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

Aleksander G. Tolstikov,^{*a} Olga V. Tolstikova^a and Genrikh A. Tolstikov^b

^a *G. K. Boreskov Institute of Catalysis, Siberian Branch of the Russian Academy of Sciences, 630090 Novosibirsk, Russian Federation. Fax: +7 3832 355 756*

^b *Novosibirsk Institute of Organic Chemistry, Siberian Branch of the Russian Academy of Sciences, 630090 Novosibirsk, Russian Federation.*

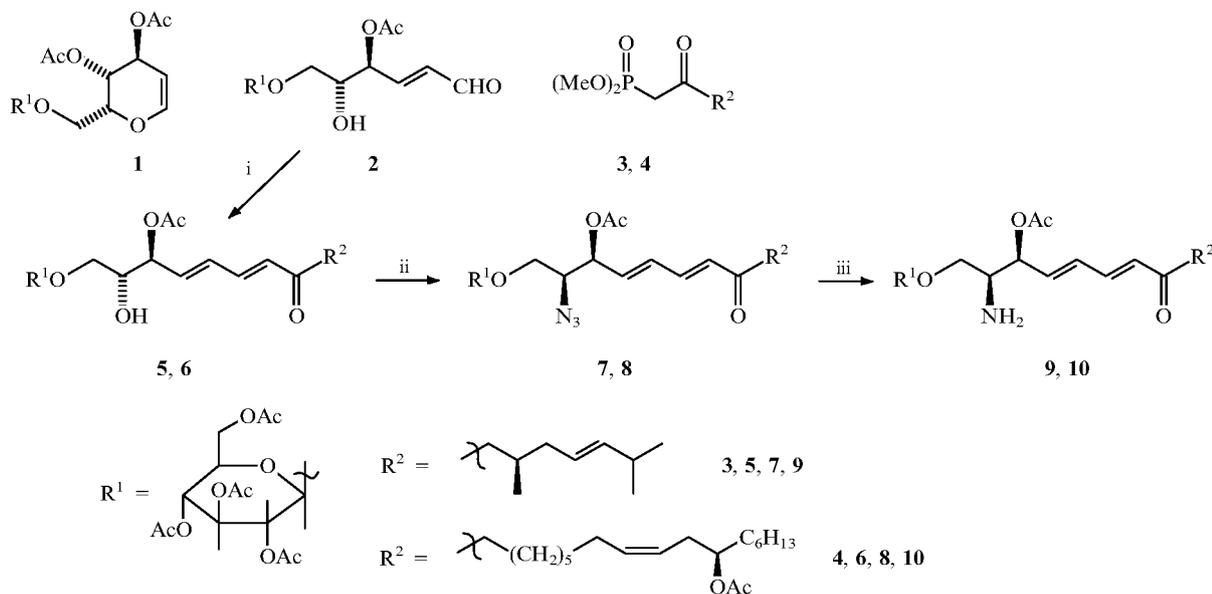
Hexa-*O*-acetyl-D-gentiobial **1** and its decyclization product (2*E*,4*S*,5*R*)-4-acetoxy-5-hydroxy-6-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyloxy)hex-2-enal **2** have been used to synthesize *O*-glycosylated aminodiols **9**, **10**, **15** that model the structure of natural lysocerebrosides. 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}

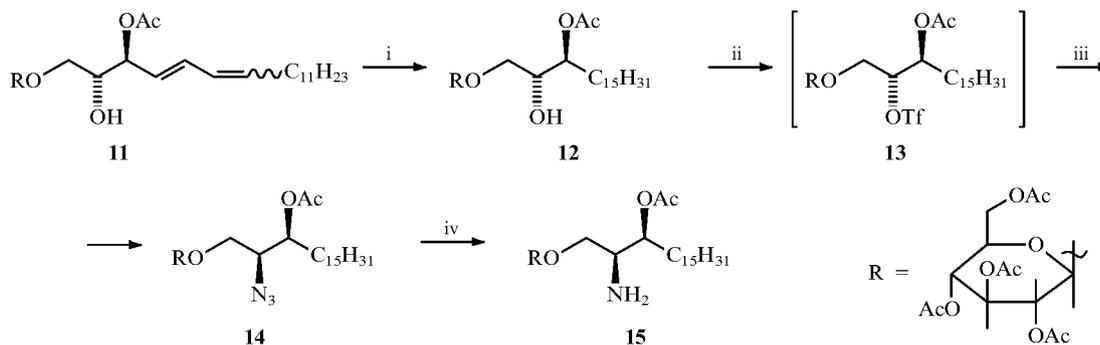
Continuing our studies in this field^{5–7} we have synthesized modified lysocerebrosides **9**, **10**, **15** intending to use them as the basic amino components with which to obtain conjugates with activated esters of arachidonic and glycyrrhizic acid derivatives. We plan not only to solve non-trivial synthetic

problems but also to look for new anti-viral and hormone-active compounds of selective and prolonged action.

We used enantioselective conversions of glycol **1** and aldehyde **2** (the product of glycol **1** acidic decyclization) as a basic Scheme for the synthesis of compounds **9**, **10**, **15**.⁷ To build the lipophilic segment of ketoaminodiols 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, CH₂Cl₂, 20 °C, 1 h; ii, (CF₃SO₂)₂O, Py, CH₂Cl₂, -10 °C, 0.5 h, then DMF, NaN₃, 20 °C, 4 h; iii, PPh₃, PhH, 45 °C, 5 h.



Scheme 2 Reagents and conditions: i, H₂, 10% Pd/C, MeCO₂Et, 20 °C, 5 h; ii, (CF₃SO₂)₂O, Py, CH₂Cl₂, -20 °C, 20 min; iii, NaN₃, DMF, CH₂Cl₂, 25 °C, 5 h; iv, PPh₃, 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 CH₂Cl₂ 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 NaN₃ 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%).

Aminodiols **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 (CF₃SO₂)₂O in the presence of pyridine in CH₂Cl₂ solution. The interaction of labile triflate **13** with NaN₃ produced azide **14** (70%). The latter was reduced by PPh₃ 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 cloprostrenol **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.

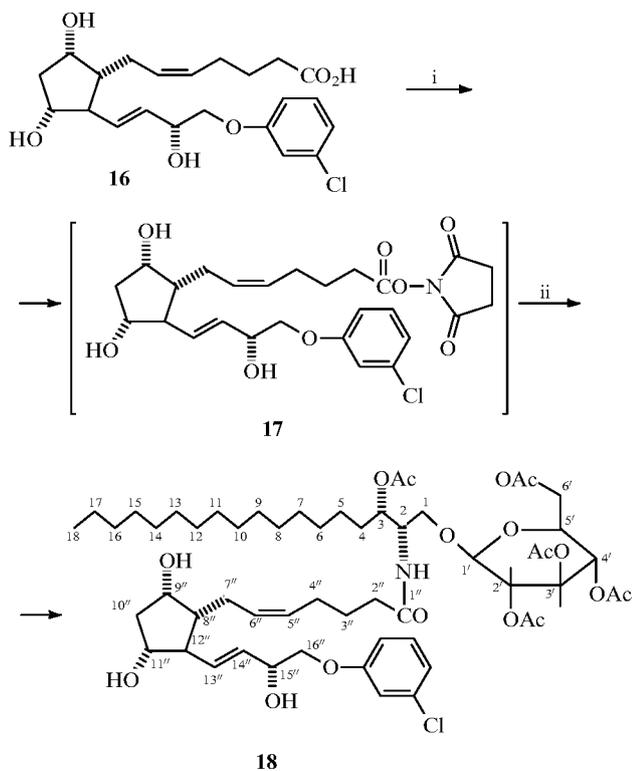
[†] Spectral data for **9**: [α]_D²⁰ -2.2° (*c* 1.8, CHCl₃); ¹³C NMR (CDCl₃) δ 17.69 (CH₃), 19.68 (C-10), 20.53, 20.64, 20.75, 20.80, 20.92 (5 CH₃CO), 25.55, 25.64 (CH₃, C-15), 29.40 (C-11), 37.18 (C-12), 48.50 (C-9), 54.44 (C-2), 61.75 (C-6'), 66.70 (C-1), 68.42 (C-2'), 70.87 (C-4'), 71.80, 71.92 (C-3', 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 CH₃CO), 200.45 (C-8);

for **18**: [α]_D²⁰ +1.2° (*c* 0.8, CCl₄); ¹³C NMR (CDCl₃) δ 14.18 (C-18), 20.50, 20.62, 20.73, 20.75, 20.78 (5 CH₃CO), 22.84 (C-17), 24.52 (C-3''), 25.40, 26.35 (C-4'', C-7''), 29.30, 29.43, 29.62, 29.75 (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*-ClC₆H₄O), 176.74 (C-1').

This study was supported by the Russian Foundation for Basic Research (grant no. 95-03-08517).

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).



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

Received: Moscow, 27th February 1996
Cambridge, 25th March 1996; Com. 6/01589A