A novel synthesis of 9-*cis*-retinoic acid and tagretin analogues via the Pauson–Khand or Heck reaction

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Abstract—The synthesis of a selection of compounds related to 9-*cis*-retinoic acid and tagretin is outlined. The methodology utilises the Pauson–Khand and Heck reaction as the key steps to prepare the intermediate aryl cyclopentenone regioisomers. © 2001 Elsevier Science Ltd. All rights reserved.

The retinoids are analogues of vitamin A, and are responsible for a variety of biological effects via activation of the retinoid family of receptors.[1] The retinoid receptors can be divided into two sub-families, the retinoic acid receptor (RAR), and the retinoid X receptor (RXR), with further sub-types (α, β, γ) also being found. As shown on Fig. 1 the endogenous ligands for these two receptor families are all-*trans*-retinoic acid (active on RAR) and 9-*cis*-retinoic acid (active on both RXR and RAR).
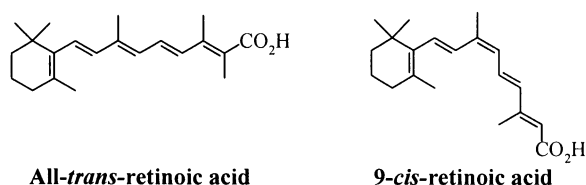

All-*trans*-retinoic acid   **9-*cis*-retinoic acid**

Figure 1.

Retinoid X receptors can form heterodimers with a variety of other nuclear receptors, including the peroxisome proliferator activated receptor (PPAR), the thyroid receptor and the orphan receptor LXR. The RXR:PPARγ heterodimer is a target in the search for compounds affecting glucose metabolism. It has been shown in vitro that ligands

selective either for RXR (rexinoids) or PPARγ (e.g. rosiglitazone) can independently activate this heterodimer and that, when they are used together, a synergistic response can be obtained.[2] This has increased the interest in RXR selective ligands, since it may provide a new or improved route to the treatment of diabetes.

During a research program in this area we were interested in preparing compounds that were both active and selective for the RXR, and ultimately the PPAR:RXR heterodimeric receptor complex. Compounds of the type shown below have been shown to bind selectively to RXR with only weak binding at RAR,[3,4] and in the case of LG 1069 (Tagretin), in vivo data has indicated anti-diabetic activity in ob/ob (obese) and db/db (diabetic) mice[2] (Fig. 2).

This paper deals with the preparation of a selection of compounds which combine in a novel way some of the structural features outlined above. The importance of the cyclopropyl or cyclopentyl ring as a potential bioisostere for the 8,9 double bond in 9-*cis*-retinoic acid has been demonstrated,[3,4] and our strategy relied on a route to the novel cyclopentenones **1** and **2** to provide suitable and versatile intermediates for further elaboration towards a series of analogues (Fig. 3). The route to these ring systems
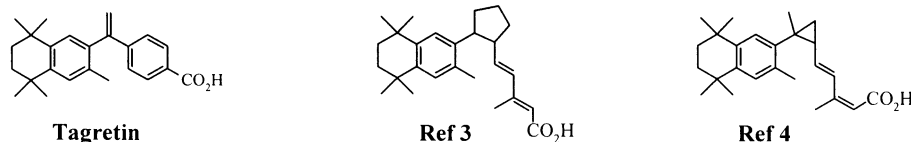

Tagretin   **Ref 3**   **Ref 4**
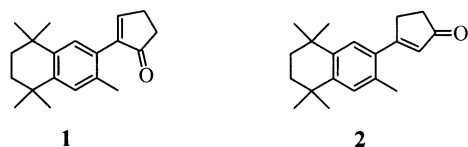
Figure 2.

Figure 3.

utilised Pauson–Khand and organopalladium coupling reactions, respectively, thus providing a convenient route to either regioisomer.

The aryl alkyne **3**, which could be prepared according to the literature procedure,[5] was treated with dicobalt octacarbonyl in petroleum ether to form the corresponding dicobalt hexacarbonyl–alkyne complex. This complex underwent intermolecular Pauson–Khand[6] reaction with ethylene using triethylamine-*N*-oxide dihydrate as the oxidative source.[7] In accordance with reactions of this type the more bulky group (the aryl moiety) is located alpha to the carbonyl moiety in the product giving cyclopentenone **1** as the sole regioisomer (Scheme 1).

It should be noted that the synthesis of **1** via Heck, Negishi or Stille coupling of the respective aryl-metal with 2-iodo-cyclopent-2-enone was also investigated. However, in each case the yields were poor (<20%) and the reactions generally not as clean.

The approach to the saturated cyclopentane required hydrogenation of enone **1** using platinum oxide, and reduction of the product with sodium borohydride gave the *cis*- alcohol **4a** (proton coupling observed between the benzylic hydrogen and the vicinal proton on hydroxy containing carbon) together with the corresponding *trans*-alcohol **4b**

(no coupling between these protons) in quantitative yield in a ratio of about 6:4. The isomers could be separated easily by flash chromatography and conversion of **4a** via Mitsunobo reaction with methyl 4-hydroxybenzoate (simplified coupling pattern of the proton at the tertiary centre consistent with inversion) and hydrolysis using potassium hydroxide gave the carboxylic acid **5**. The corresponding *trans*-isomer **4b** can be converted in a similar fashion.

The unsaturated analogue could be accessed via Luche reduction of **1**, providing the allylic alcohol **6**, which could again be coupled with methyl 4-hydroxybenzoate under Mitsunobo conditions to give the corresponding ester, which was further hydrolysed to give **7**.

Cyclopropanation of the alkene moiety of **1** was also investigated, and initially an attempt was made using dimethylsulphoxonium methyl ylide[8] but the enone was completely unreactive under these conditions. After extensive investigation it was found necessary to first prepare the allylic alcohol **6**, where the proximal alcohol moiety could then assist the cyclopropanation and counteract the detrimental presence of the bulky aryl group. It was found that upon reaction with diethylzinc and chloroiodomethane[9] the cyclopropyl alcohol could be prepared in moderate yield, and PCC oxidation of the resultant product gave the desired cyclopropyl ketone **8**. Horner–Emmons reaction using either *para* or *meta* diethyl-carbomethoxybenzyl phosphonate was found in each case to give a single isomeric product, which presumably due to steric constraints imposed by the methyl substituent on the aromatic ring completely favours formation of the *E*-isomer. In each case a small amount of transesterification of the methyl ester to an ethyl ester was observed, and this was generally
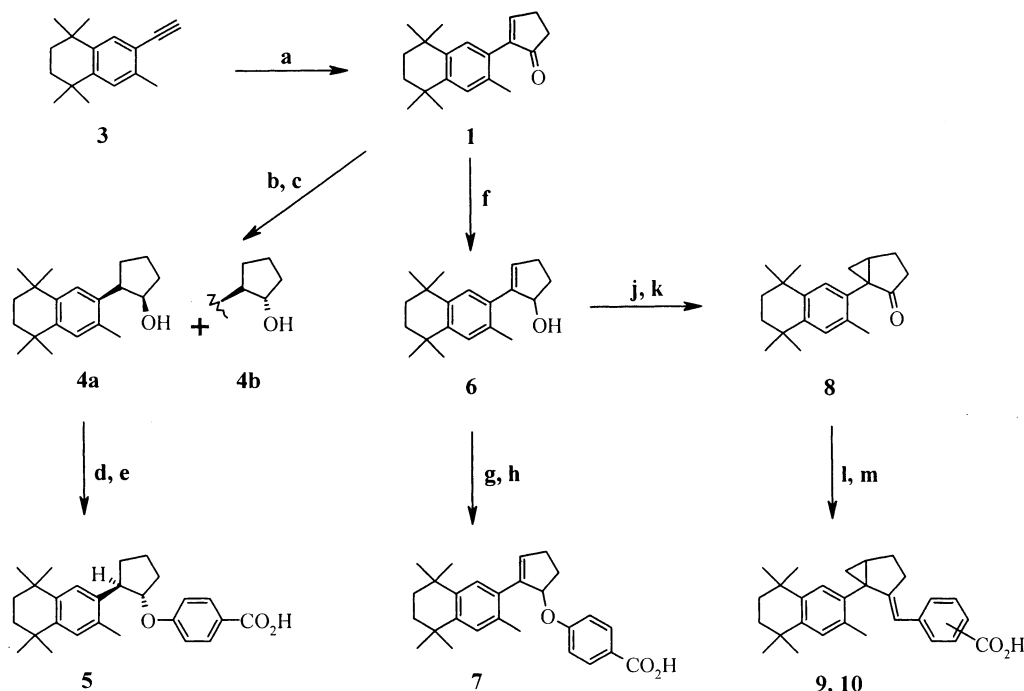
Scheme 1. *Reagents*: (a) i. Co₂(CO)₈, ii. ethylene, Me₃NO (42% over two steps); (b) 40 psi H₂, PtO₂ (78%); (c) NaBH₄ (58% *cis*, 42% *trans*); (d) HOC₆H₄CO₂CH₃, DEAD, Ph₃P (70%); (e) KOH, MeOH (79%); (f) NaBH₄, CeCl₃ (99%); (g) as for d (26%); (h) as for e (40%); (j) Et₂Zn, CH₂ICl (31%); (k) PCC (99%); (l) MeO₂CC₆H₄CH₂P(O)(OEt)₂, NaH, 15-crown-5 (*para* 60%, *meta* 75%); (m) as for d (*para* 80%, *meta* 51%).
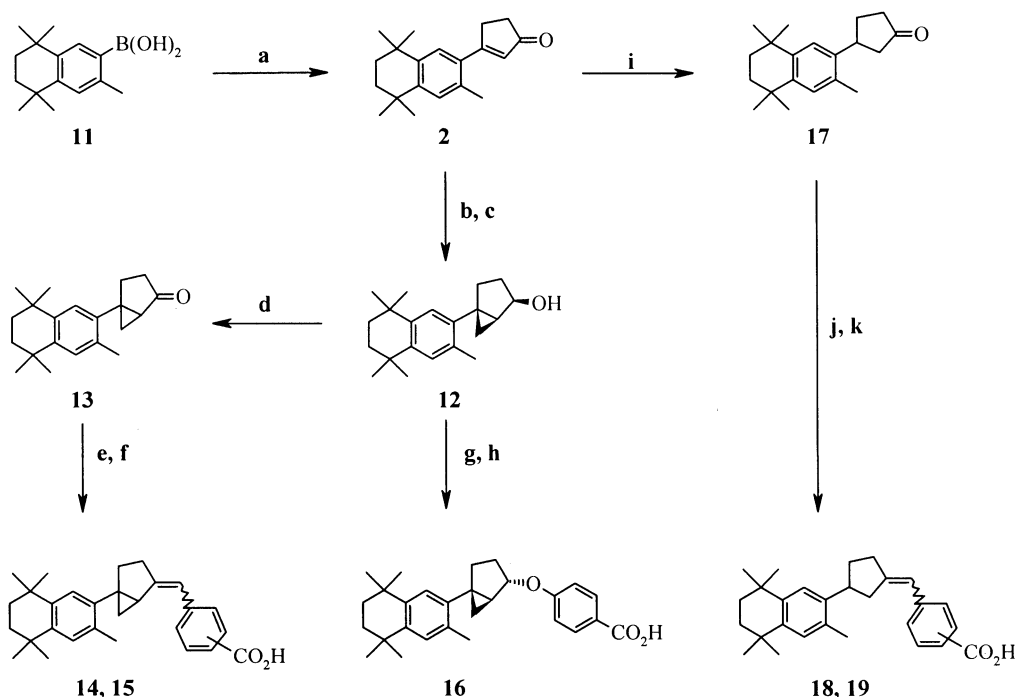
Scheme 2. *Reagents*: (a) i. PdCl$_2$(PPh$_3$)$_2$, NaOAc, 1-chlorocyclopent-1-en-3-one (65%); (b) NaBH$_4$, CeCl$_3$ (63%); (c) Et$_2$Zn, CHICl (49%); (d) PCC (97%); (e) MeO$_2$CC$_6$H$_4$CH$_2$P(O)(OEt)$_2$, NaH, 15-crown-5 (*para* 99%, *meta* 87%); (f) KOH, MeOH (*para* 75%, *meta* 57%); (g) HOC$_6$H$_4$CO$_2$CH$_3$, DEAD, Ph$_3$P (54%); (h) as for f (13%); (i) 40 psi H$_2$, PtO$_2$, KOAc (79%); (j) as for e (*para* 93%, *meta* 93%); (k) as for f (*para* 41%, *meta* 54%).

observed for the Horner–Emmons reactions described in this paper (see Section 2 for details), and may be due to some ethanol traces in the starting phosphonate (derived from an Arbuzov reaction). This was however only a transient problem since ester hydrolysis afforded the respective *para*- and *meta*- acids **9** and **10**.

The route to the regioisomeric cyclopentenone is shown in Scheme 2, and was achieved via Heck coupling of boronic acid **11** with 1-chlorocyclopent-1-en-3-one, providing **2** in 65% yield. A small amount of isomerisation of the double bond in **2** was also observed, however, the non-conjugated cyclopentenone could be readily reconverted to **2** simply by refluxing in benzene or toluene. Luche reduction gave the corresponding allylic alcohol, which was further converted to the cyclopropyl alcohol **12** (relative stereochemistry shown).

PCC oxidation of alcohol **12** to the corresponding cyclopropyl ketone **13** and Horner–Emmons hydrolysis as shown in Scheme 2 gave the respective *para*- or *meta*- *E*/*Z* aryl alkenes **14** and **15**. It proved very difficult to separate and thus define the stereochemistry of the respective *E* and *Z* compound mixtures in **14** or **15**, and only in the case of **14** a small amount of pure isomer (absolute stereochemistry not determined) could be obtained via recrystallisation. Alternatively, Mitsunobo coupling of **12** with methyl 4-hydroxybenzoate followed by ester hydrolysis gave the benzyl ether **16**.

Initial attempts to hydrogenate the enone double bond of **2** were unsuccessful, and surprisingly, conversion of this substrate was not as straightforward as anticipated. It was found that normal catalytic hydrogenation whilst providing

complete consumption of starting material gave, together with **17**, substantial amounts of a less polar by-product, resulting in poor and irreproducible reaction yields. It was thought that there could be some reduction of the ketone moiety occurring under the reaction conditions, and that the resultant allylic alcohol could be unstable especially in the presence of trace amounts of acid. We thought that base may inhibit this side reaction and it was found that by carrying out the hydrogenation in the presence of potassium acetate the desired ketone could be accessed in good yield. Finally the Horner–Emmons hydrolysis sequence as described above gave the *meta*- or *para*- carboxylic acids **18** and **19** as an *E*/*Z* mixture. The product also contained traces of two cyclopentene regioisomers formed via double bond migration into the 5-membered ring.

1. Conclusion

In summary, we have developed a new route to analogues of 9-*cis* retinoic acid and tagretin as potential ligands for the retinoid X receptor. The novel cyclopentenones **1** and **2** can be derivatised to provide compounds for comparison that incorporate single, double, or cyclopropyl moieties in the central five membered ring. Biological activity of these and additional compounds will be reported in a future communication.

2. Experimental

2.1. General methods

Melting points were determined with a Büchi melting point

apparatus B-545. IR spectra were recorded on a Perkin–Elmer Spectrum One FT-IR Spectrometer. ^{1}H NMR was recorded at 300 MHz and ^{13}C NMR at 75 MHz on a Bruker DRX 300 spectrometer. Chemical shifts are given in ppm (δ) relative to tetramethylsilane. Mass spectra were recorded on a Varian MAT 311A mass spectrometer using the peak matching method, or on a Finnigan MAT TSQ 70 mass spectrometer with electron impact (EI) ionization, Elemental analysis was performed on a Fisons EA1108 elemental analyser by Novo Nordisk Microanalytical Laboratory, Denmark. Column chromatography was performed on Macherey–Nagel Kieselgel 60 (230–440 mesh).

2.1.1. 2-(3,5,5,8,8-Pentamethyl-5,6,7,8-tetrahydronaphthalen-2-yl)cyclopent-2-enone (1).
To a stirred suspension of cobalt carbonyl (9.1 g, 27 mmol) in petroleum ether (300 mL) under nitrogen was added alkyne (**3**) (5.5 g, 24 mmol) and petroleum ether (25 mL), and the reaction stirred for 3 h at room temperature. The reaction mixture was then filtered through a pad of Celite and concentrated under reduced pressure. The crude cobalt alkyne complex was redissolved in benzene (75 mL) and exposed to an ethylene atmosphere using an ethylene filled balloon. A solution of trimethylamine-*N*-oxide dihydrate (14.4 g, 192 mmol) in methanol (75 mL) was added over 2.5 h and the reaction was stirred for 16 h. The reaction mixture was then filtered through a pad of Celite and concentrated under reduced pressure. Chromatography (hexane/ethyl acetate 2:1) gave (**1**) (2.88 g, 42%) as an off white solid mp 138–139°C. IR (KBr) 2954, 2920, 2880, 1690 (CO), 1502, 1457, 1388, 1361, 1315 cm^{-1}; δ_H (CDCl$_3$) 1.26 (6H, s, CMe$_2$), 1.27 (6H, s, CMe$_2$), 1.65 (4H, s, CH$_2$CH$_2$), 2.14 (3H, s, ArMe), 2.53–2.62 (2H, m, CH$_2$), 2.72–2.81 (2H, m, COCH$_2$), 7.04 (1H, s, ArH), 7.12 (1H, s, ArH), 7.55–7.60 (1H, m, C=CH). δ_C (CDCl$_3$) 208.2, 161.2, 147.0, 145.3, 142.5, 133.5, 129.6, 128.7, 127.9, 35.5, 35.3, 34.4, 34.3, 32.3, 32.2, 27.2, 20.4. HRMS calcd for C$_{20}$H$_{26}$O: 282.1984; found: 282.1969.

2.1.2. *cis*- and *trans*-2-(3,5,5,8,8-Pentamethyl-5,6,7,8-tetrahydronaphthalen-2-yl)cyclopentanol (4).
A mixture of (**1**) (2.0 g, 7 mmol) and platinum oxide (200 mg) in ethyl acetate (30 mL) was hydrogenated at 40 psi for three days. The catalyst was removed by filtration through a Celite pad and the solution concentrated under reduced pressure. Chromatography (hexane/ethyl actetate 5:1) gave 2-(3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydronaphthalen-2-yl)cyclopentanone (1.56 g, 78%), mp 86–86.5°C. IR (KBr) 3019, 2959, 1732 (CO), 1503, 1451, 1361 cm^{-1}; δ_H (CDCl$_3$) 1.20 (6H, s, CMe$_2$), 1.22 (3H, s, CMe), 1.23 (3H, s, CMe), 1.63 (4H, s, CH$_2$CH$_2$), 1.80–2.50 (6H, m, CH$_2$CH$_2$CH$_2$), 2.20 (3H, s, ArMe), 3.45 (1H, dd, J=13.9, 8.3 Hz, COCH), 6.88 (1H, s, ArH), 7.05 (1H, s, ArH). δ_C (CDCl$_3$) 219.1, 143.2, 142.6, 134.4, 133.5, 128.6, 125.6, 53.4, 38.7, 35.2, 35.1, 33.9, 33.7, 32.0, 31.9, 31.8, 31.7, 31.6, 21.0, 19.7. Anal. calcd for C$_{20}$H$_{28}$O; C 84.45, H 9.92. Found C 84.31, H 9.92. HRMS calcd for C$_{20}$H$_{28}$O: 284.2140; found: 284.2133.

To the product from the previous step (500 mg, 1.76 mmol) in ethanol (5 mL) and dichloromethane (0.5 mL) was added sodium borohydride (80 mg, 2.1 mmol) and the reaction

stirred for 4 h. Dilute HCl was added and the reaction partially concentrated. Water was added and the aqueous layer extracted with ether, dried and concentrated under reduced pressure. Chromatography (hexane/ethyl acetate 3:1) gave (**4a**) (288 mg, 58%) as a gum eluting first, followed by (**4b**) (210 mg, 42%) as a white solid mp 78–79°C. (**4a**) IR (KBr) 3468, 3023, 2960, 1502, 1455, 1362 cm^{-1}; δ_H (CDCl$_3$) 1.18–1.31 (12H, m, 2CMe$_2$), 1.62 (4H, s, CH$_2$CH$_2$), 1.73–2.25 (6H, m, CH$_2$CH$_2$CH$_2$), 2.29 (3H, s, ArMe), 3.16 (1H, ddd, J=11.1, 7.3, 3.8 Hz, CHCHOH), 4.20–4.26 (1H, m, CHOH), 7.08 (1H, s, ArH), 7.21 (1H, s, ArH). δ_C (CDCl$_3$) 143.4, 142.8, 134.6, 134.3, 128.9, 126.0, 73.5, 48.7, 35.6, 35.5, 34.4, 34.3, 34.2, 32.5, 32.3, 32.2, 32.1, 28.3, 22.8, 20.0. HRMS calcd for C$_{20}$H$_{30}$O 286.2297; found: 286.2288. (**4b**) IR (KBr) 3369, 3019, 2957, 1500, 1452, 1361 cm^{-1}; δ_H (CDCl$_3$) 1.22 (12H, s, 2CMe$_2$), 1.62 (4H, s, CH$_2$CH$_2$), 1.58–1.99 (4H, m, CH$_2$CH$_2$), 2.02–2.25 (2H, m, CH$_2$), 2.32 (3H, s, ArMe), 3.12 (1H, dd, J=13.9, 7.6 Hz, CHCHOH), 4.24–4.34 (1H, m, CHOH), 7.05 (1H, s, ArH), 7.10 (1H, s, ArH). δ_C (CDCl$_3$) 142.4, 142.2, 138.5, 133.5, 128.0, 123.2, 79.9, 49.7, 35.1, 35.0, 33.9, 33.8, 33.7, 31.9, 31.8, 31.8, 31.7, 29.6, 22.0, 19.6. HRMS calcd for C$_{20}$H$_{30}$O 286.2297; found: 286.2289.

2.1.3. *trans*-4-[2-(3,5,5,8,8-Pentamethyl-5,6,7,8-tetrahydronaphthalen-2-yl)cyclopentyloxy]benzoic acid (5).
To solution of (**4**) (190 mg, 0.66 mmol), triphenyl phosphine (174 mg, 0.66 mmol) and 4-carbomethoxyphenol (121 mg, 0.79 mmol) in THF was added, dropwise, diethylazodicarboxylate (DEAD), (110 mg, 0.66 mmol) in THF (0.4 mL) and the solution stirred for 4 h, whereupon a further 0.33 mmol of triphenyl phosphine, 4-carbomethoxyphenol and DEAD was added and the reaction stirred for 12 h. Concentration under reduced pressure and chromatography (hexane/ethyl acetate 6:1) gave the methyl ester of (**5**) (194 mg, 70%). IR (KBr) 3022, 2956, 1713 (CO), 1604, 1277, 1251, 1176 cm^{-1}; δ_H (CDCl$_3$) 1.20–1.32 (12H, m, 2CMe$_2$), 1.55–2.33 (6H, m, CH$_2$CH$_2$CH$_2$), 1.62 (4H, s, CH$_2$CH$_2$), 2.29 (3H, s, ArMe), 3.46 (1H, dt, J=7.7, 5.3 Hz, CHCHOAr), 3.70 (3H, s, CO$_2$Me), 4.70–4.80 (1H, m, CHOAr), 6.75 (2H, d, J=8.4 Hz, 2ArH), 7.02 (1H, s, ArH), 7.05 (1H, s, ArH) 7.93 (2H, d, J=8.4 Hz, 2ArH). δ_C (CDCl$_3$) 166.8, 162.0, 142.6, 142.6, 138.8, 132.2, 131.4, 128.7, 126.0, 123.5, 115.1, 86.0, 51.7, 47.8, 35.2, 34.0, 33.9, 32.9, 32.7, 32.0, 32.0, 31.9, 31.8, 24.1, 19.7. HRMS calcd for C$_{28}$H$_{36}$O$_3$: 420.2665; found: 420.2662.

The product from the previous step (140 mg, 0.48 mmol) and aqueous potassium hydroxide (1 mL of 6 M) in methanol (8 mL) was heated at reflux for 2 h. Water was added and the aqueous layer extracted with dichloromethane, dried and concentrated under reduced pressure. Chromatography (dichloromethane/methanol 20:1) gave (**5**) (107 mg, 79%) as a white solid mp 198°C. IR (KBr) 3020, 2961, 1675 (CO), 1605, 1294, 1250, 1172 cm^{-1}; δ_H (CDCl$_3$) 1.20–1.32 (12H, m, 2CMe$_2$), 1.55–2.33 (6H, m, CH$_2$CH$_2$CH$_2$), 1.62 (4H, s, CH$_2$CH$_2$), 2.29 (3H, s, ArMe), 3.46 (1H, dt, J=7.7, 5.3 Hz, CHCHOAr), 4.70–4.80 (1H, m, CHOAr), 6.78 (2H, d, J=8.4 Hz, 2ArH), 7.02 (1H, s, ArMe), 7.05 (1H, s, ArMe), 7.93 (2H, d, J=8.4 Hz, 2ArH). δ_C (CDCl$_3$) 171.0, 162.7, 142.6, 142.6, 138.8, 133.2, 132.1, 128.2, 123.5, 120.9, 115.2, 86.1, 47.8, 35.2, 34.0, 33.8,

32.9, 32.7, 32.0, 31.8, 24.1, 19.7. Anal. calcd for $C_{27}H_{34}O_3$; C 79.76, H 8.43. Found C 79.32, H 8.53. HRMS calcd for $C_{27}H_{34}O_3$: 406.2508; found: 406.2498

2.1.4. 2-(3,5,5,8,8-Pentamethyl-5,6,7,8-tetrahydronaphthalen-2-yl)cyclopent-2-enol (6).

To a stirred solution of (**1**) (190 mg, 0.67 mmol) in methanol (5 mL) in an ice bath was added cerium chloride heptahydrate (320 mg, 0.87 mmol) and the mixture stirred for 5 min. Sodium borohydride (35 mg, 0.92 mmol) was then added in one portion and the reaction stirred for 15 min. Diethyl ether (15 mL) and a mixture of brine (5 mL) and dilute HCl (1 mL) was added and the organic phase recovered. The aqueous layer was extracted with diethyl ether and the combined organic layers dried and concentrated under reduced pressure. Chromatography (hexane/ethyl acetate 3:1) gave (**6**) (190 mg, 99%) as an oil (deteriorates on storage). IR (KBr) 3418, 2959, 1498, 1458, 1362 cm^{-1}. δ_H (CDCl$_3$) 1.26 (12H, s, 2CMe_2), 1.65 (4H, s, CH_2CH_2), 1.81–1.98 (1H, m, CH$_a$H$_b$CH$_2$), 2.14 (3H, s, ArMe), 2.42–2.50 (2H, m, CH$_a$H$_b$CH_2), 2.52–2.69 (1H, m, CH$_a$H$_b$), 5.10–5.19 (1H, m, CHOH), 5.87 (1H, m, C=CH), 7.10 (1H, s, ArH), 7.21 (1H, s, ArH). δ_C (CDCl$_3$) 146.6, 144.6, 143.0, 134.0, 133.6, 132.8, 129.4, 127.6, 80.1, 61.3, 36.0, 34.8, 34.7, 34.2, 32.8, 32.7, 32.6, 31.5, 21.5, 15.0. HRMS calcd for $C_{20}H_{30}O$ 284.2069; found: 284.2139.

2.1.5. 4-[2-(3,5,5,8,8-Pentamethyl-5,6,7,8-tetrahydronaphthalen-2-yl)cyclopent-2-enyloxy]benzoic acid (7).

To solution of (**6**) (400 mg, 1.4 mmol), triphenyl phosphine (400 mg, 1.5 mmol) and 4-carbomethoxyphenol (240 mg, 1.5 mmol) in THF was added, dropwise, diethylazodicarboxylate (DEAD), (66 mg, 1.5 mmol) in THF (1 mL) and the solution stirred for 1.5 h. Work up as for (**5**) afforded the methyl ester of (**7**) (130 mg, 26%). IR (KBr) 3020, 2959, 1717 (CO), 1604, 1508, 1434, 1290, 1247 cm^{-1}; δ_H (CDCl$_3$) 1.12 (3H, s, CMe), 1.18 (3H, s, CMe), 1.28 (6H, s, CMe_2), 1.62 (4H, s, CH_2CH_2), 2.03–2.14 (1H, m, CH$_a$H$_b$CH$_2$), 2.29 (3H, s, ArMe), 2.36–2.83 (3H, m, CH$_a$H$_b$CH_2), 3.82 (3H, s, CO$_2$$Me$), 5.50–5.59 (1H, m, C$H$OAr), 6.11 (1H, s, C=C$H$), 6.85 (2H, d, J=8.1 Hz, 2ArH), 7.05 (1H, s, ArH), 7.18 (1H, s, ArH), 7.93 (2H, d, J=8.1 Hz, 2ArH). δ_C (CDCl$_3$) 167.3, 162.7, 144.2, 142.3, 141.9, 135.4, 133.2, 133.1, 131.9, 128.6, 127.2, 122.5, 115.5, 86.0, 52.1, 35.5, 34.3, 34.2, 32.2, 32.1, 32.0, 31.7, 30.9, 23.0, 21.3, 14.5. HRMS calcd for $C_{28}H_{34}O_3$: 418.2508; found: 418.2514.

The product from the previous step (60 mg, 0.14 mmol) and aqueous potassium hydroxide (0.8 mL of 6 M) in methanol (5 mL) was heated at reflux for 2 h. Work up as for (**5**) gave (**7**) (23 mg, 40%) as a solid mp 87.5–88.5°C. IR (KBr) 3440, 2959, 1683 (CO), 1509, 1424, 1246, 1168 cm^{-1}; δ_H (CDCl$_3$) 1.12 (3H, s, CMe), 1.18 (3H, s, CMe), 1.28 (6H, s, CMe_2), 1.62 (4H, s, CH_2CH_2), 2.03–2.14 (1H, m, CH$_a$H$_b$CH$_2$), 2.29 (3H, s, ArMe), 2.36–2.83 (3H, m, CH$_a$H$_b$CH_2), 5.50–5.59 (1H, m, CHOAr), 6.11 (1H, s, C=CH), 6.85 (2H, d, J=8.1 Hz, 2ArH), 7.05 (1H, s, ArH), 7.18 (1H, s, ArH), 7.93 (2H, d, J=8.1 Hz, 2ArH). δ_C (CDCl$_3$) 171.2, 162.9, 143.8, 142.0, 141.5, 135.1, 132.8, 132.7, 132.1, 128.3, 126.9, 122.1, 115.2, 85.7, 35.1, 35.1, 33.9, 33.8, 31.8, 31.8, 31.3, 30.5, 20.8. HRMS calcd for $C_{27}H_{32}O_3$: 404.2352; found: 404.2334.

2.1.6. E-1-(3,5,5,8,8-Pentamethyl-5,6,7,8-tetrahydronaphthalen-2-yl)bicyclo[3.1.0]hexan-2-one (8).

To a stirred solution of diethylzinc (0.36 mL, 3.5 mmol) dichloroethane (4 mL) in an ice bath was added, dropwise, chloroiodoethane (0.5 mL, 7 mmol) forming a white suspension. After 10 min compound (**6**) (500 mg, 1.8 mmol) in dichloroethane (1 mL) was added and the reaction stirred at this temperature for 5 min, then heated at 50°C for 15 min. The reaction mixture was diluted with diethyl ether and saturated ammonium chloride (8 mL) was added. The ether phase was washed with water, dried and concentrated under reduced pressure. Chromatography (hexane/ethyl acetate 4:1) gave 1-(3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-bicyclo[3.1.0]hexan-2-ol (164 mg, 31%) as a white solid mp 127–127.5°C. IR (KBr) 3415, 2958, 2920, 2863, 1501, 1457, 1361, 1049 cm^{-1}. δ_H (CDCl$_3$) 0.73 (1H, dd, J=7.3, 4.9 Hz, cyclopropCH_aH$_b$), 1.10 (1H, t, J=4.9 Hz, cyclopropCH$_a$H$_b$), 1.26 (12H, s, 2CMe_2), 1.40–1.50 (1H, m, cyclopropCH), 1.58 (1H, s, OH), 1.61 (4H, s, CH_2CH_2), 1.79–2.10 (4H, m, CH_2CH_2), 2.30 (3H, s, ArMe), 4.50 (1H, t, J=7.3 Hz, CHOH), 7.03 (1H, s, ArH), 7.18 (1H, s, ArH). δ_C (CDCl$_3$) 143.7, 142.8, 137.6, 135.2, 129.9, 128.6, 126.3, 78.9, 37.5, 35.6, 35.6, 34.3, 32.4, 32.3, 32.2, 29.6, 25.5, 25.3, 19.5, 11.0. HRMS calcd for $C_{21}H_{30}O$: 298.2297; found: 298.2283.

The product from the previous step (40 mg, 0.13 mmol), pyridinium chlorochromate (60 mg, 0.28 mmol) and dichloromethane (3 mL) was stirred for 2 h at room temperature. Removal of solvent under reduced pressure and chromatography (eluant hexane/ethyl acetate 4:1) gave (**8**) (40 mg, 99%) as a white solid mp 152.5–153.5°C. IR (KBr) 3023, 2962, 2921, 1717 (CO), 1499, 1454, 1360 cm^{-1}; δ_H (CDCl$_3$) 1.21 (3H, s, CMe), 1.23 (9H, s, 3CMe), 1.59 (1H, t, J=4.8 Hz, cyclopropCH_aH$_b$), 1.60 (1H, dd, J=7.3, 4.8 Hz, cyclopropCH$_a$H$_b$), 1.63 (4H, s, CH_2CH_2), 2.02–2.41 (5H, m, CH_2CH_2CH), 2.29 (3H, s, ArMe), 7.02 (1H, s, ArH), 7.08 (1H, s, ArH). δ_C (CDCl$_3$) 213.9, 144.5, 142.4, 135.8, 132.4, 128.8, 128.5, 126.3, 41.7, 35.6, 34.3, 32.8, 32.4, 32.3, 32.2, 29.9, 22.3, 20.3, 19.8. HRMS calcd for $C_{21}H_{28}O$: 296.2140; found: 296.2146.

2.1.7. E-4-[1-(3,5,5,8,8-Pentamethyl-5,6,7,8-tetrahydronaphthalen-2-yl)bicyclo[3.1.0]hex-2-ylidenemethyl]benzoic acid (9).

To a stirred suspension of sodium hydride (60 mg of 60% in mineral oil, 1.4 mmol) in THF (2 mL) under nitrogen was added 4-(diethoxyphosphorylmethyl)-benzoic acid methyl ester (0.4 g, 1.4 mmol) in THF (1 mL) and the mixture stirred for 20 min. A mixture of (**8**) (70 mg, 0.23 mmol) and 15-crown-5 (0.28 mL, 1.4 mmol) was added and the reaction stirred for 16 h at room temperature. Water was added and the aqueous phase extracted with diethyl ether, the combined organic layers were dried and concentrated under reduced pressure. Chromatography (hexane/ethyl acetate 4:1) gave a mixture of the methyl and ethyl ester of (**9**) (64 mg, 60%), which was used directly in the next step.

The product from the previous step (50 mg, 0.12 mmol) and aqueous potassium hydroxide (0.2 mL of 6 M) in methanol (3 mL) was heated at reflux for 2 h. Dilute HCl was added and the solvent removed under reduced pressure. Work up as for compound (**5**) gave (**9**) (42 mg, 80%) as a white solid

mp 274.5–275.2°C. IR (KBr) 3560, 2955, 1682 (CO), 1604, 1412, 1316, 1289 cm^{-1}; δ_H (CDCl$_3$) 1.00–1.78 (4H, m, cyclopropC$H_aH_bCH_c$, C$H_dH_eCH_2$), 1.20–1.30 (12H, m, 2CMe_2), 1.63 (4H, s, CH_2CH_2), 2.00–2.42 (2H, m, CH$_dH_eCH_2$), 2.15 (3H, s, ArMe), 2.71–2.85 (1H, m, CH$_dH_e$), 5.74 (1H, s, C=CH), 7.10 (1H, s, ArH), 7.22 (2H, d, J=8.2 Hz, 2ArH), 7.26 (1H, s, ArH), 7.97 (2H, d, J=8.2 Hz, 2ArH). δ_C (CDCl$_3$) 171.8, 153.7, 144.3, 143.4, 142.1, 135.9, 135.4, 129.9, 129.7, 128.2, 128.0, 125.9, 119.6, 40.2, 35.2, 34.0, 32.0, 31.9, 27.1, 26.9, 26.7, 19.5, 18.2. Anal. calcd for C$_{29}$H$_{34}$O$_2$ C 84.02, H 8.33. Found C 84.28, H 8.27. HRMS calcd for C$_{29}$H$_{34}$O$_2$: 414.2559; found: 414.2557.

2.1.8. *E*-**3-[1-(3,5,5,8,8-Pentamethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)bicyclo[3.1.0]hex-2-ylidenemethyl]benzoic acid (10).** Using the same procedure as described for compound (**9**), sodium hydride (88 mg of 60% in mineral oil, 2.2 mmol), 3-(diethoxyphosphorylmethyl)benzoic acid methyl ester (600 mg, 2.2 mmol) and (**8**) (130 mg, 0.43 mmol) in THF (2 mL) gave a mixture of the methyl and ethyl ester of (**10**) (146 mg, 75%) which was used directly in the next step.

The product from the previous step (140 mg, 0.48 mmol) and aqueous potassium hydroxide (0.5 mL of 6 M) in methanol (5 mL) was heated at reflux for 2 h. Work up as for (**9**) and recrystallisation from hexane/ethyl acetate gave (**10**) (70 mg, 51%) as a white solid mp 240–241°C. IR (KBr) 3448, 2961, 1678 (CO), 1600, 1450, 1409, 1276 cm^{-1}; δ_H (CDCl$_3$) 1.00–1.80 (4H, m, cyclopropC$H_aH_bCH_c$, C$H_dH_eCH_2$) 1.20–1.31 (12H, m, 2CMe_2), 1.65 (4H, s, CH_2CH_2), 2.00–2.47 (2H, m, CH$_dH_eCH_2$), 2.12 (3H, s, ArMe), 2.65–2.82 (1H, m, CH$_dH_e$), 5.72 (1H, s, C=CH), 7.10 (1H, s, ArH), 7.24 (1H, s, ArH), 7.30–7.45 (2H, m, 2ArH), 7.80–7.90 (2H, m, 2ArH). δ_C (CDCl$_3$) 172.7, 151.5, 143.3, 143.1, 142.0, 139.0, 136.1, 135.5, 135.4, 133.4, 129.9, 129.7, 127.7, 127.2, 119.1, 39.8, 35.3, 35.1, 33.9, 33.8, 32.0, 31.9, 29.7, 26.8, 26.4, 19.7, 18.7. HRMS calcd for C$_{29}$H$_{34}$O$_2$: 414.2559; found: 414.2559.

2.1.9. 3-(3,5,5,8,8-Pentamethyl-5,6,7,8-tetrahydronaphthalen-2-yl)cyclopent-2-enone (2). To a mixture of dichlorobis(triphenylphosphine)palladium(II) (220 mg, 0.3 mmol), sodium acetate (2.1 g, 15 mmol) and 3-chloro-cyclopentpent-2-enone (1.2 g, 10.3 mmol) in methanol (35 mL) at room temperature under nitrogen was added 5,6,7,8-tetrahydro-3,5,5,8,8-pentamethyl-2-naphthalene-boronic acid (**11**) (2.7 g, 11 mmol) and the mixture heated at reflux for 3 h, cooled to room temperature and filtered through a plug of Celite. Concentration under reduced pressure and chromatography (hexane/ethyl acetate 2:1) gave (**2**) (2.0 g, 65%) as a white solid mp 87–88°C. IR (KBr) 2959, 1677 (CO), 1610, 1584, 1454 cm^{-1}. δ_H (CDCl$_3$) 1.27 (12H, s, 2CMe_2), 1.65 (4H, s, CH_2CH_2), 2.47 (3H, s, ArMe), 2.52–2.59 (2H, m, CH_2CH_2CO), 3.01–3.10 (2H, m, CH_2CO), 6.32 (1H, s, C=CH), 7.18 (1H, s, ArH), 7.42 (1H, s, ArH). δ_C (CDCl$_3$) 209.9, 175.7, 147.1, 142.8, 133.3, 132.5, 131.6, 129.6, 125.6, 34.9, 34.9, 34.2, 34.0, 31.9, 31.8, 31.6, 21.6. HRMS calcd for C$_{20}$H$_{26}$O: 282.1984; found: 282.1988.

2.1.10. 5-(3,5,5,8,8-Pentamethyl-5,6,7,8-tetrahydronaph-

thalen-2-yl)bicyclo[3.1.0]hexan-2-ol (12). In an identical manner to compound (**6**), compound (**2**) (6.5 g, 23 mmol) in methanol (175 mL), cerium chloride heptahydrate (12.3 g, 33 mmol) and sodium borohydride (1.3 g, 33 mmol) gave 3-(3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)cyclopent-2-enol (4.1 g, 63%) as an off white solid mp 86–87°C (deteriorates on storage). IR (KBr) 3257, 2956, 1455, 1361 cm^{-1}. δ_H (CDCl$_3$) 1.25 (6H, s, CMe_2), 1.26 (6H, s, CMe_2), 1.55 (1H, s, OH), 1.62 (4H, s, CH_2CH_2), 1.65–1.89 (1H, m, CH$_aH_b$C=CH), 2.39 (3H, s, ArMe), 2.32–2.48 (1H, m, CH$_aH_b$), 2.51–2.70 (1H, m, CH$_cH_d$CHOH), 2.83–2.95 (1H, m, CH$_cH_d$), 4.99 (1H, br s, CHOH), 5.82 (1H, m, C=CH), 7.10 (1H, s, ArH), 7.13 (1H, s, ArH). δ_C (CDCl$_3$) 147.8, 144.5, 142.5, 134.5, 132.9, 131.2, 129.0, 126.5, 78.7, 36.5, 35.3, 34.4, 34.3, 34.2, 32.3, 32.1, 21.4. HRMS calcd for C$_{20}$H$_{30}$O 284.2069; found: 286.2130.

To a stirred solution of diethylzinc (0.59 mL, 5.2 mmol) in dichloroethane (15 mL) in an ice bath was added, dropwise, chloroiodoethane (0.76 mL, 10.4 mmol) forming a white suspension. After 10 min 3-(3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydronaphthalen-2-yl)cyclopent-2-enol (1.0 g, 3.5 mmol) in dichloroethane (5 mL) was added and the reaction stirred at this temperature for 5 min. Work up as described for compound (**8**) gave (**12**) (510 mg, 49%) as a white solid mp 119–120°. IR (KBr) 3240, 2955, 1502, 1457, 1361, 1061 cm^{-1}. δ_H (CDCl$_3$) 0.73 (1H, dd, J=7.3, 5.2 Hz, cyclo-propCH_aH_b), 1.12 (1H, t, J=5.3 Hz, cyclopropCH$_aH_b$), 1.26 (12H, s, 2CMe_2), 1.64 (4H, s, CH_2CH_2), 1.69–2.10 (6H, m, CH_2CH_2CHOHCH), 2.32 (3H, s, ArMe), 4.72–4.85 (1H, m, CHOH), 7.02 (1H, s, ArH), 7.15 (1H, s, ArH). δ_C (CDCl$_3$) 144.5, 143.6, 140.2, 136.1, 129.5, 129.1, 75.8, 36.6, 35.3, 35.2, 33.6, 33.4, 33.3, 33.3, 33.2, 33.0, 32.9, 31.7, 31.2, 20.4, 12.4. HRMS calcd for C$_{21}$H$_{30}$O: 298.2297; found: 298.2292.

2.1.11. 5-(3,5,5,8,8-Pentamethyl-5,6,7,8-tetrahydronaph-thalen-2-yl)bicyclo[3.1.0]hexan-2-one (13). In an identical manner to compound (**8**), a mixture of (**12**) (610 mg, 2 mmol), pyridinium chlorochromate (880 mg, 4 mmol) and dichloromethane (40 mL) gave (**13**) (590 mg, 97%) as a white solid mp 128.5–129°C. IR (KBr) 2955, 1729 (CO), 1615, 1502, 1457, 1361 cm^{-1}. δ_H (CDCl$_3$) 1.21 (6H, s, CMe_2), 1.22 (6H, s, CMe_2), 1.47 (1H, t, J=5.0 Hz, cyclo-propCH_aH_b), 1.50–1.53 (1H, m, cyclopropCH$_aH_b$), 1.65 (4H, s, CH_2CH_2), 2.03 (1H, dd, J=8.4, 3.5 Hz, cyclo-propCH$_c$), 2.10–2.40 (4H, m, CH_2CH_2), 2.33 (3H, s, ArMe), 7.07 (1H, s, ArH), 7.11 (1H, s, ArH). δ_C (CDCl$_3$) 214.8, 144.3, 142.8, 136.8, 134.6, 128.6, 127.6, 37.7, 35.2, 35.2, 34.1, 34.0, 34.0, 33.7, 32.0, 32.0, 31.9, 29.7, 20.6, 19.1. HRMS calcd for C$_{21}$H$_{28}$O: 296.2140; found: 296.2135.

2.1.12. 4-[5-(3,5,5,8,8-Pentamethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)bicyclo[3.1.0]hex-2-ylidenemethyl]-benzoic acid (14). In an identical manner to compound (**8**), sodium hydride (180 mg of 60% in mineral oil, 4.5 mmol) in THF (5 mL), 3-(diethoxyphosphorylmethyl)benzoic acid methyl ester (1.3 g, 4.5 mmol) in THF (3 mL), (**13**) (270 mg, 0.9 mmol) and 15-crown-5 (0.9 mL, 4.5 mmol) gave a mixture of the methyl and ethyl ester of (**14**) (390 mg, 99%) which were used directly in the next step.

In an identical manner to compound (**8**), the product from the previous step (390 mg) and aqueous potassium hydroxide (1 mL of 6 M) in methanol (5 mL) gave (**14**) (280 mg, 75%). A pure sample (40 mg of a gum) of one of the isomers was obtained by recrystallisation from methanol. IR (KBr) 3432, 2954, 1692 (CO), 1362, 1272 cm^{-1}; δ_H (CDCl$_3$) 0.82–0.92 (1H, m, cyclopropC*H*$_a$H$_b$), 1.13 (1H, t, *J*=5.0 Hz, cyclopropCH$_a$*H*$_b$), 1.15–1.32 (12H, m, 2C*Me*$_2$), 1.40–1.46 (1H, m, cyclopropC*H*$_c$), 1.61 (4H, s, C*H*$_2$C*H*$_2$), 1.90–2.10 (2H, m, C*H*$_2$), 2.21 (3H, s, Ar*Me*), 2.30–2.61 (2H, m, C*H*$_2$), 6.35 (1H, s, C=C*H*), 6.99 (1H, s, Ar*H*), 7.12 (1H, s, Ar*H*), 7.39 (1H, t, *J*=7.0 Hz, Ar*H*), 7.63 (1H, d, *J*=7.3 Hz, Ar*H*), 7.89 (1H, d, *J*=7.3 Hz, Ar*H*), 8.16 (1H, s, Ar*H*). HRMS calcd for C$_{29}$H$_{34}$O$_2$: 414.2559; found: 414.2546. Assignable peaks of other isomer from *E/Z* mixture. δ_H (CDCl$_3$) 2.28 (s, Ar*Me*), 6.58 (s, C=C*H*), 7.05 (1H, s, Ar*H*), 7.20 (1H, s, Ar*H*), 7.43 (1H, t, *J*=7.0 Hz, Ar*H*), 7.50 (1H, d, *J*=7.3 Hz, Ar*H*), 7.83–7.99 (1H, m, Ar*H*), 8.01 (1H, s, Ar*H*).

2.1.13. 3-[5-(3,5,5,8,8-Pentamethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)bicyclo[3.1.0]hex-2-ylidenemethyl]benzoic acid (15).
In an identical manner to compound (**8**), sodium hydride (180 mg of 60% in mineral oil, 4.3 mmol) in THF (5 mL), 4-(diethoxyphosphorylmethyl)benzoic acid methyl ester (0.1 g, 4.3 mmol) in THF (1 mL), compound (**13**) (260 mg, 0.87 mmol) and 15-crown-5 (0.09 mL, 4.3 mmol) in THF (5 mL) gave a mixture of the methyl and ethyl ester of (**15**) (320 mg, 87%) which was used directly in the next step.

In an identical manner to compound (**8**), the product from the previous step (310 mg, 0.7 mmol) and aqueous potassium hydroxide (1 mL of 6 M) in methanol (5 mL) gave (**15**) (170 mg, 57%) as a mixture of *E* and *Z* isomers in a ratio of approx. 6:4. IR (KBr) 3450, 2954, 1680 (CO), 1605, 1422, 1286 cm^{-1}; δ_H assignable as *E* and *Z* mixture (CDCl$_3$) 0.79–0.91 (cyclopropCH$_a$*H*$_b$), 1.05–1.18 (t, *J*=5.2 Hz, cyclopropC*H*$_a$H$_b$), 1.20–1.30 (m, 2C*Me*$_2$), 1.38–1.50 (cyclopropC*H*$_c$), 1.61 and 1.63 (s, C*H*$_2$C*H*$_2$), 2.20 and 2.30 (s, Ar*Me*), 1.90–2.60 (m, C*H*$_2$C*H*$_2$), 6.32 and 6.61 (s, C=C*H*), 6.98 and 7.05 (s, Ar*H*), 7.12 and 7.20 (Ar*H*), 7.30–7.55 (m, 2Ar*H*), 7.92–8.10 (m, 2Ar*H*). HRMS calcd for C$_{29}$H$_{34}$O$_2$: 414.2559; found: 414.2553.

2.1.14. 4-[5-(3,5,5,8,8-Pentamethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)bicyclo[3.1.0]hex-2-yloxy]benzoic acid (16).
To solution of (**12**) (190 mg, 0.63 mmol), triphenyl-phosphine (200 mg, 0.76 mmol) and 4-carbomethoxy-phenol (170 mg, 1.1 mmol) in THF (2 mL) at ice bath temperature was added, dropwise, diethylazodicarboxylate (DEAD), (130 mg, 0.76 mmol) in THF (1 mL) and the solution stirred for 1.5 h and a further 16 h at room temperature. Concentration under reduced pressure and chromatography afforded the methyl ester of (**16**) (110 mg, 54%). IR (KBr) 2957, 2864, 1719 (CO), 1605, 1507, 1434, 1278, 1249 cm^{-1}. δ_H (CDCl$_3$) 0.75 (1H, t, *J*=4.2 Hz, cycloprop-CH$_a$*H*$_b$), 0.92 (1H, dd, *J*=7.6, 4.3 Hz, cyclopropCH$_a$*H*$_b$), 1.15 (3H, s, C*Me*), 1.25 (9H, s, 3C*Me*), 1.62 (4H, s, C*H*$_2$C*H*$_2$), 1.76 (1H, dd, *J*=8.4, 4.3 Hz, cyclopropC*H*$_c$), 1.80–2.20 (4H, m, C*H*$_2$C*H*$_2$), 2.32 (3H, s, Ar*Me*), 3.90 (3H, s, CO$_2$*Me*), 4.91 (1H, d, *J*=5.2 Hz, C*H*OAr), 6.98 (2H, d, *J*=8.4 Hz, 2Ar*H*), 7.04 (1H, s, Ar*H*), 7.18 (1H, s,

Ar*H*), 8.01 (2H, d, *J*=8.4 Hz, 2Ar*H*). δ_C (CDCl$_3$) 167.4, 162.1, 143.5, 142.5, 138.4, 135.4, 132.0, 128.8, 128.4, 127.4, 115.5, 81.3, 52.2, 35.5, 34.3, 34.2, 33.5, 32.4, 32.3, 32.2, 29.4, 29.0, 19.2, 14.3. HRMS calcd for C$_{29}$H$_{36}$O$_3$: 432.2665; found: 432.2656.

The product from the previous step (150 mg, 0.34 mmol) and aqueous potassium hydroxide (1 mL of 5 M) in methanol (3 mL) was heated at reflux for 2 h. Work as described for (**5**) and chromatography (dichloromethane/methanol 20:1) gave (**16**) (19 mg, 13%), as a white solid mp 221–222°C. IR (KBr) 3420, 2959, 1684 (CO), 1604, 1509, 1250 cm^{-1}. δ_H (CDCl$_3$) 0.75 (1H, t, *J*=4.3 Hz, cyclo-propC*H*$_a$H$_b$), 0.92 (1H, dd, *J*=7.6, 4.3 Hz, cycloprop-CH$_a$*H*$_b$), 1.20 (12H, m, 2C*Me*$_2$), 1.62 (4H, s, C*H*$_2$C*H*$_2$), 1.70–1.85 (1H, m, cyclopropC*H*$_c$), 1.85–2.30 (5H, m, C*H*$_2$C*H*$_2$CHO*H*), 2.20 (3H, s, Ar*Me*), 4.95 (1H, d, *J*=5.3 Hz, C*H*OAr), 6.97–7.05 (3H, m, 3Ar*H*), 7.18 (1H, s, Ar*H*), 8.13 (2H, d, *J*=8.4 Hz, 2Ar*H*). δ_C (CDCl$_3$) 172.1, 162.9, 143.5, 142.6, 138.4, 135.4, 132.8, 128.8, 128.4, 115.6, 81.5, 35.6, 34.3, 34.2, 33.5, 32.3, 32.2, 29.4, 29.0, 19.2, 14.3. HRMS calcd for C$_{28}$H$_{34}$O$_2$: 418.2508; found: 418.2485.

2.1.15. 3-(3,5,5,8,8-Pentamethyl-5,6,7,8-tetrahydronaph-thalen-2-yl)cyclopentanone (17).
Compound (**2**) (950 mg, 3.3 mmol), potassium acetate (60 mg) and platinum oxide (40 mg) in ethyl acetate (25 mL) was hydrogenated at 3 atm for 24 h. Work up as described for compound (**4**) gave (**17**) (650 mg, 68%) as a white solid mp 97–98°C. IR (KBr) 3027, 2957, 2931, 1742 (CO), 1502, 1455, 1360 cm^{-1}. δ_H (CDCl$_3$) 1.22 (12H, m, 2C*Me*$_2$), 1.64 (4H, s, C*H*$_2$C*H*$_2$), 1.91–2.10 (1H, m, C*H*$_a$H$_b$), 2.20–2.50 (4H, m, CH$_a$*H*$_b$C*H*$_2$-COC*H*$_c$H$_d$), 2.30 (3H, s, Ar*Me*), 2.52–2.65 (1H, dd, *J*=14.0, 7.0 Hz, CH$_c$*H*$_d$), 3.47–3.61 (1H, m, ArC*H*), 7.03 (1H, s, Ar*H*), 7.12 (1H, s, Ar*H*). δ_C (CDCl$_3$) 219.8, 143.8, 143.2, 138.8, 133.8, 129.3, 123.6, 46.4, 39.5, 39.1, 36.0, 35.9, 34.9, 34.6, 32.8, 32.7, 32.6, 32.5, 31.0, 20.2. HRMS calcd for C$_{20}$H$_{28}$O: 284.2140; found: 284.2143.

2.1.16. 4-[3-(3,5,5,8,8-Pentamethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)cyclopentylidenemethyl]benzoic acid (18).
In an identical manner to compound (**8**), sodium hydride (190 mg of 60% in mineral oil, 4.1 mmol) in THF (5 mL), 4-(diethoxyphosphorylmethyl)benzoic acid methyl ester (1.18 g, 4.1 mmol) in THF (1 mL), compound (**17**) (235 mg, 0.82 mmol) and 15-crown-5 (0.82 mL, 4.1 mmol) gave the methyl and ethyl ester of (**18**) (315 mg, 93%) as a mixture of *E* and *Z* isomers (δ_H of C=C*H* at 6.43 and 6.49), contaminated with a trace amount of two cyclopentenes (δ_H of C=C*H* at 5.41 and 5.45), which was used directly in the next step.

In an identical manner to compound (**8**), the product from the previous step (315 mg, 0.7 mmol) and aqueous potassium hydroxide (2 mL of 5 M) in methanol (4 mL) gave (**18**) (120 mg, 41%) as a mixture of *E* and *Z* isomers, contaminated with a trace amount of two cyclopentenes. IR (KBr) 2960, 1688 (CO), 1600, 1453, 1282 cm^{-1}; δ_H assigned as *E* and *Z* mixture (CDCl$_3$) (CDCl$_3$) assignable 1.15–1.35 (12H, m, 2C*Me*$_2$), 1.62 and 1.65 (4H, s, C*H*$_2$C*H*$_2$), 1.80–3.20 (6H, m, C*H*$_2$C*H*$_2$CHC*H*$_2$), 2.30 and 2.32 (3H, s, Ar*Me*), 3.24–3.42 (1H, m, CH$_2$C*H*CH$_2$), 6.46

and 6.48 (1H, s, C=CH), 7.00–7.26 (2H, m, 2ArH), 7.34–7.58 (2H, m, 2ArH), 7.80–8.05 (2H, m, 2ArH), 11.70 (1H, br s, CO$_2H$). HRMS calcd for C$_{28}$H$_{34}$O$_2$: 402.2559; found: 402.2561.

2.1.17. 3-[3-(3,5,5,8,8-Pentamethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)cyclopentylidenemethyl]benzoic acid (19).

In an identical manner to compound (**8**), sodium hydride (190 mg of 60% in mineral oil, 4.1 mmol) in THF (5 mL), 3-(diethoxyphosphorylmethyl)benzoic acid methyl ester (1.18 g, 4.1 mmol) in THF (1 mL), compound (**17**) (235 mg, 0.82 mmol) and 15-crown-5 (1.6 mL, 8.2 mmol) gave the methyl and ethyl ester of (**19**) (315 mg, 93%) as a mixture of E and Z isomers (δ_H of C=CH at 6.44 and 6.50), contaminated with a trace amount of two cyclopentenes (δ_H of C=CH at 5.42 and 5.49) which was used directly in the next step.

In an identical manner to compound (**8**), the product from the previous step (310 mg, 0.7 mmol) and aqueous potassium hydroxide (2 mL of 5 M) in methanol (3 mL) gave compound (**19**) (160 mg, 54%) as a mixture of E and Z isomers contaminated with trace amounts of two cyclopentenes. IR (KBr) 2958, 1682 (CO), 1605, 1421, 1317, 1288 cm^{-1}; δ_H assigned as E and Z mixture (CDCl$_3$) 1.12–1.31 (12H, m, 2CMe_2), 1.62 (4H, s, CH_2CH_2), 2.25 and 2.32 (3H, s, ArMe), 1.60–3.12 (6H, m, CH_2CH_2CHCH_2), 3.25–3.48 (1H, m, CH$_2$CHCH$_2$), 6.45 and 6.47 (1H, s, C=CH), 6.98–7.23 (2H, m, 2ArH), 7.26–7.45 (2H, m, 2ArH), 7.80–8.01 (2H, m, 2ArH), 11.80 (1H, br s, CO$_2H$). HRMS calcd for C$_{28}$H$_{34}$O$_2$: 402.2559; found: 402.2542.

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