Pergamon

Tetrahedron 56 (2000) 389–395

TETRAHEDRON

Preparation of (+)-Hamabiwalactone B via Stille Coupling of an Enantiomerically Pure Stannylfuranone

Alexandre M. E. Richecœur and J. B. Sweeney*

Department of Chemistry, University of Reading, Whiteknights, Reading RG6 6AD, UK†

Received 4 August 1999; revised 13 October 1999; accepted 4 November 1999

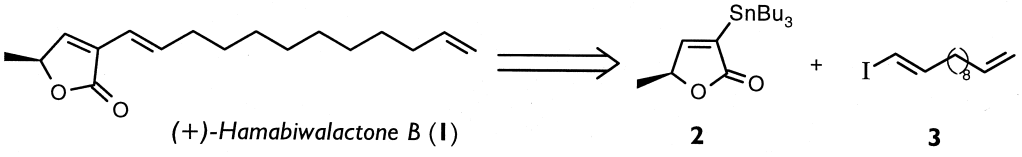
Abstract—An unambiguous and highly enantioselective total synthesis of the naturally occurring 2(5H)-furanone Hamabiwalactone B has been achieved. The key step was a palladium-catalysed cross coupling ("Stille" coupling) of the previously unreported stannylfuranone **2** with (*E*)-iodoalkene **3**. The enantiomeric purity of the synthetic natural product was ≥99%, as judged by chiral HPLC.

Introduction

Many natural and bioactive compounds contain the 2(5H)-furanone subunit;[1] consequently, we have developed a methodology to allow synthesis of such compounds via palladium-catalysed cross-coupling of 3- and 4-tributylstannyl 2(5H)-furanones with aryl iodides.[2] We here report in detail[3] the first preparation of a 3-tributylstannyl 2(5H)-furanone bearing an asymmetric centre and describe how this compound was used to synthesise and confirm the stereochemistry of Hamabiwalactone B (Scheme 1), a naturally occurring 2(5H)-furanone isolated from the roots of *Litsea Japonica* (Japanese name *Hamabiwa*) which grows in the southern part of Japan.[4] The absolute stereochemistry of the single asymmetric centre of (+)-Hamabiwalactone B was postulated as 5*S*, but not established unambiguously prior to our work and, furthermore, the optical rotation of this compound (+2.2 [*c* 0.32, $CHCl_3$]) was so low as to suggest that the isolation process may have compromised the stereogenic integrity of the asymmetric centre, given the relatively high acidity of the C5-proton.

Results and Discussion

Based on our expertise in cross-coupling reactions of 3- and 4-stannylfuranones, we expected to be able to accomplish the first total synthesis of Hamabiwalactone B by means of the chemistry outlined in Scheme 1. We, therefore, required access to two coupling partners, (5*S*)-methyl-3-tributylstannyl 2(5H)-furanone **2**, and the previously synthesised (*E*)-1-iodododeca-1,11-diene **3**. Lactone **2** had not previously been prepared in either racemic form, or as a single enantiomer prior to our synthetic efforts. Thus, we first turned our attention to the synthesis of racemic stannane **2**.



(+)-Hamabiwalactone B (**1**) **2** **3**

Scheme 1.

In the first instance, we proposed to synthesise Hamabiwalactone B in racemic form, and then to use enantiomerically pure stannylfuranone **2** to prepare **1** as a single enantiomer. Thus, we expected that the desulfurative-stannylation reaction of sulfanyl 2(5H)-furanones[2] we had used before to prepare 5-unsubstituted stannylfuranones would allow us to gain access to preparatively convenient amounts of **2**, and we sought to prepare this racemic stannylfuranone from 5-methyl-3-phenylsulfanyl-2(5H)-furanone **4**.[5] The practical realisation of this synthetic aspiration is shown in Scheme 2.

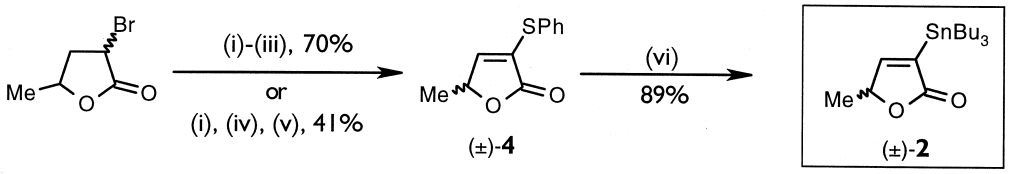
2-Bromo-5-methylbutyrolactone was reacted with sodium thiophenoxide in THF at 0°C, and the crude sulfanyl

Keywords: (+)-Hamabiwalactone B; Stille coupling; enantioselective synthesis.

* Corresponding author. E-mail: j.b.sweeney@rdg.ac.uk

† Previous address: School of Chemistry, University of Bristol, Bristol BS8 1TS, UK.

0040–4020/00/$ - see front matter
PII: S0040-4020(99)00998-9



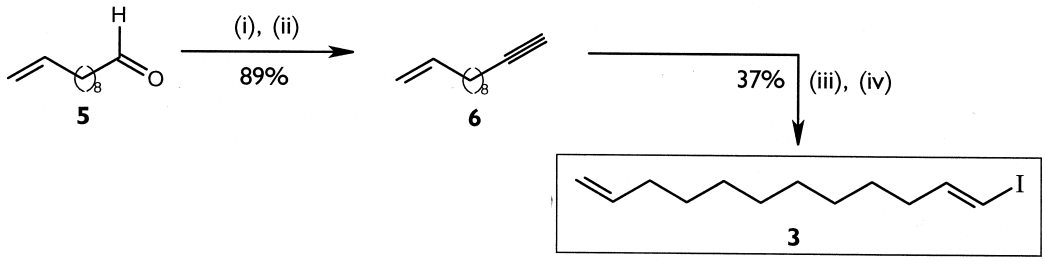
Scheme 2. Conditions: (i) NaSPh, THF, 0°C; (ii) SO_2Cl_2, CCl_4, 0°C; (iii) LiBr, Li_2CO_3, THF, reflux; (iv) *m*CPBA, CH_2Cl_2; (v) Ac_2O, 65°C; (vi) Bu_3SnH, VAZO-88®, $PhCH_3$, 100°C.

butyrolactone thereby obtained was, by a sequential chlorination–dehydrochlorination protocol, converted into sulfanyl furanone **4**, in good overall yield. Alternatively, the intermediate sulfanyl lactone could be oxidised and subjected to Pummerer rearrangement to give furanone **4**, in poorer yield. Desulfurative stannylation of **4** gave the previously unreported stannylfuranone **2** in 89% yield, the entire sequence from commercially available 2-bromo-5-methylbutyrolactone proceeding in 62% overall yield.

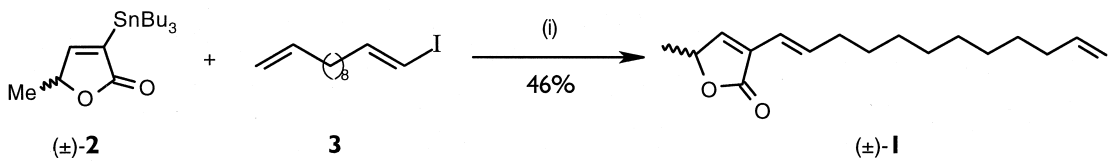
The required coupling partner, (*E*)-iodo-1,11-dodecadiene **3**, was prepared as shown in Scheme 3. Although the synthesis of (*E*)-**3** had been previously reported,[6] the reaction employed before had furnished the iododiene as a mixture of (*Z*)- and (*E*)-isomers, via reaction of 10-undecenal with an iodinated phosphonium salt, with the (*Z*)-iododiene dominating the mixture. Since the efficiency of our proposed synthesis would depend upon reaction of a single stereoisomer of **3**, we sought an alternative route and decided upon a process utilising a sequential homologation–hydroalumination–iodination transformation of commercially available 10-undecenal (Scheme 3). Thus, 10-undecenal **5** was homologated to dodeca-11-ene-1-yne **6** (previously prepared only in moderate yield via reaction of tosyloxydec-9-ene with LiC≡CH–ethylenediamine complex[7]) via Corey–Fuchs reaction[8] in excellent yield. Stereoselective *cis*-hydroalumination of **5** by DIBAL-H and reaction of the vinyl alane thus produced with elemental iodine gave (*E*)-iodoalkene **3** as a single stereoisomer; despite extensive variation of the reaction conditions, the final step of the reaction sequence always proceeded in mediocre yield. Nevertheless, we were able to prepare significant amounts of key intermediate **3** using this synthetic sequence.

Armed with our coupling partners, we turned our attention to the crucial Stille reaction. Our initial studies on coupling of **2** and **3** were not fruitful, yielding only small amounts of coupled product and returning no starting materials. After examining a wide range of catalysts and ligands, the most efficient reaction conditions we were able to discover employed tris(dibenzylideneacetone)dipalladium(II), triphenylarsine and copper(I) iodide in DMF at ambient temperature over 20 h; using this protocol, a 46% yield of (±)-Hamabiwalactone B was obtained (Scheme 4). Our synthetic material exhibited data consistent with those previously reported for the natural product.

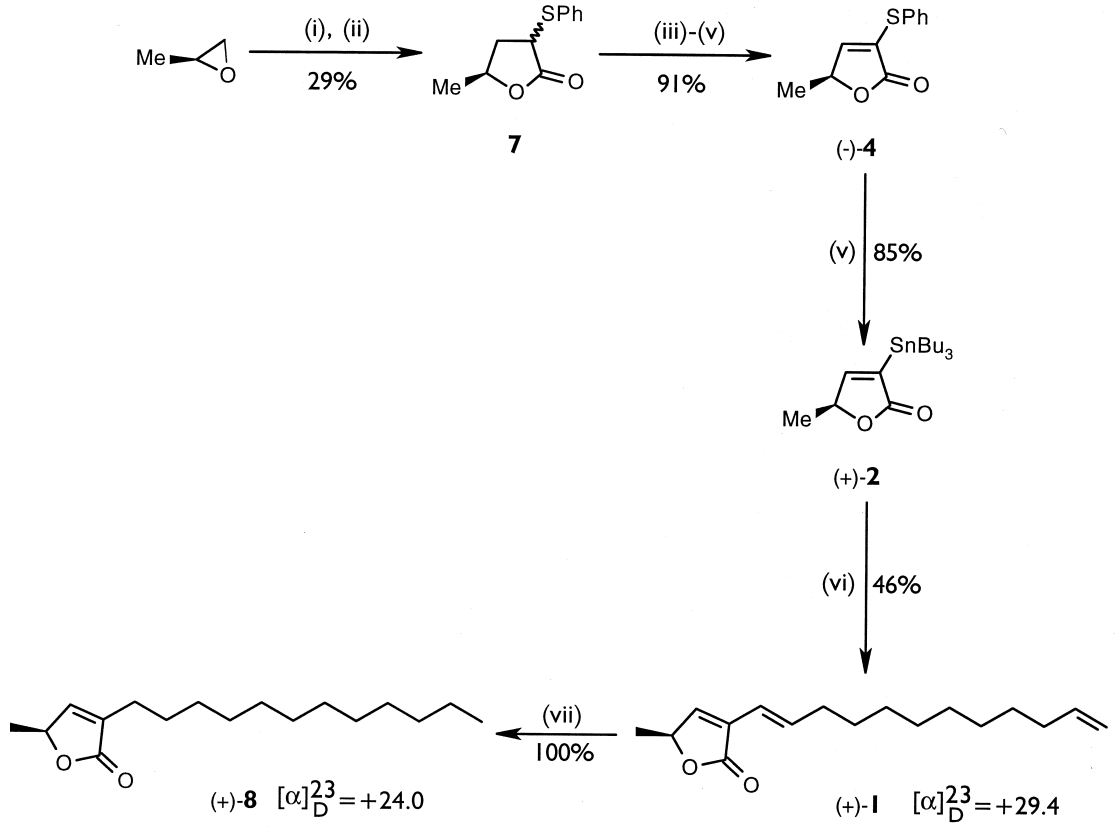
Having demonstrated the validity of our synthetic design, we immediately proceeded to attempt a first enantioselective synthesis of Hamabiwalactone-B (Scheme 5). (+)-(*S*)-5-Methyl-3-tributylstannylfuran-2(5H)-one (+)-**2**, was prepared from (−)-(*S*)-5-methyl-3-phenylsulfanyl-2(5H)-furanone (−)-**4**[9] itself prepared from (2*RS*,4*S*)-4-methyl-2-phenylsulfanylbutyrolactone **7**[9] (stereochemically homogenous at C4 but a 1:1 mixture of absolute configurations at C2) by a sequence of reactions identical to those used in the racemic synthesis. The preparation of **7** is noteworthy, in that the reported procedure for preparation



Scheme 3. Conditions: (i) CBr_4, PPh_3, Zn, CH_2Cl_2, 0°C; (ii) 2BuLi, THF, −78°C to rt; (iii) DIBAL-H, toluene, 60°C; (iv) I_2, −78°C THF.



Scheme 4. Conditions: (i) $Pd_2(dba)_3$ (0.25 mol%), $AsPh_3$ (20 mol%)$_3$, CuI (10 mol%), DMF, rt, 20 h.



Scheme 5. Conditions: (i) $PhSCH(Li)CO_2Li$, THF, 0°C; (ii) Benzene, *p*-TSA, Dean–Stark, 3 h; (iii) SO_2Cl_2, CCl_4, 0°C; (iv) LiBr, Li_2CO_3, THF, reflux; (v) Bu_3SnH, VAZO-88®, $PhCH_3$, reflux; (vi) (**3**), $Pd_2(dba)_3$, $AsPh_3$, CuI, DMF, rt, 20 h; (vii) H_2, $Pd/BaSO_4$.

of this compound, via nucleophilic ring-opening of (+)-(*S*)-propylene oxide by the dianion derived from phenylsulfanyl acetic acid as reported, does not give a clear indication of the stoichiometry required for efficient reaction ("a somewhat large excess" is the description given). Even using a five-fold equivalence of propylene oxide, the best yield we obtained for the reaction was 29%. Serendipitously, the reactions leading from sulfanyl butyrolactone **7** to stannylfuranone (+)-**2** had already been shown to proceed in good yield, and (+)-**2** was obtained in 22% overall yield from 2-phenylsulfanyl acetic acid.

When (+)-**2** was reacted with iodoalkene **3** under the conditions previously optimised in the racemic synthesis, (+)-Hamabiwalactone B was obtained. This compound exhibited $[\alpha]_D^{23}$ +29.4 (*c* 0.2 $CHCl_3$), an optical rotation of significantly greater magnitude than that reported for the natural product (+2.2 [*c* 0.32, $CHCl_3$]), but very similar to those reported for a range of other furanones bearing a C_{12}-substituent in the 3-position.[10] Analysis of our synthetic Hamabiwalactone-B using chiral HPLC[11] confirmed the stereogenic purity of our material to be ≥99%, thereby establishing the absolute stereochemistry of the single asymmetric centre of the natural product as (*S*). As further evidence in support of this deduction, we converted the natural product to 5-(*S*)-2-dodecyl-5-methyl-2(5H)-furanone **8**, whose enantiomer had previously been prepared and whose absolute configuration was proved by conversion to D-lactate.[12] The optical rotation of **8** (+24.0 [*c* 0.2, dioxan]) compared well with that of the previously reported enantiomer (−29.8 [*c* 0.2, dioxan]), reinforcing our original stereochemical assignment.

In conclusion, we have applied the Stille reaction of stannyl 2(5H)-furanones to the synthesis of (+)-Hamabiwalactone B with good effect. We are currently exploiting such reactions to the total synthesis of other naturally occurring furanones in our laboratories.

Experimental

General techniques

All organic solvents were distilled prior to use and all reagents were purified by standard procedures. 'Petrol' refers to the fraction of petroleum ether boiling within the range 40–60°C. THF was distilled from sodium benzophenone ketyl; toluene from sodium; dichloromethane, triethylamine and di-isopropylamine from calcium hydride.

Melting points were recorded on a Kofler hot-stage apparatus and are uncorrected. IR spectra were recorded on a Perkin Elmer 881 or Paragon 1000 spectrophotometer. Optical rotations were measured using a Perkin Elmer 241MC polarimeter and are quoted in 10^{-1} deg cm^2 g^{-1}. Mass spectra were recorded on a Fisons Autospec machine. ^1H and ^{13}C NMR spectra were recorded on a Jeol EX-400

spectrometer or a Bruker DPX-250 spectrometer. Unless otherwise stated, deuterochloroform was used as solvent and tetramethylsilane was used as the internal standard. Chemical shifts in ^{1}H NMR spectra are expressed as ppm downfield from tetramethylsilane, and in ^{13}C NMR, relative to the internal solvent standard. Coupling constants are quoted in Hz.

Reactions requiring anhydrous or anaerobic conditions were routinely performed under a nitrogen atmosphere in flame- or oven-dried apparatus. Flash column chromatography was performed using Merck kieselgel 60 or Fluka kieselgel 60 silica. Analytical thin layer chromatography (TLC) was performed on precoated Merck kieselgel 60 F_{254} aluminium backed plates which were visualised under UV light (254 nm), and by staining with an acidic ammonium molybdate spray.

(±)-5-Methyl-3-phenylsulfanylfuran-2(5H)-one (4). Method A. (a) A solution of 2-bromo-2-methylbutyrolactone (Aldrich) (7.5 g, 41.9 mmol) in THF (15 mL) was added dropwise over 30 min to a stirred suspension of sodium thiophenolate (6.0 g, 45.5 mmol) in THF (30 mL) cooled to 0°C. The reaction mixture was allowed to warm to ambient temperature and stirred for 72 h. The white suspension was filtered through Celite®, the filter cake washed with diethyl ether (50 mL) and the solvent removed in vacuo to give a brown oil. Purification by column chromatography (R_f 0.32, diethyl ether/petrol, 1:1) gave (±)-*cis*- and *trans*-4-methyl-2-phenylsulfanylbutyrolactone as a clear colourless oil (7.0 g, 80%), as a mixture of diastereoisomers (*cis*:*trans*=1:1). ν_{max} (neat) 1767; δ_H ($CDCl_3$) 1.33 (3H, d, *J*=6.2 Hz, diastereoisomer A), 1.37 (3H, d, *J*=6.2 Hz, diastereoisomer B), 1.83 (1H, ddd, *J*=9.1, 10.6 and 14.1 Hz, diastereoisomer A), 2.27 (1H, ddd, *J*=3.7, 8.3 and 16.1 Hz, diastereoisomer B), 2.39 (1H, ddd, *J*= 3.7, 6.2 and 16.1 Hz, diastereoisomer B), 2.74 (1H, ddd, *J*=6.2, 9.1 and 14.1 Hz, diastereoisomer A), 3.91 (1H, dd, *J*=3.7 and 8.3 Hz, diastereoisomer B), 3.99 (1H, dd, *J*=9.1 and 10.6 Hz, diastereoisomer A), 4.48–4.60 (1H, m, both diastereoisomers), 7.31–7.34 (3H, m, both diastereoisomers), 7.52–7.56 (2H, m, both diastereoisomers); *m*/*z* (EI) (Found M^+, 208.0554 (100%), $C_{11}H_{12}O_2S$ requires 208.0558).

(b) To a stirred solution of (±)-4-methyl-2-phenylsulfanylbutyrolactone (4.0 g, 20.6 mmol) in carbon tetrachloride (20 mL) cooled to 0°C was added a solution of sulfuryl chloride in carbon tetrachloride (10 mL) dropwise over 20 min. The yellow reaction mixture was stirred at 0°C for 2 h and then poured into saturated $NaHCO_3$(aq) (100 mL) (*CAUTION!*). After effervescence had subsided the mixture was extracted with dichloromethane (3×50 mL). The combined organic layers were washed with saturated $NaHCO_3$(aq) (3×50 mL), water (50 mL), saturated brine (50 mL) and dried over $MgSO_4$. The solvent was removed in vacuo to give a yellow oil. Purification by column chromatography (R_f 0.33, diethyl ether/petrol, 1:3) yielded (±)-*cis*- and *trans*-2-chloro-4-methyl-2-phenylsulfanylbutyrolactone as colourless needles (4.5 g, 96%) as a mixture of diastereoisomers (*cis*:*trans*=1:1); mp 82–83°C (pentane). ν_{max} (bromoform) 1770; δ_H ($CDCl_3$) 1.42 (3H, d, *J*=6.2 Hz, diastereoisomer A), 1.45 (3H, d, *J*=6.2 Hz, diastereoisomer B), 2.35 (1H, dd, *J*=9.2 and 14.3 Hz, diastereoisomer A), 2.49 (1H, dd, *J*=9.9 and 13.9 Hz, diastereoisomer B), 2.66 (1H, dd, *J*=5.1 and 14.3 Hz, diastereoisomer A), 2.90 (1H, dd, *J*=5.1 and 13.9 Hz, diastereoisomer B), 4.70–4.82 (1H, m, both diastereoisomers), 7.38–7.70 (5H, m, both diastereoisomers); *m*/*z* (EI) (Found M^+, 242.0161 (100%), $C_{11}H_{11}ClO_2S$ requires 242.0168).

(c) A solution of (±)-*cis*- and *trans*-2-chloro-4-methyl-2-phenylsulfanylbutyrolactone (2.6 g, 11.4 mmol) in THF (10 mL) was added to a stirred suspension of lithium bromide (3.5 g, 39.8 mmol) and lithium carbonate (2.5 g, 34.1 mmol) at ambient temperature. The reaction mixture was heated at 60°C for 1 h, cooled to ambient temperature, filtered through Celite®, the filter cake washed with diethyl ether (10 mL) and the solvent removed in vacuo to give a colourless oil. The residue was dissolved in dichloromethane (30 mL) and then washed with saturated $NaHCO_3$(aq) (30 mL), saturated brine (30 mL), dried over $MgSO_4$ and the solvent removed in vacuo. Purification by column chromatography (R_f 0.34, diethyl ether/petrol, 1:1) furnished (±)-5-methyl-3-phenylsulfanylfuran-2(5H)-one as colourless needles (2.0 g, 91%); mp 76–77°C (pentane). ν_{max} (bromoform) 1757, 1596; δ_H ($CDCl_3$) 1.38 (3H, d, *J*=6.6 Hz), 5.03 (1H, dq, *J*=1.5 and 6.6 Hz), 6.53 (1H, d, *J*=1.5 Hz), 7.42–7.43 (3H, m), 7.54–7.57 (2H, m); *m*/*z* (EI) (Found M^+, 206.0406 (64%), $C_{11}H_{10}O_2S$ requires 206.0402).

Method B. (a) To a stirred solution of (±)-4-methyl-2-phenylsulfanylbutyrolactone (7.5 g, 38.7 mmol) in dichloromethane (125 mL) cooled to 0°C was added a solution of *m*-CPBA (85%) (7.35 g, 42.6 mmol) in dichloromethane (175 mL) over 0.5 h. The reaction mixture was stirred at 0°C for 45 min and allowed to warm to ambient temperature. The solution was washed with saturated $NaHCO_3$ (2×100 mL), saturated brine (100 mL), dried over $MgSO_4$ and the solvent removed in vacuo to give a pale yellow oil which crystallised slowly. Purification by column chromatography (R_f 0.32, diethyl ether) furnished (±)-*cis*- and *trans*-4-methyl-2-phenylsulfinylbutyrolactone as colourless plates (5.1 g, 63%) as a mixture of diastereoisomers (1:1); mp 116–117°C (diethyl ether). ν_{max} (bromoform) 1760, 1141; δ_H ($CDCl_3$) 1.39 (3H, d, *J*=6.0 Hz, diastereoisomer A), 1.49 (3H, d, *J*=6.1 Hz, diastereoisomer B), 1.79 (1H, ddd, *J*=6.6, 9.2 and 14.5 Hz, diastereoisomer A), 2.02 (1H, ddd, *J*=7.7, 9.9 and 16.0 Hz, diastereoisomer B), 2.45 (1H, ddd, *J*=9.4, 9.9 and 16.0 Hz, diastereoisomer B), 2.91 (1H, ddd, *J*=5.5, 9.2 and 14.5 Hz, diastereoisomer A), 3.70 (1H, dd, *J*=5.5 and 9.2 Hz, diastereoisomer A), 3.78 (1H, dd, *J*=9.4 and 9.9 Hz, diastereoisomer B), 4.63 (1H, ddt, *J*=6.1, 8.8 and 16.0 Hz, diastereoisomer B), 4.80 (1H, ddt, *J*=6.0, 6.6 and 14.5 Hz, diastereoisomer A), 7.52–7.65 (5H, m, both diastereoisomers); *m*/*z* (EI) (Found M^+, 224.0507 (18%), $C_{11}H_{12}O_3S$ requires 224.0507).

(b) A solution of (±)-*cis*- and *trans*-4-methyl-2-phenylsulfinylbutyrolactone (0.35 g, 1.66 mmol) in acetic anhydride (5 mL) was heated at 65°C for 18 h. The reaction mixture was allowed to cool to ambient temperature and the solvent removed in vacuo to give a brown oil. Purification

by column chromatography gave (±)-5-methyl-3-phenylsulfanylfuran-2(5H)-one (**4**) as colourless needles (0.26 g, 82%). Physical data as above.

(−)-(5*S*)-5-Methyl-3-phenylsulfanylfuran-2(5H)-one (−)-(4). (a) To a solution of LDA (6.88 mmol) in THF (5 mL), cooled to 0°C, was added dropwise a solution of phenylthioacetic acid (0.58 g, 3.33 mmol) in THF (5 mL). The reaction mixture was stirred for 30 min at 0°C and became slowly opaque. The reaction mixture was then cooled to −78°C and (*S*)-propylene oxide (1.0 g, 17.2 mmol) was added in THF (3 mL). Stirring was continued for 1 h at −78°C and the reaction mixture allowed to warm to room temperature overnight. Saturated ammonium chloride solution (5 mL) was added and the solvent removed in vacuo. The residue was poured into 1N H_2SO_4 (5 mL) and the water layer extracted with diethyl ether (3×10 mL). The combined organic layers were washed with water (10 mL), brine (10 mL) and dried over $MgSO_4$. The solvent was removed in vacuo to give a brown oil. This residue was dissolved in benzene and *p*-toluene sulfonic acid (5 mg) was added. The solution was heated in a Dean–Stark apparatus for 3 h and then cooled to ambient temperature. The solvent was removed in vacuo, to give a brown oil and purification by column chromatography (R_f 0.32, diethyl ether/petrol, 1:1) gave (2*RS*,4*S*)-4-methyl-2-phenylsulfanylbutyrolactone **7**,[9] as a clear colourless oil (200 mg, 29%). ν_{max} (neat) 1767; δ_H ($CDCl_3$) 1.33 (3H, d, *J*=6.2 Hz), 1.83 (1H, ddd, *J*=9.1, 10.6 and 14.1 Hz), 2.74 (1H, ddd, *J*=6.2, 9.1 and 14.1 Hz), 3.99 (1H, dd, *J*=9.1 and 10.6 Hz), 4.48–4.60 (1H, m), 7.31–7.34 (3H, m), 7.52–7.56 (2H, m); *m*/*z* (EI) (Found M^+, 208.0554 (100%), $C_{11}H_{12}O_2S$ requires 208.0558).

(b) To a stirred solution of (4*S*)-4-methyl-2-phenylsulfanylbutyrolactone (195 mg, 0.94 mmol) in carbon tetrachloride (5 mL) cooled to 0°C was added a solution of sulfuryl chloride (0.94 g, 7.0 mmol) in carbon tetrachloride (5 mL) dropwise over 5 min. The yellow reaction mixture was stirred at 0°C for 2 h and the solvent was removed in vacuo to give a yellow oil. Purification by column chromatography (R_f 0.33, diethyl ether/petrol, 1:3) yielded (2*RS*,4*S*)-2-chloro-4-methyl-2-phenylsulfanylbutyrolactone as colourless needles (220 mg, 97%); mp 82–83°C (pentane). ν_{max} (bromoform) 1770; δ_H ($CDCl_3$) 1.42 (3H, d, *J*=6.2 Hz), 2.35 (1H, dd, *J*=9.2 and 14.3 Hz), 2.66 (1H, dd, *J*=5.1 and 14.3 Hz), 4.70–4.82 (1H, m), 7.38–7.70 (5H, m); *m*/*z* (EI) (Found M^+, 242.0161 (100%), $C_{11}H_{11}ClO_2S$ requires 242.0168).

(c) A solution of (+)-(2*RS*,4*S*)-2-chloro-4-methyl-2-phenylsulfanylbutyrolactone (200 mg, 0.83 mmol) in THF (5 mL) was added to a stirred suspension of lithium bromide (0.34 g, 3.8 mmol) and lithium carbonate (0.24 g, 3.3 mmol) at ambient temperature. The reaction mixture was heated at 60°C for 1 h, cooled to ambient temperature, filtered through Celite®, the filter cake washed with diethyl ether (10 mL) and the solvent removed in vacuo to give a colourless oil. The residue was purified by column chromatography (R_f 0.34, diethyl ether/petrol, 1:1) furnishing (−)-(5*S*)-5-methyl-3-phenylsulfanylfuran-2(5H)-one (−)-(**4**) as colourless needles (160 mg, 94%). The physical data exhibited was identical to that of the racemic material, with the addition that $[\alpha]_D^{24}=-26.6$ (*c* 1.0 $CHCl_3$).

(±)-5-Methyl-3-tributylstannylfuran-2(5H)-one (±)-(2). To a stirred solution of (±)-5-methyl-4-phenylsulfanylfuran-2(5H)-one (+)-(**4**) (0.50 g, 2.6 mmol) in deoxygenated toluene (20 mL) was added tributyltin hydride (1.5 mL, 5.2 mmol) and VAZO-88® (20 mg). The mixture was heated to 100°C for 4 h. The solvent was removed in vacuo to give a cloudy oil. Purification by column chromatography using gradient elution (R_f 0.38, petrol then diethyl ether/petrol, 1:3) afforded (±)-(5*S*)-5-methyl-3-tributylstannylfuran-2(5H)-one (±)-(**2**) as a clear colourless oil (0.87 g, 89%). ν_{max} (neat) 2953, 2869, 2850, 1735, 1582, 1463, 1147, 1115; δ_H ($CDCl_3$) 0.85–0.89 (9H, m), 0.97–1.34 (12H, m), 1.38 (3H, d, *J*=6.6 Hz), 1.42–1.60 (6H, m), 5.05 (1H, br q, *J*=6.6 Hz), 7.44 (1H, ddd, $^3J_{H-H}$=1.1 Hz, $^3J_{H-Sn}$=11.0 and 9.9 Hz); δ_C ($CDCl_3$) 9.6, 13.6, 19.2, 27.1, 28.8, 81.2, 134.7, 166.6, 177.8; *m*/*z* (CI) (Found $(M-Bu)^+$, 331.0726 (100%), $C_{13}H_{23}O_2Sn$ requires 331.0720, 270 (70), 216 (43), 176 (20).

(+)-(5*S*)-5-Methyl-3-tributylstannylfuran-2(5H)-one (+)-(2). The procedure above was employed using (−)-5-methyl-4-phenylsulfanylfuran-2(5H)-one (−)-(**4**) (150 mg, 0.73 mmol), tributyltin hydride (0.45 mL, 5.2 mmol) and VAZO-88® (2 mg). (+)-(5*S*)-5-Methyl-3-tributylstannylfuran-2(5H)-one (**2**) was obtained as a clear colourless oil (0.24 g, 85%). The physical data were identical to that obtained for the racemic material, with the addition that $[\alpha]_D^{23}=+27.9$ (*c* 1.0 $CHCl_3$).

1-Dodecen-11-yne (6). (a) Carbon tetrabromide (7.14 g, 21.5 mmol), triphenylphosphine (5.63 g, 21.5 mmol) and zinc powder (1.4 g, 21.5 mmol) were combined, cooled to 0°C and dichloromethane (100 mL) added to form a green suspension. The mixture was allowed to warm to ambient temperature and stirred for 18 h. To the now pink suspension, 10-undecenal (2.23 mL, 10.75 mmol) was added and the mixture stirred at ambient temperature for 3 h. The purple solution was poured into pentane (200 mL) and filtered through Celite®, the residue was solubilised in dichloromethane (20 mL). Pentane (50 mL) was added to reprecipitate solids, and the mixture refiltered through Celite®. The combined filtrates were pooled and the solvent removed in vacuo, to leave a colourless oil with a white solid present. Pentane (5 mL) was added and the solid triphenylphosphine oxide precipitated and removed by filtration. Removal of the solvent in vacuo and purification by column chromatography (R_f 0.73, pentane) afforded 1,1-dibromo-1,11-dodecadiene as a colourless liquid (3.3 g, 93%). ν_{max} (neat) 3074, 2924, 2853, 1640, 1463, 1440, 992, 910; δ_H ($CDCl_3$) 1.29–1.43 (12H, m), 2.05 (2H, br dd, *J*=6.8 and 7.3 Hz), 2.09 (2H, dd, *J*=7.3 and 7.3 Hz), 4.94 (1H, ddd, *J*=1.0, 1.5 and 10.3 Hz), 5.00 (1H, dd, *J*=1.0, 1.5 and 16.3 Hz), 5.83 (1H, ddt *J*=6.8, 10.3 and 16.3 Hz), 6.40 (1H, t, *J*=7.3 Hz); δ_C ($CDCl_3$) 27.7, 28.9, 29.0, 291, 29.2, 29.3, 33.2, 33.8, 88.5, 114.1, 138.9, 139.1; *m*/*z* (EI) (Found $(M)^+$, 323.9918 (4%), $C_{12}H_{20}Br_2$ requires 323.9932, 211 (40), 81 (85), 55 (100).

(b) To a stirred solution of 1,1-dibromo-1,11-dodecadiene (3.2 g, 9.8 mmol) in THF (10 mL) cooled to −78°C was

added a 2.5M solution of *n*-butyllithium in hexanes (7.9 mL, 19.7 mmol) dropwise over 15 min. The reaction mixture was stirred for 1 h at −78°C then allowed to warm to ambient temperature over 1 h. Water (20 mL) was added and the mixture extracted with pentane (3×20 mL). The combined organic extracts were washed with saturated brine (20 mL), dried over $MgSO_4$, and the solvent removed in vacuo to give a yellow oil. Purification by column chromatography (R_f 0.40, pentane) yielded 1-dodecen-11-yne (**6**) as a colourless liquid (1.6 g, 96%). ν_{max} (neat) 3311, 1641, 910; δ_H ($CDCl_3$) 1.29–1.49 (m, 12H), 1.93 (1H, t, *J*=2.6 Hz), 2.00 (2H, dd, *J*=7.0 and 7.0 Hz), 2.18 (2H, dt, *J*=2.6 and 7.0 Hz), 4.92 (1H, dd, *J*=1.1 and 10.32 Hz), 4.98 (1H, dd *J*=1.1 and 16.82 Hz), 5.81 (1H, ddt, *J*=7.0, 10.3 and 16.8 Hz); δ_C ($CDCl_3$) 18.3, 22.3, 28.4, 28.7, 28.9, 29.0, 29.3, 33.7, 68.0, 84.4, 114.1, 138.9; *m*/*z* (EI) (Found $(M)^+$, 164.1560 (18%), $C_{12}H_{20}$ requires 164.1565).

(*E*)-1-Iodo-1,11-dodecadiene (3). To a stirred solution of 1-dodecen-11-yne (**7**) (394 mg, 2.4 mmol) in toluene (5 mL) at ambient temperature was added DIBAL-H (1.5 M solution in toluene, 1.76 mL). The reaction mixture was stirred at ambient temperature for 15 min then heated to 50°C for 6 h. The solution was cooled to −50°C and iodine (0.67 g, 2.64 mmol) in THF (5 mL) was added dropwise over 15 min. The reaction mixture was then allowed to warm to ambient temperature overnight. Saturated sodium sulfate solution (0.5 mL) was added and the mixture was filtered, dried over $MgSO_4$, and the solvent removed in vacuo to give a colourless liquid. Purification by column chromatography (R_f 0.55, pentane) furnished (*E*)-1-iodo-1,11-dodecadiene (**3**), as a colourless liquid (260 mg, 37%). ν_{max} (neat) 3073, 2973, 2923, 1640, 1606, 1465, 1439, 992, 910; δ_H ($CDCl_3$) 1.28–1.38 (12H, m), 2.05 (4H, 2dd, *J*=7.3 and 14.3 Hz), 4.94 (1H, ddd, *J*=1.0, 1.5 and 10.3 Hz) 5.00 (1H, ddd, *J*=1.0, 1.5 and 16.8 Hz), 5.81 (1H, ddt, *J*=6.6, 10.3 and 16.8 Hz), 5.98 (1H, dt, *J*=1.5 and 14.3 Hz) 6.52 (1H, dt, *J*=7.3 and 14.3 Hz); δ_C ($CDCl_3$) 28.3, 28.9, 29.0, 29.3, 29.3, 29.6, 33.8, 36.0, 74.3, 114.1, 139.1, 146.7; *m*/*z* (CI) (Found $(M)^+$, 292.0709 (10%), $C_{12}H_{21}I$ requires 292.0688, 180 (56), 167 (44), 109 (38), 81 (70), 67 (69), 55 (100).

(±)-Hamabiwalactone B (1). To a stirred solution of (*E*)-1-iodo-1,11-dodecadiene (**3**) (90 mg, 0.284 mmol), triphenylarsine (20 mg, 20 mol%) and copper(I) iodide (10 mg, 10 mol%) in deoxygenated DMF (5 mL) was added (±)-5-methyl-3-tributylstannyl-furan-2(5H)-one (**2**) (105 mg, 0.258 mmol) in deoxygenated DMF (5 mL). To this mixture was added tris(dibenzylideneacetone)dipalladium(0) (3 mg, 0.25 mol%), upon which the initially deep purple solution turned deep brown in colour. The mixture was stirred overnight at ambient temperature. Removal of the solvent in vacuo and purification by column chromatography (R_f 0.32, diethyl ether/petrol, 1:3) gave (±)-Hamabiwalactone B as a colourless, clear viscous oil (31 mg, 46%). ν_{max} (neat) 1755, 1656, 1641, 1624; δ_H ($CDCl_3$) 1.28 (12H, br s), 1.42 (3H, d, *J*=6.6 Hz), 2.04 (2H, dd, *J*=7.0 and 14.0 Hz), 2.16 (2H, q, *J*=7.3 and 14.3 Hz), 4.91–5.05 (3H, m), 5.81 (1H, ddt, *J*=6.6, 10.3 and 16.8 Hz), 6.09 (1H, d, *J*=15.8 Hz), 6.79 (1H, d, *J*=7.0 and 15.8 Hz), 7.03 (1H, d, *J*=1.5 Hz); δ_C ($CDCl_3$) 19.3, 28.8, 28.9, 29.2, 29.4, 29.7, 29.8, 33.4, 33.8, 76.9, 114.1, 118.3, 129.4, 138.9, 139.2, 146.8, 172.0; *m*/*z* (EI) (Found $(M)^+$, 262.1945 (9%), $C_{17}H_{26}O_2$ requires 262.1930), 217 (6), 150 (10), 137 (30), 93 (58).

(+)-(5*S*)-Hamabiwalactone B (1). Following the procedure above, using (+)-(5*S*)-5-methyl-3-tributylstannyl-2(5H)-furanone in place of the racemate, (+)-(5*S*)-Hamabiwalactone B was obtained as a colourless, clear viscous oil (31 mg, 46%). The compound exhibited identical physical data to that obtained for the racemate, with the addition that $[\alpha]_D^{23}$=+29.4 (*c* 0.2 $CHCl_3$).

(+)-(5*S*)-3-Dodecyl-5-methylfuran-2(5H)-one (8). (+)-Hamabiwalactone (10 mg) was placed in hexane (5 mL) and palladium(0) on barium sulfate (1 mg) was added. The argon atmosphere was replaced by hydrogen and the mixture stirred at ambient temperature and atmospheric pressure for 2 min after which 2 equiv. of hydrogen had been consumed. The mixture was filtered through Celite® and the solvent removed in vacuo. Purification by column chromatography (R_f 0.32, diethyl ether/petrol, 1:3) afforded (+)-(5*S*)-3-dodecyl-5-methylfuran-2(5H)-one (**8**), as colourless needles (10 mg, 100%); mp 50°C (pentane). $[\alpha]_D^{25}$=+24.0 (*c* 0.2 dioxane); ν_{max} (bromoform) 1748, 1653; δ_H ($CDCl_3$) 0.89 (3H, t, *J*=6.2 Hz), 1.27 (20H, br s), 1.40 (3H, d, *J*=6.8 Hz), 2.28 (2H, tt, *J*=1.5 and 8.0 Hz), 5.00 (1H, qq, *J*=1.5 and 6.2 Hz), 7.00 (1H, q, *J*=1.5 Hz); δ_C ($CDCl_3$) 14.5, 19.6, 21.6, 25.1, 27.4, 27.8, 28.8, 28.9, 29.2, 29.4, 29.7, 29.8, 31.9, 77.3, 139.3, 148.8, 173.9; *m*/*z* (EI) (Found $(M)^+$, 266.2249 (57%), $C_{17}H_{30}O_2$ requires 266.2246), 221 (9), 153 (10), 139 (30), 112 (100), 69 (47), 55 (69).

Acknowledgements

We thank the University of Bristol (part-funding to A.M.E.R.), the Nuffield Foundation and ZENECA (award from Strategic Research Fund to J.B.S.) for financial support. The long-standing advice and guidance provided by Mr Glen Buchman is also gratefully and respectfully acknowledged.

References

1. Marshal, P. G. In *Rodd's Chemistry of Carbon Compounds*, 2nd ed.; Elsevier: New York, 1970; Vol. II, Part D, p 369; Knight, D. W. *Contemporary Organic Synthesis* **1994**, *1*, 287.
2. Hollingworth, G. J.; Perkins, G.; Sweeney, J. B. *J. Chem. Soc., Perkin Trans. 1* **1996**, 1913; Hollingworth, G. J.; Richecœur, A. M. E.; Sweeney, J. B. *J. Chem. Soc., Perkin Trans. 1* **1996**, 2833.
3. Richecœur, A. M. E.; Sweeney, J. B. *Tetrahedron Lett.* **1998**, *39*, 8901.
4. Tanaka, H.; Nakamura, T.; Ichino, K.; Ito, K.; Tanaka, T. *Phytochemistry* **1990**, *29*, 857.
5. Iwai, K.; Kosogi, H.; Uda, H.; Kawai, M. *Bull. Chem. Soc. Jpn.* **1977**, *50*, 242.
6. Bestmann, H. J.; Rippel, H. C.; Dostalek, R. *Tetrahedron Lett.* **1989**, *30*, 5261.
7. Taylor, S.; Hopkins, J. A.; Spangenberg, K. A.; Millen, D. W.; Grutzner, J. B. *J. Org. Chem.* **1991**, *56*, 5951.
8. Corey, E. J.; Fuchs, P. L. *Tetrahedron Lett.* **1972**, *14*, 3769.
9. Nokami, J.; Ono, T.; Kajitani, Y.; Wakabayashi, S. *Chem. Lett.*

1984, 707; Iwai, K.; Kawai, M.; Kosugi, H.; Uda, H. *Chem. Lett.* **1974**, 385.
10. Martinez, J. C.; Yoshida, M.; Gottlieb, O. R.; *Phytochemistry* **1981**, *20*, 59; Viera, P. C.; Yoshida, M.; Gottlieb, O. R.; Filho, H. F. P.; Nagem, T. J.; Filho, R. B. *Phytochemistry* **1983**, *22*, 711; Ortuno, R. M.; Bigorra, J.; Font, J. *Tetrahedron* **1988**, *44*, 5139; Nishide, K.; Aramata, A.; Kamanaka, T.; Inoue, T.; Node, M. *Tetrahedron* **1994**, *28*, 8337; Chaves, H. M.; Roque, N. F. *Phytochemistry* **1997**, *44*, 523.
11. Column: Chiralcel OB (25 cm×4.6 mm); Mobile phase: hexane/isopropyl alcohol (90:10); Detector: UV λ 250 nm, Ab 0.64 Å; Flow: 2 ml/min; Load: 10 μl of 1 mg/ml solution in mobile phase.
12. Takeda, K.; Sakurawi, K.; Ishii, H. *Tetrahedron* **1972**, *28*, 3757.