to **15**: mass spectrum parent peak at *m/e* 198, 200 (3:1); ir *inter alia* 3100 (=CH_2 stretching), 1625 (C=C stretching), and 880 cm^{-1} (=CH_2 out-of plane deformation); pmr (CCl_4) δ 4.75 (m, 1 H), 4.60 (m, 1 H), 4.10 (q, J = 7 Hz, 1 H), 2.85 (m, 1 H), 1.72 (broad s, 6 H), 1.50 (d, J = 7 Hz, 3 H), 1.09 (s, 3 H), 0.98 (d, J = 7 Hz, 3 H).

Registry No.—**1**, 7641-77-2; **5**, 20379-83-3; **8**, 40265-14-3; **9**, 50590-86-8; **12**, 50590-87-9; **13**, 51751-70-3; **15**, 19835-61-1; **16**, 41694-21-7; triethylamine, 121-44-8; tetracyanoethylene, 670-54-2.

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(3) (a) H. Hogeveen and H. C. Volger, *Recl. Trav. Chim. Pays-Bas*, **87**, 385, 1042 (1968); **88**, 353 (1969); (b) L. A. Paquette, G. R. Krow, J. M. Bollinger, and G. A. Olah, *J. Amer. Chem. Soc.*, **90**, 7147 (1968).
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(12) In cooperation with Drs. W. F. J. Huurdeman. For another synthetic pathway see H. Hogeveen and W. F. J. Huurdeman, *Tetrahedron Lett.*, 1255 (1974).

Double Bond *vs.* Cyclopropane Ring Reactivity toward Different Acids[1]

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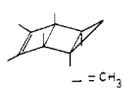
The reactions of compounds **2, 3,** and **4** with the strong acid $FHSO_3$ and with $HCl-CH_2Cl_2$ have been studied and mechanisms for these reactions are discussed. It is concluded that the reaction with $FHSO_3$ takes place at the methylene groups of the compounds investigated. The reaction with HCl, however, takes place at the cyclopropane rings of compounds **2** and **3** and possibly also of compound **4.** Tentative explanations are given, based on the different nature of the acids and different structural properties of the substrate compounds.

Some aspects of the mechanism of the protonation of cyclopropane, *e.g.*, the relative stability of the face-protonated, edge-protonated, and corner-protonated cyclopropane and the question whether the protonation occurs *via* an inversion or a retention mechanism, have been amply discussed.[2,3] Another aspect of the protonation of cyclopropane, namely the relative reactivity of cyclopropanes and double bonds, has gained less attention. From the few examples known[2d] the general trend seems to be that cyclopropane rings are more reactive toward acids than are carbon–carbon double bonds. We wish to add a new element to this discussion; it appears that in compounds containing a cyclopropane ring as well as a double bond the nature of the acid plays an important role in determining whether the cyclopropane ring or the double bond reacts first. Previously[3a] it was found that compound **1,**



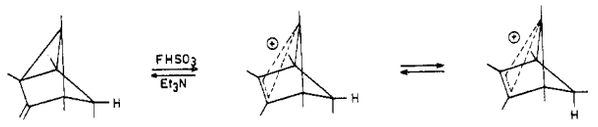
1

containing a double bond and a cyclopropane ring, reacted at the cyclopropane ring with hydrogen chloride in methylene chloride. Superacids such as $FHSO_3-SO_2ClF$, $FHSO_3-SbF_5$, $FHSO_3-SbF_5-SO_2F_2$, and $HF-BF_3$, however, did not give the product expected upon protonation of the cyclopropane ring. Perhaps reaction at the double bond occurred as the first step under the latter conditions.

Results and Discussion

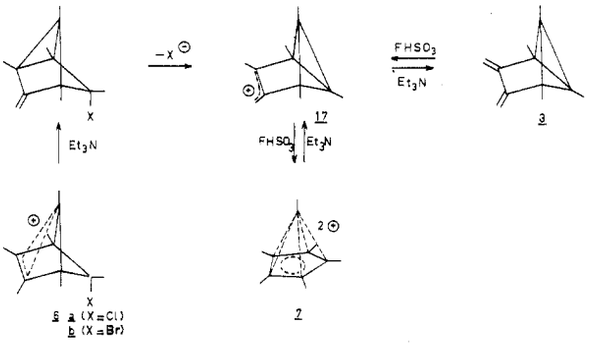
The different behavior of the superacids and $HCl-CH_2Cl_2$ toward compounds containing cyclopropane rings and double bonds was investigated with use of the model compounds **2, 3,** and **4,** containing different numbers of the reactive structural components mentioned. These model compounds are readily accessible in two-step reactions starting from hexamethyl(Dewar benzene).[1,4] In the first step the carbonium ions **5a, 6, 7,** and **8,** respectively, are generated and in the second step triethylamine abstracts a proton from these carbonium ions at the methyl group adjacent to the carbon atom bearing the highest positive charge.[4c]

Reactions with $FHSO_3$. The reactions of **2, 3,** and **4** with $FHSO_3$ show the exact reverse of the triethylamine-induced deprotonation step in the syntheses of **2, 3,** and **4.** When **2** was dissolved in $FHSO_3$ at −80°, the pmr spectrum of the solution showed the presence of a 3:1 equilibrium mixture[5] of **5a** and its endo-H isomer **5b.** Extraction



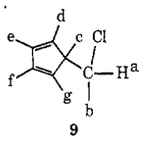
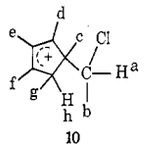
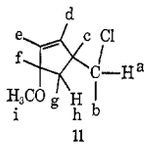
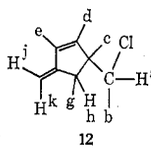
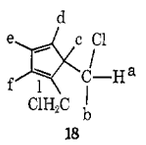
2 **5a** **5b**

of a solution of **3** in methylene chloride with $FHSO_3$ at −90° afforded the dication **7,** which presumably was ob-

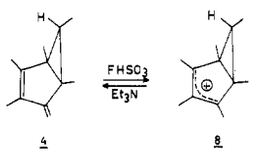


tained by successive protonation of the two methylene groups of **3.**[4b] From the literature[6,7] it is known that **4**

Table I
Pmr Spectral Data[a] of Compounds 9,[b,c] 10,[d] 11,[c] 12,[d] and 18[d]

 9	a, 4.05 (1 H, q, J = 6.5 Hz); b, 1.02 (3 H, d, J = 6.5 Hz); c, 1.08 (3 H, s); d, e, f, and g, 1.68 (3 H, broad s), 1.75 (6 H, broad s), and 1.87 (3 H, broad s)
 10	a, 4.52 (1 H, q, J = 7 Hz); b, 1.77 (3 H, d, J = 7 Hz); c, 1.38 (3 H, s); d and f, 3.00 (6 H, m); e, 2.27 (3 H, m); g,[e] 1.53 (3 H, d, J = 7 Hz); h, 3.52 (1 H, m)
 11	a,[f] 4.05 (1 H, q, J = 7 Hz); b,[f] 1.44 (3 H, d, J = 7 Hz); c, 1.01 (3 H, s); d and e, 1.59 (6 H, d); f, 1.21 (3 H, s); g,[f] 0.96 (3 H, d, J = 7 Hz); h,[f] 2.12 (1 H, q, J = 7 Hz); i, 3.01 (3 H, s)
 12	a,[f] 4.29 (1 H, q, J = 7 Hz); b,[f] 1.54 (3 H, d, J = 7 Hz); c, 1.06 (3 H, s); d and e, 1.72 (6 H, broad s); g,[f] 1.02 (3 H, d, J = 7 Jz); h,[f] 2.77 (1 H, m); j and k, 4.77 (1 H, m) and 4.67 (1 H, m)
 18	a, 4.15 (1 H, q, J = 7 Hz); b, 1.10 (3 H, d, J = 7 Hz); c, 1.13 (3 H, s); d, e, and f, 1.88 (6 H, broad s) and 1.80 (3 H, m); l, 4.27 (2 H, s)

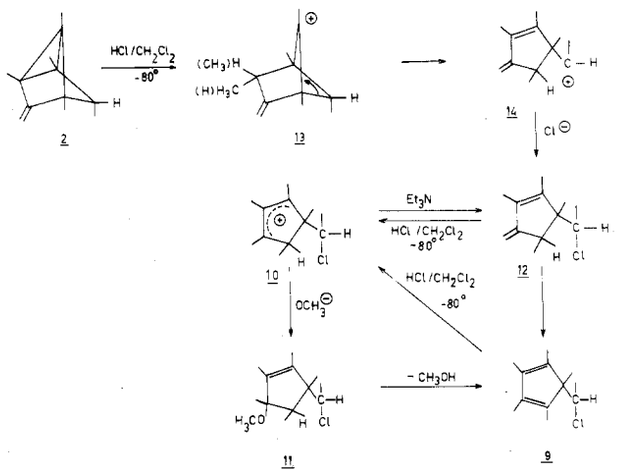
[a] δ in parts per million relative to internal TMS. [b] Reference 8b. [c] Solvent CCl_4. [d] Solvent CH_2Cl_2. [e] The peaks of this doublet show additional structure owing to coupling with methyl groups of the ring when the spectrum is recorded at 100 MHz (XL-100). [f] These assignments were confirmed by double-resonance experiments.



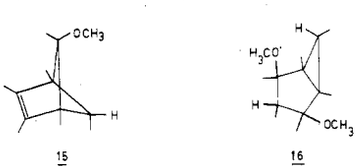
gives **8** on reaction with $FHSO_3$ at −70°. The three model compounds **2**, **3**, and **4** apparently prefer low-temperature reaction with $FHSO_3$ at the methylene groups, rather than reaction at the cyclopropane ring.

Reactions with HCl–CH_2Cl_2. The reaction of these compounds with HCl followed in part another pathway. When compound **2** was dissolved in HCl–CH_2Cl_2 (1:1 molar ratio) at −80°, the yellow solution showed a pmr spectrum which was identical with that of a solution of **9**[8] under the same conditions. This spectrum was assigned to the cyclopentenyl cation **10**, the structure of which is assigned on the basis of the pmr spectrum (see Table I) and product analysis after quenching of a solution of **10** with excess sodium methoxide in methanol at −80°. After work-up of the reaction mixture, pmr indicated compound **11** to have been formed. Assignment of structure **11** is based on the spectral data (see Table I and Experimental Section) and the observation that the product decomposed into **9** and methanol upon standing at 40° for several hours. Mechanistically two possibilities for the reaction of **2** with HCl have to be envisaged. The first possibility is double bond attack, just as in the case of $FHSO_3$. In this way cation **5a** should be formed, which exists in equilibrium with **5b**.[5,9] It is known that a solution of these ions with Cl^- as counterion, as is the case, can give **9**[9] and it is shown above that **9** is protonated under the reaction conditions. However, the reaction of **5a,b** in HCl–CH_2Cl_2 (1:1 molar ratio) was never observed to occur at −80°.[9] The second, more likely, possibility is attack at the cyclopropane ring. Experimental support for this idea was obtained in a reaction of a solution of **2** in methylene chloride with *ca.* 0.7 equiv of dry HCl gas at −80°. In this case the pmr spectrum of the solution indicated the presence of **12** together with starting material **2**. The assignment of structure **12** depends on the pmr spectrum (see Table I), the room-temperature isomerization of **12** to **9** which is enhanced enormously upon addition of a trace of acid, the protonation of **12** in HCl–CH_2Cl_2 at −80° to give cation **10**, and the independent synthesis of **12** from **10** by deprotonation with triethylamine.[4c]

From these experiments the conclusion can be drawn that HCl in CH_2Cl_2 at −80° attacks **2** at the cyclopropane ring. The reaction scheme of **2** with HCl–CH_2Cl_2 at −80° is almost complete now; only the steps from **2** to **12** are missing. Therefore we look at the six different ways in which proton addition and subsequent opening of the cyclopropane ring can occur. A reaction path *via* **13** and **14** involves only two steps and the intermediates are not extremely unstable. The five other ways either lead to different products or involve more steps, so that we propose the intermediates **13** and **14** to complete the reaction scheme.



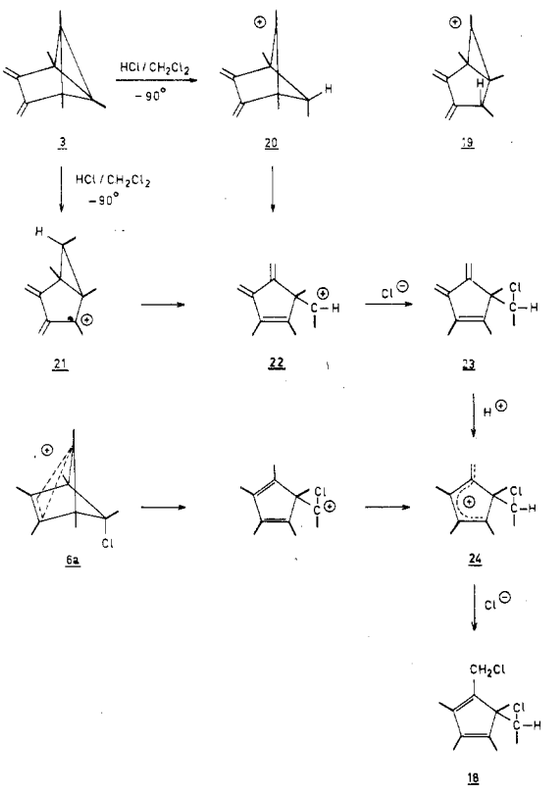
When the reaction of **2** with excess HCl (2- to 100-fold) was carried out at temperatures above −60° followed by quenching with sodium methoxide and methanol at the same temperature, the products were found to be not only **9**, **11**, and hexamethylbenzene, but also **15** (maximum amount found, 5%) and **16** (maximum 25%). The latter



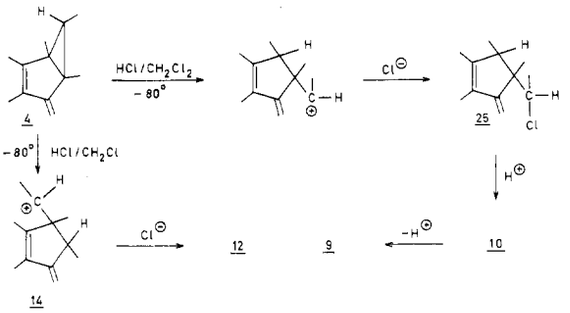
compounds have been obtained before from **5a,b**,[9] so that it is possible that at temperatures above −60° the reaction is less selective and HCl attacks the double bond as well as the cyclopropane ring.

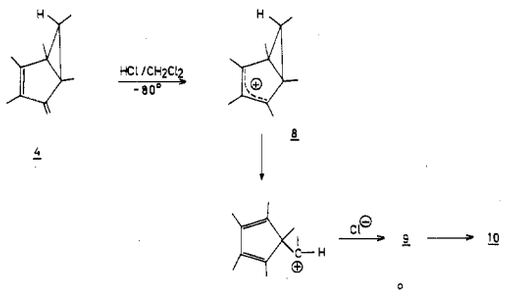
Compound **3** also shows a different behavior in reactions with $FHSO_3$ and HCl. Addition of successive portions of dry HCl to a methylene chloride solution of **3** at −90° did not give rise to observable amounts of **7** or the presumed monoprotonation product **17**.[4b] The pmr spectrum of the reaction mixture at −90° showed compound **18** to be

formed even when an excess of **3** was still present. The pmr spectrum of the reaction mixture remained unchanged upon warming to room temperature and **18** was isolated by evaporating the solvent. The assignment of structure **18** depends on the spectral data (see Table I and Experimental Section) and independent synthesis from **6a** by intramolecular rearrangement.[1b,10] It is difficult to rationalize the formation of compound **18** in the reaction of **3** with HCl by assuming protonation of a methylene group of **3** to be the first step. However, assuming initial attack on a cyclopropane ring, a reasonable mechanism can be drawn. According to Wiberg and Szeimies[11] the protonation of the bicyclobutane system is proposed to occur with retention of configuration. Owing to symmetry, only three intermediates are conceivable: **19, 20,** and **21.** Intermediate **19** is considered to be unlikely because it is energetically unfavorable and would open to a cyclohexyl ion.[12] Both intermediates **20** and **21** are possible, although **21** is expected to be the most stable one. Moreover, owing to symmetry, the formation of **21** is statistically favored by a factor of 2. Intermediates **20** and **21** are supposed to give the five-membered ring compounds **22, 23,** and **24** in subsequent steps. Finally intermediate **24,** proposed to be an intermediate also in the thermal reaction of **6a,** reacts with chloride anion to give product **18.**[1b,10]



The mechanism of the reaction of **4** with HCl in methylene chloride could not be established unambiguously. Addition of an excess of dry HCl gas to a methylene chloride solution of **4** at −80° resulted in the formation of ion **10.** This can be explained either by a reaction at the cyclopropane ring or by reaction at the double bond. In the former case six intermediates are conceivable, but only the five-membered ring compounds **12** and **25** with an exocyclic methylene group can explain the product **10.** When the reaction was carried out, however, with 0.6 equiv of HCl, so that **4** was still present, the methylene signals present in the pmr spectrum of the reaction mixture at −80° were due solely to **4.** The only other compound present in this solution was **9.** In a similar experiment with **2,** the intermediate **12** appeared to be observable under these conditions (see above). Only **25** remains therefore as a possible intermediate in the case of reaction at the cyclopropane ring and one has to assume that **25** is rapidly isomerized under the reaction conditions. The other possibility is attack at the exocyclic double bond, followed by β-fission of the resulting ion **8** and reaction with Cl^- to give **9.**[9] However, the isomerization of ion **8,**[10]





which escapes detection in these experiments, has to be assumed to occur in this medium much faster than in strongly acidic solutions,[6,7] where ion **8** has been observed at even higher temperatures. This possibility cannot be excluded, so that an unambiguous decision on the direction of the initial attack by HCl cannot be made.

Conclusions

The experiments show a striking difference between the two acids $FHSO_3$ and $HCl-CH_2Cl_2$ in their reactivity toward double bonds and cyclopropane rings in the compounds **2, 3,** and, perhaps, **4.** Literature data on $FHSO_3$,[13] $HCl-CH_2Cl_2$,[14] and liquid HCl[15] indicate that, whereas in the strong acid solvated protons are available for the reaction, this is not the case with low-temperature $HCl-CH_2Cl_2$ mixtures or liquid HCl, in which the reacting particles are polar HCl molecules. This difference obviously can change the reaction pattern dramatically.[16]

Experimental Section

Spectroscopic Measurements. Proton magnetic resonance spectra were recorded at 60 MHz using a Varian A-60D or a Jeol C60HL spectrometer equipped with a variable-temperature probe, unless otherwise stated. Chemical shifts are calculated relative to internal TMS at δ 0. Mass spectra were determined with an AEI MS9 mass spectrometer and ir spectra were obtained with use of a Perkin-Elmer 257 spectrometer; only representative peaks are given. Uv spectra were measured with a Beckman DB-G spectrophotometer.

Reaction of 2 with $FHSO_3$. Reaction of **2** with $FHSO_3$ was performed by cooling an nmr tube containing 50 mg of **2** in liquid nitrogen and subsequent introduction of 0.4 ml of $FHSO_3$. The nmr tube was warmed in a bath at −80° and stirring was applied as soon as possible.

Preparation of Solutions in $HCl-CH_2Cl_2$. The substrate (50 mg) was dissolved in methylene chloride (0.2–0.4 ml). This solution was cooled to −80° and dry HCl gas was introduced until the indicated ratio was reached as concluded from the pmr spectrum of the products.

Preparation of 11. A solution of 50 mg of **2** in 0.4 ml of $HCl-CH_2Cl_2$ (1:1 molar ratio) at −80° was poured in 800 mg of sodium

methoxide in 10 ml of methanol at −80°. The reaction mixture was warmed to room temperature, water was added, and the mixture was extracted with pentane. Washing with water, drying over anhydrous sodium sulfate, and evaporating the solvent gave 69 mg of a crude product which consisted of 95% of **11**. Standing at 40° for 1 day caused quantitative decomposition of **11** into **9** and methanol. The mass spectrum of **11** showed a parent peak at *m/e* 230 corresponding with $C_{13}H_{23}OCl$; for the pmr spectrum, see Table I.

Preparation of 18. A solution of 48 mg (0.3 mmol) of **3** in 0.4 ml of methylene chloride was cooled to −80° and dry HCl gas (0.5 mmol) was introduced. The solution was warmed to room temperature and the solvent was evaporated. The pmr spectrum of the remaining 63 mg of product indicated 80% of **18** and 15% of starting material to be present. The mass spectrum of **18** showed parent peaks at *m/e* 232, 234, and 236 (intensity ratio 9:6:1), corresponding with $C_{12}H_{18}Cl_2$; pmr spectrum, see Table I; ir *inter alia* absorption at 1620 cm^{-1}; uv λ_{max} (pentane) 275 nm.

Registry No.—**2**, 40265-14-3; **3**, 50590-86-8; **4**, 20379-83-3; **9**, 19835-61-1; **10**, 51751-32-7; **11**, 41694-19-3; **12**, 41694-21-7; **18**, 50590-88-0; HCl, 7647-01-0; $FHSO_3$, 7789-21-1.

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(16) Perturbation theory might help to explain the different behavior. The equation for the perturbation energy contains a Coulombic term and an orbital term. In the case of reactions with cations, in particular protons, the Coulombic term is the most important one and the reaction is called charge controlled. When the charge decreases, as is the case in going from a proton to a polar HCl molecule, the importance of the Coulombic term decreases and the reaction becomes orbital controlled, which means that the direction of the reaction depends on the magnitude of the frontier orbital coefficients.[17] It is obvious that charge control and orbital control will not *a priori* give rise to different reactions, but in these cases where more nucleophilic centers are available, the different reactivity toward protons and HCl might be explained by a charge-controlled reaction in the former case and an orbital-controlled reaction in the latter case. Calculations are planned to test the validity of this hypothesis.
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Bufadienolides. 26. Synthesis of Scillarenin[1,2]

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Bufalin (**1**), previously synthesized from digitoxigenin, was utilized as relay in a new synthetic route to scillarenin (**4**). Important steps in the synthesis of scillarenin included bromination and dehydrohalogenation of bufalone (**2a**) to yield scillarenone (**3**). The overall transformation from digitoxigenin also comprised the first conversion of a plant cardenolide to a plant bufadienolide (**4**).

Careful hydrolysis of, *e.g.*, proscillaridin A from the ancient Egyptian medicinal plant *Scilla maritima* yields the aglycone scillarenin (**4**).[3] The parent glycoside, proscillaridin A, is a useful clinical agent for certain cardiac problems. This 3β-rhamnose derivative of scillarenin (**4**) has also been found to be an outstandingly effective cell-growth inhibitor of the National Cancer Institute's human epidermoid carcinoma of the nasopharynx cell culture (9KB).[4]

Recently we completed partial syntheses of marinobufagin and marinobufotoxin starting with telocinobufagin (**5**) isolated from Ch'an Su.[5] The objective of the present study[6] was to extend our earlier total synthesis of bufalin[1,6,7] (**1**) to the plant bufadienolide, scillarenin[8] (**4**). The latter substance could then serve as relay in a formally continuous route[5] to telocinobufagin (**5**).

Selective chromic acid oxidation (Sarett) of bufalin (**1**) to the previously known 3-oxo derivative, bufalone (**2a**), provided a useful precursor of scillarenin (**4**). Controlled bromination of ketone **2a** with *N*-bromosuccinimide gave an epimeric mixture of the C-4 bromo derivatives (**2b**), which were dehydrobrominated in low yield using hot α-collidine or pyridine. An improved procedure involved treatment of ketone **2a** with bromine in dimethylformamide or acetic acid to give the corresponding 4-bromo derivative, which was subjected directly to dehydrobromination with lithium bromide in dimethylformamide or lithium chloride in dimethylacetamide. After preparative thin layer chromatography, scillarenone (**3**) was isolated in 30–40% yields.

A partial synthesis of scillarenone (**3**) from telocinobufagin (**5**) was also evaluated. As part of the original structural study[9] of telocinobufagin (**5**) the 3β-hydroxyl was selectively oxidized to provide ketone **2c**, which upon treatment with hot acetic acid gave scillarenone (**3**). The Meyer[9] route was conveniently modified as follows. Oxidation of telocinobufagin to ketone **2c** was accomplished in good yield with *N*-bromoacetamide and selective elimination of the tertiary 5-hydroxyl group was readily achieved using an acidic ion-exchange resin. The samples of ketone **3** prepared from bufalin and telocinobufagin were shown to be identical.

Reduction of ketone **3** to scillarenin (**4**) and thereby completion of a new formal total synthesis of this plant