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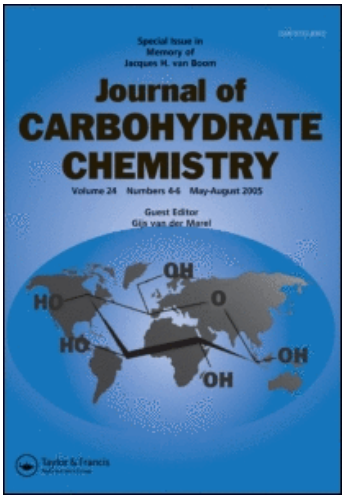

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COMMUNICATION

AN EFFICIENT SYNTHESIS OF 6,6′-DI-*O*-ACYLATED α,α-TREHALOSES†

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The potent immunostimulant and antitumor activity of trehalose 6,6′-dimycolates from mycobacteria has led to a great deal of interest in the synthesis of these glycolipids and their analogs.[1,2] To circumvent the formation of 3,6-anhydro derivatives and other by-products resulting from partial protection strategies, many of the synthetic routes to symmetrical 6,6′-diesters (including dimycolates) of trehalose have utilized trehalose intermediates fully protected at the secondary hydroxyl positions.[2,3] Recently, we described the synthesis of one such intermediate, 2,3,4,2′,3′,4′-hexakis-*O*-trimethylsilyl-α,α-trehalose (**1**), directly from trehalose dihydrate via a novel persilylation/desilylation protocol.[4] Diol **1** and related derivatives have been employed in the preparation of trehalose 6,6′-diesters both by direct acylation methods[3,5-8] and by nucleophilic displacement of 6,6′-dideoxy derivatives possessing various leaving groups on the 6 and 6′-positions.[7-12]

Most of these trehalose esterification methods, however, suffer from one or more drawbacks: direct acylation of diol **1** leads to the formation of isomeric and multiple ester by-products;[12] Mitsunobu[6,13] and carbodiimide[3,5] protocols are incompatible with 3-hydroxy acids, the main lipophilic components of naturally occurring trehalose esters;

† Dedicated to Mayer B. Goren on the occasion of his 75th birthday and in honor of his outstanding contributions to the chemistry and immunochemistry of mycobacterial glycolipids.

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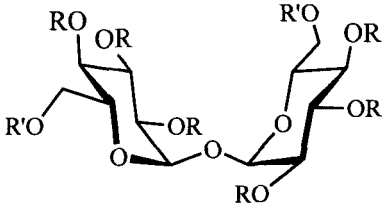
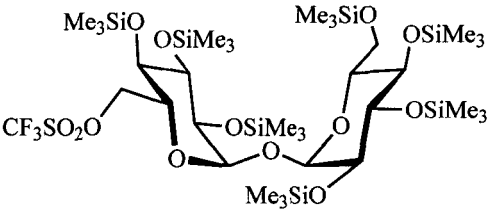
and the syntheses of 6,6′-dihalo[7,9] and other activated[8,10] derivatives of **1** are low yielding, and subsequent nucleophilic displacement with potassium salts requires crown ether catalysis and/or dipolar aprotic solvents such as a hexamethylphosphoramide. Here we describe a new procedure for the efficient preparation of trehalose diesters from **1** which overcomes these disadvantages and obviates the need for hazardous solvents and catalysts.





7

1 R = $SiMe_3$, R' = H
2 R = $SiMe_3$, R' = CF_3SO_2
3 R = $SiMe_3$, R' = n-$C_{15}H_{31}CO$
4 R = $SiMe_3$, R' = $(n\text{-}C_{14}H_{29})_2CHO$
5 R = H, R' = n-$C_{15}H_{31}CO$
6 R = H, R' = $(n\text{-}C_{14}H_{29})_2CHCO$

The biologically active[8,14] diesters **5** and **6** were synthesized in three steps from diol **1** in 65-70% overall yield by employing the highly reactive 6,6′-bis-*O*-trifluoromethanesulfonate (triflate) **2** in conjunction with the anhydrous potassium salts of palmitic and 2-tetradecylhexadecanoic acid.[15] The anhydrous salts of these acids were generated in nearly quantitative yield in ether using potassium trimethylsilanolate as an organic-soluble equivalent of potassium hydroxide.[16] A solution of the acid and $KOSiMe_3$ (1.1 equiv) was stirred for one hour at room temperature, and the precipitated potassium salt was collected under nitrogen and washed with ether. The use of $KOSiMe_3$, which is behaving presumably as a Brønsted base in the case of free carboxylic acids,[17] provides an operationally simple method for preparing pure anhydrous acid salts which appear to be more reactive than salts prepared by conventional procedures.[16]

For the syntheses of diesters **5** and **6**, diol **1** was converted in quantitative yield into the 6,6′-ditriflate **2** with trifluoromethanesulfonic anhydride and pyridine in dichloromethane at 0 °C; the use of a less nucleophilic pyridine derivative[18] was not required. The crude ditriflate **2** (homogeneous by TLC)[19] was condensed with the

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anhydrous potassium salts (2.5 equiv) of palmitic and 2-tetradecylhexadecanoic acid in cyclohexane at 80 °C to give the symmetrical hexa-*O*-trimethylsilyl 6,6′-diesters **3** and **4** in 74 and 71% yield, respectively, after purification by flash chromatography.[20] Yields were not improved by the addition of a crown ether such as *cis*-dicyclohexano-18-crown-6 (0.2 equiv). In contrast, treatment of monotriflate **7** with the potassium salt of (2*R*,3*S*)-3-hydroxy-2-tetradecyloctadecanoic acid (isocorynomycolic acid) has been reported[5] to give only a 16% yield of the expected monoester product after deprotection.[21] This result may indicate a pronounced deactivating effect by the primary trimethylsilyl group in **7** *vis-à-vis* a 6-ester group.[22]

Acid-catalyzed deprotection of diesters **3** and **4** in tetrahydrofuran (THF)-CF_3CO_2H-H_2O (4:2:1, rt, 1 h) or THF-AcOH-H_2O (6:3:1, 60 °C, 1 h) followed by chromatographic purification gave 6,6′-bis-*O*-hexadecanoyl-α,α-trehalose **5** and 6,6′-bis-*O*-(2-tetradecylhexadecanoyl)-α,α-trehalose **6** in 90-95% yield. The ^1H and ^{13}C NMR spectra of compounds **2**–**6**[19,24] were in agreement with the assigned structures and/or their reported spectral data.[5,9,25]

In summary, we have developed a highly efficient synthesis of symmetrical trehalose diesters in which *O*-alkylation of anhydrous potassium salts of carboxylic acids with ditriflate **2** is effected without the use of crown ethers or dipolar aprotic solvents. The ease of introduction and removal of the trimethylsilyl ether protecting groups also contributes to the overall convenience and practicality of this method, which should be suitable for large-scale preparation. The possibility that trehalose's conformational features (C_2 symmetry, concave shape) and ion complexing ability[26] play a role in the displacement reactions is under investigation.

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REFERENCES AND NOTES

1. T. Sakurai, I. Saiki, H. Ishida, K. Takeda and I. Azuma, *Vaccine*, **7**, 269 (1989) and references cited therein.

2. M. B. Goren, in *Handbook of Lipid Research*, Vol 6; M. Kates, Ed.; Plenum Press: New York, 1990, Ch. 5.
3. M. Nishizawa, D.M. Garcia, R. Minagawa, Y. Noguchi, H. Imagawa, H. Yamada, R. Watanabe, Y.C. Yoon and I. Azuma, *Synlett*, 452 (1996) and references cited therein.
4. D. A. Johnson, *Carbohydr. Res.*, **237**, 313 (1992).
5. A. K. Datta, K. Takayama, M. A. Nashed and L. Anderson, *Carbohydr. Res.*, **218**, 95 (1991).
6. I. D. Jenkins and M. B. Goren, *Chem. Phys. Lipids*, **41**, 225 (1986).
7. R. Toubiana, B. C. Das, J. DeFaye, B. Mompon and M.-J. Toubiana, *Carbohydr. Res.*, **44**, 308 (1975).
8. F. Numata, K. Nishimura, H. Ishida, S. Ukei, Y. Tone, C. Ishihara, I. Saiki, I. Sekikawa and I. Azuma, *Chem. Pharm. Bull.*, **33**, 4544 (1985).
9. J.-F. Tocanne, *Carbohydr. Res.*, **44**, 301 (1975).
10. R. Toubiana, C. Pizza, Y. Chapleur and B. Castro, *J. Carbohydr., Nucleosides Nucleotides*, **5**, 127 (1978).
11. A. Liav and M. B. Goren, *Chem. Phys. Lipids*, **27**, 345 (1980).
12. A. Liav and M. B. Goren, *Carbohydr. Res.*, **81**, C1 (1980).
13. J. Mulzer, A. Pointer, A. Chucholowski and G. Bruntrip, *J. Chem. Soc., Chem. Commun.*, 52 (1979).
14. M. Parant, F. Audibert, F. Parant, L. Chedid, E. Soler, J. Polonsky, and E. Lederer, *Infect. Immun.*, **20**, 12 (1978).
15. S. Kusumoto, M. Inage, T. Shiba, I. Azuma and Y. Yamamura, *Tetrahedron Lett.*, 4899 (1978).
16. E. D. Laganis and B. L. Chenard, *Tetrahedron Lett.*, **25**, 5831 (1984).
17. D. T. Grimm and J. E. Bartmess, *J. Am. Chem. Soc.*, **114**, 1227 (1992).
18. M. G. Ambrose and R. W. Binkley, *J. Org. Chem.*, **48**, 674 (1983).
19. The crude product (amorphous solid) was used in the next step without further purification. A small sample of **2**, purified by flash chromatography on silica gel with 5% EtOAc-hexanes, exhibited the following: mp 58-60 °C, $[\alpha]_D^{25}$ + 103° (*c* 1.00, $CHCl_3$); R_f 0.67 (10% EtOAc-hexanes); ^1H NMR (300 MHz, $CDCl_3$) δ 4.94 (d, 2 H, J = 3 Hz, H-1,1′), 4.62 (dd, 2 H, A part of AB system, J_{gem} = 10.5 Hz, J_{vic} = 2 Hz, H-6a,6′a), 4.53 (dd, 2 H, B part of AB system, J_{gem} = 10.5 Hz, J_{vic} = 4.5 Hz, H-6b,6′b), 4.09 (m, 2 H, H-5,5′), 3.89 (~t, 2 H, J ~ 9 Hz, H-3,3′), 3.52-3.37 (m, 4 H, H-2,2′,4,4′), 0.18, 0.16 and 0.14 (3 s, 18, 18 and 18 H, 6 $OSiMe_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 118.6 (q, J_{C-F} = 318 Hz, CF_3), 95.3, 75.1, 73.2, 72.4, 71.3, 70.6, 1.1, 0.8, 0.1; positive FAB-MS calcd for $[M + Na]^+$ 1061.2417, found 1061.2467.
20. A typical procedure is as follows. Preparation of **4**: A mixture of ditriflate **2** (0.762 g, 0.733 mmol) and potassium 2-tetradecylhexadecanoate (0.900 g, 1.83 mmol) in anhydrous cyclohexane (15 mL) was heated to reflux for 1 h. The cooled reaction mixture was filtered through a pad of silica gel and the filtrate concentrated. The residue obtained was purified by flash chromatography on silica gel (gradient elution, 0→2% EtOAc-hexanes) to give 0.850 g (71%) of **4** as a colorless oil.

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21. No experimental details for the displacement method were given in ref. 5.
22. The low yield in this case does not appear to be due to the structure of the potassium salt since condensation of ditriflate **2** with potassium (2*RS*,3*RS*)-3-hydroxy-2-tetradecyloctadecanoate (prepared from the corresponding methyl ester[23] with $KOSiMe_3$) can be effected in yields comparable to those obtained for **3** and **4** (D. A. Johnson and M. T. Livesay, unpublished results). Also, the successful condensation of the 6,6′-ditriflate of 2,3,4,2′,3′,4′-hexa-*O*-benzyl-α-D-galactopyranosyl α-D-galactopyranoside with potassium mycolate has been reported: A. Liav and M. B. Goren, *Chem. Phys. Lipids*, **51**, 9 (1989).
23. J. Polonsky and E. Lederer, *Bull. Soc. Chim. Fr.*, 504 (1954).
24. **3**: $[\alpha]_D^{25}$ + 64.5° (*c* 1.00, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 4.92 (d, 2 H, *J* = 3 Hz, H-1,1′), 4.27 (d, 2 H, A part of AB system, J_{gem} = 10 Hz, H-6a,6′a), 4.10-3.95 (m, 4 H, H-5,5′,6b,6′b), 3.90 (~t, 2 H, *J* ~ 9 Hz, H-3,3′), 3.48 (~t, 2 H, *J* ~ 9 Hz, H-4,4′), 3.44 (dd, 2 H, $J_{1,2}$ = 3 Hz, $J_{2,3}$ = 9.1 Hz, H-2,2′), 2.34 (m, AB type, 4 H, —CH_2CO—), 1.64 (m, 4 H, —CH_2CH_2CO—), 1.40-1.15 (m, 48 H, —CH_2—), 0.88 (~t, 6 H, *J* ~ 6.5 Hz, Me), 0.15, 0.14 and 0.13 (3 s, 18, 18 and 18 H, 6 $OSiMe_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.6, 94.3, 73.4, 72.6, 71.9, 70.7, 63.3, 34.2, 32.0, 29.7, 29.5, 29.4, 29.3, 29.2, 24.8, 22.7, 14.2, 1.1, 0.9, 0.2.

Anal. Calcd for $C_{62}H_{130}O_{13}Si_6$: C, 59.47; H, 10.46. Found: C, 59.27; H, 10.48.

4: $[\alpha]_D^{25}$ + 54.0° (*c* 1.41, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 4.86 (d, 2 H, *J* = 3 Hz, H-1,1′), 4.50 (d, A part of AB system, 2 H, J_{gem} = 10 Hz, H-6a,6′a), 4.0-3.8 (m, 4 H, H-5,5′,6b,6′b), 3.89 (~t, 2 H, *J* ~ 9 Hz, H-3,3′), 3.49 (~t, 2 H, *J* ~ 9 Hz, H-4,4′), 3.36 (dd, 2 H, $J_{1,2}$ = 3 Hz, $J_{2,3}$ = 9 Hz, H-2,2′), 2.35 (m, 2 H, —COCH—), 1.7-1.1 (m, 104 H, —CH_2—), 0.87 (~t, 12 H, *J* ~ 6.5 Hz, Me), 0.16, 0.14 and 0.12 (3 s, 18, 18 and 18 H, 6 $OSiMe_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.1, 94.5, 73.6, 72.8, 71.9, 62.1, 45.7, 32.6, 32.4, 32.0, 29.7, 29.6, 29.4, 27.5, 27.4, 22.7, 14.2, 1.2, 1.0, 0.3.

Anal. Calcd for $C_{90}H_{186}O_{13}Si_6$: C, 65.71; H, 11.40. Found: C, 65.78; H, 11.55.

5: mp 156-158 °C, $[\alpha]_D^{25}$ + 74.7° (*c* 1.20, $CHCl_3$); lit.[5] mp 155-158 °C, $[\alpha]_D^{20}$ + 80°); ^1H NMR (300 MHz, $CDCl_3$-CD_3OD) δ 5.11 (d, 2 H, *J* = 3 Hz, H-1,1′) 4.31 (m, 4 H, H-6,6′), 4.15-3.85 (m, 4 H, H-3,3′,5,5′), 3.56 (dd, 2 H, $J_{1,2}$ = 3 Hz, $J_{2,3}$ = 9.5 Hz, H-2,2′), 3.36 (~t, 2 H, *J* ~ 9 Hz, H-4,4′), 2.37 (~t, 4 H, *J* ~ 7.5 Hz, —$COCH_2$—), 2.21 (br s, 6 H, OH), 1.70-0.95 (m, 52 H, —CH_2—), 0.88 (~t, 6 H, *J* ~ 6.5 Hz, Me); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.4, 93.2, 72.9, 71.5, 70.1, 70.0, 63.1, 34.1, 31.9, 29.7, 29.5, 29.3, 29.2, 24.9, 22.7, 14.2.

Anal. Calcd for $C_{44}H_{82}O_{13} \cdot 1\ H_2O$: C, 63.13; H, 10.11. Found: C, 63.34; H, 9.95.

6: mp 103.5-106 °C, $[\alpha]_D^{25}$ + 47.8° (*c* 0.44, $CHCl_3$); lit.[8] wax, $[\alpha]_D^{25}$ + 47° (*c* 0.43, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$-CD_3OD) δ 5.11 (d, 2 H, *J* = 3 Hz, H-1,1′), 4.34 (m, 4 H, H-6,6′), 4.15 - 3.90 (m, 4 H, H-3,3′,5,5′), 3.56 (m, 2 H, H-2,2′), 3.31 (m, 2 H, H-4,4′), 2.37 (m, 2 H, —COCH—), 1.73 (s, 6 H, OH), 1.17-1.0 (m, 104 H, —CH_2—), 0.88 (~t, 12 H, *J* ~ 6.5 Hz, Me); ^{13}C NMR (75 MHz,

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$CDCl_3$) δ 177.5, 93.2, 72.9, 71.7, 70.7, 70.3, 63.1, 45.5, 32.0, 29.8, 29.6, 29.4, 27.4, 22.8, 14.2.

Anal. Calcd for $C_{72}H_{138}O_{13}$: C, 71.36; H, 11.48. Found: C, 71.09; H, 11.58.

25. Y. Gama, *Yukagaku*, **44**, 671 (1995).
26. C. Vicent, C. Bosso, F. H. Cano, J. L. G. de Paz, C. Foces-Foces, J. Jiménez-Barbero, M. Martín-Lomas, and S. Penadés, *J. Org. Chem.*, **56**, 3614 (1991).

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