Pergamon

Tetrahedron Vol. 51, No. 3, pp. 849-858, 1995

0040-4020/95 $9.50+0.00

0040-4020(94)00957-0

Synthesis of a Chiral 2,6-Bridged Morpholine System: *trans*-6,7-Diol Derivatives of 8-Oxa-3-azabicyclo[3.2.1]octane

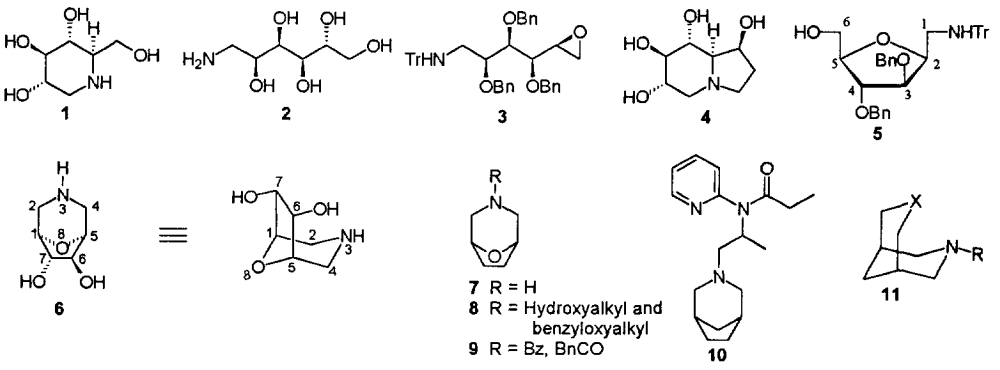
Amuri Kilonda, Elisabeth Dequeker, Frans Compernolle,* Pieter Delbeke, Suzanne Toppet, Babady-Bila,† and Georges J. Hoornaert

Departement Scheikunde, Laboratorium voor Organische Synthese, K.U.Leuven
Celestijnenlaan 200 F, 3001 Leuven-Heverlee, Belgium
† *Laboratoire de Chimie des Substances Naturelles, Université de Kinshasa*
B. P. 137 Kinshasa XI, Zaïre

Abstract: The title compound **6**, [1R-(6*endo*,7*exo*)]-8-oxa-3-azabicyclo[3.2.1]octane-6,7-diol, was derived in nine steps from 1-amino-1-deoxy-D-glucitol **2**. The key step was the acid catalyzed rearrangement of epoxide **3** to the 2,5-*cis*-disposed hydrofuran compound **5**. Linkage of the 2,5-substituents, to form the bridged secondary amine **23**, proceeded *via* mesylation of 6-OH and deprotection of 1-NH_2. Further *O*-debenzylation and (or) *N*-substitution afforded the aminodiol **6** and various *N*-alkylated derivatives. On basis of ^1H NMR analysis the chair form was assigned to the bridged morpholine ring.

INTRODUCTION

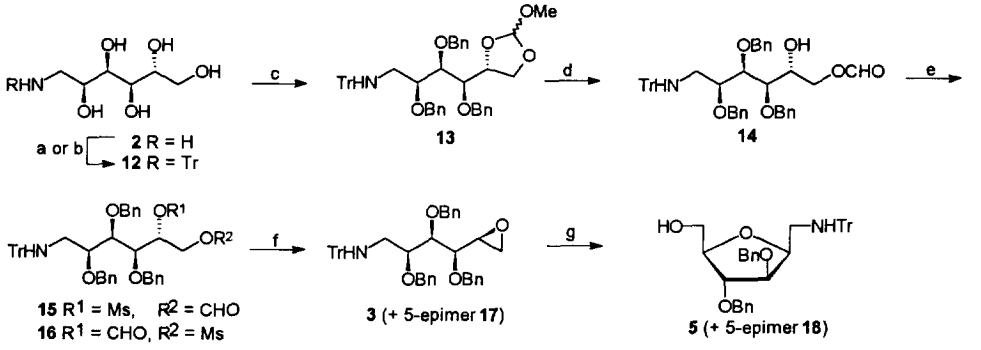
Recently we reported the synthesis of various 7-carbonyl homologues of 1-deoxynojirimycin **1**, i.e the acid, amide and ketone compounds.[1] These were derived from 1-amino-1-deoxy-D-glucitol **2** *via* a crystalline 3,4;5,6-diacetonide salt. In a concurrent sequence, 6-azido and 6-amino analogues of **1** were prepared *via* the *N*-Boc-2,3;5,6-di-*O*-isopropylidene derivative of aminoalditol **2**.[2] The present work deals with the conversion of **2** to the epoxide **3**, which might serve as an alternative precursor of the azasugars **1** (1-deoxynojirimycin) and **4** (castanospermine) and their analogues.[3] In non aqueous acidic medium, epoxide **3** rearranges to the *cis*-hydrofuran compound **5** which can be transformed to the chiral bridged aminodiol **6**.



The non chiral parent compound 8-oxa-3-azabicyclo[3.2.1]octane **7** was prepared in 1948.[4] The *N*-substituted derivatives **8** and **9** exhibit analgesic and antiinflamatory activities in mice and rats.[5] The related 3-azabicyclo[3.2.1]octane compound **10** acts as an analgesic in rats.[6] Bicyclic compounds **11** (X = heteroatom) with specific groups attached to X or incorporated into R display potent antiarrhythmic activity in animal models.[7] The herewith reported compound **6** can be viewed as a chiral analogue of the bicyclic structures **7**, **10**, and **11**.

RESULTS AND DISCUSSION

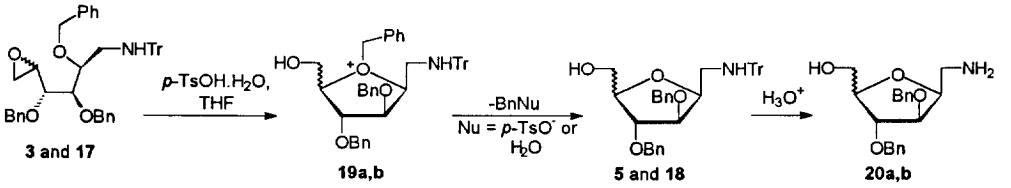
We commenced our synthesis with the aminoalditol **2** which is utilized as a precursor of the antidiabetic compound **1** and some *N*-substituted analogues.[8] The amino group of **2** was protected as the *N*-trityl derivative **12** (Scheme 1). The latter was prepared *via* initial silylation of the OH groups, *N*-tritylation, and deprotection of the trimethylsilyl groups with K_2CO_3 in methanol, in 71% overall yield. Compound **2** is not soluble in non aqueous medium. It has been reported that tritylation of amino acids in aqueous medium[9] gives low yields of *N*-tritylamino acids due to hydrolysis of trityl chloride. Whereas these difficulties can be resolved by applying the above-mentioned silyl protection method,[10] we also developed an alternative procedure to prepare compound **12** directly from the *p*-toluenesulfonate salt of **2**. In contrast to the free amine **2**, this salt is soluble in pyridine. Sequential addition of Et_3N and $(C_6H_5)_3CCl$ afforded **12** in 81% yield.



Scheme 1. *Reagents*: (a) 1) HMDS, TMSCl, pyridine, CH_2Cl_2, reflux, 3 h; 2) TrCl, Et_3N, CH_2Cl_2, 0 °C, 4 h; 3) K_2CO_3, MeOH, 4 h; (b) 1) TsOH (1 equiv.), MeOH; 2) Pyridine, Et_3N, TrCl; (c) 1) $(MeO)_3CH$, PPTS, THF, 50°C, 1-3 h; 2) NaH, DMF, BnBr, 0 °C, 1 h; (d) PPTS, aq.MeOH, THF; (e) MsCl, DMAP, Et_3N, CH_2Cl_2, room temp.; (f) MeONa, MeOH; (g) $TsOH.H_2O$ or Me_3SO_3H, THF, room temp., 10 min.

To prepare epoxide **3**, selective protection of the 5- and 6-OH groups was required. This was accomplished by heating **12** with trimethyl orthoformate and no more than 0.04 equivalents of pyridinium *p*-toluenesulfonate (PPTS) in THF at 50 °C for 1 to 3 hours. Prolonged reaction times or a higher concentration of PPTS led to less polar side products. After benzylation of the crude product with benzyl bromide and NaH in DMF, the resulting compound **13** was partially hydrolysed with aqueous methanol and PPTS to afford the pure 6-*O*-formyl ester **14** in 51% overall yield from **12**. None of the 5-*O*-formyl regioisomer was detected in the ^1H NMR spectrum. Mesylation of **14** in dichloromethane with MsCl, DMAP, and Et_3N followed by treatment with MeONa in MeOH, produced an inseparable 9:1 mixture of the epoxides **3** and **17** in 97% yield. This mixture was used in the next steps. Presumably, the formation of epoxide **17** from **14** proceeds *via* the 6-*O*-mesylate **16** which results from the base (Et_3N) catalysed

migration of the 6-*O*-formyl group of **14** to the 5-*O*-position and mesylation of the primary hydroxyl group. The *N*-benzyl-*N*-trifluoroacetyl analogue of epoxide **3** was used previously in the synthesis of 1-deoxynojirimycin and castanospermine.[3]

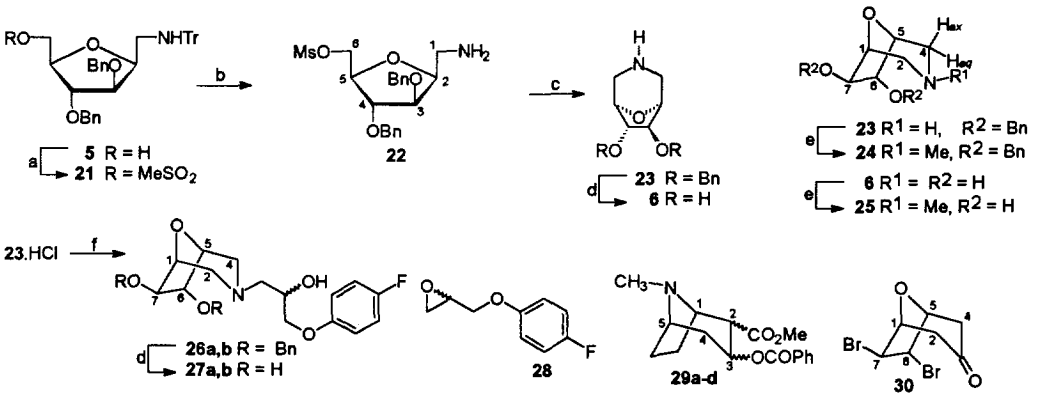


Scheme 2.

Treatment of the mixture of epoxides **3** and **17** with *p*-toluenesulfonic acid or methanesulfonic acid in THF afforded the five-membered ring compounds **5** (main product) and **18** (trace component). The mass spectra of these compounds were very similar, showing the presence of the *N*-trityl group and only two benzyl groups: ions corresponding to $[M\text{-}C_6H_5]^+$ and $[M\text{-}Tr]^+$ were detected at m/z 508 and 342 respectively. Opening of the epoxide and generation of an OH group was indicated by the introduction of one trimethylsilyl group (mass shift of 72 Daltons). In the 400 MHz ^1H NMR spectrum of compound **5** in d_6-DMSO, the primary alcohol proton was detected as a triplet centered at δ 4.70 ppm (*J* 6 Hz). The ^{13}C NMR spectrum revealed the disappearance of signals corresponding to the original epoxide **3** (δ 42.7 for C-6 and δ 53.5 ppm for C-5), and confirmed the presence of two benzyl groups. On the basis of these results and the coupling constant values observed in the ^1H NMR spectrum, the five-membered ring structure **5** was attributed to the main product. The *cis* relationship for C-1 and C-6, which implies a double inversion at C-5 (steps f and g, Scheme 1), was verified by transformation of the main product **5** to the bridged compound **23** (see below). Presumably, attack of the 2-OBn oxygen at C-5 of the protonated epoxide results in a S_N2-type cyclization and debenzylation, as depicted (Scheme 2) for both the major and the minor epoxide compounds. Similar cyclisations to hydrofuran compounds, resulting from participation of ether oxygens, have been reported previously.[11] When the mixture of epoxides **3** and **17** was heated in acidic aqueous methanol, the resulting compounds **20a** and **20b** were found to be the same (TLC, mass spectra) as those obtained indirectly *via* *N*-detritylation of **5** and **18**. The 3,4,6-tri-*O*-benzyl analogue of *cis* compound **20a** has been reported as a 5:1 mixture with the C-2 epimer.[12]

Linkage of the *cis*-disposed 2,5-substituents of compound **5** provides access to a chiral bridged morpholine system in which chirality relates to the *trans* orientation of identical substituents on the bridge carbons 6 and 7 (Scheme 3). The desired transformation (**5** → **23**) was accomplished *via* mesylation of 6-OH, acid deprotection of 1-NH_2, and heating of the primary amine salt **22.HCl** with triethylamine in dichloromethane. The cyclization could be followed through CIMS analysis of the *N*-acetylated reagent and product components (**22**, MH^+ 464 and **23**, MH^+ 368). Following chromatographic separation as the free base **23**, partial degradation was prevented by acidifying the eluates with HCl prior to evaporation. The crystalline HCl-salt was isolated in 57% yield calculated on **5**.

Difficulties were encountered in debenzylation of compound **23**. Even at 50-60 °C, only one benzyl group was removed on hydrogenation of the HCl-salt with Pd/C in methanol-acetic acid (CIMS: MH^+ 234). However, smooth debenzylation of both protecting groups was achieved by using Pearlman's $Pd(OH)_2$ catalyst with HCl in methanol. Chromatographic isolation as the free base afforded the crystalline aminodiol **6** in 94% yield.



Scheme 3. *Reagents:* (a) MsCl, DMAP, Et_3N, CH_2Cl_2, room temp.; (b) $TsOH.H_2O$ or $MeSO_3H$, MeOH, 60 °C, 30 min; (c) CH_2Cl_2, Et_3N, reflux 30 min; (d) MeOH, HCl, $Pd(OH)_2$, H_2, room temp.; (e) MeOH, CH_2O, 10% Pd/C, H_2; (f) MeOH, Et_3N, **28**, reflux, 2 h.

To characterize further the bicyclic system and to assess the biologic activity of representative compounds, we prepared some *N*-alkyl and *O*-deprotected analogues. The *N*-methyl compounds **24** and **25** were derived *via* hydrogenation of **23** and **6** with formaldehyde. Reaction of **23** with the racemic epoxide **28** in methanol at reflux temperature gave a mixture of epimeric compounds **26a,b**. Both the epimeric mixture and the chromatographically purified isomers were hydrogenated with $Pd(OH)_2$, to afford the corresponding aminodiols **27a,b**. *N*-Substitution of various amino compounds with the 3-(2-or 4-fluorophenoxy)-2-hydroxypropyl group gave rise to products showing diverse pharmacological profiles.[13-15]

Analysis of the 400 MHz ^1H NMR spectra (Table 1) clearly showed the chair conformation of the bridged morpholine ring. This form was indicated by similar ^3J-values (1.8-2.6 Hz) measured for coupling between the bridgehead protons H-1 and H-5 and the axial and equatorial neighbouring protons H-2 and H-4. The ensuing nearly identical torsional angles (*ca.* 60°) preclude alternative boat or flattened chair conformations. Supporting evidence for the chair conformation of the morpholine ring comes from a comparison with the structurally related cocaine isomers **29a-d**. For all four isomers, attribution of the chair form to the ethano bridged piperidine ring likewise rested on similar values for $^3J_{1,2}$ (2.2-3.3 Hz), $^3J_{4eq,5}$ (2.2-3.1 Hz), and $^3J_{4ax,5}$ (1.8-4.8 Hz).[16] A crystallographic study of the related ketone compound **30** also showed a chair-like conformation for the six-membered pyran ring.[17]

In the spectrum of the *N*-methyl compound **25**, equatorial *endo* protons H-2 and H-4 were differentiated by a characteristic long-range coupling (1.8 Hz). Decoupling of the low-field proton H-4*endo* removed this ^4J-coupling and also reduced the signal multiplicity for the bridgehead proton H-5 (dt→dd). The remaining dd signal relates to coupling with the *cis*-oriented protons H-6 (6.5 Hz) and H-4*exo* (2 Hz). In contrast to H-6*exo*, H-7*endo* displayed a rather sharp singlet ($\omega_{\frac{1}{2}}$ = 2 Hz) indicating torsional angles of *ca.* 90° with the *trans*-oriented protons H-6 and H-1. These data are comparable to those reported for norbornane-type compounds.[18]

In the C_6D_6 spectrum of compound **24**, signals for the bridgehead protons H-1, H-5 coincided (δ 4.1), as shown by the NOE's induced on irradiation of either H-2 or H-4. To assign the latter protons, we performed ^{13}C-{^1H} selective decoupling of H-1,H-5. This resulted in singlet signals for C-1 and C-5, and in residual couplings for C-2 and C-4 (triplet and dd, respectively) which correlated with the separations observed for each pair of protons (H-2: δ 0.1 ppm; H-4: δ 0.6 ppm). The carbons C-2 and C-4 in turn were

identified on basis of the characteristic (*anti-* and *syn-*) γ-effects[19] originating from the *exo* and *endo* benzyloxy groups (C-2: δ 58.3; C-4: δ 53.6). Finally, signals for the bridgehead protons were separated (δ 0.02 ppm) by applying a solvent mixture C_6D_6-$CDCl_3$; further ^1H-^1H decoupling confirmed the assignment of vicinal protons H-1, H-2 and H-4, H-5.

Table 1. 400 MHz 1H NMR of compounds 23, 24, and 25 in C_6D_6

	23.HCl	**24**	**25**
Proton	δ (ppm), multiplicity, *J* (Hz)	δ (ppm), multiplicity, *J* (Hz)	δ (ppm), multiplicity, *J* (Hz)
H-2*exo*	3.02, d (br), 12	2.24, dd, 11.2, 1.8	1.93, dd, 11,2.5
H-4*exo*	2.83, d (br), 12	2.14, dd, 11.6, 2.6	1.98, dd, 11.5, 2
H-2*endo*	3.52, d (br), 12	2.35, d (br), 11	2.08, dt, 11, 1.8, 1.8
H-4*endo*	2.98, d (br), 12	2.77, d (br), 11.6	2.50, dt 11.5, 1.8, 1.8
H-1	3.88, s (br)	4.10, m	3.73, s, $\omega\frac{1}{2}$: 5.5
H-7*endo*	5.12, s (br)	4.37, s (br)	3.89, s, $\omega\frac{1}{2}$: 2
H-5	3.72, d (br)	4.10, m	4.07, dt, 6.5, 2, 1.8
H-6*exo*	4.17, d, 6	4.26, dd, 6.2, 1.4	4.23, d, 6.5 Hz
CH_3	-	2.06, s	1.67, s
CH_2-Ar	4.39, 4.43, ABq, 11.5	4.38, 4.45, ABq, 11 Hz	-
CH_2-Ar	4.38, 5.05, ABq , 11.5	4.37, s	-
Ar-H	7.20-7.40, m	7.08-7.40, m	-

In the ^1H NMR spectra of the secondary amines **6** and **23**, signals for the bridge and bridgehead protons H-1, H-5, H-6, H-7 were similar to those described for the *N*-methyl compounds (see Experimental). Due to overlap and broadening effects, however, no definite assignments could be made with regard to H-2 and H-4. For the HCl-salt of **23**, some broadening of signals also was observed. The assignments shown in Table 1 were based on decoupling of H-6 and a low-field proton H-2 (tentatively assigned as H-2*endo*); NOE performed for H-2, H-4, and H-5 enhanced H-1, H-5, and H-6, respectively.

In preliminary *in vitro* experiments using various receptor systems, no significant receptor affinity was observed for the bridged morpholino compounds **6** and **23-27.**

CONCLUSION

Starting from 1-amino-1-deoxy-D-glucitol, we developed a synthetic route to a 2,6-bridged morpholine system. In these bicyclic products, chiral positions 3,4 and 2,5 of D-glucose are transposed as the bridge and bridgehead carbons 6, 7 and 5, 1 respectively. The morpholine ring, comprising positions 2, 3, and 4 as the mobile portion, was shown to be in a chair conformation implying the *endo* orientation for the amino nitrogen. In addition to the synthetic and conformational aspects discussed so far, substitution of the hydroxyl and amino groups of aminodiol **6** allows for attachment of spatially directed groups, e.g. pharmacophores and fluorophores.

EXPERIMENTAL SECTION

General methods

Melting points were uncorrected. The optical rotations were measured on a Propol polarimeter fitted with a 7 cm cell. IR spectra were recorded as thin films between NaCl plates on a Perkin-Elmer 297 grating IR spectrophotometer. ^1H and ^{13}C NMR were recorded on a Bruker AMX 400 instrument operating at 400 MHz for ^1H and 100 MHz for ^{13}C. ^1H and ^{13}C chemical shifts are reported in ppm relative to tetramethylsilane as an internal reference. *J* values are reported in Hz. Mass spectra were run on Kratos MS50 and Hewlett-Packard 5989A instruments; the ion source temperature was 150-250°C as required. Exact masses were measured at a resolution of 10,000. Analytical and preparative thin layer chromatography were performed using Merck silica gel 60 PF-224. Column chromatography was carried out using 70-230 mesh silica gel 60 (E. M. Merck). Dry solvents were freshly distilled. Solutions were dried over $MgSO_4$. 1-Amino-1-deoxy-D-glucitol was supplied by Cerestar. Elemental analysis was performed by Janssen Pharmaceutica on a Carbo Erla elemental analyser type 1106.

1-Amino-1-deoxy-1-*N*-triphenylmethyl-D-glucitol (12).

Method A : Trimethylsilyl chloride (40 ml, 77 mmol) and 1,1,1,3,3,3-hexamethyldisilazane (20 ml, 94 mmol) were added to a suspension of **2** (2.20 g, 11.3 mmol) in pyridine (10 ml) and CH_2Cl_2 (10 ml). The mixture was heated under reflux for 3 h. After cooling, the excess of reagents was destroyed by slow addition of MeOH. The solvent was removed, the oily residue was redissolved in CH_2Cl_2 and the solution washed with cold water. To the dried and cooled (0 °C) solution, TrCl (3.60 g, 12.1 mmol) and Et_3N (5 ml) were added and the mixture stirred for 4 h at 0 °C. After washing with water and evaporation of CH_2Cl_2, the residue was dissolved in MeOH (15 ml) containing K_2CO_3 (5 g). The desilylation was complete after 4 h. The mixture was evaporated to dryness and the residue distributed between CH_2Cl_2 and water. The CH_2Cl_2 phase was dried and concentrated to a small volume. This was added to an excess of hexanes and the precipitated solid collected by filtration. After three precipitations in hexanes as above, pure **12** was obtained in 71% (3.41 g) overall yield: mp 125-126°C; $[\alpha]_D^{18.5}$-9.8° (*c* 1, MeOH); ^1H NMR (400 MHz, $CDCl_3$) δ 2.35 (m, 2 H), 3.53 (m, 2 H), 3.70 (m, 4 H), 7.15-7.45 (m, 15 H); ^{13}C NMR (100 MHz, $CDCl_3$), δ 46.6 (CH_2), 63.9 (CH_2), 70.8 (C), 71.7 (CH), 72.0 (CH), 72.3 (CH), 73.4 (CH), 126.6-128.7 (aromatic CH), 145.2 (aromatic C).

Method B : To a stirred suspension of **2** (11.4 g, 60 mmol) in MeOH (150 ml) was added *p*-toluenesulfonic acid monohydrate (11.4 g, 60 mmol). After 20 min the mixture became homogeneous. The solvent was removed by co-evaporation with toluene and CCl_4, respectively. The crystalline residue was redissolved in pyridine (20 ml). Dry Et_3N (50 ml) was added followed immediately by TrCl (17 g, 60.4 mmol). After 30 min, another portion of TrCl (6 g, 21.3 mmol) was added and the reaction was allowed to proceed for 1 h. The solvent was removed and the residue was distributed between CH_2Cl_2 and water. After workup as above, compound **12** was isolated in 81% yield (20.5 g).

1-Amino-2,3,4-tri-*O*-benzyl-1-deoxy-6-*O*-formyl-1-*N*-triphenylmethyl-D-glucitol (14). Compound **12** (6.20 g, 14.6 mmol) was heated at 50 °C with $(MeO)_3CH$ (4.80 ml, 44 mmol) and PPTS (0.070 g, 0.28 mmol) in THF (25 ml) for 1.5 h. The mixture was allowed to reach room temp., and an aqueous solution of K_2CO_3 was added. After evaporation of THF, the residue was distributed between CH_2Cl_2 and water. The organic phase was dried and evaporated. The residue was dissolved in DMF (20 ml) and the solution added to a cooled (0 °C) mixture of NaH (80% dispersed in mineral oil, 2.20 g, 73 mmol) and DMF (20 ml). After 10 min of stirring, benzyl bromide (7.1 ml, 59 mmol) was added. After completion of the reaction (2 h), the excess of reagent was destroyed by slow addition of MeOH (5 ml). The solution was diluted with

CH_2Cl_2 (60 ml) and the solution washed thoroughly with water. The CH_2Cl_2 layer was dried and evaporated to afford an oily residue containing **13** as the major product. Without purification, this residue was dissolved in 100 ml of a mixture of THF/MeOH/H_2O (10/9/1). PPTS (3.17 g, 14.7 mmol) was added and the mixture stirred for 6 h. After evaporation of the solvent and column chromatography (EtOAc/hexanes: 2:3), **14** (5.4 g) was isolated as an oil in 51% overall yield from **12**. $[\alpha]_D^{20}$ -0.65° (*c* 3.5, MeOH); IR ν_{max} (cm^{-1}): 3435, 3035, 2927, 1725, 1597, 1494, 1452, 1088; ^1H NMR (400 MHz, $CDCl_3$) δ 2.25 (m, 1 H, H-1a), 2.47 (m, 1 H, H-1b), 3.58 (dd, J = 8, 4 Hz, 1 H, H-4), 3.90 (m, 2 H, H-2, H-3), 4.00 (m, 1 H, H-5), 4.18 (dd, ^2J = 12, ^3J = 6 Hz, 1 H, H-6a), 4.35 (dd, ^2J = 12, ^3J = 3 Hz, 1 H, H-6b), 4.37, 4.45 (ABq, ^2J = 11.5 Hz, 2 H, CH_2Ph, 4.49 (s, 2 H, CH_2Ph), 4.65, 4.72 (ABq, ^2J = 11.5 Hz, 2 H, CH_2Ph), 6.96-7.54 (m, 30 H, 6 *Ph*), 8.07 (s, 1 H, *H*CO-); ^{13}C NMR (100 MHz, $CDCl_3$) δ 43.4 (C-1), 65.2 (C-6), 69.7 (C-5), 70.7 (Ph_3C), 72.9, 73.2, 74.0 (3 CH_2Ph), 76.7 (C-4), 78.7, 79.2 (C-2, C-3), 126.3, 127.8, 127.8, 128.0, 128.1, 128.4, 128.5, 128.6 (aromatic *C*H), 137.4, 137.6, 137.9 (C-1' CH_2*Ph*), 145.7 (C-1' *Ph*$_3$C), 160.9 (*H*CO); HRMS calcd for $C_{41}H_{42}NO_6$ ([M-Ph]$^+$) 644.3012, found 644.3010, calcd for $C_{28}H_{32}NO_6$ ([M-Tr]$^+$) 478.2230, found 478.2237.

1-Amino-5,6-anhydro-2,3,4,-tri-*O*-benzyl-1-deoxy-1-*N*-triphenylmethyl-L-iditol (3). To a solution of **14** (2.20 g, 3.0 mmol) in dry CH_2Cl_2 (50 ml) were added MsCl (0.36 ml, 4.5 mmol), DMAP (0.372 g, 3.0 mmol), and Et_3N (0.70 ml, 9.6 mmol) at room temp. The mixture was stirred for 1 h after which time it was washed with water (3x50 ml). The organic layer was dried and evaporated to dryness. The residue was dissolved in MeOH (15 ml), MeONa (0.329 g, 6.1 mmol) was added and the solution was stirred for 2 h. Water (35 ml) was added and the solution extracted with dichloromethane (3x50 ml). The dichloromethane layer was evaporated and the residue purified by column chromatography (EtOAc/hexanes: 3:17) to afford 2.94 g (97%) of an oil which consisted of an inseparable 9:1 mixture of epoxides **3** and **17**. ^1H NMR (400 MHz, $CDCl_3$) **3**: δ 2.02 (dd, ^2J = 13, ^3J = 5 Hz, 1 H, H-1a), 2.28 (dd, ^2J = 5, $^3J_{trans}$ = 2.5 Hz, 1 H, H-6a), 2.35 (dd, ^2J = 13, ^3J = 4 Hz, 1 H, H-1b), 2.40 (t, ^2J = 5, $^3J_{cis}$ = 4 Hz, 1 H, H-6b), 3.01 (dd, J = 7, 3 Hz, 1 H, H-4), 3.12 (ddd, J = 7, 4, 2.5 Hz, 1 H, H-5), 3.83 (dd, J = 7, 3 Hz, 1 H, H-3), 3.92 (m, 1 H, H-2), 4.33, 4.47, 4.52, 4.64, 4.73, 4.78 (6 H, 3 CH_2Ph), 7.20-7.40 (39 H, *Ph*). **17:** δ 2.61 (dd, ^2J = 5 Hz, $^3J_{trans}$ = 2.5 Hz, 1 H, H-6b), 2.68 (dd, ^2J = 5 Hz, $^3J_{cis}$ = 3.5 Hz, 1 H, H-6a), 3.10 (ddd, ^3J = 5 Hz, $^3J_{cis}$ = 3.5 Hz, $^3J_{trans}$ = 2.5 Hz, 1 H, H-5), 3.28 (dd, J = 5, 2.5 Hz, 1 H, H-4). **3**: ^{13}C NMR (100 MHz, $CDCl_3$) δ 42.7 (C-6), 42.8 (C-1), 53.5 (C-5), 70.4 (*C*Ph$_3$), 71.9, 72.8, 74.5 (O*C*H$_2$Ph), 79.6, 79.9, 80.2 (C-2, C-3, C-4), 126.2-145.8 (aromatic carbons). HRMS calcd for $C_{40}H_{40}NO_4$ ([M-Ph]$^+$) 598.2957, found 598.2922, calcd for $C_{27}H_{30}NO_4$ ([M-Tr]$^+$) 432.2175, found 432.2176.

1-Amino-2,5-anhydro-3,4-di-*O*-benzyl-1-deoxy-1-*N*-triphenylmethyl-D-glucitol (5). To a solution of the 9:1 mixture of **3** and **17** (0.94 g, 1.4 mmol) in THF (20 ml) was added *p*-TsOH.H_2O (0.845 g, 4.4 mmol). After 10 min, the mixture was made alkaline with aq.K_2CO_3 and extracted with CH_2Cl_2. Column chromatography (hexanes/EtOAc: 7:3) afforded **5** (0.44 g, 53%) as an oil. $[\alpha]_D^{20}$ +18.8° (*c* 4.59, $CHCl_3$); IR: ν_{max} (cm^{-1}) 3426, 3085, 3060, 3030, 2872, 1596, 1176, 1099; ^1H NMR (400 MHz, $CDCl_3$) δ 2.45 (m, 2 H, 2 H-1), 3.61 (dd, ^2J = 11.5, ^3J = 4 Hz, 1 H, H-6a), 3.78 (dd, ^2J = 11.5, ^3J = 3 Hz, 1 H, H-6b), 4.02 (dd, J = 4.5, 1.5 Hz, 1 H, H-3), 4.05-4.09 (m, J = 3, 1.5 Hz, 2 H, H-4, H-5), 4.28 (td, J = 6, 4.5 Hz, 1 H, H-2), 4.29, 4.54 (ABq, ^2J = 12 Hz, 2 H, CH_2Ph), 4.58, 4.61 (ABq, J = 12 Hz, 2 H, CH_2Ph), 7.00-7.50 (m, 26 H, 5 *Ph*). ^{13}C NMR (100 MHz, $CDCl_3$) δ 43.2 (CH_2), 63.1 (CH_2), 70.8 (C),

71.3 (CH_2), 72.0 (CH_2), 81.0 (CH), 82.7 (CH), 82.8 (CH), 84.1 (CH), 126.2, 127.6, 127.7, 127.8, 127.9, 128.0, 128.6, (aromatic CH), 137.2 (C), 137.6 (C), 145.9 (3 C); HRMS calcd for $C_{39}H_{39}NO_4$ (M^+) 585.2879, found 585.2858. The more polar isomer **18** was isolated as a trace component by preparative TLC (hexanes/EtOAc: 7:3) and was characterized *via* mass spectral comparison with compound **5**. The isomeric compounds **5** and **18** were analysed both as the free alcohols and trimethylsilyl derivatives prepared by heating with *N,O*-bis(trimethylsilyl)trifluoroacetamide in pyridine.

[1R-(6*endo*,7*exo*)]-6,7-di-*O*-Benzyl-8-oxa-3-azabicyclo[3.2.1]octane-6,7-diol (23). To a solution of **5** (15.0 g, 25.6 mmol) in dry CH_2Cl_2 (100 ml) was added MsCl (3.20 ml, 40 mmol), DMAP (1.60 g, 13 mmol), and Et_3N (12 ml) at room temp. The mixture was stirred for 15 min after which time it was washed with water (3x50 ml). The organic layer was dried and evaporated to furnish crude **21**. Without purification, the oily residue was dissolved in 100 ml of a 1:1 mixture of concentrated HCl and MeOH. After being heated at 60 °C for 30 min, the solution was evaporated to dryness. A mixture of the crude salt **22.HCl** and Et_3N (20 ml) in CH_2Cl_2 (100 ml), was heated under reflux for 30 min (after 1 min and 30 min, respectively, samples of the solution were treated with Ac_2O for CIMS analysis). The solvent was removed and the residue purified by column chromatography (MeOH/$CHCl_3$: 3:47). To prevent partial degradation, fractions containing the free base **23** were acidified with methanolic HCl. Evaporation of the solvent afforded 5.32 g (57%) of crystalline **23**.HCl. **23:** oil, $[\alpha]_D^{20}$ -6.4° (*c* 0.6, $CHCl_3$); IR ν_{max} (cm^{-1}): 3085, 3040, 2963, 2869, 1497; ^1H NMR (400 MHz, C_6D_6) δ 2.40 (d, ^2J = 13 Hz, 1 H), 2.80 (d, ^2J = 13 Hz, 1 H), 2.95 (d, ^2J = 13 Hz, 1 H), 2.98 (d, ^2J = 13 Hz, 1 H), 3.91 (br s, 1 H, H-1), 4.01 (br s, 1 H, H-5), 4.09 (d, *J* = 2 Hz, 1 H, H-7*endo*), 4.21 (dd, *J* = 6, 2 Hz, 1 H, H-6*exo*), 4.23, 4.37 (ABq, ^2J = 12 Hz, 2 H, CH_2Ph), 4.29, 4.31 (ABq, ^2J = 12 Hz, 2 H, CH_2Ph), 7.10-7.40 (m, 15 H, *Ph*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 45.1 (CH_2) , 48.3 (CH_2), 71.3 (CH_2), 72.9 (CH_2), 76.7 (CH), 79.2 (CH), 86.0 (CH), 86.7 (CH), 127.8, 127.9, 128.4, (aromatic CH), 137.7 (aromatic C); HRMS calcd for $C_{20}H_{23}NO_3$ (M^+) 325.1688, found 325.1678; **23**.HCl, mp 60 °C; ^1H NMR (Table 1). Anal. calcd. for $C_{20}H_{24}ClNO_3.H_2O$: C, 63.24; H, 6.90; N, 3.69; O, 16.85; H_2O, 4.74. Found C, 63.43; H, 6.77; N, 3.59; O, 16.10; H_2O, 4.17.

[1R-(6*endo*,7*exo*)]-8-Oxa-3-azabicyclo[3.2.1]octane-6,7-diol (6). To a solution of **23.HCl** (0.500 g, 1.5 mmol) in MeOH (30 ml), were added 5 drops of concentrated HCl and $Pd(OH)_2$ (0.125 g). The mixture was hydrogenated in a Parr apparatus (35 psi) for 3 h. The catalyst was removed by filtration through Celite, the filtrate was evaporated and the residue purified by column chromatography on silica gel (H_2O/NH_4OH/MeOH/$CHCl_3$: 1:1:28:70) to afford 0.188 g (94%) of the crystalline aminodiol **6**: mp 195-196.6 °C; $[\alpha]_D^{20}$ -4.4° (*c* 2.3, MeOH); ^1H NMR (400 MHz, CD_3OD), δ 3.18-3.38 (m, 4 H, H-2, H-4), 4.07 (br s, 1 H, H-1), 4.20 (br s, 1 H, H-7*endo*), 4.39 (br d, *J* = 7 Hz, 1 H, H-6*exo*), 4.49 (br d, *J* = 7 Hz, 1 H, H-5); ^{13}C NMR (100 MHz, CD_3OD) δ (ppm) 44.4 (CH_2), 45.8 (CH_2), 76.2 (CH), 80.5 (2 CH), 81.7 (CH); HRMS calcd for $C_6H_{11}NO_3$ (M^+) 145.0740, found 145.0746.

[1R-(6*endo*,7*exo*)]-6,7-Di-*O*-benzyl-3-methyl-8-oxa-3-azabicyclo[3.2.1]octane-6,7-diol (24). To a solution of **23.HCl** (0.47 g, 1.4 mmol) in MeOH (30 ml), were added an aqueous solution (37%) of formaldehyde (2 ml) and 10% Pd/C (0.114 g). The mixture was hydrogenated in a Parr apparatus (35 psi) for 1 h. The catalyst was removed by filtration through Celite and the filtrate was made alkaline with methanolic ammonia. After concentration, the residue was dissolved in MeOH and the methanol solution was evaporated. This treatment was repeated several times in order to convert a more polar complex to compound **24**. The residue was dissolved in CH_2Cl_2 and the resulting solution washed with water. The organic phase was dried, and evaporated. The residue was purified by column chromatography (hexanes/EtOAc: 7:3) to

give 0.427 g (97%) of the *N*-methyl compound **24** as an oily residue: $[\alpha]_D^{20}$ +2.2° (*c* 0.96, $CHCl_3$); IR: ν_{max} (cm^{-1}) 3100-3090, 2960-2850, 1550, 1500; ^1H NMR (Table 1); ^{13}C NMR (100 MHz, C_6D_6) δ 45.6 (CH_3), 53.9 (C-4), 58.3 (C-2), 71.6 (CH_2Ph), 72.6 (CH_2Ph), 75.6, 79.1 (C-1, C-5), 86.4 (C-7), 87.4 (C-6), 127.8-128.5 (aromatic CH), 139.00 (aromatic C); HRMS calcd for $C_{21}H_{25}NO_3$ (M^+) 339.1834, found 339.1826.

[1R-(6*endo*,7*exo*)]-3-Methyl-8-oxa-3-azabicyclo[3.2.1]octane-6,7-diol (25). To a solution of **23.HCl** (0.400 g, 1.1 mmol) in MeOH (30 ml), were added 5 drops of concentrated HCl and $Pd(OH)_2$ (0.100 g). The mixture was hydrogenated in a Parr apparatus (35 psi) for 3 h. The catalyst was removed by filtration through Celite. The filtrate was evaporated and to the residue were added MeOH (30 ml), paraformaldehyde (0.13 g, 4.3 mmol) and 10% Pd/C (0.100 g). The mixture was hydrogenated in a Parr apparatus (35 psi) for 3 h. The catalyst was removed by filtration through Celite, the filtrate was evaporated and the residue was chromatographed on a silica gel column (H_2O/NH_4OH/MeOH/$CHCl_3$: 1:1:28:70) to afford 0.083 g (47% yield) of the crystalline aminodiol **25**: mp 126.6°, $[\alpha]_D^{20}$ +35.2° (*c* 0.6, $CHCl_3$); IR: ν_{max} (cm^{-1}) 3550-3400, 2960-2850; ^1H NMR (Table 1); ^{13}C NMR (100 MHz, C_6D_6) δ (ppm) 45.0 (CH_3), 55.4 (CH_2), 57.5 (CH_2), 76.8 (CH), 81.1 (CH), 82.6 (CH), 84.0 (CH); HRMS calcd for $C_7H_{13}NO_3$ (M^+) 159.0895, found 159.0902.

1-{[1R-(6*endo*,7*exo*)]-6,7-Di-*O*-benzyl-6,7-dihydroxy-8-oxa-3-azabicyclo[3.2.1]oct-3-yl}-3-*p*-fluorophenoxy-2-propanol (26a and 26b). Et_3N (1 ml) and racemic epoxide **28** (0.665g, 4.0 mmol) were added to a solution of **23.HCl** (0.992 g, 2.74 mmol) in MeOH (40 ml). The solution was heated under reflux for 30 min. The solvent was removed and the residue was purified by column chromatography (EtOAc/$CHCl_3$: 3:47). Three fractions were isolated (98% combined yield): these consisted of the pure compounds **26a** (29%, less polar) and **26b** (25%, more polar), and a mixed fraction **26a,b**. **26a**: oil, $[\alpha]_D^{20}$ -16.2° (*c* 1.01, $CHCl_3$); IR: ν_{max} (cm^{-1}) 3440, 3100-3090, 2960-2850, 1580, 1500; ^1H NMR (400 MHz, C_6D_6) δ 2.13 (br d, 1 H), 2.36-2.40 (m, 3 H), 2.56 (br d, 1 H), 2.79 (br d, 1 H), 3.75 (dd, *J* = 10, 4.5 Hz, 1 H), 3.85 (dd, *J* = 10, 5.4 Hz, 1 H), 4.04 (m, 3 H), 4.18 (br s, 1 H), 4.22 (dd, *J* = 7, 1.5 Hz, 1 H), 4.29 (s, 2 H), 4.41 (s, 2 H), 6.70-6.90 (m, 4 H), 7.20-7.40 (m, 10 H); ^{13}C NMR (100 MHz, C_6D_6) δ 50.4 (CH_2), 57.4 (CH_2), 59.7 (CH_2), 65.5 (CH), 71.2 (CH_2), 71.4 (CH_2) 73.6 (CH_2), 75.6 (CH), 78.9 (CH), 87.5 (CH), 87.8 (CH), 115.8-115.9 (aromatic CH), 127.7-128.7 (aromatic CH), 137.8, 138.7, 155.5, 158.9 (aromatic C); HRMS calcd for $C_{29}H_{32}NO_5F$ (M^+) 493.2264, found 439.2263; **26b**: oil, $[\alpha]_D^{20}$ +10.2° (*c* 1.61, $CHCl_3$); IR: ν_{max} (cm^{-1}) 3440, 3100-3090, 2960-2850, 1580, 1500; ^1H NMR (400 MHz, C_6D_6) δ 2.27 (br d, 1 H), 2.40 (m, 4 H), 2.63 (br d, 1 H), 3.69 (dd, *J* = 9, 5 Hz, 1 H), 3.83 (dd, J = 9, 5 Hz, 1 H), 3.90 (br s, 1 H), 4.04 (s, 2 H, CH_2), 4.09 (br s, 1 H), 4.15 (br d, 1 H), 4.22-4.38 (m, 4 H), 6.65-6.90 (m, 4 H), 7.20-7.40 (m, 10 H); ^{13}C NMR (100 MHz, C_6D_6) δ 53.4 (CH_2), 55.0 (CH_2), 59.9 (CH_2), 66.4 (CH), 70.9 (CH_2), 71.3 (CH_2), 73.2 (CH_2), 75.8 (CH), 78.6 (CH), 86.9 (CH), 87.6 (CH), 115.7-115.9 (aromatic CH), 127.7-128.7 (aromatic CH), 137.9, 138.4, 155.3, 158.7 (aromatic C); HRMS calcd for $C_{29}H_{32}NO_5F$ (M^+) 493.2264, found 493.2262.

1-{[1R-(6*endo*,7*exo*)]-6,7-Dihydroxy-8-oxa-3-azabicyclo[3.2.1]oct-3-yl}-3-*p*-fluorophenoxy-2-propanol (27b). To a solution of **26b** (0.200 g, 0.455 mmol) in MeOH (30 ml), were added 5 drops of concentrated HCl and $Pd(OH)_2$ (0.050 g). The mixture was hydrogenated in a Parr apparatus (35 psi) for 3 h. The catalyst was removed by filtration through Celite, the filtrate was evaporated and the residue was purified by column chromatography (MeOH/$CHCl_3$: 1:9) to afford 0.114 g (80%) of compound **27b** as an oil: $[\alpha]_D^{20}$

+16.0° (*c* 3.2, $CHCl_3$); IR: ν_{max} (cm^{-1}) 3550-3450, 3100-3090, 2960-2850, 1560; ^1H NMR (400 MHz, $CDCl_3$) δ 2.49 (m, 3 H), 2.63 (d, 1 H), 2.87 (d, 2 H), 3.82 (m, 2 H), 4.03 (m, 2 H), 4.19-4.32 (m, 3 H), 6.75-7.00 (m, 4 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 54.0 (CH_2), 54.4 (CH_2), 59.6 (CH_2), 66.7 (CH), 71.1 (CH_2), 77.2 (CH), 81.4 (CH), 81.8 (CH), 82.5 (CH), 115.6-116.1 (aromatic CH), 154.6, 158.7 (aromatic C); HRMS calcd for $C_{15}H_{20}NO_5F$ (M^+) 313.1325, found 313.1321.

Acknowledgments. The authors are indebted to the F.K.F.O. and the "Ministerie voor Wetenschapsbeleid-I.U.A.P." for financial support and to the K.U.Leuven (A. K.) and the I.W.O.N.L. (E. D.) for fellowships. They wish to thank the Firm Cerestar for generous supplies of 1-amino-1-deoxy-D-glucitol, the Firm Janssen Pharmaceutica for the receptor affinity experiments and for elemental analysis, and Mr R. De Boer for technical assistance.

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(*Received in UK* 14 *October* 1994; *accepted* 28 *October* 1994)