Synthesis of Isofagomine and a New C_6 Pyrrolidine Azasugar with Potential Biological Activity

Pieter E. R. Espeel,[a] Kathleen Piens,[b] Nico Callewaert,[b] Johan Van der Eycken*[a]

[a] Laboratory for Organic and Bioorganic Synthesis, Department of Organic Chemistry, Ghent University, Krijgslaan 281 (S.4), 9000 Gent, Belgium

[b] Laboratory for Protein Biochemistry and Biomolecular Engineering, Department of Biochemistry, Physiology and Microbiology, Ghent University, K.L. Ledeganckstraat 35, 9000 Gent, Belgium
Fax +32(9)2644998; E-mail: Johan.VanderEycken@UGent.be

Received 17 April 2008

Abstract: An efficient asymmetric synthesis of isofagomine, based on a precursor containing three differentiated hydroxyl functions, is described. The side product in the key alkylation step is converted into (2*S*,3*R*,4*R*)-2,4-bis(hydroxymethyl)-3-hydroxypyrrolidine, a new C_6 pyrrolidine azasugar, which inhibits α-glucosidase from yeast.

Keywords: asymmetric synthesis, azasugars, glycosidase inhibitors, hydroboration, ring-closing metathesis

Isofagomine (**1**) is the most representative member of the gluco-configured 1-azasugars: the ring oxygen, the anomeric carbon atom and the C-2 hydroxyl group in D-glucose (**2**) are replaced by a methylene group, a nitrogen and a hydrogen atom, respectively (Figure 1). Due to these structural features, the stable protonated form of isofagomine (**1**) shows obvious stereoelectronic similarity to the oxocarbenium ion **3**, which develops in the transition state during enzymatic hydrolysis of a glucoside while being stabilized by the enzyme.[1,2] Therefore, isofagomine (**1**) is a very potent reversible inhibitor of β-glucosidase.[3]

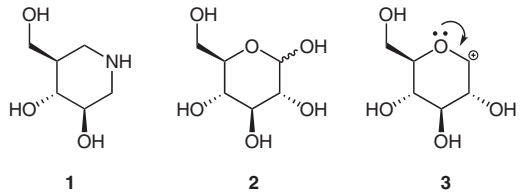
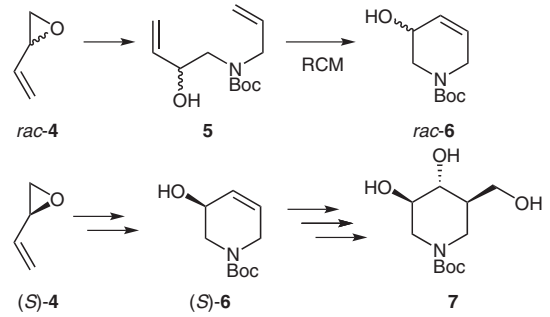


Figure 1

Syntheses of isofagomine (**1**) are numerous,[1,2] starting either from the chiral pool or from a prochiral precursor. In most cases, however, enantiomer or diastereomer separation is cumbersome. In order to turn isofagomine (**1**) into a synthetically useful and flexible chiral building block, an efficient synthesis should provide reasonable amounts of a suitably protected derivative, containing three differentiated hydroxyl functions. Most of the hitherto reported syntheses of isofagomine (**1**) lack this possibility for ready differentiation of the hydroxyl groups.

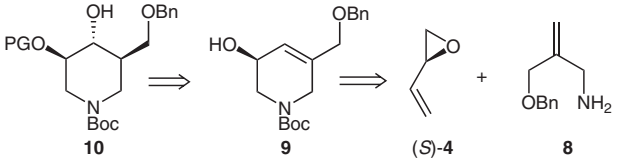
SYNLETT 2008, No. 15, pp 2321–2325
Advanced online publication: 22.08.2008
DOI: 10.1055/s-2008-1078280; Art ID: G08808ST



Scheme 1

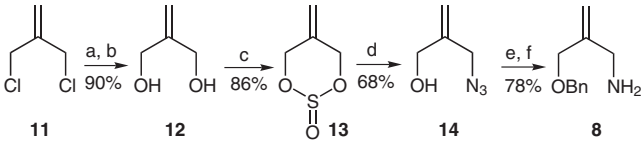
A recently published synthesis[4] of isofagomine (**1**) is based on *N*-Boc-5-hydroxy-3,4-didehydropiperidine (*rac*-**6**) as a key intermediate (Scheme 1). It is obtained by nucleophilic opening of the epoxide in vinyloxirane (*rac*-**4**) with allylamine, followed by Boc protection and ring-closing metathesis (RCM). The didehydropiperidine *rac*-**6** is then resolved via kinetic enzymatic resolution and subsequently used for the synthesis of various azasugars.[4]

We modified this reaction sequence in such a way that racemic vinyloxirane (*rac*-**4**) was replaced with (*S*)-vinyloxirane [(*S*)-**4**], thus rendering enzymatic resolution obsolete. Enantiopure (*S*)-vinyloxirane [(*S*)-**4**][5] was obtained via hydrolytic kinetic resolution with a chiral (salen) Co^{III} complex.[6] Using racemic *rac*-**6** as a reference, an enantiomeric excess of 97% ee was determined for (*S*)-**6** by chiral HPLC analysis.[7] The ee was improved to ≥99% after recrystallization from isooctane. Proceeding with (*S*)-**6**, we tried to prepare *N*-Boc-isofagomine (**7**) according to a described procedure (Scheme 1).[4] However, in our hands, two steps[8] involving the incorporation of the exocyclic methylene carbon were troublesome, rendering this synthesis unsuitable for upscaling. To circumvent these problems we devised an alternative synthesis,[9] which is depicted in the retrosynthetic scheme below (Scheme 2). The piperidine derivative **9** is prepared via alkylation of 2-benzyloxymethylallylamine (**8**) with (*S*)-vinyloxirane [(*S*)-**4**], followed by RCM. In our approach, all carbon atoms of isofagomine (**1**) are already present prior to RCM. After suitable hydroxyl protection in **9** and stereoselective hydroboration, the three hydroxyl groups in **10** are differentiated.



Scheme 2 Retrosynthesis

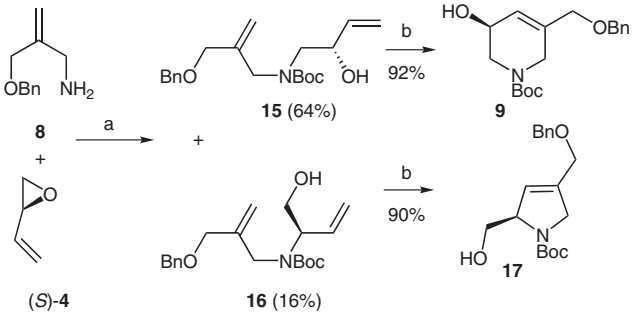
The large-scale preparation of 2-benzyloxymethylallylamine (**8**) involved a six-step sequence with an overall yield of 41% (Scheme 3). 3-Chloro-2-chloromethyl-1-propene (**11**) was converted into 2-methylidene-1,3-propanediol (**12**) via substitution with acetate and subsequent methanolysis.[10] Transformation to the cyclic sulfite **13** followed by treatment with sodium azide yielded 2-azidomethylprop-2-en-1-ol (**14**),[11] which was converted into 2-benzyloxymethylallylamine (**8**)[12] after O-benzylation and Staudinger reduction.



Scheme 3 *Reagents and conditions*: (a) AcOH, Et_3N, reflux, overnight; (b) K_2CO_3, MeOH, r.t., overnight; (c) $SOCl_2$, CCl_4, 0 °C, 50 min; (d) NaN_3, DMF, 80 °C, 15 min; (e) (i) NaH, DMF, 0 °C, 30 min; (ii) BnBr, DMF, r.t., overnight; (f) (i) Ph_3P, THF, r.t., overnight; (ii) 2 M NaOH, 80 °C, 1 h.

Opening of the epoxide in (*S*)-**4** by nucleophilic attack of **8** and subsequent amine protection led to a regioisomeric mixture **15/16** (ratio 7:3), which could be separated (Scheme 4).[12,13] Products arising from an S_N2' mechanism were not detected. Both alkylation products **15** and **16** underwent RCM upon treatment with the Grubbs second generation catalyst,[14] yielding six- and five-membered ring products **9**[12] and **17**,[15] respectively, with more than 99% ee (Figure 2). This indicates that even in the case of **16**, no racemization occurred, and a clean inversion of configuration was assumed.

In an attempt to obtain stereoselective hydroboration, we initially chose to protect the hydroxyl function in **9** with the bulky TBDPS group. However, hydroboration using



Scheme 4 *Reagents and conditions*: (a) (i) **8** (3 equiv), H_2O, 100 °C, 6 h; (ii) Boc_2O, 1 M NaOH, dioxane–H_2O, r.t., overnight; (b) Grubbs second generation catalyst (3.25 mol%), CH_2Cl_2, r.t., 48 h.

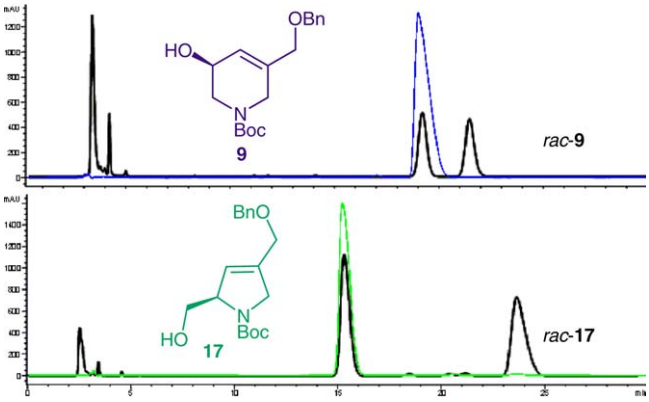


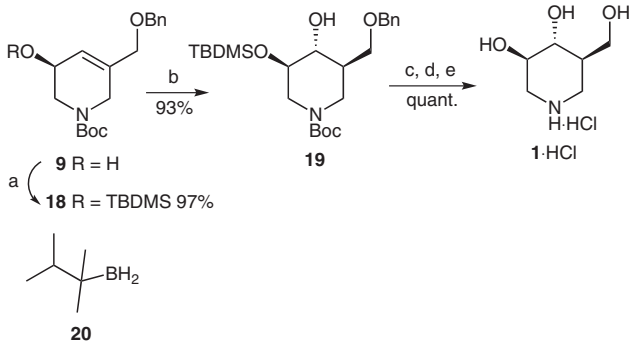
Figure 2 Chiral HPLC analysis: Chiralpak AD-H; *n*-hexane–EtOH, 95:5 (isocratic); T = 35 °C; UV detection at λ = 214 nm

9-BBN in different solvents and at elevated temperature appeared to be very sluggish, due to steric hindrance. Switching to the less sterically demanding TBDMS group rendered **18** reactive towards hydroboration with thexylborane (**20**; Scheme 5).[12,16] Standard deprotection of hydroxyl and amine protecting groups in **19** afforded the hydrochloride of isofagomine (**1**·HCl; 53% overall yield from (*S*)-**4**].

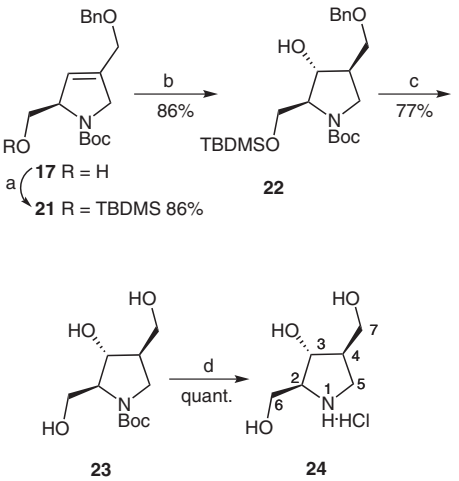
An analogous hydroboration–deprotection sequence, starting from **17**, yielded (2*S*,3*R*,4*R*)-2,4-bis(hydroxymethyl)-3-hydroxypyrrolidine hydrochloride (**24**),[15,17] a novel C_6 pyrrolidine azasugar [8% overall yield from (*S*)-**4**]. The concomitant removal of the TBDMS group during hydrogenolysis of **22** is noteworthy (Scheme 6).[18]

The ^1H NMR and ^{13}C NMR data as well as the optical rotation[19] {$[\alpha]_D$ +20 (*c* = 0.93, EtOH)} confirmed the structure of the synthesized isofagomine hydrochloride (**1**·HCl). The structure of **24** was harder to prove. Because of the conformational flexibility of five-membered rings, the ^1H–^1H vicinal coupling constants of the ring protons were useless for stereochemical assignment. Therefore, the rigid bicyclic oxazolidinone **25**[20] was synthesized[21] and submitted to a NOESY experiment: three pairs of nOe contacts supported the anticipated stereochemistry (Scheme 7).

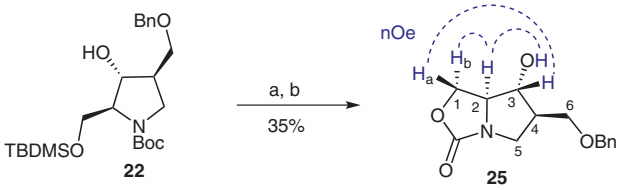
Azasugar **24** was tested for inhibition of several commercial glycosidases[22] (Table 1) and proved to be a slightly



Scheme 5 *Reagents and conditions*: (a) TBDMSCl, imidazole, DMAP, CH_2Cl_2, r.t., overnight; (b) **20** (5 equiv), THF, 0 °C → r.t., 48 h, 30% aq H_2O_2, 2 M NaOH, 0 °C, 2 h; (c) TBAF, THF, r.t., 2 h; (d) H_2, Pd/C (10%), EtOH, r.t., overnight; (e) 1 M HCl, r.t., overnight.



Scheme 6 *Reagents and conditions*: (a) TBDMSCl, imidazole, DMAP, CH_2Cl_2, r.t., overnight; (b) **20** (5 equiv), THF, 0 °C → r.t., 48 h, 30% aq H_2O_2, 2 M NaOH, 0 °C, 2 h; (c) H_2, Pd/C (10%), EtOH, r.t., 48 h; (d) 1 M HCl, r.t., overnight.



Scheme 7 *Reagents and conditions*: (a) TBAF, THF, r.t., 2 h; (b) diethylaminosulfur trifluoride (DAST), CH_2Cl_2, 0 °C→ r.t., 4 h.

Table 1 Glycosidase Inhibitor Activities (K_i [μM] at 37 °C)

Enzyme (source)	α-Glucosidase (yeast)	β-Glucosidase (almond)	α-Mannosidase (jack bean)
isofagomine **1**	86	0.11	770
azasugar **24**	65	195	no inhibition
rac-**24**	149	>1000	no inhibition

stronger inhibitor for α-glucosidase than isofagomine (**1**), but a weaker inhibitor for β-glucosidase.[3] No inhibition was observed for α-mannosidase.[23] The higher K_i values of the racemate *rac*-**24** indicate that, of the two enantiomers, the synthesized (2*S*,3*R*,4*R*)-**24** is the more potent inhibitor.

In summary, enantiopure isofagomine (**1**) was synthesized with an overall yield of 53%, starting from (*S*)-vinyloxirane [(*S*)-**4**]. Key steps included nucleophilic opening of (*S*)-vinyloxirane [(*S*)-**4**], ring-closing metathesis and stereoselective hydroboration. The regioisomeric alkylation product **16** of the epoxide opening was used in an analogous reaction sequence yielding (2*S*,3*R*,4*R*)-2,4-bis(hydroxymethyl)-3-hydroxypyrrolidine (**24**; 8% overall yield from (*S*)-**4**]. This novel C_6 pyrrolidine azasugar is a moderate inhibitor of α-glucosidase from yeast.

Acknowledgment

FWO-Vlaanderen, the Federal Government [IAP-Phase VI (2007-2011), Project P6/19] and Ghent University are greatly acknowledged for financial support. P. Espeel is indebted to FWO-Vlaanderen for a research assistant position.

References and Notes

(1) Stütz, A. E. *Iminosugars as Glycosidase Inhibitors*; Wiley-VCH: Weinheim, **1999**.
(2) Compain, P.; Martin, O. R. *Iminosugars*; Wiley: Chichester, **2007**.
(3) Dong, W.; Jespersen, T.; Bols, M.; Skrydstrup, T.; Sierks, M. R. *Biochemistry* **1996**, *35*, 2788.
(4) Ouchi, H.; Mihara, Y.; Takahata, H. *J. Org. Chem.* **2005**, *70*, 5207.
(5) $[\alpha]_D$ +20 (*c* = 1, pentane).
(6) Schaus, S.; Brandes, B.; Larrow, J.; Tokunaga, M.; Hansen, K.; Gould, A.; Furrow, M.; Jacobsen, E. *J. Am. Chem. Soc.* **2002**, *124*, 1307.
(7) Chiral HPLC analysis: Chiralcel OD-H; *n*-hexane–EtOH, 99:1 (isocratic); T = 35 °C; UV (λ = 214 nm).
(8) Incomplete stereoselective epoxidation[4] and incomplete regioselective epoxide opening with vinyl cuprate[4] both yielded an inseparable mixture of product and starting material.
(9) For a recent related approach towards racemic isofagomine (*rac*-**1**), see: Imahori, T.; Ojima, H.; Tateyama, H.; Mihara, Y.; Takahata, H. *Tetrahedron Lett.* **2008**, *49*, 265.
(10) Jautelat, M.; Artl, D.; Wieland, H. Eur Patent, EP 0110245, **1984**.
(11) Friedrich, M.; Savchenko, A.; Wächtler, A.; de Meijere, A. *Eur. J. Org. Chem.* **2003**, *11*, 2138.
(12) **Selected Experimental Details**:
O-Benzylation and Staudinger Reduction of 14: To an ice-cooled solution of **14** (12.17 g, 107.6 mmol, colorless oil) in anhyd DMF (180 mL) was added NaH (6.45 g, 60% dispersion on mineral oil, 161.3 mmol). After stirring for 30 min at 0 °C, benzyl bromide (25.6 mL, 214 mmol) was added at 0 °C and the reaction was stirred overnight (0 °C → r.t.). NaOH (60 mL, 2 M aq solution) was added and the mixture was stirred at 80 °C during 1 h. The reaction mixture was diluted with H_2O (1 L) and extracted with Et_2O (3 × 1 L). The organic phase was washed with brine (1 L) and dried (Na_2SO_4). The drying agent was filtered and the resulting clear solution was evaporated under reduced pressure. The oil was filtered over silica gel (*n*-hexane–EtOAc, 9:1) and after evaporation, the crude residue was dissolved in anhyd THF (570 mL). Ph_3P (56.4 g, 215.2 mmol) was added and the mixture was stirred overnight at r.t. NaOH (190 mL, 2 M aq solution) was added and the mixture was refluxed for 1 h. The mixture was diluted with H_2O (1 L) and extracted with CH_2Cl_2 (3 × 1 L). The organic phase was washed once with brine (0.6 L) and dried ($MgSO_4$). The drying agent was filtered and the resulting clear solution was evaporated under reduced pressure. After flash column chromatography on silica gel and purification (EtOAc–CH_2Cl_2, 8:2 + 5% Et_3N), 2-benzyloxymethylallylamine (**8**; 15 g, 84.63 mmol, 78%) was isolated as a colorless oil.
8: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.18–7.30 (m, 5 H), 5.03 (d, 2 H), 4.43 (s, 2 H), 3.97 (s, 2 H), 3.28 (s, 2 H), 1.21 (s, 2 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 147.6 (C), 138.3 (C), 128.4 (CH), 127.7 (CH), 127.7 (CH), 111.3 (CH_2), 72.1 (CH_2), 72.1 (CH_2), 44.8 (CH_2). HRMS (ES): *m*/*z* $[M + H]^+$ calcd for $C_{11}H_{15}NO$: 178.12263; found: 178.12260.

Alkylation of 2-Benzyloxymethylallylamine (8) with (*S*)-Vinyloxirane [(*S*)-4]: 2-Benzyloxymethylallylamine (**8**; 5.24 g, 29.56 mmol) was mixed with H_2O (132 μL, 7.33 mmol) in a pressure tube at 0 °C. (*S*)-Vinyloxirane [(*S*)-**4**; 0.8 mL, 9.93 mmol] was slowly added at 0 °C and the reaction vessel was sealed, heated and stirred for 6 h at 100 °C. The reaction mixture was transferred to a 100-mL round-bottomed flask and dissolved in H_2O (5.8 mL), dioxane (35 mL) and NaOH (23 mL, 1 M in H_2O). Boc_2O (9.7 g, 44.44 mmol) was added at r.t. and the reaction mixture was stirred overnight at r.t. The mixture was evaporated under reduced pressure, diluted with Et_2O (500 mL), subsequently washed with H_2O (200 mL), citric acid (200 mL, 20%) and brine (200 mL). The pooled aqueous phases were extracted with Et_2O (3 × 250 mL). The organic phases were dried ($MgSO_4$). The drying agent was filtered and the resulting clear solution was evaporated under reduced pressure. The residue (13 g) was purified by flash column chromatography on silica gel (gradient elution: *n*-hexane–EtOAc, 85:15 → 6:4) to furnish **15** (2.21 g, 6.35 mmol, 64%) and **16** (558 mg, 1.61 mmol, 16%) as colorless oils.

15: $[\alpha]_D$ 0 (*c* = 1, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 7.18–7.30 (m, 5 H), 5.75 (ddd, *J* = 5.6, 10.5, 17.1 Hz, 1 H), 5.25 (d, *J* = 17.1 Hz, 1 H), 5.08 (m, 2 H), 4.94 (s, 1 H), 4.42 (s, 2 H), 4.26 (m, 1 H), 3.87 (m, 4 H), 3.58 (br s, 1 H), 3.21 (m, 2 H), 1.36 (s, 9 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 157.5 (C), 141.9 (C), 138.4 (CH), 138.0 (C), 128.4 (CH), 127.7 (CH), 115.7 (CH_2), 113.4 (CH_2), 80.6 (C), 72.7 (CH), 72.2 (CH_2), 71.3 (CH_2), 53.7 (CH_2), 51.5 (CH_2), 28.3 (Me). HRMS (ES): *m*/*z* $[M + Na]^+$ calcd for $C_{20}H_{29}NO_4$: 370.19889; found: 370.19967.

16: $[\alpha]_D$ +9.1 (*c* = 1, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 7.18–7.30 (m, 5 H), 5.78 (m, 1 H), 5.04–5.15 (m, 4 H), 4.43 (s, 2 H), 4.26 (m, 1 H), 3.93 (m, 2 H), 3.80 (m, 2 H), 3.70 (m, 2 H), 1.37 (s, 9 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 156.3 (C), 143.0 (C), 137.9 (C), 133.9 (CH), 128.4 (CH), 127.8 (CH), 117.5 (CH_2), 113.9 (CH_2), 80.4 (C), 72.3 (CH_2), 71.7 (CH_2), 63.5 (CH_2), 62.0 (CH), 48.7 (CH_2), 28.4 (Me). HRMS (ES): *m*/*z* $[M + Na]^+$ calcd for $C_{20}H_{29}NO_4$: 370.19889; found: 370.19897.

Ring-Closing Metathesis of 15: To a solution of **15** (1.89 g, 5.44 mmol) in anhyd and degassed CH_2Cl_2 (170 mL) was added the Grubbs second generation catalyst (150 mg, 0.177 mmol) at r.t. under an argon atmosphere and the solution was stirred for 48 h. The solvent was evaporated and purified by flash column chromatography on silica gel (*n*-hexane–EtOAc, 2:1; silica gel saturated with Et_3N) to furnish **9** (1.60 g, 5 mmol, 92%) as a brown solid.

9: $[\alpha]_D$ +52.2 (*c* = 1.01, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 7.19–7.30 (m, 5 H), 5.84 (m, 1 H), 4.43 (s, 2 H), 4.16 (br s, 1 H), 3.93 (d, *J* = 18.0 Hz, 1 H), 3.89 (s, 2 H), 3.73 (d, *J* = 18.1 Hz, 1 H), 3.46 (br s, 2 H), 1.40 (s, 9 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 155.2 (C), 137.9 (C), 136.6 (C), 128.5 (CH), 127.8 (CH), 127.8 (CH), 125.4 (CH), 80.2 (C), 72.4 (CH_2), 71.5 (CH_2), 63.7 (CH), 47.7 (CH_2), 44.0 (CH_2), 28.4 (Me). HRMS (ES): *m*/*z* $[M + Na]^+$ calcd for $C_{18}H_{25}NO_4$: 342.16759; found: 342.16788.

Hydroboration of 18: Compound **18** (500 mg, 1.15 mmol) was dissolved in anhyd THF (2 mL) and a freshly prepared solution of thexylborane (**20**;[16] 5.77 mmol, 11.5 mL, 0.5 M in THF) was added at 0 °C and the reaction was stirred for 48 h (0 °C → r.t.). The reaction was quenched by adding 30% H_2O_2–2 M NaOH (1:1; 8 mL) at 0 °C and the mixture was then stirred for 2 h at 0 °C. The reaction was diluted with brine (100 mL) and extracted with CH_2Cl_2 (3 × 100 mL). After drying (Na_2SO_4), filtration and evaporation of the solvent, the residue was purified by flash chromatography on silica gel (*n*-hexane–EtOAc, 4:1), affording **19** (488 mg, 1.08 mmol, 93%) as a clear colorless oil.

19: $[\alpha]_D$ –5 (*c* = 0.97, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 7.20–7.30 (m, 5 H), 4.45 (s, 2 H), 4.06 (m, 2 H), 3.53 (br s, 2 H), 3.34 (m, 2 H), 2.54 (m, 3 H), 1.76 (m, 1 H), 1.39 (s, 9 H), 0.84 (s, 9 H), 0.06 (s, 6 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 154.6 (C), 138.2 (C), 128.4 (CH), 127.6 (CH), 127.5 (CH), 80.0 (C), 75.7 (CH), 73.3 (CH_2), 73.1 (CH), 69.4 (CH_2), 48.8 (CH_2), 45.1 (CH_2), 41.6 (CH), 28.4 (Me), 25.8 (Me), 18.1 (C), –4.4 (Me). HRMS (ES): *m*/*z* $[M + Na]^+$ calcd for $C_{24}H_{41}NO_5Si$: 452.28265; found: 452.28284

(13) Reported yields are isolated yields. The ratio of **15/16** was determined by RP-HPLC: 30% → 65% MeCN in H_2O in 60 min; Phenomenex Luna C18 (2), 5 μ, 250 × 4.6 mm.

(14) RCM can also be accomplished by the Grubbs–Hoveyda catalyst, however, not by the Grubbs first generation catalyst.

(15) Solutions of Boc-protected **17**, **21**, **22** and **23** consisted of rotamers complicating interpretation of NMR data.

(16) (a) Negishi, E.; Brown, H. C. *Synthesis* **1974**, 77. (b) Freshly prepared (according to the Aldrich Technical Bulletin AL-109) 0.5 M solution of thexylborane in THF.

(17) **24**: $[\alpha]_D$ –4.0 (*c* = 0.72, H_2O). ^1H NMR (700 MHz, D_2O): δ = 4.09 (app. t, $J_{2,3} = J_{3,4}$ = 8.0 Hz, 1 H, H-3), 3.98 (dd, $J_{2,6a}$ = 3.6 Hz, $J_{6a,6b}$ = 12.6 Hz, 1 H, H-6a), 3.86 (dd, $J_{2,6b}$ = 6.4 Hz, $J_{6a,6b}$ = 12.6 Hz, 1 H, H-6b), 3.82 (dd, $J_{4,7a}$ = 4.6 Hz, $J_{7a,7b}$ = 11.6 Hz, 1 H, H-7a), 3.73 (dd, $J_{4,7b}$ = 6.3 Hz, $J_{7a,7b}$ = 11.6 Hz, 1 H, H-7b), 3.66 (dd, $J_{4,5a}$ = 8.7 Hz, $J_{5a,5b}$ = 12.2 Hz, 1 H, H-5a), 3.58 (ddd, $J_{2,6a}$ = 3.6 Hz, $J_{2,6b}$ = 6.4 Hz, $J_{2,3}$ = 8.0 Hz, 1 H, H-2), 3.25 (dd, $J_{4,5b}$ = 9.3 Hz, $J_{5a,5b}$ = 12.2 Hz, 1 H, H-5b), 2.48 (m, 1 H, H-4). ^{13}C NMR (75 MHz, D_2O): δ = 70.9 (C-3), 65.3 (C-2), 59.5 (C-7), 57.8 (C-6), 46.2 (C-4), 45.3 (C-5). IR (HATR): 3304, 2930, 2749, 1595, 1400, 1346, 1055, 1021, 956, 820, 640 cm^{-1}. HRMS (ES): *m*/*z* $[M + H]^+$ calcd for $C_6H_{13}NO_3$: 148.09681; found: 148.09671.

(18) (a) When **19** was submitted to the same hydrogenolysis conditions, the TBDMS protecting group remained intact. (b) Ikawa, T.; Sajiki, H.; Hirota, K. *Tetrahedron* **2004**, *60*, 6189. (c) Hattori, K.; Sajiki, H.; Hirota, K. *Tetrahedron* **2001**, *57*, 2109.

(19) Jespersen, T.; Bols, M.; Sierks, M. R.; Skrydstrup, T. *Tetrahedron* **1994**, *50*, 13449.

(20) **25**: ^1H NMR (700 MHz, $CDCl_3$): δ = 7.18–7.30 (m, 5 H, Ph), 4.46 (s, 2 H, OBn), 4.41 (dd, *J* = 7.4, 9.2 Hz, 1 H, H-1b), 4.27 (dd, *J* = 2.5, 9.2 Hz, 1 H, H-1a), 3.75 (m, 2 H, H-2, H-3), 3.62 (dd, *J* = 5.2, 9.0 Hz, 1 H, H-6b), 3.40 (m, 2 H, H-5a, H-6a), 3.22 (dd, *J* = 8.2, 11.7 Hz, 1 H, H-5b), 2.70 (br s, 1 H, OH), 2.45 (m, 1 H, H-4). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 161.4 (C), 137.4 (C), 128.7 (CH), 128.1 (CH), 127.8 (CH), 78.9 (CH), 73.7 (CH_2), 71.5 (CH_2), 66.3 (CH_2), 64.1 (CH), 47.2 (CH), 46.7 (CH_2).

(21) Zhao, H.; Thurkauf, A. *Synlett* **1999**, 1280.

(22) The inhibition constants (K_i) were determined using four inhibitor concentrations within a limited range around the K_i value.

Inhibition of β-Glucosidase (Almond): K_i was determined at 37 °C using a NaH_2PO_4–Na_2HPO_4 buffer (pH 6.5; 100 mM) and 2-chloro-4-nitrophenyl-β-D-glucoside as substrate. The release of 2-chloro-4-nitrophenol was monitored continuously by measuring absorbance at λ = 405 nm. The K_i values were determined by Dixon plots.

Inhibition of α-Glucosidase (Yeast): K_i was determined at 37 °C using a NaH_2PO_4–Na_2HPO_4 buffer (pH 5.6; 100 mM) and 4-nitrophenyl-α-D-glucoside as substrate. The release of 4-nitrophenol was monitored by measuring absorbance at λ = 405 nm after addition of 10% Na_2CO_3 to samples of the reaction mixture at regular time intervals. The K_i values were

determined by Dixon plots.

Inhibition of α-Mannosidase (Jack Bean): Reactions were performed at 37 °C using a HOAc–NaOAc buffer (pH 4.5; 100 mM) containing $ZnCl_2$ (2 mM) and 4-nitrophenyl-α-D-mannoside as substrate, and were monitored analogously to the α-glucosidase assay above.

(23) No significant inhibition of the glycolysis of 4-nitrophenyl-α-D-mannoside was observed at a concentration of 1.9 mM in the presence of **24** or *rac*-**24** (1 mM).