metalate, nor does the decomposition lead to formation of $Li\{Sn[Sn(CH_3)_3]_3\}$, but only to $Sn(CH_3)_4$ and other unidentified products.

Nmr data for these species are reported in Table I. A comparison of these data with those of Shaw and Allred[11] on $(CH_3)_3SnM(CH_3)_3$ where M = a group IV element shows a similar decrease for δ_{SnCH_3} as M increases in atomic number. This trend was explained on the basis of the change in magnetic anisotropy of the system and a similar explanation may pertain here although the trend may also be accounted for on the basis of the decrease in electronegativity of the metal. The δ_{MCH} observed for the group IV systems[11] showed no trend while in our systems a general decrease in δ was noted as a function of increasing size and increasing electronegativity.

It was also noted here that J_{SnCH} increased regularly with the size of the metal while J_{SnMCH} varied as Al < Ga > In > Tl. No attempt has yet been made to establish the sign of the J_{SnMCH}, but in $Sn_2(CH_3)_6$ McFarlane[12] has established that the J_{SnSnCH} is negative. The absolute value of J_{TlCH} decreases regularly in the series $TlCH_3^{2+}$, $Tl(CH_3)_2^{+}$, and $Tl(CH_3)_3$ to the value we observe for $Tl(CH_3)_4^{-}$. The sign of J_{TlCH} is presumed to be negative since Maher and Evans have established that the sign of Tl–H coupling in $Tl(CH_3)_3$ is negative.[13] No data are available concerning the sign of the long range TlSnCH coupling constant.

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A. Thomas Weibel, John P. Oliver*
Department of Chemistry, Wayne State University
Detroit, Michigan 48202
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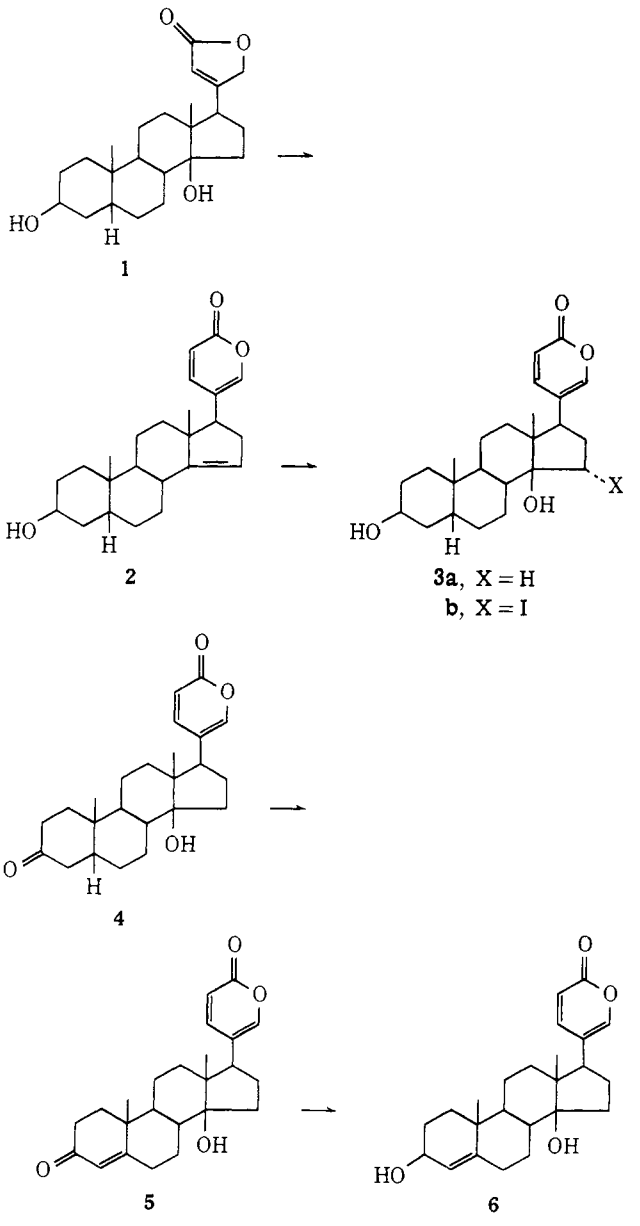
Transformation of Digitoxigenin to Scillarenin[1]

Sir:

The naturally occurring bufadienolides from toad venoms and plant sources have displayed a variety of medically interesting properties ranging from anesthetic and antineoplastic activities to heart and respiration effects.[2] Two years ago we summarized a total synthesis of the toad venom constituent bufalin (**3a**) with digitoxigenin (**1**), 14-dehydrobufalin (**2**), and resibufogenin (the related 14β,15β-epoxide) serving as relays.[3] We now wish to report a more direct route from 14-dehydrobufalin to bufalin and a total synthesis of the plant bufadienolide scillarenin (**6**)[4] employing bufalin as relay.



In a typical sequence 14-dehydrobufalin (**2**, 80 mg)[3] was treated[5] with *N*-iodosuccinimide in acetone–water (room temperature, 1 day) and the crude iodohydrin (**3b**, 79 mg) was reduced with Urushibara Ni-A[6] to complete a new synthesis of bufalin (**3a**, 54 mg, mp 240–243°).[7] Next, bufalin[3] was easily oxidized (chromium trioxide in acetic acid) to bufalone (**4**, mp 243–245°)[8] which was brominated at C-4 using *N*-bromosuccinimide in carbon tetrachloride (45 min at reflux). The α-bromo ketone (55% yield) was dehydrohalogenated (refluxing collidine for 6 hr) and scillarenone (**5**) was

(1) Parts 24 and 83, respectively, in the series Bufadienolides and Steroids and Related Natural Products. For the preceding contribution (Steroids and Related Natural Products 82), refer to P. Brown, F. Bruschweiler, and G. R. Pettit, *Helv. Chim. Acta*, **55**, 531 (1972).
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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**).

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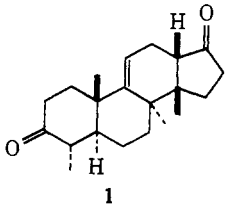
Yoshiaki Kamano, George R. Pettit*
Department of Chemistry, Arizona State University
Tempe, Arizona 85281
Received July 1, 1972

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**,



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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

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