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PAPER

Concise synthesis of the C-1–C-12 fragment of amphidinolides T1–T5†

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The C-1–C-12 segment of the amphidinolides T1–T5 has been synthesised in an efficient manner. The key transformations are highly diastereoselective rearrangement of an oxonium ylide, or metal-bound ylide equivalent, produced by intramolecular reaction of a copper carbenoid with an allylic ether, and macrocyclic fragment coupling by one-pot ring-closing metathesis and hydrogenation.

Introduction

The amphidinolides are marine natural products produced by dinoflagellates of the genus *Amphidinium* that have a symbiotic relationship with flatworms of the *Amphiscolops* species.[1] More than 30 amphidinolides have been isolated and several of them display potent cytotoxic activity.[1] However, the full biological profiles of many members of this family of natural products have not been established due to their relatively low natural abundance.

The isolation and characterisation of amphidinolides T1–T5 was first reported by Kobayashi and co-workers in 2000 and 2001 (Fig. 1).[1] Although they are not the most bioactive members of the family,[1] amphidinolides T1–T5 do display significant cytotoxic activity. They are also more structurally complex than many of the other amphidinolides and are particularly attractive synthetic targets because of their unusual structures. Amphidinolides T1–T5 possess seven stereogenic centres around the macrocyclic core and amphidinolide T2 possesses an additional stereogenic centre in its side chain (C-21). It is noteworthy that the amphidinolides T3–T5 are diastereomers, with differing configurations at C-12 and C-14, and amphidinolides T1 and T3 have a regioisomeric relationship resulting from reversal of the α-hydroxy ketone functionality at C-12 and C-13.

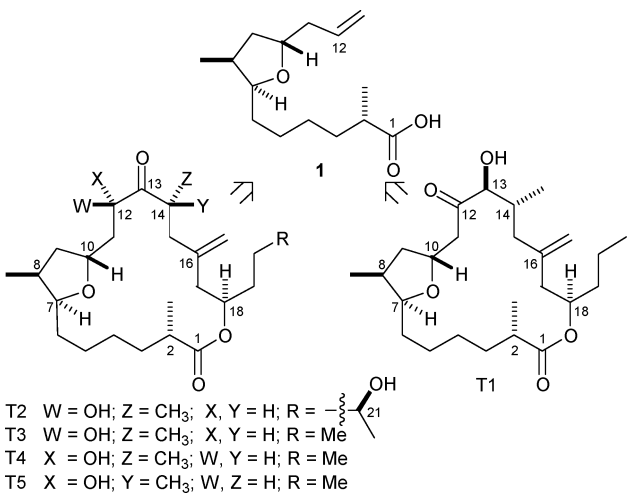

Fig. 1 Amphidinolides T1–T5 and the key fragment **1**.

Members of the amphidinolides T series have been very popular synthetic targets.[2] Fürstner and co-workers were the first to complete a total synthesis of a member of the amphidinolide T series—amphidinolide T4—in 2002 and subsequently synthesised amphidinolides T1, T3 and T5 using the same general strategy.[3,4] The groups of Ghosh (T1),[5] Jamison (T1, T4),[6] Zhao (T3),[7] Yadav (T1)[8] and, very recently, Dai (T2)[9] have also completed syntheses of members of the amphidinolide T series. However, a general modular approach, that would allow these compounds to be prepared from a common late-stage intermediate, has yet to be developed.

Results and discussion

As part of our programme concerning the total synthesis of marine natural products, we have become interested in devising a novel, general and efficient synthetic route to the amphidinolides T1–T5. This route would allow most of the compounds to be accessed by regioselective and stereoselective functionalisation at the C-12 and C-13 positions of a common macrolide intermediate. At the outset, we wished to use our oxonium ylide rearrangement methodology to construct the highly substituted tetrahydrofuran core,[10] and combine this transformation with ring-closing metathesis (RCM) reactions for macrocylic fragment coupling and formation of the complete macrolactone core of the natural products.

In most published syntheses of members of the amphidinolide T series, macrocycle formation is accomplished either by construction of the C-4–C-5 bond using RCM[3,4] or by macrolactonisation at C-1.[5,7,8] In contrast, we intend to adopt a less conventional approach and effect final ring closure by construction of the C-12–C-13 bond.[9] To accomplish this bond-forming reaction, we require

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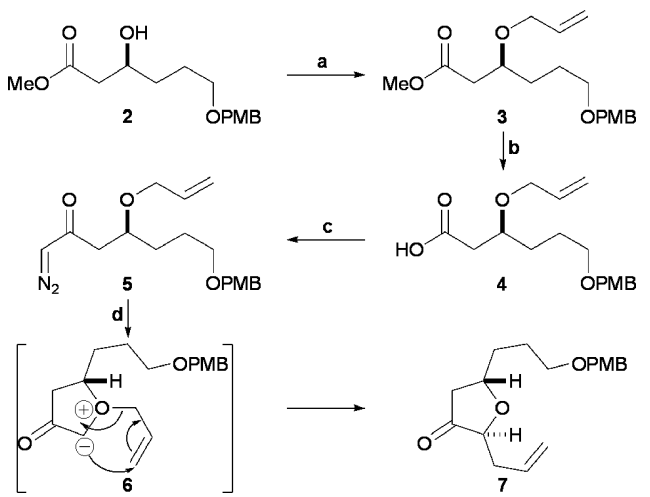
† Electronic supplementary information (ESI) available: ^{1}H and ^{13}C NMR spectra for compounds **1–3**, **5**, **7**, **13–16a**, **17**, **18**. CCDC reference number 799191. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c1ob05130j

ready access to the carboxylic acid **1**, a compound that corresponds to the C-1–C-12 fragment common to all the amphidinolides of the T series and has been used as an intermediate in several other syntheses of these natural products.[6]

The synthesis of the C-1–C-12 fragment commenced with β-hydroxy ester **2** which was prepared with >94% ee by Noyori reduction of methyl 6-[(4-methoxyphenyl)methoxy]-3-oxohexanoate (Scheme 1).[11,12] *O*-Allylation was performed by palladium-catalyzed reaction of the alcohol **2** with allyl ethyl carbonate. The resulting ester **3** was saponified to give the carboxylic acid **4** and this was converted into the diazo ketone **5** by mixed anhydride formation and reaction with diazomethane. Conversion of the ester **3** into the diazo ketone **5** was achieved with an overall yield of 85%.



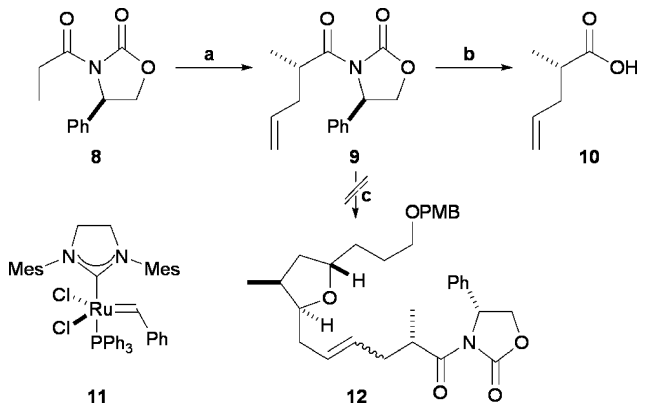
Scheme 1 *Reagents and conditions*: **a** $Pd_2(dba)_3$, dppb, $EtO_2COCH_2CHCH_2$, THF, reflux [84%]; **b** LiOH aq., THF, MeOH, rt; **c** (i) *i*-BuO_2CCl, Et_3N, Et_2O, rt, (ii) CH_2N_2, Et_2O, 0 °C → rt [85% from **3**]; **d** $Cu(acac)_2$, THF, reflux [90%, >97 : 3].

The key reaction in our synthetic route—diastereoselective dihydrofuranone formation—was accomplished by generation of a copper carbenoid from the diazo ketone **5**, followed by formation and subsequent [2,3] sigmatropic rearrangement of the free oxonium ylide **6** or its metal-bound equivalent (Scheme 1).[10] This transformation resulted in high-yielding formation of the ketone **7** as a single diastereomer as judged by NMR analysis.[10a]

The C-1–C-4 fragment was prepared from the acyl oxazolidinone **8** using standard alkylation conditions (Scheme 2).[13,4] Deprotonation of the acyl oxazolidinone **8** and reaction of the resulting enolate with allyl iodide afforded the alkylated product **9**. Cleavage of the chiral auxiliary using the Evans protocol[14] afforded the known carboxylic acid **10**.[4]

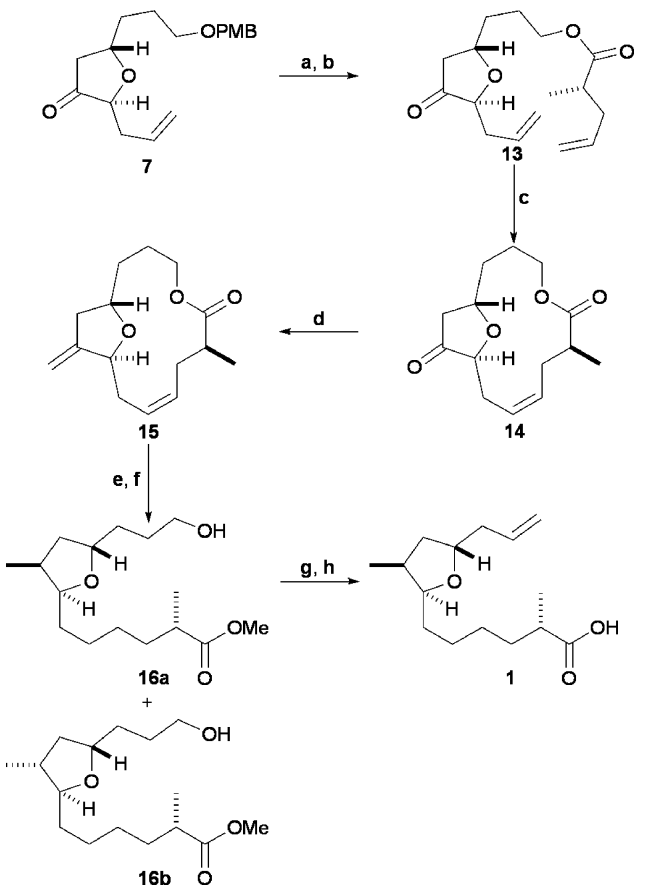
The first option was to couple the alkylated acyl oxazolidinone **9** to the allyl-substituted dihydrofuranone **7** using an alkene cross-metathesis reaction mediated by the Grubbs second-generation ruthenium catalyst (**11**).[15] However, dimeric products were obtained instead of the coupled alkene **12**, a result consistent with the finding of others that partial reaction and recycling of starting material is necessary when performing analogous cross-metathesis reactions.[5]

In order to circumvent the problematic cross-metathesis reaction, fragment coupling by intramolecular diene metathesis



Scheme 2 *Reagents and conditions*: **a** $NaN(SiMe_3)_2$, THF, −78 °C then CH_2CHCH_2I, −78 °C → rt [82%]; **b** LiOH aq., H_2O_2, THF–H_2O [100%]; **c** **7**, **11**, CH_2Cl_2, reflux.

was explored. The requisite RCM substrate **13** was prepared by removal of the PMB group from the dihydrofuranone **7** and esterification of the resulting alcohol with the carboxylic acid **10** (Scheme 3).[16] Reaction of the resulting diene **13** with the complex **11** in 1,2-dichloroethane at reflux resulted in RCM and afforded a mixture of the lactone **14** and a small amount of



Scheme 3 *Reagents and conditions*: **a** DDQ, CH_2Cl_2–H_2O, rt [93%]; **b** **10**, EDC, CH_2Cl_2, rt [70%]; **c** **11**, $Cl(CH_2)_2Cl$, reflux [72%; 15 : 1, *Z* : *E*]; **d** $Ph_3P^+CH_3\ Br^-$, $NaN(SiMe_3)_2$, THF, rt [98%]; **e** $(Ph_3P)RhCl$, H_2, PhMe, rt; **f** NaOMe, MeOH–THF, 0 → 60 °C [77% over two steps; **16a**:**16b**, 4.5 : 1]; **g** (i) *o*-$O_2NC_6H_4SeCN$, *n*-Bu_3P, CH_2Cl_2, rt, (ii) H_2O_2, rt [77%]; **h** LiOH, THF–H_2O [84%].

the *E* isomer (72%; 15 : 1, *Z* : *E*), which were not separated at this stage. The lactone **14** is crystalline and X-ray analysis of this compound confirmed our relative stereochemical assignments (Fig. 2).‡

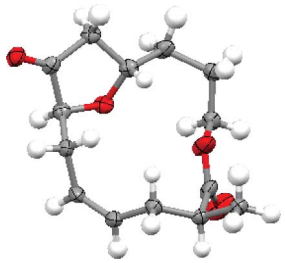


Fig. 2 The X-ray crystal structure of the lactone **14**.

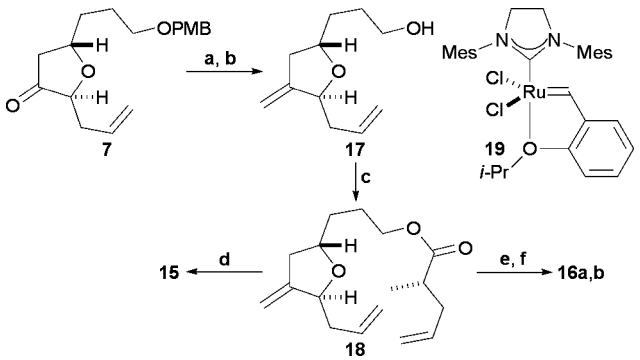
Methylenation of the keto-lactone **14** afforded the diene **15** as a mixture (3 : 1) of conformational isomers. Subsequent hydrogenation using Wilkinson's catalyst afforded a mixture of C-8 diastereomers (4.5 : 1 ratio) favouring the required diastereomer (Scheme 3). The macrolactone was then opened with sodium methoxide to give a mixture of the diastereomeric hydroxy esters **16a** and **16b** (4.5 : 1 ratio).

The structure of the major hydrogenation product was confirmed by conversion of the alcohol **16a** into the required carboxylic acid **1** (Scheme 3). Thus, reaction of the alcohol **16a** with *o*-nitrophenyl selenocyanate in the presence of tri-*n*-butylphosphine, under conditions described by Grieco,[17] followed by treatment of the resulting selenide with hydrogen peroxide resulted in selenoxide formation and elimination. Subsequent ester saponification using lithium hydroxide delivered the known carboxylic acid **1**.[6b] The structure of the acid **1** was confirmed by comparison of its data to that of authentic material.[6b]

After completing the synthesis of **1**, we established that it was possible to increase the efficiency of the route by combining the metathesis and hydrogenation reactions in a one-pot process (Scheme 4).[18] Thus, methylenation of the ketone **7** followed by removal of the PMB group afforded the alcohol **17**. Esterification of the alcohol **17** with the carboxylic acid **10** afforded the ester **18** and subsequent RCM with the Grubbs second-generation catalyst (**11**) afforded the diene **15** which was converted into the carboxylic acid **1** as before (Scheme 3). One-pot metathesis and hydrogenation using the Hoveyda–Grubbs second generation catalyst (**19**) followed by treatment of the resulting lactone with sodium methoxide delivered the esters **16a** and **16b** (4 : 1 ratio) in good yield. The level of diastereocontrol during hydrogenation was similar to that obtained when the diene **15** was hydrogenated using Wilkinson's catalyst (Scheme 3).

Conclusions

In summary, we have completed a stereoselective 11-step synthesis of the C-1–C-12 segment **1** found in the amphidinolides T1–T5 from the β-hydroxy ester **2**. The features of the route are the construction of the highly substituted tetrahydrofuran core by rearrangement of a catalytically generated oxonium ylide, or metal-bound ylide equivalent, and the deployment of a one-pot RCM and hydrogenation reaction to accomplish fragment coupling by macrolactone formation.



Scheme 4 *Reagents and conditions*: **a** $Ph_3P^+CH_3\ Br^-$, $NaN(SiMe_3)_2$, THF, rt [98%]; **b** DDQ, CH_2Cl_2–H_2O, rt [81%]; **c 10**, EDC, CH_2Cl_2, rt [86%]; **d 11**, $Cl(CH_2)_2Cl$, reflux [84%]; **e 19**, $Cl(CH_2)_2Cl$, reflux then H_2 (100 psi), 70 °C; **f** NaOMe, MeOH–THF, 60 °C [64% over two steps; 4 : 1, **16a** : **16b**].

Experimental

Methyl (*S*)-3-hydroxy-6-(4-methoxybenzyloxy)hexanoate (2)

The complex $[RuCl_2(benzene)]_2$ (5.4 mg, 1.07 μmol) and (*S*)-(−)-2,2′-bis(diphenylphosphino)-1,1′-binaphthalene (13.8 mg, 2.22 μmol) were dissolved in dry degassed DMF (0.5 mL)§ in a 5 mL vial. The mixture was stirred at 110 °C for 20 min and DMF was removed by vacuum distillation (200 mbar) at 50 °C. A solution of 6-[(4-methoxyphenyl)methoxy]-3-oxohexanoate (1.00 g, 3.57 mmol) in dry degassed methanol (2.0 mL)§ was added. The vial was transferred to a hydrogenation autoclave and the vessel was then purged three times with hydrogen. The reaction mixture was stirred at 95 °C under hydrogen (5 bar) for 18 h and then cooled to room temperature. The mixture was concentrated under reduced pressure and the residue was purified by flash chromatography on silica gel (gradient elution with petroleum ether and then petroleum ether–diethyl ether, 1 : 1) to give the ester **2** (912 mg, 91%) as a colourless oil. The enantiomeric excess of the product was determined by chiral HPLC and found to be 94% ee. R_f 0.27; (petroleum ether–diethyl ether, 1 : 3); HPLC: t_R (*S*-enantiomer) = 15.0 min, t_R (*R*-enantiomer) = 12.1 min (Chiracel OD–H, *n*-hexane–*i*-propanol, 9 : 1; 1.0 mL min^{-1}; oven temp. 25.0 °C); $[\alpha]_D^{26}$ +8.0 (*c* 1.1, $CHCl_3$); ν_{max} 3437, 2951, 2859, 1732, 1613, 1512, 1246, 1173, 1092, 1034, 818 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.50–1.82 (4H, m), 2.44 (1H, dd, J = 16.0, 8.0 Hz), 2.49 (1H, dd, J = 16.0, 4.4 Hz), 3.29 (1H, d, J = 4.0 Hz), 3.48 (2H, t, J = 6.1 Hz), 3.70 (3H, s), 3.80 (3H, s), 3.98–4.06 (1H, m), 4.44 (2H, s), 6.87 (2H, d, J = 8.4 Hz), 7.25 (2H, d, J = 8.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 26.3, 34.1, 41.7, 52.1, 55.6, 68.2, 70.2, 73.0, 114.1, 129.7, 130.6, 159.4, 173.6; LRMS (EI) m/z (intensity); 282 $[M]^+$ (6), 121 (100), 137 (78), 77 (25); HRMS (EI)

‡ The crystallographic data (excluding structure factors) for the lactone **14** have been deposited (CCDC 799191) with the Cambridge Crystallographic Data Centre. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK [fax: +44(0) 1223 336033, e-mail: deposit@ccdc.cam.ac.uk].

§ The Ru–BINAP catalyst is extremely sensitive to water and oxygen so all the glassware was flame-dried and the solvents degassed by two freeze–thaw cycles.

calcd for $C_{15}H_{22}O_5$ [M^+]: 282.1467, found: 282.1463. Anal. calcd for $C_{15}H_{22}O_5$: C, 63.81%; H, 7.85%. Found: C, 63.44%; H, 7.93%.

Methyl (*S*)-6-(4-methoxybenzyloxy)-3-(prop-2-en-1-yloxy)hexanoate (3)

Tris(dibenzylideneacetone)dipalladium(0) (8.50 mg, 9.28 μmol) and bis(diphenylphosphino)butane (15.4 mg, 36.1 μmol) were dissolved in degassed anhydrous THF (1.0 mL) followed by addition of allyl ethyl carbonate (180 μL, 1.37 mmol). To the green mixture was added by syringe, a degassed solution of the β-hydroxy ester **2** (106 mg, 0.34 mmol) in anhydrous THF (2.0 mL). The solution was then heated to 70 °C for 16 h. The resulting mixture was concentrated under reduced pressure and the residue was purified by flash chromatography on silica gel (dichloromethane–methanol, 99.5 : 0.5) to give the allyl ether **3** (102 mg, 84%) as a colourless oil: R_f 0.21 (dichloromethane–methanol, 99.5 : 0.5); R_f 0.75 (petroleum ether–diethyl ether, 1 : 3); $[\alpha]_D^{26}$ +5.6 (*c* 1.0, $CHCl_3$); ν_{max} 2953, 2923, 2854, 1737, 1613, 1513, 1458, 1247, 1172, 1097, 1036, 819 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.57–1.75 (4H, m), 2.43 (1H, dd, *J* = 15.0, 5.8 Hz), 2.57 (1H, dd, *J* = 15.0, 7.3 Hz), 3.45 (2H, t, *J* = 5.5 Hz), 3.68 (3H, s), 3.77–3.84 (1H, m), 3.80 (3H, s), 3.99 (2H, dddd, *J* = 5.5, 2.7, 1.6, 1.3 Hz), 4.43 (2H, s), 5.14 (1H, ddt, *J* = 10.3, 1.7, 1.3 Hz), 5.24 (1H, ddt, *J* = 17.2, 1.7, 1.6 Hz), 5.87 (1H, ddt, *J* = 17.2, 10.3, 5.6 Hz), 6.88 (2H, d, *J* = 9.1 Hz), 7.25 (2H, d, *J* = 9.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.6, 31.2, 39.9, 51.8, 55.4, 70.0, 70.7, 72.7, 75.7, 113.9, 117.0, 129.4, 130.7, 135.1, 159.3, 172.3; LRMS (EI) *m*/*z* (intensity): 322 $[M]^+$ (20), 121 (100), 190 (91), 137 (88), 143.1 (86); Anal. calcd for $C_{18}H_{26}O_5$: C, 67.06%; H, 8.13%. Found: C, 67.22%; H, 8.25%.

(*S*)-1-Diazo-7-(4-methoxybenzyloxy)-4-(prop-2-en-1-yloxy)heptan-2-one (5)

The methyl ester **3** (2.07 g, 6.40 mmol) was dissolved in a mixture of methanol (40 mL) and THF (60 mL). A solution of lithium hydroxide (3.78 g, 157 mmol) in water (25 mL) was added and the resulting mixture was stirred at room temperature for 1.5 h. The reaction was quenched by the addition of 1 M aqueous hydrochloric acid solution (200 mL) and diluted with EtOAc (150 mL). The layers were separated and the aqueous phase was extracted with EtOAc (3 × 150 mL). The combined organic phases were washed with brine (300 mL) and dried ($MgSO_4$) then concentrated under reduced pressure to give the carboxylic acid **4** (2.02 g), which was used without purification.

A portion of the carboxylic acid **4** (171 mg, 0.55 mmol) was dissolved in dry diethyl ether (6.0 mL) and *i*-butyl chloroformate (80.0 μL, 0.61 mmol) was added. Triethylamine (90 μL, 0.65 mmol) was added carefully to the reaction mixture and it was stirred at room temperature for 2 h. The resulting suspension was filtered and the filtrate was added directly to a freshly prepared ethereal solution of diazomethane (approximately 5 mmol in 20 mL of diethyl ether) at 0 °C, with protection of the flask from light. The mixture was stirred at 0 °C for 2 h and allowed to warm to room temperature then stirred for 14 h. Glacial acetic acid (0.60 mL, 8.25 mmol) was added dropwise until no further gas evolution was observed. The excess of acetic acid was quenched by the addition of a saturated solution of sodium hydrogencarbonate (10 mL) and the phases were separated. The aqueous phase was extracted with diethyl ether (2 × 10 mL) and the combined organic extracts were washed sequentially with water (10 mL) and brine (10 mL), then dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (petroleum ether–EtOAc, 9 : 1 → 3 : 1) to give the diazoketone **5** (151 mg, 85%) as a bright yellow oil: R_f 0.29 (petroleum ether–diethyl ether, 1 : 3); $[\alpha]_D^{27}$ +19 (*c* 1.2, $CHCl_3$); ν_{max} 2953, 2922, 2855, 2101, 1732, 1638, 1512, 1360, 1246, 1088, 1034, 924, 820 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.56–1.75 (4H, m), 2.37–2.42 (1H, m), 2.50–2.60 (1H, m), 3.45 (2H, dd, *J* = 6.3, 5.8 Hz), 3.80 (3H, s), 3.77–3.86 (1H, m), 4.01 (2H, d, *J* = 5.2 Hz), 4.42 (2H, s), 5.14 (1H, dd, *J* = 10.6, 0.7 Hz), 5.24 (1H, dd, *J* = 16.9, 0.7 Hz), 5.33 (1H, brs), 5.87 (1H, ddt, *J* = 16.9, 10.6, 5.2 Hz), 6.87 (2H, d, *J* = 8.8 Hz), 7.23 (2H, d, *J* = 8.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.6, 31.2, 46.2, 55.4, 55.6, 60.1, 70.7, 72.7, 76.0, 113.9, 117.0, 129.4, 130.7, 135.0, 159.3, 193.3; LRMS (FAB) *m*/*z* (intensity): 122 (100), 333 $[M + H]^+$ (12), 219 (8); HRMS (FAB) calcd for $C_{18}H_{25}O_4N_2$ [M + H]$^+$: 333.1814, found: 333.1817.

(2*S*,5*S*)-5-[3-(4-Methoxybenzyloxy)propyl]-2-(prop-2-en-1-yl)dihydrofuran-3(2*H*)-one (7)

Diazoketone **5** (440 mg, 1.32 mmol) in THF (12 mL) was added dropwise to a solution of copper acetylacetonate (72.0 mg, 0.28 mmol) in THF (12 mL) at reflux. The mixture was stirred at 85 °C for 40 min and then concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (petroleum ether–EtOAc, 1 : 0 → 9 : 1) to give the furanone **7** (361 mg, 90%) as a colourless oil (single stereoisomer as judged by ^1H NMR analysis): R_f 0.52; (petroleum ether–diethyl ether, 1 : 3); $[\alpha]_D^{28}$ −16 (*c* 1.0, $CHCl_3$); ν_{max} 2936, 2917, 2855, 1756, 1729, 1613, 1513, 1249, 1172, 1094, 1034, 821 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.59–1.83 (4H, m), 2.22 (1H, dd, *J* = 18.0, 6.8 Hz), 2.26–2.37 (1H, m), 2.39–2.48 (1H, m), 2.55 (1H, dd, *J* = 18.0, 6.9 Hz), 3.44–3.52 (2H, m), 3.80 (3H, s), 4.00 (1H, dd, *J* = 7.2, 4.8 Hz), 4.33–4.40 (1H, m), 4.43 (2H, s), 5.11 (1H, d, *J* = 10.1 Hz), 5.14 (1H, dd, *J* = 17.1, 1.4 Hz), 5.80 (1H, dddd, *J* = 17.1, 10.1, 7.1, 6.8 Hz), 6.87 (2H, d, *J* = 8.5 Hz), 7.25 (2H, d, *J* = 8.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 26.0, 32.4, 35.4, 42.6, 55.4, 69.6, 72.7, 75.4, 78.7, 113.9, 118.3, 129.4, 130.6, 133.2, 159.3, 216.3; LRMS (EI) *m*/*z* (intensity): 304 $[M]^+$ (15), 121 (100), 137 (100), 190 (39); HRMS (EI) calcd for $C_{18}H_{24}O_4$ $[M]^+$: 304.1675, found: 304.1672. Anal. calcd for $C_{18}H_{24}O_4$: C, 71.03%; H, 7.95%. Found: C, 70.94%; H, 8.06%.

(2*S*,5*S*)-5-(3-Hydroxypropyl)-2-(prop-2-en-1-yl)dihydrofuran-3(2*H*)-one

The furanone **7** (159 mg, 0.522 mmol) was added in one portion to a solution of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) (131 mg, 0.577 mmol) in dichloromethane (12 mL) and water (1.2 mL) at 0 °C. The reaction mixture was stirred at room temperature for 2 h and then washed sequentially with saturated aqueous sodium carbonate solution (10 mL), water (10 mL) and brine (10 mL). The organic phase was dried ($MgSO_4$) and concentrated under reduced pressure to give a residue which was purified by flash chromatography on silica gel (petroleum ether–

diethyl ether, 2 : 1 → 1 : 2) to give the alcohol (89.5 mg, 93%) as a colourless oil: R_f 0.18; (petroleum ether–diethyl ether, 1 : 3); $[\alpha]_D^{25}$ –48 (*c* 1.1, $CHCl_3$); ν_{max} 3406, 2925, 2868, 1754, 1642, 1434, 1173, 1062, 991, 920 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.58–1.83 (4H, m), 2.10 (1H, bs), 2.22 (1H, dd, *J* = 18.0, 7.2 Hz), 2.24–2.31 (1H, m), 2.35–2.42 (1H, m), 2.52 (1H, dd, *J* = 18.0, 6.8 Hz), 3.65 (2H, brs), 3.98 (1H, dd, *J* = 7.6, 4.6 Hz), 4.32–4.42 (1H, m), 5.06 (1H, dd, *J* = 10.1, 0.9 Hz), 5.09 (1H, dd, *J* = 17.0, 1.0 Hz), 5.77 (1H, ddt, *J* = 17.0, 10.1, 7.2, 6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 29.1, 32.5, 35.3, 42.7, 62.6, 75.7, 78.9, 118.5, 133.0, 215.8; LRMS (CI, isobutane) *m*/*z* (intensity): 185 $[M + H]^+$ (100), 167 (75), 71 (32); HRMS (CI, isobutane) calcd for $C_{10}H_{17}O_3$ $[M + H]^+$: 185.1178, found: 185.1180.

(*S*)-3-[(2*S*,5*S*)-4-Oxo-5-(prop-2-en-1-yl)tetrahydrofuran-2-yl]propyl 2-methylpent-4-enoate (13)

The known carboxylic acid **10**[4] (44.2 mg, 0.387 mmol) and (2*S*,5*S*)-2-allyl-5-(3-hydroxypropyl)dihydrofuran-3(2*H*)-one (45.0 mg, 0.244 mmol) were dissolved in dry dichloromethane (3.0 mL) at room temperature and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDC) (149 mg, 0.960 mmol) and 4-*N*,*N*-dimethylaminopyridine (DMAP) (101 mg, 0.827 mmol) were added. The mixture was stirred for 14 h and quenched with water (1 mL). The solution was extracted with dichloromethane (3 × 4 mL) and the organic phases were combined, washed with brine (6 mL) and then dried ($MgSO_4$). The solution was concentrated under reduced pressure and the residue was purified by flash chromatography on silica gel (petroleum ether–diethyl ether, 9 : 1 → 4 : 1) to give the ester **13** (47.6 mg, 70%) as colourless oil: R_f 0.76; (petroleum ether–EtOAc, 3 : 2); $[\alpha]_D^{26}$ –27 (*c* 1.1, $CHCl_3$); ν_{max} 2975, 2937, 2918, 1756, 1730, 1642, 1177, 1076, 993, 916 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.14 (3H, d, *J* = 6.9 Hz), 1.60–1.86 (4H, m), 2.13–2.21 (1H, m), 2.23 (1H, ddd, *J* = 18.0, 6.9, 0.9 Hz), 2.29–2.38 (3H, m), 2.51 (1H, dd, *J* = 13.9, 6.9 Hz), 2.57 (1H, dd, *J* = 17.5, 6.9 Hz), 4.01 (1H, dd, *J* = 7.4, 4.7 Hz), 4.11 (2H, t, *J* = 6.2 Hz), 4.34–4.41 (1H, m), 5.00–5.08 (2H, m), 5.09–5.18 (2H, m), 5.74 (1H, ddt, *J* = 17.0, 10.1, 6.9 Hz), 5.81 (1H, ddt, *J* = 17.1, 10.1, 7.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.7, 25.0, 32.1, 35.4, 37.9, 39.4, 42.5, 63.9, 75.2, 78.8, 117.0, 118.4, 133.1, 135.6, 176.2, 215.9; LRMS (FAB) *m*/*z* (intensity): 281 $[M + H]^+$ (22), 69 (100), 73 (93); HRMS (FAB) calcd for $C_{16}H_{25}O_4$ $[M + H]^+$: 281.1752, found: 281.1753.

(1*S*,7*S*,12*S*)-7-Methyl-5,15-dioxabicyclo[10.2.1]pentadec-9-ene-6,13-dione (14)

A solution of the diene **13** (79.2 mg, 0.282 mmol) in dry 1,2-dichloroethane (90 mL) was added slowly to a solution of the ruthenium complex **11** (21.1 mg, 24.9 μmol) in dry 1,2-dichloroethane (7 mL) at room temperature. The mixture was heated to 50 °C and stirred at this temperature for 15 min. The solvent was removed under reduced pressure and the residue was purified by flash chromatography on silica gel (petroleum ether–diethyl ether, 9 : 1 → 4 : 1) to give a mixture of the macrolactone **14** and its *E*-isomer (51.0 mg, 72%; 15 : 1, *Z* : *E*) as a colourless solid. A sample of the macrolactone **14** was recrystallised from pentane for characterisation purposes and to provide crystals suitable for X-ray diffraction studies: R_f 0.44 (petroleum ether–diethyl ether, 1 : 3); mp = 73.8–74.8 °C; $[\alpha]_D^{21}$ –28 (*c* 1.0, $CHCl_3$); ν_{max} 2921, 2850, 1756, 1730, 1260, 1083, 801 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.14 (3H, d, *J* = 6.8 Hz), 1.70–1.89 (3H, m), 2.08–2.62 (8H, m), 4.04–4.13 (2H, m), 4.30–4.37 (1H, m), 4.43 (1H, ddd, *J* = 11.3, 9.9, 1.0 Hz), 5.25–5.33 (1H, m), 5.57–5.65 (1H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.5, 24.3, 35.6, 35.9, 38.0, 40.2, 44.1, 66.0, 75.0, 79.7, 125.1, 133.2, 177.2, 217.4; LRMS (CI, isobutane) *m*/*z* (intensity): 253 $[M + H]^+$ (100), 75 (92); HRMS (CI, isobutane) calcd for $C_{14}H_{21}O_4$ $[M + H]^+$: 253.1440, found: 253.1438.

(1*S*,7*S*,12*S*,*Z*)-7-Methyl-13-methylene-5,15-dioxabicyclo-[10.2.1]pentadec-9-en-6-one (15)

To the suspension of methyltriphenylphosphonium bromide (212 mg, 593 μmol) in dry THF (5.00 mL) at 0 °C was added sodium bis(trimethylsilyl)amide (550 μL of a 1 M solution in THF, 550 μmol) and the mixture was stirred at 0 °C for 1 h. The ketone **14** (25.2 mg, 99.8 μmol) in dry THF (5.0 mL) was added and the yellow mixture was stirred at 0 °C for 1 h. The reaction was quenched by the addition of a saturated aqueous solution of ammonium chloride (10 mL). The mixture was extracted with diethyl ether (3 × 10 mL) and the combined organic phases were washed with brine (10 mL) then dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (petroleum ether to petroleum ether–diethyl ether, 9 : 1) to give the alkene **15** (24.5 mg, 98%) as a colourless oil: R_f 0.80 (petroleum ether–diethyl ether, 1 : 3); $[\alpha]_D^{21}$ –51 (*c* 1.2, $CHCl_3$); ν_{max} 2954, 2924, 2898, 2853, 1730, 1463, 1188, 968 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) (~3 : 1 mixture of conformational isomers) δ 1.13 (3H × 0.75, d, *J* = 7.2 Hz), 1.20 (3H × 0.25, d, *J* = 6.9 Hz), 1.56–1.76 (3H, m), 1.97–2.29 (5H, m), 2.43–2.64 (3H, m), 3.88–4.12 (2H, m), 4.38–4.49 (1H, m), 4.56 (1H, brs), 4.81–4.85 (1H, m), 4.96–5.01 (1H, m), 5.45–5.57 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$) (~3 : 1 mixture of conformational isomers) δ 18.4, 18.5, 25.1, 25.7, 31.8, 34.0, 34.8, 35.4, 38.3, 38.8, 40.3, 40.6, 40.7, 41.4, 65.8, 66.4, 75.3, 75.9, 79.0, 79.9, 104.3, 104.5, 126.4, 127.4, 128.9, 131.6, 151.4, 152.3, 175.8, 177.3; LRMS (CI, isobutane) *m*/*z* (intensity): 251 $[M + H]^+$ (28), 75 (100), 81 (45); HRMS (CI, isobutane) calcd for $C_{15}H_{23}O_3$ $[M + H]^+$: 251.1647, found: 251.1652.

Methyl (*S*)-6-[(2*S*,3*S*,5*S*)-5-(3-hydroxypropyl)-3-methyltetrahydrofuran-2-yl]-2-methyl-hexanoate (16a) and methyl (*S*)-6-[(2*S*,3*R*,5*S*)-5-(3-hydroxypropyl)-3-methyltetrahydrofuran-2-yl]-2-methylhexanoate (16b)

To a solution of alkene **15** (40.0 mg, 160 μmol) in dry toluene (6.0 mL) was added chlorotris(triphenylphosphine) rhodium(I) (Wilkinson's catalyst) (26 mg, 28 μmol) at room temperature. The atmosphere was purged twice with hydrogen and the mixture was stirred under an atmosphere of hydrogen at room temperature for 6 h. The mixture was filtered through a short pad of silica gel (petroleum ether–diethyl ether, 4 : 1) and the solvent was evaporated under reduced pressure to give the crude reduced lactone as a pale yellow oil. R_f 0.81 (petroleum ether–diethyl ether, 1 : 3).

Sodium in mineral oil (~10 mg, ~420 μmol) was added to dry methanol (4.0 mL) at 0 °C and the resulting mixture was

kept at 0 °C until no further gas evolution was observed. The reduced lactone (40 mg, 70 μmol) was dissolved in a mixture of dry methanol (2.0 mL) and dry THF (4.0 mL) and added to the solution of sodium methoxide. The reaction mixture was heated at 60 °C for 2 h and then quenched by the addition of a saturated aqueous solution of ammonium chloride (20 mL). The mixture was extracted with EtOAc (3 × 20 mL) and the combined organic phases were washed with brine (20 mL) and then dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (petroleum ether → petroleum ether–diethyl ether, 3 : 1) to give a mixture (4.5 : 1) of the esters **16a** and **16b** (35.1 mg, 77%) as a colourless oil. Data for **16a**: R_f 0.18 (petroleum ether–diethyl ether, 1 : 3); $[\alpha]_D^{29}$ −1.2 (*c* 1.0, $CHCl_3$); ν_{max} 3358, 2955, 2924, 2855, 2363, 1715, 1456, 1317 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.89 (3H, d, *J* = 7.0 Hz), 1.13 (3H, d, *J* = 7.0 Hz), 1.21–1.77 (14H, m), 2.17–2.27 (1H, m), 2.43 (1H, dq, *J* = 14.0, 7.0 Hz), 2.95 (1H, brs), 3.57–3.72 (2H, m), 3.66 (3H, s), 3.84–3.89 (1H, m), 4.07 (1H, qd, *J* = 7.8, 3.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.9, 17.8, 27.4, 28.2, 31.1, 34.4, 35.0, 36.8, 40.3, 41.2, 52.2, 63.8, 77.8, 82.0, 178.1; LRMS (CI, isobutane) *m/z* (intensity): 287 $[M + H]^+$ (55), 69 (100), 81 (76); HRMS (CI, isobutane) calcd for $C_{16}H_{31}O_4$ $[M + H]^+$: 287.2222, found: 287.2220.

Methyl (*S*)-6-[(2*S*,3*S*,5*S*)-3-methyl-5-(prop-2-en-1-yl)tetrahydrofuran-2-yl]-2-methylhexanoate

2-Nitrophenyl selenocyanate (88.0 mg, 0.387 mmol) and alcohol **16a** (40 mg, 0.14 mmol) were dissolved in degassed anhydrous THF (2.00 mL) followed by addition of tri-*n*-butylphosphine (93 μL, 0.34 mmol). The solution was stirred at room temperature for 2 h then the resulting brown mixture was quenched by addition of water (10 mL). The solution was extracted with EtOAc (3 × 15 mL) and the combined organic phases were washed with brine (10 mL) and then dried ($MgSO_4$). The organic solution was concentrated under reduced pressure and the residue was dissolved in THF (1 mL) and cooled to 0 °C. To this solution was added hydrogen peroxide (0.20 mL of a 27% solution in water, 1.6 mmol) and the mixture was stirred for 2 h at room temperature. The mixture was diluted with water (3 mL) and then extracted with EtOAc (3 × 5 mL). The combined organic phases were washed with brine (10 mL), dried ($MgSO_4$) and then concentrated under reduced pressure to afford the crude product. Purification by flash chromatography on silica gel (petroleum ether → petroleum ether–diethyl ether, 95 : 5) to give the alkene (31.1 mg, 77%) as a pale yellow oil: R_f 0.93; (petroleum ether–diethyl ether, 1 : 3); $[\alpha]_D^{25}$ +1.8 (*c* 1.1, $CHCl_3$); ν_{max} 2937, 2875, 2860, 1739, 1462, 1198, 1164, 913 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.89 (3H, d, *J* = 7.1 Hz), 1.14 (3H, d, *J* = 7.0 Hz), 1.23–1.50 (8H, m), 1.60–1.79 (3H, m), 2.15–2.24 (1H, m), 2.29–2.37 (1H, m), 2.43 (1H, dq, *J* = 13.9, 7.0 Hz), 3.66 (3H, s), 3.83 (1H, dt, *J* = 7.9, 5.1 Hz), 4.10 (1H, app. tt, *J* = 6.8 Hz), 5.02–5.10 (2H, m), 5.80 (1H, ddt, *J* = 17.2, 10.2, 7.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.1, 17.2, 26.6, 27.6, 30.4, 33.9, 36.0, 39.4, 39.5, 41.2, 51.6, 76.1, 81.4, 116.9, 135.2, 177.5; LRMS (CI, isobutane) *m/z* (intensity); 269 $[M + H]^+$ (18), 89 (100), 69 (76); HRMS (CI, isobutane) calcd for $C_{16}H_{29}O_3$ $[M + H]^+$: 269.2117, found: 269.2119.

(*S*)-6-[(2*S*,3*S*,5*S*)-3-Methyl-5-(prop-2-en-1-yl)tetrahydrofuran-2-yl]-2-methylhexanoic acid (1)

The methyl ester (10.2 mg, 37.2 μmol, 1.00 eq) was dissolved in a mixture of methanol (0.40 mL) and THF (0.60 mL). A solution of lithium hydroxide (27.7 mg, 1.12 mmol) in water (0.50 mL) was added and the resultant mixture was stirred at room temperature for 1.5 h. The reaction was diluted with EtOAc and the layers were separated. 1 M Aqueous hydrochloric acid (10 mL) was added to the aqueous phase and this was then extracted with EtOAc (3 × 15 mL). The combined organic phases were washed with brine (30 mL), dried ($MgSO_4$) and concentrated under reduced pressure to yield the carboxylic acid **1** (8.1 mg, 84%) as a colourless oil. R_f 0.53; (petroleum ether–diethyl ether, 1 : 3); $[\alpha]_D^{28}$ +10.2 (*c* 3.1, CH_2Cl_2) {Lit.[7b] $[\alpha]_D^{23}$ +8.4 (*c* 4.5, CH_2Cl_2)}; ν_{max} 2932, 2862, 1735, 1705, 1643, 1458, 1180, 918 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.89 (3H, d, *J* = 7.0 Hz), 1.17 (3H, d, *J* = 7.0 Hz), 1.21–1.52 (7H, m), 1.66–1.79 (3H, m), 2.16–2.25 (2H, m), 2.33 (1H, ddd, *J* = 13.8, 7.0, 5.9 Hz), 2.46 (1H, dq, *J* = 13.8, 7.0 Hz), 3.85 (1H, dt, *J* = 7.9, 5.1 Hz), 4.11 (1H, apparent tt, *J* = 6.8, 6.8 Hz), 5.01–5.10 (2H, m), 5.78 (1H, ddt, *J* = 17.2, 10.2, 7.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.1, 17.0, 26.6, 27.5, 30.4, 33.6, 36.0, 39.3, 39.4, 41.1, 76.1, 81.4, 117.0, 135.2, 182.4; LRMS (CI, isobutane) *m/z* (intensity); 255 $[M + H]^+$ (68), 75 (100), 81 (32); HRMS (CI, isobutane) calcd for $C_{15}H_{27}O_3$ $[M + H]^+$: 255.1960, found: 255.1958.

(2*S*,5*S*)-5-[3-(4-Methoxybenzyloxy)propyl]-3-methylene-2-(prop-2-en-1-yl)tetrahydrofuran

Methyltriphenylphosphonium bromide (4.20 g, 11.8 mmol) was suspended in dry THF (125 mL) and the solution was cooled to 0 °C. Sodium bis(trimethylsilyl)amide (12.0 mL of a 1 M solution in THF, 12.0 mmol) was added and the mixture was stirred at 0 °C for 1 h. A solution of the dihydrofuranone **7** (0.81 g, 2.7 mmol) in dry THF (100 mL) was added and the yellow mixture was stirred at 0 °C for 1 h. The reaction was quenched by the addition of a saturated solution of ammonium chloride (100 mL) and the mixture was extracted with diethyl ether (3 × 100 mL). The combined organic phases were washed with brine (100 mL), dried ($MgSO_4$) and then concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (petroleum ether → petroleum ether–diethyl ether, 9 : 1) to give the diene (0.79 g, 98%) as a colourless oil: R_f 0.43 (petroleum ether–diethyl ether, 3 : 1); $[\alpha]_D^{25}$ −55 (*c* 0.95, $CHCl_3$); ν_{max} 2933, 2854, 1612, 1512, 1440, 1246, 1172, 1094, 1036, 820 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.51–1.76 (4H, m), 2.24–2.36 (3H, m), 2.66 (1H, ddtd, *J* = 15.5, 6.5, 2.0, 1.8 Hz), 3.43–3.51 (2H, m), 3.81 (1H, s), 4.06 (1H, tt, *J* = 6.4, 6.3 Hz), 4.44 (3H, m), 4.87 (1H, dt, *J* = 2.1, 2.1 Hz), 5.00 (1H, dt, *J* = 2.1, 2.1 Hz), 5.08 (1H, ddt, *J* = 10.2, 2.1, 1.1 Hz), 5.12 (1H, ddt, *J* = 17.2, 2.1, 1.5 Hz), 5.85 (1H, ddt, *J* = 17.2, 10.2, 6.9 Hz), 6.88 (2H, d, *J* = 8.7 Hz), 7.26 (2H, d, *J* = 8.1 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 26.5, 32.1, 39.0, 40.2, 55.6, 70.2, 72.8, 77.6, 79.4, 105.4, 114.0, 117.3, 129.5, 131.0, 135.2, 151.5, 159.4; LRMS (EI) *m/z* (intensity): 302 $[M]^+$ (5), 121.1 (100), 82.9 (35); HRMS (EI) calcd for $C_{15}H_{23}O_3$ $[M]^+$: 302.1880, found: 302.1882.

(2*S*,5*S*)-5-(3-Hydroxypropyl)-3-methylene-2-(prop-2-en-1-yl)tetrahydrofuran (17)

The diene (960 mg, 3.17 mmol) was added in one portion to a solution of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ)

(793 mg, 3.49 mmol) in a mixture of dichloromethane (75 mL) and water (7.5 mL) at 0 °C. The reaction mixture was stirred at room temperature for 2 h and then washed sequentially with saturated aqueous sodium carbonate solution (50 mL), water (50 mL) and brine (50 mL). The organic phase was dried ($MgSO_4$) and concentrated under reduced pressure to give a residue which was purified by flash chromatography on silica gel (petroleum ether–diethyl ether, 2 : 1 → 1 : 2) to give the alcohol **17** (471 mg, 81%) as a colourless oil: R_f 0.45; (petroleum ether–diethyl ether, 1 : 3); $[\alpha]_D^{25}$ −53.6 (*c* 1.00, $CHCl_3$); ν_{max} 3356, 2933, 1714, 1641, 1433, 1375, 1238, 1110, 1056, 995, 914 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.56–1.70 (4H, m), 2.25–2.35 (3H, m), 2.61–2.63 (1H, m), 2.67 (1H, ddddd, *J* = 15.5, 6.2, 2.2, 2.0, 1.8 Hz), 3.60–3.69 (2H, m), 4.04–4.10 (1H, m), 4.46–4.50 (1H, m), 4.86 (1H, ddd, *J* = 2.2, 2.2, 2.0 Hz), 5.00 (1H, ddd, *J* = 2.2, 2.2, 2.0 Hz), 5.07 (1H, ddt, *J* = 10.2, 2.0, 1.1 Hz), 5.11 (1H, ddt, *J* = 17.1, 1.9, 1.6 Hz), 5.84 (1H, ddt, *J* = 17.1, 10.2, 6.9 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 30.1, 32.7, 39.3, 40.1, 63.2, 77.9, 79.8, 105.6, 117.6, 134.9, 151.0.

(*S*)-3-[(2*S*,5*S*)-4-Methylene-5-(prop-2-en-1-yl)tetrahydrofuran-2-yl]propyl 2-methylpent-4-enoate (18)

1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDC) (1.10 g, 7.09 mmol) and 4-*N*,*N*-dimethylaminopyridine (DMAP) (0.70 mg, 5.7 mmol) were added to a solution of the carboxylic acid **10** (0.34 g, 2.34 mmol) and alcohol **17** (0.33 g, 1.9 mmol) in dry dichloromethane (17 mL) at room temperature. The mixture was stirred for 1.5 h and quenched with water (5 mL). The solution was extracted with dichloromethane (3 × 10 mL) and the organic phases were combined, washed with brine (20 mL) and then dried ($MgSO_4$). The solution was concentrated under reduced pressure and the residue was purified by flash chromatography on silica gel (petroleum ether then petroleum ether–diethyl ether, 19 : 1) to give the ester **18** (0.45 g, 86%) as a colourless oil: R_f 0.62; (petroleum ether–diethyl ether, 9 : 1); $[\alpha]_D^{26}$ −23 (*c* 1.2, $CHCl_3$); ν_{max} 2978, 2935, 2914, 1733, 1641, 1460, 1239, 1179, 1069, 991, 912 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.14 (3H, d, *J* = 7.0 Hz), 1.44–1.80 (4H, m), 2.12–2.20 (1H, m), 2.22–2.28 (1H, m), 2.30–2.36 (2H, m), 2.4 (1H, ddt, *J* = 14.1, 7.0, 1.2 Hz), 2.50 (1H, qt, *J* = 7.0, 6.9 Hz), 2.67 (1H, ddddd, *J* = 15.5, 6.6, 2.2, 2.0, 1.8 Hz), 4.02–4.09 (3H, m), 4.42–4.45 (1H, m), 4.87 (1H, ddd, *J* = 2.2, 2.2, 2.0 Hz), 5.00 (1H, ddd, *J* = 2.2, 2.2, 2.0 Hz), 5.02–5.12 (4H, m), 5.73 (1H, ddt, *J* = 17.1, 10.2, 6.9 Hz), 5.85 (1H, ddt, *J* = 17.1, 10.2, 6.9 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 16.7, 25.4, 31.7, 37.9, 38.8, 39.4, 40.0, 64.3, 77.1, 79.3, 105.4, 117.0, 117.2, 134.8, 135.7, 151.0, 176.2; LRMS (CI, isobutane) *m*/*z* (intensity): 279 $[M + H]^+$ (40), 69.1 (100), 85.2 (87); HRMS (CI, isobutane) calcd for $C_{17}H_{27}O_3$ $[M + H]^+$: 279.1958, found: 279.1960.

(1*S*,7*S*,12*S*,*Z*)-7-Methyl-13-methylene-5,15-dioxabicyclo-[10.2.1]pentadec-9-en-6-one (15)

A solution of the triene **18** (20.1 mg, 72.2 μmol) in dry 1,2-dichloroethane (10 mL) was added slowly to a solution of the ruthenium complex **11** (3.00 mg, 3.53 μmol) in dry 1,2-dichloroethane (2.0 mL) at reflux. Three extra portions of complex **11** (3 × 3.00 mg, 3 × 3.53 μmol) were added at two-hour intervals and the mixture was stirred at reflux for 14 h. The solvent was removed under reduced pressure and the residue was purified by flash chromatography on silica gel (petroleum ether–diethyl ether, 9 : 1 → 4 : 1) to give the macrolactone **15** (15.1 mg, 84%) as a colourless oil.

Methyl (*S*)-6-[(2*S*,3*S*,5*S*)-5-(3-hydroxypropyl)-3-methyltetrahydrofuran-2-yl]-2-methylhexanoate (16a) and methyl (*S*)-6-[(2*S*,3*R*,5*S*)-5-(3-hydroxypropyl)-3-methyltetrahydrofuran-2-yl]-2-methylhexanoate (16b)

A solution of the triene **18** (21.0 mg, 72.2 μmol) in dry 1,2-dichloroethane (10 mL) was added slowly to a solution of the ruthenium complex **19** (4.50 mg, 7.20 μmol) in dry 1,2-dichloroethane (2 mL) at room temperature. The mixture was heated to reflux and stirred at this temperature for 45 min. The mixture was transferred to a hydrogenation autoclave and the vessel was then purged three times with hydrogen. The reaction mixture was stirred at 70 °C under hydrogen (6.9 bar) for 14 h and then cooled to room temperature. The mixture was filtered through a short pad of silica gel (petroleum ether–diethyl ether, 95 : 5) and the solvent was evaporated under reduced pressure to give the crude lactone (15.1 mg) as a pale yellow oil. R_f 0.81 (petroleum ether–diethyl ether, 1 : 3).

Sodium in mineral oil (~ 5 mg, ~ 210 μmol) was added to dry methanol (2.0 mL) at 0 °C and the resulting mixture was kept at 0 °C until no further gas evolution was observed. The reduced lactone (18 mg, 70 μmol) was dissolved in a mixture of dry methanol (1.0 mL) and dry THF (2.0 mL) and added to the solution of sodium methoxide. The reaction mixture was heated at 60 °C for 1 h and then quenched by the addition of a saturated aqueous solution of ammonium chloride (10 mL). The mixture was extracted with EtOAc (3 × 10 mL) and the combined organic extracts were washed with brine (10 mL) and then dried ($MgSO_4$). The solvent was removed under reduced pressure and the residue was purified by flash chromatography on silica gel (petroleum ether to petroleum ether–diethyl ether, 3 : 1) to give a mixture (4 : 1) of the esters **16a** and **16b** (13.2 mg, 64% over two steps) as a colourless oil.

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Notes and references

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