Tetrahedron 65 (2009) 5767–5775

Contents lists available at ScienceDirect

Tetrahedron

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

A synthetic approach to C-nor-D-homosteroids based on a cascade of radical cyclisations from a vinylcyclopropane-substituted acyl radical precursor

Gerald Pattenden *, Davey A. Stoker, Johan M. Winne

School of Chemistry, The University of Nottingham, Nottingham, NG7 2RD, UK

ARTICLE INFO

Article history:
Received 23 February 2009
Received in revised form 17 April 2009
Accepted 7 May 2009
Available online 13 May 2009

ABSTRACT

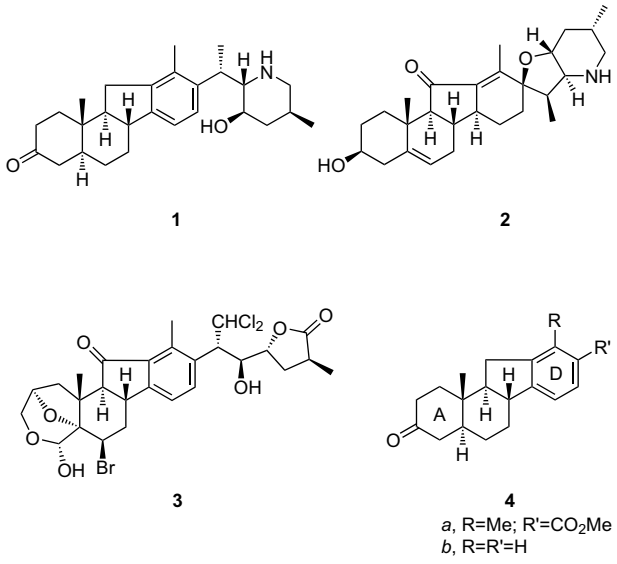
Treatment of the arylvinylcyclopropane-substituted seleno ester **5** with Bu_3SnH–AIBN, under high dilution in benzene at 80 °C, led to a 1:1 mixture of C10 methyl epimers of the C-nor-D-homosteroid ring system **24**/**25**. The homosteroid was formed from **5** via a cascade of sequential acyl 13-*endo trig* radical macrocyclisation, benzyl radical 5-*exo trig* transannulation and alkyl radical transannulation reactions (Scheme 1). The macrocyclic dienone **23** was also isolated as an intermediate in the radical cascade between **5** and **24**/**25**, and the dioxolanes **29** were interesting by-products. The cascade of radical cyclisations leading to the homosteroid **24**/**25** from the *acyl* radical precursor **5** is compared and contrasted with similar radical cascades from arylvinylcyclopropane-substituted *alkyl* radical precursors, i.e, **30**→**31** and **32b**→**38**.

1. Introduction

The C-nor-D-homosteroids comprise a small group of interesting and unusual steroids where the D-ring in the normal steroid nucleus has been expanded by one carbon, at the same time as the C-ring is contracted from a six- to a five-membered ring. Examples of these nor-homosteroids include veratramine **1** and jervine **2**, which are found in *Veratrum grandiflorum*[1] and *Veratrum californicum*,[2] respectively, and nakiterpiosin **3** isolated recently from the marine sponge *Terpios hashinota*.[3] Veratramine and jervine, together with related metabolites found in species of *Veratrum* are responsible for severe teratogenic effects, whilst other veratrum alkaloids have been used in medicine as hypotensive agents.[4] The biological profile of nakiterpiosin has not yet been determined, but the compound does display cytotoxicity against P388.

The total synthesis of veratramine **1** was first described some 40 years ago,[5,6] and recently Chen et al.[7] presented a total synthesis of nakiterpiosin **3**, at the same time revising the stereochemistry originally assigned to the natural product.[8] In this paper we describe a synthetic approach to the C-nor-D-homosteroid ring system in **1** and **3**, which uses a new cascade of radical cyclisations from a 1,2-disubstituted aromatic precursor as its basis.

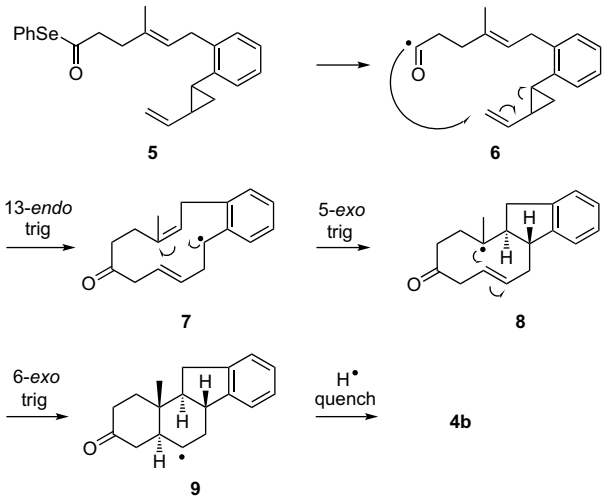
In the synthesis of veratramine **1** described by Johnson et al.,[5] the A, B and C rings of the tetracycle were elaborated in a linear, stepwise manner starting from a ring D precursor. This strategy led to the tetracyclic A-ring ketone **4a** as a key intermediate, which was then elaborated to the natural product. We conceived an approach to the tetracyclic compound **4** whereby the A, B and C rings were produced in a single step, using a cascade of radical cyclisations starting from an acyl radical intermediate.[9,10] The specific precursor we designed was compound **5**, which accommodated a γ,δ-



* Corresponding author. Tel.: +44 115 9513530; fax: +44 115 9513564.
E-mail address: gp@nottingham.ac.uk (G. Pattenden).

0040-4020/$ – see front matter © 2009 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2009.05.020

unsaturated seleno ester, as the source of the acyl radical **6**, and also a vinylcyclopropane unit designed to accept the aforementioned acyl radical as the first step in the radical cascade (Scheme 1). Thus, a 13-*endo trig* radical macrocyclisation within the acyl radical intermediate **6** would first lead to the benzylic radical intermediate **7**. Sequential 5-*exo trig* (to **8**) and 6-*exo trig* (**8** to **9**) transannular cyclisations in **7**, should then produce the tetracyclic core **4b** in veratramine in a single step event. To our knowledge acyl radical intermediates have not previously been studied in such cascade macrocyclisation–transannulation processes, and applications of vinylcyclopropanes as electrophores, i.e. radical acceptors, in carbon-to-carbon bond forming reactions are relatively sparse.

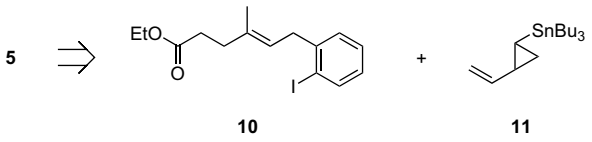


Scheme 1. Strategy for a cascade of radical cyclisations from the seleno ester **5** leading to the C-nor-D-homosteroid **4b**.

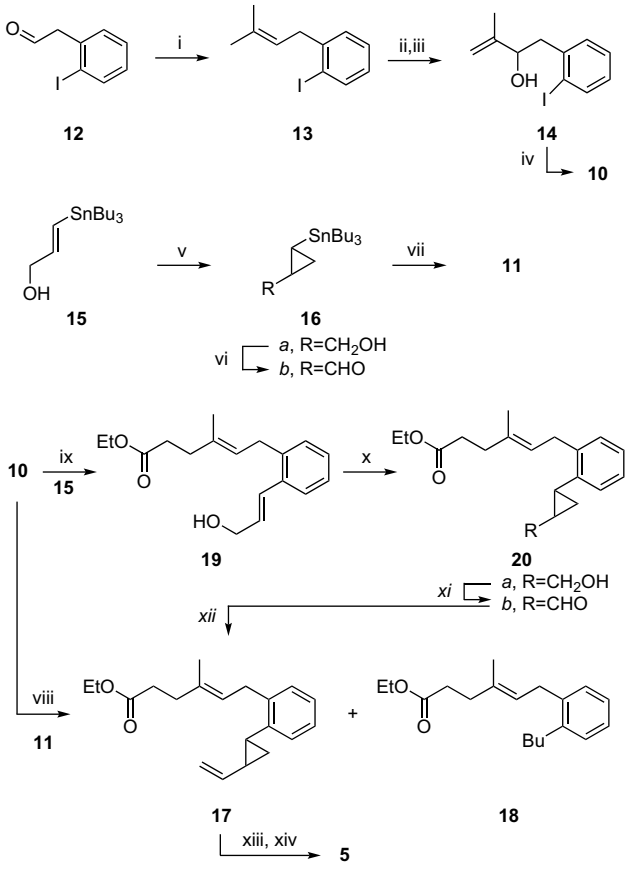
2. Results and discussion

2.1. Synthesis of the arylvinylcyclopropane-substituted seleno ester 5

The route we designed to synthesise the arylvinylcyclopropane-substituted seleno ester **5** was based on preparing the *ortho*-substituted iodobenzene **10**, followed by a Stille cross-coupling reaction[11,12] between **10** and the *E*-1,2-vinylcyclopropylstannane **11**, as the key step.



Thus, a Wittig reaction between the known phenylacetaldehyde **12**[13] and isopropyltriphenylphosphonium iodide, using *n*-BuLi as base, first gave the alkene **13** in 82% yield. Epoxidation of **13**, using *m*-CPBA, followed by rearrangement of the resulting epoxide[14] in the presence of $Al(O^iPr)_3$ next led to the allyl alcohol **14** (84%) (Scheme 2). Rearrangement of the *orthoester*[15] derived by treating **14** with triethyl orthoacetate and propionic acid at 100 °C then gave the *E*-γ-unsaturated ester **10** in 91% yield. The vinylcyclopropylstannane **11**, required for coupling to **10**, was synthesised from the known *E*-vinylstannane **15**,[16] following a Simmons–Smith cyclopropanation reaction, leading to **16a**, oxidation of **16a** to the aldehyde **16b**, and a Wittig reaction between **16b** and methylenetriphenylphosphoranylide (Scheme 2).



Scheme 2. Reagents and conditions: (i) isopropyltriphenylphosphonium iodide, BuLi, THF, 0 °C, 3 h, 82%; (ii) *m*-CPBA, DCM, 0 °C→rt, 24 h, 84%; (iii) $Al(O^iPr)_3$, tol, reflux, 12 h, 83%; (iv) propionic acid, triethyl orthoacetate, 100 °C, Dean–Stark, 4 days, 91%; (v) Et_2Zn, CH_2I_2, DCM, −50 °C→−20 °C, 48 h, 74%; (vi) IBX, DMSO, rt, 20 h, 96%; (vii) $MePPh_3Br$, NaHMDS, THF, −78 °C→rt, 12 h, 97%; (viii) $Pd(OAc)_2$, $AsPh_3$, CuI, CsF, LiCl, NMP, 80 °C, 48 h, 20%; (ix) (a) $PdCl_2(PPh_3)_2$, LiI, LiCl, DMF, 80 °C, 16 h, (b) iodine on silica, hν, benzene, rt, 12 h, 60%; (x) Et_2Zn, CH_2I_2, DCM, rt, 48 h, 82%; (xi) IBX, DMSO, rt, 12 h, 70%; (xii) $MePPh_3Br$, NaHMDS, THF, −78 °C→rt, 12 h, 93%; (xiii) LiOH, H_2O, rt, 24 h, 96%; (xiv) *N*-(phenylselenyl)phthalimide, PBu_3, rt, 24 h, 55%.

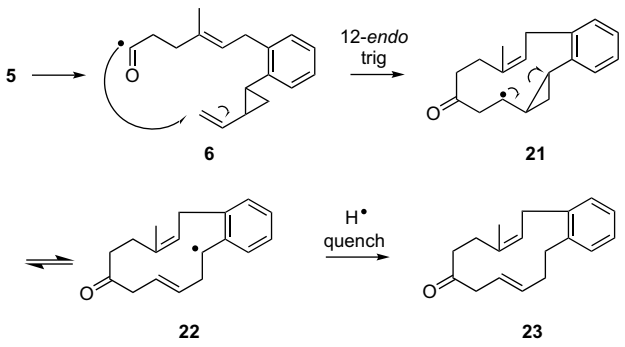
A Stille cross-coupling reaction between the iodobenzene **10** and the vinylcyclopropylstannane **11**,[17] using $Pd(OAc)_2$–$AsPh_3$ in the presence of CuI, CsF, NMP and LiCl at 80 °C led to the anticipated arylvinylcyclopropane **17** in 20% yield, but the product **18** resulting from a competitive aryl–butyl cross-coupling reaction was obtained concurrently (up to 41%). The competitive migration of an alkyl (sp^3) group in Stille reactions involving vinyl and aryl (sp^2) trialkylstannanes is very rare indeed, which is why, of course, Stille cross-coupling reactions involving sp^2 centres are so revered in synthesis. We suggest that the incidence of competitive migration of the butyl group in the stannane **11**, is associated with the 'pseudo' sp^2/sp^3 character of the carbon centres in the cyclopropane ring in **11**, and also possibly due to steric impedance between the stannane **11** and the *ortho*-substituted side-chain in the iodobenzene **10**.[18] Whatever the reason, it was frustrating to find that we were not able to separate the co-product **18** from the required arylvinylcyclopropane **17** by chromatography, on a scale sufficient to justify continuing with this particular route to the target compound **5**.

We therefore modified our approach to the vinylcyclopropane intermediate **17**, and instead first coupled the iodobenzene **10** to the *E*-vinylstannane **15**, which led to the aryl-substituted propenol **19** in 60% yield (Scheme 2). A Simmons–Smith reaction between **19** and diiodomethane in the presence of Et_2Zn next gave the *trans*-cyclopropylmethanol **20a**, which, in two straightforward steps was

then converted into the same arylvinylcyclopropane **17** to that prepared earlier from **10** and **11**. Finally, saponification of the ethyl ester group in **17**, followed by treatment of the resulting carboxylic acid with *N*-(phenylseleno)phthalimide and PBu_3 gave the phenylseleno ester **5**.

2.2. Cascade radical cyclisations leading to the C-nor-D-homosteroid 24/25

When a solution of the seleno ester **5** in benzene at 80 °C was treated with Bu_3SnH and catalytic AIBN over 8 h under high dilution, work up and chromatography resulted in the isolation of two major products, each in ca. 25% yield. The structure of one of these products, i.e. the macrocyclic dienone **23**, followed conclusively from examination of its proton and carbon NMR spectroscopic data, alongside a 2D NMR analysis. A COSY correlation analysis established pertinent proton coupling data in the macrocycle and, most importantly, confirmed that both of the alkene bonds in **23** had the *E*-configuration. The formation of the macrocyclic dienone **23** from the seleno ester **5** is the result of a 13-*endo trig* cyclisation of the acyl radical intermediate **6** into the alkene bond of the vinylcyclopropane unit in **5** producing **21**, followed by a cyclopropylmethyl-to-butenyl radical rearrangement, leading to the benzylic radical **22**, which then becomes quenched by an H• source (Scheme 3).



Scheme 3. Formation of the macrocyclic dienone **23** from the acyl radical intermediate **6**.

The second major product isolated from treatment of the seleno ester **5** with Bu_3SnH–AIBN was obtained as a crystalline solid, and preliminary analysis of its NMR spectroscopic and other data indicated that it was a 1:1 mixture of isomeric tetracyclic ketones of similar constitution to the expected C-nor-D-homosterane **4b**. Separation of the isomeric tetracycles by HPLC allowed their structures and stereochemistries to be analysed in detail by NMR spectroscopy. The ^{13}C NMR spectrum of one of the isomers showed the expected 18 carbon atoms, i.e., 6 aromatic, 11 aliphatic and 1 carbonyl resonance. A DEPT analysis then established the presence of four aromatic and three aliphatic CH signals, six CH_2 and one CH_3 signal, together with one aliphatic and two aromatic quaternary carbon centres, in the structure. The ^1H NMR spectrum was complex, showing a multiplet in the aromatic proton region, and several overlapping proton resonances between δ 1.3 and 1.9 ppm, including a double doublet (*J* 7 and 2 Hz). However, all of the proton resonances could be correlated with their carbon centres, and the carbon connectivity was established by carrying out HMQC and COSY experiments. Pertinent proton-to-proton coupling data determined between several vicinal hydrogen atoms in the ^1H NMR spectrum are collected in Figure 1, and these data allowed us to assign a *cis*, *syn*, *anti* stereochemistry **24** to this isomer of the tetracyclic ketone. Significantly, the coupling of 12 Hz between the vicinal hydrogen atoms at C8 and C9 in **24** is

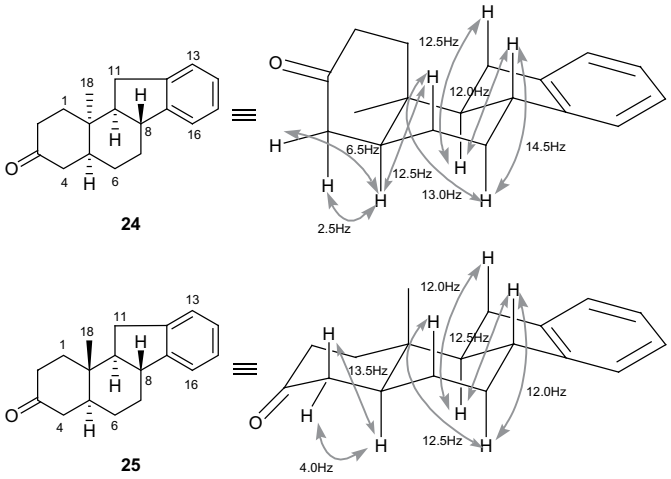
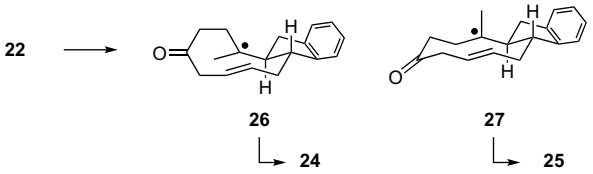


Figure 1. Pertinent vicinal proton coupling data in the ^1H NMR spectra of the isomeric tetracyclic ketones **24** and **25**.

compatible with a trans B/C ring fusion. Furthermore, the absence of diaxial vicinal coupling between the hydrogen atoms at C4 and C5, i.e. observed (*J* 6.5 and 2.5 Hz), demonstrated that the A/B ring junction cannot be trans-fused, and must therefore be cis-fused. Comparisons between the observed *J*-values shown in Figure 1, and those calculated for all possible configurations and conformations added additional support to the *cis*, *syn*, *trans* stereochemical assignment **24** to this isomer.

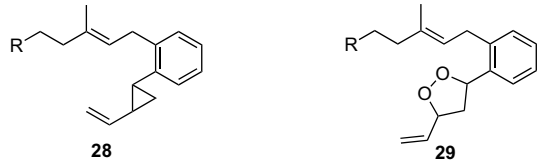
A similar analysis of the proton-to-proton coupling data between relevant vicinal hydrogen atoms in the ^1H NMR spectrum of the second isomeric tetracyclic ketone produced during the radical cascade from **5**, established that this compound had the alternative *trans*, *anti*, *trans* stereochemistry **25** (Fig. 1, with pertinent vicinal coupling data). Thus, the coupling of 12.5 Hz between the vicinal hydrogens at C8 and C9, established that the B/C ring junction is trans-fused. However, unlike the isomeric ketone **24**, the trans diaxial coupling of 13.5 Hz between the hydrogen atoms at C4 and C5 in this second isomer demonstrated that its A/B ring junction must also be trans-fused.

The isomeric tetracyclic ketones **24** and **25** are related as methyl group epimers at C10.[19] They are produced from the macrocyclic (benzylic) radical intermediate **22** as a result of a 5-*exo trig* transannulation reaction, which leads to the trans ring-fused radical intermediate **8** (cf. Scheme 1). Presumably, the methyl substituted sp^3 carbon radical centre embedded in the ten-membered ring in **8** has no stereochemical integrity, yet has sufficient conformational flexibility to present itself to the transannular double bond in the two extreme conformations **26** and **27**, which lead to the C10 methyl epimers of the tetracyclic ketone by 6-*exo trig* transannular cyclisation.



Minor products that were isolated and characterised from treatment of the seleno ester **5** with Bu_3SnH–AIBN were the compounds resulting from quenching and decarbonylation of the first-formed acyl radical species, i.e. **28a** and **28b**, together with the interesting dioxolanes **29a** and **29b**, resulting from additions of

oxygen across the cyclopropane rings of the vinylcyclopropane units in **28b** and **5**, respectively.[20]

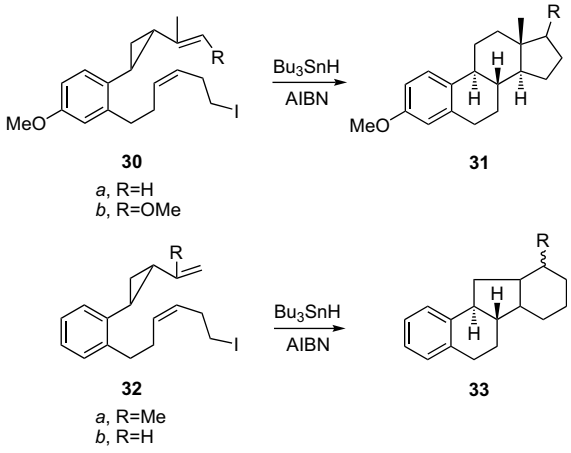


28
a, R=CHO
b, R=H

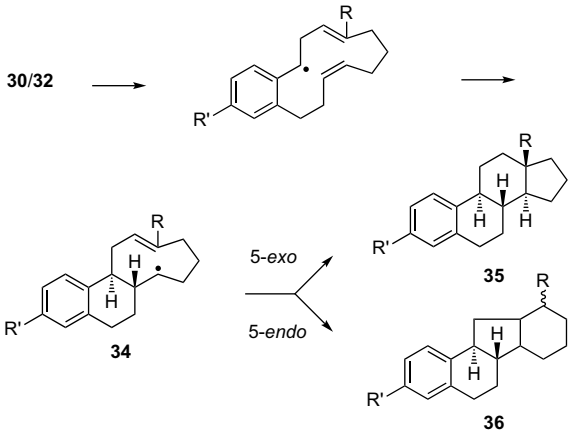
29
a, R=H
b, R=COSePh

2.3. Comparisons with related cascades leading to oestranes

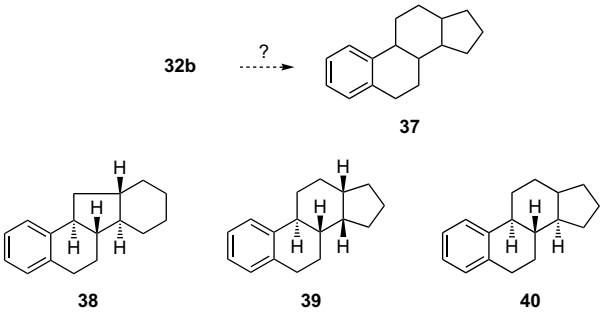
The cascade of cyclisations from the acyl radical **6** leading to the tetracycle **24**/**25** complements some of our earlier studies with the structurally related substituted vinylcyclopropanes **30** where the multiple cyclisations were triggered from *alkyl*, rather than acyl radical species.[21] The substituted vinylcyclopropanes **30** also differ from the seleno ester substrate **5** used in the present study by having two methylene groups separating the *Z*-disubstituted double bond from the aryl ring, and one less methylene group between the same double bond and the terminal CH_2I group. The substituted alkyl iodides **30a** and **30b** both underwent cascades of radical cyclisations in the presence of Bu_3SnH–AIBN, leading to the 'normal' oestrane steroid ring system products **31a** and **31b**, respectively. By contrast, when the analogous substituted iodovinylcyclopropane **32a** was treated with Bu_3SnH–AIBN, it underwent a sequence of radical cyclisations leading to the C-nor-D-homosteroid **33a** at the expense of the normal oestrane steroid by-product. The differing outcomes in the radical cascades from the iodovinylcyclopropanes **30** and **32** occur at the terminating, transannular cyclisation, event, by competing 5-*exo*/6-*endo* ring closures, viz. **34** to **35**/**36** (Scheme 4).



In a very early study of the scope for iodovinylcyclopropanes in the synthesis of oestranes by cascades of radical reactions,[22] we tentatively assigned the 'normal' steroid structure **37** with no defined stereochemistry to the polycycle resulting from treatment of **32b** with Bu_3SnH–AIBN. Over the ensuing years, and with results from other, related studies this outcome became less credulous. We therefore sought to put our minds at rest, and repeat this particular radical cascade and analyse the structures of the product in more detail. Thus, when a newly prepared sample of the iodovinylcyclopropane **32b** was treated with Bu_3SnH–AIBN, one major and two minor tetracyclic products were produced, which could be separated by reverse phase HPLC. Detailed analysis (see Supplementary data) of their NMR spectroscopic data now revealed that the major product was the C-nor-D-homo steroid **38** with the *trans, anti, trans* stereochemistry, and that the corresponding isomers **39** and **40** of the 'normal' steroid were actually minor products of the radical cascade.



Scheme 4. Dichotomous radical transannulations leading to oestranes **35** and C-nor-D-homosteroids **36**.



3. Conclusion

We have developed a new approach to C-nor-D-homosteroids, whereby the A, B and C rings are produced in a single step, using a cascade of radical cyclisations starting from an acyl radical intermediate. To our knowledge acyl radical intermediates have not previously been applied in such cascade macrocyclisation–transannulation sequences, particularly where unusual vinylcyclopropanes are used as electrophores. The outcome of the investigation has been compared and contrasted with similar, earlier, studies involving alkyl, rather than acyl, radical cascade cyclisations many of which lead to oestranes, e.g., oestrone. The research emphasises the subtle effects that substitution on the vinylcyclopropane electrophores, and the positioning of the reacting alkene bonds in the starting materials, play in determining the competition between the modes of transannular cyclisations, particularly in the final steps, in these radical cascades.

4. Experimental

4.1. General

For general details see Ref. 23. Preparative HPLC was performed on a *Polaris* 5 C18-A 10 mm×250 mm column using a *Varian Prostar 210* binary solvent delivery system and a *Varian Prostar 325* UV detector.

4.2. 1-Iodo-2-(3-methylbut-2-enyl)benzene 13

Tetrahydrofuran (2 ml) was added to a flask containing dried (high vacuum at 80 °C for 1 h) isopropyltriphenylphosphonium iodide (0.35 g, 0.8 mmol) at room temperature, under an argon atmosphere. *n*-Butyllithium (2.5 M, 0.28 ml, 0.7 mmol) was added dropwise over 5 min, to the stirred solution at 0 °C, and the mixture

was then stirred at 0 °C for 30 min. A solution of 2-(2-iodophenyl)-acetaldehyde **12**[13] (0.10 g, 0.4 mmol) in tetrahydrofuran (2 ml) was added dropwise over 5 min, at 0 °C and the mixture was stirred at 0 °C for a 3 h and then diethyl ether (5 ml) and water (5 ml) were added. The separated aqueous phase was extracted with diethyl ether (5×5 ml) and the combined organic extracts were then washed with brine (10 ml), dried and concentrated in vacuo. The residue was purified by flash column chromatography (100% petrol) on silica gel, to give the *olefin* **13** (0.10 g, 82%) as a colourless oil. ν_{max} (sol $CHCl_3$)/cm^{-1}, 2916 (s), 1562 (m); δ_H (400 MHz, $CDCl_3$), 1.76 (3H, s, C=C*Me*Me), 1.77 (3H, d, *J* 1.0 Hz, C=CMe*Me*), 3.42 (2H, d, *J* 7.0 Hz, ArCH_2), 5.27 (1H, tq, *J* 7.0 and 1.0 Hz, Me_2C=C*H*), 6.88 (1H, ddd, *J* 8.0, 7.5 and 2.0 Hz, Ar*H*), 7.20 (1H, dd, *J* 7.5 and 2.0 Hz, Ar*H*), 7.27 (1H, ddd, *J* 8.0, 7.5 and 1.0 Hz, Ar*H*), 7.82 (1H, dd, *J* 7.5 and 1.0 Hz, Ar*H*); δ_C (100 MHz, $CDCl_3$), 18.2 (q), 25.8 (q), 39.7 (t), 100.8 (s), 121.7 (d), 127.6 (d), 128.3 (d), 129.3 (d), 133.6 (s), 139.4 (d), 144.3 (s); *m*/*z* (EI) 272.0069 ($C_{11}H_{13}^{127}I$ requires 272.0062).

4.3. (±)-1-(2-Iodophenyl)-3-methylbut-3-en-2-ol 14

A solution of 3-chloroperbenzoic acid (75% in H_2O, 100 mg, 0.4 mmol) in dichloromethane (2 ml) was added dropwise over 5 min, to a stirred solution of the olefin **13** (100 mg, 0.4 mmol) in dichloromethane (2 ml) at 0 °C, under a nitrogen atmosphere. The mixture was stirred at room temperature for 24 h and then saturated sodium hydrogen carbonate (5 ml) was added. The separated aqueous phase was extracted with dichloromethane (3×5 ml) and the combined organic extracts were then washed with brine (10 ml), dried over sodium sulfate and concentrated in vacuo. The residue was purified by flash column chromatography (100% petrol) on silica gel, to give the corresponding epoxide (89 mg, 84%) as a colourless oil. ν_{max} (sol $CHCl_3$)/cm^{-1}, 2965 (s); δ_H (400 MHz, $CDCl_3$), 1.36 (3H, s, C=C*Me*Me), 1.42 (3H, s, C=CMe*Me*), 2.92–3.05 (3H, m, ArCH_2C*H*), 6.94 (1H, ddd, *J* 8.0, 7.0 and 2.0 Hz, Ar*H*), 7.28–7.34 (2H, m, 2×Ar*H*), 7.85 (1H, dd, *J* 8.0 and 1.0 Hz, Ar*H*); δ_C (100 MHz, $CDCl_3$), 19.1 (q), 24.8 (q), 40.0 (t), 58.7 (s), 63.4 (d), 100.8 (s), 128.3, 128.5 (2×d), 129.6 (d), 139.5 (d), 141.4 (s); *m*/*z* (ES) 310.9891 ($M+Na^+$, $C_{11}H_{13}O^{127}INa$ requires 310.9909).

Aluminium triisopropoxide (75 mg, 0.4 mmol) was added in one portion, to a stirred solution of the epoxide (100 mg, 0.3 mmol) in toluene (2 ml) at room temperature, under a nitrogen atmosphere. The mixture was heated to reflux for 12 h, and then cooled to room temperature and diethyl ether (5 ml) was added. The mixture was poured onto hydrochloric acid (2 M, 5 ml) and the separated aqueous phase was then extracted with diethyl ether (3×5 ml). The combined organic extracts were washed with saturated sodium hydrogen carbonate (10 ml), then dried over sodium sulfate and concentrated in vacuo. The residue was purified by flash column chromatography (5% EtOAc, 95% petrol) on silica gel, to give the *allylic alcohol* **14** (83 mg, 83%) as a colourless oil. ν_{max} (sol $CHCl_3$)/cm^{-1}, 3604 (s), 3468 (br w), 2958 (s), 1651 (m); δ_H (400 MHz, $CDCl_3$), 1.57 (1H, d, *J* 9.0 Hz, O*H*), 1.86 (3H, s, C=C*Me*), 2.84 (1H, dd, *J* 14.0 and 9.0 Hz, ArC*H*H), 3.06 (1H, dd, *J* 14.0 and 4.0 Hz, ArCH*H*), 4.36 (1H, app br d, *J* 9.0 Hz, HOC*H*), 4.88 (1H, app t, *J* 1.5 Hz, C=C*H*H), 5.03 (1H, app t, *J* 1.5 Hz, C=CH*H*), 6.92 (1H, ddd, *J* 8.0, 7.0 and 2.0 Hz, Ar*H*), 7.22–7.32 (2H, m, 2×Ar*H*), 7.84 (1H, dd, *J* 8.0 and 1.0 Hz, Ar*H*); δ_C (100 MHz, $CDCl_3$), 18.3 (q), 46.7 (t), 74.8 (d), 101.0 (s), 111.2 (t), 128.2, 128.4 (2×d), 131.1 (d), 139.7 (d), 141.2 (s), 146.9 (s); *m*/*z* (ES) 310.9892 ($M+Na^+$, $C_{11}H_{13}O^{127}INa$ requires 310.9909).

4.4. (*E*)-Ethyl 6-(2-iodophenyl)-4-methylhex-4-enoate 10

Propionic acid (0.1 ml, 1.3 mmol) was added dropwise over 2 min, to a stirred solution of the alcohol **14** (2.6 g, 9.0 mmol) in triethyl orthoacetate (35 ml, 185.0 mmol) at room temperature under a nitrogen atmosphere. The solution was heated to 100 °C under Dean–Stark conditions for 4 days, then cooled to room temperature and concentrated in vacuo. Diethyl ether (20 ml) and water (20 ml) were added, and the separated aqueous phase was then extracted with diethyl ether (3×20 ml). The combined organic extracts were washed with saturated sodium hydrogen carbonate solution (20 ml), then dried and concentrated in vacuo. The residue was purified by flash column chromatography (2% EtOAc, 98% petrol) on silica gel, to give the *unsaturated ester* **10** (2.9 g, 91%) as a colourless oil. ν_{max} (sol $CHCl_3$)/cm^{-1}, 2984 (m), 1727 (s), 1562 (m); δ_H (400 MHz, $CDCl_3$), 1.23 (3H, t, *J* 7.0 Hz, OCH_2CH_3), 1.74 (3H, app s, C=CCH_3), 2.34–2.41 (2H, m, O=CCH_2CH_2), 2.42–2.48 (2H, m, O=CCH_2CH_2), 3.41 (2H, d, *J* 7.0 Hz, ArCH_2), 4.10 (2H, q, *J* 7.0 Hz, OCH_2CH_3), 5.30 (1H, tq, *J* 7.0 and 1.0 Hz, C=C*H*), 6.88 (1H, ddd, *J* 8.0, 7.5 and 2.0 Hz, Ar*H*), 7.16 (1H, dd, *J* 7.5 and 2.0 Hz, Ar*H*), 7.26 (1H, ddd, *J* 8.0, 7.5 and 1.5 Hz, Ar*H*), 7.81 (1H, dd, *J* 7.5 and 1.5 Hz, Ar*H*); δ_C (100 MHz, $CDCl_3$), 14.2 (q), 16.4 (q), 33.1 (t), 34.6 (t), 39.5 (t), 60.3 (t), 100.7 (s), 122.4 (d), 127.7 (d), 128.3 (d), 129.1 (d), 135.5 (s), 138.3 (d), 143.8 (s), 173.3 (s); *m*/*z* (ES) 359.0499 ($M+H^+$, $C_{15}H_{20}O_2^{127}I$ requires 359.0508).

4.5. [2*E*-(Tributylstannyl)cyclopropyl]methanol 16a

Diethylzinc (1.1 M in Tol, 32 ml, 35 mmol) was added dropwise over 10 min, to a stirred solution of (*E*)-3-(tributylstannyl)prop-2-en-1-ol **15** (6.09 g, 18 mmol)[16] and diiodomethane (4.2 ml, 52 mmol) in dichloromethane (250 ml) at −50 °C, under a nitrogen atmosphere. The solution was warmed slowly to −20 °C over 2 h and stirred at this temperature for a further 48 h, before triethylamine (20 ml) was added. After warming to room temperature, water (100 ml) was added and the separated aqueous phase was then extracted with dichloromethane (3×100 ml). The combined organic extracts were washed with brine (20 ml), dried over sodium sulfate and concentrated in vacuo. The residue was purified by flash column chromatography (10% EtOAc, 90% petrol) on silica gel, to give the *cyclopropane* **16a** (4.66 g, 74%) as a colourless oil. ν_{max} (sol $CHCl_3$)/cm^{-1}, 3611 (br m), 3029 (m); δ_H (400 MHz, $CDCl_3$), 0.29–0.36 (1H, m, SnC*H*), 0.50–0.55 (2H, m, CHCH_2CH), 0.81 (6H, t, *J* 8.0 Hz, SnCH_2), 0.89 (9H, t, *J* 7.5 Hz, CH_2CH_3), 1.02–1.14 (1H, m, $HOCH_2CH$), 1.24–1.36 (6H, m, CH_3CH_2), 1.41–1.56 (6H, m, $SnCH_2CH_2$), 3.39 (1H, dd, *J* 10 and 7.5 Hz, C*H*HOH), 3.55 (1H, dd, *J* 10 and 6.5 Hz, CH*H*OH0); δ_C (100 MHz, $CDCl_3$), −2.6 (d), 7.4 (t), 8.7 (t), 13.7 (q), 18.1 (d), 27.3 (t), 29.1 (t), 69.6 (t); *m*/*z* (ES) 385.1539 ($M+Na^+$, $C_{16}H_{34}O^{120}SnNa$ requires 385.1529). These data agree with those published previously for the chiral material.[24]

4.6. 2*E*-(Tributylstannyl)cyclopropanecarbaldehyde 16b

2-Iodoxybenzoic acid (5.0 g, 17.9 mmol) was added portionwise, to a stirred solution of the alcohol **16a** (4.0 g, 11.1 mmol) in dimethylsulfoxide (80 ml) at room temperature, under a nitrogen atmosphere. The solution was stirred at room temperature for 20 h, then water (40 ml) was added and the resulting precipitate was filtered through Celite with diethyl ether (50 ml). The separated aqueous phase was extracted with diethyl ether (3×20 ml) and the combined organic extracts were washed with brine (10 ml), dried over sodium sulfate and concentrated in vacuo. The residue was purified by flash column chromatography (20% Et_2O, 80% petrol) on silica gel, to give the *aldehyde* **16b** (3.8 g, 96%) as a colourless oil. ν_{max} (sol $CHCl_3$)/cm^{-1}, 3029 (s), 1696 (s); δ_H (400 MHz, $CDCl_3$), 0.58 (1H, ddd, *J* 11.0, 8.5 and 5.5 Hz, SnC*H*), 0.88 (6H, t, *J* 8.5 Hz, SnCH_2), 0.89 (9H, t, *J* 7.0 Hz, CH_2CH_3), 1.04 (1H, ddd, *J* 8.5, 7.0 and 4.5 Hz, CHC*H*HCH), 1.24–1.37 (7H, m, CHCH*H*CH+CH_3CH_2), 1.43–1.54 (6H, m, $SnCH_2CH_2$), 1.68–1.76 (1H, m, O=CHC*H*), 8.52 (1H, d, *J* 6.5 Hz, O=C*H*); δ_C (100 MHz, $CDCl_3$), 1.7 (d), 9.0 (t), 11.2 (t), 13.7 (q), 26.9 (d), 27.3 (t), 28.9 (t), 201.6 (d); *m*/*z* (ES) 383.1359 ($M+Na^+$, $C_{16}H_{32}O^{120}SnNa$ requires 383.1373).

4.7. Tributyl(2-vinyl-*E*-cyclopropyl)stannane 11

Tetrahydrofuran (60 ml) was added to freshly dried (100 °C, 1 mmHg, 5 h) methyltriphenylphosphonium bromide (7.0 g, 19.6 mmol) at room temperature. Sodium hexamethyldisilazane (2.0 M in THF, 6.0 ml, 12.0 mmol) was added dropwise over 10 min, to the stirred solution at −78 °C, under a nitrogen atmosphere. The yellow solution was stirred at −78 °C for 30 min and then a solution of the aldehyde **16b** (3.4 g, 9.5 mmol) in tetrahydrofuran (30 ml) was added dropwise over 5 min. The mixture was stirred at −78 °C for 2 h and then allowed to warm to room temperature over 12 h. Saturated aqueous ammonium chloride solution (10 ml) was added, and the separated aqueous phase was then extracted with diethyl ether (3×20 ml). The combined organic extracts were dried over sodium sulfate and concentrated in vacuo. The residue was purified by flash column chromatography (100% petrol) on silica gel, to give the *alkene* **11** (3.3 g, 97%) as a colourless oil. ν_{max} (sol $CHCl_3$)/cm^{-1}, 3083 (w), 1631 (m); δ_H (400 MHz, $CDCl_3$), 0.11 (1H, ddd, *J* 10.5, 8.5 and 5.5 Hz, SnC*H*), 0.70–0.76 (2H, m, CHCH_2CH), 0.81 (6H, t, *J* 8.0 Hz, SnCH_2), 0.89 (9H, t, *J* 7.5 Hz, CH_2CH_3), 1.25–1.36 (6H, m, CH_3CH_2), 1.36–1.44 (1H, m, H_2C=CHC*H*), 1.44–1.56 (6H, m, $SnCH_2CH_2$), 4.80 (1H, dd, *J* 10.0 and 1.5 Hz, CH=C*H*H), 5.05 (1H, dd, *J* 17.0 and 1.5 Hz, CH=CH*H*), 5.29 (1H, ddd, *J* 17.0, 10.0 and 9.0 Hz, C*H*=CH_2); δ_C (100 MHz, $CDCl_3$), 2.6 (d), 8.7 (t), 11.5 (t), 13.7 (q), 19.4 (d), 27.3 (t), 29.1 (t), 110.5 (t), 144.6 (d); *m*/*z* (EI) 301.0986 (M−Bu, $C_{13}H_{25}^{120}Sn$ requires 301.0978).

4.8. (4*E*)-Ethyl-6-(2-((*E*)-3-hydroxyprop-1-enyl)phenyl)-4-methylhex-4-enoate 19

A solution of the aryl iodide **10** (2.50 g, 7.0 mmol) and (*E*)-3-(tributylstannyl)prop-2-en-1-ol[16] (2.60 g, 7.5 mmol) in *N*-dimethylformamide (20 ml) was added dropwise over 1 min, to flame-dried lithium chloride (0.58 g, 13.5 mmol) and lithium iodide (1.80 g, 13.0 mmol) in a Schlenk flask at room temperature, under an argon atmosphere. The mixture was degassed and bis-triphenylphosphinepalladium dichloride (0.24 g, 0.3 mmol) was added in one portion, and the mixture was then degassed again. The mixture was heated to 80 °C for 16 h, and then cooled to room temperature and poured onto water (50 ml) and ethyl acetate (50 ml). The separated aqueous phase was extracted with ethyl acetate (3×100 ml) and the combined organic extracts were then washed with water (3×20 ml), hydrochloric acid (2 M, 10 ml) and brine (50 ml), dried over sodium sulfate and concentrated in vacuo to leave a residue, which consisted of a 6:1 mixture of *Z*/*E* isomers of the allylic alcohol. Data for major *Z*-isomer: δ_H (400 MHz, $CDCl_3$), 1.20 (3H, t, *J* 7.0 Hz, OCH_2CH_3), 1.73 (3H, app s, C=CCH_3), 2.37 (2H, t, *J* 7.0 Hz, O=CCH_2CH_2), 2.43 (2H, t, *J* 7.0 Hz, O=CCH_2CH_2), 3.36 (2H, d, *J* 7.5 Hz, ArCH_2), 4.09 (2H, q, *J* 7.0 Hz, OCH_2CH_3), 4.27 (2H, dd, *J* 6.5 and 1.5 Hz, HOCH_2), 5.39 (1H, tq, *J* 7.5 and 1.0 Hz, C=C*H*), 5.94 (1H, dt, *J* 11.5 and 6.5 Hz, ArCH=C*H*), 6.65 (1H, dt, *J* 11.5 and 1.5 Hz, ArC*H*=CH), 7.07 (1H, dd, *J* 6.0 and 2.0 Hz, Ar*H*), 7.12–7.20 (2H, m, 2×Ar*H*), 7.46 (1H, dd, *J* 6.5 and 1.5 Hz, Ar*H*).

The mixture of *Z*- and *E*-isomers was dissolved in benzene (50 ml), and approximately 10 grains of iodine on silica (iodine adsorbed onto chromatographic silica with dichloromethane) were added. The mixture was left in direct sunlight for 12 h, then saturated sodium thiosulphate (50 ml) was added and the organic phase was separated and concentrated in vacuo. The residue was purified by flash column chromatography (40% Et_2O, 60% petrol) on silica gel, to give the *E*-allyl alcohol **19** (1.25 g, 60%) as a colourless oil. ν_{max} (sol $CHCl_3$)/cm^{-1}, 3611 (w), 3502 (br w), 3011 (m), 1725 (s), 1601 (w); δ_H (400 MHz, $CDCl_3$), 1.15 (3H, t, *J* 7.0 Hz, OCH_2CH_3), 1.76 (3H, app s, C=C*Me*), 2.34 (2H, t, *J* 7.0 Hz, O=CCH_2CH_2), 2.43 (2H, t, *J* 7.0 Hz, O=CCH_2CH_2), 3.38 (2H, d, *J* 7.0 Hz, ArCH_2), 4.04 (2H, q, *J* 7.0 Hz, OCH_2CH_3), 4.32 (2H, dd, *J* 5.5 and 1.0 Hz, HOCH_2), 5.24 (1H, tq, *J* 7.0 and 1.0 Hz, C=C*H*), 6.25 (1H, dt, *J* 15.5 and 5.5 Hz, ArCH=C*H*), 6.79 (1H, dt, *J* 15.5 and 1.0 Hz, ArC*H*=CH), 7.13 (1H, dd, *J* 6.0 and 2.0 Hz, Ar*H*), 7.15–7.20 (2H, m, 2×Ar*H*), 7.46 (1H, dd, *J* 6.5 and 1.5 Hz, Ar*H*); δ_C (100 MHz, $CDCl_3$), 14.1 (q), 16.2 (q), 32.3 (t), 33.0 (t), 34.5 (t), 60.4 (t), 63.9 (t), 123.9 (d), 125.9 (d), 126.3 (d), 127.7 (d), 128.5 (d), 129.3 (d), 130.1 (d), 133.9, 135.6 (2×s), 138.7 (s), 173.4 (s); *m*/*z* (ES) 311.1619 (M+Na^+, $C_{18}H_{24}O_3Na$ requires 311.1618).

4.9. (*E*)-Ethyl-6-(2-(2-(hydroxymethyl)cyclopropyl)phenyl)-4-methylhex-4-enoate 20a

Diethylzinc (1.0 M in hexanes, 520 μl, 0.5 mmol) was added dropwise over 20 min, to a stirred solution of the olefin **19** (100 mg, 0.3 mmol) and diiodomethane (84 μl, 1.0 mmol) in dichloromethane (10 ml) at room temperature, under an argon atmosphere. The mixture was stirred at room temperature for 4 h and then more diethylzinc (1.0 M in hexanes, 520 μl, 0.5 mmol) and diiodomethane (84 μl, 1.0 mmol) were added dropwise, over 20 min. The mixture was stirred at room temperature for 14 h and then ethyl acetate (50 ml) and water (50 ml) were added. The separated aqueous phase was extracted with ethyl acetate (3×20 ml), and the combined organic extracts were then washed with brine (10 ml), dried over sodium sulfate and concentrated in vacuo. The residue was purified by flash column chromatography (30% Et_2O, 70% petrol) on silica gel, to give the *cyclopropane* **20a** (86 mg, 82%) as a colourless oil. ν_{max} (sol $CHCl_3$)/cm^{-1}, 3613 (w), 3520 (br w), 3009 (m), 1726 (s), 1602 (w); δ_H (400 MHz, $CDCl_3$), 0.87–0.94 (2H, m, ArCHCH_2), 1.19 (3H, t, *J* 7.0 Hz, OCH_2CH_3), 1.38–1.45 (1H, m, $HOCH_2CH$), 1.75 (3H, d, *J* 1.0 Hz, C=CCH_3), 1.84 (1H, app dt, *J* 9.0 and 5.0 Hz, ArC*H*), 2.10 (1H, app br s, O*H*), 2.37 (2H, t, *J* 7.0 Hz, O=CCH_2CH_2), 2.44 (2H, t, *J* 7.0 Hz, O=CCH_2CH_2), 3.47 (1H, dd, *J* 16.0 and 7.0 Hz, ArC*H*H), 3.53 (1H, dd, *J* 16.0 and 7.0 Hz, ArCH*H*), 3.66 (2H, d, *J* 6.5 Hz, HOCH_2), 4.07 (2H, q, *J* 7.0 Hz, OCH_2CH_3), 5.34 (1H, app tq, *J* 7.0 and 1.0 Hz, C=C*H*), 6.99 (1H, dd, *J* 6.0 and 2.0 Hz, Ar*H*), 7.10–7.15 (3H, m, 3×Ar*H*); δ_C (100 MHz, $CDCl_3$), 12.0 (t), 14.2 (q), 16.2 (q), 19.0 (d), 23.4 (d), 31.8 (t), 33.1 (t), 34.7 (t), 60.4 (t), 66.6 (t), 123.9 (d), 125.8, 126.1, 126.2 (3×d), 128.6 (d), 134.3 (s), 139.6 (s), 140.7 (s), 173.5 (s); *m*/*z* (ES) 325.1784 (M+Na^+, $C_{19}H_{26}O_3Na$ requires 325.1774).

4.10. (*E*)-Ethyl 6-(2-(2-formylcyclopropyl)phenyl)-4-methylhex-4-enoate 20b

2-Iodoxybenzoic acid (2.75 g, 9.8 mmol) was added portionwise, to a stirred solution of the alcohol **20a** (1.85 g, 6.1 mmol) in dimethylsulfoxide (25 ml) at room temperature, under an argon atmosphere. The solution was stirred at room temperature for 12 h and then water (25 ml) was added. The mixture was filtered through Celite using diethyl ether (50 ml), and the separated aqueous phase was then extracted with diethyl ether (3×20 ml). The combined organic extracts were washed with brine (30 ml), then dried over sodium sulfate and concentrated in vacuo. The residue was purified by flash column chromatography (20% EtOAc, 80% petrol) on silica gel, to give the *aldehyde* **20b** (1.31 g, 70%) as a colourless oil. ν_{max} (sol $CHCl_3$)/cm^{-1}, 3011 (m), 1715 (br s), 1603 (w); δ_H (400 MHz, $CDCl_3$), 1.21 (3H, t, *J* 7.0 Hz, OCH_2CH_3), 1.52–1.58 (1H, m, ArCHC*H*H), 1.67–1.70 (1H, m, ArCHCH*H*), 1.71 (3H, app s, C=CCH_3), 2.05 (1H, ddd, *J* 9.0, 7.0 and 5.0 Hz, ArC*H*), 2.35 (2H, t, *J* 7.0 Hz, O=CCH_2CH_2), 2.43 (2H, t, *J* 7.0 Hz, O=CCH_2CH_2), 2.62–2.70 (1H, m, O=CHC*H*), 3.42 (2H, d, *J* 7.0 Hz, ArCH_2), 4.09 (2H, q, *J* 7.0 Hz, OCH_2CH_3), 5.28 (1H, tq, *J* 7.0 and 1.0 Hz, C=C*H*), 7.00 (1H, dd, *J* 7.5 and 1.5 Hz, Ar*H*), 7.12–7.23 (3H, m, 3×Ar*H*), 9.34 (1H, d, *J* 5.0 Hz, O=C*H*); δ_C (100 MHz, $CDCl_3$), 14.1 (q), 15.0 (t), 16.2 (q), 24.3 (d), 31.6 (t), 32.3 (d), 33.0 (t), 34.5 (t), 60.2 (t), 122.9 (d), 125.9, 126.2, 127.1 (3×d), 128.8 (d), 134.9 (s), 136.3 (s), 140.9 (s), 173.2 (s), 199.9 (s); *m*/*z* (ES) 323.1617 (M+Na^+, $C_{19}H_{24}O_3Na$ requires 323.1618).

4.11. (*E*)-Ethyl 4-methyl-6-(2-(2-vinylcyclopropyl)phenyl)hex-4-enoate 17

*4.11.1. Prepared from the aldehyde **20b***

Tetrahydrofuran (40 ml) was added to freshly dried (100 °C, 1 mmHg, 5 h) methyltriphenylphosphonium bromide (4.3 g, 12.0 mmol) at room temperature, under an argon atmosphere. A solution of sodium hexamethyldisilazane (1.0 M) in THF (5.6 ml, 5.6 mmol) was added dropwise over 15 min to the stirred solution at −78 °C. The mixture was stirred at −78 °C for 15 min and then a solution of the aldehyde **20b** (1.4 g, 4.7 mmol) in tetrahydrofuran (20 ml) was added dropwise, via canula, over 15 min. The mixture was stirred at −78 °C for a further 2 h and then allowed to warm to room temperature over 12 h. Diethyl ether (50 ml) and water (50 ml) were added, and the separated aqueous phase was then extracted with diethyl ether (3×20 ml). The combined organic extracts were dried over sodium sulfate and then concentrated in vacuo. The residue was purified by flash column chromatography (5% EtOAc, 95% petrol) on silica gel, to give the *vinylcyclopropane* **17** (1.3 g, 93%) as a colourless oil. ν_{max} (sol $CHCl_3$)/cm^{-1}, 3011 (s), 1727 (s), 1634 (m), 1602 (w); δ_H (400 MHz, $CDCl_3$), 1.05 (1H, app dt, *J* 8.5 and 5.0 Hz, ArCHC*H*H), 1.22 (3H, t, *J* 7.0 Hz, OCH_2CH_3), 1.24–1.27 (1H, m, ArCHCH*H*), 1.54–1.59 (1H, m, H_2C=CHC*H*), 1.72 (3H, app s, C=CCH_3), 1.96 (1H, ddd, *J* 8.5, 5.5 and 5.0 Hz, ArC*H*), 2.36 (2H, t, *J* 7.0 Hz, O=CCH_2CH_2), 2.43 (2H, t, *J* 7.0 Hz, O=CCH_2CH_2), 3.43 (1H, dd, *J* 16.0 and 7.0 Hz, ArC*H*H), 3.49 (1H, dd, *J* 16.0 and 7.0 Hz, ArC*H*H), 4.10 (2H, q, *J* 7.0 Hz, OCH_2CH_3), 4.96 (1H, dd, *J* 10.0 and 1.5 Hz, HC=CH*H*), 5.13 (1H, dd, *J* 17.0 and 1.5 Hz, HC=C*H*H), 5.34 (1H, app tq, *J* 7.0 and 1.5 Hz, C=C*H*), 5.58 (1H, ddd, *J* 17.0, 10.0 and 8.5 Hz, H_2C=C*H*), 6.99 (1H, dd, *J* 6.0 and 2.0 Hz, Ar*H*), 7.12–7.15 (3H, m, 3×Ar*H*); δ_C (100 MHz, $CDCl_3$), 14.2 (q), 14.6 (t), 16.2 (q), 23.0 (d), 25.7 (d), 31.6 (t), 33.2 (t), 34.7 (t), 60.3 (t), 112.4 (t), 123.6 (d), 125.7, 126.0, 126.1 (3×d), 128.4 (d), 134.4 (s), 139.5 (s), 140.9 (s), 141.0 (d), 173.4 (s); *m*/*z* (ES) 321.1817 ($M+Na^+$, $C_{20}H_{26}O_2Na$ requires 321.1825).

*4.11.2. Prepared by a Stille coupling reaction between the iodobenzene **10** and the stannane **11***

The iodobenzene **10** was coupled to the vinylcyclopropylstannane **11**, using the same reagents and conditions as those used to couple **10** to the *E*-vinylstannane **15** (for the synthesis of **19**). Work up and chromatography gave the arylvinylcyclopropane **17** (20%) and the corresponding substituted *n*-butylbenzene **18** (41%). The vinylcyclopropane **17** had identical spectroscopic properties to those recorded under section 4.11.1. The butylbenzene **18** showed: δ_H (360 MHz, $CDCl_3$), 0.96 (3H, t, *J* 7 Hz, $(CH_2)_2CH_3$), 1.30 (3H, t, *J* 7.5 Hz, OCH_2CH_3), 1.33 (2H, m, $CH_2CH_2CH_3$), 1.62 (2H, app. pentet, *J* ~7 Hz, $CH_2CH_2CH_2$), 1.71 (3H, s, CH=C*Me*), 2.2–2.4 (4H, m, $CH_2CH_2CO_2Et$), 2.55 (2H, t, *J* 7 Hz, ArCH_2), 3.22 (2H, d, *J* 6 Hz, ArCH_2CH=), 4.12 (2H, q, *J* 7.5 Hz, OCH_2CH_3), 5.80 (1H, t, *J* 6 Hz, =C*H*CH_2), 6.9–7.05 (4H, m. Ar*H*); δ_C (90 MHz, $CDCl_3$), 14.1 (2×q), 17.1 (q), 22.4 (t), 29.6 (t), 31.9 (t), 33.8 (t), 34.6 (t), 35.2 (t), 61.3 (t), 122.8 (d), 125.6 (d), 125.9 (d), 128.1 (d), 128.9 (d), 135.5 (s), 136.5 (s), 136.6 (s), 173.1 (s).

4.12. (*E*)-Phenyl-4-methyl-6-(2-(2-vinylcyclopropyl)-phenyl)hex-4-eneselenoate 5

A solution of lithium hydroxide (40 mg, 1.7 mmol) in water (2 ml) was added dropwise over 2 min, to a stirred solution of the ester **17** (150 mg, 0.5 mmol) in acetonitrile (4 ml) at room temperature. The mixture was stirred at room temperature for 24 h, then diethyl ether (1 ml) was added and the separated organic phase was extracted with water (2×5 ml) and sodium hydroxide (2 M, 5 ml). Hydrochloric acid (2 M) was added to the combined aqueous extracts until pH 1 (approximately 10 ml). The acidified aqueous phase was extracted with ethyl acetate (3×10 ml), and the combined organic extracts were dried over sodium sulfate and concentrated in vacuo, to leave the corresponding carboxylic acid (135 mg, 96%) as a colourless oil, which was used in the next step without further purification. ν_{max} (sol $CHCl_3$)/cm^{-1}, 3059 (s), 2929 (s), 1709 (w), 1600 (m); δ_H (400 MHz, $CDCl_3$), 1.05 (1H, app dt, *J* 8.5 and 5.0 Hz, ArCHC*H*H), 1.25 (1H, ddd, *J* 8.5, 6.0 and 5.0 Hz, ArCHCH*H*), 1.53–1.61 (1H, m, H_2C=CHC*H*), 1.73 (3H, app s, C=C*Me*), 1.96 (1H, ddd, *J* 8.5, 5.5 and 5.0 Hz, ArC*H*), 2.37 (2H, t, *J* 7.0 Hz, O=CCH_2CH_2), 2.49 (2H, t, *J* 7.0 Hz, O=CCH_2CH_2), 3.44 (1H, dd, *J* 16.0 and 7.0 Hz, ArC*H*H), 3.49 (1H, dd, *J* 16.0 and 7.0 Hz, ArC*H*H), 4.96 (1H, dd, *J* 10.0 and 1.5 Hz, HC=CH*H*), 5.13 (1H, dd, *J* 17.0 and 1.5 Hz, HC=C*H*H), 5.37 (1H, app tq, *J* 7.0 and 1.5 Hz, C=C*H*), 5.57 (1H, ddd, *J* 17.0, 10.0 and 8.5 Hz, H_2C=C*H*), 6.99 (1H, dd, *J* 6.0 and 2.0 Hz, Ar*H*), 7.12–7.15 (3H, m, 3×Ar*H*); δ_C (100 MHz, $CDCl_3$), 14.6 (t), 16.2 (q), 23.0 (d), 25.7 (d), 31.7 (t), 32.7 (t), 34.3 (t), 112.5 (t), 123.8 (d), 125.7, 126.0, 126.1 (3×d), 128.5 (d), 134.0 (s), 139.5 (s), 140.8 (s), 141.1 (d), 179.0 (s); *m*/*z* (ES) 271.1693 ($M+H^+$, $C_{18}H_{23}O_2$ requires 271.1693).

N-(Phenylselenyl)phthalimide (200 mg, 0.5 mmol) was added, in one portion, to a stirred solution of the carboxylic acid (110 mg, 0.4 mmol) and tributylphosphine (0.27 ml, 1.2 mmol) in benzene (1 ml) at room temperature, under an argon atmosphere. The mixture was stirred at room temperature for 24 h, then poured onto silica and purified by flash column chromatography (100% petrol) on silica gel to give the *seleno ester* **5** (90 mg, 55%) as a pale yellow oil. ν_{max} (sol $CHCl_3$)/cm^{-1}, 2924 (m), 1717 (s), 1634 (m); δ_H (400 MHz, $CDCl_3$), 1.05 (1H, app dt, *J* 8.5 and 5.0 Hz, ArCHC*H*H), 1.26 (1H, ddd, *J* 8.5, 6.0 and 5.0 Hz, ArCHCH*H*), 1.54–1.60 (1H, m, H_2C=CHC*H*), 1.73 (3H, app s, C=C*Me*), 1.96 (1H, ddd, *J* 8.5, 6.0 and 5.0 Hz, ArC*H*), 2.43 (2H, t, *J* 7.5 Hz, O=CCH_2CH_2), 2.84 (2H, t, *J* 7.5 Hz, O=CCH_2CH_2), 3.44 (1H, dd, *J* 16.0 and 7.0 Hz, ArC*H*H), 3.50 (1H, dd, *J* 16.0 and 7.0 Hz, ArCH*H*), 4.97 (1H, dd, *J* 10.0 and 1.5 Hz, HC=CH*H*), 5.14 (1H, dd, *J* 17.0 and 1.5 Hz, HC=C*H*H), 5.38 (1H, app tq, *J* 7.0 and 1.5 Hz, C=C*H*), 5.58 (1H, ddd, *J* 17.0, 10.0 and 8.5 Hz, H_2C=C*H*), 7.00 (1H, dd, *J* 6.0 and 2.0 Hz, Ar*H*), 7.13–7.16 (3H, m, 3×Ar*H*), 7.34–7.41 (3H, m, 3×Ar*H*), 7.46–7.51 (2H, m, 2×Ar*H*); δ_C (100 MHz, $CDCl_3$), 14.6 (t), 16.3 (q), 23.0 (d), 25.8 (d), 31.7 (t), 34.9 (t), 46.1 (t), 112.5 (t), 124.4 (d), 125.7, 126.0, 126.1 (3×d), 126.4 (s), 128.5 (d), 128.8 (d), 129.3 (2C d), 133.5 (s), 135.8 (2C d), 139.5 (s), 140.7 (s), 141.1 (d), 199.8 (s); *m*/*z* (ES) 433.1031 ($M+Na^+$, $C_{24}H_{26}O^{80}SeNa$ requires 433.1041).

4.13. 1,2,4a,5,6,6a,11,11a-Octahydro-11b-methyl-4*H*-benzo[*a*]fluoren-3(11b*H*)-ones 24 and 25, and (6*E*,12*E*)-8,9,14,15-tetra hydro-7-methyl-5*H*-benzo[13]annulen-10(11*H*)-one 23

A solution of tri-*n*-butyltin hydride (92 μl, 0.34 mmol) and 2,2′-azobis(isobutyronitrile) (2 mg, 0.01 mmol) in degassed benzene (20 ml), was added dropwise over 8 h via syringe pump, to a stirred solution of the seleno ester **5** (110 mg, 0.26 mmol) and 2,2′-azobis-(isobutyronitrile) (2 mg, 0.01 mmol) in degassed benzene (200 ml), at 80 °C under an argon atmosphere. The mixture was heated under reflux for a further 12 h, and then allowed to cool to room temperature and concentrated in vacuo. The residue was purified by flash column chromatography on silica (0–25% Et_2O, 100–75% petrol) to give: (i) a 1:1 mixture of angular methyl epimers of the tetracyclic ketone **24**/**25** (16.5 mg, 25%) (eluted fourth) as a crystalline solid, mp 128–129 °C (ethanol). ν_{max} (sol $CHCl_3$)/cm^{-1}, 2928 (s), 1704 (s). The epimers were separated by reverse phase preparative HPLC (MeCN/H_2O) and showed the following data: *trans*, *anti*, *trans* isomer **25** (contaminated by ~20% of the other epimer) δ_H (400 MHz, $CDCl_3$) (see numbering system on structure), 1.13 (3H, s, CH_3, *H*-18), 1.36 (1H, dddd, *J* 12.5, 12.0, 12.0 and 4.5 Hz, ArCH-C$H_{ax}H_{eq}$, *H*-7_{ax}), 1.43–1.53 (1H, m, O=C$CH_2CHCH_aH_b$, *H*-6_a), 1.51–1.60 (1H, m, O=C$H_2CH_{ax}H_{eq}$, *H*-1_{ax}), 1.56–1.62 (1H, m,

O=CCH$_2$CHCH$_a$H$_b$, *H*-6$_b$), 1.60–1.68 (1H, m, O=CCH$_2$C*H*, *H*-4), 1.67 (1H, ddd, *J* 12.5, 12.0 and 7.0 Hz, ArCHC*H*, *H*-9), 1.96 (1H, ddd, *J* 13.0, 6.5 and 2.0 Hz, O=CCH$_2$CH$_{ax}$*H*$_{eq}$, *H*-1$_{eq}$), 2.21 (1H, ddd, *J* 14.5, 4.0 and 2.0 Hz, O=CCH$_{ax}$*H*$_{eq}$CH, *H*-4$_{eq}$), 2.31 (1H, dd, *J* 14.5 and 13.5 Hz, O=CC*H*$_{ax}$H$_{eq}$CH, *H*-4$_{ax}$), 2.34–2.42 (2H, 2×m, O=CCH$_{ax}$*H*$_{eq}$CH$_2$, *H*-2$_{eq}$+ArCHCH$_{ax}$*H*$_{eq}$, *H*-7$_{eq}$), 2.49 (1H, ddd, *J* 15.0, 13.5 and 6.5 Hz, O=CCH$_{ax}$*H*$_{eq}$CH$_2$, *H*-2$_{eq}$), 2.65 (1H, dd, *J* 14.0 and 12.0 Hz, ArC*H*-$_{ax}$H$_{eq}$, *H*-11$_{ax}$), 2.73 (1H, dd, *J* 14.0 and 7.0 Hz, ArCH$_{ax}$*H*$_{eq}$, *H*-11$_{eq}$), 2.93 (1H, ddd, *J* 12.5, 12.0 and 3.5 Hz, ArC*H*, *H*-8), 7.12–7.17 (3H, m, 3×Ar*H*, *H*-14,15,16), 7.23 (1H, dd, *J* 7.0 and 2.0 Hz, Ar*H*, *H*-13); δ_C (100 MHz, CDCl$_3$), 11.6 (q, *C*-18), 28.8 (t, *C*-7), 29.5 (t, *C*-6), 31.3 (t, *C*-11), 35.6 (s, *C*-10), 38.0 (t, *C*-2), 38.4 (t, *C*-1), 44.0 (d, *C*-8), 44.3 (t, *C*-4), 46.6 (d, *C*-5), 60.7 (d, *C*-9), 122.0 (d, *C*-16), 124.6 (d, *C*-13), 126.2 (2×d, *C*-14,15), 143.0 (s, *C*-12), 146.6 (s, *C*-17), 211.4 (s, *C*-3); *cis*, *syn*, *trans* isomer **24** δ_H (400 MHz, CDCl$_3$) (see numbering system on structure), 1.33 (1H, dddd, *J* 14.5, 13.0, 12.0 and 3.5 Hz, ArCH-C*H*$_{ax}$H$_{eq}$, *H*-7$_{ax}$), 1.37 (3H, s, C*H*$_3$, *H*-18), 1.45 (1H, dddd, *J* 14.0, 13.0, 12.5 and 3.5 Hz, O=CCH$_2$CHC*H*$_{ax}$H$_{eq}$, *H*-6$_{ax}$), 1.66–1.72 (1H, m, O=CCH$_2$CH$_{ax}$*H*$_{eq}$, *H*-1$_{eq}$), 1.68–1.74 (1H, m, O=CCH$_2$CHCH$_{ax}$*H*$_{eq}$, *H*-6$_{eq}$), 1.81 (1H, ddd, *J* 12.5, 12.0 and 6.5 Hz, ArCHC*H*, *H*-9), 1.81–1.89 (1H, m, ArCH$_2$C*H*, *H*-5), 2.10 (1H, ddd, *J* 14.5, 2.5 and 2.0 Hz, O=CC*H*$_a$H$_b$CH, *H*-4$_a$), 2.17 (1H, ddd, *J* 14.0, 13.5 and 5.0 Hz, O=CCH$_2$C*H*$_{ax}$H$_{eq}$, *H*-1$_{ax}$), 2.29–2.36 (1H, m, O=CCH$_{ax}$*H*$_{eq}$CH$_2$, *H*-2$_{eq}$), 2.32–2.38 (1H, m, ArCHCH$_{ax}$*H*$_{eq}$, *H*-7$_{eq}$), 2.53 (1H, dddd, *J* 14.5, 14.0, 7.0 and 0.5 Hz, O=CC*H*$_{ax}$H$_{eq}$CH$_2$, *H*-2$_{ax}$), 2.56 (1H, dd, *J* 14.0 and 12.5 Hz, ArC*H*$_{ax}$H$_{eq}$, *H*-11$_{ax}$), 2.81 (1H, dd, *J* 14.0 and 6.5 Hz, ArCH$_{ax}$*H*$_{eq}$, *H*-11$_{eq}$), 2.82 (1H, dd, *J* 14.5 and 12.0 Hz, ArC*H*, *H*-8), 2.87 (1H, ddd, *J* 14.5, 6.5 and 0.5 Hz, O=CCH$_a$*H*$_b$CH, *H*-4$_b$), 7.11–7.18 (3H, m, 3×Ar*H*, *H*-14,15,16), 7.23 (1H, dd, *J* 7.0 and 2.0 Hz, Ar*H*, *H*-13); δ_C (100 MHz, CDCl$_3$), 24.8 (q, *C*-18), 27.1 (t, *C*-1), 29.2 (t, *C*-7), 30.2 (t, *C*-6), 31.7 (t, *C*-11), 35.1 (s, *C*-10), 37.5 (t, *C*-2), 43.2 (d, *C*-8), 44.2 (t, *C*-4), 46.2 (d, *C*-5), 59.8 (d, *C*-9), 122.0 (d, *C*-16), 124.5 (d, *C*-13), 126.1 (2×d, *C*-14,15), 143.0 (s, *C*-12), 146.6 (s, *C*-17), 212.1 (s, *C*-3); *m*/*z* (ES) 277.1570 (M+Na$^+$, C$_{18}$H$_{22}$ONa requires 277.1568); and (ii) the macrocyclic dienone **23** (16 mg, 25%) (eluted third) as a colourless oil; ν_{max} (sol CHCl$_3$)/cm^{-1}, 2920 (s), 1710 (s), 1605 (w); δ_H (400 MHz, CDCl$_3$), 1.72 (3H, d, *J* 1.5 Hz, HC=CC*H*$_3$, *H*-15), 2.33 (2H, app dd, *J* 6.0 and 4.5 Hz, O=CCH$_2$C*H*$_2$, *H*-16), 2.48 (2H, app dtd, *J* 7.5, 5.5 and 1.0 Hz, ArCH$_2$C*H*$_2$, *H*-4), 2.51 (1H, app d, *J* 12.0 Hz, O=CC*H*$_a$H$_b$CH$_2$, *H*-17$_a$), 2.52 (1H, app td, *J* 4.5 and 1.0 Hz, O=CCH$_a$*H*$_b$CH$_2$, *H*-17$_b$), 2.69 (1H, app d, *J* 5.5 Hz, ArC*H*$_a$CH$_b$CH$_2$, *H*-5$_a$), 2.70 (1H, app dd, *J* 6.0 and 5.5 Hz, ArCH$_a$C*H*$_b$CH$_2$, *H*-5$_b$), 2.91 (2H, app dd, *J* 7.0 and 1.0 Hz, O=CC*H*$_2$, *H*-1), 3.27 (2H, app d, *J* 7.0 Hz, ArC*H*$_2$CH=C, *H*-12), 5.05 (1H, app tq, *J* 7.0 and 1.5 Hz, ArCH$_2$C*H*=C, *H*-13), 5.26 (1H, app dtt, *J* 15.5, 7.5 and 1.0 Hz, O=CCH$_2$CH=C*H*, *H*-3), 5.47 (1H, app dtt, *J* 15.5, 7.0 and 1.0 Hz, O=CCH$_2$C*H*=CH, *H*-2), 7.07–7.12 (2H, m, 2×Ar*H*, *H*-7,8), 7.17 (1H, ddd, *J* 7.5, 7.0 and 2.0 Hz, Ar*H*, *H*-9), 7.24 (1H, dd, *J* 7.5 and 1.0 Hz, Ar*H*, *H*-10); δ_C (100 MHz, CDCl$_3$), 17.1 (q, *C*-15), 31.0 (t, *C*-12), 32.3 (t, *C*-16), 32.7 (t, *C*-5), 33.7 (t, *C*-4), 40.1 (t, *C*-17), 45.1 (t, *C*-1), 121.2 (d, *C*-13), 125.0 (d, *C*-2), 126.0, 126.3 (2×d, *C*-8,9), 128.7 (d, *C*-7), 130.2 (d, *C*-10), 131.9 (s, *C*-11), 134.6 (d, *C*-3), 139.0 (s, *C*-14), 139.8 (s, *C*-6), 207.9 (s, *C*-18); *m*/*z* (ES) 277.1575 (M+Na$^+$, C$_{18}$H$_{22}$ONa requires 277.1568).

The following minor compounds were also separated by chromatography: (i) the vinylcyclopropane hydrocarbon **28b** (<1 mg, 1%) as a colourless oil; δ_H (400 MHz, CDCl$_3$), 1.01 (3H, t, *J* 7.5 Hz, CH$_2$C*H*$_3$), 1.05 (1H, app dt, *J* 8.5 and 5.0 Hz, ArCHC*H*H), 1.24–1.32 (1H, m, ArCHCH*H*), 1.50–1.61 (1H, m, H$_2$C=CHC*H*), 1.71 (3H, app s, C=CC*H*$_3$), 1.99 (1H, ddd, *J* 8.5, 6.0 and 5.0 Hz, ArC*H*), 2.04 (2H, q, *J* 7.5 Hz, C*H*$_2$CH$_3$), 3.44 (1H, dd, *J* 16.0 and 7.0 Hz, ArC*H*H), 3.49 (1H, dd, *J* 16.0 and 7.0 Hz, ArCH*H*), 4.95 (1H, dd, *J* 10.0 and 1.5 Hz, HC=CH*H*), 5.13 (1H, dd, *J* 17.0 and 1.5 Hz, HC=C*H*H), 5.29 (1H, app tq, *J* 7.0 and 1.5 Hz, C=C*H*), 5.58 (1H, ddd, *J* 17.0, 10.0 and 8.5 Hz, H$_2$C=C*H*), 6.98 (1H, dd, *J* 6.0 and 1.5 Hz, Ar*H*), 7.11–7.18 (3H, m, 3×Ar*H*). Upon leaving in the open air, for 5 min, the vinylcyclopropane became oxidised producing the dioxolane **29a** (<1 mg, 1%), as a yellow oil; δ_H (400 MHz, CDCl$_3$), 1.03 (3H, t, *J* 7.5 Hz, CH$_2$C*H*$_3$), 1.75 (3H, app s, C=CC*H*$_3$), 2.06 (2H, q, *J* 7.5 Hz, C*H*$_2$CH$_3$), 2.39 (1H, app dt, *J* 12.0 and 7.5 Hz, ArCHC*H*H), 3.23 (1H, app dt, *J* 12.0 and 7.5 Hz, ArCHCH*H*), 3.35 (1H, dd, *J* 16.0 and 7.0 Hz, ArC*H*H), 3.41 (1H, dd, *J* 16.0 and 7.0 Hz, ArCH*H*), 4.89 (1H, app dt, *J* 7.5 and 7.0 Hz, H$_2$C=CHC*H*), 5.21 (1H, app tq, *J* 7.0 and 1.5 Hz, C=C*H*), 5.30 (1H, dd, *J* 10.0 and 1.5 Hz, HC=CH*H*), 5.41 (1H, dd, *J* 17.0 and 1.5 Hz, HC=C*H*H), 5.55 (1H, app t, *J* 7.5 Hz, ArC*H*), 5.93 (1H, ddd, *J* 17.0, 10.0 and 7.0 Hz, H$_2$C=C*H*), 7.19 (1H, dd, *J* 6.0 and 1.5 Hz, Ar*H*), 7.25–7.31 (3H, m, 3×Ar*H*); (ii) the saturated aldehyde **28a** (3 mg, 4%) as a yellow oil; ν_{max} (sol CHCl$_3$)/cm^{-1}, 2928 (s), 1720 (s), 1634 (m), 1605 (m); δ_H (400 MHz, CDCl$_3$), 1.05 (1H, app dt, *J* 8.5 and 5.0 Hz, ArCHC*H*H), 1.24–1.28 (1H, m, ArCHCH*H*), 1.52–1.63 (1H, m, H$_2$C=CHC*H*), 1.73 (3H, d, *J* 1.0 Hz, C=CC*H*$_3$), 1.95 (1H, ddd, *J* 8.5, 6.0 and 5.0 Hz, ArC*H*), 2.38 (2H, t, *J* 7.5 Hz, O=CCH$_2$C*H*$_2$), 2.56 (2H, td, *J* 7.5 and 2.0 Hz, O=CC*H*$_2$CH$_2$), 3.45 (1H, dd, *J* 16.0 and 7.0 Hz, ArC*H*H), 3.49 (1H, dd, *J* 16.0 and 7.0 Hz, ArCH*H*), 4.96 (1H, dd, *J* 10.0 and 1.5 Hz, HC=CH*H*), 5.13 (1H, dd, *J* 17.0 and 1.5 Hz, HC=C*H*H), 5.35 (1H, tq, *J* 7.0 and 1.0 Hz, C=C*H*), 5.58 (1H, ddd, *J* 17.0, 10.0 and 8.5 Hz, H$_2$C=C*H*), 7.00 (1H, dd, *J* 6.0 and 2.0 Hz, Ar*H*), 7.11–7.17 (3H, m, 3×Ar*H*), 9.77 (1H, t, *J* 2.0 Hz, O=C*H*); *m*/*z* (ES) 277.1565 (M+Na$^+$, C$_{18}$H$_{22}$ONa requires 277.1568); (iii) recovered seleno ester **5** (5 mg, 5%); (iv) the dioxolane **29b** (10 mg, 8%) as a colourless oil; δ_H (400 MHz, CDCl$_3$), 1.74 (3H, d, *J* 0.5 Hz, HC=CC*H*$_3$), 2.36 (1H, app dt, *J* 12.0 and 7.0 Hz, ArCHC*H*H), 2.42 (2H, t, *J* 7.5 Hz, O=CCH$_2$C*H*$_2$), 2.83 (2H, t, *J* 7.5 Hz, O=CC*H*$_2$CH$_2$), 3.18 (1H, app dt, *J* 12.0 and 7.5 Hz, ArCHCH*H*), 3.34 (1H, dd, *J* 16.0 and 7.0 Hz, ArC*H*H), 3.39 (1H, dd, *J* 16.0 and 7.0 Hz, ArCH*H*), 4.85 (1H, app dtt, *J* 7.5, 7.0 and 1.0 Hz, H$_2$C=C*H*CH), 5.27 (1H, app dt, *J* 10.0 and 1.0 Hz, HC=CH*H*), 5.28 (1H, app tq, *J* 7.0 and 0.5 Hz, C=C*H*), 5.38 (1H, app dt, *J* 17.0 and 1.0 Hz, HC=C*H*H), 5.49 (1H, app t, *J* 7.5 Hz, ArCH), 5.89 (1H, ddd, *J* 17.0, 10.0 and 7.5 Hz, H$_2$C=C*H*), 7.14 (1H, dd, *J* 7.5 and 1.5 Hz, Ar*H*), 7.33–7.40 (3H, m, 3×Ar*H*), 7.44–7.47 (3H, m, 3×Ar*H*), 7.57 (2H, dd, *J* 7.5 and 7.0 Hz, 2×Ar*H*); δ_C (100 MHz, CDCl$_3$), 16.3 (q), 31.5 (t), 34.8 (t), 45.9 (t), 48.8 (t), 79.6 (d), 82.3 (d), 119.0 (t), 124.2 (d), 125.7, 126.7, 128.1, 128.9 (4×d), 126.4 (s), 129.3 (2C d), 129.4 (d), 134.0 (s), 135.0 (d), 135.7 (2C d), 136.7 (s), 138.4 (s), 199.7 (s); *m*/*z* (ES) 465.0956 (M+Na$^+$, C$_{24}$H$_{26}$O$_3^{80}$SeNa requires 465.0945).

Acknowledgements

We thank the EPSRC (studentship to D.A.S. and fellowship to J.M.W.) and Astra Zeneca for support. We also thank Mr. Robert Kempton and Mr. Joseph Rogers for their collaboaration in reinvestigating the radical cyclisation of **32b**, and Mr. Dane Toplis for HPLC analyses and separations of oestrane and C-nor-D-homosteroid isomers.

Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2009.05.020.

References and notes

1. Saito, K. *Bull. Chem. Soc. Jpn.* **1940**, *15*, 22–27.
2. (a) Saito, K.; Suginome, H.; Takaoka, M. *Bull. Chem. Soc. Jpn.* **1934**, *9*, 15–23; (b) Fried, J.; Wintersteiner, O.; Moore, M.; Iselin, B. M.; Klingsberg, A. *J. Am. Chem. Soc.* **1951**, *73*, 2970–2971.
3. (a) Teruya, T.; Nakagawa, S.; Koyama, T.; Arimoto, H.; Kita, M.; Uemura, D. *Tetrahedron* **2004**, *60*, 6989–6993; (b) Teruya, T.; Nakagawa, S.; Koyoma, T.; Suenaga, K.; Kita, M.; Uemura, D. *Tetrahedron Lett.* **2003**, *44*, 5171–5173.
4. (a) Cooper, M. K.; Porter, J. A.; Young, K. E.; Beachy, P. A. *Science* **1998**, *280*, 1603–1607; (b) Taipale, J.; Chen, J. K.; Cooper, M. K.; Wang, B.; Mann, R. K.; Milenkovic, L.; Scott, M. P.; Beachy, P. A. *Nature* **2000**, *406*, 1005–1009; (c) Chen, J. K.; Taipale, J.; Cooper, M. K.; Beachy, P. A. *Genes Dev.* **2002**, *16*, 2743–2748; (d) Yauch, R. L.; Gould, S. E.; Scales, S. J.; Tang, T.; Tian, H,; Ahn, C. P.; Marshall, D.; Fu, L.; Januario, T.; Kallop, D.; Nannini-Pepe, M.; Kotkow, K.; Marsters, J. C.; Rubin, L. L.; de Sauvage, F. J. *Nature* **2008**, *455*, 406–410; (e) van den Brink, G. R.

Physiol. Rev. **2007**, *87*, 1343–1375; (f) Borzillo, G. V.; Lippa, B. *Curr. Top. Med. Chem.* **2005**, 147–157; (g) Lum, L.; Beachy, P. A. *Science* **2004**, *304*, 1755–1759; (h) Thron, C. D.; McCann, F. V. *Gen. Pharmacol.* **1999**, *32*, 81–89; (i) Nagata, R.; Izumi, K. *Jpn. J. Pharmacol.* **1991**, *55*, 129–137; (j) Nagata, R.; Izumi, K.; Iwata, S.-i.; Shimizu, T.; Fukuda, T. *Jpn. J. Pharmacol.* **1991**, *55*, 139–146.

5. (a) Johnson, W. S.; deJongh, H. A. P.; Coverdale, C. E.; Scott, J. W.; Burckhardt, U. *J. Am. Chem. Soc.* **1967**, *89*, 4523–4524; (b) Johnson, W. S.; Cox, J. M.; Graham, D. W.; Whitlock, H. W. *J. Am. Chem. Soc.* **1967**, *89*, 4524–4526.
6. Kutney, J. P.; Cable, J.; Gladstone, W. A. F.; Hanssen, H. W.; Nair, G. V.; Torupka, E. J.; Warnock, W. D. C. *Can. J. Chem.* **1975**, *53*, 1796–1817.
7. Gao, S.; Wang, Q.; Chen, C. *J. Am. Chem. Soc.* **2009**, *131*, 1410–1412.
8. For other synthetic studies towards veratramine **1**, jervine **2** and nakiterpiosin **3**, see: (a) Ito, T.; Ito, M.; Arimoto, H.; Takamura, H.; Uemura, D. *Tetrahedron* **2007**, *48*, 5465–5469; (b) Masamune, T.; Takasugi, M.; Murai, A.; Kobayashi, K. *J. Am. Chem. Soc.* **1967**, *89*, 4521–4523; (c) Masamune, T.; Takasugi, M.; Murai, A. *Tetrahedron* **1971**, *27*, 3369–3386.
9. Chatgilaloglu, C.; Crich, D.; Komatsu, M.; Ryu, L. *Chem. Rev.* **1999**, *99*, 1991–2069.
10. Boger, D. L.; Mathvink, R. J. *J. Org. Chem.* **1989**, *54*, 1779–1781.
11. Stille, J. K. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 508–524.
12. (a) Farina, V.; Krishnamurthy, V.; Scott, W. K. *Organic Reactions*; Wiley: New York, NY, 1997; Vol. 50; (b) Mitchell, T. N. In *Metal-Catalyzed Cross-Coupling Reactions*; de Meijere, A., Diederich, F., Eds.; Wiley-VCH: Weinheim, 2004; Chapter 3.
13. The known aldehyde **12** was conveniently prepared from 2-iodobenzaldehyde using the general homologation procedure reported earlier, see: Pedrosa, R.; Andres, C.; Iglesias, J. M. *J. Org. Chem.* **2001**, *66*, 243–250.
14. Nahmany, M.; Melman, A. *Tetrahedron* **2005**, *61*, 7481–7488.
15. Johnson, W. S.; Werthemann, L.; Bartlett, W. R.; Brocksom, T. J.; Li, T. T.; Faulkner, D. J.; Petersen, M. R. *J. Am. Chem. Soc.* **1970**, *92*, 741–743.
16. Oda, H.; Kobayashi, T.; Kosugi, M.; Migita, T. *Tetrahedron* **1995**, *51*, 695–702.
17. For a Negishi coupling involving a vinylcyclopropylzinc reagent and a vinyl iodide see: (a) Charette, A. B.; Giroux, A. *J. Org. Chem.* **1996**, *61*, 8718–8719; (b) Piers, E.; Jean, M.; Marrs, P. S. *Tetrahedron Lett.* **1987**, *28*, 5075–5078.
18. Pattenden, G.; Stoker, D. A. *Synlett*, in press.
19. The tetracyclic ketone **25** was reported earlier but no NMR data or stereochemical detail were revealed: Bhattacharyya, B. K.; Bose, A. K.; Chatterjee, A.; Sen, B. P. *J. Indian Chem. Soc.* **1964**, *41*, 479–495.
20. For earlier studies of dioxolane ring formation from arylvinylcyclopropanes in the presence of oxygen and diphenyldiselenide see: Feldman, K. S.; Simpson, R. E. *J. Am. Chem. Soc.* **1989**, *111*, 4878–4886.
21. Pattenden, G.; Gonzalez, M. A.; McCulloch, S.; Walter, A.; Woodhead, S. J. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 12024–12029.
22. Pattenden, G.; Wiedenau, P. *Tetrahedron Lett.* **1997**, *38*, 3647–3650.
23. Pattenden, G.; Stoker, D. A.; Thomson, N. M. *Org. Biomol. Chem.* **2007**, *5*, 1776–1788.
24. Charette, A. B.; Juteau, H.; Lebel, H.; Molinaro, C. *J. Am. Chem. Soc.* **1998**, *120*, 11943–11952.