Protecting groups

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Continuing the coverage in *J. Chem. Soc.*, *Perkin Trans. 1*, 1998, 4005.

Abbreviations for reagents and protecting groups: Ac, acetyl; All, allyl; Aloc, allyloxycarbonyl; AOM, *p*-anisyloxymethyl; Bn, benzyl; Boc, *tert*-butoxycarbonyl; Bts, 1,3-benzothiazol-2-yl; Bz, benzoyl; Cbz, benzyloxycarbonyl; ClAc, chloroacetyl; DCPhth, 4,5-dichlorophthaloyl; DMM, dimethylmaleoyl; DMTr, bis(*p*-methoxyphenyl)phenylmethyl; DTBB, 4,4′-di-*tert*-butylbiphenyl; Fm, fluoren-9-ylmethyl; Fmoc, fluoren-9-ylmethoxycarbonyl; HMPA, hexamethylphosphoramide; HOBT, 1-hydroxybenzotriazole; Lev, levulinoyl, 4-oxopentanoyl; mcpba, *m*-chloroperbenzoic acid; MeOTf, methyl trifluoromethanesulfonate; Mes, mesityl; MOM, methoxymethyl; MP, *p*-methoxyphenyl; MS, molecular sieves; Ms, methylsulfonyl; MsCl, methylsulfonyl chloride; MSTFA, *N*-methyl-*N*-(trimethylsilyl)trifluoroacetamide; NAP, 2-naphthylmethyl; Naph, 2-naphthyl; NDMBA, *N*,*N*′-dimethylbarbituric acid; NHS, *N*-hydroxysuccinimide; NIS, *N*-iodosuccinimide; NMP, 1-methylpyrrolidin-2-one; Npys, 3-nitro-2-pyridylsulfenyl; Phth, phthalimido; PMB, *p*-methoxybenzyl; PMBCl, *p*-methoxybenzyl chloride; PMP, *p*-methoxyphenyl; POM, (*p*-phenylphenoxy)methyl; PPTS, pyridinium toluene-*p*-sulfonate; PTC, phase transfer catalysis; PTnm, 4-methoxycarbonyl-4-nitro-2,6-dioxaspiro[5,5]undecane; PTSA, toluene-*p*-sulfonic acid; pyr, pyridine; SDMS, sialyldimethylsilyl; SEM, 2-(trimethylsilyl)ethoxycarbonyl; SES, 2-(trimethylsilyl)ethylsulfonyl; STr, triphenylmethylsulfenyl; SuOCbz, *N*-[(benzyloxycarbonyl)-oxy]succinimide; TAS-F, tris(dimethylamino)sulfonium difluorotrimethylsilicate; TBAF, tetrabutylammonium fluoride; TBDPS, *tert*-butyldiphenylsilyl; TBS, *tert*-butyldimethylsilyl; TCP, tetrachlorophthaloyl; TES, triethylsilyl; Tf, trifluoromethylsulfonyl; TFA, trifluoroacetic acid; TFAA, trifluoroacetic anhydride; TfOH, trifluoromethanesulfonic acid; THF, tetrahydrofuran; THP, tetrahydropyranyl; TIPS, triisopropylsilyl; TMEDA, *N*,*N*,*N*′,*N*′-tetramethylethylenediamine; TMS, trimethylsilyl; TMS_2O, hexamethyldisiloxane; TMSCl, trimethylsilyl chloride; TMSOTf, trimethylsilyl trifluoromethanesulfonate; TMT, trimethoxytrityl; Tnm, 2,2-bis(hydroxymethyl)-2-nitromethyloxycarbonyl; Tol, *p*-methylphenyl; Tr, trityl (triphenylmethyl); Troc, 2,2,2-trichloroethoxycarbonyl; TrS, triphenylmethylsulfenyl; Ts, *p*-tolylsulfonyl.

1 Introduction

This year's trawl through the literature has affirmed that neither improvements in selectivity nor the invention of new reactions have abated our dependence on protecting groups. As with our four previous annual reviews, our coverage is a personal selection of methods which we deemed interesting or useful. The review is organised according to the functional groups protected with emphasis being placed on deprotection conditions. Truly novel developments in protecting group chemistry are very rare and so most of the ensuing discussion pertains to the difficulties encountered—and their resolution—with the standard repertoire of protecting groups. Since most of the information we gleaned would be transparent to a keyword search, we hope to perform a useful service to our colleagues whose endeavours are perplexed by the vagaries of protecting group chemistry.

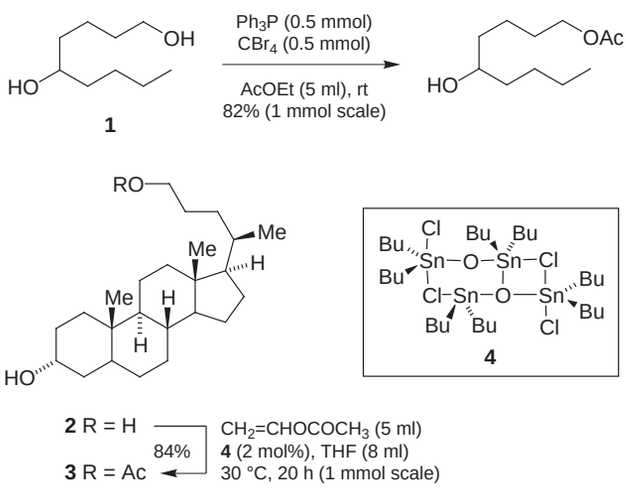
2 Hydroxy protecting groups

2.1 Esters

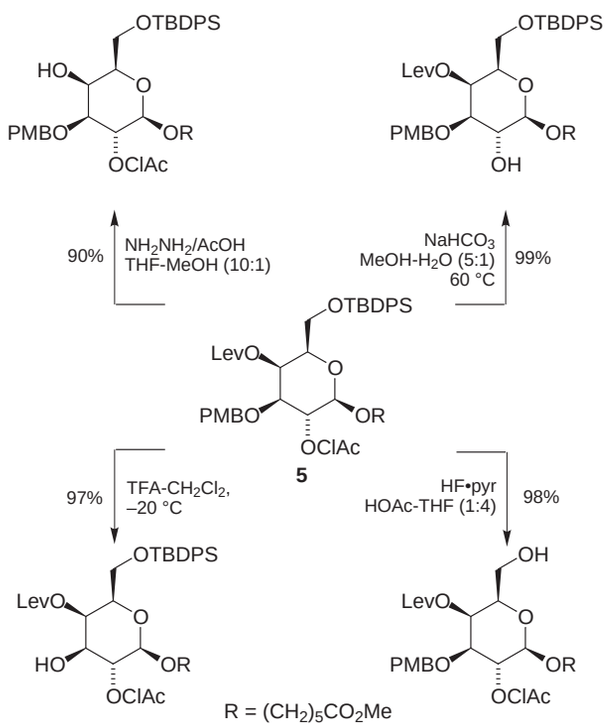
Acetylation of primary alcohols using ethyl acetate in the presence of triphenylphosphine and carbon tetrachloride has been described.[1] Primary hydroxy groups react preferentially in the presence of secondary ones (Scheme 1) although a small amount of diacetylated product is also formed—6% in the case of **1**. When ethyl acetate is replaced with methyl or ethyl formate the corresponding formates are formed but the selectivity towards a primary hydroxy group decreases. The procedure also converts tetrahydropyranyl- and *tert*-butyldimethylsilyl-protected alcohols directly into acetates and formates. Alcohols can also be acylated with alkenyl esters in the presence of a catalytic amount of 1,3-dichlorotetrabutyldistannoxane **4**.[2] A primary hydroxy group reacts preferentially over a secondary one—only 0–4% of diacylated product is observed. The catalyst **4** is available commercially or it can be easily prepared by simply mixing Bu_2SnO and Bu_2SnCl_2.

Wong and co-workers developed an efficient orthogonal protection–deprotection strategy aimed at the synthesis of pentasaccharide libraries based on the galactose derivative **5** (Scheme 2).[3] The levulinate ester, chloroacetate ester, *tert*-butyldiphenylsilyl ether and *p*-methoxybenzyl ether groups were each removed selectively and efficiently and the freed hydroxy group employed in glycosylation reactions.

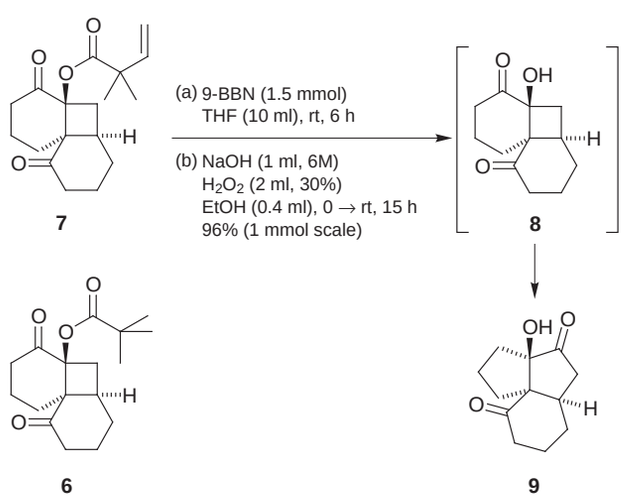
During the course of studies directed towards a synthesis of the magellanane alkaloids, Crimmins' group encountered problems with the basic hydrolysis of the tertiary pivalate in the photoaddition product **6** (Scheme 3).[4] To circumvent this difficulty, a new protecting group—2,2-dimethylpent-4-enoate (or vinyl pivalate)—was designed which is photochemically stable and fully substituted in the α-position (to preclude any α-deprotonation under basic conditions). The vinyl pivalate **7** was removed by hydroboration of the double bond followed by basic oxidation and spontaneous lactonisation. Under basic



Scheme 1



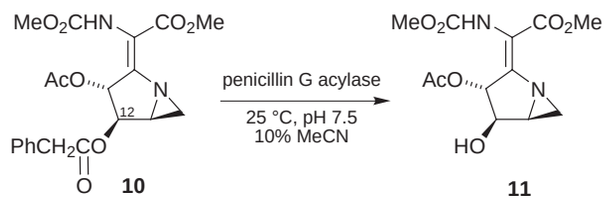
Scheme 2



Scheme 3

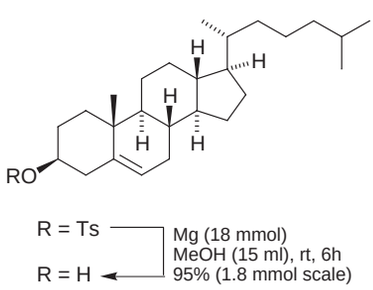
conditions the deprotected tertiary alcohol **8** rearranged to the desired product **9**. Vinyl pivalate groups can also be removed under oxidative conditions by dihydroxylation of the double bond with osmium tetroxide and *N*-methylmorpholine oxide.

The inherent instability of the aziridino[1,2-*a*]pyrrolidine substructure of the azinomycin antitumour agents is a major impediment to their synthesis. Judicious choice of a protecting group for the C12 hydroxy group is especially crucial since the free alcohol cannot be isolated. Coleman and co-workers[5,6] were able to deprotect the C12 phenylacetate **10** (Scheme 4) using immobilised penicillin G acylase; even so, the product **11** (half-life *ca.* 2 h) could only be detected as part of a mixture by NMR spectroscopy.



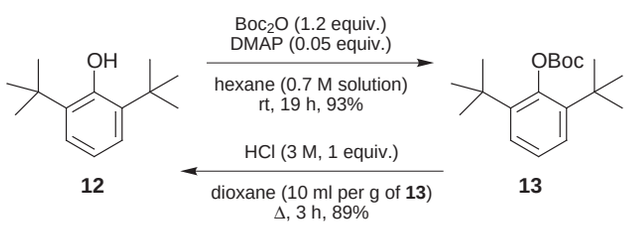
Scheme 4

Regeneration of alcohols from the corresponding tosylates can be complicated by concomitant elimination and substitution reactions. In the case of optically active tosylates, the latter leads to the epimerisation of the resulting alcohol. Magnesium in methanol has been recently reported as a reagent which cleaves alkyl and aryl tosylates in high yield and without epimerisation (Scheme 5).[7]



Scheme 5

A group from Eli Lilly developed a mild procedure for protecting hindered phenols (*e.g.* **12**, Scheme 6) as their Boc derivatives.[8] The protection was carried out in hexane which gave better results than acetonitrile or dichloromethane routinely used in this type of transformation. The deprotection studies revealed that in the case of phenols with a free *ortho* or *para* position, standard conditions (trifluoroacetic acid) caused the formation of a substantial amount of a by-product (21% in case of **13**) in which the liberated *tert*-butyl cation alkylated the aromatic ring—a reaction which was completely suppressed by using 3 M aqueous hydrochloric acid in dioxane.

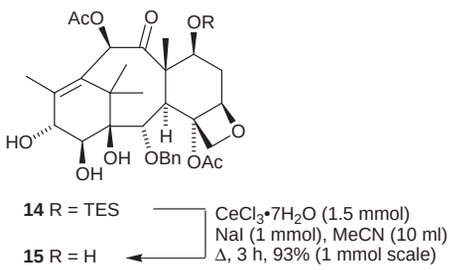


Scheme 6

2.2 Silyl ethers

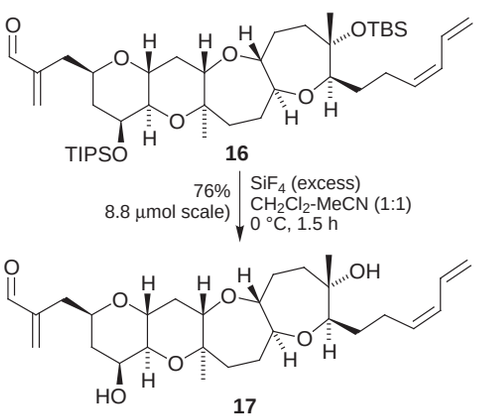
Triethylsilyl (TES), *tert*-butyldimethylsilyl (TBS), triisopropylsilyl (TIPS) and *tert*-butyldiphenylsilyl (TBDPS) groups are deprotected by cerium(III) chloride heptahydrate and sodium iodide in acetonitrile.[9] A TBS ether can also be selectively

deprotected in the presence of a TBDPS ether. More complex molecules, *e.g.* the baccatin derivative **14** (Scheme 7), can also be deprotected without migration of the acetate group or detriment to the oxetane ring. The reaction conditions do not affect acetate, benzyl, tetrahydropyranyl and *N*-Boc protecting groups but methoxymethyl ethers appear to be incompatible.



Scheme 7

In the final step of a synthesis of the hemibrevetoxin B (**17**, Scheme 8)[10] the secondary TIPS and TBS ethers were removed by stirring a solution of **16** under an atmosphere of gaseous silicon tetrafluoride according to the procedure of Corey and Yi.[11]

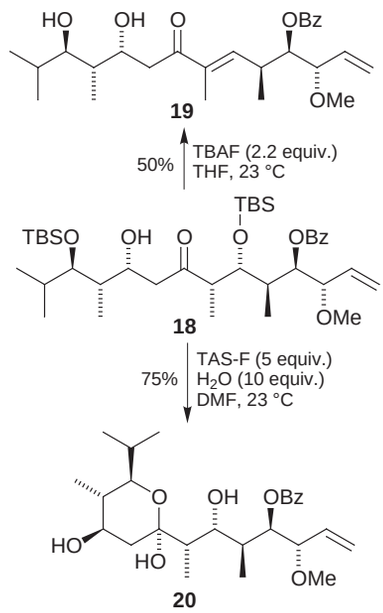


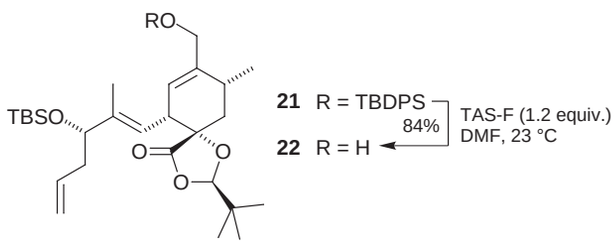
Scheme 8

A common problem attending the cleavage of silicon protecting groups is the base-catalysed dehydration of sensitive substrates. Thus attempts to remove the two TBS ethers in **18** (Scheme 9) with TBAF resulted in formation of the enone **19** in 50% yield.[12] By contrast, treatment of the same substrate with TAS-F [tris(dimethylamino)sulfonium difluorotrimethylsilicate, $(Me_2N)_3S^+F_2SiMe_3^-$] afforded the desired hemiacetal **20** in 75% yield. Using a range of complex substrates, Roush and co-workers have shown that TAS-F in DMF at room temperature is generally useful for the deprotection of TBS, TES and TBDPS ethers as well as 2-(trimethylsilyl)ethyl carbamates and 2-(trimethylsilyl)ethyl esters in base-sensitive substrates. Selective deprotections may also be achieved as exemplified by the removal of the primary TBDPS group from **21** in the presence of a secondary TBS ether. It is not yet possible to remove a secondary TES ether in the presence of a secondary TBS ether or a primary TBS ether in the presence of a secondary TBDPS ether. TAS-F is commercially available as an anhydrous solid and it can be prepared by an *Organic Syntheses* procedure.[13]

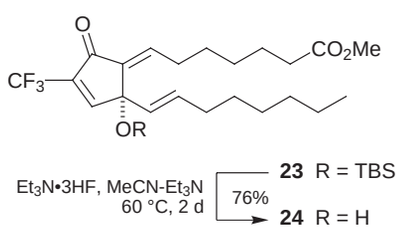
The final deprotection of the tertiary allylic TBS ether in the cross-conjugated prostanoid **23** (Scheme 10)[14] was accomplished by heating the substrate with a large excess of triethylamine tris(hydrofluoride)[15] in acetonitrile containing 10% (v/v) added triethylamine.

During a synthesis of 7-deoxypancratistatin, Keck and co-workers[16] deprotected the methoxymethyl (MOM) ether and acetonide groups in intermediate **25** (Scheme 11) with Dowex-H^+ resin in methanol at 70 °C. However, application of

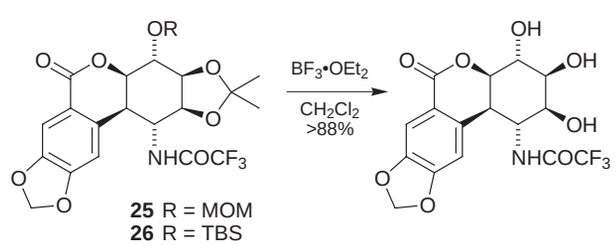




Scheme 9



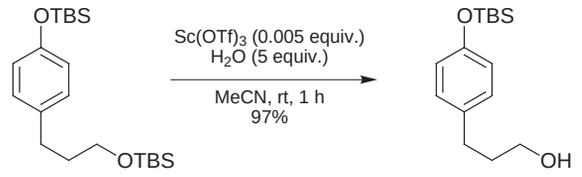
Scheme 10



Scheme 11

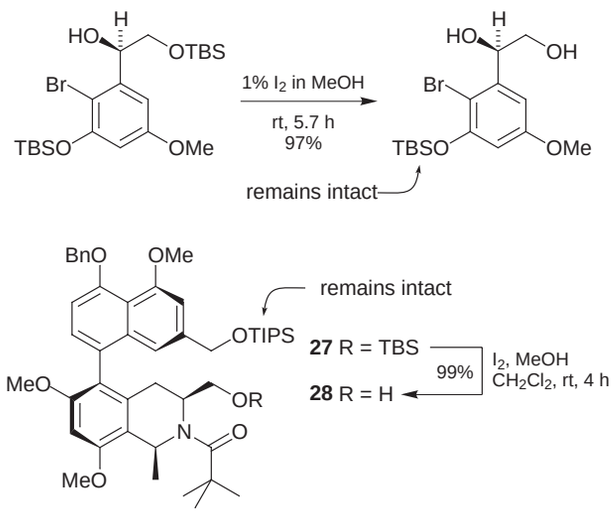
the same conditions to intermediate **26**, in which a TBS ether replaced the MOM group, were ineffective even under more forcing conditions. The acetonide was cleaved easily enough but the TBS ether was unusually recalcitrant. However both groups were cleaved efficiently using $BF_3{\cdot}OEt_2$ in dichloromethane.[17]

Treatment of primary and secondary trialkylsilyl ethers with a catalytic amount (usually 0.5 mol%) of scandium triflate and 5 equivalents of water in acetonitrile provides an efficient and practical method for deprotection.[18] Alkyl silyl ethers can be cleaved selectively in the presence of phenolic silyl ethers as illustrated in Scheme 12. TMS, TES and TBS ethers are all cleaved within 1 h whereas TIPS and TBDPS require up to 24 h but the yields are 93–98% in all cases examined.



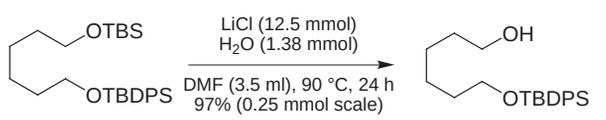
Scheme 12

Lipshutz and Keith report that 1% iodine in methanol selectively cleaves alkyl silyl ethers in the presence of aryl silyl ethers as illustrated in Scheme 13.[19] The reaction works equally well with TBS, TBDPS and TIPS ethers. The cleavage of TBDPS and TIPS ethers requires 1–1.5 days whereas TBS ethers generally cleave in less than 6 h. The rate differential is sufficient to allow selective cleavage of a primary alkyl TBS ether in the presence of a primary TIPS ether (*e.g.* **27**→**28**).



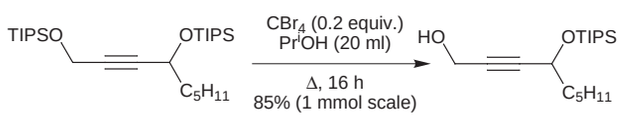
Scheme 13

The combination of lithium chloride (50 equiv.) and water (5.5 equiv.) in DMF selectively deprotects TBS ethers in the presence of TBDPS ethers (Scheme 14).[20] However, the high temperatures required (90–120 °C) makes the methodology unsuitable for thermally labile compounds.



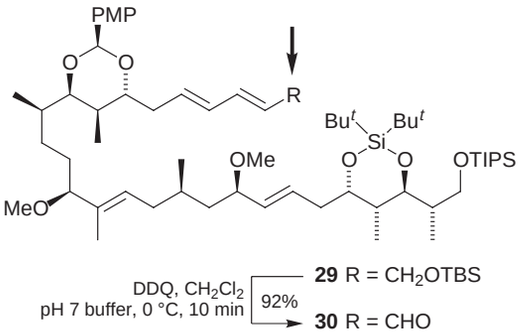
Scheme 14

Lee and co-workers[21] reported a new procedure for the deprotection of TBS, TBDPS and TIPS ethers using carbon tetrabromide (0.1 equiv.) in refluxing MeOH. In propan-2-ol, the rate of the reaction was much slower allowing the selective deprotection of a primary hydroxy group in the presence of a secondary one (Scheme 15).



Scheme 15

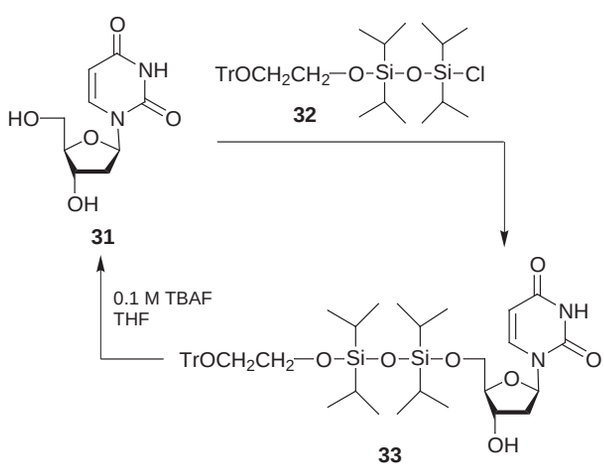
During studies directed towards the synthesis of aplyronine A, the Paterson group[22] accidentally discovered an oxidative deprotection of the allylic TBS ether in substrate **29** using DDQ to give the aldehyde **30** (Scheme 16). The survival of the potentially labile *p*-methoxyphenyl (PMP) acetal and the di-*tert*-butylsilylene protecting groups is noteworthy. A subsequent



Scheme 16

study revealed the reaction to be general though the rates of reaction varied considerably.[23] For example, the oxidative deprotection of a simple allylic TBS ether was slower indicating the beneficial effect of the diene unit but the rate could be substantially improved by switching to an allylic TES ether instead. Benzylic ethers also work well. Paterson has proposed hydride removal from the activated methylene followed by loss of the silyl group since the beneficial effect of pH 7 buffer rules out an acid-catalysed silyl ether deprotection as the first step.

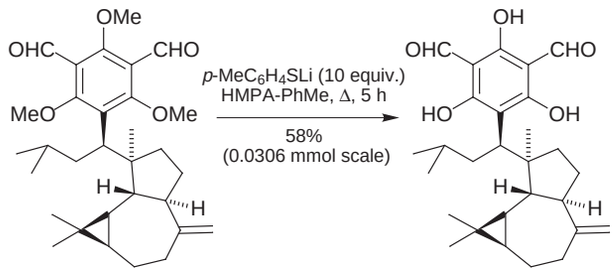
The 1,1,3,3-tetraisopropyl-3-[2-(triphenylmethoxyethoxy)]-disiloxan-1-yl protecting group has been designed for the protection of nucleoside 5′-hydroxy groups during solid phase RNA synthesis.[24] Protection involves generation of reagent **32** (Scheme 17) *in situ* by reaction of triphenylmethoxyethanol with 1,3-dichloro-1,1,3,3-tetraisopropyldisiloxane in DMF containing imidazole or pyridine as base. Addition of the alcohol **31** then generates the protected nucleoside derivative **33**. The protector is removed with TBAF or 0.01 M HCl. It is not clear what advantages this new protecting group will confer but the disadvantages are obvious: a molecular mass of 547 ($C_{33}H_{47}O_3Si_2$) with the attendant spectroscopic clutter are likely to win it few friends.



Scheme 17

2.3 Alkyl ethers

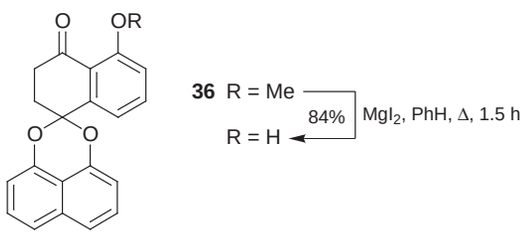
Alkyl ethers, especially methyl ethers, remain amongst the favourite protecting groups for phenols. For acid-sensitive substrates, powerful, moderately basic nucleophiles can be used to good effect. A case in point comes from the final step in the synthesis of macrocarpal C (**35**, Scheme 18)[25] involving removal of three *O*-methyl groups from the phloroglucinol derivative **34**. The use of Lewis acids such as BBr_3 was precluded by the presence of the cyclopropane ring and the exocyclic methylene. Application of a procedure by Hansson and Wickberg[26] using sodium *p*-thiocresolate in a mixture of toluene and HMPA removed only two of the methyl ethers even under forcing conditions. However, the desired transformation



Scheme 18

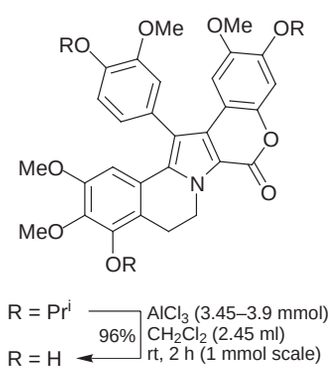
was eventually accomplished using lithium *p*-thiocresolate instead to give macrocarpal C in 58% yield.

The final step in a synthesis of the fungal spiroacetal palmarumycin CP2, deprotection of a phenolic methyl ether **36**, was achieved with magnesium iodide in refluxing benzene (Scheme 19).[27] The yield (84%) was far superior to other commonly used phenol ether deprotection conditions such as iodotrimethylsilane (32%) and sodium ethanethiolate (63%).



Scheme 19

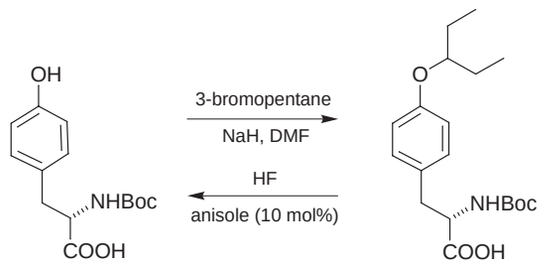
Aluminium chloride in dichloromethane cleaves isopropyl aryl ethers leaving methyl aryl ethers intact (Scheme 20).[28] Aryl halides, 1,1-dihaloalkenes, aldehydes and acetates withstand the reaction conditions but alkynes and TIPS ethers do not.



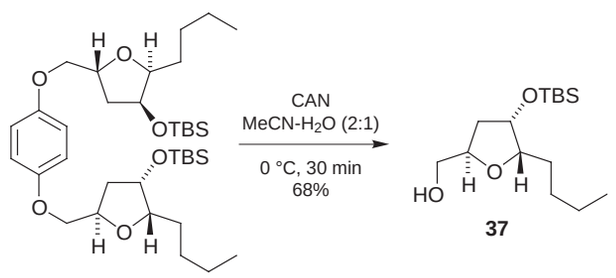
Scheme 20

The 3-pentyl group is a robust base-resistant protecting group for phenolic hydroxy groups of tyrosine in peptide synthesis using either Boc or Fmoc chemistry.[29] The protection is achieved in a one-step reaction by selective monoalkylation of the N^{a}-protected tyrosine disodium salt using 3-bromopentane in DMF (Scheme 21). The 3-pentyl group is sufficiently stable in 50% trifluoroacetic acid in dichloromethane (0.3% cleavage) and completely resistant to 20% piperidine in DMF (the reagents used to cleave Boc and Fmoc groups respectively). On the other hand, it is readily cleaved by the standard HF procedure in the presence of 10% cation scavenger like anisole or *p*-cresol which is essential to avoid alkylation of the benzene ring.

A bidirectional strategy for the synthesis of 2,3,5-trisubstituted tetrahydrofuran **37** (Scheme 22) benefited from the simultaneous protection of two primary hydroxy groups as



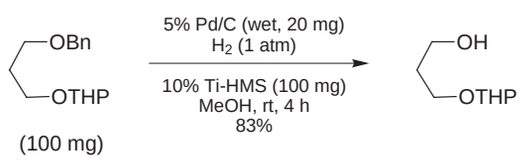
Scheme 21



Scheme 22

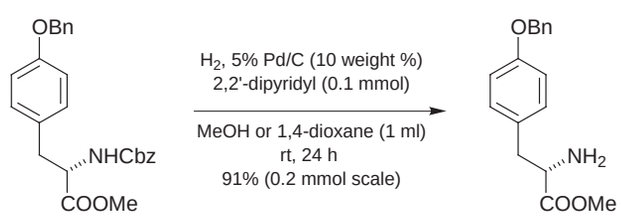
their C_2-symmetric hydroquinone ether.[30] Deprotection was achieved using ceric ammonium nitrate (CAN) in aqueous acetonitrile.

Promotion or prevention of benzyl ether hydrogenolysis can be achieved by the use of additives. For example, a titanium-loaded hexagonal mesoporous silica (Ti-HMS) accelerates deprotection of benzyl ethers under hydrogenolytic conditions.[31] The rate enhancement allows selective deprotection of benzyl ethers in the presence of TBS and THP ethers as illustrated in Scheme 23. Other acidic solid phase catalysts such as Dowex-50W × 8 or Amberlite IR-120B also accelerates hydrogenolysis of benzyl ethers but TBS and THP deprotection then competes.



Scheme 23

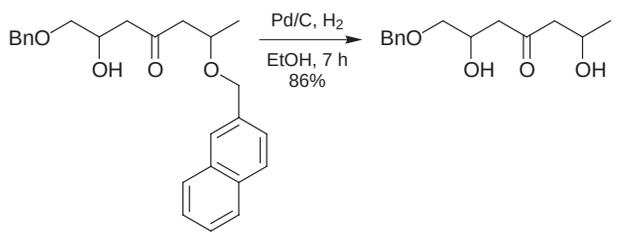
2,2′-Dipyridyl suppresses the hydrogenolysis of *O*-benzyl protected phenols allowing chemoselective reduction of double bonds, benzyl esters, nitro groups and the removal of *N*-Cbz groups in the presence of benzyl ethers (Scheme 24).[32] A similar effect of pyridine on Pd/C-catalysed hydrogenolysis of phenolic *p*-methoxybenzyl (PMB) groups has been reported.[33]



Scheme 24

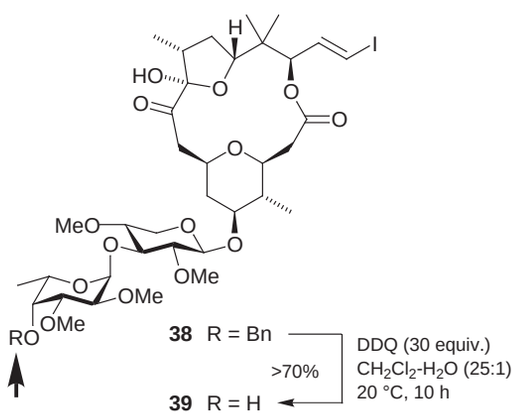
The manipulation of steric and electronic effects to tune the reactivity of protecting groups within an orthogonal set is a tried and tested technique. For example the electronic properties of the aromatic ring introduces sufficient latitude in the rate of hydrogenolysis of benzyl ether protecting groups to allow selective and sequential deprotection. Although simple benzyl ethers are cleaved more readily than their analogues bearing

CF_3, Me, OMe and *t*-Bu substituents in the *para* position, there is a need for a benzyl-type protecting group more labile than the parent system. Such a group has been reported: the 2-naphthylmethyl (NAP) group.[34] Scheme 25 illustrates the selective cleavage of a NAP group in the presence of a benzyl ether under standard hydrogenolysis conditions. A useful observation is that the 2-methylnaphthalene released during the reaction inhibits subsequent deprotection of the benzyl ether. The NAP group is stable to acidic and basic conditions, MeMgBr and DIBAL-H but shows partial decomposition with *n*-BuLi at 30 °C.



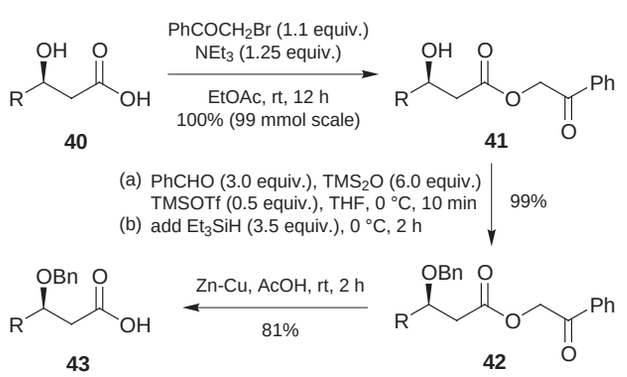
Scheme 25

At a late stage in the synthesis of polycavernoside A, the toxic agent of the red alga *Polycavernosa tsudai*, a benzyl ether had to be cleaved from the fucose residue of intermediate **38** (Scheme 26).[35] The task was accomplished by treatment of **38** with a large excess of DDQ in moist dichloromethane whereupon the debenzylated derivative **39** was obtained in >70% yield.



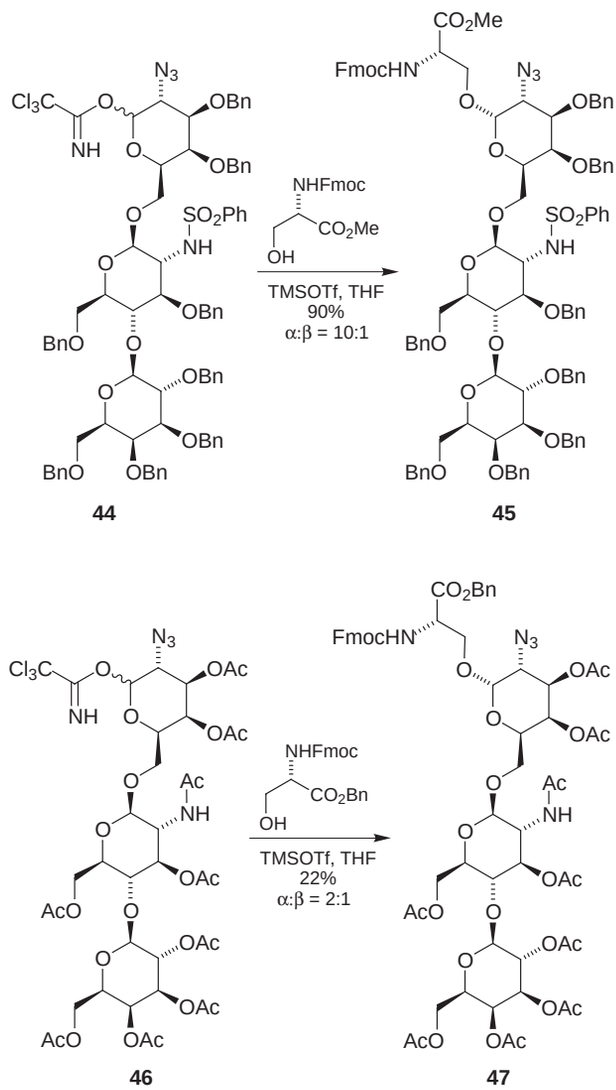
Scheme 26

Benzylation of the hydroxy group in **40** (Scheme 27)[36] was accomplished on the corresponding phenacyl ester **41** by means of a one-pot reductive benzylation.[37] Hydroxyester **41** was treated with benzaldehyde, hexamethyldisiloxane (TMS_2O) and TMSOTf in the presence of triethylsilane to give the corresponding *O*-benzyl ether **42** in 99% yield. Reductive cleavage of the phenacyl group with a zinc–copper couple then returned the acid **43**.



Scheme 27

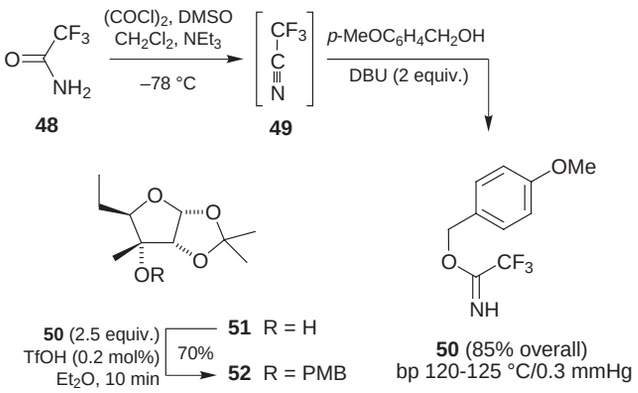
During a synthesis of the mucin-related F1a antigen, Danishefsky and co-workers[38] explored the methodology for the coupling of trisaccharide donors with serine–threonine acceptors. The protection pattern had a profound effect on the reactivity and stereoselectivity of the coupling despite the seemingly large distance of the reactive anomeric centre to the protected hydroxy groups. For example, the per-*O*-benzyl protected donor **44** (Scheme 28) was highly reactive at −78 °C, providing product **45** in 90% yield with high stereoselectivity (10:1). However, change the protecting groups to acetyl instead and the yield of **46** to **47** plummets to 22% and the stereoselectivity to 2:1. Thus, protecting groups, *via* their electronic, steric and conformational influences, coupled with solvation effects, can strongly modulate the characteristics of glycosyl donors making predictions on the efficiency and stereoselectivity of glycosidation risky.



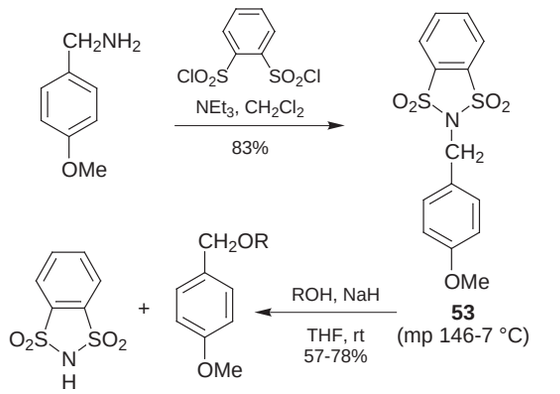
Scheme 28

Three new methods for introducing the PMB ether group have been described. Trichloroacetimidate esters are popular stable reagents for the synthesis of *tert*-butyl and benzyl ethers but the corresponding *p*-methoxybenzyl and 3,4-dimethoxybenzyl trichloroacetimidates are not stable to storage and must be prepared afresh. Furthermore, the instability of the more labile trichloroacetimidates can lead to low yields and messy reactions. Nakajima and co-workers[39] report that the analogous *p*-methoxybenzyl and 3,4-dimethoxybenzyl trifluoroacetimidates are stable compounds which can be stored for up to a month at room temperature. The synthesis of the

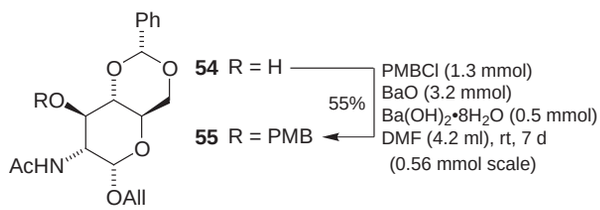
p-methoxybenzyl trifluoroacetimidate **50** is shown in Scheme 29. Treatment of trifluoroacetamide **48** with oxalyl chloride and DMSO in the presence of triethylamine gave trifluoroacetonitrile **49** which reacted *in situ* with *p*-methoxybenzyl alcohol and DBU (2 equiv.) to give the *p*-methoxytrifluoroacetimidate in 85% overall yield. The conversion of tertiary alcohol **51** to the *p*-methoxybenzyl ether **52** exemplifies the use of reagent **50** for hydroxy group protection.



Scheme 29



Scheme 30



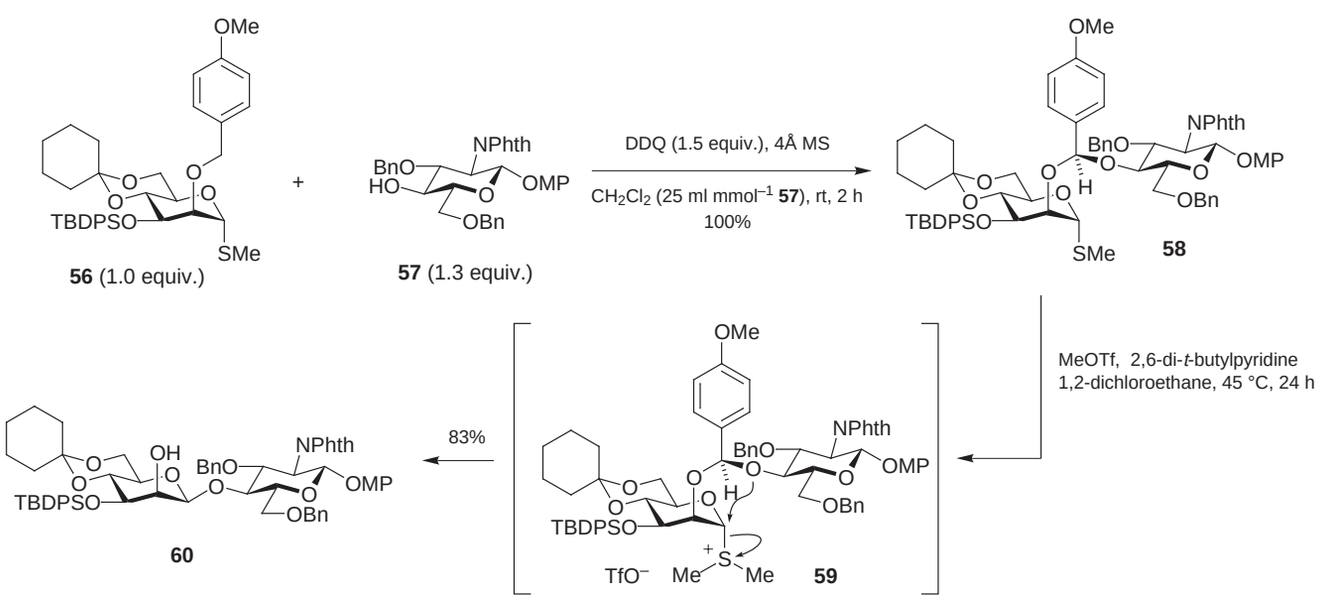
Scheme 31

A second new method for the protection of alcohols and phenols as their PMB ethers uses *N*-(4-methoxybenzyl)-*o*-benzenedisulfonimide **53** (Scheme 30) as the alkylating agent.[40] The protection step simply requires reaction of the sodium alkoxide with **53** in THF at room temperature. The disulfonimide **53** is a crystalline solid easily prepared from 4-methoxybenzylamine and *o*-benzenedisulfonyl chloride.

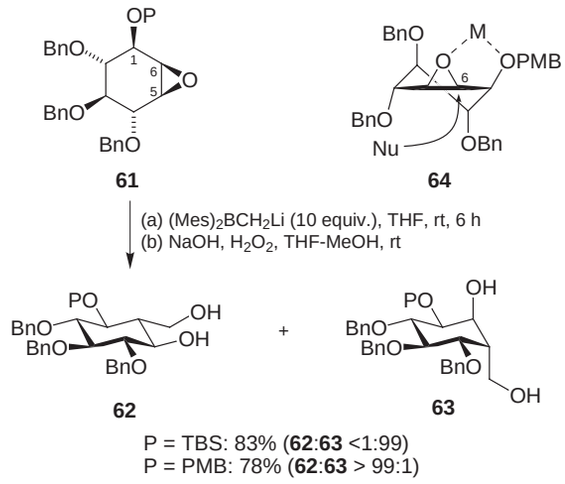
Finally, protection of the 3-hydroxy group function of the *N*-acetylglucosamine derivative **54** (Scheme 31) was accomplished by reaction of **54** with PMBCl in the presence of barium oxide and barium hydroxide in DMF.[41] The alkylation was slow (7 days) and gave the desired PMB ether **55** in 55% yield.

Ito and co-workers[42] have optimised the conditions for the stereoselective synthesis of β-manno glycosides using the intramolecular aglycon delivery approach. Thus the *p*-methoxybenzyl ether at the 2-position of the mannosyl donor **56** functions as a scaffold for the DDQ-mediated formation of the tethered intermediate **58** (Scheme 32). Subsequent activation of the anomeric α-thioglycoside by *S*-alkylation with methyl triflate triggers the intramolecular displacement of dimethylsulfane from intermediate **59** by the glucosamine-derived donor to afford the β-manno glycoside **60** in 83% yield. The rigidity of the pyranose ring system imparted by the 4,6-cyclohexylidene acetal was a significant factor controlling the efficiency of the reaction.

The nucleophilic cleavage of oxirane **61** (Scheme 33) using (lithiomethyl)dimesitylborane as a hydroxymethyl anion equivalent was a key step in a recent synthesis of the glycosidase inhibitor cyclophellitol.[43] Using oxirane **61** with P = TBS, the reaction took the expected regiochemical course giving the *trans*-diaxial diol **63** as the major product (83%, **62**:**63** < 1:99). However, the synthesis of cyclophellitol required the opposite regiochemistry giving the *trans*-diequatorial product **62**. By changing the protecting group at C1 to a PMB ether, the desired reaction took place giving **62** as the major product (78%, **62**:**63** > 99:1). The change in regioselectivity was attributed to the coordination of the PMB and oxirane oxygens as illustrated in structure **64** resulting in a locked conformation



Scheme 32

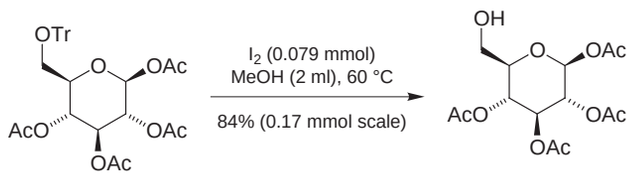


Scheme 33

in which *trans*-diaxial opening requires nucleophilic attack at C6.

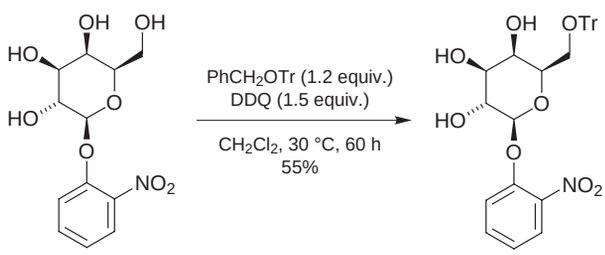
A new fluorous benzyl protecting group has been reported by Curran and co-workers.[44] Apart from being a protecting group, it also serves as a fluorous tagging group allowing easy purification of the reaction mixtures in "fluorous synthesis". This technique relies on the ability of a highly fluorinated molecule to partition into the fluorous phase in a liquid–liquid extraction between an organic and fluorous solvent. After one or more reactions are conducted and the fluorous components of each reaction separated from all non-fluorous (organic, inorganic, solid, volatile) components, the fluorous label is then cleaved and the product recovered. The application of fluorous synthesis to oligosaccharide synthesis is illustrated in Scheme 34. Reaction of D-glucal **65** with sodium hydride followed by addition of fluorous benzyl bromide (BnfBr) provides the crude tribenzyl glucal derivative **66** which is separated from organic and inorganic materials after three-phase extraction. Compound **66** is then coupled with the galactose derivative **67** using *N*-iodosuccinimide. Three phase extraction gives the iodide **68** which is then reductively deiodinated with tributyltin hydride. The tin residue (which is often difficult to remove using standard separation techniques) is then extracted into the organic phase (benzene) whereas the product **69** is isolated from the fluorous phase. After reductive debenzylation and three-phase extraction, the disaccharide derivative **70** is then acetylated to give **71** in 41% overall yield. Evaporation of the fluorous phase provided fluorous tolyl silane BnfH in 84% yield which can be brominated to regenerate the fluorous protecting group BnfBr.

A 1% (w/v) solution of iodine in methanol readily removes trityl (triphenylmethyl, Tr) and dimethoxytrityl ether groups selectively (Scheme 35).[45] Glycosidic linkages and acetate groups are well tolerated under the reaction conditions but TBS groups, which remain intact at 40 °C, are competitively deprotected at reflux. The more acid-sensitive dimethoxytrityl group is removed more rapidly and at lower temperatures than the trityl group.



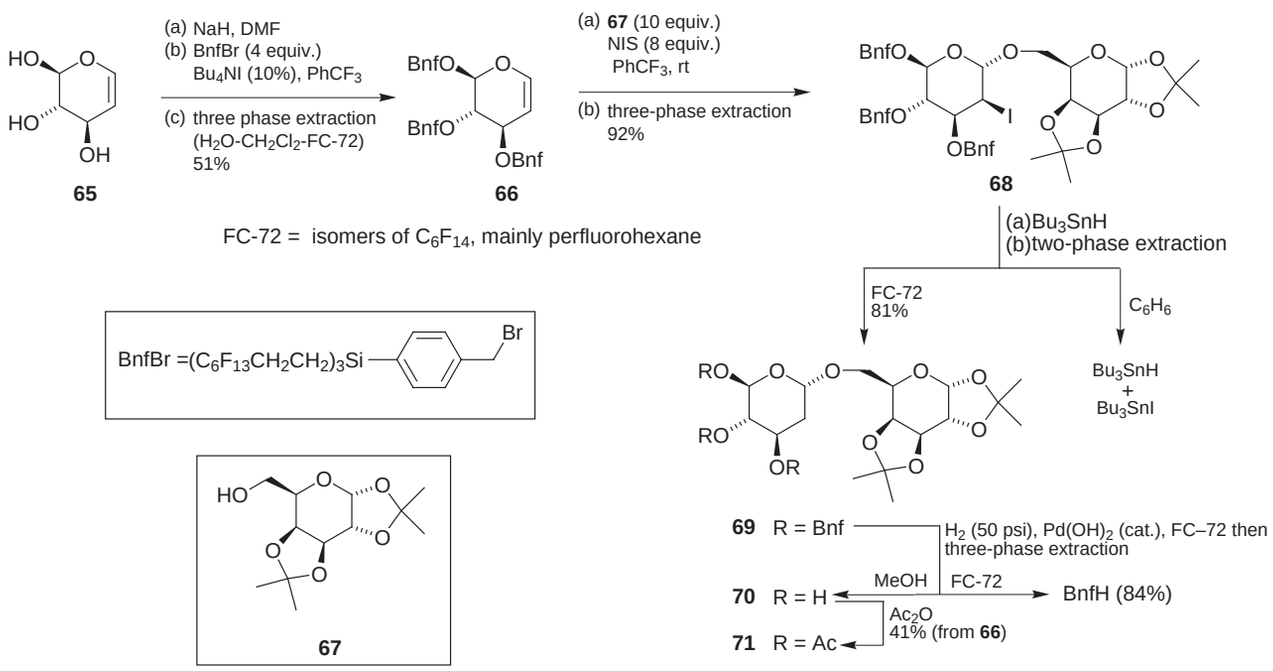
Scheme 35

Hydride abstraction from benzyl trityl ether using DDQ generates an *O*-trityl oxonium carbocation[46] which can act as a tritylating agent as illustrated in Scheme 36. The reaction works well for simple primary alcohols but the yield is moderate to low for secondary alcohols.

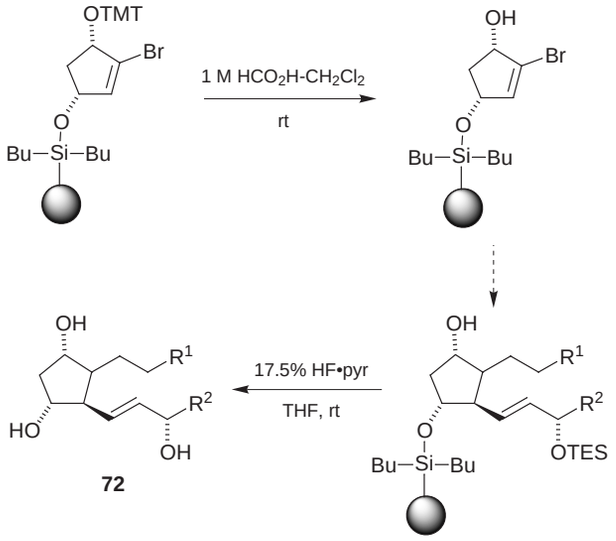


Scheme 36

The choice of a silyl linker for a solid phase synthesis of diverse prostaglandin derivatives imposed some strict boundary conditions (Scheme 37).[47] The substituents on silicon were care-



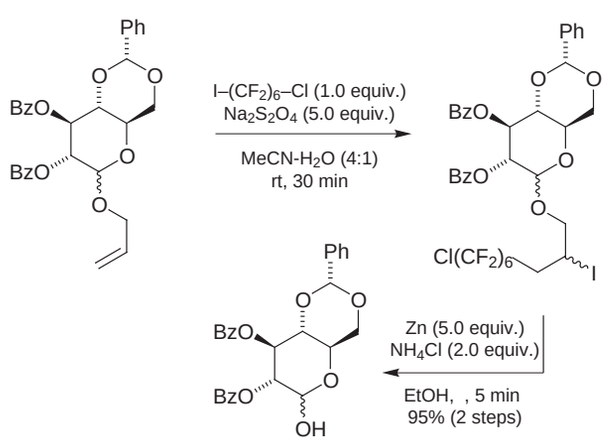
Scheme 34



Scheme 37

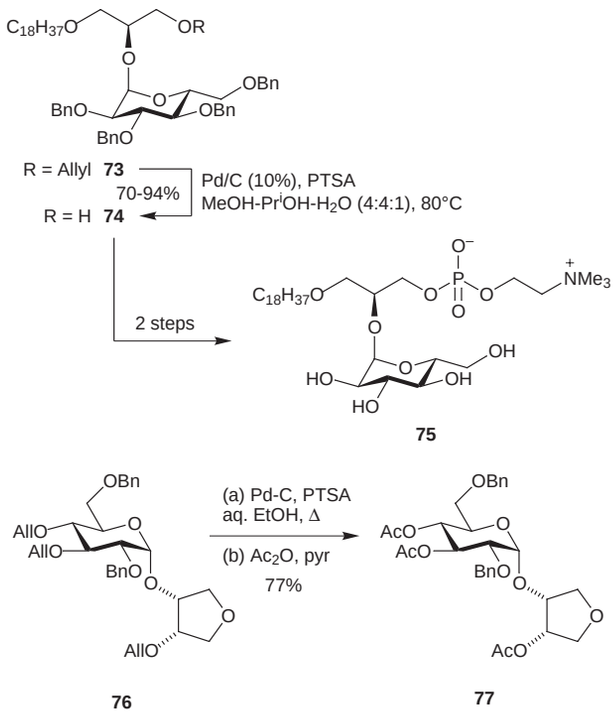
fully optimised to allow cleavage of the final product from the resin using 17.5% HF in pyridine–THF without destruction of an acid-sensitive allylic alcohol in the product **72**. The relative lability of the dibutylsilyl linker, in turn, required a protecting group for the hydroxy group which was very labile in acid. The trimethoxytrityl group served well, being cleaved with 1 M formic acid in dichloromethane at room temperature.

Allyl ethers are typically deprotected by transition metal (Pd, Rh, Ir) catalysed isomerisation of the double bond to form an enol ether which is then hydrolysed to release the hydroxy group function. Yu and co-workers [48,49] developed an alternative 2-step procedure based on perfluoroalkylation followed by reductive elimination (Scheme 38). The perfluoroalkylation is achieved using 6-chloro-1-iodoperfluorohexane in the presence of sodium dithionite in aqueous acetonitrile. Commonly used protecting groups such as benzyl, benzoyl, acetyl, benzylidene, dioxolane, TBS and *N*-phthalimide are compatible. The authors note that this new procedure offers opportunities for "fluorous synthesis" [50] of carbohydrates. The method was applied to 9 carbohydrates with yields ranging from 50 to 95%.



Scheme 38

There were two reports this year of the cleavage of allyl ethers in carbohydrates in a one-pot operation. The first came from a synthesis of [1-*O*-octadecyl-2-*O*-α-D-glucopyranosyl-*sn*-glycero(3)]phosphorylcholine (**75**, Scheme 39),[51] a derivative of platelet-activating factor (PAF), which initiates programmed cell death in keratinocytes at concentrations below 7.5 mM. The allyl ether protecting the C3 hydroxy group of the glycerol moiety in **73** was cleaved by rearrangement of the allyl ether to a prop-1-enyl ether using Pd on charcoal with simultaneous



Scheme 39

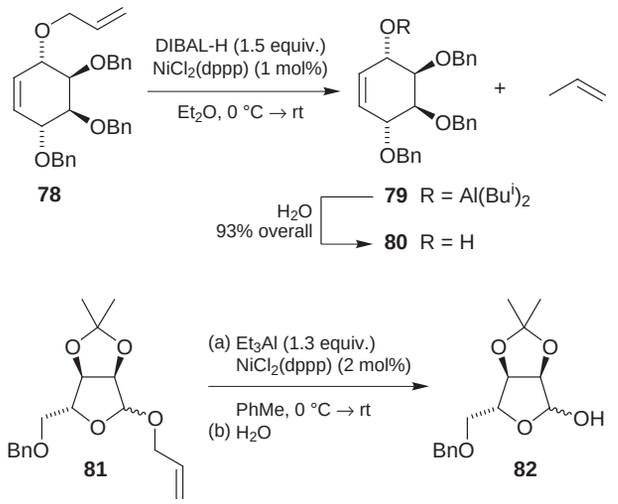
hydrolysis of the enol ether using aqueous PTSA.[52] In the second example, the three allyl groups of **76** were simultaneously deprotected [53] under similar conditions and the product isolated as its triacetate derivative **77**. The corresponding triphosphate derivative is a potent inositol triphosphate receptor ligand. Note the preservation of the acid-labile glycosidic link in both cases under these conditions.

A convenient and mild procedure for the cleavage of allyl ethers has been disclosed by Taniguchi and Ogasawara.[54] The reaction involves a Ni(0)-catalysed hydroalumination–elimination pathway leading to the direct formation of propene and an alkoxyaluminium species (*e.g.* **79**, Scheme 40). Aqueous workup then provides the deprotected alcohol in good overall yield. A number of functionalities are stable to the reaction conditions: TBS, THP, benzyl, MOM, acetyl, pivaloyl, benzoyl and PMB. The deprotection of **78** shows that primary allyl ethers cleave in preference to secondary allyl ethers. Sodium borohydride in aqueous ethanol can also be used for the cleavage. In the case of **81**, an 80% yield of the hemiacetal **82** was obtained with triethylaluminium as the reducing agent whereas DIBAL-H only afforded a 55% yield. In a different context, a German group showed that allyl ethers isomerise cleanly to (*Z*)-prop-1-enyl ethers when treated with $NiCl_2$(dppb) and lithium triethylborohydride.[55]

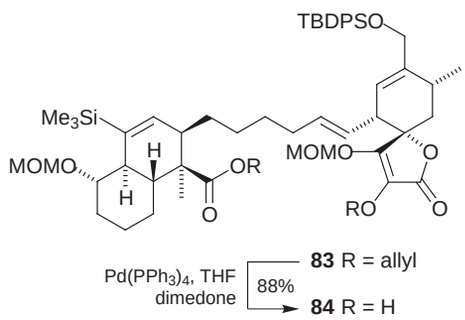
Deprotection of both the ester and the spirotetronic acid functions in the advanced chlorothricolide intermediate **83** (Scheme 41) was problematic.[56] Attempts to use a SEM ether were thwarted by decomposition caused by TBAF. Similarly attempts to remove a PMB ether with DDQ or CAN were unsuccessful owing to the instability of the product to these mild oxidants. Ultimately, simultaneous deprotection of the allyl ester and allyl tetronate using Pd(0) in the presence of dimedone proved most efficacious giving the hydroxy acid **84** in 88% yield.

2.4 Alkoxyalkyl ethers

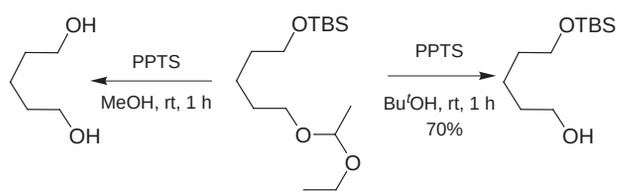
Selective deprotection of ethoxyethyl groups can be accomplished in the presence of a TBS group using pyridinium toluene-*p*-sulfonate (PPTS) (Scheme 42).[57] The use of *tert*-butyl alcohol as solvent has a crucial effect since both groups are removed in methanol. PPTS in methanol can also be used for



Scheme 40



Scheme 41



Scheme 42

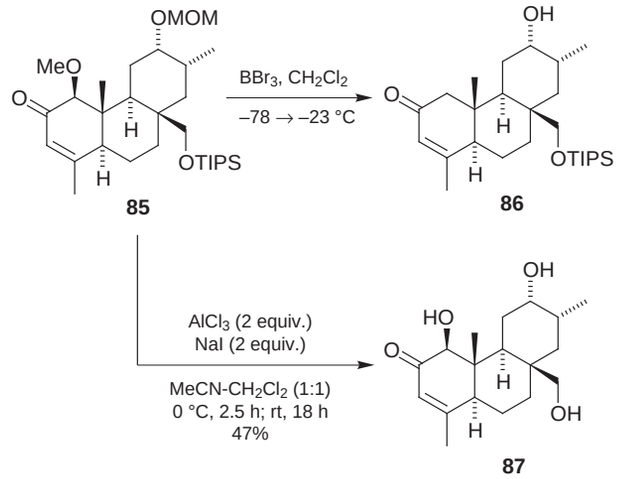
deprotecting TBS group in the presence of a Boc-protected amine.

Attempts to deprotect the methyl and methoxymethyl groups in the quassinoid intermediate **85** (Scheme 43) resulted in deoxygenation (probably *via* an intermediate α-bromo ketone) to give **86** as the major product in a complex mixture.[58] However, by using aluminium trichloride and sodium iodide in a mixture of acetonitrile and dichloromethane (1 : 1), the desired transformation occurred together with fortuitous cleavage of the TIPS group to give the target, des-D-chaparrinone (**87**) in 47% yield.

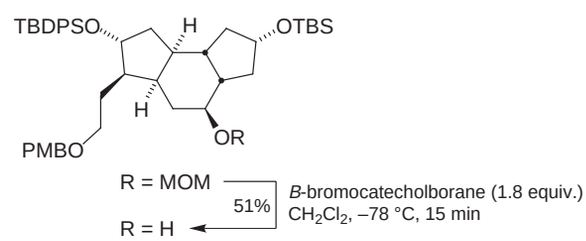
PMB ethers are generally more labile than MOM ethers towards protic or Lewis acid mediated cleavage. Nevertheless, a primary PMB ether survived the cleavage of a secondary MOM ether during a synthesis of the potent insecticidal agent spinosyn A by the Paquette group.[59] The transformation, depicted in Scheme 44, was accomplished using *B*-bromocatecholborane.[60,61]

The *p*-anisyloxymethyl group (abbreviated AOM)[62] played an important role in the synthesis of calicheamicinone reported by Clive and co-workers.[63] Its removal from the sensitive multifunctional substrate **88** (Scheme 45) was accomplished with CAN in a mixture of pyridine, methanol and water. The excellent yield of **89** (89%) attests to the mildness of the conditions.

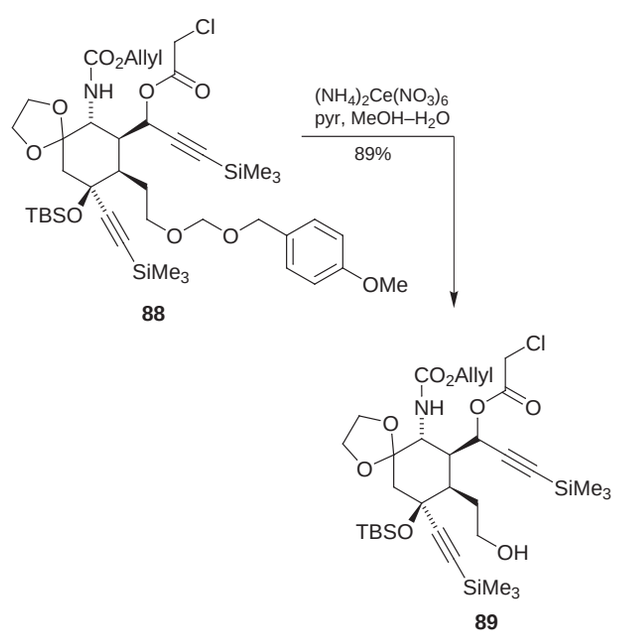
The advantages of high crystallinity were a prime motivation for the development of the (*p*-phenylphenoxy)methyl ether



Scheme 43

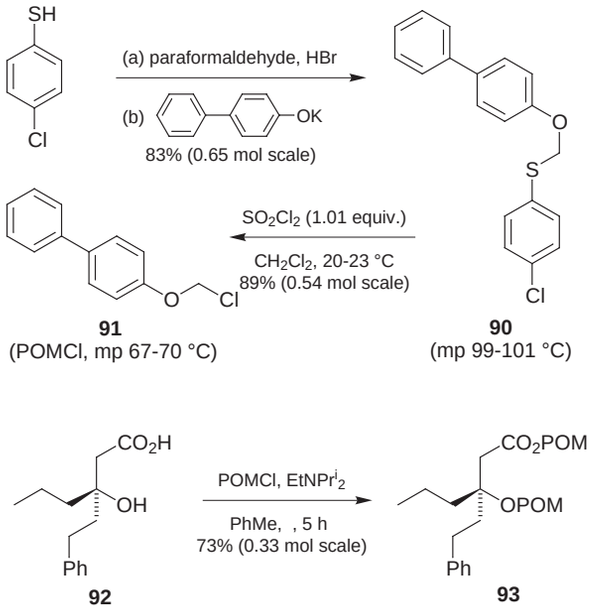


Scheme 44



Scheme 45

(POM) protecting group.[64] Reaction of *p*-chlorothiophenol with paraformaldehyde and 48% aqueous HBr afforded an intermediate bromomethyl thioether which was immediately converted to the *S*,*O*-acetal by reaction with the potassium derivative of *p*-phenylphenol. Treatment of **90** (Scheme 46) with sulfuryl chloride then afforded the crystalline 1-(chloromethoxy)-4-phenylbenzene (**91**) in 89% yield. The POM group is then introduced in the usual way, *i.e.*, by treatment of the alcohol (*e.g.* **92**) with **91** in the presence of Hünig's base. In the case of **92**, the hindered nature of the tertiary alcohol required a high temperature for the protection reaction. In a later intermediate, the POM ether was removed using methanolic sulfuric acid at room temperature.



Scheme 46

A series of three mild hydroxy group deprotections were implemented in the closing stages of the synthesis of antitumour macrolide (+)-amphidinolide J (**96**, Scheme 47) recently reported by Williams and Kissel.[65] The sequence began with the deprotection of the PMB ether in acyclic substrate **94** which occurred without 1,2-acyl migration of the acetate group. After oxidation of the aldehyde to the corresponding acid followed by Yamaguchi macrolactonisation, the protected 15-membered macrolide **95** was obtained. The allylic 2-(trimethylsilylethoxy)-methyl (SEM) ether was then deprotected under surprisingly mild conditions using pyridinium tosylate (PPTS) in refluxing *tert*-butyl alcohol. Finally, transesterification of the acetate with potassium carbonate in methanol gave the target apparently without competing ring contraction to the 14-membered macrolactone.

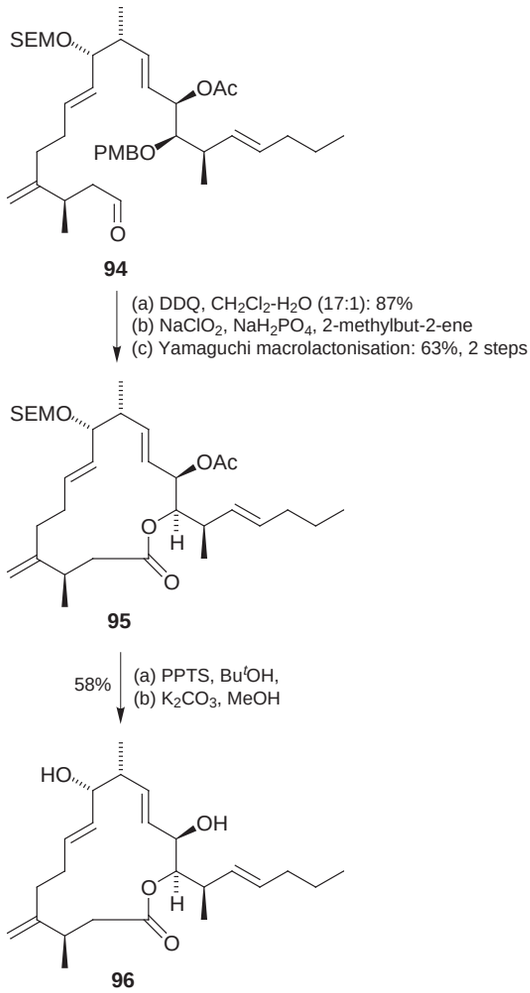
The beneficial hardiness of SEM groups was the cause of problems attending deprotection of the intermediate **97** (Scheme 48) during studies aimed at the structural elucidation of the macrolide amphidinolide L.[66] Treatment of **97** with TBAF in HMPA returned the desired diol **98** (35%) along with TES-deprotected compound **99** (33%) and the ethoxymethyl ether **100** (11%). However, when 1,3-dimethyl-3,4,5,6-tetrahydropyrimidin-2(1*H*)-one (DMPU) was used as solvent, the desired diol **98** was obtained in 82%.

A synthesis of a volatile ingredient of Yuzu fruit ("Yuzu Lactone") needed substitution of the THP ether in **101** (Scheme 49) with a bromine atom.[67] The desired transformation was achieved in one step using triphenylphosphine dibromide prepared *in situ* from triphenylphosphine and bromine.

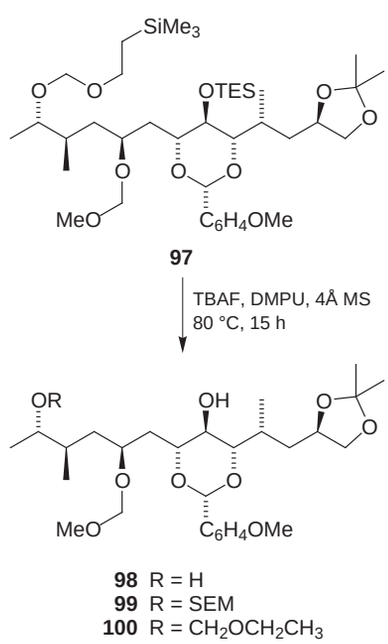
3 Thiol protecting groups

The fluoride-mediated deprotection of 2-trimethylsilylethyl thioethers is much more difficult than the corresponding ethers. In a synthesis of thiarubrine C (**104**, Scheme 50), treatment of the bis(2-trimethylsilylethyl) thioether **103** with excess TBAF resulted in only monodeprotection.[68] Cleavage of both ethers was easily achieved by conducting the cleavage with excess TBAF in the presence of trifluoroacetic anhydride presumably because of activation *via* initial acylation of the sulfur atoms. The resultant bis-trifluorothioacetate hydrolysed on workup with sodium hydrogen carbonate prior to oxidation with iodine.

Imbricatine (**105**, Scheme 51), isolated from the starfish *Dermasterias imbricata*, is responsible for eliciting the unusual swimming behaviour in the sea anemone *Stomphia coccinea.* During a synthesis of tri-*O*-methylimbricatine,[69] appendage of

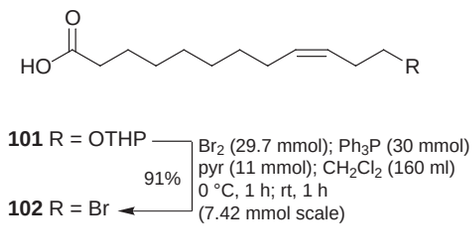


Scheme 47

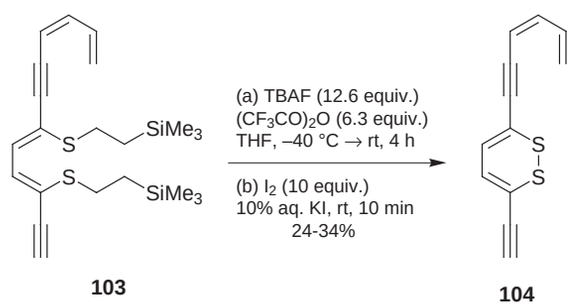


Scheme 48

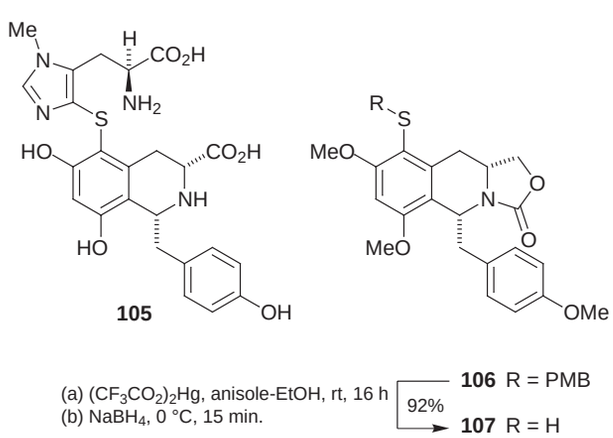
the imidazole ring required release of a thiol function from its *p*-methoxybenzyl thioether **106** using mercury(II) trifluoroacetate in ethanol containing anisole. Reduction of the resultant mercury thiolate intermediate with sodium borohydride gave the requisite thiol **107** in 92% overall yield for the two steps.



Scheme 49

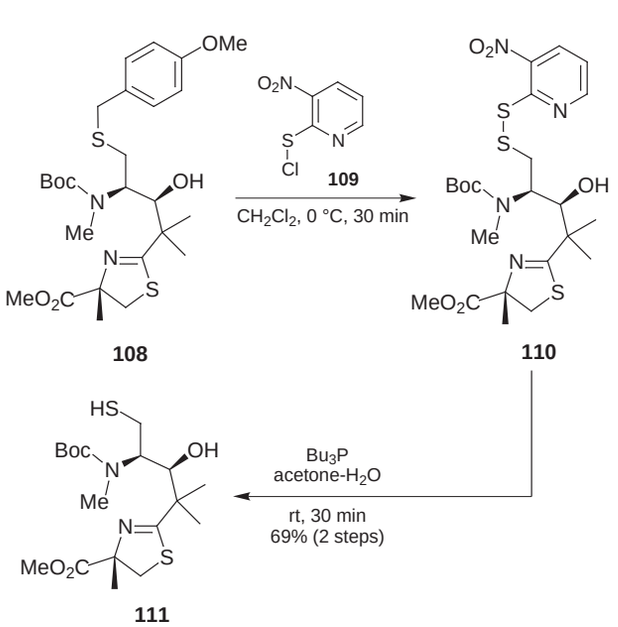


Scheme 50



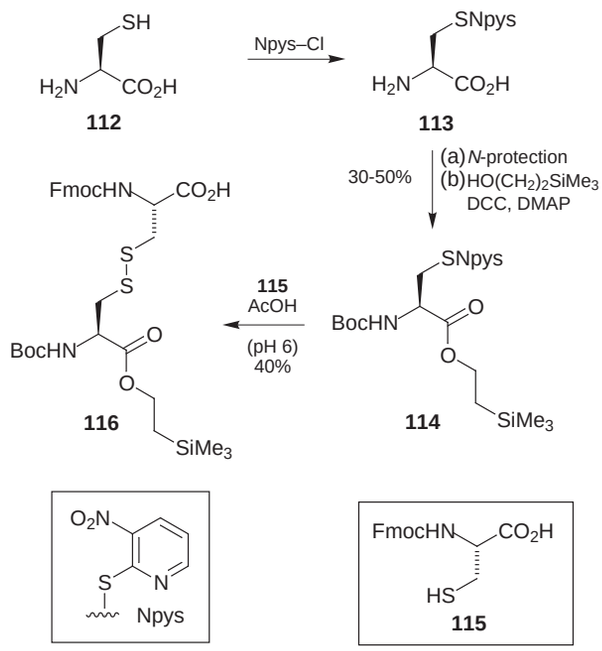
Scheme 51

A PMB group was also used to protect the thiol function in intermediate **108** (Scheme 52) *en route* to the antibiotic micacocidin.[70] The *S*-PMB group was cleaved in two steps by first reacting **108** with 3-nitro-2-pyridylsulfenyl chloride (**109**) to give the disulfide intermediate **110** which was then treated with tributyl phosphine in aqueous acetone to afford the thiol **111** in 69% overall yield for the two steps.[71,72]



Scheme 52

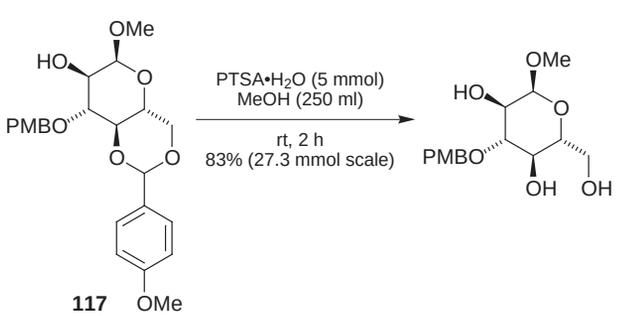
The ability of the 3-nitro-2-pyridylsulfenyl (Npys) group to serve as both a protecting and an activating group for thiols has been put to good use in a synthesis of orthogonally protected unsymmetrical cystine derivatives (*e.g.* **116**, Scheme 53).[73] The thiol moiety of cysteine **112** was transformed into the 3-nitro-2-pyridylsulfenyl (Npys) derivatives **113** followed by the protection of the amino and carboxy groups. The product **114** was then treated with the free thiol **115** at pH = 6 to afford the disulfide **116**.



Scheme 53

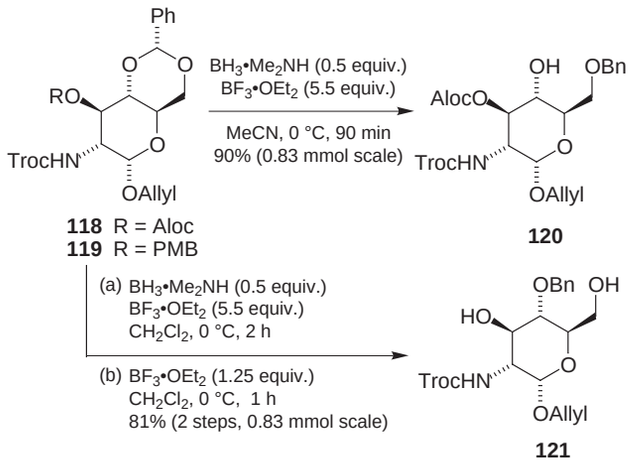
4 Diol protecting groups

A programme aimed at the synthesis of phosphatidylinositol derivatives required the selective deprotection of the *p*-methoxyphenyl acetal in **117** (Scheme 54) without detriment to the adjacent PMB ether.[74] The task was accomplished by stirring **117** in MeOH with PTSA·H_2O (pH ~ 2).



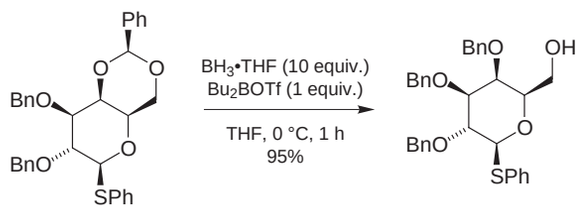
Scheme 54

This year witnessed two noteworthy examples of the reductive cleavage of 4,6-*O*-benzylidene derivatives using borane reagents. In the first example, Fukase and co-workers used the non-hygroscopic borane–dimethylamine complex in the presence of boron trifluoride etherate to cleave 4,6-*O*-benzylidene derivatives of glucose and glucosamine (Scheme 55).[36] In the case of the 3-*O*-Aloc protected derivative **118**, reductive cleavage returned the 6-*O*-benzyl ether **120** in 90% yield. However, similar reduction of the 3-*O*-PMB ether **119** gave the 4-*O*-benzyl ether **121** instead (81%) after removal of the PMB with boron trifluoride etherate.



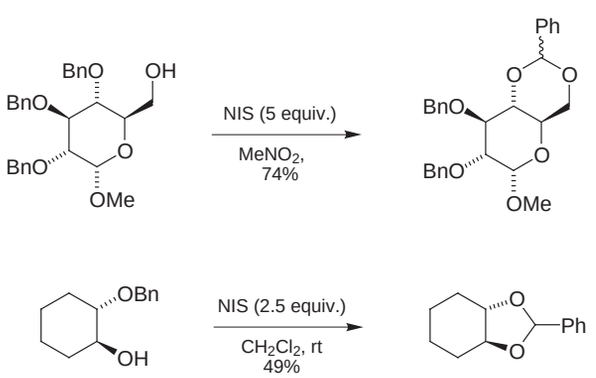
Scheme 55

The second study involved the regioselective reductive cleavage of 4,6-*O*-benzylidene acetals of various hexopyranosides with an excess of borane–tetrahydrofuran complex in the presence of dibutylboron triflate (Scheme 56).[75] Yields range from 70–95% for the 10 examples reported. Benzyl, silyl, ester and phthalimide protecting groups are compatible with the reaction conditions. Isopropylidene groups are also cleaved regioselectively (2 examples).



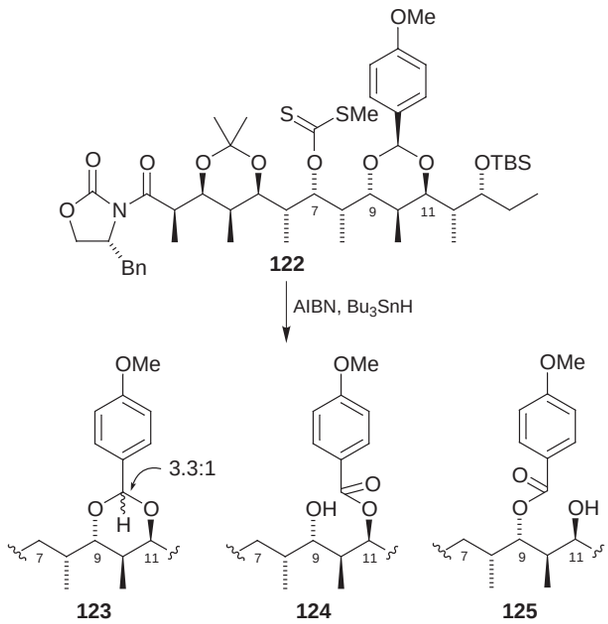
Scheme 56

N-Iodosuccinimide (NIS) accomplishes the oxidative cyclisation of 1,2-, 1,3- and 1,4-diol monobenzyl ethers to benzylidene acetals and iodine (Scheme 57).[76] The reaction requires at least 2 equiv. of NIS but frequently several additional equivalents are necessary to ensure that the reaction goes to completion. A variety of solvents (MeCN, CH_2Cl_2, $MeNO_2$) may be used. The reaction probably involves formation of an intermediate hypoiodite since substrates lacking hydroxy group functions do not participate.



Scheme 57

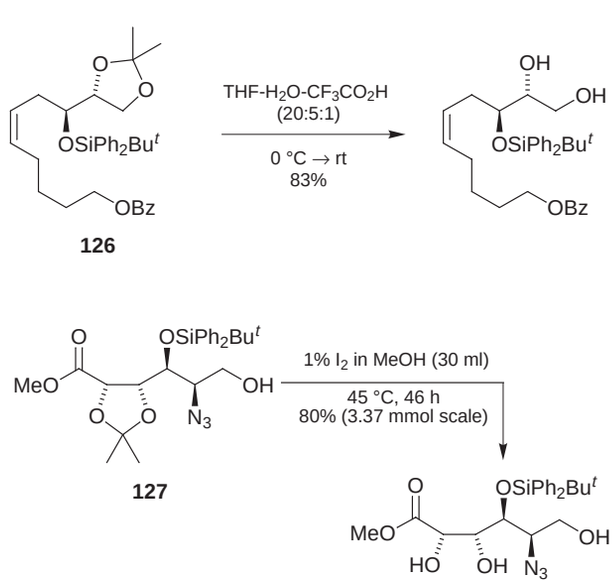
In the closing stages of a remarkably concise synthesis of 6-deoxyerythronolide B, Evans and co-workers[77] encountered some problems in the Barton deoxygenation of the xanthate ester **122** (Scheme 58). At a stoichiometry of 1.1 equiv. of Bu_3SnH per equiv. of substrate (cat. AIBN, 0.03 M in toluene, 80 °C), the desired benzylidene acetal **123** was obtained in only



Scheme 58

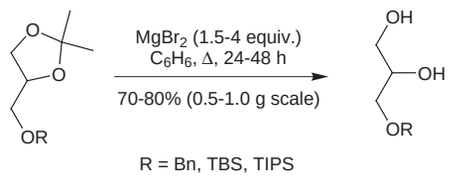
20% yield. The balance of the material was obtained as a 1:1 mixture of the deoxygenated *p*-methoxybenzoate regioisomers **124** and **125**. The formation of **124** and **125** suggested a mechanism involving radical abstraction from the benzylidene acetal by the C7 carbon radical followed by oxidative scission. The problem was eventually solved by quenching the stabilised benzylidene radical *in situ* by conducting the reaction in neat Bu_3SnH. Under these conditions the formation of **124** and **125** was completely suppressed giving the desired product **123** as a 3.3:1 mixture of acetal diastereoisomers. Acid-catalysed equilibration of the acetals then gave a single diastereoisomer in 84% yield.

Migration of silyl groups to a vicinal hydroxy group is a perennial problem. In hydrolysis of the acetonide in **126** (Scheme 59), 1,2-migration of the *tert*-butyldiphenylsilyl group was largely suppressed by using trifluoroacetic acid in aqueous THF.[78] However, application of these conditions to the acetonide **127** was not successful and a number of products resulting from 1,2-silyl migration were observed. Eventually successful cleavage of the acetonide **127** was accomplished using methanolic iodine at 45 °C.



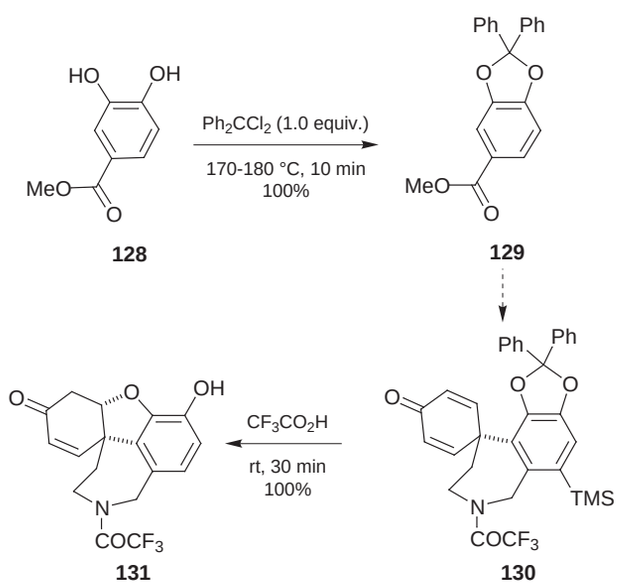
Scheme 59

Anhydrous magnesium bromide in refluxing benzene deprotects isopropylidene acetals leaving benzyl, TBS and TIPS ethers intact (Scheme 60).[79] The reagent also cleaves triphenylmethyl-protected alcohols in the presence of benzyl ethers. Isopropylidene acetals can be also deprotected with copper(II) chloride dihydrate (2 equiv.) in acetonitrile to give the corresponding diols and carbonyl compounds.[80] The reaction can be carried out with a catalytic amount of $CuCl_2 \cdot 2H_2O$ (10 mol%) but the reaction time is longer. The reagent also deprotects TBS ethers and THP acetals.



Scheme 60

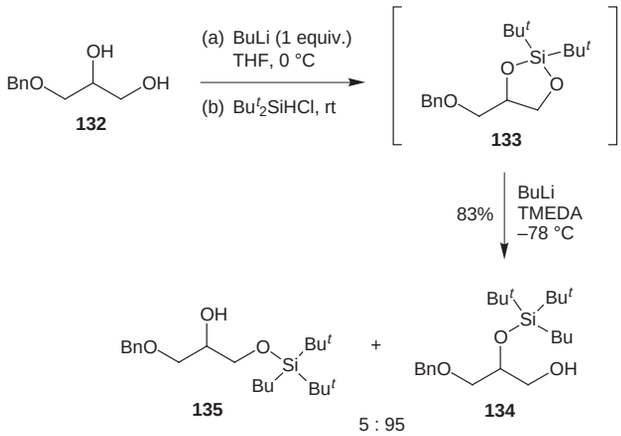
Protection of the catechol **128** (Scheme 61) as its diphenyldioxolane derivative **129** was the first step in a general approach to the galanthamine alkaloids.[81] The protection was accomplished in quantitative yield by simply heating catechol **128** with dichlorodiphenylmethane at 170–180 °C. The diphenyldioxolane ring of intermediate **130** was later cleaved with neat trifluoroacetic acid to return a catechol intermediate which underwent intramolecular addition to the dienone ring to give **131** in quantitative yield.



Scheme 61

A novel one-pot procedure for the selective protection of an internal hydroxy group of 1,2-diols has been reported.[82] The reaction of 1,2-diol **132** (Scheme 62) with 1 equiv. of BuLi followed by di-*tert*-butylchlorosilane affords cyclic silyl ether **133** with the evolution of hydrogen. Treatment of the solution with butyllithium at −78 °C in the presence of tetramethylethylenediamine (TMEDA) results in the cleavage of the Si–O bond to yield internally protected **134** as the major regioisomer. The regioselectivity of the reaction depends on the structure of the 1,2-diol and is in the range 95–99%.

Primary and secondary symmetrical diols with 2–20 carbon atoms can be selectively protected as their monotetrahydropyranyl ethers by reaction with 3,4-dihydro-2*H*-pyran in toluene or hexane catalysed by wet sulfonic acid-type ion-exchange resins.[83] The yields of the monoethers were higher than 80% while those of the corresponding diethers were lower than 5%.



Scheme 62

5 Carboxy protecting groups

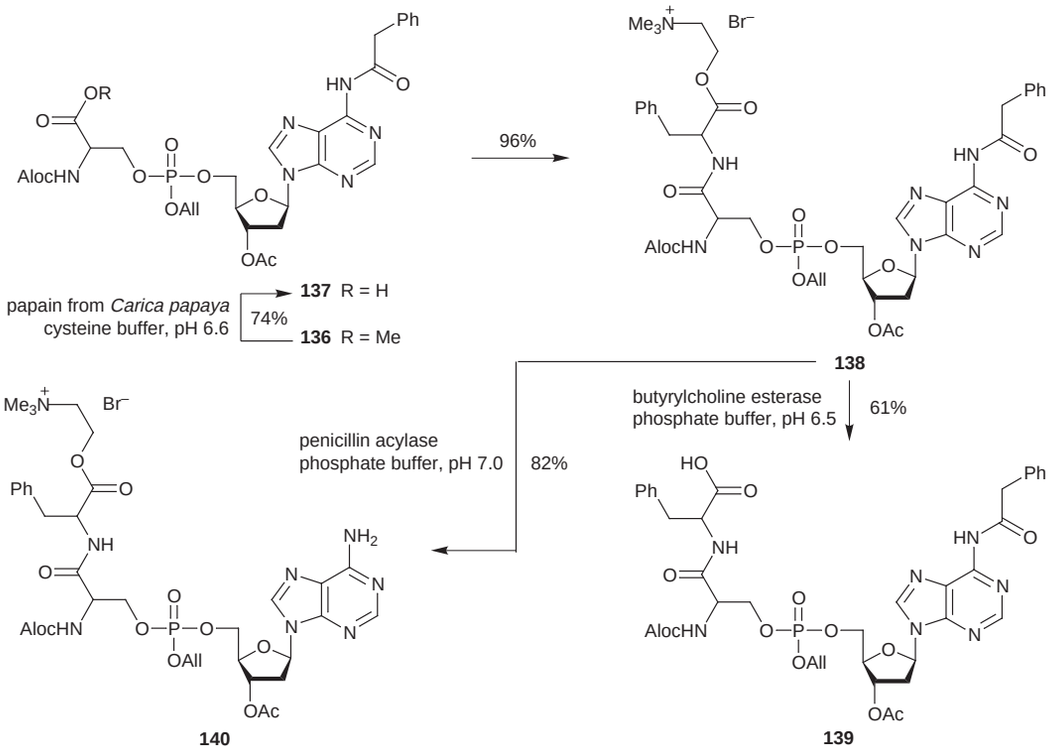
Fully protected serine- or threonine-nucleopeptides are both base-labile (the oligonucleotide suffers easy β-elimination) and acid-labile (depurination). Jungmann and Waldmann[84] report the selective deprotection of the carboxylic acids, the nucleobases and the hydroxy groups in multifunctional nucleopeptides under mild conditions using enzymes (Scheme 63). From the nucleoserine ester **136**, the C-terminal methyl ester was hydrolysed selectively with the protease papain from *Carica papaya.* However, in order to avoid complications of peptide cleavage using proteases, C-terminal deprotection using butyrylcholine esterase from horse serum was also investigated. Thus, selective hydrolysis of the choline ester **138** gave the carboxylic acid **139** in 61% yield—this being the least efficient of the dipeptide sequences investigated. Penicillin acylase catalysed removal of the phenylacetamido base protecting group to give the amine **140** in 82% yield. The 3′-acetate ester could also be selectively hydrolysed using wheat germ lipase in 64% yield (not shown).

The combination of thiophenol and a catalytic amount of potassium fluoride converts methyl esters into the corresponding acids under non-hydrolytic conditions (Scheme 64).[85] However, the high temperature (190 °C) might be incompatible with thermally sensitive compounds. Ethyl esters give generally lower yields but benzyl esters work well.

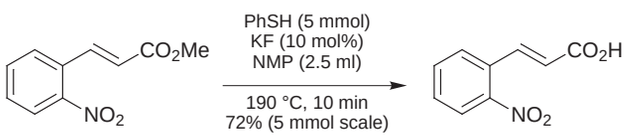
A powerful method for the selective esterification of aliphatic carboxylic acids in the presence of aromatic carboxylic acids has been reported[86] which simply entails stirring the acid at room temperature in a large excess of 2,2-dimethoxypropane containing some MeOH and HCl (10 mol%) generated *in situ* from TMSCl. The reaction is exemplified by the selective esterification of homophthalic acid (**141**, Scheme 65) which gave 95% of the monoester **142** together with 1.7% of the diester, the remainder being unreacted diacid. Alkenes, alkynes, amino, cyano, halo, hydroxy, α-keto- and nitro groups are unaffected. The reluctance of aromatic acids to undergo esterification is cogently illustrated by the fact that 2-iodobenzoic acid gave only 3.1% of the ester after 96 h in the presence of 20 mol% HCl. The reaction works with acid sensitive complex substrates too: the prostanoid ester **143** was obtained in >95% yield from the corresponding acid after 24 h.

The yellow colour of cefesone (**144**, Scheme 66) is converted into a red colour on cleavage of the β-lactam ring by β-lactamase thereby allowing determination of β-lactamase activity in biological samples.[87] In a commercial synthesis of cefesone and nitrocefin, simultaneous cleavage of the *tert*-butyl ester and isomerisation of the (*Z*)-alkene bond was accomplished using titanium tetrachloride.

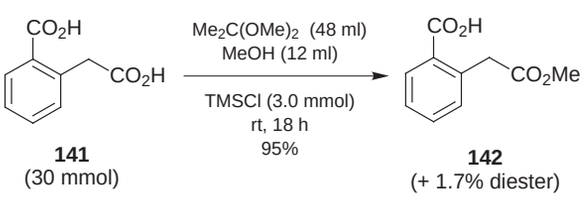
An efficient synthesis of the fungal germination inhibitor alternaric acid required an ester which survived the ruthenium catalyst used in the formation of **145** (Scheme 67).[88] Since the product was also acid-sensitive, an ester protecting group was

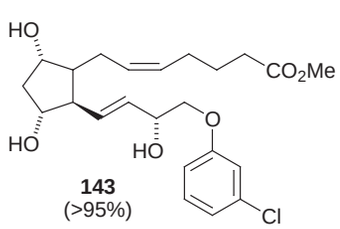


Scheme 63

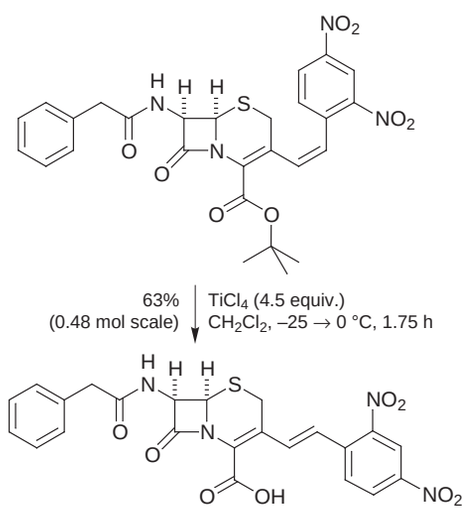


Scheme 64

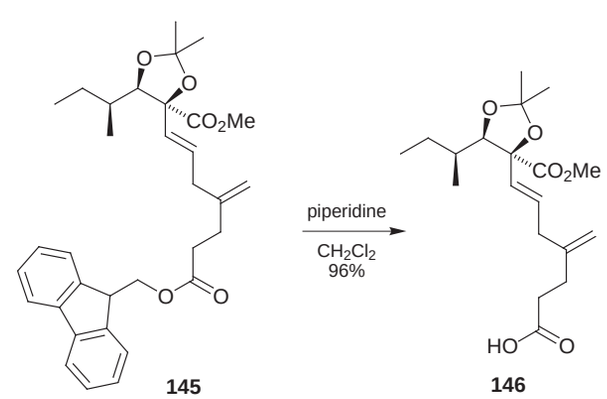




Scheme 65



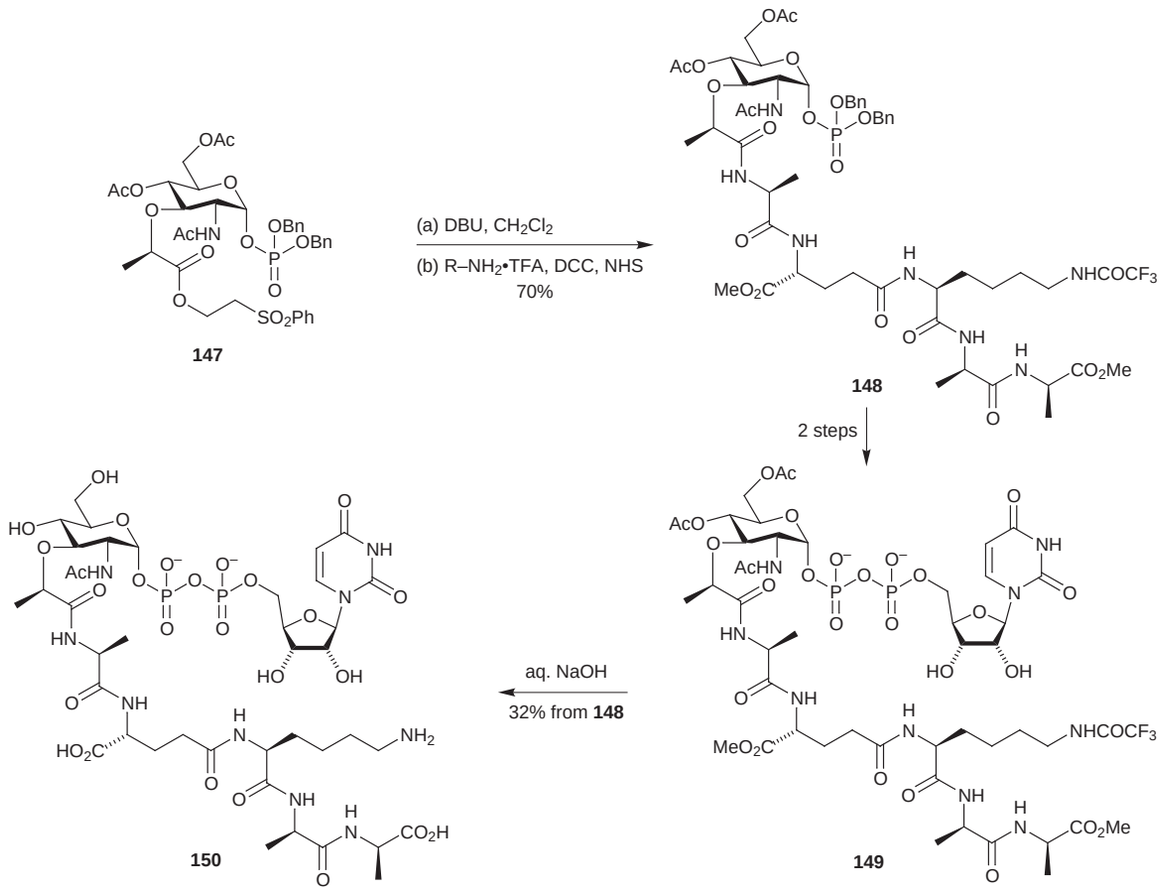
Scheme 66



Scheme 67

required which could be removed under mildly basic conditions. The fluoren-9-ylmethyl ester function served the purposes required as it was easily removed on treatment with piperidine in dichloromethane to give the required acid **146** in 96% yield.

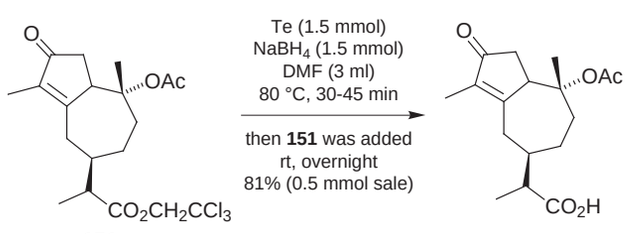
A Lilly group has devised a synthesis of the bacterial cell wall precursor UDP-*N*-acetylmuramyl-pentapeptide **150** for use in the discovery of new antibiotic agents.[89] The most widely used method for the construction of these compounds involves late stage formation of the diphosphate moiety *via* coupling of glycosyl phosphates with nucleoside 5′-morpholidophosphates (the Khorana–Moffatt procedure). Traditionally the Khorana–Moffatt process is performed after removal of all the protecting groups as the final step in glycosyl nucleotide phosphate syntheses but in the present synthesis, a protected form of peptidomuramyl phosphate **148** was used thereby requiring a set of protecting groups which could be unmasked whilst maintaining the labile anomeric diphosphate moiety intact. Scheme 68



Scheme 68

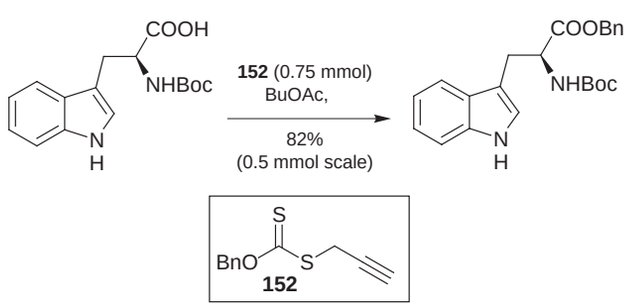
illustrates the general procedure. The carboxy group in **147** was unmasked by base-induced elimination of the 2-(phenylsulfonyl)-ethyl ester group and the pentapeptide chain constructed using standard peptide coupling methods to give **148**. Hydrogenolysis of the benzyl phosphate esters followed by the Khorana–Moffatt phosphorylation returned the fully protected target **149**. Global deprotection of two methyl esters, a trifluoroacetamide and two acetates returned the Park nucleotide **150** in 32% yield from **148**.

2,2,2-Trichloroethyl esters of carboxylic acids can be deprotected by treatment with sodium telluride in DMF (prepared *in situ* from tellurium and sodium borohydride).[90] The reaction conditions are compatible with methyl esters, acetates, TBS ethers or enones (Scheme 69), but α,β-unsaturated esters, epoxides and halides are affected by telluride anion.



Scheme 69

A new method for making benzyl esters by refluxing a carboxylic acid with xanthate **152** (Scheme 70) for several hours in toluene or butyl acetate has been described.[91] The reagent **152** is prepared in 68% yield in one step by the reaction of the sodium salt of benzyl alcohol with carbon disulfide followed by treatment with propargyl bromide. Sensitive or hindered carboxylic acids can be used and a wide range of functional groups commonly encountered in organic synthesis is tolerated. Other

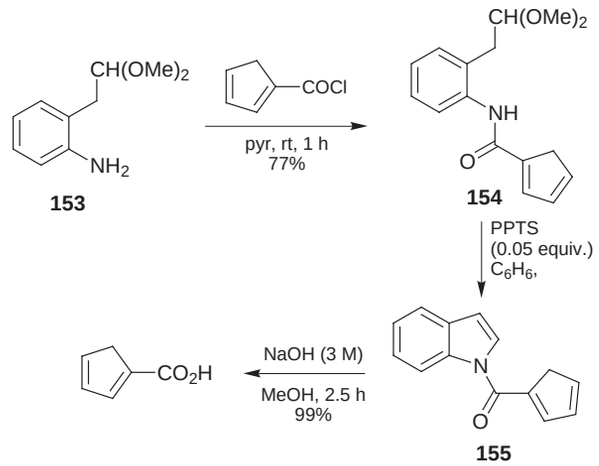


Scheme 70

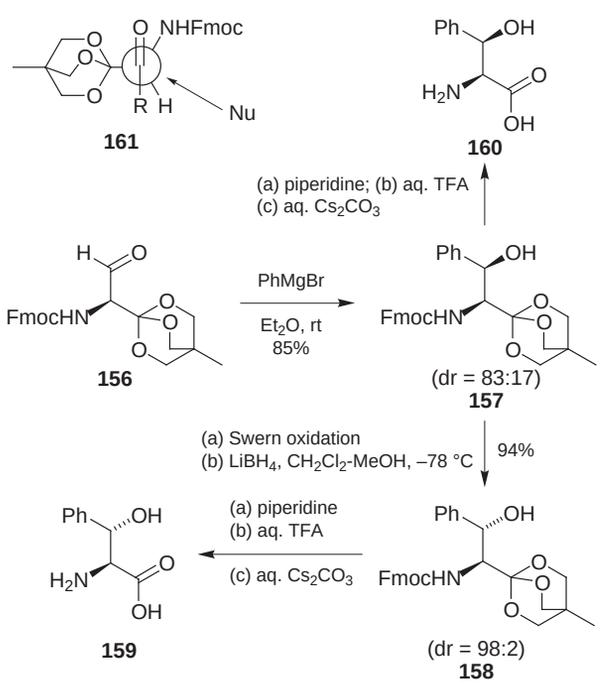
compounds like phenols, tetrazoles and hydroxypyridines (with a pK_a lower than 8–10) can also be benzylated.

A method for the relay protection of a carboxylic acid as a stable amide is exemplified by the transformations depicted in Scheme 71.[92] Amide **154** derived from 2-(2-aminophenyl)-acetaldehyde dimethyl acetal (**153**) withstands 3 M NaOH (in MeOH at rt for 2 h) and lithium borohydride (in THF at rt overnight) but hydrolysis is easily achieved *via* the corresponding indolylamide **155**.

A general stereoselective synthesis of *threo* and *erythro* β-hydroxy-α-amino acids has been described[93] which features the aldehyde **156** (Scheme 72) with the carboxy protected as its 4-methyl-2,6,7-trioxabicyclo[2.2.2]octane ortho ester derivative. Addition of Grignard reagents to aldehyde **156** gave the *threo* adducts such as **157** with good stereoselectivity. Swern oxidation of the *threo* adduct followed by low temperature reduction of the resultant ketone with lithium borohydride then afforded the corresponding *erythro* adduct **158**. The stereochemistry of the nucleophilic additions was ascribed to the large bulk of the ortho ester protecting group and is consistent with a nonchelation-controlled Felkin–Anh attack as illustrated in structure **161**.



Scheme 71

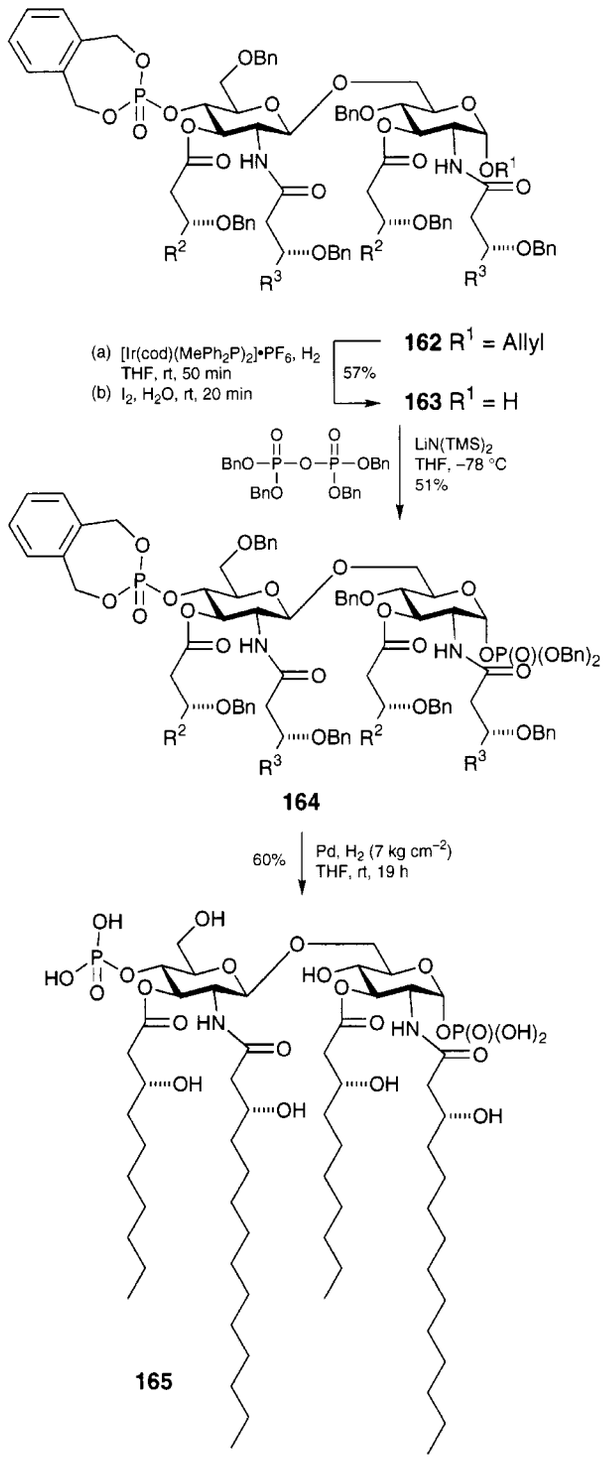


Scheme 72

6 Phosphate protecting groups

Lipid A is the active constituent of lipopolysaccharide (LPS), a cell surface glycoconjugate of Gram-negative bacteria, which stimulates immunocompetent cells to produce powerful mediators. The Fukase group synthesised the Lipid A analogue **165** (Scheme 73) having shorter lipid chains than the natural agent.[36] In the closing stages of the synthesis the allyl glycoside **162** was deprotected by isomerisation with [bis(methyldiphenylphosphine)] (1,5-cyclooctadiene)iridium(I) hexafluorophosphate to a propenyl ether which was hydrolysed with aqueous iodine. The intermediate **163** was converted to its benzyl-protected glycosyl phosphate by treatment with lithium hexamethyldisilazide in the presence of tetrabenzyl diphosphate to give the protected 1,4′-diphosphate **164**. Finally hydrogenolysis of all benzylic protecting groups using Pd black at high pressure returned the labile target **165**.

Watanabe and Nakatomi reported a synthesis of phosphatidylinositol 3,4,5-triphosphate (**172**, Scheme 74).[94] Racemic *myo*-inositol was converted to the homochiral intermediate **166** in a sequence of reactions including a chromatographic resolution of diastereoisomeric (*S*)-(+)-*O*-mandelate esters and the introduction of three phosphates protected as their fluoren-9-ylmethyl (Fm) esters. Selective monotriethylsilylation of **166**

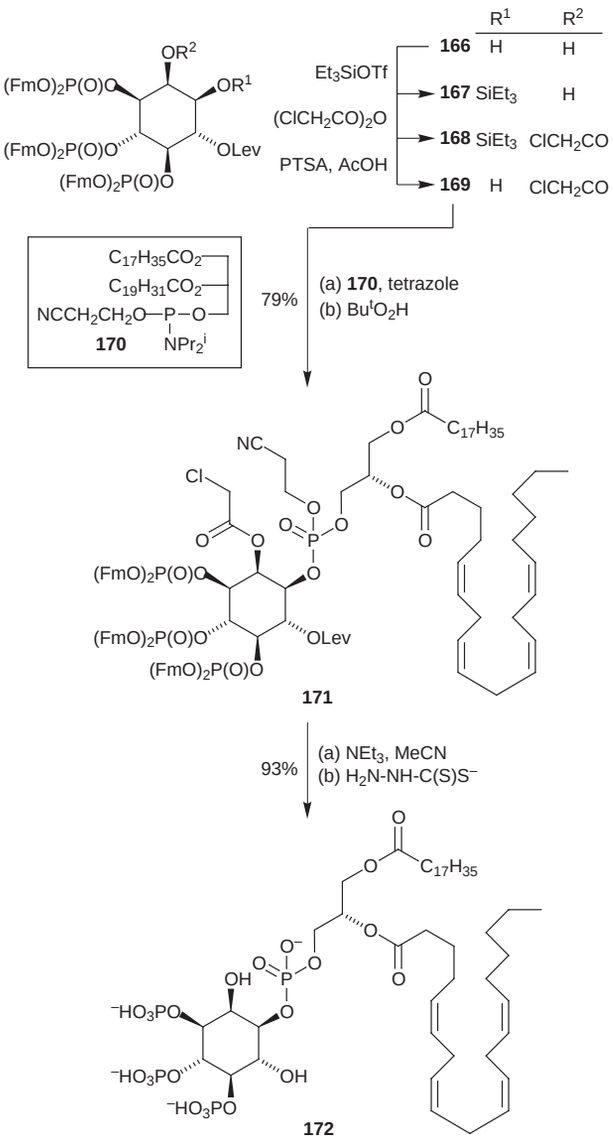


Scheme 73

was achieved with triethylsilyl triflate in the presence of 4-methyl-2,6-di-*tert*-butylpyridine as base to give **167** in 75% yield. After chloroacetylation (81%) and removal of the silyl group with PTSA in acetic acid (90%), the hydroxy group in **169** was phosphorylated using 1-stearoyl-2-arachidonyl-*sn*-glyceryl phosphoramidite (**170**) followed by oxidation to give **171** in 79% yield. Deprotection of the four phosphate functions was achieved with triethylamine for 14 h at room temperature and the synthesis completed by simultaneous cleavage of the chloroacetate and the levulinoyl (Lev) groups with hydrazinedithiocarbonate.

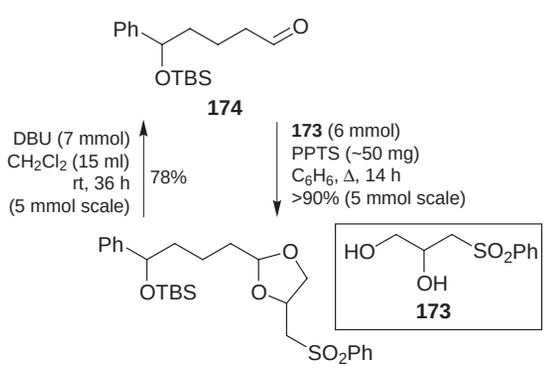
7 Carbonyl protecting groups

Chandrasekhar and Sarkar described a new base-labile protecting group for aldehydes and ketones.[95] Protection is carried



Scheme 74

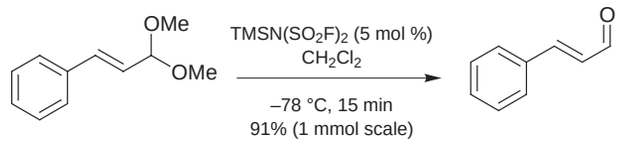
out by the reaction of diol **173** (obtained by dihydroxylation of allyl phenyl sulfone) with a carbonyl compound (*e.g.* **174**) in the presence of PPTS (Scheme 75). Cleavage is accomplished by



Scheme 75

treatment with DBU. TBS ethers, tosyl esters, THP acetals, carboxylic esters and benzoates are well tolerated. A disadvantage to the use of **173** is the introduction of two additional stereogenic centres with the unwelcome proliferation of diastereoisomers.

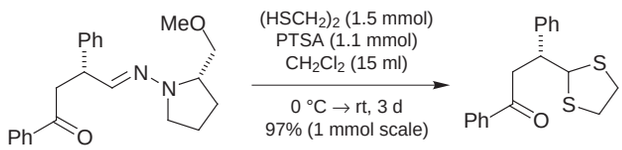
(Trimethylsilyl)bis(fluorosulfuryl)imide [$TMSN(SO_2F)_2$] deprotects acetals to form the corresponding carbonyl compounds (Scheme 76).[96] Dimethyl acetals require only catalytic



Scheme 76

amounts (5 mol%) of the reagent; however, in the case of 1,3-dioxolanes, slightly more than one equivalent has to be used.

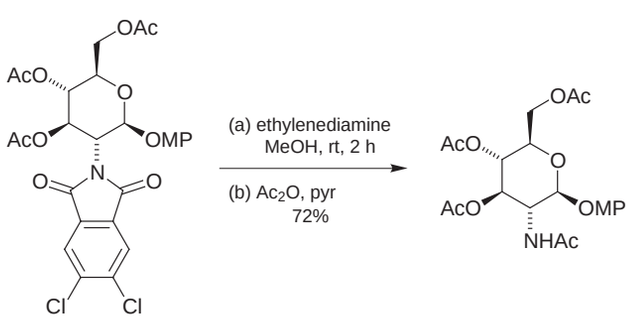
Direct dithioketalisation of *N*,*N*-dialkylhydrazones catalysed by boron trifluoride etherate or PTSA affords the corresponding dithiolanes in nearly quantitative yield (Scheme 77).[97] No racemisation is observed in optically active compounds. Aromatic carbonyl groups remain intact in the reaction conditions but aliphatic ketones undergo thioketalisation.



Scheme 77

8 Amino protecting groups

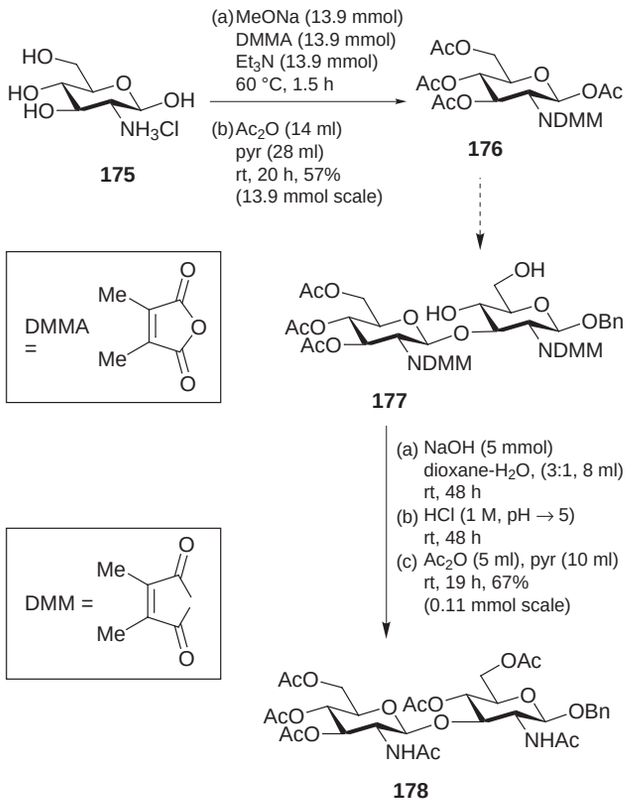
In the search for more labile variants of the phthaloyl group, Fraser-Reid[98] and Schmidt[99] introduced the tetrachlorophthaloyl (TCP) group for the *N*-protection of aminoglycosides. The TCP group is much more labile towards cleavage using ethylenediamine. The 4,5-dichlorophthaloyl (DCPhth) group has recently been evaluated for similar purposes.[100] It too is more labile than the phthaloyl group but any advantages over the TCP group were not established. Levulinoyl and chloroacetyl esters were cleaved without incident but acetate hydrolysis was accompanied by destruction of the DCPhth group in some cases. Scheme 78 exemplifies a DCPhth deprotection.



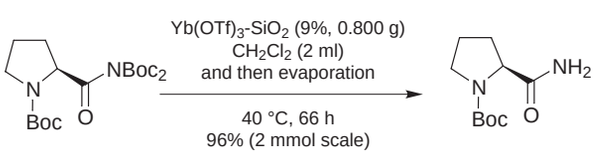
Scheme 78

The dimethylmaleoyl (DMM) group has been investigated as an amino protecting group in oligosaccharide synthesis.[101] The protection was carried out by the reaction of glucosamine hydrochloride **175** (Scheme 79) with sodium methoxide in methanol followed by dimethylmaleic anhydride (DMMA) and triethylamine. Subsequent acetylation gave the protected amino sugar derivative **176** which was then transformed into the disaccharide **177**. The removal of the two DMM groups was accomplished under weakly aqueous basic and then acidic conditions to give **178** after acetylation. The results indicated that the DMM group exhibits neighbouring group participation to enforce β linkage and is stable to acids and non-nucleophilic bases. It makes a useful alternative to other protecting groups like azido or phthalimido.

The chemoselective deprotection of *N*-Boc carboxamides by $Yb(OTf)_2$–SiO_2 can be accomplished under solvent-free conditions.[102] *N*-Boc and *N*-Cbz protected amines as well as acetonide functions survive under these conditions (Scheme 80). Cleavage of the *N*-Boc group under microwave irradiation has also been reported.[103,104]

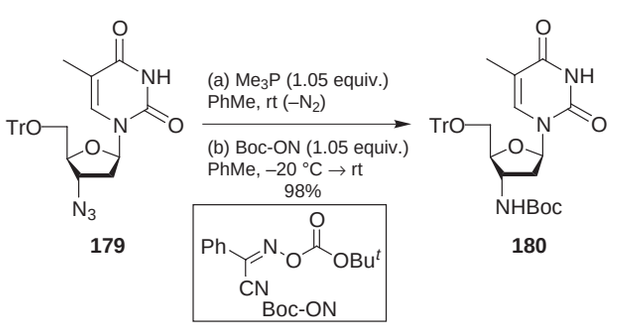


Scheme 79



Scheme 80

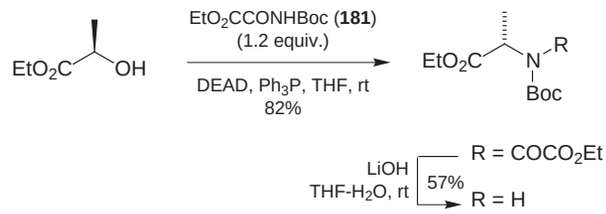
Azides react with trimethylphosphine to give phosphazene intermediates which can be trapped by addition of 2-(*tert*-butoxycarbonyloxyimino)-2-phenylacetonitrile (Boc-ON) at −20 °C to give the corresponding Boc-amines in high yield.[105] Alternatively, mixing all the components together in toluene or THF affords the Boc-amines in similar yield. The ease and efficiency of the process is illustrated by the reductive acylation of azide **179** to give **180** (Scheme 81) in 98% yield.



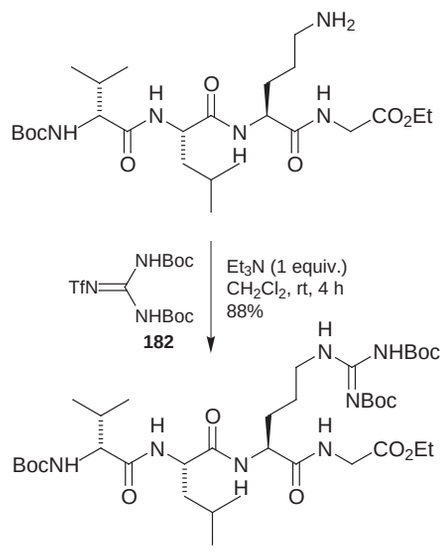
Scheme 81

N-Boc ethyl oxamate (**181**) can be directly coupled with primary and secondary alcohols under Mitsunobu conditions followed by base hydrolysis to give *N*-Boc protected amines.[106] The reaction can be used to convert optically active α-hydroxy esters into *N*-Boc protected α-amino acids (Scheme 82). No racemisation was observed during the hydrolysis step.

N,*N*′-DiBoc-*N*″-triflylguanidine **182** (Scheme 83) and the corresponding *N*,*N*′-dibenzyloxycarbonyl-(*N*,*N*′-diCbz) equivalent are a new class of guanidinylation reagents capable of



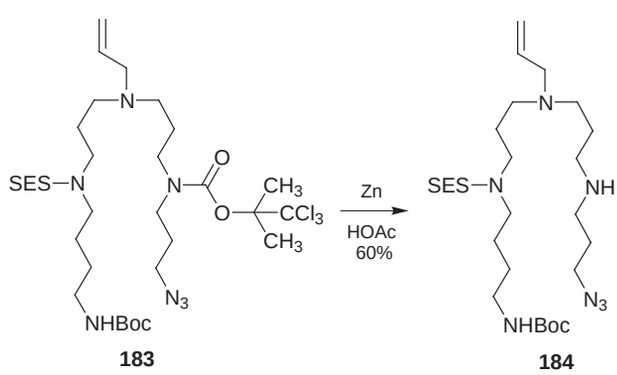
Scheme 82



Scheme 83

reacting with primary and secondary amines to afford the diprotected guanidine derivatives.[107] Difficulties are only observed with highly sterically hindered amines.

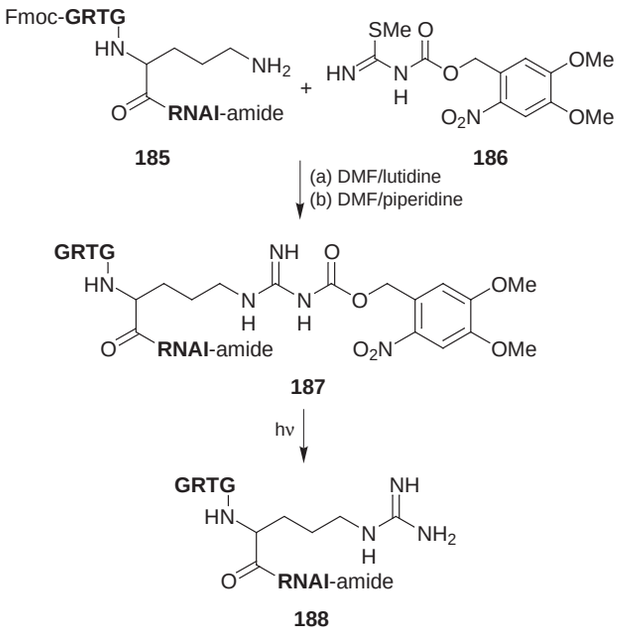
Pentamine derivative **183** (Scheme 84) was prepared and its selective deprotection examined in detail.[108] A noteworthy feature of this study was the cleavage of the 2,2,2-trichloro-*tert*-butoxycarbonyl group[109] with zinc in acetic acid at room temperature to afford the amine **184**.



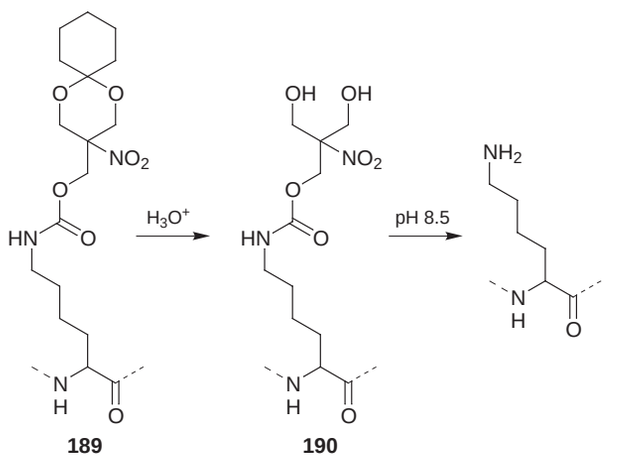
Scheme 84

Studies aimed at the evaluation of caged inhibitors of cAMP-dependent protein kinase entailed the synthesis of the ornithine-containing nonapeptide **188** *via* solid-phase peptide synthesis using the Fmoc protocol (Scheme 85).[110] The novel guanylating agent **186** was used to prepare the protected arginine intermediate **187** and the guanidine subsequently unleashed by photolysis of the nitroveratryl group.

Ramage and co-workers have developed a new relay deprotection strategy for the protection of the N^{ε}-amino group of lysine during solid phase peptide synthesis using the novel transfer active ester coupling technique.[111] The 3-nitro-1,5-dioxaspiro[5,5]undec-3-ylmethoxycarbonyl (PTnm) group in **189** (Scheme 86) is first hydrolysed to the 2,2-bis(hydroxy-



Scheme 85

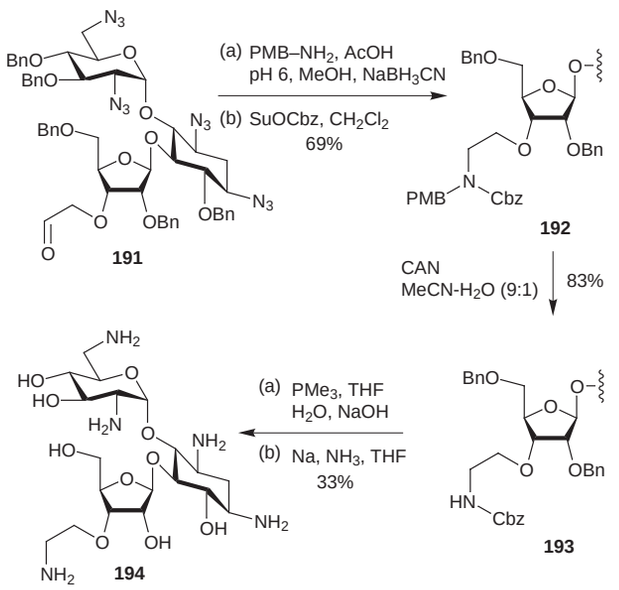


Scheme 86

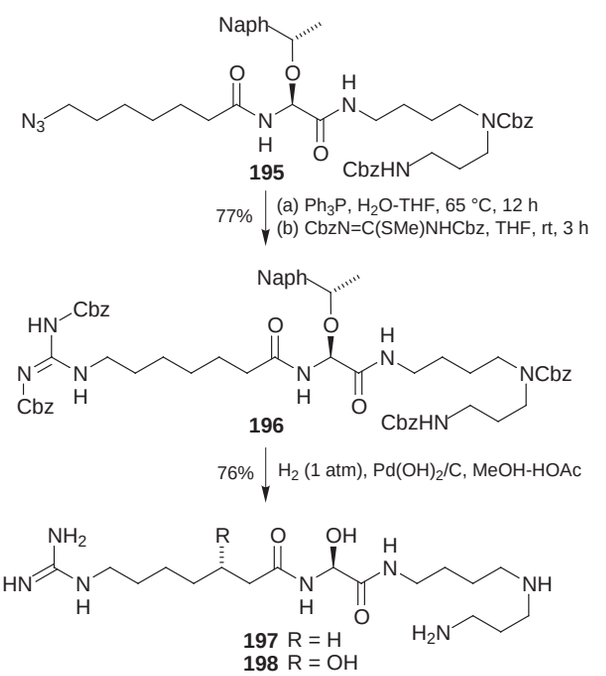
methyl)-2-nitroethyloxycarbonyl (Tnm) group **190** which is then cleaved at pH 8.5 to release the unprotected lysine residue.

A study aimed at elucidating the binding of neomycin-type aminoglycosides to ribosomal RNA required the synthesis of the tricyclic neamine core **194** (Scheme 87) having an aminoethyl linker.[112] Attempts to perform a reductive amination of the aldehyde in structure **191** using benzylamine as the nitrogen source led to an unexpected deprotection problem. During attempted dissolving metal reduction, the *N*-benzyl group was reduced to the inert Birch reduction product. To circumvent this problem, compound **191** was converted to **192** by reductive amination with *p*-methoxylbenzylamine (PMB-NH_2) followed by carbamoylation with *N*-[(benzyloxycarbonyl)-oxy]succinimide (SuOCbz). The PMB group was then oxidatively cleaved with CAN to afford **193**. The sequence was completed by reduction of the four azide functions to the corresponding amines followed by reductive cleavage of the five benzyl ethers and the Cbz group to give **194** in 33% yield.

(−)-Spergualin (**198**, Scheme 88) is an antitumour antibiotic isolated from *Bacillus laterosporus.* Recently a hemisynthetic analogue, (−)-15-deoxyspergualin (**197**) received marketing approval in Japan for the treatment of corticoresistant acute renal graft rejection. A French group[113] have reported a synthesis of **197** which benefits from a comprehensive deprotection



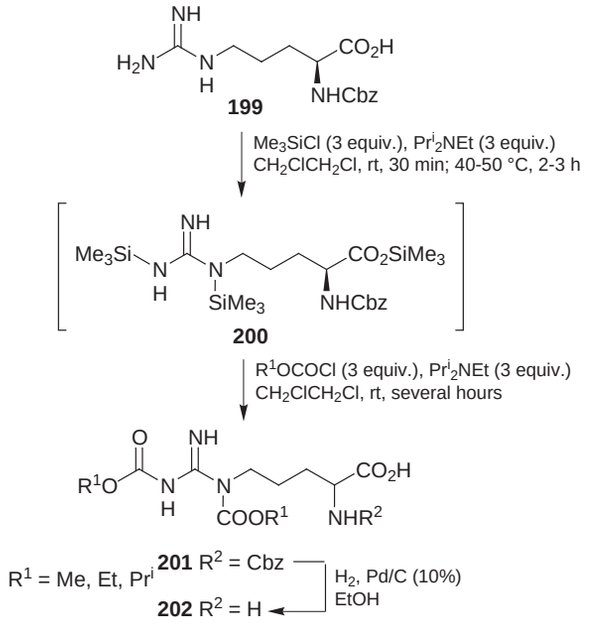
Scheme 87



Scheme 88

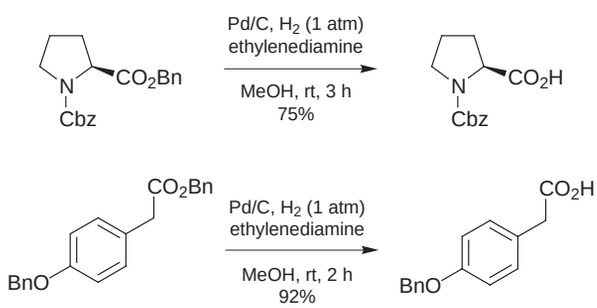
of five *O*-benzyl bonds in the final step. First, however, the unusual *N*-acyl aminal functionality in intermediate **195** was obtained in homochiral form by chromatographic resolution of a mixture of diastereoisomeric ethers derived from (*S*)-(−)-α-methylnaphthalene-2-methanol. After reduction of the azide function with triphenylphosphine, the Cbz-protected guanidine residue was introduced with *N*,*N*′-bis(benzyloxycarbonyl)-*S*-methylisothiourea.[114] Subjection of the product **196** to hydrogenolysis with Pearlman's catalyst then removed the four Cbz groups and the naphthyl ether to release the desired product **197** in 76% yield.

The use of the *N*-trimethylsilyl protected L-arginine derivative **200** (Scheme 89) in the preparation of N^{δ},N^{ω}-bis(alkoxycarbonyl)-L-arginines **202** (potential inhibitors of nitric oxide synthase) has been reported.[115] Silylation of N^{α}-Cbz (benzyloxycarbonyl) protected arginine **199** gives **200** which, without isolation, is treated with alkyl chloroformates. The resulting bis(alkoxycarbonyl) derivative **201** is then subjected to hydrogenolysis to remove the Cbz group and affords the target arginines **202**.



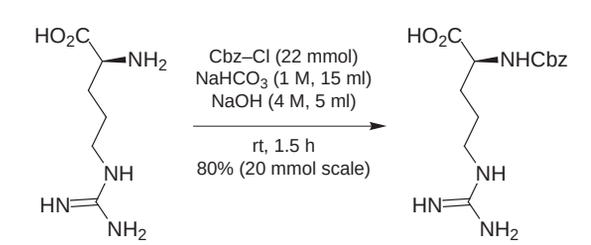
Scheme 89

Treatment of 5% Pd/C with an excess of ethylenediamine in MeOH for 48 h results in the formation of a bound 1 : 1 complex which is isolable.[116] The new catalyst displays usefully attenuated activity: olefins, acetylenes, nitro groups, azido groups and benzyl esters are reduced without harm to some Cbz groups or benzyl ethers (Scheme 90). The activity of the catalyst towards the Cbz group is strongly solvent dependent. Hydrogenolysis occurs in MeOH but not in THF with Cbz-protected aliphatic amines but aromatic amines are released even in THF. Phenolic benzyl ethers and PMB ethers are also inert towards hydrogenolysis with the new catalyst.



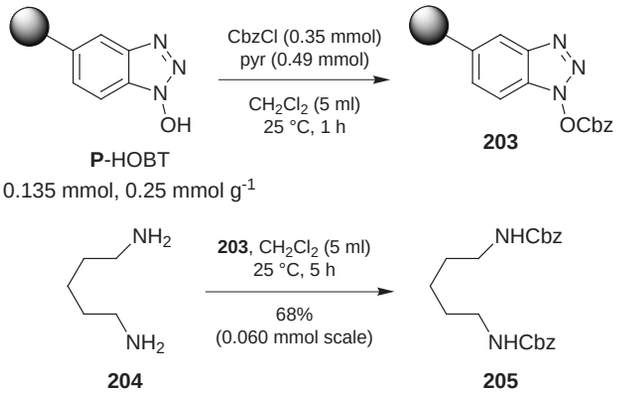
Scheme 90

Selective protection of L-arginine at the N^{α}-position (Scheme 91) was achieved using benzyl chloroformate (Cbz-Cl) in a $NaHCO_3$–NaOH buffered solution (pH 9–11).[117] If the reaction mixture was not buffered, a substantial amount of bis- and tris-Cbz derivatives was formed.



Scheme 91

Polymer-bound 1-hydroxybenzotriazole (P-HOBT) can be used for the protection of primary and secondary amines as the Cbz, Fmoc and Boc derivatives (Scheme 92).[118] The polymer was prepared from Bio-Rad SM-2 dried macroporous beads

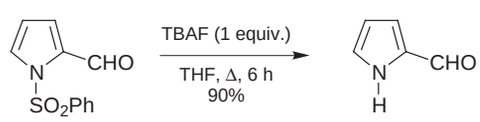


Scheme 92

(polystyrene–divinylbenzene copolymer resin, 100–200 mesh, MW cut-off 2000). After suspending in CH_2Cl_2, P-HOBT was treated with Cbz-Cl, Fmoc-Cl or $(Boc)_2O$ to give the immobilised carbonate **203**. The resulting polymer was then collected by filtration, re-suspended in CH_2Cl_2 and treated with an amine (*e.g.* **204**). The pure product **205** was obtained simply by filtering off the polymer and evaporating the filtrate. The protection can be also done in aqueous solutions for water soluble amines such as amino acids.

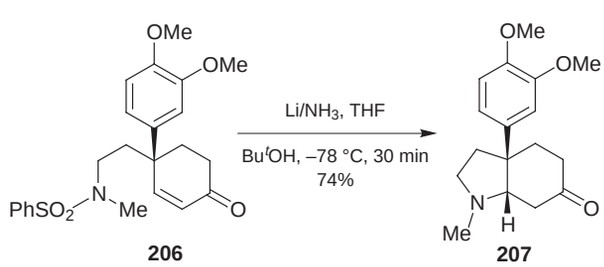
Amino acids can be protected[119] as their Fmoc derivatives by treatment with *N*-methyl-*N*-(trimethylsilyl)trifluoroacetamide (MSTFA) followed by Fmoc-*N*-succinimidyl carbonate (Fmoc-OSu).

Japanese workers[120] have deprotected *N*-methylsulfonyl and *N*-arylsulfonyl heteroaromatics with TBAF (1 equiv.) in refluxing THF (Scheme 93). It is not clear whether the TBAF used was anhydrous so the reaction may simply be a hydrolysis reaction catalysed by the basic fluoride ion.



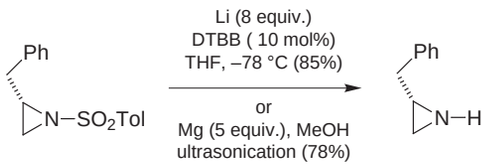
Scheme 93

The reductive cleavage of benzenesulfonamides is a well established tactic for the deprotection of secondary amines. However, the transformation depicted in Scheme 94, representing the last step in a clever synthesis of mesembrine (**207**), caught our eye because the benzenesulfonamide in **206** was cleaved under dissolving metal reduction conditions without detriment to either the aromatic ring or the enone.[121] Indeed, the survival of the enone was essential to the success of the reaction so that the amine released could undergo conjugate addition to the enone to generate the pyrrolidine ring.



Scheme 94

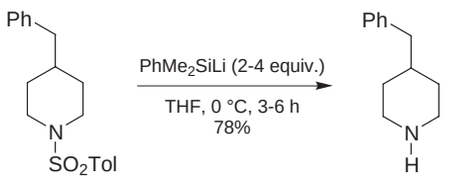
The deprotection of three different chiral *N*-sulfonyl aziridines was studied[122] under different desulfonylation conditions including various metals in liquid ammonia, SmI_2 in THF, and photodesulfonylation. The two best methods (Scheme 95) involved treatment of the substrate with excess Li powder in



Scheme 95

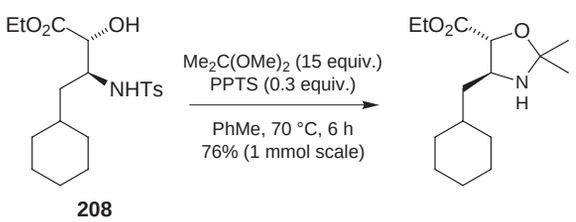
THF in the presence of a catalytic amount of 4,4′-di-*tert*-butylbiphenyl (DTBB) or magnesium metal in methanol with continuous ultrasonication.

The toluene-*p*-sulfonamides of secondary amines and indoles are cleaved by treatment with phenyldimethylsilyllithium to give the secondary amines (Scheme 96).[123] Aziridine toluene-*p*-sulfonamides are anomalous in that they undergo ring opening.



Scheme 96

Fortuitous cleavage of an *N*-tosyl group was noted during the mild acid-catalysed acetonation of the β-tosylamino-α-hydroxy ester **208** (Scheme 97).[124] The reaction was shown to be general (4 examples). Acetonation without *N*-tosyl cleavage occurred in substrates devoid of the neighbouring ester function.

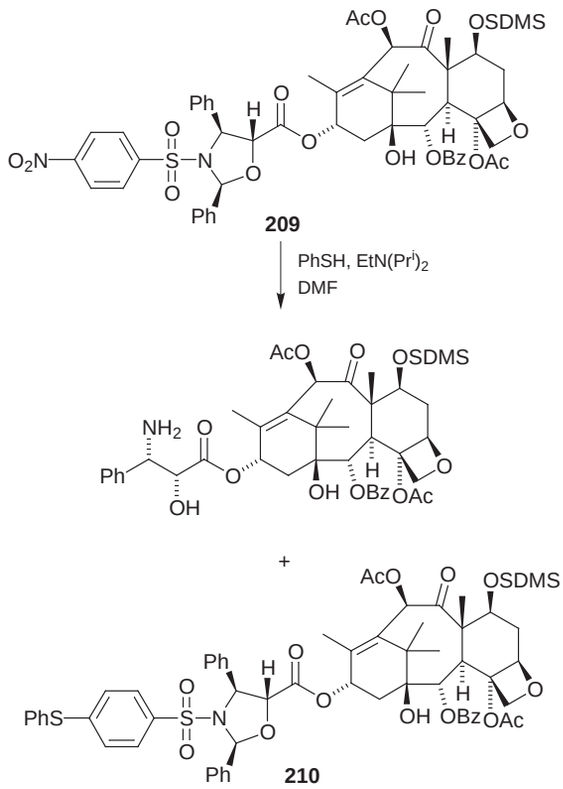


208

Scheme 97

In 1995 Fukuyama and co-workers[125] reported that phenylthiolate attacks the sulfonamide carbon of *p*-nitrobenzenesulfonamides to give Meisenheimer complexes which decompose with expulsion of the free amine. Wuts and Northuis[126] discovered that phenylthiolate addition to *p*-nitrobenzenesulfonamides is not always regioselective. For example, in the case of Taxol™ derivative **209** (Scheme 98), up to 9% of the product **210** derived from addition to the nitro carbon was observed. This diminished regioselectivity is not a steric effect but it seems to be most pronounced in the sulfonamides of cyclic amines. By contrast, *o*-nitrobenzenesulfonamides do not suffer the same problem.

A programme aimed at the synthesis of spider and wasp polyamine toxins has focused on an orthogonal deprotection–transprotection regime.[127] A previous study based on a pentamine bearing Boc, benzyl, trifluoroacetyl, pyridine-2-sulfonyl and diallyl as *N*-protecting groups foundered because debenzylation was impeded by neighbouring bulky groups and because it interfered with the deprotection of the allyl moiety. The present study is based on the use of Boc, phthalimido, allyl, pyridine-2-sulfonyl and 2-trimethylsilylethanesulfonyl (SES) groups. As can be seen from Scheme 99, each of the protecting groups could be removed selectively in good yield including the Boc group which was cleaved with trifluoroacetic acid in dichloromethane at room temperature for 30 min in 80% yield. Another advantage of the new protecting group regime is a more efficient synthesis of the fully protected pentamine derivative **211**.

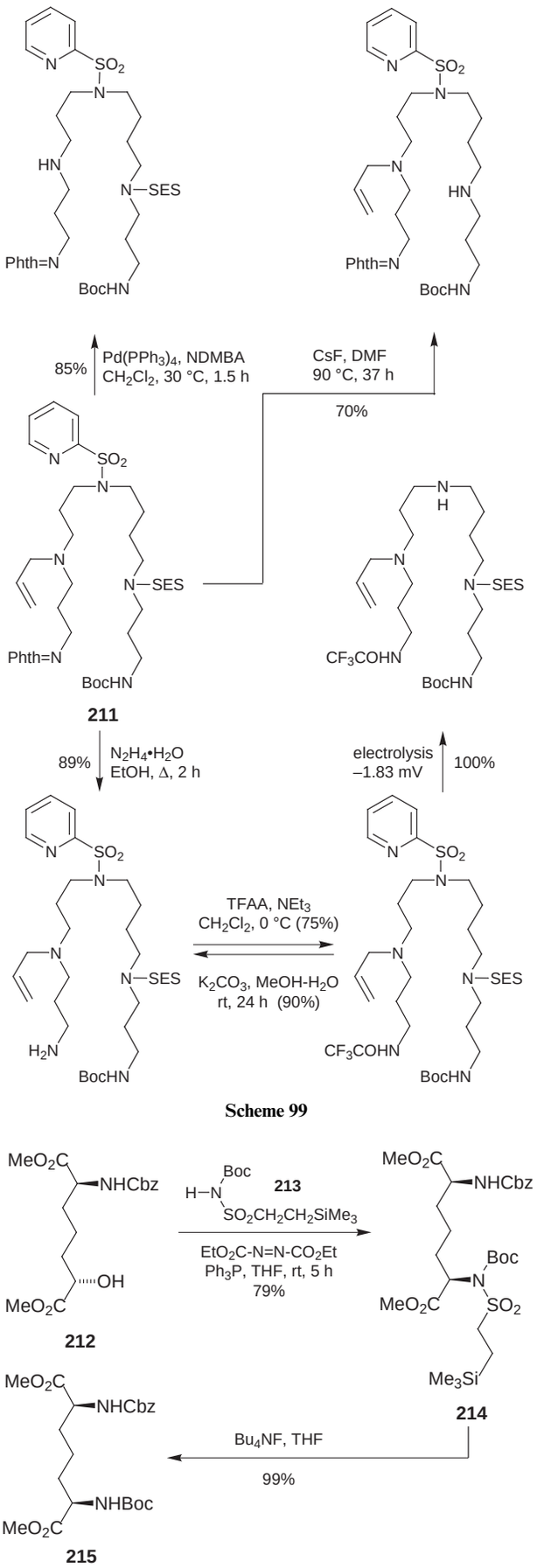


Scheme 98

meso-Diaminopimelic acid (DAP) is the key cross-linking amino acid in peptidoglycan of cell walls in Gram-negative bacteria and it is the biosynthetic precursor of L-lysine, which is a structural component of cell walls in Gram-positive bacteria. In a recent synthesis of differentially protected DAP derivatives (Scheme 100),[128] a Boc-protected amino group was introduced by Mitsunobu substitution of the hydroxy group in **212** using *tert*-butyl *N*-{[2-(trimethylsilyl)ethyl]sulfonyl}carbamate (**213**).[129] The [2-(trimethylsilyl)ethyl]sulfonyl group in **214** was then cleaved with tetrabutylammonium fluoride to give **215** in nearly quantitative yield.

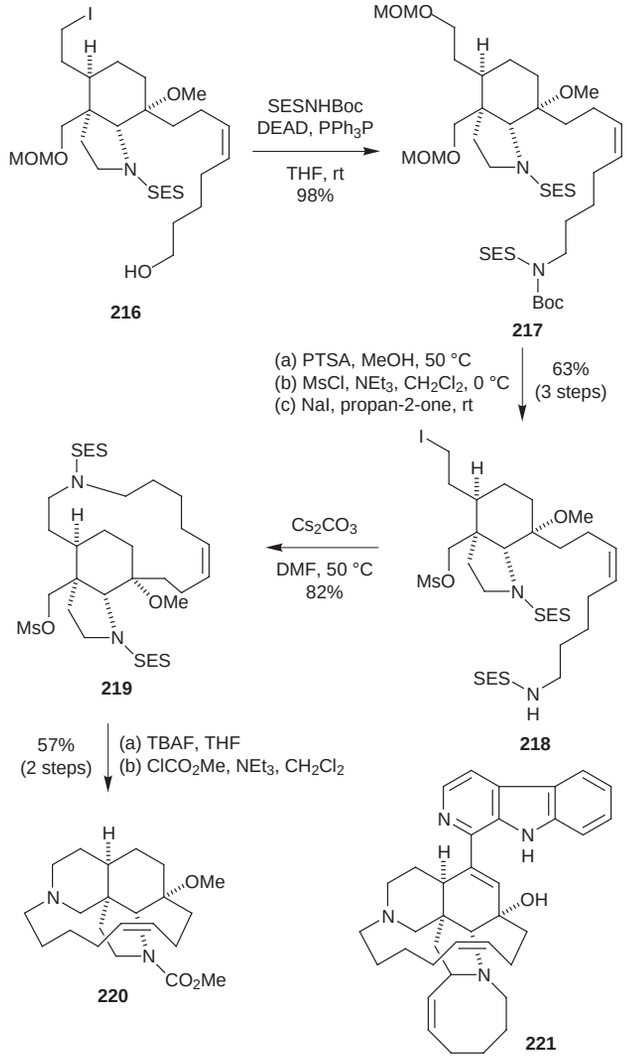
The 2-(trimethylsilyl)ethylsulfonyl (SES) group played a key role as amine protector and activator towards *N*-alkylation in a recent synthesis[130] of the ABCE ring system of manzamine A (**221**, Scheme 101). Thus nucleophilic displacement of the primary hydroxy group in **216** with the ammonia equivalent SES-NHBoc under Mitsunobu conditions returned the protected amine derivative **217** in 98% yield. Simultaneous cleavage of both MOM ethers and the Boc group using PTSA gave a diol which was converted to **218** in two further steps. Cyclisation occurred *via* *N*-alkylation of the primary SES-amide to give macrocycle **219** in 82% yield. Finally, removal of both SES groups with TBAF followed by a second intramolecular *N*-alkylation generated ring A in the target ABCE fragment **220**.

During their synthesis of diuridine monophosphates, Sekine and co-workers[131] tried to *O*-alkylate the protected nucleoside **222** (Scheme 102) by treating it with sodium hydride in THF followed by ethyl bromoacetate but the reaction resulted in formation of a considerable amount of N^3-alkylated product giving the desired *O*-alkyl derivative only in 46% yield. To avoid the N^3-alkylation **222** was converted into the *N*-triphenylmethylsulfenyl (TrS) protected uridine derivative **223** using triphenylmethylsulfenyl chloride (TrSCl) under phase transfer catalysis conditions. *O*-Alkylation of **223** worked better giving the desired product **224** in 78% yield. After replacing the 1,1,3,3-tetraisopropyldisiloxane-1,3-diyl (TIPDS) protecting group with the dimethoxytrityl (DMTr) group, the TrS group was removed in 70% yield by treatment with tributyltin hydride

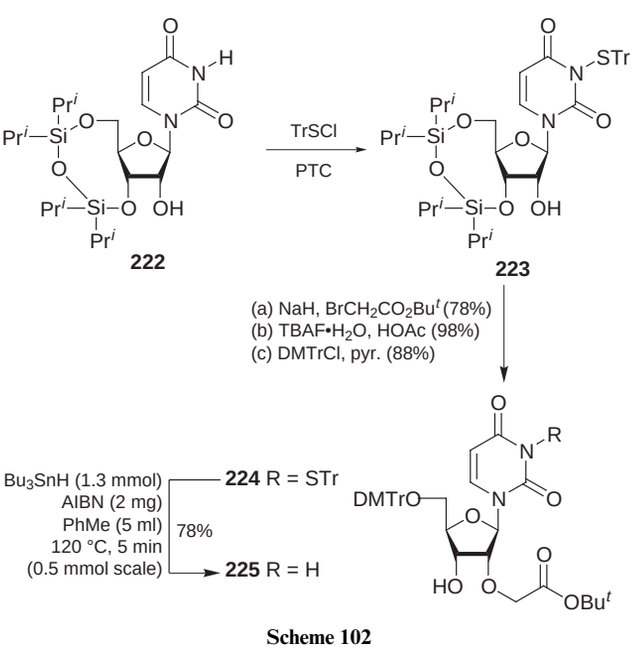


Scheme 99

Scheme 100



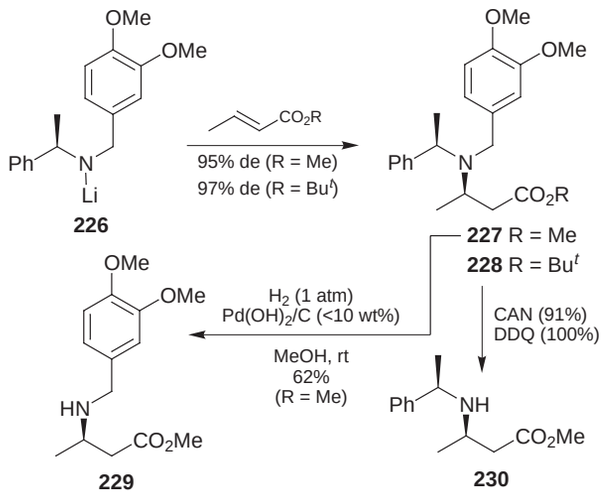
Scheme 101



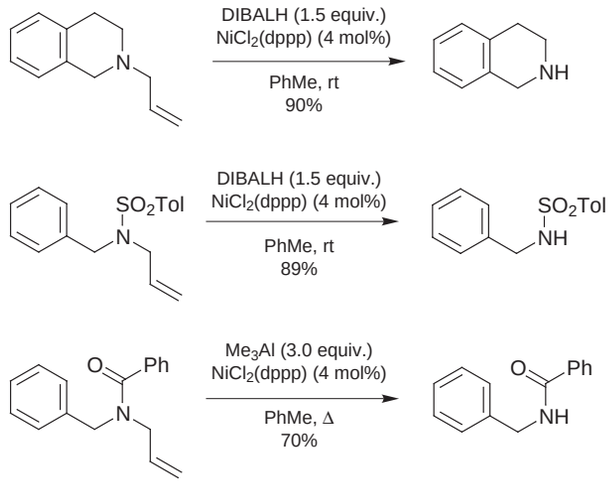
Scheme 102

in the presence of a catalytic amount of azobisisobutyronitrile (AIBN) to give **225** in 78% yield.

Davies and Ichihara showed that lithium (α-methylbenzyl)-(3,4-dimethoxybenzyl)amide (**226**, Scheme 103) can be used as an efficient differentially protected chiral ammonia equivalent in the asymmetric synthesis of β-amino acid derivatives.[132] Conjugate addition of lithium amide **226** to methyl and *tert*-butyl crotonate esters forms adducts **227** and **228** with excel-



Scheme 103



Scheme 104

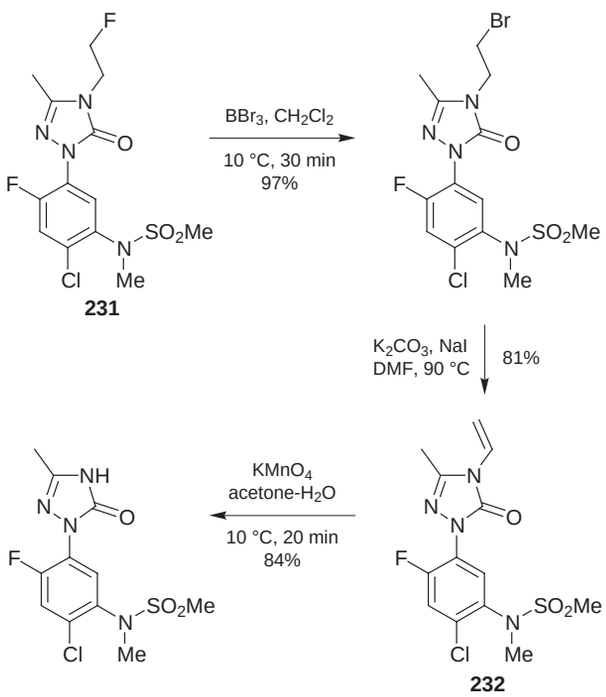
lent diastereoselectivity. Selective cleavage of the α-methylbenzyl group was accomplished using Pearlman's catalyst [$Pd(OH)_2$/C] to give the β-amino ester derivative **229** in 62% yield. Higher catalyst load and higher hydrogen pressure were required to remove both benzyl groups. However, selective removal of the 3,4-dimethoxybenzyl group could also be accomplished under oxidative conditions. Thus treatment of the *tert*-butyl ester **228** with DDQ in CH_2Cl_2–H_2O (5:1) at rt overnight afforded **230** in quantitative yield. Alternatively, treatment of **228** with CAN in MeCN–H_2O (5:1) gave **230** in 91% yield.

The *o*-nitrobenzyl group has been evaluated as a photocleavable protector for heterocyclic nitrogen compounds such as indoles, benzimidazoles and 6-chlorouracil.[133] The *o*-nitrobenzyl group was introduced by *N*-alkylation of the sodium or lithium derivative of the heterocycle (NaH or LiH) in DMF with *o*-nitrobenzyl bromide. Photocleavage was accomplished by irradiating dioxane solutions of the substrate at >320 nm. For indoles, the deprotection works best when the indole nucleus contains an electron withdrawing group (CHO, CO_2Et, CN).

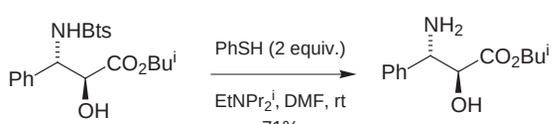
The easy deprotection of allyl ethers using Ni(0)-catalysed hydroalumination (*vide supra*) has been extended to *N*-allyl derivatives (Scheme 104).[134] Thus *N*-allylamines and *N*-allyl sulfonamides are cleaved on treatment with DIBAL-H and a catalytic amount of $NiCl_2$(dppp) in toluene at room temperature. However, *N*-allylamides undergo reduction of the carbonyl under these conditions but deallylation does occur using trimethylaluminium in refluxing toluene. Unfortunately, deprotection of *N*-allyl carbamates gives a complex mixture.

An *N*-protecting group robust enough to withstand strongly acidic conditions, aromatic nitration, catalytic hydrogenation and alkylation under basic conditions was required for the synthesis of aryl triazolinones which are inhibitors of the plant enzyme protoporphyrinogen oxidase.[135] The 2-fluoroethyl group was stable to all the required conditions but its removal required a three-step sequence depicted in Scheme 105. First substitution of the fluorine in **231** by bromine was accomplished with boron tribromide. After dehydrobromination under basic conditions, the *N*-vinyl amide in **232** was oxidatively cleaved with potassium permanganate. The overall yield for the three-step sequence was 68%.

Benzothiazolesulfonamides can be cleaved to the corresponding primary and secondary amines under mild basic conditions using benzenethiol and a base (potassium *tert*-butoxide or diisopropylethylamine) in DMF (Scheme 106).[136] The method complements the reductive conditions developed by Vedejs *et al.*[137] (Zn/HOAc–EtOH or Al–Hg/ether–H_2O).



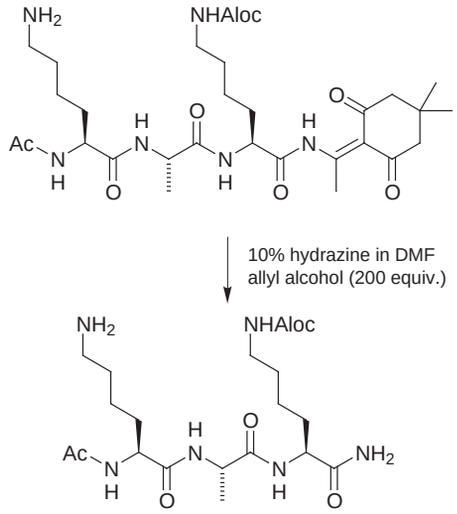
Scheme 105



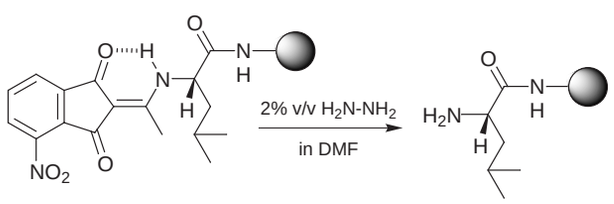
Scheme 106

A troublesome competing reaction in the hydrazinolysis of 1-(4,4-dimethyl-2,6-dioxocyclohexylidene)ethyl (Dde) protected peptides containing Aloc groups is the reduction of the alkene moiety of the Aloc group to give an *n*-propyl carbamate.[138] The competing reduction can be suppressed by conducting the hydrazinolysis in the presence of excess allyl alcohol (Scheme 107).

2-Acetyl-4-nitroindane-1,3-dione reacts with primary amines to form *N*-1-(4-nitro-1,3-dioxoindan-2-ylidene)ethyl (Nde) derivatives as stable yellow amorphous solids in good yields.[139] The Nde protecting group displays good stability towards the reagents commonly employed in solid phase peptide synthesis and its deprotection with 2% hydrazine in DMF (Scheme 108) can be easily monitored spectrophotometrically or visually. The value of the Nde group has been demonstrated in syntheses of both linear peptides and a peptide-polyamine conjugate.

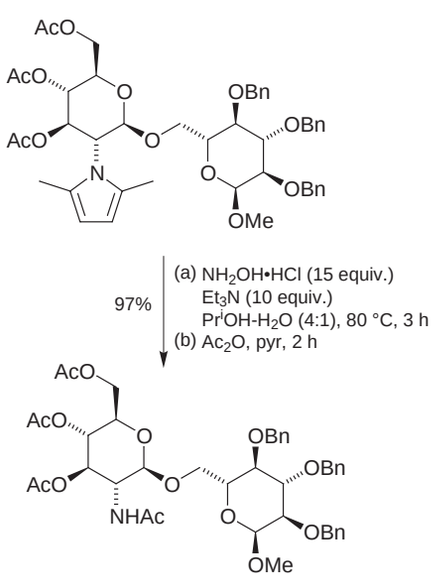


Scheme 107



Scheme 108

The 2,5-dimethylpyrrole developed over 15 years ago for the protection of primary amines[140] has been applied to the protection of 2-amino-2-deoxyglycosides.[141] It can be cleaved by treatment with hydroxylamine hydrochloride (Scheme 109) but it is stable to conditions used for removing an *N*-phthalimido group (hydrazine hydrate in refluxing EtOH). The dimethylpyrrole protecting group is easily installed by treating a primary amine with hexane-2,5-dione in the presence of triethylamine in MeOH. Although the dimethylpyrrole group is rather acid labile, it survives glycosylation using a trichloroacetimido donor and TMSOTf.



Scheme 109

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