Protecting groups

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Abbreviations for reagents and protecting groups: Ac, acetyl; All, allyl; Allocam, allyloxycarbonylaminomethyl; Alloc, allyloxycarbonyl; Bn, benzyl; Boc, *tert*-butoxycarbonyl; BBN, 9-borabicyclo[3.3.1]nonane; BOB, 4-benzyloxybutanal; Boc, *tert*-butoxycarbonyl; BOM, benzyloxymethyl; BPFOS, *tert*-butylphenyl-1*H*,1*H*,2*H*,2*H*-heptadecafluorodecyloxysilyl; Bpoc, 2-(biphenyl-4-yl)propan-2-yloxycarbonyl; Bs, benzenesulfonyl; BSA, *N*,*O*-bis(trimethylsilyl)acetamide; Bsmoc, 1,1-dioxobenzo[*b*]thiophene-2-ylmethyloxycarbonyl; Bz, benzoyl; Cbz, benzyloxycarbonyl; CAN, ceric(IV) ammonium nitrate; CEOC, 2-cyanoethoxycarbonyl; CSA, camphorsulfonic acid; ClAc, chloroacetyl; DBn, *p*-dodecyloxybenzyl; DBU, 1,8-diazabicyclo[5.4.0]undec-7-ene; DCC, dicyclohexylcarbodiimide; DDQ, 2,3-dichloro-5,6-dicyanobenzo-1,4-quinone; Ddz, 2-(3,5-dimethoxyphenyl)propan-2-yloxycarbonyl; DEAD, diethyl azodicarboxylate; DIPEA, diisopropylethylamine; DMAP, 4-dimethylaminopyridine; DME, 1,2-dimethoxyethane; DMF; dimethylformamide; DMNPC, 3,5-dimethyl-*N*-nitro-1*H*-pyrazole-1-carboximidamide; DMPU, 1,3-dimethyl-3,4,5,6-tetrahydropyrimidin-2(1*H*)-one; DMSO, dimethyl sulfoxide; DMT, 4,4′-dimethoxytrityl; $DMTSBF_4$, dimethyl(methylthio)sulfonium tetrafluoroborate; Dpm, diphenylmethyl; DTBMP, 2,6-di(*tert*-butyl)-4-methylpyridine; Dts, dithiasuccinoyl; BTTM, benzyltriethylammonium tetrathiomolybdate; FC-72, isomers of C_6F_{14}, mainly perfluorohexane; Fm, fluoren-9-ylmethyl; Fmoc, fluoren-9-ylmethoxycarbonyl; Fnam, *N*-[2,3,5,6-tetrafluoro-4-piperidinophenyl]-*N*-allyloxycarbonylaminomethyl; $TrtF_7$, 2,3,4,4′,4″,5,6-heptafluorotriphenylmethyl; HMPA, hexamethylphosphoramide; HOBT, 1-hydroxybenzotriazole; Lev, levulinoyl, 4-oxopentanoyl; MCPBA, *m*-chloroperbenzoic acid; MEM, 2-methoxyethoxymethyl; Mes, mesityl; MOM, methoxymethyl; Moz, 4-methoxybenzyloxycarbonyl; MP, *p*-methoxyphenyl; MPB, *m*-methoxybenzyl; MS, molecular sieves; Ms, methylsulfonyl; MsCl, methanesulfonyl chloride; Mspoc, 2-methylsulfonyl-3-phenylprop-2-en-1-yloxycarbonyl; NBS, *N*-bromosuccinimide; Ns, 2-nitrobenzenesulfonamide; oxone, monopersulfate compound; PAB, *p*-acetoxybenzyl; Pf, 9-phenylfluoren-9-yl; PMB, *p*-methoxybenzyl; PMBM, (*p*-methoxybenzyloxy)-methyl; PMP, *p*-methoxyphenyl; PeNB, pentadienylnitrobenzyl; PeNP, pentadienylnitropiperonyl; Poc, prop-2-ynyloxycarbonyl; PPTS, pyridinium toluene-*p*-sulfonate; pyr, pyridine; SEM, 2-(trimethylsilyl)ethoxycarbonyl; SES, 2-(trimethylsilyl)ethylsulfonyl; TAEA, tris(2-aminoethyl)amine; TBAF, tetrabutylammonium fluoride; TBDPS, *tert*-butyldiphenylsilyl; TBS, *tert*-butyldimethylsilyl; TBTU, *O*-(benzotriazol-1-yl)-*N*,*N*,*N*′,*N*′-tetramethyluronium tetrafluoroborate; Teoc, 2-trimethylsilylethoxycarbonyl; TES, triethylsilyl; Tf, trifluoromethylsulfonyl; TFA, trifluoroacetic acid; TfOH, trifluoromethanesulfonic acid; THF, tetrahydrofuran; THP, tetrahydropyranyl; Thy, thymine; TIPS, triisopropylsilyl; TMS, trimethylsilyl; TMSCl, trimethylsilyl chloride; TMSCN, trimethylsilyl cyanide; TMSI, trimethylsilyl iodide; TMSOTf, trimethylsilyl trifluoromethanesulfonate; Tr, trityl (triphenylmethyl); TrCl, trityl (triphenylmethyl) chloride; Troc, 2,2,2-trichloroethoxycarbonyl; Ts, *p*-tolylsulfonyl; Tsoc, triisopropylsilyloxycarbonyl; TsOH, toluene-*p*-sulfonic acid

1 Introduction

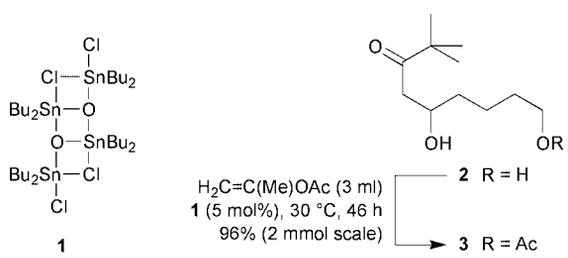
This is our sixth annual review of protecting group chemistry. The format and coverage are identical to our previous reviews. Protecting groups impinge on virtually every aspect of organic synthesis and hence comprehensive coverage of the subject is not possible—especially in areas such as carbohydrate, peptide and nucleoside chemistry which have their own niche journals. Nevertheless, we have tried to cover the most important developments in "mainstream" organic chemistry. We would welcome any suggestions from readers of useful and important developments which we may have omitted.

2 Hydroxy protecting groups

2.1 Esters

Distannoxane **1** (Scheme 1) prepared by the reaction of Bu_2SnO and Bu_2SnCl_2 catalyses the selective acylation of primary alcohols in the presence of secondary alcohols using isopropenyl acetate or acetic anhydride as the acylating agent.[1] No aqueous workup is necessary since the catalyst can be removed by simple chromatography.

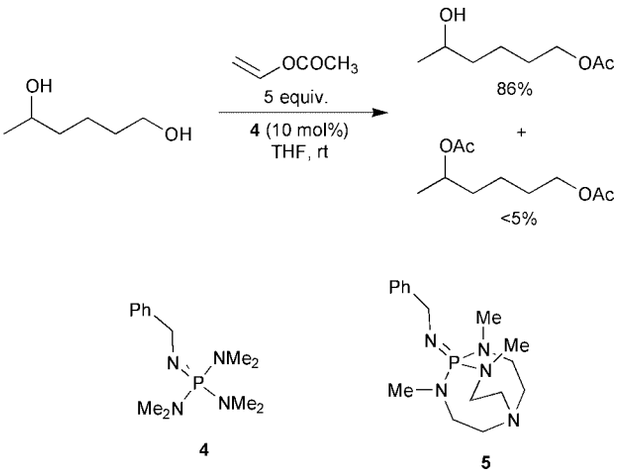
The iminophosphorane bases [$PhCH_2N{=}P(NMe_2)_3$ (**4**) and ($PhCH_2N{=}P(MeNCH_2CH_2)_3N$ (**5**)] catalyse the acylation of



Scheme 1

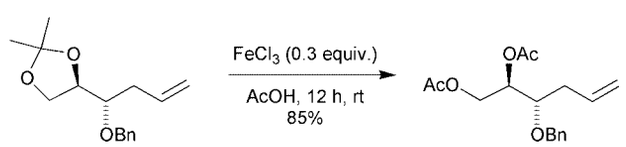
DOI: 10.1039/b003410j

primary alcohols with enol esters.[2] Acetals, epoxides, TBS ethers, disulfides, dienes, conjugated acetylenes, oxazolines, nitro compounds, and benzodioxanes are unaffected. Since secondary alcohols are inert under the reaction conditions, selective protection of primary hydroxy groups can also be achieved (Scheme 2).



Scheme 2

A protocol for the conversion of alcohols, silyl ethers and acetals to acetates using a catalytic amount of $FeCl_3$ in AcOH as the solvent has been reported (Scheme 3).[3] Alternatively 3 equiv. of AcOH in CH_2Cl_2 can also be used though the reaction times are longer. Benzyl ethers and tertiary alcohols remain intact under the reaction conditions. Acylation of alcohols can also be carried out with other acids such as CF_3COOH, HCOOH, H_2C=CHCOOH, EtCOOH, and $PrCO_2H$.



Scheme 3

Olivomycin A (**11**), a prominent member of the aureolic acid family of antitumour antibiotics, has been synthesised by the Roush group.[4] The functional density and sensitivity of the advanced intermediates required a carefully wrought protection–deprotection regime which is summarised in Scheme 4. The sequence began with the deprotection of the phenolic crotyl ether in **6** using Pd(0) and tributylstannane and reprotection of the *nascent* hydroxy group as its chloroacetate. Removal of the TES ether then unleashed the hydroxy group in the monosaccharide ring to give **7**. A glycosylation reaction was followed by treatment with NH_3 in MeOH which selectively deprotected the phenolic chlororoacetate to give **8** (78% for the two steps) which was then subjected to a second glycosidation. With the complete carbohydrate periphery now fully constructed, intermediate **9** was treated with camphorsulfonic acid in methanol to release the two side chain hydroxy groups protected as their cyclopentylidene acetal. This reaction had to be interrupted before going to completion owing to competing glycoside hydrolysis. Reprotection of the two hydroxy groups along with a third hydroxy group on the B sugar gave a tris-TES ether from which the two remaining chloroacetate groups were removed with NH_3 in MeOH to give **10**. Once again, the deprotection step had to be interrupted before going to completion because some cleavage of the isobutyrate ester on the E sugar was also observed. The heteroatom baggage accompanying the carbohydrate periphery was jettisoned in two stages. In the first stage two iodine and two bromine atoms were reductively cleaved using tributylstannane. Then two phenylthio groups and one phenylseleno group were hydrogenolysed using Raney nickel. The Raney nickel treatment conveniently cleaved the BOM ether guarding one of the phenolic hydroxy groups as well. To complete the synthesis of olivomycin A (**11**), the three remaining TES ethers were removed with Hf–pyr.

β-D-Glucopyranosyltuberonic acid isolated from *Solanum tuberosum* is a tuber inducing factor of the potato plant. Attempts to deprotect the tetraacetate of β-D-glucopyranosyltuberonic acid methyl ester (**12**, Scheme 5) using potassium cyanide or sodium hydrogen carbonate in MeOH gave 100% epimerisation of the *cis*-1,2-disubstituted cyclopentanone to the *trans*-isomer.[5] However, the tetradichloroacetate (**13**) could be deprotected in 86% yield without epimerisation by simply stirring in MeOH at room temperature for 24 h.

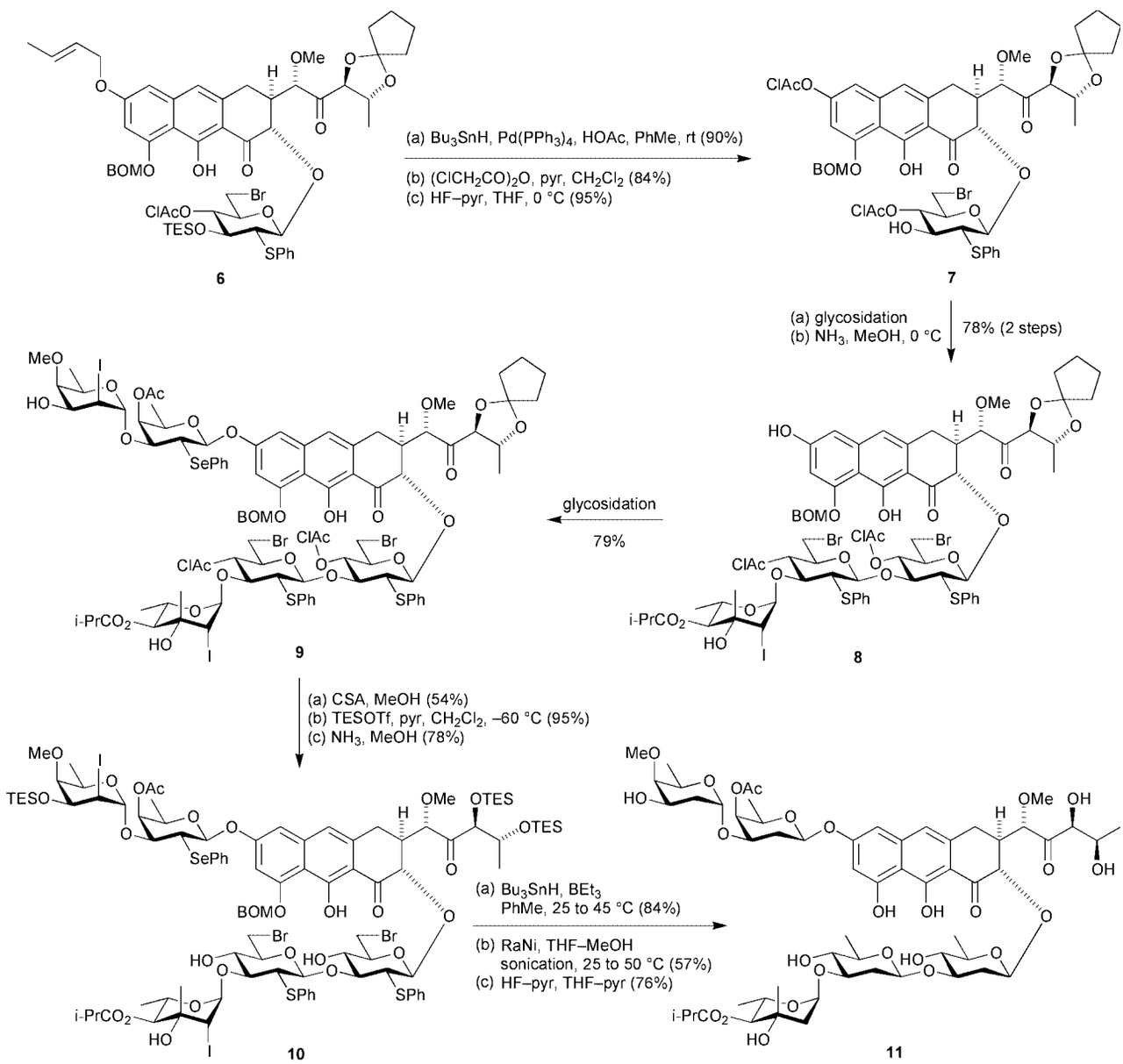
Protonation of trichloroacetimidate esters converts them into good leaving groups which have been very useful for the protection of alcohols as benzyl, *p*-methoxybenzyl, allyl, *tert*-butyl, and 2-phenylisopropyl ethers. Yu and co-workers[6] have shown that a trichloroacetimidate group can serve as a protecting group for alcohols in its own right. Trichloroacetimidate esters are easily formed by reacting the alcohol with trichloroacetonitrile in the presence of DBU and they can be cleaved using three sets of simple conditions (Scheme 6): acidic methanolysis ($TsOH·H_2O$, MeOH–CH_2Cl_2, rt), basic elimination (DBU, MeOH), and reductive elimination (Zn, NH_4Cl, EtOH). Cleavage of an isopropylidene group may compete with acidic methanolysis and prolonged deprotection using the reductive elimination conditions results in partial cleavage of acetates but not benzoates. TBS ethers are stable towards all three conditions but they can be removed with TBAF without detriment to the trichloroacetimidate group.

HF-7 (**15**, Scheme 7) is a potent neuroactive glyconucleoside disulfate from the funnel-web spider *Hololena curta* with potential for the treatment of global cerebral ischemia following cardiac arrest, drowning or carbon monoxide poisoning. A first attempt at a synthesis of HF-7 by Meinwald and co-workers[7] entailed a three-step protection sequence beginning with guanosine (**16**). First, protection of the 3′-hydroxy function as its Boc carbonate derivative was followed by protection of the 2′- and 5′-hydroxy groups as their TBS ethers and the NH_2 of the guanine as its Cbz derivative to give **17** in 45% overall yield. The 3′-hydroxy group was then unmasked using TMSOTf and collidine[8] to give **18** in 60% yield.

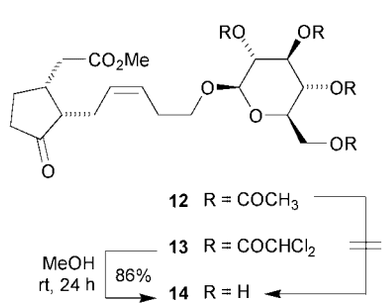
The prop-2-ynyloxycarbonyl (Poc) group is a promising protecting group for alcohols and amines which is easily introduced by reaction of the alcohol or amine with prop-2-ynyl chloroformate (bp 58–60 °C) in the presence of pyridine.[9] The Poc group is stable towards neat TFA at room temperature for 48 h allowing selective removal of a Boc group. Similarly, it survives the reductive cleavage of a benzylidene group with $BH_3·Me_2NH$–$BF_3·OEt_2$. However, treatment of a Poc group (*e.g.* **19**, Scheme 8) with 1 equivalent of dicobalt octacarbonyl in the presence of 5% TFA in dichloromethane at room temperature results in rapid cleavage to give the free alcohol **21** in 88% yield. The method depends on the high acid lability of the intermediate alkyne–Co complex **20**. Propargyl esters are cleaved with similar efficiency.

2.2 Silyl ethers

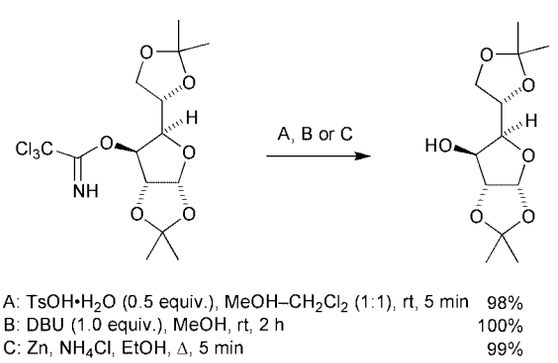
A very convenient synthesis of protected α-hydroxy aldehydes[10] which minimises protecting group manipulations exploits the known oxidation of primary and secondary TMS and TES ethers using the Swern reagent.[11–13] The method entails a selective oxidation of *primary* TMS or TES ethers of 1,2-diols, 1,2,3-triols and polyhydroxy compounds to the corresponding aldehydes. Other oxidants such as $CrO_3·2pyr$, pyridinium chlorochromate and pyridinium dichromate are generally less effective. Two examples which illustrate the efficiency of the method are given in Scheme 9.



Scheme 4



Scheme 5



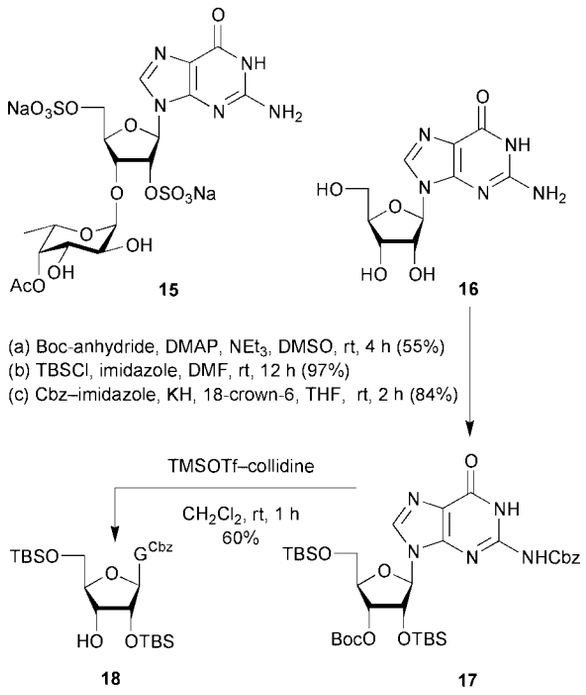
Scheme 6

During a synthesis of the angiogenesis inhibitor fumagillin (**22**, Scheme 10),[14] conversion of epoxysilane **23** to the α-hydroxyketone **24** was complicated by competing cleavage of the primary TBS ether. The task was eventually accomplished by using TBAF in THF buffered with ammonium chloride.[15]

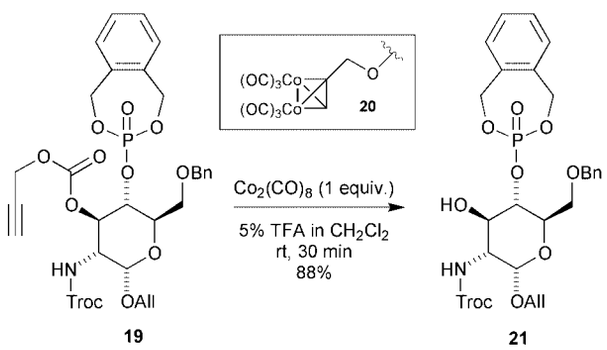
DDQ is known to deprotect TBS ethers in certain circumstances.[16] In the case of moenomycin intermediate **25** (Scheme 11), simultaneous deprotection of both a trityl group and a TBS ether in the presence of a levulinate ester and an anomeric phenylthio acetal was accomplished with DDQ in wet acetonitrile at 90 °C.[17]

tert-Butyldimethylsilyl ethers of simple alcohols, carbohydrates and nucleosides cleave on treatment with iodine monobromide (1.5 equiv.) in MeOH at room temperature (Scheme 12).[18] Acetals, PMB ethers, TBDPS ethers, esters and amides survive unscathed.

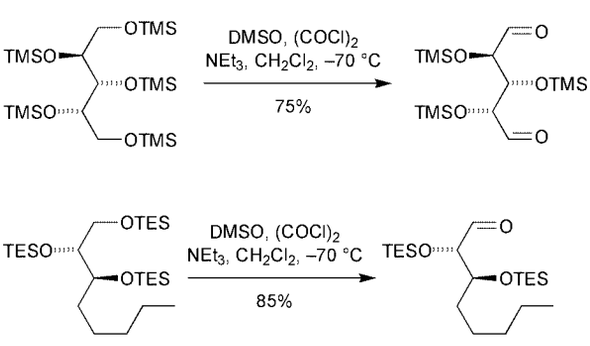
TBS ethers are cleaved under mild conditions by stirring a suspension of the substrate with an equimolar amount of zinc tetrafluoroborate in water at room temperature (Scheme 13).[19] Aldehydes, esters and urethanes are not affected and THP, allyl,



Scheme 7



Scheme 8

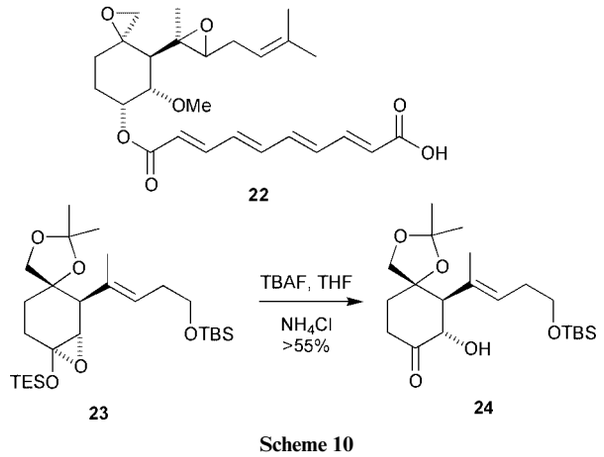


Scheme 9

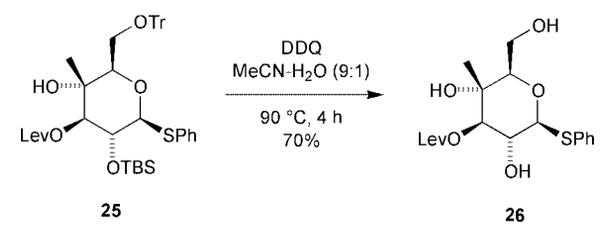
benzyl and TBDPS are inert. A co-solvent such as THF or acetonitrile may be used if required.

In order to complete a total synthesis of vancomycin, the Nicolaou group required a selective deprotection of the ring D phenolic TBS ether as a prelude to two sequential glycosidations[20] (Scheme 14). To accomplish the task selectively in the presence of three phenolic TBS ethers located on rings A and B would seem well nigh impossible. Nevertheless, conditions were found: treatment of **27** with 1 equiv. of potassium fluoride on alumina[21] in acetonitrile gave a 60% yield of the desired free phenol **28**.

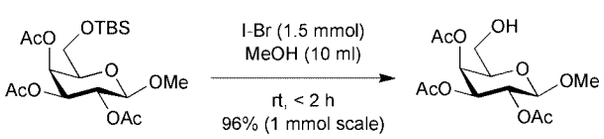
Excess oxone in aqueous methanol selectively cleaves the TBS ethers of primary alcohols in the presence of phenolic TBS ethers (*e.g.* **29**, Scheme 15).[22] Secondary TBS ethers are



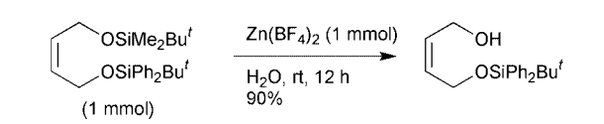
Scheme 10



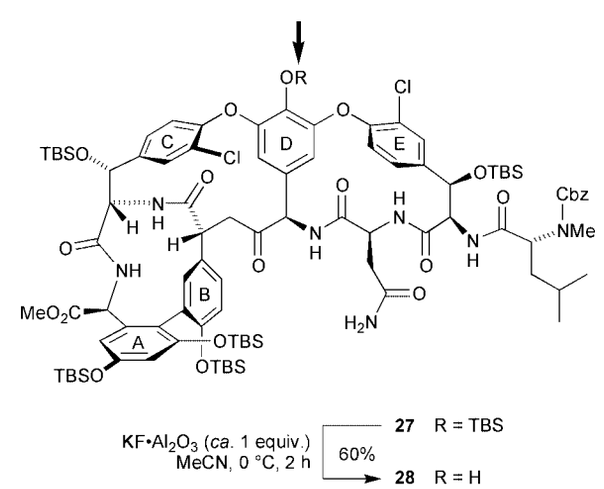
Scheme 11



Scheme 12

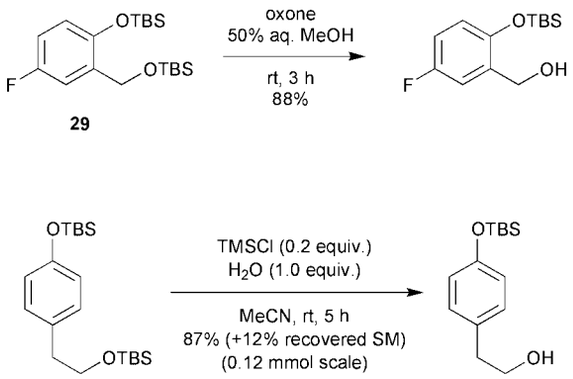


Scheme 13



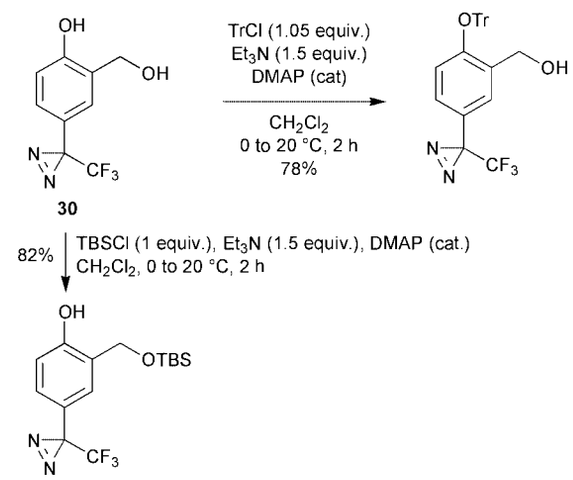
Scheme 14

unscathed as are primary TBDPS ethers. Other groups which are compatible include THP and *N*-Boc groups. The pH of the oxone solution is 2.8; however, evidence is presented to show that the TBS cleavage is not an acid-catalysed process. Primary alkyl TBS ethers can also be cleaved in the presence of phenolic TBS ethers using HCl generated *in situ* by the reaction of TMSCl with water (Scheme 15).[23] The reaction is faster if sodium iodide (0.1 equiv.) is added. All 8 examples reported involved deprotection of primary alkyl TBS ethers and no mention was made of more highly branched systems.



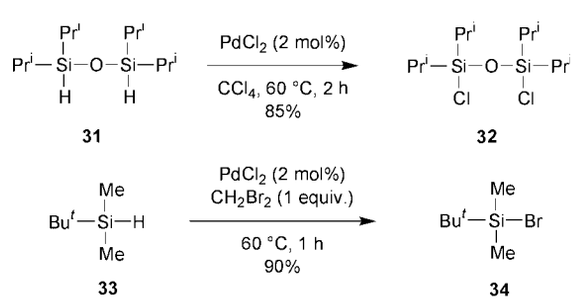
Scheme 15

Primary hydroxyalkyl phenols (*e.g.* **30**, Scheme 16) can be selectively protected either at the hydroxy group or at the phenol group by simply choosing the protecting reagent (TBS or trityl chloride) under otherwise essentially the same reaction conditions.[24] In the case of secondary hydroxyalkyl phenols, the reaction with TBS chloride is no longer selective and gives a mixture of products. On the other hand, trityl chloride affords regioselectively the *O*-protected phenol although a longer (24 h) reaction time is required.



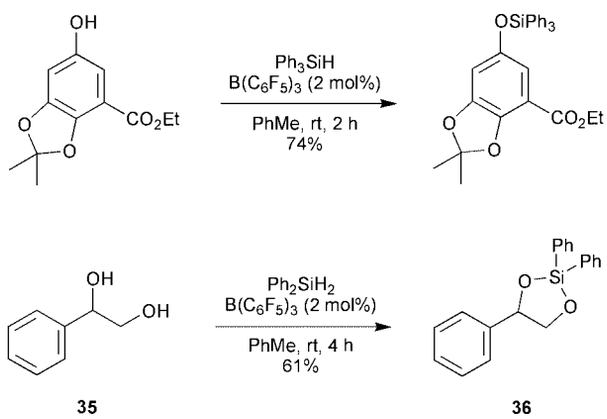
Scheme 16

A very convenient and economic method for the synthesis of halosilanes from the corresponding silanes has been described.[25] Two examples were reported beginning with treatment of 1,1,3,3-tetraisopropyldisiloxane (**31**, Scheme 17) with a catalytic amount of $PdCl_2$ in tetrachloromethane as solvent to give an 85% yield of the corresponding 1,3-dichloro-1,1,3,3-tetraisopropyldisiloxane (**32**). Similarly, treatment of *tert*-butyldimethylsilane (**33**) with 1 equivalent of dibromomethane in the presence of 2 mol% of $PdCl_2$ at 60 °C gave *tert*-butyldimethylbromosilane (**34**) in 90% yield. In the present study, the crude halosilanes were used to derivatise various nucleosides in good yields. The method should provide easy access to a range of new commercially unavailable halosilanes.



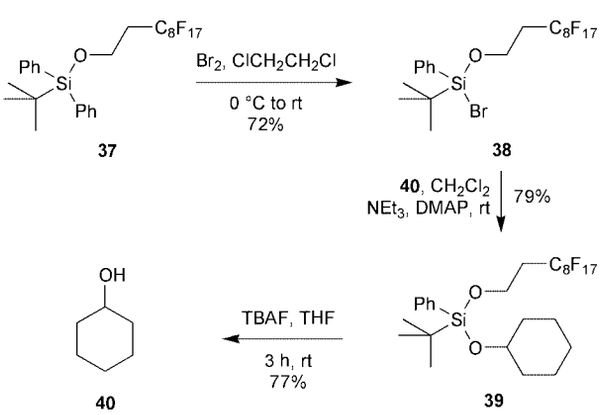
Scheme 17

The dehydrogenative silylation of alcohols can be accomplished with as little as 2 mol% of the commercial Lewis acid tris(pentafluorophenyl)borane and a silane such as Ph_3SiH or Et_3SiH (Scheme 18).[26] Primary, secondary, tertiary and phenolic hydroxy groups participate whereas alkenes, alkynes, alkyl halides, nitro compounds, methyl and benzyl ethers, esters and lactones are inert under the conditions. The stability of ether functions depends on the substrate. Thus, tetrahydrofurans appear to be inert whereas epoxides undergo ring cleavage. 1,2-Diols and 1,3-diols can also be converted to their silylene counterparts as illustrated by the conversion **35**→**36**. Hindered silanes such as Bn_3SiH and Pr^i_3SiH fail to react but Bu^tMe_2SiH and $PhMe_2SiH$ participate without difficulty. Unlike conventional base-mediated silylation reactions, sterically hindered tertiary alcohols and secondary alcohols react faster than primary alcohols; however, in a competition experiment between decan-1-ol and cyclohexanol using Ph_3SiH, the triphenylsilyl ether of decan-1-ol is formed preferentially.



Scheme 18

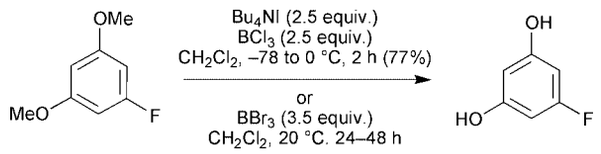
The *tert*-butylphenyl-1*H*,1*H*,2*H*,2*H*-heptadecafluorodecyloxysilyl (BPFOS) group has been developed as an acid stable protecting group for alcohols which allows protection–purification–deprotection schemes by liquid–liquid extraction with FC-72/MeCN or by solid phase extraction with fluorous reverse phase silica gel.[27] The silylating agent *tert*-butylphenyl-1*H*,1*H*,2*H*,2*H*-heptadecafluorodecyloxysilyl bromide **38** (Scheme 19) was prepared by brominolysis of the corresponding *tert*-butyldiphenylsilyl ether **37** in 72% yield. Treatment of cyclohexanol with **38** in the presence of DMAP afforded the bis-alkoxysilyl ether **39** in 79% yield. The bis-alkoxyalkyl ether **39** displayed a $t_{1/2}$ of 48 h in 0.25 M NaOMe in THF (1 : 3) but its acid stability was reduced: $t_{1/2}$ in 5% TsOH–MeOH was ~40 min. Deprotection was achieved with TBAF in THF at rt.



Scheme 19

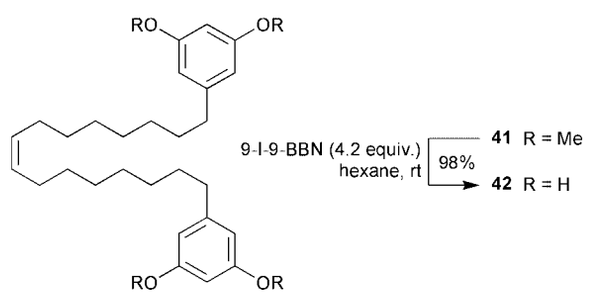
2.3 Alkyl ethers

Boron trichloride alone does not cleave isolated aryl methyl ethers at low temperature although it is effective in systems capable of chelation. However, boron trichloride together with tetrabutylammonium iodide displays enhanced reactivity allowing methyl ether cleavage at low temperature in a short time.[28] The new reagent combination is more effective than boron tribromide typically used for such ether cleavage reactions as illustrated in Scheme 20.



Scheme 20

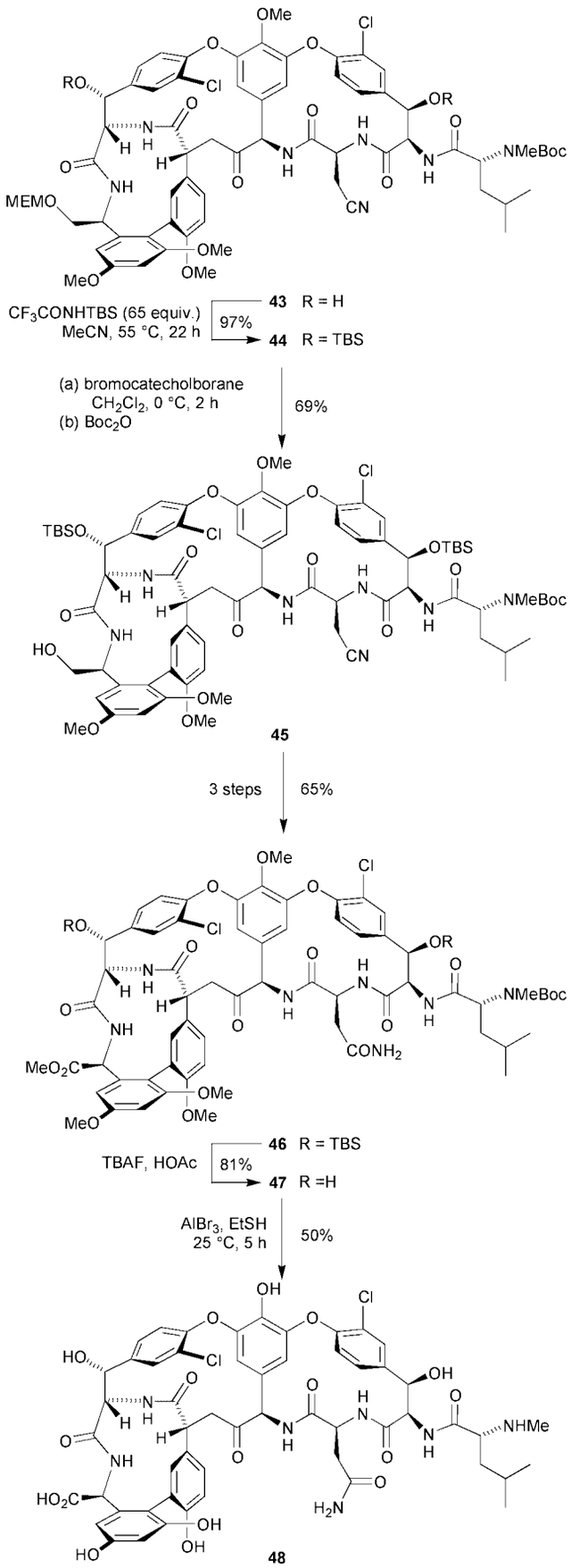
Resorcinol **42** (Scheme 21) is one of a family of simple natural products isolated from the west Australian shrub *Hakea trifurcata* which is able to cleave DNA under oxidative conditions [O_2, Cu(II)]. In the final step of a synthesis of **42**, Fürstner and Seidel required the cleavage of 4 phenolic methyl ethers.[29] Use of BBr_3 was precluded because of concomitant haloboration of the *cis*-alkene. A milder reagent which avoids haloboration is 9-iodo-9-borabicyclo[3.3.1]nonane (9-I-9-BBN).[30] Treatment of **41** with 9-I-9-BBN (4.2 equiv.) in hexane at rt gave the bis-resorcinol **42** in 98% yield. Workup of the reaction was facilitated by adding ethanolamine to the crude reaction mixture and filtering off the highly crystalline 9-BBN adduct thereof.



Scheme 21

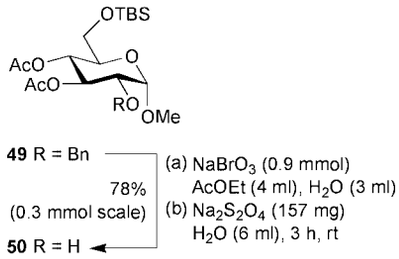
Full experimental details have been disclosed for the synthesis of vancomycin aglycone by Boger[31] and Nicolaou[32] and their respective co-workers. Scheme 22 depicts the closing steps of the Boger synthesis which entailed a series of selective deprotections in a crowded and multifunctional environment. The two free secondary hydroxy functions in intermediate **43** were first protected as their TBS ethers by reaction with a large excess of *N*-(*tert*-butyldimethylsilyl)trifluoroacetamide. Treatment of the product **44** with catecholborane removed the MEM ether along with the *N*-Boc group which had to be restored in a separate step. The *nascent* hydroxymethyl group in **45** was oxidised to a carboxylic acid which was esterified. The nitrile function was then converted to the primary amide **46**. After removal of the two TBS ethers with TBAF buffered with acetic acid, the four phenolic methyl ethers, the Boc group and the methyl ester in **47** were cleaved in a single step using a large excess of aluminium tribromide in neat ethanethiol to give vancomycin aglycone (**48**). Boger elected to carry the amide through the synthesis in latent form (as the nitrile) thereby avoiding the need for *N*-protection of the amide. Later in this review, we will see how Nicolaou was able to append a suitable protecting group onto the intact amide at a late stage.

Benzyl ethers and benzylidene acetals in carbohydrates (*e.g.* **49**, Scheme 23) can be selectively cleaved by reaction with



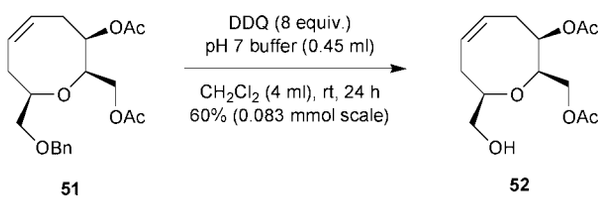
Scheme 22

sodium bromate and sodium dithionate in a mixture of ethyl acetate and water.[33] A variety of other protecting groups such as acetyl, chloroacetyl, benzoyl, pivaloyl, tosyl, TBS, trityl and isopropylidene are unaffected.



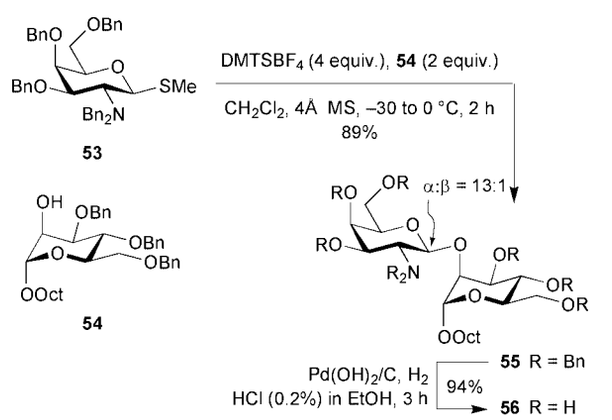
Scheme 23

The cleavage of PMB ethers with DDQ is a very common tactic in synthesis but the same reagent can also be used to cleave simple benzyl ethers.[34] An example comes from a concise approach to the red alga oxocene laurencin involving deprotection of the benzyl ether **51** (Scheme 24) in the presence of two acetate groups to give the free hydroxy group in **52** in 60% yield.[35]



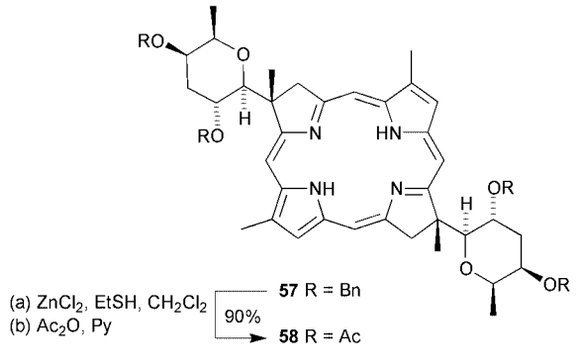
Scheme 24

1,2-*trans*-Glycosylation reactions of 2-amino-2-deoxy sugars are usually performed with amide, urethane, or phthalimide protecting groups on nitrogen and in each case the β-glycosidic link is generated with the benefit of participation by the carbonyl of the protecting group. An attempt to perform such a glycosidation using the *N*-phthalimidyl analogue of thioglycoside **53** (Scheme 25) and octyl 3,4,6-tri-*O*-benzyl-α-D-mannopyranoside (**54**) gave poor stereocontrol (α : β = 3 : 1).[36] However, the same reaction performed using the *N*,*N*-dibenzylamino group with thioglycoside activation by dimethyl(methylthio)sulfonium tetrafluoroborate ($DMTSBF_4$) gave a 13 : 1 mixture of anomers **55** in 89% yield. Subsequent comprehensive hydrogenolysis of all the benzyl groups gave the desired disaccharide **56** in 94% yield. Similar yields and selectivities were observed with a range of challenging acceptors.



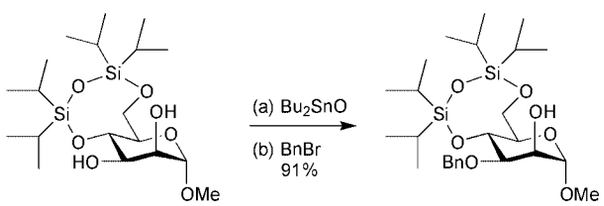
Scheme 25

The structurally unique porphyrin, tolyporphyrin A from the microalga *Tolypothrix nodosa* reverses multidrug resistance in a vinblastine-resistant population of human ovarian adenocarcinoma cells. In the closing stages of a synthesis of tolyporphyrin A, four *O*-benzyl groups were cleaved from the *C*-glycoside rings of **57** (Scheme 26) using zinc chloride and ethanethiol in dichloromethane.[37] The crude tetraol was then acetylated to give the tetraacetate **58** in 90% yield for the two steps.



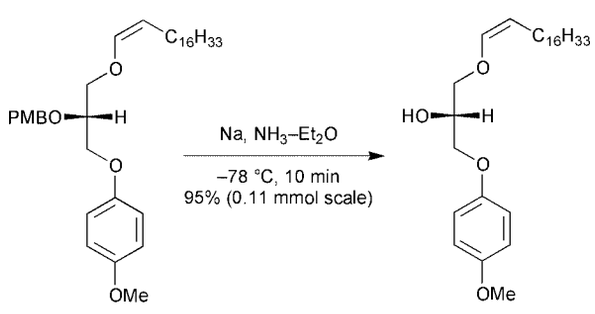
Scheme 26

Treatment of alkyl and aryl 4,6-*O*-(1,1,3,3-tetraisopropyl-1,3-disiloxane-1,3-diyl)-D-glycopyranosides with dibutyltin oxide followed by benzoyl chloride, benzyl bromide or allyl bromides gives the corresponding monoacylated or monoalkylated glycosides with excellent regioselectivity.[38] It is noteworthy that the regioselectivity of stannylene acylation is inverted compared with direct methods. The reaction is illustrated in Scheme 27.



Scheme 27

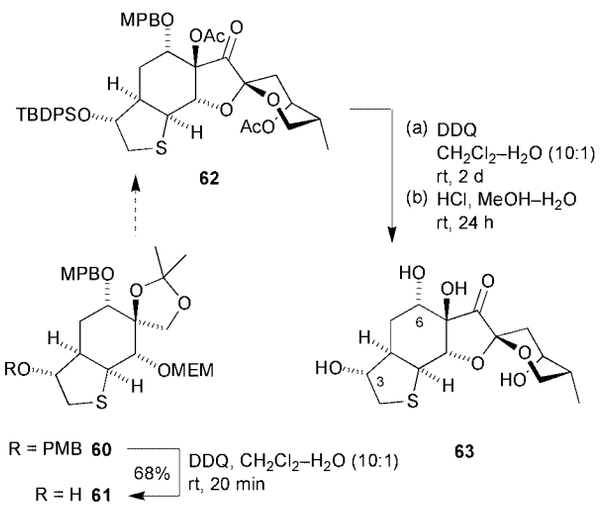
The plamalogens are phospholipids widely distributed in heart and brain tissue which may protect endothelial cells by scavenging peroxy radicals. One approach to the plamalogens was based on a glycerol derivative **59** (Scheme 28) bearing differentially protected hydroxy groups at the 2- and 3-positions.[39] Oxidative cleavage of the PMB ether with DDQ was accompanied by destruction of the *cis*-alkenyl ether but the desired deprotection was accomplished by reduction with sodium metal. The *p*-methoxyphenyl (PMP) ether protecting the 3-position survived provided the reaction time was short (10 min). However, longer times or use of lithium metal resulted in reduction of the PMP ether as well. The route ultimately foundered when the ceric ammonium nitrate used to remove the PMP ether also destroyed the *cis*-alkenyl ether. In a later, successful approach, both C-2 and C-3 hydroxy groups were protected as PMB ethers which were then cleaved with sodium in liquid ammonia.



Scheme 28

An Italian group[40] reports that cerium trichloride heptahydrate together with sodium iodide cleaves PMB ethers in refluxing acetonitrile. Compatibility data are sparse but it appears that *cis*-alkenes, benzyl ethers, THP ethers, and esters survive the reaction conditions.

A short synthesis of (+)-breynolide by Burke and co-workers[41] exploits the large difference in susceptibility of the PMB and *m*-methoxybenzyl (MPB) ethers towards oxidative hydrolysis to achieve differential protection. Thus, the PMB group in intermediate **60** (Scheme 29) was readily removed with DDQ in dichloromethane–water (10 : 1) at room temperature in only 20 min to liberate the C-3 hydroxy group. A significant factor in the choice of the MPB group for the protection of the C-6 hydroxy group was the need for its survival through several stringent steps including the acid conditions required to create the spiroacetal in intermediate **62**. The more robust MPB was later removed with DDQ, again in dichloromethane–water (10 : 1), but this time the reaction required 2 days and even then some starting material was recovered. Finally the TBDPS ether and the two acetates were hydrolysed with conc. HCl in methanol to give (+)-breynolide **63** in 88% overall yield from **62**.

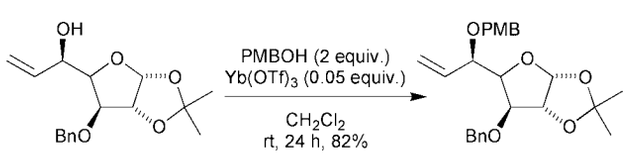


Scheme 29

Conversion of the mono-PMB ethers of 1,2- and 1,3-diols to the corresponding 1,3-dioxolanes or 1,3-dioxanes using DDQ in the absence of water is now a common ploy in synthesis. Evans *et al.*[42] recently showed that the transformation could be taken one stage further. Thus, treatment of the PMB ether **64** (Scheme 30) with 2 equivalents of DDQ resulted in two sequential cyclisations to give the bicyclic *p*-methoxyphenyl (PMP)-substituted orthoester **65** in 70% yield.

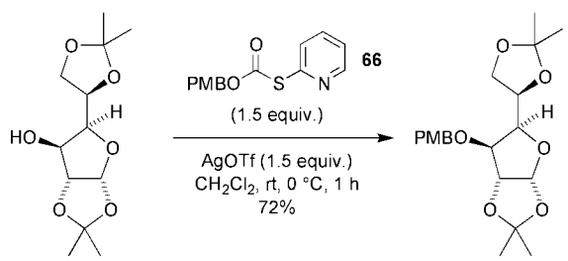
Scheme 30

Primary and secondary alcohols can be protected as PMB ethers using PMB alcohol and a catalytic amount of ytterbium(III) triflate[43] (Scheme 31). A wide variety of functional groups is tolerated like double and triple bonds, benzoates, TBS ethers, benzyl and THP ethers and isopropylidene acetals. Tertiary alcohols are inert.



Scheme 31

A new method for the conversion of primary, secondary, and tertiary alcohols to the corresponding PMB ethers has been disclosed by Hanessian and Huynh[44] (Scheme 32). The method involves reaction of the alcohol with 4-methoxybenzyl 2-pyridyl thiocarbonate (**66**) in the presence of silver(I) triflate. The reaction occurs at room temperature within 2 h and the yields are generally 72–90%. Several noteworthy features emerged from the preliminary study: no *N*-alkylation was observed with amides, carbamates and pyrimidine-type nitrogens and no ester migrations, β-eliminations, or epimerisations were noted. Reagent **66**, a yellow crystalline solid at 0 °C which can be stored for several months without noticeable decomposition, was prepared in 80% yield by the reaction of *p*-methoxybenzyl alcohol with di(2-pyridyl) thiocarbonate.

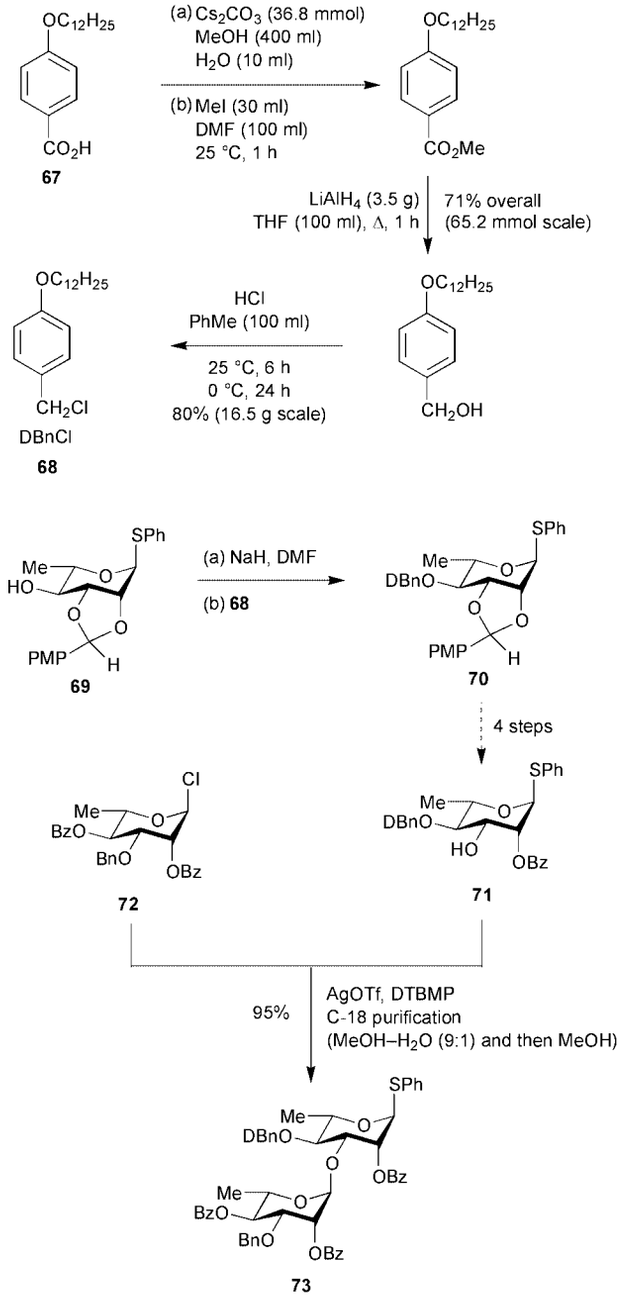


Scheme 32

p-Dodecyloxybenzyl (DBn) ethers have been developed for the synthesis and rapid isolation of disaccharides[45] (Scheme 33). Thus, treatment of thioglycoside **69** with sodium hydride followed by *p*-dodecyloxybenzyl chloride (**68**, DBnCl, prepared in three steps from *p*-dodecyloxybenzoic acid, **67**) gave the protected sugar derivative **70**. A further three steps achieved the lipophilic protecting group-tagged glycoside acceptor **71** which was then condensed with rhamnosyl donor **72**. The reaction mixture was applied to a column of Waters Preparative C_{18} 125 Å absorbent. Elution with MeOH–H_2O (9 : 1) removed the side products. Subsequent elution with MeOH afforded disaccharide **73** in >95% purity verifying that one hydrophobic DBn tag is sufficient for selective adsorption of a disaccharide onto C_{18} silica. The new technique allows rapid isolation of a disaccharide thus avoiding the conventional silica gel purification. It combines the advantages of liquid-phase oligosaccharide synthesis with the simplicity of product isolation of solid phase methods.

The *O*-benzyl group is the most common persistent protecting group in carbohydrate chemistry. It is typically cleaved by hydrogenolysis using insoluble catalysts. For the purposes of solid phase oligosaccharide synthesis, Jobron and Hindsgaul[46] have developed two new modified benzyl ethers which can be cleaved using soluble reagents. The *p*-acetoxybenzyl (PAB) group is installed by reaction of a hydroxy group (*e.g.* **76**, Scheme 34) with *p*-acetoxylbenzyl bromide (**74**) using silver trifluoromethanesulfonate in hexane–CH_2Cl_2 (1 : 1) or *p*-acetoxybenzyl trichloroacetimidate (**75**) using triflic acid in CH_2Cl_2. Removal of the PAB group from **77** begins with basic methanolysis followed by mild oxidation of phenolate anion **78** with $FeCl_3$ in Et_2O at rt for 20 min to return alcohol **76** in >95% yield. Other mild oxidants include DDQ, iodobenzene diacetate or silver carbonate on Celite. Alternatively, the phenolate can be heated in MeOH at 60 °C for 18 h to cause elimination.

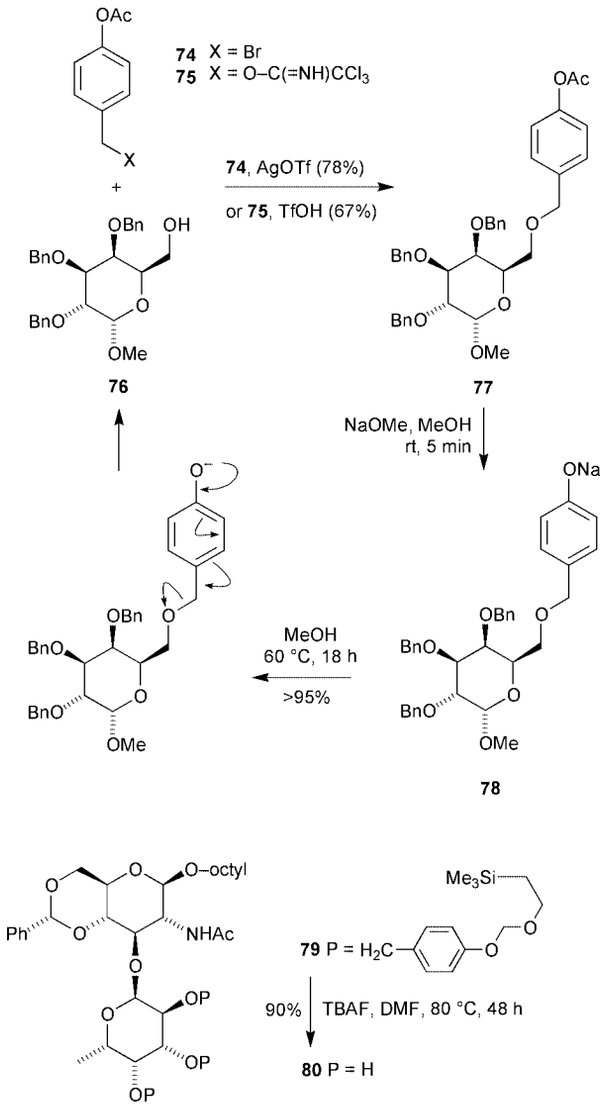
Phenolate anions generated by treatment of 2-(trimethylsilyl)ethoxymethoxybenzyl (*p*-SEM-benzyl) ethers with TBAF in DMF at 80 °C also undergo efficient elimination to give the deprotected alcohol as illustrated by the conversion of disaccharide **79** to **80**. Both new protecting groups are compatible with many of the standard manipulations in oligosaccharide synthesis and they are orthogonal to benzyl and *p*-methoxybenzyl ethers. However, both groups are cleaved under hydrogenolysis conditions (Pd/C, MeOH).



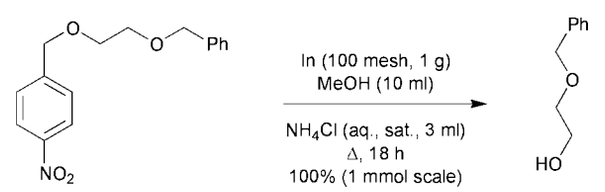
Scheme 33

Indium in aqueous methanolic ammonium chloride deprotects 4-nitrobenzyl ethers and esters leaving benzyl ethers and benzyl carbamates intact[47] (Scheme 35). Other functional groups such as aldehydes, ketones, chlorides, and heterocycles (quinoline) are unaffected by the reaction conditions. The deprotected product requires little or no further purification as the by-product (4-toluidine) is removed during the acidic work-up.

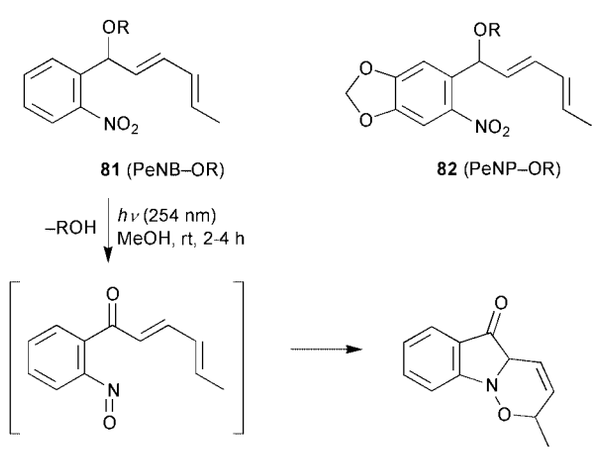
Photochemical cleavage of *o*-nitrobenzyl ethers and esters results in the formation of nitrosoarenes which can react with thiol and amine functions found typically in biological systems. In order to trap such deleterious nitrosoarenes, Pirrung *et al.*[48] developed the pentadienylnitrobenzyl (PeNB, **81**) and pentadienylnitropiperonyl (PeNP, **82**) protecting groups in which the nitrosoarene intermediate is trapped *via* an intramolecular hetero-Diels–Alder reaction (Scheme 36). PeNB groups are introduced by conventional methods by reaction of 1-(2-nitrophenyl)hexa-2,4-dien-1-ol with acid chlorides, alkyl halides or isocyanates to form esters, alkyl ethers, or carbamates respectively. The more acid-labile piperonyl derivatives



Scheme 34



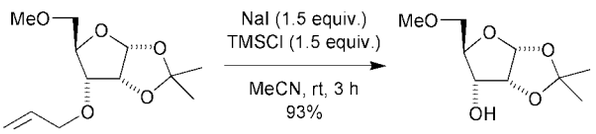
Scheme 35



Scheme 36

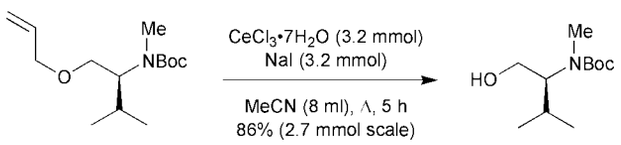
are prepared similarly. Photochemical cleavage occurs in MeOH at 254 nm for 2–4 h.

A method for the regeneration of alcohols from their allyl ethers using chlorotrimethylsilane and sodium iodide in acetonitrile has been reported (Scheme 37).[49] The yields are generally 90–98% though only fairly simple substrates have been used in the pilot study.



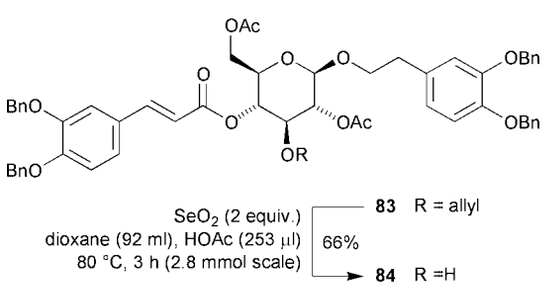
Scheme 37

A combination of cerium(III) chloride and sodium iodide in refluxing acetonitrile deprotects allyl ethers to the corresponding alcohols (Scheme 38).[50] Benzyl, THP and Boc protecting groups are compatible with the reaction conditions.



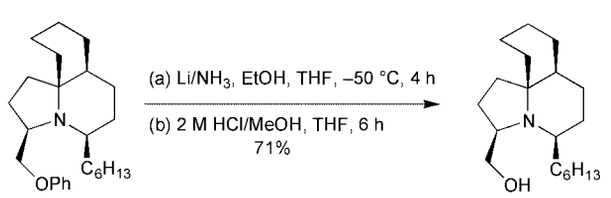
Scheme 38

A recent synthesis of acetoside should enable evaluation of its putative hepatoprotective activity, sedative effect and defence repair processing in trees. As a prelude to rhamnosylation, the allyl ether function in **83** (Scheme 39) had to be cleaved.[51] The task was accomplished using a method first published in 1970[52] involving treatment of **83** with selenium dioxide in a mixture of acetic acid and dioxane at 80 °C. The desired alcohol **84** was obtained in 66% yield.



Scheme 39

A rare example of aryl protection of a hydroxy function appeared in a synthesis of the putative structure **86** of the marine alkaloid lepadiformine[53] (Scheme 40). Birch reduction of the aryl ether in **85** followed by hydrolysis of the intermediate enol ether returned the free hydroxy group in 71% yield.

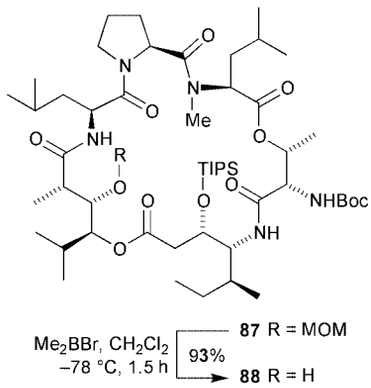


85 **86**

Scheme 40

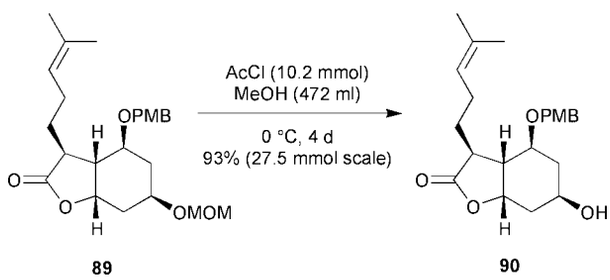
2.4 Alkoxyalkyl ethers

Deprotection of a robust MOM ether amidst a welter of polar and hydrolytically sensitive groups would not seem a trivial task. Nevertheless, the Joullié group accomplished just such a transformation in their synthesis of the antitumour didemnins.[54] Thus treatment of **87** (Scheme 41) with dimethylboron bromide in dichloromethane at low temperature liberated the desired hydroxy group in **88** in 93% yield.



Scheme 41

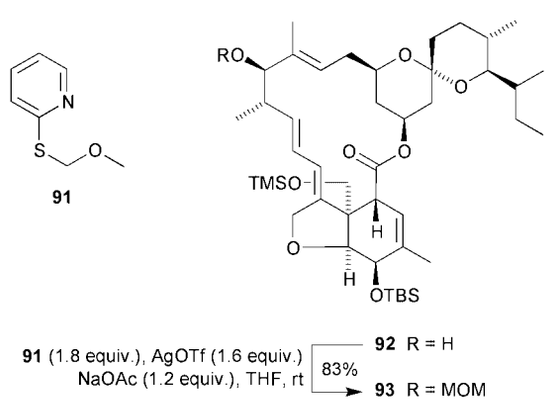
Selective deprotection of a robust MOM ether in the presence of a PMB ether was accomplished as part of a synthesis of paniculide.[55] Treatment of **89** (Scheme 42) with methanolic HCl at 0 °C for 4 days liberated the C-6 hydroxy group to give **90** in 93% yield.



89 **90**

Scheme 42

A Merck process development group has devised a new, mild procedure for the introduction of MOM groups into acid-sensitive substrates (Scheme 43).[56] The procedure is illustrated by the protection of the allylic alcohol in avermectin derivative **92** using 2-(methoxymethyl)thiopyridine (**91**), AgOTf and NaOAc in THF at room temperature. Primary, secondary and tertiary alcohols and phenols were all methoxymethylated in good yield though phenols were slower to react. Reagent **91** (bp 66 °C/0.66 mmHg) is easily prepared in 75% yield by the reaction of pyridine-2-thiol with dimethoxymethane activated by $BF_3{\cdot}OEt_2$.

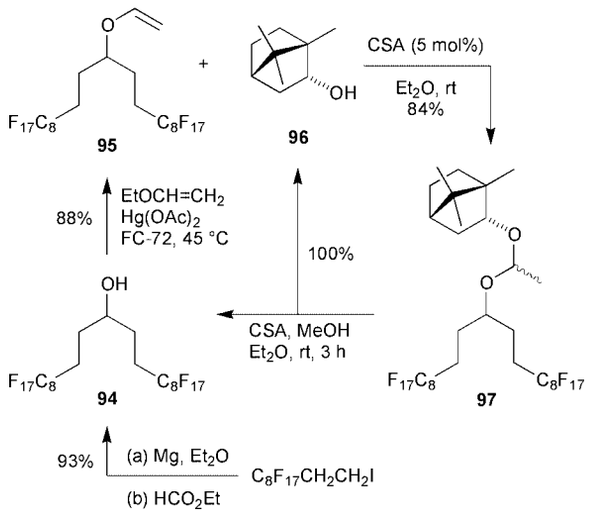


91

Scheme 43

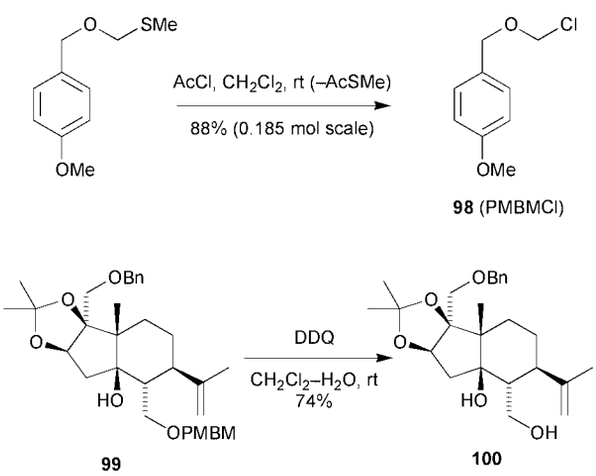
1,5-Bis(perfluorooctyl)pentan-3-yl vinyl ether (**95**) has been developed as a fluorous phase analogue of the popular ethyl vinyl ether protecting group for alcohols.[57] The preparation of

95 and its use in the protection/deprotection of a hindered 2° alcohol are illustrated in Scheme 44. Thus, treatment of an Et_2O solution of the alcohol **96** (1.0 equiv.) with **95** (3 equiv.) in the presence of CSA (5 mol%) at room temperature affords the protected derivative **97** in 84% yield after 3 h. The excess **95** can be recovered by chromatography. The reaction works equally well for primary, secondary and tertiary alcohols. Deprotection is accomplished with CSA in MeOH.



Scheme 44

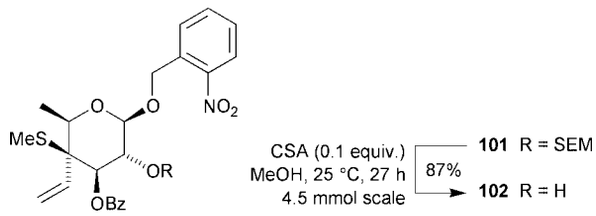
In a recent synthesis of picrotoxane sesquiterpenoids, Trost *et al.*[58] acknowledged a debt to the (*p*-methoxybenzyloxy)-methyl ether (PMBM) protecting group in achieving the target. A moderate scale synthesis of (*p*-methoxybenzyloxy)methyl chloride (**98**, Scheme 45) was described. Conditions for removal of the PMBM group are similar to those used to cleave the *p*-methoxybenzyl ether. Thus, treatment of **99** with DDQ in moist dichloromethane gave the free hydroxy group in **100** in 74% yield. The PMBM group is apparently cleaved by CAN as well but no details are given.



Scheme 45

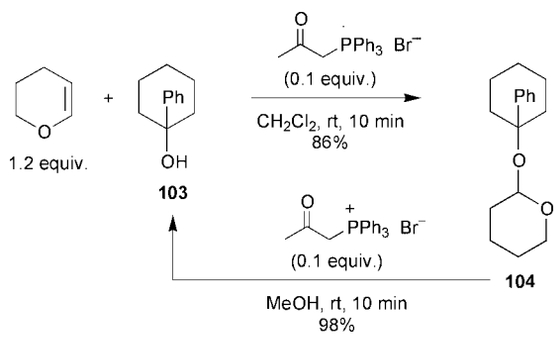
Conditions typically deployed for the deprotection of SEM ethers using TBAF in THF or DMPU resulted in complex mixtures in the case of the monosaccharide derivative **101** (Scheme 46).[59] Clean deprotection was accomplished in 87% yield using camphorsulfonic acid (0.1 equiv.) in MeOH at 25 °C.

Acetonyltriphenylphosphonium bromide catalyses the addition of alcohols to dihydropyran, ethyl vinyl ether or dihydrofuran to form the corresponding acetals.[60] As can be seen from Scheme 47, the conditions are mild enough for use with very acid-labile tertiary alcohols such as **103** without significant



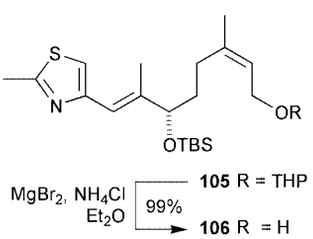
Scheme 46

dehydration. Deprotection can also be accomplished efficiently under mild conditions. For example, **104** is deprotected by stirring with acetonyltriphenylphosphonium bromide (0.1 equiv.) in MeOH at room temperature for 10 min to return the tertiary alcohol **103** in 98% yield. Acetonyltriphenylphosphonium bromide is less hygroscopic than PPTS.



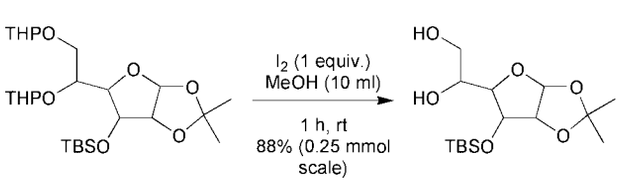
Scheme 47

Selective removal of the allylic THP ether group in epothilone B intermediate **105** (Scheme 48) without detriment to the acid-sensitive allylic TBS ether group was accomplished[61] by treatment with magnesium bromide and ammonium chloride in ether.[62]



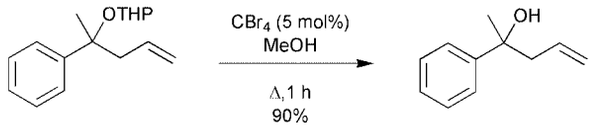
Scheme 48

Iodine in methanol deprotects tetrahydropyranyl (THP) and 4,4′-dimethoxytrityl (DMT) ethers in the presence of TBS groups[63] (Scheme 49). Also benzyl, *N*-Cbz, *N*-Boc and isopropylidene protecting groups are compatible with the reaction conditions. However, if the reaction time is extended then isopropylidene groups are cleaved.



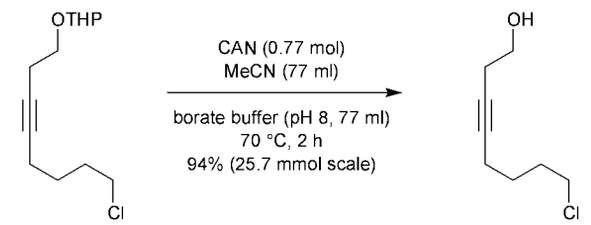
Scheme 49

In an earlier study[64] Lee and co-workers showed that acetals and ketals are cleaved with a catalytic amount of carbon tetrabromide in aqueous acetonitrile under ultrasonic irradiation. The same conditions do not affect tetrahydropyranyl ethers but switching the solvent to anhydrous MeOH and application of heat is effective (Scheme 50). No explanation has been given for the role of the carbon tetrabromide.



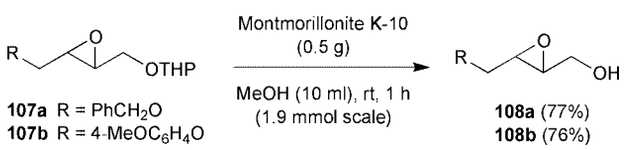
Scheme 50

A very mild method for the deprotection of THP and THF ethers entails the use of CAN (3 mol%) in MeCN and borate buffer (pH 8.0) at rt or 60 °C. Esters, nitriles, ketones, enones, halides, sulfides, alkenes, and alkynes are all compatible.[65] Trityl ethers survive the reaction conditions but ketone acetals are cleaved selectively. The method is illustrated in Scheme 51. A paper by the same group describes deprotection of ketals with CAN.[66]



Scheme 51

A Japanese group tried to deprotect THP ethers **107** but most acidic conditions affected the oxirane functionality[67] (Scheme 52). Only CAN in aqueous acetonitrile gave the desired alcohol **108a** in 74% yield but the reaction failed in the case of *p*-methoxyphenoxy derivative **107b** giving the diol **108b** (R = OH). The authors found that Montmorillonite K-10 clay in methanol allows the smooth selective deprotection of both THP ethers **107** without touching the oxirane moiety affording the alcohols **108** in 77 and 76% yield. Methoxymethyl, *tert*-butyldiphenylsilyl (TBDPS) and acetoxy groups also remained intact under the reaction conditions but ketals, TBS ethers and 2,2,2-trichloroethylimidoxy [$Cl_3CC(=NH)O$-] functionalities are unstable.



107a R = $PhCH_2O$
107b R = 4-$MeOC_6H_4O$

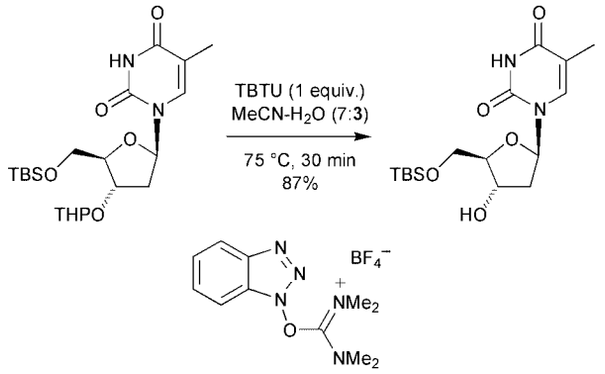
108a (77%)
108b (76%)

Scheme 52

O-(Benzotriazol-1-yl)-*N*,*N*,*N*′,*N*′-tetramethyluronium tetrafluoroborate (TBTU, **109**) selectively cleaves THP and DMT ethers in the presence of TBS ethers, isopropylidene groups, benzyl ethers, Boc groups and Cbz groups.[68] The reaction is best conducted in MeCN–H_2O (7:3) at 75 °C for brief periods (5 min to 1 h) but longer periods at rt can also be used. The hydrolysis is probably mediated by the production of HF and boric acid arising from decomposition of the tetrafluoroborate anion. If so, cheaper alternatives should be sought because TBTU is required in stoichiometric amounts and it is expensive. Scheme 53 illustrates the selective deprotection of a secondary THP group in the presence of a primary TBS group.

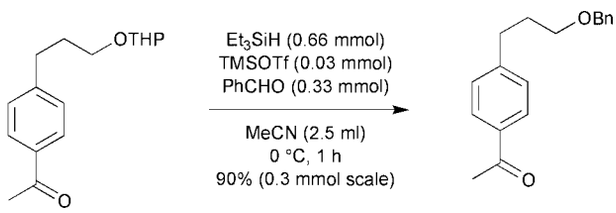
Lithium tetrafluoroborate in acetonitrile can be used as a catalyst for tetrahydropyranylation of alcohols under essentially neutral conditions.[69]

Direct conversion of THP-protected alcohols into the corresponding benzyl ethers can be performed by reaction with triethylsilane and benzaldehyde in the presence of a catalytic amount of trimethylsilyl trifluoromethanesulfonate (TMSOTf) in a one-pot procedure.[70] Benzyl ethers, benzoates and aromatic ketones (Scheme 54) remain intact in the reaction conditions. The survival of the aromatic ketone is particularly noteworthy



109 (TBTU)

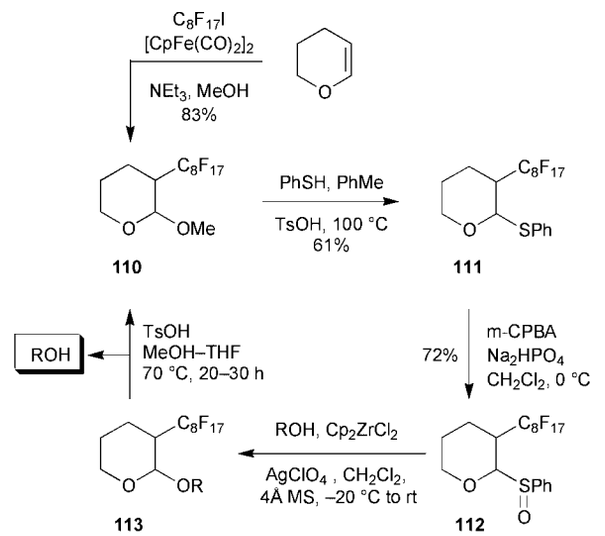
Scheme 53



Scheme 54

because it is known to be reduced by triethylsilane under acidic conditions.

The methyl acetal **110** is a strategic component of a new recyclable fluorous labelled THP protecting group protocol of Wipf and Reeves (Scheme 55).[71] Transacetalisation of **110** could not be accomplished directly owing to the potent electronic deactivation of the anomeric centre by the perfluorooctyl group. However, the requisite protection step could be accomplished by a three step procedure beginning with replacement of the methoxy group with a phenylthio group to give *O*,*S*-acetal **111** in 61% yield. The corresponding sulfoxide **112** underwent substitution by primary, secondary and tertiary alcohols using zirconocene dichloride and silver perchlorate. Purification of the THP ether **113** was accomplished by dissolving the crude product in acetonitrile and extracting 5 times with FC-72. Recovery of the alcohol was achieved by rather harsh acidic methanolysis to return the methyl acetal **110** which could be separated by repetition of the FC-72–acetonitrile partition.

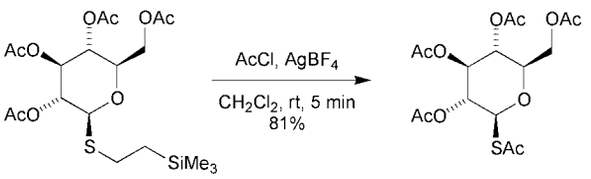


Scheme 55

3 Thiol protecting groups

The stability of 2-(trimethylsilyl)ethyl sulfides has limited their use as thiol protecting groups. For example, unlike their oxygen

counterparts, they do not undergo cleavage with TBAF even under forcing conditions. A two step procedure for the cleavage of 2-(trimethylsilyl)ethyl sulfides to thiols has been reported which involves first treatment of the 2-(trimethylsilyl)ethyl sulfide with (methylthio)dimethylsulfonium tetrafluoroborate and dimethyl sulfide to give the corresponding disulfide which is then reductively cleaved to the thiol in the second step.[72] A Swedish group has discovered mild conditions for the cleavage of 2-(trimethylsilyl)ethyl sulfides which are compatible with many of the standard transformations in carbohydrate chemistry.[73] The procedure, illustrated in Scheme 56, entails treatment of the thioether in dichloromethane with an excess of an acid chloride in the presence of silver(I) tetrafluoroborate. The resultant thioesters can then be easily hydrolysed to the thiol.



Scheme 56

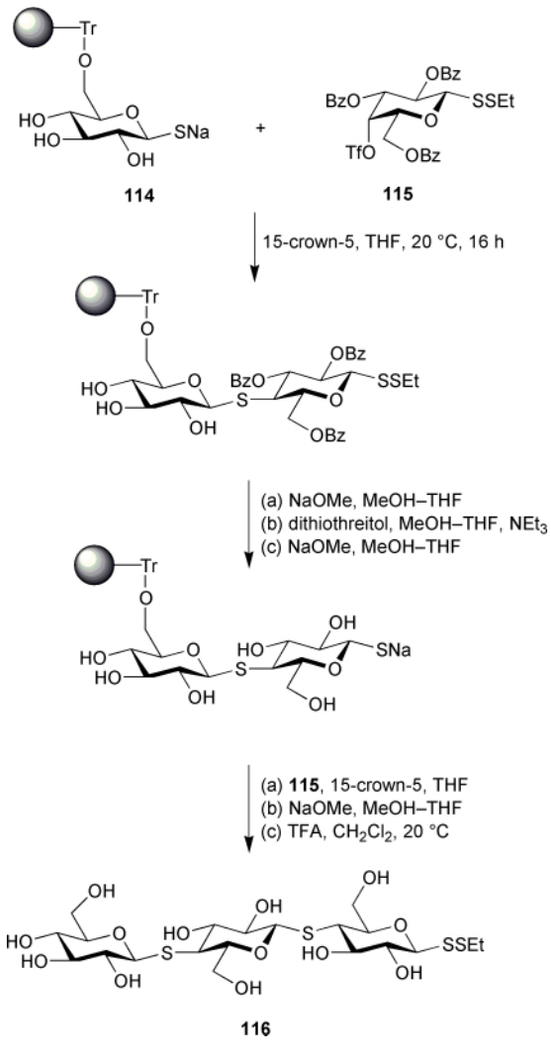
The 2-(trimethylsilyl)ethyl sulfides are stable towards TFA under conditions typically used to cleave acetals. The standard acylation and transesterification reactions are also fully compatible. Many Lewis acids are tolerated but halogenating agents react.

Thioglycosides are potential glycosidase inhibitors because they are much more stable towards enzymatic hydrolysis. Hummel and Hindsgaul[74] developed a solid phase synthesis of thio-oligosaccharides exemplified by the synthesis of the trisaccharide **116** (Scheme 57). The method exploits a highly reactive sugar thiolate **114** devoid of protecting groups as the nucleophile in a displacement reaction on triflate activated glycoside **115**. The anomeric thiol function is carried through the synthesis as its unsymmetrical ethyl disulfide which is deprotected with dithiothreitol in preparation for the next glycosidation. Finally acid cleavage from the resin gives the trisaccharide **116**.

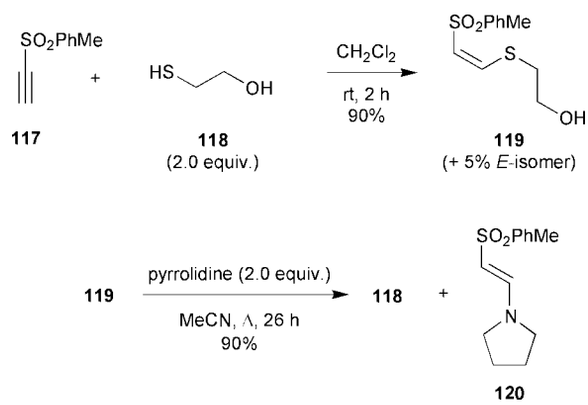
Michael addition of thiols to commercially available *p*-tolylsulfonylacetylene **117** occurs in dichloromethane in the absence of strong base to give (*Z*)-adducts preferentially.[75] Hydroxy groups need not be protected as in the case of sulfanylethanol **118** (Scheme 58). The deprotection occurs by addition–elimination of pyrrolidine in acetonitrile at rt to give the recovered thiol **118** and the (*E*)-adduct **120**.

The allyloxycarbonylaminomethyl (Allocam) group has recently been developed for the protection of thiols to complete the suite of allylic protecting groups for the common functional groups in peptides.[76] The Allocam group is stable towards piperidine in DMF under conditions used to cleave Fmoc groups but it decomposes slowly under the acidic conditions required for cleavage of *tert*-butyl esters and Boc groups (TFA in dichloromethane). The pertinent chemistry is illustrated in Scheme 59: brief treatment of cysteine hydrochloride (**121**) with one equiv. of *N*-hydroxymethylcarbamic acid allyl ester (mp 57 °C) gave the protected derivative **122** in 92% yield. The deprotection conditions are mild but the workup is tedious and the yield modest. Thus treatment of **123** with Bu_3SnH and HOAc in the presence of a Pd(0) catalyst followed by oxidative dimerisation of the liberated thiol returned cystine derivative **124** in only 65% yield.

The *N*-[2,3,5,6-tetrafluoro-4-piperidinophenyl]-*N*-allyloxycarbonylaminomethyl (Fnam) group is an alternative allylic protector for thiols with higher acid stability than the Allocam group albeit at the expense of much greater complexity.[77] The Fnam group is introduced by reacting the thiol with methyl (ethyl)(*N*-pentafluorophenyl-*N*-allyloxycarbonylaminomethyl)-



Scheme 57

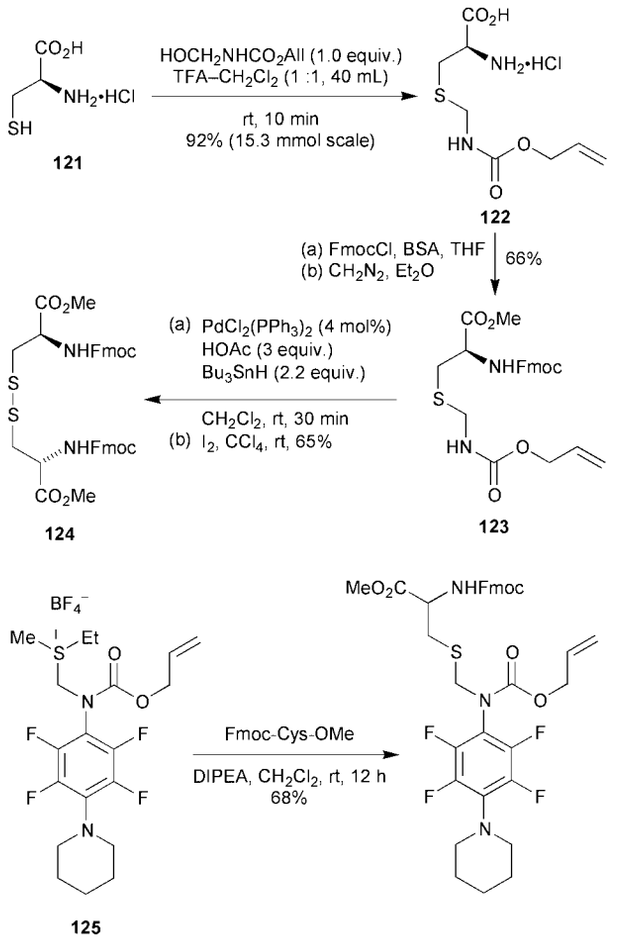


Scheme 58

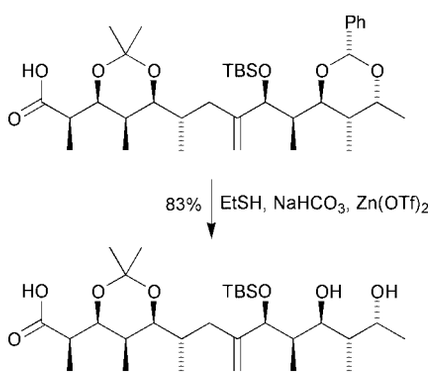
sulfonium tetrafluoroborate (**125**), prepared in four steps from pentafluoroaniline. The Fnam group is stable towards conditions for cleaving Boc groups but can be removed by Pd(0) catalysis using not only Bu_3SnH, but also *N*,*N*′-dimethylbarbituric acid and $PhSiH_3$ as allyl scavengers.

4 Diol protecting groups

A selective cleavage of a benzylidene acetal in the presence of an isopropylidene acetal was a feature of a synthesis of the macrolide antibiotic aglycone oleanolide (Scheme 60).[78] The desired transformation was accomplished in 83% yield with ethanethiol in the presence of sodium hydrogen carbonate and zinc triflate.

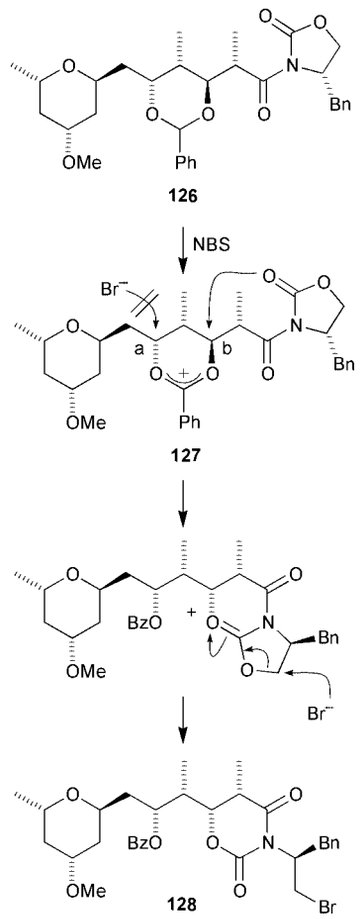


Scheme 59

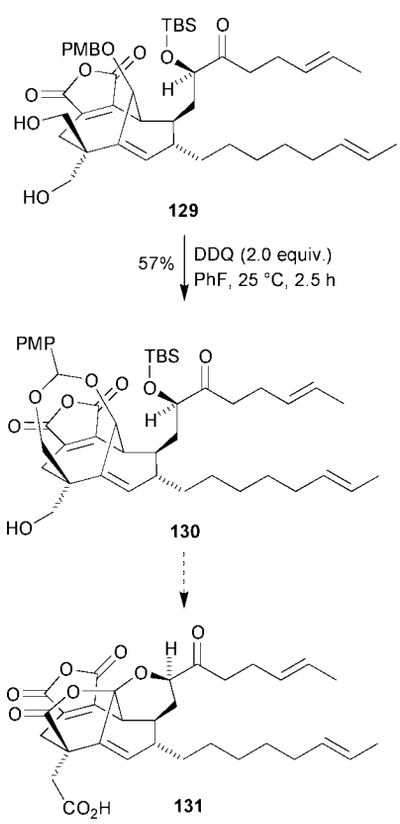


Scheme 60

More than 30 years ago Hanessian and co-workers showed that benzylidene acetals of carbohydrates cleaved regioselectively by oxidation with NBS.[79] An attempt to apply the Hanessian method to the benzylidene acetal **126** (Scheme 61)[80] was based on the premise that nucleophilic capture of the dioxonium ion **127** would occur at the less hindered site a. However, intramolecular capture at position b by the carbonyl group of the oxazolidinone moiety was faster than intermolecular attack by the bromide ion at position a resulting in formation of **128** instead.



Scheme 61

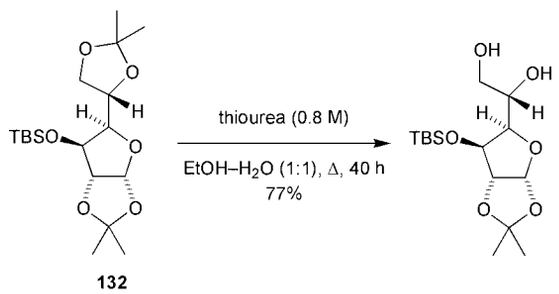


Scheme 62

One of the major synthetic achievements of 1999 was the total synthesis of CP-263,114 (**131**, Scheme 62) and its close relative CP-225,917 by the Nicolaou group.[81,82] Both compounds were originally isolated from an unidentified fungal species by scientists at Pfizer and interest in their structure was stimulated by their impressive cholesterol lowering properties through inhibition of squalene synthase. They also inhibit farnesyl transferase and hence have potential for treatment of cancer. At one stage in the elaboration of the groups pendent to the bicyclo[4.3.1]decadiene framework, it was necessary to protect one of two proximate hydroxymethyl groups in order to

initiate a selective oxidation–homologation sequence. The requisite protection was neatly accomplished by treatment of the *p*-methoxybenzyl ether **129** with DDQ in fluorobenzene whereupon ring closure to the 7-membered *p*-methoxyphenyl acetal **130** occurred in 57% yield. Whilst similar ring closures to 5- and 6-membered rings are common, the closure to a 7-membered acetal reported here is rare.

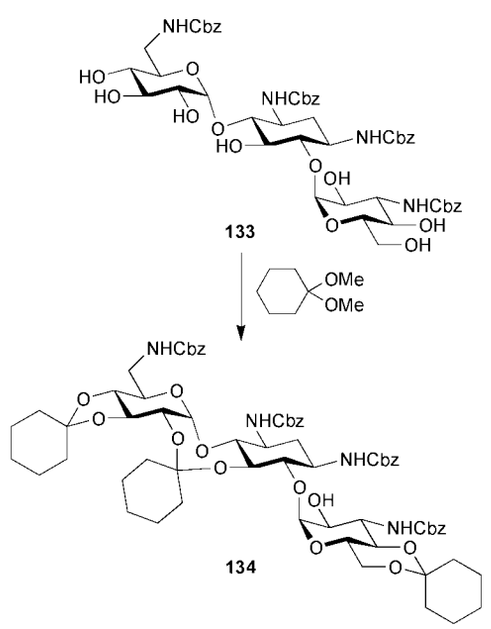
A mild method for the cleavage of certain 1,3-dioxolanes entails refluxing the substrate (*e.g.* **132**, Scheme 63) with 0.8 M thiourea in ethanol–water (1:1).[83] 1,3-Dioxolane derivatives of ketones and aldehydes are cleaved, as are THP ethers and dimethyl acetals, but MOM ethers and secondary TBS ethers appear to be inert. The mechanism of the reaction is not clear though it has been noted that a 1.0 M solution of thiourea in ethanol–water is pH 5.6.



132

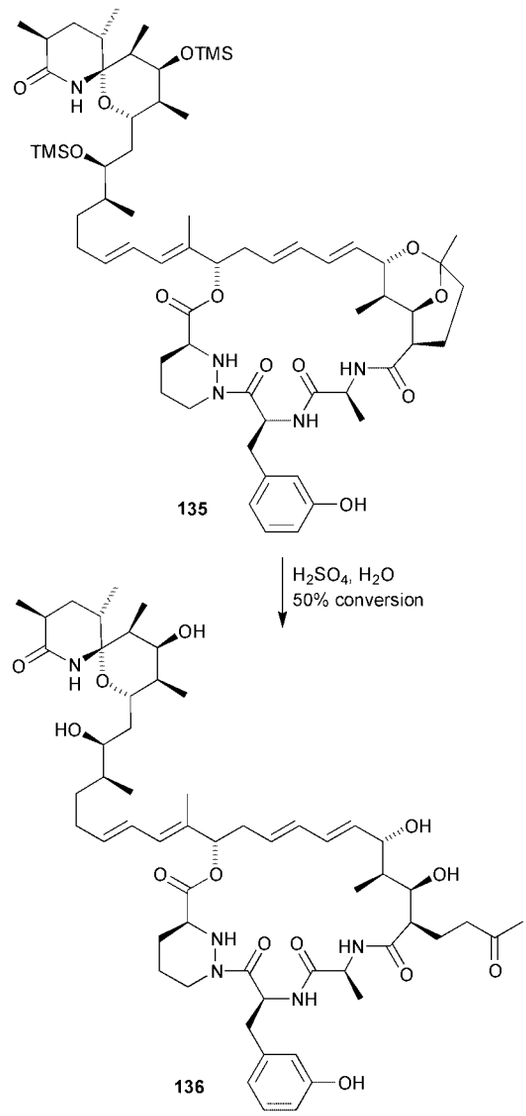
Scheme 63

During studies aimed at the synthesis of modified kanamycin antibiotics, Mobashery and co-workers[84] protected 3 pairs of proximate hydroxy groups in **133** (Scheme 64) as the corresponding cyclohexylidene acetals **134**, including one which was a *trans*-fused dioxolane and one which was incorporated into an 8-membered ring. The latter two acetals were unstable and could be selectively hydrolysed in the presence of the third, unstrained cyclohexylidene acetal.



Scheme 64

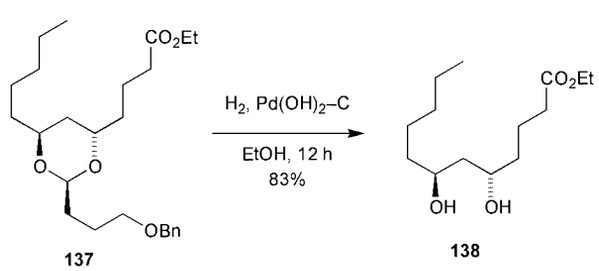
The most elegant and atom efficient method for the protection of two or more functional groups in any polyfunctional molecule involves mutual or internal protection. A good case in point has been taken from the synthesis of the immunosuppressant sanglifehrin (**136**, Scheme 65) by Nicolaou *et al.*[85] Here a 1,3-diol and a methyl ketone were internally protected as an acetal (**135**). The resultant ensemble was taken through two Stille couplings and a transprotection regime before the acetal



Scheme 65

and two TMS ethers were hydrolysed to reveal sanglifehrin A (**136**). The paper describes the final step as proceeding to 50% conversion but the *yield* is not specified.

4-Benzyloxybutanal acetals (BOB) have been recommended for the relay deprotection of 1,3-diols under very mild conditions.[86] Hydrogenolysis of the benzyloxy group in **137** (Scheme 66) produced a primary alcohol which, under the reaction conditions, undergoes intramolecular transketalisation to release the diol **138** in 83% yield. By using Pt-C instead of $Pd(OH)_2$ as the catalyst, the intermediate primary alcohol can be isolated and the subsequent transketalisation induced by treatment with PPTS in MeOH at room temperature.

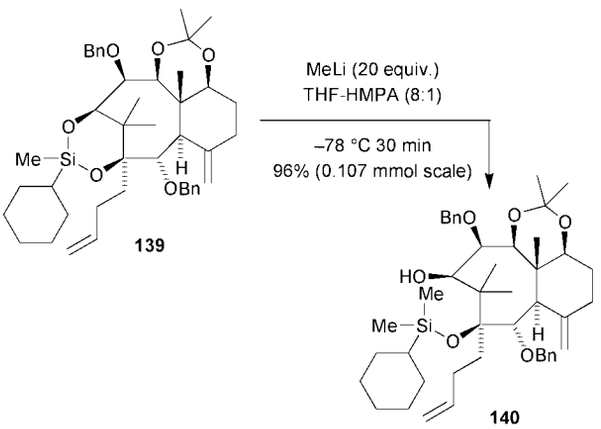


137 **138**

Scheme 66

A recent synthesis of taxol by Mukaiyama and co-workers[87] served as a vehicle for demonstrating the value of several variants of the directed aldol reaction pioneered by this group

over two decades ago. At one stage of the synthesis it was necessary to cleave a protected 1,3-diol regioselectively. The task was accomplished by the reaction of a cyclohexylmethysilylene derivative (**139**, Scheme 67) with methyllithium in the presence of HMPA to give more hindered cyclohexyldimethylsilyl ether **140** in 96% yield.



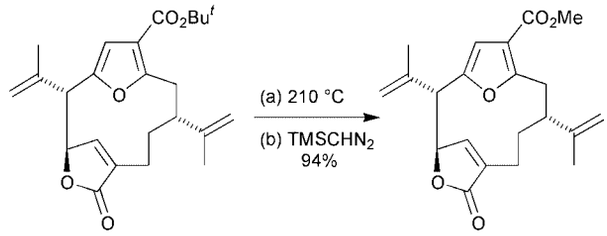
139 **140**

Scheme 67

5 Carboxy protecting groups

Nucleoproteins play a decisive role in important biological processes and their chemical synthesis hinges on the development of methods for linking the hydroxy group of a serine, a threonine or a tyrosine through a phosphodiester group to the 3′- or 5′-end of DNA or RNA. There are two major challenges to the synthesis of nucleopeptides. Firstly, the multifunctionality of the peptide–nucleotide conjugates requires the application of a variety of orthogonally stable amino, carboxy, phosphate and hydroxy groups. Secondly, fully protected serine/threonine nucleopeptides are both acid- and base-labile. Using conjugate **141** (Scheme 68) as a model, the Waldmann group[88] devised a powerful strategy for orthogonal deprotection of the four major classes of functional groups under nearly neutral conditions which exploits a combination of enzyme-labile and classical protecting groups. The conditions of the enzyme-mediated selective deprotections are so mild that neither depurination (an acid-catalysed process) nor β-elimination (a base-catalysed process) are observed.

Transesterification of the *tert*-butyl ester **146** (Scheme 69) to the corresponding methyl ester **147** is not straightforward.



146 **147**

Scheme 69

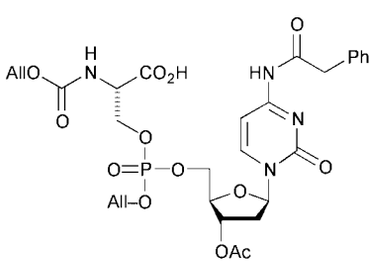
Typical acid-catalysed cleavage of the *tert*-butyl ester is precluded by the acid-sensitivity of the furan whereas basic methanolysis suffers from the electrophilicity of the unsaturated lactone. However, brief immersion of a thin layer of **146** in an oil bath preheated to 210 °C followed by treatment of the crude product with trimethylsilyldiazomethane afforded the methyl ester **147** in near-quantitative yield.[89] The elimination did not proceed in refluxing decalin (190 °C).

Attempts to convert the SEM ester of the Boc-threonine intermediate **148** (Scheme 70) to the corresponding carboxylic acid **149** using TBAF were frustrated by easy decarboxylation followed by β-elimination.[54] The desired transformation could be accomplished with HF in acetonitrile but magnesium bromide–diethyl ether in dichloromethane was an easier and safer alternative that gave the desired product **149** in quantitative yield.

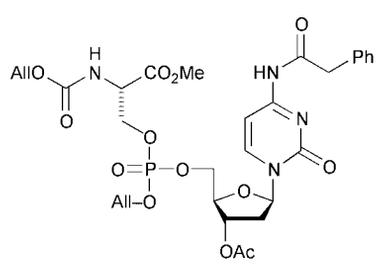
As a prelude to the construction of the macrocyclic ring of the antitumour cyclodepsipeptide tamandarin, Joullié and coworkers[90] accomplished the mild deprotection of the SEM ester **150** (Scheme 70) using magnesium bromide–diethyl ester in dichloromethane. No harm befell the Boc, TIPS, Cbz and ester functionalities.

Mild conditions for the cleavage of benzyl ethers, esters and carbamates in the presence of other easily reducible groups have been developed[91] based on earlier work of Birkofer *et al.*[92,93] Treatment of the substrate with palladium acetate and triethylamine in the presence of triethylsilane affords the deprotected product at room temperature. Examples are illustrated in Scheme 71. Competing reduction of bromoarenes, cyclopropanes or alkenes is not observed.

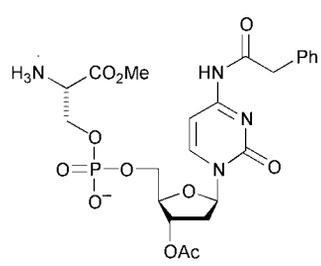
During a synthesis of the complex macrolide miyakolide, Evans *et al.* were faced with the problem of cleaving the benzyl ester **156** in the presence of the isoxazole, alkene and enoate[42] (Scheme 72). Initial attempts to achieve the desired transform-



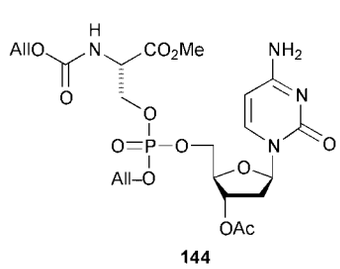
142



141

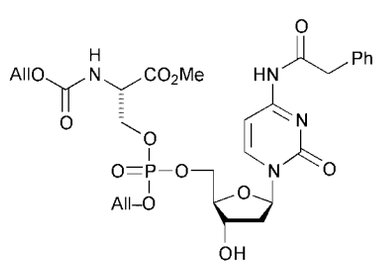


143



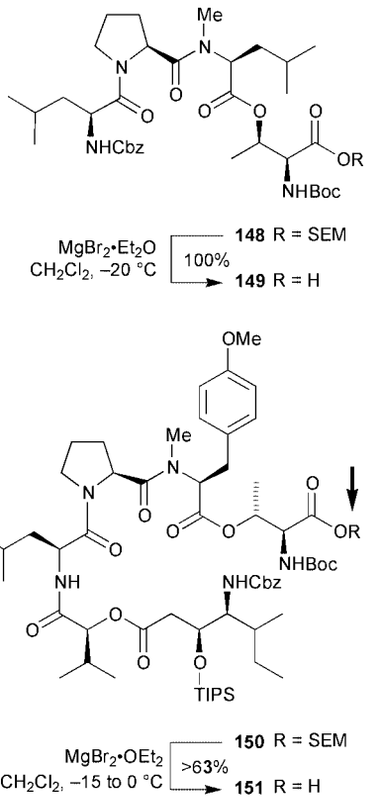
144

Product	Cleavage Conditions	Yield
142	papain, phosphate buffer pH 6.6 10 vol% acetone	91%
143	$Pd[Ph_3P]_4$, $PhSiH_3$, THF	89%
144	penicillin G acylase phosphate buffer pH 7.0, rt	77%
145	wheat germ lipase phosphate buffer pH 6.5, 37 °C	64%

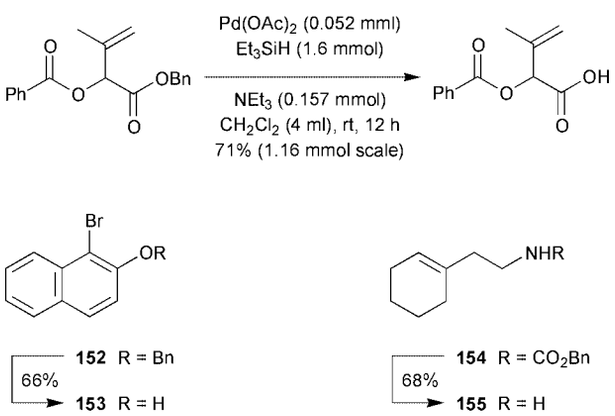


145

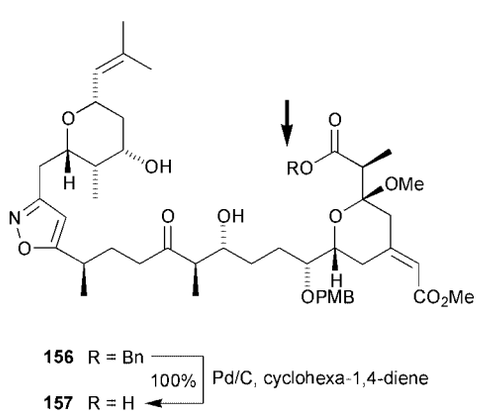
Scheme 68



Scheme 70



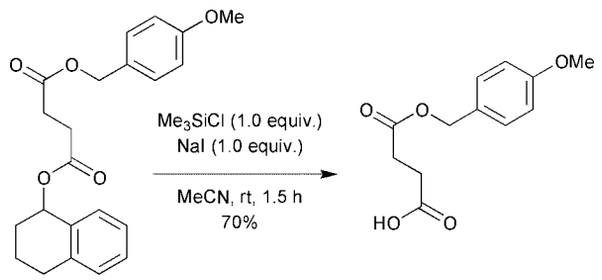
Scheme 71



Scheme 72

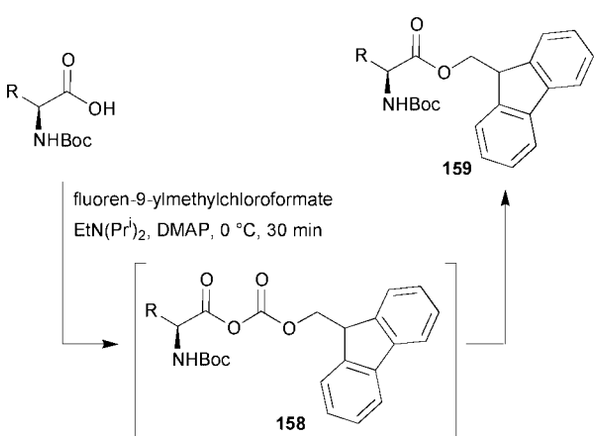
ation using transfer hydrosilylation worked on a small scale (<10 mg) but scale-up was frustrated by the hypersensitivity of the diol acid product **157**. In the end, transfer hydrogenation was a more reliable method for removing the benzyl ester (10% Pd/C, cyclohexa-1,4-diene) giving product **157** in quantitative yield.

1,2,3,4-Tetrahydro-1-naphthyl esters can be selectively cleaved in the presence of alkyl and aryl esters using sodium iodide and trimethylsilyl chloride in acetonitrile at rt—conditions which leave benzhydryl and *p*-methoxybenzyl esters intact (Scheme 73).[94] 1,2,3,4-Tetrahydro-1-naphthyl esters also cleave with TFA (in CH_2Cl_2, rt, 1 h) and H_2–Pd/C but they are stable towards sodium borohydride in MeOH at 0 °C, CAN and DDQ.



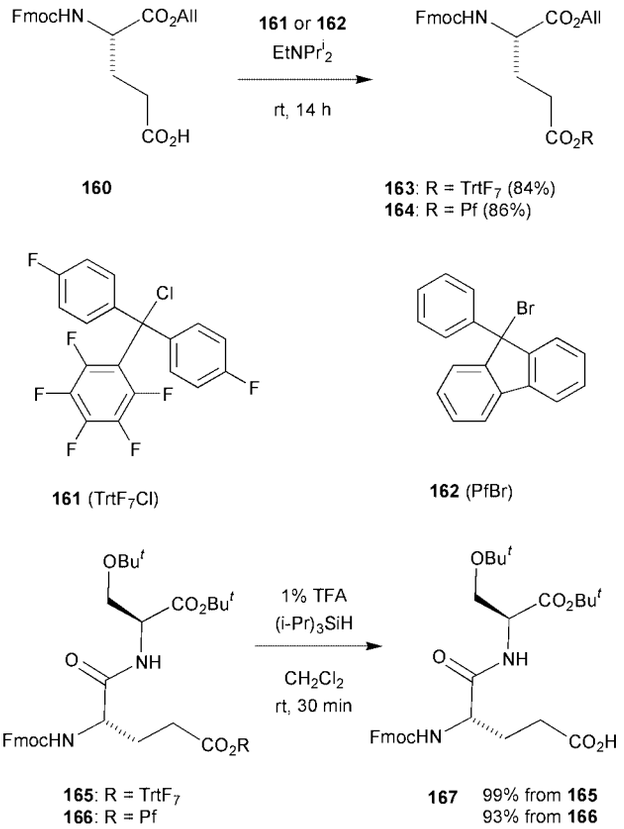
Scheme 73

N-Protected amino acids were previously converted to their fluoren-9-ylmethyl esters using fluoren-9-ylmethanol in the presence of dicyclohexylcarbodiimide[95] or with diazofluorene.[96] Alternatively, transesterification of *N*-protected amino acid 4-nitrophenyl esters with fluoren-9-ylmethanol can be used but the base, imidazole, causes some decomposition during the prolonged reaction time.[97] A new method for the preparation of fluorenylmethyl esters (Scheme 74) involves reaction of the amino acids with fluoren-9-ylmethyl chloroformate to give the intermediate carbonic anhydride **158** which undergoes spontaneous decarboxylation to the product **159** under the reaction conditions.[98] The yields are moderate to good (53–82%) except for valine which only gives a 25% yield.



Scheme 74

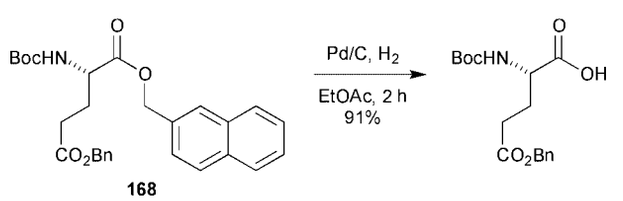
The sterically demanding 2,3,4,4′,4″,5,6-heptafluorotriphenylmethyl ($TrtF_7$) and the 9-phenylfluoren-9-yl (Pf) groups have been recommended for the protection of the γ-carboxy group of glutamic acid in peptide synthesis.[99] Both groups show a marked increase in stability over triphenylmethyl esters but they remain, nevertheless, sensitive to acid allowing removal under mild conditions. The introduction of the protecting groups is illustrated by the conversion of glutamic acid derivative **160** to the $TrtF_7$ ester **163** in 84% yield by reaction with $TrtF_7Cl$ (**161**) in diisopropylethylamine (Scheme 75). The corresponding Pf ester **164** was similarly prepared in 86% yield using 9-phenylfluoren-9-yl bromide (**162**). The $TrtF_7$ and Pf ester groups are stable in a 1 : 1 mixture of acetic acid and ethyl acetate but they are cleaved rapidly by all concentrations of TFA over 1% in dichloromethane. The cleavage is facilitated by



Scheme 75

the appropriate cationic scavengers such as triisopropylsilane. Such conditions are mild enough to preserve *tert*-butyl ethers and esters as shown by the conversion of **165** and **166** to **167**.

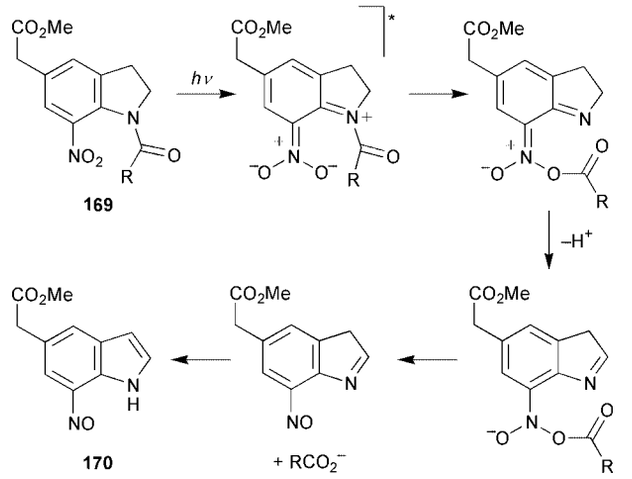
2-Naphthylmethyl esters are hydrogenolysed selectively in the presence of benzyl esters using 10% palladium on charcoal (20 mg $mmol^{-1}$) in ethyl acetate.[100] In the case of substrates bearing an α-heteroatom (*e.g.* **168** in Scheme 76), good selectivity is observed when the 2-naphthylmethyl ester resides on the carboxy adjacent to the substituent. Competing cleavage of benzyl esters can be suppressed by introducing a trifluoromethyl group at the 4-position of the phenyl ring.



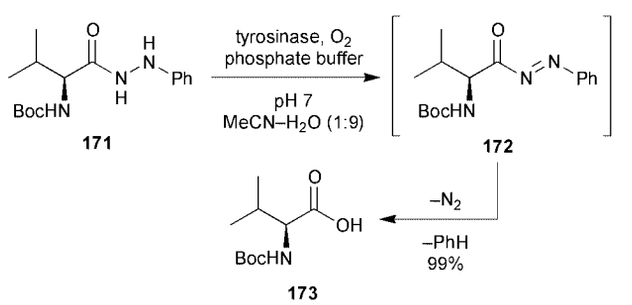
Scheme 76

1-Acyl-7-nitroindoline-5-acetic esters **169** undergo clean photolysis (351 nm laser) in neutral aqueous solution to give carboxylates and methyl 7-nitrosoindole-5-acetate (**170**) according to the mechanism proposed in Scheme 77.[101]

The Waldmann group continues its innovative programme on enzyme-cleavable protecting groups with a report on the use of the mushroom tyrosinase for the cleavage of phenylhydrazides.[102] Mushroom tyrosinase is commercially available and it tolerates up to 30% of organic solvents such as acetonitrile, dioxane or DMF. Scheme 78 illustrates the procedure. Tyrosinase is added to a solution of the substrate **171** in aqueous MeCN buffered to pH 7 with phosphate buffer whilst bubbling oxygen through the reaction mixture. The intermediate acyl diazene **172** undergoes rapid hydrolysis with loss of benzene and nitrogen to give the free acid **173**. The reaction has also been applied to four dipeptides without detriment to the *N*-terminal protecting group or the peptide bond.



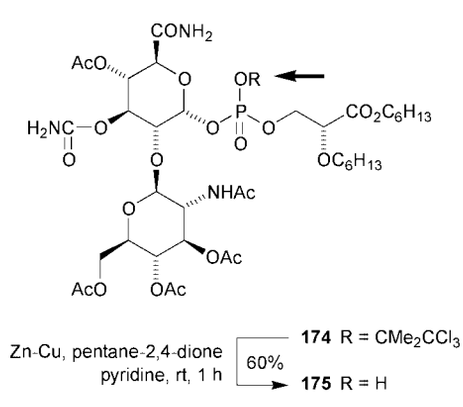
Scheme 77



Scheme 78

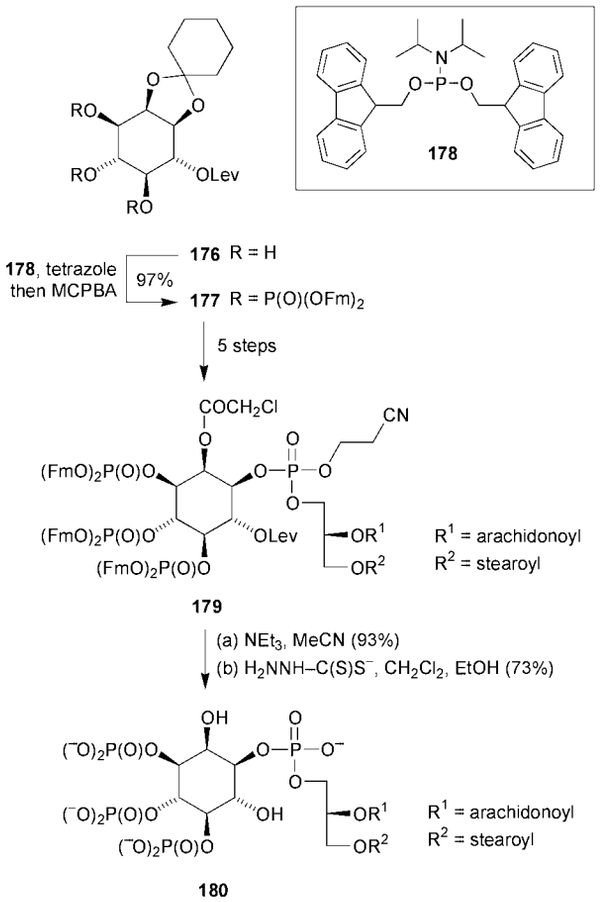
6 Phosphate protecting groups

The Welzel group[103] required a phosphodiester protecting group which could be removed under selective mild conditions as part of their synthesis of moenomycin analogues. The 2,2,2-trichloro-1,1-dimethylethoxy group served their purposes well being easily removed with freshly prepared Zn–Cu couple in pyridine in the presence of pentane-2,4-dione (Scheme 79). Pentane-2,4-dione is added to chelate the zinc cation and maintain the surface of the metal in a cleaner state.[104]

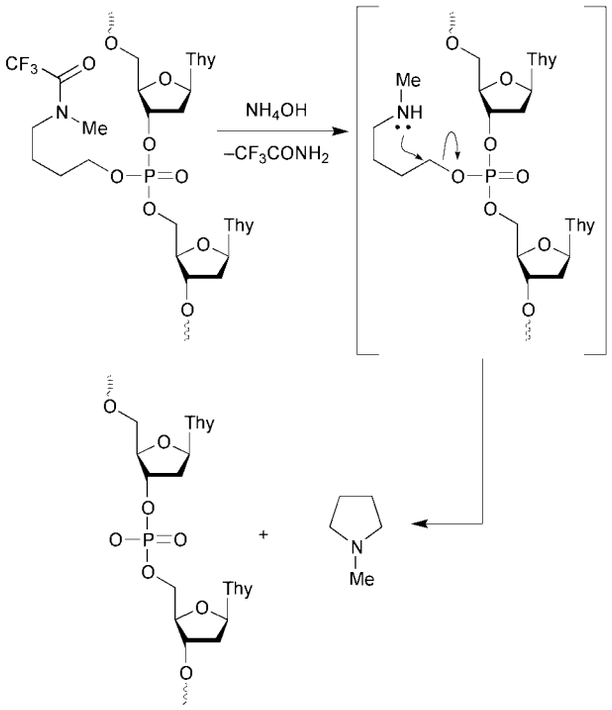


Scheme 79

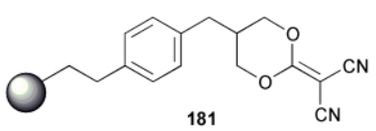
Phosphatidylinositol 3,4,5-triphosphates play an important role in activating tyrosine kinase which is implicated in cell proliferation, oncogenesis and insulin action. During a synthesis of *sn*-1-*O*-stearoyl-*sn*-2-*O*-arachidonoyl phosphatidyl-*myo*-inositol 3,4,5,-triphosphate (**180**, Scheme 80), Watanabe and Nakatomi[105] encountered difficulty removing a variety of phosphates protecting groups in the closing stages of the synthesis. Success was eventually achieved with the fluoren-9-ylmethyl (Fm) phosphate ester[106] which was introduced by reaction of triol **176** with di(fluoren-9-ylmethyl)-*N*,*N*-diisopropyl-

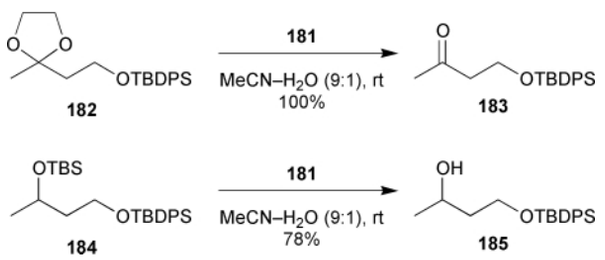


Scheme 80



Scheme 81





Scheme 82

phosphoramidite (**178**) followed by oxidation with MCPBA to give the tris-phosphotriester **177** in 97% yield. Five further routine steps were used to prepare **179** from which the cyanoethyl and fluoren-9-ylmethyl groups were removed by simple treatment with triethylamine. The chloroacetate and levulinoyl groups were finally removed with ethyldiisopropylammonium hydrazinedithiocarbonate to give the target **180**.

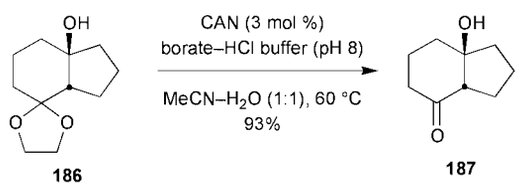
The 2-cyanoethyl group is a popular protecting group for phosphate during oligodeoxyribonuleotide synthesis using the phosporamidite method.[107] There are drawbacks though: deprotection with base (typically NH_3 or NH_4OH) releases the carcinogen acrylonitrile which can then *N*-alkylate the nucleobase—a problem which is especially acute when deprotections are conducted under preparative (*i.e.* concentrated) conditions. The Beaucage group used the 4-[*N*-methyl-*N*-(2,2,2-trifluoroacetyl)amino]butyl groups as a replacement for the 2-cyanoethyl group for the protection of phosphate.[108] Advantages include (a) higher solubility in acetonitrile; (b) higher stability in solution; and (c) deprotection generates the innocuous *N*-methylpyrrolidine. The deprotection, illustrated in Scheme 81, begins with a rate-limiting cleavage of the *N*-trifluoroacetyl group followed by rapid cyclode-esterification to produce the *O*,*O*-diphosphate. The new protecting group was applied to the solid phase synthesis of a 20-mer.

7 Carbonyl protecting groups

A polymeric dicyanoketene acetal **181** (Scheme 82), prepared by copolymerisation of a monomeric dicyanoketene acetal bearing a styrene moiety with ethylene glycol dimethacrylate, resists hydration by water at room temperature and catalyses the hydrolysis of acetals and silyl ethers.[109] MOM ethers, THP ethers and TBDPS ethers resist hydrolysis allowing selective deprotections as illustrated by the conversion of **182** to **183** and **184** to **185**. The catalyst can be recycled.

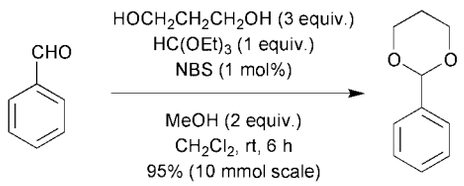
Markó and co-workers discovered that catalytic amounts of CAN catalyse the hydrolysis of dioxolane and dioxane acetals at 60 °C in the presence of a borate–HCl buffer (pH 8).[66,110] Some indication of the mildness and efficiency of the process is illustrated by the transformation depicted in Scheme 83 in which the β-hydroxyketone **187** was obtained in 93% yield without complications from dehydration. The deprotection of **186** was monitored by cyclic voltammetry and the only species present throughout the reaction was Ce(IV) indicating that the CAN acts as a highly selective Lewis acid. TIPS ethers, enones, amides, benzyl ethers and terminal alkenes are stable under the reaction conditions but *S*,*S*- and *O*,*S*-acetals,[111] TBS ethers[112] and Boc groups[113] are incompatible.

Aldehydes are converted to their 1,3-dioxane derivatives on reaction with a catalytic amount of NBS in the presence of



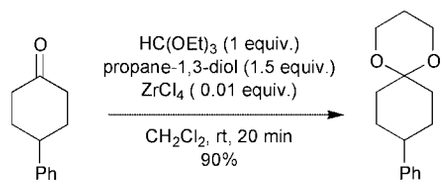
Scheme 83

propane-1,3-diol (3 equiv.) and triethyl orthoformate (1 equiv.) at rt (Scheme 84).[114] 1,3-Dioxolane derivatives can also be prepared using dimethyl tartrate. THP ethers and TBS groups are not affected and ketones react much slower and give lower yields of the acetal derivative. The role of the NBS is not clear but it may be simply acting as a source of trace amounts of HBr.



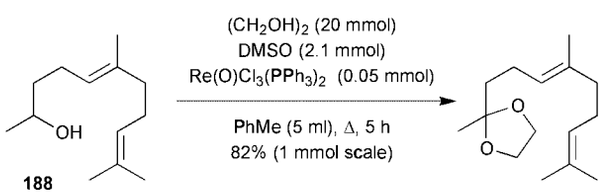
Scheme 84

Zirconium tetrachloride catalyses the transacetalisation of carbonyl compounds under mild conditions (Scheme 85).[115] A mixture of the carbonyl compound, propane-1,3-diol, and triethyl orthoformate in dichloromethane is stirred at room temperature until the reaction is complete. In the absence of the 1,3-diol, the diethyl acetal is formed. The reaction is selective for aldehydes in the presence of ketones but the selectivity diminishes when the ketone is cyclic. Thus competition experiments show that benzaldehyde and cyclohexanone give nearly a 1:1 mixture of 1,3-dioxanes. The method can also be used for the formation of thioacetals.



Scheme 85

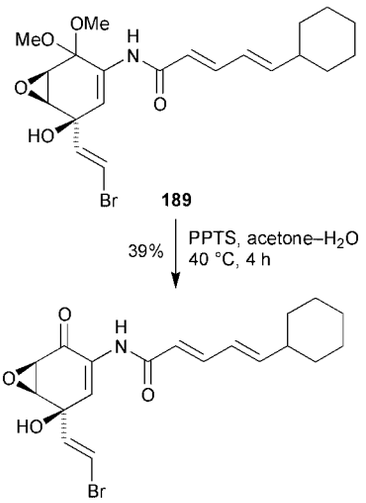
Secondary alcohols can be oxidised by DMSO and a catalytic amount of $Re(O)Cl_3(PPh_3)_2$ in the presence of ethylene glycol to give directly the ketals of the corresponding ketones (Scheme 86).[116] A small amount of the unprotected ketone (6% in the case of alcohol **188)** is sometimes formed. The analogous transformation of primary alcohols to the corresponding acetals is significantly slower, requires additional amount of DMSO, ethylene glycol and a longer reaction time.



Scheme 86

A synthesis of the epoxyquinol antibiotic nisamycin demanded the late deprotection of the dimethyl ketal **189** (Scheme 87) in the presence of an acid-sensitive tertiary allylic alcohol.[117] The desired transformation was eventually accomplished using pyridinium tosylate in aqueous acetone at 40 °C albeit in meagre yield (39%).

Dithioacetal protecting groups played a critical strategic role in the 10-year odyssey which culminated in the total synthesis of the potent marine toxin brevetoxin A by Nicolaou and coworkers.[118,119] To begin with, the mildness of the conditions required to introduce the dithioacetal group was critical to the preservation of a range of other acid sensitive protecting groups. A case in point is the conversion of ketone **190** (Scheme 88) to the dithioacetal **191** in the presence of two *tert*-



Scheme 87

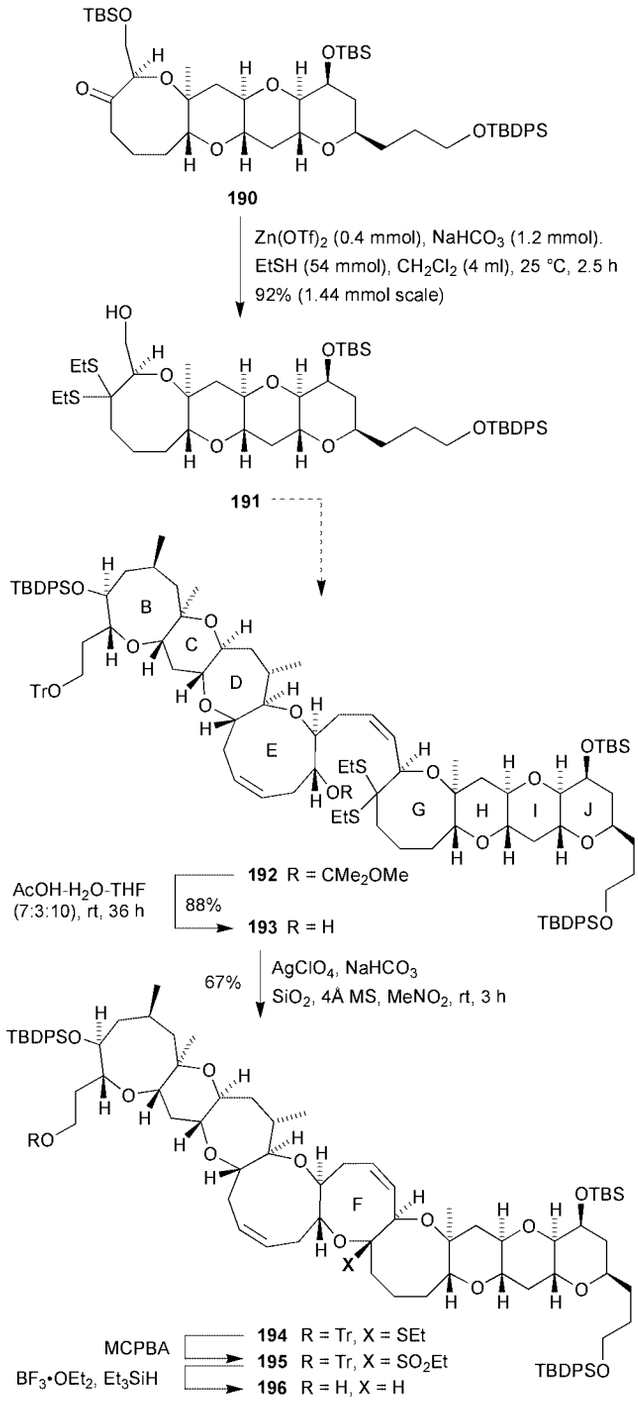
butyldimethylsilyl ethers and one *tert*-butyldiphenylsilyl ether. The task was accomplished with a large excess of ethanethiol in the presence of zinc triflate. After conjunction of the GHIJ fragment **191** with a BCDE fragment, the polycyclic fragment **192** was obtained containing 8 of the 10 rings of the natural product. Construction of the central oxocene ring (ring F) began with the mild hydrolysis of the methoxydimethylmethyl ether on ring E, whereupon the *nascent* hydroxy group in **193** served as a nucleophile in an annulation reaction activated by thiophilic silver perchlorate to generate the *O*,*S*-acetal **194**. Oxidation of the remaining thioether to a sulfone (**195**) followed by Lewis acid-promoted expulsion of ethanesulfinate afforded an oxonium ion which was captured stereoselectively to give the desired F-ring (**196**) in 68% yield from **194**. The final reductive cleavage step coincidentally performed the valuable task of removing the trityl ether protecting the side chain of ring B in preparation for the appendage of ring A. The hydroxy dithioacetal strategy was also used to construct ring G but it failed in the attempt to construct the 9-membered ring E.[120]

O,*S*-Acetals can be deprotected to the corresponding ketones using a catalytic amount of trichlorooxyvanadium in 2,2,2-trifluoroethanol under an oxygen atmosphere (Scheme 89). *S*,*S*-Acetals undergo similar deprotection but it takes much longer (182 h) to complete the reaction.[121]

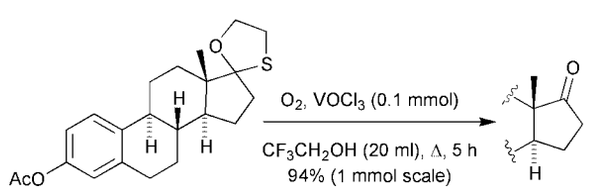
Myers and Kung reported a remarkably short synthesis of (−)-saframycin A (**203**, Scheme 90) in just 8 steps from the α-amino acid precursors **197** and **198**.[122] A key feature of the synthesis is the use of an α-amino nitrile in **198** as a latent aldehyde. Condensation of the α-amino acid precursors **197** and **198** gave an intermediate imine which underwent Pictet–Spengler cyclisation to the tetrahydroisoquinoline intermediate **199** on treatment with LiBr. After elaboration of the second tetrahydroisoquinoline ring, the final ring was constructed from **200** triggered by treatment of the α-amino nitrile with TMSCN in the presence of zinc chloride. Presumably loss of cyanide ion generated the iminium derivative **201** which cyclised and then expelled morpholine to generate another iminium ion which underwent addition of cyanide to give **202**. Three simple steps were then used to generate the natural product **203**. The high efficiency of the route enabled the synthesis of saframycin in gram quantities.

8 Amino protecting groups

The dithiasuccinoyl (Dts) group has been developed as an amino protecting group for solid phase synthesis of protected peptide nucleic acids (PNAs).[123] Treatment of the free amino group of the monomeric unit (*e.g.* **204**, Scheme 91) with bis(ethoxythiocarbonyl) sulfide gave the *N*-ethoxythiocarbonyl derivative **205**, which was silylated at the α-carboxy and



Scheme 88



Scheme 89

converted to the heterocycle **206** by reaction with (chlorocarbonyl)sulfenyl chloride. An optimised protocol for the deprotection of the Dts group using dithiothreitol in acetic acid was also developed.

(+)-Herbicidin B (**208**, Scheme 92) is a *Streptomyces* metabolite which inhibits the growth of *Xanthomonas oryzae*, the causative agent of leaf blight and selective toxicity towards dicotyledons. In the first synthesis of (+)-herbicidin B, Matsuda and co-workers encountered problems removing the *N*-benzoyl group from the advanced intermediate **207**.[124] Treatment of **207** with NaOMe or K_2CO_3 in MeOH resulted in decomposition but exposure of **207** to SmI_2 in MeOH[125] accomplished the desired deprotection. Removal of the three *O*-silyl protecting groups with TBAF returned (+)-herbicidin B in 31% overall yield.

In the closing stages of a synthesis of the antifungal agent pramanicin, Barrett and co-workers[126] deprotected the *N*-Boc lactam **209** (Scheme 93) using a procedure of Apelqvist and Wensbo[127] involving heating **209** with silica gel at 40 °C at low pressure (yield not specified). However, the deprotected lactam **210** could also be obtained in 71% yield using the conventional TFA in dichloromethane.

Deprotection of homochiral intermediate **211** (Scheme 94) with TFA unexpectedly yielded racemic diene **212**, presumably because of the acid-promoted formation of the ring-opened conjugated *N*-tosyliminium ion **213**.[128] However, the desired deprotection was accomplished without racemisation when **211** was treated with TMSI and 2,6-lutidine followed by methanolic sodium hydroxide.

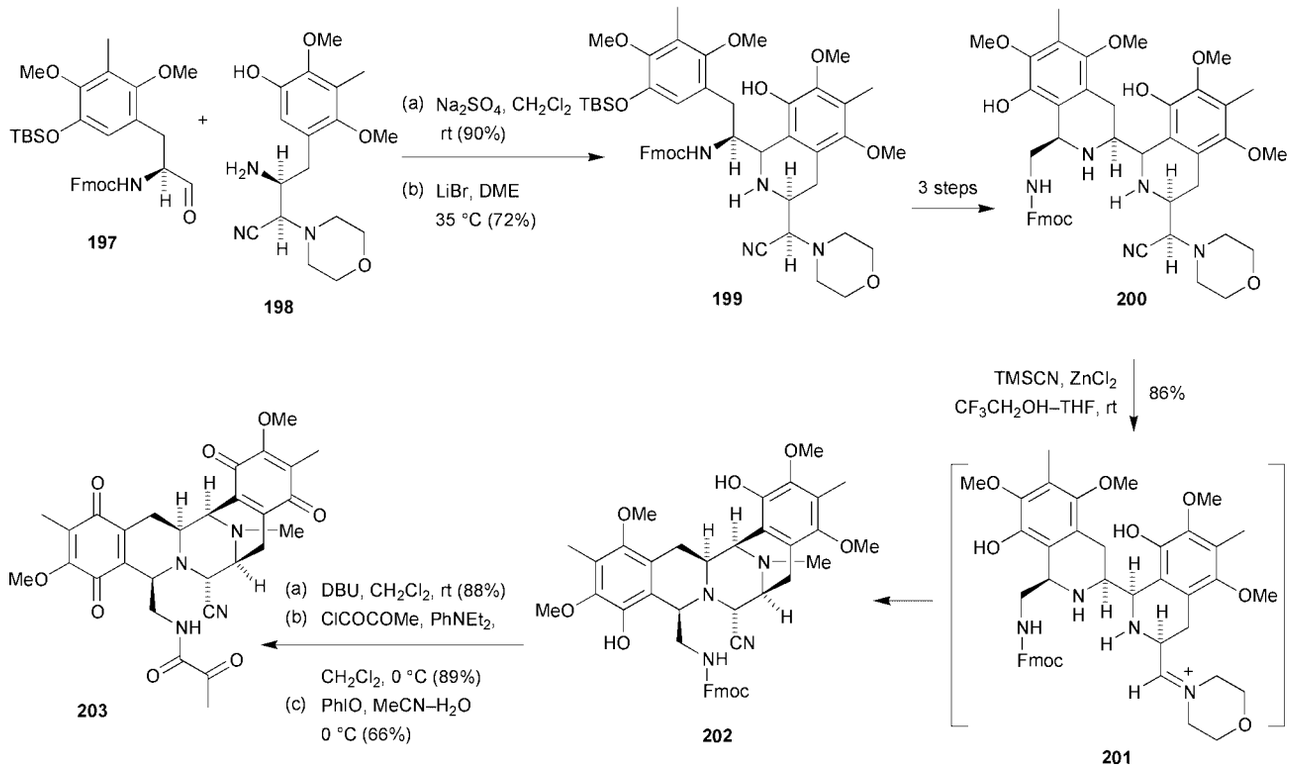
Agelastatin A (**216**, Scheme 95) is an antitumour agent isolated from the deep water sponge *Agelas dendromorpha* collected in the Coral Sea near New Caledonia. In the closing stages of a synthesis of agelastatin A by Weinreb and co-workers[129] appendage of the cyclic urea was thwarted by problems with the removal of the Boc group from intermediate **214**. Treatment of **214** with TFA at rt produced a compound which appeared to dimerise even in dilute solution. Use of triflic acid at −78 °C followed by treatment with methyl isocyanate gave mainly dimer with only traces of agelastatin. However, treatment of **214** with excess TMSI at rt gave the *O*-silyl carbamate **215** which was quenched with methyl isocyanate and dilute NaOH to give **216** in 61% overall yield.

The deprotection of PMB ethers in substrates containing dienes or trienes is frequently blighted by messy reactions. In most cases, the nature of the side reactions is not elucidated but in a recent synthesis of an unusual constituent amino acid of the protein phosphatase inhibitor motuporin, Bauer and Armstrong[130] showed that treatment of the PMB ether **217** (Scheme 96) with DDQ in the usual way afforded the product derived from oxidation of the allylic amine function to give the ketone **218** in unspecified yield.

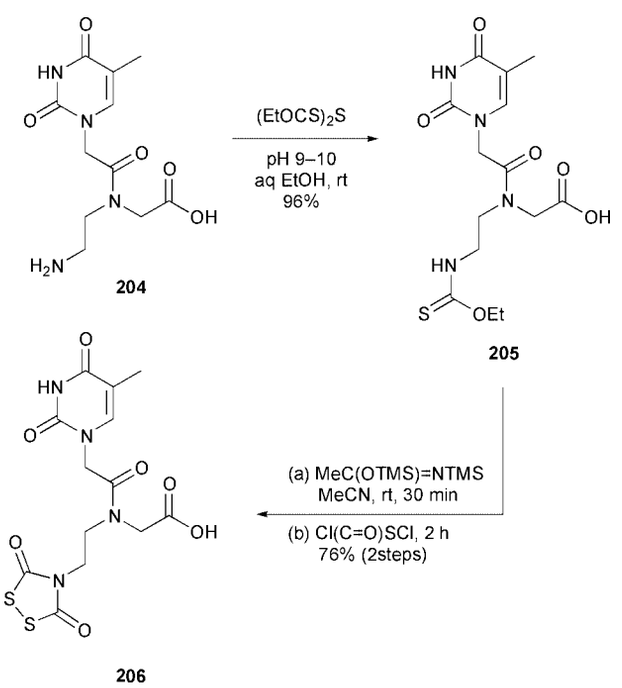
During a synthesis of the macrocyclic hexapeptide bistratamide D, the Meyers group[131] encountered a problem with a simple transformation: the hydrogenolysis of a Cbz group from **219** (Scheme 97). Under standard conditions [10% Pd/C or $Pd(OH)_2$, atmospheric pressure], no reaction occurred and the employment of liquid ammonia as solvent—a remedy for systems that suffer from sulfur poisoning[132,133]—was to no avail. Failure also attended the use of acid cleavage reagents such as boron tribromide, trifluoroacetic acid or *B*-bromocatecholborane. The problem was eventually solved by using high pressure (100 psi), a more active catalyst (Pd black) and a mixture of ethanol and triethylamine as solvent.

The 4-methoxybenzyloxycarbonyl (Moz) group previously used for the protection of amines[134–138] has been adapted for the protection of highly basic amidines.[139] The Moz group is introduced by reaction of an amidine (*e.g.* **221**, Scheme 98) with 4-methoxybenzyl 4-nitrophenyl carbonate (**222**) in the presence of pyridine. The Moz group is stable towards conditions for the alkylation of a phenol, ester hydrolysis in 1 M NaOH and peptide coupling but it was readily removed by brief exposure to 0.5% TFA in dichloromethane.

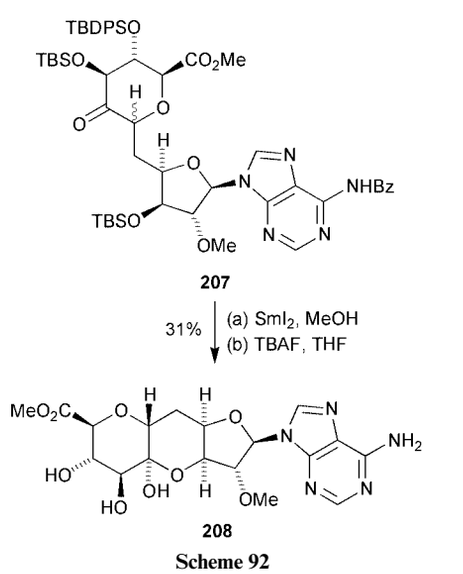
Fish do not freeze because their blood contains macromolecular antifreezes such as the antifreeze glycoprotein (AFGP) consisting of repeating units (4–55) of the glycopeptide **224** (Scheme 99). The last step in a synthesis of the glycopeptide **224**[140] entailed deprotection of the *N*-terminus protected as Moz derivative **223**. The Moz group was selected



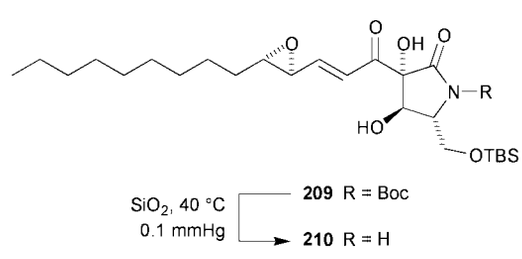
Scheme 90



Scheme 91



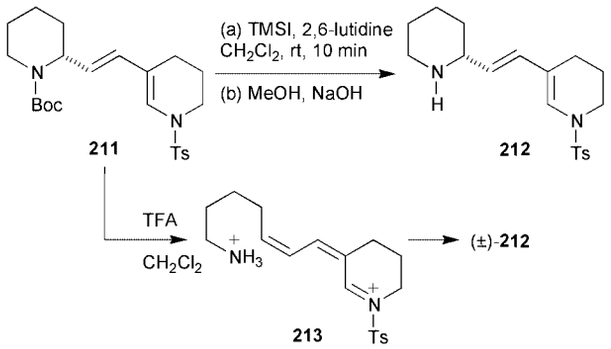
Scheme 92



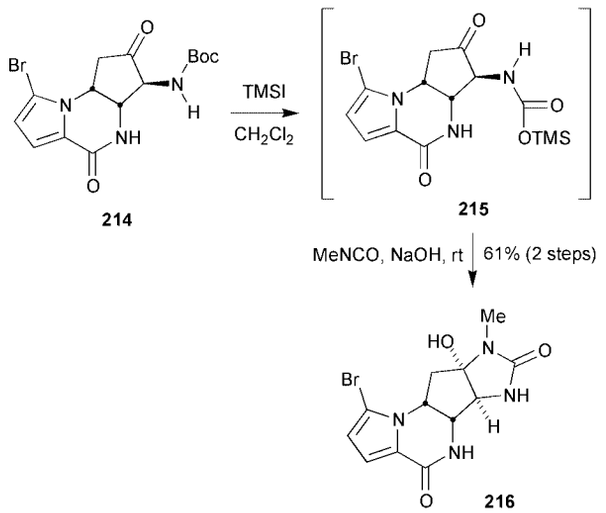
Scheme 93

because it could be removed with formic acid at room temperature for 30 min without harming the glycosidic link.

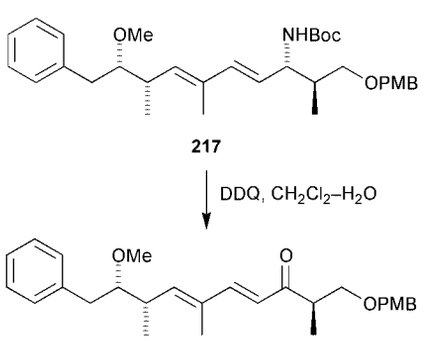
En route to a general, nonenzymatic synthesis of 3′-*O*-aminoacylated t-RNAs, Stutz and Pitsch developed a new synthetic method for the *N*-alkyloxycarbonylation of adenine and guanine nucleosides and used it for the preparation of RNA-phosphoramidites carrying photolabile sugar and nucleobase protecting groups.[141] The procedures are illustrated by the synthesis of the guanosine derivative **227** (Scheme 100). First 5′-dimethoxytrityl protected guanosine (**225**) was converted to its stannylene derivative which reacted preferentially at C-2′ with (2-nitrobenzyloxy)methyl chloride to give **226** in 80% yield. Attempts to *N*-acylate the amino function of the guanine using 2-nitrobenzyloxy chloroformate under a variety of conditions failed owing to efficient decomposition of the reagent to 2-nitrobenzyl chloride so a longer route was used. Hence, treatment of the nucleoside **226** with Ac_2O–DMAP led to quantitative acetylation of the 3′-*O*-position. Subsequent treatment with $COCl_2$–DMAP and 2-nitrobenzyl alcohol gave the desired carbamate from which the 3-*O*-acetyl protecting



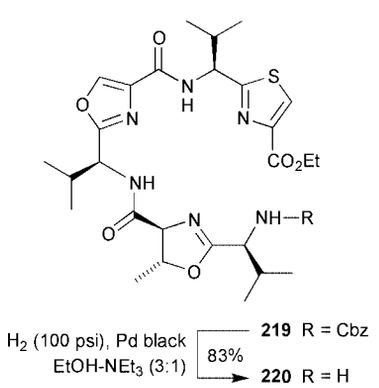
Scheme 94



Scheme 95

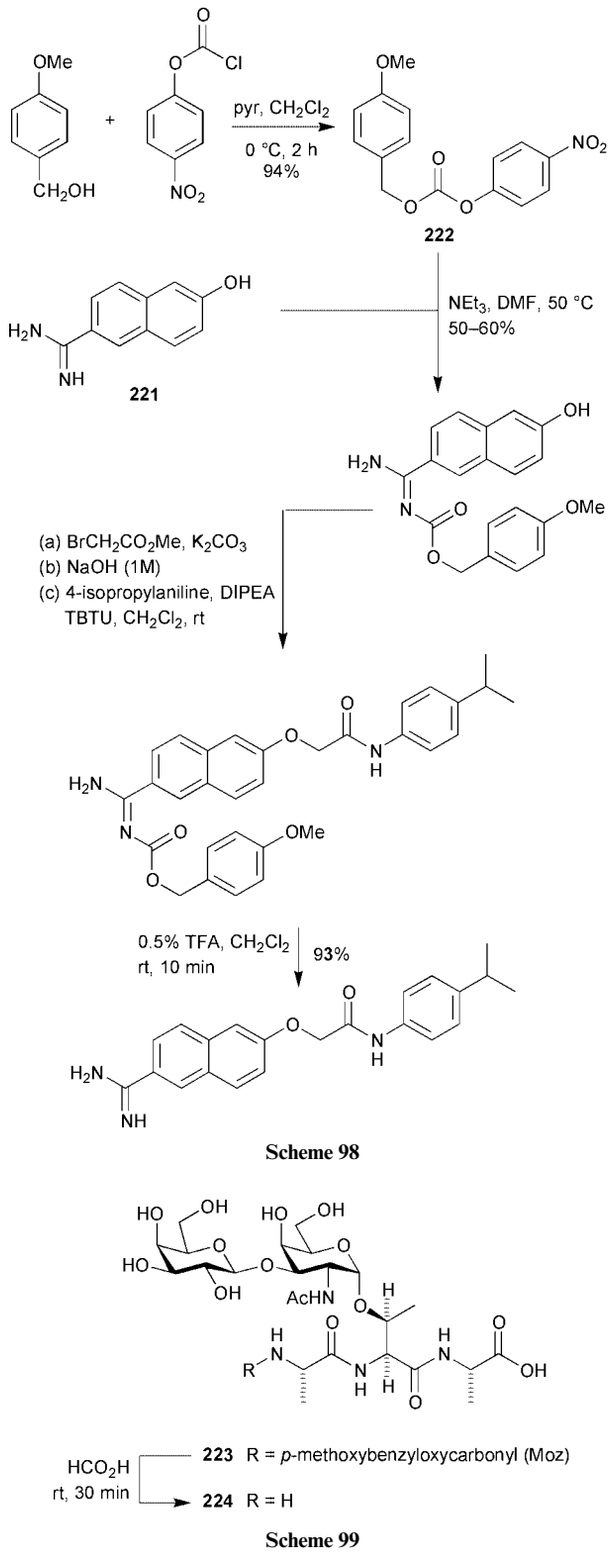


Scheme 96



Scheme 97

group was removed by basic hydrolysis. The overall yield of the 4-step sequence was 70%. Similar transformations were performed on cytosine and adenosine.

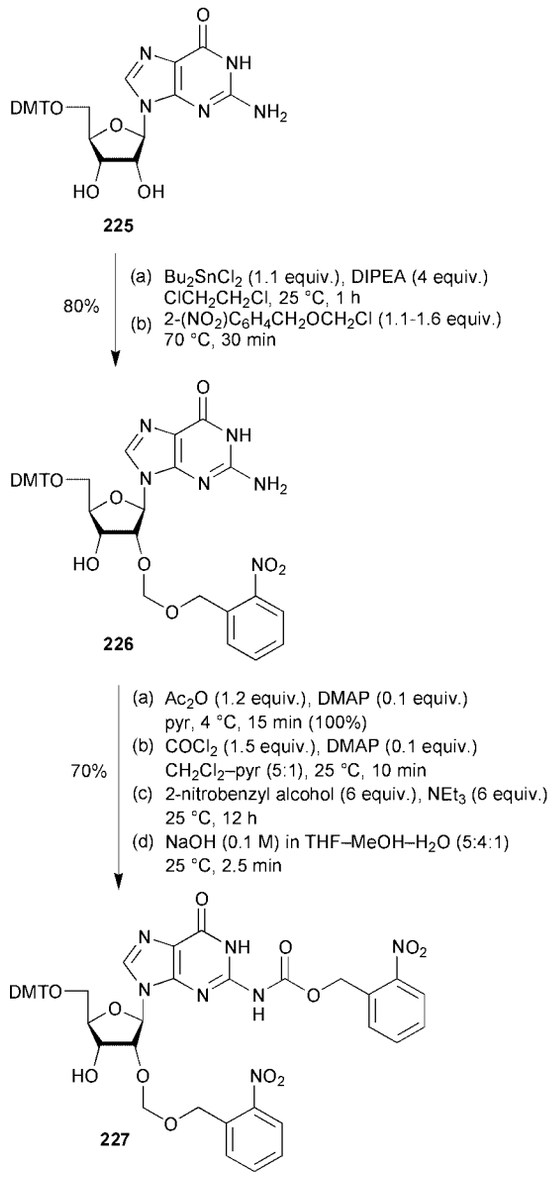


Scheme 98

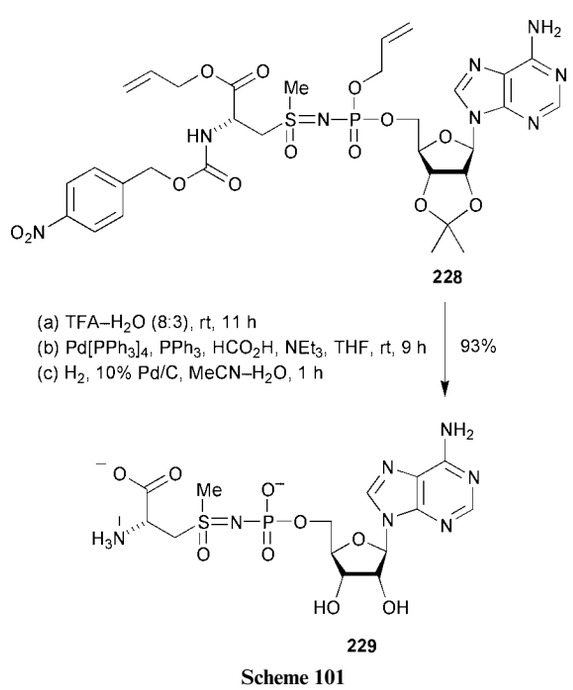
Scheme 99

Heptameric oligoribonucleotides were prepared from **227** and its relatives using the phosphoramidite activation method on solid phase and comprehensive deprotection of the heptamer was accomplished by photolysis in 50% yield.

Asparagine synthetase is a potential target for cancer chemotherapy because asparagine depletion caused by the administration of L-asparaginase is a current method for the treatment of acute lymphoblastic leukemia. The terminal steps in a synthesis of *N*-adenylated *S*-methyl-L-cysteine sulfoximine **229** (Scheme 101), a potent slow-binding inhibitor of *E. coli* asparagine synthetase-A, required a three step deprotection sequence of the fully protected intermediate **228**.[142] The sequence began with acid hydrolysis of the isopropylidene



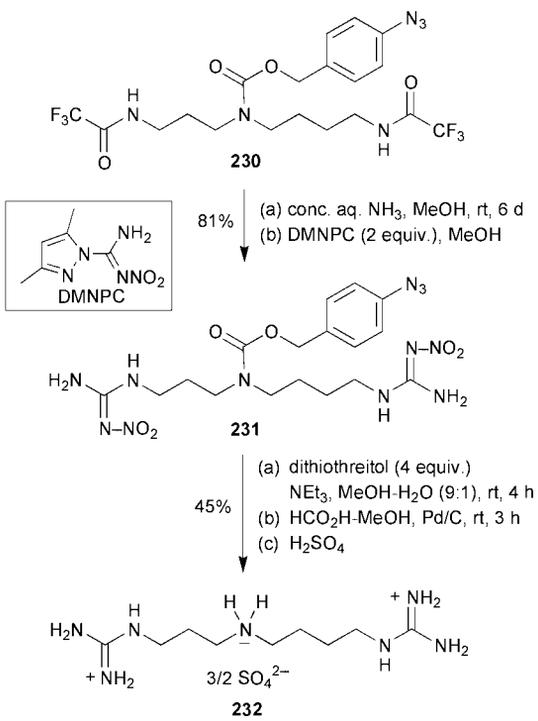
Scheme 100



Scheme 101

group followed by simultaneous deprotection of the carboxy and phosphate allyl esters using Pd(0)-catalysed reduction. Finally, the *p*-nitrobenzyloxycarbonyl protecting the amino group was removed with Pd(0)-catalysed hydrogenolysis. The overall yield of the three step sequence was 93%.

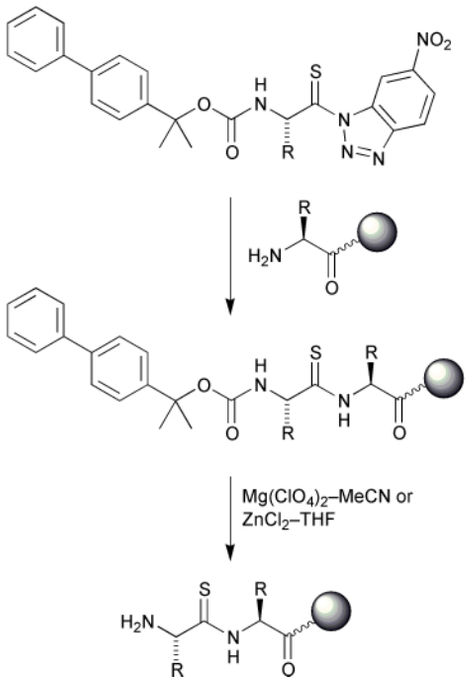
A synthesis of hirudonine sulfate (**232**, Scheme 102) from spermine by Golding and co-workers[143] is based on a mild protecting group for the N^4 of spermidine and an efficient guanylation procedure. Ammonolysis of the bis-trifluoroacetamide **230** followed by bis-nitroguanidinylation using 3,5-dimethyl-*N*-nitro-1*H*-pyrazole-1-carboximidamide (DMNPC) gave intermediate **231** in 81% yield. Removal of the 4-azidobenzyloxycarbonyl group[144] from N^4 was achieved by reduction with dithiothreitol (50% yield) whereupon the nitro group was cleaved by transfer hydrogenolysis (89%) to give the target **232**.



Scheme 102

Magnesium perchlorate or zinc chloride can act as a mild reagent for repetitive removal of *N*-terminal Bpoc [2-(biphenyl-4-yl)propan-2-yloxycarbonyl] or Ddz [2-(3,5-dimethoxyphenyl)propan-2-yloxycarbonyl] temporary protecting groups during solid phase peptide synthesis.[145] The method is especially suitable for the preparation of acid- and base-sensitive compounds like thioxo peptides (peptides in which an amide moiety is replaced by a thioamide group) as illustrated in Scheme 103. Thioxo peptides are difficult to synthesise because acidic deprotecting procedures lead to partial dethioxylation. On the other hand the repetitive treatment with base (necessary for the removal of the Fmoc protecting group) results in epimerisation. With both described reagents these side reactions can be avoided.

Carpino *et al.* have published full details for the use of the 1,1-dioxobenzo[*b*]thiophen-2-ylmethyloxycarbonyl (Bsmoc) amino protecting group for solid phase and rapid continuous solution phase syntheses of peptides.[146] The Bsmoc group is stable towards TFA (conditions for removing a *tert*-butyl ester) and tertiary amines (pyridine, diisopropylethylamine) for 24 h but deblocking occurs readily with secondary amines such as piperidine, piperazine or morpholine in DMF. Deblocking occurs (*via* nucleophilic addition followed by β-elimination) within 3–5 minutes using piperidine or tris(2-aminoethyl)amine (TAEA). The deblocking rates in DMF roughly parallel the pK_a of the secondary amine employed. A particular advantage



Scheme 103

of the Bsmoc group is that the deblocking and scavenging reactions are identical as illustrated in Scheme 104. The intermediate **233** decays over 8–10 min to give the final stable deblocking product **234.** The Bsmoc group is deprotected under milder basic conditions than the ubiquitous Fmoc group and it has the advantage that silica-bound piperazine **235** can be used for the deprotection as well as TAEA. In the latter case, the adduct **236** is water soluble, thus avoiding the need for extraction with an acidic buffer. This results in fewer complications with emulsions and loss of growing peptide into the aqueous phase and hence higher yields.

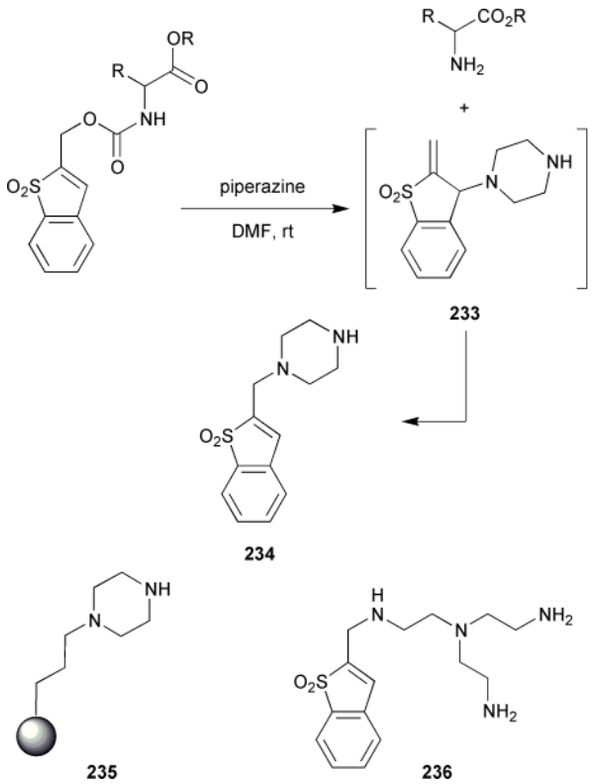
An alternative to the Bsmoc group is the 2-methylsulfonyl-3-phenyl-1-prop-2-enyloxycarbonyl (Mspoc) group which is available from 1-phenylprop-1-ene and methanesulfonyl chloride).[147] It is less prone to premature deblocking and Mspoc-protected amino acid fluorides tend to be crystalline rather than amorphous solids or foams.

As a prelude to macrolactamisation, the requisite carboxy group (protected as its benzyl ester) and the amino group (protected as its Fmoc derivative) in intermediate **237** (Scheme 105) were unleashed in a single step by transfer hydrogenolysis using 25% aqueous ammonium formate and 10% Pd/C in aqueous ethanol.[148]

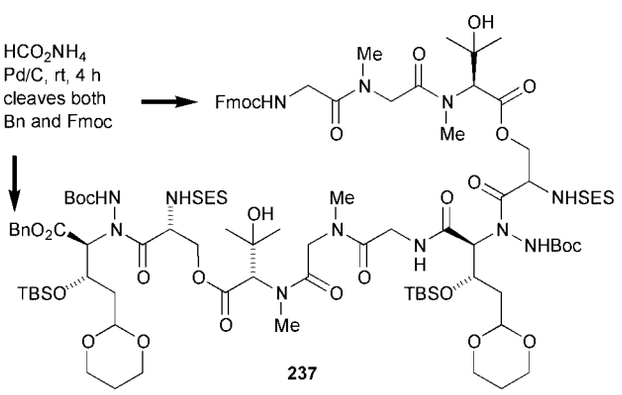
Amine–borane complexes (as allyl group scavengers) and a catalytic amount of Pd(0) deprotect allyl carbamates under nearly neutral conditions without formation of allylamines (Scheme 106).[149] The deprotection works best with $H_3N{\cdot}BH_3$ and $Me_2NH{\cdot}BH_3$ complexes. Groups such as Fmoc, Boc and OBu^t survive the reaction conditions. The method has been used for the removal of the *N*-Alloc protecting group during solid phase peptide synthesis.

The prop-2-ynyloxycarbonyl (Poc) group has been evaluated for the protection of amines.[150] It is easily introduced by treatment of the parent amines with prop-2-ynyl chloroformate[151] in aqueous dioxane with NaOH or alternatively, in dichloromethane in the presence of triethylamine and a catalytic amount of DMAP. Deprotection occurs on treatment with benzyltriethylammonium tetrathiomolybdate (BTTM, 1 equiv.) in acetonitrile with continuous ultrasonication as illustrated in Scheme 107. The Poc group appears to be stable to conditions used to remove Boc groups (*e.g.*, TFA, rt, 1 h).

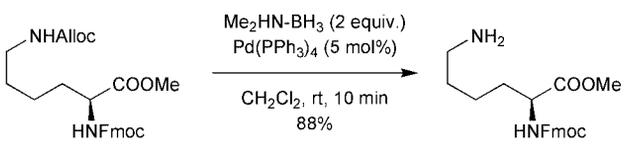
N-(2-Cyanoethoxycarbonyloxy)succinimide (**238**) is a new stable, crystalline reagent for protecting amino groups in



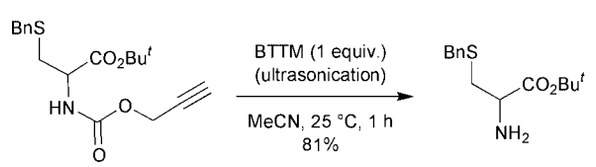
Scheme 104



Scheme 105



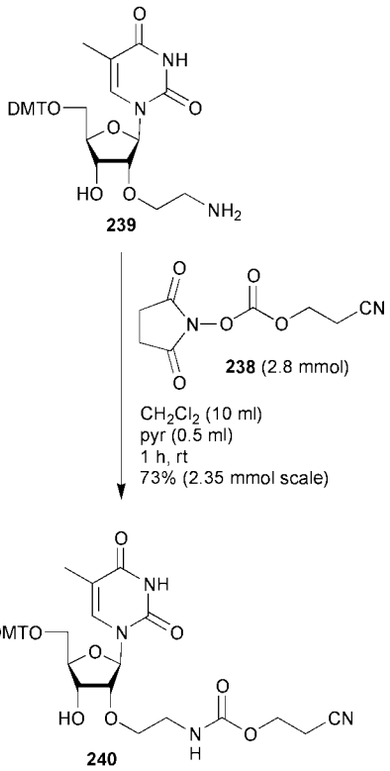
Scheme 106



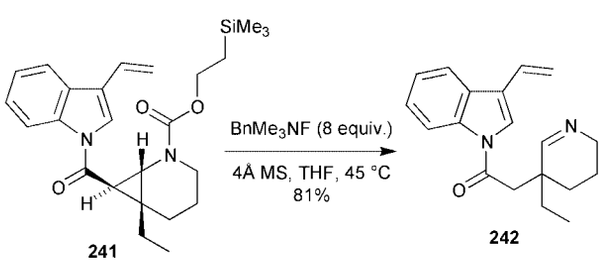
Scheme 107

nucleoside-based 2′-*O*-alkyl aminolinkers (*e.g* **239**) as their *N*-(2-cyanoethoxycarbonyl) (CEOC) derivatives (**240**) (Scheme 108).[152] After oligonucleotide formation incorporating these aminolinkers the CEOC group can be removed by β-elimination using aqueous ammonia.

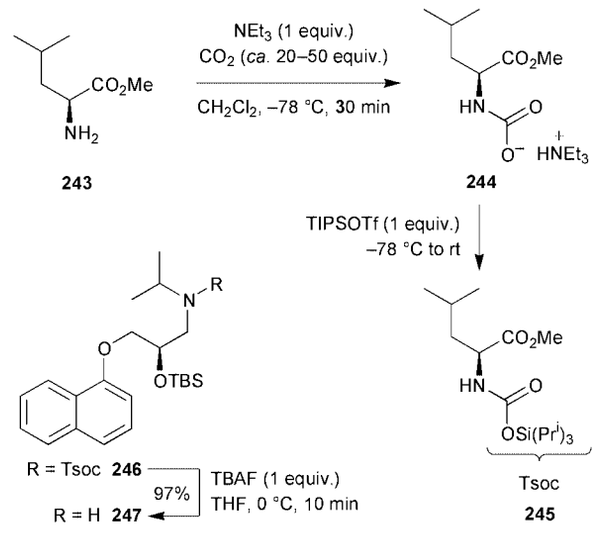
During a synthesis of (±)-eburnamonine, Grieco and Kaufman encountered problems with the deprotection of the *N*-Teoc derivative **241** (Scheme 109).[153] Use of TBAF resulted



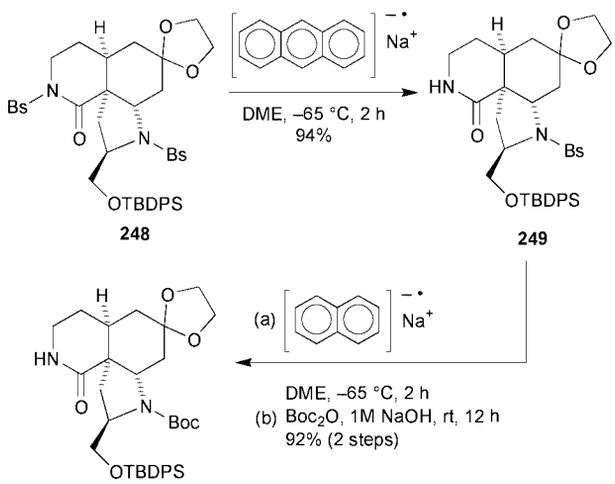
Scheme 108



Scheme 109



Scheme 110



Scheme 111

in hydrolysis of the *N*-acyl indole but pre-dried benzyltrimethylammonium fluoride[154] in THF at 45 °C together with crushed 4 Å molecular sieves gave the desired imine **242** in 81% yield.

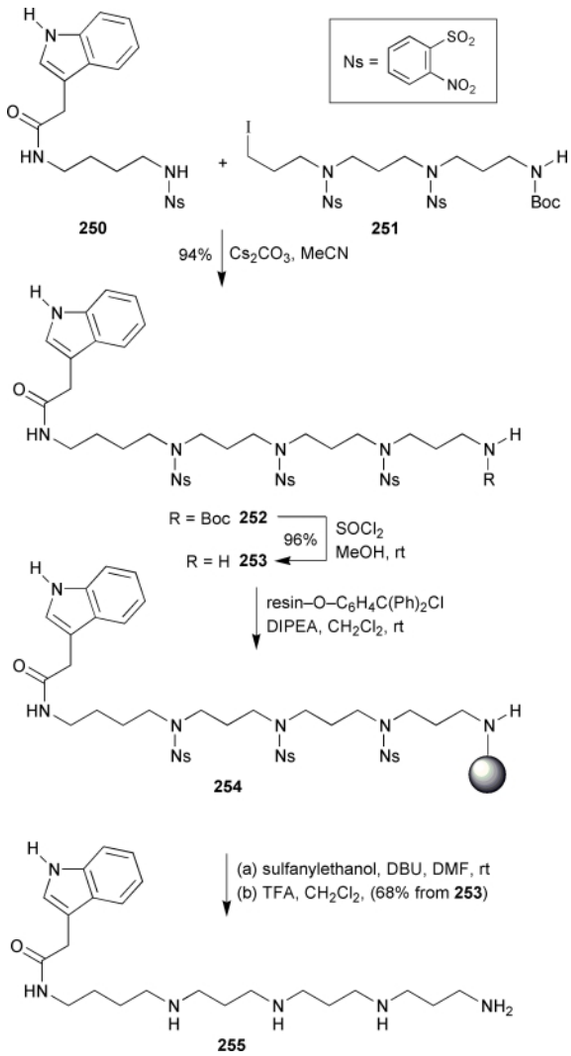
A new silicon-based protecting group, the triisopropylsilyloxycarbonyl (Tsoc) group, has been designed for the protection of primary and secondary amines.[155] *N*-Tsoc groups are easy to introduce from readily available materials: CO_2 gas or crushed dry ice is added to a solution of the amine **243** in DMF or dichloromethane containing triethylamine (1–3 equiv.) at −78 °C. After 30–60 min, the resultant carbamic acid salt **244** (Scheme 110) is treated with triisopropylsilyl triflate (1 equiv.) whereupon warming to rt followed by a standard aqueous extractive workup and chromatography on SiO_2 produces the protected amine **245**. Aniline derivatives also afford the desired carbamates but further deactivation by electron-withdrawing substituents in the *para*-position prevents the reaction from going to completion. *tert*-Butyldiphenylsilyl chloride can also be used as the silylating agent.

Deprotection of the Tsoc group is easily accomplished by treatment with TBAF (1 equiv.) in THF for 10 min—conditions which preserve secondary TBS ethers as illustrated in the deprotection of the propanol derivative **246**. Furthermore, standard peptide protecting groups such as the Boc, Cbz and Fmoc groups can be removed with little or no harm to the Tsoc group.

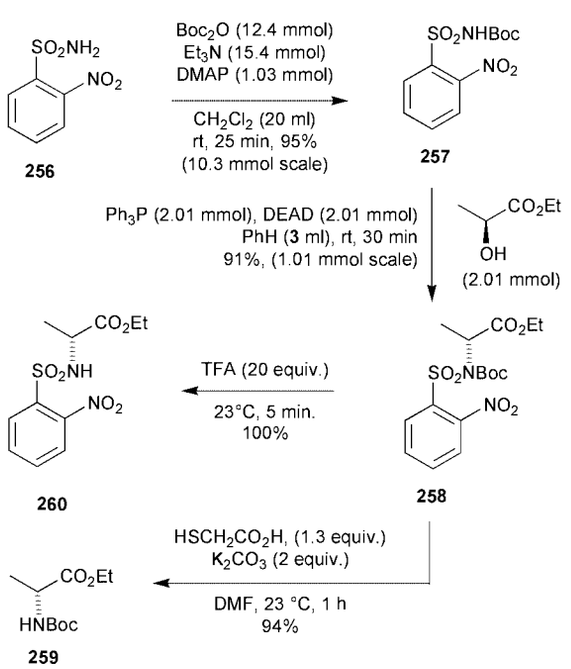
The two *N*-benzenesulfonyl (Bs) groups in manzamine intermediate **248** (Scheme 111) were sequentially removed by first treatment with sodium anthracenide to cleave the more labile amide group followed by cleavage of the *N*-Bs amine in **249** with sodium naphthalenide and re-protection as the Boc derivative.[156] Both deprotections afforded good yields.

A total synthesis of the polyamine spider toxin HO-416b (**255**, Scheme 112) has been accomplished in 12 steps (41% overall).[157] A key feature of the synthesis was the use of the 2-nitrobenzenesulfonamide (Ns) group for both the protection and activation of primary amines. We join the synthesis at the third and final *N*-alkylation of the 2-nitrobenzenesulfonamide **250** with iodoalkane **251** in the presence of Cs_2CO_3. After removal of the Boc group with HCl in methanol, the primary amine **253** was loaded onto a Merrifield resin *via* an alkoxytrityl linker. Deprotection of the three 2-nitrobenzenesulfonamide groups from the resin-bound substrate **254** with excess 2-sulfanylethanol followed by acid-catalysed release from the resin afforded the target **255** in 68% yield from **253**.

A new method for the preparation of carbamate-protected primary amines direct from the corresponding alcohols or halides has been reported by Fukuyama and co-workers (Scheme 113).[158] *N*-Alkoxycarbonyl-2-nitrobenzenesulfonamides (*e.g.* Boc derivative **257**), readily prepared by acylation of 2-nitrobenzenesulfonamide (**256**), are alkylated under either conventional or Mitsunobu conditions using alkyl halides or alcohols respectively. The product **258** is then treated with sulfanylacetic acid and potassium carbonate in DMF to remove the 2-nitrobenzenesulfonyl group giving Boc-protected amine **259**. In a similar way *N*-Alloc- and *N*-Cbz-protected primary amines can be prepared. Alternatively, the *N*-Boc, *N*-Alloc and *N*-Cbz groups can be deprotected in the presence of the 2-nitrobenzenesulfonyl group and the resulting *N*-alkylated 2-nitro-



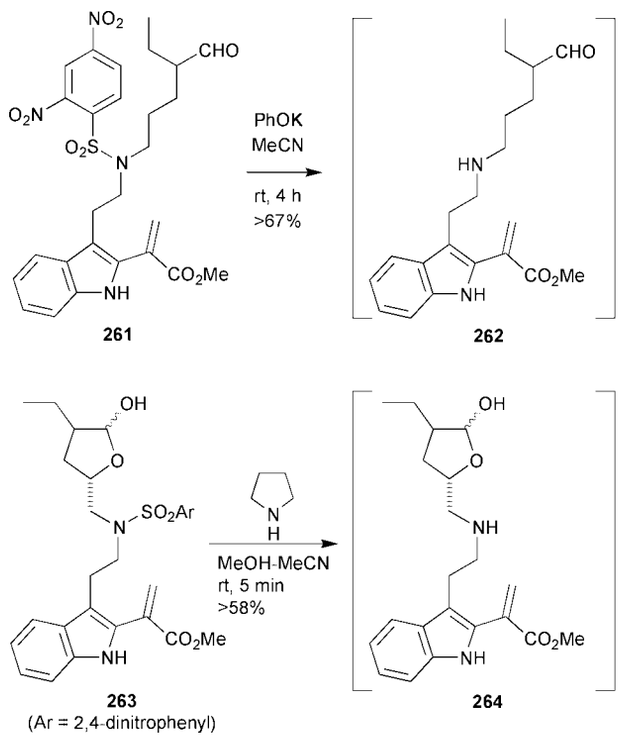
Scheme 112



Scheme 113

benzenesulfonamide **260** can then be used for the preparation of secondary amines by *N*-alkylation.

During a synthesis of the aspidosperma alkaloid vincadifformine, Fukuyama and co-workers[159] required a mild deprotection of the 2,4-dinitrobenzenesulfonyl group from the sulfonamide **261** (Scheme 114). The use of $PhSH–NEt_3$, $HSCH_2CO_2H–NEt_3$ or $PrNH_2$[160] was thwarted by competing Michael addition to the acrylate moiety. However, the harder nucleophile potassium phenoxide released the desired amino aldehyde **262** which set in motion a cascade of reactions resulting in the formation of vincadifformine in 67% yield. The failure of the same conditions to remove the 2,4-dinitrobenzenesulfonyl group from **263** was circumvented by using 5 equivalents of pyrrolidine in MeCN–MeOH (5:1) at room temperature whereupon the amino aldehyde **264** underwent a similar cascade of reactions to give tabersonine in 58% yield.



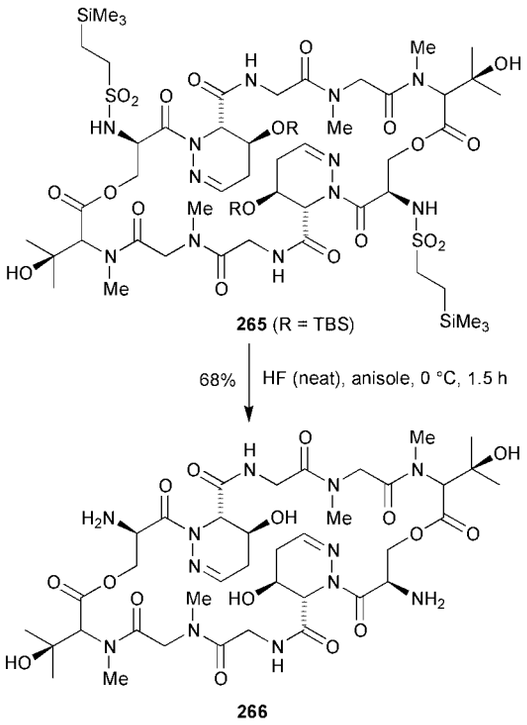
Scheme 114

Methane- and benzenesulfonamides of secondary amines can be cleaved using 1.5 equivalents of iodotrimethylsilane (generated *in situ* from chlorotrimethylsilane and sodium iodide) in refluxing acetonitrile.[161] Twelve trivial cases devoid of functionality were reported giving yields of 70–88%.

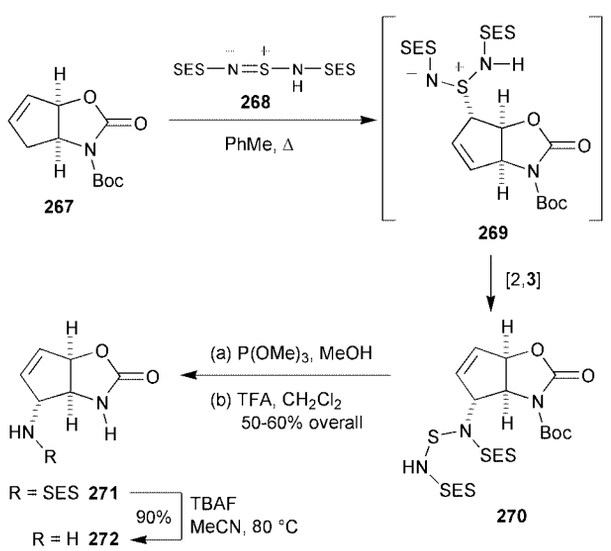
During the closing stages of a synthesis of the potent HIV reverse transcriptase inhibitors luzopeptins A–C, Boger and co-workers[148] required a cleavage of two *N*-2-(trimethylsilylethyl)-sulfonyl (SES) groups to release two primary amino groups. Treatment of **265** (Scheme 115) with TBAF or CsF led to deprotection of the two TBS ethers but left the SES groups unscathed whereas forcing conditions only gave degradation. However, both the TBS and SES groups were removed by treatment with neat HF and anisole at 0 °C to give the intermediate **266** in 68% yield.

At an early stage of the synthesis of agelastatin A, Weinreb and co-workers[129] encountered some problems with *N*-deprotection after the allylic amination of the bicyclic oxazolidinone **267** (Scheme 116) using the Sharpless–Kresze protocol.[162,163] Success was finally achieved with the SES-protected sulfodiimide enophile **268**. Intermediate **269** underwent a [2,3]-sigmatropic rearrangement to give SES-protected allylic amine derivative **270**. Reductive cleavage of the N–S bond followed by cleavage of the Boc group with TFA gave the sulfonamide **271** in 50–60% overall yield. Final deprotection of the SES group with TBAF returned the desired amine **272** in 90% yield.

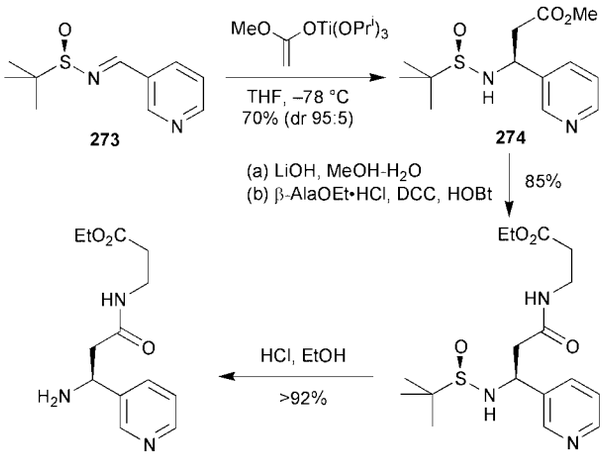
Tang and Ellman advocate the *tert*-butylsulfinyl group as a chiral directing group and Boc-surrogate for the asymmetric



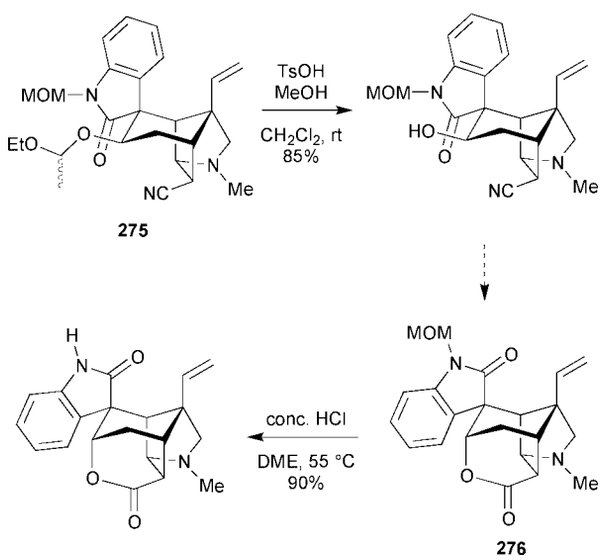
Scheme 115



Scheme 116



Scheme 117



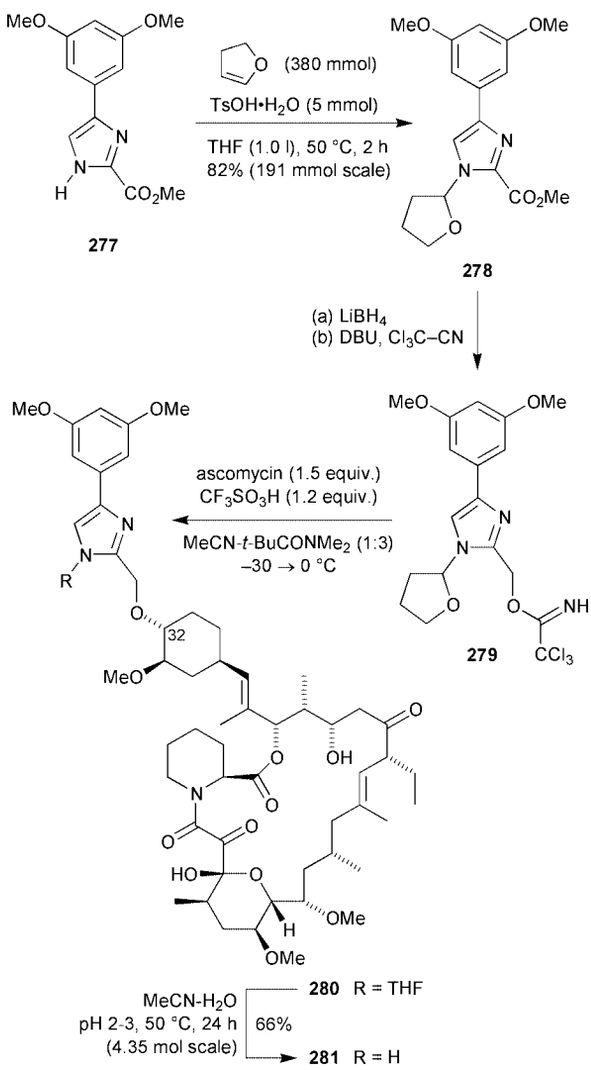
Scheme 118

synthesis of β-amino acids.[164] This dual function is illustrated by the sequence depicted in Scheme 117. Diastereoselective addition of an ester enolate to the *tert*-butylsulfinyl imine **273** gave adduct **274** in 70% yield (dr = 95 : 5). After ester hydrolysis and peptide coupling with β-alanine ethyl ester, the *tert*-butylsulfinyl group was removed by treatment with a stoichiometric amount of HCl in EtOH at room temperature.

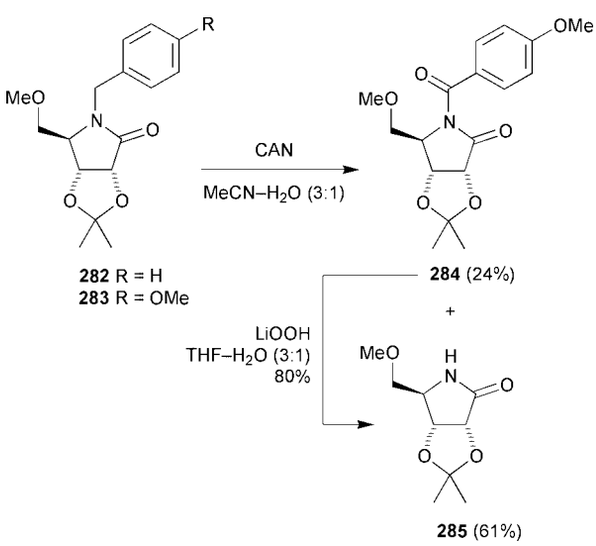
During a synthesis of the hexacyclic alkaloid gelsemine, the Overman group selected a methoxymethyl group to protect the nitrogen atom of an oxindole.[165] At one point in the synthesis, an ethoxyethyl group was removed by methanolysis from intermediate **275** (Scheme 118) without affecting the *N*-MOM group. However, in the closing stages of the synthesis, the *N*-MOM was cleaved from intermediate **276** under harsher conditions: conc. HCl in DME at 55 °C.

L-733,725 (**281**, Scheme 119) is under clinical investigation as a more potent and less toxic variant of FK-506 for the treatment of organ transplant rejection and psoriasis. The Merck process development laboratory recently described a large scale method for appending the imidazole side chain to the C-32 hydroxy group of the macrocycle in which synergistic effects of the protecting group, solvent and acid catalyst were crucial to success.[166] Because of the instability of the macrocycle (ascomycin) towards strong bases, the ether linkage between the side chain was created using the trichloroacetimidate method which, in turn, demanded an *N*-protecting group on the imidazole ring which would facilitate trichloroacetimidate cleavage to form a carbenium ion intermediate. The tetrahydrofuran-2-yl and tetrahydropyran-2-yl groups[167,168] were evaluated but the tetrahydrofuran-2-yl group was selected when a model study showed that it was cleaved with tartaric acid in MeOH at 50 °C in 9 h compared with 54 h for the corresponding tetrahydropyran-2-yl group. The tetrahydrofuran-2-yl group was introduced by treatment of the imidazole **277** with dihydrofuran using TsOH as acid catalyst. Reduction of the ester function in **278** with lithium borohydride followed by reaction with trichloroacetonitrile in the presence of a catalytic amount of DBU returned the trichloroacetimidate **279** as a stable crystalline solid in 87% overall yield from **277**. The critical coupling reaction was accomplished by treatment of ascomycin with **279** in a polar solvent mixture composed of acetonitrile and *N*,*N*-dimethylpivalamide. To complete the sequence, the tetrahydrofuranyl group was cleaved by heating a solution of **280** in MeCN–H_2O whose pH was adjusted to 2–3 with triflic acid and the product **281** isolated as its crystalline tartrate salt.

Removal of benzyl-type protecting groups to liberate lactam **285** (Scheme 120) during a synthesis of calyculin was problematic.[169] The *N*-benzyl lactam **282** failed to hydrogenolyse and



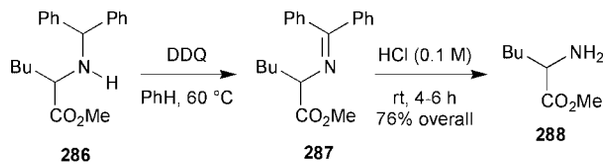
Scheme 119



Scheme 120

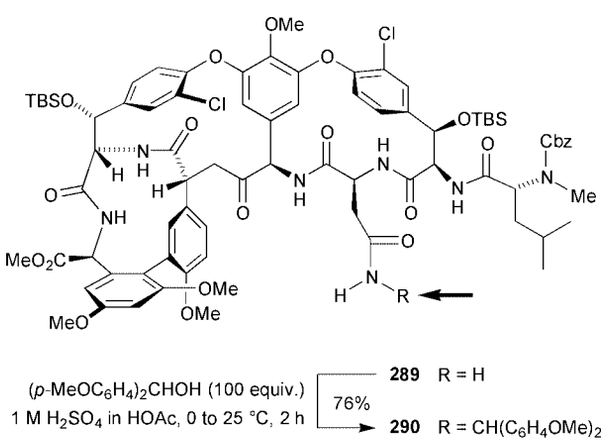
oxidative cleavage of the corresponding *N*-PMB derivative **283** with CAN[170] was accompanied by oxidation of the benzylic methylene to give the imide **284** in 24% yield together with the desired lactam **285** (61%). The yield of the desired lactam was bolstered by lithium hydroperoxide cleavage of the *N*-(*p*-methoxybenzoyl) group from **284** (80%).

A new method for the oxidative deprotection of the diphenylmethyl (Dpm) group using DDQ ($E_0 = 1000$ mV) has been described.[171] The amine (*e.g.* **286**, Scheme 121) is dissolved in benzene in the presence of crushed 4 Å molecular sieves at 60 °C. Addition of DDQ (1 equiv.) gave quantitative formation of the imine **287** after 1 h. The DDQ-derived byproducts of the reaction precipitated from the solution and were easily removed by filtration. Upon mild acid hydrolysis, the deprotected amine **288** was obtained in 76% yield.



Scheme 121

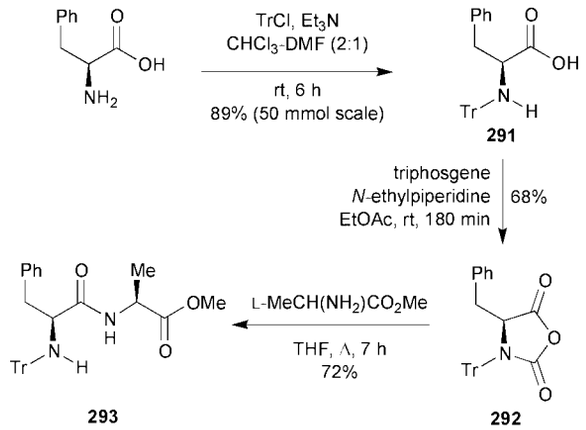
At a late stage of the synthesis of vancomycin aglycone, Nicolaou and co-workers degraded natural vancomycin to verify the structure and stereochemistry of an advanced intermediate.[32] One of the steps in the degradation required the *N*-protection of the amide function of the asparagine moiety in **289** (Scheme 122). The task was accomplished by simply treating **289** with a large excess of 4,4′-dimethoxybenzhydrol in acetic acid containing a small amount of sulfuric acid. The requisite protection occurred in 76% yield to give **290**. In the final step of the synthesis, the dimethoxybenzhydryl protecting group was removed on treatment with aluminium tribromide in neat ethanethiol. The dimethoxybenzhydryl amide was otherwise quite robust and survived many steps in the total synthesis.



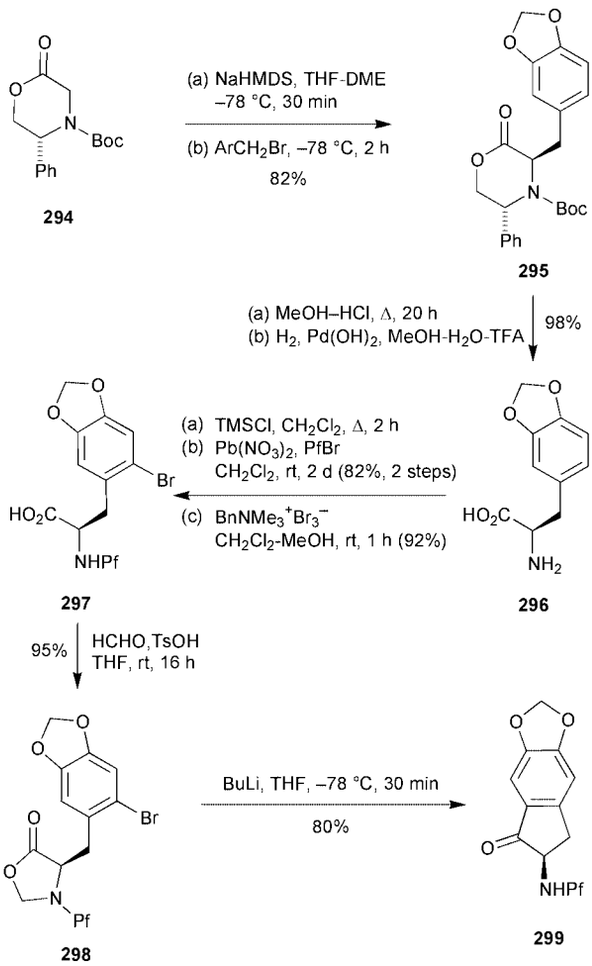
Scheme 122

The beneficial high reactivity of *N*-carboxyanhydrides (Leuchs' anhydrides) has hitherto been compromised by easy polymerisation and racemisation. Sim and Rapoport[172] report that the steric protection afforded by *N*-phenylfluorenyl- and *N*-trityl-*N*-carboxyanhydrides of α-amino acids imparts stability towards storage. Scheme 123 exemplifies their preparation and use in peptide bond formation. Thus treatment of *N*-trityl-L-phenylalanine (**291**) with triphosgene gave the crystalline *N*-carboxyanhydride **292** in 68% yield. On heating **292** with L-alanine methyl ester in THF for 7 h, the dipeptide **293** was formed in 72% yield the only by-product being carbon dioxide. No racemisation was observed.

A synthesis of the alkaloid ribasine required a supply of the (*R*)-2-aminoindanone derivative **299** (Scheme 124).[173] The high cost of D-DOPA precluded its use in the preparation of the methylenedioxy-protected dihydroxyphenylalanine **296**, a key intermediate *en route* to the target. The sequence began with the scalemic glycine equivalent **294**[174] which was alkylated in good yield to give oxazinone **295** from which the amino and carboxy groups were deprotected in a one-pot, two-step procedure involving exposure of **295** to a refluxing mixture of MeOH and



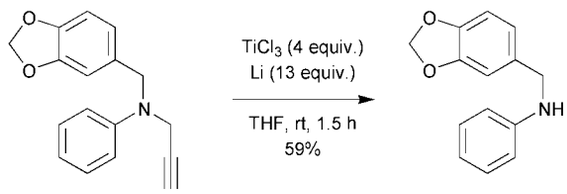
Scheme 123



Scheme 124

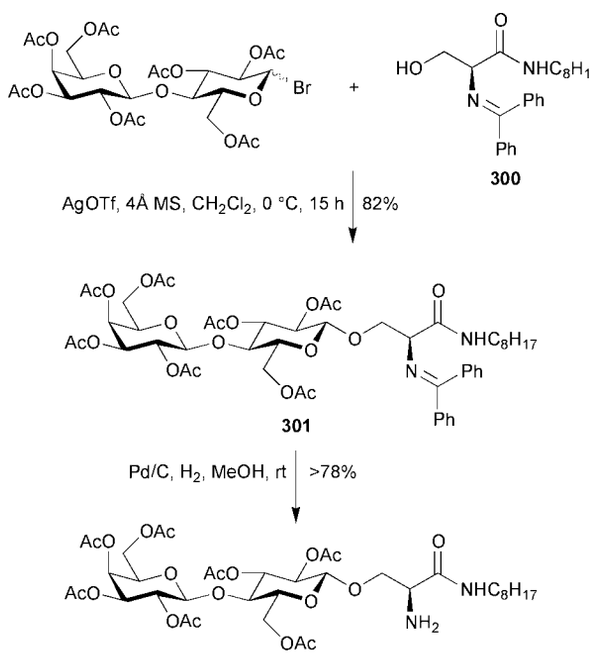
3 M HCl (6:1) for 20 h whereupon the Boc group was cleaved and the oxazinone ring hydrolysed. Hydrogenolysis of the chiral auxiliary then gave the amino acid **296** in 98% yield for the two steps. After protection of the amino group as its *N*-9-phenylfluoren-9-yl derivative,[175] a bromine atom was regioselectively introduced using benzyltrimethylammonium tribromide. The final transformation in the protecting group regime was simultaneous protection of both the amino and carboxy groups in **297** as the oxazolidinone **298**. To complete the sequence, metallation of the arene followed by intramolecular acylation gave the target **299** in 80% yield. As expected, the 9-phenylfluoren-9-yl group was an effective steric shield in preventing racemisation.

A low valent titanium reagent generated by reduction of titanium trichloride in refluxing THF cleaves *N*-propargyl groups[176] (Scheme 125). The yield is typically 55–77% but all of the cases reported (12) were devoid of any reducible functionality and so it is difficult to justify the claim that the method is mild. Some selectivity was observed: allylamines are not attacked under the conditions and propargyl ethers are cleaved faster than propargyl amines.



Scheme 125

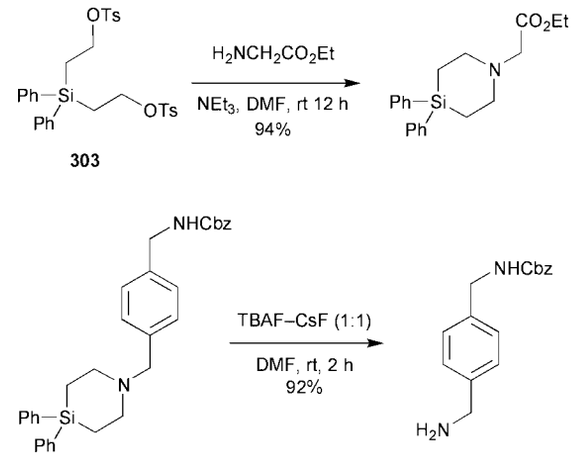
A programme aimed at the enzyme-assisted elaboration of polymer-bound glycolipids required the synthesis of the lactosyl serinamide derivative **302** (Scheme 126).[177] Protection of the glycosyl acceptor as its diphenylmethylene Schiff base[178] (**300**) greatly enhanced the yield of the glycosylation to form **301**. The protecting group was removed by hydrogenolysis to give the free amine **302** in good yield.



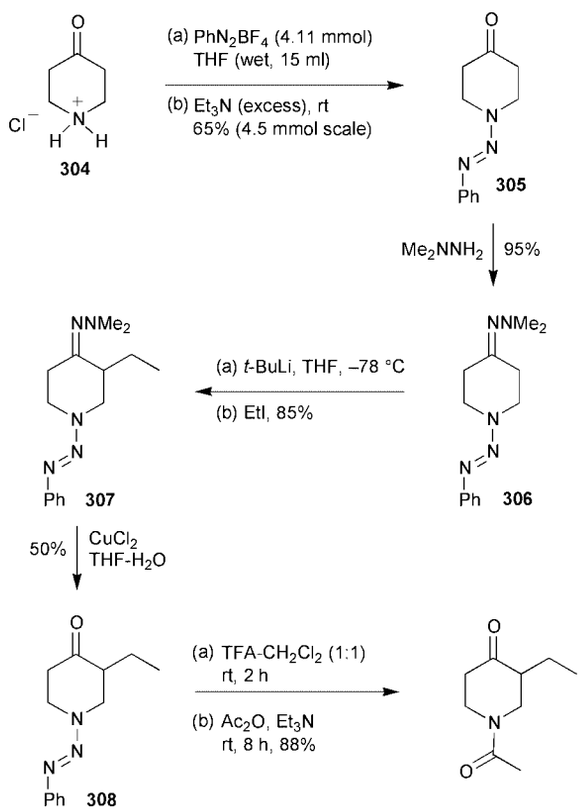
Scheme 126

The diphenylsilyldiethylene group has been developed for the protection of primary amines.[179] It is introduced by the reaction of the amine with bis[2-(*p*-tolylsulfonyloxy)ethyl]diphenylsilane (**303**, Scheme 127) which is itself prepared in 3 steps (83% overall) from diphenyldichlorosilane. More hindered secondary amines react very slowly and give, at best, monoalkylation products. Diphenylsilyldiethylene derivatives are resistant to acidic, basic or hydrogenolytic conditions required for the deprotection of Boc, phthalimide and Cbz groups. Deprotection requires an equimolar mixture of TBAF and CsF in DMF or THF at rt.

The phenyl triazene moiety has been reported as a protecting group for sensitive secondary amines like 4-piperidone (**304**, Scheme 128).[180] The protected amines (*e.g.* **305**–**308**) are resistant to Lewis acids [$Ti(OPr^i)_4$], basic hydrolysis, oxidants (PDC, H_2O_2, peracids), metal hydrides ($LiAlH_4$, $NaBH_4$), hydrogenation (Pd/C in methanol), alkylating agents (MeI at rt), alkyllithium and lithium amide bases (*t*-BuLi, LDA). However, Brønsted acids give rise to cleavage. Thus, deprotection can



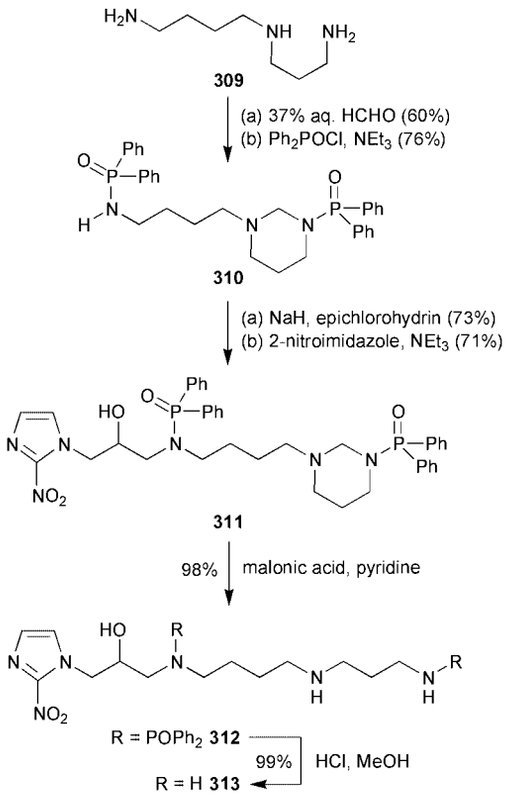
Scheme 127



Scheme 128

be easily achieved with trifluoroacetic acid. The triazene group is orthogonal to ester, amide, Cbz and other benzyl-based protecting groups.

Nitroimidazole–polyamine conjugates are potential drug delivery vehicles which exploit the polyamine uptake system of tumour cells. A Leicester group has devised a route to spermidine– and norspermidine–nitroimidazole conjugates which features the use of the *N*-phosphinoyl group as both a protector and activator.[181] The method is exemplified by the conversion of spermidine (**309**) to the conjugate **313** (Scheme 129). The sequence began with conversion of spermidine to its methylene derivative followed by *N*-phosphinoylation of the primary and secondary amines to give **310**. *N*-Alkylation of the primary phosphinamide with epichlorohydrin followed by oxirane cleavage with nitroimidazole gave conjugate **311**. Hydrolysis of the *N*,*N*-methylene acetal in **311** with malonic acid in pyridine gave **312** in 98% yield followed by acid-catalysed hydrolysis of the two phosphinoyl groups to return the desired conjugate **313** as its trihydrochloride salt.



Scheme 129

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