of these complexes is distorted by the relatively small size of the hydride ligand. On the basis of the Ir-P distances in **2**, **4**, and **6** and in *cis*-$IrH(CH_2OH)(PMe_3)_4^+PF_6^-$,[9b] the following trans influence order is obtained: H > CH_2OH > P > SH > OCH_3 > OH. This implies that the Ir-OH bond is the least covalent.[16] Indeed, this bond is 0.029 Å longer than Ir-OCH_3. This order is in agreement with the observed exchange reactivity of OH and unreactivity of SH toward methanol.

It is interesting to note the relatively small Ir-O-H angle of 91 (±7)° and the orientation of the OH ligand in **2**. For comparison, the Ir-S-H angle in **6** is 111 (±3)° with the SH pointing away from the hydride, and the Ir-O-CH_3 angle in **4** is 119.4 (±0.9)°. This may be a result of an interaction between the hydridic Ir-H and the OH proton, although the distance $H_1\cdots H_2$ of 2.441 Å is too large to represent a normal hydrogen bond. MO calculation aimed at clarifying the nature of this interaction are in progress, as are other studies on the reactivity and mechanism of formation of the above complexes.

Supplementary Material Available: Tables of fractional coordinates and isotropic thermal parameters, anisotropic thermal parameters, interatomic distances, intramolecular angles and intermolecular distances for compounds **2**, **4**, and **6** (15 pages); tables of structure factor amplitudes for **2**, **4**, and **6** (15 pages). Ordering information is given on any current masthead page.

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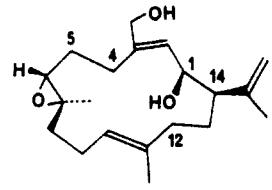

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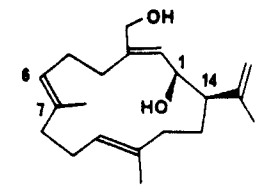

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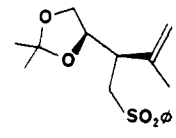

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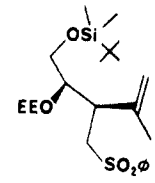

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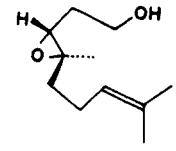

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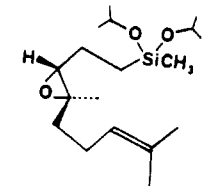

6

Total Synthesis of (-)-Asperdiol

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Received May 8, 1986

Asperdiol (**1**) is a cembranoid marine natural product which has been isolated from the extracts of Caribbean gorgonians of the *Eunicea* genus.[1] The extracts had been shown to be active in vivo against the National Cancer Institute's P-388 lymphocytic leukemia assay and several other cancer cell lines. The activity was traced to asperdiol and the structure and the absolute configuration were determined by X-ray crystallography.[1] Two total syntheses of the racemate of **1** have been described.[2] A total synthesis of (+)-desepoxyasperdiol (**2**) has been performed in our laboratory.[3] In this paper we describe the first total synthesis of (-)-asperdiol.

The presence of the C-6, C-7 epoxide in **1** made it necessary to follow an approach that differed significantly from the one used for **2**. The retrosynthetic cleavage of the macrocycle led to three fragments. The two large fragments include C-4 through C-12 and C-13 through C-2. The remaining carbon atoms, C-3 and C-20, comprise the third fragment. Each of the two large fragments included two of the asymmetric centers of the final product, therefore a convergent and enantioselective synthesis appeared possible. A synthesis of sulfone **3**, the starting point for the total synthesis, from (2*R*,3*S*)-4-benzyloxy-2,3-epoxy-1-butanol has been described.[3] It will be necessary to distinguish the two alcohol groups of **3** later in the synthesis so it is most efficient to protect them with orthogonal protecting groups at an early stage.

Acetonide exchange in dimethoxyethane-ethylene glycol was catalyzed by Amberlyst IR-120 at 45 °C for 1 h to produce the diol in 85% yield. The primary alcohol was converted to the *tert*-butyldimethylsilyl ether in 87% yield by treatment in *N*,*N*-dimethylformamide at 23 °C for 1 h with 1.2 equiv of *tert*-butyldimethylsilyl chloride and 2.5 equiv of imidazole.[4] The secondary alcohol was protected as the ethoxyethyl derivative (99% yield) by pyridinium tosylate catalyzed reaction with ethyl vinyl ether in dichloromethane. The choice of the ethoxyethyl protecting group was crucial to the success of the synthesis. This was unfortunate, because the presence of the asymmetric acetal carbon of the protecting group made the interpretation of NMR spectra tedious. The two stereocenters at C-1 and C-14 of **1** are present in **4**. The carbanion stabilizing group at C-13 allows the formation of the C-12, C-13 bond through a nucleophilic displacement reaction.

A synthesis of the C-13, C-2 fragment from homogeraniol was conceptually very simple. The asymmetric epoxidation of homoallylic alcohols according to Sharpless' conditions, however, leads to products with a modest degree of enantioselectivity.[5] Therefore an alternative approach was followed. (2*R*,3*R*)-2,3-Epoxygeraniol was prepared from geraniol.[6] The optical purity of this material was determined to be >95% by analysis of the (+)-MTPA ester.[7] The conversion of (2*R*,3*R*)-2,3-epoxygeraniol to (3*R*,4*R*)-3,4-epoxyhomogeraniol (**5**) was undertaken next. Epoxygeraniol was converted in quantitative yield to the labile mesylate by treatment with 1.2 equiv of methanesulfonyl chloride and 1.5 equiv of tri-

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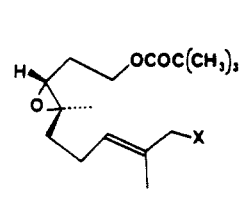
ethylamine in dichloromethane (0 °C, 15 min). The mesylate was immediately converted to the bromide by exposure for 24 h at 23 °C to 2 equiv of anhydrous lithium bromide in acetone (67% yield). Several attempts to homologate epoxygeranyl bromide failed.[8] Success was realized with (diisopropoxymethylsilyl)-methylmagnesium chloride.[9] Lithium tetrachlorocuprate[10] (0.6 mol % in tetrahydrofuran) catalyzed the coupling of the silyl Grignard reagent to form **6**. Treatment with 3 equiv of potassium hydrogen fluoride and 3.5 equiv of 30% aqueous hydrogen peroxide in *N,N*-dimethylformamide produced **5** in 52% overall yield from epoxygeranyl bromide.

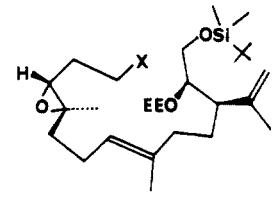
The next task was to functionalize the *E* vinyl methyl group of **5**. The alcohol was converted to the pivalate ester with 2 equiv of pivaloyl chloride in pyridine at 23 °C for 1 h (85% yield). Allylic oxidation with 5 equiv of *tert*-butyl hydroperoxide in dichloromethane at 23 °C for 24 h was catalyzed by selenium dioxide.[11]

These conditions furnished **7**, $[\alpha]_D^{22}$ +9.3° (*c* 0.17, CH_2Cl_2), in 50% yield along with 20% of recovered **6**. The conversion of **7** to allylic chloride **8** was accomplished by treatment of an ethereal solution of the allylic alcohol with an excess of carbon tetrachloride and 1.5 equiv of hexamethylphosphorus triamide for 10 min at 0 °C (79% yield.)[12]

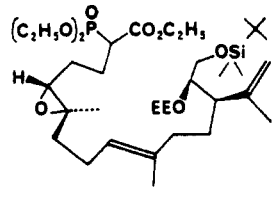
The two fragments of (−)-asperdiol were joined in 81% yield by treatment of allylic chloride **8** (1.06 equiv) with the lithio anion of sulfone **4** (1.12 equiv of *n*-butyllithium, dimethoxyethane, 20% HMPA, −78 to 0 °C, 3 h). Reductive removal of the benzenesulfonyl group from the product and simultaneous pivalate ester hydrolysis took place with 6% sodium amalgam in methanol (23 °C, 20 h) to produce **9** in 68% yield.[13] All but two of the carbon atoms of (−)-asperdiol are present in **9**. An intramolecular Horner–Emmons reaction was planned for the closure of the 14-membered ring.[3] Accordingly, carbon atoms C-3 and C-20 were introduced by converting the mesylate of **9** to iodide **10** by treatment with sodium iodide in refluxing acetone (81% yield), followed by displacement of the iodide by the sodium salt of triethylphosphonoacetate at 50 °C for 0.5 h in *N,N*-dimethylformamide in the presence of catalytic 18-crown-6 (78% yield). Phosphonate ester **11** incorporates all of the carbon atoms of **1**. Removal of the silyl protecting group with 3 equiv of tetra-*n*-butylammonium fluoride in tetrahydrofuran (95% yield) was followed by Swern oxidation (8 equiv of dimethyl sulfoxide, 10 equiv of triethylamine, 4 equiv of oxalyl chloride, −78 to 23 °C) to aldehyde **12** in 95% yield.[14] The intramolecular Horner–Emmons reaction was accomplished by treatment of a 0.003 M solution of **12** in anhydrous acetonitrile with 5 equiv of DBU and 10 equiv of lithium chloride at 23 °C for 9 h.[15] Ester **13** was obtained in 61% yield as a *single* geometrical isomer.[16] The



7 X = OH
8 X = Cl



9 X = OH
10 X = I



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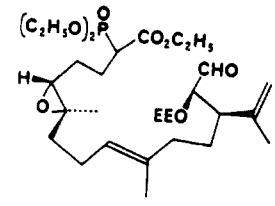

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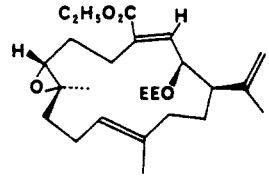

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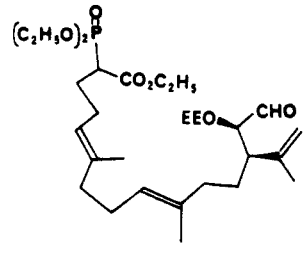
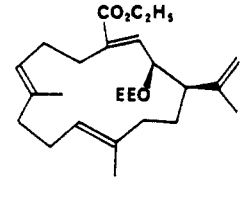


14

complete selectivity for the desired *E* isomer was unexpected because a 2:1 mixture of *E* and *Z* isomers had been obtained from the cyclization of **14**. Molecular mechanics calculations[17] indicated that the difference in the conformational energies of **13** and the C-2, C-3 *Z* isomer was the same as for **15** and the corresponding C-2, C-3 *Z* isomer, so thermodynamic control of the intramolecular Horner–Emmons reaction seems unlikely.



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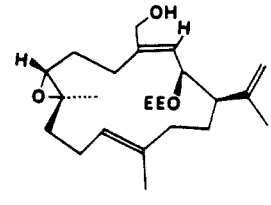

16

The synthesis of (−)-asperdiol was completed by first reducing **13** with lithium aluminum hydride in ether at −20 °C for 30 min to produce alcohol **16** in 78% yield. The hydrolysis of the ethoxyethyl group posed a problem because of the presence of the epoxide. Transannular reactions are precedented in this system.[2b] The removal of the protecting group was accomplished in 71% yield by treatment of a solution of **16** in *tert*-butyl alcohol with 1.0 equiv of pyridinium tosylate at 23 °C for 2.5 h. Synthetic (−)-asperdiol was spectroscopically identical with racemic material which was prepared by Professor W. Clark Still.[18]

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(16) The geometry of the C-2, C-3 double bond is easily determined by the chemical shift of the C-2 vinyl proton.

(17) Professor W. Clark Still's program MODEL was used to perform the NMR calculations.

The first enantioselective total synthesis of (−)-asperdiol has been accomplished in 15 steps from epoxygeranyl bromide. It is noteworthy that the trisubstituted epoxide was robust enough to survive the conditions for the nucleophilic displacement reactions which were used to form the C-12, C-13 and the C-3, C-4 bonds. The epoxide also survived the reductive desulfonylation and the intramolecular Horner–Emmons reaction. Our assumption that the cyclization to the 14-membered ring in the desepoxy series would be more straightfoward than in the epoxy series, which provided the impetus for the synthesis of (+)-desepoxyasperdiol, was shown to be false. A number of the optically pure fragments which were used for the total synthesis of **1**, particularly **4** and **7**, will be useful for the synthesis of other cembranoids.

Acknowledgment. We thank the National Institutes of Health (Grant GM-30390) for generous financial support. NSF Grant CHE 81-00240 supported the purchase of the 300-MHz NMR spectrometer. We thank Professor W. C. Still for copies of the spectra of (±)-**1** and for making a copy of the computer progam MODEL available to us.

Supplementary Material Available: Spectroscopic data for compounds **4**, **5**, **7**, **9**, **12**, and **13** and experimental procedure for the intramolecular Horner–Emmons reaction (2 pages). Ordering information is given on any current masthead page.

(18) ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.43 (d, J = 7.8 Hz, 1 H), 5.11 (t, J = 6.8 Hz, 1 H), 4.94 (br s, 1 H), 4.75 (br s, 1 H), 4.47 (dd, J = 7.7, 5.8 Hz, 1 H), 4.05 (br s, 2 H), 2.66 (dd, J = 5.9, 4.4 Hz, 1 H), 2.45–1.2 (m, 13 H), 1.74 (br s, 3 H), 1.59 (br s, 3 H), 1.17 (s, 3 H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 145.78, 139.55, 135.48, 128.76, 124.72, 113.77, 66.40, 65.87, 64.77, 60.25, 50.66, 37.55, 36.16, 28.11, 26.67, 25.94, 24.07, 22.45, 16.67, 15.86. IR (CH_2Cl_2) 3593, 3063, 2924, 1641, 1603, 1452, 1385 cm^{-1}. Mass spectrum, m/e 320 (M^+, weak) 302 ($M^+ - H_2O$), 177, 135, 108, 95, 81. Exact mass calcd for $C_{20}H_{32}O_3$ 320.2351, found 320.2357. $[\alpha]^{23}_D$ −79° (c 0.000 55, $CHCl_3$).

DNA-Mediated Photoelectron Transfer Reactions

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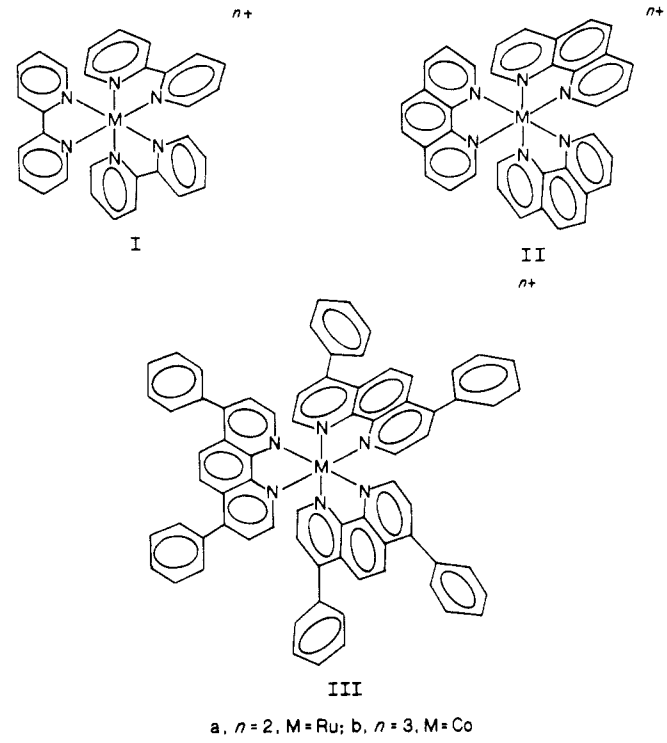
Various aspects of electron transfer involving metal centers have received intense scrutiny during the past two decades. Marcus theory[1] has provided an important theoretical framework to drive experiments.[2] Thermal and photochemical systems[3] have been developed to explore the validity of the theory and the relevance of electron transfer to biological systems.[4] For example, the efficiency of electron transfer was suggested to be attenuated by proteins, membranes, and other biological structures.[5] We report here an investigation of several donor–acceptor systems which undergo photoinduced electron transfer to examine the role of the DNA double helix in mediating electron transfer and to probe the various aspects of the DNA environment, such as local electrostatic fields, hydrophobic patches, lipophilic interactions and the dimensionality of space surrounding the double helix. A reduced dimensionality in diffusion of DNA-binding proteins was suggested as a major factor contributing to their ability to rapidly locate sequences along the DNA.[6] Another consideration of interest is whether the π-frame of the nucleic acid bases would assist the transfer of an electron across the strand in a manner similar to conductors.

The donors and acceptors employed are the polypyridyl complexes of Ru(II) and Co(III) as shown in Chart I. Several structural features prompted us to use these molecular probes, including their chirality. Binding of these complexes to DNA has been extensively studied and shows striking enantiomeric selec-

Chart I



a, n = 2, M = Ru; b, n = 3, M = Co

Table I. Electron-Transfer Rates for Various Donor–Acceptor Pairs in the Presence of DNA[a,b]

donor	acceptor	[DNA/Ru]	$K_{SV} \times 10^{-4}$, M^{-1}
$Ru(phen)_3^{2+}$	$Co(phen)_3^{3+}$	14	4.9
$Ru(phen)_3^{2+}$	$Co(phen)_3^{3+}$	18	6.0
$Ru(phen)_3^{2+}$	$Co(phen)_3^{3+}$	27	7.3
$Ru(phen)_3^{2+}$	$Co(phen)_3^{3+}$	55	8.6
$Ru(phen)_3^{2+}$	$Co(phen)_3^{3+}$	110	9.6
$Ru(bpy)_3^{2+}$	$Co(bpy)_3^{3+}$	8[c]	0.19
$Ru(bpy)_3^{2+}$	$Co(phen)_3^{3+}$	8[c]	0.35
$Ru(bpy)_3^{2+}$	$Co(DIP)_3^{3+}$	8[c]	0.83

[a] 20 mM NaCl, 110 μM calf thymus DNA, 5 mM Tris buffer, pH 7.2, typical errors are ±10%. [b] Suitable filters were placed on the excitation and emission sides to minimize any scattered and shorter wavelength light. Samples were excited at 450 nm and monitored at 600 nm. [c] These runs were made with 2 μM ruthenium, 80 μM calf thymus DNA, 50 mM NaCl, 5 mM Tris buffer, pH 7.2.

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