A Facile, Expeditious Route to the Benzooxabicyclo[3.2.1]octane System. Application to a Short, High-Yield Synthesis of Filiformin

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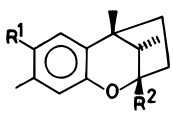
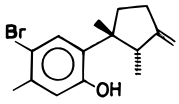
A facile and efficacious route to the benzooxabicyclo[3.2.1]octane system has been developed and applied to a synthesis of filiformin (**1**). The cycloaddition of ethylene to the methoxychromone **13** furnished the oxetanol **14** through a tandem cycloaddition and γ-hydrogen abstraction sequence. Lithium aluminum hydride reduction to the diol **15** followed by acid-catalyzed rearrangement produced benzooxabicyclooctanone (**16**), arising from exclusive external bond migration. Similarly, ethoxychromone (**17**) under the same sequence of reactions afforded the homologous bridged ketone **20**. For the synthesis of filiformin (**1**), methoxychromone **24** on ethylene cycloaddition followed by reduction of resultant oxetanol **25** with lithium aluminum hydride furnished diol **10**. Acid-catalyzed rearrangement of **10** provided the bridged ketone **11** which was brominated to give **26**. This bromo ketone had previously been converted to filiformin (**1**), and also aplysin **9**, and hence, the present work represents a short, high-yield formal synthesis of these sequiterpenes from a single starting material.

Introduction

The marine sesquiterpene filiformin and congeners constitute the only examples of naturally occurring compounds featuring a benzooxabicyclo[3.2.1]octane system.[1] The oxabicyclo[3.2.1]octane unit is, however, present in the more widely distributed sesquiterpene antibiotics, the trichothecenes.[2] The isolation of filiformin (**1**) and filiforminol (**2**) was first reported by Wells et al.[1a] from the alga *Laurencia filiformis*, which also contained the uncyclized compound, allolaurinterol (**3**). It has been suggested that **1** must be regarded as an artifact formed by spontaneous *in vitro* cyclization of **3**. Additional observation on cyclization of **3** to **1** during NMR measurements by addition of a trace of trifluoroacetic acid to a solution of **3** in $CDCl_3$ also supported this conjecture. Subsequently, several brominated analogs **4**−**6** have also been isolated.[1b]



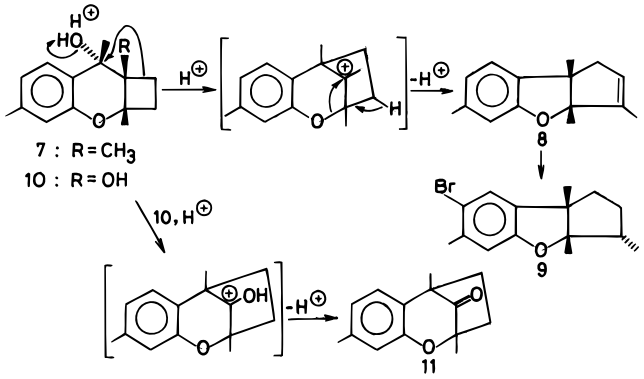


3

1: R^1=Br ; R^2=CH_3
2: R^1=Br ; R^2=CH_2OH
4: R^1=H ; R^2=CH_2Br
5: R^1=Br ; R^2=CH_2Br
6: R^1=H ; R^2=$CHBr_2$

There have been very few successful efforts at the synthesis of the ring system of **1**.[3] These have involved multistep transformations and attendant poor yields. The importance of the benzooxabicyclo[3.2.1]octane system also stems from the fact that some of the A-ring aromatic trichothecene analogs incorporating this basic unit display significant biological activity.[4] In this paper,[5] we present the full details of our expeditious and convenient approach to the benzooxabicyclo[3.2.1]octane system and its application to a short, high-yield synthesis of filiformin (**1**).

Scheme 1



Our strategy for the development of the ring system present in **1** relied on a cyclobutyl carbinol rearrangement. Previously, we had reported[6] the acid-catalyzed rearrangement of the cyclobutyl carbinol **7** involving a primary external bond migration followed by a 1,2-oxygen shift to lead to the key intermediate **8** in a highly economical synthesis of the marine sesquiterpene aplysin (**9**, Scheme 1). If a suitable modification were introduced into the carbinol such that the rearrangement were terminated with the migration of the external bond, then the benzooxabicyclo[3.2.1]octane ring system would be formed. Replacing an angular methyl group with a hydroxy group so that rapid ketonization after the initial external bond migration would result in the desired ring system (Scheme 1, **10** → **11**). Since we had already

† In part.

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(3) (a) Goldsmith, D. J.; John, T. K.; Kwong, C. D.; Painter, G. R., III. *J. Org. Chem.* **1980**, *45*, 3989. (b) Laronze, J. Y.; Boukili, R. E.; Patigny, D.; Dridi, S.; Cartier, D.; Levy, J. *Tetrahedron* **1991**, *47*, 10003.

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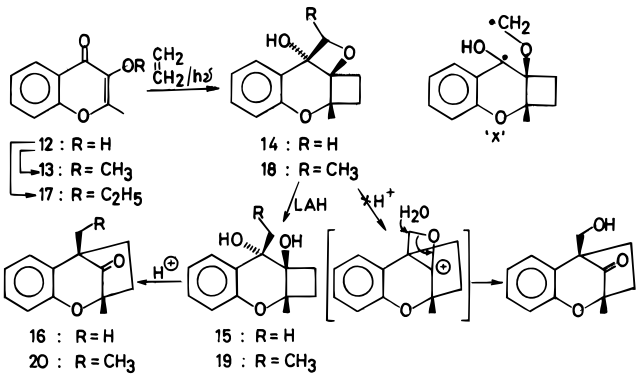
developed conditions[6] that favor a primary external bond migration in these cyclobutyl carbinol rearrangements, the proposed route appeared viable. We report here a short synthesis of filiformin (**1**) following this approach.

Results and Discussion

Generation of the required angular hydroxy substituted cyclobutyl carbinol for rearrangement studies entailed a photolytic ethylene addition to a suitably substituted 3-hydroxychromone followed by a Grignard reaction. Before synthesizing the requisite chromone, the course of the proposed strategy was studied using the known 3-hydroxy-2-methylchromone (**12**).[7] Irradiation of a benzene solution of **12** subjected to a continuous flow of ethylene gave only recovered **12**.[8] Conversion of **12** to methyl ether **13** was accomplished through reaction with methyl iodide in the presence of anhydrous potassium carbonate. Irradiation of **13** as described for **12** resulted in a gradual disappearance of **13**; after 5 h, no more **13** could be detected by TLC. The benzene was distilled off, and the viscous residue was purified by preparative TLC to furnish a solid product in 73% yield which was characterized as oxetanol **14**. Elemental analysis corresponded to a molecular formula $C_{13}H_{14}O_3$, and the IR spectrum showed the absence of a carbonyl group. The ^{1}H NMR spectrum revealed the absence of methoxy protons but showed a two-proton AB quartet at δ 4.43 and 4.56 along with a singlet at δ 2.81 corresponding to one proton assignable to a hydroxy group based on D_2O exchange experiments. The above features fit the oxetanol structure **14**, an assignment which was also borne out by subsequent transformations.

The formation of oxetanol **14** by photolytic ethylene addition to **13** can be explained in terms of a hydrogen abstraction from the methoxy substituent in the initial photoadduct by the photoexcited carbonyl group to give a 1,4-biradical X in a Norish type II process. Radical recombination then results in the oxetanol **14**. Abstraction of a γ-hydrogen in the photolysis of α-methoxy ketones to produce oxetanols is well precedented,[9] and the tandem cycloaddition and γ-hydrogen abstraction in alkene addition to α-methoxy enones has also been reported.[10] The assignement of *cis* stereochemistry to the ring juncture in **14** followed from our previous results[6] of ethylene addition to chromones, while the configuration of the oxetanol has been assigned by analogy to cognate systems.[10] Similar irradiation of ethoxychromone **17**, prepared by alkylation of **12** with ethyl iodide, furnished oxetanol **18**, in 68% yield, as a single epimer at the secondary methyl group. The homogeneity was evident from ^{1}H NMR which showed only one doublet at δ 1.35 for the secondary methyl group and a quartet at δ 4.58 for the methine hydrogen. It has not been possible to conclusively assign the configuration of this secondary methyl group but subsequent transformations remove this asymmetric center. Embedded within the oxetanol structure **14** was the desired angular hydroxy cyclobutyl carbinol system proposed as the progenitor of a cyclopentanone (bridged or fused) which would be revealed through an acid-catalyzed rearrangement, in the manner of the well-known pinacol−pinacolone rearrangement. Initial external bond migration would eventually provide the benzooxabicyclo[3.2.1]octane system (Scheme 2). To our knowledge, the potential of oxetanols has not been explored.[11] Attempted rearrangement of **14** under a few conditions ($BF_3{\cdot}Et_2O$ in benzene, sulfuric acid in petroleum ether or in nitromethane) led to a complex and unencouraging product mixture. An alternate pathway from **14** was then tried. Oxetanol **14** was reduced with lithium aluminum hydride in refluxing tetrahydrofuran, furnishing the diol **15** in excellent yield. This diol was endowed with all the features needed for the acid-catalyzed rearrangement to the benzooxabicyclo[3.2.1]-octane system (Scheme 1). The rearrangement was initially tried using $BF_3{\cdot}Et_2O$ as catalyst. Treatment of **15** in benzene with a catalytic amount of $BF_3{\cdot}Et_2O$ at ambient temperature for 1 h furnished bridged ketone **16** in very good yield as the only islated product, arising from exclusive migration of the external bond. The structural assignment of **16** followed from spectral analysis, particularly IR, which displayed a strong carbonyl absorption at 1765 cm^{-1} in agreement with the value reported for this system.[3a,4] Interestingly and indeed gratifyingly, no isomeric cyclopentanone product from initial internal bond migration was seen. The rearrangement of **15** was next carried out under different polar conditions, (i) $BF_3{\cdot}Et_2O$ or sulfuric acid in petroleum ether at −78 °C, (ii) $BF_3{\cdot}Et_2O$ or sulfuric acid in nitroethane at −78 °C, which had remarkably altered the course of the initial bond migration.[6] Even under these conditions, diol **15** furnished only bridged ketone **16** in yields ranging from 80 to 85%. Although the reasons for the exclusive external bond migration under a variety of conditions are not immediately apparent, the result provided us with a novel and facile access to the benzooxabicyclo[3.2.1]octane system. Application of the sequence of lithium aluminum hydride reduction and rearrangement to oxetanol **18** afforded bridged ketone **20** exclusively in excellent yield.

Scheme 2



With an efficient and short route to the benzooxabicyclo-[3.2.1]octane system in hand, we turned to applying this methodology to a synthesis of filiformin **1**. This required starting from 2,7-dimethyl-3-methoxychromone which

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(8) The 3-hydroxychromones were sparingly soluble in this solvent. Other solvents, like acetonitrile and THF, were tried without success.

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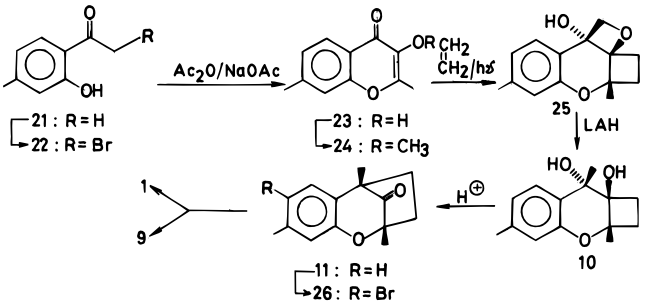
(11) For the possibly only other but unsuccessful attempt see: Schultz, A. G.; Taveras, A. G.; Kullnig, R. K. *Tetrahedron Lett.* **1990**, *31*, 849.

Scheme 3



was prepared as follows. 2-Hydroxy-4-methylacetophenone (**21**) was brominated[12] to furnish bromo ketone **22** which was then transformed to 2,7-dimethyl-3-hydroxychromone (**23**) following the procedure of Ellis et al.[7] and then methylated with methyl iodide to desired methoxychromone **24** (Scheme 3). Irradiation of a benzene solution of **24** with continuous passage of ethylene through the solution produced oxetanol **25** in 75% yield. Reduction of this oxetanol with lithium aluminum hydride in refluxing tetrahydrofuran furnished diol **10** in 95% yield as a crystalline solid. The rearrangement of diol **10**, under all the previously described conditions, followed the already established pathway to give bridged ketone **11** in yields ranging between 85 and 90%. The IR absorption at 1765 cm^{-1}, in combination with ^1H NMR and ^{13}C NMR spectral features, confirmed the structural assignment. Controlled bromination of **11** following our previous procedure[13] afforded bromo ketone **26** in good yield. The melting point and ^1H NMR spectrum of **26** were in agreement with those of an authentic sample synthesized previously by Goldsmith et al.[3a] Since this bromo ketone had served as an advanced intermediate in their synthesis of filiformin (**1**) and aplysin (**9**), our synthesis of **26** concluded a formal total synthesis of both sesquiterpenes from a single precursor. The attractive features of the synthesis are the use of readily available and inexpensive reagents and simple reaction conditions which make it a viable process.

In conclusion, an expeditious route to the benzooxabicyclo[3.2.1]octane system has been developed and applied to a short, high-yield formal synthesis of filiformin and aplysin. The synthesis revealed for the first time the potential of oxetanols as intermediates in synthesis and additionally underscored the versatility of the cyclobutyl carbinol rearrangements in providing convenient access to polycyclic frameworks of complex natural products under simple reaction conditions. This versatility forms the basis of the current, continued interest in the application of this rearrangement to natural product synthesis.[14]

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Experimental Section

General Procedures. All the compounds described herein possessing asymmetric centers are racemates. All reactions were performed under a N_2 atmosphere. Compounds isolated by the reported purification procedures were sufficiently pure for the next reaction. However, for analytical purposes, solid compounds were crystallized from suitable solvents, and melting points of such crystallized samples have been reported and are uncorrected. Liquid products were subjected to bulb to bulb distillations, and the oven temperature is designated as ot. Solvents and reagents were reagent grade materials and were further purified by conventional methods. The petroleum ether that was used is that fraction of bp 60−80 °C and light petroleum ether of bp 40−60 °C. Et_2O refers to diethyl ether. Preparative TLC was performed with silica gel 60 HF_{254} plates of 1-mm thickness. Na_2SO_4 was used to dry organic extracts.

^1H NMR spectra of $CDCl_3$ solutions were recorded at 100, 200, or 300 MHz and that of CCl_4 solutions at 60 MHz. The IR spectra are of $CHCl_3$ solutions.

2-Methyl-3-methoxychromone (13). A mixture of 2-hydroxy-3-methylchromone (**12**)[7] (810 mg, 4.6 mmol), MeI (710 mg, 5 mmol), and anhydrous K_2CO_3 (691 mg, 5 mmol) in dry acetone (25 mL) was heated under reflux with stirring for 4 h. It was then concentrated, diluted with water, and extracted with Et_2O. The ether extracts were washed with water, dried, and concentrated to afford methoxychromone **13** as a solid (740 mg, 85%): crystallized from ether−light petroleum ether; mp 102−103 °C; IR 1640 cm^{-1}; ^1H NMR (CCl_4) δ 2.40 (s, 3H), 3.89 (s, 3H), 7.17−7.76 (m, 3H), 8.10−8.30 (m, 1H). Anal. Calcd for $C_{11}H_{10}O_3$: C, 69.46; H, 5.30. Found: C, 69.63; H, 5.46.

2-Methyl-3-ethoxychromone (17). Alkylation of 2-hydroxy-3-methylchromone (**12**) (540 mg, 3.07 mmol) with EtI (624 mg, 4 mmol) in the presence of anhydrous K_2CO_3 (553 mg, 4 mmol) in dry acetone (20 mL) was carried out as per the procedure for **13** to furnish ethoxychromone **17** as an oil (490 mg, 78%): ot 95−100 °C (0.05 mmHg); IR 1640 cm^{-1}; ^1H NMR (CCl_4) δ 1.33 (t, J = 7 Hz, 3H), 2.40 (s, 3H), 4.17 (q, J = 7 Hz, 3H), 2.40 (s, 3H), 4.17 (q, J = 7 Hz, 2H), 7.10−7.74 (m, 3H), 8.06−8.26 (m, 1H). Anal. Calcd for $C_{12}H_{12}O_3$: C, 70.57; H, 5.92. Found: C, 70.46; H, 5.96.

***cis*-1,2,2a,7c-Tetrahydro-2a-methyl-7c-oxeto-9*H*-benzo[*b*]cyclobuta[*e*]pyran-7b-ol (14).** A solution of chromone **13** (440 mg) in dry thiophene-free benzene (260 mL) was irradiated through a Pyrex filter with a Hanovia 450 W mercury lamp for 5 h, during which time ethylene was bubbled through the solution. Then the solvent was evaporated under reduced pressure. The residual viscous oil was purified by preparative TLC [petroleum ether/EtOAc (9:1)] to afford **14** as a colorless crystalline solid (370 mg, 73%): crystallized from ether−light petroleum ether; mp 110−111 °C; ^1H NMR ($CDCl_3$) δ 1.40−1.52 (m, 1H), 1.58 (s, 3H), 1.68−1.86 (m, 2H), 2.34−2.48 (m, 1H), 2.81 (s, 1H, OH), 4.43 and 4.56 (ABq, J = 6.7 Hz, 2H), 6.90−7.10 (m, 2H), 7.24−7.34 (m, 1H), 7.49 (dd, J = 7.7, 1.7 Hz, 1H). Anal. Calcd for $C_{13}H_{14}O_3$: C, 71.54; H, 6.47. Found: C, 71.72; H, 6.51.

***cis*-1,2,2a,7c-Tetrahydro-2a,9-dimethyl-7c-oxeto-9*H*-benzo[*b*]cyclobuta[*e*]pyran-7b-ol (18).** Photolytic ethylene addition to chromone **17** (480 mg) in dry thiophene-free benzene (260 mL) was carried out as for **14** to furnish **18** as a solid (370 mg, 68%): crystallized from ether−light petroleum ether; mp 75−77 °C; ^1H NMR ($CDCl_3$) δ 1.39 (d, J = 6 Hz, 3H), 1.58 (s, 3H), 1.68−1.84 (m, 2H), 2.20−2.48 (m, 2H), 4.58 (q, J = 6 Hz, 1H), 6.88−7.52 (m, 4H).

Analytical data (C, H) for the oxetanol **18** could not be obtained. However, isobutane chemical ionization (IBCI) showed MH^+ at 233 corresponding to the desired molecular weight.

***cis*-1,2,2a,8a-Tetrahydro-2a,8-dimethyl-8*H*-benzo[*b*]cyclobuta[*e*]pyran-8,8a-diol (15).** To a magnetically stirred solution of oxetanol **14** (200 mg, 0.92 mmol) in dry THF (15 mL) was added LAH (35 mg, 0.92 mmol). The mixture was then vigorously refluxed for 5 h. Upon cooling, the reaction mixture was treated with saturated aqueous Na_2SO_4. The ether layer was separated, and the aqueous layer was extracted with Et_2O. The combined ether extracts were washed

with saturated brine, dried, and concentrated to afford diol **15** as a crystalline solid (190 mg, 94%): crystallized from light petroleum ether; mp 92−93 °C; ^{1}H NMR ($CDCl_3$) δ 1.39 (s, 3H), 1.55 (s, 3H), 1.60−1.74 (m, 2H), 1.86−2.06 (m, 2H), 2.13 (s, 1H, OH), 2.21 (s, 1H, OH), 6.91 (dd, J = 7.8, 1.3 Hz, 1H), 7.06−7.17 (m, 1H), 7.21−7.32 (m, 1H), 7.55 (dd, J = 7.5, 1.8 Hz, 1H). Anal. Calcd for $C_{13}H_{16}O_3$: C, 70.89; H, 7.32. Found: C, 70.86; H, 7.38.

2,3,4,5-Tetrahydro-2,5-dimethyl-2,5-methano-1-benzoxepin-10-one (16). Method A. To a magnetically stirred solution of diol **5** (90 mg) in benzene (10 mL) at rt was added a drop of freshly distilled BF_3·Et_2O. The mixture was stirred for 1 h and then treated with saturated aqueous $NaHCO_3$. The two liquid layers were separated. The aqueous layer was extracted with Et_2O. The combined organic layers were washed with water, dried, and concentrated. The residual oil was purified by preparative TLC [petroleum ether/EtOAc (98:2)] to afford the ketone **16** (70 mg, 85%): ot 78−83 °C (0.05 mmHg); IR 1765 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.43 (s, 3H), 1.44 (s, 3H), 1.78−2.08 (m, 2H), 2.20−2.66 (m, 2H), 6.74−7.26 (m, 4H). Anal. Calcd for $C_{13}H_{14}O_2$: C, 77.20; H, 6.98. Found: C, 76.85; H, 7.03.

Method B. To a magnetically stirred solution of diol **15** (90 mg) in dry petroleum ether (10 mL) at −78 °C was added a drop of concentrated H_2SO_4 or BF_3·Et_2O. The mixture was stirred at −78 °C for 1 h and then was allowed to warm to rt and then treated with saturated aqueous $NaHCO_3$. Et_2O was added. The two liquid layers were separated, and the aqueous layer was extracted with Et_2O. The combined organic layers were washed with water, dried, and concentrated. The residual oil was purified by preparative TLC as before to afford bridged ketone **16** (68 mg, 83%). This was identical with a sample prepared by method A.

Method C. To a magnetically stirred solution of the diol **15** (90 mg) in dry $EtNO_2$ (10 mL) at −78 °C was added a drop of concentrated H_2SO_4 or BF_3·Et_2O. After being stirred for 30 min, the reaction mixture was allowed to warm to 0 °C and neutralized by adding saturated aqueous $NaHCO_3$. Et_2O was added, and the layers were separated. The aqueous layer was extracted with Et_2O. The combined organic layers were washed with water, dried, and concentrated. Preparative TLC purification of the residual oil furnished ketone **16** (70 mg, 85%), identical with a sample prepared by previous methods.

***cis*-1,2,2a,8a-Tetrahydro-2a-methyl-8-ethyl-8*H*-benzo[*b*]cyclobuta[*e*]pyran-8,8a-diol (19).** Reduction with LAH of oxetanol **18** (140 mg, 0.56 mmol) via the procedure for **15** for 10 h afforded the diol **19** as a crystalline solid (120 mg, 92%): crystallized from light petroleum ether; mp 79−80 °C; ^{1}H NMR ($CDCl_3$) δ 0.62 (t, J = 7.5 Hz, 3H), 1.54 (s, 3H), 1.58−2.04 (m, 6H), 2.12 (br, 2H, OH), 6.86−7.34 (m, 3H), 7.50 (dd, J = 7.2, 2 Hz, 1H). Anal. Calcd for $C_{14}H_{18}O_3$: C, 71.77; H, 7.74. Found: C, 71.75; H, 7.79.

2,3,4,5-Tetrahydro-2-methyl-5-ethyl-2,5-methano-1-benzoxepin-10-one (20). Rearrangement of diol **19** (80 mg) was carried out as for **16** to furnish **20** as a colorless oil (60 mg, 81%): ot 85−90 °C (0.06 mmHg); IR 1763 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.06 (t, J = 7.5 Hz, 3H), 1.41 (s, 3H), 1.84−2.64 (m, 6H), 6.70−7.24 (m, 4H). Anal. Calcd for $C_{14}H_{16}O_2$: C, 77.75; H, 7.46. Found: C, 77.79; H, 7.70.

2,7-Dimethyl-3-methoxychromone (24). To a magnetically stirred suspension of $CuBr_2$ (11.84 g, 53 mmol) in dry EtOAc (25 mL) was added 2-hydroxy-4-methylacetophenone (**21**) (5.25 g, 35 mmol) in dry $CHCl_3$ (25 mL). The mixture was then refluxed until the color changed from green to amber (about 8 h). Upon cooling, it was filtered and concentrated to afford bromo ketone **22** (6.58 g, 82%): ^{1}H NMR (CCl_4) δ 2.34 (s, 3H), 4.26 (s, 2H), 6.53−6.83 (m, 2H), 7.56 (d, J = 7.5 Hz, 1H).

A mixture of the above bromo ketone **22** (6.58 g, 28.7 mmol), Ac_2O (20 mL), and anhydrous NaOAc (5 g) was heated under reflux for 2 h. Then it was cooled, diluted with water, and extracted with Et_2O. The ether extracts were washed with water, dried, and concentrated. The crude product was stirred with concentrated H_2SO_4 (10 mL) at 50 °C for 1 h. It was then cooled and diluted with water when hydroxychromone **23** precipitated out. This crude hydroxychromone (3.31 g) was filtered, dried, and directly taken in acetone (60 mL) and methylated with MeI (2.84 g) as for **13** to furnish 2,7-dimethyl-3-methoxychromone (**24**) as a solid [2.98 g, 84% (based on hydroxychromone)]: crystallized from ether; mp 91−92 °C; IR 1640 cm^{-1}; ^{1}H NMR (CCl_4) δ 2.36 (s, 3H), 2.46 (s, 3H), 3.87 (s, 3H), 7.0−7.23 (m, 2H), 8.02 (d, J = 8 Hz, 1H). Anal. Calcd for $C_{12}H_{12}O_3$: C, 70.57; H, 5.92. Found: C, 70.41; H, 5.93.

***cis*-1,2,2a,7c-Tetrahydro-2a,5-dimethyl-7c-oxeto-9*H*-benzo[*b*]cyclobuta[*e*]pyran-7b-ol (25).** Photolytic ethylene addition to chromone **24** (730 mg) in dry thiophene-free benzene (260 mL) was carried out as per procedure for **14** to furnish oxetanol **25** as a viscous oil (620 mg, 75%): ^{1}H NMR ($CDCl_3$) δ 1.40−1.50 (m, 1H), 1.58 (s, 3H), 1.70−1.78 (m, 2H), 2.32 (s, 3H), 2.37−2.44 (m, 1H), 4.42 and 4.58 (ABq, J = 7 Hz, 2H), 6.75 (br s, 1H), 6.84 (br d, J = 7.8 Hz, 1H), 7.38 (d, J = 7.8 Hz, 1H); ^{13}CMR ($CDCl_3$) δ 19.78, 21.13, 21.77, 24.05, 69.92, 78.42, 80.41, 92.05, 118.30, 120.23, 122.55, 125.62, 139.96, 151.15; HRMS calcd for $C_{14}H_{16}O_3$(M^+) 232.1099, found 232.1096.

***cis*-1,2,2a,8a-Tetrahydro-2a,5,8-trimethyl-8*H*-benzo[*b*]-cyclobuta[*e*]pyran-8,8a-diol (10).** Reduction of oxetanol **25** (480 mg, 2.07 mmol) with LAH via the procedure for **15** afforded diol **10** as a crystalline solid (460 mg, 95%): crystallized from light petroleum ether; mp 100−101 °C; ^{1}H NMR ($CDCl_3$) δ 1.38 (s, 3H), 1.55 (s, 3H), 1.62−1.66 (m, 2H), 1.92−1.97 (m, 4H), 2.34 (s, 3H), 6.75 (br s, 1H), 6.90 (br d, J = 7.8 Hz, 1H), 7.43 (d, J = 7.8 Hz, 1H); ^{13}CMR ($CDCl_3$) δ 20.99, 21.11, 24.53, 26.33, 27.91, 72.80, 82.46, 83.28, 119.18, 123.10, 123.79, 130.48, 138.19, 152.07; HRMS calcd for $C_{14}H_{18}O_3$(M^+) 234.1255, found 234.1259. Anal. Calcd for $C_{14}H_{18}O_3$: C, 71.77; H, 7.74. Found: C, 71.43; H, 7.59.

2,3,4,5-Tetrahydro-2,5,8-trimethyl-2,5-methano-1-benzoxepin-10-one (11). Rearrangement of diol **10** (120 mg) was carried out as for **16** to furnish bridged ketone **11** as a colorless oil (100 mg, 90%): ot 88−93 °C (0.3 mmHg); IR 1765 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.41 (s, 3H), 1.43 (s, 3H), 1.81−1.97 (m, 2H), 2.26 (s, 3H), 2.29−2.35 (m, 1H), 2.46−2.57 (m, 1H), 6.58 (br s, 1H), 6.71 (br d, J = 7.8 Hz, 1H), 6.91 (d, J = 7.8 Hz, 1H); ^{13}CMR ($CDCl_3$) δ 14.63, 17.87, 20.94, 32.31, 36.38, 48.60, 80.10, 116.37, 122.04, 123.94, 138.87, 151.99, 213.98; HRMS calcd for $C_{14}H_{16}O_2$(M^+) 216.1150, found 216.1152. Anal. Calcd for $C_{14}H_{16}O_2$: C, 77.75; H, 7.46. Found: C, 77.49; H, 7.50.

2,3,4,5-Tetrahydro-2,5,8-trimethyl-7-bromo-2,5-methano-1-benzoxepin-10-one (20). To a magnetically stirred solution of ketone **11** (120 mg, 0.56 mmol) in dry petroleum ether (5 mL) containing suspended anhydrous Na_2CO_3 (110 mg) was added bromine (28.9 μL) slowly until the color of bromine just persisted. After the completion of bromine addition, the reaction mixture was filtered through a short column of silica gel [petroleum ether/Et_2O (9:1)] to afford **20** as a solid (130 mg, 79%): crystallized from ether−light petroleum ether; mp 121−122 °C (lit.[3a] mp 122−123 °C); IR 1765 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.39 (s, 3H), 1.42 (s, 3H), 1.82−1.98 (m, 2H), 2.29 (s, 3H), 2.31−2.36 (m, 1H), 2.45−2.52 (m, 1H), 6.63 (s, 1H), 7.13 (s, 1H); ^{13}CMR ($CDCl_3$) δ 14.56, 17.80, 22.58, 32.25, 36.31, 48.57, 80.32, 116.07, 118.09, 127.58, 131.64, 138.31, 151.42, 213.03; HRMS calcd for $C_{15}H_{14}O_2Br$(M^+) 294.0255, found 294.0252.

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