Synthesis of (±)-likonide B (smenochromene D) using a regioselective Claisen rearrangement, separation of the enantiomers and stereochemical assignment†

Marjorie Bruder,[a] Stephen J. Smith,[b] Alexander J. Blake[a] and Christopher J. Moody*[a]

Received 21st January 2009, Accepted 25th February 2009
First published as an Advance Article on the web 27th March 2009
DOI: 10.1039/b901358j

A synthesis of the unusual ansa-bridged farnesyl hydroquinone derivative likonide B in racemic form is described. The natural product, also known as smenochromene D, was obtained from geranylacetone by a route in which the key steps are a regioselective microwave-mediated Claisen rearrangement of an aryl propargyl ether to deliver the chromene ring, and macrocyclization *via* an intramolecular Mitsunobu reaction. Subsequent HPLC on a chiral stationary phase gave the pure (+)- and (−)-enantiomers, that were studied by CD spectroscopy, thereby shedding some light on the true stereochemical nature of the two natural products (−)-smenochromene D and (+)-likonide B.

Introduction

Sesquiterpenoid quinone and hydroquinone derivatives occur widely in nature.[1–3] In 1991 Faulkner and Clardy and colleagues reported the isolation, and structure determination, of a series of unusual ansa-bridged farnesyl hydroquinones, the smenochromenes A–D (**1–4**), from a Seychelles sponge *Smenospongia* sp.[4] Some years later, Kashman and co-workers reported the isolation of two compounds, named likonide A and B (**5** and **6**), from a marine sponge *Hyatella* sp. found off the coast of Likoni, Kenya (Fig. 1).[5]

The structures and absolute configurations of the likonides were determined by detailed spectroscopic studies,[5] but their close similarity to the smenochromenes was not commented upon. Specifically, the structure and spectroscopic data for one of these compounds, smenochromene D **4**, appeared to be extremely similar to those of likonide B **6** in all respects except optical rotation: smenochromene D, $[\alpha]_D$ −68.5 (*c* 0.35, CH_2Cl_2);[4] likonide B, $[\alpha]_D$ +27 (*c* 0.08, MeOH).[5] This apparent confusion over the identity, or otherwise, of the two natural products has recently been resolved by the synthesis of (±)-smenochromene D by Trauner and co-workers,[6,7] which clearly established that smenochromene D and likonide B are identical in terms of relative stereochemistry. Hence the natural products appear to be enantiomers, or possibly, given the large discrepancy in optical rotation, to have an enantiomeric excess in the opposite sense.

Intriguingly, it was also noted that likonides A and B are formally related by a [3,3]-sigmatropic process, since Claisen rearrangement of likonide B should give likonide A (Scheme 1). However, Trauner and co-workers have recently shown that heating of likonide B **6** (= smenochromene D **4**) does not result in such a Claisen rearrangement, but rather in an alternative rearrangement to give the ring skeleton of smenochomene B.[7] It has also been proposed that another pericyclic process might be responsible for the facile racemization of smenochromene A **1** (Scheme 1),[6] since the compound was isolated as a racemate.[4]

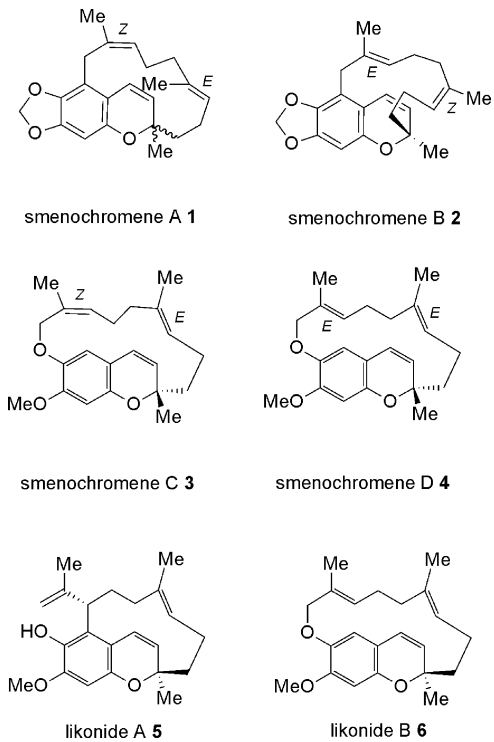
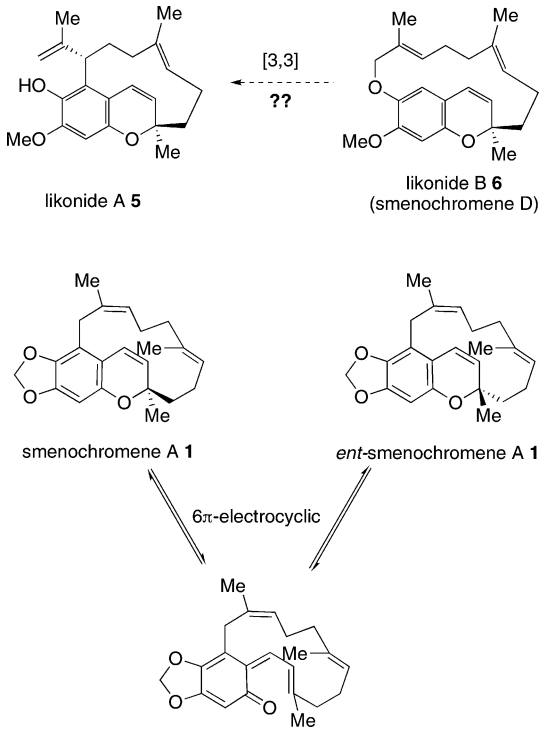


Fig. 1 Reported structures of the smenochromenes and the likonides (ref. 5 and 6).

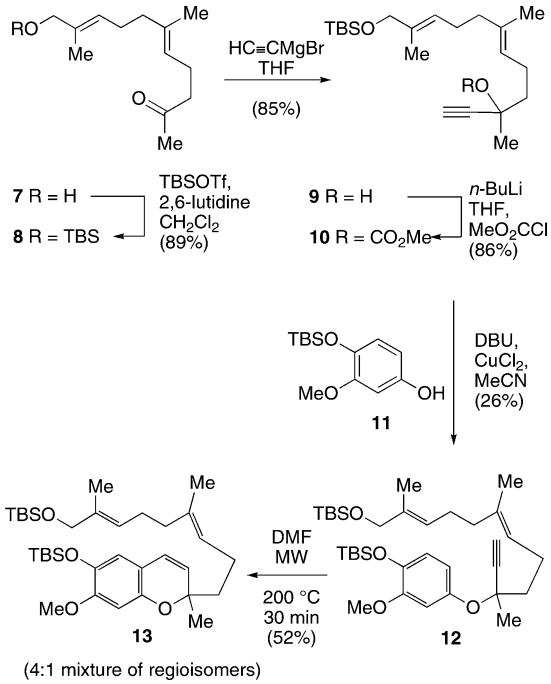
In view of the continuing interest in these and other sesquiterpene quinones and hydroquinones,[8–10] we report the details of a new synthesis of (±)-likonide B.[11] In continuation of our interest in the wide and varied use of the Claisen rearrangement in the synthesis of natural products,[12–22] a regioselectve Claisen rearrangement to form the chromene is a key step in our approach. We also describe the separation and properties of the individual

[a]*School of Chemistry, University of Nottingham, University Park, Nottingham, U.K. NG7 2RD. E-mail: c.j.moody@nottingham.ac.uk; Fax: +44 115 951 3564*
[b]*Process Research and Development, AstraZeneca R & D Charnwood, Bakewell Road, Loughborough, U.K. LE11 5RH*

† Electronic supplementary information (ESI) available: Copies of ^{1}H and ^{13}C NMR spectra. CCDC reference number 717575. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/b901358j



Scheme 1 Possible involvement of pericyclic processes in the interconversion of the likonides, and the racemization of smenochromene A.



Scheme 2

enantiomers, thereby shedding some light on the true stereochemical nature of the two natural products (–)-smenochromene D and (+)-likonide B.

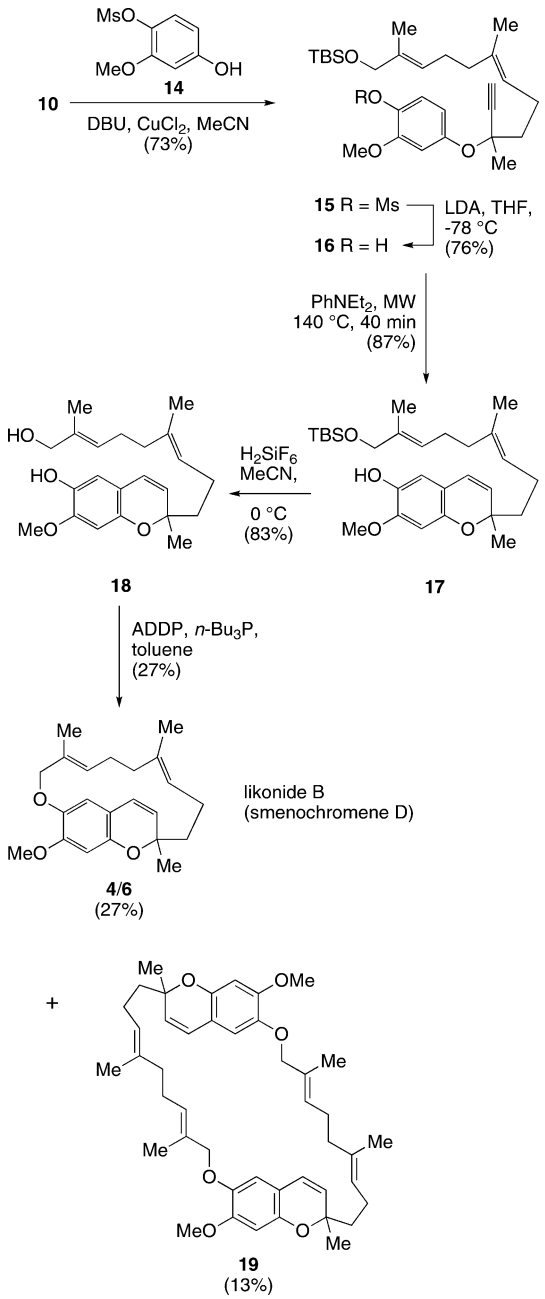
Results and discussion

Our synthesis started with the known allylic alcohol **7**, readily available from the allylic oxidation of commercial geranylacetone with selenium dioxide and *tert*-butyl hydroperoxide.[23,24] Protection as the *tert*-butyldimethylsilyl (TBS) ether **8** was followed by addition of ethynylmagnesium bromide to give tertiary alcohol **9**, and acylation with methyl chloroformate to give the tertiary propargylic alcohol carbonate **10** in preparation for coupling to a phenol. The first phenol investigated was 3-methoxy-4-*tert*-butyldimethylsiloxyphenol **11**.[25] However, attempts to couple phenol **11** with the propargylic carbonate **10** (or the corresponding trifluoroacetate) in the presence of DBU and copper(II) chloride[26,27] gave only poor yields (12–26%) of the desired propargylic ether **12**. Nevertheless, sufficient material was obtained to establish that the planned Claisen rearrangement exhibited the required regioselectivity.[27–29] Thus microwave heating[30] of **12** in DMF at 200 °C for 30 min gave the chromene **13** in a 4:1 mixture with the regioisomeric product (Scheme 2).

In order to improve the yield in the key copper catalyzed coupling step, a number of model studies were performed which established that the reaction proceeded better if an electron-withdrawing protecting group was installed on the *para*-hydroxyl group. Thus the coupling reaction of propargylic carbonate **10** was repeated using the mesyl protected phenol **14** resulting in an acceptable yield (73%) of the propargylic ether **15**. However, the Claisen rearrangement of the mesylate derivative **15** exhibited poor regioselectivity (ratio 2:1), and therefore the mesylate was cleaved using LDA in THF at low temperature.[31] Gratifyingly, the resulting phenolic propargylic ether **16** underwent a highly selective Claisen rearrangement upon microwave heating in *N*,*N*-diethylaniline at 140 °C for 40 min to give the desired chromene **17** in 87% yield with no evidence for the formation of the alternative regioisomer. Thereafter the silyl protecting group was removed from the side chain using hexafluorosilicic acid to give the precursor **18** for the macrocyclization reaction. The cyclization was effected by means of an intramolecular Mitsunobu reaction using tri-*n*-butylphosphine, 1,1′-azodicarbonyl dipiperidine (ADDP) in toluene and gave likonide B **6** (smenochromene D) in 27% yield, the poor yield probably reflecting the strained nature of the ansa-ring. A dimer, assigned as structure **19** (mixture of diastereomers), was also isolated (Scheme 3).

The NMR spectroscopic data for synthetic **6** were identical to those described for the natural products smenochromene D and likonide B,[4,5] and the aforementioned synthetic racemic material prepared by Olson and Trauner.[6] Final confirmation came from a single crystal X-ray structure determination (Fig. 2).

With a supply of synthetic racemic likonide B in hand we were able to separate the two enantiomers by preparative HPLC on a chiral stationary phase, and this allowed us to study the individual enantiomers of synthetic likonide B (= smenochromene D). The two enantiomers were studied by CD spectroscopy, and exhibited the expected spectra for pairs of enantiomers (Fig. 3). The (+)-enantiomer exhibited a positive Cotton effect at *ca.* 275 nm, and therefore could be assigned as the 3*R*-enantiomer.[5,33] Interestingly their specific rotations were $[\alpha]_D^{25}$ +180 (*c* 0.31, CH_2Cl_2) (peak 1) and $[\alpha]_D^{25}$ –176 (*c* 0.35, CH_2Cl_2) (peak 2). These values are somewhat different for those reported for the natural products: smenochromene D, $[\alpha]_D$ –68.5 (*c* 0.35, CH_2Cl_2);[4] likonide B, $[\alpha]_D$ +27 (*c* 0.08, MeOH),[5] and confirm earlier suspicions that the natural products have an enantiomeric excess in the opposite sense, and were not isolated as pure single enantiomers. This lack of



Scheme 3

optical purity in the natural products may be due to their facile racemization, possibly by the electrocyclic ring opening process proposed by Trauner for smenochromene A (Scheme 1).[6] However, heating our enantiopure material in toluene at 110 °C for 2 h left it unchanged with no evidence for racemization being observed by HPLC analysis. The use of higher temperatures were precluded by the alternative thermal rearrangement pathway reported by Trauner and co-workers.[7] Similarly, exposure of enantiopure likonide B to UV-light over a prolonged period did not result in racemization either.

In summary, we have developed a concise synthesis of (±)-likonide B, also known as smenochromene D, resolved the compound by HPLC, and, based on the optical properties of the individual enantiomers, suggest that neither of the natural

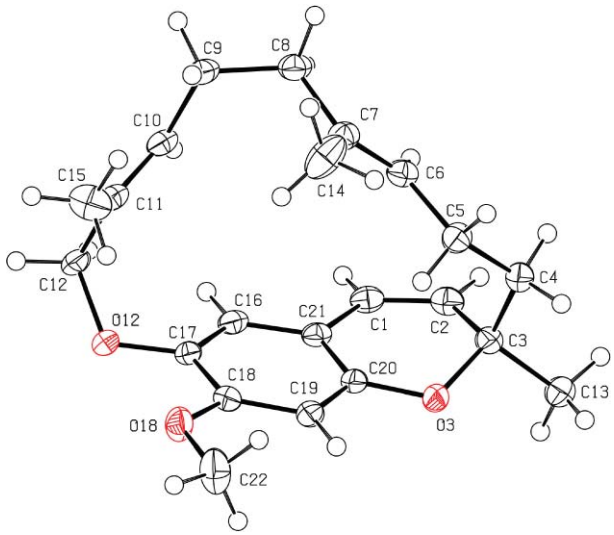


Fig. 2 X-ray crystal structure of (±)-likonide B.[32]

products were obtained optically pure. Although it has been suggested that similar compounds could undergo racemization by way of an electrocyclic ring opening–ring closure process, we can find no evidence that the single enantiomers of likonide B racemize easily. Hence, although the involvement of pericyclic processes in the racemization of these ansa-bridged farnesyl hydroquinones is an attractive proposition, there remains no experimental support for this.

Experimental section

General

Commercially available reagents were used throughout without purification unless otherwise stated. Light petroleum refers to the fraction with bp 40–60 °C. Ether refers to diethyl ether. Reactions were routinely carried out under a nitrogen or argon atmosphere. Analytical thin layer chromatography was carried out on aluminium backed plates coated with silica gel, and visualized under UV light at 254 and/or 360 nm. Chromatography was carried out on silica gel unless otherwise stated. Fully characterized compounds are chromatographically homogeneous. Infrared spectra were recorded in the range 4000–600 cm^{-1}. NMR spectra were recorded at 400 and 500 MHz (^1H frequencies, corresponding ^{13}C frequencies 100 and 125 MHz). Chemical shifts are quoted in ppm and are referenced to residual H in the deuterated solvent as the internal standard. *J* values are recorded in Hz. In the ^{13}C NMR spectra, signals corresponding to CH, CH_2, or CH_3 groups are assigned from DEPT. High and low resolution mass spectra were recorded on a time-of-flight mass spectrometer.

(5*E*,9*E*)-6,10-Dimethyl-11-*tert*-butyldimethylsiloxyundeca-5,9-dien-2-one 8. To a solution of alcohol **7**[23,24] (1.50 g, 7.13 mmol) in dry dichloromethane (36 mL) under a nitrogen atmosphere was added 2,6-lutidine (1.83 mL, 1.69 g, 15.69 mmol) and *tert*-butyldimethylsilyl triflate (1.80 mL, 2.07 g, 7.84 mmol) dropwise at room temperature. The reaction mixture was stirred for 1 h and saturated aqueous ammonium chloride (30 mL) was added. The aqueous layer was extracted once into dichloromethane (20 mL) and the combined organic extracts were washed with brine

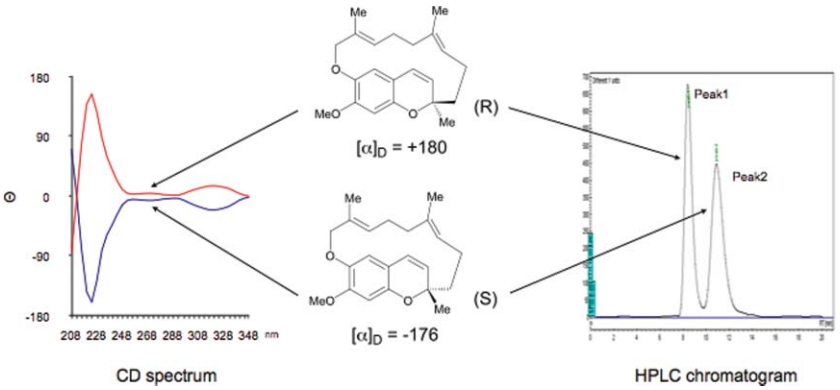


Fig. 3 CD spectra (1.5 mM in methanol) of the two enantiomers of likonide B (smenochromene D) after separation by HPLC.

(20 mL), dried over magnesium sulfate, filtered and evaporated *in vacuo*. The residue was purified by chromatography, eluting with light petroleum/ether (9:1), to give the silyl ether **8** (2.05 g, 89%) as a colourless oil; (Found: $[M+Na]^+$ 347.2376. $C_{19}H_{36}O_2Si + Na^+$ requires 347.2382); ν_{max} ($CHCl_3$)/cm^{-1} 2952, 2928, 2856, 1710, 1602, 1462, 1360, 1259, 1104; δ_H (400 MHz; $CDCl_3$) 5.35–5.31 (1 H, m, H-9), 5.08–5.05 (1 H, m, H-5), 3.97 (2 H, s, H-11), 2.45–2.41 (2 H, m, H-3), 2.27–2.21 (2 H, m, H-4), 2.11–2.06 (5 H, m, 1-Me, H-7) 2.00–1.96 (2 H, m, H-8), 1.60 (3 H, s, 10-Me), 1.57 (3 H, s, 6-Me), 0.86 (9 H, s, CMe_3), 0.04 (6 H, s, $SiMe_2$); δ_C (100 MHz; $CDCl_3$) 208.5 (C), 138.9 (C), 136.2 (C), 124.1 (CH), 122.7 (CH), 68.6 (CH_2), 43.4 (CH_2), 39.3 (CH_2), 29.9 (Me), 26.0 (CH_2), 25.8 (Me), 22.4 (CH_2), 18.2 (C), 15.9 (Me), 12.7 (Me), -5.0 (Me).

(6*E*,10*E*)-12-*tert*-Butyldimethylsiloxy-3,7,11-trimethyldodeca-6,10-dien-1-yn-3-ol 9. To a solution of ether **8** (2.00 g, 6.16 mmol) in an anhydrous mixture of THF/ether (1:1) (20 mL) at −10 °C was added ethynylmagnesium bromide (0.5 M in THF; 18.5 mL, 9.25 mmol) dropwise over a 10 min period while stirring under a nitrogen atmosphere. The mixture was stirred for further 5 h below 0 °C, and quenched with a mixture of saturated aqueous ammonium chloride (5 mL) and a hydrochloric acid (2 M; 1 mL). The mixture was extracted with ether (2 × 20 mL) and the combined organic layers were dried over magnesium sulfate, filtered and evaporated *in vacuo*. The residue was purified by chromatography, eluting with light petroleum/ether (100% to 80:20), to give the propargylic alcohol **9** (1.84 g, 85%) as a colourless oil (lit.,[34] oil); (Found: $[M+Na]^+$ 373.2530. $C_{21}H_{38}O_2Si + Na^+$ requires 373.2539); ν_{max} ($CHCl_3$)/cm^{-1} 3598, 3304, 2929, 2956, 1462, 1361, 1107; δ_H (400 MHz; $CDCl_3$) 5.37–5.34 (1 H, m, H-10), 5.20–5.16 (1 H, m, H-6), 3.99 (2 H, s, H-12), 2.45 (1 H, s, H-1), 2.35–2.10 (5 H, m, H-4, OH, H-5), 2.04–2.00 (2 H, m, H-9), 1.75–1.65 (5 H, m, H-8, 3-Me), 1.59 (3 H, s, 11-Me), 1.50 (3 H, s, 7-Me), 0.90 (9 H, s, CMe_3), 0.05 (6 H, s, $SiMe_2$); δ_C (100 MHz; $CDCl_3$) 136.0 (C), 134.4 (C), 124.6 (CH), 124.0 (CH), 87.6 (C), 71.4 (CH), 68.6 (CH_2), 68.2 (C), 43.1 (CH_2), 39.3 (CH_2), 30.2 (Me), 26.0 (CH_2), 25.9 (Me), 23.4 (CH_2), 18.4 (C), 16.0 (Me), 13.8 (Me), −5.3 (Me).

(6*E*,10*E*)-12-*tert*-Butyldimethylsiloxy-3,7,11-trimethyldodeca-6,10-dien-1-yn-3-ol methyl carbonate 10. To a solution of alcohol **9** (300 mg, 0.86 mmol) in anhydrous THF (7.5 mL) at −35 °C was added *n*-butyllithium (2.5 M in THF; 0.43 mL, 1.07 mmol) dropwise, while stirring under a nitrogen atmosphere. The mixture was stirred for further 30 min and methyl chloroformate (83 µl, 101 mg, 1.07 mmol) was added at −20 °C. The reaction mixture was stirred for 1.5 h and allowed to reach room temperature. Water (10 mL) and dichloromethane (10 mL) were added, the organic phase separated and the aqueous phase extracted with ether (2 × 10 mL). The combined organic layers were dried over magnesium sulfate, filtered and evaporated *in vacuo*. The residue was purified by chromatography, eluting with light petroleum/ether (9:1), to give the methyl carbonate **10** (301 mg, 86%) as a colourless oil; (Found: $[M+Na]^+$ 431.2585. $C_{23}H_{40}O_4Si + Na^+$ requires 431.2594); ν_{max} ($CHCl_3$)/cm^{-1} 3305, 2955, 2856, 1750, 1461, 1376, 1288, 1161, 1071; δ_H (400 MHz; $CDCl_3$) 5.38–5.34 (1 H, m, H-10), 5.15–5.11 (1 H, m, H-6), 4.00 (2 H, s, H-12), 3.76 (3 H, s, OMe), 2.59 (1 H, s, H-1), 2.24–2.17 (2 H, m, H-5), 2.14–2.09 (2 H, m, H-9), 2.03–1.95 (3 H, m, H-8, H-4), 1.88–1.80 (1 H, m, H-4), 1.72 (3 H, s, 3-Me), 1.62 (3 H, s, 11-Me), 1.59 (3 H, s, 7-Me), 0.90 (9 H, s, CMe_3), 0.05 (6 H, s, $SiMe_2$); δ_C (100 MHz; $CDCl_3$) 153.5 (C), 135.9 (C), 134.4 (C), 124.2 (CH), 122.9 (CH), 83.1 (C), 76.9 (C), 73.9 (CH), 68.6 (CH_2), 54.3 (Me), 41.2 (CH_2), 39.3 (CH_2), 26.2 (Me), 26.0 (Me), 25.9 (CH_2), 22.7 (CH_2), 18.4 (C), 15.9 (Me), 13.4 (Me), −5.3 (Me).

4-*tert*-Butyldimethylsiloxy-3-methoxyphenol 11. (a) To a solution of vanillin (1.00 g, 6.57 mmol) in anhydrous dichloromethane (30 mL) under nitrogen was added diisopropylethylamine (2.54 g, 3.40 mL, 19.72 mmol) and *tert*-butyldimethylsilyl triflate (1.81 mL, 2.08 g, 7.89 mmol) dropwise at room temperature. The mixture was stirred for 1.5 h, the solvent was removed *in vacuo* and the residue taken up in light petroleum. After filtration, the solvent was evaporated *in vacuo* and the resulting oil purified by chromatography, eluting with light petroleum/ethyl acetate (9:1), to give 4-*tert*-butyldimethylsiloxy-3-methoxybenzaldehyde (1.57 g, 89%) as a yellow oil (lit.,[35] yellow oil); (Found: $[M+Na]^+$ 289.1215. $C_{14}H_{22}O_3Si + Na^+$ requires 289.1236); ν_{max} ($CHCl_3$)/cm^{-1} 2931, 2859, 1682, 1593, 1506, 1464, 1392, 1294, 1154, 1124, 898; δ_H (400 MHz; $CDCl_3$) 9.86 (1 H, s, CHO), 7.41 (1 H, d, *J* 1.8, H-2), 7.39 (1 H, dd, *J* 8.0, 1.8, H-6), 6.97 (1 H, d, *J* 8.0, H-5), 3.88 (3 H, s, OMe), 1.01 (9 H, s, CMe_3), 0.20 (6 H, s, $SiMe_2$); δ_C (100 MHz; $CDCl_3$) 191.0 (CH), 151.3 (C), 151.0 (C), 131.0 (C), 126.2 (CH), 120.7 (CH), 110.1 (CH), 55.4 (Me), 25.6 (Me), 18.3 (C), −4.6 (Me).

(b) To a solution of 4-*tert*-butyldimethylsiloxy-3-methoxybenzaldehyde (1.00 g, 3.75 mmol) in anhydrous dichloromethane (15 mL) under a nitrogen atmosphere was added *m*CPBA (1.26 g, 5.63 mmol) portionwise at 0 °C. Following the addition, the

reaction mixture was heated at reflux (40 °C) for 2 h. The mixture was washed with saturated aqueous sodium hydrogen carbonate (2 × 10 mL), saturated aqueous sodium thiosulfate (2 × 10 mL) and again, saturated aqueous sodium hydrogen carbonate (2 × 10 mL). The organic phase was dried over magnesium sulfate, filtered and the solvent was removed *in vacuo.* The residual formate (0.94 g, 3.33 mmol) was taken up in anhydrous methanol (30 mL) and anhydrous potassium carbonate (602 mg, 4.36 mmol) was added at room temperature. The reaction mixture was stirred for 10 min and quenched with saturated aqueous ammonium chloride (30 mL). The aqueous phase was extracted several times with dichloromethane (2 × 25 mL), the combined organic phases dried over magnesium sulfate, filtered and evaporated *in vacuo.* The resulting brown oil was taken up in a minimum of light petroleum to give, on cooling, colourless crystals (800 mg, 94%) of the title compound **11**; mp 59–60 °C (lit.,[25] colourless oil); (Found: $[M+H]^+$ 255.1386. $C_{13}H_{22}O_3Si + H^+$ requires 255.1416); ν_{max} $(CHCl_3)/cm^{-1}$ 3599, 3426, 2929, 2834, 1600, 1500, 1462, 1390, 1296, 1150, 1116; δ_H (400 MHz; $CDCl_3$) 6.69 (1 H, d, *J* 8.5, H-5), 6.40 (1 H, d, *J* 2.8, H-2), 6.26 (1 H, d, *J* 8.5, 2.8, H-6), 4.78 (1 H, s, OH), 3.75 (3 H, s, OMe), 0.98 (9 H, s, CMe_3), 0.12 (6 H, s, $SiMe_2$); δ_C (100 MHz; $CDCl_3$) 151.5 (C), 150.3 (C), 138.7 (C), 120.9 (CH), 106.3 (CH), 100.6 (CH), 55.4 (Me), 25.7 (Me), 18.4 (C), –4.7 (Me).

1-*tert*-Butyldimethylsiloxy-4-[(6′*E*,10′*E*)-12′-*tert*-butyldimethylsiloxy-3′,7′,11′-tri-methyldodeca-6′,10′-dien-1′-yn-3′-yloxy]-2-methoxybenzene 12.

Method A. To a solution of propargylic alcohol **9** (200 mg, 0.57 mmol) in anhydrous acetonitrile (0.4 mL) cooled to below –5 °C was added DBU (110 μL, 112 mg, 0.74 mmol) under a nitrogen atmosphere. Trifluoroacetic anhydride (80 μL, 121 mg, 0.57 mmol) was added dropwise while maintaining the temperature below 2 °C. The resulting solution was allowed to stir at 0 °C for 1 h. Separately, to a solution of the 4-*tert*-butyldimethylsiloxy-3-methoxyphenol **11** (126 mg, 0.49 mmol) in anhydrous acetonitrile (0.4 mL) cooled to below –4 °C were added DBU (90 μL, 92 mg, 0.61 mmol) and copper(II) chloride dihydrate (1 mg) under a nitrogen atmosphere. The solution containing the trifluoroacetate (described above) was then added over a 5 min period while maintaining the temperature below 0 °C. After being stirred for 5 h below 0 °C, the mixture was concentrated *in vacuo* and the residue partitioned between water (2 mL) and ethyl acetate (6 mL). The organic layer was washed with hydrochloric acid (2 M; 2 mL), aqueous sodium hydroxide (2 M; 2 mL) and brine (2 mL), dried over magnesium sulfate, filtered and evaporated *in vacuo.* The crude product was purified by chromatography, eluting with light petroleum/ether (9:1), to give the title compound **12** (64 mg, 22%) as a colourless oil; data given below.

Method B. To a solution of the 4-*tert*-butyldimethylsiloxy-3-methoxyphenol **11** (38 mg, 0.15 mmol) in anhydrous acetonitrile (0.5 mL) cooled at –20 °C were added DBU (30 μL, 31 mg, 0.20 mmol) and anhydrous copper(II) chloride (0.1% mol) under a nitrogen atmosphere. After 20 min stirring, a solution of methyl carbonate **10** (74 mg, 0.18 mmol) in acetonitrile (0.25 mL) was added dropwise. After being stirred for 5 h below 0 °C and 18 h at room temperature, the mixture was concentrated *in vacuo* and the residue partitioned between water (2 mL) and ethyl acetate (6 mL). The organic layer was dried over magnesium sulfate, filtered and evaporated *in vacuo.* The crude product was purified by chromatography, eluting with light petroleum/ether (8:2–6:4), to give the title compound **12** (22 mg, 26%) as a colourless oil; (Found: $[M+NH_4]^+$ 604.4207. $C_{34}H_{58}O_4Si_2 + NH_4^+$ requires 604.4212); ν_{max} $(CHCl_3)/cm^{-1}$ 3304, 2929, 2856, 1601, 1504, 1463, 1361, 1309, 1153, 1110; δ_H (400 MHz; $CDCl_3$) 6.76 (1 H, d, *J* 2.6, H-2), 6.72 (1 H, d, *J* 8.6, H-5), 6.67 (1 H, dd, *J* 2.6, 8.6, H-6), 5.39–5.35 (1 H, m, H-10′), 5.18–5.15 (1 H, m, H-6′), 4.00 (2 H, s, H-12′), 3.76 (3 H, s, OMe), 2.55 (1 H, s, H-1′), 2.33–2.22 (2 H, m, H-5′), 2.16–2.10 (2 H, m, H-9′), 2.04–2.00 (2 H, m, H-8′), 1.94–1.77 (2 H, m, H-4′), 1.63 (3 H, s, 11′-Me), 1.60 (3 H, s, 7′-Me), 1.53 (3 H, s, 3′-Me), 0.99 (9 H, s, CMe_3), 0.91 (9 H, s, CMe_3), 0.13 (6 H, s, $SiMe_2$), 0.06 (6 H, s, $SiMe_2$); δ_C (100 MHz; $CDCl_3$) 150.7 (C), 149.8 (C), 140.8 (C), 135.5 (C), 134.3 (C), 124.3 (CH), 123.6 (CH), 120.1 (CH), 113.8 (CH), 107.3 (CH), 85.7 (C), 75.7 (CH), 74.6 (C), 68.6 (CH_2), 55.4 (Me), 42.4 (CH_2), 39.3 (CH_2), 26.9 (Me), 26.1 (CH_2), 26.0 (Me), 25.7 (Me), 23.0 (CH_2), 18.4 (C), 16.0 (Me), 13.4 (Me), -4.7 (Me), -5.3 (Me).

6-*tert*-Butyldimethylsilyl-2-[(3′*E*,7′*E*)-9′-*tert*-butyldimethylsiloxy-4′,8′-dimethyl-nona-3′,7′-dienyl]-7-methoxy-2-methyl-2*H*-chromen-6-ol 13. A solution of propargyl aryl ether **12** (38 mg, 0.65 mmol) in DMF (1 mL) in a sealed tube was heated at 200 °C for 30 min at 300 W in a microwave reactor. The reaction mixture was diluted with ether (5 mL), washed with brine (3 × 5 mL), water (5 mL), dried over magnesium sulfate, filtered and evaporated *in vacuo.* The oil was purified by chromatography, eluting with light petroleum/ether (9:1), to give the chromene **13** (22 mg, 52%) as an inseparable 4:1 mixture of regioisomers, as a colourless oil; (Found: $[M+Na]^+$ 609.3740. $C_{34}H_{58}O_4Si_2$ + Na^+ requires 609.3771); ν_{max} $(CHCl_3)/cm^{-1}$ 2929–2857, 1614, 1573, 1499, 1462, 1450, 1388, 1362, 1327, 1286, 1260, 1171, 1128, 1102; δ_H (400 MHz; $CDCl_3$) *major regioisomer* 6.45 (1 H, s, H-5), 6.35 (1 H, s, H-8), 6.23 (1 H, d, *J* 9.8, H-4), 5.42 (1 H, d, *J* 9.8, H-3), 5.37–5.34 (1 H, m, H-7′), 5.14–5.10 (1 H, m, H-3′), 4.00 (2 H, s, H-9′), 3.75 (3 H, s, OMe), 2.12–2.08 (4 H, m, H-2′, H-6′), 2.01–1.97 (2 H, m, H-5′), 1.76–1.62 (2 H, m, H-1′), 1.59 (3 H, s, 8′-Me), 1.57 (3 H, s, 4′-Me), 1.37 (3 H, s, 2-Me), 0.99 (9 H, s, CMe_3), 0.91 (9 H, s, CMe_3), 0.13 (6 H, s, $SiMe_2$), 0.06 (6 H, s, $SiMe_2$); the following peaks were assigned to the minor regioisomer 6.61 (1 H, d, *J* 10.0, H-4), 6.60 (1 H, d, *J* 8.7, H-7), 6.42 (1 H, d, *J* 8.7, H-8), 5.59 (1 H, *J* 10.0, H-3), 3.77 (3 H, s, OMe), 1.00 (9 H, s, CMe_3), 0.16 (6 H, s, $SiMe_2$); δ_C (100 MHz; $CDCl_3$) 151.3 (C), 147.9 (C), 138.3 (C), 135.0 (C), 134.3 (C), 127.0 (CH), 124.3 (CH), 124.2 (CH), 122.5 (CH), 118.0 (CH), 113.4 (C), 100.9 (CH), 78.2 (C), 68.6 (CH_2), 55.4 (Me), 41.0 (CH_2), 39.3 (CH_2), 26.12 (CH_2), 26.07 (Me), 26.0 (Me), 25.8 (Me), 22.6 (CH_2), 18.41 (C), 18.37 (C), 15.9 (Me), 13.4 (Me), –4.7 (Me), –5.3 (Me).

4-Methanesulfonyloxy-3-methoxyphenol 14. (a) To a solution of vanillin (1.00 g, 6.57 mmol) in anhydrous dichloromethane (20 mL) under an argon atmosphere was added *m*CPBA (2.20 g, 9.86 mmol) portionwise. Following the addition, the reaction mixture was stirred for 2.5 h at room temperature. The mixture was washed with saturated aqueous sodium hydrogen carbonate (2 × 10 mL), saturated aqueous sodium thiosulfate (2 × 10 mL) and saturated aqueous sodium hydrogen carbonate (2 × 10 mL). The organic phase was dried over magnesium sulfate, filtered and the solvent was removed *in vacuo* to give 4-hydroxy-3-methoxyphenyl formate (0.80 g, 73%) as a colourless crystals, mp 58–59 °C (lit.,[36] no mp given); (Found: $[M+H]^+$ 169.0495. $C_8H_9O_4 + H^+$ requires

169.0492); ν_{max} ($CHCl_3$)/cm^{-1} 3695, 3544, 2941, 2358, 1738, 1602, 1507, 1451, 1369, 1276, 1154, 1103; δ_H (400 MHz; $CDCl_3$) 8.30 (1 H, s, CHO), 6.96 (1 H, d, *J* 8.5, H-5), 6.67 (1 H, d, *J* 2.6, H-2), 6.64 (1 H, dd, *J* 8.5, 2.6, H-6), 5.50 (1 H, s, OH), 3.88 (3 H, s, OMe); δ_C (100 MHz; $CDCl_3$) 159.7 (CH), 146.7 (C), 143.8 (C), 142.8 (C), 114.4 (CH), 113.3 (CH), 104.6 (CH), 56.1 (Me).

(b) To a solution of 4-hydroxy-3-methoxyphenyl formate (1.77 g, 10.5 mmol) in dichloromethane (50 mL) under an argon atmosphere was added diisopropylethylamine (2.10 mL, 1.57 g, 12.1 mmol) and methanesulfonyl chloride (0.86 mL, 1.27 g, 11.0 mmol) dropwise at 0 °C. The reaction mixture was stirred for 0.5 h and washed with water. The organic layer was dried over magnesium sulfate, filtered and the solvent was removed *in vacuo.* The crude product was used without further purification and taken up in a (4:1) mixture of methanol and THF (25 mL). Anhydrous potassium hydrogen carbonate (618 mg, 6.17 mmol) was added at room temperature and the reaction mixture was stirred for 15 min. Saturated aqueous ammonium chloride (15 mL) was used to quench the reaction. The aqueous phase was extracted with ethyl acetate (3 × 25 mL), the combined organic layers were dried over magnesium sulfate, filtered and evaporated *in vacuo.* The resulting oil was dissolved in ethyl acetae–light petroleum (1:1) (5 mL) and quickly filtered through a thin layer of silica, the filtrate evaporated, and the residue crystallised from cold light petroleum to afford the title compound **14** (1.52 g, 66%) as colourless crystals; mp 92–94 °C; (Found: $[M-H]^-$ 217.0173. $C_8H_{10}O_5S$ - H requires 217.0165); ν_{max} ($CHCl_3$)/cm^{-1} 3592, 2940, 2838, 2231, 2072, 1618, 1505, 1434, 1367, 1305, 1151, 1110; δ_H (400 MHz; $CDCl_3$) 7.11 (1 H, d, *J* 8.8, H-5), 6.48 (1 H, d, *J* 2.7, H-2), 6.34 (1 H, d, *J* 8.8, 2.7, H-6), 4.88 (1 H, s, OH), 3.85 (3 H, s, OMe), 3.15 (3 H, s, Me); δ_C (100 MHz; $CDCl_3$) 158.9 (C), 153.8 (C), 132.7 (C), 125.7 (CH), 107.8 (CH), 101.7 (CH), 56.3 (Me), 38.0 (3 H, s, Me).

4-Methanesulfonyloxy-3-methoxy-((6′*E*,10′*E*)-12′-*tert*-butyldimethylsiloxy-3′,7′,11′-trimethyldodeca-6′,10′-dien-1′-yn-3′-yloxy) benzene 15. To a solution of 4-methanesulfonyl-3-methoxyphenol **14** (250 mg, 1.14 mmol) in anhydrous acetonitrile (2.5 mL) cooled to −20 °C was added DBU (205 μL, 209 mg, 1.37 mmol) and anhydrous copper(II) chloride (0.15 mg, 0.1% mol) under a nitrogen atmosphere. The mixture was stirred for 15 min and a solution of the carbonate **10** (562 mg, 1.37 mmol) in acetonitrile (3 mL) was slowly added at 0 °C. The reaction mixture was stirred below 0 °C for 5 h and at room temperature for 12 h. Water (10 mL) was added, and after extraction with ethyl acetate (2 × 10 mL), the organic layers were dried over magnesium sulfate, filtered and evaporated *in vacuo.* The residue was purified by chromatography, eluting with light petroleum/ether (7:3) to give the title compound (459 mg, 73%) as a colourless oil; (Found: $[M+Na]^+$ 573.2594. $C_{29}H_{46}O_6SSi + Na^+$ requires 573.2682); ν_{max} ($CHCl_3$)/cm^{-1} 3303, 2929, 2856, 1603, 1498, 1450, 1367, 1329, 1301, 1152, 1107, 1034; δ_H (400 MHz; $CDCl_3$) 7.20–7.17 (1 H, m, H-5), 6.86–6.83 (2 H, m, H-2, H-6), 5.39–5.35 (1 H, m, H-10′), 5.18–5.14 (1 H, m, H-6′), 4.00 (2 H, s, H-12′), 3.85 (3 H, s, OMe), 3.15 (3 H, s, Me), 2.64 (1 H, s, H-1′), 2.36–2.18 (2 H, m, H-4′), 2.15–2.10 (2 H, m, H-8′), 2.04–2.00 (2 H, m, H-9′), 1.98–1.91 (1 H, m, H-5′), 1.88–1.80 (1 H, m, H-5′), 1.63 (3 H, s, 7′-Me), 1.59 (6 H, s, 11′-Me, 3′-Me), 0.90 (9 H, s, CMe_3), 0.06 (6 H, s, $SiMe_2$); δ_C (100 MHz; $CDCl_3$) 155.3 (C), 151.5 (C), 135.8 (C), 134.3 (C), 133.4 (C), 124.2 (CH), 124.1 (CH), 123.2 (CH), 112.5 (CH), 106.2 (CH), 84.7 (C), 75.7 (CH), 75.6 (C), 68.6 (CH_2), 55.9 (Me), 42.4 (CH_2), 39.3 (CH_2), 38.0 (Me), 26.7 (Me), 26.05 (Me), 25.96 (CH_2), 22.9 (CH_2), 18.4 (C), 15.9 (Me), 13.4 (Me), −5.3 (Me).

4-[(6′*E*,10′*E*)-12′-*tert*-Butyldimethylsiloxy-3′,7′,11′-trimethyldodeca-6′,10′-dien-1′-yn-3′-yloxy]-2-methoxyphenol 16. To a solution of mesylate **15** (368 mg, 0.67 mmol) in dry THF (5.6 mL) at −78 °C was added a freshly prepared LDA solution (3.95 mL, 2.14 mmol)‡ under an argon atmosphere. The reaction mixture was stirred for 2 h at that temperature and quenched with saturated aqueous ammonium chloride (5 mL). The mixture was extracted into ethyl acetate (2 × 5 mL), dried over magnesium sulfate, filtered and the solvent removed *in vacuo.* The residue was purified by chromatography, eluting with light petroleum/ether (7:3), to give the title compound **16** (244 mg, 76%) as an orange-yellow oil; (Found: $[M+Na]^+$ 495.2903. $C_{28}H_{44}O_4Si + Na^+$ requires 495.2901); ν_{max} ($CHCl_3$)/cm^{-1} 3686, 3553, 3307, 2929, 2856, 2351, 1600, 1502, 1464, 1370, 1154, 1108; δ_H (400 MHz; $CDCl_3$) 6.80 (1 H, d, *J* 8.6 H-6), 6.78 (1 H, d, *J* 2.8, H-3), 6.71 (1 H, dd, *J* 8.6, 2.8, H-5), 5.39–5.35 (2 H, m, H-10′, OH), 5.19–5.15 (1 H, m, H-6′), 4.00 (2 H, s, H-12′), 3.85 (3 H, s, OMe), 2.56 (1 H, s, H-1′), 2.35–2.22 (2 H, m, H-5′), 2.16–2.10 (2 H, m, H-9′), 2.04–2.00 (2 H, m, H-8′), 1.94–1.87 (1 H, m, H-4′), 1.84–1.76 (1 H, m, H-4′), 1.64 (3 H, s, 7′-Me), 1.60 (3 H, s, 11′-Me), 1.53 (3 H, s, 3′-Me), 0.91 (9 H, s, CMe_3), 0.06 (6 H, s, $SiMe_2$); δ_C (100 MHz; $CDCl_3$) 148.5 (C), 146.1 (C), 141.7 (C), 135.5 (C), 134.3 (C), 124.3 (CH), 123.6 (CH), 114.9 (CH), 113.6 (C), 106.6 (CH), 85.6 (C), 76.1 (C), 74.8 (CH), 68.6 (CH_2), 55.9 (Me), 42.3 (CH_2), 39.3 (CH_2), 26.9 (CH_2), 26.1 (Me), 26.0 (Me), 23.1 (CH_2), 18.4 (C), 16.0 (Me), 13.4 (Me), −5.2 (Me).

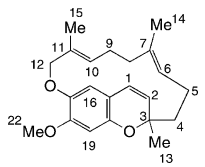
2-[(3′*E*,7′*E*)-9′-*tert*-Butyldimethylsiloxy-4′,8′-dimethylnona-3′,7′-dienyl]-7-methoxy-2-methyl-2*H*-chromen-6-ol 17. A solution of the propargyl ether **16** (98 mg, 0.21 mmol) in *N*,*N*-diethylaniline (3.5 mL) in a sealed tube was heated at 140 °C for 40 min at 300 W in a microwave reactor. The reaction mixture was concentrated and the residue was purified by chromatography, eluting with light petroleum/ether (8:2), to give the *title compound* **17** (85 mg, 87%) as a orange-yellow oil; (Found: $[M+Na]^+$ 495.2917. $C_{28}H_{44}O_4Si + Na^+$ requires 495.2901); ν_{max} ($CHCl_3$)/cm^{-1} 3630, 3553, 2929, 2856, 1628, 1583, 1501, 1458, 1360, 1290, 1124; δ_H (400 MHz; $CDCl_3$) 6.56 (1 H, s, H-5), 6.41 (1 H, s, H-8), 6.27 (1 H, d, *J* 9.8, H-4), 5.47 (1 H, d, *J* 9.8, H-3), 5.38 (1 H, m, H-7′), 5.19 (1 H, s, OH), 5.16–5.13 (1 H, m, H-3′), 4.02 (2 H, s, H-9′), 3.86 (3 H, s, OMe), 2.14–2.10 (4 H, m, H-2′, H-6′), 2.03–2.00 (2 H, m, H-4′), 1.75–1.66 (2 H, m, H-1′), 1.61 (6 H, s, 4′-Me, 8′-Me), 1.39 (3 H, s, 2-Me), 0.93 (9 H, s, CMe_3), 0.08 (6 H, s, $SiMe_2$); δ_C (100 MHz; $CDCl_3$) 146.7 (C), 146.6 (C), 139.2 (C), 135.0 (C), 134.3 (C), 127.6 (CH), 124.3 (CH), 122.4 (CH), 121.5 (CH), 113.9 (CH), 111.7 (C), 100.0 (CH), 78.1 (C), 68.6 (CH_2), 55.9 (Me), 40.9 (CH_2), 39.3 (CH_2), 26.0 (CH_2), 25.9 (Me), 25.8 (Me), 22.6 (CH_2), 18.4 (C), 15.9 (Me), 13.4 (Me), −5.3 (Me).

2-[(3′*E*,7′*E*)-9′-Hydroxy-4′,8′-dimethylnona-3′,7′-dienyl]-7-methoxy-2-methyl-2*H*-chromen-6-ol 18. To a solution of silyl ether **17** (242 mg, 0.51 mmol) in acetonitrile (10 mL) was added

‡ Lithium diisopropylamide (LDA) was prepared by the following procedure: to THF (15 mL) cooled to −78 °C was added diisopropylamine (1.97 mL, 1.47 g, 1.20 equiv) followed by *n*-butyllithium (1.61 M in hexane; 7.76 mL, 1.00 equiv). The solution was stirred at −78 °C for 30 min and used immediately.

hexafluorosilicic acid (35% w/w in water; 319 μL, 1.02 mmol) at 0 °C. The reaction mixture was stirred for 40 min and quenched with saturated aqueous sodium hydrogen carbonate (5 mL). The organic layer was separated, and the aqueous layer extracted into ethyl acetate (2 × 10 mL). The combined organic layers were washed with brine (3 × 10 mL), dried over magnesium sulfate, filtered and evaporated *in vacuo.* The residue was purified by chromatography, eluting with light petroleum/ether (1:1), to give the title compound **18** (157 mg, 83%) as an orange oil; (Found: $[M+Na]^+$ 381.2052. $C_{22}H_{30}O_4 + Na^+$ requires 381.2036); ν_{max} ($CHCl_3$)/cm^{-1} 3612, 3551, 2926, 2848, 1627, 1583, 1500, 1456, 1380, 1359, 1289, 1164, 1125; δ_H (400 MHz; $CDCl_3$) 6.56 (1 H, s, H-5), 6.38 (1 H, s, H-8), 6.26–6.23 (1 H, d, *J* 9.8, H-4), 5.46–5.43 (1 H, d, *J* 9.8, H-3), 5.39–5.35 (1 H, m, H-7′), 5.19 (1 H, s, OH-6), 5.14–5.10 (1 H, m, H-3′), 3.98 (2 H, s, H-9′), 3.84 (3 H, s, OMe), 2.13–2.08 (4 H, m, H-5′, H-1′), 2.01–1.97 (2 H, m, H-6′), 1.78–1.60 (6 H, m, H-2′, 4′-Me, OH-9′), 1.58 (3 H, s, 7′-Me), 1.36 (3 H, s, 2-Me); δ_C (100 MHz; $CDCl_3$) 146.7 (C), 146.6 (C), 139.2 (C), 134.9 (C), 134.7 (C), 127.6 (CH), 126.0 (CH), 124.3 (CH), 122.5 (CH), 117.4 (CH), 113.9 (CH), 111.7 (C), 100.1 (CH), 78.2 (C), 69.0 (CH_2), 56.0 (Me), 40.9 (CH_2), 39.2 (CH_2), 26.1 (CH_2), 26.0 (Me), 22.6 (CH_2), 15.9 (Me), 13.7 (Me).

(±)-Likonide B [(±)-smenochromene D]. Argon was bubbled



into a stirred 8 mM solution of 2-[(3*E*,7*E*)-9-hydroxy-4,8-dimethylnona-3,7-dienyl]-7-methoxy-2-methyl-2*H*-chromen-6-ol **18** (50 mg, 0.14 mmol) and 1,1′-(azodicarbonyl)-dipiperidine (105 mg, 0.42 mmol) in anhydrous toluene (17.4 mL) for 10 min at 0 °C. A first batch (40 μL) of tri-*n*-butylphosphine (140 μL, 113 mg, 0.55 mmol) was added dropwise and the reaction mixture was stirred for 20 min at 0 °C followed by the addition of a second batch of tri-*n*-butylphosphine (100 μL). The reaction mixture was allowed to reach room temperature and stirred for 24 h. A second batch of 1,1′-(azodicarbonyl)dipiperidine (105 mg, 0.42 mmol) was added at 0 °C, tributylphosphine (140 μL, 113 mg, 0.55 mmol) was added over 1 h and the mixture stirred for 8 h at room temperature. Water was added and the aqueous phase extracted into ethyl acetate (2 × 15 mL). The combined organic layers were reduced *in vacuo*, the crude product was taken up in light petroleum and filtered. The resulting filtrate was dried over magnesium sulfate, filtered and evaporated *in vacuo.* The residue was purified by chromatography, eluting with hexane/ethyl acetate (9:1), to give (i) the title compound (13 mg, 27%) as a colourless oil that slowly crystallized to give crystals suitable for X-ray analysis, mp 107–108 °C (± 7 °C) (lit.,[4] natural smenochromene D, colourless glass; lit.,[5] natural likonide B, oil; lit.,[6,7] synthetic smenochromene D, clear oil); (Found: $[M+Na]^+$ 363.1919. $C_{22}H_{28}O_3 + Na^+$ requires 363.1931); ν_{max} (DMSO)/cm^{-1} 2930, 1618, 1503, 1450, 1365, 1289, 1124; δ_H (400 MHz; DMSO) 6.61 (1 H, s, H-16), 6.38 (1 H, d, *J* 9.8, H-1), 6.34 (1 H, s, H-19), 5.41 (1 H, d, *J* 9.8, H-2), 4.87–4.85 (1 H, m, H-6), 4.78–4.74 (1 H, m, H-10), 4.38 (1 H, d, *J* 11.4, H-12), 4.07 (1 H, d, *J* 11.4, H-12′), 3.66 (3 H, s, H-22), 2.12–1.96 (4 H, m, H-9, H-5, H-8), 1.92–1.83 (1 H, m, H-5′), 1.68–1.64 (1 H, m, H-4), 1.62–1.53 (5 H, m, H-8, H-15, H-4′), 1.41 (3 H, s, H-13), 1.32 (3 H, s, H-14); δ_C (100 MHz; DMSO) 153.0 (C), 149.8 (C), 138.9 (C), 131.2 (CH), 131.0 (C), 129.6 (C), 126.3 (CH), 125.6 (CH), 123.2 (CH), 118.9 (CH), 112.9 (C), 99.9 (CH), 78.9 (CH), 78.6 (C), 55.3 (Me), 40.7 (CH_2), 38.5 (CH_2), 29.7 (Me), 24.0 (CH_2), 22.5 (CH_2), 14.2 (Me), 13.9 (Me); and (ii) a dimer assigned as **19** (13 mg, 13%) as a colourless oil (mixture of diastereoisomers); (Found: $[M+Na]^+$ 703.3943. $C_{44}H_{56}O_6 + Na^+$ requires 703.3969); δ_H (400 MHz; $CDCl_3$) 6.48 (1 H, s, ArH), 6.44 (1 H, s, ArH), 6.36 (1 H, s, ArH), 6.35 (1 H, s, ArH), 6.17 (2 H, 2d, *J* 9.8, 9.8, 2 × CH), 5.41–5.31 (4 H, 2d, *J* 9.8, 9.8, 2 × CH, m, 2 × CH=), 5.06–5.00 (2 H, m, 2 × CH=), 4.45–4.27 (4 H, m, 2 × CH_2OAr), 3.79 (6 H, s, 2 × OMe), 2.12–1.94 (12 H, m, 2 × =C(Me)CH_2CH_2, 2× =CHCH_2), 1.66–1.60 (10 H, m, 2 × Me, 2 × =CHCH_2CH_2), 1.50 (6 H, s, 2 × Me), 1.37 (3 H, s, Me), 1.33 (3 H, s, Me); δ_C (100 MHz; $CDCl_3$) 150.5 (C), 150.4 (C), 147.6 (C), 141.6 (C), 141.5 (C), 134.1 (C), 131.3 (C), 131.0 (C), 128.3 (CH), 128.0 (CH), 127.3 (CH), 127.2 (CH), 125.0 (CH), 124.9 (CH), 122.4 (CH), 113.5 (CH), 112.9 (C), 100.9 (CH), 100.8 (CH), 78.3 (C), 78.1 (C), 75.8 (CH_2), 75.7 (CH_2), 55.9 (Me), 40.6 (CH_2), 40.2 (CH_2), 38.8 (CH_2), 38.7 (CH_2), 30.3 (Me), 29.7 (Me), 26.1 (Me), 25.9 (Me), 25.3 (CH_2), 25.2 (CH_2), 22.5 (CH_2), 22.3 (CH_2), 15.6 (Me), 15.5 (Me), 13.7 (Me).

Separation of enantiomers

Column, Chiralpak OJ, 10 × 250 mm; eluant, hexane-2-propanol (98:2); 10 mg of mixture was dissolved in 1 mL of mobile phase and injected in 200 μL portions. After separation, the two enantiomers exhibited the following properties:-

Peak 1, R_t = 9.65 min [hexane–2-propanol (99:1)]; $[\alpha]_D^{25}$ +180 (*c* 0.31, CH_2Cl_2);

Peak 2, R_t = 11.4 min [hexane–2-propanol (99:1)]; $[\alpha]_D^{25}$ −176 (*c* 0.35, CH_2Cl_2).

Acknowledgements

We thank Professor Yoel Kashman for helpful exchange of information including the CD spectra of natural likonide B, Professor Dirk Trauner for copies of the NMR spectra of synthetic (±)-likonide B, and Professor Mark Searle, Laura Tye and Anita Rea for help with CD spectroscopy.

References

1 R. H. Thomson, '*Naturally Occurring Quinones*', Academic Press, 1971.
2 R. H. Thomson, '*Naturally Occurring Quinones III. Recent, advances*', Chapman and Hall, 1987.
3 R. H. Thomson, '*Naturally Occurring Quinones IV. Recent, advances*', Blackie, 1997.
4 Y. Venkateswarlu, D. J. Faulkner, J. L. R. Steiner, E. Corcoran and J. Clardy, *J. Org. Chem.*, 1991, **56**, 6271.
5 A. Rudi, Y. Benayahu and Y. Kashman, *Org. Lett.*, 2004, **6**, 4013.
6 B. S. Olson and D. Trauner, *Synlett*, 2005, 700.
7 C. P. Rosa, M. A. Kienzler, B. S. Olson, G. Liang and D. Trauner, *Tetrahedron*, 2007, **63**, 6529.
8 P. Stahl and H. Waldmann, *Angew. Chem. Int. Ed.*, 1999, **38**, 3710.
9 S. Aoki, D. Kong, K. Matsui, R. Rachmat and M. Kobayashi, *Chem. Pharm. Bull.*, 2004, **52**, 935.
10 Y. Takahashi, T. Kubota, J. Fromont and J. Kobayashi, *Tetrahedron*, 2007, **63**, 8770.
11 Preliminary communication, M. Bruder and C. J. Moody, *Synlett*, 2008, 575.

12 C. J. Moody, *J. Chem. Soc. Perkin Trans. 1*, 1984, 1333.
13 T. Martin and C. J. Moody, *J. Chem. Soc. Perkin Trans. 1*, 1988, 241.
14 C. J. Moody, K. J. Doyle, M. C. Elliott and T. J. Mowlem, *J. Chem. Soc. Perkin Trans. 1*, 1997, 2413.
15 F. Lach and C. J. Moody, *Tetrahedron Lett.*, 2000, **41**, 6893.
16 M. C. Bagley, C. J. Moody and A. G. Pepper, *Tetrahedron Lett.*, 2000, **41**, 6901.
17 C. J. Davis, T. E. Hurst, A. M. Jacob and C. J. Moody, *J. Org. Chem.*, 2005, **70**, 4414.
18 A. M. Jacob and C. J. Moody, *Tetrahedron Lett*, 2005, **46**, 8823.
19 C. S. P. McErlean, N. Proisy, C. J. Davis, N. A. Boland, S. Y. Sharp, K. Boxall, A. M. Z. Slawin, P. Workman and C. J. Moody, *Org. Biomol. Chem.*, 2007, **5**, 531.
20 C. S. P. McErlean and C. J. Moody, *J. Org. Chem.*, 2007, **72**, 10298.
21 C. L. Coombes and C. J. Moody, *J. Org. Chem.*, 2008, **73**, 6758–6762.
22 L. Guillonneau, D. Taddei and C. J. Moody, *Org. Lett.*, 2008, **10**, 4505.
23 J. E. McMurry and R. G. Dushin, *J. Am. Chem. Soc.*, 1989, **111**, 8928.
24 M. A. Umbreit and K. B. Sharpless, *J. Am. Chem. Soc.*, 1977, **99**, 5526.
25 J. Fischer, A. J. Reynolds, L. A. Sharp and M. S. Sherburn, *Org. Lett.*, 2004, **6**, 1345.
26 J. D. Godfrey, R. H. Mueller, T. C. Sedergran, N. Soundararajan and V. J. Colandrea, *Tetrahedron Lett.*, 1994, **35**, 6405.
27 For related Claisen rearrangements, see ref. 28 and the following: P. H. Kahn and J. Cossy, *Tetrahedron Lett.*, 1999, **40**, 8113.
28 S. Yamaguchi, M. Maekawa, Y. Murayama, M. Miyazawa and Y. Hirai, *Tetrahedron Lett.*, 2004, **45**, 6971.
29 For a discussion of regioselectivity in rearrangements of aryl propargyl ethers, see: S. Yamaguchi, M. Ishibashi, K. Akasaka, H. Yokoyama, M. Miyazawa and Y. Hirai, *Tetrahedron Lett.*, 2001, **42**, 1091.
30 For an earlier example of a microwave-assisted Claisen rearrangement of an aryl propargyl ether, see: F. M. Moghaddam, A. Sharifi and M. R. Saidi, *J. Chem. Res.-S*, 1996, 338.
31 T. Ritter, K. Stanek, I. Larrosa and E. M. Carreira, *Org. Lett.*, 2004, **6**, 1513.
32 CCDC-717575 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge *via* www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB21EZ, UK; fax: (+44) 1223-336-033; or deposit@ccdc.cam.ac.uk).CCDC.
33 T. Kikuchi, Y. Mori, T. Yokoi, S. Nakazawa, H. Kuroda, Y. Masada, K. Kitamura and K. Kuriyama, *Chem. Pharm. Bull.*, 1983, **31**, 106.
34 H. Takayanagi, Y. Kitano, and Y. Morinaka, 1991, PCT Application, WO9108186.
35 M. Brasholz, X. S. Luan and H. U. Reissig, *Synthesis*, 2005, 3571.
36 F. Camps, J. Coll, A. Messeguer and M. A. Pericas, *Tetrahedron Lett.*, 1981, **22**, 3895.

