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PAPER

Synthesis of benzo- and naphtho-fused bicyclo[n.3.1]alkane frameworks with a bridgehead nitrogen function by palladium-catalyzed intramolecular α′-arylation of α-nitroketones†

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The *C*-alkylation of cyclic α-nitroketones with α-halobenzyl halides in the presence of DBU followed by a Pd-catalyzed intramolecular *C*-arylation afforded benzo-and naphtho-fused bicyclo[n.3.1]alkane derivatives (n = 3, 4, 5) in excellent overall yields for the two-step sequence. In some of the reactions starting from α-nitrocyclooctanone, the major products were fused indane derivatives arising from an intramolecular attack of an intermediate Pd species onto the carbonyl group, followed by elimination.

Introduction

Areno-fused derivatives of bicyclo[n.3.1]alkane systems (Fig. 1) are present in a variety of bioactive natural and unnatural compounds. Thus, compounds of structure **1** represent a new class of opioid analgesics, designed as analogues of the benzomorphans having an exocyclic rather than endocyclic nitrogen atom.[1] The structurally related dezocine is a well-established analgesic drug, with a potency comparable to that of meperidine, but which produces dysphoria and hallucinations at high doses due to interaction with κ-opioid receptors.[2] One example of a natural product with a benzo-fused bicyclo[n.3.1]alkane framework is obtusanal B, a diterpene recently isolated from the heartwood of the Taiwanian tree *Chamaecyparis obtusa*.[3] *N*-Methylwelwistatin (also known as *N*-methylwelwitindolinone C isothiocyanate) can be considered as the biologically most relevant of the welwitindolinones, a family of structurally unusual oxindole alkaloids isolated from marine cyanobacteria.[4] It inhibits the glycoprotein P-170-mediated resistance of MCF-7/ADR tumor cells to commonly used anticancer drugs such as vinblastine, taxol, actinomycin D and daunomycin at 10^{-7} M concentrations,[5] representing a potency 20- to 100-fold that of verapamil, the reference MDR reversor.[6] Furthermore, welwistatin also behaves as an antimicrotubule agent that inhibits the polymerization of tubulin.[7] Since this is the main mechanism of action of antitumor drugs such as vincristine and vinblastine, and because P-gp-overexpressing cells show virtually no resistance to welwistatin due to its MDR reversal properties, this natural product can be considered as a good lead compound in the chemotherapy of drug-resistant tumors. Finally, huperzine A, isolated from the firmoss *Huperzia serrata*, is a centrally-acting acetylcholinesterase inhibitor that is sold as a dietary supplement for memory support in some countries and has been clinically evaluated as an anti-Alzheimer drug.[8] It is noteworthy that both *N*-methylwelwistatin and huperzine A bear nitrogen functions at a bridgehead position, which so far have been installed through a multistep approach involving a Curtius rearrangement.[9]

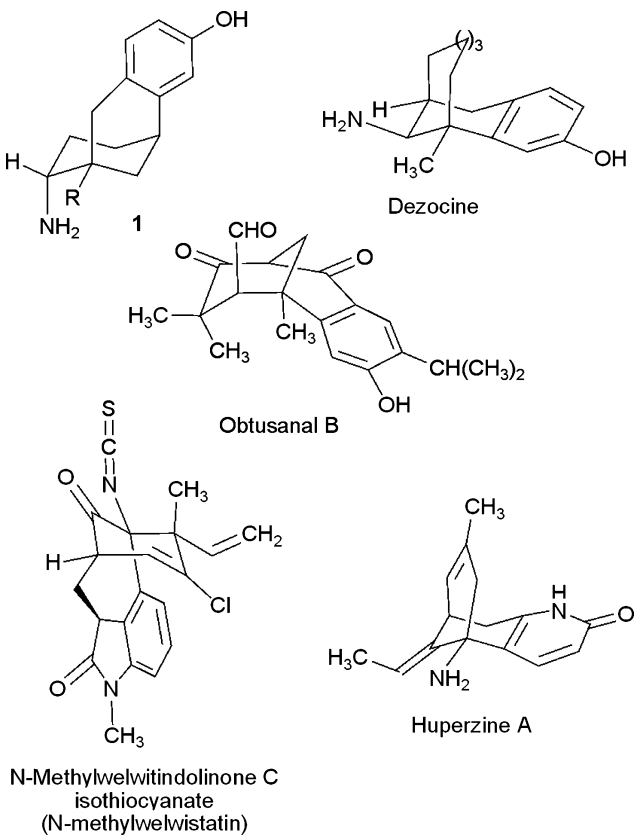

Fig. 1 Some bioactive compounds and natural products containing fused bicyclo[n.3.1]alkane frameworks.

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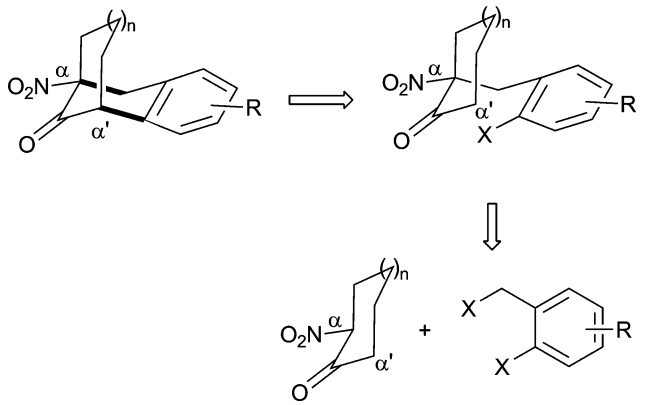
† Electronic supplementary information (ESI) available: Copies of spectra of representative compounds. See DOI: 10.1039/c0ob00526f

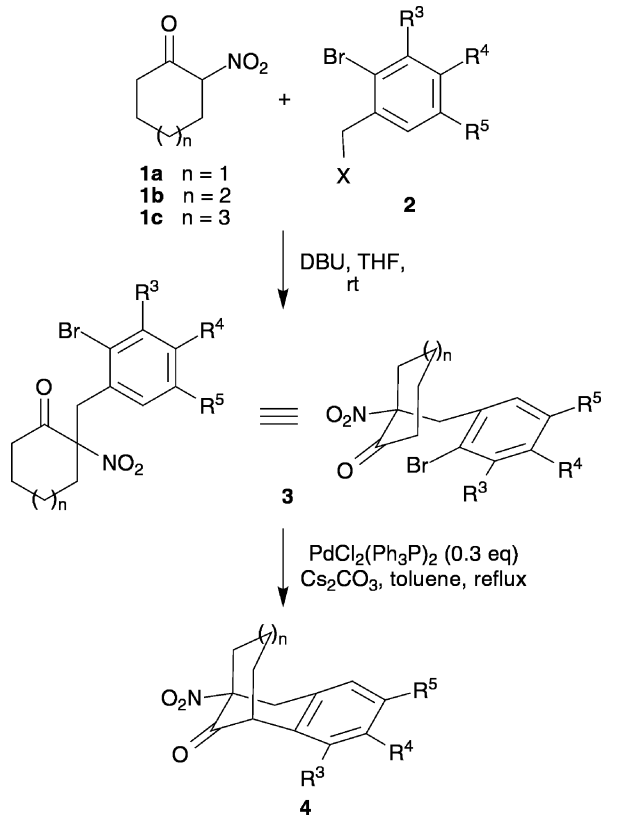
We present in this paper our findings related to the development of a new route to bicyclo[n.3.1]alkane systems from cyclic α-nitroketones, which leads to the presence of bridgehead nitrogen functions in a natural, straightforward fashion. Retrosynthetically, our plan involved an α-alkylation/α′-arylation sequence, as summarized in Scheme 1. The preparation of bicyclic compounds with a bridgehead nitro group by this strategy is unprecedented although there is mention in the literature of the synthesis of one example of a benzo-fused bicyclo[3.3.1]decane and another of a benzo-fused bicyclo[4.3.1]undecane using a similar method but starting from 6- and 7-membered cyclic α-ketoesters.[10] In spite of its straightforward appearance, our strategy involved some novel aspects that were a cause for concern in the planning stage. Thus, the intermolecular *C*-alkylation of a nitronate required for the first step can be considered problematic and indeed this type of reaction has found little application in synthesis owing to the existence of a competing *O*-alkylation process.[11] Furthermore, the direct carbon-carbon bond formation between an arene and the carbon adjacent to a carbonyl group is quite challenging, since enolate nucleophiles and aromatic halides are not good reaction partners, and it has been only recently that methods allowing this transformation have been developed, mostly based on nickel[12] or (specially) palladium-catalyzed[13] cross-coupling reactions. Nevertheless, there was no precedent for such an arylation starting from an α-nitroketone derivative.



Scheme 1 Retrosynthetic analysis of our target molecules.

Results and discussion

The *C*-alkylation of α-nitroketones **1** with dihalides **2** was assayed under a variety of conditions, and we eventually identified DBU as base and tetrahydrofuran as solvent, at room temperature, as the optimal combination. In these conditions, and contrary to literature precedent with other nitroalkanes,[11] the desired compounds **3** were the only reaction products and no trace of *O*-alkylated derivatives was observed (see the ESI for further details†). Furthermore, compounds **3** were sufficiently pure to be used for the next step without further treatment. Thus, treatment of crude **3** with dichloro-bis(diphenylphosphino)palladium in toluene, in the presence of caesium carbonate, gave the desired compounds **4**, generally in good to excellent overall yields for the *C*-alkylation/*C*-arylation sequence (Scheme 2 and Table 1). The reaction tolerates a wide range of substituents in the aromatic region, with either electron-releasing or electron-withdrawing character, and several



Scheme 2 Synthesis of compounds **4** through a palladium-catalyzed α′-intramolecular *C*-arylation reaction.

functional groups that can be used as synthetic handles, including halogen and nitro groups and oxygenated functions. The latter are particularly important because of the presence of oxygen functions in many of the natural and unnatural bioactive derivatives of the bicyclo[n.3.1]alkane system. On the other hand, the presence of an ester group precluded the intramolecular *C*-arylation step, and the only observed products in these cases were compounds **5** (Fig. 2), arising from the elimination of a molecule of nitrous acid from the starting materials. For some of the reactions starting from α-nitrocycloheptanone and α-nitrocyclooctanone (n = 2, 3), an additional product containing an indane or indene structural fragment was observed (see compounds **6** below).

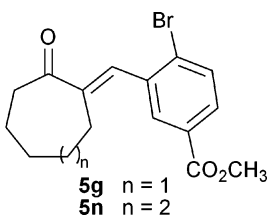


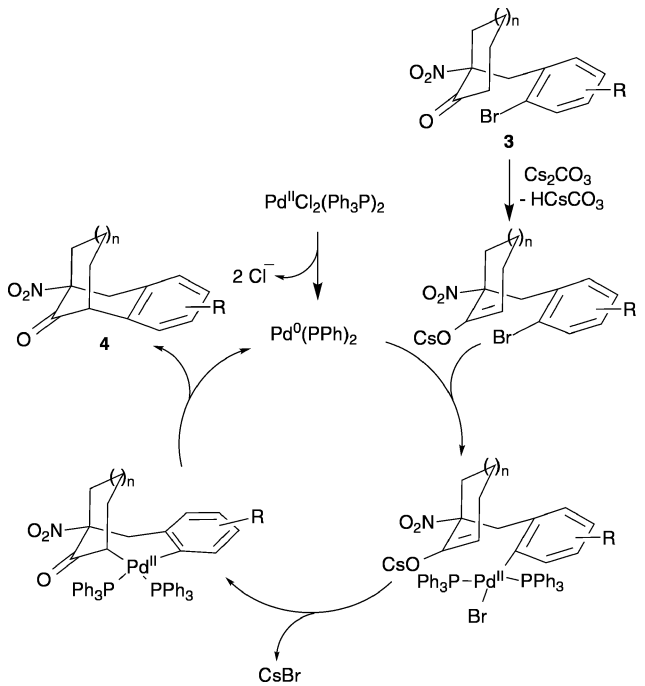
Fig. 2 Elimination products isolated from starting materials containing an ester function.

The formation of compounds **4** can be explained by the catalytic cycle summarized in Scheme 3, involving the palladation of the caesium enolate of the starting ketone, followed by an insertion step and reductive elimination of Pd leading to formation of

Table 1 Scope and yields obtained in the synthesis of benzo- and naphtho-fused bicyclo[n.3.1]alkane derivatives **4** (overall yields for the full α-alkylation/α′-arylation reaction sequence are given)

Cmpd	n	R^3	R^4	R^5	Time/h	Yield (%)
4a	1	H	H	H	4	95
4b	1	H	CH_3	H	26	98
4c	1	–CH=CH–CH=CH–		H	17	92
4d	2	H	H	H	5	80
4e	2	H	H	Cl	24	72[a]
4f	2	H	H	NO_2	9	57
4g	2	H	H	CO_2CH_3	26	0[b]
4h	2	H	CH_3	H	28	78
4i	2	H	–O–CH_2–O–		29	40[c]
4j	2	–CH=CH–CH=CH–		H	16	68
4k	3	H	H	H	5	0[d]
4l	3	H	H	Cl	45	85[a]
4m	3	H	H	NO_2	3	0[e]
4n	3	H	H	CO_2CH_3	21	0[f]
4o	3	H	CH_3	H	48	58[g]
4p	3	H	H	OCH_3	24	80
4q	3	–CH=CH–CH=CH–		H	22	88

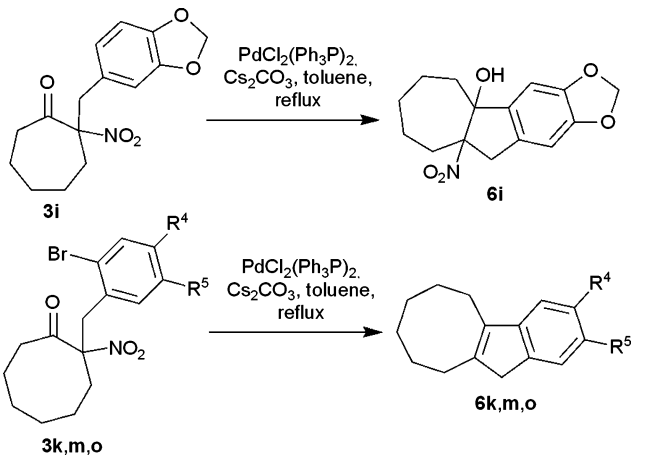
[a] Stoichiometric amounts of the Pd reagent were needed. [b] Compound **5g** was obtained instead. [c] Together with compound **6h**. [d] Compound **6j** was obtained instead. [e] Compound **6l** was obtained instead. [f] Compound **5n** was obtained instead. [g] Together with compound **6n**.



Scheme 3 Mechanism proposed for the transformation of **3** into **4**.

the final product **4**, with concomitant regeneration of the Pd(0) catalyst.

As previously mentioned, some of the reactions starting from compounds **3** derived from α-nitrocycloheptanone or α-nitrocyclooctanone led to products additional or alternative to the expected bridged systems **4**, which were identified as cycloocta[*a*]indane derivatives **6** (Scheme 4 and Table 2). Their formation involves the arylation of the carbonyl group of **3** by intramolecular nucleophilic attack of a palladium species generated from the starting halide. Such nucleophilic "Grignard-type"[14] additions of Pd species are unusual, since aryl and vinyl palladium complexes normally behave as electrophiles.[15]



Scheme 4 Isolation of cyclohepta[*a*]indene and cycloocta[*a*]indene derivatives **6** from the Pd-catalyzed cyclization of some compounds **3** derived from α-nitroheptanone and α-nitrocyclooctanone.

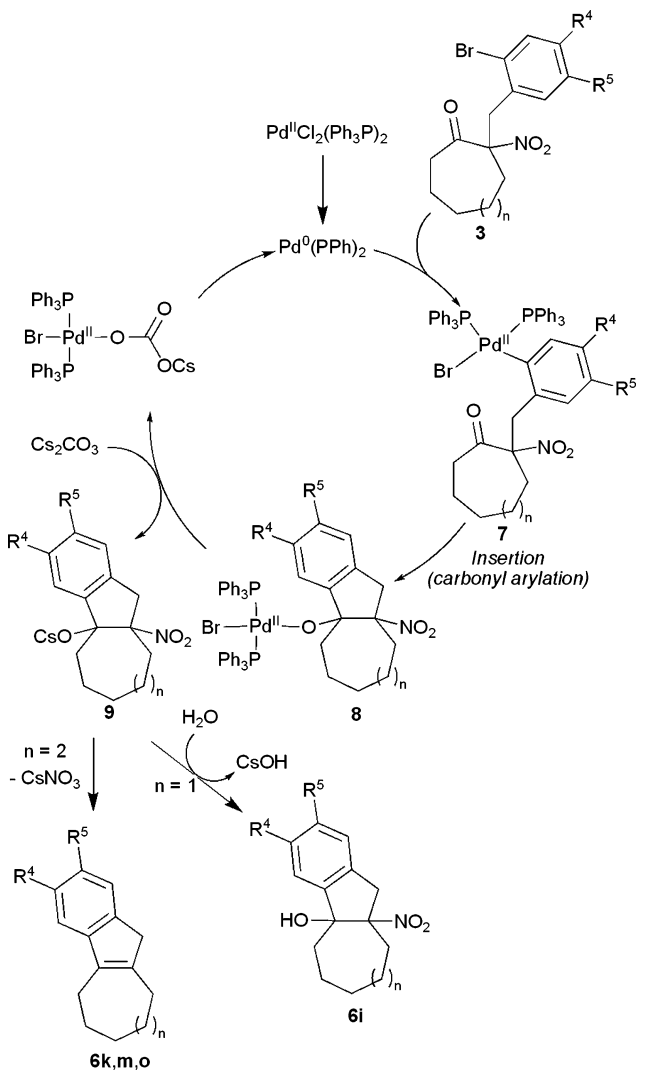
Intramolecular additions of Pd complexes onto ketones leading to fused cyclopentanol derivatives have been described by Yamamoto, who carried out these transformations in the presence of $Pd(OAc)_2$, PCy_3 (PPh_3 was ineffective) and sodium carbonate, in DMF solution, and noticed that the addition of 1-hexanol was crucial for the success of the reaction,[15] which contrasts with our results using an α-nitroketone as a starting material.

Table 2 Yields of cycloocta[*a*]indene derivatives

Cmpd.	R^4	R^5	Time/h	Yield (%)
6i	O–CH_2–O		29	30[a]
6k	H	H	5	82
6m	H	NO_2	3	85
6o	CH_3	H	48	41[b]

[a] Together with compound **4i**. [b] Together with compound **4o**.

A plausible mechanism that explains the generation of compounds **6** is shown in Scheme 5, and starts by the formation of **7**, a common intermediate for both mechanisms, followed by an insertion reaction involving an intramolecular nucleophilic attack of the palladated aromatic position onto the carbonyl group to give **8**. A final reaction with the carbonate base furnishes compound **9** and regenerates the reactive Pd(0) species. While for the few previous literature examples of this reaction the product is an alcohol arising from protonation of an intermediate similar to **9**,[14] in our case only the seven-membered system **6i** showed the same behaviour. In all other cases, the final products (**6k,m,o**) contain a double bond that arises by elimination of a molecule of caesium nitrate from **9**. Although still preliminary in this regard, our results are significant in that they offer some insights on the possibility to control the competition between the Pd-catalyzed arylation α to the carbonyl and the nucleophilic attack onto the carbonyl, which so far has not been systematically studied.[16] First, our results show that the ring size of the starting ketone has an influence on the outcome of the reaction, since the competing carbonyl insertion was generally observed only for eight-membered rings. This can be ascribed to the less rigid nature of the corresponding enolate, where the conformational flexibility of the cyclooctene ring may hinder the insertion step shown in Scheme 3, as reflected in the longer reaction times found for the formation of the bicyclic products (see Table 1). Furthermore, our results also suggest that the electron density on the aromatic ring does not greatly influence the success of the nucleophilic Pd addition, in agreement with previous observations related to the palladium-catalyzed intramolecular nucleophilic substitution at the alkoxycarbonyl group.[15b] However, the presence of two strongly electron-releasing groups favours the formation of compounds **6**, as observed for the case of **6i**, partially overcoming the tendency of seven-membered systems to afford compounds **4** exclusively.



Scheme 5 Mechanism proposed to explain the isolation of compounds **6**.

Conclusions

In summary, we have developed the first synthesis of benzo- and naphtho-fused bicyclo[n.3.1]alkane systems (n = 1–3) bearing a bridgehead nitrogen function from cyclic α-nitroketones. Our study proves that it is possible to selectively carry out the *C*-benzylation of the starting α-nitroketones in the presence of DBU in THF, without any competing *O*-alkylation. The *C*-alkylated materials, without the need for purification, were suitable substrates for Pd-catalyzed intramolecular *C*-arylation reactions, that afforded the dersired bicyclic products, normally in excellent overall yields for the alkylation–arylation sequence. The reaction showed good tolerance for functional groups, including halogen and nitro groups and oxygen functions, and the only limitation found was the absence of intramolecular cyclization when ester substituents were present in the aromatic moiety. In some of the reactions starting from α-nitrocyclooctanone, the Pd-catalyzed reaction afforded cycloocta[*a*]indene derivatives instead of the expected bicyclic compounds. Their formation can be explained by an unusual intramolecular nucleophilic attack of a palladium species onto a ketone carbonyl group, followed by elimination of a molecule of caesium nitrate.

Experimental section

General experimental information

All reagents (Aldrich, Fluka, SDS, Probus) and solvents (SDS) were of commercial quality and were used as received. Reactions were monitored by thin layer chromatography on aluminium plates coated with silica gel with fluorescent indicator (SDS CCM221254). Separations by flash chromatography were performed on silica gel (SDS 60 ACC 40–63 μm) or neutral alumina (Merck S22). Melting points were measured on a Reichert 723 hot stage microscope, and are uncorrected. Infrared spectra were recorded on a Perkin Elmer Paragon 1000 FT-IR spectrophotometer, with all compounds examined as KBr pellets or as thin films on NaCl disks. NMR spectra were obtained on Bruker Avance spectrometers operating at 250 or 300 MHz for ^{1}H and 63 or 75 MHz for ^{13}C (CAI de Resonancia Magnética Nuclear, Universidad Complutense). Mass spectra were obtained by the CAI de Espectrometría de Masas, Universidad Complutense. Elemental analyses were determined by the CAI de Microanálisis Elemental, Universidad Complutense, using a Leco 932 CHNS combustion microanalyzer.

General procedure for the *C*-alkylation of α-nitroketones. Synthesis of compounds 3

To a solution of the suitable 2-nitrocycloalkanone **1** (0.64–3.50 mmol) in dry tetrahydrofuran (5–10 ml) was added DBU (0.13–0.65 ml, 0.83–4.15 mmol). After stirring for 5 min at room temperature and under an argon atmosphere, a solution of the suitable benzylic halide (0.83–4.55 mmol) in dry THF was added, and stirring at room temperature was maintained for 2–24 h. The reaction mixture was diluted with dichloromethane (15 ml) and 2 M aqueous HCl was added until the aqueous layer was acidic. The aqueous solution was extracted with dichloromethane (3 × 10 mL), and the combined organic layers were dried over anhydrous sodium sulfate and evaporated. The residue was identified as the essentially pure compounds **3**, which were employed for the next step without further purification. Analytical samples were obtained by chromatography on silica gel using a gradient from petroleum ether to dichloromethane, and the corresponding characterization data are given below.

2-(2-Bromo-4-methylbenzyl)-2-nitrocyclohexanone (3a). Pale yellow oil. IR (NaCl): 1733 (CO), 1542 and 1386 (NO_2) cm^{-1}. ^1H NMR ($CDCl_3$, 250 MHz) δ 7.57 (dd, 1H, J = 7.9 and 1.2 Hz, H-3′); 7.29–7.15 (m, 2H, H-4′, H-5′); 7.03 (dd, 1H, J = 7.5 and 1.7 Hz, H-6′); 3.71 (d, 1H, J = 14.9 Hz, H-α); 3.56 (d, 1H, J = 14.9 Hz, H-α); 2.70–2.42 (m, 2H, H-6); 2.23–1.32 (m, 6H, H-3,4,5) ppm. ^{13}C NMR ($CDCl_3$, 63 MHz) δ 199.6 (C-1); 133.6 (C-1′); 133.1 (C-3′); 131.5 (C-6′); 129.2 (C-4′); 127.6 (C-5′); 125.9 (C-2′); 96.9 (C-2); 39.5 (C-α); 39.5 (C-6); 34.8 (C-3); 26.6 (C-5); 21.0 (C-4) ppm. Anal. Calcd for $C_{13}H_{14}NO_3Br$: C, 50.00; H, 4.48; N, 4.48. Found: C, 49.62; H, 4.13; N, 4.39.

2-(2-Bromobenzyl)-2-nitrocyclohexanone (3b). Pale yellow oil. IR (NaCl): 2943, 1732 (CO), 1543 and 1435 (NO_2), 1041; 825 cm^{-1}. ^1H NMR ($CDCl_3$, 250 MHz) δ 7.43 (d, 1H, J = 1.0 Hz, H-3′); 7.06 (dd, 1H, J = 7.8 and 1.0 Hz, H-5′); 6.90 (d, 1H, J = 7.8 Hz, H-6′); 3.66 (d, 1H, J = 14.9 Hz, H-α); 3.52 (d, 1H, J = 14.9 Hz, H-α); 2.72–2.49 (m, 3H, H-3,6); 2.33 (s, 3H, CH_3); 2.10–1.55 (m, 5H, H-3,4,5) ppm. ^{13}C NMR ($CDCl_3$, 63 MHz) δ 199.7 (C-1); 139.5 (C-4′); 133.5 (C-3′); 131.1 (C-6′); 130.3 (C-1′); 128.4 (C-5′); 125.6 (C-2′); 97.0 (C-2); 39.5 (C-α); 39.2 (C-6); 34.8 (C-3); 26.6 (C-5); 21.0 (C-4); 20.6 (CH_3) ppm. Anal. Calcd for $C_{14}H_{16}NO_3Br$: C, 51.53; H, 4.91; N, 4.29. Found: C, 51.67; H, 5.27; N, 3.91.

2-(1-Bromonaphth-2-ylmethyl)-2-nitrocyclohexanone (3c). Pale yellow solid; mp 99–100 °C (EtOH). IR (KBr) 2947; 1731 (CO); 1542 and 1355 (NO_2) cm^{-1}. ^1H NMR ($CDCl_3$, 250 MHz) δ 8.35 (dd, 1H, J = 8.4 and 0.6 Hz, H-8′); 7.84 (dd, 1H, J = 7.8 and 1.3 Hz, H-5′); 7.76 (d, 1H, J = 8.4 Hz, H-4′); 7.68–7.52 (m, 2H, H-6′,7′); 7.13 (d, 1H, J = 8.5 Hz, H-3′); 4.03 (d, 1H, J = 14.8 Hz, H-α); 3.82 (d, 1H, J = 14.8 Hz, H-α); 2.75–2.52 (m, 3H, H-3, 6); 2.17–1.91 (m, 2H, H-3, 5); 1.83–1.45 (m, 3H, H-4, 5) ppm. ^{13}C NMR ($CDCl_3$, 63 MHz) δ 199.6 (C-1); 133.7 (C-8a′); 132.3 (C-4a′); 131.8 (C-2′); 128.0; 127.9; 127.8; 127.8; 127.6; 126.7 (C-3′-8′); 126.2 (C-1′); 96.9 (C-2); 40.8 (C-α); 39.4 (C-6); 34.9 (C-3); 26.6 (C-5); 21.0 (C-4) ppm. Anal. Calcd for $C_{17}H_{16}NO_3Br$: C, 56.35; H, 4.42; N, 3.87. Found: C, 56.00; H, 4.13; N, 3.70.

2-(2-Bromobenzyl)-2-nitrocycloheptanone (3d). Pale yellow oil. IR (NaCl): 1731 (CO), 1548 and 1331 (NO_2) cm^{-1}. ^1H NMR ($CDCl_3$, 250 MHz) δ 7.50 (dd, 1H, J = 7.5 and 1.4 Hz, H-3′); 7.20–7.03 (m, 2H, H-4′, H-5′); 6.94 (dd, 1H, J = 7.5 and 1.9 Hz, H-6′); 3.64 (s, 2H, H-α); 2.60–2.51 (m, 2H, H-7); 2.11–2.02 (m, 2H, H-3); 1.70–1.40 (m, 6H, H-4,5,6) ppm. ^{13}C NMR ($CDCl_3$, 63 MHz) δ 201.6 (C-1); 133.5 (C-1′); 133.1 (C-3′); 131.3 (C-6′); 129.3 (C-4′); 127.8 (C-5′); 126.2 (C-2′); 100.2 (C-2); 40.5 (C-7); 39.5 (C-α); 31.2 (C-3); 29.4 (C-5); 26.1 (C-6); 24.3 (C-4) ppm. Anal. Calcd for $C_{14}H_{16}NO_3Br$: C, 51.53; H, 4.90; N, 4.29. Found: C, 51.55; H, 5.09; N, 4.25.

2-(2-Bromo-5-chlorobenzyl)-2-nitrocycloheptanone (3e). Pale yellow oil. IR (NaCl): 2976; 1728 (CO), 1543 (NO_2); 1463; 1348 (NO_2) cm^{-1}. ^1H NMR ($CDCl_3$, 250 MHz) δ 7.53 (d, 1H, J = 8.5 Hz, H-3′); 7.15 (dd, 1H, J = 8.5 and 2.4 Hz, H-4′); 7.05 (d, 1H, J = 2.4 Hz, H-6′); 3.69 (br s, 2H, H-α); 2.77–2.58 (m, 2H, H-7); 2.29–2.02 (m, 2H, H-3); 1.86–1.49 (m, 6H, H-4,5,6) ppm. ^{13}C NMR ($CDCl_3$, 63 MHz) δ 201.8 (C-1); 135.9 (C-1′); 134.6 (C-3′); 134.3 (C-5′); 131.7 (C-6′); 130.0 (C-4′); 124.5 (C-2′); 100.2 (C-2); 41.0 (C-7); 39.9 (C-α); 31.9 (C-3); 29.8 (C-5); 26.5 (C-6); 24.8 (C-4) ppm. Anal. Calcd for $C_{14}H_{15}NO_3ClBr$: C, 46.63; H, 4.19; N, 3.88. Found: C, 46.66; H, 4.25; N, 3.74.

2-(2-Bromo-5-nitrobenzyl)-2-nitrocycloheptanone (3f). Pale yellow oil. ^1H NMR ($CDCl_3$, 250 MHz): δ 8.03 (dd, 1H, J = 8.7 and 2.7 Hz, H-4′); 7.97 (d, 1H, J = 2.7 Hz, H-6′); 7.81 (d, 1H, J = 8.7 Hz, H-3′); 3.84 (d, 1H, J = 14.9 Hz, H-α); 3.76 (d, 1H, J = 14.9 Hz, H-α); 2.77–2.58 (m, 2H, H-7); 2.27–2.04 (m, 2H, H-3); 1.91–1.53 (m, 6H, H-4, 5, 6) ppm. ^{13}C NMR ($CDCl_3$, 63 MHz): δ 201.3 (C-1); 147.1 (C-5′); 135.9 (C-1′); 134.1 (C-3′); 133.4 (C-2′); 126.1 (C-6′); 123.8 (C-4′); 99.0 (C-2); 40.6 (C-7); 39.7 (C-α); 32.0 (C-3); 29.1 (C-5); 25.7 (C-6); 24.2 (C-4) ppm. Anal. Calcd for $C_{14}H_{16}N_2O_5Br$: C, 45.28; H, 4.04; N, 7.54. Found: C, 45.16; H, 4.10; N, 7.49.

2-(2-Bromo-5-methoxycarbonylbenzyl)-2-nitrocycloheptanone (3g). Colourless liquid. IR (neat) 2934, 2858, 1728 (2 C═O), 1548 and 1345 (NO_2), 1435, 1289 (C–O), 1261, 1118, 764 cm^{-1}. ^1H-NMR ($CDCl_3$, 250 MHz) δ 8.25 (d, J = 1.7 Hz, 1H, H-6′); 7.87 (dd, J = 1.7 and 8.1 Hz, 1H, H-4′); 7.12 (d, J = 8.1 Hz, 1H, H-3′); 3.93 (s, 3H, OMe); 3.77 (s, 2H, H-α); 2.60–2.74 (m, 2H, H-7); 2.02–2.26 (m, 2H, H-2); 1.53–1.85 (m, 6H, H-3,4,5). ^{13}C-NMR ($CDCl_3$, 62.9 MHz) δ 201.7 (C-1); 165.7 (CO_2Me); 139.2 (C-1′); 134.6 (H-6′); 131.8 (H-3′); 131.7 (H-3′); 129.1 (C-2′); 126.7 (C-5′); 100.3 (C-2); 52.9 (CO_2Me); 41.0 (C-7); 40.1 (C-α); 31.9 (C-3); 29.8 (C-5); 26.5 (C-4); 24.8 (C-6). Anal. Calcd for $C_{16}H_{18}BrNO_5$: C, 50.02; H, 4.72, N, 3.65. Found: C, 49.83; H, 4.56; N, 3.42.

2-(2-Bromo-4-methylbenzyl)-2-nitrocycloheptanone (3h). Pale yellow oil. IR (NaCl): 2952, 1731 (CO), 1543 and 1350 (NO_2), 862, 830, 674 cm^{-1}. ^1H NMR ($CDCl_3$, 250 MHz): δ 7.44 (d, 1H, J = 1.0 Hz, H-3′); 7.05 (dd, 1H, J = 7.8 and 1.0 Hz, H-5′); 6.92 (d, 1H, J = 7.8 Hz, H-6′); 3.67 (br s, 2H, H-α); 2.75–2.56 (m, 2H, H-7); 2.33 (s, 3H, CH_3); 2.28–2.05 (m, 2H, H-3); 1.84–1.49 (m, 6H, H-4,5,6) ppm. ^{13}C NMR ($CDCl_3$, 63 MHz): δ 201.7 (C-1); 139.5 (C-4′); 133.4 (C-3′); 130.8 (C-6′); 130.1 (C-1′); 128.6 (C-5′); 125.8 (C-2′); 100.2 (C-2); 40.5 (C-7); 39.1 (C-α); 31.1 (C-3); 29.3 (C-5); 26.1 (C-6); 24.2 (C-4); 20.5 (CH_3) ppm. Anal. Calcd for $C_{15}H_{18}NO_3Br$: C, 52.94; H, 5.29; N, 4.11. Found: C, 53.02; H, 5.22; N, 4.22.

2-(6-Bromobenzo[1,3]dioxol-5-ylmethyl)-2-nitrocycloheptanone (3i). White solid, mp 96 °C. IR (neat) 2934, 1731 (CO), 1542 and

1342 cm^{-1}. ^1H NMR ($CDCl_3$, 250 MHz) δ 7.02 (s, 1H, H-5); 6.53 (s, 1H, H-8); 5.99 (s, 2H, H-2); 3.64 (s, 2H, H-α); 2.59–2.77 (m, 2H, H-3′); 2.05–2.29 (m, 2H, H-7′); 1.56–1.83 (m, 6H, H-4′,5′,6′) ppm. ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ 202.2 (C-2′); 148.5 and 148.2 (C-3a, 8a); 126.7 (C-6);117.1 (C-5); 113.3 (C-7); 110.9 (C-4); 102.5 (C-1′); 100.8 (C-2); 41.1 (C-3′); 40.1 (C-α); 31.8 (C-7′); 29.9 (C-5′), 26.7 (C-4′), 24.9 (C-6′). Anal. Calcd for $C_{15}H_{16}BrNO_5$: C, 48.67; H, 4.36, N, 3.78. Found: C, 48.42; H, 4.14; N, 3.56.

2-(1-Bromonaphth-2-ylmethyl)-2-nitrocycloheptanone (3j). Pale yellow solid. IR (NaCl): 2950; 1723 (CO), 1545 and 1329 (NO_2) cm^{-1}. ^1H NMR ($CDCl_3$, 250 MHz) δ 8.31 (d, 1H, J = 8.5 Hz, H-8′); 7.88–7.42 (m, 4H, H-4′,5′,6′,7′); 7.07 (d, 1H, J = 8.5 Hz, H-3′); 4.03 (d, 1H, J = 14.7 Hz, H-α); 3.94 (d, 1H, J = 14.7 Hz, H-α); 2.71–2.56 (m, 2H, H-7); 2.18–2.03 (m, 2H, H-3);1.74–1.10 (m, 6H, H-4,5,6) ppm. ^{13}C NMR ($CDCl_3$, 63 MHz) δ 201.5 (C-1); 139.5 (C-4a′); 132.1 (C-8a′); 131.5 (C-2′); 127.8; 127.6; 127.5; 127.3; 126.6 (C-4′-8′); 126.3 (C-1′); 100.0 (C-2); 40.7 (C-7); 40.4 (C-α); 31.1 (C-3); 29.2 (C-5); 26.1 (C-6); 24.1 (C-4) ppm. Anal. Calcd for $C_{18}H_{18}NO_3Br$, M = 376: C, 57.44; H, 4.78; N, 3.72. Found: C, 57.36; H, 4.40; N, 3.68.

2-(2-Bromobenzyl)-2-nitrocyclooctanone (3k). Pale yellow oil. IR (NaCl): 2972, 1724 (CO), 1543 and 1346 (NO_2) cm^{-1}. ^1H NMR ($CDCl_3$, 250 MHz): δ 7.59 (dd, 1H, J = 7.8 and 1.3 Hz, H-3′); 7.28–7.11 (m, 2H, H-4′, H-5′); 7.03 (dd, 1H, J = 7.5 and 1.8 Hz, H-6′); 3.82 (d, 1H, J = 14.9 Hz, H-α); 3.63 (d, 1H, J = 14.9 Hz, H-α); 2.78–2.64 (m, 1H, H-8); 2.62–2.49 (m, 1H, H-8); 2.47–2.33 (ddd, 1H, J = 15.4, 8.5 and 2.8 Hz, H-3); 2.27–2.13 (ddd, 1H, J = 15.2, 8.3 and 3.2 Hz, H-3); 2.07–1.13 (m, 8H, H-4–7) ppm. ^{13}C NMR ($CDCl_3$, 63 MHz) δ 205.0 (C-1); 134.2 (C-1′); 133.6 (C-3′); 131.5 (C-6′); 129.7 (C-4′); 128.2 (C-5′); 126.5 (C-2′); 100.5 (C-2); 39.7 (C-α); 38.9 (C-8); 31.7 (C-3); 27.3 (C-7); 26.7 (C-6); 25.6 (C-5); 22.7 (C-4) ppm. Anal. Calcd for $C_{15}H_{18}NO_3Br$: C, 52.94; H, 5,29; N, 4.11. Found: C, 53.26; H, 5.28; N, 4.15.

2-(2-Bromo-5-chlorobenzyl)-2-nitrocyclooctanone (3l). Pale yellow solid; mp 96–98 °C. IR (KBr): 2934, 1725 (CO), 1543 and 1345 (NO_2), 1102, 1028 cm^{-1}. ^1H NMR ($CDCl_3$, 250 MHz): δ 7.51 (d, 1H, J = 8.5 Hz, H-3′); 7.14 (dd, 1H, J = 8.5 and 2.5 Hz, H-4′); 7.05 (d, 1H, J = 2.5 Hz, H-6′); 3.74 (d, 1H, J = 14.9 Hz, H-α); 3.62 (d, 1H, J = 14.9 Hz, H-α); 2.77–2.66 (m, 1H, H-8); 2.60–2.39 (m, 2H, H-3,8); 2.24–2.13 (m, 1H, H-3); 1.99–1.15 (m, 8H, H-4–7) ppm. ^{13}C NMR ($CDCl_3$, 63 MHz) δ 204.8 (C-1); 136.0 (C-1′); 134.6 (C-3′); 134.1 (C-4′); 131.5 (C-6′); 129.8 (C-5′); 124.4 (C-2′); 100.0 (C-2); 39.4 (C-α); 38.8 (C-8); 31.8 (C-3); 27.4 (C-7); 26.6 (C-6); 25.5 (C-5); 22.7 (C-4) ppm. Anal. Calcd for $C_{15}H_{17}NO_3ClBr$: C, 48.06; H, 4.53; N, 3.74. Found: C, 48.43; H, 4.74; N, 3.77.

2-(2-Bromo-5-nitrobenzyl)-2-nitrocyclooctanone (3m). Pale yellow oil. IR (NaCl): 2934, 1722 (CO), 1544, 1527 and 1345 (NO_2), 1031, 740 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz) δ: 8.00–7.97 (m, 2H, H-4′,6′); 7.77 (d, 1H, J = 9.2 Hz, H-3′); 3.81 (d, 1H, J = 15.0 Hz, H-α); 3.73 (d, 1H, J = 15.0 Hz, H-α); 2.76–2.47 (m, 3H, H-3,8); 2.24–2.15 (m, 1H, H-3); 1.98–1.15 (m, 8H, H-4,5,6,7) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 204.4 (C-1); 147.5 (C-5′); 136.5 (C-1′); 134.6 (C-3′); 133.7 (C-2′); 126.5 (C-6′); 124.1 (C-4′); 99.2 (C-2); 39.2 (C-α); 38.9 (C-8); 32.2 (C-3); 27.1 (C-7); 26.3 (C-6); 24.9 (C-5); 22.1 (C-4) ppm. Anal. Calcd for $C_{15}H_{17}N_2O_5Br$: C, 46.75; H, 4.41; N, 7.27. Found: C, 46.52; H, 4.09; N, 7.25.

2-(2-Bromo-5-methoxycarbonylbenzyl)-2-nitrocyclooctanone (3n). Colourless oil. IR (neat) 2934.0; 1728.2 (2 CO), 1547.8 and 1345 (NO_2); 1435.2, 1289.5, 1260.8, 1118.1, 764.4 cm^{-1}. ^1H NMR ($CDCl_3$, 250 MHz) δ 8.25 (d, J = 1.7 Hz, 1H, H-6′); 7.87 (dd, J = 1.7 and 8.1 Hz, 1H, H-4′); 7.12 (d, J = 8.1 Hz, 1H, H-3′); 3.93 (s, 3H, OMe); 3.90 (d, 1H, J = 14.9 Hz, H-α); 3.67 (d, 1H, J = 14.9 Hz, H-α); 2.60–2.74 (m, 2H, H-8); 2.02–2.26 (m, 2H, H-2); 1.15–1.90 (m, 8H, H-3,4,5,6) ppm. ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ 204.6 (C-1); 165.8 (CO_2Me); 139.4 (C-1′); 134.6 (C-6′); 131.5 (C-3′ and C-4′); 129.0 (C-2′); 126.9 (C-5′); 100.2 (C-2); 52.9 (OMe); 41.0 (C-8); 39.5 (C-α); 38.8 (C-3); 27.4 (C-6); 26.6 (C-5); 25.5 (C-7); 22.7 (C-4) ppm. Anal. Calcd for $C_{17}H_{20}BrNO_5$: C, 51.27; H, 5.06; Br, N, 3.52;. Found: C, 51.02; H, 4.87; N, 3.23.

2-(2-Bromo-4-methylbenzyl)-2-nitrocyclooctanone (3o). Pale yellow oil. IR (NaCl): 2947; 1726 (CO), 1543 and 1345 (NO_2); 1041 cm^{-1}. ^1H NMR ($CDCl_3$, 250 MHz) δ: 7.38 (d, 1H, J = 0.8 Hz, H-3′); 7.01 (dd, 1H, J = 7.9 and 1.1 Hz, H-5′); 6.88 (d, 1H, J = 7.9 Hz, H-6′); 3.74 (d, 1H, J = 14.9 Hz, H-α); 3.55 (d, 1H, J = 14.9 Hz, H-α); 2.73–2.47 (m, 2H, H-3); 2.42–2.12 (m, 5H, H-8, CH_3); 1.94–1.16 (m, 8H, H-4–7) ppm. ^{13}C NMR ($CDCl_3$, 63 MHz) δ: 204.4 (C-1); 139.3 (C-4′); 133.4 (C-3′); 130.5 (C-6′); 130.3 (C-1′); 128.4 (C-5′); 125.6 (C-2′); 99.9 (C-2); 38.6 (C-α); 38.2 (C-8); 30.9 (C-3); 26.7 (C-7); 26.1 (C-6); 25.0 (C-5); 22.1 (C-4); 20.4 (CH_3) ppm. Anal. Calcd for $C_{16}H_{20}NO_3Br$: C, 54.23; H, 5.65; N, 3.95. Found: C, 53.99; H, 5.50; N, 3.90.

2-(2-Bromo-5-methoxybenzyl)-2-nitrocyclooctanone (3p). Colourless liquid. IR (neat) 2936.2, 1724.9 (CO), 1543 and 1347 (NO_2), 1473, 1241, 1165, 1018 cm^{-1}. ^1H NMR ($CDCl_3$, 250 MHz) δ 7.45 (d, J = 8.8 Hz, 1H, H-3′); 6.71 (dd, J = 2.9 and 8.8 Hz, 1H, H-4′); 6.56 (d, J = 2.9 Hz, 1H, H-6′); 3.75 (s, 3H, OMe), 3.78 (d, J = 14.6 Hz, 1H, H-α); 3.58 (d, J = 14.9 Hz, 1H, H-α); 2.64–2.75 (m, 1H, H-8), 2.50–2.60 (m, 1H, H-8); 2.35–2.45 (m, 1H, H-3); 2.16–2.27 (m, 1H, H-3); 1.22–1.94 (m, 8H, H-4,5,6,7). ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ 204.9 (CO); 159.4 (C-5′); 134.5 (C-1′); 134.1 (C-3′); 116.8 (C-2′); 116.7 (C-6′); 115.8 (C-4′); 100.6 (C-2); 55.8 (OMe); 39.9 (C-8); 38.8 (C-3); 31.7 (C-5); 27.4 (C-6); 26.7 (C-5); 25.6 (C-7); 22.9 (C-4). Anal. Calcd for $C_{16}H_{20}BrNO_4$: C, 51.90; H, 5.44, N, 3.78. Found: C, 51.67; H, 5.32; N, 3.65.

2-(1-Bromonaphth-2-ylmethyl)-2-nitrocyclooctanone (3q). Pale yellow solid; mp 103–105 °C. IR (KBr): 2934, 1724 (CO), 1542 and 1330 (NO_2) cm^{-1}. ^1H NMR ($CDCl_3$, 250 MHz) δ: 8.35 (d, 1H, J = 8.2 Hz, H-8′); 7.,83 (d, 1H, J = 7.7 Hz, H-5′); 7.75 (d, 1H, J = 8.5 Hz, H-4′); 7.67–7.51 (m, 2H, H-6′,7′); 7.12 (d, 1H, J = 8.5 Hz, H-3′); 4.17 (d, 1H, J = 14.7 Hz, H-α); 3.87 (d, 1H, J = 14.7 Hz, H-α); 2.79–2.55 (m, 2H, H-8); 2.48–2.20 (m, 2H, H-3); 2.02–1.22 (m, 8H, H-4–7) ppm. ^{13}C NMR ($CDCl_3$, 63 MHz) δ: 204.6 (C-1); 133.7 (C-4a′); 132.4 (C-8a′); 132.0 (C-2′); 128.0 (C-4′,5′,8′); 127.7 (C-7′); 127.4 (C-3′); 126.7 (C-6′); 126.5 (C-1′); 100.1 (C-2); 40.7 (C-α); 38.4 (C-8); 31.4 (C-3); 26.8 (C-7); 26.3 (C-6); 25.2 (C-5); 22.3 (C-4) ppm. Anal. Calcd for $C_{19}H_{20}NO_3Br$: C, 58.40; H, 5.10; N, 3.50. Found: C, 58.32; H, 5.08; N, 3.43.

Pd-catalyzed cross-coupling reactions of compounds 3. General procedure

To a solution of the suitable crude compound **3** (1 mmol) in 10 ml of anhydrous toluene (previously deoxygenated by running an argon stream through the solvent while irradiating in an

ultrasound cleaning bath) was added Cs_2CO_3 (3 eq., 6 eq. for the reactions starting from **3e** and **3j**) and $PdCl_2(PPh_3)_2$ (0.3 eq., 3 eq. for the reactions starting from **3e** and **3j**). The reaction mixture was refluxed under an argon atmosphere for the times specified in Table 2. It was then diluted with ethyl acetate (20 ml) and the solution was washed with saturated aqueous NH_4Cl solution (3 × 10 ml). The organic layer was dried over anhydrous sodium sulphate and evaporated, and the residue was chromatographed on silica gel, eluting with a gradient from petroleum ether to dichloromethane, to give compounds **4** or **5**.

(±)-*cis*-5,6,7,8,9,10-Hexahydro-5,9-methano-9-nitrobenzocycloocten-11-one (4a). Pale yellow oil. IR (NaCl): 2941, 1741 (CO), 1546 and 1453 (NO_2) cm^{-1}. ^1H NMR ($CDCl_3$, 250 MHz) δ: 7.35–7.24 (m, 3H, H-Ar); 7.06–7.00 (m, 1H, H-Ar); 4.57 (dd, 1H, J = 17.2 and 1.7 Hz, H-10); 3.83 (t, 1H, J = 3.3 Hz, H-5); 3.63 (d, 1H, J = 17.3 Hz, H-10); 2.95 (ddt, 1H, J = 13.1, 5.8 and 2.4 Hz, H-8); 2.55–2.44 (m, 1H, H-8); 2.28–2.21 (m, 1H, H-6); 2.18–2.02 (m, 1H, H-6); 1.85–1.62 (m, 2H, H-7) ppm. ^{13}C NMR ($CDCl_3$, 63 MHz) δ: 201.7 (C-11); 135.6 (C-4a); 132.5 (C-10a); 128.0; 127.8; 127.7; 126.9; 95.6 (C-9); 52.5 (C-5); 41.7 (C-10); 40.4 (C-8); 36.6 (C-6); 17.8 (C-7) ppm. Anal. Calcd for $C_{13}H_{13}NO_3$: C, 67.53; H, 5.63; N, 6.06. Found: C, 67.20; H, 5.45; N, 5.89.

(±)-*cis*-5,6,7,8,9,10-Hexahydro-6,10-methano-2-methyl-6-nitrobenzocycloocten-11-one (4b). Colourless oil. IR (NaCl): 2947, 1744 (CO), 1546 and 1353 (NO_2) cm^{-1}. ^1H NMR ($CDCl_3$, 250 MHz) δ: 7.11 (br s, 2H, H-3,4); 6.84 (s, 1H, H-1); 4.51 (d, 1H, J = 17.1 Hz, H-5); 3.77 (t, 1H, J = 3.1 Hz, H-10); 3.58 (d, 1H, J = 17.1 Hz, H-5); 2.91 (ddt, 1H, J = 12.9, 6.9 and 1.8 Hz, H-7); 2.54–2.40 (m, 1H, H-7); 2.39 (s, 3H, CH_3); 2.30–2.17 (m, 1H, H-9); 2.15–2.02 (m, 1H, H-9); 1.83–1.60 (m, 2H, H-8) ppm. ^{13}C NMR ($CDCl_3$, 63 MHz) δ: 202.2 (C-11); 137.9 (C-2); 135.9 (C-10a); 129.7 (C-4a); 129.1 (C-4); 128.8 (C-3); 127.2 (C-1); 96.1 (C-6); 53.0 (C-10); 41.9 (C-5); 40.9 (C-7); 37.0 (C-9); 21.3 (CH_3); 18.3 (C-8) ppm. Anal. Calcd for $C_{14}H_{15}NO_3$: C, 68.57; H, 6.12; N, 5.71. Found: C, 68.19; H, 6.01; N, 5.51.

(±)-*cis*-7,8,9,10,11,12-Hexahydro-8,12-methano-8-nitrocycloocta[*a*]naphthalen-13-one (4c). Pale yellow solid; mp 171–172 °C. IR (KBr): 1743 (CO), 1547 and 1365 (NO_2) cm^{-1}. ^1H NMR ($CDCl_3$, 250 MHz) δ: 7.81–7.69 (m, 3H, H-Ar); 7.53–7.41 (m, 2H, H-Ar); 7.20 (d, 1H, J = 8.6 Hz, H-Ar); 4.64 (dd, 1H, J = 15.6 and 2.2 Hz, H-7); 4.48 (t, 1H, J = 3.2 Hz, H-12); 3.64 (d, 1H, J = 17.6 Hz, H-7); 2.91 (ddt, 1H, J = 13.5, 5.5 and 2.3 Hz, H-9); 2.47–2.40 (m, 1H, H-9); 2.26–2.16 (m, 2H, H-11); 1.80–1.54 (m, 2H, H-10) ppm. ^{13}C NMR ($CDCl_3$, 63 MHz) δ: 201.7 (C-13); 132.7 (C-12a); 130.2 (C-6a); 130.1 (C-12b); 129.4 (C-4a); 128.9 (C-4); 128.3 (C-5); 127.2 (C-6); 125.9 (C-3); 124.7 (C-2); 121.9 (C-1); 95.3 (C-8); 48.2 (C-12); 42.3 (C-7); 40.3 (C-9); 33.7 (C-11); 18.6 (C-10) ppm. MS (ESI), m/z: 282 (M^+ + 1). Anal. Calcd for $C_{17}H_{15}NO_3$: C, 72.59; H, 5.34; N, 4.98. Found: C, 72.70; H, 5.25; N, 4.65.

(±)-*cis*-6,7,8,9,10,11-Hexahydro-10-nitro-5*H*-5,10-methanobenzocyclononen-12-one (4d). Colourless oil. IR (NaCl): 2947, 1731 (CO), 1548 and 1348 (NO_2) cm^{-1}. ^1H NMR ($CDCl_3$, 250 MHz) δ: 7.28–7.11 (m, 4H, H-Ar); 4.08 (d, 1H, J = 15,8 Hz, H-11); 4.03 (t, 1H, J = 4.4 Hz, H-5); 3.34 (d, 1H, J = 15.8 Hz, H-11); 2.73 (dd, 1H, J = 15.1 and 7.1 Hz, H-9); 2.47–2.36 (m, 1H, H-6); 2.03–1.48 (m, 5H, H-6,7,8,9); 1.17–1.05 (m, 1H, H-7) ppm. ^{13}C NMR ($CDCl_3$, 63 MHz) δ: 201.7 (C-12); 135.0 (C-1); 132.0; 129.2; 127.8; 127.5; 127.0; 97.5 (C-10); 52.1 (C-5); 40.5 (C-11); 33.9 (C-9); 33.4 (C-6); 25.7 (C-7); 25.6 (C-8) ppm. MS (ESI), m/z: 246 (M^+ + 1). Anal. Calcd for $C_{14}H_{15}NO_3$: C, 68.57; H, 6.12; N, 5.71. Found: C, 68.20; H, 6.07; N, 5.35.

(±)-*cis*-2-Chloro-6,7,8,9,10,11-hexahydro-5*H*-10-nitro-5,10-methanobenzocyclononen-12-one (4e). Pale yellow oil. IR (NaCl): 2961, 1732 (CO), 1551 and 1350 (NO_2) cm^{-1}. ^1H NMR ($CDCl_3$, 250 MHz) δ: 7.47–7.21 (m, 3H, H-Ar); 4.08 (d, 1H, J = 16.0 Hz, H-11); 3.99 (t, 1H, J = 4.1 Hz, H-5); 3.32 (d, 1H, J = 16.0 Hz, H-11); 2.77 (dd, 1H, J = 15.0 and 7.2 Hz, H-9); 2.41–2.23 (m, 1H, H-6); 2.05–1.45 (m, 5H, H-6,7,8,9); 1.01–0.80 (m, 1H, H-7) ppm. ^{13}C NMR ($CDCl_3$, 63 MHz) δ: 200.9 (C-12); 133.9 (C-11a); 133.5 (C-4a); 133.3 (C-2); 129.1 (C-4); 128.4 (C-1); 128.1 (C-3); 97.0 (C-10); 51.7 (C-5); 40.1 (C-11); 33.8 (C-9); 33.3 (C-6); 25.6 (C-7); 25.6 (C-8) ppm. MS (ESI), m/z: 282 (M^+ + 3), 280 (M^+ + 1). Anal. Calcd for $C_{14}H_{14}NO_3Cl$: C, 60.10; H, 5.00; N, 5.00. Found: C, 59.90; H, 5.21; N, 5,33.

(±)-*cis*-6,7,8,9,10,11-Hexahydro-5*H*-2,10-dinitro-5,10-methanobenzocyclononen-12-one (4f). Pale yellow solid; mp 175–176 °C. IR (NaCl): 2937, 1734 (CO), 1552, 1522, 1436 and 1348 (NO_2) cm^{-1}. ^1H-NMR ($CDCl_3$, 250 MHz) δ: 8.23 (dd, 1H, J = 8.6 and 1.8 Hz, H-3); 8.16 (s, 1H, H-1); 7.47 (d, 1H, J = 8.7 Hz, H-4); 4.19 (d, 1H, J = 16.1 Hz, H-11); 4.11 (t, 1H, J = 4.6 Hz, H-5); 3.51 (d, 1H, J = 16.2 Hz, H-11); 2.83 (dd, 1H, J = 14.2 and 7.0 Hz); 2.48–2.40 (m, 1H); 2.08–1.84 (m, 3H); 1.68–1.40 (m, 3H) ppm. ^{13}C NMR ($CDCl_3$, 63 MHz) δ: 199.6 (C-12); 144.5 (C-2); 142.7 (C-4a); 134.0 (C-11a); 128.3 (C-4); 124.3 (C-1); 122.8 (C-3); 96.6 (C-10); 52.2 (C-5); 40.2 (C-11); 33.8 (C-6); 33.5 (C-9); 25.8 (C-8); 25.5 (C-7) ppm. Anal. Calcd for $C_{14}H_{14}N_2O_5$: C, 57.93; H, 4.82; N, 9.65. Found: C, 57.52; H, 5.03; N, 9.29.

(±)-*cis*-6,7,8,9,10,11-Hexahydro-5*H*-6,11-methano-3-methyl-10-nitrobenzocyclononen-12-one (4h). Colourless oil. IR (NaCl): 2959, 1735 (CO), 1553 and 1355 (NO_2) cm^{-1}. ^1H NMR ($CDCl_3$, 250 MHz) δ: 7.10 (br s, 2H, H-1,2); 7.04 (s, 1H, H-4); 4.04 (d, 1H, J = 15.8 Hz, H-11); 3.98 (t, 1H, J = 4.2 Hz, H-5); 3.30 (d, 1H, J = 15.7 Hz, H-11); 2.73 (dd, 1H, J = 15.1 and 7.1 Hz, H-9); 2.47–2.32 (m, 4H, H-6, CH_3); 2.09–1.48 (m, 5H, H-6,7,8,9); 1.28–1.11 (m, 1H, H-7) ppm. ^{13}C NMR ($CDCl_3$, 63 MHz) δ: 202.0 (C-12); 137.5 (C-3); 134.8 (C-4a); 129.1 (C-1); 128.9 (C-11a); 128.4 (C-2); 127.4 (C-4); 97.6 (C-10); 52.1 (C-5); 40.1 (C-11); 33.8 (C-6); 33.4 (C-9); 25.8 (C-8); 25.7 (C-7); 21.1 (CH_3) ppm. MS (ESI), m/z: 260 (M^+ + 1). Anal. Calcd for $C_{15}H_{17}NO_3$: C, 69.49; H, 6.56; N, 5.40. Found: C, 69.20; H, 6.41; N, 5.32.

(±)-*cis*-6,7,8,9,10,11,5*H*-5,11-Methano-2,3-methylenedioxy-10-nitrobenzocyclononen-12-one (4i). Colourless viscous liquid. IR (neat) 2936, 1728 (CO), 1547.7 and 1345 (NO_2), 1504, 1480, 1234, 1120, 1038, 932 cm^{-1}. ^1H NMR ($CDCl_3$, 250 MHz) δ 6.67 (s, 1H); 6.65 (s, 1H); 6.01 (dd, J = 1.3 and 4.5 Hz, 2H); 3.97 (d, J = 15.7 Hz, 1H); 3.89–3.92 (m, 1H); 3.21 (d, J = 15.7 Hz, 1H); 2.74 (dd, J = 6.7 and 15.2 Hz, 1H); 2.26–2.36 (m, 1H); 1.89–2.03 (m, 2H); 1.78–1.86 (m, 2H); 1.63–1.73 (m, 1H); 1.53–1.59 (m, 1H). ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ 201.9 (C-12); 148.1 (C-2); 147.7 (C-3); 128.5 (C-4a); 125.5 (C-11a); 109.4 (C-1); 107.0 (C-4); 101.9 (OCH_2O); 97.9 (C-10); 52.6 (C-5); 40.8 (C-11); 34.3 (C-6); 33.9 (C-9); 26.3 (C-8), 26.1 (C-7). Anal. Calcd for $C_{15}H_{15}NO_5$: C, 62.28; H, 5.23, N, 4.84 Found: C, 61.95; H, 5.01; N, 4.65.

(±)-*cis*-8,9,10,11,12,13-Hexahydro-8-nitro-7*H*-8,13-methanocyclonona[*a*]naphthalen-14-one (4j). Pale yellow oil. ^{1}H NMR ($CDCl_3$, 250 MHz) δ: 7.86–7.79 (m, 2H, H-1,4); 7.71 (d, 1H, J = 8.4 Hz, H-5); 7.51–7.40 (m, 2H, H-2,3); 7.19 (d, 1H, J = 8.4 Hz, H-6); 4.58 (t, 1H, J = 4.9 Hz, H-13); 4.10 (d, 1H, J = 16.0 Hz, H-7); 3.47 (d, 1H, J = 16.0 Hz, H-7); 2.79–2.60 (m, 2H, H-9,12); 2.10–1.74 (m, 3H, H-9,11,12); 1.68–1.56 (m, 2H, H-10); 1.18–0.95 (m, 1H, H-11) ppm. ^{13}C NMR ($CDCl_3$, 63 MHz) δ: 201.4 (C-14); 133.6 (C-13a); 131.2 (C-6a); 130.4 (C-13b); 130.1 (C-4a); 129.5 (C-4); 129.0 (C-5); 127.2 (C-6); 127.1 (C-3); 126.3 (C-2); 123.6 (C-1), 97.9 (C-8); 51.3 (C-13); 42.1 (C-7); 35.9 (C-9); 33.3 (C-12); 26.2 (C-11); 25.8 (C-10) ppm. MS (ESI), m/z: 296 (M^+ + 1). Anal. Calcd for $C_{18}H_{17}NO_3$: C, 73.22; H, 5.76; N, 4.74. Found: C, 72.95; H, 5.80; N, 4.65.

(±)-*cis*-2-Chloro-5,6,7,8,9,10,11,12-octahydro-11-nitro-5,11-methanobenzocyclodecen-13-one (4l). Pale yellow oil. IR (NaCl): 2936, 1725 (CO), 1548 and 1352 (NO_2) cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 7.22 (dd, 1H, J = 8.3 and 1.9 Hz, H-3); 7.13 (s, 1H, H-1); 7.07 (d, 1H, J = 8.3 Hz, H-4); 3.89 (d, 1H, J = 16.4 Hz, H-12); 3.76 (dd, 1H, J = 7.1 and 4.9 Hz, H-5); 3.29 (d, 1H, J = 16.5 Hz, H-12); 2.44–2.27 (m, 2H, H-6, 10); 2.20–2.02 (m, 2H, H-6,10); 1.84–1.70 (m, 1H, H-9); 1.68–1.49 (m, 3H, H-7,8,9); 1.43–1.11 (m, 2H, H-7,8) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 204.7 (C-13); 134.2 (C-4a); 134.0 (C-12a); 133.2 (C-2); 128.7 (C-1); 128.6 (C-4); 128.0 (C-3); 96.4 (C-11); 50.7 (C-5); 40.1 (C-12); 34.1 (C-6); 31.4 (C-10); 25.0 (C-8); 21.3 (C-9); 20.9 (C-7) ppm. Anal. Calcd for $C_{15}H_{16}NO_3Cl$: C, 61.33; H, 5.45; N, 4.77. Found: C, 61.16; H, 5.25; N, 4.64.

(±)-*cis*-5,6,7,8,9,10,11,12-Octahydro-3-methyl-11-nitro-5,11-methanobenzocyclodecen-13-one (4o). Colourless oil. IR (NaCl): 2933, 1723 (CO), 1548 and 1335 (NO_2) cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 7.02 (s, 2H, H-3, 4); 6.99 (s, 1H, H-4); 3.95 (d, 1H, J = 16.2 Hz, H-12); 3.82 (dd, 1H, J = 7.1 and 4.9 Hz, H-5); 3.36 (d, 1H, J = 16.2 Hz, H-12); 2.46–2.25 (m, 6H, H-7,11, CH_3); 2.18–2.14 (m, 1H, H-11); 1.88–1.60 (m, 5H, H-8–10); 1.58–1.41 (m, 1H, H-10) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 206.3 (C-13); 137.9 (C-3); 135.7 (C-4a); 129.8 (C-12a); 129.1 (C-1); 128.7 (C-2); 128.1 (C-4); 97.6 (C-11); 51.5 (C-5); 40.7 (C-12); 34.6 (C-6); 31.6 (C-10); 25.6 (C-8); 21.9 (C-9); 21.6 (CH_3); 21.3 (C-7) ppm. Anal. Calcd for $C_{16}H_{19}NO_3$: C, 70.32; H, 6.96; N, 5.13. Found: C, 69.99; H, 6.81; N, 5.08.

(±)-*cis*-2-Methoxy-5,6,7,8,9,10,11,12-octahydro-11-nitro-5,11-methanobenzocyclodecen-13-one (4p). White solid, mp 155 °C. IR (neat) 2935, 1723 (CO), 1611, 1548 and 1350 (NO_2), 1504, 1465, 1246, 1136, 10360 cm^{-1}. ^{1}H NMR ($CDCl_3$, 250 MHz) δ 7.14 (d, J = 8.6 Hz, 1H, H-4); 6.88 (dd, J = 2.4 and 8.6 Hz, 1H, H-3); 6.74 (s, 1H, H-1); 3.99 (d, J = 17.1 Hz, 1H, H-12); 3.85 (s, 3H, OMe); 3.78–3.87 (m, 1H, H-5); 3.35 (d, J = 17.1 Hz, 1H, H-12); 2.26–2.45 and 2.07–2.20 (m, 3+1H, H-7,11); 1.63–1.88 (m, 4H, H-8,9); 1.28–1.42 (m, 2H, H-10) ppm. ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ 206.3 (C-13); 159.2 (C-2); 134.2 (C-12a); 128.8 (C-4); 127.7 (C-4a); 114.2 (C-2); 114.1 (C-3); 97.5 (C-11); 55.7 (OMe); 50.9 (C-5); 41.2 (C-12); 34.7 (C-6); 31.6 (C-10); 25.6 (C-8); 21.9 (C-7); 21.2 (C-9) ppm. Anal. Calcd for $C_{16}H_{19}NO_4$: C, 66.42; H, 6.62, N, 4.84. Found: C, 66.21; H, 6.42; N, 4.63.

(±)-*cis*-7,8,9,10,11,12,13,14-Octahydro-8-nitro-8,14-methanocyclodeca[*a*]naphthalen-15-one (4q). Pale yellow solid; mp 170–171 °C. IR (KBr): 2935, 1722 (CO), 1547 and 1329 (NO_2) cm^{-1}. ^{1}H NMR ($CDCl_3$, 250 MHz) δ: 7.91 (m, 2H, H-1,4); 7.79 (d, 1H, J = 8.4 Hz, H-5); 7.61–7.49 (m, 2H, H-2,3); 7.30 (d, 1H, J = 8.4 Hz, H-6); 4.51 (dd, 1H, J = 10.6 and 7.3 Hz, H-14); 3.91 (s, 2H, H-7); 2.85–2.73 (m, 1H, H-9); 2.52–2.34 (m, 2H, H-9, 13); 2.18–2.04 (m, 1H, H-13); 1.94–1.82 (m, 2H, H-10); 1.79–1.57 (m, 4H, H-11, 12) ppm. ^{13}C NMR ($CDCl_3$, 63 MHz) δ: 204.8 (C-15); 132.9 (C-4a); 131.2 (C-14a); 130.3 (C-14b); 128.8 (C-4; C-6a); 128.0 (C-5); 126.7 (C-2); 126.2 (C-6); 125.7 (C-1); 122.2 (C-3); 95.7 (C-8); 49.6 (C-14); 40.7 (C-7); 34.2 (C-9); 32.3 (C-13); 25.9 (C-11); 23.5 (C-12); 21.1 (C-10) ppm. Anal. Calcd for $C_{19}H_{19}NO_3$: C, 73.78; H, 6.15; N, 4.53. Found: C, 73.61; H, 6.11; N, 4.67.

(*E*)-2-(2′-Bromo-4′-methoxycarbonylbenzylidene)cycloheptanone (5g). Colourless oil. IR (neat) 2934, 1728 (CO), 1548, 1435, 1289, 1260, 1118, 764 cm^{-1}. ^{1}H NMR ($CDCl_3$, 250 MHz) δ: 8.08 (d, 1H, J = 8.3 Hz, H-4′); 7.54–7.40 (m, 2H, H-2′,5′); 7.29 (s, 1H, H-α); 3.96 (s, 3H, OMe); 2.74–2.68 (m, 2H, H-7); 1.94–1.65 (m, 4H, H-3,6); 1.60–1.45 (m, 4H, H-4,5) ppm. ^{13}C NMR ($CDCl_3$, 63 MHz) δ: 204.9 (C-1); 167.1 (CO_2Me); 142.8 (C-2); 141.1 (C-1′); 134.8 (C-α); 130.3 (C-5′); 130.02 (C-3′); 129.9 (C-2′); 129.6 (C-4′); 128.1 (C-6′); 52.6 (CO_2Me); 43.8 (C-7); 31.6 (C-5); 30.3 (C-4); 28.2 (C-3); 25.8 (C-6) ppm. Anal. Calcd. for $C_{16}H_{17}BrO_3$: C, 56.99; H, 5.08. Found: C, 56.72; H, 4.89.

(*E*)-2-(2′-Bromo-4′-methoxycarbonylbenzylidene)cyclooctanone (5n). Colourless oil. IR (neat) 2934, 1729, 1693, 1288, 1255, 1112, 761 cm^{-1}. ^{1}H NMR ($CDCl_3$, 250 MHz) δ 8.25 (d, J = 1.6 Hz, 1H, H-6′); 7.86 (dd, J = 1.6 and 8.0 Hz, 1H, H-4′); 7.23 (d, J = 8.0 Hz, 1H, H-3′); 6.62 (s, 1H, H-α); 3.93 (s, 3H, CO_2Me); 2.55–2.60 (t, J = 6.0 Hz, 2H, H-8); 2.05–2.09 (m, 2H, H-3); 1.71–1.73 (m, 4H, H-4,7); 1.54–1.55 (m, 4H, H-5,6). ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ 215.3 (C-1); 165.9 (CO_2Me); 148.7 (C-2); 141.4 (C-1′); 134.1 (C-α); 131.2 (C-5′); 130.4 (C-3′); 128.9 (C-4′); 125.9 (C-6′); 123.4 (C-2′); 52.8 (CO_2Me); 43.8 (C-8); 38.7 (C-3), 28.6 (C-7), 26.7 (C-4), 25.9 (C-5), 23.6 (C-6) ppm. Anal. Calcd for $C_{17}H_{19}BrO_3$: C, C, 58.13; H, 5.45. Found: C, 57.82; H, 5.31.

2,3-Methylenedioxy-9a-nitro-4b,5,6,7,8,9,9a,10-octahydrobenzo[*a*]azulen-4b-ol (6i). Colourless liquid. IR (neat) 3508.2, 2927, 1538 and 1376 (NO_2), 1505, 1479, 1263, 1249, 1037, 937, 864 cm^{-1}. ^{1}H NMR ($CDCl_3$, 250 MHz) δ 6.74 (s, 1H, H-1); 6.67 (s, 1H, H-4); 5.98–6.01 (m, 2H, OCH_2O); 3.88 (d, J = 17.1 Hz, 1H, H-10); 3.09 (d, J = 17.1 Hz, 1H, H-10); 2.64–2.72 (m, 1H, H-9); 2.27–2.37 (m, 2H, H-9 and OH); 2.04–2.19 (m, 2H, H-5); 1.73–1.96 (m, 2H, H-6); 1.49–1.66 (m, 4H, H-7,8) ppm. ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ 149.4 (C-2); 148.2 (C-3); 137.6 (C-4a); 132.1 (C-104); 104.7 (C-2); 104.4 (C-4); 103.7 (OCH_2O); 101.8 (C-9a); 86.7 (C-4b); 43.1 (C-10); 38.3 (C-5); 37.7 (C-9); 30.1 (C-7); 23.6 (C-8); 23.3 (C-6). Anal. Calcd for $C_{15}H_{17}NO_5$: C, 61.85; H, 5.88, N, 4.81. Found:C, 61.69; H, 5.65; N, 4–58.

6,7,8,9,10,11-Hexahydro-5*H*-cycloocta[*a*]indene (6k). Colourless oil. IR (NaCl): 2907, 1467, 1260, 1020 cm^{-1}. ^{1}H NMR ($CDCl_3$, 250 MHz) δ: 7.39 (d, 1H, J = 7.2 Hz, H-4); 7.32–7.23 (m, 2H, H-1,2); 7.12 (td, 1H, J = 7.1 and 2.0 Hz, H-3); 3.32 (s, 2H, H-11); 2.64–2.55 (m, 4H, H-5,10); 1.88–1.71 (m, 6H); 1.40–1.15 (m, 2H) ppm. ^{13}C NMR ($CDCl_3$, 63 MHz) δ: 147.5 (C-4a); 145.1 (C-4b); 142.3 (C-11a); 138.8 (C-10a); 125.9 (C-3); 123.3 (C-2); 123.1 (C-1); 117.5 (C-4); 42.9 (C-11); 31.4 (C-9); 30.5 (C-10), 29.6; 27.5; 27.3

(C-6,7,8); 26.0 (C-5) ppm. MS (ESI), *m*/*z*: 199 (M^+ + 1). Anal. Calcd for $C_{15}H_{18}$: C, 90.90; H, 9.10. Found: C, 90.80; H, 9.25.

2-Nitro-6,7,8,9,10,11-hexahydro-5*H*-cycloocta[*a*]indene (6m). Pale yellow oil. IR (NaCl): 2918, 1699, 1558 and 1337 (NO_2) cm^{-1}. ^1H NMR ($CDCl_3$, 250 MHz) δ: 8.25–8.21 (m, 2H, H-Ar); 7.35–7.20 (m, 1H, H-Ar); 3.44 (s, 2H, H-11); 2.77–2.63 (m, 4H, H-5,10); 1.99–1.52 (m, 6H); 1.38–1.21 (m, 2H) ppm. ^{13}C NMR ($CDCl_3$, 63 MHz) δ: 160.2 (C-4a); 154.3 (C-2); 153.0 (C-11a); 135.5 (C-4b); 122.8 (C-10a); 120.0 (C-1); 118.3 (C-4); 117.4 (C-3); 43.0 (C-11); 31.1 (C-9); 30.9 (C-10); 30.9; 27.1; 27.0 (C-6,7,8); 26.0 (C-5) ppm. Anal. Calcd for $C_{15}H_{17}NO_2$: C, 74.07; H, 6.99; N, 5.76. Found: C, 73.81; H, 6.76; N, 5.68.

3-Methyl-6,7,8,9,10,11-hexahydro-5*H*-cycloocta[*a*]indene (6o). Colourless oil. IR (NaCl): 2920, 1612, 1444 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz) δ: 7.25 (d, 1H, J = 7.6 Hz, H-1); 7.05 (s, 1H, H-4); 6.93 (dd, 1H, J = 7.4 and 0.6 Hz, H-2); 3.26 (s, 2H, H-11); 2.60–2.52 (m, 4H, H-5,10); 2.40 (s, 3H, CH_3); 1.87–1.81 (m, 2H); 1.75–1.65 (m, 4H); 1.27 (s, 2H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 148.0 (C-4a); 145.4 (C-4b); 139.3 (C-11a); 138.8 (C-10a); 135.4 (C-3); 124.0 (C-2); 122.8 (C-1); 118.4 (C-4); 42.5 (C-11); 31.4 (C-9); 30.5 (C-10); 29.6; 27.6; 27.3 (C-6–8); 26.0 (C-5); 21.3 (CH_3) ppm. Anal. Calcd for $C_{16}H_{20}$: C, 90.56; H, 9.44. Found: C, 90.34; H-9.53.

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