Protecting groups

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REVIEW PERKIN 1

Covering: 1997
Previous review: *Contemp. Org. Synth.*, 1997, 4, 454

1 Introduction

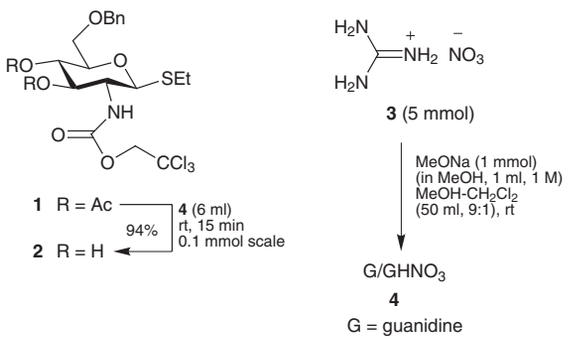
The following review covers new developments in protecting group methodology which appeared in 1997. As with our previous annual review, our coverage is a personal selection of methods which we deemed interesting or useful. Many of the references were selected through a Science Citation Index search based on the root words block, protect and cleavage; however, casual reading unearthed many facets of protecting group chemistry which are beyond the pale of a typical keyword search. Inevitably our casual reading omits whole areas in which we lack expertise and so we cannot claim comprehensive coverage of the literature. The review is organised according to the functional groups protected with emphasis being placed on deprotection conditions. A separate annual review on combinatorial chemistry appeared earlier this year which incorporates the related subject of solid phase linker chemistry.

2 Hydroxy protecting groups

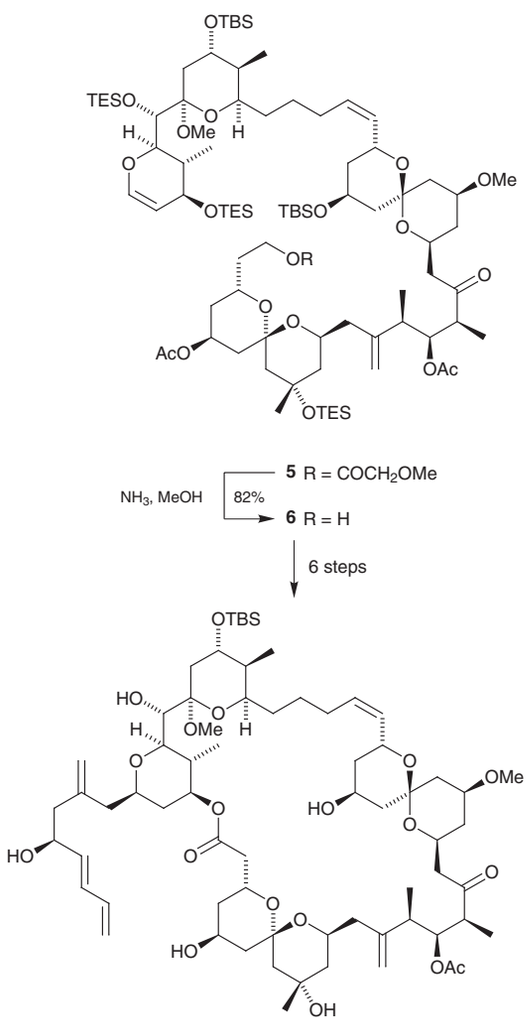
2.1 Esters

Attempts to use standard basic reagents to cleave the *O*-acetyl groups in aminosugar derivative **1** (*e.g.* MeONa in MeOH; NH_3 in MeOH; K_2CO_3 in MeOH–H_2O) also affected the *N*-Troc (2,2,2-trichloroethoxycarbonyl) group (Scheme 1).[1] The goal was finally achieved with a MeOH–CH_2Cl_2 solution of a mixture of guanidine and guanidine nitrate (**4**) [obtained by the reaction of guanidine nitrate (**3**) with 0.2 equivalents of sodium methoxide]. Both *S*- and *O*-glycosides are stable under the reaction conditions as are some standard protecting groups like NPhth (*N*-phthalimido), benzylidene and isopropylidene acetals, BnO, and Ph_2Bu^tSiO but tetrachlorophthalimido, *N*-Fmoc, and *O*-Troc protecting groups are attacked by the guanidine–guanidine nitrate reagent.

In the closing stages of an impressive synthesis of the marine antitumour agent altohyrtin C (**7**, Scheme 2), Evans and coworkers[2] exploited the higher base lability of methoxyacetates to achieve a selective deprotection in the presence of two secondary acetate functions in intermediate **5**.

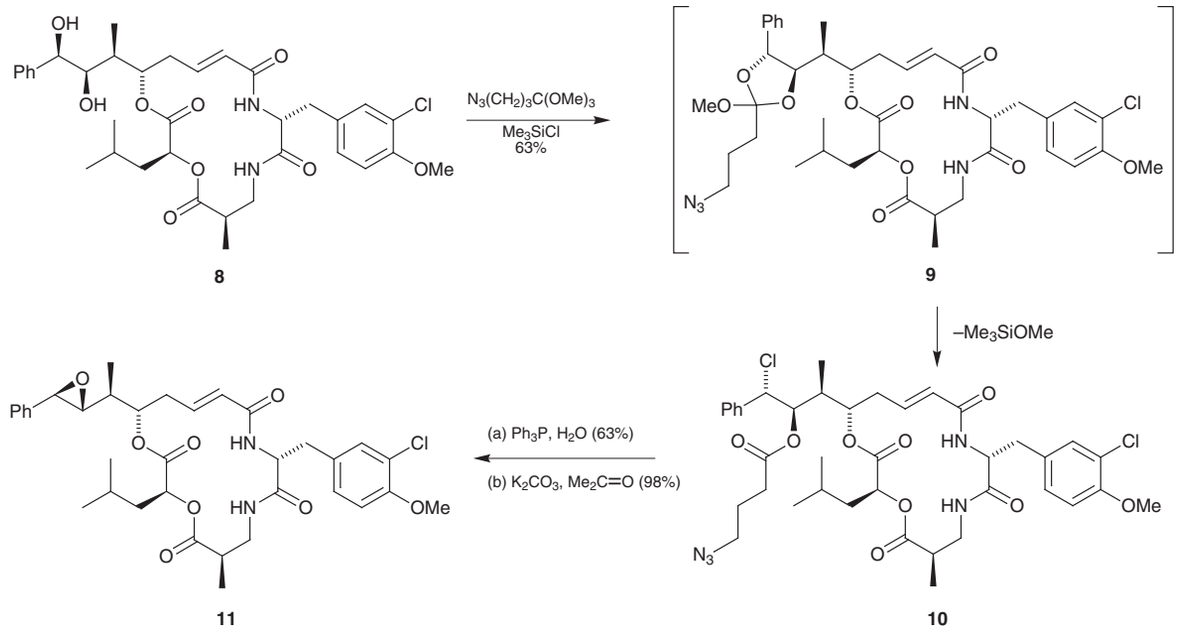


Scheme 1



Scheme 2

The penultimate step in a recent synthesis of the antitumour macrolides cryptophycin 1 (**11**) required a mild method for the introduction of the epoxide ring in the side chain[3] (Scheme 3).

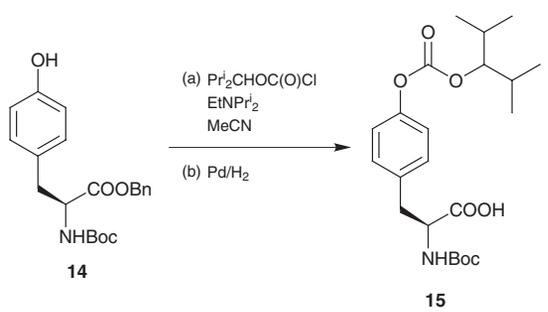


Scheme 3

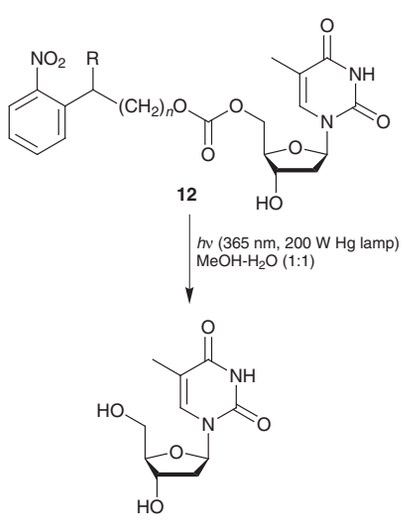
A variant of a direct method for the conversion of diols to epoxides developed by Sharpless[4] was cleverly adapted to the case at hand. Thus diol **8** was treated with the 4-azido-1,1,1-trimethoxybutane in the presence of chlorotrimethylsilane to give the cyclic orthoester **9** which decomposed under the reaction conditions with loss of Me_3SiOMe to give the chlorohydrin ester **10** (inversion). Selective reduction of the azide under Staudinger conditions produced an intermediate amino ester which underwent intramolecular lactamisation to release a hydroxy group. In the last step, the resultant chlorohydrin was converted to the cryptophycin 1 (**11**) on treatment with base.

The Hasan group[5] tested *o*-nitrobenzyloxycarbonyl (NBOC) and related groups as photolabile protectors of nucleoside 5′-hydroxy groups (Scheme 4). Generally the rates of photoremoval of 2-(*o*-nitrophenyl)ethoxycarbonyl (NPEOC) derivatives (**12**, $n = 1$) were faster than the corresponding NBOC-protected compounds (**12**, $n = 0$). Also substitution at the α-carbon had an enhancing effect. The most reactive compound had a methyl group and ethyl chain ($t_{1/2} = 0.66$ min) and the order of reactivity of **12** was found to be: R = Me, $n = 1$ > R = *o*-nitrophenyl, $n = 1$ > R = *o*-nitrophenyl, $n = 0$.

Unden and co-workers reported that the 2,4-dimethylpentan-3-yloxycarbonyl (Doc) group can be used for protecting the hydroxy group of tyrosine.[6] The protection is achieved in the reaction of tyrosine derivative **14** with 2,4-dimethylpentan-3-yl chloroformate and ethyldiisopropylamine (Scheme 5). The Doc group is 1000-fold more stable towards nucleophilic piperidine than the commonly used 2-bromobenzyloxycarbonyl (2-BrCbz) group and it is completely cleaved by hydrogen fluoride. However the 2-BrCbz group is superior in terms of acid stability (the loss of protection after 20 min in 50% trifluoroacetic acid–CH_2Cl_2 is 0.01% for 2-BrCbz group and 0.04% for Doc group).



Scheme 5

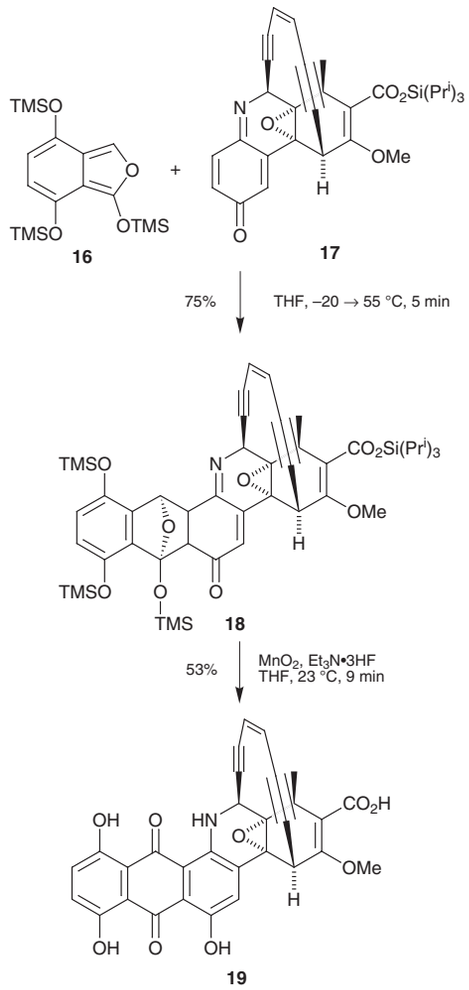


Scheme 4

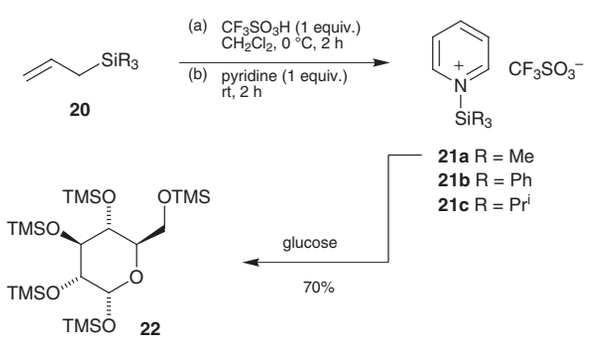
2.2 Silyl ethers

In the final steps of an elegant synthesis of dynemicin A (**19**, Scheme 6), Myers and co-workers[7] needed to deprotect the hydroquinone in Diels–Alder adduct **18** before cleavage of the sensitive bicyclic acetal followed by *in situ* oxidation to the anthraquinone in the target. This required the use of an isobenzofuran (**16**) with highly labile protecting groups for which the trimethylsilyl ether was ideally suited. Thus, brief treatment of Diels–Alder adduct **18** with excess activated manganese dioxide and triethylamine trihydrofluoride (1:1 molar ratio, *ca.* 70 equiv.) led to cleavage of the three trimethylsilyl ethers together with the triisopropylsilyl ester and the resultant product oxidised *in situ* to afford dynemicin A (**19**) in 53% yield.

N-Silylpyridinium triflates are powerful silylating agents which have been used in the preparation of enol silanes and for the silylation of carboxylic acids.[8] Olah and Klumpp report a new method for their preparation as well as their use in the silylation of alcohols[9] (Scheme 7). The salts **21a**–**c** were prepared by reaction of an allylsilane **20** with triflic acid followed



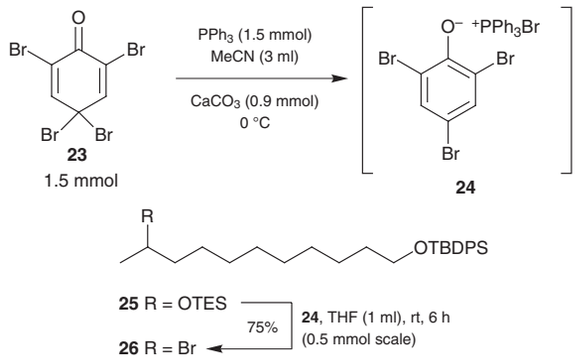
Scheme 6



Scheme 7

by addition of pyridine. They were obtained in nearly quantitative yield as crystalline solids which were stable indefinitely at room temperature in an inert atmosphere. However, the reagents are more conveniently prepared *in situ* and used immediately as silylation reagents. No aqueous workup is required to isolate the silyl ethers: the product mixture is simply diluted with pentane to complete the precipitation of the pyridinium triflate. Filtration of the product through a plug of silica gel returns the pure silyl ether.

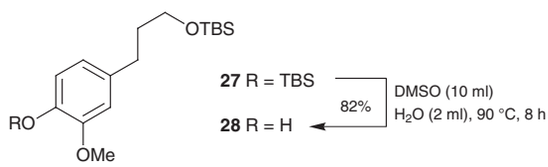
Phosphonium salt **24** (formed in the reaction of 2,4,4,6-tetrabromocyclohexa-2,5-dienone **23** with triphenylphosphine, Scheme 8) has been reported recently to transform primary and secondary alcohols and THP ethers into the corresponding bromides.[10] It can also directly convert[11] silyl ethers (*e.g.* **25**) into bromides. The reagent **24** is not isolated but is immediately treated with the corresponding silyl ether. The reaction works well with trimethylsilyl (TMS), triethylsilyl (TES) and *tert*-butyldimethylsilyl (TBS) ethers but is very slow with *tert*-



Scheme 8

butyldiphenylsilyl (TBDPS) and triisopropylsilyl (TIPS) ethers. This allows the selective bromination of **25** to give **26** in 75% yield.

Maiti and Roy[12] reported a selective method for deprotection of primary allylic, benzylic, homoallylic and aryl TBS ethers using aqueous DMSO at 90 °C (Scheme 9). All other TBS-protected groups as well as THP ethers, methylenedioxy ethers, benzyl ethers, methyl ethers and aldehyde functionalities remain unaffected. Also a benzyl TBS ether can be selectively deprotected in the presence of an aryl TBS ether.

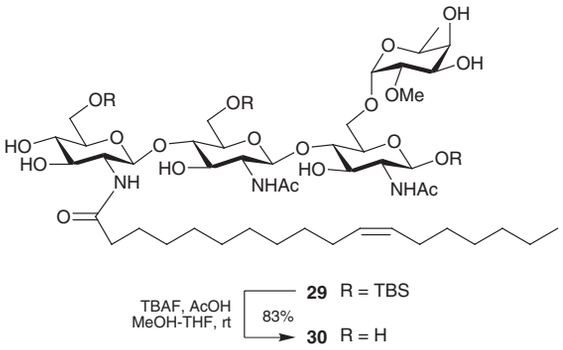


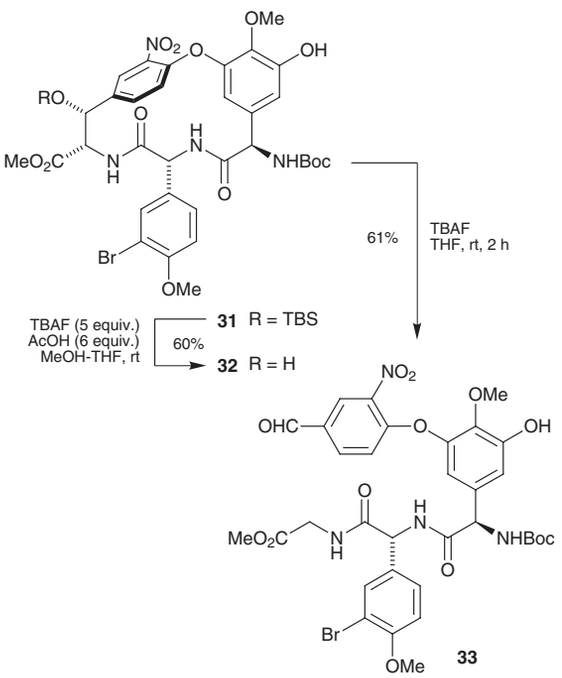
Scheme 9

Full details of Fraser-Reid's synthesis of the bacterial nodulation factor **30** NodRf-III (C18:2, MeFuc) have been published.[13] The final step of the synthesis required removal of three TBS ethers, one of which was protecting the anomeric position in **29** (Scheme 10). Anomeric deprotections using TBAF are complicated by Lobry de Bruyn–Alberda van Eckenstein rearrangements and other base catalysed degradations and mildly acidic methods (*e.g.* PPTS in MeOH at 55 °C) were fruitless even after extended reaction times. However buffering the TBAF with AcOH gave the desired target **30** in 83% yield. The problems associated with the basicity of fluoride are underscored by another recent example taken from Boger's synthesis of the vancomycin CD and DE ring systems.[14] Attempted removal of the TBS group from **31** was accompanied by retro-aldolisation of the resultant β-hydroxyphenylalanine subunit to give **33** in 61% yield. Here again, buffering the reaction mixture with AcOH suppressed the unwanted side reaction and gave the desired deprotected product **32** in 60% yield.

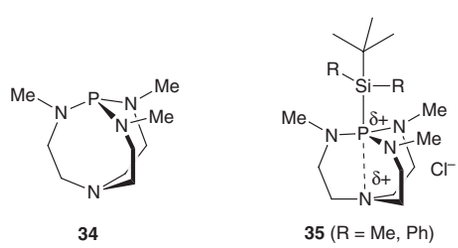
Full details of the use of a non-ionic superbase **34** (Scheme 11) as a catalyst for the silylation of alcohols using *tert*-butyldimethylsilyl chloride or *tert*-butyldiphenylsilyl chloride has been reported.[15] The reactions are carried out in acetonitrile at 24–40 °C though DMF at 24–80 °C may be needed for hindered systems. The catalyst, which is commercially available from Strem, is compatible with aldehydes, ketones, esters, nitriles and skipped dienes. The catalyst is expensive but it can be easily recycled. The catalytic effect of **34** was attributed to the formation of a transannular stabilised loose ion pair **35**.

A new synthesis of protected phenolic ethers has been reported[16] in which Ni(cyclooctadiene)$_2$ and 1,1′-bis(diphenylphosphino)ferrocene mediates the reaction of electron deficient aryl halides (*e.g.* **36a**,**b**) with sodium *tert*-butyldimethylsiloxide (Scheme 12). The reaction fails with the corresponding trimethylsilyl, triethylsilyl and triphenylsilyl derivatives. *tert*-Butyl ethers of phenols can also be prepared using sodium *tert*-butoxide.

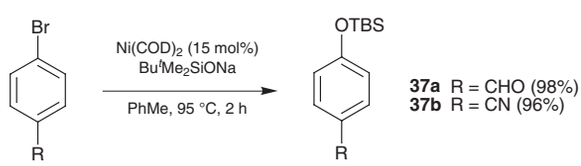




Scheme 10



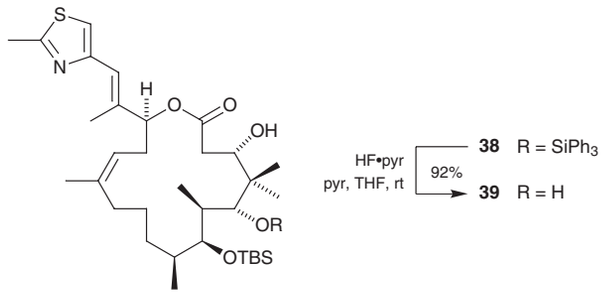
Scheme 11



Scheme 12

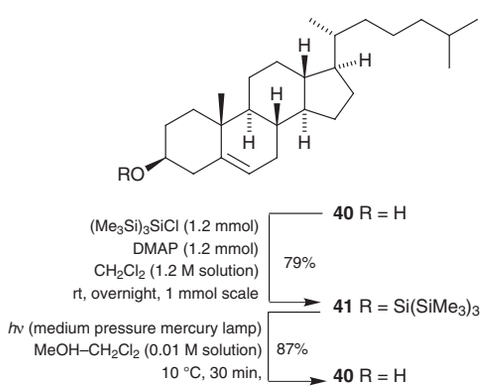
Triphenylsilyl ethers are the poor relations of the silyl ether family of protecting groups but their easy cleavage in the presence of TBS ethers offered a welcome degree of orthogonality which Danishefsky *et al.* exploited in syntheses of the epothilones (Scheme 13).[17] The triphenylsilyl group is introduced *via* the chloride in DMF using imidazole as base.

The Brook group used the tris(trimethylsilyl)silyl (sisyl) group as a new photolabile protecting group for alcohols.[18] The



Scheme 13

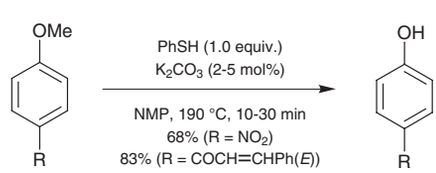
sisyl ethers are prepared by treatment of a primary or secondary alcohol with tris(trimethylsilyl)silyl chloride (derived in one step from commercial $(Me_3Si)_3SiH$ and carbon tetrachloride) and dimethylaminopyridine (DMAP) (Scheme 14). Tertiary and hindered secondary alcohols fail to give the corresponding ether presumably due to steric interactions. Sisyl ethers are stable to a variety of synthetic protocols like organometallic reagents (MeMgBr, $Ph_3P{=}CH_2$), oxidation (Jones reagent), acidic conditions (PTSA; 0.2 M HCl) and some fluoride reagents (KF and 18-crown-6; CsF). However, they are unstable in the presence of butyllithium, $LiAlH_4$ (giving a mixture of products) and tetrabutylammonium fluoride. The deprotection can be cleanly performed by photolysis using a medium pressure mercury lamp (a Hanovia lamp and a Pyrex immersion well).



Scheme 14

2.3 Alkyl ethers

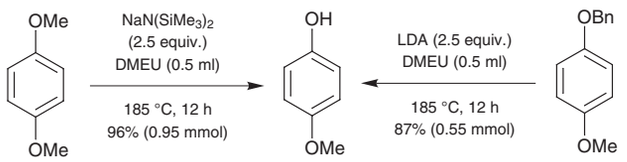
The nucleophilic cleavage of aryl alkyl ethers by alkanethiolates[19] or trimethylsilanethiolate[20] typically requires an excess of the reagent at high temperature. A recent improvement in the procedure[21] (Scheme 15) allows the use of only one equivalent of thiophenol in 1-methyl-2-pyrrolidone (NMP) using a catalytic amount (2–5 mol%) of potassium carbonate as the base. The reactions are complete in 10–30 min at 190 °C. A noteworthy feature of the procedure is the preservation of aromatic nitro and chloro substituents which are displaced with stoichiometric thiolates. Moreover, α,β-unsaturated carbonyl compounds do not undergo Michael addition of thiolate under these conditions.



Scheme 15

Hwu and co-workers reported sodium bis(trimethylsilyl)-amide $[NaN(SiMe_3)_2]$ and lithium diisopropylamide (LDA) as efficient agents for demethylation and debenzylation of alkyl ethers of phenol.[22] However, the deprotection requires quite

harsh conditions (heating at 185 °C for 12 h) which might cause decomposition of more sensitive molecules. In the case of dimethoxybenzenes (*e.g.* **42**) the selective mono-*O*-demethylation can be achieved (Scheme 16). LDA—but not sodium bis(trimethylsilyl)amide—can also selectively deprotect a benzyl ether such as **43** in the presence of a methoxy group.

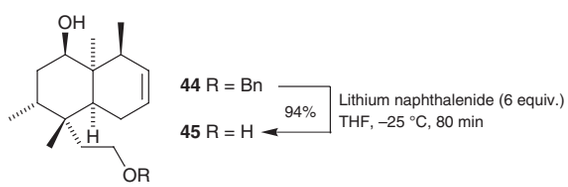


42 **43**

DMEU = 1,3-dimethylimidazolidin-2-one

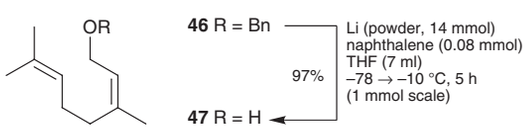
Scheme 16

Alkali metals in liquid ammonia are well known reagents for deprotecting benzyl ethers.[23] It is not then surprising that lithium naphthalenide (prepared from lithium and 1.33 equivalents of naphthalene) also proved successful in this transformation (Scheme 17).[24] The reagent seems rather harsh; however, a wide range of functionalities survive the reaction conditions like alcohols, carbon–carbon double bonds, benzene rings, and THP, silyl and methoxymethyl ethers. A ketone group can also be present but its prior conversion to an enolate is necessary.



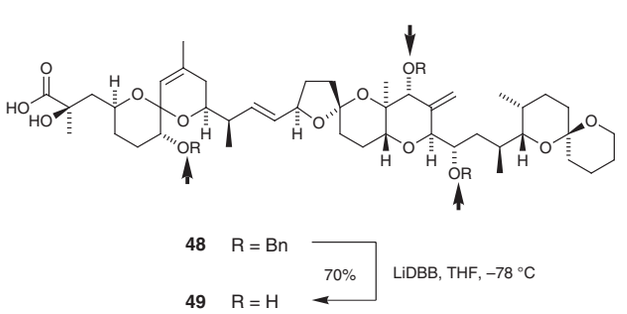
Scheme 17

A similar transformation, but with a catalytic amount of naphthalene, has been reported by Yus and co-workers.[25] Although allyl ethers are also cleaved by the procedure, the selective deprotection of benzyl groups is possible (Scheme 18). Dimethylphenylsilyloxy (but not diphenyl-*tert*-butylsilyloxy) groups can also be removed by this methodology.



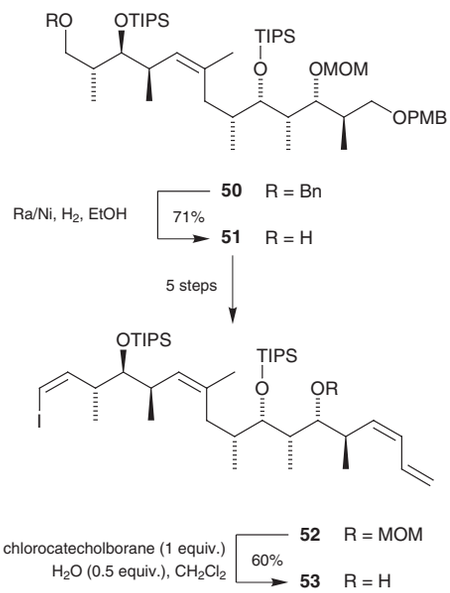
Scheme 18

The final step in a synthesis of the serine/threonine phosphatase inhibitor okadaic acid[26] (**49**) required the reductive cleavage of three benzyl ethers in the precursor **48** (Scheme 19). Previous experience had shown that over-reduction occurs readily upon debenzylation using lithium in liquid ammonia containing ethanol.[27] However, over-reduction was avoided using lithium 4,4′-di-*tert*-butylbiphenylide (LiDBB).[28]



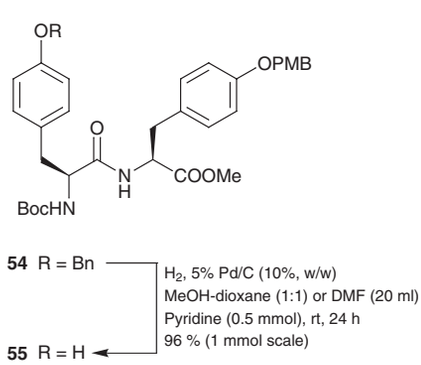
Scheme 19

Discodermolide is a polyhydroxylated lactone exhibiting potent microtubule stabilising activity similar to that of taxol. In a recent synthesis of (−)-discodermolide, Myles and co-workers[29] selectively cleaved the terminal benzyl ether in intermediate **50** (Scheme 20) using Raney nickel and hydrogen in ethanol. Reductive cleavage of the terminal *p*-methoxybenzyl PMB ether was minimised under these conditions and the trisubstituted alkene survived unscathed. Several steps later, difficulty was encountered removing the MOM ether from intermediate **52**. After extensive experimentation, the recalcitrant MOM ether was cleaved in 60% yield with 1 equiv. of chlorocatecholborane and 0.5 equiv. of water in dichloromethane.



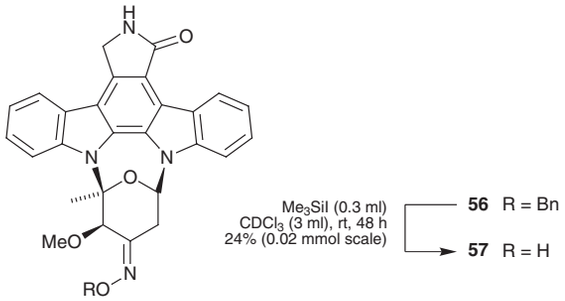
Scheme 20

Hirota and co-workers[30] reported that Pd/C catalysed hydrogenolysis of PMB protected phenols can be selectively inhibited by pyridine. This allows the selective removal of other groups like benzyl and Cbz, as well as reduction of alkenes and nitro groups in the presence of a PMB group (Scheme 21).



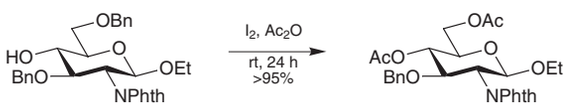
Scheme 21

Staurosporine, the first member of the glycosylated indolocarbazoles to reveal potent protein kinase C activity, has been investigated for its potential for the treatment of cancer, Alzheimer's disease, and other neurodegenerative disorders. Wood *et al.* have published[31] full details of their efficient and general route to staurosporine and other members of this family of compounds including (−)-K252a, (+)-RK286c, (+)-MLR-52 and (−)-TAN-1030a. The final step in the synthesis of (−)-TAN-1030a (**57**, Scheme 22), cleavage of an *O*-benzyl bond from an oxime, was accomplished with a large excess of iodotrimethylsilane, albeit in poor yield (24%).



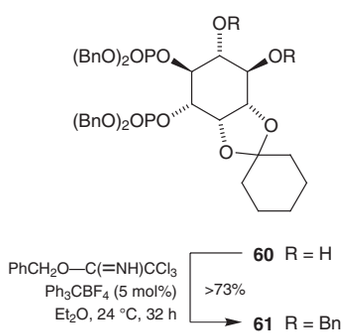
Scheme 22

Iodine is a weak Lewis acid which promotes the peracetylation of unprotected sugars. However, acetylation of *O*-benzyl protected derivatives may be accompanied by cleavage of the benzyl protecting group. Thus treatment of the glucosamine derivative **58** with iodine (100 mg g^{-1} sugar) in acetic anhydride resulted in acetylation of the hydroxy group at C4 together with selective cleavage of the primary *O*-benzyl group and its replacement by acetate to give the 4,6-di-*O*-acetyl derivative **59** in >95% yield (Scheme 23).[32]



Scheme 23

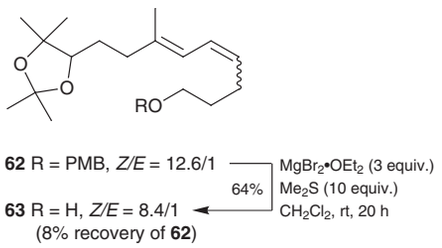
The *O*-benzylation of alcohols with benzyl trichloroacetimidate is usually accomplished using triflic acid as a catalyst. However, in a concise synthesis of the cellular messenger L-α-phosphitidyl-D-*myo*-inositol 3,4-bisphosphate,[33] trityl cation promoted benzylation of the C5 and C6 hydroxy functions was used instead (Scheme 24).[34]



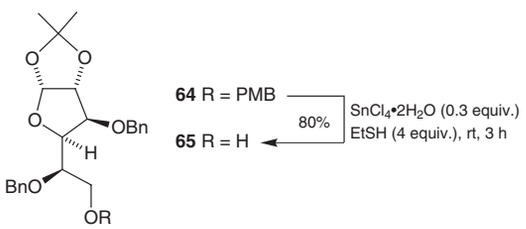
Scheme 24

Magnesium bromide–dimethyl sulfide is a mild reagent for deprotecting *p*-methoxybenzyl (PMB) ethers to the corresponding alcohols.[35] The method is specially suitable for molecules containing a 1,3-diene moiety (*e.g.* **62**, Scheme 25) because other PMB-deprotecting reagents (DDQ, CAN) are unsuccessful in these cases. However, some isomerisation of the diene is observed. Other protective groups like TBS, benzyl, benzoyl and acetonide also remain intact. On the other hand the $MgBr_2{\cdot}OEt_2$–SMe_2 system fails when the PMB group is accompanied by a methoxymethyl (MOM) or benzyloxymethyl (BOM) protecting group.

A *p*-methoxybenzyl (PMB) group can also be removed from alcohols and phenols using a catalytic amount of $AlCl_3$ or $SnCl_2{\cdot}2H_2O$ in the presence of EtSH at room temperature.[36] Under these mild conditions other protecting groups such as methyl, benzyl and TBDPS ethers, *p*-nitrobenzoyl esters, isopropylidene acetals and glycosydic moieties (Scheme 26) remain unchanged. EtSH, by trapping PMB cations, is essential to obtain the product free from impurities.

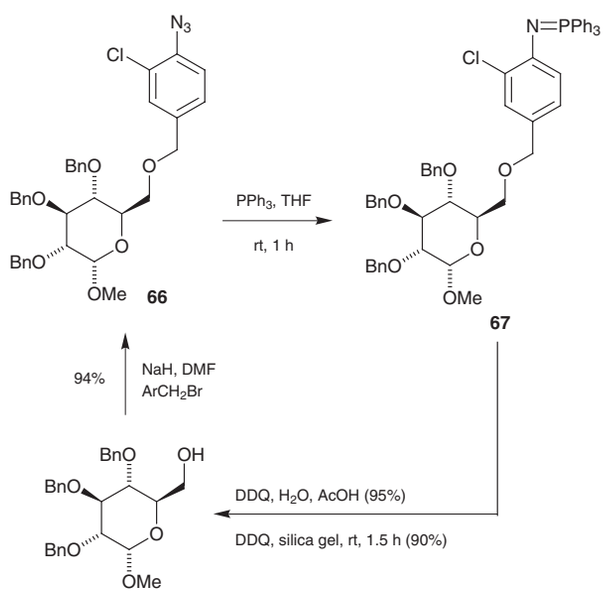


Scheme 25



Scheme 26

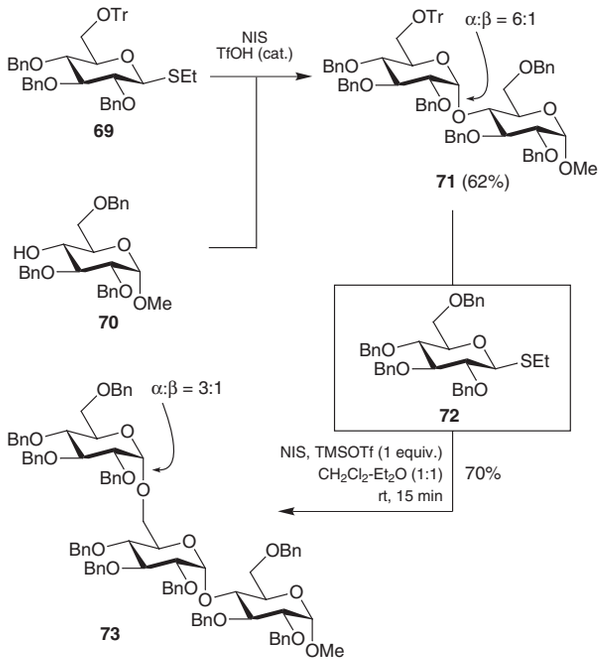
4-Azido-3-chlorobenzyl (Cl-Azb) ethers are prepared by alkylation of hydroxy groups with 4-azido-3-chlorobenzyl bromide, available in two steps from commercial 2-chloro-4-methylaniline.[37] Cl-Azb ethers are more stable than the parent 4-azidobenzyl (Azb) ether. Cl-Azb ethers were inert towards DDQ but were cleaved smoothly after conversion to the corresponding iminophosphorane (Scheme 27).



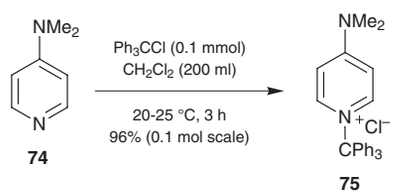
Scheme 27

6-*O*-Trityl monosaccharides are central to a strategy for the synthesis of oligosaccharides based on thioglycoside activation. Thus the trityl group in thioglycoside **69** (Scheme 28) was robust enough to withstand the arming of the thioglycoside acceptor using *N*-iodosuccinimide (NIS) in the presence of a catalytic amount of triflic acid followed by reaction with the donor **70** to give the disaccharide **71** in 62% yield.[38] The preponderance of the α-anomer was attributed to the steric effect of the trityl group. In a subsequent step, the trityl ether in **71** was cleaved and the freed hydroxy group acted as a donor when the thioglycoside **72** was armed with NIS in the presence of one equivalent of TMSOTf, whereupon the trisaccharide **73** was formed in 70% yield, again with modest α-selectivity.

4-Dimethylamino-*N*-triphenylmethylpyridinium chloride (**75**, Scheme 29) is a stable isolable salt which can be used for a clean triphenylmethylation of a primary alcohol over a second-



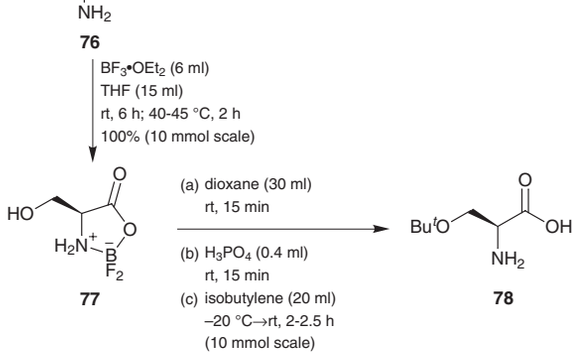
Scheme 28



Scheme 29

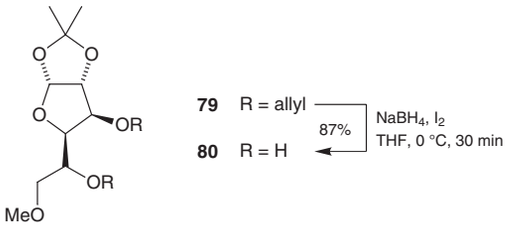
ary one.[39] Recently Hernandez and co-workers published in *Organic Syntheses*[40] a detailed large scale procedure for this reagent, slightly modifying their original method.[41]

In order to protect the hydroxy function of serine and threonine, temporary protection of α-amino and α-carboxy groups is necessary. Recently a new methodology has been developed[42] in which boron trifluoride–diethyl ether is used for the simultaneous protection of these two groups as a 2,2-difluoro-1,3,2-oxazaborolidin-5-one derivative (*e.g.* **77**, Scheme 30). Reaction of **77** with isobutylene in acidic conditions afforded selectively protected derivative **78**. In similar fashion benzyl trichloroacetimidate converts **77** into the corresponding *O*-benzyl derivative.



Scheme 30

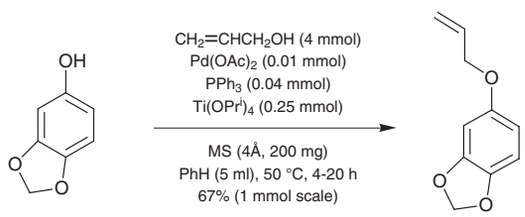
Diborane generated *in situ* by reaction of $NaBH_4$ with iodine in THF at 0 °C accomplishes the deprotection of allyl ethers under mild conditions (Scheme 31).[43] Both aryl and alkyl allyl



Scheme 31

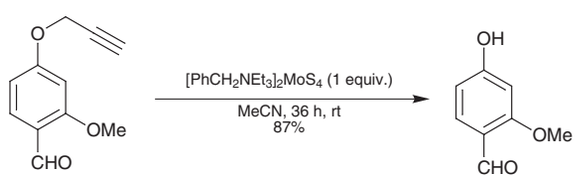
ethers are cleaved without detriment to cyano, ester, nitro, acetonide and tetrahydropyranyl groups.

Miura and co-workers[44] reported a new method for the etherification of phenols by using allyl alcohols and catalytic amounts of palladium(II) acetate and titanium(IV) isopropoxide (Scheme 32). The reaction is quite general; however, it fails in the case of 3,5-dimethoxyphenol because of the exclusive formation of a *C*-allylated product.



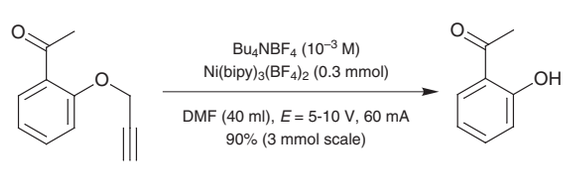
Scheme 32

Benzyltriethylammonium tetrathiomolybdate deprotects propargyl ethers and esters in acetonitrile at room temperature (Scheme 33).[45] Allyl ethers, nitro compounds, aldehydes and ketones are not affected though alkyl halides are converted to sulfides, and azides and thiocyanates are reduced.



Scheme 33

Electroreductive cleavage of propargylic aryl ethers and esters to the corresponding phenols and carboxylic acids occurs in good yield (77–99%) using Ni^{II}–bipyridine complex as catalyst.[46] Ester, cyano and, most interestingly, aryl ketone functionalities (Scheme 34) are stable under the reaction conditions. However, in the case of *o*-bromo and *o*-iodo derivatives, the halogen is quantitatively replaced with hydrogen, whereas an *o*-chloro atom is only partially reduced (20%).

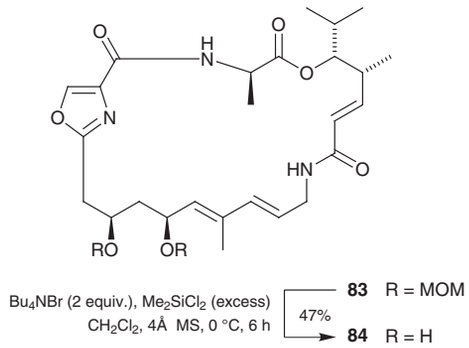


Scheme 34

2.4 Alkoxyalkyl ethers

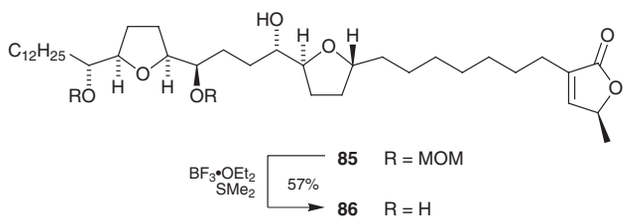
Methoxymethyl (MOM) protecting groups are quite robust and their removal is often incompatible with many functional groups. A further complication is the formation of formal derivatives on deprotection of MOM-protected 1,3-diols. Nevertheless, Ghosh and Liu[47] were able to remove two MOM groups protecting a 1,3-diol in the final step of their synthesis of the streptogramin antibiotic madumycin II (**84**, Scheme

35). The successful method employed tetrabutylammonium bromide (2 equiv.) and an excess of dichlorodimethylsilane in dichloromethane at 0 °C for 6 h.



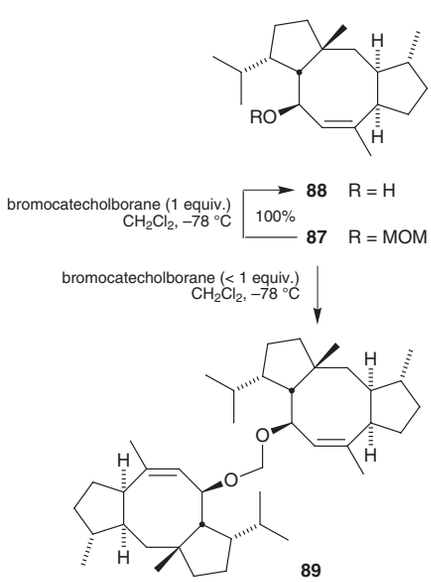
Scheme 35

The final step in a synthesis of the Annonaceous acetogenin (+)-4-deoxygigantecin[48] entailed the cleavage of two MOM ether groups using $BF_3{\cdot}OEt_2$ in the presence of SMe_2 (Scheme 36).[49]



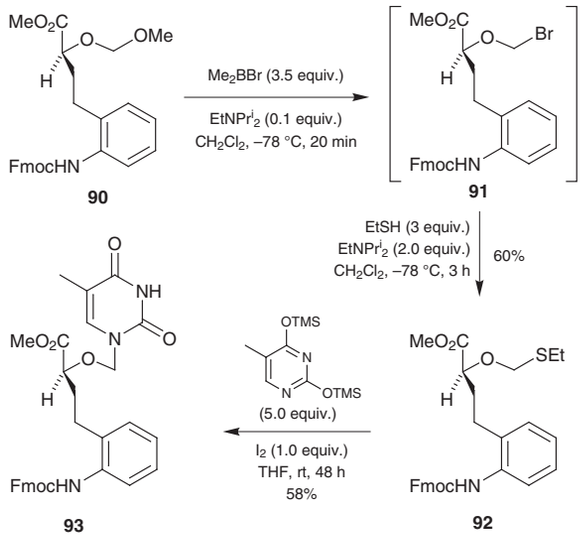
Scheme 36

During a synthesis of the diterpene epoxydictymene, the Paquette group found that easy elimination took place during the cleavage of the MOM ether in intermediate **87** (Scheme 37).[50] When 1 equiv. of bromocatecholborane in dichloromethane was used, the desired cleavage took place to give the requisite alcohol **88** in quantitative yield. However, when less than 1 equiv. was used, the dimeric species **89** was generated.



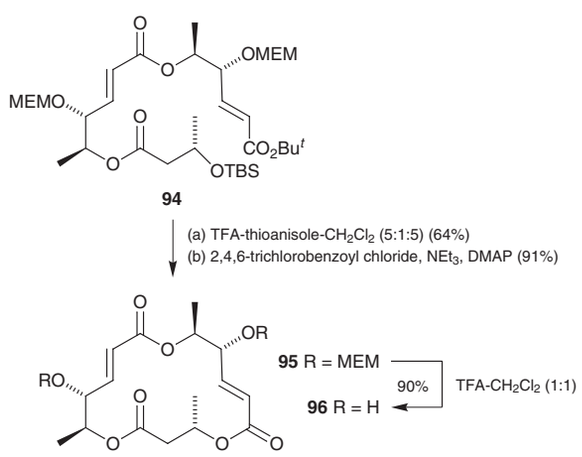
Scheme 37

Synthetic analogues of natural oligonucleotides have attracted interest for their promising applications in antisense chemotherapy.[51] In a synthesis of the thymidine acyclonucleoside analogue **93** (Scheme 38), the MOM group in **90**, normally used as a hydroxy protecting group was converted to the ethylthiomethyl ether intermediate **92** which was then used as a functional group to append thymine.



Scheme 38

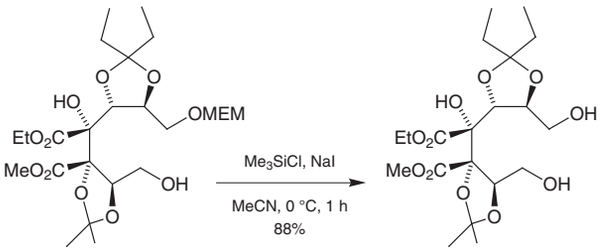
Macrosphelide A (**96**) strongly inhibits adhesion of human leukaemia HL-60 cells to human umbilical vein endothelial cells by inhibiting the binding of sialyl Lewis x to E-selectin. It is also orally active against lung metastasis of B16/BL6 melanoma in mice and it appears to be a lipoxygenase inhibitor as well. The closing steps in a recent synthesis of macrosphelide A required the stepwise release first of a hydroxy and carboxy function as a prelude to macrolactonisation and then two hydroxy groups protected as their (2-methoxyethoxy)methyl (MEM) ethers—all this without detriment to the three lactone functions.[52] The first deprotection was accomplished with a mixture of trifluoroacetic acid (TFA, 5 parts) and thioanisole (1 part) in dichloromethane (5 parts) (Scheme 39). The final deprotection of the 2 MEM groups (**95**→**96**) was accomplished in good yield with trifluoroacetic acid in dichloromethane (1 : 1).



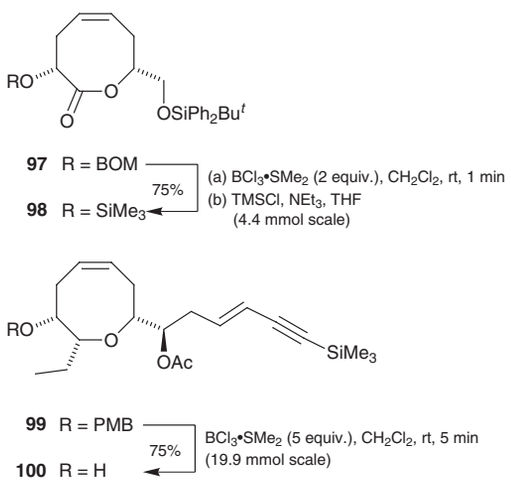
Scheme 39

A concise synthesis of zaragozic acid[53]—an inhibitor of squalene synthase—required the deprotection of a MEM ether in the presence of two dioxolane rings. This was accomplished (Scheme 40) using iodotrimethylsilane generated *in situ* by reaction of chlorotrimethylsilane and sodium iodide.[54]

In 1993 a Cambridge group showed that $BCl_3{\cdot}SMe_2$ selectively cleaved benzyl ethers in the presence of acetate and *tert*-butyldiphenylsilyl groups.[55] On the other hand trityl ethers are rapidly cleaved in the presence of benzyl ethers. The same group[56] applied the method twice in a synthesis of the marine oxocin derivative laurencin as shown in Scheme 41. Early on the benzyloxymethyl (BOM) ether **97** was cleaved in good yield and the resultant hydroxy group converted to silyl ether **98** and later



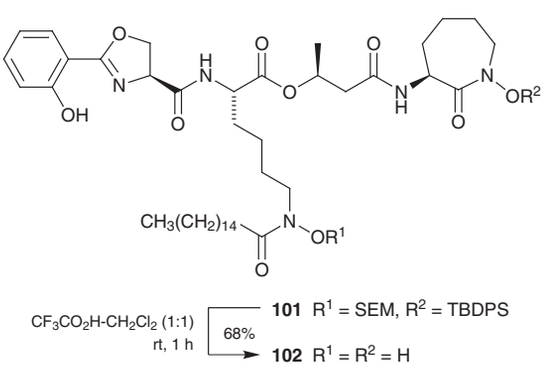
Scheme 40



Scheme 41

the *p*-methoxybenzyl ether **99** was cleaved selectively in the presence of the sensitive enyne.

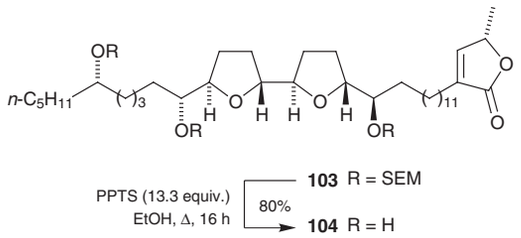
Mycobactins are a family of siderophores produced by mycobacteria to promote growth *via* iron uptake processes. Hu and Miller[57] reported a synthesis of mycobactin S (**102**, Scheme 42) which was a potent growth inhibitor of *Mycobacterium tuberculosis*. The use of a 2-(trimethylsilyl)ethoxymethyl (SEM) group to protect the hydroxamic acid residue in the N^{α}-Cbz-N^{ε}-hydroxy-N^{ε}-palmitoyl-L-lysine fragment **101** was crucial in the construction of the ester linkage. Both the SEM and *tert*-butyldiphenylsilyl (TBDPS) groups were cleaved in the final step using trifluoroacetic acid.



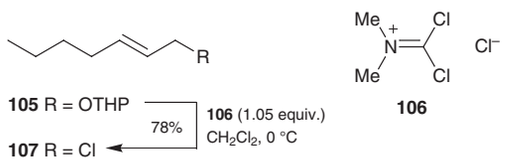
Scheme 42

A mild method for the deprotection of SEM ethers was discovered by Marshall and Chen[58] during their synthesis of the cytotoxic acetogenins aciminocin and asiminecin (**104**). In the example shown (Scheme 43), the three SEM ethers were simultaneously cleaved from **103** by heating with pyridinium tosylate (PPTS) in ethanol to give asiminecin (**104**) in 80% yield.

Mioskowski and co-workers[59] described the direct conversion of THP-protected alcohols into the corresponding chlorides using dichlorophosgeniminium chloride **106** (Scheme 44). The corresponding bromides can also be obtained if the reaction is carried out in the presence of 2 equivalents of tetrabutyl-



Scheme 43

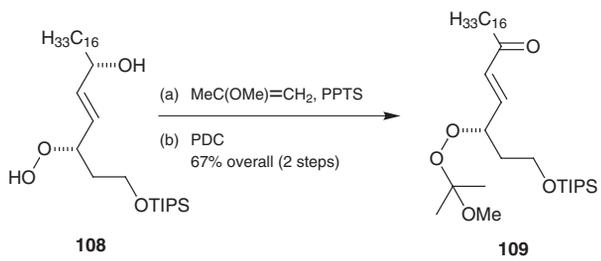


Scheme 44

ammonium bromide. The reaction works well with primary alcohols. With secondary alcohols the formation of elimination by-product is observed (which is the main product in the case of tertiary alcohols).

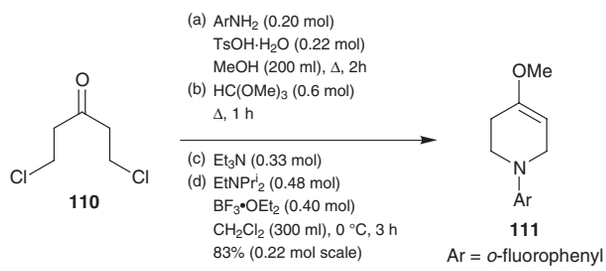
Solvent free tetrahydropyranylation of alcohols and phenols over HSZ zeolites as reusable catalysts has been reported by an Italian group.[60]

Selective protection of the hydroperoxy function in **108** (Scheme 45) using 2-methoxypropene enabled subsequent oxidation of the remaining allylic alcohol function.[61] The product **109** was converted to the marine cyclic peroxide plakorin.



Scheme 45

Acetal derivatives prepared from *N*-substituted 4-methoxy-1,2,5,6-tetrahydropyridine (*e.g.* **111**) have been used by the Reese group[62,63] for the protection of the 2′-hydroxy function in an automated solid phase synthesis of oligoribonucleotides. The drawback of this methodology was the five steps required to make **111** (and related compounds). Recently the same group reported a much shorter procedure consisting of only two steps (Scheme 46).[64]

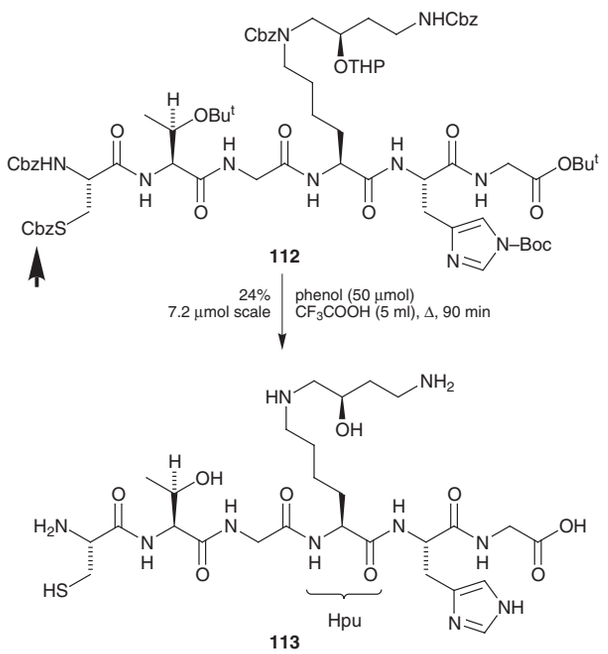


Scheme 46

3 Thiol protecting groups

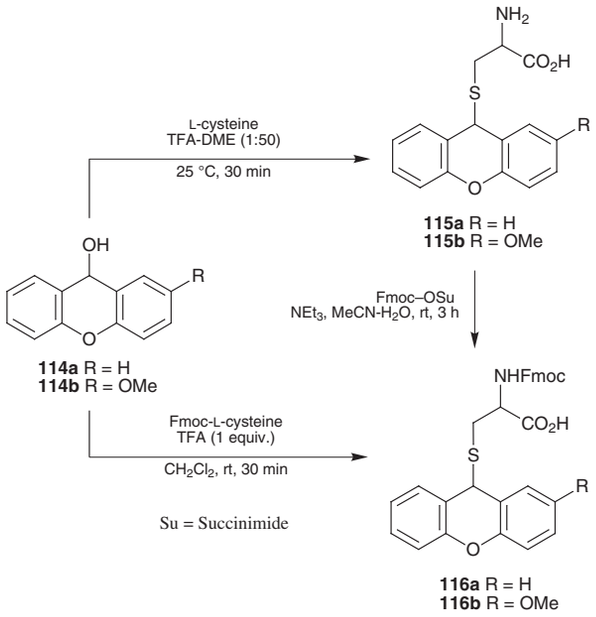
Hypusine (Hpu) is an unusual amino acid uniquely found in eLF-5A, a protein which serves as an initiation factor in all growing eukaryotic cells and which plays a critical role in the replication of human immunodeficiency virus-1 (HIV-1). Bergeron and co-workers[65] synthesised the hypusine-containing

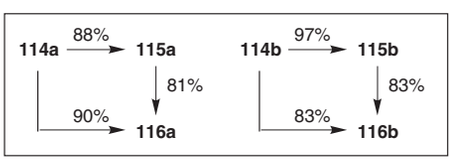
pentapeptide **113** found in eIF-5A capped at its *N*-terminus with L-cysteine (*i.e.* Cys-Thr-Gly-Hpu-His-Gly, Scheme 47) as a means of covalently linking this peptidic hapten to a carrier protein for ultimate use in raising antibodies specific to hypusine-containing epitopes. The Cbz group used to protect the cysteine thiol group was robust enough to survive aqueous sodium carbonate in DMF and typical peptide coupling conditions; however, in the final step, it was cleaved together with seven other acid-labile protecting groups, using neat refluxing trifluoroacetic acid containing phenol as a scavenger.



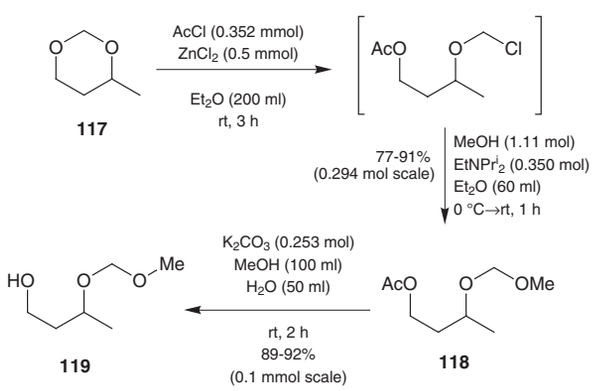
Scheme 47

S-9*H*-Xanthen-9-yl (Xan) and 2-methoxy-9*H*-xanthen-9-yl (2-Moxan) are new *S*-protecting groups for cysteine which are compatible with the base-labile N^{α}-fluoren-9-ylmethoxycarbonyl (N^{α}-Fmoc) group currently used in solid phase peptide synthesis.[66] Both groups are introduced onto sulfhydryl functions by *S*-alkylation reactions involving the corresponding xanthydrols **114a**,**b** under acid catalysis (Scheme 48). Selective removal of *S*-Xan or *S*-2-Moxan groups is best accomplished with TFA–CH_2Cl_2–Et_3SiH (1 : 98.5 : 0.5) at room temperature. Alternatively, oxidative deprotection of *S*-Xan or *S*-2-Moxan groups with iodine (10–20 equiv.) or thallium(III) tris(trifluoroacetate) (1–3 equiv.) provides the corresponding disulfides. Both groups are more labile towards acidolysis and more readily oxidised than *S*-acetamidomethyl (Acm), *S*-trityl and *S*-2,4,6-trimethoxybenzyl (Tmob) protecting groups.

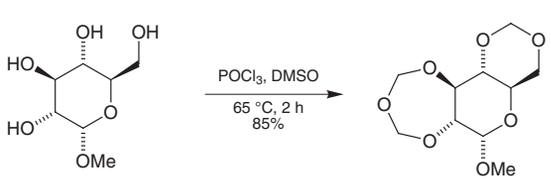




Scheme 48



Scheme 49



Scheme 50

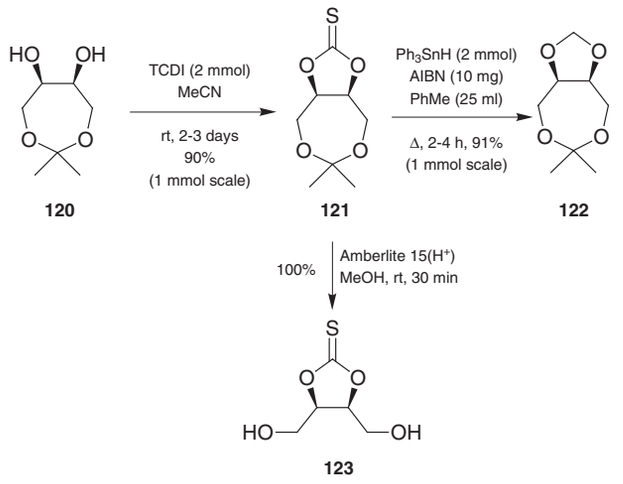
4 Diol protecting groups

A detailed large scale *Organic Syntheses* procedure has appeared for the selective MOM-protection of 1,3-diols *via* regioselective cleavage of methylene acetals (Scheme 49)[67] first communicated in 1995.[68]

Despite the relatively harsh conditions required for their removal (2 M HCl in acetone, 50 °C), methylene acetals are occasionally used in synthesis. An Italian group[69] has added $POCl_3$ and $SOCl_2$ in DMSO to the list of reagents which convert diols to methylene acetals. Whilst *syn*-1,2- and -1,3-diols give the corresponding 1,3-dioxolane and 1,3-dioxane derivatives respectively, *anti*-1,2-diols or *syn*-1,2-diols in sterically crowded environments give the corresponding 1,3,5-trioxepane derivatives as illustrated in Scheme 50. The method does not work well with simple monohydric alcohols.

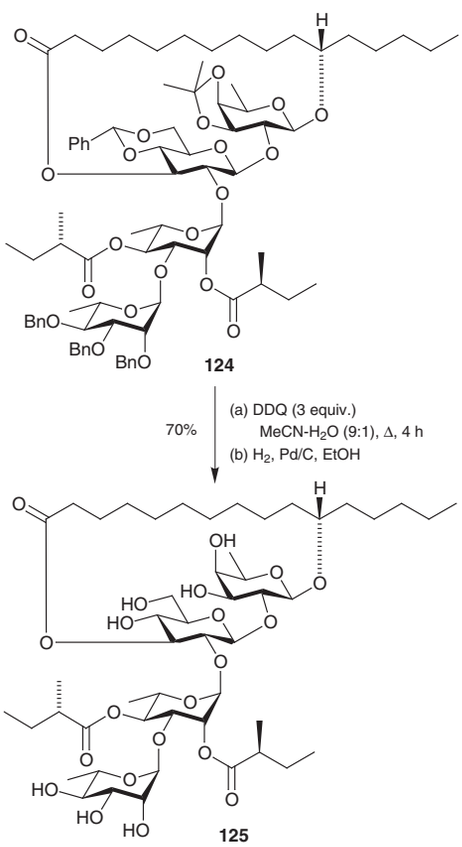
A new protecting group strategy for diols allows easy transformation of a group stable in acidic conditions into another stable in basic conditions.[70] The sequence, exemplified in Scheme 51, begins with the formation of thiocarbonate **121** by reaction of diol **120** with 1,1′-thiocarbonyldiimidazole (TCDI). The thiocarbonate moiety in **121** is stable under acidic conditions as illustrated by selective hydrolysis of the isopropylidene moiety to give **123** in quantitative yield, but the thiocarbonate reverts to the starting diol **120** by basic hydrolysis. Easy transformation of thiocarbonate **121** into methylene acetal **122** in one step by radical desulfurisation with triphenyltin hydride in the presence of AIBN gives a protecting group which is highly stable in alkaline medium while it is labile towards acid.

Tricolorin A is an unusual tetrasaccharide macrolactone isolated from *Ipomoea tricolor*, a plant used in Mexican traditional agriculture as a weed controller. Two syntheses of tri-



Scheme 51

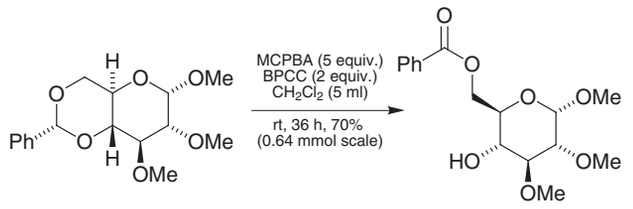
colorin A have been reported recently by the groups of Hui[71] and Heathcock.[72] The closing stages of the Hui synthesis entailed the simultaneous deprotection of a benzylidene acetal and an isopropylidene acetal (Scheme 52) using DDQ in refluxing aqueous acetonitrile. The last step, hydrogenolysis of the three benzyl ether functions in **124** gave tricolorin A (**125**).



Scheme 52

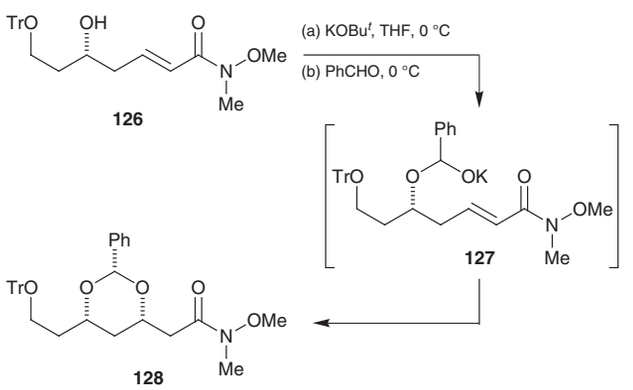
Benzylidene acetals can be cleaved to hydroxy esters using 2,2′-bipyridinium chlorochromate (BPCC) and *m*-chloroperbenzoic acid (MCPBA).[73] The selectivity of the cleavage favours the product having primary ester and secondary alcohol functionality, as shown in Scheme 53. *O*-Allyl and *O*-benzyl groups do not tolerate the reaction conditions, presumably because they undergo competitive oxidation.

The base-induced intramolecular heteroconjugate addition of the hemiacetal **127** (Scheme 54) derived from reaction of alcohol **126** with benzaldehyde was used to generate the benzylidene-protected 1,3-diol derivative **128** in 83% yield.[74]



BPCC = 2,2'-bipyridinium chlorochromate
MCPBA = *m*-chloroperbenzoic acid

Scheme 53



Scheme 54

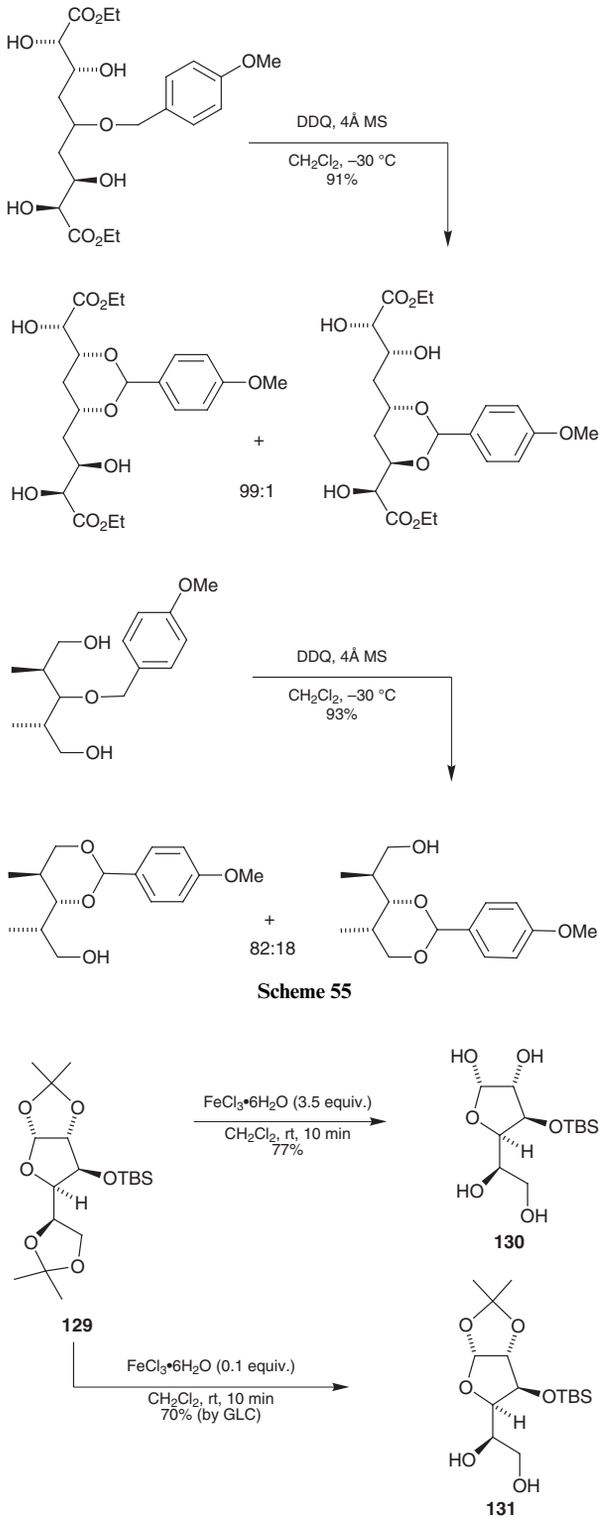
The oxidative cyclisation of mono-PMB ethers of 1,3-diols to afford the corresponding *p*-methoxyphenyl acetals was first reported by Yonemitsu and co-workers in 1982.[75] Myles and co-workers[76] have shown that oxidative cyclisation can be used to differentiate the end groups in 1,3,5-triol systems having pseudo C_2-symmetry as shown in Scheme 55.

Ferric chloride (either anhydrous or hexahydrate) absorbed on silica gel is known to promote the cleavage of acetals.[77,78] Sen and co-workers have recently reported[79] that the reaction is faster when non-absorbed $FeCl_3 \cdot 6H_2O$ in dichloromethane is used. Depending on the number of equivalents, the selective deprotection of either one or both acetal groups can be achieved (Scheme 56). In both cases, the TBS ether remains intact.

Ley has used the butane-2,3-diacetal protecting group in an expedient synthesis of several rare 6-deoxy sugars starting from cheap galactose and mannose.[80] The general procedure is illustrated in Scheme 57 by the synthesis of methyl-α-D-rhamnopyranoside (**135**, unnatural rhamnose configuration). Selective protection of the two equatorial hydroxy functions in methyl-α-D-mannopyranoside (**132**) occurred in a single step by treatment with butane-2,3-dione and trimethyl orthoformate in the presence of catalytic camphorsulfonic acid. Alternatively, the requisite protection can be accomplished using $BF_3 \cdot OEt_2$ as the catalyst. The final deprotection to give **135** was effected by hydrolysis using trifluoroacetic acid containing 10% water.

A detailed procedure for the large scale preparation of 1,1,2,2-tetramethoxycyclohexane **137** and its use in the protection of methyl α-D-mannopyranoside **138** has been described in *Organic Syntheses* (Scheme 58).[81] The paper summarised the results obtained when **137** was used for the selective protection of the *trans*-hydroxy groups in a range of sugars. Further experimental details of the methodology[82,83] and its application in oligosaccharide assembly[84,85] have also been published.

The simultaneous and selective protection of the two equatorial hydroxy groups in methyl dihydroquinate (**140**, Scheme 59) as the butane-2,3-diacetal was a key strategic feature in a synthesis of inhibitors of 3-dehydroquinate synthase.[86] Later in the synthesis, deprotection of intermediate **142** required three steps: (a) hydrolysis of the TMS ether and the butane-2,3-diacetal with trifluoroacetic acid; (b) cleavage of



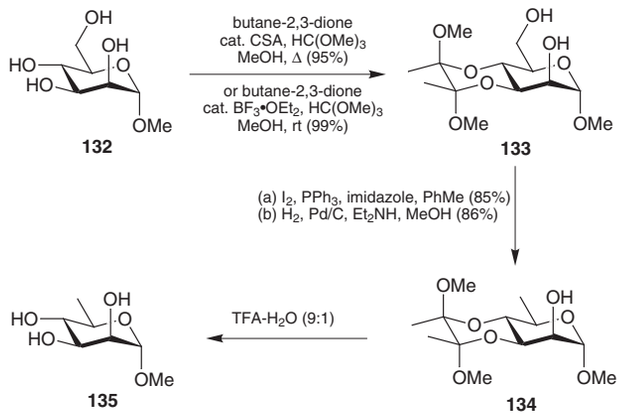
Scheme 55

Scheme 56

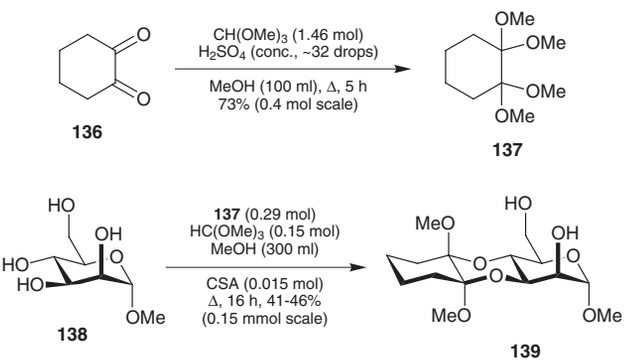
the isopropyl phosphonate with TMSBr; and (c) hydrolysis of the methyl ester with aqueous NaOH.

5 Carboxy protecting groups

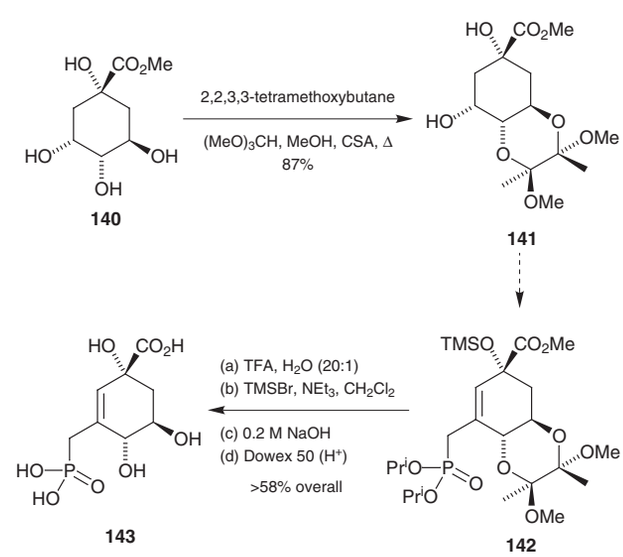
Radiosumin is isolated from the freshwater blue-green alga *Plectonema radiosum*. It is a highly potent inhibitor of trypsin and a moderately active inhibitor of plasmin and thrombin. In the last step of their synthesis of radiosumin (Scheme 60), Shioiri and co-workers[87] required an ester hydrolysis (**144**→**145**) which did not epimerise the two amino acid residues. The desired transformation was accomplished under neutral conditions through the agency of bis(tri-n-butyltin) oxide.[88]



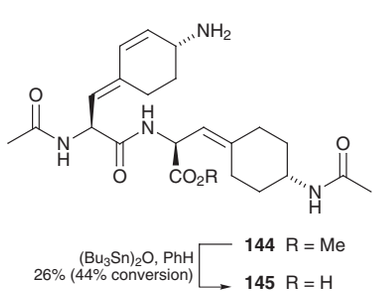
Scheme 57



Scheme 58



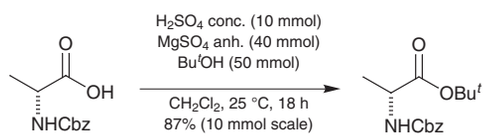
Scheme 59



Scheme 60

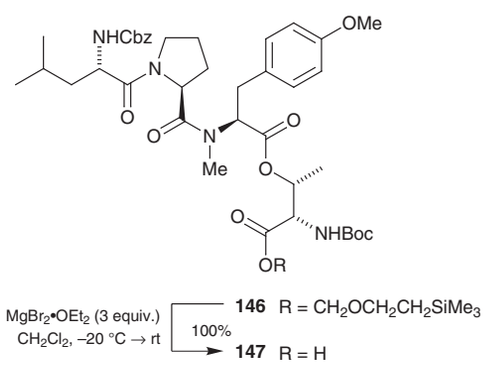
The classical method for the preparation of *tert*-butyl esters is the reaction of an acid with isobutylene in the presence of an acidic catalyst.[23] Wright and co-workers[89] reported a modified

procedure in which, instead of isobutylene, *tert*-butyl alcohol is used in the presence of a heterogeneous acid catalyst—concentrated sulfuric acid dispersed on powdered anhydrous magnesium sulfate. No internal pressure is developed during the reaction and the method is successful for various aromatic, aliphatic, olefinic, heteroaromatic and protected amino acids (Scheme 61). Also primary and secondary alcohols can be converted into the corresponding *tert*-butyl ethers using essentially the same procedure (with the exception of alcohols particularly prone to carbonium ion formation, *e.g.* 4-methoxybenzyl alcohol).



Scheme 61

2-(Trimethylsilyl)ethoxymethyl (SEM) esters are usually cleaved with HF in acetonitrile or with fluoride ion—conditions which are incompatible with acid sensitive TBS ethers and Boc groups or fluoride sensitive Fmoc groups. Joullié and coworkers[90] have explored the virtues of SEM esters for the protection of the *C*-terminus of peptides and found that many of the previous incompatibilities can be reconciled by using magnesium bromide–diethyl ether for the deprotection.[91] Protecting groups typically encountered in peptide chemistry including Boc, Cbz, Fmoc and Troc carbamates are retained. The procedure is illustrated by the efficient and selective deprotection of the didemnin tetrapeptide **146** shown in Scheme 62.



Scheme 62

Damavaricin D (**153**), a biosynthetic precursor and degradation product of streptovaricin D, inhibits RNA-directed DNA polymerase. Roush *et al.* recently accomplished a synthesis of damavaricin D which is a salutary lesson in the frustrations attending model studies.[92] Success in the synthesis was very dependent upon a carefully wrought protecting group strategy which had been thoroughly evaluated in closely related models. However, the preliminary studies were largely useless in the real system. For our present purposes we will join the synthesis at intermediate **148** (Scheme 63) and consider the selective manipulation of the five ester functions leading to the final product. Cleavage of the 2-(trimethylsilyl)ethyl ester with TBAF followed by a Curtius rearrangement on the resultant carboxylic acid returned an isocyanate intermediate which was trapped with 2-(trimethylsilyl)ethanol to give the 2-(trimethylsilyl)ethyl carbamate **149**. Selective reduction of the (*Z*)-enoate of **149** required careful control of the reaction conditions in order to avoid competing reduction on the two acetate esters. Treatment of **149** with 5 equiv. of DIBAL-H in THF at −100 to −78 °C for 1.5 h provided the (*Z*)-enal (14%), the corresponding allylic alcohol (33%) and recovered **149** (49%). After recycling **149**, the enal and allylic alcohol functions were obtained in 16 and 62% yields respectively. Conversion of the allylic alcohol to the enal by Swern oxidation followed by a Horner–Wadsworth–Emmons reaction then gave the dienoate ester **150**. Simultaneous deprotection of the nascent 2-(trimethylsilyl)ethyl ester and the 2-(trimethylsilyl)ethoxycarbonyl group with tris(dimethylamino)sulfonium difluorotrimethylsilicate (TASF) returned an amino acid which macrolactamised on treatment with *N*-methyl-2-chloropyridinium iodide to give macrolactam **151** in 76% yield for the two steps. Selective hydrolysis of the MOM group adjacent to the naphthalene amide occurred together with the acetonide to yield a triol **152** from which the allyl ether and allyl ester functions were removed by treatment with catalytic $(Ph_3P)_4Pd$ and Bu_3SnH in toluene containing HOAc.[93] Next, the two acetate functions were hydrolysed with LiOH and the carboxylic acid esterified with trimethylsilyldiazomethane. To complete the synthesis, the remaining two MOM groups were hydrolysed with aqueous TFA and the resultant diol oxidised in air to give damavaricin D (**153**).

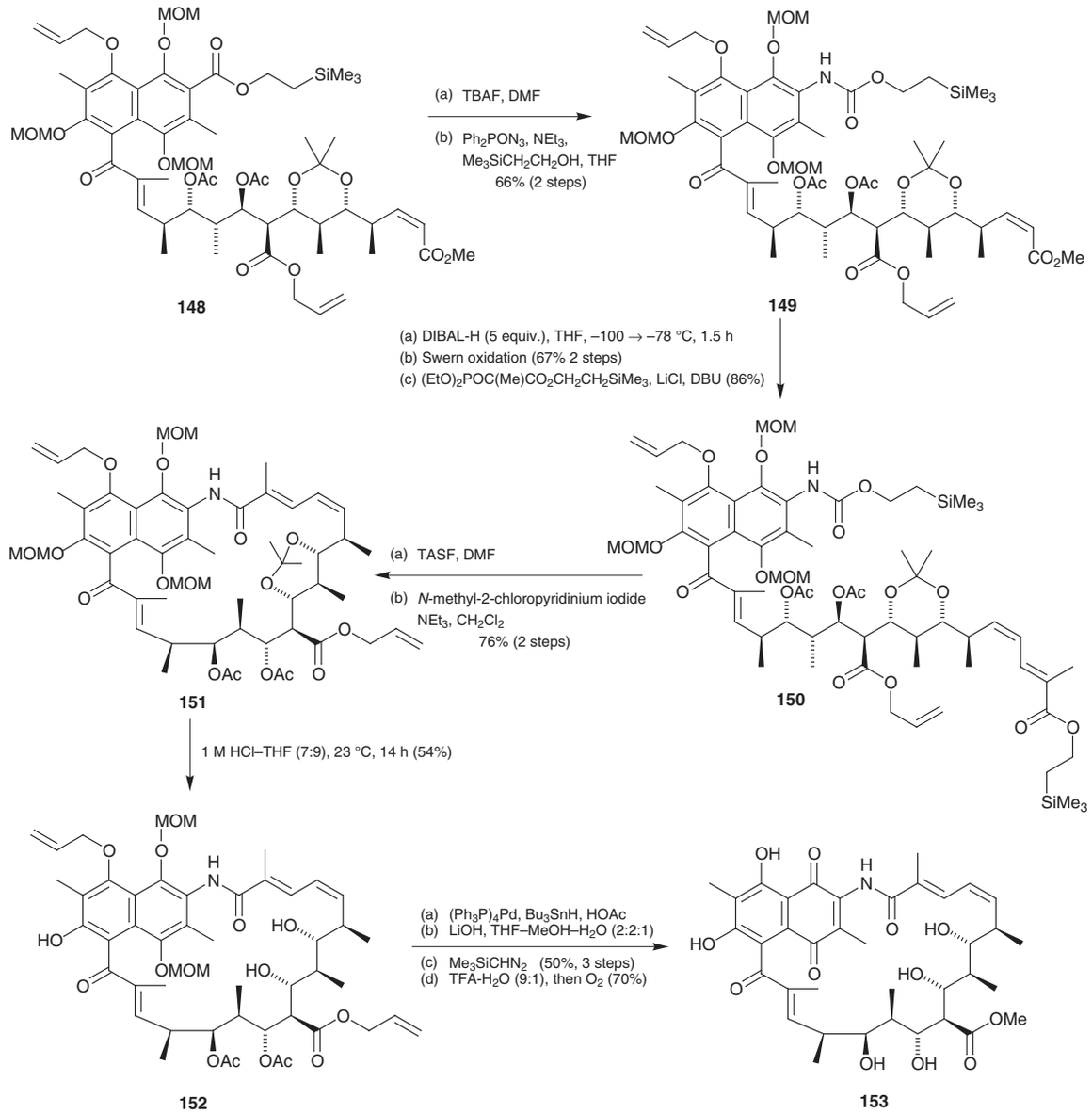
A Pfizer process development group showed that sulfinic acids or the corresponding salts, in the presence of a catalytic amount of $Pd(PPh_3)_4$, efficiently cleave the C–O bond of allyl esters and ethers as well as the C–N bond of *N*-allyl amines in dichloromethane or methanolic THF at room temperature.[94] The reaction works equally well with but-2-enyl, cinnamyl, 2-chloroprop-2-enyl and 2-methylprop-2-enyl esters. Most of the 19 examples reported used toluene-*p*-sulfinic acid or its sodium salt, but other sulfinates worked equally well such as sodium thiophene-2-sulfinate, sodium 4-chloro-3-nitrobenzenesulfinate, sodium *tert*-butylsulfinate, monosodium *p*-sulfinobenzoate and sodium formaldehyde sulfoxylate (Rongalit). To demonstrate the power of the method, various allylic esters (**154a**–**e**, Scheme 64) of the highly sensitive penem system were removed efficiently with sodium toluene-*p*-sulfinate, whereas other allyl scavengers such as carboxylic acids, morpholine, dimedone and *N*,*N*′-dimethylbarbituric acid led to poor results.

A major problem in the synthesis of serine or threonine phosphopeptides is the selective removal of *N*- or *C*-terminal protecting groups without causing β-elimination of the phosphate moiety—a transformation that occurs at pH > 8. Sebastian and Waldmann showed that heptyl esters were enzyme-labile carboxy protecting groups that could be cleaved under conditions mild enough to preserve phosphate residues.[95] A synthesis of phosphopentapeptide **158** representing a consensus sequence of the Raf-1 kinase (Scheme 65) illustrates the value of both the enzyme deprotection technique as well as the use of Pd^0-catalysed deprotection of allyl phosphates, carbamates and carboxylates.

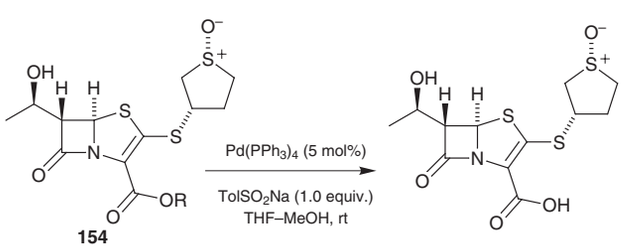
The carbamoylmethyl (CAM) group developed by Martinez[96] was employed as a carboxy protecting group in the construction of the Cys-Thr-Gly fragment **160** of the eIF-5A hapten[65] (*vide supra*). The synthesis began with *N*-Boc-Gly-CAM ester from which the tripeptide **159** was constructed using standard methodology. The CAM ester was removed with sodium carbonate in aqueous DMF to give the desired fragment **160** in 77% yield (Scheme 66). Note the survival of the *S*-Cbz function under these conditions.

The Givens group[97] have reported the use of the *p*-hydroxyphenacyl group as a new photoactivated protecting group for carboxy functions. Irradiation of buffered solutions of the ester **161** at room temperature led to rapid release of γ-aminobutyric acid (**162**) with the concomitant formation of *p*-hydroxyphenylacetic acid (**164**, Scheme 67).

The 3′,5′-dimethoxybenzoin (DMB) system can photorelease a variety of functional groups with *ca.* 350 nm irradiation. A recent study[98] of the mechanism of the reaction using nanosecond laser flash photolysis led to the suggestion that the primary step in the photorelease is a charge transfer interaction of the electron-rich dimethoxybenzene ring with the electron-



Scheme 63



	R	Time (min)	Yield
a	$CH_2C(Cl)=CH_2$	105	97%
b	$CH_2C(CH_3)=CH_2$	130	94%
c	$CH_2CH=CHCH_3$	35	91%
d	$CH_2CH=CHPh$	30	94%
e	$CH_2CH=CH_2$	25	87%

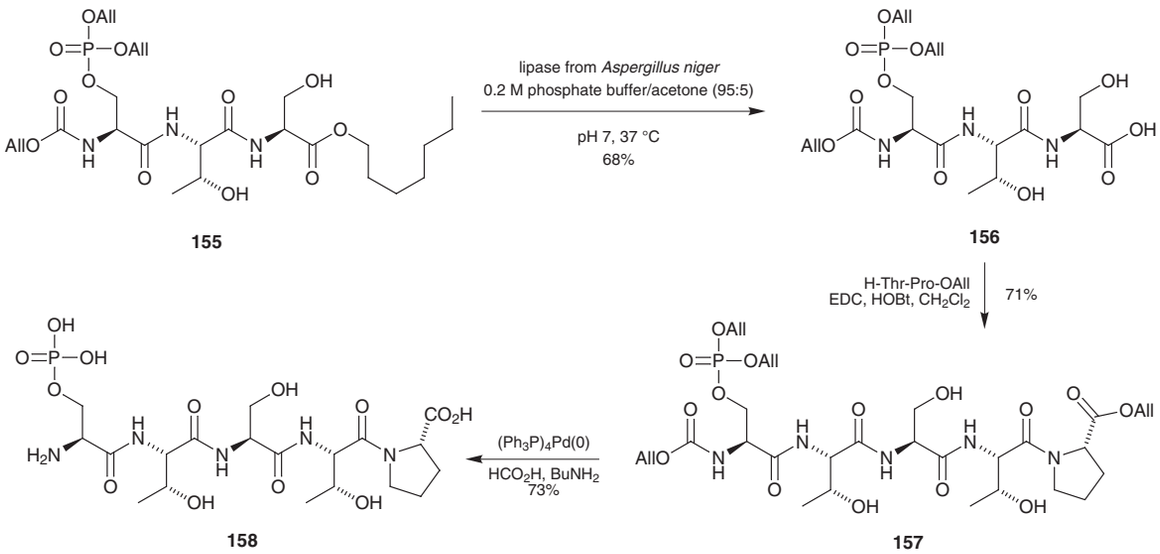
Scheme 64

deficient oxygen of the n,π* singlet excited acetophenone, to form an intramolecular exciplex **166** which can return to **165** or react to give cation **167** (Scheme 68). This mechanism accounts for the high efficiency of the substitution pattern of the methoxy groups as well as the absence of solvent-substitution or radical-derived products in 3′,5′-dimethoxybenzoin photochemistry.

During a synthesis of the challenging cyclodepsipeptide antibiotic enopeptin B, Schmidt and co-workers[99] required an acid labile protecting group that could be removed in the presence of a *tert*-butyl ester and a sensitive pentenedioyl system. The task was accomplished using a *tert*-butyldiphenylsilyl ester which was removed from the fragment **169** using aqueous HF in acetonitrile–THF (Scheme 69).

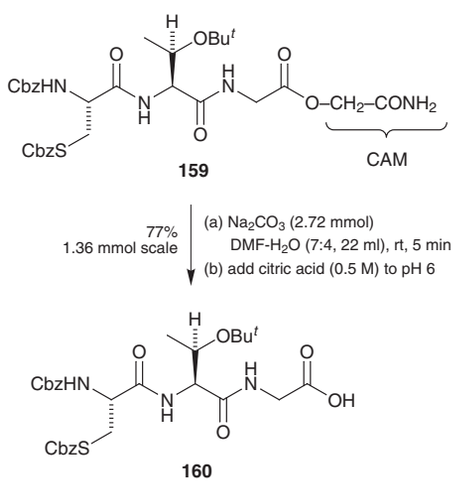
An alternative synthesis of Corey's OBO group has been reported by Charette and Chua[100] (Scheme 70). Imino and iminium triflates derived from secondary and tertiary amides respectively, react with 2,2-bis(hydroxymethyl)propan-1-ol in the presence of pyridine to give the orthoester. Primary amides cannot be used as substrates because they dehydrate to the nitrile under the reaction conditions.

A new method for the protection of polyfunctionalised carboxylic acids involves a zirconocene-catalysed epoxy ester–ortho ester rearrangement.[101] A synthesis of a γ-hydroxyleucine derivative **174** illustrates the method (Scheme 71). The epoxy ester **172** prepared from (2*S*)-2-(benzyloxycarbonylamino)-succinic acid 4-methyl ester **171** was treated with zirconocene dichloride in the presence of silver(I) perchlorate to give the 2,7,8-trioxabicyclo[3.2.1]octane (ABO) derivative **173** in 99% yield. Reaction of the remaining ester function with excess methylmagnesium bromide followed by hydrolysis gave the target molecule **174**. The ABO ortho ester derivatives of a number of amino acids were prepared in 90–100% yield by this



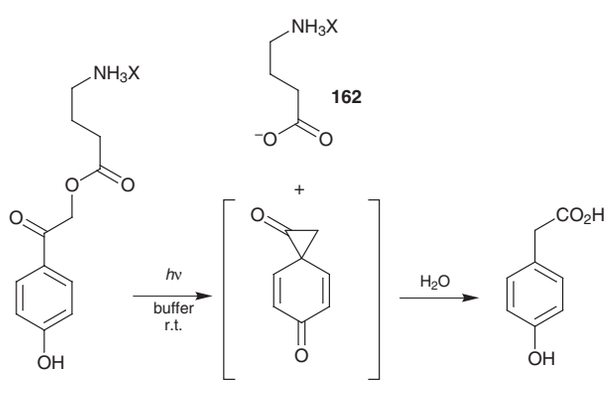
155 156 157 158

Scheme 65



159 160

Scheme 66

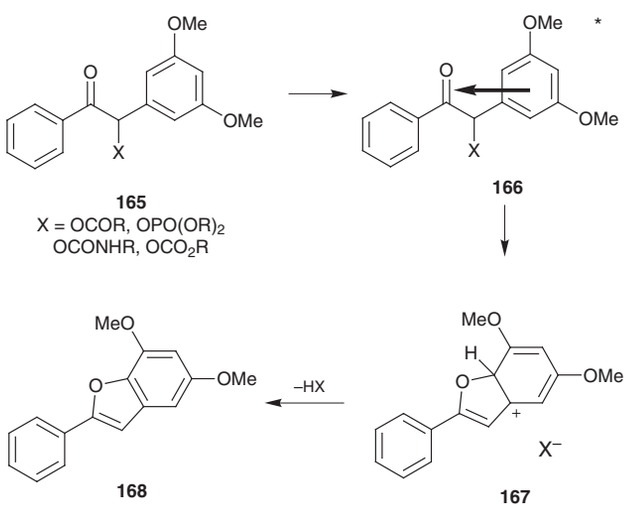


161 162 163 164

Scheme 67

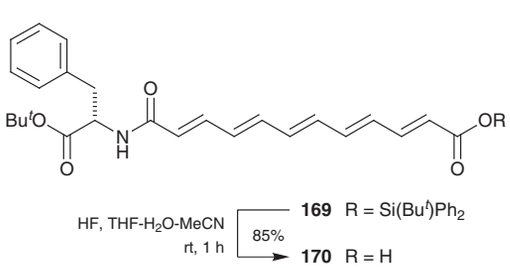
procedure. A potentially useful feature of the new ABO protecting group is its greater stability towards mild acid hydrolysis than the 2,6,7-trioxabicyclo[2.2.2]octane (OBO) ortho ester.[102] Thus, OBO groups hydrolyse in 2 min with pyridinium tosylate in aqueous methanol whereas the corresponding ABO group requires 22 h.

A synthesis of α-hydroxy-β-homoarginine derivative **177** (Scheme 72) was accomplished[103] by the addition of [tris-(methylthio)methyl]lithium[104] to the aldehyde **175** followed by Hg^{2+}-catalysed methanolysis of the resultant orthothioester **176**.



165 166 167 168

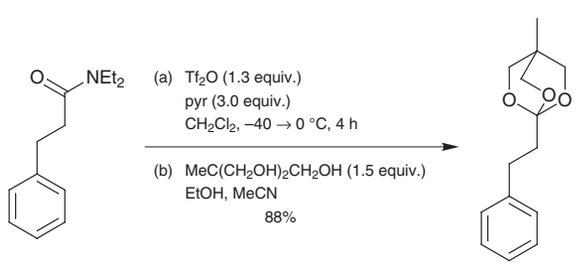
Scheme 68



169 R = Si(Bu^t)Ph$_2$

170 R = H

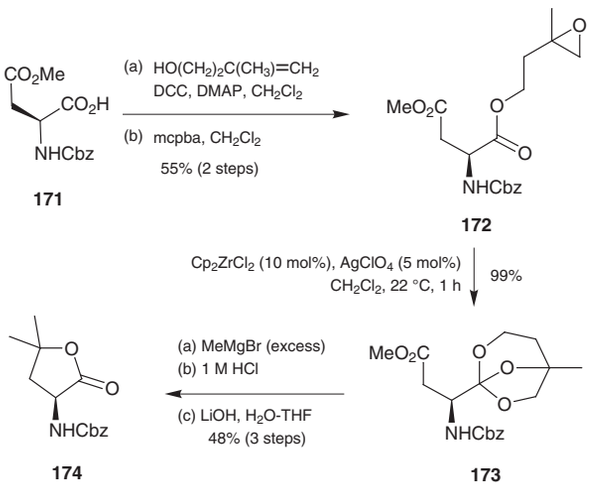
Scheme 69



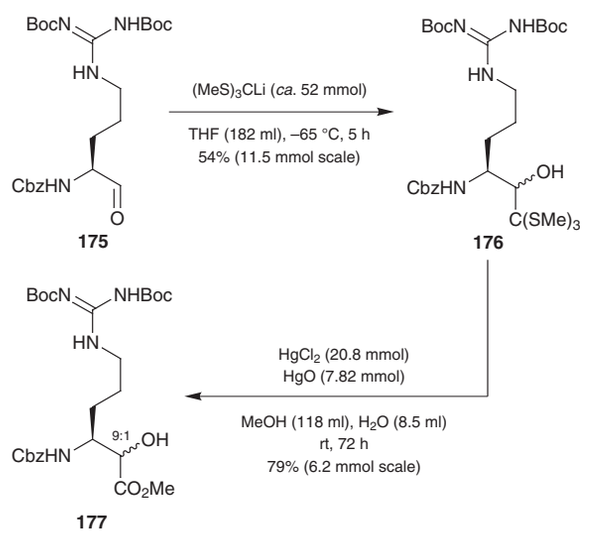
Scheme 70

6 Phosphate protecting groups

The (*N*-trifluoroacetylamino)butyl and (*N*-trifluoroacetylamino)pentyl groups have been reported as alternatives to



Scheme 71

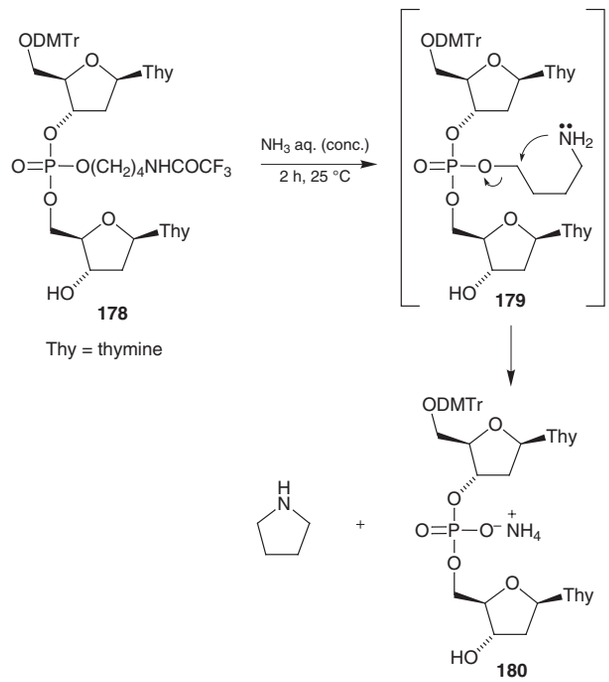


Scheme 72

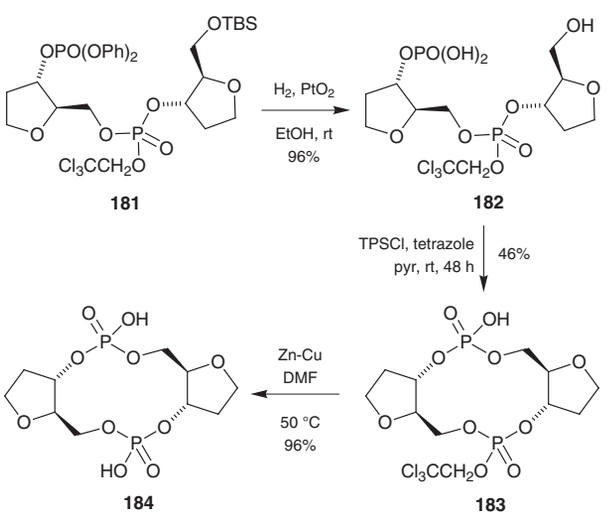
the traditional 2-cyanoethyl phosphate protecting group in the solid phase synthesis of nucleosides.[105] They can be removed from oligonucleotides (*e.g.* **178**) by treatment with conc. aqueous ammonia at ambient temperature (Scheme 73). Note that cleavage of 2-cyanoethyl phosphates is usually carried out in non-nucleophilic basic conditions using DBU. The deprotection kinetics, examined in the case of dimer **178**, showed that the initial rate-limiting cleavage of the *N*-trifluoroacetyl group was followed by a rapid cyclodeesterification of the intermediate **179**. Complete conversion occurred within 2 h at 25 °C producing phosphodiester **180** and innocuous pyrrolidine. By comparison, deprotection of a 2-cyanoethyl group releases acrylonitrile which can form an addition by-product with nucleobases.

The C_2-symmetric cyclic bis(phosphate) **184**, a potent inhibitor of oligonucleotide processing enzymes including RNA integrase, was synthesised from 2-deoxy-D-ribose in 18% overall yield.[106] The synthesis required two orthogonal phosphate protecting groups (Scheme 74). In the closing stages of the synthesis the diphenyl phosphate ester **181** was hydrogenolysed to generate the free acid, which promoted concomitant cleavage of the TBS ether. Cyclisation of **182** was accomplished with 2,4,6-triisopropylbenzenesulfonyl chloride (TPSCl) giving **183** in a 46% yield. Finally, reductive cleavage of the trichloroethyl group with zinc–copper alloy returned the target in 96% yield.

Recent studies on the *myo*-inositol cycle have revealed a family of pyrophosphoryl *myo*-inositol pentaphosphates (PP-

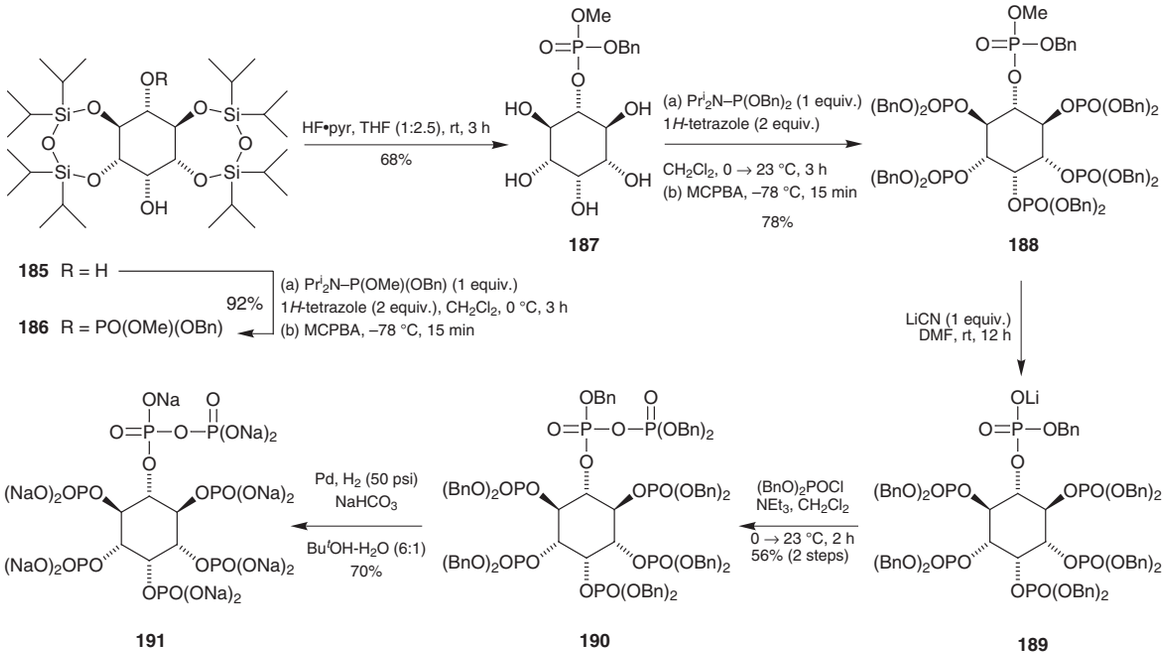


Scheme 73

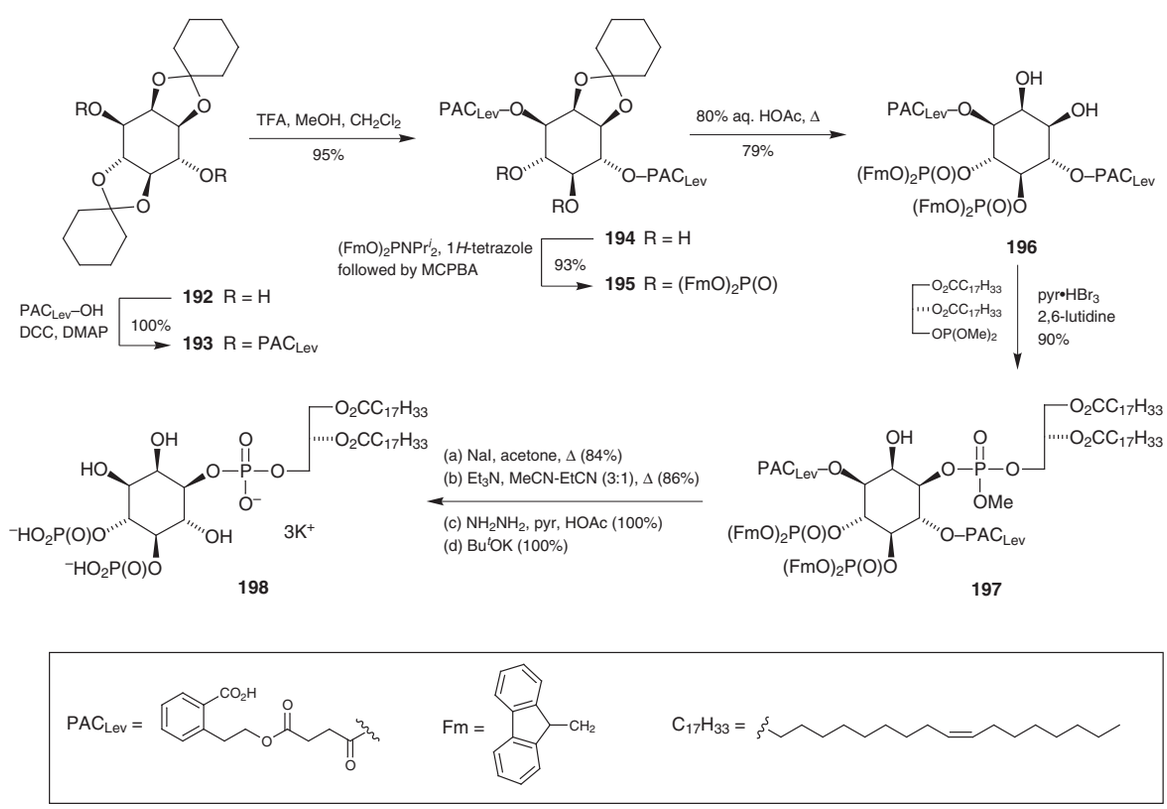


Scheme 74

$InsP_5$) and related bis-pyrophosphates which have an unusually high metabolic turnover consistent with the speculation that they act as phosphate donors for unidentified kinases. The Falck group[107] have described a stereocontrolled synthesis of 5-PP-D-*myo*-$InsP_5$ (**191**) outlined in Scheme 75 which illustrates how a single phosphate residue in a hexakisphosphate derivative can be transformed selectively to a pyrophosphate. The readily available *myo*-inositol bis-disilanoxylidene **185** was phosphorylated selectively at the less hindered equatorial C5 hydroxy group. Desilylation of **186** required carefully controlled conditions as more basic or acidic reagents such as TBAF, HF or TFA afforded a complex mixture. The desilylation was best achieved using HF·pyridine complex whereupon the desired pentaol **187** was produced in 68% yield. Phosphorylation of the liberated hydroxy groups gave hexakisphosphate **188**. Then conversion of the C5 phosphate to the corresponding pyrophosphate was initiated by specific cleavage of the phosphate methyl ester using one equivalent of lithium cyanide at room temperature. The resultant lithium salt **189** was coupled immediately with dibenzyl chlorophosphonate to give the protected pyrophosphate derivative **190**. Finally the sequence was completed by hydrogenolysis of the benzyl phos-



Scheme 75

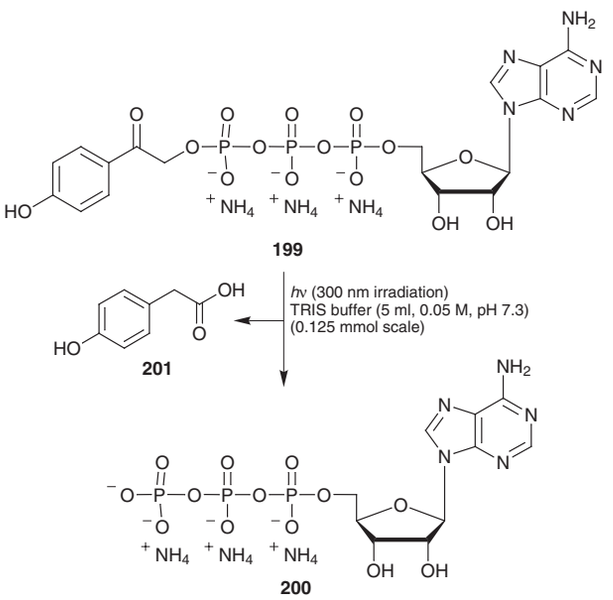


Scheme 76

phate esters in the presence of sodium hydrogen carbonate to give the target **191**. A similar sequence was used to prepare 2-PP-D-*myo*-InsP$_5$.

A recent synthesis of a DL-1,2-di-*O*-oleoyl-*sn*-glyceryl phosphate analogue of phosphatidylinositol 4,5-bisphosphate **198** (Scheme 76) incorporated fluoren-9-ylmethyl (Fm) esters as protecting groups for phosphate.[108] The synthesis began with the protection of the 3,6-dihydroxy functions in the inositol derivative **192** as their 2-[2-(levulinoyloxy)ethyl]benzoyl (PAC$_{Lev}$) esters.[109] Phosphorylation of the 4,5-diol functions with difluorenylmethyl phosphoramidite gave the fluoren-9-ylmethyl diester **195** after oxidation of the phosphite intermediate with *m*-chloroperoxybenzoic acid. Subsequent regioselective phosphorylation of the 1-hydroxy function in diol **196** gave the triphosphate **197** which completed the assembly of the components of the target. The deprotection regime began with the 1-phosphate group (NaI) followed by the fluorenylmethyl phosphates at the 4- and 5-positions using triethylamine. The first Fm group in each phosphate was removed at room temperature and the mixture then heated to remove the second Fm group. Finally, the PAV$_{Lev}$ esters were removed by reaction with hydrazine in pyridine and acetic acid and the resultant hydroxyethylbenzoates were treated with KOBu^t to afford the final product **198**.

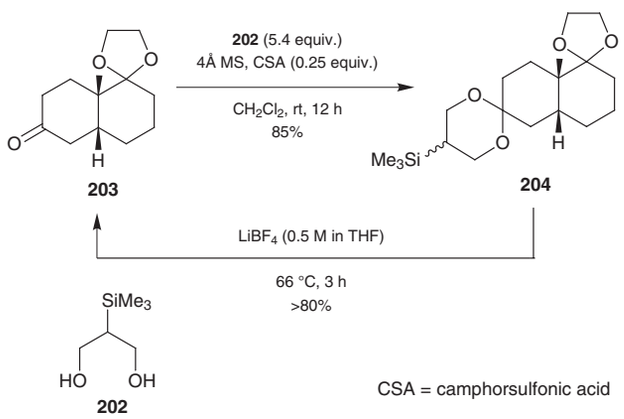
Photoactivated protective groups play an important role in the study of biochemical mechanisms, allowing the rapid and efficient release of bioactive compounds in the tested environment. Recently Park and Givens[110] demonstrated that *p*-hydroxyphenacyl groups can be used to trigger the photorelease of adenosine 5′-triphosphate (ATP, **200**) from the protected nucleotide **199** when irradiated at wavelengths between 300–350 nm (Scheme 77). *p*-Hydroxyphenacyl phototrigger compares favourably with other photoactivated protecting groups (*e.g.* desyl) because it has no chiral centres and has a better aqueous buffer solubility. Also, the by-product of the photolysis—*p*-hydroxyphenylacetic acid **201**—does not compete for the incident radiation in the 300–400 nm region, which improves the yield of the photolysis.



Scheme 77

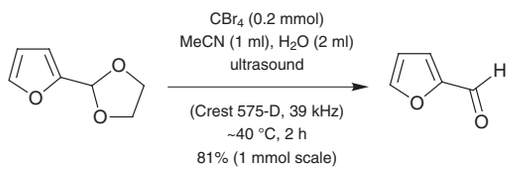
7 Carbonyl protecting groups

Lipshutz and co-workers[111] devised a new carbonyl protecting group which involves the formation of 'cyclo-SEM' derivatives (*e.g.* **204**, Scheme 78) in the reaction with 2-trimethylsilylpropane-1,3-diol (**202**). The deprotection is achieved with lithium tetrafluoroborate in THF which also allows the selective unmasking of one carbonyl group in **204** (only 2–3% of the corresponding diketone is observed). The choice of solvent can affect the selectivity of the deprotection; *e.g.* in MeCN the cyclo-SEM group as well as standard 1,3-dioxane and 1,3-dioxolane derivatives are removed.



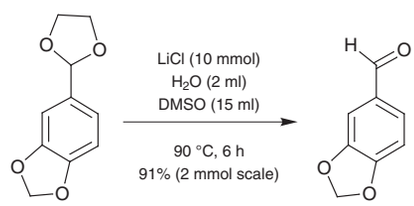
Scheme 78

Lee and Cheng[112] reported that acetals and ketals can be deprotected to the corresponding carbonyl compounds using a catalytic amount of carbon tetrabromide in acetonitrile–water mixture under either ultrasound or thermal (reflux) conditions (Scheme 79). Ultrasound conditions are milder; *e.g.* acetals containing strong electronegative substituents (like *p*-nitrobenzaldehyde derivatives) remain intact.



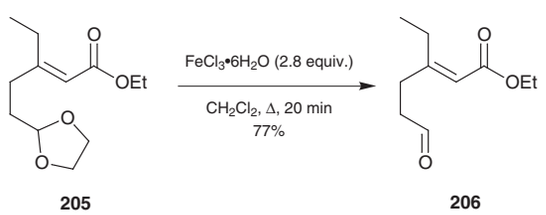
Scheme 79

A method for the cleavage of acetals and ketals to the corresponding carbonyl compounds using lithium chloride and water in DMSO at elevated temperatures (90–130 °C) has been described.[113] The method is limited to systems which give α,β-unsaturated aldehydes and ketones. Diaryl and saturated compounds remain intact allowing selective deprotection, as illustrated in Scheme 80.



Scheme 80

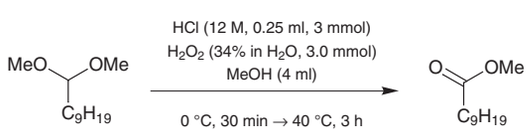
Ferric chloride hexahydrate in dichloromethane is a mild reagent for deprotecting acetals (Scheme 81) and the method is compatible with some acid sensitive groups.[79] For example, **205** was inert to olefin isomerisation under the conditions even after long reaction times.



Scheme 81

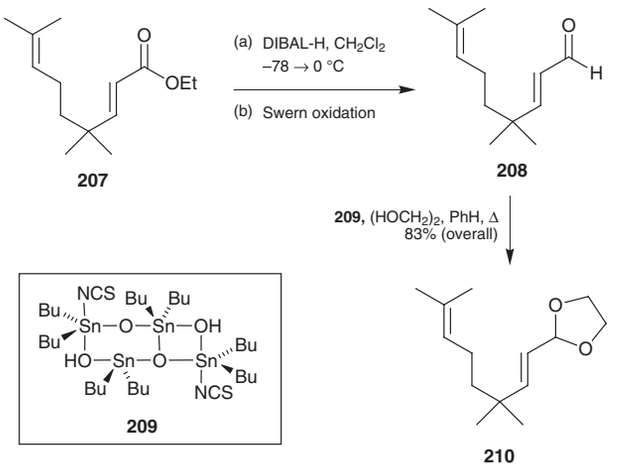
1,3-Dioxolanes are cleaved[114] in good yield using 1.5 equivalents of $CeCl_3$–$7H_2O$ in acetonitrile at room temperature. The deprotection can be hastened by adding a catalytic amount of sodium iodide and/or by heating to reflux. It is not possible to ascertain from the 13 examples cited whether these new conditions offer tangible benefits over the traditional aqueous acidic conditions.

One step conversion of acetals to esters can be achieved with hydrogen peroxide and hydrochloric acid in alcohols (Scheme 82).[115] The reaction works well with saturated compounds but with α,β-unsaturated acetals the yield is low due to competitive addition of HCl to the olefin.



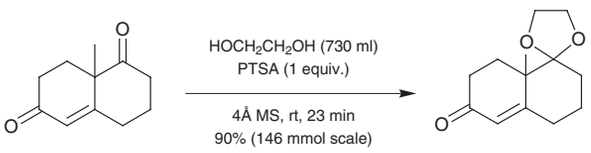
Scheme 82

Acetalisation of α,β-unsaturated carbonyl compounds is often difficult with conventional acid catalysts. In 1992 Otera and co-workers[116] reported that distannoxanes (*e.g.* **209**, Scheme 83) are extremely active catalysts for acetalisation. The reaction proceeds under almost neutral conditions and thus is recommended for sensitive compounds like enones and enals. Recently Malacria and co-workers[117] successfully used **209** for the protection of unsaturated aldehyde **208**.



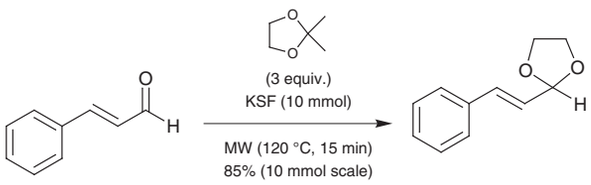
Scheme 83

The classical ketalisation of the Wieland–Miescher ketone **211** (ethylene glycol, benzene, PTSA, reflux) (Scheme 84) is capricious. It results in moderate yields of **212** due to the formation of the corresponding bisketal and also because of the presence of unreacted **211** in the reaction mixture. However, selective ketalisation of **211** can be achieved in high yield using ethylene glycol as solvent and a stoichiometric amount of PTSA.[118]



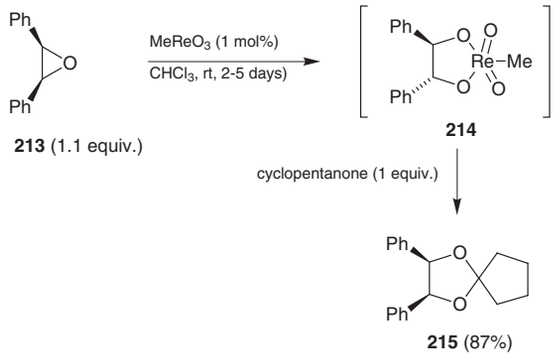
Scheme 84

Solvent free acetalisation of aldehydes and ketones under microwave irradiation has been described by Hamelin and co-workers.[119] Methyl or ethyl orthoformates, ethylene glycol or 2,2-dimethyl-1,3-dioxolane can be used as reagents and PTSA or montmorillonite clay KSF as a catalyst (Scheme 85).



Scheme 85

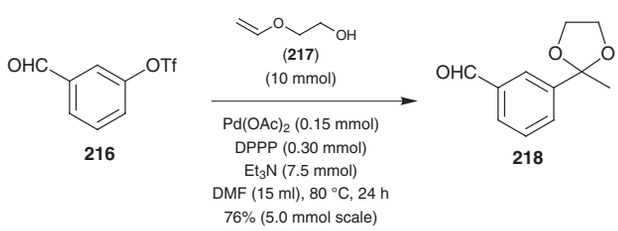
A new synthesis of dioxolanes from oxiranes and carbonyl compounds has been reported[120] which is catalysed by methylrhenium trioxide. The stereochemistry of the starting oxirane is retained in the final product owing to two inversions in the sequence depicted in Scheme 86. Aldehydes and cyclic ketones give good yields but acyclic ketones such as pentan-3-one and cyclic conjugated enones such as cyclohexenone give poor to modest yields. In some cases the bis(alkoxy)rhenium(VII) complexes **214** could be detected. Ketene acetals and oxazolidines



Scheme 86

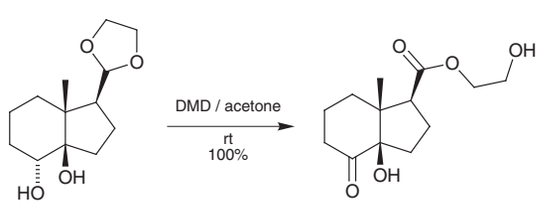
can also be formed from the analogous reaction of oxiranes with ketenes and aldimines respectively.

Cyclic ketals of acetophenone can be prepared directly by the reaction of aryl triflates, bromides or iodides (*e.g.* **216**, Scheme 87) with hydroxyalkyl vinyl ethers (*e.g.* **217**) in the presence of a catalytic amount of palladium(II) acetate and 1,3-bis(diphenylphosphino)propane (DPPP).[121] The example illustrated in Scheme 87 is especially noteworthy since the protected methyl ketone was introduced in the presence of a reactive aldehyde functionality.



Scheme 87

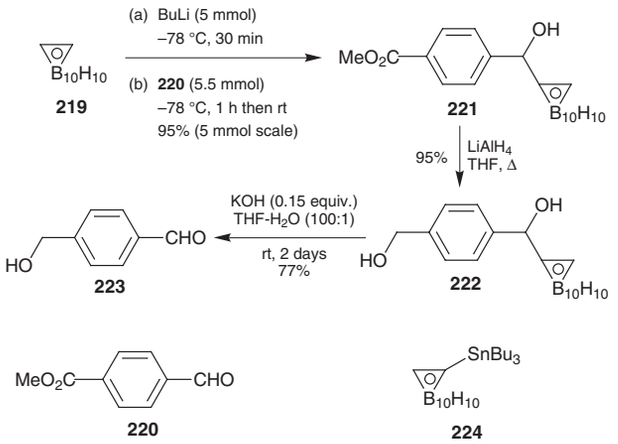
Acetals are susceptible to oxidation by ozone and dioxolane derivatives are especially reactive giving 2-hydroxyethyl esters at a rate comparable with the oxidation of alkenes.[122] Frigerio and co-workers[123] recently showed that dimethyldioxirane (DMD) also effects the oxidation of dioxolanes in good yield. In the single example illustrated in Scheme 88, the secondary alcohol function is also oxidised to a ketone.



Scheme 88

Deprotection of thioacetals using clay supported ammonium nitrate[124–126] and zirconium sulfophenyl phosphonate[127] has also been reported recently.

Yamamoto and co-workers[128] reported a new protecting group for aldehydes and ketones which is based on the reaction of a carbonyl compound (*e.g.* **220**, Scheme 89) with lithiocarborane (formed by treatment of *o*-carborane **219** with *n*-butyllithium). The addition product **221**, unlike acetals, is stable under aqueous protic acid and Lewis acid conditions. The adduct can be easily converted back into the corresponding carbonyl compound under basic conditions using a catalytic amount of KOH in aqueous THF. The practical application of the methodology is illustrated in Scheme 89. Reduction of the ester group in **221** by lithium aluminium hydride gave alcohol **222** which, after deprotection of the carbonyl function,

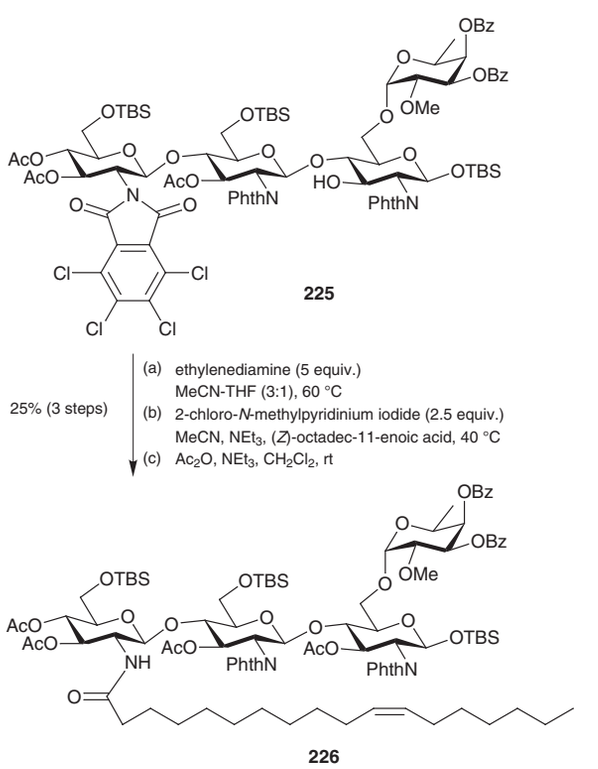


Scheme 89

yielded hydroxy aldehyde **223**. Chemoselective protection of an aldehyde in the presence of a ketone can also be accomplished using *o*-carboranyltributylstannane **224** and a catalytic amount of $Pd_2dba_3{\cdot}CHCl_3$.

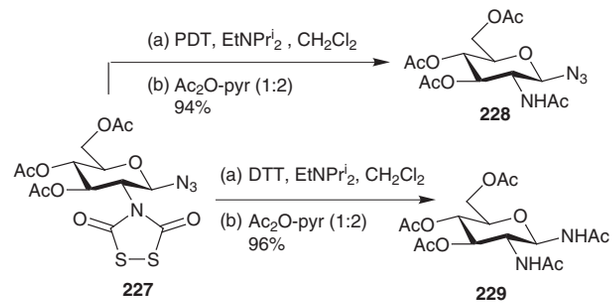
8 Amino protecting groups

A key element in Fraser-Reid's synthesis of nodulation factor NodRf-III (C18:1, MeFuc) was the use of a tetrachlorophthaloyl (TCP) group to provide *N*-differentiation of the linear glucosamine backbone.[13] Thus installation of the (*Z*)-octadec-11-enoyl group on the terminal glucosamine began by selective deprotection of the TCP group in tetrasaccharide **225** (Scheme 90) using only 5 equivalents of ethylenediamine. After amide bond formation and esterification of any deprotected acetates, the two remaining phthalimide (Phth) groups were removed by heating **226** in EtOH at 90 °C for 34 h with 500 equivalents of ethylenediamine.



Scheme 90

In the course of studies concerning the development of orthogonal protecting group schemes for glycopeptide synthesis, the selectivity between the reduction of *N*-dithiasuccinyl (N-Dts) and azido functionalities has been investigated.[129] By use of propane-1,3-dithiol (PDT) in the presence of diisopropylethylamine (DIPEA), it is possible to reduce selectively the *N*-Dts group of **227** (Scheme 91) without affecting the azido group. On the other hand, the more reactive dithiothreitol (DTT)–DIPEA reduced both groups affording **229** in 96% yield after acetylation.



Scheme 91

During their synthesis of disaccharide **234** bearing an ethanolamine phosphate group (PEA), van Boom and coworkers[130] reported the first example of immobilised penicillin-G acylase mediated deblocking of an *N*-phenylacyl-protected PEA moiety. The introduction of the protected phosphate group was achieved in the reaction of disaccharide **230** (Scheme 92) with phosphoramidite **232**. Oxidation of the intermediate phosphite triester with *tert*-butyl hydroperoxide and triethylamine was accompanied by the simultaneous deprotection of the 2-cyanoethyl group. The resulting protected phosphodiester **231** was subjected to hydrogenation (to cleave the Cbz and benzyl groups) followed by treatment with immobilised penicillin-G acylase (Seperase G) to remove the *N*-phenylacetyl group from the PEA moiety.

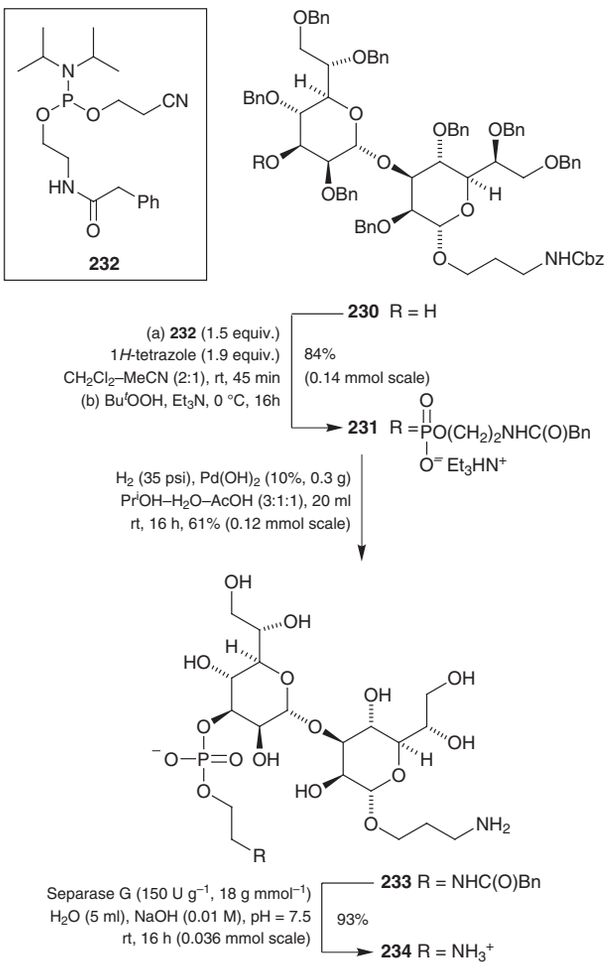
A similar application of penicillin-G acylase for the deprotection of *N*-phenylacetyl-protected nucleobases in oligonucleotides has been reported by the Waldmann group.[131]

The use of a picolinoyl group as an electrochemically removable protecting group for amines in peptide synthesis has been reported.[132] The protection step is carried out by treating an amino acid ester or peptide (*e.g.* **235**, Scheme 93) with pipecolinic acid (Pic-OH), 1-hydroxybenzotriazole (HOBT), *N*-methylmorpholine (NMM) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC). The picolinoyl protecting group is then removed from the tripeptide **237** by electrolysis at $E = -1300$ mV *vs.* saturated calomel electrode (SCE). The deprotection can be performed selectively in the presence of tosyl, benzyloxycarbonyl, *O*-benzyl, *tert*-butoxycarbonyl and *O*-*tert*-butyl groups. However, two groups turned out to be incompatible: trichloroethoxycarbonyl (Troc) (probably because of competitive cleavage of the C–Cl bond) and fluoren-9-ylmethoxycarbonyl (solubility problems).

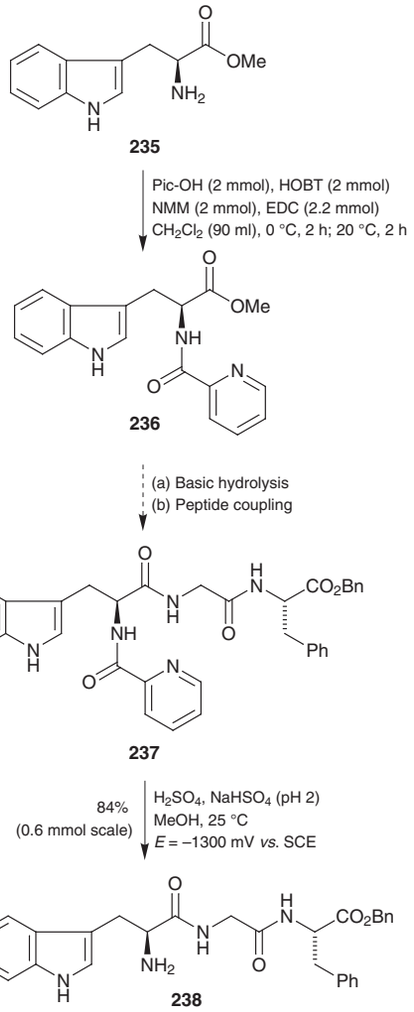
The pent-4-enoyl group[133] has been used for protection of an α-amino function during the synthesis of aminoacylated transfer RNA's (Scheme 94).[134] The protection step is carried out by treating the methyl ester of (*S*)-valine **239** with pent-4-enoic anhydride. The product **240** was then attached to a nucleotide to give **241**. Deblocking was then effected by treatment with iodine.

Stannic chloride in ethyl acetate is a new reagent for the deprotection of bis-Boc substituted guanidines[135] (*e.g.* **243**, Scheme 95). The reagent is milder than the trifluoroacetic acid typically used and gives good yields of the corresponding solid guanidinium chlorides **244** whereas trifluoroacetate salts are difficult to crystallise.

During a synthesis of the serine protease inhibitor cyclotheonamide B, a Dutch group[103] found that under many acidic conditions, the *O*-(*tert*-butyl)tyrosine in the dipeptide **245**



Scheme 92

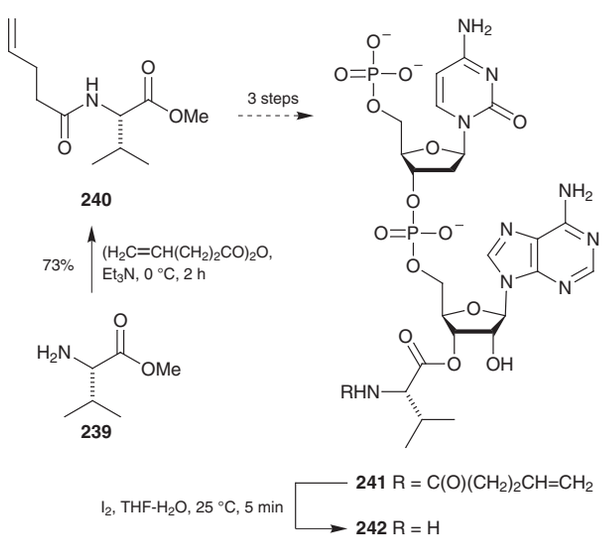


Scheme 93

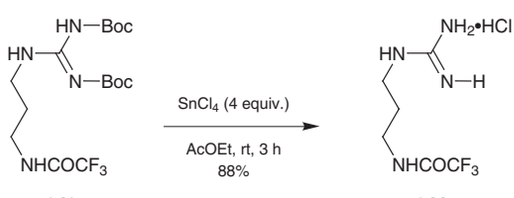
(Scheme 96) cleaved more rapidly than the *N*-Boc group. Fortunately, using the conditions of Ohfune and co-workers,[136,137] the *N*-Boc group could be cleaved selectively using TMSOTf followed by aqueous workup. The extreme sensitivity of an *O*-(*tert*-butyl)tyrosine derivative towards careful treatment with HCl in ethyl acetate (1 M, 500 mol%) was also recently established in a study aimed at selective cleavage of *N*-Boc groups in the presence of other acid-labile protecting groups such as *tert*-butyl esters, aliphatic *tert*-butyl ethers, *S*-Boc groups and *S*-trityl ethers.[138]

During the early stages of Myers' synthesis of dynemicin A,[7] deprotection of the Boc group in **247** (Scheme 97) was required in order to effect internal amidation for the preparation of the quinolone **248**. Initial experiments confirmed that the enol ether function in **247** was too labile to the acidic conditions usually associated with Boc deprotection (*e.g.* trifluoroacetic acid in dichloromethane). However, by heating **247** in the weakly acidic 4-chlorophenol (180 °C, 30 min) the Boc group was cleaved while preserving the enol ether function to give the quinolone **248** in 84% yield. 4-Chlorophenol was the optimal solvent for the deprotection/amidation since aprotic solvents such as diphenyl ether gave very slow reaction and phenol itself was slower and gave a messy reaction with by-products derived from reaction with the phenol.

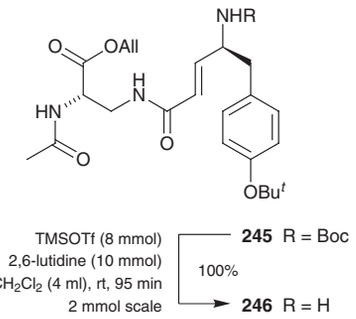
The azinomycins are antitumour antibiotics isolated from the culture broth of strain *Streptomyces griseofuscus* S42227. During a study directed towards the synthesis of the aziridine core of the azinomycins, Coleman and Carpenter[139] had encountered difficulties in removing the benzyloxycarbonyl (Cbz) group from the aziridine **249** (Scheme 98). For example, hydrogenolysis using various palladium catalysts [Pd–C, Pd-$(OH)_2$, Pd black, Pd–Al_2O_3] was incompatible with the bromo-



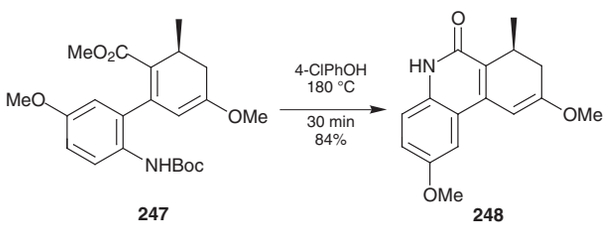
Scheme 94



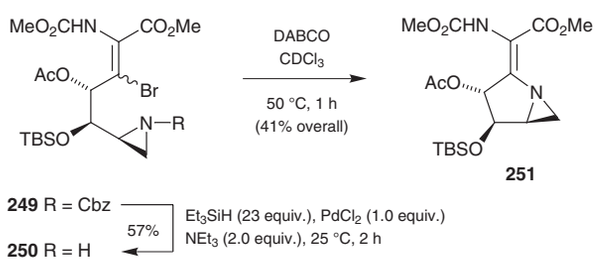
Scheme 95



Scheme 96



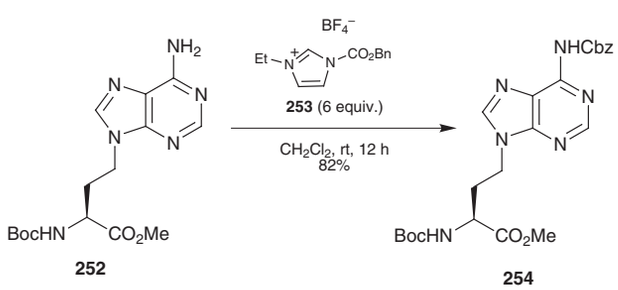
Scheme 97



Scheme 98

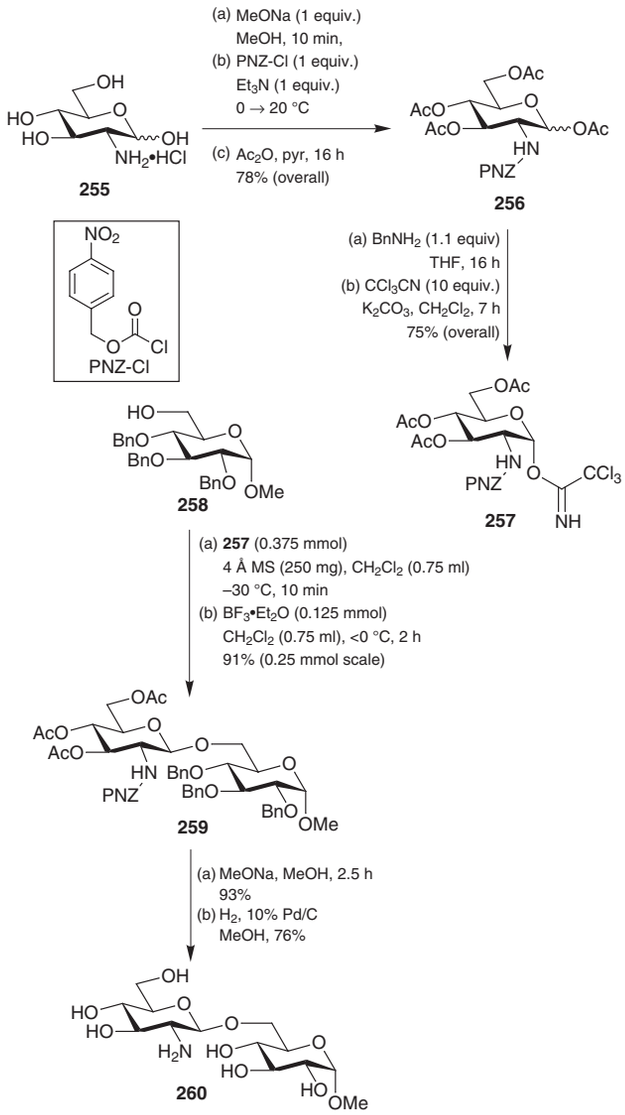
alkene. Success was eventually achieved using the conditions of Birkofer:[140] $PdCl_2$, Et_3SiH, NEt_3, 25 °C.

Peptide nucleic acid (PNA) analogues of DNA have attracted interest as potential regulators of gene expression owing to their ability to invade duplex DNA, thereby forming PNA : DNA heteroduplexes. During a synthesis of the requisite α-amino acids harbouring the four DNA bases in the side chain, difficulty was encountered protecting the N^6-amino group of the adenine in compound **252** as its Cbz derivative.[141] Treatment with benzyl chloroformate under all the usual conditions did not give clean or efficient acylation. However, when 1-(benzyloxycarbonyl)-3-ethylimidazolium tetrafluoroborate (**253**, Rapoport's reagent[142]) was used instead, the desired acylation was both clean and efficient (Scheme 99).



Scheme 99

The *p*-nitrobenzyloxycarbonyl (PNZ) *N*-protecting group has been reported as a participating group in the stereoselective formation of 2-amino-β-glucosides (Scheme 100).[143] The protection was carried out in the reaction of glucosamine hydrochloride **255** with sodium methoxide in methanol followed by *p*-nitrobenzyl chloroformate (PNZ-Cl) and triethylamine. Subsequent acetylation gave the protected amino-sugar **256** in 81% overall yield. The trichloroacetamide **257** was formed by regioselective deacetylation with benzylamine followed by treatment with Cl_3CCN in the presence of potassium carbonate. Glycosidation of **258** with the glycosyl donor **257** was carried out using boron trifluoride–diethyl ether as a promoter to give the disaccharide **259** in 91% yield. This result indicates that the combination of the PNZ moiety with anomeric trichloroacetimidate activation achieves β-glycosidation in high yield with high stereoselectivity. Finally the PNZ group was removed by hydrogenolysis along with *O*-benzyl ethers to give **260** in 76% yield. Alternatively the PNZ group can be deprotected selectively by sodium dithionite under neutral conditions where benzyl ethers and carboxylate esters remain intact. Since *O*-acetyl groups can be removed by treatment with MeONa–MeOH in the presence of the PNZ group, this makes the PNZ group effectively an orthogonal protecting group in oligosaccharide synthesis.



Scheme 100

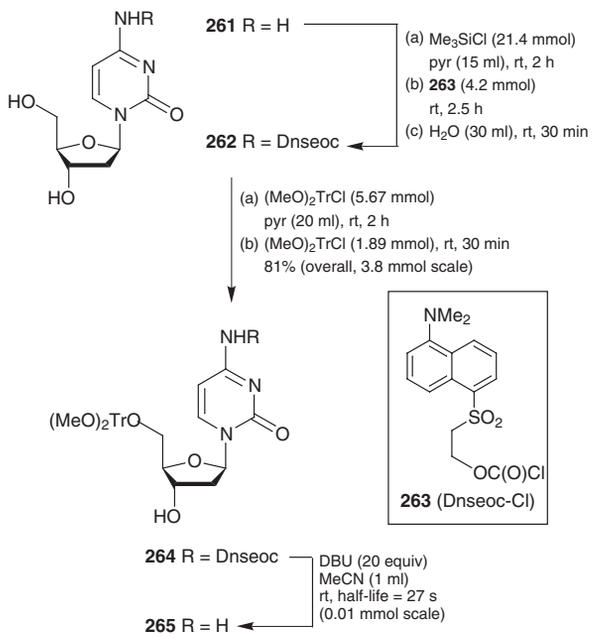
A German group[144] has introduced the [(2-{[5-(dimethylamino)-1-naphthyl]sulfonyl}ethoxy)carbonyl] group (Dnseoc) for protection of amino function in nucleobases during oligonucleotide synthesis (Scheme 101). The nucleoside (*e.g.* **261**) could be protected directly in the reaction with Dnseoc-Cl (**263**) and *N*-methyl-1*H*-imidazole. However a better result was obtained when the two hydroxy groups were temporarily transformed into TMS ethers followed by reaction with **263** and desilylation. The crude product **262** was then treated with 4,4′-

dimethoxytrityl chloride to afford protected nucleoside **264** in 81% overall yield from **261**. Deprotection of the nucleobase was achieved by reaction with excess 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU). Kinetic experiments showed that the rate of deprotection was much faster than the previously used [2-(4-nitrophenyl)ethoxy]carbonyl (Npeoc) group. In most cases complete deprotection occurred within 30 min.

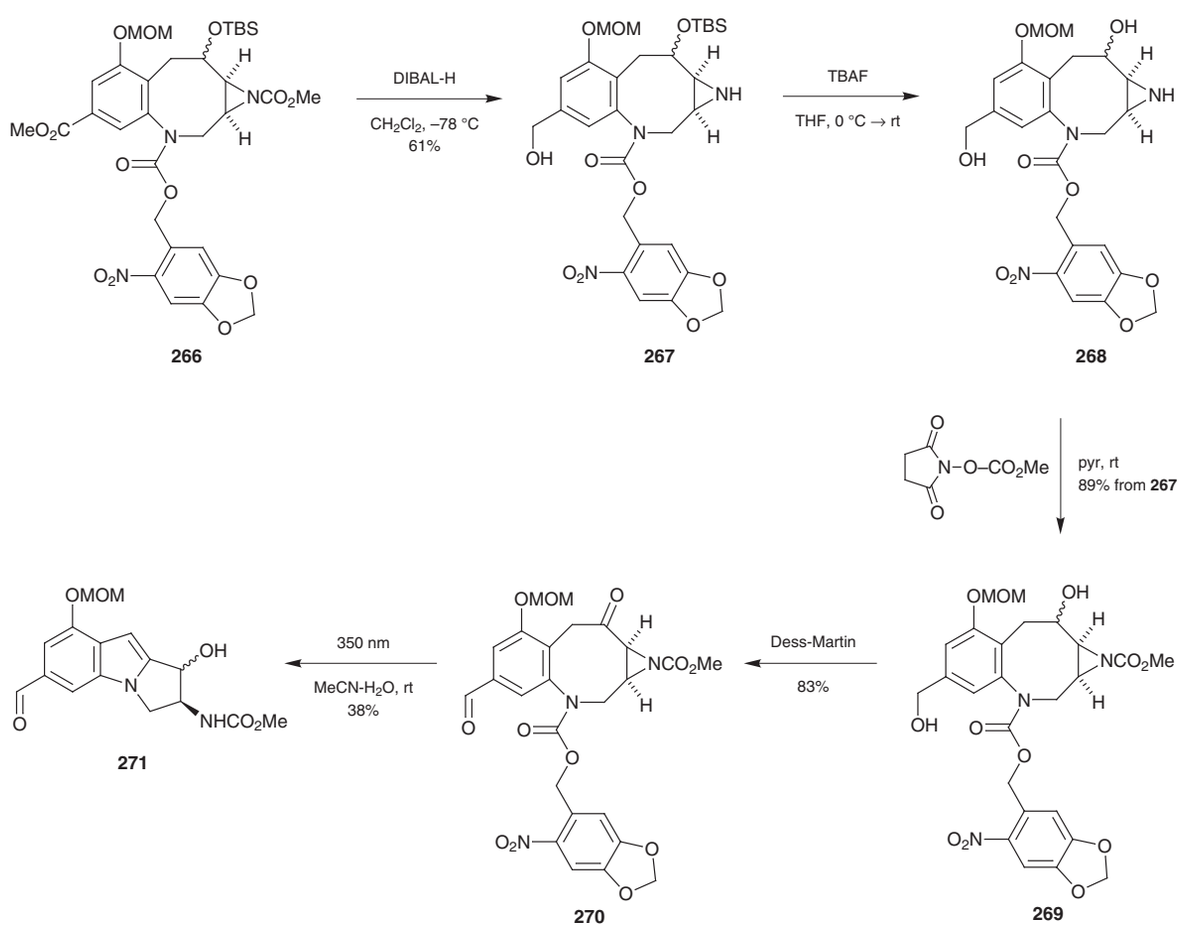
FR 900482 isolated from the fermentation broth of *Streptomyces sandaensis* shows promising anti-tumour activity owing to its ability to cross-link DNA. In studies directed towards the synthesis of FR 900482, Rollins and Williams[145] were unable to deprotect the TBS ether in intermediate **266** (Scheme 102) without prior deprotection of the adjacent aziridine. Simultaneous *N*-deprotection and reduction of the ester function was accomplished in 61% yield using DIBAL-H without competing reduction of the 6-nitroveratryloxycarbonyl (Nvoc) group. Cleavage of the TBS ether with TBAF followed by restoration of the methoxycarbonyl group using *N*-(methoxycarbonyloxy)succinimide gave **269** in 89% yield for the two steps. After Dess–Martin oxidation to the keto aldehyde **270**, the Nvoc group was removed photochemically to give the target mitosene derivative **271** in 38% yield.

Carpino *et al.* have invented a new base-sensitive amino protecting group which is more labile than the ubiquitous Fmoc group.[146] The 1,1-dioxobenzo[*b*]thiophene-2-methoxycarbonyl (Bsmoc) group is introduced *via* its chloroformate or *N*-hydroxysuccinimide derivative and it is stable to peptide coupling in solution or solid phase using acyl fluorides or *in situ* activation *via* ammonium or phosphonium salts. The Bsmoc group is stable towards tertiary amines (pyridine, diisopropylethylamine) for 24 h but deblocking occurs (*via* nucleophilic addition followed by β-elimination) within 3–5 min using piperidine or tris(2-aminoethyl)amine (TAEA). In Fmoc chemistry the deblocking event generates dibenzofulvene which is subsequently scavenged—an event which may not be very efficient on solid phases. However, a particular advantage of the Bsmoc group is that the deblocking and scavenging reactions are identical as illustrated in Scheme 103. The intermediate **273** decays over 8–10 min to give the final stable deblocking product **274**.

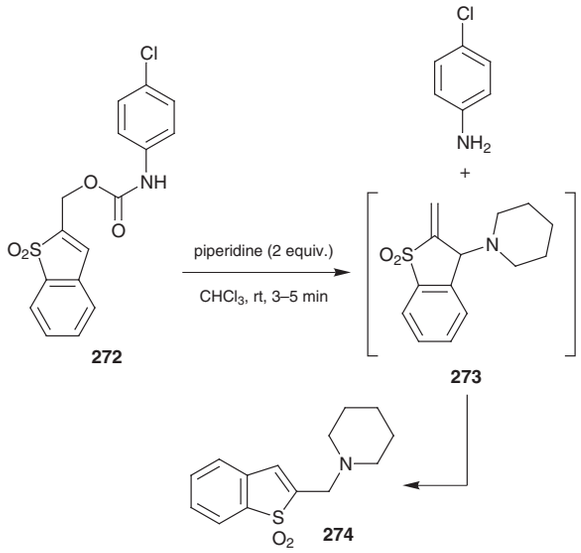
A synthesis of Bsmoc-$(Leu)_3$-OFm illustrates the selective deblocking of the *N*-Bsmoc in the presence of a fluoren-9-ylmethyl (Fm) ester. Thus, treatment of Bsmoc-Leu-OFm with 2% TAEA in dichloromethane followed by coupling with



Scheme 101



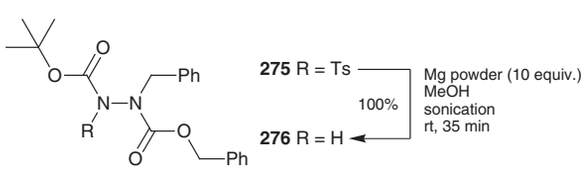
Scheme 102



Scheme 103

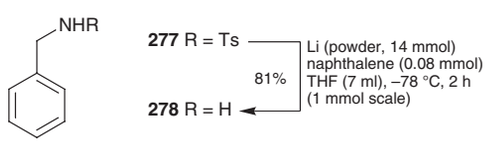
Bsmoc-Leu-F and subsequent repetition of the procedure produced the target tripeptide. However, selective cleavage of the fluoren-9-ylmethyl ester could be accomplished using 10% *N*-methylcyclohexylamine or diisopropylamine in dichloromethane.

Magnesium in anhydrous methanol has been reported as a reagent for the removal of arylsulfonyl groups from *N*-arylsulfonylcarbamates and *N*-acylsulfonamides[147] (Scheme 104). The deprotection is carried out under ultrasonic conditions and is compatible with other nitrogen protecting groups like *N*-benzyl, *N*-benzyloxycarbonyl (*N*-Cbz) and *N*-*tert*-butoxycarbonyl (N-Boc). However an *N*-2,2,2-trichloroethoxycarbonyl (*N*-Troc) group undergoes a known alkyl halide reduction giving rise to the *N*-2,2-dichloroethoxycarbonyl (*N*-Doc) derivative. Furthermore, transesterification takes place when the protected esters of amino acids are used.



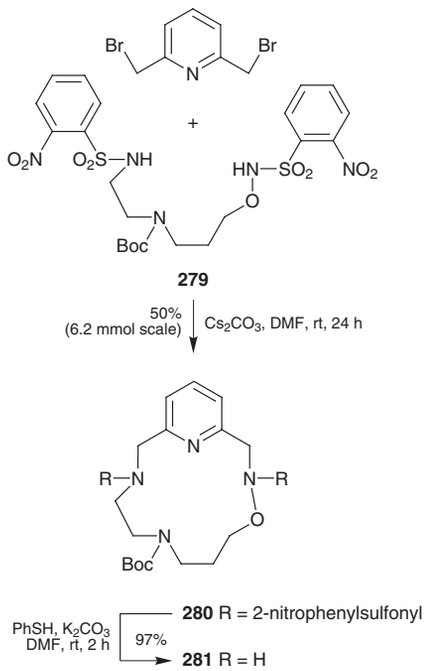
Scheme 104

The use of excess lithium powder and a catalytic amount of naphthalene to cleave toluene-*p*-sulfonamides has been reported.[25] The procedure is chemoselective in so far as benzylic derivative **277** affords the amine **278** without any cleavage of the benzylic moiety (Scheme 105). Deprotection of the corresponding mesyl (methanesulfonyl) derivatives fails but it works well in the case of *N*,*N*-disubstituted sulfonamides. The removal of tosyl, mesyl and benzyl groups from disubstituted carboxamides can also be achieved by the reported methodology.



Scheme 105

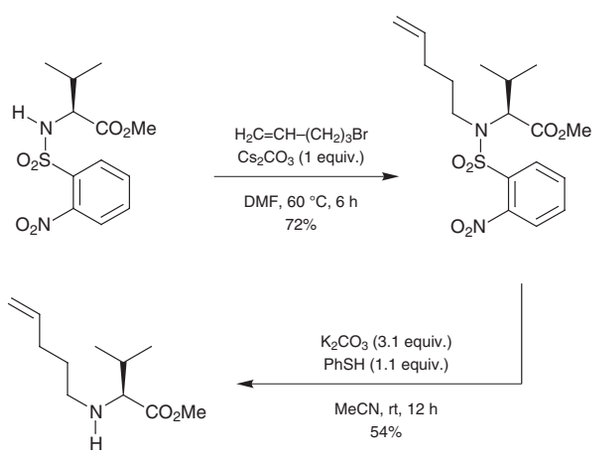
Scheme 106 shows the synthesis of one of three scaffolds used in a solution phase combinatorial search for polyazapyridinophanes with potent antibacterial activity.[148] Alkylation of the bis-2-nitrobenzenesulfonyl-protected[149] derivative **279** with 2,6-di(bromomethyl)pyridine gave the macrocycle **280**



Scheme 106

from which the arylsulfonyl groups were removed selectively using benzenethiol in the presence of potassium carbonate. 4-Nitrobenzenesulfonamides, which are cleaved under similar mild conditions, have been used to alkylate amino acids.[150]

The 2- and 4-nitrophenylsulfonamide derivatives of amino acids are useful substrates for mono-*N*-alkylation using only caesium carbonate as the base (Scheme 107).[151] The sulfonamide can then be easily cleaved in high yield by S_NAr reaction between the *N*-alkylated sulfonamide and potassium phenylthiolate in acetonitrile to give the *N*-alkylated α-amino esters without racemisation.



Scheme 107

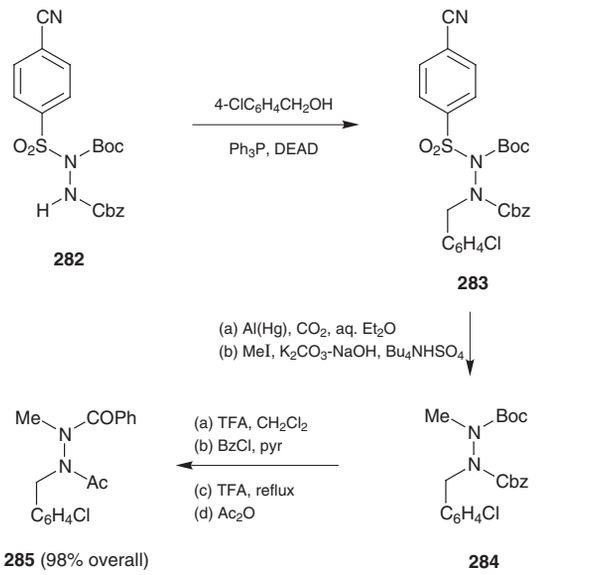
Hydrazine **282** harbouring three orthogonal protecting groups has been prepared (two steps from H_2N-NHCbz, 87%) and used for the stepwise synthesis of tetrasubstituted hydrazine derivatives[152] as illustrated in Scheme 108. Mitsunobu alkylation of **282** gave **283** from which the 4-cyanophenylsulfonyl group was removed by reduction and the resultant product then alkylated under phase transfer conditions to give **284**. Cleavage of the Boc group with dilute TFA allowed the introduction of the third group, a benzoyl. Finally cleavage of the Cbz group in refluxing neat TFA and acetylation returned the tetrasubstituted hydrazine derivative **285** in 98% overall yield.

A sequence for the glycosidation of glycals with concomitant

acetamidation previously developed by Danishefsky *et al.*[153] has now been extended to a synthesis of a model glycopeptide in the form of an asparagine-linked pentasaccharide[154] (Scheme 109). We join the synthesis at the pentasaccharide stage when the final iodoanthracenesulfonamidation is initiated using iodonium bis(collidine) perchlorate to give the iodosulfonamide derivative **287**, which was then treated with tetrabutylammonium azide to give the glycosyl azide **289** *via* the *N*-sulfonylaziridine intermediate **288**. After acetylation of the sulfonamide, the 9-anthrylsulfonyl group was removed under very mild conditions using thiophenol in the presence of base. Earlier in the same synthesis, benzenesulfonamide was used as the nucleophilic partner in which case the phenylsulfonyl group was removed using sodium naphthalenide.

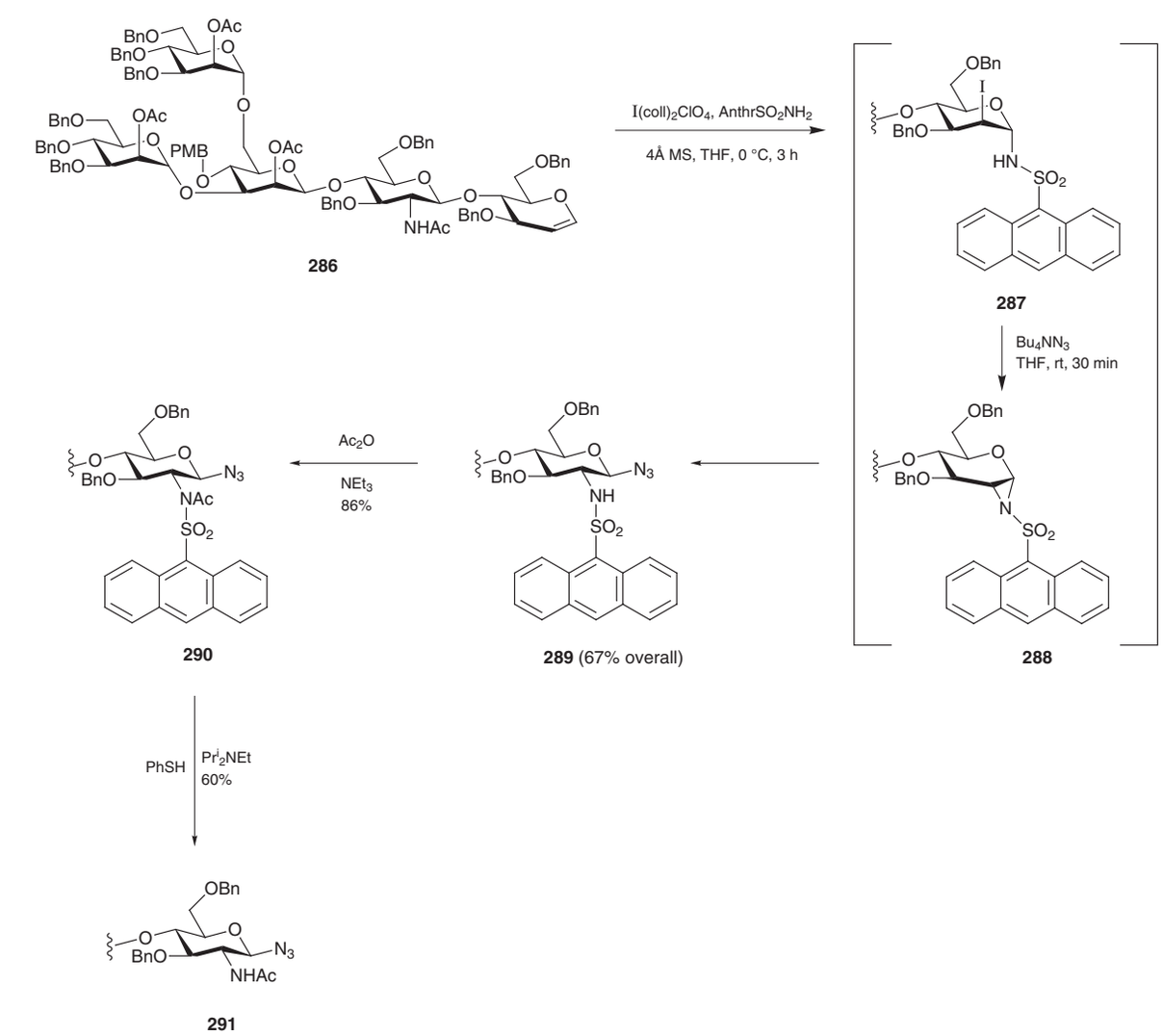
Weinreb *et al*. have reported the use of the *tert*-butylsulfonyl (Bus) group as a new protecting group for amines.[155] The Bus group is introduced (Scheme 110) by reaction of the amine with *tert*-butylsulfinyl chloride followed by oxidation of the sulfinamide with dimethyldioxirane, *m*-chloroperbenzoic acid, or $RuCl_3$ (cat.)/$NaIO_4$. This two-step procedure is a consequence of the instability of *tert*-butylsulfonyl chloride; indeed, *tert*-butylsulfinyl chloride itself is also unstable though it can be stored neat in a freezer indefinitely. The Bus group is stable towards strong alkyllithium and Grignard reagents, 0.1 M HCl in MeOH (20 °C, 1 h), 0.1 M TFA in dichloromethane (20 °C, 1 h), or pyrolysis at 180 °C. However, Bus-protected secondary amines can be cleaved with 0.1 M triflic acid in dichloromethane containing anisole as a cation scavenger at 0 °C for 15–30 min whilst primary amines are released more slowly at room temperature. It is also possible to cleave Bus-protected secondary amines with neat TFA in anisole at room temperature overnight whereas the corresponding primary sulfonamides are unscathed under the same conditions.

Trimethylsilylethanesulfonyl chloride (SES-Cl) is a reagent used to protect amines as their corresponding sulfonamides.[23]



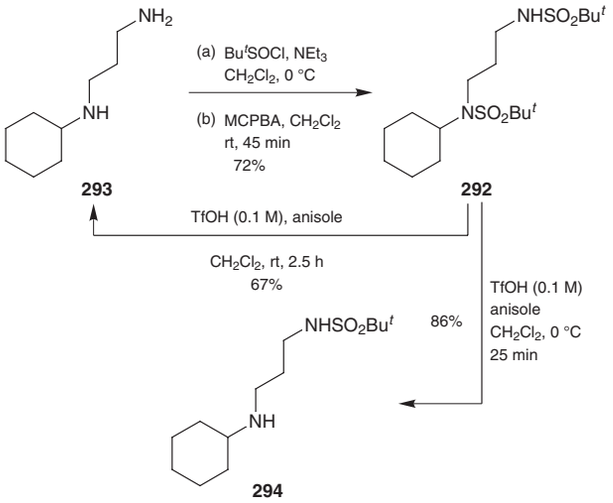
282 **283** **284** **285** (98% overall)

Scheme 108



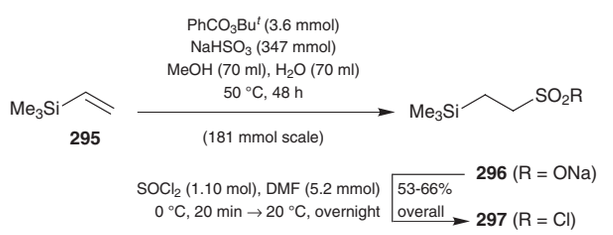
286 **287** **288** **289** (67% overall) **290** **291**

Scheme 109



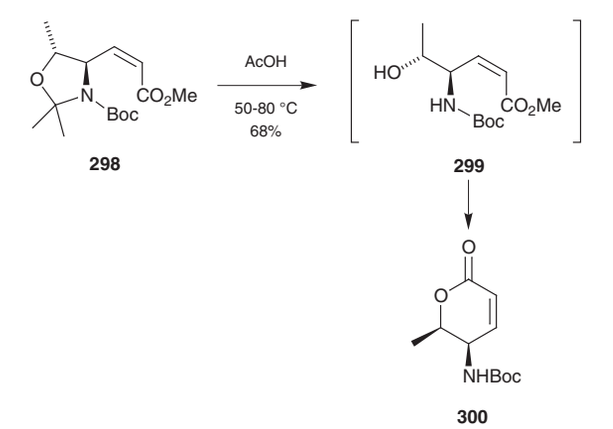
Scheme 110

Recently an improved large scale preparation of this reagent has been published in *Organic Syntheses* (Scheme 111).[81] In the first step sodium bisulfite was added to trimethylvinylsilane (**295**) in the presence of a catalytic amount of *tert*-butyl perbenzoate. The resulting crude sodium sulfonate **296** was then treated with thionyl chloride and a catalytic amount of DMF to afford the corresponding sulfonyl chloride **297** in 53–66% overall yield.



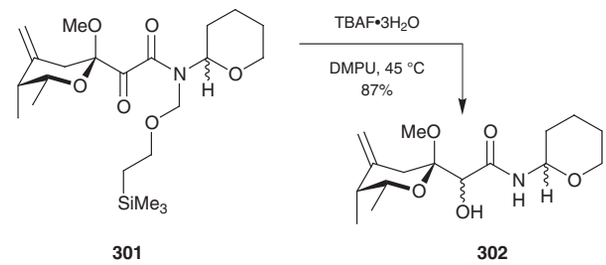
Scheme 111

Neat acetic acid at 50–80 °C cleaved the aminal protecting group in **298** (Scheme 112) selectively without harm to the acid labile *N*-Boc group.[156] Lactonisation of the open chain intermediate **299** occurred under these conditions whereas most other methods produced mixtures of the desired lactone **300** together with varying amounts of the hydroxy ester **299**. Lactone **300** was used in a synthesis of deoxy aminohexoses.



Scheme 112

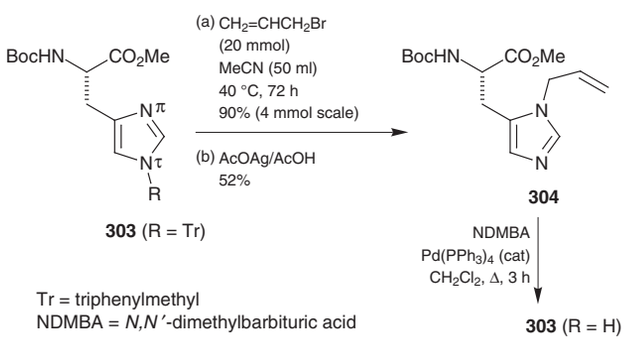
During model studies directed towards the synthesis of the marine antitumour agent mycalamide, Hoffmann and co-workers[157] discovered a reduction reaction which accompanied the deprotection of an *N*-SEM [2-(trimethylsilyl)ethoxymethyl] amide derivative **301** (Scheme 113). Treatment of **301** with TBAF in DMPU at 45 °C returned the α-hydroxy amide **302** in excellent yield as a 3 : 1 mixture of diastereoisomers. Whilst the nature of the reducing agent is unknown, the authors speculate that it must have been triggered by a reagent of the type N-CH_2-O- or F-CH_2-O- derived from cleavage of the SEM group. The reduction was a welcome and useful surprise since the nascent hydroxy group is present in the natural product.



Scheme 113

The SEM group can also be used for the regioselective protection of the N^1 position of uracil allowing the selective alkylation of the nitrogen at the 3-position.[158]

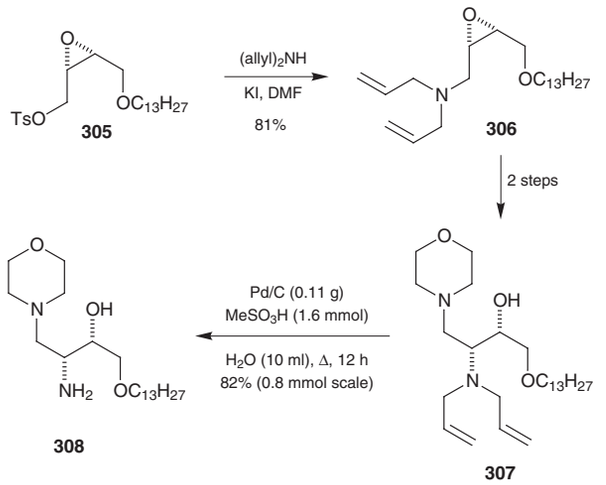
Protection of the imidazole nucleus of histidine derivatives (*e.g.* **303**, R = H, Scheme 114) during peptide synthesis is highly recommended to avoid racemisation at the α-carbon of the corresponding acid-activated species. Guibé and co-workers[159] reported that the allyl group at the N^{π} position could be used for this purpose. The regioselective protection of the imidazole nucleus was achieved in two steps starting from N^{τ}-trityl derivative **303** by (a) reaction with the excess of allyl bromide and (b) removal of the trityl group from the resulting ammonium salt with silver acetate in acetic acid. Basic hydrolysis of **304** (aqueous 1 M NaOH–methanol) followed by DCC mediated peptide coupling of the corresponding acid occurred with good (97%) conservation of enantiomeric purity. Selective removal of the allyl group was then achieved by treatment with a catalytic amount of tetrakis(triphenylphosphine)palladium(0) either in the presence of *N*,*N*′-dimethylbarbituric acid or $PhSiH_3$ and acetic acid.



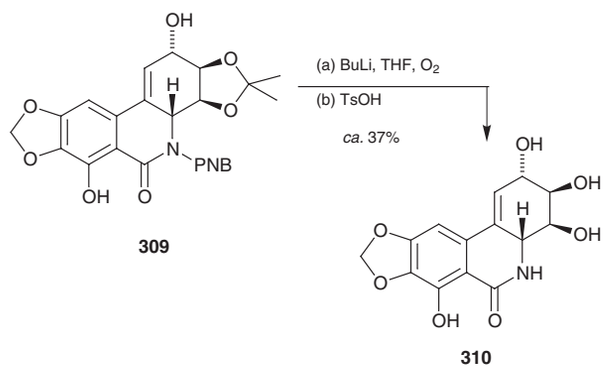
Scheme 114

During their synthesis of a potential inhibitor of glucosylceramide synthase Rayner and co-workers[160] encountered difficulties in deprotecting the amino group in intermediate **307** (Scheme 115). Under conditions previously successful for this transformation—$(Ph_3P)_3RhCl$–MeCN–H_2O—only very low yields of the desired product **308** were obtained. The problem was finally overcome by modifying the previously published procedure of Picq and co-workers[161] (Pd/C, $MeSO_3H$ and water) to afford **308** in 82% yield.

In the closing stages of a recent synthesis of narciclasine, Rigby and Mateo[162] encountered difficulties removing the PMB group protecting the amide nitrogen in intermediate **309** (Scheme 116). The usual oxidative methods were to no avail but an old desperate method of Williams[163] eventually succeeded.



Scheme 115



Scheme 116

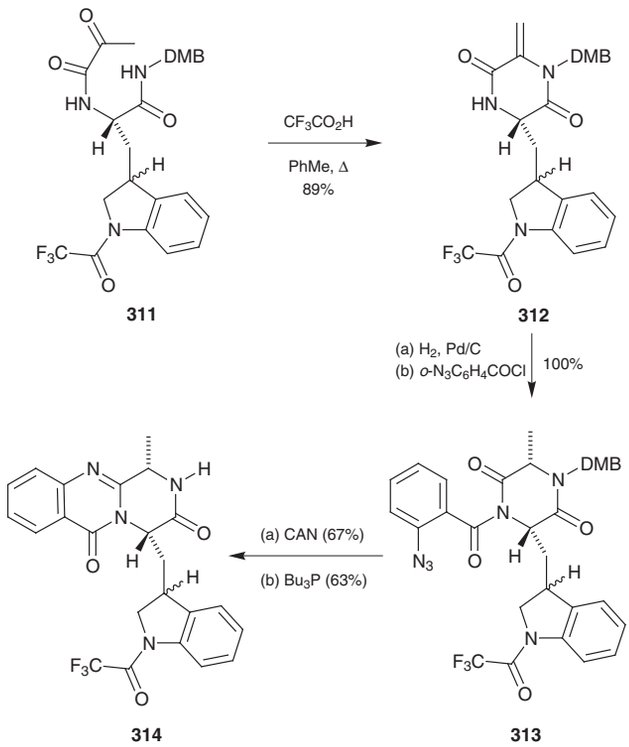
Thus treatment of the diol **309** with excess BuLi in THF whilst bubbling oxygen through the solution cleaved the PMB group and the natural product **310** was obtained by acid hydrolysis of the acetonide. The yield was low but no doubt welcome nevertheless.

The fumiquinazolines are moderately cytotoxic metabolites isolated from fungi isolated from fish. In the synthesis of fumiquinazoline G (Scheme 117), He and Snider[164] used a 2,4-dimethoxybenzyl group (DMB) to protect an amide nitrogen in two important steps: the cyclisation of **311** to **312** and acylation step (b) in the conversion of **312** to **313**. Note that the DMB group is inert to the hydrogenation conditions. The DMB group was finally removed with CAN prior to closure of the quinazoline ring, which completes the skeleton of the target.

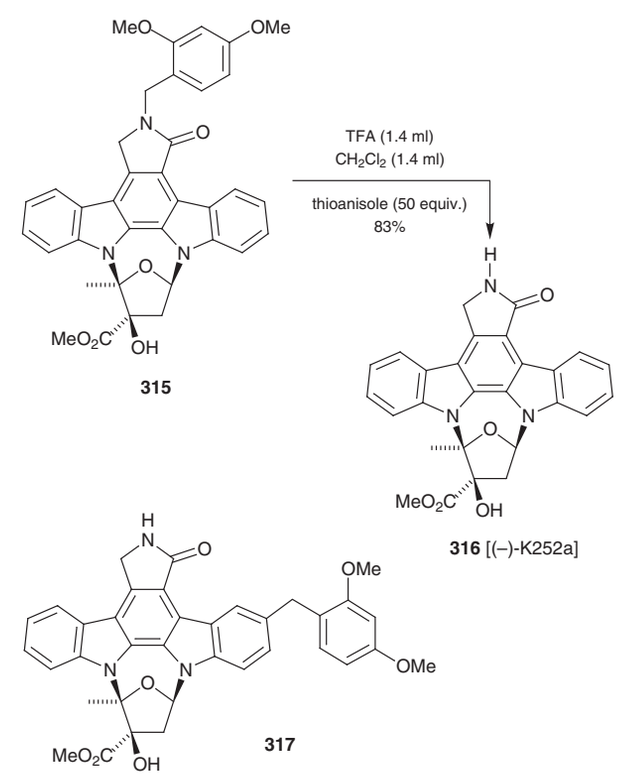
After Raphael *et al.*[165] had encountered problems in the cleavage of an *N*-benzyl group protecting the indole pyrrolidone ring system Wood *et al.*[166] elected to use the acid labile 2,4-dimethoxybenzyl group which was successfully cleaved in the final step of their synthesis of the indolocarbazole (−)-K252a (Scheme 118) using trifluoroacetic acid (TFA). In the absence of the thioanisole scavenger, an appreciable amount of **317** was formed.

The di(*p*-anisyl)methyl group is a useful protector for the amino function during a synthesis of arylglycines *via* a Mannich reaction between an aldimine of glyoxylic acid and an arylboronic acid (Scheme 119).[167] The di(*p*-anisyl)methyl protector is easily removed with hot 70% aqueous acetic acid.

Orienticin C is a member of the vancomycin family of antibiotics used for the treatment of methicillin resistant *Staphylococcus aureus* infections. The Evans synthesis[168] of orienticin C exploited the 4,4′-dimethoxydiphenylmethyl (Ddm) protecting group for the asparagine unit; because it survived the synthesis intact until the final step (shown in Scheme 120), it helped minimise epimerisation during peptide coupling, and it suppressed the vexatious aspartate–isoaspartate rearrangement.[169]



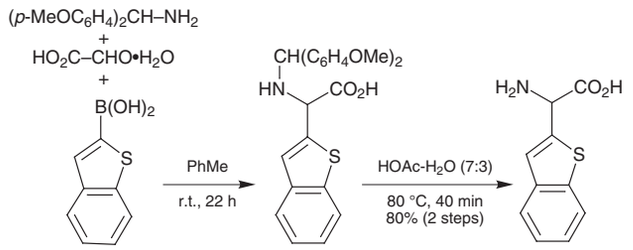
Scheme 117



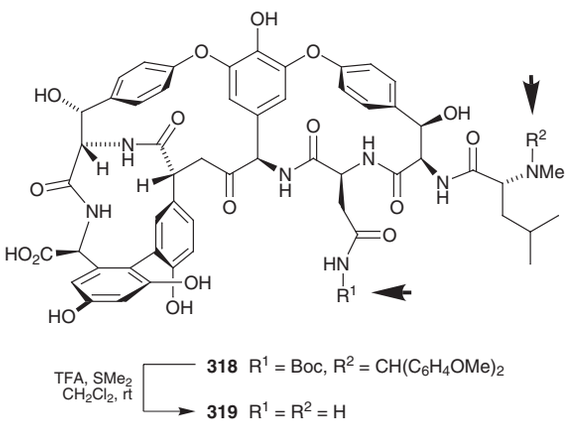
Scheme 118

The Ddm group, together with the Boc group, were removed by treatment of **318** with trifluoroacetic acid to give the desired product. In this preliminary communication the yield of the final three steps is not specified.

The trityl group is well established for the *N*-protection of amino acids and other primary amine derivatives but the more labile methoxy-substituted trityl derivatives have received scant attention. Golding *et al.* recently reported the use of 4,4′-dimethoxytrityl tetrafluoroborate ($DMT^+BF_4^-$) and 4,4′,4″-trimethoxytrityl tetrafluoroborate ($TMT^+BF_4^-$) as useful reagents for the protection of primary and some secondary



Scheme 119



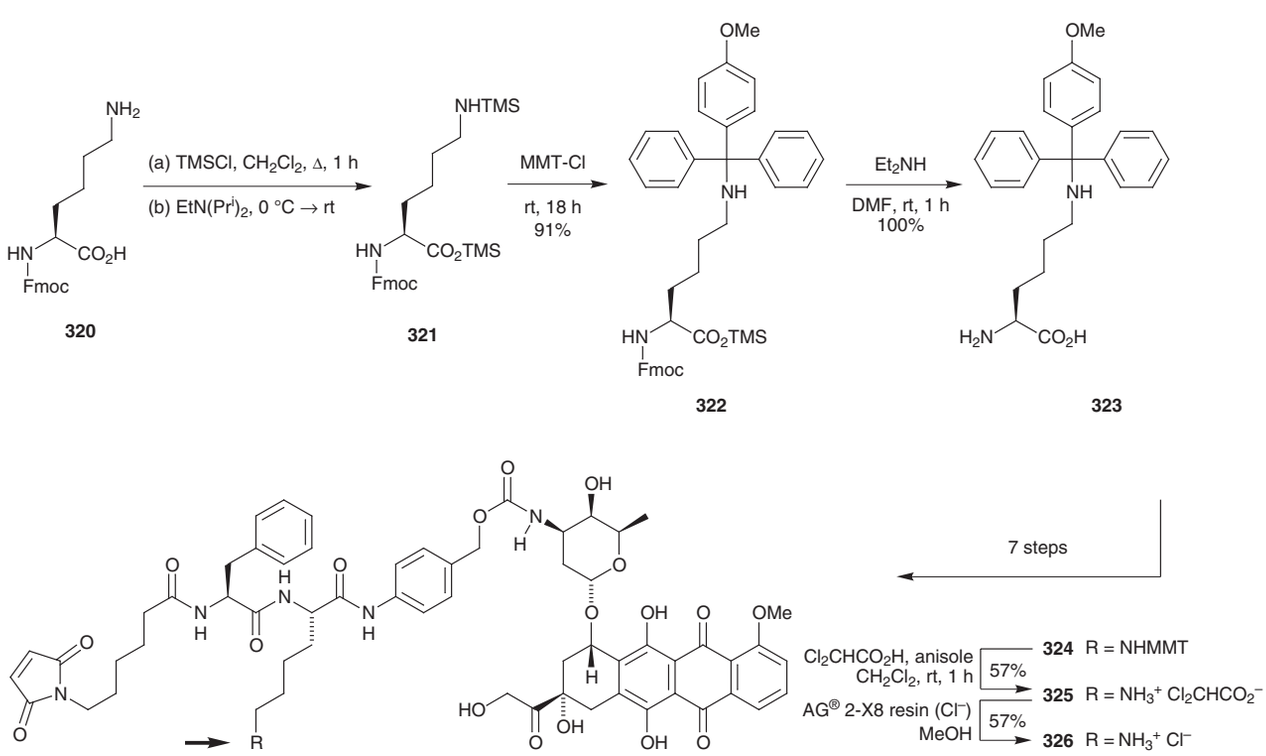
Scheme 120

amines.[170] The latter reagent is stable indefinitely in air. Protected amines are obtained either by reaction of $DMT^+BF_4^-$ or $TMT^+BF_4^-$ with the amine or by alkylating DMT- or TMT-amine (available from $DMT^+BF_4^-$ and $TMT^+BF_4^-$ by treatment with ammonia). Alkylation of DMT- or TMT-amines stops after monoalkylation. The DMT and TMT amines are far more stable than their corresponding ethers and require relatively strongly acidic conditions even for the TMT group. For example, DMT amines are cleaved with 2 M HCl in THF (1 : 1) at room temperature whereas the TMT derivatives are cleaved with 0.05–0.5 M HCl under similar conditions.

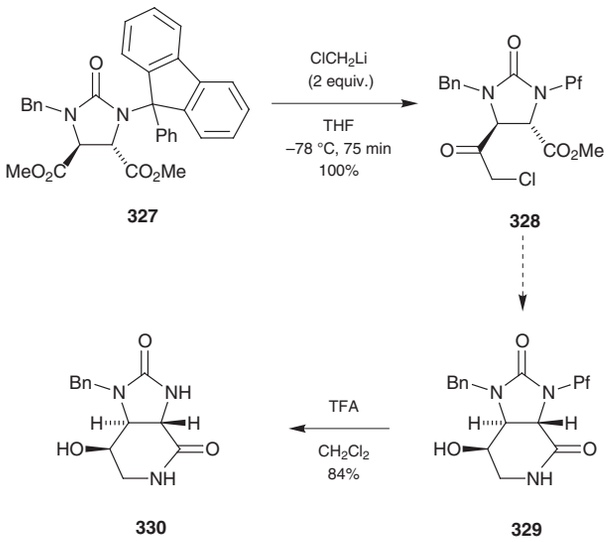
Bristol-Myers Squibb have developed a technique for targeting anti-cancer pro-drugs using monoclonal antibodies that are specifically internalised by the tumour cells.[171] The pro-drugs are then released by cathepsin B cleavage of a maleimidocaproyl Phe-Lys linker attached through a self-immolative *p*-aminobenzyloxycarbonyl spacer. One of the synthetic challenges in the synthesis of the pro-drug is its sensitivity to common deprotection regimes used for amino groups such as TFA in dichloromethane (Boc), hydrogenation (Cbz), Pd (allyloxycarbonyl, Alloc) and secondary amines (Fmoc). A particularly vexing problem was the protection of the terminal amino group of lysine. The problem was solved by using a monomethoxytrityl (MMT) group which was introduced as shown in Scheme 121. Lys(MMT) (**323**) was prepared from Fmoc-Lys (**320**) by a one-pot tritylation procedure in which both the amino and carboxy groups are temporarily silylated with TMSCl followed by removal of the Fmoc group with diethylamine. The Lys(MMT) (**323**) was then incorporated into pro-drugs harbouring doxorubicin, taxol and mitomycin C as the warheads. In the case of the doxorubicin pro-drug **324**, the MMT group was cleaved from the lysine using dichloroacetic acid in the presence of anisole at room temperature. Under these conditions the lysine was protonated, thereby preventing addition of the amino group to the maleimide residue leading to the formation of polymeric products.

The 9-phenylfluoren-9-yl (Pf) protecting group offers steric protection to functional groups in its periphery. A Spanish group[172] has shown that the certain chiral *N*-(9-phenylfluoren-9-yl)-α-amido esters react with organolithium reagents to give the corresponding enantiomerically pure ketones in good yield. For example, the imidazolidinone **327** (Scheme 122) reacted with chloromethyllithium to give ketone **328** in quantitative yield. The protecting group was later removed from intermediate **329** by acidolysis to give **330**, a core structure of the streptothricin antibiotics.

The [2+2] cycloaddition of ketenes generated from acid chlorides and a tertiary organic base with imines (the Staudinger reaction) is an important reaction in the commercial synthesis of the azetidin-2-one ring system. Unfortunately, the reaction has hitherto been limited mostly to imines prepared from non-enolisable aldehydes. Palomo and co-workers[173] have shown that *N*-[bis(trimethylsilyl)methyl]imines of enolisable

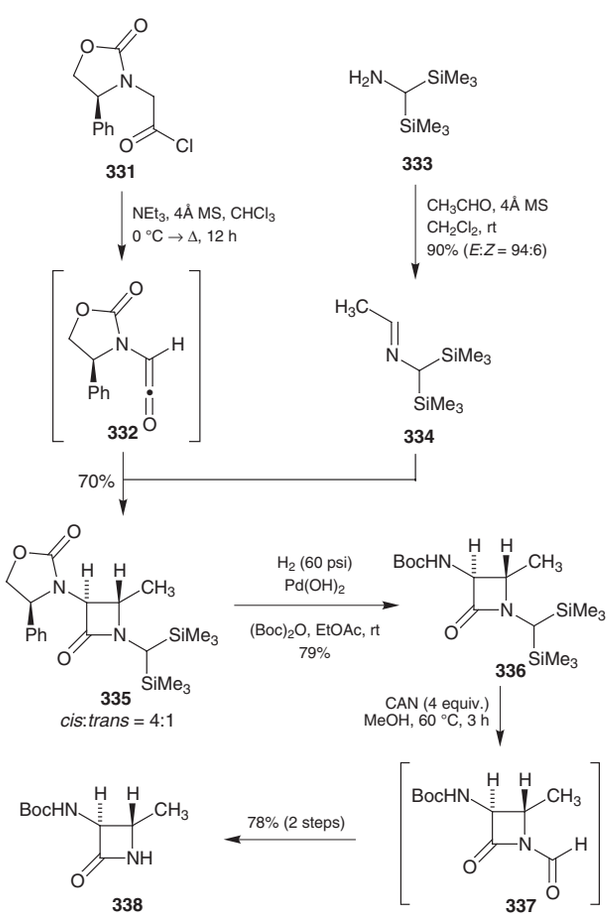


Scheme 121



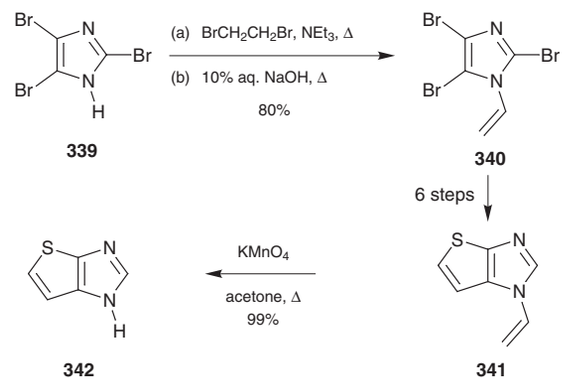
Scheme 122

aldehydes (*e.g.* **334**, Scheme 123) are stable and isolable reagents which undergo easy and efficient [2+2] cycloaddition with homochiral aminoketene **332**. The mild deprotection of the bis(trimethylsilyl)methyl and phenyloxazolidinone *N*-protecting groups was accomplished with cerium(IV) ammonium nitrate (CAN) and hydrogen/$Pd(OH)_2$ respectively. Alternatively, the latter protecting group can be cleaved with lithium in liquid ammonia.



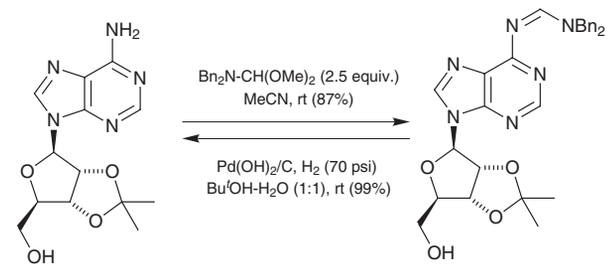
Scheme 123

The bromine atoms in 1-protected 2,4,5-tribromoimidazole can be sequentially replaced through selective Br→Li (or MgBr) exchange strategies. However, application of this strategy to the synthesis of polyfunctionalised imidazoles has been hampered by lack of a suitable *N*-protecting group. For example, previous attempts to convert various 1-protected 2,4,5-tribromoimidazoles to the thieno[2,3-*d*]imidazole **342** (Scheme 124) failed owing to the instability of the product to the acidic or basic conditions required for *N*-deprotection. Hartley and Iddon[174] have shown that the vinyl group survives the three halogen metal exchange reactions used to convert 1-vinyl-2,4,5-tribromoimidazole (**340**) to the thienoimidazole **341**. Oxidative cleavage of the vinyl group in **341** using ozone in methanol (dimethyl sulfide workup) or potassium permanganate in refluxing acetone gave the desired parent thieno[2,3-*d*]-imidazole **342** in excellent yield.



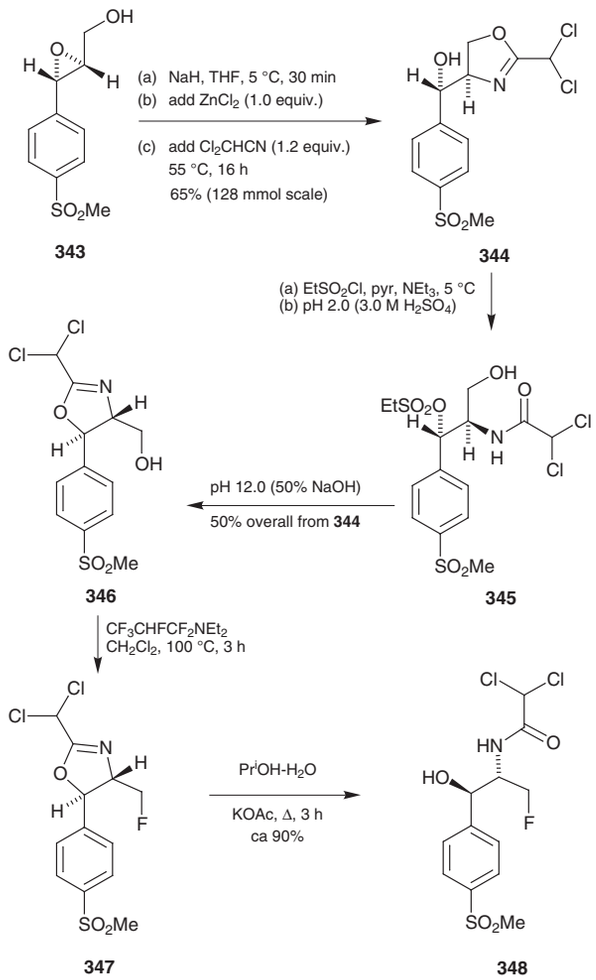
Scheme 124

A French group[175] have shown that *N*,*N*-dibenzylformamidine derivatives serve as useful protecting groups for the protection of the primary amino function of guanine and adenine groups in nucleotide synthesis. The *N*,*N*-dibenzylformamidine derivatives are prepared (Scheme 125) by reaction of the primary amino function with dibenzylformamide dimethyl acetal prepared *in situ* by reaction of dimethylformamide dimethyl acetal with dibenzylamine (3 equiv.) in refluxing acetonitrile for 20 h. *N*,*N*-Dibenzylformamidines are cleaved by hydrogenolysis using $Pd(OH)_2$ (0.5–5.0 equiv.) in Bu′OH–H_2O (1 : 1) at 70 psi.

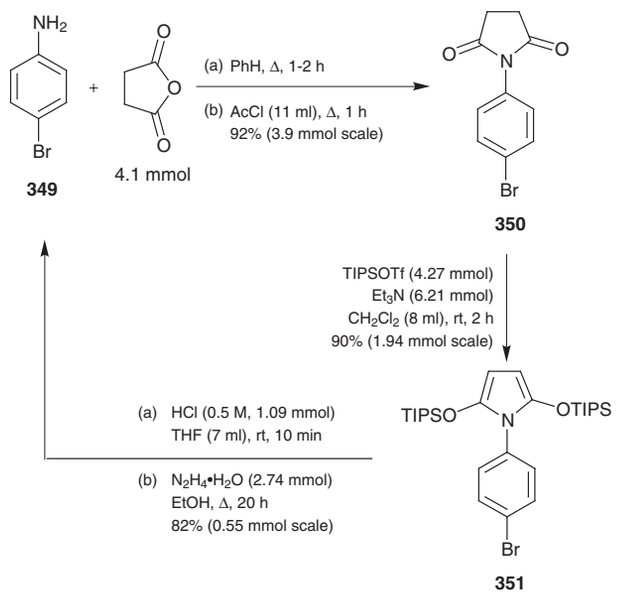


Scheme 125

The process research group[176] at Schering-Plough have devised an asymmetric synthesis of the broad spectrum antibiotic florfenicol (**348**, Scheme 126) which made good strategic use of a (dichloromethyl)oxazoline group as a protecting group which is eventually incorporated in the final product after transformation to a dichloroacetamide. Treatment of the homochiral epoxy alcohol **343** with sodium hydride followed by zinc chloride gave a zinc alkoxide, which reacted with dichloroacetonitrile to introduce the (dichloromethyl)oxazoline moiety. The zinc chloride was added to suppress the Payne rearrangement. After conversion of the hydroxy function in **344** to its ethanesulfonate, the oxazoline was hydrolysed to the dichloroacetamide derivative **345**. Intramolecular displacement of the ethanesulfonate group (inversion) regenerated the oxazoline ring which protected the hydroxy and amino functions during the conversion of the free hydroxy group in **346** to the fluoro derivative **347**. Finally, hydrolysis of the oxazoline ring at pH 5.0 gave the crystalline florfenicol (**348**).



Scheme 126



Scheme 127

Primary amines can be protected as their 2,5-bis[(triisopropylsilyl)oxy]pyrrole (Bipsop) derivatives.[177] The two step protection sequence is shown in Scheme 127. In the first step the amine (*e.g.* **349**) is transformed into the corresponding imide **350** by reaction with succinic anhydride followed by cyclodehydration of the intermediate amide acid with acetyl chloride. In the second step the imide **350** is treated with triisopropylsilyl triflate (TIPSOTf) in the presence of triethylamine to give the desired pyrrole derivative **351**. The bis[(triisopropylsilyl)oxy]-pyrrole ring is stable to strong bases such as organolithium reagents (−78 to 20 °C), heating at temperatures up to 150 °C, and chromatography on neutral alumina. Removal of the Bipsop protecting group can be accomplished under mild conditions by sequential reaction first with dilute acid followed by refluxing the intermediate succinimide with hydrazine in ethanol.

The first total synthesis of haliclamine A (**357**, Scheme 128) was achieved by stepwise inter- and intra-molecular *N*-alkylations of 3-alkylpyridine derivatives.[178] To avoid polymerisation or intramolecular *N*-alkylation of **353** during coupling of **352** and **353**, the nucleophilic nitrogen in **352** was protected as its *N*-oxide. Mesylation of the alcohol function in **354** resulted in expedient deoxygenation of the *N*-oxide whence macrocyclisation of intermediate **355** gave the bispyridinium salt **356**. Reduction with sodium borohydride completed the synthesis.

9 Miscellaneous protecting groups

Roberts and co-workers[179] were looking for a protecting group for arenesulfonic acids which, on the one hand, would be compatible with a wide range of standard organic synthesis methodologies, but on the other hand, could be removed under relatively mild conditions. It turned out that neopentyl (2,2-dimethylpropyl) esters (*e.g.* **359**, Scheme 129) served this purpose well, withstanding such reagents as *tert*-butyllithium, vinylmagnesium bromide, CrO_3, NBS/benzoyl peroxide, H_2/RaNi, DIBAL-H, NaI, $HONH_2$, NaH, aq. HBr or NaOH. Deprotection could be easy accomplished by heating the ester with excess tetramethylammonium chloride in DMF.

Sulfate monoesters in carbohydrates can be protected as their trifluoroethyl ester.[180] The protected sulfates were prepared by treatment of the carbohydrate (*e.g.* **361**, Scheme 130) with sulfur trioxide–pyridine complex followed by reaction of the crude monosulfate with trifluorodiazoethane. The resulting 2,2,2-trifluoroethyl ester **362** was stable to sodium methoxide in methanol, which allowed selective acetate methanolysis to give **363**. The removal of the sulfate protecting group was achieved with potassium *tert*-butoxide in *tert*-butyl alcohol. Apart from sodium methoxide, 2,2,2-trifluoroethyl sulfates were also stable to tetrabutylammonium fluoride, trifluoroacetic acid in ethanol and catalytic hydrogenation, but not to dilute sulfuric acid (the entire sulfate moiety was cleaved).

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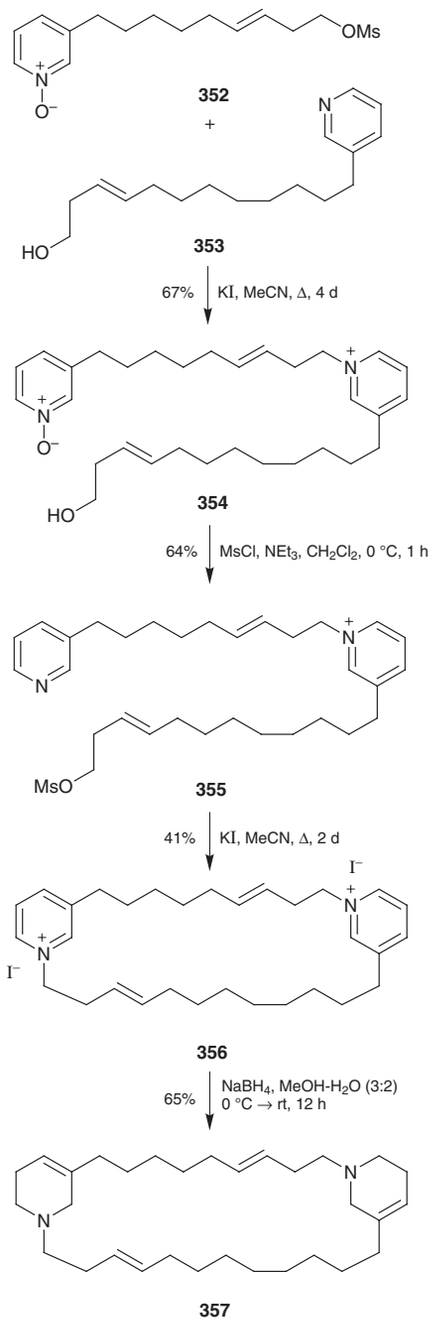
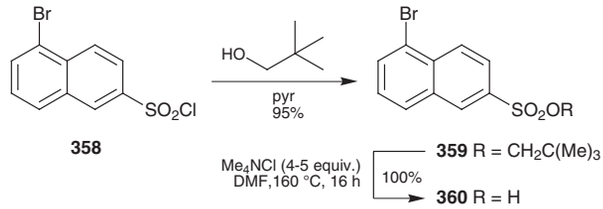
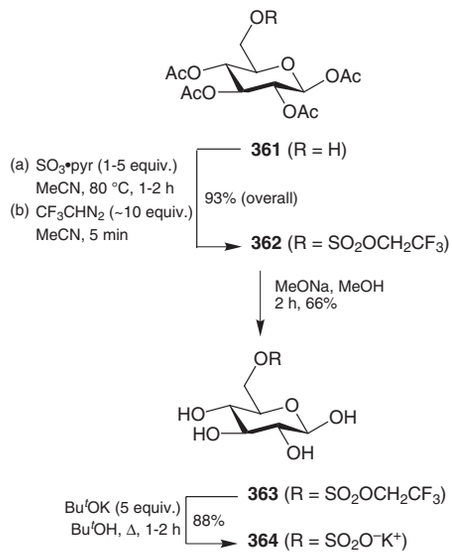


Scheme 128



Scheme 129



Scheme 130

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