Available online at www.sciencedirect.com
ScienceDirect
Tetrahedron
Tetrahedron 63 (2007) 4500–4509

Total synthesis of cyercene A and the biomimetic synthesis of (±)-9,10-deoxytridachione and (±)-ocellapyrone A

Raphaël Rodriguez,[a] Robert M. Adlington,[a,*] Serena J. Eade,[a] Magnus W. Walter,[c] Jack E. Baldwin[a] and John E. Moses[b,*]

[a]*The Chemistry Research Laboratory, University of Oxford, Mansfield Road, Oxford OX1 3TA, UK*
[b]*The School of Pharmacy, University of London, 29-39 Brunswick Square, London WC1N 1AX, UK*
[c]*Lilly Research Centre, Eli Lillyand Company Ltd, Erl Wood Manor, Sunninghill Road, Windlesham GU20 6PH, UK*

Received 23 November 2006; revised 19 February 2007; accepted 8 March 2007
Available online 13 March 2007

Dedicated to the memory of Professor D. John Faulkner

Abstract—This paper summarises our detailed study towards the biomimetic synthesis of the complex polypropionate derived natural product (±)-9,10-deoxytridachione. A previous study based on the elaboration of functionalised γ-pyrones allowed us to synthesise cyercene A. The same efficient methodology has been applied for the elaboration of a more complex fully conjugated γ-pyrone polyene. Our approach centred on a key tandem Suzuki-coupling/electrocyclisation reaction, which supports a possible biosynthetic pathway for this class of natural products. A related compound was obtained during our studies, which we identified as the correct structure of ocellapyrone A.

1. Introduction

1.1. Background

Over the last 30 years, many structurally novel polypropionate derived metabolites have been isolated from marine organisms as diverse as bacteria, sponge and molluscs. Pyrone containing polypropionate compounds are characteristically produced by a restricted group of marine molluscs of the order *Sacoglossan*.[1] These creatures have developed a symbiotic relationship with active chloroplasts from algae in order to synthesise, in their own tissue, secondary metabolites involved in defence against predators. Such compounds, which are formally derived from a polyketide pathway, are associated with specific ecophysiological functions of the molluscs, and may also act as mediators in tissue regeneration.[2] The diverse range of biological activities expressed is the consequence of the impressive structural diversity associated with this superfamily of natural products.

Indeed, these metabolites display an unusual and diverse array of molecular architectures, often comprising compounds with pyrone units appended to a polyene or polyene derived carbon-frame/side chain. For example, Figure 1 displays a range of structures including unsaturated conjugated polyenes such as cyercene A (**1**),[3] 1,3-cyclohexadiene core units such as 9,10-deoxytridachione (**2**)[4] and tridachiahydropyrone (**5**),[5] bicyclo[3.1.0]hexene metabolites including photodeoxytridachione (**7**),[6] bicyclo[4.2.0]octadiene (e.g., ocellapyrone A (**10**)[7–9]) and their corresponding oxidised metabolites such as tridachione (**3**),[10] tridachiapyrone I (**4**),[11] tridachiahydropyrone B (**6**),[11,5b] tridachiapyrone E (**8**),[12] tridachiapyrone F (**9**),[12] ocellapyrone B (**11**)[8,9] and elysiapyrone B (**12**).[13] It is noteworthy that the nitrophenyl pyrones spectinabilin (**13**)[14] and SNF compounds[15] **14** and **15** isolated from the actinomycete *Streptomyces spectabilis* exhibit similar structural complexities.

Fascinated by the structural diversity of the natural products created by these astonishing marine organisms, Faulkner undertook a research programme in the late 1970s dedicated to the isolation and characterisation of new metabolites.[4] This pioneering work uncovered many interesting compounds and their chemical relationships. A most representative example was provided independently by Scheuer and Faulkner, both demonstrating the in vivo[6] and in vitro[4] photochemical conversion of (−)-9,10-deoxytridachione (**2**) into (−)-photodeoxytridachione (**7**). Ireland and Faulkner proposed that (−)-9,10-deoxytridachione (**2**) undergoes a $[_{\sigma}2_a+_{\pi}2_a]$ rearrangement to (−)-photodeoxytridachione (**7**), which is chemically reasonable since optical activity was retained in the product. However, it could also be proposed that during the in vivo conversion, (−)-**2** undergoes a

Keywords: Total synthesis; Natural products; Electrocyclisation; Reaction cascade.
* Corresponding authors. Tel.: +44 (0)20 7753 5804; fax: +44 (0)20 7753 5935 (J.E.M.); e-mail: john.moses@pharmacy.ac.uk

0040–4020/$ - see front matter © 2007 Published by Elsevier Ltd.
doi:10.1016/j.tet.2007.03.057

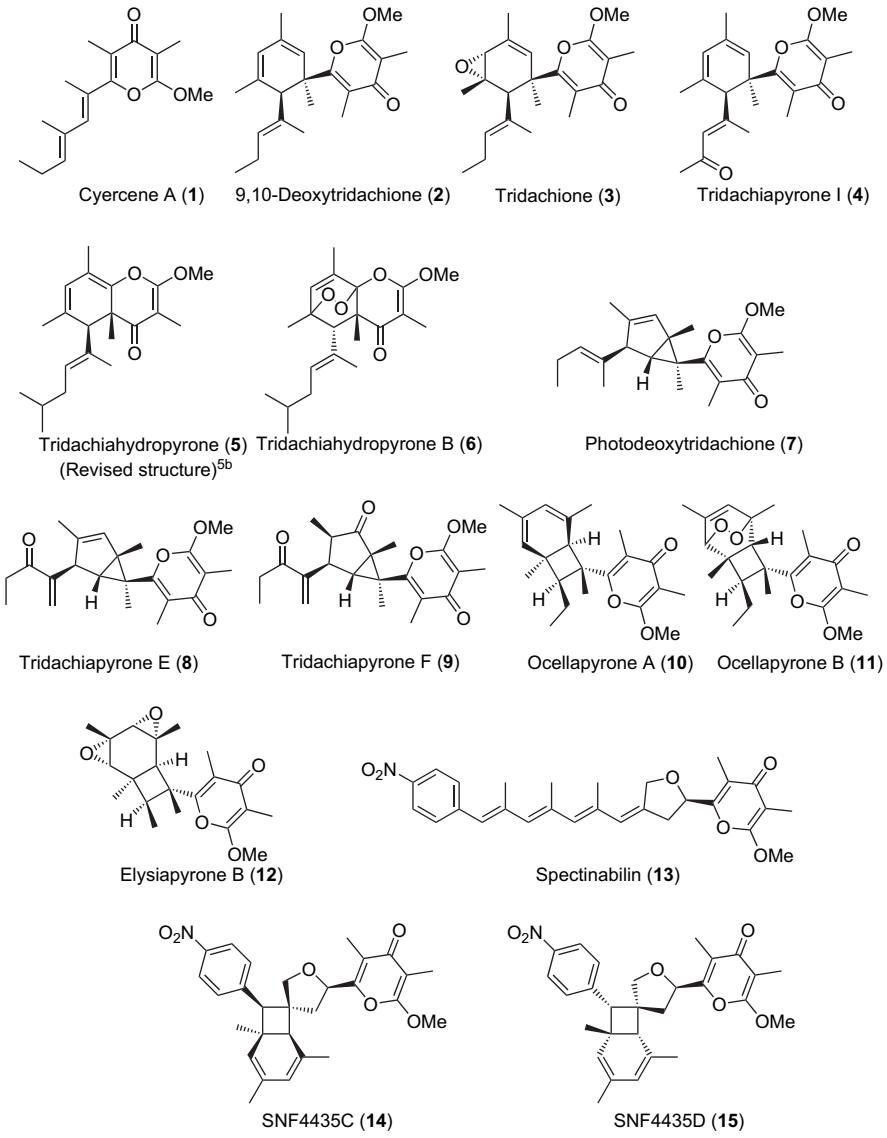


Figure 1. Representative structural diversity of polypropionate metabolites containing γ-pyrones.

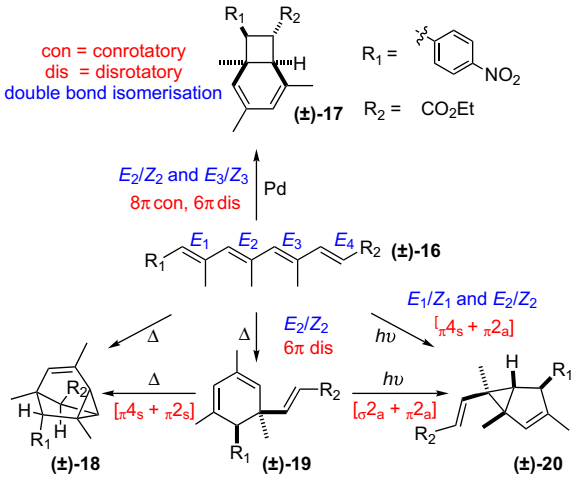
retro-electrocyclisation providing an achiral tetraene, which subsequently undergoes a photochemical enzyme mediated Diels–Alder cycloaddition giving **7** in enantiopure form. Jones, however, has recently proposed a diradical process to be involved in this transformation.[16]

1.2. Previous study

Intrigued by the noteworthy $[_{\sigma}2_a+_{\pi}2_a]$ transformation of (−)-**2** into (−)-**7** and the possible chemical relationship existing between other polypropionate metabolites, we investigated model reactions involving simple polyene substrates.[17] This study allowed us to demonstrate the ability of conjugated polyenes to undergo selective cascade isomerisations–pericyclisations, forming a range of complex core structures under a judicious choice of reaction conditions. Such polyenes were found to be versatile reactive substrates and highly sensitive to their environment such as light, temperature or the presence of a palladium catalyst.

Thus, we have demonstrated several different modes of thermal and photochemical reactions affording structurally diverse scaffolds from relatively simple (*E*,*E*,*E*,*E*)-tetraene precursors. In the examples illustrated in Scheme 1, polyene (±)-**16** was encouraged to undergo selective *E*/*Z* double bond isomerisation under a variety of reaction conditions, resulting in the necessary geometry for cascade electrocyclisations to ensue. Several of the model core structures such as (±)-**17**, (±)-**19** and (±)-**20** shared common features with the *Sacoglossan* polypropionate metabolites described above, which led us to propose a general biosynthetic rationale to explain the origin of these natural products through cascade electrocyclisations.[17] We proposed that many complex polypropionate metabolites may be biosynthetically derived from conjugated linear polyenes via double bond isomerisations, thermal and/or photochemical electrocyclisations, [4+2] cycloadditions and photoinduced [2+2] concerted rearrangements, generating significant structural diversity. Scheme 2 describes our proposed hypothesis of a general biosynthetic pathway for representative polypropionate metabolites containing γ-pyrones and describes possible chemical relationship existing between them. A single polyene precursor (*E*,*E*,*E*,*E*)-**21** could, after photochemical or thermal selective double bond isomerisation, convert

into the polyene intermediates (*E*,*Z*,*E*,*E*)-**22**, (*E*,*Z*,*Z*,*E*)-**23**, (*Z*,*E*,*E*,*E*)-**24** and (*Z*,*Z*,*E*,*E*)-**25**, which could subsequently undergo photochemically or thermally allowed pericyclic processes to provide metabolites **2**, **7** and **5**, respectively. Furthermore, selective late stage oxidation could lead to the related metabolites including **3**, **4**, **6**, **8** and **9**.



Scheme 1. Complex core structures derived from polyene precursors.

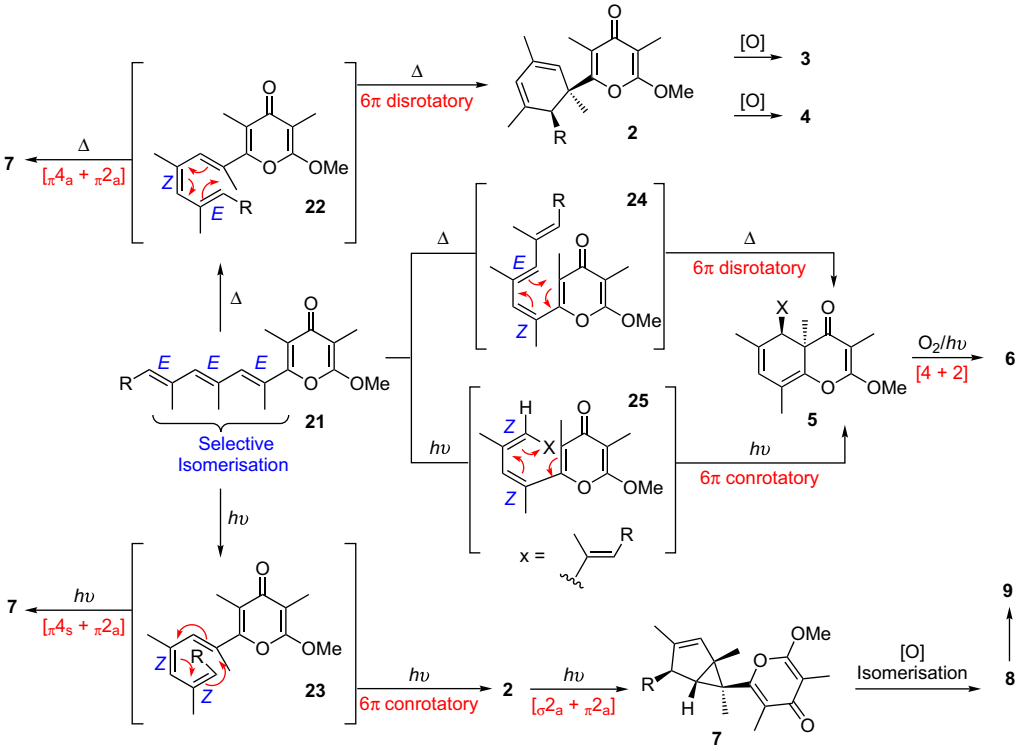
As part of our continuing efforts directed towards the biomimetic synthesis of natural products,[18,19] we became interested in the polypropionate derived (±)-9,10-deoxytridachione (**2**) due to its unusual molecular architecture and biological activity. Compound (−)-**2** was isolated as a single enantiomer by Faulkner and has attracted much attention with respect to understanding the chemical processes involved in its biosynthesis and biosynthetic transformations.[4,10] We have recently reported the first total synthesis of this natural product in racemic form, which involved a tandem Suzuki cross coupling/disrotatory electrocyclisation process.[7] We now report a complete account of our studies, which includes an efficient preparation of cyercene A (**1**) using a novel methodology, and its application to the biomimetic synthesis of both natural products (±)-9,10-deoxytridachione (**2**) and (±)-ocellapyrone A (**10**).

2. Results and discussion

2.1. Model study: synthesis of cyercene A (1)

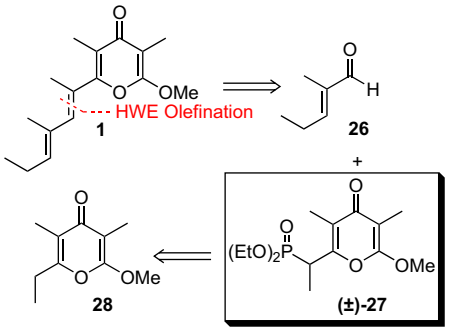
Cyerce cristallina is a *Sacoglossan* species whose body volume is mainly due to the presence of dorsal appendages aposematically coloured in red and white. When attacked by predators, this mollusc secretes presumably toxic mucus and, if molested further, detaches its cerata, which then exhibit prolonged contractions and carry on secreting large amount of mucus. After the autonomic process, the mollusc provides a striking example of regeneration by completely reproducing the cerata within a week. Intrigued by the unusual display of tissue regeneration for such a complex organism, Di Marzo and co-workers undertook a research programme, aimed at characterising some of the chemical substances involved in both chemical defence and regenerative process.[3] Several products were isolated and cyercene A (**1**) was found to be central in the tissue regeneration phenomena.[3,20]

A retrosynthetic analysis of this very interesting natural product reveals the commercially available aldehyde **26** (Scheme 3) and the phosphono-γ-pyrone unit (±)-**27**, which we believed could be coupled in a stereoselective manner to furnish



Scheme 2. Proposed biosynthetic relationship between several γ-pyrone containing compounds.

the target compound in a single step. Structurally related non-methylated phosphono-pyrones have been reported by Koester and Hoffmann, however there are no reports of their use in Horner–Wadsworth–Emmons olefinations.[21] Further disconnection of the functionalised pyrone building block gives rise to the known pyrone **28**. Our desire to utilise a Horner–Wadsworth–Emmons type approach for the coupling was based upon the well-known ability of such reagents to generate *E*-trisubstituted olefins stereoselectively.[22] It was also desirable to install the double bond in one step, thus avoiding additional dehydration protocols necessary in existing aldol-type methodology utilised in related studies with α-pyrones.[23]



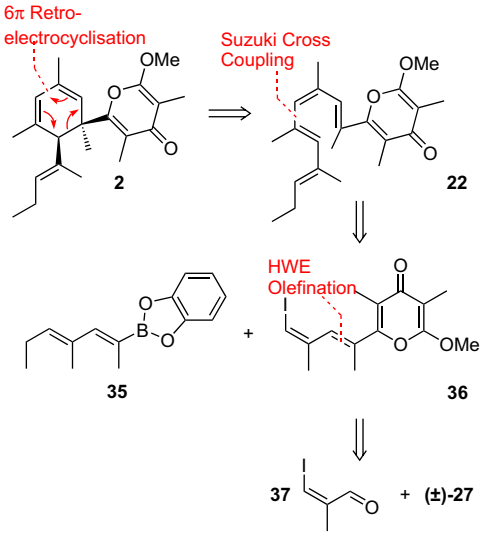
Scheme 3. Cyercene A retrosynthetic analysis.

Our synthesis of cyercene A (**1**) commenced with the readily available 2-ethyl-6-methoxy-3,5-dimethylpyran-4-one (**28**) shown in Scheme 4.[21,23] Deprotonation of **28** using lithium hexamethyldisilazide at −78 °C in tetrahydrofuran, followed by quenching of the resulting anion with the Davis oxaziridine,[24] lead to the functionalised hydroxypyrone (±)-**33** in good yield. The product was then smoothly converted into the corresponding mesylate in high yield and was easily purified by flash silica gel chromatography to provide (±)-**34**. Treatment of the latter with the sodium salt of diethyl phosphite in DMF at 0 °C successfully generated the desired Horner–Wadsworth–Emmons reagent (±)-**27** in good yield. Finally, treatment of the commercially available aldehyde **26** with the lithium salt of (±)-**27** at −78 to 20 °C successfully yielded the target natural product cyercene A (**1**) as the major stereoisomer [*E*:*Z*>16:1] in excellent yield.[25] All spectral data were in agreement with those described for the natural product.[3] We have also investigated several other olefination protocols using similar enals, including a Julia-type coupling and a Reformatsky approach. Both strategies involved the corresponding iodo-pyrone rather than the Horner–Wadsworth–Emmons reagent. Unfortunately, such protocols were abandoned, suffering from very low yields.

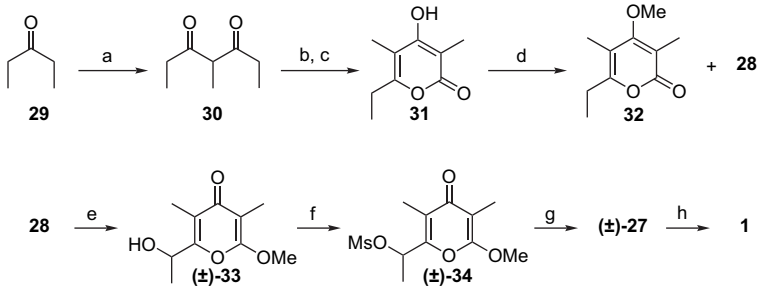
With the above example, we had synthesised a novel γ-pyrone Horner–Wadsworth–Emmons reagent, which we anticipated could be employed in the synthesis of more complex polypropionate derived natural products. Having this methodology in hand, and our expertise in polyene rearrangements,[17] we next engaged in the biomimetic synthesis of the more complex polyene derived metabolite (±)-9,10-deoxytridachione (**2**).

2.2. Application of methodology to the synthesis of complex metabolites

(−)-9,10-Deoxytridachione (**2**) was isolated from the molluscs *Tridachiella diomedea*[4] (Mexican dancer) and *Placobranchus ocellatus*.[6] This natural product seemed suitable for our continuing studies since we envisaged that relatively simple chemical manipulations may allow access to a range of related metabolites including **3**, **4**, **7**, **8** and **9** (Scheme 2). Scheme 5 depicts a retrosynthetic rationale towards (±)-**2**. Thus, a retro thermal 6π-disrotatory electrocyclisation reveals the (*E*,*Z*,*E*,*E*)-conjugated γ-pyrone-tetraene **22**, which we, Ireland and Faulkner,[4] have considered as a possible biosynthetic precursor to **2**. However, we also appreciated that **2**



Scheme 5. (±)-9,10-Deoxytridachione retrosynthetic analysis.

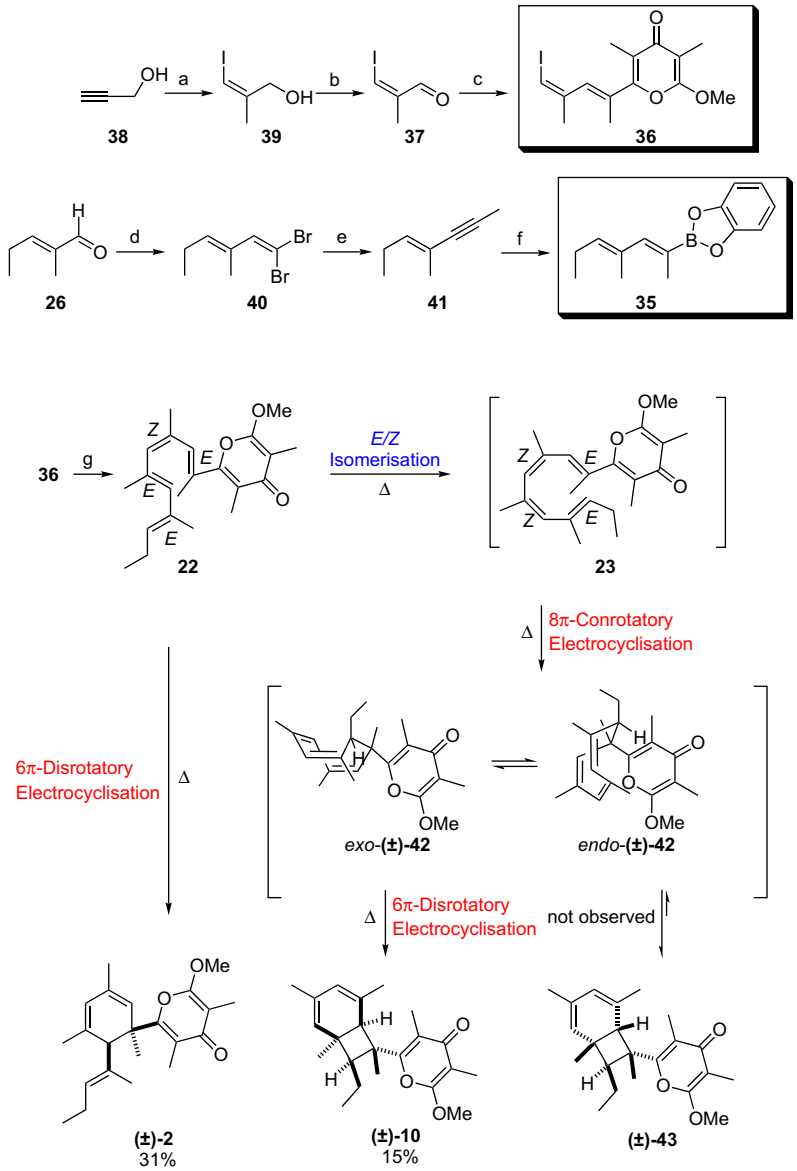


Scheme 4. Reagents and conditions: (a) NaH, Et_2O, then ethyl propionate, 0 °C to rt, 12 h, 52%; (b) DIPA, ^nBuLi, THF, 0 °C, 30 min, then solid CO_2; (c) Ac_2O, rt, 12h, 59% over two steps; (d) Me_2SO_4, Li_2CO_3, refluxing acetone, 48 h, 42% for **32**, 55% for **28**; (e) LHMDS, THF, −78 °C, 30 min, then Davis's reagent, 10 min, 76%; (f) Et_3N, MsCl, DCM, 0 °C, 30 min, 92%; (g) NaH, diethylphosphite, DMF, 0 to 60 °C, then (±)-**34**, 0 °C to rt, 12 h, 84%; (h) LHMDS, DMF, −78 °C then **26**, then −78 °C to rt over 1 h, 87%.

may be biosynthetically derived through a photochemical 6π-conrotatory electrocyclisation process[17c,d] of the corresponding (*E*,*Z*,*Z*,*E*)-tetraene **23** (Scheme 2). Although both thermal and photochemically induced 6π-electrocyclisation processes have been reported with related polyene systems, to our knowledge, such transformations had not been demonstrated with conjugated γ-pyrone containing polyenes. Considering the known photochemical relationship between **2** and **7**,[4,6] we assumed that polyene **22** was more suitable for our study. Avoiding photochemical conditions would allow us to prepare (±)-**2** selectively without its subsequent conversion into (±)-**7**.

Thus, disconnection of **22** revealed the known conjugated vinyl-boronic ester **35**[26] and vinyl iodide **36**, which we believed would be ideal partners for a Suzuki coupling reaction.[27] Further analysis of fragment **36** revealed the Horner–Wadsworth–Emmons olefination reagent (±)-**27**, which was previously used in the preparation of cyercene A (**1**), and the known readily available iodo-aldehyde **37**.[28]

Our synthesis commenced with the condensation of aldehyde **37**, obtained in two steps from propargyl alcohol,[28] with the lithium salt of (±)-**27**, at −78 to 20 °C in THF, to give the conjugated vinyl iodide **36** as the major stereoisomer [*E*:*Z*>6:1] in an unoptimised 39% yield (Scheme 6). Subsequent Suzuki cross coupling between **36** and boronic ester **35**, the latter obtained efficiently in three steps from **26**,[26] was performed using standard conditions at 80 °C.[29] The insoluble palladium salts were removed from the reaction mixture by a quick filtration on florisil®. ^{1}H NMR of the crude reaction mixture showed the presence of four new alkenyl signals [δ_H ($CDCl_3$) 5.32–5.41 (br m), 5.85 (br s), 5.98 (br s) and 6.42 (br s)] characteristic of



Scheme 6. Reagents and conditions: (a) MeMgBr, CuI, Et_2O, −10 °C to rt, then ICl, −10 °C to rt, 16 h, 45%; (b) MnO_2, DCM, rt, 12 h, 99%; (c) (±)-**27**, LHMDS, THF, −78 °C to rt, 1 h, 39%; (d) PPh_3, CBr_4, DCM, rt, 2 h, 96%; (e) BuLi, THF, then MeI, −78 °C to rt over 2 h, then stirred 16 h, 40%; (f) catecholborane neat, 90 °C, 4 h, 99%; (g) $Pd(PPh_3)_4$, **35**, THF, then aqueous KOH, 80 °C, 2 h, 65% (crude product **22**), then benzene, 120 °C, 1 h, 31% for (±)-**2**, 15% for (±)-**10**.

a conjugated tetraene,[17d,e] leading us to conclude the major constituent of the crude mixture to be compound **22**.

Crude **22** was heated in a sealed tube in benzene at 120 °C for 1 h in the absence of light. A mixture comprising two main compounds was obtained, which we were unable to separate by silica gel chromatography. However, purification by reverse phase C-18 HPLC facilitated the separation of the two compounds.[30] The spectral data for the major compound isolated (31% yield), corresponded to the natural product (±)-**2**,[4] and was presumably formed via a 6π-disrotatory electrocyclisation from polyene **22**.

The other unexpected compound obtained in 15% yield possesses the same structural bicyclo[4.2.0]octadiene core as the spectinabilin (**13**) derived immunosuppressants SNF 4435 C (**14**) and D (**15**) (Fig. 1), and is formally derived from isomerisation of (*E*,*Z*,*E*,*E*)-**22** to (*E*,*Z*,*Z*,*E*)-**23**, followed by thermally allowed consecutive 8π-conrotatory and sterically favoured 6π-disrotatory electrocyclisations.[17f,19a,c,31,32] The *exo*-structure (±)-**10** proposed for this compound was based upon extensive NOE measurements. Recently, two natural products were isolated from the mollusc *P. ocellatus* by Manzo et al.[8] for which structures **43** and **11** were proposed. The *endo*-structure of **43** had indirectly been assigned by structural comparison with **11** for which 2D NMR analysis has been carried out.[8] However, the NMR data (^{1}H and ^{13}C) collected by us for compound (±)-**10** were identical to those described for **43** by Manzo et al. We did not observe any traces of (±)-**43** during our synthesis and a structural reassignment for the newly isolated natural product ocellapyrone A was suggested. More recently, in a similar study, Trauner observed similar results and confirmed the structure correction after X-ray analysis of a related compound derived from (±)-**43**.[9] In his recent report, Trauner observed the formation of (±)-**43** as the major isomer along with small quantities of (±)-**10** starting from the same polyene **22** at lower temperature (45 °C). A higher temperature (120 °C) used during our experiment allowed us to isolate compound (±)-**10** as a single product. However, if formed, (±)-**43** could convert into the *endo*-(±)-**42** intermediate at high temperature via a 6π retro-electrocyclisation and subsequently displaces the equilibrium towards the most stable *exo* conformer, the latter yielding natural product (±)-**10**. In a comparable study, Trauner also reported the conversion of (±)-**43** into ocellapyrone B ((±)-**11**) via a [4+2] cycloaddition with singlet oxygen. However, **43** has still not been isolated itself as a natural product.

3. Conclusion

In conclusion, we have described the first total synthesis of cyercene A (**1**) and (±)-9,10-deoxytridachione ((±)-**2**) in a biomimetic fashion, demonstrating experimentally a chemical relationship between a fully conjugated polyene-γ-pyrone and a complex natural product. The results from this study strengthen our general biosynthetic proposal that compounds of these classes are most likely derived through pericyclic processes of linear polyene precursors. The co-isolation of (±)-ocellapyrone A ((±)-**10**) during our synthesis also strongly supports this biosynthetic hypothesis on the grounds that both natural products have been isolated from the same mollusc *P. ocellatus*. This successful, flexible methodology previously created for the synthesis of cyercene A will be further optimised in our laboratory, and used to probe for the preparation of other polypropionate metabolites. This example further demonstrates the power of such biomimetic approaches, which allowed us in this particular case to obtain the unexpected, recently isolated natural product (±)-**10**.

4. Experimental

4.1. General procedures

All reagents were purified by standard techniques reported in Ref. 35 or used as supplied from commercial sources, as appropriate. Solvents were distilled before use, unless otherwise stated. Anhydrous dichloromethane was obtained by heating to reflux over calcium hydride for an hour followed by distillation under argon. Anhydrous diethyl ether and anhydrous THF were obtained by heating to reflux over sodium–benzophenone for 1 h followed by distillation under argon. Anhydrous DMF was purchased from the Sigma–Aldrich Company and used without any further purification. Solvents were removed under reduced pressure using a Buchi R110 or R114 Rotavapor. Final traces of solvent were removed from samples using an Edwards E2M5 high vacuum pump with pressure below 2 mmHg. All experiments were carried out under inert atmosphere unless otherwise stated. ^{1}H NMR spectra were recorded using Bruker DPX 200, DQX 400, AMX 500 and DRX 500 instruments. For ^{1}H spectra recorded in $CDCl_3$, CD_3OD and C_6D_6, chemical shifts are quoted in parts per million (ppm) and are referenced to the residual solvent peak. The following abbreviations are used: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad. Proton assignments and stereochemistry are supported by ^{1}H–^{1}H COSY and NOESY where necessary. Data are reported in the following manner: chemical shift (integration, multiplicity, coupling constant if appropriate). Coupling constants (*J*) are reported in hertz to the nearest 0.5 Hz. ^{13}C NMR spectra were recorded using Bruker DPX 200, Bruker DQX 400 and Bruker AMX 500 instruments. Carbon spectra assignments are supported by DEPT-135 spectra, ^{13}C–^{1}H (HMQC and HMBC) correlations where necessary. Flash column chromatography was carried out using Sorbsil™ C60 (40–63 mm, 230–400 mesh) silica gel. Thin layer chromatography was carried out on glass plates pre-coated with Merck silica gel 60 F254, which was visualised either by quenching of UV fluorescence or by dipping in a solution of $KMnO_4$ ($KMnO_4$ (3 g), KOH (0.3 g), K_2CO_3 (20 g) and water (300 mL)) followed by heating, as appropriate. Melting points were recorded using a Cambridge Instruments Gallen™ III Kofler Block melting apparatus or a Buchi 510 capillary apparatus and are uncorrected.

Infrared spectra were recorded either as a thin film between NaCl plates or KBr disc on a Perkin-Elmer Paragon 1000 Fourier Transform spectrometer with internal referencing. Absorption maxima are reported in wavenumbers (cm^{-1}) and the following abbreviations are used: s, strong; br, broad; m, medium; w, weak. Low-resolution mass spectra were recorded on V. G. Micromass ZAB 1F and V. G. Masslab instruments as appropriate with modes of ionisation being

indicated as CI, EI, ES or APCI with only molecular ions. High-resolution mass spectrometry was performed on a Waters 2790-Micromass LCT electrospray ionisation mass spectrometer, on a V. G. autospec chemical ionisation mass spectrometer and a Thermo Electron LTQ-FT Mass Spectrometer.

4.1.1. 4-Methyl-3,5-heptanedione (30).[33] Compound **30** was prepared according to the procedure of Konopelski et al.[33]

Colourless oil; bp 188 °C/766 mmHg [lit.,[33] 190 °C/750 mmHg]; ν_{max}/cm^{-1} (film) 1710s; ^1H NMR (400 MHz, $CDCl_3$): δ_H 1.01 (6H, t, J=7.0 Hz), 1.29 (3H, d, J=7.0 Hz), 2.47 (4H, q, J=7.0 Hz), 3.67 (1H, q, J=7.0 Hz); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ_C 7.5, 12.7, 34.7, 60.0, 207.3.

4.1.2. 6-Ethyl-4-hydroxy-3,5-dimethyl-2*H*-pyran-2-one (31).[21] Compound **31** was prepared according to the procedure of Koester and Hoffmann.[21] White powder; ν_{max}/cm^{-1} (KBr disc) 2975br, 1684s, 1552s; ^1H NMR (400 MHz, $CDCl_3$): δ_H 1.16 (3H, t, J=7.5 Hz), 1.95 (3H, s), 1.98 (3H, s), 2.51 (2H, q, J=7.5 Hz); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ_C 8.6, 9.6, 11.6, 24.2, 98.3, 106.9, 159.9, 165.9, 166.9.

4.1.3. 2-Ethyl-6-methoxy-3,5-dimethyl-4*H*-pyran-4-one (28) and 6-ethyl-4-methoxy-3,5-dimethyl-2*H*-pyran-2-one (32).[23] Compounds **28** and **32** were prepared according to a modified route of Takano et al.[23] A mixture of pyrone **31** (10.0 g, 59.5 mmol), dimethyl sulfate (15.0 g, 119.0 mmol) and Li_2CO_3 (13.3 g, 180.0 mmol) in acetone (100 mL) was heated to reflux for 48 h. After cooling, the reaction mixture was diluted with Et_2O (100 mL) and filtered through Celite®. The filtrate was concentrated under reduced pressure and purified by flash silica gel chromatography (4:1, 30–40 PE/EtOAc).

Elution first yielded α-pyrone **32** (4.54 g, 42%) as a yellow oil. R_f 0.35 (4:1, 30–40 PE/EtOAc); ν_{max}/cm^{-1} (film) 1705s, 1573s, 1360m, 1067w; ^1H NMR (400 MHz, $CDCl_3$): δ_H 1.11 (3H, t, J=7.5 Hz), 1.85 (3H, s), 1.93 (3H, s), 2.44 (2H, q, J=7.5 Hz), 3.73 (3H, s); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ_C 9.7, 10.0, 11.6, 24.2, 60.1, 108.5, 109.0, 160.0, 166.2, 168.4.

Further elution yielded γ-pyrone **28** (5.95 g, 55%) as a white crystalline solid. R_f 0.15 (4:1, 30–40 PE/EtOAc); mp 46–47 °C; ν_{max}/cm^{-1} (KBr disc) 1668s, 1592s, 1464m, 1175w; ^1H NMR (400 MHz, $CDCl_3$): δ_H 1.26 (3H, t, J=7.5 Hz), 1.82 (3H, s), 1.91 (3H, s), 2.60 (2H, q, J=7.5 Hz), 3.94 (3H, s); ^{13}C NMR (100.6 Hz, $CDCl_3$): δ_C 6.8, 9.7, 11.2, 24.1, 55.2, 99.2, 117.6, 159.1, 162.1, 181.1.

4.1.4. (±)-2-(1-Hydroxy-ethyl)-6-methoxy-3,5-dimethyl-pyran-4-one ((±)-33). To a solution of THF (30 mL) containing γ-pyrone **28** (3.00 g, 16.5 mmol) at −78 °C under an atmosphere of argon was slowly added LHMDS (18.1 mL of a 1 M solution, 18.1 mmol) with stirring. The solution changed from colourless to a bright red whilst allowed to stir at −78 °C for 30 min. A solution of Davis's reagent[24] (5.17 g, 19.8 mmol) in THF (15 mL) was then added cautiously to the pyrone anion, and allowed to stir for a further 10 min. The reaction was then quenched by the addition of satd aq NH_4Cl (20 mL). The crude mixture was extracted with EtOAc (2×50 mL), followed by washing of the organic fraction with brine (2×50 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure to give a yellow oil. The crude residue was purified by flash silica gel chromatography (1:1, 30–40 PE/EtOAc) to give the title compound as a white powder (2.48 g, 76%). R_f 0.20 (EtOAc); mp 78–80 °C; ν_{max}/cm^{-1} (KBr disc) 3301br s, 1660s, 1569s; ^1H NMR (400 MHz, $CDCl_3$): δ_H 1.49 (3H, d, J=6.5 Hz), 1.84 (3H, s), 1.92 (3H, s), 4.02 (3H, s), 4.97 (1H, q, J=6.5 Hz); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ_C 6.8, 9.1, 20.1, 55.4, 64.1, 99.4, 117.7, 158.2, 162.3, 181.4; HRMS [(ES)$^+$] calculated for $C_{10}H_{15}O_4$ [MH$^+$]: 199.0970, found 199.0971.

4.1.5. (±)-Methanesulfonic acid 1-(6-methoxy-3,5-dimethyl-4-oxo-4*H*-pyran-2-yl)ethyl ester ((±)-34). Et_3N (1.13 mL, 8.11 mmol) was slowly added to a solution of γ-hydroxypyrone (±)-**33** (1.00 g, 5.07 mmol) in DCM (10 mL) at 0 °C under argon. The solution was allowed to stir for 2 min, followed by the slow dropwise addition of methane sulfonyl chloride (0.87 g, 7.60 mmol). The reaction mixture was allowed to stir for a further 30 min at 0 °C, by which time a white precipitate of $Et_3N\cdot HCl$ had formed. The reaction was then quenched by the addition of satd aq NH_4Cl (20 mL), and the mixture was extracted with DCM (2×40 mL), followed by washing of the organic fraction with brine (2×40 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure to give a yellow solid. The crude residue was purified by flash silica gel chromatography (4:1, 30–40 PE/EtOAc) to give the title compound as a white solid (1.29 g, 4.67 mmol, 92%). R_f 0.50 (EtOAc); mp 100–103 °C; ν_{max}/cm^{-1} (KBr disc) 1672s, 1584s, 1349s, 1180s; ^1H NMR (400 MHz, $CDCl_3$): δ_H 1.72 (3H, d, J=6.5 Hz), 1.84 (3H, s), 2.09 (3H, s), 2.99 (3H, s), 4.03 (3H, s), 5.86 (1H, q, J=6.5 Hz); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ_C 6.9, 9.5, 18.9, 38.9, 55.6, 72.9, 100.5, 120.7, 151.6, 162.2, 180.1; HRMS [(ES)$^+$] calculated for $C_{11}H_{17}O_6S$ [MH$^+$]: 277.0746, found 277.0750.

4.1.6. (±)-[1-(6-Methoxy-3,5-dimethyl-4-oxo-4*H*-pyran-2-yl)-ethyl]phosphonic acid diethyl ester ((±)-27). To a stirred suspension of sodium hydride (155 mg of 60% dispersion in paraffin oil, 3.8 mmol) in DMF (1 mL) at 0 °C was slowly added diethyl phosphite (426 μL, 3.31 mmol). The solution was allowed to stir for 30 min at 0 °C, and then for a further 30 min at 60 °C. The solution was then cooled in an ice bath to 0 °C, followed by the cautious addition of a solution of mesylate (±)-**34** (760 mg, 2.75 mmol) in DMF (1 mL). The reaction mixture was warmed to rt and allowed to stir overnight, then quenched by the addition of satd aq NH_4Cl (1 mL). The crude mixture was extracted with EtOAc (2×5 mL), followed by washing of the organic fraction with water (2×5 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure to give a yellow oil. The crude residue was purified by flash silica gel chromatography (EtOAc) to give the title compound as a pale yellow oil (738 mg, 84%). R_f 0.15 (EtOAc); ν_{max}/cm^{-1} (oil) 2984s, 1666s, 1600s; ^1H NMR (400 MHz, $CDCl_3$): δ_H 1.24 (3H$_A$, t, J=7.0 Hz), 1.30 (3H$_B$, t, J=7.0 Hz), 1.54 (3H, dd, J=18.0,

7.0 Hz), 1.83 (3H, s), 1.96 (3H, br s), 3.41 (1H, dq, J=23.5, 7.0 Hz), 3.99 (3H, s), 4.01–4.18 ($4H_{AB}$, m); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ_C 6.8, 10.1, 11.9, 16.4, 34.9 (d, J=141.0 Hz), 55.5, 62.7 (C_A), 63.4 (C_B), 99.3, 119.9, 153.3, 162.1, 180.4; HRMS [(ES)$^+$] calculated for $C_{14}H_{24}O_6P$ [MH$^+$]: 319.1311, found 319.1314.

4.1.7. Cyercene A (1).[3] To a solution of DMF (1 mL) containing phosphono-pyrone (±)-**27** (35.0 mg, 0.11 mmol) at −78 °C was added LHMDS (120 μL of a 1 M solution in THF, 0.12 mmol). The solution was allowed to stir for 10 min, by which time the solution had attained a bright yellow colour, followed by the dropwise addition of aldehyde **26** (10.7 mg, 12 μL, 0.11 mmol). The mixture was allowed to warm to rt over 1 h, then quenched by the addition of satd aq NH_4Cl (1 mL). The crude mixture was extracted with EtOAc (2×5 mL), followed by washing of the organic fraction with water (2×5 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure to give a yellow oil. The crude residue was purified by flash silica gel chromatography (4:1, 30–40 PE/EtOAc) to give the title compound as a colourless oil (25.0 mg, 0.095 mmol, 87%). All spectral data were identical in all respects to the natural material.[3] ν_{max}/cm^{-1} (oil) 1650s, 1605s, 1585s; ^1H NMR (500 MHz, $CDCl_3$): δ_H 1.04 (3H, t, J=7.5 Hz), 1.84 (3H, br s), 1.87 (3H, br s), 2.01 (3H, br s), 2.04 (3H, br s), 2.16 (2H, m), 3.96 (3H, s), 5.53 (1H, br t, J=7.0 Hz), 6.11 (1H, s); ^{13}C NMR (125.7 MHz, $CDCl_3$): δ_C 6.8, 11.8, 13.7, 16.0, 16.2, 21.4, 55.1, 99.2, 117.6, 125.5, 130.8, 135.8, 139.4, 159.1, 161.8, 181.5; HRMS [(ES)$^+$] calculated for $C_{16}H_{23}O_3$ [MH$^+$]: 263.1647, found 263.1651.

4.1.8. (*Z*)-3-Iodo-2-methylprop-2-en-1-ol (39).[28] Compound **39** was prepared according to the procedure of Hénaff and Whiting.[28] ν_{max}/cm^{-1} (oil) 3300br, 3010s, 2980s, 1600s, 1050m; ^1H NMR (200 MHz, $CDCl_3$): δ_H 1.92 (3H, d, J=1.5 Hz), 4.20 (2H, s), 5.95 (1H, q, J=1.5 Hz); ^{13}C NMR (125.7 MHz, $CDCl_3$): δ_C 21.6, 66.8, 74.9, 146.6.

4.1.9. (*Z*)-3-Iodo-2-methylprop-2-enal (37).[28,34] The title compound was prepared according to a procedure of Porco et al.[34] as unstable yellow crystals, which were conserved in the dark at −20 °C, and used in the next step without further purification; ν_{max}/cm^{-1} (NaCl plate) 2940s, 1680s; ^1H NMR (200 MHz, $CDCl_3$): δ_H 2.52 (3H, d, J=1.5 Hz), 7.24 (1H, q, J=1.5 Hz), 9.26 (1H, s).

4.1.10. 2-(4-Iodo-1,3-dimethylbuta-1,3-dienyl)-6-methoxy-3,5-dimethylpyran-4-one (36). To a dry flask containing a magnetic stirrer bar were added pyrone (±)-**27** (320 mg, 1.01 mmol) and dry THF (2 mL). The flask was purged with argon, and cooled to −78 °C, followed by the addition of a solution of LHMDS (1.10 mL of a 1 M THF solution, 1.10 mmol). The mixture was allowed to stir for 30 min by which time the solution became bright red. A solution of aldehyde **37** (290 mg, 1.48 mmol) in THF (2 mL) was added and the reaction allowed to warm to rt over the course of 1 h. The reaction was quenched by the addition of brine (5 mL), and extracted with EtOAc (2×10 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure to give a crude brown solid. The crude residue was purified by flash silica gel chromatography (9:1, 30–40 PE/EtOAc) to give the title compound as a white solid (143 mg, 0.39 mmol, 39%) [E:Z>6:1]. R_f 0.50 (1:1, 30–40 PE/EtOAc); mp 88–91 °C; ν_{max}/cm^{-1} (KBr disc) 1654s, 1589s, 1464s, 1325m, 1255m, 1169w; ^1H NMR (500 MHz, $CDCl_3$): δ_H 1.88 (3H, s), 1.99 (3H, br d, J=1.5 Hz), 2.08 (3H, br s), 2.12 (3H, s), 3.98 (3H, s), 6.17 (1H, br s), 6.26 (1H, q, J=1.5 Hz); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ_C 7.3, 12.5, 16.8, 24.6, 55.8, 80.2, 99.8, 118.9, 130.8, 137.1, 143.7, 157.8, 162.3, 181.6; HRMS [(ES)$^+$] calculated for $C_{14}H_{18}IO_3$ [MH$^+$]: 361.0301, found 361.0308.

4.1.11. 1,1-Dibromo-3-methylhexa-1,3-diene (40).[26] Compound **40** was prepared according to the procedure of Paterson and Perkins.[26] ν_{max}/cm^{-1} (KBr disc) 1716s, 1643s; ^1H NMR (400 MHz, $CDCl_3$): δ_H 1.02 (3H, t, J=7.5 Hz), 1.87 (3H, s), 2.09 (2H, qd, J=7.5, 7.5 Hz), 5.63 (1H, t, J=7.5 Hz), 6.94 (1H, s); ^{13}C NMR (62.9 MHz, $CDCl_3$): δ_C 13.5, 15.2, 21.4, 85.3, 131.0, 137.6, 140.9.

4.1.12. (*E*)-4-Methylhept-4-en-2-yne (41).[26] Compound **41** was prepared according to the procedure of Paterson and Perkins.[26] ν_{max}/cm^{-1} (film) 2970m, 2935m, 2252m; ^1H NMR (500 MHz, $CDCl_3$): δ_H 0.95 (3H, t, J=7.5 Hz), 1.73 (3H, d, J=0.5 Hz), 1.92 (3H, s), 2.05 (2H, qd, J=7.5, 7.5 Hz), 5.73 (1H, br t, J=7.5 Hz); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ_C 3.9, 13.4, 17.0, 21.4, 81.5, 82.6, 117.3, 138.1.

4.1.13. 2-(1,3-Dimethylhexa-1,3-dienyl)benzo[1,2,3]dioxaborole (35).[26] Compound **35** was prepared according to a modified procedure of Paterson and Perkins.[26] In a dry Schlenk tube was placed alkyne **41** (500 mg, 4.63 mmol) and freshly distilled catecholborane (555 mg, 4.63 mmol). The mixture was heated at 90 °C for 4 h, then cooled to rt. The resulting yellow oil needed no further purification (1.06 g, >99%). ν_{max}/cm^{-1} (oil) 2965s, 1595s, 1474m, 1411s; ^1H NMR (500 MHz, $CDCl_3$): δ_H 1.04 (3H, t, J=7.5 Hz), 1.96 (3H, s), 2.10 (3H, s), 2.24 (2H, qd, J=7.5, 7.0 Hz), 5.70 (1H, t, J=7.0 Hz), 7.08–7.17 (3H, m), 7.24 (2H, m); ^{13}C NMR (125.7 MHz, $CDCl_3$): δ_C 13.7, 15.2, 16.2, 21.5, 95.7, 112.2, 122.3, 132.9, 137.4, 148.5, 149.6; HRMS [(CI)$^+$] calculated for $C_{14}H_{18}$ $^{11}BO_2$ [MH$^+$]: 229.1399, found 229.1389.

4.1.14. (±)-9,10-Deoxytridachione ((±)-2)[4] and ocellapyrone A ((±)-10).[8] In a dry Schlenk tube, vinyl-iodide **36** (207 mg, 0.57 mmol) and tetrakis(triphenylphospine) palladium(0) (33 mg, 5 mol %) were stirred for 10 min in the dark, at 20 °C in THF (2 mL). To the reaction mixture was then added borane **35** (154 mg, 0.67 mmol) in THF (1 mL) via cannula, and the reaction heated at 80 °C under argon. After 5 min, KOH aq (1.2 mL, 1M) was added. The reaction was stirred for 2 h at 80 °C, cooled to rt, and extracted with diethyl ether (3×50 mL). The combined organic layers were washed with brine (2×50 mL), dried over magnesium sulfate, then concentrated under reduced pressure to give a brown oil. The oil was quickly subjected to chromatography over florisil®, to remove the catalyst mixture, which gave crude tetraene **22** as the major product (130 mg, 66%). Compound **22** (for which the ^1H NMR displays four new alkenyl signals in the NMR spectra [δ_H ($CDCl_3$) 5.32–5.41 (br m), 5.85 (br s), 5.98 (br s), 6.42 (br s)] characteristic of a conjugated tetraene), was taken immediately in a sealed tube,

and heated in benzene (2 mL) at 120 °C under argon for 1 h in the dark. After evaporation of the solvent under reduced pressure, the brown oil obtained was purified by silica gel (preparative TLC; 90:10, 30–40 PE/EtOAc) to afford a mixture of compounds (60 mg), including the title compounds (±)-**2** and (±)-**10** (by ^{1}H NMR).[30] Following separation of the isomers by reverse phase C-18 HPLC [CH_3CN/H_2O, 6:4] both compounds ((±)-**2**, 31% and (±)-**10**, 15%) were fully characterised by NMR and mass spectrometry. All spectral data recorded were identical in all respects to the natural material for both compounds (±)-**2**[4] and (±)-**10**.[8]

For (±)-**2**: R_f 0.60 (3:1, 30–40 PE/EtOAc); ν_{max}/cm^{-1} (film) 2960s, 2929s, 2873m, 2859m, 1729s, 1662m, 1616m, 1599w, 1462m, 1404w, 1378w, 1274m, 1166w, 1123w, 1072m, 1040m, 984w; ^{1}H NMR (500 MHz, $CDCl_3$): δ_H 0.71 (3H, t, J=7.5 Hz), 1.33 (3H, s), 1.44 (3H, s), 1.73 (3H, s), 1.74–1.80 (2H, m), 1.79 (3H, d, J=1.5 Hz), 1.83 (3H, s), 2.06 (3H, s), 2.72 (1H, s), 3.99 (3H, s), 5.06 (1H, t, J=7.0 Hz), 5.59 (1H, s), 5.68 (1H, s); ^{13}C NMR (125.6 MHz, $CDCl_3$): δ_C 6.8, 12.2, 13.7, 14.1, 21.0, 21.5, 22.3, 26.8, 47.5, 55.3, 59.4, 98.6, 119.9, 122.3, 124.2, 127.7, 130.8, 132.0, 134.8, 161.0, 161.6, 181.1; HRMS [(ESI)$^+$] calculated for $C_{22}H_{31}O_3$ [MH$^+$]: 343.2268, found 343.2268.

For compound (±)-**10**: R_f 0.55 (3:1, 30–40 PE/EtOAc); ν_{max}/cm^{-1} (film) 2959m, 2929m, 2874w, 2857w, 1728w, 1661s, 1616s, 1459m, 1405m, 1375m, 1317m, 1290m, 1246m, 1168m, 1129w, 1036w; ^{1}H NMR (500 MHz, $CDCl_3$): δ_H 0.89 (3H, t, J=7.5 Hz), 1.15 (3H, s), 1.25 (3H, s), 1.55–1.61 (1H, m), 1.70–1.81 (1H, m), 1.74 (3H, d, J=1.5 Hz), 1.77 (3H, s), 1.88 (3H, s), 1.97 (3H, s), 2.41 (1H, dd, J=11.5, 3.0 Hz), 3.12 (1H, s), 4.01 (3H, s), 5.07 (1H, s), 5.62 (1H, s); ^{13}C NMR (125.6 MHz, $CDCl_3$): δ_C 7.2, 9.8, 13.3, 15.5, 18.9, 22.2, 23.5, 32.5, 38.1, 47.3, 49.2, 57.2, 57.3, 100.6, 116.7, 122.9, 125.4, 129.9, 130.2, 162.2, 164.9, 182.0; HRMS [(ES)$^+$] calculated for $C_{22}H_{31}O_3$ [(MH)$^+$]: 343.2268, found 343.2266.

Acknowledgements

We thank Lilly Research Center, Erl Wood Manor, Windlesham for their assistance in purification and characterisation of compounds (±)-**2** and (±)-**10**. We would also like to thank Dr. Sébastien Brückner, Dr. Tim Claridge and Dr. Babara Odell for helpful discussions. Thanks to the EPSRC for funding J.E.M.

References and notes

1. For an excellent review, see: Davies-Coleman, M. T.; Garson, M. J. *Nat. Prod. Rep.* **1998**, *5*, 477–492.
2. Cimino, G.; Ciavatta, M. L.; Fontana, A.; Gavagnin, M. *Bioactive Compounds from Natural Sources*; Tringali, C., Ed.; Taylor and Francis: London, 2001; Chapter 15, pp 577–637.
3. Vardaro, R. R.; Di Marzo, V.; Crispino, A.; Cimino, G. *Tetrahedron* **1991**, *47*, 5569–5576.
4. Ireland, C.; Faulkner, D. J. *Tetrahedron* **1981**, *37*, 233–240.
5. (a) Gavanin, M.; Mollo, E.; Cimino, G.; Ortea, J. *Tetrahedron Lett.* **1996**, *37*, 4259–4262; (b) Jeffery, D. W.; Perkins, M. V.; White, J. M. *Org. Lett.* **2005**, *7*, 1581–1584.
6. Ireland, C.; Scheuer, P. J. *Science* **1979**, *205*, 922–923.
7. Moses, J. E.; Adlington, R. M.; Rodriguez, R.; Eade, S. J.; Baldwin, J. E. *Chem. Commun.* **2005**, 1687–1689.
8. Manzo, E.; Ciavatta, M. L.; Gavagnin, M.; Mollo, E.; Wahidulla, S.; Cimino, G. *Tetrahedron Lett.* **2005**, *46*, 465–468.
9. Miller, A. K.; Trauner, D. *Angew. Chem., Int. Ed.* **2005**, *44*, 4602–4606.
10. Ireland, C.; Faulkner, D. J.; Solheim, B. A.; Clardy, J. *J. Am. Chem. Soc.* **1978**, *100*, 1002–1003.
11. Fu, X.; Hong, E. P.; Schmitz, F. J. *Tetrahedron* **2000**, *56*, 8989–8993.
12. Ksebati, M. B.; Schmitz, F. J. *J. Org. Chem.* **1985**, *50*, 5637–5642.
13. Cueto, M.; D'CroZ, L.; Maté, J. L.; San-Martín, A.; Darias, J. *Org. Lett.* **2005**, *7*, 415–418.
14. Kakinuma, K.; Hanson, C. A.; Rinehart, K. L., Jr. *Tetrahedron* **1976**, *32*, 217–222.
15. (a) Kurosawa, K.; Takahashi, K.; Tsuda, E. *J. Antibiot.* **2001**, *54*, 541–547; (b) Takahashi, K.; Tsuda, E.; Kurosawa, K. *J. Antibiot.* **2001**, *54*, 548–553.
16. Zuidema, D. R.; Miller, A. K.; Trauner, D.; Jones, P. B. *Org. Lett.* **2005**, *7*, 4959–4962.
17. (a) Brückner, S.; Baldwin, J. E.; Adlington, R. M.; Claridge, T. D. W.; Odell, B. *Tetrahedron* **2004**, *60*, 2785–2788; (b) Moses, J. E.; Baldwin, J. E.; Adlington, R. M.; Cowley, A. R.; Marquez, R. *Tetrahedron Lett.* **2003**, *44*, 6625–6627; (c) Brückner, S.; Baldwin, J. E.; Moses, J.; Adlington, R. M.; Cowley, A. R. *Tetrahedron Lett.* **2003**, *44*, 7471–7473; (d) Moses, J. E.; Baldwin, J. E.; Brückner, S.; Eade, S. J.; Adlington, R. M. *Org. Biomol. Chem.* **2003**, *1*, 3670–3684; (e) Moses, J. E.; Baldwin, J. E.; Marquez, R.; Adlington, R. M.; Claridge, T. D. W.; Odell, B. *Org. Lett.* **2003**, *5*, 661–663; (f) Moses, J. E.; Baldwin, J. E.; Marquez, R.; Adlington, R. M.; Cowley, A. R. *Org. Lett.* **2002**, *4*, 3731–3734.
18. For a recent review, see: Moses, J. E.; Adlington, R. M. *Chem. Commun.* **2005**, 5945–5952.
19. For recent examples, see: (a) Jacobsen, M. F.; Moses, J. E.; Adlington, R. M.; Baldwin, J. E. *Tetrahedron* **2006**, *62*, 1675–1689; (b) Rodriguez, R.; Moses, J. E.; Adlington, R. M.; Baldwin, J. E. *Org. Biomol. Chem.* **2005**, *3*, 3488–3495; (c) Jacobsen, M. F.; Moses, J. E.; Adlington, R. M.; Baldwin, J. E. *Org. Lett.* **2005**, *7*, 2473–2476; (d) Jacobsen, M. F.; Moses, J. E.; Adlington, R. M.; Baldwin, J. E. *Org. Lett.* **2005**, *7*, 641–644; (e) Tchabanenko, K.; Adlington, R. M.; Cowley, A. R.; Baldwin, J. E. *Org. Lett.* **2005**, *7*, 585–588; (f) Schwaebisch, D.; Tchabanenko, K.; Adlington, R. M.; Cowley, A. R.; Baldwin, J. E. *Chem. Commun.* **2004**, 2552–2553; (g) Rodriguez, R.; Adlington, R. M.; Moses, J. E.; Cowley, A.; Baldwin, J. E. *Org. Lett.* **2004**, *6*, 3617–3619; (h) Moses, J. E.; Commeiras, L.; Baldwin, J. E.; Adlington, R. M. *Org. Lett.* **2003**, *5*, 2987–2988; (i) Baldwin, J. E.; Claridge, T. W. D.; Culshaw, A. J.; Heupel, F. A.; Lee, V.; Spring, D. R.; Whitehead, R. C.; Boughtflower, R. J.; Mutton, I. M.; Upton, R. J. *Angew. Chem., Int. Ed.* **1998**, *37*, 2661–2663.
20. Di Marzo, V.; Vardaro, R. R.; Petrocellis, L. D.; Villani, G.; Minei, R.; Cimino, G. *Experientia* **1991**, *47*, 1221–1227.
21. Koester, G.; Hoffmann, R. W. *Liebigs Ann. Chem.* **1987**, 987–990.

22. Wadsworth, W. S., Jr.; Emmons, W. D. *J. Am. Chem. Soc.* **1961**, *83*, 1733–1738.
23. Hatakeyama, S.; Ochi, N.; Takano, S. *Chem. Pharm. Bull.* **1993**, *41*, 1358–1361.
24. Davis, F. A.; Stringer, O. D. *J. Org. Chem.* **1982**, *47*, 1774–1775.
25. Moses, J. E.; Baldwin, J. E.; Adlington, R. M. *Tetrahedron Lett.* **2004**, *45*, 6447–6448.
26. Paterson, I.; Perkins, M. V. *J. Am. Chem. Soc.* **1993**, *115*, 1608–1610.
27. (a) Reeder, M. R.; Meyers, A. I. *Tetrahedron Lett.* **1999**, *40*, 3115–3118; (b) Miyaura, N.; Satoh, Y.; Hara, S.; Suzuki, A. *Bull. Chem. Soc. Jpn.* **1986**, *59*, 2029–2031.
28. Hénaff, N.; Whiting, A. *Tetrahedron* **2000**, *56*, 5193–5204.
29. Miyaura, N.; Ishiyama, T.; Sasaki, H.; Ishikawa, M.; Satoh, M.; Suzuki, A. *J. Am. Chem. Soc.* **1989**, *111*, 314–321.
30. ^{1}H NMR of the product mixture before HPLC purification indicated that the ratio of compounds [(±)-**2**:(±)-**10**] was approximately [1:1].
31. Parker, K. A.; Lim, Y.-H. *J. Am. Chem. Soc.* **2004**, *126*, 15968–15969.
32. For an excellent review concerning biosynthetic and biomimetic electrocyclisation, see: Beaudry, C. M.; Malerich, J. P.; Trauner, D. *Chem. Rev.* **2005**, *105*, 4757–4778.
33. Eid, C. N., Jr.; Konopelski, J. P. *Tetrahedron* **1991**, *47*, 975–992.
34. Shen, R.; Lin, C. T.; Bowman, E. J.; Bowman, J. B.; Porco, J. A., Jr. *J. Am. Chem. Soc.* **2003**, *125*, 7889–7901.
35. Perrin, D. D.; Armarego, W. L. F. *Purification of Laboratory Chemicals*, 3rd ed.; Pergamon: Oxford, 1988.