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Free-radical mediated synthesis of enantiomerically pure, highly functionalized inositols from carbohydrates

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Abstract

We report the synthesis, free-radical cyclization of precursors 1,2,7-trideoxy-7-iodo-3,4:5,6-di-*O*-isopropylidene-D-*gluco*-hept-1-enitol (**1**), methyl 7-*O*-acetyl-6-*O*-benzyl-8-bromo-2,3,8-trideoxy-4,5-*O*-isopropylidene-D-*gluco*-oct-2-enonate (**2**) and 5-*O*-acetyl-4-*O*-benzyl-6-bromo-6-deoxy-2,3-*O*-isopropylidene-D-glucose-*O*-benzyloxime (**3**), readily prepared from D-glucose, and some selected transformations of the carbocycles obtained from these intermediates. In compound **1** we have installed a terminal double bond and an iodide as radical acceptor and leaving group, respectively. Compounds **2** and **3** are ε-bromo aldehydes substituted with α,β-unsaturated ester and oxime ether functions as radical traps, respectively. The tributyltin hydride mediated ring closure of these radical precursors have afforded a series of interesting, diverse and highly functionalized carbocycles which can be considered useful building blocks for the synthesis of branched-chain cyclitols, aminocyclitols and aminoconduritols. In these processes, a good chemical yield and high stereoselectivity has been found in the newly formed stereocenters. Particularly interesting has been the finding that the stereochemical outcome of the free-radical cyclization is independent of the ratio of isomers (*E* or *Z*) in oxime ether **3**. These results show the power and the state of art of this strategy for the stereocontrolled synthesis of enantiomerically pure inositols from carbohydrates.

Keywords: Carbocyclization; Free-radicals; Tributyltin hydride; Inositols; Carbohydrates

1. Introduction

During the last 13 years we have developed a series of new, free-radical based methodologies[1–4] for the synthesis of enantiomerically pure, highly functionalized carbocycles ('inositols') from carbohydrates.[5,6]

In this paper we describe some of our recent developments in the free-radical cyclization of acyclic, conveniently functionalized radical precursors.[5] We report here the synthesis and free-radical cyclization of the radical precursors **1**–**3** (Schemes 1 and 2), and some selected subsequent transformations of the carbocycles obtained. In compound **1** (Scheme 1), we have installed a terminal double bond and an iodide, as radical acceptor and leaving group, respectively. Compounds **2** and **3** (Scheme 2) are ε-bromo aldehydes substituted with α,β-unsaturated ester and oxime ether functions, respectively. These radical precursors should afford a series of interesting, diverse and highly functionalized inositols, useful building blocks for the synthesis of branched-chain cyclitols, aminocyclitols and aminoconduritols.[7]

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2. Results and discussion

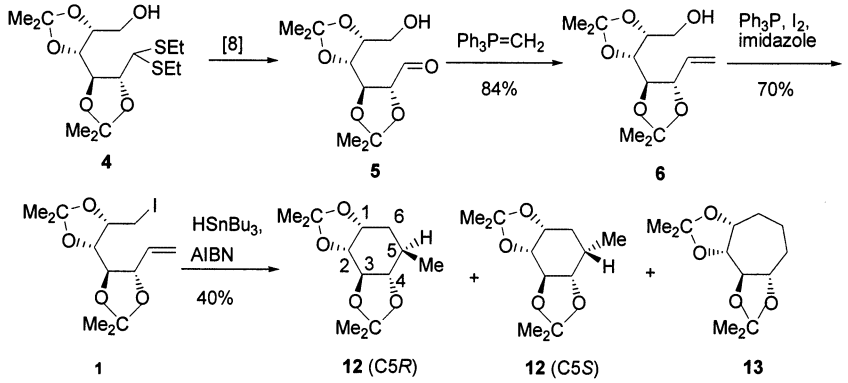
Synthesis of the radical precursors **1**–**3**.— The synthesis of **1** has been achieved from alcohol **4** (Scheme 1). After aldehyde deprotection as described,[8] to give aldehyde **5**, followed by Wittig reaction, final iodination of alcohol **6**, under Garegg's conditions,[9] afforded iodide **1**.

The synthesis of the radical precursor **2** and **3** has been performed from a common intermediate, aldehyde **11**, under standard conditions, as shown in Scheme 2. This aldehyde has been synthesized from **7**, a very well known building block prepared by us several years ago.[10] This synthetic sequence provided the desired compound after selective acid hydrolysis of the 1,2-*O*-isopropylidene group at C-5 and C-6 to give **8** (70% yield), bromination at C-6 yielding halosugar **9** (61%), acetylation of the hydroxyl at C-5 and final deprotection of the masked aldehyde at C-1 giving aldehyde **11** via compound **10**. These transformations afforded the desired intermediates in good yield and multigram quantities (see Section 3). All new compounds showed good analytical and spectroscopic data.

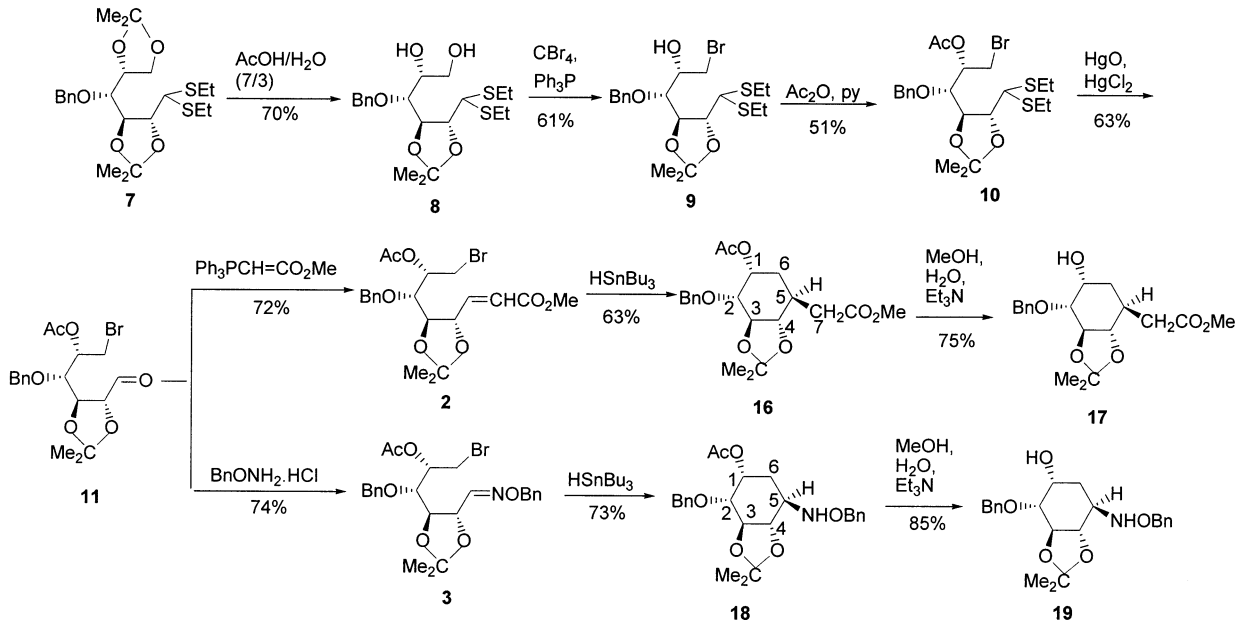
Wittig reaction on aldehyde **11** afforded the expected α,β-unsaturated ester **2**, isolated as an inseparable mixture of *E* (H-2: 6.66 ppm, $J_{1,2}$ 15.6, $J_{2,3}$ 6.0 Hz) and *Z* (H-2: 6.19 ppm, $J_{1,2}$ 11.5, $J_{2,3}$ 8.6 Hz) isomers in 72% combined yield, which were processed together in the next free-radical cyclization.

The synthesis of oxime ether **3** was achieved under the standard conditions in 74% yield from aldehyde **11** (Scheme 2). During the isolation we could obtain, and analyze by ^{1}H NMR spectroscopy, pure isomer *E*-**3** [δ 7.46 (d, $J_{1,2}$ 6.4 Hz, 1 H, H-1)], a mixture of isomers *E*-**3** and *Z*-**3**, in a 1:1 ratio, and pure isomer *Z*-**3** [δ 6.94 (d, $J_{1,2}$ 5.0 Hz, 1 H, H-1)]. This allowed us for the first time in our free-radical projects[11] to study the influence of the geometry at the double bond of the oxime ether in the yield and in the stereochemical outcome of the 6-*exo*-trig[12] free-radical cyclization.

6-exo-*Trig free-radical cyclization of precursors* **1**–**3**.—Free-radical cyclization of precursor **1**, under standard conditions mediated by tributyltin hydride and AIBN, provided carbocycle **12**(C5*R*), unidentified product **a** and unidentified product **b** (Scheme 1), in 40% overall yield and in a 2:0.1:0.4 ratio (determined by coupled GLC–MS analysis in the crude reaction mixture), respectively. After column chromatography, we were able to isolate major resulting product, carbocycle **12**(C5*R*), in 86% diastereomerically pure form. After extensive spectroscopic analysis we could analyze the relevant vicinal coupling constant around carbon C-5 ($J_{4,5}$ 10.0 Hz); this is a typical data for axial(H-4)–axial(H-5) protons, which allowed us to assign as *R* the absolute configuration at C-5. In summary, compound **12**(C5*R*) was the expected 6-*exo*-trig cyclization derivative. We have hypothesized that the other two detected minor compounds resulting in the carbocyclization reaction, products **a** and **b**, possibly corresponded to the other two possible isomeric cyclization products: the epimer at C-5, **12**(C5*S*), and the 7-endo product, **13**. This



Scheme 1.



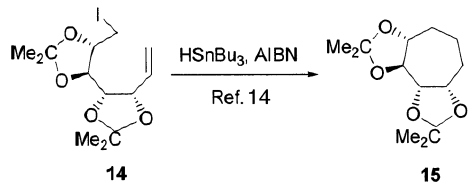
Scheme 2.

was based on the comparative analysis of the mass spectra corresponding to these products, obtained in the coupled GLC–MS experiment. These two products showed almost identical mass spectrum [similar to **12**(C5*R*) mass spectrum], but unfortunately, no unequivocal proof could be obtained about their real identity. Independently of the exact nature of these secondary products, the present carbocyclization has been highly stereo- and regioselective, the major isomer being the 6-*exo*-trig product and the C5*R* isomer, [**12**(C5*R*)].

The stereochemical outcome of this process is quite similar and follows the expected trends observed in our previous results in related substrates during the 6-*exo*-trig free-radical cyclization reactions.[11] According to Beckwith,[13] major isomer results from the free-radical cyclization of the radical species in a chair-like conformation with most of the substituents in preferred pseudo-equatorial orientation.

The formation of the exclusive 6-*exo*-trig product in this case was rather surprising in view of the Redlich's results on the cyclization of radical precursor **14** to give carbocycle **15** (Scheme 3).[14] This is indeed an unique 7-*endo*-trig ring case closure in a sugar derivative. Apparently, this result proves that for the final result of a free-radical cyclization not only is important the presence of the isopropylidene protecting groups for defining the course of the radical cyclization, but the relationship between the stereogenic sequence of the asymmetric carbons and the location of the carbon centered radical and the radical trap. In compound **1** the primary radical is vicinal to a syn-isopropylidene group, while in Redlich's example, in compound **14**,[14] the primary radical is vicinal to an anti-isopropylidene group.

These results moved us to test the free-radical cyclization of precursor **2** (Scheme 2). It was of interest to see whether a simple isopropylidene group, of anti configuration and located vicinal to the carbon that becomes the radical acceptor, could efficiently direct the stereochemical outcome of the process. The free-radical cyclization of this precursor, under the usual conditions, afforded only **16** (Scheme 2) in 63% yield, diastereomerically pure at newly formed stereocenter. The basic



Scheme 3.

hydrolysis of **16** gave alcohol **17** in 75% yield. The stereochemistry at the newly formed stereocenter in **16** was easily established by analysis of the ^{1}H NMR spectrum and selective ^{1}H–^{1}H decoupling experiments. Doing that, and as expected, for a chair-like conformation, we analyzed proton H-4 at 3.07 ppm, with typical axial–axial vicinal coupling constants ($J_{3,4}$ 9.0, $J_{4,5\alpha}$ 10.8 Hz), which allowed us to establish as *S* the absolute configuration at C-5. Similar data and identical conclusions were also obtained from the analysis of **17**. In summary, the stereochemical outcome of this cyclization was the same which we have observed in other previous studies,[5] and clearly indicates that the presence of only one isopropylidene group at C-2 and C-3 is enough for a total control of the stereochemistry during the ring closure. An additional bonus, due to the type of the radical acceptor, was the absence of endo cyclization products.

The free-radical cyclization of a C–N double bond-containing radical acceptor (the oxime ether **3**) (Scheme 2) was very interesting. Cyclization of the mixture of oximes *E*-**3** + *Z*-**3**, in a 1:1 ratio, using the slow addition of reagents technique (see Section 3), afforded **18** in poor yield (20%) accompanied with other more complex products whose structure could not be determined. When the cyclization was performed with pure precursor (*E*)-**3** in the standard conditions, but at 0.01 M in toluene, and using the 'one-pot' addition technique, only **18** was obtained but in a poor yield (27%). Finally, for precursor (*Z*)-**3** in the standard conditions, but at 0.05 M in toluene, and using again the 'one-pot' addition technique, only **18** was obtained in a good yield (73%). This compound, after basic hydrolysis, afforded alcohol **19** in 85% yield (Scheme 2). Compounds **18** and **19** showed analytical and spectroscopic data in good agreement with these structures. Careful analysis of the ^{1}H NMR spectrum of derivative **18** along with selective ^{1}H–^{1}H decoupling experiments allowed us to assign the chemical shifts and determine relevant coupling constants for configurational determination ($J_{5,6\beta}$ 11.0 Hz). This value clearly showed that the configuration at the newly formed stereocenter was *R*. In addition, selective NOE experiments showed strong effects between H-2 and H-1/H-4, between H-5 and H-3, and between H-4 and H-6β. In summary, in spite of the moderate chemical yield for the cyclization, this ring closure has been always completely stereoselective giving the expected β-substituted isomer at C-5, in agreement with the cyclization of precursor **2** (see above). We have also observed that the stereoselectivity of the cyclization is independent of the *E*/*Z* ratio in the precursor, obtaining always the same pure major isomer. This is a fact that Bartlett and colleagues could demonstrate for the 5-*exo*-trig free-radical cyclization of precursors derived from sugars having oxime ethers as radical traps,[15] but a conclusion that we could not demonstrate until now in our similar and pioneered 6-*exo*-trig free-radical cyclizations on sugar templates.

In summary, these results prove that the free-radical cyclization strategy is one of the most efficient and convenient methods for the synthesis of differently substituted and functionalized inositols.

3. Experimental

General methods.—Reactions were monitored by TLC using precoated silica gel aluminum plates containing a fluorescent indicator (E. Merck, 5539). Detection was done by UV (254 nm) followed by charring with sulfuric–AcOH spray, 1% aq $KMnO_4$ solution or 0.5% phosphomolybdic acid in 95% EtOH. Anhydrous Na_2SO_4 was used to dry organic solutions during work-ups and the removal of solvents was carried out under vacuum with a rotary evaporator. Flash-column chromatography was performed using silica gel 60 (230–400 mesh, E. Merck) and hexane–EtOAc mixtures as eluent unless otherwise stated. ^{1}H spectra were recorded with a Varian VXR-300(400)S spectrometers, using tetramethylsilane as an internal standard and ^{13}C NMR spectra were recorded with a Bruker WP-200-SY. Values with (*) can be interchanged. The coupled GLC–MS experiment was run in a column. Compounds **4**, **5** and **7** were prepared according to published procedures.[8,10]

General method for free-radical cyclization.—To a solution of the precursor in toluene (0.02 M), previously deoxygenated by bubbling Ar into the solution, under Ar, at reflux, a solution of AIBN (0.5 equiv) and Bu_3SnH (2 equiv) was slowly added via syringe pump in the indicated time. The mixture was heated until complete reaction, the solvent was removed, the residue dissolved in a mixture of 1:1 ethyl ether–15% aq solution of KF and stirred vigorously overnight. Then, the organic layer was separated, dried, filtered, evaporated and the residue was submitted to chromatography (eluting with hexane–EtOAc mixtures) to give the product.

1,2-Dideoxy-3,4:5,6-di-O-*isopropylidene*-D-gluco-*hept-1-enitol* (**6**).—To a suspension of hemiacetal **5** (1.15 g, 4.41 mmol) and methyltriphenylphosphonium bromide (4.91 g, 13.7 mmol, 3.1 equiv) in dry THF (7 mL), cooled at −20 °C, under Ar, *n*-BuLi (5.5 mL, 8.8 mmol, 1.6 M in hexane) was slowly added. The mixture was warmed at rt, stirred for 2 h and quenched with an aq satd solution of ammonium chloride. Then, the mixture was diluted with CH_2Cl_2, washed with an aq satd solution of $NaHCO_3$, brine, dried, filtered and evaporated. The residue was submitted to flash chromatography (7:3 hexane–EtOAc) to give **6** (960 mg, 84%): oil; $[\alpha]_D^{25}$ −12° (*c* 0.23, $CHCl_3$); IR (film) *v* 3460 (OH), 2986, 2936 1380, 1216, 1050 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 5.79 (ddd, $J_{1,2}$ 17.3, $J_{1',2}$ 10.1, $J_{2,3}$ 7.6 Hz, 1 H, H-2), 5.41 (dm, 1 H, H-1), 5.28 (dm, 1 H, H-1′), 4.45 (dd, $J_{3,4}$ 8.6 Hz, 1 H, H-3), 4.23 (dt, $J_{6,7}$ 5.2, $J_{5,6}$ 6.7 Hz, 1 H, H-6), 4.05 (dd, $J_{4,5}$ 1.7 Hz, 1 H, H-5), 3.76 (t, $J_{7,OH}$ 5.2 Hz, 2 H, 2 H-7), 3.68 (dd, 1 H, H-4), 2.84 (t, 1 H, OH), 1.50, 1.42 (6 H), 1.35 [3 s, $2 \times OC(CH_3)_2$, 12 H]; ^{13}C NMR (75 MHz, $CDCl_3$): δ 134.4 (C-2), 120.1 (C-1), 109.8, 108.8 [2 C, $2 \times OC(CH_3)_2O$], 79.3 (C-3), 78.2 (C-6), 77.2 (C-5), 73.3 (C-3), 61.3 (C-7), 27.1, 26.8, 26.4, 25.5 [4 C, $2 \times OC(CH_3)_2O$]; EIMS (70 eV): *m*/*z* 243 ([$M^+ - 15$], 12), 141 (5), 127 (21), 113 (10), 98 (36), 69 (52), 43 (100). Anal. Calcd for $C_{13}H_{22}O_5$: C, 60.45; H, 8.58. Found: C, 60.30; H, 8.81.

1,2,7-Trideoxy-7-iodo-3,4:5,6-di-O-*isopropylidene*-D-gluco-*hept-1-enitol* (**1**).—A solution of **6** (116 mg, 0.45 mmol) in dry toluene (5.4 mL), under Ar and at reflux, was treated with triphenylphosphine (284 mg, 1.1 mmol, 2.4 equiv), imidazole (74 mg, 1.1 mmol, 2.4 equiv) and iodine (172 mg, 0.7 mmol, 1.5 equiv). After 30 min the mixture was cooled, and the mixture was washed with a 10% aq solution of $NaHCO_3$ and brine. The organic phase was separated, dried, the solvent was evaporated, and the residue submitted to chromatography (99:1 hexane–EtOAc) affording **1** (115 mg, 70%): oil; $[\alpha]_D^{25}$ −9° (*c* 0.57, $CHCl_3$); IR (film) *v* 2985, 2934, 1455, 1380, 1216, 1061 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 5.82 (ddd, $J_{1,2}$ 17.4, $J_{1',2}$ 10.1, $J_{2,3}$ 7.3 Hz, 1 H, H-2), 5.43 (dm, 1 H, H-1), 5.31 (dm, 1 H, H-1′), 4.51 (q, $J_{6,7} = J_{5,6} = J_{6,7'}$ 7.0 Hz, 1 H, H-6), 4.39 ($J_{3,4}$ 8.5 Hz, 1 H, H-3), 4.08 (dd, $J_{4,5}$ 1.7 Hz, 1 H, H-5), 3.77 (dd, 1 H, H-4), 3.38 (dd, $J_{7,7'}$ 2.5 Hz, 2 H, 2 H-7), 1.52, 1.43 (6 H), 1.38 [3 s, $2 \times OC(CH_3)_2$, 12 H]; ^{13}C NMR (75 MHz, $CDCl_3$): δ 134.6 (C-2), 119.9 (C-1), 109.8, 109.3 [2 C, $2 \times OC(CH_3)_2O$], 79.1 (C-3), 78.4 (C-4), 77.9 (C-6), 74.2 (C-5), 27.2, 26.9, 26.7, 25.5 [4 C, $2 \times OC(CH_3)_2O$], 2.5 (C7); EIMS (70 eV): *m*/*z* 368 ([$M^{\bullet+}$], 1), 353 ([$M^+ - 15$], 12), 241 (13), 183 (23), 155 (10), 127 (52), 108 (21), 98 (100). Anal. Calcd for $C_{13}H_{21}IO_4$: C, 42.40; H, 5.75. Found: C, 42.36; H, 5.81.

Carbocyclization of radical precursor **1**.—Compound **1** (88.6 mg, 0.24 mmol) was submitted to the procedure in Section 3.2 (time for the slow addition: 9 h, and 24 for additional reaction time) to give Fraction (**A**) [15 mg of a mixture of **12**(C5*R*) ($t_r = 16.84$ min, in the GLC–MS experiment) and product **a** ($t_r = 19.27$ min, in the GLC–MS experiment), in a 93:7 ratio, according to GLC] and Fraction (**B**) [6 mg of a mixture of **12**(C5*R*), product **b** ($t_r = 17.91$ min, in the GLC–MS experiment), and product **a**, in a 51:10:39 ratio, respectively]. Total yield: 21 mg (40%). **12**(C5*R*) (86% diastereomerically pure) [1L(1,2,4/3,5)-1,2:3,4-di-*O*-isopropylidene-5-*C*-methylcyclohexan-1,2,3,4-tetrol]: oil; $[\alpha]_D^{25}$ −44° (*c* 0.52, $CHCl_3$); IR (film) *v* 2984, 2927, 1456, 1381, 1232, 1055 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 4.29 (td, $J_{1,2} = J_{1,6\beta}$ 4.9, $J_{1,6\alpha}$ 1.7 Hz, 1 H, H-1), 4.13 (dd, $J_{2,3}$ 9.0 Hz, 1 H, H-2), 3.52 (t, $J_{3,4}$ 9.2 Hz, 1 H, H-3), 2.94 (t, $J_{4,5}$ 10.0 Hz, 1 H, H-4), 2.26 (ddd, $J_{6\alpha,6\beta}$ 15.5, $J_{5,6\alpha}$ 4.7 Hz, 1 H, H-6α), 1.75 (m, 2 H, H-5,

H-6β), 1.51, 1.42, 1.41, 1.35 [4 s, 2 × $OC(CH_3)_2O$], 1.05 (d, *J* 6.5 Hz, 3 H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 110.1, 108.9 [2 C, 2 × $OC(CH_3)_2O$], 81.8 (C-3), 81.0 (C-4), 78.6 (C-2), 74.5 (C-1), 35.3 (C-6), 28.6, 26.9, 26.2 (2 C) [4 C, 2 × $OC(CH_3)_2O$], 17.8 (CH_3); EIMS (70 eV): *m*/*z* 227 ([$M^+ - 15$], 100), 169 (39), 127 (39), 109 (61), 81 (92). Anal. Calcd for $C_{13}H_{22}O_4$: C, 64.44; H, 9.15. Found: C, 64.37; H, 9.31.

4-O-*Benzyl*-*2,3*-O-*isopropylidene*-D-*glucose diethyl dithioacetal* (**8**).—Compound **7** (9.6 g, 21 mmol) was treated with 7:3 AcOH–water (50 mL) at rt overnight. The solvent was removed and the residue was submitted to chromatography (4:1 hexane–EtOAc) to give diol **8** (6.5 g, 70%): oil; $[\alpha]_D^{25}$ −178° (*c* 0.11, $CHCl_3$); IR (film) *v* 3600–3100, 3030, 3010, 2920, 1425, 1345, 1225, 1050 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.36–7.34 (m, 5 H, $OCH_2C_6H_5$), 4.70 (q, *J* 11.3 Hz, 2 H, $OCH_2C_6H_5$), 4.42–4.37 (m, 2 H), 4.01–3.97 (m, 1 H), 3.88 (d, $J_{1,2}$ 4.6 Hz, 1 H, H-1), 3.81–3.77 (m, 3 H), 3.10–3.00 (br s, 1 H, OH), 2.80–2.60 (m, 4 H, 2 × SCH_2CH_3), 2.65–2.58 (br s, 1 H, OH), 1.45, 1.43 [2 s, $OC(CH_3)_2O$], 1.23 (t, *J* 7.5 Hz, 6 H, 2 × SCH_2CH_3); EIMS (70 eV): *m*/*z* 308 (16), 297 (8), 223 (12), 136 (20), 135 (37), 91 (100). Anal. Calcd for $C_{20}H_{32}O_5S_2$: C, 57.66; H, 7.74; S, 15.39. Found: C, 57.47; H, 7.61; S, 15.22.

4-O-*Benzyl*-*6*-*bromo*-*6*-*deoxy*-*2,3*-O-*isopropylidene*-D-*glucose diethyl dithioacetal* (**9**).—Compound **8** (1.5 g, 3.6 mmol) was dissolved in dry THF (45 mL) and treated with triphenylphosphine (1.88 g, 7.2 mmol, 2 equiv) and carbon tetrabromide (3.5 g, 10.8 mmol) at rt for 45 min. The solvent was removed and the residue was submitted to chromatography (3:2 hexane–EtOAc) to give bromide **9** (1.0 g, 61%): oil; $[\alpha]_D^{25}$ −16° (*c* 0.69, $CHCl_3$); IR (film) *v* 3560–3200, 3025, 2970, 1465, 1390, 1220, 1130 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.37–7.35 (m, 5 H, $OCH_2C_6H_5$), 4.69 (q, *J* 11.3 Hz, 2 H, $OCH_2C_6H_5$), 4.41 (d, *J* 3.3 Hz, 2 H), 4.12 (q, *J* 6.0 Hz, 1 H, H-5), 3.03 (d, *J* 6.0 Hz, 1 H, OH), 2.77–2.61 (m, 4 H, 2 × SCH_2CH_3), 1.46, 1.43 [2 s, $OC(CH_3)_2O$], 1.25 (t, *J* 7.3 Hz, 6 H, 2 × SCH_2CH_3); EIMS (70 eV): *m*/*z* 479–481 ([$M^+ + 1$], 2), 451 (4), 419 (28), 385 (28), 325 (24), 301 (51), 287 (33), 250 (26), 171 (34), 91 (100). Anal. Calcd for $C_{20}H_{31}BrO_4S_2$: C, 50.10; H, 6.52; S, 13.37. Found: C, 50.22; H, 6.31; S, 13.45.

5-O-*Acetyl*-*4*-O-*benzyl*-*6*-*bromo*-*6*-*deoxy*-*2,3*-O-*isopropylidene*-D-*glucose diethyl dithioacetal* (**10**).—Compound **9** (1.0 g, 2.1 mmol) was treated with Ac_2O (9.5 mL) and pyridine (9.4 mL) at rt overnight. The solvent was removed and the residue was submitted to chromatography (17:3 hexane–EtOAc) to give bromide **10** (590 mg, 51%): oil; $[\alpha]_D^{25}$ −7° (*c* 0.55, $CHCl_3$); IR (film) *v* 3020, 2980, 1720, 1465, 1340, 1250–1180, 1100–1025 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.35–7.26 (m, 5 H, $OCH_2C_6H_5$), 5.23 (ddd, $J_{5,6}$ 7.2, $J_{5,4}$ 2.8, $J_{5,6'}$ 4.4 Hz, 1 H, H-5), 4.76 (q, *J* 11.4 Hz, 2 H, $OCH_2C_6H_5$), 4.33 (dd, $J_{2,3}$ 7.7, $J_{1,2}$ 5.7 Hz, 1 H, H-2), 4.23 (dd, $J_{4,3}$ 7.3 Hz, 1 H, H-4), 3.97–3.93 (m, 2 H, H-6′, H-3), 3.83 (d, 1 H, H-1), 3.67 (dd, $J_{6,6'}$ 11.5 Hz, 1 H, H-6), 2.76–2.71 (m, 4 H, 2 × SCH_2CH_3), 2.13 (s, 3 H, $OCOCH_3$), 1.43, 1.38 [2 s, 6 H, $OC(CH_3)_2O$], 1.25 (t, *J* 7.5 Hz, 6 H, 2 × SCH_2CH_3); EIMS (70 eV): *m*/*z* 459–461 (2, 2), 4512–414 (4, 4), 385–387 (4, 4), 327–329 (7, 7), 135 (51), 91 (100). Anal. Calcd for $C_{22}H_{33}BrO_5S_2$: C, 50.67; H, 6.38; S, 12.29. Found: C, 50.44; H, 6.31; S, 12.17.

Methyl 7-O-*acetyl*-*6*-O-*benzyl*-*8*-*bromo*-*2,3,8*-*trideoxy*-*4,5*-O-*isopropylidene*-D-*gluco*-*oct*-*2*-*enonate* (**2**).—Compound **10** (590 mg, 1.13 mmol) was dissolved in 18:1 acetone–water. Then, mercuric oxide (490 mg, 2.26 mmol) and mercuric chloride (614 mg, 2.26 mmol) were added. The mixture was refluxed overnight. The flask was cooled, the solvent evaporated, and the residue was dissolved in CH_2Cl_2, washed with a 5% aq solution of KI, brine, dried, filtered, and evaporated. The crude was submitted to chromatography (3:1 hexane–EtOAc) to give aldehyde **11** (298 mg, 63%) which was immediately used. To an aliquot of this aldehyde (228.3 mg, 0.55 mmol), dissolved in dry toluene (10 mL), methoxycarbonyltriphenylphosphorane (273 mg, 0.82 mmol, 1.5 equiv) was added, and the mixture was stirred for 24 h at rt. The solvent was removed and the residue was submitted to chromatography (7:3 hexane–EtOAc) to give **2** (186.6 mg, 72%), as an inseparable mixture

of *E* and *Z* isomer in a 1.4:1 ratio: oil; IR ($CHCl_3$) *v* 2986, 1726, 1438, 1373, 1071 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.44–7.28 (m, 5 H, $OCH_2C_6H_5$), 6.66 (dd, $J_{2,3}$ 15.6, $J_{3,4}$ 6.0 Hz, 1 H, H-3(*E*)), 6.19 (dd, $J_{2,3}$ 11.5, $J_{3,4}$ 8.6 Hz, 1 H, H-3(*Z*)), 5.98 (dd, $J_{2,4}$ 1.0 Hz, 1 H, H-2(*Z*)), 5.90 (dd, $J_{2,4}$ 1.3 Hz, 1 H, H-2(*E*)), 5.70 (ddd, $J_{4,5}$ 15.8 Hz, 1 H, H-4(*Z*)), 5.28–5.14 (m, 2 H), 4.84 (q, *J* 11.1 Hz, 2 H, (*Z*)-$OCH_2C_6H_5$), 4.71 (q, *J* 11.5 Hz, 2 H, (*Z*)-$OCH_2C_6H_5$), 4.45 (ddd, $J_{4,5}$ 14.3 Hz, 1 H, H-4(*E*)), 3.98–3.60 (m, 3 H), 3.73 (s, 3 H, (*E*)-CO_2CH_3), 3.68 (s, 3 H, (*Z*)-CO_2CH_3), 2.10 (s, 3 H, (*E*)-$OCOCH_3$), 2.09 (s, 3 H, (*Z*)-$OCOCH_3$), 1.40, 1.38, 1.37 (3 s, $OC(CH_3)_2$); EIMS (70 eV): *m*/*z* 455–457 ([$M^+ - 15$], 8/8), 247 (25), 167 27), 127 (54), 91 (100). Anal. Calcd for $C_{21}H_{27}BrO_7$: C, 53.51; H, 5.77. Found: C, 53.55; H, 5.63.

Carbocyclization of radical precursor **2**.—Compound **2** (146.3 mg, 0.3 mmol) was submitted to the procedure in Section 3.2 by adding quickly $HSnBu_3$ (161 μL, 0.6 mmol, 2 equiv) and AIBN (24.6 mg, 0.5 equiv) in one single operation, to give product **16** (77 mg, 63%) after chromatography (4:1 hexane–EtOAc). Compound **16** [1L(1,2,4/3,5)-1-*O*-acetyl-2-*O*-benzyl-3,4-*O*-isopropylidene-5-*C*-methoxycarbonylmethylcyclohexan-1,2,3,4-tetrol]: oil; IR (film) *v* 2986, 1738, 1437, 1372, 1241, 1092 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.32–7.21 (m, 5 H, $OCH_2C_6H_5$), 5.46 (q, $J_{1,2} = J_{1,6\alpha} = J_{1,6\beta}$ 3.0 Hz, 1 H, H-1), 4.75 (q, *J* 12.5 Hz, 2 H, $OCH_2C_6H_5$), 3.83 (t, $J_{3,4} = J_{2,3}$ 9.5 Hz, 1 H, H-3), 3.64 (s, 3 H, CO_2CH_3), 3.56 (dd, 1 H, H-2), 3.07 (dd, $J_{4,5\alpha}$ 10.8 Hz, 1 H, H-4), 2.65 (dd, $J_{7,7'}$ 15.2, $J_{7,5\alpha}$ 4.0 Hz, 1 H, H-7), 2.50–2.00 (m, 4 H, H-5α, H-7′, 2 H-6), 2.08 (s, 3 H, $OCOCH_3$), 1.43, 1.40 [2 s, $OC(CH_3)_2O$]; ^{13}C NMR (75 MHz, $CDCl_3$): δ 172.1, 170.2 ($OCOCH_3$, CO_2CH_3), 137.9–127.5 ($OCH_2C_6H_5$), 110.3 [$OC(CH_3)_2O$], 80.3 (C-3)*, 78.5 (C-2), 77.8 (C-4)*, 71.0 ($OCH_2C_6H_5$), 68.4 (C-1), 51.6 (CO_2CH_3), 36.7 (C7)*, 33.6 (C-6)*, 32.3 (C-5), 26.9, 26.8 [2 C, $OC(CH_3)_2O$], 21.1 ($OCOCH_3$); EIMS (70 eV): *m*/*z* 392 (2), 377 ([$M^+ - 15$], 6), 334 (6), 303 (17), 226 (19), 168 (46), 91 (100). Anal. Calcd for $C_{21}H_{28}O_7$: C, 64.27; H, 7.19. Found: C, 64.37; H, 7.11.

1L(1,2,4/3,5)-2-O-Benzyl-3,4-O-isopropylidene-5-C-methoxycarbonylmethylcyclohexan-1,2,3,4-tetrol (**17**).—Compound **16** (33 mg, 0.084 mmol) was treated with a mixture of 1:4:5 triethylamine, water and MeOH (1 mL) at rt for 2 days. The solvent was removed and the crude was submitted to chromatography (7:3 hexane–EtOAc) to give **17** (22 mg, 75%): oil; $[\alpha]_D^{25}$ −9° (*c* 0.14, $CHCl_3$); IR (film) *v* 3454, 2930, 1739, 1436, 1372, 1237, 1096 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.32–7.21 (m, 5 H, $OCH_2C_6H_5$), 4.77 (q, *J* 12.0 Hz, 2 H, $OCH_2C_6H_5$), 4.09 (m, $W_{h/2}$ 1.4 Hz, 1 H, H-1), 3.89 (t, $J_{3,4} = J_{2,3}$ 9.5 Hz, 1 H, H-3), 3.67 (s, 3 H, $-CO_2CH_3$), 3.54 (dd, $J_{2,1}$ 3.4 Hz, 1 H, H-2), 3.08 (dd, $J_{4,5\alpha}$ 10.7 Hz, 1 H, H-4), 2.66 (dd, $J_{7,7'}$ 15.0, $J_{7,5\alpha}$ 4.4 Hz, 1 H, H-7), 2.60–2.12 (m, 5 H, OH, H-5α, H-7′, 2 H-6), 1.43, 1.40 [2 s, $OC(CH_3)_2O$]; EIMS (70 eV): *m*/*z* 168 (10), 140 (9), 107 (9), 91 (100). Anal. Calcd for $C_{19}H_{26}O_6$: C, 65.13; H, 7.48. Found: C, 65.29; H, 7.55.

5-O-Acetyl-4-O-benzyl-6-bromo-6-deoxy-2,3-O-isopropylidene-D-glucose O-benzyloxime (**3**).—Aldehyde **11** (443 mg, 1.06 mmol) was dissolved in CH_2Cl_2 (19 mL) and treated with *O*-benzylhydroxylamine hydrochloride (192 mg, 1.1 mmol, 1.1 equiv), pyridine (91 mg, 1.1 mmol, 1.1 equiv) and water (ten drops). The mixture was stirrred at rt for 24 h. The mixture was diluted with more CH_2Cl_2, washed with brine, dried, filtered and the solvent was removed. The residue was submitted to chromatography (19:1 hexane–EtOAc) to give pure compound (*E*)-**3** (120 mg), (*E*) + (*Z*)-**3** (229 mg, in a 1:1 ratio) and pure (*Z*)-**3** (156 mg). Total: 405 mg (74% yield). (*E*)-**3**: oil; IR (film) *v* 3064, 3032, 2987, 1745, 1455, 1372, 1242, 1083, 1025 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.46 (d, $J_{1,2}$ 6.4 Hz, 1 H, H-1), 7.37–7.31 (m, 10 H, $2 \times OCH_2C_6H_5$), 5.15–5.10 (m, 1 H, H-5), 5.12 (s, 2 H, $OCH_2C_6H_5$), 4.67 (q, *J* 11.3 Hz, 2 H, $OCH_2C_6H_5$), 4.58 (dd, $J_{2,3}$ 8.1, $J_{1,2}$ 6.3 Hz, 1 H, H-2), 4.11 (dd, $J_{4,3}$ 3.6 Hz, 1 H, H-3), 3.87 (dd, $J_{5,6}$ 2.8, $J_{6,6'}$ 11.3 Hz, 1 H, H-6), 3.73 (dd, $J_{4,5}$ 4.8 Hz, 1 H, H-4), 3.70 (dd, $J_{5,6'}$ 6.5 Hz, 1 H, H-6′), 2.08 (s, 3 H, $OCOCH_3$), 1.41, 1.38 [2 s, 6 H, $OC(CH_3)_2O$]; ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.7 ($OCOCH_3$), 147.6 (C-1), 137.8-127.9 ($2 \times OCH_2C_6H_5$), 110.0 [$OC(CH_3)_2O$], 79.0, 76.5, 76.2–74.8 ($2 \times OCH_2C_6H_5$), 73.9, 73.4, 32.0

(C-6), 26.5–26.4 [OC(CH_3)$_2$O], 20.8 (OCOCH_3); EIMS (70 eV): m/z 506–504 ([$M^+ - 15$], 2, 1), 464–462 (1, 1), 296 (13), 234 (10), 181 (9), 91 (100). Anal. Calcd for $C_{25}H_{30}BrNO_6$: C, 57.70; H, 5.81; N, 2.69. Found: C, 57.47; H, 5.61; N, 2.77. (*Z*)-**3**: oil; IR (film) ν 3064, 3032, 2987, 1745, 1455, 1372, 1242, 1083 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.38–7.18 (m, 10 H, 2 × $OCH_2C_6H_5$), 6.94 (d, $J_{1,2}$ 5.0 Hz, 1 H, H-1), 5.20–5.13 (m, 2 H, H-5, H-2), 5.16–5.09 (2 d, J 11.4 Hz, 2 H, $OCH_2C_6H_5$), 4.44 (q, J 11.5 Hz, 2 H, $OCH_2C_6H_5$), 4.09 (dd, $J_{3,4}$ 1.8, $J_{3,2}$ 7.3 Hz, 1 H, H-3), 3.92 (m, 1 H, H-4), 3.91 (dd, $J_{5,6}$ 7.1, $J_{6,6'}$ 11.6 Hz, 1 H, H-6), 3.61 (dd, $J_{5,6'}$ 6.5 Hz, 1 H, H-6′), 2.12 (s, 3 H, $OCOCH_3$), 1.39 [s, 6 H, OC(CH_3)$_2$O]; ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.6 ($OCOCH_3$), 151.6 (C-1), 137.7–127.1 (2 × $OCH_2C_6H_5$), 110.7 [$OC(CH_3)_2O$], 79.9, 77.1, 76.9–74.6 (2 × $OCH_2C_6H_5$), 73.9, 71.4, 32.4 (C-6), 26.3 [2 C, OC(CH_3)$_2$O], 20.9 (OCOCH_3); EIMS (70 eV): m/z 464–462 (1, 1), 428–430 (1, 1), 370–372 (2, 2), 354 (4), 296 (13), 234 (9), 181 (8), 91 (100). Anal. Calcd for $C_{25}H_{30}BrNO_6$: C, 57.70; H, 5.81; N, 2.69. Found: C, 57.65; H, 5.90; N, 2.53.

Carbocyclization of radical precursor **3**

*Carbocyclization of radical precursor (*E*)-***3*** + (Z)-***3*** (1:1).* This mixture (159 mg, 0.3 mmol) was treated according Section 3.2 (slow addition in 6 h, and additional heating at 100 °C for 10 h) to give **18** (26 mg, 20%).

*Carbocyclization of radical precursor pure (*E*)-***3***.* This compound (105 mg, 0.2 mmol) was treated according to Section 3.2 (0.01 M in toluene, 'one-pot' addition, and additional heating at 100 °C for 2 h) to give (**18**) (24 mg, 27%).

*Carbocyclization of radical precursor pure (Z)-***3***.* This compound (134 mg, 0.26 mmol) was treated according to Section 3.2 (0.05 M in toluene, 'one-pot' addition, and additional heating at 100 °C for 5 h) to give **18** (86 mg, 73%). [1*L*(1,2,4/3,5)-1-*O*-Acetyl-2-*O*-benzyl-5-benzyloxyamino-3,4-*O*-isopropylidenecyclohexan-1,2,3,4-tetrol] (**18**): oil; $[\alpha]_D^{25}$ −23° (*c* 1.05, $CHCl_3$); IR (film) ν 3031, 2985, 1739, 1497, 1454, 1372, 1238, 1093 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.35–7.31 (m, 10 H, 2 × $OCH_2C_6H_5$), 5.88 (br s, 1 H, $NHOCH_2C_6H_5$), 5.55 (dt, $J_{1,2} = J_{1,6\alpha}$ 3.2, $J_{1,6\beta}$ 3.0 Hz, 1 H, H-1), 4.69 (q, J 13.2 Hz, 2 H, $OCH_2C_6H_5$), 4.68 (s, 2 H, $OCH_2C_6H_5$), 3.88 (dd, $J_{3,4}$ 10.1, $J_{2,3}$ 10.3 Hz, 1 H, H-3), 3.61 (dd, 1 H, H-2), 3.41–3.33 (m, 2 H, H-4, H-5), 2.20 (dt, $J_{5,6\alpha}$ 3.2, $J_{6\alpha,6\beta}$ 14.7 Hz, 1 H, H-6α), 2.09 (s, 3 H, $OCOCH_3$), 1.60 (ddd, $J_{5,6\beta}$ 11.0 Hz, 1 H, H-6β), 1.47, 1.45 [2 s, 6 H, $OC(CH_3)_2O$]; ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.1 ($OCOCH_3$), 137.8–127.5 (2 × $OCH_2C_6H_5$), 110.9 [$OC(CH_3)_2O$], 77.69 (C-3), 77.64 (C-2), 77.2 (C-4), 77.1–71.1 (2 × $OCH_2C_6H_5$), 68.5 (C-1), 57.1 (C-5), 32.0 (C-6), 26.9, 26.8 [$OC(CH_3)_2O$], 21.1 ($OCOCH_3$); EIMS (70 eV): m/z 441 ([$M^{\bullet+}$], 12), 440 ([$M^+ - 1$], 34), 382 (25), 181 (15), 105 (111), 91 (100). Anal. Calcd for $C_{25}H_{31}NO_6$: C, 68.01; H, 7.08; N, 3.17. Found: C, 67.96; H, 7.18; N, 3.43.

[1L(1,2,4/3,5)-2-O-Benzyl-5-benzyloxyamino-3,4-O-isopropylidenecyclohexan-1,2,3,4-tetrol] (**19**).—Acetate **18** (96.8 mg, 0.22 mmol) was treated with a with a mixture of 1:4:5 triethylamine, water and MeOH (1 mL) at rt for 2 days. The solvent was removed and the crude was submitted to chromatography (7:3 hexane–EtOAc) to give **19** (75 mg, 85% yield): oil; $[\alpha]_D^{25}$ 2° (*c* 0.35, $CHCl_3$); IR (film) ν 3477, 3030, 2929, 1496, 1454, 1371, 1232, 1091, 1027 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.38–7.27 (m, 10 H, 2 × $OCH_2C_6H_5$), 5.80 (br s, 1 H, $NHOCH_2C_6H_5$), 4.76 (q, J 11.9 Hz, 2 H, $OCH_2C_6H_5$), 4.70 (s, 2 H, $OCH_2C_6H_5$), 4.12 (m, 1 H, H-1), 3.93 (t, $J_{3,4} = J_{2,3}$ 9.3 Hz, 1 H, H-3), 3.57 (dd, $J_{2,1}$ 3.3 Hz, 1 H, H-2), 3.41 (dt, $J_{5,4} = J_{5,6\beta}$ 10.7, $J_{5,6\alpha}$ 3.9 Hz, 1 H, H-5), 3.37 (dd, 1 H, H-4), 2.25 (dt, $J_{1,6\alpha}$ 3.9, $J_{6\alpha,6\beta}$ 14.4 Hz, 1 H, H-6α), 1.55–1.48 (m, 1 H, H-6β), 1.45 [s, 6 H, $OC(CH_3)_2O$]; EIMS (70 eV): m/z 350 ([$M^{\bullet+}$], 8), 188 (5), 91 (100). Anal. Calcd for $C_{23}H_{29}NO_5$: C, 69.15; H, 7.32; N, 3.51. Found: C, 69.06; H, 7.27; N, 3.33.

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