bond prevented the use of the 2-chloroindole reduction route[9] and finally the partial reduction of the lactam **6a** to (±)-hobartine (**1**)[10] was achieved with LAH in ethereal solution. An insoluble derivative precipitated in each run and the reaction had to be completed by submitting the extracted products to repeated reductions (45–55%). Final transformation of hobartine into aristoteline was envisaged as a cationic cyclization of the terpene trisubstituted double bond and the indole nucleus. In the event refluxing of (±)-**1** in concentrated HCl solution for 8 h resulted in cyclization (62%) to (±)-aristoteline (**3**).[11]

In an analogous fashion (+)-**4b**, prepared from (−)-β-pinene,[2a] was condensed with isatin to yield **5b**[12] (98%), which was reduced with KBH_4 to **6b**[13] (56%) and then with LAH to give (+)-makomakine (**2**)[14] (40%). Bick et al.[4] recently cyclized (+)-makomakine (**2**) to (+)-aristoteline (**3**) under aqueous HBr treatment (10%); in boiling concentrated HCl (3 h), synthetic (+)-**2** was converted into (+)-aristoteline (**3**)[15] in 50% yield. The optical purity of synthetic aristoteline (**3**) and makomakine (**2**) was 90% since the optical purity of the commercially available (−)-β-pinene was only 90%.

These two route provide a short approach (four and five steps) to the heretofore rare *Aristotelia* alkaloids. We are currently investigating modifications of this scheme to improve both its yield and flexibility.

Acknowledgment. We thank Professors I. R. C. Bick and M. Hesse for reference samples and spectra.

Registry No. (±)-**1**, 82769-16-2; (+)-**2**, 79559-56-1; (+)-**3**, 57103-59-0; (±)-**4a**, 68036-85-1; (+)-**4b**, 82731-94-0; (±)-**5a**, 82731-95-1; **5b**, 82731-96-2; **6a**, 82731-97-3; **6b**, 82731-98-4; isatin, 91-56-5; (−)-α-pinene, 7785-26-4; (−)-β-pinene, 18172-67-3.

Supplementary Material Available: Experimental data for compounds (3 pages). Ordering information is given on any current masthead page.

(9) Kubo, A.; Nakai, T. *Synthesis* **1980**, 365–366.
(10) (±)-**1**: mp 166–167 °C; UV, ^1H NMR, and mass spectra were identical with those of natural (−)-hobartine.
(11) (±)-**3**: mp 173–175 °C; UV, ^1H NMR, and mass spectra were identical with those of natural (+)-aristoteline; the IR spectrum (KBr) of the racemic compound was slightly different from that of (+)-**3**.
(12) **5b**: UV (EtOH) λ_{max} 209 nm, 257, 315; IR ($CHCl_3$) 1615, 1635, 1705, 3200 cm^{-1}; ^1H NMR (60 MHz, $CDCl_3$) δ 1.42, 1.52 (2 s, 6 H), 3.15 (m, 1 H), 4.80 (m, 1 H), 4.92 (m, 1 H), 8.65 (br s, 1 H), 8.72 (m, 1 H); MS, *m/z* 93 (100), 136, 143, 170, 171, 306 (M^+, 10), 307, 308.
(13) **6b**: UV (EtOH) λ_{max} 213 nm, 252, 282; IR ($CHCl_3$) 1620, 1705, 3220 cm^{-1}; ^1H NMR (60 MHz, $CDCl_3$) δ 1.10, 1.25 (2 s, 6 H), 4.60 (m, 1 H), 4.78 (m, 1 H), 6.80–7.50 (m, 4 H), 8.00 (br s, 1 H); MS, *m/z* 93, 130, 132, 158, 164, 174, 178, 215, 217, 295, 310 (M^+, 100).
(14) (+)-**2**: amorphous; $[\alpha]_D$ +107° (*c* 1.01, $CHCl_3$) (lit.[4] $[\alpha]_D$ +131.2°); the spectral data are identical with those described in ref 4; the 400-MHz ^1H NMR spectrum is in full agreement with structure **2**.
(15) (+)-**3**: $[\alpha]_D$ +13° (*c* 0.71, MeOH) (lit.[5a] $[\alpha]_D$ +16°).

Catherine Mirand, Georges Massiot, Jean Lêvy*
ERA/CNRS No. 319
Faculté de Pharmacie
F51096 Reims Cedex, France
Received April 13, 1982

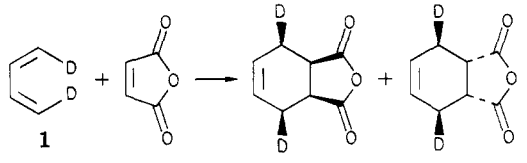
Endo Preference in the Diels–Alder Cycloaddition of Butadiene and Maleic Anhydride

Summary: The reaction of deuterium-labeled 1,3-butadiene with maleic anhydride reveals an 85/15 preference for endo adducts at 80 °C in benzene ($\delta\Delta G^{\ddagger} \sim 1.2$ kcal/mol). Since the endo transition state is sterically disfavored here, this represents a particularly simple measurement of the minimum energy advantage associated with electronic explanations of the Alder endo rule.

Sir: The general observation of endo selectivity in the Diels–Alder synthesis is an important aspect of the usefulness of this reaction. The selectivity, referred to as the Alder endo rule,[1] has been noted for dienophile substituents that are both saturated and unsaturated, that range from moderately electron donating to powerfully electron withdrawing, and that range from sterically simple to complex.[2] In this paper we present our determination of the endo selectivity in a parent system, perhaps the least complex measured to date, that between butadiene and maleic anhydride.

A number of experiments and theoretical arguments have been presented that support several explanations for the endo rule. Endo orientation is argued to be stabilized by inductive[3] or charge-transfer[4] interactions for both unsaturated and saturated groups and by stabilizing secondary orbital overlap[1,5] for unsaturated dienophile substituents. Steric factors, particularly those of the type exemplified by the interactions between the methylene protons of cyclopentadiene and exo oriented dienophiles, have been argued to disfavor the exo transition state by either crowding[6] or by forcing poor alignment of the interacting orbitals.[7]

In the reaction of butadiene with maleic anhydride the ratio of endo to exo transition states can be determined by proper deuterium labeling. We have previously described the synthesis[8] and mechanistic usefulness[9] of *cis,cis*-1,4-dideuterio-1,3-butadiene (**1**). We report here that **1** leads to a mixture of 85% endo and 15% exo in its reaction with maleic anhydride.



1 *exo*-**2** (15%) *endo*-**3** (85%)

Reaction of **1** with maleic anhydride can be conveniently accomplished at 80 °C, in benzene solution (sealed tube). Under these conditions the reaction product is completely stable and the ratio of products **2** and **3** directly reflects the ratios of exo and endo transition states. The assignment of structure derives from two separate chemical shift studies. In both the ene anhydride **4** and *cis*-epoxy anhydride **5**, the H_aH_b methylene protons appear as well-resolved separate resonances. In both cases the lower field of the two signals also shows the strongest response to $Eu(fod)_3$; for example $\Delta\delta$/equivalent of $Eu(fod)_3$ = 280 Hz vs. 165 Hz, for **4**, in benzene [**4**] = 0.26 M. This strongly

(1) Alder, K.; Stein, G. *Angew. Chem.* **1937**, *50*, 510.
(2) Martin, J. G.; Hill, R. K. *Chem. Rev.* **1961**, *61*, 537–562. This is a comprehensive review of stereochemical features of the Diels–Alder reaction.
(3) Wassermann, A. *J. Chem. Soc.* **1935**, 825, 1511; **1936**, 432; *Trans. Faraday Soc.* **1939**, *35*, 841; and "Diels–Alder Reactions"; Elsevier: New York, 1965.
(4) Woodward, R. B.; Baer, H. *J. Am. Chem. Soc.* **1944**, *66*, 645.
(5) (a) Woodward, R. B.; Katz, T. J. *Tetrahedron* **1959**, *5*, 70. (b) Hoffmann, R.; Woodward, R. B. *J. Am. Chem. Soc.* **1965**, 87, 4388. Woodward, R. B.; Hoffmann, R. *Angew. Chem. Int. Ed. Engl.* **1969**, *8*, 781.
(6) This feature was first summarized forcefully by Martin and Hill in ref 2.
(7) Herndon, W. C.; Hall, L. H. *Tetrahedron Lett.* **1967**, 3095.
(8) Stephenson, L. M.; Gemmer, R. V.; Current, S. P. *J. Org. Chem.* **1977**, *42*, 212.
(9) (a) Stephenson, L. M.; Gemmer, R. V.; Current, S. *J. Am. Chem. Soc.* **1975**, *97*, 5909. (b) Graham, C. R.; Stephenson, L. M. *Ibid.* **1977**, *99*, 7098.

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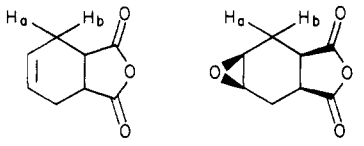
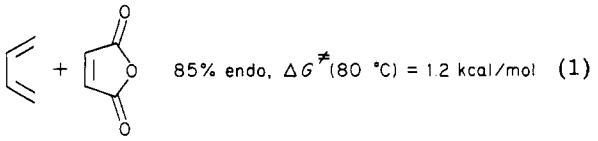
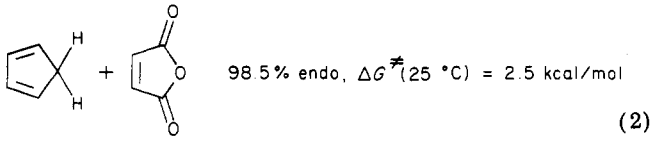


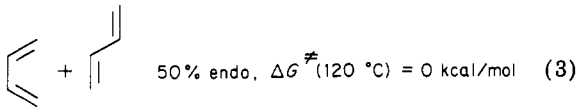
4 5

suggests that the low-field proton is cis to the anhydride. Since the low-field proton is also that which primarily remains undeuterated when 1 is employed, the major product is 3, as shown, and the predominant transition state is endo.

This experiment is in general agreement with other studies of this reaction.[10] Comparison of reactions 1 and 2 suggest that steric factors are important in forcing endo selectivity but are not an exclusive influence. Comparison of 1 and 3 also suggests that maleic anhydride is better disposed than is butadiene to take advantage of factors favoring endo selectivity.







The present result is particularly important in that it does not involve steric *destabilization* of exo transition states as a factor in endo selectivity. Indeed, in the case of butadiene plus maleic anhydride we would presume that steric repulsions in the endo transition state must be the larger. Thus the 1.2 kcal/mol favoring of endo must represent a *minimum* intrinsic energy advantage that one can associate with an electronic explanation of the Alder endo rule.

Acknowledgment. The work has been supported by the National Science Foundation Grant CHE-8012233.

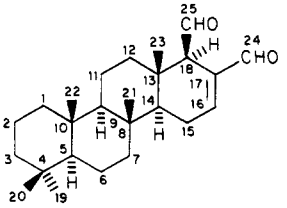
(10) Most recently see Houk, K. N. *Tetrahedron Lett.* **1970**, 2621. By comparing cyclopentene to cyclopentadiene as dienophiles, Houk concludes that the second double bond stabilizes the endo transition state by 2.5–5.0 kcal/mol. This was ascribed to a secondary orbital interaction.

L. M. Stephenson,* D. E. Smith, S. P. Current
Hydrocarbon Research Institute
University of Southern California
Los Angeles, California 90089
Received July 16, 1982

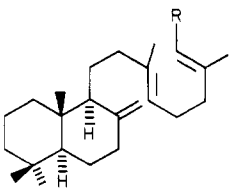
Biogenetic-Type Synthesis of Scalaranes

Summary: The *E*- and *Z*-isoprenologues **2a** and **3a** of methyl *ent*-copalate undergo stereospecific cationic cyclization to tetracyclic substances belonging to the scalarane class of sesterterpenes.

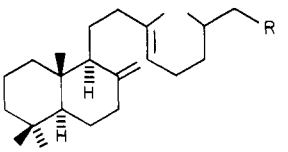
Sir: Certain sponges of the order Dictyoceratidae contain tetra- or pentacyclic sesterterpenes exemplified by the scalaradials (1), which exhibit various biological activities.[1,2] No synthesis of a scalarane is on record and there is no information on their biosynthesis. It has been proposed that the scalaranes arise by a triterpene-like cyclization of a geranylfarnesol precursor initiated at the isopropylidene group.[3] However, it is also possible that, like copalol or *ent*-copalol pyrophosphate in the biogenesis of tri- and tetracyclic diterpenes,[4] the isoprenologue **2b** of *ent*-copalol pyrophosphate is a way station on the enzymic route to the scalaranes. In the present communication we report stereospecific cationic cyclizations that stimulate this process and also describe elaboration of functionalities present in some naturally occurring scalaranes.[5]



1



2a, R = CO_2Me
b, R = CH_2OPP
c, R = CH_2OH



3a, R = CO_2Me
b, R = CH_2OH

After failure of several other approaches, **2a** and **3a** were synthesized conveniently as follows. Combination of manool (4) and ethyl acetoacetate under Carroll reaction[6] conditions afforded 13*E* ketone **5** and its *Z* isomer (2:1, 70%), readily distinguished by ^{13}C NMR spectroscopy[7] and separated by HPLC. Condensation of **5** with trimethyl phosphonoacetate (NaH, Me_2SO)[8] then gave **2a** and **3a** (2:1, 75%), also easily distinguished by NMR spectroscopy[9] and separated by HPLC.

(1) (a) Cimino, G.; De Stefano, S.; Minale, L.; Trivellone, E. *J. Chem. Soc., Perkin Trans. 1* **1977**, 1587 and references cited therein. (b) Cafieri, F.; De Napoli, L.; Fattorusso, E.; Santacroce, C.; Sica, D. *Tetrahedron Lett.* **1977**, 477. (c) *Experientia* **1977**, *33*, 994. (d) *Gazz. Chim. Ital.* **1977**, *107*, 71. (e) Kashman, Y.; Rudi, A. *Tetrahedron* **1977**, *33*, 2997. (f) Cafieri, F.; De Napoli, L.; Iengo, A.; Santacroce, C. *Experientia* **1978**, *34*, 300. (g) Cimino, G.; Cafieri, F.; De Napoli, L.; Fattorusso, E. *Tetrahedron Lett.* **1978**, 2041. (h) Cimino, G.; De Stefano, S.; Di Luccia, A. *Experientia* **1979**, *35*, 1277. (i) Kashman, Y.; Zviely, M. *Tetrahedron Lett.* **1979**, 3879. (i) Kazlauskas, R.; Murphy, P. T.; Wells, R. J.; Daly, J. J. *Aust. J. Chem.* **1980**, *33*, 1783. (k) Walker, R. P.; Thompson, J. E.; Faulkner, D. J. *J. Org. Chem.* **1980**, *45*, 4976; (l) Kikuchi, H.; Tsukitani, Y.; Shimizu, I.; Kobayashi, M.; Kitagawa, I. *Chem. Pharm. Bull.* **1981**, *29*, 1492.

(2) Different authors have used different numbering systems for these compounds that are known as scalaranes. We use the one of ref 1j.

(3) Cordell, G. A. *Phytochemistry* **1974**, *14*, 2343.

(4) For references, see (a) Coates, R. M.; Cavender, P. L. *J. Am. Chem. Soc.* **1980**, *102*, 6358. (b) Drengler, K. A.; Coates, R. M. *J. Chem. Soc., Chem. Commun.* **1980**, 856.

(5) For biomimetic acid catalyzed cyclizations leading to other polycyclic systems, see (a) Johnson, W. S. *Angew. Chem., Int. Ed. Engl.* **1976**, *15*, 9. (b) Johnson, W. S. *Bioorg. Chem.* **1976**, *5*, 51. (c) Van Tamelen, E. E. *Pure Appl. Chem.* **1981**, *20*, 1259.

(6) Carroll, M. F. *J. Chem. Soc.* **1941**, 507.

(7) For the 13*E* isomer: C-12 δ 38.38 (t), 13-Me δ 15.92 (q); for the 13*Z* isomer, C-12 30.51 (t), 13-Me 23.28 (q). All new compounds gave satisfactory high-resolution mass spectra and were pure by ^1H and ^{13}C NMR criteria. ^1H NMR spectra were run at 270 MHz, ^{13}C NMR spectra at 67.89 MHz in $CDCl_3$ solution.

(8) Greenwald, R.; Chaykovsky, M.; Corey, E. *J. Org. Chem.* **1963**, *28*, 1128.

(9) For **2a**, 17-Me δ 2.18, 18.84 (q), C-15 41.00 (t); for **3a**, 17-Me δ 1.89, 25.53 (q), C-16 33.48 (t). $LiAlH_4$ reduction of **2a** or **3a** gave **2c** or **3b**.

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