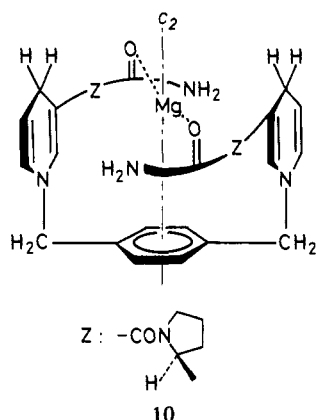


evidence, combined with the stereochemical outcome that the enantiomeric excess of the product mandelate was at a maximum by the use of equimolar bis(NAH) **1** and Mg, shows that the stereochemical requirements are accommodated well in the stoichiometric *intramolecular* chelation complex which exhibits 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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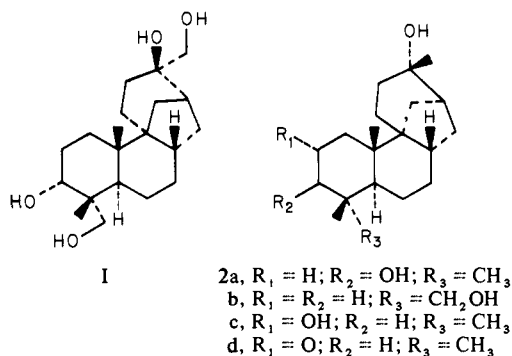
Total Synthesis of (±)-Maritimidol

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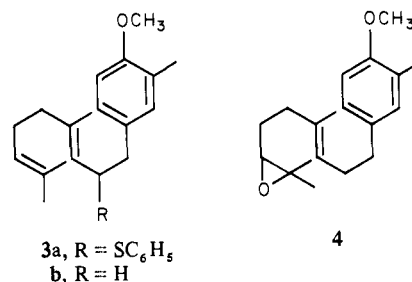
Diterpenoids of the aphidicolane (**1**)-stemodane (**2**) type, including aphidicolin (**1**) as well as maritimidol (**2a**) and other *Stemodia* components (**2b-d**), have attracted attention not only because of their novel structures but also because of certain biomedical and pharmacological properties.¹⁻⁴ We wish now to



(1) Aphidicolin, a fungal metabolite with antiviral and antimetabolic properties,² finds use as an inhibitor of DNA synthesis. Maritimidol,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.

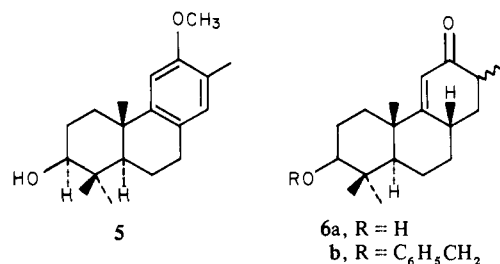
disclose the first maritimidol (±) total synthesis, a stereospecific, nonrelay route which parallels in significant respects the probable biogenesis of this natural product.⁵

Alkylation of phenylgeranyl thioether⁶ anion (generated by the action of 1.1 equiv of *n*-C₄H₉Li on the thioether in THF at -78 °C) with 2-methyl-4-(chloromethyl)anisole⁷ (1.1 equiv in THF at -78 °C) gave rise to the coupling product **3a** (85% after chromatography on SiO₂). Reductive desulfurization with Li



(3 equiv in NH₃ 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-H₂O at 0 °C, then excess K₂CO₃ in CH₃OH at room temperature, followed by SiO₂ chromatography).

As a variant of the biocyclization process, Lewis acid treatment (BF₃·Et₂O or SnCl₄) of oxide **4** in aprotic solvent (CH₂Cl₂ or CH₃NO₂ at 0 °C; C₆H₆ at 25 °C) produced 25-50% hydrophenanthrene **5**,⁹ initially as a clear gum but crystalline (mp 103-105 °C) after SiO₂ chromatography. In order to prepare



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 NH₃-THF-C₂H₅OH at reflux), generating, after hydrolysis (10:1 CH₃OH-7 N aqueous HCl at room temperature) of the intermediary enol ether, the conjugated enone **6a**, mp 55-57 °C (51% after SiO₂ chromatography).¹⁰

On successive exposure to LiN[CH(CH₃)₂]₂ (3.4 equiv in THF at 25 °C) and (CH₃)₂-*t*-C₄H₉SiCl (3.2 equiv in refluxing THF),

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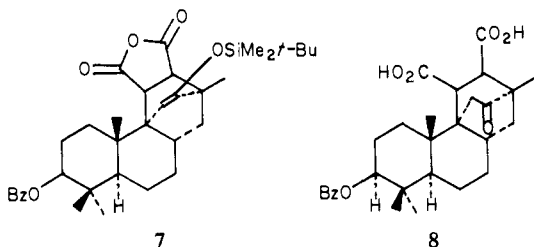
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(8) IR 2959, 1495, 1250 cm⁻¹; 60-MHz NMR (CDCl₃) δ 1.18 (3 H, s), 1.22 (3 H, s), 1.58 (3 H, s), 2.15 (3 H, s), 2.30-2.70 (3 H, m), 3.78 (3 H, s), 4.90-5.40 (1 H, m), 6.45-6.95 (3 H, m).

(9) IR 3413, 2941, 1489, 1252, 1200, 1033, 733 cm⁻¹; 60-MHz NMR (CDCl₃) 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).

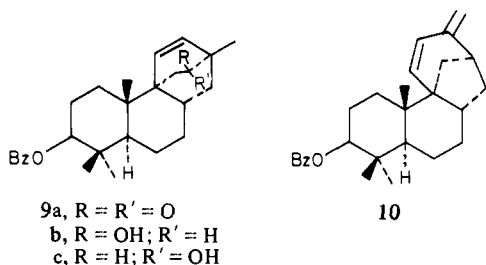
(10) IR 3450, 2940, 1670, 1605 cm⁻¹; 60-MHz NMR (CDCl₃) δ 0.87 (3 H, s), 1.03 (3 H, s), 1.08 (3 H, d, *J* = 6 Hz), 1.13 (3 H, s), 3.05-3.40 (1 H, m), 5.70-5.90 (1 H, m).

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 $90^\circ C$), involving approach from the overall less hindered β face, produced pentacycle **7**. Since the adduct was unstable, it was hydrolyzed



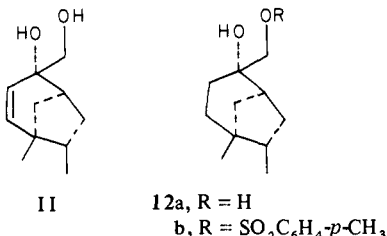
(3:2 5% aqueous KOH- $(CH_3)_2CO$ at reflux) (84% from **6b**) to the keto acid **8**,¹¹ which in the crude, amorphous state was oxidatively decarboxylated with $Pb(OAc)_4$ in O_2 -saturated pyridine at $90^\circ C$, giving (21% after SiO_2 chromatography) the unsaturated ketone **9a**¹² (mp $134-136^\circ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

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



induced a [2.2.2] \rightarrow [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 ($-10^\circ C \rightarrow$ 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 $173-176^\circ C$; 41% overall from **10**). Exposure of the latter of $TsCl$



(pyridine at $25^\circ C$) yielded monotosylate **12b** (81%) which was transformed to (\pm)-maritimidol benzyl ether through the agency of $LiHB(C_2H_5)_3$ (100 equiv in THF at $25^\circ C$, followed by $NaOH-H_2O_2$ workup). Debzylation was effected by Li in NH_3 at reflux, giving (\pm)-maritimidol (after HPLC, 60% from **12b**) (mp $212.5-214^\circ C$; 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 methodology² involves the formation of a cyclobutanone by cycloaddition of a ketone-bearing anion-stabilizing group to a derivative of cyclopentene or cyclopentadiene followed by regioselective cleavage of the strained ring with carbon nucleophiles. An alternative strategy³ 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 chloride⁴ **2a** (0.032 mol) in hexane (120 mL) containing cyclopentadiene (0.2 mol) (Scheme I). Workup and distillation yielded pure **3a** (70%, mp $68^\circ C$).⁵ The activating effect of a chlorine substituent on

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(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.