Carbohydrate Research, 130 (1984) 261–269
Elsevier Science Publishers B.V., Amsterdam – Printed in The Netherlands

SYNTHESIS OF A CHIRAL 1,7-DIOXASPIRO[5,5]UNDECENE. A MODEL FOR THE SPIROACETAL SUBUNIT OF AVERMECTIN B_{1a}*

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(Received December 30th, 1983; accepted for publication, February 16th, 1984)

ABSTRACT

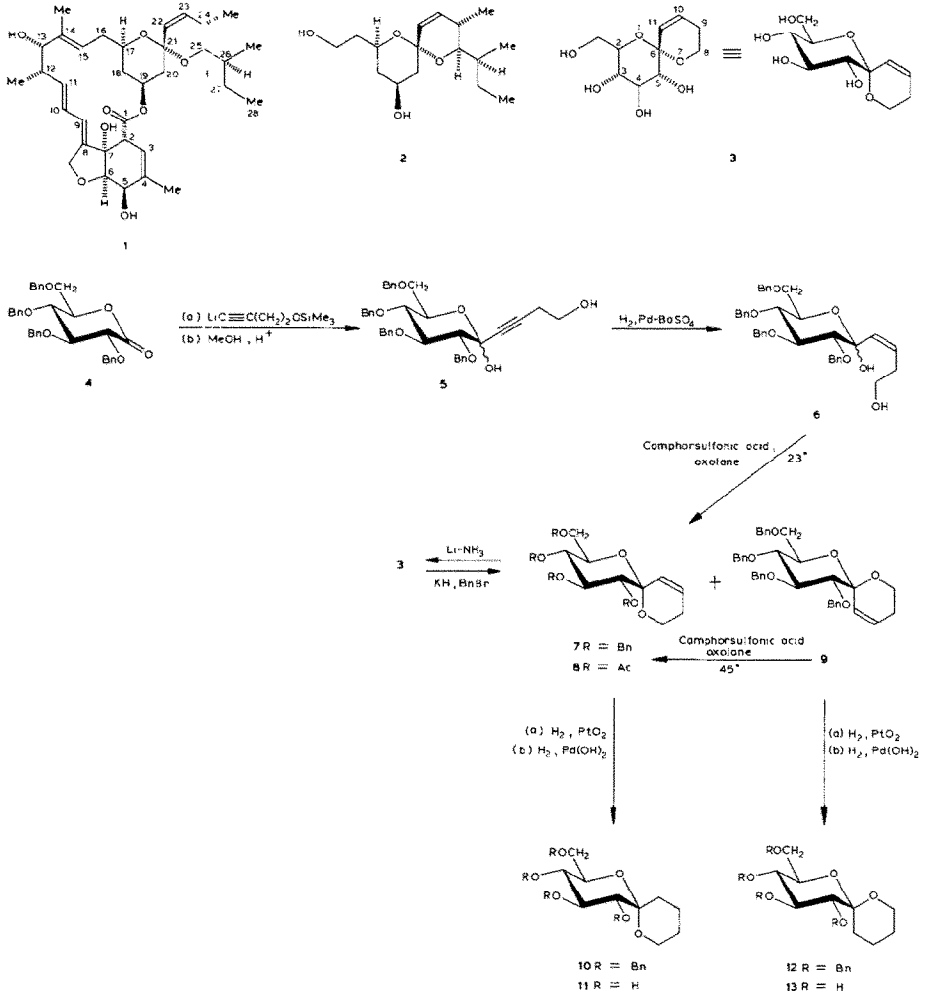
The stereocontrolled synthesis of a chiral, polyhydroxy 1,7-dioxaspiro-[5,5]undecene from D-glucose is described. The bicyclic system with a different pattern of substitution can be found in a number of biologically important natural products such as the avermectins and the milbemycins.

INTRODUCTION

Several biologically important natural products contain a dioxaspiroacetal unit as part of their unique molecular architecture[1,2]. Specifically, 1,6-dioxaspiro-[4,4]nonane and -[4,5]undecane units, with or without substituents in either ring, are encountered in the structures of chalcogran[3] or various aggregation substances[4], respectively. Related subunits are found in the structurally intriguing ionophore antibiotics[5], as a mosaïc of alternating or repeating units. The major sex-pheromone of the olive fly has been identified as 1,7-dioxaspiro[5,5]undecane, an assignment which was verified by a synthesis[6]. This symmetrically disposed, spiroacetal motif is also found in vastly more complex molecules containing an intricate array of chiral centers and functional groups. Thus, the calcium-binding ionophore A 23187 (ref. 7) and the potent anthelmintic group of antibiotics comprising the avermectins[8] and the milbemycins[9] offer awe-inspiring examples of such structures. In spite of their structural divergence and degree of complexity, all these natural products are endowed with a unique orientation of atoms around the spiroacetal carbon atom. Thus, by virtue of the semi-rigid structure of the spiroacetal unit and the anticipated stereoelectronic consequences of the anomeric effect[10,11], the corresponding subunits in these molecules adopt a spatial arrangement which is often predictable. Indeed, extensive X-ray crystallographic studies have confirmed the generality of this phenomenon[5]. We have previously referred to this preference as "anomeric stereoselection"[2,12], which arises from the highly diastereoselective acetalization of a dihydroxyketone progenitor in such a manner

*Dedicated to Professor Raymond U. Lemieux.
†NSERCC post-doctoral fellow, 1982–83.

0008-6215/84/$ 03.00



so as to satisfy the stereoelectronic requirements of the anomeric and exo-anomeric effects[13].

Achievements in the synthesis of ionophore antibiotics have been monumental, particularly with the conquest of such targets as A-23187 (ref. 14), lasalocid[15], monensin[16], and milbemycin B_3 (ref. 17), among others. The avermectins remain as unconquered targets, although efforts along these lines are under study in several laboratories including ours. Thus, we recently completed the total synthesis[18] of the chiral spiroacetal subunit **2** of avermectin B_{1a} aglycon[19] **1**, by relying on the chiron approach*. In concurrent work, Baker *et al.*[22] have described the preparation of key intermediates for the ultimate synthesis of milbemycin B_1 and aver-

*We have recently used the term "chiron" to describe an enantiomerically pure synthon. See, for example, ref. 20. For a mathematical interpretation of the term "chiron" as it relates to asymmetry in molecules, see ref. 21.

mectin A_1 aglycons. Clearly, the main challenge in these endeavors resides in the stereocontrolled synthesis of the highly functionalized, chiral backbone of the intended acetal. Once assembled, the spiroacetalization may be expected to follow a reasonably predictable course to lead to the desired diastereoisomer in preponderance, if not exclusively. Under thermodynamic control, the product may be expected to exist entirely with the anticipated gauche orientation of the O–C–O bonds comprising the anomeric (spiroacetal) center. It has been shown that bicyclic acetals having an axial orientation of alkoxy anomeric substituents are stabilized by at least 6.3 kJ/mol compared to the alternate anomer[23].

Examination of the structures of the 1,7-dioxaspiro[5,5]undecene subunit in avermectin B_{1a} aglycon revealed functional and stereochemical features not uncommon to carbohydrate-type progenitors, inasmuch as we are dealing with two pyranosidic, internal glycosides. Thus, the left-hand portion could be formally related to a 2,4-dideoxy-D-*threo*-hexose(2,4-dideoxy-D-glucose), and the right-hand side to a highly branched, unsaturated analog. Indeed, the recognition of such symmetry and functional elements is the very basis of the chiron approach[20,23] used in the assembly[18] of the subunit **2**. Model studies seemed necessary at the inception of this project, and it was concluded that the chiral polyhydroxylated spiroketal derivative **3** would constitute a reasonable, initial target to test out the strategies of stereocontrolled bond-formation at the anomeric center, the compatibility of functional and protecting groups, and finally, the stereochemical outcome of the spiroacetalization reaction. Clearly, the most practical entry into the desired system consists in a stereocontrolled attack upon an appropriately O-substituted D-glucono-1,5-lactone by a bifunctional nucleophile. The functional requirements of the right-hand portion of **3** reduced the choice of nucleophile to the lithium salt of an *O*-protected acetylenic alcohol. Lindlar hydrogenation would thus ensure the generation of the desired *cis* double-bond, while the terminal hydroxyl group would lead to the internal glycoside. The reaction of carbohydrate lactones with metal acetylides to provide acetylenic lactols has precedent in the literature[24]. More recently, Lancelin *et al.*[25] have utilized this reaction to prepare *C*-alkynyl β-D-glucopyranosides by Lewis acid-catalyzed reduction[26] of the lactol. In general, the addition of organolithium reagents to esters leads to the corresponding tertiary alcohols and, in this context, the obtention of the acetylenic lactols as initially demonstrated[24] is of interest. Chabala and Vincent[27] have subsequently shown that 5-pentanolide and 4-butanolide and, to a lesser extent, 6-hexanolide react with lithium acetylides to give the corresponding α,β-ynones. Related studies directed at the preparation of spirocyclic acetals also utilized the condensation of lactones with lithium acetylides[13,28–30]. Alternative routes to these spiroacetals could take advantage of other strategies, such as a hetero Diels–Alder reaction for example[31].

RESULTS AND DISCUSSION

We chose readily available 2,3,4,6-tetra-*O*-benzyl-D-glucono-1,5-lactone[32] (**4**)

as our starting material for reasons of compatibility and convenience. Treatment of **4** with the lithium salt of 1-trimethylsilyloxy-3-butyne, followed by a workup under mildly acidic conditions afforded a mixture of anomers of the acetylenic lactol derivative **5** in 92% yield*. Partial catalytic hydrogenation of the triple bond in the presence of palladium-on-barium sulfate gave a high yield of the corresponding *cis*-olefins **6**, which, upon treatment with camphorsulfonic acid led to a 4:3 mixture of the spiroacetals **7** and **9**, readily separable by flash-column chromatography[32]. Their constitutional structures as well as anomeric configurations were ascertained by spectroscopic means. Thus, irradiation of the vinylic proton, closest to the anomeric center in the crystalline α-D-glucoside **7**, resulted in a 8–9% signal enhancement for H-2 in the glucopyranosyl ring (17% n.O.e.), reflecting the relative spatial dispositions of the two protons in question. On the other hand, when the corresponding vinylic proton of the other isomer **9** was irradiated, signals for H-3 and -5 in the D-glucopyranosyl ring were enhanced ($\approx$27% n.O.e. for each), as would be expected from the structure. The thermodynamic instability of **9** was evidenced by its ready anomerization under the conditions of original spiroacetalization, except for the temperature which was kept at 45°. Removal of the benzyl protecting groups from **7** was achieved by a dissolving metal reduction which afforded the desired model spiroacetal **3** in 83% yield. Benzylation of the latter compound led to the original product **7**, and acetylation gave the syrupy tetraacetate **8**. Catalytic hydrogenation in the presence of platinum oxide of compounds **7** and **9** led, in each case, to the saturated spiroacetal derivatives **10** and **12**, respectively. Debenzylation was achieved in the presence of palladium hydroxide-on-charcoal to give the saturated spiroacetals **11** and **13**, respectively.

Thus, whereas the reaction of the lithium acetylide with the lactone **3** was not initially stereocontrolled, the desired spiroacetal **7** could be obtained, in high yield and efficiency, simply by anomerization of the kinetic mixture of products. Once again, the fundamental importance of the anomeric and exo-anomeric effects, which are magnified in the spiroacetal structures because of restricted rotamer populations, are manifest and revealing.

EXPERIMENTAL

*General methods***. — Optical rotations were determined with a Perkin–Elmer No. 241 polarimeter. ^{1}H-N.m.r. spectra were recorded, for solutions in chloroform-*d* with tetramethylsilane as internal standard, at 90 MHz with a Bruker WH-90 spectrometer, unless otherwise noted and at 400 MHz with a Bruker WH-400 spectrometer. I.r. spectra were recorded as neat films with a Perkin–Elmer No.

*Treatment of the alkoxide generated in the reaction with methyl trifluoromethanesulfonate led to a ~1:1 mixture of methyl glycosides which could be isolated individually. Equilibration (methanol–camphorsulfonic acid) gave a 2:1 mixture of α- and β-glycosides.

**The purity of syrupy compounds was not ascertained by elemental analyses (Editor).

781 spectrophotometer. Chemical-ionization (isobutane) mass spectra were recorded with a V.G. Micromass 12-12 and electron-impact mass spectra with a Kratos MS 902 instrument, respectively. Column chromatography was effected on Baker silica gel (60–200 mesh). Flash chromatography[33] was performed on Merck silica gel 60 (230–400 mesh). Dichloromethane was distilled in the presence of P_2O_5. Oxolane and diethyl ether were distilled from sodium diphenylketyl.

*2,3,4,6-Tetra-*O*-benzyl-*D*-gluco-1,5-lactone* (**4**). — To a stirred solution of 2,3,4,6-tetra-*O*-benzyl-D-glucopyranose (5.4 g, 10 mmol) in dichloromethane (150 mL) containing powdered molecular sieves (3A, 10 g) was added pyridinium chlorochromate (10 g, 46 mmol) in one portion. After 45 min, the dark suspension was diluted with diethyl ether (300 mL) and hexane (150 mL), and filtered through a silica gel column (80 g). The column was washed with a further 300 mL of diethyl ether, and the combined filtrates were evaporated to dryness to give **4** (5.13 g, 95%) as a syrup[32], $[\alpha]_D$ +73.2° (*c* 4.14, $CHCl_3$); ν_{max}^{film} 1755 cm^{-1} (lactone); ^{1}H-n.m.r.: δ 7.4–7.2 (m, 20 H, Ar), 5.0–3.66 (m, 14 H, $PhCH_2$ and aliph.); c.i.–m.s.: *m/z* 539 (MH^+), 357 ($MH^+ - 2\,PhCH_2\cdot$).

*2,3,4,6-Tetra-*O*-benzyl-1-*C*-(4-hydroxy-1-butynyl)-α,β-*D*-glucopyranose* (**5**). — To a solution of 1-trimethylsilyloxy-3-butyne (380 mg, 2.7 mmol) in anhydrous diethyl ether (10 mL) at −15° was added dropwise 1-butyllithium (1.57 mL, 1.56M). After being stirred at −15° for 20 min, the acetylide was added dropwise to a solution of lactone **4** (1.1 g, 2.04 mmol) in anhydrous ether (40 mL), at −15°, *via* a double-tip needle. The solution was stirred for an additional 45 min after which dilute ammonium chloride solution was added, and the mixture partitioned between ethyl acetate and NaCl solution. The organic layer was evaporated to dryness and the residue dissolved in methanol (100 mL) containing pyridinium *p*-toluenesulfonate (0.5 g). The solution was stirred for 1 h at room temperature, the methanol evaporated, and the residue flash chromatographed (1:1 ethyl acetate–hexane) to give **5** (1.14 g, 92%) as a syrup, ν_{max}^{film} 3350 (OH), 2240 cm^{-1} (w, C≡C); ^{1}H-n.m.r.: δ 7.4–7.2 (m, 20 H, Ar), 5.1–3.5 (m, 16 H, $PhCH_2$ and aliph.), 3.3–2.6 (bm, 2 H, 2 OH), 2.5–2.3 (~q, 2 H, C≡C–CH_2); c.i.–m.s.: *m/z* 483 ($MH^+ - H_2O - PhCH_2OH$), 375 ($MH^+ - H_2O - 2PhCH_2OH$).

*2,3,4,6-Tetra-*O*-benzyl-1-*C*-(4-hydroxy-1-Z-butenyl)-α,β-*D*-glucopyranose* (**6**). — A solution of acetylene derivative **5** (920 mg, 1.5 mmol) in ethyl acetate (8 mL) and pyridine (0.8 mL) containing 5% palladium-on-barium sulfate (60 mg) was stirred under hydrogen at atmospheric pressure. After 2 h at room temperature, the mixture was filtered, the filtrate diluted with ethyl acetate (50 mL) and washed with aqueous copper sulfate and then NaCl solution, and the organic phase dried ($MgSO_4$) and evaporated to give olefin **6** as a syrup (750 mg, 81%), after flash chromatography (3:2 hexane–ethyl acetate); ν_{max}^{film} 3350 cm^{-1} (OH); ^{1}H-n.m.r. (400 MHz): δ 7.4–7.2 (m, 20 H, Ar), 5.75, 5.7 (2 d, 1 H, *J* 12 Hz, C*H*=CH–CH_2), 5.6–5.55 (2 ddd, 1 H, CH=C*H*–CH_2), 5.0–3.4 (m, 16 H, $C_6H_5CH_2$ and aliph.), 2.75, 2.6, 2.36 (3 m, 2 H, CH_2OH). This material was used without further purification in the next step.

(3S,4S,5R)-Tribenzyloxy - (2R) - benzyloxymethyl - 1,7 - dioxa - (6R,S) - spiro-[5,5]undec-10-ene (**7, 9**). — Diol **6** (790 mg, 1.29 mmol) was stirred for 5 h at room temperature in oxolane (10 mL) containing camphorsulfonic acid (100 mg). The solution was diluted with ethyl acetate and washed successively with aqueous $NaHCO_3$ and NaCl, dried ($MgSO_4$), and evaporated to give spiroacetals **7** (433 mg, 56%), m.p. 93.5–94°, $[\alpha]_D$ +53.5° (*c* 1.39, dichloromethane), and **9** (312 mg, 41%), $[\alpha]_D$ +36.7° (*c* 0.90, dichloromethane) after flash chromatography (4:1 hexane–ethyl acetate); ν_{max}^{film} (**7** and **9**): no OH strech at 3350 cm^{-1}.

Compound **7** *[(6R)]*. ^{1}H-N.m.r. (400 MHz, benzene-d_6): δ 7.35–7.05 (m, 20 H, Ar), 5.74 (dd, 1 H, *J* 5.7, 10 Hz, H-10), 5.35 (ddd, 1 H, *J* 1, 2.8, 10 Hz, H-11), 4.91, 4.85, 4.65, 4.44 (4 AB, 8 H, 4 CH_2Ph), 4.36 (dd, 1 H, *J* 9.4, 9.4 Hz, H-4), 4.12 (ddd, 1 H, *J* 1.8, 4, 10.1 Hz, H-2), 3.91 (dd, 1 H, *J* 9.1, 10 Hz, H-3), 3.81 (m, 1 H, H-8), 3.8 (dd, 1 H, *J* 4.1, 10.7 Hz, H-12), 3.69 (dd, 1 H, *J* 1.8, 10.7 Hz, H-12′), 3.6 (bdd, 1 H, *J* 6, 10.8 Hz, H-8′), 3.45 (d, 1 H, *J* 9.5 Hz, H-5), 2.08 (m, 1 H, H-9), 1.33 (m, 1 H, H-9′); c.i.–m.s.: *m/z* 593 (MH^+), 486 (MH^+ – $PhCH_2O\cdot$), 377 (MH^+ – 2 $PhCH_2OH$), 240 (MH^+ – 2 $PhCH_2OH$ – $PhCH_2O\cdot$ – CH_2O).

Anal. Calc. for $C_{38}H_{40}O_6$: C, 77.00; H, 6.80. Found: C, 77.07; H, 6.83.

Compound **9** *[(6S)]*. ^{1}H-N.m.r. (400 MHz): δ 7.35–7.15 (m, 20 H, Ar), 6.24 (bdd, 1 H, *J* 5.3, 10.4 Hz, H-10), 6.11 (ddd, 1 H, *J* 1.2, 2.4, 10.4 Hz, H-11), 4.82, 4.78 4.68, 4.60 (4 AB, 8 H, 4 CH_2Ph), 4.18 (ddd, 1 H, *J* 3.5, 11.7, 11.7 Hz, H-8), 3.92 (dd, 1 H, *J* 6.3, 11.1 Hz, H-8′), 3.8 (dd, 1 H, *J* 8.6, 9.0 Hz, H-4), 3.74–3.65 (m, 4 H, H-2,3,12,12′), 3.58 (d, 1 H, *J* 9.1 Hz, H-5), 2.41 (m, 1 H, H-9), 1.96 (m, 1 H, H-9′); c.i.–m.s.: *m/z* 593 (MH^+), 486 (MH^+ – $PhCH_2O\cdot$), 378 (MH^+ – $PhCH_2OH$ – $PhCH_2O\cdot$), 240 (MH^+ –2 $PhCH_2OH$ – $PhCH_2O\cdot$ – CH_2O).

(3S,4S,5R)-Tribenzyloxy - (2R) - benzyloxymethyl - 1,7 - dioxa - (6R) - spiro-[5,5]undecane (**10**). — Hydrogen was bubbled through a stirred solution of spiroacetal **7** (76 mg, 0.128 mmol) in ethyl acetate (5 mL) containing PtO_2 (25 mg) until reduction of the olefin was complete (t.l.c.; ~30 min). The catalyst was filtered off and washed with ethyl acetate. Evaporation of the solvent afforded spiroacetal **10** (76 mg, quant.), $[\alpha]_D$ +19.8° (*c* 1.10, chloroform); ^{1}H-n.m.r.: δ 7.5–7.2 (m, 20 H, Ar), 5.0–3.2 (m, 16 H, –CH_2O– and –CHO–), 1.9–1.3 [m, 6 H, –C(CH_2)$_3$$CH_2O$–]; c.i.–m.s.: *m/z* 595 (MH^+), 487 (MH^+ – $PhCH_2OH$), 379 (MH^+ – 2 $PhCH_2OH$), 271 (MH^+ –3 $PhCH_2OH$), 151 (MH^+ – 2 $PhCH_2OH$ – $PhCH_2O\cdot$ – $PhCH_2OCH_2\cdot$).

(3S,4S,5R)-Tribenzyloxy - (2R) - benzyloxymethyl - 1,7 - dioxa - (6S) - spiro-[5,5]undecane (**12**). — Reduction **9**, *via* the procedure described for the conversion of **7** to **10**, afforded **12** (quant.), $[\alpha]_D$ +18.3° (*c* 1.22, chloroform); ^{1}H-n.m.r.: δ 7.4–7.2 (m, 20 H, Ar), 5.1–3.5 (m, 16 H, –CH_2O– and –CHO–), 2.1–1.5 [m, 6 H, –C(CH_2)$_3$$CH_2O$–]; c.i.–m.s.: *m/z* 595 (MH^+), 487 (MH^+ – $PhCH_2OH$), 379 (MH^+ – 2 $PhCH_2OH$), 271 (MH^+ –3 $PhCH_2OH$), 151 (MH^+ – 2 $PhCH_2OH$ – $PhCH_2O\cdot$ – $PhCH_2OCH_2\cdot$).

(3S,4S,5R)-Trihydroxy - (2R) - hydroxymethyl - 1,7 - dioxa - (6R) - spiro-[5,5]undecane (**11**). — Hydrogen was bubbled through a stirred solution of

spiroacetal **10** (66 mg, 0.11 mmol) in methanol (1.5 mL) containing $Pd(OH)_2$ (30 mg). After 4 h, the catalyst was removed by filtration and the solvent evaporated. The residue was chromatographed on silica gel (4:1 chloroform–2-propanol) affording tetrol **11** (21 mg, 81%) as a syrup, $[\alpha]_D$ +73.5° (*c* 1.05, chloroform); ν_{max}^{film} 3350 cm^{-1} (OH); ^{1}H-n.m.r. (400 MHz; acetone-d_6): δ 4.23 (bs, 1 H, OH), 3.83 (bdd, 1 H, C*H*OH), 3.75–3.56 (m, 5 H, 2 CH_2O–, C*H*OH), 3.45 (m, 1 H, C*H*OH), 3.33 (bdd, 1 H, *J* 9.2, 9.2 Hz, C*H*OH), 3.0 (bs, 3 H, 3 OH), 2.05–1.83 (m, 2 H, CH_2), 1.57–1.36 (m, 4 H, CH_2–CH_2); c.i.–m.s.: *m/z* 235 (MH^+), 217 ($MH^+ - H_2O$), 199 ($MH^+ - 2\,H_2O$), 169 ($MH^+ - H_2O$ – HO· – $HOCH_2$·).

(3S,4S,5R) - Trihydroxy - (2R) - hydroxymethyl - 1,7 - dioxa - (6S) - spiro[5,5]-undecane (**13**). — Debenzylation of **12**, *via* the procedure described for the conversion of **10** to **11**, afforded **13** (78%) as a syrup, $[\alpha]_D$ +66.4° (*c* 1.95, chloroform); ν_{max}^{film} 3350 cm^{-1} (OH); ^{1}H-n.m.r. (400 MHz; acetone-d_6 + D_2O): δ 3.86–3.83 (m, 1 H, C*H*OH), 3.72–3.60 (m, 5 H, 2 CH_2O–, C*H*OH), 3.5–3.1 (m, 2 H, 2 C*H*OH), 2.05–1.8 (m, 2 H, CH_2), 1.6–1.3 (m, 4 H, CH_2CH_2); c.i.–m.s.: *m/z* 235 (MH^+), 217 ($MH^+ - H_2O$), 199 ($MH^+ - 2\,H_2O$), 169 ($MH^+ - H_2O$ – HO· – $HOCH_2$·).

(3S,4S,5R) - Trihydroxy - (2R) - hydroxymethyl - 1,7 - dioxa - (6R) - spiro[5,5]-undec-10-ene (**3**). — A solution of **7** (258 mg, 0.44 mmol) in oxolane (4 mL) was added dropwise to a solution of lithium (35 mg, 5 mmol) in liquid ammonia (12 mL) at −33°. After 10 min, ethanol was added until the blue color disappeared, and the solution was allowed to warm to room temperature. The solution was then partitioned between ethyl acetate and water, and the aqueous phase evaporated to dryness. The residue was dissolved in water (5 mL), and the solution passed through a plug of Dowex 50W-X8 (H^+) cation-exchange resin and evaporated to dryness to give tetrol **3** (84 mg, 83%) as a syrup, $[\alpha]_D$ +29.1° (*c* 1.58, methanol), after chromatography on silica gel (3:1 chloroform–2-propanol); ν_{max}^{film} 3350 cm^{-1} (OH); ^{1}H-n.m.r. (400 MHz; D_2O): δ 6.14 (ddd, 1 H, *J* 1.6, 6.0, 10.0 Hz, H-10), 5.49 (dd, 1 H, *J* 1.2, 10.2 Hz, H-11), 3.72 (m, 2 H, H-8,8′), 3.70–3.28 (m, 5 H, H-2,3,4 and CH_2OD), 3.27 (d, 1 H, *J* 9.7 Hz, H-5), 2.2 (m, 1 H, H-9), 1.83 (m, 1 H, H-9′); c.i.–m.s.: *m/z* 233 (MH^+), 215 ($MH^+ - H_2O$), 197 ($MH^+ - 2\,H_2O$).

Benzylation of 3,4,5-trihydroxy-2-hydroxymethyl-1,7-dioxa-(6R)-spiro-[5,5]undec-10-ene (**3**). — To a solution of tetrol **3** (5 mg, 22 μmol) in *N,N*-dimethylformamide (0.2 mL) and *N,N′,N″*-hexamethylphosphoramide (0.1 mL) was added KH (0.13 mmol) at 0°. After 15 min, benzyl bromide (0.1 mL) was added and the mixture allowed to warm to room temperature. After 8 h, water was added and the solution extracted with ethyl ether. The extract was washed with NaCl solution, dried ($MgSO_4$), and evaporated to give spiroacetal **7** (8.3 mg, 65%) after chromatography on silica gel (9:1 hexane–ethyl acetate).

(3S,4S,5R) - Triacetoxy - (2R) - acetoxymethyl - 1,7 - dioxa - (6R) - spiro[5,5]-undec-10-ene (**8**). — A solution of tetrol **3** (15.7 mg, 68 μmol) in pyridine (0.5 mL) containing acetic anhydride (0.1 mL) and 4-dimethylaminopyridine (5 mg) was stirred overnight at room temperature. The solution was diluted with ethyl acetate (15 mL) and washed successively with aqueous $CuSO_4$, H_2O, and NaCl solution, dried

($MgSO_4$), and evaporated. The residue was chromatographed on silica gel (7:3 hexane–ethyl acetate) to give tetraacetate **8** (22 mg, 81%) as a syrup, $[\alpha]_D$ +51.7° (*c* 0.98, dichloromethane); ν_{max}^{film} 1750 cm^{-1} (OAc); ^{1}H-n.m.r. (400 MHz): δ 6.16 (bdd, 1 H, *J* 5.4, 10.1 Hz, H-10), 5.60 (ddd, 1 H, *J* 1.1, 2.7, 10.1 Hz, H-11), 5.52 (dd, 1 H, *J* 9.7, 9.8 Hz, H-4), 5.13 (dd, 1 H, *J* 9.9, 9.6 Hz, H-3), 5.09 (d, 1 H, *J* 10.1 Hz, H-5), 4.26 (dd, 1 H, *J* 4.6, 12.3 Hz, H-12), 4.13 (m, 1 H, H-2), 4.09 (dd, 1 H, *J* 2.3, 12.7 Hz, H-12′), 3.89 (m, 2 H, H-8,8′), 2.37 (m, 1 H, H-9), 2.10 (s, 3 H, OAc), 2.03 (s, 6 H, 2 OAc), 1.99 (s, 3 H, OAc), 1.93 (m, 1 H, H-9′); m.s.: *m/z* 385 (33.6, $M^+ - CH_3\cdot$), 341 ($M^+ - AcO\cdot$), 325 ($M^+ - HOAc - CH_3\cdot$), 281 ($M^+ - HOAc - AcO\cdot$), 221 ($M^+ - 2\,HOAc - AcO\cdot$).

Isomerization of spiroacetal **9** *to* **7**. — A solution of spiroacetal **9** (290 mg, 0.49 mmol) in oxolane (U.S.P.; 10 mL) containing camphorsulfonic acid (200 mg) was stirred for 8 h at 45°. The solution was diluted with ethyl acetate (20 mL), washed with aqueous $NaHCO_3$ and then NaCl solution, dried ($MgSO_4$), and evaporated to give spiroacetal **7** (252 mg, 87%) after crystallization from ether–hexane.

ACKNOWLEDGMENTS

The authors thank the Natural Sciences and Engineering Research Council of Canada for a fellowship to A.U. and for financial assistance. They also acknowledge the generous financial support and encouragement from Merck–Frost Laboratories. They thank Dr. Phan Viet Tan for recording high-resolution, 400-MHz ^{1}H-n.m.r. spectra and for the n.O.e. measurements, as well as Michael Evans for the mass spectra. They also acknowledge the valuable technical assistance by Mrs. Ani Glamyan.

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