Synthesis of Cycloheptenols from Carbohydrates by Ring-Closing Metathesis

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The metathesis reaction of suitable functionalized dienes has resulted in an elegant and efficient strategy for the synthesis of a variety of carbocyclic ring systems.[1]

In this context, the ring-closing metathesis (RCM) of chiral, polyfunctionalized 1,ω-dienes, leading to densely functionalized, enantiomerically pure cyclopentenes or cyclohexenes, has been reported.[2] Despite these efforts, the ring-closing metathesis (RCM) of chiral, polyoxygenated 1,8-nonadienes leading to polyfunctionalized cycloheptene derivatives has remained unexplored.[1f−i] This is surprising in view of the large number of natural products containing a seven-membered-ring carbocycle as structural motif[3] with remarkable biological activities.[4,5]

We now report that a variety of cycloheptenols[6] can be synthesized in enantiomerically pure form, in high chemical yield and extremely mild conditions, by ring-closing metathesis of acyclic, chiral polyoxygenated 1,8-nonadiene precursors derived from carbohydrates. In addition, these results gave us the opportunity to describe the critical effects of the absolute configurations at the stereocenters and/or protecting groups around the olefinic bonds in the course of the ring-closing metathesis.[7]

For our initial studies we selected D-mannose as starting material and the readily available derivative **1**[2a] as key intermediate (Scheme 1). Allylmagnesium bromide addition to this lactol gave the expected diol **2** as a mixture of isomers [**2a**(C6*R*)/**2b**(C6*S*): 7/3)] in 85% chemical yield, that were easily separated by flash chromatography and independiently transformed. The formation of major *R* isomers in the addition of Grignard-like reagents to carbohydrate derived lactols is well documented[8] and has been used in several synthetic schemes. From compound **2a**, and following standard protocols, the corresponding diacetylated **3a**, dibenzylated **4** and the silylated/acetylated **6**, precursors were easily obtained. Analogously, from compound **2b** we prepared the corresponding diacetylated **3b** derivative. All new molecules showed excellent analytical and spectroscopic data, in good agreement with the structures shown in Scheme 1 (see the **Supporting Information**).

With these compounds in our hands, we tested the carbocyclization protocol. After some experimentation, conditions were found to promote efficient ring-closing reactions. The RCM of compounds **2**−**4** and **6**, mediated by benzylidenebis(tricyclohexylphosphine)dichlororuthenium (**7**) as catalyst (10%), afforded the cycloheptenols **8**−**13** (Scheme 1) (see the **Experimental Section**). Under these conditions, at room temperature and using methylene chloride (0.02 M) as solvent, the free alcohol **2a** gave the carbocycle **8** in a slow (7 days), incomplete, and low-yielding reaction [45% (70%)].[9] Conversely, its epimer **2b** gave the RCM product **9** after 6 h, in 85% yield. Very interestingly, all the di-*O*-protected deriva-

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(9) The RCM reaction of precursor **2a** using methylene chloride at reflux gave the same result [45% (70%) after 7 days]. When toluene was tested as solvent the yield [17% (26%) after 2 days] was worse and extended decomposition was observed.

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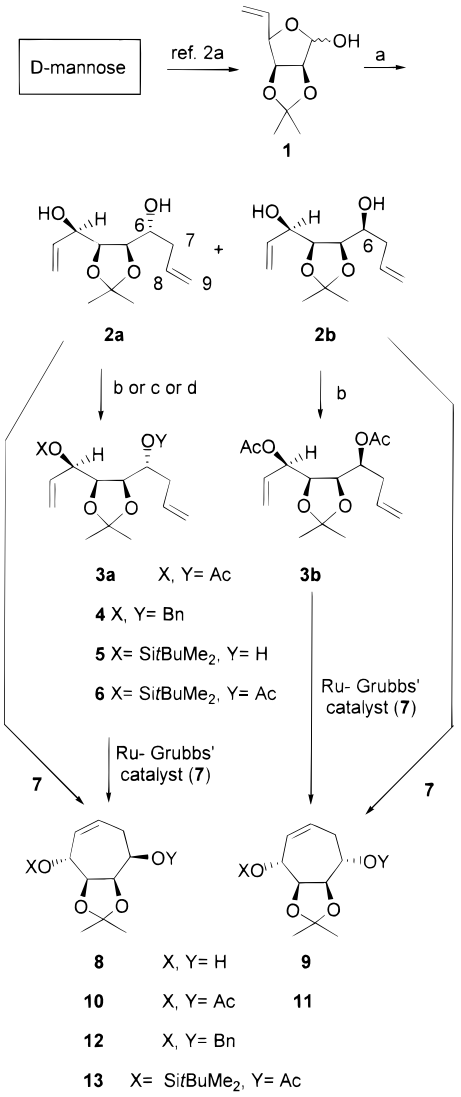
Scheme 1[a]



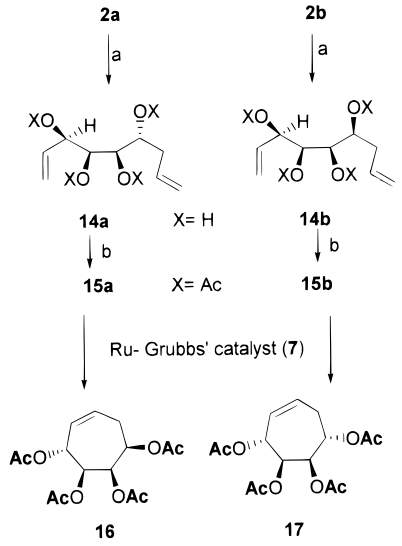
[a] Reagents: (a) $CH_2{=}CHCH_2MgBr$, THF, 0 °C (85%); (b) Ac_2O, py, rt (for **2a** to **3a**: 99%; for **2b** to **3b**: 90%); (c) BnBr, NaH, THF (for **2a** to **4**: 99%); (d) (i) $ClSitBuMe_2$, py (65%), (ii) Ac_2O, py (99%) [for **2a** *via* **5** to **6**).

tives **3a**, **4**, and **6**, derived from **2a**, afforded the carbocyclization products **10** (1 h, 95%), **12** (1 h, 90%), and **13** (40 min, 99%), respectively, in fast reactions in very good chemical yields. In agreement with this and not surprisingly, the diacetate precursor **3b**, derived from compound **2b**, gave the cycloheptenol derivative **11** in the fastest reaction time (20 min) and in an equally high chemical yield (96%).

To test the presumed entropic assistance to the cyclization process[10] derived from the pre-exinting *syn* 1,3-dioxolane ring at C4−C5[11] in our substrates, compounds **2a** and **2b** were submitted to acid hydrolysis and acetylation to give open-chain precursors **15a** and **15b**, *via* alcohols **14a** and **14b**, respectively (Scheme 2) (see the **Supporting Information**). To our great satisfaction, products **15a** and **15b**, under the same experimental conditions, afforded the carbocycles **16** (6 h, 90%) and **17** (2 h, 85%) in excellent yields and mild conditions (see the **Experimental Section**). For correlation purposes,

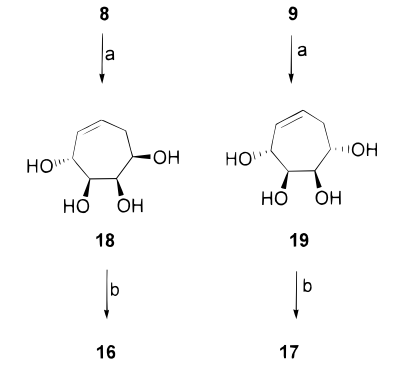
(10) Edwards, S. D.; Lewis, T.; Taylor, R. J. K. *Tetrahedron Lett.* **1999**, *40*, 4267.

Scheme 2[a]



[a] Reagents: (a) $AcOH/H_2O$ (for **2a** to **14a**: 99%; for **2b** to **14b**: 99%); (b) Ac_2O, py, rt (for **14a** to **15a**: 99%; for **14b** to **15b**: 99%).

Scheme 3[a]



[a] Reagents: (a) $AcOH/H_2O$ (for **8** to **18**: 90%; for **9** to **19**: 85%); (b) Ac_2O, py, rt (for **18** to **16**: 98%; for **19** to **17**: 81%).

these products were also obtained by acid hydrolysis and acetylation of carbocycles **8** and **9** (Scheme 3), respectively. The effect of the protected hydroxyl functions were evident again when, in the standard metathesis conditions, fully deprotected poliol precursors **14a** and **14b** prooved to be very reluctanct to react and were recovered unchanged, after one week reaction time.

From the results reported above several conclusions can be drawn: (a) open chain or conformationally restricted precursors are good substrates for the RCM reaction; (b) the absolute stereochemistry at the "allyl-part" of the 1,8-nonandiene precursor has a deep influence in the course of the RCM reaction; (c) the different steric crowding around the olefinic bonds probably allowed the first formal [2 + 2] cycloaddition/cycloreversion

(11) The importance of preexisting heterocycles in selected positions and orientations on acyclic precursors for successful carbocyclization processes has been demostrated in our laboratory: (a) Marco-Contelles, J.; Ruiz, P.; Martínez, L.; Martínez-Grau, A. *Tetrahedron* **1993**, *49*, 6669. (b) Marco-Contelles, J.; Bernabé, M.; Ayala, D.; Sánchez, B. *J. Org. Chem.* **1994**, *59*, 1234 [for an application of the results reported in this paper, see: (c) Gómez, A. M.; Danelón, G. O.; Valverde, S.; López, J. C. *J. Org. Chem.* **1998**, *63*, 9626; *Corrigendum*: *J. Org. Chem.* **1999**, *64*, 7280]. (d) Marco-Contelles, J.; Pozuelo, C.; Jimeno, M. L.; Martínez, L.; Martínez-Grau, A. *J. Org. Chem.* **1992**, *57*, 2625. (e) Marco-Contelles, J.; Martínez-Grau, A. *Chem. Soc. Rev.* **1998**, *27*, 155.

processes[1] to take place at the less hindered C8=C9 bond;[12] (d) these effects are minimized in protected (acetylated or benzylated) derivatives, leading to differently protected cycloheptenols in good yields, in fast reactions, under mild reaction conditions.

The observations found in this work can be rationalized in terms of the preferred conformations, due to possible powerful coordination between the −OH at C-6 on the Ru=C8 carbene,[13] in the transition states for the RCM reaction, that bring more reactive, closer and paralel the double bonds to be metathesized, minimizing other possible unfavorable interactions. Similarly, for the protected acetyl derivatives (**3a**, **3b**, **6**, **15a** and **15b**) the oxygen at the carbonyl is expected to effectively and efficiently to coordinate with the ruthenium carbene center in six-membered chelate structures promoting fast RCM reactions. Identical observations have been reported in other substrates,[7] but to the best our knowledge these critical structure−reactivity relationships have not been described before in open-chain sugar templates.[14]

In summary, the results reported here are noteworthy and constitute one of the best known synthetic alternatives for the preparation of enantiomerically pure, highly functionalized cycloheptene derivatives, comparing very well with other methods, in terms of simplicity, efficiency and chemical yields. These compounds, **8**−**13**, **16**−**19**, can be considered as molecules ("homo-deoxy-conduritols")[15] with high potential biological and synthetic interest. Work in this direction is beeing pursued in our laboratory and will be reported in due course.

Experimental Section

General Methods. See ref 11d.

General Protocol for the Ring-Closing Metathesis. A degassed solution of the 1,8-diene precursor, in dry methylene chloride (0.02 M), under argon, was treated with catalyst **7** (10%). The mixture was stirred at room temperature, until complete reaction (TLC analysis). The solvent was removed and the residue submitted to flash chromatography (eluting with hexane/ethyl acetate mixtures) to isolate the pure cycloheptenols.

(1*R*,2*R*,3*S*,4*R*)-2,3-*O*-(1-Methylethylidene)cyclohept-5-ene-1,2,3,4-tetrol (8). Following the general protocol for the RCM reactions compound **2a** (68.6 mg, 0.3 mmol) gave carbocycle **8** [27 mg, 45% (70%); flash chromatography hexane/ethyl acetate: 75/25]: oil; $[\alpha]^{25}_D$ −43 (*c* 0.56, $CHCl_3$); IR (KBr) *v* 3400 (OH), 1640 cm^{-1}; ^1H NMR ($CDCl_3$) *δ* 5.58 (br d, *J* = 12.4 Hz, 1 H), 5.48 (br d, *J* = 12.4 Hz, 1 H), 4.82 (br d, *J* = 7.3 Hz, 1 H), 4.22−4.19 (m, 2 H), 4.09 (dd, *J* = 9.1 Hz, *J* = 7.3 Hz, 1 H), 2.67 (br s, 1 H), 2.65 (br d, *J* = 19.0 Hz, 1 H), 2.49 (br s, 1 H), 2.28 (br d, *J* = 19.0 Hz, 1 H), 1.54, 1.39 (s, s, 3 H, 3 H); ^{13}C NMR ($CDCl_3$) *δ* 130.1, 124.3, 108.3, 81.7, 77.8, 69.4, 67.3, 31.2, 27.3, 24.7; MS (70 eV) *m*/*z* 185 (M^+-15, 10), 70 (100). Anal. Calcd for $C_{10}H_{16}O_4$: C, 59.98; H, 8.05. Found: C, 59.72; H, 7.79.

(1*S*,2*R*,3*S*,4*R*)-2,3-*O*-(1-Methylethylidene)cyclohept-5-ene-1,2,3,4-tetrol (9). Following the general protocol for the RCM reactions compound **2b** (85.7 mg, 0.39 mmol) gave carbocycle **9** (65 mg, 85%; flash chromatography, hexane/ethyl acetate: 75/25): oil; $[\alpha]^{25}_D$ −10 (*c* 0.35, $CHCl_3$); IR (KBr) *v* 3400 (OH), 1640 cm^{-1}; ^1H NMR ($CDCl_3$) *δ* 5.57−5.45 (m, 2 H), 4.42 (br d, *J* = 8.7 Hz, 1 H), 4.12 (dd, *J* = 8.7 Hz, *J* = 8.0 Hz, 1 H), 4.10−4.08 (m, 1 H), 4.04 (dd, *J* = 9.5 Hz, *J* = 8.0 Hz, 1 H), 2.69 (d, *J* = 1.6 Hz, 1 H), 2.64 (d, *J* = 1.7 Hz, 1 H), 2.47 (br d, *J* = 17.6 Hz, 1 H), 2.27−2.15 (m, 1 H), 1.48, 1.37 (s, s, 3 H, 3H); ^{13}C NMR ($CDCl_3$) *δ* 129.9, 124.9, 108.9, 81.1, 80.1, 68.8, 68.5, 34.1, 27.7, 24.9. MS (70 eV) *m*/*z* 185 (M^+ − 15, 9), 70 (100). Anal. Calcd for $C_{10}H_{16}O_4$: C, 59.98; H, 8.05. Found: C, 59.82; H, 8.33.

(1*R*,2*R*,3*S*,4*R*)-1,4-Di-*O*-acetyl-2,3-*O*-(1-methylethylidene)-cyclohept-5-ene-1,2,3,4-tetrol (10). Following the general protocol for the RCM reactions compound **3a** (92.2 mg, 0.29 mmol) gave carbocycle **10** (79.4 mg, 95%; flash chromatography, hexane/ethyl acetate: 80/20): oil; $[\alpha]^{25}_D$ −58 (*c* 0.75, $CHCl_3$); IR (KBr) *v* 1720 ($OCOCH_3$), 1640 cm^{-1}; ^1H NMR ($CDCl_3$) *δ* 5.80−5.74 (m, 1 H), 5.58 (br dt, *J* = 12.9 Hz, *J* = 3.7 Hz, 1 H), 5.49−5.41 (m, 2 H), 4.42−4.32 (m, 2 H), 2.71 (ddq, *J* = 1.7 Hz, *J* = 7.0 Hz, *J* = 19.0 Hz, 1 H), 2.35 (br d, *J* = 19.0 Hz, 1 H), 2.13 (s, 3 H), 2.12 (s, 3 H), 1.45, 1.35 (s, s, 3 H, 3H); ^{13}C NMR ($CDCl_3$) *δ* 170.1, 169.9, 127.6, 126.7, 108.9, 77.5, 76.9, 70.7, 69.4, 30.5, 26.5, 24.4, 21.2, 21.1; MS (70 eV) *m*/*z* 284 (M^+, 1), 43 (100). Anal. Calcd for $C_{14}H_{20}O_6$: C, 59.14; H, 7.09. Found: C, 59.19; H, 6.85.

(1*S*,2*R*,3*S*,4*R*)-1,4-Di-*O*-acetyl-2,3-*O*-(1-methylethylidene)-cyclohept-5-ene-1,2,3,4-tetrol (11). Following the general protocol for the RCM reactions compound **3b** (84.7 mg, 0.26 mmol) gave carbocycle **11** (64.3 mg, 96%; flash chromatography, hexane/ethyl acetate: 80/20): mp 88−90 °C; $[\alpha]^{25}_D$ −52 (*c* 0.67, $CHCl_3$); IR (KBr) *v* 1720 ($OCOCH_3$), 1640 cm^{-1}; ^1H NMR ($CDCl_3$) *δ* 5.67 (ds, *J* = 9.9 Hz, *J* = 2.3 Hz, 1 H), 5.56 (dqt, *J* = 12.3 Hz, *J* = 3.1 Hz, 1 H), 5.33 (ds, *J* = 12.3 Hz, *J* = 1.3 Hz, 1 H), 5.23 (ddd, *J* = 3.3 Hz, *J* = 9.3 Hz, *J* = 11.4 Hz, 1 H), 4.32 (dd, *J* = 6.7 Hz, *J* = 9.3 Hz, 1 H), 4.22 (dd, *J* = 6.7 Hz, *J* = 9.9 Hz, 1 H), 2.47 (ddm, *J* = 3.3 Hz, *J* = 18.6 Hz, 1 H), 2.25 (ddm, *J* = 11.4 Hz, *J* = 18.6 Hz, 1 H), 2.10 (s, 3 H), 2.07 (s, 3 H), 1.43 and 1.34 (s, s, 3 H, 3H); ^{13}C NMR ($CDCl_3$) *δ* 170.0, 169.9, 128.9, 125.4, 109.7, 78.3, 77.4, 70.7, 70.6, 31.6, 27.5, 25.4, 21.2, 21.0; MS (70 eV) *m*/*z* 284 (M^+, 1), 43 (100). Anal. Calcd for $C_{14}H_{20}O_6$: C, 59.14; H, 7.09. Found: C, 59.40; H, 7.25.

(1*R*,2*R*,3*S*,4*R*)-1,4-Di-*O*-benzyl-2,3-*O*-(1-methylethylidene)-cyclohept-5-ene-1,2,3,4-tetrol (12). Following the general protocol for the RCM reactions compound **4** (74.6 mg, 0.29 mmol) gave carbocycle **12** (63 mg, 90%; flash chromatography, hexane/ethyl acetate: 85/15): oil; $[\alpha]^{25}_D$ −36 (*c* 0.58, $CHCl_3$); IR (KBr) *v* 3010, 1650 cm^{-1}; ^1H NMR ($CDCl_3$) *δ* 7.34−7.23 (m, 10 H), 5.62 (ddt, *J* = 12.2 Hz, *J* = 3.7 Hz, *J* = 1.9 Hz, 1 H), 5.59 (br d, *J* = 12.2 Hz, 1 H), 4.69 (d, *J* = 12.1 Hz, 1 H), 4.68 (d, *J* = 12.2 Hz, 1 H), 4.67−4.65 (m, 1 H), 4.64 (d, *J* = 12.1 Hz, 1 H), 4.60 (d, *J* = 12.2 Hz, 1 H), 4.43 (t, *J* = 7.8 Hz, 1 H), 4.25 (dd, *J* = 7.8 Hz, *J* = 1.7 Hz, 1 H), 4.07 (ddd, *J* = 6.6 Hz, *J* = 3.2 Hz, *J* = 1.7 Hz, 1 H), 2.59 (dddt, *J* = 1.9 Hz, *J* = 3.8 Hz, *J* = 6.6 Hz, *J* = 17.1 Hz, 1 H), 2.26 (br d, *J* = 17.1 Hz, 1 H), 1.50 and 1.36 (s, s, 3 H, 3H); ^{13}C NMR ($CDCl_3$) *δ* 138.7, 137.5, 129.6, 128.2, 127.7−127.2 (12 C), 108.2, 79.6, 78.5, 75.8, 75.7, 72.2, 71.6, 31.3, 26.5, 24.2; MS (70 eV) *m*/*z* 380 (M^+, 1), 91 (100). Anal. Calcd for $C_{24}H_{28}O_4$: C, 75.76; H, 7.42. Found: C, 75.48; H, 7.22.

(1*R*,2*R*,3*S*,4*R*)-1-*O*-Acetyl-4-*tert*-butyldimethylsilyl-2,3-*O*-(1-methylethylidene)cyclohept-5-ene-1,2,3,4-tetrol (13). Following the general protocol for the RCM reactions compound **6** (22.0 mg, 0.049 mmol) gave carbocycle **13** (17.6 mg, 99%; flash chromatography, hexane/ethyl acetate: 85/15): oil; $[\alpha]^{25}_D$ −11 (*c* 0.49, $CHCl_3$); IR (KBr) *v* 3010, 1640 cm^{-1}; ^1H NMR ($CDCl_3$) *δ* 5.66 (ddd, *J* = 7.5 Hz, *J* = 3.7 Hz, *J* = 1.5 Hz, 1 H), 5.59 (ddd, *J* = 13.1 Hz, *J* = 4.6 Hz, *J* = 2.0 Hz, 1 H), 5.56 (dt, *J* = 13.1 Hz, *J* = 3.7 Hz, 1 H), 4.66 (br t, *J* = 5.3 Hz, 1 H), 4.33 (t, *J* = 7.6 Hz, 1 H), 4.29 (dd, *J* = 8.0 Hz, *J* = 1.5 Hz, 1 H), 2.64 (br dd, *J* = 7.5 Hz, *J* = 19.0 Hz, 1 H), 2.34 (dt, *J* = 19.0 Hz, *J* = 3.7 Hz, 1 H), 2.09 (s, 3 H), 1.44, 1.33 (s, s, 3 H, 3H), 0.92, 0.10 (s, 9 H; s, 6 H); ^{13}C NMR ($CDCl_3$) *δ* 170.0, 130.3, 126.7, 108.4, 79.8, 77.5, 70.4, 69.2, 31.2, 26.4, 25.8 (3 C), 24.2, 21.3, 18.2, −4.6, −4.8; MS (70 eV) *m*/*z* 356 (M^+, 1), 181 (100). Anal. Calcd for $C_{18}H_{32}O_5Si$: C, 60.64; H, 9.05. Found: C, 60.55; H, 9.32.

(1*R*,2*R*,3*S*,4*R*)-1,2,3,4-Tetra-*O*-acetyl-cyclohept-5-ene-1,2,3,4-tetrol (16). Following the general protocol for the RCM reactions compound **15a** (24.9 mg, 0.069 mmol) gave carbocycle **16** (20.5 mg, 89%; flash chromatography, hexane/ethyl acetate: 70/30): oil; $[\alpha]^{25}_D$ + 10 (*c* 0.46, $CHCl_3$); IR (KBr) *v* 1720

(12) The RCM reactions are very sensitive to steric hindrance close to the double bonds to be metathesized: Fürstner, A., Langemann, K. *Synthesis* **1997**, 792.

(13) Examples of formation of chelates in RCM: (a) Delgado, M.; Martín, J. D. *J. Org. Chem.* **1999**, *64*, 4798. (b) Fürstner, A., Langemann, K. *J. Am. Chem. Soc.* **1997**, *119*, 9130. (c) Kirkland, T. A.; Grubbs, R. H. *J. Org. Chem.* **1997**, *62*, 7310. (d) Kingsbury, J. S., Harrity, J. P. A.; Bonitatebus, P. J. Jr.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1999**, *121*, 791.

(14) See ref 2e for some recent, interesting results, regarding the influence of the absolute stereochemistry of the different hydroxyl protecting groups in sugar templates, on the course of RCM reactions.

(15) (a) Balci, M.; Sutbeyaz, Y.; Secen, H. *Tetrahedron* **1990**, *46*, 3715. (b) Vogel, P.; Fattori, D.; Gasparini, F.; Le Drian, C. *Synlett* **1990**, 393.

($OCOCH_3$), 1640 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.83 (ddd, J = 10.3 Hz, J = 4.0 Hz, J = 2.6 Hz, 1 H), 5.73 (dddd, J = 12.0 Hz, J = 6.7 Hz, J = 4.1 Hz, J = 2.6 Hz, 1 H), 5.55 (d, J = 1.6 Hz, 1 H), 5.50 (dt, J = 12.0 Hz, J = 2.9 Hz, 1 H), 5.03 (dd, J = 10.3 Hz, J = 2.3 Hz, 1 H), 4.86 (ddd, J = 11.6 Hz, J = 3.1 Hz, J = 2.2 Hz, 1 H), 2.82−2.64 (m, 1 H), 2.16 (s, 3 H), 2.15−2.02 (m, 1 H), 2.01 (s, 3 H), 1.96 (s, 3 H), 1.95 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 169.9, 169.8, 169.7, 169.5, 131.7, 125.5, 72.0, 70.5, 69.4, 68.4, 26.6, 20.9 (2 C), 20.8, 20.6; MS (70 eV) m/z 183 (3), 43 (100). Anal. Calcd for $C_{15}H_{20}O_8$: C, 54.87; H, 6.14. Found: C, 54.69; H, 6.40.

(1*S*,2*R*,3*S*,4*R*)-1,2,3,4-Tetra-*O*-acetylcyclohept-5-ene-1,2,3,4-tetrol (17). Following the general protocol for the RCM reactions compound **15b** (31.4 mg, 0.088 mmol) gave carbocycle **17** (26 mg, 90%; flash chromatography, hexane/ethyl acetate: 70/30): oil; $[\alpha]^{25}_D$ −24 (*c* 0.3, $CHCl_3$); IR (KBr) υ 1720 ($OCOCH_3$), 1640 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.74 (dt, J = 10.6 Hz, J = 5.9 Hz, 1 H), 5.72−5.65 (m, 2 H), 5.43 (dd, J = 7.0 Hz, J = 2.7 Hz, 1 H), 5.36 (dd, J = 8.6 Hz, J = 2.7 Hz, 1 H), 5.01 (dt, J = 7.0 Hz, J = 5.4 Hz, 1 H), 2.50 (t, J = 5.4 Hz, 1 H), 2.10 (s, 3 H), 2.09 (s, 3 H), 2.07 (s, 3 H), 2.03 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 169.7, 169.6 (2 C), 169.5, 129.9, 127.1, 71.9, 69.6, 69.3, 68.3, 27.8, 20.9, 20.8, 20.7 (2 C); MS (70 eV) m/z 183 (3), 43 (100). Anal. Calcd for $C_{15}H_{20}O_8$: C, 54.87; H, 6.14. Found: C, 54.80; H, 6.35.

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Supporting Information Available: Experimental procedures and characterization data for compounds **2a,b**−**6**, **14a,b**, **15a,b**, **18**, and **19**. This material is available free of charge via the Internet at http:/pubs.acs.org.

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