

Novel *O*- and *N*-Linked Inositol Oligomers: A New Class of Unnatural Saccharide Mimics

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Abstract: Several *N*- as well as *O*-linked inositol oligomers were synthesized by a chemo-enzymatic approach. Whole-cell fermentation of bromobenzene with *E. coli* JM109(pDTG601) furnished a chiral *cis*-dienediol which was converted into its vinyl epoxide and vinyl aziridine, respectively. Two-fold epoxide/aziridine openings catalyzed by Yb(OTf)₃ served as the key step in the synthesis of *N*-linked analogs, whereas a convergent approach furnished the *O*-linked inositol oligomers. Their synthesis is described and structural comparisons drawn to higher oligomers of *L-chiro*- and *neo*-inositol oligomers.

Key words: oligosaccharides, ring-opening, epoxides, aziridines, inositols

The structural diversity of carbohydrates surpasses that of peptides in its combinatorial possibilities.¹ The domain of unnatural saccharides further expands the number of possible structures as a result of increased opportunities for the substitution of atoms or functional groups within a particular sugar framework.² Some time ago we embarked on a study of a fascinating new class of compounds – oligoinositols – represented by the general formula **1**, in which the presence of an additional chiral carbon center substantially increases the number of possible structures when compared to the corresponding oligosaccharides (Figure 1).^{3,4}

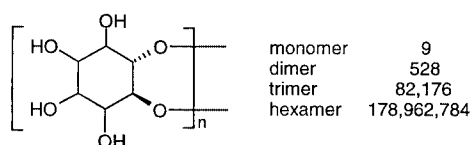


Figure 1 Combinatorial possibilities of oligoinositols⁴

Oligoinositols resemble oligosaccharides in conformation, molecular volume, and hydrogen-bonded secondary structure. The last aspect has already been demonstrated by both crystal structure and molecular modeling studies.⁵ Because such compounds lack the glycosidic linkage, they may become ideal candidates for screening as carbohydrate analogs for oral rather than intravenous applications in cases where their biological activities would mimic those of natural sugars. Obvious applications of these compounds are their use as heparin analogs, insulin

mediators, or inhibitors of natural glycosidase enzymes.^{2,3,6} In addition, compounds of this type have the potential for serving as multi-functional scaffolds in parallel synthesis, metal sequestering agents,⁵ and novel materials containing primary as well as secondary chirality, the last being a function of the β -turn feature resulting from *trans*-1,2-linkage. In this paper, we report the synthesis of a series of heteroatom-linked oligomers featuring primarily the *L-chiro*-inositol stereochemical motif as shown in Figure 2.

Oxygenated dimer **2**, which features the *L-chiro*-amino-inositol-*proto*-quercitol configuration, has been prepared and shown to sequester calcium ions from aqueous solution and to form extended helical chelates.⁵

Dimers **3**, **4**, and **5** are described in this manuscript: **5** has an additional hydroxylic site when compared to **2** whereas **3** and **4** are *N*-linked rather than *O*-linked entities. Their preparation, shown in Schemes 1 and 2, is reasonably straightforward and lends itself to iterative coupling eventually to produce higher oligomers of any of these compounds.

Bromocyclohexadiene-*cis*-diol (**6**),⁷ produced by whole-cell fermentation of bromobenzene with JM109-(pDTG601), an organism that expresses toluene dioxygenase (TDO), is converted in two steps to either vinyloxirane **7**⁸ or *N*-tosyl vinylaziridine **8**.^{8,9} These compounds serve as electrophilic partners in the subsequent coupling reaction.

Conduramine oligomers **9** and **10** were obtained by a one-pot procedure in which vinyloxirane **7** or vinylaziridine **8** were treated with ammonia and the resulting aminoalcohol or *trans*-diamine was subsequently reacted with vinyloxirane **7**, to produce **9** (79%) or **10** (94%), respectively (Scheme 1). Dehalogenation of **9** with Bu₃SnH/AIBN in THF provided **11** in 83% yield. The hydroxyl groups in **11** were protected selectively as acetates (89%) followed by conversion of the secondary amine into its trifluoroacetamide to provide **12** in 88% yield. An analogous strategy provided **14** starting from **10** by first protecting the alcohol as the acetate (93%), then transforming the amine to its trifluoroacetamide (98%), and subsequently dehalogenating **13** with Bu₃SnH/AIBN in THF (73%). The hydroxylation of the double bonds in **12** was achieved with OsO₄(cat.)/NMNO followed by protection of the *cis*-diols as their acetonides to give **15** in 53% yield. A similar reaction sequence provided **16** starting from **14** in 61% yield. Basic hydrolysis of the acetate and the trifluoroacet-

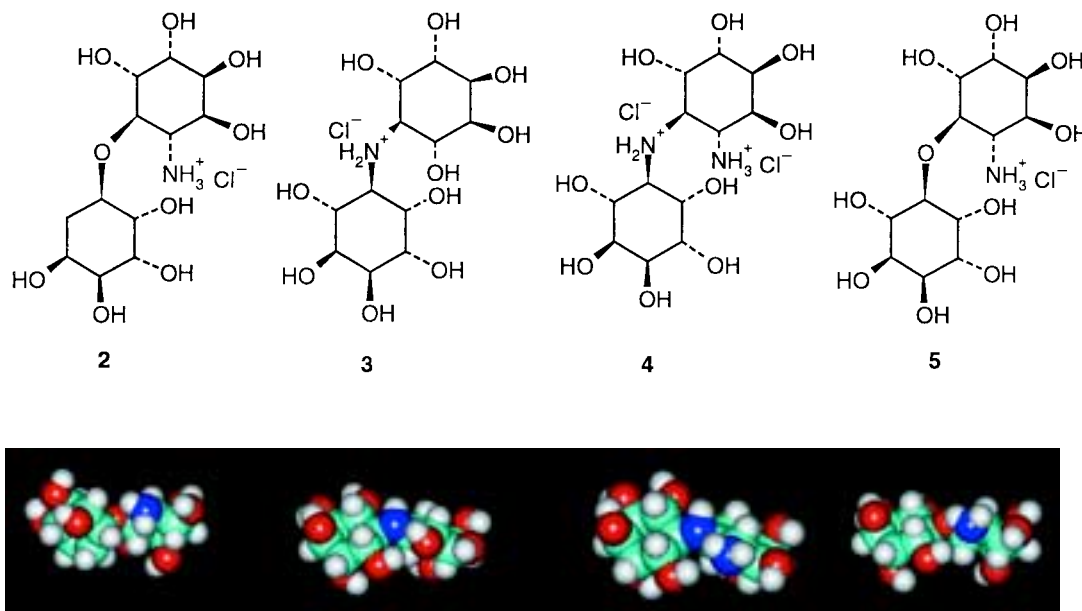
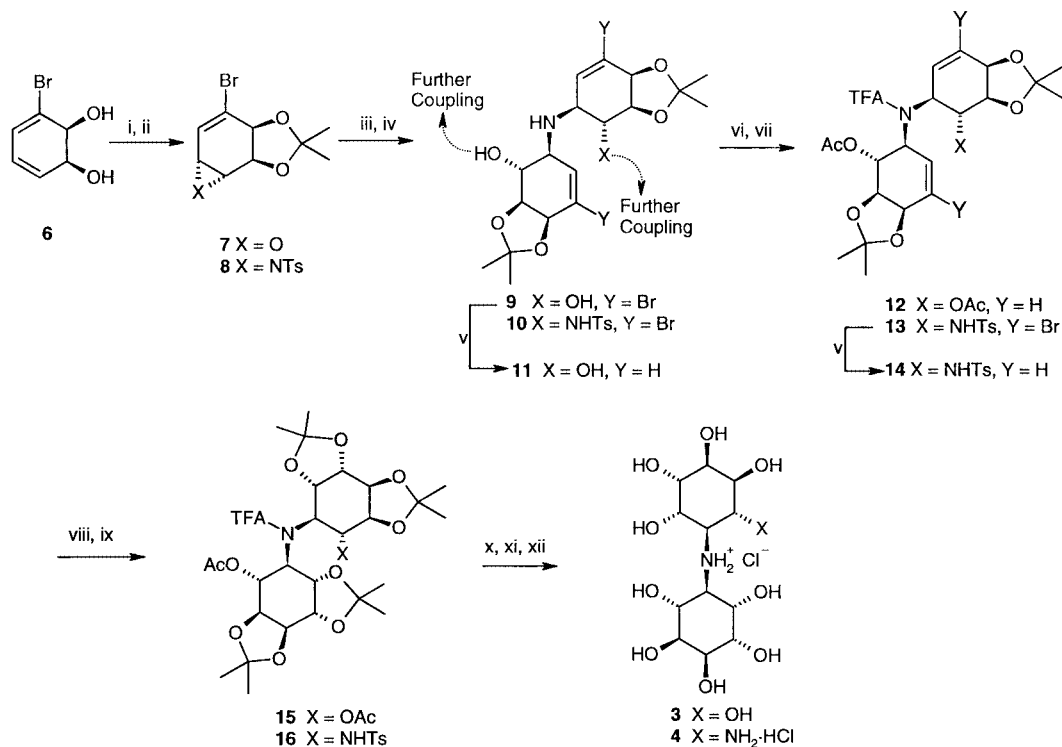


Figure 2 Structures and molecular modeling of *O*- and *N*-linked *L*-chiro-inositol dimers

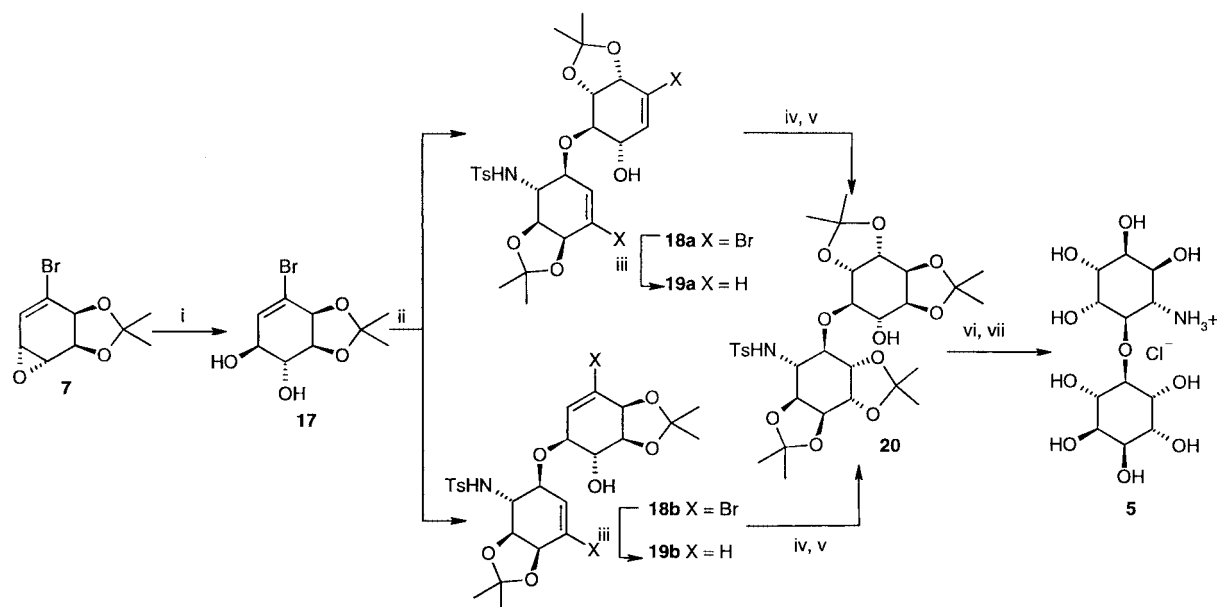
amide, followed by removal of the acetonides with MeOH–HCl provided the hydrochloride salt **3** in 87% yield. In analogy, the acetate and trifluoroacetamide in **16** were removed under basic conditions (57%), and the sulfonamide was removed with Na in liquid ammonia (84%), followed by acidic hydrolysis to give **4** in 77% yield.

In the preparation of the *O*-linked inositol oligomer **5**, a convergent approach was pursued, because of the inherent C_2 symmetry of the molecule. The ring opening of vinylloxirane **7** with KOH furnished the *trans*-diol **17** (63%),¹⁰ which was utilized as a nucleophile at either hydroxyl site and reacted with vinylaziridine **8** to yield **18a** and **18b** (52% total).¹¹ Vinyl bromide **18a** was debrominated under



Scheme 1 Synthesis of *N*-linked inositol oligomers **3** and **4**

i) DMP, H^+ ; ii) mCPBA or PhINTs; iii) $Yb(OTf)_3$, NH_3 ; iv) **7**, dioxane; v) Bu_3SnH , AIBN; vi) Ac_2O , pyridine, DMAP; vii) $(CF_3CO)_2O$, pyridine, DMAP, Δ ; viii) OsO_4 , NMNO, H_2O , acetone; ix) DMP, H^+ ; x) MeOH, NaOMe; xi) Na, $NH_3(l)$; xii) HCl, MeOH



Scheme 2 Synthesis of *O*-linked inositol oligomer **5**

i) KOH, DMSO, Δ ; ii) BF_3OEt_2 , **8**; iii) Bu_3SnH , AIBN; iv) OsO_4 , NMNO, H_2O , acetone; v) DMP, H^+ ; vi) Na, $\text{NH}_3(l)$; vii) HCl, MeOH

the same conditions used for the *N*-linked analogs to give **18b** in 68% yield. The latter was hydroxylated (OsO_4/NMNO) and the resulting *cis*-diols protected as acetones to provide **20** in 60% yield over two steps. The same strategy was applied to convert **18a** into **20**. The amine moiety in **20** was deprotected with $\text{Na}/\text{NH}_3(l)$, followed by deprotection of the acetals under acidic conditions to yield **5** in 52% yield as depicted in Scheme 2.

Thus, the *O*-linked analog **5** has been prepared in six steps and 5% overall yield. Similarly, **3** has been attained in seven steps and 17% yield, and **4** in eight steps and 10% yield, respectively.

The NMR analyses of these compounds have shown interesting symmetry properties. For example, the NMR spectrum of oligomer **3** in D_2O proved to be symmetrical, showing only a total of six ring protons, even though the molecule is not a *meso* compound.

The inhibition properties of these compounds towards glycosidic enzymes are the focus of our current research.¹²

The properties of the dimers described in this manuscript provide an opportunity for investigation of higher oligomers. In principle, the iterative coupling of compounds derived from **7** and **8** can be continued in a controlled manner indefinitely, either at the conduritol/conduramine stage (**9**, **10**), or at the stage of fully hydroxylated entities **3–5**. The latter, of course, would generate multiple possibilities for structural diversity if performed with the fully deprotected hydroxylated materials. On the other hand, the coupling in the former series is amenable to complete control since only two (and sometimes one) nucleophilic sites are available. The oligomers in the fully oxygenated series can further be classified as homogeneous, for example if composed of only one repeating monomer (i.e. inos-

itol), or heterogeneous, in which the monomeric coupling partners are synthons reflecting the ultimate stereochemistry of any of the nine isomeric inositols. That such a variance would alter secondary structure in the resulting oligomers is illustrated in Figure 3, where the comparison of *L-chiro*- and *neo*-inositols is made for dimers, tetramers and octamers. Trimers in both series have been synthesized as have the pentamers,³ hexamers,¹³ and octamers¹³ in the *L-chiro* series. The two series show marked differences in their secondary helical structures.

Such properties could be exploited in the design of, for example, water-soluble catalysts. It seems that serious secondary structure alterations could be attained by judicious “programming” of the coupling events for eventual design of multitudes of oligomers composed of alternating (random or planned) sequences of inositol units. These endeavors form the current focus of our research and will be reported in due course.

All non-aqueous reactions were performed using standard techniques for the exclusion of moisture and air. Melting points were recorded on a Hoover Unimelt apparatus and are uncorrected. IR spectra were recorded on a Perkin-Elmer FT-IR or on a Perkin-Elmer Spectrum one FT-IR spectrometer. ^1H and ^{13}C NMR spectra were recorded on a Varian Gemini (300 MHz), a Varian VXR (300 MHz), and a Mercury 300 (300 MHz) instrument. All chemical shifts are referenced to TMS or residual undeuterated solvent. Optical rotation was measured on a Perkin Elmer 341 instrument. All combustion analyses were performed by Atlantic Microlab, Norcross GA. Mass spectra were recorded by the analytical division at the University of Florida, Gainesville.

Bis-[6-[(1*R*,2*S*,3*S*,6*S*)-4-bromo-2,3-*O*-isopropylidencyclohex-4-ene-1,2,3-triol]}amine (9**)**

A 2-neck round-bottom flask equipped with a dry-ice condenser was charged with epoxide **7** (1.934 g, 7.833 mmol) and $\text{Yb}(\text{OTf})_3$

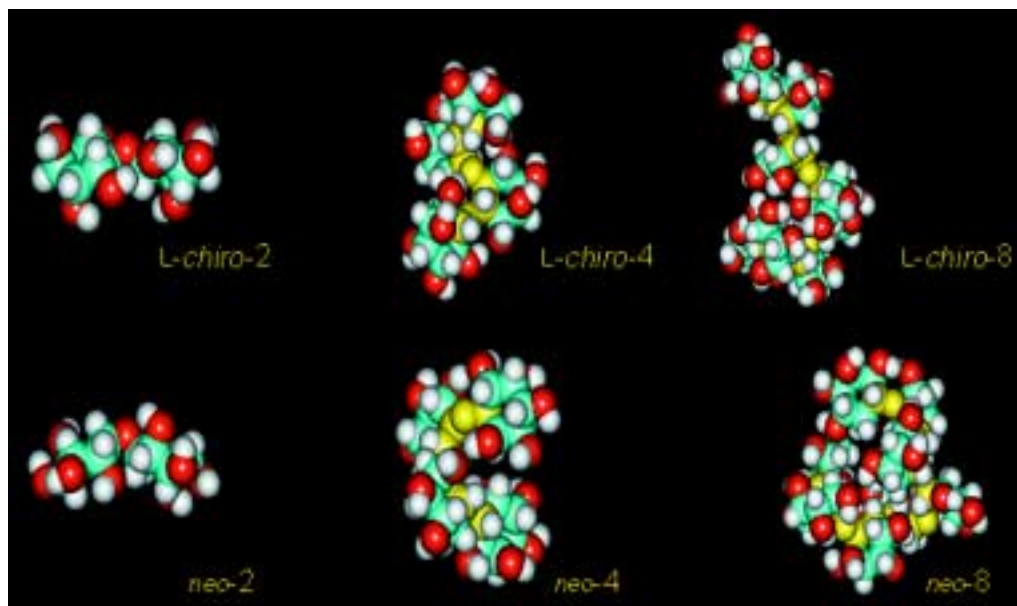


Figure 3 Molecular modeling of higher oligomers of *L-chiro*- and *neo*-inositols¹⁴

(971 mg, 1.566 mmol). Ammonia (approx. 20 mL) was condensed into the reaction vessel and allowed to reflux for 8 h, after which it was allowed to evaporate. To the solid residue was added a solution of epoxide **7** (2.1 g, 8.505 mmol) in 1,4-dioxane (20 mL) and the mixture was heated to reflux for 24 h. After cooling to r.t., the solvent was removed under reduced pressure and the residue purified by flash-chromatography (hexanes–EtOAc, 1:1) to yield **9** (3.136 g, 78%) as a yellow foam.

$[\alpha]_{\text{D}}^{27} = +52.3$ ($c = 0.90$, CHCl_3).

IR (KBr): $\nu = 3448, 2987, 2934, 1382, 1219, 1073 \text{ cm}^{-1}$.

$^1\text{H NMR}$ (CDCl_3 , 300 MHz): $\delta = 6.21$ (d, $J = 1.9$ Hz, 2H), 4.68 (d, $J = 6.5$ Hz, 2H), 4.16 (dd, $J = 8.7, 6.5$ Hz, 2H), 3.49 (t, $J = 8.8$ Hz, 3H), 3.20 (dt, $J = 8.8, 1.5$ Hz, 2H), 1.54 (s, 6H), 1.42 (s, 6H).

$^{13}\text{C NMR}$ (CDCl_3 , 75 MHz): $\delta = 133.9, 119.4, 110.9, 78.3, 77.2, 71.9, 57.2, 28.3, 26.0$.

HRMS (m/z): $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{18}\text{H}_{26}\text{NB}_2\text{O}_6$: 512.0108; found: 512.0278.

Anal. Calcd for $\text{C}_{18}\text{H}_{25}\text{Br}_2\text{NO}_6$: C, 42.29; H, 4.93; N, 2.74. Found: C, 42.22; H, 4.94; N, 2.60.

Bis-{6-[(1*R*,2*S*,3*R*,6*S*)-2,3-*O*-isopropylidene-cyclohex-4-ene-1,2,3-triol]}amine (11**)**

Compound **9** (407 mg, 0.796 mmol) was dissolved in anhyd THF and degassed with argon for 20 min. AIBN (13 mg, 0.079 mmol) was added and the mixture heated to reflux after which Bu_3SnH (514 μL , 1.911 mmol) was added. The reaction was allowed to reflux for 4.5 h and then cooled to r.t. The solvent was removed in vacuo and the residue purified by flash-chromatography (EtOAc) to yield 232 mg (83%) of the title compound as a white solid.

Mp = 159–160 °C; $[\alpha]_{\text{D}}^{30} = -13.8$ ($c = 1.55$, CHCl_3).

IR (KBr): $\nu = 3424, 2989, 2926, 1381, 1258, 1210, 1068 \text{ cm}^{-1}$.

$^1\text{H NMR}$ (CDCl_3 , 300 MHz): $\delta = 5.90$ (m, 4H), 4.63 (dd, $J = 6.8, 2.0$ Hz, 2H), 4.13 (dd, $J = 8.8, 6.7$ Hz, 2H), 3.72 (s, 3H), 3.48 (dd, $J = 9.0$ Hz, 2H), 3.22 (d, $J = 9.2$ Hz, 2H), 1.51 (s, 6H), 1.39 (s, 6H).

$^{13}\text{C NMR}$ (CDCl_3 , 75 MHz): $\delta = 132.8, 124.0, 110.0, 78.1, 72.4, 72.3, 55.5, 28.1, 25.6$.

HRMS (m/z): $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{18}\text{H}_{28}\text{NO}_6$: 354.1917; found: 354.1925.

Anal. Calcd for $\text{C}_{18}\text{H}_{27}\text{NO}_6$: C, 61.17; H, 7.70; N, 3.96. Found: C, 60.88; H, 7.92; N, 3.87.

Bis-{6-[(1*R*,2*R*,3*R*,6*S*)-1-*O*-acetyl-2,3-*O*-isopropylidene-cyclohex-4-ene-1,2,3-triol]}trifluoroacetamide (12**)**

Amine **11** (323 mg, 0.914 mmol) was dissolved in anhyd CH_2Cl_2 in a flame-dried flask under a static argon atmosphere and a spatula tip of DMAP was added. The reaction mixture was cooled to 0 °C followed by addition of pyridine (211 μL , 2.61 mmol) and Ac_2O (185 μL , 1.94 mmol). The solution was stirred at 0 °C for 1 h and then slowly allowed to warm to r.t. After 10 h, the mixture was quenched with MeOH (0.3 mL), stirred for 20 min and concentrated in vacuo. The resulting yellow oil was purified by flash-chromatography (hexanes–EtOAc, 3:2) to yield the *O*-diacetate of **11** as white solid (356 mg, 89%). This material (910 mg, 2.08 mmol) was dissolved in anhyd pyridine (20 mL) in a flame-dried thick-wall tube under argon atmosphere and trifluoroacetic anhydride (1.5 mL) was added. The tube was sealed and heated in an oil-bath to 100 °C for 2 h. The mixture was allowed to cool to r.t., diluted with MeOH (50 mL) and concentrated under reduced pressure. The residue was co-evaporated several times with toluene and the resulting brown oil purified by flash-chromatography (hexanes–EtOAc, 3:2) to yield amide **12** (980 mg, 88%) as an off-white foam.

$[\alpha]_{\text{D}}^{28} = +52.4$ ($c = 0.75$, CHCl_3).

IR (film on NaCl): $\nu = 2988, 2935, 2360, 1752, 1703, 1373, 1223, 1064 \text{ cm}^{-1}$.

$^1\text{H NMR}$ (CDCl_3 , 300 MHz): $\delta = 6.01$ (dt, $J = 10.2, 2.5$ Hz, 1H), 5.91 (dt, $J = 10.0, 3.2$ Hz, 1H), 5.87 (dd, $J = 9.4$ Hz, 1H), 5.64 (d, $J = 10.4$ Hz, 1H), 5.58 (dd, $J = 10.4, 2.4$ Hz, 1H), 5.19 (br s, 1H), 4.64 (br s, 1H), 4.57 (m, 2H), 4.44 (dd, $J = 5.2$ Hz, 1H), 4.17 (d, $J = 9.8$ Hz, 1H), 4.10 (dd, $J = 9.1, 6.1$ Hz, 1H), 2.18 (s, 3H), 2.06 (s, 3H), 1.49 (s, 3H), 1.40 (s, 3H), 1.38 (s, 3H), 1.35 (s, 3H).

$^{13}\text{C NMR}$ (CDCl_3 , 75 MHz): $\delta = 170.5, 169.8, 157.0$ (q, $J = 36$ Hz), 132.7, 130.9, 126.0, 124.2, 115.9 (q, $J = 288$ Hz), 111.1, 110.7, 77.5, 72.8, 72.7, 71.4, 70.2, 69.2, 57.4, 57.3, 28.2, 28.0, 26.7, 26.4, 21.3, 21.1.

HRMS (m/z): $[M - CH_3]^+$ calcd for $C_{23}H_{27}NO_9F_3$: 518.1638; found: 518.1657.

Anal. Calcd for $C_{24}H_{30}NO_9F_3$: C, 54.03; H, 5.67; N, 2.63. Found: C, 54.28; H, 5.73; N, 2.55.

Bis-{6-[(1R,2S,3R,6S)-1-O-acetyl-2,3,4,5-di-O-isopropylidencyclohex-4-ene-1,2,3,4,5-pentol]}trifluoroacetamide (15)

Amide **12** (893 mg, 1.674 mmol) was dissolved in a mixture (15 mL) of acetone– H_2O – t -BuOH (100:10:1), followed by addition of NMNO (706 mg, 6.026 mmol) and a small crystal of solid OsO_4 . After 48 h, an additional portion of NMNO (400 mg, 3.414 mmol) was added. The reaction was quenched after 50 h by addition of an excess of 10% aq sodium bisulfite and allowed to stir for 15 min. After adjusting the pH value to ~3 with 1 M HCl, the mixture was extracted with EtOAc (4×200 mL) and the combined organic layers were washed with sat. aq $NaHCO_3$ (20 mL), dried ($MgSO_4$), and concentrated in vacuo to yield 780 mg of a brown semi-solid of the corresponding tetrol. This material was dissolved in CH_2Cl_2 (30 mL) and DMP (4 mL) and a catalytic amount of p -TsOH was added. The reaction was allowed to stir at r.t. for 14 h. The mixture was diluted with EtOAc (100 mL), washed with sat. aq $NaHCO_3$ (10 mL), dried (Mg_2SO_4) and concentrated under reduced pressure to give the tetraacetone **15** (559 mg, 53% over two steps) as an off-white foam.

$[\alpha]_D^{27} = -71.2$ ($c = 0.8$, $CHCl_3$).

IR (KBr): $\nu = 2989, 2941, 1762, 1701, 1457, 1374, 1220, 1054$ cm^{-1} .

1H NMR ($CDCl_3$, 300 MHz): $\delta = 5.76$ (dd, $J = 11.0, 8.9$ Hz, 1H), 5.15 (dd, $J = 10.6, 7.1$ Hz, 1H), 4.92 (dd, $J = 7.9$ Hz, 1H), 4.84 (dd, $J = 6.1, 1H$), 4.46 (m, 3H), 4.05–4.30 (m, 3H), 3.89 (dd, $J = 9.9$ Hz, 1H), 3.48 (dd, $J = 11.3, 5.6$ Hz, 1H), 2.18 (s, 3H), 2.07 (s, 3H), 1.61 (s, 3H), 1.53 (s, 3H), 1.51 (s, 3H), 1.49 (s, 3H), 1.45 (s, 3H), 1.36 (s, 3H), 1.31 (s, 3H), 1.30 (s, 3H).

^{13}C NMR ($CDCl_3$, 75 MHz): $\delta = 170.9, 169.1, 159.1$ (q, $J = 36$ Hz), 116.1 (q, $J = 290$ Hz), 110.7, 109.9, 109.7, 109.6, 78.4, 77.5, 76.7, 76.2, 75.8, 73.8, 68.5, 67.8, 60.2, 57.8, 28.1, 27.5, 27.4, 26.6, 25.6, 25.3, 24.8, 21.8, 21.1.

HRMS (m/z): $[M + H]^+$ calcd for $C_{30}H_{43}NO_{13}$: 682.2686; found: 682.2647.

Anal. Calcd for $C_{30}H_{42}F_3NO_{13}$: C, 53.86; H, 6.21; N, 2.05; Found: C, 53.09; H, 6.22; N, 1.98.

Bis-{6-[(1R,2S,3R,6S)-cyclohexa-1,2,3,4,5-pentol]}amine Hydrochloride (3)

Compound **15** (444 mg, 0.707 mmol) was dissolved in a 0.1 M solution of NaOMe in MeOH (10 mL) and stirred at r.t. for 4 h. The mixture was concentrated under reduced pressure and the residue loaded on a flash-chromatography column (EtOAc–hexanes, 3:1) to yield an off-white foam (310 mg, 88%), which was dissolved in MeOH (9 mL) and treated with concd HCl (500 μ L). The mixture was allowed to stand at r.t. for 20 h after which a white, crystalline precipitate had been formed. The crystals were filtered off and washed with MeOH–acetone (2×2 mL, 1:1). Concentration and crystallization of the mother liquor gave additional precipitate which was combined with the former to yield hydrochloride **3** (200 mg, 75% over two steps) as white crystals.

$[\alpha]_D^{30} = -61.9$ ($c = 1.0$, H_2O).

IR (KBr): $\nu = 3444, 3321, 1577, 1440, 1383, 1333, 1207, 1091$ cm^{-1} .

1H NMR (D_2O , 300 MHz): $\delta = 4.19$ (dd, $J = 10.6, 2.3$ Hz, 2H), 4.09 (m, 4H), 3.99 (dd, $J = 10.2$ Hz, 2H), 3.92 (dd, $J = 10.3$ Hz, 2H), 3.84 (dd, $J = 9.1, 2.0$ Hz, 2H).

^{13}C NMR (D_2O , 75 MHz): $\delta = 71.8, 71.1, 71.0, 69.6, 67.7, 62.4$.

HRMS (m/z): M^+ calcd for $C_{12}H_{24}NO_{10}$: 342.1400; found: 342.1410.

Anal. Calcd for $C_{12}H_{24}NO_{10}Cl$: C, 38.15; H, 6.40; N, 3.71. Found: C, 38.21; H, 6.66; N, 3.60.

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- The ratio of **18a**:**18b** seems to vary considerably with the reaction scale. Although we have separated **18a** and **18b** to establish their regiochemistry, it is not necessary to do so for preparative runs, since both ultimately yield **20**.
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- All molecular modeling was performed with SPARTAN SGI version 5.1.1, available from Wavefunction Inc., on a Silicon Graphics O².