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Stereocontrolled Synthesis of Modified Galactocerebroside

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Based on (4*S*,5*R*,2*E*)-3-*O*-(2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranosyl)-6-*O*-acetyl-5-hydroxyhex-2-enal, (2*S*,3*S*,4*E*,6*E*)-3-*O*-β-D-galactopyranosyl-2-*N*-hexadecanoyl-8-oxo-4,6-sphingadienine has been synthesized in its pentaacetate form.

In our recent publication we reported on a new method for the relative stereocontrolled synthesis of low molecular mass *O*-glycosides with non-carbohydrate aglycones.[1] The method was demonstrated to be useful as applied to the synthesis of chiral precursors for cerebrosides.[2] In order to proceed with our research programme, we have developed a synthetic procedure to obtain the pentaacetate of modified galactocerebroside **6**. Acidic opening of the dihydropyran ring in hexa-*O*-acetyl-β-D-lactal **1**[1] afforded a starting chiral unit as (4*S*,5*R*,2*E*)-3-*O*-(2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranosyl)-6-*O*-acetyl-5-hydroxyhex-2-enal **2**. Coupling of aldehyde **2** with dimethyl-2-oxododecylphosphonate in the presence of KOH gave a 75% yield of *O*-glycoside **3**. The latter was reacted with trifluoromethanesulfonic acid anhydride (Tf_2O) in pyridine, followed by a single-step treatment of the resultant product with NaN_3 in the presence of *N*,*N*-dimethylformamide (DMF) to give azide **4** in 46% yield. The azide **4** was subsequently reduced with triphenylphosphine, which afforded lysocerebroside **5** in 60% yield. The latter was *N*-acylated with hexadecanoyl chloride in the presence of triethylamine and a catalytic amount of 4-dimethylaminopyridine (DMAP), which led to an 82% yield of the required (2*S*,3*S*,4*E*,6*E*)-3-*O*-β-D-galactopyranosyl-2-*N*-hexadecanoyl-8-oxo-4,6-sphingadienine pentaacetate **6**. The structures of all the compounds obtained were confirmed by

their IR, UV, ^1H and ^{13}C NMR spectroscopic data and also by the results of their elemental analysis.†

We have proposed thereby a common approach for synthetic preparations of cerebrosides and their analogues showing enantiomeric purity, *via* acidic decyclization of glycals from disaccharides to *O*-glycosylated α,β-unsaturated aldehydes that are subsequently alkenated by the appropriate phosphonates or phosphoranes.

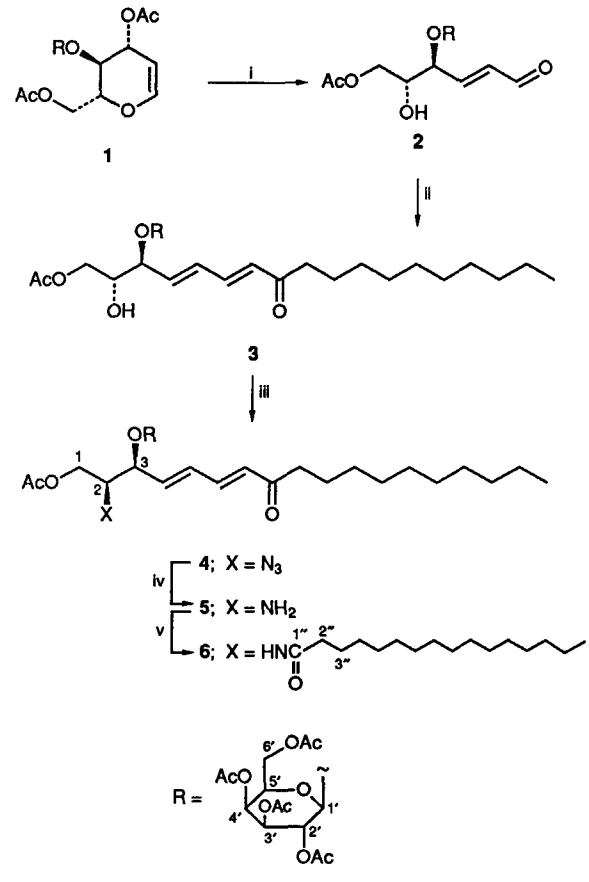
References

1 G. A. Tolstikov, A. G. Tolstikov, O. F. Prokopenko and V. N. Odinokov, *Synthesis*, 1990, 533.

2 A. G. Tolstikov, O. F. Prokopenko, R. Kh. Yamilov and G. A. Tolstikov, *Mendeleev Commun.*, 1991, 64.

† *Spectroscopic assignments* for compound **3**: $[\alpha]_D^{20}$ 9.4° (*c* 2.7, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 0.82 (t, 3H, 18-H, *J* 6.5 Hz), 1.21–1.37 (m, 14H, 11-H–17-H), 1.51–1.65 (m, 2H, 10-H), 1.98, 2.02, 2.04, 2.06, 2.09 (5s,15H, $5CH_3CO$), 2.54 (t, 2H, 9-H, *J* 7.3 Hz), 3.72 (dd, 1H, 1-H_a, J_{gem} 11.1, $J_{1a,2}$ 7 Hz), 3.87 (m, 1H, 5′-H), 3.92 (br s, 1H, OH), 4.06–4.23 (m, 4H, 6′-H, 1-H_b, 2-H), 4.32 (m, 1H, 3-H), 4.62 (d, 1H, 1′-H, $J_{1',2'}$ 7.9 Hz), 5.02 (dd, 1H, 3′-H, $J_{3',2'}$, 10.3, $J_{3',4'}$ 3.45 Hz), 5.22 (dd, 1H, 2′-H, $J_{2',1'}$ 7.9, $J_{2',3'}$ 10.35 Hz), 5.39 (m, 1H, 4′-H), 6.15 (dd, 1H, 4-H, $J_{4,5}$ 15.3, $J_{4,3}$ 6.7 Hz), 6.20 (d, 1H, 7-H, $J_{7,6}$ 15.5 Hz), 6.45 (dd, 1H, 5-H, $J_{5,4}$ 15.3, $J_{5,6}$ 10.7 Hz), 7.12 (dd, 1H, 6-H, $J_{6,7}$ 15.5, $J_{6,5}$ 10.75 Hz); ^{13}C NMR ($CDCl_3$) δ 14.07 (18-C), 20.51, 20.60, 20.71, 20.81 ($5CH_3CO$), 22.65 (17-C), 24.26 (10-C), 29.31, 29.43, 29.48, 29.56 (11-C–15-C), 31.89 (16-C), 40.94 (9-C), 61.35 (6′-C), 64.91 (1-C), 67.04 (4′-C), 69.12 (3′-C), 70.84 (2′-C), 70.98 (5′-C), 71.97 (2-C), 82.05 (3-C), 101.53 (1′-C), 130.85 (5-C), 131.61 (7-C), 138.20 (4-C), 140.48 (6-C), 169.66, 170.02, 170.18, 170.29, 171.35 ($5CH_3CO$), 200.59 (8-C).

Compound **6**: $[\alpha]_D^{20}$ − 17.3° (*c* 1.7, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 0.82 (t, 3H, 18-H, *J* 6.7 Hz), 0.88 (t, 3H, 16″-H, *J* 6.8 Hz), 1.15–1.42 (m, 38H, 11-H–17-H, 4″-H–15″-H), 1.65 (m, 4H, 10-H, 3″-H), 1.97, 2.02, 2.05, 2.07, 2.12 (5s, 15H, $5CH_3CO$), 2.28 (t, 2H, 2″-H, *J* 7.5 Hz), 2.53 (t, 2H, 9-H, *J* 7.4 Hz), 3.85 (m, 1H, 5′-H), 3.97 (dd, 1H, 1-H_a, J_{gem} 11.2, $J_{1,2}$ 7.1 Hz), 4.03 (m, 3H, 1-H_b, 6′-H), 4.32 (m, 2H, 2-H, 3-H), 4.51 (d, 1H, 1′-H, $J_{1',2'}$ 7.8 Hz), 4.97 (dd, 1H, 3′-H, $J_{3',2'}$ 10.5, $J_{3',4'}$ 3.2 Hz), 5.18 (dd, 1H, 2′-H, $J_{2',3'}$ 10.5, $J_{2',1'}$ 7.9 Hz), 5.35 (m, 1H, 4′-H), 5.84 (d, 1H, HN, *J* 8.8 Hz), 6.08 (dd, 1H, 4-H, $J_{4,3}$ 6.6, $J_{4,5}$ 15.4 Hz), 6.15 (d, 1H, 7-H, $J_{7,6}$ 15.7 Hz), 6.32 (dd, 1H, 5-H, $J_{5,6}$ 10.7, $J_{5,4}$ 15.4 Hz). 7.05 (dd, 1H, 6-H, $J_{6,5}$ 10.7, $J_{6,7}$ 15.75 Hz); ^{13}C NMR ($CDCl_3$) δ 14.11, 14.16 (18-C, 16″-C), 20.48, 20.53, 20.64, 20.76, 21.03 ($5CH_3CO$), 22.66, 22.67 (17-C, 15″-C), 24.16, 24.84 (10-C, 3″-C), 29.12, 29.34, 29.42, 29.47, 29.61, 29.64, 29.67, 30.05 (11-C–15-C, 4″-C–13″-C), 31.87, 31.89 (16-C, 14″-C), 34.06 (2″-C), 40.81 (9-C), 51.53 (2-C), 60.38 (1-C), 61.17 (6′-C), 66.83 (4′-C), 69.02 (3′-C), 70.58, 70.85 (2′-C, 5′-C), 79.74 (3-C), 130.88 (5-C), 131.02 (7-C), 138.55 (4-C), 140.51 (6-C), 169.99, 170.12, 170.26, 170.32, 170.76 ($5CH_3CO$), 173.56 (1″-C), 200.65 (8-C).



Scheme 1 *Reagents and conditions*: i, 0.01 mol dm^{-3} H_2SO_4, cat. $HgSO_4$, dioxane, 25 °C, 6 h; ii, $(MeO)_2P(O)CH_2(CO)C_{10}H_{21}$, KOH, CH_2Cl_2, 25 °C, 1 h; iii, Tf_2O, Py, CH_2Cl_2, − 10 °C, 15 min; then NaN_3, DMF, 25 °C, 4 h; iv, Ph_3P, PhH, 45 °C, 1 h; then H_2O, 45 °C, 24 h; v, $ClCO(CH_2)_{14}Me$, Et_3N, cat. DMAP, CH_2Cl_2, 0 °C, 1 h

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