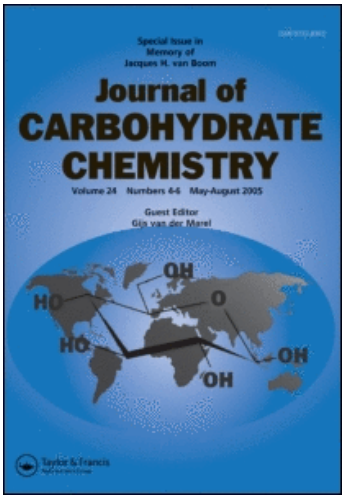

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ORTHOESTER CLAISEN REARRANGEMENT OF A D-GLUCOSE-DERIVED SPIROCYCLIC SUBSTRATE

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ORTHOESTER CLAISEN REARRANGEMENT OF A D-GLUCOSE-DERIVED SPIROCYCLIC SUBSTRATE

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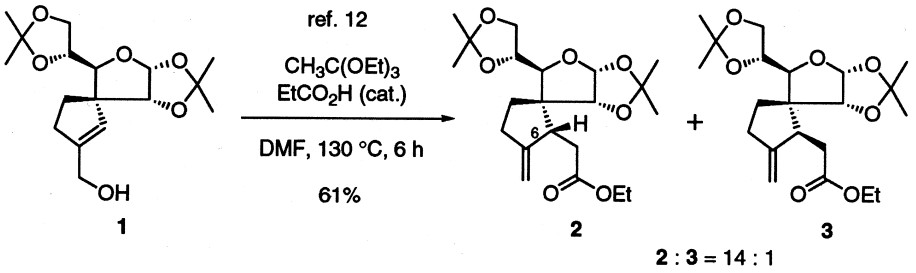
ABSTRACT

The Claisen rearrangement of a spiro compound 1 derived from 1,2:5,6-di-*O*-isopropylidene-α–D-glucofuranose, with triethyl orthopropionate afforded the rearrangement products 4, 5, and 6 as a 1:2.5:10 diastereomeric mixture. The reaction of 1 with trimethyl orthobutyrate provided a 1:3 mixture of 7 and 8. In both cases, the σ-bond formation proceeded predominantly from the β-side. This stereochemical outcome was opposite to that observed in the case of the rearrangement of 1 with triethyl orthoacetate.

INTRODUCTION

The Claisen rearrangement and its variants are powerful synthetic tools for the preparation of stereochemically complex materials.[1-3] As part of continuing interests in the transformation of carbohydrates into a variety of multifunctionalized building blocks, we have studied the orthoester Claisen rearrangements of some carbohydrate-derived allylic alcohols.[4-10] Recently, we reported that the thermal treatment of **1**,[11] a spiro compound carrying the 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranosyl moiety, with triethyl orthoacetate in the presence of a catalytic amount of propanoic acid afforded the Claisen rearrangement products **2** and **3** with a high level (α:β =14:1) of diastereoselectivity at C-6 (Scheme 1).[12] Spiro compounds are frequently found in nature as core skeletons of a variety of natural terpenoids, represented by spirovetivane (vetispirane), acorane, and chamigrane-type sesquiterpenoids (Figure 1).[13] Accordingly, enantiomerically pure multifunc-



Scheme 1.

tionalized spiro compounds would serve as versatile building blocks for spirocyclic sesquiterpenoids synthesis. For the purpose of introducing an α-substituted alkoxycarbonylmethyl group as a side chain in the spiro cyclopentane moiety, we have investigated the Claisen rearrangement of allylic alcohol **1** with triethyl orthopropionate or trimethyl orthobutyrate. Herein, we describe the results of the reactions of **1** with the two α-substituted orthoacetates.

RESULTS AND DISCUSSION

The Claisen rearrangement of **1** with triethyl orthopropionate in the presence of a catalytic amount of propanoic acid in DMF at 130 °C for 4 h provided an inseparable mixture of the rearrangement products **4**, **5**, and **6** (1:2.5:10) in a combined yield of 87% (Scheme 2). The stereochemistries of the newly introduced stereogenic carbon centers in **4**, **5**, and **6** were established through conversion of the mixture into bicyclic derivatives **14**, **15**, and **16** (*vide infra*). Surprisingly, apparent β-selectivity (α:β = **4**+**5**:**6** = 1:2.8), regarding the configuration at C-6, was observed in this reaction. This stereochemical outcome was opposite to that observed in the case of the Claisen rearrangement of **1** with triethyl orthoacetate as depicted in Scheme 1.

The Claisen rearrangement of **1** with trimethyl orthobutyrate was carried out under analogous conditions used for those depicted in Schemes 1 and 2 (Scheme 3). A 10% yield of the rearrangement product was obtained. To improve the yield of the product, we sought more efficient reaction conditions. As a result, the addi-

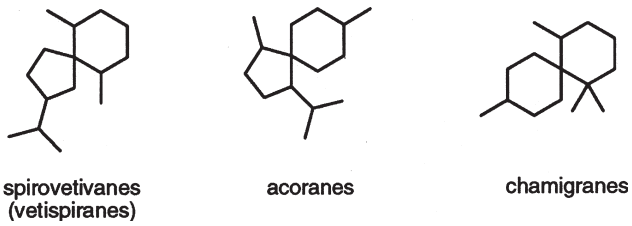


Figure 1.

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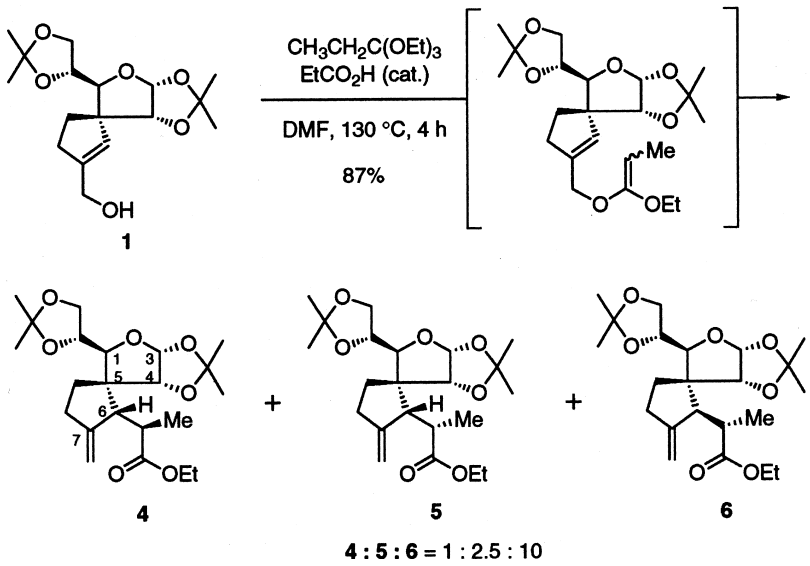
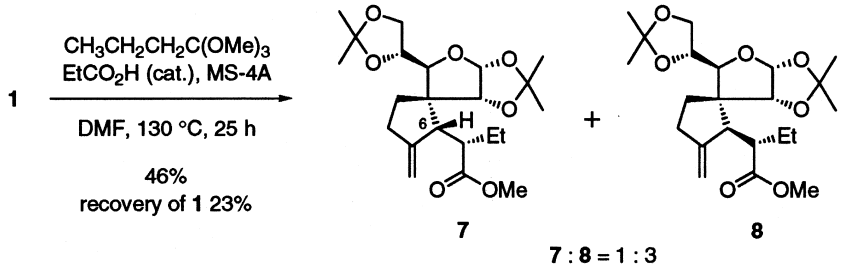


Scheme 2.

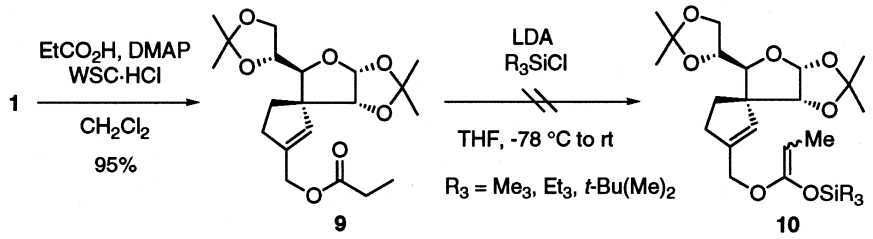
tion of powdered molecular sieves 4A (MS-4A) was found to be effective. In the presence of MS-4A, the reaction produced a 46% combined yield of the rearrangement products **7** and **8** (1:3) as an inseparable mixture, and unreacted **1** was recovered in 23% yield. Similar to the case of the Claisen rearrangement of **1** with triethyl orthopropionate, the β-isomer **8** was formed preferentially.

We also prepared the substrate **9** for the Ireland-Claisen rearrangement by acylation of **1** (Scheme 4). However, treatment of **9** with lithium diisopropylamide (LDA) and subsequent addition of trialkylsilyl chloride gave neither silyl ketene acetal **10** nor the rearrangement product. In fact, in many cases, **9** was recovered or decomposition occurred. We investigated the Ireland-Claisen rearrangement of **9** no further.

To ensure the stereochemical assignment of the rearrangement products **4-8**, we carried out the following chemical transformation (Scheme 5). Diisobutylaluminium hydride (Dibal-H) reduction of the mixture of **4**, **5**, and **6** provided a 1:2.5

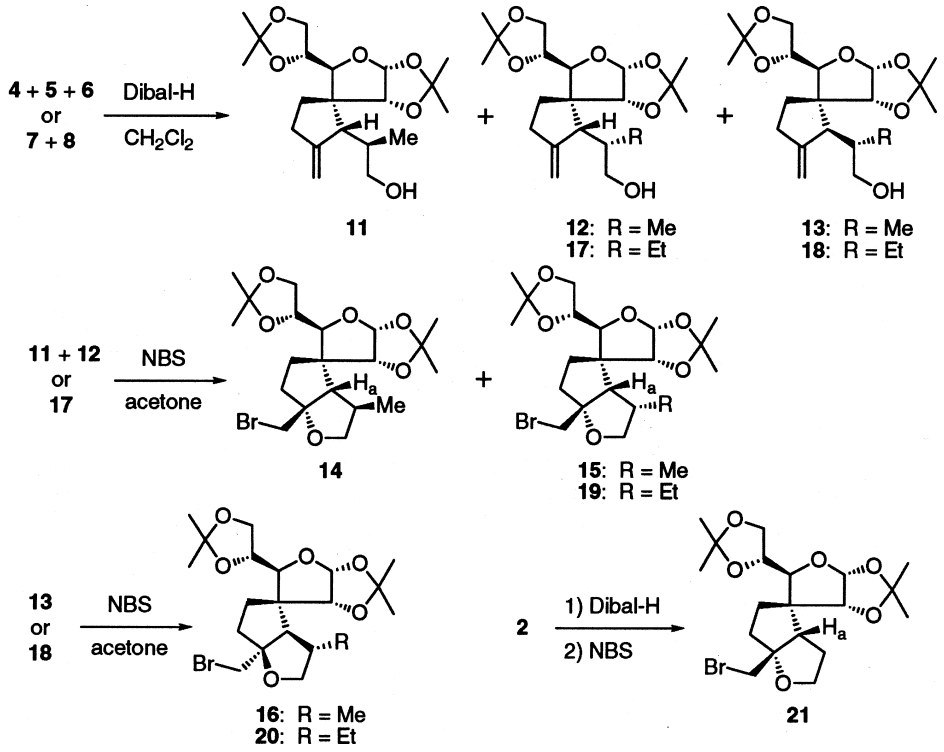


Scheme 3.



Scheme 4.

inseparable mixture of **11** and **12** (20%), and **13** (72%), respectively. The mixture of **11** and **12** was treated with *N*-bromosuccinimide (NBS) to give a mixture of **14** and **15** in 94% yield. Compound **13** was also subjected to bromoetherification with NBS to give **16** in 97% yield. Analogously, the mixture of **7** and **8** was reduced to **17** and **18**, which were readily separated by chromatography on silica gel. The bromoetherification of **17** or **18** provided **19** or **20** in overall yield of 20% or 64%, respectively, from the mixture of **7** and **8**. The structures of the conformationally rigid compounds **14-16**, **19** and **20** were determined by ^{1}H NMR analysis that included NOE difference experiments (Figure 2). In the NOE difference experiments



Scheme 5.

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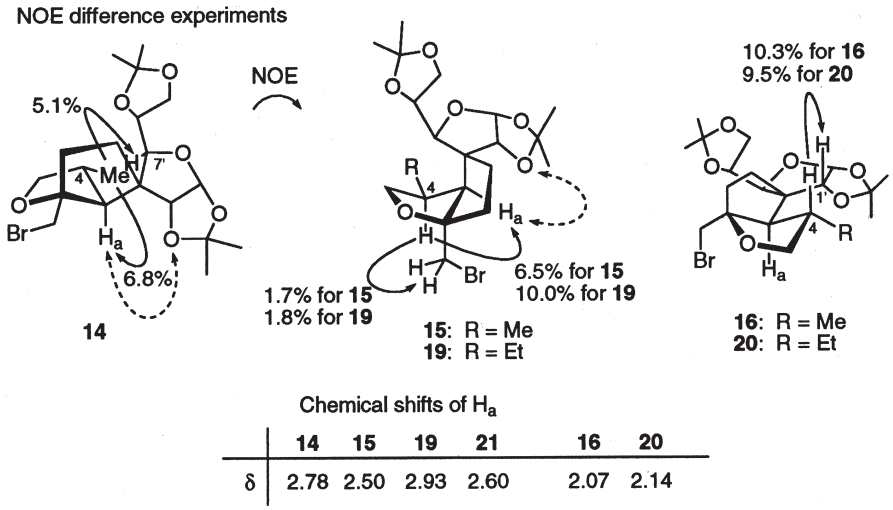

Chemical shifts of H_a

	14	15	19	21	16	20
δ	2.78	2.50	2.93	2.60	2.07	2.14

Figure 2.

for **14**, signal enhancements of H-7' and angular H_a were observed when the Me group at C-4 was irradiated. In the cases of **15** and **19**, signal enhancements of CH_2Br and H_a were observed when H-4 was irradiated. On the other hand, NOE was observed between H-1′ and H-4 in **16** and **20**. Furthermore, the signals for H_a in **14**, **15**, and **19** appeared at lower field than those in **16** and **20** due to the proximity of H_a to one of the isopropylidene oxygens of **14**, **15**, and **19**. Also the chemical shift of H_a in **21**, prepared from **2** by Dibal-H reduction followed by bromoetherification with NBS (Scheme 5), was observed at a lower field as with **14**, **15**, and **19**.

In the Claisen rearrangement of **1** with triethyl orthoacetate (Scheme 1), the σ-bond formation proceeded predominantly from the α-side to avoid the steric hindrance expected in the presence of the isopropylidene group fused with the tetrahydrofuran ring.[12] In contrast, the β-isomers **6** and **8** were obtained both as the major rearrangement products in the present studies. Regarding the transition states of the Claisen rearrangements described above, four chair-like transition states for the rearrangement of **1** with α-substituted orthoacetates are possible (Figure 3).[14] In transition states **TS-A** or **TS-B**, a steric repulsion generated between alkyl group (Me or Et) and the furanosyl ring (**TS-A**) or a 1,3-diaxial repulsion (**TS-B**) is present. Consequently, it is likely that these steric interactions make **TS-A** and **TS-B** less stable than **TS-C** leading to the major products **6** or **8**. Another transition state **TS-D** appears to be much more destabilized in the presence of severe nonbonded interactions as shown.

In conclusion, we have investigated the Claisen rearrangement of **1** with triethyl orthopropionate or trimethyl orthobutyrate, which provided practical access to enantiomerically pure highly functionalized spiro compound building blocks.

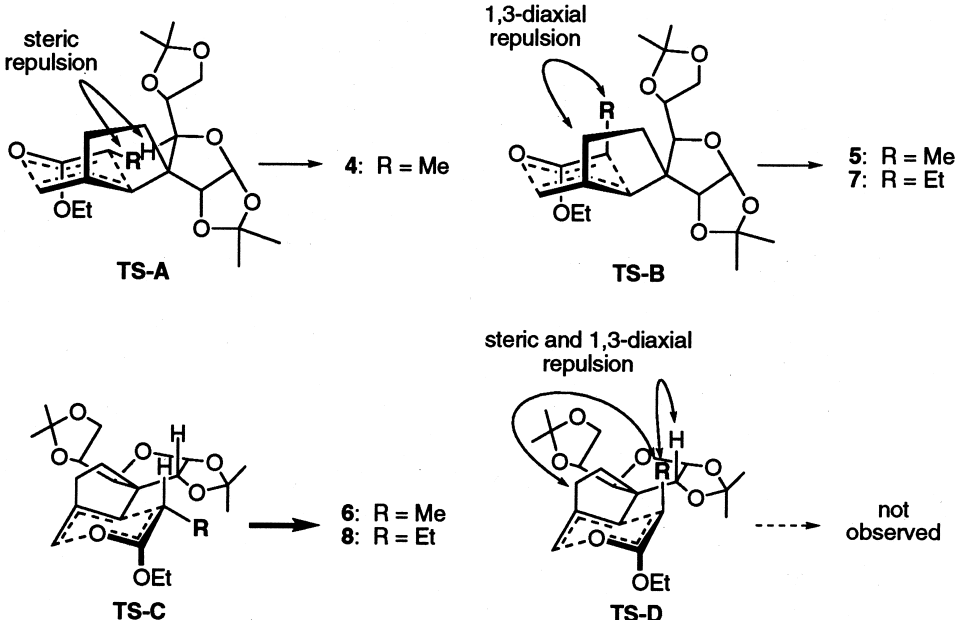

Figure 3.

EXPERIMENTAL

General methods. Melting points are uncorrected. Specific rotations were measured in a 10 mm cell. ^{1}H NMR spectra were recorded by a JEOL JNM-GSX 270 (at 270 MHz) in $CDCl_3$ solution with tetramethylsilane as an internal standard. ^{13}C NMR spectra were recorded at 68 MHz in $CDCl_3$ solution. High-resolution mass spectra (HRMS) were measured by a JEOL JMS-GCMATE spectrometer (EI, 70 eV). Thin-layer chromatography (TLC) was performed on Merck Kieselgel 60 F_{254} plates. Crude reaction mixtures and extractive materials were purified by chromatography on silica gel 60 K070 (Katayama Chemical) or Wakogel C-300 (Wako). Unless otherwise described, reactions were carried out at ambient temperature. Combined organic extracts were dried over anhydrous Na_2SO_4. Solvents were removed from the reaction mixture or combined organic extracts by concentration under reduced pressure using an evaporator at a bath temperature at 35–45 °C.

(1*S*,3*R*,4*R*,5*R*,6*R*)-6-[(1*R*)- (**4**), (1*S*,3*R*,4*R*,5*R*,6*R*)-6-[(1*S*)- (**5**), and (1*S*,3*R*,4*R*,5*R*,6*S*)-6-[(1*S*)-1-(Ethoxycarbonyl)ethyl]-3,4-(isopropyl-idenedioxy)-1-[(1*R*)-1,2-(isopropylidenedioxy)ethyl]-7-methylene-2-oxa-spiro[4.4]nonane (**6**). To a stirred solution of **1** (101 mg, 0.309 mmol) in DMF (2 mL) were added triethyl orthopropionate (1 mL) and propanoic acid (2% solution in DMF, 12 μL, 3 μmol). The mixture was stirred at 130 °C for 4 h and concentrated in vacuo with

the aid of toluene. The residue was purified by column chromatography on silica gel (EtOAc:hexane, 1:8) to provide 110 mg (87%) of an inseparable mixture of **4**, **5**, and **6** (1:2.5:10) as a colorless oil: TLC, R_f 0.56 (EtOAc:hexane, 1:2); IR (neat) 2980, 2940, 2890, 1730, 1650, 1460 cm^{-1}; ^1H NMR (270 MHz) signals attributable to **5** δ 1.15 (d, *J*=7.0 Hz, 3 H, CH_3-1 of the side chain at C-6), 1.28 (t, *J*=7.3 Hz, 3 H, OCH_2CH_3), 1.31, 1.31, 1.40, 1.54 (4s, 3 Hx4, $C(CH_3)_2$x2), 1.41 (m, 1 H, H-9), 1.73 (m, 1 H, H-9), 2.93 (m, 2 H, H-8, 8), 3.30 (m, 1 H, H-1 of the side chain at C-6), 3.41 (m, 1 H, H-6), 3.90–4.16 (m, 6 H, OCH_2CH_3, H-1, and H-1, 2, 2 of the side chain at C-1), 4.35 (d, *J*=2.9 Hz, 1 H, H-4), 4.70 (q, *J*=1.8 Hz, 1 H, C=C*H*H), 4.93 (q, *J*=1.8 Hz, 1 H, C=CH*H*), 5.62 (d, *J*=2.9 Hz, 1 H, H-3), signals attributable to **6** δ 1.27 (t, *J*=7.1 Hz, 3 H, OCH_2CH_3), 1.31, 1.31, 1.40, 1.52 (4s, 3 H•4, $C(CH_3)_2$x2), 1.33 (d, *J*=7.3 Hz, 3 H, CH_3-1 of the side chain at C-6), 1.41 (m, 1 H, H-9), 1.73 (m, 1 H, H-9), 2.43 (m, 2 H, H-8, 8), 2.93 (m, 1 H, H-6), 3.23 (dq, *J*=4.4, 7.3 Hz, 1 H, H-1 of the side chain at C-6), 3.90–4.16 (m, 6 H, OCH_2CH_3, H-1, and H-1, 2, 2 of the side chain at C-1), 4.48 (d, *J*=3.3 Hz, 1 H, H-4), 4.87 (q, *J*=1.8 Hz, 1 H, C=C*H*H), 4.92 (q, *J*=1.8 Hz, 1 H, C=CH*H*), 5.61 (d, *J*=3.3 Hz, 1 H, H-3); ^{13}C NMR (68 MHz) signals attributable to **5** δ 13.2, 14.2, 25.3, 26.2, 26.4, 27.1, 29.1, 32.4, 39.8, 48.2, 58.7, 60.2, 67.6, 73.6, 84.1, 86.3, 103.4, 107.6, 109.1, 112.4, 151.4, 175.5, signals attributable to **6** δ 14.1, 17.3, 25.3, 26.2, 26.4, 27.0, 28.4, 31.3, 40.5, 50.1, 58.7, 60.1, 68.1, 73.7, 83.5, 86.1, 103.8, 107.2, 109.1, 112.0, 152.0, 175.8. HRMS: Calcd for $C_{21}H_{31}O_7$ $[(M–CH_3)^+]$ *m/z* 395.2070. Found 395.2068.

(1*S*,3*R*,4*R*,5*R*,6*R*)- (**7**) and (1*S*,3*R*,4*R*,5*R*,6*S*)-3,4-(Isopropylidenedioxy)-1-[(1*R*)-1,2-(isopropylidenedioxy)ethyl]-6-[(1*S*)-1-(methoxycarbonyl)propyl]-7-methylene-2-oxa-spiro[4.4]nonane (**8**). The following reaction was carried out under Ar. To a stirred solution of **1** (61.0 mg, 0.187 mmol) in DMF (1 mL) were added trimethyl orthobutyrate (0.5 mL), propanoic acid (2% solution in DMF, 7 μL, 2 μmol), and powdered molecular sieves 4A (120 mg). The mixture was stirred at 130 °C for 25 h, and the molecular sieves were removed by filtration and washed well with EtOAc. The combined filtrate and washings were washed with H_2O (30 mL x 3), and the organic layer was dried and concentrated in vacuo with the aid of toluene. The residue was purified by column chromatography on silica gel (EtOAc:hexane, 1:7) to provide 35.3 mg (46%) of an inseparable mixture of **7** and **8**, and 13.9 mg (23%) of **1** was recovered. The diastereomeric mixture of **7** and **8** (**7:8** = 1:3) was obtained as a colorless oil: TLC, R_f 0.58 (EtOAc:hexane, 1:2); IR (neat) 2980, 2940, 2880, 1730, 1650, 1460 cm^{-1}; ^1H NMR (270 MHz) signals attributable to **7** δ 0.91 (t, *J*=6.8 Hz, 3 H, CH_2CH_3), 1.30, 1.31, 1.40, 1.54 (4s, 3 Hx4, $C(CH_3)_2$x2), 1.33 (m, 1 H, H-9), 1.59–2.00 (m, 3 H, H-9, CH_2CH_3), 2.40 (m, 2 H, H-8, 8), 2.95 (m, 1 H, H-1 of the side chain at C-6), 3.26 (m, 1 H, H-6), 3.68 (s, 3 H, OCH_3), 3.88–4.06 (m, 3 H, H-1, 2, 2 of the side chain at C-1), 4.15 (d, *J*=5.9 Hz, 1 H, H-1), 4.34 (d, *J*=2.9 Hz, 1 H, H-4), 4.77 (m, 1 H, C=C*H*H), 4.94 (m, 1 H, C=CH*H*), 5.62 (d, *J*=2.9 Hz, 1 H, H-3), signals attributable to **8** δ 0.94 (t, *J*=7.2 Hz, 3 H, CH_2CH_3), 1.30, 1.33, 1.39, 1.52 (4s, 3 Hx4, $C(CH_3)_2$x2), 1.33

(m, 1 H, H-9), 1.59–2.00 (m, 3 H, H-9, CH_2CH$_3$), 2.40 (m, 2 H, H-8, 8), 2.83 (m, 1 H, H-6), 3.08 (ddd, J=3.3, 5.9, 8.8 Hz, 1 H, H-1 of the side chain at C-6), 3.65 (s, 3 H, OCH$_3$), 3.88–4.06 (m, 3 H, H-1, 2, 2 of the side chain at C-1), 4.10 (d, J=5.9 Hz, 1 H, H-1), 4.54 (d, J=3.1 Hz, 1 H, H-4), 4.89 (q, J=1.7 Hz, 1 H, C=CHH), 4.94 (q, J=1.7 Hz, 1 H, C=CHH), 5.61 (d, J=3.1 Hz, 1 H, H-3); ^{13}C NMR (68 MHz) signals attributable to **7** δ 12.8, 22.1, 24.8, 26.2, 26.4, 27.2, 29.0, 31.8, 46.6, 48.5, 51.3, 58.3, 67.6, 73.7, 83.4, 85.9, 103.9, 108.4, 109.0, 112.4, 150.4, 175.7, signals attributable to **8** δ 12.3, 24.8, 25.3, 26.3, 26.4, 27.0, 28.1, 31.5, 47.9, 49.5, 51.2, 59.1, 67.5, 73.6, 84.1, 86.2, 103.6, 108.0, 108.8, 112.0, 151.5, 175.7. HRMS: Calcd for $C_{21}H_{31}O_7$ [(M–CH$_3$)$^+$] *m/z* 395.2070. Found 395.2071.

(1*S*,3*R*,4*R*,5*R*)-3,4-(Isopropylidenedioxy)-1-[(1*R*)-1,2-(isopropylidenedioxy)ethyl]-7-[1-(propionyloxy)methyl]-2-oxaspiro[4.4]non-6-ene (**9**). To a cooled (0 °C) stirred solution of **1** (203 mg, 0.622 mmol) in CH_2Cl_2 (4 mL) were added propanoic acid (0.70 mL, 0.93 mmol), 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (17.9 mg, 0.933 mmol), and 4-(dimethylamino)pyridine (15.1 mg, 0.124 mmol). The mixture was stirred for 3 h, diluted with H_2O (30 mL) and extracted with CH_2Cl_2 (15 mL x 3). The combined extracts were dried and concentrated in vacuo. The residue was purified by column chromatography on silica gel (EtOAc:hexane, 1:5) to provide 226 mg (95%) of **9** as a colorless oil: TLC, R_f 0.57 (EtOAc:hexane, 1:2); $[\alpha]_D^{26}$ +72.5° (*c* 1.81, $CHCl_3$); IR (neat) 2990, 2940, 2880, 1740, 1460 cm^{-1}; ^{1}H NMR (270 MHz) δ 1.16 (t, J=7.5 Hz, 3 H, CH$_2$CH_3), 1.29, 1.31, 1.35, 1.55 (4s, 3 Hx4, C(CH$_3$)$_2$x2), 1.55 (m, 1 H, H-9), 2.08 (ddd, J=5.5, 7.9, 13.5 Hz, 1 H, H-9), 2.36 (q, J=7.5 Hz, 2 H, CH_2CH$_3$), 2.38-2.45 (m, 2 H, H-8, 8), 3.95-4.10 (m, 4 H, H-1 and H-1, 2, 2 of the side chain at C-1), 4.27 (d, J=3.5 Hz, 1 H, H-4), 4.64 (s, 2 H, H-1, 1 of the side chain at C-7), 5.61 (t, J=1.5 Hz, 1 H, H-6), 5.72 (d, J=3.5 Hz, 1 H, H-3); ^{13}C NMR (68 MHz) δ 9.1, 25.3, 26.2, 26.7, 26.9, 27.5, 28.2, 32.3, 61.9, 62.7, 67.8, 74.1, 81.4, 88.7, 104.1, 109.1, 112.0, 127.0, 141.9, 174.2. HRMS: Calcd for $C_{19}H_{27}O_7$ [(M–CH$_3$)$^+$] *m/z* 367.1757. Found 367.1756.

(1*S*,3*R*,4*R*,5*R*,6*R*)-6-[(1*R*)- (**11**), (1*S*,3*R*,4*R*,5*R*,6*R*)-6-[(1*S*)- (**12**), and (1*S*,3*R*,4*R*,5*R*,6*S*)-6-[(1*S*)-1-(Hydroxymethyl)ethyl]-3,4-(isopropylidenedioxy)-1-[(1*R*)-1,2-(isopropylidenedioxy)ethyl]-7-methylene-2-oxa-spiro[4.4]nonane (**13**). The following reaction was carried out under Ar. To a cooled (–78 °C) stirred solution of the mixture of **4**, **5**, and **6** (63.5 mg, 0.155 mmol) in CH_2Cl_2 (2 mL) was added Dibal-H (1.00 M solution in toluene, 0.50 mL, 0.50 mmol). The mixture was stirred at –78 °C for 30 min and quenched with H_2O (0.5 mL). The precipitated solids were removed by filtration through a Celite-pad and washed well with CH_2Cl_2. The combined filtrate and washings were diluted with H_2O (60 mL) and extracted with CH_2Cl_2 (30 mL x 3). The combined extracts were dried and concentrated in vacuo. The residue was purified by column chromatography on silica gel (EtOAc:hexane, 1:3) to provide 11.6 mg (20%) of an inseparable mixture of **11** and **12** and 41.0 mg (72%) of **13**. The diastereomeric mixture of **11** and **12** (**11:12** = 1:2.5) was obtained as a colorless oil: TLC, R_f 0.31 (EtOAc:hexane, 1:2); IR

(neat) 3480, 2980, 2930, 2880, 1650, 1460 cm^{-1}; ^1H NMR (270 MHz) signals attributable to **11** δ 1.05 (d, *J*=6.6 Hz, 3 H, CH_3-1 of the side chain at C-6), 1.30, 1.33, 1.44, 1.53 (4s, 3 Hx4, $C(CH_3)_2$x2), 1.43 (m, 1 H, H-9), 1.70 (m, 1 H, H-9), 2.04–2.18 (m, 3 H, H-8, 8 and H-1 of the side chain at C-6), 2.84 (m, 1 H, H-6), 3.32 (dd, *J*=6.2, 11.0 Hz, 1 H, C*H*HOH), 3.54 (m, 1 H, CH*H*OH), 3.89–4.17 (m, 4 H, H-4, and H-1, 2, 2 of the side chain at C-1), 4.31 (d, *J*=5.9 Hz, 1 H, H-1), 4.97 (m, 1 H, C=C*H*H), 5.03 (m, 1 H, C=CH*H*), 5.66 (d, *J*=3.3 Hz, 1 H, H-3), signals attributable to **12** δ 0.87 (d, *J*=7.0 Hz, 3 H, CH_3-1 of the side chain at C-6), 1.30, 1.33, 1.38, 1.53 (4s, 3 Hx4, $C(CH_3)_2$x2), 1.43 (m, 1 H, H-9), 1.70 (m, 1 H, H-9), 2.34–2.51 (m, 3 H, H-8, 8 and H-1 of the side chain at C-6), 2.80 (m, 1 H, H-6), 3.54 (m, 2 H, CH_2OH), 3.89–4.17 (m, 4 H, H-1, and H-1, 2, 2 of the side chain at C-1), 4.36 (d, *J*=3.0 Hz, 1 H, H-4), 4.82 (m, 1 H, C=C*H*H), 4.95 (m, 1 H, C=CH*H*), 5.63 (d, *J*=3.0 Hz, 1 H, H-3); ^{13}C NMR (68 MHz) signals attributable to **11** δ 18.9, 25.6, 26.2, 27.1, 27.3, 28.0, 29.7, 36.2, 51.5, 60.0, 66.2, 68.4, 74.4, 81.5, 87.4, 102.6, 108.9, 109.5, 111.8, 151.5, signals attributable to **12** δ 13.5, 25.5, 26.5, 26.5, 27.1, 29.1, 32.3, 35.6, 48.1, 59.4, 67.0, 67.1, 73.5, 84.4, 86.2, 103.6, 108.6, 108.7, 112.2, 151.2. HRMS: Calcd for $C_{19}H_{29}O_6$ [$(M–CH_3)^+$] *m/z* 353.1964. Found 353.1968. Compound **13** was obtained as a colorless oil: TLC, R_f 0.22 (EtOAc:hexane, 1:2); $[\alpha]_D^{20}$ +44.9° (*c* 2.10, $CHCl_3$); IR (neat) 3480, 2985, 2935, 2880, 1650, 1460 cm^{-1}; ^1H NMR (270 MHz) δ 1.12 (d, *J*=7.0 Hz, 3 H, CH_3-1 of the side chain at C-6), 1.31, 1.33, 1.39, 1.54 (4s, 3 Hx4, $C(CH_3)_2$x2), 1.46 (m, 1 H, H-9), 1.70 (m, 1 H, H-9), 2.38–2.56 (m, 3 H, H-8, 8 and H-1 of the side chain at C-6), 2.74 (m, 1 H, H-6), 3.46 (dd, *J*=7.3, 11.0 Hz, 1 H, C*H*HOH), 3.71 (dd, *J*=5.7, 11.0 Hz, 1 H, CH*H*OH), 3.90–4.12 (m, 4 H, H-1, and H-1, 2, 2 of the side chain at C-1), 4.41 (d, *J*=3.1 Hz, 1 H, H-4), 4.90 (q, *J*=1.8 Hz, 1 H, C=C*H*H), 4.94 (q, *J*=1.8 Hz, 1 H, C=CH*H*), 5.63 (d, *J*=3.1 Hz, 1 H, H-3); ^{13}C NMR (68 MHz) δ 17.7, 25.3, 26.4, 26.5, 27.2, 29.0, 32.0, 36.3, 50.7, 58.9, 66.0, 67.6, 73.5, 83.3, 86.1, 103.9, 107.7, 109.0, 112.2, 151.8. HRMS: Calcd for $C_{19}H_{29}O_6$ [$(M–CH_3)^+$] *m/z* 353.1964. Found 353.1966.

(1*R*,1′*R*,4*R*,5*S*,5′*R*,6*R*,7′*S*)- (**14**) and (1*R*,1′*R*,4*S*,5*S*,5′*R*,6*R*,7′*S*)-1-(Bromomethyl)-7′-[(1*R*)-1,2-(isopropylidenedioxy)ethyl]-3′,3′,4-trimethyl-2,2′,4′,6′-tetraoxa-spiro[bicyclo[3.3.0]octane-6,8′-bicyclo[3.3.0]octane] (**15**). To a cooled (0 °C) stirred solution of the mixture of **11** and **12** (11.6 mg, 0.0315 mmol) in acetone (1 mL) was added *N*-bromosuccinimide (8.4 mg, 0.047 mmol). The mixture was stirred at 0 °C for 10 min, diluted with EtOAc (20 mL), and washed with saturated aqueous $Na_2S_2O_3$ (10 mL x 2), saturated aqueous $NaHCO_3$ (10 mL), and saturated brine (10 mL), successively. The organic layer was dried and concentrated in vacuo. The residue was purified by column chromatography on silica gel (EtOAc:hexane, 1:8) to provide 13.3 mg (94%) of a 1:2.5 mixture of **14** and **15** (1:2.5) as white solids: TLC, R_f 0.53 (EtOAc:hexane, 1:2); IR (neat) 2980, 2940, 2880, 1450 cm^{-1}; ^1H NMR (270 MHz) signals attributable to **14** δ 1.04 (d, *J*=6.4 Hz, 3 H, CH_3 at C-4), 1.33, 1.35, 1.40, 1.52 (4s, 3 Hx4, $C(CH_3)_2$x2), 1.81–2.07 (m, 4 H, H-7, 7, 8, 8), 2.50 (d, *J*=7.8 Hz, 1 H, H-5), 2.76 (m, 1 H, H-4), 3.39 (t, *J*=9.1 Hz, 1 H, H-3), 3.48 (d, *J*=10.7 Hz, 1 H, C*H*HBr), 3.67 (d, *J*=10.7 Hz, 1 H,

CH*H*Br), 3.81–4.21 (m, 5 H, H-1′, 3 and H-1, 2, 2 of the side chain at C-7′), 4.24 (d, *J*=6.4 Hz, 1 H, H-7'), 5.72 (d, *J*=3.9 Hz, 1 H, H-5′), signals attributable to **15** δ 1.31 (d, *J*=7.3 Hz, 3 H, CH_3 at C-4), 1.32, 1.38, 1.43, 1.52 (4s, 3 Hx4, $C(CH_3)_2$x2), 1.81–2.07 (m, 4 H, H-7, 7, 8, 8), 2.66 (m, 1 H, H-4), 2.78 (d, *J*=6.8 Hz, 1 H, H-5), 3.58 (d, *J*=10.3 Hz, 1 H, C*H*HBr), 3.75 (t, *J*=8.3 Hz, 1 H, H-3), 3.78 (d, *J*=10.3 Hz, 1 H, CH*H*Br), 3.81–4.21 (m, 5 H, H-3, 7′ and H-1, 2, 2 of the side chain at C-7′), 4.47 (d, *J*=3.2 Hz, 1 H, H-1′), 5.60 (d, *J*=3.2 Hz, 1 H, H-5′); ^{13}C NMR (68 MHz) signals attributable to **14** δ 17.2, 25.5, 26.1, 26.8, 27.2, 28.7, 35.2, 37.0, 40.2, 57.4, 59.0, 68.3, 74.5, 77.2, 81.7, 86.0, 93.8, 103.5, 109.4, 111.9, signals attributable to **15** δ 14.5, 25.5, 26.1, 26.6, 27.2, 31.6, 36.1, 38.5, 39.5, 53.6, 58.9, 69.7, 73.3, 75.3, 84.1, 85.1, 94.3, 104.0, 109.8, 112.0. HRMS: Calcd for $C_{19}H_{28}BrO_6$ [$(M–CH_3)^+$] *m/z* 431.1069. Found 431.1073.

(1*S*,1′*R*,4*S*,5*R*,5′*R*,6*R*,7′*S*)-1-(Bromomethyl)-7′-[(1*R*)-1,2-(isopropylidenedioxy)-ethyl]-3′,3′,4-trimethyl-2,2′,4′,6′-tetraoxaspiro[bicyclo[3.3.0]octane-6,8′-bicyclo[3.3.0]-octane] (**16**). As described for the preparation of **14** and **15**, compound **13** (30.7 mg, 0.0833 mmol) was treated with NBS to provide 36.4 mg (97%) of **16** as colorless crystals: mp 94.0–95.5 °C; TLC, R_f 0.49 (EtOAc:hexane, 1:2); $[\alpha]_D^{19}$ +27.4° (*c* 1.82, $CHCl_3$); IR (neat) 2990, 2960, 2935, 2880, 1460 cm^{-1}; ^{1}H NMR (270 MHz) δ 1.15 (d, *J*=6.6 Hz, 3 H, CH_3 at C-4), 1.31, 1.39, 1.43, 1.52 (4s, 3 Hx4, $C(CH_3)_2$x2), 1.56–1.89 (m, 3 H, H-7, 7, 8), 2.06 (m, 1 H, H-8), 2.07 (d, *J*=5.5 Hz, 1 H, H-5), 2.59 (m, 1 H, H-4), 3.39 (t, *J*=9.1 Hz, 1 H, H-3), 3.70 (d, *J*=10.4 Hz, 1 H, C*H*HBr), 3.81 (dd, *J*=6.8, 8.1 Hz, 1 H, H-2 of the side chain at C-7′), 3.86 (d, *J*=10.4 Hz, 1 H, CH*H*Br), 3.87 (d, *J*=9.2 Hz, 1 H, H-7′), 3.96 (ddd, *J*=5.5, 6.8, 9.2 Hz, 1 H, H-1 of the side chain at C-7′), 4.09 (dd, *J*=7.9, 9.1 Hz, 1 H, H-3), 4.19 (dd, *J*=5.5, 8.1 Hz, 1 H, H-2 of the side chain at C-7′), 4.35 (d, *J*=3.1 Hz, 1 H, H-1′), 5.57 (d, *J*=3.1 Hz, 1 H, H-5′); ^{13}C NMR (68 MHz) δ 18.8, 25.5, 26.4, 26.7, 27.1, 29.1, 36.9, 37.8, 40.0, 59.1, 60.7, 69.7, 73.0, 74.4, 84.7, 88.0, 95.3, 103.2, 109.7, 112.0. HRMS: Calcd for $C_{19}H_{28}BrO_6$ [$(M–CH_3)^+$] *m/z* 431.1069. Found 431.1070.

(1*S*,3*R*,4*R*,5*R*,6*R*)- (**17**) and (1*S*,3*R*,4*R*,5*R*,6*S*)-6-[(1*S*)-1-(Hydroxymethyl) propyl]-3,4-(isopropylidenedioxy)-1-[(1*R*)-1,2-(isopropylidenedioxy)ethyl]-7-methylene-2-oxa-spiro[4.4]nonane (**18**). As described for the preparation of **11**, **12** and **13**, the mixture of **7** and **8** (29.9 mg, 0.0728 mmol) was treated with Dibal-H to provide 6.1 mg (22%) of **17** and 19.6 mg (70%) of **18**. Compound **17** was obtained as a colorless oil: TLC, R_f 0.40 (EtOAc:hexane, 1:2); $[\alpha]_D^{18}$ +58.5° (*c* 0.27, $CHCl_3$); IR (neat) 3500, 2990, 2960, 2940, 1650, 1460 cm^{-1}; ^{1}H NMR (270 MHz) δ 0.95 (t, *J*=7.3 Hz, 3 H, CH_2CH_3), 1.32, 1.32, 1.40, 1.54 (4s, 3 Hx4, $C(CH_3)_2$x2), 1.13–1.45 (m, 3 H, H-9, CH_2CH_3), 1.75 (m, 1 H, H-9), 2.17 (m, 1 H, H-1 of the side chain at C-6), 2.45 (m, 2 H, H-8, 8), 2.96 (m, 1 H, H-6), 3.56 (t, *J*=10.5 Hz, 1 H, C*H*HOH), 3.79 (dd, *J*=3.9, 10.5 Hz, 1 H, CH*H*OH), 3.86–4.12 (m, 3 H, H-1, 2, 2 of the side chain at C-1), 4.17 (d, *J*=6.4 Hz, 1 H, H-1), 4.34 (d, *J*=2.9 Hz, 1 H, H-4), 4.88 (q, *J*=1.7 Hz, 1 H, C=C*H*H), 4.95 (q, *J*=1.7 Hz, 1 H, C=CH*H*), 5.64 (d, *J*=2.9 Hz, 1 H, H-3); ^{13}C NMR (68 MHz) δ 12.8, 21.6, 25.6, 26.3, 26.3, 27.1, 29.1, 31.9, 42.5, 47.5, 58.7, 64.4, 67.9, 73.5, 83.0, 85.7, 104.0, 107.9, 109.3, 112.4,

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151.2. HRMS: Calcd for $C_{20}H_{31}O_6$ [$(M–CH_3)^+$] *m/z* 367.2121. Found 367.2122. Compound **18** was obtained as a colorless oil: TLC, R_f 0.23 (EtOAc:hexane, 1:2); $[\alpha]_D^{18}$ +50.4° (*c* 0.89, $CHCl_3$); IR (neat) 3500, 2980, 2960, 2840, 1650, 1460 cm^{-1}; ^1H NMR (270 MHz) δ 1.00 (t, *J*=7.3 Hz, 3 H, CH_2CH_3), 1.31, 1.33, 1.39, 1.54 (4s, 3 Hx4, $C(CH_3)_2$x2), 1.47 (m, 1 H, H-9), 1.59–1.78 (m, 3 H, H-9, CH_2CH_3), 2.20 (m, 1 H, H-1 of the side chain at C-6), 2.46 (m, 2 H, H-8, 8), 2.88 (m, 1 H, H-6), 3.54 (dd, *J*=6.1, 11.0 Hz, 1 H, C*H*HOH), 3.70 (dd, *J*=5.1, 11.0 Hz, 1 H, CH*H*OH), 3.89–4.11 (m, 4 H, H-1 and H-1, 2, 2 of the side chain at C-1), 4.40 (d, *J*=3.3 Hz, 1 H, H-4), 4.87 (q, *J*=1.8 Hz, 1 H, C=C*H*H), 4.92 (q, *J*=1.8 Hz, 1 H, C=CH*H*), 5.64 (d, *J*=3.3 Hz, 1 H, H-3); ^{13}C NMR (68 MHz) δ 12.5, 24.8, 25.4, 26.4, 26.6, 27.2, 29.2, 32.4, 43.2, 47.7, 58.9, 65.1, 67.9, 73.6, 83.5, 86.2, 104.1, 107.4, 109.1, 112.3, 152.2. HRMS: Calcd for $C_{20}H_{31}O_6$ [$(M–CH_3)^+$] *m/z* 367.2121. Found 367.2129.

(1*R*,1′*R*,4*S*,5*S*,5′*R*,6*R*,7′*S*)-1-(Bromomethyl)-4-ethyl-7′-[(1*R*)-1,2-(isopropylidene-dioxy)ethyl]-3′,3′-dimethyl-2,2′,4′,6′-tetraoxaspiro[bicyclo[3.3.0]octane-6,8′-bicyclo[3.3.0]octane] (**19**). As described for the preparation of **14** and **15**, compound **17** (6.1 mg, 0.016 mmol) was treated with NBS to provide 6.7 mg (91%) of **19** as colorless crystals: mp 76.0–78.0 °C; TLC, R_f 0.59 (EtOAc:hexane, 1:2); $[\alpha]_D^{18}$ +30.2° (*c* 0.34, $CHCl_3$); IR (neat) 2980, 2960, 2940, 2880, 1460 cm^{-1}; ^1H NMR (270 MHz) δ 0.94 (t, *J*=7.3 Hz, 3 H, CH_2CH_3), 1.32, 1.36, 1.42, 1.52 (4s, 3 Hx4, $C(CH_3)_2$x2), 1.40–2.09 (m, 6 H, H-7, 7, 8, 8, CH_2CH_3), 2.41 (m, 1 H, H-4), 2.93 (d, *J*=6.6 Hz, 1 H, H-5), 3.51 (d, *J*=10.1 Hz, 1 H, C*H*HBr), 3.59 (d, *J*=10.1 Hz, 1 H, CH*H*Br), 3.81–4.09 (m, 5 H, H-3, 3, 7′ and H-1, 2 of the side chain at C-7′), 4.18 (dd, *J*=5.5, 8.1 Hz, 1 H, H-2 of the side chain at C-7′), 4.41 (d, *J*=2.7 Hz, 1 H, H-1′), 5.62 (d, *J*=2.7 Hz, 1 H, H-5′); ^{13}C NMR (68 MHz)δ? 14.3, 20.5, 25.4, 26.2, 26.6, 27.2, 32.0, 35.6, 39.7, 46.1, 51.9, 58.6, 69.5, 73.2, 73.6, 83.0, 84.8, 94.1, 104.5, 109.7, 112.3. HRMS: Calcd for $C_{20}H_{30}BrO_6$ [$(M–CH_3)^+$] *m/z* 447.1205. Found 447.1205.

(1*S*,1′*R*,4*S*,5*R*,5′*R*,6*R*,7′*S*)-1-(Bromomethyl)-4-ethyl-7′-[(1*R*)-1,2-(isopropylidene-dioxy)ethyl]-3′,3′-dimethyl-2,2′,4′,6′-tetraoxaspiro[bicyclo[3.3.0]octane-6,8′-bicyclo[3.3.0]octane] (**20**). As described for the preparation of **14** and **15**, compound **18** (19.6 mg, 0.0512 mmol) was treated with NBS to provide 21.7 mg (92%) of **20** as a colorless oil: TLC, R_f 0.68 (EtOAc:hexane, 1:2); $[\alpha]_D^{18}$ +36.2° (*c* 1.09, $CHCl_3$); IR (neat) 2980, 2960, 2935, 2880, 1460 cm^{-1}; ^1H NMR (270 MHz) δ 0.86 (t, *J*=7.3 Hz, 3 H, CH_2CH_3), 1.31, 1.38, 1.42, 1.51 (4s, 3 Hx4, $C(CH_3)_2$x2), 1.54–1.93 (m, 5 H, H-7, 7, 8, CH_2CH_3), 2.08 (m, 1 H, H-8), 2.14 (d, *J*=4.8 Hz, 1 H, H-5), 2.50 (m, 1 H, H-4), 3.49 (t, *J*=8.6 Hz, 1 H, H-3), 3.67 (d, *J*=10.5 Hz, 1 H, C*H*HBr), 3.80 (d, *J*=10.5 Hz, 1 H, CH*H*Br), 3.83 (dd, *J*=6.7, 8.1 Hz, H-2 of the side chain at C-7′), 3.86 (d, *J*=9.2 Hz, 1 H, H-7′), 3.96 (ddd, *J*=5.7, 6.7, 9.2 Hz, 1 H, H-1 of the side chain at C-7′), 4.16 (t, *J*=8.6 Hz, 1 H, H-3), 4.19 (dd, *J*=5.7, 8.1 Hz, 1 H, H-2 of the side chain at C-7′), 4.34 (d, *J*=3.1 Hz, 1 H, H-1′), 5.57 (d, *J*=3.1 Hz, 1 H, H-5′); ^{13}C NMR (68 MHz) δ 12.8, 25.5, 26.4, 26.7, 27.1, 28.1, 29.2, 36.9, 37.9, 46.7, 57.1, 60.7, 69.7, 73.1, 73.2, 84.6, 87.8, 94.8,

103.4, 109.7, 112.0. HRMS: Calcd for $C_{20}H_{30}BrO_6$ [$(M–CH_3)^+$] *m/z* 447.1205. Found 447.1201.

(1*R*,1′*R*,5*S*,5′*R*,6*R*,7′*S*)-1-(Bromomethyl)-7′-[(1*R*)-1,2-(isopropylidenedioxy)ethyl]-3′,3′-dimethyl-2,2′,4′,6′-tetraoxaspiro[bicyclo[3.3.0]octane-6,8′-bicyclo[3.3.0]octane] (**21**). As described for the preparation of **11**, **12** and **13**, the 14:1 mixture of **2** and **3**[12] (33.5 mg, 0.0845 mmol) was treated with Dibal-H to provide 29.6 mg (99%) of a 14:1 mixture of the alcohols as a colorless oil: TLC, R_f 0.24 (EtOAc:hexane, 1:2); $[\alpha]_D^{17}$ +58.5° (*c* 1.48, $CHCl_3$); IR (neat) 3480, 2990, 2960, 2940, 2880, 1650, 1460 cm^{-1}; ^1H NMR (270 MHz) for the major isomer δ 1.28, 1.34, 1.42, 1.52 (4s, 3 Hx4, $C(CH_3)_2$x2), 1.40 (m, 1 H, H-9), 1.75–1.91 (m, 2 H, H-9 and H-1 of the side chain at C-6), 2.16 (m, 1 H, H-1 of the side chain at C-6), 2.48 (m, 2 H, H-8, 8), 2.71 (m, 1 H, H-6), 3.65–4.18 (m, 6 H, C*H*$_2$OH, H-1 and H-1, 2, 2 of the side chain at C-1), 4.27 (d, *J*=3.3 Hz, 1 H, H-4), 4.90 (q, *J*=2.4 Hz, 1 H, C=C*H*H), 4.91 (q, *J*=2.4 Hz, 1 H, C=CH*H*), 5.66 (d, *J*=3.3 Hz, 1 H, H-3); ^{13}C NMR (68 MHz) for the major isomer δ 25.5, 26.3, 26.3, 27.0, 27.5, 28.7, 31.9, 44.0, 57.9, 61.9, 68.5, 73.6, 81.4, 85.5, 104.0, 105.8, 109.5, 112.3, 152.8. HRMS: Calcd for $C_{18}H_{27}O_6$ [$(M–CH_3)^+$] *m/z* 339.1808. Found 339.1815.

As described for the preparation of **14** and **15**, the 14:1 mixture of the alcohols (29.6 mg, 0.0835 mmol) was treated with NBS to provide 33.1 mg (91%) of a 14:1 mixture of **21** and its isomer as a colorless oil: TLC, R_f 0.50 (EtOAc:hexane, 1:2); $[\alpha]_D^{16}$ +56.0° (*c* 1.66, $CHCl_3$); IR (neat) 2990, 2960, 2940, 2880, 1460 cm^{-1}; ^1H NMR (270 MHz) for the major isomer **21** δ 1.31, 1.38, 1.43, 1.51 (4s, 3 Hx4, $C(CH_3)_2$x2), 1.54–2.11 (m, 4 H, H-7, 7, 8, 8), 2.30 (m, 2 H, H-4, 4), 2.60 (dd, *J*=5.0, 8.3 Hz, 1 H, H-5), 3.66 (d, *J*=10.3 Hz, 1 H, C*H*HBr), 3.81 (d, *J*=10.3 Hz, 1 H, CH*H*Br), 3.82–4.01 (m, 5 H, H-3, 3, 7′ and H-1, 2 of the side chain at C-7′), 4.19 (dd, *J*=5.7, 8.3 Hz, 1 H, H-2 of the side chain at C-7′), 4.29 (d, *J*=3.1 Hz, 1 H, H-1'), 5.57 (d, *J*=3.1 Hz, 1 H, H-5′); ^{13}C NMR (68 MHz) for the major isomer **21** δ 25.6, 26.4, 26.7, 27.1, 29.7, 32.0, 37.3, 39.3, 50.5, 59.9, 68.9, 69.6, 73.0, 84.3, 87.3, 94.2, 103.3, 109.7, 112.2. HRMS: Calcd for $C_{18}H_{26}BrO_6$ [$(M–CH_3)^+$] *m/z* 417.0912. Found 417.0906.

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