Total Synthesis of (+)-4-Oxo-5,6,9,10-tetradehydro-4,5-secofuranoeremophilane-5,1-carbolactone via Novel Lactone Construction through Allene Intramolecular Cycloaddition

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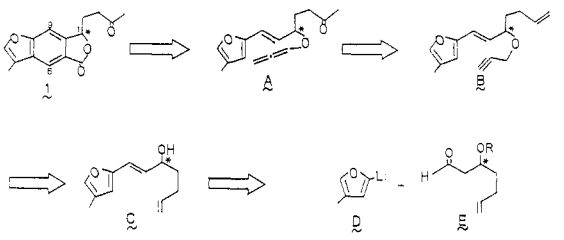
The first asymmetric synthesis of the title compound **1** is described. The crucial step is a facile construction of the tricyclic lactone, the basic skeleton of **1**, via allene intramolecular cycloaddition. Methyl (*R*)-(−)-3-hydroxyhept-6-enoate (**3**) was converted into the (*R*)-propargyl ether **8** in six steps. Base treatment (*t*-BuOK/*t*-BuOH, 83 °C) of **8** caused a smooth cyclization via the intramolecular Diels–Alder reaction of the allenyl ether intermediate to give **9**, which on successive hydration and oxidation provided the lactone **10** as a mixture of diastereomers. Aromatization of **10** afforded a single product (**11**), which was subjected to the Wacker oxidation to give (*R*)-(+)-**1**.

Organic synthesis has developed into an important tool for determining the structure of natural products, hence complementing modern spectral methods.[1] In this context, asymmetric synthesis via chiral synthons (chirons)[2] provides a useful method for assignment of the absolute configuration of natural products.[3]

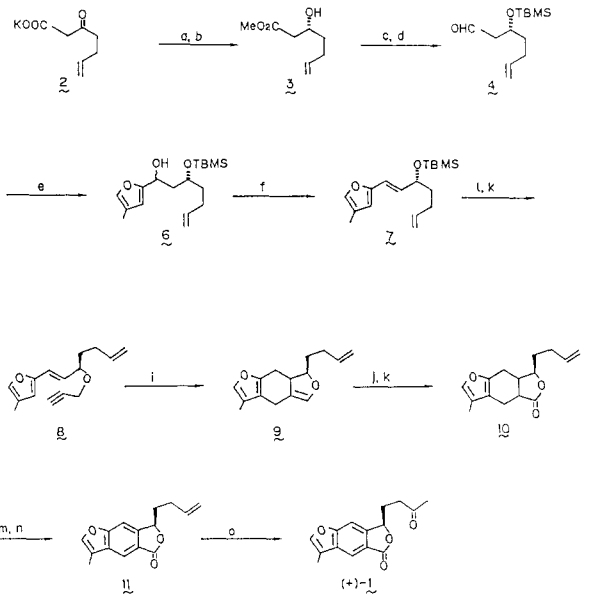
Benzofuran lactone **1** was isolated from the aerial parts of the South African Composite *Euryops hebecarpus* by Bohlmann et al.[4] The unusual secofuranoeremophilane structure of **1** and its unprecedented biogenesis[4] are noteworthy. Although the gross structure of **1** was determined by spectroscopic means[4] as well as synthesis,[5] the absolute configuration remains unclear.[6] The method used in the racemic synthesis,[5] however, was not applicable to the asymmetric synthesis. Herein, we report on the first total synthesis of (+)-**1** based on the allene intramolecular cycloaddition strategy[7] using an optically active starting material, i.e., (*R*)-**3**.[8] The results of this work may provide important information about the absolute configuration of natural **1** as well as the biogenetically related compounds.[4]

Recently, we have developed a new method of lactone synthesis[7c] via intramolecular Diels–Alder (D.A.) reaction of allenyl ethers[7] followed by a hydration–oxidation procedure. Now, we planned to take advantage of this methodology for construction of the basic skeleton (tricyclic lactone) of optically active **1** as outlined in Scheme I. Thus, chiral **1** is considered to be formed by the intramolecular D.A. reaction of chiral ether **A**, which in turn can be prepared from furyl anion **D** and optically active aldehyde **E** via **C** and **B** due to easy isomerization of the propargyl ether to the allenyl ether[7] as well as oxidation (Wacker oxidation)[9] of the terminal olefin to the acetyl group (Scheme I).

Scheme I



Scheme II[a]



[a] (a) Bakers' yeast, D-glucose, KH_2PO_4, H_2O, 25 °C; (b) MeOH, concentrated H_2SO_4, 25 °C; (c) *t*-$BuMe_2SiCl$, imidazole, DMF; (d) DIBAH, toluene, −78 °C; (e) 2-bromo-4-methylfuran, *n*-BuLi (1.1 equiv), THF, −78 °C; (f) $(PhO)_3P^+MeI^-$, HMPA, 25 °C; (g) *n*-Bu_4NF, THF; (h) *n*-BuLi, propargyl bromide, benzene/DMSO (1:1); (i) *t*-BuOK (8 equiv), *t*-BuOH, 83 °C; (j) 5% CSA, CH_3CN/H_2O (2:1); (k) Ag_2CO_3, Celite, benzene, reflux; (l) LDA, PhSeCl, HMPA, THF, −78 °C; (m) 30% H_2O_2, pyridine, CH_2Cl_2, 0 °C; (n) DDQ, benzene, 25 °C, then reflux; (o) $PdCl_2$ (5 mol %), CuCl (1 equiv), O_2, wet DMF, 25 °C.

(1) See, for example: (a) Nicolaou, K. C.; Veale, C. A.; Webber, S. E.; Katerinopoules, H. *J. Am. Chem. Soc.* **1985**, *107*, 7515. (b) Kozikowski, A. P.; Park, P. *Ibid.* **1985**, *107* 1763.

(2) Hanessian, S. *Total Synthesis of Natural Products: The 'Chiron' Approach*; Pergamon: New York, 1983.

(3) Corey, E. J.; Magriotis, P. A. *J. Am. Chem. Soc.* **1987**, *109*, 287.

(4) Bohlmann, F.; Zdero, C.; Grenz, M. *Chem. Ber.* **1974**, *107*, 2730.

(5) Bohlmann, F.; Fritz, G. *Tetrahedron Lett.* **1981**, *22*, 95.

(6) No data concerning optical rotation of natural **1** have been available due to the very limited amount of **1** isolated: private communication from Professor F. Bohlmann.

(7) (a) Hayakawa, K.; Yodo, M.; Ohsuki, S.; Kanematsu, K. *J. Am. Chem. Soc.* **1984**, *106*, 6735. (b) Hayakawa, K.; Yamaguchi, Y.; Kanematsu, K. *Tetrahedron Lett.* **1985**, *26*, 2689. (c) Hayakawa, K.; Ohsuki, S.; Kanematsu, K. *Ibid.* **1986**, *27*, 947. (d) Hayakawa, K.; Yasukouchi, T.; Kanematsu, K. *Ibid.* **1986**, *27*, 1837. (e) Hayakawa, K.; Ohsuki, S.; Kanematsu, K. *Ibid.* **1986**, *27*, 4205.

(8) $[\alpha]^{24}_D$ −22.7° (*c* 1.3, $CHCl_3$), >99% ee: Hirama, M.; Shimizu, M.; Iwashita, M. *J. Chem. Soc., Chem. Commun.* **1983**, 599.

(9) Tsuji, J.; Shimizu, I.; Yamamoto, K. *Tetrahedron Lett.* **1976**, 2975.

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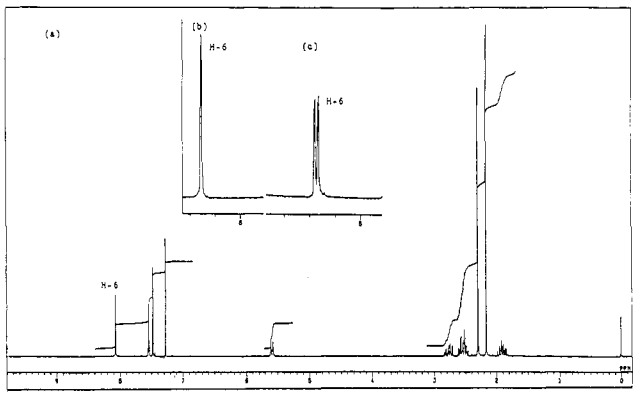

Figure 1. ^{1}H NMR spectra (270 MHz) of (a) (+)-1, (b) (+)-1 in the presence of Eu(hfc)$_3$ (14 mol %) and (c) (±)-1 in the presence of Eu(hfc)$_3$ (21 mol %).

The synthesis (Scheme II) began with asymmetric reduction (bakers' yeast) of **2**[7a] to (*R*)-**3** according to the method of Hirama et al.[8] Silylation of **3** with *tert*-butyldimethylchlorosilane (TBMSCl)/imidazole in DMF and DIBAH reduction (toluene, −78 °C) gave aldehyde **4**, $[\alpha]^{25}_D$ +0.8° (*c* 1.4 $CHCl_3$), in 85% yield. Treatment of **4** with 2-lithio-4-methylfuran (**5**) (THF, −78 °C), generated by reaction of 2-bromo-4-methylfuran[10] and *n*-BuLi (1 equiv), afforded a diastereomeric mixture (1:1) of alcohols **6**, which was subjected to dehydration under neutral conditions [$(PhO)_3P^+MeI^-$, HMPA][11] to give **7**, $[\alpha]^{28}_D$ +26.2° (*c* 1.1 MeOH), in 75% yield from **4**. Desilylation of **7** (*n*-Bu_4NF, THF; 96%) followed by alkylation [*n*-BuLi, C_6H_6/DMSO (1:1); propargyl bromide, 0 °C] afforded the propargyl ether **8** (54%), $[\alpha]^{27}_D$ +176.0° (*c* 1.1 MeOH), besides unreacted alcohol (39%) which was repeatedly propargylated to give more **8**.

With the requisite **8** in hand, the stage was set to employ the key lactone synthesis via intramolecular Diels–Alder reaction of allenyl ether (like A).[7c] Thus, treatment of **8** with excess *t*-BuOK in *t*-BuOH at reflux (83 °C, 1 h) provided a quantitative yield of **9**, which was immediately treated with 5% camphorsulfonic acid (CSA) in H_2O/CH_3CN (1:2) to give the lactol (59%) followed by oxidation with Fetizon's reagent[12] (Ag_2CO_3, Celite) in C_6H_6 (80 °C) to give a diastereomeric mixture of lactones **10** (74%). Conversion of **10** into the benzofuran was carried out by stepwise dehydrogenation via oxidative elimination (30% H_2O_2, pyridine, CH_2Cl_2, 0 °C) of the initially formed phenyl selenide (LDA, THF, −78 °C; PhSeCl, 60%) followed by aromatization with DDQ (C_6H_6, 25–80 °C) to give **11** (38%), $[\alpha]^{26}_D$ +70.8° (*c* 1.26, $CHCl_3$). Finally, Wacker oxidation of **11** [$PdCl_2$ (5 mol %), CuCl (1 equiv), wet DMF, 25 °C][9] gave (+)-**1**. $[\alpha]^{27}_D$ +75.6° (*c* 1.1, $CHCl_3$), in 94% yield. The synthetic (+)-**1** was identical with the natural product in spectroscopic (^{1}H NMR, IR, UV, MS) properties except for the unknown optical rotation.[6,13] We have also synthesized racemic **1**, mp 115–116 °C (lit.[5] mp 120 °C), in a similar way, starting with racemic **3** obtained by the $NaBH_4$ reduction (EtOH, 95%) of the ethyl ester of **2**. In determining the enantiomeric purity of (+)-**1** obtained above, it was shown that the H-6 protons (δ 8.07) of racemic **1** could be nicely resolved in the 270-MHz ^{1}H NMR spectrum by using Eu(hfc)$_3$[14] as the chiral shift reagent (Figure 1). Hence subsequent ^{1}H NMR experiments demonstrated that the above synthesis generated (+)-**1** in >98% enantiomeric purity.

While the absolute configuration of natural **1** still remains unknown due to the unavailability of the optical rotation,[4,6] the above asymmetric synthesis clearly indicated that it can be immediately assigned as the *R* configuration as shown in (+)-**1** if the natural product is dextrorotatory, and the *S* configuration if levorotatory.

Experimental Section

General. The melting points were measured with a Yanagimoto micro melting point apparatus and are uncorrected. The ^{1}H NMR spectra were taken with a Hitachi R-600 spectrometer (unless otherwise noted) or JEOL JNM-GX 270 spectrometer with tetramethylsilane as an internal standard; chemical shifts are expressed in δ values. IR spectra were taken with a JASCO IR A-100 infrared spectrophotometer. Optical rotations were determined on a JASCO DIP-360 polarimeter. Mass spectra were determined on a JEOL-D-300 equipped with a JMA 3100/3500 at an ionization voltage of 70 eV. UV spectra were determined with a Shimadzu UV-260 spectrophotometer. For thin layer chromatographic (TLC) analysis, Merck precoated TLC plates (Kieselgel 60 F_{254}, 0.2 mm) were used, and column chromatography was done by using Merck Kieselgel 60 (70–200 mesh) as the stationary phase. Gas chromatographic (GLC) analysis was performed on a Simadzu GC-8A gas chromatograph using a CBP1 capillary column. Purity of all samples was estimated (>95%) on the basis of 270-MHz NMR, TLC, and GLC analyses. Bakers' yeast was purchased from Oriental Yeast Co., Ltd.

Methyl (*R*)-(−)-3-Hydroxyhept-6-enoate (3). This represents a modification of the procedure described by Hirama et al.[8] A solution of ethyl 3-oxohept-6-enoate (1.7 g, 0.01 mmol) and aqueous 1 M KOH (25 mL) in ethanol (40 mL) was stirred at 25 °C for 20 h. The ethanol was removed in vacuo and the residue was diluted with water (200 mL). The resulting solution was added to a prestirred (30 min) suspension of bakers' yeast (66 g), D-glucose (75 g), KH_2PO_4 (157 mg), and $MgSO_4$ (79 mg) in water (200 mL), and the mixture was stirred vigorously at 25 °C for 2 days with occasional addition of D-glucose (30 g, every 6 h). After Celite (99 g) was added, the mixture was stirred for an additional 30 min and filtered through a pad of Celite. The filtrate was acidified to pH 2 with concentrated HCl and then extracted with ether (3 × 200 mL). The organic extract was washed with brine (200 mL), dried over anhydrous $MgSO_4$, and evaporated in vacuo.

The crude product was dissolved in methanol (120 mL) and concentrated H_2SO_4 (2 mL) was added. After being stirred for 15 h at room temperature, the mixture was concentrated by evaporation of the solvent under the reduced pressure, diluted with ether, and washed successfully with water, 10% aqueous $NaHCO_3$, and brine. The organic layer was dried over $MgSO_4$ and evaporated in vacuo. The residue was chromatographed on a silica gel column by using hexane/ethyl acetate (7:1) as an eluent to give **3** (520 mg, 33%) as a pale yellow oil: IR (neat) 3500, 1720, 1620 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 6.19–5.54 (1 H, m), 5.15–4.87 (2 H, m), 4.27–3.89 (1 H, m), 3.71 (3 H, s), 2.96 (1 H, d, *J* = 4.2 Hz, D_2O exchangeable), 2.46 (2 H, d, *J* = 7.2 Hz), 2.26–2.04 (2 H, m), 1.75–1.52 (2 H, m); $[\alpha]^{24}_D$ −22.0° (*c* 1.27, $CHCl_3$).

(*R*)-(+)-3-(*tert*-Butyldimethylsiloxy)-6-heptenal (4). To a stirred solution of alcohol **3** (1.7 g, 11 mmol) in DMF (5 mL) at room temperature was added *tert*-butyldimethylchlorosilane (2.1 g, 14 mmol) and imidazole (1.8 g, 27.5 mmol). After 3 h at room temperature, the reaction mixture was poured into brine (20 mL) and extracted with ethyl acetate (3 × 40 mL). The combined extracts were washed with brine (20 mL) and dried over Na_2SO_4. The solvent was removed under reduced pressure, and the crude product was purified by column chromatography on silica gel using hexane–ethyl acetate (40:1) as an eluent to give methyl (*R*)-(−)-3-(*tert*-butyldimethylsiloxy)hept-6-enoate (2.58

(10) Knight, D. W.; Rustidge, D. C. *J. Chem. Soc., Perkin Trans. 1* **1981**, 679.
(11) Verheyden, J. P. H.; Moffatt, J. G. *J. Org. Chem.* **1970**, *35*, 2319.
(12) Mckillop, A.; Young, D. W. *Synthesis* **1979**, 401.
(13) We are grateful to Professor F. Bohlmann for identification of (+)-1 with authentic sample by spectral comparison.
(14) Tris[3-[(heptafluoropropyl)hydroxymethylene]-(+)-camphorato]europium(III).

g, 90%) as a colorless oil: IR (neat) 1740, 1640, 1090 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.10–5.54 (1 H, m), 5.15–4.58 (2 H, m), 4.19 (1 H, t, J = 6.0 Hz), 3.68 (3 H, s), 2.47 (2 H, d, J = 6.0 Hz), 2.26–1.94 (2 H, m), 1.94–2.26 (2 H, m), 0.89 (9 H, s), 0.08 (s, 6 H); $[\alpha]^{25}_D$ −14.4° (c 1.42, $CHCl_3$).

To a solution of the above ester (2.58 g, 9.9 mmol) in dry toluene (20 mL) was added dropwise diisobutylaluminum hydride (DIBAL-H) (1 M solution in hexane, 11.9 mL, 11.9 mmol) at −78 °C under Ar, and the resulting mixture was stirred at this temperature for 1 h. After saturated $NaHSO_4$ (10 mL) was added, the mixture was warmed up to room temperature and extracted with ether (3 × 40 mL). The combined extracts were washed successively with saturated $NaHSO_4$ and brine (2 × 20 mL) and dried over Na_2SO_4 and the solvent was removed under the reduced pressure. The residue was subjected to a column chromatography on silica gel using hexane/ethyl acetate (20:1) to give **4** (1.93 g, 85%) as a pale yellow oil, bp 90–98 °C/20 mmHg (Kugelrohr): IR (neat) 1720, 1640, 1260, 1100 cm^{-1}; ^1H NMR ($CDCl_3$) δ 9.81 (1 H, t, J = 2.4 Hz), 6.06–5.51 (1 H, m), 5.13–4.88 (2 H, m), 4.22 (1 H, m), 2.52 (2 H, dd, J = 6.0, 2.4 Hz), 2.18–1.94 (2 H, m), 1.80–1.56 (2 H, m), 0.87 (9 H, s), 0.07 (6 H, s); $[\alpha]^{25}_D$ +0.84° (c 1.43, $CHCl_3$). Anal. Calcd for $C_{13}H_{26}O_2Si$: C, 64.39; H, 10.82. Found: C, 64.42; H, 10.79.

(3*R*)-1-Hydroxy-1-[2-(4-methylfuryl)]-3-(*tert*-butyldimethylsiloxy)-6-heptene (6). To a stirred solution of 2-bromo-4-methylfuran (2.26 g, 12.7 mmol) in dry THF (10 mL) at −78 °C under Ar was added dropwise n-BuLi (1.6 M solution in hexane, 8.2 mL, 12.7 mmol). The resulting orange solution was stirred at −78 °C for 1.5 h and then a THF solution of **4** (1.9 g, 8.4 mmol) was added. After being stirred at this temperature for 1.5 h, the reaction mixture was poured into water (5 mL) containing a few drops of concentrated HCl and extracted with ether (3 × 30 mL). The combined extracts were washed with brine (2 × 10 mL) and dried over $MgSO_4$, and the solvent was removed under the reduced pressure. The residue was subjected to a medium pressure column chromatography on silica gel using hexane/ethyl acetate (20:1) to give a diastereomeric mixture of **6** (1.6 g, 60%) as a yellow oil: IR (neat) 3400, 1640 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.12 (1 H, q, J = 1.2 Hz), 6.10 (1 H, s), 5.91–5.52 (1 H, m), 5.13–4.86 (3 H, m), 4.23–3.86 (1 H, m), 3.19 and 2.99 (1 H, each d, J = 6.0 Hz, D_2O exchangeable), 2.00 (3 H, d, J = 1.2 Hz), 1.94–1.26 (6 H, m), 0.91 (9 H, s), 0.09 (6 H, s); MS, m/z (relative intensity) 306 ($M^+ - H_2O$, 3.5), 75 (100).

(3*R*)-1-[2-(4-Methylfuryl)]-3-(*tert*-butyldimethylsiloxy)-1(*E*),6-heptadiene (7). A solution of crude **6** obtained as above from **4** (2.26 g, 12.7 mmol) in HMPA (5 mL) was added to a stirred mixture of methyltriphenoxyphosphonium iodide (MIPI) (12.5 g, 30.0 mmol) in HMPA (40 mL) under Ar at room temperature. After 1.5 h, the mixture was diluted with aqueous 10% KOH (50 mL) and extracted with ether (3 × 60 mL). The combined extracts were washed successively with brine and water and dried over Na_2SO_4, and the solvent was removed under reduced pressure. The residue was subjected to a column chromatography on silica gel using hexane/ethyl acetate (30:1) to give **7** (3.6 g, 71% from **4**) as a pale yellow oil: IR (neat) 1640, 1090 cm^{-1}; 270-MHz ^1H NMR ($CDCl_3$) δ 7.10 (1 H, q, J = 1.2 Hz), 6.27 (1 H, dd, J = 15.8, 0.3 Hz), 6.07 (1 H, dd, J = 15.8, 5.9 Hz), 6.08 (1 H, s), 5.87–5.78 (1 H, m), 5.05–4.92 (2 H, m), 4.26 (1 H, q, J = 5.8, Hz), 2.00 (3 H, d, J = 1.2 Hz), 1.68–1.56 (2 H, m), 0.91 (9 H, s), 0.06 (3 H, s), 0.04 (3 H, s); $[\alpha]^{28}_D$ +26.2° (c 1.1, MeOH).

(*R*)-1-[2-(4-Methylfuryl)]-3-(2-propynyloxy)-1(*E*),6-heptadiene (8). To a solution of **7** (4.02 g, 13.6 mmol) in dry THF (50 mL) was added n-Bu_4NF (1 M solution in THF, 27.3 mL, 27.3 mmol). After being stirred at room temperature for 4 h, the reaction mixture was poured into brine (50 mL) and extracted with ether (3 × 60 mL). The combined extracts were washed with brine (2 × 10 mL) and dried over anhydrous $MgSO_4$. The solvent was removed under reduced pressure to give the crude alcohol (2.57 g): IR (neat) 3300, 3025, 1630 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.16 (1 H, br s), 6.40 (1 H, d, J = 15.6 Hz), 6.20 (1 H, br s), 6.11 (1 H, dd, J = 15.6, 7.8 Hz), 5.81–5.55 (1 H, m), 5.15–4.87 (2 H, m), 4.24 (1 H, br q, J = 4.8 Hz), 1.99 (1 H, d, J = 1.2 Hz), 2.36–1.48 (5 H, m).

The above crude product was dissolved in a 1:1 mixture (60 mL) of dry benzene and Me_2SO and cooled in a water bath under Ar. To this stirred solution was added dropwise 1.6 M n-BuLi in hexane (13.1 mL, 20.4 mmol), and the mixture was stirred at room temperature for 1.5 h. After propargyl bromide (7.3 mL, 81.6 mmol) was added, the mixture was stirred at room temperature for 4 h and then quenched with ice water (50 mL). The mixture was extracted with ether (3 × 80 mL) and the organic layers were washed with brine and dried over Na_2SO_4. The solvent was removed under reduced pressure, and the crude product was purified by column chromatography on silica gel with hexane/ethyl acetate (30:1–10:1 gradient) to give **8** (1.64 g, 53%) and the unreacted alcohol (600 mg, 19%) in the order of elution. Compound **8**: IR ($CHCl_3$) 3320, 1640, 1600 cm^{-1}; 270-MHz ^1H NMR (C_6D_6) δ 6.86 (1 H, q, J = 0.3 Hz), 6.27 (1 H, d, J = 16 Hz), 6.03 (1 H, dd, J = 16.0, 7.9 Hz), 5.88 (1 H, br s), 5.83–5.70 (1 H, 10-lines, m), 5.01–4.84 (2 H, m), 4.01 (1 H, dd, J = 15.8, 2.5 Hz), 3.87 (1 H, dd, J = 15.8, 2.5 Hz), 4.02–3.95 (1 H, m), 2.20–2.14 (2 H, m), 2.02 (1 H, t, J = 2.5 Hz), 1.74 (3 H, d, J = 1.2 Hz), 1.84–1.71 (1 H, m), 1.64–1.50 (1 H, m); MS, m/z (relative intensity) 230 (M^+, 2.1), 55 (100); high resolution MS calcd for $C_{15}H_{18}O_2$ 230.1306, found 230.1308; $[\alpha]^{27}_D$ +176.0° (c 1.05, MeOH).

(7*R*)-3-Methyl-7-(3-butenyl)-4,7,7a,8-tetrahydro-1,6-dioxa-*s*-indacene (9). A solution of **8** (447 mg, 1.94 mmol) and t-BuOK (1.1 g, 9.5 mmol) in t-BuOH (20 mL) was stirred at room temperature for 1 h under Ar and then refluxed (83 °C) for 1 h. After cooling, the reaction mixture was diluted with ether (40 mL), washed successively with brine and water, and dried over Na_2SO_4. The solvent was removed in vacuo to give **9** (440 mg, 98%): ^1H NMR ($CDCl_3$) δ 7.05 (1 H, br s), 6.22 (1 H, br s), 6.04–5.57 (1 H, m), 5.17–4.90 (2 H, m), 4.43–4.16 (1 H, m), 3.07–2.69 (4 H, m), 2.72–1.60 (5 H, m), 1.92 (3 H, d, J = 1.2 Hz).

(7*R*)-3-Methyl-7-(3-butenyl)-4,4a,5,7,7a,8-hexahydro-1,6-dioxa-*s*-indacen-5-one (10). To a solution of **9** (440 mg, 1.94 mmol) in a mixture of CH_3CN (10 mL) and H_2O (5 mL) was added dropwise a solution of (±)-10-camphorsulfonic acid (CSA) (500 mg) in CH_3CN–H_2O (3:2, 10 mL), and the mixture was stirred at room temperature for 4 h. After dilution with ether (50 mL), the reaction mixture was washed successively with brine and saturated $NaHCO_3$ (2 × 20 mL) and dried over Na_2SO_4, and the solvent was removed under reduced pressure. The residue was subjected to medium pressure column chromatography on a silica gel using hexane/ethyl acetate (10:1–7:1) as eluent to give a diastereomeric mixture of lactols (278 mg, 59% from **9**): IR ($CHCl_3$) 3400, 1638 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.07 (1 H, br s), 6.10–5.42 (1 H, m), 5.27–4.88 (3 H, m), 4.02 (1 H, br q, J = 6.6 Hz), 3.74 (1 H, br s), 2.94–1.67 (10 H, m), 1.92 (3 H, d, J = 1.2 Hz).

A suspension of Fetizon's reagent[12] ($AgNO_3$/Celite) (3.12 g, 5.5 mmol) in benzene (10 mL) was heated under reflux for 1 h in an apparatus fitted with a Dean–Stark trap. After cooling, the above crude lactol (136 mg, 0.548 mmol) dissolved in dry benzene (5 mL) was added and the mixture was refluxed for a further 7 h. The reaction mixture was cooled and the precipitate was filtered off through a pad of Celite that was washed well with ether. The combined filtrate was evaporated under the reduced pressure and the residue was chromatographed on a silica gel column by with hexane/ethyl acetate (20:1–10:1) to give a diastereomeric mixture of **10** (100 mg, 74%): IR ($CHCl_3$) 1770, 1210, 1640 cm^{-1}; 270-MHz ^1H NMR ($CDCl_3$) δ 7.08, 7.06, 7.04 (1 H, 2:3:1, each br s), 5.92–5.74 (1 H, m), 5.29–5.02 (2 H, m), 4.50 (1 H, ddd, J = 8.7, 5.2, 3.7 Hz), 3.31–1.81 (10 H, m), 1.98 (3 H, d, J = 1.3 Hz); MS, m/z (relative intensity) 246 (M^+, 100).

(*R*)-3-Methyl-7-(3-butenyl)-5,7-dihydro-1,6-dioxa-*s*-indacen-5-one (11). To a stirred solution of LDA (1.97 mmol) prepared from diisopropylamine (200 mg, 1.97 mmol) and n-BuLi (1.4 mL of 1.56 M solution in hexane) in dry THF (1 mL) was added **10** (404 mg, 1.64 mmol) in THF (1 mL) at −78 °C. After 40 min, PhSeCl (347 mg, 1.81 mmol) in THF (2 mL) containing HMPA (0.3 mL, 1.81 mmol) was added rapidly. The mixture was stirred at this temperature for 4 h and diluted with ether (50 mL). The organic layer was washed successively with brine and saturated $NaHCO_3$, dried over Na_2SO_4, and evaporated in vacuo. The residue was chromatographed on a silica gel column with hexane/ethyl acetate (1:0–10:1) to give a diastereomeric mixture of keto selenides (395 mg, 60.0%): IR ($CHCl_3$) 1760, 1615, 1560, 1460 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.72–7.19 (5 H, m), 7.09 (1 H, q, J = 1.2 Hz), 6.08–5.62 (1 H, m), 5.08–4.79 (2 H, m), 4.05 (1 H, td, J = 10.8, 3.0 Hz), 2.94 (1 H, d, J = 16.8 Hz), 2.56 (1 H, d, J = 16.8

Hz), 2.36–1.41 (7 H, m), 1.84 (3 H, d, J = 1.2 Hz).

To a solution of the above selenide (395 mg, 0.985 mmol) in CH_2Cl_2 (10 mL) containing pyridien (0.1 mL) were added at 0 °C three 0.1-mL portions of 15% hydrogen peroxide at 15-min intervals. The reaction mixture was stirred at 0 °C for 1 h, quenched with CH_2Cl_2 (40 mL), and washed successively with saturated $NaHCO_3$, brine, and water. The organic layer was dried over Na_2SO_4 and evaporated in vacuo to give crude (*R*)-3-methyl-7-(3-butenyl)-7,7a-dihydro-1,6-dioxa-*s*-indacen-5(8*H*)-one: IR (neat) 1740, 1630, 1585, 1515, 900 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.95 (1 H, q, J = 1.8 Hz), 5.85–5.31 (1 H, m), 5.04 (1 H, s), 5.01–4.74 (2 H, m), 4.36–4.05 (1 H, m), 3.00–2.84 (2 H, m), 2.15–0.85 (5 H, m), 1.68 (3 H, d, J = 1.8 Hz).

The crude product was dissolved in dry benzene (15 mL) under Ar, and 2,3-dichloro-5,6-dicyano-*p*-benzoquinone (DDQ) (268 mg, 1.18 mmol) was added in benzene (9 mL). The mixture was stirred at room temperature for 40 min and refluxed for 1 h. The residue was passed through a short pad of alumina with CH_2Cl_2 as the eluent and the solvent was evaporated in vacuo. The residue was chromatographed on silica gel by using hexane/ethyl acetate (9:1) to give **11** (91 mg, 38%) as colorless viscous oil: IR ($CHCl_3$) 1750, 1640, 1370, 1090 cm^{-1}; 270-MHz ^1H NMR ($CDCl_3$) δ 8.07 (1 H, d, J = 0.5 Hz), 7.53 (1 H, q, J = 1.2 Hz), 7.43 (1 H, t, J = 1.2 Hz), 5.87–5.81 (1 H, m), 5.56 (1 H, dd, J = 8.2, 3.0 Hz), 5.13–5.00 (2 H, m), 2.29 (3 H, d, J = 1.2 Hz), 2.27–2.17 (2 H, m), 2.25–2.21 (2 H, m); MS, m/z (relative intensity) 242 (M^+, 11.9) 200 ($M^+ - C_3H_6$, 100); high resolution MS calcd for $C_{15}H_{14}O_3$ 242.0942, found 242.0946; $[\alpha]^{26}_D$ +70.79° (*c* 1.26, $CHCl_3$).

(*R*)-4-Oxo-5,6,9,10-tetradehydro-4,5-secofurano-eremophilane-5,1-carbolactone (1). Cuprous chloride (21.1 mg, 0.21 mmol) and palladium chloride (7.1 mg, 0.04 mmol)) were suspended in DMF (1 mL) containing a trace of H_2O. The mixture was stirred vigorously under oxygen atmosphere until absorption of oxygen ceased (about for 3 h). Then **11** (52 mg, 0.21 mmol) dissolved in DMF (2 mL) was added and the mixture was stirred vigorously under oxygen at room temperature for 2 h. The reaction mixture was poured into 3 N HCl, extracted with ether (3 × 30 mL), and washed successively with saturated $NaHCO_3$ and brine (2 × 10 mL). The solvent was removed under reduced pressure. The residue was subjected to column chromatography on silica gel using hexane/ethyl acetate (3:1) to give **1** (52 mg, 94%) as colorless crystals: mp 105–106 °C (ether/*n*-hexane); UV λ_{max} (ether) 228 nm (log ϵ 4.64), 248 (3.81), 263 sh (3.61), 295 (3.41), 304 sh (3.27); IR (CCl_4) 1705, 1760 cm^{-1}; 270-MHz ^1H NMR ($CDCl_3$) δ 8.06 (1 H, d, J = 0.8 Hz), 7.54 (1 H, q, J = 1.3 Hz), 7.47 (1 H, t, J = 0.8 Hz), 5.58 (1 H, ddd, J = 8.5, 3.0, 0.8 Hz), 2.81–2.70 (1 H, m), 2.61–2.45 (2 H, m), 1.98–1.84 (1 H, m), 2.29 (3 H, d, J = 1.3 Hz), 2.16 (3 H, s); MS, m/z (relative intensity) 258 (M^+, 15.6), 200 ($M^+ - C_3H_6O$, 100); high resolution MS calcd for $C_{15}H_{14}O_4$ 258.0891, found 258.0890; $[\alpha]^{27}_D$ +75.6° (*c* 1.05, $CHCl_3$). Anal. Calcd for $C_{15}H_{14}O_4$: C, 69.74; H, 5.47. Found: C, 69.88; H, 5.58.

Probing Ergot Alkaloid Biosynthesis: Synthesis and Feeding of a Proposed Intermediate along the Biosynthetic Pathway. A New Amidomalonate for Tryptophan Elaboration

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The total synthesis of the diastereomeric amino acids **2** and their *N*-trideuteriomethyl analogues has been carried out. These compounds represent possible intermediates along the biosynthetic pathway from 4-(γ,γ-dimethylallyl)tryptophan (**1**) to the ergot alkaloids (e.g., **3a**). The synthetic scheme features the preparation of an (indolylvinyl)metallic reagent from 4-ethynylindole via a hydrostannylation/metal–metal exchange sequence, as well as the preparation of dimethyl [*N*-methyl-*N*-[(2,2,2-trichloroethoxy)carbonyl]amino]malonate, a new amidomalonate reagent for tryptophan elaboration. Incorporation experiments with *Claviceps sp.* SD58 followed by GC–MS analysis of the major alkaloid, elymoclavine, showed that neither diastereomer of **2**-d_3 is an ergot alkaloid precursor.

The ergot alkaloids represent a pharmacologically interesting class of natural products that find important clinical use and that consequently still command the attention of both synthetic and medicinal chemists.[1]

In spite of the considerable efforts that have been devoted to understanding the biosynthesis of the ergot alkaloids, a number of unsolved problems remain.[2a] Tryptophan was established as a precursor to the ergot alkaloids by Mothes et al. in 1958,[2b] and Floss et al. showed that the L isomer is incorporated with almost complete retention of the α hydrogen and the amino nitrogen.[2c] Further studies gave support to the idea that *R*-mevalonic acid is then incorporated into the ergot alkaloids by way of dimethylallyl pyrophosphate.[2d] An enzyme-catalyzed reaction between tryptophan and dimethylallyl pyrophosphate thus provides 4-(γ,γ-dimethylallyl)tryptophan (DMAT, **1**) as the first pathway-specific intermediate in ergot biosynthesis. While other studies have convincingly demonstrated that DMAT is converted to elymoclavine

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