Tetrahedron Vol. 48, No. 15, pp. 3131-3138, 1992
Printed in Great Britain

0040-4020/92 $5.00+.00

Studies on the Synthesis of 8-Alkyl-8-aryl-2-azabicyclo[3.3.1]nonan-7-ones. A Short Synthetic Route to Functionalized 8-Alkyl Derivatives[1]

Josep Bonjoch*, Núria Casamitjana, Josefina Quirante, Carme Garriga, and Joan Bosch

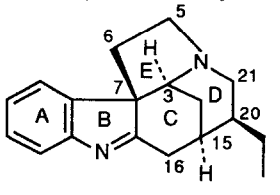
Laboratory of Organic Chemistry, Faculty of Pharmacy, University of Barcelona,08028-Barcelona, Spain

(Received in UK 23 December 1991)

Key Words: 2-Cyanopiperidine; modified Polonovski reaction; 2-azabicyclo[3.3.1]nonan-7-ones; Wadsworth-Emmons condensation; 5-functionalized 2-oxopentyl synthon

Abstract: Two approaches to 8-alkyl-8-aryl-2-azabicyclo[3.3.1]nonan-7-ones are explored. They are based on the cyclization of an α-alkyl α-aryl ketone upon an iminium salt generated from 2-cyanopiperidine **13** and on the arylation of 8-alkyl-2-azabicyclo[3.3.1]nonan-7-one **20**. An efficient, short synthetic route to 8-alkyl-2-azabicyclo[3.3.1]nonan-7-ones, using phosphonate **16** as a 5-functionalized 2-oxopentyl synthon, is reported.

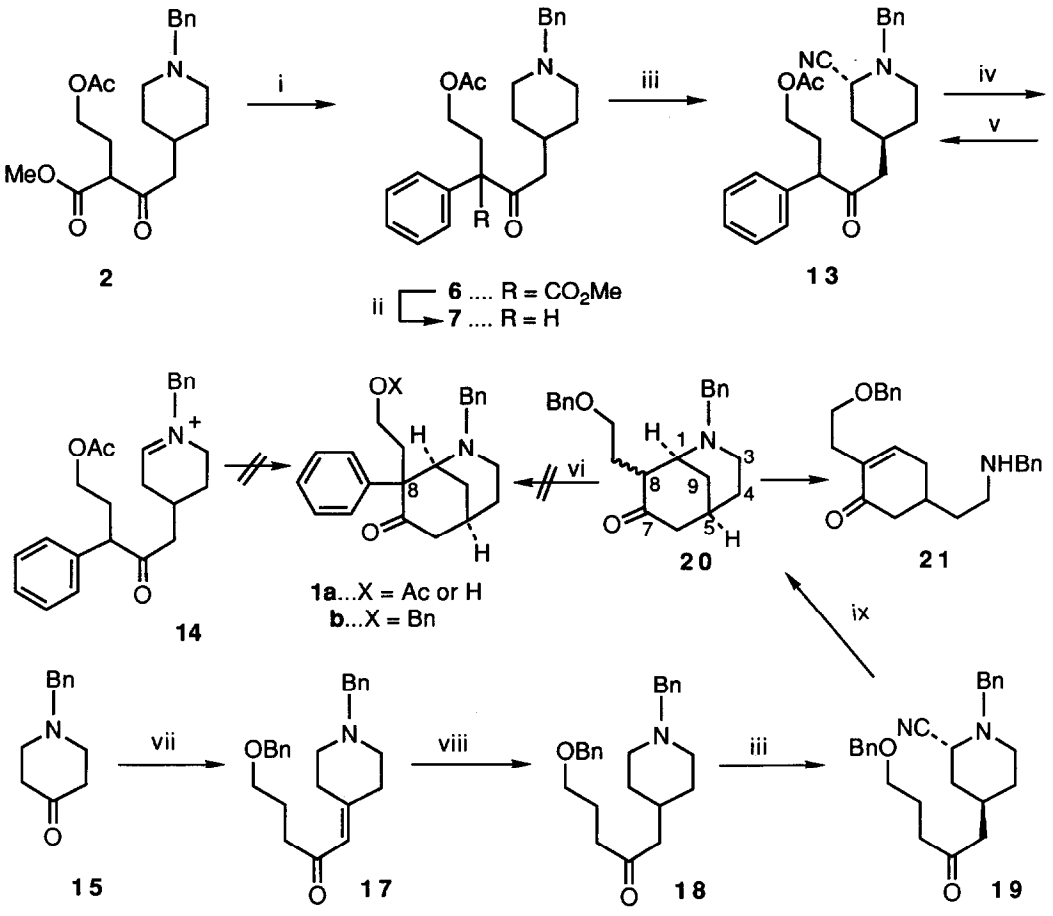
The formation of the quaternary C-7 center of pentacyclic *Strychnos* indole alkaloids has proved to be the crucial step in most total synthesis of these alkaloids.[2] This center corresponds to C-8 of the 2-azabicyclo[3.3.1]nonane (morphan) moiety (the CD ring substructure of *Strychnos* alkaloids). With the final aim of the synthesis of *Strychnos* alkaloids from tricyclic CDE ring precursors by elaboration of the indole ring in the last synthetic steps,[2c] in previous papers we have reported synthetic routes to both 8-alkyl-[1,3] and 8-aryl-2-azabicyclo[3.3.1]nonan-7-ones.[4,5] They are based on the closure of the carbocyclic ring (bond formed C_1-C_8) by a Mannich-type cyclization between an iminium salt (usually generated from a 2-cyanopiperidine) and the α-position of a ketone.



Tubifoline

We report now the results of applying the same methodology to the synthesis of 8-alkyl-8-aryl derivatives **1**, *i.e.* having the quaternary C-8 center, either by cyclization of an appropriate α-alkyl α-aryl ketone **13** or by arylation at the ketone α-position of a previously cyclized 8-alkylmorphan derivative **20** (Scheme 1).

The required keto nitrile **13** was prepared by a modified Polonovski reaction[6] from piperidine **7**, which, in turn, was obtained by arylation of the α-alkylated β-keto ester **2** followed by



Scheme 1. Reagents and Conditions: (i) $C_6H_5Pb(OAc)_3$, pyridine, $CHCl_3$, 40%; (ii) DMSO, LiCl, 36%; (iii) a. *m*-CPBA, CH_2Cl_2, 0° C, 1 h; b. TFAA, -15° C, 1 h; c. aq. KCN, NaOAc, pH 4-5, 30 min, 68% for **13**; 72% for **19**; (iv) TsOH, benzene, reflux, overnight; (v) KCN, pH 4-5; (vi) $(C_6H_5)_2ICl$, K^tBuO, 32%; (vii) $(EtO)_2POCH_2CO(CH_2)_3OBn$ (**16**), KOH, EtOH-H_2O, room temperature, 4 h, 88%; (viii) H_2, PtO_2, 81%; (ix) 12 N aq. HCl-MeOH (1:9), 40 h, reflux, 66%.

decarbalkoxylation of the resulting product **6**.[7] However, in contrast with similar cyclizations to 8-alkyl- or 8-arylmorphan derivatives, attempts to cyclize **13** to the target morphan **1a** were unsuccessful. This failure cannot be attributed to an inefficient procedure in generating the intermediate iminium cation **14**, but probably to steric factors,[10] since formation of **14** was confirmed by trapping it from the crude reaction mixture with potassium cyanide.

The second alternative we have explored for the synthesis of C-8 disubstituted systems **1** was the direct arylation at the ketone α-position of morphan **20**, which was prepared in good overall yield in four steps from 1-benzyl-4-piperidone (**15**). Wadsworth-Emmons condensation of **15** with the novel phosphonate reagent **16**, followed by catalytic hydrogenation, gave 4-

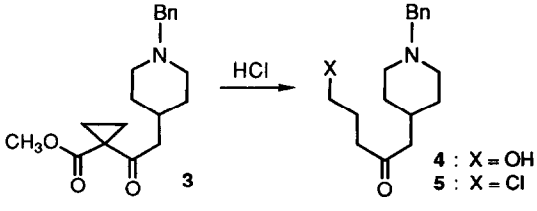
(oxopentyl)piperidine **18** in 71% overall yield. This straightforward introduction of a suitably functionalized C_5 chain at the piperidine 4-position represents a significant improvement of previous synthesis of 8-alkyl-2-azabicyclo[3.3.1]nonan-7-ones.[1,3] α-Cyanation of piperidine **18** by the modified Polonovski reaction[6] and further acid-promoted cyclization of the resulting 2-cyanopiperidine **19** were also accomplished in good yields to give an *exo-endo* mixture (approximately 1:2 ratio) of morphans **20**. However, treatment of **20** with diphenyliodonium chloride[11] did not lead to the expected 8-arylmorphan **1b**, cyclohexenone **21** being obtained as the only identifiable product instead. Formation of **21** evidences that β-amino ketone **20** has undergone a retro-Michael reaction, a process that had already been observed from some 8-substituted 2-azabicyclo[3.3.1]nonan-7-ones.[4b]

Although the above approaches have proved to be useless for the construction of the quaternary C-8 center in morphan derivatives, the use for the first time of phosphonate **16** as a 5-functionalized 2-oxopentyl synthon and the efficient short synthesis of 8-alkyl-2-azabicyclo[3.3.1]nonan-7-ones deserve interest.

EXPERIMENTAL

The NMR spectra were recorded in $CDCl_3$ on a Varian Gemini-200 spectrometer with TMS as internal standard. Chemical shifts are reported in ppm (δ) downfield from TMS and coupling constants (*J*) in Hz. IR spectra were taken with a Perkin-Elmer 1600 FT spectrometer and only noteworthy absorptions (reciprocal centimeters) are listed. TLC was carried out on SiO_2 and the spots were located with UV light or iodoplatinate reagent. Flash chromatography was carried out on SiO_2 (230-400 mesh, SDS). Microanalyses were performed by Centro de Investigación y Desarrollo (C.S.I.C.), Barcelona.

Methyl α-(2-Acetoxyethyl)-1-benzyl-4-piperidineacetoacetate (2) was prepared by alkylation of methyl 1-benzyl-4-piperidineacetoacetate with 2-bromoethyl acetate in the presence of sodium hydride (1.05 equiv) by the previously reported procedure.[3] Flash chromatography (99.5:0.5 methylene chloride-methanol) of the crude product afforded **2**[3] (60%) and the cyclopropyl derivative **3** (16%). Compound **3**: IR ($CHCl_3$) 1735, 1710; ^{1}H-NMR 1.27 (qd, *J* = 12, 3, H-3ax and H-5ax), 1.42 (s, cyclopropyl), 1.62 (dm, *J* = 12, H-3eq and H-5eq), 1.85 (m, H-4), 1.97 (td, *J* = 12, 2.5, H-2ax and H-6ax), 2.75 (d, *J* = 6.5, 4-CH_2), 2.83 (dm, *J* = 12, H-2eq and H-6eq), 3.47 (s, CH_2Ar), 3.71 (s, OCH_3), 7.29 (s, ArH); ^{13}C-NMR 18.1(cyclopropyl), 31.5 (C-4), 31.8 (C-3, C-5), 34.3 (*ipso* -cyclopropyl), 48.2 (4-CH_2), 52.0 (OCH_3), 53.3 (C-2, C-6), 63.2 (NCH_2Ar), 126.8(*p*-Ar), 128.1 (*m*-Ar), 129.1 (*o*-Ar), 138.4 (*ipso*-Ar), 171.5 (COO), 204.3 (CO). Anal. Calcd for $C_{19}H_{25}NO_3$: C, 72.39; H, 8.00; N, 4.44. Found: C, 72.34; H, 8.04; N, 4.40.



Treatment of **3** with refluxing aqueous 4 N HCl for 3 h followed by a conventional work-up and flash chromatography (98:2 methylene chloride-methanol) gave **1-benzyl-4-(5-hydroxy-2-oxopentyl)piperidine** (**4**; 34%) and (95:5 methylene chloride-methanol) **1-benzyl-4-(5-chloro-2-oxopentyl)piperidine** (**5**; 29%).

Compound **4**: IR ($CHCl_3$) 1710; ^{1}H-NMR 1.25 (qd, J = 12, 3, H-3ax and H-5ax), 1.63 (dm, J = 13, H-3eq and H-5eq), 1.72-1.90 (m, CH_2 and H-4), 1.98 (td, J = 12, 2.5, H-2ax and H-6ax), 2.36 (d, J =7, 4-CH_2), 2.54 (t, J = 7, $COCH_2$), 2.85 (dm, J = 12, H-2eq and H-6eq), 3.48 (s, CH_2Ar), 3.64 (t, J = 7 , CH_2O), 7.31 (s, ArH); ^{13}C-NMR 26.1 (CH_2), 31.4 (C-4), 31.8 (C-3, C-5), 39.9 ($COCH_2$), 49.1 (4-CH_2), 53.2 (C-2, C-6), 61.5 (CH_2O), 63.2 (CH_2Ar), 127.0, 128.1, 129.3, 137.9 (Ar), 211.3 (CO). Anal. Calcd for $C_{16}H_{23}NO_2.1/2H_2O$: C, 71.07; H, 8.90; N, 5.10. Found: C, 71.10; H, 8.46; N, 4.49. Compound **5**: ^{1}H-NMR 1.27 (qd, J = 12, 3, H-3ax and H-5ax), 1.63 (dm, J =12, H-3eq and H-5eq), 1.8-2.1 (m, H-2ax, H-6ax, H-4, CH_2), 2.35 (d, J = 6.5, 4-CH_2), 2.58 (t, J = 4, $COCH_2$), 2.85 (dm, J = 12, H-2eq and H-6eq), 3.48 (s, CH_2Ar), 3.57 (t, J = 7, CH_2Cl), 7.30 (s, ArH); ^{13}C-NMR 25.9 (CH_2), 31.6 (C-4), 31.8 (C-3, C-5), 39.7 (CH_2CO), 44.3 (CH_2Cl), 49.4 (4-CH_2), 53.3 (C-2, C-6), 63.2 (CH_2Ar), 127.0, 128.3, 129.3, 138.3 (Ar), 209.5 (CO).

Methyl α-(2-Acetoxyethyl)-1-benzyl-α-phenyl-4-piperidineacetoacetate (6). β-Keto ester **2** (857 mg, 2.28 mmol), phenyllead triacetate[12] (1.58 g, 2.51 mmol), and pyridine (0.55 ml, 6.84 mmol) were stirred in anhydrous chloroform (94 ml) at 55-60° C for 24 h. The reaction mixture was diluted with chloroform and washed with 3N hydrochloric acid. The aqueous phase was washed with chloroform, and the combined organic extracts were extracted with 10% aqueous sodium carbonate, dried, and evaporated. Flash chromatography (99.5:0.5 chloroform-diethylamine) gave pure arylated β-keto ester **6** (412 mg, 40%) as an oil and the starting β-keto ester **2** (126 mg); IR ($CHCl_3$) 1735-1710; ^{1}H-NMR 1.30 (m, H-3ax and H-5ax), 1.60 (dm, J =13, H-3eq and H-5eq), 1.70-2.04 (m, H-4, H-2ax, and H-6ax), 1.96 (s, CH_3), 2.15 (dd, J = 17, 5.5, 1H, $COCH_2$), 2.33 (dd, J = 17, 7 Hz, 1H, $COCH_2$), 2.47 and 2.67 (2m, CH_2), 2.82 (dm, J = 13, H-2eq and H-6eq), 3.46 (s, CH_2Ar), 3.81 (s, OCH_3), 3.71 and 3.98 (2m, OCH_2), 7.25-7.37 (m, ArH); ^{13}C-NMR 20.8 (CH_3), 31.4 and 31.6 (C-3, C-5), 31.5 (C-4), 34.0 (CH_2), 45.8 (CH_2CO), 52.5 (OCH_3), 53.5 and 53.5 (C-2, C-6), 61.1 (CH_2O), 63.3 (CH_2Ar), 66.7 (C), 127.0, 127.9, 128.0, 128.2, 128.8, 129.3, 135.8 (Ar), 170.6 ($COOCH_3$), 171.1 ($COCH_3$), 203.5 (CO). Anal. cald for $C_{27}H_{33}NO_5$: C, 71.80; H, 7.37; N, 3.10. Found: C, 71.53; H, 7.74; N, 2.99.

1-Benzyl-4-(3-phenyl-5-acetoxy-2-oxopentyl)piperidine (7). A solution of β-keto ester **6** (800 mg, 1.8 mmol) in DMSO (3.6 ml) containing lithium chloride (112 mg, 2.7 mmol) and water (0.1 ml, 5.4 mmol) was stirred at 160° C for 3h. The reaction mixture was extracted with ether, and the combined organic extracts were washed with brine, dried, and evaporated. Flash chromatography (chloroform) of the residue gave ketone **7** (250 mg, 36%); IR ($CHCl_3$) 1735-1715; ^{1}H-NMR 1.37 (ddd, J = 13, H-3ax and H-5ax), 1.62 (dm, J = 13, H-3eq and H-5eq), 1.72-2.14 (m, H-4, H-2ax, and H-6ax), 2.01 (s, CH_3), 2.29 (d, J = 7, CH_2CO), 2.35 (m, CH_2), 2.90 (dm, J = 12, H-2eq and H-6eq), 3.54 (s, CH_2Ar), 3.71 (t, J = 7, CHCO), 4.0 (m, CH_2O), 7.27-7.35 (m, ArH); ^{13}C-NMR 20.9 (CH_3), 30.7 and 31.1 (C-3, C-5), 31.3 (C-4), 31.5 (CH_2), 48.0 (CH_2CO), 53.2 and 53.3 (C-2, C-6), 59.9 (CHCO), 62.4 (CH_2O), 62.9 (CH_2Ar), 127.4, 127.6, 128.3, 129.1, 129.5, 137.0 (Ar), 170.3 (COO), 208.1 (CO). Anal. Calcd. for $C_{25}H_{31}NO_3.1/2\ H_2O$: C, 74.59; H, 8.01; N, 3.48. Found: C, 74.60; H, 7.56; N, 3.65.

1-Benzyl-4-(3-phenyl-2-oxopropyl)piperidine (8). Method A. To a cooled (-78° C) solution of *N*-isopropylcyclohexylamine (5.2 ml, 31 mmol) in anhydrous THF (70 ml) was added under nitrogen 1.6 M *n*-butyllithium in hexane (19.3 ml, 31 mmol). After 1 h at -78° C, a solution of ethyl 1-benzyl-4-piperidineacetate (4.04 g, 15.5 mmol) in THF was ad-ded, and the mixture was stirred at -78° C for 10 min. Then, phenylacetyl chloride (2.4 g, 15.5 mmol) was added. After 10 min at -78° C, the reaction mixture was quenched with 20% hydrochloric acid and allowed to warm up to room temperature. The two phases were separated, and the aqueous one was basified with saturated aqueous sodium carbonate and ex-tracted with methylene chloride. The combined organic extracts were dried and evaporated. *N*-

Isopropylcyclohexylamine was removed by distillation. Flash chromatography (99:1 methylene chloride-methanol) gave **ethyl 1-benzyl-α-(phenylacetyl)-4-piperidineacetate** (**9**, 1.23 g, 21%; 38% based on the recovered starting ester); IR ($CHCl_3$) 1713, 1737; ^{1}H-NMR 1.21 (t, J = 7, CH_3), 2.86 (dm, J = 12, H-2eq and H-6eq), 3.42 (d, J = 10, CH), 3.47 (s, CH_2Ar), 3.77 (s, CH_2CO), 4.11 (q, J = 7, OCH_2), 7.2-7.3 (m, ArH); ^{13}C-NMR 13.8 (CH_3), 29.5, 29.7 (C-3, C-5), 35.4 (C-4), 49.8 (CH_2CO), 53.1 (C-2, C-6), 61.2 (OCH_2), 63.1 (CH_2Ar), 63.8 (*C*HCO), 127.0, 127.1, 128.2, 128.7, 129.2, 129.7, 131.1, 138.3 (Ar), 168.5 (COO), 202.4 (CO). Anal. Calcd. for $C_{24}H_{29}NO_2$: C, 75.95; H, 7.70; N, 3.69. Found: C, 75.98; H, 7.66; N, 3.68.

A mixture of β-keto ester **9** and 3 N hydrochloric acid was refluxed for 4h. The mixture was cooled, basified with 2N aqueous sodium hydroxide, and extracted with methylene chloride. The extracts were dried and evaporated. Flash chromatography (99:1 methylene chloride-methanol) gave ketone **8** (1.98 g, 70%) as an oil. The spectroscopic data of **8** were identical to those previously reported.[4b]

Method B. A solution of diisopropylamine (1.95 ml, 14.0 mmol) in anhydrous THF (30 ml) was treated with *n*-BuLi (8.1 ml, 13.0 mmol, 1.6 M in hexanes) at 0° C. After stirring at 0° C for 30 min, the solution was cooled to -78° C, and a solution of *tert*-butyl phenylacetate (2.5 g, 13.0 mmol) in THF (30 ml) was added dropwise. After stirring at -78° C for 45 min, a solution of ethyl 1-benzyl-4-piperidineacetate (1.5 g, 5.7 mmol) in THF (30 ml) was added dropwise. The resulting solution was stirred at -78° C for 1.25 h, and then warmed to -40° C for 1.5 h. Finally, the reaction was stirred at 0° C for 1 h. The reaction mixture was then treated with 315 ml of pH 7 buffer (3 M KH_2PO_4) and extracted with methylene chloride. The organic extracts were washed with 1.2 N hydrochloric acid. The aqueous phase was basified with 10% aqueous sodium carbonate and extracted with methylene chloride. The organic extracts were dried and evaporated. Flash chromatography (99.5:0.5 methylene chloride-methanol) provided 443 mg (20%; 60% based on recovered starting material) of ***tert*-butyl 1-benzyl-α-phenyl-4-piperidineacetoacetate** (**10**) as an oil and 1 g of starting piperidineacetate; IR ($CHCl_3$) 1713, 1737; ^{1}H-NMR 1.16 (qd, J = 12, 3, H-3ax, H-5ax), 1.45 (s, 9H, CH_3), 1.53 (dm, J = 12, H-3eq, H-5eq), 1.8 (m, H-4), 1.93 (td, J =12, 2.5, H-2ax, H-6ax), 2.33 and 2.43 (2 dd, J =16, 2.5, CH_2CO), 2.79 (dm, J = 12, H-2eq, H-6eq), 3.44 (s, CH_2Ar), 4.60 (s, CHAr), 7.26-7.32 (m, Ar); ^{13}C-NMR 27.6 (CH_3), 31.2 (C-4), 31.4, 31.7 (C-3, C-5), 48.0 (CH_2CO), 53.3 (C-2, C-6), 63.2 (CH_2Ar), 65.9 (CHAr), 81.9 (C), 126.9, 128.0, 128.1, 128.7, 129.5, 132.7, 138.4 (Ar), 167.6 (COO), 203.4 (CO).

To a solution of anhydrous *p*-toluenesulfonic acid (430 mg, 2.5 mmol) in anhydrous toluene (20 ml) was added a solution of **10** (704 mg, 1.85 mmol) in toluene. The resulting mixture was refluxed for 2h. The solvent was evaporated, and the residue was partitioned between 10% aqueous sodium carbonate and methylene chloride. The aqueous phase was extracted with methylene chloride, and the combined organic extracts were dried and evaporated. Flash chromatography (98:2 methylene chloride- methanol) gave ketone **8** (438 mg, 77%) as an oil.

***trans*-1-Benzyl-4-(3-phenyl-5-acetoxy-2-oxopentyl)-2-piperidinecarbonitrile (13)**. A solution of *m*-chloroperbenzoic acid (95 %, 166 mg, 0.89 mmol) in anhydrous methylene chloride (6 ml) was added over 15 min to a stirred solution of ketone **7** (320 mg, 0.81 mmol) in anhydrous methylene chloride (6 ml) maintained at 0° C under argon atmosphere. Stirring was continued at 0°C for 1 h. After the resulting solution had been cooled at -15° C, trifluoroacetic anhydride (0.46 ml, 3.26 mmol) was added dropwise, and the mixture was stirred at -15° C for 1 h and at room temperature for 15 min. Potassium cyanide (159 mg, 2.44 mmol) in water (10 ml) was then added and the pH adjusted to 5 by the addition of solid sodium acetate. The two phase mixture was vigorously stirred for 30 min, basified with 10 % aqueous sodium carbonate, and extracted with methylene chloride. The organic extracts were washed with water, dried, and evaporated. Flash chromatography (methylene chloride) gave nitrile **13** (230 mg, 68%); IR ($CHCl_3$) 1730, 1710;

^{1}H-NMR 1.38 (td, J = 12.5, 4, H-3ax), 1.80 (dq, J = 12.5, 3, H-3eq), 2.01 (s, CH_3), 2.30 (d, J = 7, 4-CH_2), 2.75 (m, H-6eq), 3.4-4.1 (m, OCH_2, ArCH, CH_2Ar, H-2eq), 7.30 (m, ArH); ^{13}C-NMR 20.5 (CH_3), 27.6 (C-4), 30.3 (CH_2), 30.8 (C-3), 33.7 (C-5), 47.0 (CH_2CO), 48.7 (C-6), 51.3 (C-2), 52.2 (CHAr), 59.9 (OCH_2), 62.0 (CH_2Ar), 116.1 (CN), 127.2, 127.5, 128.2, 128.4, 128.8, 129.0, 137.5 (Ar), 170.9 (COO), 207.5 (CO). Anal. Calcd. for $C_{26}H_{30}N_2O_3.H_2O$: C, 71.53; H, 7.39; N, 6.41. Found: C, 71.57; H, 7.23; N, 6.08.

Diethyl 5-Benzyloxy-2-oxopentylphosphonate (16). To a suspension of sodium hydride (3.06 g, 0.133 mol, 55-60 % in oil, washed with hexane) in 150 ml of anhydrous THF was added dropwise under argon a solution of freshly distilled diethyl 2-oxopropylphosphonate[13] (10 g, 62 mmol) in THF (25 ml). The resulting mixture was stirred at room temperature for 2 h and cooled to 0 °C. Then, *n* -butyllithium (40 ml, 64 mmol, 1.6 M in hexane) was added dropwise. After stirring for 30 min, a solution of benzyl 2-iodoethyl ether[14] (14.8 g, 56 mmol) in THF (25 ml) was added. The mixture was warmed to room temperature and stirred for 1 h. The reaction mixture was quenched at 0 °C by the addition of 5 % hydrochloric acid (60 ml) and the product was extracted with methylene chloride. The extracts were washed with brine, dried, and evaporated. Flash chromatography (98:2 methylene chloride-methanol) afforded phosphonate **16** (12.2 g, 60%): IR (NaCl) 1710; ^{1}H-NMR 1.62 (t, J = 7, CH_3), 1.91 (quint, J = 6.5, CH_2), 2.74 (t, J = 6.5, CH_2CO), 3.08 (d, J = 22.5, PCH_2), 3.48 (t, J = 6.5, OCH_2), 4.11 (q, J = 7, OCH_2), 4.47 (s, CH_2Ar), 7.15-7.35 (m, ArH); ^{13}C-NMR 15.6 and 15.7 (CH_3), 23.1 (CH_2), 40.2 (CH_2CO), 40.5 and 43.1 (PCH_2), 61.9 (CH_2CH_3), 68.6 (OCH_2), 72.4 (CH_2Ar), 127.3, 128.1, 138.1 (Ar), 201.6 (CO). Anal. Calcd for $C_{16}H_{25}O_5P$: C, 58.54; H, 7.62. Found: C, 58.59; H, 7.64.

1-Benzyl-4-(5-benzyloxy-2-oxopentylidene)piperidine (17). To a solution of phosphonate **16** (1.34 g, 4.08 mmol) and potassium hydroxide (230 mg, 4.10 mmol) in 5 ml of ethanol-water (30:7) at 5 °C were slowly added 0.66 ml (22.2 mmol) of 1-benzyl-4-piperidone (**15**). The mixture was stirred at room temperature for 4 h. Ethanol was evaporated, and the residue was extracted with ether. The extracts were dried and evaporated to give, after flash chromatography (6:4 hexane-AcOEt), 1.34 g (88%) of piperidine **17**: IR ($CHCl_3$) 1683, 1623; ^{1}H-NMR 1.90 (quint, J = 6, CH_2), 2.29 (t, J = 5.5, 2H, 3-H), 2.35-2.75 (m, 6 H, 2-H, 6-H, CH_2), 2.96 (t, J = 5.5, 2H, 5-H), 3.49 (t, J = 6, OCH_2), 3.52 (s, NCH_2Ar), 4.48 (s, OCH_2Ar), 6.00 (s, 1 H, =CH), 7.28-7.34 (m, ArH); ^{13}C-NMR 23.9 (CH_2), 29.2 (C-3), 36.6 (C-5), 40.8 (CH_2CO), 54.0 and 54.4 (C-2, C-6), 62.5 (NCH_2Ar), 69.4 (OCH_2), 72.7 (OCH_2Ar), 121.8 (=CH), 127.2, 127.7, 128.3, 128.4, 129.0,129.2, 138.2, 138.6 (Ar), 157.8 (C-4), 201.4 (CO). Anal. Calcd for $C_{24}H_{29}NO_2$: C, 79.33; H, 7.98; N, 3.85. Found: C, 79.20; H, 8.09; N, 3.88.

1-Benzyl-4-(5-benzyloxy-2-oxopentyl)piperidine (18). A solution of piperidine **17** (1.12 g, 3.1 mmol) in ethanol (60 ml) was hydrogenated at room temperature and atmospheric pressure over platinum oxide (34 mg). When the absorption ceased, the catalyst was filtered off and the filtrate was evaporated. Flash chromatography (ethyl acetate) afforded 890 mg (81 %) of piperidine **18**: IR ($CHCl_3$) 1709; ^{1}H-NMR 1.23 (qd, J = 12.5, 3.5, H-3ax and H-5ax), 1.60 (dm, J = 12.5, H-3eq and H-5eq), 1.86 (quint, J = 7, CH_2), 1.7-1.9 (m, 4-H), 1.95 (td, J = 11.7, 2.4, H-2ax and H-6ax), 2.30 (d, J = 6.7, 4-CH_2), 2.48 (t, J = 7, CH_2CO), 2.82 (dm, J = 11.7, H-2eq, H-6eq), 3.45 (t, J = 7, OCH_2), 3.46 (s, NCH_2Ar), 4.46 (s, OCH_2Ar), 7.29-7.31 (m, ArH); ^{13}C-NMR 23.4 (CH_2), 31.4 (C-4), 31.9 (C-3, C-5), 39.8 (CH_2CO), 49.3 (4-CH_2), 53.3 (C-2, C-6), 63.2 (NCH_2Ar), 69.1 (OCH_2), 72.7 (OCH_2Ar), 126.9, 127.6, 128.1, 128.4, 129.2, 138.4 (Ar), 210.3 (CO). Anal. Calcd for $C_{24}H_{31}NO_2.1/2H_2O$: C, 76.97; H, 8.61; N, 3.74. Found: C, 77.07; H, 8.57; N, 3.51.

***trans*-1-Benzyl-4-(5-benzyloxy-2-oxopentyl)-2-piperidinecarbonitrile (19)** was prepared as reported above for **13**. Piperidine **18** (540 mg, 1.5 mmol) was treated sequentially with *m*-chloroperbenzoic acid (70%, 395 mg, 18.9 mmol), trifluoroacetic anhydride (0.45 ml, 3.25 mmol), and potassium cyanide (190 mg, 3.0 mmol). After work-up and flash chromatography (1:1 hexane-ethyl acetate), cyanopiperidine **19** was obtained (421 mg, 72%): IR ($CHCl_3$) 2223, 1712; ^{1}H-NMR 1.22 (qd, J = 13.5, 4.5, H-5ax), 1.42 (td, J = 13.5, 4.5, H-3ax), 1.70 (dm, J = 13.5, H-5eq), 1.88 (quint, J = 6.5, CH_2), 1.7-2.0 (m, H-3eq), 2.0-2.3 (m, H-4ax), 2.33 (d, J = 7, 4-CH_2), 2.50 (t, J = 6.5, CH_2CO), 2.3-2.6 (m, H-6ax), 2.79 (dm, J = 13.5, H-6eq), 3.47 (t, J = 6.5, OCH_2), 3.53 and 3.69 (2d, J = 13, NCH_2Ar), 3.72 (deformed t, J = 3.3, H-2eq), 4.47 (s, OCH_2Ar), 7.29-7.35 (m, ArH); ^{13}C-NMR 23.5 (CH_2), 27.9 (C-4), 31.0 (C-5), 34.0 (C-3), 39.6 (CH_2CO), 48.4 and 48.9 (4-CH_2, C-6), 51.4 (C-2), 60.0 (NCH_2Ar), 69.0 (OCH_2), 72.7 (OCH_2Ar), 116.3 (CN), 127.6, 128.4, 128.5, 128.8, 129.0, 136.9, 138.3 (Ar), 209.1 (CO). Anal. Calcd for $C_{25}H_{30}N_2O_2$. 1/2 H_2O: C, 75.16; H, 7.82; N, 7.01. Found: C, 75.20; H, 7.42; N, 6.66.

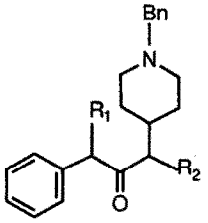
2-Benzyl-8-(2-benzyloxyethyl)-2-azabicyclo[3.3.1]nonan-7-one (20). A solution of 2-cyanopiperidine **19** (268 mg, 0.69 mmol) in methanol (10 ml) containing 12 N hydrochloric acid (1 ml) was refluxed for 40h under argon. Methanol was evaporated and the residue was basified with 10 % aqueous sodium carbonate and extracted with methylene chloride. The extracts were dried and evaporated. Flash chromatography (1:1 hexane-ethyl acetate) gave *exo* -**20** (46 mg, 18 %) and *endo* -**20** (119 mg, 48 %). *exo*-**20**: IR (NaCl) 1700; ^{1}H-NMR 1.53 (dm, J = 12, H-4eq), 1.65-2.00 (m, 5H), 2.3-2.5 (m, H-3ax, H-6eq, and H-5), 2.63 (dd, J = 16.5, 5.5, H-6ax), 2.65 (masked, H-3eq), 2.90 (br. t, J = 7, H-8eq), 3.04 (br. s, H-1eq), 3.45 (t, J = 6.5, OCH_2), 3.62 (s, NCH_2Ar), 4.44 (s, OCH_2Ar), 7.22-7.32 (m, ArH); ^{13}C-NMR 28.9 (C-5), 28.9 (C-9), 30.8 (C-4), 32.1 (8-CH_2), 44.5 (C-6), 44.8 (C-3), 58.5 (C-1), 59.1 (NCH_2), 67.8 (OCH_2), 73.0 (OCH_2Ar), 127.1, 127.7, 127.9, 128.4, 128.5, 128.8, 138.4, 138.9 (Ar), 215.2 (C-7). Anal. Calcd for $C_{24}H_{29}NO_2$: C, 79.30; H, 8.04; N, 3.85. Found: C, 79.35; H, 8.01; N, 3.72. *endo*-**20**: IR (NaCl): 1700; ^{1}H-NMR 1.21 (dm, J = 12, H-4eq), 1.60 (dq, J = 12, 2, H-9 *anti*), 1.70 - 2.10 (m, 4-Hax and 8-Hax), 2.2-2.7 (m, 8 H), 3.18 (br. s, H-1eq), 3.46 (m, OCH_2), 3.73 and 3.89 (2d, J = 13.5, NCH_2Ar), 4.34 and 4.42 (2d, J = 11.5, OCH_2Ar), 7.26-7.32 (m, ArH); ^{13}C-NMR 26.0 (8-CH_2), 26.4 (C-4), 28.2 (C-9), 29.9 (C-5), 41.7 (C-3), 47.1 (C-6), 51.2 (C-8), 57.6 (C-1), 58.1 (NCH_2), 67.8 (OCH_2), 72.6 (OCH_2Ar), 127.0, 127.6, 127.8, 128.3, 128.4, 128.6, 138.7, 140.2 (Ar), 213.4 (C-7). Anal Calcd for $C_{24}H_{29}NO_2$: C, 79.30; H, 8.04; N, 3.85. Found: C, 79.55; H, 7.91; N, 3.61.

Attempted Arylation of 20. To a solution of potassium *tert*-butoxide (70.5 mg, 0.63 mmol) in freshly distilled *tert*-butanol (8 ml) was added, under nitrogen, a solution of ketone **20** (228 mg, 0.63 mmol) in *tert*-butanol (1 ml) and then diphenyliodonium chloride (200 mg, 0.63 mmol). The reaction mixture was heated at 70° C for 48 h. The solvent was evaporated, and the residue was partitioned between brine and methylene chloride. The aqueous phase was extracted with methylene chloride, and the combined organic extracts were dried and evaporated. Flash chromatography (1:3 hexane-methylene chloride) gave **2-(2-benzyloxyethyl)-6-(2-benzylaminoethyl)-2-cyclohexenone (21**; 73 mg, 32%): ^{13}C-NMR 29.5 (2-CH_2), 32.4 (5-CH_2), 32.5 (C-4), 33.4 (C-5), 44.4 (NCH_2), 46.3 (C-6), 54.6 (NCH_2Ar), 68.7 (CH_2O), 72.7 (OCH_2Ar), 131.0 (C-2), 146.0 (C-3), 199.1 (CO).

Acknowledgment. This work was supported by the DGICYT (Spain, project PB 88-0316).

REFERENCES AND NOTES

1. Part 17 in the series Functionalized 2-Azabicyclo[3.3.1]nonanes. For Part 16: N. Casamitjana, J. Gràcia, J. Bonjoch, and J. Bosch, *Tetrahedron Lett*, submitted.
2. a) J. Bosch and J. Bonjoch, 'Studies in Natural Products Chemistry: Pentacyclic *Strychnos* Indole Alkaloids,' Vol. 1, ed. by Atta-ur-Rahman, Elsevier, Amsterdam, 1988, pp. 31-88; b) J. Harley-Mason, *Pure Appl. Chem.*, **1975**, *41*, 167-174; c) J. Bonjoch, N. Casamitjana, J. Quirante, M. Rodríguez, and J. Bosch, *J. Org. Chem.*, **1987**, *52*, 267-275; d) M. Amat, A. Linares, and J. Bosch, *J. Org. Chem.*, **1990**, *55*, 6299-6312; e) M. E. Kuehne, D. A. Frasier, and T. D. Spitzer, *J. Org. Chem.*, **1991**, *56*, 2696-2700; f) J. M. Fevig, R. W. Marquis Jr., and L. E. Overman, *J. Am. Chem. Soc.*, **1991**, *113*, 5085-5086.
3. J. Bonjoch, N. Casamitjana, J. Quirante, A. Torrens, A. Paniello, and J. Bosch, *Tetrahedron*, **1987**, *43*, 377-381.
4. a) J. Bonjoch, J. Quirante, M. Rodríguez, and J. Bosch, *Tetrahedron*, **1988**, *44*, 2087-2092; b) J. Bonjoch, J. Quirante, D. Solé, J. Castells, M. Galceran, and J. Bosch, *Tetrahedron*, **1991**, *47*, 4417-4428.
5. For other synthesis of 8-aryl-2-azabicyclo[3.3.1]nonan-7-ones, see: S. Blechert, *Synthesis*, **1989**, 71-82.
6. D. S. Grierson, *Org. React.*, **1990**, *39*, 85-295.
7. Alternate methods of preparing **7** failed. Thus, although **8**[4b,8] was alkylated (LDA) with ethyl bromoacetate to give **11**[9] (82%) and the dianion (NaH, then BuLi) derived from **9** reacted with methyl iodide to give **12** (33%), neither **8** nor **9** could be alkylated with 2-bromo-(or iodo)-ethyl acetate under a variety of experimental conditions.



	R_1	R_2
7	CH_2CH_2OAc	H
8	H	H
9	H	CO_2Et
10	CO_2tBu	H
11	CH_2CO_2Et	H
12	CH_3	CO_2Et

8. Additionaly, **8** was prepared from ethyl 1-benzyl-4-piperidineacetate by two alternate procedures, either *via* β-keto ester **9** or *tert*-butyl ester **10** (see Experimental).
9. Compound **11**: ^{1}H-NMR 1.21 (t, J = 7, CH_3), 1.30 (m, 2H), 1.62 (dm, J = 12, H-3eq and H-5eq), 1.85 (m, 3H), 2.01 (td, J = 12, 2.5, H-2ax and H-6ax), 2.37 (d, J =6.5, CH_2CO), 2.51 (dd, J = 17, 4.5, 1H, CH_2CO_2), 2.86 (dm, J = 12, H-2eq and H-6eq), 3.20 (dd, J =17, 10, 1H, CH_2CO_2), 3.50 (s, CH_2Ar), 4.09 (q, J = 7, OCH_2), 4.11 (dd, J =11, 5, CHAr), 7.30 (m, ArH); ^{13}C-NMR 13.8 (CH_3), 30.8 (C-4), 30.9 (CH_2), 31.3 (C-3, C-5), 36.6 (CH_2COO), 47.6 (CH_2CO), 53.1 (C-2, C-6), 54.3 (CHAr), 60.3 (OCH_2), 62.8 (CH_2Ar), 127.1, 127.6, 128.1, 128.2, 129.0, 137.2, 137.4 (Ar), 172.1 (COO), 208.2 (CO).
10. For some consequences of the steric crowding between an equatorial C-8 substituent and the piperidine nitrogen substituent, see references 3 and 4b.
11. R. M. Moriarty and R. K. Vaid, *Synthesis*, **1990**, 431-447.
12. R. P. Koyzord, J. Morgan, and J. T. Pinhey, *Aust. J. Chem.* **1985**, *38*, 1147-1153.
13. G. Sturtz, *Bull. Soc. Chim. Fr.*, **1967**, 1345-1353.
14. Prepared by reaction of benzyl 2-bromoethyl ether (D. Grobelny, P. Maslak, and S. Witek, *Tetrahedron Lett.* **1979**, 2639-2642) with sodium iodide in 2-butanone at reflux temperature for 48 h.