

Atropisomerisation in sterically hindered α,β -disubstituted cyclopentenones derived from an intermolecular cobalt(0)-mediated Pauson–Khand reaction†

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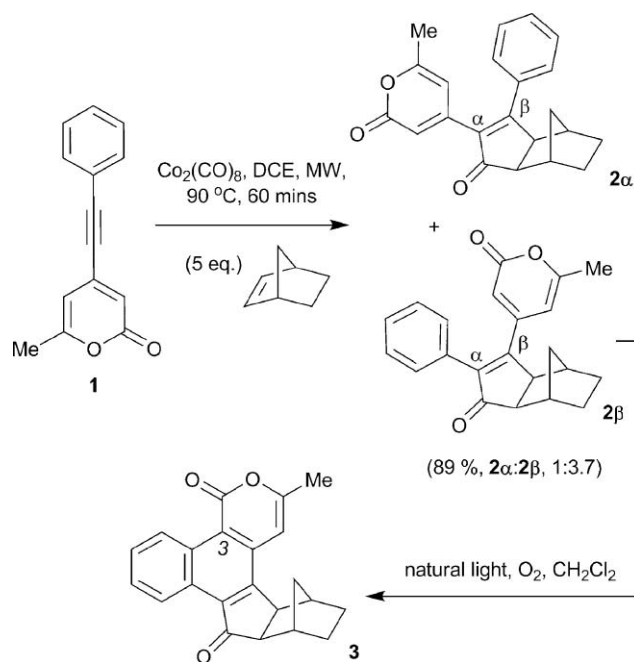
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4-(2-Phenylethynyl)-2*H*-chromen-2-one reacts with norbornene and $\text{Co}_2(\text{CO})_8$ in an intermolecular Pauson–Khand reaction by focused microwave dielectric heating. Two regioisomeric products are formed; the electron-deficient coumarin moiety preferentially occupies the β -position of the cyclopentenone ring system, whereas the phenyl occupies the α -position. The sterically hindered α,β -(2,3)-disubstituted cyclopentenone regioisomeric products exhibit pronounced atropisomerisation, and the magnitude of the energetic barrier to interconversion between these atropisomers is dependent on the relative position of the coumarin moieties. Interconversion is slow when the coumarin is found in the α -position, whereas interconversion is relatively fast when found in the β -position.

Introduction

Intermolecular Pauson–Khand (PK) reactions¹ of alkynes with alkenes (especially norbornene and its derivatives), mediated by stoichiometric quantities of $\text{Co}_2(\text{CO})_8$, have been of continued interest to the academic community, both in terms of applications² and mechanistic studies.³ Whilst the reactions of internal alkynes (e.g. **1**) under conventional heating are slow, microwave (MW) heating⁴ dramatically improves the rate of the reactions. Reaction of **1**,⁵ norbornene and $\text{Co}_2(\text{CO})_8$ under MW irradiation generates two regioisomeric products, **2 α** or **2 β** , in 89% yield (ratio = 1 : 3.7; Scheme 1). 2-Pyrone (2*H*-pyran-2-one) and phenyl moieties can be considered sterically near equivalent, therefore it was predicted⁶ and proven that the major regioisomeric product possessed the phenyl group in the α -position and the electron-deficient 2-pyrone in the β -position of the cyclopentenone ring (**2 β**) (note: α/β notation^{6a} has been used to distinguish between the two regioisomeric PK cycloadducts in the past; here, 2-pyrone is the primary ring system).⁷ Interestingly, **2 β** participated in a light induced C3-regioselective 6π -electrocyclisation/oxidative aromatisation reaction to give **3**. In this study we have extended our investigations to replacement of the 2-pyrone moiety with an electronically related coumarin (2*H*-chromen-2-one). The larger coumarin moiety is expected, on steric grounds, to alter the regioselectivity of the PK reaction.⁸ In addition, we anticipated that PK products containing the coumarin motif could exhibit atropisomerisation.



Scheme 1 PK reaction of **1** with norbornene and $\text{Co}_2(\text{CO})_8$.

Results and discussion

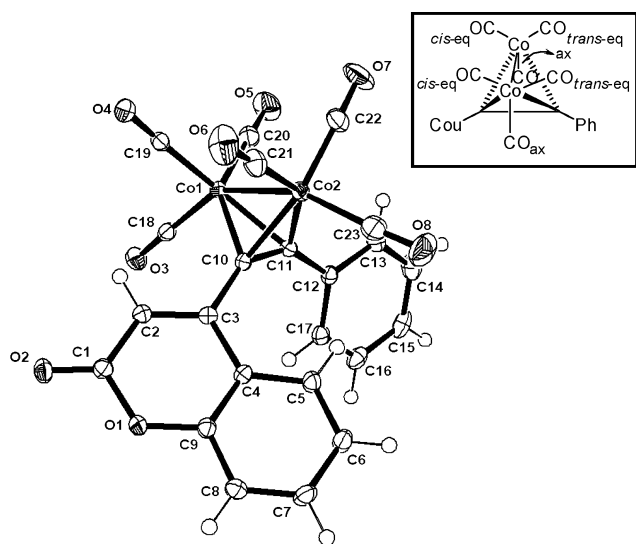
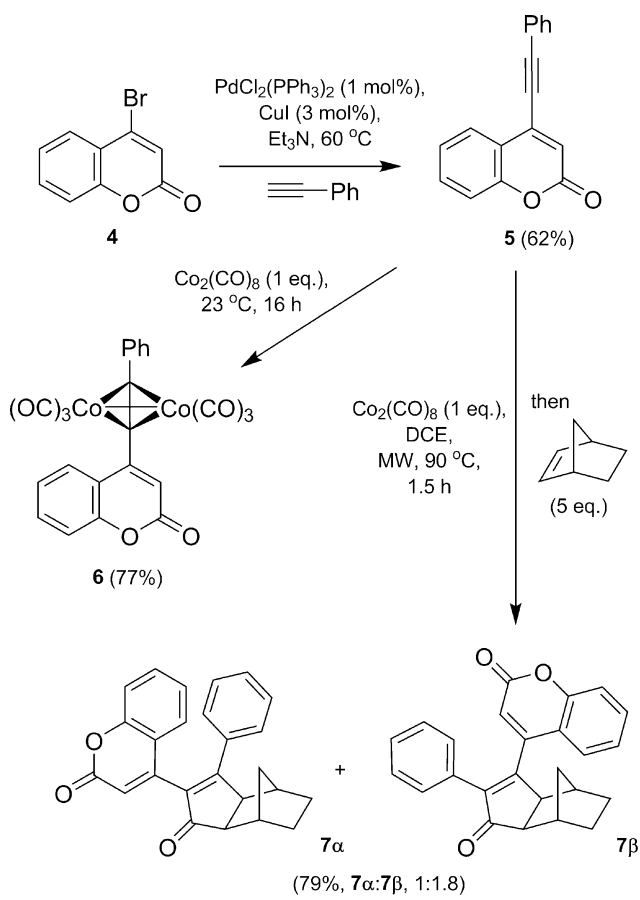
Alkynylcoumarin **5** was readily prepared in 62% yield by Sonogashira alkylation of known⁹ compound **4** using a $\text{PdCl}_2(\text{PPh}_3)_2$ precatalyst and CuI co-catalyst at low loadings in the presence of Et_3N (Scheme 2).¹⁰ Prior to conducting the PK reaction, intermediate complex **6** was independently prepared by a reaction of equimolar quantities of **5** and $\text{Co}_2(\text{CO})_8$ at 23 °C for 16 h, affording **6** in 77% yield after chromatography on silica gel.

The X-ray crystal structure of **6** (Fig. 1) shows the expected structural connectivity for this type of complex.¹¹ Labile CO ligands are found in both *cis*-equatorial positions, indicated by the longer Co–CO bond lengths, e.g. $\text{Co}_1\text{–CO}_{\text{cis-eq}}$ (1.8304(17) Å) and $\text{Co}_2\text{–CO}_{\text{cis-eq}}$ (1.8264(19) Å), and one *trans*-equatorial position

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† Electronic supplementary information (ESI) available: X-Ray diffraction data, refinement information and Cartesian coordinates. CCDC reference numbers 780325 and 780326. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c0ob00264j.

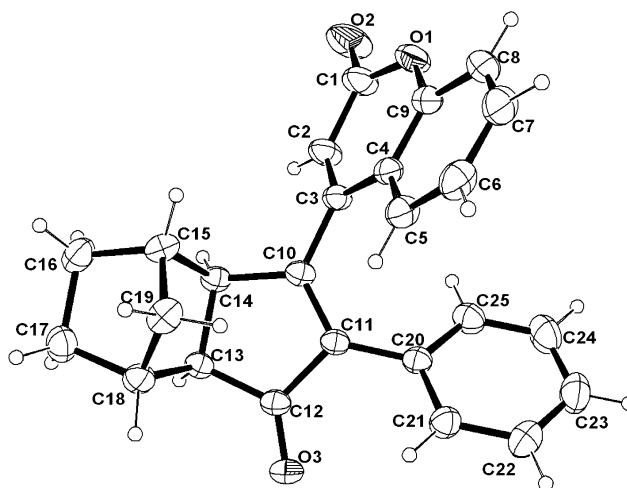


($\text{Co}_1\text{-CO}_{\text{trans-eq}}$ (1.8302(19) Å). The other *trans*-equatorial position exhibits a significantly shorter bond distance, e.g. $\text{Co}_2\text{-CO}_{\text{trans-eq}}$ (1.8090(19) Å). This difference is likely due to the orientation and electronic deficiency of the coumarin moiety, relative to each cobalt atom, which affects the strength of one of the *trans*-

equatorial CO ligands. In terms of the PK reaction, the crystal structure indicates that the initial 'CO loss' could occur from either *cis*- or *trans*-equatorial sites in **6**.

PK reaction of **5**: A 1,2-dichloroethane (DCE) solution of **5** in the presence of an equimolar amount of $\text{Co}_2(\text{CO})_8$ was reacted at 23 °C for 1 h (TLC analysis confirming complete loss of **5**). Norbornene (~ 5 eq.) was then added and the mixture heated in a CEM Discover microwave at 90 °C for 1.5 h, which gave two isolatable regioisomeric products **7α** and **7β** in 79% yield in a ratio of 1 : 1.8, respectively.

It was anticipated that the electron-withdrawing coumarin moiety would appear preferentially in the β-position of the newly formed cyclopentenone ring. However, any dominant steric effects could place the larger coumarin moiety into the α-position. **7β** was predicted to be the major regioisomer based on electronic grounds and this was confirmed unambiguously as the major regioisomer crystallised from CDCl_3 , giving crystals suitable for X-ray diffraction (Fig. 2).



(determined at 298 K). Thermal ellipsoids are shown at 30% probability.

At 303 K, the ^1H NMR spectra of the two regioisomeric products **7α** and **7β** are markedly different. **7β** exhibits broad proton signals indicative of an exchange process, whereas **7α** exhibits two sets of sharp proton signals sharing similar chemical shifts. Variable temperature (VT) ^1H NMR experiments (500 MHz) for **7β** were recorded at 10 K intervals between 223 K and 323 K (Fig. 3).

At low temperatures, the singlet expected for the C3 proton of the coumarin in **7β** appears as two separate resonances at 6.72 and 6.04 ppm. Increasing the temperature to ca. 293 K results in coalescence and increasing the temperature to 323 K leads to the sharpening of the resulting averaged signal. The standard Gibbs' free energy (ΔG°), using the equilibrium constant K derived at 223 K for the two species, is 0.6 kJ mol^{-1} .

Molecular models show that there is restricted rotation about the single C–C bond connecting the coumarin moiety to the cyclopentenone framework. The barrier to rotation about this bond is large enough that, under the appropriate conditions, it is possible to observe two conformers (atropisomers). The VT spectra show that increasing temperature allows these conformers to interconvert thermally. From the spectroscopic data, it is

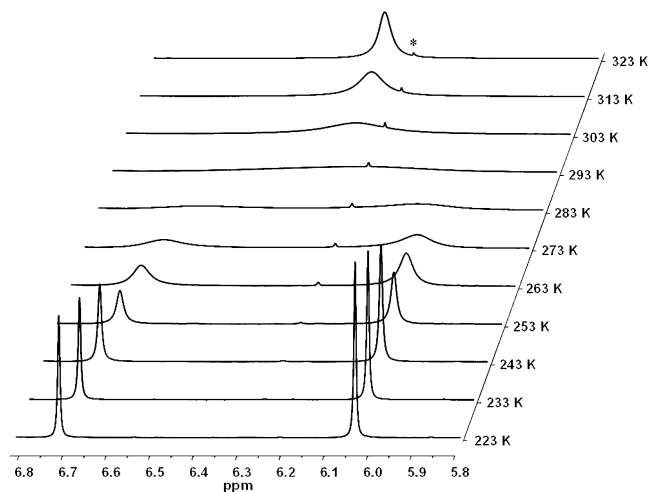


Fig. 3 VT ^1H NMR (500 MHz) spectra of 7β in CDCl_3 between 6.8–5.8 ppm for temperatures 223 K to 323 K. * Trace impurity.

possible to obtain the activation parameters for the observed exchange process for 7β .

Using *gNMR* software,¹² we were able to simulate the line shape of the experimentally observed spectra to gain the rate constants for the exchange process at a number of temperatures. An Arrhenius plot of $1/T$ against $\ln k$ gives a straight line with slope $-E_a/R$, allowing the activation energy to be estimated (55.3 kJ mol^{-1}). In addition, an Eyring plot of $\ln(k/T)$ against $1/T$ afforded a straight line plot (Fig. 4, $R^2 = 0.9964$) from which the enthalpy ($\Delta H^\ddagger = (51.8 \pm 1.79) \text{ kJ mol}^{-1}$) and entropy $\Delta S^\ddagger = (-11.85 \pm 6.52) \text{ J mol}^{-1} \text{ K}^{-1}$ of activation were determined. The small ΔS^\ddagger value is in keeping with exchange being intramolecular, and the ΔH^\ddagger value indicates that the barrier to rotation is primarily enthalpic. These data indicate that the free energy of activation (ΔG^\ddagger) at 303 K is (55.4 ± 2.66) kJ mol^{-1} .

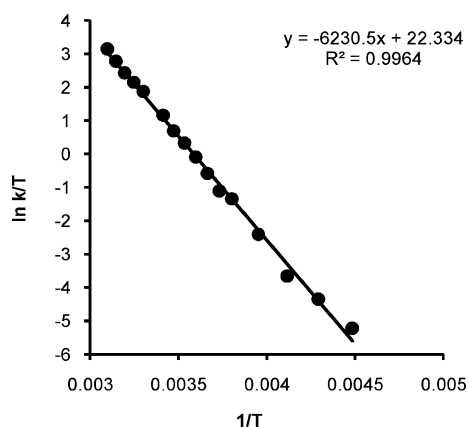


Fig. 4 Eyring plot of $\ln(k/T)$ vs. $1/T$ for rate constants obtained by simulation of ^1H NMR spectra at temperatures between 223 K and 323 K for compound 7β .

For the minor isomer $7a$, the two separate atropisomers $7a_A$ and $7a_B$ are clearly distinguishable at room temperature, and there is no indication of an exchange process occurring. Variable

temperature ^1H NMR experiments on $7a$ in d_8 -toluene recorded at higher temperatures showed some line-broadening of the proton signals, however, no evidence for coalescence was observed up to 65°C . Therefore, the activation energy required for interconversion of the atropisomers derived from $7a$ is higher than 7β .

DFT calculations at the B3LYP level on the two sets of atropisomers (derived from both $7a$ and 7β , Fig. 5) have allowed the theoretical activation parameters for interconversion of the atropisomers derived from each regioisomer to be determined.

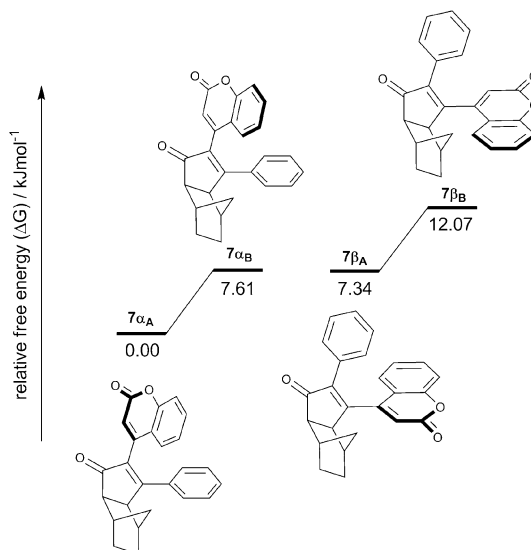


Fig. 5 Relative free energies calculated for the four atropisomers of 7 .

The theoretical values for the activation parameters for isomer 7β are in good agreement with the experimentally observed values, with a difference in ΔG^\ddagger of 0.6 kJ mol^{-1} between the value calculated for **TS-1** and the experimentally-determined value (Fig. 6). The interconversion of $7a_A \rightarrow 7a_B$ is calculated to be less favoured than that of $7\beta_A \rightarrow 7\beta_B$, with ΔG^\ddagger being *ca.* 23 kJ mol^{-1} higher. This difference supports the experimental observation that no exchange is observed at room temperature for $7a$. Substituting the calculated value of ΔH^\ddagger for $7a$ into $\Delta H^\ddagger = E_a - RT$ allows the activation energy for the interconversion to be estimated. At 303 K, the activation energy for the process is approximately 75.7 kJ mol^{-1} . This is 20 kJ mol^{-1} higher than the value calculated for the major isomer 7β (from the Arrhenius plot).

By substituting the calculated values of ΔH^\ddagger and ΔS^\ddagger into equation $\ln(k/T) = \ln(k_B/h) - (\Delta H^\ddagger/RT) + (\Delta S^\ddagger/R)$, the rate constant for the exchange process could be estimated at various temperatures. From the values calculated for 7β , an estimated rate constant of 2240 s^{-1} at 303 K was determined. The estimated rate constant by *gNMR* at 303 K was determined to be 1960 s^{-1} , showing a reasonable correlation between the calculated and observed values. From the values calculated for $7a$, a rate constant of approximately 0.2 s^{-1} is estimated, confirming that at room temperature, exchange is expected to be slow on the NMR timescale.

The relative energies obtained for the four atropisomers indicate that the regioisomer with the coumarin moiety in the α -position is the energetically most favourable regioisomer, with a difference of 7.3 kJ mol^{-1} between the two lowest energy atropisomers $7a_A$ and

\ddagger Neither regioisomer $7a$ or 7β undergoes a natural ligand-induced 6π -electrocyclisation/oxidative aromatisation reaction (in contrast to 2β).

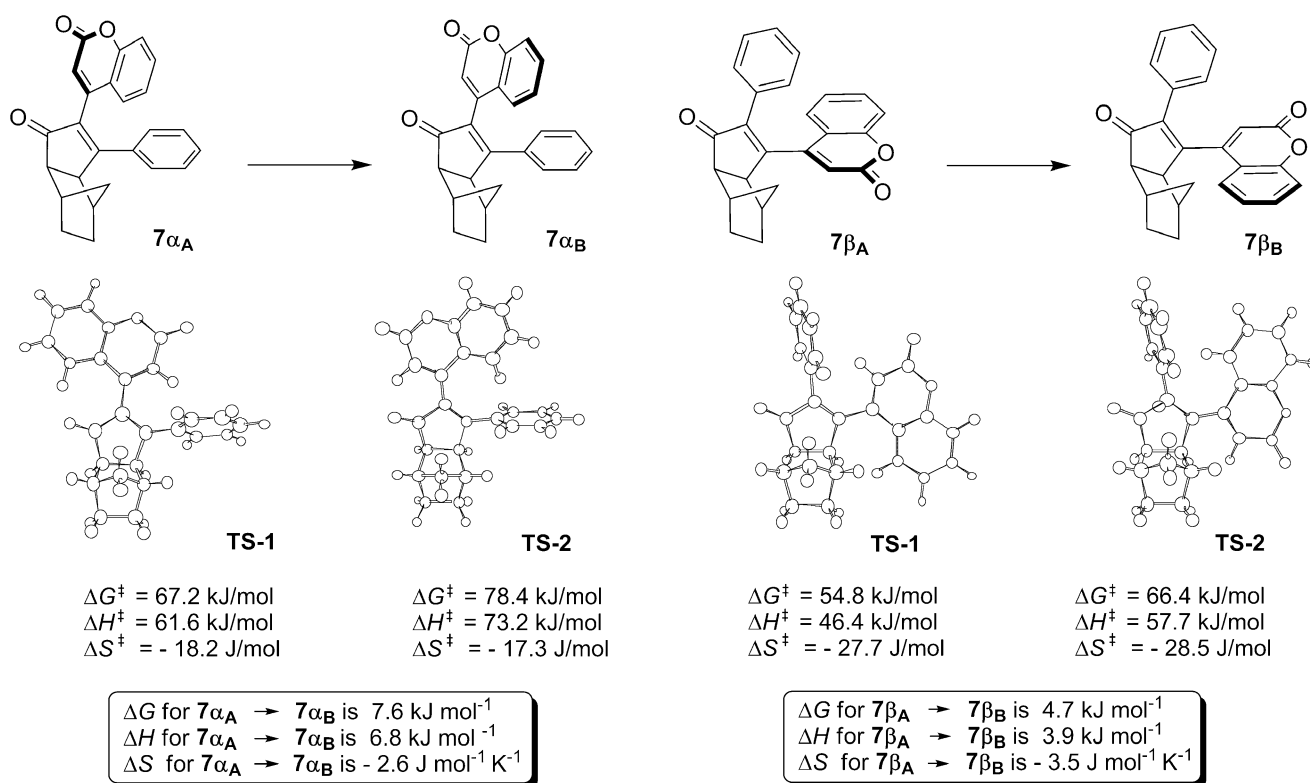


Fig. 6 Theoretically determined energetic parameters for both of the regioisomeric products 7α and 7β . For each process, two different transition state structures were calculated considering the clockwise and anticlockwise rotations about the single C–C bond connecting the coumarin moiety to the cyclopentenone framework.

$7\beta_A$ (for each regioisomer). The calculations also show that the two atropisomers of 7β are closer in energy than the two isomers of 7α , with $7\beta_A$ being 4.7 kJ mol^{-1} more stable than $7\beta_B$, and $7\alpha_A$ being 7.6 kJ mol^{-1} more stable than $7\alpha_B$.

Conclusions

In this paper we have demonstrated that 4-(2-phenylethynyl)-2H-chromen-2-one **5** reacts with norbornene and $\text{Co}_2(\text{CO})_8$ in an intermolecular Pauson–Khand reaction. The electron deficient moiety preferentially occupies the β -position of the cyclopentenone. However, both regioisomeric cyclopentenone products 7α and 7β exhibit atropisomerisation. The magnitude of the energetic barrier to interconversion between these atropisomers is dependent on the relative position of the coumarin substituent. Interconversion is slow when the coumarin is found in the α -position, whereas interconversion is relatively fast when found in the β -position. It is interesting to note this is a rare instance¹³ where atropisomerisation has been observed in the formation of PK-type cyclopentenone products.

Experimental section

Computational studies by DFT

Density functional theory (DFT) calculations at the B3LYP level¹⁴ were performed to calculate the structures of the isomers and the transition states. Frequency calculations were also performed to confirm the characteristics of the calculated structures as minima

or transition states. Calculations of intrinsic reaction coordinates (IRC)¹⁵ were also performed on transition states to confirm that such structures are indeed connecting two minima. The standard 6-31G basis set was used.¹⁶ All calculations were carried out with the Gaussian 03 software package.¹⁷

General experimental details

Solvents were dried where necessary using standard procedures prior to use and stored under an argon atmosphere. DCE refers to 1,2-dichloroethane. Nitrogen gas was oxygen-free and was dried immediately prior to use by passage through an 80 cm column containing sodium hydroxide pellets and silica. Argon gas was used directly *via* balloon transfer or on a Schlenk line. TLC analysis was performed routinely using Merck 5554 aluminium backed silica plates. Compounds were visualised using UV light (254 nm) and a basic aqueous solution of potassium permanganate. ^1H NMR spectra were recorded at either 400 MHz using a JEOL ECX 400 spectrometer, with ^{13}C NMR spectra recorded on the same instrument at 100 MHz (^1H decoupled); or at 500 MHz on a Bruker AV 500 spectrometer, with ^{13}C NMR spectra recorded on the same instrument at 125 MHz (^1H decoupled). Chemical shifts are reported in parts per million (δ) relative to CHCl_3 at δ 7.24 (^1H) or 77.0 (^{13}C). Coupling constants (J values) are reported in Hertz (Hz), and spin multiplicities are indicated by the following symbols: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), br (broad). Full details of the X-ray diffraction studies are given in the ESI.†

4-(2-Phenylethynyl)-2H-chromen-2-one (5). 4-Bromo-2H-chromen-2-one **4** (1.0 g, 4.7 mmol) and phenylacetylene (580 mg, 0.62 mL, 5.6 mmol), PdCl₂(PPh₃)₂ (33 mg, 1 mol%), CuI (27 mg, 3 mol%) and dry acetonitrile (7 mL) were added to an oven dried Schlenk tube charged with a magnetic stirrer bead. Dry triethylamine (1.5 eq.) was added and the reaction was heated at reflux for 16 h. On completion, the reaction mixture was washed with H₂O (10 mL), extracted with CH₂Cl₂ (3 × 20 mL), dried over MgSO₄, filtered and the solvent removed *in vacuo*. Purification by recrystallisation from hot EtOH, afforded the *title compound* as a cream solid (720 mg, 62%). M.p. > 119 °C (decomposes). ¹H NMR (400 MHz, CDCl₃): δ = 6.63 (s, 1H; coumarin), 7.34–7.38 (m, 2H; coumarin), 7.41–7.47 (m, 3H; Ph), 7.57 (ddd, *J* = 8.2, 7.4, 1.6 Hz, 1H; coumarin), 7.65 (m, 2H; Ph), 7.96 (dd, *J* = 8.2 Hz, 1.6 Hz, 1H; coumarin). ¹³C NMR (100.5 MHz, CDCl₃): δ = 82.8 (4°), 102.1 (4°), 117.0 (CH), 118.4 (CH), 118.4 (4°), 121.1 (4°), 124.5 (CH), 126.7 (CH), 128.7 (CH), 130.2 (CH), 132.2 (CH), 132.3 (CH), 137.2 (4°), 153.5 (4°), 160.2 (4°). *v*_{max} (CH₂Cl₂, cm⁻¹) 2211, 1751, 1730, 1719, 1607, 1557, 1491, 1451, 1374, 1324, 1250, 1189, 1146, 1126, 936. LR(ESI-MS): *m/z*: 247{(MH)⁺, 100}. HR(ESI-MS): *m/z*: calcd for C₁₇H₁₁O₂: 247.0754; found: 247.0750 [M+H]⁺.

[μ₂-4-(2-Phenylethynyl)-2H-chromen-2-one]-hexacarbonyl dicobalt (6). Equimolar quantities of dicobalt octacarbonyl (239 mg, 0.7 mmol) and the alkyne **5** (720 mg, 0.7 mmol) were added to a Schlenk tube containing a magnetic stirrer bead. Dry THF (6 mL per mmol) was added and the reaction was stirred for 16 h at room temperature (23 °C). The solvent was removed *in vacuo* and the crude product purified by chromatography on silica gel eluting with hexane–ethyl acetate mixtures (1 : 0 to 9 : 1, v/v), which afforded the *title compound* as a black crystalline solid (286 mg, 77%). ¹H NMR (500 MHz, CDCl₃): δ = 6.82 (s, 1H; coumarin), 7.04 (ddd, *J* = 8.3, 7.3, 1.1 Hz, 1H; coumarin), 7.33 (dd, *J* = 8.0, 1.4 Hz, 1H; coumarin), 7.35–7.39 (m, 3H; Ph), 7.41 (dd, *J* = 8.3, 1.0 Hz, 1H; coumarin), 7.44–7.46 (m, 2H; Ph), 7.50 (ddd, *J* = 8.6, 7.3, 1.1 Hz, 1H; coumarin). ¹³C NMR (125 MHz, CDCl₃): δ = 82.3 (4°), 95.9 (4°), 116.7 (CH), 117.4 (4°), 117.5 (CH), 123.7 (CH), 126.4 (CH), 128.7 (CH), 129.3 (CH), 129.9 (CH), 132.2 (CH), 137.0 (4°), 153.4 (4°), 154.4 (4°), 160.8 (4°), 198.2 (br, M–CO). *v*_{max} (CH₂Cl₂, cm⁻¹) 2097, 2064, 2037, 1716, 1606, 1549, 1350, 1271, 1264, 1188. LR(ESI-MS): *m/z*: 533{(MH)⁺, 100}. HR(ESI-MS): *m/z*: calcd for C₂₃H₁₁Co₂O₈: 532.9112; found: 532.9091 [M+H]⁺. Found – C, 51.83; H, 1.98. C₂₃H₁₀Co₂O₈ requires C, 51.91; H, 1.89.

Pauson–Khand reaction of compound 5. Equimolar quantities of dicobalt octacarbonyl (171 mg, 0.5 mmol) and compound **5** (124 mg, 0.5 mmol) were added to a microwave tube containing a magnetic stirrer bar. 1,2-Dichloroethane (2 mL) was added and the reaction mixture was stirred for 60 min at room temperature (23 °C). After this time, norbornene (235 mg, 2.5 mmol) was added and the reaction tube was placed in a microwave reactor (100 W, 90 °C). Any build-up in pressure was released from the vessel at 10 min intervals during the first hour of the reaction. The reaction was monitored by TLC analysis and heated until the intermediate cobalt complex (**6**) could no longer be detected. On completion, the solvent was removed *in vacuo* and the crude products purified by chromatography on silica gel eluting with hexane–EtOAc (1 : 0

to 7 : 3, v/v) to afford two regioisomeric products **7a** (52 mg, 28%) and **7β** (93 mg, 52%).

Data for (3aRS,4SR,7RS,7aSR)-6-Methyl-4-(1-oxo-3-phenyl-3a,4,5,6,7,7a-hexahydro-1H-4,7-methanoinden-2-yl)-2H-chromen-2-one (7a). M.p. > 88 °C (decomposes). ¹H NMR (500 MHz, 303 K, CDCl₃) (quoted as a mixture of atropisomers): δ = 1.08 (d, *J* = 10.8 Hz, 0.8H; H-8), 1.22–1.27 (m, 1.8H; H-8), 1.39 (d, *J* = 10.8 Hz, 1H; H-8), 1.44–1.52 (m, 3.6H; H-5,6-endo), 1.67–1.80 (m, 3.6H; H-5,6-exo), 2.24–2.28 (br, 1.8H; H-7a), 2.60 (d, *J* = 5.4 Hz, 1H), 2.62–2.66 (m, 1.6H; H-7 + H-4), 2.66–2.69 (br, 1H; H-7), 3.39 (d, *J* = 5.4 Hz, 1H; H-3a), 3.43 (d, *J* = 5.4 Hz, 0.8H; H-3a), 6.00 (s, 0.8H; C3-coumarin), 6.45 (s, 1H; C3-coumarin), 6.88–6.95 (m, 1.8H), 7.26–7.33 (m, 9.8H), 7.34–7.41 (m, 3.6H), 7.43–7.47 (d, 1H), 7.55–7.59 (m, 1H). ¹³C NMR (125 MHz, 303 K, CDCl₃): δ = 28.6 (CH₂), 28.7 (CH₂), 28.9 (CH₂), 29.1 (CH₂), 31.7 (CH₂), 32.4 (CH₂), 38.7 (CH), 39.2 (CH), 39.4 (CH), 39.8 (CH), 50.7 (CH), 51.5 (CH), 54.4 (CH), 54.7 (CH), 116.5 (CH), 116.8 (4°), 117.2 (CH), 117.4 (CH), 117.7 (CH), 118.7 (4°), 123.8 (CH), 124.6 (CH), 125.8 (CH), 126.3 (CH), 128.2 (CH), 128.3 (CH), 129.0 (CH), 131.0 (CH), 131.7 (CH), 132.2 (CH), 133.0 (4°), 133.6 (4°), 136.6 (4°), 138.4 (4°), 147.6 (4°), 149.6 (4°), 153.9 (4°), 154.1 (4°), 160.2 (4°), 160.3 (4°), 172.7 (4°), 174.1 (4°), 206.1 (4°), 206.6 (4°). *v*_{max} (CH₂Cl₂, cm⁻¹) 2963, 2877, 1755, 1723, 1695, 1628, 1606, 1559, 1450, 1380, 1371, 1327, 1198, 1183. LR(ESI-MS): *m/z*: 369{(MH)⁺, 100}. HR(ESI-MS): *m/z*: calcd for C₂₅H₂₁O₃: 369.1485; found: 369.1493 [M+H]⁺.

Data for (3aRS,4SR,7RS,7aSR)-6-Methyl-4-(1-oxo-2-phenyl-3a,4,5,6,7,7a-hexahydro-1H-4,7-methanoinden-3-yl)-2H-chromen-2-one (7β). M.p. > 196 °C (decomposes). ¹H NMR (500 MHz, 303 K, CDCl₃): δ = 1.15 (d, *J* = 10.6 Hz, 1H; H-8), 1.28–1.34 (m (overlapping d, *J* = 10.6 Hz), 2H; H-8), 1.37–1.43 (m, 1H; H-5,6-endo), 1.63–1.74 (m, 2H; H-5,6-exo), 2.12–2.28 (br, 1H; H-4), 2.60 (d, *J* = 5.5 Hz, 1H; H-7a), 2.69 (br, 1H; H-7), 3.01 (d, *J* = 5.5 Hz, 1H; H-3a), 5.72–6.65 (br, 1H), 7.04–7.24 (m, 6H), 7.38–7.42 (m, 2H), 7.44–7.62 (br s, 1H). ¹³C NMR (125 MHz, 303 K, CDCl₃): δ = 28.4 (CH₂), 28.8 (CH₂), 31.6 (br, CH₂), 37.6 (CH), 40.0 (CH), 52.0 (br, CH), 54.1 (CH), 114.4 (4°), 117.5 (CH), 124.5 (br, 4°), 125.9 (4°), 128.3 (CH), 128.4 (CH), 128.8 (CH), 129.8 (br, 4°), 132.5 (CH), 145.9 (br, CH), 153.8 (4°), 156.3 (4°), 159.9 (4°), 207.2 (4°). *v*_{max} (CH₂Cl₂, cm⁻¹) 2963, 2877, 1726, 1707, 1606, 1562, 1494, 1450, 1372, 1322, 1183, 1105. LR(ESI-MS): *m/z*: 391{(MNa)⁺, 100}. HR(ESI-MS): *m/z*: calcd for C₂₅H₂₀NaO₃: 391.1305; found: 391.1318 [M+Na]⁺.

Acknowledgements

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