Pergamon

SCIENCE DIRECT®

Tetrahedron Letters 44 (2003) 2633–2636

TETRAHEDRON LETTERS

Synthesis of a model bicyclic core related to *Microscleroderma spirophora* steroids

Anand Mayasundari, Ulf Peters and David G. J. Young*

Department of Chemistry, University of Tennessee, Knoxville, TN 37996, USA

Received 31 January 2003; revised 5 February 2003; accepted 7 February 2003

Abstract—An approach to the strained B,C-bicyclic nucleus of a heterocyclic class of steroids is described. The approach relies on a sigmatropic shift for installation of the strained bridge.

In connection with our program aimed at the synthesis of strained bridgehead olefins, we undertook the stereocontrolled synthesis of structures related to the bicyclic nucleus of steroids isolated from *Microscleroderma spirophora* (Fig. 1).[1] As shown in Scheme 1 retrosynthetic analysis involved assembly of the bicyclic core using a sigmatropic shift where epoxide ring strain was used as a driving force for rearrangement to the bridgehead diene.[2]

As outlined in Scheme 2, addition of vinyl Grignard to iodocyclohexenone **5** followed by PCC oxidation afforded the rearranged product **7**.[3] The resulting ketone was reduced with sodium borohydride and cerium trichloride in methanol to yield alcohol **8**.[4] Directed Grignard cross coupling afforded the hexatriene **9** in 44% overall yield for four steps.[5,6]

Synthesis of the bicyclic core was completed by directed stereoselective introduction of the bridging oxygen using *tert*-butyl hydroperoxide and vanadium to afford **10** (Scheme 3).[7] As anticipated, heating **10** in the presence of triethylamine led to smooth Cope conversion to the target oxabicyclic **11**.[8,9]

Structural proof for **11** was obtained through preparation of the derived benzoate which yielded X-ray quality crystals. The ORTEP of **12** is shown in Figure 2 where the ester oxygen and bridging oxygen are poised on the same face of the ring system.

Turning to the synthesis of the second analog (Scheme 4), **11** was acylated with acetic anhydride and 4-DMAP. The resulting material was deprotonated with lithium diisopropylamide, silylated with

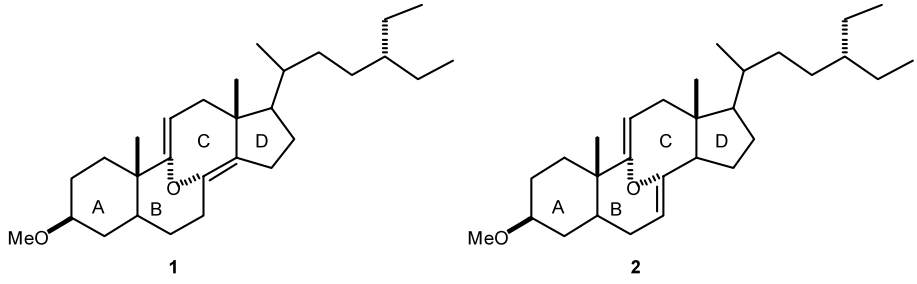
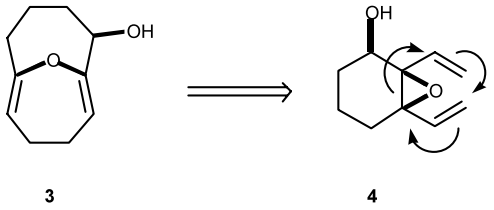


Figure 1.

* Corresponding author.

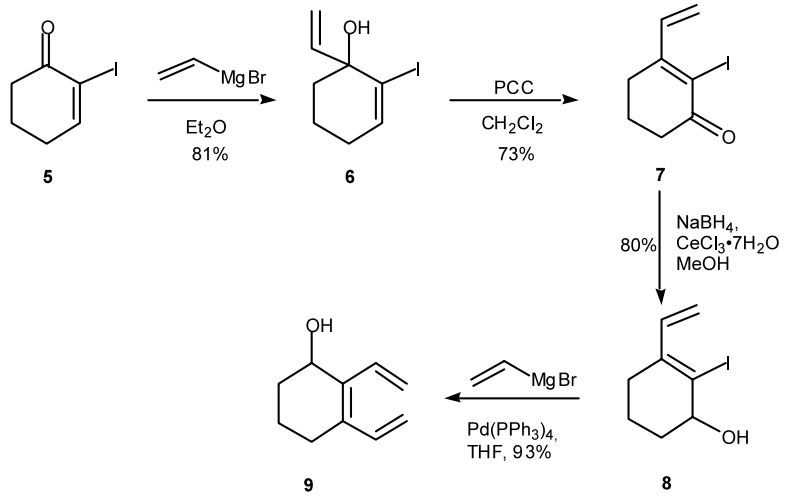
0040-4039/03/$ - see front matter
doi:10.1016/S0040-4039(03)00378-2



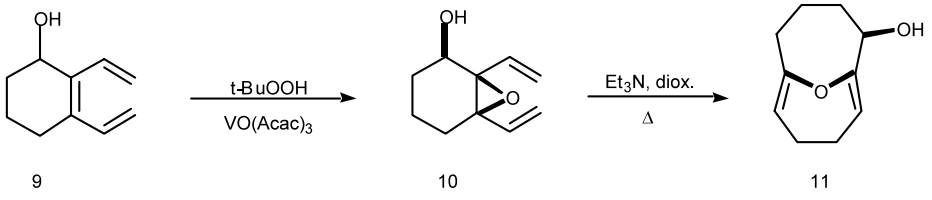
Scheme 1. Retrosynthetic analysis of **3**.

tert-butyldimethylsilyl chloride and DMPU, and then warmed to room temperature to afford the rearranged diene **13** via Ireland–Claisen rearrangement.[10]

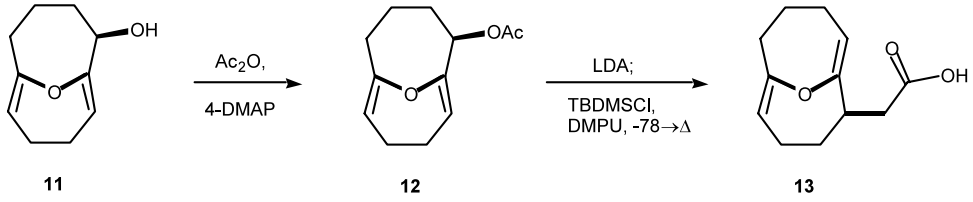
In summary two strained analogs of steroidal systems have been synthesized using a Cope rearrangement strategy. The synthesis of analog **11** required six steps and proceeded in 13% yield while the synthesis of analog **13** included two additional steps for 10% overall yield.[11] Further transformations of these structures are being investigated and will be reported in due course.



Scheme 2. Preparation of hexatriene.



Scheme 3. Preparation of model compound **11**.



Scheme 4. Rearrangement of acetate **12**.

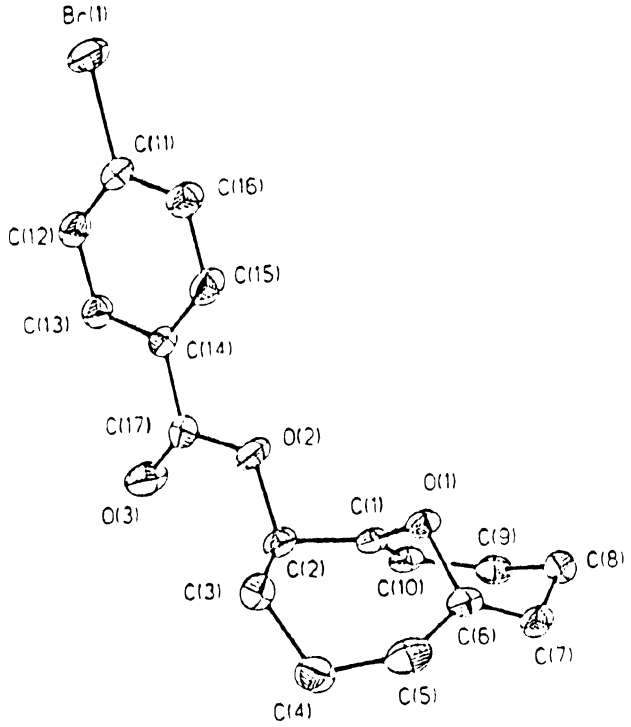


Figure 2. ORTEP of **12**.

References

1. Costantino, V.; Fattorusso, E.; Mangoni, A.; Aknin, M.; Gaydou, E. M. *Steroids* **1994**, *59*, 181.
2. Von Zezschwitz, P.; Voigt, K.; Lansky, A.; Noltemeyer, M.; de Meijere, A. *J. Org. Chem.* **1999**, *64*, 3806.
3. (a) Babler, J. H.; Coghlan, M. J. *Synth. Commun.* **1976**, *6*, 469; (b) Dauben, W. G.; Michno, D. M. *J. Org. Chem.* **1977**, *42*, 682; (c) Sundararaman, P.; Herz, W. *J. Org. Chem.* **1977**, *42*, 806.
4. Germal, A. L.; Luche, J. L. *J. Am. Chem. Soc.* **1981**, *103*, 5454.
5. Mayasundari, A.; Young, D. G. J. *Tetrahedron Lett.* **2001**, *42*, 203.
6. *Procedure for **8** to **9***: To a solution of 8.97 g (35.9 mmol) of **8** in 90 mL of THF was added 117.4 mg (102 μmol) of $Pd(PPh_3)_4$. The reaction stirred 10 min, was cooled to −78°C, and 89.7 mL (89.7 mmol) of CH_2=CHMgBr was added over 30 min. The reaction was warmed to room temperature stirred for 12 h and quenched with saturated aqueous ammonium chloride. The layers were separated, and the aqueous phase was extracted with three 100-mL portions of ether. The combined organic layers were washed with 100 mL of brine, dried ($MgSO_4$) and concentrated in vacuo. The residue was chromatographed over 175 g of silica gel (eluted with dichloromethane) to afford 4.99 g (33.18 mmol, 93%) of **9**.
7. Sharpless, K. B.; Michaelson, R. C. *J. Am. Chem. Soc.* **1973**, *95*, 6136.
8. *Procedure for **10** to **11***: To 99.3 mg (0.60 mmol) of epoxide **10** in 15 mL of 1,4-dioxane at room temperature was added 0.17 mL (1.2 mmol) of triethylamine. The reaction was warmed to 80°C and stirred 10 h, then cooled to room temperature and concentrated in vacuo. The residue was chromatographed over 5 g of silica gel eluted with hexanes–ether, 1:1) to yield 66 mg (66%) of **11** as a yellow oil.
9. Ireland, R. E.; Wipf, P.; Xiang, J. N. *J. Org. Chem.* **1991**, *56*, 3572.
10. *Procedure for **12** to **13***: To a solution of 0.73 mL of diisopropylamine in 6 mL of THF at 0°C was added 3.6 mL of a 1.5 M solution of *n*-BuLi in hexanes over 5 min. After stirring at 0°C for 10 min, the solution was cooled to −78°C and acetate **12** was added over 10 min as a solution of 5 mL of THF. The reaction stirred for 40 min at −78°C, then 887 mg (5.9 mmol) of TBDMSCl in 4.5 mL of THF was added over 5 min, followed 4 min later by 4.3 mL of DMPU. The reaction stirred 15 min at −78°C, warmed to room temperature, and was heated under reflux for 18 h. After cooling to room temperature, the solution was extracted with two 25-mL portions of 2N aqueous NaOH, and the aqueous phase was then acidified with 6N aqueous HCl. The resulting solution was extracted with three 40-mL portions of diethyl ether and the combined organic layers were washed with 30 mL of brine, dried ($MgSO_4$) and concentrated in vacuo. The residue was chromatographed over 65 g of SiO_2 (eluted with hexanes–ethyl acetate 1:1) to afford 768 mg (3.69 mmol, 69%) of **13** as a pale yellow solid.
11. *Selected data for new compounds*:
    Compound **6**: ^{1}H NMR ($CDCl_3$): δ 6.57–6.52 (m, 1H), 5.79 (ddd, 1H), 5.33–5.18 (m, 2H), 2.19–1.89 (m, 5H), 1.81–1.60 (m, 2H); ^{13}C NMR ($CDCl_3$): δ 142.99, 141.37, 114.85, 109.33, 74.75, 36.17, 29.42, 18.83. HRMS (EI) calcd for $C_8H_{11}IO$: m/z 249.9855. Found: m/z 249.9848.
    Compound **7**: ^{1}HNMR ($CDCl_3$): δ 7.02 (dd, 1H), 5.78 (d, 1H), 5.58 (d, 1H), 2.68–2.59 (m, 4H), 2.25–1.96 (m, 2H); ^{13}C NMR ($CDCl_3$): δ 192.96, 158.68, 142.65, 124.07, 110.40, 37.23, 28.07, 21.81. HRMS (EI) calcd for C_8H_9IO: m/z 247.9698. Found: m/z 247.9693.
    Compound **8**: ^{1}H NMR ($CDCl_3$): δ 6.64 (dd, 1H), 5.36 (dd, 1H), 5.21 (d, 1H), 4.36 (q, 1H), 2.43–2.30 (m, 2H), 2.27–2.16 (m, 1H), 2.01–1.63 (m, 4H); ^{13}C NMR ($CDCl_3$): δ 142.14, 140.24, 117.93, 110.57, 74.41, 32.10, 27.77, 17.95. HRMS (EI) calcd for $C_8H_{11}IO$: m/z 249.9855. Found: m/z 249.9864.
    Compound **9**: ^{1}H NMR ($CDCl_3$): δ 6.98–6.80 (m, 2H), 5.46 (d, 1H), 2.18–2.05 (m, 1H), 1.97–1.88 (m, 1H), 1.82–1.55 (m, 4H); ^{13}C NMR ($CDCl_3$): δ 135.28, 133.90, 133.85, 132.56, 115.42, 114.66, 63.87, 30.58, 25.77, 16.60. HRMS (EI) calcd for $C_{10}H_{14}O$: m/z 150.1045. Found: m/z 150.1047.
    Compound **10**: ^{1}H NMR ($CDCl_3$): δ 5.84–5.68 (m, 2H), 5.42–5.21 (m, 4H), 4.12–4.06 (m, 1H), 2.16 (d, 1H), 1.95–1.90 (m, 2H), 1.65–1.54 (m, 3H), 1.39–1.32 (m, 1H); ^{13}C NMR ($CDCl_3$): δ 135.94, 134.01, 119.16, 117.88, 68.64, 68.46, 67.59, 29.63, 26.76, 16.61. HRMS (EI) calcd for $C_{10}H_{14}O_2$: m/z 166.0994. Found: m/z 166.0991.
    Compound **11**: ^{1}H NMR ($CDCl_3$): δ 5.00–4.97 (m, 1H), 4.91–4.87 (m, 1H), 4.18 (dd, 1H), 2.87–2.76 (m, 1H); ^{13}C NMR ($CDCl_3$): δ 163.37, 159.81, 114.74, 110.51, 72.36, 34.28, 32.81, 24.08, 22.04, 21.74. HRMS (EI) calcd for $C_{10}H_{14}O_2$: m/z 166.0994. Found: m/z 166.0994.

Compound **12**: ^{1}H NMR ($CDCl_3$): δ 5.28 (dd, 1H), 5.14 (dd, 1H), 4.93 (t, 1H), 2.92–2.80 (m, 1H), 2.56–2.46 (m, 1H), 2.24 (t, 2H), 2.02 (s, 3H), 1.99–1.70 (m, 5H), 1.43–11.30 (m, 1H); ^{13}C NMR ($CDCl_3$): δ 170.55, 164.17, 155.76, 118.52, 110.40, 74.58, 33.14, 30.80, 24.59, 22.91, 21.51, 21.37. HRMS (EI) calcd for $C_{12}H_{16}O_3$: m/z 208.1099. Found: m/z 208.1097.

Compound **13**: ^{1}H NMR ($CDCl_3$): δ 11.40 (s, 1H), 5.11 (dd, 1H), 5.01–4.97 (m, 1H), 3.00–2.97 (m, 1H), 2.83 (dd, 1H), 2.69–2.51 (m, 3H), 2.45–2.25 (m, 2H), 1.94–1.67 (m, 4H), 1.59–1.49 (m, 1H), 1.35–1.23 (m, 1H); ^{13}C NMR ($CDCl_3$): δ 178.90, 161.26, 159.68, 112.71, 110.92, 39.43, 35.12, 34.70, 32.34, 28.12, 24.31, 20.13. HRMS (EI) calcd for $C_{12}H_{16}O_3$: m/z 208.1099. Found: m/z 208.1098.