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The synthesis of a natural product family: from debromoisolaurinterol to the aplysins

David C. Harrowven,[a,*] Matthew C. Lucas[a] and Peter D. Howes[b]

[a]*Department of Chemistry, The University, Southampton S017 1BJ, UK*
[b]*Medicinal Chemistry 2, GlaxoWellcome Medicines Research Centre, Gunnels Wood Road, Stevenage, Herts SG1 2NY, UK*

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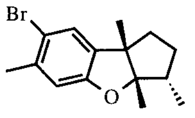
Abstract—Total syntheses of (±)-aplysin **1**, (±)-debromoaplysin **2**, (±)-isoaplysin **3**, (±)-aplysinol **4**, (±)-debromoaplysinol **5**, (±)-aplysinal **6**, (±)-isolaurinterol **7** and (±)-debromoisolaurinterol **8** are described. Key features are a diastereoselective, sulfur mediated radical cyclisation of diene **12** to give **35**; a new radical to polar crossover sequence mediated by $Bu_3Sn^{\cdot}$ that transforms diene **12** into (±)-debromoisolaurinterol **8**; and a series of biomimetic cyclisation and oxidation reactions. © 2001 Elsevier Science Ltd. All rights reserved.

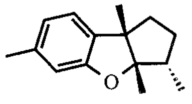
1. Background

During a programme to identify natural anti-tumour agents of marine origin, Yamamura and Hirata observed that crude extracts of the *Aplysia* sea hare displayed significant biological activity.[1] Among the chemical constituents identified in the extract was an unusual tricyclic sesquiterpene which they named aplysin **1**.[1–6] Several related compounds were subsequently identified, including debromoaplysin **2**, isoaplysin **3**,[7] aplysinol **4**,[3] debromoaplysinol **5**,[4] and aplysinal **6**.[5] The co-occurrence of brominated and non-brominated aplysins in all known natural sources prompted speculation that the debromo-analogues scavenged reactive halogens from the marine environment before they could inflict damage on the host. The aplysins are also believed to act as anti-feedants, preventing the predatory advances of other marine organisms.[8]

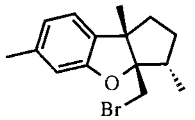
Natural sources of the aplysins are limited. They have been identified in North American opisthobranchs and the red sea alga *Laurencia*. It is believed that the latter is responsible for the synthesis of aplysins in nature as both the *Aplysia* sea hare and opisthobranchs feed on *Laurencia* and aplysins are accumulated in the gut of both molluscs.[8,9]



1 aplysin



2 debromoaplysin



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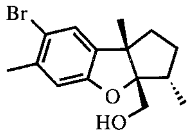
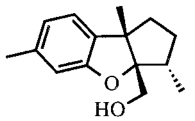
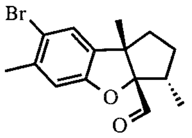


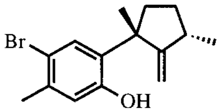
4 aplysinol



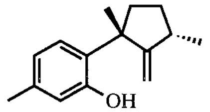
5 debromoaplysinol



6 aplysinal



7 isolaurinterol



8 debromoisolaurinterol

From a synthetic viewpoint the aplysins offer an interesting challenge. In particular, the need to establish three contiguous stereogenic centres while constructing a sterically demanding tricyclic skeleton requires special attention. Several syntheses of aplysin **1** have been reported using a variety of strategies.[10,11] To date only Venkateswaran has developed a route applicable to the more demanding members of this series, modifying an earlier synthesis of aplysin **1** to address isoaplysin **3** and aplysinol **4**.[8]

Keywords: terpenes and terpenoids; natural products; radicals and radical reactions; cyclisations; oxygen heterocycles.

* Corresponding author. Tel.: +23-8059-3302; fax: +23-8059-3781; e-mail: dch2@soton.ac.uk

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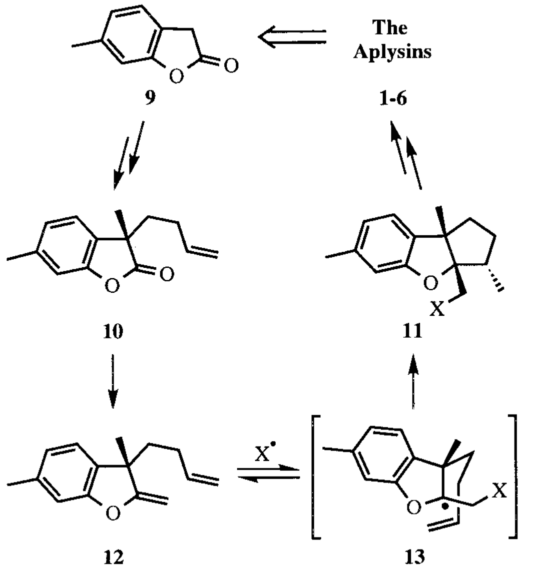
2. Our strategy

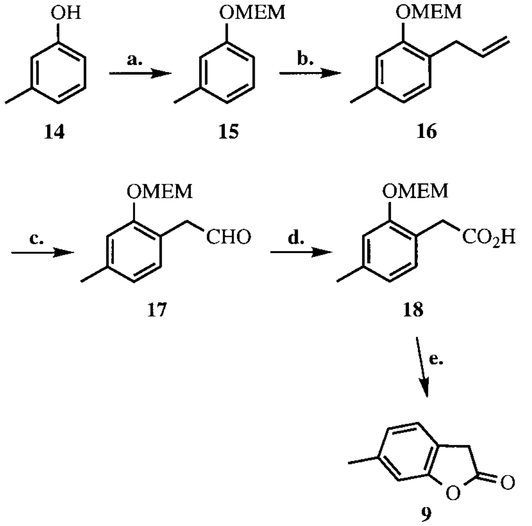
Our interest in radical reactions and the synthesis of naturally occurring arenes led us to consider the approach outlined in Scheme 1.[12] We hoped that an electrophilic radical generated in the presence of diene **12** would first add to the terminus of the enol ether giving **13**. A 5-*exo*-trig cyclisation through a chair-like transition state[13] followed by a hydrogen atom quench would then provide **11**, an advanced precursor of all the aplysins.



Scheme 1.

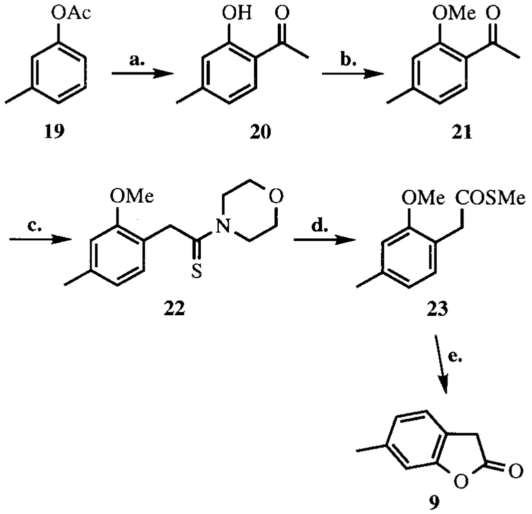
3. Synthesis of 6-methylbenzofuran-2-one

Our first task was to secure a synthesis of 6-methylbenzofuran-2-one **9**. To that end, the ethoxymethyl ether **15** derived from *meta*-cresol **14** was metallated with *t*-butyllithium and then allylated.[14] Ozonolysis of the resulting alkene **16** next provided aldehyde **17** which was smoothly oxidised to the corresponding acid **18** with Jones' reagent and lactonised to **9** using PPTS (Scheme 2).

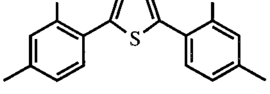


Scheme 2. *Reagents and conditions:* **a.** NaH, MEMCl, Et$_2$O, DMF, 3h, 94%; **b.** *t*-BuLi, pentane, 0°C, 7h; CuI.P(OEt)$_3$, THF, −78°C, 30 min.; CH$_2$=CHCH$_2$Br, RT, 22h, 78%; **c.** O$_3$, CHCl$_3$, −78°C, 40 min.; PPh$_3$, RT, 5h, 70%; **d.** CrO$_3$, 2M H$_2$SO$_4$, acetone, RT, 72%; **e.** PPTS, PhCH$_3$, Δ, 20h, 50%.

Though effective for the synthesis of **9**, the hazards associated with using *t*-butyllithium on a large scale led us to develop an alternative approach. This began with the acetate **19** derived from *meta*-cresol. When exposed to zirconium(IV) chloride at room temperature under ultrasound irradiation **19** was smoothly transformed into acetophenone **20**.[15] Sequential protection of the phenol as its methyl ether **21**, Willgerodt-Kindler oxidation to thioamide **22** and alkylation and hydrolysis provided thioester **23**.[16,17] Finally, exposure to boron trichloride effected simultaneous deprotection of the methyl ether and lactonisation giving benzofuranone **9** (Scheme 3).



Scheme 3. *Reagents and conditions:* **a.** ZrCl$_4$, ultrasound irradiation, DCM, RT, 24h, 93%; **b.** Me$_2$SO$_4$, KOH, acetone, RT, 15h, 97%; **c.** morpholine, S$_8$, 100°C, 24h, 76%; **d.** MeI, H$_2$O, THF, Δ, 18h, 90%; **e.** BCl$_3$, DCM, 0°C to RT, 15h, 46%.



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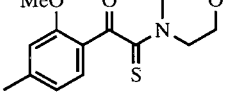

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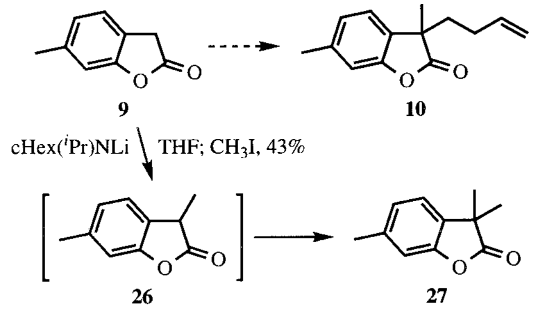
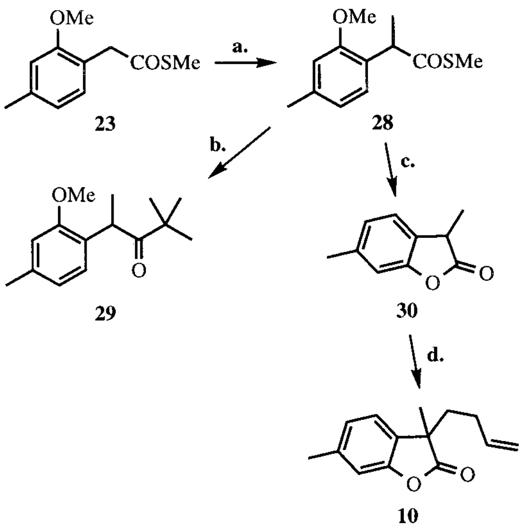
It is worth noting that the Willgerodt-Kindler reaction furnished two major side products, thiophene **24** (the identity of which was confirmed by X-ray crystallography) and thioxoketone **25**. Fortunately, the yield of each diminished as the scale of the reaction was increased.

4. Synthesis of diene 12

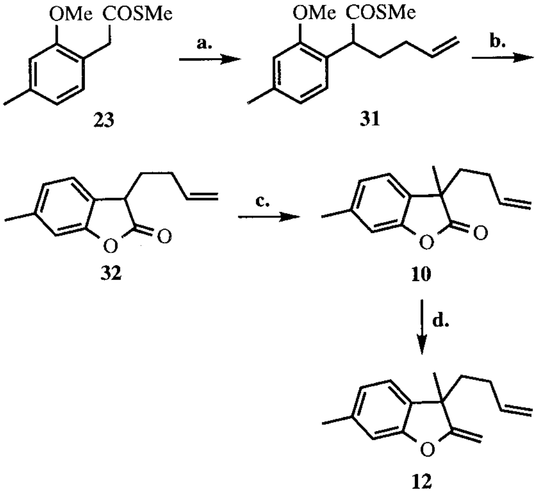
Several difficulties were experienced at this juncture. For example, attempts to alkylate the enolate derived from **9** with 4-butenyl bromide returned only recovered starting material while methylation with methyl iodide furnished the dialkylated product **27** rather than **26** (Scheme 4).



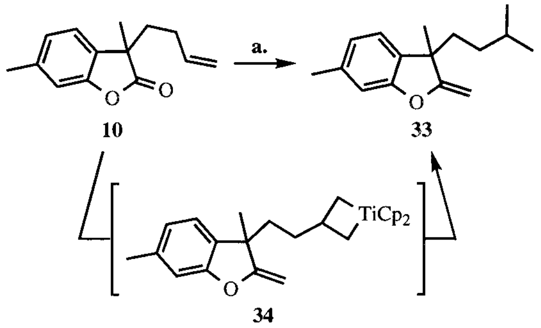
Scheme 4.



Scheme 5. *Reagents and conditions:* **a.** *t*-BuLi, TMEDA, THF, −60°C, 10 min.; MeI, RT, 2h, 96%; **b.** *t*-BuLi, THF, −78°C, 1h; CH$_2$=CHCH$_2$CH$_2$Br, RT, 71%; **c.** BCl$_3$, DCM, 0°C, 2h, 71%; **d.** *c*-Hex(*i*-Pr)NLi, HMPA, THF −78°C, 30 min; CH$_2$=CHCH$_2$CH$_2$I, RT, 2h, 92%.



Scheme 6. *Reagents and conditions:* **a.** *t*-BuLi, TMEDA, THF, −60°C, 10 min.; CH$_2$=CHCH$_2$CH$_2$I, −78°C, 1h, RT, 8h, 54%; **b.** BCl$_3$, DCM, 0°C, 2h, 71%; **c.** *c*-Hex(*i*-Pr)NLi, HMPA, THF, −78°C to 0°C, 15 min; MeI, −78°C to 0°C, 2h, 84%; **d.** 2.8 equiv. Cp$_2$TiCl$_2$, 7.8 equiv. AlMe$_3$, PhMe, −78°C to RT, 30 min., 54% [+28% **10**].

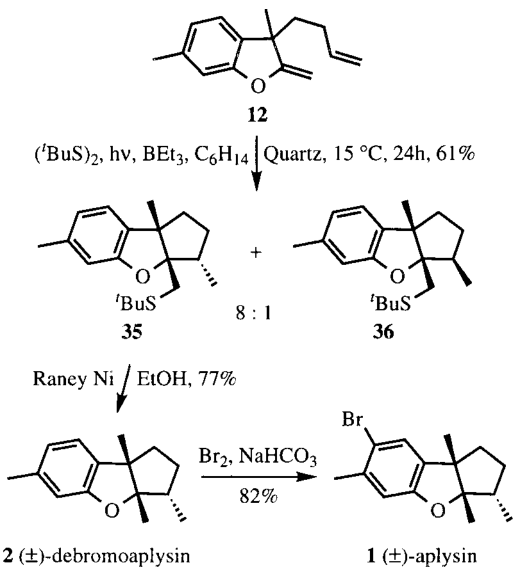


Scheme 7. *Reagents and conditions:* **a.** 6 equiv. Cp$_2$TiCl$_2$, 12 equiv. AlMe$_3$, PhMe, −78°C to RT, 30 min., 79%.

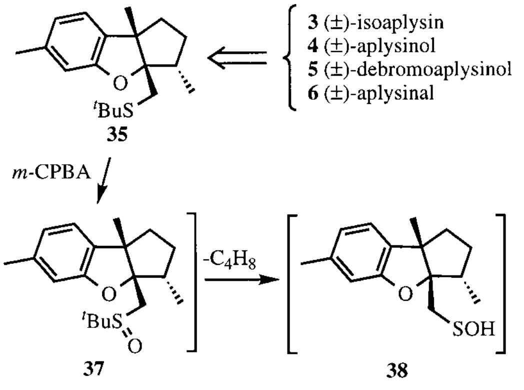
Pleasingly, deprotonation of **23** with *t*-BuLi was facile and quenching with methyl iodide gave **28** in 96% yield. However, attempts to effect the deprotonation of **28** with *t*-BuLi led to ketone **29** rather than the desired enolate. To circumvent this difficulty lactonisation of **28** to benzofuranone **30** was effected through the action of boron trichloride. Deprotonation and alkylation with 4-iodobut-2-ene then gave the *bis*-alkylated lactone **10** in 92% yield (Scheme 5).

The alternative sequence involving homoallylation of **23** to **31**, lactonisation to **32** and methylation to **10** was also effective. Synthesis of diene **12** was then accomplished by exposure of lactone **10** to Tebbe's reagent (Scheme 6).[18]

Though the conversion of lactone **10** to diene **12** proceeded in modest yield, much of the remaining mass balance was recovered starting material which was easily recycled. Interestingly, attempting to push the reaction to completion by using the Tebbe reagent in vast excess effected both methyleneation of the carbonyl and methylation of the terminal alkene giving **33** in 79% yield. We presume that the secondary reaction proceeds via a metallocyclobutane such as **34** which protonates on work up (Scheme 7).[19]



Scheme 8.



Scheme 9.

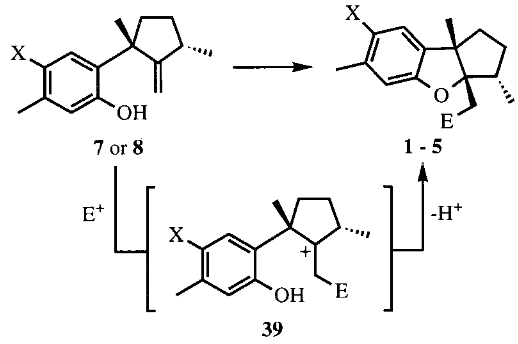
5. The total synthesis of (±)-aplysin and (±)-debromoaplysin

We were now in a position to test our key step.[20] Pleasingly, irradiation of a hexane solution of **12** containing di-*t*-butyl disulfide gave tricycles **35** and **36** in 61% yield as a partially separable 8:1 mixture of diastereoisomers. That the stereochemical course of the reaction had followed the predicted path (Scheme 1) was confirmed through hydrogenolysis of the major diastereoisomer with Raney nickel to (±)-debromoaplysin **2**. On treatment with bromine, **2** was rapidly transformed into (±)-aplysin **1** (Scheme 8). Both synthetic samples displayed spectral and physical characteristics identical to those reported by others: an X-ray analysis provided further confirmation of structure.[21]

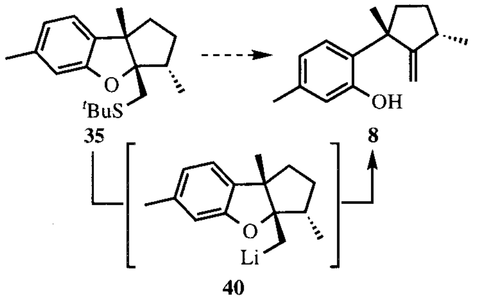
6. Approaches to the other aplysins

Unfortunately, all attempts to functionalise sulfide **35** in order to access the more demanding aplysins met with failure. For example, oxidation of the sulfide with *m*-CPBA proceeded smoothly but led to loss of the *t*-butyl group, presumably via the electrocyclic elimination **37**→**38**. Manipulation of the resulting product, the identity of which we were uncertain of, proved intractable (Scheme 9).

In attempting to overcome this difficulty the cyclisation of **12** was repeated using diphenyl disulfide. Surprisingly, under a range of cyclisation conditions the starting material **12** was returned in near quantitative yield. Attempts to transform the carbon to sulfur bond into a more useful functional group with mercury(II) salts likewise met with failure. Indeed, where new products could be identified the yields obtained were of no synthetic utility.



Scheme 10.



Scheme 11.

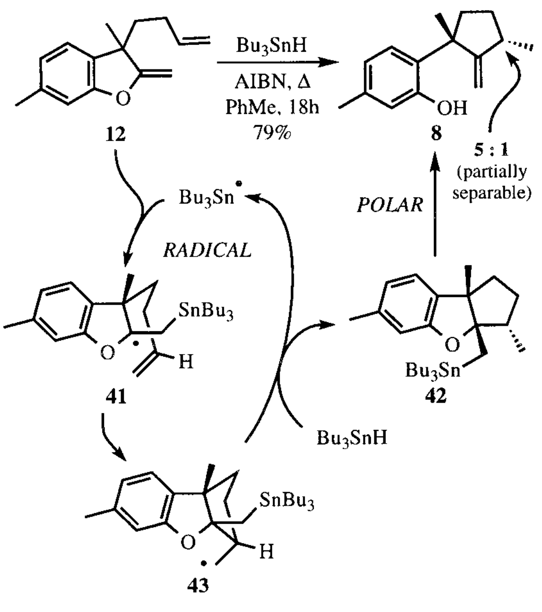
6.1. A biomimetic approach: from isolaurinterols to aplysins

At this juncture we decided to change our strategy.[22] Though the biosynthesis of the aplysins has yet to be rigorously established,[22] the co-occurrence of the isolaurinterols and aplysins in *Laurencia* and the sea hare *Aplysia* led us to conclude that the isolaurinterols might serve as precursors to the aplysins in nature.[6,23] Thus, addition of a suitable electrophile to isolaurinterol **7** or debromoisolaurinterol **8** would lead to cation **39**. Interception by the proximal phenol would then give rise to an aplysin (Scheme 10).

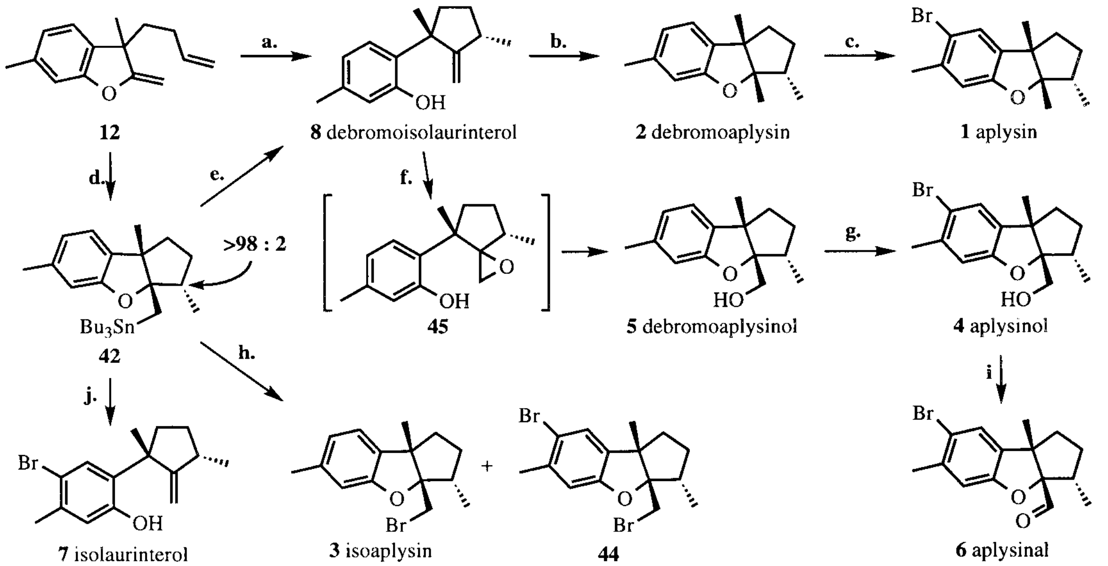
Our plan was to effect the metallation of sulfide **35** so as to induce scission of the benzofuran to debromoisolaurinterol **8** (Scheme 11). Alas, we had no success in that regard so our attention turned to the possibility of effecting the novel radical to polar crossover sequence outlined in Scheme 12.[24]

6.2. A new radical to polar crossover reaction

To our delight, a synthesis of (±)-debromoisolaurinterol **8** was readily accomplished through exposure of diene **12** to



Scheme 12.



Scheme 13. *Reagents and conditions:* **a.** Bu_3SnH, AIBN, PhMe, 80°C, 18h, 79%; **b.** acidic $CDCl_3$, RT, 16h, 100%; **c.** Br_2, $NaHCO_3$, DCM, 0°C, 30 min, 82%; **d.** Bu_3SnH, AIBN, C_6H_{14}, hν, 15°C, 20h, 69%; **e.** PhMe, reflux, 18h, 82% (+**42**, 12%); **f.** *m*-CPBA, DCM, 0°C, 24h, 52% (+**8**, 10%; +**45**, 12%); **g.** Br_2, $NaHCO_3$, $CHCl_3$, 0°C, 1h, 51% (+**5**, 24%); **h.** as **g.** giving **3**, 47% and **44**, 47%; **i.** Dess-Martin periodinane, DCM, RT, 2h, 96%; **j.** NBS, $CHCl_3$, reflux, 72h, 50% (+**42**, 18%).

tributylstannyl radicals formed under standard conditions using thermolysis to initiate the breakdown of AIBN. This provided **8** as a 5:1 mixture of diastereoisomers in 79% yield (Scheme 12).

Though reasonable, diastereoselectivity was improved dramatically by conducting reactions at 15°C using light to induce cleavage of the initiator. Under these conditions the tricyclic stannane **42** was provided as a 98:2 mixture of diastereoisomers in 69% yield. Refluxing a toluene solution of **42** for 24 h then gave (±)-debromoisolaurinterol **8** in 82% yield together with 12% recovered stannane **42** (Scheme 13).

Acid catalysed cyclisation of (±)-debromoisolaurinterol **8** to (±)-debromoaplysin **2** was extremely facile. Indeed, when a $CDCl_3$ solution of this compound was allowed to stand for 16 h prior to NMR analysis a quantitative conversion to (±)-debromoaplysin **2** was observed ($CDCl_3$ stored over anhydrous potassium carbonate failed to induce cyclisation). Bromination of **2** then provided aplysin **1** in 82% yield. Epoxidation of **8** with *m*-CPBA likewise induced spontaneous cyclisation to give (±)-debromoaplysinol **5** in 52% yield together with traces of recovered starting material (10%) and an oxirane intermediate **45** (12%). Bromination of **5** then gave (±)-aplysinol **4** which was smoothly oxidised to (±)-aplysinal **6** on treatment with the Dess–Martin periodinane reagent.[25]

Attempts to effect conversion of (±)-debromoisolaurinterol **8** into (±)-isoaplysin **3** and (±)-isolaurinterol **7** through direct halogenation were less rewarding, affording complex mixtures containing these materials, recovered **8** and dibromide **44**. However, exposing a cooled solution of stannane **42** to bromine gave (±)-isoaplysin **3** in an acceptable 47% yield while simply refluxing a chloroform solution of **42** with NBS gave (±)-isolaurinterol **7** in 50% yield (Scheme 13).[24]

7. Conclusion

We have completed total syntheses of all the known aplysin and isolaurinterol natural products and provided evidence that each is derived in nature from **8**. Additionally, we have developed a new method for effecting a vinyl group transfer from oxygen to carbon involving a radical to polar crossover reaction mediated by tributyltin hydride, viz. **12**→**8**. The remarkable diastereoselectivity attained in the free radical cyclisations **12**→**35** and **12**→**42** is also noteworthy.

8. Experimental

8.1. General remarks

Melting points were obtained using a Mel-Temp (II) apparatus and are uncorrected. UV spectra were recorded on a Pye Unicam SP800 spectrometer. IR spectra of oils and solutions were recorded on a Perkin–Elmer 1600 series Fourier transform infrared spectrometer using NaCl cells. For most solids, IR spectra were recorded directly using a Bio-Rad FTS 135 Fourier transform infrared spectrometer equipped with a Golden Gate Single Reflection Diamond ATR. NMR spectra were recorded on a Bruker AC300 (operating at 300 MHz for ^1H and at 75 MHz for ^{13}C) or a Bruker AM400 (operating at 400 MHz for ^1H and at 100 MHz for ^{13}C). Chemical shifts (δ_H) are reported as values in parts per million relative to tetramethylsilane (δ_H 0.00, δ_C 0.00) or residual $CHCl_3$ (δ_H 7.27, δ_C 77.2). Mass spectra were recorded on a variety of instruments either in house or at the EPSRC mass spectrometry centre, Swansea.

All reactions were magnetically stirred under an inert atmosphere. Photochemical reactions were performed in a Quartz reaction vessel with irradiation from a 125W medium pressure mercury lamp and were water cooled.

Reactions were monitored by thin layer chromatography using Macherey–Nagel Alugram Sil G/UV$_{254}$ precoated aluminium foil plates of layer thickness 0.25 mm. Compounds were visualised firstly by UV irradiation, then by exposure to iodine vapour and finally by heating plates exposed to solutions of phosphomolybdic acid in ethanol. Column chromatography was performed on Sorbsil 60 silica (230–400 mesh), slurry packed and run under low pressure.

Hexane was dried over calcium hydride and degassed using ultrasound irradiation prior to use. Ether refers to diethyl ether and petrol refers to the fraction of petroleum ether in the boiling point range 40–60°C. Details of our synthesis of **23** from **19** have been reported previously.[17a] Importantly, when the Willgerodt-Kindler oxidation of **21** was conducted on a 50 g scale the desired product **22** was furnished in 67% yield together with thiophene **24** (17%) and thioxoketone **25** (7%). The structure of **24** has been revised following X-ray crystallograpic analysis. 4-Iodobut-1-ene was prepared following the procedure as described by Fry et al. and Hoarau et al.[26]

8.1.1. 1-(Ethoxymethoxy)-3-methylbenzene (15).[27] Prepared following the procedure of Ronald et al.[14] To a stirred suspension of sodium hydride (26.6 g, 666 mmol) in dry ether (160 mL) and DMF (40 mL) under nitrogen and with cooling to 0°C was added *meta*-cresol **14** (24.0 g, 23.2 mL, 222 mmol) over 25 min. Once effervescence had ceased (~10 min), chloromethyl ethyl ether (21.0 g, 20.6 mL, 222 mmol) was added via syringe over 15 min. The reaction mixture was warmed to ambient temperature and stirred for 5 h, then quenched by slow addition of water (50 mL). The mixture was extracted into ether (3×50 mL), then the combined organic extracts were washed with water (50 mL) and brine (40 mL) then dried ($MgSO_4$), filtered and concentrated in vacuo to a yellow oil (43 g). Purification by chromatography (silica, petrol) gave **15** (34.8 g, 210 mmol, 94%) as a colourless oil; IR (neat, cm^{-1}) ν_{max} 3038m, 2977s, 2791w, 1586s, 1491s, 1458s, 1410m, 1393s, 1252s, 1150s, 1106s, 910m; UV (MeOH, nm) λ_{max} (ϵ_{max}) 278 (700), 271 (750), 266 inf (600); ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 7.21 (1H, dd, J=7.9, 7.7 Hz, Ar*H*), 6.91 (1H, s, Ar*H*), 6.89 (1H, d, J=7.7 Hz, Ar*H*), 6.85 (1H, d, J=7.9 Hz, Ar*H*), 5.25 (2H, s, OCH_2O), 3.75 (2H, q, J=7.1 Hz, OCH_2CH_3), 2.35 (3H, s, $ArCH_3$), 1.25 (3H, t, J=7.1 Hz, OCH_2CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 157.6 (*C*, Ar), 139.7 (*C*, Ar), 129.4 (*C*H, Ar), 122.7 (*C*H, Ar), 117.1 (*C*H, Ar), 113.3 (*C*H, Ar), 93.3 (OCH_2O), 64.3 (OCH_2CH_3), 21.7 ($ArCH_3$), 15.3 (OCH_2CH_3); LRMS (CI) *m/z* 166 (M^+, 90%), 136 ($[MH-C_2H_5]^+$, 40%), 108 (75%).

8.1.2. 1-Allyl-2-(ethoxymethoxy)-4-methylbenzene (16). Prepared following the procedure of Ziegler et al.[28] Thus, a solution of *tert*-butyllithium (44.2 mL of a 1.5 M solution in pentane, 66.3 mmol) was transferred to a flask and maintained at 0°C under an atmosphere of nitrogen. To this was added 1-(ethoxymethoxy)-3-methylbenzene **15** (11.0 g, 66 mmol) in pentane (100 mL) via cannula over 3 min with vigorous stirring. After 1 h stirring was halted and the anion allowed to settle over 6 h. The bright yellow supernatant was removed via cannula, the anion cooled to −78°C and resuspended in dry THF (100 mL). Copper(I) iodide triethylphosphite complex (24.8 g, 70 mmol) was added in a single portion and the mixture stirred for 30 min. Allyl bromide (7.99 g, 5.71 mL, 66 mmol) was added dropwise over 5 min. After stirring for 1 h the reaction mixture was warmed to ambient temperature and stirred for 22 h. The reaction mixture was diluted with dichloromethane (100 mL) and washed repeatedly with ca. $NH_{3\,(aq)}$ (10×200 mL) until no more blue discolouration of the ammonia solution was observed. The combined aqueous phases were washed with dichloromethane (100 mL) then the combined organic phases were washed with water (2×80 mL) and brine (60 mL), then dried ($MgSO_4$), filtered and concentrated in vacuo to a yellow oil (21.0 g). Purification by chromatography (silica, 10% ethyl acetate in petrol) gave **16** (10.7 g, 51.8 mmol, 78%) as a pale yellow oil; IR (neat, cm^{-1}) ν_{max} 3077m, 2977s, 2900s, 1638s, 1613s, 1582s, 1508s, 1442bs, 1392s, 1317s, 1248s, 1016bs, 912s, 716w; UV (MeOH, nm) λ_{max} (ϵ_{max}) 282 (850), 274 (900); ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 7.07 (1H, d, J=7.5 Hz, Ar*H*), 6.97 (1H, s, Ar*H*), 6.81 (1H, d, J=7.4 Hz, Ar*H*), 6.02 (1H, ddt, J=16.7, 10.2, 6.4 Hz, $=CH$), 5.28 (2H, s, OCH_2O), 5.07 (1H, dd, J=16.7, 1.5 Hz, $=CHH$), 5.04 (1H, br. d, J=10.2 Hz, $=CHH$), 3.78 (2H, q, J=7.1 Hz, OCH_2CH_3), 3.41 (2H, d, J=6.4 Hz, $ArCH_2$), 2.37 (3H, s, $ArCH_3$), 1.28 (3H, t, J=7.1 Hz, OCH_2CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 155.1 (*C*, Ar), 137.5 ($=CH$), 137.5 (*C*, Ar), 129.9 (*C*H, Ar), 126.3 (*C*, Ar), 122.5 (*C*H, Ar), 115.3 ($=CH_2$), 115.0 (*C*H, Ar), 93.3 (OCH_2O), 64.4 (CH_2CH_3), 34.3 ($ArCH_2$), 21.6 ($ArCH_3$), 15.3 (CH_2CH_3); LRMS (APCI) *m/z* 206 (M^+, 20%), 161 (100%), 147 (45%); HRMS (CI) *m/z* Found MH^+: 207.1385, $C_{13}H_{19}O_2$ requires 207.1385.

8.1.3. 2-[2-(Ethoxymethoxy)-4-methylphenyl]acetaldehyde (17). Prepared following the procedure of Knowles and Thompson.[29] Thus, a stirred solution of alkene **16** (5.00 g, 24.3 mmol) in chloroform (90 mL) was cooled to −78°C and ozone bubbled through the solution for 40 min (at which time a pale blue colour persisted). Oxygen was bubbled through the mixture for 15 min then triphenylphosphine (12.78 g, 48.6 mmol) was added. The mixture was warmed to ambient temperature and stirred for 5 h. The pale yellow solution was concentrated in vacuo to a cloudy yellow residue (20.5 g). Purification by chromatography (silica, 0–5% ethyl acetate in petrol) gave **17** (3.56 g, 17.1 mmol, 70%) as a colourless oil; IR (neat, cm^{-1}) ν_{max} 2977s, 2901s, 2818m, 1725s, 1614m, 1583m, 1508s, 1444m, 1391s, 1007bs, 811m; UV (MeOH, nm) λ_{max} (ϵ_{max}) 280 (850), 274 (850); ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 9.60 (1H, t, J=2.0 Hz, CHO), 7.05 (1H, d, J=7.5 Hz, Ar*H*), 7.00 (1H, s, Ar*H*), 6.82 (1H, d, J=7.5 Hz, Ar*H*), 5.25 (2H, s, OCH_2O), 3.71 (2H, q, J=7.1 Hz, OCH_2CH_3), 3.62 (2H, d, J=2.0 Hz, CH_2CHO), 2.36 (3H, s, $ArCH_3$), 1.24 (3H, t, J=7.1 Hz, CH_2CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 200.5 (CHO), 155.6 (*C*, Ar), 139.3 (*C*, Ar), 131.2 (*C*H, Ar), 122.7 (*C*H, Ar), 118.7 (*C*, Ar), 114.8 (*C*H, Ar), 93.1 (OCH_2O), 64.6 (CH_2CH_3), 45.5 (CH_2CHO), 21.7 ($ArCH_3$), 15.2 (CH_2CH_3); LRMS (APCI) *m/z* 208 (M^+, 10%), 163 (50%), 133 (80%); HRMS (CI) *m/z* Found $[M+NH_4]^+$: 226.1443, $C_{12}H_{20}NO_3$ requires 226.1443.

8.1.4. 2-[2-(Ethoxymethoxy)-4-methylphenyl]acetic acid (18). Prepared following the procedure of Jones et al.[30] Thus, to a stirred solution of aldehyde **17** (3.00 g, 14.4 mmol) in acetone (100 mL) was added Jones reagent (9.0 mL, 57.7 mmol) over 20 min at ambient temperature. Stirring was continued for a further 5 min after addition was complete, then to the turquoise mixture was added water (200 mL). The reaction mixture was extracted with ether (5×20 mL) then the organic phases were combined, washed with water (2×20 mL) then brine (20 mL), dried ($MgSO_4$), filtered and concentrated in vacuo to a yellow oil (3.58 g). Purification by chromatography (silica, 50% ether in petrol) gave **18** (2.32 g, 10.4 mmol, 72%) as a colourless oil; IR (neat, cm^{-1}) ν_{max} 3300–2900bs, 2978m, 1710s, 1616w, 1585w, 1510m, 1258m, 1154m, 1012s, 846w; UV (EtOH, nm) λ_{max} (ϵ_{max}) 276 (650); ^1H NMR (300 MHz, $CDCl_3$) δ_H 10.2 (1H, br. s, CO_2H), 7.09 (1H, d, J=7.5 Hz, ArH), 6.98 (1H, s, ArH), 6.81 (1H, d, J=7.5 Hz, ArH), 5.28 (2H, s, OCH_2O), 3.72 (2H, q, J=7.2 Hz, OCH_2CH_3), 3.63 (2H, s, CH_2COOH), 2.38 (3H, s, ArCH_3), 1.25 (3H, t, J=7.2 Hz, CH_3CH_2); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 178.5 (C=O), 155.4 (C, Ar), 139.2 (C, Ar), 130.9 (CH, Ar), 122.5 (CH, Ar), 120.0 (C, Ar), 114.9 (CH, Ar), 93.1 (OCH_2O), 64.5 (CH_2CH_3), 35.8 (ArCH_2), 21.7 (ArCH_3), 15.2 (CH_2CH_3); LRMS (CI) m/z 224 (M^+, 80%), 165 ($[M-C_2H_5OCH_2]^+$, 100%); HRMS (CI) m/z Found MH^+: 225.1125, $C_{12}H_{17}O_4$ requires 225.1127.

8.1.5. 6-Methyl-2,3-dihydrobenzo[*b*]furan-2-one (9).[31–33] To a stirred solution of 2-[2-(ethoxymethoxy)-4-methylphenyl]acetic acid **18** (0.150 g, 0.67 mmol) in toluene (80 mL) was added pyridinium *para*-toluenesulfonate (20 mg, 0.08 mmol) and the mixture heated at reflux under a soxhlet containing 3 Å molecular sieves for 20 h. The reaction was cooled to ambient temperature and the toluene removed in vacuo to give a brown oil (0.160 g). Purification by chromatography (silica, 10–20% ether in petrol) afforded **9** as a colourless oil that crystallised upon standing to a colourless solid. Recrystallisation from petroleum ether gave lactone **9** (50 mg, 0.34 mmol, 50%) as colourless needles, mp 68–70°C (petrol) [Lit. 73°C;[31] lit. 66–69°C (hexane)];[32] IR ($CHCl_3$, cm^{-1}) ν_{max} 2917w, 1796s, 1633m, 1504m, 1228m, 1203m, 1156m, 1064s, 950s, 840w; UV (MeOH, nm) λ_{max} (ϵ_{max}) 273 (600); ^1H NMR (300 MHz, $CDCl_3$) δ_H 7.16 (1H, d, J=7.5 Hz, ArH), 6.95 (1H, d, J=7.5 Hz, ArH), 6.95 (1H, s, ArH), 3.70 (2H, s, ArCH_2CO), 2.39 (3H, s, ArCH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 174.7 (C=O), 154.9 (C, Ar), 139.5 (C, Ar), 124.9 (CH, Ar), 124.4 (CH, Ar), 120.0 (C, Ar), 111.5 (CH, Ar), 33.0 (ArCH_2), 21.8 (ArCH_3); LRMS (APCI) m/z 149 (MH^+, 5%), 148 (M^+, 15%), 147 (60%), 109 (100%); Anal. Found: C, 72.86; H, 5.34; $C_9H_8O_2$ requires C, 72.96; H, 5.44.

Alternatively, to a stirred solution of thioester **23** (1.00 g, 4.76 mmol) in dichloromethane (25 mL) cooled to 0°C and under nitrogen was added boron trichloride (6.19 mL of a 1 M solution, 6.19 mmol) via syringe over 30 s. The reaction mixture was stirred for 1 h then warmed to ambient temperature and stirred for 2 h. Further boron trichloride (6.19 mL of a 1 M solution, 6.19 mmol) was added and stirring continued for 15 h. The reaction was then quenched by the addition of water (10 mL) and extracted with dichloromethane (3×20 mL). The combined organic phases were washed with NaOH (2 M, 20 mL) and brine (10 mL) then dried ($MgSO_4$), filtered and concentrated in vacuo to a yellow oil. Purification by chromatography (silica, 10–20% ether in petrol) gave **9** (325 mg, 2.20 mmol, 46%) as a colourless solid.

8.1.6. 3,3,6-Trimethyl-2,3-dihydrobenzo[*b*]furan-2-one (27).[34] Following the procedure of Padwa et al.[35] To a stirred solution of *N*-isopropylcyclohexylamine (0.105 g, 0.12 mL, 0.74 mmol) and HMPA (0.24 g, 0.24 mL, 1.35 mmol) in THF (10 mL) under nitrogen and with cooling to −78°C was added *tert*-butyllithium (0.43 mL of a 1.7 M solution in hexane, 0.74 mmol) over 1 min. The mixture was stirred for 15 min, warmed to 0°C over 30 min, then recooled to −78°C. A solution of lactone **9** (0.100 g, 0.68 mmol) in THF (5 mL) was added dropwise over 1 min. After 4 h the reaction mixture was warmed to ambient temperature over 30 min then partitioned between dichloromethane (10 mL) and water (10 mL). The aqueous layer was extracted with dichloromethane (3×5 mL) then the combined organic phases were washed with water (10 mL) and brine (10 mL), dried ($MgSO_4$), filtered and concentrated in vacuo to a yellow oil (0.57 g). Purification by chromatography (silica, 0–5% ether in petrol) afforded **27** (0.052 g, 0.30 mmol, 43%) as a colourless oil; IR (neat, cm^{-1}) ν_{max} 2974m, 2930m, 1808s, 1630m, 1596w, 1501m, 1143m, 1110m, 1033s, 950s, 819m; UV (MeOH, nm) λ_{max} (ϵ_{max}) 273 (1500); ^1H NMR (300 MHz, $CDCl_3$) δ_H 7.10 (1H, d, J=7.4 Hz, ArH), 6.97 (1H, d, J=7.4 Hz, ArH), 6.95 (1H, s, ArH), 2.38 (3H, s, ArCH_3), 1.49 (6H, s, ArC(CH_3)$_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 181.5 (C=O), 152.4 (C, Ar), 139.1 (C, Ar), 130.8 (C, Ar), 125.0 (CH, Ar), 122.5 (CH, Ar), 111.6 (CH, Ar), 42.9 (ArC(CH_3)$_2$), 25.5 (ArC(CH_3)$_2$), 21.8 (ArCH_3); LRMS (APCI) m/z 177 (MH^+, 5%), 176 (M^+, 100%), 148 ($[M-CO]^+$, 40%).

8.1.7. Methyl 2-(2-methoxy-4-methylphenyl)propanethioate (28). To a stirred solution of thioester **23** (13.72 g, 65.0 mmol) in THF (150 mL) and TMEDA (14.8 mL, 98.0 mmol) at −70°C and under nitrogen was added *tert*-butyllithium (43.0 mL of a 1.5 M solution in pentane, 65 mmol) over 30 min. After 5 min a solution of methyl iodide (13.9 g, 6.1 mL, 98.0 mmol) in THF (15 mL) was added over 15 min. After 2 h the reaction mixture was warmed to ambient temperature. After 16 h, water (75 mL) was added and the aqueous phase extracted with ether (3×50 mL). The organic extracts were combined and washed with saturated aqueous sodium thiosulfate (60 mL) and brine (60 mL) then dried ($MgSO_4$), filtered and concentrated in vacuo to a yellow oil (17.1 g). Purification by chromatography (silica, 5% ether in petrol) gave **28** (14.0 g, 62.5 mmol, 96%) as a colourless oil; IR (neat, cm^{-1}) ν_{max} 2974w, 1684s, 1612m, 1581w, 1505m, 1265m, 1040m, 940m, 814w; UV (MeOH, nm) λ_{max} (ϵ_{max}) 280 (2500); ^1H NMR (300 MHz, $CDCl_3$) δ_H 7.17 (1H, d, J=7.7 Hz, ArH), 6.80 (1H, d, J=7.7 Hz, ArH), 6.73 (1H, s, ArH), 4.28 (1H, q, J=7.0 Hz, ArCH), 3.84 (3H, s, OCH_3), 2.37 (3H, s, ArCH_3), 2.24 (3H, s, SCH_3), 1.50 (3H, d, J=7.0 Hz, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 202.8 (C=O), 157.1 (C, Ar), 139.9 (C, Ar), 128.3 (CH, Ar), 125.6 (C, Ar), 121.5 (CH, Ar), 111.9 (CH, Ar), 55.6 (OCH_3), 46.9 (ArCH), 21.8 (ArCH_3), 17.4 ($CHCH_3$), 11.9 (SCH_3); LRMS m/z (APCI) 150 ($[M-CH_3SCO+H]^+$, 10%), 149 ($[M-CH_3SCO]^+$, 100%); HRMS (CI) m/z Found $[M+NH_4]^+$: 242.1213, $C_{12}H_{20}NO_2S$ requires 242.1215.

8.1.8. 2,2-Dimethyl-4-[4-methyl-2-(methyloxy)phenyl]-3-pentanone (29). To a stirred solution of the thioester **28** (0.150 g, 0.67 mmol) in THF (5 mL) cooled to −78°C and under nitrogen was added *tert*-butyllithium (0.39 mL of a 1.7 M solution in pentane, 0.67 mmol) over 1 min. After 15 min, 4-bromo-1-butene (0.095 g, 0.070 mL, 0.70 mmol) was added over 1 min. After 2 h, the mixture was warmed to ambient temperature over 2 h. After 14 h, water (5 mL) was added and the mixture extracted with ether (3×5 mL). The combined organic extracts were washed with water (5 mL) and brine (5 mL) then dried ($MgSO_4$), filtered and concentrated in vacuo to a yellow oil (0.45 g). Purification by chromatography (silica, 0 to 10% ether in petrol) gave **29** (0.112 g, 0.48 mmol, 71%) as a colourless oil; IR (neat, cm^{-1}) ν_{max} 2869m, 1702s, 1612m, 1581m, 1506s, 1263s, 1191m, 1042s, 926w, 816m; UV (MeOH, nm) λ_{max} (ϵ_{max}) 279 (3500); ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 7.09 (1H, d, J=7.4 Hz, Ar*H*), 6.73 (1H, d, J=7.4 Hz, Ar*H*), 6.68 (1H, s, Ar*H*), 4.72 (1H, q, J=6.9 Hz, ArC*H*), 3.86 (3H, s, OCH_3), 2.34 (3H, s, ArCH_3), 1.28 (3H, d, J=6.9 Hz, CHCH_3), 1.05 (9H, s, C(CH_3)$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 217.4 (*C*═O), 155.8 (*C*, Ar), 137.8 (*C*, Ar), 127.8 (*C*H, Ar), 126.8 (*C*, Ar), 121.5 (*C*H, Ar), 111.6 (*C*H, Ar), 55.5 (OCH_3), 44.9 (*C*(CH_3)$_3$), 37.9 (Ar*C*H), 26.8 (C(CH_3)$_3$), 21.6 (ArCH_3), 19.6 (CHCH_3); LRMS (CI) *m*/*z* 235 (MH^+, 6%), 149 ($[M-C_4H_9CO]^+$, 100%); HRMS (CI) *m*/*z* Found $[M+NH_4]^+$: 252.1963, $C_{15}H_{26}NO_2$ requires 252.1964;

8.1.9. 3,6-Dimethyl-2,3-dihydrobenzo[*b*]furan-2-one (30). To a stirred solution of thioester **28** (14.5 g, 64.7 mmol) in dichloromethane (250 mL) at 0°C and under nitrogen was added boron trichloride (77.6 mL of a 1.0 M solution in heptane, 77.6 mmol) dropwise over 5 min. After 30 min at 0°C the reaction mixture was warmed to ambient temperature and water (100 mL) added. The phases were separated and the aqueous phase was extracted with ether (3×50 mL). The combined organic extracts were washed with 1 M HCl (2×30 mL), 1 M NaOH (50 mL), water (50 mL) and brine (50 mL) then dried ($MgSO_4$), filtered and concentrated in vacuo to a colourless oil (9.80 g). Purification by chromatography (silica, 0 to 5% ether in petrol) gave **30** (7.37 g, 45.5 mmol, 71%) as a colourless oil which crystallised on standing to a colourless solid. Recrystallisation from petroleum ether gave large cubic crystals, mp 35–37°C (petrol); IR (neat, cm^{-1}) ν_{max} 2978w, 2932w, 1804vs, 1630m, 1594w, 1499w, 1452w, 1425m, 1258m, 1095s, 1027s, 941s; UV (MeOH, nm) λ_{max} (ϵ_{max}) 274 (1800); ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 7.13 (1H, d, J=7.5 Hz, Ar*H*), 6.96 (1H, d, J=7.5 Hz, Ar*H*), 6.92 (1H, s, Ar*H*), 3.69 (1H, q, J=7.5 Hz, ArC*H*), 2.39 (3H, s, ArCH_3), 1.56 (3H, d, J=7.5 Hz, CHCH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 178.6 (*C*═O), 153.7 (*C*, Ar), 139.4 (*C*, Ar), 125.9 (*C*, Ar), 124.9 (*C*H, Ar), 123.6 (*C*H, Ar), 111.5 (*C*H, Ar), 38.4 (Ar*C*H), 21.8 (ArCH_3), 16.2 (CHCH_3); LRMS (CI) *m*/*z* 180 ($[M+NH_4]^+$, 100%), 162 (M^+, 24%), 134 (20%); Anal. Found: C, 74.33; H, 6.19; $C_{10}H_{10}O_2$ requires C, 74.06; H, 6.21.

8.1.10. Methyl 2-[4-methyl-2-(methyloxy)phenyl]-5-hexenethioate (31). To a stirred solution of the thioester **23** (2.10 g, 10.0 mmol) in THF (10 mL) cooled to −78°C and under nitrogen was added *tert*-butyllithium (7.70 mL of a 1.3 M solution in pentane, 10.0 mmol) via syringe over 90 s. The reaction mixture was stirred for 10 min then 4-iodo-1-butene (2.60 g, 14.2 mmol) in THF (5 mL) was added dropwise via syringe over 90 s. After 1 h the reaction mixture was warmed to ambient temperature and stirred for a further 8 h. Water (20 mL) and ether (20 mL) were added then the aqueous phase extracted with ether (3×20 mL). The combined organic extracts were washed with saturated sodium thiosulfate (20 mL) then brine (20 mL), dried ($MgSO_4$), filtered and concentrated in vacuo to a yellow oil (3.10 g). Purification by column chromatography (silica, 0–3% ether in petrol) gave **31** (1.42 g, 5.40 mmol, 54%) as a colourless oil; IR (neat, cm^{-1}) ν_{max} 3075w, 2929m, 2863w, 1688s, 1640w, 1612w, 1582w, 1506m, 1266m, 1040m, 795w; UV (MeOH, nm) λ_{max} (ϵ_{max}) 280 (2600); ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 7.16 (1H, d, J=7.7 Hz, Ar*H*), 6.78 (1H, br. d, J=7.7 Hz, Ar*H*), 6.72 (1H, s, Ar*H*), 5.80 (1H, ddt, J=16.8, 10.3, 6.4 Hz, ═C*H*), 5.02 (1H, dd, J=16.8, 1.7 Hz, ═CH*H*), 4.97 (1H, br. d, J=10.3 Hz, ═C*H*H), 4.25 (1H, t, J=7.4 Hz, ArC*H*), 3.83 (3H, s, OCH_3), 2.36 (3H, s, ArCH_3), 2.23 (3H, s, SCH_3), 2.27–2.14 (1H, m, C*H*HCH_2CH═), 2.02 (2H, app. q, J=7.0 Hz, CH_2CH═), 1.94–1.80 (1H, m, CH*H*CH_2CH═); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 201.8 (*C*═O), 157.3 (*C*, Ar), 138.8 (*C*, Ar), 138.1 (═*C*H), 128.6 (*C*H, Ar), 124.0 (*C*, Ar), 121.6 (*C*H, Ar), 115.2 (═CH_2), 112.0 (*C*H, Ar), 55.7 (OCH_3), 51.5 (Ar*C*H), 31.6 (CH_2), 31.4 (CH_2), 21.8 (ArCH_3), 11.9 (SCH_3); LRMS (APCI) *m*/*z* 265 (MH^+, 20%), 189 ($[M-CH_3SCO]^+$, 20%), 101 (100%); HRMS (CI) *m*/*z* Found M^+: 264.1182, $C_{15}H_{20}O_2S$ requires 264.1184.

8.1.11. 3-(3-Butenyl)-6-methyl-2,3-dihydrobenzo[*b*]furan-2-one (32). To a stirred solution of thioester **31** (0.34 g, 1.29 mmol) in dichloromethane (10 mL) cooled to 0°C and under nitrogen was added boron trichloride (1.55 mL of a 1 M solution, 1.55 mmol) via syringe over 30 s. The reaction mixture was stirred for 1 h then warmed to ambient temperature and stirred for 2 h. Water (5 mL) was added then the aqueous phase was extracted with ether (3×10 mL). The combined organic phases were washed with dilute HCl (2 M, 10 mL), NaOH (2 M, 10 mL), water (10 mL) and brine (10 mL) then dried ($MgSO_4$), filtered and concentrated in vacuo to a yellow oil (0.35 g). Purification by chromatography (silica, 0–5% ether in petrol) gave **32** (0.21 g, 1.04 mmol, 81%) as a colourless oil; IR (neat, cm^{-1}) ν_{max} 3078w, 2978w, 2925w, 1802s, 1630m, 1594w, 1500m, 1260m, 1065s, 947m; UV (MeOH, nm) λ_{max} (ϵ_{max}) 272 (2000); ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 7.15 (1H, d, J=7.5 Hz, Ar*H*), 6.96 (1H, d, J=7.5 Hz, Ar*H*), 6.92 (1H, s, Ar*H*), 5.79 (1H, ddt, J=17.1, 10.1, 6.6 Hz, ═C*H*), 5.04 (1H, dd, J=17.1, 1.5 Hz, ═CH*H*), 5.01 (1H, br. d, J=10.1 Hz, ═C*H*H), 3.70 (1H, app. t, J=6.5 Hz, ArC*H*), 2.38 (3H, s, ArCH_3), 2.26–2.14 (2H, m, CH_2CH_2), 2.14–1.98 (2H, m, CH_2CH_2); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 177.7 (*C*═O), 154.0 (*C*, Ar), 139.4 (*C*, Ar), 136.9 (*C*H, Ar) 136.9 (═*C*H), 124.9 (*C*H, Ar), 124.3 (*C*, Ar), 124.0 (*C*H, Ar), 116.3 (═CH_2), 42.6 (Ar*C*H), 30.5 (CH_2), 30.1 (CH_2), 21.8 (ArCH_3); LRMS (CI) *m*/*z* 243 ($[M+CH_3CN]^+$, 20%), 203 (MH^+, 50%), 202 (M^+, 40%), 101 (100%); HRMS (CI) *m*/*z* Found M^+: 202.0986, $C_{13}H_{14}O_2$ requires 202.0994.

8.1.12. 3-(3-Butenyl)-3,6-dimethyl-2,3-dihydrobenzo[*b*]-furan-2-one (10). Prepared following the procedure of Padwa et al.[35] Thus, to a stirred solution of *N*-isopropylcyclohexylamine (3.40 mL, 15.8 mmol) in THF (30 mL) and HMPA (4.9 mL, 28.3 mmol) at −78°C and under nitrogen was added *sec*-butyllithium (13.9 mL of a 1.14 M solution in cyclohexane, 15.8 mmol) over 30 s. After 10 min the mixture was warmed to 0°C (over 30 min) then recooled to −78°C. Lactone **30** (1.83 g, 11.3 mmol) in THF (10 mL) was added via syringe over 30 s. After 10 min a solution of the 1-iodo-3-butene (4.10 g, 22.5 mmol) in THF (10 mL) was added over 30 s. After 12 h the reaction mixture was warmed to ambient temperature and stirred for 12 h. Water (15 mL) and ether (15 mL) was added and the phases separated. The aqueous phase was extracted with ether (3×15 mL) then the combined organic extracts were washed with saturated aqueous sodium thiosulfate solution (20 mL) and brine (20 mL), then dried ($MgSO_4$), filtered and concentrated in vacuo to a yellow oil. Purification by chromatography (silica, petrol then 5% ether in petrol) gave **10** (2.25 g, 10.4 mmol, 92%) as a colourless oil; IR (neat, cm^{-1}) ν_{max} 3079w, 2929m, 1806vs, 1633m, 1596w, 1500m, 1453m, 1259m, 1029s, 948s, 815m; UV (MeOH, nm) λ_{max} (ϵ_{max}) 274 (1450); ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 7.07 (1H, d, *J*=7.6 Hz, Ar*H*), 6.98 (1H, br. d, *J*=7.6 Hz, Ar*H*), 6.94 (1H, s, Ar*H*), 5.63 (1H, ddt, *J*=17.3, 9.6, 6.6 Hz, C*H*=), 4.94–4.84 (2H, m, =C*H*$_2$), 2.39 (3H, s, ArC*H*$_3$), 2.11–1.72 (4H, m, C*H*$_2$C*H*$_2$), 1.48 (3H, s, C*H*$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 180.9 (*C*=O), 153.0 (*C*, Ar), 139.2 (*C*, Ar), 137.0 (=*C*H), 128.7 (*C*, Ar), 125.1 (*C*H, Ar), 122.8 (*C*H, Ar), 115.5 (=*C*H$_2$), 111.5 (*C*H, Ar), 47.2 (Ar*C*), 38.2 (*C*H$_2$), 29.3 (*C*H$_2$), 24.8 (C*C*H$_3$), 21.8 (Ar*C*H$_3$); LRMS (APCI) *m/z* 258 ($[MH+CH_3CN]^+$, 20%), 217 (MH$^+$, 100%), 216 (M$^+$, 40%), 111 (20%), 101 (75%); HRMS (EI) *m/z* Found: M$^+$, 216.1151, $C_{14}H_{16}O_2$ requires 216.1150.

Alternatively, to a stirred solution of *N*-isopropylcyclohexylamine (0.70 mL, 4.27 mmol) in THF (15 mL) and HMPA (1.29 mL, 7.42 mmol) at −78°C and under nitrogen was added *sec*-butyllithium (3.0 mL of a 1.4 M solution in cyclohexane, 4.26 mmol). After 10 min the mixture was warmed to 0°C then recooled to −78°C. Lactone **32** (0.75 g, 3.71 mmol) in THF (10 mL) was added via syringe over 4 min. After 15 min a solution of methyl iodide (0.79 g, 0.35 mL, 5.57 mmol) in THF (5 mL) was added over 2 min. After 30 min the reaction mixture was warmed to ambient temperature and stirred for 1 h. Water (10 mL) and ether (10 mL) was added and the phases separated. The aqueous phase was extracted with ether (3×15 mL) then the combined organic extracts were washed with saturated aqueous sodium thiosulfate solution (20 mL) and brine (20 mL), then dried ($MgSO_4$), filtered and concentrated in vacuo to a yellow oil (1.9 g). Purification by chromatography (silica, 0 to 2% ether in petrol) gave **10** (0.67 g, 3.10 mmol, 84%) as a colourless oil.

8.1.13. 3-(3-Butenyl)-3,6-dimethyl-2-methylene-2,3-dihydrobenzo[*b*]furan (12). Prepared following the procedure of Cannizzo and Grubbs.[36] Thus, trimethylaluminium (14.4 mL of a 2 M solution in heptane, 28.8 mmol) was added via syringe to titanocene dichloride (2.56 g, 10.28 mmol) and the mixture stirred at ambient temperature for 24 h. The mixture was cooled to −78°C then THF (10 mL) added followed by a solution of lactone **10** (0.80 g, 3.70 mmol) in THF (10 mL) dropwise over 5 min. After 30 min the mixture was warmed to ambient temperature and stirred for a further 20 h. THF (10 mL) was added and the mixture cooled to 0°C. Sodium hydroxide (1.15 g, 28.8 mmol) in water (3 mL) was added dropwise then the reaction mixture was filtered through a pad of celite. The celite was washed with ether (3×20 mL) and the combined filtrates dried ($MgSO_4$), filtered and concentrated in vacuo to a cloudy yellow oil (1.05 g). Purification by chromatography (silica, 0 to 1% ether in petrol) firstly gave diene **12** (0.43 g, 2.01 mmol, 54%) as a colourless oil; IR (neat, cm^{-1}) ν_{max} 3072w, 2864m, 1685s, 1640m, 1618s, 1595m, 1140s, 960s, 911w, 809m; UV (MeOH, nm) λ_{max} (ϵ_{max}) 283 (3050), 235 (10100); ^{1}H NMR (300 MHz, C_6D_6) δ_H 6.75–6.68 (2H, m, 2×Ar*H*), 6.64 (1H, d, *J*=7.7 Hz, Ar*H*), 5.64 (1H, ddt, *J*=16.5, 10.7, 6.1 Hz, =C*H*), 4.94–4.84 (2H, m, CH=C*H*$_2$), 4.82 (1H, d, *J*=2.4 Hz, =C*H*H), 4.04 (1H, d, *J*=2.4 Hz, =CH*H*), 2.05 (3H, s, ArC*H*$_3$), 1.78–1.50 (3H, m), 1.40–1.25 (1H, m), 1.23 (3H, s, C*H*$_3$); ^{13}C NMR (75 MHz, C_6D_6) δ_C 170.8 (=*C*), 157.4 (*C*, Ar), 138.4 (*C*, Ar), 138.3 (=*C*H), 130.7 (*C*, Ar), 122.9 (*C*H, Ar), 122.5 (*C*H, Ar), 114.3 (*C*H$_2$=CH), 110.2 (*C*H, Ar), 82.9 (C=*C*H$_2$), 47.5 (Ar*C*), 42.5 (*C*H$_2$CH=), 29.6 (C*C*H$_2$), 29.2 (C*C*H$_3$), 21.3 (Ar*C*H$_3$); LRMS (APCI) *m/z* 230 ($[M+H_2O]^+$, 10%), 215 (MH$^+$, 50%), 214 (M$^+$, 100%), 126 (10%), 111 (25%), 85 (15%); HRMS (EI) *m/z* Found M$^+$: 214.1347, $C_{15}H_{18}O$ requires 214.1358; then recovered **10** (0.22 g, 1.02 mmol, 28%).

8.1.14. 3,6-Dimethyl-3-(3-methylbutenyl)-2-methylene-2,3-dihydrobenzo[b]furan (33). Prepared following a modified procedure of Cannizzo and Grubbs.[36] Thus, trimethylaluminium (27.8 mL of a 2 M solution in heptane, 55.5 mmol) was added via syringe to titanocene dichloride (6.92 g, 27.8 mmol) and toluene (10 mL) under argon and at ambient temperature. After 24 h the mixture was cooled to −78°C and to it was added a solution of lactone **10** (1.20 g, 5.56 mmol) in THF (10 mL) over 5 min. After 30 min the mixture was warmed to ambient temperature. After 24 h the mixture was cooled to 0°C and sodium hydroxide (2.2 g, 55.5 mmol) in water (5 mL) was carefully added. The mixture was dried ($MgSO_4$) then filtered through a pad of celite. The cake was washed thoroughly with ether (3×50 mL) then the filtrate was concentrated in vacuo to a red residue. Purification by chromatography (silica, petrol) gave **33** (1.00 g, 4.39 mmol, 79%) as a colourless oil; IR (neat, cm^{-1}) ν_{max} 2956m, 2925m, 2868w, 1684m, 1618m, 1595m, 1498m, 1325w, 1141s, 958s, 806s; UV (MeOH, nm) λ_{max} (ϵ_{max}) 283 (2650); ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.08 (1H, d, *J*=7.5 Hz, Ar*H*), 6.91 (1H, d, *J*=7.5 Hz, Ar*H*), 6.84 (1H, s, Ar*H*), 4.79 (1H, d, *J*=2.6 Hz, =C*H*H), 4.26 (1H, d, *J*=2.6 Hz, =CH*H*), 2.47 (3H, s, ArC*H*$_3$), 1.86 (1H, app. td, *J*=12.8, 4.4 Hz, C*H*HCH$_2$), 1.71 (1H, app. td, *J*=12.8, 4.4 Hz, CH*H*CH$_2$), 1.55–1.50 (1H, m, C*H*(CH$_3$)$_2$), 1.52 (3H, s, C*H*$_3$), 1.21 (1H, tdd, *J*=12.8, 6.8, 4.4 Hz, C*H*HCH(CH$_3$)$_2$), 0.93 (3H, d, *J*=7.1 Hz, CH(C*H*$_3$)$_2$), 0.91 (3H, d, *J*=6.8 Hz, CH(C*H*$_3$)$_2$), 0.86 (1H, tdd, *J*=12.8, 6.8, 4.4 Hz, CH*H*CH(CH$_3$)$_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 171.0 (=*C*), 156.9 (*C*, Ar), 138.3 (*C*, Ar), 131.0 (*C*, Ar), 122.7 (*C*H, Ar), 122.5 (*C*H, Ar), 110.0 (*C*H, Ar), 82.6 (=*C*H$_2$), 47.6 (Ar*C*), 41.1 (*C*H$_2$), 33.8 (*C*H$_2$), 29.7 (*C*H$_3$C), 28.3 (*C*H(CH$_3$)$_2$), 22.7 (CH(*C*H$_3$)), 22.6 (CH(*C*H$_3$)), 21.7 (Ar*C*H$_3$); LRMS (APCI) *m/z* 231 (MH$^+$, 70%), 230 (M$^+$, 90%), 165 (50%), 111 (100%); HRMS

(EI) *m/z* Found MH$^+$: 231.1754, $C_{16}H_{23}O$ requires 231.1749.

8.1.15. rel-(3*S*,3a*S*,8b*S*)-(3,6,8b-Trimethyl-2,3,3a,8b-tetrahydro-1*H*-benzo[*b*]cyclopenta[*d*]furan-3-yl)methyl (*tert*-butyl) sulfide (35). A stirred solution of diene **12** (0.40 g, 1.87 mmol) and di-*tert*-butyl disulfide (1.67 g, 1.81 mL, 9.35 mmol) in degassed hexane (100 mL) was irradiated with UV light (Quartz filter). Triethylborane (1.0 mL of a 1 M solution in hexanes, 1 mmol) was added via syringe. After 16 h, saturated ammonium chloride (20 mL) was added and the phases separated. The aqueous phase was extracted with ether (3×15 mL) then the organic phases were combined and washed with brine (20 mL), dried ($MgSO_4$), filtered and concentrated in vacuo to an orange oil (2.15 g). Purification by chromatography (silica, 0 to 2% ether in petrol) gave **35** (0.34 g, 1.12 mmol, 61%) as a yellow oil which was determined by NMR to be a 8:1 mixture of diastereomers. Further purification by chromatography (silica, 5 to 10% dichloromethane in petrol) gave firstly a mixture of *cis* and *trans* isomers **35** and **36** then pure **35** as a colourless oil; IR (neat, cm^{-1}) ν_{max} 2955s, 2862m, 1620w, 1593s, 1499s, 1320w, 1280s, 1160m, 948s, 852w; UV (MeOH, nm) λ_{max} (ϵ_{max}) 284 (4000); ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 6.91 (1H, d, *J*=7.4 Hz, Ar*H*), 6.67 (1H, d, *J*=7.4 Hz, Ar*H*), 6.58 (1H, s, Ar*H*), 2.99 (1H, d, *J*=12.2 Hz, SC*H*H), 2.87 (1H, d, *J*=12.2 Hz, SCH*H*), 2.30 (3H, s, $\mathrm{ArC}H_3$), 2.17 (1H, m, C*H*CH_3), 1.87 (1H, app. dd, *J*=11.2, 7.1 Hz), 1.72–1.58 (3H, m), 1.51 (3H, s, $\mathrm{C}H_3$), 1.34 (9H, app. s, $\mathrm{C(C}H_3)_3$), 1.14 (3H, d, *J*=6.8 Hz, $\mathrm{C}H_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 159.0 (*C*, Ar), 137.9 (*C*, Ar), 133.4 (*C*, Ar), 122.2 (*C*H, Ar), 121.0 (*C*H, Ar), 109.2 (*C*H, Ar), 99.2 (O*C*), 55.4 (Ar*C*), 43.8 ($C\mathrm{HCH_3}$), 42.4 ($C\mathrm{H_2}$), 42.2 ($C\mathrm{CH_3}$), 32.8 ($C\mathrm{H_2}$), 31.5 ($C\mathrm{H_2}$), 30.7 ($\mathrm{C(}C\mathrm{H_3)_3}$), 23.6 ($\mathrm{C}C\mathrm{H_3}$), 21.5 ($\mathrm{Ar}C\mathrm{H_3}$), 13.8 ($\mathrm{CH}C\mathrm{H_3}$); LRMS (CI) *m/z* 305 (MH$^+$, 60%), 304 (M$^+$, 40%), 249 ($[M-C_4H_7]^+$, 70%), 83 (100%); HRMS (EI) *m/z* Found M$^+$, 304.1858, $C_{19}H_{28}OS$ requires 304.1861. A pure sample of the *cis* isomer could not obtained. Spectral peaks in a ^{1}H NMR spectra of an enriched sample that were attributed to **36** follow: δ_H (300 MHz, $CDCl_3$) 6.91 (1H, d, *J*=7.4 Hz, Ar*H*), 6.68 (1H, d, *J*=7.4 Hz, Ar*H*), 6.57 (1H, s, Ar*H*), 3.34 (1H, d, *J*=13.2 Hz, S*H*H), 3.19 (1H, d, *J*=13.2 Hz, SH*H*), 2.29 (3H, s, $\mathrm{ArC}H_3$), 2.13 (1H, app. dq, *J*=13.2, 6.6 Hz, C*H*CH_3), 1.87 (1H, app. dd, *J*=11.4, 6.1 Hz), 1.71–1.58 (3H, m), 1.49 (3H, s, $\mathrm{C}H_3$), 1.35 (9H, app. s, $\mathrm{C(C}H_3)_3$), 1.16 (3H, d, *J*=6.8 Hz, $\mathrm{CHC}H_3$).

8.1.16. rel-(3*S*,3a*S*,8b*S*)-[(3,6,8b-Trimethyl-2,3,3a,8b-tetrahydro-1*H*-benzo[*b*]cyclopenta[*d*]furan-3-yl)methyl]-(tributyl)stannane (42). A mixture of diene **12** (0.50 g, 2.34 mmol), tri-*n*-butyltin hydride (1.36 g, 1.24 mL, 4.67 mmol) and AIBN (0.19 g, 1.17 mmol) in degassed hexane (110 mL) was irradiated with UV (Quartz filter) at 15°C and under nitrogen. After 20 h the solvents were removed in vacuo and the residue purified by chromatography (silica, petrol) to give **42** (0.815 g, 1.61 mmol, 69%) as a colourless oil; IR (neat, cm^{-1}) ν_{max} 2953s, 2924s, 2866m, 1619w, 1592m, 1499s, 1456s, 1269s, 1125s, 1068s, 945s, 801s; UV (MeOH, nm) λ_{max} (ϵ_{max}) 286 (3800); ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 6.88 (1H, d, *J*=7.5 Hz, Ar*H*), 6.62 (1H, d, *J*=7.5 Hz, Ar*H*), 6.45 (1H, s, Ar*H*), 2.28 (3H, s, $\mathrm{ArC}H_3$), 1.90–1.75 (2H, m), 1.70–1.55 (2H, m), 1.50–1.18 (15H, m), 1.32 (3H, s, $\mathrm{C}H_3$), 1.11 (3H, d, *J*=6.6 Hz, $\mathrm{CHC}H_3$), 0.88 (9H, app. t, *J*=7.2 Hz, $3\times\mathrm{C}H_3$), 0.73 (6H, m, $3\times\mathrm{SnC}H_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 159.1 (*C*, Ar), 137.8 (*C*, Ar), 133.7 (*C*, Ar), 122.6 (*C*H, Ar), 120.6 (*C*H, Ar), 109.4 (*C*H, Ar), 102.4 (O*C*), 54.9 (Ar*C*), 49.0 ($C\mathrm{HCH_3}$), 43.0 ($C\mathrm{H_2}$), 31.4 ($C\mathrm{H_2}$), 29.3 ($3\times\mathrm{SnCH_2}C\mathrm{H_2}$, [residual $J=_{117/119Sn}-{}^{13}C$ 20 Hz]), 27.6 ($3\times\mathrm{SnCH_2CH_2}C\mathrm{H_2}$, [residual $J=_{117/119Sn}-{}^{13}C$ 58 Hz]), 24.1 ($C\mathrm{CH_3}$), 21.6 ($\mathrm{Ar}C\mathrm{H_3}$), 17.4 ($\mathrm{Sn}C\mathrm{H_2C}$), 13.9 ($\mathrm{CH}C\mathrm{H_3}$), 13.8 ($3\times\mathrm{SnCH_2CH_2CH_2}C\mathrm{H_3}$), 10.6 ($3\times\mathrm{Sn}C\mathrm{H_2}$, [residual $J=_{119Sn}-{}^{13}C$ 325 Hz, residual $J=_{117Sn}-{}^{13}C$ 311 Hz]); LRMS (APCI) *m/z* 449 ($[M-C_4H_9]^+$, 100%), 447 (90%), 445 (40%), 341 ($[M-(C_4H_9)_3]^+$, 5%), 276 (40%), 274 (35%), 272 (15%), 220 ($[M-Sn(C_4H_9)_3]^+$, 35%), 218 (35%), 216 (25%); HRMS (EI) *m/z* Found MH$^+$: 507.2642, $C_{27}H_{47}OSn$ requires 507.2649.

8.1.17. 2-[rel-(1*R*,3*S*)-1,3-Dimethyl-2-methylenecyclopentyl]-5-methylphenol ((±)-debromoisolaurinterol) (8). Stannane **42** (0.100 g, 0.198 mmol) in toluene (5 mL) was heated at reflux under nitrogen for 18 h. The mixture was concentrated in vacuo then purified by chromatography (silica, petroleum ether then 5% ether in petroleum ether) to give firstly recovered starting material **42** (12 mg, 0.002 mmol, 12%) as a colourless oil then (±)-debromoisolaurinterol **8** (35 mg, 0.163 mmol, 82%) as a colourless oil; IR (neat, cm^{-1}) ν_{max} 3453bs, 3069w, 3026w, 2978m, 2958s, 2870m, 1641w, 1622w, 1570w, 1503m, 1372m, 1291m, 1137m, 805s; UV (MeOH, nm) λ_{max} (ϵ_{max}) 270 (10100); ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 7.22 (1H, d, *J*=8.4 Hz, Ar*H*), 6.74 (1H, dd, *J*=8.4, 1.2 Hz, Ar*H*), 6.68 (1H, d, *J*=1.2 Hz, Ar*H*), 5.59 (1H, s, ArO*H*), 5.11 (1H, d, *J*=2.0 Hz, =C*H*H), 4.97 (1H, d, *J*=2.0 Hz, =CH*H*), 2.86 (1H, dtt, *J*=9.1, 7.0, 2.2 Hz, C*H*CH_3), 2.30 (3H, s, $\mathrm{ArC}H_3$), 2.25 (1H, ddd, *J*=12.9, 8.0, 6.6 Hz, C*H*HCH_2CH), 2.06 (1H, dddd, *J*=12.9, 8.8, 7.2, 6.6 Hz, C*H*HCH), 1.60 (1H, dt, *J*=12.9, 7.1 Hz, CH*H*CH_2CH), 1.48 (3H, s, $\mathrm{C}H_3$), 1.40–1.30 (1H, m), 1.22 (3H, d, *J*=7.0 Hz, $\mathrm{CHC}H_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 165.8 (=*C*), 153.9 (*C*, Ar), 138.0 (*C*, Ar), 130.2 (*C*, Ar), 127.9 (*C*H, Ar), 121.6 (*C*H, Ar), 119.0 (*C*H, Ar), 106.8 ($=C\mathrm{H_2}$), 50.1 (Ar*C*), 39.5 ($C\mathrm{H_2}$), 38.0 ($C\mathrm{HCH_3}$), 31.5 ($C\mathrm{H_2}$), 28.1 ($C\mathrm{H_3C}$), 21.3 ($\mathrm{Ar}C\mathrm{H_3}$), 20.9 ($C\mathrm{H_3CH}$); LRMS (APCI) *m/z* 217 (MH$^+$, 15%), 216 (M$^+$, 30%), 163 (15%), 146 (40%), 105 (100%); HRMS (EI) *m/z* Found M$^+$: 216.1504, $C_{15}H_{20}O$ requires 216.1514. The spectral characteristics were consistent with literature values.[6,23]

Alternatively, a solution of diene **12** (100 mg, 0.47 mmol), tributyltin hydride (270 mg, 0.25 mL, 0.93 mmol) and AIBN (38 mg, 0.23 mmol) in toluene (10 mL) was heated at reflux under nitrogen for 18 h. The mixture was then cooled to ambient temperature and concentrated in vacuo to a colourless oil. Purification by chromatography (silica, 5% ether in petroleum ether) gave (±)-debromoisolaurinterol **8** (17 mg, 0.079 mmol, 28%) as a colourless oil; and then a mixture of (±)-debromoisolaurinterol **8** and (±)-epidebromoisolaurinterol (2-[rel-(1*R*,3*S*)-1,3-dimethyl-2-methylenecyclopentyl]-5-methylphenol) (80 mg, 0.37 mmol, 79%) as a 5:1 mixture of diastereoisomers. Signals in the NMR spectrum attributed to (±)-epidebromoisolaurinterol follow: ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 7.29 (1H, obsc. d, Ar*H*), 5.65 (1H, s, ArO*H*), 5.12 (1H, d, *J*=2.0 Hz, =C*H*H), 5.02 (1H, d, *J*=2.0 Hz, =CH*H*), 1.46

(3H, s, C*H*$_3$), 1.23 (3H, d, *J*=7.0 Hz, CHC*H*$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 165.5 (=*C*), 131.0 (*C*, Ar), 127.4 (*C*H, Ar), 118.8 (*C*H, Ar), 106.2 (=*C*H$_2$), 49.7 (Ar*C*), 39.7 (*C*H$_2$), 38.7 (*C*HCH$_3$), 32.3 (*C*H$_2$), 27.4 (*C*H$_3$), 20.0 (CH*C*H$_3$) with other signals being obscured by **8**.

8.1.18. rel-(3*S*,3a*S*,8b*S*)-3,3a,6,8b-Tetramethyl-2,3,3a,8b-tetrahydro-1*H*-benzo[*b*]cyclopenta[*d*]furan ((±)-debromoaplysin) (2).[8,10] Prepared following the procedure of Pettit and van Temelen.[37] Thus, to a suspension of Raney nickel (ca. 1 g, 17 mmol) in ethanol (4 mL) was added a solution of sulfide **35** (42 mg, 0.14 mmol) in ethanol (2 mL) and the mixture heated at reflux. After 40 h the mixture was cooled and filtered through a pad of Celite. The Celite was extracted with chloroform (80 mL) using a Soxhlet apparatus. The combined organic phases were concentrated in vacuo to a colourless oil (29 mg). Purification by chromatography (silica, 5 to 10% dichloromethane in petrol) gave (±)-debromoaplysin **2** (23 mg, 0.11 mmol, 77%) as a colourless oil; IR (neat, cm^{-1}) ν_{max} 2954s, 2866m, 1619w, 1593m, 1499s, 1280s, 1123m, 1009m, 948m, 801m; UV (MeOH, nm) λ_{max} (ϵ_{max}) 285 (2400); ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 6.93 (1H, d, *J*=7.4 Hz, Ar*H*), 6.66 (1H, d, *J*=7.4 Hz, Ar*H*), 6.54 (1H, s, Ar*H*), 2.29 (3H, s, ArC*H*$_3$), 1.90–1.70 (2H, m), 1.66–1.53 (2H, m), 1.33 (3H, s), 1.29 (3H, s), 1.25–1.15 (1H, m), 1.12 (3H, d, *J*=6.6 Hz, C*H*$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 159.0 (*C*, Ar), 138.0 (*C*, Ar), 133.8 (*C*, Ar), 122.7 (*C*H, Ar), 120.9 (*C*H, Ar), 109.5 (*C*H, Ar), 99.0 (O*C*), 55.2 (*C*CH$_3$), 46.3 (*C*H), 42.8 (*C*H$_2$), 31.4 (*C*H$_2$), 23.7 (OC*C*H$_3$), 21.6 (Ar*C*H$_3$), 20.2 (C*C*H$_3$), 13.3 (CH*C*H$_3$); LRMS (APCI) *m/z* 217 (MH$^+$, 10%), 216 (M$^+$, 20%), 100 (100%); HRMS (EI) *m/z* Found M$^+$: 216.1507, $C_{15}H_{20}O$ requires 216.1514. These spectral and physical characteristics were consistent with literature values.[8,10]

Alternatively, a solution of (±)-debromoisolaurinterol **8** (10.0 mg, 0.046 mmol) in commercial deuteriochloroform (1 mL) was stood at ambient temperature for 16 h. Concentration in vacuo gave (±)-debromoaplysin **2** (10 mg, 0.046 mmol, 100%) as a colourless oil.

8.1.19. rel-(3*S*,3a*S*,8b*S*)-7-Bromo-3,3a,6,8b-tetramethyl-2,3,3a,8b-tetrahydro-1*H*-benzo[*b*]cyclopenta[*d*]furan ((±)-aplysin) (1).[8,10] Prepared following the procedure of Nemoto et al.[38] Thus, to a stirred solution of (±)-debromoaplysin **2** (14 mg, 0.065 mmol) and sodium hydrogen carbonate (8.7 mg, 0.140 mmol) in chloroform (5 mL) at 0°C was added a solution of bromine (0.97 mL of a 0.1 M solution in chloroform, 0.097 mmol). After stirring at ambient temperature for 10 min, concentration in vacuo gave a pale brown residue (40 mg). Purification by chromatography (silica, 5 to 10% dichloromethane in petrol) gave (±)-aplysin **1** (16 mg, 0.053 mmol, 82%) as a white crystalline solid which was recrystallised from methanol to give a white powder, mp 96–98°C (methanol) [Lit. 98–100°C (methanol)];[8] IR ($CHCl_3$, cm^{-1}) ν_{max} 2956s, 2849m, 1479m, 1460s, 1391m, 1308w, 1192w, 1006m, 904w, 846w; UV (MeOH, nm) λ_{max} (ϵ_{max}) 296 (2950), 234 (5500); ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 7.15 (1H, s, Ar*H*), 6.60 (1H, s, Ar*H*), 2.31 (3H, s, ArC*H*$_3$), 1.90–1.50 (4H, m), 1.32 (3H, s), 1.29 (3H, s), 1.20–1.05 (1H, obscured m), 1.11 (3H, d, *J*=6.8 Hz, C*H*$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 158.3 (*C*, Ar), 137.1 (*C*, Ar), 136.4 (*C*, Ar), 126.7 (*C*H, Ar), 114.1 (*C*, Ar), 111.0 (*C*H, Ar), 100.0 (O*C*), 54.5 (Ar*C*), 46.2 (*C*H), 42.7 (*C*H$_2$), 31.3 (*C*H$_2$), 23.5 (*C*H$_3$), 23.3 (*C*H$_3$), 20.1 (C*C*H$_3$), 13.2 (CH*C*H$_3$); LRMS (CI) *m/z* 296 ([M(^{81}Br)]$^+$, 70%), 294 ([M(^{79}Br)]$^+$, 100%), 100 (50%); HRMS (EI) *m/z* Found M$^+$: 294.0616, $C_{15}H_{19}BrO$ requires 294.0619. These spectral and physical characteristics were consistent with literature values.[1]

8.1.20. rel-(3*S*,3a*S*,8b*S*)-3,6,8b-Trimethyl-2,3,3a,8b-tetrahydro-1*H*-benzo[*b*]cyclopenta[*d*]furan-3-yl]methanol ((±)-debromoaplysinol) (5).[8] To a stirred solution of debromoisolaurinterol **8** (110 mg, 0.51 mmol) in dichloromethane (4 mL) at 0°C and under argon was added *m*-CPBA (105 mg, 0.61 mmol). After 24 h, the solution was diluted with dichloromethane (20 mL), washed with sodium thiosulfate (20 mL) and sodium hydrogen carbonate (20 mL), then dried ($MgSO_4$), filtered and concentrated in vacuo to a yellow gum (90 mg). Purification by chromatography (silica, petrol then 5% ether in petrol) gave firstly recovered **8** (11 mg, 0.05 mmol, 10%) as a colourless oil, secondly 2-[rel-(4*S*,7*S*)-4,7-dimethyl-1-oxaspiro[2.4]hept-4-yl]-5-methylphenol **45** (14 mg, 0.06 mmol, 12%) as a colourless oil; IR (neat, cm^{-1}) ν_{max} 3417s, 3268s, 2964s, 1730m, 1621m, 1503s, 1290s, 1121w, 933m, 803s; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 7.71 (1H, s, ArO*H*), 7.08 (1H, d, *J*=7.8 Hz, Ar*H*), 6.72 (1H, br. s, Ar*H*), 6.67 (1H, br. d, *J*=7.8 Hz, Ar*H*), 2.93 (1H, d, *J*=4.3 Hz, OC*H*H), 2.73 (1H, d, *J*=4.3 Hz, OCH*H*), 2.61 (1H, m), 2.34 (1H, m, C*H*CH$_3$), 2.23 (3H, s, ArC*H*$_3$), 2.14–2.04 (1H, m), 1.68–1.58 (1H, m), 1.31 (3H, s, C*H*$_3$), 0.93–0.71 (1H, m), 0.74 (3H, d, *J*=7.0 Hz, CHC*H*$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 158.8 (*C*, Ar), 138.4 (*C*, Ar), 127.1 (*C*, Ar), 127.0 (*C*H, Ar), 121.4 (*C*H, Ar), 120.5 (*C*H, Ar), 73.6 (*C*O), 51.5 (*C*H$_2$O), 46.1 (Ar*C*), 36.3 (*C*H$_2$), 35.2 (*C*HCH$_3$), 30.0 (*C*H$_2$), 24.8 (*C*H$_3$), 20.7 (Ar*C*H$_3$), 15.8 (*C*H$_3$CH); LRMS (CI) *m/z* 232 (M$^+$, 90%), 201 (58%), 159 (100%); HRMS (CI) *m/z* Found [M+NH$_4$]$^+$: 250.1806, $C_{15}H_{24}NO_2$ requires 250.1807; and finally (±)-debromoaplysinol **5** (57 mg, 0.26 mmol, 52%) as a yellow solid which, after recrystallisation from hexane was furnished as a white powder; mp 103–105°C (hexane) [Lit. 79–80°C (petrol)];[8] IR (solid, cm^{-1}) ν_{max} 3427m, 2947s, 2867m, 1620w, 1593s, 1500s, 1455s, 1268s, 1044m, 999s, 854m; UV (MeOH, nm) λ_{max} (ϵ_{max}) 284 (2600); ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 6.93 (1H, d, *J*=7.5 Hz, Ar*H*), 6.70 (1H, br. d, *J*=7.5 Hz, Ar*H*), 6.60 (1H, br. s, Ar*H*), 3.87 (1H, dd, *J*=12.1, 4.3 Hz, C*H*HOH), 3.74 (1H, dd, *J*=12.1, 8.6 Hz, CH*H*OH), 2.31 (3H, s, ArC*H*$_3$), 1.94–1.80 (2H, m), 1.76 (1H, dd, *J*=8.6, 4.3 Hz, CH$_2$O*H*), 1.71–1.60 (2H, m), 1.50 (3H, s, C*H*$_3$), 1.23–1.11 (1H, m), 1.11 (3H, d, *J*=6.8 Hz, C*H*$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 159.3 (*C*, Ar), 138.2 (*C*, Ar), 133.7 (*C*, Ar), 122.6 (*C*H, Ar), 121.6 (*C*H, Ar), 109.4 (*C*H, Ar), 99.6 (O*C*), 64.4 (*C*H$_2$OH), 54.6 (Ar*C*), 42.8 (*C*HCH$_3$), 42.7 (*C*H$_2$C), 32.0 (*C*H$_2$CH), 23.2 (*C*H$_3$C), 21.6 (Ar*C*H$_3$), 14.1 (*C*H$_3$CH); LRMS (APCI) *m/z* 233 (MH$^+$, 100%), 232 (M$^+$, 30%), 215 ([MH−H$_2$O]$^+$, 30%), 111 (20%), 105 (15%); HRMS (CI) *m/z* Found MH$^+$: 233.1536, $C_{15}H_{21}O_2$ requires 233.1542; Anal. Found: C, 77.58; H, 8.63; $C_{15}H_{20}O_2$ requires C, 77.55; H, 8.68. The spectral characteristics were consistent with literature values.[4,8]

8.1.21. rel-(3*S*,3a*S*,8b*S*)-7-Bromo-3,6,8b-trimethyl-2,3,3a,8b-tetrahydro-1*H*-benzo[*b*]cyclopenta[*d*]furan-3-

yl]methanol ((±)-aplysinol) (4).[8] Following a modified procedure of Nemoto et al.[38] Thus, to a stirred solution of (±)-debromoaplysinol **5** (25 mg, 0.107 mmol) and sodium hydrogen carbonate (16 mg, 0.216 mmol) in chloroform (3 mL) at 0°C was added bromine (0.86 mL of a 0.125 M solution in chloroform, 0.107 mmol) dropwise over 2 min. After 1 h the mixture was concentrated in vacuo and purified by chromatography (silica, 10% ether in petrol) to give firstly recovered **5** (6 mg, 0.26 mmol, 24%) then (±)-aplysinol **4** (19 mg, 0.06 mmol, 57%) as a white solid. Recrystallisation from carbon tetrachloride gave white needles, mp 154–156°C (CCl_4) [Lit. 151–153°C (CCl_4)];[8] IR (solid, cm^{-1}) ν_{max} 3186m, 2957m, 2933m, 2871m, 1579m, 1375s, 1234s, 1156s, 1100s, 841s, 790m; UV (MeOH, nm) λ_{max} (ϵ_{max}) 292 (1680); ^1H NMR (400 MHz, $CDCl_3$) δ_H 7.16 (1H, s, Ar*H*), 6.66 (1H, s, Ar*H*), 3.85 (1H, dd, *J*=12.2, 2.5 Hz, C*H*HOH), 3.71 (1H, dd, *J*=12.2, 8.1 Hz, CH*H*OH), 2.33 (3H, s, ArCH_3), 1.92–1.78 (2H, m), 1.75–1.58 (3H, m), 1.47 (3H, s, CH_3), 1.20–1.10 (1H, m), 1.09 (3H, d, *J*=7.0 Hz, CHCH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 174.2 (*C*, Ar), 137.1 (*C*, Ar), 136.3 (*C*, Ar), 126.4 (*C*H, Ar), 114.8 (*C*, Ar), 110.8 (*C*H, Ar), 100.3 (*C*O), 64.0 (*C*H_2O), 54.7 (*C*), 42.5 (*C*H_2), 42.4 (*C*HCH_3), 31.7 (*C*H_2), 23.2 (Ar*C*H_3), 22.9 (*C*H_3), 13.9 (CH*C*H_3); LRMS (APCI) *m/z* 313 ($M(^{81}Br)H^+$, 40%), 312 ($M(^{81}Br)^+$, 100%), 310 ($M(^{79}Br)H^+$, 38%), 310 ($M(^{79}Br)^+$, 98%), 295 ($[M(^{81}Br)H-H_2O]^+$, 55%), 293 ($[M(^{79}Br)H-H_2O]^+$, 50%), 233 ($[MH-Br]^+$, 20%); HRMS (EI) *m/z* Found M^+: 310.0569, $C_{15}H_{19}BrO_2$ requires 310.0568. These spectral and physical characteristics were consistent with literature values.[3,8]

8.1.22. (rel-3*S*,3a*S*,8b*S*)-7-Bromo-3,6,8b-trimethyl-2,3,3a,8b-tetrahydro-1*H*-benzo[*b*]cyclopenta[*d*]furan-3a-carbaldehyde ((±)-aplysinal) (6). To a stirred solution of (±)-aplysinol **4** (4.0 mg, 0.013 mmol) in dichloromethane (1 mL) under argon and at ambient temperature was added Dess–Martin periodinane (10.9 mg, 0.026 mmol). After 2 h, the mixture was purified by chromatography (silica, 20% ether in petroleum ether) to give (±)-aplysinal **6** (3.8 mg, 0.0123 mmol, 96%) as a colourless solid; mp 87–89°C (petrol); IR (solid, cm^{-1}) ν_{max} 2958m, 2930m, 1731vs, 1580w, 1483s, 1377s, 1264m, 1150s, 1099m, 941w; ^1H NMR (400 MHz, $CDCl_3$) δ_H 9.69 (1H, s, C*H*O), 7.09 (1H, s, Ar*H*), 6.72 (1H, s, Ar*H*), 2.55–2.45 (1H, m, C*H*CH_3), 2.29 (3H, s, ArCH_3), 1.85 (1H, dd, *J*=11.5, 5.6 Hz, CC*H*H), 1.73–1.63 (2H, m), 1.24 (3H, s, CH_3), 1.24–1.15 (1H, m), 0.95 (3H, d, *J*=6.8 Hz, CHCH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 204.4 (*C*HO), 160.2 (*C*, Ar), 139.5 (*C*, Ar), 135.8 (*C*, Ar), 127.9 (*C*H, Ar), 117.1 (*C*, Ar), 113.1 (*C*H, Ar), 105.5 (O*C*), 60.3 (*C*CH_3), 44.5 (*C*H_2), 44.0 (*C*HCH_3), 33.2 (*C*H_2), 25.6 (Ar*C*H_3), 24.8 (*C*H_3C), 14.6 (CH*C*H_3); LRMS (CI) *m/z* 310 (MH^+, 60%), 281 ($[M-CHO]^+$, 70%), 239 (100%); HRMS (CI) *m/z* Found $[M+NH_4]^+$: 326.0747, $C_{15}H_{21}BrNO_2$ requires 326.0756. These spectral characteristics were consistent with literature values.[5]

8.1.23. rel-(3*S*,3a*S*,8b*S*)-7-Bromo-3a-(bromomethyl)-3,6,8b-trimethyl-2,3,3a,8b-tetrahydro-1*H*-benzo[*b*]cyclopenta[*d*]furan (44) and rel-(3*S*,3a*S*,8b*S*)-3a-(bromomethyl)-3,6,8b-trimethyl-2,3,3a,8b-tetrahydro-1*H*-benzo[*b*]cyclopenta[*d*]furan ((±)-isoaplysin) (3).[8] Prepared following a modified procedure of Nemoto et al.[23] To a stirred solution of the stannane (0.15 g, 0.30 mmol) and sodium hydrogen carbonate (43 mg, 0.59 mmol) in chloroform (10 mL) at 0°C and under nitrogen was added a solution of bromine (3 mL of a 0.1 M solution in chloroform, 0.30 mmol) over 2 min. After 5 min the mixture was concentrated in vacuo to a brown residue. Purification by chromatography (silica, petrol then 2% ether in petrol) gave firstly dibromide **44** (53 mg, 0.14 mmol, 47%) as a white solid; mp 126–128°C (methanol); IR (solid, cm^{-1}) ν_{max} 2954m, 2931m, 2868w, 1581m, 1484s, 1394s, 1378s, 1267s, 1230m, 1140m, 1105w, 911s; UV (MeOH, nm) λ_{max} (ϵ_{max}) 292 (2470); ^1H NMR (400 MHz, $CDCl_3$) δ_H 7.15 (1H, s, Ar*H*), 6.68 (1H, s, Ar*H*), 3.70 (1H, d, *J*=11.3 Hz, C*H*HBr), 3.56 (1H, d, *J*=11.3 Hz, CH*H*Br), 2.34 (3H, s, ArCH_3), 2.16 (1H, app. dq, *J*=12.7, 6.7 Hz, C*H*CH_3), 1.94–1.85 (1H, m), 1.77–1.58 (2H, m), 1.52 (3H, s, CH_3), 1.33–1.11 (1H, obscured m), 1.13 (3H, d, *J*=6.7 Hz, CHCH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 158.2 (*C*, Ar), 137.5 (*C*, Ar), 135.9 (*C*, Ar), 126.3 (*C*H, Ar), 115.0 (*C*H, Ar), 111.0 (*C*H, Ar), 98.1 (O*C*), 55.8 (Ar*C*), 43.9 (*C*HCH_3), 42.9 (*C*H_2C), 34.5 (*C*H_2Br), 31.6 (CH_2*C*H_2CH), 23.4 (*C*H_3), 22.9 (Ar*C*H_3), 13.8 (CH*C*H_3); LRMS (CI) *m/z* 391 376 ($(M(^{81}Br^{81}Br))^+$, 50%), 374 ($M^+(^{81}Br^{79}Br)$, 100%), 372 ($M^+(^{79}Br^{79}Br)$, 45%), 296 ($[M(^{81}Br)-Br]^+$, 25%), 294 ($[M(^{79}Br)-Br]^+$, 23%); HRMS (EI) *m/z* Found M^+: 371.9726, $C_{15}H_{18}Br_2O$ requires 371.9724; then (±)-isoaplysin **3** (42 mg, 0.14 mmol, 47%) as a colourless oil; IR (neat, cm^{-1}) ν_{max} 2953s, 2931s, 2867m, 1622m, 1593s, 1499s, 1456s, 1424s, 1378m, 1271s, 1137m, 947s; UV (MeOH, nm) λ_{max} (ϵ_{max}) 284 (3750); ^1H NMR (300 MHz, $CDCl_3$) δ_H 6.92 (1H, d, *J*=7.4 Hz, Ar*H*), 6.70 (1H, br. d, *J*=7.6 Hz with fine splitting, Ar*H*), 6.61 (1H, br. d, *J*=0.5 Hz, Ar*H*), 3.70 (1H, d, *J*=11.2 Hz, C*H*HBr), 3.59 (1H, d, *J*=11.2 Hz, CH*H*Br), 2.31 (3H, s, ArCH_3), 2.20 (1H, app. dq, *J*=13.4, 6.7 Hz, C*H*CH_3), 1.90 (1H, app. dd, *J*=12.0, 6.7 Hz, CCH_3C*H*H), 1.75–1.65 (2H, m), 1.53 (3H, s, CH_3), 1.30–1.12 (1H, obscured m), 1.13 (3H, d, *J*=6.7 Hz, CHCH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 158.9 (*C*, Ar), 138.4 (*C*, Ar), 133.2 (*C*, Ar), 122.3 (*C*H, Ar), 121.6 (*C*H, Ar), 109.5 (*C*H, Ar), 97.4 (O*C*), 55.7 (Ar*C*), 43.9 (*C*HCH_3), 42.8 (*C*H_2), 34.8 (*C*H_2Br), 31.7 (*C*H_2), 23.1 (*C*H_3), 21.7 (Ar*C*H_3), 14.0 (CH*C*H_3); LRMS (APCI) *m/z* 297 ($M(^{81}Br)H^+$, 90%), 296 ($M(^{81}Br)^+$, 80%), 295 ($M(^{79}Br)H^+$, 100%), 294 ($M(^{79}Br)^+$, 65%), 165 (30%), 111 (35%), 100 (65%); HRMS (EI) *m/z* Found M^+: 294.0620, $C_{15}H_{19}BrO$ requires 294.0619. These spectral characteristics were consistent with literature values.[7,8]

8.1.24. 2-[rel-(1*R*,3*S*)-1,3-Dimethyl-2-methylenecyclopentyl]-5-methylphenol ((±)-isolaurinterol) (7).[23] A solution of stannane **42** (0.150 g, 0.30 mmol) and *N*-bromosuccinimide (51 mg, 0.29 mmol) in chloroform (5 mL) was stirred at 0°C under argon for 18 h. The mixture was then heated at reflux. After 72 h the mixture was concentrated and purified by chromatography (silica, petrol then 2% ether in petrol) to give firstly recovered starting material **42** (28 mg, 0.05 mmol, 18%) as a colourless oil then (±)-isolaurinterol **7** (43 mg, 0.146 mmol, 50%) as a colourless oil; IR (CH_2Cl_2, cm^{-1}) ν_{max} 3442m, 2958s, 2870m, 1644w, 1612w, 1390s, 1242m, 1165s, 903m, 669m; UV (MeOH, nm) λ_{max} (ϵ_{max}) 285 (2005); ^1H NMR (400 MHz, $CDCl_3$) δ_H 7.45 (1H, s, Ar*H*), 6.74 (1H, s, Ar*H*), 5.55 (1H, s, ArO*H*), 5.10 (1H, d, *J*=2.0 Hz, =C*H*H), 4.94 (1H, d, *J*=2.0 Hz,

=CH*H*), 2.85 (1H, m, C*H*CH$_3$), 2.31 (3H, s, ArC*H*$_3$), 2.20 (1H, ddd, *J*=13.0, 7.8, 6.8 Hz, C*H*HCH$_2$), 2.06 (1H, app. ddt, *J*=12.8, 8.8, 7.3 Hz, C*H*HCHCH$_3$), 1.60 (1H, dt, *J*=12.8, 7.1 Hz, CH*H*CH$_2$CH), 1.45 (3H, s, C*H*$_3$), 1.46–1.35 (1H, m), 1.21 (3H, d, *J*=7.1 Hz, CHC*H*$_3$); ^{13}C NMR (75 MHz, CDCl$_3$) δ_C 165.4 (=*C*), 153.4 (*C*, Ar), 137.6 (*C*, Ar), 133.2 (*C*, Ar), 131.7 (*C*H, Ar), 120.9 (*C*H, Ar), 116.0 (*C*, Ar), 107.4 (=*C*H$_2$), 50.3 (Ar*C*), 39.6 (*C*H$_2$), 38.1 (*C*HCH$_3$), 31.7 (*C*H$_2$), 28.2 (*C*H$_3$C), 22.7 (Ar*C*H$_3$), 21.5 (CH*C*H$_3$); LRMS (APCI) *m/z* 297 (M(^{81}Br)H$^+$, 35%), 296 (M(^{81}Br)$^+$, 100%), 295 (M(^{79}Br)H$^+$, 40%), 294 (M(^{79}Br)$^+$, 90%); HRMS (CI) *m/z* Found M$^+$: 294.0615, C$_{15}$H$_{19}$BrO requires 294.0619. These spectral characteristics were consistent with literature values.[6,23]

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