Protecting groups

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Reviewing the literature published in 1994

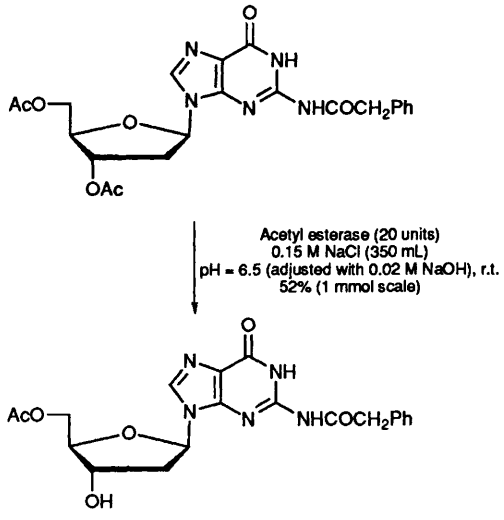
1 Introduction

The following review covers new developments in protecting group methodology which appeared in 1994. The review is not comprehensive but a selection of methods which we deemed interesting or useful. In addition to examples gleaned from casual reading, the references were selected through a Science Citation Index search based on the root words block, protect, and cleavage. The review is organized according to the functional groups 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.

2 Hydroxyl protecting groups

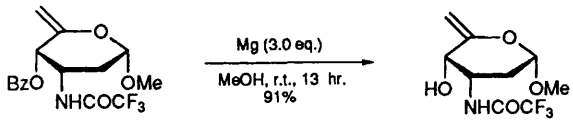
2.1 Esters

Biotransformations continue to make significant contributions to protecting goup technology. For example, the acetyl esterase enzyme from the *flavedo* of oranges chemo- and regio-selectively removes acetyl groups from carbohydrates and nucleosides (**Scheme 1**).[1] However, the exquisite gentleness and selectivity of the reaction exacts its price: 350 mL of solvent are needed for 1 mmol of substrate. In another example, Fujii and co-workers[2] reported a simple strategy for the generation of catalytic antibodies which can regioselectively and stereoselectively deprotect acylated carbohydrates.



Scheme 1

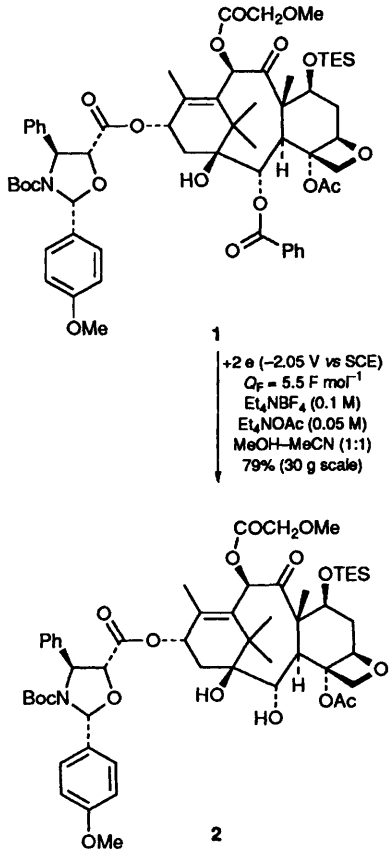
Magnesium metal in methanol (*i.e.* magnesium methoxide) deprotects alkyl esters selectively by transesterification in the order *p*-nitrobenzoate > acetate > benzoate > pivaloate ≫ trifluoroacetamide (**Scheme 2**)[3].



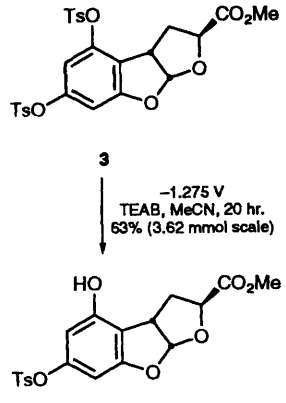
Scheme 2

Electrochemical methods are not a stock in trade of the typical synthetic chemist but two recent reports amply illustrate the potential of the method. In the first report, a new route to semisynthetic docetaxel analogues (**Scheme 3**) was accomplished by the selective electrochemical cleavage of the 2-benzoate as the key reaction.[4] The optimized electrochemical reduction of **1** in a mixture of methanol and acetonitrile in the presence of tetraethylammonium acetate and acetate buffer at $E -2.0$ to -2.05 V *versus* SCE (5.5 F mol^{-1} used) gave the 2-debenzoyl taxoid **2** in 79% yield on a 30 g scale.

In the second example, electrochemical reductive cleavage was a ploy used to selectively remove only one of the tosyl groups from the bistosylate **3** during a synthesis of the furobenzofuran precursors of the carcinogenic aflatoxins B[5] (**Scheme 4**).

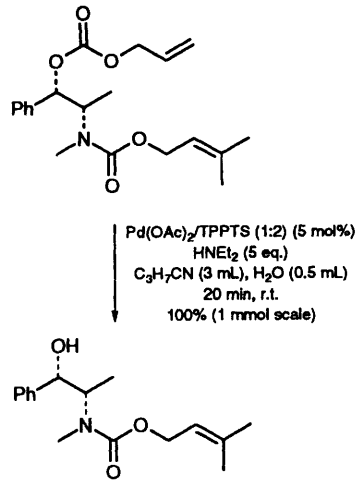


Scheme 3



Scheme 4

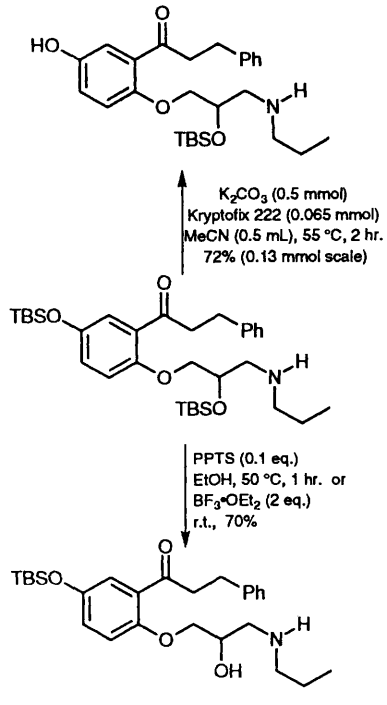
Genêt and co-workers[6,7] have reported the removal of allyloxycarbonyl (Aloc) groups from protected alcohols using a water soluble Pd^0 catalyst [prepared *in situ* from $Pd(OAc)_2$ and trisodium 3,3′,3″-phosphinetriyltribenzenesulfonate (TPPTS)] with diethylamine as allyl scavenger. **Scheme 5** illustrates the selective deprotection of an Aloc group without affecting a neighbouring dimethylallylcarbamate. The best result is obtained in a biphasic butyronitrile–water system with 5% of Pd^0.



Scheme 5

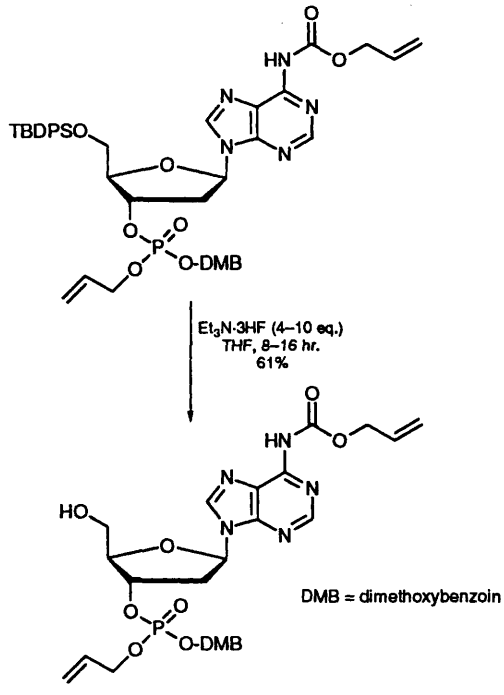
2.2 Silyl ethers

Selective cleavage of primary and secondary TMS, TIPS, TBS, and TBDPS ethers has been accomplished with neutral alumina by stirring in the presence of a non-polar solvent like hexane.[8] The deprotection rate depends on the steric bulk of the silicon substituents, following the order TMS ≫ TBS ~ TIPS > TBDPS. The procedure can discriminate between different silyl groups located at equivalent positions of the same molecule, affording the corresponding monoprotected alcohols in very good yields. Potassium carbonate/Kriptofix 222 deprotects phenolic silyl ethers[9] and under these conditions the alkanolic silyl ethers remain unaffected. On the other hand PPTS or $BF_3 \cdot OEt_2$ removes only alcoholic silyl ethers (**Scheme 6**).



Scheme 6

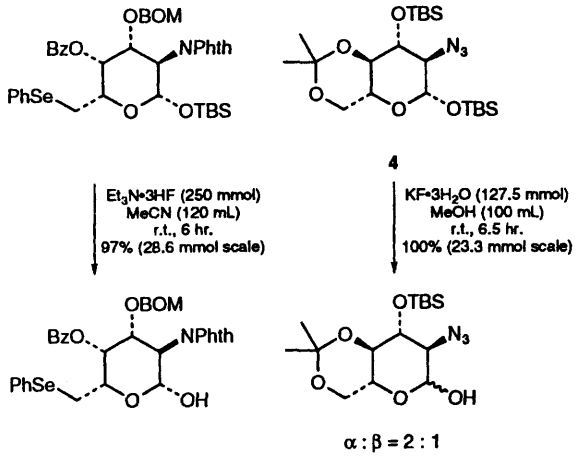
Pirrung and co-workers[10] reported a new method of deprotecting nucleosides and nucleotides bearing silyl protecting groups using commercially available triethylamine trihydrofluoride (**Scheme 7**). Work-up is accomplished by simple evaporation and chromatography thereby avoiding aqueous work-up. Excess triethylamine was added before work-up in some cases, but products of depurination were not observed even in its absence despite the seemingly acidic nature of the reagent. It is also harmless to pivaloyl, allyl, dimethoxybenzoin (DMB), and cyanoethyl protection.



Scheme 7

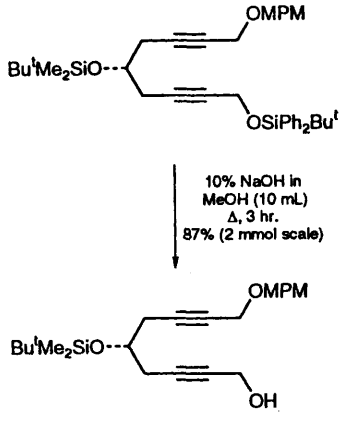
During a recent synthesis of the antibiotic tunicamycin, Myers, and co-workers[11] required mild and efficient methods for the large-scale deprotection of anomeric TBS ethers. The first procedure (**Scheme 8**) uses triethylamine trihydrofluoride to accomplish the task in 97% yield. The second procedure effected deprotection of the pure α-glycoside **4** in quanatitative yield using the trihydrate of KF in MeOH but the product was obtained as a mixture of anomers (α:β = 2:1). Note the selective removal of the anomeric TBS ether in the case of **4**. Kremsky and Sinha[12] have reported that TBS and TIPS ethers can be removed from nucleosides under mild conditions by treatment with a mixture of potassium fluoride trihydrate and 18-crown-6 in DMF or THF at room temperature. Both acid and base-labile protecting groups are unaffected.

t-Butyldiphenylsilyl ethers or triphenylsilyl ethers are readily cleaved at room temperature using HF generated *in situ* from the reaction of $BF_3 \cdot OEt_2$ with 4-methoxysalicylaldehyde.[13] The reaction time needed for complete deprotection is faster than



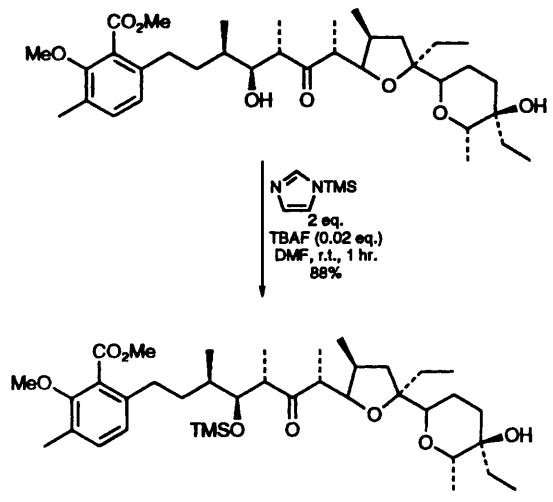
Scheme 8

TBAF or $BF_3 \cdot OEt_2$ alone. t-Butyldiphenylsilyl ethers are usually more difficult to cleave than t-butyldimethylsilyl ethers — especially in acid — but **Scheme 9** shows a selective deprotection of a primary TBDPS ether in the presence of a secondary TBS ether using 10% NaOH in reluxing MeOH.[14]

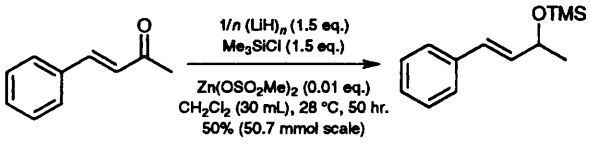


Scheme 9

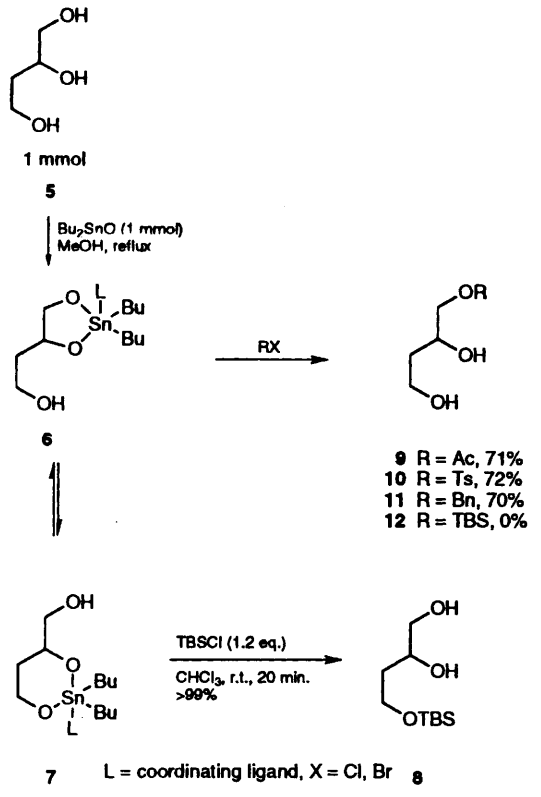
A new silylation of base-sensitive alcohols has been described by Tanabe and co-workers.[15] The procedure uses silazanes in the presence of a catalytic amount (~0.02 eq.) of tetrabutylammonium fluoride (TBAF) (**Scheme 10**). The use of more hindered silazanes such as the bissilyl derivative of 5,5-dimethylhydantoin allows regioselective TMS or TBDMS protection of primary hydroxy groups in the presence of secondary and tertiary ones. The same research group also found that hydrosilanes and disilanes can be used instead of silazanes in TBAF-catalysed protection of primary and secondary alcohols.[16] TMS protected alcohols can be prepared directly from carbonyl compounds via reductive silylation.[17] The procedure is limited to ketones and nonenolizable aldehydes and is accomplished by treating them with lithium hydride, TMSCl and a



Scheme 10



Scheme 11

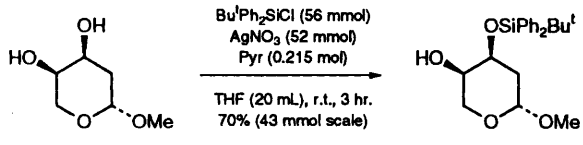


Scheme 12

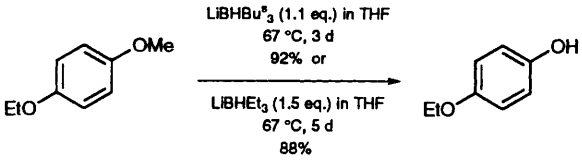
catalytic amount of zinc salts or zinc powder (**Scheme 11**).

Regioselective protection of the primary hydroxy groups in butane-1,2,4-triol **5** was achieved via stannanediyl acetal methodology.[18] Although stannanediyl acetal formation can give either **6** or **7**, silylation (TBDMSCl, 1.2 eq.) occurs exclusively at the primary hydroxy of the 1,3-diol system to give **8** in >99% yield (**Scheme 12**); however, acylation, tosylation, and benzylation occur preferentially at the primary hydroxy group of the 1,2-diol system to give **9**, **10**, and **11** respectively.

The silylation of hindered alcohols is greatly accelerated by the use of silyl triflates in place of the chlorides. The one silyl protecting group for which the triflate procedure is precluded is the t-butyldiphenylsilyl group whose triflate cannot be prepared in the usual way owing to easy protiodesilylation of the aromatic rings. However, the rate of silylation with t-$BuPh_2SiCl$ can be boosted with the aid of silver nitrate.[19] In the example shown in **Scheme 13**, silylation of an equatorial hydroxyl occurred preferentially over its adjacent axial neighbour.



Scheme 13

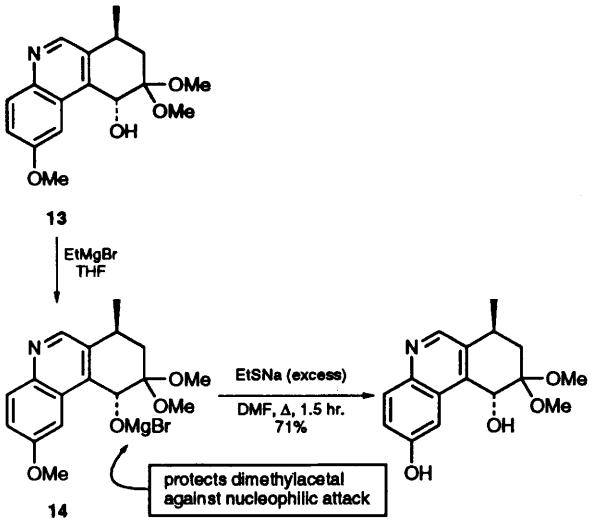


Scheme 14

2.3 Alkyl ethers

Methyl aryl ethers can be demethylated[20] using L-Selectride and SuperHydride (**Scheme 14**). L-Selectride is the more effective reagent while electron-poor arenes work best. Ethyl ethers react much slower than methyl ethers so selective deprotection is possible.

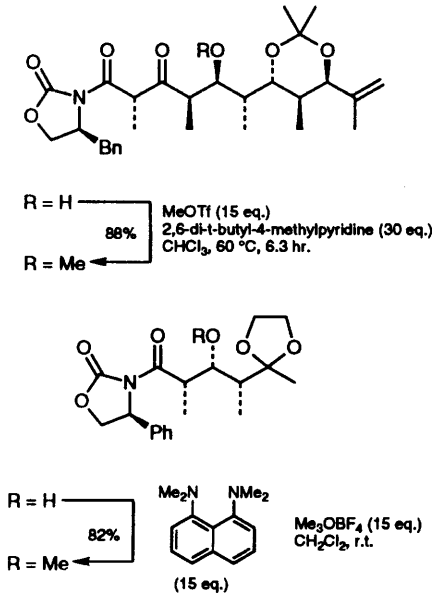
During a synthesis of quinone imine precursors to the dynemicins, Myers and co-workers[21] encountered problems with the lability of the dimethyl acetal function in **13** (**Scheme 15**) whilst removing the robust phenolic methyl group using sodium thioethoxide in hot DMF. These workers found that prior conversion of the free hydroxy function in the substrate into the magnesium salt **14**



Scheme 15

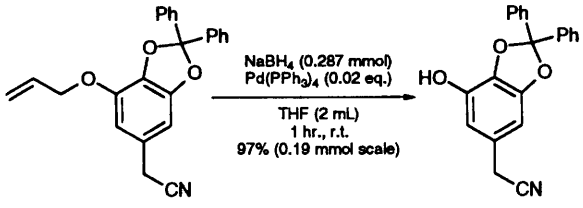
by reaction with EtMgBr afforded protection for the dimethylacetal under the strenuous conditions of nucleophilic demethylation.

For all its simplicity, the *O*-methylation of alcohol functions in polyoxygenated natural products and their precursors can be very inefficient. Evans and co-workers[22] systematically investigated some of the known mild methods in the search for optimum conditions. **Scheme 16** depicts two of the procedures which were especially fruitful. Both methods suffer from the high cost of the bases required.



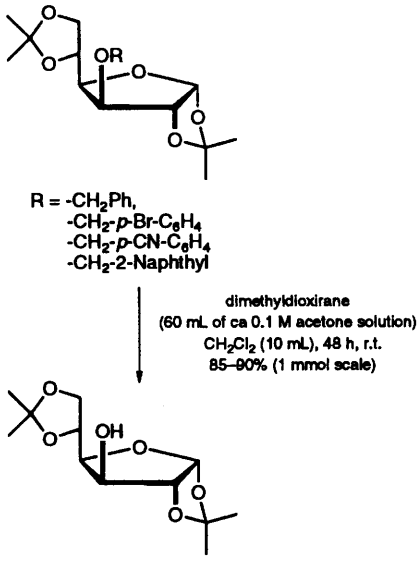
Scheme 16

The allyl group in its various guises has gained favour as a hydroxyl protecting group due to its stability under basic and acidic conditions. Zhu and co-workers[23] reported a way of removing this group from protected phenols using sodium borohydride and a catalytic amount of $Pd(PPh_3)_4$ (**Scheme 17**). A range of reducible functional groups are compatible like nitro groups, acetals, carboxylic acids, nitriles, carbamates, and imides. However, allyl esters are cleaved selectively in the presence of allyl ethers.



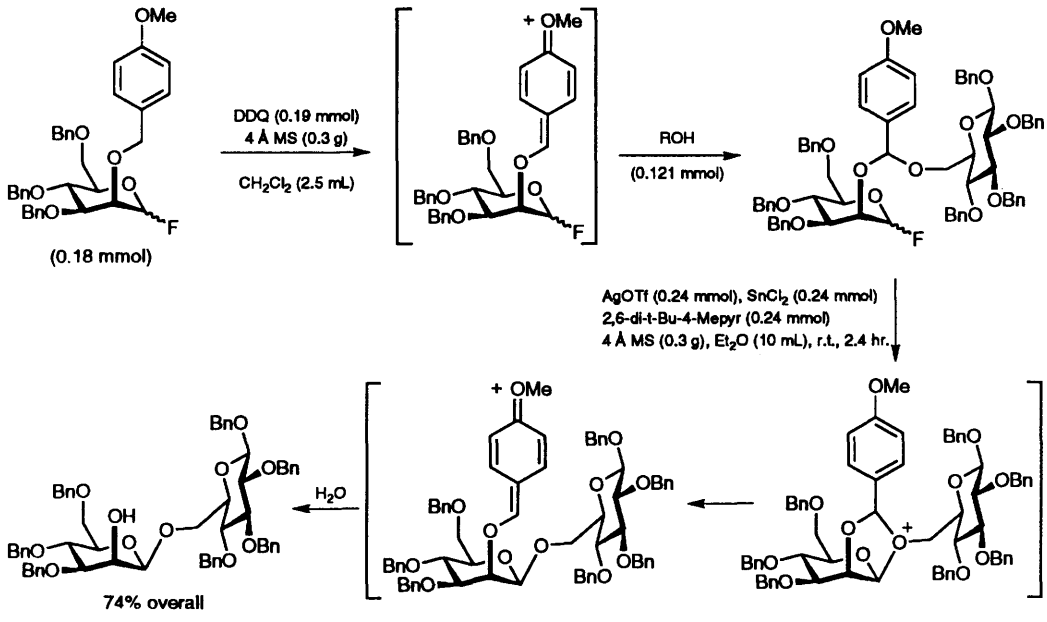
Scheme 17

Benzyl ethers are amongst the oldest and most often used protecting groups typically removed by hydrogenolysis or dissolving metal reduction. A study on the oxidative debenzylation using dimethyldioxirane carried out by Csuk and co-workers[24] showed that the reaction proceeds well with benzyl ethers of primary and secondary alcohols and the method is compatible with silyl ethers (**Scheme 18**). Isopropylidiene acetals are stable but benzylidene acetals are cleaved. The deprotection of *p*-bromo, *p*-cyano and 2-naphthylmethyl ethers can also be accomplished. Due to its



Scheme 18

1,2-*cis*-arrangement and the stereoelectronically disfavoured anomeric equatorial C–O linkage, construction of *β*-mannosides based on conventional technology is difficult to achieve. Ito and Ogawa have recently devised an ingenious solution to the problem (**Scheme 19**) by using the well known oxidative lability of *p*-methoxybenzyl ethers to create a temporary anchor that fixes the position of the nucleophilic partner in a *p*-methoxyphenyl acetal.[25] In the subsequent glycosidation step the



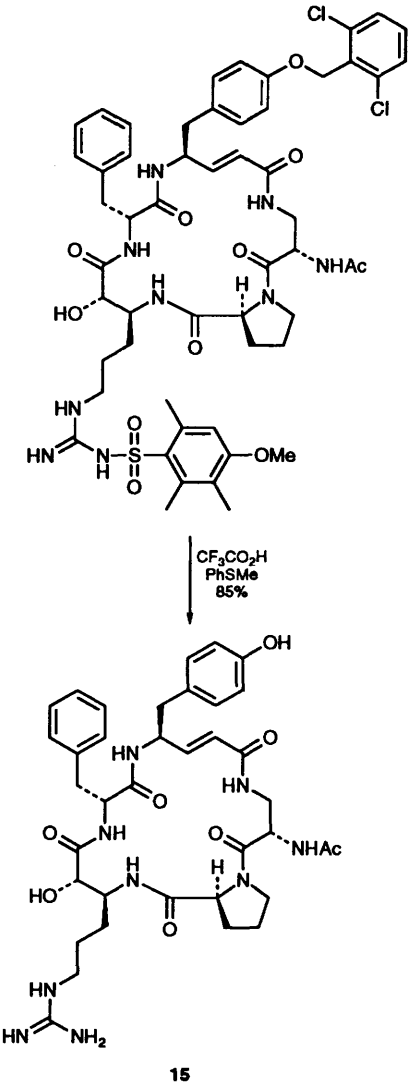
Scheme 19

neighbouring acetal ensures delivery of the nucleophilic partner from the β-face giving an intermediate whose capture by water results in stereospecific formation of the desired β-mannoside.

A recent synthesis of the thrombin inhibitor cyclotheonamide B (**15**) was notable for the use of the simultaneous deprotection of an arginine 4-methoxy-2,3,6-trimethylbenzenesulfonyl group and a phenolic 2,6-dichlorobenzyl ether using trifluoroacetic acid in the presence of thioanisole as a carbocation scavenger.[26] Both protecting groups survived dilute HCl in dioxane, LiOH in aqueous THF, TMSOTf (used to remove a Boc group), TBAF (used to cleave a trimethylsilylethyl ester), and a Dess–Martin oxidation (**Scheme 20**).

Falck and co-workers[27] have described a novel protecting group for primary and secondary alcohols prepared from commercial 1,1,1,3,3,3-hexafluoro-2-phenylisopropyl (HIP) alcohol using DEAD and Ph_3P (**Scheme 21**). The oustanding chemical resistance of the HIP group compares favourably with other standard ether protectors such as methyl, benzyl, and trityl. HIP ethers are stable over an unusually broad pH range as well as being resistant to oxidants, nucleophiles (MeLi, N_2H_4), Lewis acids ($BF_3 \cdot OEt_2$), and various reducing agents. However, lithium aluminium hydride causes partial (<30%) cleavage of primary HIP ethers under forcing conditions. Results from the selective removal of several representative alcohol protecting groups in the presence of a HIP moiety are summarized in **Table 1**.

The susceptibility of trifluoromethyl ethers to lithium naphthalenide (LiNaphth) can be exploited for the preferential deprotection of HIP ethers in the presence of other protecting groups. Many common functional groups such as amides, carboxylic acids, unconjugated olefins, and



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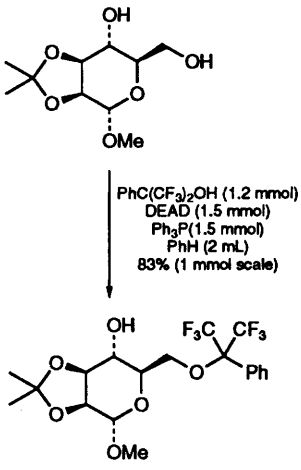
Scheme 20



Scheme 21

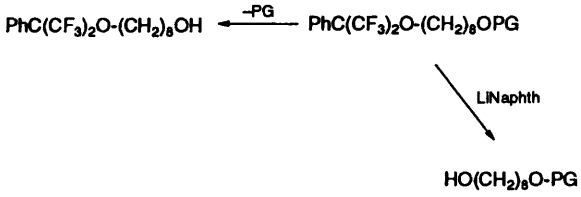


Table 1 PG removal

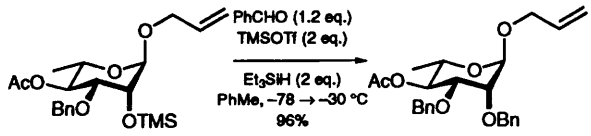
Entry	PG	Reaction conditions	T/hr.	Yield (%)	HIP* removal yield (%)
1	Tr	$SnCl_2$, CH_2Cl_2	4	89	81
2	THP	*p*-TsOH, MeOH	1	93	89
3	MEM	Me_3SiCl, NaI/MeCN	6	88	86
4	Bn	Pd/C, H_2/MeOH	1	91	71
5	MPM	DDQ, CH_2Cl_2/H_2O	3	92	74
6	t-$BuPh_2Si$	Bu_4NF, THF	1	95	73
7	Bz	KOH, MeOH		97	0

*HIP = -$C(CF_3)_2Ph$

acetylenes are compatible with the HIP deprotection conditions whilst others, *e.g.* esters, epoxides, ketones, and halides, are labile. With stoichiometric LiNaphth, deprotection is rapid (<1 h) even at −78 °C; on a preparative scale, the cleavage is more conveniently conducted using Li sand and a catalytic amount of naphthalene, although the reaction requires more time to reach completion.

Direct preparation of benzyl ethers from of TMS ethers of primary and secondary alkyl alcohols has been reported by Hatakeyama and co-workers[28] (**Scheme 22**). Ester, lactone, and glycosidic acetal functionalities are unaffected.

The growing interest in the solid phase synthesis of small organic molecules has stimulated a fresh

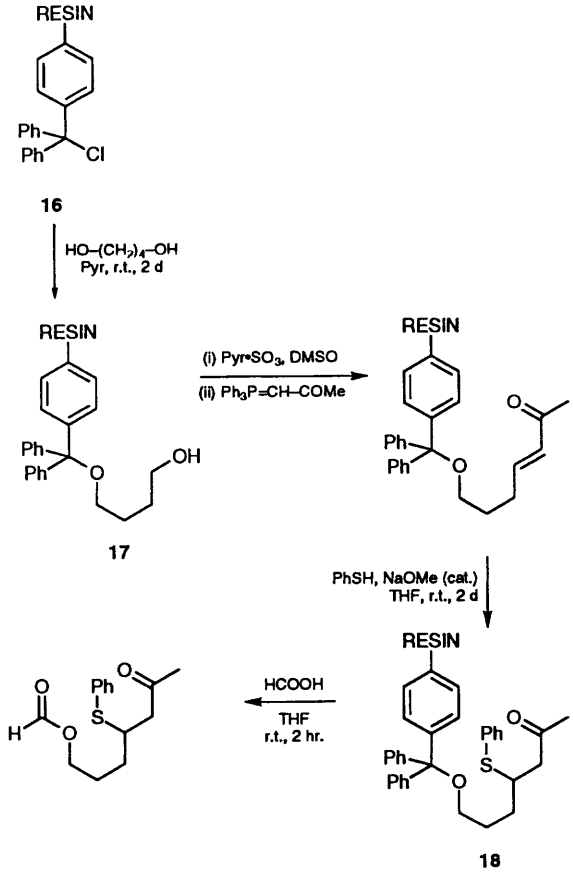


Scheme 22

appraisal of traditional organic synthesis in a polymeric environment. One such recent study[29] examined Horner–Emmons and conjugate addition chemistry on short aliphatic chains linked to a solid support (**Scheme 23**). Reaction of butane-1,4-diol with the tritylated[30] polystyrene **16** gave the monoprotected alcohol **17** which was converted into the adduct **18** using traditional organic transformations without any penalty in efficiency. Release of the adduct was accomplished by simply treating the polymer beads with formic acid in THF at room temperature. Having validated the basic protocol, the authors extended their study to the generation of combinatorial libraries.

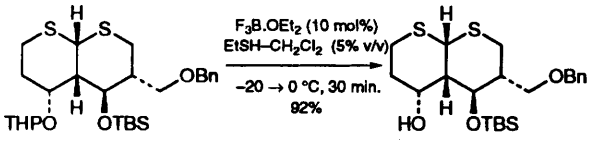
2.4 Alkoxyalkyl ethers

Tetrahydropyranyl (THP) ethers can be selectively cleaved in the presence of TBS ethers, MOM ethers, benzyl ethers, and mesitylene acetals using



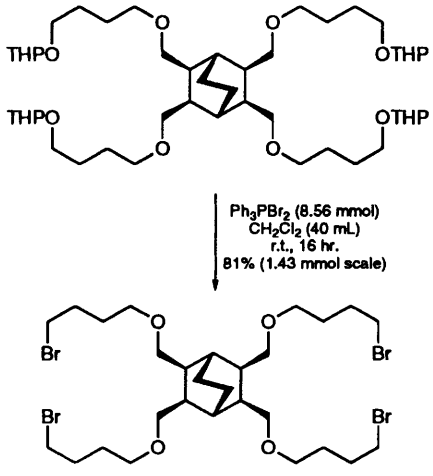
Scheme 23

10 mol% $BF_3 \cdot OEt_2$ in dichloromethane containing EtSH as a carbocation scavenger; BBr_3, $ZnCl_2$, and $ZnBr_2$ also work.[31] An example is shown in **Scheme 24.**



Scheme 24

Tanemura and co-workers[32] have reported that THP ethers can be deprotected with DDQ in methanol–water solution giving the parent alcohols in very good yields. Sonnet's[33] one-pot direct conversion of tetrahydropyranyl ethers into bromoalkanes using $Ph_3P \cdot Br_2$ complex was used in quadruplicate for the conversion shown in **Scheme 25.**[34]

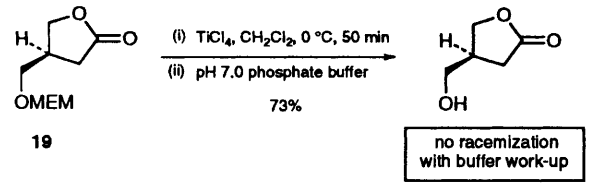


Scheme 25

A tetrahydropyranylation of primary and secondary alcohols using (zinc chloride)-impregnated alumina[35] is mild (room temperature), solvent free, and the procedure does not need an aqueous work-up.

Deprotection of the homochiral MEM ether **19** was complicated by racemization owing to reversible intramolecular transesterification. Schröer and Welzel found that racemization could be prevented by using a phosphate buffer (pH 7.0) during work-up.[36] Even then the product must be immediately used in the next step if the valuable stereogenicity is to be preserved (**Scheme 26**).

During a synthesis of the antifungal polyene macrolide roxaticin (**24**) (**Scheme 27**), Rychnovsky and Hoye[37] were faced with the daunting task of selectively releasing and distinguishing only the first two of the nine hydroxy functions (at C-1 and C-3) in the fully protected intermediate **20**. The



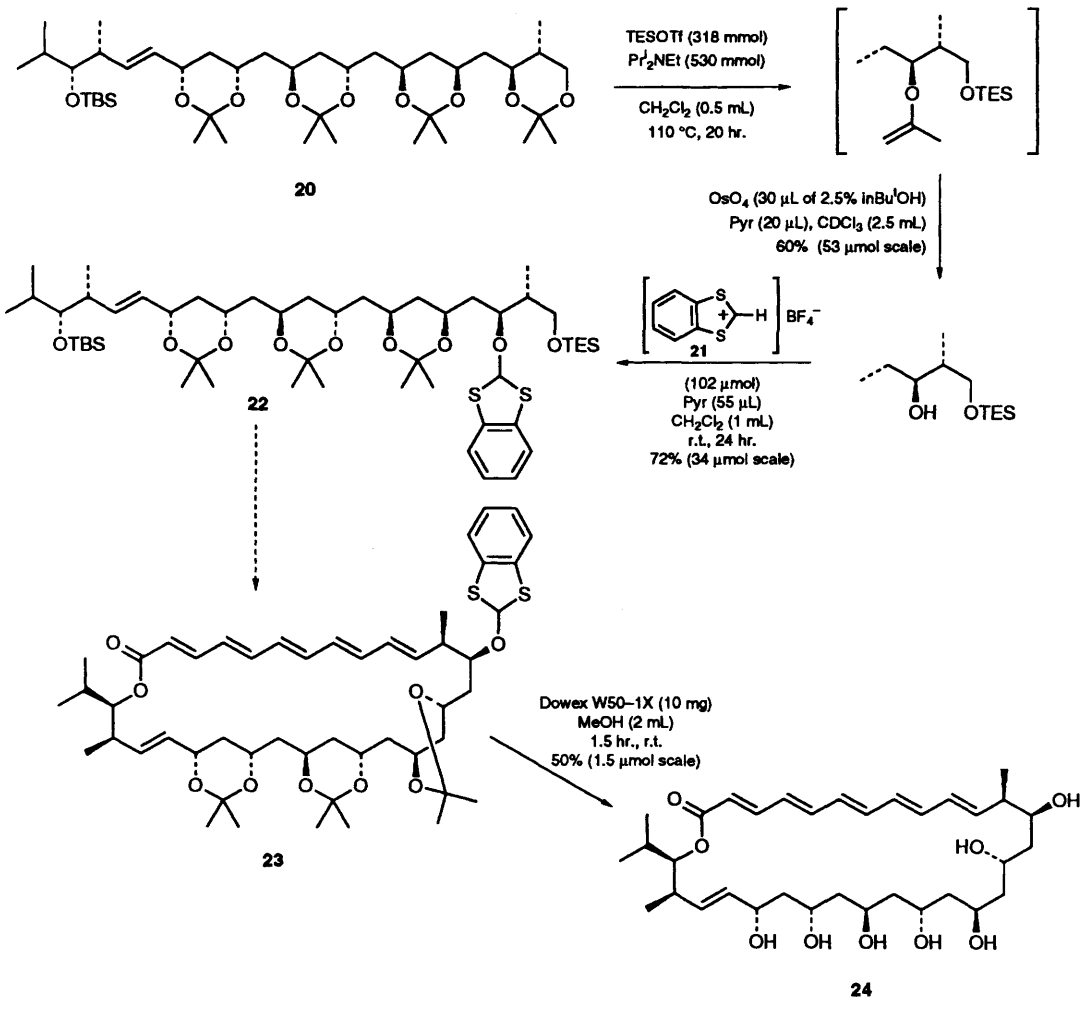
Scheme 26

successful three-step protocol involved first selective electrophilic cleavage of the terminal dioxane ring using TESOTf at elevated temperature thereby placing a TES group at C-1 and an isopropenyl ether at C-3. The isopropenyl ether was then cleaved in the second step using OsO_4 and finally the C-3 hydroxyl function was reprotected by reaction with 1,3-benzodithiolyl tetrafluoroborate (**21**) according to the procedure of Sekine and Hata.[38]. The resultant 1,3-benzodithiolan-2-yl (BDT) ether was stable to the conditions required to remove the TES ether of intermediate **22** in preparation for construction of the macrocycle in intermediate **23**. In the final step of the synthesis, the remaining three dioxane rings and the BDT ether were cleaved using an acid ion-exchange resin in MeOH.

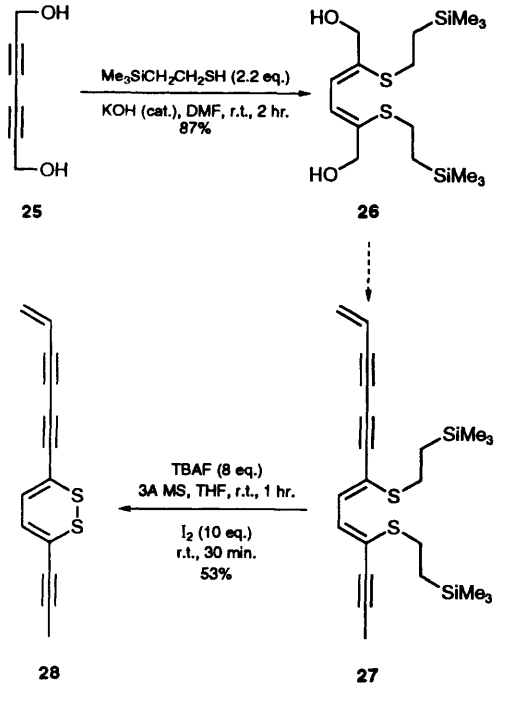
3 Thiol protecting groups

For the synthesis of the highly labile antibiotic thiarubrine A (**28**) (**Scheme 28**), Koreeda and Yang[39] required a method for introducing a protected thiol which could be carried through the synthesis unscathed until the end. The 2-(trimethylsilyl)ethyl group which had previously served well in the protection of esters and alcohols (in the form of the SEM group) was chosen for its robust character. Thus, a double base-catalysed addition of 2-(trimethylsilyl)ethanethiol to the diyne **25** gave the symmetrical dienedithiol derivative **26** in excellent yield. After further elaboration to the triyne **27**, the two thiol functions were released by treatment with TBAF and the construction of the 1,2-dithiine ring completed by oxidation with iodine to give the target in 53% yield for the two steps.

Guibé and co-workers[40] reported a new allylic protecting group for thiols in general and cysteine in paticular — allyloxycarbonylaminomethyl (Allocam). *S*-Allocam derivatives are readily prepared by acid-catalysed condensation of thiols with allyl *N*-hydroxymethyl carbamate **29** (**Scheme 29**). Deprotection can be achieved using a palladium catalyst, tributyltin hydride, and acetic acid — the latter being essential to prevent formation of allyl thioethers. The reaction leads to a mixture of the thiol, its tributyltin derivative, and minor amounts of disulfide. For the sake of convenience, the crude reaction mixtures were therefore treated with iodine and the deprotected products isolated as their disulfide derivatives. *S*-Allocam derivatives are stable under the basic deprotection conditions of



Scheme 27



Scheme 28

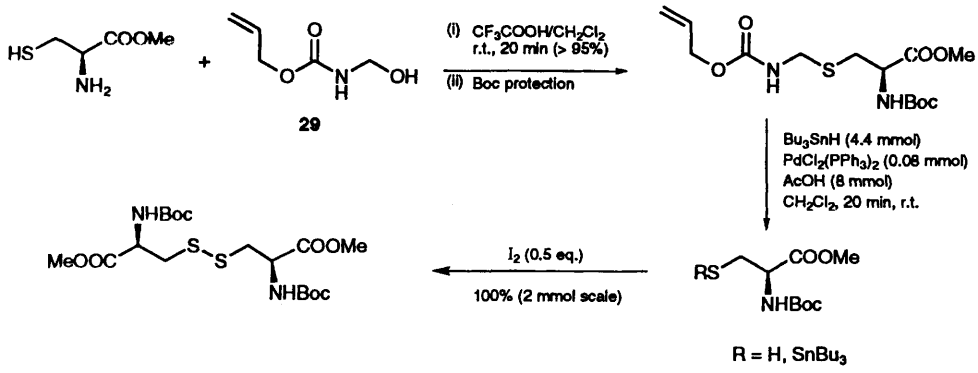
Fmoc derivatives but only marginally stable in the acidic conditions of Bu^t ester and Boc removal.

4 Diol protecting groups

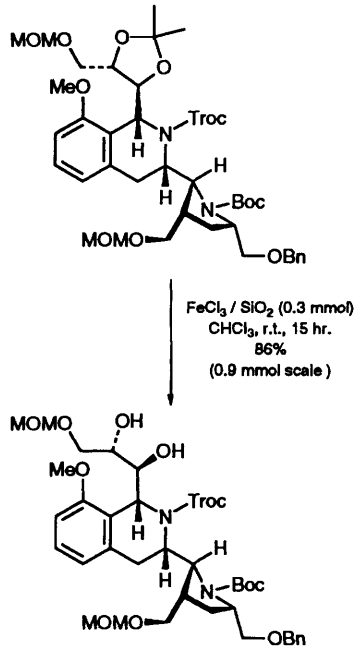
Selective cleavage of an acetonide in the presence of two MOM ethers, a Troc group, and a Boc group was accomplished with the aid of ferric chloride adsorbed onto silica gel (**Scheme 30**).[41]

Dowex 50W-X8 in 90% methanol has been shown to efficiently cleave a terminal acetonide in the presence of an internal acetonide (**Scheme 31**).[42]

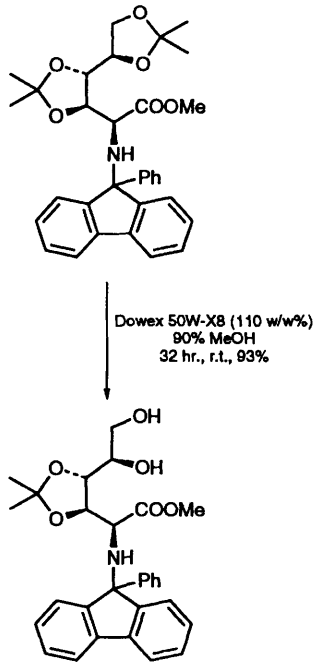
The Ley group has devised new methods for the simultaneous protection of two adjacent hydroxyl functions in carbohydrate derivatives.[43] For example, cyclohexane-1,2-diacetals allow protection of diequatorial 1,2-diols especially in *manno*-type sugars where regioselective introduction of 3,4-protection is difficult. For rhamnosides[44] this was, until now, only possible by a four-step sequence. In the example shown (**Scheme 32**), the requisite protection was accomplished by acid-catalysed transacetalization between methyl α-mannoside (**31**) and 1,1,2,2-tetramethoxy-cyclohexane (**30**). In this case, vicinal protection



Scheme 29



Scheme 30



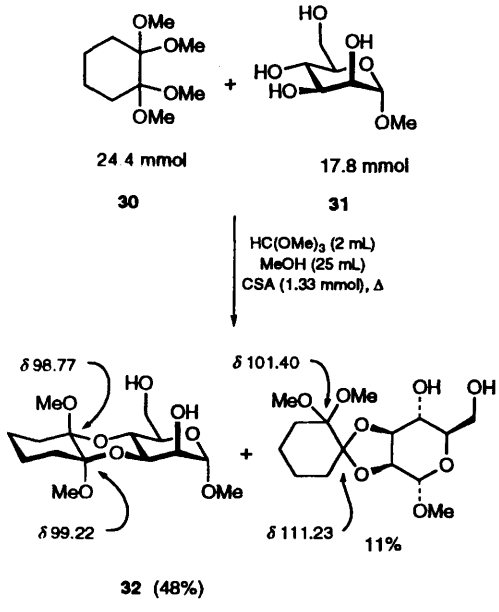
Scheme 31

includes a minor amount of axial–equatorial protection of the 2,3-hydroxyls as well. The resultant cyclohexane-1,2-diacetals **32** are readily deprotected on brief treatment with trifluoroacetic acid/water (19:1).

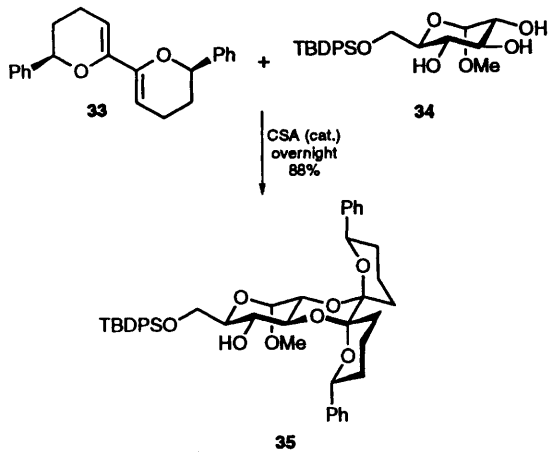
On the other hand the protection of D-glucopyranose **34** (**Scheme 33**) presents problems, because here all secondary OH groups are *trans*-diequatorially arranged; thus tetramethoxycyclohexane **30** gives a mixture of 2,3- and 3,4-protected glucosides. If, however, the homochiral bis-dihydropyran **33** is used, one regioisomer (**35**) can be prepared in high yield.[45]

5 Carboxyl protecting groups

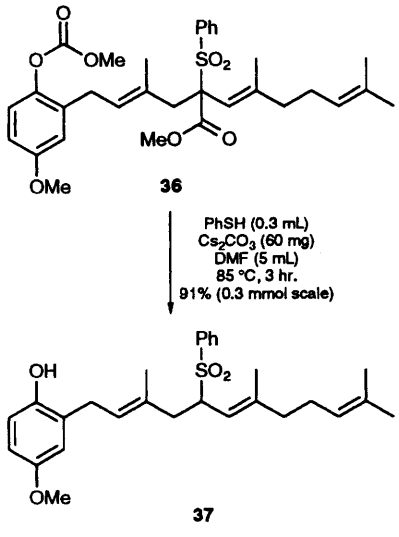
The very high nucleophilicity of caesium phenylthiolate[46] was used to cleave both a hindered methyl ester and a methyl carbonate in the tetraprenylbenzoquinol derivative **36** (**Scheme 34**) under comparatively mild conditions (DMF,



Scheme 32



Scheme 33



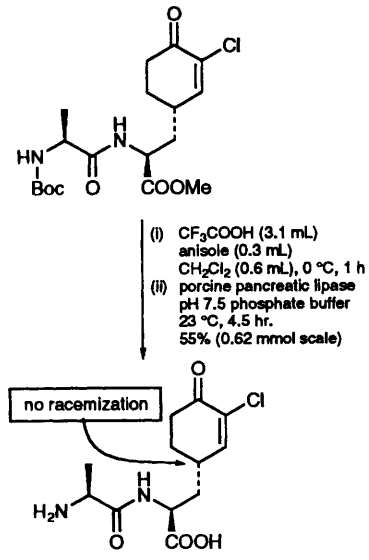
Scheme 34

85 °C).[47] The phenolic methyl ether in the product **37** survived unscathed.

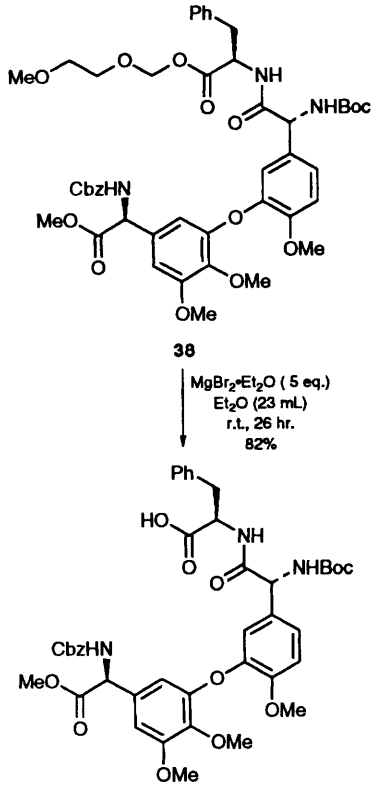
Chlorotetaine is an irreversible inhibitor of glucosamine-6-phosphate synthetase and thereby interferes with cell wall biosynthesis. The terminal steps of a synthesis of chlorotetaine are shown in **Scheme 35** in which deprotection of an *N*-terminal amino group is a prelude to the final enzymatic hydrolysis of a methyl ester function.[48] Critical to the success of the synthesis was the suppression of easy racemization at the ring juncture in the ester hydrolysis step by using porcine pancreatic lipase.

Anson and Montana reported a way of deprotecting benzyl esters under neutral conditions using *N*-bromosuccinimide and dibenzoyl peroxide in carbon tetrachloride.[49] It provides an alternative method to hydrogenolysis but it fails when the substrate contains a tertiary amide functionality.

The 2-methoxyethoxy (MEM) group is a well known protector for alcohols but its use in the protection of carboxylic acids is rare. **Scheme 36** depicts the deprotection of a MEM ester **38** under



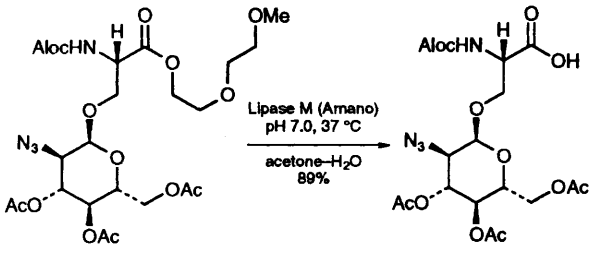
Scheme 35



Scheme 36

mild conditions without harm to the Cbz or Boc groups and without racemization of the arylglycine units.[50] MEM esters can also be cleaved readily on treatment with $AlCl_3$–*N*,*N*-dimethylaniline in dichloromethane to give the parent carboxylic acid in high yield[51] and the same conditions can be used to cleave methyl, benzyl, methoxymethyl, methylthiomethyl, and β-(trimethylsilyl) ethoxymethyl esters as well.

The Kunz group has been at the forefront of development of new strategies and tactics for the synthesis of glycopeptides which compound all the difficulties inherent in manipulating acid-sensitive carbohydrates and base-sensitive peptides. A noteworthy new tactic from these workers[52] uses lipase M from *Mucor javanicus* for the hydrolysis of the C-terminus of peptide components of glycopeptides as illustrated by the model shown in **Scheme 37**. 2-[2-Methoxyethoxy]ethyl (MEE) esters are especially valuable substrates because they confer wetability and solubility in water and so ensure that the esters of hydrophobic peptide sequences will be hydrolysable. Moreover, lipases generally lack protease activity making them selective for hydrolysis of ester functions only.



Scheme 37

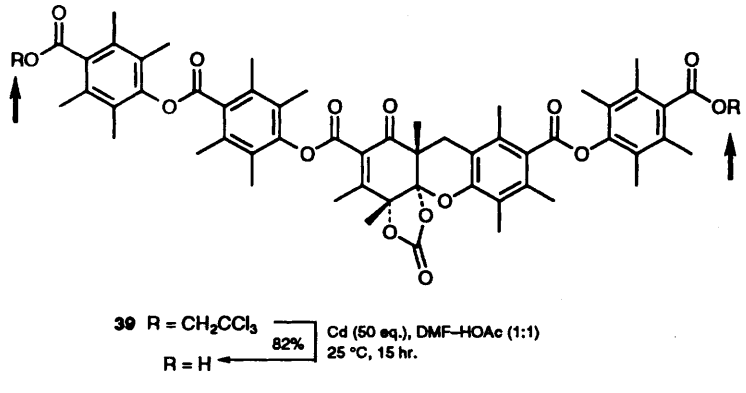
Reductive cleavage of 2,2,2-trichloroethyl esters and carbamates is usually accomplished with Zn in the presence of a proton source such as NH_4Cl or acetic acid. However, in a recent synthesis of the potent phospholipase A_2 inhibitor thielocin A1b, a 2,2,2-trichloroethyl ester was cleaved from the complex substrate **39** using cadmium in a mixture of DMF and acetic acid (**Scheme 38**).[53]

Of the many approaches toward the development of useful protecting groups for peptide synthesis, the concept of converting a stable protecting group into a labile protecting group (relay deprotection[54]) has been fruitful. The same concept can be applied to linkers for solid phase peptide synthesis in which the linker also serves as a C-terminal protecting group.

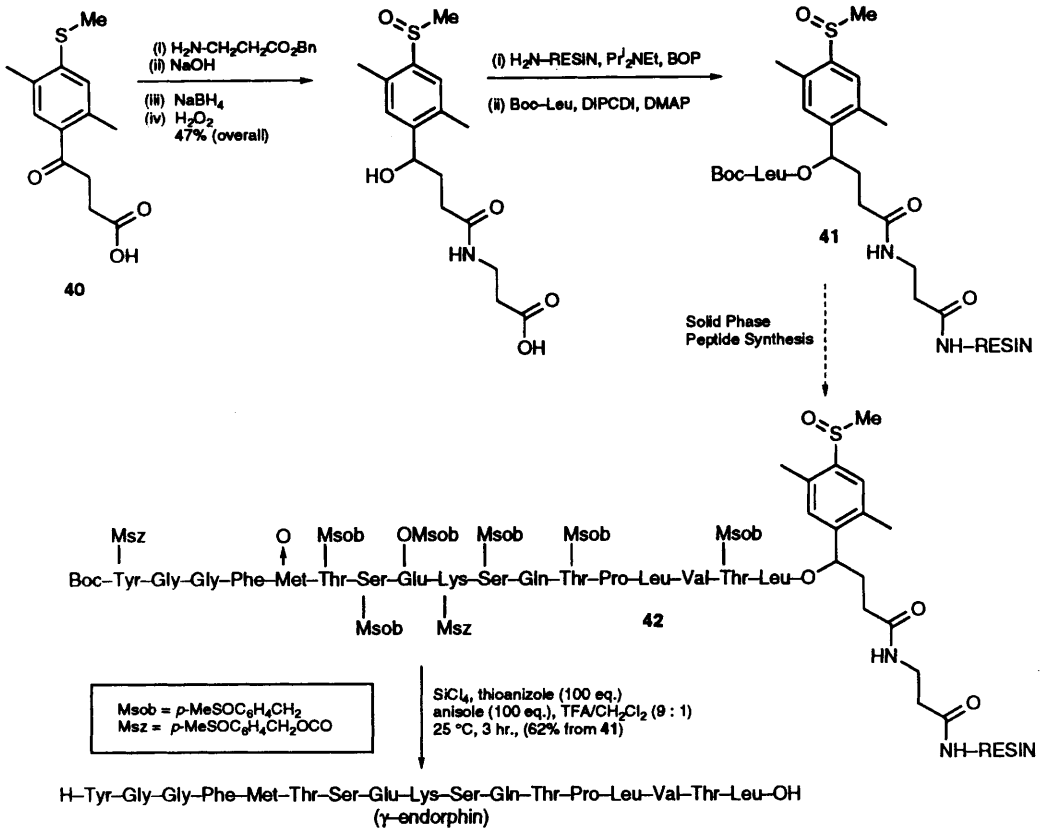
A recent synthesis of γ-endorphin by Kiso and co-workers[55] adapted a relay deprotection strategy based on the *p*-(methylsulfinyl)benzyl (Msob) group of Samanen and Brandies[56] for the design of a new linker: 4(2,5-dimethyl-4-methylsulfinylphenyl)-4-hydroxybutanoic acid (DSB) (**40**) (**Scheme 39**). The linker was appended to an aminomethylated polystyrene-resin and then coupled with C-terminal amino acid Boc-Leu to give **41**. The acid stability of *p*-(methylsulfinyl)benzyl type groups enabled selective removal of the Boc-protecting group from reagent **41** which could be used in solid phase peptide synthesis to prepare the protected resin-bound peptide **42**. The deprotection of all protecting groups as well as the cleavage of the peptide from the resin was achieved in one-pot by reductive acidolysis using tetrachlorosilane, thioanisole, anisole, and trifluoroacetic acid. Under these conditions all Msob-derived protecting groups were smoothly reduced to the corresponding labile sulfide form and then cleaved by acidolysis to give γ-endorphin in 62% yield.

In a recent solid phase synthesis of arylacetic acids,[57] a linker was required with the seemingly irreconcilable property of being stable towards the basic conditions of enolate alkylation and Suzuki coupling but also labile towards cleavage with hydroxide or amines. A relay deprotection approach based on Kenner's *N*-acylsulfonamide linker[58] served the purpose as shown in **Scheme 40**. Under basic conditions the arylsulfonamide (pK_a 2.5) is deprotonated and hence inert towards nucleophilic attack during the alkylation (**43**→**44**) and Suzuki coupling (**44**→**45**) steps. However, cleavage from the resin was accomplished by first converting the *N*-acylsulfonamide **45** into its *N*-methylated derivative **46** which is now quite labile towards nucleophilic attack.

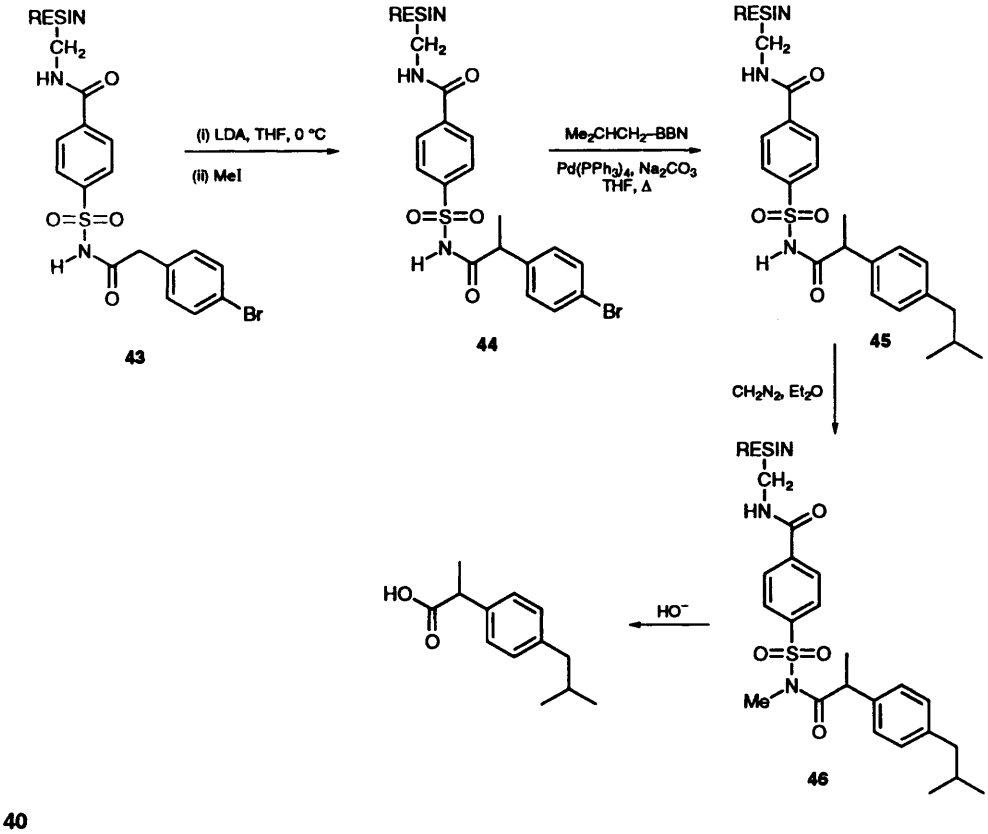
Cleavage of peptide segments linked to resins by allyl linkers using hydrostannolytic allyl transfer was originally reported by Loffet.[59] Giralt and co-workers[60] showed that the procedure (which uses tributyltin hydride in presence of $(Ph_3P)_4PdCl_2$) is compatible with Fmoc protecting groups. Alternatively, the cleavage reaction may be carried out using *N*-methylaniline in a 2:2:1 mixture of



Scheme 38



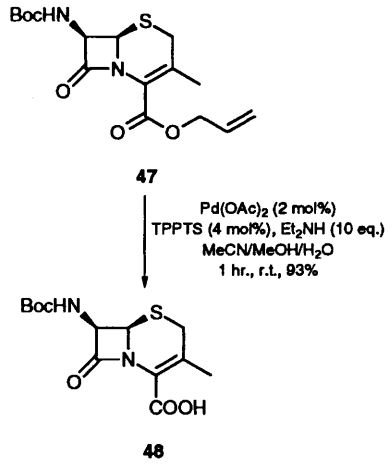
Scheme 39



Scheme 40

DMSO/THF/0.5 M HCl in the presence of $(Ph_3P)_4Pd$. The weaker basicity of the *N*-methylaniline compared with the usual morpholine suppresses competing deprotection of Fmoc groups.

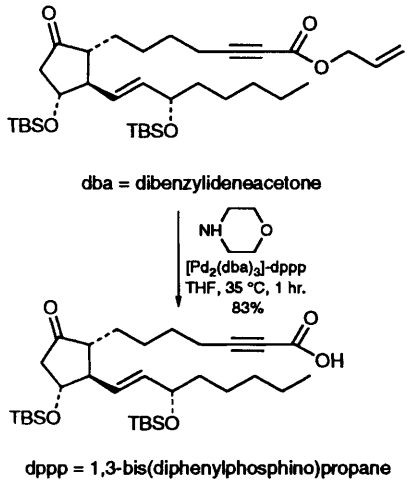
Genêt and co-workers[6] devised a water soluble Pd^0 catalyst [prepared *in situ* from $Pd(OAc)_2$ and trisodium 3,3′,3″-phosphinetriyltribenzenesulfonate (TPPTS)] which can be used to deprotect base sensitive penem allyl ester **47** (**Scheme 41**). The free carboxylic acid **48** was obtained in high yield and almost pure form by simple evaporation.



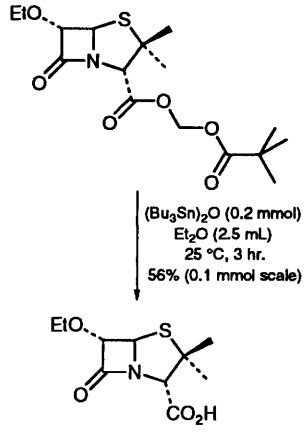
Scheme 41

Allyl alk-2-ynoates can be readily converted into alk-2-ynoic acids by reaction with morpholine in the presence of a palladium-diphenylphosphinopropane catalyst, thus providing a deprotection of allyl esters of 2,2,3,3-tetradehydro-PGE_1 (**Scheme 42**).[61] Ruthenium-catalysed reductive cleavage of allylic esters with formic acid and triethylamine has also been reported.[62]

Bis(tributyltin) oxide has been known for some time as a mild reagent for non-hydrolytic cleavage of carboxylic esters.[63] The reaction is carried out in aprotic solvents under essentially neutral conditions and is thus compatible with other acid- or base-sensitive functional groups. Recently a comprehensive study[64] revealed that bis(tributyltin) oxide shows a high level of chemoselectivity between methyl and ethyl esters *versus* t-butyl esters and lactones. (Pivaloyloxy)methyl carboxylates can also be cleaved in the presence of the base sensitive β-lactam moiety (**Scheme 43**). However, sterically hindered esters do not cleave and the method is not compatible with a fluoroalkyl group.



Scheme 42

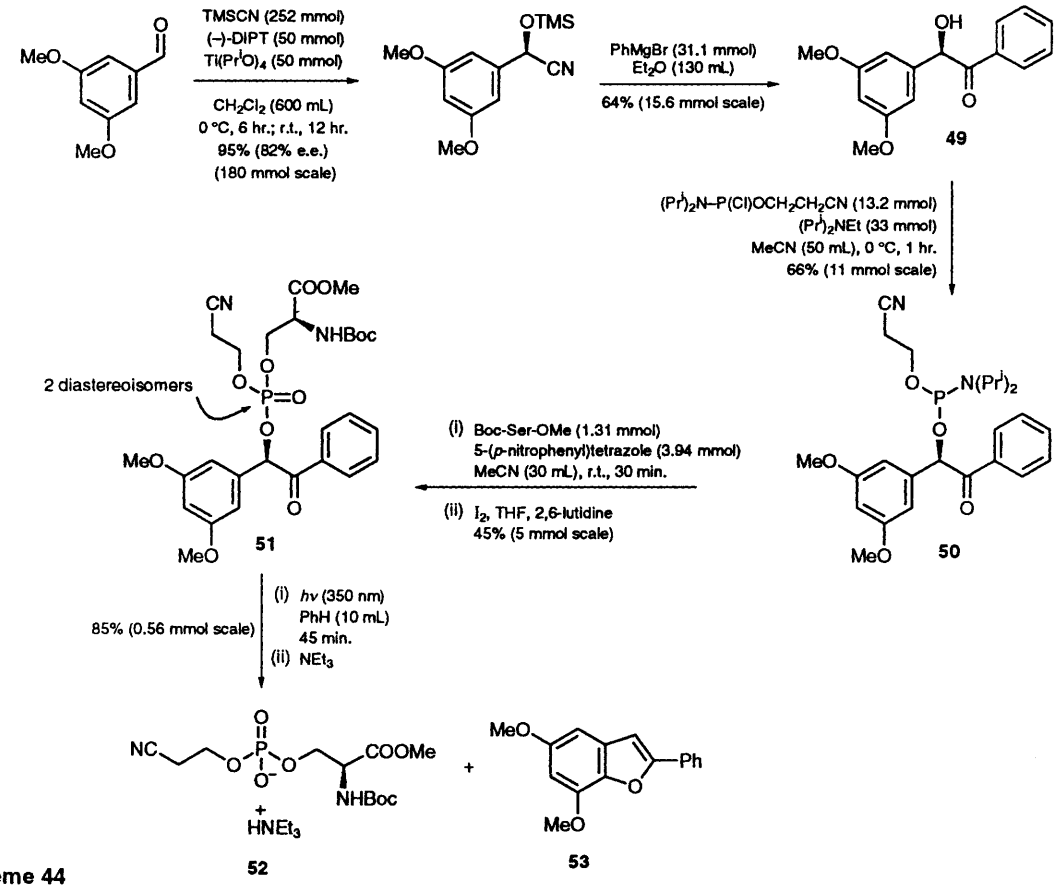


Scheme 43

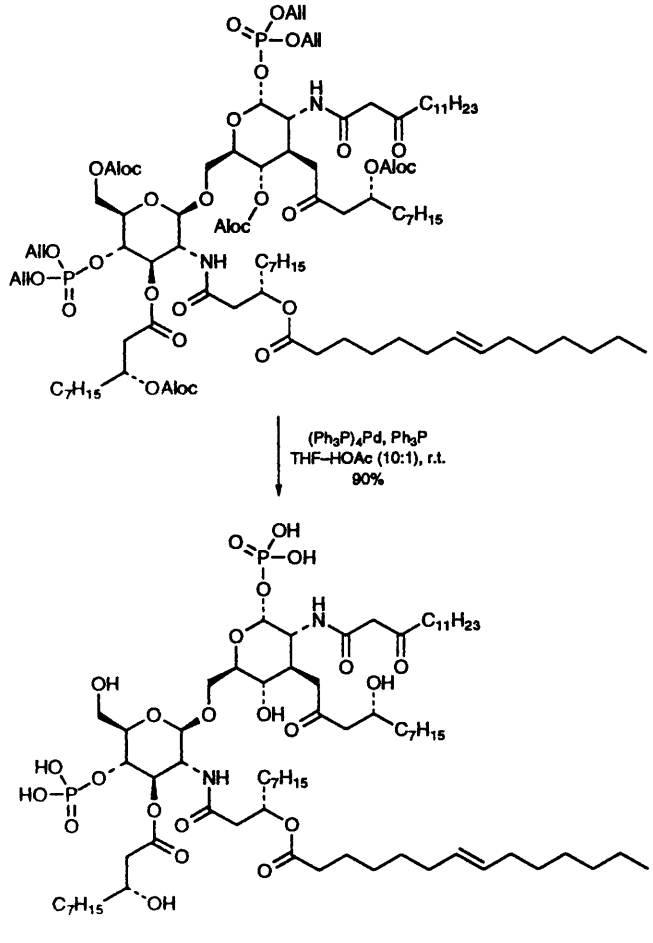
6 Phosphate protecting groups

In 1971 Sheehan[65] showed that 3′,5′-dimethoxybenzoin (DMB) esters are photochemically cleaved with high quantum yield (0.64) to the corresponding carboxylic acid and the relatively inert 2-phenyl-5,7-dimethoxybenzofuran (**53**). Givens[66] and Pirrung[67] have extended these observations to the protection of phosphotriesters. An asymmetric synthesis of 3′,5′-dimethoxybenzoin (**Scheme 44**) via the benzaldehyde cyanohydrin minimizes the number of diastereoisomers created in the phosphorylation of chiral alcohols. Thus reaction of **49** with 2′-(cyanoethoxy)(*N*,*N*′-diisopropylamino)chlorophosphine afforded the phosphoramidite **50** which then reacted with Boc-Ser-OMe to give the two diastereoisomeric phosphotriesters **51**. Photodeprotection gave the desired phosphodiester **52** (85%) along with **53**. Baldwin has used 3′,5′-dimethoxybenzoin for the photolabile protection of inorganic phosphate.[68]

The allyl group in its many guises has rapidly gained favour for the protection of alcohols (allyl carbonates, allyl ethers), carboxylic acids (allyl esters), amines (allyl carbamates), and more recently, phosphates.[69] **Scheme 45** illustrates the value of the allyl group for the deprotection of complex substrates under very mild conditions.[70] By using Pd^0 in a mixture of THF and acetic acid, 4 alcohol functions protected as their allyloxycarbonate (aloc derivatives) and two phosphotriesters protected and their allyl ester derivatives were deprotected simultaneously in 90% yield without injury to the remaining acid and base sensitive functionality.



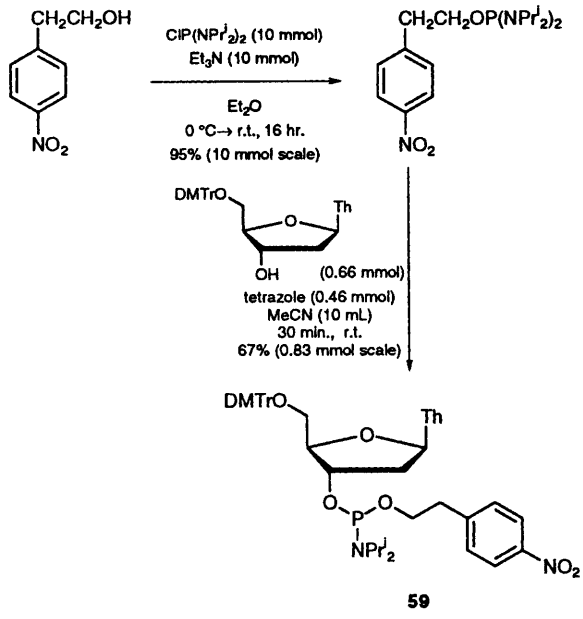
Scheme 44



Scheme 45

The 2-(trimethylsilyl)ethyl (TMSE) has been used successfully as a protecting group for phosphate monoester synthesis.[71] It can be removed by treatment with tetrabutylammonium fluoride or HF in acetonitrile. Recently, Wada and Sekine have reported that TMSE is an effective protecting group for the internucleotidic phosphate in oligonucleotide synthesis.[72] Reaction of protected phosphitylating reagent **55** (**Scheme 46**) with 5′-*O*-dimethoxytritylthymidine **54** afforded the phosphoramidite building block **56** in 80–6% yield. The TMSE-phosphoramidite **56** was then condensed with thymidine 3′-*O*-succinate bound to controlled pore glass (CPG) **57** in the presence of 1*H*-tetrazole. After oxidation with iodine and the subsequent capping reaction using acetic anhydride and DMAP, the protected dimer **58** was obtained in 99% yield.

p-Nitrophenylethyl (Npe) groups are useful for phosphate protection during the preparation of oligonucleotides (**Scheme 47**).[73] After phosphoramidite **59** was transformed into an oligonucleoside, the protecting group was removed using DBU. Npe protecting groups are superior to the 2-cyanoethyl group owing to diminished alkylation side-reaction during deprotection.



59

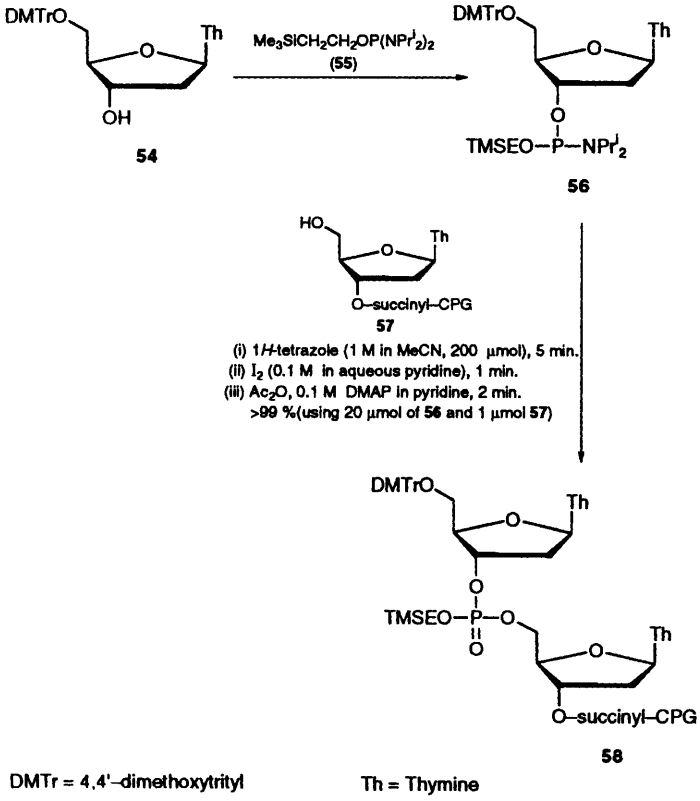
DMTr = 4,4'-dimethoxytrityl Th = Thymine

Scheme 47

7 Carbonyl protecting groups

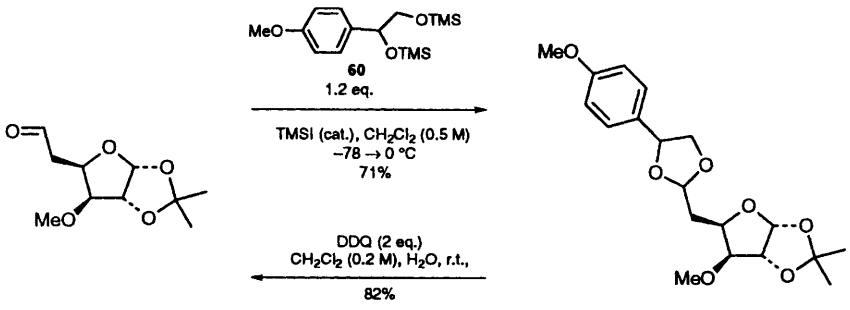
7.1 *O,O*-Acetals

Aldehydes and ketones can be protected as *p*-methoxyphenylethylene acetals and ketals using bis-trimethylsilyl ether **60** and a catalytic amount of TMSI.[74] Deprotection is accomplished under mild conditions with DDQ and water in dichloromethane. Other acetals and ketals are not affected (**Scheme 48**)

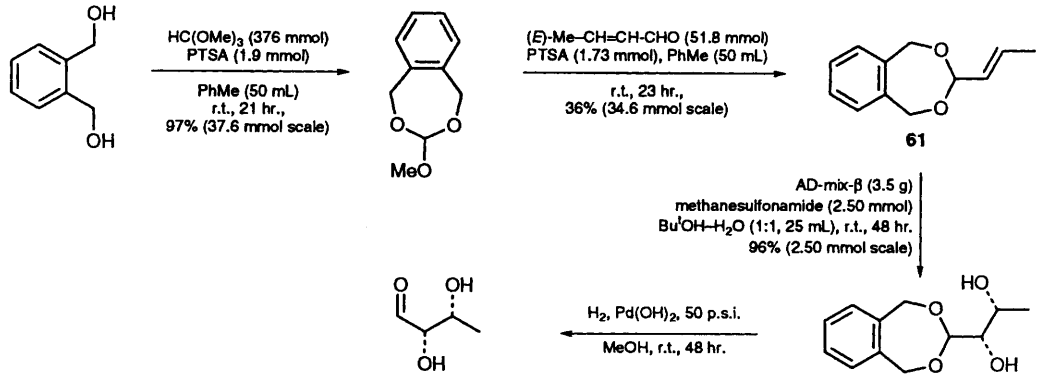


DMTr = 4,4'-dimethoxytrityl Th = Thymine

Scheme 46



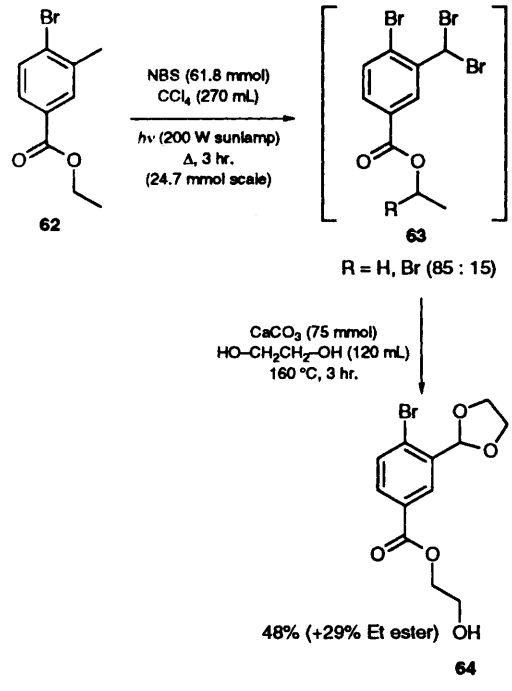
Scheme 48



Scheme 49

Wong and co-workers[75] recently exploited the hydrogenolytic lability of 1,5-dihydro-3*H*-2,4-benzodioxepin derivatives for the preparation of some acid-labile dihydroxyaldehyde derivatives generated by the Sharpless asymmetric dihydroxylation as illustrated in **Scheme 49**. In the example shown, the required protected alkene **61** was generated in modest yield by acetal exchange with 3-methoxy-1,5-dihydro-3*H*-2,4-benzodioxepin. Acid hydrolysis can also be used to release the aldehyde.

The conversion of an aryl methyl group into a dioxolane is hardly a typical method but its feasibilty is illustrated by the two-step procedure shown in **Scheme 50**. The first step, a double radical bromination under photochemical conditions, converts **62** into the 1,2-dibromoalkane **63**. In this case the bromination of the methyl group is accompanied by a small amount of bromination of the ester methylene function. In the second step, a double displacement of the bromine atoms in **63** by ethylene glycol at 160 °C produces the dioxolane **64** as a mixture of ethyl and hydroxyethyl esters.[34]

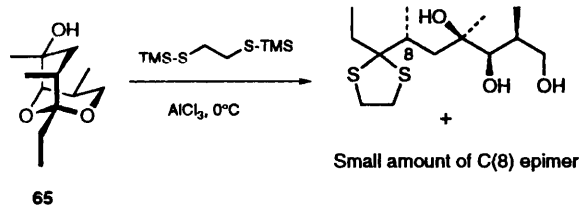


Scheme 50

7.2 *S,S*-Acetals

Direct conversion of the ketal function in **65** into a dithioketal moiety (**Scheme 51**)[76] was accomplished with aluminium trichloride in order to minimalize the epimerization at C-(8) — a problem which attends other Lewis acids such as titanium tetrachloride.

Deprotection of 1,3-dithianes to the corresponding carbonyl compounds has been achieved by treatment with 1.5 equivalents of DDQ in acetonitrile–water (9:1)[77] and by irradiation



Scheme 51

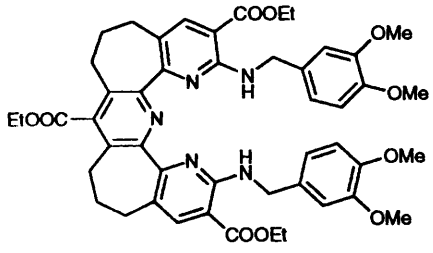
($\gamma > 360$ nm) of a dichloromethane solution of the dithioacetal or ketal with a pyrylium salt and molecular oxygen.[78]

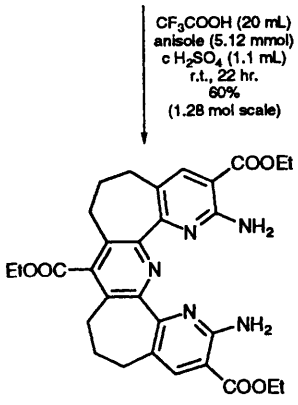
8 Amino protecting groups

Hydrazinolysis which is typically used to deprotect phthalimide derivatives can also be used to deprotect *N*-[1-(4,4-dimethyl-2,6-dioxocyclohexylidene)ethyl (Dde) groups which are easily introduced by reaction of an amine (for example cadaverine as shown in **Scheme 52**) with 2-acetyldimedone (**66**).[79] Dde groups are stable to 20% piperidine in DMF, the reagent frequently used to remove Fmoc groups, but is readily removed by 2% hydrazine in DMF within minutes. The driving force for the Dde deprotection is the formation of 3,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydro-1*H*-indazole and this can be monitored by the UV absorption at either 270 or 290 nm. The example shown in **Scheme 52** comes from a synthesis of the spider toxins nephilatoxin-9 and -11.

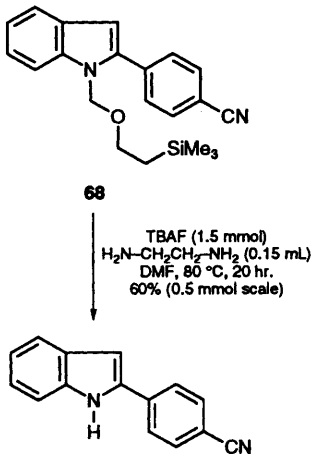
Two amine functions protected as their *N*-(3,4-dimethoxyphenyl)methyl derivatives in the pentacyclic tripyridine **67** (**Scheme 53**) were released on treatment with trifluoroacetic acid in the presence of anisole as a carbocation scavenger.[80]

Attempts to remove the [(trimethylsilyl)ethoxy]methyl (SEM) group from the indole derivative **68** (**Scheme 54**) using TBAF in THF gave poor yields[81] — a problem which had been previously encountered by others.[82] The best and most consistent results were obtained by using

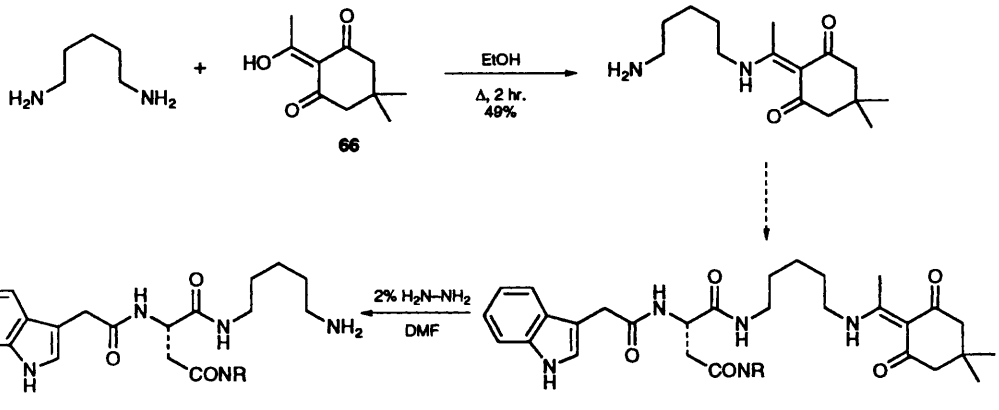




Scheme 53



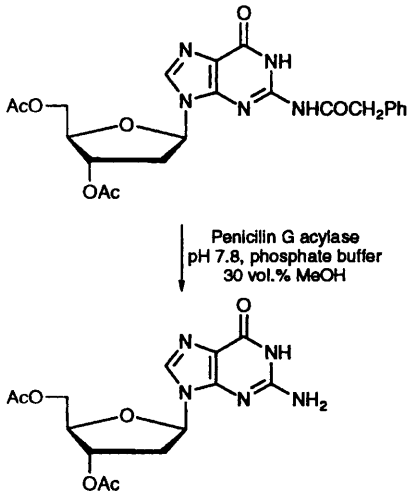
Scheme 54



Scheme 52

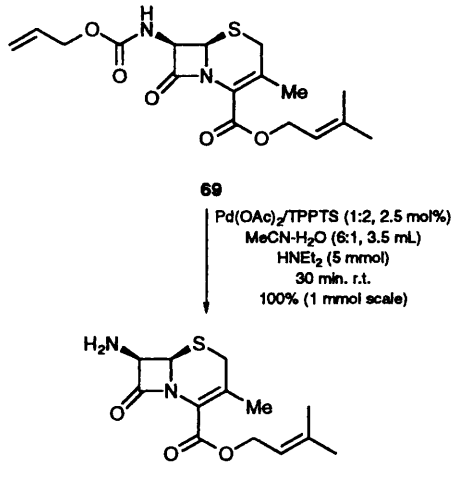
TBAF in DMF in the presence of an excess of ethylenediamine.[83]

Waldman and co-workers reported[1] the chemoselective enzymatic liberation of the amino functions present in the nucleobases of *O*-acetylated nucleosides by penicillin G acylase mediated hydrolysis of the corresponding phenylacetamides (**Scheme 55**).



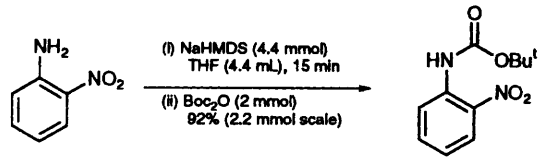
Scheme 55

Allyloxycarbamate protected cephalosporin **69** (**Scheme 56**) are selectively and quantitatively cleaved using a Pd^0 water soluble catalyst [prepared *in situ* from $Pd(OAc)_2$ and trisodium 3,3′,3″-phosphinetriyltribenzenesulfonate (TPPTS)] under homogeneous conditions without affecting the dimethylallyl carboxylate.[7]



Scheme 56

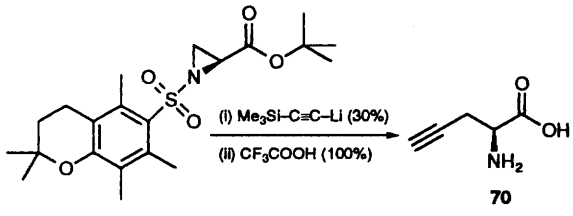
Aryl amines are converted into their Boc derivatives by treatment with two equivalents of sodium hexamethyldisilazide in THF followed by one equivalent of di-t-butylcarbonate.[84] This procedure works on a wide variety of both electron-rich and electron-deficient aryl amines (**Scheme 57**).



Scheme 57

Joullié and co-workers[85] reported that Fmoc can be removed from *N*-protected amino acids and dipeptides by potassium fluoride/18-crown-6 in the presence of methyl, ethyl, t-butyl, benzyl, and *p*-methoxybenzyl esters.

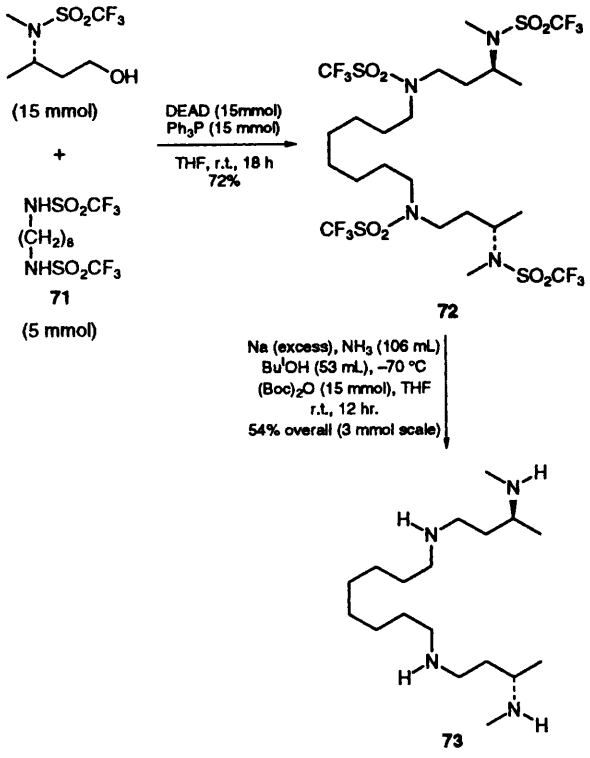
Ramage originally designed the 2,2,5,7,8-pentamethylchroman-6-sulfonyl (pmc) group for the protection of the highly basic guanidine function in arginine based on earlier observations that electron donating substituents on arylsulfonamides greatly facilitate protonolysis.[86,87] Church and Young[88] have used the pmc group to activate an aziridine ring during nucleophilic cleavage with lithium trimethylsilylacetylide (**Scheme 58**). Simultaneous removal of the TMS, t-butyl ester, and pmc groups occurred in quantitative yield on treatment with trifluoroacetic acid to give the amino acid derivative **70**.



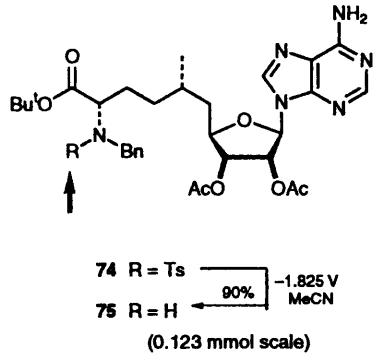
Scheme 58

A recent synthesis of spermine and spermidine analogues for use as tumour growth inhibitors made good strategic use of the trifluoromethanesulfonyl group as both a protecting group and an activating group (**Scheme 59**).[89] The high acidity of the *N*-trifluoromethanesulfonamides of primary amines (pK_a 7.5 compared with 11.7 for the corresponding tosyl derivatives) was sufficient to enable a double alkylation of the octane-1,8-diamine derivative **71** under Mitsunobu conditions. All four of the trifluoromethanesulfonyl groups were then removed from the alkylation product **72** using sodium in a mixture of ammonia and t-BuOH to give the tetra-amine **73**.

Deprotection of *N*-(arylsulfonyl)amines can be problematic. Electrolytic cleavage offers a method which tolerates a range of functionality. Thus, electrolysis of the *N*-tosylamide **74** (**Scheme 60**) gave the corresponding amine **75** in 90% yield.[90] Vedejs and Lin have also shown[91] that *N*-(arylsulfonyl) amines can be deprotected efficiently using SmI_2 in a refluxing mixture of the substrate in THF and *N,N′*-dimethylpropyleneurea (DMPU). Diaryl



Scheme 59



Scheme 60

disulfides and aryl mercaptans are amongst the sulfur-containing by-products. The study revealed that phenylsulfonyl groups cleave faster than tosyl groups but primary and secondary sulfonamides cleave at about the same rate.

β-Tosylethylamine **76** (**Scheme 61**) is a readily prepared reagent that can be used to synthesize *N*-tosylethyl-protected amido compounds, which can be deprotected with potassium t-butoxide.[92] Thus, deprotection of β-lactam **77** gave no evidence of ring-opening or epimerization.

9 Books and Reviews

1 'Protecting Groups', P.J. Kocienski, 1994, Thieme Verlag, Stuttgart, 1994.

2 'Applications of Combinatorial Technologies to Drug Discovery, 1. Background and Peptide Combinatorial Libraries', M.A. Gallop, R.W. Barrett, W.J. Dower, S.P.A. Fodor, and E.M. Gordon, *J. Med. Chem.*, 1994, **37**, 1233.

3 'Applications of Combinatorial Technologies to Drug Discovery. 2. Combinatorial Organic Synthesis, Library Screening Strategies, and Future Directions', E.M. Gordon, R.W. Barrett, W.J. Dower, S.P.A. Fodor, and M.A. Gallop, *J. Med. Chem.*, 1994, **37**, 1385.

4 'Convergent Solid-Phase Peptide Synthesis', P. Lloyd-Williams, F. Albericio, and E. Giralt, *Tetrahedron*, 1993, **49**, 11065.

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6 'The Chemistry of 2-Oxazolines (1985-Present)', T.G. Gant and A.I. Meyers, *Tetrahedron*, 1994, **50**, 2297.

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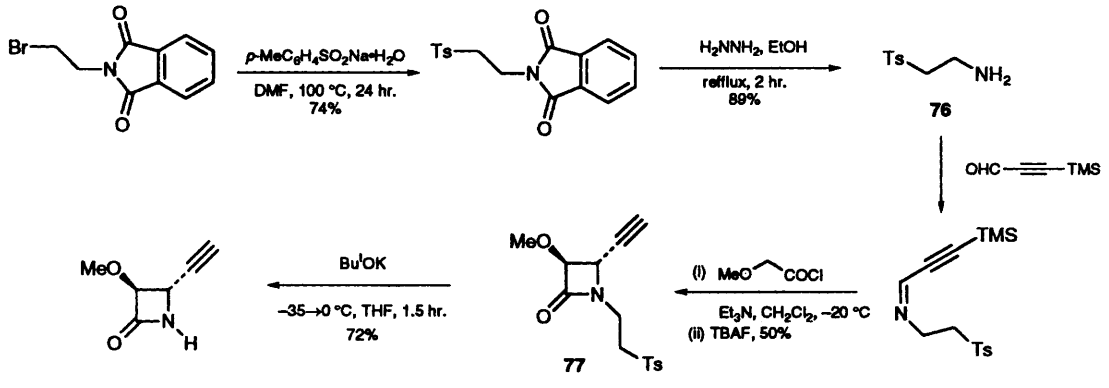

Scheme 61

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