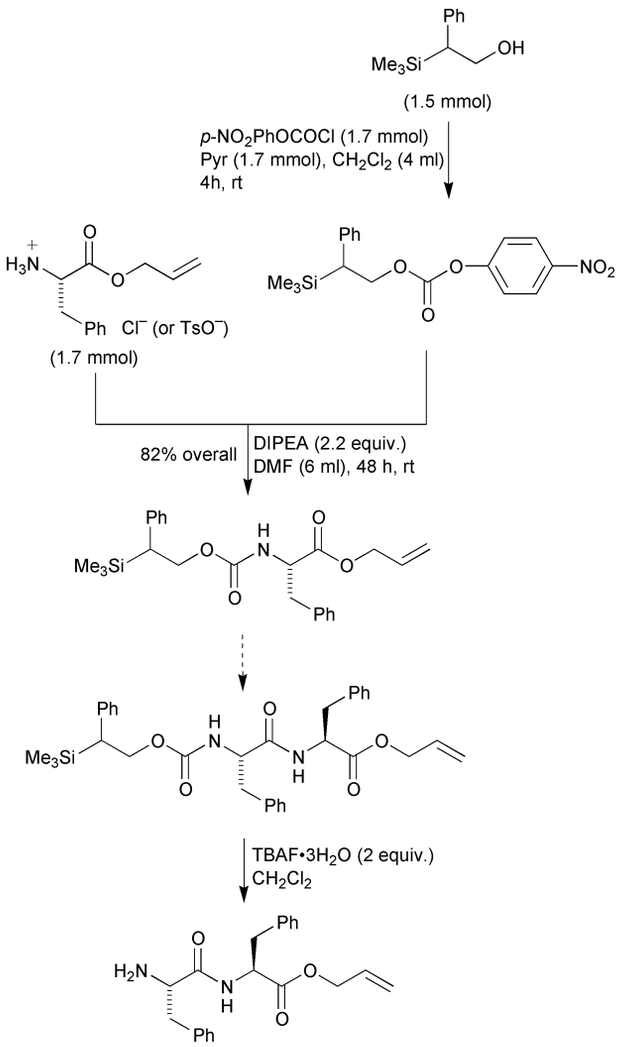
Scheme 85

A significant side reaction occurs during the deprotection of N^{in}-cyclohexyloxycarbonyl-protected tryptophan-containing peptides using HF in the presence of *p*-cresol as the cation scavenger.[127] In the case of the model compound **152** (Scheme 86), 88.6% of the desired indole **153** was obtained together with the by-product **154** (10.6%). However, use of HF with Fmoc-Leu (10 equiv.) as the cation scavenger at −5 °C gave **153** (99.5%) with no further complications.



Scheme 86

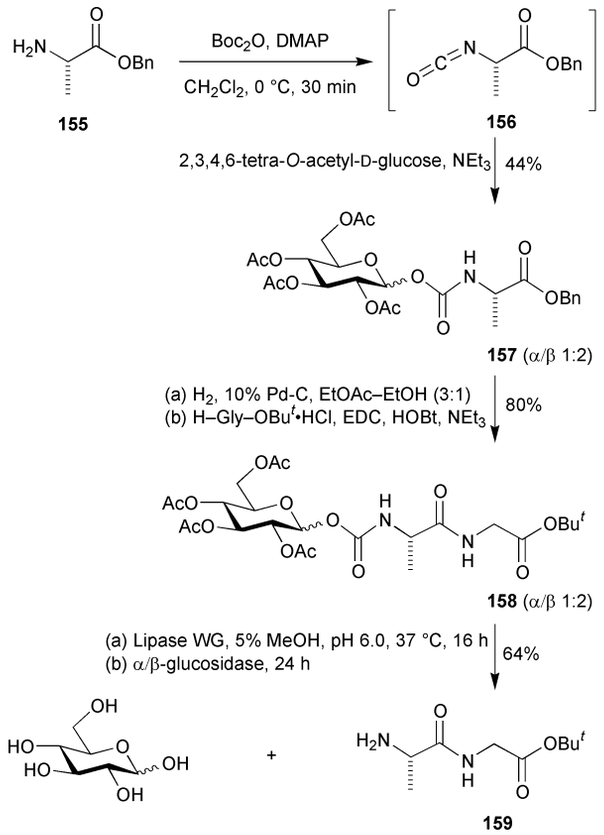
The trimethylsilylethyl system [*e.g.* the trimethylsilylethoxycarbonyl (Teoc) group for amines[128]] is a useful protecting moiety thanks to the mild conditions for deprotection using fluoride anion.[44,45] Recently Kunz and co-workers[129] reported that the (2-phenyl-2-trimethylsilyl)ethoxycarbonyl (Psoc) group, which incorporates a phenyl group in the α position relative to the silyl group, has higher reactivity towards fluoride-induced fragmentation leading to fewer side reactions. The Psoc group is stable under the usual conditions applied in peptide synthesis, *e.g.* using HATU–HOAt or TBTU–HOBt. An application of the new protecting group in peptide synthesis is illustrated in Scheme 87.



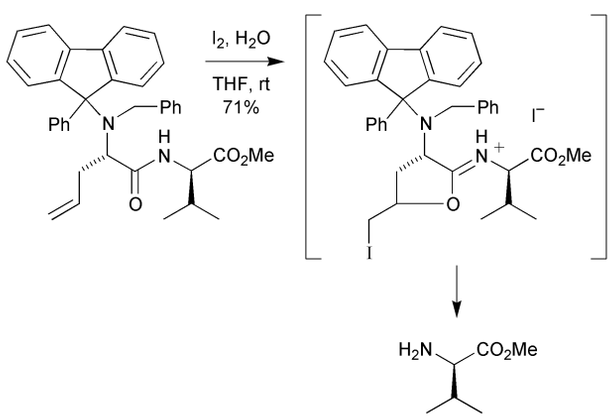
Scheme 87

Protection of the *N*-terminus of peptides as their tetra-*O*-acetyl-D-glucopyranosyloxycarbonyl and tetra-*O*-acetyl-D-galactopyranosyloxycarbonyl urethane derivatives affords a very mild method for deprotection using two tandem biotransformations.[130] The method is illustrated in Scheme 88. L-Alanine benzyl ester was converted to its isocyanate derivative **156** which was treated with 2,3,4,6-tetra-*O*-acetyl-D-glucose to afford the urethane **157** in 44% yield. After hydrogenolysis of the benzyl ester, peptide chain elongation using glycine *tert*-butyl ester afforded the dipeptide **158**. Cleavage of the urethane protecting group was accomplished in two steps: first, the 4 acetyl groups were hydrolysed using a lipase and then the glycosidic bond was cleaved with α/β-glucosidase to afford **159** in 64% yield. A synthesis of the tetrapeptide, L-leucyl-L-seryl-L-prolyl-*O*-(*tert*-butyl)-L-serine *tert*-butyl ester using the tetra-*O*-acetyl-D-galactopyranosyloxycarbonyl urethane established that a *tert*-butyl ester could be cleaved with TFA in 98% yield without detriment to the glycosidic bond.

N-Acylation of racemic amino acids with *N*-benzyl-*N*-(9-phenylfluoren-9-yl)-(*S*)-2-aminopent-4-enoic acid affords diastereoisomeric amides that are easily separated by column chromatography.[131] The degree of separation does not depend on the side chain substitution of the amino acid. The amino acid is then recovered by treatment of the amide with iodine and water as illustrated in Scheme 89.



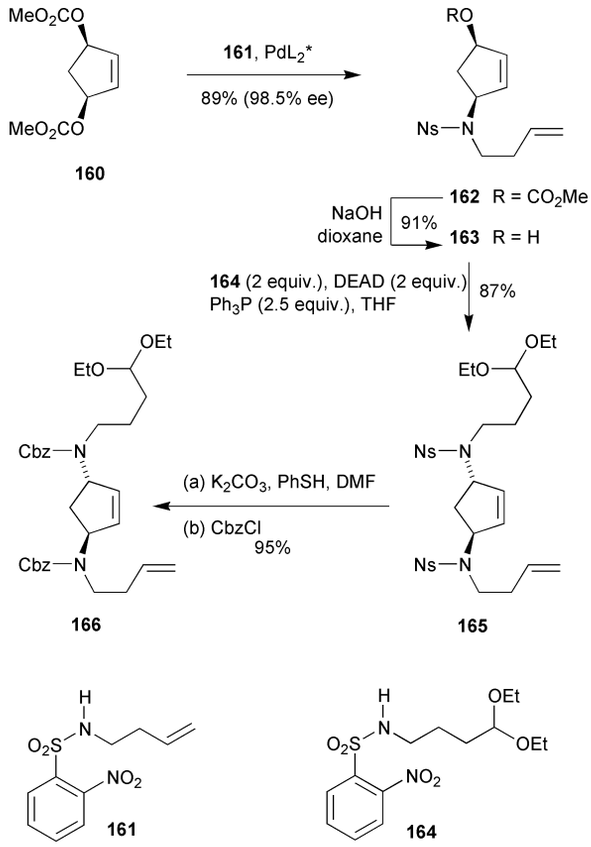
Scheme 88



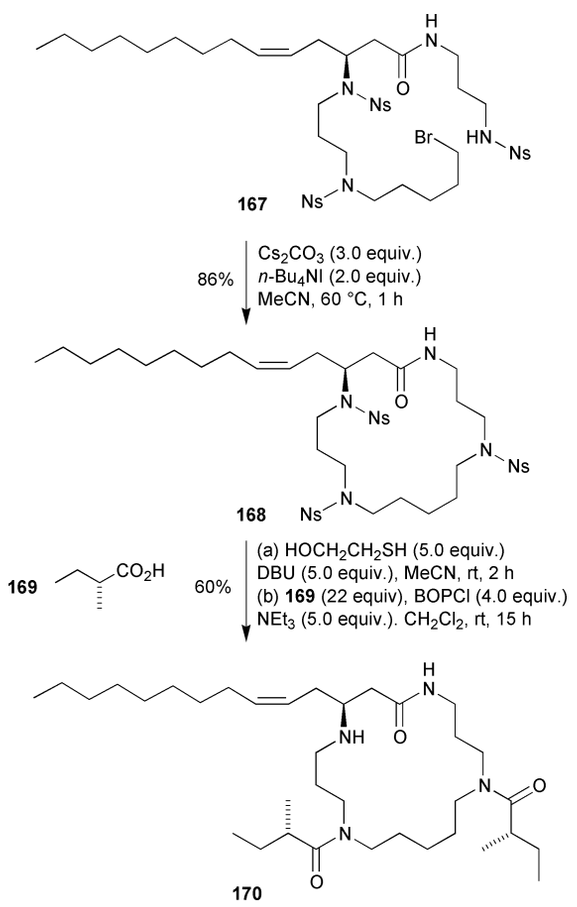
Scheme 89

A synthesis of the tetraponerines by Stragies and Blechert uses the *o*-nitrobenzenesulfonamide group in its dual role as a protecting group and as an activator for the N–H bond.[132] In the first step (Scheme 90), a Pd(0)-catalysed asymmetric allylic alkylation of the *o*-nitrobenzenesulfonamide **161** using the dicarbonate **160** gave the monoalkylation product **162** in 89% yield (98.5% ee). After hydrolysis of the remaining carbonate group, a Mitsunobu reaction using the *o*-nitrobenzenesulfonamide **164** as the nucleophile gave the bis-sulfonamide **165**. Transprotection of the two *o*-nitrobenzenesulfonamide groups to the corresponding Cbz groups occurred in one pot using first, mild cleavage with thiophenol and potassium carbonate, followed by addition of CbzCl to give **166** in 95% yield.

Lipogrammistatin A (**170**, Scheme 91) is isolated from the skin mucus of grammitised fish. Fukuyama and co-workers[133] accomplished an efficient synthesis of **170** in which the *o*-nitrobenzenesulfonamide group served as both an activator and protecting group. Thus, upon heating a mixture of sulfonamide **167**, tetrabutylammonium iodide and caesium carbonate in acetonitrile, cyclisation occurred to give



Scheme 90



Scheme 91

168 in 86% yield. After removal of the three Ns groups in **168** with excess mercaptoethanol and DBU, the resultant triamine was selectively diacylated with (*S*)-2-methylbutyric

acid (**169**) and BOPCl to give **170** in 60% overall yield from **168**.

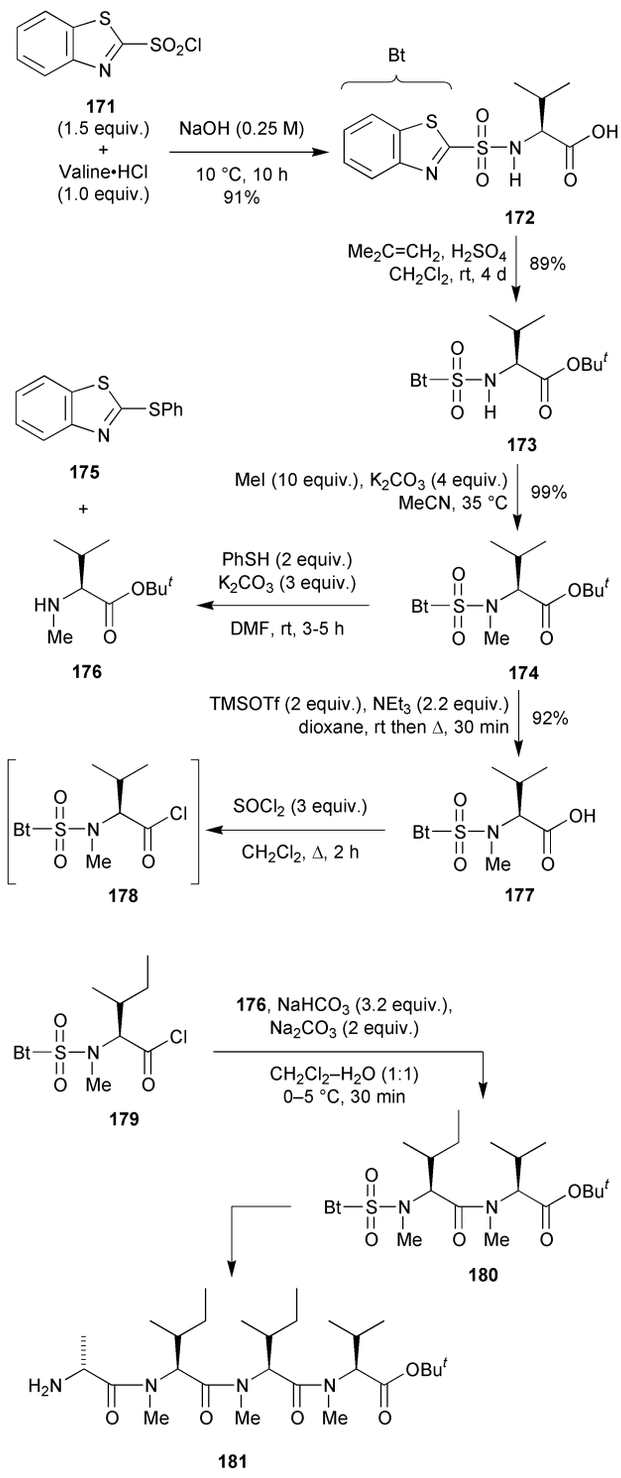
Vedejs and Kongkittingam reported a protocol for the solution-phased synthesis of hindered *N*-methylated peptides based on the use of the benzothiazol-2-ylsulfonyl group as both a protecting and activating group.[134] The relevant chemistry is depicted in Scheme 92 using valine as a prototypical amino acid. Thus, *N*-protection of valine with benzothiazol-2-ylsulfonyl chloride (**171**) under Schotten–Baumen conditions gave the sulfonamide derivative **172** in 91% yield. The corresponding *tert*-butyl ester **173** was then *N*-methylated using iodomethane and potassium carbonate in 99% yield. The benzothiazol-2-ylsulfonyl activating group was removed under mild conditions by simply treating **174** with thiophenol and potassium carbonate to give *N*-methylvaline *tert*-butyl ester **176** and 2-phenylthiobenzothiazole **175**. The benzothiazol-2-ylsulfonyl protecting group was then used to prepare the amino acid chloride **178** in two steps beginning with the removal of the *tert*-butyl ester with TMSOTf in refluxing dioxane followed by reaction of carboxylic acid **177** with thionyl chloride. The isoleucine acid chloride **179**, prepared in an analogous fashion, was coupled with **176** under mildly basic conditions to give the dipeptide **180**. After deprotection of **180** with thiophenol, two further cycles produced the tetrapeptide **181** corresponding to cyclosporin 8–11 tetrapeptide subunit **181**. A major benefit of this route is the easy purification of the product peptides using simple extraction methods rather than chromatography or solid-phase techniques.

A general method for the attachment of a chiral β-phenylalanine to a polymer support using a traceless silyl linker has been developed[135] that exploits the *tert*-butylsulfinyl group as both a chiral auxiliary and a Boc-surrogate.[136] The chiral auxiliary role is manifest in the first step shown in Scheme 93 in which an asymmetric addition of the titanium enolate **183** of methyl acetate to the *tert*-butylsulfinyl imine **182** occurs in 79% yield (dr 99 : 1). Hydroboration of the terminal alkene in **184**, followed by a Suzuki coupling of the borane intermediate with bromopolystyrene, gave the polymer-bound β-amino acid derivative **185** from which the *tert*-butylsulfinyl group was removed on brief treatment with 50% TFA in dichloromethane to give the dipeptide **186**. After further elaboration to a tripeptide intermediate, the product was cleaved from the solid support by treatment with 50% TFA in dichloromethane for 24 h.

A robust *N*-MOM group installed early in a synthesis of gelsemine survived 11 steps before it was severed with TMSI generated *in situ* from TMSCl and NaI in the penultimate step (Scheme 94).[137]

Catalytic transfer hydrogenation using 10% Pd/C in the presence of cyclohexa-1,4-diene as the hydrogen donor selectively cleaves tertiary benzylamines and reduces alkenes while leaving benzyl and benzyloxymethyl (BOM) ethers intact (Scheme 95).[138] The reaction is cleaner when conducted in the presence of acetic acid. Selective cleavage of benzylamines in the presence of benzyl ethers using catalytic hydrogenation is known[139–141] as is selective reduction of alkenes in the presence of benzyl ethers.[142]

Oxidative cleavage of tertiary, acyclic tri-, di- and mono-*N*-benzylamines can be effected with CAN (2.1 equiv.) in aqueous acetonitrile.[143] The reaction fails in the presence of *N*-Me or *N*-Et groups, and it fails when the *N*-atom is embedded in a ring. Unbranched *N*-benzylic substituents cleave preferentially over α-branched *N*-benzylic substituents. *N*-Benzyl secondary amines are inert to further oxidation. The oxidative cleavage reaction is chemoselective: *N*-benzyl deprotection occurs in the presence of *N*-benzyl amides, *O*-benzyl ethers, *O*-benzyl esters, *O*-benzyl phenolates and *S*-benzyl ethers. Oxidation of tertiary *N*-benzyl-*N*-4-methoxybenzyl-substituted amines is indiscriminate suggesting that initial single electron oxidation by CAN occurs at the tertiary nitrogen rather than the arene ring of



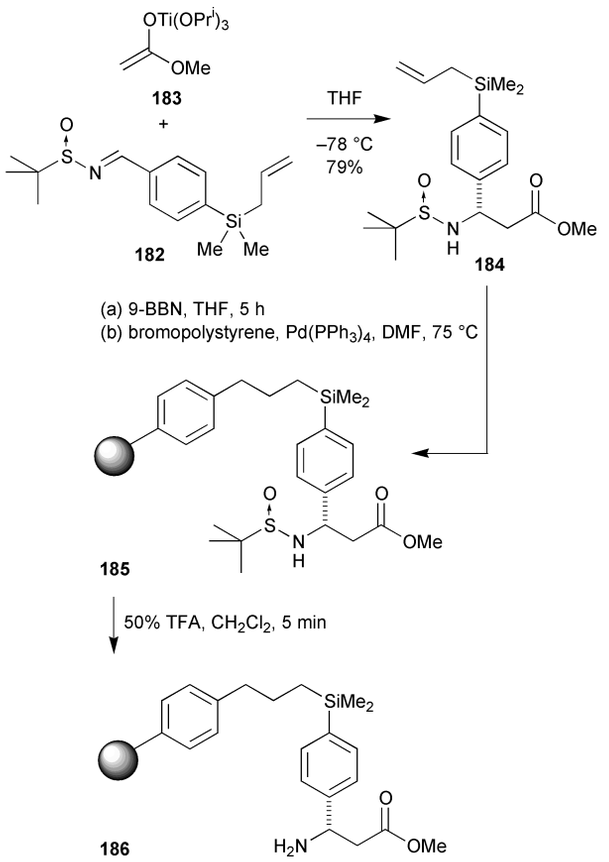
Scheme 92

the *N*-benzyl substituent. Scheme 96 illustrates the potential efficiency and selectivity of the reaction.

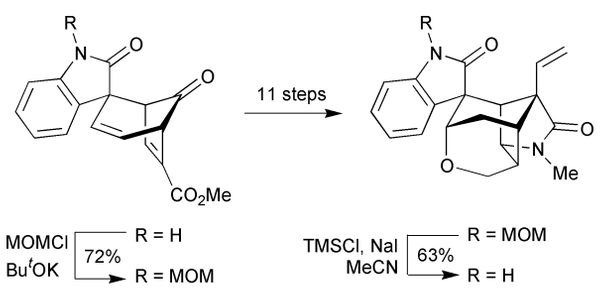
CAN or DDQ perform selective mono-debenzylation of tertiary amines with two benzyl substituents.[144] In the case of dienylamine **187**, which has a homoallylic C–N bond (Scheme 97), only DDQ can be used, whereas CAN leads to fragmentation. Mono-benzyl tertiary and dibenzyl secondary amines are inert towards both reagents.

Ytterbium triflate catalyses the deprotection of *N*- and *O*-trityl derivatives at room temperature in the presence of water (1 equiv.) (Scheme 98).[145] *N*-Boc, *O*-TIPS, methylene acetals and pentafluorobenzyl esters are not affected.

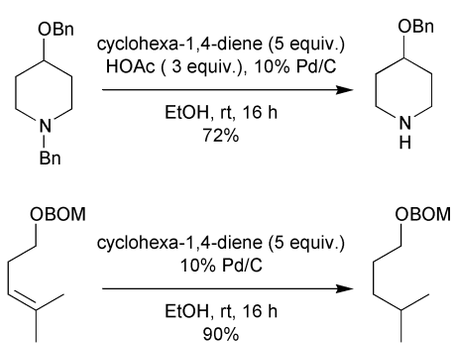
The final step in a very brief synthesis of (−)-spirotryprostatin B **190** (Scheme 99) required the cleavage of the *N*-SEM group from the spiroindolone **188**.[146] After some



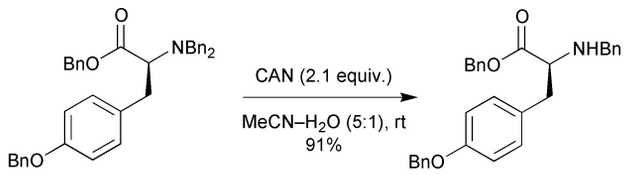
Scheme 93



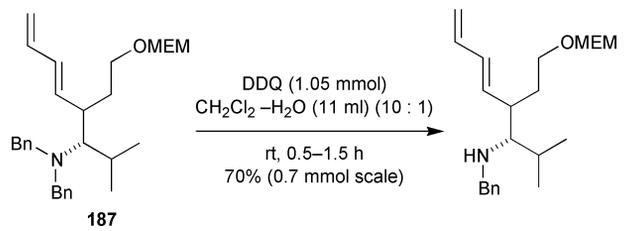
Scheme 94



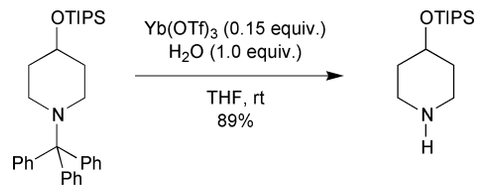
Scheme 95



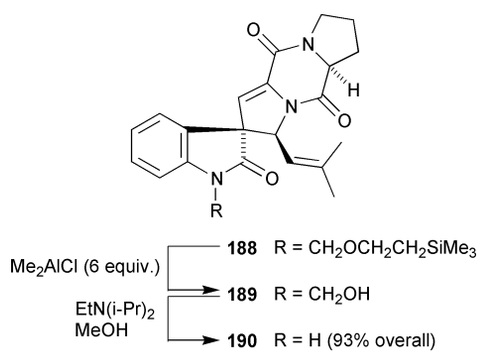
Scheme 96



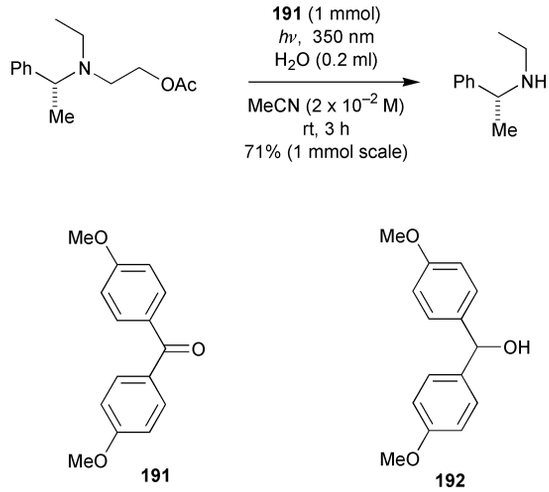
Scheme 97



Scheme 98



Scheme 99



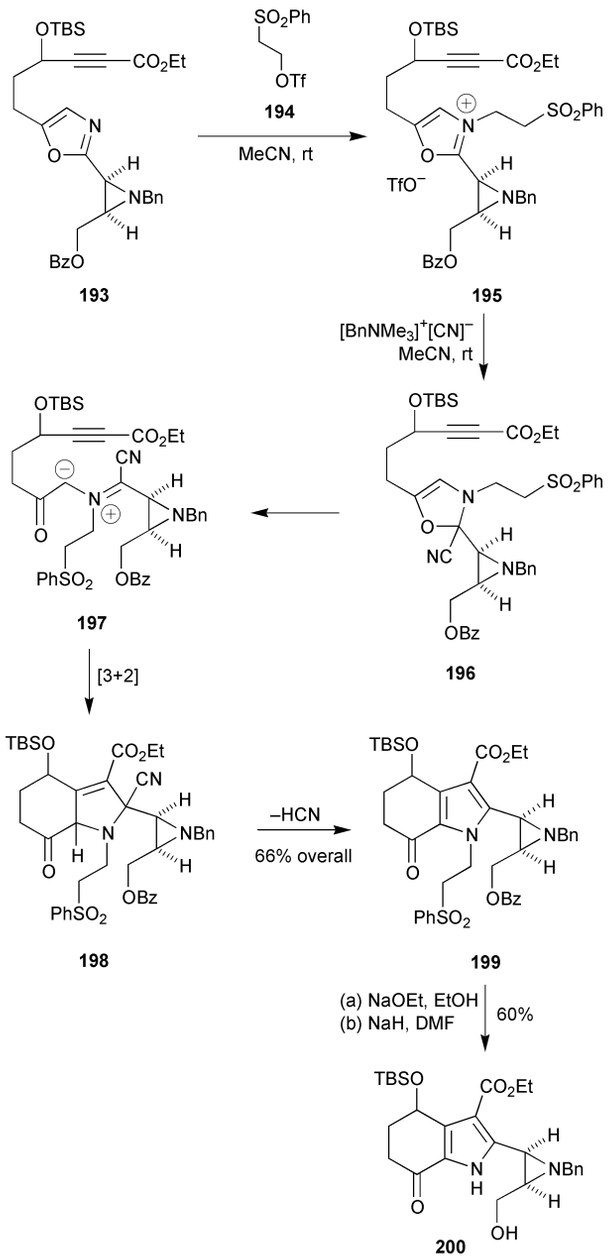
Scheme 100

experimentation, the *N*-SEM group was discharged in high yield by initial exposure to Me_2AlCl (6 equiv.) followed by heating the resultant *N*-hydroxymethyl derivative **189** with diisopropylethylamine in MeOH to remove the unit of formaldehyde.

The *N*-(2-acetoxyethyl) protecting group can be cleaved photochemically on irradiation at 350 nm in the presence of 4,4′-dimethoxybenzophenone (**191**) in wet acetonitrile.[147] The irradiation is performed in a Rayonet RPR-200 photoreactor equipped with six low-pressure mercury lamps (RPR-3500A, 350 nm, 24 W). No epimerisation is observed when a chiral amine is used (Scheme 100). The deprotection is accompanied by the reduction of 4,4′-dimethoxybenzophenone to the corresponding alcohol **192**. The process is limited to tertiary amines as secondary amines are recovered unchanged.

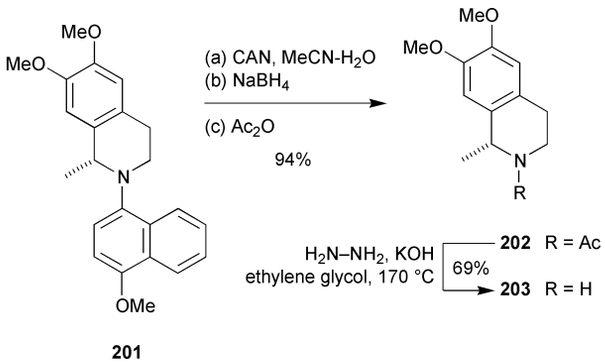
A synthetic approach to aziridinomitosene derivatives[148] based on the intramolecular [3 + 2]-cycloaddition of azome-

thine ylides to alkynyl esters, exploited the rarely used 2-(phenylsulfonyl)ethyl group[149,150] as both an activator and an *N*-protecting group. The sequence (Scheme 101) began with the selective *N*-alkylation of the oxazole ring **193** in the presence of the aziridine using 2-(phenylsulfonyl)ethyl triflate **194** (mp 63–64 °C), which is prepared from the corresponding alcohol in 86% using triflic anhydride and pyridine. Addition of an excess of benzyltrimethylammonium cyanide to the quaternary ammonium salt **195** induced a sequence of reactions that gave the pyrrole derivative **199** in 66% overall yield. After ethanolysis of the benzoate ester in **199**, the 2-(phenylsulfonyl)ethyl group was removed by a β-elimination reaction with sodium hydride in DMF to give the free pyrrole **200** in 60% yield.



Scheme 101

The final stages of a synthesis of the tetrahydroisoquinoline alkaloid salsolidine[151] (**203**, Scheme 102) were impeded by difficulties with the oxidative cleavage of the *N*-4-methoxynaphthyl group in **201**. Treatment of **201** with CAN in aqueous acetonitrile failed to provide **203** in detectable yield owing to further reactions of the product **203** with the 1,4-naphthoquinone by-product. By adding sodium borohydride to the reaction mixture, the 1,4-naphthoquinone was reduced to the corresponding naphthalene-1,4-diol thereby allowing isolation of salsolidine in 94% yield as its acetamide **202**.



Scheme 102

Chirally modified glycinimide derivatives are useful and common reagents for the asymmetric synthesis of α-amino acids. In most of the examples reported so far, the amino group is converted to an imine that serves the dual role of protector and activator of the α-position. A recent brief survey of chirally modified glycinimide derivatives reveals two distinct types of reagents. In the first type, exemplified by reagents **204**[152] and **205**,[153] the chiral auxiliary and the protecting group are one and the same. In the second group, exemplified by reagents **206**[154] and **207**[155] the roles of chiral auxiliary and amino protector are played by two different appendages. In the latter type, the diphenylmethyleneimino group has been a common feature owing to its ease of introduction and hydrolysis. A new type-2 reagent (**211**) has been explored by Guillena and Nájera[156] based on 1,5-dimethyl-4-phenylimidazolidin-2-one as the chiral auxiliary. Scheme 103 depicts the synthesis of **211** and illustrates its use in an asymmetric alkylation reaction. The glycinimide intermediate **210** was converted to its diphenylmethyleneamino derivative **211** using diphenylmethanimine ($Ph_2C{=}NH$) by the procedure of O'Donnell and Polt.[157]

9 Miscellaneous protecting groups

A synthesis of the kedarcidin core structure foundered temporarily because the TBS groups located on the alkyne termini in **214** (Scheme 104) could not be cleaved with TBAF owing to concurrent elimination of hydrogen bromide to give the corresponding tetrayne.[158] The undesired elimination could be suppressed by buffering the reaction with a phenol. Under optimum conditions, treatment of **214** with TBAF and 2-nitrophenol ($pK_a = 7.22$) in THF at 0 °C followed by slow warming of the reaction mixture to room temperature over 17 h afforded the desired triyne product **215** in 87% yield. The efficacy of the acidic buffer was strongly dependent on acidity. Thus phenol ($pK_a = 10$) or *p*-bromophenol ($pK_a = 8.42$) led to greater amounts of elimination, whereas more acidic additives such as 2,6-dichlorophenol ($pK_a = 6.79$) or pentachlorophenol ($pK_a = 4.4$) retarded the rate of desilylation to the point of impracticality.

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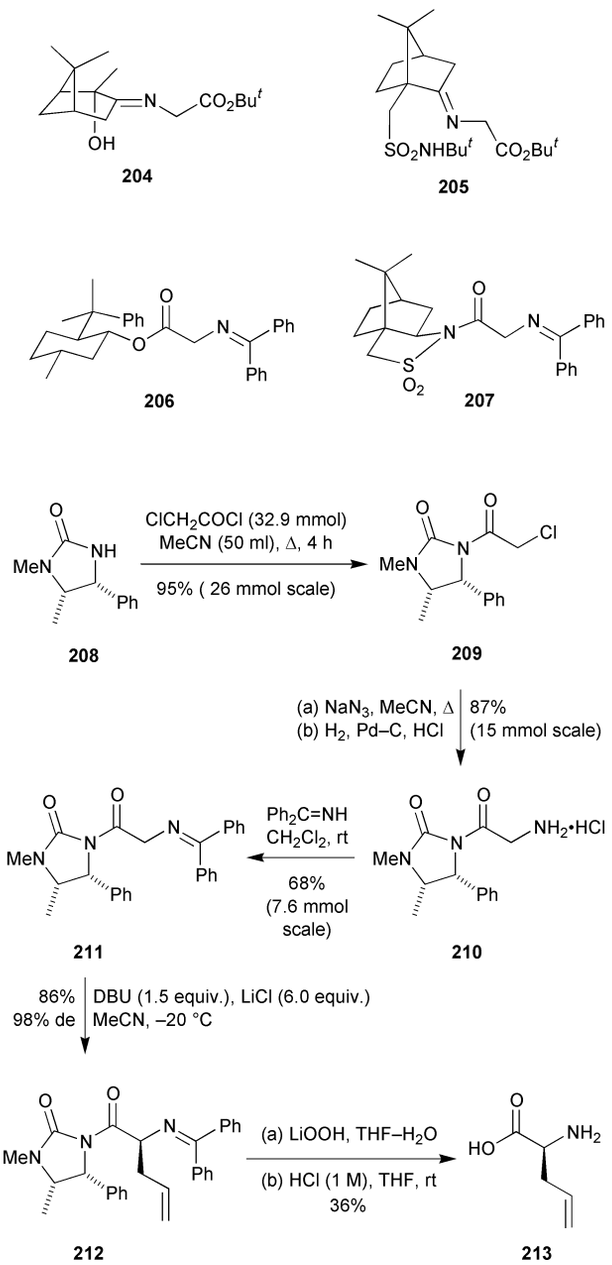
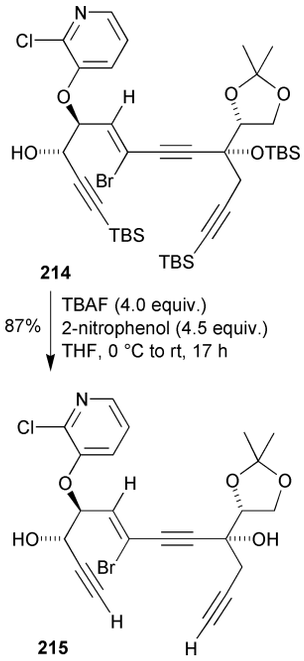


Scheme 103



Scheme 104

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