Pergamon

Tetrahedron Letters 41 (2000) 7313–7315

TETRAHEDRON LETTERS

Lipophilic prodrugs of 1-deoxynojirimycin derivatives

Sandra Fouace[a] and Michel Therisod[b,*]

[a]*SESNAB, Pôle Sciences et Technologie, Université de La Rochelle, 17042 La Rochelle cedex, France*
[b]*LCBB, Bât. 420, ICMO, Université Paris-Sud, 91405 Orsay cedex, France*

Received 8 June 2000; accepted 9 July 2000

Abstract

We report a new synthesis of Miglitol, and its conversion to a lipophilic prodrug. The same procedure permits the preparation of a prodrug of 1-desoxynojirimycin and probably of other 1-deoxynojirimycin derivatives.

Inhibitors of α-glucosidases are of interest for two possible therapeutic actions:

- Antiviral: as inhibitors of α-glucosidases I and II, they can block the biosynthesis of viral glycoproteins (e.g. gp 120 of HIV).[1]
- Antidiabetic: as inhibitors of intestinal sucrase or phosphorylases, they can slow down the catabolism of sugars and lower the blood content in glucose.[2]

The latter activity can be a drawback if the drugs are to be used as antivirals, causing diarrhea and hypoglycaemia.[3]

Iminosugars, especially 1-deoxynojirimycine (1-dNJ) derivatives, have been shown to inhibit the development of HIV in vitro.[4] As drugs in vivo, however, they show an important hepatic toxicity, making lipophilic prodrugs promising derivatives. These prodrugs can avoid a rapid degradation in the liver by travelling as chilomicrons through the lymphatic system.[5] Miglitol (*N*-(2-hydroxyethyl)-1-deoxynojirimycine) is only available from Bayer (as BAY m1099). Its synthesis has been patented several times by this company.[6] This compound has been extensively studied, mainly for its antidiabetic potency.[7]

We report herein a new synthetic route to Miglitol, based on the strategy employed by Ganem to prepare 1-dNJ[8] (Fig. 1).

Our method shortcuts 1-dNJ itself, by introducing the hydroxyethyl group at an early stage. Two diastereomeric bromomercuric intermediates **1a** and **2a** are obtained, which can be easily separated by chromatography before their transformation into **1b** and **2b**, respectively.[10] The

* Corresponding author. Tel: +33-1-69156311; fax: +33-1-69157281; e-mail: therisod@icmo.u-psud.fr

0040-4039/00/$ - see front matter
PII: S0040-4039(00)01229-6

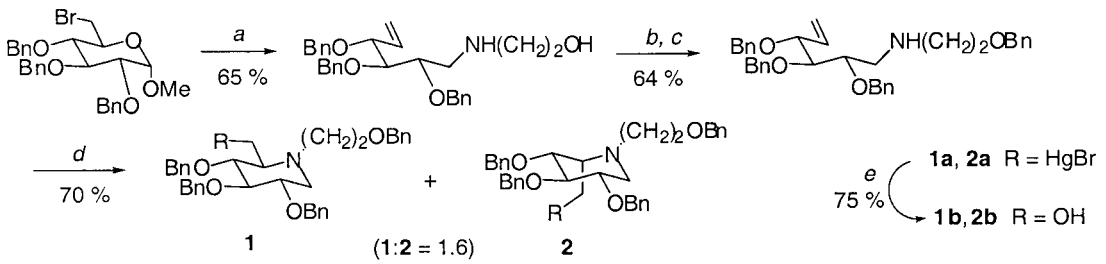

Figure 1. (*a*) Zn, $HO(CH_2)_2NH_2$, $NaBH_3CN$, $PrOH/H_2O$, reflux, 3 h; (*b*) NaH, BnCl, DMF; (*c*) $ClCOOCHClCH_3$, toluene/MeOH, reflux, 4 h;[9] (*d*) $HgOCOCF_3$, THF, rt, 12 h, then aq. $KHCO_3/KBr$; (*e*) $O_2/NaBH_4$, DMF

amount of the desired stereomer **1b** can be significantly improved by transformation of **2b** through the sequence: oxidation (Swern), epimerisation (DBU), reduction ($NaBH_4$). Compound **1b** was quantitatively deprotected by hydrogenolysis to give Miglitol.

One free hydroxyl group of the partly protected intermediate **1b** obtained, permits an easy coupling to cholesterol hemisuccinate **3**, to give, after hydrogenolysis, a lipophilic conjugate of Miglitol and cholestanol **4** (Fig. 2).

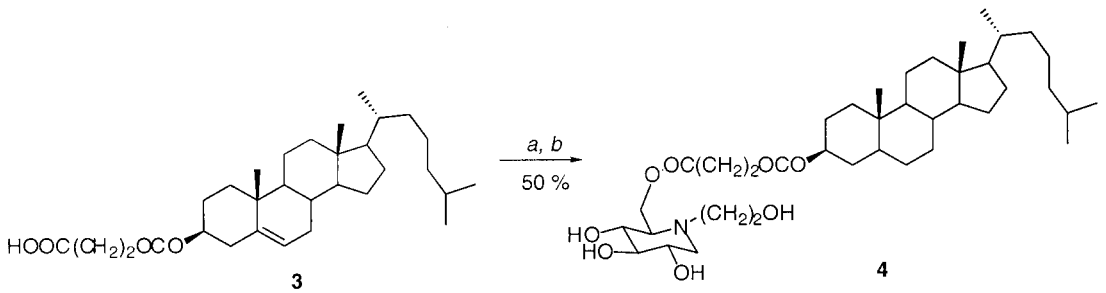

Figure 2. (*a*) (1) $SOCl_2$, DMF/toluene, 0°C to rt, 12 h; (2) NEt_3, **1b**, DCM, 2 h (55%); (*b*) H_2, Pd–C, EtOH (92%)

The same method can be employed for the synthesis of conjugates of 1-dNJ itself. We used the 55:25 diastereoisomeric mixture of protected intermediates **1c** and **2c** obtained in the Ganem synthesis. This gave a mixture of conjugates easily separated by chromatography (Fig. 3).

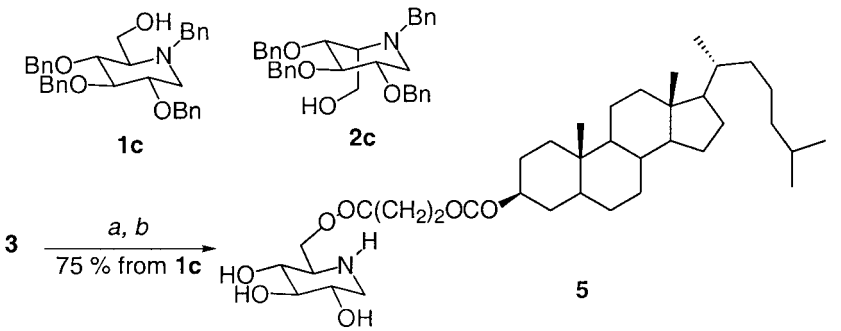

Figure 3. (*a*) (1) $SOCl_2$, DMF/toluene, 0°C to rt, 12 h; (2) NEt_3, **1c+2c**, DCM, 2 h (81%); (3) column chromatography; (*b*) H_2, Pd–C, EtOH (93%)

The same procedure could most probably be applied to other active derivatives of 1-dNJ and other iminosugars. The pharmacodynamics of these prodrugs of Miglitol and 1-dNJ will be estimated in animals.

Acknowledgements

We are grateful to Région Poitou-Charentes for financial support to S.F. We thank Prof. Y. Letourneux and Prof. L. Elkhiel for useful discussions and help.

References

1. Jacob, G. S. *Curr. Opin. Struct. Biol.* **1995**, *5*, 605–611.
2. Scheen, A. J. *Drugs* **1997**, *54*, 355–368.
3. Scofield, A. M.; Fellows, L. E.; Nash, R. J.; Fleet, G. W. J. *Life Sci.* **1988**, *39*, 645–650.
4. Gruters, R. A.; Neefjes, J. J.; Tersmette, M.; de Goede, R. E. Y.; Tulp, A.; Huisman, H. G.; Miedema, F.; Ploegh, H. L. *Nature* **1987**, *330*, 74–77.
5. Porter, C. J. H. *Crit. Rev. Ther. Drug Carrier Systems* **1997**, *14*, 333–393.
6. Kinast, G.; Schedel, M.; Köbernick, W. Eur. Pat. 49858, 1982.
7. Joubert, P. H.; Veuter, C. P.; Joubert, H. F.; Hillebrand, I. *Eur. J. Pharmacol.* **1985**, *28*, 705–708.
8. Bernotas, R. C.; Ganem, B. *Tetrahedron Lett.* **1985**, *26*, 1123–1126.
9. Kapnang, H.; Charles, G. *Tetrahedron Lett.* **1983**, 3233–3236.
10. Analytical data. Compound **1b**: ^{1}H NMR (400 MHz, $CDCl_3$), δ (ppm) 2.32 (m, 2H, H-1, H-5), 2.49 (td, 1H, J = 14.6, 3.6 Hz, N–CH_2–CH_2–), 3.03 (m, 1H, N–CH_2–CH_2–), 3.11 (dd, 1H, J = 11.4, 4.5 Hz, H-1), 3.46 (m, 2H, N–CH_2–CH_2–), 3.54 (m, 2H, H-2, H-3), 3.62 (t, 1H, H-4, J = 9.1 Hz), 3.78 (dd, 1H, J = 12.4, 1.4 Hz, H-6), 3.87 (dd, 1H, J = 12.4, 2.7 Hz, H-6′), 4.48, 4.52, 4.58–4.68, 4.82, 4.93, 4.94 (8H, O–CH_2–Ph), 7.29 (m, 20H, Ar); ^{13}C NMR (100 MHz, $CDCl_3$), δ (ppm) 51.1 (N–CH_2–CH_2–), 55 (C-1), 57.9 (C-6), 65.5 (C-5), 67.6 (N–CH_2–CH_2–), 72.9, 73.2, 75.3, 75.5 (O–CH_2–Ph), 77.9 (C-4), 78 (C-3), 86.7 (C-2); MS: 568 (M^+, 1), 536 (29), 446 (11), 91 (100). Compound **4**: ^{1}H NMR (400 MHz, CD_3OD), δ (ppm) 0.69 (s, 3H, CH_3-18), 0.85 (s, 3H, CH_3-19), 0.87 (d, 3H, J = 6.6 Hz, CH_3-27), 0.88 (d, 3H, J = 6.6 Hz, CH_3-26), 0.92 (d, 3H, J = 6.6 Hz, CH_3-21), 2.63–2.69 (m, 7H, NCH_2CH_2OH, $OCOCH_2CH_2COO$, H-1, H-6), 3.02 (m, 2H, NCH_2CH_2OH, H-1′), 3.30–3.63 (m, 5H, H-2, H-3, H-4, H-6, H-6′), 3.9 (m, 2H, NCH_2CH_2OH), 4.58 (m, 1H, H-3a chol.); IR: 3459, 1737, 2924, 3030–3092. MS (ESI): 679.1 $(M+H)^+$ (calc. for $C_{39}H_{67}NO_8$: 677.48). Compound **5**: ^{1}H NMR (400 MHz, CD_3OD), δ (ppm) 0.69 (s, 3H, CH_3-18), 0.85 (s, 3H, CH_3-19), 0.87 (d, 3H, J = 6.7 Hz, CH_3-27), 0.88 (d, 3H, J = 6.6 Hz, CH_3-26), 0.92 (d, 3H, J = 6.6 Hz, CH_3-21), 2.64–2.69 (m, 6H, $OCOCH_2CH_2COO$, H-1, H-1′), 3.38–3.45 (m, 1H, H-5), 3.73 (m, 1H, H-3a chol.), 3.94 (m, 3H, H-2, H-3, H-4), 4.38 (m, 1H, H-6), 4.43 (dd, 1H, J = 12, 4.5 Hz, H-6′); ^{13}C NMR (100 MHz, CD_3OD), δ (ppm) 12.5, 12.7, 19.2, 23, 23.2 (CH_3-18, CH_3-19, CH_3-21, CH_3-26, CH_3-27), 29.7, 29.8 ($COCH_2CH_2COO$), 35.1 (C-1), 46 (C-5), 55.6 (C-3a chol.), 63.5 (C-6), 67.6, 68, 69.3 (C-2, C-3, C-4); MS (ESI): 633.8 $(M+H)^+$ (calc. for $C_{37}H_{63}NO_7$: 633.46).