isolated (15–20% yields, mp 247–249°, M^+ 382)[9] by preparative thin-layer chromatography. Reduction[4] of scillarenone to scillarenin (**6**, mp 230–232°) was easily realized by several different methods of which lithium tri-*tert*-butoxyaluminum hydride (tetrahydrofuran solution, 0° for 5 hr) and lithium borohydride (tetrahydrofuran solution, 0° for 5 hr) afforded the best results (approximately 75% yields). The synthetic specimen of scillarenin was identical (by mixture melting point determination, thin-layer chromatographic and infrared spectral comparison) with an authentic sample kindly provided by Dr. W. Haede.[4]

The preceding more direct route to bufalin has also been accomplished by way of analogously prepared bromohydrin and chlorohydrin intermediates but the 15α-chloro substituent proved considerably more resistant to hydrogenolysis. Completion of the above synthetic route from bufalin to scillarenin represents the first chemical transformation of a plant cardenolide (**1**) to a plant bufadienolide (**6**).

Acknowledgment. This investigation was supported by Public Health Service Research Grant No. 5-RO1-CA11451-02, 5-RO1-CA11451-03, and CA-10612-04 from the National Cancer Institute.

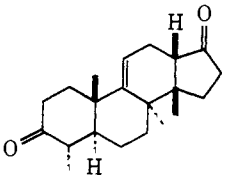
(9) A. von Wartburg, *Helv. Chim. Acta*, 47, 1228 (1964).

Yoshiaki Kamano, George R. Pettit*
Department of Chemistry, Arizona State University
Tempe, Arizona 85281
Received July 1, 1972

Steroidal Antibiotics. Total Synthesis of the Fusidic Acid Tetracyclic Ring System[1]

Sir:

The steroidal antibiotics of the fusidane series, *i.e.*, fusidic acid,[2] helvolic acid,[3] and cephalosporin P_1,[4] have proved to be valuable remedies in combating infections caused by staphylococci. The fusidane series is a new type of tetracyclic triterpene representing an intermediate between squalene and lanosterol. From the synthetic standpoint, this tetracyclic nucleus offers many challenges, the two most important being the presence of 8α- and 14β-methyl groups with the absence of a 13β-methyl group and the possession of a trans–syn–trans configuration in the A–B–C ring portion of the tetracyclic system. We should like to report the total synthesis of the tetracyclic compound (±)-**1**,



1

a degradation product of fusidic acid,[5] which can, in turn, serve as an intermediate in the synthesis of the antibiotic. The synthetic scheme is outlined in Scheme I.

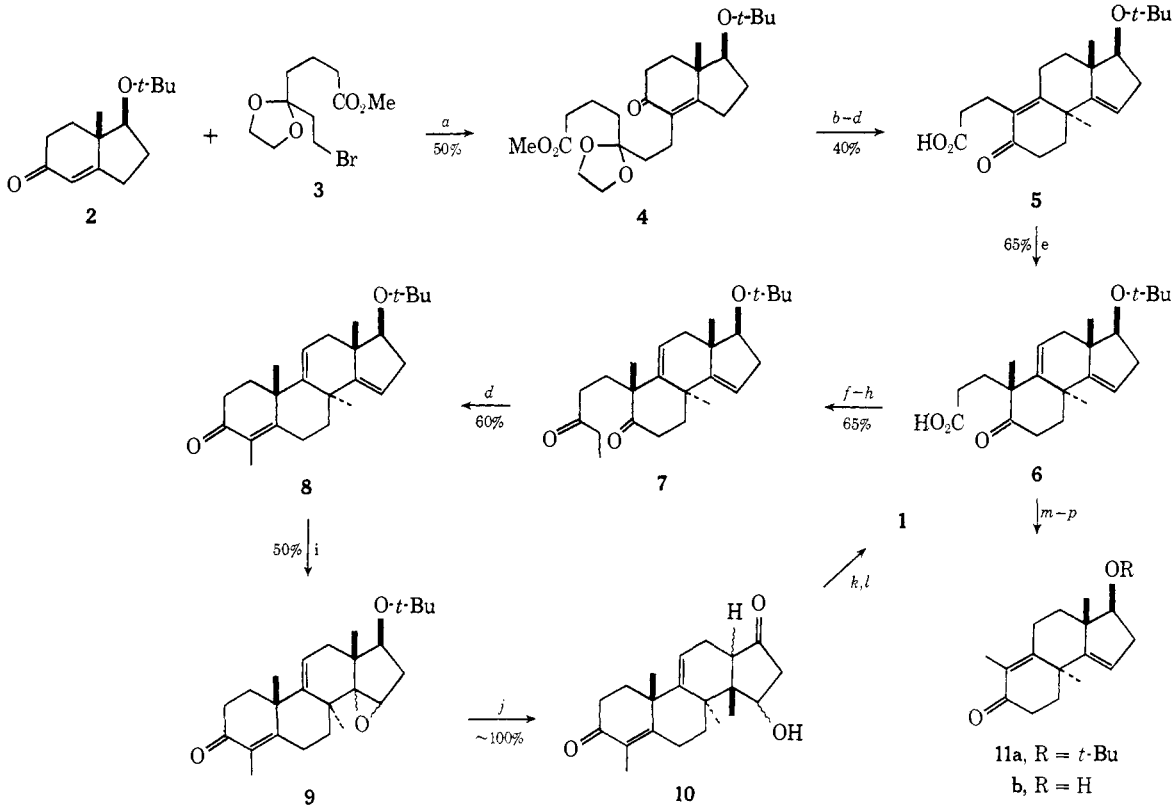
Alkylation of enone **2**[6] with the bromoketal ester **3**[7] yielded **4**[8] which was then alkylated with methyl iodide; the ketal hydrolyzed and the resulting 1,5-diketone cyclized with Triton B to produce tricyclic enone **5**. Methylation of **5** with methyl iodide to give keto acid **6** (mp 121–123°) was best accomplished by using potassium hydroxide in aqueous *tert*-butyl alcohol as the base; these conditions minimized polyalkylation. The stereochemistry of quaternary centers at C-8 and C-10 was established in the following manner. The methyl ester of **6** was allowed to react with sodium dimethyl ethylphosphonate and the resulting β-ketophosphonate upon reaction with sodium methoxide underwent a reverse Michael reaction to yield tricyclic enone **11a** which upon acid treatment gave the known tricyclic 8α-methylenone **11b**.[9] Since the 17β-hydroxy derivative of **6** was isomeric with the known 8α,10α-dimethyl compound,[10] the stereochemistry of the C-10 methyl group in **6** has a β configuration.

The keto acid **6** was converted to ethyl ketone **7** (mp 64–66°) *via* the acid chloride using lithium diethylcuprate and the diketone cyclized with Triton B to give tetracyclic enone **8** (mp 119–121°). This enone upon reaction with 1.1 equiv of *m*-chloroperbenzoic acid in methylene chloride at 0° for 30 hr yielded epoxide **9** in 50% yield and an isomeric epoxide in 30% yield. A benzene solution of **9** was allowed to react with purified $BF_3 \cdot Et_2O$ for 2 min at 25° and the rearranged ketol **10**, derived by hydrolysis of the $\Delta^{13(17)}$-enol ether first formed, obtained in nearly quantitative yield. The ketol **10** was heated with a 0.1% benzene solution of *p*-toluenesulfonic acid and the desired conjugated cyclopentenone derivative obtained in 50% yield. This material was reduced with Li, NH_3, and *t*-BuOH,[11] and the reaction mixture directly chromatographed upon silica gel to yield crystalline (±)-**1**, mp 182–185°, in 20% yield.[12] The nmr spectrum of (±)-**1** was virtually superimposible upon a spectrum of (+)-**1** obtained from fusidic acid.[13]

Unequivocal proof of the structure and stereochemistry of (±)-**1** was achieved by X-ray crystallography (see Figure 1).[14] Crystals of (±)-**1** are monoclinic

(1) This work was supported by Grant No. CY-04284, National Cancer Institute, U. S. Public Health Service.
(2) W. O. Godtfredsen, W. von Daeline, S. Vangedal, A. Marquet, D. Arigoni, and A. Malera, *Tetrahedron*, 21, 3505 (1965).
(3) S. Iwasaki, M. I. Sair, H. Igarshi, and S. Okuda, *Chem. Commun.*, 1119 (1970).
(4) T. G. Halsall, E. R. H. Jones, G. Lowe, and C. E. Newall, *ibid.*, 685 (1966); P. Oxley, *ibid.*, 729 (1966).
(5) P. A. Diassi, G. W. Krakower, I. Bacso, and H. Ann Van Dine, *Tetrahedron*, 22, 3443 (1966).
(6) Z. G. Hajos, R. A. Micheli, D. R. Parrish, and E. P. Oliveto, *J. Org. Chem.*, 32, 3008 (1967).
(7) Methyl 7-bromo-5-ethylenedioxyheptanoate (**3**) was prepared from 4-carbomethoxybutyryl bromide, ethylene, and aluminum bromide.
(8) All substances gave analytical and spectral data consistent with the postulated structures.
(9) J. Bordner, R. H. Stanford, Jr., and R. E. Dickerson, *Acta Crystallogr., Sect. B*, 26, 2107 (1970).
(10) The stereochemistry of C-8 and C-10 in this reference compound was established by X-ray analysis (J. Bordner, private communication).
(11) H. A. Smith, B. J. L. Huff, W. J. Powers, III, and D. Caine, *J. Org. Chem.*, 32, 2851 (1967).
(12) This yield represents a minimal value since no attempt was made to isolate the more soluble C/D trans isomer and the overreduced products.
(13) Comparison sample kindly supplied by Dr. P. A. Diassi.
(14) The X-ray crystallographic study was kindly performed for us by D. L. Ward, A. Zalkin, and D. H. Templeton of this department and the complete data will be published. For the computer program which drew the projection drawing, see C. K. Johnson, ORTEP, Oak Ridge National Laboratory, Oak Ridge, Tenn., 1965, Report No. ORNL-3794.

Scheme I



[a] NaH, DMSO. [b] KO-*t*-Bu, MeI. [c] Aqueous HOAc. [d] Triton B. [e] KOH, *t*-BuOH, MeI. [f] NaOH. [g] $(COCl)_2$. [h] $LiEt_2Cu$. [i] *m*-$ClC_6H_4CO_3H$, 0°. [j] $BF_3 \cdot Et_2O$. [k] *p*-TsOH, Bz. [l] Li, NH_3, *t*-BuOH. [m] CH_2N_2. [n] (MeO)$POCHCH_3Na$. [o] NaOMe, MeOH. [p] $HClO_4$–THF.

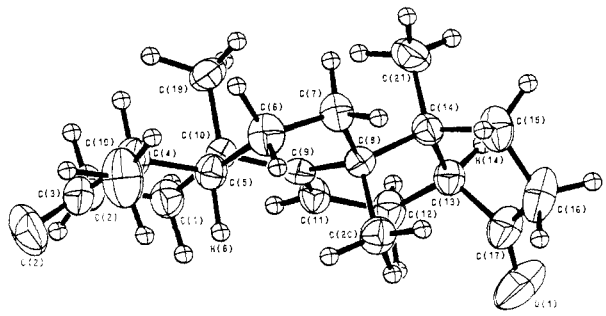


Figure 1. Projection drawing of **1**. The ring carbon atoms are numbered in the standard fashion.

with space group $C2/c$ and $a = 19.562$ (6), $b = 11.915$ (4), and $c = 15.623$ (4) Å, and $\beta = 107.84$ (4)°. There are eight molecules in the unit cell and 1124 data where $I > 3\sigma(I)$ were utilized. All C and O atoms were refined anisotropically and all H atoms refined isotropically. The final R value was 3.4%. Data were obtained with a Picker FACS-I automatic diffractometer with graphite monochromatized molybdenum Kα radiation.

It is to be noted that earlier generalities[15, 16] with regard to the stereochemistry of the alkylation of enones upon which this present synthesis was planned were, indeed, followed in this group of compounds. The ultimate success of the synthesis relied upon the acid-catalyzed rearrangement of an angular methyl group upon the opening of an epoxide (the Westphalen rearrangement). It had been shown[17] that this rearrangement involved a nearly planar cationic reaction complex followed by the migration of the group which could achieve maximum coplanarity with the p orbital of the cationic center. Examination of a molecular model of the tetracyclic cation at C-14 formed from **9** clearly showed that only the C-13 angular methyl group met this criterion and, thus, the rearrangement would be expected to yield **10** as found.

Acknowledgment. The authors are indebted to the Hoffmann-La Roche Co. for kindly supplying the bicyclic enone starting material.

(15) F. H. Bottom and F. J. McQuillin, *Tetrahedron Lett.*, 1975 (1967); 459 (1968).

(16) R. E. Ireland, D. A. Evans, D. Glover, G. M. Rubottom, and H. Young, *J. Org. Chem.*, **34**, 3717 (1969).

(17) J. M. Coxon, M. P. Hartshorn, and C. N. Muir, *Chem. Commun.*, 1591 (1970), and earlier papers.

W. G. Dauben,* G. Ahlgren, T. J. Leitereg
W. C. Schwarzel, M. Yoshioko
Department of Chemistry, University of California
Berkeley, California 94720

Received August 18, 1972

Fluxional Nature of Benzo- and Naphthocyclooctatetraeneiron Carbonyl Complexes

Sir:

Contrary to statements in the literature,[1] shift isomerism of 3,4,5,6-*tetrahapto*benzocyclooctatetraeneiron tricarbonyl (**1**) and its 2,3-naphtho analog **2** is sufficiently rapid to label them fluxional molecules.

(1) J. A. Elix and M. V. Sargent, *J. Amer. Chem. Soc.*, **91**, 4734 (1969).