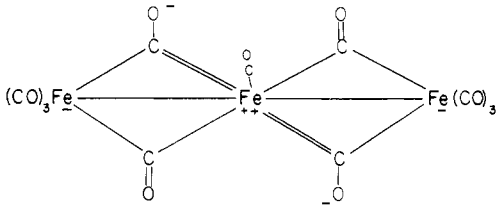
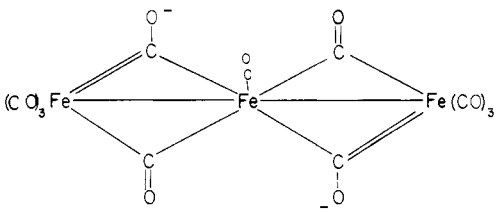
cluster might be described as an inverted umbrella, the handle being the unique carbonyl bound to Fe(1). The least-squares plane defined by the bridging carbonyl carbon atoms C(2), C(3), C(4), and C(5) is 0.36 Å below Fe(1) and above Yb(1) and Yb(2) by 0.56 and 0.48 Å, respectively. The terminal Fe(2) and Fe(3) atoms are slightly below this plane, by 0.06 and 0.02 Å, respectively.

The bonding iron–iron distances are similar to those found in the electronically equivalent (48 electron) triiron clusters $[Fe_3(CO)_9(\mu\text{-}CO)(\mu_3\text{-}CO)]^{2-}$,[4] $[Fe_3(CO)_{10}(\mu\text{-}H)(\mu\text{-}CO)]^-$,[8a] and $Fe_3(CO)_{10}(\mu\text{-}CO)_2$.[8b] The latter three clusters have their iron atoms at the corners of an isosceles triangle, the geometry usually found for trimetallic cluster molecules.[9] The geometry of the $[Fe_3(CO)_7(\mu\text{-}CO)_4]^{2-}$ cluster (Figure 2 shows the averaged bond angles and lengths within the cluster) has been greatly perturbed by the presence of the two $[Yb(C_5Me_5)_2]^+$ units, which have forced four carbonyl groups into bridging positions. The Fe(1)CO(4)-CO(5) and Fe(1)CO(2)CO(3) fragments may be viewed as metallaacetonylacetonate groups coordinated in a chelating fashion to the two ytterbium(III) centers.[10] Thus, the $Fe_3(CO)_{11}^{2-}$ cluster may be viewed, in an electronic sense, by the valence bond structures shown below (IIa and IIb), in which each of the terminal



IIa

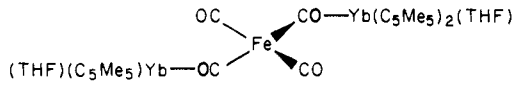


IIb

iron atoms have 18 valence electrons and the central iron atom has 16 valence electrons. These valence bond structures are only approximations to the true electronic structure, and a molecular orbital treatment will be much better. However, the valence bond representations emphasize the formal analogy to that of a metallaacetonylacetonate ligand. In order to act as a chelating ligand, the $[Fe_3(CO)_{11}]^{2-}$ distorts by breaking an Fe–Fe bond. This process does not require much energy since the Fe–Fe bond energy in $Fe_3(CO)_{12}$ is estimated to be ca. 19 kcal mol^{-1},[11] most certainly less than that of four ytterbium–oxygen bonds.

A rich reaction chemistry is suggested by the "opened" geometry of the $[Fe_3(CO)_{11}]^{2-}$ cluster. However, toluene solutions of the $[(C_5Me_5)_2Yb]_2[Fe_3(CO)_{11}]$ cluster did not react with H_2 or CO at 18 atm during a 24-period.

In order to examine reactions of the complete set of binary iron carbonyls with the ytterbium(II) metallocene, we have studied the reaction of $Fe(CO)_5$ with 2 molar equiv of $Yb(C_5Me_5)_2(OEt_2)$. The reaction gives $[Yb(C_5Me_5)_2(thf)]_2[Fe(CO)_4]$ after crystallization from tetrahydrofuran.[12] The complex gives $Fe(CO)_4(SnPh_3)_2$ upon reaction with Ph_3SnCl, as shown by infrared spectroscopy.[13] Thus, the complex may be formulated as the tetracarbonylferrate, III, analogous to the well-known sodium salt, $Na_2Fe(CO)_4$.[14]



III

Acknowledgment. This work was supported by the Director, Office of Energy Research, Office of Basic Energy Sciences, Chemical Sciences Division of the U.S. Department of Energy under contract Number W-7406-ENG-48. We also thank the NSF for a grant to the Chemistry Department used to purchase the X-ray diffractometer. We thank a referee for helpful comments.

Registry No. $[(Me_5C_5)_2Yb]_2[Fe_3(CO)_7(\mu\text{-}CO)_4]$, 80878-91-7; $[(Me_5C_5)_2Yb(thf)]_2[Fe(CO)_4]$, 80890-27-3; $Fe_2(CO)_9$, 15321-51-4; $Fe_3(CO)_{12}$, 17685-52-8; $Fe(CO)_5$, 13463-40-6; $(Me_5C_5)_2Yb(OEt_2)$, 74282-47-6.

Supplementary Material Available: A listing of thermal and positional parameters (6 pages). Ordering information is given on any current masthead page.

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(12) Anal. Calcd for $C_{52}H_{76}FeO_6Yb_2$: C, 52.1; H, 6.39. Found: C, 51.6; H, 6.42. ^{1}H NMR (THF-d_8, 26 °C) a single resonance was observed at δ 9.52 ($\nu_{1/2}$ = 144 Hz). Hydrolysis of a sample dissolved in benzene gave a mixture of Me_5C_5H and tetrahydrofuran in area ratio 2:1 by ^{1}H NMR spectroscopy; IR ν(CO) (Nujol): 2004 w, 1980 w, 1961 w, 1928 s, 1922 s, 1753 m sh, 1741 s, 1711 s, 1648 m sh, and 1608 s br cm^{-1}.
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Stereospecific Synthesis of the C30–C43 Segment of Palytoxin by Macrocyclically Controlled Remote Asymmetric Induction

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Received November 23, 1981

We recently reported that the conformational structure of macrocyclic compounds provides a unique, well-defined medium through which widely separated asymmetric centers may interact effectively.[1] This conclusion follows from the observation that simple monosubstituted macrolactones and macrocycloalkanones undergo a variety of highly stereoselective addition reactions that appear to be controlled by the conformation(s) of the macrocycle involved. Mechanistic points aside, the major value of that work lies in its implications to the synthesis of complex arrays of stereocenters on conformationally flexible molecular frameworks. In this communication, we describe our first application of the approach as a central strategy for the control of acyclic stereochemistry. Thus the lypophilic segment (**1**, R, R′ = H) of the complex marine toxin palytoxin[2] (**1**, R = $C_{29}H_{51}O_{16}N_2$, R′ = $C_{81}H_{142}O_{36}N$) was prepared stereospecifically from propylene oxide via the medium ring lactone **2** (see Figure 1).

Selection of an appropriate macrocyclic intermediate for the effective control of stereochemistry is crucial to the success of our approach to remote asymmetric induction. The requirements for such an intermediate would be simply that it be prepared easily and that it react via a conformation that will yield the desired relative stereochemistry at newly formed asymmetric centers. As described below, the evaluation of potential systems in the context of these requirements may be assisted by molecular mechanics calculations.[3] These simple calculations are quite revealing with respect to conformations and strain energies and suggest here that

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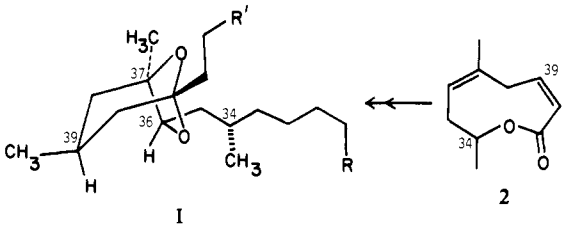

Figure 1.

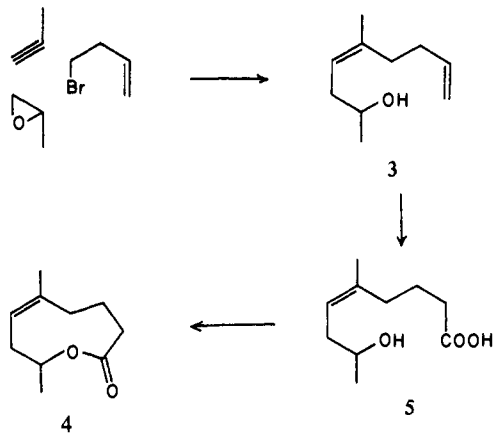

Figure 2.

the nine-membered lactone **2** could provide a valuable template for the control of the remote C39 chiral center by the single primordial chiral center at C34 (palytoxin numbering system). Remaining asymmetry at C36 and C37 could then be established with 1,3 control from C39 by an intramolecular, stereospecific addition to the *Z*-trisubstituted double bond (see Figure 2).

The carbon framework of the desired macrolactone **2** was prepared in a single step by copper-catalyzed addition of butenylmagnesium bromide to propyne followed by in situ trapping with propylene oxide[4] by using the procedure of Normant[5] and Helquist[6] (75% yield). The resulting alcohol (**3**) was protected (dihydropyran, *p*-TsOH), hydroborated (a, 9-BBN; b, NaOOH), oxidized (PDC, DMF), and deprotected (a, *p*-TsOH, MeOH; b, KOH) in 76% overall yield to the required hydroxy acid **4**. While high dilution lactonization should produce the required macrolide **5**, the poor yields (<20%) typically found for the formation of saturated nine-membered lactones might be expected to render the planned scheme impractical. In the instance of **5**, however, the presence of a *Z*-olefinic linkage could provide a substantial enthalpic, as well as entropic, benefit to the desired cyclization by the elimination of important transannular repulsions in the product. Molecular mechanics calculations using the MM2 force field[7] support this suggestion and indicate that the most stable conformation of **5** should be almost 6 kcal/mol more stable than the most stable conformation of 8-methyloctanolide itself. With use of the 2-thiopyridyl ester method of Corey,[8] the desired lactonization seems to reflect these advantages since it proceeds to give **5** (mass spectrum: M + 1, m/e = 169) in 71% isolated yield (10% diolide formation) from **4**.

In preparation for introduction of the C39 asymmetric center, lactone **2** (^{1}H NMR ($CDCl_3$) δ 6.48 (1 H, ddd, J = 3, 7, 9 Hz), 5.88 (1 H, dd, J = 2,9 Hz), 5.30 (1 H, br d, J = 7 Hz), 4.87 (1 H, m), 3.70 (1 H, dt, J = 3, 11 Hz), 2.54 (1 H, m), 2.35 (1 H, dd, J = 8, 11 Hz), 2.08 (1 H, ddd, J = 1, 3, 11 Hz), 1.67 (3 H, s), 1.38 (3 H, d, J = 6 Hz)) was prepared from **5** by enolate selenation (a, $LiNiPr_2$, THF; b, PhSeBr) and oxidation/elimination ($NaIO_4$, MeOH) (66% yield). We anticipated that the reaction of dimethylcuprate with **2** would yield the desired *cis*-dimethyl product (**6**). This expectation was based on analogy with cuprate reactions of closely related lactones as well as analysis by the computational scheme we described previously.[1] The computations[9] indicated that the most stable conformer of **2** (shown in Figure 3) and another closely related one should contribute overwhelmingly to the predominant reaction pathway and lead to the *cis*-dimethyl product. Experimentally, a single adduct was produced (92% yield) with Me_2CuLi–BF_3[10] at −78 °C as shown by capillary VPC (25 m of carbowax 20 M flexible silica capillary), 250-MHz proton NMR spectrometry ($CDCl_3$) δ 5.25 (1 H, br t, J = 8 Hz), 4.86 (1 H, m), 2.65 (1 H, dd, J = 9, 12 Hz), 2.25 (3 H, m), 1.93 (2 H, m), 1.67 (3 H, s), 1.25 (3 H, d,

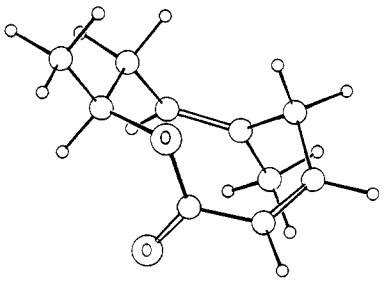

Figure 3.

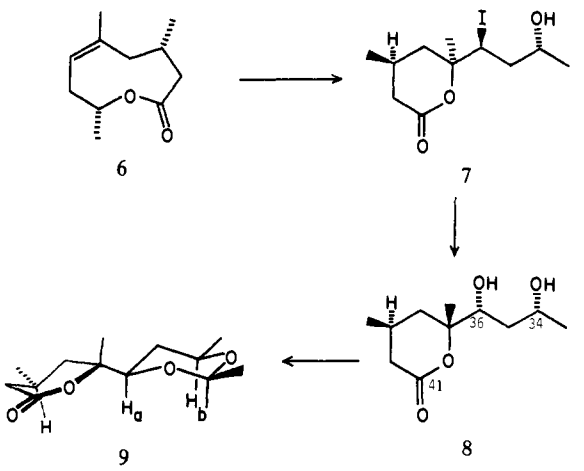

Figure 4.

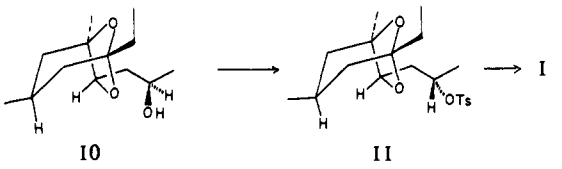

Figure 5.

(4) Both enantiomers of propylene oxide are readily available from lactic acid: B. Seuring and D. Seebach, *Helv. Chim. Acta*, **60**, 1175 (1977); L. R. Hillis and R. C. Ronald, *J. Org. Chem.*, **43**, 3348 (1981).

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(9) The low-energy conformations of lactone **2** were found by using a ring-generating computer program that exhaustively generated all possible rings having 0.5–3.5-Å closure distances and 50–170° closure angles at a resolution of 15° for each dihedral angle having a central single bond. The resulting 468 rings were subjected to MM2 strain-energy minimization and 7 unique conformations having strain energies within 5 kcal/mol of the ground state were found. The relative strain energies of these conformers were 0.0, 0.45, 0.67, 2.17, 2.66, 3.24, and 4.77 kcal/mol. Each of these conformers was then appropriately converted into the geometrically equivalent β-methyl enolate and was energy minimized again. The lowest energy form of **2** (see Figure 3 for ORTEP diagram) turned out to give the lowest form of the β-methyl enolate. Based on all of the product enolate energies and assuming exclusive peripheral cuprate addition, a Boltzmann distribution at −78 °C gave an expected cis:trans ratio of 96:4.[1]

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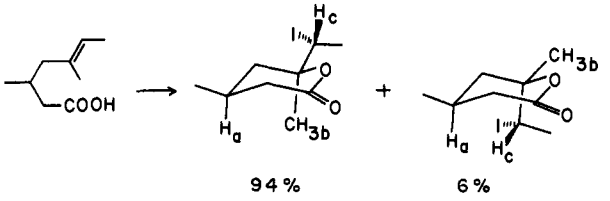

Figure 6.

J = 7 Hz), 1.07 (3 H, d, J = 7 Hz)), and ^{13}C NMR ($(CDCl_3)$ δ 20.26, 23.91, 24.63, 32.07, 36.72, 38.31, 42.29, 69.66, 121.58, 138.63, 173.44). With the C39 asymmetry effectively incorporated, saponification (KOH–MeOH–H_2O) and iodolactonization (KI_3, $NaHCO_3$, H_2O) proceeded with high 1,3-asymmetric induction to yield the equatorial iodoalkyl derivative as the only product (**7**, 82%)[11] (see Figure 4). Saponification (KOH–H_2O) and subsequent acidification (HCl–H_2O) inverted both asymmetric centers via an intermediate epoxy acid and led directly to **8** (mp 92–94 °C, 95% yield). Although the relative configuration of C34 and C36 in **9** were readily determined by ^1H NMR (H_a and H_b are axial), the remaining stereochemistry was best proven by an X-ray crystallographic analysis of **8**, which confirmed the stereochemistry shown above.[12]

Transformation to the palytoxin segment **1** (R, R′ = H) required three final operations: (1) side-chain addition at C41; (2) internal ketalization; (3) side-chain addition at C34 with retention of configuration. The first of these constructions caused some difficulty in that organometallic addition to C41 was quite sluggish and tended toward double addition. Although a completely satisfactory solution that avoids the problems of 1,3-diaxial interactions has yet to be discovered, it was found that treatment of **8** with excess EtMgBr in chloroform at −30 °C for 6 h gave a 69% yield (50% conversion) of the required ketal **10** (see Figure 5).

While our original plan for C34 side-chain addition involved a double inversion sequence in which an intermediate C34 bromide is displaced by an alkylcuprate, the required bromide (from tribromoimidazole, Ph_3P;[13] 96%) turned out to be unreactive under a variety of conditions with dibutylcuprate. In examining other potential leaving groups, it was found that the tosylate of **10** gave acceptable coupling with Bu_2CuLi in Et_2O (−20 °C). Our final problem then became to prepare the tosylate **11** by inversion at C34. While this could be accomplished along known lines ((1) PhCOOH, Ph_3P, DEAD;[14] (2) KOH–H_2O; (3) TsCl, C_5H_5N; 50% overall yield), a more concise route was found that used lithium tosylate with triphenylphosphine/diethylazodicarboxylate in THF and led directly to **11** in 52% yield. This reaction presumably proceeded by a process similar to that of the Mitsunobu alcohol inversion.[14] It is anticipated that improvements in the procedure will lead to increased product yields in this potentially useful reaction. Final conversion to **1** was effected as outlined above in 47% yield with the balance of the material being isolated as elimination products.[15]

Registry No. 1 (R = R′ = H), 80764-92-7; **2**, 80764-93-8; **3**, 80764-94-9; **4**, 80764-95-0; **5**, 80764-96-1; **6**, 80764-97-2; **7**, 80764-98-3; **8**, 80764-99-4; **9**, 80765-00-0; **10**, 80765-01-1; tosylate **10**, 80765-02-2; tosylate **11**, 80795-31-9; propylene oxide, 75-56-9; butenyl bromide, 5162-44-7; propyne, 74-99-7.

(11) Similar 1,3-asymmetric induction was observed previously by Kenneth R. Shaw with the related olefinic acid shown in Figure 6. The stereochemistry of the cyclization followed from NOE studies on the major product which showed a 12–15% enhancement of CH_{3b} on irradiation of H_a. Corresponding irradiation of the minor product showed a comparable enhancement of H_c.

(12) We thank Drs. J. P. Springer and E. H. Cordes at Merck, Sharp & Dohme Research Laboratories, Rahway, NJ, for their assistance in conducting the X-ray crystallographic analysis of **8**.

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Biomimetic Synthesis of Dibromophakellin

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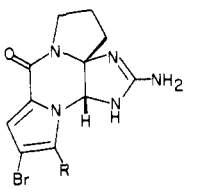
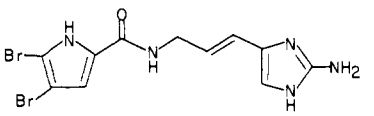
Received November 30, 1981

Marine rather than terrestrial organisms produce a structurally broad spectrum of intriguing metabolites containing guanidine units. Among these, tetrodotoxin, saxitoxin, cypridina luciferin, and the zoanthoxanthins received most attention in the past.[1] The two phakellins **1** and **2**,[2,3] isolated from *Phakellia flabellata*, a



1 R = Br
2 R = H



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sponge, and oroidin (**3**),[4] from *Agelas oroides*, another sponge, belong to a more recently discovered group of marine products containing both bromopyrrole and guanidine substituents. The structure of dibromophakellin (**1**), confirmed by X-ray analysis[2] of its acetate, is noteworthy because despite the presence of both aminoacetal and diaminoketal functionalities the substance exhibits considerable stability toward hydrolytic agents. Oroidin (**3**) and dibromophakellin (**1**) are isomers and are undoubtedly biogenetically related.[5] Neither metabolite has been synthesized, but rather than synthesize oroidin (**3**) and attempt isomerization to dibromophakellin (**1**), we decided to investigate the oxidative cyclization of dihydrooroidin (**9**) (see Chart I) and the brominative cyclization of the halogen-free compound **11**, processes that we hoped to be related to the biosynthesis of the metabolites.

The initial phase of the synthesis was concerned with the preparation of dihydrooroidin (**9**). Commercially available L-(+)-citrulline (**4**) was converted to its ethyl ester **5** with ethanolic hydrogen chloride. Reduction of **5** with sodium amalgam under strict pH control was followed by condensation of the crude aldehyde with cyanamide at pH 4.5. Cyclization with 15% aqueous hydrochloric acid gave 2-amino-4(5)-(3-ureidopropyl)imidazole (**6**) purified as the picrate, mp 203–206 °C dec (73% overall yield).[6] The corresponding hydrochloride (97%), mp 130–142 °C dec, was hydrolyzed with 4 N NaOH (reflux, 8 h)[7] to the hydroscopic amine **7**, best stored in the form of its crystalline dihydrochloride, mp 215–217 °C dec (yield >70%). Acylation was accomplished by condensation with **8**[8] in dimethylformamide in the presence of 3 equiv of sodium carbonate (20 °C, 4–5 h). Dihydrooroidin **9** (free base) [mp 118–121 °C (from methanol), UV max (CH_3OH) 274 nm (ϵ 13 400); IR (Nujol) 1685, 1625, 1590, 1525 cm^{-1}; NMR (Me_2SO-d_6) δ 1.69 (quin, 2, J = 7.5 Hz), 2.34 (t, 2, J = 7.5 Hz), 3.25 (m, 2), 6.24 (s, 1), 6.83 (s, 1), 8.04 (t, 1, J = 4.5 Hz, exch), 5.5 (br, 1, exch), 7.0 (br, 4, exch)] was

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