Pergamon

Tetrahedron 57 (2001) 6011–6017

TETRAHEDRON

Stereoselective synthesis and conformational analysis of *cis*-5-(2-nitrophenyl)-2-azabicyclo[3.3.0]octan-6-ones

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Received 8 November 2000; revised 25 April 2001; accepted 10 May 2001

Abstract—A short route to *cis*-5-(2-nitrophenyl)-2-azabicyclo[3.3.0]octanes involving ozonolysis of 2-allyl-2-(2-nitrophenyl)-1,3-cyclopentanedione followed by double reductive amination is described. The preferred conformations of the azabicyclic ring system in these compounds are reported.

1. Introduction

The 5-aryl-2-azabicyclo[3.3.0]octane framework I[1] is found in the *Melodinus* quinoline alkaloids[2] (e.g. meloscine), in the vindolinine group of indole alkaloids[3] (e.g. tuboxenine), and in the structurally unique compound calebassinine-1.[4] The only total synthesis for these monoterpenoid alkaloids reported thus far is Overman's synthesis of meloscine (Fig. 1).[5,6]

In this paper, we describe a synthetic entry to 5-(2-nitrophenyl)-2-azabicyclo[3.3.0]octan-6-ones, which were envisaged as the starting building blocks for the synthesis of the afore-mentioned alkaloids, since they incorporate three of their rings and possess suitable functionalities for assembling the rest of the skeleton.

Four procedures have been described for the preparation of compounds with the framework I (Scheme 1): (i) Overman[7] exploited the tandem cationic aza-Cope rearrangement/Mannich cyclization for the preparation of this type of compounds using 2-amino-1-(1-arylvinyl)cyclobutanols as intermediates (last bond formed C1–C5). (ii) Remuson[8] used the cyclization of an allylsilane upon an α-acyliminium salt (last bond formed C1–C8). (iii) Baldwin's[9] key step consisted of an intramolecular nitrone/alkene cycloaddition, followed by reduction of the labile N–O bond and lactamization. (iv) Pearson[10] formed the azabicyclic system by a [3+2]cycloaddition promoted by a 2-azaallyl anion upon an alkene. It is noteworthy that none of these routes incorporate a functionalization in the aryl group which can be further elaborated into indoline or quinoline units.

Keywords: amination; conformation; cyclopentanones; nitro compounds; nitrogen heterocycles.

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2. Results and discussion

2.1. Synthesis of 5-(2-nitrophenyl)-2-azabicyclo[3.3.0]-octan-6-ones

The synthetic approach to 5-(2-nitrophenyl)-2-azabicyclo-[3.3.0]octane derivatives here described is based on an extension of our previous work on the synthesis of 3a-(2-nitrophenyl)octahydroindol-4-ones,[11] a class of compounds that have proved to be useful intermediates for the total synthesis of *Strychnos* alkaloids[12] including strychnine itself.[13]

Our approach involves the elaboration of the pyrrolidine ring by introduction of the amino moiety by a double reductive amination process: first, in an intermolecular way (N2–C3 bond formed), upon the aldehyde of the tricarbonyl derivative resulting from the ozonolysis of 2-allyl-2-(2-nitrophenyl)-1,3-cyclopentanedione and then, in an

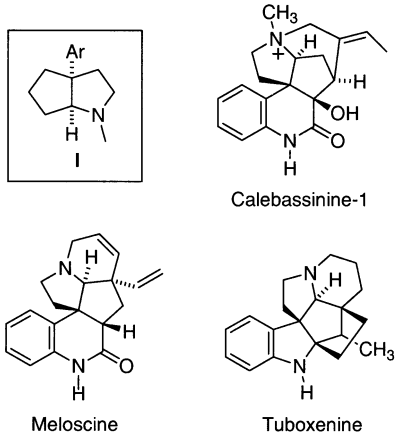

Figure 1.

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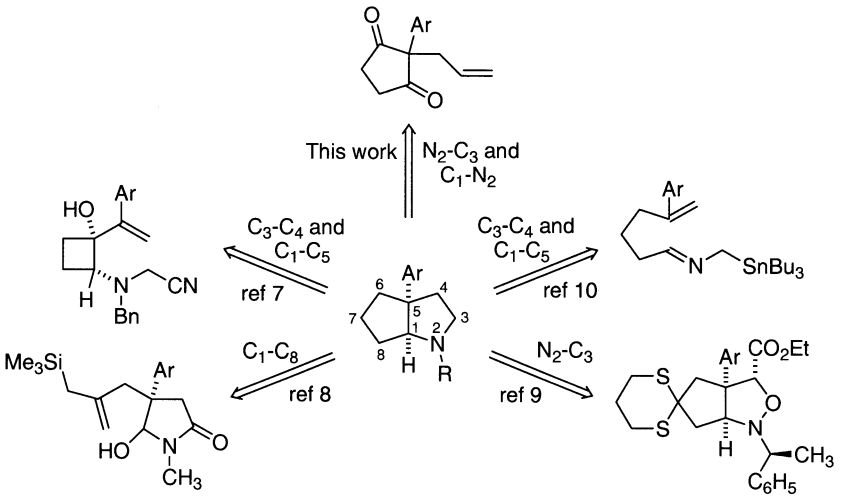
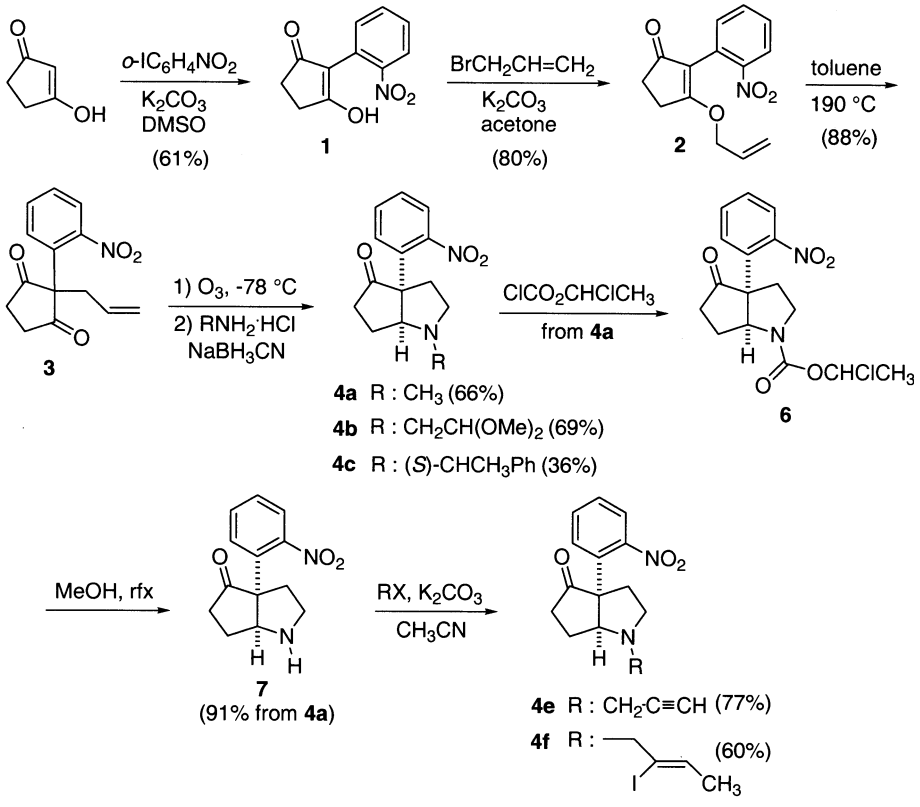


Scheme 1. Synthetic approaches to *cis*-5-aryl-2-azabicyclo[3.3.0]octanes.

intramolecular manner (C1–N2 bond formed), upon one of the two enantiotopic ketone carbonyl groups.

Direct arylation of 1,3-cyclopentanedione[14] by a nucleophilic aromatic substitution reaction, using potassium carbonate as a base and 2-iodonitrobenzene as the arylating agent in DMSO (85–90°C, 3 h), afforded dione **1** in 61% yield, the enolic form being the favoured tautomer (Scheme 2). As in the cyclohexanedione series,[11] the elaboration of the quaternary carbon center was accomplished by *O*-allylation and subsequent Claisen rearrangement. Thus, treatment of dione **1** with allyl bromide and K_2CO_3 provided allyl vinyl ether **2**, which, on heating at 190°C, was converted to the α,α-disubstituted cyclopentanedione **3** in 70% overall yield.

Having obtained the prochiral dione **3**, we undertook the elaboration of the pyrrolidine ring. Thus, ozonolysis of the allyl group of dione **3**, followed by reaction of the ozonide intermediate with methylamine hydrochloride and sodium cyanoborohydride, stereoselectively gave the *cis* azabicyclo derivative **4a** in 66% yield. As a minor by-product dione **5a** was isolated from the reaction of the secondary amine intermediate with the formaldehyde formed during the reduction of the ozonide. This competing process, not observed in the 1,3-cyclohexanedione series, indicates that in the



Scheme 2. Synthesis of 5-(2-nitrophenyl)-2-azabicyclo[3.3.0]octan-6-ones.

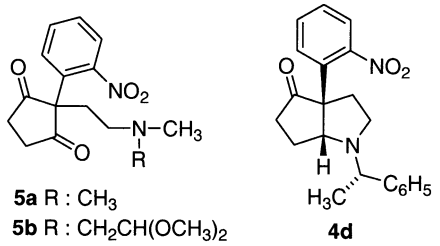


Figure 2.

5,5-membered series the intramolecular attack of the secondary amine upon the ketone carbonyl group is slower than in the 6,5-membered series. Operating as above, but using 2,2-dimethoxyethylamine as the aminocyclization agent, azabicyclo **4b** was isolated in 69% yield together with small amounts of dione **5b**.

The use of (*S*)-1-phenylethylamine[15] in the sequence of ozonolysis-double reductive amination from dione **3** afforded enantiopure *cis* azabicyclic compound **4c** in 36% yield together with minor amounts of the other *cis* derivative **4d**, the diastereoselectivity of the process being analogous to that observed in the 6,5-membered homoderivative.[11] (for the determination of the absolute configuration of **4c**, see below) (Fig. 2).

The valuable secondary amine **7** was prepared from **4a** by treatment with α-(chloroethyl) chloroformate and subsequent heating of the resulting carbamate, **6** in a methanol solution. Starting from enantiopure **4c**, and following the same procedure although with more drastic reaction conditions, (−)-**7** was obtained. Alkylation of the secondary amine **7**, introducing functionalized side chains upon the nitrogen atom, broadens the access to 5-aryl-2-azabicyclo-[3.3.0]octanone derivatives. For example, azabicyclos **4e** and **4f** were prepared by reaction of **7** with propargyl bromide and (*Z*)-1-bromo-2-iodo-2-butene, respectively.

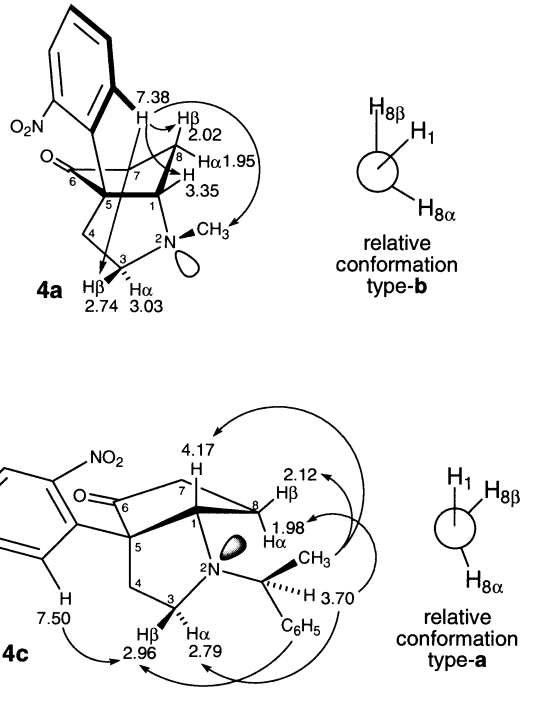


Figure 3.

2.2. Spectroscopic analysis of azabicyclic derivatives

The stereochemistry of **4a** was established by NMR, using COSY and NOESY experiments, which allowed the *cis* configuration and the conformation depicted in Fig. 3 to be determined. Strong through space interactions between H-6′ of the phenyl substituent and the *N*-methyl group, H-1, H-3β and H-8β[16] indicated that these groupings are all *syn*-related. The half-chair cyclopentane conformation type-**b**[17] can be deduced from the observation of H-1 as a doublet of doublets (J=5 and 2 Hz) in the ^{1}H NMR spectrum, involving estimated dihedral angles near to −45 and 75° between H-1 and the *cis* and *trans* H-8 hydrogens, repectively. Thus, compound **4a** must exist preferentially in a conformation with the *N*-Me group on the β-face (*trans* to C-8 and H-3α), the *cis* H-1 and H-3β hydrogens being identically shielded by the *syn*-Me group and the anti electron pair.[18] The spectral data indicated that compound **4b** as well as the propargyl derivative **4e** and vinyl iodide **4f** have similar conformational characteristics (see Section 3 and Table 1).

The conformational behavior of enantiopure compounds **4c** and **4d** was different with respect to the *N*-alkylderivatives **4a**, **4b**, **4e** and **4f**, since the cyclopentane ring changes towards a preferred type-**a**[17] half-chair conformation (dihedral angles near to 45 and 140°), as can be deduced from the coupling constants for H-1 (dd, J=7.5 and 5.5 Hz). Moreover, the nitrogen lone pair is now located on the top face and the bulky 1-phenylethyl substituent is on the concave, sterically more congested, bottom face of the *cis*-azabicyclo[3.3.0]octane ring system. The predominant conformation of **4c** shown in Fig. 3 was confirmed on the basis of 2D NOE data, which in turn afforded diagnostic evidence for the (1*S*,5*R*) configuration of **4c**.

The NOESY experiment on **4c** showed off-diagonal cross-peaks connecting H-1 and H-8 with a methyl proton, thus indicating their spatial proximity. The distance between these protons would increase in the derivative with the opposite configuration at the ring junction. The NOESY spectrum also showed interactions between the benzylic proton and the C-3 and C-8 *endo* protons, thus corroborating the absolute configuration of **4c**, which is the same as that of alkaloids incorporating the *cis*-5-aryl-2-azabicyclo-[3.3.0]octane subunit in their backbone (see Fig. 1).

Interestingly, the secondary amine **7** also adopts a type-**a** half-chair conformation. Comparison of the ^{1}H NMR signals for H-3β (δ 3.36) and H-1 (δ 4.19) of secondary amine **7** with the corresponding signals of *N*-methyl derivative **4a** (H-3β δ 2.74; H-1 δ 3.35) showed that the *N*-methyl group caused an upfield shift in both of these hydrogens, as expected from a conformational switch.

The most significant differences in the ^{13}C NMR data (Table 1) that can be used to diagnose the preferred conformation for azabicyclos **4**(**a**–**f**), and **7** are the chemical shifts of the carbonyl group. Compounds with type-**a**

Table 1. ^{13}C NMR chemical shifts of 5-(2-nitrophenyl)-2-azabicyclo[3.3.0]octan-6-ones

	C-1	C-3	C-4	C-5	C-6	C-7	C-8	C-1′	C-2′	C-3′	C-4′	C-5′	C-6′
4a[a]	74.1	55.3	35.0	63.2	217.1	36.0	21.9	133.9	149.7	125.1	127.9	132.4	130.1
4b[a]	73.4	54.3	35.6	62.6	216.3	36.3	22.9	134.2	149.5	125.2	127.9	132.6	130.1
4c[a]	70.9	49.5	34.3	62.5	215.1	36.7	21.0	136.3	148.5	125.1	127.8	132.9	130.5
4d[a]	71.2	49.8	34.8	62.4	215.3	36.4	22.9	136.3	148.4	125.1	127.8	132.8	130.3
4e[a]	70.7	51.9	35.0	62.9	216.0	36.2	23.1	134.2	149.5	125.2	127.9	132.5	130.1
4f[a]	71.6	51.5	35.3	62.9	217.2	35.4	22.3	134.0	149.5	125.1	127.9	132.5	130.4
6[a,b]	67.8–68.5	46.0–46.8	31.4–32.4	61.7–62.9	210.6–212.1	35.9–36.1	26.7–27.8	133.9–134.4	147.2–147.7	126.3–126.5	128.7–129.6	133.9–134.4	128.7–129.6
7	70.6	46.5	36.1	64.2	215.0	37.1	26.9	135.4	148.0	125.7	128.0	133.2	129.5

In ppm relative to TMS. Recorded at 50.3 MHz.

[a] Substituent signals: **4a**, 39.0 (NCH_3); **4b**, 53.2 (NCH_2), 53.8 (OCH_3), 103.3 (CH); **4c**, 21.8 (CH_3), 60.2 (NCHAr), 126.9 (CH), 128.3 (CH), 145.2 (C); **4d**, 23.3 (CH_3), 60.8 (NCHAr), 126.9 (CH), 128.3 (CH), 144.7 (C); **4e**, 39.8 (NCH_2), 73.0 (C), 78.4 (CH); **4f**, 21.6 (CH_3), 64.1 (N CH_2), 109.1 (=CI), 131.4 (=CH); 6, 25.2–25.3 (CH_3), 82.7–82.9 (OCHCl), 151.0–151.3 (NCOO).

[b] In the description of the NMR data of this compound a hyphen is used to indicate that the spectrum is complex due to the existence of diastereomers and rotamers.

Table 2. ^{13}C NMR chemical shifts of 2-(2-nitrophenyl)cyclopentanone derivatives **1**–**3** and **5**

	C-1	**C-2**	C-3	C-4	C-5	C-1′	C-2′	C-3′	C-4′	C-5′	C-6′
1	184.0	113.5	184.0	30.4	30.4	125.4	148.4	123.7	126.9	131.9	131.5
2[a]	201.3	117.0	184.2	25.3	33.8	125.3	148.3	124.5	128.1	132.6	131.9
3[a]	209.6	64.4	209.6	36.0	36.0	131.0	148.0	126.0	128.8	134.1	131.6
5a[a]	209.7	63.5	209.7	35.5	35.5	130.6	147.5	126.0	128.8	134.1	131.3
5b[a]	209.6	63.7	209.6	35.4	35.4	130.5	147.2	126.0	128.8	134.1	131.4

In ppm relative to TMS. Recorded at 50.3 MHz.
[a] Substituent signals: 2, 70.7, 119.0, 131.5 ($OCH_2CH{=}CH_2$); 3, 36.8, 120.9, 130.0 ($CH_2CH{=}CH_2$); **5a**, 30.3, 45.2, 53.5 ($CH_2CH_2N(CH_3)_2$); **5b**, 29.4, 43.1, 52.0, 53.6, 58.5, 102.3 ($CH_2CH_2N(CH_3)CH_2CH(OCH_3)_2$).

conformation show the carbonyl carbon at a higher field (δ 215) than those with type-**b** conformation (δ 216–217).

The same conformational behavior of the more sterically demanding compound **4c** and the secondary amine **7** suggests that the steric factor alone is not responsible for the conformational switch, the presence of the *o*-nitro substituent being an important factor in the conformational behavior of these compounds.

3. Experimental

3.1. General

^1H- and ^{13}C NMR spectra (Tables 1 and 2) were recorded in $CDCl_3$ solution, using Me_4Si as internal standard. Chemical shifts are reported in ppm downfield (δ) from Me_4Si. IR spectra were recorded on a Nicolet 205 FT infrared spectrophotometer and only noteworthy absorptions are listed. Melting points were determined in a capillary tube and are uncorrected. Optical rotations were measured on a Perkin–Elmer 241 polarimeter. TLC was carried out on SiO_2 (silica gel 60 F_{254}, Merck), and the spots were located with UV light, iodoplatinate reagent or 1% aqueous $KMnO_4$. Chromatography refers to flash chromatography and was carried out on SiO_2 (silica gel 60, SDS, 230–400 mesh ASTM). Drying of organic extracts during workup of reactions was performed over anhydrous Na_2SO_4. Evaporation of solvents was accomplished with a rotatory evaporator. Microanalyses were performed by Centro de Investigación y Desarrollo (CSIC), Barcelona.

3.1.1. 2-(2-Nitrophenyl)-1,3-cyclopentanedione (1). A mixture of 1,3-cyclopentanedione (5 g, 51 mmol), anhydrous K_2CO_3 (14 g, 102 mmol), and *o*-iodonitrobenzene[19] (15.2 g, 61.2 mmol) in DMSO (50 ml) was heated to 85–90°C for 4 h. After cooling, the mixture was poured into water. The resulting solution was acidified with concentrated hydrochloric acid and extracted with CH_2Cl_2. The combined organic extracts were washed with brine, dried, and concentrated to give a brown foam, which was chromatographed (CH_2Cl_2 to CH_2Cl_2, 5% MeOH) affording dione **1** (6.8 g, 61%). IR (KBr) 3500–2350, 1530, 1378 cm^{-1}. ^1H NMR (300 MHz) δ 2.64 (br, 4H, H-4 and H-5), 7.38 (ddd, J=8.1, 6.6, and 2.2 Hz, 1H), 7.52–7.63 (m, 2H), 7.90 (dd, J=8.4 and 1 Hz, 1H). Anal. calcd for $C_{11}H_9NO_4$ (219.19): C, 61.80; H, 4.14; N, 6.39. Found: C, 61.88; H, 4.45; N, 5.97.

3.1.2. 3-Allyloxy-2-(2-nitrophenyl)-2-cyclopentenone (2). A mixture of dione **1** (5 g, 22.8 mmol), anhydrous K_2CO_3 (6.3 g, 45.5 mmol), and allyl bromide (2.25 ml, 26 mmol) in anhydrous acetone (100 ml) was stirred at reflux temperature for 3 h. The solvent was removed, and the residue was partitioned between water and CH_2Cl_2. The aqueous layer was extracted with CH_2Cl_2. The combined organic extracts were washed with water, dried, and concentrated to give an oil, which was chromatographed (CH_2Cl_2) affording enol ether **2** (4.7 g, 80%). IR ($CHCl_3$) 1687, 1625, 1600, 1526, 1381, 1352 cm^{-1}. ^1H NMR (300 MHz) δ 2.65 (m, 2H), 2.86 (m, 2H), 4.69 (dt, J=5.4 and 1.5 Hz, 2H, CH_2O), 5.32 (ddt, J=10.5, 2.5, and 1.5 Hz, 1H), 5.32 (ddt, J=17.2, 2.5, and 1.5 Hz, 1H), 5.94 (ddt, J=17.2, 10.5, and 5.4 Hz, 1H), 7.43 (ddd, J=8.2, 7.3, and 1.5 Hz, 1H, H-4′), 7.49 (dd, J=7.8 and 1.5 Hz, 1H, H-6′), 7.60 (ddd, J=7.8, 7.3, and 1.2 Hz, 1H, H-5′), 7.95 (dd, J=8.2 and 1.2 Hz, 1H, H-3′). Anal. calcd for $C_{14}H_{13}NO_4$ (259.27): C, 64.85; H, 5.05; N, 5.40. Found: C, 64.49; H, 5.01; N, 5.43.

3.1.3. 2-Allyl-2-(2-nitrophenyl)-1,3-cyclopentanedione (3). A solution of enol ether **2** (6 g, 23.1 mmol) in anhydrous toluene (60 ml) was stirred at 180–190°C in a sealed tube for 12 h. After the solvent was evaporated, the residue was crystallized (EtOAc) affording dione **3** (5.28 g, 88%); mp 145–146°C (white needles). IR (KBr) 1724, 1523, 1353 cm^{-1}. ^1H NMR (200 MHz) δ 2.86 (d, J=7 Hz, 2H, CH_2), 2.98 (s, 4H, CH_2CO), 5.24 (dd, J=10 and 1 Hz, 1H), 5.29 (dd, J=17 and 1 Hz, 1H), 5.71 (ddt, J=17, 10, and 7 Hz, 1H), 7.52 (td, J=8 and 1.5 Hz, 1H), 7.66–7.78 (m, 2H), 8.13 (dd, J=8 and 1.5 Hz, 1H). Anal. calcd for $C_{14}H_{13}NO_4$ (259.27): C, 64.85; H, 5.05; N, 5.40. Found: C, 64.56; H, 5.11; N, 5.35.

3.1.4. *cis*-2-Methyl-5-(2-nitrophenyl)-2-azabicyclo[3.3.0]-octan-6-one (4a). A stirred solution of dione **3** (2.86 g, 11 mmol, 1 equiv.) in CH_2Cl_2 (100 ml) at −78°C was charged with a constant stream of ozone. After 2.5 h, the solution turned characteristic pale blue and was purged with oxygen. The solvent was removed with a rotatory evaporator without warming, and the residue was dissolved in MeOH (40 ml). To this solution were added first a solution of methylamine hydrochloride (3 g, 44 mmol, 4 equiv.) in MeOH (50 ml) and then sodium cyanoborohydride (345 mg, 5.5 mmol, 0.5 equiv.). After being stirred for 30 min, an additional portion of sodium cyanoborohydride (345 mg, 5.5 mmol, 0.5 equiv.) was added and stirring was continued for 1 h. At this time, an additional portion of sodium cyanoborohydride (1 g, 16.5 mmol, 1.5 equiv.) was added, and stirring was continued for 2.5 h. The reaction was quenched with 1N hydrochloric acid (30 ml) and the stirring was continued for 30 min. After removal of the

methanol under reduced pressure, the aqueous mixture was extracted with ether, and the organic layers were discarded. The aqueous layer was made alkaline with solid K_2CO_3 and extracted with CH_2Cl_2. The organic extracts were dried and concentrated to give an oil, which was chromatographed. Elution with CH_2Cl_2-1% MeOH afforded ketone **4a** (1.9 g, 66%), whereas elution with CH_2Cl_2–3% MeOH gave 2-[2-(dimethylamino)ethyl]-2-(2-nitrophenyl)-1,3-cyclopentanedione (**5a**, 140 mg, 5%).

Ketone **4a**: IR (film) 1738, 1530, 1363 cm^{-1}. ^1H NMR (500 MHz)[16] δ 1.95 (dddd, J=13.5, 9.5, 3, and 2 Hz, 1H, H-8α), 2.02 (dddd, J=14, 13.5, 9.5, and 5 Hz, 1H, H-8β), 2.36 (ddd, J=19, 9.5, and 3 Hz, 1H, H-7), 2.36 (s, 3H, NCH_3), 2.36–2.40 (m, 2H, H-4), 2.61 (dt, J=19 and 9.5 Hz, 1H, H-7), 2.74 (q, J=9 Hz, 1H, H-3β), 3.03 (ddd, J=9, 7, and 4 Hz, 1H, H-3α), 3.35 (dd, J=5 and 2 Hz, 1H, H-1), 7.36 (ddd, J=8, 7.5, and 1.5 Hz, 1H, H-4′), 7.38 (dd, J=7.5 and 1 Hz, 1H, H-6′), 7.51 (ddd, J=8, 7.5, and 1.5 Hz, 1H, H-5′), 7.67 (dd, J=7.5 and 1 Hz, 1H, H-3′). Anal. calcd for $C_{14}H_{16}N_2O_3$ (260.30): C, 64.60; H, 6.20; N, 10.76. Found: C, 64.34; H, 6.22; N, 10.75.

Dione **5a**: ^1H NMR δ 2.22 (s, 6H, NCH_3), 2.27 (s, 4H), 2.90–3.20 (m, 4H), 7.55 (t, J=8 Hz, 1H), 7.65 (d, J=8 Hz, 1H), 7.80 (t, J=8 Hz, 1H), 8.10 (d, J=8 Hz, 1H).

3.1.5. *cis*-2-(2,2-Dimethoxyethyl)-5-(2-nitrophenyl)-2-azabicyclo[3.3.0]octan-6-one (4b). Operating as above, from dione **3** (0.5 g, 1.9 mmol) and 2,2-dimethoxyethylamine hydrochloride (815 mg, 7.7 mmol), ketone **4b** (448 mg, 69%) and 2-[2-[*N*-(2,2-Dimethoxyethyl)methylamino]ethyl]-2-(2-nitrophenyl)-1,3-cyclopentanedione (**5b**, 63 mg, 9%) were obtained after chromatography (CH_2Cl_2-1% MeOH to CH_2Cl_2-4% MeOH).

Ketone **4b**: IR (film) 1737, 1529, 1360 cm^{-1}. ^1H NMR (500 MHz)[16] δ 1.97 (dddd, J=13, 10, 3, and 2 Hz, 1H, H-8α), 2.11 (m, 1H, H-8β), 2.32–2.47 (m, 3H, H-4 and H-7), 2.63–2.72 (m, 2H, H-7 and CH_2N), 2.85 (dd, J=13 and 5.5 Hz, 1H, CH_2N), 2.92 (q, J=8.5 Hz, 1H, H-3β), 3.18 (td, J=8.5 and 3 Hz, 1H, H-3α), 3.35 (s, 6H, OCH_3), 3.66 (br d, J=5 Hz, 1H, H-1), 4.42 (t, J=5.5 Hz, 1H, $CH(OMe)_2$), 7.40 (t, J=7.5 Hz, 1H, H-4′), 7.43 (d, J=7.5 Hz, 1H, H-6′), 7.55 (t, J=7.5 Hz, 1H, H-5′), 7.75 (d, J=7.5 Hz, 1H, H-3′). Anal. calcd for $C_{17}H_{22}N_2O_5$ (334.24): C, 61.07; H, 6.63; N, 8.37. Found: C, 60.78; H, 6.81; N, 8.20.

Dione **5b**: ^1H NMR (200 MHz) δ 2.35 (s, 3H, NCH_3), 2.40–2.70 (m, 4H), 2.90–3.25 (m, 4H), 3.30–3.50 (m, 2H), 3.37 (s, 6H, $(OMe)_2$), 4.45 (t, J=5.5 Hz, 1H, $CH(OMe)_2$), 7.52 (t, J=8 Hz, 1H), 7.62 (d, J=8 Hz, 1H), 7.75 (t, J=8 Hz, 1H), 8.09 (d, J=8 Hz, 1H).

3.1.6. (1*S*,5*R*)-2-[(*S*)-2-(1-Phenylethyl)]-5-(2-nitrophenyl)-2-azabicyclo[3.3.0]octan-6-one (4c). Operating as above, from dione **3** (0.9 g, 3.4 mmol) and (*S*)-α-methylbenzylamine hydrochloride (570 mg, 3.6 mmol), using *i*-PrOH as the solvent in the reductive amination step, ketone **4c** (425 mg, 36%) and the (1*R*,5*S*)-isomer (**4d**, 47 mg, 4%) were obtained after chromatography (hexane to 8:2 hexane–EtOAc).

Ketone **4c**: $[\alpha]_D$=−107 (*c* 0.3, MeOH). mp 93–95°C. IR (film) 1742, 1531, 1358 cm^{-1}. ^1H NMR (500 MHz)[16] δ 1.34 (d, J=7 Hz, 3H, CH_3), 1.98 (m, 1H, H-8α), 2.12 (m, 1H, H-8β), 2.19 (ddd, J=15, 9.5, and 8 Hz, 1H, H-4), 2.42 (ddd, J=15, 8, and 4.5 Hz, 1H, H-4), 2.53 (ddd, J=19, 10.5, and 7 Hz, 1H, H-7), 2.71 (ddd, J=19, 10.5, and 5.5 Hz, 1H, H-7), 2.79 (td, J=9.5 and 4.5 Hz, 1H, H-3α), 2.96 (dt, J=9.5 and 8 Hz, 1H, H-3β), 3.70 (q, J=7 Hz, 1H, NCHAr), 4.17 (dd, J=7.5 and 5.5 Hz, 1H, H-1), 7.21–7.33 (m, 5H, ArH), 7.44 (td, J=8 and 1 Hz, 1H, H-4′), 7.50 (dd, J=8 and 1 Hz, 1H, H-6′), 7.63 (td, J=8 and 1 Hz, 1H, H-5′), 7.87 (dd, J=8 and 1 Hz, 1H, H-3′). Anal. calcd for $C_{21}H_{22}N_2O_3$ (350.04): C, 71.98; H, 6.33; N, 7.99. Found: C, 71.74; H, 6.36; N, 7.96.

Ketone **4d**: ^1H NMR (300 MHz)[16] δ 1.39 (d, J=6.6 Hz, 3H, CH_3), 2.02–2.16 (m, 2H), 2.23 (dt, J=14.1 and 8.5 Hz, 1 H, H-4), 2.36–2.52 (m, 2H), 2.76 (ddd, J=19, 10, and 6.6 Hz, 1H, H-7), 2.99 (td, J=9.3 and 3.3 Hz, 1H, H-3α), 3.16 (dt, J=9.3 and 7.8 Hz, 1H, H-3β), 3.68 (q, J=6.6 Hz, 1H, NCHAr), 3.74 (dd, J=7.5 and 6 Hz, 1H, H-1), 7.18–7.65 (m, 8H), 7.83 (dd, J=8 and 1.5 Hz, 1H, H-3′).

3.1.7. *cis*-2-[(1-Chloroethoxy)carbonyl]-5-(2-nitrophenyl)-2-azabicyclo[3.3.0]octan-6-one (6). A mixture of amine **4a** (0.96 g, 3.71 mmol) and α-chloroethyl chloroformate (5 ml) was heated at reflux for 6 h. The mixture was diluted with Et_2O and washed with 10% hydrochloric acid. The organic layer was dried and concentrated to give carbamate **6** (1.3 g, quantitative). ^1H NMR (200 MHz) δ 1.80 (m, 3H, CH_3), 1.86–2.98 (m, 5H), 3.15–4.98 (m, 4H), 6.53 (m, 1H, CHCl), 7.40–7.78 (m, 3H), 8.09 (d, J=7.5 Hz, 1H).

3.1.8. *cis*-5-(2-Nitrophenyl)-2-azabicyclo[3.3.0]octan-6-one (7). A solution of carbamate **6** (1.3 g, 3.71 mmol) in MeOH (15 ml) was heated at reflux for 3 h. The solvent was evaporated, and the residue partitioned between dichloromethane and saturated aqueous K_2CO_3. The organic layer was dried and concentrated, and the residue was chromatographed (CH_2Cl_2-2% MeOH) to give amine **7** (826 mg, 91%). ^1H NMR (500 MHz)[16] δ 1.78 (dddd, J=13.5, 10.5, 7.5, and 6.5 Hz, 1H, H-8α), 2.18 (ddd, J=15, 9.5, and 7.5 Hz, 1H, H-4), 2.40–2.48 (m, 2H, H-4 and H-8β), 2.54 (ddd, J=19, 10.5, and 7.5 Hz, 1H, H-7), 2.69 (ddd, J=19, 10.5, and 4.5 Hz, 1H, H-7), 3.36 (m, 2H, H-3), 4.19 (dd, J=8 and 6.5 Hz, 1H, H-1), 7.34 (dd, J=8 and 1 Hz, 1H, H-6′), 7.41 (td, J=8 and 1 Hz, 1H, H-4′), 7.58 (td, J=8 and 1 Hz, 1H, H-5′), 7.87 (dd, J=8 and 1 Hz, 1H, H-3′). Anal. calcd for $C_{13}H_{14}N_2O_3$ (246.27). 1/2H_2O: C, 61.17; H, 5.92; N, 10.97. Found: C, 61.01; H, 5.71; N, 10.84.

3.1.9. (1*S*,5*R*)-5-(2-Nitrophenyl)-2-azabicyclo[3.3.0]octan-6-one [(−)7]. Using a procedure similar to that described for the preparation of (±)-**7** from **6**, compound **4c** (100 mg, 0.28 mmol) was heated with α-chloroethyl chloroformate (5 ml) and then with MeOH (3 ml) to give (−)-7 (30 mg, 45%) as an oil. $[\alpha]_D$=−203 (*c* 0.4, MeOH).

3.1.10. *cis*-5-(2-Nitrophenyl)-2-propargyl-2-azabicyclo-[3.3.0]octan-6-one (4e). To a solution of **7** (150 mg, 0.6 mmol) in CH_3CN (10 ml) were added propargyl bromide (0.14 ml, 1.2 mmol) and K_2CO_3 (168 mg, 1.2 mmol). After stirring at 50°C for 3 h, the solvent was evaporated, and the residue was partitioned between water and CH_2Cl_2.

The organic extract was concentrated and chromatographed (0.5% MeOH in CH_2Cl_2) to give **4e** (134 mg, 77%) as an oil. ^{1}H NMR (200 MHz) 1.85–2.05 (m, 1H), 2.05–2.20 (m, 2H), 2.20–2.50 (m, 3H), 2.70 (dt, J=19 and 9.5 Hz, 1H, H-7), 3.02–3.20 (m, 2H), 3.52 (d, J=2.6 Hz, NCH_2), 3.75 (d, J=5 Hz, 1H, H-1), 7.35–7.45 (m, 2H), 7.55 (t, J=8 Hz, 1H), 7.75 (d, J=8 Hz, 1H). Anal. calcd for $C_{16}H_{16}N_2O_3$ (284.29): C, 67.59; H, 5.67; N, 9.85. Found: C, 67.25; H, 5.73: N, 9.76.

3.1.11. *cis*-2-[(*Z*)-2-iodo-2-butenyl]-5-(2-nitrophenyl)-2-azabicyclo[3.3.0]octan-6-one (4f). To a solution of **7** (740 mg, 3 mmol) in CH_3CN (10 ml) were added (*Z*)-1-bromo-2-iodo-2-butene (1.5 g, 6 mmol) and K_2CO_3 (829 mg, 6 mmol). After stirring at room temperature for 3 h, the solvent was evaporated, and the residue was partitioned between water and CH_2Cl_2. The dried organic extract was concentrated and chromatographed (1:1, hexane–CH_2Cl_2) to give 769 mg (60%) of **4f** as an oil. IR (film) 1745, 1534, 1363 cm^{-1}; ^{1}H NMR δ 1.77 (d, J=6.4 Hz, 3H, CH_3), 1.94–2.10 (m, 2H), 2.30–2.50 (m, 2H), 2.65–2.90 (m, 2H), 3.03 (m, 1H), 3.26 and 3.56 (2d, J=14 Hz, 1H each, NCH_2), 3.66 (t, J=3.6 Hz, 1H, H-1), 5.83 (q, J=6.4 Hz, 1H, =CH), 7.24–7.60 (m, 3H), 7.71 (d, J=8 Hz, 1H). Anal. calcd for $C_{17}H_{19}IN_2O_3$ (426.25): C, 47.90; H, 4.49, N, 6.57. Found: C, 47.80; H, 4.41; N, 6.59.

Acknowledgements

Financial support for this research was provided by DGES (Spain) through Grants PB94-0214 and PB97-0877. Support for DURSI, Catalonia (1999SGR-00078 and 1999SGR-00079) is also acknowledged. R. C. was on leave from the University of Zacatecas (México) with a fellowship.

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