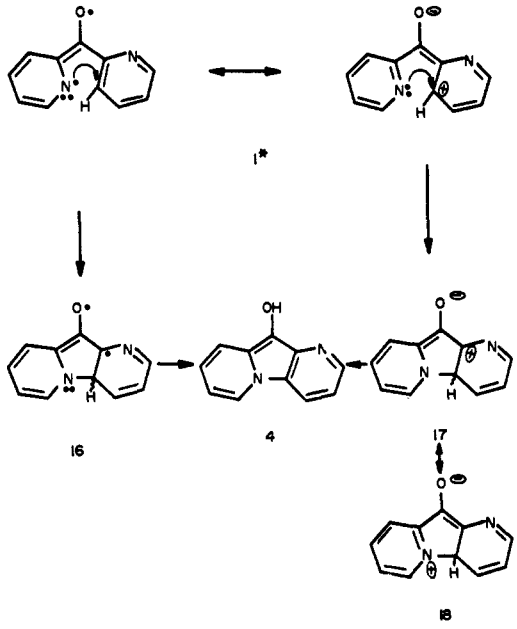
Scheme III



tures of the n–π^* excited state, namely the radical or dipolar form. The electronic distribution of the resonance forms of the excited state could conceivably produce species **16** from the radical or **17** from the dipolar structure of **1**[29b] on the reaction path to final product **4** (Scheme III). The same is proposed for **9–11**. Similar intermediates, as the zwitterion **17**, along reaction paths have been suggested and reported by Clark, *et al.*,[30] for the photocyclization of anilinopyridines to carbolines and by Linschitz and his coworkers,[31] who discussed the mechanism of oxidative photocyclization of diphenylamine to carbazole.

A considerable body of information concerning the photochemical reactions of conjugated unsaturated ketones can be rationalized on the basis of a positive charge being developed on the carbon atom β to the carbonyl group in the product-controlling state.[32] This would support the dipolar formulation for the excited state of **1**,[29b] presumably the lowest n–π^* triplet, which leads to the zwitterion **18**, a resonance form of **17**, and subsequent prototropism to **4**. Further details and related experiments will be published later.

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(33) From work done in partial fulfillment of requirements for the Ph.D. degree at The George Washington University.

Charles R. Hurt[33]
Goddard Space Flight Center, NASA
Greenbelt, Maryland 20771

Nicolae Filipescu*
Department of Chemistry, The George Washington University
Washington, D. C. 20007

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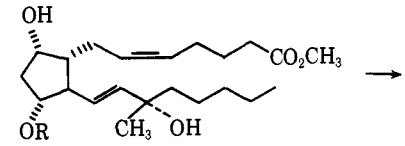
(15*S*)-15-Methylprostaglandins

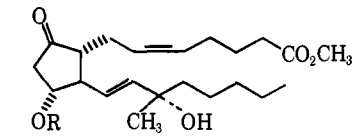
Sir:

Following studies designed to determine whether prostaglandins inert to the action of the enzyme 15-hydroxyprostaglandin dehydrogenase[1] might yet retain biological activity, we reported the preparation of several 15-methylprostaglandins and initial bioassay results.[2] We report now the preparation of (15*S*)-15-methylprostaglandin E_2, methyl ester (15-methyl PGE_2, methyl ester (**4**)). This substance and its precursor, (15*S*)-15-methylprostaglandin $F_{2\alpha}$, methyl ester (15-methyl $PGF_{2\alpha}$, methyl ester (**1**)), are the most potent prostaglandins reported to date.

Selective silylation of 15-methyl $PGF_{2\alpha}$, methyl ester (**1**),[2,3] mp 55–56° (ether–hexane), $[\alpha]D$ +26° (*c*



1, R = H
2, R = trimethylsilyl (TMS)



3, R = TMS
4, R = H

1.00, 95% ethanol) at C-11 was accomplished using an excess of trimethylsilyldiethylamine[4] in acetone at −45°. The resulting monotrimethylsilyl derivative **2**,[3] mp 33–35° (hexane), was oxidized with Collins reagent[5,6] to give ketone **3** which, without purification, was treated with aqueous methanol containing a trace of acetic acid. This process gave, after silica gel chromatography using mixtures of ethyl acetate and Skellysolve B, 15-methyl PGE_2, methyl ester (**4**)[3] as an oil, $[\alpha]D$ −72° (*c* 1.53, chloroform) in 45% yield from **1**.

The (*S*) configurational assignment of C-15 in **1**, originally based on relative tlc mobilities and biological activities in a wide assortment of prostaglandin C-15 epimeric pairs,[2] was confirmed by an X-ray crystallographic determination[7] of the iodophenacyl ester of 15-methyl $PGF_{2\alpha}$.

Neither 15-methyl $PGF_{2\alpha}$, methyl ester (**1**) nor 15-methyl PGE_2, methyl ester (**4**) (nor the corresponding free acids[2]) was a substrate for pig-lung 15-hydroxyprostaglandin dehydrogenase.[8] Methyl esters of $PGF_{2\alpha}$ and 15-methyl $PGF_{2\alpha}$ have similar potencies *in vitro* on the gerbil colon and *in vivo*, given intravenously, on

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the blood pressure of the rat.[8] Duration of action of the 15-methylprostaglandin was significantly longer in the latter test.[8,9] Similarly, the methyl esters of PGE_2 and 15-methyl PGE_2 have approximately equal potency as stimulants of gerbil colon *in vitro* and, *in vivo*, both were vasodepressors in the anesthetized rat, given intravenously.[8] At low doses, duration of the vasodepressor effect was longer for the 15-methyl analog than for PGE_2, methyl ester.[8] Finally, based on *in vivo* experiments using the pregnant uterus as an end point, both 15-methyl $PGF_{2\alpha}$ and 15-methyl PGE_2 methyl esters appear to be at least five–ten times the activity of the respective parent prostaglandins in the monkey[10,11] and up to several hundred times more potent in man.[12,13] These observations indicate that for the methyl esters of $PGF_{2\alpha}$ and PGE_2, the introduction of a 15-methyl group interferes with inactivation by 15-hydroxyprostaglandin dehydrogenase, results in a slower overall rate of metabolism, and increases apparent potency.[11–13]

Acknowledgments. The authors gratefully acknowledge discussions with Professors S. Bergstrom and B. Samuelsson, as well as the technical assistance of J. M. Baldwin.

(9) Duration of vasodepressor activity was determined near the middle of the dose–response range.[8]

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E. W. Yankee,* G. L. Bundy
The Upjohn Company
Kalamazoo, Michigan 49001
Received December 27, 1971

Studies on the Total Synthesis of Steroidal Antibiotics. I. An Efficient, Stereoselective Method for the Formation of *trans-syn-trans*-Perhydrophenanthrene Derivatives[1]

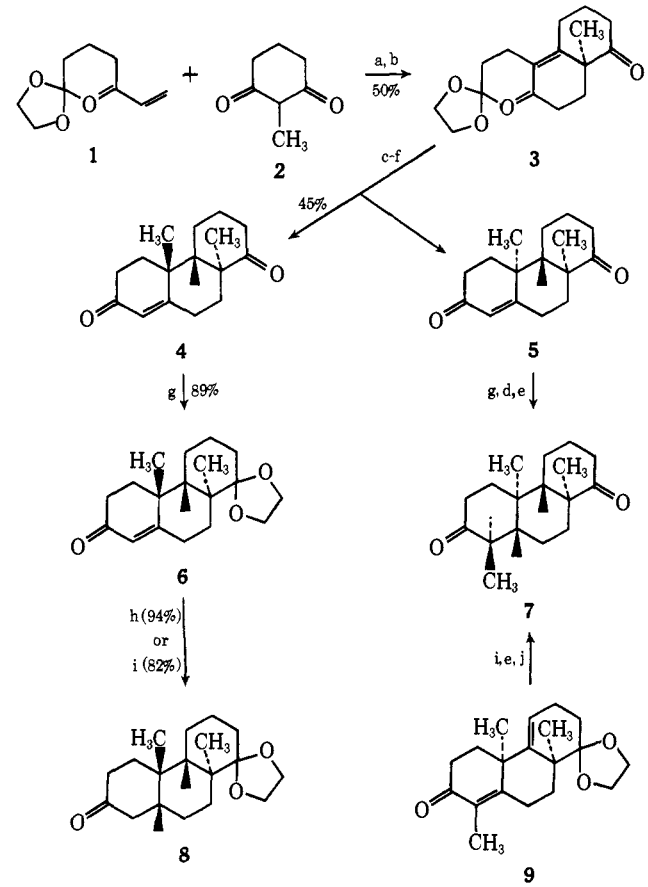
Sir:

From a synthetic standpoint one of the more challenging aspects of the structure of the steroidal antibiotics, such as fusidic[2a] and helvolic acids,[2b] is the trans-syn-trans configuration of the portion that makes up the A, B, and C rings of the tetracyclic system. This arrangement constrains the B ring in a boat conformation and thus severely circumscribes the applicable synthetic sequences. We report here an investigation of this problem that has led to the development of an efficient and potentially general reaction sequence for the stereoselective construction of tricyclic models related to the ABC ring system of these antibiotics.

To define more clearly the stereochemical limitations of well used synthetic methods as well as focus on model compounds of some possible utility for the fusidic acid synthesis itself, we chose the syn-trans enedione **4** as the key substrate (Chart I[3]). Crucial to the synthesis of this enedione **4** was the reductive methylation[4] of the α,β-unsaturated ketone **3** which resulted in the formation of two isomeric trans-fused ketones in a ratio of 6:1. The predominate isomer was converted to the desired enedione **4**, and the same procedure converted the minor isomer to the enedione **5**. This minor component served to establish the stereochemical outcome of the sequence through its conversion to the saturated dione **7**, which was also available from the ketone ketal **9** of established stereochemistry.[5]

Some precedence[6] suggested that metal–ammonia reduction of the enone system in a syn-trans molecule such as **4** might lead to the desired trans-syn-trans system, and, before investigating more devious procedures, we pursued this approach. However, a single saturated ketone ketal **8** was obtained in high yield from the lithium or potassium–ammonia reduction of the ketone ketal **6**, and this material was identical[3] with the ketone ketal obtained in virtually quantitative yield through catalytic hydrogenation of the same substrate. Molecular models of the ketone ketal **6** reveal the boat conformation of the B ring of this

Chart I. Synthesis of Syn-Trans Enedione **4** and Derivatives[a]



[a] a, NEt_3, CH_3OH; b, C_4H_9N, KOH, $C_6H_5CH_3$, Δ; c, $(CH_2OH)_2$, *n*-C_6H_{14}, *p*-TsOH, Δ; d, Li, NH_3, THF; CH_3I; e, H_3O^+; f, KOH, EtOH, Δ; g, $(CH_2OH)_2$, *n*-C_5H_{12}–CH_2Cl_2, *p*-TsOH; h, H_2, Pd/C, EtOH; i, K(Li), NH_3, THF; EtOH; $CrO_3 \cdot Py_2$, CH_2Cl_2; j, H_2, Pd/C, HOAc, 8 *N* H_2CrO_4, acetone. See ref 3.

(1) This investigation was supported by Public Health Service Research Grant AM 14160 from the National Institute of Arthritis and Metabolic Diseases.

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