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Desymmetrization of trehalose *via* regioselective DIBAL reductive ring opening of benzylidene and substituted benzylidene acetals†

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Trehalose dibenzylidene and substituted dibenzylidene acetals were reductively opened either at O6 or O4 in a regioselective manner by using a DIBAL stock solution prepared in toluene or dichloromethane, respectively, to achieve desymmetrization of the trehalose core. The method was applied to synthesize various biologically important unsymmetrically substituted trehalose glycoconjugates, including a mycobacterial trisaccharide, a 4-*epi*-trehalosamine analog and a maradolipid.

Trehalose **1** [α-D-Glc-(1 → 1)-α-D-Glc] (Fig. 1) is a C_2 symmetric, non-reducing disaccharide present in several organisms. Trehalose glycolipids and lipooligosaccharides form an important class of biologically active compounds, most of which are related to *M. tuberculosis*[1–5] while some are found in fungi and worms. These glycoconjugates are challenging synthetic targets due to their highly amphiphilic character and structural diversity, which includes additional functional groups, chiral centres of the side chains and, most importantly, the point of attachments to the trehalose core. Some of them comprise a non-symmetrically substituted trehalose core with substituents attached at O4 or O6. For example (Fig. 1), a maradolipid **2** was recently isolated[6] from *C. elegans* and it has been correlated with the dauer larvae resistance. It is the first diacylated trehalose glycolipid found in the animal kingdom and also the first 6,6′-unsymmetrically substituted trehalose glycolipid reported so far.

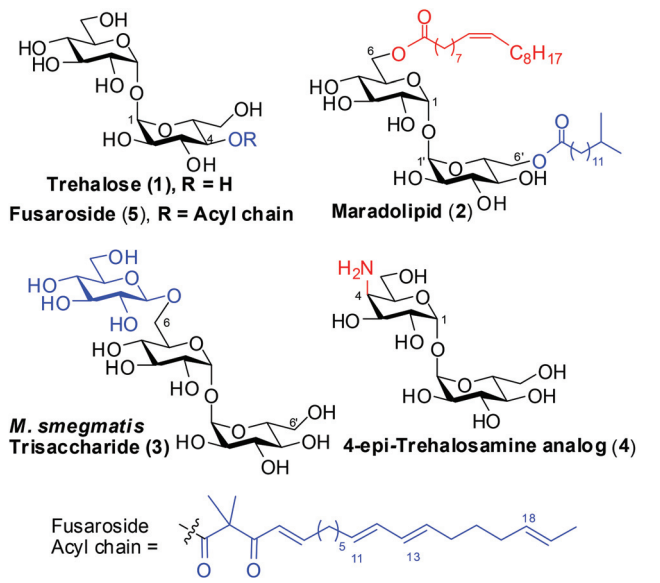

Fig. 1 Various biologically important glycans containing unsymmetric trehalose core.

Likewise, trisaccharide **3** from *M. fortuitum*[7] and *M. smegmatis*,[8] consisting of a β-linked D-glucosyl unit attached to one of the O6 of the trehalose, is a representative member of a group of O4/O6 linked trehalose based oligosaccharides which are thought to impart stability to mycobacteria during stress and latency. Trisaccharide **3** was earlier isolated from yeast as well.[9] Several trehalosamine derivatives have been evaluated for their potential antibiotic activity.[10,11] The C4 epimer of the 4-amino-4-deoxy-α,α-trehalose **4** is an attractive target.[12] Very recently, a unique trehalose glycolipid fusaroside **5** was isolated[13] from an endophytic fungus, *Fusarium* sp. LN-11. It is composed of a trehalose unit attached at O4 to the carboxylic carbon of a rare, branched long-chain fatty acid (C20 : 4) comprising a conjugated diene moiety and a conjugated ketone moiety. Fusaroside **5** has been shown to be moderately active against brine shrimp larvae. Similarly, several other unsymmetrical trehalose glycoconjugates are shown to be involved in a wide range of biological activities.[1,2]

Synthesis of unsymmetrically substituted trehalose glycoconjugates is a formidable task as it requires either the differentiation of eight hydroxyl groups of trehalose **1**[5] or stereoselective construction of 1,1-α,α-linkage between the two appropriately protected glucose units.[14] Installation of this α,α-1,1-linkage *via* coupling of protected D-glucose derivatives

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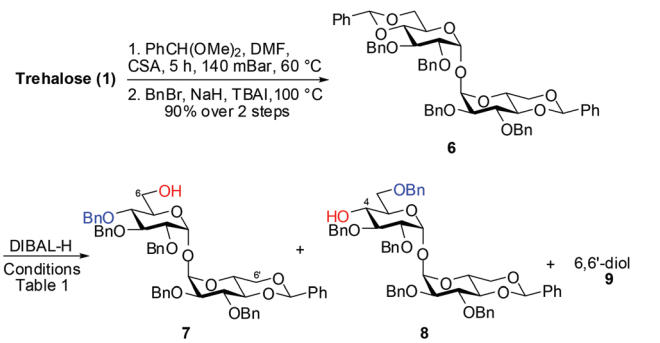
is very difficult, as not one but two anomeric linkages are formed simultaneously. To tackle this problem, Bertozzi and coworkers developed an intramolecular aglycon delivery (IAD) approach for stereoselective formation of α,α-1,1-linkage.[15,16] An alternative approach is to use commercially available trehalose. However, desymmetrization of the C_2 symmetrical disaccharide trehalose **1** *via* regioselective protection is again a challenge. Most of the trehalose glycoconjugates have modifications at C4 or C6 positions of trehalose. A number of methods have been reported for selective O6 mono-protection of trehalose[5,17–21] whereas reports on selective O4 functionalization[22–24] are rare and involve longer protection deprotection sequences.

Regioselective reductive ring opening of 4,6-*O*-benzylidene and substituted 4,6-*O*-benzylidene acetals is routinely used to obtain the 6-OH or 4-OH derivatives of various sugars.[25–34] We envisioned that a selective ring opening of only one of the 4,6-*O*-benzylidene groups of the trehalose dibenzylidene acetals, carried out under controlled conditions, would give access to unsymmetrically substituted trehalose derivatives. Although seemingly straightforward, this approach has not been developed for desymmetrization of trehalose. As such, there are only a few reports on the reductive ring opening of symmetrical 4,6,4′,6′-di-*O*-benzylidene derivatives of trehalose to obtain the corresponding symmetric diols.[11,16,35–37] For the mono-opening of bis-acetals, Wessel and Minder reported that in the case of an unsymmetrical 3-deoxy 4,6,4′,6′-di-*O*-benzylidene trehalose derivative, the benzylidene acetal close to the deoxy centre is found to be more reactive under $NaCNBH_3$/HCl conditions, leading to the corresponding 4-OH (51%) as a major product along with the minor 6-OH (22%).[38] However, this method does not apply to naturally occurring C_2 symmetric trehalose. Recently, Bertozzi and coworkers observed that the reaction of a 4,6,4′,6′-di-*O*-dibenzylidene derivative with the $NaCNBH_3$–TfOH combination led to an inseparable mixture of 4-mono and 4,4′-di opened products in modest yields.[35] To the best of our knowledge, there are no reports on the regioselective O6 mono-opening of trehalose dibenzylidene acetals. Herein, we present the first systematic study to establish the reaction conditions of regioselective DIBAL reductive ring opening of benzylidene and substituted benzylidene acetals of trehalose to give facile access to the corresponding 6-OH or 4-OH derivatives of trehalose. Application of this method to the synthesis of trehalose glycoconjugates **2–4** is demonstrated.

From the array of reagent combinations available for the ring opening of benzylidene acetals, we opted for DIBAL owing to its operational simplicity and the flexibility to change the course of the reaction to obtain either 6-OH or 4-OH derivatives by merely changing the solvent and temperature conditions. Takano *et al.*[32] first employed DIBAL for the regioselective ring opening of benzylidene acetals. Subsequently, Mitsunobu and coworkers[33] extended these studies to carbohydrates and found that the bulk and orientation of the C3 protecting group play a crucial role in determining the mode of regioselection. Nokami and coworkers[34] further showed that the regioselectivity of the DIBAL reductive ring opening can be controlled by using DIBAL stock solutions prepared in different solvents. Thus, in the case of methyl 2,3-di-*O*-benzyl-4,6-benzylidene-α-D-glucoside, the reaction with DIBAL in toluene gives predominantly the corresponding 6-OH product, whereas the 4-OH product was obtained as a major product when the same reaction was carried out in dichloromethane stock solution. With this background, we conducted a series of experiments on trehalose di-benzylidene acetals. Our results indicate that by carefully tuning the temperature conditions and equivalents of the DIBAL stock solution prepared in toluene or dichloromethane, desymmetrization of the C_2 symmetric trehalose core can be achieved to access the 4-OH or 6-OH trehalose derivatives, respectively.

We began our experiments with the known di-*O*-benzylidene derivative **6**[39] (Scheme 1) which was conveniently prepared by di-benzylidenation of trehalose **1**,[40] followed by benzylation (90%, 2 steps). A systematic study of the regioselective ring opening of **6** using DIBAL in toluene or dichloromethane to obtain the corresponding 6-OH **7** and 4-OH **8** was conducted first. The regioselectivity of ring opening was determined by analyzing the 2D NMR spectra of **7** and **8**. Their COSY spectra showed a correlation of the OH proton with either H6 or H4. This was also confirmed by carrying out the acetylation of 6-OH **7** and 4-OH **8** and observing the downward movement of two (CH_2) or one (CH) proton in ^{1}H NMR, by ~0.5 or 1.5 ppm, respectively. This general procedure was followed for characterization of all the ring opening products reported in the study (see ESI†). The reaction conditions and results are summarized in Table 1. First, compound **6** in toluene was treated with 10 equiv. of 1.5 M DIBAL (supplied as a 25 wt% stock solution in toluene) at −10 °C (entry 1). The starting material was consumed in 1 h and two new, clearly separable spots were seen on TLC, the proportion of which remained unchanged even after 24 h. From this reaction, we obtained the non-symmetric 6-OH derivative **7** in 61% yield along with the C_2 symmetric 6,6′-di-OH trehalose derivative **9**[41] (29%). In order to suppress the formation of **9**, resulting from the ring opening of the second benzylidene acetal, the reaction was conducted at −18 °C using 8 equiv. DIBAL (entry 2). Although this reaction generated the 6-mono opened product **7** exclusively, it was sluggish and led to the recovery of the



Scheme 1 Preparation and ring opening of trehalose dibenzylidene acetal **6**.

Table 1 Regioselective ring opening of benzylidene acetal in **6**

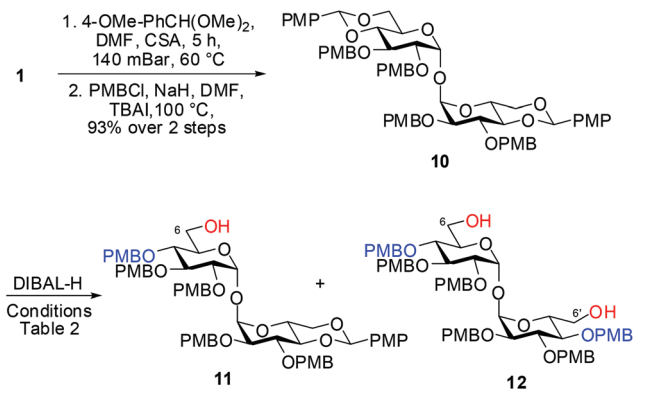
Entry	Reagent (equiv.)	DIBAL (equiv.)	Solvent (mL per 0.1 g)	*T* (°C)	Time (h)	Yield (%) 6	7	8	9
1	DIBAL in toluene	10	Toluene	−10	24	—	61	—	29
2	DIBAL in toluene	8	Toluene	−18	5	36	40	—	—
3[a]	DIBAL in toluene	8	Toluene	−18 to rt	1	—	78	—	19
4[a]	**DIBAL in toluene**	**5**	**Toluene**	**−18 to rt**	**1.5**	**—**	**89**	**—**	**Trace**
5	DIBAL in CH_2Cl_2	5	Neat	rt	1	—	70	—	14
6	**DIBAL in CH_2Cl_2**	**5**	**Neat**	**0**	**1**	**—**	**25**	**60**	**—**
7	DIBAL in CH_2Cl_2	5	Neat	−18 to −10	1	90	—	Trace	—

[a] DIBAL was added at −18 °C and the reaction was immediately moved to rt.

unreacted starting material to the extent of 36%. There was no progress in the reaction after 1 h. To alleviate the reactivity, the DIBAL addition was carried out at −18 °C and the reaction was immediately moved to rt. Under these conditions the desired **7** was obtained in 78% yield but the di-opened product **9** (19%) was encountered again as a minor product (entry 3). Finally, reducing the amount of DIBAL to 5 equiv. under the same conditions circumvented the formation of the di-opened product giving **7** in 89% yield (entry 4). With such success in selective O6 mono opening of **6**, we turned our attention to the O4 mono opening. We first conducted the ring opening reaction using DIBAL stock solution (1 M in dichloromethane) at rt. To our surprise, the reaction generated the 6-opened product **7** (70%) along with the 6,6′-diol **9** (14%). However, the regioselectivity of the reaction was reversed when the same reaction was conducted at 0 °C (entry 6) leading to 4-OH **8** (60%) as a major product and 6-OH **7** (25%) as a minor product. Further reducing the reaction temperature to −18 °C to −10 °C did not help and the starting material was recovered to the extent of 90% (entry 7). Compound **8** had been prepared earlier in 25% overall yield from **6** *via* regioselective benzylidene hydrolysis followed by tin mediated benzylation.[24] ^{1}H NMR data of **8** was in complete agreement with the reported data.

In order to expand the scope of the reaction, we turned our attention to the substituted benzylidene acetals. For this purpose, the *p*-methoxybenzylidene acetal **10** (Scheme 2) was obtained using similar conditions from trehalose **1** in excellent yield (93%, 2 steps). The results of the regioselective DIBAL reductive ring opening of *p*-methoxybenzylidene acetals in **10** are summarized in Table 2. Since *p*-methoxybenzyl (PMB) ethers are more electron donating, as anticipated, compound **10** proved to be more reactive than **6**. Thus, reaction of **10** with 1.5 M DIBAL (supplied as 25 wt% in toluene) under the conditions earlier optimized for **6** for selective mono opening (−18 °C to rt, 1.5 h) in fact furnished the diol **12** (90%) in a rapid manner (entry 1). Conducting the same reaction with a lesser amount of DIBAL (3 equiv.) allowed isolation of the desired 6-OH **11** (34%) along with major 6,6′-diol (61%) (entry 2). The best results were obtained when the DIBAL (3 equiv.) addition was carried out in an ice-salt bath at −18 °C and the reaction was quenched after 15 min without moving it to rt. Under these conditions, the desired 6-OH **11** was obtained in 83% yield (entry 3). Our attempts to open the PMP acetal in **10** in an O4 selective manner, however, met with little success (entries 4–6). The corresponding 4-OH compound could not be obtained; instead **11** and **12** were generated each time. The reaction was too sluggish at −78 °C to allow any conversion.

We next tested the 2-naphthylidene acetal **14** which was efficiently prepared from the known per-*O*-TMS trehalose **13**[36,42] *via* bis-naphthylidenation using 2-naphthaldehyde and TMSOTf[43] catalyst followed by removal of TMS groups using TBAF and its subsequent PMB protection in excellent yield (Scheme 3). The reaction conditions and results of the naphthylidene ring opening reactions of **14** with DIBAL in toluene or CH_2Cl_2 to access the corresponding 6-OH **15** and 4-OH **16** are summarized in Table 3. The conditions earlier optimized for the benzylidene acetal **6** equally worked well for the 6-opening of acetal in **14** using 1.5 M DIBAL in toluene (5 equiv., −18 °C to rt, 1 h) leading to the desired 6-OH **15** in 81% yield (entry 1). For the O4 opening of acetal in **14**, 1 M DIBAL in CH_2Cl_2 was added at 0 °C. However, this reaction afforded 6-OH **15** in 76% yield. Conducting the reaction at −20 °C led to generation of the 4-OH **16** in minor amounts along with major 6-OH **15**. The best results were obtained when the reaction was conducted at −30 °C (entry 4) giving the desired 4-OH **16** (52%) as a major product along with 6-OH **15** (8%) in minor proportions; substantial starting material was recovered (29%).



Scheme 2 Preparation and ring opening studies of Di-PMP acetal **10**.

Table 2 Regioselective ring opening of *p*-OMe-benzylidene acetal in **10**

Entry	Reagent (equiv.)	DIBAL (equiv.)	Solvent (mL per 0.1 g)	*T* (°C)	Time (h)	Yield (%) **11**	Yield (%) **12**
1[a]	DIBAL in toluene	5	Toluene	−18 to rt	1.5	—	90
2[a]	DIBAL in toluene	3	Toluene	−18 to rt	1.5	34	61
3	**DIBAL in toluene**	**3**	**Toluene**	**−18**	**0.25**	**83**	**Trace**
4	DIBAL in CH_2Cl_2	3	Neat	0	0.5	38	45
5	DIBAL in CH_2Cl_2	3	Neat	−45	0.75	25	60
6[b]	DIBAL in CH_2Cl_2	3	Neat	−78	2	—	—

[a] DIBAL was added at −18 °C and the reaction was immediately moved to rt. [b] Starting material was recovered quantitatively.

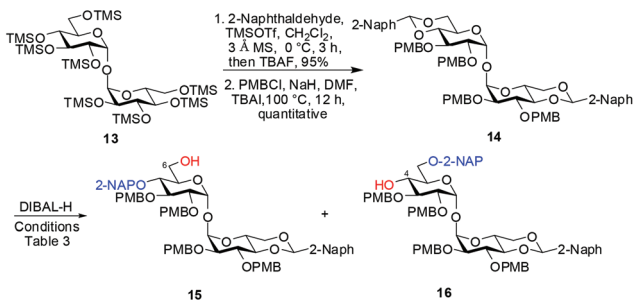
Table 3 Regioselective ring opening of 2-Naph acetal in **14**

Entry	Reagent (equiv.)	DIBAL (equiv.)	Solvent (mL per 0.1 g)	*T* (°C)	Time (h)	Yield (%) **14**	Yield (%) **15**	Yield (%) **16**
1[a]	**DIBAL in toluene**	**5**	**Toluene**	**−18 to rt**	**1**	7	**81**	—
2	DIBAL in CH_2Cl_2	5	Neat	0	1.5	—	76	—
3	DIBAL in CH_2Cl_2	5	Neat	−20	2	—	53	28
4	**DIBAL in CH_2Cl_2**	**5**	**Neat**	**−30**	**2**	**29**	**8**	**52**

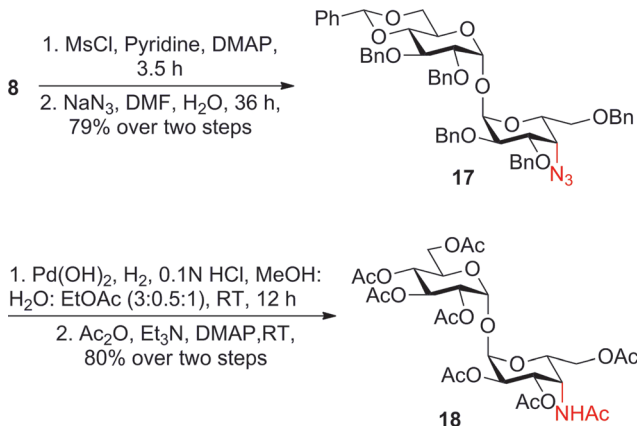
[a] DIBAL was added at −18 °C and the reaction was immediately moved to rt.

Recent mechanistic studies[44–46] have indicated that the regioselectivity of the ring opening reaction depends on a complex interplay of several factors including the solvent, temperature, time, steric factors and the nature of the reducing agent as well as the Lewis acid catalyst.[31] The exact reasons for the observed reversal of selectivity, upon changing the solvent, in the absence of Lewis acid, remain obscure. From a purely practical point of view, this study gives rapid access to the 6-OH (**7**, **11** and **15**) and 4-OH (**8** and **16**) derivatives of trehalose in which a benzylidene or substituted acetal is present at one terminus and the remaining hydroxyls are protected as benzyl or substituted benzyl ethers. These unsymmetrically substituted derivatives can be used for synthesizing a variety of trehalose glycoconjugates as exemplified by the synthesis of **2–4**.

Scheme 4 delineates a short synthesis of the 4-*epi*-trehalosamine analog **4** from **8**. The 4-OH group of **8** was converted into a mesylate group, which was subsequently displaced by sodium azide to obtain the 4-azido trehalose derivative **17** (79%, 2 steps) with inversion of configuration at C4.



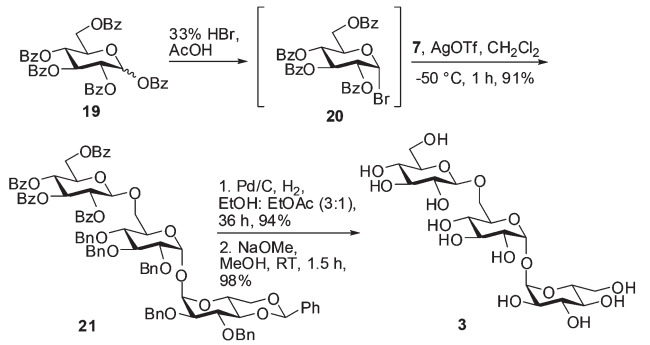
Scheme 3 Preparation and ring opening of Di-2-Naph acetal **14**.



Scheme 4 Synthesis of a 4-*epi*-trehalosamine analog.

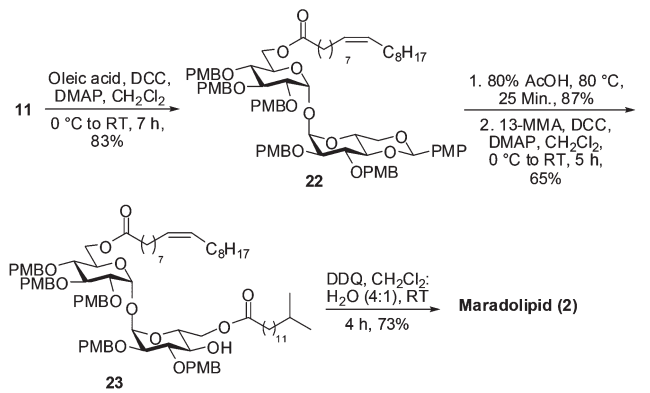
Hydrogenolysis of **17** furnished the 4-amino trehalose derivative **4** which was characterized as its per-acetate derivative **18**. The structure of compound **18** was confirmed by comparison of its ^{1}H NMR and ^{13}C NMR with the literature data.[12]

An efficient synthesis of the trisaccharide **3** found in *Mycobacterium smegmatis*,[7] *Mycobacterium fortuitum*[8] and yeast[9] is presented in Scheme 5. Known D-glucosyl per-*O*-benzoate **19** was first converted into the corresponding glycosyl bromide **20**, which was coupled as such with 6-OH **7** as an acceptor using silver triflate as a promoter to afford the protected trisaccharide **21** (91%). Hydrogenolysis followed by debenzoylation afforded the target trisaccharide **3** in excellent yields. The spectral data of **3** were in perfect agreement with the data of the isolated one.[9] Compound **3** has been earlier synthesized by a different route.[47]



Scheme 5 Synthesis of trisaccharide **3**.

Maradolipid **2** has gained considerable attention from the synthetic community since its isolation in 2010.[6] We reported the first synthesis of **2**[42] using regioselective acylation of the 6,6′-diol trehalose hexa-*O*-TMS derivative as a key step. Subsequently, other groups reported the syntheses of **2**[48–50] and its thioglycoside analog[51] along similar lines employing regioselective acylation as a symmetry breaking step. Herein we report a conceptually different route for synthesis of compound **2** using regioselective reductive ring opening of PMB acetal as a key step (Scheme 6). Benzyl groups are rendered unsuitable for the synthesis of trehalose glycolipids containing lipid chains with unsaturation, because the double bond and the acyl function are susceptible to hydrogenolysis or Birch reduction conditions, respectively. PMB groups on the other hand are orthogonal to these functionalities, as they can be easily cleaved under oxidative conditions by using CAN or DDQ. Accordingly the 6-OH **11** was acylated with oleic acid using DCC and DMAP to obtain **22** (83%). The *p*-methoxybenzylidene acetal in **22** was selectively hydrolyzed using 80% acetic acid and the freed 4,6-diol was regioselectively acylated with 13-methyl myristic acid under DCC conditions to afford **23** (65%). The PMB groups in **23** were removed using DDQ in a facile manner to deliver a maradolipid **2**. The data of **2** corroborated well the earlier reported data of the maradolipid.[6,42] It is expected that coupling of the 4-OH derivative **16** with the appropriate long chain acid can be utilized for the synthesis of



Scheme 6 Synthesis of a maradolipid **2**.

fusaroside **5**. Efforts in this direction are currently underway in our laboratory.

Conclusions

In conclusion, we have established the conditions for desymmetrization of the trehalose core *via* DIBAL reductive ring opening of benzylidene and substituted benzylidene acetals, for the first time, by controlling the reagent stoichiometry, solvent and temperature. The methodology is applied for the synthesis of unsymmetrically substituted trehalose glycolipids and oligosaccharides. The short and convenient method would certainly find its use in the synthesis of complex trehalose glycoconjugates.

Acknowledgements

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