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]

(10) K. T. Kirton, G. Duncan, T. Oesterling, and A. Forbes, *Ann. N. Y. Acad. Sci.*, **180**, 445 (1971).

(11) K. T. Kirton and A. D, Forbes, *Prostaglandins*, in press.

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(13) M. Bygdeman, *et al.*, *Lancet*, submitted for publication.

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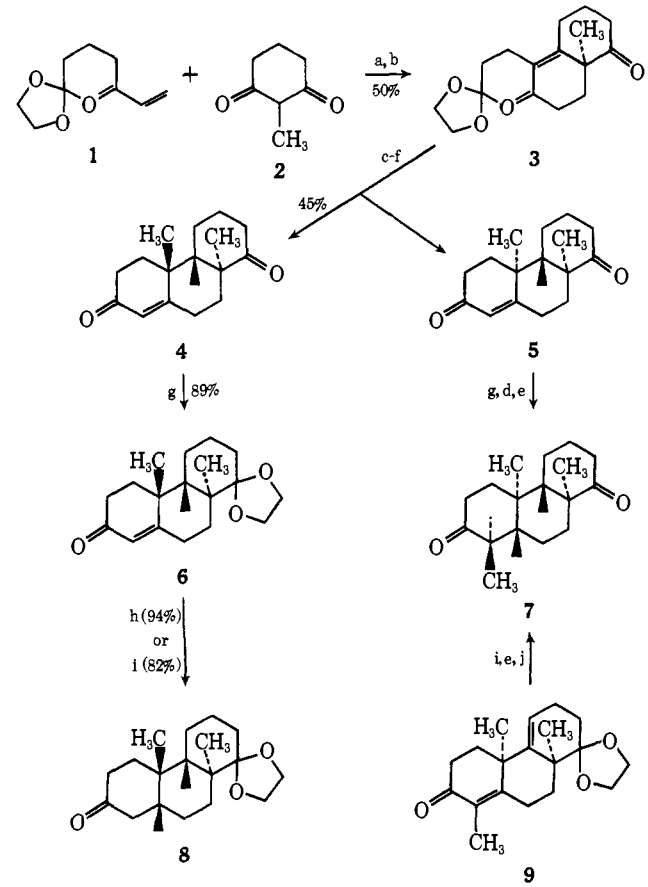
Studies on the Total Synthesis of Steroidal Antibiotics. I. An Efficient, Stereoselective Method for the Formation of *trans-syn-trans*-Perhydrophenanthrene Derivatives[1]

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]

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.

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

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

(2) (a) W. O. Godtfredsen, W. von Daehne, S. Vangedal, A. Marquet, D. Arigoni, and A. Melera, *Tetrahedron*, **21**, 3505 (1965); (b) S. Iwasaki, M. I. Sair, H. Igarashi, and S. Okuda, *Chem. Commun.*, 1119 (1970).

(3) All new compounds were characterized by ir and nmr spectra and had satisfactory (±0.2%) combustion analyses. Sample identities were determined by mixture melting point and spectral (ir, nmr) and chromatographic (tlc, glpc) comparison.

(4) G. Stork, P. Rosen, N. Goldman, R. V. Coombs, and J. Tsuji, *J. Amer. Chem. Soc.*, **87**, 275 (1965).

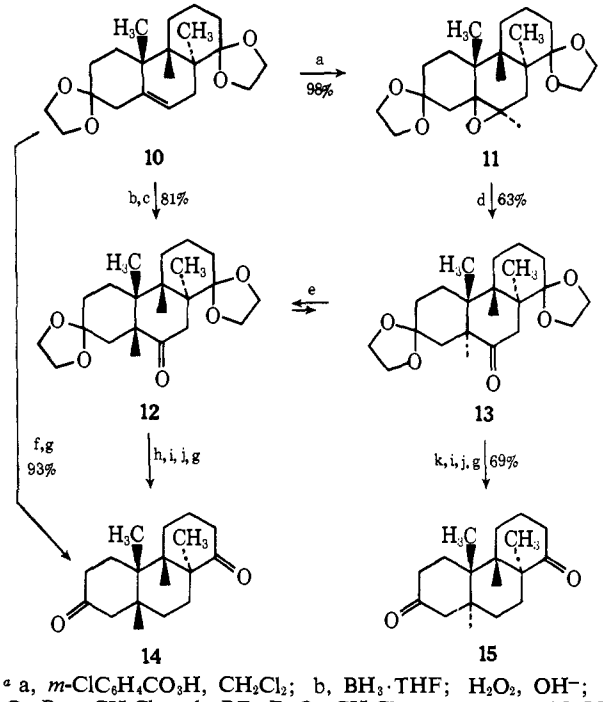
(5) R. E. Ireland, S. E. Baldwin, D. J. Dawson, M. I. Dawson, J. E. Dolfini, J. Newbould, W. S. Johnson, M. Brown, R. J. Crawford, P. F. Hudrlik, G. H. Rasmussen, and K. K. Schmiegel, *ibid.*, **92**, 5743 (1970).

(6) E. Farkas, J. M. Owen, M. Debono, R. M. Molloy, and M. M. Marsh, *Tetrahedron Lett.*, 1023 (1966).

system and clearly show that it is only the β face of the enone portion of the molecule that is unhindered and accessible to intermolecular approach. Thus, catalytic hydrogenation of the ketone ketal **6** results in the formation of the cis-syn-trans ketal ketone **8**, and the same stereochemical outcome attends the metal–ammonia reduction process. This result is probably a reflection of steric strain inherent in such syn-trans tricyclic structures.

Another approach to this problem is through the diketal **10** of the enedione **4** [$(CH_2OH)_2$, C_6H_6, *p*-TsOH, 93%] (Chart II). Again access to the α face of this

Chart II. Synthesis of Trans-Syn-Trans Diketone **15**[a]



[a] a, *m*-$ClC_6H_4CO_3H$, CH_2Cl_2; b, $BH_3 \cdot THF$; H_2O_2, OH^-; c, $CrO_3 \cdot Py_2$, CH_2Cl_2; d, $BF_3 \cdot Et_2O$, CH_2Cl_2; e, aqueous NaOH, EtOH; f, H_2, 10% Pd/C, EtOH; g, H_3O^+; h, Li, NH_3; EtOH; i, *n*-BuLi, DME, HMPA, $ClPO(NMe_2)_2$; j, Li, $EtNH_2$, THF; k, $LiAlH_4$, Et_2O. See ref 3.

molecule is severely restricted, and intermolecular reagents may only reasonably approach its β side. Catalytic hydrogenation of the diketal **10** and then deketalization substantiates this analysis, since *only* the cis-syn-trans diketone **14**,[3] also available on hydrolysis of the monoketal **8**, is formed.

These observations make it apparent that the formation of the desired trans AB ring fusion through an *intermolecular* process is unlikely, and efficient access to this system would better depend on the *intramolecular* transfer of an α-oriented hydrogen to the ring fusion. Such a sequence was realized when the boron trifluoride catalyzed rearrangement of β oxide **11** afforded the diketal ketone **13**. On treatment of this diketal ketone **13** with aqueous ethanolic hydroxide for 2 hr at reflux, an invariant mixture (90:10 by nmr analysis) of the *cis*-**12** and *trans*-**13** isomers was reached. The cis isomer **12** was isolated from this mixture and shown to be identical[3] with the diketal ketone prepared by hydroboration and then oxidation of the diketal **10**. Evidence that a mixture of *cis-syn-trans*-**12** and *trans-syn-trans*-**13** isomers in the ratio of 90:10 is at equilibrium under these basic conditions was apparent from an identical isomerization study of the pure cis isomer **12**.

Final confirmatory evidence of the accuracy of the structural assignments made for the two diketal ketones **12** and **13** was found in the removal[7] of the carbonyl group and the formation of the diketones **14** and **15**. In both cases this transformation was accomplished *without* isomerization of the AB ring fusion, since distinctly different diketones resulted and one, the diketone **14**, was identical[3] with the cis-syn-trans material prepared above.

The stereochemical result of this epoxidation–rearrangement sequence relies on the easy intermolecular steric access of the peracid to the β face of the unsaturated diketal **10** and the subsequent concerted intramolecular character of the oxide → ketone transformation. *None* of the isomeric cis diketal ketone **12** could be detected in the product from this sequence, and the success of the scheme in this functionalized system suggests that the process will generally be applicable to the formation of other trans-syn-trans structures.

(7) R. E. Ireland and G. Pfister, *Tetrahedron Lett.*, 2145 (1969); D. C. Muchmore, Ph.D. Thesis, California Institute of Technology, 1970.

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Regio- and Stereoselective Methyl Migrations in Silver(I)-Promoted Rearrangements of Tricyclo[3.2.0.0^{2,4}]heptanes[1]

Sir:

Since the original recognition of the capability of Ag^+ to promote structural bond reorganizations of molecules endowed only with strained σ bonds,[2] considerable exploration of the field has occurred[3] and other transition metals of equal effectiveness have been found.[4] Although a general mechanistic theory in explanation of the observed structural changes has progressed into a formative stage,[1,3b,4a] new aspects of the novel rearrangement capability of Ag^+ are certain to emerge. We wish now to report just such an unusual, mechanistically informative development in silver(I) chemistry.

In a series of experiments designed to test for substituent effects on the Ag^+-promoted rearrangement of the tricyclo[3.2.0.0^{2,4}]heptane ring system, we had occasion to treat **1**[5] with small amounts of silver

(1) Part IX of the series entitled "Silver(I) Ion Catalyzed Rearrangements of Strained σ Bonds." For the previous paper, see L. A. Paquette and S. E. Wilson, *J. Amer. Chem. Soc.*, **93**, 5934 (1971).

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