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Bioorganic & Medicinal Chemistry Letters 15 (2005) 3071–3075
Bioorganic & Medicinal Chemistry Letters

Total asymmetric synthesis of (−)-conduramine B-1 and of its enantiomer. *N*-Benzyl derivatives of conduramine B-1 are β-glucosidase inhibitors

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Received 31 January 2005; revised 1 April 2005; accepted 14 April 2005
Available online 4 May 2005

Abstract—The 'naked sugars' (+)- and (−)-7-oxabicyclo[2.2.1]hept-5-en-2-one have been converted into (−)-conduramine B-1 ((−)-**3**) and its enantiomer (+)-**3**, respectively. They have been condensed with a variety of aldehydes in the presence of $NaBH(OAc)_3$. The *N*-substituted derivatives **4** and *ent*-**4** so-obtained have been tested against two α-glucosidases, two amyloglucosidases, two β-glucosidases and one β-xylosidase for their inhibitory activities. Although (−)-**3** and (+)-**3** do not inhibit any of these enzymes at 1 mM concentration, *N*-benzylated derivatives of (−)-conduramine B-1 are selective and competitive inhibitors of β-glucosidases with K_i in low micromolecular range.

Gaucher's disease is the most prevalent of the lysosomal storage disorders.[1] The deficiency of the enzyme glucosylceramide β-glucosidase leads to accumulation of its nondegradable substrate glucosylceramide in monocyte-macrophage cells. Patients with Gaucher's disease exhibit hepatosplenomegaly, anemia, bone lesions and respiratory failure, with or without progressive neurological disorders. Current therapeutic strategies include expensive enzyme replacement and substrate depletion.[2] Unfortunately, the efficacy to neurological symptoms of this therapy is low.[3] The addition of competitive β-glucosidase inhibitor such as *N*-(*n*-nonyl)-1-deoxynojirimycin (**1**) (Fig. 1) to cultured cells stabilizes glucosylceramide β-glucosidase. The activity of the variant enzyme is enhanced to such an extent that significant improvement of therapeutic values could be achieved.[4,5] This represents an example of specifically acting chemical chaperones.[6] Recently, *N*-octyl-β-valienamine (**2**)[7] has also been found to act as a chemical chaperone to accelerate transport and maturation of F213I mutant β-glucosidase and it may have a potential as drug in the treatment of Gaucher's disease. Less polar compounds than **1** and **2** should pass more readily through the blood–brain barrier.

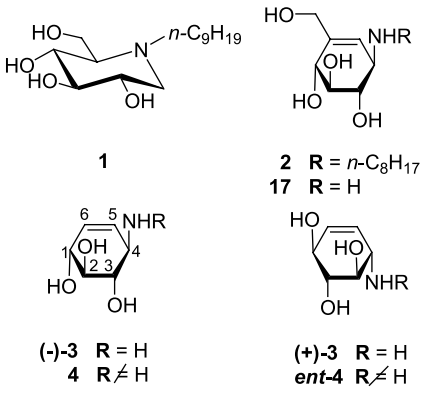

Figure 1.

We have thus examined whether conduramine B-1 (**3**), which can be seen as a de(hydroxymethyl) derivative of β-valienamine, would not be a β-glucosidase inhibitor.[8] We report here its total, asymmetric synthesis and its inhibitory activity towards two α-glucosidases, two amyloglucosidases, two β-glucosidases and one β-xylosidase. Neither (−)-**3**, nor (+)-**3** did inhibit any of these enzymes at 1 mM concentration. Interestingly,

Keywords: Asymmetric synthesis; Conduramine B-1; β-Glucosidases; Inhibition; Naked sugars.
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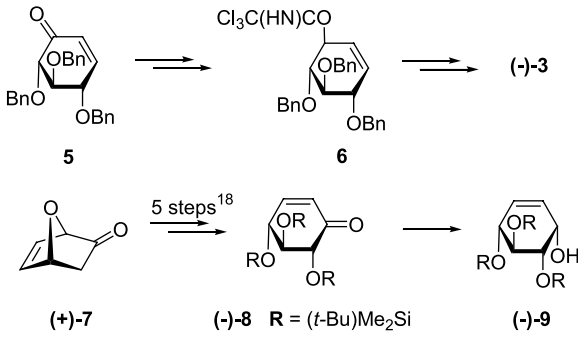
doi:10.1016/j.bmcl.2005.04.023

however, *N*-benzylation of conduramine B-1 generates derivatives **4** that are β-glucosidase inhibitors in the low micromolecular range. As expected, enantiomers *ent*-**4** do not inhibit, or inhibit poorly the same β-glucosidases. A few conduramine B-1 derivatives **4** are weak inhibitors of β-xylosidase from *Aspergillus niger*.

Racemic conduramine B-1[9] ((±)-**3**) tetraacetate has been prepared first in 1962 by Nakajima et al.[10] A protected form of (−)-**3** has been obtained through dynamic kinetic asymmetric transformation of (±)-conduritol B[11] tetrakis(3,3,3-trichloropropionates) by Trost et al.[12] Unprotected conduramine B-1 (−)-**3** was prepared first by Stick and co-workers[13] through Overman rearrangement[14] of trichloroacetamidate **6**. The latter compound was derived from methyl D-glucopyranoside following a multistep process involving the formation of enone **5** (Scheme 1).[15]

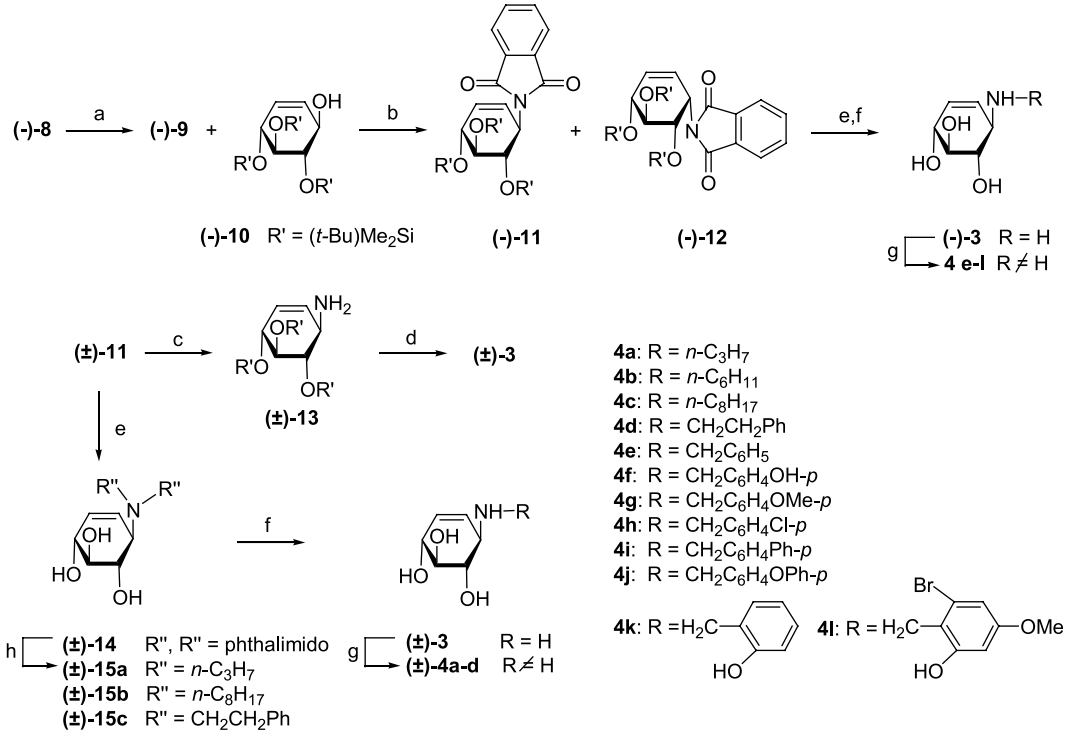


Scheme 1.

We report here a new synthesis of (−)-**3** applying our 'naked sugar' methodology[16] and which converts (+)-7-oxabicyclo[2.2.1]hept-5-en-2-one[17] ((+)-**7**) into enone (−)-**8** and into (−)-conduritol F ((−)-**9**).[18,19] The same method starting with (−)-**7** allowed one to prepare (+)-*ent*-conduramine B-1 ((+)-**3**) for the first time.

Reduction of cyclohexenone (−)-**8** with $NaBH_4/CeCl_3 \cdot 7H_2O$ in methanol (0 °C, 3 h) gave a 2.5:1 mixture of alcohols (−)-**9** and (−)-**10** in 98% yield.[18] Treatment of this mixture with phthalimide, diethyl azodicarboxylate and triphenylphosphine (all in 1.25 equiv)[20] in dry toluene (0 °C, 12 h) provided a 4:1 mixture of *N*-substituted phthalimides (−)-**11** and (−)-**12** (87%) that were separated by flash column chromatography on silica gel (Scheme 2).

In order to study the reactions of these phthalimides we reacted racemic (±)-**11** (51% yield based on (±)-**8**) with an excess of hydrazine (5 equiv of $NH_2NH_2 \cdot H_2O$, MeOH, 5 h, 65 °C). This furnished amine (±)-**13** in 77% yield. Unfortunately, desilylation ($Bu_4NF \cdot 3H_2O$, THF) of (±)-**13** gave (±)-**3** which could not be purified. Thus, we turned back to enantiomerically pure (−)-**11** and undertook its desilylation under acidic conditions (1% *p*-toluenesulfonic acid in MeOH, 30 min under



Scheme 2. Reagents and conditions: (a) $NaBH_4/CeCl_3 \cdot 7H_2O$/MeOH, 0 °C, 3 h; (b) phthalimide, EtOOCN=NCOOEt, Ph_3P/toluene, 0 °C, 12 h/separation by flash chromatography; (c) $NH_2NH_2 \cdot H_2O$, MeOH, 5 h, 65 °C; (d) $Bu_4NF \cdot 3H_2O$/THF, 20 °C, 15 min; (e) 1% TsOH in MeOH, 65 °C, reflux, 30 min; (f) 40% $MeNH_2$ in H_2O, 20 °C, 45 min, solvent evaporation in vacuo, filtration on Dowex-50W-X2 (H^+ form)/2 N NH_4OH; (g) RCHO (1 equiv), $NaBH(OAc)_3$ (1.4 equiv)/MeOH, 20 °C/2–5 h/yield: 81–99%; (h) RCHO (2.4 equiv), $NaBH(OAc)_3$ (3.4 equiv)/MeOH, 20 °C/2–5 h/yield: 49–68%.

reflux). This provided (−)-**14**, the treatment of which with 40% aqueous solution of methylamine[21] (20 °C, 45 min), followed by filtration on acidic Dowex-50W-X2, (H^+) gave (−)-**3** (elution with 2 N NH_4OH) in 95% yield (Scheme 2).

The *N*-substituted derivatives (±)-**4a**–**d**, enantiomerically pure **4e**–**l** and *N*,*N*-disubstituted derivatives (±)-**15a**–**c** were prepared by standard reductive amination of corresponding aldehydes.[22] Starting with 'naked sugar' (−)-**7**, (+)-*ent*-conduramine B-1 ((+)-**3**) and its *N*-substituted derivatives were obtained in the same way.[23–25]

We have tested compounds (−)-**3** and (+)-**3**, (±)-**4e**–**l** some of their enantiomers *ent*-**4e**–**l**, (−)-**14**, (+)-*ent*-**14** and (±)-**15a**–**c** for their inhibitory activities towards seven commercially available glycosidases. The data are summarized in Table 1.

Ogawa et al.[27] have found that β-valienamine (**17**) (Fig. 1) does not inhibit β-glucocerebrosidase whereas *N*-alkyl derivatives can be potent inhibitors of this enzyme. Thus, our finding is that conduramine B-1 ((−)-**3**) does not inhibit β-glucosidases from yeast and rice whereas *N*-substituted derivatives **4** do, is not a surprise. They also found that **17** and its *N*-alkyl derivatives inhibit α-glucosidase from yeast. This is not the case with the *N*-alkyl derivatives of conduramine B-1 ((±)-**4a**–**d**).[28] The latter, however, are moderate inhibitors of β-glucosidase from almonds (IC_{50} = 32 μM for R = *n*-hexyl and CH_2CH_2Ph). *N*,*N*-Disubstitution with *n*-propyl, *n*-octyl or β-phenylethyl groups leads to very bad β-glucosidase inhibitors ((±)-**15a**–**c**). However, *N*-monosubstitution with benzyl moieties as in **4e**–**j** generates the best and the most selective β-glucosidase inhibitors. The same compounds **4e**–**j** neither recognize α-glucosidases nor amyloglucosidases. The best inhibitors are **4e**,**i** and **j** with inhibition constant K_i = 10, 8 and 13 μM, respectively (Table 1). Lineweaver–Burk plots establish that they are competitive inhibitors. The most potent inhibitor **4i** of β-glucosidase from almonds is also the best inhibitor of β-glucosidase from *Caldocellum saccharolyticum*.

In summary, a new, total asymmetric synthesis of (−)-conduramine B-1 ((−)-**3**) has been developed. The same method has been used to prepare its enantiomer (+)-**3**.

Table 1. Inhibitory activity of (−)-conduramine B-1 ((−)-**3**) and *N*-substituted derivatives, and of some of their enantiomers[a,b,c]

Inhibitor		Enzyme						
Compounds	R=	α-Glucosidase		Amyloglucosidase		β-Glucosidase		β-Xylosidase
		Yeast	Rice	*Aspergillus niger*	*Rhizopus* mold	Almonds	*Caldocellum saccharolyticum*	*Aspergillus niger*
(−)-**3**	H	ni	ni	ni	ni	ni	ni	ni
(+)-**3**	H	ni	ni	ni	ni	ni	ni	ni
(±)-**4a**	*n*-C_3H_7	ni	ni	ni	30%	80%, IC_{50} = 66	nm	ni
(±)-**4b**	*n*-C_6H_{13}	ni	ni	ni	ni	92%, IC_{50} = 32	nm	ni
(±)-**4c**	*n*-C_8H_{17}	ni	ni	ni	ni	85%, IC_{50} = 69	nm	ni
(±)-**4d**	CH_2CH_2Ph	ni	ni	ni	ni	86%, IC_{50} = 32	nm	ni
4e	Bn	ni	ni	ni	ni	96%, IC_{50} = 32 K_i = 10 (C)	43%	74%
ent-**4e**		ni	ni	63%	72%	51%	ni	ni
4f	$CH_2C_6H_4OH$-*p*	ni	ni	31%	57%	93%, IC_{50} = 72	56%	67%
ent-**4f**		ni	ni	94%	85%	26%	ni	ni
4g	$CH_2C_6H_4OMe$-*p*	ni	ni	ni	ni	95%, IC_{50} = 52 K_i = 25 (C)	68%	74%
ent-**4g**		ni	ni	63%	72%	51%	ni	ni
4h	$CH_2C_6H_4Cl$-*p*	ni	ni	ni	ni	96%, IC_{50} = 35	84%, IC_{50} = 185	ni
ent-**4h**		ni	ni	45%	72%	82%	ni	ni
4i	$CH_2C_6H_4Ph$-*p*	ni	ni	ni	ni	97%, IC_{50} = 32 K_i = 8 (C)	94%, IC_{50} = 35	ni
ent-**4i**		ni	ni	ni	ni	56%	ni	ni
4j	$CH_2C_6H_4OPh$-*p*	ni	ni	ni	ni	97%, IC_{50} = 43 K_i = 13 (C)	71%, IC_{50} = 52	ni
ent-**4j**		ni	ni	ni	ni	ni	ni	ni
4k		41%	ni	ni	29%	ni	ni	ni
ent-**4k**		ni	ni	42%	41%	ni	ni	ni
4l		ni	ni	ni	ni	ni	43%	ni
ent-**4l**		ni	ni	ni	ni	ni	ni	ni
(±)-**15a**	*n*-C_3H_7	ni	ni	ni	ni	36%	ni	ni
(±)-**15b**	*n*-C_8H_{17}	ni	ni	ni	ni	ni	83%	ni
(±)-**15c**	CH_2CH_2Ph	ni	ni	ni	ni	36%	ni	ni

Percentage of inhibition at 1 mM concentration of the inhibitor, IC_{50} and K_i in μM, when measured. Optimal pH, 35 °C.

[a] For conditions of measurement, see Ref. 26.

[b] (C): competitive (Lineweaver–Burk plots), ni: no inhibition at 1 mM concentration; nm: not measured.

[c] Both phthalimides (−)-**14** and (+)-*ent*-**14** were devoid of inhibitory activity towards the enzymes tested here.

Although conduramine B-1 does not inhibit β-glucosidases (from almonds and from *C. saccharolyticum*) and β-xylosidase from *A. niger*, its *N*-benzyl derivatives are good competitive inhibitors of these enzymes. The most potent β-glucosidase inhibitor, *N*-(*p*-phenylbenzyl)-conduramine B-1 (**4i**) is also the most selective inhibitor. Because of their relative important hydrophobicity, *N*-benzyl derivatives of conduramine B-1 should be tested for their ability to act as chemical chaperones and for their therapeutic potential for the Gaucher's disease.

Acknowledgements

We are grateful to the Office Fédéral de la Recherche et de la Science (OFES, No. 030738, European FP6 project, TRIoH) for financial support. We thank also Mr. Martial Rey, F. Sepúlveda and S. Reddy Dubbaka for their technical help and Professor Inmaculada Robina, University of Seville, for useful discussions.

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23. All compounds were obtained in analytically pure form and fully characterized. Data of (+)-**3**: $[\alpha]_{589}^{25}$ +173 (c = 0.29, MeOH); IR (film): 3340, 2860, 1650, 1615, 1575, 1400 cm^{-1}; UV (MeOH): δ_{max} 207 (ε = 965); ^1H NMR (400 MHz, CD_3OD): δ 5.62, 5.54 (2H, 2ddd, $J_{1,6} \cong J_{1,5} \cong J_{6,4} \cong J_{5,4}$ = 2.4, $J_{5,6}$ = 10.2, H-5, H-6), 4.09 (1H, m, H-1), 3.42 (1H, dd, $J_{2,3}$ = 9.8, $J_{3,4}$ = 7.8, H-3), 3.47–4.26 (2H, m, H-2, H-4); ^{13}C NMR (100.6 MHz, CD_3OD): δ 131.3, 129.7 (2d, 162, C-5, C-6), 77.8, 77.7 (2d, 143, C-2, C-3), 73.8 (d, 144, C-1), 55.7 (d, 139, C-4). Anal. Calcd for $C_6H_{11}NO_3$ (145.074): C, 49.65, H, 7.64. Found: C, 50.01; H, 7.51.

24. Data of (+)-*ent*-**4e**: $[\alpha]_{589}^{25}$ +87 (c = 0.075, MeOH); IR (KBr): 3405, 1610, 1545, 1420, 1210, 1125 cm^{-1}; UV (MeOH): δ_{max} 260 (ε = 360), 258 (350), 215 (3290); ^1H NMR (400 MHz, CD_3OD): δ 7.45–7.30 (5H, m), 5.76–5.72 (2H, m, H-5, H-6), 4.12 (dd, $J_{1,2}$ = 7.9, $J_{1,6}$ = 3.2, H-1), 4.05, 3.93 (2d, ^2J = 12.9, H_2C(Bn)), 3.59 (dd, $J_{2,3}$ = 10.0, $J_{3,4}$ = 8.7, H-3), 3.46 (dd, $J_{3,4}$ = 8.7, $J_{4,5}$ = 3.2, H-4), 3.43 (dd, $J_{2,3}$ = 10.0, $J_{1,2}$ = 7.9, H-2); ^{13}C NMR (100.6 MHz, CD_3OD): δ 138.8 (s), 132.9, 126.1 (2d, 162, C-5, C-6), 130.0, 129.7, 128.8 (3d, 160, CH_{ar}), 77.9 (d, 145, C-2), 73.9 (d, 138, C-3), 73.4 (d, 147, C-1), 61.4 (d, 136, C-4), 50.8 (t, 137). Anal. Calcd for $C_{13}H_{17}NO_3$ (235.121): C, 66.36; H, 7.28; N, 5.95. Found: C, 65.87; H, 7.01; N, 6.04.

25. Data of (+)-*ent*-**4i**: $[\alpha]_{589}^{25}$ +107 (c = 0.15, MeOH); IR (KBr): 3365, 2855, 1560, 1410, 1340, 1125, 1040 cm^{-1}; UV (MeOH): δ_{max} 268 (ε = 6370), 249 (7160), 217 (5450); ^1H NMR (400 MHz, CD_3OD): δ 7.68–7.61 (4H, m), 7.54–7.32 (5H, m), 5.85 (ddd, $J_{5,6}$ = 10.4, $J_{4,5}$ = 2.0, $J_{1,5}$ = 1.9, H-5), 5.80 (1H, ddd, $J_{5,6}$ = 10.4, $J_{4,6}$ = 2.1, $J_{1,6}$ = 2.0, H-6), 4.15, 4.03 (2d, ^2J = 13.0), 4.12 (1H, dd, $J_{1,2}$ = 7.9, $J_{1,6}$ = 2.0, H-1), 3.63 (dd, $J_{2,3}$ = 9.7, $J_{3,4}$ = 8.8, H-3), 3.53 (dd, $J_{3,4}$ = 8.8, $J_{4,5}$ = 3.1, H-4), 3.45 (dd, $J_{2,3}$ = 9.7, $J_{1,2}$ = 7.9, H-2); ^{13}C NMR (100.6 MHz, CD_3OD): δ 142.6, 141.6, 135.1 (3s), 134.7 (d, 163, C-5), 131.0, 129.9, 128.6, 128.4, 127.9 (5d, 160), 123.9 (d, 158, C-6), 77.7 (d, 139, C-2), 73.1, 73.0 (2d, 144, C-1, C-3), 61.4 (d, 141, C-4), 49.9 (t, 142); HRMS (MALDI-TOF): calcd for $C_{19}H_{21}NO_3Na$: 334.1419 [M+Na^+]. Found: 334.1414.

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28. *N*-Benzylation of α-valienamine[29] and 2-(aminomethyl)-pyrrolidine-3,4-diols[22] also enhances their inhibitory activities and selectivities towards glycosidases.

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