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Palladium catalysed bis- and tris-cyclisations furnishing fused cyclopropyl carbo/heterocycles

Ronald Grigg,* Uthai Sakee, Visuvanathar Sridharan, Sukanthini Sukirthalingam and Ravishanker Thangavelauthum

Molecular Innovation Diversity and Automated Synthesis (MIDAS) Centre, School of Chemistry, Leeds University, Leeds LS2 9JT, UK

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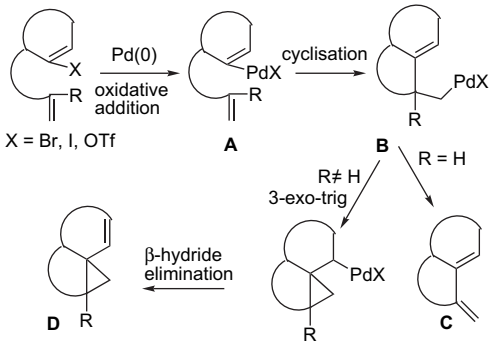
Abstract—Catalytic bis- and tris-cyclisation of a series of acyclic carbo- and heterocyclic precursors results in formation of two or three rings, two or three C–C bonds and two asymmetric tetrasubstituted C-centres regio- and stereoselectively in excellent yield.

1. Introduction

Palladium catalysed cascade reactions provide valuable strategies for the constructions of fused, bridged and spiro carbo/heterocyclic systems.[1,2] Furthermore such cascades have demonstrated their utility for the construction of small strained rings. We and others have reported palladium catalysed cyclisations leading to di-, tri- and tetracyclic compounds containing fused cyclopropane rings.[3–10] Additionally palladium catalysed tandem cyclisation–cyclopropanation is a novel way of assembling a variety of carbo/heterocyclic skeletons with concomitant engineering of considerable additional molecular complexity not available via classical methods for the formation of cyclopropanes such as the reaction of diazo compounds with alkenes catalysed by Rh,[11a–e] Ru,[11f] Cu,[12] Pd[13] and Pt[14] complexes, and Pt[15a] and Au[15b] catalysed cycloisomerisation.

In this paper we report full details of palladium catalysed bis- and tris-cyclisation cascades affording fused/spiro cyclopropyl carbo/heterocycles.[3a–c] A general palladium catalysed bis-cyclisation cascade is shown in Scheme 1.

Oxidative addition of Pd(0) to the carbon–halide/triflate bond gives a vinyl palladium(II) species **A**. Cyclisation of **A** onto a proximal alkene gives the alkyl palladium(II) intermediate **B**. When R=H then **B** may undergo a β-hydride elimination to give **C**. If R≠H a second cyclisation occurs to form the tricyclic cyclopropane **D**.



Scheme 1.

2. Bis-cyclisation cascades

2.1. 5-*exo-trig*/3-*exo-trig* Cascades

2.1.1. Carbocyclic systems. Enol triflates **3a–c** were prepared (Scheme 2) to explore palladium catalysed 5-*exo-trig*/3-*exo-trig* cascades forming tricyclic cyclopropanes. Thus **1a–c** were treated with 1.1 mol equiv ^{t}BuOK in ^{t}BuOH and 4-iodo-2-methylbut-3-ene to give **2a–c** in good yields. Subsequent treatment of **2a–c** with Comins triflating agent[16] in the presence of LDA at −78 °C afforded enol triflates **3a–c** in 77–81% yields.

When enol triflate **3a** was reacted in the presence of 10 mol % $Pd(OAc)_2$, 20 mol % PPh_3, Na_2CO_3 (2 mol equiv), Et_4NCl (1 mol equiv) in boiling acetonitrile it afforded **4** as a single diastereoisomer in 88% yield. The bond forming sequence is detailed in Scheme 3. The relative stereochemistry of **4** was established by NOE studies on **5**, which was prepared

* Corresponding author. Tel.: +441133436501; fax: +441133436530; e-mail: r.grigg@leeds.ac.uk

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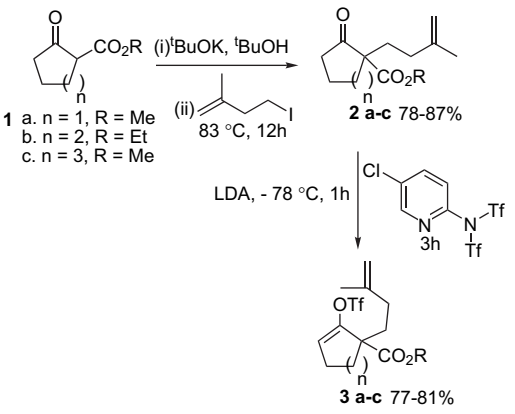
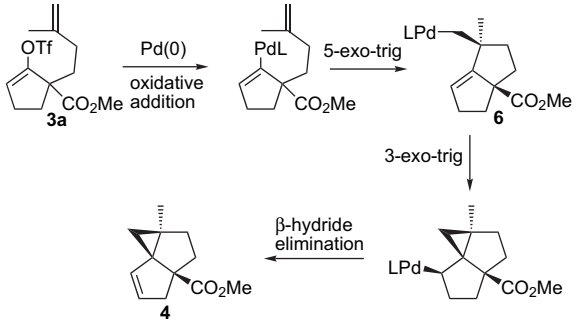
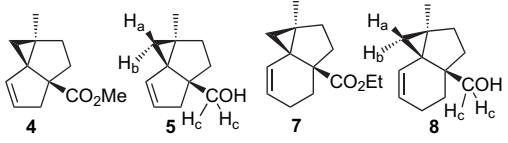


Scheme 2.



Scheme 3.

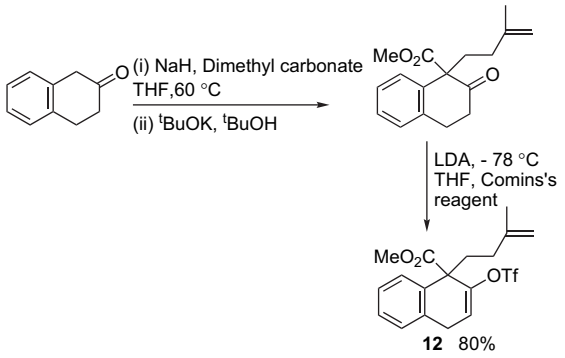
by $LiAlH_4$ reduction of **4**. Thus irradiation of both of the diastereotopic protons H_c (δ 3.45) resulted in 3% enhancement of the signal for the proton H_a (δ 0.90) showing that the cyclopropane ring and the $-CH_2OH$ group are cis-related.



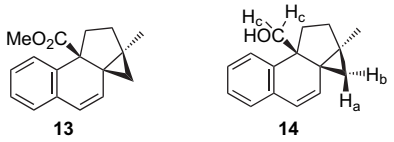
In a similar manner the analogous six-membered enol triflate **3b** underwent consecutive stereo- and regiospecific 5-*exo-trig* and 3-*exo-trig* cyclisations to give the 3/5/6-ring system **7** in 73% yield. The relative stereochemistry was established by NOE studies on **8**, which was obtained by $LiAlH_4$ reduction of **7**. Irradiation of both of the diastereotopic protons H_c (δ 3.45) resulted in 2.5% enhancement of the signal for H_a (δ 1.05).

The seven-membered ring enol triflate **3c** cyclised under similar conditions to afford a 2:1:1 mixture of **9**, **10** and **11** in 75% yield (Scheme 4). In this case double bond isomerisation proved more facile than in the case of the 3/5/5- and 3/5/6-ring systems. It would be expected that addition of Ag^+ or Tl^+ salts[17,18] would suppress double bond isomerisation (vide infra **21**, **22**). Indeed addition of TlOAc (1.2 mol equiv) and reducing the reaction time to 5 h afforded **9** (76%) as the sole product.

The vinyl triflate **12** was prepared in 70% yield from β-tetralone in three steps by carboxymethylation, alkylation and triflation (Scheme 5) in order to study the formation of a tetracyclic cyclopropyl system. Cyclisation of **12** under the same conditions as described above afforded **13** in 90% yield. The relative stereochemistry of **13** was also established by $LiAlH_4$ reduction to give **14** followed by NOE studies. Irradiation of both of the diastereotopic H_c protons (δ 3.45) resulted in enhancement (2.5%) of the signal for H_a (δ 0.90) thus establishing their cis-relationship.



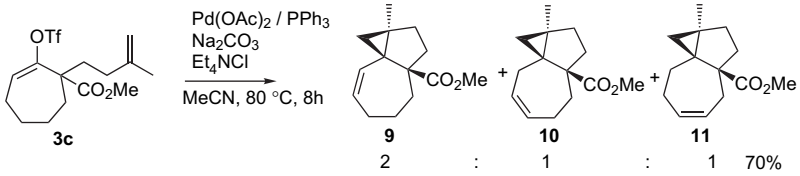
Scheme 5.



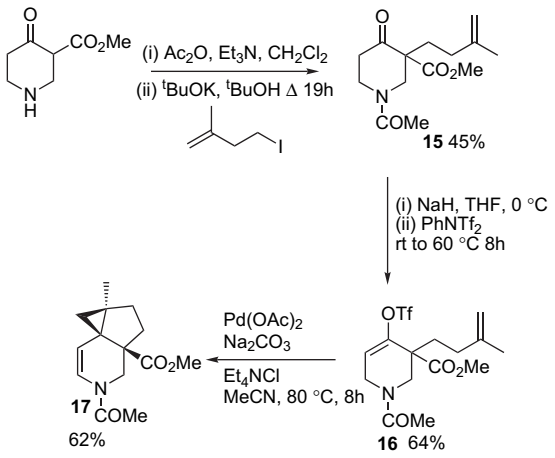
2.1.2. Heterocyclic systems. Enol triflate **16** was synthesised in three steps in good yield (Scheme 6). Methyl 4-oxopiperidine-3-carboxylate was *N*-acetylated in the presence of Et_3N in CH_2Cl_2. The alkyl side chain was then introduced in the presence of ^{t}BuOK as base. Triflation of **15** was carried out using McMurry's method[19] to afford **16** in 64% yield.

Enol triflate **16** successfully underwent a palladium catalysed 5-*exo-trig*/3-*exo-trig* cyclisation cascade to give **17** as a single stereoisomer in 62% yield.

A further heterocyclic precursor, vinyl bromide **18**, was prepared from 2,3-dibromocyclohexene and 2-methyl-2-propen-1-ol in 68% yield. It cyclised in the presence of 5 mol % $PdCl_2(PPh_3)_2$, Et_4NCl (1 mol equiv) and Zn dust

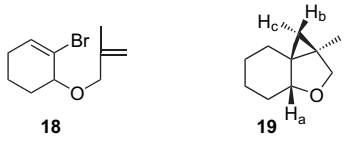


Scheme 4.



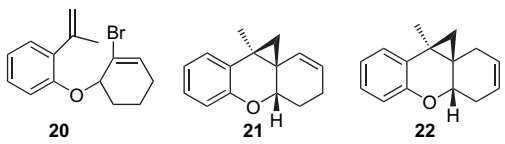
Scheme 6.

(2 mol equiv) in MeCN at 80 °C to afford **19** in 50% yield. There are two potential roles for the Zn dust: (a) as a reductant of Pd(II) to Pd(0) and (b) as a halogen sink[20] promoting formation of a more reactive, coordinatively unsaturated palladium intermediate. The relative stereochemistry of **19** was established by NOE studies. Thus irradiation of proton H_a (δ 3.92) effected enhancement (2%) of the signal of H_b (δ 1.10) establishing that the cyclopropane ring and H_a are cis-related.

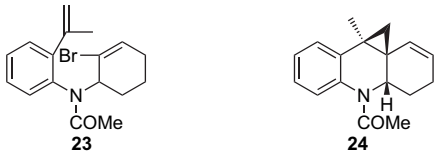


2.2. 6-*exo-trig*/3-*exo-trig* Cascades

Vinyl halide **20** was synthesised in 55% yield from 2-hydroxyacetophenone and 2,3-dibromocyclohex-1-ene in boiling THF, followed by a Wittig reaction. Under standard palladium catalysed cyclisation conditions **20** gave a 10:1 mixture of **21** and **22** in 71% yield via successive 6-*exo-trig* and 3-*exo-trig* cyclisations. The isomeric product **22** was suppressed by using modified reaction conditions previously developed by us.[18] Thus when the reaction was repeated with 10 mol % $Pd(OAc)_2$, 20 mol % PPh_3 and 1.2 mol equiv TlOAc in boiling MeCN, **21** was obtained as the sole product in 76% yield.

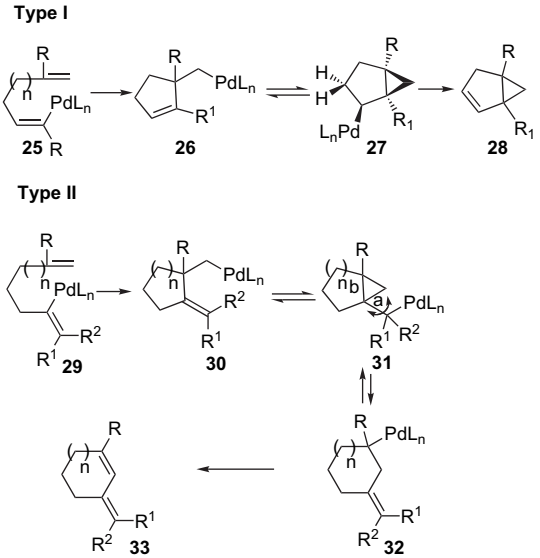


We briefly looked at the *N*-analogue of **20**. Compound **23** was prepared in 70% yield from *N*-acetyl-2-isopropenylaniline in two steps by acetylation followed by alkylation. Cyclisation of **23** under our standard conditions over 8 h afforded **24** in a disappointing 37% yield. However, addition of Zn dust (2 mol equiv) improved the yield from 37 to 72% and reduced the reaction time to 3 h.



All the foregoing cyclopropyl forming cyclisations proceed regio- and stereoselectively and involve the formation of two rings, two C–C bonds and two chiral tetrasubstituted C-centres.

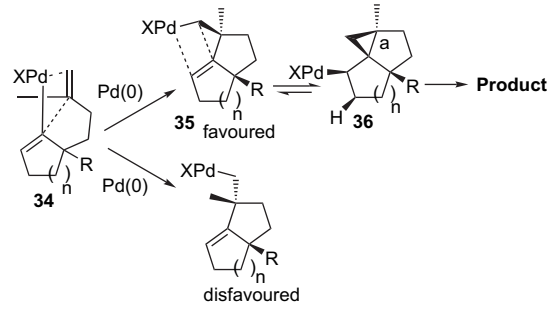
2.2.1. Mechanism. Cyclopropanation as an integral part of palladium catalysed cascades is often concealed by rearrangement of a cyclopropylcarbinylpalladium intermediate with accompanying ring expansion in appropriate cases. This process was first identified and explained, essentially simultaneously, by Torii[21] and Negishi.[22] Negishi formalised the rearrangement in terms of type I **25** and type II **29** substrates (Scheme 7).[22] The key difference is that a type I substrate is processed via intermediate **27** in which the required *syn* alignment of bonds β to the palladium only allows either equilibration with **26** or β-H elimination to form **28**. In contrast type II substrates **29** proceed via **31**, which can equilibrate with **30** but additionally now possess a rotatable bond **31** (↷) allowing the palladium to attain a *syn* alignment with either cyclopropyl bond a or b. *syn* Alignment with bond b triggers a cyclopropylcarbinylpalladium ring expansion affording **32** and subsequently **33** (or double bond isomer) in which the diagnostic olefinic geometry (R^1/R^2) has been inverted.[23] For very elegant examples of stereochemical control of such processes see Torii et al.[21] Solvent effects on type II processes have been interpreted in terms of equilibration of **31** and **32**.[24]



Scheme 7.

A stereochemical feature not heretofore discussed is the influence of an allylic stereocentre in the type I substrates, which is present in **3a–c**, **16**, **20** and **23** in this work. The fusion of a new five- or six-membered ring onto an existing 5–7-membered ring in these examples always results in a cis-arrangement of the allylic substituent and the

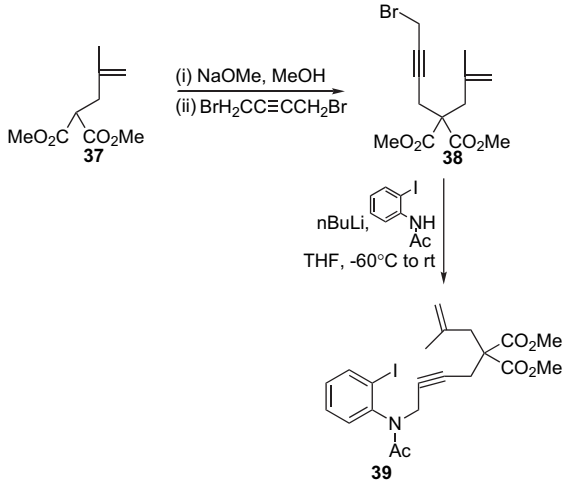
cyclopropyl ring (vide infra). Mechanistically the initial cyclisation pre-ordains all the subsequent cascade stereochemistry (Scheme 8) and is controlled by the four-centre C–Pd/alkene transition state **34**, ease of coordination of the alkene and (presumably) tether length. The reaction then proceeds via a second four-centre transition state **35** to product. The initial cyclisation **34**→**35** places the CH_2PdX group on the *exo* face of a bowl shaped transition state minimising steric interactions. The second cyclisation affords **36**, which lacks the rotatable C–C bond necessary to effect a *syn* relationship between the Pd–C bond and the cyclopropyl 'a' bond in **36**.



Scheme 8.

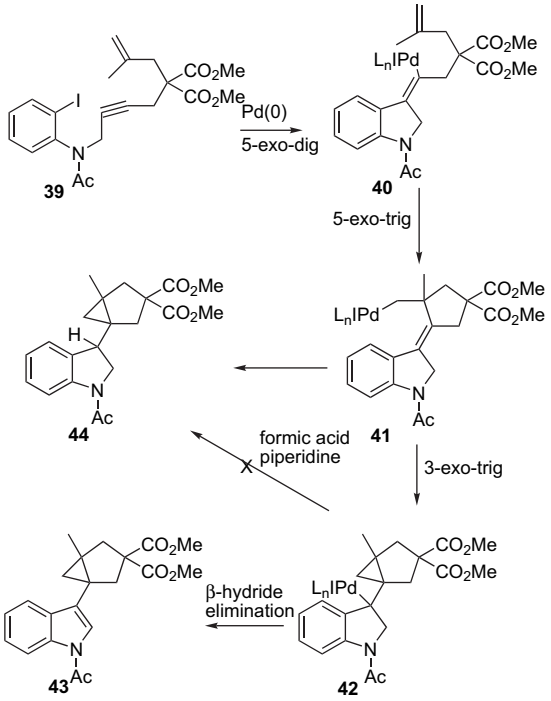
2.3. Tris-cyclisation cascades

Tris-cyclisation substrate **39** was prepared in two steps via sequential alkylation procedures in good yield (Scheme 9).



Scheme 9.

Under our standard palladium catalysed conditions **39** undergoes an initial 5-*exo-dig* cyclisation to give a vinyl palladium intermediate **40**, followed by a 5-*exo-trig* cyclisation process forming an alkyl palladium intermediate **41**, which then undergoes a 3-*exo-trig* cyclisation followed by β-hydride elimination to give **44** in 62% yield (Scheme 10).[3a] Addition of formic acid and piperidine as hydride ion source in place of Na_2CO_3 also afforded **44**. This indicates that all three cyclisation processes: 5-*exo-dig*, 5-*exo-trig* and 3-*exo-trig* are faster than hydride ion capture processes and also that β-hydride elimination **42**→**43** is faster than hydride ion capture e.g. **42**→**44**. This process results in formation of three rings, three C–C bonds, and two chiral tetrasubstituted C-centres.



Scheme 10.

3. Summary

We have demonstrated novel regio- and stereoselective palladium catalysed bis- and tris-cyclisation cascades allowing access to polyclic cyclopropyl carbo- and heterocycles, regio- and stereoselectively in good yields. The stability of the cyclopropyl products arises by suppression of the cyclopropylcarbinyl palladium(II) rearrangement due to lack of a rotatable C–C bond, which prevents a *syn* alignment between the Pd–C bond and the relevant cyclopropyl C–C bond. Related cyclisations[7–10] were reported subsequent to our preliminary communications.[3]

4. Experimental

4.1. General

Melting points were determined on a Reichert hot-stage apparatus and are uncorrected. Mass spectral data were obtained from a VG Autospec instrument operating at 70 eV (EI and FAB) or ZD 2000 electrospray instrument (ES). Accurate molecular masses were obtained from the EPSRC Swansea Mass Spectroscopy service using perfluorotributylamine or polyethylenimine as an internal standard. Microanalyses were obtained using a Carbo Erba MOD11016 instrument. IR spectra were determined on a Nicolet Magna FT-IR 560 spectrometer. The IR samples were prepared as thin films by evaporation of a solution of the compound in DCM onto a germanium plate. Nuclear magnetic resonance spectra were recorded on QE 300 and Bruker 400 instruments operating at, 300 and 400 MHz, respectively. Solvents

were dried according to established methods, unless purchased dry from Aldrich in sure-seal bottles. Palladium acetate was supplied by Johnson Matthey and used as received. The term ether refers to diethyl ether and the term petrol refers to the 40–60 °C boiling point fraction of petroleum ether.

4.2. General procedure for alkylation of 2-oxocycloalkane carboxylates

2-Methyl-4-iodo-1-butene (1 mmol) was added to a stirred solution of methyl 2-oxocycloalkane carboxylate (1 mmol) and KO^{t}Bu (1 mmol) in Bu^{t}OH (10 ml). The solution was slowly heated to boiling and maintained under reflux for 19 h. After cooling, the mixture was treated with water to dissolve precipitated salts and extracted with ether (3×25 ml). The combined ether extracts were washed with saturated brine, dried ($MgSO_4$) and evaporated in vacuo to leave an oil, which was purified by column chromatography or kugelrohr distillation.

4.2.1. Methyl 1-(3-methyl-3-butenyl)-2-oxocyclopentane carboxylate (2a). 2-Methyl-4-iodo-1-butene (6.89 g, 35 mmol), methyl 2-oxocyclopentane carboxylate (5.0 g, 35 mmol) and 1 M potassium *tert*-butoxide in *tert*-butanol (42 ml) were reacted by the general method. Workup in the usual way followed by distillation afforded the product (6.0 g, 81%) as a colourless oil, bp 77–79 °C/0.03 mmHg. Found: C, 68.35; H, 8.40; $C_{12}H_{18}O_3$ requires C, 68.55; H, 8.50%; δ_H: 1.75 (s, 3H, Me), 1.91–2.30 (m, 10H, 5×CH_2), 3.75 (s, 3H, OMe), 4.70 (s, 2H, =CH_2); *m*/*z* (%): 210 (M^+, 1), 151 (4), 142 (100), 110 (89), 55 (36) and 41 (28); ν_{max}: 1770, 1680, 1485, 1280, 1190 and 930 cm^{-1}.

4.2.2. 1-(3-Methyl-3-butenyl)-1-methoxycarbonyl-2-cyclopentenol triflate (3a). *n*-Butyllithium (19.64 ml, 1.6 M solution in hexane, 0.03 mol) was added slowly via a syringe to a stirred solution of diisopropylamine (4.4 ml, 0.031 mol) in freshly distilled THF (10 ml) while maintaining the temperature between −30 and −20 °C. The resulting solution was stirred at that temperature for 0.5 h. Compound **2a** (6 g, 0.028 mol) in THF (10 ml) was added dropwise at −78 °C and the resulting solution stirred at −78 °C for 1 h. *N*-(5-Chloro-2-pyridyl)triflimide (12.3 g, 0.031 mol) in THF (15 ml) was then added dropwise at −78 °C and the resulting solution maintained at that temperature for 3 h. After allowing the reaction mixture to come to room temperature, water was added, the mixture extracted with ether, washed with 10% NaOH and the organic extracts dried ($MgSO_4$) and evaporated. The residual oil was distilled under vacuum to afford the product (7.5 g, 77%) as a colourless oil, bp 82–85 °C/0.03 mmHg. Found: C, 45.80; H, 5.00; S, 9.50; F, 16.60; $C_{13}H_{17}F_3O_5S$ requires: C, 45.60; H, 4.95; S, 9.35; F, 16.65%; δ_H: 1.72 (s, 3H, Me), 1.92–2.54 (m, 8H, 4×CH_2), 3.72 (s, 3H, OMe), 4.75 (d, 2H, *J* 10 Hz, =CH_2), 5.78 (s, 1H, CH=C); *m*/*z* (%): 342 (M^+, 1), 273 (100), 149 (7), 133 (50), 108 (94), 69 (80), 55 (47) and 41 (56); ν_{max} (film): 2880, 1700, 1610, 1380, 1200, 1190 and 820 cm^{-1}.

4.2.3. 1-(3-Methyl-3-butenyl)-1-ethoxycarbonyl-2-cyclohexenol triflate (3b). *n*-Butyllithium (14.44 ml, 1.6 M solution in hexane, 0.023 mol) was added slowly via a syringe to a stirred solution of diisopropylamine (3.23 ml, 0.023 mol) in THF (10 ml) while maintaining the temperature between −30 and −20 °C. The resulting solution was stirred at that temperature for 0.5 h. Compound **2b** (5 g, 0.02 mol) in THF (10 ml) was added dropwise at −78 °C and the solution was stirred at −78 °C for 1 h. *N*-(5-Chloro-2-pyridyl)triflimide (8.24 g, 0.02 mol) in THF (15 ml) was then added dropwise at −78 °C and the resulting mixture maintained at −78 °C for 3 h. The solvent was then removed under reduced pressure and the residue partitioned between water (100 ml) and dichloromethane (150 ml). The water layer was extracted with dichloromethane (100 ml) and the combined dichloromethane extracts dried ($MgSO_4$) and evaporated. The residue was purified by flash chromatography (SiO_2) eluting with 1:1 v/v ether–petroleum ether to afford the product (6.5 g, 83%) as a pale yellow oil, bp 96–102 °C/0.02 mmHg. Found: C, 48.75; H, 5.70; S, 8.60; F, 15.25; $C_{15}H_{21}F_3O_5S$ requires: C, 48.65; H, 5.65; S, 8.65; F, 15.4%; δ_H: 1.27 (t, 3H, *J* 6 Hz, Me), 1.73 (s, 3H, =CMe), 1.31–2.47 (m, 10H, 5×CH_2), 4.23 (m, 2H, OCH_2), 4.71 (m, 2H, =CH_2) and 5.91 (m, 1H, =CH); *m*/*z* (%): 370 (M^+, 1), 325 (5), 302 (100), 221 (11), 69 (93), 55 (63) and 41 (47); ν_{max} (film): 1735, 1425, 1220, 1150, 1100, 1040, 920, 840 and 775 cm^{-1}.

4.2.4. Methyl 1-(3-methyl-3-butenyl)-2-oxocycloheptane carboxylate (2c). Prepared from 2-methyl-4-iodo-1-butene (12.6 g, 0.06 mol) and methyl 2-oxocycloheptane carboxylate (10 g, 0.058 mol) in 1 M potassium *tert*-butoxide in *tert*-butanol (70 ml) by the general procedure. The yellow solution was heated slowly to reflux and maintained there for 19 h. The solvent was then removed under reduced pressure and the residue partitioned between water (150 ml) and dichloromethane (200 ml). The water layer was extracted with dichloromethane (100 ml) and the combined dichloromethane extracts dried ($MgSO_4$) and evaporated. The residue was purified by flash chromatography (SiO_2) eluting with 1:4 v/v ether–petroleum ether to afford the product (12.2 g, 87%) as a colourless oil, bp 90–93 °C/0.03 mmHg. Found: C, 70.35; H, 9.20; $C_{14}H_{22}O_3$ requires: C, 70.60; H, 9.25%; δ_H: 1.72 (s, 3H, Me), 1.43–2.61 (m, 14H, 7×CH_2), 3.71 (s, 3H, OMe), 4.70 (m, 2H, =CH_2); *m*/*z* (%): 238 (M^+, 1), 207 (5), 170 (100), 138 (95), 110 (37) and 55 (18); ν_{max} (film): 2900, 1730, 1450, 1220 and 910 cm^{-1}.

4.2.5. 1-(3-Methyl-3-butenyl)-1-methoxycarbonyl-2-cycloheptenol triflate (3c). *n*-Butyllithium (28.9 ml, 1.6 M solution in hexane, 0.046 mol) was added slowly via a syringe to a stirred solution of diisopropylamine (6.46 ml, 0.046 mol) in THF (15 ml) while maintaining the temperature between −30 and −20 °C and stirring continued at this temperature for a further 0.5 h. Compound **2c** (10 g, 0.04 mol) in THF (10 ml) was then added dropwise at −78 °C, and the solution was stirred at −78 °C for 1 h. *N*-(5-Chloro-2-pyridyl)triflimide (16.48 g, 0.04 mol) in THF (15 ml) was added dropwise at −78 °C and the resulting mixture maintained at −78 °C for 3 h. The solvent was then removed under reduced pressure and the residue partitioned between water (200 ml) and dichloromethane (240 ml). The water layer was extracted with dichloromethane (100 ml) and the combined dichloromethane extracts dried ($MgSO_4$) and evaporated. The residue was purified by flash chromatography (SiO_2) eluting with 1:16 v/v ether–petroleum ether to afford the product (12.8 g, 81%)

as a pale yellow oil, bp 102–104 °C/0.02 mmHg. Found: C, 48.50; H, 5.65; S, 8.70; F, 15.10; $C_{15}H_{21}F_3O_5S$ requires: C, 48.65; H, 5.65; S, 8.65; F, 15.40%; δ_H: 1.70 (s, 3H, Me), 1.88–2.18 (m, 12H, 6×CH_2), 3.75 (s, 3H, OMe), 4.7 (m, 2H, C=CH_2), 6.01 (m, 1H, =CH); *m/z* (%): 370 (M^+, 1), 302 (51), 152 (77), 69 (100) and 55 (43); ν_{max} (film): 3300, 2900, 1740, 1410, 1210, 1170, 1000 and 890 cm^{-1}.

4.2.6. Methyl 1a-methyl-1,1a,2,3-tetrahydrocyclopropa[*c*]pentalene-3a(4*H*)-carboxylate (4). Enol triflate **2a** (0.3 g, 0.87 mmol) was added to a stirred suspension of $Pd(OAc)_2$ (0.019 g, 0.087 mmol), PPh_3 (0.046 g, 0.175 mmol), Na_2CO_3 (0.185 g, 1.75 mmol) and Et_4NCl (0.145 g, 0.87 mmol) in acetonitrile (8 ml). The resulting mixture was boiled under reflux under a nitrogen atmosphere for 8 h. The solvent was then removed under reduced pressure and the residue partitioned between water (50 ml) and dichloromethane (50 ml). The water layer was extracted with dichloromethane (50 ml) and the combined dichloromethane extracts dried ($MgSO_4$) and evaporated. The residue was purified by flash chromatography (SiO_2) eluting with 1:16 v/v ether–petroleum ether to afford the product (0.15 g, 89%) as a colourless oil; δ_H: 0.95 and 1.00 (2×d, 2×1H, *J* 6 Hz, cyclopropyl H), 1.08 (s, 3H, Me), 1.80–2.14 (m, 4H, 2×CH_2), 2.36 and 2.92 (2×d, 2×1H, *J* 16 Hz, CH_2), 3.54 (s, 3H, OMe), 5.43 and 5.75 (2×m, 2×1H, 2×=CH); *m/z* (%): 192 (M^+, 15), 133 (100), 115 (16), 91 (49) and 39 (19); ν_{max} (film): 1720, 1600, 1445, 1380, 1300, 1260, 1200, 1080, 800 and 735 cm^{-1}.

4.2.7. (1a-Methyl-1,1a,2,3-tetrahydro-cyclopropa[*c*]pentalen-3a(4*H*)-yl) methanol (5). Compound **4** (0.15 g, 0.781 mmol), in dry ether (9 ml) was added dropwise to the stirred suspension of $LiAlH_4$ (0.03 g, 0.781 mmol) in ether (6 ml). The resulting suspension was boiled under reflux for 2 h, cooled and the excess $LiAlH_4$ decomposed by successive addition of H_2O (1 ml), 15% NaOH (1 ml) and H_2O (2 ml). After the addition was complete, the solution was stirred for 1 h, filtered and the precipitate washed with ether (2×20 ml). The combined ether layers were dried ($MgSO_4$), concentrated in vacuo and the residue purified by column chromatography eluting with 1:2 v/v ether–petroleum ether to afford the product (0.102 g, 80%) as a colourless oil. Found: C, 80.50; H, 10.00; $C_{11}H_{16}O$ requires: C, 80.50; H, 9.75%; δ_H: 0.821 and 0.952 (2×d, 2×1H, *J* 6 Hz, cyclopropyl H), 1.06 (s, 3H, Me), 1.30–1.84 (m, 5H, 2×CH_2 and OH), 2.28 and 2.43 (2×d, 2H, *J* 16 Hz, CH_2), 3.41 and 3.49 (2×d, 2H, *J* 10 Hz, OCH_2) and 5.49 and 5.75 (2×br s, 2×1H, =CH_2); *m/z* (%): 164 (M^+, 8), 133 (100), 105 (50), 91 (61), 79 (16), 55 (14) and 41 (17); ν_{max} (film): 3475, 1730, 1485, 1290, 1180 and 760 cm^{-1}.

4.2.8. Ethyl 1a-methyl-1,1a,2,3,4,5-hexahydro-3a*H*-cyclopropa[*c*]indene-3a-carboxylate (7). Enol triflate **3b** (0.3 g, 0.81 mmol) was added to a suspension of $Pd(OAc)_2$ (0.018 g, 0.081 mmol), PPh_3 (0.042 g, 0.l62 mmol), Na_2CO_3 (0.171 g, 1.62 mmol) and Et_4NCl (0.134 g, 0.81 mmol) in acetonitrile (8 ml). The resulting mixture was boiled under reflux under a nitrogen atmosphere for 8 h. The solvent was then removed under reduced pressure and the residue partitioned between water (60 ml) and dichloromethane (60 ml). The water layer was extracted with dichloromethane (60 ml) and the combined dichloromethane extracts dried ($MgSO_4$) and evaporated. The residue was purified by flash chromatography (SiO_2) eluting with 1:16 v/v ether–petroleum ether to afford the product (0.12 g, 71%) as a colourless oil. Found: C, 76.20; H, 9.15; $C_{14}H_{20}O_2$ requires: C, 76.35; H, 9.10%; δ_H: 0.52 (d, 1H, *J* 6 Hz, cyclopropyl H), 1.03 (s, 3H, Me), 1.21 (t, 3H, *J* 6 Hz, Me), 1.23–2.07 (m, 9H, 4×CH_2 and cyclopropyl H), 4.05 (m, 2H, OCH_2), 5.23 and 5.72 (2×m, 2×1H, 2×=CH); *m/z* (%): 220 (M^+, 3), 147 (100), 131 (31), 105 (61) and 91 (62); ν_{max} (film): 2900, 1740, 1650, 1460, 1400, 1380, 1280, 1200, 1090, 1050, 975 and 700 cm^{-1}.

4.2.9. (1a-Methyl-1,1a,2,3,4,5-hexahydro-3a-cyclopropa[*c*]inden-3a-yl) methanol (8). Compound **7** (0.1 g, 0.454 mmol) in dry ether (8 ml) was added dropwise to a stirred suspension of $LiAlH_4$ (0.018 g, 0.454 mmol) in ether (8 ml). The resulting suspension was boiled under reflux for 2 h, cooled and the excess $LiAlH_4$ destroyed by successive addition of H_2O (1 ml), 15% NaOH (1 ml) and H_2O (2 ml). After the addition was complete, the solution was stirred for 1 h, filtered and the precipitate washed with ether (2×15 ml). The combined ether layers were dried ($MgSO_4$), concentrated in vacuo and the residue purified by column chromatography eluting with 1:4 v/v ether–petroleum ether to afford the product (0.063 g, 78%) as a colourless oil. Found: C, 81.00; H, 10.20; $C_{12}H_{18}O$ requires: C, 80.90; H, 10.10%; δ_H: 0.35 and 1.02 (2×d, 2×1H, *J* 5 Hz, cyclopropyl H), 1.16 (s, 3H, Me), 1.30–2.12 (m, 9H, 4×CH_2 and OH), 3.46 and 3.75 (2×d, 2H, *J* 10 Hz, OCH_2), 5.19 and 5.23 (2×br s, 2×1H, CH=CH); *m/z* (%): 178 (M^+, 9), 147 (100), 117 (27), 105 (43), 91 (64), 77 (18) and 41 (16); ν_{max} (film): 3330, 1480, 1390, 1045 and 940 cm^{-1}.

4.2.10. Methyl 1a-methyl-1,1a,2,3,5,6-hexahydrocyclopropa[*c*]azulene-3a(4a*H*)-carboxylate (9). (a) Enol triflate **3c** (0.2 g, 0.54 mmol) was added to a suspension of $Pd(OAc)_2$ (0.012 g, 0.054 mmol), PPh_3 (0.028 g, 0.l08 mmol), Na_2CO_3 (0.114 g, 1.08 mmol) and Et_4NCl (0.089 g, 0.54 mmol) in acetonitrile (6 ml). The resulting mixture was boiled under reflux under a nitrogen atmosphere for 9 h. The solvent was then removed under reduced pressure and the residue partitioned between water (50 ml) and dichloromethane (50 ml). The water layer was extracted with dichloromethane (60 ml) and the combined dichloromethane extracts dried ($MgSO_4$) and evaporated. The residue was purified by flash chromatography (SiO_2), eluting with 1:16 v/v ether–petroleum ether, to afford **9** (0.035 g, 30%), and a 1:1 mixture of **10** and **11** (0.053 g, 45%) as colourless oils. Found (mixed isomers): C, 76.20; H, 9.15; $C_{14}H_{20}O_2$ requires: C, 76.35; H, 9.05%; **9** δ_H: (500 MHz): 0.42 and 1.00 (2×d, 2×1H, *J* 5.0 Hz, cyclopropyl H), 1.14 (s, 3H, Me), 1.5–2.2 (m, 10H, 5×CH_2), 3.68 (s, 3H, OMe), 5.10 (dd, 1H, *J* 12.0, 2.6 Hz, =CH) and 5.7 (ddd, 1H, *J* 12.0, 6.8, 3.0 Hz, =CH); **10** and **11** (1:1 mixture) δ_H: 0.02 and 0.73 (2×d, 2H, *J* 5 Hz, cyclopropyl H), 0.08 and 0.54 (2×d, 2H, *J* 5 Hz, cyclopropyl H), 1.12 and 1.23 (2×s, 6H, 2×Me), 1.43–2.42 (m, 20H, 10×CH_2), 3.16 (d, 1H, *J* 3 Hz, =CH), 3.64 and 3.65 (2×s, 6H, 2×OMe), 5.63 (m, 2H, HC=CH), 5.98 (m, 1H, =CH); *m/z* (%): 220 (M^+, 22), 161 (100), 160 (50), 145 (42), 105 (95) and 77 (17); ν_{max} (film): 1730, 1650, 1450, 1250, 1200, 1110, 1080, 1020 and 840 cm^{-1}.

(b) Repeating the reaction but with a reaction time of 5 h and the addition of TlOAc (0.315 g, 1.2 mmol) afforded **9** (76%) as the sole product.

4.2.11. Methyl 1-(3-methyl-3-butenyl)-2-tetralone-1-carboxylate (12). 2-Methyl-4 iodo-1-butene (2.05 g, 10.7 mmol) was added to a stirred solution of 1-carbomethoxy-2-tetralone (2 g, 9.8 mmol) and KO^{t}Bu (1.21 g, 10.7 mmol in 1 M solution of ^{t}BuOH). The pale yellow solution was boiled under reflux for 10 h, cooled, water added to dissolve the precipitate and extracted with ether (3×20 ml). The combined ether extracts were washed with saturated brine (50 ml), dried ($MgSO_4$) and evaporated in vacuum to leave an oil, which was distilled under reduced pressure to afford the product (1.5 g, 57%) as a colourless oil, bp 120–122 °C/0.01 mmHg. Found: C, 74.75; H, 7.60; $C_{17}H_{20}O_3$ requires: C, 75.00; H, 7.35%; δ_H: 1.61 (s, 3H, Me), 2.29–3.19 (m, 8H, 4×CH_2), 3.6 (s, 3H, OMe), 4.60 and 4.46 (2×s, 2×1H, =CH_2), 7.21–7.24 (m, 4H, ArH); *m*/*z* (%): 272 (M^+, 1), 204 (46), 172 (100), 129 (22), 115 (34), 77 (6) and 65 (3); ν_{max} (film): 1780, 1700, 1550, 1505, 1440, 1410, 1370, 1280, 1140 and 960 cm^{-1}.

4.2.12. Methyl 1-(3-methylbut-3-enyl)-2-trifluoromethylsulfonyloxy-1,4-dihydronaphthalene-1-carboxylate (12). 1-Carbomethoxy-1-(3-methylbut-3-enyl)-2-tetralone (1.15 g, 4.2 mmol) in THF (8 ml) was added dropwise at −78 °C to a stirred solution of lithium diisopropylamide [from *n*-BuLi (3.17 ml, 1.6 M solution in hexane, 5.0 mmol) and diisopropylamine (0.71 ml, 5.0 mmol)] in THF (10 ml). The resulting solution was stirred at −78 °C for 1 h and *N*-(5-chloro-2-pyridyl)triflimide (1.74 g, 4.86 mmol) in THF (10 ml) was then added dropwise with stirring and the resulting mixture stirred at −78 °C for 3 h. The solvent was then removed under reduced pressure and the residue partitioned between water (100 ml) and dichloromethane (150 ml). The water layer was extracted with dichloromethane (100 ml), the combined dichloromethane extracts dried ($MgSO_4$) and evaporated. The residue was purified by flash chromatography (SiO_2) eluting with 1:4 v/v ether–petroleum ether to afford the product (1.1 g, 65%) as a colourless oil. Found: C, 53.04; H, 4.70; S, 8.00; F, 14.30; $C_{18}H_{19}F_3O_5S$ requires: C, 53.45; H, 4.70; S, 7.90; F, 14.1%; δ_H: 1.44–2.27 (m, 6H, 3×CH_2), 1.63 and 3.70 (2×s, 2×3H, 2×Me), 4.62 and 4.65 (2×s, 2×1H, =CH_2), 6.23–6.26 (m, 1H, =CH), 7.19–7.33 (m, 4H, ArH); *m*/*z* (%): 404 (M^+, 1), 345 (4), 289 (100), 255 (12), 69 (69) and 41 (45); ν_{max} (film): 1780, 1450, 1270, 1175, 1060, 1000, 930, 840 and 740 cm^{-1}.

4.2.13. Methyl 7a-methyl-6b,7,7a,8-tetrahydrocyclopropa[3,4] cyclopenta[1,2-*a*] naphthalene (13). Enol triflate **12** (0.3 g, 0.742 mmol) was added to a stirred suspension of $Pd(OAc)_2$ (0.016 g, 0.074 mmol), PPh_3 (0.038 g, 0.148 mmol), Na_2CO_3 (0.157 g, 1.48 mmol) and Et_4NCl (0.122 g, 0.742 mmol) in CH_3CN (10 ml). The resulting mixture was boiled under reflux for 8 h. The solvent was then removed under reduced pressure and the residue partitioned between water (50 ml) and dichloromethane (50 ml). The water layer was extracted with dichloromethane (50 ml), the combined dichloromethane extracts dried ($MgSO_4$) and evaporated. The residue was subjected to flash chromatography (SiO_2) eluting with 1:4 v/v ether–petroleum ether to afford a solid, which was crystallised from ether–petroleum ether to give the product (0.17 g, 90%) as colourless prisms, mp 59–61 °C. Found: C, 80.35; H, 7.15; $C_{17}H_{18}O_2$ requires: C, 80.30; H, 7.10%; δ_H: 0.77 and 1.25 (2×d, 2×1H, *J* 5 Hz, cyclopropyl H), 1.11 (s, 3H, Me), 1.58–2.56 (m, 4H, 2×CH_2), 3.58 (s, 3H, OMe), 5.59 and 6.53 (2×d, 2×1H, *J* 9 Hz, =CH), 7.08–7.35 (m, 4H, ArH); *m*/*z* (%): 254 (M^+, 12), 195 (100), 179 (32), 165 (37) and 77 (3); ν_{max} (film): 750, 1500, 1410, 1260 and 750 cm^{-1}.

4.2.14. (6a-Methyl-5,6,6a,7-tetrahydro-4b*H*-cyclopropa[2,3] cyclopenta[1,2-*a*] naphthalen-4b-yl) methanol (14). Compound **13** (0.045 g, 0.177 mmol) in dry ether (8 ml) was added dropwise to a stirred suspension of $LiAlH_4$ (0.0068 g, 0.177 mmol) in ether (6 ml). The resulting suspension was boiled under reflux for 2 h, cooled, and the excess $LiAlH_4$ destroyed by careful successive addition of H_2O (0.5 ml), 15% NaOH (0.5 ml) and H_2O (1 ml). After the addition was complete, the solution was stirred for 1 h, filtered and the precipitate washed with ether (2×20 ml). The combined ether layers were dried ($MgSO_4$), concentrated in vacuo and the residue subjected to column chromatography eluting with 1:8 v/v ether–petroleum ether to afford the product (0.033 g, 82%) as a colourless oil. Found: 226.1355; $C_{16}H_{18}O$ requires: 226.1357; δ_H: 0.78 and 1.42 (2×d, 2H, *J* 5 and 4 Hz, cyclopropyl H), 1.26 (s, 3H, Me), 1.5–2.48 (m, 5H, 2×CH_2+OH), 3.64 and 3.75 (2×d, 2H, *J* 11 Hz, OCH_2), 5.70 and 6.67 (2×d, 2H, *J* 9 Hz, 2×=CH), 7.25–7.45 (m, 4H, ArH); *m*/*z* (%): 226 (M^+, 25), 195 (100), 77 (8), 65 (4) and 43 (4).

4.2.15. Methyl 1-acetyl-3-(3-methyl-3-butenyl)-4-oxopiperidine-3-carboxylate (15). Methyl 1-acetyl-4-oxopiperidine-3-carboxylate (2.00 g, 10.05 mmol) was added to a stirred solution of KO^{t}Bu (1.17 g, 10.42 mmol) in DMSO (20 ml). The resulting solution was stirred at room temperature for 1 h, when 2-methyl-4-iodo-1-butene (2.00 g, 10.2 mmol) was added and stirring continued at room temperature for a further 14 h. The solution was then diluted with water (30 ml) and extracted with EtOAc (3×30 ml). The combined ethyl acetate extracts were washed with saturated brine (50 ml), dried ($MgSO_4$) and evaporated under reduced pressure. The residual oil was purified by column chromatography (SiO_2) eluting with 10:1 v/v ether–petroleum ether to afford the product (1.25 g, 46%) as a pale yellow oil. Found: C, 62.70; H, 8.05; N, 5.25; $C_{14}H_{21}NO_4$ requires: C, 62.90; H, 7.90; N, 5.25%; δ_H: 1.61–2.37 (m, 10H, 5×CH_2), 1.65 (s, 3H, =CMe), 2.18 (s, 3H, COMe), 3.49 (s, 3H, OMe), 4.8 (s, 2H, =CH_2); *m*/*z* (%): 267 (M^+, 4), 239 (27), 199 (78), 69 (36), 55 (51) and 43 (100); ν_{max} (film): 2800, 1720, 1690, 1500, 1410 and 1290 cm^{-1}.

4.2.16. Methyl 1-acetyl-3-(3-methyl-3-butenyl)-4-trifluoromethylsulfonyloxy piperidine-3-carboxylate (16). Compound **15** (0.2 g, 0.75 mmol) in THF (5 ml) was added dropwise to a suspension of NaH (0.043 g, 1.8 mmol) in freshly distilled THF (10 ml) at 0 °C. The resulting mixture was allowed to warm to room temperature and then $PhNTf_2$ (0.28 g, 0.786 mmol) in THF (6 ml) was added dropwise and the mixture heated at 60 °C for 8 h. The solvent was then removed under reduced pressure and the residue partitioned between water (50 ml) and dichloromethane (50 ml). The water layer was extracted with dichloromethane (50 ml)

and the combined dichloromethane extracts dried ($MgSO_4$) and evaporated. The residue was purified by flash chromatography (SiO_2) eluting with 1:8 v/v ether–petroleum ether to afford the product (0.19 g, 64%) as a colourless oil. Accurate mass: 399.0961; $C_{15}H_{20}F_3N0_6S$ requires: 399.0963; δ_H: 1.11–4.3 (m, 8H, 4×CH_2), 1.66 (s, 3H, =CMe), 2.16 (s, 3H, COMe), 3.69 (s, 3H, CO_2Me), 4.63 and 4.7 (2×s, 2H, =CH_2), 5.8 (br s, 1H, =CH); *m/z* (%): 399 (M^+, 7), 368 (12), 331 (40), 266 (76), 198 (47), 166 (100), 69 (72) and 43 (83); ν_{max} (film): 3400, 1800, 1700, 1480, 1260, 1200, 1140 and 930 cm^{-1}.

4.2.17. Methyl 2-acetyl-5a-methyl-1,2,5,5a,6,7-hexahydro-7a*H*-cyclopropa[2,3] cyclopenta[1,2-*c*] pyridine-7a carboxylate (17). The enol triflate **16** (0.13 g, 0.325 mmol) was added to a stirred suspension of $Pd(OAc)_2$ (0.007 g, 0.0325 mmol), PPh_3 (0.017 g, 0.065 mmol), Na_2CO_3 (0.069 g, 0.651 mmol) and Et_4NCl (0.053 g, 0.325 mmol) in CH_3CN (8 ml). The resulting mixture was stirred and boiled under reflux for 8 h. Standard workup followed by column chromatography eluting with 4:1 v/v ether–petroleum ether afforded the product (0.05 g, 62%) as a colourless oil. Found: C, 67.50; H, 7.80; N, 5.50; $C_{14}H_{19}NO_3$ requires: C, 67.50; H, 7.65; N, 5.60%; δ_H: 0.6 and 1.2 (d, 2H, *J* 5 Hz, cyclopropyl H), 1.12 (s, 3H, Me), 1.1–1.8 (m, 6H, 3×CH_2), 2.02 (s, 3H, COMe), 3.63 (s, 3H, OMe) and 6.62 and 7.27 (2×m, 2×H, 2×=CH); *m/z* (%): 249 (M^+, 33), 206 (93), 189 (77), 146 (100) and 43 (57); ν_{max} (film): 1720, 1450, 1375, 1250, 1110, 1080 and 1040 cm^{-1}.

4.2.18. 2-Bromocyclohex-2-en-1-yl 2-methylprop-2-en-1-yl ether (18). 2-Methyl-2-propen-1-ol (0.546 g, 7.57 mmol) in THF (5 ml) was added to a stirred suspension of NaH (0.45 g, 60% dispersion in oil, 9 mmol) in freshly distilled THF (10 ml) at 0 °C and stirring continued for 1 h at room temperature. 2,3-Dibromocyclohexene (2 g, 8.7 mmol) was then added and stirring continued for a further 8 h at room temperature at which time the solvent was removed under reduced pressure and the residue partitioned between water (50 ml) and dichloromethane (50 ml). The water layer was extracted with dichloromethane (50 ml) and the combined dichloromethane extracts dried ($MgSO_4$) and evaporated. The residue was distilled under reduced pressure to afford the product (1.2 g, 68%) as a colourless oil, bp 62–65 °C/0.25 mmHg. Accurate mass: 230.0305; $C_{10}H_{15}BrO$ requires: 230.0306; δ_H: 1.50–2.05 (m, 6H, 3×CH_2), 1.74 (s, 3H, Me), 3.79 (br s, 1H, OCH), 3.98 (m, 2H, OCH_2), 4.82 and 4.94 (2×s, 2×lH, =CH_2), 6.14–6.16 (m, 1H, =CH); *m/z* (%): 232 (M^+, 1), 230 (M^+, 1), 175 (31), 151 (35), 79 (100), 55 (34) and 41 (15); ν_{max} (film): 3200, 1670, 1470, 1350, 1100 and 910 cm^{-1}.

4.2.19. 1a-Methyl-1a,2,4,5-tetrahydro-1*H*,3a*H*-cyclopropa[*c*] [1] benzofuran (19). Vinyl bromide **18** (0.05 g, 0.216 mmol) was added to a stirred suspension of $PdC1_2(PPh_3)_2$ (0.015 g, 0.0216 mmol), Zn dust (0.028 g, 0.432 mmol) and Et_4NCl (0.035 g, 0.216 mmol) in CH_3CN (5 ml) and the resulting mixture was stirred and boiled under reflux for 2 h. Standard workup followed by column chromatography eluting with 1:4 v/v ether–petroleum ether afforded the product (0.016 g, 50%) as a colourless oil. Accurate mass: 150.1045; $C_{10}H_{14}O$ requires: 150.1044; δ_H: 0.529 and 0.964 (2×d, 2×1H, *J* 4.4 and 4.5 Hz, cyclopropyl H), 1.1 (s, 3H, Me), 1.43–2.13 (m, 4H, 2×CH_2), 3.61 and 3.72 (2×d, 2H, *J* 8.1 Hz, OCH_2), 3.87–3.93 (m, 1H, OCH), 5.15–5.19 (m, 1H, =CH), 5.69–5.72 (m, 1H, =CH); *m/z* (%): 150 (M^+, 34), 135 (27), 91 (100), 55 (23) and 41 (31); ν_{max} (film): 1750, 1500, 1090 and 740 cm^{-1}.

4.2.20. 6-(2-Acetylphenoxy)-l-bromocyclohexene. 2-Hydroxyacetophenone (1.8 g, 0.013 mol) in freshly distilled THF (15 ml) was added to a stirred suspension of NaH (0.634 g, 60% dispersion in oil, 0.013 mol) in freshly distilled THF (10 ml) at 0 °C. The resulting mixture was stirred for 1 h at room temperature when 2,3-dibromohexene (3.2 g, 0.013 mol) was added and the resulting mixture was boiled under reflux for 8 h. The solvent was then removed under reduced pressure and the residue partitioned between water (70 ml) and dichloromethane (100 ml). The water layer was extracted with dichloromethane (100 ml) and the combined dichloromethane layers dried ($MgSO_4$) and evaporated. The residue was distilled under reduced pressure to give the product (1.9 g, 49%) as a colourless oil, bp 140–148 °C/0.03 mmHg. Found: C, 56.90; H, 5.20; Br, 27.30; $C_{14}H_{15}BrO_2$ requires: C, 56.95; H, 5.05; Br, 27.10%; δ_H: 1.05–2.21 (m, 6H, 3×CH_2), 2.66 (s, 3H, COMe), 4.8 (br s, 1H, OCH), 6.39–6.41 (m, 1H, =CH), 6.95–7.75 (m, 4H, ArH); *m/z* (%): 296 (M^+, 2), 294 (M^+, 2), 215 (13), 160 (23), 121 (21), 79 (100) and 43 (22); ν_{max} (film): 2900, 1700, 1630, 1510, 1480, 1330, 1270, 1000 and 780 cm^{-1}.

4.2.21. 2-Bromocyclohex-2-en-1-yl 2-isopropenylphenyl ether (20). *n*-Butyllithium (5.16 ml, 1.6 M solution in hexane, 8.27 mmol) was added to a stirred suspension of methyltriphenylphosphonium bromide (2.95 g, 8.27 mmol) in ether (40 ml) under nitrogen and stirring continued at room temperature for an hour. 6-(2-Acetylphenoxy)-l-bromocyclohexene (1.22 g, 4.13 mmol) in ether (20 ml) was added dropwise over 30 min. The resulting mixture was stirred for 15 h, then diluted with water (20 ml) and extracted with ether (3×20 ml). The combined ether extracts were dried ($MgSO_4$), evaporated in vacuo and the residue distilled to afford the product (0.64 g, 53%) as colourless oil, bp 100–110 °C/0.02 mmHg. Found: C, 61.45; H, 5.85; Br, 27.30; $C_{15}H_{17}BrO$ requires: C, 61.45; H, 5.80; Br, 27.30%; δ_H: 1.65–2.03 (m, 6H, 3×CH_2), 2.06 (s, 3H, Me), 4.69 (br s, 1H, CH), 4.96, 5.02 (2×s, 2×1H, =CH_2), 6.26 (m, 1H, =CH) and 6.84–7.14 (m, 4H, ArH); *m/z* (%): 294 (M^+, 3), 292 (M^+, 3), 213 (21), 134 (100), 91 (30) and 79 (93).

4.2.22. 10b-Methyl-1,5,5a,10b-tetrahydro-4*H*-cyclopropaxanthene (21). Vinyl bromide **20** (0.15 g, 0.508 mmol) was added to a stirred suspension of $Pd(OAc)_2$ (0.011 g, 0.0508 mmol), PPh_3 (0.026 g, 0.101 mmol) and TlOAc (0.162 g, 0.616 mmol) in CH_3CN (8 ml). The resulting mixture was stirred and boiled under reflux for 5 h. The solvent was then removed under reduced pressure and the residue partitioned between water (50 ml) and dichloromethane (50 ml). The water layer was extracted with dichloromethane (50 ml) and the combined dichloromethane extracts dried ($MgSO_4$) and evaporated. The residue was purified by flash chromatography (SiO_2) eluting with 1:2 v/v ether–petroleum ether to afford the product **21** (0.074 g, 76%) as a pale yellow oil. Accurate mass: 212.1209; $C_{15}H_{16}O$ requires: 212.1209; δ_H: 0.872 and 1.36 (2×d, 2H, *J* 5 Hz, cyclopropyl H), 1.40 (s, 3H, Me), 1.18–2.23 (m, 4H, 2×CH_2),

4.27 (m, 1H, OCH), 5.35 and 5.70 (2×m, 2×1H, 2×=CH), 6.70–7.24 (m, 4H, ArH); *m/z* (%): 212 (M^+, 21), 197 (42), 91 (18), 77 (13) and 32 (100); ν_{max} (film): 1620, 1505, 1470, 1240 and 770 cm^{-1}.

4.2.23. *N*-Acetyl-*N*-(2-bromocyclohex-2-enyl)-2-isopropenylaniline (23). *N*-Acetyl-2-isopropenylaniline (1.74 g, 0.01 mol) in freshly distilled THF (15 ml) was added to a stirred suspension of NaH (0.58 g, 0.0l2 mol, 60% dispersion in oil) in THF (10 ml) at 0 °C. The resulting mixture was stirred for 1 h at room temperature when 2,3-dibromocyclohexene (2.77 g, 0.011 mol) was added and stirring continued for further 8 h. The solvent was then removed under reduced pressure and the residue partitioned between water (100 ml) and dichloromethane (150 ml). The water layer was extracted with dichloromethane (100 ml) and the combined dichloromethane extracts dried ($MgSO_4$) and evaporated. The residual pale yellow solid was crystallised from ether–petroleum ether to give the product (2.32 g, 70%) as pale yellow prisms, mp 86–88 °C. Found: C, 61.00; H, 6.00; N, 4.05; Br, 24.10; $C_{17}H_{20}BrNO$ requires: C, 61.05; H, 5.95; N, 4.20; Br, 23.95%; δ_H: 1.15–2.08 (m, 6H, 3×CH_2), 1.80 (s, 3H, =CMe), 2.02 (s, 3H, COMe), 4.94 and 5.14 (2×s, 2×1H, =CH_2), 5.61–5.73 (m, 1H, NCH), 6.15–6.23 (m, 1H, =CH), 7.20–7.34 (m, 4H, ArH); *m/z* (%): 335 (M^+, 1), 333 (M^+, 1), 254 (100), 212 (12), 174 (17), 91 (51) and 43 (39); ν_{max} (Nujol): 3400, 3050, 1790, 1480, 1320, 1080 and 820 cm^{-1}.

4.2.24. 6-Acetyl-10b-methyl-1,4,5,5a,6,10b-hexahydrocyclopropa[1]acridine (24). Vinyl bromide **23** (0.05 g, 0.0149 mmol) was added to a stirred suspension of $PdCl_2(PPh_3)_2$ (0.01 g, 0.0149 mmol), Zn dust (0.019 g, 0.299 mmol) and Et_4NCl (0.024 g, 0.149 mmol) in CH_3CN (5 ml). The resulting mixture was stirred and boiled under reflux for 4 h. The solvent was then removed under reduced pressure and the residue partitioned between water (30 ml) and dichloromethane (30 ml). The water layer was extracted with dichloromethane (30 ml) and the combined dichloromethane layers dried ($MgSO_4$) and evaporated. The residue was purified by flash chromatography (SiO_2) eluting with 1:4 v/v ether–petroleum ether to afford the product (0.0275 g, 73%) as a pale yellow oil. Found: C, 80.65; H, 7.60; N, 5.25; $C_{17}H_{19}NO$ requires: C, 80.65; H, 7.50; N, 5.55%; δ_H: 0.96 and 1.36 (2×d, 2×1H, *J* 6 Hz, cyclopropyl H), 1.46 (s, 3H, Me), 2.14 (s, 3H, COMe), 1.1–2.4 (m, 4H, 2×CH_2), 5.10 and 5.49 (2×d, 2H, *J* 11 Hz, =CH), 5.75–5.8 (m, 1H, NCH), 6.95–7.43 (m, 4H, ArH); *m/z* (%): 253 (M^+, 35), 238 (7), 210 (61), 160 (100), 77 (19) and 43 (25); ν_{max} (Nujol): 3000, 1690, 1490, 1410 and 750 cm^{-1}.

4.2.25. Dimethyl 4-bromobut-2-ynyl-2-methylprop-2-enylmalonate (38). Dimethyl 2-methylprop-2-enylmalonate (9.31 g, 0.05 mol) was slowly added to a methanolic solution of sodium methoxide [prepared from Na (1.15 g) and absolute MeOH (25 ml)] and stirred the mixture at room temperature for 15 min. 1,4-Dibromobut-2-yne (12.71 g, 0.06 mol) was then added and stirring continued at room temperature for a further 16 h when water (25 ml) was added and the mixture extracted with ether (3×40 ml). The combined ether layers were washed with brine, dried over anhydrous $MgSO_4$ and evaporated. The residual oil was distilled to give the product as a pale yellow liquid (5.0 g, 32%), bp 105–110 °C/0.1 mmHg. Found: C, 49.30; H, 5.45; $C_{13}H_{17}BrO_4$ requires: C, 49.23; H, 5.40%; δ_H: 2.90, 2.83 and 1.66 (3×s, 2H, 2H and 3H, C=CCH_2, CH_2 and C=CCH_3), 3.75 and 3.88 (2×s, 2H and 3H, CH_2Br and OCH_3), 4.85 and 4.92 (2×d, 2×1H, *J* 1.3 Hz, C=CH_2); *m/z* (%): 319 and 317 (1.6), 177 (100), 145 (16), 117 (40), 59 (28); ν_{max} (film): 2237, 1735, 1434, 1276, 1206, 1183 cm^{-1}.

4.2.26. Dimethyl {4-[acetyl (2-iodophenyl) amino] but-2-yn-1-yl}(2-methylprop-2-en-1-yl) malonate (39). *n*-BuLi (4.2 ml of 1.6 M solution in hexane, 0.0066 mol) was added from a syringe to a cooled solution (0–4 °C) of *N*,*N*-diisopropylamine (0.84 ml, 0.006 mol) in dry THF (25 ml) under an atmosphere of N_2 and stirring and cooling continued for 15 min. The reaction mixture was then cooled to −60 °C, a solution of 2-iodoacetanilide (1.56 g, 0.006 mol) in dry THF (10 ml) was added and the mixture stirred at −60 °C for 15 min. A solution of **38** (1.903 g, 0.006 mol) in THF (5ml) was added next and the mixture allowed to warm to room temperature with stirring over 15 h. The mixture was then quenched with a saturated solution of NH_4Cl (20 ml) and extracted with ether (3×25 ml). The combined ether layers were dried over anhydrous $MgSO_4$, evaporated and the residue purified by flash column chromatography, eluting with 7:3 v/v ether–petroleum ether to give the product (1.44 g, 49%), which crystallised as colourless plates from ether–petroleum ether, mp 63–65 °C. Found: C, 50.60; H, 4.85; N, 2.70; I, 25.70; $C_{21}H_{24}INO_5$ requires: C, 50.70; H, 4.86; N, 2.82; I, 25.52%; δ_H: 1.52 and 1.71 (2×s, 2×3H, $COCH_3$ and C=CCH_3), 2.6 5 and 2.71 (2×s, 2×2H, 2×CH_2), 3.62 and 3.63 (2×s, 2×3H, 2×$COOCH_3$), 4.63 and 4.78 (2×s, 2×1H, C=CH_2), 3.70 and 4.96 (2×dd, 2×1H, *J* 17.2 and 2 Hz, NCH_2), 7.06 and 7.39 (2×m, 2H and 1H, ArH), 7.87 (dd, 1H, *J* 7.8 and 1.7 Hz, ArH); *m/z* (%): 497 (M^+, 42), 482 (50), 370 (22), 366 (92), 312 (25), 244 (100), 177 (28); 43; ν_{max} (KBr): 1736, 1666, 1469, 1280, 1206, 1194 cm^{-1}.

4.2.27. Dimethyl 1-(1-acetyl-1*H*-indol-3-yl)-5-methylbicyclo [3.1.0] hexane-3,3-dicarboxylate (43). A mixture of **39** (0.248 g, 0.0005 mol), $Pd(OAc)_2$ (0.011 g, 10 mol %), PPh_3 (0.026 g, 20 mol %), Na_2CO_3 (0.046 g, 0.0005 mol) and Et_4NCl (0.082 g, 0.0005 mol) in dry acetonitrile (7 ml) was heated at 70 °C for 0.5 h. The palladium residue was filtered off, the solvent evaporated, the residue dissolved in EtOAc (15 ml) and washed with water (15 ml). The organic layer was separated, dried over anhydrous $MgSO_4$ and evaporated to leave a brown solid, which was purified by preparative TLC, eluting with 3:2 v/v ether–petroleum ether to give the product (0.12 g, 65%) as a colourless solid, which became an amorphous pale yellow solid when exposed to air. Found: C, 66.85; H, 6.30; N, 3.45; $C_{21}H_{23}NO_5 \cdot 0.5H_2O$ requires: C, 66.65; H, 6.39; N, 3.70%; δ_H: 0.66 (br s, 2H, CH_2), 0.93 and 2.52 (2×s, 2×3H, $COCH_3$ and CH_3), 2.57 (d, 1H, *J* 13.7 Hz), 2.85 (m, 3H), 3.66 and 3.67 (2×s, 2×3H, 2×CH_3), 7.13 –7.29 (m, 2H, ArH), 7.50 and 8.34 (2×d, 2×lH, *J* 7.2 Hz, ArH); *m/z* (%): 369 (M^+, 100), 327 (25), 250 (29), 208 (70), 49 (57), 47 (43), 43 (37).

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