Stereoselective Synthesis of Polycyclic Ring Systems via the Tandem Diels–Alder Reaction

Jeffrey D. Winkler*,[1,†] Sanghee Kim,[†] Kevin R. Condroski,[‡] Amparo Asensio,[‡] and K. N. Houk*,[‡]

Department of Chemistry, The University of Pennsylvania, Philadelphia, Pennsylvania 19104, and Department of Chemistry and Biochemistry, University of California, Los Angeles, California 90025

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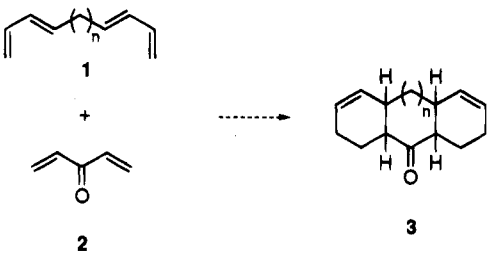
Summary: Intermolecular Diels–Alder reaction of a monoprotected bis-diene with a bis-dienophile, followed by deprotection of the second diene moiety and a second *intramolecular* Diels–Alder reaction, leads to the stereoselective construction of polycyclic ring systems with high levels of stereochemical control.

The application of organic chemical reactions in tandem can lead to the efficient formation of structurally and stereochemically complex structures from relatively simple starting materials.[2] While the sequential performance of two Diels–Alder reactions to generate polycyclic structures has been reported by several groups,[3] the preparation of polycyclic systems from two acyclic precursors, as outlined in Scheme 1, has received less attention.[4,5] The success of such a process, which would necessarily involve sequential intermolecular and intramolecular Diels–Alder cycloaddition reactions, depends critically on the careful orchestration of the reactivity of the four species (two dienes and two dienophiles) of this system, especially in the case where the formation of the central ring is entropically unfavorable (i.e., $n = 2$ or 3; seven- or eight-membered ring formation). We report herein that this tandem process leads to the formation of polycyclic ring systems (Scheme 1; $n = 1$, 3) with exceedingly high degrees of stereochemical control. *Four new stereogenic centers are established on the central ring in the course of this tandem process!* We have also discovered that the use of Lewis acid catalysis in these reactions not only magnifies the endo-exo selectivity of the intramolecular cyclization, but also changes the stereochemical outcome of the Diels–Alder reaction via conformational control of the Diels–Alder dienophile.

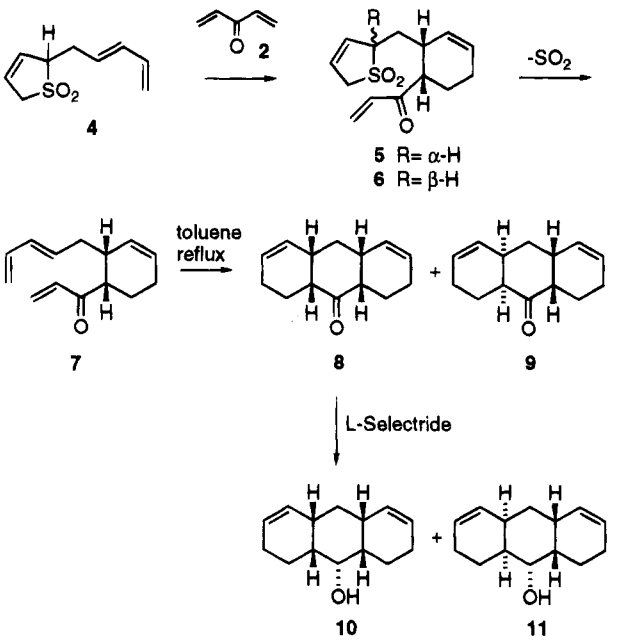
We have examined the reaction of bis-dienes in which one of the diene moieties is protected as a sulfolene ring (Scheme 2).[6] This simple manipulation permits the controlled formation of the first ring by intermolecular Diels–Alder cyclization, with the caveat that the temperature for the first cycloaddition must be lower than that required for the extrusion of SO_2.

The requisite sulfolene diene **4** (Scheme 2) was prepared by alkylation of butadiene sulfone with 2,4-pentadienyl bromide as described by Chou.[7] Condensation of **4** with divinyl ketone **2** in the presence of $ZnCl_2$ (2 equiv, 25 °C, 20 h) led to the formation of a 1:1.1 ratio of the diastereomeric mono-Diels–Alder adducts **5** and **6** in 85% yield. The cis relationship of the substituents on the cyclohexene ring could be established for both of the diastereomeric products by ^1H NMR and was confirmed by single crystal X-ray analysis.

Scheme 1



Scheme 2



The transfer of stereochemical information in the intramolecular Diels–Alder reaction was next examined. Heating the diastereomeric adducts **5** and **6** in refluxing toluene led, via extrusion of SO_2, to the diene intermediate **7**. Under these reaction conditions, intramolecular Diels–Alder cyclization with the second dienophile moiety occurred, leading to the formation of the second and third rings in this cascade and the isolation of two tricyclic ketodienes **8** and **9** in a 17:1 ratio in 77% yield.[8] The relative stereochemistry of the major adduct **8** could be established by ^1H NMR analysis of the reduction product obtained on reaction of **8** with L-Selectride. The

† The University of Pennsylvania.

‡ University of California.

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(1) Recipient of the American Cyanamid Young Faculty Award (1989–1992) and a National Institutes of Health Research Career Development Award (1988–1993).

(2) For an excellent review, see: Ho, T. L. *Tandem Reactions in Organic Synthesis*; Wiley-Interscience: New York, 1992.

(3) Trost, B. M.; Shimizu, M. *J. Am. Chem. Soc.* **1982**, *104*, 4299. Paquette, L. A.; Wyvratt, M. J.; Berk, H. C.; Noerck. R. E. *J. Am. Chem. Soc.* **1978**, *100*, 5845.

(4) For the application of this strategy to the synthesis of the fluorenone ring system, see: Kraus, G. A.; Taschner, M. J. *J. Am. Chem. Soc.* **1980**, *102*. 1974.

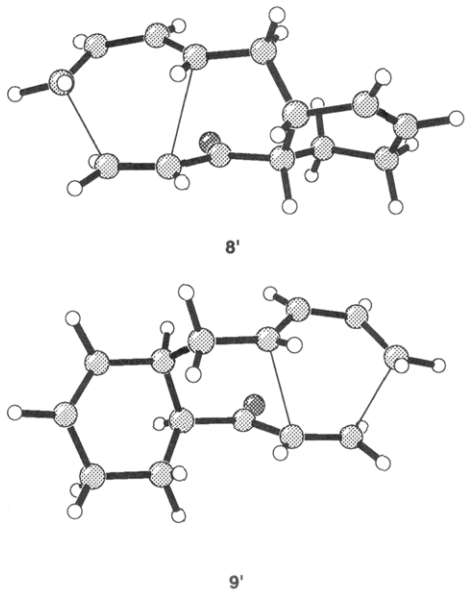
(5) For the preparation of a tetracyclic ring system from a single acyclic precursor, see: Goldberg, D. R.; Hansen, J. A.; Giguere, R. J. *Tetrahedron Lett.* **1993**, 8003.

(6) For a very recent example of alkylated sulfolenes as diene precursors for intramolecular Diels–Alder reactions, see: Chou, S. S. P.; Lee, C. S.; Cheng, M. C.; Tai, H.-P. *J. Org. Chem.* **1994**, *59*, 2010.

(7) (a) Chou, T.; Tso, H.; Lin, L. C. *J. Org. Chem.* **1986**, *51*, 1000. (b) Chou,T.; Tso, H.; Hung, S. C. *J. Org. Chem.* **1987**, *52*, 3394. (c) Chou,T.; Tso, H.; Chang, L. *J. Chem. Soc., Perkin Trans. 1* **1985**, 515.

0022-3263/94/1959-6879$04.50/0

Scheme 3

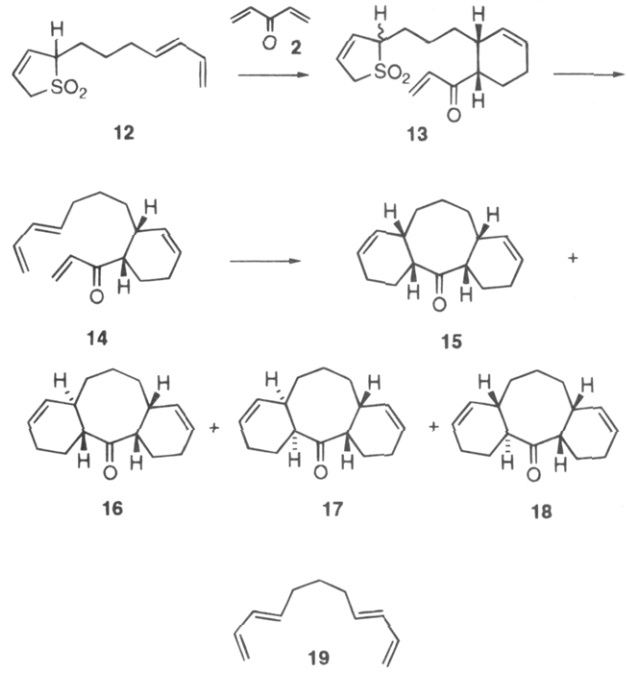


product alcohol **10** exhibits eight lines in the ^{13}C NMR spectrum, which is consistent with the structure shown in Scheme 2, but not with the alcohol **11** (derived from reduction of **9**), which contains neither a plane nor an axis of symmetry.[9]

The selective formation of the cis-syn-cis adduct **8** is consistent with the diastereomeric transition state structures **8'** and **9'** shown in Scheme 3, which were generated by a systematic Monte Carlo conformational search and subsequent energy minimizations using the force field method described by one of us for internally activated Diels–Alder reactions, a study that revealed that cycloaddition occurs predominantly through the s-cis conformation of the dienophile.[10] The calculations predict a product distribution of **8** and **9** in a ratio of 22:1, respectively (E_{rel} = 2.4 kcal/mol at 384 K), which is in excellent agreement with the experimentally observed product ratio (17:1).

To determine the importance of the sulfolene protection group in the observed efficiency of this reaction sequence, the reaction of divinyl ketone with 1,3,6,8-nonatetraene was examined under two different reaction conditions. First, exposure of a 0.1 M solution of diene and dienophile to 2 equiv of $ZnCl_2$ at 25 °C led to the formation of a 1.3:1 mixture of **8** and **9** in 41% yield. No change in the product ratio or yield was observed on dilution (to 0.01 M) and heating the reaction mixture, in analogy to the reaction conditions reported for the conversion of **4** to **8** and **9**. It was also found that a <12% yield of multiple products was obtained (including **8** and **9** in a 2:1 ratio) on refluxing a solution of **2** and the tetraene in the absence of Lewis acid. These results underscore the utility of the sulfolene-based process that we have developed.

Scheme 4



The formation of tricyclic systems in which the central ring is an eight-membered ring provides an important test for the generality of this process, since the intramolecular cycloaddition reaction might not be expected to compete efficiently with intermolecular cycloaddition. Reaction of **12**, prepared from butadiene sulfone and heptadienyl bromide, with divinyl ketone, **2**, in the presence of 2 equiv of $ZnCl_2$ at 25 °C led to the formation of a ca. 1:1 ratio of two inseparable endo Diels–Alder adducts **13** in 74% yield. Thermolysis of this mixture (toluene reflux, 30 min) led to the formation of a single diene **14** in quantitative yield, which on prolonged heating (5 mM in toluene, 36 h) led to the selective formation of two of the four possible diastereomeric tricyclic products **15** and **16** in a 1.1:1 ratio in 80% yield (Scheme 4). It is interesting to note that only one of the two possible endo Diels–Alder adducts (**15** and not **17**) and only one of the two possible exo Diels–Alder adducts (**16** and not **18**) is formed under the thermal reaction conditions.

Intramolecular Diels–Alder cycloaddition in the presence of $EtAlCl_2$ led to the predominant formation of the cis-anti-cis product **17**, along with **15**, **16**, and the trans-syn-cis isomer **18** (55% yield in a 8.5:2.2:1.0:1.8 ratio as determined by ^1H NMR of the crude reaction mixture).[11,12] While the endo/exo selectivity (**15** + **17**/**16** + **18**) is increased relative to the thermal process (4:1 vs 1.1:1), it is striking that the Lewis acid does not promote the formation of **15** (the major product of the thermal reaction) but instead leads to the selective formation of **17**, the formation of which was not observed under the thermal (non-Lewis acid) reaction conditions.

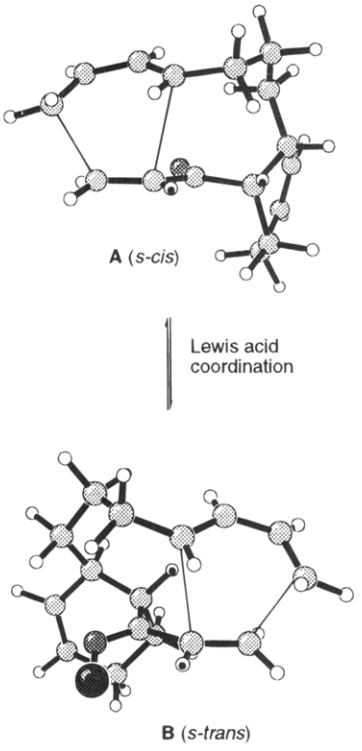
Both the thermal and Lewis acid-catalyzed results are consistent with the transition state structures shown in Scheme 5, in which the black spheres represent a Lewis acid. The s-cis formation of the dienophile as shown in

(8) All new compounds were fully characterized by full spectroscopic (NMR, IR, high-resolution MS) data. Yields refer to spectroscopically and chromatographically homogeneous (>95%) materials. Spectral data for **8**: ^1H NMR ($CDCl_3$, 500 MHz, δ) 5.66–5.63 (m, 2H), 5.60–5.57 (m, 2H), 2.53–2.49 (m, 4H), 2.11–1.96 (m, 4H), 1.88–1.76 (m, 2H), 1.65–1.60 (m, 3H), 1.49–1.42 (m, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz, δ) 217.1, 129.8, 126.7, 47.9, 35.6, 32.3, 24.7, 22.8; IR (neat, cm^{-1}): 3020, 2920, 2850, 1690, 1430. Spectral data for **9**: ^1H NMR ($CDCl_3$, 500 MHz, δ) 5.72–5.65 (m, 2H), 5.58–5.52 (m, 2H), 2.65–2.57 (m, 2H), 2.51–2.45 (m, 2H), 2.17–1.92 (m, 6H), 1.80 (t, 2H, J = 6.1Hz), 1.58–1.51 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz, δ) 215.2, 130.1, 128.2, 46.7, 34.3, 33.5, 22.4, 22.5; IR (neat, cm^{-1}) 3020, 2920, 2850, 1690, 1430.

(9) For the assignment of stereochemistry in a related manner in the triquinane series, see: Eaton, P. E.; Giordano, C.; Schloemer, G.; Vogel, U. *J. Org. Chem.* **1976**, *41*, 2238.

(10) Raimondi, L.; Brown, F. K.; Gonzalez, J.; Houk, K. N. *J. Am. Chem. Soc.* **1992**, *114*, 4796. The force field was implemented in MACROMODEL, Version 4.0 (Mohamadi, F.; Richards, N.; Guida, W.; Liskamp, R.; Caufield, C.; Chang, G.; Hendrickson, T.; Still, W. C. *J. Comput. Chem.* **1990**, *11*, 440) incorporating changes necessary for compatibility of these parameters with the MM2* force field.

Scheme 5



A leads to the selective formation of products in which the hydrogens marked with asterisks have a cis stereochemical relationship on the eight-membered ring (the same relative stereochemistry observed in the formation of **8** from **7** in Scheme 2). However, we have previously demonstrated that Lewis acid complexation changes the preferred dienophile conformation from s-cis (as shown in Schemes 3 and 5) to s-trans.[10] Cyclization via the Lewis acid-complexed s-trans conformer **B** leads to the predominant formation of **17**, in which the two angular hydrogens α to the carbonyl have a trans stereochemical relationship on the eight-membered ring. While numerous examples exist for the enhancement of endo/exo selectivities in the Diels–Alder reaction by Lewis acid catalysis,[13] this is the first example of asymmetric induction in the Diels–Alder reaction via control of the dienophile conformation (s-cis vs s-trans) by Lewis acid complexation.

To determine the utility of the sulfolene ring in this very efficient eight-membered ring formation, the thermal reaction of 1,3,8,10-undecatetraene, **19**, with divinyl ketone was examined. Reaction of **19** with **2** (20 mM in toluene, reflux) led to the formation of six isomeric products in 25% yield. Under Lewis acidic conditions (vide supra), a 4:4:1:1 mixture of products was obtained in 17% yield. The utility of this sulfolene-mediated tandem process for the preparation of polycyclic systems with high levels of selectivity has been demonstrated. The scope of this process is currently under active investigation in our laboratory, and our results will be reported in due course.

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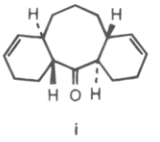
Supplementary Material Available: Experimental procedures, compound characterization data, and copies of NMR spectra (32 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

(11) Spectral data for compounds **14**–**17**. **14**: ^{1}H NMR ($CDCl_3$, 500 MHz, δ) 6.45 (dd, 1H, J = 16.0, 10.0 Hz), 6.40–6.31 (m, 2H), 5.98 (dd, 1H, J = 15.0, 10.0 Hz), 5.57–5.39 (m, 3H), 5.05 (d, 1H, J = 16.7 Hz), 4.92 (d, 1H, J = 10.2 Hz), 2.99–2.92 (m, 1H), 2.55–2.45 (m, 1H), 2.15–1.92 (m, 4H), 1.78–1.71 (m, 2H), 1.98–1.92 (m, 1H), 1.35–1.06 (m, 3H); ^{13}C NMR ($CDCl_3$, 125MHz, δ) 205.5, 137.2, 135.1, 134.9, 131.1, 129.5, 127.7, 127.1, 114.8, 48.5, 36.0, 32.6, 31.2, 26.9, 24.7, 19.2; IR (neat, cm^{-1}) 3020, 2915, 1700, 1675, 1610. **15**: ^{1}H NMR ($CDCl_3$, 500 MHz, δ) 5.71–5.65 (m, 2H), 5.57–5.51 (m, 2H), 2.97–2.90 (m, 2H), 2.80–2.71 (m, 2H), 2.16–1.90 (m, 2H), 1.80–1.70 (m, 4H), 1.65–1.53 (m, 4H), 1.46–1.18 (m, 4H); ^{13}C NMR ($CDCl_3$, 125 MHz, δ) 216.0, 131.5, 125.9, 48.2, 38.1, 32.3, 28.0, 23.9, 20.6; IR (neat, cm^{-1}) 3030, 2940, 2870, 1685, 1450, 1300. **16**: ^{1}H NMR ($CDCl_3$, 500 MHz, δ) 5.70–5.58 (m, 3H), 5.45–5.40 (m, 1H), 3.15–3.08 (m, 1H), 2.68 (ddd, 1H, J = 10.2, 6.3, 2.5 Hz), 2.52–2.48 (m, 1H), 2.36–1.92 (m, 5H), 1.82–1.40 (m, 6H), 1.25–1.11 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz, δ) 219.3, 132.4, 131.9, 126.5, 126.1, 51.0, 49.6, 44.1, 32.9, 32.6, 32.0, 26.0, 25.5, 25.0, 23.5, 16.6; IR (neat, cm^{-1}): 3030, 2940, 2870, 1685, 1450, 1300. **17**: ^{1}H NMR ($CDCl_3$, 500 MHz, δ) 5.63–5.53 (m, 4H), 2.81–2.69 (m, 4H), 2.17–2.08 (m, 2H), 2.03–1.93 (m, 2H), 1.89–1.78 (m, 4H), 1.60–1.49 (m, 2H), 1.49–1.38 (m, 4H); ^{13}C NMR ($CDCl_3$, 125 MHz, δ) 218.9, 131.8, 126.0, 49.7 (br), 37.0 (br), 29.3, 25.4, 23.9, 19.5; in toluene-d_8 (355 K, 125 MHz, δ) 215.3, 132.5, 126.3, 50.1, 37.7, 30.0, 25.9, 24.5, 20.3; IR (neat, cm^{-1}) 3030, 2940, 2870, 1685, 1450, 1300.

(12) The stereochemical assignments for structures **15**–**18** were made in the following manner. As indicated in ref 11, homogeneous samples and spectral data were obtained for three of the four stereoisomeric ketones. Two of the compounds exhibit nine lines in the ^{13}C spectrum and therefore contain a plane of symmetry, while the third isomer exhibits 16 lines (no symmetry). The separated symmetrical ketones were then submitted to ketone reduction conditions. Ketone **15**, on exposure to L-Selectride (2 equiv, tetrahydrofuran, −78 → 25 °C), gave a single alcohol in which the symmetry of the starting ketone was preserved [^{13}C spectrum (eight lines): δ 134.8, 124.5, 82.5, 41.3, 38.2, 31.4, 25.6, 25.7]. In contrast, ketone **17** underwent reduction only on exposure to an excess of lithium aluminum hydride (10 equiv, diethyl ether, reflux) to give an alcohol product that had lost the symmetry of the starting ketone [^{13}C spectrum (14 lines): δ 133.3 (br), 126.0 (br), 74.84, 48.2, 42.3, 41.1, 32.4, 30.0, 27.7, 27.0, 26.5, 25.2, 21.2, 18.2]. Finally, treatment of **17** with 25% sodium methoxide in methanol at reflux led to the formation of **16** and another isomer of **17** to which the structure **i** was tentatively assigned. By exclusion, the fourth isomeric ketone was therefore assigned the structure **18** as shown in Scheme 4.



i

(13) For excellent general discussions, see: (a) Roush, W. In *Advances in Cycloaddition*; Padwa, A., Ed.; JAI Press, Inc.: Greenwich, 1990; Vol. 2, pp 91–146. (b) Taschner, M. In *Organic Synthesis: Theory and Applications;* Hudlicky, T., Ed.; JAI Press, Inc.: Greenwich, 1989; Vol. 1, pp 1–102. (c) Oppolzer, W. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 876.