Available online at www.sciencedirect.com
ScienceDirect
Tetrahedron Letters 48 (2007) 5919–5922
Tetrahedron Letters

Diastereoselectivity in an electrocyclization reaction of cyclopentadienones

Michael Harmata,[a,*] Pinguan Zheng,[a] Peter R. Schreiner[b] and Armando Navarro-Vázquez[c]

[a] *Department of Chemistry, University of Missouri-Columbia, Columbia, Missouri 65211, USA*
[b] *Institute of Organic Chemistry, Justus-Liebig University, Heinrich-Buff-Ring, 58, 35392 Giessen, Germany*
[c] *Departamento de Química Orgánica Facultade de Química, Universidade de Santiago de Compostela, 15782 Santiago de Compostela, Spain*

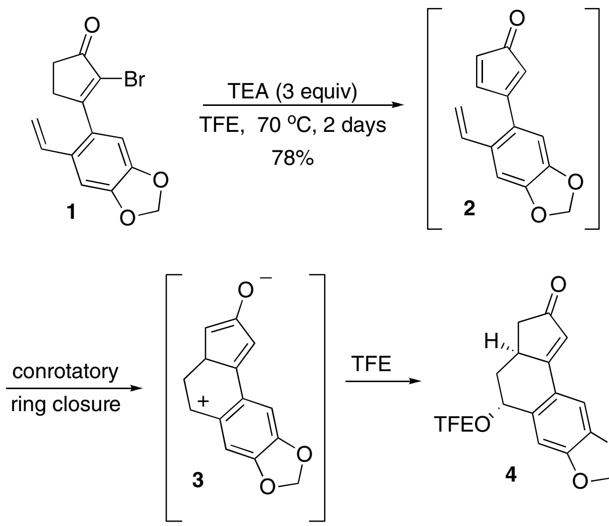
Received 2 May 2007; revised 1 June 2007; accepted 4 June 2007
Available online 9 June 2007

Abstract—Two cyclopentadienones were generated and both underwent conrotatory electrocyclization as expected based on Woodward–Hoffmann rules. This result lends support to the idea that these ring-closing reactions are, in fact, pericyclic processes.

Electrocyclic reactions represent a powerful method for creating rings efficiently and stereoselectively.[1] A number of strategies are available for conducting and catalyzing such reactions. Recently, we reported the use of 'deantiaromatization' as a driving force for the electrocyclization of a set of cyclopentadienones, in conjunction with studies ultimately directed at the synthesis of hamigeran B.[2] For example, treatment of **1** with triethylamine in trifluoroethanol (TFE) for 2 days at 70 °C resulted in the formation of **4** in 78% yield. Presumably, cyclopentadienone **2** was generated from **1** by a 1,4-elimination. Cyclization and trapping then proceeded to afford **4** as shown in Scheme 1.

As a pericyclic process, this cyclization should proceed stereospecifically in a conrotatory fashion, as it involves 8π-electrons. To probe this, we prepared two isomeric precursors and examined their cyclizations to establish whether this is the case. This Letter contains the details of that study.

The two substrates required for this study were prepared from the halogen–metal exchange reaction between **5** and **6** with *n*-BuLi followed by transmetalation with $CeCl_3$.[3] The organocerium reagents were reacted with **7** and the products **8** and **9** were obtained in 85% and 16% (80% based on recovered starting material) yields after hydrolysis (Scheme 2).[4] The low (unoptimized) yield for **9** can be ascribed to steric effects, but may also be due to the quality (e.g., dryness) of the $CeCl_3$.[5] In our hands, drying protocols for this salt do not always produce consistent results.[6]



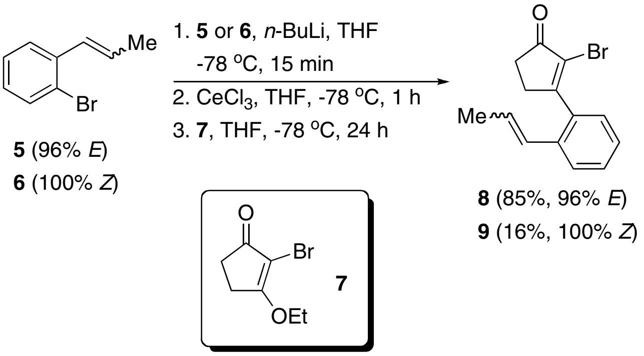
Scheme 1. Cyclization through deantiaromatization.

With the pure *E* and *Z* cyclopentenones in hand, electrocyclic reactions were carried out under standard reaction

---

* Corresponding author. Tel.: +1 573 882 1097; fax: +1 573 882 2754; e-mail: HarmataM@missouri.edu

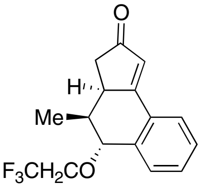
0040-4039/$ - see front matter
doi:10.1016/j.tetlet.2007.06.011



Scheme 2. Preparation of starting materials.

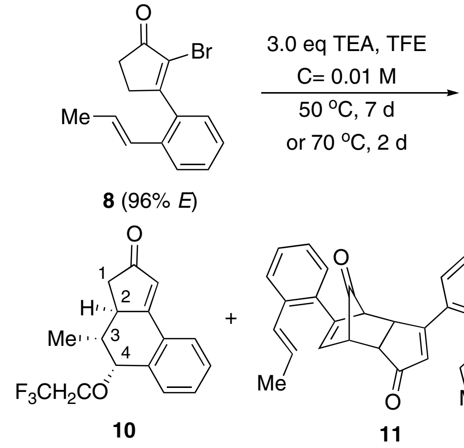
conditions (50 °C, 7 days or 70 °C, 2 days).[7] When E isomer **8** (96% E; 24:1, E:Z)[8] was treated with triethylamine at 50 °C for 7 days, the desired cyclization adduct **10** was isolated in 43% yield with nearly complete diastereoselectivity (10:1), accompanied by 33% recovered starting material and some cyclopentadienone dimer **11** (Scheme 3).[9] The diastereoselectivity in the formation of **10** was not complete as the starting material **8** contained some **9** (4%). The change in the product ratio *vis-à-vis* the ratio of starting materials suggested that **9** reacted more efficiently than **8**. The ratio of **8**, **10**, and **11** in the crude reaction mixture was 0.39:0.51:0.10 by ^{1}H NMR.

The amount of dimer increased significantly when **8** was stirred in TFE at 70 °C for 2 days. The expected product **10** was isolated in 39% yield and (**8**, **10**, and dimer: 0.33:0.48:0.19). The stereochemistry of **10** was determined by X-ray crystallography and is consistent with our proposed conrotatory cyclization mechanism.[10] NMR data (Fig. 1) in solution are also in agreement with the X-ray data as evident from the observed NOE signals between H_2 and the methyl group and also between the H_3 and H_4 protons.



12

In contrast to **8**, when the Z isomer **9** was treated with base, the reaction was surprisingly clean. Product **12** was isolated in 56% yield as a single diastereomer, together with 27% recovered starting material.[7,11] Since the product could not be crystallized, the stereochemical assignment of **12** was based on the analysis of NOESY experiments and scalar coupling constants.[12] First, the observed $^{3}J_{H3-H4}$ coupling constant of 2.2 Hz agrees better with the computed equatorial–equatorial constant, using the Hassnoot–Altona empirical equation[13] of 2.0 Hz. Placing the trifluoroethoxy group in the equatorial position gives an equatorial axial computed ^{3}J constant of 4.4 Hz; secondly, no cross peak between H_2 and H_4 was observed in the NOESY experiment.



Scheme 3. Cyclization of **8**.

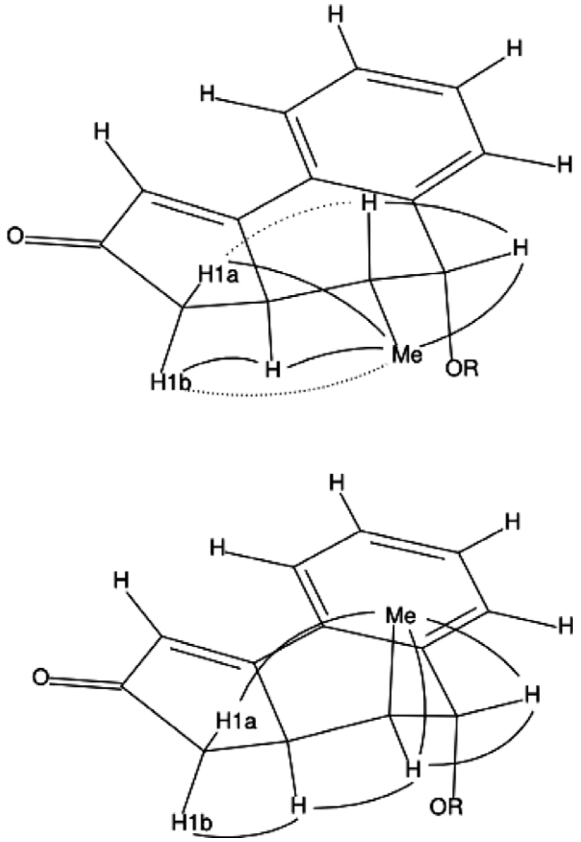
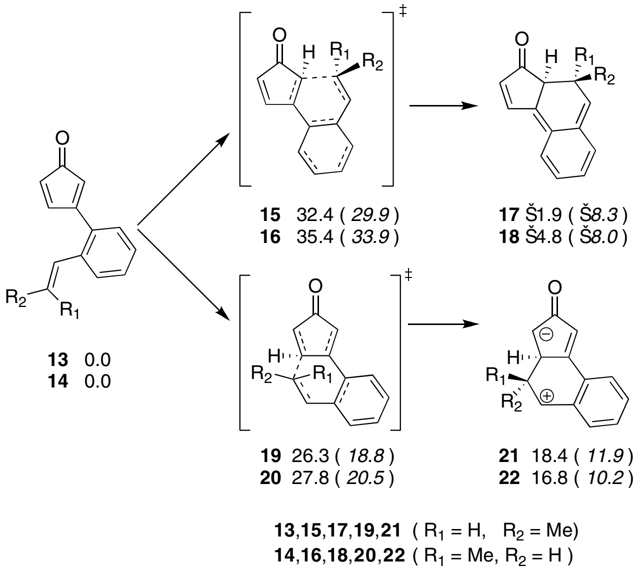


Figure 1. NOE correlations for **10** (top) and **12** (bottom). Dashed lines indicate weak NOEs.

We have investigated the proposed pericyclic processes by means of DFT computations. An unrestricted broken-spin-symmetry (UBS)[14] procedure was used for structures with a biradicaloid character. The structures were optimized at the B3LYP[15]/6-31G* level upon which single point energies were computed at B3LYP/6-311+G**. Solvation effects in trifluoroethanol were modeled using the continuum PCM[16] model, employing ethanol parameters as provided in Gaussian03 but with a relative permitivity ε of 26.73 and effective solvent radius of 0.3 Å; single point energies were computed at the PCM-B3LYP/6-311+G** level as well. Harmonic



Scheme 4. Activation and reaction B3LYP/6-311+G**//B3LYP/6-31G* $\Delta G_{298.15\,K}$ free energies. Regular font: gas phase values, italics: PCM (TFE) data.

frequencies were computed on all optimized structures to verify the nature of the stationary points and to obtain thermochemical quantities. Reported free energies $\Delta G_{298.15\,K}$ were obtained by inclusion of B3LYP/6-31G* thermochemical corrections in the B3LYP/6-311+G** computations.[17]

The computations (Scheme 4) help elucidate the somewhat unexpected finding that **9** is better behaved than **8**. This can be rationalized in terms of the relative energies of the zwitterionic intermediates **21** and **22**. Although the position of the methyl group over the π-system in transition state **20** results in a slightly higher activation free energy for the formation of zwitterion **22** as compared to **21**, formation of the former is less endothermic, which, as a consequence, results in a faster overall process, making side reactions less competitive. Alternatively, the electrocyclization might be reversible. The computational data suggest reversibility should be more important for the cyclization of **13** than **14**. This would result in the regeneration of **13**, from zwitterion **21**, allowing it to engage in side reactions and thus lowering the yield of **10**. As previously observed,[2] the conrotatory process for **13** and **14** is kinetically and thermodynamically favored over the disrotatory cyclizations involving transition states **15** and **16**, respectively.

In conclusion, we uncovered new evidence for an 8π-electron conrotatory mechanism for the cyclization reaction of cyclopentadienones. Further studies of the mechanism of this process and applications to synthesis are underway.

Acknowledgements

This work was supported by the National Science Foundation to whom we are grateful. Thanks to Dr. Charles L. Barnes for acquisition of X-ray data. A.N. thanks the Centro de Supercomputación de Galicia (CESGA) for computer time.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2007.06.011.

References and notes

1. (a) Beaudry, C. M.; Malerich, J. P.; Trauner, D. *Chem. Rev.* **2005**, *105*, 4757; (b) Frontier, A. J.; Collison, C. *Tetrahedron* **2005**, *61*, 7577.
2. Harmata, M.; Zheng, P.; Schreiner, P. R.; Navarro-Vázquez, A. *Angew. Chem., Int. Ed.* **2006**, *45*, 1966.
3. Narayanan, B. A.; Bunnelle, W. H. *Tetrahedron Lett.* **1987**, *28*, 6261.
4. Compound **8**: 85% yield; pale yellow solid; mp: 92–93 °C; IR (film): 2908.9, 1707.6, 1613.6, 1433.8, 1184.5 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.56 (d, *J* = 7.5 Hz, 1H), 7.37 (td, *J* = 7.5, 1.0 Hz, 1H), 7.30 (td, *J* = 7.5, 1.0 Hz, 1H), 7.14 (dd, *J* = 7.5, 1.0 Hz, 1H), 6.19–6.27 (m, 2H), 2.93–2.95 (m, 2H), 2.71–2.73 (m, 2H), 1.87 (d, *J* = 5.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 202.2, 174.0, 135.6, 134.4, 130.1, 129.7, 128.8, 127.6, 127.4, 126.8, 125.7, 34.2, 33.9, 19.5; HRMS Calcd for $C_{14}H_{13}BrO$ M$^+$, 276.0144; found, 276.0137. Compound **9**: 16% yield (80% based on recovered starting material); solid, mp: 64–65 °C; IR: 3015.2, 1715.8, 1613.6 cm^{-1}; ^{1}H NMR 300 MHz, $CDCl_3$): δ 7.24–7.45 (m, 4H), 6.33 (d, *J* = 11.4, 1H), 5.83 (dt, *J* = 11.4, 7.0 Hz, 1H), 2.93–2.96 (m, 2H), 2.67–2.70 (m, 2H), 1.75 (dd, *J* = 7.0, 1.7 Hz, 3H); ^{13}C NMR (75.0 MHz, $CDCl_3$): δ 201.5, 173.3, 134.9, 134.6, 129.8, 129.0, 128.8, 127.5, 126.8, 126.7, 124.3, 33.2, 32.3, 14.4; HRMS Calcd for $C_{14}H_{13}BrO$ M$^+$, 276.0144; found, 276.0137.
5. The reactivity of cerium chloride is dependent on the manner in which the cerium chloride is activated. See also: (a) Conlon, D. A.; Kumke, D.; Moeder, C.; Hardiman, M.; Hutson, G.; Sailer, L. *Adv. Synth. Catal.* **2004**, *346*, 1307; (b) Evans, W. J.; Feldman, J. D.; Ziller, J. W. *J. Am. Chem. Soc.* **1996**, *118*, 4581.
6. Other methods were used for dehydrating $CeCl_3{\cdot}7H_2O$: (a) Takeda, N.; Imamoto, T. *Org. Synth.* **1999**, *76*, 228; (b) Paquette, L. A. *Encyclopedia of Reagents for Organic Synthesis*; Wiley: Chichester, 1995 pp 1031.
7. *Typical electrocyclic reaction procedure*: To a trifluoroethanol (10.3 mL) solution of *E*-**8** (28.7 mg, 0.103 mmol) was added triethylamine (43 μL, 0.31 mmol). The resulting mixture was heated under certain conditions (method A: 50 °C, 7 days; method B: 70 °C, 2 days). The reaction was monitored by TLC. After the completion of the reaction, trifluoroethanol was evaporated and the residue was dissolved in CH_2Cl_2 and washed with 1 N HCl, saturated $NaHCO_3$, H_2O and brine. The extract was dried over $MgSO_4$ and the solvent was removed by a rotavap. Column chromatography (15% EtOAc, 30% EtOAc) gave the desired product.
8. The *E*/*Z* ratio was derived from the respective alkenes by proton NMR.
9. Compound **10** (from **8**): Method A: 43% yield (33%, recovered starting material); method B: 39% yield (27% recovered starting material). Colorless crystal, mp: 132–133 °C; IR: *v* 2917.1, 1687.1, 1670.8, 1593.1, 1270.3, 1151.8, 1115.1 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$): δ

7.78–7.81 (m, 1H), 7.44–7.51 (m, 2H), 7.29–7.33 (m, 1H), 6.44 (d, $J = 2.2$ Hz, 1H), 4.39 (d, $J = 2.4$ Hz, 1H), 3.78–3.94 (m, 2H), 3.44–3.54 (m, 1H), 2.75 (dd, $J = 18.0$, 6.4 Hz, 1H), 2.25 (dd, $J = 18.0$, 4.1 Hz, 1H), 1.95–2.08 (m, 1H), 1.29 (d, $J = 6.8$ Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 207.3, 173.6, 135.8, 131.0 130.3, 130.0, 129.7, 127.8, 125.1, 124.0 (q, $J_{C\text{–}F} = 279.2$ Hz), 81.1, 66.2 (q, $J_{C\text{–}F} = 34.1$ Hz), 41.1, 40.5, 40.4, 15.6; HRMS Calcd for $C_{16}H_{15}F_3O_2Na$ $[M+Na]^+$, 319.0916; found, 319.0902.

10. Crystallographic data (excluding structure factors) for the structure of compounds in this Letter has been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 637396 (**10**). Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44 0 1223 336033 or e-mail; deposit@ccdc.cam.ac.uk].
11. Compound **12** (from **9**): Method A: 56% yield (27% recovered starting material). solid, mp: 55–56 °C; IR: ν 2966.1, 2925.3, 1699.4, 1597.2, 1278.5, 1151.8, 1102.8 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.74–7.77 (m, 1H), 7.37–7.53 (m, 3H), 6.52 (d, $J = 1.5$ Hz, 1H), 4.41 (d, $J = 2.2$ Hz, 1H), 3.80–4.06 (m, 3H), 2.67 (dd, $J = 18.6$, 6.8 Hz, 1H), 2.53–2.59 (m, 1H), 2.35 (dd, $J = 18.6$, 3.5 Hz, 1H), 0.73 (d, $J = 7.1$ Hz, 3H); ^{13}C NMR (75.0 MHz, $CDCl_3$): δ 207.9, 171.5, 133.1, 131.8, 131.5, 129.8, 129.3, 127.0, 126.3, 123.8 (q, $J_{C\text{–}F} = 279.2$ Hz), 82.5, 66.1 (q, $J_{C\text{–}F} = 34.1$ Hz), 38.3, 37.8, 34.7, 10.2; HRMS Calcd for $C_{16}H_{15}F_3O_2Na$ $[M+Na]^+$, 319.0916; found, 319.0923.
12. Coupling constants were computed using the NMRDev program [http://desoft03.usc.es/armando/software.html] on B3LYP/6-31G* optimized structures.
13. Hassnoot, C. A. G.; De Leeuw, F. A. A. M.; Altona, C. *Tetrahedron* **1980**, *36*, 2783.
14. (a) Gräfenstein, E.; Kraka, E.; Filatov, M.; Cremer, D. *Int. J. Mol. Sci.* **2002**, *3*, 360; (b) Schreiner, P. R.; Navarro-Vázquez, A.; Prall, M. *Acc. Chem. Res.* **2005**, *38*, 29.
15. (a) Becke, A. D. *J. Chem. Phys.* **1993**, *98*, 5648; (b) Lee, C.; Yang, w.; Parr, R. G. *Phys. Rev. B* **1988**, *37*, 785.
16. Miertus, S.; Scrocco, E.; Tomasi, J. *Chem. Phys.* **1981**, *55*, 11.
17. Frisch, M. J. et al.; GAUSSIAN03, Revision B.05, Gaussian: Wallingford, CT, 2004.