Syntheses and Glycosidase Inhibitory Activities of 2-(Aminomethyl)-5-(hydroxymethyl)pyrrolidine-3,4-diol Derivatives

by **Florence Popowycz**, **Sandrine Gerber-Lemaire***, **Catherine Schütz**, and **Pierre Vogel**

Institute of Chemical Sciences and Engineering, Swiss Federal Institute of Technology, EPFL-BCH, CH-1015 Lausanne

New 2-(aminomethyl)-5-(hydroxymethyl)pyrrolidine-3,4-diol derivatives were synthesized from (5*S*)-5-[(trityloxy)methyl]pyrrolidin-2-one (**6**) (*Schemes 1* and *2*) and their inhibitory activities toward 25 glycosidases assayed (*Table*). The influence of the configuration of the pyrrolidine ring on glycosidase inhibition was evaluated. (2*R*,3*R*,4*S*,5*R*)-2-[(benzylamino)methyl]-5-(hydroxymethyl)pyrrolidine-3,4-diol ((+)-**21**) was found to be a good and selective inhibitor of α-mannosidase from jack bean ($K_i = 1.2$ μM) and from almond ($K_i = 1.0$ μM). Selectivity was lost for the non-benzylated derivative (2*R*,3*R*,4*S*,5*R*)-2-(aminomethyl)-5-(hydroxymethyl)pyrrolidine-3,4-diol ((+)-**22**) which inhibited α-galactosidases, β-galactosidases, β-glucosidases, and α-*N*-acetylgalactosaminidase as well.

Introduction. – Enzymes that are involved in the synthesis and processing of oligosaccharides, such as glycosidases and glycosyltransferases, are important catalysts for the specific assembly of oligosaccharide structures on proteins [1] and sphingolipids [2]. The design and preparation of selective inhibitors of these enzymes [3] is of high interest, as these molecules can be used to modulate cellular functions. Moreover they may provide potential drugs in new therapeutic strategies [4]. In particular, swainsonine (**1**), a natural inhibitor of Golgi α-mannosidase II containing a 4-amino-4-deoxymannofuranoside unit [5], reduces certain tumors and hematological dysfunctions [6] (*Fig.*). Nevertheless, some side effects resulted in limitations for the development of this compound in medicinal treatments. The search for new α-mannosidase inhibitors that might be used as antimetastatic agents is an important field of investigation, and some synthetic analogues of swainsonine have also shown interesting properties [7]. Recently, we reported that (2*R*,3*R*,4*S*) and (2*S*,3*R*,4*S*)-2-(aminomethyl)pyrrolidine-3,4-diol derivatives, such as **3a** and **4**, are selective and competitive inhibitors of α-mannosidases [8].

Inspired by the work of *Saotome* and co-workers [9], we wondered whether the introduction of a hydroxymethyl substituent at the C(5) position of the pyrrolidine ring could enhance the enzymatic inhibitory activity of our aromatic derivatives. We report here the syntheses and inhibitory activities toward glycosidases of 2-(aminomethyl)-5-(hydroxymethyl)pyrrolidine-3,4-diol derivatives **5**.

Results and Discussion. – Following the procedure reported by *Ikota* and co-workers [10], the semi-protected lactam **6** was converted to the diastereoisomeric alcohols (−)-**9** and (−)-**10** *via* the allylic alcohols **7**, which were obtained as a mixture of unseparable diastereoisomers (*Scheme 1*). Mesylation of the secondary alcohols **7**

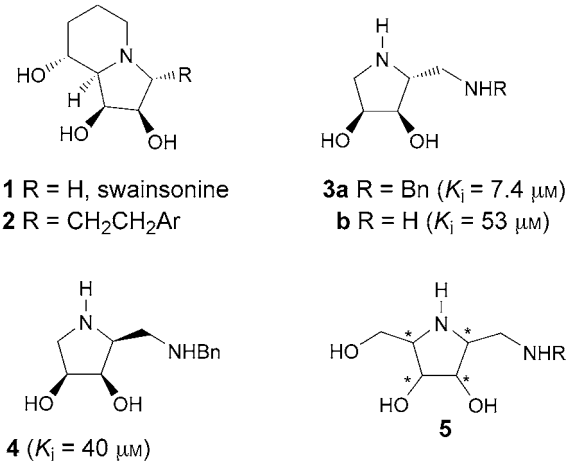


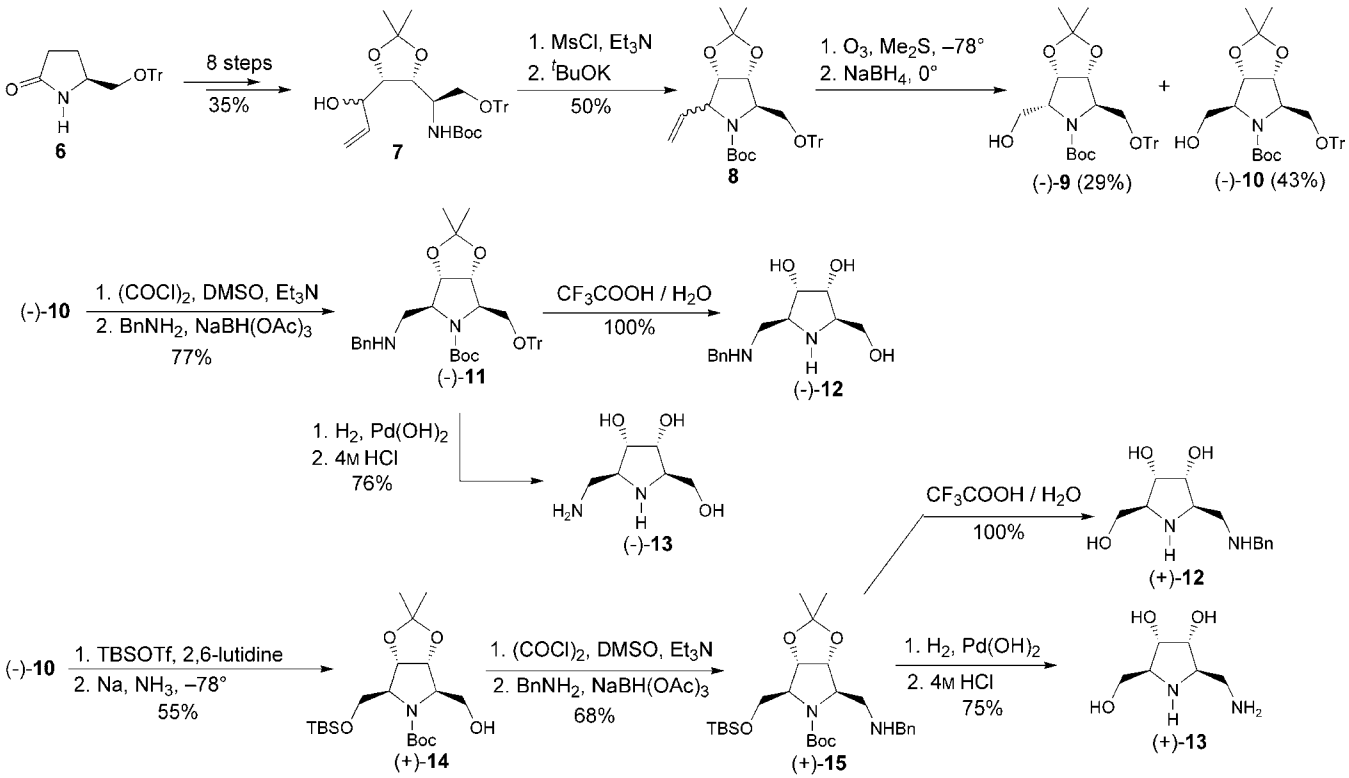
Figure. *Swainsonine* (**1**) *and synthetic analogues as α-mannosidase inhibitors.* K_i for α-mannosidase from jack bean.

followed by treatment with ^{t}BuOK induced cyclization to give the protected pyrrolidines **8** in 50% yield. Ozonolysis of the olefin moiety and reductive treatment of the resulting aldehydes afforded (−)-**9** and (−)-**10** in 29 and 43% yields, respectively. The major stereoisomer (−)-**10** was first oxidized under *Swern* conditions [11] and submitted to reductive amination in the presence of benzylamine to generate the protected diamine (−)-**11** in 77% yield. Acidic hydrolysis of all the protective groups afforded (−)-**12** in quantitative yield. The corresponding free diamino derivative (−)-**13** was obtained after cleavage of the benzyl group and treatment with HCl. It was possible to generate the related enantiomers by transformation of the tritylated alcohol. For this purpose, alcohol (−)-**10** was silylated under classical conditions (^{t}BuMe$_2$SiOTf, 2,6-lutidine (=2,6-dimethylpyridine), 0°), and *Birch* reduction of the resulting bis-ether allowed rapid and efficient removal of the trityl protecting group. All other attempts (HCOOH, TsOH, $ZnBr_2$, Me_2SiCl/phenol, $H_2/Pd(OH)_2$) failed to give the semiprotected derivative (+)-**14**. Following the procedure described before, the benzylamino derivative (+)-**12** and the corresponding diamino derivative (+)-**13** were obtained *via* (+)-**15** in 68 and 51% yield, respectively (starting from (+)-**14**).

To generate other stereoisomers of this family, alcohol (−)-**9** was protected as a silyl ether (→(−)-**16**) and submitted to *Birch* reduction (*Scheme 2*). However, the so-formed alcoholate intermediate readily cyclized at the carbamate moiety to provide the bicyclic derivative (−)-**17** in excellent yield[1]). In the case of the isomer derived from (−)-**10**, the bulky trityl and *tert*-butyldimethylsilyl groups are located on the same face of the pyrrolidine ring so that the carbamate group may be pushed down on the opposite face of the ring. As a result, the cyclization was not observed within the reaction time. For isomer (−)-**9**, it was necessary to turn to a methoxymethyl (MOM) protective group (→(−)-**18**) to avoid this side reaction and to isolate the free alcohol

[1]) Such derivatives are often observed in the multi-step synthesis of pyrrolidine derivatives [12].

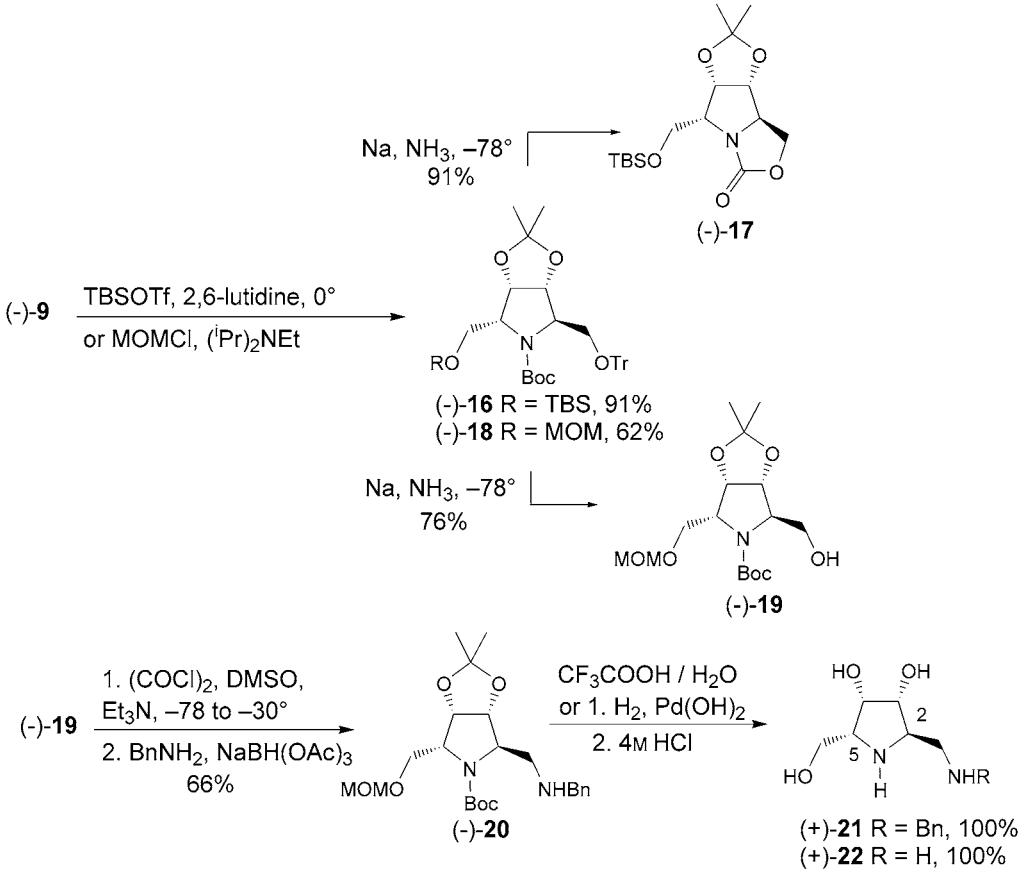
Scheme 1. *Synthesis of (2S,3S,4R,5R)- and (2R,3R,4S,5S)-2-(Aminomethyl)-5-(hydroxymethyl)pyrrolidine-3,4-diol Derivatives*



Tr = Ph_3C, Boc = ^{t}BuOC(O), Bn = $PhCH_2$, TBS = ^{t}BuMe$_2$Si

(−)-**19** in 76% yield. Oxidation under *Swern* conditions followed by reductive amination in the presence of benzylamine afforded, after appropriate deprotection of the intermediate (−)-**20**, the benzylamino derivative (+)-**21** and the diamino derivative (+)-**22**.

Scheme 2. *Synthesis of (2*R*,3*R*,4*S*,5*R*)-2-(Aminomethyl)-5-(hydroxymethyl)pyrrolidine-3,4-diol Derivatives*



Tr = Ph_3C, Boc = ^{t}BuOC(O), TBS = ^{t}BuMe_2Si, MOM = $MeOCH_2$, Bn = $PhCH_2$

Compounds (−)-**12**, (−)-**13**, (+)-**12**, (+)-**13**, (+)-**21**, and (+)-**22** were tested for their inhibitory activities toward 25 commercially available glycosidases[2]), and the results were compared with the activities of the previously reported inhibitors **3**. The data are summarized in the *Table* for galactosidases, glucosidases, mannosidases, and one *α-N*-acetylgalactosaminidase. Our derivatives did not show any inhibitory activity at 1 mM concentration toward *α*-L-fucosidases from bovine epididymis and from human placenta, *β*-mannosidase from *Helix pomatia*, *β*-xylosidase from *Aspergillus niger*, and *β-N*-acetylglucosaminidases from jack bean and from bovine epididymis A and B.

[2]) For detailed experimental conditions, see [13].

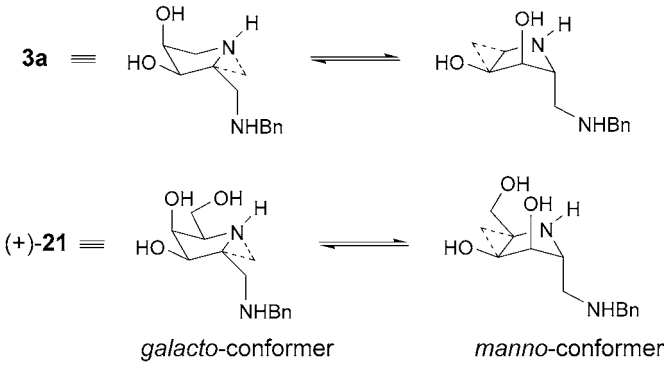
Table. *Inhibitory Activities of 3,4-Dihydroxy-5-(hydroxymethyl)-2-yl Derivatives.* Percentage of inhibition at 1 mM concentration, IC_{50} and K_i in μM, optimal pH. All inhibitions are competitive, except when indicated. M = mixed-type inhibition, n.i. = no inhibition at 1 mM concentration.

	3a	**3b**	(−)-**12**	(+)-**12**	(−)-**13**	(+)-**13**	(+)-**21**	(+)-**22**
α-Galactosidase:								
coffee bean	n.i.	n.i.	n.i.	n.i.	n.i.	72%	92%	100%
Aspergillus niger	n.i.	n.i.	n.i.	n.i.	n.i.	n.i.	n.i.	44%
E. coli	n.i.	n.i.	n.i.	n.i.	n.i.	n.i.	n.i.	63%
β-Galactosidase:								
E. coli	24%	92%	n.i.	n.i.	n.i.	97%	n.i.	83%
bovine liver	26%	n.i.	45%	59%	n.i.	n.i.	30%	86%
Aspergillus niger	n.i.	24%	n.i.	n.i.	n.i.	n.i.	n.i.	n.i.
Aspergillus orizae	n.i.	60%	n.i.	n.i.	n.i.	n.i.	n.i.	43%
jack bean	n.i.	76%	37%	n.i.	n.i.	n.i.	n.i.	40%
β-Glucosidase:								
almond	68%	97%	n.i.	51%	31%	36%	41%	99%
Caldocellum saccharolyticum	n.i.	93%	n.i.	41%	40%	n.i.	58%	97%
α-Mannosidase:								
jack bean	92% $IC_{50}=60$ $K_i=7.4$	81% $IC_{50}=170$ $K_i=53$	n.i.	n.i.	n.i.	n.i.	100% $IC_{50}=6.2$ $K_i=1.2$(M)	97%
almond	69% $IC_{50}=230$ $K_i=71$	51% $IC_{50}=1000$	n.i.	21%	n.i.	n.i.	98% $IC_{50}=4.5$ $K_i=1.0$	97%
α-*N*-Acetylgalactosaminidase:								
chicken liver	n.i.	n.i.	n.i.	n.i.	n.i.	n.i.	99% $IC_{50}=2.3$ $K_i=24$	99%

As we already observed for the aminopyrrolidinediol **3b**, derivatives that bear a primary amino group at the lateral side chain are moderate to strong inhibitors of a wide range of enzymes. In particular, aminopyrrolidinediol (+)-**22** is a strong inhibitor of α-galactosidase from coffee bean (100% inhibition at 1mM), β-glucosidases from almond and *Caldocellum saccharolyticum* (99% and 97% at 1mM), α-mannosidase from jack bean and almond (each 97% at 1mM), and α-*N*-acetylgalactosaminidase from chicken liver (99% at 1mM). This lack of selectivity is probably due to the small size of the pyrrolidine derivative that can enter the active site of various enzymes without any specificity due to its flexibility. Introduction of an aromatic substituent at the primary amino group resulted in significative enhancement of the enzymatic selectivity, in particular for the (2*R*,3*R*,4*S*,5*R*) derivative (+)-**21** that appeared to be the most promising inhibitor of this study. This compound demonstrated competitive inhibition (*Lineweaver–Burk* plots) of α-mannosidase from almond ($IC_{50}=4.5$ μM, $K_i=1$ μM) and α-*N*-acetylgalactosaminidase from chicken liver ($IC_{50}=2.3$ μM, $K_i=24$ μM) and mixed-type inhibition of α-mannosidase from jack bean ($IC_{50}=6.2$ μM, $K_i=1.2$ μM). In comparison with derivative **3a**, which has no substituent at C(5) of the pyrrolidine ring, we observed not only enhancement of the inhibitory activity toward α-mannosidases (increase of a factor 70 for the inhibition of α-mannosidase from almond), but also found good inhibition of α-*N*-acetylgalactosaminidase.

These inhibitions can result from the different conformations adopted by the pyrrolidine ring that can either mimic a galactopyranoside or a mannopyranoside (*Scheme 3*). In derivative **3a**, the absence of a hydroxymethyl group at C(5) resulted in a complete loss of the binding to galactosidases. As expected, we also observed that the absolute configuration of the stereogenic centers of the pyrrolidine ring has a crucial influence on the inhibitory activities as the other isomers (−)-**12** and (+)-**12** exhibited poor or no inhibition toward the glycosidases tested.

Scheme 3. *Possible Conformations Adopted by the Pyrrolidine Ring*



Conclusions. – We have synthesized polysubstituted five-membered iminoalditols from (5*S*)-5-[(trityloxy)methyl]pyrrolidin-2-one (**6**) with various configurations. Evaluation of their inhibitory activities toward glycosidases demonstrated that only the (2*R*,3*R*,4*S*,5*R*) derivative exhibits interesting properties with strong inhibiton of α-mannosidases and α-*N*-acetylgalactosaminidase due to the different conformations that can adopt the pyrrolidine ring. Moreover, the introduction of a hydroxymethyl substituent at C(5) of the pyrrolidine ring led to significative enhancement of the inhibitory activity toward α-mannosidases in comparison with the nonsubstituted derivative. Exchange of the benzyl group in (+)-**21** for other aromatic systems might lead to better α-mannosidase inhibitors.

This work was supported by the *Swiss National Science Foundation* (Grant N° 2100-063567.00/1) and the *Office Fédéral de l'Enseignement et de la Recherche* (COST D13/0001/99).

Experimental Part

General. All commercially available reagents (*Fluka, Aldrich*) were used without further purification. Solvents were dried by standard methods. Light petroleum ether refers to the fraction boiling at 40–60°. Liquid/solid flash chromatography (FC): silica-gel *60* (*Merck* No. 9385; 240–400 mesh). TLC: *Merck* silica-gel $60F_{254}$ plates; detection by UV light, *Pancaldi* reagent ($(NH_4)_6MoO_4$, $Ce(SO_4)_2$, H_2SO_4, H_2O) or $KMnO_4$. IR Spectra: *Perkin-Elmer 1420* spectrometer. Optical rotations: *Jasco DIP-370* polarimeter; $[\alpha]_D$ in 10^{-1} deg cm^2 g^{-1}. ^{1}H-NMR Spectra: *Bruker ARX-400* spectrometer, at 400 MHz; δ(H) in ppm rel. to the solvent's residual signal ($CHCl_3$, δ(H) 7.27°; CH_3OD, δ(H) 3.31) as internal reference, *J* in Hz; all ^{1}H assigments were confirmed by 2D-COSY-45 and 2D-NOESY experiments. ^{13}C-NMR Spectra: same instrument as for ^{1}H but at 100.6 MHz; δ(C) in ppm rel. to the solvent's signal ($CDCl_3$, δ(C) 77.0°; CD_3OD, δ(C) 49.2) as internal reference, *J* in Hz; all ^{13}C

assignments were confirmed by 2D-HMQC. MS: *Nermag R 10-10C*, chemical ionization (NH_3) mode; *m/z* (amu) (% rel. to base peak). Elemental analyses: *Ilse Beetz*, D-96301 Kronach.

tert-*Butyl (3a*S,*4*S,*6*R,*6a*R*)-4-[(Benzylamino)methyl]-tetrahydro-2,2-dimethyl-6-[(trityloxy)methyl]-5*H-*[1,3]dioxolo[4,5-*c*]*pyrrole-5-carboxylate* ((−)-**11**). To a soln. of oxalyl chloride (81 µl, 0.94 mmol, 1.15 equiv.) in CH_2Cl_2 (4 ml), cooled to −78°, was added DMSO (140 µl, 1.97 mmol, 2.4 equiv.). After 20 min, alcohol (−)-**10** (446 mg, 0.82 mmol, 1 equiv.) in anh. CH_2Cl_2 (8 ml) was added dropwise. After 20 min, Et_3N (571 µl, 4.1 mmol, 5 equiv.) was added, and the mixture was warmed to −30° for 20 min. The mixture was poured into H_2O (15 ml) and extracted with CH_2Cl_2 (3 × 20 ml). The combined extract was washed with brine (20 ml), dried ($MgSO_4$), and evaporated to afford a pale yellow oil. Sodium triacetoxyborohydride (243 mg, 1.15 mmol, 1.4 equiv.) was added portionwise to a stirred soln. of the crude aldehyde (0.82 mmol, 1 equiv.) and benzylamine (0.82 mmol, 1 equiv.) in 1,2-dichloroethane (8 ml). After stirring at r.t. overnight, the soln. was poured into sat. aq. $NaHCO_3$ soln. (10 ml) and extracted with CH_2Cl_2 (3 × 10 ml). The combined org. extract was dried ($MgSO_4$) and evaporated. FC (silica gel, AcOEt/light petroleum ether 1:1) afforded (−)-**11** (400 mg, 77% (2 steps)). Colorless oil. $[\alpha]_{589}^{25} = -28$, $[\alpha]_{577}^{25} = -31$, $[\alpha]_{546}^{25} = -35$, $[\alpha]_{435}^{25} = -57$, $[\alpha]_{405}^{25} = -69$ ($c = 0.37$, CH_2Cl_2). UV (MeCN) 271 (33000), 214 (31560). IR (film): 3445, 3060, 2980, 2935, 1690, 1490, 1450, 1395, 1215, 1160, 1130, 1065, 1000, 900, 870, 755, 700. ^{1}H-NMR (400 MHz, $CDCl_3$): 7.47–7.25 (*m*, 20 arom. H); 4.70–4.62 (*m*, H−C(3a), H−C(6a)); 4.17 (*m*, H−C(6)); 4.04–3.84 (*m*, H−C(4)); 3.65–3.52 (*m*, PhCH_2); 3.38–3.04 (*m*, 2 H−C(1″)); 2.74 (*dd*, ^3J(1′,4) = 4.7, ^2J = 11.7, 1 H−C(1′)); 2.67–2.54 (*m*, 1 H−C(1′)); 1.49 (*s*, Me_2C); 1.38 (*s*, *t*Bu): 1.36 (*s*, Me_2C). ^{13}C-NMR (101 MHz, $CDCl_3$): 154.3 (*s*, NCOO); 143.6 (*s*, arom. C); 140.4 (*s*, arom. C); 128.8, 128.3, 128.0, 127.8, 127.1, 126.8 (6*d*, arom. C); 111.6 (*s*, Me_2CO); 86.4 (*s*, Ph_3C); 83.2, 82.3 (2*d*, C(3a), C(6a)); 79.8 (*s*, Me_3CO); 64.6 (2*d*, C(4), C(6)); 63.2 (*t*, C(1″)); 53.6 (*t*, PhCH_2); 51.1 (*t*, C(1′)); 28.3 (*q*, Me_3C); 27.3 (*q*, Me); 25.5 (*q*, Me). CI-MS (NH_3): 635 (100, $[M+H]^+$), 391 (10), 335 (4), 243 (91), 198 (25), 128 (68), 91 (27, $PhCH_2^+$). Anal. calc. for $C_{40}H_{46}N_2O_5$ (634.85): C 75.68, H 8.09, N 4.41; found: C 75.74, H 8.07, N 4.38.

*(2*S,*3*S,*4*R,*5*R*)-2-[(Benzylamino)methyl]-5-(hydroxymethyl)pyrrolidine-3,4-diol* ((−)-**12**). A soln. of (−)-**11** (48 mg, $7.561 \cdot 10^{-5}$ mol) in CF_3COOH (4 ml) and H_2O (0.5 ml) was stirred at r.t. for 45 min. Evaporation and FC (silica gel, MeCN/NH_4OH soln. 4:1) afforded (−)-**12** (19 mg, 100%). Pale yellow oil. $[\alpha]_{589}^{25} = -4$, $[\alpha]_{577}^{25} = -5$, $[\alpha]_{435}^{25} = -5$, $[\alpha]_{435}^{25} = -9$, $[\alpha]_{405}^{25} = -12$ ($c = 0.59$, H_2O). UV (MeCN): 260 900), 206 (6600). IR (film): 3210, 1695, 1680, 1650, 1435, 1200, 1135. ^{1}H-NMR (400 MHz, MeOD): 7.48–7.36 (*m*, 5 arom. H); 4.07 (*s*, PhCH_2); 3.99 (*dd*, ^3J(4,3) = 5.1, ^3J(4,5) = 5.1, H−C(4)); 3.85 (*dd*, ^3J(3,4) = 5.1, ^3J(3,2)) = 5.2, H−C(3)); 3.71 (*dd*, ^3J(1″,5)) = 4.0, ^2J = 11.3, 1 H−C(1″)); 3.63 (*dd*, ^3J(1″,5) = 4.7, ^2J = 11.3, 1 H−C(1″)); 3.43 (*m*, H−C(2)); 3.35 (*m*, H−C(5)); 3.08 (*dd*, ^3J(1′,2) = 4.7, ^2J = 12.7, 1 H−C(1′)); 2.89 (*dd*, ^3J(1′,2)) = 8.5, ^2J = 12.7, 1 H−C(1′)). ^{13}C-NMR (101 MHz, MeOD): 137.2 (*s*, arom. C), 131.1 (*d*, ^1J(C,H) = 159, 2 arom. C), 130.8 (*d*, ^1J(C,H) = 161, 2 arom. C), 130.4 (*d*, ^1J(C,H) = 161, arom. C), 75.9 (*d*, ^1J(C,H) = 143, C(3)); 74.1 (*d*, ^1J(C,H) = 148, C(4)), 66.5 (*d*, ^1J(C,H) = 141, C(5)), 63.3 (*t*, ^1J(C,H) = 143, C(1″)); 62.3 (*d*, ^1J(C,H) = 142, C(2)), 54.2 (*t*, ^1J(C,H) = 140, PhCH_2), 51.2 (*t*, ^1J(C,H) = 141, C-(1′)). CI-MS (NH_3): 253 (100, $[M+H]^+$), 221 (6), 163 (3), 146 (10), 132 (58), 120 (71), 115 (67), 91 (56, $PhCH_2^+$).

*(2*S,*3*S,*4*R,*5*R*)-2-(Aminomethyl)-5-(hydroxymethyl)pyrrolidine-3,4-diol* ((−)-**13**). A soln. of (−)-**11** (104 mg, 0.16 mmol) and 10% $Pd(OH)_2$/C (20 mg) in MeOH (3 ml) was stirred at r.t. for 12 h. The mixture was filtered through a pad of *Celite* and evaporated: pale oil (68 mg, 76%). This crude intermediate was stirred at r.t. for 30 min in a 4M aq. HCl soln. (2.5 ml). Evaporation and FC (silica gel, MeCN/NH_4OH soln. 4:1) afforded (−)-**13** (20 mg, 100%). Pale yellow oil. $[\alpha]_{589}^{25} = -4$, $[\alpha]_{577}^{25} = -5$, $[\alpha]_{546}^{25} = -7$, $[\alpha]_{435}^{25} = -13$ ($c = 0.26$, H_2O). UV(MeCN): 295 (1300), 260 (1280), 212 (3200). IR (film): 3500–3000, 1650, 1455, 1205, 800, 700. ^{1}H-NMR (400 MHz, D_2O): 4.33 (*dd*, ^3J(3,4) = 5.0, ^3J(3,2) = 7.6, H−C(3)); 4.29 (*dd*, ^3J(4,5) = 3.7, ^3J(4,3) = 5.0, H−C(4)); 3.97 (*dd*, ^3J(1″,5) = 3.4, ^2J = 12.0, 1 H−C(1″)); 3.92–3.83 (*m*, 1 H−C(1″), H−C(2), H−C(5)); 3.57 (*AB*, 2 H−C(1′)). ^{13}C-NMR (101 MHz, D_2O): 75.0 (*d*, ^1J(C,H) = 148, C(3)); 72.6 (*d*, ^1J(C,H) = 154, C(4)); 68.6 (*d*, ^1J(C,H) = 149, C(5)); 61.1 (*d*, ^1J(C,H) = 148, C(2)); 60.6 (*t*, ^1J(C,H) = 146, C(1″)); 41.0 (*t*, ^1J(C,H) = 146, C(1′)). CI-MS (NH_3): 163 (6, $[M+H]^+$), 146 (8), 132 (100), 115 (11), 84 (9).

tert-*Butyl (3a*S,*4*S,*6*R,*6a*R*)-4-{[[*(tert-*Butyl)dimethylsilyl]oxy}methyl}tetrahydro-6-(hydroxymethyl)-2,2-dimethyl-5*H-*[1,3]dioxolo[4,5-*c*] *pyrrole-5-carboxylate* ((+)-**14**). To a soln. of (−)-**10** (503 mg, 0.92 mmol) in CH_2Cl_2 (15 ml), cooled to 0°, were added 2,6-lutidine (267 µl, 2.30 mmol, 2.5 equiv.) and ^{t}BuMe$_2$SiOTf (296 µl, 1.29 mmol, 1.4 equiv.). After stirring for 10 min at 0°, the mixture was diluted with CH_2Cl_2 (20 ml) and poured into sat. aq. $NaHCO_3$ soln. (20 ml). The aq. layer was extracted with CH_2Cl_2 (3 × 20 ml). The combined extract was washed with brine (10 ml), dried ($MgSO_4$), and evaporated. FC (silica gel, Et_2O/light petroleum ether 1:9) afforded intermediate fully protected pyrrolidine (354 mg, 58%) as a colorless oil.

Metallic Na (185 mg, 8.0 mmol, 15 equiv.) was added to liq. NH_3 (10 ml; condensed at −78°). A soln. of the fully protected pyrrolidine (354 mg, 0.54 mmol) in THF (5 ml) was added dropwise. After stirring at −78° for

20 min, solid NH_4Cl was added, and the mixture was allowed to warm up to r.t. The residue was diluted with MeOH, filtrated on a pad of *Celite*, and evaporated. Purification by FC (silica gel, AcOEt/light petroleum ether 1:4) afforded (+)-**14** (211 mg, 94%). Colorless oil. $[\alpha]_{589}^{25} = +10$, $[\alpha]_{577}^{25} = +11$, $[\alpha]_{546}^{25} = +13$, $[\alpha]_{435}^{25} = +22$, $[\alpha]_{405}^{25} = +25$ ($c = 0.75$, CH_2Cl_2). UV (MeCN): 285 (20700). IR (film): 3445, 2935, 2885, 2860, 1695, 1675, 1470, 1395, 1335, 1255, 1215, 1175, 1110, 1065, 1005, 975, 940, 840, 780. ^{1}H-NMR (400 MHz, $CDCl_3$): 4.81–4.71 (*m*, H–C(3a)); 4.68–4.54 (*m*, H–C(6a)); 4.40–3.58 (*m*, H–C(4), H–C(6), 2 H–C(1′), 2 H–C(1″)); 1.51 (*s*, Me_2C); 1.48 (*s*, ^{t}Bu); 1.36 (*s*, Me_2C); 0.93 (*s*, Me_3CSi); 0.12 (*s*, Me_2Si). ^{13}C-NMR (101 MHz, $CDCl_3$): 154.1 (NCOO); 111.5 (Me_2CO); 82.1, 81.6, 81.5, 80.9 (C(3a), C(6a)); 80.7, 80.3 (Me_3CO); 66.7, 66.3, 65.8, 64.8, 63.9, 63.6, 63.1 (C(4), C(6), C(1′), C(1″)); 28.4 (^{t}Bu); 27.6 (Me_2C); 26.0 (Me_3CSi); 25.5 (Me_2C); 18.6 (Me_3CSi); −5.5, −5.6 (Me_2Si). CI-MS (NH_3): 418 (18, $[M+H]^+$), 362 (15), 318 (56), 304 (45), 260 (29), 228 (11), 202 (55), 172 (100), 116 (7), 75 (28). Anal. calc. for $C_{20}H_{39}NO_6Si$ (417.65): C 57.52, H 9.41, N 3.35; found C 57.56, H 9.54, N 3.44.

tert-*Butyl (3a*R,*4*R,*6*S,*6a*S)*-4-[(Benzylamino)methyl]-6-{[[(*tert-*butyl)dimethylsilyl]oxy}methyl}tetrahydro-2,2-diemethyl-5*H*-[1,3]dioxolo[4,5-*c*]pyrrole-5-carboxylate* ((+)-**15**). As described for (−)-**11**, with oxalyl chloride (23 µl, 0.26 mmol, 1.15 equiv.), CH_2Cl_2 (1.5 ml), DMSO (39 µl, 0.55 mmol, 2.4 equiv.), (+)-**14** (94 mg, 0.23 mmol), CH_2Cl_2 (2.5 ml), and Et_2N (160 µl, 1.15 mmol, 5 equiv.). Workup with H_2O (10 ml), CH_2Cl_2 (3 × 10 ml), and brine (10 ml). Then with sodium triacetoxyborohydride (68 mg, 0.32 mmol, 1.4 equiv.), crude aldehyde (0.23 mmol), benzylamine (25 µl, 0.23 mmol), and 1,2-dichloroethane (3 ml) (12 h). Workup with sat. aq. $NaHCO_3$ soln. (5 ml) and CH_2Cl_2 (3 × 5 ml). FC (silica gel, AcOEt/light petroleum ether 1:4) afforded (+)-**15** (1:1 mixutre of rotamers α and β; 79 mg, 68% (2 steps)). Colorless oil. $[\alpha]_{589}^{25} = +22$, $[\alpha]_{577}^{25} = +22$, $[\alpha]_{546}^{25} = +25$, $[\alpha]_{435}^{25} = +33$, $[\alpha]_{405}^{25} = +34$ ($c = 0.49$, CH_2Cl_2). UV (MeCN) 270 (4100), 208 (9030). IR (film): 3335, 2955, 2930, 2860, 1695, 1470, 1455, 1395, 1335, 1255, 1215, 1175, 1115, 1065, 975, 835, 780, 735, 700. ^{1}H-NMR (400 MHz, $CDCl_3$): 7.34–7.24 (*m*, 5 arom. H); 4.69 (*m*, H–C(3a)); 4.60 (*m*, H–C(6a)); 4.02–3.55 (*m*, H–C(4), H–C(6), PhCH_2, 2 H–C(1″)); 2.87–2.60 (*m*, 2 H–C(1′)); 1.47 (*s*, ^{t}Bu); 1.40 (*s*, Me_2C); 1.34 (*s*, Me_2C); 0.89 (*s*, Me_3CSi); 0.04, 0.03 (2 s, Me). ^{13}C-NMR (101 MHz, $CDCl_3$): 154.5 (*s*, NCOO); 140.4 (*s*, arom. C); 128.3 (*d*, ^1J(C,H) = 159, 2 arom. C); 128.0 (*d*, ^1J(C,H) = 160, 2 arom. C); 126.9 (*d*, ^1J(C,H) = 158, arom. C); 111.5 (*s*, Me_2CO); 83.7 (d, ^1J(C,H) = 153, C(6a)$_\alpha$); 83.2 (*d*, ^1J(C,H) = 156, C(6a)$_\beta$); 81.9 (*d*, ^1J(C,H) = 151, C(3a)$_\beta$); 81.1 (*d*, ^1J(C,H) = 157, C(3a)$_\alpha$); 79.9 (*s*, Me_3CO); 66.0, 64.7 (2*d*, ^1J(C,H) = 144, ^1J(C,H) = 142, C(4), C(6)); 63.2 (*t*, ^1J(C,H) = 142, C(1″)$_\beta$); 62.7 (*t*, ^1J(C,H) = 144, C(1″)$_\alpha$), 53.7 (*t*, ^1J(C,H) = 132, PhCH_2); 51.2 (*t*, ^1J(C,H) = 136, C(1′)), 28.4 (*q*, ^1J(C,H) = 126, ^{t}Bu); 27.4 (*q*, ^1J(C,H) = 127, Me_2C); 26.0 (*q*, ^1J(C,H) = 125, Me_3CSi); 25.5 (*q*, ^1J(C,H) = 126, Me_2C); 18.4 (*s*, Me_3CSi); −5.4 (*q*, ^1J(C,H) = 120, Me_2Si). CI-MS: 507 (100, $[M+H]^+$), 449 (1), 228 (3), 154 (9), 120 (42), 91 (11).

tert-*Butyl (3a*S,*4*R,*6*R,*6a*R*)-4-[{[(*tert-*Butyl)dimethylsilyl]oxy}methyl]tetrahydro-2,2-dimethyl-6-[(trityloxy)methyl]-5*H*-[1,3]dioxolo[4,5-*c*]pyrrole-5-carboxylate* ((−)-**16**). As described for (+)-**14** with alcohol (−)-**9** (574 mg, 1.05 mmol), CH_2Cl_2 (17 ml), 2,6-lutidine (305 µl, 2.63 mmol, 2.5 equiv.), and ^{t}BuMe$_2$Si (338 µl, 1.47 mmol, 1.4 equiv.) (omitting the Na/NH_3 treatment) (−)-**16** (631 mg, 91%). Colorless oil. $[\alpha]_{589}^{25} = -60$, $[\alpha]_{577}^{25} = -63$, $[\alpha]_{546}^{25} = -68$, $[\alpha]_{435}^{25} = -114$, $[\alpha]_{405}^{25} = -134$ ($c = 0.59$, CH_2Cl_2). UV (MeCN) 262 (2200), 210 (28300). IR (film): 3435, 2955, 2855, 1695, 1450, 1370, 1255, 1215, 1165, 1085, 1000, 840, 755, 705. ^{1}H-NMR (400 MHz, $CDCl_3$): 7.42–7.24 (*m*, 15 arom. H); 4.87–4.48 (*m*, H–C(3a), H–C(6a), 1 H–C(1′)); 4.15–4.05 (*m*, H–C(4), H–C(6)); 3.87 (*m*, 1 H–C(1′)); 3.36–3.04 (*m*, 2 H–C(1″)); 1.53 (*s*, Me_2C); 1.49 (*s*, Me_2C); 1.34 (*s*, ^{t}Bu); 0.94 (*s*, Me_3CSi); 0.11 (*s*, Me_2Si). ^{13}C-NMR (101 MHz, $CDCl_3$): 154.3 (NCOO); 143.6 (arom. C); 128.6, 127.9, 127.1 (arom C); 111.5 (Me_2CO); 86.5 (Ph_3CO); 80.3 (C(3a), C(6a)); 80.2 (Me_3CO); 65.0, 63.6 (C(4), C(6)); 63.5 (C(1″)); 60.5 (C(1′)); 28.4 (^{t}Bu); 26.5 (Me_2C); 25.9 (Me_3CSi); 25.0 (Me_2C); 18.5 (Me_3CSi); −5.5 (*q*, Me_2CSi). CI-MS (NH_3): 660 (7, $[M+H]^+$), 286 (5), 243 (100), 165 (16), 105 (7). Anal. calc. for $C_{39}H_{53}NO_6Si$ (659.98): C 70.98, H 8.09, N 2.12; found: C 70.91, H 8.03, N 2.09.

*(3a*R,*3b*R,*8*R,*8a*S*)-8-{[[(*tert-*Butyl)dimethylsilyl]oxy}methyl]tetrahydro-4*H,*6*H*-[1,3]dioxolo[3,4]pyrrolo[1,2-*c*]oxazol-6-one* ((−)-**17**). As described for (+)-**14** (omitting the *t*BuMe$_2$SiO Tf/2,6-lutidine treatment) with Na (42 mg, 1.84 mmol, 15 equiv.), NH_3 (5 ml), (−)-**16** (81 mg, 0.12 mmol), and THF (2 ml) (NH_4Cl (0.5 g) for workup): (−)-**17** (39 mg, 91%). $[\alpha]_{589}^{25} = -9$, $[\alpha]_{577}^{25} = -11$, $[\alpha]_{546}^{25} = -14$, $[\alpha]_{435}^{25} = -25$, $[\alpha]_{405}^{25} = -30$ ($c = 0.37$, CH_2Cl_2). UV (MeCN): 334 (470), 206 (3700). IR (film): 3500, 2930, 2855, 1765, 1705, 1470, 1395, 1255, 1215, 1080, 840, 775. ^{1}H-NMR (400 MHz, $CDCl_3$): 4.91 (*dd*, ^3J(8a,3a) = 6.4, ^3J(8a,8)) = 6.4, H–C(8a)); 4.56 (*dd*, ^3J(4,3b) = 8.3, ^2J = 9.4, H–C(4)); 4.47 (*dd*, ^3J(3a,8a) = 6.4, ^3J(3a,3b) = 6.3, H–C(3a)); 4.32 (*dd*, ^3J(4,3b) = 3.4, ^2J = 9.4, H–C(4)); 4.17 (*m*, H–C(8)); 3.93 (*m*, H–C(3b)); 3.89 (*dd*, ^3J(1′,8) = 6.6, ^2J = 10.5, H–C(1′)); 3.75 (*dd*, ^3J(1′,8) = 7.2, ^2J = 10.5, H–C(1′)); 1.53 (*s*, Me_2C); 1.33 (*s*, Me_2C); 0.91 (*s*, Me_3CSi); 0.09 (*s*, Me_2Si). ^{13}C-NMR (101 MHz, $CDCl_3$): 160.3 (*s*, NCOO); 114.8 (*s*, Me_2CO); 84.5 (*d*, ^1J(C,H) = 154, C(3a)); 81.2 (*d*, ^1J(C,H) = 158, C(8a)); 66.8 (*d*, ^1J(C,H) = 153, C(4)); 62.9 (*d*, ^1J(C,H) = 152, C(3b)); 61.3 (*d*, ^1J(C,H) = 144, C(8)); 60.7 (*t*,

^1J(C,H) = 145, C(1′)); 27.0 (*q*, ^1J(C,H) = 127, *Me*$_2$C); 25.8 (*q*, ^1J(C,H) = 125, Me$_3$*C*Si); 25.0 (*q*, ^1J(C,H) = 127, Me$_2$C); 18.3 (*s*, Me$_3$CSi); −5.5 (*q*, ^1J(C,H) = 119, Me$_2$Si). CI-MS (NH_3): 344 (28, $[M+H]^+$), 328 (7), 304 (1), 286 (37), 243 (18), 228 (22), 198 (25), 184 (44), 154 (79), 142 (100), 129 (61), 89 (6), 75 (28). Anal. calc. for $C_{16}H_{29}NO_5Si$ (343.51): C 55.95, H 8.51 ; found: C 56.10, H 8.52.

tert-*Butyl (3a*S,*4*R,*6*R,*6a*R*)-Tetrahydro-4-[(methoxymethoxy)methyl]-2,2-dimethyl-6-[(trityloxy)methyl]-5*H*-[1,3]dioxolo[4,5-*c*]pyrrole-5-carboxylate* (−)-**18**. To a soln. of (−)-**9** (104 mg, 0.19 mmol) in CH_2Cl_2 (3 ml), cooled to 0°, were added *N*-ethyldiisopropylamine (196 µl, 1.14 mmol, 6 equiv.) and $MeOCH_2Cl$ (58 µl, 0.76 mmol, 4 equiv.). The mixture was allowed to warm to r.t. for 12 h. The soln. was diluted with CH_2Cl_2 (5 ml) and washed with 1M HCl. The aq. layer was extracted with CH_2Cl_2 (3 × 5 ml) and the combined org. extract dried ($MgSO_4$) and evaporated. FC (silica gel (AcOEt/light petroleum ether 1:4)) afforded (−)-**18** (78 mg, 62%). Colorless oil. $[\alpha]_{589}^{25} = -53$, $[\alpha]_{577}^{25} = -55$, $[\alpha]_{546}^{25} = -63$, $[\alpha]_{435}^{25} = -106$, $[\alpha]_{405}^{25} = -123$ (*c* = 0.56, CH_2Cl_2). UV (MeCN): 260 (2020), 212 (25500). IR (film): 3060, 2980, 1700, 1600, 1490, 1450, 1370, 1250, 1210, 1155, 1045. ^{1}H-NMR (400 MHz, $CDCl_3$): 7.42–7.12 (*m*, 15 arom. H); 4.95 (*m*, H−C(6a)); 4.72 (*AB*, OCH_2O); 4.50 (*m*, H−C(3a)); 4.36–3.80 (*m*, H−C(4), H−C(6), 2 H−C(1′)); 3.46 (*m*, 1 H−C(1″)); 3.42 (*s*, MeO); 3.12 (*m*, 1 H−C(1″)); 1.60 (*s*, Me$_2$C); 1.53 (*s*, Me$_2$C); 1.35 (*s*, ^{t}Bu). ^{13}C-NMR (101 MHz, $CDCl_3$): 154.3 (NCOO); 143.5 (arom. C); 128.5, 128.0, 127.2 (arom. C); 111.2 (Me$_2$*C*O); 97.1 (OCH_2O); 81.4 (C(3a)); 80.3 (Me$_3$*C*O); 80.0 (C(6a)); 65.3 (C(4)); 63.7 (C(1′)); 63.5 (C(1″)); 61.6 (C(6)); 55.2 (MeO); 28.4 (^{t}Bu); 26.0 (*Me*$_2$C), 24.8 (*Me*$_2$C). CI-MS (NH_3): 590 (2, $[M+H]^+$), 527 (0.4), 348 (3), 292 (2), 243 (100), 216 (48), 165 (63). Anal. calc. for $C_{35}H_{43}NO_7$ (589.76): C 71.28, H 7.35; found: C 71.64, H 7.69.

tert-*Butyl (3a*R,*4*R,*6*R,*6a*S*)-Tetrahydro-4-(hydroxymethyl)-6-[(methoxymethoxy)methyl]-2,2-dimethyl-5*H*-[1,3]dioxolo[4,5-*c*]pyrrole-5-carboxylate* ((−)-**19**). As described for (−)-**17**, with Na (198 mg, 8.6 mmol, 30 equiv.), NH_3 (10 ml), (−)-**18** (169 mg, 0.29 mmol), and THF (4 ml) (NH_4Cl (0.8 g) for workup): (−)-**19** (76 mg, 76%). Colorless oil. $[\alpha]_{589}^{25} = -65$, $[\alpha]_{577}^{25} = -70$, $[\alpha]_{546}^{25} = -77$, $[\alpha]_{435}^{25} = -130$, $[\alpha]_{405}^{25} = -153$ (*c* = 0.46, CH_2Cl_2). UV (MeCN): 271 (780), 198 (6670). IR (film): 3460, 2980, 1695, 1660, 1455, 1370, 1250, 1210, 1040. ^{1}H-NMR (400 MHz, $CDCl_3$): 4.81 (*dd*, ^3J(6a,3a) = 6.3, ^3J(H−6a,6) = 6.2, H−C(6a)); 4.67 (*AB*, OCH_2O); 4.47 (br. *s*, H−C(3a)); 4.10–3.86 (*m*, H−C(4), H−C(6), H−C(1′)); 3.81 (*t*, ^3J(1″,6) = 9.3, H−C(1″)); 3.74 (*dd*, ^3J(1′,4) = 4.8, ^2J = 11.4, H−C(1′)); 3.40 (*s*, MeO); 1.55 (*s*, Me$_2$C); 1.49 (*s*, ^{t}Bu); 1.38 (*s*, Me$_2$C). ^{13}C-NMR (101 MHz, $CDCl_3$): 154.3 (*s*, NCOO); 111.5 (*s*, Me$_2$*C*O); 96.7 (*t*, ^1J(C,H) = 165, O*C*H$_2$O); 80.9 (*d*, ^1J(C,H) = 158, C(3a)); 80.2 (*s*, Me$_3$*C*O); 78.5 (*d*, ^1J(C,H) = 153, C(6a)); 65.4 (*d*, ^1J(C,H) = 146, C(4)); 64.9 (*t*, ^1J(C,H) = 147, C(1′)); 62.9 (*t*, ^1J(C,H) = 145, C(1″)); 60.4 (*d*, ^1J(C,H) = 144, C(6)); 55.2 (*q*, ^1J(C,H) = 142, MeO); 28.4 (*q*, ^1J(C,H) = 127, ^{t}Bu); 26.0 (*q*, ^1J(C,H) = 127, *Me*$_2$C); 24.8 (*q*, ^1J(C,H) = 127, *Me*$_2$C). CI-MS (NH_3): 349 (11), 348 (6, $[M+H]^+$), 216 (10), 202 (2), 185 (13), 172 (100), 154 (7), 126 (5), 85 (2). Anal. calc. for $C_{16}H_{29}NO_7$ (347.43): C 55.32, H 8.41; found: C 55.30, H 8.32.

tert-*Butyl (3a*R,*4*R,*6*R,*6a*S*)-4-[(Benzylamino)methyl]tetrahydro-6-[(methoxymethoxy)methyl]-2,2-dimethyl-5*H*-[1,3]dioxolo[4,5-*c*]pyrrole-5-carboxylate* ((−)-**20**). As described for (−)-**11**, with oxalyl chloride (22 µl, 0.25 mmol, 1.15 equiv.), CH_2Cl_2 (1.5 ml), DMSO (37 µl, 0.52 mmol, 2.4 equiv.), (−)-**19** (76 mg, 0.22 mmol, 1 equiv.), CH_2Cl_2 (2.5 ml), and Et_3N (152 µl, 1.09 mmol, 5 equiv.). Workup with H_2O (10 ml), CH_2Cl_2 (3 × 10 ml), and brine (10 ml). Then with sodium triacetoxyborohydride (65 mg, 0.31 mmol, 1.4 equiv.), crude aldehyde (0.22 mmol), benzylamine (24 µl, 0.23 mmol, 1 equiv.), and 1,2-dichloroethane (2 ml) (12 h). Workup with sat. aq. $NaHCO_3$ soln. (5 ml) and CH_2Cl_2 (3 × 5 ml): (−)-**20** (55 mg, 57% (2 steps)). Pale yellow oil. $[\alpha]_{589}^{25} = -65$, $[\alpha]_{577}^{25} = -70$, $[\alpha]_{546}^{25} = -79$, $[\alpha]_{435}^{25} = -133$, $[\alpha]_{405}^{25} = -160$ (*c* = 0.62, CH_2Cl_2). UV (MeCN): 261 (2530), 207 (17000). IR (film): 3340, 2980, 2935, 1700, 1495, 1455, 1370, 1280, 1245, 1165, 1115, 1050, 1000. ^{1}H-NMR (400 MHz, MeOD): 7.37–7.24 (*m*, 5 arom. H); 4.83 (*dd*, ^3J(6a,3a) = 6.0, ^3J(6a,6) = 5.9, H−C(6a)); 4.67 (*m*, H−C(3a)); 4.63 (*s*, O*CH*$_2$O); 4.31–3.83 (*m*, 2 H−C(1″)); 3.86 (*m*, H−C(6)); 3.80–3.74 (*m*, H−C(4), PhCH$_2$); 3.38 (*s*, MeO); 2.70 (*m*, 2 H−C(1′)); 1.48 (*s*, Me$_2$C); 1.35 (*s*, ^{t}Bu, Me$_2$C). ^{13}C-NMR (101 MHz, MeOD): 157.1 (*s*, NCOO); 142.0 (*s*, arom. C); 130.3 (*d*, ^1J(C,H) = 160, 4 arom. C); 129.0 (*d*, ^1J(C,H) = 161, arom. C); 113.3 (s, Me$_2$*C*O); 98.7 (*t*, ^1J(C,H) = 161, OCH_2O); 83.7 (*d*, ^1J(C,H) = 159, C(3a)); 82.4 (*s*, Me$_3$*C*O); 81.7 (*d*, ^1J(C,H) = 160, C(6a)); 66.7 (*d*, ^1J(C,H) = 152, C(4)); 66.3 (*d*, ^1J(C,H) = 147, C(1″)); 62.7 (*d*, ^1J(C,H) = 140, C(6)); 56.4 (*q*, ^1J(C,H) = 135, MeO); 55.4 (*t*, ^1J(C,H) = 134, Ph*C*H$_2$); 50.4 (*t*, C(1′)); 29.5 (*q*, ^1J(C,H) = 127, Me$_3$C); 27.3, 25.9 (2*q*, ^1J(C,H) = 127, Me$_2$C). CI-MS (NH_3): 437 (2, $[M+H]^+$), 375 (1), 216 (2), 184 (7), 143 (2), 120 (33), 91 (100, $PhCH_2^+$). Anal. calc. for $C_{23}H_{36}N_2O_6$ (436.57): C 63.28, H 8.31; found: C 63.38, H 8.36.

*(2*R,*3*R,*4*S,*5*R*)-2-[(Benzylamino)methyl]-5-(hydroxymethyl)pyrrolidine-3,4-diol* ((+)-**21**). As described for (−)-**12**, with (−)-**20** (24 mg, $5.497 \cdot 10^{-5}$ mol), CF_3COOH (2 ml), and H_2O (0.25 ml) (30 min): (+)-**21** (14 mg, 100%). Colorless oil. $[\alpha]_{589}^{25} = +6$, $[\alpha]_{577}^{25} = +7$, $[\alpha]_{546}^{25} = +8$, $[\alpha]_{435}^{25} = +14$ (*c* = 0.64, MeOH). UV (MeCN): 266 (640), 198 (2400). IR (film): 3280, 2920, 1655, 1580, 1460, 795. ^{1}H-NMR (400 MHz, D_2O): 7.53–7.47 (*m*, 5 arom. H); 4.21 (*dd*, ^3J(4,3) = 4.0, ^3J(4,5) = 3.7, H−C(4)); 4.05 (*s*, PhC*H*$_2$); 3.99 (*dd*, ^3J(3,4)) = 4.0,

$^3J(3,2))=8.2$, H–C(3)); 3.85 (*dd*, $^3J(1'',5)=6.6$, $^2J=11.5$, 1 H–C(1″)); 3.71 (*dd*, $^3J(1'',5))=6.6$, $^2J=11.5$, 1 H–C(1″)); 3.36 (*m*, H–C(2), H–C(5)); 3.08 (*dd*, $^3J(1',2)=4.4$, $^2J=12.5$, 1 H–C(1′)); 2.93 (*dd*, $^3J(1',2)=9.0$, $^2J=12.5$, 1 H–C(1′)). ^{13}C-NMR (101 MHz, D_2O): 134.2 (arom. C); 131.6 (2 arom. C); 131.4 (2 arom. C); 130.9 (arom. C); 78.3 (C(3)); 74.3 (C(4)); 62.5, 60.8 (C(2), C(5), C(1″)); 54.6 (Ph*C*H_2); 53.1 (C(1′)). ESI-MS: 253.34.

*(2*R*,3*R*,4*S*,5*R*)-2-(Aminomethyl)-5-(hydroxymethyl)pyrrolidine-3,4-diol* ((+)-**22**). As described for (−)-**13**, with (−)-**20** (110 mg, 0.250 mmol), 10% $Pd(OH)_2$/C (20 mg), and MeOH (5 ml). Then with the pale yellow oily intermediate (86 mg, 100%) and 4M HCl (5 ml) (1 h). (+)-**22** (40 mg, 100%). Colorless oil.

Data of Intermediate tert-*Butyl (3a*R*,4*R*,6*R*,6a*S*)-4-(Aminomethyl)tetrahydro-6-[(methoxymethoxy)methyl]-2,2-dimethyl-5*H*-[1,3]dioxolo[4,5-c]pyrrole-5-carboxylate:* $[\alpha]_{589}^{25}=-80$, $[\alpha]_{577}^{25}=-80$, $[\alpha]_{546}^{25}=-92$, $[\alpha]_{435}^{25}=-154$, $[\alpha]_{405}^{25}=-182$ ($c=0.46$, CH_2Cl_2). UV (MeCN): 263 (640), 198 (9050). IR (film): 3380, 2980, 2935, 1695, 1455, 1370, 1280, 1245, 1210, 1165, 1115, 1050, 1000. ^{1}H-NMR (400 MHz, MeOD): 4.82 (*m*, H–C(6a)); 4.67 (*m*, H–C(3a)); 4.64 (*s*, O*C*H_2O); 4.36–4.11 (*m*, 2 H–C(1″)); 3.90 (*m*, H–C(6)); 3.79 (*dd*, $^3J(4,3)=9.1$, $^3J(4,1')=9.2$, H–C(4)); 3.39 (*s*, MeO); 2.84 (*m*, 2 H–C(1′)); 1.50 (*s*, Me_2C, *t*Bu); 1.37 (*s*, Me_2C). ^{13}C-NMR (101 MHz, MeOD): 156.9 (*s*, NCOO); 113.5 (*s*, Me_2*C*O); 98.6 (*t*, ^1J(C,H) = 161, O*C*H_2O); 83.0 (*d*, ^1J(C,H) = 146, C(3a)); 81.6 (*s*, Me_3*C*O); 81.5 (*d*, ^1J(C,H) = 158, C(6a)); 66.8 (*t*, ^1J(C,H) = 141, C(1″)); 66.7 (*d*, ^1J(C,H) = 156, C(4)); 62.4 (*d*, ^1J(C,H) = 142, C(6)); 56.4 (*q*, ^1J(C,H) = 136, MeO); 43.4 (*t*, ^1J(C,H) = 148, C(1′)); 29.7 (*q*, ^1J(C,H) = 127, *Me*$_3$C); 27.3, 25.9 (2*q*, ^1J(C,H) = 127, *Me*$_2$C). CI-MS (NH_3): 347 (1, $[M+H]^+$), 291 (2), 241 (6), 216 (22), 184 (100), 154 (24), 126 (17), 98 (42), 84 (24). Anal. calc. for $C_{16}H_{30}N_2O_6$ (346.44): C 55.47, H 8.73; found: C 55.71, H 8.69.

*Data for (+)-***22**: $[\alpha]_{589}^{25}=+17$, $[\alpha]_{577}^{25}=+28$, $[\alpha]_{546}^{25}=+34$, $[\alpha]_{435}^{25}=+59$, $[\alpha]_{405}^{25}=+71$ ($c=0.13$, H_2O). UV (MeCN): 269 (605), 260 (605), 202 (270). IR (film): 3600–2980, 1680, 1630, 1455, 1435, 1200, 800, 700. ^{1}H-NMR (400 MHz, D_2O): 4.42 (*m*, H–C(4)); 4.37 (*dd*, $^3J(3,4))=3.7$, $^3J(3,2))=9.5$, H–C(3)); 4.11–4.00 (*m*, H–C(5), 2 H–C(1″)); 3.90 (*m*, H–C(2)); 3.61 (*m*, 2 H–C(1′)). ^{13}C-NMR (101 MHz, D_2O): 76.6 (*d*, ^1J(C,H) = 142, C(3)); 71.9 (*d*, ^1J(C,H) = 157, C(4)); 65.4 (*d*, ^1J(C,H) = 151, C(5)); 59.9 (*t*, ^1J(C,H) = 141, C(1″)); 59.4 (*d*, ^1J(C,H) = 144, C(2)); 41.5 (*t*, ^1J(C,H) = 142, C(1′)). EI-MS: 163.38.

REFERENCES

[1] R. Kornfeld, S. Kornfeld, *Ann. Rev. Biochem*. **1985**, *54*, 631; K. W. Morenem, R. B. Trimble, A. Herscovics, *Glycobiology* **1994**, *4*, 113; A. Varki, *Glycobiology* **1993**, *3*, 97; P. R. Crocker, T. Feizi, *Curr. Opin. Struct. Biol*. **1996**, *6*, 679; R. A. Dwek, *Chem. Rev*. **1996**, *96*, 683; I. Brockhausen, *Biochim. Biophys. Acta* **1999**, *1473*, 67.

[2] T. D. Butters, R. A. Dwek, F. M. Platt, *Chem. Rev*. **2000**, *100*, 4683.

[3] A. J., Kirby, *Acc. Chem. Res*. **1984**, *17*, 305; D. G. Gorenstein, *Chem. Rev*. **1987**, *87*, 1047; M. L. Sinnott, *Chem. Rev*. **1990**, *90*, 1171; J. H. Jeong, B. W. Murray, S. Takayama, C. H. Wong, *J. Am. Chem. Soc*. **1996**, *118*, 4227; B. Ganem, *Acc. Chem. Res*. **1996**, *29*, 340; M. Bols, *Acc. Chem. Res*. **1998**, *31*, 1; T. D. Heightman, A. T. Vasella, *Angew. Chem., Int. Ed*. **1999**, *38*, 750; Y. Ichikawa, Y. C. Lin, D. P. Dumas, G. J. Shen, E. Garcia-Jonceda, M. A. Williams, R. Bayer, C. Ketcham, L. E. Walker, J. C. Paulson, C. H. Wong, *J. Am. Chem. Soc*. **1992**, *114*, 9283; L. Qiao, B. W. Murray, M. Shimazakin, J. Schultz, C. H. Wong, *J. Am. Chem. Soc*. **1996**, *118*, 7653; I. Jefferies, B. R. Bowen, *Bioorg. Med. Chem. Lett*. **1997**, *7*, 1171; M. M. Palcic, L. D. Heerze, O. P. Srivastava, O. J. Hindsgaul, *Biol. Chem*. **1989**, *264*, 17174.

[4] B. Fernandes, U. Sagman, M. Auger, M. Demetrio, J. W. Dennis, *Cancer Res*. **1991**, *51*, 718; K. M. Robinson, M. E. Begovic, M. E. Rhinerhardt, E. W. Heineke, J. B. Ducep, P. R. Kastner, F. N. Marshall, C. Danzin, *Diabetes* **1991**, *40*, 825; F. M. Platt, G. Reinkensmeier, R. A. Dwek, T. D. Butters, *J. Biol. Chem*. **1997**, *272*, 19365; F. Lapierre, K. Holme, L. Lam, R. J. Tressler, N. Storm, J. Wee, R. J. Stack, J. Castellot, D. J. Tyrrell, *Glycobiology* **1996**, *6*, 355; A. Mehta, N. Zizmann, P. M. Rudd, T. M. Block, R. A. Dwek, *FEBS Lett*. **1998**, *430*, 17; T. Kolter, *Angew. Chem., Int. Ed*. **1997**, *36*, 1955; Q. J. Fan, S. Ishii, N. Asano, Y. Suzuki, *Nat. Med*. **1999**, *5*, 112; T. Cox, R. Lachman, C. Hollack, J. Aerts, S. van Weely, M. Hrebicek, F. Platt, T. Butters, R. Dwek, C. Moyses, I. Gow, D. Elstein, A. Zimran, *Lancet* **2000**, *355*, 1481.

[5] S. M. Colegate, P. R. Dorling, C. R. Huxtable, *Austr. J. Chem*. **1979**, *32*, 2257; S. L. White, T. Nagai, S. K. Akiyama, E. J. Reeves, K. Grzegorzewski, K. Olden, *Cancer Commun*., **1991**, *3*, 83; K. Olden, P. Breton, K. Grzegorzewski, Y. Yasuda, B. L. Gause, O. A. Oredipe, S. A. Newton, S. L. White, *Pharmacol.Ther*. **1991**, *50*, 285; N. Asano, *J. Enzyme Inhibition* **2000** *15*, 215; J. Carver, J. W. Dennis, P. Shah, US Patent 5773239A, 30 June, 1998 (*Chem. Abstr*. **1998**, *129*, 95683).

[6] A. D. Elbein, R. D. Molyneux, 'Iminosugars as Glycosidase Inhibitors; Nojirimycin and Beyond', Ed. A. E. Stütz, Wiley-VCH, Weinheim, 1999, Chapt.11, p. 216.
[7] P. E. Goss, J. Baptiste, B. Fernades, M. Baker, J. W. Dennis, *Cancer Res.* **1994**, *54*, 1450; P. E. Goss, C. L. Reid, D. Bailey, J. W. Dennis, *Clin. Cancer Res.* **1997**, *3*, 1077; P. D. Rye, N. V. Bovin, E. V. Vlasova, R. A. Walker, *Glycobiology* **1995**, *5*, 385.
[8] F. Popowycz, S. Gerber-Lemaire, E. Rodriguez-García, C. Schütz, P. Vogel, *Helv. Chim. Acta* **2003**, *86*, 1914.
[9] C. Saotome, C. H. Wong, O. Kanie, *Chem. Biol*. **2001**, *8*, 1061.
[10] N. Ikota, H. Nakagawa, S. Ohno, K. Noguchi, K. Okuyama, *Tetrahedron* **1998**, *54*, 8985.
[11] A. J. Mancuso, S. L. Huang, D. Swern, *J. Org. Chem*. **1978**, *43*, 2480; T. Tidwell, *Org. React*. **1990**, *39*, 287.
[12] A. K. Forrest, R. R. Schmidt, G. Hunter, I. Jibril, *J. Chem. Soc. Perkin Trans. 1* **1984**, 1981; A. Defoin, T. Sifferlen, J. Streith, *Synlett* **1997**, 1294.
[13] A. Brandi, S. Cicchi, F. M. Cordero, B. Frignoli, A. Goti, S. Picasso, P. Vogel, *J. Org. Chem*. **1995**, *60*, 6806.

Received October 16, 2003