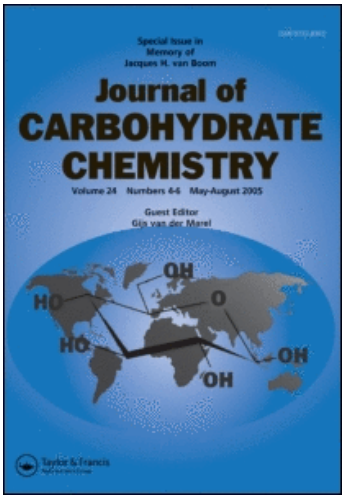

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SYNTHESIS OF C-LINKED SUGAR BUTENOLIDES AND THEIR CONVERSION INTO C-LINKED ISOXAZOLIDINE SACCHARIDES *

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SYNTHESIS OF C-LINKED SUGAR BUTENOLIDES AND THEIR CONVERSION INTO C-LINKED ISOXAZOLIDINE SACCHARIDES*

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ABSTRACT

Synthesis of C-linked isoxazolidines was achieved by addition of nitrone to C-linked sugar butenolides, which in turn were prepared by iodolactonisation on the chiral template derived from diacetone glucose.

Key Words: C-linked sugar butenolides; C-linked isoxazolidine saccharides; iodolactonization; Bioactive carbohydrates

INTRODUCTION

Increased awareness of the vital role played by carbohydrates in natural and disease processes prompted the development of synthetic routes a number of years ago for bioactive carbohydrates.[1] A variety of new glycosubstances which can be either C-saccharides or C-linked saccharides were synthesised as glycosyl mimics,[2–4] for purposes of pharmacological properties evaluation. Butenolides and butanolides, component structures of several natural[5–9] and bioactive[10] compounds and useful build-

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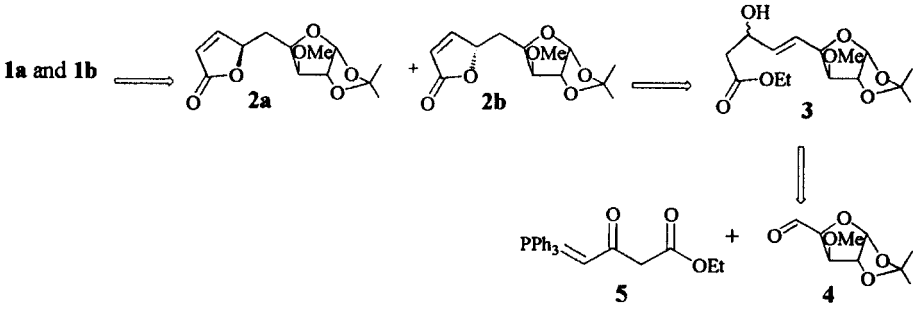
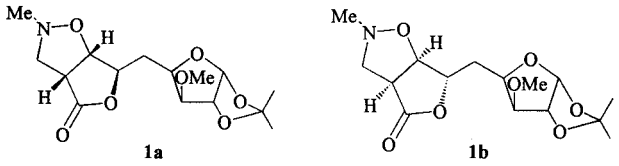


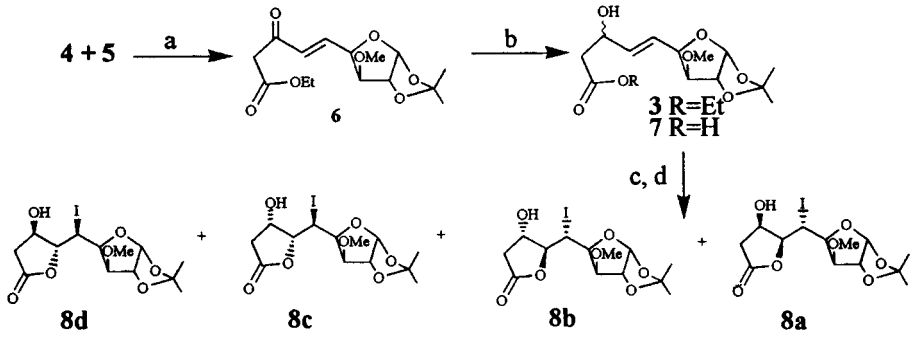
Scheme 1. Retrosynthetic analysis.

ing blocks[11] for the synthesis of several complex natural products, have become important synthetic targets.[11–13] Because of their biological activity[14] as well as structural implications,[15–16] there is an enormous amount of interest in the preparation of bicyclic isoxazolidine[17] compounds. In continuation of our studies on the synthesis of ''new glycosubstances'',[18–26] herein, we report the synthesis of sugar linked butenolides and their conversion into new sugar linked isoxazolidine derivatives.



RESULTS AND DISCUSSION

From the retro synthetic analysis (Scheme 1) of **1a** and **1b**, it was envisaged that the butenolides **2a** and **2b** would be appropriate late stage intermediates, that could



Scheme 2. Reagents: a) benzene, reflux, 5 h; b) $CeCl_3.7H_2O$, $NaBH_4$, MeOH, 0°C-rt, 3 h; c) 1N aq LiOH, DME, 0°C-rt, 5 h; d) I_2, sat. aq $NaHCO_3$, THF, 0°C, 5 h.

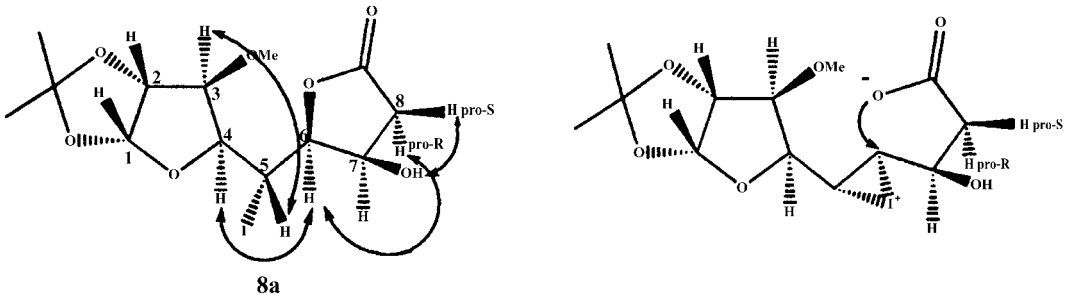
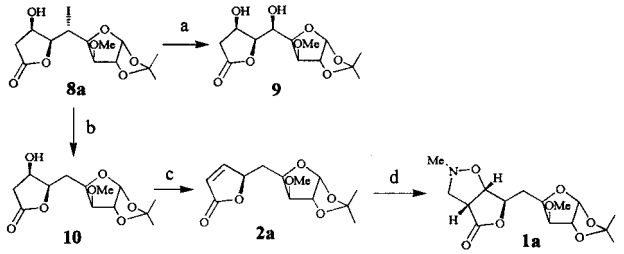


Figure 1. NOE diagram for **8a** and iodonium ion intermediate.

be realized from **3**, which in turn resulted from the condensation of aldehyde **4** and ylide **5**.

Accordingly, aldehyde[27] **4** (Scheme 2), on Wittig olefination with ethyl 3-oxo(triphenylphosphorylidene)butanoate[28] (**5**) in benzene at reflux, gave **6** as an inseparable keto–enol mixture, which on reduction with $CeCl_3.7H_2O$-$NaBH_4$ in MeOH under Luche's[29] conditions afforded **3** as an inseparable mixture. Hydrolysis of **3** with 1 N aq LiOH gave **7**, which on reaction with I_2[30] in the presence of aq $NaHCO_3$ gave a mixture of **8a**–**d**, as judged by TLC analysis. Purification by column chromatography gave one major compound ($R_f = 0.4$) in pure form, while the remaining three isomers were inseparable.

Based on the literature precedents,[18–26] where the iodonium ion formation from the less hindered side and opening of the three membered ring from the opposite side has been described, it was assumed that the major compound should be either **8a** or **8b** (Figure 1). The structure of major compound was assigned as **8a**, by extensive NMR studies. In the ^{1}H NMR spectrum of **8a**, the *trans* orientation of H5 (t, 4.22 ppm) with respect to both H4 and H6 was evident from the large J values between H4–H5 ($J_{4,5} = 10.2$ Hz) and H5–H6 ($J_{5,6} = 9.5$ Hz). The observed NOE between H6–H7, H6–$H8_{pro\text{-}R}$ and H7OH–$H8_{pro\text{-}S}$ unambiguously fixed the stereochemistry at C7 (*R*), while the relative orientation of lactone ring to sugar ring was confirmed from the char-



Scheme 3. Reagents: a) $NaHCO_3$, CH_3CN-H_2O (2:1), reflux, 12 h; b) $NaCNBH_3$, cat. *n*-$BuSnCl_3$, AIBN, *t*-BuOH, reflux, 4 h; c) Ac_2O, Et_3N, CH_2Cl_2, DMAP, rt, 5 h; d) $(CH_2O)n$, MeNHOH.HCl, C_6H_6, reflux, 4.5 h.

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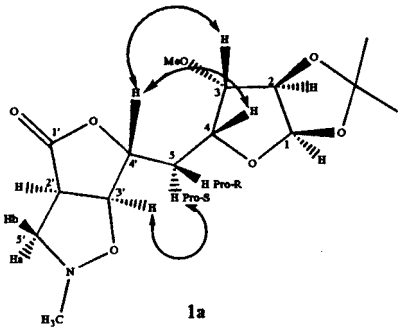
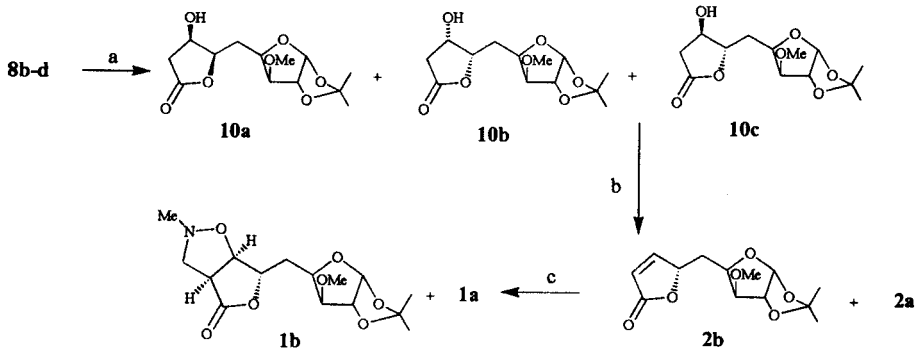


Figure 2. NOE diagram for **1a**.

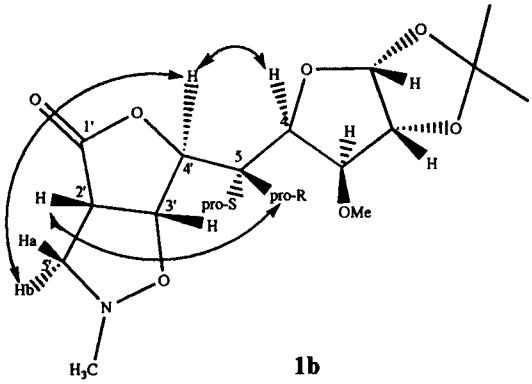
acteristic NOE between H4–H6 and H3–H5 (Figure 1). Lactone **8a** was treated with $NaHCO_3$ in aq CH_3CN at reflux (Scheme 3) to afford C-linked disaccharide **9**.

In a further study, deiodination of **8a** with *n*-Bu_3SnCl (Cat)-$NaCNBH_3$ gave butanolide **10**, which on acetylation (Ac_2O, Et_3N, cat. DMAP) afforded butenolide **2a**. Reaction of **2a** with the nitrone derived from the formaldehyde and CH_3NHOH in benzene at reflux gave isoxazolidine **1a** as a single isomer as judged from the spectral data. $J_{3',4'} \cong 0$ implies that H4′ is *trans* to H3′, while $J_{2',3'} = 7.0$ Hz indicates that H2′ is *cis* to H3′. The two five membered rings are therefore *cis* fused. Some of long distance NOEs are shown in Figure 2. The couplings $J_{4'5pro\text{-}S} = 5.4$, $J_{4,5pro\text{-}S} = 8.0$, $J_{4,5pro\text{-}R} = 5.4$ and $J_{4'5pro\text{-}R} = 5.7$ Hz, indicate absence of a single predominant isomer for **1a**. Unlike **8a**, **1a** might exist in several rotomeric forms about C4–C5 and C4′–C5, resulting in effective averaging of the couplings involving H5a and H5b.

Similarly, a mixture of **8b–d** was subjected to deiodination (Scheme 4) to give **10a–c**, which on acetylation furnished **2a** and **2b** as an inseparable mixture. Finally, reaction of **2a** and **2b** with HCHO–CH_3NHOH furnished **1a** and **1b**, after chromatographic separation. Structure of **1a** was identical to that prepared earlier, while **1b** was found to be epimeric at C-6, C-7 and C-8 to **1a**. $J_{3',4'} \cong 0$ in **1b** also indicates that



Scheme 4. Reagents: a) $NaCNBH_3$, $BuSnCl_3$, cat. AIBN, *t*-BuOH, reflux, 4 h; b) Ac_2O, Et_3N, CH_2Cl_2, DMAP, rt, 5 h; c) $(CH_2O)n$, MeNHOH.HCl, C_6H_6, reflux, 4.5 h.



1b

Figure 3. NOE diagram for **1b**.

the H4′ is *trans* to H3′ while H2′ and H3′ are *cis* with J = 8.4 Hz. Characteristic NOEs like H4–H4′, H2′–$H5_{pro\text{-}R}$ (Figure 3) and the large couplings between $J_{4',5pro\text{-}S} = 9.2$, $J_{4,5pro\text{-}R} = 8.6$ Hz indicate the relative orientation of two rings is such that the sugar and lactone oxygen are in *cis* orientation.

Thus, sugar linked butenolides were synthesized adopting Wittig and iodo lactonisation reactions and converted them into useful new glycosubstances such as C-disaccharide and sugar linked isoxazolidines. Due to the ready availability of reagents, simple reaction conditions and readily extendable functionalities on the new products, the present protocol and the butenolide precursors should find wide applications for the synthesis of several ''new glycosubstances''.

EXPERIMENTAL

General procedure. Solvents were dried over standard drying agents and freshly distilled prior to use. ^{1}H NMR (200 MHz, 400 MHz, 500 MHz) and ^{13}C NMR (50 MHz, 100 MHz, 125 MHz) spectra were recorded in deuteriochloroform solution with tetramethylsilane as an internal reference on Varian Gemini-200 MHz, Unity-400 MHz and INOVA-500 MHz spectrometers and J values are given in Hz. 2D experiments like DQCOSYand NOESY were carried out with 2X192 transitions. The NOESY experiments were performed with mixing time of 0.4 seconds. Optical rotations were measured with a JASCO DIP-370 instrument and $[\alpha]_D$ values are in units of 10^{-1}deg cm^2g^{-1}. Organic solutions were dried over anhydrous Na_2SO_4 and concentrated below 40°C under vacuum. HRMS were recorded on V G Autospec Mass Spectrometer at 5 or 7 K resolution using perfluoro kerosene as an internal reference. Infrared (IR) are reported in wavenumbers (cm^{-1}). The nomenclature mentioned in the experimental section was adopted from ACD/Name version 1.0β, ACD Inc., Toronto, Canada.

Wittig reaction of 4 (synthesis of 6). A mixture of **4** (9.0 g, 44.5 mmol) and **5** (26.06 g, 66.8 mmol) in benzene (100 mL) was heated at reflux for 5 h. The reaction mixture was cooled to room temperature after completion of the reaction and the

solvent removed under vacuum. The residue on purification by column chromatography (silica gel, 60–120 mesh, EtOAc-hexane, 1:9) furnished compound **6** (8.5 g) in 61% yield as an inseparable keto–enol mixture in 6:4 ratio as a syrup. ^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.20–1.35 (m, 6H, CH_3,OCH_2CH_3), 1.52 (s, 3H, CH_3), 3.38 (s, 3H, OCH_3), 3.55 (s, 2H, H-8,8′ of keto form), 3.75 (d, 1H, J 4.2 Hz, H-3), 4.20 (q, 2H, J 6.2 and 13.7 Hz, OCH_2CH_3), 4.52–4.60 (m, 1H, H-2), 4.70–4.80 (m, 1H, H-4), 5.90 (d, 1H, J 4.2 Hz, H-1), 6.12 (d, 1H, J 15.6 Hz, H-6), 6.46 (d, 1H, J 15.6, H-8), 6.62 (dd, 1H, J 5.6 and 15.6 Hz, H-5 of keto form), 6.92 (dd, 1H, J 5.6 and 15.6 Hz, H-5 of enol form), 11.82 (s, 1H, enolic OH); ^{13}C NMR ($CDCl_3$, 200 MHz): 13.9, 14.0, 26.0, 26.6, 47.3, 58.0, 58.1, 60.0, 61.1, 79.3, 79.6, 817, 82.0, 85.5, 91.7, 104.64, 104.8, 111.6, 111.8, 126.2, 129.7, 132.4, 141.2, 166.9, 168.1, 172.6, 191.4; EIMS: *m*/*z* 313 ($M^+ - 1$, 5%), 299 ($M^+ - 15$, 15%), 253 (20%), 196 (35%), 115 (100%), 103 (80%); EI-HRMS: Calculated for $C_{14}H_{19}O_7$ ($M^+ - 15$): 299.113078, found: 299.112039.

Ethyl 3-hydroxy-5-[6-methoxy-2,2-dimethyl-(3a*R*,5*R*,6*S*,6a*R*)perhydrofuro[2,3-*d*][1,3] dioxol-5-yl]-(3*R*/*S*,4*E*)pentenoate (3). A mixture of compound **6** (7.3 g, 24 mmol) and $CeCl_3.7H_2O$ (10.3 g, 27.8 mmol) in methanol (40 mL) was cooled to 0°C and treated with $NaBH_4$ (1.2 g, 34.8 mmol) in portions. The reaction mixture was allowed to stir at room temperature for 3 h. Methanol was removed under vacuum, treated with water (100 mL) and extracted with EtOAc (3×50 mL). Combined organic layers were successively washed with water (50 mL), brine (50 mL), dried (Na_2SO_4) and purified by column chromatography (silica gel, 60–120 mesh, EtOAc-hexane, 1:3) to afford alcohols **3** (5.2 g) in 71% yield as a syrup. $[\alpha]_D - 42.80°$ (*c* 0.5, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.20–1.34 (m, 6H, CH_3,OCH_2CH_3), 1.48 (s, 3H, CH_3), 2.40–2.62 (m, 2H, H-8,8′), 3.36 (s, 3H, OCH_3), 3.54–3.63 (m, 1H, H-3), 4.25 (q, 2H, J 7.5 and 14.7 Hz, OCH_2CH_3), 4.48–4.62 (m, 3H, H–2,4,7), 5.80–5.88 (d, 3H, J 4.2 Hz, H-1,5,6); ^{13}C NMR ($CDCl_3$, 200 MHz): 13.9, 26.0, 26.5, 41.2, 57.9, 60.5, 68.0, 80.1, 81.9, 85.5, 104.5, 111.2, 124.5, 135.2 (2C allylic carbon), 171.7; EIMS: *m*/*z* 301 ($M^+ - 15$, 5%),167 (15%), 155 (60%), 127 (15%), 85 (100%), 43 (75%); EI-HRMS: Calculated for $C_{14}H_{21}O_7$ ($M^+ - 15$): 301.128728, found: 301.128817.

Ethyl 3-hydroxy-5-[6-methoxy-2,2-dimethyl-(3a*R*,5*R*,6*S*,6a*R*)perhydrofuro[2,3-*d*][1,3] dioxol-5-yl]-(3*R*/*S*,4*E*)pentenoic acid (7). A mixture of compound **3** (5.1 g, 16.1 mmol) in DME (40 mL) at 0°C was treated with aq LiOH (40 mL, 1N 40.3 mmol) dropwise and stirred at room temperature. After 5 h the reaction mixture was neutralized with acetic acid, the solvent removed under reduced pressure and the residue extracted with EtOAc (5×50 mL). Combined organic layers were dried (Na_2SO_4) and concentrated under vacuum to afford acids **7** (4.5 g) in 98% yield as a syrup. $[\alpha]_D - 105.6°$ (*c* 0.5, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.30 and 1.50 (2 s, 6H, 2 CH_3), 2.50–2.70 (br s, 2H, H-8,8′), 3.38 (s, 3H, OCH_3), 3.62–3.68 (br s, 1H, H-3), 4.50–4.95 (m, 4H, H-2,4,7,OH), 5.84–5.95 (m, 3H, H-1,5,6); EIMS: *m*/*z* 273 ($M^+ - 15$, 3%), 127 (30%), 85 (100%), 59 (50%), 43 (50%); EI-HRMS: Calculated for $C_{12}H_{17}O_7$ ($M^+ - 15$): 273.097428, found: 273.097537.

Iodolactonisation of 7 (synthesis of 8a–8d). A mixture of **7** (4.4 g, 15.2 mmol) and saturated aqueous $NaHCO_3$ (15 mL) in ether (15 mL) was cooled to 0°C and treated with an ice cold solution of iodine (11.6 g, 45.8 mmol) in THF (15 mL). The flask was

protected from light and the reaction mixture stirred for 5 h at 0°C. After completion of the reaction (TLC, EtOAc-hexane, 1:1, $R_f = 0.5$) it was quenched with saturated aqueous sodium sulfite, diluted with saturated aq $NaHCO_3$ (50 mL) and extracted with ether (2×50 mL). The ethereal layer was washed with brine (60 mL), dried (Na_2SO_4) and solvent removed in vacuum to afford a mixture of compounds **8a**, **8b**, **8c** and **8d** (4.4 g) in 71% overall yield. Purification of residue by column chromatography (silica gel, finer than 200 mesh, EtOAc-hexane, 1:3) first gave a mixture of **8b**, **8c** and **8d** (2.8 g, 44.4%), second eluted was **8a** (1.6 g, 25.3%) as a syrup. **8a**: $[\alpha]_D - 50.80°$ (*c* 0.5, $CHCl_3$); ^1H NMR (DMSO-d_6, 500 MHz): δ 1.27 and 1.42 (2 s, 6H, 2 CH_3), 2.33 (d, 1H, $J_{8pro\text{-}R,8pro\text{-}S}$ 17.2 Hz, H-$8_{pro\text{-}S}$), 2.88 (dd, 1H, $J_{7,8pro\text{-}R}$ 5.1 Hz, H-$8_{pro\text{-}R}$), 3.39 (s, 3H, OCH_3), 3.87 (d, 1H, $J_{3,4}$ 2.9 Hz, H-3), 4.22 (t, 1H, $J_{4,5}$ 10.2 , $J_{5,6}$ 9.5 Hz, H-5), 4.37 (dd, 1H, H-4), 4.51 (ddd, 1H, $J_{6,7}$ 3.3 Hz, H-7), 4.55 (dd, 1H, H-6), 4.69 (d, 1H, $J_{1,2}$ 3.8 Hz, H-2), 5.54 (d, 1H, $J_{7,OH}$ 4.9 Hz, OH), 5.94 (d, 1H, H-1); FAB-MS: *m/z* 415 ($M^+ + 1$, 48%), 399 ($M^+ - 15$, 62%), 357 (60%), 339 (55%), 297 (95%), 169 (100%); mixture of **8b**, **8c** and **8d**: $[\alpha]_D - 31.75°$ (*c* 0.5, $CHCl_3$); ^1H NMR ($CDCl_3$, 200 MHz): δ 1.25 and 1.45 (2 s, 6H, 2 CH_3), 2.33–3.12 (m, 2H, H-8,8′), 3.25, 3.40 and 3.46 (3 s of 1:6:2 ratio integrations, each s 3H, OCH_3), 3.83 and 3.90 (2 d, 2:1 ratio, 1H, $J_{3,4}$ 3.2 and 2.8 Hz, H-3), 4.14–4.60 (m, 1H, H-5), 4.26–4.34 (m, 1H, H-4), 4.40–4.60 (m, 2H, H-4,7), 4.65 (d, 1H, $J_{1,2}$ 4.1 Hz, H-2), 4.80 (m, 1H, H-6), 5.82 and 5.90 (2 d 3:1, 1H, $J_{1,2}$ 4.2 Hz, H-1).

Hydrolysis of iodide 8a (9). A mixture of **8a** (0.5 g, 1.2 mmol) and $NaHCO_3$ (0.101 g, 1.2 mmol) in CH_3CN–H_2O (10 mL, 2:1) was heated at reflux for 12 h. Acetonitrile was removed under vacuum, the residue diluted with EtOAc (60 mL), washed with water (40 mL), brine (40 mL), dried (Na_2SO_4) and concentrated under vacuum. Crude product was purified by column chromatography (silica gel, 60–120 mesh, EtOAc-hexane, 1:1) to afford **9** (0.313 g) in 85% yield as a syrup: $[\alpha]_D - 5.86°$ (*c* 1.16, $CHCl_3$); ^1H NMR ($CDCl_3$, 500 MHz): δ 1.34 and 1.49 (2 s, 6H, 2 CH_3), 1.50 (br s, 2H, 2 OH) 2.59 (dd, 1H, $J_{7,8'}$ 6.8, $J_{8,8'}$ 17.6 Hz, H-8′), 2.88 (dd, 1H, $J_{7,8}$ 7.8 Hz, H-8), 3.48 (s, 3H, OCH_3), 3.95 (d, 1H, $J_{3,4}$ 3.6 Hz, H-3), 4.15 (dd, 1H, $J_{4,5}$ 2.3, $J_{5,6}$ 5.9 Hz, H-5), 4.28 (t, 1H, H-4), 4.30 (t, 1H, $J_{6,7}$ 5.0 Hz, H-6), 4.61 (d, 1H, $J_{1,2}$ 3.8 Hz, H-2), 4.77 (ddd, 1H, H-7), 5.99 (d, 1H, H-1); ^{13}C-NMR ($CDCl_3$, 50 MHz): 26.2, 26.9, 36.9, 57.7, 68.1, 69.7, 78.5, 81.3, 86.3, 86.6, 104.8, 112.3, 174.7; FAB-MS: *m/z* 327 ($M^+ + 23$, 85%), 305 ($M^+ + 1$, 10%), 289 ($M^+ - 15$, 35%), 247 (100%), 229 (45%), 197 (30%), 65 (47%); FAB-HRMS: Calculated for $C_{13}H_{21}O_8$ ($M^+ + 1$): 305.123643, found: 305.123528.

4-Hydroxy-5-[6-methoxy-2,2-dimethyl-(3a*R*,5*R*,6*S*,6a*R*)perhydrofuro[2,3-*d*][1,3]dioxol-5-ylmethyl](4*R*,5*S*)-2H,3H,4H-2-furanone (10). A mixture of **8a** (1.0 g, 2.42 mmol), $NaCNBH_3$ (0.30 g, 4.8 mmol) and $^nBu_3SnCl$ (.078 g, 0.24 mmol) in *tert*-butyl alcohol (1 mL) was heated up to 80°C, then a catalytic amount of AIBN (0.025 g) was added to the mixture and heating was continued for 4 h. Solvent was removed in vacuum and the residue purified by column chromatography (silica gel, 60–120 mesh, EtOAc-hexane, 2:3) to give **10** (0.647 g) in 92% yield as a syrup. $[\alpha]_D - 68.87°$ (*c* 1.1, $CHCl_3$); ^1H NMR ($CDCl_3$, 200 MHz): δ 1.30 and 1.48 (2 s, 6H, 2 CH_3), 2.28 (t, 2H, J 6.9 Hz, H-5,5′), 2.52 (dd, 1H, J 1.3, 15.1 Hz, H-8), 2.75 (dd, 1H, J 5.9, 15.3 Hz, H-8′), 3.13 (br s, 1H, OH), 3.42 (s, 3H, OCH_3), 3.65 (d, 1H, J 3.68 Hz, H-3), 4.40–4.42 (m, 1H, H-4), 4.41–4.52 (m, 1H, H-7), 4.56 (d, 1H, J 4.6 Hz, H-2),

4.59–4.70 (m, 1H, H-6), 5.84 (d, 1H, J 4.6 Hz, H-1); FAB-MS: *m/z* 289 ($M^+ + 1$, 35%), 273 ($M^+ - 15$, 10%), 259 (18%), 176 (12%), 154 (100%), 137 (75%), 120 (15%), 107 (28%); FAB-HRMS: Calculated for $C_{13}H_{21}O_7$ ($M^+ + 1$): 289.128728, found: 289.129833.

5-[6-Methoxy-2,2-dimethyl-(3a*R*,5*R*,6*S*,6a*R*)perhydrofuro[2,3-*d*][1,3]dioxol-5-ylmethyl]-(5*R*)-2H-2-furanone (2a). A solution of **10** (0.6 g, 2.08 mmol) in CH_2Cl_2 (12 mL) was sequentially treated with Et_3N (0.87 mL, 6.25 mmol), Ac_2O (0.29 mL, 3.12 mmol) and catalytic DMAP (0.025 g) and stirred at room temperature for 5 h. The reaction mixture was diluted with CH_2Cl_2 (5 mL) and washed with water (30 mL), brine (30 mL), dried (Na_2SO_4) and concentrated under vacuum. The residue was purified by column chromatography (silica gel, 60–120 mesh, EtOAc-hexane, 1:4) to afford **2a** (0.35 g) in 63% yield as a syrup. $[\alpha]_D - 35.43°$ (*c* 0.5, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.25 and 1.48 (2 s, 6H, 2 CH_3), 1.95–2.14 (m, 2H, H-5,5′), 3.35 (s, 3H, OCH_3), 3.56 (d, 1H, J 3.7 Hz, H-3), 4.30–4.40 (m, 1H, H-4), 4.52 (d, 1H, J 3.7 Hz, H-2), 4.05–4.20 (m, 1H, H-6), 5.78 (d, 1H, J 3.76 Hz, H-1), 6.0–6.10 (m, 1H, H-8), 7.50 (d, 1H, J 5.6 Hz, H-7); FAB-MS: *m/z* 293 ($M^+ + 23$, 95%), 271 ($M^+ + 1$, 60%), 255 ($M^+ - 15$, 35%), 213 (72%), 181 (82%), 133 (100%), 107 (70%); FAB-HRMS: Calculated for $C_{13}H_{19}O_6$ ($M^+ + 1$): 271.118164, found: 271.117320.

6-[6-Methoxy-2,2-dimethyl-(3a*R*,5*R*,6*S*,6a*R*)perhydrofuro[2,3-*d*][1,3]dioxol-5-ylmethyl]-2-methyl-(3a*R*,6*R*,6a*S*)perhydrofuro[3,4-*d*]isoxazol-4-one (1a). To a mixture of *N*-methyl hydroxylamine hydrochloride (0.185 g, 2.2 mmol) and Et_3N (0.46 mL, 3.3 mmol) in benzene (10 mL), was added paraformaldehyde (0.066 g, 2.2 mmol) and the reaction mixture was heated at reflux for 1 h. The reaction mixture was cooled to room temperature, treated with compound **2a** (0.270 g, 10 mmol) in benzene (2 mL) and again allowed to reflux for 4.5 h. It was cooled to room temperature, diluted with EtOAc (20 mL), washed sequentially with water (30 mL), brine (30 mL), dried (Na_2SO_4) and concentrated in vacuum. The residue was purified by column chromatography (silica gel, 60–120 mesh, EtOAc-hexane, 1:2) to furnish compound **1a** (0.29 g) in 88% yield: $[\alpha]_D - 5.63°$ (*c* 0.5, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 1.31 and 1.46 (2 s, 6H, CH_3), 2.07 (ddd, 1H, $J_{4,5pro\text{-}S}$ 8.0, $J_{4',5pro\text{-}S}$ 5.4 and $J_{5pro\text{-}S,5pro\text{-}R}$ 14.6 Hz, H-5pro-S), 2.13 (dt, 1H, $J_{4,5pro\text{-}R}$ 5.4 and $J_{4',5pro\text{-}R}$ 5.7 Hz, H-5pro-R), 2.65 (t, 1H, $J_{2',5'a}$ 6.7, $J_{5'a,5'b}$ 9.3 Hz, H-5′a), 2.71 (s, 3H, N-CH_3), 3.42 (s, 3H, OCH_3), 3.52 (d, 1H, H-5′b), 3.58 (t, 1H, $J_{2'3'}$ 7.0 Hz, H-2′), 3.63 (d, 1H, $J_{3,4}$ 3.2 Hz, H-3), 4.28 (ddd, 1H, H-4), 4.58 (d, 1H, $J_{1,2}$ 3.8 Hz, H-2), 4.67 (t, 1H, H-4′), 4.73 (d, 1H, H-3′), 5.85 (d, 1H, H-1); ^{13}C NMR($CDCl_3$, 50 MHz): δ 26.31, 27.76, 29.69, 31.91, 44.29, 49.49, 57.68, 61.03, 75.30, 81.25, 84. 72, 104.71, 111.74 (2C), 177.14; FAB-MS: *m/z* 330 ($M^+ + 1$, 100%), 329 (M^+, 58%), 255 ($M^+ - 15$, 12%), 240 (8%), 229 (10%), 213 (8%), 185 (5%); FAB-HRMS: Calculated for $C_{15}H_{23}NO_7$ (M^+): 329.147452, found: 329.148587.

Iodolactonisation of 8b, 8c and 8d (synthesis of 10a, 10b and 10c). A mixture of **8b–8d** (2.75 g, 6.6 mmol), $NaCNBH_3$ (0.836 g, 13.3 mmol) and *n*-Bu_3SnCl (0.021 g, 0.66 mmol) in *tert*-butyl alcohol (20 mL) was heated up to 80°C, then a catalytic amount of AIBN (0.025 g) was added to the mixture and heating continued for 4 h. The reaction

was worked up as described for **10** to afford **10a–c** (1.78 g) in 94% yield as an inseparable mixture. ^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.32 and 1.50 (2 s, 6H, 2 CH_3), 1.98–2.90 (m, 4H, H-5,5′,8,8′), 3.45 (s, 3H, OCH_3), 3.62 (d, 1H, J 3.60 Hz, H-3), 4.16–4.35 (m, 1H, H-4), 4.35–4.64 (m, 3H, H-2,6,7), 5.85 (d, 1H, J 3.6 Hz, H-1); EI-MS: *m/z* 273 ($M^+ - 15$, 20%), 200 (15%), 171 (18%), 145 (60%), 99 (10%), 71 (100%), 43 (90%).

5-[6-Methoxy-2,2-dimethyl-(3a*R*,5*R*,6*S*,6a*R*)perhydrofuro[2,3-*d*][1,3]dioxol-5-ylmethyl]-(5*R*/*S*)-2H-2-furanone (2a and 2b). A solution of **10a–c** (1.72 g, 5.9 mmol) in CH_2Cl_2 (20 mL) was sequentially treated with Et_3N (2.49 mL, 17.9 mmol), Ac_2O (1.18 mL, 8.9 mmol) and catalytic DMAP (0.04 g). The reaction mixture was worked up as described for **2a** to afford **2a** and **2b** (0.96 g) in 60% yield as an inseparable mixture. $[\alpha]_D - 44.18°$ (*c* 0.5, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.24 and 1.44:1.26, and 1.48 (1:2) (4 s, 6H, 2 CH_3), 1.98–1.20 and 1.95–2.14 (1:2) (2 m, each 2H, H-5,5′), 3.35 and 3.37 (2 s, each 3H, OCH_3), 3.56 (d, 1H, J 3.7 Hz, H-3), 4.09–4.22 and 4.30–4.40 (1:2) (2 m, each 1H, H-4), 4.52 (d, 1H, J 3.7 Hz, H-2), 4.05–4.22 (m, 1H, H-6), 5.73–5.85 (m, 1H, H-1), 6.0–6.12 (m, 1H, H-8), 7.50 (d, 1H, J 5.6 Hz, H-7); EI-MS: *m/z* 255 ($M^+ - 15$, 25%), 181 (32%), 127 (70%), 71 (100%), 43 (45%);

6-[6-Methoxy-2,2-dimethyl-(3a*R*,5*R*,6*S*,6a*R*)-perhydrofuro[2,3-*d*][1,3]dioxol-5-ylmeth-yl]-2-methyl-(3a*R*/*S*,6*R*/*S*,6a*S*/*R*)perhydrofuro[3,4-*d*]isoxazol-4-one (1a and 1b). To a solution of *N*-methyl hydroxylamine hydrochloride (0.54 g, 6.6 mmol) and Et_3N (1.38 mL, 9.9 mmol) in benzene (25 mL) paraformaldehyde (0.198 g, 6.6 mmol) was added and reaction mixture heated at reflux for 1 h. The reaction mixture was cooled to room temperature and treated with **2a** and **2b** (0.81 g, 3.0 mmol) in benzene (5 mL) and the reaction mixture heated at reflux for 4.5 h and worked up as described for **1a** to afford the mixture of **1a** and **1b**, which was purified by column chromatography (silica gel, 60–120 mesh, EtOAc-hexane, 1:2). First eluted was *6-[6-methoxy-2, 2-di methyl-(3aR,5R,6S,6aR)perhydrofuro[2,3-d][1,3]dioxol-5-ylmethyl]-2-methyl-(3aR,6R,6aS)perhydrofuro[3,4-d]isoxazol-4-one* (**1a**) (0.45 g), in 45.5% yield, which was identical with the compound prepared earlier from pure **8a**. Second eluted was *6-[6-methoxy-2,2-d methyl-(3aR,5R,6S,6aR)perhydrofuro[2,3-d][1,3]dioxol-5-ylmethyl]-2-methyl-(3aS,6S,6aR)perhydrofuro[3,4-d]isoxazol-4-one* (**1b**) (0.39 g) in 39.3% yield. **1b**: $[\alpha]_D - 84.40°$ (*c* 1.2, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 1.32, 1.49(2s, 6H, $2CH_3$), 1.94(ddd, 1H, $J_{4,5pro\text{-}S}$ 4.4, $J_{4',5Pros\text{-}S}$ 9.2, $J_{5pro\text{-}R,5pro\text{-}S}$ 14.5 Hz, H-$5_{pro\text{-}s}$), 2.06(ddd, 1H, $J_{4,5pro\text{-}R}$ 8.6, $J_{4',5pro\text{-}R}$ 4.6 Hz, H-$5_{pro\text{-}R}$), 2.62(m, 1H, H-5′a), 2.74(s, 3H, N-CH_3), 3.12(m, 1H, H-2′), 3.23(m, 1H, 5′b), 3.40(s, 3H, OCH_3), 3.62(d, 1H, $J_{3,4}$ 3.1 Hz, H-3), 4.32(ddd, 1H, H-4), 4.57(d, 1H, $J_{1,2}$ 3.8 Hz, H-2), 4.59(m, 1H, H-4′), 4.67(d, 1H, $J_{2',3'}$ 8.4 Hz, H-3′), 5.85(d, 1H, H-1) ; FAB-MS: *m/z* 330 ($M^+ + 1$, 65%), 329 (M^+, 50%), 281 (30%), 267 (10%), 221 (40%), 213 (8%), 147 (100%).

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