Enantioselective Synthesis of Bicyclo[4.4.1]undecane-2,7-dione via Samarium(II)-Mediated Fragmentation of a Cyclopropane Precursor

Sherif El Sheikh, Nina Kausch, J. Lex, J.-M. Neudörfl, Hans-Günther Schmalz*

Institut für Organische Chemie, Universität zu Köln, Greinstr. 4, 50939 Köln, Germany
Fax +49(221)4703064; E-mail: schmalz@uni-koeln.de

Received 4 April 2006

Abstract: An efficient six-step synthesis of bicyclo[4.4.1]undecane-2,7-dione was elaborated. Key steps include an enantioselective oxazaborolidine-catalyzed borane reduction (CBS reduction) of 2,3,4,6,7,8-hexahydronaphthalene-1,5-dione to the corresponding diol, and a subsequent (*syn*-diastereoselective) cyclopropanation. Oxidation then gives tricyclo[4.4.1.0^{1,6}]undecane-2,7-dione (>99% ee) which on treatment with two equivalents of samarium(II) iodide undergoes cleavage of the central cyclopropane bond to yield the target compound without any loss of stereochemical information.

Key words: asymmetric synthesis, chirality, cyclopropane, fragmentation, samarium diiodide

Among the group of small bridged bicyclic molecules, the bicyclo[4.4.1]undecane substructure is quite rarely encountered. Naturally occuring examples include the marine natural products spiniferin[1] (**1**) and isocyclocitrinol[2] (**2**). The most famous non-natural representative of this ring system is E. Vogel's 1,6-methano[10]annulene[3] (**3**, R = H, Figure 1).[4]

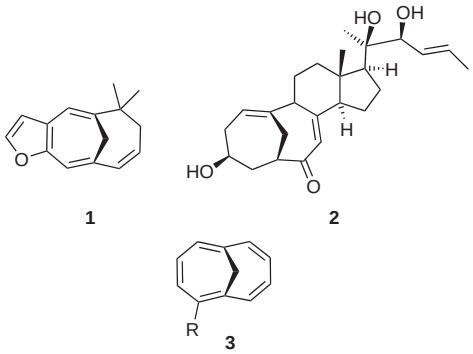


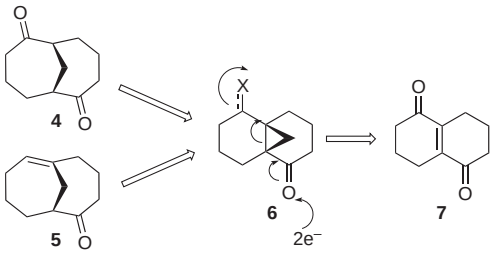
Figure 1 Compounds containing the bicyclo[4.4.1]undecane substructure

The only common synthetic approach to bicyclo[4.4.1]undecane derivatives with an unfunctionalized C_1-bridge is based on the norcaradiene-cycloheptatriene rearrangement, i.e., a 6π-electrocyclic ring-opening. Thus, tricyclo[4.4.1.0^{1,6}]undeca-2,4-diene precursors yield bicyclo[4.4.1]undecatrienes as depicted in Equation 1.[3,5,6]

Equation 1 Norcaradiene-cycloheptatriene rearrangement

While the electrocyclic approach is perfectly suitable for the synthesis of structures like **1**, it cannot easily be applied to the synthesis of products with a more complex substitution pattern and/or a higher degree of saturation. Especially, the conditions commonly employed to build up the required norcaradiene precursors (DDQ or bromination/dehydrobromination)[3,4] are not necessarily compatible with a range of functional groups.

Recently, we became interested in functionalized bicyclo[4.4.1]undecanes such as **4** and **5**. While **5** can be considered as a model compound for **2**, we were particularly interested in the synthesis of the C_2-symmetric compound **4** (Scheme 1). Due to the inherent chirality of this compound we consider it to represent a valuable building block for the elaboration of new chiral ligands. The lower homologues of **4**, bicyclo[3.3.1]nonane-2,6-dione and bicyclo[2.2.1]heptane-2,5-dione have already found successful application as building blocks for chiral ligands.[7,8]



Scheme 1 Concept for the synthesis of compounds **4** and **5** via reductive fragmentation

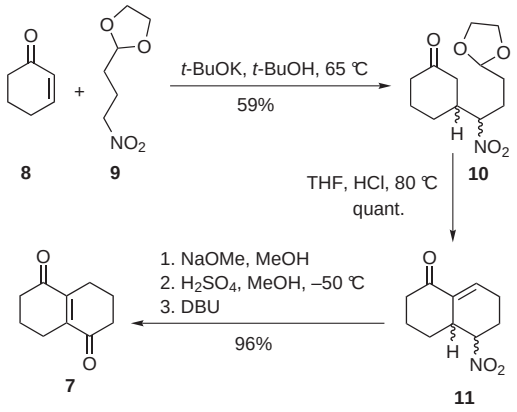
The reason why chiral bicyclo[4.4.1]undecanes have never found application in enantioselective chemistry was certainly the lack of an efficient synthetic entry to this class of compounds.[9]

As a new strategy we envisioned that appropriately functionalized tricyclic systems of type **6** should undergo fragmentation of the central bond upon treatment with reducing agents such as zinc or samarium(II)-iodide (Scheme 2). Therefore, we decided to prepare tricyclo[4.4.1.0^{1,6}]undecane-2,7-dione (**6a**, X = O) to investigate its reductive fragmentation using samarium(II)-iodide.[10]

SYNLETT 2006, No. 10, pp 1527–1530
Advanced online publication: 12.06.2006
DOI: 10.1055/s-2006-941599; Art ID: G12106ST

Retrosynthetic analysis of **6** suggests enedione **7** as a precursor. The common synthesis of **7** by perhydrogenation of napththalene-1,5-diol followed by two oxidation steps[11] is of limited practical value due to low overall yields, costly reagents, and long reaction times. This prompted us to elaborate a new synthesis of this compound.

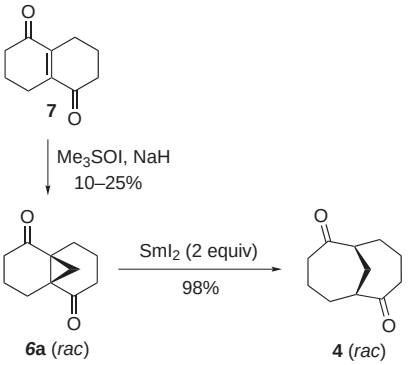
Our synthesis of enedione **7**, which allows easy access to multigram quantities of the compound, is shown in Scheme 2. At first, base-catalyzed Michael addition of the protected 4-nitrobutanal (**9**)[12] to cyclohexenone (**8**) afforded **10** in 59% yield as a mixture of stereoisomers. Subsequent acid-catalyzed cyclization proceeded with virtually quantitative yield to give nitroketone **11**, again as a mixture of stereoisomers. The final conversion of **11** to the enedione **7** was achieved employing modified Nef conditions[13] and subsequent isomerization with DBU. It proved to be important to conduct the hydrolysis of the intermediate nitronate at low temperature under anhydrous conditions to prevent decomposition of the product that was observed under classical (aqueous) conditions.



Scheme 2 A practical synthesis of enedione **7**

While all our attempts to convert **7** into the tricycle *rac*-**6a** under various Simmons–Smith-type conditions failed, we succeeded to obtain the desired cyclopropane at least in low yields (10–25%) by treatment of **7** with dimethylsulfoxonium methylide.[14] With compound *rac*-**6a** in hand we were ready to probe the key fragmentation. Indeed, reaction of *rac*-**6a** with two equivalents of samarium(II) iodide in THF at room temperature furnished bicyclo[4.4.1]undecane-2,7-dione (*rac*-**4**) in virtually quantitative yield (Scheme 3).

Having thus demonstrated the general feasibility of the concept, we turned our attention towards the elaboration of a more efficient and, in particular, enantioselective synthesis of the key intermediate **6a**. We envisioned that the introduction of the methylene bridge could be achieved after reduction of both carbonyl groups of **7**. Using a chiral reducing agent to prepare the C_2-symmetric diol **13**, the directing and activating effect of the two *cis*-oriented hydroxyl groups could possibly be utilized for a *syn*-diastereoselective cyclopropanation.

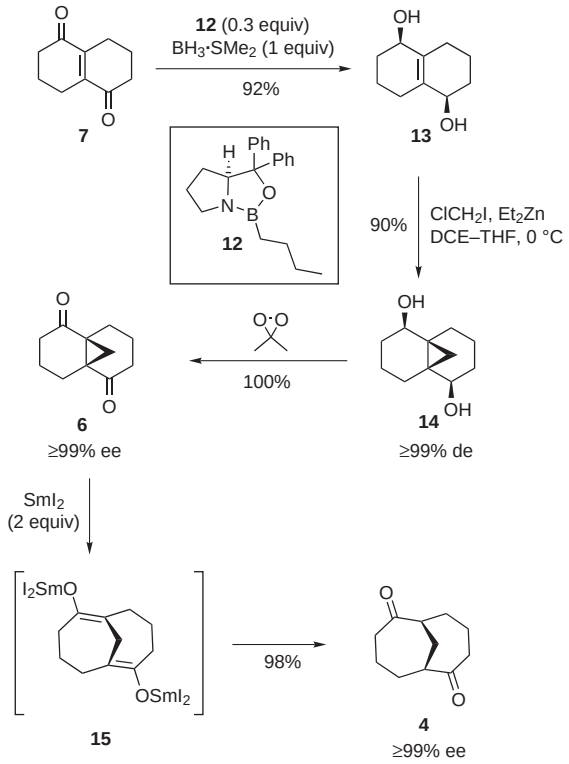


Scheme 3 Synthesis of racemic diketone **4**

For this purpose, enedione **7** was subjected to an oxazaborolidine-catalyzed borane reduction (CBS reduction)[15] furnishing the *cis*-diol **13** in 92% yield as a single stereoisomer (Scheme 4). While attempts to cyclopropanate **13** under Simmons–Smith conditions (Zn/Cu couple, CH_2I_2) failed due to complete decomposition, we finally succeeded to achieve the desired transformation using the diethylzinc/chloroiodomethane reagent.[16] The tricyclic diol **14**, which was again obtained as a single diastereomer, could be converted to the rather unstable diketone **6** either by Jones oxidation (84%) or with dimethyldioxirane[17] (100%). The optically active diketone was then also subjected to the established fragmentation conditions (2 equiv SmI_2, THF, r.t.) to give bicyclo[4.4.1]undecane-2,7-dione (**4**), again in almost quantitative yield (Scheme 4). The enantiomeric purity of this product ($[\alpha]_D^{20}$ –105.0, *c* 0.765, $CHCl_3$) was determined to >99% ee by gas chromatography using a chiral stationary phase.

The proven stereospecificity of the reductive fragmentation (Scheme 4) is remarkable since the chirality centers of tricycle **6** are destroyed during the fragmentation. Obviously, the intermediate dienolate **14** retains the absolute stereochemical information due to its inherent non-planar (chiral) nature.[18] At this point it should be mentioned that unsymmetrically substituted bicyclo[4.4.1]undecanes in which both bridgehead carbons are planarized by being part of a double bond (e.g., **3**, R …H) are configurationally stable planar chiral molecules.[18]

The absolute configuration of the synthesized compounds was assigned as follows: based on the reliable model of Corey for the CBS reduction[15] we were confident that the configuration of the diol **13**, prepared using the (*S*)-proline-derived catalyst **12**, was *R*,*R* as shown in Scheme 4. The *syn*-directing effect of allylic hydroxyl groups in Simmons–Smith-type cyclopropanations is well established.[16] The relative configuration of the cyclopropanation product **14** obtained from **13** was also confirmed by NOE measurements. Thus, the absolute configuration of the oxidation product **6** must be *S*,*S*. For geometrical reasons, the stereospecific reductive fragmentation of (*S*,*S*)-**6** can only lead to **4** with the shown *R*,*R*-configuration. This



Scheme 4 Enantioselective synthesis of diketone **4**

assignment is supported by the CD spectrum of compound **4**, which displays a pronounced negative Cotton effect at about 300 nm (Figure 2).[19]

An X-ray crystal structure analysis of **4** reveals that this compound adopts a conformation in which the two carbonyl groups point 'downward' (away from the methylene bridge). The distance between the two oxygen atoms is only 4.4 Å (Figure 3). This not only suggests that stereoselective addition reactions could be possible but also that diimine or dioxime derivatives of **4** may be interesting chiral chelate ligands for metal complexation.

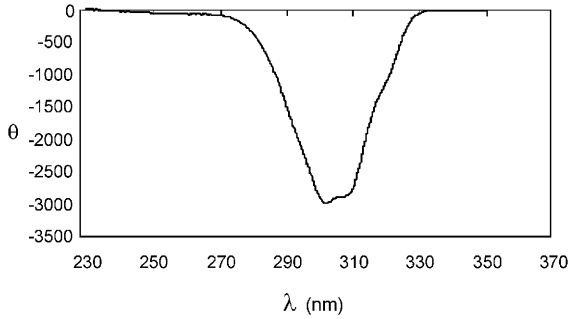


Figure 2 CD spectrum of **4** in MeOH

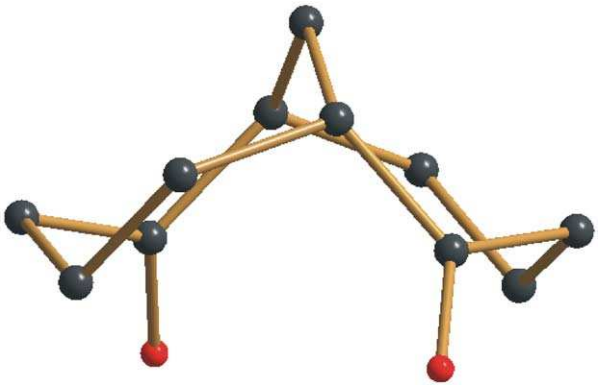


Figure 3 Structure of **4** in the crystalline state (H atoms not shown)

In conclusion, we have elaborated a novel and fully enantioselective synthesis of the C_2-symmetric diketone **4**, which proceeds in only six steps starting from cyclohexenone. Current research in this laboratory is directed towards further development of this chemistry and in particular towards the synthesis of new C_2-symmetric ligands derived from **4** (or *ent*-**4**) and their application in enantioselective catalysis.

(1*S*,2*R*,6*S*,7*R*)-Tricyclo[4.4.1.0^{1,6}]undecane-2,7-diol (14)

A 1 M solution of Et_2Zn in hexane (87 mL, 87 mmol) was added to 1,2-dichloroethane (135 mL) at 0 °C under Ar. Then, ICH_2Cl (13 mL, 178 mmol) was added over 5 min and the resulting cloudy solution was stirred for an additional 5 min after which a solution of diol **13** (2.44 g, 14.5 mmol) in 45 mL of THF was added all at once. The cooling bath was removed and the reaction mixture was stirred overnight. Sat. NH_4Cl solution (25 mL) was added, the organic phase was separated, washed with H_2O (2 × 50 mL) and brine (2 × 50 mL), dried over $MgSO_4$ and evaporated, leaving 2.35 g (90%) of **14** as a colorless crystalline solid.

Mp 126–127 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.77 (dd, 2 H, $^3J_1$ = 9.4 Hz, $^3J_2$ = 5.7 Hz), 1.59–1.82 (m, 6 H), 1.40–1.52 (m, 2 H), 1.34 (br s, 2 H, OH), 1.12–1.27 (m, 2 H), 0.90–1.03 (m, 2 H), 0.57 (s, 2 H, H-11) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 74.6 (d, C-2 and C-7), 46.3 (t), 30.5 (t), 30.0 (t), 20.4 (t), 15.9 (t, C-11) ppm. IR (ATR): 3326 (s), 2927 (s), 2856 (s), 1452 (m), 1322 (w), 1267 (m), 1206 (w), 1152 (m), 1060 (s), 1024 (s), 952 (m), 936 (m), 902 (m), 831 (m), 734 (m) cm^{-1}. MS (EI, 70 eV): *m/z* (%) = 182 (1) [M]$^+$, 164 (20) [M – H_2O]$^+$, 149 (25), 131 (35), 117 (35), 105 (40), 91 (100), 79 (80), 67 (40), 55 (40), 39 (60). HRMS (EI): *m/z* calcd for $^{12}C_{11}H_{18}$ $^{16}O_2$ [M]$^+$: 182.1307; found: 182.131.

(1*S*,6*S*)-Tricyclo[4.4.1.0^{1,6}]undecane-2,7-dione (6)

Method A: with Dimethyldioxirane

Diol **14** (20 mg, 0.11 mmol) was dissolved in acetone (0.7 mL). To this was added a 0.7 M solution of dimethyldioxirane in acetone (7 mL) portion wise over 8 h. After stirring overnight, the reaction mixture was evaporated under reduced pressure, leaving 19.5 mg (100%) of **6** as a colorless crystalline solid.

Method B: with Chromic Acid

Diol **14** (250 mg, 1.37 mmol) was dissolved in 20 mL of acetone, cooled to 0 °C and treated with Jones reagent until an orange color persisted. After stirring the mixture for an additional 10 min, *i*-PrOH (10 mL) was added and the reaction mixture was evaporated to a volume of 5 mL under reduced pressure. Then, H_2O (100 mL) was added, and the solution was extracted with MTBE (4 × 100

mL). The combined organic layers were dried over $MgSO_4$ and evaporated to yield 206 mg (84%) of **6** as colorless crystals.

Compound **6** was essentially pure according to GC, TLC and NMR analysis. Further purification was achieved by column chromatography (SiO_2), albeit with substantial loss of material due to decomposition on the column.

Mp 119–120 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.24–2.41 (m, 4 H), 1.95–2.14 (m, 4 H), 1.51–1.83 (m, 6 H) ppm; the cyclopropane protons resonate at 1.70 ppm as a singlet. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 207.2 (s), 39.4 (s), 36.2 (t), 21.9 (t), 17.9 (t), 17.7 (t) ppm. IR (ATR): 3079 (w), 2941 (m), 2871 (m), 1682 (s), 1636 (w), 1484 (w), 1447 (m), 1411 (w), 1382 (w), 1342 (m), 1248 (m), 1234 (m), 1202 (w), 1144 (m), 1085 (w), 871 (s), 859 (s), 829 (m), 646 (w) cm^{-1}. MS (EI, 70 eV): *m/z* (%) = 178 (20) $[M]^+$, 164 (5), 150 (90), 135 (85), 120 (60), 112 (50), 93 (55), 79 (100), 64 (30), 55 (65), 39 (60). HRMS (EI): *m/z* calcd for $^{12}C_{11}H_{14}{}^{16}O_2$ $[M]^+$: 178.0994; found: 178.099. $[\alpha]_D^{20}$ –46.3 (*c* 1.0, $CHCl_3$).

(1*R*,6*R*)-Bicyclo[4.4.1]undecane-2,7-dione (4)

To of a freshly prepared 0.1 M solution of SmI_2 in THF (8.6 mL, 0.86 mmol) was added, dropwise and with stirring, a solution of diketone **6** (77 mg, 0.43 mmol) in THF (7 mL) at r.t. The initially deep blue solution turned brownish-yellow immediately. After 2 min, sat. NH_4Cl solution (15 mL) was added and the reaction mixture was extracted with MTBE (3 × 30 mL). The combined organic layers were washed with brine (3 × 30 ml), dried over $MgSO_4$ and evaporated under reduced pressure. The crude product was filtered over SiO_2 (EtOAc) to afford 76 mg (98%) of a colorless, crystalline solid. Mp 124–126 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.77–2.82 (m, 2 H), 2.60–2.69 (m, 2 H), 2.31–2.52 (m, 6 H), 1.70–1.80 (m, 2 H), 1.35–1.61 (m, 4 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 212.6 (s), 49.0 (d), 42.8 (t), 30.2 (t), 29.0 (t), 21.4 (t) ppm. IR (ATR): 2940 (m), 2874 (w), 2840 (w), 1689 (s), 1461 (w), 1449 (m), 1434 (w), 1317 (m), 1214 (w), 1181 (m), 1151 (w), 1127 (w), 1058 (w), 1044 (w), 992 (m), 928 (m), 886 (w), 782 (w) cm^{-1}. MS (EI, 70 eV): *m/z* (%) = 180 (40) $[M]^+$, 162 (10), 152 (2), 139 (35), 125 (25), 111 (35), 97 (45), 84 (80), 69 (50), 55 (100), 41 (70). $[\alpha]_D^{20}$ –105, $[\alpha]_{546}^{20}$ –130.6, $[\alpha]_{405}^{20}$ –376.0, $[\alpha]_{365}^{20}$ –659.5, $[\alpha]_{334}^{20}$ 1599.2 (*c* 0.765, $CHCl_3$). GC (Agilent HP-6890 system, 6-T-2,3-Me-β-cyclodextrin 25 m fused silica capillary column, 250 μm diameter, gas type: H_2 (0.6 bar), inlet temperature 150 °C, detector temperature 220 °C, temperature program: 40 °C (10 min) to 150 °C (75 min): t_R (1*R*,6*R*) = 68.114 min (99.62%), t_R (1*S*,6*S*) = 69.361 min (0.38%), 99% ee. HRMS (EI): *m/z* calcd for $^{12}C_{11}H_{16}{}^{16}O_2$ $[M]^+$: 180.1150; found: 180.115; Anal. Calcd for C, 73.3; H, 8.95. Found: C, 72.98; H, 8.98.

Acknowledgment

This work was supported by the Fonds der Chemischen Industrie. We thank Dr. Mathias Schäfer for mass spectrometric measurements and Andreas Adler for assistance in gas chromatographic and HPLC analytic techniques.

References and Notes

(1) Cimino, G.; De Stefano, S.; Minale, L.; Trivellone, E. *Tetrahedron Lett.* **1975**, 3727.
(2) Amagata, T.; Amagata, A.; Tenney, K.; Valeriote, F. A.; Lobkovsky, E.; Clardy, J.; Crews, P. *Org. Lett.* **2003**, *5*, 4393.
(3) Vogel, E.; Roth, H. D. *Angew. Chem.* **1964**, *76*, 145.
(4) The bicyclo[4.4.1]undecane ring system (with a functionalized C_1-bridge) also occurs as a substructure in some other more complex polycyclic natural products such as ingenol. For a leading reference, see: Montalt, J.; Linker, F.; Ratel, F.; Miesch, M. *J. Org. Chem.* **2004**, *69*, 6715.
(5) Vogel, E.; Klug, W.; Breuer, A. *Org. Synth., Coll. Vol. VI* **1988**, 731.
(6) Marshall, J. A.; Conrow, R. E. *J. Am. Chem. Soc*. **1983**, *105*, 5679.
(7) (a) Otomaru, Y.; Kina, A.; Shintani, R.; Hayashi, T. *Tetrahedron: Asymmetry* **2005**, *16*, 1673. (b) Otomaru, Y.; Tokunaga, N.; Shintani, R.; Hayashi, T. *Org. Lett.* **2005**, *7*, 307.
(8) Berkessel, A.; Schröder, M.; Sklorz, C. A.; Tabanella, S.; Vogl, N.; Lex, J.; Neudörfl, J. M. *J. Org. Chem.* **2004**, *69*, 3050.
(9) For a synthesis of *rac*-**4** by $Pb(OAc)_4$-mediated cleavage of a pinacol, see: Kakiuchi, K.; Kumanoya, S.; Kobiro, K.; Tobe, Y.; Odaira, Y. *Bull. Chem. Soc. Jpn.* **1990**, *63*, 3358.
(10) For the reductive fragmentation of 1,4-diketones using samarium(II) iodide, see: (a) Williams, D. B. G.; Blann, K.; Holzapfel, C. W. *J. Chem. Soc,. Perkin Trans. 1* **2001**, 219. For the reductive cleavage of cyclopropyl ketones, see also: (b) Batey, R. A.; Motherwell, W. B. *Tetrahedron Lett.* **1991**, *32*, 6649. (c) Kim, Y. H.; Lee, I. S. *Heteroat. Chem.* **1992**, *3*, 509. (d) Batey, R. A.; Harling, J. D.; Motherwell, W. B. *Tetrahedron* **1996**, *52*, 11421. (e) Molander, G. A.; Alonso-Alija, C. *Tetrahedron* **1997**, *53*, 8067. (f) Lee, P. H.; Lee, J.; Kim, H.-C. *Bull. Korean Chem. Soc.* **2000**, *21*, 207. (g) Aulenta, F.; Hölemann, A.; Reißig, H.-U. *Eur. J. Org. Chem.* **2006**, *7*, 1733.
(11) McChesney, J. D. *J. Pharm. Sci.* **1979**, *68*, 1116.
(12) Horni, A.; Hubacek, I.; Hesse, M. *Helv. Chim. Acta* **1994**, *77*, 579.
(13) (a) Chamakh, A.; M'hirsi, M.; Villiéras, J.; Lebreton, J.; Amri, H. *Synthesis* **2000**, 295. (b) Pinnick, H. K. *Org. React.* **1990**, *38*, 655.
(14) Corey, E. J.; Chaykovsky, M. *J. Am. Chem. Soc.* **1962**, *84*, 867.
(15) (a) Corey, E. J.; Bakshi, R. K.; Shibata, S. *J. Am. Chem. Soc.* **1987**, *109*, 5551. (b) For a review, see: Corey, E. J.; Helal, C. J. *Angew. Chem., Int. Ed. Engl.* **1986**, *15*, 37.
(16) (a) Miyano, S.; Hashimoto, H. *Bull. Chem. Soc. Jpn.* **1973**, *46*, 892. (b) Miyano, S.; Izumi, Y.; Fujii, H.; Hashimoto, H. *Synthesis* **1977**, 700. (c) Denmark, S. E.; Edwards, J. P. *J. Org. Chem.* **1991**, *56*, 6974.
(17) (a) Murray, R. W.; Singh, M. *Org. Synth., Coll. Vol. IX* **1998**, 288. (b) Adam, W.; Bialas, J. *Chem. Ber.* **1991**, *124*, 2377.
(18) Kuffner, U.; Schlögl, K. *Tetrahedron Lett.* **1971**, *21*, 1773.
(19) The homologous (1*R*,5*R*)-bicyclo[3.3.1]nonane-2,6-dione also displays a negative Cotton effect: (a) Berg, U.; Butkus, E. *J. Chem. Res., Synop.* **1993**, 116. (b) Application of the octant rule to compound **4** also predicts a negative Cotton effect for the *R*,*R*-enantiomer, see: (b) Moffitt, W.; Woodward, R. B.; Moscowitz, A.; Klyne, W.; Djerassi, C. *J. Am. Chem. Soc.* **1961**, *83*, 4013.