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Regioselective Protection and Functionalization of Trehalose[#]

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Abstract

Trehalose containing glycolipids (e.g. TDM, TDCM, sulfolipids, maradolipids, etc.), and lipooligosaccharides are attractive synthetic targets due to their potent biological activities and complex structures. This review gives an account of the methods developed over past fifty years for regioselective protection of trehalose polyol to access symmetric and unsymmetrical derivatives of trehalose and their applications to the synthesis of diverse glycoconjugates.

Keywords : Trehalose, Regioselective protection, Mycobacterial glycolipids, Lipooligosaccharides, Trehalose glycoconjugates

Introduction

Trehalose **1** [α-D-Glc-(1→1)-α-D-Glc] is a naturally occurring C_2 symmetric, non reducing disaccharide.[1-3] Several trehalose containing glycolipids and lipooligosaccharides are found in mycobacteria,[4-21] while a few are isolated from fungi and worms.[22,23] These glycoconjugates are attractive synthetic targets. The challenges in their synthesis include, (i) their highly amphiphilic character, and (ii) their structural diversity arising through their large number of functional groups (esters, double bonds, COOH, SO_4 etc.), additional chiral centres of the side chains, and the point of attachments to the trehalose core. Moreover, some of them comprise a non-symmetrically substituted trehalose core with substituents attached at O2, O3, O4 or O6.

A few representative examples of biologically significant trehalose based glycoconjugates are shown in Figure 1. Trehalose dimycolate (TDM, cord factor) **2**[6] represents a class of symmetrical 6,6′-disubstituted glycolipids from *Mycobacterium tuberculosis* (MTb) while structurally similar trehalose dicorynomycolate (TDCM) **3**[14] is found in *Corynebacterium spp*. A maradolipid **4** bearing oleic acid and 13-methylmyristic acid is a first example of 6,6′-unsymmetrically substituted glycolipids recently found in *C. elegans*.[22] Glycolipid **5** is a representative example of mycobacterial lipooligosaccharides[15,16] wherein a carbohydrate moiety is attached to one of the termini of the trehalose core at O6, whereas fusaroside **6** recently isolated[23] from an endophytic fungus, *Fusarium* sp. LN-11, comprises trehalose unit attached at O4 to a rare, branched and polyunsaturated long-chain fatty acid. Likewise, diacylated sulfoglycolipid (Ac_2SGL) **7**[17] and sulfolipid SL-1 **8**[18-21] are examples of highly complex, un-symmetrically substituted glycolipids from MTb. Such complex target molecules demand a careful selection of orthogonal protecting groups for masking and unmasking the hydroxyl groups without disturbing the delicate functionalities.

Synthesis of trehalose glycoconjugates has been an area of intense research for long. Due to their diverse structures and important immunogenic activities these compounds have continued to attract immense attention from synthetic chemists and biologists.[24,25] The distribution, structure and biological properties of trehalose glycolipids have been extensively reviewed by Asselineau *et al.* in 1978.[7] Khan *et al.* recently reviewed synthesis and biological activities of trehalose glycolipids.[14] Strategically, the regioselectively differentiated trehalose core can be accessed in two different ways, (1) by stereoselective coupling of selectively protected two glucose units and (2) *via* regioselective protection of natural and abundant trehalose. The first route entails a difficult to achieve stereoselective 1,2-*cis* glycosylation of glucopyranosyl donors. Moreover, the glycosylation involves simultaneous formation of two glycosidic linkages leading to four possible stereoisomers (α,α; α,β; β,α; β,β), the proportion of which depends on the reaction conditions. The progress in the development of methodologies for construction of 1,1-α,α-glycosidic bond of trehalose has been reviewed recently by us.[26] The other way is to differentiate the hydroxyl groups of commercially available trehalose, which is again a difficult task since six secondary hydroxyl groups with similar reactivity have to be dealt with. Nevertheless, over past fifty years several impressive protocols have

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been developed for this purpose. This review is focused on the strategies and methodologies developed for regioselective protection of trehalose to construct symmetrical and un-symmetrical trehalose derivatives and their applications in the synthesis of the natural and unnatural trehalose glycoconjugates.

Regioselective protection of trehalose polyol

The inter-relationship between the eight hydroxyl groups of the C_2 symmetric trehalose is shown in the Figure 2. Most of the literature methods to prepare symmetric and un-symmetrical derivatives of trehalose are focused mainly on the differentiation of 6,6′-hydroxyl groups from the rest of the hydroxyls, asserting the fact that there are numerous examples wherein diverse functionalities are present at 6,6′-positions and also that it is the simplest differentiation owing to the higher reactivity of the primary hydroxyl groups. The most common bulky protecting groups employed for this purpose are trityl,[27-52] and tosylate/mesylates.[53-69] Occasionally, TBS/TBDPS,[37,70-72] groups are also used. The TMS group has been tactically used to differentiate the primary hydroxyls of trehalose based on the faster rate of hydrolysis of the primary

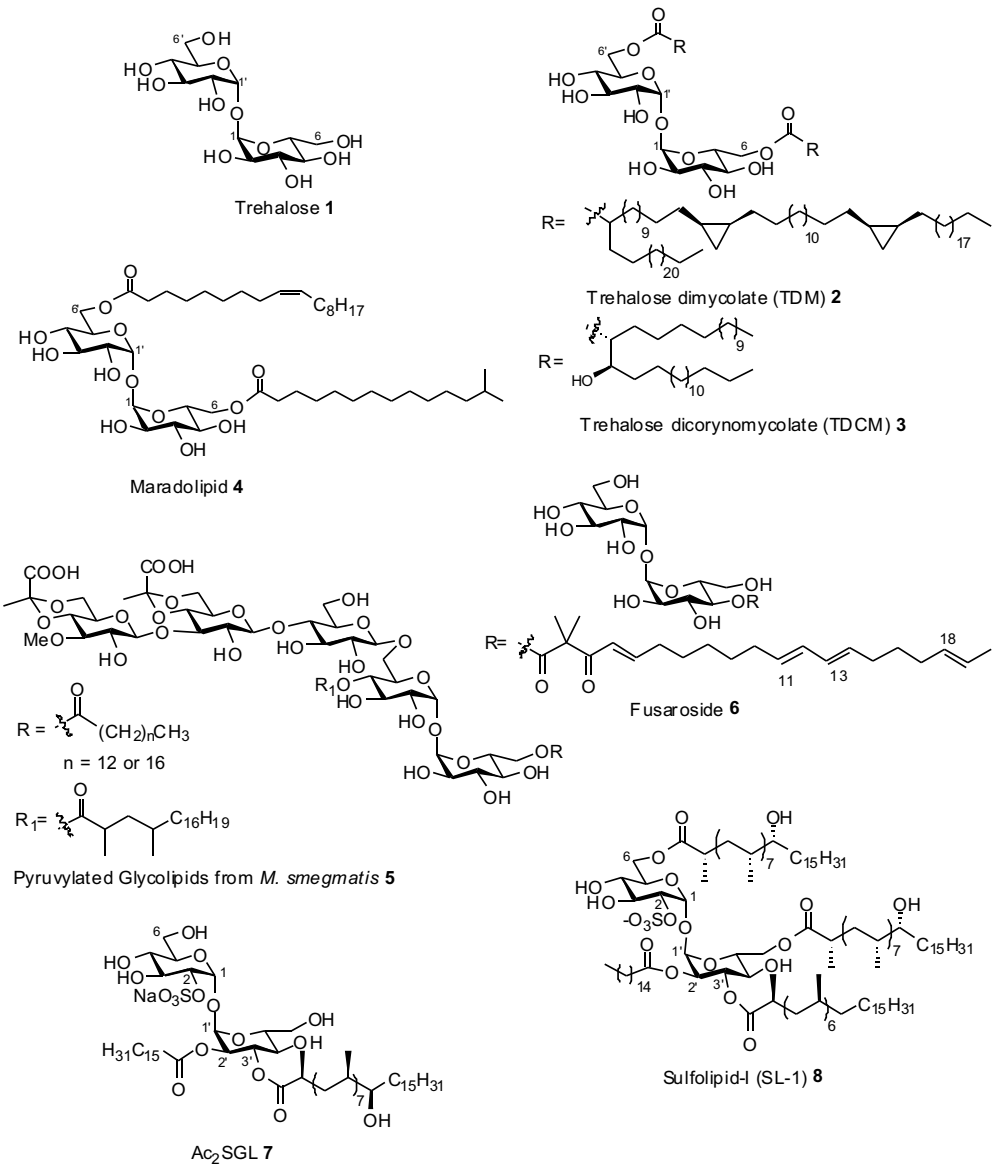


Figure 1: Naturally occuring trehalose glycolipids and lipooligosaccharides.

TMS groups.[73-85,88] In addition, direct functionalization of primary hydroxyl groups[91-116] and enzymatic reactions[87,117-124] have been also reported. The inter-relationship between various hydroxyls allows selective formation of diverse acetals. Strategically, first the 4,6-hydroxyl groups with 1,3-*cis* relationship are masked in the form of 4,6-di-*O*-benzylidene acetals revealing the 2,3-diols, which can be further differentiated based on the higher acidity of the 2-OH or the higher nucleophilicity of 3-OH.[178-193] The 4,6-diols as well as 2,3-*trans*-diol moieties can be protected by cyclohexylidene acetal,[168-172] isopropylidene acetal,[171-177] silyl acetals[194-197] and other cyclic acetal protecting groups.[198-200] Importantly, the benzylidene acetals can be further reductively cleaved to expose 6-OH[89,137-138] or 4-OH[89,137,152-163] groups under a variety of conditions. These methods have been used to synthesize symmetrical trehalose glycoconjugates and ingeniously employed for de-symmetrization of the C_2 symmetric trehalose core to access un-symmetrically substituted trehalose natural products. These methods are categorically discussed in the following sections.

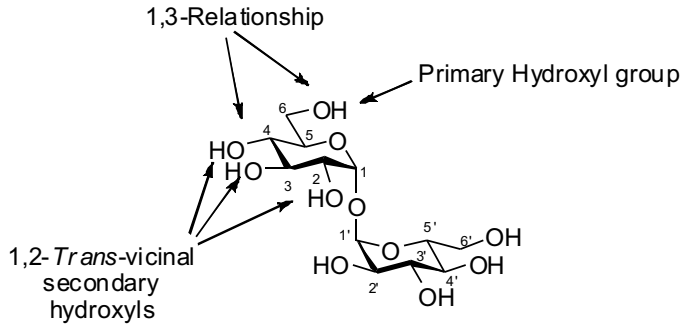
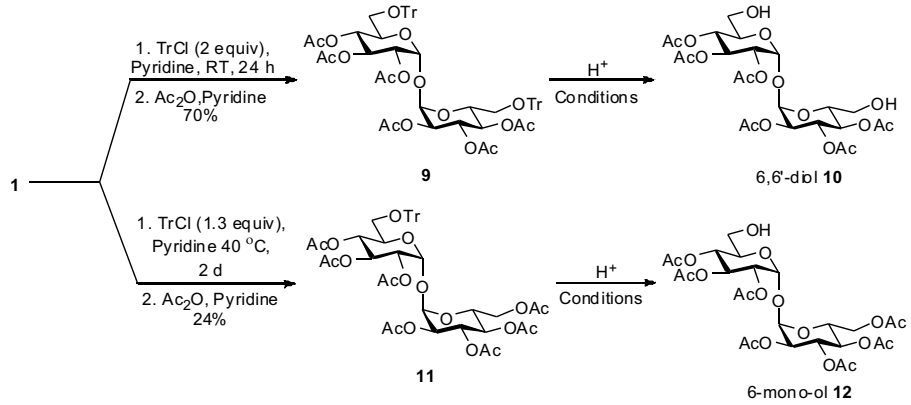


Figure 2: Inter-relationship of hydroxyl groups in trehalose **1**.

Tritylation

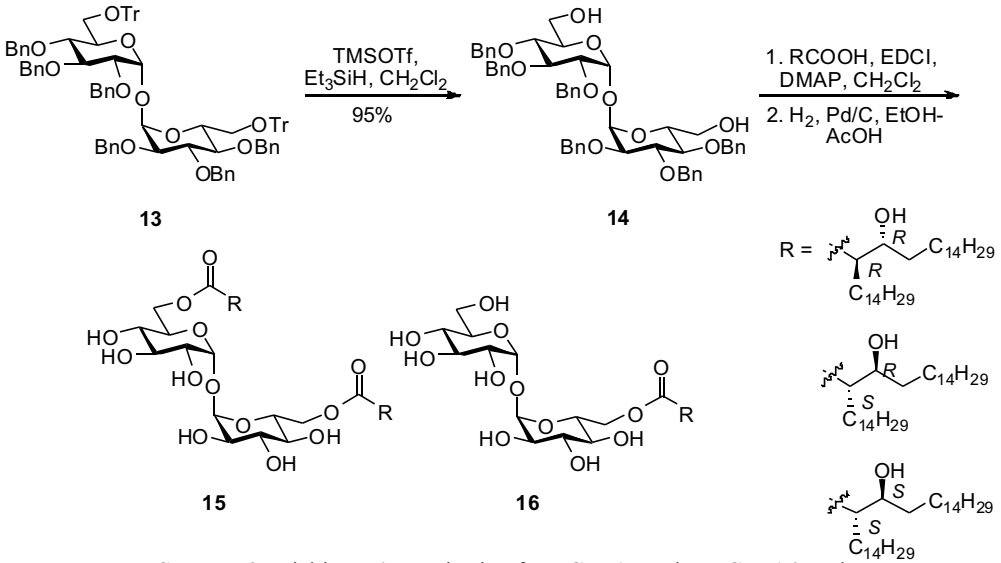
One of the frequently used methods for differentiation of O6/ O6, O6′ of trehalose is tritylation. The ease to carry out selective protection of primary hydroxyl groups in the presence of secondary ones by using bulky trityl protecting group and its facile deprotection under mild acidic conditions has made it a method of choice. Bredereck[27] in 1930, first used trityl group as a tool to differentiate the primary hydroxyl groups of the trehalose (Scheme 1). Thus, treatment of trehalose with 2 equiv. of trityl chloride in pyridine at RT for 24 h, followed by acetylation afforded the 2,2′,3,3′,4,4′-hexa-*O*-acetyl derivative **9** (70%) with the two primary hydroxyl groups protected as trityl ethers, which were selectively removed by using HBr in AcOH to give 6,6′-diol **10** in 48% yields. Improved yields for hydrolysis were reported later by the use of 80% acetic acid,[28] *p*-TSA/MeOH,[29] or Et_3SiH/TMSOTf combination.[30] The same sequence of reactions using 1.3 equiv. of trityl chloride gave access to 6-*O*-mono-trityl **11** (24%) which upon acid hydrolysis afforded 6-mono-OH derivative **12**. Both the symmetric and unsymmetrical derivatives have been used for the synthesis of several natural and unnatural derivatives of trehalose.



Scheme 1: Mono- and di-tritylation of trehalose.

Liav and Goren[28,31-33] were the first to use this method for the synthesis of important bacterial glycolipid TDCM and its analogs. They first converted trehalose into 6,6′-ditrityl trehalose, which upon benzylation (BnBr, NaH) gave its 6,6′-ditrityl 2,2′,3,3′,4,4′-hexa-*O*-benzyl derivative **13**. Then trityl groups were deprotected using 80% AcOH and the so obtained 2,2′,3,3′,4,4′-hexa-*O*-benzyl 6,6′ diol **14** was converted into its corresponding di-mesylate, which was subsequently displaced with potassium salt of the (D/L) corynomycolic acid to obtain the corresponding dicorynomycolate derivative. This method of introducing acyl chains was found to be superior over the alternate method of acylation of diol using corresponding acyl chloride. The 6-mono-mycoloyl and 6-mono-corynomycoloyl derivatives were also prepared by using 6-*O*-acetyl-2,2′,3,3′,4,4′-hexa-*O*-benzyl derivative, which was obtained as a by-product in the trityl deprotection step.[32]

On similar lines, Nishizawa and co-workers prepared all the four possible analogs of trehalose dicorynomycolates (Scheme 2).[34-36] The trityl groups of **13** were removed using Et_3SiH and TMSOTf[30] to obtain the 6,6′-diol **14**. The corynomycolic acid and its diastereomers were prepared by chiral induction procedures.[36] EDCI mediated coupling of **14** with these chiral acids, followed by catalytic hydrogenation afforded the symmetric TDCM **15** in good yields. They also prepared mono-corynomycolates **16** and several other synthetic analogs by varying the alkyl chain length. All the analogs were tested for their immunogenic activity. The natural anolog and its anti isomer showed highest antitumor as well as inhibitory activity in experimental lung metastasis based on the immunoadjuvant activity.



Scheme 2: Nishizawa's synthesis of TDCM **15** and TMCM **16** analogs.

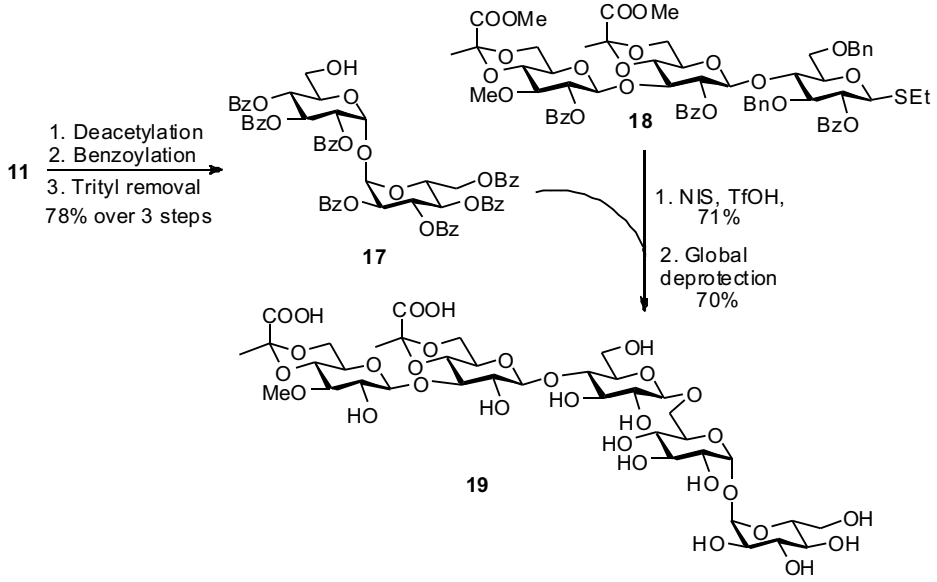
Parthasarathy and co-workers[37] also used a similar strategy to prepare a few synthetic analogs of TDM, which were found to impart desiccation resistance to membranes. Liu and co-workers[38] extended the strategy for the synthesis of several analogs of anti-invasive agent Brartemicin *via* acylation of **14** under Mitsunobu conditions. The synthetic analog 6,6′-bis(2,3-dimethoxybenzoyl)-α,α-D-trehalose was shown to be more immuno-potent than the natural product.

In addition to the trehalose glycolipids, the 6,6′-diol derivatives were also utilized for construction of diverse hybrid molecular architecture including glycophanes (hybrid cyclodextrin-cyclophane),[29,39] and bridged and double calixarene-trehalose[40] *via* coupling of the primary alcohol with the corresponding benzyl chlorides or acyl chlorides, respectively. The 6,6′-diol **10** was transformed *via* azide displacement of mesylate to obtain its corresponding 6,6′-diamino-analog,[41] which was converted into amide derivatives.[42-44] The 6,6′-diol **14** was also utilized for the synthesis of unnatural heterocyclic derivatives of trehalose.[45] Very recently, this strategy was used to prepare guanidine functionalized trehalose derivatives which were able to pass through the blood-brain barrier (BBB).[46] These molecules are potential therapeutic agents for Huntington's disease. Many 6,6′-phosphine trehalose based chiral ligands and their complexes have been also prepared by Tom Chang and co-workers *via* selective

tritylation strategy. These complexes have been shown to be synthetically useful in obtaining enantioselectivity in various conversions.[47] The 6,6′-diol **14** was also used for homologation of trehalose at 6,6′-positions. For instance, compound **14** was converted to 6,6′-di-iodo derivative which upon elimination followed by oxidation of thus formed alkene was transformed into the L-iduronic acid derivative corresponding to trehalose.[48] Alternatively, the 2,2′,3,3′,4,4′-hexa-*O*-benzoyl 6,6′-diol was converted into its triflate which was displaced with KCN to form the 6,6′-di-cyano derivative. Its reduction to amine and further reductive amination with 1-hydroxy-2-butanone afforded ethambutol-trehalose hybrid.[49]

The unsymmetrical 6-OH trehalose derivative obtained *via* selective mono-tritylation was also useful in synthesizing pyruvylated glycolipid pentasaccharide from *M. smegmatis*.[15-16] The synthesis of the pentasaccharide moiety, devoid of the pyruvylate groups on the terminal sugars, was first accomplished by Lipták and co-workers.[50] Later, Ziegler and co-workers came up with a strategy for the assembly of pyruvylated sugars and thereby synthesized the core pyruvylated pentasaccharide (Scheme 3).[51] Accordingly, mono-trityl derivative **11** upon a three step sequence involving deacetylation, benzoylation and detritylation afforded the 6-OH trehalose derivative **17** (78%), which was smoothly glycosylated with the requisite trisaccharide thioglycoside **18** (71%) and subsequent global deprotection afforded the core pentasaccharide **19** (70%). Synthesis of the terminal trisaccharide thioglycoside donor **18** was achieved by coupling of the monomeric sugar pyruvate by using trichloroacetimidate coupling method.

The unsymmetrical 2,2′,3,3′,4,4′,6-hepta-*O*-benzyl trehalose derivative has been also used for the attachment of a fluorophore *N*-methyl-6-oxyquinolinium betaine to trehalose by displacement of 6-OTf by nitrogen functionality.[52]



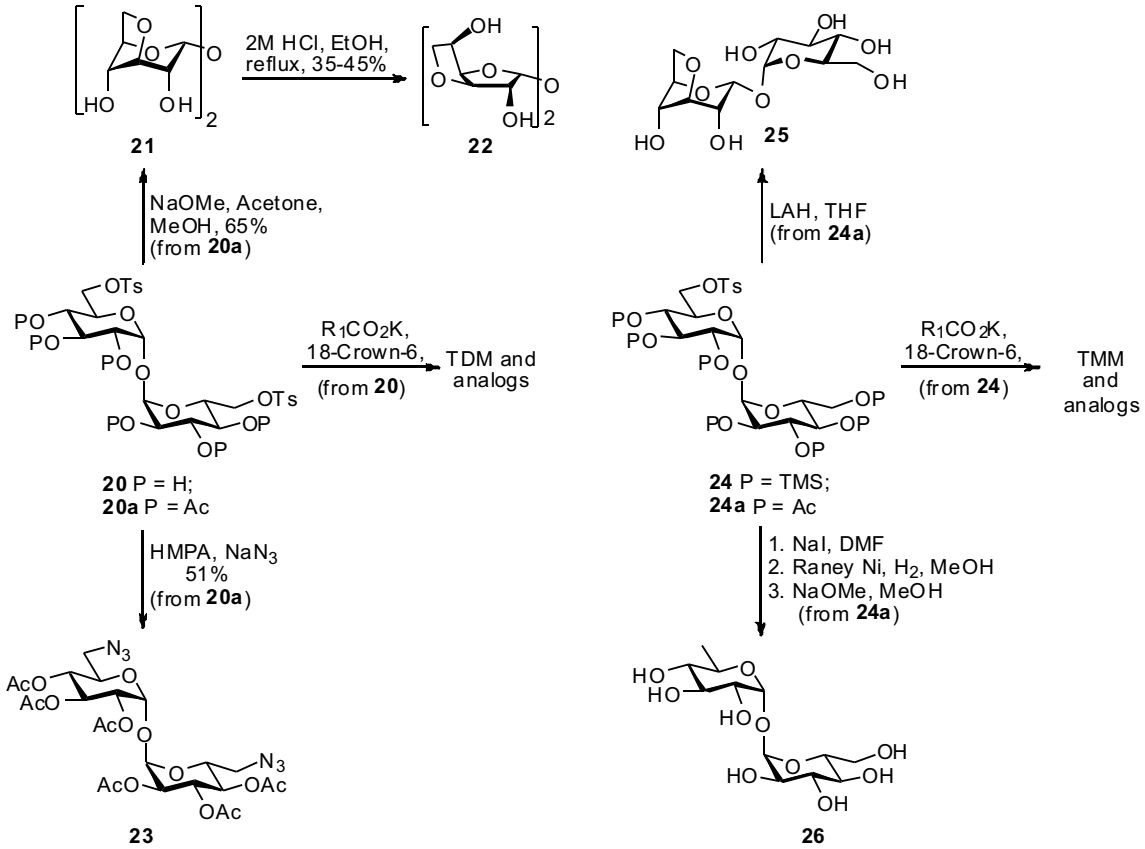
Scheme 3: Synthesis of pyruvylated pentasaccharide core **19** of the glycolipid from *M. smegmatis*.

Tosyl and Mesyl derivatives

Protection of trehalose with tosyl or mesyl protecting groups at the primary position helps in two ways, (i) it differentiates the primary hydroxyl groups from the six secondary hydroxyls and (ii) it transforms the primary OH into a good leaving group.[53-69] Polonsky *et. al.* used the 6,6′-di-*O*-tosyl trehalose **20** (Pyridine, TsCl) for the synthesis of cord factor (TDM) and its various symmetric and unsymmetrical analogs *via* direct displacement with the potassium salt of the corresponding acid (Scheme 4).[56-58] The method is conceptually attractive as minimal protecting groups (i.e. only tosylates) are used and the TDMs could be synthesized just in two steps avoiding lengthy protection-deprotection sequence. However, it had a few drawbacks including the formation of 3,6-anhydro trehalose products, and other by-products that were difficult to separate from the desired diesters.

The ditosylate **20a** prepared from trehalose *via* tosylation followed by acetylation was advantageously used for preparation of 3,6:3′,6′-dianhydrotrehalose[59] **21**, which was rearranged to its furanoid form **22** *via* an acid catalyzed rearrangment.[60] Compound **20a** has been

also used in the preparation of diazido trehalose derivatives **23** *via* azide displacement of tosylates.[61] The 6,6′-diazidotrehalose was used in the synthesis of trehalose capped β-cyclodextrins.[62-64] A carbonyl insertion was carried out on ditosyl trehalose **20a** by reacting it with sodium dicarbonylcyclopentadienyliron (NaFp) and CO to extend the chain and prepare trehalose homologs, 6-deoxy-α-D-gluco-heptopyranosyl-(1→1)-6-deoxy-α-D-gluco-heptopyranoside, and bis(heptosuranic acid).[65] Similarly, the 6-*O*-mono mesylate derivatives of trehalose **24**[53] were used for the synthesis of unsymmetrical trehalose derivatives such as 3,6-anhydrotrehalose derivative **25**,[66] 6-deoxy trehalose[67] **26**, 6-monomycoloyl trehalose analogs.[58,66-68] The 6-*O*-monotosyl trehalose was converted into 6-monoazide trehalose which was then coupled with amino acids to form pentapeptide trehalose derivative.[69]

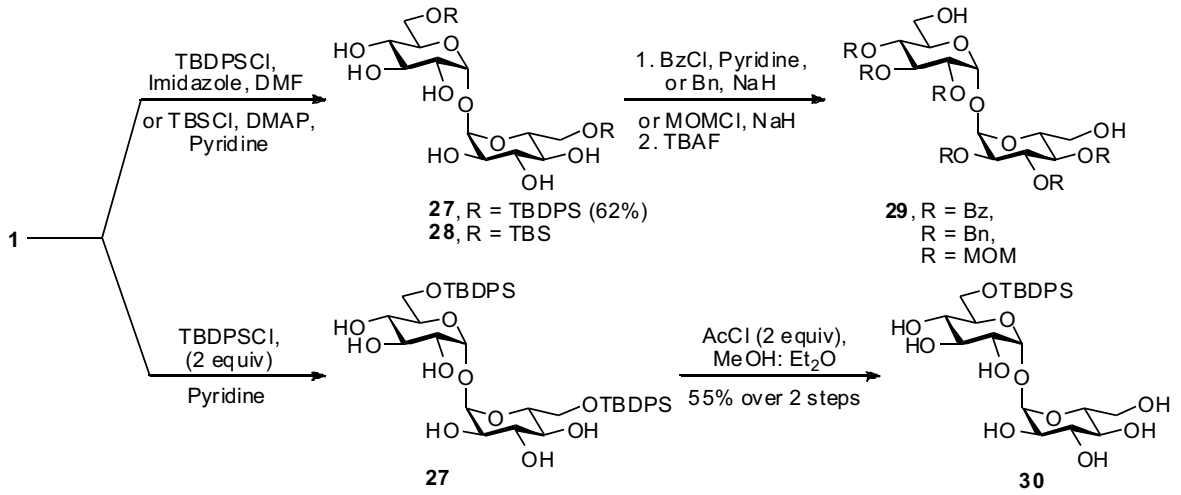


Scheme 4: Transformations of di-sulfonated and mono-sulfonated derivatives of trehalose.

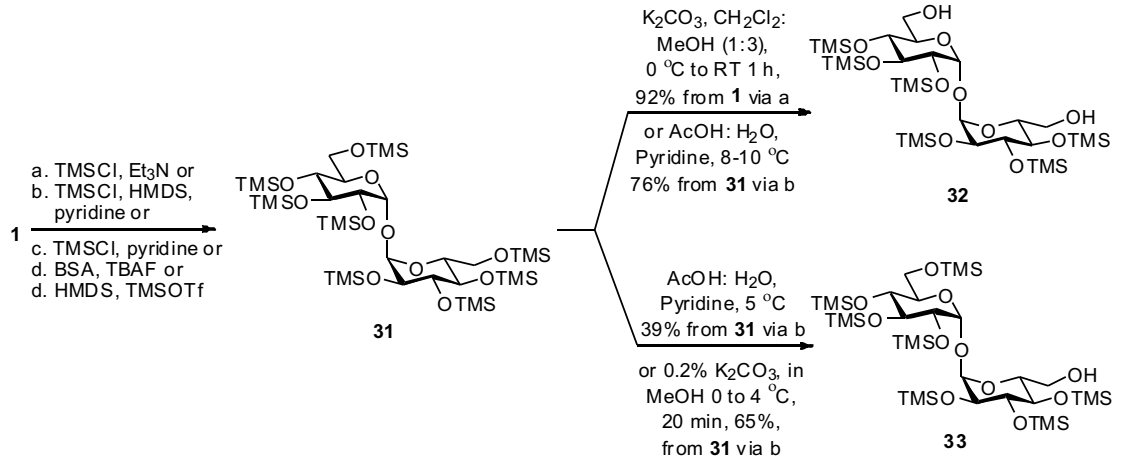
TBS and TBDPS protecting groups

Being bulky protecting groups, TBS and TBDPS serve the same purpose of selectively protecting primary alcohols of trehalose (Scheme 5). A general route constitutes a di-silylation of trehalose to obtain di-TBDPS **27** or di-TBS **28** in good yields. The remaining secondary hydroxyls are then protected with an orthogonal protecting group (e.g. Bz, Bn, MOM) and the TBS/TBDPS groups are subsequently removed to expose the 6,6′-diols **29** which could be modified. Parthasarathy and co-workers[37] prepared trehalose-di-oleyl derivative starting from 6,6′-di-TBDPS protected compound **27** through MOM protection of secondary OH groups, TBDPS deprotection, 6,6′-di-*O*-tosylation and nucleophilic displacement using oleyl alkoxide (oleyl alcohol and NaH). Bertozzi and co-workers used 6,6′-di-TBS trehalose **28** for the synthesis of 6,6′-dideoxytrehalose *via* benzoylation, TBS deprotection and xanthate reduction.[70] Sanki *et al.* used compound **27**, *via* benzylation, removal of TBDPS, oxidation of C6 and further Horner-Wadsworth-Emmons reaction, for extending the carbon chain at 6,6′-position for synthesizing α-keto and α-ketoamide derivatives of trehalose as possible antigens for mycobacterial strain.[71]

However, the 6-mono-TBDPS derivative of trehalose is difficult to prepare. In general, mono-functionalization of trehalose, which is the most straightforward way of desymmetrization of trehalose, is usually low-yielding. Recently, Benjamin Davis and co-workers conducted flow chemistry kinetic studies to generate data so as to gain insight into this long standing problem.[72] From their studies, they developed a batch process for large scale production of mono-TBDPS trehalose **30** (Scheme 5). This reverse modification route involves, first carrying out a high yielding di-TBDPS-protection of trehalose to obtain **27**, which is then subjected to selective mono-deprotection using AcCl and methanol in CH_2Cl_2 to afford **30** (55% over two steps). This method has a great synthetic application as it directly gives access to the unsymmetrical derivatives of trehalose including 6-mono-phosphate, 6-fluoro, 6-bromo, and 6-azido trehalose.[24] These derivatives were selectively incorporated into *MTb* as probes of function and for imaging purpose. Moreover, the relatively higher stability of TBDPS group over trityl group under acidic conditions provides flexibility in the synthesis of non-symmetrical trehalose derivatives.



Scheme 5: Selective mono and di-TBDPS/TBS protection of trehalose.

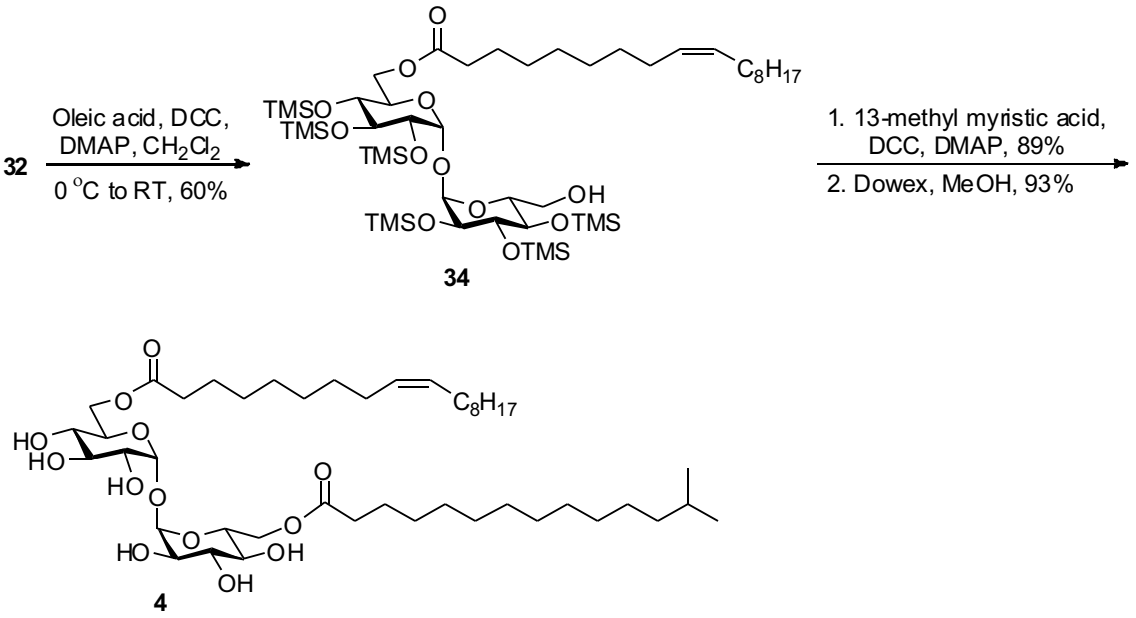


Scheme 6: Regioselective deprotection of primary TMS ethers in trehalose octaTMS **31**.

TMS protecting groups

TMS groups are one of the important protecting groups in trehalose chemistry. The advantages of using TMS groups include, (i) TMS groups are easy to introduce, (ii) they improve the solubility of trehalose in organic solvents, (iii) they are fairly stable, (iv) the primary TMS ethers could be hydrolyzed or acetylated selectively in the presence of secondary TMS ethers, (v) global deprotection could be achieved instantly and cleanly under mild conditions without disturbing the double bonds or acyl chains, in contrast to benzyl or acetyl groups.

Taubiana and co-workers first prepared the hexa-trimethylsilyl trehalose in two steps from trehalose and used it in the synthesis of trehalose 6,6′-dipalmitate.[73] Their method involved per-*O*-silylation of trehalose using TMSCl and HMDS in pyridine to obtain trehalose octa-TMS **31** and selective removal of primary hydroxyls of **31** using methanolic K_2CO_3 to obtain 2,2′,3,3′,4,4′-hexa-*O*-TMS trehalose **32** (90%) (Scheme 6). Use of TMSCl in pyridine in the first step also give similar results.[74,75] In our experience, using triethylamine (Et_3N) in place of pyridine for the formation of octa-TMS offers practical advantages over pyridine method, as Et_3N is easy to evaporate. Also, use of CH_2Cl_2 as a co-solvent in the hydrolysis reaction helps solubilizing the reactants and expedites the formation of **32**.[76] Subsequently, Gensler and Alam in 1977 prepared **32** (76%) and 2,2′,3,3′,4,4′,6-hepta-*O*-TMS trehalose **33** (39%) under controlled conditions using aqueous acetic acid.[74,75] They used the methodology to link the sugar covalently to the bovine serum albumin and human serum albumin and evaluated it for immunomodulating antitumor activity. Johnson and co-workers[77,78] developed a one-pot method to prepare diol **32**[78] and subsequently applied it for synthesis of trehalose dipalmitate *via* the nucleophilic displacement of 6,6′-bis-triflate derivative with the potassium salt of palmitic acid. Their variant involves per-*O*-silylation of trehalose using *N*,*O*-bis(trimethylsilyl)acetamide (BSA) and a catalytic amount of tetrabutylammonium fluoride (TBAF). The labile primary TMS groups were then removed *in situ* by adding K_2CO_3 in methanol at 0 °C in the same pot to give 6,6′-diol **32** in 83% yield. Datta and co-workers applied Taubiana's method to prepare diol **32** and used it to synthesize trehalose 6-mono and trehalose 6,6′-dicorynomycolates and their simpler analogs by controlling the amount of carboxylic acid used in the dicyclohexylcarbodiimide (DCC) mediated coupling.[79] They also prepared 6-mono-OH **33** (65%) by using 0.2% methanolic K_2CO_3 under controlled conditions and used it for synthesis of 6-mono-ester analogs. A few syntheses of trehalose 6,6′-diesters have been reported recently using this method.[80-82] On similar lines, Block and co-workers extended this strategy for the synthesis of the mono and di-phosphate derivatives of trehalose.[83] Very recently, Wang and co-workers used a combination of hexamethyldisilazide (HMDS) and cat. TMSOTf for per-*O*-silylation of **1**.[84]



Scheme 7: Synthesis of a maradolipid **4**.

In 2010, Kurzchalia and co-workers isolated a structurally unique class of glycolipids from the dauer larvae of *C. elegans* termed maradolipids.[22] The maradolipids were present as a mixture of at least sixty different glycolipids and the heterogeneity is resulting from the structural variation in the side chain alone.[85] The major component of maradolipids was identified as 6-*O*-oleoyl-6′-*O*-13-methylmyristoyl trehalose **4**. We carried out the first synthesis of the major component of maradolipid **4**, employing monoacylation of 6,6′-diol **32** as a key de-symmetrization step (Scheme 7).[76] A DCC mediated coupling of oleic acid with **32** using reverse addition strategy afforded 6-*O*-oleyl derivative **34 (**60%). The remaining free hydroxyl group was acylated using 13-methylmyristic acid, followed by treatment with Dowex acidic resin to afford maradolipid in 45% overall yield over 5 steps. This route is particularly useful for rapidly synthesizing various analogs of maradolipid. Knölker and co-worker used a similar strategy to prepare ten members of maradolipid family including **4,** using EDCI as a coupling agent.[85] Subsequently, Grindley and co-workers reported a protecting group free synthesis of **4** and analogs *via* direct TBTU mediated acylation[86] while Csuk and co-workers reported a chemo-enzymatic version along the similar lines employing regioselective acylation as a symmetry breaking step.[87]

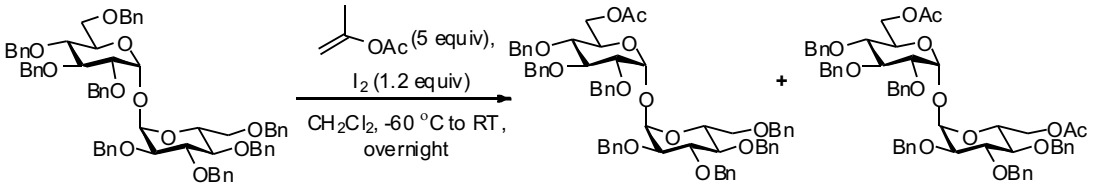
Synthesis of a thioglycoside analog of **4** is also reported.[88] Recently, we reported a conceptually different synthesis of maradolipid **4** *via* regioselective O6 DIBAL-reductive ring opening of trehalose benzylidene acetal.[89]

Regioselective acetolysis of per-*O*-benzyl trehalose

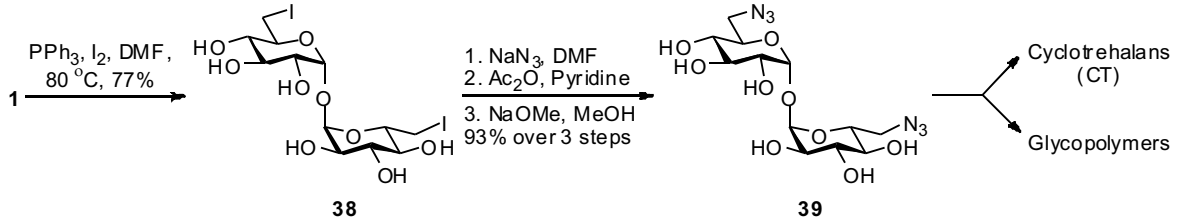
Benzyl groups are considered to be robust and therefore used as permanent protecting groups in the synthesis of complex glycans. Recently, Iadonisi and co-workers reported a very useful method for selective acetolysis of the primary benzyl group of various sugars by using isopropenyl acetate promoted by I_2 or by using I_2, Et_3SiH combination.[90] The octabenzyl-trehalose **35** was subjected to controlled acetolysis in CH_2Cl_2 to afford a separable mixture of 6-mono **36** and 6,6′-di-*O*-acetylated derivatives **37** in 41% and 25% yields, respectively (Scheme 8).

Direct functionalization of trehalose

In 1972, Hanessian and Lavallée[91,92] extended their strategy of direct bromination of primary sugar alcohols to trehalose and prepared 6-bromotrehalose (37%) and 6,6′-dibromotrehalose (62%) by reacting trehalose directly with triphenylphosphine and *N*-bromosuccinimide (NBS). Corresponding 6-chloro, 6-iodo and 6,6′-di-halo derivatives of trehalose were also



Scheme 8: Regioselective acetolysis of primary benzyl groups.

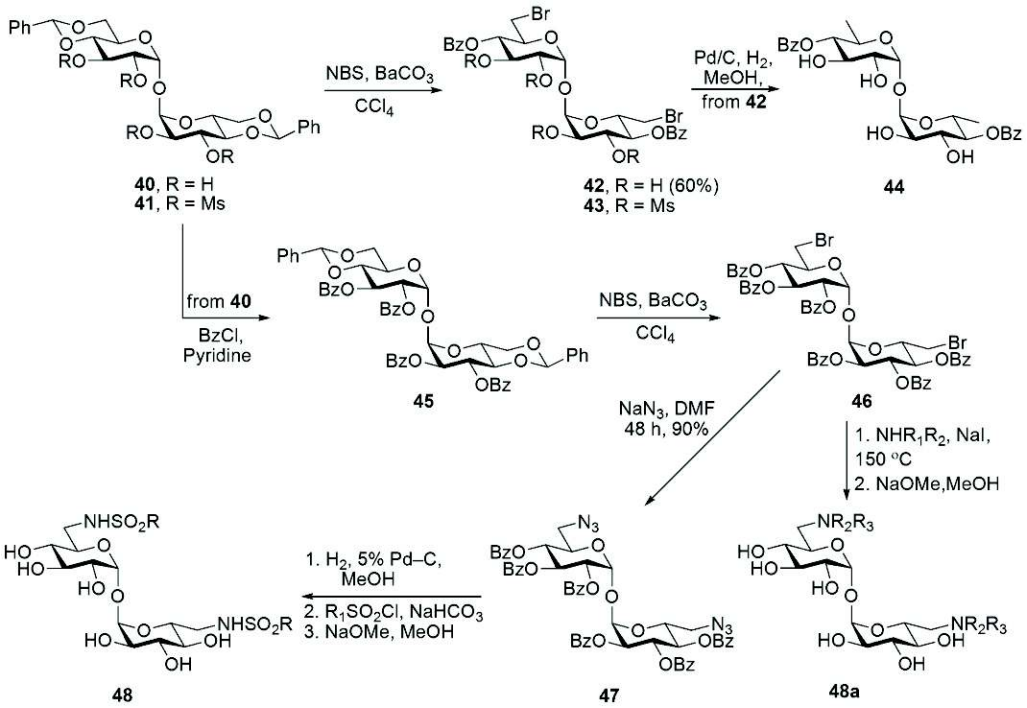


Scheme 9: Direct iodination of trehalose and synthesis of 6,6'-diazidotrehalose.

prepared. The methodology was used for the synthesis of several 6-mono-and 6,6′-difunctionalized trehalose derivatives such as 6-aminotrehalose,[92,93] cord factor and its analogs,[73,94] and guanidine glycosides of trehalose[95,96] *via* displacement of the primary bromide group with suitable nucleophiles.

Mitsunobu reaction has been also used for the direct functionalization of unprotected trehalose at the primary position, to synthesize cord factor and its analogs using diisopropyl azodicarboxylate (DIAD), triphenylphosphine (PPh_3) and the corresponding acid.[97-99] The direct conversion of trehalose to its 6,6′-di-iodo derivative **38**[100] and its subsequent azide displacement to obtain 6,6′-diazido **39** was a key step in the synthesis of trehalose based cyclodextrin analogs (cyclotrehalans) (Scheme 9).[100-106] The diazido derivative **38** has been also utilized for synthesizing glycopolymers of trehalose *via* click reaction with dialkyne-amide co-monomers containing 1,2, or 3 Boc-protected secondary amines.[107,108]

Trehalose was selectively functionalized at the primary position to obtain 6-mono or 6,6′-



Scheme 10: Opening of benzylidene acetal with NBS and transformations of the 6,6'-dibromotrehalose.

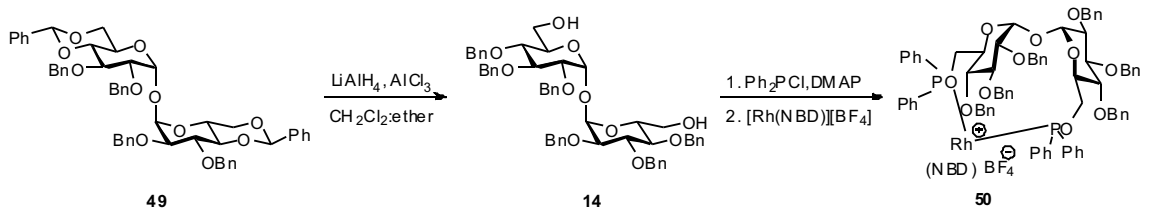
phosphates,[109,110] cord factor analogs,[111] trehalose dipeptide,[112] carboxymethyl and quaternary ammonium derivatives of trehalose[113] and pseudo-cord factor analogs with 6,6′-dicarboxyltrehalose[114] *via* selective oxidation of the primary alcohol.[115] A synthesis of cord factor analog is also reported using $(Bu_3Sn)_2O$ mediated regioselective acylation of **1** with corresponding acyl chloride.[116]

Enzymatic and chemo-enzymatic routes

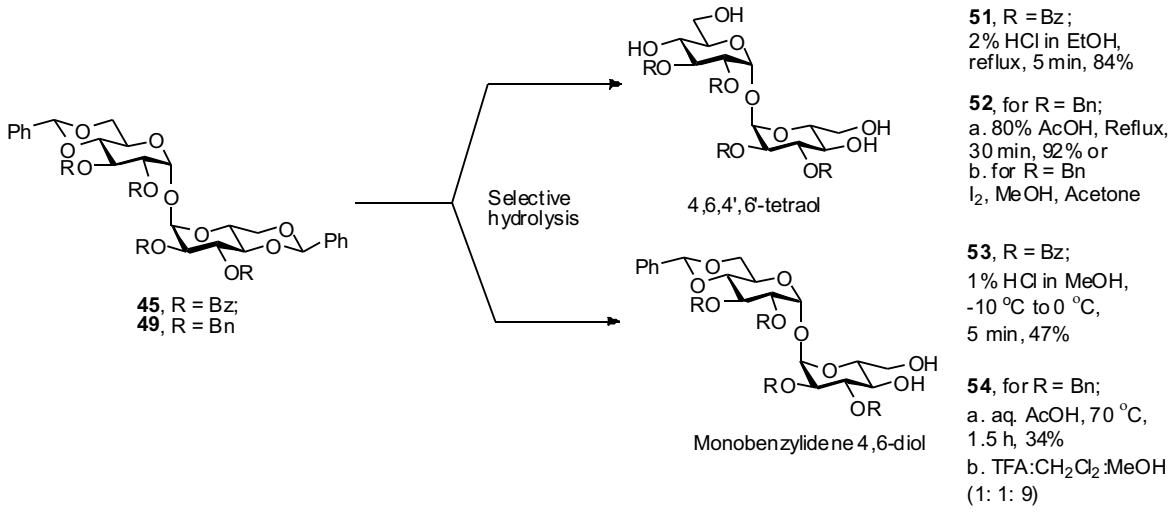
Various enzymes have been used for the synthesis of 6-acyl and 6,6′-diacyl trehaloses.[87,117-124] Trehalose was glycosylated stereospecifically at O3, O4 or O6 positions to obtain diverse oligosaccharides.[125-129] Very recently, Csuk and co-workers reported a chemo-enzymatic synthesis of a maradolipid.[87] They used alcalase from *Bacillus licheniformis* for carrying out mono-acylation of trehalose as a key desymmetrization step. The intermediate monoester was then acylated by chemical means *via* Mitsunobu reaction using DIAD, PPh_3 and HMPA.

Benzylidene acetals for regioselective differentiation of trehalose

Over the years, benzylidene acetals have been used as a useful tool for protecting the 4,6-diols of trehalose for its conversion into symmetric and non-symmetric derivatives. Generally, the 4,6-diols are masked in the form of benzylidene acetals to expose the 2,3-diols, which can then be protected with different protecting



Scheme 11: Regioselective benzylidene ring opening of **49** and synthesis of organometallic complex **50**.



Scheme 12: Partial or complete hydrolysis of benzylidene acetal of **45** and **49**.

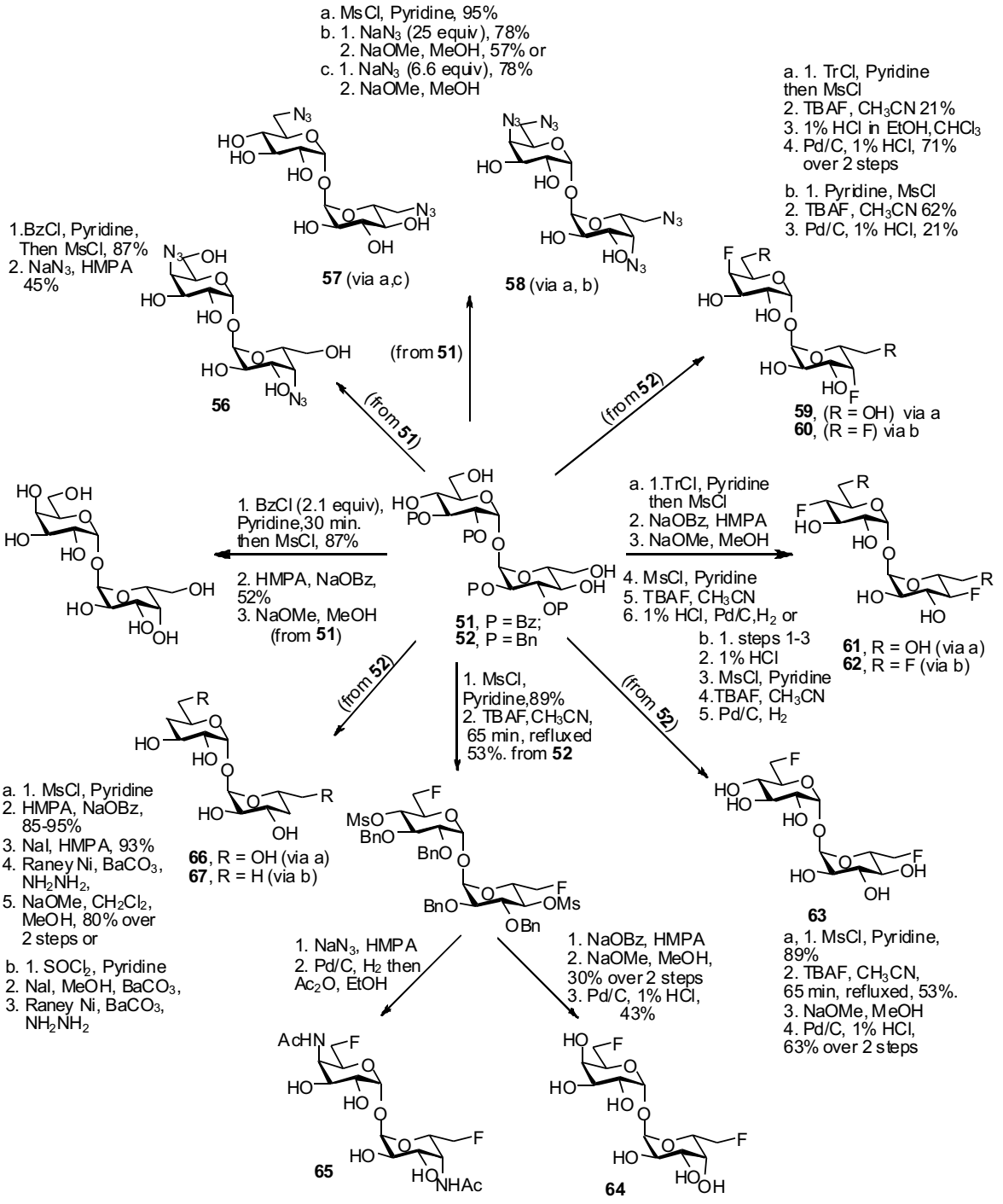
groups. The benzylidene acetals can be hydrolyzed completely to access 4,4′,6,6′-tetraols.[130-132] Alternatively, partial hydrolysis of a dibenzylidene derivative of trehalose or partial benzylidenation of trehalose under controlled conditions affords mono-benzylidene protected trehalose derivatives.[70,133,134] Moreover, the benzylidene derivatives can be regioselectively cleaved under reductive conditions to access 4-OH or 6-OH trehalose derivatives or they can be oxidatively opened using Hanessian's conditions[135] of NBS to obtain 6,6′-dibromo compounds. These useful transformations constitute a well-established route to access regioselectively protected trehalose derivatives.

Hanessian and Plessas[135] in 1969 attempted the first ever ring opening reaction of di-benzylidene trehalose **40**/**41** to produce 6,6′-dibromotrehalose derivatives **42**/**43** (60%). Hydrogenation of **42** afforded the C6 deoxygenated trehalose derivatives **44** (Scheme 10). The NBS method was extended by Reynolds and co-workers to benzoylated derivative **45** to obtain the corresponding dibromo derivative **46**, which upon azide displacement gave 6,6′-diazido derivative **47** in excellent yields.[136] Compounds **46** and **47** were in turn converted into various alkylamine and sulphonamide derivatives **48** bearing different alkyl or sulphonamide chains.

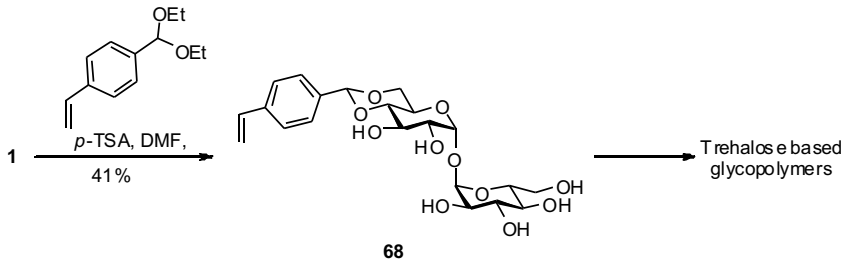
RajanBabu and co-workers[137] prepared trehalose 6,6′-diol **14** from trehalose di-benzylidene acetal derivative **49** *via* regioselective reductive ring opening using LAH-$AlCl_3$ combination (Scheme 11). The 6,6′-diol **14** was further converted into chiral organometallic complex **50** with Rh metal, which was used for enantioselective hydrogenation of dehydroamino acids.[137,138]

Richardson and co-workers published a series of papers on chemical modification of trehalose *via* manipulation of 4,6-*O*-benzylidene acetals.[139] Their pioneering work led to the synthesis of trehalose based synthetic deoxy, amino, fluoro- and galacto- analogs.

Acid catalyzed hydrolysis of the benzylidene acetals is used to gain access to both symmetric 4,4′,6,6′-tetraol and un-symmetrical 4,6-diol by controlling the reaction conditions (Scheme 12). The protected dibenzylidene acetal **45** was hydrolyzed by using 2% ethanolic HCl[130] under reflux conditions to obtain the tetra-ol derivative **51**. Similarly, hydrolysis of **49** is reported by using 80% acetic acid[131] or I_2 in methanol.[132] On the other hand,



Scheme 13: Syntheses of various amino-, fluoro-, and deoxytrehaloses by Richardson and co-workers.



Scheme 14: Synthesis of monobenzylidene acetal **68**

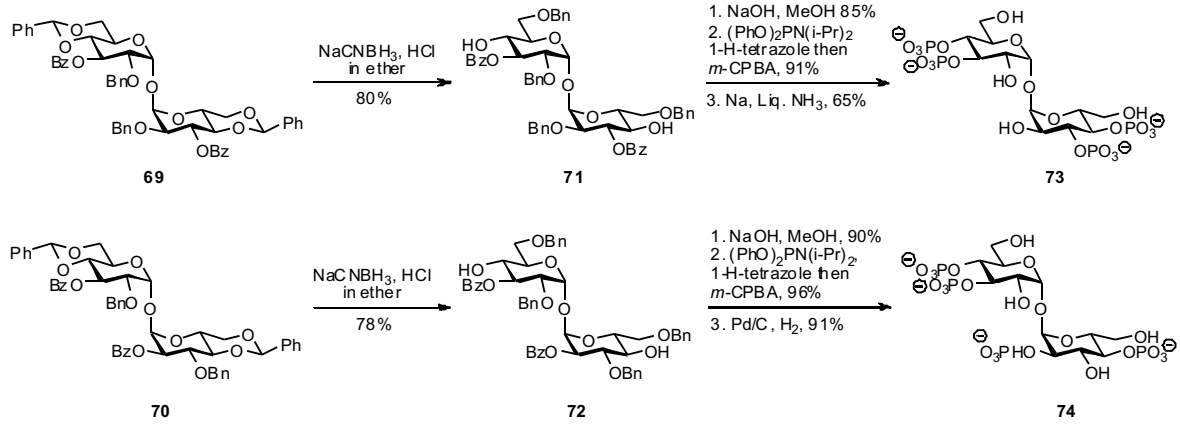
selective mono-benzylidene derivatives **53**/**54** were obtained using 1% HCl in Methanol[133] or aq. AcOH, 70 °C,[134] or TFA- methanol conditions.[70]

The tetra-ol **51** and **52** were transformed into panoply of derivatives using various displacement reactions (Scheme 13). For example, **51** was converted into galactotrehalose derivative **55** by displacement of the mesylates.[130] Similarly, 4,4′-diazido **56** or 6,6′-diazido **57** and 4,4′,6,6′-tetraazido derivative **58** of trehalose were synthesized by azide displacement of corresponding mesylates.[140] The 6,6′-hydroxyls in **52** were protected as trityl ethers and the remaining 4,4′-hydroxyls were converted into mesylates which were concomitantly displaced by TBAF to generate 4,4′-difluoro derivative **59**.[141] Similarly, a direct mesylation of tetra-ol **52** followed by treatment with excess TBAF and refluxing for prolonged time (5 d) gave 4,4′,6,6′-tetrafluoro galacto trehalose derivative **60**.

The 6,6′-dityrityl-4,4′-dimesyl-trehalose was converted to galactotrehalose by displacement of the two 4,4′-mesylate groups with NaOBz.[142] The 4,4′-diol obtained after saponification was mesylated and converted to 4,4′-difluorotrehalose **61.** Alternatively, after the gluco-galacto epimerization step, deprotection of trityl group, mesylation of 4,4′,6,6′-tetraol and subsequent fluoride displacement of mesylates give access to the tetrafluoro derivative **62**. Similarly treatment of the 4,4′,6,6′-tetramesylate with TBAF for 65 min under reflux conditions followed by global deprotection offered 6,6′-di-fluoro trehalose **63**, which was similarly transformed *via* 4,4′-epimerization into 6,6′-di-fluoro galactotrehalose **64** and 4,4′-diamino-6,6′-difluorotrehalose **65**.[143]

Richardson and co-workers also prepared 4,4′-di-deoxy and 4,4′,6,6′-tetra-deoxy derivatives of trehalose **66** and **67** by reductive dehalogenation of the corresponding iodide or chloride, respectively, by using hydrazine hydrate and Raney-Ni.[144] Apart from these analogs, many research groups developed syntheses of cord factors and their analogs using tetra-ol **52** as starting material *via* displacement of sulfonates or by direct acylation.[132,144-148]

The unsymmetrical mono-benzylidene acetal **54** was used for the synthesis of the mono-fluoro,[149] mono-



Scheme 15: Opening of benzylidene acetals in **69** and **70** using $NaCNBH_3$ and synthesis of tetraphosphates **73** and **74**.

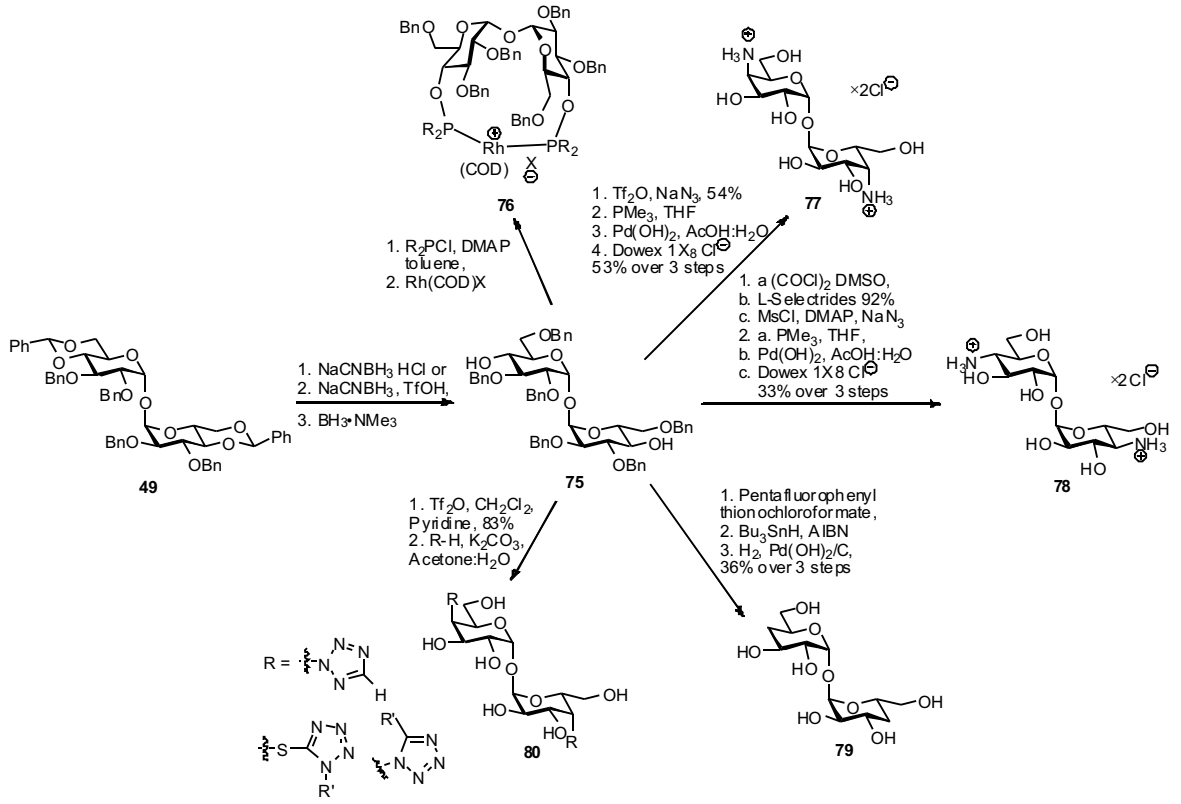
amino,[143] 4,6-difluoro,[150] galactoglucotrehalose,[151,152] 4,6-diamino derivatives using similar strategies.[143] 4,6-Diol **54** was also utilized in the synthesis of oligosaccharides containing unsymmetrical trehalose core *via* O6 benzylation followed by glycosylation at O4.[153-155]

A direct method to prepare a substituted mono-benzylidene trehalose derivative was recently reported by Maynard and co-workers (Scheme 14). Reaction of 4-vinylbenzaldehyde diethyl acetal and cat. *p*-TSA with trehalose afforded 4-vinyl-benzylidene derivative **68** (41%) along with a significant amount of the corresponding di-benzylidene product. Compound **68** was used for synthesizing a trehalose glycopolymer.[156,157]

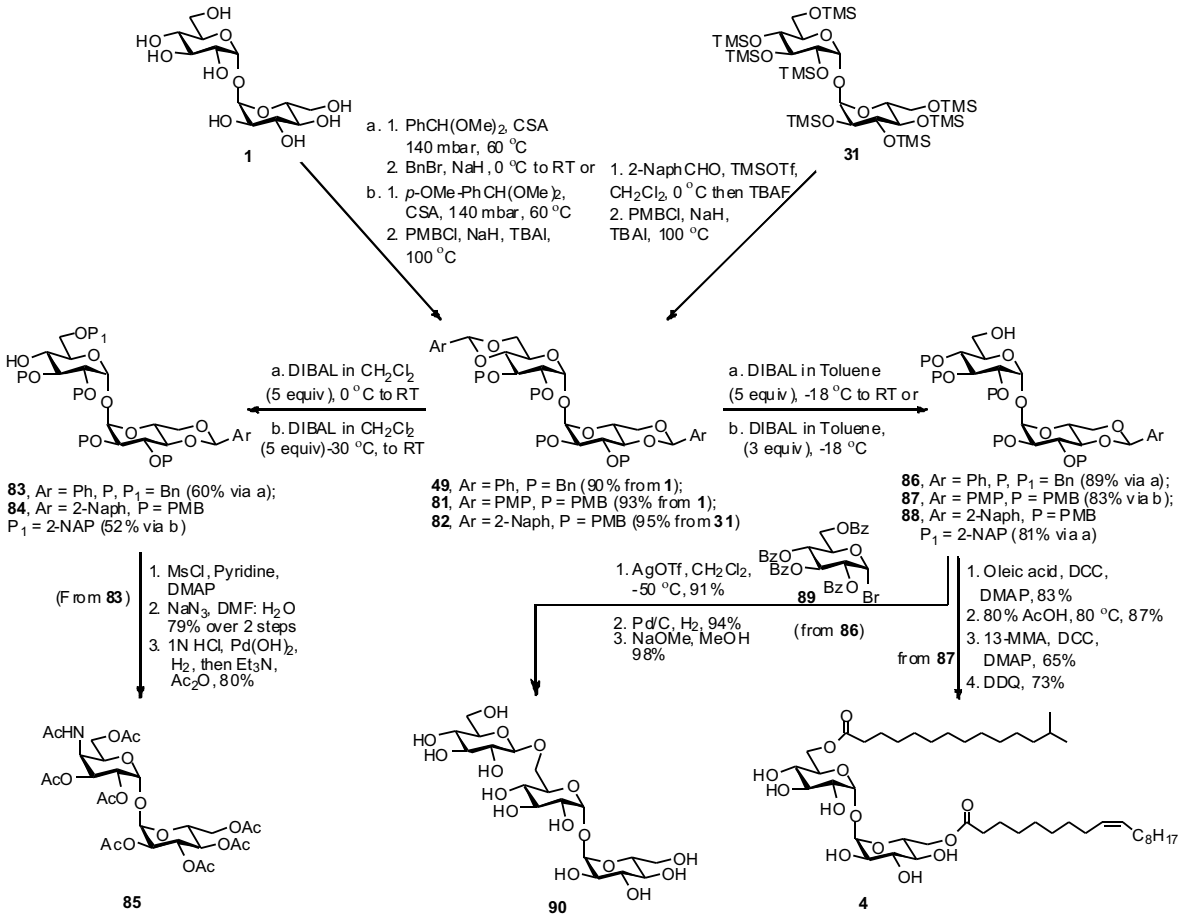
Richardson and co-workers prepared the 4,4′-diol derivatives *via* benzylidene hydrolysis followed by selective tritylation of the primary hydroxyls.[141] Reductive opening of the benzylidene acetal regioselectively at 4,4′-positions is another efficient way which has been accomplished by use of $NaCNBH_3$ in combination with various acid catalysts,[70,158-160] $BH_3{\cdot}NMe_3$-$AlCl_3$[161] and Et_3SiH-$FeCl_3$[163] combinations.

Potter and co-workers reported synthesis of 2,4,3′,4′- and 3,4,3′,4′-tetraphosphonates by regioselective ring opening of trehalose dibenzylidene acetal derivatives bearing benzyl and benzoyl groups at 2,3-position (Scheme 15).[158]

The symmetric and unsymmetrical derivatives **69** and **70** were synthesized by using tin-mediated reactions. Reductive ring opening reactions of **69** and **70** using $NaCNBH_3$ and HCl, went well producing the ring opened product **71** and **72** in 80% and 78% yields, respectively. The tetra-ols obtained after saponification of the benzoyl groups were phosphorylated and catalytic debenzylation resulted in symmetrically and un-symmetrically phosphorylated trehalose derivatives **73** and **74**.



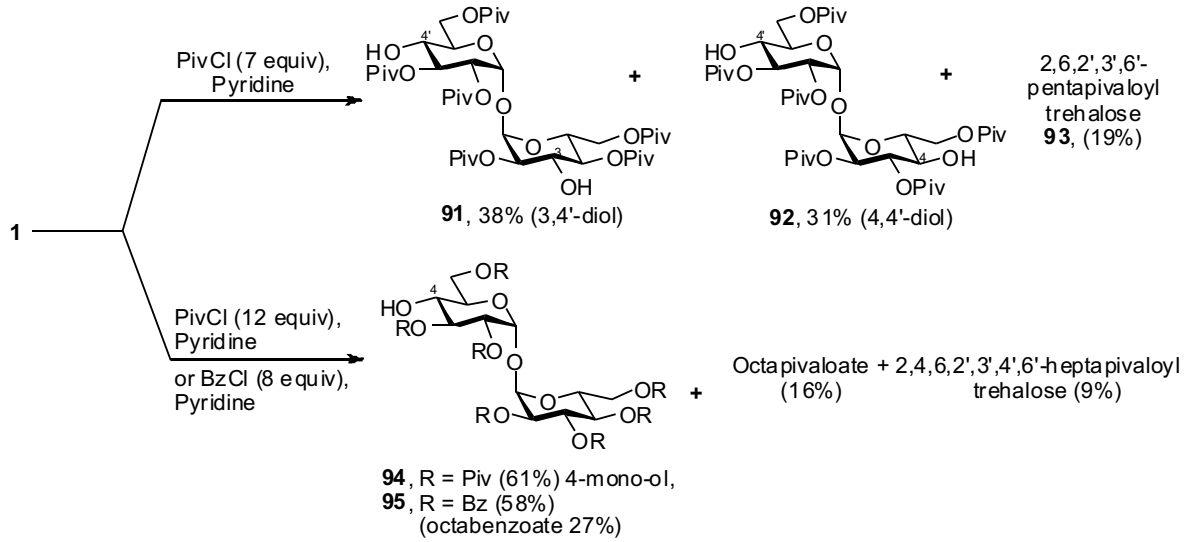
Scheme 16: Regioselective opening of benzylidene acetals in **49** at 4,4′-position, and transformations of 4,4′-diol **75**.



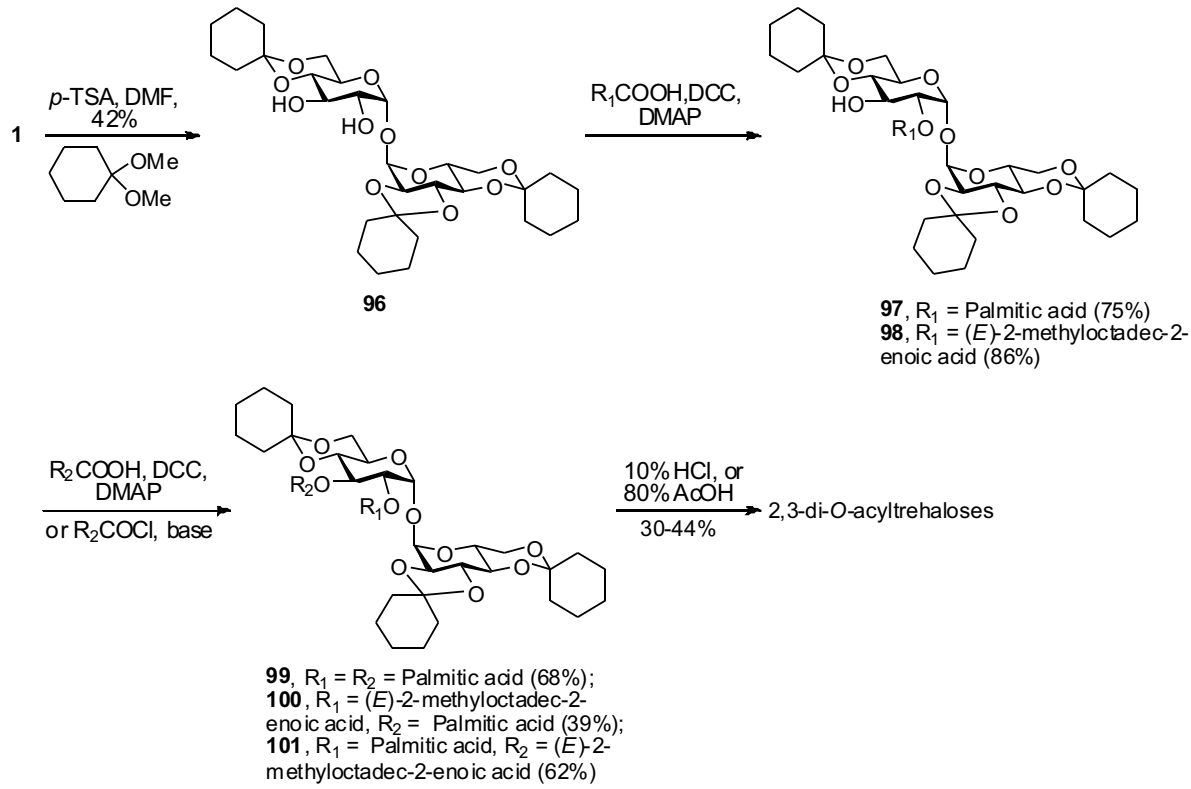
Scheme 17: Regioselective opening of one of the benzylidene acetal of **49**, **81**, **82** and Synthesis of **85**, **90** and maradolipid **4**.

RajanBabu and co-workers (Scheme 16) also reported the opening of the dibenzylidene acetal **49** at 4,4′-positions using $NaCNBH_3$/HCl to obtain the symmetric derivative **75**.[137] Further the diol **75** was converted into bisphosphinite ligands which were complexed with Rh metal to form a complex **76** which was further used for enantioselective hydrogenation of dehydroamino acids.[137,138] Tom Chang and co-workers prepared **75** by ring opening of **49** using $BH_3.NMe_3$ and employed it in the synthesis of trehalose 4,4′-diammonium hydrochloride derivative **77** *via* displacements of the corresponding triflates by azides with inversion of configurations.[161] Alternatively they also employed Swern oxidation of the 4,4′-diol **75** followed by L-Selectride reduction to effect epimerization followed by mesylation and azide displacement to access **78**. The compounds were screened for their biological activities against *Mycobacterium smegmatis*.[161,162] Bertozzi and co-workers used $NaCNBH_3$ and TfOH combination to obtain **75** and prepared a 4,4′-dideoxy derivative **79** by deoxygenation of the free hydroxyl groups *via* xanthate reduction.[70] dos Santos *et. al.* synthesised 4,4′-substituted heterocyclic derivatives of trehalose **80** by S_N2 displacement of the 4,4′-bis-triflate intermediate with inversion of configurations.[160]

Regioselective reductive opening of one of the benzylidene acetals constitutes a short route for desymmetrization of trehalose. Recently, we carried out a systematic study to establish conditions for selective ring opening of only one of the 4,6-*O*-benzylidene groups of the trehalose dibenzylidene acetals and substituted benzylidene acetals at O6 or O4, by using DIBAL solution in toluene or in CH_2Cl_2, respectively to get access to un-symmetrically substituted 6-OH and 4-OH trehalose derivatives (Scheme 17).[89] This method is especially useful for synthesis of various un-symmetrically substituted trehalose glycoconjugates.



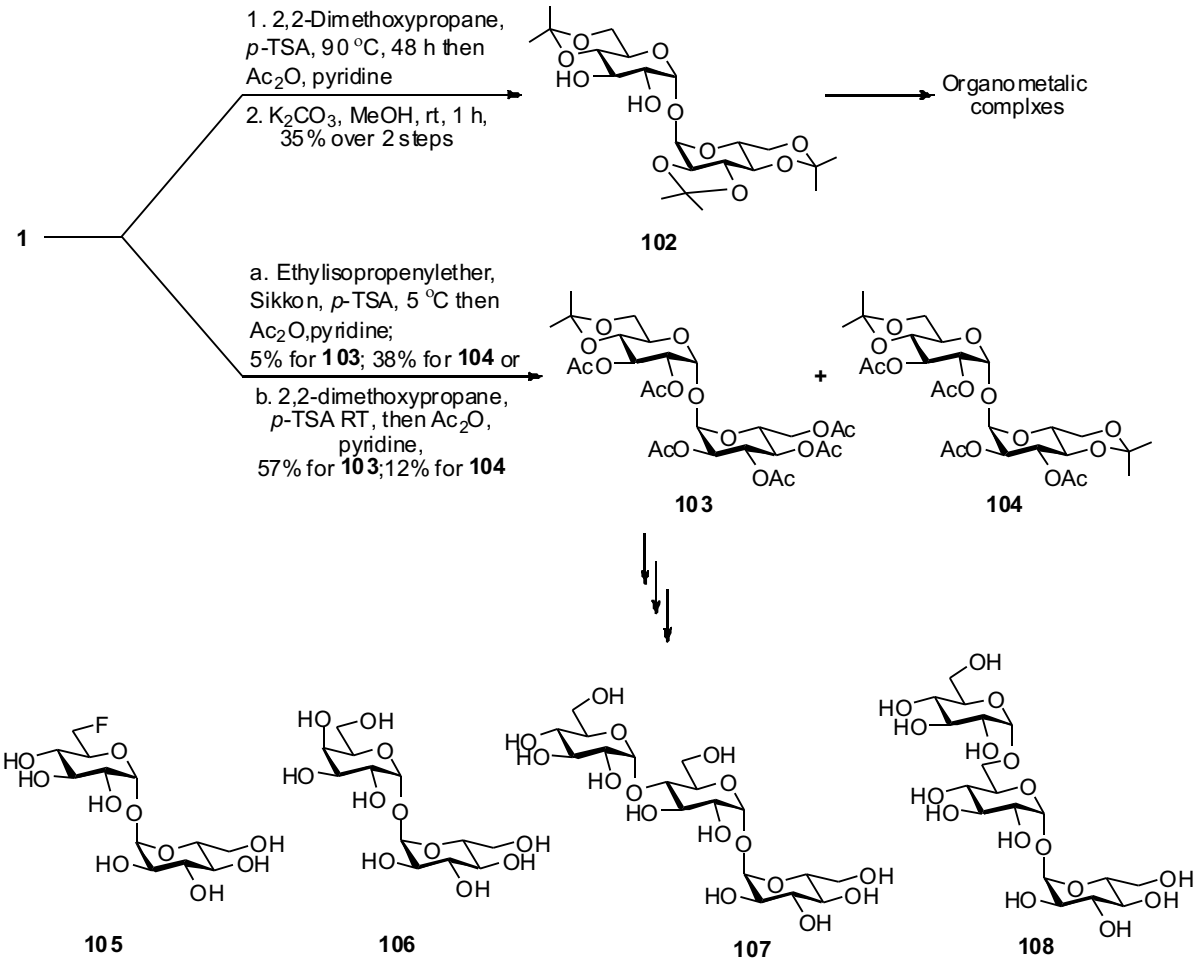
Scheme 18: Regioselective pivaloylation or benzoylation of trehalose.



Scheme 19: Synthesis tricyclohexylidene acetal and 2,3-diacyl trehaloses by Wallace and Minnikin.

Compound **49** when subjected to regioselective ring opening using 5 equiv. DIBAL in CH_2Cl_2, effected ring opening of only one benzylidene acetal at 4-position to give 4-OH derivative **83** (60%). On the other hand, reaction of **49** with DIBAL in toluene afforded 6-OH derivative **86** (89%) with complete reversal of regioselectivity. Substituted benzylidene acetals **81** and **82** also gave good selectivity in acetal opening with DIBAL in toluene to afford 6-OH derivatives **87** (83%) and **88** (81%). The reaction of the 2-naphthylidene acetal **82** with DIBAL in CH_2Cl_2 was also successful and produced **84** with a free 4-OH, whereas PMP acetal **81** was proved to be very reactive towards the DIBAL and regioselectivity in the ring opening could not be reversed.

The unsymmetrical derivatives **83, 84, 86-88** are suitable for synthesis of trehalose glycoconjugates as the necessary protecting group pattern is established and the substituted benzylidene acetals and the PMB group can be removed in the final step without disturbing sensitive functionalities. The free 4-OH **83** was converted to its azido epimer by displacement of the corresponding triflate (79%), removal of the protecting groups followed by acetylation to afford compound **85** (80%). The 6-OH derivative **86**, was used for the synthesis of trisaccharide **90** *via* its stereoselective coupling with glycosyl bromide **89** (91%) followed by global deprotection (92% over 2 steps). Compound **87** with a free 6-OH group, was utilized in the synthesis of a maradolipid **4** *via* a sequence of DCC mediated coupling of **87** with oleic



Scheme 20: Synthesis of acetonide derivatives of trehalose and their transformations.

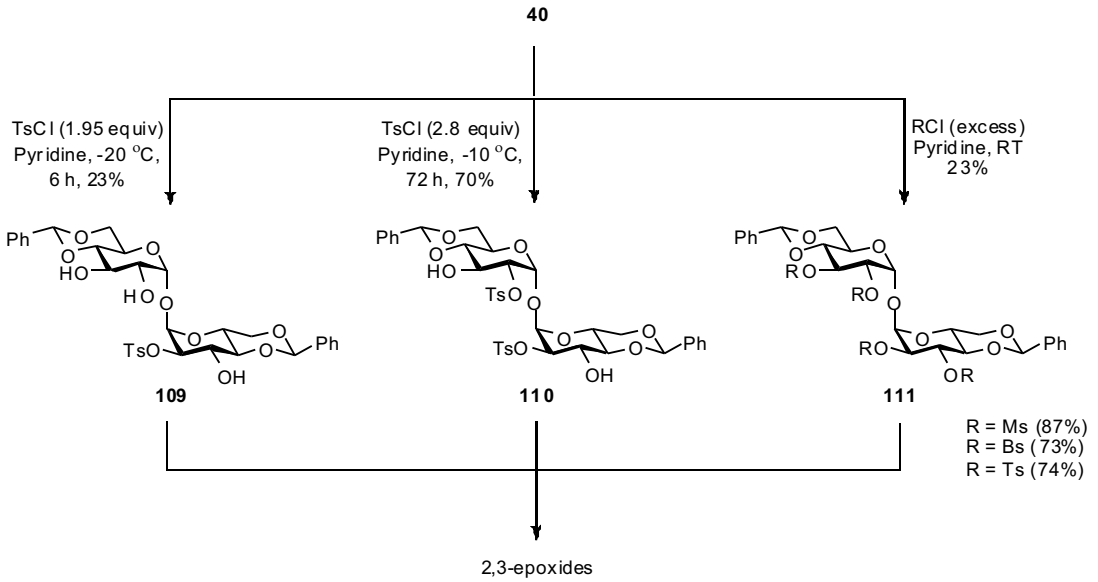
acid (83%), acid catalyzed hydrolysis of PMP acetal (87%), selective acylation of primary hydroxyl group with 13-methyl myristic acid (65%) and oxidative removal of PMB groups using DDQ (73%).

The 4-OH derivatives of trehalose can also be obtained by direct acylations (Scheme 18). Richardson and co-workers reported that treatment of trehalose with 7 equiv. of pivaloyl chloride in pyridine gives a mixture of 3,4′-diol **91** (38%), 4,4′-diol **92** (31%) and 3,4,4′-triol **93** (19%), while treatment with 12 equiv. of PivCl gives the 4-OH hepta-pivaloate derivative **94** (61%) as a major product along with the octa-pivaloate (16%) and 3-OH trehalose derivatives (9%).[164] Similarly, Nashed and co-workers reported a reaction of trehalose with 8 equiv. of BzCl that afforded 4-OH hepta-benzoate derivative **95** (58%) along with the octabenzoate (27%).[165-167] The unsymmetrical 4-OH derivatives **94** and **95** were transformed into various gluco- and galacto- trehalose derivatives (chloro, azido, amino, hydroxy) *via* nucleophilic displacements.[166,167]

Tricyclohexylidene acetal

One of the most elegant examples of desymmetrization of trehalose core using regioselctive protection is perhaps the tricyclohexylidene derivative **96** prepared in one step by Wallace and Minnikin (Scheme 19). Reaction of trehalose with 1,1-dimethoxycyclohexane (8 equiv.) and cat. *p*-TSA afforded unsymmetrical **96** (42%) along with symmetrical dicyclohexylidene derivative (39%). The obvious merit of this method lies in generating an unsymmetrical derivative of trehalose with 2,3-hydroxyl groups free for further functionalization. Wallace and Minnikin used it further for synthesizing diacyltrehalose isolated from *Mycobacterium fortuitum* and its analogs.[168-170] Interestingly, a DCC mediated coupling of 2,3-diol **96** with palmitic acid or (*E*)-2-methyloctadec-2-enoic acid afforded the 2-acyl derivatives **97** (75%) and **98** (86%), respectively, with high regioselectivity. Sequential acylation of **97** under the same conditions gave 2,3-di-palmitoyl trehalose **99** (68%). Alternatively, the second acylation on **97** and **98** were done under basic conditions using stoichiometric acid chloride and imidazole or 4-pyrollidinopyridine to obtain **100** (39%) and **101** (62%), respectively. The cyclohexylidene acetals were removed by treatment with aqueous acid (with 10% HCl at 85 °C or 3:1 acetic acid: water at 85 °C) to furnish 2,3-diacyl trehaloses.

The tricyclohexylidene derivative **96** was contemporaneously used by RajanBabu and co-workers[137] and Uemura and co-workers[171,172] for the synthesis of chiral 2,3-bisphosphinites by reacting with diarylphosphine chloride with cat. DMAP as a base. The bisphosphinite ligands were complexed readily with Rh (I) metal salt followed by removal of tricyclohexylidene acetals to synthesize chiral trehalose based metal complexes. Both the protected and unprotected complexes were used for asymmetric hydrogenation of dehydroamino acids and their esters in high enantioselectivity.

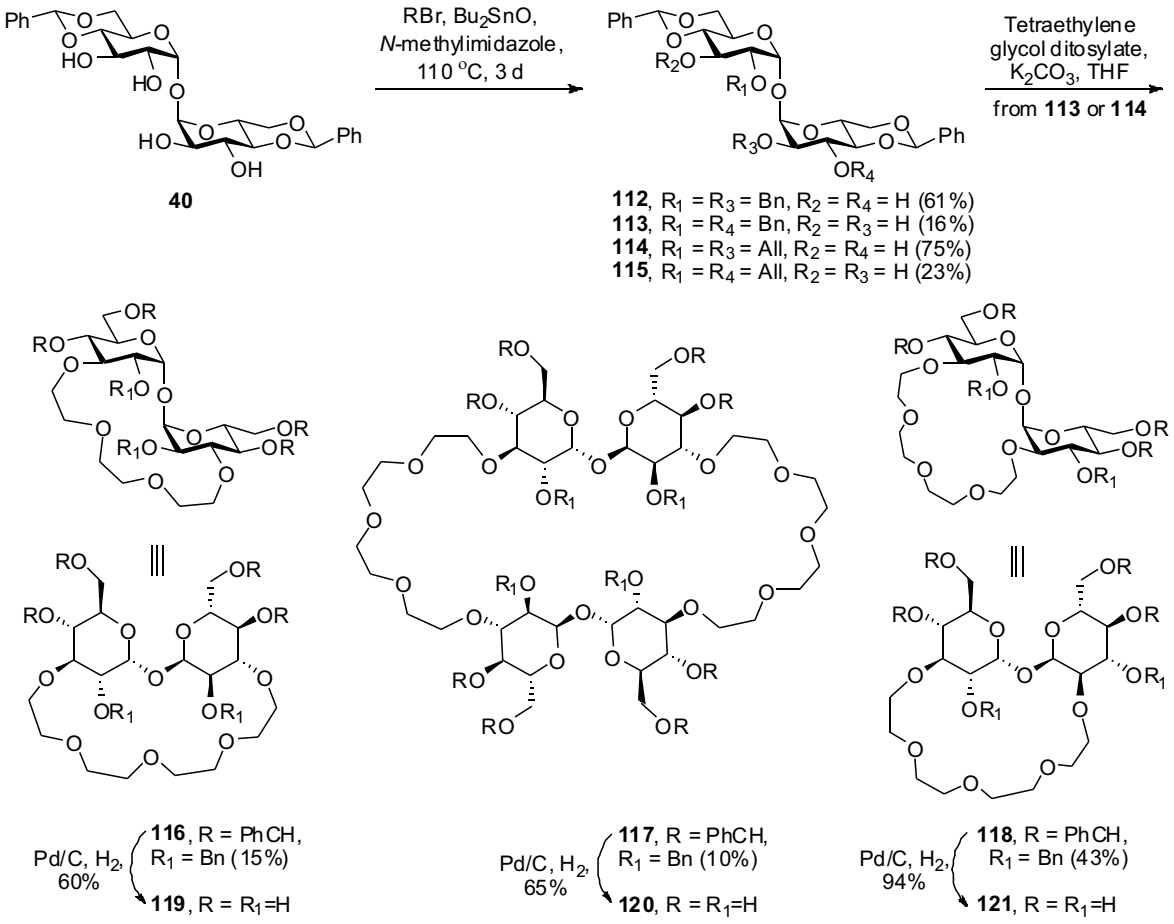


Scheme 21: Synthesis of regioselectively tosylated derivatives of **40**.

Uemura and co-workers also used the tri-isopropylidene acetal (acetonide) as an alternative to the tricyclohexylidene acetal.[171,172] Reaction of trehalose with 2,2-dimethoxypropane in DMF and cat. *p*-TSA at 90 °C gives (after per-*O*-acetylation and Zémplen deacetylation) a similarly tri-protected 2,3-diol trehalose derivative **102** (35%) (Scheme 20).[171] Earlier Bar-Guilloux and co-workers reported that the reaction conducted at 0-5 °C using ethylisopropenyl ether and a dehydrating agent Sikkon gives a mixture of mono and diacetonide derivatives **103** (5%) and **104** (38%).[173] The monoacetonide **103** was obtained with improved yields of 57% by carrying out the reaction of trehalose with 2,2-dimethoxypropane in the presence of *p*-TSA as acid catalyst.[174,175] The 4,6-diol prepared by deprotection of acetonide has been used for the synthesis of unsymmetrical fluorotrehalose **105** as well as galacto-trehalose **106**,[173] and also for the synthesis of 4- or 6-monoglycosylated trehalose derivatives **107** and **108**.[174] Lipták and co-workers employed the monoacetonide derivative **103** for the synthesis of the tetrasaccharide from *M. kansasii*.[176] Azuma and co-workers also utilized the unsymmetric 4,6-diol to prepare 6-deoxy-6-mycoloylamino trehalose and further joined it with 6-*O*-(aminoacyl)-muramoyl dipeptide using a succinic acid unit.[177]

Regioselective transformations at O2 and O3 positions by making use of benzylidene acetal

Tosylation of trehalose dibenzylidene acetal **40** under basic conditions offers 2-*O* selectivity (Scheme 21). By controlling the stoichiometry of the tosyl chloride in pyridine and temperature, the 2-monotosyl trehalose **109** (1.95 equiv. TsCl, -20 °C, 6 h, 23%), 2,2′-ditosyl trehalose **110** (2.8 equiv. TsCl, -10 °C, 72 h, 70%), and



Scheme 22: Regioselective Bu_2SnO mediated alkylations of **40**, and synthesis of trehalose based crown ether analogs.

2,2′,3,3′-tetratosyl trehalose **111** (excess TsCl, RT, 74%) were obtained.[178] Richardson and co-workers ingeniously utilized these compounds for the synthesis of the 2,3-mono or 2,3,2′,3′-diepoxides by base catalyzed displacement of the sulfonates.[178] These epoxides were further exploited for the synthesis of the 2,2′-dideoxytrehalose,[179] 3,3′-dideoxytrehalose,[180,181] 2-deoxy 2-aminotrehalose,[179] 2,3-dideoxy 2-aminotrehalose,[181,182] and other symmetric or unsymmetrical deoxy derivatives of trehalose as well as C-4 epimers of cord factor.[183-187]

The di- or tri-ester derivatives prepared by regioselective tosylation[188,189] or benzoylation[189,190] of trehalose were converted *via* oxidation of the unprotected 3-OH or 3,3′-diols into 3-monoketo or 3,3′-diketo derivatives, respectively, which were eventually transformed into the *allo*-analogs of trehalose through stereoselective reductions.[188-190]

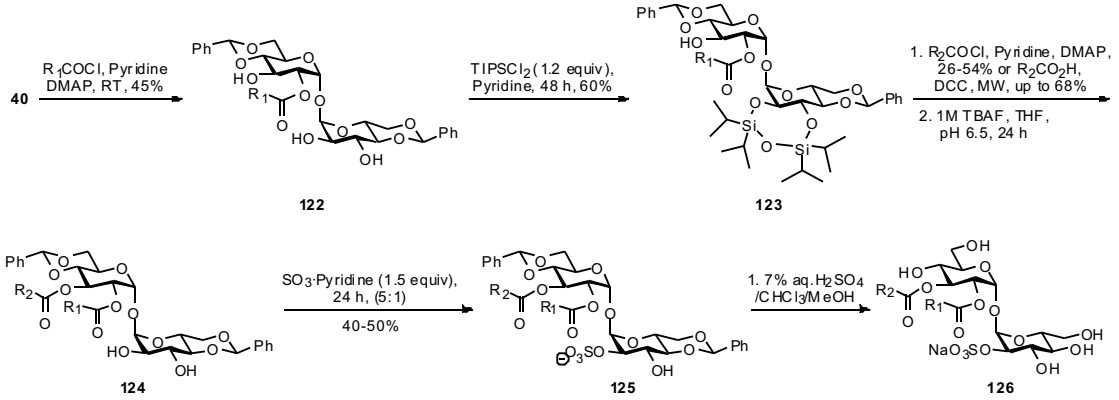
Very recently, Zhang and co-workers prepared 2- or 3-dodecyltrehalose derivatives by controlled alkylation of tetra-ol **40** with dodecyl bromide employing NaH as base.[191] The 2-*O*- and 3-*O*-monoalkylated derivatives were obtained as a 1:1 mixture in 40% yield.

Tin-mediated reactions

Penadés and co-workers reported that Bu_2SnO mediated alkylation of tetra-ol **40** give good 2-O selectivity (Scheme 22).[192] They obtained 2,2′-di-*O*-benzyl-4,6;4′,6′-di-*O*-benzylidene trehalose **112** (61%) along with 2,3′-di-*O*-benzyl-4,6;4′,6′-di-*O*-benzylidene trehalose **113** (16%) in the presence of *N*-methylimidazole as catalyst. The reaction was found to be less selective in the absence of the imidazole catalyst (**112**, 33% and **113**, 12%). Using this method, they also prepared the *O*-allylated derivatives *viz.* 2,2′-di-*O*-allyl-4,6;4′,6′-di-*O*-benzylidene **114 (**75%), and 2,3′-di-*O*-allyl-4,6;4′,6′-di-*O*-benzylidene trehalose **115** (23%). The 3,3′-diol derivative **112** was reacted with the ditosylate tetraethylene glycol with K_2CO_3 as a base under reflux conditions in THF to obtain two crown ether derivatives *viz.* mono-*trehalo*-3,3′-tetraethylene glycol **116** (15%) and bis-*trehalo*-3,3′-tetraethylene glycol **117** (10%), while the reaction of 2,3′-diol **113** resulted in single crown ether **118** (43%).[193] Global deprotection of **116-118** afforded trehalose containing chiral crown ethers **119-121.**

Synthesis of Ac_2SGL

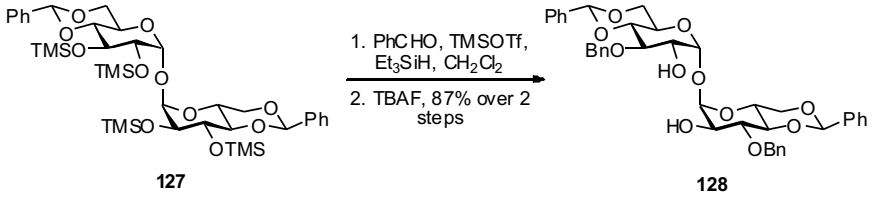
Sulfated trehalose glycolipids are studied due to their potent immunogenic activity. Goren and co-workers showed that sulfation of the tetraol **40** can be carried out regioselectively at O2 using SO_3·pyridine complex in 40% yield while the O3 isomer is isolated in minor amounts (8%).[194] In 1993, Baer and Wu devised a general strategy for the synthesis of 2,3- and 2,3′-diacyl trehalose making use of Bu_2SnO mediated selective acylation reactions.[195] Under the conditions, reaction of tetraol **40** with palmitoyl chloride (1.2 equiv.) gave a monoacylated 2′,3,3′-triol in 66% yields. The 2-monoester triol was then protected at 2′,3′-position as a silylidene acetal with 1,3-dichloro-1,1,3,3-tetraisopropyl disiloxane in 40% yield and the remaining hydroxyl group was acylated to obtain fully protected 2,3-diacyl trehalose. On the other hand, tin-mediated acylation using 2 equiv. of palmitoyl chloride resulted in a 2,3′-diacylated product in 35% yields. The silylidine and benzylidene acetals were smoothly removed using 1 M TBAF in dioxane and I_2 in methanol,



Scheme 23: Synthesis of Ac_2SGL analogs by Prandi and co-workers.

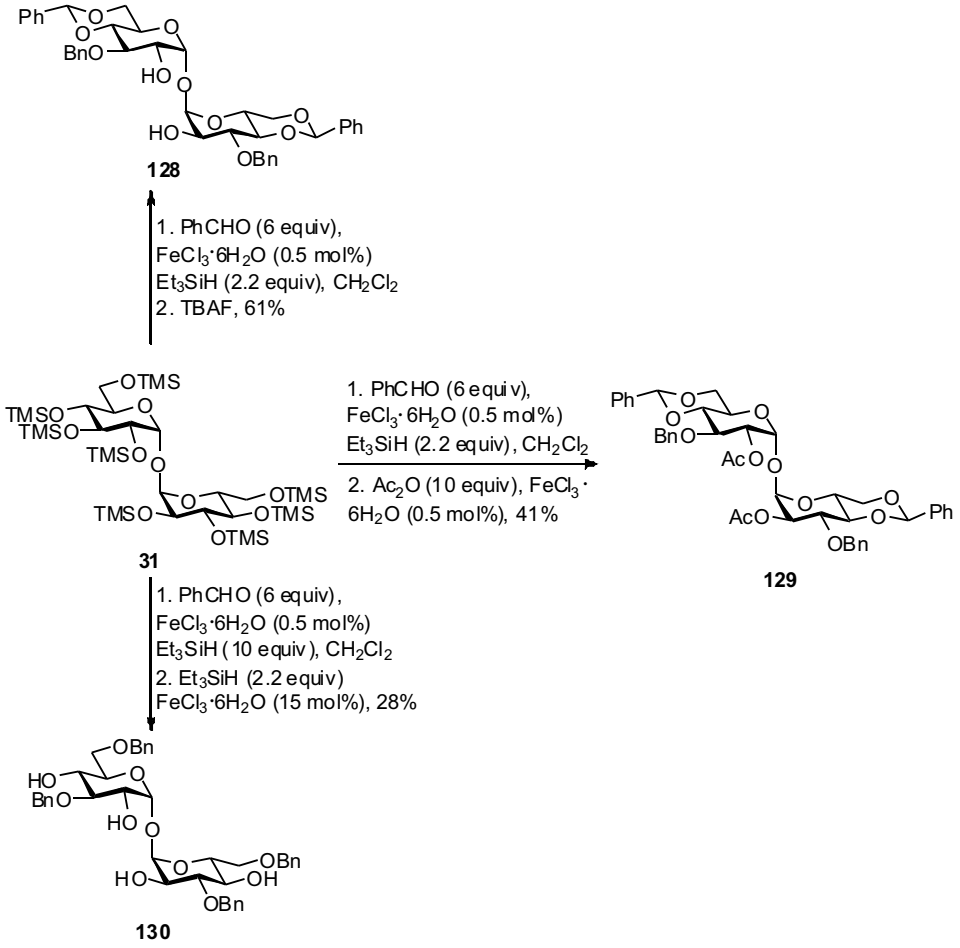
respectively, in 80% overall yields.

In 2004 Gilleron *et al.* isolated 2,3-diacyl-2′-sulfate-α,α-trehalose (Ac_2SGL) from *Mycobacterium tuberculosis* and is considered to be a potent TB antigen.[17] In 2008, Prandi and co-workers employed a modified strategy to achieve the first synthesis of analogs of the natural Ac_2SGL in which the hydroxyphthioceranoyl moiety had been replaced by less complex esters (Scheme 23).[196] By obviating the tin-mediated acylation, palmitoylation was successfully carried out on **40** using palmitoyl chloride in pyridine to obtain 2-monopalmitoyl derivative **122** (45%), which was then silylidenated with 1,3-dichloro-1,1,3,3-tetraisopropyl disiloxane (60%) to get the same intermediate **123** synthesized earlier by Baer and Wu. The remaining hydroxyl was acylated with several non-



127 **128**

Scheme 24: Reductive benzylation of **127** at 3,3'-position by Hung and co-workers.



128 **31** **129** **130**

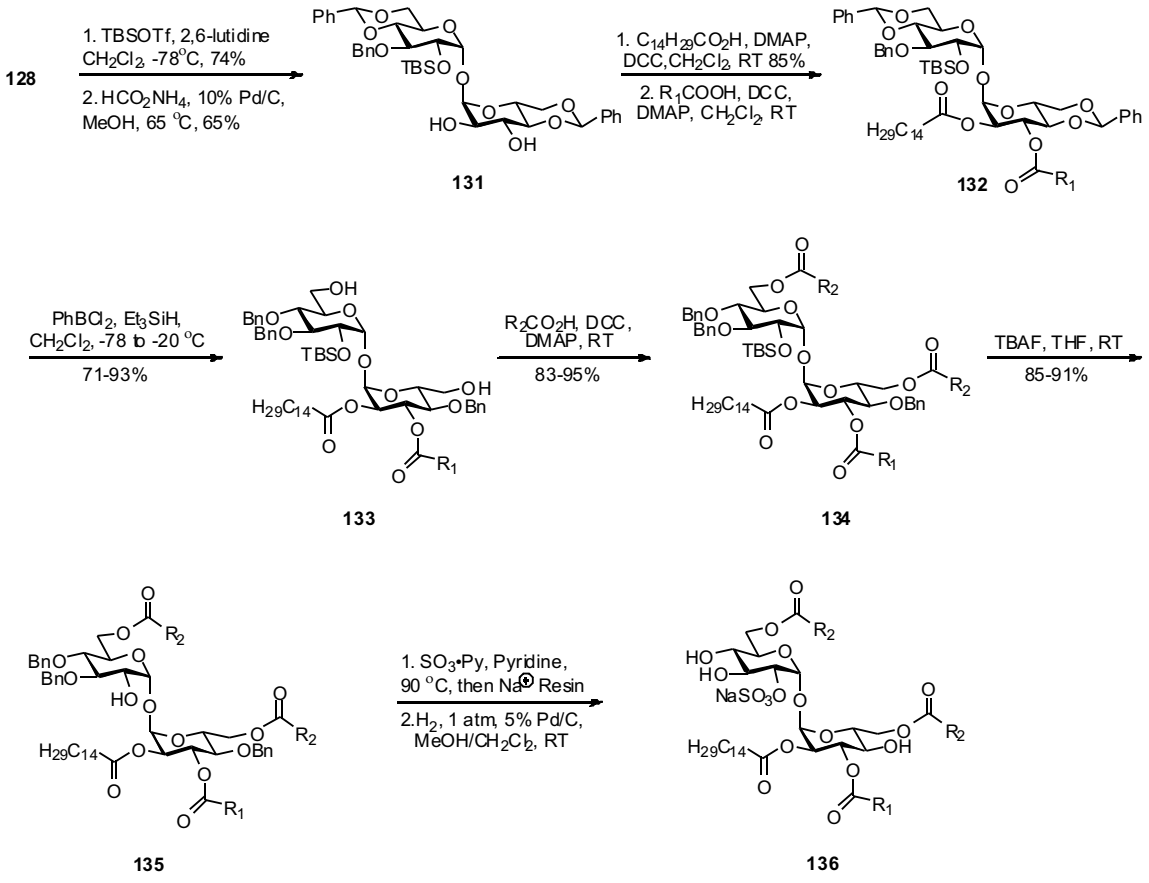
Scheme 25: Beau's one-pot protection strategy for trehalose.

methylated to polymethylated analogs of hydroxyphthioceranic acid of variable chain length (yields upto 68%).[196] Removal of the silyl protection using TBAF in AcOH (pH 6.5) generated the 2,3-diol **124** in 90% yield. A regioselective sulfation with SO_3-pyridine generated the corresponding 2-*O*-sulfated analog as a major product along with the 3-*O*-sulfated by-product (ratio 5:1, 40-50%) **125**. The protecting groups were removed by acid hydrolysis to obtain the corresponding sulfated diacyl trehalose derivatives **126**.

Recently, Minnaard and co-workers synthesized the hydroxyphthioceranic acid and thereby completed the first synthesis of Ac_2SGL **7** essentially using Prandi's method.[197] The difficulties encountered in the second acylation step during analog preparation due to the steric crowding of silylidine acetal were circumvented by conducting the acylation of hydroxyphthioceranic acid using 2,4,6-trichlorobenzoyl chloride in Et_3N and DMAP catalyst. Also, the regioselective sulfation was carried out cleanly using 2,2,2-trichloroethoxysulfuryl-*N*-methylimidazolium triflate in 61% yield.

Regioselective 3,3′-reductive etherification of trehalose dibenzylidene acetal

Regioselective tosylation and Bu_2SnO mediated alkylation or acylation can be used to protect the 2,2′-positions. The selective protection of 3,3′-hydroxyl groups is also desired as many trehalose based glycolipids are functionalized at the O2 position. Hung and co-workers developed the reductive 3-*O*-etherification strategy for monosaccharides and the same was extended to the disaccharides including trehalose.[201] 2,2′,3,3′-Tetra-*O*-TMS-4,6;4′,6′-dibenzylidene trehalose **127** was subjected to reductive etherification using benzaldehyde and triethylsilane in the presence of TMSOTf as a catalyst (Scheme 24). Deprotection of the remaining TMS group by using TBAF in the same pot generated 3,3′-di-OBn derivative



Scheme 26: Synthesis of SL-1 analogs by Beau and co-workers.

128 (87%).

One-pot protection of trehalose

One-pot protection strategy is well established for monosaccharides,[202-204] but it is not much explored for trehalose due to increased number of hydroxyl groups and complexity. Beau and co-workers (Scheme 25) extended the one-pot protection strategy for the synthesis of regioselectively protected trehalose derivatives.[163] The octa-TMS-trehalose **31** was subjected to 4,6,4′,6′-dibenzylidene acetal formation using PhCHO and $FeCl_3 \cdot 6H_2O$ catalyst followed by reductive etherification using Et_3SiH, to produce **128** (61% yield) in a one-pot manner. A sequential benzylidene formation, reductive benzylation and acetylation afforded fully protected **129** (41%). Likewise, a one-pot benzylidene formation, reductive benzylation and regioselective ring opening at 4,4′-positions using Et_3SiH gave **130** (28%).

Synthesis of SL-1

SL-1 is a mycobacterial sulfated glycolipid isolated by Middlebrook *et al*.[18] in 1959 and characterized and identified as a virulence factor of MTb by Goren[19-21] in 1970. It is a trehalose based tetraacyl derivative sulfated at 2-position of one of the glucose units. The nonsulfated glucose unit is acylated at 2′ and 3′ with palmitic or stearic acid at 2′ and thioceranic acid at 3′-position. The primary 6 and 6′ positions bear hydroxythioceranoyl group. Due to the high degree of regioselectivity in acylation and chiral polymethylated side chains there is no total synthesis reported for this molecule to date. Bertozzi and co-workers synthesized a simpler analog of SL-1 *via* IAD approach.[205] Complex trehalose glycolipids such as SL-1 analogs provide a perfect testing ground for any regioselective protection protocol. Very recently, Beau and co-workers came up with a strategy for the synthesis of SL-1 analogs with simpler acyl chains at the appropriate positions and the sulfate group at 2-position (Scheme 26).[206] The key intermediate 3,3′-di-OBn derivative **128** was obtained as described earlier using one-pot protection. Selective monosilylation of one of the 2-hydroxyl groups was employed as a symmetry breaking operation. Controlled debenzylation using Pd/C in the presence of ammonium formate resulted in the deprotection of the less hindered benzyl group at 3′-position to generate 2,3-diol **131**. DCC mediated di-acylation of **131** with palmitic acid or sequential monoacylations with palmitic acid and monomethylated acids offered compound **132**. At this stage, the dibenzylidene acetals were opened at 6,6′-position to obtain 6,6′-diol **133**, which was acylated with the monomethylated acid to obtain tetraacyl trehalose **134**. The TBS group was selectively deprotected by using TBAF providing 2′-OH derivative **135**. Sulfation of the mono-ol **135** with $SO_3 \cdot$pyridine followed by catalytic hydrogenolysis gave tetraacylated sulfolipids **136.**

Conclusion

Trehalose containing glycoconjugates have thus received immense attention from synthetic chemists. Progress in this area has always been centred on the ways to differentiate the hydroxyl groups of trehalose. Over the years, several protecting group strategies have been developed, for this purpose, including various ethers, acetals as well as ester-type protecting groups. These protocols have opened up new doorways to access a diverse array of symmetrical and unsymmetrical trehalose derivatives. The efforts have culminated into syntheses of a variety of glycolipids such as DATs, SL-1 analogs, maradolipids and Ac_2SGL as well as other trehalose glycoconjugates. The ready access to trehalome would help in understanding the biological functions of trehalose glycoconjugates over the years to come.

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