ORGANIC LETTERS

2004
Vol. 6, No. 16
2713−2716

Memory of Chirality in the Transannular Cyclization of Cyclodecenyl Radicals

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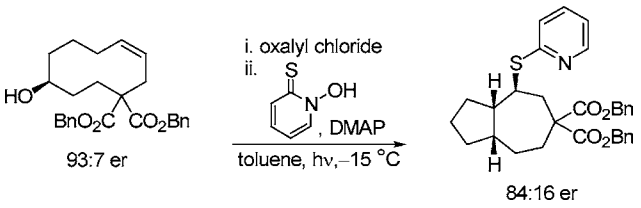
Received May 24, 2004

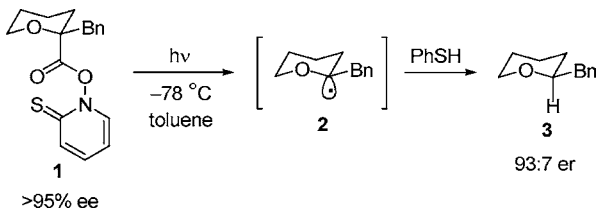
ABSTRACT



The transannular cyclization of an enantioenriched cyclodecenyl radical proceeds in a 5-*exo* fashion to produce scalemic bicyclo[5.3.0]-decanes. This cyclization is notable because it demonstrates chirality transfer through conformational memory of an unstabilized secondary radical.

The field of stereoselective radical reactions has rapidly advanced with the emergence of both chiral auxiliary based and chiral Lewis acid based approaches.[1] More recently, "memory of chirality"[2,3] has emerged as another strategy for enantioselective radical reactions.[4] Previous work in our laboratory has demonstrated memory of chirality in the hydrogen abstraction of an anomeric-stabilized tetrahydropyranyl radical (Scheme 1).[5] We hoped to extend this methodology to include an unstabilized secondary radical in the transannular cyclization of a cyclodecenyl radical. The cyclodecenyl radical system was chosen on the basis of its rigidity and potential to undergo a transannular cyclization[6] faster than a conformational change that would result in racemization. In addition, the potential for cyclodecenes to provide 5,7-fused ring systems and the presence of these hydroazulene skeletons in natural products makes cyclodecenes an attractive target for radical reactions.

Scheme 1. Memory of Chirality in Hydrogen Abstraction of a Tetrahydropyranyl Radical



To investigate chirality transfer in the transannular cyclization, we chose cyclodecene **4** as our test substrate (Scheme 2). Radical deoxygenation of **4** via its mixed oxalate generates a cyclodecenyl radical that cyclizes in a 5-*exo* fashion to produce 5,7-fused bicycle **5**. The potential for the chiral radical precursor **4** to undergo an enantioselective cyclization is dependent upon the rate of the transannular cyclization. If a radical generated from optically pure mixed

(1) (a) Sibi, M. P.; Porter, N. A. *Acc. Chem. Res.* **1999**, *32*, 163−171. (b) Curran, D. P.; Porter, N. A.; Giese, B. *Stereochemistry of Radical Reactions*; VCH: New York, 1996.

(2) Kawabata, T.; Fuji, K. *Top. Stereochem.* **2003**, *23*, 175−205.

(3) In alkylations: (a) Carlier, P. R.; Zhao, H.; DeGuzman, J.; Lam, P. C.-H. *J. Am. Chem. Soc.* **2003**, *125*, 11482−11483. (b) Seebach, D.; Sting, A. R.; Hoffmann, M. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 2708−2748.

(4) (a) Curran, D. P.; Liu, W.; Chen, C. H.-T. *J. Am. Chem. Soc.* **1999**, *121*, 11012−11013. (b) Giese, B.; Wettstein, P.; Stahelin, C.; Barbosa, F.; Neuburger, M.; Zehnder, M.; Wessig, P. *Angew. Chem., Int. Ed.* **1999**, *38*, 2586−2587. (c) Sauer, S.; Schumacher, A.; Barbosa, F.; Giese, B. *Tetrahedron Lett.* **1998**, *39*, 3685−3688.

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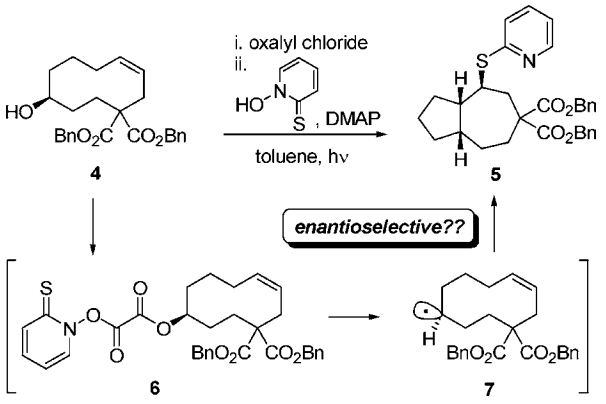
(6) Beckwith, A. L. J.; Bowry, V. W.; Schiesser, C. H. *Tetrahedron* **1991**, *47*, 121−130.

10.1021/ol049038x CCC: $27.50
Published on Web 07/09/2004

Scheme 2. Radical Cyclization via Deoxygenation



oxalate **6** underwent a transannular cyclization (path a) before conformational interconversion (path b), enantioenriched products would be obtained (Figure 1).

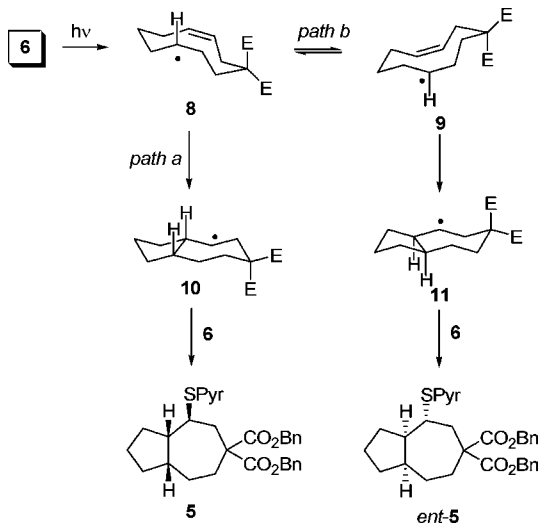


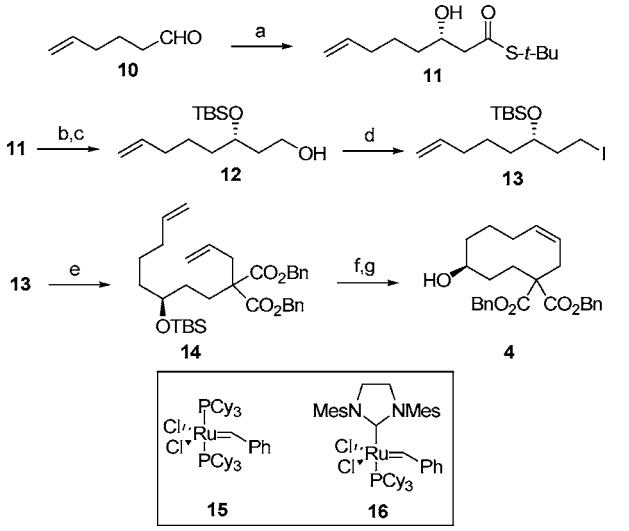
Figure 1. Racemization pathway.

Racemization would occur through a disfavored chair/boat interconversion. This is an example of memory of chirality because the chiral information is held by the conformation of the radical intermediate and not the radical center.

We set out to synthesize the radical precursor **4** through a ring-closing metathesis of the bisolefin **14** (Scheme 3). The synthesis of bisolefin **14** began with Mukaiyama−Keck aldol condensation of 5-hexenal with the trimethylsilyl ketene acetal derived from *tert*-butyl thioacetate to afford thioester **11** in 89% yield and 89% ee. Silyl ether formation followed by reduction of the ester provided alcohol **12** in 93% over two steps. Conversion of the resultant alcohol to the iodide **13** and coupling with anionic allyl dibenzylmalonate furnished the requisite bisolefin **14** (90%, 2 steps).

With the cyclization precursor **14** in hand, we investigated the ring-closing metathesis utilizing ruthenium alkylidenes,

Scheme 3. Synthesis of Radical Precursor[a]



[a] Reaction conditions: (a) 1-*tert*-butylthio-1-(trimethylsilyl) oxoethene, (*R*)-BINOL, Ti(O*i*Pr)$_4$, 4 Å MS, ether, −35 °C, 89%, 89% ee. (b) TBSOTf, 2,6-lutidine, CH_2Cl_2, 100%. (c) DIBALH, CH_2Cl_2, −25 °C, 93%. (d) I_2, PPh_3, CH_2Cl_2, imidazole, 0 °C, 94%. (e) NaH, allyl dibenzylmalonate, THF, 0 °C to rt, 96%. (f) 20 mol % **16**, CH_2Cl_2, 1 mM, 40 °C, 16 h, 88%. (g) TBAF, THF, 0 °C to rt, 95%.

such as those developed by Grubbs.[7] Initial studies employing **15** as a catalyst (1 mM, CH_2Cl_2, 40 °C) did not provide the desired 10-membered carbocycle; instead, only acyclic dimer products were observed. However, it was found that Grubbs' second-generation catalyst **16** was effective in forming the strained ring in good yield (88%) under high dilution conditions (1 mM in substrate).

The ring-closing metathesis product was isolated as a mixture of alkene products (ca. 1:1.7), initially assigned as the *E*- and *Z*-cyclodecenes. This result was expected since ring-closing metathesis in the synthesis of large rings generally gives mixtures of olefin isomers.[7b,8] However, attempts to separate the alkene products, both as the silyl ethers and the deprotected alcohols, were unsuccessful by a variety of chromatographic methods. This result and the inability to enrich one isomer over the other by chemical means[9] led us to consider the alkene products were not olefin isomers but rather conformational isomers. Variable temperature NMR studies were conducted to confirm the presence of two different conformers. ^{1}H NMR experiments carried out from −30 to 100 °C in toluene-d_8 showed coalescence of the doubled peaks at temperatures at and above 37 °C (Figure 2). This coalescence temperature corresponds to an interconversion barrier of ca. 15.5 kcal/

(7) (a) Scholl, M.; Ding, S.; Lee, C. W.; Grubbs, R. H. *Org. Lett.* **1999**, *1*, 953−956. (b) Grubbs, R. H.; Chang, S. *Tetrahedron* **1998**, *54*, 4413−4450. (c) Grubbs, R. H.; Kirkland, T. A. *J. Org. Chem.* **1997**, *62*, 7310−7318.

(8) (a) Lee, C. W.; Grubbs, R. H. *Org. Lett.* **2000**, *2*, 2145−2147. (b) Furstner, A.; Muller, T. *Synlett* **1997**, 1010−1011. (b) Furstner, A.; Langemann, K. *Synthesis* **1997**, 792−803.

(9) Selective dihydroxylation with α-AD-mix (60% conversion) returned the starting cyclodecene of the same isomeric ratio.

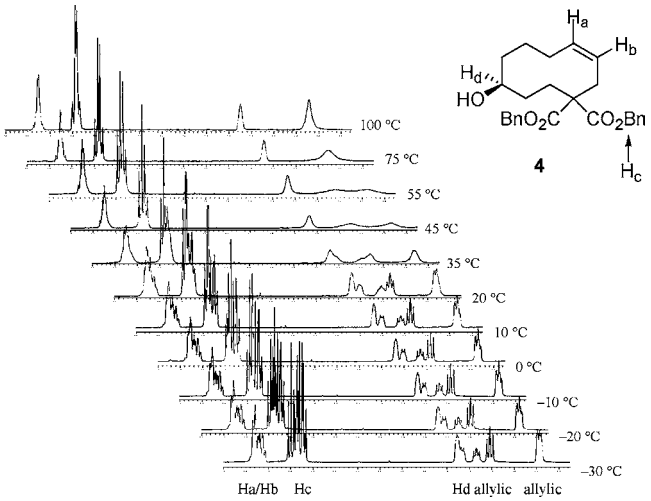
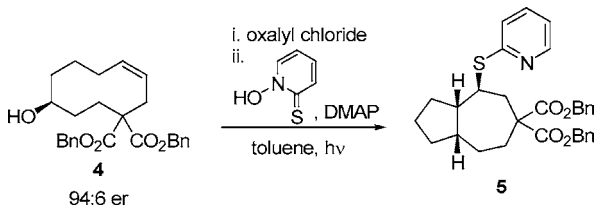


Figure 2. Variable-temperature ^{1}H NMR studies: 5.6−2.5 ppm.

mol. Thus, the ring-closing metathesis provided a single alkene isomer, determined to be the *Z*-cyclodecene by NOE measurements, as a 1:1.7 mixture of conformational isomers.[10]

Our attention was then turned to the radical cyclization. Cyclodecene **4** was treated with oxalyl chloride, followed by *N*-hydroxy pyridine thione and catalytic DMAP to generate mixed oxalate **6** in situ. Photolysis of the reaction mixture led to bicyclo[5.3.0]decane **5**, demonstrating that the cyclodecenyl radical, from deoxygenation of **4**, cyclized in a 5-*exo* fashion to generate the bicyclo[5.3.0]decane **5**.

Table 1. Radical Cyclization Results

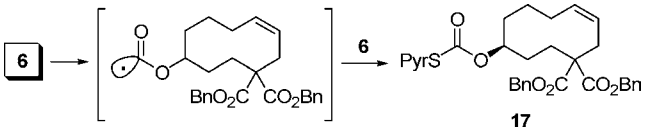


entry[a]	temp (°C)	yield (%)	er[b]
1	23	88	63:37
2	0	67	79:21
3	−15	51	84:16
4	−35	43	84:16

[a] Reaction mixtures were photolyzed with a 500-W tungsten lamp. [b] Enantiomeric ratio determined by chiral HPLC analysis (Diacel OD-H column), 90:10 hexanes/IPA, 0.9 mL/min.

Trapping of the intermediate carbon radical with the thiopyridyl group occurred from the convex face of the bicycle, providing **5** as a single diastereomer (NOE). Notably, the transannular cyclization proceeded with significant chirality transfer. At room temperature, the 5,7-fused product **5** was obtained in 63:37 er from the 94:6 er of the starting material (Table 1, entry 1). Higher levels of enantioselectivity were reached by lowering the temperature to 0 °C to obtain products of 79:21 er. Interestingly, the same er (84:16) was obtained at both −15 and −35 °C, suggesting a limit in the enantioselectivity observed. The yields ranged from 43% to 88%, and products were accompanied with significant amounts of the monodecarboxylated and trapped side product **17**, demonstrating that the fragmentation is a stepwise process (Scheme 4).

Scheme 4. Stepwise Fragmentation Leads to Side Product **17**



The variation in enantioselectivity observed may be due to the presence of two conformers in the starting substrate. Energy minimization calculations of the cyclodecenol methyl ester using MacroModel (MM2 force field) strongly suggests two boat-chair-boat conformers, BCB-1 and BCB-2, as the lowest energy conformers present (Figure 3). Further analysis

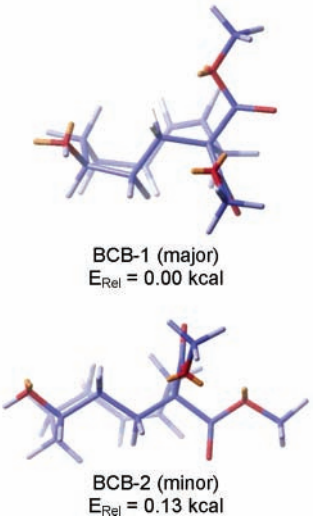


Figure 3. Low-energy conformers of cyclodecenol methyl ester.

reveals direct cyclization of BCB-2 leads to the *cis*-fused product, whereas direct cyclization of BCB-1 leads to the *trans*-fused product (Figure 4). The *trans*-fused product is not observed, so the major conformer may undergo a conformational change prior to cyclization to provide the *cis*-fused product, potentially leading to an erosion in the enantioselectivity.

The presence of two distinct conformers was not anticipated and may have a deleterious effect on the selectivity of

(10) Isomeric ratio was determined by ^{1}H NMR at −30 °C and varied slightly at different temperatures: 1:1.71 (−30 °C), 1:1.66 (−20 °C), 1:1.60 (−10 °C).

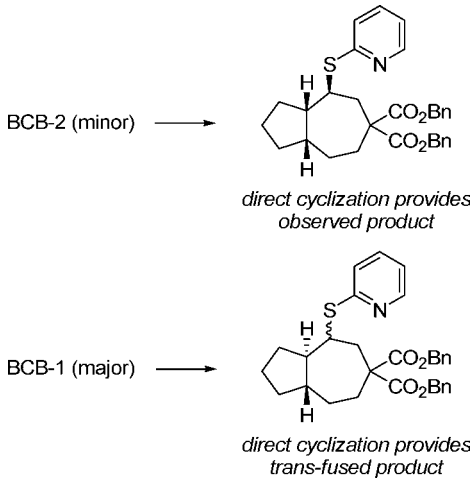


Figure 4. Fate of conformers of cyclodecenol **4**.

the reaction. The minor computational conformer can directly cyclize to provide the observed product with little consequence to the enantioselectivity; however, the major computational conformer must undergo a conformational change to provide the observed product. Furthermore, the increase in enantioselectivity and decrease in yield may be a consequence of the minor conformer cyclizing faster than the major conformer. Despite the presence of these two conformers, we have shown that the cyclization of cyclodecenyl radicals proceeds with 90% chirality transfer at −15 and −35 °C, thus demonstrating memory of chirality in the transannular cyclization of an unstabilized secondary radical.

Acknowledgment. The National Institutes of Health (GM 65338) provided financial support.

Supporting Information Available: Experimental procedures and spectral data for compounds **4**, **5**, and **10**−**14**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL049038X