Protecting groups

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Reviewing the literature published in 1995
Continuing the coverage in *Contemporary Organic Synthesis*, 1995, **2**, 315

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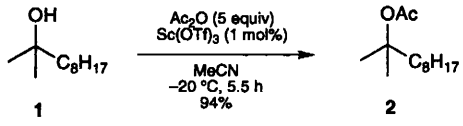
1 Introduction

This review covers new developments in protecting group methodology which appeared in 1995. As with our previous annual review,[1] the coverage is a personal selection of methods which we deemed interesting or useful. In addition to examples gleaned from reading the literature, the references were selected through a Science Citation Index search based on the root words 'block', 'protect' and 'cleavage'. The review is organised according to the type of functional group protected with emphasis being placed on deprotection conditions. In the accompanying schemes, transformations for which the scale is specified imply that full experimental details were provided in the original reference. Owing to the intense current interest in solid phase synthesis, we have also included recent developments in new linkers.

2 Hydroxy protecting groups

2.1 Esters

DMAP increases the rate of acylation of alcohols with acid anhydrides by a factor of 10^4. In the case of compound **1**, the use of DMAP as a catalyst at room temperature after 5.5 h yielded less than 1% of **2** (**Scheme 1**). By contrast, Yamamoto and

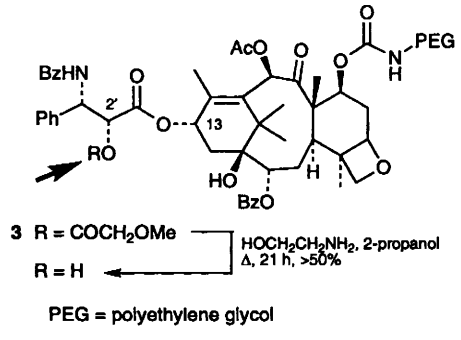


Scheme 1

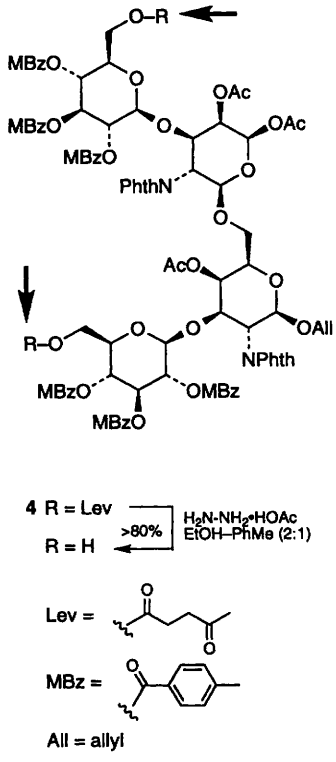
co-workers[2] showed that scandium triflate (1 mol%) accomplished the desired esterification in 94% yield at −20 °C. Scandium triflate is especially useful for large-scale synthesis because as little as 0.1 mol% can be used.

During a synthesis of water soluble taxol derivatives modified with polyethylene glycol (PEG), considerable difficulty was encountered in selectively removing an ester protecting group from the 2′ position (**Scheme 2**).[3] When R = Ac, hydrolysis with $NaHCO_3$ was slow and was accompanied by partial hydrolysis of the C13 side chain. The chloroacetyl group was too hydrolytically labile to offer adequate protection. However, the methoxyacetate **3**, which hydrolyses *ca.* 20 times faster than acetate, was cleaved with excess ethanolamine without rupture of the C13 side chain.

Relay deprotection is a powerful technique for the selective deprotection of functional groups in a polyfunctionalised substrate.[4] A good example that emerged this year (**Scheme 3**) comes from a synthesis of the circulating anodic antigen secreted by the parasite *Schistosoma mansoni*.[5] The two primary alcohol functions in the tetrasaccharide **4** were deprotected selectively in the presence of secondary acetate and *p*-toluate esters and phthalimide functions, using hydrazine buffered with



Scheme 2



Scheme 3

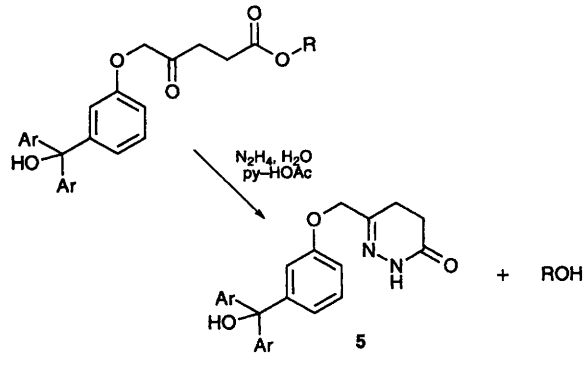
acetic acid according to the procedure of van Boom and Burgers.[6]

Levulinate esters are useful for the deprotection of alcohols under essentially neutral conditions using hydrazine hydrate. A levulinic acid derivative bearing a trityl alcohol functionality has been developed by Leikauf and Köster (**Scheme 4**) to serve as a reporter functionality.[7] The deprotection is easily assayed colorimetrically by treating the cleavage product **5** with 5% Cl_2CHCO_2H in dichloromethane to give a trityl cation with λ_{max} 513 nm (ε 78500).

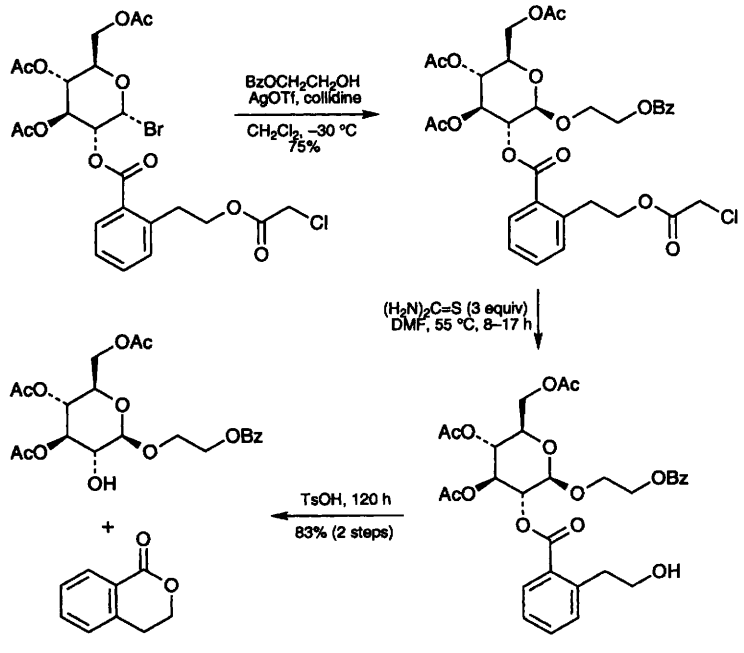
Another relay deprotection method reported this year for the selective deprotection of ester functions in carbohydrate derivatives[8] is illustrated in **Scheme 5**. The 2-(2-chloroacetoxyethyl)benzoyl group (abbreviated CAEB) functions as a temporary 1,2-*trans*-directing protecting group for glycosyl donors. It is stable to hydrogenolysis and can be cleaved with thiourea without affecting acetyl, benzoyl, benzyl and benzylidene groups.

2.2 Silyl ethers

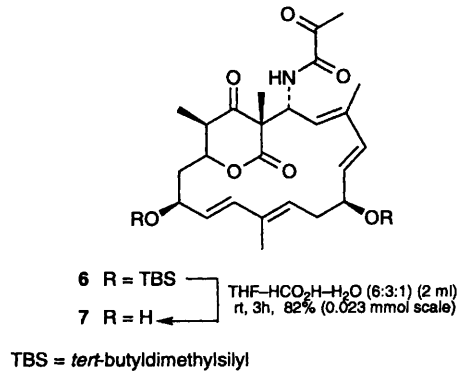
In the final step of a synthesis of the antitumour antibiotic lankacidin C, Kende and co-workers[9] were faced with the difficult deprotection of the bis-TBS



Scheme 4



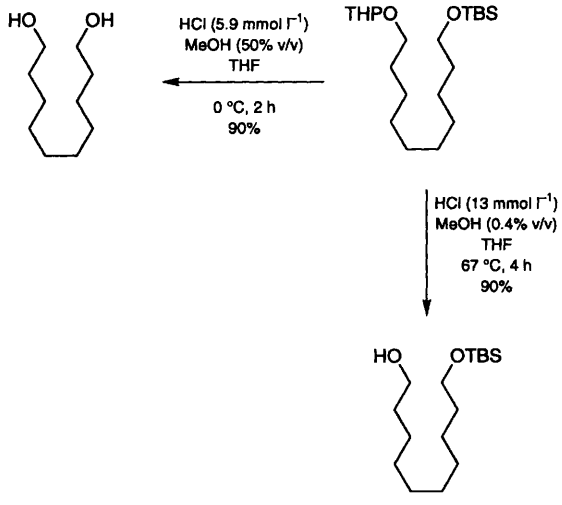
Scheme 5



Scheme 6

ether **6** (**Scheme 6**) without cleavage of the delicate oxanedione ring. Desilylation of **6** failed with all variants of fluoride or HF, but was finally achieved using aqueous formic acid at 20 °C for 3 h to produce in 82% yield the target molecule **7**.

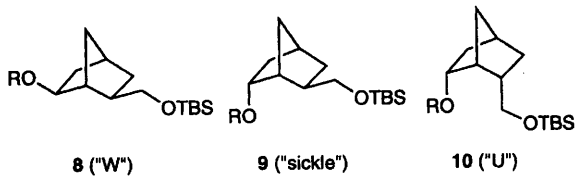
The solvent dependence of the rate of solvolysis of TBS ethers[10] has useful implications for selective deprotections. Thus, dilute methanolic HCl in anhydrous THF (<0.5% MeOH, *ca.* 10^{-2} mol l^{-1}) cleaves THP ethers and 1-ethoxyethyl ethers, whereas TBS ethers remain intact even at elevated temperatures (**Scheme 7**). However both acetal and TBS groups can be cleaved if the amount of MeOH is increased to 50%.



Scheme 7

The kinetics of the desilylation reactions of a range of sulfonylated and methoxylated norbornyl silyl ethers established a correlation between the geometry of the σ-relay and the rate of desilylation.[11] Desilyation rates generally decrease in the order W > sickle-like > U as shown in the table accompanying **Scheme 8**.

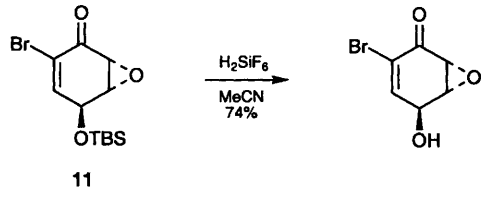
The search for an expanded repertoire of reagents for the cleavage of TBS (TBDMS, *tert*-butyldimethylsilyl) ethers in sensitive substrates is



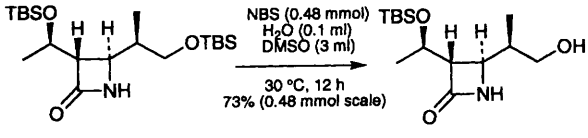
R	k_{obs} x 10^{-3} min^{-1}		
	8	**9**	**10**
Me	5.6	2.3	0.4
Ts	15.4	4.3	1.3

Scheme 8

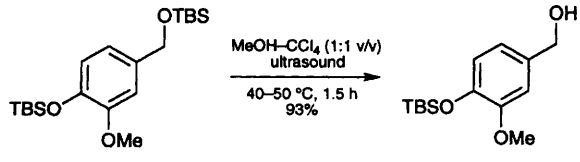
illustrated by three recent examples. First, Johnson and Miller[12] accomplished the deprotection of the TBS ether **11** in the presence of an acid-labile oxirane ring using fluorosilicic acid in acetonitrile (**Scheme 9**). Second, a Japanese group[13] exploited the known lability of TBS ethers towards NBS in the presence of water[14,15] to accomplish selective deprotection of a primary TBS ether in the presence of a secondary TBS ether in β-lactams (**Scheme 10**). Finally, Lee and co-workers[16] reported a new method of selective deprotection of TBS ethers of primary alcohols using sonication (**Scheme 11**). Under the reaction conditions TBS ethers of phenols as well as secondary and tertiary alcohols remain intact but TBS ethers of primary alcohols can be deprotected in the presence of a primary TBDPS ether. Numerous functionalities are also resistant *e.g.* $-CO_2R$, $-OR$, $-NR_2$, $-Cl$, $-COR$, $-CHO$ and $-CONR_2$.



Scheme 9

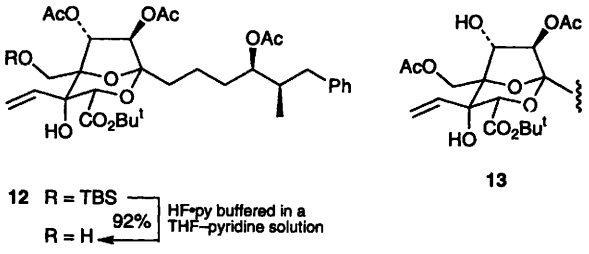


Scheme 10



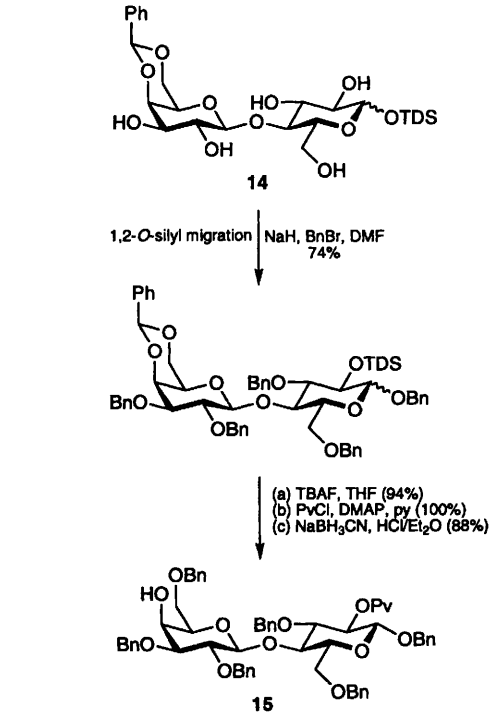
Scheme 11

The removal of a silyl ether protecting group without competing migration of a proximate ester function can be difficult. In a synthesis of zaragozic acid, Carreira and Du Bois[17] suppressed formation of the migration product **13** by deprotecting the TBS ether **12** with the HF·pyridine complex in THF buffered with pyridine (**Scheme 12**).



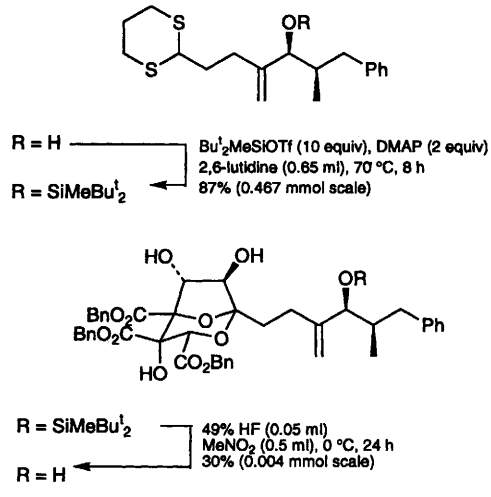
Scheme 12

1,2-*O*-Silyl migration is another competing process which is usually considered a nuisance. However, Lassaletta and Schmidt[18] recently exploited the reaction to good effect in a synthesis of the glycosphingolipid precursor **15** which had previously required a 14-step sequence from lactose (**Scheme 13**). Thus treatment of **14** (four steps from lactose) with NaH and benzyl bromide in DMF caused 1,2-*O*-silyl migration of the thexyldimethylsilyl (TDS) group thereby protecting the 2-hydroxyl function whilst the remaining free hydroxy functions were *O*-benzylated. After replacement of the TDS group with a pivaloyl group, the benzylidene acetal was cleaved reductively to give the desired fragment **15** in only eight steps overall from lactose.



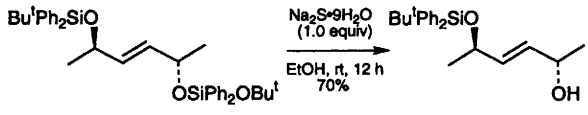
Scheme 13

The additional steric bulk in methyldi-*tert*-butylsilyl ethers makes them more stable than the ubiquitous *tert*-butyldimethylsilyl ether group toward nucleophilic attack. They are also more difficult to introduce and remove as shown by the transformations depicted in **Scheme 14** taken from Nicolaou's synthesis of zaragozic acid.[19]



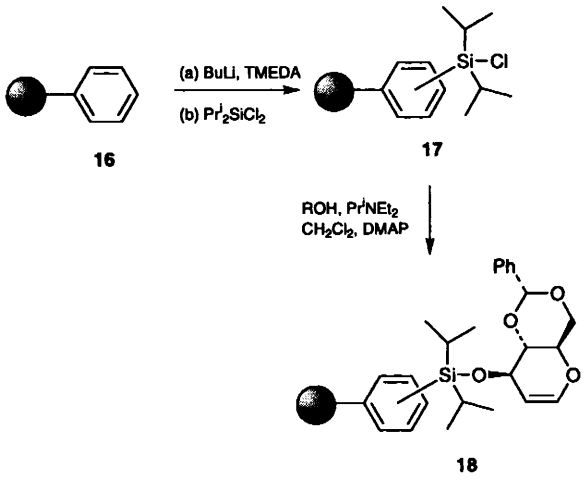
Scheme 14

tert-Butoxydiphenylsilyl ethers are an inexpensive alternative to *tert*-butyldiphenylsilyl ethers,[20] with comparable stability. Schmittberger and Uguen have shown[21] that *tert*-butoxydiphenylsilyl (DPTBOS) ethers are cleaved slowly using $Na_2S·9H_2O$ in dry ethanol or methanol at room temperature (rt) – conditions which preserve *tert*-butyldimethylsilyl (TBS) and *tert*-butyldiphenylsilyl (TBDPS) ethers (**Scheme 15**). Control experiments established that the cleavage was not caused by the basic reaction conditions (pH 11.9).



Scheme 15

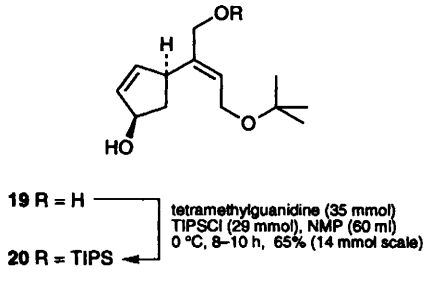
The Danishefsky research group reported a solid phase synthesis of the Lewis b antigen in which the oligosaccharide was constructed stepwise from a glycal bound to the polymer *via* a silane linker.[22] The linker was prepared by the metallation of 1% divinylbenzene–styrene copolymer **16** followed by reaction with diisopropyldichlorosilane (**Scheme 16**).



Scheme 16

The resulting chlorosilane **17** was then used to attach the primer glycal unit as a silyl ether **18**. The fully developed oligosaccharide was finally cleaved from the polymer with TBAF and HOAc in THF. A very similar strategy has been devised for the solid phase synthesis of 2′-deoxyribose oligonucleotides.[23]

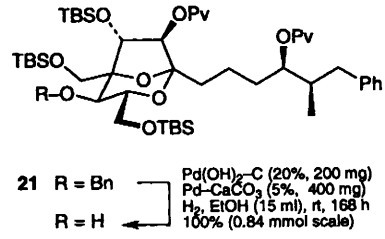
During a monumental synthesis of strychnine, the research group of Overman[24] encountered difficulties with the simple selective protection of the primary alcohol function in the diol **19** as its (triisopropylsilyl) TIPS ether (**Scheme 17**). The best method involved treatment of the diol **19** with 2 equiv. of TIPSCl and 2.2 equiv. of 1,1,3,3-tetramethylguanidine at 0 °C in *N*-methylpyrollidinone until the diol could no longer be detected by TLC. This treatment provided the readily separable monosilyl ether **20** in 65% yield together with the bis-silyl ether in 33% yield.



Scheme 17

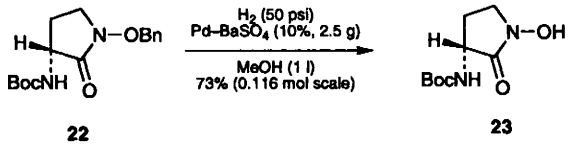
2.3 Alkyl ethers

During their synthesis of zaragozic acid, Carreira and Du Bois[17] found that catalytic hydrogenolysis of **21** using Pearlman's catalyst [$Pd(OH)_2$] was accompanied by removal of the TBS groups as well. For reasons which are not clear, the unwanted silyl deprotection could be suppressed by using Pd on $CaCO_3$ together with $Pd(OH)_2$ as the catalyst (**Scheme 18**).



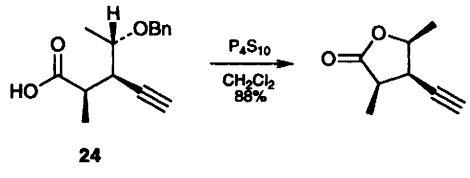
Scheme 18

Nikam and co-workers[25] found that Pd–$BaSO_4$ is an efficient catalyst for the hydrogenolysis of the benzyl hydroxamate **22** to give the corresponding hydroxamic acid **23** (**Scheme 19**). With Pd–C, reductive cleavage of the N–O bond was observed.

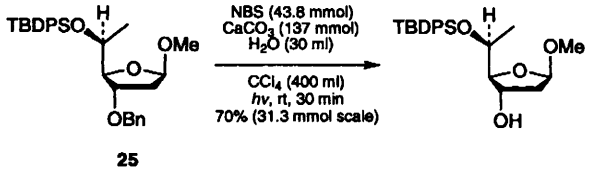


Scheme 19

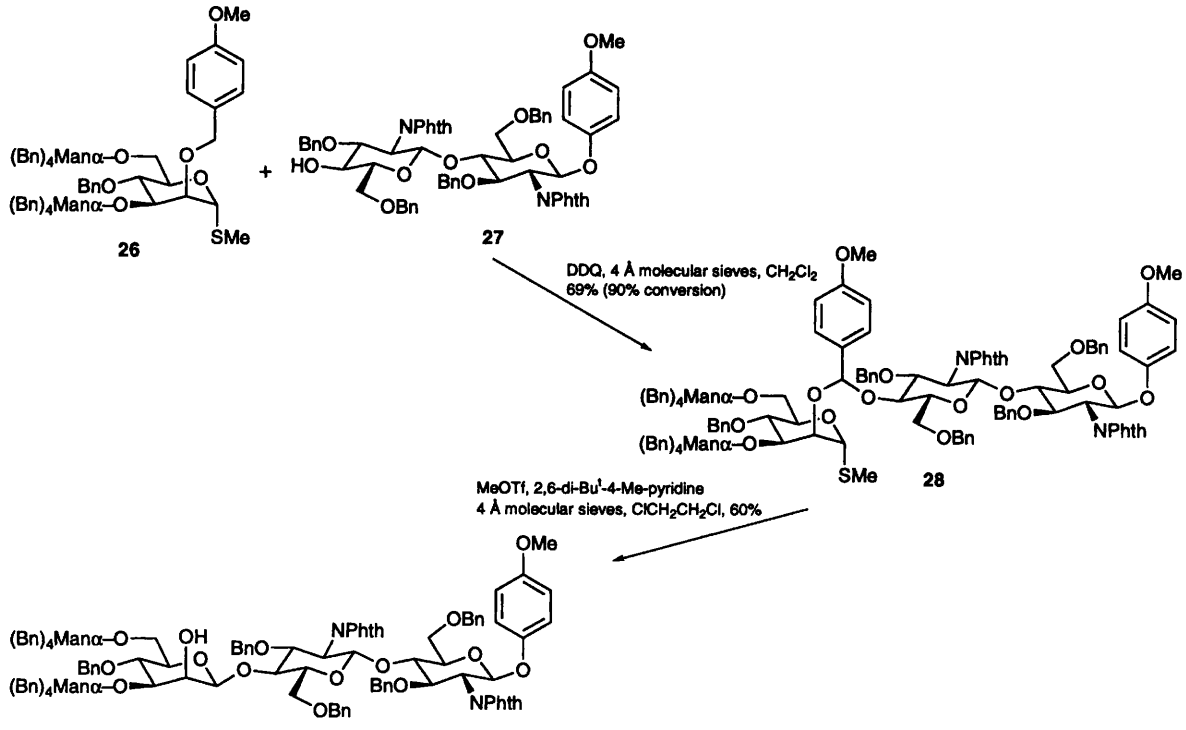
Two rare methods for cleaving benzyl ethers were reported in 1995. Cleavage of benzyl ethers with P_4S_{10} does not appear to be a general reaction, but this reagent works well with the carboxylic acid **24** where intramolecular participation is possible (**Scheme 20**).[26] Photochemically induced bromination of a benzyl ether followed by hydrolysis of the resulting bromohydrin derivative[27] was used to deprotect the benzyl ether function in furanoside **25** (**Scheme 21**).[28]



Scheme 20



Scheme 21

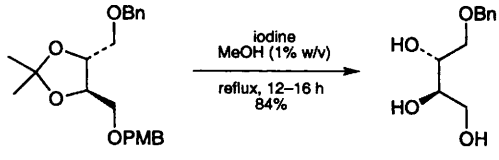


Scheme 22

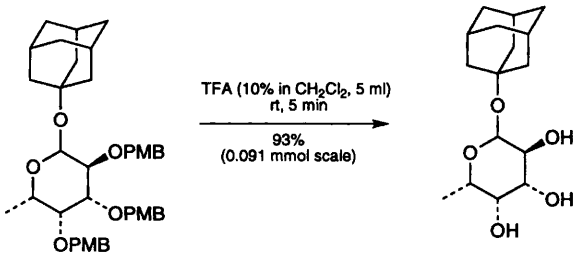
The oxidative conditions normally used to deprotect *p*-methoxybenzyl ethers provide a method for stereodirected glycosylation as illustrated by a synthesis of the pentasaccharide core structure of an asparagine-linked glycoprotein oligosaccharide (**Scheme 22**).[29] The technique involved the generation of a mixed acetal **28** on oxidation of the *p*-methoxybenzyl ether in the trimannoside donor **26** in the presence of chitobiose derivative **27**. Activation of the methylthio group in **28** by *S*-alkylation induced intramolecular creation of the crucial β-mannoside link.

The acid lability of *p*-methoxybenzyl (PMB) groups has long been appreciated but rarely exploited in deprotection chemistry. **Scheme 23** shows that PMB ethers can be removed selectively with TFA without detriment to a glycosidic link, and the survival of a trisaccharide under similar conditions suggests that PMB groups may be used in oligosaccharide synthesis.[30]

During the course of a synthesis in which the removal of an isopropylidene group in the presence of both a PMB ether and a benzyl ether was required, it was discovered[31] that iodine in methanol[32] cleaved not only the isopropylidene acetal, but also the PMB ether (**Scheme 24**). The deprotection proceeds with a 1% (w/v) solution of iodine in methanol at reflux.



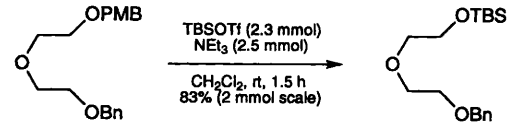
Scheme 24



PMB = *p*-methoxybenzyl

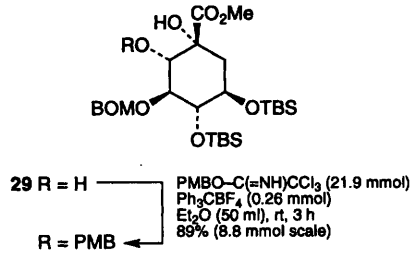
Scheme 23

The combined use of TBSOTf (*tert*-butyldimethylsilyl trifluoromethanesulfonate) and NEt_3 readily cleaves *p*- or *o*-methoxybenzyl ethers to give directly the corresponding TBS ethers in high yields (**Scheme 25**).[33] TES (triethylsilyl) ethers can be prepared likewise.



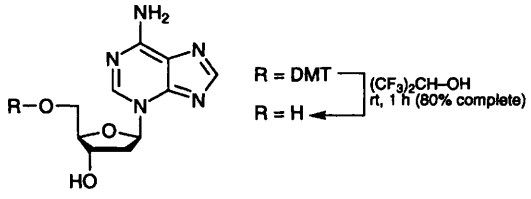
Scheme 25

Falck and co-workers[34] recently accomplished the selective protection of the hindered secondary alcohol **29** using *p*-methoxybenzyl trichloroacetimidate in the presence of a catalytic amount of trityl tetrafluoroborate as catalyst according to the procedure of Nakajima (**Scheme 26**).[35]



Scheme 26

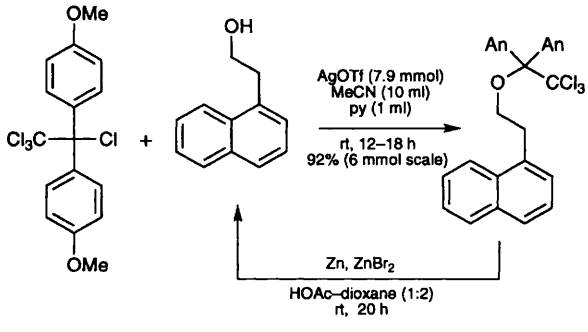
Leonard and Neelima have shown[36] that 1,1,1,3,3,3-hexafluoropropan-2-ol (pK_a 9.3) removes the 4,4′-dimethoxytrityl (DMT) protecting group from the 5′-hydroxyl group of acid-sensitive nucleosides and nucleotides without competing *N*-glycosyl cleavage (**Scheme 27**). The reaction is easily followed by the appearance of a bright orange colour (λ_{max} 498 nm) due to the dimethoxytrityl carbocation.



5′-*O*-(4,4′-dimethoxytrityl)isoadenosine

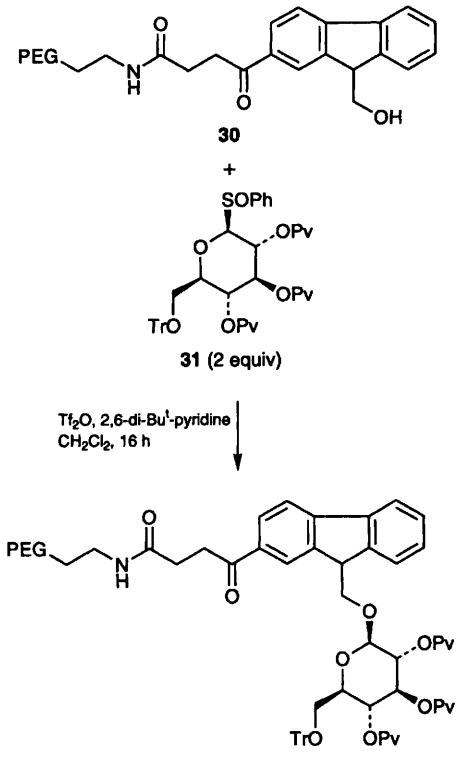
Scheme 27

Ugi and co-workers[37] have recommended 1,1-dianisyl-2,2,2-trichloroethyl ethers (abbreviated DATE) for the protection of alcohols (**Scheme 28**). DATE ethers are stable to conc. HCl–MeOH–dioxane (1:2:2), Cl_2CHCO_2H–CH_2Cl_2 (3:97), and conc. NH_3–dioxane (1:1), but they are readily cleaved by reduction with a mixture of Zn and $ZnBr_2$ in HOAc–dioxane (1:2).



Scheme 28

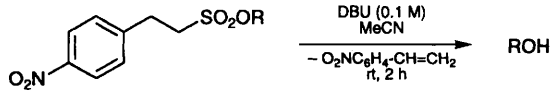
A new base-labile anchoring group consisting of 9-(hydroxymethyl)fluorene-2-succinic acid coupled to aminoethyl polyethylene glycol (**30**) was developed for the synthesis of oligosaccharides on polymer supports using 1-(phenylsulfinyl)glycosides as donors.[38] The polymer-supported **30** was primed with the first monosaccharide residue **31** as shown in **Scheme 29**.



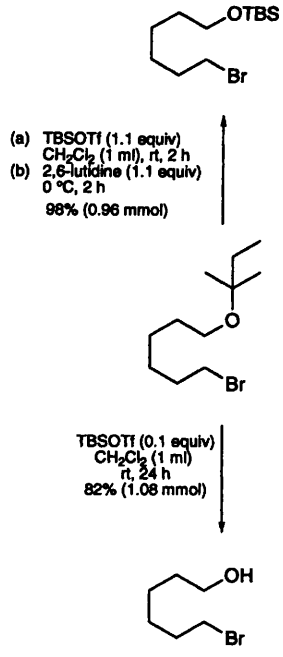
Scheme 29

The 2-(4-nitrophenyl)ethylsulfonyl (Npes) group is a base-labile protecting group for hydroxy functions in nucleoside synthesis (**Scheme 30**).[39] The Npes group is stable to the acidic conditions used to remove trityl and TBS groups but it is cleaved on treatment with DBU in MeCN at room temperature in 2 h. The Npes group is not removed rapidly by fluoride ions and it is more labile than 2-(4-nitrophenyl)ethyl (Npe) and 2-(4-nitrophenyl)ethoxycarbonyl (Npeoc) groups. Npes group are introduced by reaction of the alcohol function with 2-(4-nitrophenyl)ethylsulfonyl chloride and pyridine.

tert-Butyl and *tert*-amyl (2-methylbut-2-yl) ethers are cleaved by treatment with a catalytic amount of



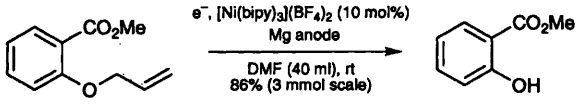
Scheme 30



Scheme 31

TBSOTf (**Scheme 31**).[40] When a stoichiometric amount of triflate is used (followed by 2,6-lutidine) the same ethers can be converted directly into the corresponding TBS ethers. Methoxy, allyloxy, lactone, bromo, trimethylsilylalkynyl and alkenyl groups are tolerated.

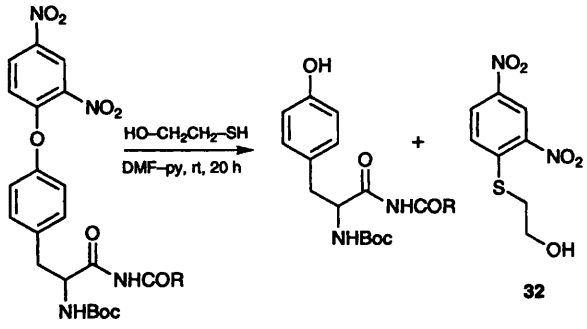
Olivero and co-workers[41] reported that the cationic complex $[Ni(bipy)_3](BF_4)_2$ is a good catalyst for the electrochemical cleavage of the O–C (allyl) bond of allyl ethers, affording the parent alcohols or phenols in good yield, under mild conditions (**Scheme 32**). The electrochemical method is based on the use of a single-compartment cell, fitted with a sacrificial magnesium anode. Reaction is carried out in DMF at a constant current, with 10 mol% of catalyst with respect to the starting allyl ether. The electrochemical set-up is very simple and allows the deprotection on a preparative scale. The method is selective for allyl ethers; homoallyl ethers or enol ethers are not cleaved under these conditions.



bipy = 2,2'-bipyridine

Scheme 32

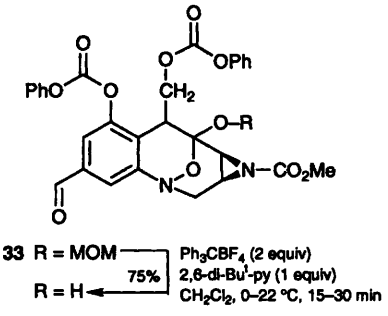
The 2,4-dinitrophenyl (Dnp) group is useful for the selective exposure of the aryl hydroxy function of tyrosine without compromising the protecting groups of other tyrosine residues or amino groups in post-assembly peptide modifications such as phosphorylation.[42] The deprotection is easily accomplished with mercaptoethanol and the course of the deprotection can be monitored by the appearance of the thioether **32** [λ_{max} 341 nm ($\varepsilon = 12500$)] (**Scheme 33**).



Scheme 33

2.4 Alkoxyalkyl ethers

In the closing stages of a synthesis of mitomycin derivative FR-900482, the densely functionalised intermediate **33** had to be shorn of its robust MOM (methoxymethyl) protector (**Scheme 34**).[43] The task was accomplished with trityl fluoroborate under conditions devised some years ago by Kishi.[44]



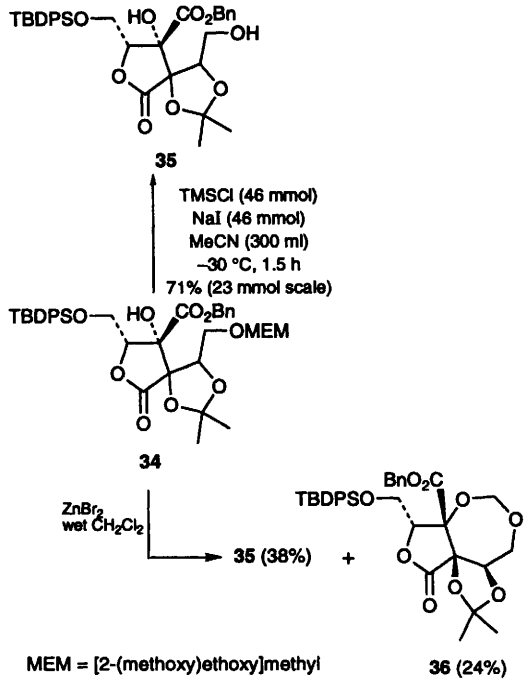
MOM = methoxymethyl

Scheme 34

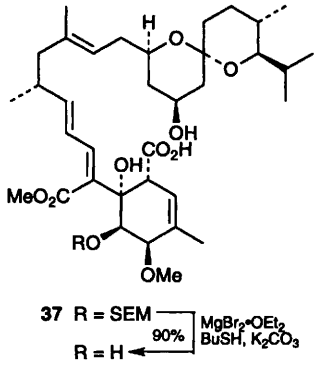
Attempts to deprotect the MEM ether **34** using $ZnBr_2$ in wet CH_2Cl_2[45,46] gave the desired primary alcohol **35** (38%) together with the dioxepane derivative **36** (24%) (**Scheme 35**).[19] Fortunately, cleavage of the MEM {[2-(methoxy)ethoxy]methyl} ether with TMSI, generated *in situ* from reaction of TMSCl with NaI, gave **35** (71%) free of contamination by **36**.

During a synthesis of the milbemycins, Thomas and co-workers[47] required a mild deprotection of SEM ether **37**. Magnesium bromide etherate in the presence of butanethiol and K_2CO_3 accomplished the desired deprotection in 90% yield (**Scheme 36**).

Selective protection of the 2'-hydroxy group of *N*-acyl-*O*-di(*tert*-butyl)silane-3',5'-diyl nucleoside



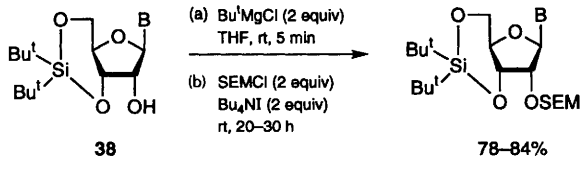
Scheme 35



Scheme 36

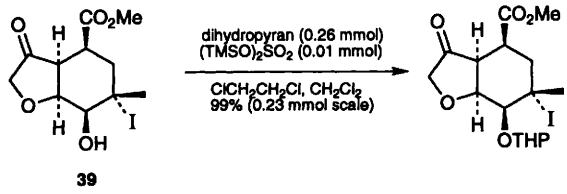
derivatives **38** can be accomplished with 2-[(trimethylsilyl)ethoxy]methyl chloride (SEMCl) using Bu^tMgCl as the base (**Scheme 37**).[48] The usual conditions (SEMCl, Hünig's base) are complicated by *N*-alkylation.

There are probably more methods for tetrahydropyranylation of alcohols than entries in Don Giovanni's catalogue. Nevertheless, White and



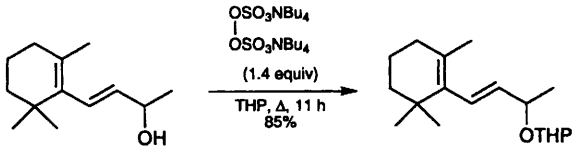
Scheme 37

co-workers[49] had great difficulty protecting the secondary alcohol function in **39** using a selection of the many methods published. Success was finally achieved using bis(trimethylsilyl) sulfate[50] as catalyst in 1,2-dichloroethane (**Scheme 38**). The anhydrous, essentially neutral conditions are mild and efficient. Another rare catalyst reported for the tetrahydropyranylation of alcohols with 3,4-dihydro-2*H*-pyran is dicyanoketene ethylene acetal.[51]



Scheme 38

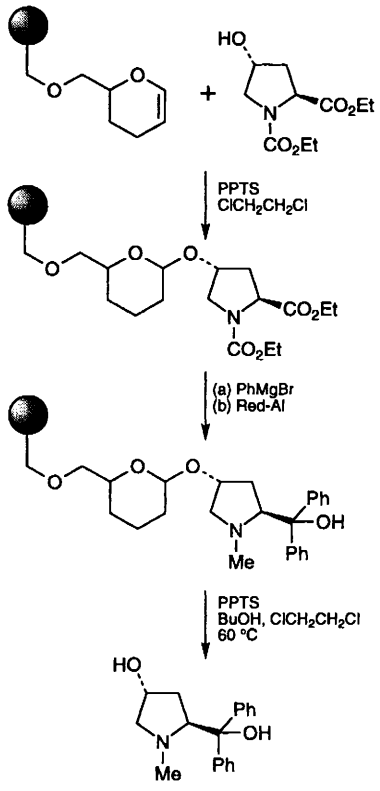
A new procedure for oxidative tetrahydropyranylation of alcohols involves reaction of tetrahydropyran (THP) and tetrabutylammonium peroxydisulfate (**Scheme 39**).[52,53] Olefins, sulfides and acetals survive intact because the reaction proceeds under nearly neutral conditions.



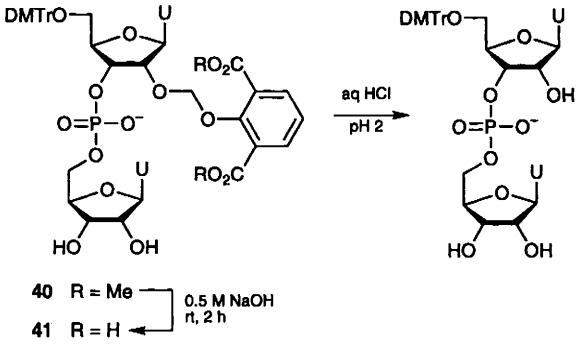
Scheme 39

For the solid phase synthesis of 2-pyrrolidine methanol ligands, Liu and Ellman[54] required a linker which was stable to Grignard reagents and Red-Al®. The THP group served the purpose and benefitted from easy cleavage from the resin using PPTS (**Scheme 40**). Reductive cleavage of a THP ether with a combination of boron trifluoride etherate and sodium cyanoborohydride has been reported by Srikrishna and co-workers.[55]

The 2-hydroxyisophthalate formaldehyde acetal (HIFA) group has been recommended for the protection of 2′-hydroxy functions of nucleosides during automated machine synthesis of RNA oligomers.[56] As the diester (*e.g.* **40**, **Scheme 41**), HIFA groups are relatively stable to the acidic conditions used to deprotect dimethoxytrityl groups during chain elongation, but alkaline hydrolysis produces the corresponding diacid **41** which is labile towards dilute HCl. The authors estimate a 42-fold increase in the rate of hydrolysis at pH 1 and 1320-fold increase at pH 3 compared with the diester **40**. The four step sequence required to introduce the protecting group is likely to limit its appeal.



Scheme 40



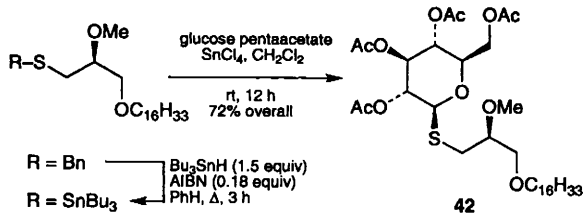
Scheme 41

3 Thiol protecting groups

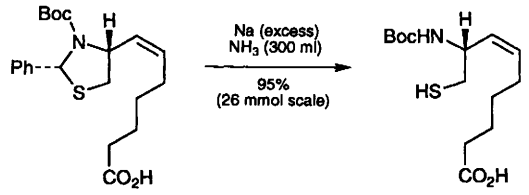
Deprotection of *S*-benzyl groups using Bu_3SnH gives tributylstannyl sulfides[57] which are effective thioglycosidation agents[58] as illustrated in the synthesis of the thioglycolipid **42** (**Scheme 42**).

During an economical synthesis of (+)-biotin from L-cysteine, a Belgian group[59] accomplished protection of both an amino group and a thiol as a thiazolidine. The thiazolidine ring was later cleaved very efficiently using dissolving metal reduction as shown in **Scheme 43**.

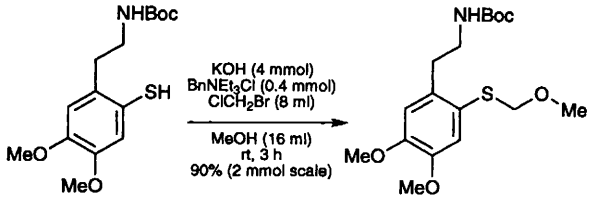
Protection of a thiol as its MOM derivative can be accomplished by treating the thiol with base and $ClCH_2Br$ in MeOH as shown in **Scheme 44**. Alcohols and carboxylic acids do not react.[60]



Scheme 42



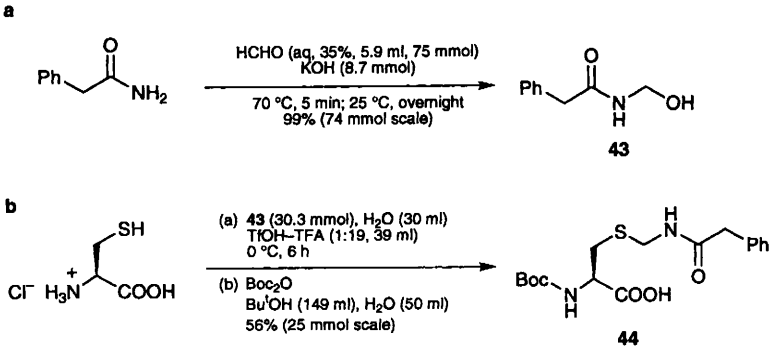
Scheme 43



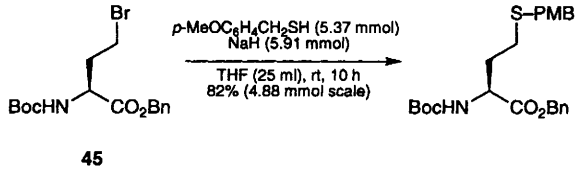
Scheme 44

Albericio and co-workers[61] reported that the phenylacetamidomethyl (Phacm) group can be used to protect the thiol function of cysteine during Boc and Fmoc solid-phase peptide synthesis. The Phacm group can be introduced onto L-cysteine by reaction with *N*-(hydroxymethyl)phenylacetamide **43** in the presence of trifluoromethanesulfonic acid (TfOH) (**Scheme 45**). The crude intermediate is then treated with di-*tert*-butyl dicarbonate (or Fmoc-succinimide) to give the appropriate fully protected Boc derivative **44** (or corresponding Fmoc derivative). The advantages of using the Phacm group in peptide synthesis stem from the fact that, apart from chemical means (iodine or thallium salts), it can also be removed enzymatically by the action of penicillin amidohydrolase at neutral pH. This makes it orthogonal with the common cysteine protecting groups, such as 4-methylbenzyl, trityl and fluorenylmethyl.

An orthogonally protected L-homocysteine has been prepared[62] by simple displacement of a bromine from **45** by sodium *p*-methoxybenzylthiolate as shown in **Scheme 46**. The *S*-*p*-methoxybenzyl group is stable to conditions used for the removal of Boc groups (TFA, room temperature) or NaOH used to hydrolyse benzyl esters but it can be cleaved by boiling TFA[63] or $Hg(OCOCF_3)_2$ at 0 °C.[64]



Scheme 45



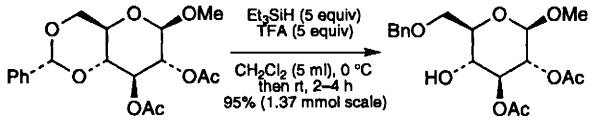
Scheme 46

4 Diol protecting groups

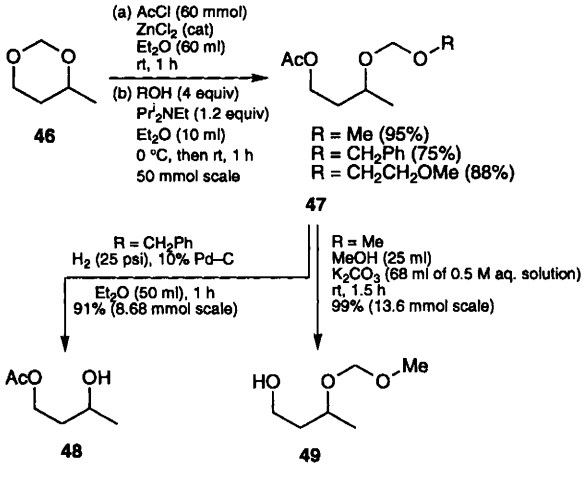
A two-step method for the differential functionalization of 1,2- and 1,3-diols involves reaction of cyclic acetals with acetyl chloride in the presence of zinc chloride followed by conversion of the resulting chloromethyl ether into an alkoxymethyl ether (**Scheme 47**).[65] When the procedure is applied to the unsymmetrically substituted acetal **46**, the product **47** has the acetate at the less hindered centre. By the proper choice of alcohol (methyl or benzyl alcohol) the subsequent step can give rise to a compound with a protected primary **48** or secondary **49** hydroxy group.

One of the most useful and widely utilised methods for differentiating the C-4 hydroxy group of sugars involves the reductive regioselective opening of a 4,6-*O*-benzylidene acetals. DeNinno and co-workers[66] reported a new procedure using trifluoroacetic acid and triethylsilane (**Scheme 48**). Both benzyl and acetate protecting groups are tolerated, although the acetate protected compounds react faster and more cleanly.

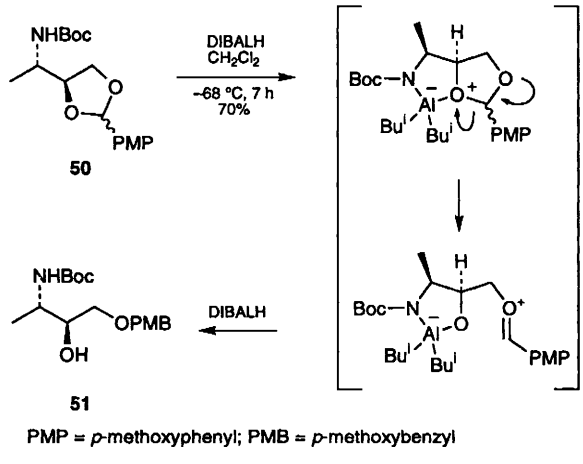
Reductive cleavage of the *p*-methoxyphenyl (PMP) methylene acetal **50** can be performed with excellent regioselectivity using DIBAL-H at low temperature but the major product **51** is the secondary alcohol rather than the expected primary alcohol (**Scheme 49**).[67] The observed regioselectivity can be attributed to a directing effect by the nitrogen of the vicinal carbamate. A similar result had been previously observed by Takano[68] in benzylidene acetals with a vicinal alcohol or ether group.



Scheme 48

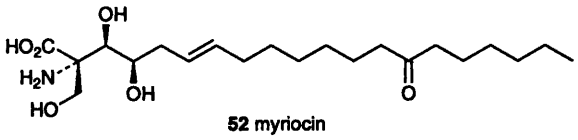


Scheme 47

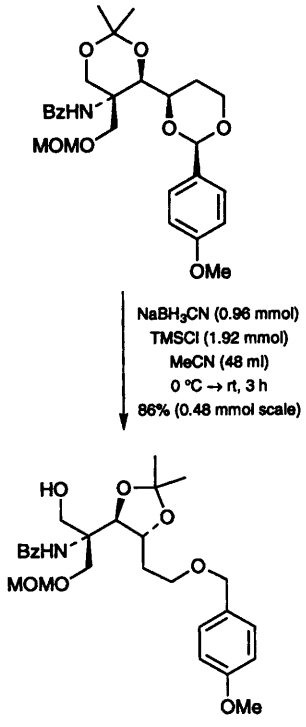


Scheme 49

During a synthesis of myriocin **52**, a Japanese research group[69] accomplished the selective reductive cleavage of a PMP methylene acetal with concomitant rearrangement of a 1,3-dioxane to a 1,3-dioxolane (**Scheme 50**).



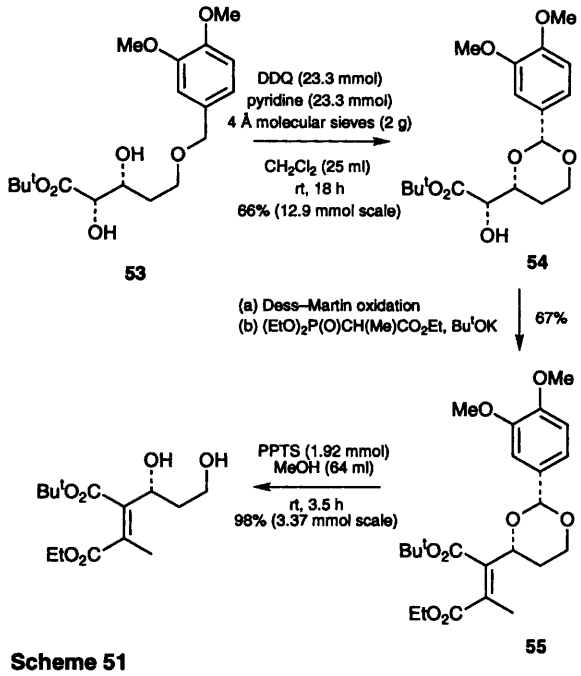
52 myriocin



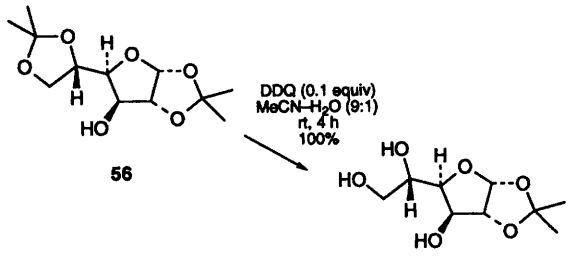
Scheme 50

In a synthesis of the protein phosphatase inhibitor tautomycin, the Oikawa group[70] used the superior hydrolytic lability of the dimethoxybenzylidene acetal in the synthesis of a maleate side chain as shown in **Scheme 51**. Thus treatment of the 3,4-dimethoxybenzyl ether **53** with DDQ caused oxiditive cyclisation to take place to give the 3,4-dimethoxybenzylidene acetal **54**. Two further steps converted **54** into the maleate derivative **55** which was then deprotected using PPTS in MeOH. The corresponding *p*-methoxyphenylmethylene (*p*-methoxybenzylidene) acetal was labile towards the Wadsworth–Emmons reaction and suffered epimerisation.

A Spanish research group[71] has thoroughly evaluated DDQ as a reagent for the deprotection of acetals[72] and thioacetals[73] in carbohydrate derivatives. The use of 0.1–0.4 equiv. of DDQ in MeCN–H_2O (9:1) cleaves isopropylidene groups at between room temperature (rt) and 80 °C without affecting tosyl, benzoyl, benzyl or acetate groups, though at elevated temperature some acyl migration may occur. Monosubstituted dioxolanes (*e.g.* **56**, **Scheme 52**) are more readily hydrolysed than bicyclic, spiro



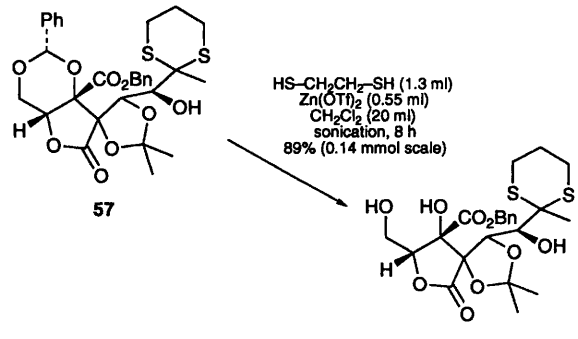
Scheme 51



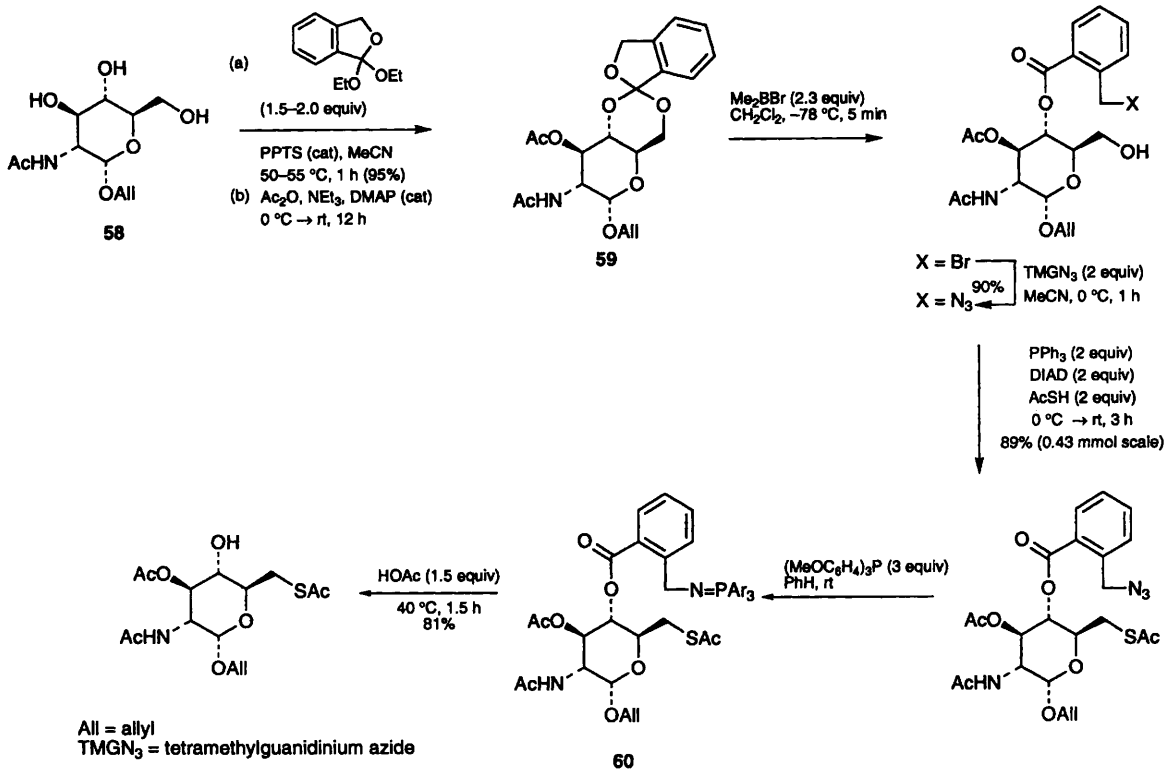
Scheme 52

and disubstituted systems, and 1,3-dioxanes are more labile than 1,3-dioxolanes. Removal of dithioacetals requires 2 equiv. of DDQ at 80 °C.

During a synthesis of zaragozic acid, the Nicolaou group[19] required the selective destruction of the benzylidene acetal **57** in the presence of an isopropylidene acetal (**Scheme 53**). The task was accomplished in 89% yield using zinc triflate and ethane-1,2-dithiol with the aid of sonication.



Scheme 53



Scheme 54

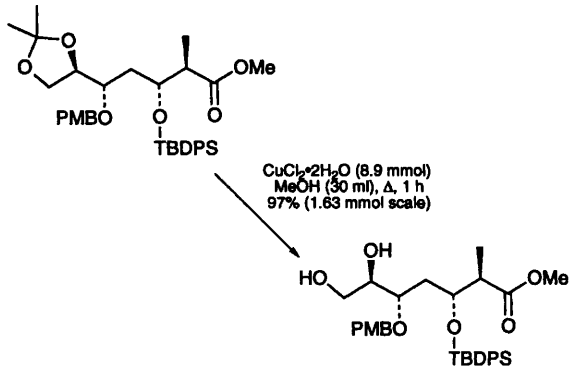
An efficient strategy for regiocontrolled differentiation of the 4,6-positions of pyranosides has been developed using dimethylboron bromide-mediated cleavage of phthalide orthoesters.[74] The procedure illustrated in **Scheme 54** began with reaction of glycoside **58** with a phthalide orthoester in acetonitrile or DMF in the presence of catalytic PPTS to give the 4,6-*O*-protected orthoester **59** in excellent yield as a single diastereomer. High selectivity for generation of the C4 benzoate was achieved by employing 2.3 equiv. of dimethylboron bromide. Two important features to be noted are:

(i) the reaction proceeds smoothly with no complications from competitive cleavage of the anomeric acetal of the sugar, and
(ii) the sterically demanding secondary (C4) hydroxy group is protected over a free primary (C6) hydroxy group.

To complete the sequence, selective cleavage of the benzoate moiety in the presence of the three additional acyl functionalities was accomplished using tris(4-methoxyphenyl)phosphine in the presence of glacial acetic acid. Presumably this reaction involves intramolecular transacylation of the phosphoranylideneamine **60**.

During a synthesis of lankacidin C, a selective hydrolysis of an isopropylidene group without harm to a PMB ether was accomplished efficiently using $CuCl_2 \cdot 2H_2O$ in MeOH at reflux (**Scheme 55**).[9]

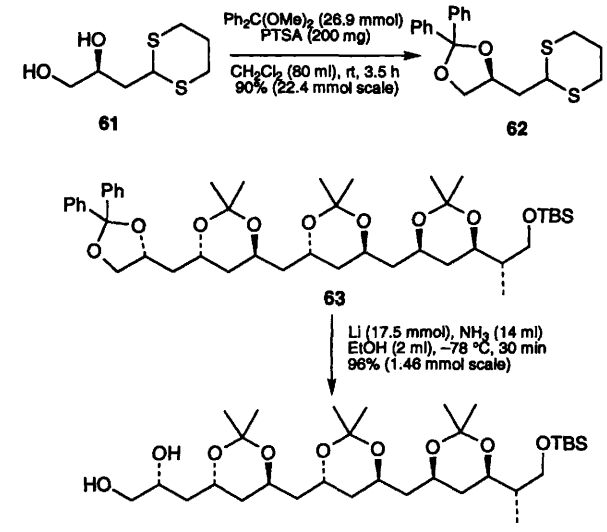
2,2-Diphenyl-1,3-dioxolanes are seldom used in synthesis but **Scheme 56** gives some indication of



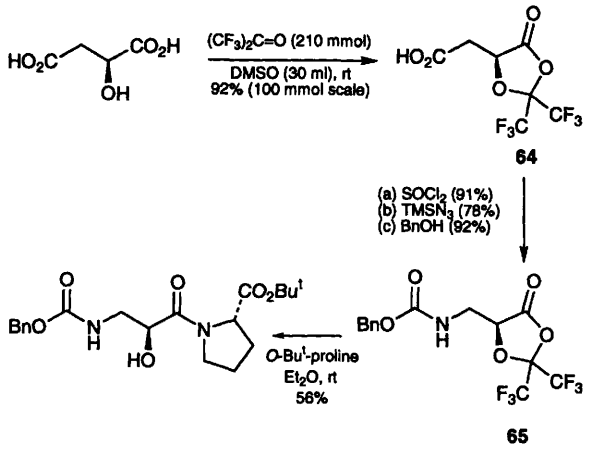
Scheme 55

their potential.[75] Treatment of the diol **61** with benzophenone dimethyl acetal gave the dioxolane derivative **62** which was then elaborated to the fully protected polyol chain **63**. Selective unmasking of the terminal 1,2-diol was accomplished by reductive cleavage of the 2,2-diphenyl-1,3-dioxolane with lithium in liquid ammonia – conditions which left the seven remaining hydroxy functions fully protected.

Simultaneous protection of the hydroxy group and activation of the C1 carboxyl group of malic acid was accomplished by formation of the dioxolanone **64** by reaction of malic acid with hexafluoroacetone in DMSO (**Scheme 57**).[76] The remaining unprotected carboxyl was transformed into an



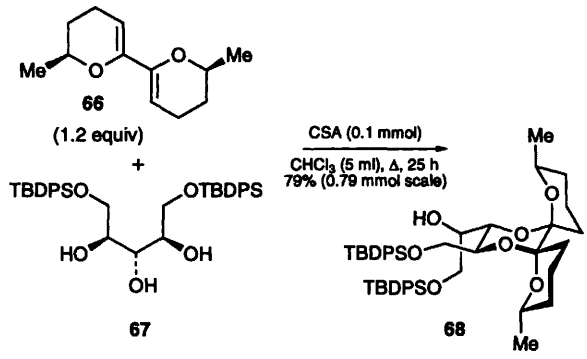
Scheme 56



Scheme 57

amino group *via* Curtius rearrangement. The highly electrophilic dioxolanone **65** was then used to acylate proline *tert*-butyl ester under mild conditions without the need for further deprotection of the alcohol or activation of the carboxyl function.

The Ley group[77] has reported details of a new method for regio- and enantio-selective differentiation of symmetrical polyols (**Scheme 58**). Reaction of the enantiopure diene **66** with the 1,5-disilylated xylitol **67** in boiling chloroform containing a catalytic amount of CSA gave the protected polyol **68** as the only isolated product. The reaction is completely diastereoselective and the product formed is the most thermodynamically stable in which the two side chain methyl groups and the two hydroxylated side chains on the dioxane ring are equatorially orientated, with the spirocentres fully stabilised anomerically. Removal of the dispiroketal moiety can be achieved using 95% aqueous TFA. Similarly protected sugars have been used in a one-pot synthesis of oligosaccharides.[78]

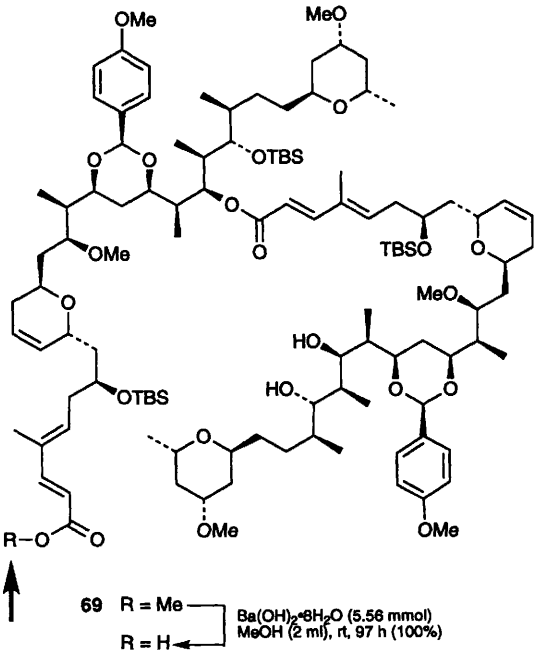


Scheme 58

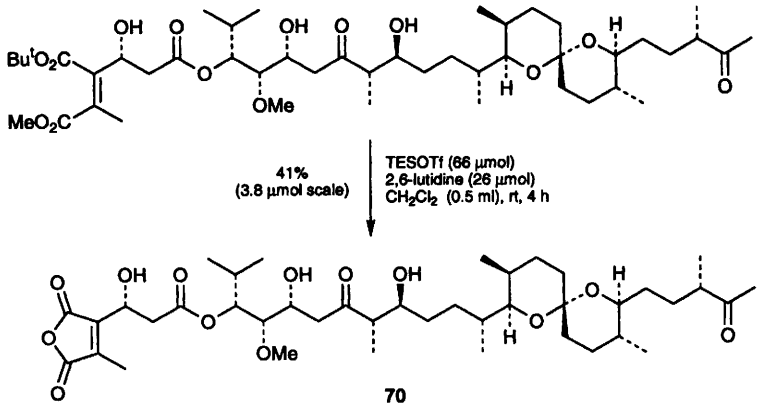
5 Carboxyl protecting groups

At a late stage in the synthesis of the macrodiolide swinholide, Paterson and co-workers[79] were faced with the problem of hydrolysing a terminal methyl dienoate ester **69** (**Scheme 59**) without competing hydrolysis of a similar internal ester. The problem was compounded by the potential elimination of TBSOH and oxene ring scission to generate a highly conjugated system. The desired transformation was eventually achieved in quantitative yield using barium hydroxide hydrate in methanol.

The final step of the synthesis of the protein phosphatase inhibitor tautomycin **70** involved selective deprotection of the *tert*-butyl ester of the maleate side chain with concomitant anhydride formation (**Scheme 60**).[80] Protic acids which had worked in model studies failed owing to destruction of the anhydride product **70**. However, the reaction proceeded in modest yield using 17.4 equiv. of



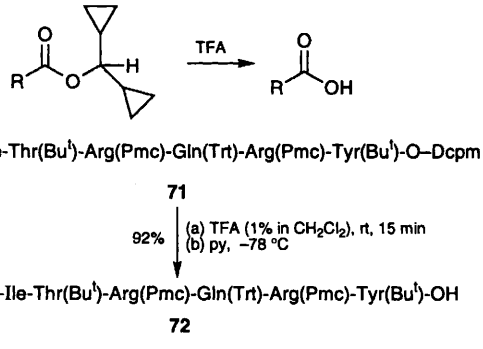
Scheme 59



Scheme 60

TESOTf in the presence of 2,6-lutidine. The more reactive TMSOTf gave only decomposition.

Carpino and co-workers[80] have reported two new protecting groups which take advantage of the easy solvolysis of cyclopropylmethyl systems: the dicyclopropylmethyl (Dcpm) group for carboxyl and the dimethylcyclopropyl (Dmcp) group for amide protection (*vide infra*). Protection of acids with Dcpm group (prepared by reaction of the acid with dicyclopropylcarbinol and DCC) is especially useful where its selective removal is later necessary in the presence of other acid sensitive groups. **Scheme 61** illustrates deblocking of the peptide **71** by TFA to form **72** in which a *tert*-butyl ether and *N*-trityl group remained intact.



Scheme 61

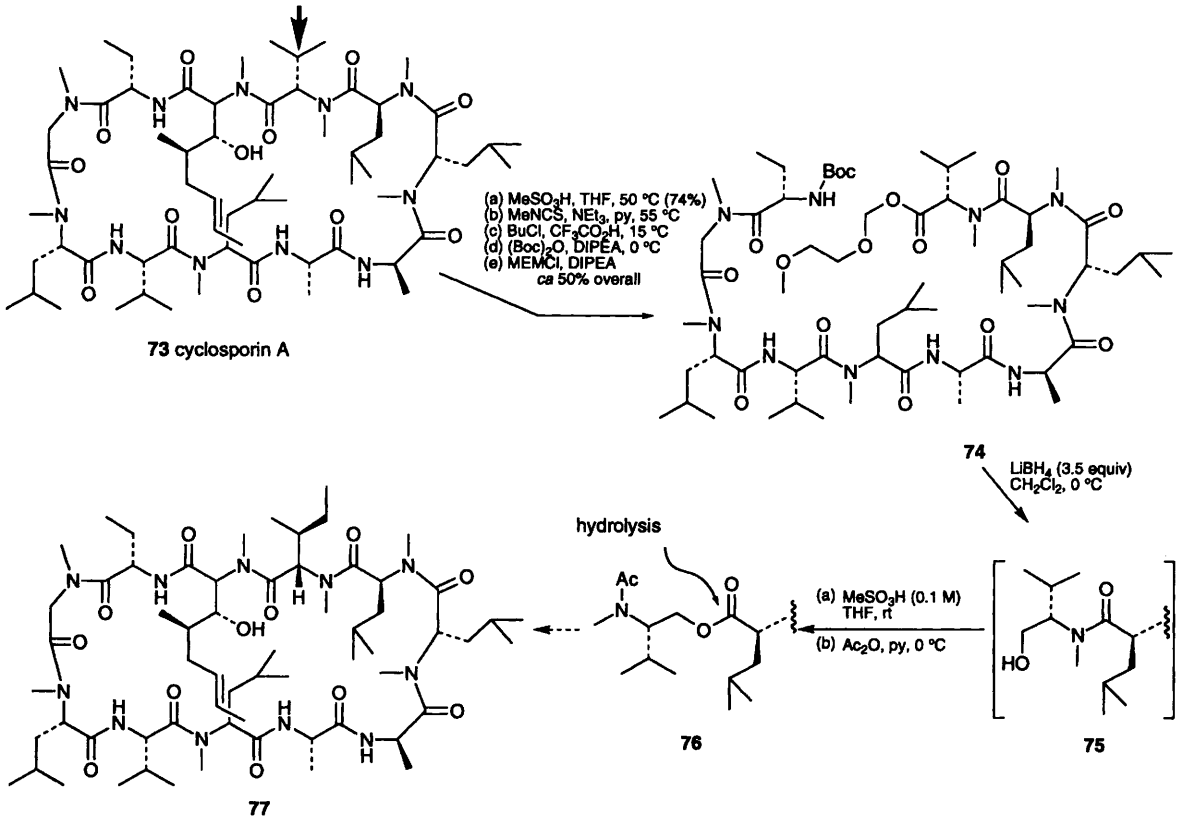
As part of a programme aimed at probing the molecular recognition of the immunosuppressant cyclosporin A **73** and its protein receptor, the Schreiber group[81] required the replacement of the valine group (arrow) in cyclosporin A with a sterically more demanding isoleucine group (**Scheme 62**). The multistep procedure began with controlled degradation of natural cyclosporin A to the linear peptide **74** in which the amino and carboxyl termini were protected as their Boc and MEM ester derivatives respectively. The MEM (methoxyethoxymethyl) ester, with its favourable metal-binding properties, was essential for the subsequent reduction step (**74**→**75**) as all other combinations of common esters and reducing agents failed. Following reduction to the alcohol **75**, an acid catalysed *N*→*O* shift and *N*-acylation produced the rearranged ester **76** which could be hydrolysed to give an intermediate from which the ring was reconstructed with incorporation of the desired isoleucine to give the target **77**.

At a late stage in the synthesis of the potent protein serine–threonine phosphatase inhibitor motuporin (**Scheme 63**), Valentekovich and Schreiber[82] achieved macrolactamisation of the pentapeptide **78** by a four-step process beginning with reductive removal of the phenacyl ester group followed by pentafluorophenyl ester formation at the *C*-terminus. *N*-Terminal Boc group deprotection, followed by dilution and neutralisation with excess Hünig's base, gave the desired macrocycle **79** in 55% yield. A recent report suggests[83] that phenacyl esters may also be removed oxidatively as illustrated by the example in **Scheme 64**.

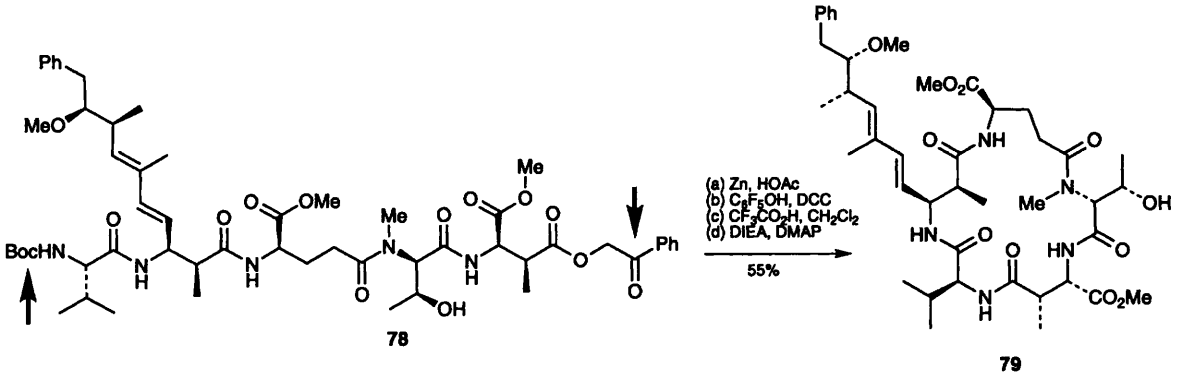
The very mild conditions required to deblock allyl esters continues to attract attention. Thus, a Japanese group[84] has described the use of $Pd(OAc)_2$ in H_2O as a less expensive and more practical alternative to the unstable $Pd[PPh_3]_4$ for the deprotection of β-lactam allyl esters (e.g. **80**) (**Scheme 65**). The water is beneficial in promoting reduction of Pd^{II} to Pd^0.

Seitz and Kunz[85] have advanced the art of solid phase synthesis by developing a novel allylic anchor whose virtues were exemplified in a synthesis of protected and unprotected *O*-glycosylated Mucin-type glycopeptides. Anchoring through allyl esters not only allows peptide derivatives to be detached without affecting acid- and base-labile structural elements, but also provides orthogonal stability relative to the temporary protecting groups commonly used in solid phase peptide synthesis. In the example shown (**Scheme 66**) the glycopeptide segment **81** was detached with Pd^0 catalysis using *N*-methylaniline as the nucleophile.

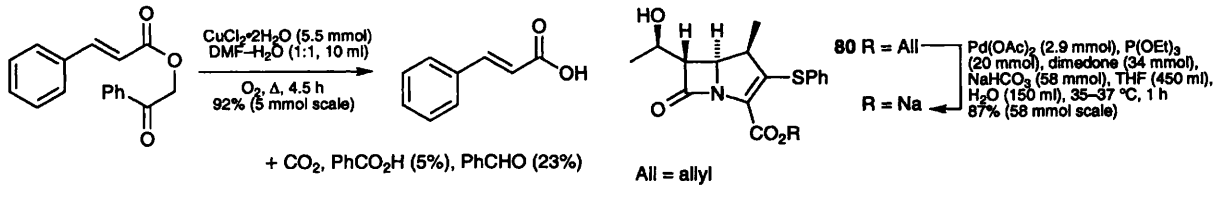
Benzylic esters activated by electron-donating groups on the aromatic ring are now common



Scheme 62



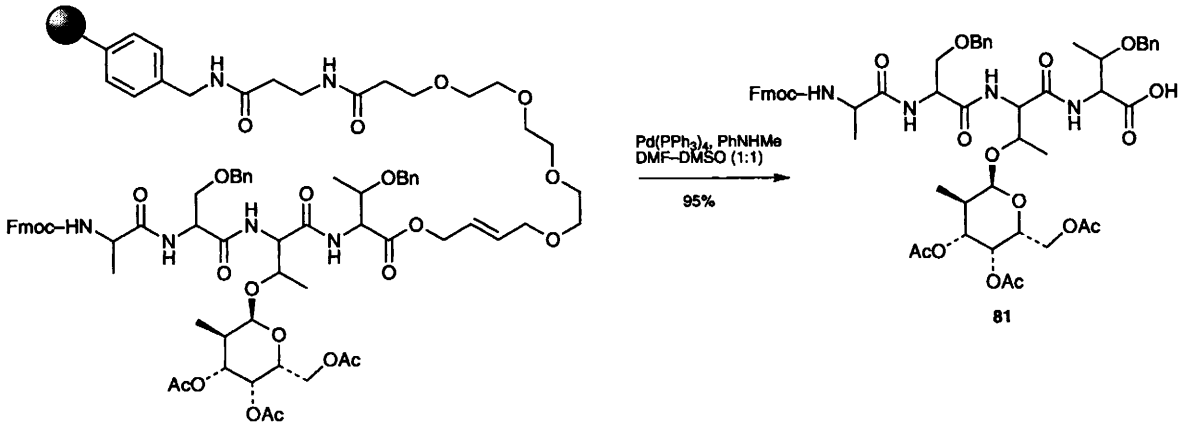
Scheme 63



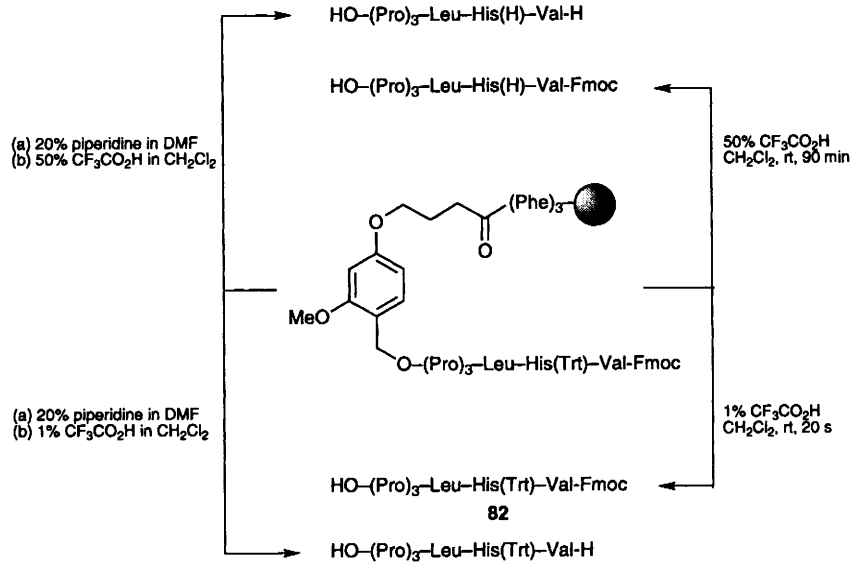
Scheme 64

Scheme 65

elements of linkers in solid phase synthesis. Their cleavage can be accomplished under acidic or basic conditions. For example, the peptide H-(Val-His-Leu-Pro-Pro-Pro)$_8$-OH corresponding to the *N*-terminal domain of the abundant maize protein γ-zein has been synthesised by the Giralt group (**Scheme 67**).[86] The protected precursor Fmoc-(Val-His(Trt)-Leu-Pro-Pro-Pro)-OH **82** was synthesised on a solid phase using the highly acid-labile 4-[4-(hydroxymethyl)-3-methoxyphenoxy]butyric acid



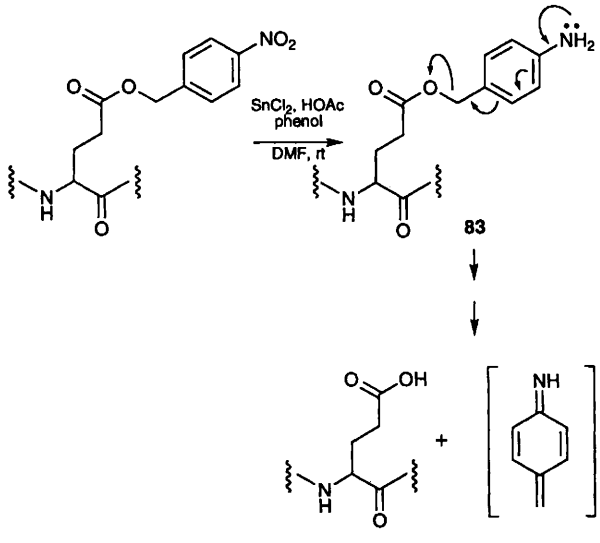
Scheme 66



Scheme 67

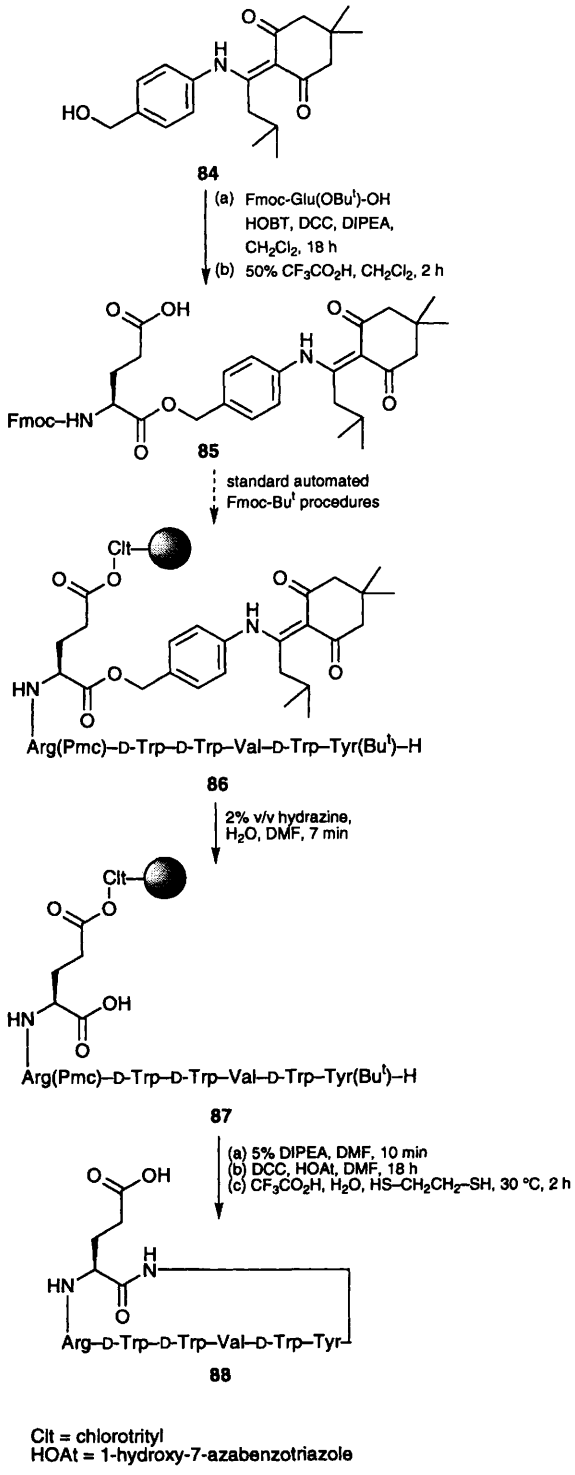
(HMPB) of Riniker[87] as handle. An important feature of this synthetic strategy is the posssibility of obtaining the peptide sequence at different levels of protection by varying the cleavage program. Note the efficient cleavage of the protected segment from the resin by treatment with 1% TFA in dichloromethane with complete retention of the *N*-trityl group protecting the imidazole ring in histidine.

A solid phase supported peptide synthesis strategy using *p*-nitrobenzyl esters, thioethers and carbamates for side chain protection has been described (**Scheme 68**).[88] The *p*-nitrobenzyl side chain-protected amino acids of lysine, cysteine, glutamic acid and aspartic acid were synthesised and incorporated into short peptides by standard Fmoc methodology on polystyrene resin. Deprotection was carried out under mildly acidic reducing conditions using a solution of $SnCl_2$, HOAc and phenol in DMF at room temperature. The deprotection takes advantage of the easy 1,6-elimination of the intermediate *p*-aminobenzyl ester **83**.



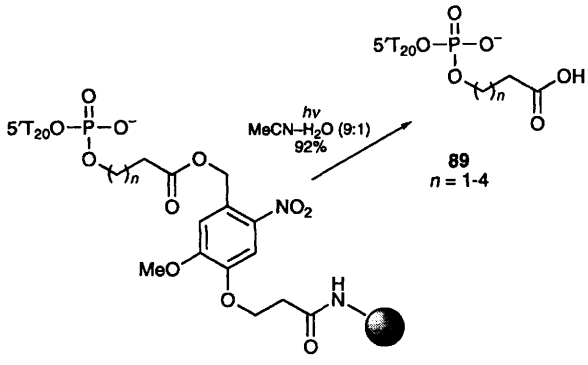
Scheme 68

4-{*N*-[1-(4,4-Dimethyl-2,6-dioxocyclohexylidene)-3-methylbutyl]amino}benzyl ester (Dmab) is a new carboxy protecting group that is based on the safety-catch principle and can be used orthogonally with Fmoc–Bu^t peptide chemistry.[89] It is cleaved with 2% v/v hydrazine–H_2O–DMF at room temperature within minutes. The key component, 4-{*N*-[1-(4,4-dimethyl-2,6-dioxocyclohexylidene)-3-methylbutyl]amino}benzyl alcohol **84** was easily prepared as pale yellow crystals (mp 154–157 °C) in *ca.* 70% yield by reaction of 4-aminobenzyl alcohol and 2-(3-methylbutyryl)dimedone in refluxing THF. The value of Dmab is illustrated by a synthesis of a cyclic heptapeptide fragment **88** as shown in **Scheme 69**. Thus esterification of **84** with Fmoc-Glu(OBu^t)-OH using DCC followed by cleavage of the *tert*-butyl ester with TFA gave the Dmab ester **85**. The free carboxyl group was then attached to a 2-chlorotrityl chloride polystyrene resin in preparation for further elaboration to the heptapeptide **86**. Removal of the Dmab group by hydrazinolysis then gave a resin-bound heptapeptide **87** which was cyclised. Finally treatment with acid accomplished simultaneous removal the side chain protecting groups and cleavage from the resin to give the target heptapeptide **88**.



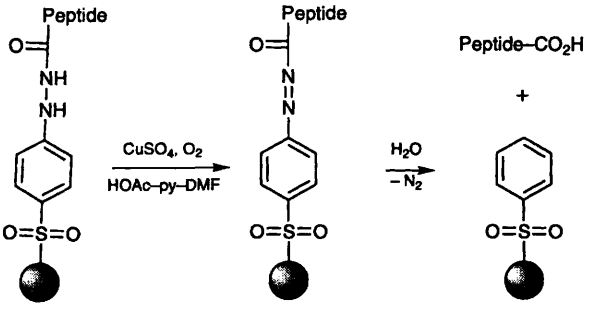
Scheme 69

Incorporation of a veratrole moiety into an *o*-nitrobenzyl component of a solid phase linker enhances its photolability. The method was applied to the synthesis of the eicosameric 3′-alkyl carboxylic acids **89** (**Scheme 70**).[90] Photocleavage occurred in 92% yield using the band-pass-filtered output of a high pressure Hg–Xe lamp (800 W). The cleavage conditions are mild enough to tolerate phosphodiester and nucleobase protecting groups.



Scheme 70

A polymer-bound phenylhydrazide group may be used to protect a C-terminal carboxyl function of a growing peptide.[91] The phenylhydrazide group serves as a linker which can be easily removed under mild oxidative conditions using Cu^{II} and molecular oxygen (**Scheme 71**). The phenylhydrazide linker is compatible with acid- and base-labile protecting groups.

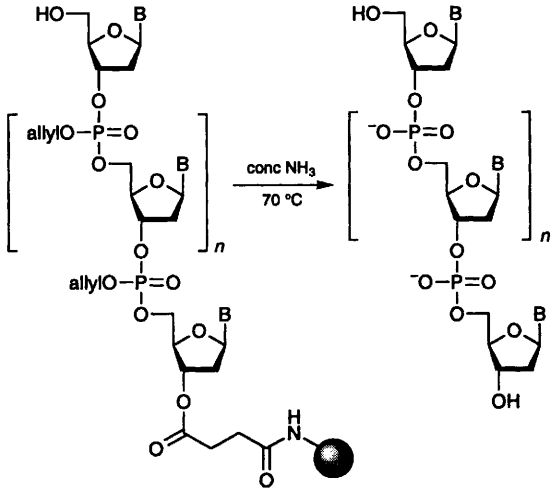


Scheme 71

6 Phosphate protecting groups

Some years ago Bannwarth and co-workers[92,93] developed bis(allyloxy)(diisopropylamino)phosphine as a phosphinylating agent which could be used for the phosphorylation of hydroxy functions in amino acids after activation by tetrazole followed by oxidation. The allyl protecting groups were later removed with Pd^0 and Ph_3P leading to the phosphorylated derivatives. Recently *N*-Boc-*O*-diallylphosphoryl serine and *N*-Boc-*O*-diallylphosphoryl threonine were synthesised by the Bannwarth procedure and used to synthesise *O*-phosphorylated peptides in the Boc mode of solid phase synthesis.[94] The allyl groups were removed with Pd^0, Ph_3P and formic acid.

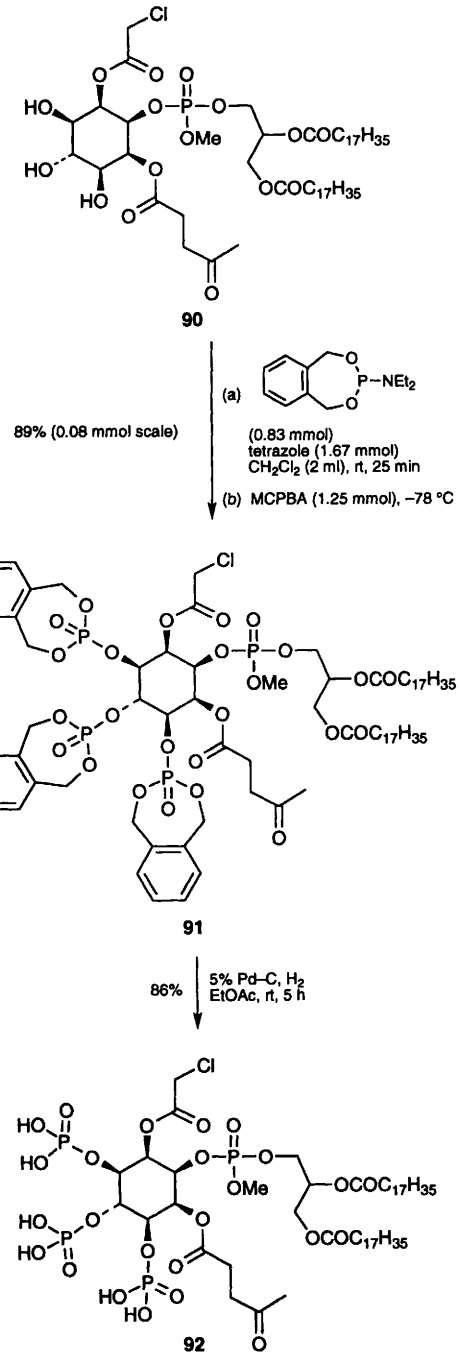
A Hofmann-La Roche group[95] investigated approaches to the solid phase synthesis of peptide–DNA hybrids using the Fmoc strategy for peptide synthesis and the phosphoramidite approach for DNA synthesis. The allyl protecting group used for the phosphate was stable to the DBU used to cleave the Fmoc group but difficulties were experienced optimising allyl cleavage using Pd catalysis, especially when the substrate was bound to a solid support. A useful development is the discovery that allyl phosphates are cleaved with concentrated ammonia under the same conditions used to cleave the oligonucleotide from its solid support as illustrated in **Scheme 72**.



Scheme 72

The hexafluoroisobutyl group $[(CF_3)_2CHCH_2]$ has recently been recommended as another base-labile protecting group for phosphate which is compatible with the phosphoramidite protocol.[96] It is removed under the same conditions as the 2-cyanoethyl group but the phosphoramidite precursors are more stable to heat and therefore easier to purify.

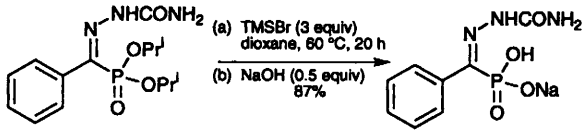
Distearoylphosphatidyl-*myo*-inositol 3,4,5-tris-(dihydrogen phosphate) (PIP_3) **92** (**Scheme 73**) is formed in the plasma membrane and is implicated in cell proliferation and oncogenesis. The Watanabe



Scheme 73

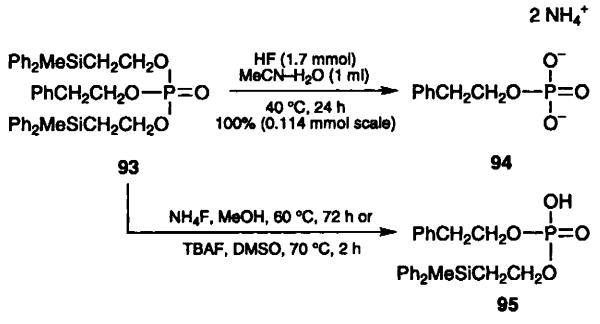
group[97] introduced the three phosphate groups via reaction of triol **90** with *o*-xylylene *N*,*N*-diethylphosphoramidite followed by oxidation. The 3,4,5-tris-*O*-(*o*-xylylenedioxyphosphanyloxy)-*myo*-inositol intermediate **91** was then cleaved by hydrogenolysis in good yield.

McKenna[98] first introduced TMSBr as a general reagent for cleaving methyl or ethyl phosphonate esters. Salomon and Breuer[99] found that, in some cases, isopropyl phosphonates cleaved more efficiently when TMSBr was used in excess in dioxane as illustrated in **Scheme 74**.



Scheme 74

Following the precedent set by Chao[100] and Sawabe,[101] the preparation and cleavage of bis[2-(methyldiphenylsilyl)ethyl] alkyl phosphates and the corresponding bis[2-(trimethylsilyl)ethyl] alkyl phosphates were examined in detail by Freeman and co-workers.[102] Treatment of the triester **93** (**Scheme 75**) with TBAF or NH_4F removes only one 2-(trialkylsilyl)ethyl group to give the diester **95**, whereas treatment with a solution of HF in $MeCN–H_2O$ gives the phosphate monoester **94** (as its ammonium salt) in quantitative yield. Cleavage can also be accomplished with TFA. The methyldiphenylsilyl derivative reacted slower than the (trimethylsilyl)ethyl analogue.

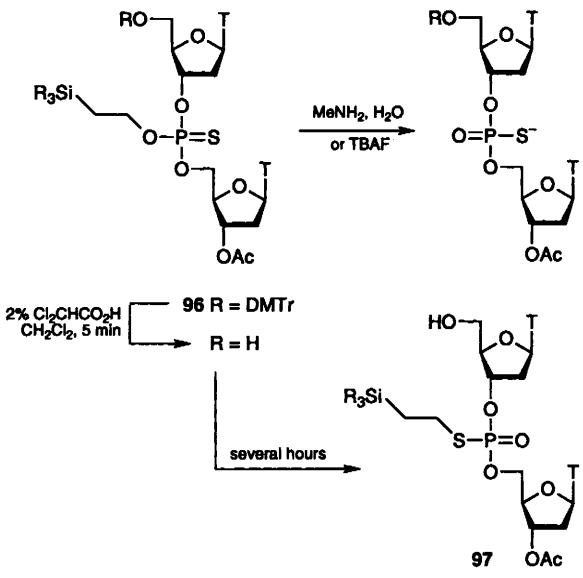


Scheme 75

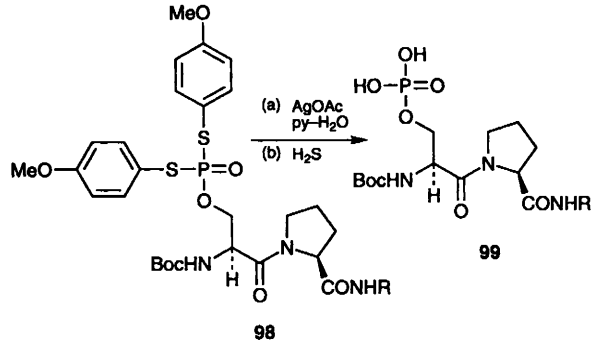
Krotz and co-workers[103] have employed β-(trialkylsilyl)ethyl phosphorothioates in oligonucleotide synthesis. The *O,O,O*-trialkyl phosphorothioate **96** could be deprotected with $MeNH_2–H_2O$ or TBAF as shown in **Scheme 76**. Removal of the dimethoxytrityl protecting group from **96** was accomplished with 2% Cl_2CHCO_2H in dichloromethane for 5 min but prolonged exposure to these conditions resulted in a thiono–thiolo rearrangement to give the *O,O,S*-trialkyl phosphorothioate **97**. The ease of the rearrangement depended on the substitution on silicon: trimethylsilyl rearranged fastest; methyldiphenylsilyl was slowest.

Peptides containing phosphoserine or phosphothreonine can be prepared[104] using *O*[*S,S*-bis(*p*-methoxyphenyl)phosphorodithioyl] groups as shown in **Scheme 77**. Deprotection takes place on treating the phosphopeptide **98** with AgOAc in aqueous pyridine to give the corresponding phosphomonoester **99**.

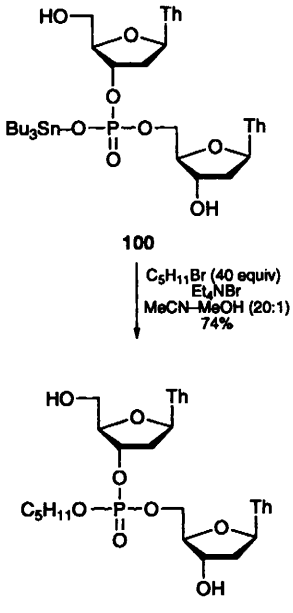
O-Alkylation of phosphates *via* tributylstannyl salts was applied to dinucleotides such as thymidyl(3′-5′)thymidine **100** as shown in **Scheme 78**. Note the absence of hydroxy group protection.[105]



Scheme 76



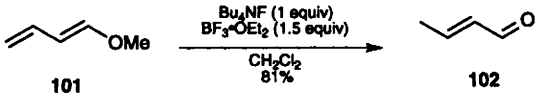
Scheme 77



Scheme 78

7 Carbonyl protecting groups

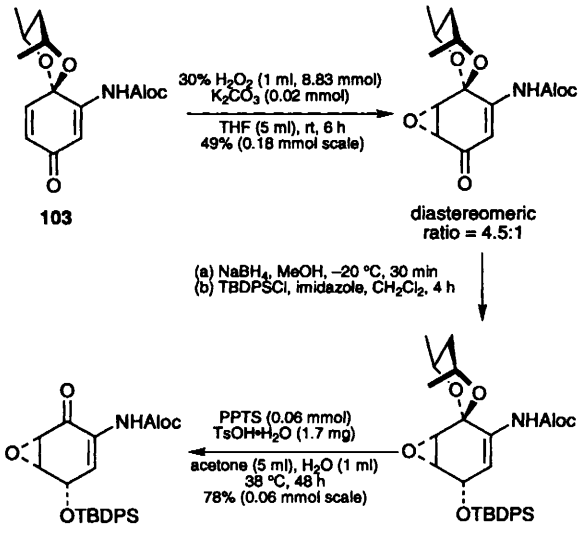
Hydrolysis of enol ethers to aldehydes is generally achieved in the presence of strong mineral acids such as aq. HCl, H_2SO_4 and $HClO_4$. Yamamoto and co-workers[106] reported that combination of a protic acid or Lewis acid with Bu_4NF forms milder reagents which are effective for deprotecting acid-labile enol ethers (**Scheme 79**). For example, treatment of 1-methoxybuta-1,3-diene **101** with Bu_4NF and $BF_3{\cdot}OEt_2$ (or Bu_4NF and HCl) gave the corresponding unsaturated aldehyde **102** in 81% yield whereas the uncomplexed acids $BF_3{\cdot}OEt_2$, HCl or $AlCl_3{\cdot}OEt_2$ failed.



101 102

Scheme 79

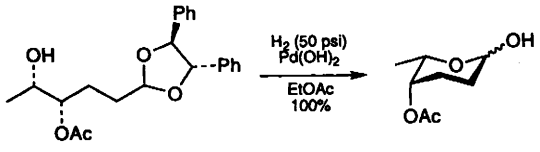
The acetal **103** prepared from (2*R*,4*R*)-pentane-2,4-diol served two useful functions in Wipf's synthesis of the epoxyquinol core of the manumycin antibiotics.[107] First, it afforded diastereocontrol in the epoxidation reaction depicted in **Scheme 80**. Secondly, the axial methyl group in the acetal ring introduced a beneficial level of strain which enabled the hydrolysis of the acetal to occur without destruction of the product. When both methyl groups in the acetal occupy equatorial positions, the hydrolysis could not be accomplished.



Scheme 80

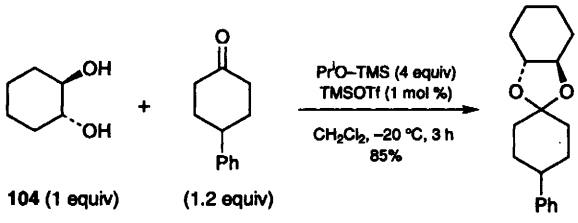
The mild conditions used for hydrogenolysis of benzyl ethers have been adapted[108] to the deprotection of a 4,5-diphenyl-1,3-dioxolane as illustrated in **Scheme 81**.

In 1980 Noyori and co-workers[109] reported a synthesis of dioxolanes under mild conditions by



Scheme 81

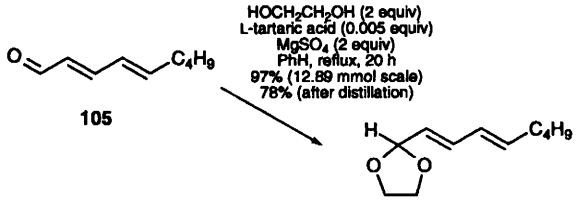
reaction of a ketone or aldehyde with ethylene glycol bis(trimethylsilyl) ether in the presence of TMSOTf. More convenient conditions have been developed[110] which generate the bis(trimethylsilyl) ether *in situ* by reaction of the diol (e.g. **104**) with a *sec*- or *tert*-alkoxysilane in the presence of 1 mol% TMSOTf as shown in **Scheme 82**. Lanthanoid sulfonates have also been found to be good catalysts for acetalisation of aldehydes and ketones with methyl orthoformate.[111]



104 (1 equiv) (1.2 equiv)

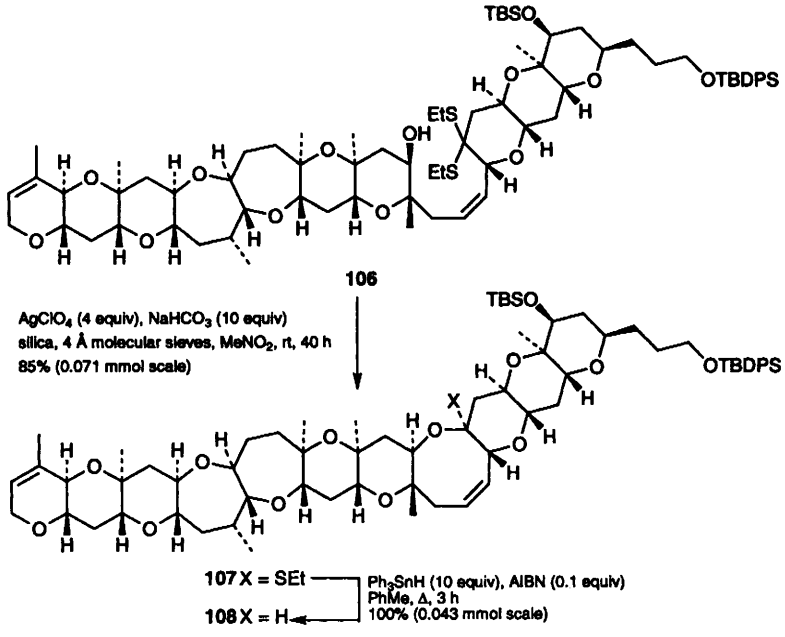
Scheme 82

Acetalisation of unsaturated aldehydes can be troublesome because of low yields and side reactions like migration and isomerisation of the double bond. Lu's group[112] examined the influence of the acidic component in the reaction of aldehydes with ethylene glycol and found that the best results are obtained when tartaric acid is used. In the case of compound **105** (**Scheme 83**), less than 2% of double bond-isomerised acetal was observed; with stronger acids like *p*-TsOH or succinic acid, 12 and 4% were observed respectively. The presence of magnesium sulfate was also crucial in order to achieve a high yield of the desired products.



Scheme 83

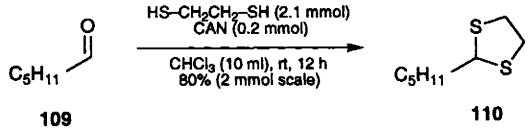
An *S*,*S*-acetal has played a key role in the formation of the 2,3,7,8-tetrahydro-6*H*-oxocine ring in Nicolaou's synthesis of brevetoxin (**Scheme 84**).[113] Ag^I-assisted cyclisation of the intermediate **106** first generated an *O*,*S*-acetal **107** from which the unwanted ethylthio group was excised under radical



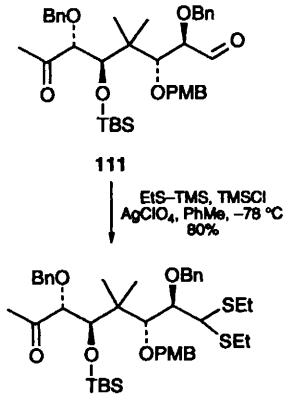
Scheme 84

conditions to give the requisite tetrahydrooxocine **108**.

Two new methods for the formation of *S,S*-acetals appeared recently. In the first method (**Scheme 85**),[114] aldehydes (*e.g.* **109**) are converted into their 1,3-dithiolanes (*e.g.* **110**) using ceric ammonium nitrate (CAN) and ethane-1,2-dithiol. High yields are obtained at room temperature (rt) in the presence of ketones. Alicyclic ketones may be protected at elevated temperature but aromatic and aliphatic ketones remain unaffected. In the second method (**Scheme 86**),[115] selective acetalisation of an aldehyde in the presence of a ketone **111** using Ag^I-catalysed thioacetalisation with EtS–TMS and TMSCl was used in a synthesis of a fully functionalised B-ring system of taxol.



Scheme 85

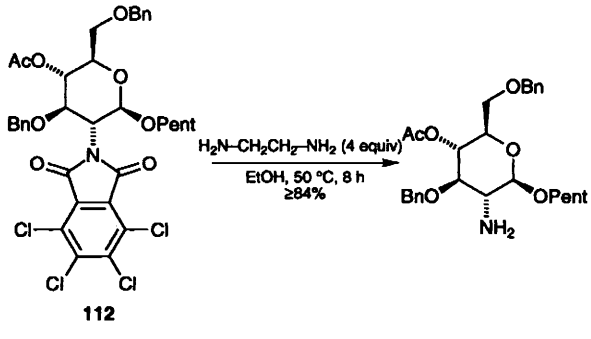


Scheme 86

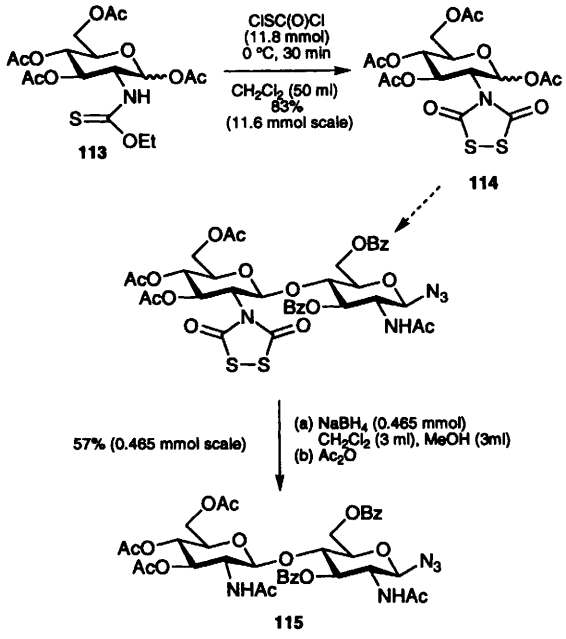
8 Amino protecting groups

The enhanced electron deficiency of tetrachlorophthalimides (abbreviated TCP) makes them much easier to cleave than the standard phthalimide function.[116] For example the tetrachlorophthalimide **112** (**Scheme 87**) was deprotected with four equiv of ethylenediamine in EtOH at 50 °C for 8 h. Under the same conditions the analogous phthalimide survived unscathed. It is noteworthy that the withdrawal of electron density imparted by the four chlorine atoms did not impair the neighbouring group participation of the TCP group in glycosidation reactions.

Although the dithiasuccinoyl (Dts) group has been used for the protection of amines for some time, the Meldal group[117] was the first to use it in the stereoselective β-glycosylation of amino sugars.



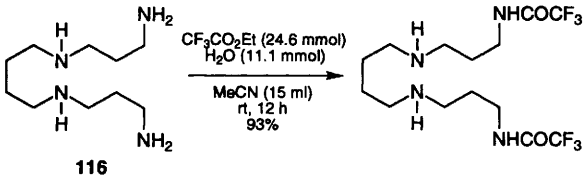
Scheme 87



Scheme 88

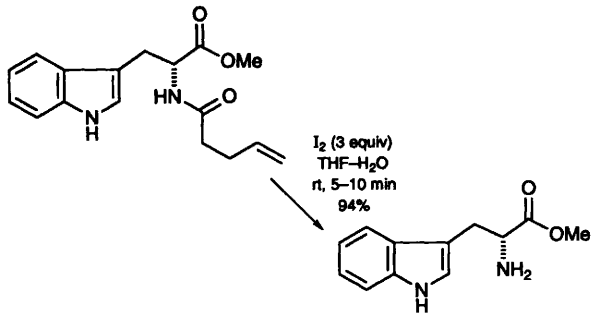
In the example illustrated in **Scheme 88**, the Dts group in **114** was introduced by reaction of the ethoxythiocarbonyl derivative **113** with chlorocarbonylsulfenyl chloride. Later in the sequence, removal of the Dts group was achieved using sodium borohydride (without affecting the azido group), followed by *N*-acetylation to give **115**. The mild conditions of the cleavage are compatible with most *O*- and *N*-protecting groups.

Selective trifluoroacetylation of primary amines in the presence of secondary amines (*e.g.* **116**) can be accomplished by reaction with ethyl trifluoroacetate in THF, MeCN or dioxane at 0 °C to rt (**Scheme 89**).[118,119] The product is isolated simply by evaporation of the solvent and liberated ethanol. The same conditions accomplish selective monotrifluoroacetylation of secondary diamines.[120]



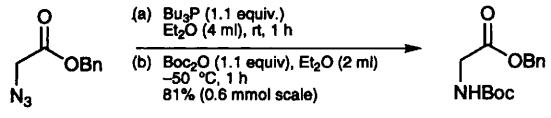
Scheme 89

Primary and secondary amines are readily protected as *N*-pent-4-enoyl derivatives by reaction with pent-4-enoic anhydride. Deprotection is rapidly and efficiently achieved under mild conditions by treatment with three equiv of iodine in aqueous THF for 5–10 min (**Scheme 90**).[121] These deprotection conditions do not affect oxidisable funtionalities including *p*-methoxybenzyl ethers and alkyl sulfides. Aloc groups, however, appear to be incompatible.



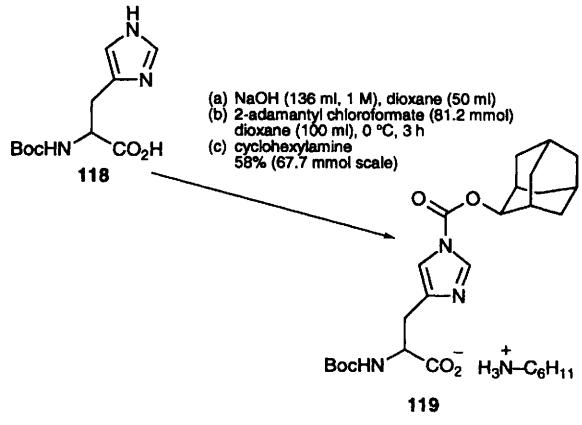
Scheme 90

The formation of Boc-protected primary amines directly from azides (H_2, Pd–C, Boc_2O) has been known for some time.[122] Afonso[123] has now reported a new method which is based on reaction of azides (*e.g.* **117**) with tributylphosphine followed by addition of di-*tert*-butyl dicarbonate (**Scheme 91**). The procedure is useful if functional groups are present which are incompatible with catalytic hydrogenation conditions.



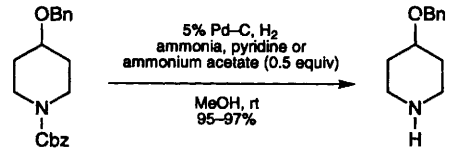
Scheme 91

Protection of the imidazole ring of histidine with a 2-adamantyloxycarbonyl (2-Adoc) group is accomplished by reaction of N^{α}-protected (Cbz or Boc) histidine derivatives (*e.g.* **118**) with 2-adamantyl chloroformate (**Scheme 92**).[124] The 2-Adoc group in **119** is both stable to Boc-deprotecting conditions, and easily and rapidly removable by anhydrous HF or 1 M trifluoromethanesulfonic acid and thioanisole in TFA. In addition, the N^{im}-2-Adoc group effectively suppresses racemisation of the histidine residue. The benefits of N^{im}-2-Adoc protection were illustrated in a solid phase synthesis of thyrotropin-releasing hormone.



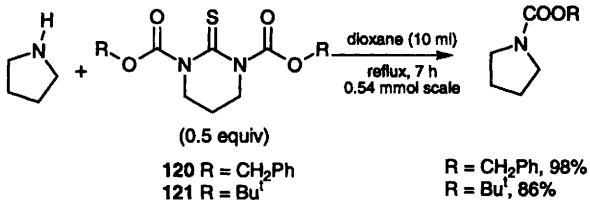
Scheme 92

Sajiki has reported that ammonia, pyridine, or ammonium acetate inhibit the Pd–C catalysed hydrogenolysis of benzyl ethers whilst olefins, Cbz groups, benzyl esters and azides are reduced smoothly (**Scheme 93**).[125]



Scheme 93

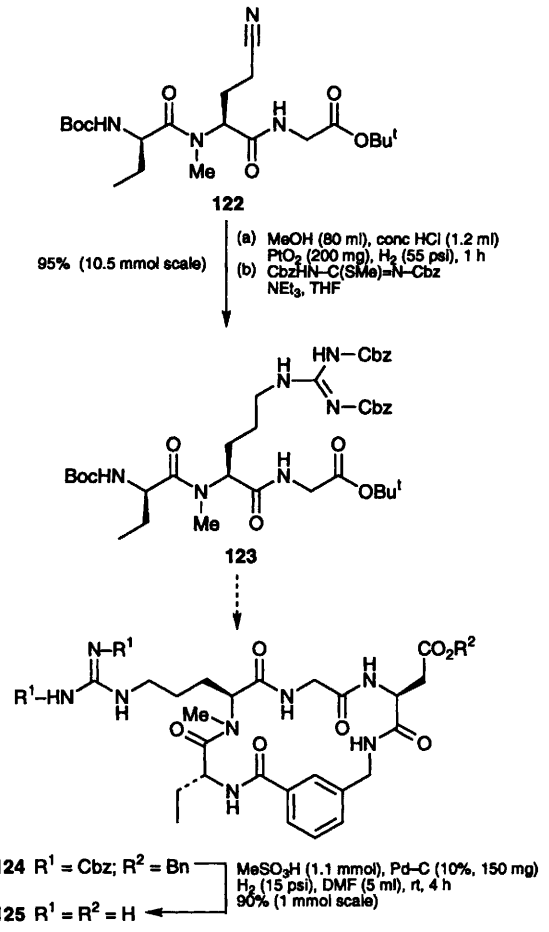
Matsumura and co-workers[126] report that cyclic thioureas (like **120** and **121**) efficiently transfer alkoxycarbonyl groups under mild and neutral conditions (**Scheme 94**). These reagents are reasonably stable to air, moisture and heat — properties which make them much easier to handle than, for instance, benzyl chloroformate and di-*tert*-butyl dicarbonate.



Scheme 94

During a recent synthesis of the antithrombitic cyclic peptide antagonist **125** of glycoprotein IIb/IIIa, an arginine was protected as the bis-Cbz derivative (**Scheme 95**).[127] The protected arginine was synthesised from the tripeptide **122** by catalytic hydrogenation of the nitrile function to a primary amine. Subsequent reaction with *N,N'*-bis(benzyloxycarbonyl)-*S*-methylthioisourea[128] introduced the protected guanidine function **123** in a single step in good yield. After elaboration to the cyclic derivative **124**, the Cbz and benzyl ester functions were removed simultaneously by hydrogenolysis to give the desired target **125** in 90% yield.

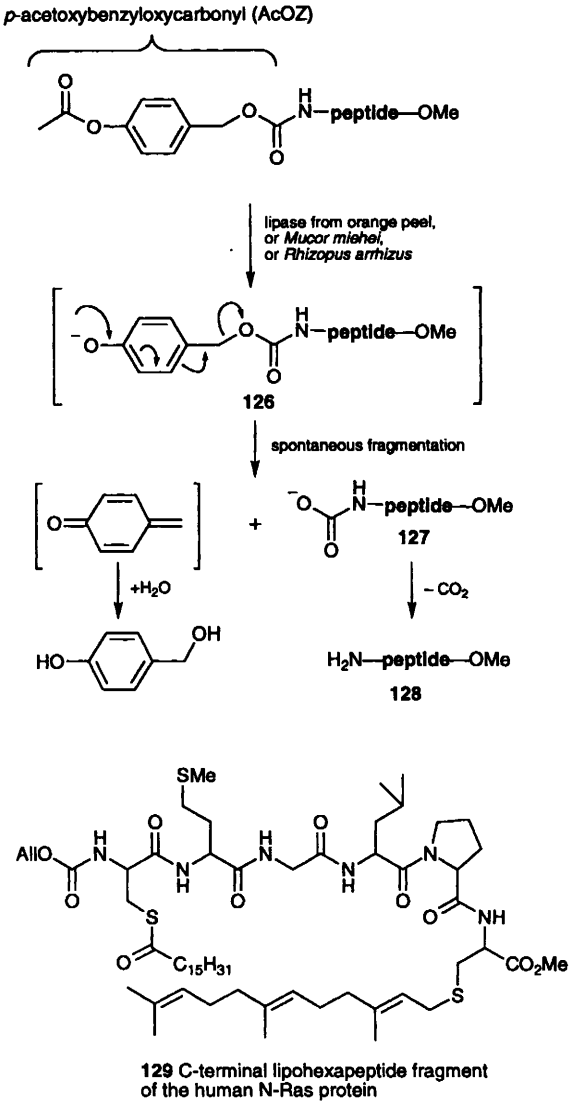
In the search for protecting groups compatible with the synthesis of highly sensitive peptide conjugates, Waldmann and Nägele[129] have developed a new urethane protecting group, the *p*-acetoxybenzyloxycarbonyl (AcOZ) group, which can be cleaved enzymatically under mild conditions using lipases from orange peel, *Mucor miehei*, or *Rhizopus arrhizus*. Electric eel acetyl choline esterase can also be used. In all cases the acetyl group is cleaved leading to a phenoxide intermediate **126** which fragments spontaneously to a quinone methide intermediate and a carbamate **127**. Decarboxylation of the carbamate then returns the deprotected *N*-terminus of the peptide fragment **128**. The value of the methodology was demonstrated in a synthesis of the lipohexapeptide C-terminus **129** of the human Ras protein – a protein implicated in growth-factor mediated transduction of extracellular signals across the cell membrane (**Scheme 96**). The challenge in a synthesis of **129** is the lability of the *S*-farnesyl group (incompatible with acid conditions used to remove Boc groups) and the *S*-palmitoyl group (spontaneous hydrolysis at pH 6–7).



Scheme 95

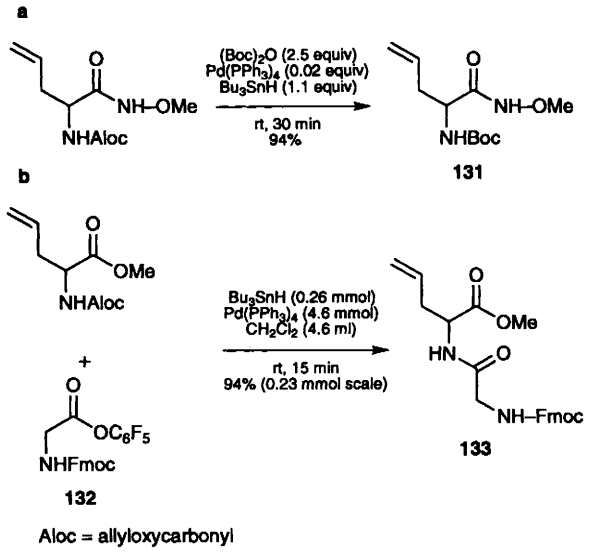
A novel method for the enzymatic synthesis of sialylglycoconjugates on a polymer support has been described.[130] A primer polymer **130** (**Scheme 97**) having *N*-acetyl-D-glucosamine residues attached through a phenylalanine-containing linker was elongated with galactosyl and sialyl transferases. The resulting sialo-oligosaccharide was cleaved with α-chymotrypsin.

Three research groups have reported conditions for the transacylation of allyloxycarbonyl (Aloc) groups. Pd-Catalysed deprotection of Aloc groups using Bu_3SnH in the presence of carboxylic anhydrides, acid chlorides and activated esters was described by Speckamp and co-workers.[131] A useful example is the removal of the Aloc group in the presence of *tert*-butyl carbonate, which, in essence, amounts to transprotection to a Boc-protected α-amino acid derivative (*e.g.* **131**, **Scheme 98a**).



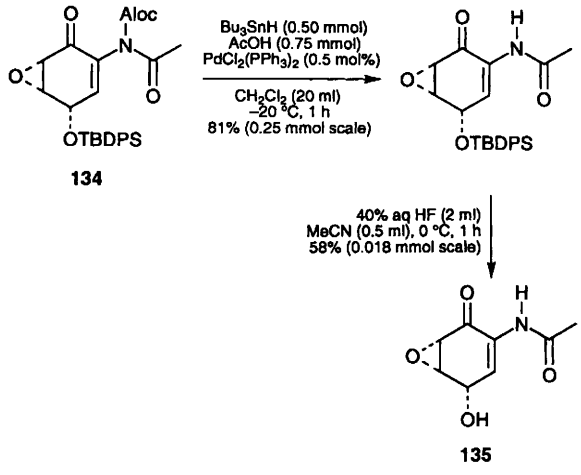
Scheme 96

More importantly, the use of activated *N*-protected α-amino esters (*e.g.* **132**) leads to a dipeptide (*e.g.* **133**) as shown in **Scheme 98b**. This new one-pot method for peptide coupling proceeds under mild conditions in excellent yield and without noticeable racemisation. Beugelmans and co-workers[132] have described the use of sodium borohydride as hydride donor in similar transformations. Finally, Pd^0-catalysed cleavage or transacylation of allyl carbamates, carboxylates and phenoxides in the presence of phenylsilane or *N*-methyl-*N*-(trimethylsilyl)trifluoroacetamide has been reported by Guibé and co-workers.[133]

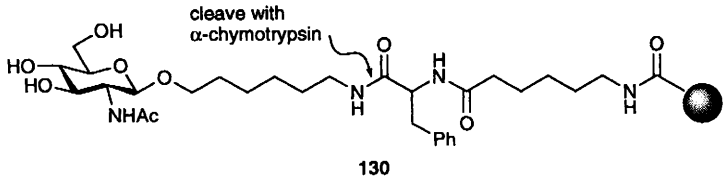


Scheme 98

The extremely broad functional group tolerance of the Pd-catalysed N-deprotection of the Aloc groups in **134** was a crucial design feature in a synthesis of the epoxyquinol core **135** of the manumycin family of antitumour antibiotics (**Scheme 99**).[107] The final desilylation step was complicated by the base sensitivity of **135**, but HF in MeCN at 0 °C accomplished removal of the TBDPS group where TBAF had failed.

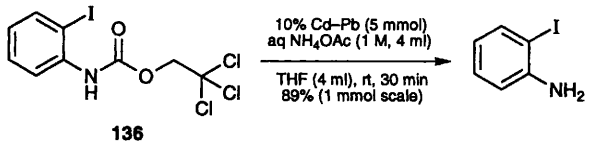


Scheme 99



Scheme 97

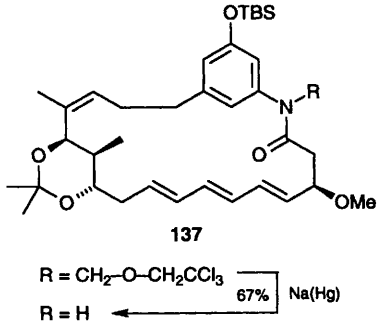
The readily prepared Cd–Pb couple cleaves 2,2,2-trichloroethoxycarbonyl (Troc) groups rapidly (30–45 min) and efficiently (90–95%) at pH 7.0 (**Scheme 100**).[134] 5 Equiv. of Cd per Troc group are optimal. Unactivated halogens (including iodine, *e.g.* as in **136**) survive but nitro and azide groups are reduced. Troc esters are deprotected much faster than the corresponding carbamates or carbonates.



136

Scheme 100

During a synthesis of the ansamycin antibitoics trienomycin A and F, Smith and co-workers[135] found that the choice of protecting group for the amide function in intermediate **137** proved to be unexpectedly critical: *p*-methoxybenzyl and 2-(trimethylsilyl)ethoxymethyl (SEM) moieties could not be removed without extensive decomposition under oxidative (*e.g.* DDQ, CAN) or acidic conditions, respectively. However, the 2,2,2-trichloroethoxymethyl unit, which had previously been deployed for hydroxy group protection by Evans,[136] was successfully cleaved using Na(Hg) (**Scheme 101**).

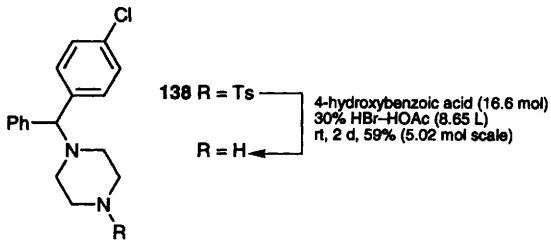


137

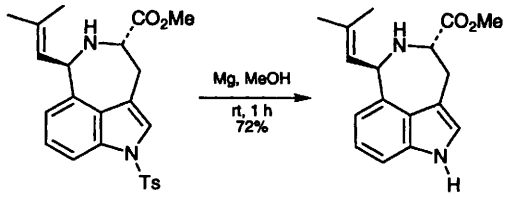
Scheme 101

During a large scale synthesis of cetirizine hydrochloride, an antihistamine agent for the treatment of allergic syndromes, Opalka and co-workers[137] used HBr and phenol[138,139] for the reductive removal of the N–Ts group from **138**. However, under these conditions, removal of phenolic by-products complicated workup on a large scale. When 4-hydroxybenzoic acid was used in place of phenol, most of the 4-hydroxybenzoic acid derivatives crystallised out on addition of the crude reaction mixture to water, the remainder being removed by base extraction of the filtrate (**Scheme 102**).

During a synthesis of clavicipitic acid, a Japanese group[140] cleaved an indole *N*-tosyl group with Mg in



Scheme 102



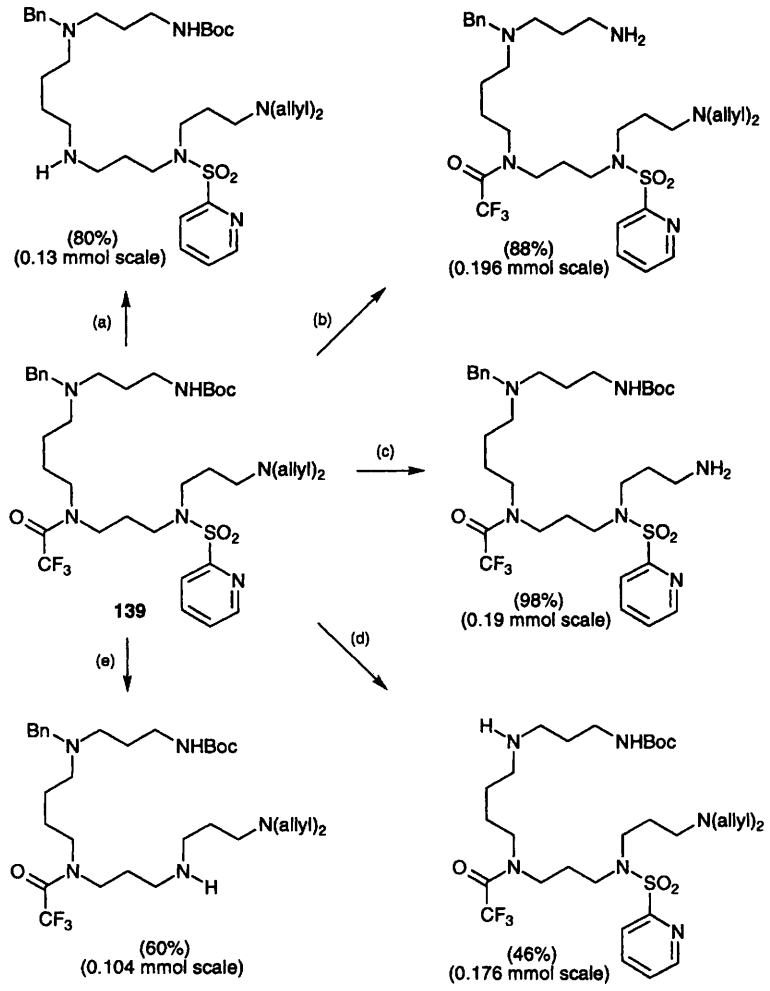
Scheme 103

MeOH without racemisation of the α-amino ester (**Scheme 103**).

The reductive cleavage of *N*-(arylsulfonyl)amines with SmI_2 reported in 1994 requires refluxing THF and DMPU, the latter being added to increase the reduction potential of the Sm.[141] However, Hesse and co-workers[142,143] have shown that the pyridine-2-sulfonyl group is cleaved without using DMPU or HMPA because of its lower LUMO energy. Thus the *N*-(pyridine-2-sulfonyl) group provides a new method for the protection of primary amines, arylamines and amino acid derivatives. The resulting sulfonamides are obtained in good yields and are frequently crystalline, and they can be deprotected under mild conditions by using SmI_2 in THF at rt or by electrolysis. The *N*-(pyridine-2-sulfonyl) group was one of five orthogonal amino protecting groups developed for polyamine synthesis as illustrated in **Scheme 104** by the selective deprotections of the 1,16-diamino-4,8,13-triazahexadecane **139**.

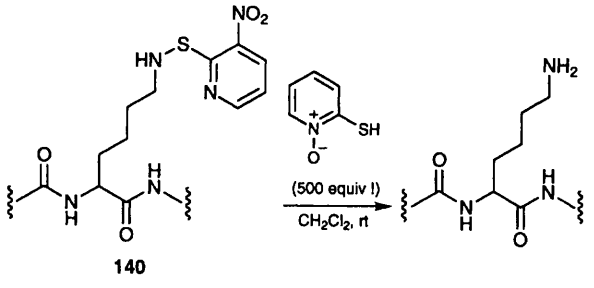
The 3-nitropyridine-2-sulfenyl (Npys) group is stable to TFA and 88% formic acid but it is easily removed with: (a) 0.1 M HCl in dioxane, (b) triphenylphosphine–pentachlorophenol or (c) 2-mercaptopyridine-*N*-oxide.[144] However, Npys groups on a peptide attached to a polymer support are significantly more difficult to cleave than the corresponding solution phase deprotections. Rajagopolan and co-workers[145] showed that 2-mercaptopyridine-*N*-oxide in large excess (500 equiv) will cleanly and efficiently cleave the Npys group from lysine residues in polymer-bound peptides **140** (**Scheme 105**).

Genet and co-workers[146,147] have reported that mono- and di-allylamines can be cleaved using Pd^0 catalysis and 2-mercaptobenzoic acid as an allyl trapping agent. Tertiary amines like **141** react much faster than secondary amines (as **142**) and at room temperature selective deprotection of one allyl group can be achieved (**Scheme 106**). Removal of

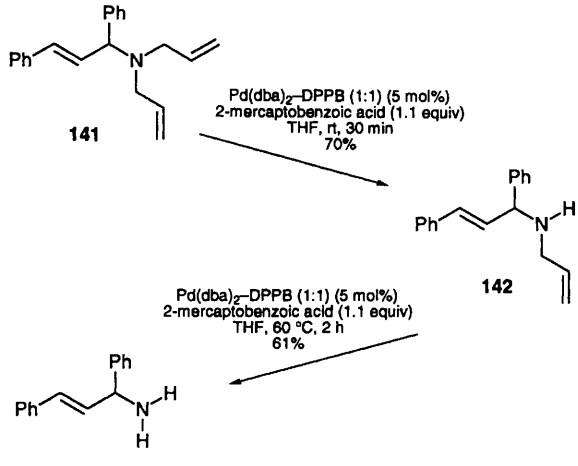


Reagents and conditions: (a) K_2CO_3, MeOH, rt, 2 h; (b) CF_3CO_2H, CH_2Cl_2, rt, 2.5 h; (c) $Pd(PPh)_4$, *N,N'*-dimethylbarbituric acid, CH_2Cl_2, 35 °C, 1.5 h; (d) $ClCOCHClCH_3$, CH_2Cl_2, –10 °C, 12 h then MeOH, NEt_3, Δ, 12 h; (e) SmI_2, THF, rt, 12 h

Scheme 104



Scheme 105



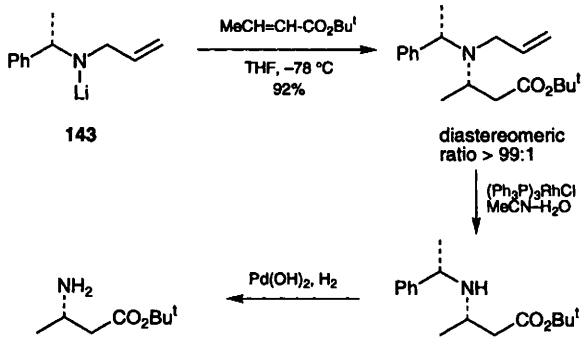
dba = dibenzylideneacetone
DPPB = 1,4-bis(diphenylphosphino)butane

Scheme 106

the remaining allyl group in **142** requires a higher temperature (60 °C).

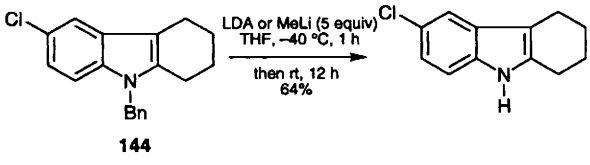
Davies and co-workers[148,149] have extended the range of enantiomerically pure lithium amide bases which undergo conjugate addition to unsaturated esters with a good to excellent diastereomeric ratio

(dr). Lithium [α-methylbenzyl]amide **143**, for example, (**Scheme 107**) can serve as a differentially protected chiral ammonia equivalent for the asymmetric synthesis of β-amino acids and β-lactams. The allyl group is deprotected first using Rh-catalysed isomerisation–hydrolysis whereas the benzyl group is removed by hydrogenolysis using $Pd(OH)_2$ as the catalyst.



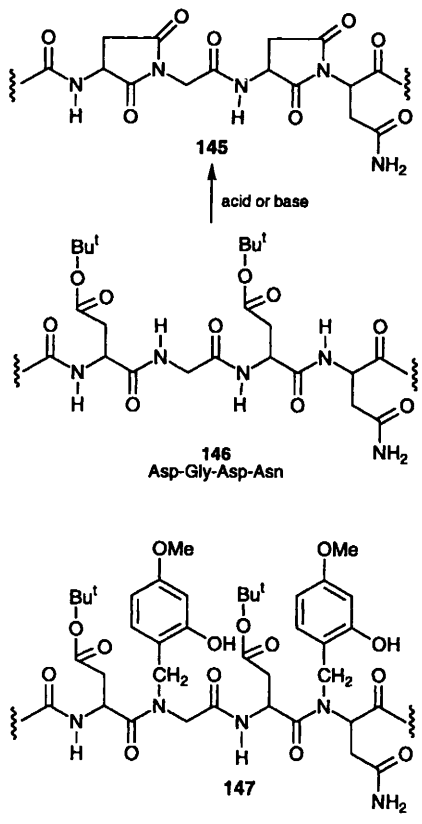
Scheme 107

The reaction of *N*-benzylindoles (*e.g.* **144**) with lithium diisopropylamide or methyllithium (5 equiv.) results in debenzylation (**Scheme 108**). The reaction probably occurs *via* a carbene mechanism. The yields are generally 40–60%.



Scheme 108

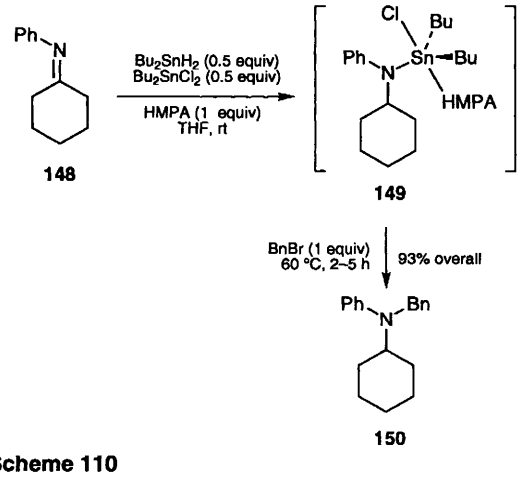
The formation of aspartimide (cyclic imide) involving aspartic acid residues is one of the most serious side reactions in solid phase peptide synthesis. The reaction is catalysed by base or by strong acid and leads to racemisation and/or isomerisation of the affected residue. Furthermore, although the aspartimide ring is hydrolysed in neutral and alkaline media, attack at both carbonyl groups may occur leading to a mixture of α- and β-aspartyl peptides. In the Fmoc-*tert*-butyl strategy of synthesis, the problem is especially acute at Asp-Asn and Asp-Gly sequences (**146**→**145**) as illustrated in **Scheme 109**. In a synthesis of an *N*-terminal, 20 residue fragment of ferredoxin,[150] aspartimide formation was completely suppressed using *N*-2-hydroxy-4-methoxybenzyl (Hmb) backbone protection[151,152] at the two vulnerable Asp-Gly-Asp-Asn sites **147**. Deprotection and cleavage of the completed peptide fragment with 95% TFA–5% ethanedithiol returned a homogeneous product devoid of aspartimide contaminents. Another approach to the suppression of aspartimide



Scheme 109

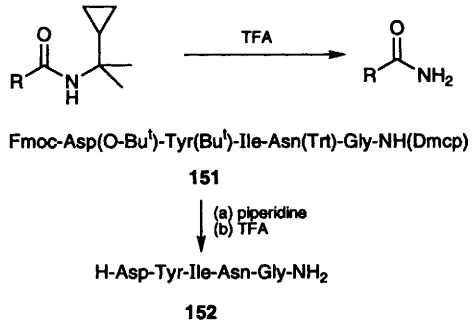
formation in solid phase peptide synthesis was reported by Karlström and Undén.[153] Protection of the aspartic acid carboxyl as its β-2,4-dimethyl-3-pentyl ester suppresses aspartimide formation under acidic or basic conditions and it is easier to cleave in TFA ($t_{1/2}$ 40 h at 4 °C) compared with the corresponding cyclohexyl ester ($t_{1/2}$ 500 h) which is commonly used.

The highly coordinated tin hydride Bu_2SnClH in HMPA reduces imines (*e.g.* **148**) to intermediate tin amides **149** whose alkylation with benzyl bromide or allyl bromide affords the corrersponding *N*-allyl or *N*-benzyl tertiary amines (*e.g.* **150**, **Scheme 110**).[154]



Scheme 110

Carpino and co-workers[80] have shown that the enhanced acid lability of the dimethylcyclopropylmethyl (Dmcp) group compared with the dicyclopropylmethyl group (*vide supra*) made it useful for the *N*-protection of peptide amides (**Scheme 111**). Previously, peptide amides were obtained *via* initial assembly of an ester and subsequent ammonolysis. However, Dmcp-protected amides can be introduced directly. In the case of pentapeptide **151**, treatment with piperidine first removed the Fmoc group and subsequent treatment with TFA deblocked all remaining protecting groups to afford peptide **152** in excellent quality.

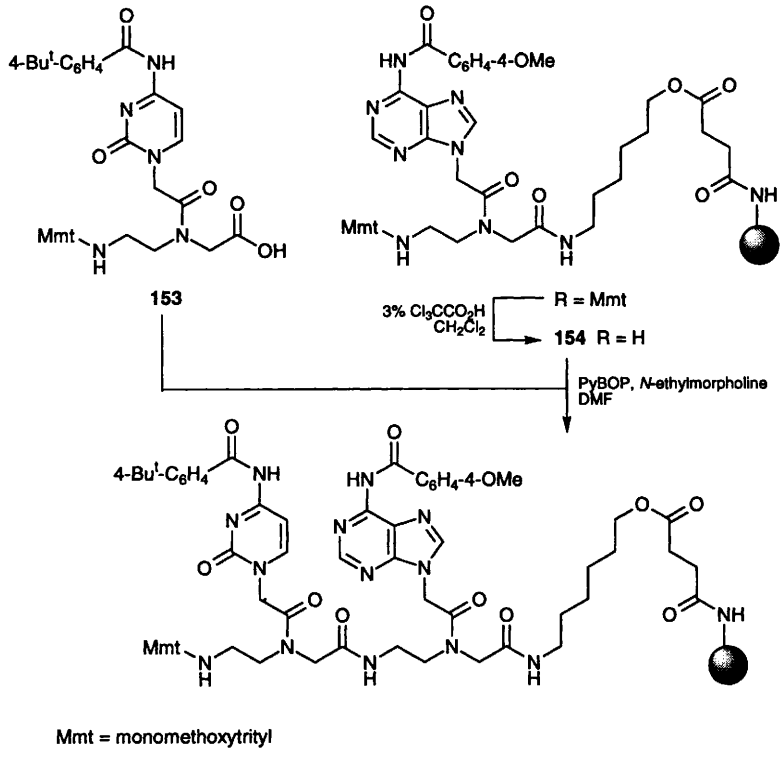


Scheme 111

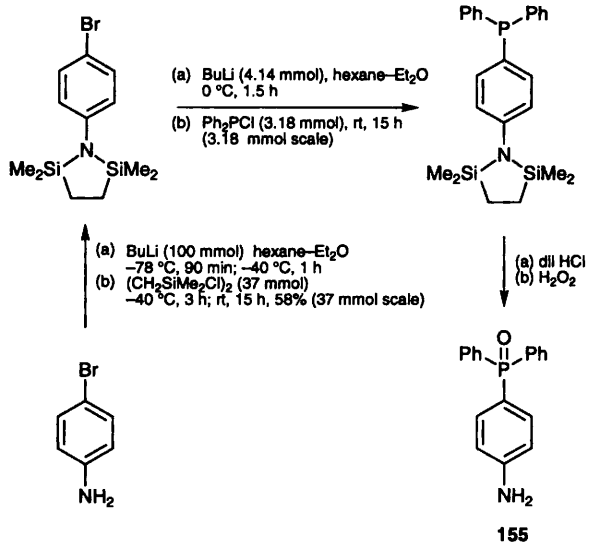
Polyamide (or peptide) nucleic acids (PNAs) are oligomers of nucleobase-derivatised *N*-(2-aminoethyl)glycine which recognise and bind strongly to specific DNA or RNA sequences. PNA oligomers have a number of properties which make them potentially useful as antisense therapeutics and as diagnostic tools. A Hoechst group[155] has devised a synthesis of novel monomethoxytrityl (Mmt) protected monomers (*e.g.* **153**) which can be attached sequentially to a supported primer **154**. Each cycle is preceded by a mild acid-catalysed deprotection of the Mmt group as shown in **Scheme 112**. PNAs of mixed base composition have been prepared by this strategy.

Whitaker and co-workers[156] have given ample testimony to the value of STABASE protection of amino groups in their recent synthesis of (4-aminophenyl)diphenyl phosphine oxide **155**, summarised in **Scheme 113**.

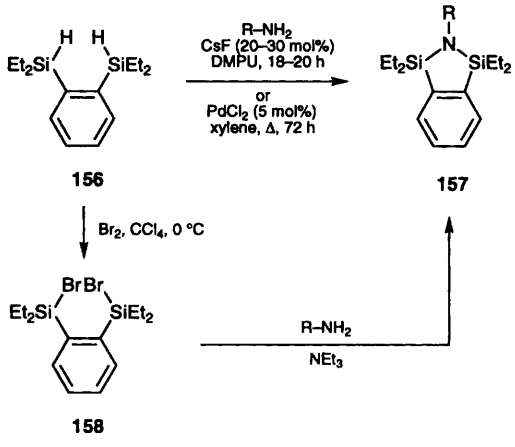
In the search for new variants of the STABASE protecting group for amines which are more stable to hydrolysis and chromatography, Davis and Gallagher[157] prepared 1,1,3,3-tetraethyl-1,3-disilaisoindolines (abbreviated TEDI) by the three routes shown in **Scheme 114**. First the disilane **156** was treated with a primary amine in the presence of CsF (20–30 mol%) in DMPU to give the TEDI **157**. Second, the same disilane and primary amine reacted in the presence of $PdCl_2$ (5 mol%) after heating in xylene. Finally a two step procedure involving prior formation of bis(bromosilane) **158** followed by reaction with the primary amine in the presence of NEt_3 accomplished the synthesis of TEDI **157**. Compound **157** was about 75 times more stable towards water than the corresponding STABASE derivative and it was more stable to column chomatography. However, **157** could be hydrolysed in AcOH–Et_2O (1:4) with a half-life of 53 minutes.



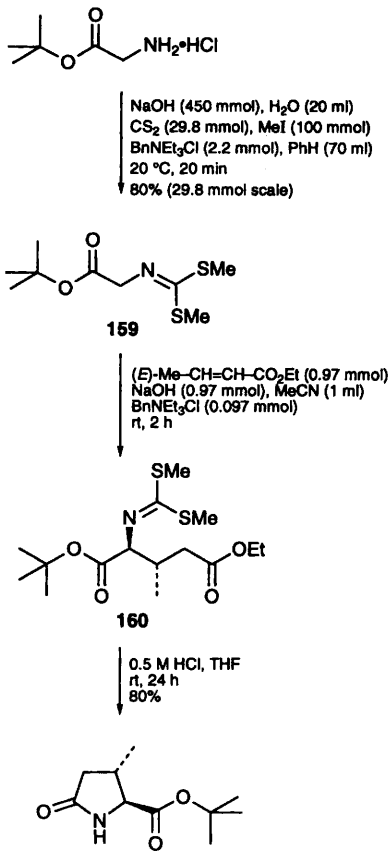
Scheme 112



Scheme 113



Scheme 114



Scheme 115

The *N*-bis(methylthio)methyleneamine derivative **159** of glycine underwent a highly anti-stereoselective conjugate addition to ethyl (*E*)-butenoate to give the adduct **160** (dr 49:1).[158] Hydrolysis of the protecting group resulted in lactamisation (**Scheme 115**).

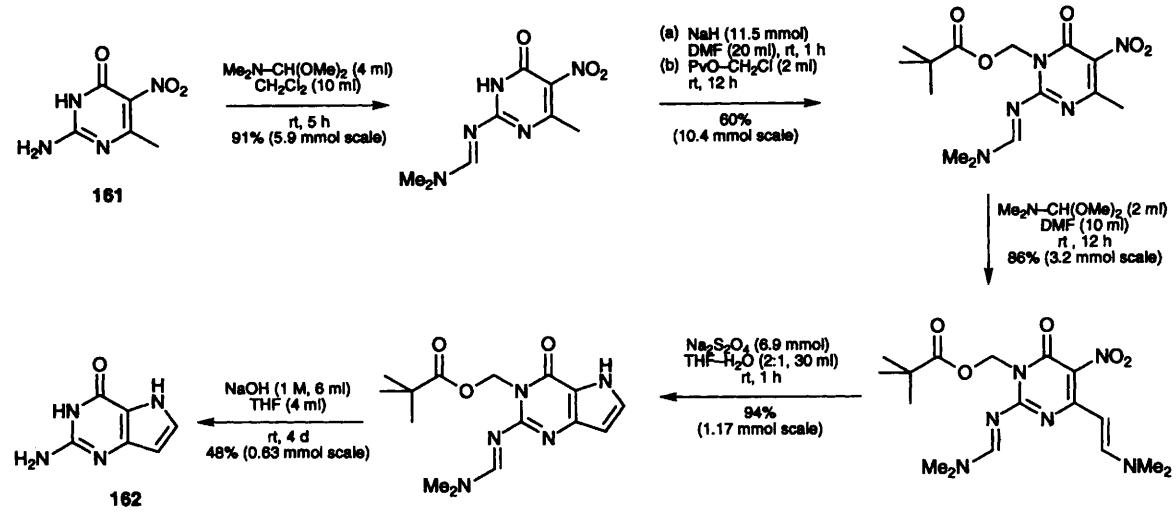
During a synthesis of pyrrolo[2,3-*e*]pyrimidine folate analogues, Taylor and Young[159] required protection of the amino and amido groups of the pyrimidinone **161** *en route* to the intermediate 9-deazaguanine **162** (**Scheme 116**). The dimethylaminomethylene protecting group was introduced first by reaction of **161** with dimethylformamide dimethylacetal. The amido nitrogen was then protected as its pivaloyloxymethyl derivative – a reaction which was accompanied by 15% *O*-alkylation. The protecting groups were removed simultaneously using aqueous NaOH.

Coote and co-workers[160] described the utility of 1,2,4-oxadiazol-5(4*H*)-ones **164** and 5-benzyloxy-1,2,4-oxadiazoles **165** as both precursors to, and protecting groups for amidine functionality (**Scheme 117**). The former compounds are stable in basic conditions and can be easy prepared from amidoximes **163**. Both protecting groups may be readily removed upon hydrogenation, liberating the parent amidine.

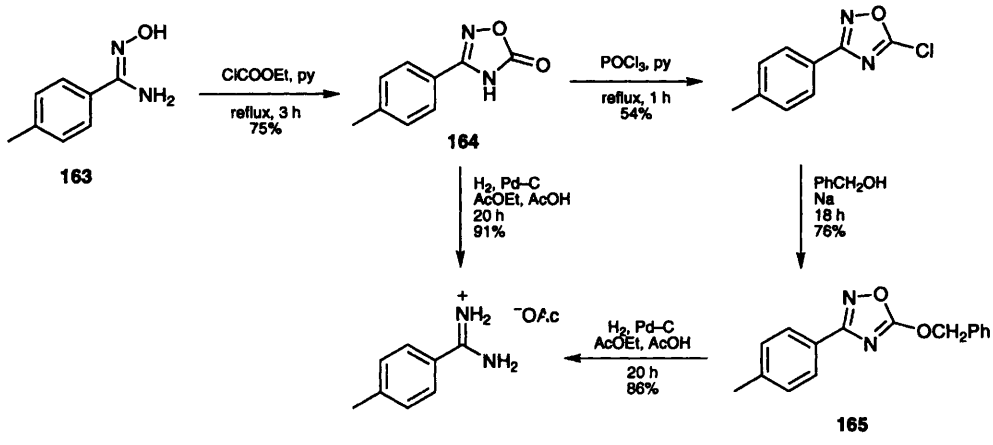
A fast conjugate addition occurs when uridines and thymidines (*e.g.* **166**) are treated with methyl propiolate in the presence of DMAP. **Scheme 118** shows that *N*-[(*E*)-2-(methoxycarbonyl)vinyl]uridine **167** is readily cleaved by nucleophiles such as pyrrolidine or methylamine thereby affording a new N3 protection protocol.[161] The adducts are stable to non-aqueous acid but they are hydrolysed by aqueous acid.

A model of the BC ring system of the antibiotic sakyomycin required cleavage of a 2,4-dinitrophenylamine derivative **168** to release a very sensitive amine **169**. The cleavage was achieved slowly under mild conditions using a basic ion exchange resin (IRA-400) in aqueous acetone (**Scheme 119**).[162]

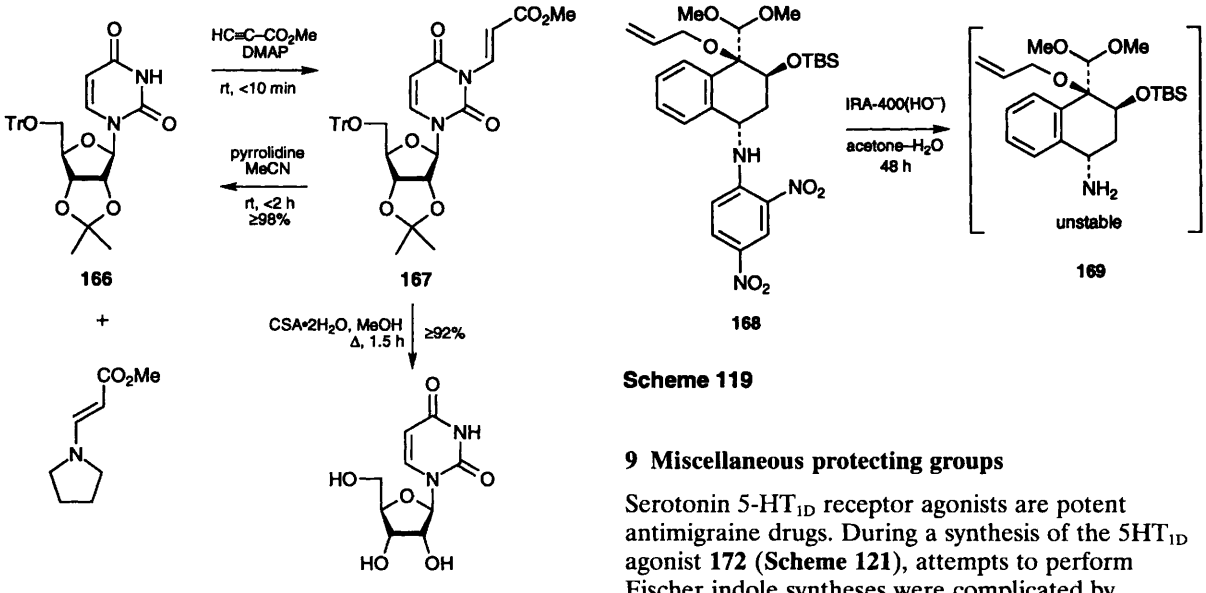
A new large scale synthesis of β-amino alcohols from amino acids exploits enaminonitriles as protecting groups for amines.[163] The efficiency of the sequence was largely compromised by the modest yields obtained in the final hydrolysis step in the example shown (**Scheme 120**). The cyano group in the enaminonitrile intermediate **170** was quite robust, withstanding attack by alkyllithiums, Grignard reagents, and borohydride at elevated temperature.



Scheme 116



Scheme 117

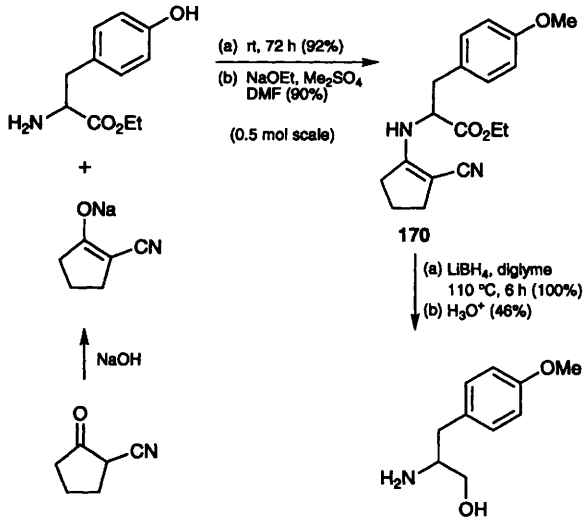


Scheme 118

Scheme 119

9 Miscellaneous protecting groups

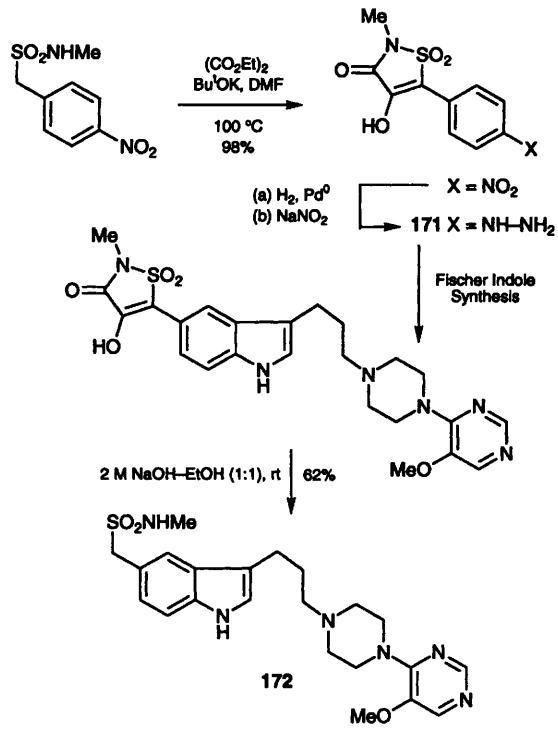
Serotonin 5-HT_{1D} receptor agonists are potent antimigraine drugs. During a synthesis of the $5HT_{1D}$ agonist **172** (**Scheme 121**), attempts to perform Fischer indole syntheses were complicated by elimination of the methylaminosulfonyl group.[164] By



Scheme 120

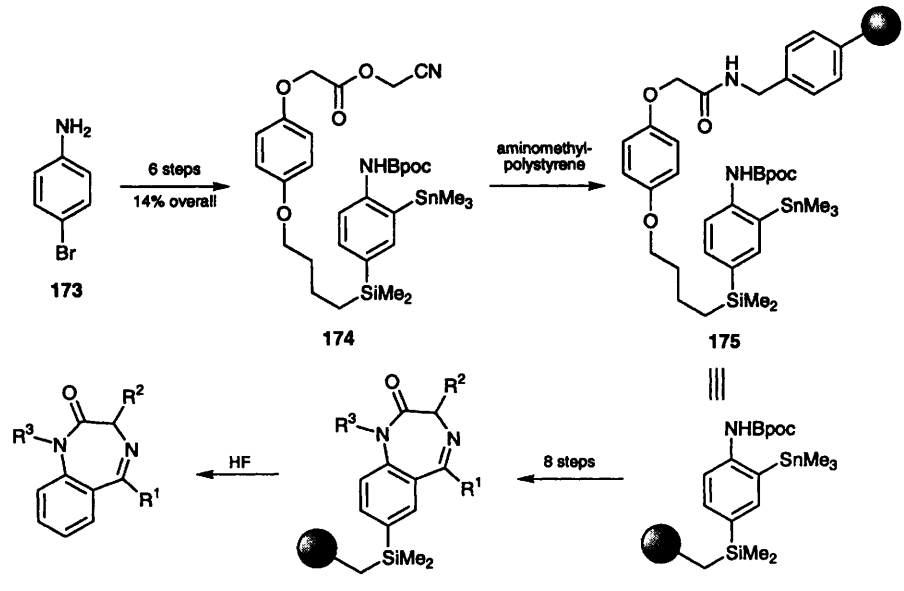
masking the methylaminosulfonyl group (while retaining its pendent methyl group) as a 4-hydroxy-2-methyl-3(2*H*)-isothiazolone-1,1-dioxide **171**, the requisite Fischer indole synthesis was successful. The protecting group was cleaved in the last step by treatment with 2 M NaOH in EtOH.

A key aspect of any solid phase synthesis is the means by which a molecule is linked to the solid support. Perhaps the easiest linkage occurs through a functional group such as an amino group or a carboxyl group which is retained intact or in modified form in the final product after cleavage. Alternatively, a spectator functional group can be appended to the target structure purely for purposes of linkage. However, the spectator group may confer unwanted properties on the cleaved target. An alternative approach would involve linkage through



Scheme 121

a spectator functional group that can be easily replaced by a proton leaving no trace of the solid phase synthesis. Plunkett and Ellman[165] have developed a 'traceless' linker for the solid phase synthesis of benzodiazepine derivatives based on protonolysis of arylsilanes (**Scheme 122**). The (aminoaryl)stannane which serves as a primer group in the synthesis was first attached to a 4-(alkoxy)-phenoxyacetic acid group through a silane linkage and the whole (**174**) then appended to an (amino-

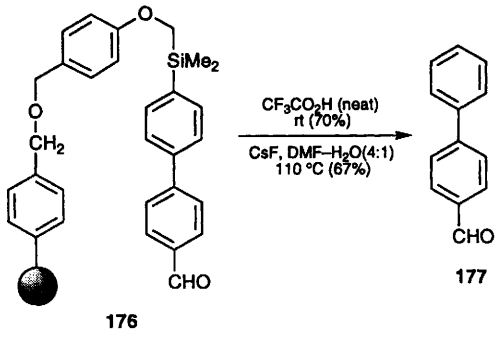


Bpoc = 2-(*p*-biphenylyl)isopropyloxycarbonyl

Scheme 122

methyl)polystyrene resin (**175**). After elaboration of the diazepinone system, cleavage was accomplished with anhydrous HF. Note that the aryl–silicon bond is stable to the trifluoroacetic used to cleave Boc groups owing to the extremely electron-poor nature of the protonated benzodiazepine. The detractions to this route are: (a) the large number of steps required to engineer the arene **173** into a structure **174** which can be attached to the resin and (b) the harsh conditions of anhydrous HF cleavage.

Veber and co-workers[166] have reported the synthesis of some arylsilane linkers attached to a polystyrene resin **176** which generate an unsubstituted aryl ring **177** on cleavage with either neat TFA or CsF in hot aqueous DMF (**Scheme 123**). The authors claim that the cleavage conditions are mild enough to tolerate sensitive substrates.



Scheme 123

Acknowledgement

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