A permanganate mediated approach to the synthesis of *cis*-solamin

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Abstract

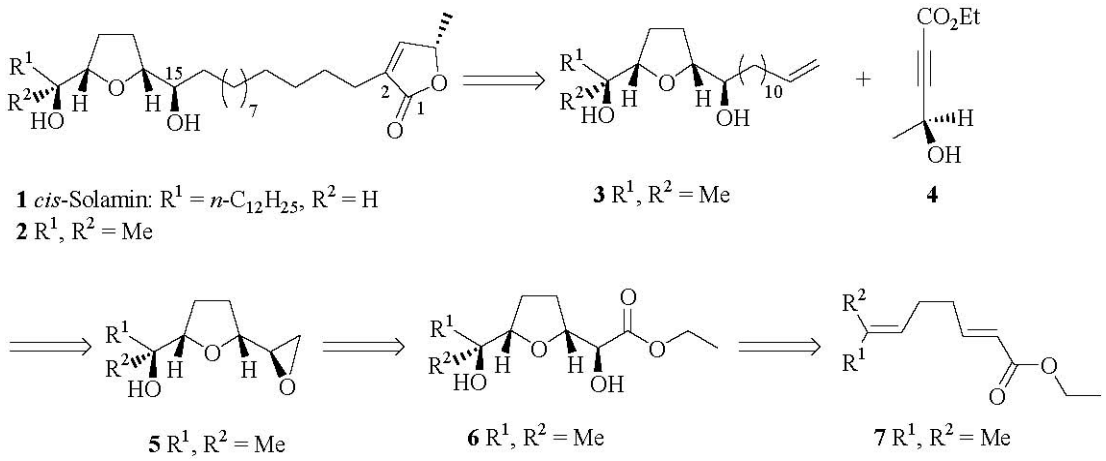
A model study directed towards the synthesis of the Annonaceous acetogenin *cis*-solamin (1) is reported. The key step in the synthesis involved the permanganate-promoted oxidative cyclisation of ethyl (*E*)-7-methylocta-2,6-dienoate (**7**) to afford a tetrahydrofuran diol **6**. The remaining C_1-C_{13} portion of the target was introduced using an organocopper-mediated opening of epoxide **5**, followed by a ruthenium-catalysed Alder−ene reaction. Significantly, no protecting groups were required during the assembly of the fragments.

Keywords: Permanganate, *cis*-solamin, oxidative cyclization, furan, epoxide, ene reaction

Introduction

The Annonaceous acetogenins are natural products isolated from the plant family, Annonaceae (custard-apple family). They are derived from C32 or C34 fatty acids combined with a 2-propanol unit at C2 that typically forms part of a terminal α,β-unsaturated γ-lactone (butenolide). In addition, one or more 2,5-disubstituted tetrahydrofuran (THF) rings are often present in the hydrocarbon backbone, which may carry oxygen substituents or unsaturation along its length. Considerable interest has been shown in the Annonaceous acetogenins, largely due to their cytotoxicity both towards healthy cells, but particularly cancerous cells.[1,2] Their mechanism of action involves ATP deprivation as a result of inhibition of the NADH: ubiquinone oxoreductase present in complex I of the mitochondrial electron transport system, and the ubiquinone-linked NADH oxidase that is active in plasma membranes of cancerous cells.[3] Other biological properties such as immunosuppressive, pesticidal, antiprotozoal, antifeedant, anthelmintic and antimicrobial activities have been reported,[1,4-6] further fuelling interest in these natural products.
A substantial number of total syntheses of Annonaceous acetogenins have now been published,[1,7] and some studies towards the synthesis of biologically active analogues have appeared.[8-10] Most of the synthetic work to date has focused on the preparation of compounds with *trans*-2,5-disubstituted THF rings, whereas the synthesis of the *cis*-isomers has been comparatively neglected.[11,12]

Here we describe an approach to the synthesis of the core and right hand portions of the Annonaceous acetogenin *cis*-solamin (**1**). Our strategy centres on the use of a permanganate oxidative cyclisation of a 1,5-diene to produce the *cis*-2,5-disubstituted THF diol core (Scheme 1).[13-16] In this way, four of the five stereocentres present within the target molecule will be introduced with control of relative stereochemistry in a single synthetic step. Ultimately, control of absolute stereochemistry will be achieved using a chiral auxiliary.[17-18]



Scheme 1. Approach to *cis*-2,5-disubstituted THF-containing acetogenins employing a permanganate–promoted oxidative cyclisation.

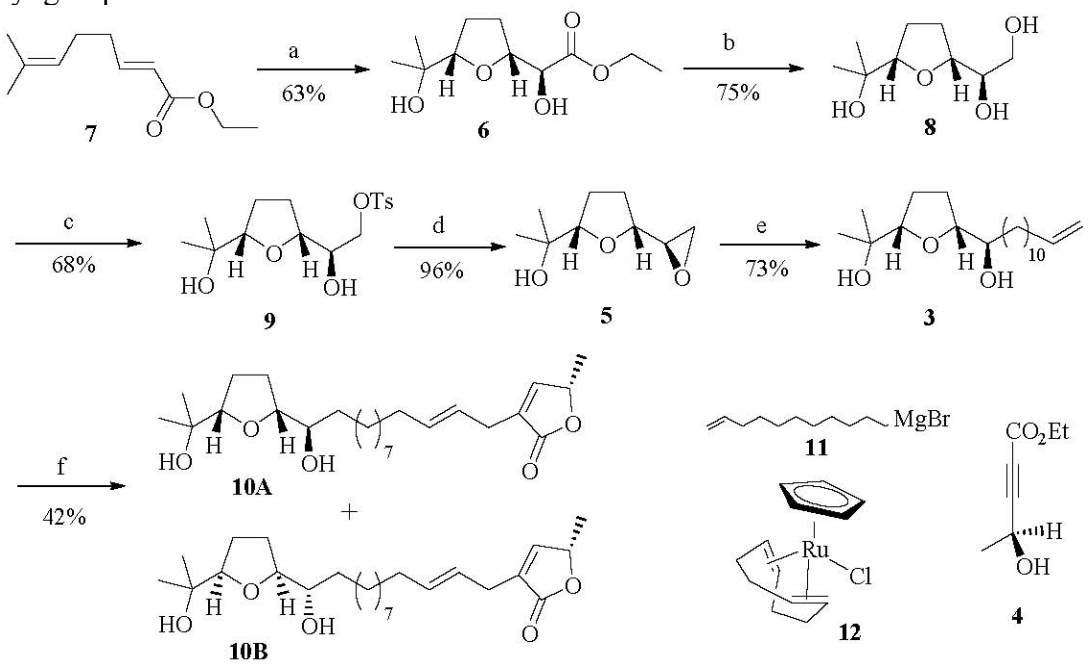
The butenolide ring present in **2** would be prepared using a ruthenium-catalysed Alder−ene reaction developed by Trost.[19] Introduction of the required alkenyl chain would be carried out using an organocopper mediated opening of epoxide **5**, which in turn would derive from ester **6**.

Results and Discussion

Our synthesis of the model compound **2** began with the 1,5-diene **7**, prepared in two steps from 2-methylbut-3-en-2-ol.[20,21] Oxidative cyclisation of diene **7** gave the desired THF diol **6** in good yield (63 %) as a single diastereoisomer.[22] Reduction of ester **6** produced the polar triol **8**, which underwent selective tosylation to afford diol **9**. Formation of the key epoxide intermediate **5** occurred rapidly when a methylene chloride solution of **9** was treated with DBU. The C3–C13 carbon atoms present in the target were introduced using a copper-catalysed Grignard reaction to give the terminal alkene **3**, required for the formation of the butenolide ring in the subsequent step.

The Trost ruthenium-catalysed Alder−ene reaction between alkene **3** and optically enriched alkyne **4**‡ gave the desired diastereoisomeric butenolides **10A** and **10B** (indistinguishable by nmr) in satisfactory yield in a 5:1 ratio with the uncyclised regioisomer which is typically observed in these reactions.[19] It is noteworthy that the use of protecting groups was avoided

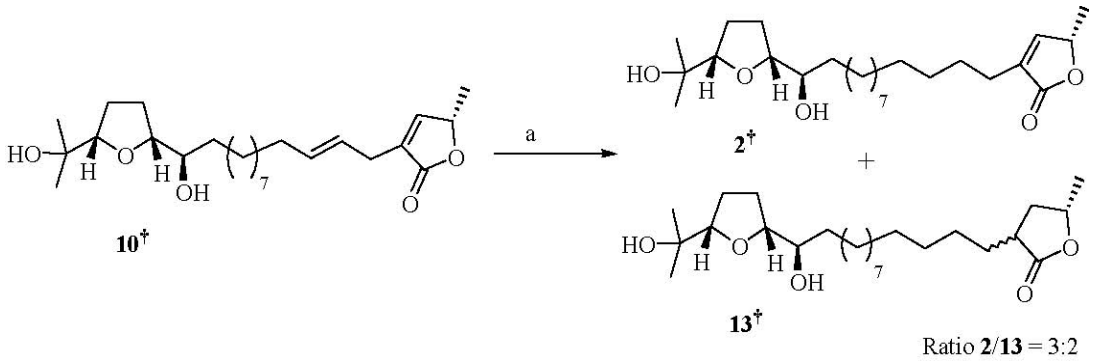
during the assembly of the fragments, with both the copper-catalysed Grignard opening of epoxide **5** and the ruthenium-catalysed Alder−ene reaction proceeding in the presence of free hydroxyl groups.



Scheme 2. Synthesis of model Annonaceous acetogenin **2**.
Reagents and conditions: a) $KMnO_4$, AcOH, buffer pH 6.5, acetone, -20 °C; b) $NaBH_4$, THF, H_2O; c) TsCl, DMAP, Et_3N, CH_2Cl_2; d) DBU, CH_2Cl_2; e) **11**, CuI, THF; f) **4**, CpRu(COD)Cl (**12**), benzene/EtOH, sealed vessel, Δ.

With compound **10** in hand, we were in a position to investigate the selective reduction of the disubstituted olefin. The reduction was carried out in a steel bomb at 2−4 atmospheres of H_2, giving a 3:2 mixture (nmr) of the desired butenolide **2** (two diastereoisomers) and over reduced lactone **13** (possible 4 diastereoisomers) in near quantitative yield. Although efforts to separate **2** and **13** were unsuccessful, we are confident that the over reduction observed here will be avoided when we come to tackle *cis*-solamin itself by more careful control of H_2 pressure.[23] Unfortunately, we were not able to demonstrate this on the model substrate, as insufficient material was available to attempt the reaction a second time.

In conclusion, a short synthesis to the central THF ring and right hand side-chain of *cis*-solamin has been achieved. In the key step a permanganate oxidative cyclisation of a 1,5-diene was used to generate four of the five stereocentres present in the natural product. The THF diol functionality was shown to be compatible with the organocopper and ruthenium catalysed Alder−ene reactions that will ultimately be used in the synthesis of *cis*-solamin. An asymmetric synthesis of *cis*-solamin by this approach is currently under investigation.



Scheme 3 Attempted selective reduction of **10**.
Reagents and conditions: a) $Rh(PPh_3)_3Cl$, H_2 (2-4 bar), benzene/EtOH.

Experimental Section

General Methods. ^{1}H-NMR and ^{13}C-NMR were recorded on 300 or 400 MHz spectrometers (300 or 400 MHz, ^{1}H-NMR respectively and 75 or 100 MHz, ^{13}C-NMR respectively) in deuterated chloroform ($CDCl_3$) with chloroform (δ 7.26 ppm ^{1}H, δ 77.5 ppm ^{13}C) as the internal standard unless stated otherwise. IR spectra were recorded on a Nicolet Impact 400 spectrometer, fitted with a Spectra-Tech Thunderdome accessory. The abbreviations s (strong), m (medium), w (weak) and br (broad) are used when reporting the data. Melting points were obtained in open capillary tubes and are uncorrected. All non-aqueous reactions were carried out under an inert atmosphere of N_2, in oven-dried glassware unless otherwise stated. The following solvents were distilled before use: THF (from Na/benzophenone) and CH_2Cl_2 (from CaH_2) and where appropriate, other reagents and solvents were purified by standard techniques.[24] TLC was performed on aluminium-backed plates coated with silica gel 60 with an F_{254} indicator; the chromatograms were visualised under UV light and/or by staining with phosphomolybdic acid (20 % solution in ethanol) or $KMnO_4$. Flash column chromatography was performed with 40-63 μm silica gel (Merck). The buffer solution used in the permanganate oxidative cyclisation is an aqueous 4:1 mixture of 1/16 M KH_2PO_4 & 1/16 M Na_2HPO_4 at pH 6.5.

Ethyl (2*S)-2-hydroxy-2-[(2*R**,5*S**)-5-(1-hydroxy-1-methylethyl)tetrahydro-2-furanyl]ethanoate (6).** A solution of 0.4 M $KMnO_4$ (6.60 mL, 2.6 mmol, 1.6 eq) and acetic acid (265 μL, 4.6 mmol, 2.8 eq) was added dropwise over 10 min to a mixture of diene **7** (300 mg, 1.7 mmol), buffer (1.16 mL) and acetone (20 mL) at –20 °C (internal). The reaction was quenched after a further 2 min by addition of ice-cooled $Na_2S_2O_5$ (sat. aq, 40 mL) and ice (20 g). Ether (50 mL), NaCl (10 g) and $NaHCO_3$ (aq, 20 mL) were added and the organic layer separated. The aqueous layer was extracted with CH_2Cl_2 (2 x 30 mL). The organic layers were combined and dried (Na_2SO_4), before concentrating *in vacuo* to give a yellow oil (350 mg). Purification by column chromatography on silica gel (3:72:33:2 EtOAc/hexane) gave the title compound **6** (241 mg, 1.0 mmol, 63 %) as a white solid. Recrystallisation from EtOAc/hexane gave white crystals of mp

44-45 °C; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 4.43 (1H, ddd, *J* = 2.2, 4.4, 6.6 Hz, C**H**CHOH), 4.34-4.21 (2H, m, OC**H$_2$**CH$_3$), 4.14 (1H, d, *J* = 2.0 Hz, C**H**CO$_2$), 3.78 (1H, t, *J* = 7.0 Hz, C**H**C(CH$_3$)$_2$), 3.22 (2H, br, OH), 2.20-1.83 (4H, m, C**H$_2$**C**H$_2$** (THF)), 1.34 (3H, t, *J* = 7.2 Hz, C**H$_3$**CH$_2$O) 1.29 (3H, s, (C**H$_3$**)$_2$COH), 1.15 (3H, s, (C**H$_3$**)$_2$COH); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 173.6 (C), 86.7 (CH), 80.0 (CH), 74.0 (CH), 72.1 (C), 61.9 (CH$_2$), 28.2 (CH$_2$), 28.1 (CH$_3$), 26.3 (CH$_2$), 25.2 (CH$_3$), 14.3 (CH$_3$); IR *v* 3350(br), 1737(s), 1364(s), 1264(s), 1199(s), 1158(s), 1121(s), 1078(s), 1026(s) cm^{-1}; LRMS (CI) *m/z* 233 (10 %, [M+H]$^+$), 250 (20 %, [M+NH$_4$]$^+$), 215 (100 %, [M+H-H$_2$O]$^+$) Da; HRMS (EI) calcd for $C_{11}H_{21}O_5$ *m/z* 233.1389, found 233.1391.

(1*R)-1-[(2*R**,5*S**)-5-(1-Hydroxy-1-methylethyl)tetrahydro-2-furanyl]ethane-1,2-diol (8).** To a solution of ester **6** (200 mg, 0.86 mmol) and $NaBH_4$ (66 mg, 1.7 mmol) in THF (25 mL) at rt was added H_2O (0.5 mL). After 16 h a 1:1 solution of MeOH/CH_2Cl_2 (8 mL) was added. After 10 min the solution was concentrated *in vacuo* to give an oil. Purification by column chromatography on silica gel (1:191:9 MeOH/CH_2Cl_2) gave the title triol **8** (123 mg, 0.65 mmol, 75 %) as a white solid. Recrystallisation from EtOAc/hexane gave white crystals of mp 49-51 °C; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 4.11-4.05 (1H, m, C**H**CHOH), 3.80 (1H, t, *J* = 7.0 Hz, C**H**C(CH$_3$)$_2$OH), 3.74-3.60 (2H, m, C**H$_2$**OH), 3.56-3.49 (1H, m, C**H**OH), 2.53 (3H, br s, OH), 2.10-1.83 (4H, m, C**H$_2$** (THF)), 1.20 (3H, s, (C**H$_3$**)$_2$COH), 1.05 (3H, s, (C**H$_3$**)$_2$COH); ^{13}C-NMR δ (75 MHz, $CDCl_3$) 86.7 (CH), 80.2 (CH), 74.2 (CH), 72.0 (C), 65.3 (CH$_2$), 28.5 (CH$_2$), 27.9 (CH$_3$), 26.0 (CH$_2$), 25.4 (CH$_3$); IR *v* 3442(br), 3309(br), 3139(br), 1163(s), 1152(s), 1129(s), 1080(s), 1066(s), 1050(s) cm^{-1}; LRMS (CI) *m/z* 191 (10 %, [M+H]$^+$), 208 (20 %, [M+NH$_4$]$^+$), 173 (100 %, [MH$^+$-H$_2$O]); HRMS (EI) calcd for $C_9H_{19}O_4$ *m/z* 191.1283, found 191.1280.

(2*R)-2-Hydroxy-2-[(2*R**,5*S**)-5-(1-hydroxy-1-methylethyl)tetrahydro-2-furanyl]ethyl 1-benzenesulfonate (9).** To a solution of triol **8** (55 mg, 0.29 mmol), tosyl chloride (110 mg, 0.58 mmol) and DMAP (4 mg, 0.03 mmol) in CH_2Cl_2 (10 mL) was added Et_3N (0.3 mL, 2 mmol). After 16 h CH_2Cl_2 (40 mL) and brine (20 mL) were added, the organic phase was separated, dried (Na_2SO_4) and concentrated *in vacuo* to give a colourless oil (160 mg). Purification by column chromatography using silica gel (3:7 EtOAc/CH_2Cl_2) gave the title compound **9** (69 mg, 0.20 mmol, 68 %) as a colourless oil. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.73 (2H, d, *J* = 8.0 Hz, C**H**), 7.27 (2H, d, *J* = 8.0 Hz, C**H**), 4.10-4.00 (2H, m, C**H$_2$**OTs), 3.99-3.94 (1H, m, C**H**CHOH), 3.80 (1H, t, *J* = 7.0 Hz, C**H**C(CH$_3$)$_2$OH) 3.66 (1H, dt, *J* = 4.0, 8.0 Hz, C**H**OH), 3.26 (2H, br, OH), 2.35 (3H, s, C**H$_3$**Ar), 1.98-1.72 (4H, m, C**H$_2$** (THF)), 1.15 (3H, s, (C**H$_3$**)$_2$COH) 1.04 (3H, s, (C**H$_3$**)$_2$COH); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 145.3 (C), 133.2 (C), 130.3 (CH), 128.4 (CH), 86.8 (CH), 78.6 (CH), 72.5 (C), 72.1 (CH), 72.0 (CH$_2$), 28.6 (CH$_2$), 28.1 (CH$_3$), 26.3 (CH$_2$), 26.1 (CH$_3$), 22.0 (CH$_3$); IR *v* 3360(br), 1737(m), 1596(m), 1456(m), 1358(s), 1190(s), 1175(s), 1096(s), 1076(s) cm-1; LRMS (ES+) *m/z* 711 (50 %, [2M+Na]$^+$), 367 (100 %, [M+Na]$^+$), 345 (25 %, [M+H]$^+$); HRMS (EI) calcd for $C_{16}H_{25}O_6S$ *m/z* 345.1372, found 345.1359.

2-(2*S,5*R**)-5-[(2*R**)Oxiran-2-yl]tetrahydro-2-furanyl-2-propanol (5).** To a solution of tosylate **9** (186 mg, 0.54 mmol) in CH_2Cl_2 (15 mL) at 0 °C was added DBU (90 mg, 0.59 mmol) dropwise by syringe. The reaction was allowed to warm to rt and stirred for 12 h. Concentration *in vacuo* gave a yellow oil, which was purified by column chromatography on silica gel (1:40

MeOH/CH_2Cl_2) to afford the title compound **5** (89 mg, 0.52 mmol, 96 %) as a yellow oil. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 4.11 (1H, ddd, *J* = 3.0, 5.5, 7.5 Hz, ROC**H**), 3.78 (1H, t, *J* = 7.0 Hz, C**H**C$(CH_3)_2$OH), 3.09-3.02 (2H, m, C**H**OCH_2, O**H**), 2.85 (1H, dd, *J* = 3.0, 5.0 Hz, C**H$_2$**OCH), 2.79 (1H, dd, *J* = 4.0, 5.0 Hz, C**H$_2$**OCH), 2.18-1.81 (4H, m, C**H$_2$** (THF)), 1.20 (3H, s, (C**H$_3$**)$_2$COH), 1.05 (3H, s, (C**H$_3$**)$_2$COH); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 87.1 (CH), 76.7 (CH), 71.4 (C), 54.7 (CH), 44.3 (CH_2), 29.6 (CH_2), 28.0 (CH_3), 25.8 (CH_2), 25.2 (CH_3); IR *v* 3455(br), 1470(m), 1381(m), 1361(m), 1258(m), 1177(m), 1156(s), 1109(s), 1071(s), 1032(s) cm^{-1}; LRMS (CI) *m/z* 190 (25 %, $[M+NH_4]^+$), 173 (20 %, $[M+H]^+$), 155 (100 %, $[M+H-H_2O]^+$); HRMS (CI) calcd for $C_9H_{17}O_3$ *m/z* 173.1178, found 173.1181.

(1*R)-1-[(2*R**,5*S**)-5-(1-Hydroxy-1-methylethyl)tetrahydro-2-furanyl]-12-tridecen-1-ol (3).** A solution of undec-10-enylmagnesium bromide (**11**) in THF (3.5 mL of 0.2 M, 0.7 mmol) was added to a suspension of CuI (28 mg, 0.15 mmol) in THF (10 mL) at 0 °C. After 10 min stirring, the solution was cooled to –70 °C (internal) whereupon it went grey. A solution of epoxide **5** (25 mg, 0.14 mmol) in THF (2 mL) was added dropwise. After 45 min the reaction mixture was quenched by the addition of an aqueous solution of saturated NH_4Cl /NH_4OH (9:1, 30 mL). Ether (60 mL) was added and the organic phase separated. The organic phase was then washed with brine (20 mL), dried (Na_2SO_4) and concentrated *in vacuo* to give a yellow oil (250 mg). Purification by column chromatography on silica gel (3:7 EtOAc/hexane) gave the title THF diol **3** (32 mg, 0.10 mmol, 73 %) as a white solid. Recrystallisation from EtOAc/hexane gave white crystals of mp 30-33 °C; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 5.74 (1H, tdd, *J* = 6.5, 10.0, 17.0 Hz, C**H**=CH_2), 4.92 (1H, dd, *J* = 2.0, 17.0 Hz, C**H**H=CH(E)), 4.85 (1H, dd, *J* = 2.0, 10.0 Hz, C**H**H=CH(Z)), 3.76 (1H, q, *J* = 6.5 Hz, C**H**CHOH), 3.71 (1H, t, *J* = 7.0 Hz, C**H**C$(CH_3)_2$OH), 3.40-3.34 (1H, m, C**H**OHCH_2), 2.49 (2H, br, OH), 1.98 (2H, q, *J* = 6.5 Hz, C**H$_2$**CH=CH_2), 1.90-1.61 (4H, m, C**H$_2$**C**H$_2$** (THF)), 1.20 (3H, s, (C**H$_3$**)$_2$COH), 1.48-1.18 (18H, m, (C**H$_2$**)$_9$$CH_2$CH=$CH_2$), 1.06 (3H, s, (C**H$_3$**)$_2$COH); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 139.6 (CH), 114.5 (CH_2), 86.5 (CH), 82.9 (CH), 74.8 (CH), 72.0 (C), 34.6 (CH_2), 34.2 (CH_2), 30.1 (CH_2), 30.0 (CH_2), 30.0 (CH_2), 30.0 (CH_2), 29.9 (CH_2), 29.5 (CH_2), 29.3 (CH_2), 28.8 (CH_2), 27.9 (CH_3), 26.5 (CH_2), 26.1 (CH_2), 25.5 (CH_3); IR *v* 3376(br), 1640(m), 1463(s), 1377(m), 1362(m), 1162(s), 1081(s), 995(s) cm^{-1}; LRMS (ES+) *m/z* 675 (50 %, $[2M+Na]^+$), 653 (5 %, $[2M+H]^+$), 349 (100, $[M+Na]^+$); HRMS (EI) calcd for $C_{20}H_{39}O_3$ *m/z* 327.2899, found 327.2901.

(5*S*)-3-(*E*,13*R)-13-Hydroxy-13-[(2*R**,5*S**)-5-(1-hydroxy-1-methylethyl)tetrahydro-2-furanyl]-2-tridecenyl-5-methyl-2,5-dihydro-2-furanone (10).** Under an atmosphere of argon, a bright orange solution of the ruthenium complex **12** (3 mg, 0.02 mmol, 5 mol %) in degassed CH_3OH (1 mL) was added by syringe to a stirred solution of alkene **3** (56 mg, 0.17 mmol) and alkyne **4** (24.5 mg, 0.17 mmol)[19] in degassed CH_3OH (4 mL). The solution was heated at reflux for 2.5 h. After cooling to rt the mixture was diluted with ether (30 mL), filtered and concentrated *in vacuo* to give an orange oil (75 mg). Purification by column chromatography on silica gel (1:40 CH_3OH/CH_2Cl_2), gave butenolide **10** (30 mg, 0.07 mmol, 42 %) as a yellow oil. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 6.99 (1H, d, *J* = 1.5 Hz, C**H**=CCO_2), 5.56 (1H, dt, *J* = 15.1, 6.5 Hz, C**H**=CHCH_2CCO_2), 5.46 (1H, dt, *J* = 15.1, 6.5 Hz, C**H**CH_2CCO_2), 5.01 (1H, dq, *J* = 1.5, 6.5

Hz, C**H**CH_3), 3.83 (1H, q, *J* = 6.2 Hz, C**H**CHOH), 3.76 (1H, t, *J* = 7.0 Hz, C**H**C$(CH_3)_2$OH), 3.44 (1H, q, *J*= 5.5 Hz, C**H**OH), 2.94 (2H, d, *J* = 6.5 Hz, C$\mathbf{H_2}$CCO_2), 2.50 (2H, br, O**H**), 2.04 (2H, q, *J* = 6.6 Hz, C$\mathbf{H_2}$CH=CHCCO_2), 1.96-1.69 (4H, m, C$\mathbf{H_2}$C$\mathbf{H_2}$ (THF)), 1.40 (3H, d, *J* = 6.5 Hz, C$\mathbf{H_3}$CH), 1.27 (3H, s, (C$\mathbf{H_3}$)$_2$COH), 1.51-1.25 (16H, m, (C$\mathbf{H_2}$)$_\mathbf{8}$CHOH), 1.13 (3H, s, (C$\mathbf{H_3}$)$_2$COH); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 173.6 (C), 149.5 (CH), 134.3 (CH), 133.7 (C), 124.4 (CH), 86.3 (CH), 82.6 (CH), 77.7 (CH), 74.6 (CH), 71.7 (C), 34.3 (CH_2), 32.6 (CH_2), 29.8 (CH_2), 29.7 (CH_2), 29.7 (CH_2), 29.5 (CH_2), 29.4 (CH_2), 29.3 (CH_2), 28.5 (CH_2), 28.5 (CH_2), 27.6 (CH_3), 26.2 (CH_2), 25.9 (CH_2), 25.2 (CH_3), 19.3 (CH_3); IR *ν* 3420(br), 2849(s), 1739(s), 1462(s), 1376(m), 1240(s), 1084(m) cm^{-1}; LRMS (ES+) *m/z* 868 (30 %, $[2M+Na]^+$), 445 (100 %, $[M+Na]^+$), 423 (25 %, $[M+H]^+$); HRMS (ES+) calcd for $C_{25}H_{42}O_5Na$ *m/z* 445.2924, found 445.2923.

Compounds 2 & 13. In a steel bomb were placed butenolide **10** (30 mg, 0.07 mmol) and Wilkinson's catalyst (7 mg, 0.007 mmol) in a 1:1 solution of benzene/ethanol (3 mL). After 3 cycles of nitrogen/evacuation, H_2 (2-4 bar) was introduced. The mixture was stirred at rt for 18 h. After releasing the pressure, $CHCl_3$ (10 mL) was added and the mixture filtered, resulting in a brown liquor that was concentrated *in vacuo* and then purified by column chromatography on silica gel (50 % EtOAc/hexane). This gave a yellow oil that contained butenolide **2** and the over reduced lactone **13** as a 3:2 inseparable mixture (28 mg, 95 %).

Compound **2** (selected data): ^{1}H-NMR (300 MHz, $CDCl_3$) δ 6.99 (1H, d, *J* = 1.5 Hz, C**H**=CCO_2), 4.99 (1H, dq, *J* = 1.5, 6.5 Hz, C**H**CH_3), 3.84 (1H, q, *J* = 6.2 Hz, C**H**CHOH), 3.76 (1H, t, *J* = 7.0 Hz, C**H**C$(CH_3)_2$OH), 3.44 (1H, q, *J*= 5.5 Hz, C**H**OH), 2.24 (2H, t, *J* = 7.4 Hz, C$\mathbf{H_2}$CCO_2); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 173.9 (C), 148.9 (CH), 134.3 (CH), 86.2 (CH), 82.6 (CH), 75.1 (CH), 74.4 (CH); LRMS (ES+) of mixture *m/z* 447 (100 %, $[M+Na]^+$), 425 (65 %, $[M+H]^+$).

Compound **13** (selected data): ^{1}H-NMR (300 MHz, $CDCl_3$) δ 4.51-4.41 (1H, m, C**H**CH_3), 3.84 (1H, q, *J* = 6.2 Hz, C**H**CHOH), 3.76 (1H, t, *J* = 7.0 Hz, C**H**C$(CH_3)_2$OH), 3.44 (1H, q, *J*= 5.5 Hz, C**H**OH) (THF protons coincidental for both compounds); LRMS (ES+) of mixture *m/z* 449 (70 %, $[M+Na]^+$), 427 (40 %, $[M+H]^+$).

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References and Notes

‡ Ethyl (4*S*)-4-hydroxy-2-pentynoate (**4**) was prepared by the method of Trost *et al.*[19] Spectroscopic data agreed with that published.[19] Optical purity was assessed by polarimetry

$[\alpha]^{20}_D$ –26.7° (*c*. 0.232, $CHCl_3$) Lit. $[\alpha]^{25}_D$ –28.4° (*c*. 0.206, $CHCl_3$). [19]

† Only one diastereoisomer for each compound (**2** and **13**) is shown in scheme 3.

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