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Cycloheptenols from carbohydrates

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Abstract

The first ring-closing metathesis of chiral, polyoxygenated, differently *O*-substituted, acyclic 1,8-nonadienes is reported. Compared with other methods, this is one of the best synthetic alternatives for the preparation of enantiomerically pure, highly functionalized cycloheptenol derivatives in terms of simplicity, efficiency and chemical yields. © 2000 Elsevier Science Ltd. All rights reserved.

Seven-membered ring carbocycles occur frequently in a number of natural products[1] which have remarkable biological activities.[2] Therefore, a variety of synthetic methods have been reported for the asymmetric synthesis[3] of seven-membered carbocyclic frameworks.[4] In spite of these efforts and in view of the few methods available for the enantioselective synthesis of differently substituted cycloheptanes,[3,5] we decided to investigate[6] the ring-closing metathesis (RCM)[7] of chiral, polyoxygenated 1,8 nonadienes. We now report that a variety of cycloheptenols can be synthesized in enantiomerically pure form, in high chemical yield and under extremely mild conditions. In addition to the potential utility of this synthetic approach, these results gave us the opportunity to describe the critical effects of the absolute configurations at the stereocenters or protecting groups around the olefinic bonds in the course of the ring-closing metathesis of acyclic, chiral polyoxygenated 1,ω-diene precursors derived from sugars.[8]

For our initial attempts we selected the precursors **1** (C6 *R*), **2** (C6 *S*), **3** (C6 *R*), **4** (C6 *R*), **5** (C6 *R*) and **6** (C6 *S*), readily available from D-mannose as described[8a] and standard chemical manipulation. The RCM of compounds **1**–**6**,[9] mediated by benzylidene-bis(tricyclohexylphosphine)dichlororuthenium (**7**) as catalyst (10%), afforded the cycloheptenols **8**–**13** (Scheme 1).[10] Under these conditions, at room temperature and methylene chloride (0.02 M) as solvent, free alcohol **1** (C6 *R*) gave the carbocycle **8** (Scheme 1) in a slow, incomplete and low yielding reaction.[11a] By contrast, and to our great satisfaction, the epimeric alcohol **2** (C6 *S*) gave the RCM product **9** (Scheme 1) in a fast (6 h), complete and high yielding reaction (85%).[11b] Very interestingly, the diprotected derivatives **3**–**5**, derived from **1** (C6 *R*), afforded the corresponding carbocyclization products **10**–**12** in fast reactions in extremely high chemical yields (Scheme 1).[11c] In agreement with this and not surprisingly, the diacetate precursor (**6**), derived

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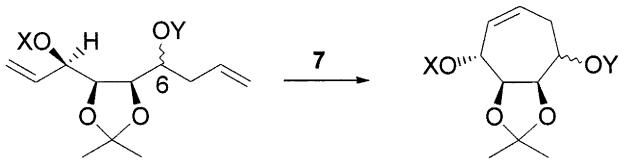
from compound **2** (C6 *S*), gave the cycloheptenol derivative **13** (Scheme 1) in the fastest reaction time (20 min) and in an equally consistent chemical yield (96%).[11c]



1 (C6 *R*)	X, Y= H	**8** [45% (70)%, 7 days]
2 (C6 *S*)	X, Y= H	**9** (85%, 6 h)
3 (C6 *R*)	X, Y= Ac	**10** (95%, 1 h)
4 (C6 *R*)	X, Y= Bn	**11** (90%, 1 h)
5 (C6 *R*)	X= Si*t*BuMe$_2$, Y= Ac	**12** (99%, 40 min)
6 (C6 *S*)	X, Y= Ac	**13** (96%, 20 min)

Scheme 1.

In summary, the results reported here are noteworthy and constitute a useful synthetic alternative for the preparation of enantiomerically pure, highly functionalized cycloheptenol derivatives, comparing very well with other methods, in terms of simplicity, efficiency and chemical yields. Note that no special experimental conditions, techniques or complicated equipment or materials are necessary to perform these carbocyclization reactions; obviously, these facts enhance the synthetic potential of the present process. In addition, we have observed that the stereochemical arrangement and/or the type of the functional groups in the chiral, polyoxygenated, differently substituted, acyclic 1,8-nonadienes strongly affect the course of the RCM reaction,[11] giving new insights into this new and useful synthetic procedure. Work is now in progress to extend these results to other related substrates in order to present a mechanistic rationale for these observations.

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9. The synthesis of precursors **1**–**6** will be described elsewhere.
10. General protocol for the ring-closing metathesis. A degassed solution of the 1,8-diene precursor (**1**–**6**), in dry methylene chloride (0.02 M), under argon, was treated with catalyst **7** (10%). The mixture was stirred at room temperature, until the reaction was complete (TLC analysis). The solvent was removed and the residue submitted to flash chromatography (eluting with hexane/ethyl acetate mixtures) to isolate the pure cycloheptenols. Spectroscopic data. Compound **8**. ^{1}H NMR ($CDCl_3$) δ 5.58 (br d, *J*=12.4 Hz, 1H), 5.48 (br d, *J*=12.4 Hz, 1H), 4.82 (br d, *J*=7.3 Hz, 1H), 4.22–4.19 (m, 2 H), 4.09 (dd, *J*=9.1 Hz, *J*=7.3 Hz, 1 H), 2.67 (br s, 1H), 2.65 (br d, *J*=19.0 Hz, 1H), 2.47 (br s, 1H), 2.28 (br d, *J*=19.0 Hz, 1H), 1.54 and 1.39 (s, s, 3H, 3H); ^{13}C NMR ($CDCl_3$) δ 130.1 (CH), 124.3 (CH), 108.3 (C_q), 81.7 (CH), 77.8 (CH), 69.4 (CH), 67.3 (CH), 31.2 (CH_2), 27.3 and 24.7 (CH_3). Compound **10**. ^{1}H NMR ($CDCl_3$) δ 5.80–5.74 (m, 1H), 5.58 (br dt, *J*=12.9 Hz, *J*=3.7 Hz, 1H), 5.49–5.41 (m, 2H), 4.42–4.32 (m, 2H), 2.71 (ddq, *J*=1.7 Hz, *J*=7.0 Hz, *J*=19.0 Hz, 1H), 2.35 (br d, *J*=19.0 Hz, 1H), 2.13 (s, 3H), 2.12 (s, 3H), 1.45 and 1.35 (s, s, 3H, 3H); ^{13}C NMR ($CDCl_3$) δ 170.1 (C_q), 169.9 (C_q), 127.6 (CH), 126.7 (CH), 108.9 (C_q), 77.5 (CH), 76.9 (CH), 70.7 (CH), 69.4 (CH), 30.5 (CH_2), 26.5 (CH_3), 24.9 (CH_3), 21.2 (CH_3), 21.1 (CH_3). Compound **11**. ^{1}H NMR ($CDCl_3$) δ 7.34–7.23 (m, 10H), 5.62 (ddt, *J*=12.2 Hz, *J*=3.7 Hz, *J*=1.9 Hz, 1H), 5.59 (br d, *J*=12.2 Hz, 1H), 4.69 (d, *J*=12.1 Hz, 1H), 4.68 (d, *J*=12.2 Hz, 1H), 4.67–4.65 (m, 1H), 4.64 (d, *J*=12.1 Hz, 1H), 4.60 (d, *J*=12.2 Hz, 1H), 4.43 (t, *J*=7.8 Hz, 1H), 4.25 (dd, *J*=7.8 Hz, *J*=1.7 Hz, 1H), 4.07 (ddd, *J*=6.6 Hz, *J*=3.2 Hz, *J*=1.7 Hz, 1H), 2.59 (dddt, *J*=1.9 Hz, *J*=3.8 Hz, *J*=6.6 Hz, *J*=17.1 Hz, 1H), 2.26 (br d, *J*=17.1 Hz, 1H), 1.50 and 1.36 (s, s, 3H, 3H); ^{13}C NMR ($CDCl_3$) δ 138.7 and 137.5 (C_q), 129.6 (CH), 128.2 (CH), 127.7–127.2 (CH), 108.2 (C_q), 79.6 (CH), 78.5 (CH), 75.7 (CH), 72.2 and 71.6 (CH_2), 69.4 (CH), 31.3 (CH_2), 26.5 (CH_3), 24.2 (CH_3).
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