Pergamon

Tetrahedron 57 (2001) 7409–7416

TETRAHEDRON

Studies towards the biomimetic synthesis of the nonadrides CP-225,917 and CP-263,114

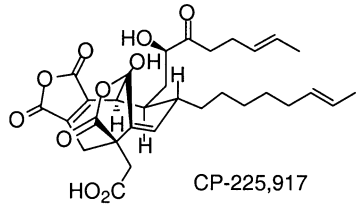
Jack E. Baldwin,* Robert M. Adlington, Fanny Roussi, Paul G. Bulger, Rodolfo Marquez and Alexander V. W. Mayweg

The Dyson Perrins Laboratory, University of Oxford, South Parks Road, Oxford OX1 3QY, United Kingdom

Received 25 April 2001; revised 6 June 2001; accepted 28 June 2001

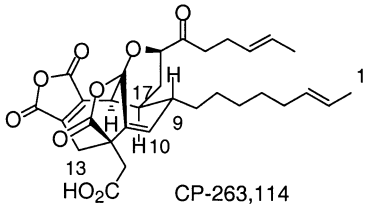
Abstract—Intramolecular cyclisations of dimeric bis-anhydride compounds have been investigated, to help elucidate the biosynthesis of the nonadride family of compounds. Short and efficient syntheses of these bis-anhydride compounds, together with their cyclisations to yield analogues of glaucanic and *iso*-glaucanic acid, are described herein.

In the late 1990's Pfizer laboratories reported the isolation and structure elucidation of two new natural products, CP-225,917 **1** and CP-263,114 **2**.[1] The CP compounds have been classified as the most complex members of the nonadride class of compounds. Structurally, they present a nine-membered ring onto which a maleic anhydride moiety is annealed, which, combined with the 6 stereocentres present, makes them an extremely challenging synthetic target. It is this structural complexity combined with their significant biological activity (inhibition of squalene synthase and RAS-farnesyl transferase), which has made them attractive synthetic targets, as demonstrated by the work recently published.[2]



CP-225,917

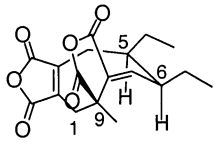
1



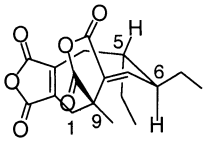
CP-263,114

2

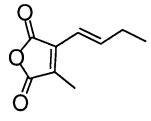
The core structure of the CP compounds is closely related to that of glaucanic acid **3**, simply differing in the stereochemistry at the C_9 position and the C_{10}–C_{11} double bond geometry. Therefore, the understanding and development of a biosynthetic route to both glaucanic acid **3** and *iso*-glaucanic acid **4** could prove extremely beneficial in understanding how these complicated natural products are formed, and could lead to a short biomimetic synthetic route to the CP compounds.



3



4



5

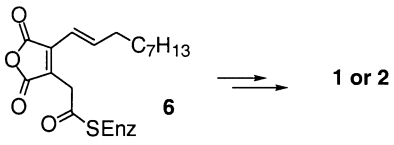
Sutherland and co-workers[3] originally proposed that glaucanic acid **3**, and *iso*-glaucanic acid **4** are produced in vivo by the head to head dimerisation of the C-9 anhydride **5**. In his in vitro experiments however, Sutherland was only able to isolate *iso*-glaucanic acid **4**, through what he proposed to be a concerted [6π+4π] cyclodimerisation.

Sulikowski, in a related approach,[4] has recently proposed the idea that the CP compounds might be derived from the dimerisation of anhydride **6**, through a similar biosynthetic pathway as that for the formation of glaucanic acid **3** (Scheme 1).

Keywords: nonadrides; biomimetic synthesis; intramolecular cyclisation; bis-anhydride dimers.

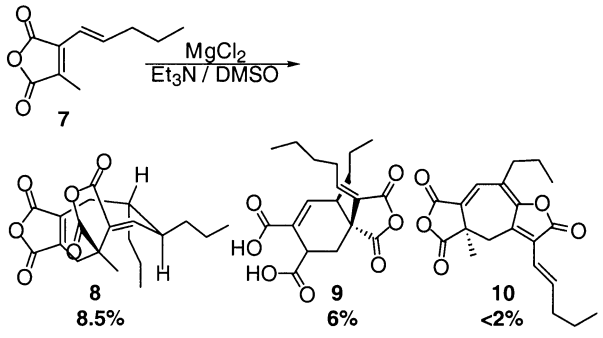
* Corresponding author. Tel.: +44-1865-275-670; fax: +44-1865-275-632; e-mail: jack.baldwin@chem.ox.ac.uk

0040–4020/01/$ - see front matter
PII: S0040-4020(01)00706-2



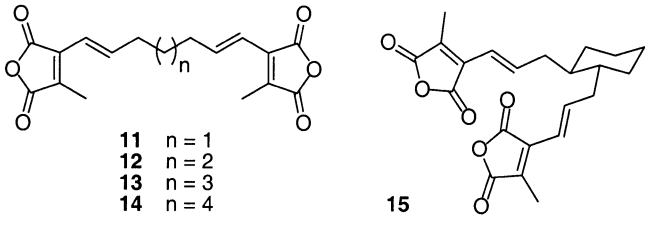
Scheme 1.

Our group has long been interested in the biosynthesis of both glaucanic **3** and *iso*-glaucanic acid **4** with a view to understanding and establishing its potential for a one-pot biomimetic synthesis of the nine membered ring core of the CP compounds.[5] Our previous results showed that the dimerisation of anhydride **7** afforded the bis-anhydride **8** (same relative stereochemistry as *iso*-glaucanic acid **4**), as well as the dimerisation products **9** and **10**. The formation of both **9** and **10** suggested a stepwise dimerisation process via successive Michael additions. In addition, we were also able to show that the pathway for the formation of **9** is a reversible process[5] (Scheme 2).

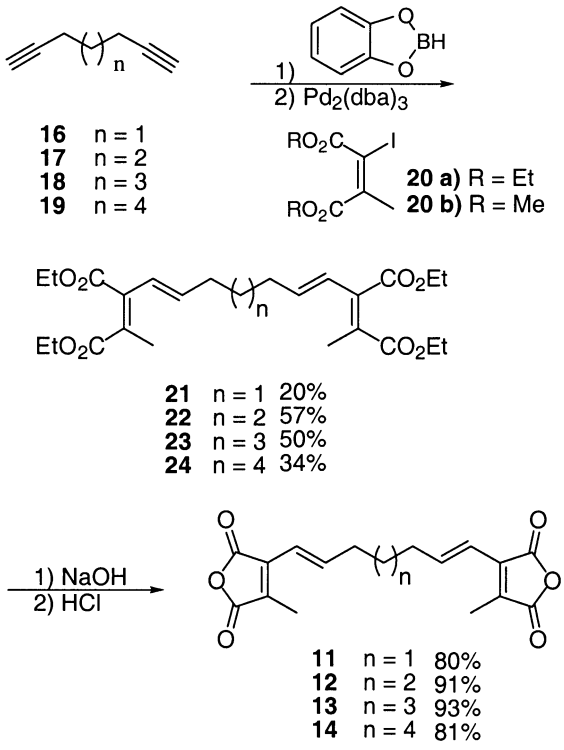


Scheme 2.

As part of our continuing efforts in this area, we wish to report further progress in investigating the glaucanic acid biosynthesis, focusing on the effect that the tethering of the anhydride subunits would have on the Michael addition selectivity, and the double bond geometry and stereochemical configurations at C_5, C_6 and C_9 (glaucanic acid **3** numbering). Thus, with this in mind, the tethered systems **11**–**15** were efficiently synthesised and the cyclisations attempted.

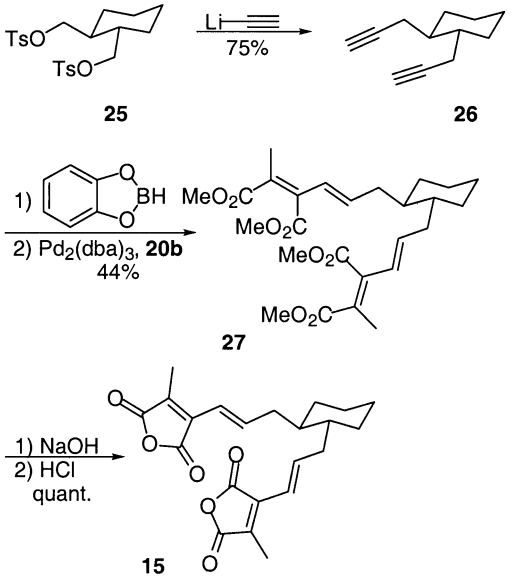


The synthesis of the simple alkyl tethers was accomplished in three steps beginning with the commercially available diynes **16**–**19**. Hydroboration followed by Suzuki coupling[6] with 2-iodo-3-methyl diethyl maleate[5] **20a** gave the desired maleate dimers **21**–**24**. These maleate dimers were then converted to the corresponding anhydrides through ester saponification, followed by acid treatment. The desired anhydrides **11**–**14** were thus obtained efficiently and without need of further purification (Scheme 3).



Scheme 3.

The synthesis of the cyclic tether began with readily available *trans* bis-tosyl derivative **25**.[7] The bis-tosylate **25**, was alkynylated to provide bis-alkyne **26**, which was then hydroborated and immediately coupled with diethyl maleate **20b**,[5] as above, to afford the desired tetra-ester **27** in good yield. Finally, saponification and acid catalysed anhydride formation provided the desired cyclohexyl derivative **15** quantitatively (Scheme 4).



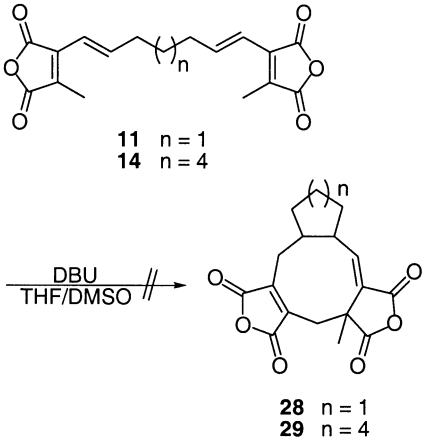
Scheme 4.

The intramolecular cyclisations of the tethered anhydrides **11**–**15** were then investigated, with interesting results. All

reactions were performed under high dilution conditions (1 mmol starting material per 100 mL solvent), whilst at the same time, the effect of base, solvent and temperature employed were investigated. Both triethylamine and diisopropylethylamine (1.1 equiv.) failed to react with the starting anhydrides even at high temperatures (refluxing THF, acetonitrile, or toluene). Moreover, deuterium oxide quenching experiments failed to incorporate deuterium onto the starting anhydride, demonstrating that no deprotonation had taken place. DBU, however, proved extremely successful at deprotonation, as indicated by the formation of deep red coloured reaction mixtures.

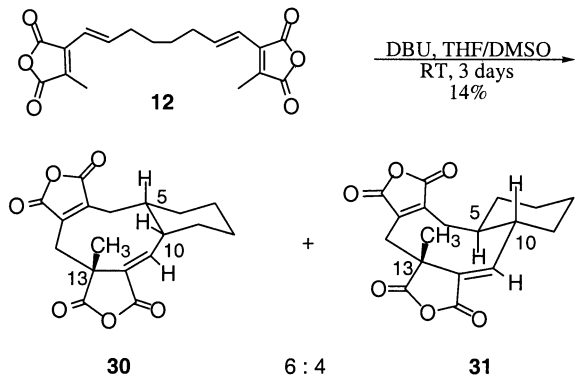
The choice of solvent on the other hand, was not as dramatic as the base involved. Although the reaction was found to proceed in acetonitrile, cleaner reaction mixtures were obtained when either THF or DMSO was employed. A mixture of THF and DMSO (4:1), however, provided the best compromise between ease of use and anion solvation. It was determined that even though deprotonation using DBU could occur at low temperatures (−78–0°C), the newly formed anions failed to react at temperatures lower than 20°C. It is also worth noting that in contrast to previous results,[5] the addition of either zinc chloride or magnesium chloride failed to improve the yields and relative amounts of the cyclised products obtained.

Submission of anhydrides **11** and **14** to the optimised reaction conditions for varying lengths of time (24–168 h) failed to yield any of the desired cyclised products **28** and **29**, causing instead decomposition of starting material. Although the lack of cyclisation of bis-anhydride **14** could be rationalised due to the inherent difficulty in generating a [7.6.0] bicyclic system **29**, it is less clear why the [7.3.0] bicyclic system **28** did not form (Scheme 5).



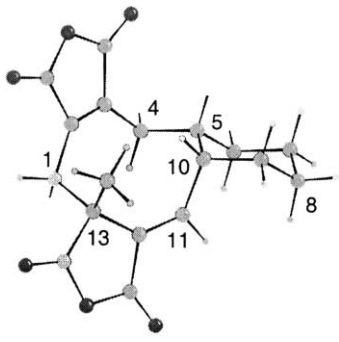
Scheme 5.

Anhydride **12** however, afforded two very clean [7.4.0] bicyclic products **30** and **31** in a 3:2 ratio in reasonable isolated yield. This 3:2 ratio of diastereomers remained constant despite change of temperatures (20–60°C), and various reaction times (24–72 h). The low yield was due not only to competing polymerisation of the starting material during the reaction, but also due to the sensitivity of the products to purification by flash column chromatography on silica gel (Scheme 6).



Scheme 6.

Selective crystallisation of anhydride **30** from deuterated chloroform, followed by X-ray analysis confirmed its structure as a [7.4.0] bicyclic bis-anhydride with a *cis* C_5–C_{10} ring junction, analogous to glaucanic acid **3**.[8] Furthermore, the C_{13} methyl group is positioned *syn* to H_5 and H_{10}, with the trisubstituted double bond presenting an *E*-configuration. nOe experiments performed upon **30** indicated a through space interaction between the C_{13} methyl group and both H_5 and H_{10}.

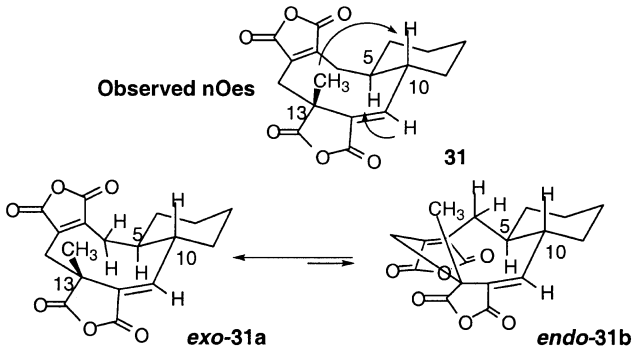


30

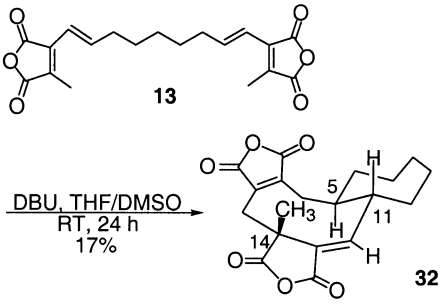
The structure of the *trans* [7.4.0] bis-anhydride **31**, on the other hand is consistent with an analogue of *iso*-glaucanic acid **4**, presenting a *trans* C_5–C_{10} ring junction as well as a *cis* relation between the C_{13} methyl and H_{10} as shown by nOe correlations. The trisubstituted double bond however, shows the same *E*-configuration as in compound **30**, as demonstrated by the strong nOe between H_{11} and H_5 which is absent in **30**. Low temperature NMR experiments however, failed to show a doubling of the signals, which would be consistent with a significant barrier to interconversion between the probable *exo*-**31a** and *endo*-**31b** nine-membered ring conformational isomers (Scheme 7).

The cyclisation of bis-anhydride **13** on the other hand, was complete in 24 h. ^{1}H NMR analysis of the crude product mixture indicated the presence of a single bicyclic [7.5.0] compound, together with polymeric material. Unfortunately, the bicycle **32** proved to be just as unstable to silica gel chromatography as the previously described [7.4.0] bicycles, and could only be isolated in 17% yield (Scheme 8).

Since a single crystal was not obtained, the structure and relative stereochemistry of the bicycle **32** were determined

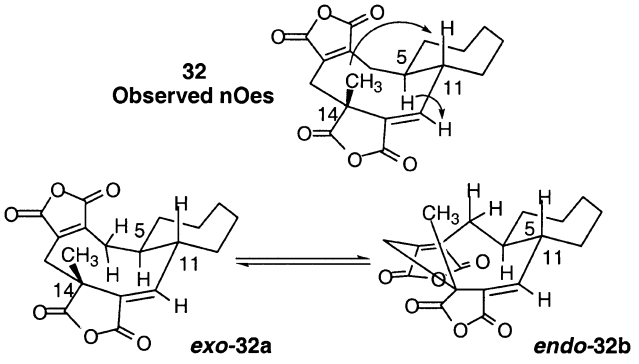


Scheme 7.



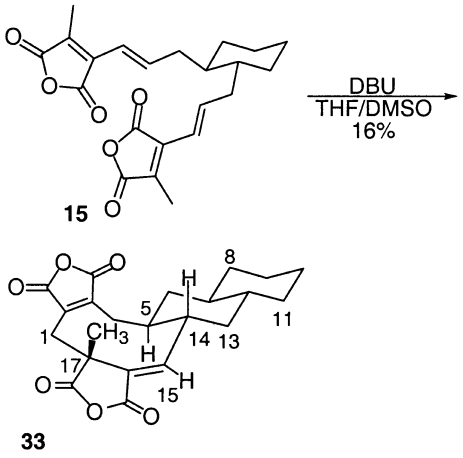
Scheme 8.

by one- and two-dimensional nOe experiments. We believe that this bicyclic product has a *trans*-fused structure similar to those of the [7.4.0] bicyclic product **31** and *iso*-glaucanic acid **4**, as demonstrated by the nOes between C_{14} methyl group and H_{11}, and between H_{12} and H_5. Low-temperature NMR experiments on the other hand, showed the probable presence of both the *exo*-**32a** and *endo*-**32b** conformational isomers, distinguishable only by the characteristic nOe from H_5 to H_4 and H'_4 present in the *exo* conformer **32a** (Scheme 9).



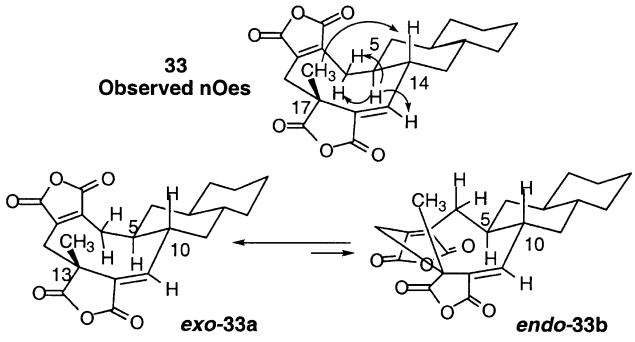
Scheme 9.

Finally, the cyclisation of cyclohexyl derivative **15**, was attempted under the same previously described conditions. In this particular instance, cyclisation proceeded cleanly to yield a tricyclic product **33** in 16% yield as white needles, unsuitable for X-ray analysis. NMR data on the other hand, provided clear evidence of both the *trans* decalin structure and the *trans* C_5–C_{14} ring junctions, through both coupling constants and nOe experiments. Furthermore, the *E* configuration of the trisubstituted double bond was then confirmed by the nOes observed between H_{15} and H_5, [and H_{15}–H_{13}], similar to those observed for both compounds **31** and **32** (Scheme 10).



Scheme 10.

The *exo* relationship between the two anhydride units was then confirmed by the diagnostic nOe between H_5 and both H_4 and H'_4. Low temperature NMR experiments on the other hand, failed to cause a doubling of the signals, which made us consider the possibility of a higher energy barrier to interconversion between the *exo* tricycle **33a** and its corresponding *endo* isomer **33b** relative to that of the bicyclic compound **32**, possibly similar in magnitude to that of bicyclic compound **31** (Scheme 11).



Scheme 11.

In an attempt to further understand the factors governing the observed equilibria, computational studies were then undertaken. Geometrical optimisation of the cyclised bis-anhydrides were carried out using the semi-empirical PM3 and AM1 methods.[9] The relative energy difference between each set of *exo* and *endo* isomers are provided in Table 1.

Both methods predict, as expected, a significant energy difference between the *exo* and the *endo* isomers in the *cis* fused [7.4.0] bicyclic system **30**. The energy difference between the *exo* and *endo* conformers decreases

Table 1. Semi-empirical PM3 and AM1 calculated heats of formation

System	*Exo* (**a**)	*Endo* (**b**)	ΔH_f (kcal mol^{-1})
PM3 **30** *cis*	−217.9	−210.7	7.2
AM1 **30** *cis*	−197.4	−189.01	8.3
PM3 **31** *trans*	−218.7	−219.1	0.4
AM1 **31** *trans*	−196.4	−198.0	1.6
PM3 **32** *trans*	−220.7	−220.7	0.0
AM1 **32** *trans*	−202.1	−201.4	0.7
PM3 **33** *trans*	−234.4	−232.5	1.9
AM1 **33** *trans*	−218.2	−215.7	2.5

significantly as the ring junction is changed from *cis* to *trans* (systems **31** and **32**), with the exception of tricycle **33**, in which the decalin unit seems to provide a slightly higher interconversional barrier. These calculated energy values are in agreement with the conformer populations as observed by NMR, with the exception of bicyclic conformer **32**, in which the conformational exchange predicted has not been detected.

Mechanistically, we propose that the formation of the six- and seven- membered cycles, as well as that of the decalin system, precedes that of the nine-membered ring through transition states **34** and **36**. These transition states then generate the corresponding cyclohexyl intermediates **35** and **37** with the corresponding relative configuration at the ring junction set in place. Once the cycloalkyl rings are in place, this would then provide the stability and rigidity necessary to allow nine-membered ring formation through what we believe to be *exo*-oriented double-Michael additions (Scheme 12).

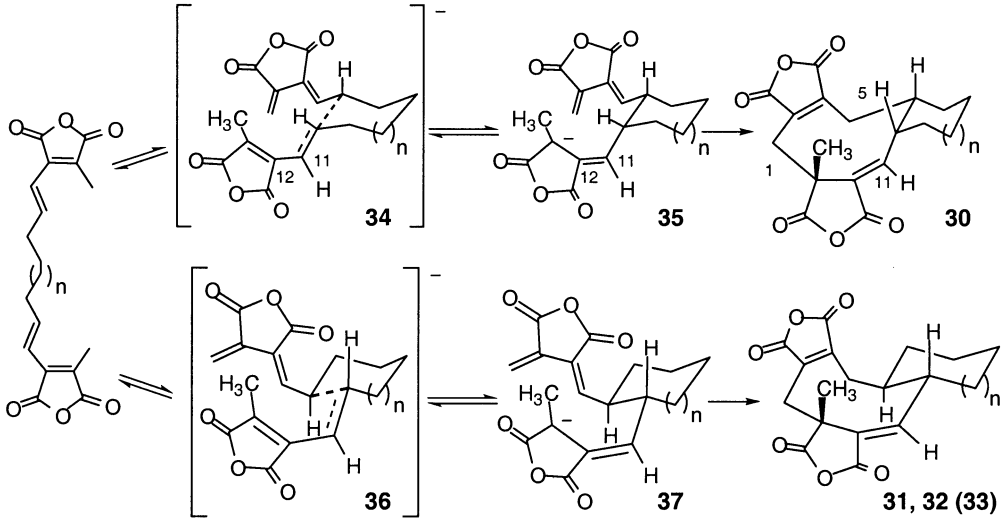
In conclusion, we have demonstrated the outcome of linking both anhydride units in a biomimetic synthesis of the nonadrides. We believe that these linkers bring together the anhydride termini, not unlike the way an enzyme might bring two anhydride monomers before cyclisation. We are currently undertaking both experimental and computational studies in order to further elucidate, and expand the scope of this interesting biomimetic cyclisation. The results of these studies will be published shortly.

1. Experimental

1.1. General

All solvents and reagents were purified by standard techniques or used as supplied from commercial sources as appropriate. Flash chromatography was carried out on 230–400 mesh silica gel or 70–230 mesh aluminium oxide. Analytical TLC was performed on silica gel F-254 plates of 0.2 mm thickness. ^{1}H- and ^{13}C NMR spectra were recorded on Varian Gemini 200, Bruker AC200, Bruker DPX400, Bruker AMX500 and Bruker AM500 instruments. Chemical shifts are quoted in parts per million (ppm) and are referenced to the residual solvent peak. Coupling constants (*J*) were recorded in Hertz (Hz), and are quoted to the nearest 0.5 Hz. IR spectra were recorded using a Perkin–Elmer Paragon 1000 Fourier Transform spectrometer. Low resolution mass spectra were recorded on Fisons V.G. platform APCI instrument or a VG Masslab 20-250 (CI/DCI). High resolution mass spectra were recorded on a VG ZAB-E instrument. Microanalyses were performed by 'Elemental Microanalysis Limited', Hameldown Road, Okehampton, Devon, EX20 1UB. Melting points were obtained using a Büchi 510 capillary apparatus and are uncorrected.

1.1.1. Cyclohexyl bis-alkyne 26. To a stirred suspension of lithium acetylide ethylene diamine complex (2.721 g, 29.55 mmol, 4.0 equiv.) in dry dimethyl sulphoxide (20 mL) was added the known ditosylate **25**[7] (3.360 g, 7.42 mmol, 1.0 equiv.) in portions over 5 min at 8°C. The mixture was stirred under argon at 8°C for 30 min then at 20°C for 5 h, then quenched with sat. aq. ammonium chloride (50 mL). The mixture was then partitioned between water (50 mL) and hexanes (50 mL). The aqueous layer was extracted with hexanes (4×50 mL), and the combined organic layers were washed with brine (2×70 mL), dried over $MgSO_4$, filtered and concentrated in vacuo. Purification by column chromatography (hexanes) provided 889 mg (75%) of the known[7] bis-alkyne **26** as a colourless oil. R_f 0.3 (hexanes); δ_H (400 MHz; $CDCl_3$) 1.25–1.29 (4H, m), 1.43–1.46 (2H, m), 1.72–1.74 (2H, m), 1.79–1.83 (2H, m), 1.98 (2H, t, *J*=3 Hz), 2.26–2.29 (4H, m).



Scheme 12.

1.2. General procedure for the synthesis of maleate dimers 21–24 and 28

Catecholborane (2.1 equiv.) was added dropwise to the neat bis-alkyne (1.0 equiv.) at 20°C under argon. The mixture was stirred at 80°C for 24 h. The mixture was then cooled to 20°C, dissolved in dimethoxyethane (1 mL $mmol^{-1}$ of alkyne) and added to a solution of 2-iodo-3-methyl diethyl maleate **20a**[5] (2.0 equiv.) and $Pd_2(dba)_3$ (0.06 equiv.) in dimethoxyethane (20 mL $mmol^{-1}$ of alkyne). After 10 min 3 M aq. potassium phosphate (3.6 equiv.) was added, and the mixture refluxed for 6 h. After cooling to 20°C the mixture was filtered through Celite, washing the pad thoroughly with diethyl ether. The filtrate was added to sat. aq. ammonium chloride, the layers were separated and the aqueous layer extracted three times with diethyl ether. The combined organic layers were washed once with brine, dried over $MgSO_4$, filtered and concentrated in vacuo. The crude material was finally purified by flash column chromatography on silica gel.

1.2.1. Maleate dimer 21. The crude material was purified by flash column chromatography (2:1 diethyl ether/hexanes) to give the desired dimer in 20% yield from **16** (1.0 g, 10.85 mmol) as a yellow oil: R_f 0.18 (2:1 diethyl ether/hexanes). δ_H(200 MHz; $CDCl_3$) 1.20 (6H, t, J=7 Hz), 1.26 (6H, t, J=7 Hz), 1.53 (2H, quint, J=7 Hz), 1.92 (6H, s), 2.16 (4H, q, J=7 Hz), 4.12 (4H, q, J=7 Hz), 4.24 (4H, q, J=7 Hz), 5.86 (2H, dt, J=16, 7 Hz), 6.28 (2H, d, J=16 Hz); δ_C (50.3 MHz; $CDCl_3$) 13.5, 14.0 (2Cs), 27.6, 32.8, 61.0, 61.1, 124.4, 124.5, 139.7, 141.0, 166.9, 168.8; ν_{max}(film)/cm^{-1} 2968, 2926, 1731, 1705; Anal. calcd for $C_{25}H_{36}O_8$: C 64.62, H 7.82, found: C 64.31, H 7.90; m/z (APCI$^+$): 419 ($M-C_2H_5O^+$).

1.2.2. Maleate dimer 22. The crude material was purified by flash column chromatography (9:5 diethyl ether/hexanes) to give the desired dimer in 57% yield from **17** (1.09 g, 10.24 mmol) as white crystals: R_f 0.20 (9:5 diethyl ether/hexanes). δ_H (200 MHz; $CDCl_3$) 1.28 (6H, t, J=7 Hz), 1.34 (6H, t, J=7 Hz), 1.44 (4H, m), 1.99 (6H, s), 2.21 (4H, m), 4.19 (4H, q, J=7 Hz), 4.32 (4H, q, J=7 Hz), 5.94 (2H, dt, J=16, 7 Hz), 6.34 (2H, d, J=16 Hz); δ_C(50.3 MHz; $CDCl_3$) 14.0, 14.5 (2Cs), 27.3, 33.8, 61.5, 61.6, 124.6, 124.8, 140.7, 141.6, 167.5, 169.4; ν_{max}(film)/cm^{-1} 3041, 2958, 1721, 1265; Anal. calcd for $C_{26}H_{38}O_8$: C 65.24, H 8.01, found: C 65.34, H 8.33; m/z (APCI$^+$): 433 ($M-C_2H_5O^+$); mp 56°C, (ether/hexane).

1.2.3. Maleate dimer 23. The crude material was purified by flash column chromatography (8:5 diethyl ether/hexanes) to afford the expected dimer in 50% yield from **18** (506 mg, 4.21 mmol) as a yellow oil: R_f 0.19 (8:5 diethyl ether/hexanes). δ_H (200 MHz; $CDCl_3$) 1.28 (12H, m), 1.41 (6H, m), 1.99 (6H, s), 2.19 (4H, m), 4.19 (4H, q, J=7 Hz), 4.31 (4H, q, J=7 Hz), 5.93 (2H, dt, J=16, 7 Hz), 6.33 (2H, dt, J=16, 1.5 Hz); δ_C(50.3 MHz; $CDCl_3$) 14.0, 14.5, 28.9, 29.1, 29.3, 33.9, 61.5, 61.6, 124.5, 124.7, 141.1, 141.7, 167.5, 169.4; ν_{max}(film)/cm^{-1} 3020, 2984, 1720; Anal. calcd for $C_{27}H_{40}O_8$: C 65.82, H 8.19, found: C 66.08, H 8.50; m/z (APCI$^+$): 515 (MNa^+).

1.2.4. Maleate dimer 24. The crude residue was purified by flash column chromatography (7:5 diethyl ether/hexanes) to afford the desired dimer in 34% yield from **19** (1.0 g, 7.45 mmol) as white crystals: R_f 0.22 (7:5 diethyl ether/hexanes). δ_H (200 MHz; $CDCl_3$) 1.33 (20H, m), 1.99 (6H, s), 2.17 (4H, m), 4.19 (4H, q, J=7 Hz), 4.32 (4H, q, J=7 Hz), 5.95 (2H, dt, J=16, 7 Hz), 6.33 (2H, dt, J=16, 1.5 Hz); δ_C(50.3 MHz; $CDCl_3$) 13.8, 14.4, 28.9, 29.2, 30.1, 30.6, 33.8, 61.4, 124.3, 124.5, 141.1, 141.6, 167.3, 169.1; ν_{max}(film)/cm^{-1} 2975, 2927, 2857, 1732, 1716, 1259; Anal. calcd for $C_{28}H_{42}O_8$: C 66.38, H 8.36, found: C 66.64, H 8.33; m/z (APCI$^+$): 461 ($M-C_2H_5O^+$); mp 46°C (ether/hexane).

1.2.5. Maleate dimer 28. The crude product was purified by flash column chromatography (1:1 diethyl ether/hexanes) to afford the desired tetraester in 44% yield from **26** (2.36 g, 14.73 mmol) as a pale yellow syrup: R_f 0.15 (1:1 hexanes/diethyl ether). δ_H (400 MHz; $CDCl_3$) 0.93–0.97 (2H, m), 1.14–1.20 (4H, m), 1.64–1.70 (4H, m), 2.00 (6H, s), 2.02–2.08 (2H, m), 2.46 (2H, dd, J=14, 6.5 Hz), 3.75 (6H, s), 3.86 (6H, s), 5.90 (2H, ddd, J=16, 8.5, 6.5 Hz), 6.32 (2H, d, J=16 Hz); δ_C (400 MHz; $CDCl_3$) 13.5, 25.9, 31.9, 37.8, 41.3, 52.3, 52.3, 124.0, 125.1, 139.7, 141.4, 167.5, 169.5; ν_{max}(film)/cm^{-1} 2925, 2854, 1732, 1626, 1601, 1435, 1313, 1265, 1201, 988,770, 733; HRMS: $C_{26}H_{36}O_8Na$ calcd: 499.2308; found: 499.2317 (MNa^+); m/z (CI$^+$): 494 (57%, MNH_4^+), 477 (9, MH^+), 445 (100), 430 (11), 385 (16), 352 (10), 305 (8).

1.3. General procedure for conversion of anhydrides

To a stirred solution of maleate intermediate (1.0 equiv.) in absolute ethanol (35 mL $mmol^{-1}$ of maleate) was added 3 M aq. lithium hydroxide (50 equiv.) in one portion at 20°C. The mixture was stirred for 2 days at 20°C, then adjusted to pH1 with 1 M aq. HCl. The mixture was extracted four times with ethyl acetate. The combined organic layers were dried over $MgSO_4$, filtered and concentrated in vacuo to afford the expected bis-anhydrides, which were used without further purification.

1.3.1. Anhydride dimer 11. The crude product was obtained in 80% yield from **21** (1.04 g, 3.29 mmol) as a pale yellow amorphous solid: R_f 0.27 (7:2 hexanes/ethyl acetate). δ_H (200 MHz; $CDCl_3$) 1.73 (2H, quint, J=7.5 Hz), 2.11 (6H, s), 2.34 (4H, q, J=7.5 Hz), 6.27 (2H, dt, J=16, 0.5 Hz), 7.11 (2H, dt, J=16, 7 Hz); δ_C (50.3 MHz; $CDCl_3$) 9.3, 27.2, 33.7, 117.8, 135.6, 136.9, 146.4, 164.5, 166.2; ν_{max}(film)/cm^{-1} 3053, 2987, 2937, 1829, 1768; HRMS: $C_{17}H_{16}O_6{\cdot}NH_4$ calcd: 334.129, found: 334.129 (MNH_4^+); m/z (APCI$^+$): 317 (MH^+).

1.3.2. Anhydride dimer 12. The crude product was obtained in 91% yield from **22** (2.70 g, 5.60 mmol) as an orange amorphous powder: R_f 0.31 (7:2 hexanes/ethyl acetate). δ_H(200 MHz; $CDCl_3$) 1.64 (4H, m), 2.19 (6H, s), 2.36 (4H, m), 6.31 (2H, dt, J=16, 1.5 Hz), 7.17 (2H, dt, J=16, 7 Hz); δ_C (50.3 MHz; $CDCl_3$) 9.8, 28.5, 34.6, 118.0, 135.8, 137.5, 147.5, 165.0, 166.8; ν_{max}(film)/cm^{-1} 3054, 2981, 2935, 2852, 1813, 1766; HRMS: $C_{18}H_{18}O_6{\cdot}NH_4$ calcd: 348.145, found: 348.145 (MNH_4^+); m/z (APCI$^+$): 311 (MH^+).

1.3.3. Anhydride dimer 13. The crude product was obtained in 93% yield from **23** (1.32 g, 2.69 mmol) as a brown amorphous solid: R_f 0.27 (4:1 hexanes/ethyl acetate). δ_H (200 MHz; $CDCl_3$) 1.62 (6H, m), 2.11 (6H, s), 2.28 (4H, m), 6.24 (2H, dt, J=16, 1.5 Hz), 7.13 (2H, dt, J=16, 7 Hz); δ_C(50.3 MHz; $CDCl_3$) 9.8, 28.7, 29.2, 34.7, 117.8, 135.7, 137.6, 147.9, 165.0, 166.8; ν_{max}(film)/cm^{-1} 3009, 2934, 1820, 1759; HRMS: $C_{19}H_{20}O_6{\cdot}NH_4$ calcd: 362.161, found: 362.160 (MNH_4^+); m/z (CI^+): 362 (MNH_4^+).

1.3.4. Anhydride dimer 14. The crude product was obtained in 81% yield from **24** (1.81 g, 3.58 mmol) as a brown amorphous powder: R_f 0.29 (4:1 hexanes/ethyl acetate). δ_H (200 MHz; $CDCl_3$) 1.40 (8H, m), 2.12 (6 H, s), 2.30 (4H, m), 6.25 (2H, dt, J=16, 1.5 Hz), 7.13 (2H, dt, J=16, 7 Hz); δ_C(50.3 MHz; $CDCl_3$) 9.8, 28.7, 29.4, 34.8, 117.7, 135.6, 137.6, 148.2, 165.1, 166.8; ν_{max}(film)/cm^{-1} 2971, 2934, 2858, 1735, 1698, 1628, 1622, 1599; Anal. calcd for $C_{20}H_{22}O_6$: C 67.03, H 6.19, found: C 66.82, H 6.26; m/z ($APCI^+$): 359 (MH^+).

1.3.5. Anhydride dimer 15. The crude product was obtained in quantitative yield from **27** (4.09 g, 8.59 mmol) as a pale brown solid: R_f 0.37 (4:1 hexanes/ethyl acetate). δ_H (400 MHz; $CDCl_3$) 1.04–1.10 (2H, m), 1.21–1.25 (2H, m), 1.32–1.37 (2H, m), 1.68–1.77 (4H, m), 2.12 (6H, s), 2.15–2.21 (2H, m), 2.57 (2H,dd, J=14, 7 Hz), 6.26 (2H, d, J=16 Hz), 7.14 (2H, ddd, J=16, 8, 7 Hz).

1.4. General procedure for the intramolecular bis-anhydride cyclisations

To a stirred solution of the crude bis-anhydride (1.0 equiv.) in dry tetrahydrofuran (78 mL $mmol^{-1}$ of bis-anhydride) and dry dimethyl sulphoxide (22 mL $mmol^{-1}$ bis-anhydride) was added 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) (1.1 equiv.) dropwise over 10 min at 20°C. The mixture was stirred under argon for the time indicated, then quenched by the addition of 3 M aq. HCl (1 mL/mL THF). The mixture was extracted four times with ethyl acetate, dried over $MgSO_4$, filtered and concentrated in vacuo to afford the crude product.

1.4.1. Bicyclic compounds 30 and 31. The reaction was performed according to the general procedure and stirred for 72 h. The crude material obtained was purified by flash column chromatography on silica gel (3:1 hexanes/ethyl acetate+1% formic acid) to afford the product as a pale yellow liquid in 14% yield from **12** (500 mg, 1.51 mmol) and as a mixture of two inseparable isomers **30** and **31**: R_f 0.25 (7:2 hexanes/ethyl acetate). The bicyclic compound **31** was then selectively crystallised from $CDCl_3$ as clear cubic crystals.

ν_{max}(film)/cm^{-1} 2929, 2857, 1836, 1767; HRMS: $C_{18}H_{18}O_6{\cdot}NH_4$ calcd: 348.146, found: 348.145 (MNH_4^+); m/z ($APCI^+$): 331 (MH^+); Bicyclic compound **30**. δ_H (200 MHz; $CDCl_3$) 1.44 (1H, m), 1.49 (3H, s), 1.56–1.74 (6H, m), 1.92 (1H, m), 2.05 (1H, t, J=12.5 Hz), 2.19 (1H, m), 2.43 (1H, m), 2.61 (2H, m), 3.28 (1H, d, J=13.5 Hz), 7.49 (1H, d, J=12.5 Hz); δ_C(100.6 MHz; $CDCl_3$) 19.1, 19.4, 25.9, 28.3, 29.3, 30.8, 31.8, 35.8, 45.3, 48.8, 130.8, 139.4, 147.4, 147.5, 164.1, 164.7, 165.4, 173.8; mp 200–202°C; Bicyclic compound **31**. δ_H(200 MHz; $CDCl_3$) 1.20–1.40 (2H, m), 1.55 (3H, s), 1.57–1.90 (6H, m), 1.92 (1H, m), 2.0 (1H, m), 2.44 (1H, dd, J=13, 4.5 Hz), 2.60 (2H, m), 3.31 (1H, d, J=13.5 Hz), 6.97 (1H, d, J=11 Hz); δ_C (100.6 MHz; $CDCl_3$) 19.3, 24.1, 25.6, 25.7, 29.8, 31.8, 32.9, 41.1, 43.8, 48.6, 129.3, 140.8, 146.7, 150.9, 164.0, 164.7, 165.4, 173.8.

1.4.2. Bicyclic compound 32. The reaction was performed according to the general procedure and stirred for 24 h. The crude material obtained was purified by flash column chromatography on silica gel (7:2 hexanes/ethyl acetate) to afford a yellow oil which was triturated in 10:1 hexanes/diethyl ether to give the bicyclic product in 17% yield from **13** (2.05 g, 4.70 mmol) as a white amorphous powder: R_f 0.19 (4:1 hexanes/ethyl acetate). δ_H(200 MHz; $CDCl_3$) 1.42–1.79 (10H, m), 1.61 (3H, s), 1.94 (1H, m), 2.23 (1H, m), 2.59 (2H, m), 3.04 (1H, d, J=14 Hz), 3.13 (1H, d, J=14 Hz), 7.04 (1H, d, J=12 Hz); δ_C (125.7 MHz; $CDCl_3$) 23.3, 26.3, 27.4, 29.9, 31.9, 33.0, 33.2, 34.3, 44.1, 44.8, 49.0, 126.5, 141.3, 147.4, 152.1, 164.6, 165.6 (2Cs), 174.3; ν_{max}(film)/cm^{-1} 2926, 2884, 1835, 1768, 1664; mp 209–210°C; HRMS: $C_{19}H_{20}O_6{\cdot}NH_4$ calcd: 362.161, found: 362.160 (MNH_4^+); m/z ($APCI^+$): 345 (MH^+).

1.4.3. Bicyclic compound 33. The reaction was performed according to the general procedure and stirred for 5 h. The crude material obtained was purified by flash column chromatography on silica gel (7:2 hexanes/ethyl acetate) to afford a yellow oil which was triturated in 8:1 hexanes/diethyl ether to give the bicyclic product in 16% yield from **15** (3.30 g, 8.59 mmol) as a white powder. R_f 0.3 (4:1 Hexane/EtOAc); δ_H (500 MHz; $CDCl_3$) 0.84–0.95 (4H, m), 1.00–1.05 (2H, m), 1.09–1.16 (1H, m), 1.20–1.28 (3H, m), 1.56 (3H, s), 1.63 (1H, dt, J=13.5, 3 Hz), 1.68–1.74 (2H, m), 1.89 (1H, dt, J=13.5, 3 Hz), 1.95 (1H, ddd, J=11.5, 10.5, 3.5 Hz), 2.01–2.05 (1H, m), 2.43 (1H, dd, J=12.5, 4.5 Hz), 2.57 (1H, d, J=13.5 Hz), 2.61 (1H, dd, J=12.5, 3.5 Hz), 3.30 (1H, d, J=13.5 Hz), 7.00 (1H, d, J=11.5 Hz); δ_C (400 MHz; $CDCl_3$) 19.4, 26.1, 26.2, 29.6, 32.9, 32.9, 33.2, 38.8 (2Cs), 40.8, 41.2, 42.4, 43.6, 48.6, 129.2, 140.8, 146.7, 150.8, 164.1, 165.3, 165.5, 173.8; ν_{max}(KBr)/cm^{-1} 2924, 2854, 1833, 1784, 1768, 1664, 1447, 1292, 1232, 938; mp >230°C; HRMS: $C_{22}H_{24}O_6{\cdot}NH_4$ calcd: 402.192, found 402.191 (MNH_4^+); m/z (CI^+) 402 (100%, MNH_4^+), 299 (5).

Acknowledgements

We wish to thank the EPSRC for student awards for P. G. B. and A. V. W. M. and 'La Ligue Nationale Contre Le Cancer' for post-doctoral funding for F. R. We wish to acknowledge Dr T. Claridge and Dr B. Odell for invaluable assistance with the NMR spectroscopy and Dr D. Watkin from the Department of Chemical Crystallography, Oxford for assistance with the X-ray Crystallographic analysis of **30**.

References

1. (a) Dabrah, T. T.; Harwood, H. J.; Jankovich, N. D.; Kaneko,

T.; Li, J. C.; Lindsey, S.; Moshier, P. M.; Subashi, T. A.; Therrien, M.; Watts, P. C. *J. Antibiot.* **1997**, *50*, 1–7. (b) Dabrah, T. T.; Kaneko, T.; Massefski, W.; Whipple, E. B. *J. Am. Chem. Soc.* **1997**, *119*, 1594–1598.

2. (a) Toyota, M.; Majo, V. J.; Ihara, M. *Tetrahedron Lett.* **2001**, *42*, 1555–1558. (b) Tan, Q.; Danishefsky, S. *J. Angew. Chem., Int. Ed. Engl.* **2000**, *39*, 4509–4511. (c) Yoshimitsu, T.; Yanagisawa, S.; Nagaoka, H. *Org. Lett.* **2000**, *2*, 3751–3754. (d) Davies, H. M. L.; Ren, P. D. *Tetrahedron Lett.* **2000**, *41*, 9021–9024. (e) Bio, M. M.; Leighton, J. L. *Org. Lett.* **2000**, *2*, 2905–2907. (f) Clive, D. L. J.; Sun, S. Y.; Gagliardini, V.; Sano, M. K. *Tetrahedron Lett.* **2000**, *41*, 6259–6263. (g) Waizumi, N.; Itoh, T.; Fukuyama, T. *J. Am. Chem. Soc.* **2000**, *122*, 7825–7826. (h) Sheehan, S. M.; Lalic, G.; Chen, J. S.; Shair, M. D. *Angew. Chem., Int. Ed. Engl.* **2000**, *39*, 2714–2715. (i) Chen, C.; Layton, M. E.; Sheehan, S. M.; Shair, M. D. *J. Am. Chem. Soc.* **2000**, *122*, 7424–7425. (j) Davies, H. M. L.; Calvo, R. L.; Townsend, R. J.; Ren, P. D.; Churchill, R. M. *J. Org. Chem.* **2000**, *65*, 4261–4268. (k) Devaux, J. F.; O'Neil, S. V.; Guillo, N.; Paquette, L. A. *Collect. Czech. Chem. Commun.* **2000**, *65*, 490–510. (l) Nicolaou, K. C.; Jung, J. K.; Yoon, W. H.; He, Y.; Zhong, Y. L.; Baran, P. S. *Angew. Chem., Int. Ed. Engl.* **2000**, *39*, 1829–1832. (m) Starr, J. T.; Carreira, E. M. *Angew. Chem., Int. Ed. Engl.* **2000**, *39*, 1415–1421. (n) Diederichsen, U. *Nachr. Chem. Tech. Lab.* **1999**, *47*, 1423–1427. (o) Nicolaou, K. C.; He, Y.; Fong, K. C.; Yoon, W. H.; Choi, H. S.; Zhong, Y. L.; Baran, P. S. *Org. Lett.* **1999**, *1*, 63–66. (p) Meng, D. F.; Tan, Q.; Danishefsky, S. *J. Angew. Chem., Int. Ed. Engl.* **1999**, *38*, 3197–3201. (q) Clive, D. L. J.; Zhang, J. H. *Tetrahedron* **1999**, *55*, 12059–12068. (r) Yoshimitsu, T.; Yanagiya, M.; Nagaoka, H. *Tetrahedron Lett.* **1999**, *40*, 5215–5218. (s) Clive, D. L. J.; Sun, S. Y.; He, X.; Zhang, J. H.; Gagliardini, V. *Tetrahedron Lett.* **1999**, *40*, 4605–4609. (t) Meng, D. F.; Danishefsky, S. *J. Angew. Chem., Int. Ed. Engl.* **1999**, *38*, 1485–1488. (u) Nicolaou, K. C.; Baran, P. S.; Zhong, Y. L.; Choi, H. S.; Yoon, W. H.; He, Y.; Fong, K. C. *Angew. Chem., Int. Ed. Engl.* **1999**, *38*, 1669–1675. (v) Nicolaou, K. C.; Baran, P. S.; Zhong, Y. L.; Fong, K. C.; He, Y.; Yoon, W. H.; Choi, H. S. *Angew. Chem., Int. Ed. Engl.* **1999**, *38*, 1676–1678. (w) Bio, M. M.; Leighton, J. L. *J. Am. Chem. Soc.* **1999**, *121*, 890–891. (x) Nicolaou, K. C.; Baran, P. S.; Jautelat, R.; He, Y.; Fong, K. C.; Choi, H. S.; Yoon, W. H.; Zhong, Y. L. *Angew. Chem., Int. Ed. Engl.* **1999**, *38*, 549–552. (y) Chen, C.; Layton, M. E.; Shair, M. D. *J. Am. Chem. Soc.* **1998**, *120*, 10784–10785. (z) Frontier, A. J.; Danishefsky, S. J.; Koppel, G. A.; Meng, D. F. *Tetrahedron* **1998**, *54*, 12721–12736. (aa) Waizumi, N.; Itoh, T.; Fukuyama, T. *Tetrahedron Lett.* **1998**, *39*, 6015–6018. (bb) Kwon, O. Y.; Su, D. S.; Meng, D. F.; Deng, W.; D'Amico, D. C.; Danishefsky, S. J. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 1877–1880. (cc) Kwon, O. Y.; Su, D. S.; Meng, D. F.; Deng, W.; D'Amico, D. C.; Danishefsky, S. J. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 1880–1882. (dd) Armstrong, A.; Critchley, T. J.; Mortlock, A. A. *Synlett* **1998**, 552–553. (ee) Nicolaou, K. C.; Postema, M. H. D.; Miller, N. D.; Yang, G. *Angew. Chem., Int. Ed. Engl.* **1998**, *36*, 2821–2823. (ff) Sgarbi, P. W. M.; Clive, D. L. J. *Chem. Commun.* **1997**, 2157–2158. (gg) Nicolaou, K. C.; Harter, M. W.; Boulton, L.; Jandeleit, B. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 1194–1196.
3. Huff, R. K.; Moppett, C. E.; Sutherland, J. K. *J. Chem. Soc.* **1972**, 2584–2590.
4. (a) Sulikowski, G. A.; Agnelli, F.; Corbett, R. M. *J. Org. Chem.* **2000**, *65*, 337–342. (b) Spencer, P.; Agnelli, F.; Williams, J. H.; Keller, P. N.; Sulikowski, G. A. *J. Am. Chem. Soc.* **2000**, *122*, 420–421.
5. Baldwin, J. E.; Beyeler, A.; Cox, R. J.; Keats, C.; Pritchard, G. J.; Adlington, R. M.; Watkin, D. J. *Tetrahedron* **1999**, *55*, 7363–7374.
6. Suzuky, A. *Pure Appl. Chem.* **1985**, *12*, 1749–1758.
7. Volk, T.; Bernicke, D.; Bats, J.; Schmalz, H. G. *Eur. J. Inorg. Chem.* **1998**, 1883–1905.
8. The atomic coordinates for **30** are available on request from the Cambridge Crystallographic Data Centre, University Chemical Laboratory, Lensfield Road, Cambridge CB2 1EW (Deposition number CCDC 164448). The crystallographic numbering system differs from that used in the text; therefore any request should be accompanied by the full literature citation of this paper.
9. White, J. D.; Kim, J.; Drapela, N. E. *J. Am. Chem. Soc.* **2000**, *122*, 8665–8671.