with the largest residual peaks in the final difference map of −0.22 and +0.22 e Å^{-3}.

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Supplementary Material Available: Structure drawings of **7** and **20**, tables of atomic coordinates and isotropic thermal parameters, bond lengths, bond angles, anisotropic thermal parameters, and hydrogen atoms coordinates and isotropic displacement parameters for **7** and **20**, and a discussion of features of the X-ray structures of **7** and **20** (13 pages). Ordering information is given on any current masthead page.

Stereocontrolled Synthesis of (±)-Debromoaplysin, (±)-Aplysin, (±)-Debromoaplysinol, (±)-Aplysinol, and (±)-Isoaplysin

Sujay Biswas, Arun Ghosh, and Ramanathapuram V. Venkateswaran*

Department of Organic Chemistry, Indian Association for the Cultivation of Science, Jadaupur, Calcutta, 700 032, India

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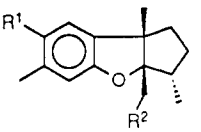
Stereocontrolled synthesis in racemic form of the title marine sesquiterpenes is described. Alkylation of styrenol **6** with α-bromopropanoic acid furnished acid **7**. Similar alkylation with α-bromo-β-methoxypropanoic acid provided acid **8**. Intramolecular cycloaddition of the ketene generated from the acid chloride of **7** afforded cyclobutanone **9** whereas **8** led to a mixture of **10** and **11**, but following a modified condition **10** could be obtained exclusively. Regioselective ring expansion of **9** and **10** to cyclopentanones **13** and **15** followed by addition of methylmagnesium iodide and dehydration provided olefins **16** and **17**. Hydrogenation of these using Pd–C catalyst lacked selectivity, but PtO_2 showed selectivity, affording (±)-**2** and **19**, respectively. Controlled bromination of **2** furnished (±)-aplysin (**1**), and **19** yielded **21**. Demethylation of **19** afforded (±)-debromoaplysinol (**3**). Similarly **21** furnished (±)-aplysinol (**4**). Bromination of **3** resulted in (±)-isoaplysin (**5**).

The red alga *Laurencia* and the sea hare *Aplysia* species provide a rich haul of halogenated sesquiterpenes.[1] Aplysin (**1**)[2] belongs to the first class of halogenated sesquiterpenes isolated from marine sources. The presumptive precursor of **1**, debromoaplysin (**2**)[2] and the related debromoaplysinol (**3**),[3] aplysinol (**4**),[2,4] and isoaplysin (**5**)[5] have also been isolated from these sources. These sesquiterpenes represent a new structural type, and some of them also display antifeedant properties which help protect the host mollusks from raptorial advances. The co-occurrence of the unhalogenated forms suggests the possibility of these functioning as antioxidants to scavenge reactive halogens. Commensurate with the novel structure and associated properties of these compounds have also been synthetic efforts. These efforts have spanned several years,[6] resulting in the synthesis of **1** and **2**. Recently we disclosed[7] a short and stereocontrolled synthesis of **1** and **2**. We now provide details of this and the first synthesis of **3**, **4**, and **5** in racemic form with full stereocontrol.

We envisaged development of the tricarbocyclic framework through a one-carbon ring enlargement of appropriately substituted dihydrocyclobutabenzofuranones, readily accessible from intramolecular cycloaddition of a



1: R^1 = Br; R^2 = H
2: R^1 = R^2 = H
3: R^1 = H; R^2 = OH
4: R^1 = Br; R^2 = OH
5: R^1 = H; R^2 = Br

phenoxy ketene onto an *ortho-situated* styrene. Indeed in recent years such an intramolecular ketene–alkene cycloaddition[8] has emerged as an important and versatile method for synthesis of polycyclic compounds. Further with a simple modification in the substrate at the initial stage, a single starting material should serve the synthetic requirements for all of the targeted natural products. Successful application of this methodology has led to the synthesis of **1**–**5** in good overall yields as shown below.

The starting material chosen was the styrenol **6**.[9] This already incorporates two of the methyl groups present in **1**–**5**, and introduction of the bromine atom into the aromatic ring as necessary for **1** and **4** can be effected at the last stage of the synthesis as already established.[6b] The styrenol **6** was alkylated in the presence of sodium hydride with α-bromopropanoic acid and furnished the phenoxypropanoic acid **7** in 63% yield (Scheme I). This acid, as its sodium salt, was reacted with oxalyl chloride to provide an acid chloride[10] which on treatment with Et_3N in benzene at reflux resulted in generation of the ketene and concomitant intramolecular cycloaddition[11] to afford the

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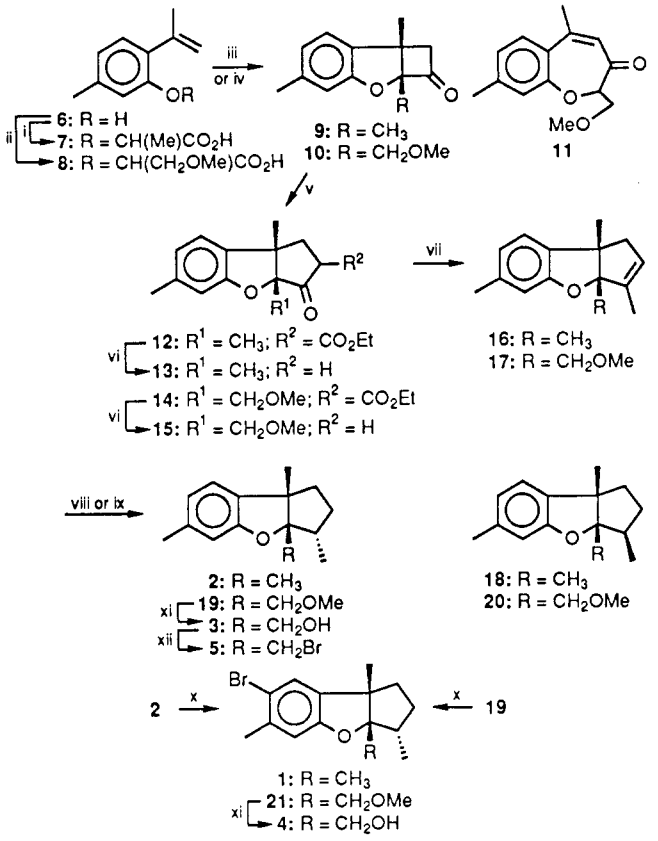
(8) For a recent review of this phenomenon, see: Snider, B. B. *Chem. Rev.* **1988**, *88*, 793.
(9) Divakar, K. J.; Rao, A. S. *Synth. Commun.* **1976**, 423.
(10) We have found it more expedient to make the acid chloride by this procedure than direct reaction with oxalyl chloride which gave some problems.

0022-3263/90/1955-3498$02.50/0

Scheme I[a]



[a] Reagents: (i) NaH, $MeCH(Br)CO_2H$, THF; (ii) NaH, $MeOCH_2$–$CH(Br)CO_2H$, THF; (iii) (a) NaOEt, (b) $(COCl)_2$, then Et_3N, benzene reflux; (iv) *p*-TsCl, Et_3N, benzene, reflux; (v) BF_3Et_2O, N_2CHCO_2Et; (vi) LiCl, DMSO, H_2O, 160 °C; (vii) MeMgI, Et_2O, then $POCl_3$, pyridine; (viii) Pd/C, EtOH; (ix) PtO_2 EtOH; (x) Br_2, Na_2CO_3, petroleum; (xi) Me_3SiCl, NaI, CH_3CN; (xii) CBr_4Ph_3P, benzene.

cyclobutanone **9** in 86% yield. The stereochemistry assigned to **9** followed from well-established analogies.[11] The next step in the synthesis entailed a ring enlargement of the cyclobutanone to a cyclopentanone. In order to facilitate subsequent introduction of a methyl group, regioselective homologation involving migration of the primary carbon in ketone **9** was deemed most favorable. Furthermore a precedent[12] was already available relating to mode of bond migration in differently substituted cyclobutanones where a propensity for preferential migration of the less encumbered bond was observed. Following this cue, ring enlargement of **9** with ethyl diazoacetate in presence of BF_3·Et_2O proceeded regioselectively and furnished the β-keto ester **12**, which on heating in aqueous DMSO in presence of LiCl[13] disengaged the ethoxycarbonyl group to deliver in 75% overall yield the cyclopentanone **13**. No trace of the other isomer was discernible from GC or ^1H NMR analysis. The structure of **13** was easily deduced from the ^1H NMR spectrum where the four aliphatic methylene protons appeared as a multiplet at δ 1.8–2.5 and expectedly in the other isomer these protons which would flank a carbonyl group would display a different (AB) pattern. Additional corroboration followed from further transformations leading to the natural products. Thus the sequence of reactions has led to the assemblage of the basic tricarbocyclic framework of **1** and **2** in good yields and with full stereocontrol. Interaction of **13** with methylmagnesium iodide followed by dehydration of the ensued carbinol afforded the tricyclic olefin **16** in 88% yield. The formation of olefin **16** while confirming structure **13** also completed a formal synthesis of **2** and **1** in view of an earlier synthesis[6b] from **16**. But on account of our inability to obtain a comparison data, we opted to effect the required transformations comprising the two steps of hydrogenation and bromination to complete the synthesis. Initially we carried out hydrogenation of **16** using palladium on carbon as catalyst, based on literature precedents[6a,d] that such a catalytic hydrogenation of the corresponding 7-bromoalkene resulted in selective uptake of hydrogen from the exo face to produce a single isomer. However we found that under this condition **16** furnished a mixture of (±)-debromoaplysin (**2**) and the isomer **18** quantitatively in 3:2 ratio. These were separated by preparative-layer chromatography, and the identity of **2** was established by comparison of the ^1H NMR spectrum with that of an authentic sample. The chief difference between the two isomers was the upfield shift of the secondary methyl doublet in isomer **18** compared to **2**. We next carried out the hydrogenation using Adam's catalyst (PtO_2), and as reported[6b] this showed pronounced selectivity and afforded (±)-**2** smeared with only traces (ca. 3%) of **18**. This was further purified by preparative-layer chromatography to obtain pure **2**, and a controlled bromination[6b] furnished (±)-aplysin (**1**), identical in melting point and spectrum with an authentic sample.

Encouraged by the success attending the synthesis of **1** and **2**, we then applied this methodology to the synthesis of **3**, **4**, and **5**. The primary requirement here was to introduce an angular hydroxymethyl group at C-3a which related back to the choice of an appropriate alkylating agent in the first step of the synthesis. We settled on α-bromo-β-methoxypropanoic acid[14] as the suitable alkylating agent. This would incorporate the required hydroxymethyl in the form of a methyl ether which could be subsequently cleaved to reveal the hydroxy function. Alkylation of the styrenol **6** with this alkylating agent, using sodium hydride as before, furnished the phenoxypropanoic acid **8** in 60% yield. Conversion of **8** to the acid chloride followed by treatment with Et_3N as described above led unexpectedly to a 1:1 mixture of the desired cyclobutanone **10** and the intramolecular acylation product **11** in 92% combined yield. These were easily separated by preparative-layer chromatography. The structure of **11** followed from analytical and spectral data. It showed absorption in the IR at 1655 cm^{-1} indicative of the α,β-unsaturated carbonyl group. In the ^1H NMR spectrum it displayed a doublet at δ 2.33 for the vinylic methyl and a broad singlet at δ 6.35 due to vinylic hydrogen. We believe this product arose from cyclization of the acid-chloride induced by some HCl present during the oxalyl chloride reaction (originating perhaps from high ambient humidity at time of reaction).[15] While this aspect is being looked into in more detail, we were pleased to find that

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(12) Liu, H. J.; Ogino, T. *Tetrahedron Lett.* **1973**, 4937.
(13) Krapcho, A. P. *Synthesis* **1982**, 805, 893.

(14) (a) Vishwakarma, L. C.; Walia, J. S. *J. Indian Chem. Soc.* **1976**, *53*, 156. (b) *Organic Syntheses*; Wiley: New York, 1955; Collect. Vol. III, p 774.
(15) Such intramolecular acylation products in intramolecular cycloadditions of certain keteniminium salts with alkenes having a trans allylic hydrogen have been encountered (cf. ref 8). A recent study [Kher, S. M.; Kulkarni, G. H.; Mitra, R. B. *Synth. Commun.* **1989**, *19*, 597] involving acid **7** concludes that the intramolecular acylation is the preferred pathway. However, our results clearly demonstrate this is not so, and cyclobutanones can be obtained in excellent yield, following a proper set of conditions. Thus acylation presumably takes place at the acid chloride stage rather than through involvement of ketene. This aspect is being evaluated in detail.

when acid 8 was subjected to the one-pot procedure developed by Brady[16] for the intramolecular ketene–alkene cycloadditions involving heating a mixture of 8, *p*-toluenesulfonyl chloride, and Et_3N in benzene at reflux, it furnished only the cyclobutanone **10** in 83% yield. This also displayed identical behavior as **9** in the next steps involving ring enlargement with ethyl diazoacetate in presence of $BF_3{\cdot}Et_2O$ to regioselectively provide β-keto ester **14** and subsequent deethoxycarbonylation to the cyclopentanone **15** in 77% overall yield. Reaction of this ketone with methylmagnesium iodide followed by dehydration of the resultant carbinol afforded in 86% yield the tricyclic olefin **17**. At this juncture we were prompted by our previous observation on **16** to study the course of hydrogenation of **17**. Interestingly this also on hydrogenation using palladium on carbon as catalyst yielded a mixture of debromoaplysinol methyl ether (**19**) and the isomer **20** in a 3:2 proportion, underscoring the lack of selectivity in the hydrogenation of these systems under these conditions. Separation of these isomers was not considered expedient since hydrogenation using Adam's catalyst followed the earlier course and furnished selectively **19**. This also could be brominated successfully following previous controlled conditions and provided aplysinol methyl ether (**21**) in 84% yield. Unmasking of the protected hydroxy group in **19** was accomplished through demethylation induced by an in situ generated iodotrimethylsilane[17] and furnished in 90% yield (±)-debromoaplysinol (**3**), mp 79–80 °C. Similar demethylation of **21** afforded (±)-aplysinol (**4**) in 60% yield, mp 151–53 °C. Bromination of debromoaplysinol (**3**) with CBr_4 in presence of triphenylphoshine as previously reported[5] completed the synthesis of (±)-isoaplysin (**5**). The identities of synthetic **3**, **4**, and **5** were secured through consonant ^1H NMR spectra with those of authentic samples.

In summary, we have described a short and stereocontrolled approach for the synthesis of the marine sesquiterpenes **1–5** from a single starting material, employing the intramolecular ketene–alkene cycloaddition as a key step. This attests to the viability of this useful technique for synthesis of polycyclic compounds and in the present instance provides a short route to the above mentioned compounds in good overall yield.

Experimental Section

General. All reactions were carried out in a nitrogen atmosphere. Melting points and boiling points are uncorrected, and melting points were taken in an open capillary in a sulfuric acid bath. All of the dry solvents and reagents were prepared from reagent grade materials by conventional methods. Petroleum refers to the fraction of bp 60–80 °C and ether refers to diethyl ether. Product purities were routinely checked by TLC. Preparative-layer chromatography was done with silica gel 60 HF_{254} (E. Merck) plates, thickness 1 mm. Drying of organic layers was done with sodium sulfate.

^1H NMR spectra were determined at 200 MHz on a Varian XL-200 spectrometer in $CDCl_3$ solution. Peak positions are indicated in ppm downfield from internal TMS in δ units. IR spectra were recorded on Perkin-Elmer 298 infrared spectrophotometer and were taken in chloroform solution. Gas chromatographic analyses were done on a Shimadzu GC-9A instrument using column OV-17 (2 m) and nitrogen as carrier gas.

2-(2-Isopropenyl-5-methylphenoxy)propanoic Acid (7). To a magnetically stirred solution of 2-isopropenyl-5-methylphenol (4.2 g, 28.3 mmol) and α-bromopropanoic acid (4.34 g, 28.3 mmol) in dry THF (30 mL) at −10 °C was added sodium hydride (2.26 g, 65% dispersion in mineral oil, 61 mmol) portionwise during 45 min. Stirring was continued at −10 °C for 20 min and at room temperature for 30 min. The reaction mixture was then refluxed with vigorous stirring for 10 h. Upon cooling the reaction was diluted with water, acidified with dilute HCl (6 N), and extracted with ether. The ether extract was washed with water, dried, and concentrated.

The residue was chromatographed through silica gel with 15% ethyl acetate in petroleum to afford **7** as a crystalline solid (3.9 g, 63%), crystallized from petroleum: mp 58–60 °C; ^1H NMR δ 1.67 (d, J = 6 Hz, 3 H), 2.16 (dd, J = 0.5, 0.9 Hz, 3 H), 2.34 (s, 3 H), 4.82 (q, J = 6 Hz, 1 H), 5.11 (m, 1 H), 5.17 (m, 1 H), 6.64 (m, 1 H), 6.82 (br d, J = 8 Hz, 1 H), 7.14 (d, J = 8 Hz, 1 H).

Anal. Calcd for $C_{13}H_{16}O_3$: C, 70.89; H, 7.32. Found: C, 70.68; H, 7.40.

***cis*-2a,7b-Dihydro-2a,5,7b-trimethylcyclobuta[*b*]benzofuran-2(1*H*)-one (9).** A dilute solution of sodium methoxide in methanol was added dropwise to a solution of the phenoxypropanoic acid **7** (2.2 g, 10 mmol) in double distilled methanol (20 mL) containing phenolphthalein (2 drops) until a permanent pink color persisted. Methanol was removed under anhydrous conditions, and the last traces of methanol were removed by azeotropic distillation with benzene (3 times). The sodium salt of the acid was dried well under vacuum.

To a magnetically stirred suspension of the above sodium salt in dry benzene (20 mL) at 0 °C was added oxalyl chloride (5.08 g, 40 mmol). The mixture was stirred at 0 °C for 30 min, at room temperature for another 30 min, and finally at 50–60 °C for 30 min. The excess oxalyl chloride was removed under vacuum by distillation with fresh addition of benzene (3 times). The crude acid chloride was diluted with dry benzene (100 mL) and filtered to remove sodium chloride. The filtered solution was added dropwise to a refluxing solution of triethylamine (2.12 g, 21 mmol) in dry benzene (150 mL) over 5 h. After the addition was complete, it was refluxed with continuous stirring for another 5 h. The mixture was cooled and filtered. The filtrate was concentrated, and the residual oil was subjected to chromatography over silica gel. Elution with 2% ethyl acetate in petroleum afforded **9** as a colorless liquid (1.75 g, 86%): bp 95–100 °C/(0.07 mmHg); IR 1780 cm^{-1}; ^1H NMR δ 1.52 (s, 3 H), 1.57 (s, 3 H), 2.30 (s, 3 H), 3.15 and 3.23 (AB q, J = 17.8 Hz, 2 H), 6.66 (br s, 1 H), 6.76 (m, 1 H), 7.09 (d, J = 7.6 Hz, 1 H).

Anal. Calcd for $C_{13}H_{14}O_2$: C, 77.2; H, 6.98. Found: C, 77.12; H, 7.19.

***cis*-1,2,3a,8b-Tetrahydro-3a,6,8b-trimethylcyclopenta[*b*]benzofuran-3-one (13).** To a magnetically stirred and cooled (−10 °C) solution of **9** (1.01 g, 5 mmol) and $BF_3{\cdot}Et_2O$ (1.06 g, 7.5 mmol) in dry ether (30 mL) was added ethyl diazoacetate (855 mg, 7.5 mmol) slowly during 25 min. Stirring was continued at −10 °C for another 30 min and at room temperature for 3 h. The cold reaction mixture was quenched by addition of saturated aqueous sodium hydrogen carbonate. The ether layer was separated, and the aqueous layer was extracted with ether. The combined ethereal layer was washed with saturated brine and dried. The residual oil after removal of ether was distilled to yield the β-keto ester **12** (1.17 g, 81%): bp 130–135 °C (0.1 mmHg); IR 1750 (br), 1650 cm^{-1}; ^1H NMR δ 1.28 (t, J = 7 Hz, 3 H), 1.32 (s, 3 H), 1.58 (s, 3 H), 2.31 (s, 3 H), 2.61 and 2.89 (AB q, J = 15 Hz, 2 H), 4.2 (q, J = 7 Hz, 2 H), 6.69 (br s, 1 H), 6.76 (m, 1 H), 7.09 (d, J = 8 Hz, 1 H).

A mixture of the above β-keto ester **12** (250 mg, 0.87 mmol), water (0.5 mL), lithium chloride (200 mg, 5 mmol), and DMSO (5 mL) was heated under reflux with stirring for 6 h in an oil bath at 165–170 °C. It was then cooled, diluted with cold water, and extracted with ether. The ethereal layer was washed with water, dried, and concentrated. The residual oil was chromatographed over silica gel. Elution with 5% ethyl acetate in petroleum furnished the tricyclic ketone **13** (173 mg, 92%): bp 100–105 °C (0.15 mmHg); IR 1750 cm^{-1}; ^1H NMR δ 1.33 (s, 3 H), 1.38 (s, 3 H), 2.29 (s, 3 H), 1.8–2.5 (m, 4 H), 6.61 (br s, 1 H), 6.75 (m, 1 H), 7.03 (d, J = 7.6 Hz, 1 H).

Anal. Calcd for $C_{14}H_{16}O_2$: C, 77.75; H, 7.46. Found: C, 77.62; H, 7.58.

***cis*-3a,8b-Dihydro-3,3a,6,8b-tetramethyl-1*H*-cyclopenta[*b*]benzofuran (16).** To a magnetically stirred solution of

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(17) Olah, G. A.; Narang, S. C.; Gupta, B. G. B.; Malhotra, R. *J. Org. Chem.* **1979**, *44*, 1247.

methylmagnesium iodide [prepared from magnesium (25 mg, 0.001 g-atom) and methyl iodide (149 mg, 1 mmol) in dry ether (5 mL)] was added a solution of tricylic ketone **13** (170 mg, 0.8 mmol) in dry ether (4 mL) at room temperature. The reaction mixture was then heated under reflux for 3 h, cooled to 0 °C, decomposed with dilute H_2SO_4 (2 N), and stirred at room temperature for 10 min. After separating the ether layer, the aqueous layer was extracted with ether. The combined ether layer was washed with saturated sodium hydrogen carbonate, saturated brine, and water, dried, and concentrated to afford a colorless oil.

The above crude Grignard product was taken in pyridine (3 mL) and cooled to 0 °C, and with stirring phosphorus oxychloride (350 mg, 2.3 mmol) was added. The reaction mixture was stirred at room temperature for 24 h, diluted with H_2SO_4 (7 N), and extracted with ether. The ethereal layer was washed with saturated sodium hydrogen carbonate and saturated brine and dried. The oil obtained after removal of ether was subjected to preparative-layer chromatography using 1% ethyl acetate in petroleum. This afforded the desired olefin **16** (149 mg, 88%): bp 70–80 °C (0.2 mmHg); ^{1}H NMR δ 1.28 (s, 3 H), 1.42 (s, 3 H), 1.72 (ddd, J = 1.72, 0.9, 0.7 Hz, 3 H), 2.59 (m, 2 H), 5.4 (br, 1 H), 6.56 (br s, 1 H), 6.68 (m, 1 H), 7.0 (d, J = 7.6 Hz, 1 H).

Anal. Calcd for $C_{15}H_{18}O$: C, 84.07; H, 8.47. Found: C, 83.99; H, 8.50.

***cis*-2,3,3a,8b-Tetrahydro-3,3a,6,8b-tetramethyl-1*H*-cyclopenta[*b*]benzofuran [(±)-Debromoaplysin (2)] and Isomer 18. Method A.** The tricyclic alkene **16** (50 mg, 0.23 mmol) was hydrogenated in the presence of 10% Pd–C (4.2 mg) in double-distilled ethanol (5 mL) under atmospheric pressure. After 2 h the catalyst was filtered off and the filtrate was concentrated under reduced pressure to afford a colorless oil (50 mg). GC analysis showed this to be a mixture of two components in a ratio of 3:2 t_R 1.8 min (major) and 2.25 min (minor) at 180 °C. The ^{1}H NMR spectrum also displayed two doublets for the secondary methyl at δ 0.98 and 1.11 in 2:3 ratio.

These two compounds were separated by preparative-layer chromatography using 1% ethyl acetate in petroleum. The less polar component corresponded to (±)-debromoaplysin (**2**) (30 mg): ^{1}H NMR δ 1.11 (d, J = 6.6 Hz, 3 H), 1.29 (s, 3 H), 1.32 (s, 3 H), 2.28 (s, 3 H), 6.53 (br s, 1 H), 6.64 (br d, J = 6.8 Hz, 1 H), 6.92 (d, J = 7.4 Hz, 1 H).

The more polar component (20 mg), the isomer **18**, showed the following spectral features: ^{1}H NMR δ 0.98 (d, J = 7.3 Hz, 3 H), 1.27 (s, 3 H), 1.30 (s, 3 H), 2.28 (s, 3 H), 6.50 (br s, 1 H), 6.66 (m, 1 H), 6.93 (d, J = 7.6 Hz, 1 H).

Method B. The tricyclic alkene **16** (70 mg, 0.32 mmol) in double-distilled ethanol (4 mL) was hydrogenated using platinum oxide (12.3 mg) as catalyst. After 2 h the mixture was filtered through a short column of silica gel with petroleum. Removal of the solvent under reduced pressure furnished (±)-**2** as a colorless liquid (70 mg). GC analysis showed this to be 97% pure. This was further purified by preparative-layer chromatography using 1% ethyl acetate in petroleum. Extraction of the major band yielded pure (±)-debromoaplysin (**2**), bp 100–110 °C (0.15 mmHg). ^{1}H NMR data was identical with that of a sample obtained from method A.

Anal. Calcd for $C_{15}H_{20}O$: C, 83.28; H, 9.32. Found: C, 83.02; H, 9.52.

***cis*-2,3,3a,8b-Tetrahydro-3,3a,6,8b-tetramethyl-7-bromo-1*H*-cyclopenta[*b*]benzofuran [(±)-Aplysin (1)].** To debromoaplysin (30 mg, 0.138 mmol) taken in petroleum (2 mL) containing suspended anhydrous sodium carbonate (21.8 mg) was added bromine (7.1 μL) slowly until the color of bromine just persisted. Within 2 min, after the completion of bromine addition, the reaction mixture was filtered through a short column of silica gel with 10% ether in petroleum. This afforded (±)-aplysin (**1**) as a crystalline solid (32 mg, 75%): crystallized from methanol, mp 98–100 °C (lit.[6] mp 100–101 °C); ^{1}H NMR δ 1.09 (d, J = 6.7 Hz, 3 H), 1.27 (s, 3 H), 1.30 (s, 3 H), 2.30 (s, 3 H), 6.58 (s, 1 H), 7.13 (s, 1 H).

Anal. Calcd for $C_{15}H_{19}OBr$: C, 61.03; H, 6.49. Found: C, 61.11; H, 6.73.

2-(2-Isopropenyl-5-methylphenoxy)-3-methoxypropanoic Acid (8). Alkylation of styrenol **6** (4.4 g, 29.7 mmol) with α-bromo-β-methoxypropanoic acid (5.44 g, 29.7 mmol) in presence of sodium hydride (3.12 g, 50% dispersion in oil, 65 mmol) in dry THF (30 mL) was carried out as for **7** to furnish **8** (4.5 g, 60%): crystallized from petroleum, mp 57–59 °C; ^{1}H NMR δ 2.13 (dd, J = 0.9, 0.5 Hz, 3 H), 2.31 (s, 3 H), 3.44 (s, 3 H), 3.89 (br d, 2 H), 4.82 (t, J = 4 Hz, 1 H), 5.09 (m, 1 H), 5.15 (m, 1 H), 6.65 (br s, 1 H), 6.80 (m, 1 H), 7.10 (d, J = 7.5 Hz, 1 H).

Anal. Calcd for $C_{14}H_{18}O_4$: C, 77.03; H, 8.31. Found: C, 76.96; H, 8.49.

***cis*-2a,7b-Dihydro-2a-(methoxymethyl)-5,7b-dimethylcyclobuta[*b*]benzofuran-2-(1*H*)-one (10). Method A.** Via procedure for **7**, the acid **8** (375 mg, 1.5 mmol) furnished a crude product in 92% yield which showed two spots on TLC. These two were separated by preparative-layer chromatography using 2% ethyl acetate in petroleum.

The less polar band afforded a crystalline solid (160 mg, 46%) and corresponded to the desired cyclobutanone **10**: Crystallized from petroleum, mp 55–56 °C; IR 1785 cm^{-1}; ^{1}H NMR δ 1.68 (s, 3 H), 2.30 (s, 3 H), 3.13 and 3.31 (AB q, J = 17.6 Hz, 2 H), 3.43 (s, 3 H), 3.83 and 3.89 (AB q, J = 10.4 Hz, 2 H), 6.67 (br s, 1 H), 6.78 (br d, J = 7 Hz, 1 H), 7.11 (d, J = 7.6 Hz, 1 H).

Anal. Calcd for $C_{14}H_{16}O_3$: C, 72.39; H, 6.94. Found: C, 72.45; H, 6.92.

The more polar band corresponded to **11** (160 mg, 46%): bp 150–160 °C (0.15 mmHg); IR 1655 cm^{-1}; ^{1}H NMR δ 2.33 (d, J = 1 Hz, 3 H), 2.37 (s, 3 H), 3.44 (s, 3 H), 3.82 (q, A of ABX, J_{AB} = 10.9 Hz, 1 H), 3.94 (q, B of ABX, J_{BA} = 10.9 Hz, 1 H), 4.36 (q, X of ABX, J_{AX} = 2.79, J_{BX} = 7.21 Hz, 1 H), 6.35 (br s, 1 H), 7.01 (br s, 1 H), 7.06 (m, 1 H), 7.38 (d, J = 7.97 Hz, 1 H).

Anal. Calcd for $C_{14}H_{16}O_3$: C, 72.39; H, 6.94. Found: C, 72.37; H, 7.01.

Method B. To a magnetically stirred and refluxing solution of triethylamine (4.04 g, 40 mmol) and *p*-toluenesulfonyl chloride (2.03 g, 16 mmol) in dry benzene (100 mL) was added dropwise a solution of the acid **8** (2 g, 8 mmol) in dry benzene (100 mL) during 5 h. After the addition was complete, the mixture was refluxed for another 6 h. Then the reaction mixture was cooled and washed with water and concentrated to one-third of the volume. This concentrated solution was stirred with aqueous sodium hydroxide (250 mL, 3%) for 10 h. The benzene layer was separated, washed with water, and concentrated. The residual oil on silica gel chromatography with 2% ethyl acetate in petroleum afforded **10** as a crystalline solid (1.54 g, 83%): crystallized from petroleum, mp 55–56 °C. This was identical with sample obtained from method A.

Application of this one-pot procedure to acid **7** also furnished the cyclobutanone **9** in a yield of 83%.

***cis*-3-Oxo-1,2,3a,8b-tetrahydro-3a-(methoxymethyl)-6,8b-dimethyl-3*H*-cyclopenta[*b*]benzofuran (15).** Ring expansion of **10** (1.11 g, 4.8 mmol) was carried out as for **9** and furnished a β-keto ester **14** (1.27 g, 82%): bp 135–140 °C (0.1 mmHg); IR 1750 (br), 1650 cm^{-1}. Deethoxycarbonylation as before followed by chromatgraphic purification yielded the cyclopentanone **15** as a colorless solid (0.94 g, 94%): crystallized from ether–petroleum, mp 68–70 °C; IR 1750 cm^{-1}; ^{1}H NMR δ 1.46 (s, 3 H), 2.28 (s, 3 H), 3.32 (s, 3 H), 3.75 and 3.91 (AB q, J = 8.7 Hz, 2 H), 6.59 (br s, 1 H), 6.76 (br d, J = 8 Hz, 1 H), 7.04 (d, J = 7.6 Hz, 1 H).

Anal. Calcd for $C_{15}H_{18}O_3$: C, 73.14; H, 7.37. Found: C, 72.98; H, 7.15.

***cis*-3a,8b-Dihydro-3,6,8b-trimethyl-3a-(methoxymethyl)-1*H*-cyclopenta[*b*]benzofuran (17).** Grignard reaction with methylmagnesium iodide on **15** (740 mg, 3 mmol) and dehydration via the procedure for **13** afforded the alkene **17** (630 mg, 86%): bp 135–140 °C (0.15 mmHg); ^{1}H NMR δ 1.38 (s, 3 H), 1.76 (ddd, J = 1.7, 0.8, 0.8 Hz, 3 H), 2.28 (s, 3 H), 3.39 (s, 3 H), 3.64 and 3.78 (AB q, J = 9.6 Hz, 2 H), 5.60 (br, s, 1 H), 6.60 (br s, 1 H), 6.70 (br d, J = 8 Hz, 1 H), 7.02 (d, J = 7.3 Hz, 1 H).

Anal. Calcd for $C_{16}H_{20}O_2$: C, 78.65; H, 8.25. Found: C, 78.58; H, 8.43.

***cis*-2,3,3a,8b-Tetrahydro-3,6,8b-trimethyl-3a-(methoxymethyl)-1*H*-cyclopenta[*b*]benzofuran [(±)-Debromoaplysinol Methyl Ether (19)] and Isomer 20. Method A.** Catalytic hydrogenation of **17** in presence of 10% Pd–C as for **16** led to a mixture of **19** and **20**. GC analysis showed these to be in a proportion of 3:2, t_R 3.64 min (major) and 4.88 min, at 180 °C: ^{1}H NMR δ 1.02, 1.10 (2 d, 3 H, in 2:3 proportions), 1.38, 1.40 (2 s, 3 H, 2:3 proportions), 2.28 (s, 3 H), 3.36, 3.40 (2 s, 3 H,

3:2 proportions), 6.62 (br s, 1 H), 6.68 (br d, J = 8 Hz, 1 H), 6.90 (d, J = 7.4 Hz, 1 H).

Method B. Hydrogenation was carried out using platinum oxide as catalyst. This afforded only **19** in 95% yield: bp 125–130 °C (0.15 mmHg); ^{1}H NMR δ 1.10 (d, J = 6.7 Hz, 3 H), 1.40 (s, 3 H), 2.28 (s, 3 H), 3.36 (s, 3 H), 3.53 (s, 2 H), 6.63 (br s, 1 H), 6.67 (br d, J = 8 Hz, 1 H), 6.90 (d, J = 7.4 Hz, 1 H).

Anal. Calcd for $C_{16}H_{22}O_2$: C, 78.01; H, 9.00. Found: C, 77.92; H, 9.12.

***cis*-2,3,3a,8b-Tetrahydro-3,6,8b-trimethyl-3a-(methoxymethyl)-7-bromo-1*H*-cyclopenta[*b*]benzofuran [(±)-Aplysinol Methyl Ether (21)].** Bromination of **19** was carried out as for **2** and provided the methyl ether of aplysinol (**21**) in 84% yield: bp 154–157 °C (0.2 mmHg); ^{1}H NMR δ 1.08 (d, J = 6.7 Hz, 3 H), 1.40 (s, 3 H), 2.30 (s, 3 H), 3.34 (s, 3 H), 3.49 and 3.54 (AB q, J = 10.5 Hz, 2 H), 6.64 (s, 1 H), 7.13 (s, 1 H).

Anal. Calcd for $C_{16}H_{21}O_2Br$: C, 59.08; H, 6.50. Found: C, 58.85; H, 6.63.

***cis*-2,3,3a,8b-Tetrahydro-3,6,8b-trimethyl-3a-(hydroxymethyl)-1*H*-cyclopenta[*b*]benzofuran [(±)-Debromoaplysinol (3)].** To a magnetically stirred solution of **19** (200 mg, 0.81 mmol) and sodium iodide (244 mg, 1.62 mmol) in dry acetonitrile (2 mL) was added trimethylsilyl chloride (105.5 mg, 0.97 mmol) at room temperature. Stirring was continued at room temperature for 4 h. The reaction mixture was diluted with water and extracted with ether. The ether layer was washed with water and dried. The residue obtained after removal of the solvent was subjected to preparative-layer chromatography using 5% ethyl acetate in petroleum. This furnished **3** as a crystalline solid (169 mg, 90%): crystallized from petroleum, mp 79–80 °C; ^{1}H NMR δ 1.10 (d, J = 6.7 Hz, 3 H), 1.48 (s, 3 H), 2.29 (s, 3 H), 3.73 and 3.85 (AB q, J = 12.5 Hz, 2 H), 6.59 (br s, 1 H), 6.70 (br d, J = 8 Hz, 1 H), 6.93 (d, J = 7.3 Hz, 1 H).

A 100-MHz ^{1}H NMR spectrum was fully consonant with the spectrum (100 MHz) of an authentic sample.

Anal. Calcd for $C_{15}H_{20}O_2$: C, 77.55; H, 8.63. Found: C, 77.46; H, 8.53.

***cis*-2,3,3a,8b-Tetrahydro-3,6,8b-trimethyl-3a-(hydroxymethyl)-7-bromo-1*H*-cyclopenta[*b*]benzofuran [(±)-Aplysinol (4)].** (±)-Aplysinol methyl ether (**21**) (300 mg, 0.92 mmol) was subjected to demethylation as for **19**. The crude product was subjected to preparative-layer chromatography using 5% ethyl acetate in petroleum. Extraction of the band yielded (±)-**4** as a crystalline solid (172 mg, 60%): crystallized from CCl_4, mp 151–153 °C; ^{1}H NMR δ 1.08 (d, J = 6.6 Hz, 3 H), 1.48 (s, 3 H), 2.32 (s, 3 H), 3.8 (m, 2 H), 6.67 (s, 1 H), 7.16 (s, 1 H).

A 100-MHz ^{1}H NMR spectrum was fully consonant with the spectrum (100 MHz) of an authentic sample.

Anal. Calcd for $C_{15}H_{19}O_2Br$: C, 57.87; H, 6.15. Found: C, 57.82; H, 6.42.

***cis*-2,3,3a,8b-Tetrahydro-3,6,8b-trimethyl-3a-(bromomethyl)-1*H*-cyclopenta[*b*]benzofuran [(±)-Isoaplysin (5)].** A mixture of (±)-debromoaplysinol (**3**) (70 mg, 0.30 mmol), carbon tetrabromide (360 mg, 1.08 mmol), and triphenylphosphine (315 mg, 1.20 mmol) in dry benzene (9 mL) was heated under reflux with continuous stirring for 2 h. Removal of the solvent afforded an oil which was subjected to preparative-layer chromatography using 1% ethyl acetate in petroleum. Extraction of the band afforded (±)-isoaplysin (**5**) (49 mg, 56%): bp 125–130 °C (0.15 mmHg); ^{1}H NMR δ 1.12 (d, J = 6.70 Hz, 3 H), 1.52 (s, 3 H), 2.29 (s, 3 H), 3.58 and 3.68 (AB q, J = 11.1 Hz, 2 H), 6.67 (br s, 1 H), 6.71 (br d, J = 8 Hz, 1 H), 6.91 (d, J = 7.6 Hz, 1 H).

Anal. Calcd for $C_{15}H_{19}OBr$: C, 61.01; H, 6.44. Found: C, 60.99; H, 6.48.

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