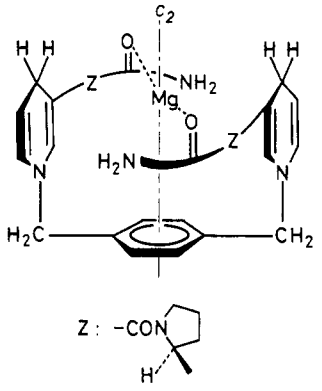
evidence, combined with the stereochemical outcome that the enantiomeric excess of the product mandelate was at a maximum by the use of equimolar bis(NAH) **1** and Mg, shows that the stereochemical requirements are accommodated well in the stoichiometric *intramolecular* chelation complex which exhibits the highest stereospecificity and is unaffected by an excess of metal ion.

It then seems likely that the operating bis(NAH) **1** assumes a C_2 conformation with the specific pro-*R* or pro-*S* hydrogens of the two juxtaposed equivalent dihydropyridine nuclei disposed outside and the C_2 axis passing through the interposing Mg and the center of the *p*-xylene bridge (**10**).



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Acknowledgment. This work was supported in part by a grant in aid (521316) from the Ministry of Education of Japan for which we are deeply grateful.

(11) E. T. Stiller, S. A. Harris, J. Finkelstein, J. C. Keresztesy, and K. Folkers, *J. Am. Chem. Soc.*, **62**, 1785 (1940).

Total Synthesis of (±)-Maritimol

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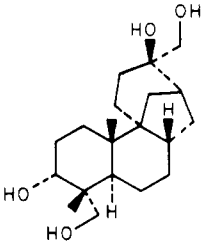
Received April 20, 1981

Diterpenoids of the aphidicolane (**1**)–stemodane (**2**) type, including aphidicolin (**1**) as well as maritimol (**2a**) and other Stemodia components (**2b–d**), have attracted attention not only because of their novel structures but also because of certain biomedical and pharmacological properties.[1–4] We wish now to disclose the first maritimol (±) total synthesis, a stereospecific, nonrelay route which parallels in significant respects the probable biogenesis of this natural product.[5]



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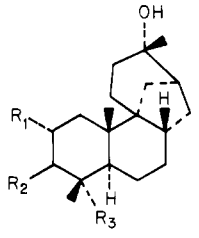
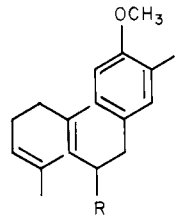


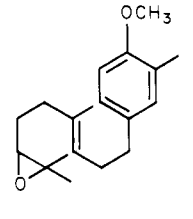
2a, $R_1 = H$; $R_2 = OH$; $R_3 = CH_3$
b, $R_1 = R_2 = H$; $R_3 = CH_2OH$
c, $R_1 = OH$; $R_2 = H$; $R_3 = CH_3$
d, $R_1 = O$; $R_2 = H$; $R_3 = CH_3$

(1) Aphidicolin, a fungal metabolite with antiviral and antimitotic properties,[2] finds use as an inhibitor of DNA synthesis. Maritimol,[3] stemodinol (**2b**),[3] stemodinol (**2c**),[4] and stemodinone (**2d**)[4] occur in *stemodia maritima* L. (Scrophulariaceae), a plant used in the Caribbean for treatment of venereal disease.

Alkylation of phenylgeranyl thioether[6] anion (generated by the action of 1.1 equiv of n-C_4H_9Li on the thioether in THF at −78 °C) with 2-methyl-4-(chloromethyl)anisole[7] (1.1 equiv in THF at −78 °C) gave rise to the coupling product **3a** (85% after chromatography on SiO_2). Reductive desulfurization with Li



3a, $R = SC_6H_5$
b, $R = H$



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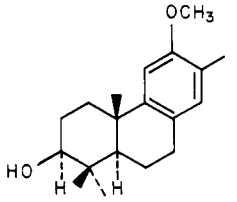
(3 equiv in NH_3 at −78 °C) generated (90%) polyene **3b** [bp 111 °C (0.03 mmHg)], which was converted via the terminal bromohydrin to the epoxide **4** (71% from **3b**)[8] (first 1.1 equiv of NBS in 5:1 THF–H_2O at 0 °C, then excess K_2CO_3 in CH_3OH at room temperature, followed by SiO_2 chromatography).

As a variant of the biocyclization process, Lewis acid treatment (BF_3·Et_2O or $SnCl_4$) of oxide **4** in aprotic solvent (CH_2Cl_2 or CH_3NO_2 at 0 °C; C_6H_6 at 25 °C) produced 25–50% hydrophenanthrene **5**,[9] initially as a clear gum but crystalline (mp 103–105 °C) after SiO_2 chromatography. In order to prepare



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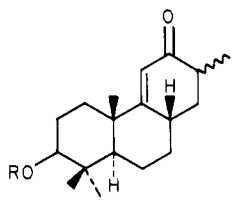

6a, $R = H$
b, $R = C_6H_5CH_2$

for the Diels–Alder reaction planned for construction of a fourth ring, the aromatic moiety in **5** was subjected to a Birch-type reduction (200 equiv of Li in 4:1:1 NH_3–THF–C_2H_5OH at reflux), generating, after hydrolysis (10:1 CH_3OH–7 N aqueous HCl at room temperature) of the intermediary enol ether, the conjugated enone **6a**, mp 55–57 °C (51% after SiO_2 chromatography).[10]

On successive exposure to $LiN[CH(CH_3)_2]_2$ (3.4 equiv in THF at 25 °C) and $(CH_3)_2$-t-C_4H_9SiCl (3.2 equiv in refluxing THF),

(2) Brudret, K. M.; Dalziel, W.; Hesp, B.; Jarvis, J. A.; Neidle, S. *Chem. Commun.* **1972**, 1027.
(3) Hufford, C. D.; Guerrero, R. O.; Doorenbos, N. J. *J. Pharm. Sci.* **1976**, *65*, 778.
(4) Manchand, P. S.; White, J. D.; Wright, H.; Clardy, J. *J. Am. Chem. Soc.* **1973**, *95*, 2705.
(5) (a) For successful synthetic approaches to aphidicolin, see: Trost, B. M.; Nishimura, Y.; Yamamoto, K. *J. Am. Chem. Soc.* **1979**, *101*, 1328. McMurry, J. E.; Andrus, A.; Ksander, G. M.; Musser, J. H.; Johnson, M. A. *Ibid.* **1979**, *101*, 1330. (b) Total synthesis of (±)-aphidicolin: Corey, E. J.; Tius, M. A.; Das, J. *Ibid.* **1980**, *102*, 1742. (c) Total synthesis of (±)-stemodin (**2c**) and (±)-stemodinone (**2d**): Corey, E. J.; Tius, M. A.; Das, J. *Ibid.* **1980**, *102*, 7612.
(6) Altman, L. J.; Ash, L.; Marson, S. *Synthesis* **1974**, 129.
(7) Wenner, W. *J. Org. Chem.* **1951**, *16*, 457.
(8) IR 2959, 1495, 1250 cm^{-1}; 60-MHz NMR ($CDCl_3$) δ 1.18 (3 H, s), 1.22 (3 H, s), 1.58 (3 H, s) 2.15 (3 H, s), 2.30–2.70 (3 H, m), 3.78 (3 H, s), 4.90–5.40 (1 H, m), 6.45–6.95 (3 H, m).
(9) IR 3413, 2941, 1489, 1252, 1200, 1033, 733 cm^{-1}; 60-MHz NMR ($CDCl_3$) δ 0.90 (3 H, s), 1.08 (3 H, s), 1.22 (3 H, s), 2.16 (3 H, s), 2.20–2.37 (1 H, m), 2.73–2.90 (1 H, m), 3.24–3.40 (1 H, m), 3.80 (3 H, s), 6.71 (1 H, s), 6.82 (1 H, brs).
(10) IR 3450, 2940, 1670, 1605 cm^{-1}; 60-MHz NMR ($CDCl_3$) δ 0.87 (3 H, s), 1.03 (3 H, s), 1.08 (3 H, d, J = 6 Hz), 1.13 (3 H, s), 3.05–3.40 (1 H, m), 5.70–5.90 (1 H, m).

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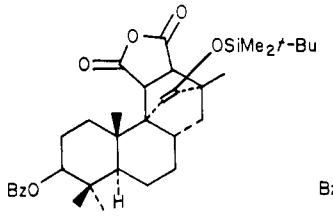
the benzyl ether (**6b**) of ketone **6a** was transformed quantitatively into the corresponding silyl enol ether, reaction of which (unpurified) with maleic anhydride (3.6 equiv in $C_6H_5CH_3$ at 90 °C), involving approach from the *overall* less hindered β face, produced pentacycle **7**. Since the adduct was unstable, it was hydrolyzed



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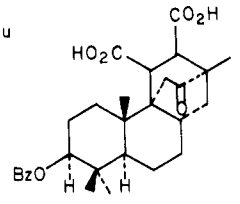

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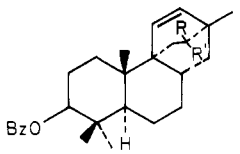
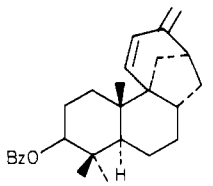
(3:2 5% aqueous KOH–$(CH_3)_2CO$ at reflux) (84% from **6b**) to the keto acid **8**,[11] which in the crude, amorphous state was oxidatively decarboxylated with $Pb(OAc)_4$ in O_2-saturated pyridine at 90 °C, giving (21% after SiO_2 chromatography) the unsaturated ketone **9a**[12] (mp 134–136 °C; ether–hexane).

Reduction of **9a** with $NaBH_4$ (10 equiv in C_2H_5OH at 25 °C) produced (85%) in a 70:30 ratio (by HPLC) the two alcohols **9b** and **9c**. Tosylation of **9b** (excess TsCl in pyridine at 40 °C)



9a, R = R′ = O
b, R = OH; R′ = H
c, R = H; R′ = OH



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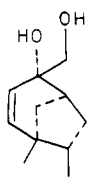
induced a [2.2.2] → [3.2.1] skeletal rearrangement, similar to that in the presumed biosynthesis of the stemodane system, with formation (77%) of the conjugated diene **10**.[13]

Oxidation of **10** with OsO_4 in $(C_2H_5)_2O$ and 2 equiv of pyridine (−10 °C → room temperature) proceeded regio- and stereoselectively generating glycol **11**, which was directly hydrogenated (freshly prepared Pt-black in C_2H_5OH at room temperature and 1 atm) to the saturated tetracycle **12a** (after HPLC, mp 173–176 °C; 41% overall from **10**). Exposure of the latter of TsCl



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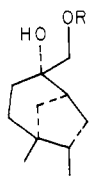

12a, R = H
b, R = $SO_2C_6H_4$-*p*-CH_3

(pyridine at 25 °C) yielded monotosylate **12b** (81%) which was transformed to (±)-maritimol benzyl ether through the agency of $LiHB(C_2H_5)_3$ (100 equiv in THF at 25 °C, followed by $NaOH–H_2O_2$ workup). Debenzylation was effected by Li in NH_3 at reflux, giving (±)-maritimol (after HPLC, 60% from **12b**) (mp 212.5–214 °C; ether–hexane) indistinguishable from the natural product on the basis of chromatographic as well as NMR, IR, and MS spectral comparisons.

(11) IR (KBr) 2955, 1731, 1698, 1179; 100 MHz NMR ($CDCl_3$ + Me_2SO-d_6) δ 0.85 (3 H, s), 0.96 (3 H, s), 1.05 (3 H, s), 1.20 (3 H, s), 2.40–3.45 (4 H, m), 4.40 and 4.63 (2 H, AB, J = 12 Hz), 7.33 (5 H, brs).

(12) IR 2916, 1718, 1241, 1221, 729, 678 cm^{-1}; 100-MHz NMR ($CDCl_3$) δ 0.88 (3 H, s), 0.99 (3 H, s), 1.10 (3 H, s), 1.15 (3 H, s), 2.03 and 2.50 (2 H, AB, J = 18 Hz), 2.80-3.00 (1 H, m), 4.43 and 4.70 (2 H, AB, J = 12 Hz), 5.83 (1 H, d, J = 8 Hz), 6.43 (1 H, d, J = 8 Hz), 7.32(5 H, brs).

(13) UV λ_{max} (EtOH) 236 nm; 100-MHz NMR ($CDCl_3$) δ 0.93 (3 H, s), 1.02 (3 H, s), 1.15 (3 H, s), 1.95–2.20 (2 H, m), 2.75–3.00 (2 H, m), 3.30–3.55 (2 H, m), 4.41 and 4.67 (2 H, AB, J = 12 Hz), 4.44 (1 H, Brs), 4.58 (1 H, t, J = 1.5 Hz), 5.93 (1 H, dd, J = 10 Hz, 1.5 Hz), 6.08 (1 H, d, J = 10 Hz), 7.31 (5 H, brs).

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A Short, Economical, and Stereoselective Route to Prostaglandins by Vicinal Alkylation of Cyclopentadiene

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An unusual number of elegant and ingenious routes to prostaglandins have been explored with success.[1] Recently we have initiated studies of a general approach to this important class of hormones which possess a common structural feature, namely, two vicinal carbon chains attached to a functionalized cyclopentane ring. Our approach has capitalized on the possibility of adding regio- and stereoselectivity two carbon chains on a suitably substituted cyclopentane ring. The methodology[2] involves the formation of a cyclobutanone by cycloaddition of a ketone-bearing anion-stabilizing group to a derivative of cyclopentene or cyclopentadiene followed by regiospecific cleavage of the strained ring with carbon nucleophiles. An alternative strategy[3] is based on the conjugate addition of a cuprate reagent to a cyclopentenone followed by trapping of the intermediate enolate with electrophiles.

The present communication outlines an application of this general methodology to an exceptionally short and economical synthesis of advanced intermediates which can be easily converted into primary prostaglandins and their analogues. *In the present approach, a new reagent, (carbomethoxy)chloroketene* (**1a**), *is used for the stereoselective introduction of both side chains and functionality on cyclopentadiene.*

(Carbomethoxy)chloroketene (**1a**) was generated in situ at room temperature by dropwise addition (7 h) of triethylamine (0.032 mol) in dry hexane (420 mL) to a solution of acid chloride[4] **2a** (0.032 mol) in hexane (120 mL) containing cyclopentadiene (0.2 mol) (Scheme I). Workup and distillation yielded pure **3a** (70%, mp 68 °C).[5] The activating effect of a chlorine substituent on

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(2) (a) Cossement, E.; Binamé, R.; Ghosez, L. *Tetraheron Lett.* **1974**, 997. (b) Ghosez, L. *Int. Congr. Ser.*—Excerpta *Med.* **1979**, *No.* **457**, 93. (c) Michel, Ph.; O'Donnell, M.; Binamé, R.; Ghosez, L.; Declercq, J. P.; Germain, G.; Arte, E.; Van Meerssche, M. *Tetrahedron Lett.* **1980**, 2577.

(3) (a) Stork, G.; Isabe, M. *J. Am. Chem. Soc.* **1975**, *97*, 6260. (b) Patterson, J. W.; Fried J. H. *J. Org. Chem.* **1974**, 39, 2506. (c) Posner, E. H.; Sterling, S. J.; Whitten, C. E.; Lentz, C. M.; Brunelle, D. J. *J. Am. Chem. Soc.* **1975**, *97*; *Tetrahedron Lett.* **1974**, 2591. (d) Schwarts, J.; Loots, M. J.; Kosugi, M. *J. Am. Chem. Soc.* **1980**, *102*, 1333.

(4) The acid chloride **2a** could be readily prepared by chlorination of monomethyl malonate with SO_2Cl_2 in ether and subsequent reaction with PCl_5. The crude acid chloride contained 10% of dichlorinated material but was used without further purification.

(5) All new compounds gave correct elemental analysis and satisfactory spectral data.

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