Protecting groups

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Reviewing the literature published in 1996
Continuing the coverage in *Contemporary Organic Synthesis*, **1996**, *3*, 397

1 Introduction

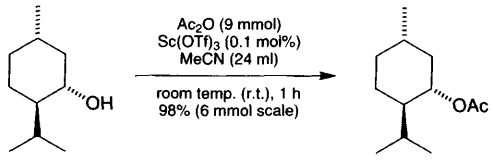
Our chronicle of the triumphs and tribulations of protecting group chemistry follows the pattern set in our previous reviews with one exception: our coverage of solid phase linker chemistry has been curtailed because the volume of work published on solid phase synthesis has expanded to the point where it is no longer feasible to do justice to the subject in a single review. Therefore, a separate review dedicated exclusively to solid phase synthesis has been prepared by Dr R. Brown (*Contemp. Org. Synth.*, 1997, **4**, 216).

Other recently published reviews in the area of protecting group chemistry are given in Section 10.

2 Hydroxy protecting groups

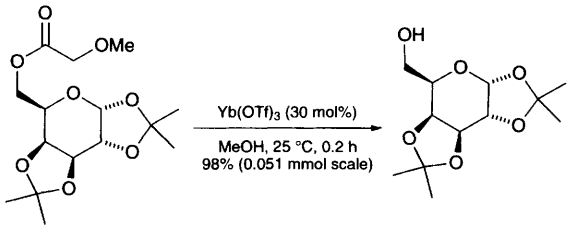
2.1 Esters

Yamamoto and co-workers have demonstrated[1] that commercially available scandium trifluoromethanesulfonate (triflate) is a remarkably active acid catalyst for the acylation of alcohols with acid anhydrides (**Scheme 1**). Its catalytic activity is higher than other acylation catalysts such as 4-dimethylaminopyridine–triethylamine or tributylphosphine. This, according to the authors, makes scandium triflate the most effective acylation catalyst reported to date. However, its acidic properties take their toll—in the case of allylic and some tertiary alcohols, migration or elimination by-products are observed.



Scheme 1

Inanaga and co-workers have developed a new method for the deprotection of the methoxyacetyl group, in which ytterbium(III) triflate acts as a Lewis acid catalyst in methanol to promote the transesterification[2] (**Scheme 2**). The methoxyacetyl group can be removed selectively in the presence of cohabiting acetate and benzoate groups but also such acid-labile ether protecting groups as tetrahydropyranyl (THP), *tert*-butyldimethylsilyl (TBS), *tert*-butyldiphenylsilyl (TBDPS), and methoxyethoxymethyl (MEM) ethers. The catalyst can be recovered easily and reused without serious loss of its catalytic activity.



Scheme 2

Xu and co-workers[3] have reported that magnesium methoxide in methanol cleaves esters affording the corresponding alcohols in good yields. Selective deprotection was possible and the order of reactivity of different esters was found to be: *p*-nitrobenzoate > acetate > benzoate > pivaloate > > acetamide.

As part of a programme aimed at the development of serodiagnostics and synthetic vaccines based on carbohydrates, the van Boom group[4] investigated the synthesis of tetrameric fragments corresponding to the cell wall phenolic glycolipids of *Mycobacterium kansasii* serovars II and IV. A key issue in the synthesis was the construction of an α-glycosidic link between a 1-thio-α-D-mannopyranoside donor and

an L-fucopyranoside acceptor using *N*-iodosuccinimide and TfOH. The authors found that the efficiency and stereoselectivity of the glycosylation was strongly dependent on the protecting group at C-2 in the mannoside donor. The 2-dibromomethylbenzoyl group, first developed by Reese and co-workers[5] in 1979, proved especially efficacious as shown in **Scheme 3**. Not only did it aid the twin tasks of efficient and stereoselective glycosylation, but it was also easily cleaved without incident to the 4-*O*-acetyl group in the fucosyl moiety. The cleavage was accomplished with silver perchlorate in aqueous acetone to give the 2-*O*-(2-formyl)benzoyl derivative **1** which was then treated with morpholine to complete the deprotection.

Recombinases and topisomerases cleave DNA into two shorter strands by nucleophilic attack of a tyrosine hydroxy on an internucleotide phosphodiester to give one strand bound to the enzyme *via* a tyrosine phosphodiester and another free strand. The process can reverse and the two strands recombine or the 5′-hydroxy of a different free oligonucleotide strand can attack the phosphoryltyrosine. For a study of the strand-joining reactions catalysed by recombinases and topoisomerases, a solid phase synthesis of oligonucleotides terminated by 3′-phosphoryltyrosine was developed which began with the release of the phenolic hydroxy function of a tyrosine protected as its levulinate ester[6] (**Scheme 4**). The relay deprotection was initiated by mild reduction of the keto group of the levulinate ester **2** by sodium borohydride. The resultant hydroxy ester **3** underwent intramolecular transesterification. The free hydroxy of tyrosine then assumed the role of the first 5′-hydroxy in a standard solid phase oligonucleotide synthesis.

An improved solid phase support has been prepared for oligonucleotide synthesis which exploits the *o*-nitrobenzyl intramolecular photochemical redox reaction to accomplish retrieval of the oligonucleotide from the solid support.[7] A synthesis of the primed support is shown in **Scheme 5**.

The 2-(trimethylsilyl)ethyl ester protecting group was crucial because it was easily cleaved in the presence of the acid-labile dimethoxytrityl (DMTr) group and the hydrolytically labile carbonate in **8**. A salient virtue of the new photolabile linker in **10** was its rapid and easy scission using a commonly available source of UV light (365 nm) under conditions which cause minimal photodamage.

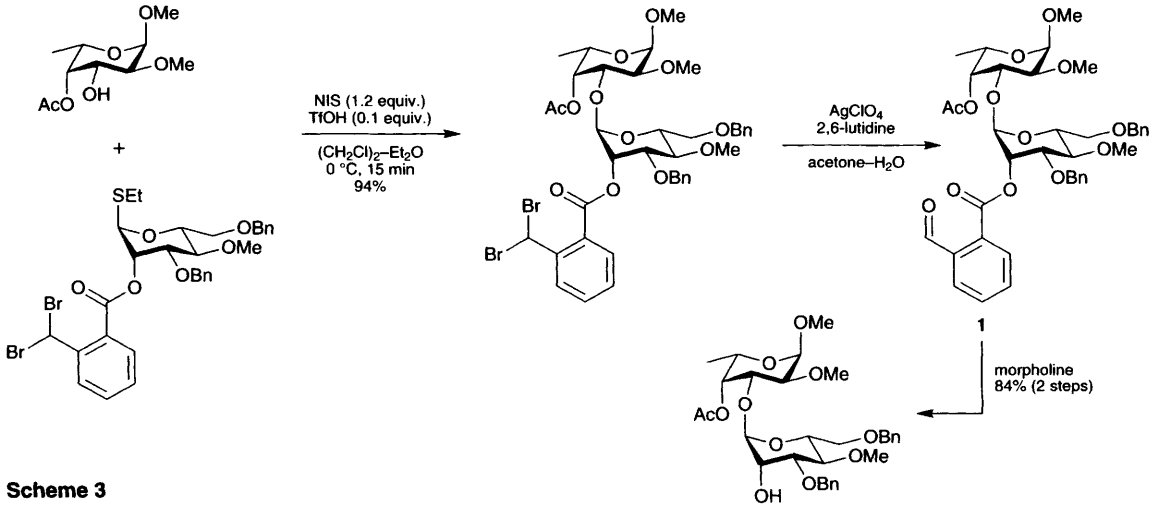
2.2 Silyl ethers

Ammonium fluoride was used twice[8] to deprotect TBS ethers during a synthesis of the antifungal agent FR-900848. The second deprotection, involving the sensitive pentacyclopropane **11** (**Scheme 6**) was accomplished in over 49% yield on treatment with 20 equiv. of ammonium fluoride. Attempts to use TBAF were accompanied by problems with purification.

Friesen and Trimble investigated the site selectivity in the α-silyl lithiation of TBS groups which competes with the metallation of the enol ether in 3,4,6-tris-(*O*-*tert*-butyldimethylsilyl)-D-glucal (**13**) using Bu^{t}Li as the base[9] (**Scheme 7**). Metallation of **13** with 4 equiv. of Bu^{t}Li followed by a D_2O quench returned **15** with the percentages of deuterium incorporation shown. In the case of 3,4-bis-*O*-(*tert*-butyldimethylsilyl)-6-deoxyglucal derivative (**14**), α-silyl metallation at the C-4 TBS was a very minor pathway leading to **16**.

During a synthesis of heptaamino acid substituted β-cyclodextrins, Stoddart and co-workers[10] converted the primary OTBS groups in **17** directly to the corresponding bromoalkane **18** using $Ph_3P{\cdot}Br_2$ according to the procedure of Palomo and co-workers[11] (**Scheme 8**).

Wilson and Keay reported the cleavage of silyl protected [TBS, triethylsilyl (TES) and TMS] phenols by treatment with catalytic amount of $PdCl_2(MeCN)_2$ in refluxing acetone containing 5 equiv. of water.[12] The procedure does not require an aqueous workup.



Scheme 3

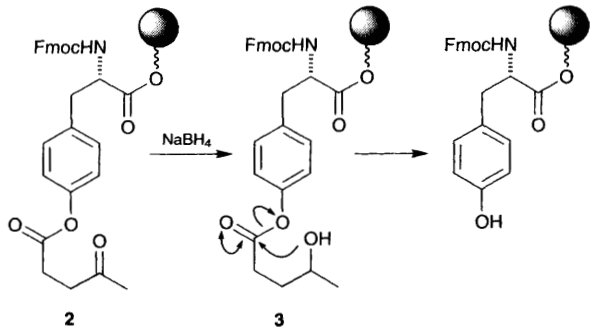
The final step in a recent synthesis of the antifungal agent paulacandulin D involved deprotection of five *O*-silyl groups including a TES group, a di-*tert*-butylsilylene group and two phenolic triisopropylsilyl (TIPS) ethers[13] (**19**, **Scheme 9**). Acid conditions were precluded by the acid lability of the side chain. Use of TBAF was complicated by problems in separating the product from tetrabutylammonium salts. However, the desired global deprotection was accomplished with tris(dimethylamino)sulfonium difluorotrimethylsilicate (TASF).

Johnson and Taubner reported[14] that *N,O*-bis(*tert*-butyldimethylsilyl)acetamide (BTBSA) can be used for efficient *tert*-butyldimethylsilylation of alcohols (including tertiary and hindered secondary ones) in the presence of a catalytic amount of tetrabutylammonium fluoride (TBAF) or another source of fluoride. The procedure can be used for the selective protection of primary hydroxy groups in the presence of secondary ones (**Scheme 10**) and secondary in the presence of tertiary. However, the selective protection of 1,2-diols fails due to the migration of silyl group caused by the basic fluoride.

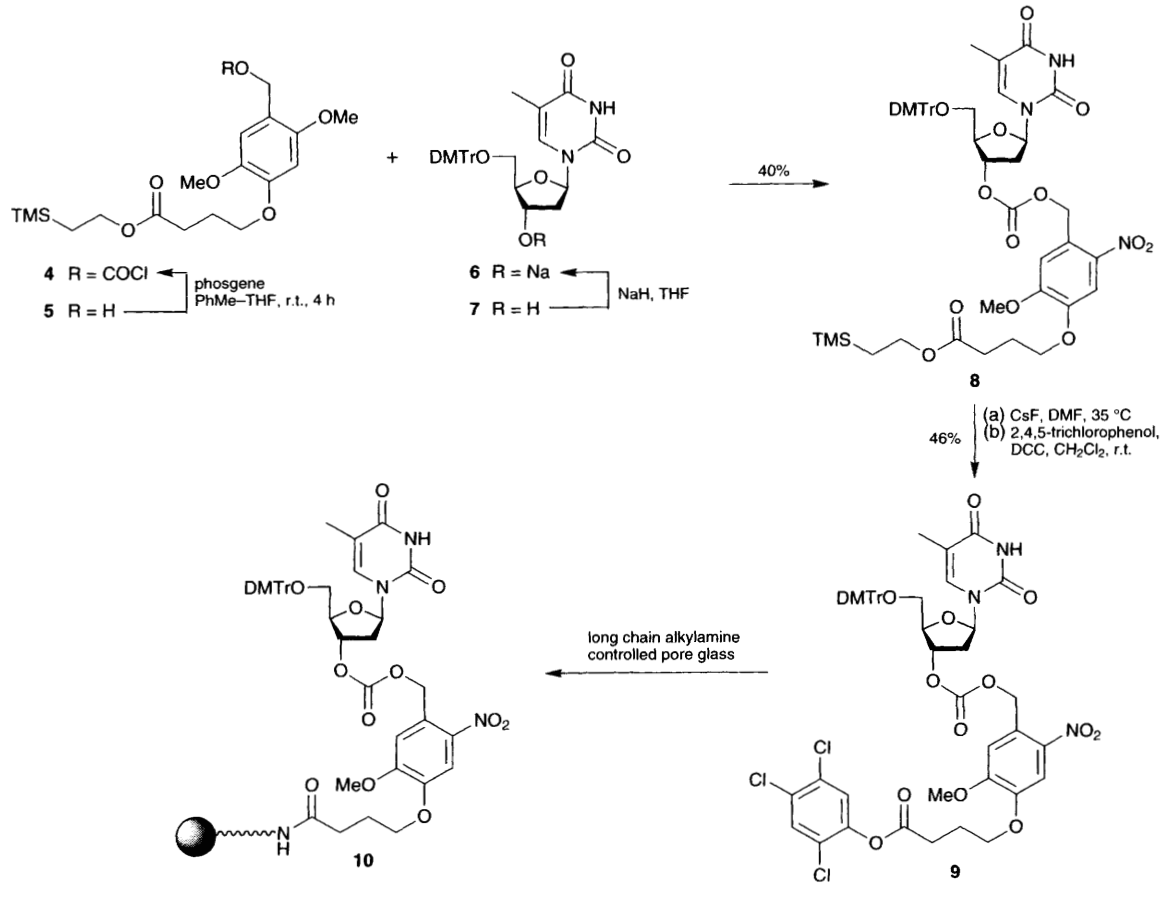
In a synthesis of carbocyclic thymidine analogues, a Ciba group[15] used *N*-*tert*-butyldimethylsilyl-*N*-methylacetamide[16] to accomplish the double silylation of the diol **20** (**Scheme 11**). The choice of this particular silylating agent was based on the results of extensive experiments on the corresponding bromo derivative which had proved difficult to silylate using standard conditions.

Singh and co-workers have reported[17] that TBS and THP ethers can be cleaved by brief treatment with ceric(IV) ammonium nitrate (CAN) in methanol at 0 °C. Primary TBS-protected alcohols can be deprotected selectively in the presence of THP ethers and ketals.

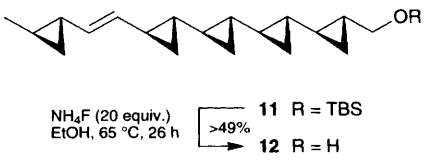
Oriyama and co-workers[18] described a one-step transformation of THP ethers into the corresponding silyl protected alcohols by reaction with trialkylsilyl trifluoromethanesulfonates followed by triethylamine. For example, the dialkylsilylene deriv-



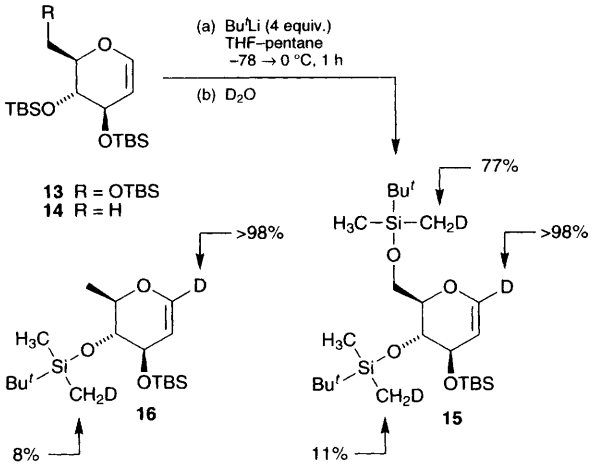
Scheme 4



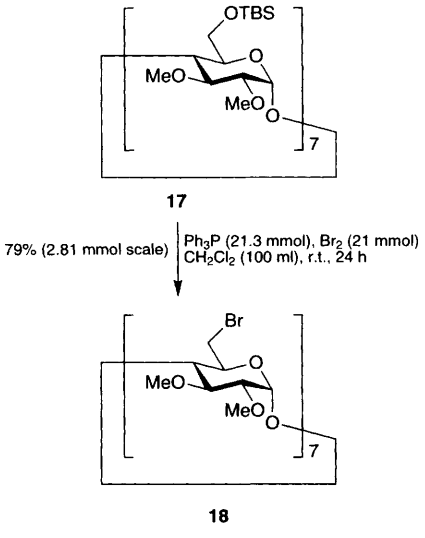
Scheme 5



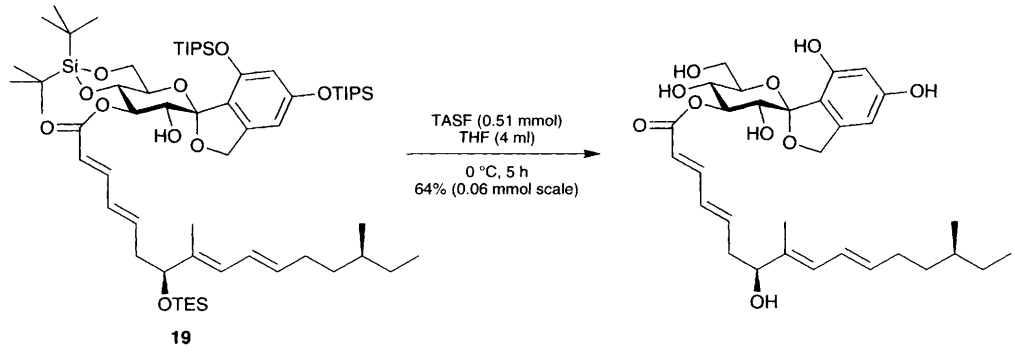
Scheme 6



Scheme 7



Scheme 8



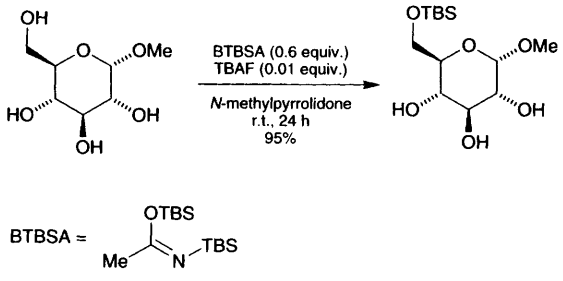
Scheme 9

ative of 1,3-diol **22** was obtained directly from the corresponding bis(tetrahydropyranyl ether) **21** (**Scheme 12**).

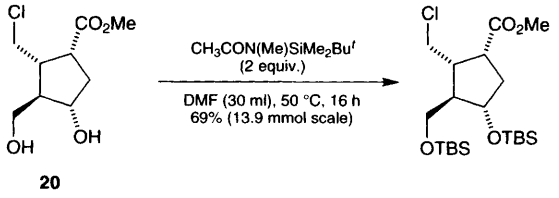
Selective deprotection of silyl ethers under mild conditions was a key feature in the closing stages of a synthesis of the macrolide antibiotic oleandomycin aglycon **27** (**Scheme 13**) by Evans and Kim.[19] First, the TIPS ether at C-13 was selectively removed in the presence of the C-9 TBS ether using triethylammonium fluoride. The triethylammonium fluoride was prepared from HF·pyridine complex and triethylamine. The excess base was removed *in vacuo* and the resultant white crystalline solid **24** was stored under argon. After macrocyclisation of diol **24**, the C-9 TBS ether was removed using HF·pyridine complex without detriment to the adjacent oxirane. After oxidation of the C-9 hydroxy, the synthesis was completed by removal of the benzylidene acetal using hydrogenolysis. The overall yield for the sequence was greater then 50%.

Protection of the C-17 hydroxy of the discodermolide intermediate **28** (**Scheme 14**) was problematic.[20] The TBS ether was stable to all deprotection conditions compatible with the molecule and the TES ether was too labile to survive subsequent steps. However, the diethylisopropysilyl ether (DEIPS) offered an increment of stability over the TES group and was subsequently cleaved, along with the three TBS ethers, using toluene-*p*-sulfonic acid in aqueous THF. The DEIPSOTf required for the conversion of **28** to **29** was prepared from DEIPSCl[21] and triflic acid.[22]

The Stork group pioneered the use of temporary attachment of two reactants through a tether in order to promote stereocontrolled intramolecular reaction. The method has been especially fruitful in the construction of β-mannopyranosides where the vicinal *cis* (axial) β-hydroxy group blocks access to the β-face. Recently Stork and La Clair[23] have reported further examples of the 'temporary silicon connection method' first reported in 1992 for the β-glycosidation of mannose derivatives *via* sulfoxide activation. We join the route (**Scheme 15**) after the tethering of the two monosaccharide units with dimethyldichlorosilane. Directed glycosidation occurred on treatment of the axial phenyl sulfoxide **30** with triflic anhydride.



Scheme 10



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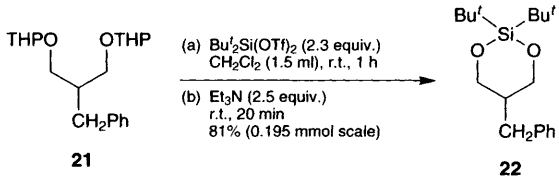
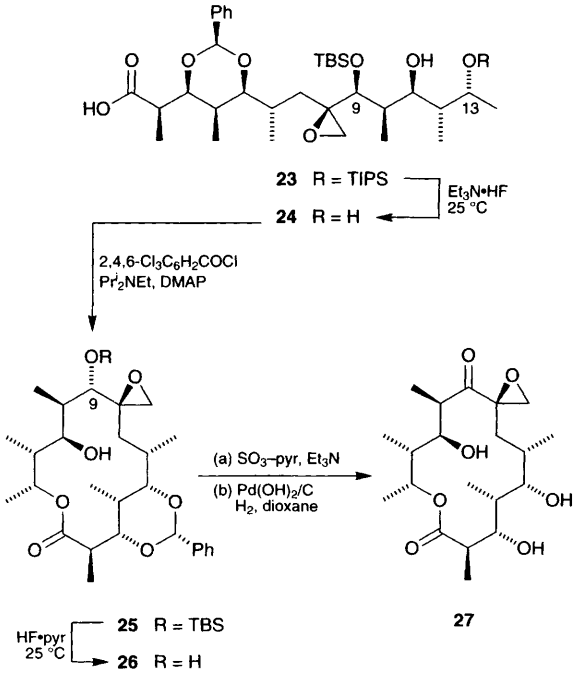
Scheme 11



21 **22**

Scheme 12



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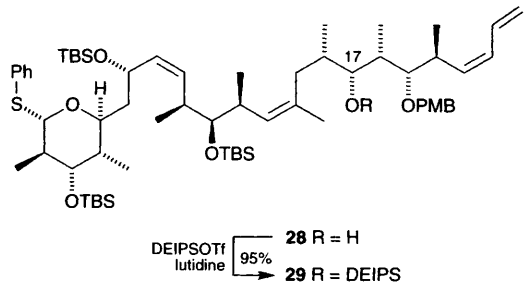
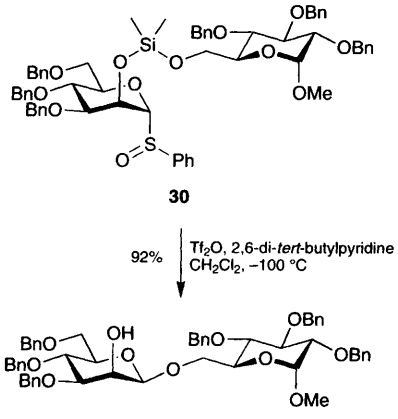
Scheme 13



Scheme 14



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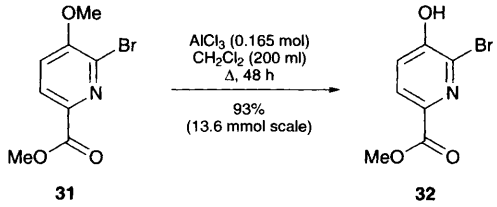
Scheme 15

2.3 Alkyl ethers

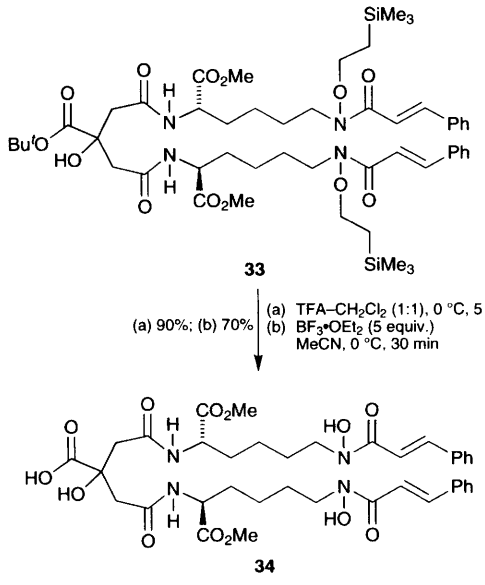
Attempts[24] to demethylate the methyl ether **31** (**Scheme 16**) using $AlCl_3$ and NaCl at 150 °C for 2 min[25] led to a clean reaction but both the methyl ester and the methyl ether were cleaved (98%). By using $AlCl_3$ alone in refluxing dichloromethane,[26,27] the desired pyridinol **32** was obtained in 93% yield after 48 h.



31 **32**

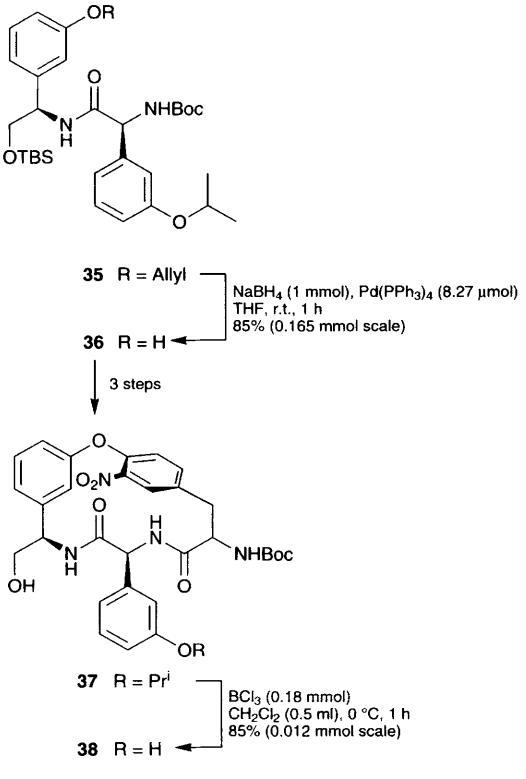
Scheme 16

During a recent synthesis of the siderophore nannochelin A (**34**, **Scheme 17**),[28] the hydroxamate residues were protected as their *O*-[2-(trimethylsilyl)ethyl] ethers **33**. To complete the synthesis, the *tert*-butyl ester in **33** was first cleaved with trifluoroacetic acid and the hydroxamic acid residues then freed with $BF_3 \cdot OEt_2$.



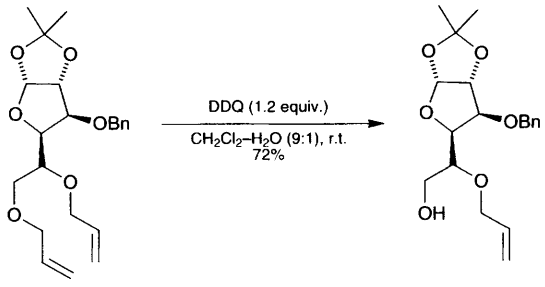
Scheme 17

A French group[29] has designed and synthesised modified carboxy binding pockets of the glycopeptide antibiotics vancomycin and teicoplanan. A key issue in their synthesis was the orthogonal protection of phenolic hydroxy groups and **Scheme 18** illustrates the use of allyl and isopropyl ethers *en route* to the advanced intermediate **38**. The mild conditions for the deprotection of allyl ether **35** are noteworthy.[30,31]



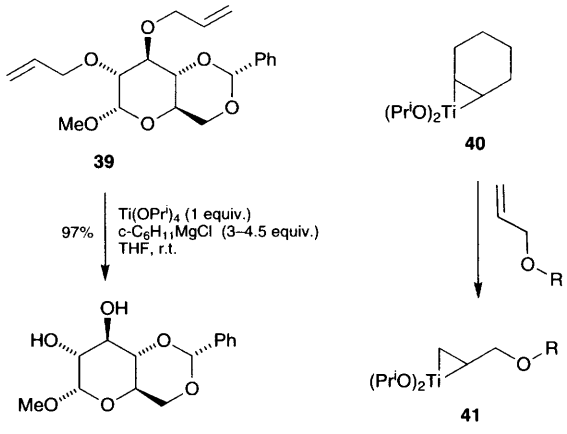
Scheme 18

Yadav and co-workers[32] have reported a new method for deprotecting primary allyl ethers using DDQ as oxidising reagent (**Scheme 19**). Secondary allyl ethers (including anomeric positions) as well as benzyl, acetoxy and TBS protecting groups remain intact under the reaction conditions.



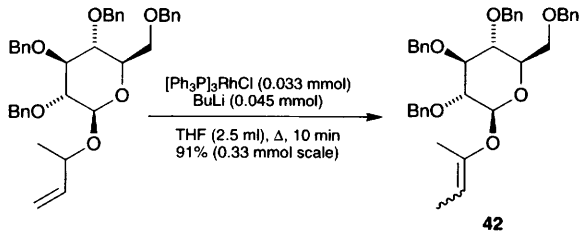
Scheme 19

Lee and Cha[33] described the selective cleavage of allyl ethers to alcohols by use of a reagent prepared from titanium(IV) tetraisopropoxide and commercially available Grignard reagents like *n*-butyl- or cyclohexyl-magnesium chloride. Neither benzylidene acetals (as in **39**) nor more highly substituted allylic ethers were affected under the reaction conditions (**Scheme 20**). This selectivity stems from the reaction mechanism which in the first step involves formation of the titanacyclopropane intermediate **40**. Ligand exchange with unsubstituted allyl ethers affords intermediate **41** which then undergoes β-elimination to give the deprotected alcohol.



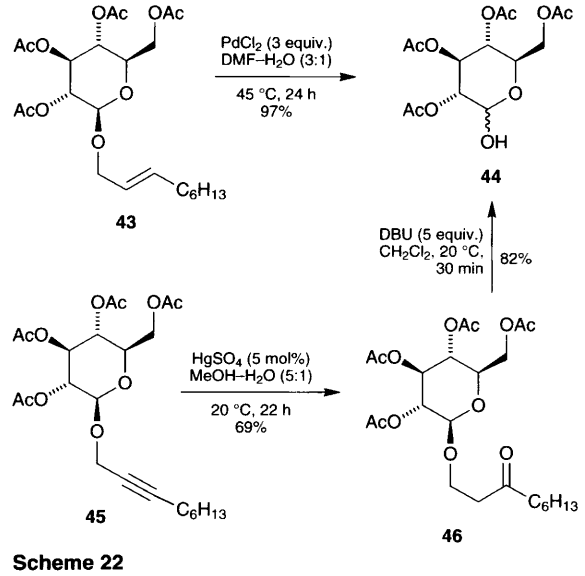
Scheme 20

The isomerisation of allyl ethers to enol ethers by Wilkinson's catalyst in refluxing aqueous ethanol, which is a typical first step in the deprotection of allyl ethers, is accompanied by reduction of the double bond to the propyl ether. However, treatment of $[Ph_3P]_3RhCl$ with BuLi results in a rhodium catalyst which is able to isomerise a wide range of substituted and unsubstituted allylic ethers without competing reduction.[34] In the example shown in **Scheme 21**, the crude enol ether **42** can be cleaved by treatment with $HgCl_2$–HgO in acetone to give the corresponding lactol in 93% yield.



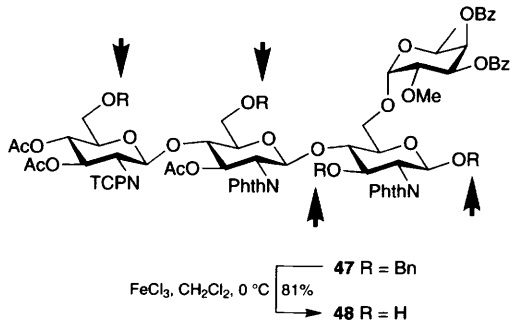
Scheme 21

A major obstacle in the synthesis of the moenomycin antibiotics is the insolubility of synthetic intermediates. The Welzel group[35] has addressed the problem of solubility by using lipophilic groups at the anomeric centre of saccharide intermediates. The deprotection conditions for two model examples are shown in **Scheme 22**. Thus, treatment of the nonenyl ether **43** with excess $PdCl_2$ in aqueous DMF returned glucose tetraacetate **44**. Alternatively, hydration of the nonynyl derivative **45** followed by base-catalysed elimination of the β-alkoxy ketone **46**, likewise returned **44** in 57% yield for the two steps. The alkyne-based protocol was extended to advanced moenomycin intermediates which displayed the requisite solubility characteristics.



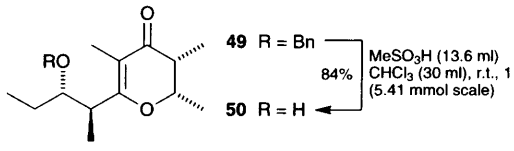
Scheme 22

Nodulation factors are secreted by bacteria as signalling devices that launch the early steps in the formation of root nodules in leguminous plants. The Fraser-Reid group[36] used ferric chloride to deprotect four benzyl ethers at a late stage of the synthesis of the complex tetrasaccharide **48** which is an intermediate in the synthesis of the nodulation factor produced by *Rhizobium fredii* (**Scheme 23**).The synthesis is also noteworthy for the use of the tetrachlorophthalimide group (TCP) to accomplish *N*-differentiation of the terminal glucosamine residue.



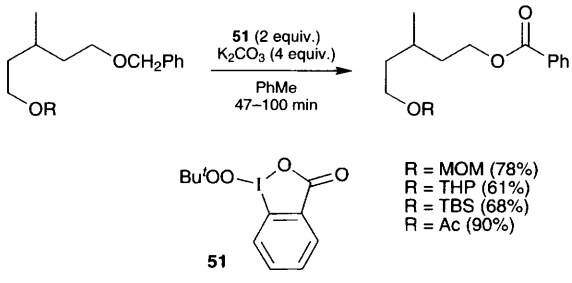
Scheme 23

In the closing stages of a highly stereoselective synthesis of the sex pheromone of the drugstore beetle *Stegobium paniceum*, Matteson and co-workers[37] found that debenzylation of the benzyl ether **49** could be conveniently accomplished with methanesulfonic acid in chloroform (**Scheme 24**).



Scheme 24

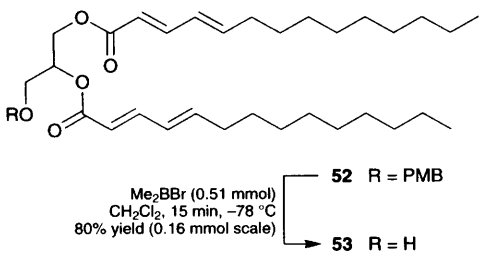
Oxidation of benzyl ethers to the corresponding esters by 1-(*tert*-butylperoxy)-1,2-benziodoxol-3(1*H*)-one (**51**) has been described by Ochiai and co-workers.[38] Since esters can be readily hydrolysed under basic conditions, this method provides a convenient alternative to the usual reductive deprotection. The reaction is carried out in the presence of alkali metal carbonates and the conditions are mild enough to be compatible with other hydroxy protecting groups such as methoxymethyl (MOM), THP, TBS and acetoxy (**Scheme 25**). Compound **51** can be also used for oxidation of allyl ethers; however, the yields are lower (40–60% for unsubstituted allyl groups).



Scheme 25

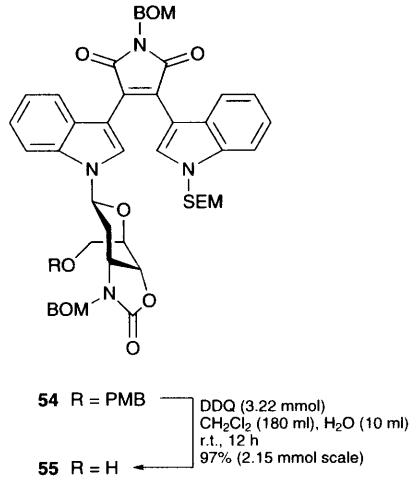
During their synthesis of polymerisable 1,2-diacylglycerols **53** (**Scheme 26**), O'Brien and co-workers[39] needed a suitable protecting group which could be removed in the presence of sensitive dienoyl groups. The *p*-methoxybenzyl (PMB) ether served this

purpose well and deprotection of **52** using Me_2BBr proceeded without migration of an acyl group or detriment to the polymerisable dienoyl group.



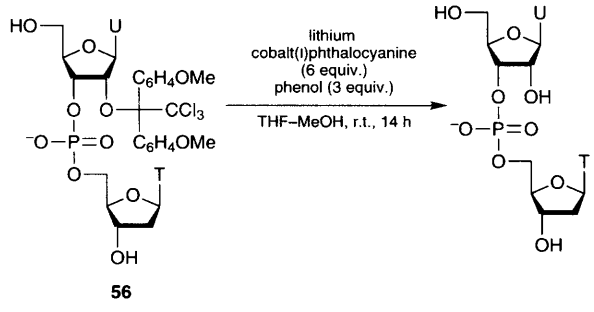
Scheme 26

A PMB ether was selectively cleaved from the indole glycoside **54** in the presence of *N*-SEM and *N*-BOM (benzyloxymethyl) groups (**Scheme 27**) using the standard oxidative conditions (DDQ).[40]



Scheme 27

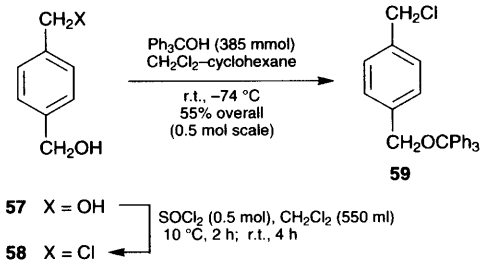
The 1,1-dianisyl-2,2,2-trichloroethyl (DATE) group has been used as a new 2′-hydroxy protecting group of ribonucleotides.[41] To exemplify the procedure, the dinucleotide **56** (**Scheme 28**) was constructed using a conventional DNA synthesiser and the DATE group cleaved quantitatively by lithium cobalt(I)phthalocyanine.



56

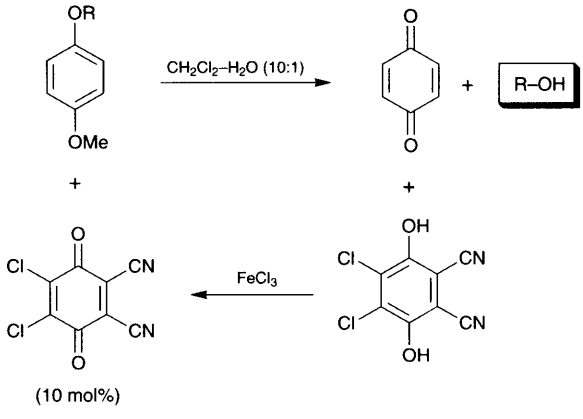
Scheme 28

During a synthesis of an HIV-1 protease inhibitor, protection of the alcohol function in **58** (**Scheme 29**) was complicated by the presence of a reactive benzylic chloride.[42] Although the trityl, MEM or silyl groups could be incorporated under standard basic conditions, considerable *O*-alkylation *via* the benzylic chloride competed leading to multiple products and low yields. However, acid-catalysed tritylation worked well. The optimum conditions involved monochlorination of diol **57** with thionyl chloride followed by immediate conversion of the crude benzylic chloride **58** to the trityl ether **59** using trityl alcohol and the residual HCl liberated during the chlorination step.



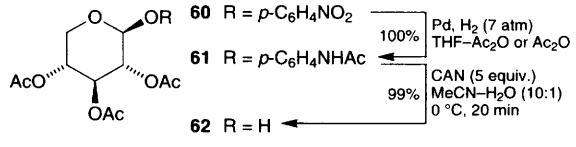
Scheme 29

4-Methoxy- and 3,4-dimethoxy-benzyl ethers can be deprotected with 10 mol% DDQ in dichloromethane–water (10:1) by using $FeCl_3$ (3 equiv.) to recycle the hydroquinone by-product[43] (**Scheme 30**). Acetate esters, TBS, MOM, THP, and benzylidene acetal groups survive.



Scheme 30

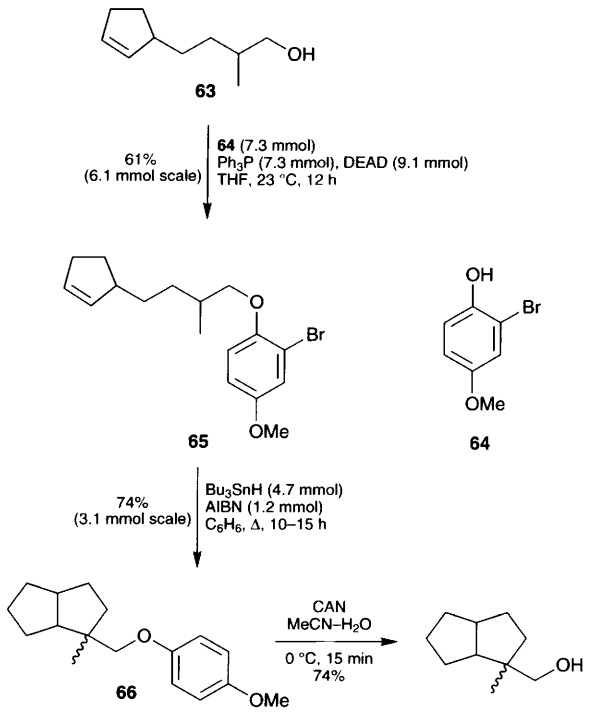
The use of the *p*-nitrophenyl group for anomeric protection of carbohydrates has been reported.[44] The protected glycosides (*e.g.* **60**, **Scheme 31**), which are easily prepared by the reaction of *p*-nitrophenol with acetylated glycosyl bromides, can be deprotected *via* hydrogenation to the corresponding acetamidophenyl glycoside **61** followed by oxidative cleavage with ceric ammonium nitrate (CAN).



Scheme 31

The 2-bromo-4-methoxyphenyl group has been introduced by Curran and co-workers[45] to act both

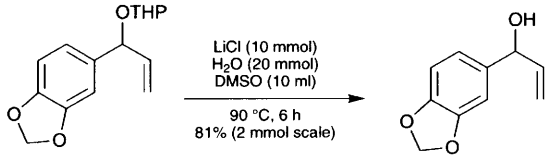
as a hydroxy protecting and radical translocating group. It protects an alcohol before and after its use as a translocating group to generate a radical from a C–H bond β to the protected alcohol. The protecting group is introduced by Williamson ether synthesis or Mitsunobu reaction using 2-bromo-4-methoxyphenol **64**. The resultant 2-bromo-4-methoxyphenyl ether (*e.g.* **65**, **Scheme 32**) is then treated with tributyltin hydride and AIBN to generate a radical on the phenyl ring which then initiates a radical translocation–cyclisation sequence. The final product **66** is then deprotected using standard conditions (CAN).



Scheme 32

2.4 Alkoxyalkyl ethers

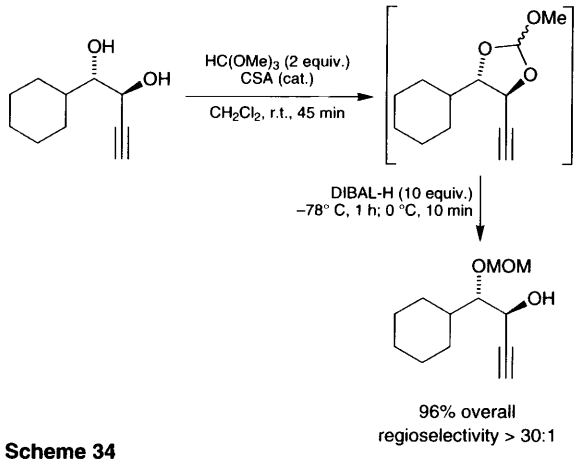
Maiti and co-workers[46] reported a new method for removal of THP protecting group using a combination of lithium chloride and water in DMSO at 90 °C (**Scheme 33**). Under the reaction conditions other acid-sensitive groups like methylenedioxy ether remain unaffected.



Scheme 33

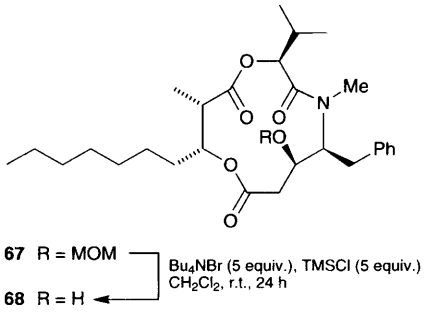
Rao and co-workers[47] have reported copper(II) chloride in dichloromethane as a effective catalyst for tetrahydropyranylation of alcohols.

A MOM ether can be introduced onto the more sterically hindered alcohol of a vicinal diol *via* the the regioselective reductive cleavage of the intermediate orthoester prepared *in situ* from the diol and trimethyl orthoformate.[48] The procedure was examined in ten substrates by Friesen and Vanderwal[49] who confirmed the high regioselectivity (generally >30:1) as illustrated in **Scheme 34**.



Scheme 34

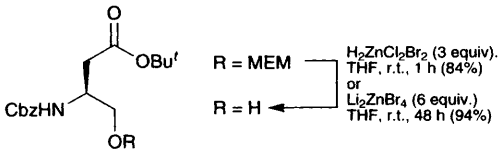
Drug resistance may be caused by the over-expression of P-glycoprotein, a 170–200 kDa transmembrane protein that acts as an ATP-dependent drug efflux pump. Hapalosin, a cyclodepsipeptide isolated from the blue-green alga *Hapalosiphon welwitschii*, inhibits the P-glycoprotein efflux pump and thus may have potential for reversing drug resistance. In a recent synthesis of hapalosin (**68**, **Scheme 35**), Ghosh *et al.*[50] removed a MOM ether group from **67** in the final step using a mixture of tetrabutylammonium bromide (5 equiv.) and TMSCl (5 equiv.).[51]



Scheme 35

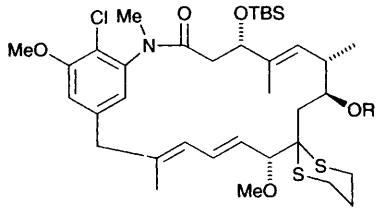
A modification of the zinc halide-mediated cleavage of the MEM ether group has been described[52] which can be used with substrates which otherwise chelate the zinc reagent without undergoing deprotection. The modification uses tetrahalozincate reagents formed by adding two molar equivalents of etheral hydrogen chloride or of lithium halide to the zinc halide reagent. **Scheme 36** exemplifies the reaction. Esters and aryl ethers are

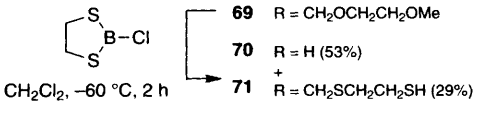
unaffected after 48 h although TBS ethers cleaved slowly (*ca.* 5%).



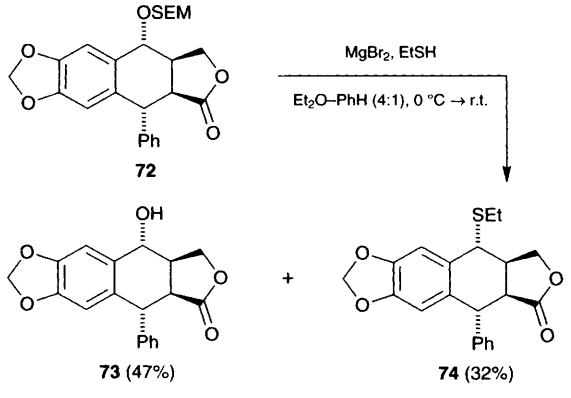
Scheme 36

The use of thiols to assist Lewis-acid mediated cleavage of acetals can result in the formation of thioethers. In the closing stages of a synthesis of maytansinol, Bénéchie and Khuong-Huu found[53] that cleavage of the MEM ether in intermediate **69** (**Scheme 37**) to the alcohol **70** using freshly prepared 2-chloro-1,3,2-dithioborolane[54] according to the procedure of Williams and Sakdarat[55] was accompanied by the thiol **71**—a by-product which had hitherto escaped notice. Similarly, treatment of the podophylotoxin derivative **72** (**Scheme 38**) with magnesium bromide and ethanethiol[56] cleaved the SEM ether function to give the desired alcohol **73** as the major product together with the thioether **74**, presumably the result of capture of a quinomethane intermediate by the ethanethiol.[57]



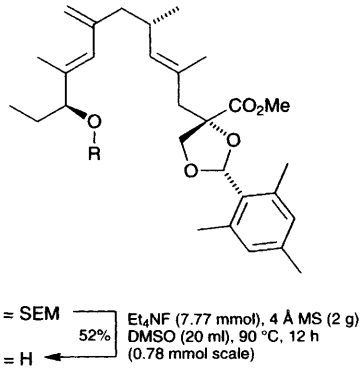


Scheme 37



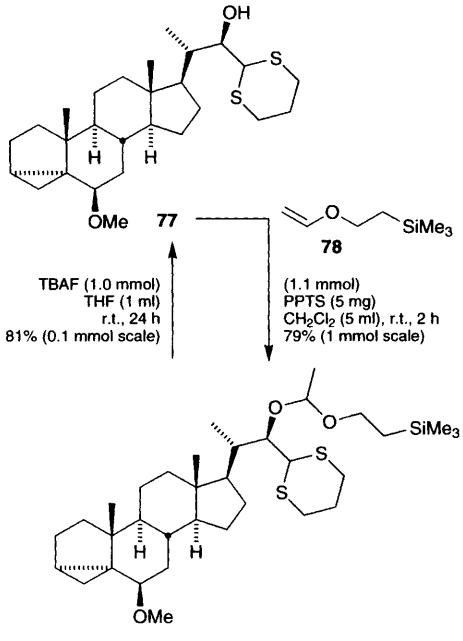
Scheme 38

The SEM ether **75** (**Scheme 39**) was cleaved by tetraethylammonium fluoride in hot DMSO in the presence of powdered molecular sieves to give the secondary alcohol **76** in 52% yield.[58]



Scheme 39

Koreeda and co-workers[59] described the application of a novel hydroxy-protecting group—1-[2-(trimethylsilyl)ethoxy]ethyl (SEE). It can be envisaged as a hybrid between the 1-(ethoxy)ethyl (EE) and the 2-[(trimethylsilyl)ethoxy]methyl (SEM) group because it combines the ease of protection of EE group and the ease of deprotection of the SEM group. Protection of alcohols (*e.g.* **77**, **Scheme 40**) can be realised under very mildly acidic conditions typical for EE group in the reaction with 2-(trimethylsilyl)ethyl vinyl ether (**78**) in the presence of a catalytic amount of pyridinium toluene-2-sulfonate (PPTS). It is noteworthy that SEE ether formation proceeds smoothly even with highly acid-sensitive alcohols such as **77**. Deprotection, on the other hand, can be carried out under mild conditions with tetrabutylammonium fluoride (TBAF). Removal of EE group usually requires acidic aqueous or alcoholic condition which may affect other acid sensitive groups in the molecule.



Scheme 40

Aplyronine A is a 24-membered macrolide which is a potent antitumour agent isolated from the sea

hare *Aplysia kurodai*. Aplyronine A contains two free hydroxy groups and four hydroxy groups entombed in ester functionality. **Scheme 41** depicts the closing stages of a synthesis of aplyronine A by the Yamada group[60] featuring a carefully wrought three-fold orthogonal deprotection sequence designed to sequentially expose two of the four hydroxy groups for esterification whilst retaining the two free hydroxy groups at C-9 and C-25. Selection of a suitable protecting group for the C-29 hydroxy group was crucial to the success of the synthesis. Initially a [(4-methoxybenzyl)oxy]methyl ether[61,62] was selected but its removal at a later stage in the synthesis could not be accomplished without destruction of the $\alpha,\beta,\gamma,\delta$-unsaturated lactone moiety. However, the enhanced lability of the analogous [(3,4-dimethoxybenzyl)oxy]methyl group[63] towards DDQ enabled the selective release of the C-29 hydroxy in intermediate **83** in preparation for its esterification with *N,N*-dimethylalanine. The requisite [(3,4-dimethoxybenzyl)oxy]methyl group was installed by the alkylation of the secondary hydroxy group in intermediate **81** with [(3,4-dimethoxybenzyl)oxy]methyl chloride **80** prepared by reaction of the corresponding (methylthio)methyl ether **79** with sulfuryl chloride. The hydroxy at C-7 was exposed by treatment of the (methylthio)methyl ether in **84** with silver nitrate buffered with 2,6-lutidine and then esterified with *N,N,O*-trimethylserine to give **85**. To complete the synthesis of aplyronine A, the remaining hydroxy groups at C-9 and C-25 were deprotected with HF·pyridine complex in pyridine—conditions mild enough to accomplish the requisite deprotection without ring enlargement of the macrocyclic lactone through transesterification with the nascent C-25 hydroxy group.

In the closing stages of a recent synthesis of the potent antitumour agent FR900482 by the Terashima group[64] simultaneous reductive cleavage of a BOM-protected benzyl alcohol and a benzyl ether was achieved by catalytic hydrogenolysis. The preservation of the benzylic C–O bond in **87** (arrow in **Scheme 42**) is noteworthy.

Use of the *p*-nitrobenzyloxymethyl group as a novel protecting group for the 2′-hydroxy of ribonucleosides has been reported.[65] It is less hindered than the TBS group used previously which leads to much faster coupling times. It is also stable to acid and base, but is easily removed by treatment with fluoride ion.

3 Thiol protecting groups

The final step (**Scheme 43**) in a synthesis of the antitumour depsipeptide FR-901,228 (**89**) involved simultaneous deprotection of two thiol groups in intermediate **88** protected as their *S*-trityl derivatives and disulfide bridge formation using iodine in methanol.[66]

The Baldwin group[67] accomplished a stereocontrolled synthesis of (2*R*,3*R*)-3-mercaptoaspartic acid derivative **91** from L-aspartic acid using *S*-(2,4-dimethoxybenzyl)-4-methylbenzenethiosulfonate (**90**) as an electrophilic sulfenylating agent (**Scheme 44**). The thiol is obtained as its 2,4-dimethoxybenzyl (DMOB) ether which can be removed using mercury(II) trifluoroacetate. The crystalline sulfenylating agent **90** was prepared in two steps from commercial 2,4-dimethoxybenzyl alcohol.

Ecteinascidin 743 is an exceedingly potent antitumour agent of marine origin whose clinical evaluation has been seriously hampered by inadequate supplies from natural sources. Corey and co-workers[68] have recently completed an elegant total synthesis of ecteinascidin 743 which employs a fluoren-9-ylmethyl group ($FlCH_2$) for the protection of a cysteinyl thiol. **Scheme 45** depicts a series of steps conducted in one pot by which the ten-membered lactone bridge was constructed in 79% overall yield. The first step in the sequence involved formation of the sulfoxonium salt **93** by reaction of hydroxydienone **92** with the Swern reagent. Elimination of DMSO then generated the quinomethane **94** which underwent intramolecular conjugate addition of the thiolate **95** released by treatment of the 9-fluorenylmethyl group with excess *N-tert*-butyl-*N′,N′,N″,N″*-tetramethylguanidine.

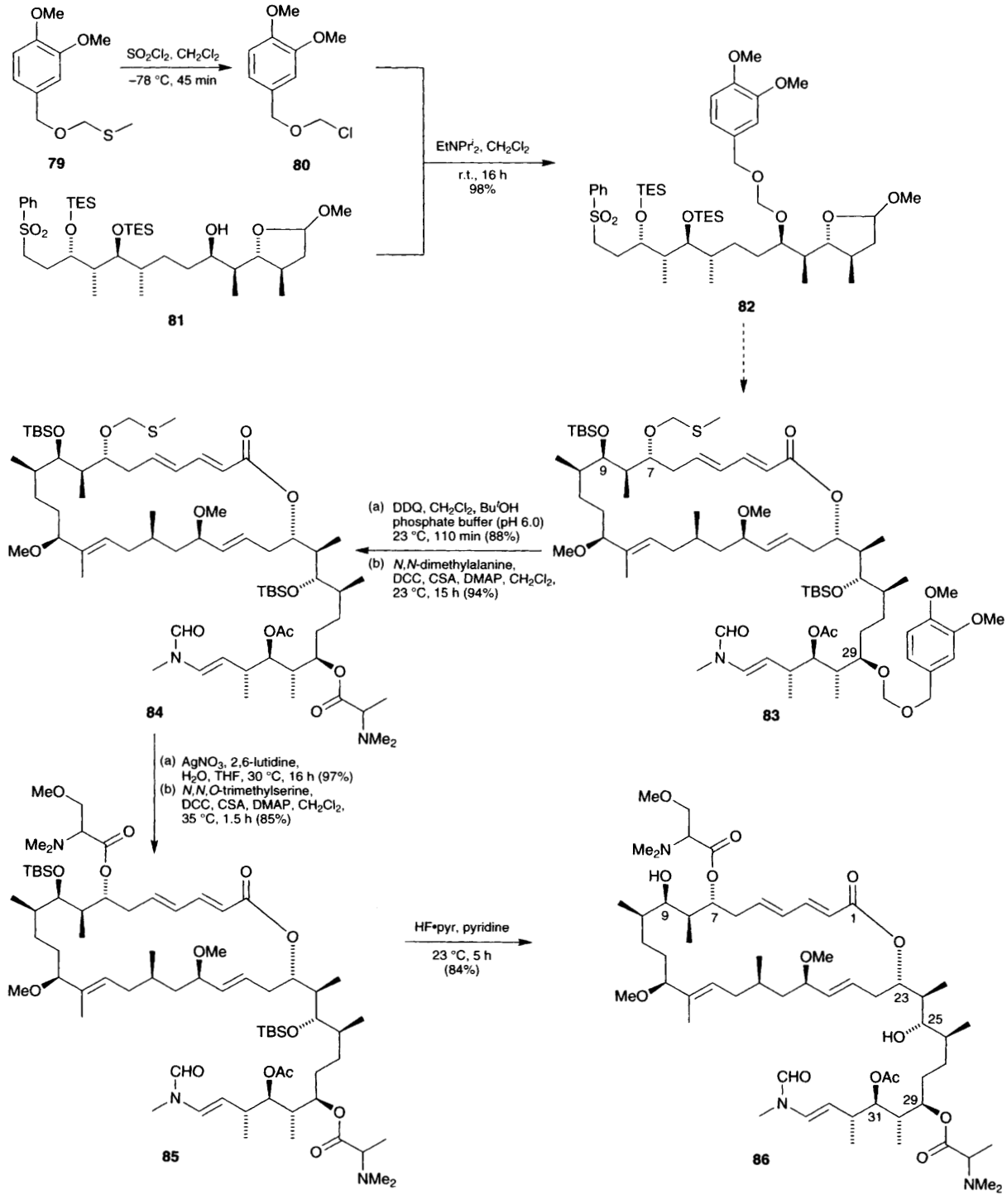
4 Diol protecting groups

Saito and co-workers[69] reported the selective cleavage of acetals derived from 1,2- or 1,3-diols bearing neighbouring hydroxy groups (e.g. **96**, **Scheme 46**) by treatment initially with $BH_3{\cdot}SMe_2$ followed by $BF_3{\cdot}OEt_2$. The C–O bond proximate to the hydroxy group was reduced selectively to diol **97**. Borane compares favourably with alanc reagents previously used for the same purpose because of much shorter reaction times.

The clinical efficacy of paclitaxel for the treatment of solid tumours has stimulated the search for new analogues with improved therapetic potential. A recent study by a Dutch group[70] focused on the synthesis and modification of 7-deoxypaclitaxel derived from natural taxine isolated from the dried needles of *Taxus baccata*. A significant chemical feature of this study was the extensive use of acetal-type protecting groups for the various hydroxy groups present in the molecule. **Scheme 47** illustrates a few of the selective reactions which were employed to expose hydroxy functions on the periphery of the molecule. A case in point is the derivative **98** with three different acetal protecting groups. The ethoxyethyl acetal protecting the 2′-hydroxy was the most labile: treatment of **98** with H_2O–HOAc–THF (2:2:1) at room temperature was sufficient to remove it in good yield. Removal of the ethoxyethyl and the isopropylidene acetal protecting the 1,2-diol at C-9 and C-10 was accomplished by increasing the concentration of acetic acid (H_2O–HOAc–THF = 2:4:1) and raising the temperature to 40 °C. Finally, cleavage of the benzylidene acetal in **99** without detriment to the isopropylidene acetal was accomplished under

oxidative conditions using *tert*-butyl hydroperoxide in the presence of palladium acetate to give the monobenzoate ester **100** in modest yield.

Galbonolide B (**102, Scheme 48**) is a 14-membered macrolide with potent antifungal activity against the human pathogens *Candida albicans* and *Rhodotorula rubra* as well as the agricultural pests *Botrytis cinerea* and *Pseudomonas lachrymans*. The last step in a recent synthesis of galbanolide B required the release of a 1,2-diol protected as a dioxolane derivative.[58] A number of different aryl acetal protecting groups were investigated. When the aryl group was Ph, 3-MeO-C_6H_4 or 4-Me-C_6H_4, the allylic lactone moiety hydrolysed preferentially. On the other hand activated acetals such as 2-MeO-C_6H_4, 4-MeO-C_6H_4 and 4-PhO-C_6H_4 were too unstable towards acid to survive the synthetic sequence unscathed. However, 2,4,6-trimethylbenzylidene substituted dioxolane **101** was stable enough to survive the necessary synthetic steps but

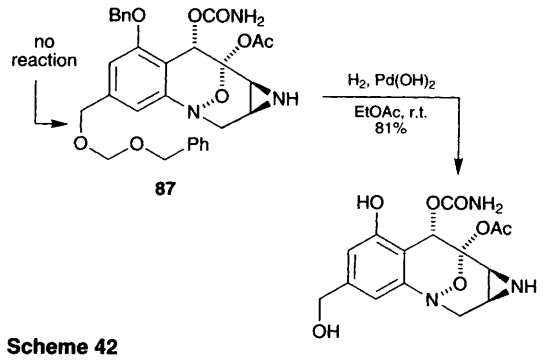


Scheme 41

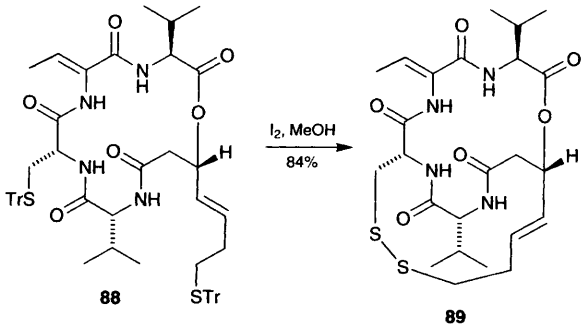
hydrolysed efficiently on brief exposure to aqueous acetic acid at room temperature.

During the application of *n*-pentenyl glycoside methodology to the stereoselective construction of the tetrasaccharyl cap portion of *Leishmania* lipophosphoglycan, Arasappan and Fraser-Reid[71] achieved the reductive cleavage of the benzylidene acetal **103 (Scheme 49)** with triethylsilane–trifluoroacetic acid[72] without affecting the chloroacetate function.

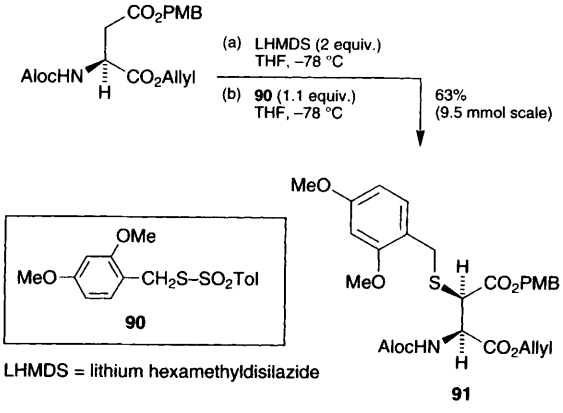
Treatment of 4,6-*O*-*p*-methoxybenzylidene acetals of mono- and di-saccharides with DDQ in the presence of halide salts gave the 6-deoxy-chloro or -bromo-4-*O*-*p*-methoxybenzoates exclusively in ~90% yield[73] **(Scheme 50)**. In the presence of water the corresponding 6- and 4-*O*-*p*-methoxybenzoates with unprotected hydroxy groups in the 4- and



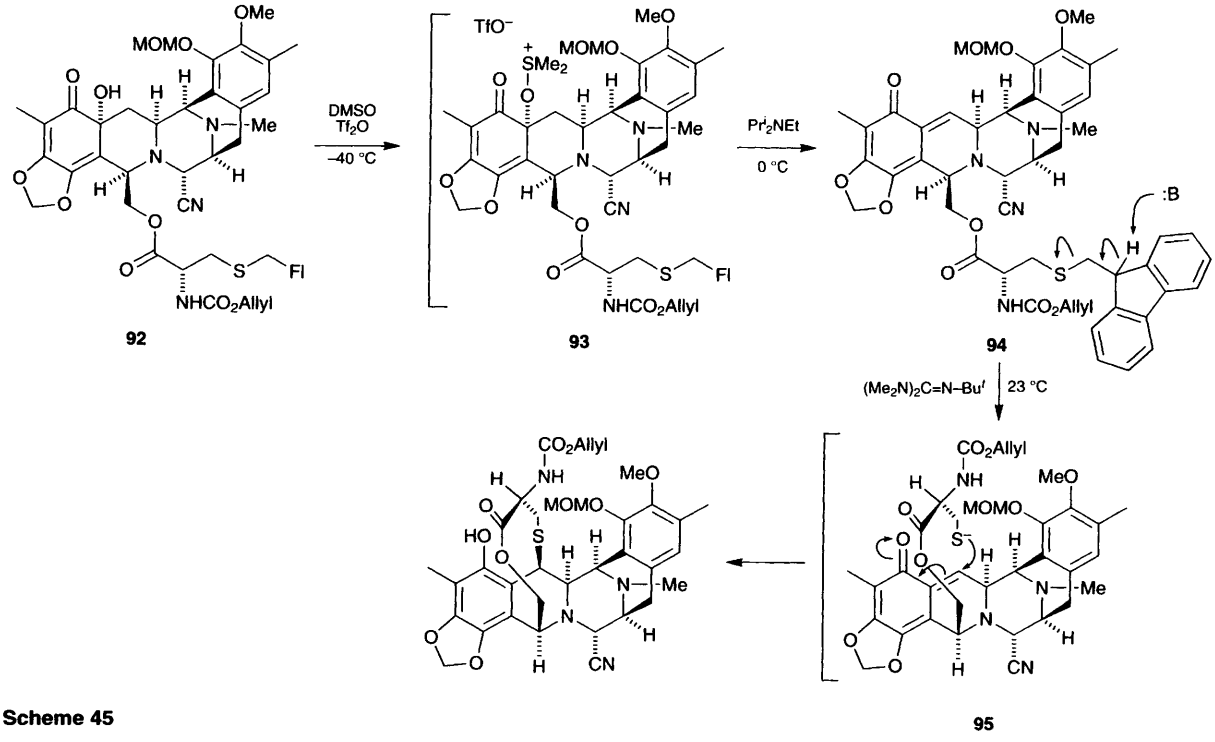
Scheme 42



Scheme 43



Scheme 44



Scheme 45

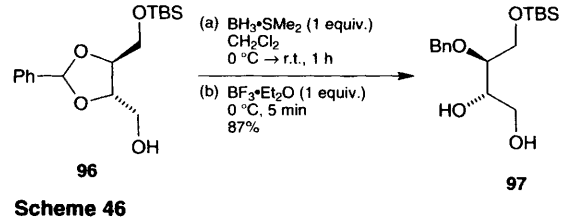
6-position were obtained in the ratio ~4:1 in 85–98% yield.

Schreiber and co-workers[20] used a procedure of Evans and Gauche-Prunet[74] to create a benzylidene acetal with high 1,3-asymmetric induction *via* addition of an alkoxide to benzaldehyde followed by intramolecular conjugate addition of the resultant hemiacetal derivative. Thus, treatment of **104** (**Scheme 51**) with benzaldehyde and catalytic KHMDS provided benzylidene acetal **105** as a single isomer in 73% yield.

Deacetonation of **106** (**Scheme 52**) in a mixture of acetic acid and water under reflux conditions was unexpectedly accompanied by cleavage of the interglycosidic linkage and partial removal of the TBDPS group.[75] However, a high yielding and smooth transformation of **106** into **107** was attained by unleashing the 1,2-*O*-isopropylidene function with HOAc–H_2O containing ethylene glycol.

In the closing stages of Danishefsky's synthesis of Taxol[76], the cyclic carbonate **108** (**Scheme 53**) was converted selectively to the benzoate ester **109**—a transformation which was precedented in the earlier Taxol syntheses of Holton[77] and Nicolaou.[78]

Ley and co-workers pioneered the use of chiral bisdihydropyrans for selective diol protecting agents.[79] Recently they have added two more



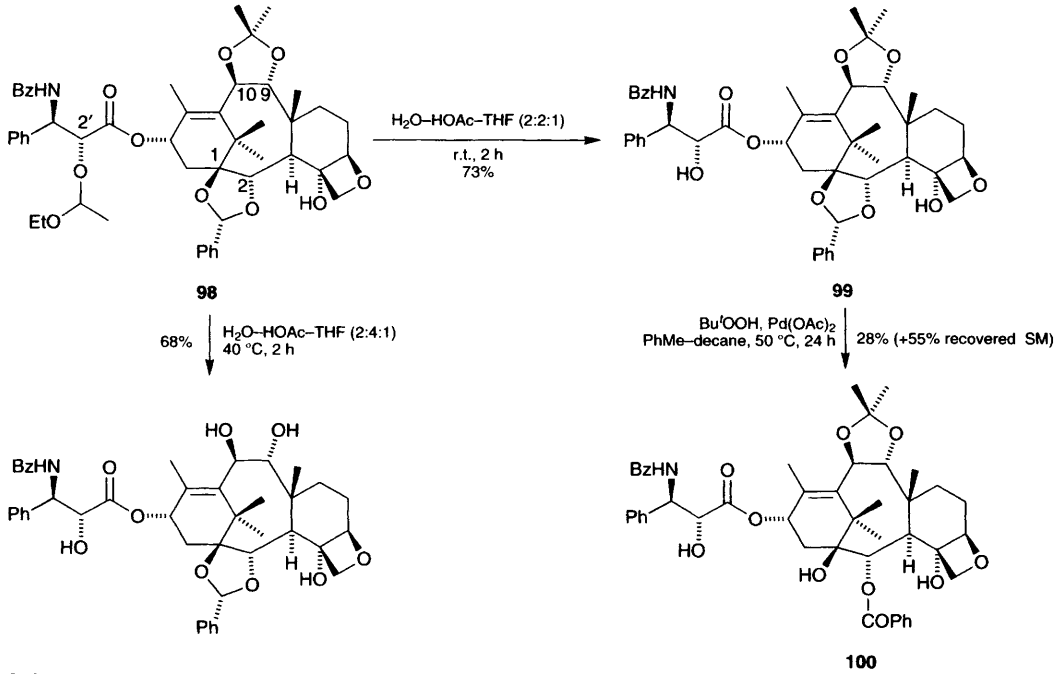
96 **97**

Scheme 46

reagents to their repertoire:[80,81] dibromide **110** and disulfide **111** (**Scheme 54**). They both react with one enantiomer of the racemic diol **112** to give dispiroketals **113** and **114**. The advantage of these dispiroketals stems from the fact that they can be easily deprotected by β-elimination. In the case of dispiroketal **113**, treatment with lithium 4,4′-di-*tert*-butylbiphenyl (LDBB) gave the corresponding cyclohexanediol **112** with high enantiomeric purity. In order to deprotect the disulfide **114**, it was first oxidised to disulfone **115** using *m*-chloroperbenzoic acid (MCPBA). This facilitates deprotonation of the acidic α-proton with a base such as lithium hexamethyldisilazide (LHMDS) which on subsequent β-elimination gave homochiral diol **112**. Bisdihydropyrans **110** and **111** can also be used for the selective protection of diequatorial diol pairs in glucose derivatives.

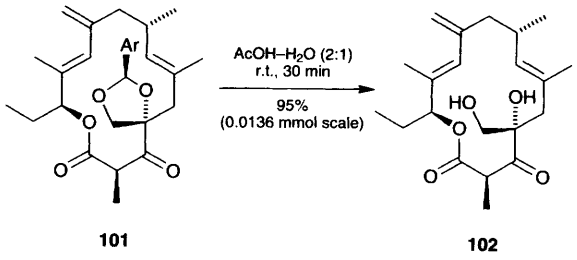
Another contribution from Ley's group[82] was the improved procedure for protecting 1,2-diols by using directly α-diketones rather than the corresponding 1,2-diacetals previously reported.[79] Thus, reaction of commercial phenanthrene-9,10-quinone **117** (**Scheme 55**) with methyl α-D-mannopyranoside **116** and trimethyl orthoformate in the presence of camphorsulfonic acid gave **118** in which two diequatorial hydroxy groups are selectively protected. Unfortunately phenanthrene 9,10-diacetals have proved inert to hydrogenolysis or hydrolysis.

Frost and co-workers[83] described the use of 2,2,3,3-tetramethoxybutane (TMB) as a reagent for the selective protection of vicinal diequatorial diols to give butane 2,3-bisacetal (BBA) protected derivatives. The reaction is illustrated in **Scheme 56** by the conversion of methyl α-D-mannoside (**119**) to the diacetal **120** in 91% yield. TMB is cheaper and easier to prepare (especially in large scale) than



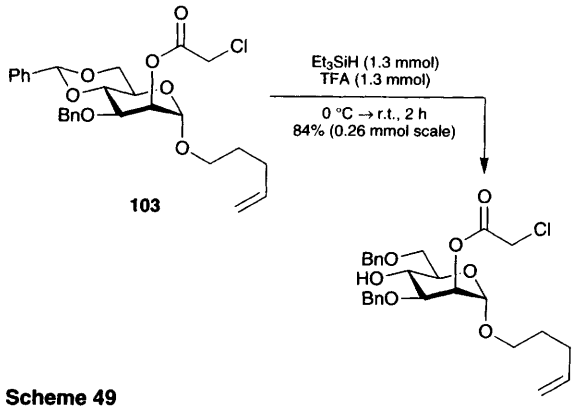
98 **99** **100**

Scheme 47



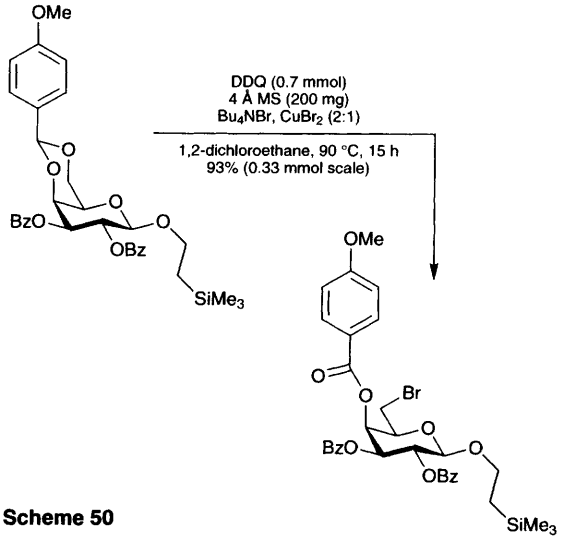
101 102

Scheme 48

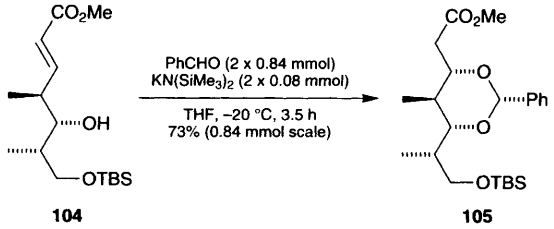


103

Scheme 49

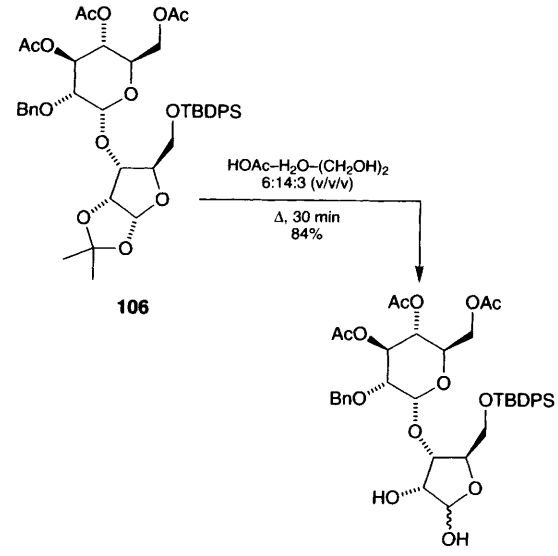


Scheme 50



104 105

Scheme 51



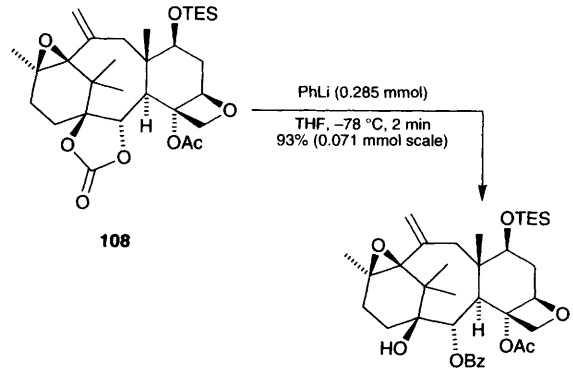
106 107

Scheme 52

other reagents serving the same purpose such as 3,3′,4,4′-tetrahydro-6,6′-spirobis-2*H*-pyran (bis-DHP) and 1,1,2,2,-tetramethoxycyclohexane (TMC)[79]. In the case of **119**, bis-DHP failed to perform the analogous protection and reaction with TMC proceeded in only 48% yield. The BBA group is compatible with a wide variety of reagents and can be deprotected with aqueous trifluoroacetic acid in methylene chloride.

5 Carboxy protecting group

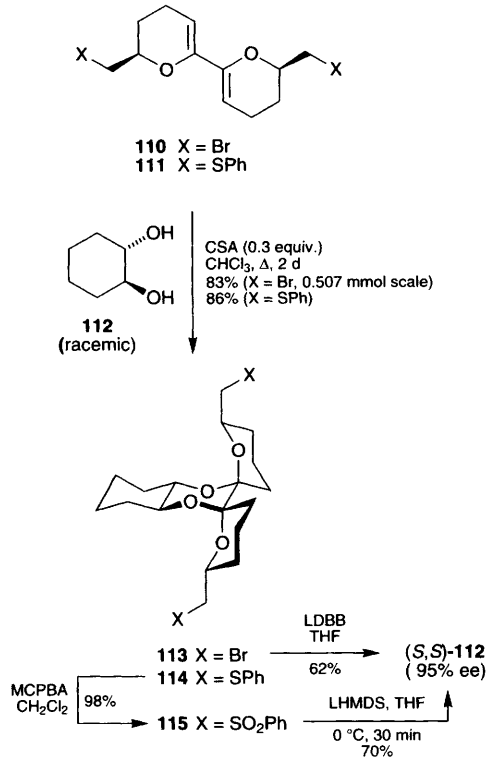
During a synthesis of the protein kinase C inhibitor balanol, Lampe and co-workers[84] found that deprotection of the *tert*-butyl ester **121** with trifluoroacetic or formic acid was accompanied by substantial quantities of a debenzylated by-product (**Scheme 57**). The same side reaction accompanied thermolytic cleavage of the *tert*-butyl ester in neutral solvents presumably due to acid catalysis by the carboxylic acid product **122**. However, thermolysis in quinoline at 205 °C led cleanly to the desired benzophenone carboxylic acid **122** in 68% yield.



108 109

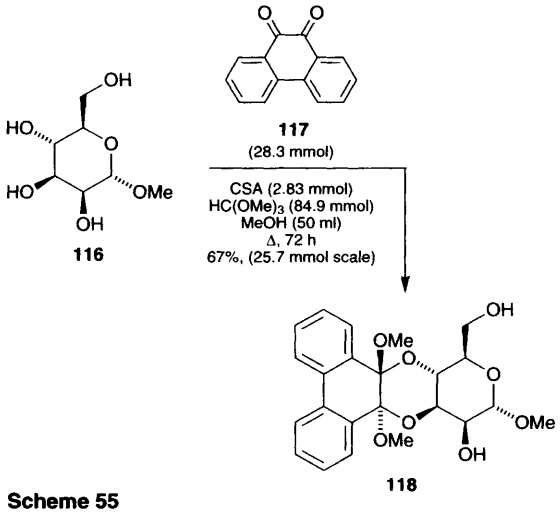
Scheme 53

When Fmoc-protected aspartic acid is used in solid phase peptide synthesis, deprotection of the Fmoc group in the final peptide by piperidine is complicated by aspartimide formation. However, protection of the terminal carboxy as its β-3-methylpentan-3-yl ester (Mpe) minimises this side

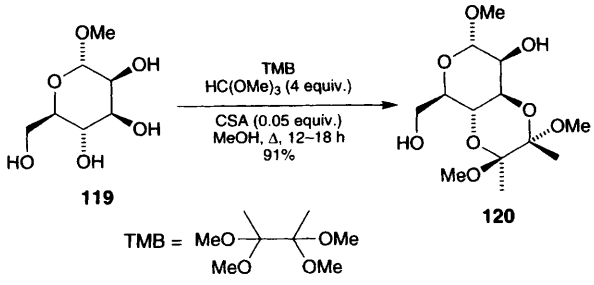


LDBB = lithium 4,4'-di-*tert*-butylbiphenyl

Scheme 54



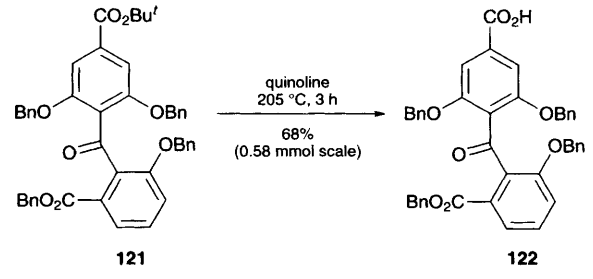
Scheme 55



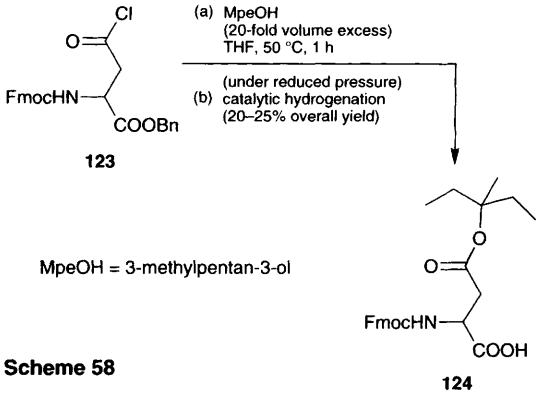
Scheme 56

reaction.[85] The preparation of the protected aspartic acid **124** is carried out by reaction of the chloride **123** with 3-methylpentan-3-ol followed by catalytic hydrogenation (**Scheme 58**). The Mpe group gives significantly better protection against base-catalysed aspartimide formation (25%) than the previously used β-*tert*-butyl and β-1-adamantyl groups (58% and 81% respectively).

Somatostatin is a tetradecapeptide hormone which inhibits the release of several hormones and neurotransmitters. In the pursuit of an inhibitor of somatostatin, Smith and co-workers[86] synthesised the complex analogue **130** (**Scheme 59**) which incorporates a carefully terraced set of selective deprotections of carboxylic acids together with their amino partners to enable sequential construction of the three rings. The sequence began by anchoring a partially protected tripeptide to a resin *via* a β-aspartyl ester to give the chlorotrityl ester **125**. Solid phase peptide synthesis transformed **125** to the fully elaborated peptide chain in **126**. The first ring was constructed after acidolysis [0.75% trifluoroacetic acid (TFA)] of the *N*-trityl and chlorotrityl ester groups to give the monocycle **127**. Palladium(0)-catalysed deprotection of an *N*-Aloc and allyl ester is the prelude to the construction of the second ring giving bicycle **128**. Then treatment of **128** with 50% trifluoroacetic acid in aqueous dichloromethane removed a *tert*-butyl ester, an *N*-Boc and a *tert*-butyl ether (on threonine) to give the precursor whose cyclisation completed the construction of the third and final ring in **129**. The remaining Fmoc and Cbz groups remaining on the two lysine residues were finally cleaved in the usual way to give the somatostatin analogue **130**.



Scheme 57

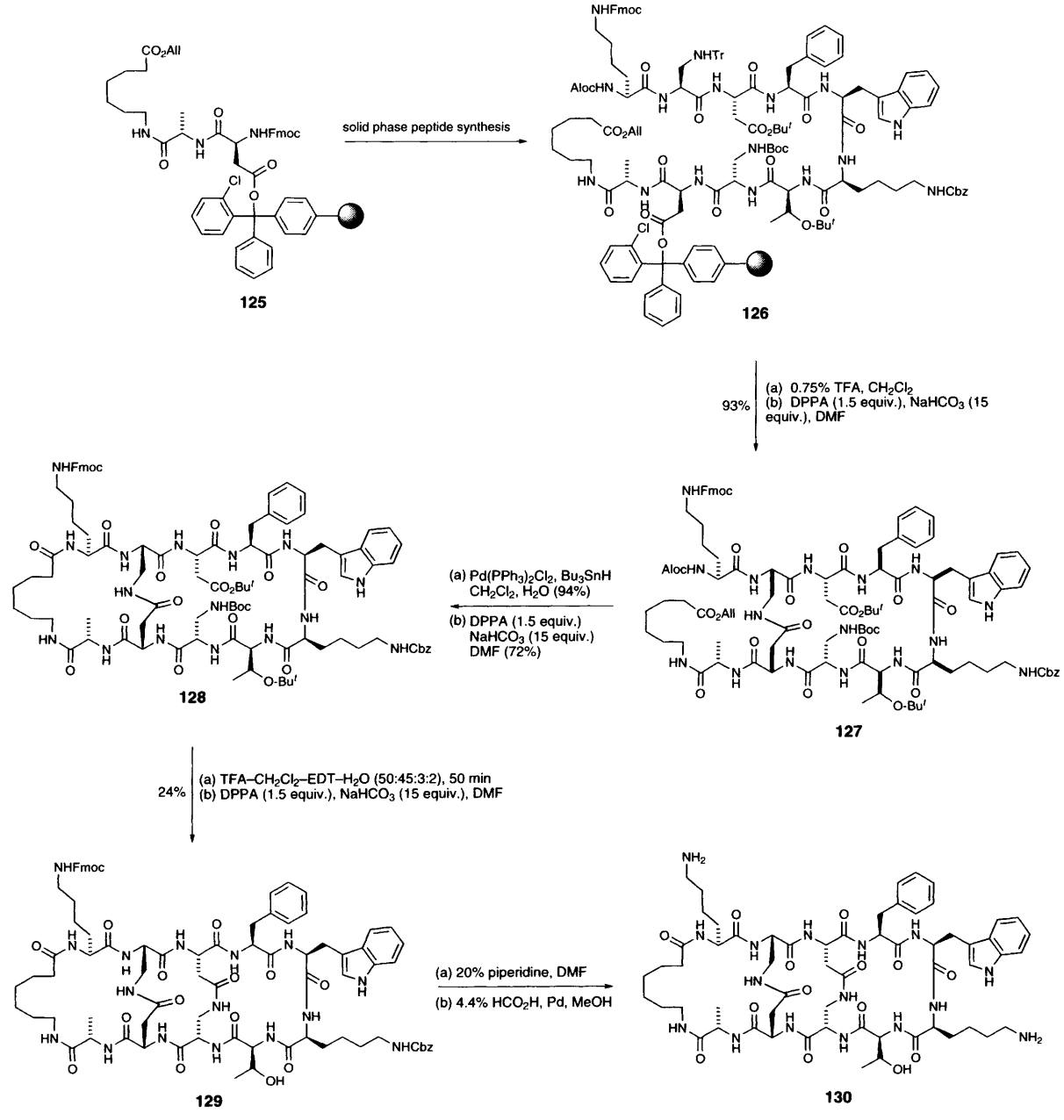


123 124

Scheme 58

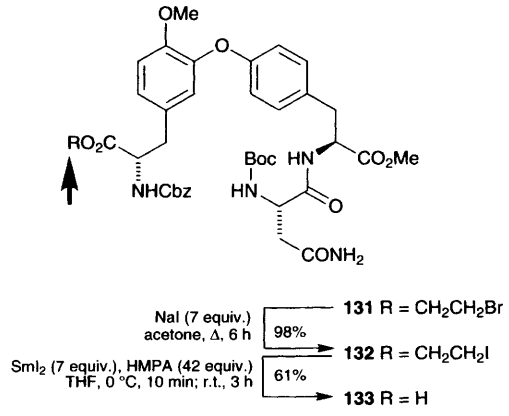
Pearson and co-workers[87] used a 2-bromoethyl ester to protect carboxy group during a synthesis of the immunopotentiator OF 4949 III (**Scheme 60**). The 2-bromoethyl ester proved sturdy enough to survive the coupling and metallation reactions leading to **131** but it was easily removed after halogen exchange to the 2-iodoethyl ester **132** which was then reductively cleaved with samarium diiodide using HMPA as an additive.

Fastrez and co-workers[88] found mild conditions for selective cleavage of the methoxymethyl (MOM) ester from penam sulfone **134** (**Scheme 61**). The best results were obtained by overnight incubation of **134** at 21 °C in a mixture of methanol and water (60% MeOH) to afford **135** quantitatively. Standard



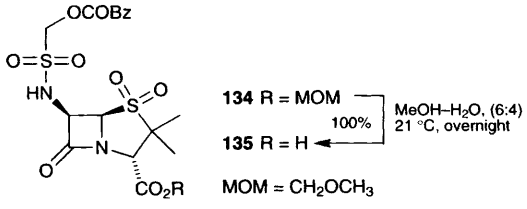
125 126 127 128 129 130

Scheme 59



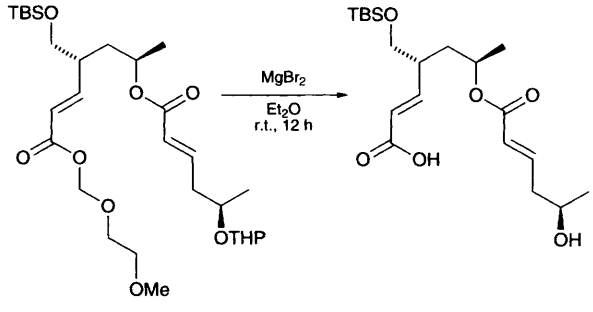
Scheme 60

conditions like aqueous HCl or $MgBr_2$ were accompanied by some β-lactam degradation.



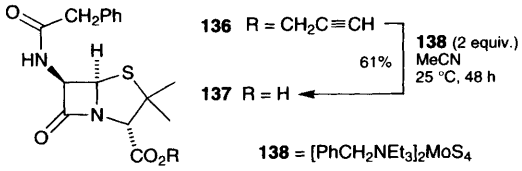
Scheme 61

A key step in the synthesis of the macrodiolide bartanol was the simultaneous deprotection of a THP ether and a MEM ester using magnesium bromide in ether overnight at room temperature[89] (**Scheme 62**).



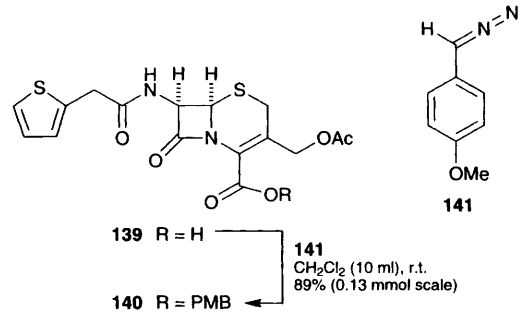
Scheme 62

Prop-2-ynyl esters have been reported as a new protecting group for carboxylic acids.[90] Deprotection is accomplished with benzyltriethylammonium tetrathiomolybdate **138** (**Scheme 63**). The mildness of the conditions is well illustrated by the deprotection of prop-2-ynyl ester of penicillin G (**136**) which has a sensitive β-lactam unit. Prop-2-ynyl esters can be deprotected selectively in the presence of acetyl, benzyl, *tert*-butyl or allyl esters.



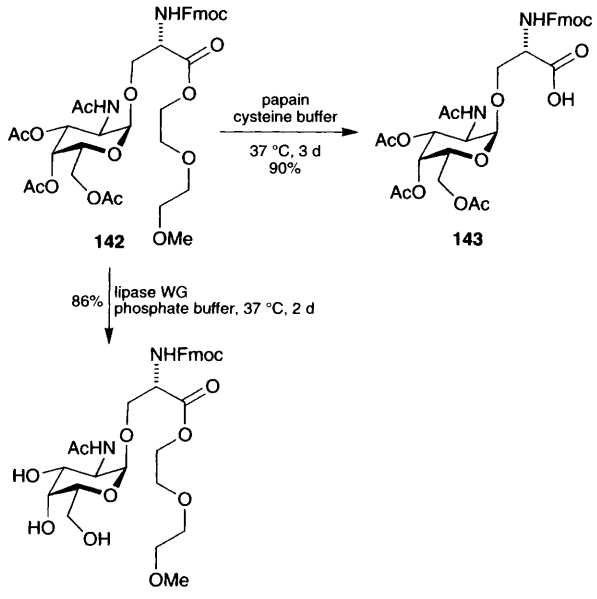
Scheme 63

Protection of the C-9 carboxy function of cephalosporins can be problematic due to the extreme base sensivity of most cephems: the carboxylate itself is a sufficiently good base to cause isomerisation of the double bond from the Δ-3 to the Δ-2 position. Waddell and Santorelli[91] reported a very mild method of the preparation of allyl and PMB esters of cephalosporins (*e.g.* **140**, **Scheme 64**) using the corresponding acid (*e.g.* **139**) and diazoalkanes (*e.g.* **141**). The use of dichloromethane as a solvent is crucial in order to have a high rate of reaction and hence minimise by-products. The requisite diazo compounds can be easily prepared from *N*-*p*-methoxybenzyl- or *N*-allyl-*O*-ethylcarbamates which are transformed first into corresponding *N*-nitroso derivatives followed by the reaction with sodium methoxide.



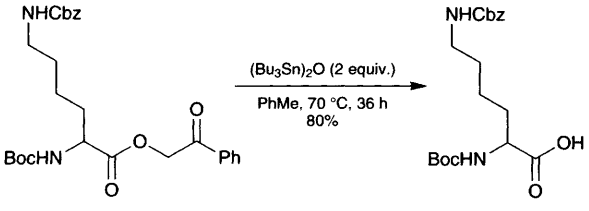
Scheme 64

The preparation of glycopeptides containing *O*-glycosidic links between serine or threonine imposes stringent limits on protecting group protocols. Under acidic conditions anomerisation or glycosidic cleavage may occur whereas at pH >11, β-elimination of the carbohydrate may occur. The Kunz group[92] has disclosed details of the selective *C*-terminal deprotection of *O*-glycopeptide (methoxyethoxy)ethyl (MEE) esters under mild conditions (pH 6.6, 37 °C) by enzymatic hydrolysis using papin or lipase M from *Mucor javanicus* as exemplified by the selective hydrolysis of **142** to **143** (**Scheme 65**). On the other hand, selective deprotection of acetate functions from the saccharide portion of **142** was accomplished by enzymatic hydrolysis with lipase WG from wheat germ.



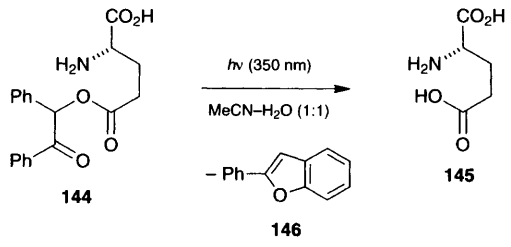
Scheme 65

Phenacyl, methyl and benzyl esters of various *N*-α-Boc, *N*-α-Cbz or *N,N*-dimethylamino-protected amino acids and dipeptides, as well as esters of *N*-α-protected amino acids linked to Wang and Pam resins, can be cleaved to the corresponding carboxylic acids on heating with bis(tributyltin) oxide in aprotic solvents[93] (**Scheme 66**). There is no racemisation of the amino acid and peptide products. However there are some limitations to the method: removal of tin residues from the product can diminish the yield and the Cbz group (but not a Boc) may undergo competitive cleavage.



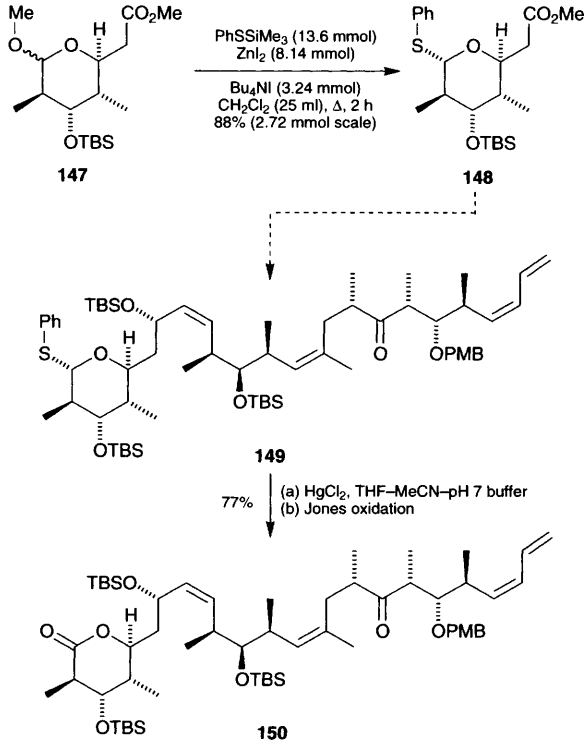
Scheme 66

The photochemistry of 2-oxo-1,2-diphenylethyl (desyl) derivatives first reported by Sheehan and co-workers more than 30 years ago[94,95] has recently been adapted[96] to the release of endogenous amino acid neurotransmitters. Photolysis at 350 nm of solutions of γ-*O*-desyl glutamate **144** in 1:1 H_2O–MeCN cleanly produced free glutamate **145** (**Scheme 67**). Biologically inert 2-phenylbenzo[*b*] furan **146** was the only photoproduct detectable by HPLC. Attempts to use the desyl phototrigger for the release of *N*-desyl derivatives were less successful.



Scheme 67

An important issue in Schreiber's synthesis of discodermolide[20] was the choice of functionality to mask the lactone until late in the synthesis. The lactone was protected in its lower oxidation state, as the lactol, by a thiophenyl group (**Scheme 68**). The *O,S*-acetal **148** was prepared by treatment of the anomeric mixture of acetals **147** with $PhSSiMe_3$, ZnI_2, and Bu_4NI to give a 2:1 mixture of anomeric *O,S*-acetals which were separated by chromatography. Towards the end of the synthesis, the lactone was recreated by Hg^{2+}-catalysed hydrolysis of the *O,S*-acetal in **149** followed by Jones oxidation to lactone **150** in 77% yield for the two steps.



Scheme 68

6 Phosphate protecting groups

Stimulation of an extracellular G-protein coupled receptor induces intracellular calcium mobilisation *via* the second messenger D-*myo*-inositol 1,4,5-triphosphate (IP3) which is then implicated in smooth muscle contractility, secretion, neuronal excitability, the activation of inflammatory cells, and cell proliferation. The adenophostins are IP3

receptor agonists isolated from *Penicillium brevicompactin* with 100 times greater binding affinity than the natural ligand IP3. The van Boom group[75] has reported a synthesis of adenophostin A which features the use of a base-labile 2-(methylsulfonyl) ethyl (MSE) group for phosphate protection. We join the closing stages of the synthesis (**Scheme 69**) when the 3′-*O*-glucosyladenosine derivative **151** was transformed to the protected phosphate **153** using *N*,*N*-diisopropylbis[2-(methylsulfonyl)ethyl]phosphoramidite **152** followed by *in situ* oxidation of the intermediate phosphite triester. Sequential removal of the base labile benzoyl and MSE groups, the acid-labile 4,4′-dimethoxytrityl groups (DMT), and finally hydrogenolysis of the benzyl ether gave adenophostin A (**154**).

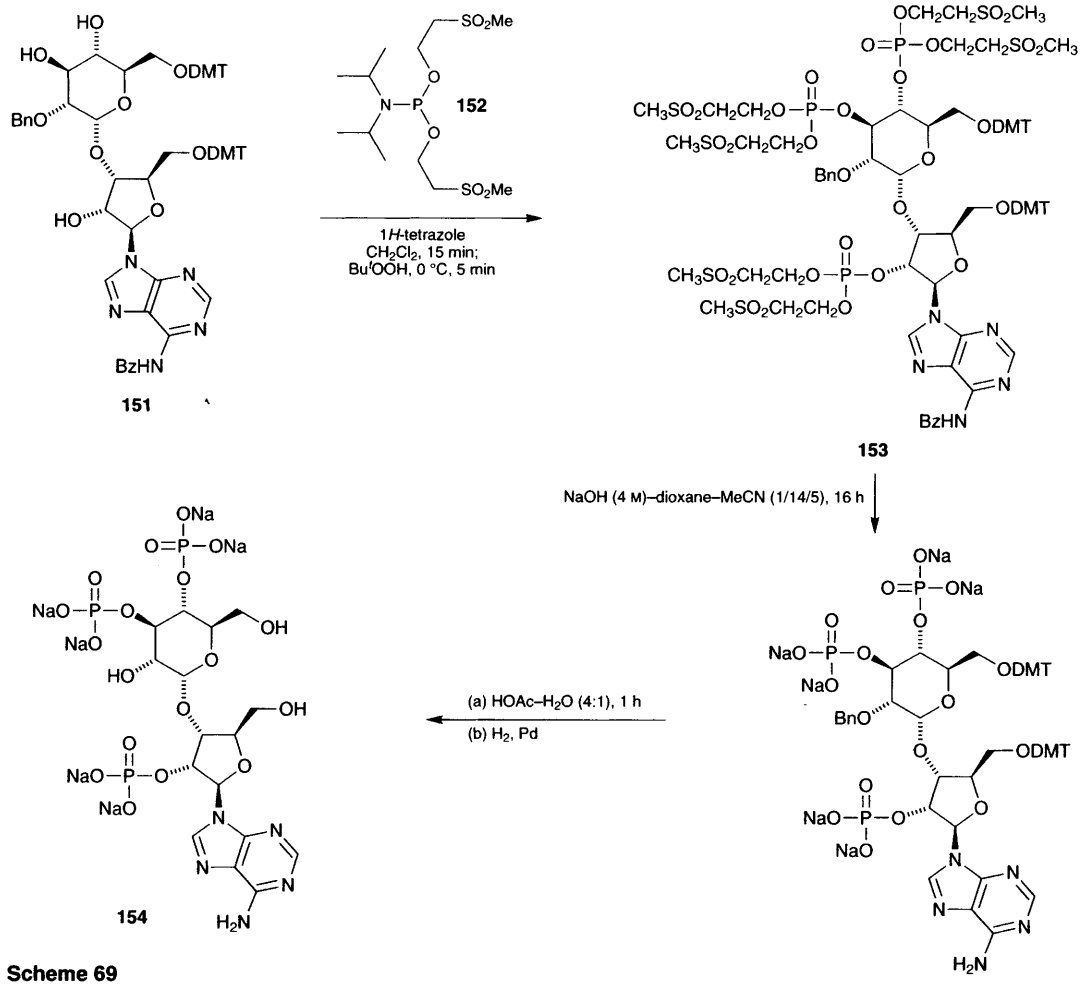
The Pirrung group[97] developed a method for the preparation of short DNA sequences using light to deprotect a nucleoside-2′-phosphotriester prior to coupling with the free 5′-hydroxy nucleotide. The dimethoxybenzoin (DMB) group was used as the photolabile protecting group for the 3′-phosphate whilst 2-cyanoethyl (CE) was effective as the second protecting group on the phosphotriester **155**. The method for preparing the protected nucleotide units as well as the photocleavage is illustrated in **Scheme 70**.

4-Cyanobut-2-enyl as a cheap replacement for 2-cyanoethyl group for internucleotide phosphate protection has been reported.[98] This group is stable to acidic conditions and can be deprotected using aqueous ammonia.

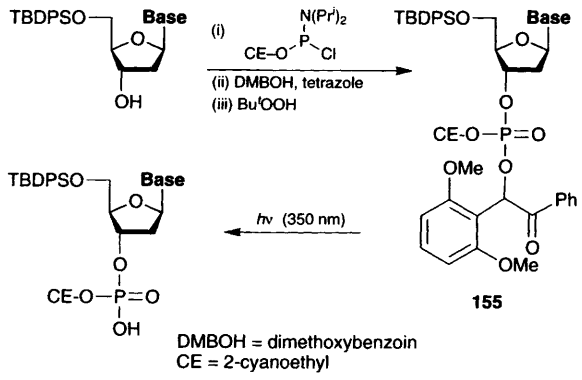
7 Carbonyl protecting groups

The marine natural product (−)-α-kainic acid (**159**, **Scheme 71**) has attracted considerable interest owing to its potent neurotransmitting activity. A recent synthesis of **159** by Hanessian and Ninkovic[99] uses a trimethylstannyl group as a latent aldehyde. Thus oxidation of stannane **156** with cerium(IV) ammonium nitrate (CAN) produced the dimethyl acetal **157**. Attempts to hydrolyse the acetal function with TsOH or $SnCl_2 \cdot H_2O$[100] led to epimerisation at C-4. However, treatment of **157** with bromodimethylborane[101] at −78 °C gave the desired aldehyde **158** in quantitative yield without any detectable epimerisation.

During a synthesis of the sesquiterpene (+)-taylorione,[102] deprotection of the dioxolane **160** (**Scheme 72**) using anhydrous carbon tetrabromide and triphenylphosphine[103] was superior in yield or economy to the standard techniques of acetal hydrolysis such as TsOH in aqueous acetone (66%).



Scheme 69



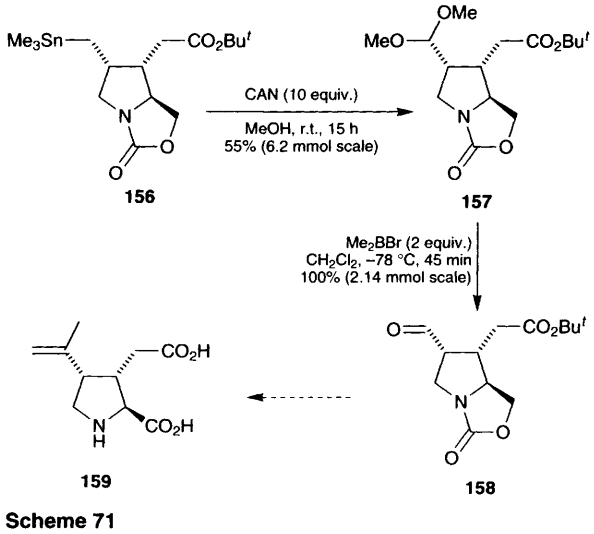
Scheme 70

Under these conditions aliphatic ketals cleave but aliphatic acetals are inert.

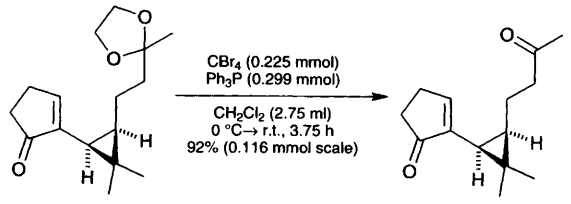
Fujioka and co-workers[104] have developed a synthesis of chiral 1,4-diols from the ene acetal prepared from the corresponding aldehyde and homochiral hydrobenzoin. In the first step (**Scheme 73**), treatment of the acetal **161** with I(coll)$_2$ClO$_4$ in the presence of 2-methoxyethanol gave the dioxocane **163** (four diastereoisomers) *via* the oxonium ion intermediate **162**. After reductive removal of the iodine, the methoxyethoxy acetal group in **164** was displaced by a Grignard reagent with retention of configuration to give pure dioxocane **165** after chromatography. Finally, cleavage of the chiral auxiliary using calcium in liquid ammonia returned the 1,4-diol **166** in 92% yield. An analogous procedure was used to generate homochiral 1,5-diols.

Curini and co-workers reported a convenient method for the deprotection of 1,3-dithiolanes and 1,3-dithianes using Oxone® (potassium hydrogen persulfate) and wet alumina.[105] Other functional groups like double bonds (e.g. compound **167**, **Scheme 74**) and acetates remain intact.

Mehta and Uma[106] described the use of 'oxides of nitrogen' as a reagent for deprotection of thioacetals.



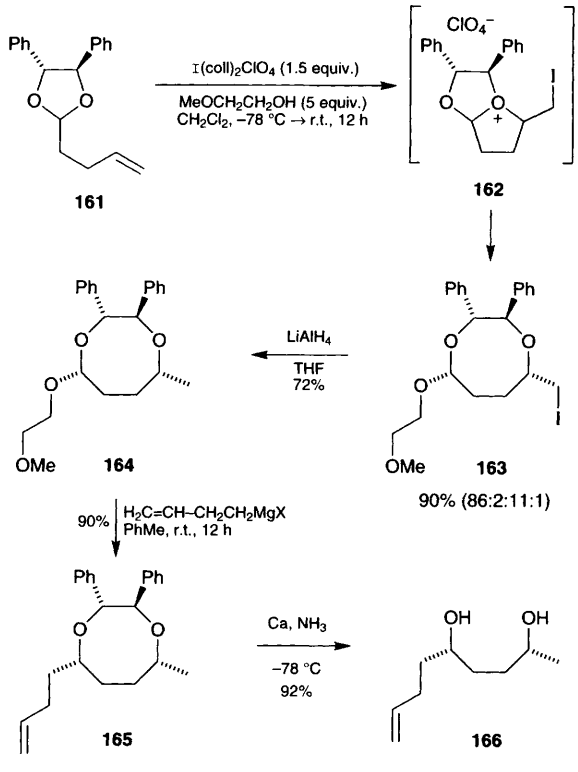
Scheme 71



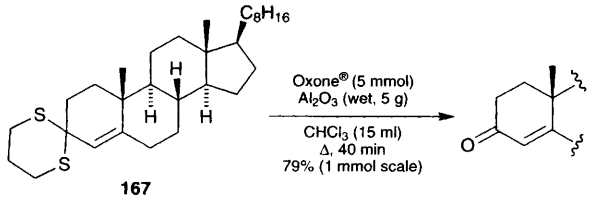
Scheme 72

An investigation of the mechanism of silver-promoted *S,S*-acetal cleavage using ^{13}C NMR spectroscopy suggested a symmetrical intermediate.[107] X-Ray analysis of a crystalline 1:1 adduct of 2-methyl-1,3-dithiane with silver nitrate revealed the bridged structure **168** (**Scheme 75**). Subsequent reaction of the complex with water is the rate limiting step in the ring opening process. Previous workers[108] had inferred a different bridged structure **169** based on kinetic studies.

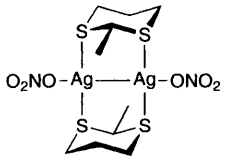
Komatsu and co-workers reported that *S,S*-acetals can be deprotected with air in the presence of a



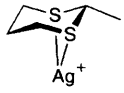
Scheme 73



Scheme 74



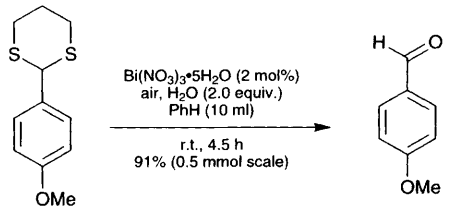
168



169

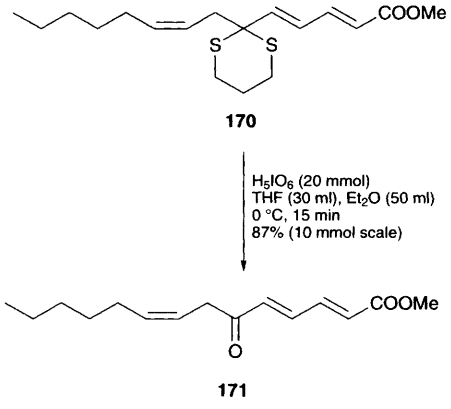
Scheme 75

catalytic amount of bismuth(III) nitrate pentahydrate to regenerate the original carbonyl compounds in good to excellent yields[109] (**Scheme 76**). Under an argon atmosphere the reaction scarcely proceeded, which suggests that oxidation by molecular oxygen is involved as a key step in the deprotection. When the reaction was sluggish, it was considerably facilitated by the additional presence of a secondary bismuth(III) salt *i.e.* bismuth chloride, as an auxiliary additive. Benzene was the best solvent, followed by toluene and acetonitrile.



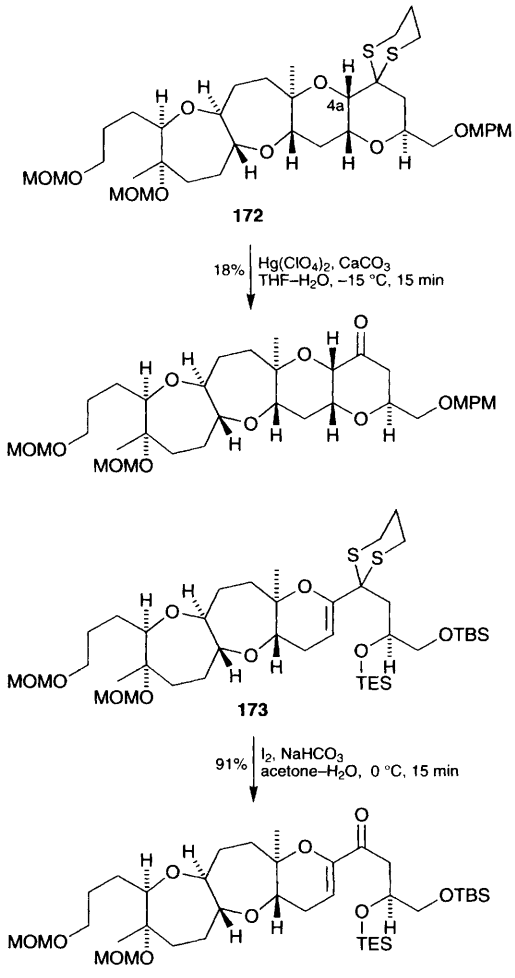
Scheme 76

A new method of deprotecting dithioacetals, oxathioacetals and sulfoxidothioacetals using periodic acid has been published by Shi and co-workers.[110] The mildness of the reagent is well illustrated by the case of dithioacetal **170** which gives ketone **171** without migration of the (*Z*)-double bond or destroying the dienyl ester moiety (**Scheme 77**). Other acid sensitive groups like TBS ethers and acetals also remain intact in the reaction conditions. The latter case is noteworthy taking into account how difficult it is to cleave thioacetals under classical hydrolytic conditions.



Scheme 77

Attempts to deprotect the dithiane in the advanced hemibrevetoxin intermediate **172** (**Scheme 78**) were thwarted by low yields and messy reactions under a wide range of conditions[111] [MeI, $NaHCO_3$, acetone–H_2O; $(CF_3CO_2)_2IPh$, MeCN–H_2O; NIS, $AgNO_3$, MeCN–H_2O; I_2, $NaHCO_3$, acetone–H_2O]. The best results were obtained with $Hg(ClO_4)_2$, $CaCO_3$, THF–H_2O at −15 °C. Reasoning that the problem was caused by participation of the ring oxygen atom at C-4a, the deprotection was later accomplished in 91% yield with I_2 under mildly basic conditions on the intermediate **173** in which oxygen participation is blocked.

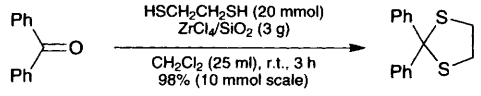


Scheme 78

The full details on oxidative removal of 1,3-dithiane protecting groups by DDQ (2,3-dichloro-5,6-dicyano-*p*-benzoquinone) have been published.[112] The method allows the selective cleavage of 1,3-dithianes in the presence of 1,3-dithiolanes and diphenyl dithioacetals.

Patney and Margan[113] reported a new method for thioacetalisation of carbonyl compound using ethane-1,2-dithiol and catalytic amount of anhydrous zirconium(IV) chloride dispersed on silica gel. The high reactivity of the catalyst is clearly demonstrated by the fact that even less reactive aromatic ketones (*e.g.* benzophenone **174**, **Scheme 79**) react at room temperature to give the corre-

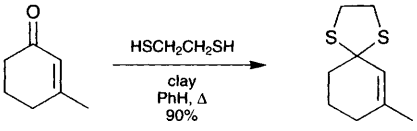
sponding dithioacetals in high yields. The method can be used to protect α,β-unsaturated aldehydes but fails in case of α,β-unsaturated ketones.



174

Scheme 79

Natural kaolinic clay is an efficient catalyst for the acetalisation of aldehydes and thioacetalisation of aldehydes and ketones.[114] The special feature of the catalytic process is that α,β-unsaturated ketones (*e.g.* **175**, **Scheme 80**) undergo protection without the shift of the double bond to β,γ-position. Aldehydes can be protected in the presence of ketones.



175

Scheme 80

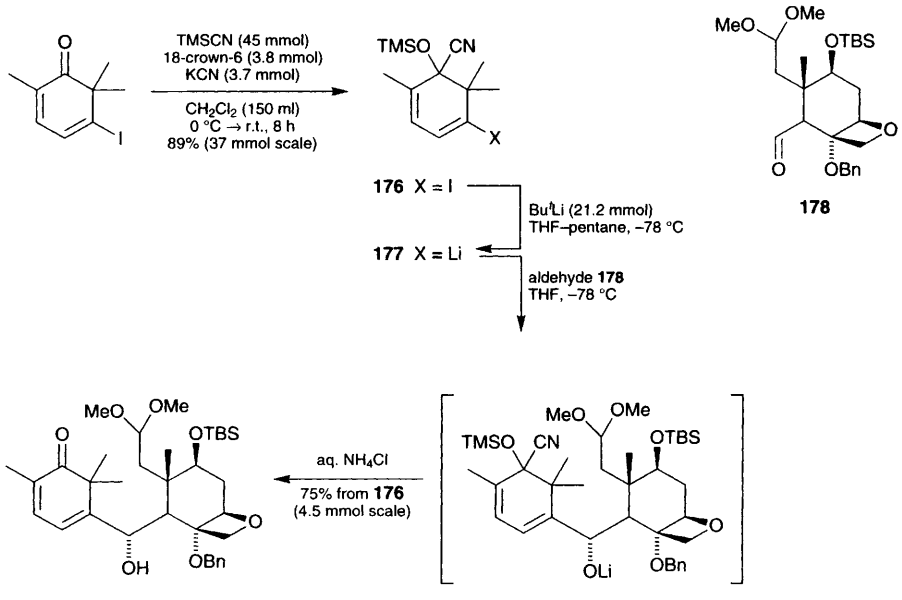
O-Trimethylsilyl cyanohydrins are not robust but they do offer the opportunity for temporary protection of a carbonyl group which must soon be deprotected under mild conditions. For example, a key fragment linkage reaction in the synthesis of Taxol and baccatin III by Danishefsky and co-workers[76] involved generation of the lithium reagent **177** (**Scheme 81**) and its condensation with aldehyde **178** to give a single adduct in which the *O*-trimethylsilyl cyanohydrin was easily hydrolysed on workup. The compatibility of the alkenyllithium with a nitrile function at low temperature in this sequence was noteworthy.

8 Amino protecting groups

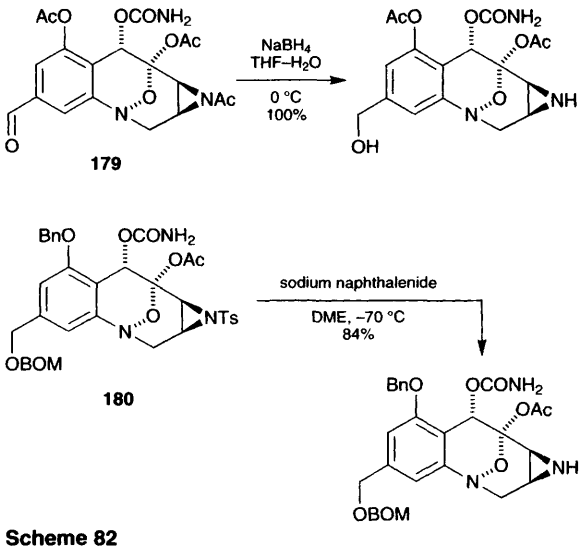
The usual resilience of amides in the presence of nucleophiles does not extend to amides of aziridines in which strain diminishes the deactivation of the amide carbonyl through resonance. A case in point comes from a recent synthesis of the potent antitumour agent FR900482 by the Terashima group.[64,115] Simultaneous reduction of the carbonyl group and deprotection of the *N*-acetylaziridine in **179** (**Scheme 82**) was accomplished with sodium borohydride without detriment to the phenolic ester. Later in the same synthesis, an aziridinyl tosyl group was cleaved with sodium naphthalenide without affecting the N–O bond or the benzyl or BOM ether groups in **180**.

Fraser-Reid has provided further testimony as to the value of the tetrachlorophthalimide (TCP) group for the protection of primary amines in aminoglycoside and glycopeptide synthesis.[116] Amongst the many advantages of the TCP group are (a) the low cost of tetrachlorophthalide; (b) high crystallinity; (c) its easy cleavage with ethylenediamine; (d) the easy removal of the highly insoluble cleavage product. Benzoate esters survive the cleavage as illustrated in **Scheme 83**. Cleavage of the TCP group was accomplished with ethylenediamine (1.8 equiv.) in a mixture of acetonitrile, tetrahydrofuran and ethanol at 60 °C. The solvent composition is significant: in the presence of methanol significant racemisation and complete transesterification were observed. Acetate esters are less robust than the corresponding benzoates.

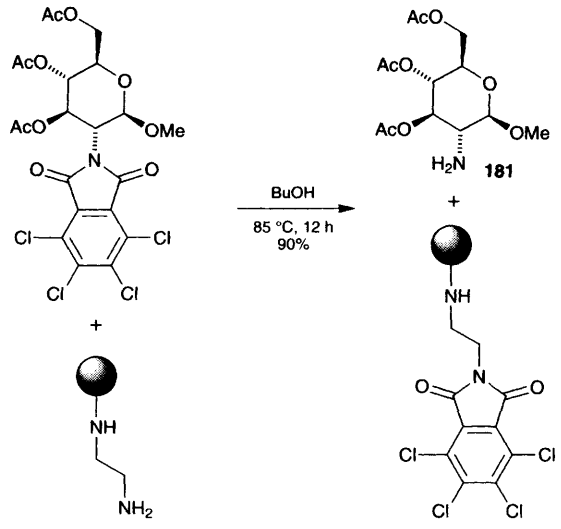
Stangier and Hindsgaul have shown that TCP groups can be removed from carbohydrate derivatives using alkyldiamines immobilised on polystyrene



Scheme 81



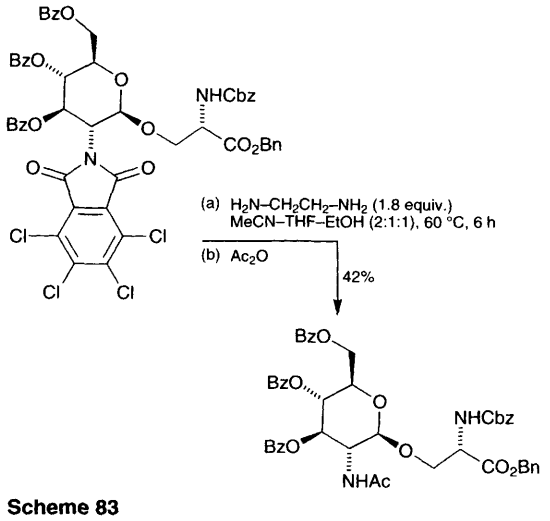
Scheme 82



Scheme 84

beads[117] (**Scheme 84**). The protecting group and reagent remain on the beads and the free amino sugar **181** is recovered in 81–96% yield by simple filtration and evaporation. The survival of the acetate functions using the bound variant of the diamine is noteworthy.

Barany and co-workers[118] have described an 'active ester' approach to the synthesis of 2-acetamido-2-deoxy-β-D-glucopyranose *O*-glycosides with the side chain hydroxy groups of serine and threonine which are building blocks for the solid phase synthesis of glycopeptides. At the heart of the active ester approach is the use of pentafluorophenyl (Pfp) esters in the dual role of protection and activation of the carboxy group of the amino acid. However, the procedure poses special problems arising from the 2-amino substituent in the glycosyl donor: activation of donors with a 2-*N*-acyl group (*e.g.* chloroacetyl, trichloroacetyl, allyloxycarbonyl, and



Scheme 83

2,2,2-trichloroethoxycarbonyl) provides relatively unreactive oxazoline intermediates whereas the phthaloyl group requires prolonged base treatment at elevated temperatures for its removal. The dithiasuccinoyl (Dts) group, on the other hand, provides protection equivalent to the ubiquitous phthaloyl group but has the advantage of being removed rapidly without affecting the Pfp ester by reduction with zinc in the presence of acetic anhydride to give the requisite *N*-acetyl group directly. The sequence for the introduction of the Dts group and its subsequent reductive cleavage is illustrated in **Scheme 85**. The Dts group can also be removed by thiolysis with mercaptoethanol or *N*-methylmercaptoacetamide.[119–121]

The *n*-pent-4-enoyl group, which has proved a powerful tool in carbohydrate synthesis,[122] has been adapted for the protection of nucleobases during solid phase oligonucleotide synthesis. Thus the simultaneous oxidation of the internucleotidic H-phosphonate link as well as deprotection of the nucleobases of the model support-bound dimer **182** (**Scheme 86**) was achieved on simple treatment with iodine (2% in pyridine–H_2O, 98:2, 30 min).

The 2,4-dimethylpentan-3-yloxycarbonyl (Doc) group has been recommended for the protection of tryptophan in Boc solid phase peptide synthesis.[123] It protects the tryptophan against *tert*-butylation during deprotection of *tert*-butyl esters and Boc groups (50% CH_2Cl_2–TFA); however, it is removed during cleavage of the peptide from the resin with strong acid. **Scheme 87** illustrates a method for introducing the Doc group (illustrated in structure **183**). Doc protection for the imidazole ring of histidine combines several features that make it useful for solid phase peptide synthesis using Boc chemistry.[124] It is readily cleaved by liquid HF, stable to trifluoroacetic acid, and soluble in nonpolar organic solvents. Although the Doc group is also highly resistant to nucleophiles, thereby

avoiding N^{im} to N^{π} transfer and premature cleavage by other nucleophiles during solid phase synthesis, it is cleaved rapidly by 5% hydrazine in DMF (half-life 5 min). Comparison with the 2-adamantyloxycarbonyl (Adoc) group, another urethane-type protecting group for histidine, is instructive: the Adoc group had a half-life of 12 min in 20% piperidine in DMF whereas the Doc group had a half-life of 84 h.

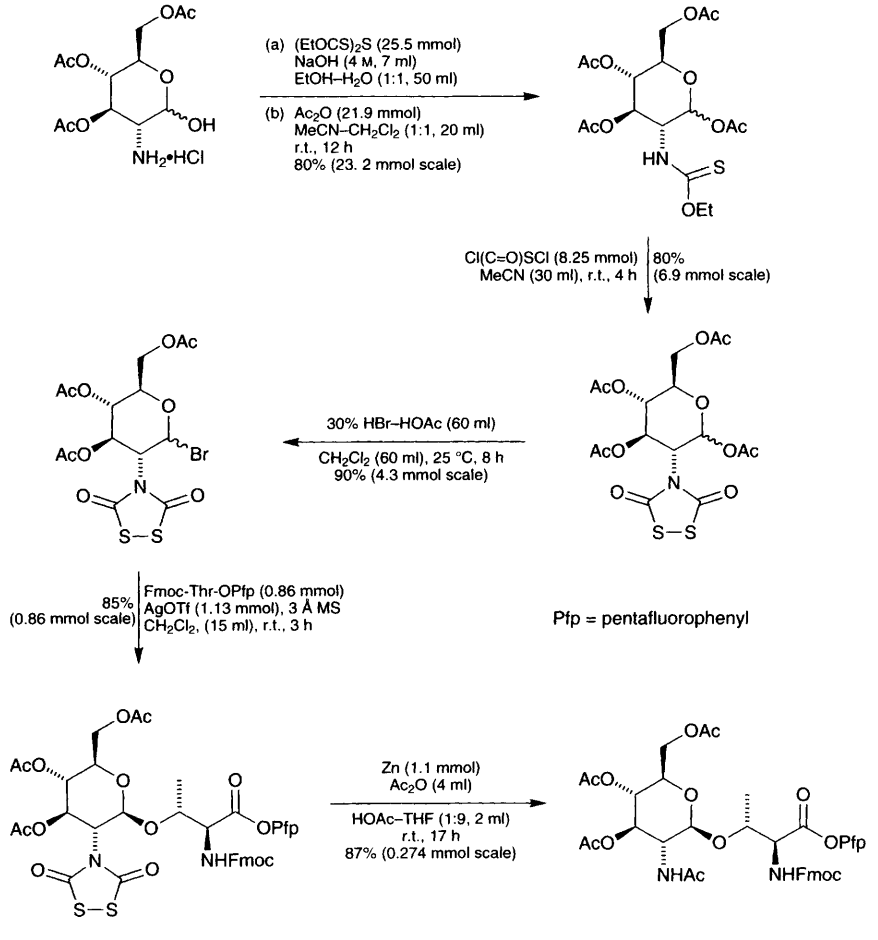
Hwu and co-workers[125] reported that *tert*-butoxycarbonyl (Boc) protected amines, alcohols and thiols can be efficiently deprotected using a catalytic (0.2 equiv.) amount of cerium(IV) ammonium nitrate (CAN) in acetonitrile. Under the reaction conditions several acid sensitive groups survive including isopropylidene, (dimethylamino)methylidene, *tert*-butyldimethylsilyl and acyl functionalities. Functionalities such as benzyl esters as well as indole, pyrimidine and phthalimide nuclei also remain intact. In the case of esters of amino acids (*e.g.* **184**, **Scheme 88**), the deprotected product **185** is obtained without any detectable racemisation.

Cavelier and Enjalbal[126] reported the selective removal of *N*-Boc protection in the presence of either TBS or TBDPS ethers (*e.g.* dipeptide **186**, **Scheme 89**) using a saturated solution of HCl in ethyl acetate. The choice of solvent is crucial to get high selectivity; in methanol the fully deprotected product is obtained.

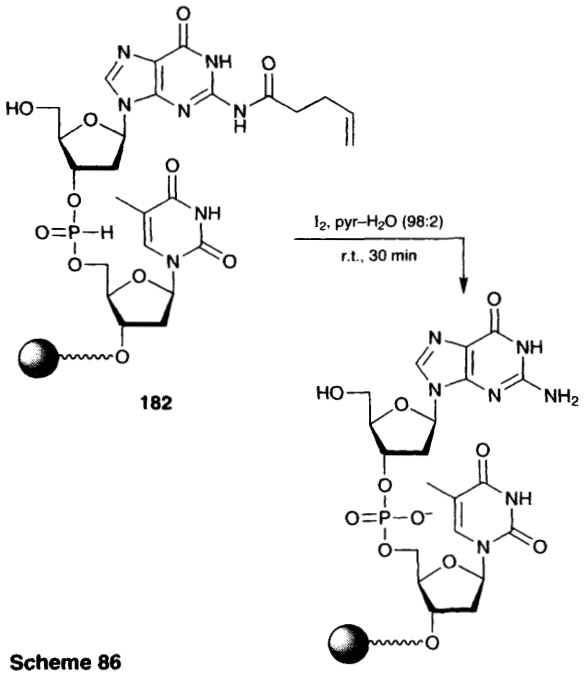
A combination of silicon tetrachloride and phenol as a reagent for the deblocking of Boc-protected amino groups in solid phase peptide synthesis has been reported.[127]

Boc-protection of hindered amino acids using the standard conditions [NaOH, dioxane, H_2O and di-*tert*-butyl dicarbonate $(Boc)_2O$] gives only modest yields because the destruction of the Boc_2O competes with the acylation. Much improved yields are obtained by running the reaction in acetonitrile in the presence of the soluble tetramethylammonium salt of the amino acid[128] (**Scheme 90**).

The van Boom laboratory[129] has reported a synthesis of the tyramine spacer-containing tetramer **189**, a derivative of the phenolic glycolipid of *Mycobacterium kansasii* serovar I. An early attempt to construct **189** (**Scheme 91**) using a Cbz protecting group for the tyramine nitrogen failed owing to unexpected deprotection during a radical deoxygenation of a thiocarbonate using Bu_3SnH in refluxing toluene. The authors modified their procedure and used the phenacetyl unit in **188** to protect the tyramine nitrogen, removing it in the final step using immobilised Penicillin-G acylase. Note that the acetate ester function survived unscathed.

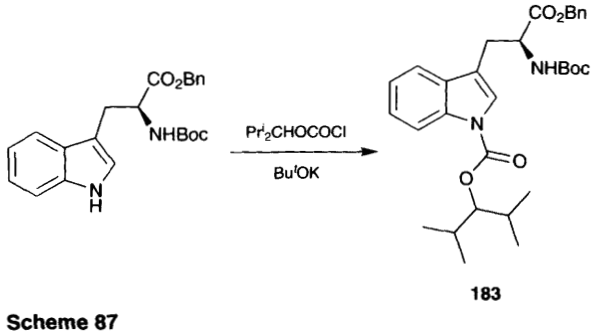


Scheme 85



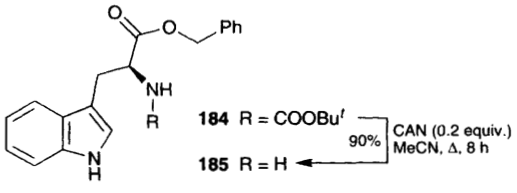
182

Scheme 86

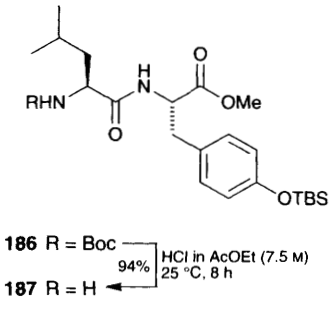


183

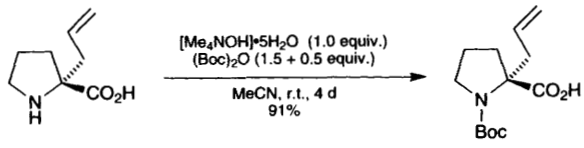
Scheme 87



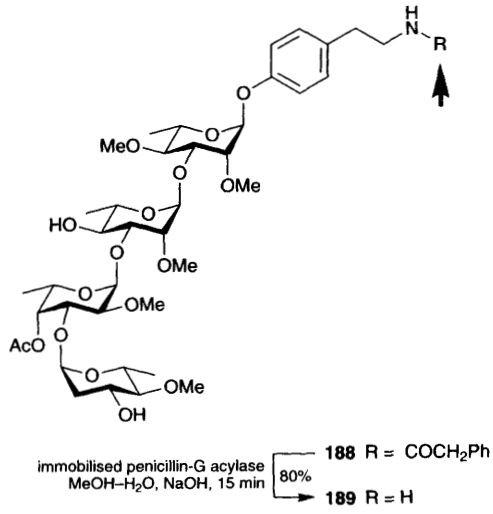
Scheme 88



Scheme 89

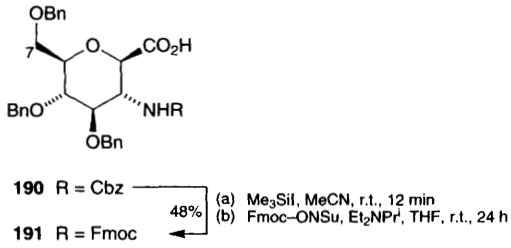


Scheme 90



Scheme 91

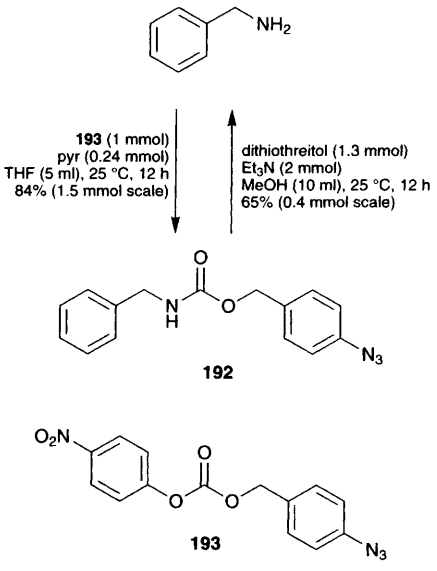
In a synthesis of peptides containing sugar amino acids, the Fmoc-protected building block **191** (**Scheme 92**) was required.[130] Attempts to prepare **191** from **190** using catalytic hydrogenolysis or TFA and thioanisole were frustrated by competing cleavage of the benzyl ethers. The best results for selective cleavage of the Cbz group were obtained using trimethylsilyl iodide in acetonitrile[131] though C-7–*O*-benzyl ether cleavage was still observed to some extent. The resultant free amine was trans-protected to its Fmoc derivative using fluoren-9-ylmethyl succinimidyl carbonate (Fmoc–ONSu).



Scheme 92

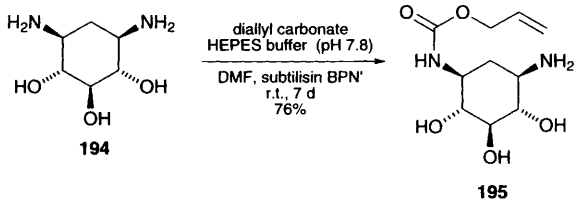
Griffin and co-workers[132] reported the use of 4-azidobenzyloxycarbonyl (ACBZ) groups for the protection of amines. The protection is achieved by the reaction of an amine with 4-azidobenzyl 4-nitrophenyl carbonate (**193**, **Scheme 93**). Alternatively the protected aromatic amine can be prepared directly by the treatment of 4-azidobenzyl alcohol with an aryl isocyanate. In the deprotection

procedure, 4-azidobenzyloxycarbamates (*e.g.* **192**) undergo rapid reduction in the presence of dithiothreitol (*threo*-1,4-dimercaptobutane-2,3-diol), and the resultant 4-aminobenzyloxycarbamates undergo immediate cascade degradation to release the target amine. Since azide reduction can be done under very mild conditions, the ACBZ group may be removed in the presence of other amine-protecting groups.



Scheme 93

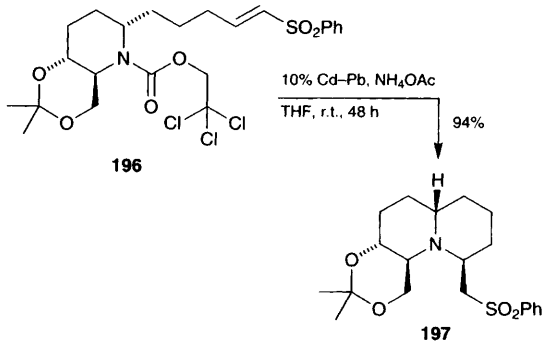
Wong and co-workers.[133] described a novel enzymatic method for the protection of amines with homocarbonates and subtilisin BPN′ or lipase from *Candida cylindracea* (CCL) as enzymes. Diallyl carbonate turns out to be the most useful substrate for the reaction. With the aid of subtilisin BPN′, *meso*-2-deoxystreptamine **194** (**Scheme 94**) was converted into carbamate **195** with excellent chemo- and enantio-selectivity (>99% ee) despite five possible sites of reaction.



HEPES = 4-(2-hydroxyethyl)piperazine-1-ethanesulfonic acid

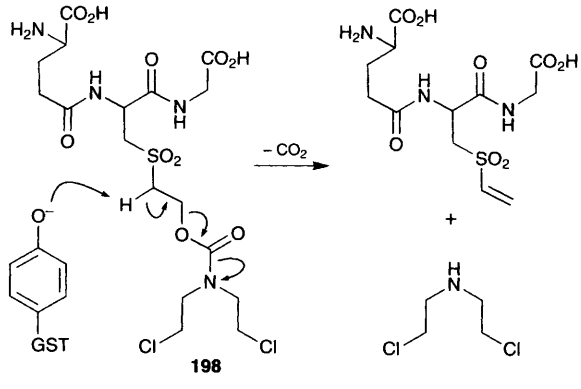
Scheme 94

During a synthesis of the marine antitumour alkaloid clavepictine, Momose and co-workers[134] constructed the *cis*-quinolizidine core **197** (**Scheme 95**) by an intramolecular Michael addition initiated by the reductive deprotection of the *N*-Troc (Troc = 2,2,2-trichloroethylcarbamoyl) group in substrate **196** using Cd-Pb alloy.[135]



Scheme 95

A major cellular defence mechanism utilises the tripeptide glutathione in conjunction with glutathione *S*-transferase (GST) as a scavenger for toxic electrophiles. In many types of cancer tissue, elevated levels of GST have been observed thereby offering an opportunity for selective targeting. For example,[136] the glutathione analogue **198** (**Scheme 96**) binds to GST in which a proximate tyrosine causes release of a nitrogen mustard protected as its [2-(alkylsulfonyl)ethyl]carbamate. The powerful alkylating agent then causes destruction of the cell.



Scheme 96

The deprotection of *N*-sulfonylated amides can be achieved under neutral conditions by reaction with Bu_3SnH in boiling toluene.[137] The deprotection works well with *N*-benzoyl and related amides (e.g. **199**, **Scheme 97**) but *N*-acetyl derivatives are inert under the reaction conditions.

Scheme 97

The Danishefsky group.[138] reported a synthesis of the Hakomori MBr1 glycosphingolipid (**201**, **Scheme**

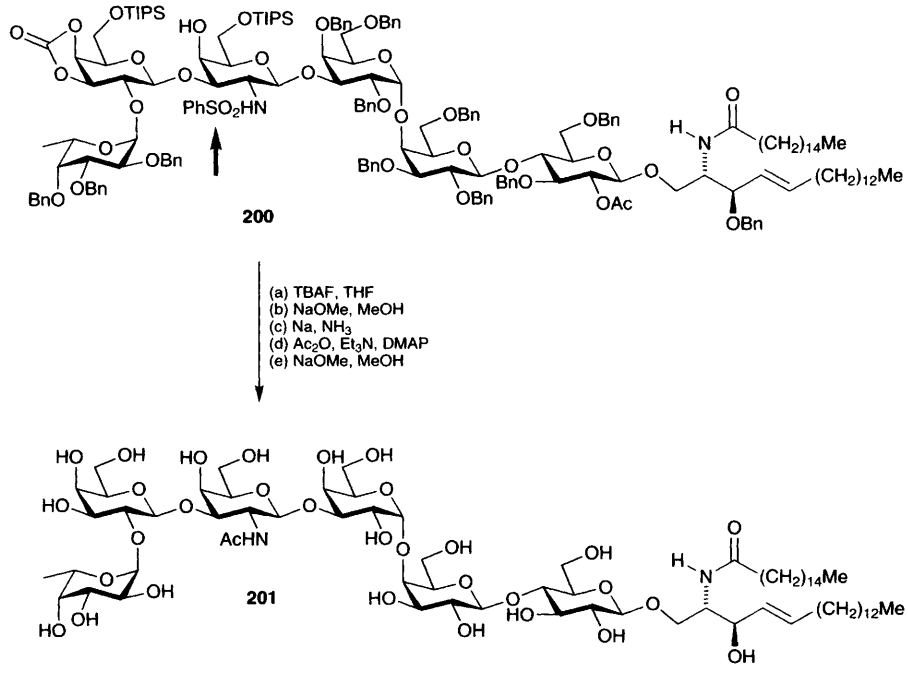
98) which is a human breast cancer antigen. The last five steps of the synthesis were all concerned with protecting group manipulations. Treatment of **200** with TBAF followed by sodium methoxide–methanol resulted in cleavage of the two TIPS groups, an acetate, and the cyclic carbonate (94% for the two steps). The 12 benzyl groups and the lone phenylsulfonamido groups were then reductively cleaved by sodium in liquid ammonia. Finally, exhaustive acetylation followed by deacetylation with sodium methoxide–methanol returned the target antigen **201** in 72% overall yield for the five steps.

Progress on the synthesis of the phenanthridone alkaloid pancratistatin[139] was impeded when the tosyl group from the *N*-tosyl lactam **203** (**Scheme 99**) could not be removed reductively (sodium amalgam, sodium naphthalenide, samarium diiodide); reduction of the lactam carbonyl to the hemiaminal occurred instead. The problem was solved at the expense of six additional steps by removing the tosyl group from the earlier precursor **202** before closure of the lactam ring. Thus acylation of the tosylamide moiety in **202** gave the *N*-tosylcarbamate **205** whereupon reductive cleavage of the tosyl group was easily accomplished using sodium–anthracene[140] in DME at −75 °C. The yield of carbamate **206** after removal of the TBS group with TBAF was 82%. A further six steps then accomplished the synthesis of the target intermediate **204**.

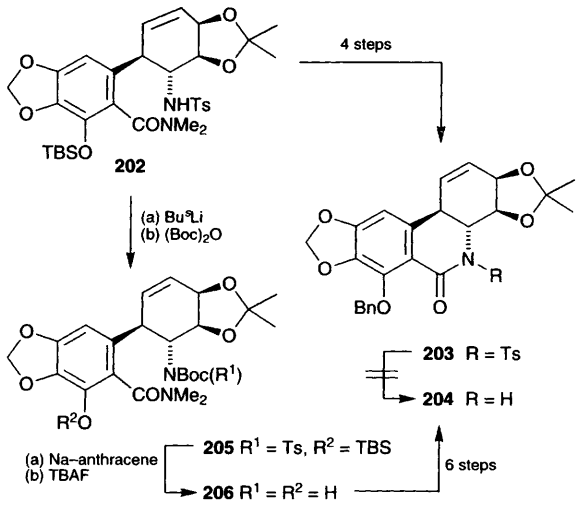
Cai and Soloway[141] prepared a series of spermine and spermidine ligands harbouring a carborane moiety in an attempt to target brain tumours using boron neutron capture therapy. Owing to the incompatibility of the carborane system with strong bases, acid labile protecting/activating groups for the nitrogen were required. The mesitylsulfonyl group served both functions admirably. Cleavage was accomplished in the final step using conc. HCl in refluxing ethanol to give the hydrochloride salt of the spermine derivative **208** (**Scheme 100**).

The Vedejs group[142] has reported two new heteroarene-2-sulfonyl chlorides for the protection of amino groups as sulfonamides during peptide synthesis (**Scheme 101**). Benzothiazole-2-sulfonyl chloride (**209**, 'betsyl' chloride, BtsCl) and 5-methyl-1,3,4-thiadiazole-2-sulfonyl chloride (**210**, 'thisyl' chloride, ThsCl) were prepared from the corresponding thiols by oxidation with excess chlorine in aqueous acetic acid. Both compound were crystalline and stable for months in the freezer but they gradually decomposed with loss of sulfur dioxide on standing at room temperature. Simple amines react rapidly with **209** and **210** under aprotic conditions whereas zwitterionic amino acids were best protected using a suspension of the sulfonyl chloride in aqueous sodium hydroxide while maintaining the pH in the range 10–10.5. This method gave crystalline *N*-Bts and *N*-Ths derivatives in 92–97% yield with alanine, valine, phenylalanine, proline and phenylglycine. The Bts group is cheaper but the Ths group reacts faster in the *N*-protection step and it has better solubility and crystallinity in some cases.

The stability of the Bts group towards typical orthogonal deprotection conditions was assayed using *N*-Bts-phenylglycine (Bts-Phg) as a substrate. Thus, Bts-Phg survived conditions that cleave Boc (trifluoroacetic acid, 2 days at room temperature) or Fmoc (diethylamine, DMF, 21 h, room temperature). Slow cleavage did occur in trifluoroacetic acid–thiophenol after 2 days at room temperature (*ca.* 25%) and Z hydrogenolysis conditions (H_2, Pd/C, EtOAc) resulted in partial cleavage and catalyst poisoning. *N*-Bts-proline was cleaved with



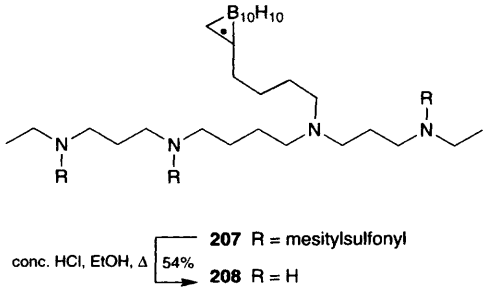
Scheme 98



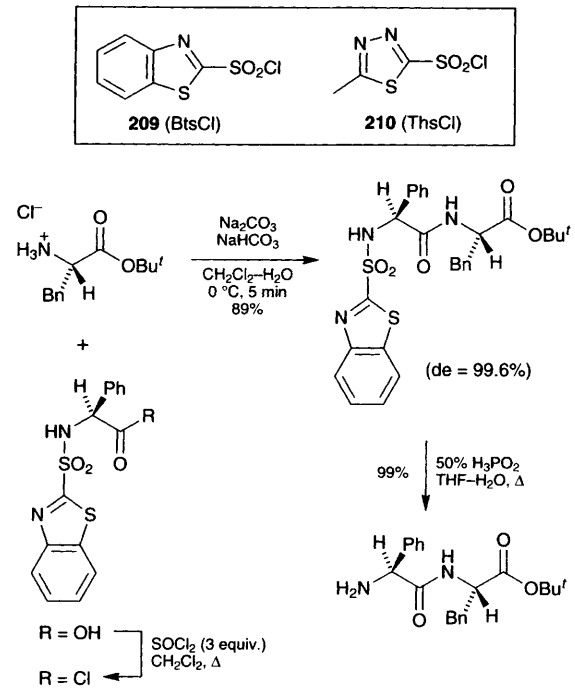
Scheme 99

2.5 M NaOH at room temperature after 12 h with very little racemisation whereas Bts-Phg required harsher conditions: 1.0 M NaOH at 90–100 °C for 24 h in which case racemisation was nearly complete. Removal of the *N*-Bts or *N*-Ths groups was best accomplished at room temperature by treatment with (a) Zn, HOAc–EtOH, (b) Al(Hg), ether–H_2O, or (c) 50% H_3PO_2 in DMF. Alternatively, deprotection can be accomplished using sodium dithionite or sodium hydrogen sulfite in refluxing EtOH–H_2O. **Scheme 101** illustrates one of the prime virtues of the new protecting groups: they are stable to the conditions required to make acid chlorides which can be used in peptide coupling with hindered amino acids without the need for additives.

Boger and co-workers.[143] used Weinreb's [2-(trimethylsilyl)ethyl]sulfonyl (SES) group[144] to protect the amino group of a serine residue during a total synthesis of the potent antitumour decadepsipeptide (−)-sandramycin (**Scheme 102**). Removal of the two SES protecting groups from the symmetrical intermediate **211** was accomplished with TBAF (10 equiv.) in the presence of Boc_2O (30 equiv.) at room temperature so that the liberated amine could be trapped as its Boc derivative before it could react with the proximate ester function—a reaction which occurred under the more basic conditions associated with TBAF alone. The mildness of the reaction conditions were welcome

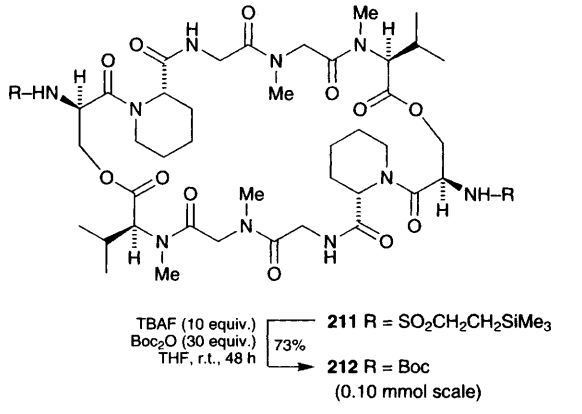


Scheme 100



Scheme 101

and fortuitous since deprotection of SES-protected amines usually requires higher reaction temperatures (50–100 °C). The authors speculate that Boc acylation precedes and activates the subsequent SES deprotection. Under the acidic conditions of the Boc deprotection, the liberated amine is protonated and therefore cannot react with the ester function.

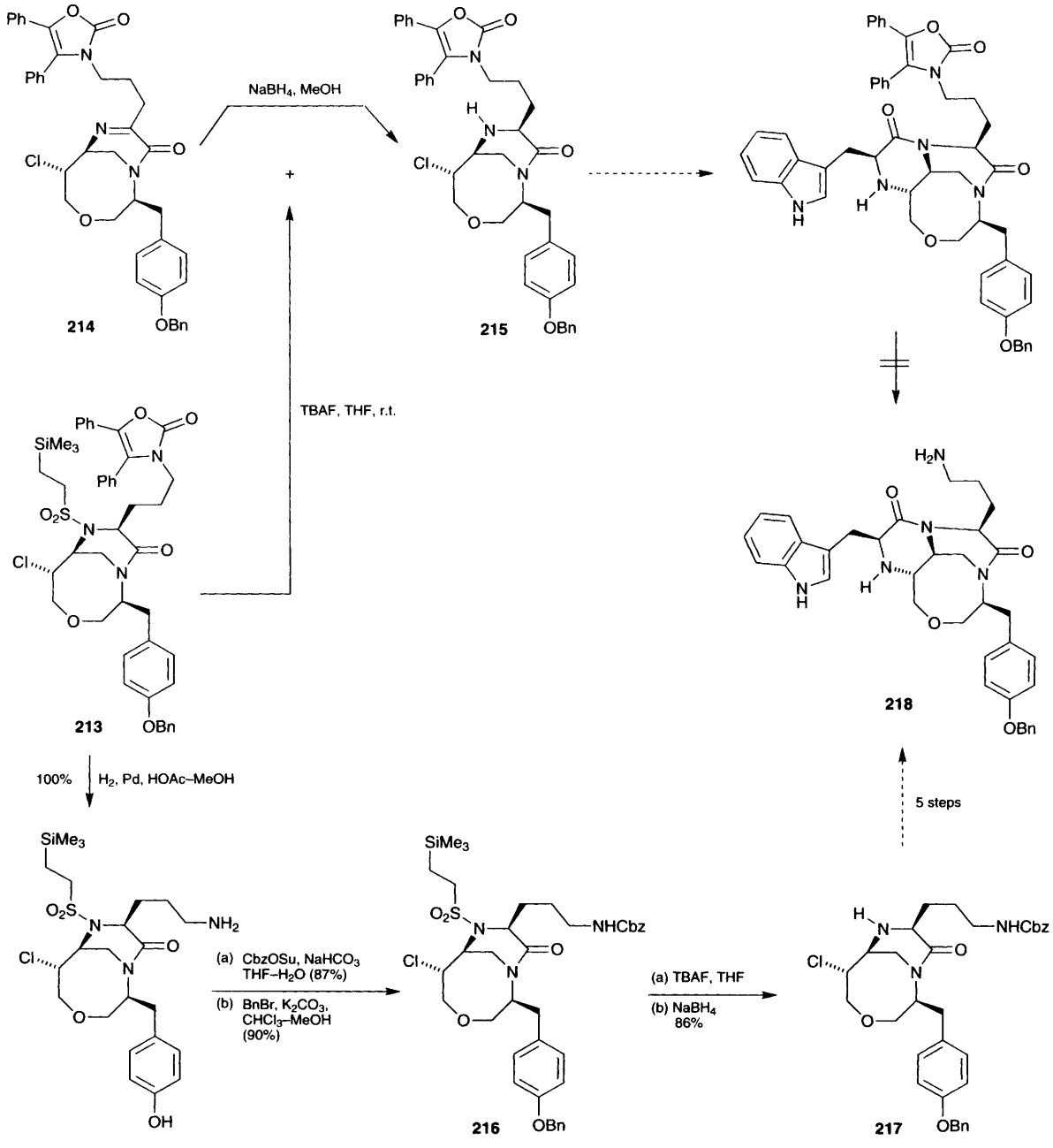


Scheme 102

A synthesis of a peptidomimetic designed to mimic the α-amylase inhibitor tendamistat was beset by a number of problems including complications with protecting groups. The synthesis required a robust protection scheme for the two nitrogens of ornithine. Kozlowski and Bartlett[145] chose the SES group to protect the α-nitrogen and the seldom used diphenyloxazolone group[146] to protect the δ-nitrogen (**Scheme 103**). For the purposes of this discussion, we consider the efforts to convert **213** to the tricyclic

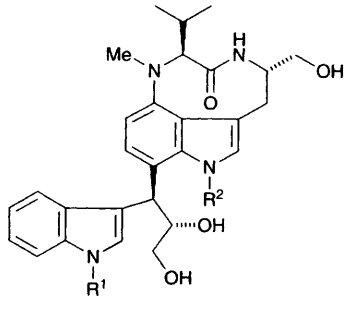
derivative **218**. Deprotection of the SES group in **213** with TBAF occurred at room temperature to give **215** together with an unprecedented β-elimination by-product **214**—the ease of deprotection and the side reaction being a consequence of the severe steric crowding in the substrate. Fortunately, the imine in **214** could be reduced to **215** with sodium borohydride. Problems were then encountered in the deprotection of the δ-amino function. In spite of a number of precedents for removal of the diphenyloxazolone group under mild conditions,[147–150] its cleavage under hydrogenolytic conditions was preceded by cleavage of the phenolic benzyl ether whereupon the more forcing conditions required for removal of the diphenyloxazolone also attacked the indole. Success was finally achieved by a detour involving inversion of the deprotection sequence. Thus, simultaneous deprotection of the oxazolone and benzyl ether groups followed by reprotection gave the Cbz-protected derivative **216** in good yield. Now removal of the SES group with TBAF gave the free amide **217** which was converted to the desired target **218** in five further steps.

Cytoblastin (**220**) is an immunomodulator produced by *Streptoverticillium eurocidium*. Recently Moreno and Kishi.[151] completed a synthesis of cytoblastin which established its stereochemistry. In the last step of the synthesis, a SES and a SEM group protecting the two indole nitrogens were removed from intermediate **219** (**Scheme 104**)



Scheme 103

simultaneously. Whilst removal of the SES was fast, the SEM group resisted cleavage under the usual conditions.[152,153] Success was eventually achieved by performing the deprotection in neat TBAF under vacuum, whence the rate of deprotection was observed to increase with the degree of vacuum suggesting that the rate determining step involves an equilibrium between the hemiaminal and the free indole NH.



219 R^1 = SES, R^2 = SEM
220 $R^1 = R^2$ = H
90%
TBAF (neat)
0.1 mmHg

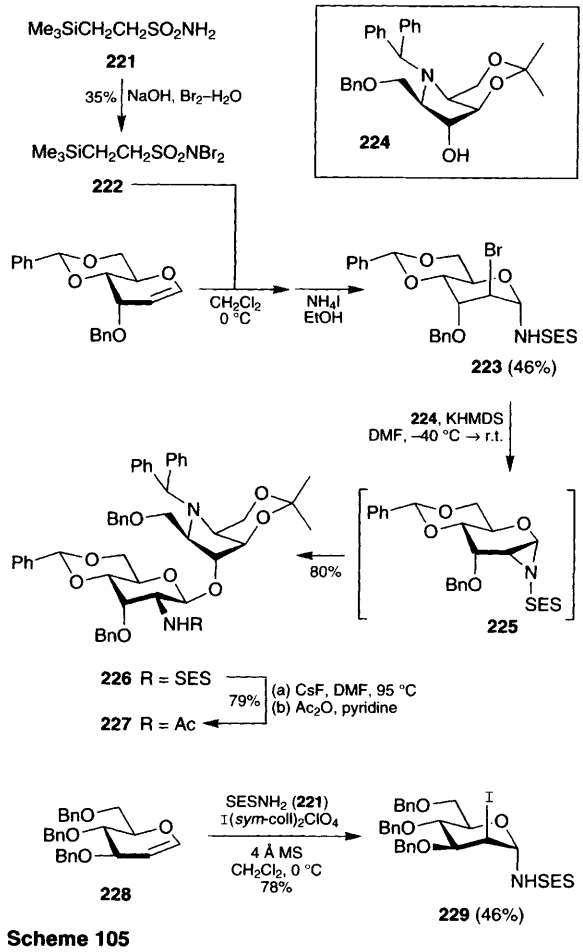
Scheme 104

A key step in a synthesis of the chitinase inhibitor allosamidin by Griffith and Danishefsky[154] used *N,N*-dibromo-2-(trimethylsilyl)ethanesulfonamide (**222**) as an electrophilic sulfonamidoglycosylation reagent (**Scheme 105**). The initial *N*-bromosulfonamide adduct (not shown) was reduced with ammonium iodide to give the 2-(trimethylsilyl)ethanesulfonyl (SES) protected amine derivative **223** in 46% yield. Treatment of the adduct **223** with potassium hexamethyldisilazide (KHMDS) in the presence of the pyrrolidine **224** gave the SES-protected disaccharide **226** *via* nucleophilic cleavage of the *N*-sulfonylaziridine **225**. Removal of the SES protecting group was accomplished in 79% yield using caesium fluoride in hot DMF. The authors noted that in some cases, the addition of one equivalent of acetic anhydride was necessary to drive the deprotection to completion. In another briefer variant of the methodology, tri-*O*-benzyl-D-glucal (**228**) was treated with 2-(trimethylsilyl)ethanesulfonamide (**221**) in the presence of iodonium di-sym-collidine perchlorate to give a 78% yield of the *trans*-iodosulfonamide **229** which could be used as a substrate in silver-assisted glycosylation.

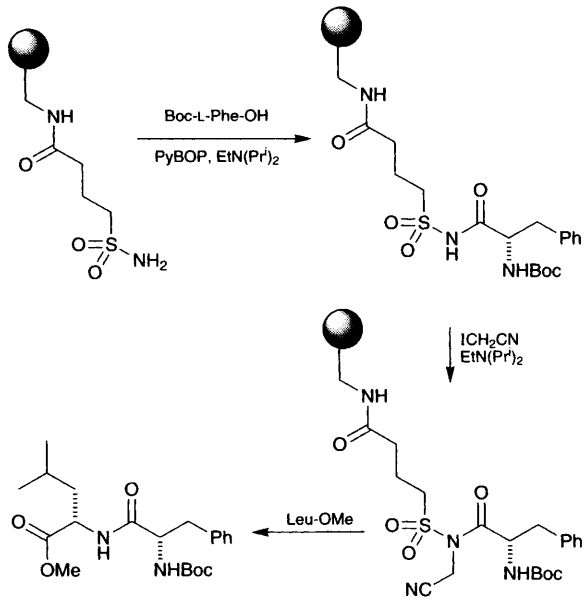
Owing to their stability to acidic and basic conditions, acylsulfonamides are useful linkers for acyl functions to solid supports. Cleavage of the acyl function from the support can be achieved by first activating the sulfonamide through *N*-methylation[155] followed by reaction with alcohols or amines to give ester or amide products respectively. In many cases the reactivity of the *N*-methylsulfonamide is poor but replacement of the methyl by a cyanomethyl group results in at least a 100-fold increase in the rate of cleavage[156] **Scheme 106** illustrates the procedure for peptide synthesis. Unfortunately, a small amount of epimerisation (1.2–1.5%) is observed during the sequence.

During their work on metallation of the methyl group in 5-methyltetrazole **230** (**Scheme 107**), Huff and co-workers[157] required a suitable protecting group for the N-2 position of the tetrazole nucleus. They found that trityl (triphenylmethyl) group (Tr) suits this purpose perfectly for the following reasons: (i) crystalline *N*-trityl-5-methyltetrazole **231** can be prepared in high yield by the reaction of **230** with trityl chloride as a single regioisomer (formation of a mixture of *N*-regioisomers with other protecting groups had been reported previously); (ii) the trityl group was inert to the deprotonation and trapping conditions; (iii) the trapped product (e.g. **232**) can be easily deprotected with anhydrous HCl in dichloromethane.

Overstimulation of mammalian CNS receptors after cerebral ischaemia and trauma can result in irreversible brain damage. Certain polyamine toxins from wasps and spiders block the ionotropic glutamate receptors which mediate signal transduction and offer the prospect of neuroprotection. A solid phase synthesis of polyamine conjugates has been described[158] which utilises the 2-chlorotrityl chloride resin as both a primary amine protector and solid support, and exploits the ability of 2-acetyldimedone



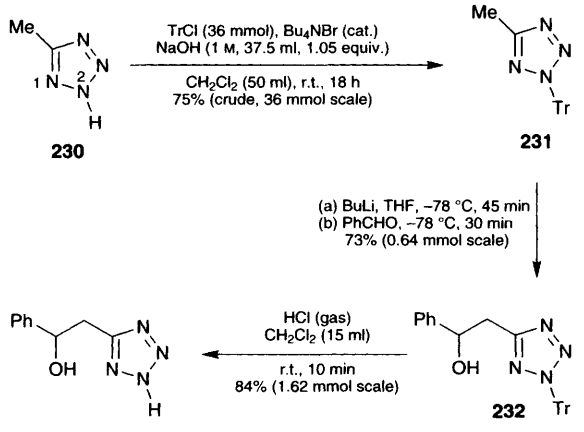
Scheme 105



Scheme 106

to react specifically with primary amines (e.g. **233**) to give a *N*-[1-(4,4-dimethyl-2,6-dioxocyclohexylidene)-ethyl] (Dde) group (**234**, **Scheme 108**). After protection of the remaining secondary amino functions as *N*-Boc derivatives, deprotection of the Dde group with 2% hydrazine restored the primary amino group in **235** which was then elaborated to philanthotoxin-433 (**236**).

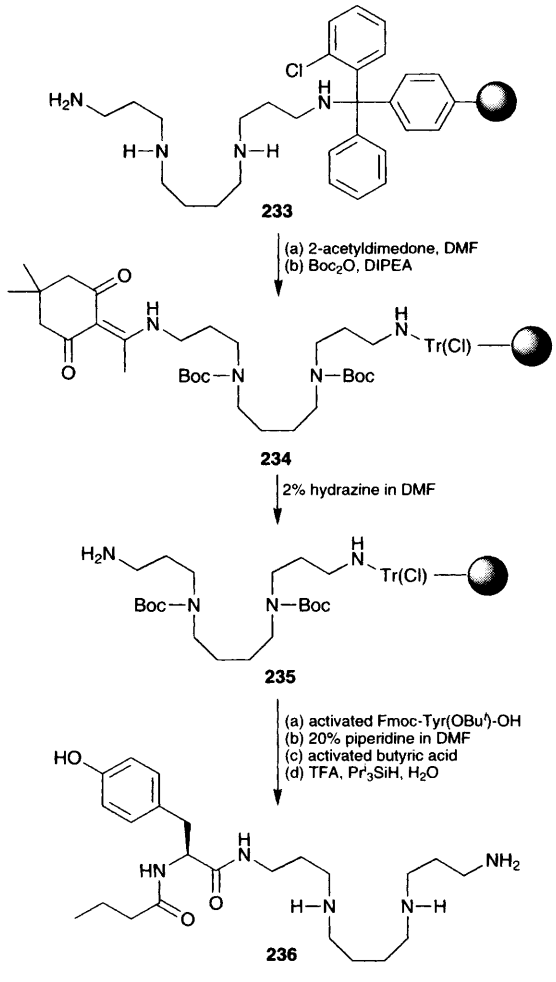
Alkoxyalkyl protection of amidic NH was a core feature in Danishefsky's synthesis of the indolocarbazole alkaloid staurosporine.[40] Staurosporine is a potent inhibitor of protein kinase C and it possesses immunosuppressant activity as well as reversing multidrug resistance. The SEM group was removed from the indole **237** with TBAF to give **238** in 74% yield (**Scheme 109**). Towards the end of the synthesis, the two BOM groups in **239** were cleaved by hydrogenolysis. The authors report sonication of the hydrogenolysis reaction mixture for 20 min prior to stirring at room temperature overnight—a detail presumably introduced to ensure exposure of fresh catalyst surface to the reactants.



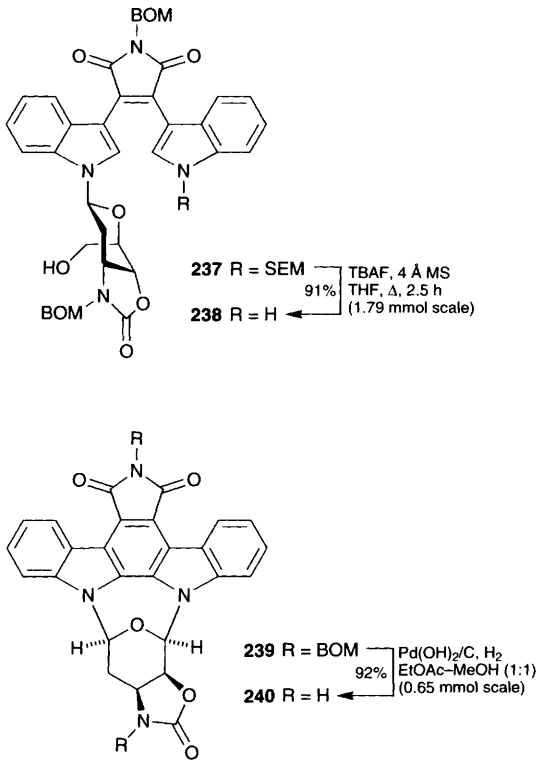
Scheme 107

During a synthesis of nucleoside analogues, Edstrom and co-workers[159] required an N^1 protecting group for pyrrolo[2,3-*d*]pyrimidine-2,4-diones that could be selectively removed in the presence of N^3 benzyloxymethyl (BOM) (or methoxymethyl) group and N^7 *p*-nitrophenylethyl (PNPE) groups. The methylthiomethyl (MTM) group fulfils all requirements though selective deprotection requires three steps (**Scheme 110**): (1) reaction of the fully protected compound **241** with sulfuryl chloride to give chloromethyl derivative **242**; (2) hydrolysis of **242** with aqueous THF in the presence of SiO_2 to give hydroxymethyl derivative **243**; (3) thermal extrusion of formaldehyde from **243** to afford deprotected compound **244**.

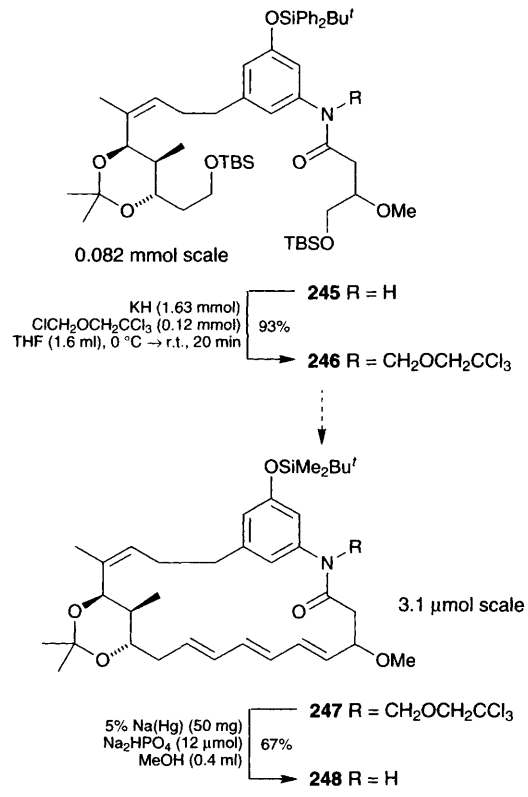
In the closing stages of a synthesis of the novel ansamycin antibiotic trienomycin A, Smith and co-workers[160] found that the choice of amide protecting group for intermediate **245** to be unexpectedly critical (**Scheme 111**). After considerable experimentation with other derivatives (Boc, PMB, SEM), the (2,2,2-trichloroethoxy)methyl group was found to satisfy the needs of the synthesis. Treatment of **245** with chloromethyl 2,2,2-trichloroethyl ether and KH in THF provided the tertiary amide **246** in 93% yield. After conver-



Scheme 108



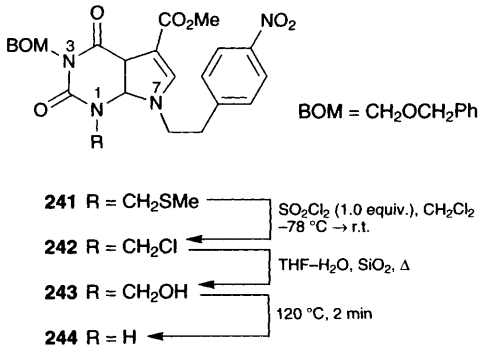
Scheme 109



Scheme 111

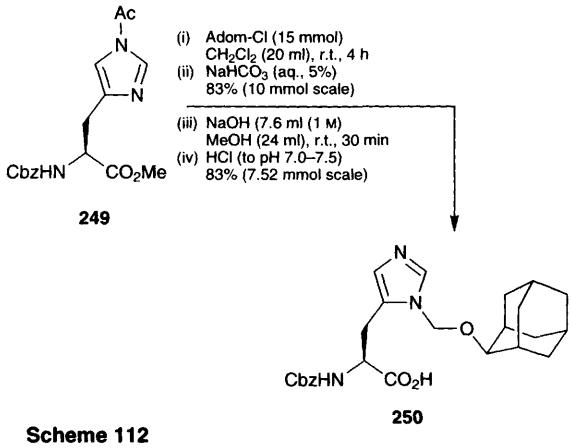
sion of **246** to triene **247**, the protecting group was removed by reductive elimination using buffered sodium amalgam (67% yield). The resultant amide **248** was converted to trienomycins A and F in five further steps. For the use of the (2,2,2-trichloroethoxy)methyl group for the protection of hydroxy functions see Evans' synthesis of cyctovaricin.[161]

A synthesis of thyrotropin-releasing hormone was used to illustrate the benefits of the 2-adamantyloxymethyl (Adom) group for the protection of histidine during solid-phase peptide synthesis.[162] Thus Cbz-(N^{π}-2-adamantyloxymethyl)histidine (**250**) was prepared by from histidine derivative **249** by reaction with 2-adamantyloxymethyl chloride (Adom-Cl) followed by ester hydrolysis as shown in



Scheme 110

Scheme 112. The Adom group was stable to TFA and piperidine–DMF (20%) at room temperature up to 48 h but was rapidly cleaved by triflic acid–TFA–thioanisole or anhydrous HF.

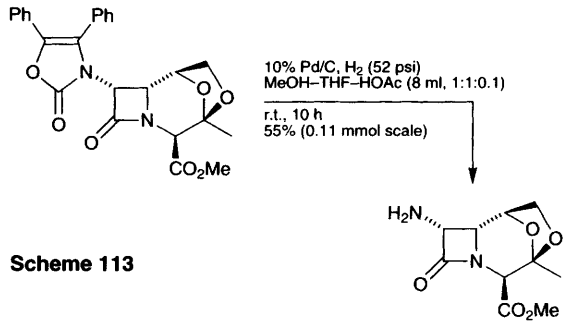


Scheme 112

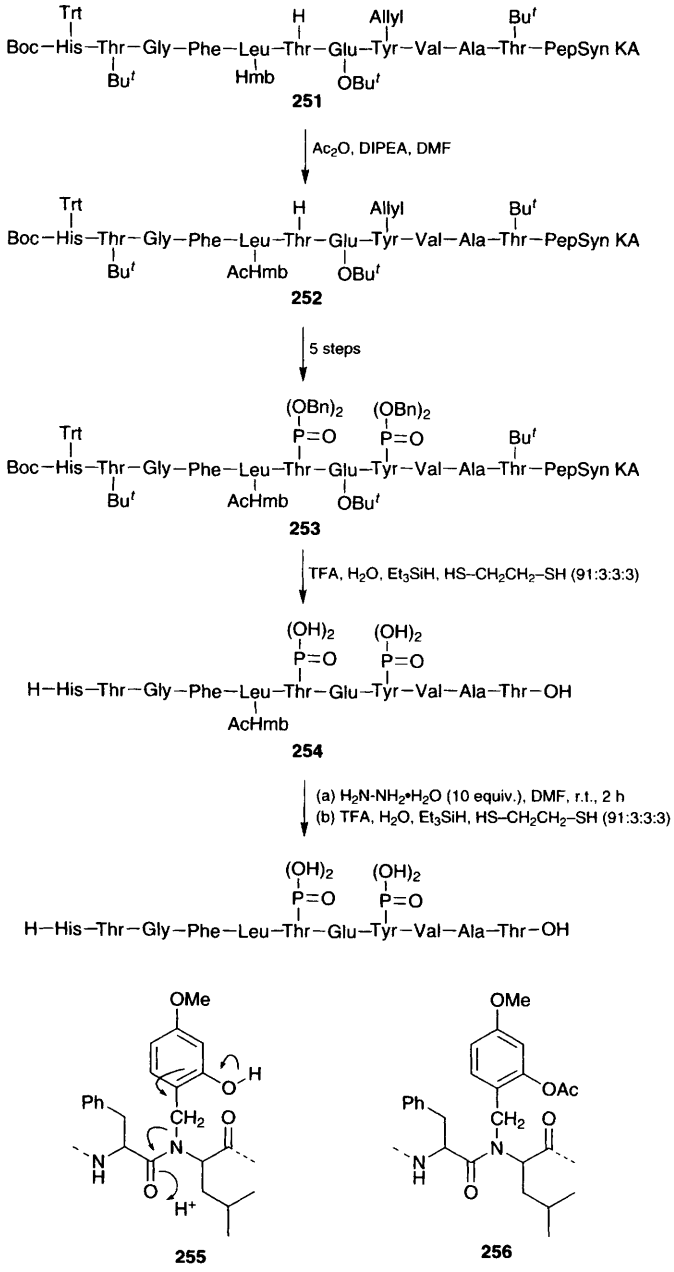
The 4,5-diphenyloxazo-2(3*H*)-one group (abbreviated Ox) first developed by Sheehan and Guziec[146] is very stable towards hydrolysis under acidic or basic conditions and Ox-protected compounds tend to be crystalline, highly fluorescent solids. In the

example[163] shown in **Scheme 113**, the Ox group was best cleaved by hydrogenolysis using 10% Pd/C at 52 psi of hydrogen pressure in methanol–THF containing some acetic acid. The by-product of the hydrogenolysis is 1,2-diphenylethane.

During an attempted solid phase synthesis of the bis-phosphorylated decapeptide encompassing residues 178–188 from the MAP kinase ERK-2, considerable difficulty was caused by peptide chain association and aggregation mediated through intra- and inter-molecular hydrogen bonding. Reasoning that the phenylalanyl–leucyl bond was the offending sequence, Johnson and co-workers[164] substituted the phenylalanyl–leucyl amide N–H bonds with the acid-labile *N*-(2-hydroxy-4-methoxybenzyl)(Hmb) protecting group (**251**, **Scheme 114**). The deleterious aggregation effects were thereby suppressed leading



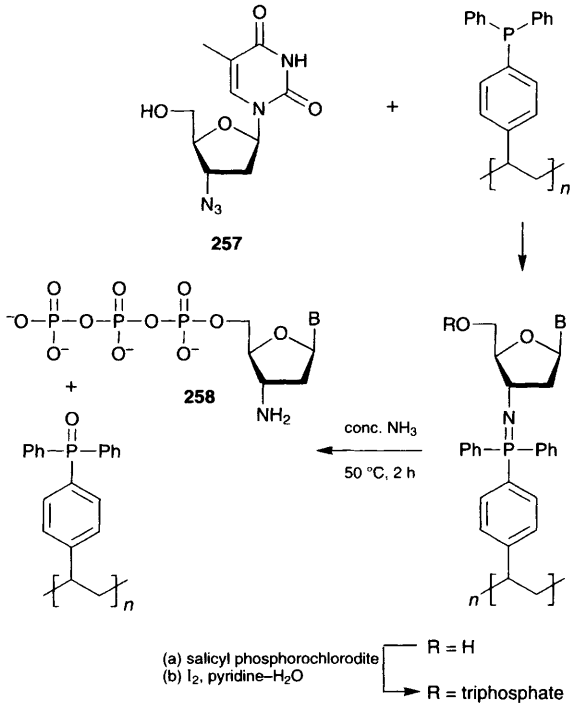
Scheme 113



Scheme 114

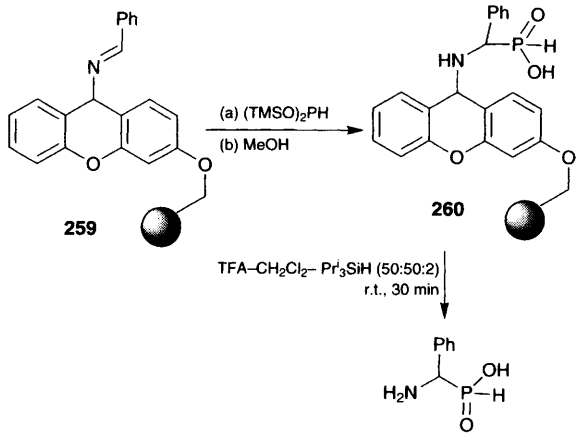
to greatly improved crude product purity. Three features of the sequence outlined in **Scheme 114** deserve comment. First, the acid lability of the Hmb group depends on the free 2-hydroxy group on the aromatic ring (as shown in structure **255**) and hence it must itself be protected as an acetate ester (**252** and structure **256**) in order to prevent its irreversible phosphorylation. Secondly, the acid-stability of the protected Hmb acetate is evident from the deprotection of the *N*-trityl, *O*-Bu^t, and benzyl phosphate groups with TFA (transformation **253**→**254**). Finally, the acid-lability of the Hmb was restored on hydrazinolysis of the acetate **254**.

A German group[165] has shown that polymer-bound triphenylphosphine is suitable for reduction of 2′- or 3′-azidonucleosides to the corresponding aminoglycosides. Since the nucleoside remains bound to the polymer support *via* a stable phosphinimine linkage, chemical manipulations can be performed on the nucleoside whilst the amino group remains protected by the polymer. In the example shown (**Scheme 115**), the 5′-triphosphate of 3′-amino-2′,3′-dideoxythymidine **258** was prepared in 70–75% overall yield based on azidonucleoside **257**.



Scheme 115

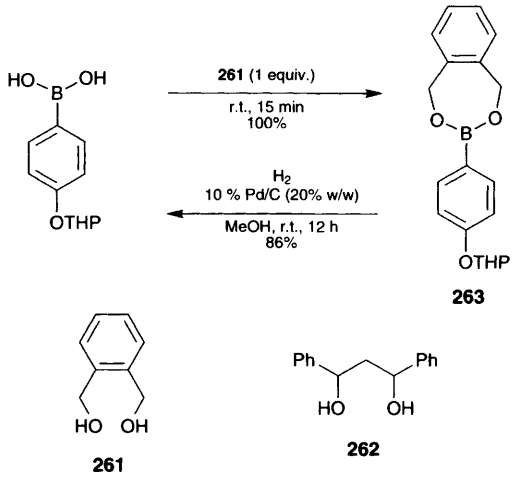
A new solid phase synthesis of phosphinic acids was reported which exploits the acid-lability of 9-amino-xanthenyl groups to release the final product.[166] The procedure entails addition of bis(trimethylsilyl)phosphonite to 9-aryl- or 9-alkyl-iminoxanthen-3-yloxymethyl polystyrene (e.g. **259**, **Scheme 116**) followed by treatment of the resin-bound adduct **260** with 50% TFA.



Scheme 116

9 Miscellaneous protecting groups

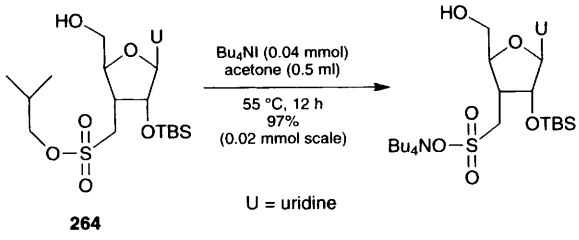
Two reducible protecting groups for boronic acids have been reported by Morin and co-workers[167] (**Scheme 117**). Diol **261** has the advantage that after deprotection by hydrogenolysis, the by-product (*o*-xylene) can be easily removed by evaporation. However, the protected compounds (*e.g.* **263**) are quite susceptible to hydrolysis. Esters derived from diol **262** are more stable but deprotection produces non-volatile 1,3-diphenylpropane which has to be removed by extraction.



Scheme 117

Xie and Widlanski[168] described the application of the isobutyl group for the protection of sulfonates during a synthesis of nucleoside analogues. These esters are stable to prolonged storage and a variety of reaction conditions that degrade isopropyl or ethyl sulfonates. On the other hand, removal of the isobutyl group is easier than removal of the isopropyl group and can be accomplished by treat-

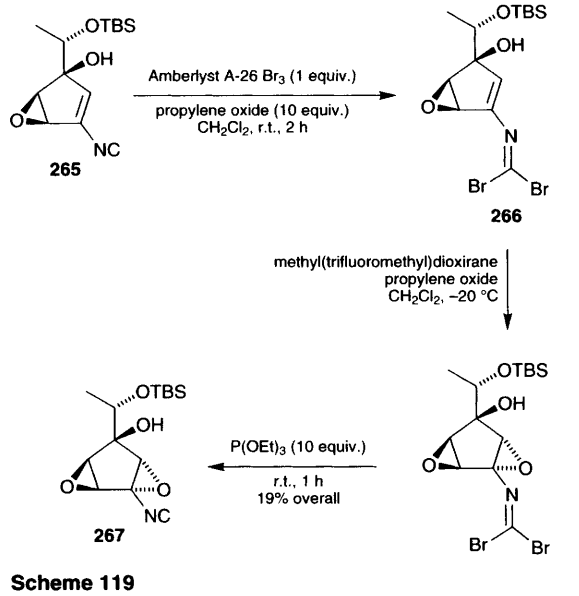
ment of the sulfonate (e.g. **264**) with tetrabutylammonium iodide (**Scheme 118**).



264

Scheme 118

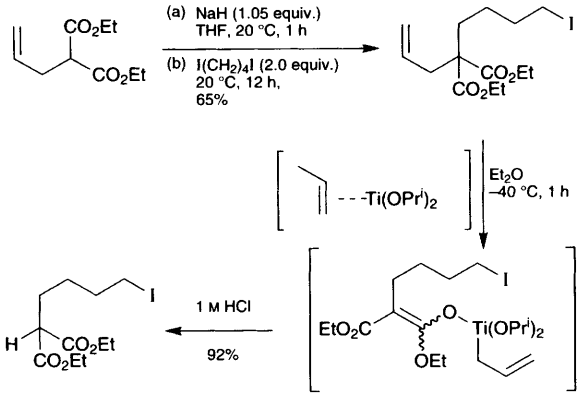
During a synthesis of the isonitrile metabolite trichoviridin, it was necessary to shield the isonitrile function in intermediate **265** from oxidation to the corresponding isocyanate[169] (**Scheme 119**). The task was accomplished by protection of the isonitrile as its bromine adduct conveniently prepared by bromination with a polymer-bound bromine reagent. Successive treatment of the dibromoimine adduct **266** with methyl(trifluoromethyl)dioxirane followed by triethylphosphite returned the TBS ether of trichoviridin (**267**).



265 **266** **267**

Scheme 119

A common complication attending the malonic ester synthesis is the prevention of dialkylation. A Japanese group[170] found that monoalkylation could be controlled by protecting one of the acidic hydrogens with an allyl group. Removal of the allyl group was accomplished using (η^2-propene)Ti(OPr^i)$_2$ readily generated *in situ* by reaction of Ti(OPr^i)$_4$ with 2 equiv. of Pr^{i}MgBr (**Scheme 120**).



Scheme 120

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