was concentrated in vacuo. High-vacuum distillation of the crude product gave 19.3 g of *N*-formylpiperidine, bp ~60–70 °C (0.1–0.2 mmHg), and 69.6 g (43.7% yield) of tripiperidinomethane, bp 98–106 °C (0.05–0.1 mmHg) [lit.[5] bp 107–110 °C (0.1 mm)]; NMR ($CDCl_3$) δ 1.43 (br s, 18, $(CH_2)_3$), 2.58 (br s, 12, CH_2N), 3.12 (s, 1, $HC(N)_3$).

2-Cyano-3-piperidinoacrylamide. Tripiperidinomethane (58.4 g, 0.22 mol) and cyanoacetamide (16.8 g, 0.20 mol) were combined in 200 mL of ethanol and stirred for 4.5 h at room temperature. After the mixture cooled, the crystals were filtered, washed, and dried to give 25.3 g (71%) of 2-cyano-3-piperidinoacrylamide: mp 159–161 °C; NMR ($CDCl_3$) δ 1.70 (s, 6, $(CH_2)_3$), 3.50 and 3.90 (2 br s, 4, $N(CH_2)_2$), 5.95 (br s, exchanges with D_2O, 2, NH_2), 7.90 (s, 1, =CH).

Anal. Calcd for $C_9H_{13}N_3O$: C, 60.32; H, 7.31; N, 23.45. Found: C, 60.39; H, 7.39; N, 23.53.

2-(3,4,5-Trimethoxybenzyl)-3-piperidinoacrylonitrile. Tripiperidinomethane (1.86 g, 7 mmol) and 3-(3,4,5-trimethoxyphenyl)propionitrile (1.11 g, 5 mmol) were combined quickly and heated for 18 h at 135 °C (pot temperature) under house vacuum (125 mmHg). The resultant brown oil was taken up in ether (3 mL) and placed on a short silica gel column. The column was washed with dichloromethane and the washings were concentrated to an oil which solidified on standing. The product was washed with ether (3 × 10 mL) and dried to yield 0.88 g (55.5%) of a beige solid (mp 100–101.5 °C), whose NMR spectrum was consistent with the desired structure. A second crop of light yellow solid (mp 86–92 °C) was isolated from the combined ether washings. NMR analysis showed the second crop to be an 85:15 mixture of expected product and starting nitrile. The combined assayed yield for the two crops was 1.075 g (68.0%).

Acknowledgment. We express our appreciation to Dr. David A. Yeowell for his support of this work and for useful comments and suggestions. The competent technical assistance of Mr. Steven L. Cook and Miss Eddie M. Lyon is also gratefully acknowledged.

Registry No. 5 (R = H, R_2 = CH_3, R_3 = C_6H_5), 93-61-8; **5** (R = H, R_2 = C_2H_5, R_3 = C_6H_5), 5461-49-4; **5** (R = CH_3, R_2 = CH_3, R_3 = C_6H_5), 579-10-2; **6** (R_1 = CH_3, R_2 = CH_3, R_3 = C_6H_5), 121-69-7; **6** (R_1 = C_2H_5, R_2 = CH_3, R_3 = C_6H_5), 613-97-8; **7**, 22630-09-7; **8** (X = O, Y = CN, Z = CO_2Et), 6630-64-4; **8** (X = O, Y = CN, Z = $CONH_2$), 25229-97-4; **8** (X = O, Y = CO_2Et, Z = CO_2Et), 62648-61-7; **8** (X = O, Y = *p*-ClC_6H_4, Z = CN), 74552-29-7; **8** (X = CH_2, Y = CN, Z = $CONH_2$), 72915-03-8; **8** (X = O, Y = 3,4,5-$(OMe)_3C_6H_2CH_2$, Z = CN), 30077-81-7; **8** (X = CH_2, Y = 3,4,5-$(OMe)_3C_6H_2CH_2$, Z = CN, 30077-83-9; **9**, 22630-08-6; tris(2,6-dimethylmorpholino)methane, 72915-01-6; tris(*N*-methylpiperazino)methane, 22630-10-0; *N*-methylaniline, 100-61-8; *N*-formylpiperidine, 2591-86-8; *N*-formylmorpholine, 4394-85-8; *N*-ethylmorpholine, 100-74-3; $HC(OCH_3)_3$, 149-73-5; $HC(OC_2H_5)_3$, 122-51-0; $CH_3C(OCH_3)_3$, 1445-45-0; $CH_3(C_6H_5)NH$, 100-61-8; $C_2H_5(C_6H_5)NH$, 103-69-5; piperidine, 110-89-4; morpholine, 110-91-8; 2,6-dimethylmorpholine, 141-91-3; *N*-methylpiperazine, 109-01-3; $HC(O\text{-}i\text{-}Pr)_3$, 4447-60-3; $CH_2(CN)CO_2Et$, 105-56-6; $CH_2(CN)CONH_2$, 107-91-5; $CH_2(p\text{-}ClC_6H_4)CN$, 140-53-4; $CH_2(3,4,5\text{-}(OMe)_3C_6H_2CH_2)CN$, 49621-50-3; $CH_2(CO_2Et)_2$, 105-53-3.

Preparation and Rearrangement of Trichothecane-Like Compounds. Synthesis of Aplysin and Filiformin

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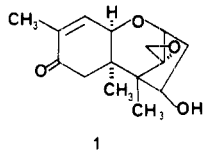
Received March 21, 1980

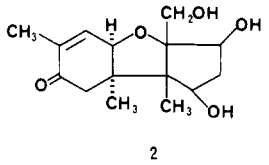
The preparation of three trichothecane-like compounds, olefin **9** and epoxides **10** and **23**, is reported. Subjection of **9** to conditions of acid-catalyzed rearrangement followed by hydrogenation leads to (±)-aplysin. The anti epoxide **10** also undergoes rearrangement but with migration of the aryl group rather than the pyranyl oxygen to give **26**. Syn epoxide **23** does not undergo skeletal rearrangement. Hydrogenation of olefin **9** affords (±)-filiformin.

Introduction

The trichothecane group of sesquiterpenoid fungal metabolites undergoes a variety of acid-catalyzed rearrangements.[1] Trichothecolone, **1**, for example, when treated with aqueous acid affords the rearranged apotrichothecane triol **2**.[2] The ring system and the substituents

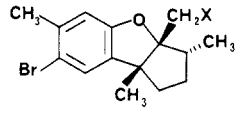


1

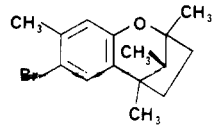


2

at the junction positions of the two five-membered rings of this apotrichothecane bear a striking resemblance to the structural features of several members of the laurane class of marine natural products.[3,4] In particular, the relationship can be seen between rearrangement product **2** and aplysin, **3**,[5] and aplysinol, **4**.[5,6] In addition, the bridged ring system of **1** is mirrored in the structure of another laurane substance, filiformin, **5** (a compound of somewhat dubious natural parentage).[7]



3, X = H
4, X = OH



5

(1) (a) Tamm, Ch. *Fortschr. Chem. Org. Naturst.* **1974**, *31*, 64. (b) Schumacher, R.; Gutzwiller, J.; Tamm, Ch. *Helv. Chim. Acta* **1971**, *54*, 2080. (c) Godtfredsen, W. O.; Vangedal, S. *Acta Chem. Scand.* **1965**, *19*, 1088. (d) Adams, P. M.; Hanson, J. R.; *J. Chem. Soc., Perkin Trans. 1* **1972**, 2783.

(2) Gutzwiller, J.; Mauli, R.; Sigg, H. P.; Tamm, Chm. *Helv. Chim. Acta* **1964**, 47, 2234.

(3) Nakanishi, K.; Goto, T.; Ito, S.; Natori, S.; Nozoe, S. "Natural Products Chemistry"; Academic Press: New York, 1974; Vol. 1., pp 154–161.

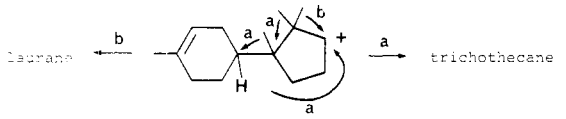
(4) Schuer, P. J. "Chemistry of Marine Natural Products"; Academic Press: New York, 1973.

(5) Yamamura, S.; Hirata, Yi; *Tetrahedron* **1963**, *19*, 1963.

(6) McMillan, J. A.; Paul, I. C.; Caccamese, S.; Rinehart, K. L. *Tetrahedron Lett.* **1976**, 4219.

0022-3263/80/1945-3989$01.00/0

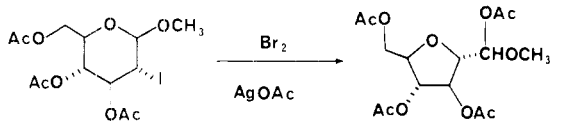
While a strong family relationship clearly exists between these two groups of natural products it must be noted that the laurane compounds are neither direct descendants nor progenitors of the trichothecanes on the sesquiterpene family tree. The two groups do share a common ancestor (other than farnesol), however, and the "missing link" which connects them is presumably a cuparane intermediate equivalent to cation 6.[8] Differing modes of sub-



6

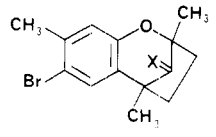
stituent migration, indicated by arrows a and b in structure **6**, lead to the contrasting patterns of methyl substitution found in **1** vs. **3–5**.

As noted above, the rearrangement of the epoxytrichothecane skeleton to the laurane (apotrichothecane) structure is characteristic for the fungal compounds. Outside of this structural class, however, the rearrangement of similar dioxaspirooctanes appears to be unknown,[9] though some related processes have been found in sugar chemistry,[10] for example, the conversion of **7** to **8**.[10a] The

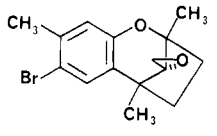


7 8

question of the generality of this type of rearrangement remains, however, since the reaction of the halo sugar is driven by the formation of an energetically favorable intermediate oxonium ion. In this report we describe an investigation of the rearrangement of two trichothecane-like compounds, olefin **9** and epoxide **10**, and the application of their reactivity to the synthesis of aplysin, filiformin, and an isomer of aplysinol.



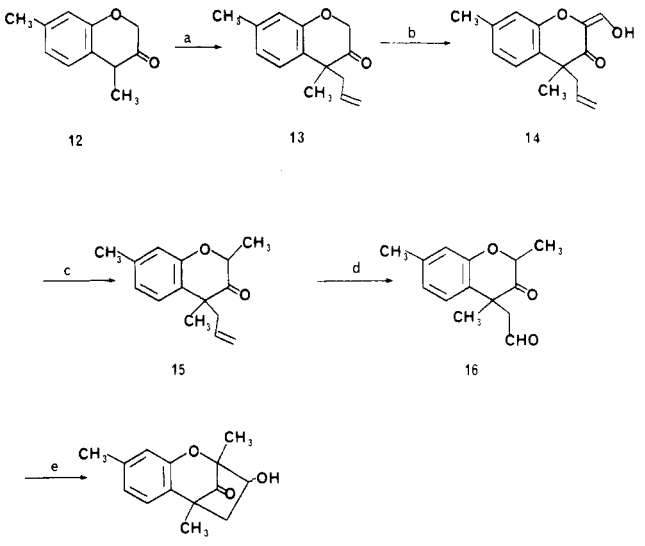
9, X = CH_2
11, X = O



10

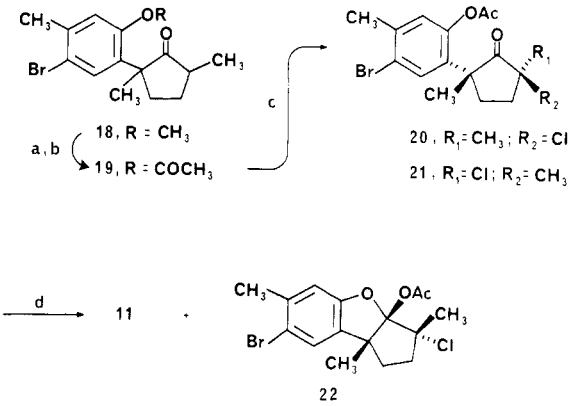
Preparation of Trichothecane-Like Substrates. The key intermediate required for the preparation of **9** and **10** was tricyclic ketone **11**. Two approaches to the construction of **11** were followed. The first, based on ketone

Scheme I[a]



[a] a, $BrCH_2CH{=}CH_2$, KO-*t*-Bu; b, $HCO_2CH_2CH_3$, NaH; c, NaH, CH_3I, KOH; d, OsO_4; e, $NaOCH_3$.

Scheme II[a]

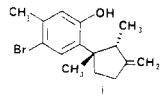


[a] a, $NaSCH_2CH_3$; b, NaH, CH_3COCl; c, SO_2Cl_2; d, DBN.

12[11] as a starting material, is shown in Scheme I. Monoallylation of **12** afforded **13** which was then methylated in standard fashion via the derived α-formyl derivative **14** to afford the dialkylated chromanone **15**. Subjection of the latter to cleavage of the allyl double bond by the action of osmium tetraoxide–sodium periodate[12] yielded **16** as a mixture of epimers. Subsequent exposure of **16** to a sevenfold excess of sodium methoxide in methanol[13] afforded **17** in 71% yield. All attempts to derivatize and remove the hydroxyl group of this rather fragile ketol proved unsuccessful, however.

An alternative approach to the construction of the oxabicyclic system of aromatic trichothecanes has been described by Anderson and co-workers.[14] In this route the central pyran ring is formed by displacement of an α-halo atom of a cyclopentanone by the oxygen of an α'-(*o*-hydroxyaryl) group. Our application of this methodology to the successful preparation of **11** (Scheme II) proceeded from the substituted cyclopentanone **18**, previously re-

(7) Kazlauskas, R.; Murphy, P. T.; Quinn, R. J.; Wells, R. J., *Aust. J. Chem.* **1976**, *29*, 2533. Filliformin is suggested to occur in extracts of *Laurencia filiformin* by virtue of the spontaneous in vitro cyclization of allolaurinterol (i).



(8) (a) Achilladelis, B.; Adams, P. M.; Hanson, J. R. *J. Chem. Soc., Perkin Trans. 1* **1972**, 1425. (b) Adams, P. M.; Hanson, J. R. *J. Chem. Soc., Chem. Commun.* **1971**, 1414. (c) Adams, P. M.; Hanson, J. R. *J. Chem. Soc., Perkin Trans. 1* **1972**, 586.

(9) Inkegami, S.; Ohichi, J.; Akaboshi, S. *Chem. Pharm. Bull.* **1975**, *23*, 2701. These authors report that 1,5-dioxaspiro-2,5-octane, unlike its 5-thia analogue, does not undergo skeletal rearrangement.

(10) (a) Lemieux, R. U.; Fraser-Ried, B. *Can. J. Chem.* **1964**, *42*, 547. (b) Bera, B. C.; Foster, A. B.; Stacey, M. *J. Chem. Soc.* **1956**, 4531. (c) Chan, W.-P.; Gross, P. H. *J. Org. Chem.* **1980**, *45*, 1369.

(11) Still, W. C.; Goldsmith, D. J. *J. Org. Chem.* **1970**, *35*, 2282.

(12) Pappo, R.; Allen, D. S.; Lemieux, R. U.; Johnson, W. S. *J. Org. Chem.* **1956**, *21*, 478.

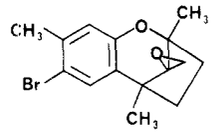
(13) Fujimoto, Y.; Yokura, S.; Nakamura, T.; Morikawa, T.; Tatsun, T. *Tetrahedron Lett.* **1974**, 2523.

(14) (a) Anderson, W. K.; Lee, G. E. *J. Org. Chem.* **1980**, *45*, 501. (b) Anderson, W. K.; LaVoie, E. J.; Lee, G. E. *Ibid.* **1977**, *42*, 1045.

ported by Hirata[15] in the original synthesis of aplysin.

When keto acetate **19** was exposed to sulfuryl chloride promoted chlorination, a mixture of epimers in the ratio of 2:1 was obtained. The major epimer is assumed to be the trans isomer **20** on the basis that the least hindered approach to **19** should be trans to the aryloxy group and the subsequent finding that the desired tricyclic ketone **11** is formed in 61% yield upon treatment of the mixture with DBN in benzene. A second product, **22**, presumably derived from the *cis*-chloro ketone **21** was also isolated in low yield.

Ketone **11** readily yielded the desired olefinic substrate **9** by Wittig methylenation. In the case of the epoxide substrate, the specific stereochemistry shown in **10** was required, i.e., an anti arrangement of the oxiranyl and pyranyl oxygens. Only this isomer should be capable of synchronous epoxide opening and oxygen migration. Eventually, both isomers, **10** and **23**, were prepared



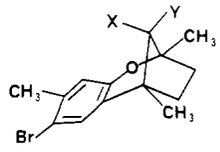
23

Stereochemistry of Epoxidation. Olefin **9** was treated with *m*-chloroperbenzoic acid to afford a single epoxide. The same epoxide was obtained when ketone **11** reacted with dimethyloxosulfonium methylide.[16] Conversely, the reaction of **11** with dimethylsulfonium methylide[16] yielded an epimeric epoxide.

A clear-cut assignment of stereochemistry could not be made for these epoxides on the basis of their spectral characteristics. However, from the fact that only the product from peracid and oxosulfonium methylide epoxidation undergoes the skeletal rearrangement discussed in the following section, it is clear that this compound has the anti configuration **10**. The epoxide obtained with the sulfonium ylide, therefore, is **23**.[17]

The stereochemical outcome of these epoxidation reactions is surprising. The most accessible side of the double bond of **9** or of the carbonyl group of **11** would appear to be, from the examination of molecular models, syn with respect to the aromatic ring. Yet both of the kinetically controlled epoxidation reactions, peracid oxidation[18] and dimethylsulfonium methylide methylene transfer,[16,19] occur from the seemingly more hindered face of the reaction site. Our results indicate, however, that the aromatic region of **9** and **11** is the more encumbered one, presumably due to the effective size of the π system. This conclusion is reinforced, moreover, by the finding that catalytic hydrogenation of olefin **9** yields a single material, the "natural product" filiformin, **5**.[7] The stereochemical assignment of filiformin is unequivocal.[7] For example, both our synthetic material and the reported natural compound show high-field signals in the NMR for the apical methyl group. In the proton spectrum the methyl signal appears at 0.7 ppm while in the ^{13}C NMR spectrum it appears at 7 ppm. These positions are compatible only with a syn relationship of the methyl group and the aromatic ring.

The stereochemistry of epoxidation with sulfur ylide reagents has been shown to be a function of the oxidation state of the sulfur atom. Oxosulfonium methylides usually afford products explainable on the basis that the reactions are equilibrium-controlled processes, ones in which reversibility of attack at a carbonyl carbon allows for formation of the least hindered betaine intermediates. For the reaction of **11** with the oxosulfonium ylide, two betamines are possible, a and b. On the basis of our con-



a, X = O^-, Y = $CH_2SO(CH_3)_2$

b, X = $CH_2SO(CH_3)_2$, Y = O^-

clusions regarding the relative hindrance of the groups on opposite sides of the one carbon bridge of **9** and **11**, betaine a should be the favored intermediate. Yet the ultimate product of this reaction, epoxide **10**, is clearly derived from betaine b. This result may be rationalized by assuming that electronic rather than steric factors determine the relative energies of a and b. Intermediate a contains a negatively charged oxygen in close proximity to both the aromatic ring system and one of the pyranyl oxygen unshared electron pairs. As a consequence this "less hindered" intermediate may be unstable relative to b, the precursor of the observed product **10**.

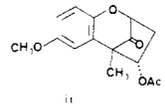
Rearrangement Results. Acid-catalyzed rearrangements of the trichothecane-like intermediates **9**, **10**, and **23** were carried out. When olefin **9** was exposed to the action of toluenesulfonic acid in benzene a rearranged material, dehydroaplysin (**24**),[15,20] was obtained in 66% yield. Saturation of the double bond of **24** gave racemic aplysin identical in all respects, including melting point, with the racemic synthetic material recently reported by Ronald.[20] In contrast, the *syn*-epoxide **23** yielded no identifiable skeletal rearrangement products in the presence of acid catalysts. For example, HCl in methanol promoted reaction gave only a chlorohydrin, **25**, which was reconverted to **23** upon treatment with base. The *anti*-epoxide **10**, however, underwent quantitative rearrangement in the presence of either BF_3/etherate or toluenesulfonic acid to yield **26**, the result of *aryl* migration, rather than a 1,2 shift of the pyranyl oxygen. An X-ray determination[21] of the structure of **27**, the acetate derived from **26**, demonstrated that this rearrangement product has a substitution pattern isomeric with that of natural aplysinol **4**. Catalytic hydrogenation of **26** also produced a saturated alcohol **28**[22] which differed spectroscopically from **4**.

We have thus observed two different modes of rearrangement of our trichothecane-like substrates **9** and **10**: one involving aryl migration, **10** → **26**, and the other involving apparent oxygen migration, **9** → **24**. The latter

(15) Yamada, K.; Yazawa, H.; Uemura, D.; Toda, M.; Hirata, Y. *Tetrahedron* **1969**, *25*, 3509.

(16) (a) Corey, E. J.; Chaykovsky, M. *J. Am. Chem. Soc.* **1965**, *87*, 1353. (b) House, H. O. "Modern Synthetic Reactions", 2nd ed.; W. A. Benjamin: Menlo Park, CA, 1972; p 718.

(17) The epoxide obtained by Anderson and Lee[14a] by treatment of ii with dimethylsulfonium methylide is assigned, without conclusive evidence, the anti configuration. On the basis of our findings this product is more likely to be the syn compound.



ii

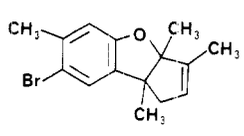
(18) Lynch, B. M.; Pausacker, K. H. *J. Chem. Soc.* **1955**, 1525.

(19) Johnson, C. R. *Acc. Chem. Res.* **1973**, *6*, 341.

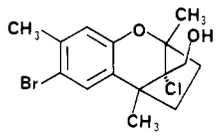
(20) Ronald, R. C. *Tetrahedron Lett.* **1976**, 4413. A total synthesis of optically active aplysin has been reported recently; see: Ronald, R. C.; Gewali, M. B.; Ronald B. P. *J. Org. Chem.* **1980**, *45*, 2224.

(21) The details of this structural study will be reported elsewhere.

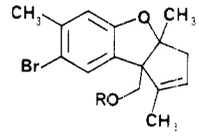
(22) The stereochemistry of reduction product **28** is assumed on the basis of hydrogenation from the convex face of **26**.



24

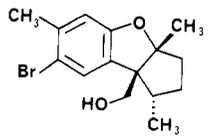


25



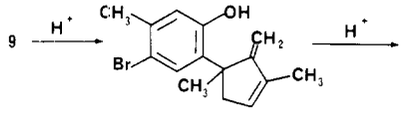
26, R = H

27, R = $COCH_3$



28

process, however, may not involve a concerted 1,2 shift. An alternative pathway for the reaction of **9** may occur by protonation of the pyranyl oxygen followed by elimination to form diene **29**. This substance upon protonation of the



29

exo double bond would then cyclize to form **24**. However, if diene **29** is an intermediate in the rearrangement process it must be consumed rapidly. In attempting to follow the course of the conversion of **9** → **24** by NMR we were unable to detect the presence of signals attributable to **29**. No definitive statement of the generality of dioxaspirooctane rearrangements can be made therefore. Results from the investigation of the acid-catalyzed rearrangements of other pyranyl epoxides will be reported later.

Experimental Section

General. Melting points were obtained in glass capillaries with a Thomas Uni-Melt apparatus. Infrared spectra were determined with Perkin-Elmer Model 257, 457, and 727 spectrophotometers. Nuclear magnetic resonance spectra were obtained with Varian Associates EM-360 and CFT-20 spectrometers and chemical shifts are reported in parts per million (δ) relative to an internal tetramethylsilane reference. Nominal mass spectra were recorded with either a Varian Associates M-66 or Finnigin 4000 spectrometer. Microanalyses werre performed by Atlantic Microlabs, Atlanta, GA, and precise mass measurements were carried out with the Varian M-66 instrument. Reagents and solvents were purified by standard methods.

4,7-Dimethyl-4-(2′-propenyl)chroman-3-one (13). To a cooled stirred solution of 0.97 g (24.1 mmol) of potassium in 10 mL of anhydrous degassed *tert*-butyl alcohol under a nitrogen atmosphere was added 4.38 g (25 mmol) of **12**[11] in 15 mL of *tert*-butyl alcohol. Allyl bromide (8.8 mL) was then added in one portion. Stirring of the mixture was continued for 2 h at room temperature. Standard workup (dilution with water, extraction with ether) afforded an oil which was kugelrohr distilled to give **13** (4.5 g, 84%): bp 130 °C (0.5 torr); IR (neat) 1735, 1650 cm^{-1}; NMR (CCl_4) 1.36 (s, 3), 2.25 (s, 3), 2.45 (m, 2), 4.30 (AB q, J = 17 Hz), 4.80 (m, 1) 5.05 (m, 1) 5.20–5.80 (m, 1), 6.82 (m, 3); mass spectrum (70 eV), m/e 216, 175, 147, 120, 91.

Anal. Calcd for $C_{14}H_{16}O_2$: C, 77.78; H, 7.41. Found: C, 77.70; H, 7.49.

2,4,7-Trimethyl-4-(2′-propenyl)chroman-3-one (15). To a stirred, cooled (10 °C) suspension of 0.5 g (10.23 mmol) of 50% sodium hydride–mineral oil dispersion in 25 mL of anhydrous ether and 0.05 mL of ethanol under a nitrogen atmosphere was added in a dropwise fashion over 1 h a solution of 2.5 g (10.23 mmol) of ketone **13** in 1.46 g (19.5 mmol) of ethyl formate. The reaction was stirred for 18 h at ambient temperature. Unreacted hydride was destroyed with ethanol. Water (20 mL) was added and the phases were separated. The aqueous solution was washed with ether, acidified with cold 6 N HCl, and extracted with ether. Workup of the latter ether extracts in the usual manner afforded, after short-path distillation, 0.9 g (80%) of the α-formyl ketone **14**; NMR ($CDCl_3$) 1.59 (s, 3), 2.30 (s, 3), 2.30–2.82 (m, 2), 4.80–5.73 (m, 3), 6.80–7.3 (m, 3), 8.80 (s, 1).

To a stirred, cooled suspension of washed (benzene, three times) sodium hydride–mineral oil suspension (0.2 g, 4. mmol) in 20 mL of dry 1,2-dimethoxyethane was added 0.88 g of **14** in dropwise fashion. After 1 h at room temperature 1.27 g (9.0 mmol) of methyl iodide was added over 40 min. The reaction mixture was then stirred for 3 h at room temperature and for 12 h at 40 °C. Solvent was then removed by distillation and 60 mL of 10% aqueous KOH was added. After an additional 12 h the reaction was worked up in standard fashion (ether extraction) to yield, after short-path distillation [bp 133–135 °C (0.5 torr)], 1.92 g (64%) of **15**: IR (CCl_4) 1730 cm^{-1}; NMR (CCl_4) δ 1.42 (2 d, 3), 1.41 (s, 3), 2.35 (s, 3), 2.54 (m, 2), 4.20 (2 q, 1), 4.73–5.50 (m, 3), 6.72–7.03 (m, 3).

Anal. Calcd for $C_{15}H_{18}O_2$: C, 78.23; H, 7.88. Found: C, 78.17; H, 7.89.

2,4,7-Trimethyl-3-chromanone-4-acetaldehyde (16). A mixture of 15 mL of ether, 15 mL of water, 1.5 g (6.5 mmol) of **15**, and 17.0 mg (0.65 mmol) of osmium tetroxide was stirred during the addition, over 40 min, of 2.93 g (13.7 mmol) of finely powdered sodium metaperiodate. The temperature was maintained between 24 and 26 °C during the addition and for 80 min thereafter. Water (50 mL) was then added to the pale yellow mixture and it was subsequently extracted with two 50-mL portions of ether. The ether solution was washed with 1% aqueous NaOH and dried and the solvent removed. Kugelrohr distillation [bp 120–122 °C (0.25 torr)] of the residue gave 1.03 g (68%) of **19**: IR (CCl_4) 2740, 1730 cm^{-1}; NMR (CCl_4) δ 1.23 (s, 3), 1.30–1.60 (m, 3), 2.30 (s, 3), 2.68–3.40 (m, 2), 4.50 (q, 1), 6.80–6.94 (m, 3), 9.48 (d, 1); precise mass calcd for $C_{14}H_{16}O_3$ m/e 232.109 98, found m/e 232.109 58.

Aldol Cyclization of 16 (17). Keto aldehyde **16** (0.2 g, 0.9 mmol) was dissolved in 5 mL of absolute methanol to which was added a solution of 0.142 g (6.2 mmol) of sodium in 10 mL of absolute methanol. The mixture was heated at reflux for 35 min, concentrated to half-volume in vacuo, and then poured onto ice. The mixture was then extracted with ether and the ether solution dried and evaporated in vacuo. Chromatography of the residue on silica gel afforded 0.15 g (71%) of **17** as an oil: IR (CCl_4) 3640, 3520, 1769 cm^{-1}; NMR (CCl_4) 1.25 (s, 3), 1.28 (s, 3), 1.62 (d of d, J = 14, J = 4 Hz, 1), 2.95 (d of d, J = 14, J = 9 Hz, 1), 4.25 (d of d, J = 9, J = 4 Hz, 1), 6.61 (m, 3); precise mass calcd for $C_{14}H_{16}O_3$ m/e 232.109 98, found m/e 232.107 89.

2,5-Dimethyl-2-(2-acetoxy-4-methyl-5-bromophenyl)-cyclopentanone (19). A. Cleavage of the Methyl Ether of 18. Methoxy ketone **18**[15] (4 g, 12.9 mmol) in 25 mL of dry DMF was added dropwise to a solution (5 mL) of sodium thioethoxide (prepared from 1.99 g, 32.1 mmol, of ethanethiol and 1.48 g, 32.1 mmol, of 50% sodium hydride–oil dispersion) which was maintained at 95 °C with stirring for 3 h. After cooling, the reaction mixture was poured into water and the latter then extracted with ethyl acetate. Removal of the dried solvent afforded the crude demethylated material as a mixture of phenolic and hemiketal isomers.

B. Acetylation. The crude product from A was converted to its sodium salt (50% sodium hydride–oil dispersion, 0.69 g, 15 mmol; ether, 10 mL; room temperature), the solution was cooled to −30 °C, and 1.6 g (20 mmol) of acetyl chloride was added with vigorous stirring. After 10 min the mixture was poured into ice-cold 10% HCl. Workup with ether in the usual fashion gave a solution which was filtered through silica gel to yield, after solvent removal, acetate **19**: 3.0 g (69%); mp 114–115 °C; IR ($CHCl_3$) 1775–1735 (br), 1620 cm^{-1}; NMR (CCl_4) δ 1.24 (d, 3), 1.34 (s, 3), 2.22 (s, 3), 5.35 (s, 3), 6.98 (s, 1), 7.53 (s, 1).

Anal. Calcd for $C_{16}H_{19}BrO_3$: C, 56.64; H, 5.65. Found: C, 56.66; H, 5.68.

Chlorination of Ketone 19 (20 and 21). To a stirred, cold (0 °C) solution of keto acetate **19** (3 g, 8.85 mmol) in 20 mL of CCl_4 was added 1.89 g (13.3 mmol) of freshly distilled sulfuryl chloride. The ice bath was removed and stirring was continued for 15 h at room temperature. Ice and water were then added to the reaction mixture, the layers were separated, and the aqueous

phase was extracted with CH_2Cl_2. The organic extracts were then washed with water, 10% K_2CO_3 solution, and saturated salt solution. Drying (Na_2CO_3) and removal of solvent gave 3.4 g (99%) of **20** and **21**: IR ($CHCl_3$) 1740, 1610 cm^{-1}; NMR (CCl_4) δ 1.56 (3 H, s), 1.66 and 1.72 (s, s, 3), 2.20 (m, 4), 2.28 (br s, 3), 2.40 (br s, 3), 6.95 (s, 1 H), 7.34 (s, 1 H). Integration of the methyl signals at 1.66 and 1.72 ppm indicated an isomer ratio of 2:1 **20**–**21**.

Anal. Calcd for $C_{16}H_{18}BrClO_3$: C, 51.43; H, 4.85. Found: C, 51.55; H, 4.92.

Cyclization of Chloro Ketone Mixture 20 and 21 (11 and 22). DBN (1.3 g, 11 mmol) was added to a cold (0 °C) stirred solution of 3.4 g (9 mmol) of **20** and **21** in benzene. The cooling bath was removed and the mixture was stirred at room temperature for 15 min. Benzene was removed in vacuo and the residue was chromatographed on silica gel (hexane followed by 19:1 hexane–ether). From the more polar fractions there was isolated the bridged ketone **11** (1.08 g, 61% based on the proportion of **20** in the chloro ketone mixture): mp 122–123 °C; IR ($CHCl_3$) 1765, 1605, 1550 cm^{-1}; NMR ($CDCl_3$) δ 1.37 (s, 3), 1.42 (s, 3), 2.27 (s, 3), 1.5–2.3 (m, 4), 6.61 (s, 1), 7.11 (s, 1).

Anal. Calcd for $C_{14}H_{15}BrO_2$: C, 56.96; H 5.12. Found: C, 56.86; H, 5.19.

Rechromatography of the nonpolar fractions (silica gel, hexane) afforded crystalline **22**: mp 123–125 °C; IR ($CDCl_3$) 1755, 1615 cm^{-1}; NMR ($CDCl_3$) δ 1.45 (s, 3), 1.69 (s, 3), 1.91 (m, 4), 2.06 (s, 3), 2.33 (s, 3), 6.72 (s, 1), 7.14 (s, 1); mass spectrum, *m/e* 374, 372, 332, 330, 228, 226.

Preparation of Olefin 9. To a solution of 1.12 mmol of methylenetriphenylphosphorane, prepared in the standard fashion using butyllithium, in 10 mL of dry THF was added 0.25 g (0.85 mmol) of ketone **11** in 5 mL of THF. After 12 h at reflux temperature the THF was removed in vacuo. The residue was taken up in hexane (100 mL) and the solution was washed with water and brine. Removal of the dried solvent, followed by chromatrography (silica gel, hexane), gave olefin **9** (0.22 g, 89%): mp 93–94 °C; IR ($CHCl_3$) 1620, 1565 cm^{-1}; NMR (CCl_4) δ 1.45 (s, 3), 1.49 (s, 3), 2.22 (s, 3), 1.6–2.2 (m, 4), 4.86 (s, 1), 4.99 (s, 1), 6.46 (s, 1), 7.08 (s, 1).

Anal. Calcd for $C_{15}H_{17}BrO_2$: C, 61.44; H, 5.84; Br, 27.27. Found: C, 61.40; H, 5.84; Br, 27.23.

Preparation of (±)-Filiformin (5). Olefin **9** (0.046 g, 0.16 mmol) was hydrogenated over 10% Pd on carbon (0.005 g) in ethyl acetate at 1 atm. Filtration of the catalyst and removal of solvent gave 0.045 g (96%) of (±)-filiformin: mp 61–62 °C (95% ethanol); IR annd ^1H and ^{13}C NMR spectra were identical with those reported[7] for the natural product; precise mass calcd for $C_{15}H_{19}BrO$ *m/e* 294.064 64, found 294.061 93.

Conversion of 9 to Dehydroaplysin (24). A solution of olefin **9** (0.06 g, 0.21 mmol) and a catalytic amount of *p*-toluenesulfonic acid in 20 mL of benzene was heated at reflux with stirring for 5 h. The cooled solution was then washed twice with water, the organic layer was dried, and the solvent was removed in vacuo. The residue was purified by preparative TLC (silica gel, hexane) to yield 0.04 g (66%) of (±)-dehydroaplysin, spectroscopically identical with the material previously reported by Ronald.[20]

(±)-Aplysin (3). Hydrogenation of **24** (0.04 g, 0.137 mmol) by the procedure given for **5** afforded, after preparative TLC (silica gel, hexane) and crystallization from 95% ethanol, 0.02 g (50%) of (±)-aplysin. The melting point, 96–98 °C, was identical with that of a sample of (±)-aplysin similarly recrystallized and was undepressed on admixture; IR, ^1H ^{13}C NMR, and mass spectra were identical with those of authentic material.[20]

Preparation of *anti*-Epoxide 10. A. Peracid Oxidation of 9. Olefin **9** (0.07 g, 0.24 mmol) in 5 mL of $CHCl_3$ was treated with 0.041 g (0.24 mmol) of *m*-chloroperbenzoic acid for 24 h at room temperature. After dilution with 50 mL of $CHCl_3$, the solution was washed with ice-cold 5% NaOH and then with water. Removal of dried solvent gave epoxide **10** as an oil (0.07 g, 95%): IR ($CHCl_3$) 1616, 1560 cm^{-1}; NMR ($CDCl_3$) δ 1.1 (s, 3), 1.2 (s, 3), 2.12 (m, 4), 2.24 (s, 3), 2.75 (d, J = 5 Hz, 1), 2.94 (d, J = 5 Hz, 1), 6.62 (s, 1), 7.18 (s, 1).

Anal. Calcd for $C_{15}H_{17}BrO_2$: C, 58.26; H, 5.55. Found: C, 58.09; H, 5.60.

B. Oxosulfonium Ylide Reaction. Ketone **11** (0.2 g, 0.68 mmol) in 5 mL of Me_2SO (containing sufficient THF for homogeneous solution) was added to a mixture of 0.74 mmol of dimethyloxosulfonium methylide[16] in 5 mL of Me_2SO. The mixture was heated at 55 °C under nitrogen for 1.5 h. Standard workup and chromoatgraphy (silica gel, hexane/CH_2Cl_2) gave 0.16 g (76%) of **10**.

Preparation of *syn*-Epoxide 23. A THF solution (10 mL) of ketone **11** (0.2 g, 0.68 mmol) was added to a stirred solution of 0.68 mmol of dimethylsulfonium methylide[17] in 10 mL of Me_2SO at −10 °C. The mixture was stirred for an additional 15 min at −10 °C and for 15 min at room temperature. Ice, water, and saturated salt solution were then added and the solution was extracted with ether. Standard workup gave 0.19 g of a light yellow oil which was chromatographed (silica gel, ether–hexane) to yield oxirane **23** (0.15 g, 72%): mp 115–117 °C; IR ($CHCl_3$) 2980, 2940, 2895, 1610, 1555, 1390 cm^{-1}; NMR ($CDCl_3$) δ 1.04 (s, 3), 1.20 (s, 3), 1.4–2.1 (m, 4), 2.23 (s, 3), 2.89 (d, J = 4 Hz), 3.06 (d, J = 4 Hz), 6.53 (s, 1), 7.06 (s, 1); precise mass calcd for $C_{15}H_{17}BrO_2$ *m/e* 308.041 07, found 308.039 65.

Acid-Catalyzed Rearrangement of *anti*-Epoxide 10 (26). A benzene solution (50 mL) of **10** (0.07 g, 0.23 mmol) containing a catalytic amount of *p*-toluenesulfonic acid was heated under reflux for 6 h. Standard workup gave **26** (0.07 g).

The same product, **26**, was produced by treatment of **10** with BF_3–etherate in benzene solution at room temperature: IR ($CHCl_3$) 3600, 1615, 1565 cm^{-1}; NMR ($CDCl_3$) δ 1.57 (s, 3), 1.63 (br s, 3), 2.36 (s, 3), 2.72 (m, 2), 3.81 (d, J = 12 Hz, 1), 4.18 (d, J = 12 Hz, 1), 5.65 (m, 1), 6.78 (s, 1), 7.40 (s, 1); mass spectrum, *m/e* 310, 308, 292, 290, 279, 277, 265, 263, 239, 237, 211, 198, 183.

Acetylation of 26 (27). Alcohol **26** (0.28 g, 0.9 mmol) was acetylated (acetic anhydride, 1 mL; pyridine, 10 mL) to afford, after workup and crystallization from pentane, acetate **27** (0.27 g, 85%): mp 90–91 °C; IR ($CHCl_3$) 2960, 2890, 1740, 1621, 1590, 1485, 1385, 1245; NMR ($CDCl_3$) δ 1.51 (s, 3), 1.68 (m, 3), 2.08 (s, 3), 2.38 (s, 3), 2.70 (m, 2), 4.13 (d, J = 12 Hz, 1), 4.83 (d, J = 12 Hz, 1), 5.65 (m, 1), 6.78 (s, 1), 7.40 (s, 1); precise mass calcd for $C_{17}H_{19}BrO_3$ *m/e* 350.050 17, found 350.051 75.

Hydrogenation of 26 (28). Hydrogenation of 0.07 g (0.23 mmol) of **26** over 10% Pd on carbon at 1 atm in ethyl acetate gave after preparative TLC purification (silica gel, 1:4 ether–hexane) 0.035 g (49%) of **28**: mp 72–73 °C; IR ($CHCl_3$) 3650, 3500, 1625, 1685 cm^{-1}; NMR ($CDCl_3$) δ 0.9 (d, J = 7 Hz, 3), 1.5 (s, 3), 2.3 (s, 3), 3.76 (s, 2), 6.6 (s, 1), 7.1 (s, 1); mass spectrum, *m/e* 312, 310, 281, 279, 255, 253, 289, 287, 200; precise mass calcd for $C_{15}H_{19}BrO_2$ *m/e* 310.056 81, found 310.053 89.

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