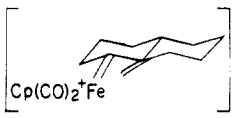
The isomeric cyclopropanes **7** and **8** exhibit quite different ^1H and ^{13}C NMR spectra.[25] Compared to **7**, **8** shows much more fully resolved and interpretable signals for the cyclopropyl protons; thorough decoupling experiments permit us to make peak assignments that are in accord with earlier data for related cyclopropanes.[23c,26]

Of significance is that the stereochemistry of the intramolecular cyclopropanation to give **7** is not only the opposite of the alternative *inter*molecular cyclopropanation routes shown above, but it is also the opposite of closely related cases of *intra*molecular cyclopropanations of diazo compounds.[4a,23b,27] We tentatively rationalize the stereochemical outcome of our reaction by hypothesizing a chair-like transition state **10** leading to **7**.[28]



10

The trans stereochemistry of **7** coincides with formerly proposed structures of the natural product cycloeudesmol (the structural assignment of which has been revised recently)[23,29] and with key intermediates in syntheses of other compounds.[30] Of potential importance is that our reaction may provide an approach to angularly alkylated, fused ring systems of defined stereochemistry,[28,31] a point which we are continuing to pursue in general.

Acknowledgment. We are grateful for the financial support provided by the National Science Foundation (Grant CHE 8120466) and the donors of the Petroleum Research Fund, administered by the American Chemical Society. The 300-MHz NMR spectrometer used in this work was purchased in part with funds provided by the NSF Instrumentation Program (Grant 8114412).

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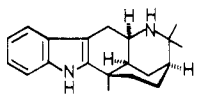
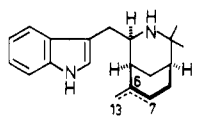
Stereocontrolled Total Syntheses of (-)-Hobartine and (+)-Aristoteline via an Intramolecular Nitrone-Olefin Cycloaddition

Summary: The *Aristotelia* alkaloids (-)-hobartine and (+)-aristoteline have been synthesized from indole and (*S*)-1-*p*-menthen-8-ylamine (**7**) in 11 steps (19%) via an intramolecular nitrone-olefin 1,3-dipolar cycloaddition.

Sir: Several species of plants from the genus *Aristotelia* contain a series of novel, structurally similar $C_{20}N_2$ indole alkaloids.[1] Distinguishing characteristics of these bases include tryptamine and nonrearranged geranyl subunits that have been functionalized and cyclized to varying degrees. (+)-Aristoteline (**1**), the major component in many species,[1a,2] (-)-hobartine (**2**),[1g] and (+)-makomakine (**3**)[1f] are representative examples.



(+)-1



(-)-2 Δ6,7

(+)-3 Δ6,13

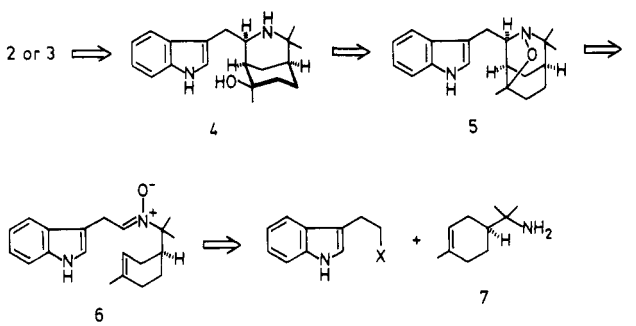
Of the previous synthetic entries into this class of alkaloids,[1e,3] two reports describe syntheses of hobartine and makomakine and the conversion of each to aristoteline by treatment with concentrated hydrochloric acid.[3a,b] Although these routes to makomakine were both direct and enantioselective, the hobartine produced by each approach was necessarily racemic even when optically active starting materials were used. More recently, an asymmetric synthesis of (-)-hobartine was achieved via a biomimetic iminium ion cyclization.[3c]

(24) Becker, K. B. *Helv. Chim. Acta* **1977**, *60*, 68.
(25) **7**: ^1H NMR (300 MHz, $CDCl_3$) δ 0.96-2.08 (several m, 15 noncyclopropyl H), 0.73 (unresolved m, 2 cyclopropyl H), 0.17 (unresolved m, 1 cyclopropyl H); ^{13}C NMR (75 MHz, $CDCl_3$, apparent coincidence of 2 C) δ 39.32, 38.40, 33.23, 27.33, 27.25, 25.80, 23.94, 23.24, 17.35, 15.44. **8**: ^1H NMR (300 MHz, $CDCl_3$) δ 0.75-2.04 (several m, 15 non-cyclopropyl H), 0.66 (m, cyclopropyl methine H), 0.28 (apparent t, J = 4 Hz, endo cyclopropyl H), 0.14 (dd, J = 9, 4 Hz, exo cyclopropyl H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 38.75, 33.45, 30.85, 26.51, 26.42, 25.64, 23.15, 22.23, 17.95, 17.46, 15.93.
(26) (a) Closs, G. L.; Moss, R. A. *J. Am. Chem. Soc.* **1964**, *86*, 4042. (b) Dauben, W. G.; Wipke, W. T. *J. Org. Chem.* **1967**, *32*, 2976. (c) Traynham, J. G.; Dehm, J. S.; Green, E. E. *Ibid.* **1968**, *33*, 2587. (d) Poulter, C. D.; Boikess, R. S.; Brauman, J. I.; Winstein, S. *J. Am. Chem. Soc.* **1972**, *94*, 2291. (e) Hahn, R. C.; Howard, P. H. *Ibid.* **1972**, *94*, 3143. (f) Jefferies, P. R.; Knox, J. R.; Scaf, B. *Aust. J. Chem.* **1973**, *26*, 2199. (g) Payne, T. G.; Jefferies, P. R. *Tetrahedron* **1973**, *29*, 2575. (h) Mathias, R.; Weyerstahl, P. *Chem. Ber.* **1979**, *112*, 3041. (i) Alder, A. P.; Wolf, H. R.; Jeger, O. *Helv. Chim. Acta* **1981**, *64*, 198.
(27) (a) McMurry, J. E.; Blaszczak, L. C. *J. Org. Chem.* **1974**, *39*, 2217. (b) Mori, K.; Ohki, M.; Kobayashi, A.; Matsui, M. *Tetrahedron* **1970**, *26*, 2815. A key factor in governing the stereochemistry in our case may be the absence of other ring substituents in substrate **6** compared to earlier examples (see especially ref 4a).
(28) For leading references pertaining to the stereochemistry of related cyclizations, see: (a) Deslongchamps, P. "Stereoelectronic Effects in Organic Chemistry"; Pergamon: Oxford, 1983; p 307. (b) Lansbury, P. T.; Demmin, T. R.; DuBois, G. E.; Haddon, V. R. *J. Am. Chem. Soc.* **1975**, *97*, 394. (c) Johnson, W. S.; Elliott, J. D.; Hanson, G. J. *J. Am. Chem. Soc.* **1984**, *106*, 1138. (d) Nishizawa, M.; Takenaka, H.; Hayashi, Y. *Ibid.* **1985**, *107*, 522. (e) van Tamelen, E. E.; Faler, D. L. *Proc. Natl. Acad. Sci. U.S.A.* **1985**, *82*, 1879. For a summary of mechanistic proposals for cyclopropanations using organoiron reagents, see ref 7j.
(29) (a) Moss, R. A.; Chen, E. Y. *J. Org. Chem.* **1981**, *46*, 1466. (b) Suzuki, T.; Furusaki, A.; Kikuchi, H.; Kurosawa, E.; Katayama, C. *Tetrahedron Lett.* **1981**, *22*, 3423. (c) Chen, E. Y. *J. Org. Chem.* **1985**, *49*, 3245.
(30) (a) Ireland, R. E.; Marshall, D. R.; Tilley, J. W. *J. Am. Chem. Soc.* **1970**, *92*, 4754. (b) Dailey, O. D.; Fuchs, P. L. *J. Org. Chem.* **1980**, *45*, 216. (c) Tsuda, Y.; Kashiwaba, N.; Kajitani, M.; Yasui, J. *Chem. Pharm. Bull.* **1981**, *29*, 3424.
(31) Stork, G.; Clark, G.; Weller, T. *Tetrahedron Lett.* **1984**, *25*, 5367.

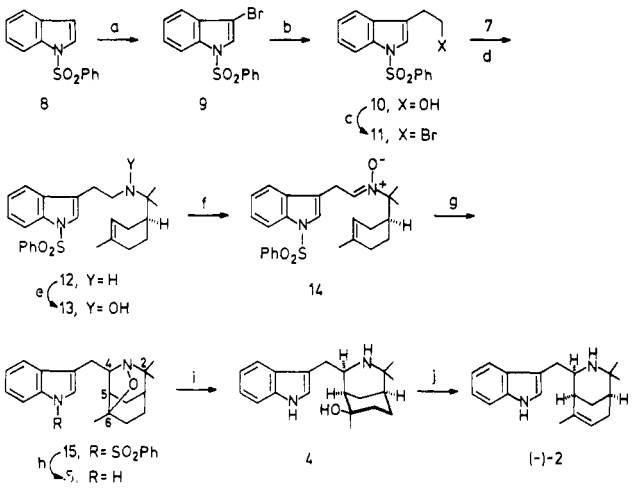
(1) (a) Anderson, B. F.; Robertson, G. B.; Avey, H. P.; Donovan, W. F.; Bick, I. R. C.; Bremner, J. B.; Finney, A. J. T.; Preston, N. W.; Gallagher, R. T.; Russel, G. B. *J. Chem. Soc., Chem. Commun.* **1975**, 511-512. (b) Bick, I. R. C.; Hai, M. A.; Preston, N. W.; Gallagher, R. T. *Tetrahedron Lett.* **1980**, 545-546. (c) Hai, M. A.; Preston, N. W.; Kyburz, R.; Schöpp, E.; Bick, I. R. C.; Hesse, M. *Helv. Chim. Acta* **1980**, *63*, 2130-2134. (d) Bick, I. R. C.; Hai, M. A. *Tetrahedron Lett.* **1981**, 3275-3276. (e) Chaichit, N.; Gatehouse, B. M.; Bick, I. R. C.; Hai, M. A.; Preston, N. W. *J. Chem. Soc., Chem. Commun.* **1979**, 874-875. (f) Bick, I. R. C.; Hai, M. A. *Heterocycles* **1981**, *16*, 1301-1303. (g) Kyburz, R.; Schöpp, E.; Bick, I. R. C.; Hesse, M. *Helv. Chim. Acta* **1979**, *62*, 2539-2546. (h) Bick, I. R. C.; Hai, M. A.; Preston, N. W. *Heterocycles* **1983**, *20*, 667-669. (i) Bick, I. R. C.; Bremner, J. B.; Preston, N. W.; Calder, I. C. *J. Chem. Soc., Chem. Commun.* **1971**, 1155-1156. (j) Ros, H.; Kyburz, R.; Preston, N. W.; Gallagher, R. T.; Bick, I. R. C.; Hesse, M. *Helv. Chim. Acta* **1979**, *62*, 481-487. (k) For a recent review of the *Aristotelia* alkaloids and their biogenesis, see: Saxton, J. E. In "Indoles"; Saxton, J. E., Ed.; Wiley: New York, 1983; Part 4, Chapter 11, pp 47-62.
(2) Bhakuni, D. S.; Silva, M.; Matlin, S. A.; Sammes, P. G. *Phytochemistry* **1976**, *16*, 574-576. Zabel, V.; Watson, W. H.; Bittner, M.; Silva, M. *J. Chem. Soc., Perkin Trans. 1* **1980**, 2842-2844.
(3) (a) Mirand, C.; Massiot, G.; Lévy, J. *J. Org. Chem.* **1982**, *47*, 4170-4171. (b) Stevens, R. V.; Kenney, P. M. *J. Chem. Soc., Chem. Commun.* **1983**, 384-386. (c) Darbre, T.; Nussbauer, C.; Borschberg, H. J. *Helv. Chim. Acta* **1984**, *67*, 1040-1052.

0022-3263/85/1950-5900$01.50/0

Scheme I



Scheme II[a]



[a] (a) Br_2, propylene oxide, room temperature, 83%; (b) *t*-BuLi, BF_3, ethylene oxide, 87%; (c) CBr_4, Ph_3P, room temperature, 94%; (d) $NaHCO_3$, CH_3CN, 15 h, 69%; (e) *m*-CPBA, 0 °C, CH_2Cl_2; (f) O_2, $Cu(OAc)_2$, 0 °C, 20 min; (g) Δ, $PhCH_3$, 5 h, 64% from **12**; (h) 6% Na(Hg), Na_2HPO_4, 0 °C, 40 min, 91%; (i) Zn, AcOH/H_2O, 50 °C, 1.5 h, 96%; (j) TFA, Δ, 12 h; 77%.

In our approach to the hobartine ring system (shown retrosynthetically in Scheme I), we envisioned an intramolecular nitrone–olefin 1,3-dipolar cycloaddition as the key step (i.e., **6** → **5**). This would subsequently produce alcohol **4** as the precursor to the target alkaloids. The requisite isoxazolidine ring (**5**) was predicted from Dreiding models to be the major product from a regioselective and stereospecific (*Z*)-nitrone–olefin cycloaddition.[4] It was anticipated that a nitrone such as **6** would be available in optically pure form from (*S*)-1-*p*-menthen-8-ylamine (**7**) and a tryptophyl unit.

The successful realization of this strategy is shown in Scheme II. Amine **7** was prepared in two steps (62%) from (−)-α-pinene as reported,[5] $[\alpha]^{28}_D$ −64 ± 4° (neat) [lit[3c] $[\alpha]^{25}_D$ −106° (*c* 2.1, EtOH)]. Bromination of *N*-(phenylsulfonyl)indole (**8**)[6] gave the C-3 bromo derivative **9**[8,9] (83%), mp 122–123 °C. Treatment of **9** with *tert*-butyllithium (Et_2O, −105 °C) followed by the rapid sequential addition of boron trifluoride etherate[7] and ethylene oxide afforded *N*-(phenylsulfonyl)tryptophol (**10**)[8] (87%; oil). This was efficiently converted to bromide **11**[8,9] (94%), mp 117–118 °C, with carbon tetrabromide/triphenylphosphine.[10] Alkylation of amine **7** with bromide **11** was accomplished in boiling acetonitrile in the presence of sodium bicarbonate to give amine **12**[8,9] (69%), mp 78–78.5 °C, $[\alpha]^{28}_D$ −32.8 ± 0.6° (*c* 6.12, EtOH).

The crucial oxidation of amine **12** to nitrone **14** was most efficiently carried out in two stages. Thus, treatment of **12** with *m*-chloroperbenzoic acid (*m*-CPBA)[11] gave hydroxylamine **13**,[8] characterized as the oxalate salt (mp 172 °C dec).[9] Further oxidation of **13** was achieved by bubbling oxygen through a solution of **13** (CH_2Cl_2, 0 °C) containing a catalytic amount of cupric acetate[12] to yield nitrone **14**.[8] This appeared to be a single geometric isomer, predicted to be *Z*, as evidenced by the clean triplet at δ 6.95 (*J* = 5 Hz) in the ^1H NMR spectrum. The intramolecular cycloaddition of **14** proceeded smoothly in refluxing toluene (5 h)[13] to afford a single cycloadduct **15**[8,9] (64% from **12**), mp 134–135 °C, $[\alpha]^{28}_D$ −51 ± 2° (*c* 3.74, $CHCl_3$), as judged by TLC and NMR spectroscopy.

(4) For recent, leading references on intramolecular nitrone–olefin cycloadditions in the synthesis of natural products, see: Oppolzer, W., Ed. "Tetrahedron Symposia-in-Print"; Pergamon: New York, 1985; Vol. 41, No. 21, pp 3447–3568. Schwartz, M. A.; Willbrand, A. M. *J. Org. Chem.* **1985**, *50*, 1359–1365.

(5) Pancrazi, A.; Kabore, I.; Khuong-Huu, O. *Bull. Chim. Soc. Fr.* **1977**, 162–164.

(6) Saulnier, M. G.; Gribble, G. W. *J. Org. Chem.* **1982**, *47*, 757–761.

(7) Eis, M. J.; Wrobel, J. E.; Ganem, B. *J. Am. Chem. Soc.* **1984**, *106*, 3693–3694.

(8) **9**: IR ($CDCl_3$) 1605, 1585, 1445, 1370, 1265 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.15–8.15 (c, 9 H), 7.63 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ 137.5, 134.1, 134.0, 129.6, 129.3, 126.7, 125.7, 124.6, 123.9, 120.0, 113.4, 99.7. **10**: IR ($CDCl_3$) 3605, 3450, 1610, 1450, 1370, 1280, 1180, cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.17–8.17 (c, 10 H), 3.87 (t, *J* = 6 Hz, 2 H), 2.90 (t, *J* = 6 Hz, 2 H), 2.05 (br s, 1 H); ^{13}C NMR ($CDCl_3$) δ 137.9, 135.0, 133.6, 130.8, 129.1, 126.5, 124.7, 123.4, 123.1, 119.7, 119.4, 113.5, 61.4, 28.1. **11**: IR ($CDCl_3$) 1605, 1450, 1370, 1175, cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.15–8.05 (c, 10 H), 3.60 (m, 2 H), 3.23 (m, 2 H). **12**: IR ($CDCl_3$) 3480, 1605, 1445, 1370, 1175 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.00–8.10 (c, 10 H), 5.30 (br m, 1 H), 2.80 (br s, 4 H), 0.90–2.10 (c, 8 H), 1.58 (br s, 3 H), 0.91 (s, 6 H); ^{13}C NMR ($CDCl_3$) δ 137.7, 134.9, 133.2, 130.5, 128.7, 126.1, 124.3, 122.7, 121.0, 120.5, 119.1, 113.3, 53.6, 40.5, 39.9, 30.7, 26.2, 25.9, 23.8, 23.7, 23.3, 22.9; mass spectrum [no M^+ (*m/e* 436) was seen at normal magnification], *m/e* 341, 284, 253, 166, 130, 81, 71, 57 (base). **13**: IR ($CDCl_3$) 3600, 3495, 1610, 1455, 1370, 1180 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.05–8.05 (c, 10 H), 5.30 (br m, 1 H), 4.55 (br s, 1 H), 2.90 (br s, 4 H), 0.90–2.10 (c, 7 H), 1.61 (br s, 3 H), 0.97 (s, 6 H); ^{13}C NMR ($CDCl_3$) δ 138.2, 135.1, 133.9, 133.5, 131.1, 129.1, 126.6, 124.5, 123.0, 122.9, 121.6, 120.9, 119.4, 113.6, 63.2, 50.4, 40.9, 31.2, 26.8, 24.1, 23.3, 18.5, 18.2. **14**: IR ($CDCl_3$) 1670, 1635, 1605, 1575, 1450, 1370, 1175 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.20–8.20 (c, 10 H), 6.95 (t, *J* = 5 Hz, 1 H), 5.32 (br m, 1 H), 3.90 (d, *J* = 5 Hz, 2 H), 1.0–2.1 (c, 7 H), 1.63 (br s, 3 H), 1.42 (s, 3 H), 1.38 (s, 3 H). **15**: IR ($CDCl_3$) 1450, 1370, 1215, 1175 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.17–8.15 (c, 10 H), 3.63 (t, *J* = 7 Hz, 1 H), 2.92 (dd, *J* = 7, 5 Hz, 2 H), 1.0–2.2 (c, 8 H), 1.33 (s, 3 H), 1.23 (s, 3 H), 1.00 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 138.0, 135.0, 133.5, 131.0, 129.0, 126.5, 124.5, 123.3, 123.0, 121.3, 119.6, 113.6, 83.8, 67.0, 62.7, 46.3, 36.7, 31.1, 28.7, 28.6, 27.4, 26.7, 22.5; mass spectrum, *m/e* 450 (M^+), 365, 309, 297, 270, 180 (base), 81, 77, 56. **5**: IR ($CDCl_3$) 3490, 1460, 1380, 1240 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.30 (br s, 1 H), 6.90–7.80 (c, 5 H), 3.87 (t, *J* = 6 Hz, 1 H), 3.12 (skewed d, *J* = 6 Hz, 2 H), 1.0–2.3 (c, 8 H), 1.42 (s, 3 H), 1.28 (s, 3 H), 1.13 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 136.2, 127.5, 122.3, 121.6, 119.0, 118.8, 113.7, 111.2, 84.0, 67.8, 62.9, 45.8, 37.0, 31.3, 29.1, 28.9, 27.6, 27.0, 26.8, 22.6; mass spectrum, *m/e* 310 (M^+), 295, 267, 225, 210, 196, 180, 157, 130 (base). **4**: IR ($CDCl_3$) 3610, 3490, 3420, 3300, 1620, 1460, 1380, 1340, 1255 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.35 (br s, 1 H), 6.90–7.85 (c, 5 H), 3.10–3.80 (c, 3 H), 1.00–2.80 (c, 10 H), 1.28 (s, 3 H), 1.02 (br s, 6 H); ^{13}C NMR ($CDCl_3$) δ 136.4, 127.5, 122.3, 121.6, 119.0, 118.9, 114.1, 111.1, 74.6, 57.2, 53.5, 42.9, 36.1, 35.9, 32.2, 31.0, 30.4, 29.1, 26.4, 24.6; mass spectrum, *m/e* 312 (M^+), 311, 310, 297, 294, 279, 255, 200, 182 (base), 164, 130, 56. **2**: IR ($CHCl_3$) 3490, 1625, 1610, 1460, 1430, 1420, 1385, 1340, 1080, 1010 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.35 (br s, 1 H), 6.80–7.80 (c, 5 H), 5.65 (br s, 1 H), 3.50 (br t, *J* = 8 Hz, 1 H), 0.80–3.00 (c, 9 H), 1.80 (br s, 3 H), 1.13 (s, 3 H), 1.07 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 136.3, 133.4, 127.4, 124.7, 122.4, 121.5, 118.8, 113.2, 111.0, 54.5, 53.6, 38.1, 35.0, 31.6, 29.9, 29.2, 27.8, 25.76, 25.68; mass spectrum, *m/e* 294 (M^+), 279, 237, 222, 199, 180, 164 (base), 130. **1**: IR ($CHCl_3$) 3480, 1610, 1465, 1385, 1295, 1175 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.85 (br s, 1 H), 6.95–7.65 (c, 4 H), 3.60–3.80 (br d, 1 H), 1.0–3.3 (c, 10 H), 1.41 (s, 3 H), 1.26 (s, 3 H), 1.05 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 142.6, 136.0, 128.1, 120.9, 119.0, 118.1, 110.4, 104.3, 53.2, 50.4, 39.3, 35.9, 35.6, 33.1, 29.1, 28.6, 27.8, 27.6, 25.4, 25.1; mass spectrum, *m/e* 294 (M^+), 279 (base), 237, 222, 211, 194, 182, 167, 143.

(9) A satisfactory elemental analysis (C, H, N, and S, Br, if present, ±0.15%) was obtained for this new compound.

(10) Chen, S. Y.; Joullie, M. M. *Synth. Commun.* **1984**, *14*, 591–592.

(11) Büchi, G.; Luk, K. C.; Kobbe, B.; Townsend, J. M. *J. Org. Chem.* **1977**, *42*, 244–246.

(12) Hamer, J.; Macaliso, A. *Chem. Rev.* **1964**, *64*, 473–495.

(13) Black, D. St.-C.; Crozier, R. F.; Davis, V. C. *Synthesis* **1975**, 205–221.

Although the regioselectivity of the cycloaddition could not be established solely from the ^1H NMR spectrum of the product, an off-resonance $^{13}C\{^1H\}$ NMR experiment[14] clearly established the structure of **15** to be as shown in Scheme II. This was deduced from the three nonaromatic, relatively low-field ^{13}C NMR resonances at δ 62.7, 67.0, and 83.9 assigned to (hobartine numbering) C(2), C(4), and C(6) (or C(5) had cycloaddition proceeded in the other sense). Thus, the resonances at δ 62.7 and 83.9 were found to arise from *quaternary* carbons, a result consistent only with structure **15**. The carbon α to oxygen in the other possible cycloadduct would not have been quaternary, and only one quaternary downfield resonance would have been observed.

The next task was the reductive cleavage of the isoxazolidine ring. The N–O bond of **15** was completely inert to all neutral and basic reducing systems investigated.[15] Upon treatment with buffered sodium amalgam,[16] **15** was smoothly converted[17] to isoxazolidine **5**[8] (91%), mp 210–210.5 °C, $[\alpha]^{28}_D$ −41 ± 2° (*c* 3.36, $CHCl_3$). The reluctance of similar isoxazolidines toward reduction has been noted by others.[18] However, **5** was cleanly reduced to the desired alcohol **4**[8,9] (96%), mp 145.5–146.5 °C, $[\alpha]^{28}_D$ +65 ± 2° (*c* 3.64, $CHCl_3$), by using zinc/aqueous acetic acid.[19] Treatment of **4** with *p*-toluenesulfonic acid (benzene, reflux, 30 min) afforded a mixture of (−)-hobartine (**2**) (50%) and (+)-aristoteline (**1**) (28%), separated by radial thick layer chromatography. Dehydration of **4** with neat trifluoroacetic acid (reflux, 12 h) produced (−)-hobartine (77%) exclusively. The (−)-hobartine obtained, mp 152.5–153.5 °C, $[\alpha]^{28}_D$ −27 ± 3 (*c* 1.69, $CHCl_3$) [lit.[1g] mp 149–150.5 °C, $[\alpha]^{20}_D$ −20 ± 3° (*c* 1.66, $CHCl_3$); lit.[3c] mp 151 °C, $[\alpha]^{25}_D$ −28° (*c* 1.2, $CHCl_3$)] gave spectra (IR, 300-MHz ^1H NMR, ^{13}C NMR, mass spectrum) identical with those of the natural product. In addition, our synthetic (+)-aristoteline (**1**)[8,20] was identical with a sample of the natural product (TLC, IR, ^1H NMR, ^{13}C NMR, mass spectrum).

Attempts to convert alcohol **4** to (+)-makomakine (**3**) were only partially successful. Thus, treatment of **4** with phosphorus oxychloride (pyridine, 3 h, 70 °C) gave a mixture (68%) of (−)-hobartine (**2**) and makomakine (**3**) in a ratio of ca. 88:12 (^1H NMR).

To summarize, we have described a convergent, stereocontrolled synthesis of (−)-hobartine in which a single chiral center (**7**) was elaborated into three through a highly regioselective and stereospecific intramolecular nitrone–olefin 1,3-dipolar cycloaddition. The synthetic sequence, while somewhat longer than the previous syntheses of hobartine, compares quite favorably in its overall efficiency.

Acknowledgment. This investigation was supported in part by PHS Grant GM-30761 awarded by the National Institutes of Health, the donors of the Petroleum Research Fund, administered by the American Chemical Society, and Merck Sharp and Dohme Research Laboratories. We also thank Professors I. R. C. Bick and M. Hesse for samples and spectra of natural hobartine, makomakine, and aristoteline and the National Science Foundation for funds to purchase a Varian XL-300 NMR spectrometer.

Supplementary Material Available: Complete experimental details (7 pages). Ordering information is given on any current masthead page.

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Received August 13, 1985

(14) Performed on a Varian XL-300 instrument with the proton decoupling frequency offset 2500 Hz.
(15) Aluminum amalgam,[16] sodium amalgam,[16] and $LiAlH_4$ in refluxing tetrahydrofuran (on **5**) were tried.
(16) Keck, G. L.; Fleming, S.; Nickell, D.; Weider, P. *Synth. Commun.* **1979**, *9*, 281–286.
(17) Sundberg, R. J.; Bloom, J. D. *J. Org. Chem.* **1981**, *46*, 4836–4842.
(18) See: DeShong, P.; Dicken, C. M.; Leginus, J. M.; Whittle, R. R. *J. Am. Chem. Soc.* **1984**, *106*, 5598–5602 and references cited therein.
(19) Iida, H.; Watanabe, Y.; Tanaka, M.; Kibayashi, C. *J. Org. Chem.* **1984**, *49*, 2412–2418.
(20) The sign of the $[\alpha]_D$ of **1** was found to be positive in agreement with ref 3c although an accurate value could not be obtained because of insufficient material.

The Synthesis and Relative Configuration of (±)-Lirionol

Summary: The synthesis of C-9 epimers **1** and **2** of the natural lignan lirionol is described. The relative configuration of the natural material is thereby established as **2** contrary to the previous assignment.

Sir: Lirionol, an unusual tetracyclic bridged lignan, was isolated from the bark of *Liriodendron tulipfera* and assigned[1] the structure and relative stereochemistry **1** from spectroscopic and biogenetic considerations. The bicyclo[3.3.1]nonadienone feature, constituting the central BC rings of lirionol, betrayed its probable biogenetic origin from a 1-aryl tetralin precursor and invited an attempt at synthesis by simple Friedel–Crafts cyclization to form the 3,4-bond of the molecule. Such a plan requires an efficient means for the stereocontrolled elaboration of an all-trans 1,2,3-substituted tetralin (e.g., **12**, Chart I) and we addressed this problem by application of the methods previously developed in our laboratory for the synthesis of (±) podophyllotoxin.[2,3] We now report the successful outcome of these efforts, the synthesis of both C-9 epimers **1** and **2** and the revision of the relative stereochemistry of lirionol.

Deprotonation of 2,3,4-trimethoxy-*N*,*N*-diethylbenzamide with *sec*-butyllithium–TMEDA and quenching the resultant 6-lithio species with 2,3,4-trimethoxybenzaldehyde was followed by lactonization of the amide–alcohol to provide[4] the phthalide **3** in 62% overall yield. Reduction with DIBAL-H in methylene chloride produced a mixture of diastereomeric lactols **4**, used after purification but without separation to generate the 1-arylisobenzofuran **5**, which was reacted[5] in situ with dimethyl acetylenedicarboxylate to yield (61% from **3**) the bicyclo adduct **6**. Thus all the carbon atoms of lirionol were assembled by this short sequence in 38% overall yield and in a convergent fashion.

Hydrogenolysis of **6** with 5% Pd/charcoal in ethyl acetate at 60 psi provided the all-cis tetralin **7** in 74% yield with no trace of any C-1 epimer. This was a surprising result, contrary to previous experience[2,6] with palladium-catalyzed hydrogenolysis. We are investigating the structural and stereochemical dependence of this reaction

(1) Chen, C.-L.; Chang, H.-M. *Phytochemistry* **1978**, *17*, 779. Neither a sample of natural lirionol nor spectra of it or any derivatives could be obtained.
(2) Rodrigo, R. *J. Org. Chem.* **1980**, *45*, 4538.
(3) Rajapaksa, D.; Rodrigo, R. *J. Am. Chem. Soc.* **1981**, *104*, 4725.
(4) de Silva, S. O.; Watanabe, M.; Snieckus, V. *J. Org. Chem.* **1979**, *44*, 4802.
(5) Keay, B. A.; Plaumann, H. P.; Rajapaksa, D.; Rodrigo, R. *Can. J. Chem.* **1983**, *61*, 1977.
(6) Rylander, P. N. "Catalytic Hydrogenation in Organic Synthesis"; Academic Press: New York, 1979.

0022-3263/85/1950-5902$01.50/0