CH=NBu) (II)[10] and that compound II can also be formed by using H_2O as a source of hydrogen in a reaction analogous to the WGS reaction (reaction 9). Reaction 9 is proposed to occur

$$RhOEP(H) + BuNC \rightarrow RhOEP(CH{=}NBu) \quad (8)$$

$$(RhOEP)_2 + H_2O + 3BuNC \rightarrow 2RhOEP(CH{=}NBu) + BuNCO \quad (9)$$

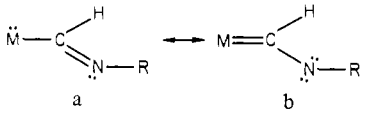
through an intermediate analogous to the metallocarboxylic acid in the WGS reaction. The RhOEP(H) produced in reactions

$$(RhOEP)_2 + BuNC + H_2O \rightarrow RhOEP(C(OH){=}NBu) + RhOEP(H) \quad (10)$$

$$RhOEPnC(OH){=}NBu) \rightarrow RhOEP(H) + BuNCO \quad (11)$$

10 and 11 subsequently reacts with BuNC to produce the formimidoyl complex II by reaction 8.

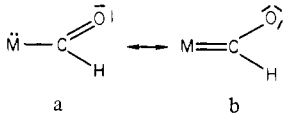
The C–N stretching frequency for RhOEP(CH=NBu) (ν_{CN} = 1624 cm^{-1}) is similar to that of $(\eta^5\text{-}C_5Me_5)_2Zr(H)(CH{=}NCH_3)$ (ν_{CN} = 1617)[9] and organic analogues ($\nu_{CN} \sim 1625$) but is substantially higher than values reported for metalloformimidoyls ($\nu_{C=N}$ = 1550–1580 cm^{-1})[6-8] where back-π-bonding (resonance structure b) is expected to be more important. Similarly, the



a b

ν_{CO} value of 1700 cm^{-1} for RhOEP(CHO) is higher than for any previously reported metalloformyl (ν_{CO} = 1570–1640).[11]

Prior to this report, $\eta^5\text{-}C_5H_5Re(Ph_3P)(NO)(CHO)$ was the only metalloformyl to be structurally characterized.[12] A relatively short Re–C distance (2.055 Å), the C–O bond distance of 1.22 Å, and a ν_{CO} of 1558 cm^{-1} indicate the importance of back-π-bonding (resonance structure b) in this complex. RhOEP(CHO)



a b

has a much shorter C–O distance (1.175 Å) and higher ν_{CO} (1700 cm^{-1}), suggesting that the $Rh^{III}OEP$ unit may be relatively ineffective in back-π-bonding with the formyl group. RhOEP(CHO) is more like an organic aldehyde (resonance structure a) than previously reported metalloformyls, and this may be expected to produce different patterns of formyl group reactivity. The short Rh–C distance of 1.869 (6) Å in I compared to 2.031 (6) Å in $RhOEP(CH_3)$[13] is partially attributed to the differences in carbon hybridization.

The ability of rhodium octaethylporphyrin dimer to activate and transfer hydrogen to carbon monoxide indicates relevance to Fischer–Tropsch chemistry. We are presently studying the reactivity patterns of the coordinated formyl group in I, including hydrogen reduction, and evaluating the conditions required to establish a catalytic cycle. RhOEP(H) is the first of a potential large class of metallomacrocycles that could produce related chemistry. Mechanistic studies of reaction 1 and a survey of carbon monoxide reactivity with metallomacrocycle hydrides are expected to reveal the generality of formyl complex formation with metallomacrocycles and establish criteria for stabilizing the coordinated formyl unit. We presently believe that the rigid macrocycle, relatively high metal oxidation state [Rh(III)], and the normal covalent bond forming ability of rhodium(II) all contribute to stabilizing the metalloformyl unit in RhOEP(CHO).

Acknowledgment. This work was supported by the donors of the Petroleum Research Fund, administered by the American Chemical Society (Grant 5-22799), and NSF MRL Grant DMR-7923647.

Registry No. I, 79666-16-3; II, 80010-78-2; CO, 630-08-0; RhOEP(H), 63372-77-0; $(RhOEP)_2$, 63439-10-1; BuNC, 2769-64-4.

(10) Reactions 8 and 9 are virtually quantitative when carried out in sealed NMR tubes using C_6D_6 as the solvent and fivefold excesses of BuNC and H_2O. Rh(CH=NBu) can be isolated as an air-stable crystalline solid by removing the solvent under vacuum. RhOEP(—CH=NBu): IR (Nujol mull) $\nu_{C=N}$ = 1624 cm^{-1}; ^1H NMR (C_6D_6) δ -2.48 (—CH=NBu, $J(CH{=}NCH_2)$ = 6.0 Hz), $\delta_{CH=NCH_2-}$ 0.36; Porphyrin resonances $\delta_{C\text{-}H}$ = 10.42, δ_{CH_2} = 4.11, δ_{CH_3} 2.06.

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A Formal Total Synthesis of Fusidic Acid[1]

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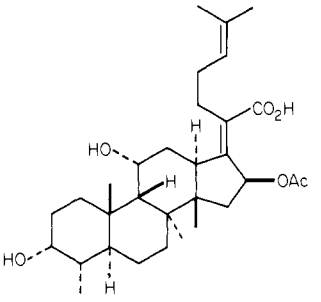
Of the many tetracyclic triterpenes of the dammarane series, fusidic acid (**1**) is the most potent antibiotic, and it possesses the broadest spectrum of biological activity.[3] Since it was first reported in 1962,[4] the clinical importance of **1** has been established,[5] and a wealth of knowledge has been accumulated in regard to its chemical modification and degradation.[3] We now report the formal total synthetic of fusidic acid.



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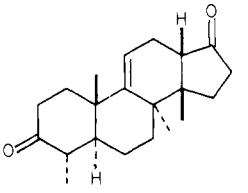

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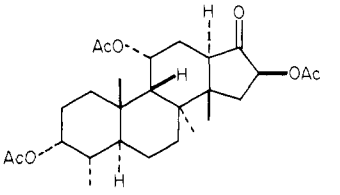

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(1) This research was supported by Grant CA 64284, National Cancer Institute, and Grant GM 27320, National Institute of General Medical Sciences, U. S. Public Health Service.

(2) National Research Service Award, 1979–1981, National Institute of Allergy and Infectious Diseases.

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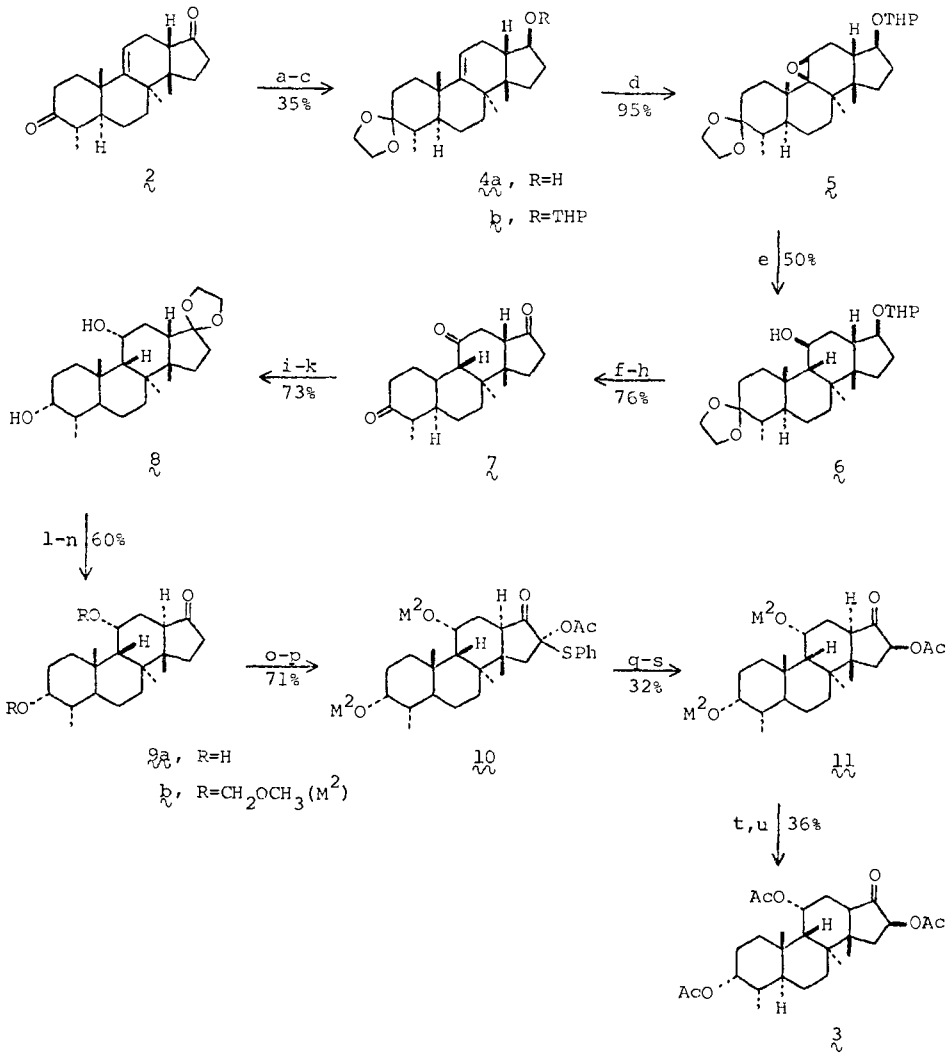
Scheme I[a]



[a] (a) $HOCH_2CH_2OH$, TsOH. (b) $LiAlH_4$. (c) DHP, TsOH. (d) MCPBA. (e) Li, $H_2NCH_2CH_2NH_2$. (f) CrO_3, pyridine. (g) 80% aqueous AcOH. (h) CrO_3, HOAc. (i) H_2, PtO_2. (j) $HOCH_2CH_2OH$, TsOH. (k) $LiAlH_4$. (l) 80% aqueous AcOH. (m) NaOH. (n) $CH_3OCH_2NEt_3^+Cl^-$. (o) LDA, $(PhS)_2$. (p) $Pb(OAc)_4$. (q) MCPBA. (r) Δ. (s) H_2, Pd/C. (t) CF_3CO_2H. (u) Ac_2O, AcOH, TsOH.

Among studies directed toward the total synthesis of fusidic acid,[6] a synthesis of diketone **2**, in racemic form, which possesses the basic tetracyclic skeleton of **1** has been reported from this laboratory.[7] Subsequently, the elaboration of ketone **3**, a degradation product of **1**,[8] to fusidic acid has been achieved.[9] In order to complete the formal total synthesis of **1**, our objective was the conversion of **2** to **3**. This conversion is outlined in Scheme I.

Ketalization of **2**[10] gave the C-3 monoketal which was reduced with $LiAlH_4$, and the major product **4a** (mp 162–164 °C)[11,12] was assigned the 17β configuration on the basis of NMR and chemical correlation studies. The alcohol was converted to the tetrahydropyranyl ether **4b**; the overall yield for these three steps was 35%. In order to introduce the 9β-H and the 11α-OH structural features in one step, the reductive opening of the 9α,11α-epoxide in the natural 13α-H series was studied, and it was found that this process yielded only the 9α-H product, a result due to protonation stable ring system. To hinder attack on the α face by use of steric congestion, the 9β,11β-epoxide **5**[11,12] in the unnatural 13β-H series was prepared. Treatment of **5** with lithium in ethylenediamine (45 °C) gave 50% of the 9β-H derivative **6**[11,12] and 30% of the related 9α-H isomer. This result confirmed our expectation related to the utility of the unnatural 13β-H series for this transformation.

Oxidation of **6** with Collins reagent gave the C-11 ketone derivative from which the protecting groups were removed to give the 17β-hydroxy-3,11-dione (mp 158–159 °C).[11,13] This material upon oxidation with chromium trioxide in acetic acid gave the known triketone **7**.[4] Regio- and stereoselective reduction of the carbonyl groups at C-3 and C-11 was accomplished in the following manner. Hydrogenation of **7** over PtO_2 gave the known 3α-alcohol[8a] which was treated with ethylene glycol to give the C-17 monoketal (mp 147–148 °C).[11,12] Reduction of this latter material with $LiAlH_4$ gave diol **8** (mp 183–184 °C).[11,12] Again, the configuration at C-13 presumably controls the stereochemistry of the reduction at C-11 by steric congestion of the α face, making

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(10) Compound **2** represents a relay intermediate in the synthesis. The compound used in this present work has been obtained by degradation of fusidic acid,[8] and therefore, all subsequent compounds are in the optically active series. The synthetic **2**[7] has not been resolved.

(11) ^1H NMR and IR spectra are in accord with assigned structure.

(12) Molecular formula established by elemental analysis.

(13) Molecular formula established by high-resolution mass spectrometry.

attack from the β face favored.

The 13β-H configuration having served its function was inverted to the more stable, natural 13α-H configuration. In the 11-deoxy series, the 13α configuration is only slightly favored (60%),[8] but in the present case, the introduction of the 11α-hydroxy group introduces yet another unfavorable 1,3-diaxial interaction to the 13β-H configuration, and thus, a greater preponderance of the 13α-H material was expected.[14] Diol ketal **8** was hydrolyzed in 80% aqueous acetic acid followed by epimerization of the resulting ketone with aqueous NaOH. A 5:1 mixture of the 13α-H/13β-H ketones was obtained, and pure **9a** (mp 201–202 °C)[11,12,15] was isolated in 67% overall yield from **8**. The diolone **9a** was methoxymethylated to **9b** (mp 90–91 °C) in 89% yield by using (methoxymethyl)triethylammonium chloride[16] in refluxing chloroform; other methods bring about loss of stereochemical purity at C-13.

Completion of the synthesis now required only the introduction of the 16β-acetoxy group and manipulation of protecting groups. Extensive investigation indicated that chemistry at C-16 in **9b** occurs predominantly from the α face and that, once obtained, a 16α functionality could not be successfully inverted. Our strategy thus became to use the α-face selectivity in this series by introducing the oxygen functionality at C-16 *first*, followed by introduction of the C-16 hydrogen. A variety of methods for accomplishing this conversion can be conceived; however, the hydrogenation of Δ^{15}-enol acetate[15,16] seemed particularly appropriate for this system. Trost and co-workers have developed a facile conversion of ketones to α-acetoxy enones,[17] and this chemistry became the key to the completion of the synthesis.

Phenylsulfenylation[17a] of **9b** gave the 16-(phenylthio)ketone[11,13] in 76% yield as a mixture of isomers at C-16, and treatment of this mixture with lead tetraacetate[17b,c] gave **10**[11,12] as predominantly only isomer in 93% yield. Oxidation of **10** to the C-16 sulfoxide was troublesome; however, treatment with MCPBA and pyrolysis of the resulting sulfoxide gave a 32% yield of acetoxy enone which could be hydrogenated in quantitative yield to give **11**[11,13] with none of the 16α-acetoxy compound detectable. Removal of the methoxymethyl protecting groups (4:1:1 CF_3CO_2H–H_2O–THF) gave the 16β-acetoxy-3,11-diol in 57% yield which was identical by NMR, IR, and TLC with material obtained by ozonolysis of dihydrofusidic acid. The diol was converted to the triacetate **3** with Ac_2O/AcOH/TsOH in 63% yield to complete the formal total synthesis of fusidic acid.

A fundamental feature of this synthesis is the use of the shape of the molecule by control of the stereochemistry at centers C-9, C-11, and C-13 to guide reactions to the α or the β face of the molecule.

Acknowledgment. We are greatly indebted to Dr. W. O. Godtfredsen of Leo Pharmaceutical Products, Copenhagen, for the generous supply of fusidic acid which made this study possible.

Registry No. 1, 6990-06-3; **2**, 14253-81-7; **3**, 14185-98-9; **4a**, 79970-95-9; **4b**, 79970-96-0; **5**, 79970-97-1; 9b-**6**, 79970-98-2; 9α-**6**, 80008-82-8; **7**, 5609-46-1; **8**, 79970-99-3; 13α-**9a**, 80008-83-9; 13β-**9a**, 80008-84-0; **9b**, 79971-00-9; 16α-(phenylthio)-**9b**, 79971-01-0; 16β-(phenylthio)-**9b**, 79971-02-1; **10**, 79971-03-2; **11**, 79971-04-3; **11** acetoxyenone, 79971-05-4; 17β-hydroxy-**7**, 80008-85-1; **8** 11-ketone, 79971-06-5; **11** (M^2 = H), 14424-42-1.

(14) This concept has been discussed earlier by Godtfredsen[4b] and on a related compound showed that after simple passage through a column of basic alumina a 1:1 mixture was obtained.

(15) R. Bucourt and M. Legrand (*C. R. Hebd. Seances Acad. Sci.* **1964**, *258*, 3491) have reported a mp of 223 °C for this compound. Their work has been repeated, and the material we obtained was identical in physical and spectral properties with the compound reported in this present study.

(16) The reagent was prepared in analogy to the use by Corey of (methoxyethoxymethyl)triethylammonium chloride for the attachment of MEM groups under mild condition (*Tetrahedron Lett.* **1976**, 809). Subsequently, Teisseire (*Tetrahedron Lett.* **1980**, 2051) also reported the use of the same methodymethyl salt.

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Structural Effects on the Photopolymerization of Bilayer Membranes

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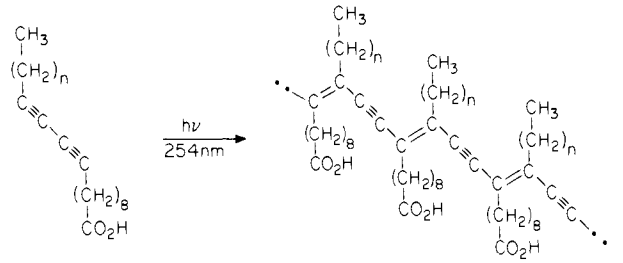
Received September 8, 1981

The conformational preference of phosphatidylethanolamines and phosphatidylcholines in bimolecular-layer membranes has been determined by low-angle X-ray diffraction[1] and NMR[2,3] data. In this conformation the glycerol backbone is approximately perpendicular to the plane of the bilayer, and the two fatty acid chains extend unequal distances into the bilayer membrane. In contrast, synthetic bilayer-forming surfactant molecules such as dialkyl dimethylammonium salts, reported by Kunitake and his colleagues,[4] have planes of symmetry which suggest that both chains will penetrate equally into the bilayer membrane.

We wish to report studies on molecules analogous to both the biological and synthetic lipids which contain conjugated diacetylene moieties in the long alkyl chains. These lipid diacetylenes form bilayer structures when suspended in aqueous buffers. The formation of vesicles in sonicated samples has been demonstrated by electron microscopy.[6,7] The ultraviolet-light-initiated polymerization of the diacetylenes in these hydrated lipid bilayers has been described.[5-7] The bilayer structure is retained after polymerization (Figure 1).[6,7] Our studies now demonstrate remarkable differences in photosensitivity which are interpretable in terms of the expected conformational preference of the molecules.



We have prepared samples of lipid diacetylenes based on phosphatidylcholine (**1**),[7] a dialkyl dimethylammonium salt (**2**),[8] and a dialkylphosphate (**3**).[8] The photosensitivity of each membrane was evaluated under conditions of maximum sensitivity,

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(8) Compound **2** was prepared by the reaction of the acid chloride of 10,12-tricosadiynoic acid with bis(2-hydroxyethyl)dimethylammonium chloride using 4-(dimethylamino)pyridine as catalyst. The product was purified by gel permeation and silicic acid chromatography followed by recrystallization from acetone: NMR ($CDCl_3$) δ 0.9 (t, 6 H, CH_3C), 1.4 (br s, 56 H, CH_2), 2.2 (m, 12 H, CH_2CO, $CH_2C{\equiv}$), 3.5 (s, 6 H, CH_3N), 4.2 and 4.6 (m, each 4 H, CH_2O and CH_2N); IR (CCl_4) 1737 and 1260 (CO_2R), 2300, 2400 (w, C≡C) cm^{-1}. Compound **3** was prepared from 10,12-tricosadiyn-1-ol and phosphoryl chloride by a method similar to that of Kunitake et al.[4c] The crude crystalline material was recrystallized from hexane at 0 °C: NMR ($CDCl_3$) δ 0.9 (*t*, 6 H, CH_3), 1.3 (br s, 50 H, CH_2), 2.2 (br t, 8 H, $CH_2C{\equiv}$), 3.7 (br s, 4 H, CH_2O); IR (film) 3400 (br, w, OH), 1230 (P(=O)OH) cm^{-1}.

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