Total, Asymmetric Synthesis of (+)-Castanospermine,[1] (+)-6-Deoxycastanospermine, and (+)-6-Deoxy-6-fluorocastanospermine

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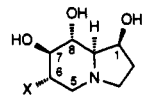
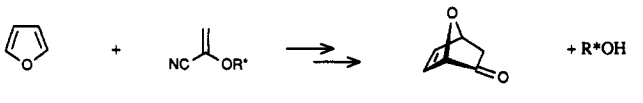
Bromination of the dibenzyl acetal of (-)-(1*S*,4*S*)-7-oxabicyclo[2.2.1]hept-5-en-2-one ((-)-**5**) led to (+)-(1*S*,5*S*,6*S*,7*S*)-6-*endo*-(benzyloxy)-5-*exo*-bromo-7-oxabicyclo[2.2.1]heptan-2-one (**25**). Baeyer-Villiger oxidation of **25** gave 2-*O*-benzyl-3-bromo-3,5-dideoxy-β-L-*arabino*-hexofuranosidurono-6,1-lactone (**26**). Methanolysis of **26** afforded the corresponding methyl (methyl αβ-L-arabinofuranosid)uronates (**27** + **28**). The α anomer **27** was reduced with DIBAH into methyl 2-*O*-benzyl-3-bromo-3,5-dideoxy-β-L-*arabino*-hexofuranoside (**29**). Mesylation of the primary alcohol, followed by treatment with NH_3 gave methyl 2-*O*-benzyl-3,5,6-trideoxy-3,6-imino-β-L-*lyxo*-hexofuranoside (**32**). Acetylation of the amine with $ClCH_2COCl$, acetolysis of the methyl furanoside followed by Arbuzov condensation with $(EtO)_3P$, and then intramolecular Horner-Emmons reaction led to (5*S*,6*S*,7*S*)-7-hydroxy-5-(benzyloxy)-1-azabicyclo[4.3.0]non-3-en-2-one (**37**). Base-catalyzed hydrolysis of the corresponding epoxide **43** ((1*S*,6*S*,7*S*,8*R*,8a*S*)-8-(benzyloxy)-6,7-epoxy-1-hydroxyoctahydroindolizidin-5-one) followed by reduction of the lactam and deprotection of the alcoholic functions afforded (+)-castanospermine ((+)-**1**). The conversion of (-)-**5** into (+)-**1** was highly stereoselective, requiring the isolation of 10 synthetic intermediates and with an overall yield of 15.2%. Reduction of **43** with $BH_3 \cdot Me_2S$ or its treatment with $HF \cdot Et_3N$ allowed one to prepare readily (+)-6-deoxycastanospermine ((+)-**2**) and 6-deoxy-6-fluorocastanospermine ((+)-**3**). The crystal structure of (+)-**3** is also reported.

Castanospermine ((+)-**1**) is a polyhydroxylated indolizidine isolated first in 1981 by Hohenschultz et al.[3] from seeds of the monotypic Australian rainforest and riverine tree *Castanospermum australe*. More recently,[4] it has been found in dried pod of *Alexa leiopetala* Sandwith and in seven other species of the same genus. The structure (relative configuration) of (+)-**1** was established by X-ray radiocrystallography first,[3] and then (absolute configuration) through chemical correlation by Bernotas and Ganem.[5] Castanospermine has generated much interest because it is a potent inhibitor of various glucosidases including lysomal α-glucosidase,[6] α- and β-glucosidase in fibroplast extracts,[6] the glycoprotein processing enzyme glucosidase I[7] as well as being a powerful inhibitor of β-xylosidase[6] and sucrase.[8] The ability of (+)-**1** to disrupt glycoprotein processing has resulted in the use of this compound to modify biosynthesis; it might provide more insight into the role of oligosaccharides in glycoprotein function.[9] Very interesting is the fact that (+)-**1** is able to inhibit experimental metastasis of some cancers.[10] Furthermore, it inhibits replication of human immunodeficiency virus (HIV) syncytium formation[11] and other virus replication.[12]



(+)-**1** X=OH
(+)-**2** X=H
(+)-**3** X=F



4 (-)-**5**

Ganem and Bernotas[5] have proposed a first synthesis of (+)-**1** which was inspired logically from the resemblance of (+)-**1** with D-glucopyranose. A short synthesis of 1-deoxynojirimycin (1,5-dideoxy-1,5-imino-D-glucitol) from D-glucose was developed,[13] and then an efficient two carbon chain elongation process (via the corresponding 6-carb-

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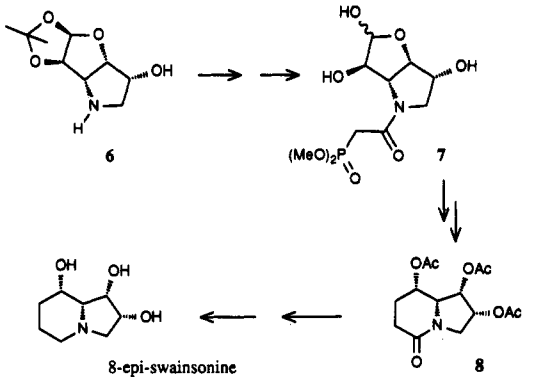
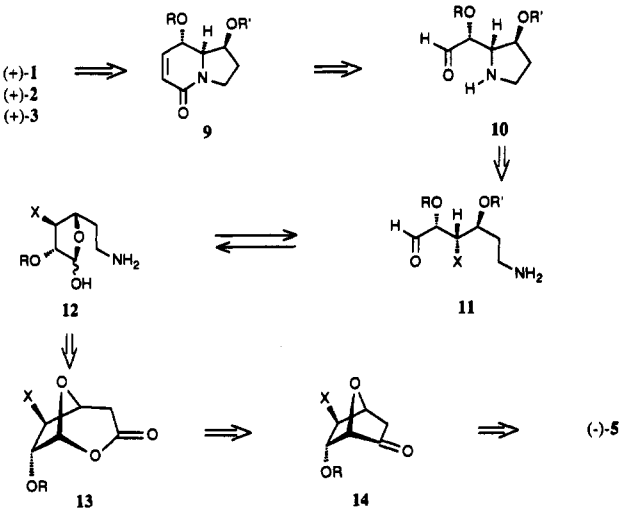
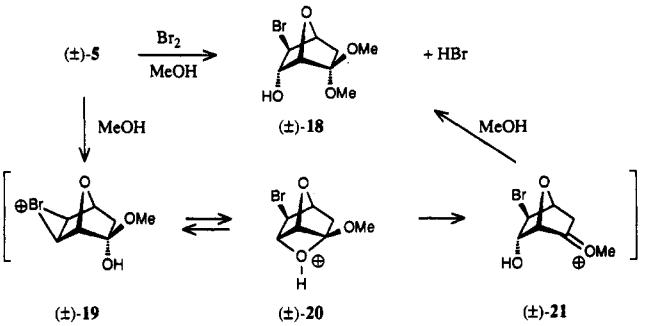
Scheme I



Scheme II



Scheme III



aldehyde) was found to complete the synthesis of (+)-1.[14] The second approach proposed by Hashimoto and co-workers[15] uses mannose as starting material. Fleet and co-workers[16] have obtained 6-epi- and 1,6-diepicastanospermine from L-gulonolactone, and Richardson and co-workers derived 1-deoxycastanospermine from D-glucose[17] and 1,8-dideoxy-6-epicastanospermine from a 2-azido-altropyranoside derivative.[18] We report here a high stereoselective, total synthesis of (+)-1 starting with (−)-(1*S*,4*S*)-7-oxabicyclo[2.2.1]hept-5-en-2-one ((−)-**5**), a "naked sugar"[19]) obtained readily optically pure in two steps from furan and 1-cyanovinyl (1*R*')-camphanate (**4**).[20,21] The first syntheses of (+)-6-deoxycastanospermine ((+)-**2**) and (+)-6-deoxy-6-fluorocastanospermine ((+)-**3**) are also reported. We also report the crystal structure of (+)-**3** by X-ray diffraction.

Retrosynthetic Plan

We wished to develop a method that would allow us to prepare not only natural castanospermine (+)-**1**, but also its enantiomer (−)-**1** and derivatives in which some of the hydroxy groups could be exchanged by other substituents, with centers C(6), C(7), C(8), and C(8a) conserving, or not, the gluco relative configuration. We have adopted a general strategy involving intermediate **9** with an unsaturated six-membered ring annulated to a pyrrolidine system (see Scheme II), the stereoselectivity of the substitution at C(6) and C(7) should be controlled by steric factors resulting from the geometry of the 1-azabicyclo[4.3.0]nonane system or/and by the substituent at C(8). In their synthesis of 8-episwainsonine, Austin and co-workers[22] showed that intramolecular Horner–Emmons reaction of the phosphonate **7** derived from pyrrolidine **6** by condensation with $(MeO)_2PO\text{-}CH_2COOH$ gives a 47% yield of the corresponding lactam **8** after catalytic hydrogenation and acetylation (Scheme I).[23]

In analogy, the α,β-unsaturated lactam **9** should be derived from aldehyde **10** or an equivalent synthetic intermediate. The pyrrolidine ring in **10** would be generated through an intramolecular S_N2 displacement of the 6-amino-5,6-dideoxy-*arabino*-hexose derivative **11** in which the OH group at C(3) has been replaced by an adequate leaving group X. the furanose **12** form of **11** should be derived from the corresponding lactone **13** expected[19,24] to be formed with high regioselectivity in the Baeyer–Villiger oxidation of the 7-oxanorbornan-2-one **14** bearing at C(5) the leaving group X in the exo position and at C(6) a protected alcohol function in the *endo* position. This kind of compound can be obtained, in principle, in one step by

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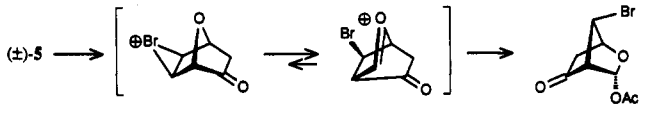
electrophilic addition of 7-oxanorborn-5-en-2-one, the electrophile attacking the exo face of the endocyclic double bond and the nucleophile being captured in the endo position of C(6) due to the electron-releasing effect of the homoconjugated carbonyl group.[25,26] Thus bromination of (−)-5 in an appropriate nucleophilic solvent ROH might lead to the desired derivative 14 in which X = Br.

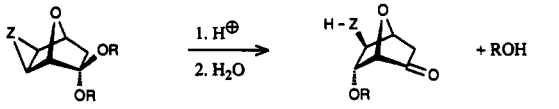
Results and Discussion

Addition of Br_2 to the racemic enone (±)-5[24a] in Ac_2O + AcOH (−50 °C, 5 min) gave the unstable bromide (±)-17 in moderate yield. The latter arises from a Wagner–Meerwein (pinacolic) rearrangement of the bromonium ion intermediate (±)-15 into the oxycarbenium ion intermediate (±)-16,[28] which is then trapped with AcOH. Interestingly, and as in the case of the reaction of 5,6-*exo*-epoxy-7-oxabicyclo[2.2.1]heptan-2-one in $Ac_2O/HSO_3F/CH_2Cl_2$ which gave mostly 5-oxo-2-oxabicyclo[2.2.1]heptane-2,7-diyl diacetates, the 1,2-shift of the acyl group in (±)-15 appears to be favored over that of the alkyl group.[29]



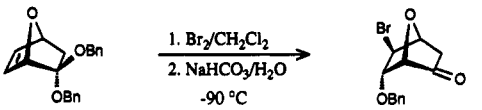
(±)-15 (±)-16 (±)-17

Addition of Br_2 to (±)-5 in MeOH (−50 °C to 20 °C, 15 h) gave bromohydrin (±)-18 (43%, isolated) together with products by decomposition. This result can be interpreted in terms of the mechanism shown in Scheme III involving the formation of a hemiacetal, due to MeOH addition to the ketone moiety of (±)-5, and bromination of the endocyclic double bond, leading to intermediate (±)-19. The latter ion undergoes then 1,3-migration of the *endo*-hydroxy group via (±)-20 to generate onium ion intermediate (±)-21. Acid-catalyzed rearrangements of 3,8-dioxatricyclo[3.2.1.$0^{2,4}$]octan-6-one[29] and 3-aza-8-oxatricyclo-[3.2.1.$0^{2,4}$]octan-6-one acetals[30] (22) given the corresponding 5-*exo*,6-*endo*-disubstituted 7-oxanorbornan-2-ones 23 in high yield following similar mechanisms as that shown in Scheme III. Thus, the observation of (±)-5 + Br_2 + 2



22 Z=O; NCOR'; R=Me; CH_2Ph=Bn 23

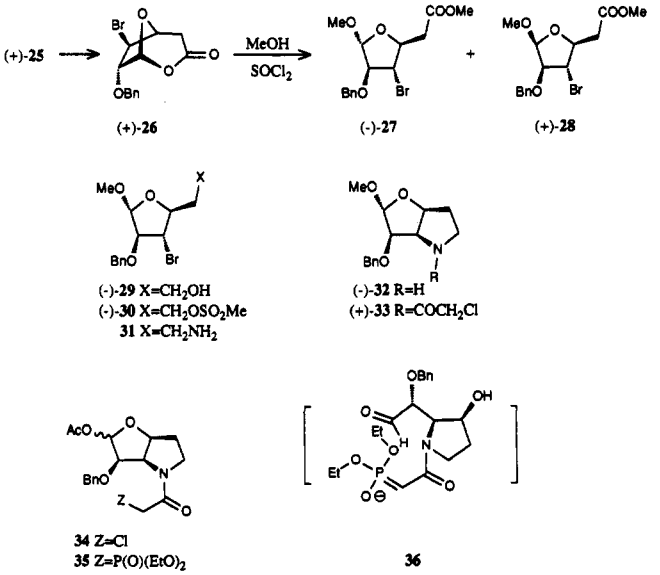
MeOH → (±)-18 + HBr suggested that bromination of an acetal of (±)-5 might undergo a similar rearrangement and generate the desired protected bromohydrin in a good yield. This was indeed the case with the dibenzyl acetal (−)-24 (obtained by treatment of optically pure enone (−)-5[19] with $BnOSiMe_3$ and $CF_3SO_3SiMe_3$ in CH_2Cl_2)[29] which reacted with Br_2 in CH_2Cl_2 at −90 °C to give (+)-25 isolated in 98% yield. The reaction with Br_2, and the quenching with aqueous $NaHCO_3$ had to be carried out at −90 °C to avoid concurrent decomposition and formation of benzyl bromide.



(−)-24 (+)-25

Baeyer–Villiger oxidation of (+)-25 with mCPBA (metachloroperbenzoic acid) in CH_2Cl_2 containing $NaHCO_3$ (20 °C) gave lactone (+)-26 (95%). Treatment of (+)-26 with MeOH and $SOCl_2$ led to a 4:1 mixture of the methyl furanosides (−)-27 + (+)-28 (100%) from which (+)-28 could be separated by crystallization and reequilibrated with (−)-27 by treatment with $MeOH/SOCl_2$. Reduction of uronate (−)-27 with diisobutylaluminium hydride (DIBAL) in THF/toluene gave alcohol (−)-29 quantitatively, the bromide being not reduced under these conditions. The corresponding methanesulfonate (−)-30 (obtained by treatment of (−)-29 with CH_3SO_2Cl/pyridine/CH_2Cl_2) with 24% NH_3 in EtOH/H_2O 1:1 (45 °C, 1 day) afforded the primary amine 31 which generated the pyrrolidine (−)-32 under the conditions of its formation (99% yield, 95% pure by ^1H NMR). The methanesulfonate derived from the minor furanoside (+)-28 was decomposed under these conditions!

Reaction of (−)-32 with $ClCH_2COCl$ in pyridine/CH_2Cl_2 furnished the chloroacetamide (+)-33 (79% based on (−)-27). The methyl furanoside moiety in (+)-33 was transformed into the corresponding acetyl furanoside 34 (88%) by treatment with Ac_2O/H_2SO_4 at 0 °C (2 h).[23g] Arbuzov reaction on 34 ($P(OEt)_3$, 130 °C) gave the corresponding phsphonoacetamide 35, which was not isolated and treated immediately with K_2CO_3 in EtOH (20 °C, 3 days) giving product 37 which arose from the intramolecular Horner–Emmons condensation of the intermediate aldehyde 36. Acetylation (Ac_2O/DMAP) of 37 afforded (+)-38 (49% based on (−)-27).



(+)-26 (−)-27 (+)-28

(−)-29 X=CH_2OH
(−)-30 X=CH_2OSO_2Me
31 X=CH_2NH_2

(−)-32 R=H
(+)-33 R=$COCH_2Cl$

34 Z=Cl
35 Z=P(O)(EtO)$_2$

36

Addition of Br_2(AcOH, 20 °C) to (±)-38 gave dibromide (±)-39 as major product of reaction. The same reaction in the presence of AgOAc (AcOH/Ac_2O, 10 °C)[31] afforded a 1.5:1 mixture of monobromides 40 and (+)-41. As expected for bicyclo[4.3.0]nonene derivatives, the endo face

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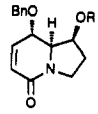
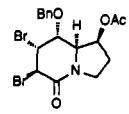
of the C(6)–C(7) double bond in (+)-38 is more sterically

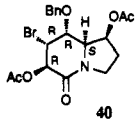


37 R=H
(+)-38 R=Ac

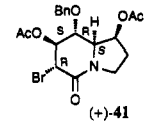


(±)-39

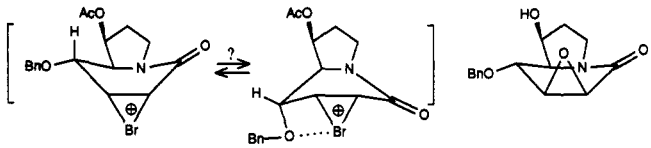
hindered than its exo face, thus favoring the electrophilic attack that gives the bromonium ion intermediate 42. It is possible also[32] that the allylic benzyloxy group at C(8) stabilizes the onium ion as shown with the hypothetical conformer 42'. In agreement with the Fürst–Plattner rule[33] which favors the formation of trans-diaxial products, nucleophilic quenching of 42 was expected to be favored at C(6) rather than at C(7). This was indeed the case for Br^-, but the selectivity was not significant in the case of AcO^-.



40

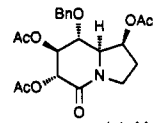


(+)-41

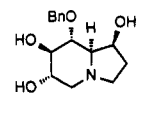


42 42' 43

The mixture of protected bromohydrins 40 + (+)-41 was methanolyzed ($MeOH/SOCl_2$, 20 °C) and then treated with a base (2-(*tert*-butylimino)-2-((diethylamino)imino)-1,3-dimethylperhydro-1,3,2-diazaphosphorine on polystyrene (BEMP), CH_3CN, 20°C) to give epoxide 43 (75%), which could not be purified by column chromatography on silica gel. The latter was hydrolyzed in the presence of the same base ($BEMP/CH_3CN/H_2O$, 100 °C) and then acetylated (Ac_2O, DMAP) to yield lactan (+)-44 (42%, based on (+)-38). The nucleophile attack of C(6) was expected to be favored with respect to the C(7) attack on the basis of an electronic factor (α-position to the amide moiety) and of steric hindrance due to the benzyloxy group at C(8) which retards the nucleophilic attack at C(7). In this case, the Fürst–Plattner rule[33] would have predicted a preferred attack of center C(7) rather than C(6).



(+)-44



45

Lactam 44 has the same configuration at C(1), C(6), C(7), C(8), and C(8a) as in (+)-castanospermine ((+)-1). This was established by its 360-MHz ^1H NMR spectrum which showed typical vicinal coupling constants ^3J(H–C(6),H–C(7)) = ^3J(H–C(7),H–C(8)) = ^3J(H–C(8),H–C(8a)) = 9.5 Hz for axial protons of a chair cyclohexane conformation.[34] Reduction of the lactam with $BH_3{\cdot}Me_2S$ (THF, 20 °C), followed by methanolysis (MeOH, K_2CO_3, 60 °C), afforded the partially protected castanospermine derivative 45 (95%). Debenzylation (H_2/Pd–C) of 45 furnished (+)-1 in 97% yield. The physical and spectal data of (+)-1 so

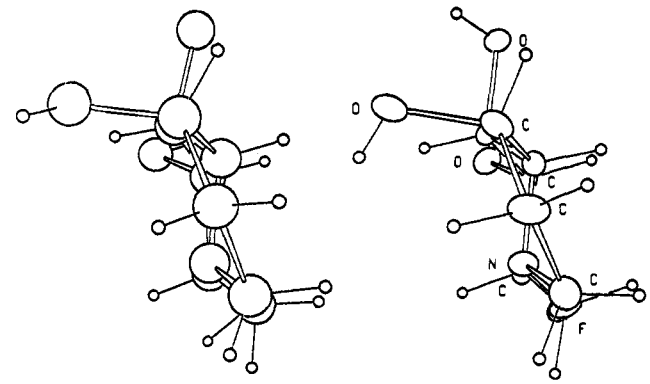
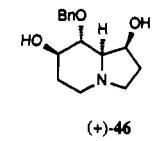


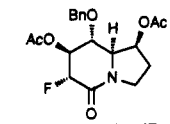
Figure 1. Projections of crystal structures of (+)-1 and (+)-3.

obtained were identical with those of an authentic sample of natural (+)-castanospermine.

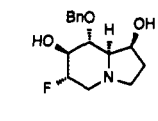
Treatment of epoxy lactam 43 with $BH_3{\cdot}Me_2S$ in anhydrous THF led to a mixture of compounds from which the partially protected 6-deoxycastanospermine (+)-46 could be isolated (25%). No other amine derivative was detected in the reaction mixture. Hydrogenolysis of the benzylic ether gave (+)-2 (97%). Treatment of 43 with $HF{\cdot}Et_3N$ led to a stereoselective ring opening of the epoxide moiety with attack of C(6) by the fluoride anion. After acetylation (+)-47 (52%) was isolated. Reduction of (+)-47 with $BH_3{\cdot}Me_2S$ in anhydrous THF, followed by hydrolysis of the acetates ($HCl/MeOH/H_2O$, 70 °C) afforded the partially protected 6-deoxy-6-fluorocastanospermine (+)-48 (83%). Hydrogenolysis of the benzylic ether gave (+)-3 (93%).



(+)-46



(+)-47



(+)-48

The structures of (+)-2, (+)-3, and derivatives (+)-46 to (+)-48 were secured by their spectral data and by their comparison with those reported for (+)-1.[3,5,14,15] For all these compounds, the ^1H NMR spectra suggested conformations ($^NC_7$ chair for the six-membered ring) similar to that of (+)-1.[14,15] The pK_a values of the conjugate acids of (+)-1, (+)-2, and (+)-3 have been determined (titrimetric method) to be 6.01 ± 0.01, 7.31 ± 0.02, and 5.09 ± 0.01, respectively, at 25 °C (H_2O).

Because the biological properties of (+)-3 will have to be compared with those of (+)-1, we have determined the crystal structure of (+)-3 by X-ray diffraction and compared it with that published for (+)-1.[3] As already suggested by the solution ^1H NMR spectra, the polyhydroxylated indolizidines (+)-1 and (+)-3 have similar topologies in the crystalline state as illustrated by their projections (Figure 1) in a plane perpendicular to the pseudo-C_2 axis of their five-membered rings passing through the carbon atom C(2) and the middle of the C(8a)–N(4) bond (see also the supplementary material).

Conclusion

(+)-Castanospermine has been derived from (−)-7-oxabicyclo[2.2.1]hept-5-en-2-one ((−)-5 in 15.2% overall yield). The method is highly stereoselective and requires the isolation of 10 intermediate products (see the experimental Section). The α,β-unsaturated lactam 37, as well as the corresponding epoxide 43, are potential intermediates for the preparation of analogues of castanospermine as illustrated with the syntheses of 6-deoxy ((+)-2) and 6-deoxy-6-fluoro derivatives ((+)-3). Since (+)-7-oxabicy-

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clo[2.2.1]hept-5-en-2-one ((+)-5) is as readily available as (−)-5,[19] (−)-castanospermine and its derivatives can be prepared with the same ease.

Experimental Section

General remarks, see ref 21.

(±)-(1*RS*,3*SR*,4*SR*,7*SR*)-7-Bromo-5-oxo-2-oxabicyclo-[2.2.1]hept-3-yl Acetate ((±)-17). Bromine (0.18 mL, 3.45 mmol) was added dropwise in 5 min to a stirred solution of (±)-7-oxabicyclo[2.2.1]hept-5-en-2-one ((±)-5, 0.38 g, 3.45 mmol)[24a] in Ac_2O (4 mL) cooled to −60 °C. After the mixture was stirred at −60 °C for 5 more min, $NaHCO_3$ (0.5 g) was added, and the mixture allowed to reach 0 °C. It was then poured into H_2O (100 mL) and extracted with CH_2Cl_2 (40 mL, three times). The solvent was evaporated and the Ac_2O was eliminated by azeotropic distillation with toluene, in vacuo. The residue was recyrstallized from Et_2O: 0.2 g (34%) of colorless crystals; mp 86–90 °C dec; ^1H NMR (250 MHz, $CDCl_3$) δ 6.64 (dd, J = 3.5, 1.0, HC(2-exo)), 4.80 (m, ^3J = 2.5, 1.0, 0.5, ^4J(HC(2),HC(4)) = ^4J(HC(1),HC(4)) = 1.0, HC(4)), 4.34 (dd, J = 1.5, 0.5, HC(7)), 3.20 (m, ^3J = 3.5, 1.5, ^4J(HC(1),-HC(5)) = ^4J(HC(1),HC(4)) = 1.0, HC(1)), 2.76 (d, ^2J = 18.5, ^3J = 1.0, HC(5-endo)), 2.48 (ddd, ^2J = 18.5, ^3J = 2.5, ^4J = 1.0. HC(5-exo)), 2.09 (s, CH_3CO).

(±)-(1*RS*,2*RS*,3*SR*,4*RS*)-3-*exo*-Bromo-6,6-dimethoxy-7-oxabicyclo[2.2.1]heptan-2-*endo*-ol ((±)-18). A 1 M solution of Br_2 in anhydrous MeOH (1.4 mL) was added dropwise to a vigourously stirred solution of (±)-7-oxabicyclo[2.2.1]hept-5-en-2-one ((±)-5, 150 mg, 1.4 mmol) in MeOH (5 mL) cooled to −70 °C. The temperature was allowed to reach 20 °C overnight. The red solution was poured into a saturated aqueous solution of $NaHCO_3$, and the mixture was extracted with CH_2Cl_2 (40 mL, five times). After filtration on cotton and solvent evaporation, the residue was recrystallized twice from CH_2Cl_2/petroleum ether, yielding 150 mg (43%) of colorless crystals: mp 129–131 °C; IR (KBr) ν 3380, 2995, 2975, 2920, 1450, 1400; ^1H NMR (360 MHz, $CDCl_3$) δ 4.61 (br d, J = 6.0, HC(4)), 4.57 (m, HC(2)), 4.41 (d, J = 10.5, OH), 4.36 (br d, J = 5.0, HC(1)), 3.76 (d, J = 3.0, HC(3)), 3.38 and 3.33 (2 s, 2 MeO), 2.15 (dd J = 13.0, 6.0, HC(5-exo)), 1.97 (d, J = 13.0, HC(5-endo)); MS (CI, NH_3) 223 (54), 222 (19), 221 (56), 220 (12), 173 (100).

(1*S*,4*S*,5*S*,6*S*)-6-*endo*-(Benzyloxy)-5-*exo*-bromo-7-oxabicyclo[2.2.1]heptan-2-one ((+)-25). A solution of Br_2 (0.8 mL, 15.6 mmol) in anhydrous CH_2Cl_2 (25 mL) was added dropwise (in 60 min) to a vigourously stirred solution of dibenzyl acetal of (−)-(1S,4S)-7-oxabicyclo[2.2.1]hept-5-en-2-one ((−)-24,[19,29] 4.5 g, 14.6 mmol) in anhydrous CH_2Cl_2 (50 mL) cooled to −90 °C, under Ar atmosphere. A saturated aqueous solution of $NaHCO_3$ (20 mL) was added dropwise with stirring at −90 °C, and the mixture was allowed to warm up to 0 °C. The mixture was then poured into saturated aqueous solution of $NaHCO_3$ (150 mL) and extracted with CH_2Cl_2 (30 mL, five times). After drying ($MgSO_4$) and solvent evaporation, the residue was crystallized from Et_2O/petroleum ether, yielding 4.25 g (98%) of colorless crystals: mp 92–92.5 °C; ^1H NMR (360 MHz, $CDCl_3$) δ 7.43–7.33 (m, C_6H_5), 4.89 (d, J = 6.5, HC(4)), 4.62 & 4.60 (2 d, J = 11.5, Bn), 4.48 (s, HC(6) + HC(1)), 4.01 (s, HC(5)), 2.61 (dd, J = 18.0, 6.5, HC(3-exo)), 2.29 (d, J = 18.0, HC(3-endo)); $[\alpha]^{20}_{589}$ = +69°, $[\alpha]^{20}_{578}$ = +72°, $[\alpha]^{20}_{546}$ = +81°, $[\alpha]^{20}_{436}$ = +129°, $[\alpha]^{20}_{365}$ = +160° (c = 10 g/dm^3, CH_2Cl_2).

(±)-6-*endo*-(Benzyloxy)-5-*exo*-bromo-7-oxabicyclo[2.2.1]-heptan-2-one ((±)-25). The same procedure was followed as for (+)-25, starting with (±)-5,5-bis(benzyloxy)-7-oxabicyclo[2.2.1]-hept-2-ene ((±)-24),[29] mp 74–74.5 °C.

2-*O*-Benzyl-3-bromo-3,5-dideoxy-β-L-*arabino*-hexofuranosidurono-6,1-lactone ((+)-26, (1*S*,5*S*,6*S*,7*S*)-7-*endo*-(Benzyloxy)-6-*exo*-bromo-2,8-dioxabicyclo[3.2.1]octan-3-one). $NaHCO_3$ (5 g) and then m-chloroperbenzoic acid (9.0 g, Aldrich 80–90%) were added to a stirred solution of (+)-25 (11.7 g, 39.4 mmol) in CH_2Cl_2 (150 mL) cooled to 5 °C. After the mixture was stirred at 25 °C for 15 h, KF (4.7 g) was added, and the resultant mixture was stirred at 25 °C for 3 h. The precipitate was filtered off on Celite, and the solvent was evaporated. The residue was recrystallized from Et_2O (100 mL) and petroleum ether (150 mL), yielding 11.8 g (96%) of colorless crystals: mp 115–116 °C; ^1H NMR (360 MHz, $CDCl_3$) δ 7.37 (br s, C_6H_5), 5.90 (d, J = 4.0, HC(1)), 4.74 (d, J = 7.0, HC(5)), 4.70 & 4.60 (2 d, J = 11.5, Bn), 4.56 (d, J = 4.0, HC(7)), 4.08 (s, HC(6)), 3.13 (dd, J = 18.5, 7.0, HC(4-exo)), 2.69 (d, J = 18.5, HC(4-endo)); $[\alpha]^{20}_{589}$ = +135°, $[\alpha]^{20}_{578}$ = +140°, $[\alpha]^{20}_{546}$ = +160°, $[\alpha]^{20}_{436}$ = +274°, $[\alpha]^{20}_{365}$ = +439° (c = 10 g/dm^3, CH_2Cl_2).

(±)-2-*O*-Benzyl-3-bromo-3,5-dideoxy-β-D,L-*arabino*-hexofuranosidurono-6,1-lactone ((±)-26). The same procedure was followed as for (+)-26, starting with (±)-25: mp 107.5–108 °C.

Methyl (Methyl 2-*O*-benzyl-3-bromo-3,5-dideoxy-α-L-arabinofuranosid)uronate ((−)-27) and Methyl (Methyl 2-*O*-benzyl-3-bromo-3,5-dideoxy-β-L-*arabino*-hexofuranosid)uronate ((+)-28). $SOCl_2$ (2 mL) was added dropwise into a stirred suspension of (+)-26 (4.2 g, 13.4 mmol) in MeOH (40 mL) at 25 °C. After having stood at 25 °C for 4 days, the mixture was cooled to 0 °C and $NaHCO_3$ (7 g) was added portionwise in 10 min under vigourous stirring. The solvent was evaporated, the residue was dissolved in a saturated aqueous solution of $NaHCO_3$, and the mixture was extracted with CH_2Cl_2 (40 mL, five times). The extracts were combined and dried ($MgSO_4$), and the solvent was evaporated. The residue was crystallized form Et_2O (30 mL) and petroleum ether (25 mL) at −20 °C (3 days), yielding 0.78 g (16.2%) of a 1:5 mixture of (−)-27 and (+)-28. The mother liquor was evaporated and dried under vacuum, yielding 4.0 g (82.1%) of pure (−)-27. The crystalline mixture of (−)-27 + (+)-28 was dissolved in MeOH (7 mL) and treated as above with $SOCl_2$. Separation by column chromatography on silica gel (Lobar B, ether, R_f((−)-27) = 0.6, R_f((+)-28) = 0.4) gave 640 mg of (−)-27 and 120 mg of (+)-28. Global yield of (−)-27:4.64 g (97.8%).

Characteristics of (−)-27: colorless crystals; mp 32–35 °C; ^1H NMR (360 MHz, $CDCl_3$) δ 7.42–7.31 (m, C_6H_5), 4.90 (d, J = 1.5, HC(1)), 4.71 and 4.63 (2 d, J = 12.0, Bn), 4.53 (ddd, J = 9.0, 8.5, 4.0, HC(4)), 4.21 (dd, J = 5.0, 1.5, HC(2)), 3.82 (dd, J = 9.0, 5.0, HC(3)), 3.74 (s, $COOCH_3$), 3.38 (s, MeO), 2.83 (dd, J = 16.0, 4.0), and 2.63 (dd, J = 16.0, 8.5, H_2C(5)); $[\alpha]^{20}_{589}$ = −45°, $[\alpha]^{20}_{578}$ = −46.5°, $[\alpha]^{20}_{546}$ = −52.5°, $[\alpha]^{20}_{436}$ = −82°, $[\alpha]^{20}_{365}$ = −114° (c = 10 g/dm^3, CH_2Cl_2).

Characteristics of (+)-28: colorless crystals; mp 70–70.5 °C; ^1H NMR (360 MHz, $CDCl_3$) δ 7.43–7.29 (m, C_6H_5), 4.78 and 4.75 (2 d, J = 12.0, Bn), 4.61 (d, J = 4.0, HC(1)), 4.56 (ddd, J = 9.5, 7.5, 4.0, HC(4)), 4.14 (dd, J = 9.5, 7.5, HC(3)), 4.08 (dd, J = 9.5, 4.0, HC(2)), 3.74 (s, $COOCH_3$), 3.38 (s, MeO), 2.81 (dd, J = 15.5, 4.0), and 2.58 (dd, J = 15.5, 9.5, H_2C(5)); $[\alpha]^{20}_{589}$ = +89°, $[\alpha]^{20}_{578}$ = +93°, $[\alpha]^{20}_{546}$ = +105°, $[\alpha]^{20}_{436}$ = +174°, $[\alpha]^{20}_{365}$ = +265° (c = 10 g/dm^3, CH_2Cl_2).

(±)-Methyl (Methyl 2-*O*-benzyl-3-bromo-3,5-dideoxy-α-D,L-*arabino*-hexofuranosid)uronate ((±)-27) and (±)-Methyl (Methyl 2-*O*-benzyl-3-bromo-3,5-dideoxy-β-D,L-*arabino*-hexofuranosid)uronate ((±)-28). The same procedure was followed as for (−)-27 + (+)-28, starting with (±)-26. Characteristics of (±)-27: colorless oil. Characteristics of (±)-28: colorless crystals; mp 64–65 °C.

Methyl 2-*O*-Benzyl-3-bromo-3,5-dideoxy-β-L-*arabino*-hexofuranoside ((−)-29). A 1.2 M solution of diisobutylaluminium hydride in toluene (60 mL, 72 mmol) was added in 10 min to a stirred solution of (−)-27 (10.75 g, 29.9 mmol) in anhydrous THF (100 mL) at −50 °C under Ar atmosphere. The temperature was allowed to reach −20 °C in 30 min, and the mixture was stirred for 5 h. Aqueous HCl (3 N, 100 mL) was added under vigourous stirring, and after 5 min at 25 °C, a saturated aqueous solution of NH_4Cl (100 mL) was added, and the mixture was extracted with AcOEt (100 mL, twice). The extracts were combined and dried ($MgSO_4$), and the solvent was evaporated, yielding 9.93 g (100%) of a colorless oil. An analytical sample of (−)-29 was,obtained by purification of 260 mg of this oil by column chromatography on silica gel (Lobar B, ether), yielding 240 mg (96%) of a colorless oil: ^1H NMR (360 MHz, $CDCl_3$) δ 7.44–7.31 (m, C_6H_5), 4.92 (d, J = 1.5, HC(1)), 4.72 and 4.63 (2 d, J = 12.0, Bn), 4.31 (ddd, J = 9.5, 9.0, 3.5, HC(4)), 4.21 (dd, J = 5.0, 1.5 HC(2)), 3.85 (br t, J = 6.0, H_2C(6)), 3.78 (dd, J = 9.5, 5.0, HC(3)), 3.38 (s, MeO), 2.21–2.06 and 1.93–1.83 (2 m, H_2C(5)); $[\alpha]^{20}_{589}$ = −47.5°, $[\alpha]^{20}_{578}$°, $[\alpha]^{20}_{546}$ = −55°, $[\alpha]^{20}_{436}$ = −87°, $[\alpha]^{20}_{365}$ = −121.5° (c = 10 g/dm^3, CH_2Cl_2).

Methyl 2-*O*-Benzyl-3-bromo-3,5-dideoxy-6-*O*-(methylsulfonyl)-β-L-*arabino*-hexofuranoside ((−)-30). CH_3SO_2Cl (2.8 mL, 36 mmol) was added dropwise to a stirred solution of crude

(−)-**29** (9.93 g, 30 mmol) in anhydrous Et_3N (5.0 mL, 36 mmol) and anhydrous CH_2Cl_2 (60 mL) cooled to 0 °C. After stirring at 0 °C for 2.5 h, the mixture was poured into a mixture of ice (50 g) and a saturated aqueous solution of $NaHCO_3$ (100 mL). The mixture was extracted with CH_2Cl_2 (50 mL, four times). The extracts were combined and dried ($MgSO_4$), and the solvent was evaporated to dryness in vacuo, yielding 12.63 g (100%) of a yellowish oil. An analytical sample of (−)-**30** was obtained by purification of 240 mg by column chromatography on silica gel (Lobar B, ether), yielding 230 mg (96%) of a colorless oil: ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.42–7.31 (m, C_6H_5), 4.89 (d, J = 1.5, HC(1), 4.69 & 4.61 (2 d, J = 12.0, Bn), 4.40 (m, $H_2C(6)$), 4.24 (td, J = 9.0, 3.5, HC(4)), 4.21 (dd, J = 5.0, 1.5, HC(2)), 3.71 (dd, J = 9.0, 5.0, HC(3)), 3.25 (s, MeO), 3.05 (s, CH_3SO_2), 2.38–2.28 and 2.04–1.93 (2 m, $H_2C(5)$); $[\alpha]^{20}_{589}$ = −43°, $[\alpha]^{20}_{578}$ = −44.5°, $[\alpha]^{20}_{546}$ = −50°, $[\alpha]^{20}_{436}$ = −79.5°, $[\alpha]^{20}_{365}$ = −112.5° (c = 11 g/dm^3, CH_2Cl_2).

Methyl 2-*O*-Benzyl-3,5,6-trideoxy-3,6-imino-β-L-*lyxo*-hexofuranoside ((−)-32). A mixture of crude (−)-**30** (5.71 g, 14.1 mmol), EtOH (120 mL), and 24% aqueous NH_3 (120 mL) was heated to 45 °C for 24 h. After concentration to ca. 100 mL in vacuo, KOH (3 g) and ice (100 g) were added. The mixture was extracted with CH_2Cl_2 (40 mL, five times). The extracts were combined, and the solvent was evaporated to dryness, yielding 3.48 g (99.4%) of a colorless oil. An analytical sample of (−)-**32** was obtained by purification of 100 mg by column chromatography on neutral alumina (Et_2O/MeOH, 10:1), yielding 65 mg (65%) of a colorless oil: ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.38–7.30 (m, C_6H_5), 4.92 (d, J = 1.5, HC(1)), 4.68 (td, J = 5.0, 1.5, HC(4)), 4.64 (m, Bn), 3.92 (dd, J = 6.5, 1.5, HC(2)), 3.86 (dd, J = 6.5, 5.0, HC(3)), 3.34 (s, MeO), 3.10–2.92 (m, $H_2C(6)$), 2.12 (br s, NH), 1.99 (dddd, J = 13.5, 6.0, 2.5, 1.5), and 1.84 (dddd, J = 13.5, 10.0, 7.5, 5.0, $H_2C(5)$); $[\alpha]^{20}_{589}$ = −83°, $[\alpha]^{2-}_{578}$ = −86°, $[\alpha]^{20}_{546}$ = −97°, $[\alpha]^{20}_{436}$ = −154°, $[\alpha]^{20}_{365}$ = −218° (c = 10 g/dm^3, CH_2Cl_2).

Methyl 2-*O*-Benzyl-*N*-(chloroacetyl)-3,5,6-trideoxy-3,6-imino-β-L-*lyxo*-hexofuranoside ((+)-33). Anhydrous pyridine (2.26 mL, 28 mmol) and then $ClCH_2COCl$ (2.22 mL, 28 mmol) were added dropwise to a stirred solution of (−)-**32** (3.48 g, 14 mmol) in anhydrous CH_2Cl_2 (50 mL) cooled to −5 °C. The temperature was allowed to reach 8 °C in 2 h with stirring. The mixture was poured into a mixture of ice (50 g) and 1 N HCl (120 mL) and extracted with CH_2Cl_2 (30 mL, 6 times). Each extract was washed with saturated aqueous solution of $NaHCO_3$ (50 mL). The extracts were combined and the solvent was evaporated. The residue was purified by column chromatography on silica gel (150 g, AcOEt), yielding 2.59 g (79%) of a colorless oil: ^{1}H NMR (250 MHz, $CDCl_3$) (3:1 mixture of two rotamers) δ 7.42–7.24 (m, C_6H_5), 4.93:4.98 (s, HC(1)), 4.83:4.80 (dd, J = 6.5, 6.0, HC(3)), 4.54 (s, 2 H): 4.78 and 4.48 (2 d, J = 12.5, Bn), 4.12:3.94 (d, J = 6.0, HC(2)), 4.01 and 3.90:3.79 and 3.71 (2 d, J = 12.5, $ClCH_2CO$), 3.68 (ddd, J = 10.0, 8.0, 2.0, HC(6)), 3.48 (td, J = 10.0, 7.0, HC(6)), 3.30:3.35 (MeO), 2.20–1.86 (m, $H_2C(5)$); $[\alpha]^{20}_{589}$ = +67.5°, $[\alpha]^{20}_{578}$ = +70.5°, $[\alpha]^{20}_{546}$ = +81.5°, $[\alpha]^{20}_{436}$ = +151°, $[\alpha]^{20}_{365}$ = +265° (c = 10 g/dm^3, CH_2Cl_2).

Acetyl 2-*O*-Benzyl-3,5,6-trideoxy-3,6-imino-α-L-*lyxo*-hexofuranoside (34α) and Acetyl 2-*O*-Benzyl-3,5,6-trideoxy-3,6-imino-β-L-*lyxo*-hexofuranoside (34β). Concentrated H_2SO_4 (1.5 g) was added dropwise to a stirred solution of (+)-**33** (2.94 g, 9.02 mmol) in Ac_2O (30 mL) cooled to 0 °C. After the mixture was stirred at 5 °C for 2 h, $NaHCO_3$ (3 g) was added portionwise. After 5 min at 0 °C, the mixture was poured into ice (50 g) and a saturated aqueous solution of $NaHCO_3$ (100 mL) and extracted with CH_2Cl_2 (70 mL, four times). Each extract was washed with brine (50 mL). The extracts were combined, the solvent was evaporated, and the excess of Ac_2O was eliminated by azeotropic distillation with toluene (300 mL, then 100 mL, twice, rotatory evaporator). The yellowish residue was purified by column chromatography on silica gel (AcOEt), yielding 3.59 g (87.5%) of a yellowish oil that can be used in the next synthetic step. Analytical samples of **34α** and **34β** were obtained on separating 150 mg by column chromatography on silica gel (Lobar B, AcOEt), yielding 112 mg (74%) of **34α** and 11 mg (7%) of **34β**. Characteristics of **34α**: yellowish oil; ^{1}H NMR (250 MHz, $CDCl_3$) (major rotamer) δ 7.40–7.27 (m, C_6H_5), 6.23 (s, HC(1)), 4.90–4.80 (m, HC(3) + HC(4)), 4.64 and 4.54 (2 d, J = 11.0, Bn), 4.22 (d, J = 6.0, HC(2)), 4.02 and 3.90 (2 d, J = 12.5, $ClCH_2CO$), 3.68 (ddd, J = 10.5, 8.0, 2.5) and 3.49 (ddd, J = 10.5, 10.4, 7.0, $H_2C(6)$), 2.25–2.00 (m, $H_2C(5)$), 2.07 (s, Ac); (minor rotamer) δ 6.29 (s, HC(1)), 4.04 (d, J = 6.0, HC(2), 3.67 (s, $ClCH_2CO$), 2.12 (s, Ac); $[\alpha]^{20}_{589}$ = +65°, $[\alpha]^{20}_{578}$ = +68°, $[\alpha]^{20}_{546}$ = +78°, $[\alpha]^{20}_{436}$ = +144°, $[\alpha]^{20}_{365}$ = +250° (c = 10 g/dm^3, CH_2Cl_2). Characteristics of **34β**: yellowish oil; ^{1}H NMR (250 MHz, $CDCl_3$, 2 rotamers 1:1) δ 7.40–7.20 (m, C_6H_5), 6.32 and 6.22 (2 d, J = 3.5, HC(1)), 4.97–4.47 (m, 4 H, HC(3), HC(4), Bn), 4.36 and 3.98 (2 d, J = 12.5, $ClCH_2CO$), 4.14–3.35 (m, HC(2), $H_2C(6)$, $ClCH_2CO$), 2.22–1.88 (m, $H_2C(5)$), 2.10 and 2.08 (2 s, Ac).

(5*S*,6*S*,7*S*)-7-Acetoxy-5-(benzyloxy)-1-azabicyclo[4.3.0]-non-3-en-2-one ((+)-38). A mixture of **34α** + **34β** (1.57 g, 4.44 mmol) and triethyl phosphite (8 mL) was heated to 130 °C for 7 h. The excess of $(EtO)_3P$ was distilled off under vacuum, and the residue was dried in vacuum (1 Torr, 130 °C, 15 min). After addition of EtOH (50 mL) and K_2CO_3 (1.3 g), the mixture was stirred at 20 °C for 3 days. Water (100 mL) was added, and the mixture was extracted with CH_2Cl_2 (200 mL, and then 50 mL, six times). The extracts were combined and dried ($MgSO_4$), and the solvent was evaporated. Anhydrous pyridine (5 mL), Ac_2O (5 mL), and 4-(dimethylamino)pyridine (10 mg) were added, and the mixture was allowed to stand at 20 °C for 2 days. The excess of reagents was distilled off by azeotropic distillation with toluene (100 mL, then 50 mL, twice, rotatory evaporator), and the residue was purified by column chromatography on silica gel (100 g, AcOEt). The main fraction (R_f = 0.3) yielded 960 mg (72%) of a colorless oil: ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.40–7.28 (m, C_6H_5), 6.62 (dd, J = 10.0, 1.5, HC(4)), 5.92 (dd, J = 10.0, 2.0, HC(3)), 5.44 (ddd, J = 3.6, 3.5, 3.4, HC(7)), 4.68 and 4.50 (2 d, J = 12.0, Bn), 4.46 (ddd, J = 11.5, 2.0, 1.5, HC(5)), 3.86 (dd, J = 11.5, 3.6, HC(6)), 3.74 (ddd, J = 11.0, 9.5, 1.5) and 3.48 (ddd, J = 11.0, 10.9, 7.5, $H_2C(9)$), 2.20–1.96 (m, $H_2C(8)$), 1.88 (s, Ac); UV (CH_3CN) λ 210 (ε 16 000), 220 (7200), 230 (1660), 240 (1330), 250 (1700), λ_{max} 257 (1800), 270 (1300), 280 (840), 300 (180); $[\alpha]^{25}_{589}$ = +161°, $[\alpha]^{25}_{578}$ = +166°, $[\alpha]^{25}_{546}$ = +187°, $[\alpha]^{25}_{436}$ = +281°, $[\alpha]^{25}_{365}$ = +328° (c = 10 g/dm^3, CH_2Cl_2).

(5*RS*,6*RS*,7*RS*)-1-Acetoxy-5-(benzyloxy)-1-azabicyclo-[4.3.0]non-3-en-2-one ((±)-38). The same procedure was followed as for (+)-**38**, starting with the mixture of (±)-**27** and (±)-**28**: colorless crystals; mp 91.5–92.5 °C.

(1*RS*,6*RS*,7*SR*,8*SR*,8a*SR*)-1-Acetoxy-8-(benzyloxy)-6,7-dibromooctahydroindolizidin-5-one ((±)-39). A 1 M solution of Br_2 in AcOH (0.4 mL, 0.4 mmol) was added dropwise to a stirred solution of (±)-**38** (30 mg, 0.1 mmol) in AcOH (0.3 mL). After 3 h at 20 °C, H_2O (50 mL) was added and the mixture extracted with CH_2Cl_2 (30 mL, three times). The extracts were combined, the solvent was evaporated, and the excess of AcOH was distilled off by azeotropic distillation with toluene. The residue was crystallized from Et_2O, yielding 28 mg (61%) of colorless crystals: mp 162–168 °C dec; ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.40–7.30 (m, C_6H_5), 5.40 (q, J = 2.5, HC(1)), 4.80 (m, HC(6), HC(7)), 4.68 and 4.16 (2 d, J = 12.5, Bn), 4.20 (dd, J = 9.0, 2.0, HC(8)), 3.94 (dd, J = 9.0, 2.5, HC(8a)), 3.80–3.50 (m, $H_2C(3)$), 2.18–2.05 (m, $H_2C(2)$), 1.86 (s, Ac).

(1*S*,6*R*,7*R*,8*R*,8a*S*)-8-(Benzyloxy)-7-bromo-1,6-diacetoxyoctahydroindolizidin-5-one (40) and (1*S*,6*R*,7*S*,8*R*,8a*S*)-8-(Benzyloxy)-6-bromo-1,7-diacetoxyoctahydroindolizidin-5-one ((+)-41). A freshly prepared 1 M Br_2 solution in Ac_2O (3 mL) was added dropwise in 10 min to a stirred suspension of (+)-**38** (300 mg, 1 mmol) and AgOAc (600 mg, 3.6 mmol) in AcOH (3 mL) and Ac_2O (1.5 mL) at 9 °C and under Ar atmosphere. After stirring at 9 °C for 15 min, the mixture was poured into H_2O (100 mL) and ice (50 g) and extracted with AcOEt (100 mL, three times). The extracts were combined, washed with H_2O (80 mL, three times), and dried ($MgSO_4$), the solvent was evaporated, and the excess of Ac_2O was distilled off by azeotropic distillation with toluene (20 mL, then 4 mL, four times, rotatoray evaporator), yielding 700 mg of a yellowish oil, 1.5:1 mixture of **40** + (+)-**41** that can be used for the next step. Analytical samples of **40** and (+)-**41** were obtained in the following way. A 200-mg portion of **40** + (+)-**41** was purified by column chromatography on silica gel (20 g, AcOEt/petroleum ether, 1:1, R_f = 0.5), yielding 140 mg (70%) of a colorless oil that crystallized on adding Et_2O (4 mL, 20 °C), giving 40 mg (20%) of (+)-**41**. Evaporation of the mother liquor yielded a 5:1 mixture of **40**/(+)-**41**. Characteristics of **40**: ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.40–7.25 (m, C_6H_5), 5.72 (d, J = 2.8, HC(6)), 5.44 (ddd, J =

3.0, 2.5, 2.4, HC(1)), 4.66 and 4.45 (2 d, J = 12.0, Bn), 4.49 (dd, J = 2.8, 2.5, HC(7)), 3.94 (dd, J = 8.5, 3.0, HC(8a)), 3.70 (dd, J = 8.5, 2.5, HC(8)), 3.80–3.52 (m, $H_2C(3)$), 2.18–2.10 (m, $H_2C(2)$), 2.08 and 1.93 (2 s, 2 Ac). Characteristics of (+)-41: colorless crystals; mp 126–127 °C; ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.40–7.25 (m, C_6H_5), 5.58 (dd, J = 6.5, 6.4, HC(7)), 5.38 (ddd, J = 3.5, 3.4, 1.5, HC(1)), 4.68 and 4.52 (2 d, J = 11.5, Bn), 4.35 (d, J = 6.4, HC(6)), 3.91 (dd, J = 9.0, 3.5, HC(8a)), 3.76 (dd, J = 9.0, 6.5, HC(8)), 3.70–3.55 (m, $H_2C(3)$), 2.20–2.07 (m, $H_2C(2)$), 2.12 and 1.93 (2 s, 2 Ac); $[\alpha]^{25}_{589}$ = +123°, $[\alpha]^{25}_{578}$ = +128°, $[\alpha]^{25}_{546}$ = +146°, $[\alpha]^{25}_{436}$ = +252°, $[\alpha]^{25}_{365}$ = +401° (c = 10 g/dm^3, CH_2Cl_2).

(1*S*,6*S*,7*S*,8*R*,8a*S*)-8-(Benzyloxy)-6,7-epoxy-1-hydroxyoctahydroindolizidin-5-one (43). $SOCl_2$ (0.5 mL) was added dropwise to a stirred solution of the crude 1.5/1 mixture of **40** + (+)-**41** (derived from 300 mg of (+)-**38** (1 mmol)) in MeOH (10 mL) under Ar. After stirring at 20 °C for 17 h, the solvent was evaporated and the residue was dissolved in CH_3CN (10 mL). After addition of 2-(*tert*-butylimino)-2-(diethylamino)-1,3-dimethylperhydro-1,3,2-diazaphosphorine on polystyrene (900 mg, 2 mmol), the suspension was stirred at 20 °C for 35 min. The polymer supported base was filtered off, and the solvent was evaporated, giving an oily residue. An analytical sample of **43** was obtained by purifying 40 mg by column chromatography on silica gel (1 g, AcOEt, R_f = 0.3), yielding, 20 mg (50%) of a colorless oil: ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.45–7.36 (m, C_6H_5), 4.86 and 4.64 (2 d, J = 12.0, Bn), 4.35 (m, HC(1)), 3.88 (dd, J = 10.0, 0.7, HC(8)), 3.76 (dd, J = 10.0, 3.0, HC(8a)), 3.66 (ddd, J = 11.5, 8.5, 2.0, HC(3)), 3.56 (dd, J = 3.5, 0.7, HC(7)), 3.43 (J = 11.5, 7.5, H'C(3)), 3.38 (d, J = 3.5, HC(6)), 2.04–1.88 (m, $H_2C(2)$), 1.54 (br d, J = 4.0, HO).

(1*S*,6*R*,7*S*,8*R*,8a*S*)-8-(Benzyloxy)-1,6,7-triacetoxyoctahydroindolizidin-5-one ((+)-44). The crude epoxide **43** (before chromatography) resulting from the transformation of 300 mg of (+)-**38** (1 mmol) was dissolved in CH_3CN (2 mL) and H_2O (16 mL). After the addition of 2-(*tert*-butylimino)-2-(diethylamino)-1,3-dimethylperhydro-1,3,2-diazaphosphorine on polystyrene (450 mg), the suspension was stirred at 100 °C for 4.5 h. The polymer was filtered off, and the solvent was evaporated. The residue was dissolved in anhydrous pyridine (4 mL) and Ac_2O (4 mL), and 4-(dimethylamino)pyridine (10 mg) was added. After 2 days at 20 °C, the solvent was evaporated, and the excess of pyridine and Ac_2O was distilled off by azeotropic distillation with toluene (70 mL, then 15 mL, twice, rotatory evaporator). The residue was taken with 0.5 N HCl (20 mL) and extracted with CH_2Cl_2 (10 mL, four times). The extracts were combined, and the solvent was evaporated. The residue was purified by column chromatography on silica gel (3 g, AcOEt), yielding 250 mg (R_f = 0.5) of a colorless oil which crystallizes from Et_2O, giving 174 mg (42%, based on (+)-**38**) of colorless crystals: mp 97–98 °C; ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.40–7.20 (m, C_6H_5), 5.62 (t, J = 9.5, HC(7)), 5.38 (m, HC(1)), 5.10 (d, J = 9.5, HC(6)), 4.66 and 4.54 (2 d, J = 11.0, Bn), 3.88 (t, J = 9.5, HC(8)), 3.74 (dd, J = 9.5, 3.0, HC(8a)), 3.60 (m, $H_2C(3)$), 2.22–2.00 (m, $H_2C(2)$), 2.12, 2.06, and 1.98 (3 s, 3 Ac); $[\alpha]^{20}_{589}$ = +136°, $[\alpha]^{20}_{578}$ = +142°, $[\alpha]^{20}_{546}$ = +162°, $[\alpha]^{20}_{436}$ = +280°, $[\alpha]^{20}_{365}$ = +451° (c = 10 g/dm^3, CH_2Cl_2).

(1*RS*,6*SR*,7*RS*,8*SR*,8a*RS*)-8-(Benzyloxy)-1,6,7-triacetoxyoctahydroindolizidin-5-one ((±)-44). The same procedure was followed as for (+)-**44**, starting with (±)-**38**: colorless crystals; mp 198–199 °C.

(1*S*,6*S*,7*R*,8*R*,8a*R*)-8-(Benzyloxy)-1,6,7-trihydroxyoctahydroindolizidine (45). A 10 M solution of BH_3·Me_2S in THF (0.6 mL, Aldrich) was added dropwise to a stirred suspension of (+)-**44** (150 mg, 0.36 mmol) in anhydrous THF (3 mL). After stirring at 20 °C for 15 h, H_2O (4 mL) was added dropwise, and then MeOH (8 mL) and K_2CO_3 (200 mg) were added. After heating to 60 °C for 2 h, the solvent was evaporated and the residue was taken up with AcOEt (10 mL). The precipitate was filtered off and the solvent was evaporated. The residue was purified by column chromatography on silica gel (3 g, CH_2Cl_2/MeOH, 5:1, R_f = 0.25), yielding 95 mg (95%) of a colorless oil: ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.43–7.28 (m, C_6H_5), 4.85 (2 d, J = 11.5, Bn), 4.28 (ddd, J = 4.5, 3.5, 2.0, HC(1)), 3.72 (ddd, J = 10.5, 9.0, 5.0, HC(6)), 3.59 (t, J = 9.0, HC(8)), 3.45 (t, J = 9.0, HC(7)), 3.19 (dd, J = 10.5, 5, HC(5)), 3.13 (td, J = 8.0, 2.0, HC(3)), 2.29–2.10 (m, HC(2), HC(3)), 1.97 (t, J = 10.5, H'C(5)), 1.95 (dd, J = 9.0, 3.5, HC(8a)), 1.86–1.75 (m, H'C(2)).

(+)-Castanospermine ((+)-1). A mixture of **45** (84 mg), THF (1 mL), H_2O (0.2 mL), and 10% Pd/C (100 mg) was degassed and pressurized (1 atm) with H_2. After stirring at 20 °C for 24 h, the precipitate was filtered off on Celite and rinsed with MeOH. The filtrate was concentrated in vacuo, and the residue was dissolved in H_2O (6 mL). The aqueous solution was washed with CH_2Cl_2 (3 mL, five times). Each organic layer was extracted with water (4 mL). The aqueous phases were combined and basic Amberlite IRA 68 (500 mg, previously washed with H_2O) was added, and the suspension was stirred for 20 min. After filtration, the solvent was evaporated and the residue was dried in vacuo, yielding 55 mg (97%) of a colorless oil that crystallized slowly. Recrystallization from EtOH (4 mL) yielded 41 mg of pure (+)-1: colorless crystals; mp 208–209 °C dec (lit. mp 212–215 °C,[3] 207–210 °C[15]); ^{1}H NMR (360 NMR (360 MHz, D_2O) δ 4.38 (ddd, J = 7.0, 4.5, 1.5, HC(1)), 3.61 (ddd, J = 10.5, 9.0, 5.0, HC(6)), 3.56 (dd, J = 10.0, 9.0, HC(8)), 3.29 (t, J = 9.0, HC(7)), 3.15 (dd, J = 11.0, 5.0, HC(5)), 3.06 (ddd, J = 9.5, 9.0, 2.0, HC(3)), 2.29 (dddd, ^2J = 14.0, ^3J = 7.0, 9.0, 2.0, HC(2)), 2.20 (td, ^2J = ^3J = 9.0, H'C(3)), 2.04 (dd, ^2J = 11.0, ^3J = 10.5, H'C(5)), 2.01 (dd, J = 10.0, 4.5, HC(8a)), 1.68 (dddd, ^2J = 14.0, ^3J = 9.5, 9.0, 1.5, H'C(2)). The same characteristics were observed with a sample of natural (+)-1 supplied by Sigma Chemical Company, St. Louis, MO 63178 (C3784): ^{13}C NMR (90.55 MHz D_2O) δ 79.4 (d, ^{J}(C,H) = 145, C(7)), 71.8 (d, 140, C(8a)), 70.5 (d, 145, C(8)), 70.0 (d, 150, C(1)), 69.3 (d, 145, C(6)), 55.7 (t, 140, C(5)), 51.9 (t, 140, C(3)), 33.1 (t, 135, C(2)); $[\alpha]^{20}_{589}$ = +81°, $[\alpha]^{20}_{578}$ = +83°, $[\alpha]^{20}_{546}$ = +93.5°, $[\alpha]^{20}_{436}$ = +153°, $[\alpha]^{20}_{365}$ = +235° (c = 2.2 g/dm^3, H_2O) [lit. $[\alpha]^{25}_{589}$ = +79.7° (c = 9.3 g/dm^3),[3] +71° (c = 2.7 g/dm^3),[14] $[\alpha]^{19}_{D}$ = +7.9° (c = 2 g/dm^3)[15]]; MS (70 eV) 189 (M^+, 19), 172 (10), 171 (10), 149 (11), 145 (67), 128 (14), 100 (15), 99 (13), 98 (15), 86 (100), 85 (16), 84 (11), 71 (16), 70 (22), 69 (11), 68 (20), 60 (32), 58 (27), 57 (65), 56 (17), 55 (21), 45 (33). Anal. Calcd for $C_8H_{15}NO_4$ (189.21): C, 50.78; H, 7.99; N, 7.40. Found: C, 50.85; H, 7.96; N, 7.44.

(±)-Castanospermine ((±)-1). The same procedure was followed as for **45** and (+)-1, starting with (±)-**44**: colorless crystals; mp 189–190 °C.

(1*S*,7*R*,8*R*,8a*R*)-8-(Benzyloxy)-1,7-dihydroxyoctahydroindolizidine ((+)-46). BH_3·Me_2S (4 mL) was added dropwise to a stirred solution of **43** (740 mg, 90% pure, 2.43 mmol). After stirring at 20 °C for 4 days, the mixture was cooled to 0 °C, and H_2O (15 mL) and then 3 N HCl (15 mL) were added dropwise with stirring. The mixture was heated to 60 °C for 4 h, and the solvent was evaporated. The residue was purified by column chromatography on Dowex-H^+ (20 g). The elution started with 1:5 MeOH/H_2O (60 mL) and continued with H_2O (50 mL), then with MeOH (50 mL), and finally with 1 N NH_3 in 1:1 MeOH/H_2O. The main fraction gave 480 mg of yellowish oil which was purified by column chromatography on silica gel (30 g, CH_2Cl_2/MeOH, 10:1), yielding 158 mg (25%) of a colorless oil: ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.42–7.20 (m, 5 H), 4.92 and 4.76 (2 d, ^2J = 12.0, CH_2Ph), 4.32 (m, HC(1)), 3.56 (ddd, J = 11.0, 9.0, 5.0, HC(7)), 3.50 (t, J = 9.0, HC(8)), 3.15 (m, $H_{eq}C(3)$), 3.02 (ddd, ^2J = 11.5, ^3J = 4.5, 2.5, $H_{eq}C(5)$), 2.30–1.60 (m, 7 H, $H_{ax}C(3)$, $H_{ax}C(5)$, $H_2C(6)$, $H_2C(2)$); $[\alpha]^{25}_{589}$ = +3.2°, $[\alpha]^{25}_{578}$ = +3.5°, $[\alpha]^{25}_{546}$ = +3.5°, $[\alpha]^{25}_{436}$ = +4.2°, $[\alpha]^{25}_{365}$ = +7.1°, (c = 6.2 g/dm^3, CH_2Cl_2).

(1*S*,7*R*,8*R*,8a*R*)-1,7,8-Trihydroxyoctahydroindolizidine (6-Deoxycastanospermine, (+)-2). A mixture of (+)-**46** (158 mg, 0.6 mmol), MeOH (1 mL), H_2O (0.4 mL), HCOOH (0.4 mL), and 10% Pd/C (20 mg) was degassed and then pressurized with H_2 (1 atm.). After shaking at 20 °C for 16 h, the precipitate was filtered off (rinsing with MeOH) and the solvent was evaporated. The residue was dissolved in H_2O and purified by column chromatography of Dowex 50 XH^+ (2 g). The elution started with H_2O (4 mL), then with 1 N NH_3, yielding 108 mg (97%) of a yellowish oil: ^{1}H NMR (250 MHz, D_2O) δ 4.36 (ddd, J = 7.0, 5.0, 2.0, HC(1)), 3.54–3.44 (m, HC(7), HC(8)), 3.20 (ddd, ^2J = 9.5, ^3J = 9.0, 2.5, $H_{eq}C(3)$), 2.94 (ddd, ^2J = 11.5, ^3J = 4.5, 2.5, $H_{eq}C(5)$), 2.27 (dddd, ^2J = 14.0, ^3J = 9.0, 7.0, 2.5, $H_aC(2)$), 2.12 (ddd, ^2J = ^3J = 9.0, $H_{ax}C(3)$), 2.08 (dd, ^3J = 9.0, 5.0, HC(8a)), 1.93 (dddd, ^2J = 13.0, ^3J = 4.5, 2.5, 2.5, $H_{eq}C(6)$), 1.89 (dddd, ^2J = 14.0, ^3J = 9.0, 9.0, 2.0, $H_bC(2)$), 1.64–1.56 (m, $H_{ax}C(6)$); $[\alpha]^{25}_{589}$ = +36°, $[\alpha]^{25}_{578}$ = +37.4°, $[\alpha]^{25}_{546}$ = +40°, $[\alpha]^{25}_{436}$ = +71°, $[\alpha]^{25}_{365}$ = +72° (c = 25 g/dm^3, EtOH).

(1*S*,6*R*,7*S*,8*R*,8a*R*)-1,7-Diacetoxy-8-(benzyloxy)-6-fluorooctahydro-5-indolizidin-5-one ((+)-47). A mixture of

43 (102 mg, 0.32 mmol), HF·Et_3N (3 mL), and BEMP on polystyrene (150 mg) was heated to 95 °C for 2 days and then poured into a saturated aqueous $NaHCO_3$ solution (30 mL). The mixture was extracted with AcOEt (30 mL, four times); the extracts were combined and dried ($MgSO_4$), and the solvent was evaporated. The yellowish residue (150 mg) was mixed with Ac_2O (0.5 mL), pyridine (0.5 mL), and 2-(dimethylamino)pyridine (1 mg) and stirred at 20 °C for 4 days. The solvent was removed by azeotropic distillation with toluene (twice), and the residue was purified by column chromatography on silica gel (4 g, AcOEt). The main fraction was purified by column chromatography (SiO_2, Lobar B, AcOEt). After crystallization from Et_2O, 66 mg (52%) was obtained: colorless crystals; mp 132–138 °C (for the racemate (±)-47: mp 178–179 °C); ^1H NMR (250 MHz, $CDCl_3$) δ 7.40–7.22 (m, 5 H), 5.62 (ddd, $^3J(H,F)$ = 14.5, ^3J = 8.5, 9.5, HC(7)), 5.36 (m, HC(1)), 4.82 (dd, $^2J(H,F)$ = 48, $^3J(H,H)$ = 8.5, HC(6)), 4.65 and 4.55 (2 d, ^2J = 11.5, CH_2Ph), 3.84 (td, $^3J(H,H)$ = 9.5, $^4J(H,F)$ = 1.5, HC(8)), 3.75 (dd, $^3J(H,H)$ = 9.5, 3.0, HC(8a)), 3.62 (m, $H_2C(3)$), 2.19–2.10 (m, $H_2C(2)$), 2.13 and 1.97 (2 s, 2 Ac); $[\alpha]^{25}_{589}$ = +162°, $[\alpha]^{25}_{578}$ = +168°, $[\alpha]^{25}_{546}$ = +192°, $[\alpha]^{25}_{436}$ = +331°, $[\alpha]^{25}_{365}$ = +531° (c = 10 g/dm³, CH_2Cl_2).

(1*S*,6*S*,7*S*,8*R*,8a*R*)-8-(Benzyloxy)-6-fluoro-1,7-dihydroxyoctahydroindolizidine ((+)-48). A 10 M solution BH_3·Me_2S in THF (0.4 mL) was added to a solution of (+)-47 (207 mg, 0.55 mmol) in anhydrous THF (3 mL). After the mixture was stirred at 20 °C for 24 h, 3 N HCl (1 mL) was added dropwise and then MeOH (3 mL) was also added. After the mixture was heated to 70 °C for 4 h, the solvent was evaporated and the residue was dissolved in MeOH (3 mL). $NaHCO_3$ (1 g) was added portionwise, and the mixture was diluted with CH_2Cl_2 (5 mL). The precipitate was filtered off (Celite), and the solvent was evaporated. The residue was purified by column chromatography on silica gel (10 g, CH_2Cl_2/MeOH, 10:1). The main fraction (R_f = 0.5) was purified further by column chromatography on silica gel (Lobar B, CH_2Cl_2/MeOH 15:1, R_f = 0.3), yielding 127 mg (83%) of colorless oil: ^1H NMR (250 MHz, $CDCl_3$) δ 7.50–7.26 (m, 5 H), 4.88 and 4.84 (2 d, ^2J = 11.5, CH_2Ph), 4.54 (dddd, $^2J(H,F)$ = 51, ^3J = 14, 8.5, 5.5, HC(6)), 4.30 (m, HC(1)), 3.75 (ddd, $^3J(H,F)$ = 15, ^3J = 9, 8.5, HC(7)), 3.60 (t, ^3J = 9.0, HC(8)), 3.33 (ddd, ^2J = 10.0, ^3J = 5.5, 2.0, $H_{eq}C(5)$), 3.4 (m, $H_{eq}C(3)$), 2.33–2.13 (m, $H_{ax}C(3)$, HC(2), $H_{ax}C(5)$), 2.00 (dd, ^3J = 9.0, 3.5, HC(8a)), 1.87–1.74 (m, $H_bC(2)$); $[\alpha]^{25}_{589}$ = +52°, $[\alpha]^{25}_{578}$ = +54°, $[\alpha]^{25}_{546}$ = +61°, $[\alpha]^{25}_{436}$ = +98°, $[\alpha]^{25}_{365}$ = +149° (c = 4.2 g/dm³, CH_2Cl_2).

(1*S*,6*S*,7*S*,8*R*,8a*R*)-6-Fluoro-1,7,8-trihydroxyoctahydroindolizidine (6-Deoxy-6-fluorocastanospermine, (+)-3). Same procedure as for (+)-2, starting with (+)-48 (127 mg, 0.45 mmol). Yield: 80 mg (93%) of a white solid. Recrystallization from EtOH (0.3 mL) and Et_2O (3 mL) at −20 °C gave 60 mg of colorless crystals: mp 142–143 °C. For the racemic (±)-3: mp 154–155 °C dec; IR (KBr) ν 3360, 2980, 2960, 2935, 2910, 2800, 1475, 1435, 1380, 1315, 1295, 1275, 1250, 1225, 1200, 1170, 1145, 1130, 1090, 1075, 1055, 1000, 980, 955, 855 cm^{-1}; ^1H NMR (250 MHz, D_2O) δ 4.44 (dddd, 1 H, $^2J(H,F)$ = 50, $^3J(H,H)$ = 10.5, 9.0, 5.5, HC(6)), 4.36 (m, HC(1)), 3.64–3.50 (m, HC(7), HC(8)), 3.30 (ddd, ^2J = 10.5, ^3J = 5.5, $^3J(H,F)$ = 2.2, $H_{eq}C(D)$), 3.09–3.04 (m, $H_{eq}C(3)$), 2.37–2.17 (m, $H_{ax}C(5)$, $H_{ax}C(3)$, $H_aC(2)$), 2.03 (dd, ^3J = 9.5, 4.5, HC(8a)), 1.94–1.83 (m, HC(2)); ^{13}C NMR (62.9 MHz, D_2O) δ 91.0 (dd, $^1J(C,F)$ = 174, $^1J(C,H)$ = 155, C(6)), 77.4 (dd, $^2J(C,F)$ = 17.3 $^1J(C,H)$ = 145, C(7)), 71.3 (d, $^1J(C,H)$ = 130, C(8a)), 69.6 (d, $^1J(C,H)$ = 155, C(1)), 68.4 (dd, $^3J(C,F)$ = 11.1, $^1J(C,H)$ = 145, C(8)), 52.8 (td, $^1J(C,H)$ = 140, $^2J(C,F)$ = 26.0, C(5)), 51.6 (t, $^1J(C,H)$ = 140, C(3)), 33.0 (t, $^1J(C,H)$ = 135, C(2)); MS (CI, NH_3) 193 (10), 192 (M + 1, 100), 191 (15), 190 (10), 174 (24), 173 (23), 154 (14), 147 (50), 118 (9), 86 (9), 82 (9); $[\alpha]^{25}_{589}$ = +88°, $[\alpha]^{25}_{578}$ = +92°, $[\alpha]^{25}_{546}$ = +104°, $[\alpha]^{25}_{436}$ = +170°, $[\alpha]^{25}_{365}$ = +267° (c = 1.6 g/dm³, EtOH). Anal. Calcd for $C_8H_{14}FNO_3$ (191.20): C, 50.25; H, 7.38; N, 7.33. Found: C, 50.36; H, 7.37; N, 7.28.

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Registry No. (+)-1, 79831-76-8; (±)-1, 123284-48-0; (+)-2, 130948-07-1; (+)-3, 131635-62-6; (±)-3, 131722-90-2; (−)-5, 94482-75-4; (±)-5, 94482-73-2; (±)-17, 131635-63-7; (±)-18, 131635-64-8; (−)-24, 131722-80-0; (±)-24, 115140-08-4; (+)-25, 131722-81-1; (±)-25, 123190-65-8; (+)-26, 131697-89-7; (±)-26, 123190-66-9; (−)-27, 131635-65-9; (±)-27, 123190-67-0; (+)-28, 131635-66-0; (±)-28, 123190-63-6; (−)-29, 131635-67-1; (−)-30, 131635-68-2; (−)-32, 131724-03-3; (+)-33, 131722-82-2; α-34, 131722-83-3; β-34, 131722-91-3; (+)-38, 131722-84-4; (±)-38, 123190-72-7; (±)-39, 131635-69-3; 40, 131722-85-5; (+)-41, 131722-86-6; 43, 131722-87-7; (+)-44, 131722-88-8; (±)-44, 123190-76-1; 45, 131722-89-9; (+)-46, 131635-70-6; (+)-46 diacetate, 131635-73-9; (+)-47, 131635-71-7; (±)-47, 131722-92-4; (+)-48, 131635-72-8.

Supplementary Material Available: IR, ^{13}C NMR, and MS spectral data, as well as elemental analyses of all new compounds (+)-25 to (−)-30, (−)-32 to 34, (−)-38 to (+)-41, 43 to (+)-48; X-ray crystallographic results on (+)-3, with stereoview of unit cell (16 pages). Ordering information is given on any current masthead page.

Ascent of the Aldose Series by Four Carbon Atoms: Total Synthesis of D-*glycero*-D-*talo*-L-*talo*-Undecose Pentaacetonide

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Enantiomerically pure undecose acetonide **9** was synthesized, through heptose intermediate **5**, starting with D-glyceraldehyde acetonide (**1**). The key steps were two consecutive four-carbon homologations, each consisting of four reactions: (i) stereoselective elongation of the aldehyde precursor with 2-(trimethylsiloxy)furan, giving C_{n+4} butenolide templates **2** and **6**, (ii) anti-selective cis-dihydroxylation of the butenolide double bond, giving fully functionalized lactones **3** and **7**, (iii) lactone ring opening and protection, giving open-chain methyl esters **4** and **8**, and (iv) DIBAL reduction to aldoses **5** and **9**. At the end of the eight-step sequence, undecose **9** was prepared in a 5.1% overall yield, which corresponded to a 69.5% average yield per step.

The elongation of "short" homochiral progenitors by suitable carbon fragments is a prominent method of ascending the carbohydrate series.[1] Ingenious approaches to the stereocontrolled assembly of natural and synthetic

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