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Hexa-*O*-acetyl-D-gentiobial in enantioselective synthesis of lysocerebrosides and their conjugates

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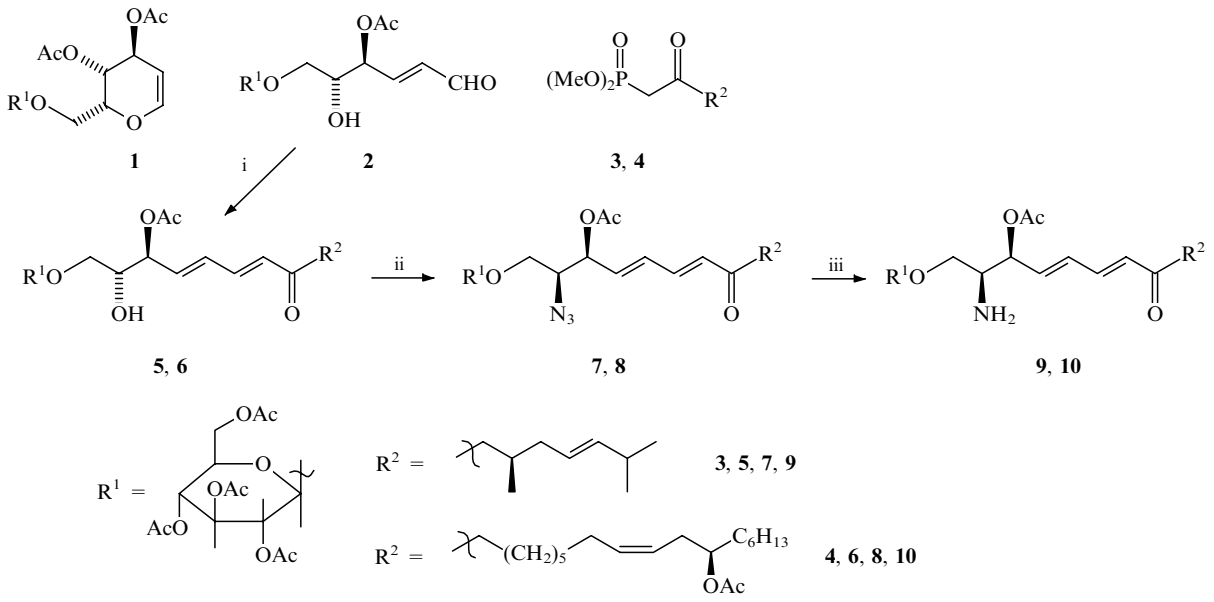
Hexa-*O*-acetyl-D-gentiobial 1 and its decyclization product (2*E*,4*S*,5*R*)-4-acetoxy-5-hydroxy-6-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyloxy)hex-2-enal 2 have been used to synthesize *O*-glycosylated aminodiols 9, 10, 15 that model the structure of natural lysocerebrosides. Compounds 9, 10, 15 can serve as basic components to produce *N*-acylated conjugates with derivatives of arachidonic and glycyrrhizic acids.

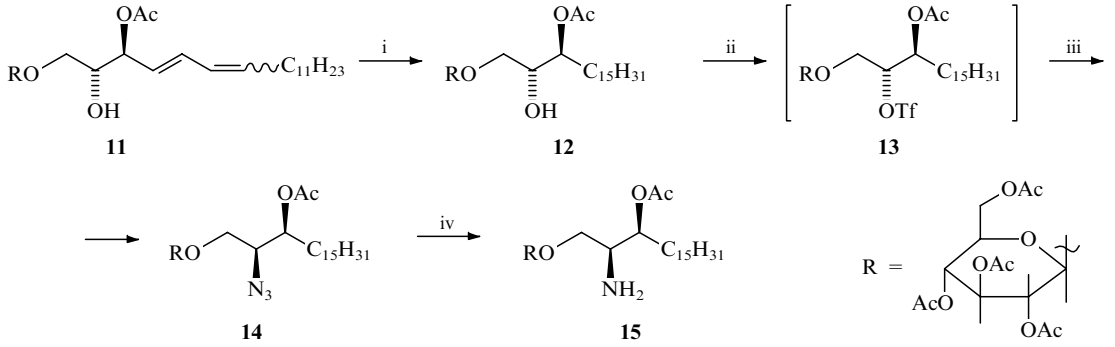
Among natural glycosphingolipids and their synthetic analogues there appear to be many compounds which exhibit valuable biological activity, some of which show antiviral activity.[1–4]

Continuing our studies in this field[5–7] we have synthesized modified lysocerebrosides **9**, **10**, **15** intending to use them as the basic amino components with which to obtain conjugates with activated esters of arachidonic and glycyrrhizic acid derivatives. We plan not only to solve non-trivial synthetic problems but also to look for new anti-viral and hormone-active compounds of selective and prolonged action.

We used enantioselective conversions of glycal **1** and aldehyde **2** (the product of glycal **1** acidic decyclization) as a basic Scheme for the synthesis of compounds **9**, **10**, **15**.[7] To build the lipophilic segment of ketoaminodiol molecules **9**, **10** we used the well-known phosphonates **3**, **4**.[8] (2*R*,3*S*,4*E*,6*Z*)-3-Acetoxy-2-hydroxy-1-(2,3,4,6-tetra-*O*-acetyl-β-glucopyranosyloxy)octadeca-4,6-diene **11**,[7] which we synthesized earlier,



Scheme 1 *Reagents and conditions*: i, **3** or **4**, KOH, CH_2Cl_2, 20 °C, 1 h; ii, $(CF_3SO_2)_2O$, Py, CH_2Cl_2, −10 °C, 0.5 h, then DMF, NaN_3, 20 °C, 4 h; iii, PPh_3, PhH, 45 °C, 5 h.



Scheme 2 *Reagents and conditions*: i, H_2, 10% Pd/C, $MeCO_2Et$, 20 °C, 5 h; ii, $(CF_3SO_2)_2O$, Py, CH_2Cl_2, −20 °C, 20 min; iii, NaN_3, DMF, CH_2Cl_2, 25 °C, 5 h; iv, PPh_3, PhH, 45 °C, 8 h.

served as a starting compound to produce *O*-glycoside **15**.

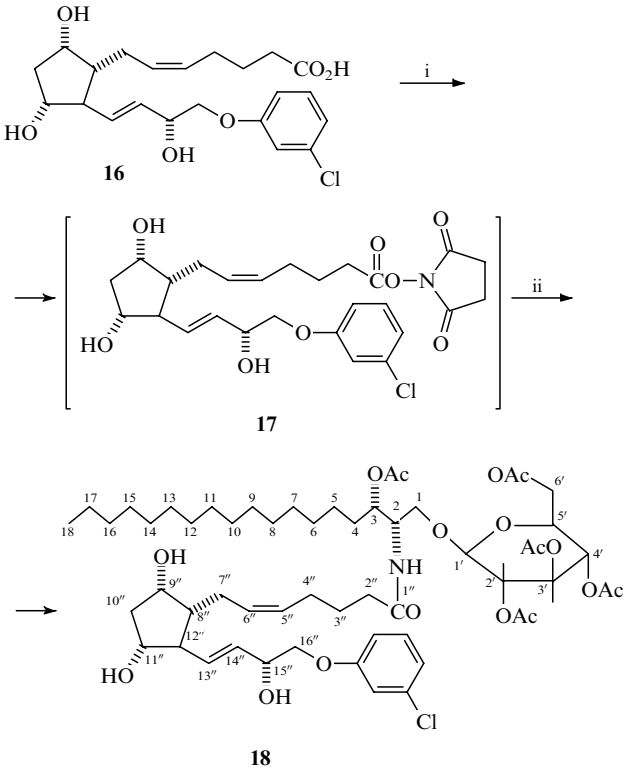
According to Scheme 1, aldehyde **2** reacts with phosphonates **3** and **4** in the presence of equimolar amounts of KOH suspended in CH_2Cl_2 producing dienones **5** and **6** in yields of 72% and 80%, respectively. The reaction of compound **5** with trifluoromethanesulfonic acid anhydride and treatment of the reaction product *in situ* with NaN_3 in DMF produces azide **7** in 56% yield. In the same manner we synthesized azide **8** (64%). The reduction of azides **7**, **8** with triphenylphosphine under slight heating (45 °C) in benzene solution completes the synthesis of desired ketoaminodiols **9** (75%) and **10** (82%).

Aminodiol **15** synthesis (Scheme 2) required a three-stage conversion of initial *O*-glycoside **11**. Complete hydrogenation of **11** catalysed by 10% Pd/C in ethyl acetate solution produced the saturated product **12** in 82% yield. The product was then treated with $(CF_3SO_2)_2O$ in the presence of pyridine in CH_2Cl_2 solution. The interaction of labile triflate **13** with NaN_3 produced azide **14** (70%). The latter was reduced by PPh_3 to produce modified lysocerebroside **15** (85%).

We obtained conjugate **18** (Scheme 3) *via* aminoacylation of lysocerebroside **15** by activated oxysuccinimide ester **17**. The latter was previously synthesized *via* interaction of cloprostenol **16** with *N*-hydroxysuccinimide (HOSu) and *N*,*N*′-dicyclohexylcarbodiimide (DCC) in the THF.[9] The yield of desired product **18** after chromatographic purification on a silica gel column was 32%. Elemental analysis and spectroscopic data confirm the structure of all compounds obtained.[†] A separate paper concerning the synthesis of conjugates with glycyrrhizic acid will follow later.

[†] Spectral data for **9**: $[\alpha]_D^{20}$ −2.2° (*c* 1.8, $CHC1_3$); ^{13}C NMR ($CDC1)_3$ δ 17.69 (CH_3), 19.68 (C-10), 20.53, 20.64, 20.75, 20.80, 20.92 (5 CH_3CO), 25.55, 25.64 (CH_3, C-15), 29.40 (C-11), 37.18 (C-12), 48.50 (C-9), 54.44 (C-2), 61.75 (C-6′), 66.70 (C-1), 68.42 (C-2′), 70.87 (C-4′), 71.80, 71.92 (C-3′, C-5′), 72.62 (C-3), 100.79 (C-1′), 124.36 (C-13), 130.97, 131.12, 131.56 (C-5, C-7, C-14), 139.50 (C-4), 140.65 (C-6), 169.82, 170.12, 170.29, 170.54, 170.83 (5 CH_3CO), 200.45 (C-8);

for **18**: $[\alpha]_D^{20}$ +1.2° (*c* 0.8, CCl_4); ^{13}C NMR ($CDCl_3$) δ 14.18 (C-18), 20.50, 20.62, 20.73, 20.75, 20.78 (5 CH_3CO), 22.84 (C-17), 24.52 (C-3″), 25.40, 26.35 (C-4″, C-7″), 29.30, 29.43, 29.62, 79.75 (C-5, C-15), 31.97 (C-16), 33.01, 33.32 (C-2″, C-4), 42.76 (C-10″), 50.32, 52.38, 55.62 (C-8″, C-2, C-12″), 61.82 (C-6′), 67.12 (C-1), 68.54 (C-2′), 70.85, 70.92 (C-4′, C-15″), 71.80, 71.93, 71.98, 72.54, 72.80 (C-3′, C-5′, C-16″, C-9″, C-3), 101.08 (C-1′), 128.10, 129.15, 129.72, 134.95 (C-5″, C-6″, C-13″, C-14″), 113.20, 116.12, 121.36, 130.29, 135.19 (*m*-ClC_6H_4O), 176.74 (C-1″).



Scheme 3 *Reagents and conditions*: i, HOSu, DCC, THF, 25 °C, 10 h; ii, **15**, THF–1,4-dioxane, 25 °C, 48 h.

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References

1 K. Mori and T. Kiusho, *Liebigs Ann. Chem.*, 1991, **12**, 1309.
2 S. Hirsch and J. Kashman, *Tetrahedron*, 1989, **45**, 3897.
3 A. P. Kozikowski and J. P. Wu, *Tetrahedron Lett.*, 1990, **31**, 4309.
4 A. Kazuo, H. Koro, S. Yasuo and V. Kasuyuki, *Chem. Abstr.*, 1991, **115**, 176634t, 76.
5 A. G. Tolstikov, R. Kh. Yamilov, O. F. Prokopenko and G. A. Tolstikov, *Mendeleev Commun.*, 1992, 96.
6 A. G. Tolstikov, R. Kh. Yamilov, L. V. Spirikhin and G. A. Tolstikov, *Mendeleev Commun.*, 1992, 108.
7 A. G. Tolstikov, O. F. Prokopenko, R. Kh. Yamilov and G. A. Tolstikov, *Mendeleev Commun.*, 1991, 64.
8 A. G. Tolstikov, R. Kh. Yamilov, I. A. Kukovinets and G. A. Tolstikov, *Bioorg. Khim.*, 1993, **19**, 337 (*Russ. J. Bioorg. Chem.*, 1993, **19**, 182).
9 L. A. Baltina, S. A. Ryzhova, E. V. Vasil'eva and G. A. Tolstikov, *Bioorg. Khim.*, 1994, **20**, 55 (*Russ. J. Bioorg. Chem.*, 1994, **20**, 40).

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