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TOTAL SYNTHESIS OF (±)APLYSIN AND (±)DEBROMOAPLYSIN[1]

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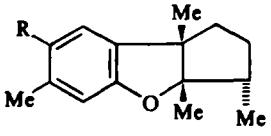
Abstract—Aplysin **1** and debromoaplysin **2**, sesquiterpenes isolated from *Aplysia kurodai* were synthesized in racemic form by two routes. Some rearrangement reactions, encountered during the synthetic work, are described.

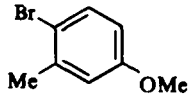
FROM *Aplysia kurodai*, a kind of mollusca, isolation of several bromo compounds was reported[2] and the structures of aplysin **1** and aplysinol, bromine-containing sesquiterpenes determined.[3] A bromo compound, laurinterol was obtained from *Laurencia intermedia* and the structure elucidated.[4] The stereochemical aspect of laurinterol was established by X-ray analysis of the acetate.[5] Since laurinterol was transformed into aplysin,[4] the structure of aplysin including stereochemistry was established as shown in **1**.

We describe here the synthesis, in racemic form, of aplysin **1** and debromoaplysin **2** which is also a natural product.

As a starting material for the synthesis 3-methyl-4-bromo-anisole **3**[6] was selected. The reason for this choice, in spite of the presence of rather reactive bromine in the



1: R = Br
2: R = H



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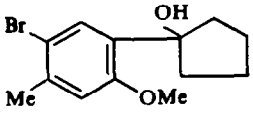

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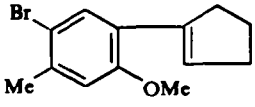

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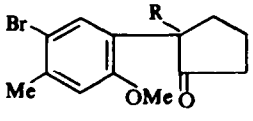
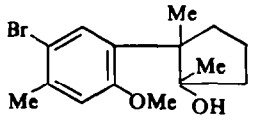


6: R = H
7: R = Me



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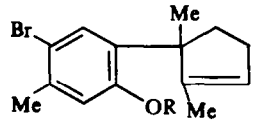
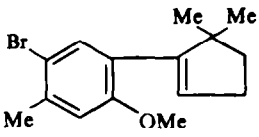


9: R = Me
26: R = H



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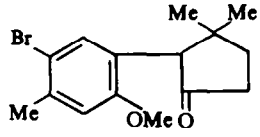

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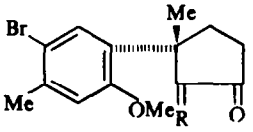
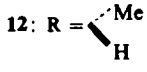
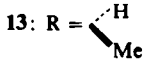
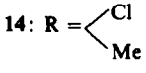
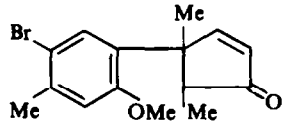


12: R = 

13: R = 

14: R = 



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molecule, was that the bromination at an appropriate stage (e.g. **2** → **1**) after construction of the gross structure of aplysin would not afford a monobromo compound corresponding to **1** but produce a mixture of dibromo- and tribromo-derivatives.[7] Selective metallation at C-6 position of the anisole **3** was achieved with phenyl lithium in ether under the condition specified in the Experimental. The lithium derivative of **3** generated *in situ*, reacted with cyclopentanone to give a cyclopentanol **4**. During the distillation of the crude alcohol **4** under reduced pressure, dehydration occurred, affording a crystalline cyclopentene **5**, the structure of which was confirmed by spectral evidence: in the NMR spectrum two sharp singlets due to aromatic protons appeared at δ 6·65 and δ 7·28, indicating that the condensation occurred between the C-6 position of the anisole **3** and cyclopentanone. Conversion of the cyclopentene **5** to a cyclopentanone **6** was examined under various conditions. Hydroboration of **5**, followed by chromic acid oxidation afforded the desired product **6** in poor yield (ca. 15%). Monoperphthalic acid oxidation of **5** produced a complex mixture, from which the ketone **6** was obtained, again in poor yield (13%). Preparation of the ketone **6** was most conveniently achieved by performic acid oxidation of **5** (62% yield).

Methylation at the benzylic C atom alpha to the CO function was effected by treating the cyclopentanone **6** with sodium hydride in 1,2-dimethoxyethane and then

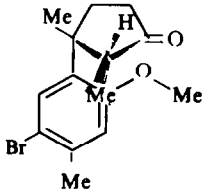
with methyl iodide to give the product **7** in good yield (96%).* The ketone **7** was treated with methyl magnesium iodide in benzene at reflux temperature, affording an alcohol **8** together with the unreacted ketone **7**. Crude product **8**, after separation from the ketone **7** by column chromatography, was dehydrated with benzene–50% sulphuric acid to give a cyclopentene **9**. In contrast, when the alcohol **8** was heated in benzene containing a small amount of *p*-toluenesulphonic acid, dehydration accompanied by a rearrangement occurred, resulting in formation of a cyclopentene **10**, which was further converted to a ketone **11** having no secondary Me group.

The normal dehydration product **9** was smoothly oxidized by performic acid to give a mixture of diastereoisomeric cyclopentanones, **12**(m.p. 149–151°) and **13** (m.p. 83–85°) in the ratio of 14:1. The major product **12** obtained in 70% yield was isomerized to **13** by brief treatment with methanolic sodium methoxide. Assignment of the stereostructures **12** and **13** to two products was mainly based on the following NMR spectral evidence. Although the NMR spectra of two ketones **12** and **13** were similar, a remarkable difference was observed regarding the signal of a secnodary Me group: while the ketone **12** showed the signal at δ 0·64 (doublet, J = 7 c/s), the corresponding signal appeared at δ 0·97 (doublet, J = 7 c/s) in **13**. From the inspection of the molecular model, it was deduced that the secondary Me group *cis* to the aryl group would, to a considerable extent, be shielded by an anisotropic effect of the aryl group. Since the signal of a secondary Me group in **12** appeared at an unusually high field (δ 0·64) in the NMR spectrum, the Me group must be *cis* to the aryl group and situated over the plane of the benzene ring in **12**.†

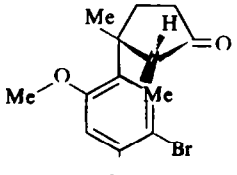
Chlorination at a methine C atom alpha to the CO function of the ketone **12** was readily effected by treating with sulphuryl chloride. In this reaction, only a single diastereoisomer **14** was produced, stereochemistry of which remained unsettled. A severe steric compression must exist in the chloro ketone **14**, because the two adjacent C atoms of the cyclopentanone ring are fully substituted. It was anticipated therefore that on demethylation of the OMe group of **14** an intramolecular displacement of the Cl atom by the phenolic oxygen would occur with ease owing to the steric compression. Thus the conditions were searched for demethylation of the OMe group of **14**. Since the compound **14** was rather unstable, various reagents[8] including $AlCl_3$-benzene, BF_3 etherate, and HBr–AcOH were examined on the ketone **12** as a model compound, resulting in recovery of **12**. It was found that only two reagents, boron

* The yield of the compound **7** was largely dependent on the solvent employed: using other solvents, such as dioxane, THF and benzene, the methylated product **7** was obtained in yields between 20–30%.

† Although two conformations **12a** and **12b** were conceivable, the former seemed to be an actual one, because there must exist a large nonbonding interaction between a OMe and a benzylic Me group in the latter, **12b**.

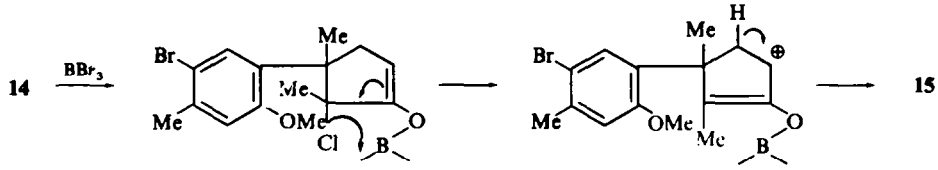


12a

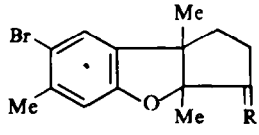


12b

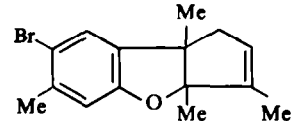
trichloride and boron tribromide were effective for the purpose. The chloro ketone **14**, when treated with boron tribromide in methylene chloride, afforded a cyclized product **16** in 20% yield. From the reaction mixture an additional product was obtained in 18% yield, which proved to be a cyclopentenone derivative **15**. The conjugated ketone **15** could arise from the ketone **14** via intermediates **A** and **B**.



The decreased reactivity of the CO group in the ketone **16** made it somewhat difficult to combine one carbon unit to the CO carbon: among the reactions examined for this purpose Grignard reaction was found to be satisfactory.



16: R = O



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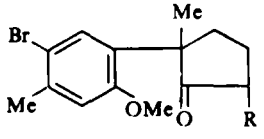
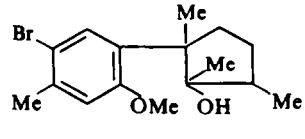
17: R = 

The ketone **16** reacted smoothly with methyl magnesium iodide at room temperature to give an alcohol **17** in high yield. The resulting alcohol **17** was easily dehydrated with phosphoryl chloride and pyridine to give a single product, a cyclopentene **18**. Catalytic hydrogenation of **18** in ethanol, using 10% Pd-C as catalyst gave a crystalline product, which was shown to be identical with natural aplysin in spectral (IR, UV, NMR and Mass) and gas chromatographic behaviour. On catalytic hydrogenation of **18** in the presence of platinum oxide (±)debromoaplysin was also obtained together with (±)aplysin. It was found that (±)aplysin **1** was readily transformed into (±)debromoaplysin **2** by catalytic hydrogenation in the presence of platinum oxide.

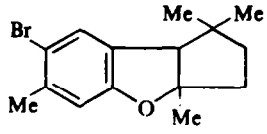
We have further achieved the synthesis of racemic aplysin by another route, starting from the ketone **7**. In order to introduce a Me group into a methylene carbon alpha to the CO function of **7**, the following reactions were conducted on the ketone **7**. Condensation of **7** with ethyl formate in the presence of sodium methoxide in benzene



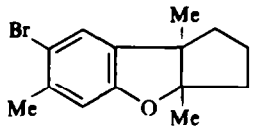
19: R = CHO
20: R = Me



21



24



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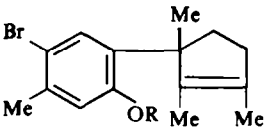
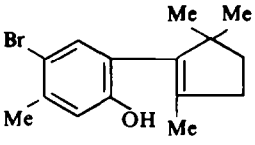


22: R = Me
28: R = H



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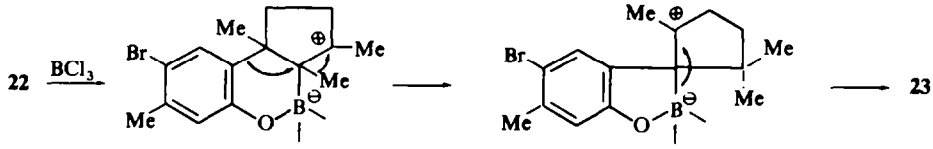
afforded a formyl derivative **19**, which was treated with methyl iodide in acetone containing potassium carbonate. Hydrolysis of the resulting product led to a single product, a cyclopentanone **20**. Although the CO group in **20** was, to some extent, sterically hindered, the reaction with methyl lithium or methyl magnesium iodide took place, affording an alcohol **21** in moderate yield.*

Dehydration of the alcohol **21** was achieved by refluxing in 50% sulphuric acid–benzene, leading to a cyclopentene **22**. The OMe group in **22** resisted demethylation under a variety of conditions[8] ($AlCl_3$-benzene, HCl–AcOH, HBr–AcOH, HI, BF_3 etherate, toluidine hydrochloride, pyridine hydrochloride, piperidine–sodium hydride; at room temperature and/or elevated temperatures). In many cases **22** was recovered and sometimes black tar together with **22** resulted. Boron trichloride was found to be effective for demethylation of the OMe group in **22**, affording a phenolic compound **23**. However, rearrangement occurred during the demethylation, since the product obtained by an acid-catalysed cyclization of the phenolic compound **23** lacked a secondary Me group. Spectral properties of the cyclized product were consistent with the structure **24**. The product **24** isomeric with aplysin **1** showed four singlets due to Me groups at δ 0·90, 1·15, 1·48 and 2·33 (aromatic Me) respectively in the NMR spectrum: the first three singlets clearly indicated the presence of three tertiary Me



C D

* It should be noted that the CO group of **20** was more reactive than that of the isomer **12**. No reaction took place between **12** and MeMgI under the conditions used for **20**. The ketone **20** reacted with $Ph_3P{=}CH_2$, affording a terminal methylene compound in low yield, while no reaction occurred with **12**. The very low reactivity of the CO group in **12** could be accounted for by considering the conformation **12a**. In this, the OMe group blocks one side of the CO group, making it difficult for the CO carbon to be converted to a tetrahedral form. The above explanation for the unusually low reactivity of **12** seems more plausible, considering the reactivity of the cyclized ketone **16**. Thus, as described, **16** reacted with Grignard reagent smoothly, and it reacted with $Ph_3P{=}CH_2$ and $Me_2S{=}CH_2$ to some extent, while the ketone **12** did not react at all.

groups. The product **24** also showed a sharp singlet at δ 2·80 (1H), which was assigned to a benzylic proton with no adjacent hydrogens.* For comparison the compound **9** was treated with boron trichloride. In this case a phenolic product **26** without rearrangement was obtained, which was cyclized to a compound **27**.

The phenol **23** would possibly be formed from **22** as follows: addition of the Lewis acid to a double bond would generate a carbonium ion **C**, and after the successive rearrangement of Me and aryl groups, a new double bond conjugated with the aryl group would be formed via the intermediate **D**. Since many attempts to demethylate the OMe group of **22** under acidic conditions were unsuccessful, demethylation was examined in non-acidic media. Grignard reagent was found to be satisfactory. The cyclopentene **22**, when heated in methyl magnesium iodide in a sealed tube at 165–170°, afforded a mixture of phenolic compounds containing **28**. The mixture was treated with *p*-toluenesulphonic acid in acetic acid. The resulting mixture was separated by repetition of preparative gas chromatography; (±)aplysin **1** (10% yield from **22**) and (±)debromoaplysin **2** (3–5% yield from **22**) were obtained. In addition a colourless liquid product† (15% yield from **22**) was obtained, which was isomeric with aplysin.

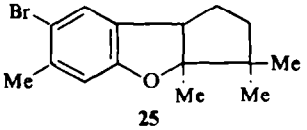
EXPERIMENTAL

All m.ps were uncorrected. UV spectra were determined in MeOH on a Beckman DK2 spectrophotometer and a Perkin–Elmer Model 202 spectrophotometer. IR spectra were recorded on a JASCO IR-S spectrophotometer. NMR spectra were recorded on a Varian A-60 spectrometer; only prominent peaks are cited; chemical shifts are given in ppm relative to internal TMS; s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; coupling constants are given in c/s. Mass spectra were obtained on a Hitachi RMU-6D mass spectrometer equipped with an all glass inlet system and operating with an ionization energy of 70 eV. GLC analysis and separation were performed on a Hitachi K-52 instrument and a Yanagimoto Model GCG-2 instrument. TLC was carried out on silica gel G (E. Merck, A.G., Germany) and column chromatography on silicic acid (100 mesh, Mallinckrodt, U.S.A.), and alumina (E. Merck, A.G., Germany).

1-(2'-Methoxy-4'-methyl-5'-bromophenyl) pentene **5**

All operations were carried out under N_2. A PhLi soln was prepared by adding portionwise 12·4 g (1·79 mole) metallic Li to 134 g (0·87 mole) bromobenzene in 500 ml anhyd ether with stirring. To the stirred soln of PhLi, 155 g (0·77 mole) of **3** was added dropwise at room temp. The mixture was stirred for 18 hr

* The structure **25** was also conceivable for the cyclized product. However a signal due to a benzylic proton appeared as a sharp singlet, which would not be expected from the structure **25**.



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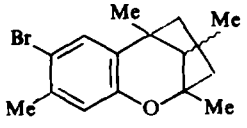
† Although the structure of this product could not be established, the product would be either the stereoisomer regarding the secondary Me group of **1** or a structural isomer **29**.



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at room temp and refluxed for 8 hr. After cooling, 63·2 g (0·75 mole) cyclopentanone was added with ice-bath cooling and stirring. After 15 min at 0° and then 1 hr at room temp, the mixture was carefully poured onto ice–water. The mixture was extracted with ether 3 times. The combined ethereal soln was washed with H_2O and a sat NaCl aq and dried over $MgSO_4$. After removal of ether, the residual oil crystallized on standing. The crude alcohol **4** was distilled under reduced press (b.p. 160–180°/3 mm) to give a solid, which was recrystallized from 95% EtOH to give pure **5**, 68 g (33% yield), m.p. 56–57°; UV maxima, 313 mμ (log ε, 3·63), 302 mμ (3.68), 260 mμ (4·09); IR (KBr) 1610, 1545, 835 (strong, $-\overset{|}{C}=\overset{|}{C}-H$) cm^{-1}; NMR (CCl_4) 2·35 (3H, s, aromatic Me), 3·80 (3H, s, OMe), 6·27(1H, m, vinyl H), 6·65 (1H, s, aromatic H), 7·28 (1H, s, aromatic H); Mass,* M^+ 268 and 266. (Found: C, 58·61; H, 5·68; Br, 29·61. $C_{13}H_{15}OBr$ requires: C, 58·43; H, 5·65; Br, 29·91%).

2-(2′-Methoxy-4′-methyl-5′-bromophenyl) cyclopentanone **6**

(a) *Hydroboration–oxidation method.* Brown's procedure[9] was applied to **5**.

(b) *Preparation by performic acid oxidation.* To a stirred suspension of 49·1 g (0·18 mole) of **5** in 158 ml 85% formic acid, 22 g (0·19 mole) of a 30% H_2O_2 soln was added dropwise under ice-bath cooling. When the mixture was gradually warmed with stirring all the crystals dissolved and then a crystalline solid deposited again. The mixture was kept at 40° for 3 hr and at room temp for 1 day. Water was added and the resulting solid was washed with H_2O, a 10% KOH aq and pet ether for removal of unreacted **5** and dried. Recrystallization from EtOH gave crystals of **6**, 32·0 g (62% yield), m.p. 131–132°; UV max, 285 mμ (log ε, 3·30); IR (KBr) 1732, 1605, 1555 cm^{-1}; NMR (CCl_4) 2·38 (3H, s, aromatic Me), 2·2–3·2 (7H, complex pattern), 3·75 (3H, s, OMe), 6·74 (1H, s, aromatic H), 7·18 (1H, s, aromatic H); Mass, M^+ 284 and 282. (Found: C, 55·23; H, 5·44. $C_{13}H_{15}O_2Br$ requires: C, 55·17; H, 5·34%).

2-Methyl-2-(2′-methoxy-4′-methyl-5′-bromophenyl) cyclopentanone **7**

To a stirred soln of 8·5 g (0·03 mole) of **6** in 100 ml of 1,2-dimethoxyethane was added 0·8 g (0·033 mole) of NaH and the reddish mixture was kept at 70° for 2 hr under N_2. After dropwise addition of 6 g (0·042 mole) MeI, the yellow mixture was stirred at 70° for 1 hr and then at reflux temp for 1 hr. The mixture was poured onto ice–water and extracted with benzene 3 times. The combined benzene layers were washed with H_2O and dried over $MgSO_4$. Evaporation of benzene gave a slightly yellow crystalline solid. Recrystallization from 95% EtOH gave crystals, **7**. The mother liquor was concentrated and the residue was chromatographed on neutral alumina with $CHCl_3$ to give crystals, **7**. The total amount of **7**; 8·5 g (96% yield), m.p. 121–122°; UV maxima, 289 mμ (log ε, 3·33), 283 mμ (3·34); IR (KBr) 1738, 1603, 1552 cm^{-1}; NMR (CCl_4) 1·32 (3H, s, Me), 2·39 (3H, s, aromatic Me), 3·72 (3H, s, OMe), 6·72 (1H, s, aromatic H), 7·33 (1H, s, aromatic H); Mass, M^+ 298 and 296. (Found: C, 56·38; H, 5·66; Br, 27·11. $C_{14}H_{17}O_2Br$ requires: C, 56·55; H, 5·73; Br, 26·93%).

1,2-Dimethyl-2-(2′-methoxy-4′-methyl-5′-bromophenyl) cyclopentanol **8** *and 2,3-Dimethyl-3-(2′-methoxy-4′-methyl-5′-bromophenyl) cyclopentene* **9**

A soln of MeMgI was prepared from 2·47 g (0·1 mole) Mg and 18·5 g (0·13 mole) MeI in anhyd ether (200 ml) under N_2. Ether was distilled off and dried benzene (300 ml) was added. To the stirred Grignard soln, 20·7 g (0·07 mole) of **7** in benzene (70 ml) was added dropwise at 70°. The mixture was refluxed under N_2 for 10 hr and poured onto ice-dil HCl. The benzene layer was separated and the aqueous layer was extracted twice with benzene. The combined benzene extract was washed with H_2O and dried over $MgSO_4$. On removal of benzene, a crystalline mixture (ca. 21 g) of **8** and unreacted **7** remained. The mixture was roughly separated by column chromatography on silicic acid (250 g) with $CHCl_3$ to give crude **8** (ca. 9 g; IR (KBr), 3550, 1605, 1550 cm^{-1}) and **7**. A soln in benzene (90 ml) of **8** (9 g) containing some **7** was mixed with 50% H_2SO_4 (18 ml) and the mixture was refluxed with stirring for 3 hr. The benzene layer was separated, washed with H_2O, a sat $NaHCO_3$ aq and H_2O and dried over $MgSO_4$. Evaporation of benzene afforded a crystalline residue, which was chromatographed over silicic acid (100 g) with $CHCl_3$ to give pure **9** and the unreacted **7**. The recovered total amount of **7** in two steps was 14 g. The cyclopentene **9** was recrystallized from 95% EtOH; 4·8 g, m.p. 88–89°; UV maxima, 289 mμ (log ε, 3·36), 283 mμ (3·37); IR (KBr) 1645, 1600, 1550 cm^{-1}; NMR (CCl_4) 1·42 (3H, s, Me), 1·57 (3H, d, J = 2 c/s, allyl coupling, $Me-\overset{|}{C}=CH-$), 2·34

* Owing to the presence of almost equal amounts of two bromine isotopes (Br^{79} and Br^{81}) two mass numbers are cited as M^+.

(3H, s, aromatic Me), 3·80 (3H, s, OMe), 5·44 (1H, m, vinyl H), 6·70 (1H, s, aromatic H), 7·18 (1H, s, aromatic H); Mass, M^+ 296 and 294. (Found: C, 61·20; H, 6·77. $C_{15}H_{19}OBr$ requires: C, 61·07; H, 6·49%).

2-(2'-Methoxy-4'-methyl-5'-bromophenyl)3,3-dimethylcyclopentene **10** *and 2-(2'-Methoxy-4'-methyl-5'-bromophenyl) 3,3-dimethylcyclopentanone* **11**

A mixture of 3·3 g of the alcohol **8** in benzene (100 ml) containing 1·5 g *p*-toluenesulfonic acid and 1·5 g $CaCl_2$ were placed in a flask fitted with a water-separator. The mixture was refluxed for 1·5 hr and after cooling was washed repeatedly with a dil $NaHCO_3$ aq. The benzene soln was further washed with H_2O and a sat NaCl aq and dried over $MgSO_4$. Evaporation of benzene afforded a crystalline **10** (3·3 g). IR spectrum of which was similar to that of **9** but different in the finger print region. To a stirred suspension 2·9 g crude **10** in 99% formic acid (20 ml), 1·6 ml 30% H_2O_2 aq was added dropwise under cooling. The suspension was stirred at 0° for 30 min and at room temp overnight. Water (150 ml) was added and the resulting ppt was collected by filtration, washed with H_2O, a 2% NaOH aq and again with H_2O and dried (2·7 g). Since TLC analysis (CCl_4) showed the presence of unreacted **10**, the mixture was chromatographed on silicic acid (50 g): unreacted **10** was eluted with CCl_4 and the elution with $CHCl_3$ afforded **11**. Recrystallization from benzene–hexane gave pure **11**, 2·2 g, m.p. 134–135°; UV maxima, 292 mμ (log ε, 3·42), 285 mμ (3·43); IR (KBr) 1733, 1605, 1555 cm^{-1}; NMR (CCl_4) 0·78 (3H, s, Me), 1·12 (3H, s, Me), 2·35 (3H, s, aromatic Me) 3·37 (1H, s, benzylic H), 3·70 (3H, s, OMe), 6·65 (1H, s, aromatic H), 6·93 (1H, s, aromatic H); Mass, M^+ 312 and 310. (Found: C, 57·68; H, 6·12. $C_{15}H_{19}O_2Br$ requires: C, 57·93; H, 6·16%).

2,3-Dimethyl-3-(2'-methoxy-4'-methyl-5'-bromophenyl) cyclopentanones **12, 13**

To a stirred suspension of 2·36 g (0·008 mole) of **9** in 85% formic acid (16 ml), 1·2 ml 30% H_2O_2 aq was added dropwise under ice–bath cooling. The mixture was stirred at 0° for 30 min and at room temp overnight. Water was added and the ppt was collected by filtration, washed with H_2O, a 10% NaOH aq and H_2O, and dried. The ppt (2·2 g) was chromatographed on silicic acid (40 g) with $CHCl_3$: early fractions afforded an oily material (0·25 g), which was further purified by preparative TLC ($CHCl_3$–CCl_4, 2:1) to give, on standing in a refrigerator, a crystalline product **13**; later fractions yielded a crystalline solid **12**, 1·77 g, (recrystallization from 95% EtOH, 70% yield), m.p. 149–151° (sealed tube); UV maxima, 289 mμ (log ε, 3·39), 282 mμ (3·38); IR (KBr) 1745, 1605, 1550 cm^{-1}; NMR (CCl_4) 0·64 (3H, d, J = 7 c/s, Me—CH—), 1·32 (3H, s, Me), 2·35 (3H, s, aromatic Me), 3·78 (3H, s, OMe), 6·67 (1H, s, aromatic H), 7·20 (1H, s, aromatic H); Mass, M^+ 312 and 310. (Found: C, 57·74; H, 6·13; Br, 25·52. $C_{15}H_{19}O_2Br$ requires: C, 57·93; H, 6·16; Br, 25·70%).

13, 120 mg (recrystallization from 95% EtOH, ca. 5% yield), m.p. 83–85°; IR (KBr) 1735, 1600, 1545 cm^{-1}; NMR (CCl_4) 0·97 (3H, d, J = 7 c/s, Me—CH—), 1·18 (3H, s, Me), 2·35 (3H, s, aromatic Me), 3·84 (3H, s, OMe), 6·72 (1H, s, aromatic H), 7·24 (1H, s, aromatic H); Mass, M^+ 312 and 310. (Found: C, 57·86; H, 6·13; Br, 25·73. $C_{15}H_{19}O_2Br$ requires: C, 57·93; H, 6·16; Br, 25·70%).

Isomerization of the ketone **12** *to the ketone* **13**

A soln of **12** (30 mg) in MeOH (2 ml) containing MeONa (10 mg) was refluxed for 2 hr and was concentrated under reduced press. The resulting mixture was diluted with H_2O, neutralized with a 10% HCl aq and extracted with benzene. The extract was washed with H_2O and dried over $MgSO_4$. On removal of the solvent an oily material was obtained. The oily mixture was separated by preparative TLC ($CHCl_3$–CCl_4, 2:1) to give the starting **12** and the isomer **13** (8 mg), which was identified by IR and TLC comparison.

2-Chloro-2,3-dimethyl-3-(2'-methoxy-4'-methyl-5'-bromophenyl) cyclopentanone **14**

To a stirred soln of 0·78 g (0·0025 mole) of **12** in anhyd CCl_4 (6 ml) a soln of 0·4 g (0·003 mole) SO_2Cl_2 was added dropwise under ice-bath cooling. The mixture was stirred at 0° for 1 hr and at room temp overnight, and poured onto ice–water with vigorous stirring. The organic layer was separated and washed with H_2O, a sat $NaHCO_3$ aq soln and H_2O and dried over $MgSO_4$. Evaporation of CCl_4 afforded a pale yellow oily material (0·86 g), which was chromatographed on silicic acid with CH_2Cl_2 to give oily **14**, 0·67 g (78% yield). The product was shown to be distillable and to be almost pure by GLC analysis (the purity was more than 83%); IR (CCl_4) 1763, 1600, 1540 cm^{-1}; NMR (CCl_4) 1·18 (3H, s, Me), 1·68 (3H, s, Me), 2·33 (3H, s, aromatic

Me), 3·64 (3H, s, OMe), 6·64 (1H, s, aromatic H), 7·47 (1H, s, aromatic H); Mass, M^+ 348, 346 and 344 with intensities (ca. 1:4:3) expected for the compound containing one Br and one Cl.

Action of BBr_3 *on the chloroketone* **14**

To a stirred soln of 2·1 g (0·0061 mole) of **14** in benzene (13 ml), a soln of 2·0 g (0·0080 mole) BBr_3 in benzene (2 ml) was added dropwise under ice-bath cooling. The mixture was stirred at room temp for 2 days and poured onto ice–water. The benzene layer was separated and washed with H_2O, a sat $NaHCO_3$ aq, H_2O and a sat NaCl aq successively and dried over Na_2SO_4. On evaporation of the solvent, a brown oily residue was obtained, which showed two spots on a TLC plate (benzene as solvent). The mixture was chromatographed on silicic acid (ca. 100 g), using $CHCl_3$ as solvent: early fractions afforded a crystalline solid, which was recrystallized from EtOH to give the pure **16**; from the later fractions **15** was isolated (recrystallization from i-PrOH).

15: 334 mg (18% yield), m.p. 82–83°; UV maxima, 289 mμ (log ε, 3·40), 284 mμ (3·41); IR ($CHCl_3$) 1715, 1600, 1545 cm^{-1}; NMR (CCl_4) 1·15 (3H, d, J = 6·3 c/s, Me—CH—), 1·34 (3H, s, benzylic Me), 2·34 (3H, s, aromatic Me), 2·52 (1H, q, J = 6·3 c/s, —CH—Me), 3·80 (3H, s, OMe), 6·06 (1H, d, J = 6·0 c/s, vinyl H), 6·72 (1H, s, aromatic H), 7·16 (1H, s, aromatic H), 7·71 (1H, d, J = 6·0 c/s, vinyl H); Mass, M^+ 310 and 308. (Found: C, 58·31; H, 5·63. $C_{15}H_{17}O_2Br$ requires: C, 58·26; H, 5·55%).

16: 346 mg (20% yield), m.p. 132–133°; UV max, 294 mμ (log ε, 3·52); IR ($CHCl_3$) 1760, 1615, 1580 cm^{-1}; NMR (CCl_4) 1·28 (3H, s, Me), 1·31 (3H, s, Me), 2·27 (3H, s, aromatic Me), ca. 1·5–2·3 (4H, complex pattern), 6·48 (1H, s, aromatic H), 7·03 (1H, s, aromatic H); Mass, M^+ 296 and 294. (Found: C, 56·93; H, 5·93; Br, 27·38. $C_{14}H_{15}O_2Br$ requires: C, 57·00; H, 5·13; Br, 27·09%).

Formation of the cyclopentene **18** *via the cyclopentanol* **17**

A soln of MeMgI was prepared from 40 mg Mg and 285 mg MeI in anhyd ether (5 ml) under N_2. To this soln, an ethereal soln (1 ml) of 238 mg (0·81 mmole) of **16** was added. The mixture was kept at reflux temp for 3 hr, and the resulting complex was, after cooling, decomposed with 2N H_2SO_4. The ethereal layer was separated, washed with a sat $NaHCO_3$ aq (twice), H_2O (twice) and a sat NaCl aq and dried over $MgSO_4$. On removal of ether, a colourless product remained, which was purified by column chromatography on silicic acid with $CHCl_3$ to give a colourless liquid, **17**, 208 mg (ca. 83% yield); IR (CCl_4) 3650 cm^{-1}. To a stirred soln of 208 mg (0·67 mmole) of **17** in dried pyridine (4 ml), 287 mg (2·0 mmoles) of $POCl_3$ was added dropwise under ice-bath cooling. The mixture was stirred at room temp for 24 hr, diluted with 20% H_2SO_4 and extracted with two 10 ml portions benzene. The combined benzene extract was washed with sat $NaHCO_3$ aq, H_2O and a sat NaCl aq, and dried over $MgSO_4$. Evaporation of benzene afforded a slightly coloured product, which showed one spot on a TLC plate (benzene as solvent). The product was purified by column chromatography over silicic acid with benzene to give a colourless liquid **18**, which was shown to be distillable and homogeneous (by GLC analysis); 140 mg (72% yield from **17**); IR (CCl_4) 1615, 1580 cm^{-1}; NMR (CCl_4) 1·25 (3H, s, Me), 1·35 (3H, s, Me), 1·67 (3H, d, J = 1·5 c/s, vinyl Me), 2·26 (3H, s, aromatic Me), 2·50 (2H, m, —CH_2—), 5·34 (1H, m, vinyl H), 6·50 (1H, s, aromatic H), 7·08 (1H, s, aromatic H).

(±)*Aplysin* **1** *from the cyclopentene* **18**

(a) The cyclopentene **18** (24 mg) was hydrogenated in the presence of 10% Pd–C (2 mg) in EtOH (2 ml) under atm press. Within 2 hr, 1 mole equiv H_2 was absorbed. After removal of the catalyst the soln was concentrated under reduced press to give a crystalline solid, which was recrystallized from EtOH; (±)-**1**, 20 mg (85% yield); m.p. 101–102°; UV maxima, 295 mμ (log ε, 3·59), 235 mμ (3·86); IR (CCl_4) 1615, 1580 cm^{-1}; NMR (CCl_4) 1·10 (3H, d, J = 6·0 c/s, Me—CH—), 1·25 (3H, s, Me), 1·30 (3H, s, Me), 2·30 (3H, s, aromatic Me), 6·50 (1H, s, aromatic H), 7·07 (1H, s, aromatic H); Mass, M^+ 296 and 294. (Found: C, 61·14; H, 6·34; Br, 27·07. $C_{15}H_{19}OBr$ requires: C, 61·02; H, 6·44; Br, 27·07%). The spectral data were identical with those of natural aplysin.

(b) Catalytic hydrogenation of **18** (108 mg) was carried out in the presence of PtO_2 (10 mg) in EtOH (20 ml) under atm press. The catalyst was filtered off and the filtrate concentrated under reduced press to give a residue, containing two compounds by GLC analysis performed on an SE-30 cloumn (20 m) at 220°. Two substances were separated by preparative TLC with n-hexane, using continuous development

technique: a crystalline product was obtained by extraction from silica gel layer with $CHCl_3$–MeOH (7 : 3), which was shown to be (±)aplysin **1** (63 mg); a liquid product was isolated, which proved to be (±)debromoaplysin **2** (42 mg). Pure **2** was obtained by preparative GLC on Carbowax 20 M (2 m column at 185°; He as carrier gas). Spectral properties of synthetic **2** were identical with those of natural **2**.

Preparation of (±)debromoaplysin **2** *from (±)aplysin* **1**

Synthetic aplysin **1** (7 mg) was catalytically hydrogenated with PtO_2 (2 mg) in EtOH (2 ml) under atm press. After removal of the catalyst the soln was concentrated to give (±)-**2**.

2,5-*Dimethyl*-2-(2′-*methoxy*-4′-*methyl*-5′-*bromophenyl*)-*cyclopentanone* **20**

To a stirred suspension of 0·57 g (0·011 mole) MeONa in anhyd benzene (10 ml), a soln of 1·5 g (0·005 mole) of **7** and 0·78 g (0·010 mole)HCOOEt in benzene (5 ml) was added dropwise under ice-bath cooling. The mixture in the flask fitted with a $CaCl_2$-tube was stirred at room temp overnight and poured onto ice–water. The benzene layer was separated and extracted with a 10% NaOHaq. From the benzene layer the starting material **7** (0·29 g) was recovered. The aqueous alkaline soln was, after washing with benzene, acidified with a 10% HClaq. The aqueous acidic soln was extracted with benzene 3 times and the benzene extract washed with H_2O and dried over $MgSO_4$. Evaporation of benzene afforded **19**, 1·25 g (ca. 75% yield); IR (KBr) 1735 (shoulder), 1710, 1675, 1620, 1600, 1560 cm^{-1}; Mass, M^+ 326 and 324.

The crude **19** was directly employed for the next step. A soln of 1 g (0·003 mole) of **19**, 1·4 g (0·009 mole) MeI and 0·48 g (0·0035 mole) K_2CO_3 in anhyd acetone (5 ml) was refluxed for 20 hr. A white ppt appeared within 5 hr. Evaporation of acetone afforded a solid, to which H_2O was added.

The mixture was extracted with benzene and the benzene extract washed with a 10% NaOHaq and H_2O and dried over $MgSO_4$. On removal of benzene, an oily product (0·82 g) remained, which was dissolved in 95% EtOH (5 ml)–10% KOH (1·5 ml). The aqueous alkaline EtOH soln was refluxed for 15 min and evaporated. To the residual mixture, H_2O–benzene was added and the benzene layer separated. The benzene extract was washed with H_2O and dried over $MgSO_4$. On removal of benzene, a crystalline solid was obtained, which was recrystallized from n-hexane (or 95% EtOH) to give pure **20**, 0·5 g (31% yield from **7**), m.p. 134–136°; UV max, 283 mμ (log ε, 3·36); IR (KBr) 1735, 1610, 1545 cm^{-1}; NMR (CCl_4) 1·15 (3H, d, J = 7·0 c/s, Me—CH—), 1·25 (3H, s, Me), 2·36 (3H, s, aromatic Me), 3·70 (3H, s, OMe), 6·70 (1H, s, aromatic H), 7·35 (1H, s, aromatic H); Mass, M^+ 312 and 310. (Found: C, 57·90; H, 6·22; Br, 25·62. $C_{15}H_{19}O_2Br$ requires: C, 57·93; H, 6·16; Br, 25·70%).

1,2,5-*Trimethyl*-2-(2′-*methoxy*-4′-*methyl*-5′-*bromophenyl*)-*cyclopentanol* **21**

A soln of MeMgI was prepared from 0·38 g Mg and 2·5 g (0·017 mole) MeI in anhyd ether (ca. 70 ml). Ether was distilled off and dried benzene (50 ml) was added. To the Grignard soln a soln of 3 g (0·0096 mole) of **20** in benzene (10 ml) was added at room temp. The soln was refluxed for 10 hr and poured onto ice–dil H_2SO_4. The benzene layer was separated, washed with H_2O, a sat $NaHCO_3$aq and H_2O and dried over $MgSO_4$. Evaporation of benzene afforded a crystalline solid (3·05 g), which was chromatographed on silicic acid with $CHCl_3$ to give **21** (crude), ca. 3 g, m.p. 136–138° (recrystallization from 95% EtOH); UV maxima, 288 mμ (log ε, 3·31), 282 mμ (3·31); IR (KBr) 3520 cm^{-1}; NMR (CCl_4) 0·80 (3H, s, Me), 1·00 (3H, d, J = 6 c/s, Me—CH—), 1·23 (3H, s, Me), 2·38 (3H, s, aromatic Me), 3·08 (1H, s, OH), 3·94 (3H, s, OMe), 6·74 (1H, s, aromatic H), 7·30 (1H, s, aromatic H). (Found: C, 59·19; H, 7·03. $C_{16}H_{23}O_2Br$ requires: C, 58·77; H, 7·03%).

1,2,3-*Trimethyl*-3-(2′-*methoxy*-4′-*methyl*-5′-*bromophenyl*)-*cyclopentene* **22**

A soln of crude **21** (3·0 g) in benzene (20 ml) was mixed with 50% H_2SO_4 (7 ml). The mixture was refluxed with stirring for 3 hr and poured onto ice–water. The benzene layer was separated, washed with H_2O, sat $NaHCO_3$aq and H_2O, and dried over $MgSO_4$. Evaporation of benzene afforded a solid, which was chromatographed on silicic acid (50 g) with $CHCl_3$. The crystalline **22** was obtained: 1·2 g, m.p. 124·5–125·5° (recrystallization from 95% EtOH); UV maxima, 288 mμ (log ε, 3·37), 282 mμ (3·37); IR (KBr) 1600, 1550 cm^{-1}; NMR (CCl_4) 1·38 (3H, s, Me), 1·46 (3H, s, Me), 1·70 (3H, s, Me), 2·33 (3H, s, aromatic Me), 3·78 (3H, s, OMe), 6·65 (1H, s, aromatic H), 7·05 (1H, s, aromatic H); Mass, M^+ 310 and 308. (Found: C, 62·34; H, 7·13; Br, 25·56. $C_{16}H_{21}OBr$ requires: C, 62·19; H, 6·85; Br, 25·86%).

Action of BCl_3 *on the cyclopentene* **22**: *formation of the rearranged product* **23**

A soln of 0·62 g (0·002 mole) of **22** in CH_2Cl_2 (2 ml) was added to ca. 0·8 ml BCl_3 in a flask cooled in an acetone–dry ice bath (bath temp ca. −50°). The mixture was kept in the bath for 10 hr and at room temp for further 5 hr. After removal of the solvent the residue was mixed with H_2O. The mixture was extracted with benzene and the benzene extract was washed with H_2O, $NaHCO_3$aq and H_2O and dried over $MgSO_4$. Evaporation of benzene afforded a dark red-brown oily material (0·65 g), which was chromatographed on silicic acid (10 g) with $CHCl_3$ to give a colourless liquid, the rearranged phenol **23** (0·43 g); UV maxima, 297 mμ (shoulder), 291 mμ (no intensities were measured); IR (film) 3400 cm^{-1}; NMR (CCl_4) 0·98 (3H, s, Me), 1·18 (3H, s, Me), 1·57 (3H, s, Me—C=C—), 2·40 (3H, s, aromatic Me), 3·75 (1H, s, OH), 6·80 (1H, s, aromatic H), 7·08 (1H, s, aromatic H).

Cyclization of the rearranged phenol **23**

A soln of 0·43 g of crude **23** and 0·1 g *p*-toluenesulphonic acid in AcOH (20 ml) was refluxed for 2 hr. Evaporation of AcOH under reduced press gave an oily product, to which was added a $NaHCO_3$ aq. The mixture was extracted with benzene and the benzene extract was washed with H_2O and dried over $MgSO_4$. On removal of benzene, a liquid substance was obtained, which was chromatographed on silicic acid (10 g) with $CHCl_3$. The liquid product obtained was further purified by repeating GLC separation, using Carbowax 20 M (2 m column; column temp, 235°; He as carrier gas) and Apiezon L (2 m column; column temp, 225°; He as carrier gas). A colourless liquid **24**, 0·045 g was obtained; UV maxima, 297 mμ (shoulder), 291 mμ, 231 mμ (no intensities were measured); IR (film) no OH band, 1610, 1570 cm^{-1}; NMR (CCl_4) 0·90 (3H, s, Me), 1·15 (3H, s, Me) 1·48 (3H, s, Me), 2·33 (3H, s, aromatic Me), 2·80 (1H, s, benzylic H), 6·57 (1H, s, aromatic H), 7·20 (1H, s, aromatic H); Mass, M^+ 296 and 294. (Found: C, 61·42; H, 6·22. $C_{15}H_{19}OBr$ requires: C, 61·02: H, 6·44%).

Preparation of the compound **27** *via the cyclopentene* **26**

A soln of 0·59 g of **9** and ca. 0·8 ml BCl_3 in CH_2Cl_2 (2 ml) was kept in an acetone–dry ice bath (bath temp ca. −50°) for 5 hr. Evaporation of the solvent afforded a white residue, which was hydrolysed with H_2O. The mixture was extracted with benzene and the benzene extract was washed with H_2O, sat $NaHCO_3$ aq and H_2O and dried over $MgSO_4$. On removal of benzene, an oily material remained, which was chromatographed on silicic acid (20 g) with $CHCl_3$ to give a semicrystalline **26**, 0·44 g; IR (CCl_4) 3400 (phenolic OH), 1610, 1585, 1520 cm^{-1}; NMR (CCl_4) 1·46 (6H, s, two Me), 2·42 (3H, s, aromatic Me), 3·70 (1H, s, OH), 7·17 (1H, s, aromatic H), 7·83 (1H, s, aromatic H).

To a soln of 0·4 g of crude **26** in AcOH (20 ml), 0·1 g of *p*-toluenesulphonic acid was added. The mixture was refluxed for 2 hr, concentrated under reduced press and diluted with H_2O. The resulting aqueous mixture was extracted with benzene and the benzene extract was washed with a dil NaOH aq and H_2O and dried over $MgSO_4$. Evaporation of benzene afforded an oily material (0·34 g), which was chromatographed on silicic acid (10 g) with $CHCl_3$ to give crude crystals, **27**. Recrystallization from 95% EtOH yielded pure **27**, 0·07 g, m.p. 51–52°; IR (KBr) 1610, 1580 cm^{-1}; NMR (CCl_4) 1·32 (3H, s, Me), 1·37 (3H, s, Me), 2·32 (3H, s, aromatic Me), 6·52 (1H, s, aromatic H), 7·20 (1H, s, aromatic H); Mass, M^+ 282 and 280. (Found: C, 60·12; H, 6·16. $C_{14}H_{17}OBr$ requires: C, 60·05; H, 6·12%).

Action of methyl magnesium iodide on the cyclopentene **22**: *the phenol* **28**

To an ethereal soln of MeMgI prepared from 0·97 g Mg and 6·3 g (0·045 mole) MeI, 1·2 g (0·004 mole) of **22** was added. Ether was evaporated and the residual mixture placed in a sealed tube, heated gradually and kept at 165–170° (bath temp) for 5 hr. After cooling, the reaction mixture was diluted with dil H_2SO_4–ice and extracted with ether. The ethereal extract was washed with H_2O, sat $NaHCO_3$ aq and H_2O and dried over $MgSO_4$. On removal of ether crude brown oily **28** was obtained, 1·1 g; IR (film) 3450 cm^{-1} (phenolic OH).

(±)*Aplysin* **1**, (±)*debromoaplysin* **2** *and the isomer of aplysin from the phenol* **28**

A soln of 1·1 g of crude **28** and 0·35 g *p*-toluenesulfonic acid in AcOH (56 ml) was refluxed for 2 hr. Evaporation of AcOH under reduced press afforded oily material, to which H_2O was added. The mixture was extracted with ether and the ethereal extract was successively washed with a dil $NaHCO_3$ aq and H_2O, and dried over $MgSO_4$. Evaporation of ether afforded a coloured oily mixture, which was chromatographed over silicic acid (20 g) with $CHCl_3$ to give a slightly yellow oil, 0·95 g. Preparative GLC separation of the

mixture was repeatedly performed on Carbowax 20 M (2 m column with i.d. 8 mm; column temp, 240°; He as carrier gas; flow rate 30 ml/min) and Apiezon L (2 m column with i.d. 8 mm; column temp, 230°; He as carrier gas; flow rate 55 ml/min). Three products were obtained in a pure state: 28 mg (3% yield from **22**) of (±)-**2** (retention time with a Carbowax 20 M column, 5·4 min), 93 mg (10% yield from **22**) of (±)-**1** (m.p. 99–100°; retention time 15·5 min), and 140 mg (15% yield from **22**) of the isomer of aplysin (retention time 19·3 min). The identification of synthetic **1** and **2** with natural products was made by spectral (UV, IR, NMR, and mass) and GLC comparison. The spectral properties of the isomer of aplysin were as follows: UV maxima, 294 mμ (log ε, 3·57), 236 mμ (3·68); IR (film) 1610, 1580 cm^{-1}; a distinct difference of IR spectra between (±)-**1** and the isomer (liquid) was that a strong band appeared at 1195 cm^{-1} in (±)-**1** and a corresponding one was observed at 1100 cm^{-1} in the isomer; NMR (CCl_4) 0·98 (3H, d, J = 7·0 c/s, Me—CH(Br)—), 1·24 (3H, s, Me), 1·30 (3H, s, Me), 2·30 (3H, s, aromatic Me), 1·5–2·5 (4H, broad, $—CH_2—CH_2—$), 6·50 (1H, s, aromatic H), 7·08 (1H, s, aromatic H); Mass, M^+ 296 and 294. (Found: C, 61·14; H, 6·34. $C_{15}H_{19}OBr$ requires: C, 61·02; H, 6·44%).

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