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TOTAL SYNTHESIS OF ARTHROBACILIN A

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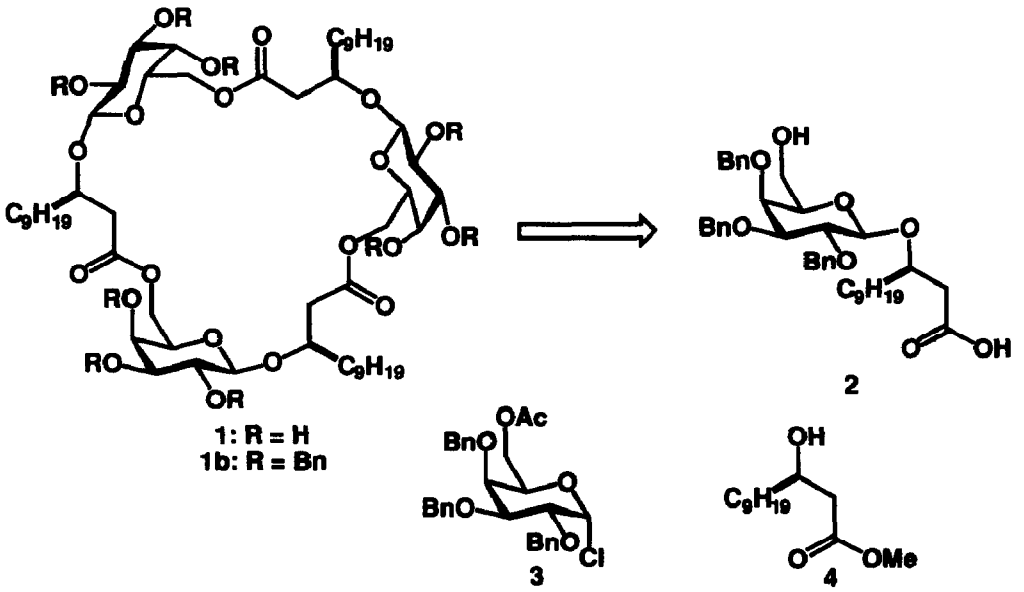
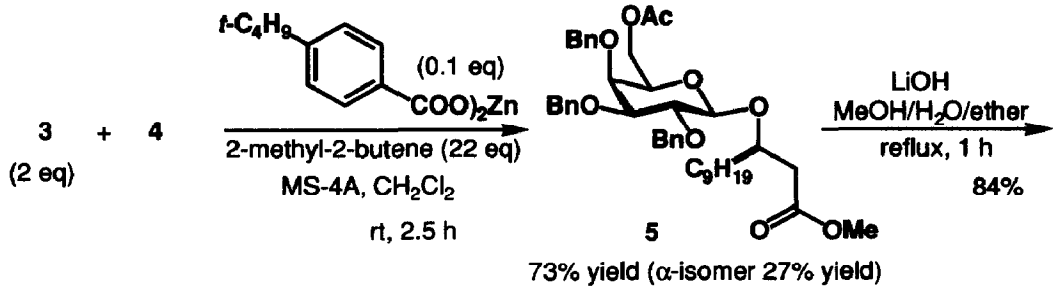
Abstract: Novel cyclic glycolipids, arthrobacilin A and its analogues, have been synthesized by means of unique DCC/DMAP•HCl promoted oligomerization/cyclization, zinc salt catalyzed β-selective glycosylation, and Noyori's BINAP/Ru catalyzed asymmetric reduction.

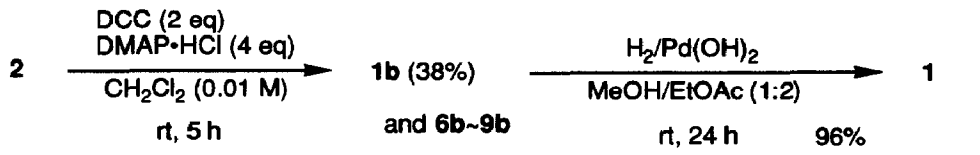
Arthrobacilin A (**1**) was isolated from the culture broth of *Arthrobactor sp.* NR2967 as a cell growth inhibitor. The unique structure, which is the sole example belonging to the category of cyclic glycolipid, has been established by NMR experiments as well as some chemical derivations in 1992.[1] As we have developed an efficient zinc salt catalyzed glycosylation procedure,[2,3] we have been interested in a total synthesis of this novel cyclic glycolipid and focussed on the possibility of oligomerization/cyclization sequence to give **1b** from monomeric ω-hydroxylic acid **2**. Noyori's BINAP/Ru catalyzed asymmetric reduction of β-ketoesters should be the most promising procedure for the introduction of the desired *R* chirality on the fatty acid residue **4**.[4,5] We assumed that zinc *p-tert*-butylbenzoate would accelerate the glycosylation of **3** and **4** remarkably in β-selective manner.[3]

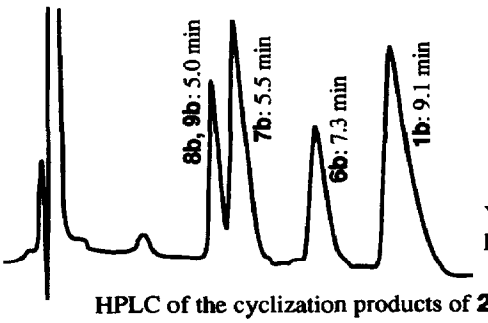


A mixture of methyl (*R*)-2-hydroxydodecanoate [(*R*)-**4**] and 2,3,4-tri-*O*-benzyl-6-*O*-acetyl-α-D-galactopyranosyl chloride (**3**, 2 eq) was heated at reflux in dichloromethane in the presence of zinc *p-tert*-

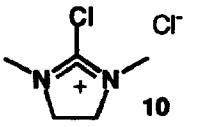
butylbenzoate (0.1 eq), molecular sieves 4A, and 2-methyl-2-butene (22 eq) for 2.5 h providing β-galactoside **5** in 73% yield along with α-isomer in 27% yield after column chromatography on silica gel.[3] Simultaneous hydrolysis of the methyl ester and the acetyl group of **5** was achieved by LiOH in methanol/water/ether (3:1:4) to give ω-hydroxylic acid **2** in 84% yield. A 0.01M dichloromethane solution of the monomeric glycoside **2** was treated with dicyclohexylcarbodiimide (DCC, 2 eq) and *N,N*-dimethylaminopyridine•HCl (DMAP•HCl, 4 eq) at room temperature for 5 h providing a mixture of cyclic oligomers in quantitative yield.[6] This mixture was subjected to HPLC (YMC sil A-003, 4.6 x 250 mm column, hexane/ethyl acetate 9:1 as an eluant) affording trimer **1b** (rt 9.1 min) in 38% yield along with tetramer **6b** (rt 7.3 min, 19% yield), dimer **7b** (rt 5.5 min, 21% yield), and mixture of pentamer **8b** and hexamer **9b** (rt 5.0 min, 14% yield).[8] $Pd(OH)_2$ catalyzed hydrogenolysis of nine benzyl groups of **1b** in methanol/ethyl acetate (1:2) at room temperature for 24 h gave arthrobacilin A (**1**) in 96% yield. This product showed parent peak at *m/z* 1103.6323 $(M+Na)^+$ in high resolution FAB mass spectrum (calcd for $C_{54}H_{96}O_{21}Na$: 1103.6342). Other spectral features were also indistinguishable from those of natural product. Tetramer **6**, dimer **7**, pentamer **8** and hexamer **9** were also characterized by high resolution FAB mass spectra after deprotection.[7] Biological activities of these arthrobacilin analogues are currently under investigation. It is interesting to note that the oligomerization/ cyclization reaction of **2** in dichloromethane (0.01 M) promoted by 2-chloro-1,3-dimethylimidazolinium chloride (**10**)[8] along with DMAP afforded only the dimer **7b** selectively in 70% yield.



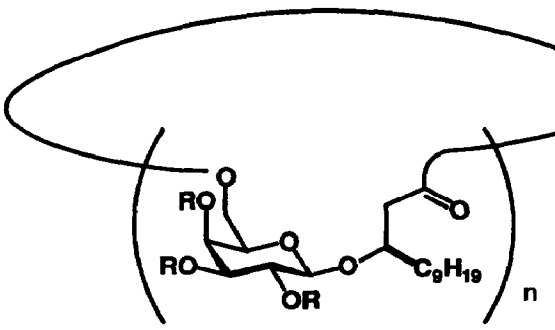




HPLC of the cyclization products of **2** with DCC/DMAP•HCl

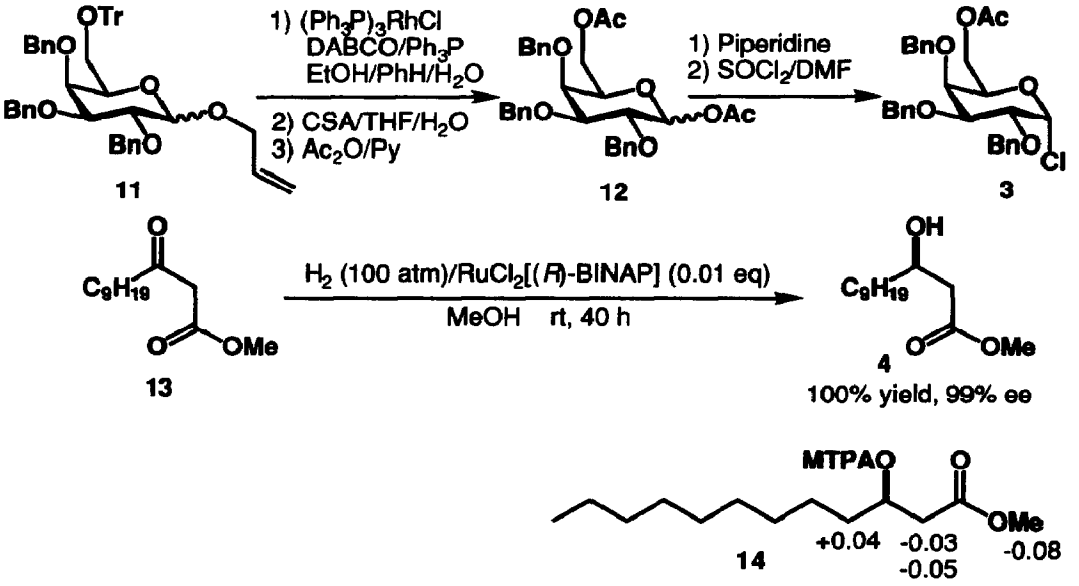


YMC Sil A-003 column, 4.6 x 250 mm
hexane/ethyl acetate 9:1, 3.5 mL/min



6: R = H, n = 4
6b: R = Bn, n = 4
7: R = H, n = 2
7b: R = Bn, n = 2
8: R = H, n = 5
8b: R = Bn, n = 5
9: R = H, n = 6
9b: R = Bn, n = 6

Galactosyl chloride **3** and (*R*)-2-hydroxydodecanoic acid (**4**) were prepared as follows. Allyl 2,3,4-tri-*O*-benzyl-6-*O*-trityl-β-D-galactopyranoside (**11**) prepared from D-galactose (28% yield) was treated with tristriphenylphosphinerhodium chloride (0.01 eq), DABCO (0.2 eq), triphenylphosphine (0.1 eq), in ethanol/benzene/water (7:3:1) for 2 h at reflux temperature, and the crude isomerization products were hydrolyzed and then acetylated to give diacetate **12** in 94% yield. Selective hydrolysis of the acetate on anomeric position by piperidine and subsequent chlorination with $SOCl_2$ afforded the glycosylation donor **3** in 96% yield. Methyl 2-oxododecanoate (**13**) was reduced by hydrogen (100 atm) in the presence of $RuCl_2$[(*R*)-BINAP] (0.01 eq) in methanol at room temperature for 40 h to give alcohol **4** in 100% yield.[5,6] Optical purity of the reduction product was at least 99% ee based on 400 MHz ^{1}H NMR analysis of the derived MTPA esters. Although the reliable empirical rule has been established that the *R* catalyst provides *R* alcohols in the Noyori's BINAP/Ru catalyzed asymmetric reduction of a variety of carbonyl compounds, *R* stereochemistry of our reduction product **4** was further confirmed by Kusumi's modified MTPA method.[9] The Δ δ values are illustrated in **14**.



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University and Dr. T. Ohtsuka of Nippon Roche Research Center for supplying natural arthrobacilin A for identification. High resolution FAB mass spectra were determined by Nippon Roche Research Center, and we hereby appreciate. We also thank to Ono Pharmaceutical Co. Ltd. for financial aid.

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6. Boden, E. P.; Keck, G. E. *J. Org. Chem.*, **1985**, *50*, 2394.
7. Spectral data of arthrobacilin analogs were; **6**: *m/z* 1463.8463 $(M+Na)^+$ [calcd for $C_{72}H_{128}O_{28}Na$: 1463.8490]; $[\alpha]_D^{22}$ -21.7° (*c* 0.8, $CHCl_3$); FT IR (film) ν 3407, 2924, 2855, 1740, 1458, 1375, 1262, 1130, 1076, 781, 606 cm^{-1}; ^1H NMR (200 MHz in C_5D_5N) δ 0.82 (3H, t, *J* = 6.3 Hz), 1.09-1.28 (12H, m), 1.57 (1H, m), 1.78 (3H, m), 2.87 (1H, dd, *J* = 15.0, 5.6 Hz), 3.39 (1H, dd, *J* = 15.0, 7.0 Hz), 4.13 (1H, dd, *J* = 9.2, 4.1 Hz), 4.23 (1H, t,*J* = 6.3 Hz), 4.40 (2H, m), 4.57 (1H, br), 4.94 (3H, m); ^{13}C NMR (50 MHz, C_5D_5N) δ 14.3 q, 22.9 t, 25.6 t, 29.6 t, 29.9 t, 30.0 t, 30.2 t, 32.1 t, 35.8 t, 42.1 t, 64.1 t, 69.8 d, 72.4 d, 73.5 d, 75.0 d, 77.9 d, 105.8 d, 171.6 s. **7**: *m/z* 743.4210 $(M+Na)^+$ [calcd for $C_{36}H_{64}O_{14}Na$: 743.4194]; $[\alpha]_D^{23}$ +20.9° (*c* 1.2, MeOH/$CHCl_3$ 2:1); FT IR (film) ν 3576, 3378, 3302, 2926, 1736, 1468, 1223, 693 cm^{-1}; ^1H NMR (400 MHz in C_5D_5N) δ 0.82 (3H, t, *J* = 6.9 Hz), 1.14-1.35 (12 H, m), 1.65 (2H, m), 1.90 (2H, m), 2.84 (1H, dd, *J* = 14.9, 11.6 Hz), 3.95 (1H, dd, *J* = 14.9, 3.3 Hz), 4.10 (1H, dd, *J* = 9.4, 2.8 Hz), 4.28 (2H, m), 4.40 (1H, dd, *J* = 9.4, 7.7 Hz), 4.52 (1H, br), 4.74 (1H, d, *J* = 11.0 Hz), 4.83 (1H, d, *J* = 7.7 Hz), 5.06 (1H, d, *J* = 11.0 Hz); ^{13}C NMR (100 MHz in C_5D_5N) δ 14.2 q, 22.9 t, 25.6 t, 29.6 t, 29.9 t, 29.9 t, 29.9 t, 32.0 t, 35.9 t, 42.8 t, 66.1 t, 70.4 d, 72.2 d, 73.6 d, 75.0 d, 79.2 d, 107.2 d, 171.7 s. Separation of **8** and **9** was achieved by ODS column chromatography using a mixture of MeOH/H_2O/AcOH (20:1:1) as eluant. **8**: $[\alpha]_D^{23}$ -1.5° (*c* 0.5, $CHCl_3$); FT IR (film) ν 3414, 2924, 2855, 1738, 1458, 1377, 1260, 1078, 801 cm^{-1}; ^1H NMR (600 MHz in C_5D_5N) δ 0.85 (3H, t, *J* = 7.1 Hz), 1.19-1.33 (12H, m), 1.58 (1H, m), 1.72 (1H, m), 1.82 (2H, m), 2.90 (1H, dd, *J* = 15.4, 7.1 Hz), 3.32 (1H, dd, *J* = 15.4, 6.0 Hz), 4.13 (1H, dd, *J* = 9.3, 3.2 Hz), 4.21 (1H, t, *J* = 6.5 Hz), 4.40 (1H, dd, *J* = 9.3, 7.3 Hz), 4.44 (1H, br d, *J* = 3.0 Hz), 4.58 (1H, m), 4.93 (1H, d, *J* = 7.3 Hz), 4.94-5.03 (2H, m); ^{13}C NMR (150 MHz in C_5D_5N) δ 14.3 q, 22.9 t, 25.5 t, 29.6 t, 29.9 t, 30.0 t, 30.2 t, 32.1 t, 35.6 t, 41.8 t, 63.9 t, 69.6 d, 72.3 d, 73.4 d, 74.9 d, 77.6 d, 105.4 d, 171.6 s; MS (FAB) *m/z* 1824.0658 $(M+Na)^+$ [calcd for $C_{90}H_{160}O_{35}Na$: 1824.0638]. and **9**: $[\alpha]_D^{23}$ -1.3° (*c* 0.3, $CHCl_3$); FT IR (film) ν 3426, 2924, 1740, 1667, 1456, 1379, 1080, 803 cm^{-1}; ^1H NMR (600 MHz in C_5D_5N) δ 0.85 (3H, t, *J* = 7.1 Hz), 1.17-1.32 (12H, m), 1.58 (1H, m), 1.72 (1H, m), 1.83 (2H, m), 2.90 (1H, dd, *J* = 15.1, 5.8 Hz), 3.30 (1H, dd, *J* = 15.1, 7.1 Hz), 4.13 (1H, dd, *J* = 9.3, 1.7 Hz), 4.18 (1H, br t, *J* = 6.6 Hz), 4.39 (1H, t, *J* = 9.3 Hz), 4.43 (1H, br), 4.56 (1H, m), 4.90 (1H, m), 4.95-5.02 (2H, m); ^{13}C NMR (150 MHz in C_5D_5N) δ 14.3 q, 22.9 t, 25.5 t, 29.6 t, 29.9 t, 30.0 t, 30.2 t, 32.1 t, 35.5 t, 41.7 t, 63.9 t, 69.6 d, 72.3 d, 73.3 d, 74.9 d, 77.5 d, 105.3 d, 171.6 s; MS (FAB) *m/z* 2184.2751 $(M+Na)^+$ [calcd for $C_{108}H_{192}O_{42}Na$: 2184.2786].
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