DOI: 10.1002/ejoc.201201370

Benzannulated Cycloheptanones from Binaphthyl Platforms

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Keywords: Helical structures / Density functional calculations / NMR spectroscopy / Multiple quantum NMR

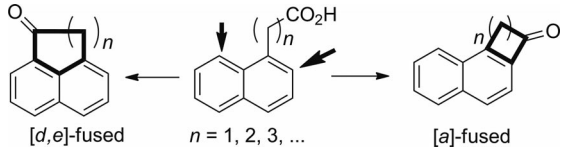
Preparations of benzannulated cycloheptanones starting from unique binaphthyl molecular platforms are described. Binaphthyl acetic acids proved suitable percursors for fused cycloheptanone architectures. Seven-membered rings embedded in binaphthyl units were selectively generated by use of Eaton's reagent. Isomeric helical architectures arising from electrophilic cyclisation processes at second reaction sites in the precursors could also be obtained under different acidic conditions. Unambiguous discrimination between isomeric geometries was provided by multiple quantum NMR sequences. DFT calculations were performed and gave evidence of different behaviour of the substrates towards intramolecular electrophilic substitution. The theoretical approach confirmed the experimental results, agreeing completely with X-ray data.

Introduction

Benzannulated cycloalkanones have been a focus of continuous interest over the last decades. Textbook and advanced methodologies to install small- to medium- and large-sized carbocycles in phenyl or naphthyl derivatives have been developed.[1] Such motifs based on cycloheptanone cores are key intermediates in the preparation of complex molecular architectures and natural products.[2] The presence both of distorted and of planar units usually induces a deformation of the overall carbon framework, a key factor in the modulation of properties of porphyrin-like compounds,[3] potent tumourigenic activity[4] and inhibition of mammalian aminopeptidases.[5]

In this large family of fused molecules, we became interested in naphthylannulated cycloheptanones. In this context, naphthyl alkanoic acids or derivatives are common and obvious starting materials for the elaboration of naphthylcycloalkanone backbones. Electrophilic activation of the acid derivative and further cyclisation can afford two products, however. As shown below, cyclisation is dependent on the ease of generation of the electrophile, the nucleophilicities of the two reaction sites and the alkyl chain length.

Cyclisation reactions of 2-(1-naphthyl)acetic acid derivatives (n = 1, Scheme 1) exclusively afforded the expected [*d,e*]-fused acenaphthenone motif.[6] In contrast, (1-naphthyl)propionic acid derivatives (n = 2) gave mainly mixtures of both [*d,e*]- and [*a*]-fused motifs – phenalenone and naphthylcyclopentanone, respectively – depending on experimental conditions and the use of the carboxylic acid or the acyl chloride as substrate.[6,7] A further increase in the length of the alkyl chain by one carbon atom, to give (1-naphthyl)-butanoic acid (n = 3), led to the exclusive formation of the [*a*]-fused naphthylcyclohexanone.[8] In these cases, the [*d,e*]-fused naphthylcycloheptanone motif was not reported (Scheme 1). Attempts to modify the selectivity through incorporation of a rigid phenyl group in the alkyl chain remained unsuccessful.[9]



Scheme 1. Access to naphthylcycloalkanones from ω-(1-naphthyl)-alkanoic acids.

Interestingly, the influence of further rigidification of such substrates on the cyclisation process and issues of selective synthetis have not yet been reported. By a similar analysis, the unique analogously substituted nonplanar bi-

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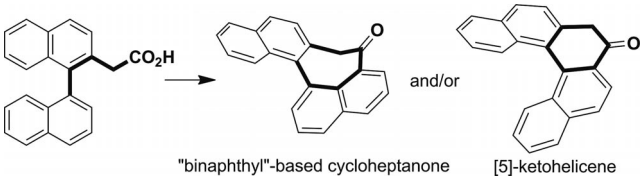
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/ejoc.201201370.

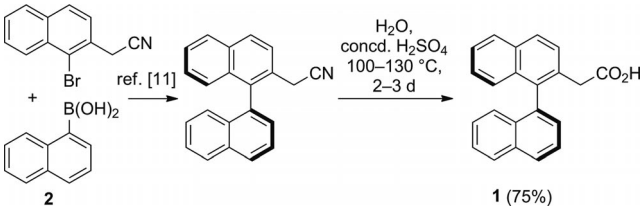
naphthyl core would be expected to afford either the [*d*,*e*]-fused cycloheptanone derivative or the [*a*]-fused [5]-ketohelicene. In this work we show that a binaphthyl platform incorporating an electrophilic carboxylic acid moiety (Scheme 2) is a suitable starting material for the preparation of angular fused cycloheptanones (brown cyclisation site in Figure 2, below). Depending on the reaction conditions and the relative nucleophilicities of the two reactions sites, a second cyclisation process (green cyclisation site in Figure 2) can also take place, allowing the formation of [5]-helicene derivatives (Scheme 2). The formation of binaphthyl-based cycloheptanones is confirmed by multiple quantum NMR sequences, X-ray analysis and theoretical calculations.



Scheme 2. Access to angular cycloheptanones and/or [5]-helicene motifs starting from binaphthyl precursors.

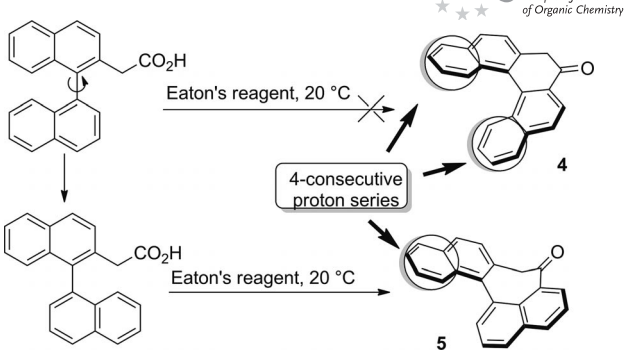
Results and Discussion

Our first goal was to prepare carboxylic acid **1** (Scheme 3) from easily accessible precursors. As shown, compound **1** was readily obtained through Suzuki coupling between naphthalene boronic acid and nitrile **2**.[10] The transformation of the nitrile group was achieved in H_2O by treatment with conc. H_2SO_4 at 100–130 °C to afford the carboxylic acid **1** in high yield.



Scheme 3. Preparation of carboxylic acid **1**.

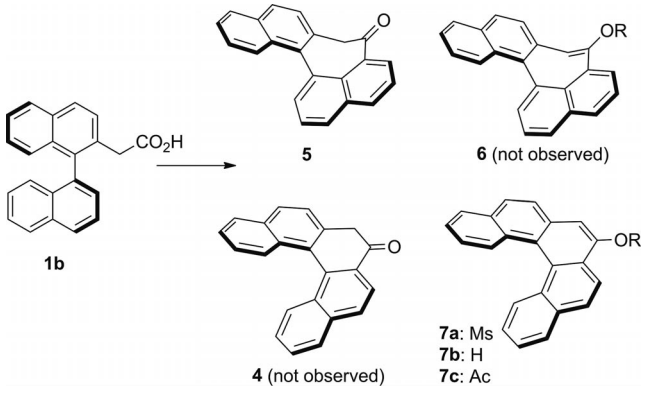
Gratifyingly, acid **1** underwent smooth cyclisation into a new cyclic ketone on treatment with Eaton's reagent [$MeSO_3H$ (MSA), P_2O_5] at room temperature (Scheme 4).[11] The proton NMR spectra clearly supported the obtainment of a methyl ketone fragment, exhibiting two doublets at δ = 4.36 and 3.90 ppm corresponding to the geminal protons α to the carbonyl moiety. The presence of a carbonyl group was detected by IR and exact mass analyses and confirmed the general structure of this molecule.



Scheme 4. Possible ketone architectures accessible from carboxylic acid **1**.

Careful examination of NMR spectra raised the problem of the cyclisation site and the possibility of the obtainment of seven-membered ring ketone **5**, arising from rotation of one naphthyl group around the binaphthyl axis and cyclisation at the brown site in Figure 2, below, rather than the more classical and expected six-membered ring ketone **4**.

The two structures are isomers. The determination of the exact molecular architecture was successfully achieved by means of a multiple quantum NMR sequence (MQS).[12] Indeed, such a sequence, initially developed for particularly crowded proton NMR spectra of multicomponent mixtures, proved very useful in our case and allowed us to discriminate multiple proton patterns on an aromatic core. As shown in Scheme 5, the two possible isomeric structures have different substitution patterns: one four-consecutive-proton series for compound **5** and two four- consecutive-proton series in the case of the ketone **4**. As shown below, the MQS unambiguously showed the presence of only one four-consecutive-proton pattern (labelled a–d), characteristic of the seven-membered ring ketone structure **5** (Figure 1).



Scheme 5. Possible architectures obtained.

Attempts to optimise the reaction led to mixtures of several products depending on the reaction conditions. Scheme 5 shows the possible architectures obtained and Table 1 lists reactions conditions together with ratios between plausible products.

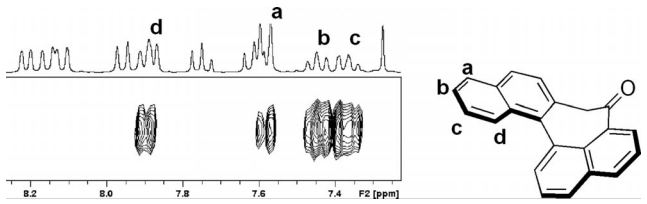


Figure 1. Characteristic MQS and assignment of Ha–Hd protons for ketone **5**.

Table 1. Preparation of compounds **5**–**7**.

Entry	Conditions	Conv.[a] [%]	Ratio **5**/**7**	Yield [%]
1	MSA, P_2O_5, 20 °C	50	100:0	**5** (40)
2	MSA, P_2O_5, 25 °C	100	55:45[b]	**5** (51)/**7a** (38)
3	MSA, P_2O_5, reflux	100	_[c]	_[c]
4	MSA, P_2O_5, DCE, 80 °C	100	42:58[b]	**5** (40)/**7a** (55)
5	AcOH, Ac_2O, $ZnCl_2$	100	40:60	**7c** (63)

[a] Levels of conversion were determined from NMR spectra of the crude materials. [b] Products were not isolated, but were obtained as a mixture of **7a** (major) and **7b**. [c] These reaction conditions led to degradation of both reactants.

At 25 °C, with Eaton's reagent, two types of architectures were obtained in similar amounts (Entry 2). Characteristic NMR signals showed the presence of the ketone **5**, which was isolated in 51% yield. Careful analysis of NMR spectra revealed the presence of two additional products. With the absence of aliphatic protons allowing the formation of compound **4** to be ruled out, the presence of singlets could correspond to the formation of the enol forms **6** and/or **7**. Again, NMR Q4–Q1 correlation unambiguously showed the presence of [5]-helicene architectures. Indeed, the presence of two characteristic four-consecutive-proton patterns is in full agreement with **7**, thus ruling out the possible enol form of the seven-membered ring ketone **6**. We were indeed able to isolate compound **7a** (R = OMs), plausibly arising from the mesylation of the parent six-membered enol **7b**, in 38% yield. Although **7b** (R = H) could not be isolated, its formation could be shown by the presence of a characteristic singlet in the NMR spectra and was confirmed by mass analysis. It was assumed that **7b** was in fact produced first under the acidic conditions, but was rapidly transformed into the corresponding mesylate **7a**.

Heating of **1** at reflux in MSA afforded only degradation byproducts (Entry 3). In contrast, heating of **1** at 80 °C in DCE (1,2-dichloroethane) led to the formation of both **5** and **7a** in a 4:6 ratio (Entry 4). A change from Eaton's reagent to AcOH/$ZnCl_2$ in Ac_2O led to the formation of **7c** (R = Ac, 63% yield), resulting from in situ acetylation of the parent **7b** enol form, as the sole product.

It is worth noting that neither the ketone **4** nor the enol **6** could be isolated. In the [5]-helicene series, the enol form **7b** could plausibly be directly converted into sulfonate **7a** or acetate **7c** derivatives depending on the reaction conditions. In contrast, the twisting of the seven-membered ring likely favoured the formation of the ketone **5** over the corresponding nonplanar potential enol form **6**, which was indeed not observed. MQS again proved a useful tool for unambiguous discrimination between architectures in these series (see the Supporting Information). Compounds **5** and the helicenes **7** are the result of the reaction of a common electrophile, generated from the parent carboxylic acid in the presence of a proton source, at two different cyclisation sites (green and brown sites in Figure 2). As confirmed by quantum chemical calculations[12] at the B3LYP/6-31+G(d,p) level of theory,[13] the two sites have similar capabilities for cyclisation, their similar HOMO coefficients confirming the potential for formation of both products.

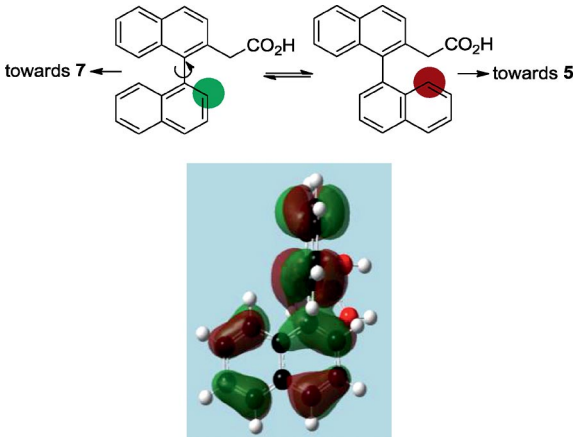
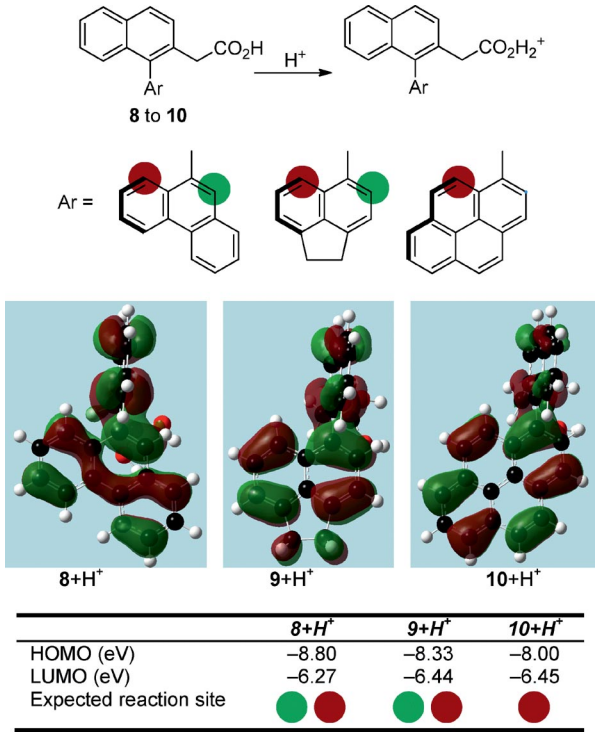


Figure 2. DFT calculations for carboxylic acid **1** + H^+.

In the light of these first results we next focused on three new carboxylic acid derivatives, incorporating phenanthrene, acenaphthene and pyrene subunits (Figure 3). Our objective was to determine whether we could influence the balance between the two cyclisation sites.

DFT calculations afforded insightful forecasts as shown below.

The theoretical approach revealed different behaviour of substrates **8**–**10** towards intramolecular electrophilic substitution. In their HOMOs, protonated substrates **8** and **9** each displayed two valid atomic orbital coefficients, thus potentially affording two products arising from electrophilic substitution at both cyclisation sites. In contrast, the HOMO of the protonated acid **10** showed the presence of a nodal plane responsible for a unique nucleophilic site that would lead to exclusive cyclisation to form the seven-membered ring ketone. Interestingly, the substrate **10**, bearing the pyrene unit, would be expected to afford the best cyclisation results because its protonated form exhibited the highest HOMO value (–8.00 eV) and the strongest interaction between frontier orbitals (1.55 eV). In contrast, as shown by their lower HOMO values, ranging from –8.80 to –8.33 eV, and increased interactions, ranging from 2.53 to 1.89 eV, the two protonated substrates **8** and **9**, respectively, appeared less nucleophilic and less reactive towards the cyclisation process. Carboxylic acids **8**–**10** were prepared as in Scheme 1, through Suzuki couplings followed by hydrolysis of the resulting nitriles under strongly acidic reaction conditions (Figure 4).



	8+H+	9+H+	10+H+
HOMO (eV)	–8.80	–8.33	–8.00
LUMO (eV)	–6.27	–6.44	–6.45
Expected reaction site			

Figure 3. HOMO representations for isovalues at 98%.

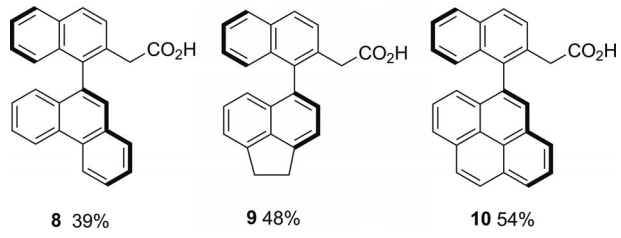
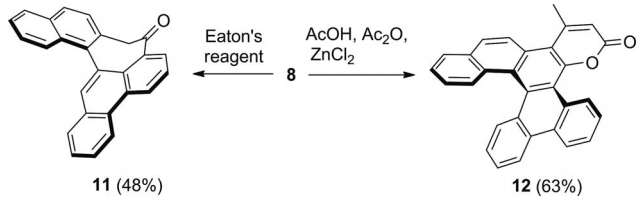


Figure 4. Carboxylic acids **8**–**10**.

Compounds **8**–**10** were obtained in 39, 48 and 54% yields, respectively (Figure 4). Under hydrolysis conditions, no traces of cyclisation products were detected in the crude materials.

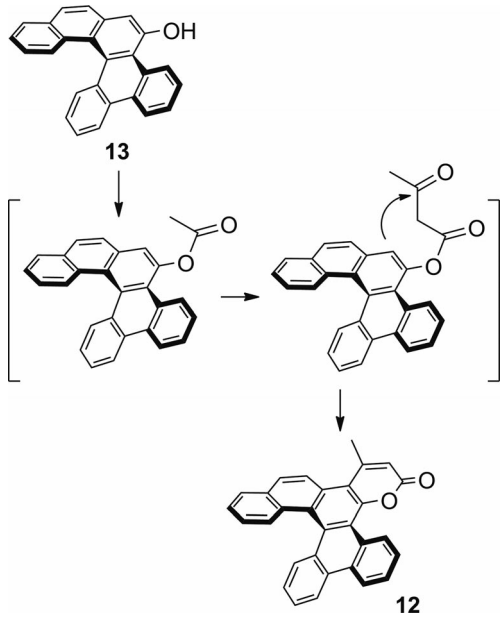
Carboxylic acids **8**–**10** were next subjected to cyclisation under acidic conditions. Surprisingly, when **8** and Eaton's reagent were mixed together at 25 °C, the seven-membered ring ketone **11** was obtained as the sole product in a fair 48% yield (Scheme 6).



Scheme 6. Preparation of ketone **11** and helicene **12**.

Unfortunately, attempts to achieve the formation of the helicene architecture by increasing the reaction temperature failed, in good agreement with theoretical calculations. Although the formation of a second architecture could not be fully ruled out, heating of **8** in MSA at reflux led to intractable mixtures and did not allow us to gain more information. Gratifyingly, though, a change from MSA to AcOH, Ac_2O and $ZnCl_2$ at 120 °C proved successful and allowed us to obtain helicene **12** selectively in a good 63% yield.

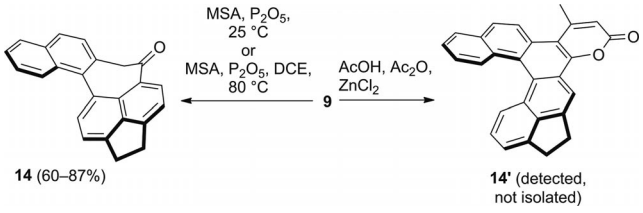
The formation of the helicene **12** can be explained in terms of the following mechanism (Scheme 7), which plausibly involves enol **13** as the first intermediate formed. Compound **13** was not isolated but was probably acetylated under those reaction conditions. A Claisen-type reaction under acidic conditions followed by a final cyclisation step would occur from the newly formed ketoacetate intermediate under acidic catalysis conditions.[14]



Scheme 7. Plausible mechanism for the formation of helicene **12**.

Both ketone **11** and helicene **12** were characterized by NMR spectroscopy. Again, MQS allowed clear discrimination between both architectures (see the Supporting Information).

Similarly, the carboxylic acid **9** was subjected to electrophilic substitution with MSA as the proton source (Scheme 8).

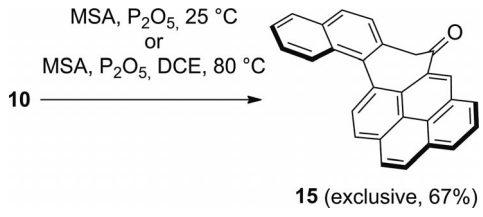


Scheme 8. Preparation of the ketone **14**.

At 25 °C or in DCE at 80 °C, we were able to isolate the ketone **14** as the exclusive cyclisation product in yields ranging from 60 to 87%. The architecture **14′**, which might be obtained with AcOH, Ac_2O and $ZnCl_2$ as cyclisation

conditions, could not be isolated. Its presence could, however, be detected by mass spectroscopy analysis. In this case, observed yields higher than 80% are nevertheless indicative of an almost exclusive product and suggest a major impact of the substitution of the naphthalene core on the electrophilic cyclisation process. The presence of only one four-consecutive-proton series, characteristic of the seven-membered ring ketone structure, was observed by MQS (see ESI).

Finally, the ketone **15** (Scheme 9) was obtained as the exclusive cyclisation product, as expected from theoretical calculations. Indeed, **15** was the sole compound formed during the MSA-promoted cyclisation process whatever reactions conditions, such as temperature and dilutions, were used. Even the use of AcOH, Ac_2O and $ZnCl_2$ at 120 °C for 48 h led exclusively to ketone **15**. No traces of the possible helicene analogues to **7c** or **12**, previously obtained under such reactions conditions, could be detected, confirming exclusive selectivity observed when starting from the carboxylic acid **10**. MQS results were in good agreement with the structure of ketone **15**, which contains the characteristic four-consecutive-proton series.



Scheme 9. Preparation of ketone **15**.

Single crystals of **15** suitable for X-ray analysis (Figure 5) could be obtained by slow evaporation of an ethyl acetate solution.[15] X-ray analysis confirmed the formation of a seven-membered ring arising from cyclisation at the *peri*-position of the pyrene moiety. The strained conformation adopted by the seven-membered ring embedded in the bisaromatic core including one pyrene and one naphthalene fragment, might explain the absence of enolisation even in a concentrated acidic medium. As depicted in Figure 5, the presence of a central nonplanar seven-membered ring dictates the overall geometry of the molecular architecture.

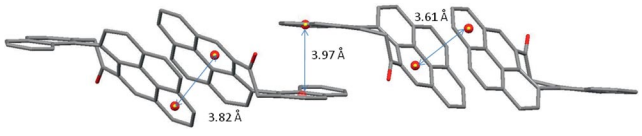


Figure 5. Single-crystal X-ray diffraction analysis of ketone **15**.

Two different intermolecular π–π interactions between planar fragments of the molecule dictate the molecular arrangement. Two adjacent molecules are linked together through two consecutive pyrene units with an average distance of 3.74 Å on one hand, and two naphthalene units with a distance of 3.97 Å on the other hand.

As shown in Figure 6, the optimised geometry obtained from theoretical calculations is in good agreement with X-ray data; relevant comparison of selected data is given in Table 2.

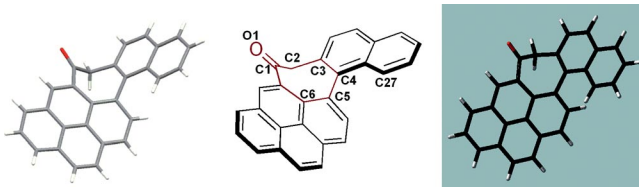


Figure 6. Comparison between X-ray-determined structure **15** (left) and theoretical data [gas phase B3LYP/6-31+G(d,p)] (right).

Table 2. Selected geometric data and comparison for ketone **15**.

Entry	Geometric parameters	X-ray cyrstal structure determination	Quantum chemical calculation
1	C1–O1 [Å]	1.223	1.2228
2	C4–C5 [Å]	1.497	1.4952
3	C5–C27 [Å]	2.980	2.9882
4	C1–C2–C3 [°]	104.8	106.4
5	C1–C2–C3–C4 [°]	65.6	66.36
6	C3–C4–C5–C6 [°]	–54.7	–53.23

The geometric comparisons focused mainly on the seven-membered ring, which is central to the overall molecular architecture. Interestingly, geometric optimisation achieved through quantum chemical calculation proved reliable for the solid-state geometrical parameters. As an example, the C=O double bond and C4–C5 bond that link the two planar fragments together revealed very high levels of accuracy (Entries 1 and 2). In addition, the calculated and determined C5–C27 interatomic distances are almost identical (Entry 3). Moreover, the C1–C2–C3 angle (Entry 4) and the dihedral angles (Entries 5 and 6) that characterize the contortion of the seven-membered ring are very close.

The absorption and emission spectra of **5**, **11**, **14** and **15** in CH_2Cl_2 are shown in Figure 7. As expected, compounds **5** and **14**, which differ from one another only by an ethylene fragment, exhibited closely similar absorption data. The presence of an extended aromatic system, such as in **11** and **15**, bearing a phenanthrene and a pyrene unit, respectively, induced broad red-shifted absorption peaks in comparison with **5**.

Interestingly, the emission spectra of all of the cycloheptanones each exhibited at least two emission peaks, suggesting similar behaviour of all targeted ketones. In fact, all the ketones seem to behave as two structurally independent units. The first (naphthyl, phenanthrenyl, acenaphthyl and pyrenyl), directly linked to the ketone moiety and the second (naphthalenyl), correspond to withdrawing and donating groups, respectively. In this context, each emission spectrum would reflect the presence of a monomer and an exciplex, characterized by the clear presence of two emission peaks and a broad red-shifted emission of the exciplex. The nonplanar and rigid molecular arrangement of the two aromatic units linked together through the cycloheptanone core rather restrict cofacial interactions between the two

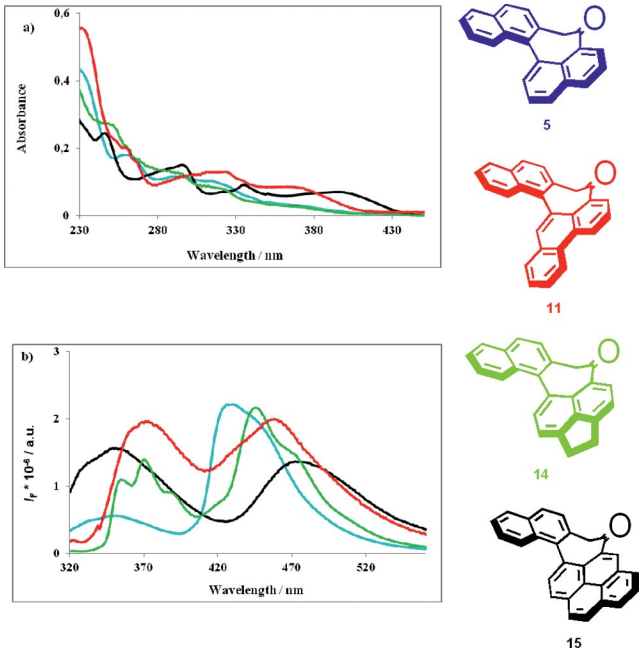


Figure 7. a) Absorption spectra of 10 μM solutions of **5**, **14** and **15** and a 94 μM solution of **11** in CH_2Cl_2. b) Fluorescence spectra of **5** (λ_{exc} = 293 nm), **11** (λ_{exc} = 323 nm), **14** (λ_{exc} = 293 nm) and **15** (λ_{exc} = 295 nm) in CH_2Cl_2.

aromatic planes within the same molecule.[16] The excitation transfer between the donor and acceptor moieties thus most plausibly occurred through intermolecular interactions between two exci-partners. The most pronounced bathochromic shift between the two emission peaks is observed in the pyrenyl series, which is consistent with previous reports in extended aromatic series.[17]

Conclusions

In summary, we have shown that benzannulated cycloheptanones can be efficiently prepared from versatile binaphthyl molecular platforms. Several binaphthyl acetic acids, each containing two potential cyclisation sites, have been studied. Seven- and six-membered rings were generated selectively, depending on the reaction conditions and on the relative nucleophilicities of the precursor cyclisation sites. Multiple quantum NMR sequences allowed clear discrimination between potential isomeric molecular architectures arising from cyclisation at different sites. DFT predictive calculations were performed; they agreed completely with the observed selectivity and were confirmed by the X-ray data to be highly reliable.

Experimental Section

General: Unless otherwise noted, all starting materials were obtained from commercial suppliers and used without purification. Petroleum ether was distilled under argon. NMR spectra were recorded with 400 MHz, 300 MHz and 200 MHz Bruker spectrometers. Chemical shifts are reported in ppm relative to the residual solvent peaks (δ =7.26 ppm for $CHCl_3$, 5.32 ppm for $[D_2]$dichloromethane, 3.58 ppm for $[D_8]$THF for ^1H spectra and δ =77.00 ppm for $CDCl_3$, 53.8 ppm for $[D_2]$dichloromethane, 67.4 ppm for $[D_8]$-THF) for ^{13}C spectra. HRMS data were recorded with an Autospec Ultima (Waters/Micromass) device with a resolution of 5000 RP at 5%. 1-Bromo-2-(cyanomethyl)naphthalene was prepared as described in reference S1 in the Supporting Information. UV/Vis analyses were performed with a Perkin–Elmer UV/Vis/NIR Lambda 19 spectrophotometer; 1 cm path quartz cells were used for the measurements. Steady-state fluorescence measurements were recorded with a FluoroMax-3 spectrofluorimeter with a 150 W Xenon lamp and a slit width of 5 nm. For all measurements, the samples used for fluorescence are the same for UV/Vis.

Typical Procedure for the Preparation of Carboxylic Acid 1: Concentrated H_2SO_4 (4 mL) was added at 0 °C to a stirred suspension of nitrile reactant (0.46 mmol) in H_2O. The mixture was stirred at 130 °C for 2 d. The resulting solution was extracted with dichloromethane (4 × 10 mL). The organic phase was then washed with water. The combined organic layers were dried, filtered and concentrated under vacuum. The crude product was purified by flash chromatography. After purification on silica gel (PE/EtOAc 50:50), **1** was obtained (108 mg, 75%) as a yellow solid. ^1H NMR (300 MHz, $CDCl_3$): δ = 10.70 (br., 1 H), 8.05–7.90 (m, 4 H), 7.65–7.56 (m, 2 H), 7.42–7.50 (m, 3 H), 7.30–7.17 (m, 4 H), 3.47 (m, 2 H, CH_2) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 177.4, 137.4, 135.9, 133.6, 133.4, 132.7, 132.6, 130.1, 128.3, 128.3, 128.3, 128.2, 128.2, 127.9, 127.7, 126.8, 126.3, 126.1, 126.0, 125.8, 125.5, 39.1 ppm. IR: $\tilde{\nu}$ = 3150, 2450, 1703, 1405, 1290, 1225, 824, 759 cm^{-1}. HRMS (ESI): calcd. for $C_{22}H_{16}O_2Na$ $[M + Na]^+$ 335.1057; found 335.1048.

Compound 8: After purification on silica gel (PE/EtOAc 50:50), **8** was obtained (100 mg, 39%) as a brown solid. ^1H NMR (300 MHz, $CDCl_3$): δ = 10.32 (br., 1 H), 8.82 (d, J = 8.2 Hz, 2 H), 8.06–7.83 (m, 3 H), 7.78–7.64 (m, 4 H), 7.59–7.28 (m, 6 H), 3.78–3.37 (m, 2 H, CH_2) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 177.0, 137.2, 134.5, 133.6, 132.7, 131.7, 130.4, 130.3, 129.1, 128.7, 128.2, 128.1, 127.9, 127.7, 127.6, 127.3, 126.9, 126.8, 126.7, 126.3, 126.2, 126.0, 125.8, 122.8, 122.6, 39.1 ppm. IR: $\tilde{\nu}$ = 3039 (OH), 1698 (CO) cm^{-1}. HRMS (ESI): calcd. for $C_{25}H_{17}$ $[M - CO_2 - H]^-$ 317.1334; found 317.1330.

Compound 9: After purification on silica gel (PE/EtOAc 50:50), **9** was obtained (75 mg, 48%) as a brown solid. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.93 (t, J = 8.5 Hz, 2 H), 7.55 (d, J = 8.5 Hz, 1 H), 7.48–7.29 (m, 5 H), 7.27–7.19 (m, 2 H), 6.89 (d, J = 7.5 Hz, 1 H), 3.63–3.42 (m, 6 H, CH_2) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 177.9, 146.0, 139.3, 137.1, 133.4, 132.6, 130.9, 130.2, 129.8, 128.0, 127.7, 127.4, 126.8, 126.5, 126.4, 126.1, 126.0, 125.5, 120.9, 119.4, 119.0, 39.6, 30.4, 30.1 ppm. IR: $\tilde{\nu}$ = 3050 (OH), 1701 (CO) cm^{-1}. HRMS (ESI): calcd. for $C_{24}H_{17}O_2$ $[M - H]^-$ 337.1249; found 337.1229.

Compound 10: After purification on silica gel (PE/EtOAc 50:50), **10** was obtained (59 mg, 54%) as a yellow solid. ^1H NMR (300 MHz, $CDCl_3$): δ = 8.16 (d, J = 7.8 Hz, 1 H), 8.10 (d, J = 8.1 Hz, 1 H), 8.04 (s, 1 H), 7.95–7.78 (m, 6 H), 7.69 (d, J = 8.5 Hz, 1 H), 7.47 (d, J = 8.5 Hz, 1 H), 7.38–7.29 (m, 2 H), 7.15–7.08 (m, 1 H), 6.97 (d, J = 7.5 Hz, 1 H), 3.42–3.25 (m, 4 H, CH_2) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 177.2, 137.9, 133.6, 133.4, 132.7, 131.4, 131.1, 131.0, 130.5, 128.4, 128.3, 128.2, 127.9, 127.8 (2 C), 127.7, 127.5, 127.0, 126.4, 126.2, 126.1, 125.9, 125.3, 125.2, 124.8 (2 C), 124.7, 39.1 ppm. IR: $\tilde{\nu}$ = 3026 (OH), 1702 (CO) cm^{-1}. HRMS (ESI): calcd. for $C_{28}H_{18}O_2Na$ $[M + Na]^+$ 409.1203; found 409.1204.

Typical Procedure for Cyclisation of Carboxylic Acids with Eaton's Reagent: Acid **1** (190 mg, 0.6 mmol) in DCE (2 mL) was solubilized in MSA (10 mL)/P_2O_5 (20 mg) and the red solution was stirred at room temperature for 3 d. The resulting dark red solution was poured into ice (50 g), and the aqueous phase was extracted with dichloromethane (3 × 20 mL) The combined organic layers were dried, filtered and concentrated under vacuum. The crude product was purified by flash chromatography on silica gel (PE/EtOAc 9:1) to give the ketone **5** (91 mg, 51%) as a yellow paste and the helicene **7a** (86 mg, 38%) as a brown solid.

Ketone 5: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.20 (d, J = 7.1 Hz, 1 H, 17-H), 8.15 (d, J = 8.3 Hz, 1 H, 15-H), 8.11 (t, J = 8.1 Hz, 1 H, 14-H), 7.95 (d, J = 8.4 Hz, 1 H, 4-H), 7.93–7.85 (m, 3 H, 5-H, 12-H), 7.75 (t, J = 6.9 Hz, 1 H, 13-H), 7.64–7.57 (m, 3 H, 8-H, 3-H, 16-H), 7.47–7.42 (m, 1 H, 6-H), 7.39–7.34 (m, 1 H, 7-H), 4.34 (d, J = 10.8 Hz, 1 H, 22-H), 3.90 (d, J = 10.8 Hz, 1 H, 22-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 192.2, 135.7, 135.5, 134.3, 134.0, 133.9, 133.8, 133.4, 132.7, 130.4, 130.0, 129.9, 129.6, 129.5, 128.4, 126.7, 126.4, 126.3, 125.3, 125.1, 124.9, 51.1 ppm. IR: $\tilde{\nu}$ = 1674 (CO) cm^{-1}. HRMS (ESI): calcd. for $C_{22}H_{15}O$ $[M + H]^+$ 295.1204; found 295.1123.

Helicen-13-yl Methanesulfonate 7a: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.47 (d, J = 8.6 Hz, 1 H, 8-H), 8.42 (d, J = 8.6 Hz, 1 H, 18-H), 8.20 (d, J = 8.5 Hz, 1 H, 3-H), 8.02 (d, J = 8.8 Hz, 1 H, 4-H), 7.99–7.94 (m, 4 H, 22-H, 13-H, 15-H, 5-H), 7.84 (d, J = 8.6 Hz, 1 H, 14-H), 7.60–7.48 (m, 2 H, 6-H, 16-H), 7.31–7.25 (m, 2 H, 7-H, 17-H), 3.28 (s, 3 H, SO_2Me) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 143.7, 132.6, 132.5, 131.3, 130.4, 130.3, 129.1, 128.9, 128.8, 128.6, 128.5, 128.0, 127.9, 127.1, 126.6, 126.0, 125.9, 125.7, 124.9, 124.8, 118.8, 118.6, 37.9 ppm. IR: $\tilde{\nu}$ = 1445 (S=O), 1171 (S–O) cm^{-1}. HRMS (ESI): calcd. for $C_{23}H_{16}O_3SNa$ $[M + Na]^+$ 395.0718; found 395.0671.

Ketone 11: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.05 (d, J = 8.3 Hz, 1 H, 15-H), 8.84 (d, J = 8.1 Hz, 1 H, 26-H), 8.32 (d, J = 8.4 Hz, 1 H, 17-H), 8.09 (s, 1 H, 12-H), 8.00–7.93 (m, 2 H, 4-H, 23-H), 7.93 (d, J = 8.4 Hz, 1 H, 5-H), 7.85–7.65 (m, 3 H, 25-H, 16-H, 24-H), 7.61–7.57 (m, 2 H, 8-H, 3-H), 7.47–7.42 (m, 1 H, 6-H), 7.35–7.21 (m, 1 H, 7-H), 4.48 (d, J = 10.8 Hz, 1 H, 22-H), 3.92 (d, J = 10.8 Hz, 1 H, 22-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 192.2, 136.1, 135.8, 134.9, 133.8, 133.0, 131.2, 131.1, 130.6, 130.2, 130.1, 129.5, 129.2, 128.9, 128.4, 128.1, 127.6, 127.5, 126.6, 126.5, 126.1, 125.7, 125.3, 125.0, 122.8, 50.9 ppm. IR: $\tilde{\nu}$ = 1698 (CO) cm^{-1}. HRMS (ESI): calcd. for $C_{26}H_{16}O$ $[M + H]^+$ 345.1281; found 345.1279.

Ketone 14: ^{1}H NMR (200 MHz, $CDCl_3$): δ = 8.18 (d, J = 7.5 Hz, 1 H, 17-H), 7.97 (d, J = 7.8 Hz, 1 H, 12-H), 7.93–7.86 (m, 2 H, 4-H, 5-H), 7.83 (d, J = 7.6 Hz, 1 H, 8-H), 7.61–7.55 (m, 2 H, 13-H, 3-H), 7.44–7.33 (m, 3 H, 6-H, 16-H, 7-H), 4.27 (d, J = 11.0 Hz, 1 H, 22-H), 3.90 (d, J = 11.0 Hz, 1 H, 22-H), 3.59–3.50 (m, 4 H, 23-H, 24-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 192.6, 152.9, 147.6, 139.8, 135.4, 134.8, 133.8, 132.4, 132.4, 131.5, 130.1, 129.3, 128.9, 128.3, 128.2, 127.2, 127.0, 126.1, 125.1, 119.3, 118.8, 51.7, 30.9, 30.4 ppm. IR: $\tilde{\nu}$ = 1672 (CO) cm^{-1}. HRMS (ESI): calcd. for $C_{24}H_{17}O$ $[M + H]^+$ 321.1279; found 321.1283.

Ketone 15: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.86 (s, 1 H, 17-H), 8.39–8.11 (m, 6 H, 25-H, 27-H, 24-H, 23-H, 13-H, 12-H), 8.09 (t, J = 7.7 Hz, 1 H, 26-H), 7.98 (d, J = 8.3 Hz, 1 H, 4-H), 7.91 (d, J = 7.5 Hz, 1 H, 8-H), 7.58 (d, J = 8.4 Hz, 1 H, 3-H), 7.44 (d, J = 7.6 Hz, 1 H, 5-H), 7.44–7.35 (m, 1 H, 7-H), 7.35–7.29 (m, 1 H, 6-H), 4.40 (d, J = 10.7 Hz, 1 H, 22-H), 4.01 (d, J = 10.7 Hz, 1 H, 22-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 192.5, 135.7, 134.5, 133.8, 133.1, 132.7, 132.4, 131.6, 131.2, 131.0, 130.0, 129.4, 129.0, 128.7, 128.6, 128.4, 128.2, 127.6, 127.1, 126.7, 126.6, 126.4, 126.3, 125.8, 125.5, 125.3, 124.4, 50.7 ppm. IR: $\tilde{\nu}$ = 1676 (CO) cm^{-1}. HRMS (ESI): calcd. for $C_{28}H_{15}O$ $[M - H]^-$ 367.1220; found 367.1123.

Typical Procedure for Cyclisation of Carboxylic Acids with AcOH/Ac_2O/$ZnCl_2$: Acid **1** (50 mg, 0.16 mmol) was solubilized in an AcOH/Ac_2O (3:2) mixture (10 mL), and then $ZnCl_2$ (436 mg, 3.2 mmol, 20.0 equiv.) was added. The solution was stirred at reflux for 48 h. H_2O (10 mL) was added to the resulting dark solution, and the aqueous phase was extracted with EtOAc (3 × 20 mL); the organic phase was then washed with H_2O (20 mL). The combined organic layers were dried, filtered and concentrated under vacuum. The crude product was purified by flash chromatography on silica gel (PE/EtOAc 6:4) to give the helicene **7c** (35 mg, 63%) as a yellow solid.

Helicene 7c: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.49 (d, J = 8.7 Hz, 1 H, 18-H), 8.44 (d, J = 8.7 Hz, 1 H, 8-H), 7.97–7.80 (m, 6 H, 15-H, 14-H, 13-H, 5-H, 4-H, 3-H), 7.68 (s, 1 H, 22-H), 7.58–7.48 (m, 2 H, 6-H, 16-H), 7.32–7.23 (m, 2 H, 7-H, 17-H), 2.55 (s, 3 H, 23-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 169.6, 145.2, 132.5, 132.4, 131.7, 130.7, 130.6, 129.3, 129.0, 128.6, 128.1, 128.0, 127.9, 127.8, 126.7, 126.2, 126.0, 125.8, 125.3, 124.7, 125.5, 118.9, 118.6, 21.1 ppm. IR: $\tilde{\nu}$ = 1797 (CO) cm^{-1}. HRMS (ESI): calcd. for $C_{22}H_{13}O$ $[M - MeCO]^-$ 293.1770; found 293.1760.

Helicene 12: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 10.11 (d, J = 9.0 Hz, 1 H, 3-H), 9.14 (d, J = 7.8 Hz, 1 H, 23-H), 8.74 (d, J = 8.0 Hz, 1 H, 26-H), 8.57 (d, J = 9.0 Hz, 1 H, 15-H), 8.18 (d, J = 8.0 Hz, 1 H, 8-H), 8.10 (d, J = 8.1 Hz, 1 H, 4-H), 8.07 (d, J = 9.0 Hz, 1 H, 18-H), 7.96 (d, J = 7.0 Hz, 1 H, 5-H), 7.80–7.75 (m, 2 H, 25-H, 24-H), 7.61 (t, J = 6.0 Hz, 1 H, 16-H), 7.49 (t, J = 6.0 Hz, 1 H, 6-H), 7.26–7.16 (m, 2 H, 17-H, 7-H), 6.49 (s, 1 H, 29-H), 2.59 (s, 3 H, Me) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 180.1, 162.9, 155.7, 134.1, 132.1, 131.0, 130.9, 130.5, 130.4, 130.1, 129.6, 129.5, 128.7, 128.5, 128.2, 127.8, 127.6, 127.5, 127.4, 126.3, 126.0, 124.8, 123.8, 123.6, 123.5, 123.4, 121.2, 116.3, 113.9, 19.9 ppm. IR: $\tilde{\nu}$ = 1655 (CO) cm^{-1}. HRMS (ESI): calcd. for $C_{30}H_{19}O_2$ $[M + H]^+$ 411.1386; found 411.1385.

Supporting Information (see footnote on the first page of this article): ^{1}H NMR, ^{13}C NMR and multiple quantum NMR spectra and DFT calculations.

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Received: October 16, 2012
Published Online: December 6, 2012

