Tetrahedron 69 (2013) 6639–6647

Contents lists available at SciVerse ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Enynone dihydroxylation–cyclisation as a route to densely functionalised 3(2*H*)-furanone derivatives: an approach to the core of the zaragozic acids

Mehrnoosh Ostovar, Charles M. Marson *

Department of Chemistry, University College London, Christopher Ingold Laboratories, 20 Gordon Street, London WC1H OAJ, UK

A R T I C L E I N F O

Article history:
Received 19 March 2013
Received in revised form 15 May 2013
Accepted 28 May 2013
Available online 4 June 2013

Keywords:
3(2*H*)-Furanone
Dihydroxylation
Cyclisation
Zaragozic acid

A B S T R A C T

The synthesis of an advanced intermediate is described that could secure the polyoxygenated core of zaragozic acids and related natural products. The key strategy employs a two-step synthesis of the 3(2*H*)-furanone ring system by catalytic dihydroxylation-mercury(II)/acid-catalysed cyclisation with concomitant deprotection. The scope of the 3(2*H*)-furanone synthesis has been evaluated, and this ring system is shown to remain intact in multi-step reaction sequences. Access to novel, highly oxygenated 3(2*H*)-furanone derivatives has been achieved.

1. Introduction

Natural products containing a tetrahydrofuran ring or a partially saturated furan core (e.g., Fig. 1) often possess pronounced biological activity, and include polyether antibiotics, such as monensin and halichondrin B;[1] inhibitors of serine-threonine proteases, such as the caliculins;[2] and inhibitors of squalene synthase, such as the zaragozic acids.[3–6] The 3(2*H*)-furanone ring system,[7] a Michael acceptor, is present in various sesquiterpenoids possessing anti-inflammatory activity[8] and in a number of naturally occurring anti-tumour agents[9] and bacterial glycosides.[10] The 3(2*H*)-furanone inotilone is a naturally occurring potent COX-2 inhibitor.[11]

The introduction of densely oxygenated functionalities in multiple locations on tetrahydropyran and tetrahydrofuran rings still presents a challenge, and one relevant to many classes of natural products.[1–12] 5-*exo*-Tet cyclisations of epoxy alcohols are often used to prepare 2-hydroxymethyl-substituted tetrahydrofurans;[13] however, the corresponding 5-*endo*-tet cyclisations to give 3-

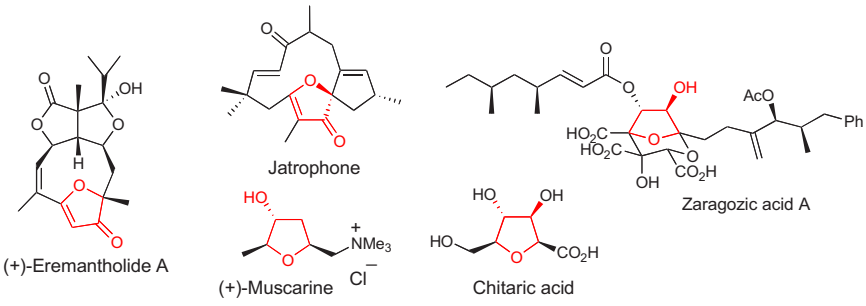


Fig. 1. Some natural products containing 3-oxygenated dihydro- and tetrahydrofuran ring systems.

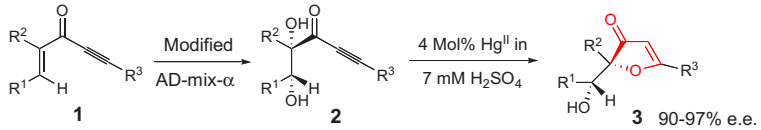
* Corresponding author. Fax: +44 (0) 20 7679 7463; e-mail address: c.m.marson@ucl.ac.uk (C.M. Marson).

0040-4020/$ – see front matter © 2013 Published by Elsevier Ltd.
http://dx.doi.org/10.1016/j.tet.2013.05.125

hydroxytetrahydrofurans are disfavoured, as are cyclisations of hydroxymethyl enones to give 3(2*H*)-furanones. Moreover, epoxy alcohol cyclisations afford tetrahydrofurans rather than dihydrofuran systems, as present, for example, in the anti-cancer agents eremantholide A[9b,14] and jatrophone[9c,15] (Fig. 1). We considered that limitations on access to 3-oxygenated dihydro- and tetrahydrofuran ring systems (Fig. 1) might be countered by catalytic asymmetric synthesis of 3(2*H*)-furanones from enynones using a Sharpless dihydroxylation[16]–cyclisation protocol[17] (Scheme 1), and wished to explore the extent to which that reaction could be applied to the synthesis of natural product ring systems. Compared with other methods for the synthesis of 3(2*H*)-furanones,[18] including acid-catalysed cyclodehydration of α-hydroxy-1,3-diketones,[19] base-catalysed ring closures,[20] and other metal-catalysed cyclisations,[21] the dihydroxylation–cyclisation protocol of Scheme 1 has several notable features, being regioselective, diastereoselective and in many cases enantioselective.[17]

However, reaction of **12** with PBr_3 at 0 °C in diethyl ether gave rise to extensive decomposition. Since a convergent route to ynone **1** was not available, and in case the alkyne was participating in side-reactions, the corresponding diester **15** was prepared by reaction of PBr_3 with the Baylis–Hillman adduct **14**. The allylic bromide **15** was obtained in 69% yield, but displacement with $PhCH_2ONa$ gave only the S_N2' product **16**, none of the required S_N2 product **8** (R=Bn, X=O^{t}Bu) being isolated.

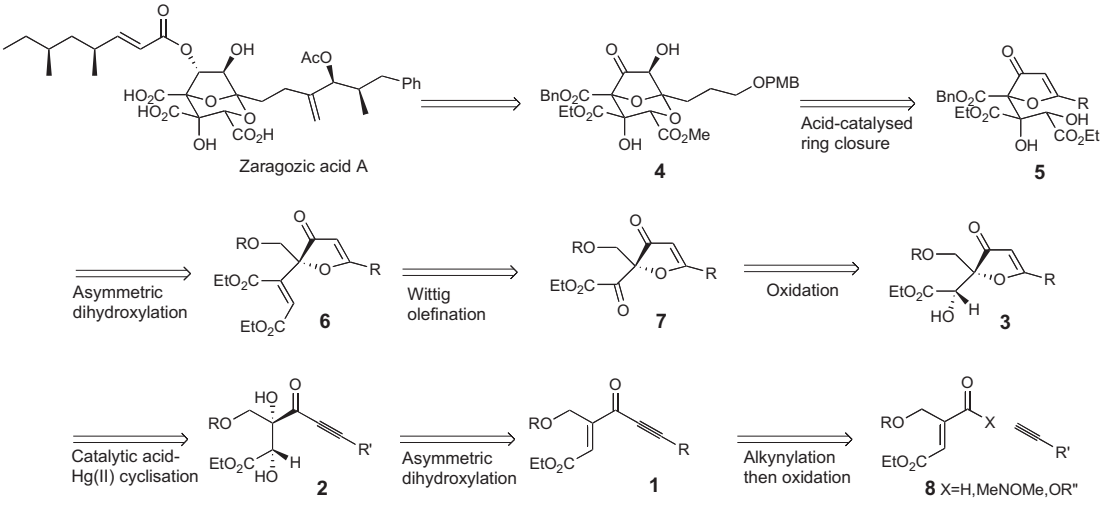
These unexpected difficulties led to a revision of the approach to ynones **1** and consideration of a strategy involving olefination of a pyruvic ester (Scheme 4). Dihydroxylation of *tert*-butyl acrylate afforded **17**, which underwent acylation at the primary position to give acetate **18**, which with BAIB–TEMPO[25] afforded pyruvate ester **19** via a convenient and scaleable route. Wittig olefination afforded a quantitative yield of a 2.7:1 mixture of the triesters **8a** and **8b**, respectively, which were separated by column chromatography.



Scheme 1. Catalytic asymmetric synthesis of substituted 3(2*H*)-furanones.[17]

The core of the zaragozic acids was selected, its construction being envisaged by two cyclisations onto the alkynyl unit, as part of a synthetic sequence that would also provide a rigorous test of the scope of the 3(2*H*)-furanone synthesis (Scheme 1) in multi-step reactions. Additionally, an achiral enynone of type **1** (Scheme 2) might be cyclised, modified and a further two chiral, oxygenated centres created by a second Sharpless asymmetric dihydroxylation[22] to give the advanced intermediate **5** (Scheme 2).

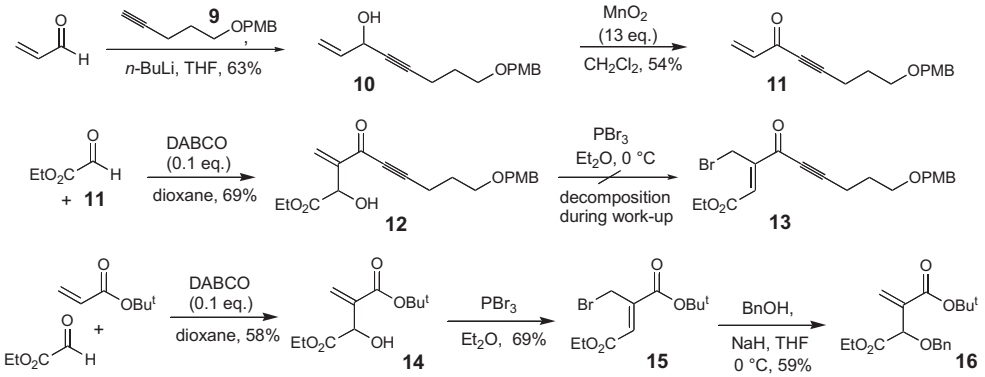
Given that appropriate aldehydes were not available, an alkynyl anion addition would now be to a carboxy group rather than an aldehyde; a Weinreb amide partner was sought, which from previous work[17] was known to be compatible with the required dihydroxylation–cyclisation protocol of Scheme 1. Hydrolysis of **8a** (1:1 TFA/CH_2Cl_2, 99%) afforded **20a**, which with thionyl chloride formed quantitatively the unstable acid chloride **21a** that was immediately reacted with *N*,*O*-dimethylhydroxylamine to give the



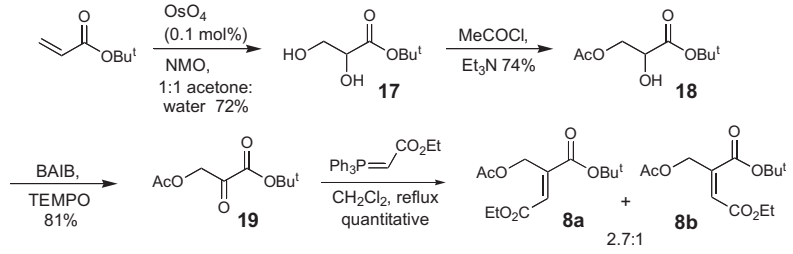
Scheme 2. Retrosynthetic analysis for construction of the core of zaragozic acid A via a 3(2*H*)-furanone. R′=$(CH_2)_3$OPMB.

2. Results and discussion

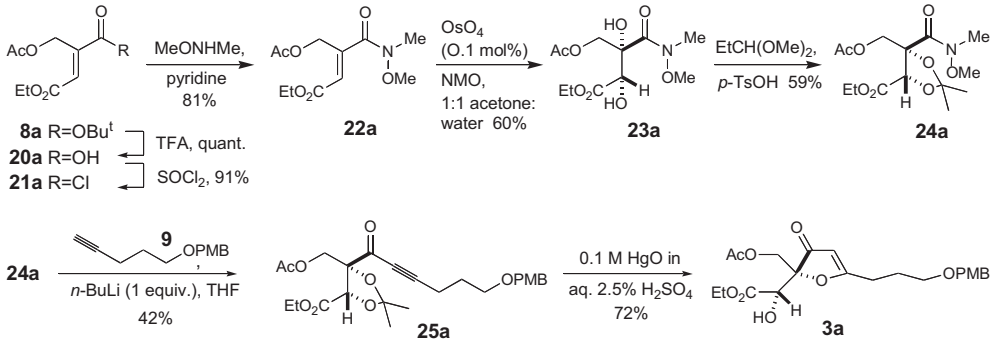
γ-Substituted unsaturated esters of type **1** appear to be unknown, and **8** are little known.[23] The carbon framework of **1** was readily assembled by an addition of the alkynyl anion of **9** to acrolein, followed by oxidation with MnO_2 to give **11**, which participated in a Baylis–Hillman reaction with ethyl glyoxylate to give **12** (Scheme 3). Such allylic alcohols are known to undergo efficient S_N2' displacement to give the corresponding allyl bromides.[24] Weinreb amide **22a** (Scheme 5). Unfortunately, this amide proved resistant to dihydroxylation using AD-mix reagents,[26] so a racemic synthesis was developed. Osmylation under Upjohn conditions[27] afforded **23a** as a single diastereoisomer, which was protected as the acetal **24a**. Addition of the alkynyl anion of **9** afforded the ynone **25a**, which underwent both deprotection and cyclisation when treated with catalytic quantities of Hg(II) and sulfuric acid, a reagent system that also effects cyclisation of 1-alkynyl-2,3-epoxy alcohols to 2,3-dihydro-4*H*-pyran-4-ones.[28]



Scheme 3. A Baylis–Hillman approach to γ-substituted unsaturated esters.



Scheme 4. Synthesis of acetoxymethylmaleate and succinate esters.



Scheme 5. Synthesis of *rel*-(2*S*,2′*S*)-2,3-dihydro-3(2*H*)-furanone **3a**.

The same sequence of reactions was performed on the stereoisomer **20b**, obtained by hydrolysis of **8b**, led ultimately to the 3(2*H*)-furanone **3b** (Scheme 6), the diastereoisomer of **3a** obtained above. Schemes 5 and 6 illustrate the reliability and stereointegrity of these methods for the preparation of polysubstituted 3(2*H*)-furanones.

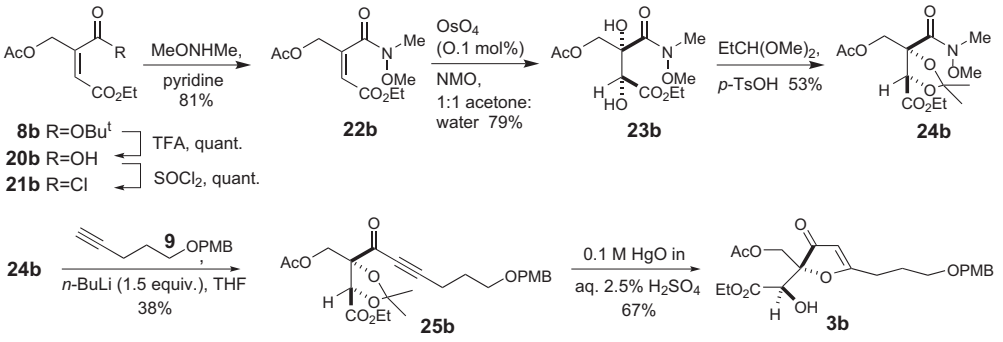
The α-hydroxy ester **3a** was oxidised using the Dess–Martin periodinane to give the unusual and unstable pyruvate ester **7** (Scheme 7), which was subjected to Wittig olefination without further purification to give the single diastereoisomer **6**. This compound was resistant to dihydroxylation with AD-mix reagents, as was the case for diesters **22**. However, dihydroxylation under Upjohn conditions[27] afforded a mixture of the diastereoisomers **5a** and **5b**. The major diastereoisomer was isolated but could not be unequivocally assigned. Despite the precedent for the conjugate addition of alcohols to 3(2*H*)-furanones under acidic conditions, a variety of reagents did not afford evidence for the formation of the bicyclo compound **4a**, containing the core oxygenated framework of zaragozic acid, or any other bicyclo system.

Neither *p*-TsOH (10 mol %) in CH_2Cl_2 at reflux, nor $AuCl_3$ (2 mol %) in methanol effected cyclisation. Osmium tetroxide-catalysed dihydroxylation of the double bond in the ring, which could have accelerated cyclisation, could not be achieved using Upjohn conditions.[27] A bromo-etherification of the ring double bond in **5** was attempted using *N*-bromosuccinimide, and an epoxidation using *m*-chloroperoxybenzoic acid was also attempted, but again cyclisation could not be achieved. Nevertheless, precedent suggests that cyclisation to the desired bicyclo cores should be achievable, and further investigation is warranted. The methodology presented here would then permit access to a diverse selection of novel compounds containing the 4,8-dioxabicyclo[3.2.1] octane core.

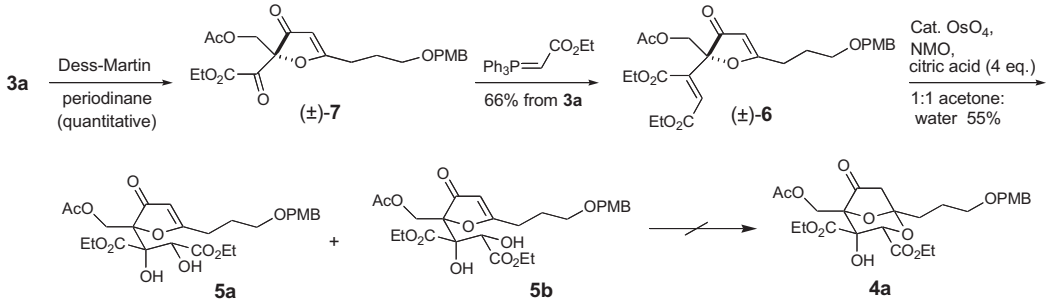
3. Experimental section

3.1. General

All chemicals were used as supplied. Solvents used were reagent grade, and anhydrous THF, diethyl ether, dichloromethane and



Scheme 6. Synthesis of *rel*-(2*S*,2′*R*)-2,3-dihydro-3(2*H*)-furan-2-one **3b**.



Scheme 7. Progression of (±)-**7** towards the zaragozic acid core.

acetonitrile were obtained from an Anhydrous Engineering (USA) solvent system after passing through an alumina column. Glassware was flame-dried prior to use. Compound homogeneity was monitored by ascending thin-layer chromatography, performed on Merck 0.2 mm aluminium-backed silica gel 60 F_{254} plates and visualised using UV radiation at 254 nm or by staining with vanillin, potassium permanganate, anisaldehyde or ninhydrin. Column chromatography was performed using Merck 0.040–0.063 mm, 230–400 mesh silica gel. Petroleum ether refers to the 40–60 °C boiling fraction, unless otherwise stated. Evaporation refers to the removal of solvent under reduced pressure. Melting points were determined using an Electrothermal 9100 instrument, and are uncorrected. Infrared (IR) spectra were recorded on a Shimadzu 100 FT-IR 8700 instrument or a Perkin–Elmer Precisely Spectrum 100 FT-IT spectrometer with ATR, either as neat powders or as thin films. ^{1}H NMR spectra were recorded on a Bruker AMX300, AMX-400, AVANCE-500 and AVANCE-600 spectrometers; chemical shifts are reported in δ parts per million (ppm) relative to the internal reference tetramethylsilane. Mass spectra were obtained on Micromass 70-SE and MAT 900XP instruments.

The following compounds were prepared according to the literature: ethyl (triphenylphosphanylidene)acetate.[29]

*3.1.1. 8-(4-Methoxybenzyloxy)-oct-1-en-4-yn-3-ol (**9**).* To a solution of 4-pentyn-1-ol (1.00 g, 11.8 mmol) in dry dichloromethane (10 mL) 20 °C under an atmosphere of nitrogen, was added a solution of freshly prepared *p*-methoxybenzyl trichloroacetimidate (6.71 g, 23.7 mmol) in dichloromethane (3 mL) in a slow stream. After 5 min, pyridinium *p*-toluenesulfonate (1.49 g, 5.94 mmol) was added in one portion. The mixture was stirred at room temperature for 3 h and then quenched with solid sodium hydrogen carbonate followed by saturated aqueous sodium hydrogen carbonate (10 mL). The resulting mixture was diluted with dichloromethane (5 mL). The organic layer was separated, and the aqueous layer was extracted with dichloromethane (3×10 mL). The combined organic layers were dried over $MgSO_4$, filtered and evaporated. Chromatography of the residue on silica gel (1:15 ethyl acetate/petroleum ether) gave **9** (2.40 g, 98%) as a colourless oil; IR ν_{max} (cm^{-1}) 3292, 2935, 2857, 2117, 1611; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.27 (2H, d, *J*=8.6 Hz), 6.88 (2H, d, *J*=8.6 Hz), 4.44 (2H, s), 3.80 (3H, s), 3.55 (2H, t, *J*=6.2 Hz), 2.31 (2H, td, *J*=7.1, 2.7 Hz), 1.95 (1H, t, *J*=2.7 Hz), 1.86–1.78 (2H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.2, 130.6, 129.2, 113.8, 84.0, 72.7, 68.5, 68.4, 55.3, 28.7, 15.3; LRMS *m*/*z* (+CI, %) 204 (18), 203 (49), 121 (100); HRMS+CI calcd for $C_{13}H_{16}O_2$ 204.1145, found: 204.1145.

*3.1.2. 8-(4-Methoxybenzyloxy)-oct-1-en-4-yn-3-ol (**10**).* To a solution of 1-(4-methoxybenzyloxy)pent-4-yne (**9**) (2.00 g, 9.79 mmol) in dry tetrahydrofuran (5 mL) under an atmosphere of nitrogen was added dropwise *n*-butyllithium (2.5 M in hexane, 4.85 mL, 12.1 mmol) at −78 °C over 5 min. After the mixture was stirred at this temperature for 45 min, acrylaldehyde (0.98 mL, 14.6 mmol) was added. The mixture was allowed to warm to 20 °C over 30 min. When no aldehyde remained (45 h, by TLC), the mixture was quenched with saturated aqueous ammonium chloride (5 mL) and the organic layer was extracted with diethyl ether (3×10 mL). The combined organic layers were washed with brine (10 mL), dried over $MgSO_4$, filtered and evaporated. Chromatography of the residue on silica gel (1:3 ethyl acetate/petroleum ether) gave **10** (1.6 g, 63%) as a colourless oil; IR ν_{max} (cm^{-1}) 3403, 2934, 2860, 2213, 1671, 1611; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.25 (2H, d, *J*=8.6 Hz), 6.87 (2H, d, *J*=8.6 Hz), 5.93 (1H, m), 5.40 (1H, dd, *J*=17.0, 1.2 Hz), 5.16 (1H, dd, *J*=10.0, 1.2 Hz), 4.80 (1H, d, *J*=3.3 Hz), 4.42 (2H, s), 3.79 (3H, s), 3.51 (2H, t, *J*=6.2 Hz), 2.34 (2H, td, *J*=7.1, 1.9 Hz), 1.92–1.88 (2H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.2, 137.6, 130.5, 129.3, 115.9, 113.8, 86.4, 79.4, 72.6, 68.4, 63.3, 55.3, 28.7, 15.6; LRMS *m*/*z* (+CI, %) 243 (5), 121 (100); HRMS+CI calcd for $[M-OH]^+$ $C_{16}H_{19}O_2$ 243.1385, found: 243.1395.

*3.1.3. 8-(4-Methoxybenzyloxy)-oct-1-en-4-yn-3-one (**11**).* A solution of 8-(4-methoxybenzyloxy)-oct-1-en-4-yn-3-ol (**10**) (1.20 g,

4.61 mmol) in dichloromethane (3 mL) was added in one portion to a stirred suspension of manganese dioxide (5.21 g, 60.0 mmol) in dichloromethane (50 mL) under an atmosphere of nitrogen. Stirring was continued at 20 °C for 24 h. Then the mixture was filtered through Celite, and the Celite thoroughly washed with dichloromethane (25 mL). The combined organic filtrates were evaporated. Chromatography of the residue (1:22 ethyl acetate/petroleum ether) gave **11** (0.65 g, 54%) as a yellow oil; IR ν_{max} (cm^{-1}) 2939, 2217, 1725, 1648, 1612; ^1H NMR (600 MHz, $CDCl_3$) δ 7.26 (2H, d, J=8.6 Hz), 6.89 (2H, d, J=8.6 Hz), 6.50 (1H, dd, J=17.3, 0.9 Hz), 6.38 (1H, m), 6.14 (1H, dd, J=10.2, 1.0 Hz), 4.42 (2H, s), 3.80 (3H, s), 3.56 (2H, t, J=6.0 Hz), 2.56 (2H, t, J=7.0 Hz), 1.92–1.88 (2H, m); ^{13}C NMR (150 MHz, $CDCl_3$) δ 179.1, 159.2, 138.0, 133.4, 130.3, 113.8, 95.0, 78.7, 72.7, 68.0, 55.3, 28.0, 16.0; LRMS m/z (+CI, %) 259 (13), 241 (53), 217 (40), 157 (100), 121 (61); HRMS+CI calcd for $C_{16}H_{19}O_3$ 259.1334, found: 259.1326.

*3.1.4. Ethyl 2-hydroxy-9-(4-methoxybenzyloxy)-3-methylene-4-oxonon-5-ynoate (**12**).* 1,4-Diazabicyclo[2.2.2]octane (4.3 mg, 0.038 mmol) was added in one portion at 0 °C to a solution of 8-(4-methoxybenzyloxy)-oct-1-en-4-yn-3-one (**11**) (0.10 g, 0.38 mmol) and ethyl glyoxylate (0.12 g of 50% w/w solution in toluene, 0.58 mmol) in dioxane (0.4 mL). The mixture was kept at 20 °C for 5 h, then poured into hydrochloric acid (0.3 mL, 10%) and the aqueous layer was extracted with ethyl acetate (3×2 mL). The combined organic layers were dried over $MgSO_4$, filtered and evaporated. Chromatography of the residue on silica gel (1:2 ethyl acetate/petroleum ether) gave **12** (90 mg, 69%) as a colourless oil; IR ν_{max} (cm^{-1}) 3443, 2932, 2857, 2213, 1735, 1644, 1512; ^1H NMR (600 MHz, $CDCl_3$) δ 7.26 (2H, d, J=8.6 Hz), 6.89 (2H, d, J=8.6 Hz), 6.58 (1H, s), 6.27 (1H, s), 4.92 (1H, s), 4.45 (2H, s), 4.24 (2H, q, J=7.1 Hz), 3.81 (3H, s), 3.55 (2H, t, J=5.9 Hz), 2.57 (2H, t, J=7.1 Hz), 1.92–1.88 (2H, m), 1.23 (3H, t, J=7.1 Hz); ^{13}C NMR (150 MHz, $CDCl_3$) δ 177.8, 172.3, 159.2, 146.2, 133.3, 130.2, 129.3, 113.8, 95.8, 78.4, 72.7, 69.7, 68.0, 62.3, 55.3, 27.9, 16.0, 14.1; LRMS m/z (+CI, %) 361 (15), 240 (50), 121 (100), 103 (50); HRMS+CI calcd for $C_{20}H_{25}O_6$ 361.1651, found: 361.1669.

*3.1.5. 4-tert-Butyl-1-ethyl-2-hydroxy-3-methylenesuccinate (**14**).* 1,4-Diazabicyclo[2.2.2]octane (0.17 g, 1.56 mmol) was added in one portion at 0 °C to a solution of *tert*-butyl acrylate (2.0 g, 15.6 mmol) and ethyl glyoxylate (4.76 g of a 50% w/w solution in toluene, 23.4 mmol) in dioxane (15 mL). The mixture was kept at room temperature for 48 h, then poured into hydrochloric acid (5 mL, 10%) and the aqueous layer extracted with ethyl acetate (3×20 mL). The combined organic layers were dried over $MgSO_4$, filtered and evaporated. Chromatography of the residue on silica gel (1:3 ethyl acetate/petroleum ether) gave **14** (2.08 g, 58%) as a yellow oil; IR ν_{max} (cm^{-1}) 3499, 2980, 2935, 1738, 1713, 1636; ^1H NMR (600 MHz, $CDCl_3$) δ 6.21 (1H, s), 5.78 (1H, s), 4.73 (1H, s), 4.17 (2H, m), 1.42 (9H, s), 1.20 (3H, t, J=7.1 Hz); ^{13}C NMR (150 MHz, $CDCl_3$) δ 172.5, 164.3, 139.4, 128.2, 81.8, 71.3, 62.2, 27.9, 14.0; LRMS m/z (+ES, %) 254 (45), 197 (100); HRMS+ES calcd for $C_{11}H_{18}NaO_5$ 253.1052, found: 253.1049.

*3.1.6. 4-tert-Butyl-4-ethyl-2-bromomethylbut-2-enedioate (**15**).* To a round-bottomed flask containing 4-*tert*-butyl-1-ethyl-2-hydroxy-3-methylenesuccinate (**14**) (1.00 g, 4.34 mmol) in dry diethyl ether (10 mL) under an atmosphere of nitrogen, was added phosphorus tribromide (0.42 mL, 4.34 mmol) at 0 °C. The mixture was stirred for 1 h, then quenched by dropwise addition of water (10 mL). The organic layer was separated and the aqueous layer was extracted with diethyl ether (2×10 mL). The combined organic layers were dried over $MgSO_4$, filtered and the filtrate evaporated. Chromatography of the residue on silica gel (20:1 petroleum ether/ethyl acetate) gave **15** (0.87 g, 69%) as a colourless oil; IR ν_{max} (cm^{-1}) 2980, 2935, 1716, 1645; ^1H NMR (400 MHz, $CDCl_3$) δ 6.70 (1H, s), 4.67 (2H, s), 4.25 (2H, q, J=7.1 Hz), 1.51 (9H, s), 1.31 (3H, t, J=7.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.9, 163.7, 144.2, 127.7, 83.0, 61.2, 27.9, 23.0, 14.1; LRMS m/z (+CI, %) 293 (22), 238 (98), 237 (100); HRMS+CI calcd for $C_{11}H_{18}BrO_4$ 293.0389, found: 293.0385.

*3.1.7. 4-tert-Butyl-1-ethyl-2-benzyloxy-3-methylene succinate (**16**).* To a solution of benzyl alcohol (30 mg, 0.28 mmol) in dry tetrahydrofuran (2.0 mL) at 0 °C was added sodium hydride (60% in mineral oil, 14 mg, 0.36 mmol) in one portion. The mixture was stirred for 1 h, then transferred by means of a double-tipped ended needle, dropwise over 10 min to a stirred solution of 1-*tert*-butyl-4-ethyl-2-bromomethyl-but-2-enedioate (**15**) (75 mg, 0.26 mmol) in tetrahydrofuran (2.0 mL), maintained at 0 °C. The mixture was stirred for 1 h at room temperature and then quenched by dropwise addition of water (3 mL). The aqueous layer was separated and extracted with diethyl ether (3×5 mL). The combined organic layers were dried over $MgSO_4$, filtered and evaporated. Chromatography of the residue on silica gel (1:7 ethyl acetate/petroleum ether) gave **16** (48 mg, 59%) as a colourless oil; IR ν_{max} (cm^{-1}) 2979, 2933, 1714; ^1H NMR (400 MHz, $CDCl_3$) δ 7.36–7.27 (5H, m), 6.33 (1H, s), 5.91 (1H, s), 4.75 (1H, s), 4.61–4.67 (2H, m), 4.16 (2H, q, J=7.1 Hz), 1.44 (9H, s), 1.22 (3H, t, J=7.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.0, 164.5, 138.1, 137.3, 128.6, 128.1, 128.0, 127.2, 81.7, 76.4, 72.2, 61.4, 28.2, 14.3; LRMS m/z (+ES, %) 343 (33), 287 (100); HRMS+ES calcd for $C_{18}H_{24}NaO_5$ 343.1521, found: 343.1521.

*3.1.8. 4-tert-Butyl 2,3-dihydroxypropionate (**17**).* *N*-Methylmorpholine-*N*-oxide (18.4 g, 94.4 mmol), then osmium tetroxide (0.21 g, 0.1 mol %; CAUTION: TOXIC) were added to a solution of *tert*-butyl acrylate (11.0 g, 85.8 mmol) in and mixture of acetone (260 mL) and water (260 mL) at 0 °C. The mixture was stirred at room temperature for 72 h, after which saturated aqueous sodium sulfite (170 mL) was added and the mixture then stirred for a further 15 min, prior to dilution with water (170 mL). The aqueous portion was extracted with dichloromethane (3×300 mL) and the organic layers were combined, washed with brine (400 mL) and dried over $MgSO_4$, then evaporated. Chromatography of the residue on silica gel (1:1 petroleum ether/diethyl ether) gave **17** (10.0 g, 72%) as a colourless oil; IR ν_{max} (cm^{-1}) 3424, 2978, 2931, 1728; ^1H NMR (600 MHz, $CDCl_3$) δ 4.14 (1H, t, J=3.8 Hz), 3.86 (1H, dd, J=11.6, 3.2 Hz), 3.78 (1H, dd, J=11.6, 4.1 Hz), 2.85 (2H, br s), 1.49 (9H, s); ^{13}C NMR (150 MHz, $CDCl_3$) δ 172.3, 83.2, 71.8, 64.3, 28.0; LRMS m/z (+CI, %) 163 (100), 107 (50); HRMS+CI calcd for $C_7H_{15}O_4$ 163.0970, found: 163.0974.

*3.1.9. 4-tert-Butyl 3-acetoxy-2-hydroxypropionate (**18**).* To a stirred solution of *tert*-butyl 2,3-dihydroxypropionate (**17**) (10.0 g, 61.6 mmol) in dichloromethane (80 mL) at 0 °C was added triethylamine (11.3 mL, 80.1 mmol) dropwise over 15 min. After 0.5 h, acetyl chloride (4.8 mL, 68 mmol) was added dropwise over 40 min at 0 °C. The mixture was stirred for 2 h, then quenched with water (20 mL). The organic layer was separated and the aqueous layer was extracted with dichloromethane (3×20 mL), dried over $MgSO_4$, filtered and the filtrate evaporated. Chromatography of the residue on silica gel (1:4 diethyl ether/petroleum ether) gave **18** (9.32 g, 74%) as a white solid, mp 56–58 °C; IR ν_{max} (cm^{-1}) 3443, 2979, 2936, 1730; ^1H NMR (300 MHz, $CDCl_3$) δ 4.37–4.19 (3H, m), 3.25 (1H, br d, J=5.6 Hz), 2.10 (3H, s), 1.41 (9H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.1, 170.6, 83.2, 69.4, 65.7, 27.8, 20.6; LRMS m/z (+FAB, %) 227 (73), 176 (100); HRMS+FAB calcd for $C_9H_{16}NaO_5$ 227.0895, found: 227.0892.

*3.1.10. 4-tert-Butyl 3-acetoxy-2-oxopropionate (**19**).* To a solution of *tert*-butyl 3-acetoxy-2-hydroxypropionate (**18**) (3.0 g, 14.6 mmol) in dichloromethane (180 mL) were added TEMPO (0.34 g, 2.2 mmol) and iodobenzene diacetate (7.09 g, 22.0 mmol) at room temperature. The mixture was stirred for 24 h and then quenched

with aqueous sodium thiosulfate (50 mL, 10%). The aqueous layer was extracted with dichloromethane (3×50 mL). The combined organic layers were dried over $MgSO_4$ and the filtered solution was evaporated. Chromatography of the residue on silica gel (1:4 diethyl ether/petroleum ether) gave **19** (2.40 g, 81%) as a yellow oil; IR ν_{max} (cm^{-1}) 2980, 2900, 1729; ^1H NMR (400 MHz, $CDCl_3$) δ 5.08 (2H, s), 2.16 (3H, s), 1.53 (9H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 187.5, 170.0, 158.3, 85.1, 66.6, 27.7, 20.3; LRMS *m/z* (+CI, %) 203 (19), 161 (100); HRMS+CI calcd for $C_9H_{15}O_5$ 203.0920, found: 203.0902.

*3.1.11. (E) and (Z)-1-tert-Butyl 4-ethyl-2-acetoxymethylbut-2-enedioate (**8a**) and (**8b**).* To a solution of ethyl (triphenylphosphanylidene)-acetate (7.36 g, 21.1 mmol) in dichloromethane (40 mL) at reflux was added *tert*-butyl 3-acetoxy-2-oxo-propionate (**19**) (2.86 g, 14.1 mmol) in dichloromethane (20 mL) dropwise over 20 min. The mixture was heated at reflux for 2 h; TLC indicated that no ketone remained and showed two new spots corresponding to the products (2.7:1 trans- to cis-isomers). The solvent was evaporated and the residue was redissolved in the minimum volume of dichloromethane and applied to a silica gel column. Chromatography of the residue (1:8 diethyl ether/petroleum ether) gave **8a** (2.8 g, 73%) as a yellow oil; IR ν_{max} (cm^{-1}) 2980, 1732, 1716, 1655; ^1H NMR (400 MHz, $CDCl_3$) δ 6.78 (1H, s), 5.17 (2H, s), 4.40 (2H, q, *J*=7.1 Hz), 2.07 (3H, s), 1.48 (9H, s), 1.28 (3H, t, *J*=7.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.2, 164.8, 164.3, 141.6, 130.0, 82.5, 61.2, 58.1, 27.9, 20.6, 14.0; LRMS *m/z* (+FAB, %) 295 (80), 217 (100), 199 (55), 176 (90), 155 (71); HRMS+FAB calcd for $C_{13}H_{20}NaO_6$ 295.1158, found: 295.1159. 2D NOE analysis did not show long-range interaction of the olefinic hydrogen atom with the methylene group.

A reaction using *tert*-butyl 3-acetoxy-2-oxo-propionate (**19**) (0.35 g, 1.73 mmol) was carried out and worked up as above. Chromatography (1:5 diethyl ether/petroleum ether) gave **8b** (92 mg, 27%) as an orange oil; IR ν_{max} (cm^{-1}) 2981, 1735, 1722, 1660; ^1H NMR (400 MHz, $CDCl_3$) δ 6.59 (1H, s), 4.74 (2H, s), 4.18 (2H, q, *J*=7.2 Hz), 2.07 (3H, s), 1.47 (9H, s), 1.25 (3H, t, *J*=7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.9, 164.9, 164.4, 141.8, 122.4, 83.0, 61.2, 63.1, 61.0, 27.9, 20.6, 14.1; LRMS *m/z* (+ES, %) 295 (20), 239 (100); HRMS+ES calcd for $C_{13}H_{20}NaO_6$ 295.1158, found: 295.1156. 2D NOE analysis showed a long-range interaction of the olefinic hydrogen atom with the methylene group.

*3.1.12. (E)-4-Ethyl-2-acetoxymethylbut-2-enedioate (**20a**).* To a solution of (*E*)-1-*tert*-butyl-4-ethyl-2-acetoxymethyl-but-2-enedioate (**8a**) (0.80 g, 2.93 mmol) in dichloromethane (10 mL), trifluoroacetic acid (10 mL) was added at 0 °C and the mixture was stirred for 2 h at 20 °C. Volatile material was removed under reduced pressure to leave **20a** (0.63 g, quantitative) as an orange oil requiring no purification; IR ν_{max} (cm^{-1}) 3700–2400, 2983, 1721, 1660; ^1H NMR (500 MHz, $CDCl_3$) δ 7.00 (1H, s), 5.19 (2H, s), 4.23 (2H, q, *J*=7.1 Hz), 2.02 (3H, s), 1.30 (3H, t, *J*=7.1 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.6, 169.7, 164.4, 138.7, 133.1, 67.2, 61.5, 20.6, 14.0; LRMS *m/z* (+CI, %) 217 (46), 157 (100); HRMS+CI calcd for $C_9H_{13}O_6$ 217.0712, found: 217.0715.

*3.1.13. (E)-4-Ethyl-4-acetoxy-3-chlorocarbonylbut-2-enedioate (**21a**).* To a solution of (*E*)-4-ethyl 2-acetoxymethylbut-2-enedioate (**20a**) (0.63 g, 2.93 mmol) in dichloromethane (20 mL) cooled in an ice-bath under nitrogen, was added thionyl chloride (0.57 mL, 7.93 mmol) dropwise with stirring. The mixture was then heated under nitrogen at reflux at 60 °C. When the reaction was complete, as indicated by TLC analysis, the solvent and the excess thionyl chloride were evaporated under reduced pressure at 40 °C to give **21a** (0.63 g) as a dark brown oil, which was used directly in the next step; IR ν_{max} (cm^{-1}) 2981, 2910, 1783, 1726.

*3.1.14. (E)-Ethyl-4-acetoxy-3-(methoxymethylcarbamoyl)-but-2-enoate (**22a**).* To a solution of ethyl (*E*)-4-acetoxy-3-chlorocarbonylbut-2-enoate (**21a**) (0.63 g, 2.68 mmol) in dichloromethane (10 mL) at 0 °C was added *N,O*-dimethylhydroxylamine hydrochloride (0.44 g, 4.56 mmol) followed by pyridine (0.87 mL, 10.7 mmol). The mixture was stirred at 20 °C; progress of the reaction was monitored by TLC. On completion, (usually 3 h) the mixture was acidified using aqueous hydrochloric acid (2 M, 5 mL), and the aqueous layer was extracted with dichloromethane (3×5 mL). The combined organic layers were washed with saturated aqueous sodium hydrogen carbonate (2×15 mL) followed by brine (15 mL). The organic layer was dried over $MgSO_4$, filtered and evaporated. The residue was purified by column chromatography (1:1 ether/petroleum ether) to give **22a** (0.56 g, 81%) as an orange oil; IR ν_{max} (cm^{-1}) 2982, 2940, 1744, 1716, 1653; ^1H NMR (300 MHz, $CDCl_3$) δ 5.98 (1H, s), 5.38 (2H, s), 4.17 (2H, q, *J*=7.1 Hz), 3.60 (3H, s), 3.20 (3H, s), 1.99 (3H, s), 1.25 (3H, t, *J*=7.1 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.0, 168.0, 164.7, 149.0, 120.6, 61.4, 61.0, 60.9, 30.8, 20.6, 14.1; LRMS *m/z* (+CI, %) 260 (100), 200 (26); HRMS+CI calcd for $C_{11}H_{18}NO_6$ 260.1134, found: 260.1143.

*3.1.15. rel-(2S,3S)-Ethyl 3-acetoxymethyl-2,3-dihydroxy-N-methoxy-N-methylsuccinate (**23a**).* *N*-Methylmorpholine-*N*-oxide (0.17 g, 1.27 mmol) then osmium tetroxide (14.7 mg, 5 mol %; CAUTION: TOXIC) were added to a solution of ethyl (*E*)-4-acetoxy-3-(methoxymethylcarbamoyl)-but-2-enoate (**22a**) (0.30 g, 1.15 mmol) in a mixture of acetone (3.5 mL) and water (3.5 mL) at 0 °C. The mixture was stirred at room temperature for 48 h, after which saturated aqueous sodium sulfite (3 mL) was added, and the mixture stirred for a further 15 min, then diluted with water (3 mL). The aqueous portion was extracted with dichloromethane (4×10 mL), dried over $MgSO_4$, filtered and evaporated. Chromatography of the residue on silica gel (2:1 ethyl acetate/petroleum ether) gave **23a** (0.20 g, 60%) as a yellow oil; IR ν_{max} (cm^{-1}) 3423, 2983, 2910, 1738, 1650; ^1H NMR (500 MHz, $CDCl_3$) δ 4.75 (1H, s), 4.53 (1H, d, *J*=11.6 Hz), 4.49 (1H, d, *J*=8.0 Hz), 4.45 (1H, d, *J*=11.6 Hz), 4.29–4.25 (2H, m), 3.72 (3H, s), 3.26 (3H, s), 1.97 (3H, s), 1.29 (3H, t, *J*=7.1 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.8, 170.4, 170.1, 79.5, 72.0, 65.6, 62.4, 60.7, 33.7, 21.0, 14.1; LRMS *m/z* (+CI, %) 294 (100), 276 (59), 260 (48); HRMS+CI calcd for $C_{11}H_{20}NO_8$ 294.1189, found: 294.1182.

*3.1.16. rel-(4S,5S)-Ethyl 5-acetoxymethyl-5-(methoxymethylcarbamoyl)-2,2-dimethyl-[1,3]-dioxolane-4-carboxylate (**24a**).* To a solution of (±)-ethyl 3-acetoxymethyl-2,3-dihydroxy-*N*-methoxy-*N*-methylsuccinate (**23a**) (0.18 g, 0.61 mmol) in benzene (1.00 mL; CAUTION: TOXIC) were added 2,2-dimethoxypropane (0.12 g, 1.22 mmol) and *p*-toluenesulfonic acid monohydrate (5.82 mg, 0.03 mmol). The mixture was heated at reflux for 24 h in a Dean and Stark apparatus containing freshly activated 4 Å molecular sieves. The mixture was concentrated and dried in vacuo. The residue was purified by silica gel column chromatography (1:1 ethyl acetate and petroleum ether) to give **24a** (0.12 g, 59%) as a yellow oil; IR ν_{max} (cm^{-1}), 2985, 2940, 1747, 1655; ^1H NMR (300 MHz, $CDCl_3$) δ 5.40 (1H, s), 4.61 (1H, d, *J*=11.5 Hz), 4.32 (1H, d, *J*=11.5 Hz), 4.20–4.12 (2H, m), 3.71 (3H, s), 3.25 (3H, s), 1.99 (3H, s), 1.56 (3H, s), 1.35 (3H, s), 1.27 (3H, t, *J*=7.1 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.8, 169.9, 168.8, 111.7, 85.8, 77.9, 63.1, 61.5, 61.0, 27.2, 27.1, 25.8, 20.6, 14.1; LRMS *m/z* (+CI, %) 334 (100), 260 (26); HRMS+CI calcd for $C_{14}H_{24}NO_8$ 334.1502, found: 334.1491.

*3.1.17. rel-(4S,5S)-Ethyl 5-acetoxymethyl-5-[6-(4-methoxybenzyloxy)-hex-2-ynoyl]-2,2-dimethyl-[1,3]-dioxolane-4-carboxylate (**25a**).* To a solution of 1-(4-methoxybenzyloxy)-pent-4-yne (**9**) (1.74 g, 8.55 mmol) in dry THF (30 mL) under nitrogen was added *n*-butyllithium (1.6 M in hexane, 5.3 mL, 8.55 mmol) dropwise over 10 min at −78 °C. The mixture was warmed to −20 °C for 1 h, then cooled to −78 °C. Then the mixture was added to a −78 °C cold solution of (±)-ethyl 5-acetoxymethyl-5-(methoxymethylcar-

bamoyl)-2,2-dimethyl-[1,3]-dioxolane-4-carboxylate (**24a**) (1.90 g, 5.70 mmol) in dry THF (20 mL) by means of a double-tipped needle. After stirring the mixture for 3 h at −78 °C, saturated aqueous ammonium chloride (15 mL) was added and the mixture was warmed to room temperature. Water was added until two clear layers had formed. The aqueous layer was separated and extracted with diethyl ether (3×30 mL). The combined organic layers were dried over $MgSO_4$, filtered and evaporated. Chromatography of the residue on silica gel (1:4 ethyl acetate/petroleum ether) gave **25a** (1.13 g, 42%) as a yellow oil; IR ν_{max} (cm^{-1}), 3012, 2937, 2839, 2209, 1745, 1675, 1612; ^1H NMR (400 MHz, $CDCl_3$) δ 7.25 (2H, d, J=8.8 Hz), 6.88 (2H, d, J=8.8 Hz), 5.00 (1H, s), 4.44 (2H, s), 4.43 (1H, d, J=12.0 Hz), 4.35 (1H, d, J=12.0 Hz), 4.30–4.20 (2H, m), 3.81 (3H, s), 3.54 (2H, t, J=6.0 Hz), 2.58 (2H, t, J=7.2 Hz), 2.04 (3H, s), 1.97–1.81 (2H, m), 1.62 (3H, s), 1.48 (3H, s), 1.31 (3H, t, J=7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 184.1, 170.0, 167.6, 159.2, 130.2, 129.3, 113.9, 113.8, 113.5, 100.2, 87.9, 78.6, 72.7, 67.9, 62.8, 61.9, 55.3, 27.8, 27.4, 26.6, 20.6, 16.3, 14.1; LRMS m/z (+ES, %) 499 (100), 396 (70); HRMS+ES calcd for $C_{25}H_{32}NaO_9$ 499.1944, found: 499.1953.

*3.1.18. rel-(2S)-Ethyl {(S)-2-acetoxymethyl-5-[3-(4-methoxybenzyloxy)-propyl]-3-oxo-2,3-dihydrofuran-2-yl}-2-hydroxyacetate (**3a**).* To (±)-ethyl-5-acetoxymethyl-5-[6-(4-methoxybenzyloxy)-hex-2-ynoyl]-2,2-dimethyl-[1,3]-dioxolane-4-carboxylate (**25a**) (35 mg, 0.07 mmol) in acetone (5 mL, HPLC grade) was added acidified mercury(II) oxide solution (0.3 mL, 0.1 M), obtained by dissolving yellow mercury(II) oxide in aqueous 2.5% sulfuric acid. The mixture was stirred for 24 h then neutralised by the addition of powdered sodium hydrogen carbonate. The mixture was stirred for a further 1.5 h, filtered and the filtrate evaporated. The residue was dissolved in diethyl ether (10 mL) and the solution was washed with water (10 mL). The aqueous layer was extracted with ether (2×10 mL), and the combined extracts washed with saturated aqueous sodium hydrogen carbonate (10 mL) then brine (10 mL), and dried over $MgSO_4$, filtered and evaporated. The residue was purified by flash column chromatography (1:1 petroleum ether/ethyl acetate) to give **3a** (23 mg, 72%) as a colourless oil; IR ν_{max} (cm^{-1}), 3650–3040, 2935, 1742, 1704, 1594, 1512; ^1H NMR (300 MHz, $CDCl_3$) δ 7.24 (2H, d, J=8.6 Hz), 6.87 (2H, d, J=8.6 Hz), 5.47 (1H, s), 4.56 (1H, d, J=12.1 Hz), 4.48 (1H, d, J=8.8 Hz), 4.42 (2H, s), 4.37 (1H, d, J=12.1 Hz), 4.28 (2H, q, J=7.1 Hz), 3.80 (3H, s), 3.62–3.30 (2H, m), 2.62 (2H, t, J=6.9 Hz), 2.00 (3H, s), 1.97–1.89 (3H, m), 1.31 (3H, t, J=7.1 Hz); ^{13}C NMR (150 MHz, $CDCl_3$) δ 200.7, 194.7, 170.4, 170.3, 159.5, 130.2, 129.6, 114.0, 104.7, 89.1, 73.0, 71.0, 68.6, 62.9, 55.5, 28.1, 26.5, 22.6, 20.8, 14.3; LRMS m/z (+ES, %) 459 (100), 339 (5); HRMS+ES calcd for $C_{22}H_{28}NaO_9$ 459.1631, found: 459.1631.

*3.1.19. (Z)-4-Ethyl-2-acetoxymethylbut-2-enedioate (**20b**).* To a solution of (*E*)-1-*tert*-butyl-4-ethyl-2-acetoxymethyl-but-2-enedioate (**8a**) (9.00 g, 33.0 mmol) in dichloromethane (90 mL), trifluoroacetic acid (90 mL) was added at 0 °C and the mixture was stirred for 3.5 h at 20 °C. Volatile material was removed under reduced pressure to leave **20b** (7.14 g, quantitative) as an orange oil requiring no purification; IR ν_{max} (cm^{-1}) 3680–2220, 2985, 1717, 1656; ^1H NMR (400 MHz, $CDCl_3$) δ 6.34 (1H, s), 4.87 (2H, s), 4.27 (2H, q, J=7.1 Hz), 2.10 (3H, s), 1.30 (3H, t, J=7.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.0, 166.7, 166.3, 141.5, 125.2, 63.0, 62.6, 20.7, 13.8; LRMS m/z (+ES, %) 239 (46), 157 (100); HRMS+ES calcd for $C_9H_{12}NaO_6$ 239.0532, found: 239.0538.

*3.1.20. (Z)-4-Ethyl-4-acetoxy-3-chlorocarbonylbut-2-enedioate (**21b**).* To a solution of (*Z*)-4-ethyl 2-acetoxymethylbut-2-enedioate (**20b**) (8.00 g, 37.0 mmol) in dichloromethane (260 mL) cooled in an ice-bath under nitrogen, was added thionyl chloride (7.2 mL, 0.10 mol) dropwise with stirring. The mixture was then heated under nitrogen at reflux at 60 °C. When the reaction was complete, as indicated by TLC analysis, the solvent and the excess thionyl chloride were evaporated under reduced pressure at 40 °C to give **21b** (9.0 g) as a dark brown oil, which was used directly in the next step; IR ν_{max} (cm^{-1}) 1780.

*3.1.21. (Z)-Ethyl-4-acetoxy-3-(methoxymethylcarbamoyl)-but-2-enoate (**22b**).* To a solution of ethyl (*Z*)-4-acetoxy-3-chlorocarbonylbut-2-enoate (**21b**) (8.68 g, 37.0 mmol) in dichloromethane (110 mL) at 0 °C was added *N*,*O*-dimethylhydroxylamine hydrochloride (6.13 g, 62.8 mmol) followed by pyridine (12 mL, 0.148 mol). The mixture was stirred at 20 °C; progress of the reaction was monitored by TLC. On completion, the mixture was acidified using aqueous hydrochloric acid (2 M, 40 mL), and the aqueous layer was extracted with dichloromethane (2×40 mL). The combined organic layers were washed with saturated aqueous sodium hydrogen carbonate (2×120 mL) followed by brine (15 mL). The organic layer was dried over $MgSO_4$, filtered and evaporated. The residue was purified by column chromatography (1:1 ether/petroleum ether) to give **22b** (6.1 g, 81%) as an orange oil; IR ν_{max} (cm^{-1}) 2981, 2943, 1743, 1716, 1655; ^1H NMR (400 MHz, $CDCl_3$) δ 5.95 (1H, s), 5.29 (2H, s), 4.13 (2H, q, J=7.1 Hz), 3.56 (3H, s), 3.20 (3H, s), 1.95 (3H, s), 1.23 (3H, t, J=7.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.4, 169.9, 164.6, 148.9, 120.3, 69.0, 61.9, 61.2, 60.7, 20.5, 13.9; LRMS m/z (+ES, %) 282 (100); HRMS+ES calcd for $C_{11}H_{17}NaNO_6$ 282.0954, found: 282.0954.

*3.1.22. rel-(2S,3S)-Ethyl 3-acetoxymethyl-2,3-dihydroxy-N-methoxy-N-methylsuccinate (**23b**).* *N*-Methylmorpholine-*N*-oxide (4.41 g, 37.6 mmol) then osmium tetroxide (0.31 mg, 5 mol %; CAUTION: TOXIC) were added to a solution of ethyl (*E*)-4-acetoxy-3-(methoxymethylcarbamoyl)-but-2-enoate (**22b**) (6.25 g, 25.1 mmol) in a mixture of acetone (75 mL) and water (75 mL) at 0 °C. The mixture was stirred at room temperature for 48 h, after which saturated aqueous sodium sulfite (50 mL) was added, and the mixture stirred for a further 15 min, then diluted with water (50 mL). The aqueous portion was extracted with dichloromethane (4×150 mL), dried over $MgSO_4$, filtered and evaporated. Chromatography of the residue on silica gel (2:1 ethyl acetate/petroleum ether) gave **23b** (5.80 g, 79%) as a yellow oil; IR ν_{max} (cm^{-1}) 3421, 2980, 2909, 1736, 1648; ^1H NMR (400 MHz, $CDCl_3$) δ 4.78 (1H, s), 4.54 (1H, d, J=11.3 Hz), 4.50 (1H, d, J=8.0 Hz), 4.46 (1H, d, J=11.3 Hz), 4.30–4.26 (2H, m), 3.73 (3H, s), 3.27 (3H, s), 1.98 (3H, s), 1.30 (3H, t, J=7.1 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.8, 170.4, 169.9, 79.4, 71.9, 65.5, 62.4, 60.7, 33.7, 20.6, 14.0; LRMS m/z (+ES, %) 316 (100), 239 (12), 227 (20); HRMS+ES calcd for $C_{11}H_{19}NaNO_8$ 316.1008, found: 316.1020.

*3.1.23. rel-(4R,5S)-Ethyl 5-acetoxymethyl-5-(methoxymethylcarbamoyl)-2,2-dimethyl-[1,3]-dioxolane-4-carboxylate (**24b**).* To a solution of (±)-ethyl 3-acetoxymethyl-2,3-dihydroxy-*N*-methoxy-*N*-methylsuccinate (**23b**) (5.0 g, 17 mmol) in benzene (25 mL; CAUTION: TOXIC) were added 2,2-dimethoxypropane (5.22 mL, 42.6 mmol) and *p*-toluenesulfonic acid monohydrate (0.16 g, 0.85 mmol). The mixture was heated at reflux for 48 h in a Dean and Stark apparatus containing freshly activated 4 Å molecular sieves. The mixture was concentrated and dried in vacuo. The residue was purified by silica gel column chromatography (1:1 ethyl acetate and petroleum ether) to give **24b** (3.0 g, 53%) as a yellow oil; IR ν_{max} (cm^{-1}), 2985, 2940, 1747, 1655; ^1H NMR (400 MHz, $CDCl_3$) δ 5.39 (1H, s), 4.59 (1H, d, J=11.5 Hz), 4.31 (1H, d, J=11.5 Hz), 4.28–4.12 (2H, m), 3.69 (3H, s), 3.23 (3H, s), 1.97 (3H, s), 1.55 (3H, s), 1.34 (3H, s), 1.25 (3H, t, J=7.1 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.9, 168.7, 166.5, 111.6, 85.7, 77.8, 63.0, 61.8, 61.4, 34.0, 27.1, 25.7, 20.5, 14.0; LRMS m/z (+ES, %) 356 (100); HRMS+ES calcd for $C_{14}H_{23}NaNO_8$ 356.1321, found: 356.1327.

3.1.24. rel-(4S,5S)-Ethyl 5-acetoxymethyl-5-[6-(4-methoxybenzyloxy)-hex-2-ynoyl]-2,2-dimethyl-[1,3]-dioxolane-4-carboxylate

(***25b***). To a solution of 1-(4-methoxybenzyloxy)-pent-4-yne (**9**) (2.70 g, 13.5 mmol) in dry THF (50 mL) under nitrogen was added *n*-butyllithium (1.6 M in hexane, 8.4 mL, 13.5 mmol) dropwise over 10 min at −78 °C. The mixture was warmed to −20 °C for 1 h, then cooled to −78 °C. Then the mixture was added to a −78 °C cold solution of (±)-ethyl 5-acetoxymethyl-5-(methoxymethylcarbamoyl)-2,2-dimethyl-[1,3]-dioxolane-4-carboxylate (**24b**) (3.0 g, 9.0 mmol) in dry THF (20 mL) by means of a double-tipped needle. After stirring the mixture for 3 h at −78 °C, saturated aqueous ammonium chloride (10 mL) and then water (25 mL) were added. The mixture was allowed to warm to room temperature, then water was added until two clear layers had formed. The aqueous layer was separated and extracted with diethyl ether (3×70 mL). The combined organic layers were dried over $MgSO_4$, filtered and evaporated. Chromatography of the residue on silica gel (1:3 ethyl acetate/petroleum ether) gave **25b** (1.63 g, 38%) as a yellow oil; IR ν_{max} (cm^{-1}), 3012, 2937, 2839, 2209, 1748, 1675, 1612; ^1H NMR (400 MHz, $CDCl_3$) δ 7.20 (2H, d, J=8.6 Hz), 6.83 (2H, d, J=8.6 Hz), 4.94 (1H, s), 4.38 (2H, s), 4.34 (1H, d, J=12.1 Hz), 4.27 (1H, d, J=12.1 Hz), 4.25–4.15 (2H, m), 3.76 (3H, s), 3.49 (2H, t, J=5.6 Hz), 2.53 (2H, t, J=7.2 Hz), 1.98 (3H, s), 1.87–1.78 (2H, m), 1.56 (3H, s), 1.43 (3H, s), 1.29 (3H, t, J=7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 184.0, 169.9, 167.5, 159.1, 130.1, 129.1, 113.7, 113.4, 100.1, 87.8, 78.5, 76.7, 67.8, 62.7, 61.8, 60.3, 55.1, 27.7, 27.3, 26.4, 20.5, 16.2, 13.9; LRMS m/z (+ES, %) 499 (100), 396 (8); HRMS+ES calcd for $C_{25}H_{32}NaO_9$ 499.1944, found: 499.1942.

*3.1.25. rel-(2R)-Ethyl {(S)-2-acetoxymethyl-5-[3-(4-methoxybenzyloxy)-propyl]-3-oxo-2,3-dihydrofuran-2-yl}-2-hydroxyacetate (**3b**).* To (±)-ethyl-5-acetoxymethyl-5-[6-(4-methoxybenzyloxy)-hex-2-ynoyl]-2,2-dimethyl-[1,3]-dioxolane-4-carboxylate (**25b**) (0.80 g, 1.67 mmol) in acetone (50 mL, HPLC grade) was added acidified mercury(II) oxide solution (2.5 mL, 0.1 M), obtained by dissolving yellow mercury(II) oxide in aqueous 2.5% sulfuric acid. The mixture was stirred for 24 h then neutralised by the addition of powdered sodium hydrogen carbonate. The mixture was stirred for a further 1.5 h, filtered and the filtrate evaporated. The residue was dissolved in diethyl ether (25 mL) and the solution was washed with water (40 mL). The aqueous layer was extracted with ether (2×25 mL), and the combined extracts washed with saturated aqueous sodium hydrogen carbonate (50 mL) then brine (50 mL), and dried over $MgSO_4$, filtered and evaporated. The residue was purified by flash column chromatography (1:1 petroleum ether/ethyl acetate) to give **3b** (0.49 g, 67%) as a colourless oil; IR ν_{max} (cm^{-1}), 3650–3040, 2935, 1742, 1704, 1594, 1512; ^1H NMR (400 MHz, $CDCl_3$) δ 7.19 (2H, d, J=8.6 Hz), 6.83 (2H, d, J=8.6 Hz), 5.43 (1H, s), 4.52 (1H, d, J=12.0 Hz), 4.44 (1H, d, J=8.8 Hz), 4.40 (2H, s), 4.32 (1H, d, J=12.0 Hz), 4.25 (2H, q, J=7.1 Hz), 3.75 (3H, s), 3.60–3.30 (2H, m), 2.58 (2H, t, J=6.9 Hz), 1.95 (3H, s), 1.90–1.82 (3H, m), 1.27 (3H, t, J=7.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 201.0, 194.4, 170.0, 169.9, 159.1, 129.9, 129.2, 112.9, 104.3, 88.8, 72.6, 70.6, 68.2, 65.5, 55.1, 27.7, 26.1, 22.2, 20.4, 14.0; LRMS m/z (+ES, %) 459 (100), 297 (13); HRMS+ES calcd for $C_{22}H_{28}NaO_9$ 459.1631, found: 459.1617.

*3.1.26. rel-Ethyl {(R)-2-acetoxymethyl-5-[3-(4-methoxybenzyloxy)-propyl]-3-oxo-2,3-dihydrofuran-2-yl}-2-oxoacetate (**7**).* To a solution of *rel*-(2*S*)-ethyl {(*S*)-2-acetoxymethyl-5-[3-(4-methoxybenzyloxy)-propyl]-3-oxo-2,3-dihydrofuran-2-yl}-2-hydroxyacetate (**3a**) (40 mg, 0.09 mmol) in dichloromethane (2 mL) at room temperature were added sodium hydrogen carbonate (38 mg, 0.45 mmol) and Dess–Martin periodinane (58 mg, 0.13 mmol). After stirring for 2 h, saturated aqueous sodium hydrogen carbonate (2 mL) and saturated aqueous sodium sulfite (2 mL) were added. The mixture was stirred for 0.5 h, then the aqueous layer was separated and extracted with dichloromethane (2×8 mL). The combined organic layers were washed with brine (4 mL), dried over $MgSO_4$, filtered and evaporated. The crude product **7** (40 mg, quantitative) was very unstable and used directly for the next step without further purification; IR ν_{max} (cm^{-1}) 2945, 2893, 2832, 1747, 1702, 1601; ^1H NMR (600 MHz, $CDCl_3$) δ 7.26 (2H, d, J=8.6 Hz), 6.89 (2H, d, J=8.6 Hz), 5.61 (1H, s), 5.52 (1H, d, J=2.5 Hz), 5.14 (1H, d, J=2.5 Hz), 4.45 (2H, s), 4.13 (2H, q, J=7.1 Hz), 3.82 (3H, s), 3.52 (2H, t, J=7.6 Hz), 2.06 (3H, s), 2.00–1.93 (2H, m), 1.26 (3H, t, J=7.1 Hz); ^{13}C NMR (150 MHz, $CDCl_3$) δ 187.5, 186.1, 171.2, 159.3, 153.4, 130.1, 129.3, 113.8, 105.3, 96.9, 72.7, 26.0, 21.1, 14.2; LRMS m/z (+FAB, %) 457 (32), 433 (30), 335 (44) 274 (52), 241 (100); HRMS+FAB calcd for $C_{22}H_{26}NaO_9$ 457.1474, found: 457.1469.

*3.1.27. rel-Diethyl 2-{(R)-2-acetoxymethyl-5-[3-(4-methoxybenzyloxy)-propyl]-3-oxo-2,3-dihydrofuran-2-yl}-(Z)-but-2-enedioate (**6**).* To a solution of crude (±)-ethyl {2-acetoxymethyl-5-[3-(4-methoxybenzyloxy)-propyl]-3-oxo-2,3-dihydrofuran-2-yl}-2-oxo-acetate (**7**) (40 mg, 0.09 mmol) in dichloromethane (2 mL) at room temperature was added ethyl (triphenylphosphanylidene)acetate (47 mg, 0.13 mmol). The mixture was stirred for 1 h, after which time the reaction was shown to be complete by TLC. The solvent was evaporated and the residue was dissolved in a small amount of dichloromethane and applied to a silica gel column. Chromatography (1:2 ethyl acetate/petroleum ether) afforded **6** (35 mg, 76% overall, from **3a**) as a colourless oil; IR ν_{max} (cm^{-1}) 2977, 2938, 1717, 1645, 1601; ^1H NMR (400 MHz, $CDCl_3$) δ 7.26 (2H, d, J=8.6 Hz), 6.89 (2H, d, J=8.6 Hz), 6.33 (1H, s), 5.48 (1H, s), 4.61 (1H, d, J=12.0 Hz), 4.44 (2H, s), 4.37 (1 H, d, J=12.0 Hz), 4.31 (2H, m), 4.19 (2H, q, J=7.1 Hz), 3.82 (3H, s), 3.50 (2H, t, J=6.0 Hz), 2.66 (2H, t, J=7.6 Hz), 2.04 (3H, s), 1.93 (2H, m), 1.31 (3H, t, J=7.1 Hz), 1.26 (3H, t, J=7.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.8, 193.5, 169.8, 164.4, 163.7, 159.3, 142.5, 130.1, 129.3, 121.3, 113.8, 103.3, 87.7, 72.7, 68.1, 65.1, 62.0, 61.3, 55.3, 27.6, 26.3, 20.6, 14.0, 13.9; LRMS m/z (+ES, %) 457 (32), 527 (100); HRMS+ES calcd for $C_{26}H_{32}NaO_{10}$ 527.1893, found: 527.1905.

*3.1.28. rel-(2S,3S)-Diethyl 2-{(S)-2-acetoxymethyl-5-[3-(4-methoxybenzyloxy)-propyl]-3-oxo-2,3-dihydrofuran-2-yl}-2,3-dihydroxysuccinate (**5a**) or (**5b**).* Citric acid (38 mg, 0.19 mmol) was added to a solution of (±)-diethyl 2-{2-acetoxymethyl-5-[3-(4-methoxybenzyloxy)-propyl]-3-oxo-2,3-dihydrofuran-2-yl}-(*Z*)-but-2-enedioate (**6a**) (50 mg, 0.10 mmol) in a mixture of acetone (2 mL) and water (2 mL). Osmium tetroxide (2.5 mg, 0.01 mmol; CAUTION: TOXIC) was then added, followed by 4-methylmorpholine-*N*-oxide (11.6 mg, 0.10 mmol). The mixture was stirred for 4 h at room temperature. Acetone was removed on a rotary evaporator. Saturated aqueous sodium sulfite (2 mL) was added to the aqueous residue, which was stirred for 10 min and then extracted with dichloromethane (4×8 mL). The combined organic layers were dried over $MgSO_4$, filtered and evaporated to give a 2:1 mixture of diastereoisomers, as shown in the ^1H NMR spectrum. Chromatography of the residue on silica gel (ethyl acetate) gave a single diastereoisomer, **5a** or **5b** (28 mg, 55%) as a colourless oil; IR ν_{max} (cm^{-1}) 3463, 2937, 1741, 1704; ^1H NMR (600 MHz, $CDCl_3$) δ 7.26 (2H, d, J=8.6 Hz), 6.90 (2H, d, J=8.6 Hz), 5.54 (1H, s), 4.95 (1H, s), 4.86 (1H, d, J=12.0 Hz), 4.75 (1H, d, J=12.0 Hz), 4.45 (2H, s), 4.29–4.18 (4H, m), 3.82 (3H, s), 3.51 (2H, t, J=6.0 Hz), 2.59 (2H, m), 1.95 (3H, s), 1.90 (2H, m), 1.33 (3H, t, J=7.1 Hz), 1.26 (3H, t, J=7.1 Hz); ^{13}C NMR (150 MHz, $CDCl_3$) δ 201.7, 193.0, 170.2, 169.9, 169.2, 159.3, 130.1, 129.3, 113.8, 105.3, 90.6, 80.9, 72.8, 72.0, 68.3, 63.8, 63.0, 62.5, 55.3, 27.5, 26.5, 20.6, 14.0; LRMS m/z (+ES, %) 561 (100), 539 (5); HRMS+ES calcd for $C_{26}H_{34}NaO_{12}$ 561.1948, found: 561.1953.

References and notes

1. (a) Faul, M. M.; Huff, B. E. *Chem. Rev.* **2000**, *100*, 2407; (b) Ireland, R. E.; Meissner, R. S.; Rizzacasa, M. A. *J. Am. Chem. Soc.* **1993**, *115*, 7166; (c) Aicher, T. D.; Buszek, K. R.; Fang, F. G.; Forsyth, C. J.; Jung, S. H.; Kishi, Y.; Matelich, M. C.; Scola, P. M.; Spero, D. M.; Yoon, S. K. *J. Am. Chem. Soc.* **1992**, *114*, 3162.

2. Evans, D. A.; Gage, J. R.; Leighton, J. L. *J. Am. Chem. Soc.* **1992**, *114*, 9434.
3. (a) Nakamura, S. *Chem. Pharm. Bull.* **2005**, *53*, 1; (b) Armstrong, A.; Blench, T. J. *Tetrahedron* **2002**, *58*, 9321; (c) Koert, U. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 773.
4. For total syntheses of zaragozic acid A see: (a) Hirata, Y.; Nakamura, S.; Watanabe, N.; Kataoka, O.; Kurosaki, T.; Anada, M.; Kitagaki, S.; Shiro, M.; Hashimoto, S. *Chem.—Eur. J.* **2006**, *12*, 8898 (also zaragozic acid C); (b) Tomooka, K.; Kikuchi, M.; Igawa, K.; Suzuki, M.; Keong, P.-H.; Nakai, T. *Angew. Chem., Int. Ed.* **2000**, *39*, 4502; (c) Caron, S.; Stoermer, D.; Mapp, A. K.; Heathcock, C. H. *J. Org. Chem.* **1996**, *61*, 9126; (d) Nicolaou, K. C.; Nadin, A.; Leresche, J. E.; Yue, E. W.; La Greca, S. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 2190.
5. For total syntheses of zaragozic acid C see: (a) Nakamura, S.; Hirata, Y.; Kurosaki, T.; Anada, M.; Kataoka, O.; Kitagaki, S.; Hashimoto, S. *Angew. Chem., Int. Ed.* **2003**, *42*, 5351; (b) Armstrong, A.; Barsanti, P. A.; Jones, L. H.; Ahmed, G. *J. Org. Chem.* **2000**, *65*, 7020; (c) Carreira, E. M.; Bu Bois, J. *J. Am. Chem. Soc.* **1995**, *117*, 8106; (d) Evans, D. A.; Barrow, J. C.; Leighton, J. L.; Robichaud, A. J.; Sefkow, M. *J. Am. Chem. Soc.* **1994**, *116*, 12111.
6. For formal total syntheses of zaragozic acids see: (a) Wang, Y.; Metz, P. *Chem.—Eur. J.* **2011**, *17*, 3335; (b) Bunte, J. O.; Cuzzupe, A. N.; Daly, A. M.; Rizzacasa, M. A. *Angew. Chem., Int. Ed.* **2006**, *45*, 6376.
7. Haug, T. T.; Kirsch, S. F. *Targets Heterocycl. Syst.* **2009**, *13*, 57.
8. Sakamoto, H. T.; Flausino, D.; Castellano, E. E.; Stark, C. B. W.; Gates, P. J.; Lopes, N. P. *J. Nat. Prod.* **2003**, *66*, 693.
9. (a) Baraldi, P. G.; Guarneri, M.; Mandredini, S.; Simoni, D.; Balzarini, J.; De Clercq, E. *J. Med. Chem.* **1989**, *32*, 284; (b) Boeckman, R. K.; Yoon, S. K.; Heckendorn, D. K. *J. Am. Chem. Soc.* **1991**, *113*, 9682; (c) Kupchan, S. M.; Sigel, C. W.; Matz, M. J.; Renauld, J. A. S.; Haltiwanger, R. C.; Bryan, R. F. *J. Am. Chem. Soc.* **1970**, *92*, 4476; (d) Martin, A. S.; Rovirosa, J.; Muñoz, O.; Chen, M. H. M.; Guneratne, R. D.; Clardy, J. *Tetrahedron Lett.* **1983**, *24*, 4063.
10. Kirmizigul, S.; Goren, N.; Yang, S.-W.; Cordell, G. A.; Bozok-Johansson, C. *J. Nat. Prod.* **1997**, *60*, 378.
11. Wangun, H. V. K.; Härtl, A.; Kiet, T. T.; Hertweck, C. *Org. Biomol. Chem.* **2006**, *4*, 2545.
12. (a) Rosales, A.; Estévez, R. E.; Cuerva, J. M.; Oltra, J. E. *Angew. Chem., Int. Ed.* **2005**, *44*, 319; (b) Nakamura, I.; Yamamoto, Y. *Chem. Rev.* **2004**, *104*, 2127; (c) Dieters, A.; Martin, S. F. *Chem. Rev.* **2004**, *104*, 2199.
13. (a) Simpson, G. L.; Heffron, T. P.; Merino, E.; Jamison, T. F. *J. Am. Chem. Soc.* **2006**, *128*, 1056; (b) Nicolaou, K. C.; Prasad, C. V. C.; Somers, P. K.; Hwang, C.-K. *J. Am. Chem. Soc.* **1989**, *111*, 5330.
14. Li, Y.; Hale, K. J. *Org. Lett.* **2007**, *9*, 1267.
15. Han, Q.; Wiemer, D. F. *J. Am. Chem. Soc.* **1992**, *114*, 7692.
16. For some of the few reports of enantioselective dihydroxylation of α,β-unsaturated ketones see: (a) Cox, R. J.; de Andrés-Gomez, A.; Godfrey, C. A. *Org. Biomol. Chem.* **2003**, *18*, 3173; (b) Walsh, P. J.; Sharpless, K. B. *Synlett* **1993**, 605.
17. Marson, C. M.; Edaan, E.; Morrell, J. M.; Coles, S. J.; Hursthouse, M. B.; Davies, D. T. *Chem. Commun.* **2007**, 2494.
18. For non-enantioselective methods of constructing the 3(2*H*)-furanone ring system see: (a) Winkler, J. D.; Oh, K.; Asselin, S. M. *Org. Lett.* **2005**, *7*, 387; (b) Manfredini, S.; Baraldi, P. G.; Bazzanini, R.; Guarneri, M.; Simoni, D.; Balzarini, J.; De Clercq, E. *J. Med. Chem.* **1994**, *37*, 2401; (c) Sampson, P.; Roussis, V.; Drtina, D. J.; Koerwitz, F. L.; Wiemer, D. F. *J. Org. Chem.* **1986**, *51*, 2525; (d) Chimichi, S.; Boccalini, M.; Cosimelli, B.; Viola, G.; Vedaldi, D.; Dall'Acqua, F. *Tetrahedron Lett.* **2002**, *43*, 7473; (e) Andersen, S. H.; Sharma, K. K.; Torssell, K. B. G. *Tetrahedron* **1983**, *39*, 2241; (f) Antonioletti, R.; Bonadies, F.; Scettri, A. *Tetrahedron Lett.* **1987**, *28*, 2297.
19. (a) Jerris, P. J.; Smith, A. B., III. *J. Org. Chem.* **1981**, *46*, 577; (b) Smith, A. B., III; Levenberg, P. A.; Jerris, P. J.; Scarborough, R. M., Jr.; Wovkulich, P. M. *J. Am. Chem. Soc.* **1981**, *103*, 1501.
20. (a) Poonoth, M.; Krause, N. *J. Org. Chem.* **2011**, *76*, 1934; (b) Shamshina, J. L.; Snowden, T. S. *Tetrahedron Lett.* **2007**, *48*, 3767; (c) Langer, P.; Krummel, T. *Chem. Commun.* **2000**, 967; (d) Kato, K.; Nouchi, H.; Ishikura, K.; Takaishi, S.; Motodate, S.; Tanaka, H.; Okudaira, K.; Mochida, T.; Nishigaki, R.; Shigenobu, K.; Akita, H. *Tetrahedron* **2006**, *62*, 2545; (e) Villemin, D.; Jaffrés, P.-A.; Hachémi, M. *Tetrahedron Lett.* **1997**, *38*, 537.
21. (a) Qi, C.; Jiang, H.; Huang, L.; Yuan, G.; Ren, Y. *Org. Lett.* **2011**, *13*, 5520; (b) Egi, M.; Azechi, K.; Saneto, M.; Shimizu, K.; Akai, S. *J. Org. Chem.* **2010**, *75*, 2123; (c) Bunnelle, E. M.; Smith, C. R.; Lee, S. K.; Singaram, S. W.; Rhodes, A. J.; Sarpong, R. *Tetrahedron* **2008**, *64*, 7008; (d) Crone, B.; Kirsch, S. F. *Angew. Chem., Int. Ed.* **2006**, *45*, 5878; (e) Liu, Y.; Liu, M.; Guo, S.; Tu, H.; Zhou, Y.; Gao, H. *Org. Lett.* **2006**, *8*, 3445; (f) Kirsch, S. F.; Binder, J. T.; Liébert, C.; Menz, H. *J. Org. Chem.* **2007**, *72*, 5435; (g) Silva, F.; Reiter, M.; Mills-Webb, R.; Sawicki, M.; Klär, D.; Bensel, N.; Wagner, A.; Gouverneur, V. *J. Org. Chem.* **2006**, *71*, 8390.
22. Kumar, D. N.; Rao, B. V. *Tetrahedron Lett.* **2004**, *45*, 2227.
23. (a) Patel, R. M.; Argade, N. P. *Synthesis* **2009**, 374; (b) Gabriele, B.; Costa, M.; Salerno, G.; Chiusoli, G. P. *J. Chem. Soc., Perkin Trans. 1* **1994**, 83; (c) Chou, T.-S.; Knochel, P. *J. Org. Chem.* **1990**, *55*, 4791.
24. (a) Marson, C. M.; Pink, J. H.; Hall, D.; Hursthouse, M. B.; Malik, A.; Smith, C. *J. Org. Chem.* **2003**, *68*, 792; (b) Huang, H.; Xiongcai, D. J.; Qiu, M.; Zheng, Z. *Org. Lett.* **2006**, *8*, 3359.
25. De Mico, A.; Margarita, R.; Parlanti, L.; Vescovi, A.; Piancatelli, G. *J. Org. Chem.* **1997**, *62*, 6974.
26. Bennani, Y. L.; Sharpless, K. B. *Tetrahedron Lett.* **1993**, *34*, 2079.
27. VanReenen, V.; Kelly, R. C.; Cha, D. Y. *Tetrahedron Lett.* **1973**, *23*, 1976.
28. Marson, C. M.; Harper, S.; Oare, C. A.; Walsgrove, T. *J. Org. Chem.* **1998**, *63*, 3798.
29. Gagey, N.; Neveu, P.; Benbrahim, C.; Goetz, B.; Aujard, I.; Baudin, J.-B.; Jullien, L. *J. Am. Chem. Soc.* **2007**, *129*, 9986.