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# Diastereoselectivity in the Intramolecular Nitrone, Oxime, and Nitrile Oxide Cycloaddition Reactions. Synthesis of Amino Inositol Derivatives as α-Glucosidase Inhibitors

Norton P Peet, Edward W Huber, and Robert A Farr*

Merrell Dow Research Institute, 2110 East Galbraith Road, Cincinnati, OH 45215

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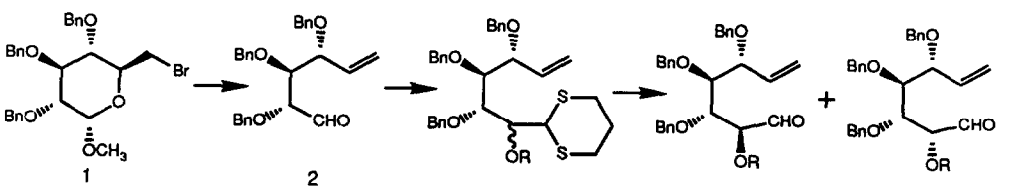
**Abstract:** The diastereoselectivity in the intramolecular 1,3-dipolar cycloaddition reactions of 4 and 5 (R=Bn, 4-MeOBn) was examined.

The 1,3-dipolar cycloaddition of nitrones,[1] nitrile oxides,[1] and oximes[1,2] to olefins is a powerful synthetic tool for the preparation of 1,3-amino alcohols and/or protected aldols. Recently, the intramolecular nitrile oxide cycloaddition (INOC) and nitrone cycloaddition reactions of olefinic aldehydes derived from sugars have been applied to the synthesis of hydroxylated aminocyclopentane and cyclohexane derivatives[3] and the β-glucosidase inhibitor cyclophellitol.[4] We have examined and compared these cycloaddition reactions during the synthesis of α-glucosidase inhibitors **9**, **10**, and **19**

Bromide **1**, prepared in 67% overall yield from methyl-α-D-glucopyranoside, was cleaved with zinc dust to aldehyde **2** as described by Bernet and Vasella[5] (Scheme 1). Without isolation, **2** was converted to dithianes **3a,b** [n-BuLi, 1,3-dithiane, 0°C, 2 h;[6] NaH, DMF, BnBr or 4-$CH_3OC_6H_4CH_2Cl$ (MPM-Cl), 0-25°C, 1 h] in 67% and 69% overall yields, respectively. Hydrolysis of dithianes **3a** (3 equiv NCS, 3.3 equiv $AgNO_3$, 80% aq $CH_3CN$)[7] gave a 50% yield of a 4:1 mixture of **4a** and **5a**, while hydrolysis of **3b** (1.6 equiv NCS, 2.0 equiv $AgClO_4$, 90% aq acetone) gave a 67% yield of a 2 5:1 mixture of **4b** and **5b**; some epimerization of **5a,b** to **4a,b** under the reaction conditions was observed using partially separated dithianes **3a,b**. The configurations of **4** and **5** were assigned after subsequent conversion to their intramolecular cycloaddition products. Aldehydes **4a,b** and **5a,b** were readily separated by flash chromatography[8] (10-15% EtOAc in cyclohexane) prior to cyclization

**Scheme 1**

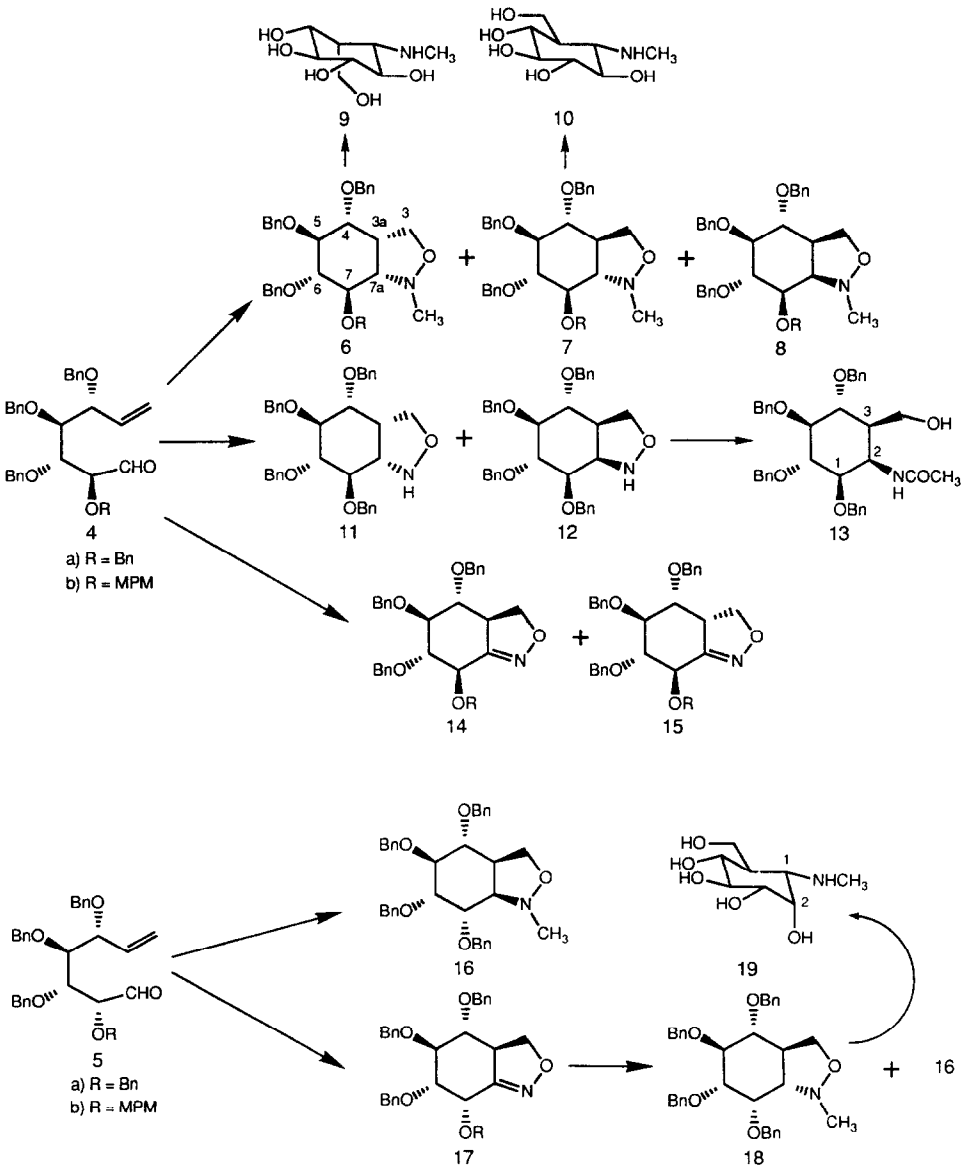



1 2 3 4 5

a) R = Bn
b) R = MPM

Reaction of D-*ido*-hept-6-enose derivative **4a** with $CH_3NHOH$ in refluxing $CH_3OH$ for 3 h gave a 60% yield of **6a** and 16% of **7a** (Scheme 2). Similarly, **4b** gave 69% of **6b** and 17% of **7b**, in addition, 2.6% of **8b** was isolated (order of elution, 25% EtOAc in cyclohexane: **8b**, **6b**, **7b**). The stereochemistry at the bridgehead carbons and C-7 was assigned based on $^1H$ NMR coupling constants (Table) and 2D NOE experiments For **6a**, strong NOE correlations were observed between $H_{7a}$ and $H_{3a}$ confirming the *cis* configuration at the

## Scheme 2



ring junction. An NOE is also observed between $H_{7a}$ and $H_6$ indicating the diaxial configuration of these protons. The lack of an NOE between $H_{3a}$ and $H_{7a}$ for **7a** supports the trans ring junction, and a unique NOE between $H_4$ and $H_{7a}$ indicates they are oriented 1,3-diaxial For **8b**, the large coupling for $J_{3a,4}$ and the smaller couplings for $J_{7,7a}$ and $J_{7a,3a}$ support the stereochemistry shown.

Reaction of **4a** with $NH_2OH$ HCl ($CH_3ONa$, $CH_3OH$, 2 h) gave a 3·1 ratio of *anti*·*syn* oximes [$^1H$ NMR ($CDCl_3$) δ 7 49 ($J$=7.5 Hz) and 6.94 ($J$=6.0 Hz) for RC<u>H</u>=NOH] which upon prolonged heating (toluene, 110°C, 18 h; xylenes, 137°C, 21 h) gave 52% of a 2:1·1 mixture of isoxazolidines **11** and **12**, in addition to 13% of recovered oximes. The less polar cycloadduct was N-methylated ($CH_3I$, $K_2CO_3$, acetone) to give **6a**. The stereochemistry of **12** was inferred from **13**, which was obtained by reductive cleavage (Zn, 85% aq HOAc) of **12** followed by acetylation The $^1H$ NMR ($CDCl_3$) of **13** showed a narrow multiplet (δ 4 70) for $H_2$ consistent only with two equatorial-axial couplings; a strong NOE was observed between $H_2$ and both $H_1$ and $H_3$

**Selected Vicinal Coupling Constants (Hz) for Cycloadducts**

| Compound | $J_{3a,4}$ | $J_{4,5}$ | $J_{5,6}$ | $J_{6,7}$ | $J_{7,7a}$ | $J_{7a,3a}$ |
|---|---|---|---|---|---|---|
| **6a** | 5 | * | 8 | 9 | 8 | 8 |
| **7a** | 10 | 9 | * | * | 9 | 10 |
| **8b** | 10 | * | 9 | 9 | 4 | 5 |
| **14** | 9 | 9 | * | 8 | -- | -- |
| **15** | 5 | 4 | 3 | 2 | -- | -- |
| **16** | 10 | 7 | 4 | 2 | 6 | * |
| **17** | 10 | 9 | 9 | 4 | -- | -- |
| **18** | 10 | 8 | 9 | 3 | <4 | 10 |

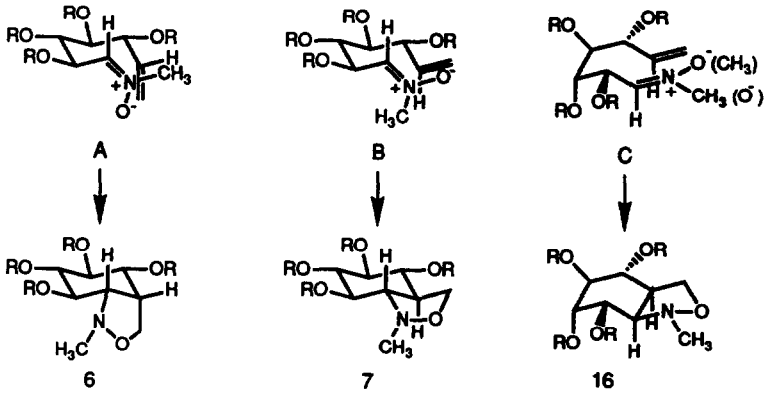
* not measured due to overlap of signals

*In situ* oxidation of the crude oximes of **4a** to the nitrile oxide (aq NaOCl, $CH_2Cl_2$) gave an 86% yield of a 64·36 mixture of isoxazolines **14a** and **15a**. For **15a**, only small (equatorial-equatorial and equatorial-axial) couplings were observed, indicating the compound was not in a chair conformation Also, the typical 1,3-diaxial NOE correlations were not observed An identical ratio of diastereomers **14b** and **15b** was obtained from the INOC reaction of **4b**. The diastereoselectivity observed in the INOC reaction is in accord with the proposed transition state[9] for the reaction (Interestingly, 4-hydroxy-**14a** (prepared from L-glucose) was recently reported to be the <u>sole</u> product (70%) of the INOC reaction of the corresponding hydroxy analog of **4a** [4])

In contrast, the intramolecular nitrone cycloaddition of D-gulo-hept-6-enose derivative **5a** gave **16** in 67% yield with high diastereoselectivity; only minor amounts of other uncharacterized cycloadducts were detected The coupling constants observed for **16** indicate this compound assumes a twist-boat conformation NOE data indicate a 1,3-diaxial orientation between $H_{3a}$ and $H_5$ (and thus the stereochemistry shown for $H_{3a}$). The stereochemistry of $C_{7a}$ in **16** was not definitively determined due to overlap of signals but was confirmed upon methylation/reduction of **17a** (*vide infra*). The INOC reaction of **5a,b** showed similarly high diastereoselectivity and **17a,b** were isolated in 82% and 76%

yields, respectively. For **17a** the stereochemistry at $C_{3a}$ was established based on the large axial-axial coupling for $J_{3a,4}$ and an observed NOE between $H_{3a}$ and $H_5$. Methylation [$(CH_3)_3O^+BF_4^-$, $CH_3NO_2$] of **17a** followed by $NaBH_4$ reduction[10] in EtOH gave a 55% yield of a 36:64 mixture of **18**:**16**. Coupling constants for **18** indicate the six-membered ring is in a chair conformation with $H_{7a}$ axial. NOE's are observed between $H_{7a}$ and both $H_6$ and $H_7$.

The stereochemical outcome of the nitrone cyclization of **4a,b** can be rationalized by examination of the transition states **A** and **B** for cyclization. Chair-like transition state **A** leading to *cis* products **6** requires a Z-nitrone for maximal orbital overlap, while chair-like transition state **B** leading to *trans* isoxazolidines **7** requires an E-nitrone for good orbital overlap.[11] The preponderance of **6** over **7** may be merely a consequence of the preferential formation of the Z-nitrones, as the $^1H$ NMR ($CDCl_3$) of the crude nitrones derived from **4a** showed predominantly a doublet (J=7 Hz) at $\delta$ 6.59, indicative of a Z-nitrone;[12] the signal for the E-nitrone could not be discerned. The formation of minor product **8b** requires a boat-like transition state.[11] We examined the cycloaddition of the oximes of **4a**, expecting that perhaps the predominantly formed anti-oxime might retain its stereochemical integrity upon conversion to its E-nitrone tautomer to give more of the *trans* product via a transition state analogous to **B**. However, only *cis* products **11** and **12** were isolated. The higher temperatures necessary for the oxime cycloaddition may make cyclization through a boat-like transition state (leading to **12**) more energetically favorable. In fact, the presence of a pseudo-axial benzyloxy substituent at C-2 precludes cyclization via either chair transition state, and cyclization of the nitrones derived from **5a** leads exclusively to *cis* derivative **16** via the boat-like transition state **C**; good orbital overlap can be achieved in **C** with either a Z or E nitrone.




Catalytic hydrogenation (HOAc, Pd black) of **6a**, **7a**, and **18** gave amino inositols **9**, **10**, and **19**, respectively. All three compounds were inactive at 1 mM against rat intestinal sucrase. Against pig kidney $\alpha$-glucosidase I, **19**, possessing an $\alpha$-OH group at C-2, had an $IC_{50}$ of 0.5 mM, while **10** and **9** had $IC_{50}$'s of 2 mM and >2 mM, respectively. The

weak activity of these amino inositols vs α-glucosidase is in sharp contrast to the reported potent activity of our related aminocyclopentane derivatives vs α-mannosidase.[3a]

## EXPERIMENTAL

Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Silica Gel 60 (230-400 mesh ASTM, EM Science) was used for all flash chromatographies Nuclear magnetic resonance spectra were recorded on Varian VXR-300 and Gemini-300 NMR spectrometers. Chemical shifts are reported versus tetramethylsilane (TMS). Coupling constants are reported in Hertz (Hz). As appropriate, $^1H$-$^1H$ and $^1H$-$^{13}C$ shift correlation spectroscopy (COSY and HETCOR, respectively), 2D nuclear Overhauser effect (NOESY), and 2D homonuclear J-resolved (HOM2DJ) experiments were performed to aid in spectral interpretation and assignments. Mass spectra were recorded on either a Finnigan MAT 4600 or a VG Analytical Limited ZAB2-SE mass spectrometer using chemical ionization with $CH_4$ as the reagent gas IR spectra were recorded on a Perkin-Elmer Model 1800 FT-IR spectrophotometer

***6,7-Dideoxy-2,3,4,5-tetrakis-O-(phenylmethyl)-D-gulo/ido-hept-6-enose, Cyclic 1,3-Propanediyl Mercaptals (3a).*** To a stirred solution of 4.45 g (37.0 mmol) of 1,3-dithiane in 100 ml dry THF at -25 to -30°C under nitrogen was added 23 2 mL (37 mmol) of 1 6M n BuLi/hexane. After 1 h a solution of 11.87 g (28.50 mmol) of freshly prepared crude aldehyde **2**, prepared from bromide **1** according to the procedure of Bernet and Vasella,[5] in 20 mL dry THF (+ 2 x 3 mL rinses) was added. After 2 h (the bath temperature rose to 5°C) the reaction mixture was poured into aqueous $NH_4Cl$ and extracted twice with ether The combined extracts were washed with brine, dried ($MgSO_4$), and concentrated in vacuo. The residue was dissolved in 30 mL dry DMF and the resulting solution (+ 2 x 2 mL DMF rinses) was added to a vigorously stirred suspension of NaH [1.52 g (38.0 mmol) of 60% dispersion which was first washed 3 x with pentane] in 30 mL dry DMF at 0°C. Benzyl bromide (3 56 mL, 29 9 mmol) was then added dropwise The reaction mixture was allowed to warm to 25°C overnight (the reaction is complete in less than 1 h) before being quenched with aqueous $NH_4Cl$. The mixture was diluted with water and extracted twice with ether. The extracts were washed twice with water, brine, and dried ($MgSO_4$). Concentration in vacuo and flash chromatography of the residue eluting with 10% EtOAc in cyclohexane gave 12.00 g (67%) of **3a** as an orange oil. A portion was resubjected to chromatography eluting with 5% EtOAc in cyclohexane to obtain the analytical sample as a pale straw-colored oil: IR (neat) $\nu_{max}$ 3080, 3050, 3020, 2920, 2880, 2850, 1700, 1493, 1450, 1085, 1065, 1025, 733, 695 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 7 4-7 2 (m, 20 H), 5.92-5.77 (m, 1 H), 5 32-5.1 (m, 2 H), 5 01 (d, 0 5 H), 4.88-4 5 (m, 6 5 H), 4.4-4.28 (m, 2 H), 4 18-3 63 (m, 4 H), 2.86-2.57 (m, 4 H), 2.08-1 76 (m, 2 H); mass spectrum, m/z 655 ($M^+$+29), 627 ($M^+$+1), 519, 197, 181, 119, 107, 91 (100). Anal Calcd for $C_{38}H_{42}O_4S_2$. C, 72.81; H, 6.75; S, 10.23. Found· C, 73.09; H, 6.78; S, 10.09.

***6,7-Dideoxy-2-[(4-methoxyphenyl)methoxy]-3,4,5-tris-O-(phenylmethyl)-D-gulo/ido-hept-6-enose, Cyclic 1,3-Propanediyl Mercaptals (3b).*** An identical procedure utilizing 25.05 g (47.5 mmol) of bromide 1 and subsequently 6.75 mL (49.8 mmol) of 4-methoxybenzyl chloride gave 23.75 g (76%) of dithianes **3b** contaminated by 7% of methyl-6-deoxy-2,3,4-tris(phenylmethoxy)-α-D-glucopyranoside. A portion of the material was rechromatograph eluting with 4%, then 5% EtOAc in cyclohexane to give the analytical sample: IR (neat) $\nu_{max}$ 2934, 2898, 1514, 1454, 1248, 1086, 1068, 1028, 752, 736, 698 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 7.38-7.22, (m, 17 H), 6.83 (d, 1 H, J=4.6 Hz), 6.80 (d, 1 H, J=4.6 Hz), 5.91-5.77 (m, 1H), 5.32-5.11 (m, 2 H), 4.95 - 4.67 (m, 4 H), 4.64-4.56 (m, 2 H), 4.48 (d, 0 5 H, J=10.7 Hz), 4.40-4.27 (m, 1.5 H), 4.17-3.79 (m, 4.5 H), 3.78 and 3.77 (2s, 3 H), 3.71 (t, 0.5 H, J=5.3 Hz), 2.86-2.56 (m, 4 H), 2.09-1.78 (m, 2 H); mass spectrum, m/z 697 ($M^+$+41), 685 ($M^+$+29), 657 ($M^+$1), 227, 121, 107 (100), 91. Anal. Calcd for $C_{39}H_{44}O_5S_2$: C, 71.31; H, 6.75; S, 9.76. Found: C, 71.21, H, 6.84; S, 9.55.

***6,7-Dideoxy-2,3,4,5-tetrakis-O-(phenylmethyl)-D-ido-hept-6-enose (4a) and 6,7-Dideoxy-2,3,4,5-tetrakis-O-(phenylmethyl)-D-gulo-hept-6-enose (5a).*** A solution of 5.661 g (9.03 mmol) of dithianes **3a** in 11 mL $CH_3CN$ (+ 2 x 3 mL $CH_3CN$ rinses) was added rapidly to a vigorously stirred solution of 3.566 g (26.7 mmol) of N-chlorosuccinimide (NCS) and 5.084 g (29.9 mmol) of $AgNO_3$ in 165 mL aqueous 80% $CH_3CN$. AgCl separated immediately. The mixture was stirred for 45 min. Saturated aqueous $Na_2S_2O_3$, $Na_2CO_3$, and NaCl solutions were added and after 10-15 min the mixture was diluted with EtOAc/$H_2O$ and filtered through filter aid. The organic layer was separated from the filtrate and the aqueous layer was extracted with additional EtOAc. The combined extracts were washed with dilute aqueous NaCl, saturated aqueous NaCl, and dried ($MgSO_4$). The solvent was removed in vacuo and the residue purified by flash chromatography eluting with first 10%, then 15% EtOAc in cyclohexane to give 0.510 g (10.5%) of **5a** and 1.954 g (40%) of the more polar **4a** as colorless oils. For **5a**: IR (neat) $\nu_{max}$ 3060, 3030, 2865, 1732, 1499, 1458, 1090, 1070, 1032, 740, 700 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 9 69 (d, 1 H, J=1.3 Hz), 7.33-7.22 (m, 20 H), 5.89-5.77 (m, 1 H), 5.30 (bs, 1 H), 5.26 (m, 1 H), 4 76 (d, 1 H, J=11.3 Hz), 4.71 (d, 1 H, J=11.3 Hz), 4.64 (d, 1 H, J=11.3 Hz), 4.60 (d, 1 H, J=11.7 Hz), 4.56 (d, 1 H, J=11.6 Hz), 4.55 (d, 1 H, J=11.3 Hz), 4.33 (d, 1 H, J=11.7 Hz), 4.31 (d, 1 H, J=11.6 Hz), 4.14 (dd, 1 H, J=7.3, 5.8 Hz), 4.05-3 99 (m, 2 H), 3 73 (t, 1 H, J=5.5 Hz); $^{13}$NMR ($CDCl_3$) δ 201.57, 138.22, 138.13, 138.01, 137.38, 135.00, 128.42, 128 31, 128 27, 128.22, 127.98, 127.91, 127.88, 127.80, 127.64, 127 58, 127 55, 119.19, 84.24, 81.31, 81.02, 80.70, 75.05, 73.88, 72.46, 70.49; mass spectrum, m/z 537 ($M^+$+1), 429, 337, 181, 107, 91 (100); exact mass calcd for $C_{35}H_{37}O_5$ 537.2641, found 537.2654. For **4a**: IR (neat) $\nu_{max}$ 3055, 3025, 2860, 1725, 1493, 1450, 1110, 1085, 1065, 1025, 733, 695 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 9.59 (s, 1 H), 7.34-7.20 (m, 20 H), 5 84-5.71 (m, 1 H), 5 27 (dd, 1 H, J=10.5, 1.6 Hz), 5.18 (dd, 1 H, J=17.3, 1.2 Hz), 4.73 (d, 1 H, J=12.0 Hz), 4 68 (d, 1 H, J=10 8 Hz), 4.63 (d, 1 H, J=12 Hz), 4.59 (d, 1 H, J=11 Hz), 4.58 (d, 1 H, J=11 8 Hz), 4.52 (d, 1 H, J=11 5 Hz), 4.30 (d, 1 H, J=12.0 Hz), 4 24 (d, 1 H, J=11 7 Hz), 4.01 (t, 1 H, J=4.6 Hz), 3.88 (dd, 1 H, J=7.1, 5.9 Hz), 3.79 (t, 1 H, J=5 2 Hz), 3 67 (d, 1 H, J=4 6 Hz); $^{13}$C NMR

($CDCl_3$) δ 200.82, 138.08, 137.70, 137.30, 135.21, 128.48, 128.38, 128.36, 128.31, 128.23, 128.16, 128.05, 127.90, 127.66, 127.51, 119.12, 81.07, 80.40, 80.22, 79.77, 74.68, 74.15, 72.96, 70.42; mass spectrum, m/z 537 ($M^+$+1), 429, 321, 231, 181, 91 (100); exact mass calcd for $C_{35}H_{37}O_5$ 537.2641, found 537.2598.

***6,7-Dideoxy-2-[(4-methoxyphenyl)methoxy]-3,4,5-tris-O-(phenylmethyl)-D-ido-hept-6-enose (4b) and 6,7-Dideoxy-2-[(4-methoxyphenyl)methoxy]-3,4,5-tris-O-(phenylmethyl)-D-gulo-hept-6-enose (5b).*** Modification of the above procedure used in the preparation of **4a/5a**, employing 1.61 equiv of NCS and 2.01 equiv $AgClO_4$ in aqueous 90% acetone, gave a 67% yield of **4b/5b** after flash chromatography of the crude product through a very short column of silica gel eluting with 15% EtOAc in cyclohexane. Careful rechromatography eluting with 10-12.5% EtOAc in cyclohexane gave **5b** followed by **4b** in a 1:2 ratio. However, the mixture was normally used in the cylcoaddition reactions due to the lability of the aldehydes. For **5b**: $^1H$ NMR ($CDCl_3$) δ 9.68 (s, 1 H), 7.3-7.22 (m, 15 H), 7.18 (d, 2 H, J=8.7 Hz), 6.81 (d, 2 H, J=8.7 Hz), 5.89-5.77 (m, 1 H), 5.27 (d, 1 H, J=15.9 Hz), 5.26 (d, 1 H, J=11.8 Hz), 4.75 (d, 1 H, J=11.3 Hz), 4.70 (d, 1 H, J=11.3 Hz), 4.63 (d, 1 H, J=11.3 Hz), 4.54 (d, 1 H, J=11.5 Hz), 4.54 (d, 1 H, J=11.2 Hz), 4.52 (d, 1 H, J=11.5 Hz), 4.29 (d, 1 H, J=11.6 Hz), 4.28 (d, 1 H, J=11.5 Hz), 4.14 (dd, 1 H, J=7.3, 6.1 Hz), 4.0-4.01 (m, 2 H), 3.73 (t, 1 H, J=5.3 Hz), 3.68 (s, 3 H). For **4b**: $^1H$ NMR ($CDCl_3$) δ 9.58 (s, 1 H), 7.32-7.20 (m, 15 H), 7.16 (d, 2 H, J=8.7 Hz), 6.85 (d, 2 H, J=8.6 Hz), 5.84-5.72 (m, 1 H), 5.28 (dd, 1 H, J=10.4 and 1.8 Hz), 5.18 (ddd, 1 H, J=17.3, 1.8, and 0.7 Hz), 4.68 (d, 1 H, J=10.9 Hz), 4.64 (d, 1 H, J=12.0 Hz), 4.63 (d, 1 H, J=11.5 Hz), 4.60 (d, 1 H, J=10.7 Hz), 4.58 (d, 1 H, J=11.8 Hz), 4.52 (d, 1 H, J=11.5 Hz), 4.26 (d, 1 H, J=11.8 Hz), 4.25 (d, 1 H, J=11.8 Hz), 3.86 (dd, 1 H, J=7.5 and 5.7 Hz), 3 81 (s, 3 H), 3.66 (d, 1 H, J=4.6 Hz).

***(-)-(3aα,4β,5α,6β,7α,7aα)-Octahydro-1-methyl-4,5,6,7-tetrakis(phenylmethoxy)-2,1-benzisoxazole (6a) and (3aα,4α,5β,6α,7β,7aβ)-Octahydro-1-methyl-4,5,6,7-tetrakis(phenylmethoxy)-2,1-benzisoxazole (7a).*** A solution (suspension) of $CH_3NHOH$ (NaCl) in 10 mL $CH_3OH$ [prepared from 230 mg (4.26 mmol) of $CH_3ONa$ and 362 mg (4.33 mmol) of $CH_3NHOH{\cdot}HCl$] was added to a stirred solution of 1.904 g (3.55 mmol) of **4a** in 40 mL $CH_3OH$ and the resulting solution was heated at reflux under nitrogen for 4 h, then allowed to stir at 25°C for 2.5 days. The solution was partially concentrated in vacuo. The residue was diluted with water and extracted twice with EtOAc/cyclohexane. The combined extracts were washed with water, brine, and dried ($MgSO_4$). Concentration in vacuo and flash chromatography of the residue eluting with 23% EtOAc in cyclohexane gave 1.21 g (60%) of *cis* isomer **6a** and 0.321 g (16%) of the more polar *trans* isomer **7a** as white solids. Recrystallization of each from ether/pentane gave **6a** as fine white needles and **7a** as matted white crystals. For **6a**: mp 58.5-61°C; IR (KBr) $\nu_{max}$ 2882, 1496, 1454, 1358, 1114, 1086, 1070, 736, 698 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 7.33-7.25 (m, 20 H), 4.93 (d, 1 H, J=11 Hz), 4.93 (d, 1 H, J=10 9

Hz), 4.83 (d partially obscured by peak at δ 4.815, 1 H), 4.815 (s, 2 H), 4.78 (s, 82 H), 4.71 (d, 1 H, J=11.8 Hz), 4.62 (d, 1 H, J=11.8 Hz), 4.15 (8dd, 1 H, J=9.0, 8.7 Hz), 3.90 (t, 1 H, J=8.7 Hz), 3.82-3.69 (m, 3 H), 3.48 (dd, 1 H, J=9.0, 8.0 Hz), 3.32 (m, 1 H, J=9.0, 8.7, 8.3 Hz), 2.99 (t, 1 H, J=8.3 Hz), 2.68 (s, 3 H); $^{13}$C NMR ($CDCl_3$) δ 138.83, 138.54, 138.36, 138.14, 128.33, 128.26, 128.23, 128.19, 128.10, 128.02, 127.99, 127.86, 127.79, 127.72, 127.69, 127.62, 127.55, 127.44, 127.37, 83.14, 81.10, 77.62, 75.12, 75.04, 74.92, 72.69, 70.04, 67.02, 44.98, 42.34; mass spectrum, m/z 594 ($M^+$+29), 566 ($M^+$+1), 476, 107, 91 (100); $[\alpha]_D^{25}$ -13.3° (c 1.1, $CHCl_3$). Anal. Calcd for $C_{36}H_{39}NO_5$: C, 76.43; H, 6.95; N, 2.48. Found: C, 76.48; H, 7.01; N, 2.36. For **7a**: mp 85-87.5°C; IR (KBr) $\nu_{max}$ 2910, 2854, 1496, 1454, 1356, 1158, 1142, 1130, 1086, 1068, 1050, 736, 696 cm$^{-1}$; $^1$H NMR ($CDCl_3$) δ 7.33-7.24 (m, 20 H), 4.93-4.84 (m, 4 H), 4.84 (d, 1 H, J=10.9 Hz), 4.72 (d, 1 H, J=11.5 Hz), 4.705 (d, 1 H, J=10.9 Hz), 4.55 (d, 1 H, J=11.5 Hz), 4.02 (t, 1 H, J=6.9 Hz), 3.77-3.65 (m, 3 H), 3.59 (dd, 1 H, J=10.5, 7.1 Hz), 3.56 (dd, 1 H, J=10.9, 8.5 Hz), 2.80 (s, 3 H), 2.57 (dq, 1 H, J=7.0, 10.7 Hz), 2.37 (dd, 1 H, J=11.1, 9.4 Hz); $^{13}$C NMR ($CDCl_3$) δ 138.37, 138.31, 137.94, 137.88, 128.47, 128.40, 127.96, 127.92, 127.83, 127.75, 127.68, 127.64, 87.02, 85.93, 82.73, 79.77, 76.10, 75.96, 74.60, 73.87, 70.58, 67.80, 50.41, 47.60; mass spectrum, m/z 594 ($M^+$+29), 566 ($M^+$+1), 476, 107, 91 (100). Anal. Calcd for $C_{36}H_{39}NO_5$: C, 76.43, H, 6.95; N, 2 48. Found: C, 76.35; H, 6.99; N, 2.31.

***(-)-(3aα,4β,5α,6β,7α,7aα)-Octahydro-7-[(4-methoxyphenyl)methoxy]-1-methyl-4,5,6-tris-(phenylmethoxy)-2,1-benzisoxazole (6b), (-)-(3aα,4α,5β,6α,7β,7aβ)-Octahydro-7-[(4-methoxyphenyl)methoxy]-1-methyl-4,5,6-tris(phenylmethoxy)-2,1-benzisoxazole (7b), and (+)-(3aα,4α,5β,6α,7β,7aα)-Octahydro-7-[(4-methoxyphenyl)methoxy]-1-methyl-4,5,6-tris(phenylmethoxy)-2,1-benzisoxazole (8b).*** Using a similar procedure in which the reactants were heated at reflux for 22 h, **8b**, **6b**, and **7b** were obtained in yields of 2.6, 69, and 17%, respectively, after flash chromatography eluting with 25% EtOAc in cyclohexane. *Cis* isomer **8b** was recrystallized from cylcohexane to give fine colorless needles. *Cis* isomer **6b** was obtained as a pale straw-colored oil which partially crystallized upon standing; trituration with pentane gave a white solid. *Trans* isomer **7b** was obtained as matted white needles after recrystallization from ether/pentane. For **6b**: mp 59-61°C; IR (neat) $\nu_{max}$ 3030, 2952, 2884, 1612, 1514, 1496, 1454, 1358, 1302, 1248, 1210, 1172, 1156, 1112, 1070, 1030, 822, 736, 698 cm$^{-1}$; $^1$H NMR ($CDCl_3$) δ 7.38-7.22 (m 17 H), 6.83 (d, 2 H, J=7.4 Hz), 4.9-4.74 (m, 6 H), 4.72 (d, 1 H, J=12 Hz), 4.63 (d, 1 H, J=12 Hz), 4.16 (t, 1 H, J=8.7 Hz), 3.90 (t, 1 H, J=8.5 Hz), 3.82-3.67 (m, 3 H), 3.76 (s, 3 H), 3.46 (t, 1 H, J=8.4 Hz), 3.33 (m, 1 H), 2.98 (t, 1 H, J=7.9 Hz), 2.69 (s, 3 H); mass spectrum, m/z 636 ($M^+$+41), 624 ($M^+$+29), 596 ($M^+$+1), 488, 121, 92, 91 (100); $[\alpha]_D^{25}$ -22.7° (c 1.00, $CHCl_3$). Anal. Calcd for $C_{37}H_{41}NO_6$: C, 74.60; H, 6.94; N, 2.35. Found: C, 74.72; H, 6.95; N, 2.19. For **7b**: mp 77-79°C; IR (KBr) $\nu_{max}$ 2910, 1514, 1354, 1250, 1144, 1130, 1062, 1044, 990, 754, 734, 696 cm$^{-1}$; $^1$H NMR ($CDCl_3$) δ 7.37-7.23 (m, 15 h), 7.20 (d, 2 H, J=8.5 Hz), 6.82 (d, 2 H, J=8.5 Hz), 4.91 (s, 2 H), 4.90 (s, 2 H), 4.78 (d, 1 H, J=10.4 Hz), 4.70 (d,

1 H, J=11.5 Hz), 4.64 (d, 1 H, J=10.4 Hz), 4.54 (d, 1 H, J=11.5 Hz), 4.02 (t, 1 H, J=6.7 Hz), 3.77-3.50 (m, 5 H), 3.71 (s, 3 H), 2.82 (s, 3 H), 2.64-2.50 (m, 1 H), 2.35 (dd, 1 H, J=11, 9.6 Hz); mass spectrum, m/z 624 ($M^+$+29), 596 ($M^+$+1), 137, 121, 107, 92, 91 (100); $[\alpha]_D^{25}$ -12.0° (c 0.61, $CHCl_3$). Anal. Calcd for $C_{37}H_{41}NO_6$: C, 74.60; H, 6.94; N, 2.35. Found: C, 74.50; H, 7.01, N, 2.25. For **8b**: mp 128-133°C; IR(KBr) $\nu_{max}$ 2888, 1614, 1516, 1248, 1108, 1088, 1070, 1038, 1030, 734, 696 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 7.34-7.22 (m, 17 H), 6.85 (d, 2 H, J=8.5 Hz), 4.95 (d, 2 H, J=11.3 Hz), 4.86 (d, 1 H, J=10.8 Hz), 4.82 (d, 1 H, J=11.3 Hz), 4.79 (d, 1 H, J=10.7 Hz), 4.68 (d, 1 H, J=11.3 Hz), 4.62 (d, 2 H, J=12.4 Hz), 4.02-3.95 (m, 2 H), 3.89-3.73 (m, 6 H), 3.56 (t, 1 H, J=9.2 Hz), 3.04 (dd, 1 H, J=5.0, 4.3 Hz), 2.84 (s, 3 H), 2.52-2.44 (m, 1 H); $^{13}C$ NMR ($CDCl_3$) δ 159.49, 139.01, 138.87, 138.78, 130.48, 129.56, 128.59, 128.51, 128.16, 128.10, 127.90, 127.73, 127.63, 127.58, 113.88, 85.80, 81.62, 79.66, 79.51, 75.48, 75.40, 74.98, 73.19, 68.40, 67.66, 55.15, 48.79, 47.54; mass spectrum, m/z 636 ($M^+$ + 41), 624 ($M^+$ + 29), 596 ($M^+$ + 1), 518, 488, 121, 92, 91 (100); $[\alpha]_D^{25}$ + 61.2° (c 0.16, $CHCl_3$). Anal. Calcd for $C_{37}H_{41}NO_6$: C, 74.60; H, 6.94; N, 2.35. Found: C, 74.87; H, 7.04; N, 2.15.

***1,2-Dideoxy-2-(hydroxymethyl)-1-(methylamino)-myo-inositol Hydrochloride (9).*** Hdrogenation of a solution of 826 mg (1.46 mmol) of **6a** in 25 mL HOAc containing 192 mg Pd black as catalyst in a Parr hydrogenation apparatus for 2 days gave, after removal of solvent, addition of dilute HCl, and concentration *in vacuo*, a crystalline solid. Recrystallization from $CH_3CN/CH_3OH$ gave 269 mg (76%) of **9** as pale amber crystalline granules: mp 201° dec; IR (KBr) $\nu_{max}$ 3412, 3298, 3196, 3122, 1616, 1466, 1104, 1080,1044, 1034, 1022, 1014, 946 $cm^{-1}$; $^1H$ NMR (DMSO-$d_6$, $D_2O$) δ 3.82-3.76 (m obscured by HOD peak), 3.66 (dd, 1 H, J=10.9, 8.9 Hz), 3.60 (dd, 1 H, J=11.0, 9.4 Hz), 3.38 (dd, 1 H, J=9.9, 5.1 Hz), 3.14 (dd, 1 H, J=9.6, 9.1 Hz), 2.98 (t, 1 H, J=9.1 Hz), 2.96 (dd, 1 H, J=11.1, 4.4 Hz), 2.63 (s, 3 H), 2.47-2.39 (m, 1 H, J=9.0, 4.4 Hz); $^{13}C$ NMR (DMSO-$d_6$) δ 76.29, 73.10, 70.41, 69.76, 60.63, 55.91, 40.30, 31.99; mass spectrum, m/z 248 ($M^+$+41), 236 ($M^+$+29), 208 ($M^+$+1, 100), 190, 116. Anal. Calcd for $C_8H_{17}NO_5 \cdot HCl$: C, 39.43; H, 7.45; N, 5.75. Found: C, 39.62; H, 7.69; N, 5.59.

***1,2-Dideoxy-2-(hydroxymethyl)-1-(methylamino)-scyllo-inositol (10).*** Similar hydrogenation of a solution of 322 mg (0.569 mmol) of **7a** in 16 mL aqueous 80% HOAc containing 101 mg Pd black for 3 days gave, after flash chromatography eluting with 3:1:2 $CH_3OH$:conc $NH_4OH$:$CH_2Cl_2$ and lyophilization from water, 108 mg (92%) of **10** as a hygroscopic faint beige foam: $^1H$ NMR ($D_2O$) δ 3.89 (dd, 1 H, J=11.6, 3.9 Hz), 3.84 (dd, 1 H, J=11.6, 3.1 Hz), 3.51 (dd, 1 H, J=9.9, 9.2 Hz), 3.44-3.23 (m, 3 H), 2.65 (dd, 1 H, J=11.3, 10.5 Hz), 2.39 (s, 3 H), 1.65 (tt, 1 H, J=10.9, 3.5 Hz); $^{13}C$ NMR ($D_2O$) δ 79.47, 78.12, 75.37, 73.55, 61.96, 61.16, 45.81, 33.58; mass spectrum, m/z 248 ($M^+$+41), 236 ($M^+$+29), 208 ($M^+$+1, 100), 190; exact mass calcd for $C_8H_{18}NO_5$ 208.1185, found 208.1188.

***2-[(Acetyl)amino]-2,3-dideoxy-3-(hydroxymethyl)-1,4,5,6-tetrakis-O-(phenylmethyl)-D-myo-inositol (13).*** A solution (suspension) of $NH_2OH$ (NaCl) in 2 mL $CH_3OH$ [prepared from 99 mg (1.8 mmol) of $CH_3ONa$ and 136 mg (1.96 mmol) of $NH_2OH \cdot HCl$] was added to a stirred

solution of 627 mg (1.17 mmol) of **4a** in 9 mL $CH_3OH$ under nitrogen. After 2 h the solution was concentrated in vacuo and the residue partitioned between EtOAc/cyclohexane and water. The organic layer was washed with water and then concentrated in vacuo. The residue (655 mg) was dissolved in 25 mL toluene and the solution was heated at reflux under nitrogen for 18 h; the toluene was removed in vacuo and replaced with 25 mL xylenes and the solution was heated at reflux for 21 h. Removal of the solvent and flash chromatography of the residue (622 mg) eluting with 26-35% EtOAc/cyclohexane gave 81 mg (13%) of recovered oximes followed by 336 mg (52%) of a 68:32 mixture of **11**/**12** as determined by integration of the multiplets at δ 2.96 and 2 65. Compounds **11** and **12** were partially separable, but their $^1H$ NMR spectra were partially broadened and poorly resolved. The purified less polar isomer from a similar experiment was identified as **11** by conversion to **6** in 57% yield by treatment with 1.2 equiv $CH_3I/K_2CO_3$ in acetone at 25°C for 18 h.

The mixture of **11**/**12** from above was dissolved in 10 mL of aqueous 85% HOAc at 55-60°C and treated with 255 mg (3.90 mmol) activated Zn dust After 30 min, the solution was decanted and partially concentrated in vacuo. The residue was diluted with aqueous NaOH and extracted twice with ether. The combined extracts were washed with water and brine, dried ($MgSO_4$), and concentrated in vacuo. The crude amino alcohols were dissolved with stirring in 5 mL $CH_2Cl_2$ at 0°C containing 197 μL (1 41 mmol) of $Et_3N$, and 100 μL (1 41 mmol) $CH_3COCl$ was added dropwise. After 30 min the solution was diluted with ether, washed with water and brine, and dried ($MgSO_4$). Concentration in vacuo gave 355 mg of a mixture of acetates which were partially separated by careful flash chromatography eluting with first 30:35:35, then 45:20:35 EtOAc/cyclohexane/$CH_2Cl_2$, to give 196 mg of 1-[(acetyl)amino]-2-[(acetyloxy)methyl]-1,2-dideoxy-3,4,5,6-tetrakis-*O*-(phenylmethyl)-*myo*-inositol, mp 88-90°C, and 98 mg of a mixture from which pure **13** was isolated by recrystallization from first cyclohexane/EtOAc, then ether/pentane: mp:173.5-176.5°C; IR (KBr) $\nu_{max}$ 1655, 1544, 1088, 1071, 697 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 7.34-7.23 (m, 20 H), 5.48 (d, 1 H, J=7.6 Hz), 4.95 (d, 1 H, J=10.5 Hz), 4 92 (d, 1 H, J=10.5 Hz), 4.83 (d, 2 H, J=10.6 Hz), 4.81 (d, 1 H, J=10.5 Hz), 4.70 (m, 1 H), 4.59 (d, 1 H, J=11.3 Hz), 4.50 (d, 1 H, J=10.9 Hz), 4.46 (d, 1 H, J=10.5 Hz), 3.97 (m, 1 H), 3.70 (dd, 1 H, J=9.6, 4.9 Hz), 3.65-3.54 (m, 2 H), 3.34-3.20 (m, 2 H), 2.09 (s, 3 H), 1.91 (m, 1 H), 1.65 (bs, 1 H); $^{13}C$ NMR ($CDCl_3$) δ 173 26, 138.32, 137.81, 137 33, 128.55, 128.46, 128.41, 128.04, 127.99, 127.94, 127.91, 127.87, 127.83, 127.74, 85.68, 82 34, 79.60, 78.51, 75.96, 75.36, 71.69, 59.91, 46.04, 44.92, 23.26; mass spectrum, m/z 624 ($M^+$+ 29), 596 ($M^+$+ 1, 100), 578; exact mass calcd for $C_{37}H_{42}NO_6$ 596.3012, found 596 3013 Anal Calcd for $C_{37}H_{41}NO_6$· C, 74.60; H, 6.94; N, 2.35. Found: C, 73 73; H, 6.97; N, 2.28

***(-)-(3aα,4α,5β,6α,7β)-3,3a,4,5,6,7-Hexahydro-4,5,6,7-tetrakis(phenylmethoxy)-2,1-benzisoxazole (14a) and (+)-(3aα,4β,5α,6β,7α)-3,3a,4,5,6,7-Hexahydro-4,5,6,7-tetrakis(phenylmethoxy)-2,1-benzisoxazole (15a).*** A solution (suspension) of $NH_2OH$ (NaCl) in 5 mL $CH_3OH$ [prepared from 313 mg (5.79 mmol) of $CH_3ONa$ and 424 mg (6.10 mmol) of $NH_2OH·HCl$] was added to a stirred solution of 1.954 g (3 64 mmol) of **4a** in 15 mL $CH_3OH$ under nitro-

gen. After 18 h the solution was concentrated in vacuo and the residue partitioned between EtOAc/cyclohexane and water. The organic layer was washed with water then concentrated in vacuo. The residue (2.00 g) was dissolved in 45 mL $CH_2Cl_2$ and the solution cooled to 0°C. To the vigorously stirred solution was added 9.7 mL of commercial bleach. The reaction mixture was allowed to stir at 25°C for 3 days, then diluted with water and extracted with EtOAc/cyclohexane. The extracts were washed with water and then concentrated in vacuo to give 1.99 g of semi-solid. After recrystallization of the crude product mixture from hexane/EtOAc, 918 mg (46%) of **14a** was obtained as colorless crystals. Flash chromatography of the mother liquor eluting with 13% EtOAc in cyclohexane gave 577 mg (29%) of **15a** as a colorless oil and a mixture of **14a/15a** from which 128 mg (6.4%) of additional **14a** was isolated after recrystallization from hexane/EtOAc. For **14a**: mp 117.5-119.5°C; IR (KBr) $\nu_{max}$ 3032, 2890, 2872, 1498, 1454, 1356, 1132, 1092, 1070, 738, 698 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 7.41-7.23 (m, 20 H), 5.04 (d, 1 H, J=11.5 Hz), 4.98 (d, 1 H, J=10.7 Hz), 4.94 (d, 1 H, J=10.7 Hz), 4.84 (d, 1 H, J=11.5 Hz), 4.83 (d, 1 H, J=10.7 Hz), 4.82 (d, 1 H, J=10.7 Hz), 4.67 (d, 1 H, J=11.5 Hz), 4.60 (d, 1 H, J=11.5 Hz), 4.44 (dd, 1 H, J=10.3, 8.5 Hz), 4.36 (m, 1 H), 3.89 (t, 1 H, J=8.5 Hz), 3 72-3.62 (m, 2 H), 3.47-3.40 (m, 1 H), 3.36-3.26 (m, 1 H); $^{13}C$ NMR ($CDCl_3$) δ 154.57, 138.23, 138.17, 137.82, 137.56, 128.55, 128.40, 128.38, 128.34, 128.11, 128.06, 128.05, 128.01, 127.86, 127.83, 127.74, 127.73, 127.70, 84.90, 83.69, 81.16, 77.38, 76.16, 76.05, 74.63, 73.19, 72.77, 52.44; mass spectrum, m/z 590 ($M^+$+41), 578 ($M^+$+29), 550 ($M^+$+1), 107, 91 (100); $[\alpha]_D^{25}$ -35.6° (c 0.95, $CHCl_3$). Anal. Calcd for $C_{35}H_{35}NO_5$: C, 76.48; H, 6.42; N, 2.55. Found: C, 76.44; H, 6.47; N, 2 46. For **15a**: IR ($CHCl_3$ film) $\nu_{max}$ 3030, 2886, 1496, 1454, 1104, 1072, 1028, 736, 698 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 7.34-7.18 (m, 20 H), 4.67 (d, 1 H, J=11.9 Hz), 4.65 (d, 1 H, J=12.1 Hz), 4.64 (d, 1 H, J=11.7 Hz), 4.63 (d, 1 H, J=11 9 Hz), 4.49 (bs, 1 H), 4.47 (d, 1 H, J=12.1 Hz), 4.43 (d, 1 H, J=12 1 Hz), 4.41 (d, 1 H, J=11.7 Hz), 4.36 (d, 1 H, J=12.1 Hz), 4.35-4.32 (m, 2 H), 4.01 (m, 1 H), 3.86 (td, 1 H, J=10.5, 5.1 Hz), 3.83 (t, 1 H, J=4.0 Hz), 3.76 (dt, 1 H, J=1.8, 4.5 Hz), $^{13}C$ NMR ($CDCl_3$) δ 154.60, 137.81, 137.76, 137.63, 128.34, 127.90, 127.86, 127.83, 127.76, 127.72, 127.67, 79.05, 75.57, 75.52, 72.56, 72.48, 71.62, 71.41, 70.74, 69.02, 46.28; mass spectrum, m/z 550 ($M^+$ + 1), 442, 107, 91(100); $[\alpha]_D^{25}$ + 33.8° (c 1.23, $CHCl_3$). Anal. Calcd for $C_{35}H_{35}NO_5$· C, 76.48; H, 6.42; N, 2.55. Found: C, 76.44; H, 6 41; N, 2.48.

***(-)-(3aα,4α,5β,6α,7β)-3,3a,4,5,6,7-Hexahydro-7-[(4-methoxyphenyl)methoxy]-4,5,6-tris-(phenylmethoxy)-2,1-benzisoxazole (14b).*** Using a similar procedure in which a 3·1 mixture of aldehydes **4b** and **5b** were utilized as starting materials, 18% of **17b** and 35% of **14b** were isolated after flash chromatography eluting with **13**, then 15% EtOAc in cyclohexane. For **14b**: mp 133-135°C; IR (KBr) $\nu_{max}$ 2881, 1511, 1247, 1158, 1132, 1091, 1070, 737, 699 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 7.35-7.22 (m, 17 H), 6.82 (d, 2 H, J=8.7 Hz), 4.96 (d, 1 H, J=10.9 Hz), 4.96 (d, 1 H, J=10.6 Hz), 4.93 (d, 1 H, J=10.2 Hz), 4.82 (d, 2 H, J=10.4 Hz), 4.80 (d, 1 H, J=10.8 Hz), 4.60 (d, 1 H, J=11.3 Hz), 4.58 (d, 1 H, J=11.5 Hz), 4.42 (dd, 1 H, J=10 4, 8.5 Hz), 4.33 (m, 1 H), 3.89 (t, 1 H, J=8.5 Hz), 3 73 (s, 3 H), 3.71-

3.60 (m, 2 H), 3.47-3.39 (m, 1 H), 3.33-3.22 (m, 1 H); $^{13}C$ NMR ($CDCl_3$) δ 159.58, 154.87, 138.43, 138.31, 137.97, 129.96, 129.86, 129.78, 128.66, 128.52, 128.45, 128.23, 128.16, 128.10, 127.99, 127.85, 127.80, 113.83, 84.80, 83.58, 81.06, 76.92, 76.03, 75.96, 74.51, 72.72, 72.64, 55.05, 52.22; mass spectrum, m/z 608 ($M^+$+29), 580 ($M^+$+1), 137, 121 (100), 107, 92, 91; $[\alpha]_D^{25}$ -34.6° (c 1.1, $CHCl_3$). Anal. Calcd for $C_{36}H_{37}NO_6$: C, 74.59; H, 6.43; N, 2.42. Found: C, 74.79; H, 6.54; N, 2.34.

***(+)-(3aα,4α,5β,6α,7α,7aα)-Octahydro-1-methyl-4,5,6,7-tetrakis(phenylmethoxy)-2,1-benzisoxazole (16).*** Using the same procedure for the preparation of **6-8**, **16** was obtained as a near colorless oil in 67% yield after flash chromatography eluting with 25% EtOAc in cyclohexane: IR (neat) $\nu_{max}$ 2872, 1454, 1092, 1074, 1028, 736, 698 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 7.36-7.22 (m, 20 H), 4.81 (d, 1 H, J=11.4 Hz), 4.68 (d, 1 H, J=12.2 Hz), 4.63 (d, 1 H, J=12.2 Hz), 4.61 (d, 1 H, J=11.6 Hz), 4.58 (d, 1 H, J=11.7 Hz), 4.56 (d, 2 H, J=11.3 Hz), 4.52 (d, 1 H, J=11.8 Hz), 4.07 (dd, 1 H, J=8.7, 6.7 Hz), 3.86 (dd, 1 H, J=6.9, 3.9 Hz), 3.80 (dd, 1 H, J=3.9, 2.0 Hz), 3.71 (dd, 1 H, J=6.1, 2.1 Hz), 3.69 (dd, 1 H, J=10.6, 7.5 Hz), 3.68 (dd, 1 H, J=8.6, 3.5 Hz), 2.92 (m, 2 H), 2.67 (s, 3 H); $^{13}C$ NMR ($CDCl_3$) δ 138.51, 138.36, 138.31, 138.11, 128.39, 128.34, 127.80, 127.75, 127.69, 127.63, 83.92, 80.98, 77.61, 77.22, 74.06, 72.49, 72.31, 69.58, 69.27, 46.77, 45.46; mass spectrum, m/z 606 ($M^+$ + 41), 594 ($M^+$ + 29), 566 ($M^+$ + 1), 107, 92, 91(100); exact mass calcd for $C_{36}H_{40}NO_5$ 566.2906, found 566.2858; $[\alpha]_D^{25}$ + 50.5° (c 0.78, $CHCl_3$). Anal. Calcd for $C_{36}H_{39}NO_5$: C, 76.43; H, 6.95; N, 2.48. Found: 76.94; H, 6.94; N, 2.40.

***(+)-(3aα,4α,5β,6α,7α)-3,3a,4,5,6,7-Hexahydro-4,5,6,7-tetrakis(phenylmethoxy)-2,1-benzisoxazole (17a).*** Using the same procedure for the preparation of **14/15**, **17a** was obtained as white crystals in 82% yield after flash chromatography eluting with 17.5% EtOAc in cyclohexane. Recrystallization from ether/pentane gave **17a** as white granules: mp 90.5-93°C; IR (KBr) $\nu_{max}$ 3032, 2924, 2872, 1496, 1454, 1358, 1098, 1074, 1046, 1028, 854, 736, 696 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 7.41-7.21 (m, 20 H), 5.03 (d, 1 H, J=10.7 Hz), 4.83 (d, 1 H, J=11.8 Hz), 4.82 (d, 1 H, J=10.4 Hz), 4.63 (d, 2 H, J=12.4 Hz), 4.58-4.56 (m, 2 H), 4.51 (d, 1 H, J=3.5 Hz), 4.46 (d, 1 H, J=12.4 Hz), 4.35 (dd, 1 H, J=10.7, 8.5 Hz), 4.15 (t, 1 H, J=9.3 Hz), 3.82 (t, 1 H, J=8.5 Hz), 3.52 (td, 1 H, J=10.4, 8.5 Hz), 3.44 (dd, 1 H, J=9.8, 3.5 Hz), 3.35 (dd, 1 H, J=9.8, 9.0 Hz); $^{13}C$ NMR ($CDCl_3$) δ 154.66, 138.54, 137.99, 137.65, 136.89, 128.48, 128.40, 128.36, 128.32, 128.15, 127.99, 127.83, 127.78, 127.60, 82.19, 81.93, 80.85, 76.02, 74.41, 73.35, 72.39, 70.92, 68.85, 50.83; mass spectrum, m/z 590 ($M^+$+41), 578 ($M^+$+29), 550 ($M^+$+1,100), 107, 91; $[\alpha]_D^{25}$ +47.7° (c 0.93, $CHCl_3$). Anal. Calcd for $C_{35}H_{35}NO_5$: C, 76.48; H, 6.42; N, 2.55. Found: C, 76.60, H, 6.39; N, 2.44.

***(+)-(3aα,4α,5β,6α,7α)-3,3a,4,5,6,7-Hexahydro-7-[(4-methoxyphenyl)methoxy]-4,5,6-tris(phenylmethoxy)-2,1-benzisoxazole (17b).*** Using a similar procedure, **17b** was obtained in 76% yield after purification by flash chromatography eluting with 17% EtOAc in cyclohexane. Recrystallization from cyclohexane gave **17b** as matted white crystals: mp

118-120°C; IR (KBr) $\nu_{max}$ 2932, 2884, 1512, 1454, 1244, 1098, 1076, 1028, 858, 734, 696 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 7.39-7.23 (m, 17 H), 6.88 (d, 2 H, J=8.6 Hz), 5.03 (d, 1 H, J=10.6 Hz), 4.84 (d, 1 H, J=11.5 Hz), 4.82 (d, 1 H, J=10.6 Hz), 4.60 (d, 1 H, J=11.5 Hz), 4.59 (d, 1 H, J=12.1 Hz), 4.55 (s, 2 H), 4.50 (d, 1 H, J=3.5 Hz), 4.40 (d, 1 H, J=12.1 Hz), 4.36 (dd, 1 H, J=10.7, 8.5 Hz), 4.13 (dd, 1 H, J=9.5, 9.0 Hz), 3.82 (t, 1 H, J=8.5 Hz), 3.81 (s, 3 H), 3.52 (td, 1 H, J=10.4, 8.5 Hz), 3.44 (dd, 1 H, J=9.8, 3.5 Hz), 3.34 (dd, 1 H, J=9.8, 9.0 Hz); $^{13}C$ NMR ($CDCl_3$) δ 159.76, 155.08, 138.78, 138.23, 137.88, 130.48, 129.04, 128.69, 128.55, 128.35, 128.20, 128.04, 127.97, 127.82, 113.92, 82.26, 81.92, 80.79, 76.04, 74.43, 73.32, 72.25, 70.45, 68.17, 55.16, 50.76; mass spectrum, m/z 620 ($M^+$+41), 608 ($M^+$+29), 580 ($M^+$+1), 137, 121, 107, 91 (100), 79; $[\alpha]_D^{25}$ +55.1° (c 1.08, $CHCl_3$). Anal. Calcd for $C_{36}H_{37}NO_6$: C, 74.59; H, 6.43; N, 2.42. Found: C, 74.55, H, 6.39; N, 2.33.

***(3aα,4α,5β,6α,7α,7aβ)-Octahydro-1-methyl-4,5,6,7-tetrakis(phenylmethoxy)-2,1-benzisoxazole (18).*** To a stirred solution of 773 mg (1.41 mmol) of **17a** in 8 mL 99% $CH_3NO_2$ under nitrogen was added 237 mg (1.60 mmol) of trimethyloxonium tetrafluoroborate. After 1 h an additional 42 mg (0.28 mmol) of Meerwein's salt was added and the solution was stirred for 2 h. Concentration in vacuo gave 1.007 g of tacky pale amber glass. An ice cold solution of 114 mg (3.01 mmol) of $NaBH_4$ in 10 mL EtOH was added to 890 mg (1.25 mmol) of the glass with swirling and ice bath cooling. The stirred solution was allowed to warm to 25°C overnight. The excess $NaBH_4$ was quenched with HOAc and the reaction mixture was diluted with aqueous KOH and extracted with several portions of EtOAc. The combined extracts were washed with brine, dried ($MgSO_4$), and concentrated in vacuo to give 692 mg of a pale yellow oil. This was combined with 196 mg of material from similar reductions and purified by flash chromatography on silica gel eluting with first 17.5%, then 30% EtOAc in cyclohexane to give, along with 320 mg (35%) of **16** as a colorless oil, 180 mg (20%) of the more polar **18** as a white solid: $^1H$ NMR ($C_6D_6$) δ 7.49 (d, 2 H, J=7.3 Hz), 7.36 (m, 4 H), 7.24-7.05 (m, 14 H), 4.98 (d, 1 H, J=11 Hz), 4.96 (d, 1 H, J=12 Hz), 4.82 (d, 1 H, J=11.1 Hz), 4.72 (d, 1 H, J=12 Hz), 4.61 (d, 1 H, J=11.9 Hz), 4.49 (d, 1 H, J=11.9 Hz), 4.47 (s, 2 H), 4.22 (dd, 1 H, J=9.2, 8.5 Hz), 4.11 (pseudo t, 1 H, J=3.3 Hz), 3.74 (bs, 1 H), 3.44-3.39 (m, 2 H), 3.305 (dd, 1 H, J=10.2, 8.5 Hz), 3.27 (dd, 1 H, J=9.2, 2.7 Hz), 2.51 (s, 3 H), 1.78 (bd, 1 H, J=9.2 Hz); $^{13}C$ NMR ($C_6D_6$) δ 139.92, 139.26, 139.07, 128.57, 128.38, 128.31, 128.23, 128.11, 127.99, 127.93, 127.86, 127.76, 127.68, 127.42, 84.54, 83.47, 81.12, 75.83, 73.97, 73 24, 72.51, 72.05, 70.90, 68.64, 46.90, 44.71.

***1,6-Dideoxy-6-(hydroxymethyl)-1-(methylamino)-myo-inositol (19).*** Hydrogenation of a solution of 180 mg (0.318 mmol) of **18** in 10 mL of aqueous 80% HOAc containing 54 mg Pd black in a Parr shaker for 3 days gave 54 mg of crude material. Flash chromatography eluting with 3:1:2 $CH_3OH$: conc $NH_4OH$:$CH_2Cl_2$ gave 33 mg of colorless oil which was dissolved in 3 mL aqueous HOAc at 45°C and treated with Zn dust for 1.5 h. Concentration in vacuo and rechromatography gave 24 mg of **19** as a colorless oil: $^1H$ NMR ($D_2O$, external

DSS) δ 4.24 (t, 1 H, J=2.7 Hz), 3.91 (dd, 1 H, J=11.5, 3.0 Hz), 3.83 (dd, 1 H, J=11.5, 5.2 Hz), 3.60 (pseudo t, 1 H, J=9.7 Hz), 3.39 (dd, 1 H, J=10.1, 2.9 Hz), 3.27 (dd, 1 H, J=10.8, 9.2 Hz), 2.78 (dd, 1 H, J=11.6, 2.6 Hz), 2.45 (s, 3 H), 1.77 (m, 1 H); mass spectrum, m/z 248 ($M^+$+41), 236 ($M^+$+29), 208 ($M^+$+1, 100), 190; exact mass calcd for $C_8H_{18}NO_5$ 208.1185, found 208.1187.

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