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SYNTHESES AND CHARACTERIZATION OF FOUR DIASTEREOMERS OF TREHALOSE-6, 6'-DICORYNOMYCOLATES (TD BH32)

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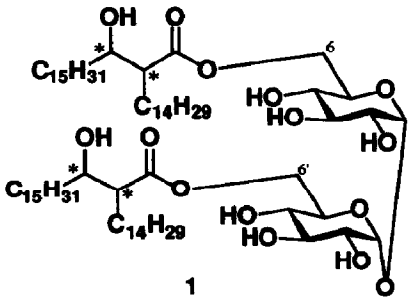
Abstract: Four diastereomers of trehalose-6,6'-dicorynomycolates (TD BH-32) have been synthesized selectively by DCC/DMAP•HCl mediated diesterification of protected trehalose with corynomicolic acid and its all possible isomers, each of which was prepared in enantiomerically pure form.

Glycolipids of mycobacteria so called cord factor, trehalose-6, 6'-dimycolate (TDM),[1] have been accepting significant attention due to their various biological activities.[2] TDM as well as a number of synthetic analogs with high molecular weight α-branched β-hydroxy fatty acid have been investigated dealing with the structure activity relationship.[3, 4, 5, 6] In 1985, Azuma and coworkers reported that a diastereomeric mixture of trehalose-6,6'-dicorynomycolate [TD BH32 (**1**)] shows significant peritoneal macrophage activation but low toxicity in mice.[7] We have been interested in this area from the standpoint on a relationship between the absolute configurations of the α and β positions of the corynomycolic acid residue and biological activities. Although the absolute structure of natural corynomycolic acid was established to be 2*R*, 3*R* based on the synthetic studies[8, 9] pure TD BH32 has not yet been prepared. Thus, we would like to describe herein the syntheses and characterization of four diastereomers of TD BH32 (**1a-1d**). Isolation of trehalose-6,6'-dicorynomycolates from *Corynebacterium matruchotii* was reported recently,[10] and thus this investigation means the first total synthesis of the natural product **1a** as well.



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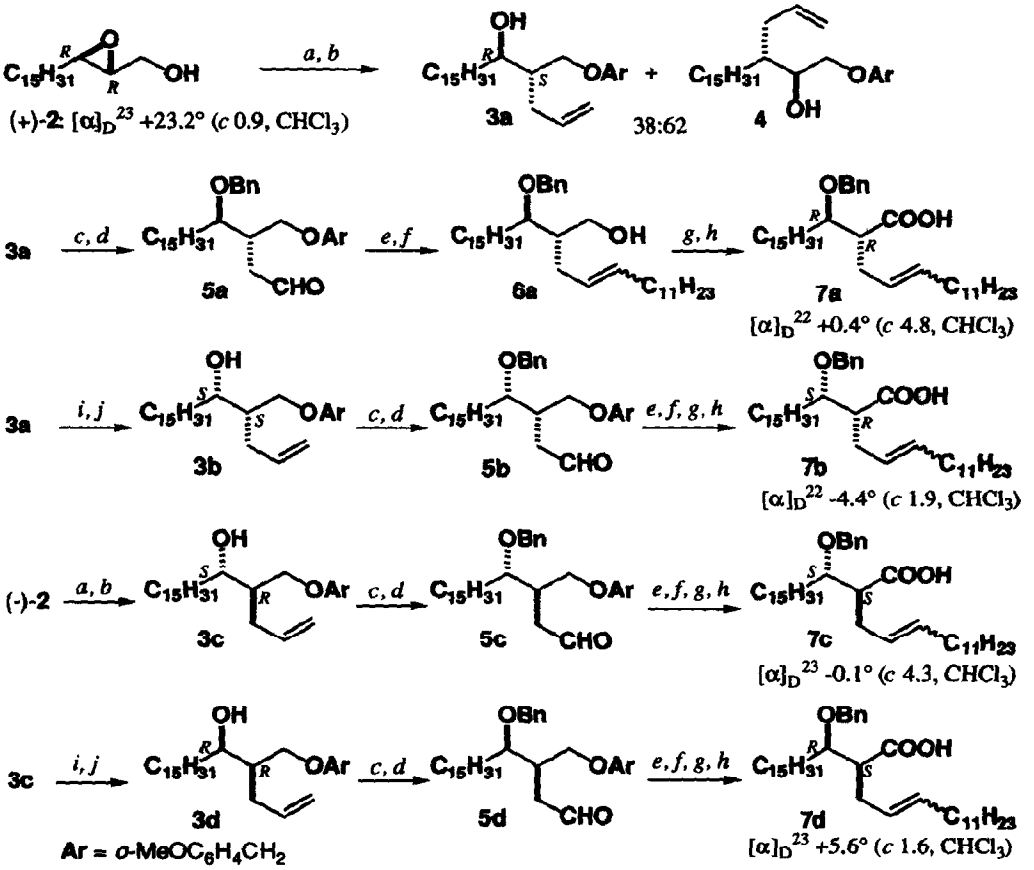
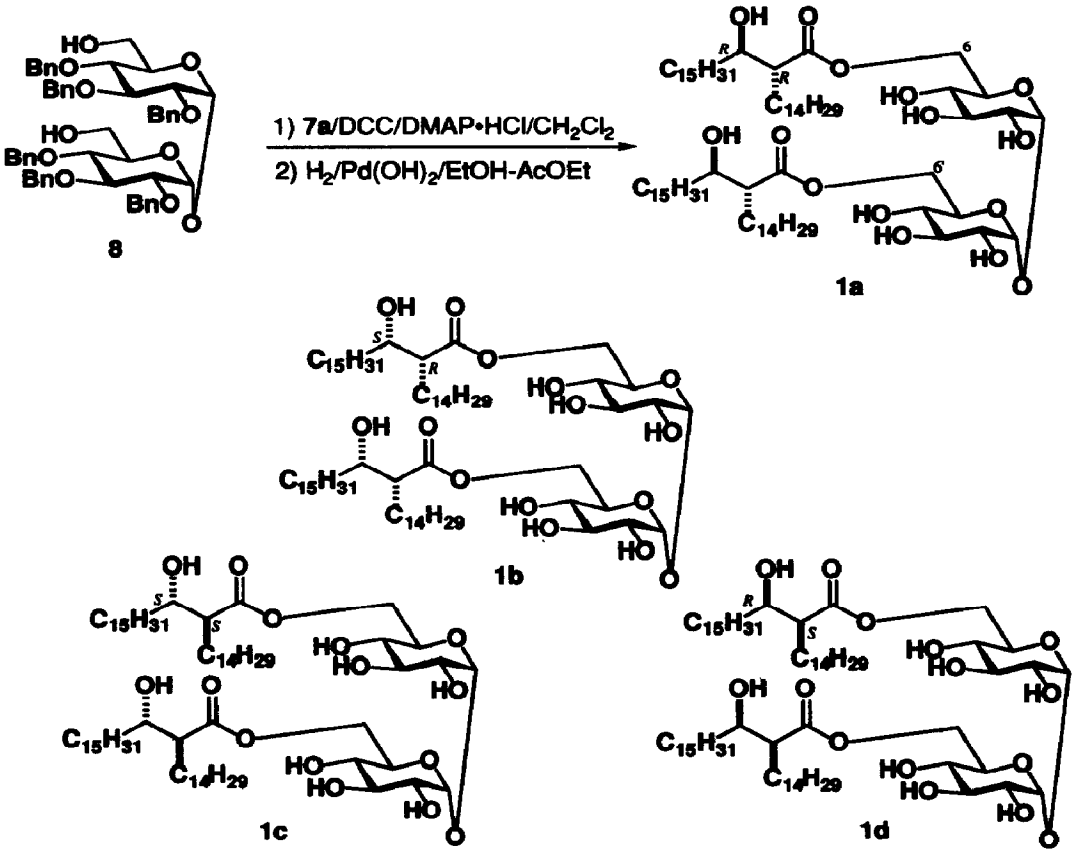
The optically pure epoxide [(2*R*, 3*R*)-(+)-**2**], $[\alpha]_D^{23}$ +23.2° (*c* 0.9, $CHCl_3$), quantitatively prepared by the Katsuki-Sharpless catalytic asymmetric epoxidation of 2-octadecenol using D-(-)-DIPT in CH_2Cl_2,[11] was converted into *o*-methoxybenzyl ether in 80% yield. Reaction of the resulting methoxybenzyl ether with allylmagnesium bromide in THF afforded 3*R* alcohol **3a** and 2*S* alcohol **4** quantitatively in a ratio of 38:62. Separation of **3a** and **4** was achieved by HPLC using YMC D-Sil-5 120A (20 x 250 mm) column with hexane and ethyl acetate (15:1) as an eluant. The hydroxyl group of **3a** was protected as its benzyl ether and the double bond was cleaved by Lemieux-Johnson oxidation to give aldehyde **5a**, which upon Wittig reaction with the ylide derived

from triphenyldodecanoylphosphonium bromide followed by DDQ oxidation[12] afforded a mixture of *E* and *Z* olefinic alcohols **6a** in 60% overall yield. Sequential Swern oxidation, and $NaClO_2$ oxidation[13] afforded (2*R*, 3*R*)-carboxylic acid **7a**, $[\alpha]_D^{22}$ +0.4° (*c* 4.8, $CHCl_3$), in 50% yield. The stereochemistry of 3*R* hydroxyl group of **3a** was inverted via mesylation and following reaction with potassium superoxide[14] to give (2*S*, 3*S*)-alcohol **3b** in 84% yield.[15] The alcohol **3b** was subjected to the same operations as employed for **3a** affording (2*R*, 3*S*)-carboxylic acid **7b**, $[\alpha]_D^{22}$ -4.4° (*c* 1.9, $CHCl_3$). The enantiomeric epoxide (2*S*, 3*S*)-(-)-**2**, $[\alpha]_D^{23}$ -23.0° (*c* 0.4, $CHCl_3$),[11] was similarly transformed into (2*S*, 3*S*)-carboxylic acid **7c**, $[\alpha]_D^{23}$ -0.1° (*c* 4.3, $CHCl_3$), via (2*R*, 3*S*)-alcohol **3c** and aldehyde **5c**. The 3*S*-hydroxy group of **3c** was inverted to give (2*R*, 3*R*)-compound **3d** which was further transformed into (2*S*, 3*R*)-carboxylic acid **7d**, $[\alpha]_D^{23}$ +5.6° (*c* 1.6, $CHCl_3$).



a *o*-$MeOC_6H_4CH_2Cl$/NaH/THF-DMF (3:1), rt, 7 h *b* CH_2=$CHCH_2MgCl$/THF, -78→0°C, 6 h *c* NaH/$PhCH_2Br$/THF-DMF (3:1), rt, 12 h *d* OsO_4/$NaIO_4$/THF-H_2O (1:1), rt, 4 h *e* $Ph_3PCH_2C_{11}H_{23}Br$/BuLi/THF, -78°C→rt, 2 h *f* DDQ/CH_2Cl_2-H_2O (10:1), rt, 2 h *g* $(COCl)_2$/DMSO/Et_3N/CH_2Cl_2, -78°C, 1.5 h *h* $NaClO_2$/NaH_2PO_4/2-methyl-2-butene/*t*-BuOH-H_2O (4:1), rt, 30 min *i* MsCl/Py, rt, 2 h *j* 18-Crown-6/KO_2/DMSO-DME (1:1), 0°C, 1.5 h

Four optically pure carboxylic acids **7a**-**7d** in hand, we then examined their condensations with α,α-trehalose derivative **8**. Trehalose dimycolates have previously been prepared in moderate yields by coupling the ditosylate of trehalose with potassium salt of the corresponding fatty acid under vigorous conditions,[16] by Mitsunobu reaction of trehalose with the fatty acid,[17] or by DCC-DMAP mediated coupling of TMS protected trehalose and corynomycolic acids protected as TBS ether (DL- or racemic).[18] We tried the condensation of **8** with **7a** (2.5 equiv) in the presence of DCC (5 equiv), DMAP•HCl (8 equiv),[19] and MS 4A in dichloromethane at room temperature for 5 days, and the diester was obtained in 99% yield. This diester was subjected to catalytic hydrogenation in the presence of $Pd(OH)_2/C$ in EtOH-EtOAc (1:1) to give trehalose 6,6'-dicorynomycolates **1a**, $[\alpha]_D^{23}$ +55.1° (*c* 0.13, $CHCl_3$), quantitatively, after purification by HPLC using ODS column (4.6 x 200 mm) eluted with MeOH-$CHCl_3$ (5:2). NMR spectrum of **1a** in DMSO-d_6-CF_3COOH was identical with that of natural product at least at the reported range (3 to 5 ppm).[10] Stereoisomeric dicorynomycolates **1b**, $[\alpha]_D^{23}$ +29.0° (*c* 0.13, $CHCl_3$), **1c**, $[\alpha]_D^{23}$ +38.6° (*c* 0.13, $CHCl_3$), and **1d**, $[\alpha]_D^{24}$ +46.3° (*c* 0.13, $CHCl_3$), were prepared analogously from **7b**, **7c**, and **7d**, respectively, and characterized.[20] Investigations of the biological activities of **1a**-**1d** are currently being undertaken.



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20. Spectral data of **1a**: FT IR (film) 3385, 2928, 2855, 1730, 1466, 1377, 1267, 1150, 1107, 1076, 1053, 1022, 993, 943, 806, 721, 581 cm^{-1}; ^1H NMR (600 MHz in C_5D_5N) δ 0.87 (12H, t, J = 7.1 Hz), 1.28-1.40 (90H, m), 1.43 (2H, m), 1.50 (2H, m), 1.60 (4H, m), 1.74-1.88 (8H, m), 1.98 (2H, m), 2.91 (2H, m), 4.16 (2H, t, J = 9.5 Hz), 4.21 (2H, m), 4.29 (2H, dd, J = 9.5, 3.7 Hz), 4.69 (2H, t, J = 9.5 Hz), 4.86 (2H, dd, J = 11.7, 5.7 Hz), 5.15 (4H, m), 5.86 (2H, d, J = 3.7 Hz), 6.27 (2H, br s); ^{13}C NMR (50 MHz in C_5D_5N) δ 14.4q, 23.0t, 26.4t, 28.2t , 29.5t, 29.7-30.4t, 32.2t, 35.5t, 54.0d, 64.4t, 71.6d, 72.4d, 72.6d, 73.4d, 74.8d, 96.1d, 175.1s.
1b: FT IR (film) 3368, 2924, 2855, 1734, 1464, 1377, 1271, 1177, 1148, 1109, 1074, 1051, 993, 806, 714 cm^{-1}; ^1H NMR (600 MHz in C_5D_5N) δ 0.88 (12H, t, J = 7.0 Hz), 1.28-1.41 (90H, m), 1.45 (2H, m), 1.53 (2H, m), 1.64 (4H, m), 1.70-1.87 (8H, m), 1.98 (2H, m), 2.92 (2H, m), 4.18 (2H, t, J = 9.4 Hz), 4.24 (2H, m), 4.28 (2H, dd, J = 9.3, 3.7 Hz), 4.70 (2H, t, J = 9.3 Hz), 4.82 (2H, dd, J = 11.7, 5.4 Hz), 5.09 (2H, m), 5.25 (2H, br d, J = 11.7 Hz), 5.90 (2H, d, J = 3.7 Hz), 6.33 (2H, br d, J = 1.5 Hz); ^{13}C NMR (50 MHz in C_5D_5N) δ 14.4q, 23.0t, 26.3t, 28.2t , 29.4t, 29.7-30.1t, 32.2t, 35.6t, 54.2d, 64.1t, 71.8d , 72.2d, 72.5d, 73.5d, 74.8d, 95.8d, 175.1s.
1c: FT IR (film) 3374, 2928, 2855, 1732, 1466, 1377, 1273, 1177, 1150, 1109, 1076, 991, 941, 806, 721, 586 cm^{-1}; ^1H NMR (600 MHz in C_5D_5N) δ 0.87 (12H, t, J = 6.8 Hz), 1.22-1.38 (94H, m), 1.49 (2H, m), 1.58 (2H, m), 1.64 (2H, m), 1.84 (4H, m), 2.11 (4H, m), 2.89 (2H, m), 4.15 (2H, t, J = 9.0 Hz), 4.31 (4H, m), 4.70 (2H, t, J = 8.8 Hz), 4.83 (2H, dd, J = 11.5, 5.7 Hz), 5.12 (2H, m), 5.20 (2H, br d, J = 11.5 Hz), 5.89 (2H, d, J = 3.7 Hz), 6.28 (2H, br d, J = 6.1 Hz); ^{13}C NMR (50 MHz in C_5D_5N) δ 14.4q, 23.0t, 26.8t, 28.4t, 29.7-30.1t, 32.2t, 36.2t, 53.8d, 64.4t , 71.7d, 72.3d, 72.4d, 73.4d, 74.7d, 95.9d, 175.2s. .
1d: FT IR (film) 3362, 2924, 2855, 1732, 1466, 1182, 1148, 1107, 1053, 991, 806, 721 cm^{-1}; ^1H NMR (600 MHz in C_5D_5N) δ 0.87 (12H, t, J = 7.0 Hz), 1.25-1.43 (92H, m), 1.48 (2H, m), 1,60 (2H, m), 1.67 (2H, m), 1.87 (6H, m), 2.14 (4H, m), 2.90 (2H, m), 4.22 (2H, t, J = 9.3 Hz), 4.27 (4H, m), 4.72 (2H, t, J = 9.3 Hz), 4.91 (2H, dd, J = 11.7, 5.1 Hz), 5.12 (2H, m), 5.12 (2H, br d, J = 11.0 Hz), 5.88 (2H, d, J = 3.7 Hz), 6.25 (2H, br d, J = 5.9 Hz); ^{13}C NMR (50 MHz in C_5D_5N) δ 14.4q, 23.0t, 26.7t, 28.3t , 29.3t, 29.7-30.1t, 32.2t, 36.3t, 54.0d, 64.1t, 71.7d, 72.1d, 72.4d, 73.4d, 74.9d, 96.1d, 175.4s.

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