Pergamon

Tetrahedron, Vol. 53, No. 4, pp. 1391-1402, 1997

0040-4020/97 $17.00 + 0.00

PII: S0040-4020(96)01051-4

Synthesis of 2-Azabicyclo[3.3.1]nonanes by means of (Carbamoyl)dichloromethyl Radical Cyclization

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Abstract: A new procedure for the synthesis of 2-azabicyclo[3.3.1]nonanes by intramolecular carboradical cyclization of 4-(trichloroacetamido)cyclohexenes substituted with an electron withdrawing substituent (ester or nitrile) is described. The procedure allows the preparation of synthetically interesting azabicyclos **14** and **15** in nearly 70% yield.

The synthesis of 2-azabicyclo[3.3.1]nonane derivatives[1] has been achieved by several procedures either from piperidine derivatives or from carbocyclic compounds,[2] but the construction of the bridged nucleus by means of ring closure promoted by a carboradical process has not been described until our recent synthesis of the heteroyohimban alkaloid melinonine-E, which possesses an unique pentacyclic skeleton embodying the 2-azabicyclo[3.3.1]nonane framework.[3] This azabicyclic bridged system constitutes the skeleton of the two natural products (bromocavernicolenone,[4] and kopsone[5]) recently isolated. Moreover the 2-azabicyclo[3.3.1]nonane occurs as subunit of the novel immunosuppressant FR901483[6] as well as numerous alkaloids of several types (e.g. morphine, strychnine, daphniphyllidine,...).

In this paper we describe a general entry to the 2-azabicyclo[3.3.1]nonane nucleus by intramolecular cyclization of 3-aza-6-heptenyl radicals.[7] Several types of carboradical precursors have been used to generate β-nitrogen containing radicals.[8-18] The usefulness of each precursor in inducing successful cyclization depends on the substrate type, the required process (4-endo-, 5-exo-....), and the method and conditions used to carry out the reaction (hydride method, atom transfer procedure, initiation type, temperature, dilution...).[19] In spite of the profused development in the use of β-nitrogen containing radicals to synthesize 5-membered rings, and more recently 4-membered rings,[20] its usefulness in the synthesis of six-membered rings has been scarcelly exploited so far.[21,22]

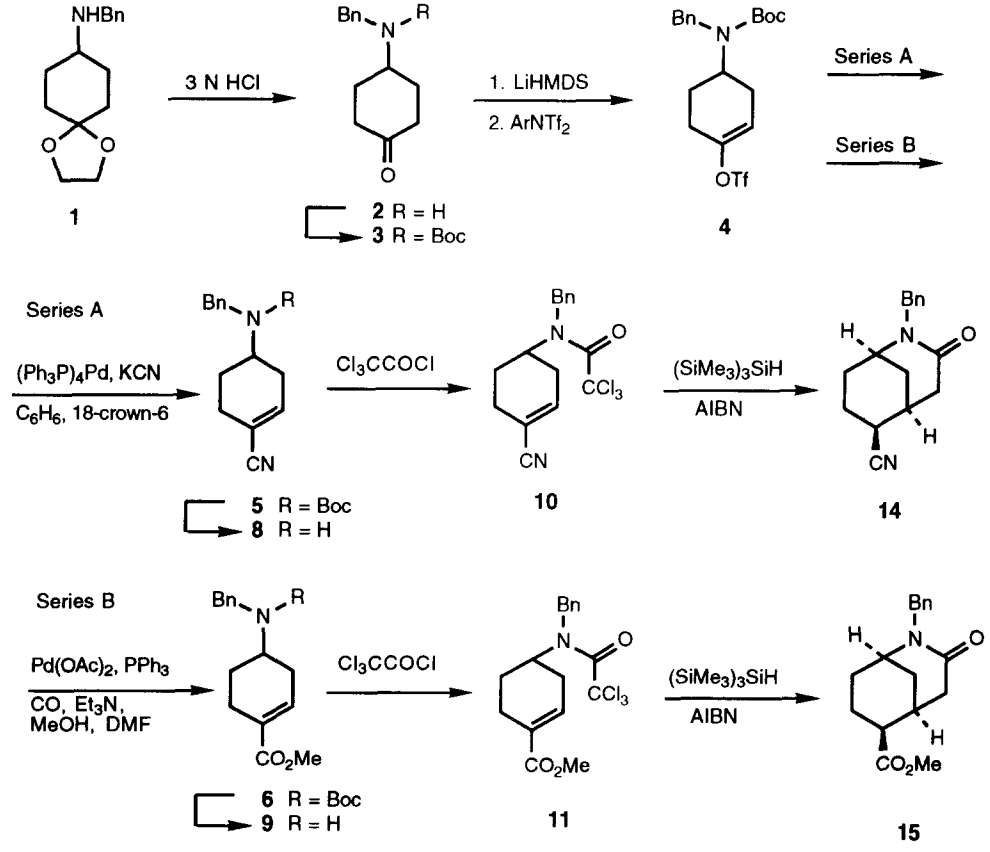
In order to develope our synthesis of 2-azabicyclo[3.3.1]nonanes we chose the trichloroacetamido group as the carboradical precursor because it could be generated in a single operation step from the corresponding amine in contrast to other procedures which required more elaborate processes. The use of other haloacetamides, equally available, was also considered in our work. Moreover, the amido group present might be useful in further synthetic operations as has occurred in our synthesis of melinonine-E.[3] Although considerable attention has been directed towards the synthesis of nitrogen-containing heterocycles by using radical cyclizations, the use of trichloroacetamides as precursors of α-carbamoyl radicals has been limited,[9,23] despite the good results observed in their cyclization upon electron-poor double bonds.

Results and Discussion

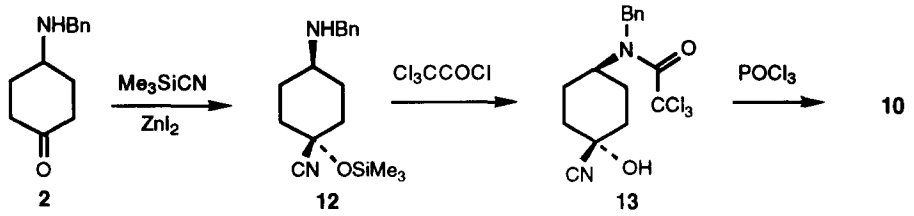
Our synthetic approach began with cyclohexanone **2**[24] which is readily available from 1,4-cyclohexanedione monoethylene acetal in two steps. Thus, the latter, after reductive amination by reaction with benzylamine followed by treatment with sodium borohydride, gave benzylamino derivative **1**[25] which, upon hydrolysis, led to the desired ketone **2**.

In order to generate the double bond that will act as the radical acceptor[26] in the ring closure step and desymmetrizes the cyclohexane derivative **2** we adopt a methodology which could be extrapolated to an enantioselective version in the future. After protection of the secondary amine **2** as the carbamate **3**, we generated the vinyl triflate **4** using LiHMDS as a base[27] and *N*-(5-chloro-2-pyridyl)triflimide as sulfonylating agent.[28]

Treatment of enol triflate **4** with potassium cyanide in the presence of $Pd(PPh_3)_4$ and 18-crown-6 in benzene provides the corresponding α,β-unsaturated nitrile **5** in 51% yield.[29] On the other hand, the same vinyl triflate **4** upon palladium-mediated carbonylation-methoxylation[30] gave rise to α,β-unsaturated ester **6**.[31] Deprotection of cyclohexenes **5** and **6** followed by trichloroacetylation, in both series, of secondary amines **8** and **9** gives the required amidocyclohexenes **10** and **11**. The α,β-unsaturated nitrile **10** was also prepared in a



Scheme 1. Synthesis of 2-azabicyclo[3.3.1]nonanes



Scheme 2. (The major *trans* isomers were depicted)

more straightforward manner in this racemic series by formation[32] of trimethylsilylcyanohydrin **12** from ketone **2** followed by trichloroacetylation to give **13**, which upon dehydration[33] with $POCl_3$ allows the formation of nitrile **10** in 44% overall yield for the required three-steps from ketone **2** (Scheme 2).

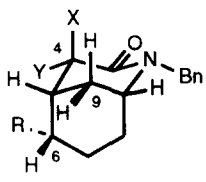
The radical cyclizations of **10** and **11** were carried out with tris(trimethylsilyl)silane (TTMSS)[34] as the radical mediator (Table 1). When compound **10** was treated with TTMSS (2 equiv) and 0.1 equiv of AIBN in refluxing benzene (0.12 M) over a period of 16 h, the expected cyclization to the 2-azabicyclo[3.3.1]nonane ring system took place (66% yield) to give a mixture of **14** (minor amounts) and its C-4 chloro and dichloro substituted derivatives **17** and **16**, respectively. As expected, treatment of both chlorinated compounds with Zn brought about the hydrogenolysis of C-Cl bonds to provide the nitrile **14** as a single stereoisomer. When the cyclization was conducted in the presence of 3.5 equiv of TTMSS, the cyclized product **14** was directly obtained in 57% yield together with 17% of chloro derivative **17**. The relative configuration at C-6 in **14** (equatorial cyano group) was deduced from the multiplicity (qd, J = 13.5 and 4 Hz) of H-7ax (assigned from the 2D NMR spectra), which indicates the axial disposition for the proton at C-6. This configuration is the expected one taking into account that hydrogen abstraction by radicals in cyclic systems occurs from the most accessible face.[35] The stereochemistry of all azabicyclos synthesized was established from their ^{13}C NMR data (Table 2) by considering the existence or the absence of γ-effects upon C-4, C-6 or C-9.[36]

From the synthetic standpoint, the best results in this radical cyclization were achieved when we used ester **11** as proradical. Under the same conditions, azabicyclo **15** was isolated in nearly 70% yield, indicating that in this case the reduction of C-Cl bond in C-4 is easier.

The above cyclizations of trichloroacetamidocyclohexenes **10** and **11** not only provides a synthetic entry to the 2-azabicyclo[3.3.1]nonane ring system but also constitutes one of the scarce examples of synthetically useful 6-exo-trig cyclizations from 3-aza-6-heptenyl radicals.[37] In addition, it is noteworthy that the dichloromethylcarbamoyl radicals, generally considered to have an electrophilic nature, underwent cyclization onto electron-poor double bonds in good yield.

Table 1. Radical Cyclization of 10 and 11 Providing 14 or 15

Compd	Reagent	Compounds	
10	TTMSS (2 equiv)	**16** (17%)	**17** (48%)
10	TTMSS (3.5 equiv)	**14** (57%)	**17** (17%)
11	TTMSS (2 equiv)	**15** (41%)	**18** (21%)
11	TTMSS (3.5 equiv)	**15** (68%)	



	R	X	Y
14	CN	H	H
15	CO_2Me	H	H
16	CN	Cl	Cl
17	CN	H	Cl
18	CO_2Me	H	Cl

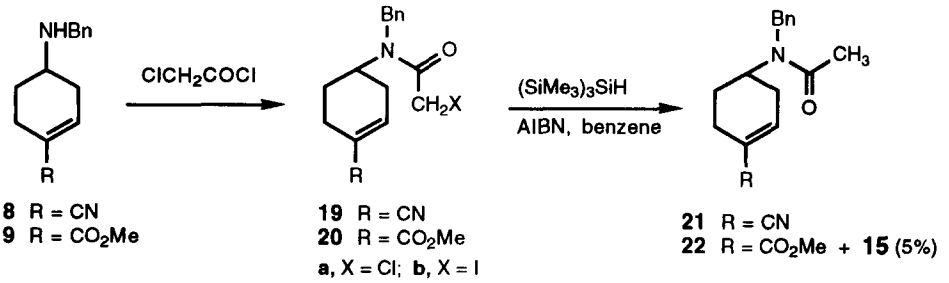
Table 2. ^{13}C NMR Data (δ) of 2-Azabicyclo[3.3.1]nonanes 14-18[a]

Compd	C-1	C-3	C-4	C-5	C-6	C-7	C-8	C-9	CH_2Ar[b]	Other
14	49.5	169.2	33.7	29.7	32.8	20.4	27.5	31.0	48.3	120.8
15	50.3	170.3	33.8	29.4	46.2	18.6	28.1	32.3	48.1	173.9 / 51.7
16	50.4	164.0	84.2	46.9	32.7	20.4	27.9	30.3	49.4	119.9
17	50.1	166.3	57.3	36.2	31.2	20.4	27.7	32.8	49.1	120.5
18	51.0	166.9	58.3	37.2	45.0	17.9	27.9	33.7	49.2	173.6/ 51.8

[a] In $CDCl_3$ (50.3 MHz). Values for compounds **14** and **15** were assigned on the basis of HMQC spectra. [b] Phenyl ring carbons were found at δ 127.7 (±0.1), 127.9 (±0.1), 128.8 (±0.1), and 136.5 (±0.5).

Finally, we examined the behaviour of iodoacetamides **19b** and **20b** in front of the radical cyclization process. The acylation of secondary amines **8** and **9**, performed with chloroacetyl chloride, afforded the chloroacetamides **19a** and **20a** which gave the required iodoacetamides by reaction with sodium iodide in acetonitrile at room temperature. Acetamides **19** and **20** showed the presence of two rotamers in a ratio *ca.* 7:3 by ^1H NMR. The ^{13}C NMR indicates the rotamer *Z* to be predominant, its benzylic carbon, *anti* to oxygen atom of amide, appearing more deshielded (~3 ppm) than in the *E* isomer, whereas the *syn* located C-4 resonates at a more shielded field (~ 3.5 ppm). Although the major conformer in each case (***Z*-19b** and ***Z*-20b**) generates a radical which is topologically prohibited from cyclizing, it is known that the temperature in which the cyclization attempts were carried out, increasing the rate of rotation around the amide bond, allows the conversion of *syn* radicals to *anti* radicals that can cyclize.[12a] However, we have not observed a cyclized compound starting from nitrile **19b**, the reduced acetamide **21** being the sole product isolated. Starting from ester **20b** we isolated the reduced acetamide **22** and minor amounts (5% yield) of the cyclized product **15**. The reduced products **21** and **22** can be derived from the initially generated carbamoylmethyl radical either by direct reduction or a 1,5-hydrogen shift followed by reduction of the allylic radical formed.[38]

In summary, although 6-exo-trig radical cyclizations are relatively slow, such reactions of α-(carbamoyl)dichloromethyl radicals, generated from **10** and **11**, proved to be effective. These acetamides underwent cyclisation to furnishe the bridged azabicyclo derivatives **14** and **15** in good yields, using 3.5 equiv of hydride reagent, the process being stereoselective. The presence of the chlorine atoms in the radical intermediates is indispensable, as is shown by the inefficiency of the cyclization of α-carbamoylmethyl radicals generated from iodoacetamides **19** and **20**.



8 R = CN
9 R = CO_2Me

19 R = CN
20 R = CO_2Me
a, X = Cl; **b**, X = I

21 R = CN
22 R = CO_2Me + **15** (5%)

Scheme 3. (Compounds **19** and **20** are depicted in their minor *E* conformation around the amide bond, whereas **21** and **22** are depicted in their major *Z* rotamer)

EXPERIMENTAL

General. ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ solution at 300 MHz and 75.4 MHz, respectively, or at 200 MHz and 50.3 MHz, respectively. In addition, 2D NMR COSY and HMQC experiments were performed on a Varian XL-500 instrument. Chemical shifts are reported as δ values (ppm) relative to internal Me_4Si. Infrarred spectra were recorded on a Nicolet 205 FT-IR spectrophotometer. Mass spectra were determined on a Hewlett-Packard 5988 A mass spectrometer or on a Autospec-VG (HRMS). TLC was performed on SiO_2 (silica gel 60 F_{254}, Merck). The spots were located by UV light and a 1% $KMnO_4$ solution or hexachloroplatinate reagent. Chromatography refers to flash column chromatography and was carried out on SiO_2 (silica gel 60, SDS, 230-400 mesh). All reactions were carried out under an argon or nitrogen atmosphere with dry, freshly distilled solvents under anhydrous conditions, unless otherwise noted. Drying of organic extracts during the work-up of reactions was performed over anhydrous Na_2SO_4. Melting points were determined in a capillary tube on a Büchi apparatus and are uncorrected. Microanalyses were performed by the "Centro de Investigación y Desarrollo" (CSIC), Barcelona.

4-Benzylaminocyclohexanone (2).[25] A mixture of benzylamine (7.8 ml, 71.7 mmol) and 1,4-cyclohexanedione monoethylene acetal (10 g, 64 mmol) in CH_2Cl_2 (50 ml) was stirred for 4 h with activated 4 Å molecular sieves. The resulting suspension was filtered through a short pad of Celite and the filtrate evaporated to dryness. To the residue dissolved in MeOH (150 ml) and cooled at 0 °C, was added $NaBH_4$ (4.8 g, 128 mmol) and the mixture stirred for an additional 4 h. Then, H_2O (10 ml) was added to the reaction mixture and MeOH was evaporated. The residue was dissolved in CH_2Cl_2 and washed with brine. Evaporation of the dried extracts afforded **4-benzylaminocyclohexanone ethylene acetal (1**, 15.3 g, 96%) as an orange oil, which was used without further purification in the next step: IR (NaCl) 3125; ^1H NMR 1.30-1.90 (m, 8H), 2.58 (m, 1H , H-4_{ax}), 3.77 (s, 2H, CH_2Ph), 3.89 (s, 4 H, OCH_2), 7.20-7.35 (m, 5H, ArH); ^{13}C NMR 29.8 (C-3 and C-5), 32.5 (C-2 and C-6), 50.9 (NCH_2), 54.0 (C-4), 63.8 (OCH_2), 108.3 (C-1), 126.4, 127.6, 128.0, and 140.5 (Ar).

A solution of **1** (14.8 g, 60 mmol) in THF (81 ml) and hydrochloric acid (3 N, 89 ml) was heated at reflux for 10 h. The mixture was rotary evaporated, and the residue, cooled at 0 °C, basified with aqueous NaOH (2.5 N), and extracted with CH_2Cl_2. Evaporation of the dried extracts gave ketone **2** (11.5 g, 88%), which was used without further purification in the next step: IR (NaCl) 3300, 1713; ^1H NMR 1.74 (m, 2H, H-3_{ax} and H-5_{ax}), 2.02-2.14 (m, 2H, H-3_{eq} and H-5_{eq}), 2.22-2.34 and 2.46-2.58 (2m, 4H, H-2 and H-6), 3.0 (m, 1H, H-4_{ax}), 3.84 (s, 2H, CH_2Ph), 7.22-7.34 (m, 5H, ArH); ^{13}C NMR 31.8 (C-3 and C-5), 38.2 (C-2 and C-6), 51.4 (NCH_2), 52.7 (C-4), 126.9, 127.9, 128.4, and 140.2 (Ar), 211.4 (C-1).

4-[Benzyl(*tert*-butoxycarbonyl)amino]cyclohexanone (3). To a solution of ketone **2** (2 g, 9.8 mmol) in MeOH (15 ml) and Et_3N (1.5 ml) was added di-*tert* -butyl dicarbonate (3.86 g, 17.7 mmol) and the mixture was heated at 60 °C for 2 h. The solvent was evaporated, the residue was treated with hydrochloric acid (1 N) until pH 2-3, and the resulting solution was extracted with CH_2Cl_2. The organic extracts were washed with brine, dried and evaporated to give an oil, which was crystallized from isopropanol to give **3** (2.6 g, 85%) as a white solid: mp 101-104 °C; IR (KBr) 1710, 1676; ^1H NMR 1.43 (br s, 9H, CH_3), 1.70-2.10 (m, 4H, H-3 and H-5), 2.27-2.50 (m, 4H, H-2 and H-6), 4.39 (br s, 2H, CH_2Ph), 4.5 (m, 1H, 4-H), 7.15-7.35 (m, 5H, ArH); ^{13}C NMR 28.2 (CH_3), 29.8 (C-3 and C-5), 39.9 (C-2 and C-6), 46.8 (NCH_2), 53.4 (C-4), 80.1 (C), 126.4, 126.7, 128.2, and 139.6 (Ar), 155.4 (NCO), 209.5 (CO). Anal. Calcd for $C_{18}H_{25}NO_3$: C, 71.24, H, 8.31, N, 4.62. Found: C, 71.21; H, 8.38, N; 4.62.

4-[Benzyl(*tert*-butoxycarbonyl)amino]cyclohexenyl trifluoromethanesulfonate (4). To a solution of ketone **3** (170 mg, 0.55 mmol) in THF (5 ml) cooled at -78 °C was added LiHMDS (0.6 ml, 0.6 mmol, 1 M in THF) and the resultant solution was stirred for 2 h. *N*-(5-Chloro-2-pyridyl)triflimide (294 mg, 0.83 mmol) was added and the reaction mixture was allowed to warm to room temperature. Stirring was continued for 5 h and after solvent removal the residue was dissolved in Et_2O, and washed with 2 N aqueous NaOH and 2 N

aqueous HCl. Evaporation of the dried organic extracts afforded a residue which was purified by chromatography (3% EtOAc in hexane) to give **4** (189 mg, 72%) as a clear oil: IR (NaCl) 1692, 1415; ^{1}H NMR 1.42 (br s, 9H, CH_3), 1.82 (m, 1H, H-5_{eq}), 1.95 (qd, J = 12 and 6 Hz, 1H, H-5_{ax}), 2.15-2.60 (m, 3H), 4.23 (m, 1H, H-4_{ax}), 4.39 (br s, 2H, CH_2Ph.), 5.65 (m, $W_{1/2}$ = 10 Hz, 1H, H-2), 7.15-7.40 (m, 5 H, ArH); ^{13}C NMR 26.7 (C-6), 27.2 (C-5), 27.5 (C-3), 28.1 (CH_3), 47.4 (NCH_2), 50.9 (C-4), 80.1 (C), 112.0, 116.2, 120.4, and 124.6 (CF_3), 117.0 (C-2), 126.4, 126.8, 128.3, and 139.4 (Ar), 147.8 (C-1), 155.3 (CO). Anal. Calcd for $C_{19}H_{24}F_3NO_5S$: C, 52.41; H, 5.56; F, 13.09; N, 3.22; S 7.36. Found: C, 52.45; H, 5.62; F, 12.69; N, 3.24; S, 7.22.

4-[Benzyl(*tert*-butoxycarbonyl)amino]-1-cyclohexenecarbonitrile (5). A suspension of triflate **4** (129 mg, 0.3 mmol), potasium cyanide (77 mg, 1.2 mmol), tetrakis(triphenylphosphine)palladium (0) (20.4 mg, 0.017 mmol), and 18-crown-6 (812 mg, 0.04 mmol) in benzene (0.6 ml) was heated at reflux temperature for 6 h. Then, the reaction mixture was partitioned between Et_2O (10 ml) and H_2O (10 ml) and extracted with Et_2O. Evaporation of the dried ethereal extracts left a residue which was purified by chromatography (5% MeOH in CH_2Cl_2) to give **5** (48 mg, 51%) as a white solid: mp 60-63 °C (EtOAc); IR (KBr) 2250, 1695; ^{1}H NMR 1.43 (br s, 9H, CH_3), 1.20-2.50 (m, 6H), 4.15 (m, 1H, H-4_{ax}), 4.39 (br s, 2H, CH_2Ph), 6.50 (br s, 1H, H-2), 7.15-7.35 (m, 5H, ArH); ^{13}C NMR 26.3 (C-6), 27.5 (C-5), 28.4 (CH_3), 30.0 (C-3), 47.6 (NCH_2), 50.9 (C-4), 80.3 (C), 111.8 (C-1), 119.0 (CN), 126.6, 127.0, 128.4, and 139.4 (Ar), 143.6 (C-2), 155.0 (CO). Anal. Calcd for $C_{19}H_{24}N_2O_2$ 1/4 H_2O: C, 72.01; H, 7.79; N, 8.84. Found: C, 71.65; H, 7.91; N, 8.44.

Methyl 4-[Benzyl(*tert*-butoxycarbonyl)amino]-1-cyclohexenecarboxylate (6). To a solution of triflate **4** (716 mg, 1.64 mmol), in MeOH (2.8 ml, 69 mmol) were added triethylamine (0.45 ml, 3.23 mmol), palladium acetate (11 mg, 0.05 mmol), triphenylphosphine (25 mg, 0.09 mmol), and DMF (6.3 ml). The reaction mixture was purged with carbon monoxide and stirred under a 3 atm pressure of CO overnight at room temperature. Then, Et_2O (100 ml) and H_2O (50 ml) were added. The ether layer was washed with water until neutral, dried, and evaporated to give a residue which was subjected to chromatography (7% EtOAc in hexane). The initial elution gave ester **6** (367 mg, 65%) as a clear oil: IR (NaCl) 1713, 1690; ^{1}H NMR (COSY) 1.40 (br s, 9 H, CH_3), 1.69 (qd, J = 12 and 5 Hz, 1H, H-5_{ax}), 1.78 (m, 1H, H-5_{eq}), 2.27 (m, 3 H, H-3 and H-6_{ax}), 2.47 (dm, J = 10 Hz, 1H, H-6_{eq}), 3.70 (s, 3H, OCH_3), 4.20 (m, 1H, H-4_{ax}), 4.37 (s, 2H, CH_2Ph), 6.82 (m, $W_{1/2}$ = 10 Hz, 1H, H-2), 7.18-7.31 (m, 5 H, ArH); ^{13}C NMR (HMQC) 24.9 (C-6), 26.8 (C-5), 28.3 (CH_3), 29.8 (C-3), 47.1 (NCH_2), 51.6 (C-4, OCH_3), 80.0 (C), 126.5, 126.7, 128.3, and 139.8 (Ar), 129.6 (C-1), 138.0 (C-2), 155.6 (NCO), 167.3 (CO). Anal. Calcd for $C_{20}H_{27}NO_4$: C, 69.56; H, 7.82; N, 4.05. Found: C, 69.45; H, 7.88; N, 4.01. Further elution gave **methyl 5-[benzyl(*tert*-butoxycarbonyl)amino]-1-cyclohexenecarboxylate (7**, 20 mg, 3%) as a clear oil: IR (NaCl) 1740, 1689; ^{1}H-NMR 1.40 (br s, 9H, CH_3), 1.73 (qd, J =12 and 5 Hz, 1H, H-5_{ax}), 1.83 (m, 1H, H-5_{eq}), 2.17 (br s, 1H, H-3_{ax}), 2.41 (m, 2H, H-6_{ax}. and H-6_{eq}), 2.54 (dd, J=15 and 4 Hz, 1H, H-3_{eq}), 3.83 (s, 3H, OCH_3), 4.15 (s, 1H, H-4_{ax}), 4.39 (br s, 2H, CH_2Ph), 6.85 (m, J =10 Hz, 1H, H-2), 7.17-7.30 (m, 5H, ArH); ^{13}C NMR (HMQC) 22.9 (C-3), 26.2 (C-4), 28.3 (CH_3), 30.7 (C-6), 47.5 (NCH_2), 52.4 (C-4, OCH_3), 80.1 (C), 126.6, 126.9, 128.3, and 139.5 (Ar), 135.1 (C-1), 147.2 (C-2), 164.4 (CO).

4-Benzylamino-1-cyclohexenecarbonitrile (8). Trifluoroacetic acid (3 ml, 39.2 mmol) was added dropwise to an ice-cooled solution of **5** (200 mg, 0.6 mmol) in CH_2Cl_2 (1 ml) and the mixture stirred for 1 h at room temperature. The reaction mixture was concentrated and the residue recrystallized from Et_2O to give the trifluoroacetate salt of **8** as a white solid: mp 180 °C (dec). The free amine **8** was obtained by partitioning the trifluoroacetate salt between EtOAc and 2 N aqueous NaOH. The organic layer was washed with brine, dried and evaporated to afford the pure secondary amine **8** (105 mg, 77%) as a clear oil: IR (NaCl): 3400, 2400; ^{1}H NMR 1.5 (dtd, J = 13, 9.5 and 6 Hz, 1 H, H-5_{ax}), 1.9-2.1 (m, 5 H), 2.84 (dddd, J = 10, 7, 5 and 2 Hz, 1H, H-4_{ax}), 6.54 (m, $W_{1/2}$ = 10 Hz, 1H, H-2), 7.20-7.40 (m, 5H, ArH); ^{13}C NMR 25.5 (C-6), 27.6 (C-5), 32.8 (C-3), 50.3 (C-4), 50.9 (NCH_2), 112.0 (C-1), 119.3 (CN), 126.9, 127.9, 128.4, and 140.0 (Ar), 143.0 (C-2). HRMS calcd for $C_{14}H_{16}N_2$ 212.1313, found 212.1313.

Methyl 4-Benzylamino-1-cyclohexenecarboxylate (9). Operating as above, from carbamate **6** (513 mg, 1.5 mmol), trifluoroacetic acid (6.94 ml, 90.7 mmol) and CH_2Cl_2 (2 ml), the trifluoroacetate salt of **9** was obtained as a white solid: mp 196-197 °C (Et_2O). Anal. Calcd for $C_{17}H_{20}F_3NO_4$: C, 56.82; H, 5.61; N, 3.90. Found: C, 57.03; H, 5.60, N, 3.82. As above, free amine **9** (279 mg, 76%) was obtained as a clear oil: IR (NaCl) 3300,1712; ^1H NMR (500 MHz) 1.50 (dtd, J = 13, 10 and 5.5 Hz, 1H, H-5_{ax}), 1.55 (br s, 1H, NH), 1.94 (m, $W_{1/2}$ = 12, 1H, H-5eq), 2.05 (m, 1H, 3-H), 2.22 (m, 1H, H-6), 2.47 (m, 2H, H-3 and H-6), 2.82 (dddd, J = 11, 7.75, 5 and 2.5 Hz, 1 H, H-4_{ax}), 3.70 (s, 3H, OCH_3), 3.80 and 3.84 (2 d, J = 13 Hz, 2H, CH_2Ph), 6.89 (m, $W_{1/2}$ = 10 Hz, 1 H, H-2), 7.21-7.33 (m, 5 H, ArH); ^{13}C NMR (HMQC) 23.0 (C-6), 28.1 (C-5), 32.7 (C-3), 50.9 (NCH_2), 51.2 (OCH_3), 51.4 (C-4), 126.8, 127.9, 128.2, and 140.0 (Ar), 129.8 (C-1), 137.4 (C-2), 167.3 (CO). Anal. Calcd for $C_{15}H_{19}NO_2$: C, 73.44; H, 7.81; N, 5.71. Found C, 73.33; H, 7.84; N, 5.66.

4-Benzylamino-1-trimethylsilyloxycyclohexane-1-carbonitrile (12). To a solution of cyclohexanone **2** (5 g, 25.2 mmol) in CH_2Cl_2 (36 ml) was added zinc iodide (315 mg, 0.98 mmol) and trimethylsilylcyanide (6.76 ml, 50.4 mmol). The reaction mixture was heated at 65 °C for 2 h. Then, the solvent was evaporated and the residue was taken up with Et_2O and filtered. The filtrate was evaporated to dryness to give *O*-silyl cyanohydrin **12** (4.6 g, 86%) as a mixture of *cis-trans* isomers in a ratio 1:3, as a yellow oil, which was used in the next step without further purification: IR (NaCl) 2220; ^1H NMR (*trans*-**12**)1.52 (ddd, J = 13, 10 and 2.5 Hz, 2 H, H-3_{ax}. and H-5_{ax}), 1.63 (td, J = 12.5 and 3 Hz, 2 H, H-2_{ax}. and H-6_{ax}), 2.01 (dm, J = 13 Hz, 2 H, H-3_{eq} and H-5eq), 2.19 (dm, J = 13 Hz, 2 H, H-2_{eq} and H-6_{eq}), 2.55 (tt, J = 10 and 4 Hz, 1H, H-4_{ax}), 7.20-7.40 (m, 5 H, ArH); ^{13}C NMR (*cis*-**12**) 1.3 (CH_3), 27.3 (C-3 and C-5), 35.7 (C-2 and C-6), 51.0 (NCH_2), 54.0 (C-4), 68.7 (C-1), 122.2 (CN); (*trans*-**12**) 1.4 (CH_3), 29.4 (C-3 and C-5), 37.6 (C-2 and C-6), 51.0 (NCH_2), 54.0 (C-4), 70.8 (C-1), 121.5 (CN), 127.0, 128.0, 128.4, and 140.2 (Ar). HRMS calcd for $C_{17}H_{26}N_2OSi$: 302.1814, found 302.1813.

4-(*N*-Benzyltrichloroacetamido)-1-hydroxy-1-cyclohexanecarbonitrile (13). To a solution of **12** (500 mg, 1.6 mmol) in CH_2Cl_2 (1 ml) was added pyridine (0.27 ml, 3.46 mmol) and the mixture was cooled to 0 °C. Then, trichloroacetyl chloride (0.28 ml, 2.52 mmol) in CH_2Cl_2 (1.5 ml) was added dropwise. After 12 h of stirring at room temperature the reaction mixture was concentrated. The resulting residue was dissolved in CH_2Cl_2 and washed with 1 N aqueous HCl, saturated aqueous K_2CO_3, and brine. The organic phase was dried and evaporated to leave a residue which was purified by chromatography (CH_2Cl_2) to give **13** (494 mg, 79%) as a mixture of epimers *cis* and *trans* in a 1:3 ratio: white solid mp, 84-86 °C (CH_2Cl_2); IR (KBr) 1671; ^1H NMR 1.5-2.5 (m, 8H), 4.55 (m, 1H, H-4_{ax}), 4.62 (s, 2 H, CH_2Ph), 7.10-7.45 (m, 5 H, ArH); ^{13}C NMR (*cis*-**13**) 23.8 (C-3 and C-5), 35.5 (C-2 and C-6), 47.9 (NCH_2), 57.2 (C-4), 64.7 (C-1), 93.3 (CCl_3), 121.0 (CN), 125,9, 127,0, 128.5, and 136.8 (Ar), 160.6 (CO); (*trans*-**13**) 26.7 (C-3 and C-5), 36.6 (C-2 and C-6), 47.9 (NCH_2), 57.2 (C-4), 68.9 (C-1), 93.3 (CCl_3), 120.6 (CN), 126.1, 127.1, 128.6, and 136.8 (Ar), 160.7 (CO). Anal. Calcd for $C_{16}H_{15}Cl_3N_2O_2$: C, 51.15; H, 4.56; Cl, 28.31; N, 7.46. Found: C, 50.91; H, 4.56; Cl, 28.78; N, 7.08.

4-(*N*-Benzyltrichloroacetamido)-1-cyclohexenecarbonitrile (10) *Method A*. Operating as above, from amine **8** (200 mg, 0.94 mmol), pyridine (0.11 ml, 1.23 mmol), trichloroacetyl chloride (0.15 ml, 1.35 mmol) and CH_2Cl_2 (2.5 ml), and after chromatography (5% EtOAc in hexane) trichloroacetamide **10** (262 mg, 77%) was isolated. *Method B*. To a solution of cyanohydrin **13** (596 mg, 1.42 mmol) in pyridine (3.6 ml) cooled to 0 °C was added slowly $POCl_3$ (0.83 ml, 8.95 mmol). The reaction mixture was stirred at room temperature for 24 h and then concentrated. The resulting residue was dissolved in CH_2Cl_2 and washed with 1 N aqueous HCl and brine. The organic phase was dried and evaporated to leave a residue which was purified by chromatography (CH_2Cl_2) to give **10** (457 mg, 65%) as a white solid: mp 162-165 °C (EtOAc); IR (KBr) 2214, 1674; ^1H NMR 1.70-2.60 (m, 6H), 4.52 and 4.70 (2d, J = 16 Hz, 2H, CH_2Ph), 4.80 (m, 1H, H-4_{ax}), 6.49 (br s, 1H, H-2), 7.00-7.45 (m, 5H, ArH); ^{13}C NMR 26.1 (C-6), 27.1 (C-5), 29.5 (C-3), 47.5 (NCH_2), 54.0 (C-4), 93.3 (CCl_3), 112.1 (C-1), 118.4 (CN), 125.9, 127.3, 128.7, and 137.0 (Ar), 142.1 (C-2), 160.2 (CO). Anal. Calcd for $C_{16}H_{15}Cl_3N_2O$: C, 53.73; H, 4.23; N, 7.83. Found: C, 53.75; H, 4.32; N, 7.77.

Methyl 4-(*N*-Benzyltrichloroacetamido)-1-cyclohexenecarboxylate (11). Operating as above (Method A), from amine **9** (200 mg, 0.82 mmol), pyridine (0.07 ml, 0.85 mmol), trichloroacetyl chloride (0.14 ml, 1.22 mmol) and CH_2Cl_2 (2 ml), and after chromatography (5% EtOAc in hexane) chloroacetamide **11** (224 mg, 70%) was isolated: IR (KBr) 1707, 1670; ^1H NMR 1.52-2.54 (m, 6H), 3.72 (s, 3H, OCH_3), 4.54 and 4.70 (2 d, J = 15 Hz, CH_2Ph), 4.80 (m, 1H, H-4_{ax}), 6.58 (m, $W_{1/2}$ = 10 Hz, 1H, H-2), 7.10-7.40 (m, 5H, ArH); ^{13}C NMR 24.6 (C-6), 26.7 (C-5), 29.4 (C-3), 47.6 (NCH_2), 51.7 (OCH_3), 55.1 (C-4), 93.4 (CCl_3), 126.1, 127.2, 128.6, and 137.0 (Ar), 129.9 (C-1), 136.4 (C-2), 160.8 (NCO), 166.9 (CO). Anal. Calcd for $C_{17}H_{18}Cl_3NO_3$: C, 52.26; H, 4.64; Cl, 27.22; N, 3.59. Found: C, 52.13; H, 4.61; Cl, 27.41; N, 3.56.

Radical cyclization of 10. General Procedure. With 2 Equiv of $(SiMe_3)_3SiH$. A suspension of α,β-unsaturated nitrile **10** (130 mg, 0.36 mmol) and AIBN (12 mg, 0.07 mmol) in benzene (2.7 ml) was heated to reflux. Then, TTMSS (0.22 ml, 0.72 mmol) was added dropwise and the reaction mixture was stirred at this temperature for 21 h. After evaporation of the solvent the residue was chromatographed (2% MeOH in CH_2Cl_2). The first eluate gave **(1*RS*,5*RS*,6*SR*)-2-benzyl-4,4-dichloro-3-oxo-2-azabicyclo[3.3.1]nonane-6-carbonitrile (16)** (20 mg, 17%) as a white solid: mp 173-175 °C (EtOAc); IR (NaCl) 1672; ^1H NMR 1.20-2.40 (m, 5H), 2.66 (dm, J = 14.5 Hz, 1H, H-9*S*), 3.02 (dt, J = 12.5 and 3.5 Hz, 1H, H-6_{ax}), 3.30 (m, $W_{1/2}$ = 9 Hz, 1H, H-1_{eq}), 3.56 (br s, 1H, H-5_{eq}), 3.94 and 5.31 (2d, J = 15 Hz, 2H, CH_2Ph), 7.20-7.50 (m, 5H, ArH); ^{13}C NMR, Table 2; HRMS calcd for $C_{16}H_{16}Cl_2N_2O$ 322.0640, found 322.0648. The second eluate gave **(1*RS*,4*SR*,5*RS*,6*SR*)-2-benzyl-4-chloro-3-oxo-2-azabicyclo[3.3.1]nonane-6-carbonitrile (17)** (70 mg, 48%): IR (NaCl) 2240, 1655; ^1H NMR 1.50 (m, 1H, H-8_{ax}), 1.85-2.15 (m, 5 H), 2.80-3.00 (m, 2 H, H-5_{eq} and H-6_{ax}), 3.53 (m, $W_{1/2}$ = 10 Hz, 1 H, H-1_{eq}), 4.01 and 5.22 (2d, J =15 Hz, 2 H, CH_2Ph), 4.82 (d, J = 6.2 Hz, 1H, H-4_{ax}), 7.10-7.30 (m, 5 H, ArH); ^{13}C NMR, Table 2; HRMS calcd for $C_{16}H_{17}ClN_2O$ 288.1029, found 288.1035.

(1*RS*,5*SR*,6*SR*)-2-Benzyl-3-oxo-2-azabicyclo[3.3.1]nonane-6-carbonitrile (14). Operating as above, α,β-unsaturated nitrile **10** (267 mg, 0.74 mmol) in benzene (6 ml) was treated with AIBN (85 mg, 0.52 mmol) and 3.5 equiv of TTMSS (0.80 ml, 2.60 mmol), and the crude material was chromatographed (2% MeOH in CH_2Cl_2). The first eluate gave **17** (16 mg, 17%) as a white solid. The second eluate gave **14** (108 mg, 57%) as a white solid: mp 70-71 °C (CH_2Cl_2); IR (NaCl) 2230, 1648; ^1H NMR (500 MHz) 1.38 (tq, J = 13.5 and 2.5 Hz, 1H, H-8ax), 1.67 (dm, J = 12 Hz, 1H, H-9*S*), 1.75 (qd, J =13.5 and 4 Hz, 1H, H-7_{ax}), 1.82 (dm, J =14 Hz, 1H, H-8_{ax}), 1.92 (dm, J = 13 Hz, 1H, H-7_{eq}), 1.95 (dm, J = 13 Hz, 1H, H-9*R*), 2.5 (br s, 1H, H-5_{eq}), 2.72-2.82 (m, 3H, H-4_{ax}, H-4_{eq} and H-6_{ax}), 348 (br s, 1H, H-1_{eq}), 3.96 and 5.21 (2 d, J = 15 Hz, 2H, CH_2Ph), 7.21-7.32 (m, 5H, ArH); ^{13}C NMR, Table 2. Anal. Calcd for $C_{16}H_{18}N_2O$: C, 75.56, H, 7.13, N, 11.02. Found: C, 75.39; H, 7.12; N, 10.90.

To a solution of monochlorinated bicyclo **17** (40 mg, 0.14 mmol) in absolute MeOH (2 ml) was added ammonium chloride (45 mg, 0.83 mmol) and after cooling to 0 °C powdered zinc (90 mg, 1.4 mmol) was added. The reaction mixture, after 24 h at room temperature, was filtered through Celite and the filtrate evaporated and chromatographed to afford **14** (27 mg, 70%). From dichlorinated bicyclo **16** (40 mg, 0.12 mmol), MeOH (3 ml), ammonium cloride (89 mg, 1.6 mmol) and powdered zinc (180 mg, 2.7 mmol), by the same procedure, bicyclo **14** (22 mg, 70%) was obtained.

Radical cyclization of 11. With 2 equiv of TTMSS. Following the general procedure, α,β-unsaturated ester **11** (121 mg, 0.25 mmol) in benzene (2.2 ml) was treated with AIBN (20 mg, 0.10 mmol) and 2 equiv of TTMSS (0.19 ml, 0.51 mmol), and the crude material was chromatographed (2% MeOH in CH_2Cl_2). The first eluate gave **(1*RS*,4*SR*,5*RS*,6*SR*) methyl 2-benzyl-4-chloro-3-oxo-2-azabicyclo[3.3.1]nonane-6-carboxylate (18)** (21 mg, 21 %) as a white solid: IR (KBr) 1732,1654; ^1H NMR 1.42 (tdd, J = 13, 4.5 and 2.5 Hz, 1H, H-8_{ax}), 1.91 (dt, J = 13 and 3 Hz, 1H, H-9*R*), 1.65-2.14 (m, 4H), 2.52 (dt, J =13 and 3 Hz, 1H, H-6_{ax}), 3.28 (m, $W_{1/2}$ = 13 Hz, 1 H, H-5_{eq}), 3.52 (br s, 1 H, H-1_{eq}), 4.00 and 5.22 (2 d, J =15 Hz, 2 H, CH_2Ph),4.72 (d, J = 6.5

Hz, 1 H, H-4_{ax}), 7.20-7.40 (m, 5 H, ArH); ^{13}C NMR, Table 2. HRMS calcd for $C_{17}H_{20}ClNO_2$ 321.1130, found 321.1130. The second eluate gave **15** (36 mg, 41%) as a white solid: for analytical data, *vide infra*.

(1*RS*,5*SR*,6*SR*) Methyl 2-Benzyl-3-oxo-2-azabicyclo[3.3.1]nonane-6-carboxylate (15). Following the general procedure, ester **11** (68 mg, 0.17 mmol) in benzene (1.4 ml) was treated with AIBN (31 mg, 0.18 mmol) and 3.5 equiv of TTMSS (0.18 ml, 0.59 mmol), and the crude material was chromatographed (2% MeOH in CH_2Cl_2) to give **15** (34 mg, 68%) as a white solid: mp 123-124 °C (CH_2Cl_2); IR (KBr) 1731, 1638; ^1H NMR (500 MHz) 1.33 (tdd, J =13.5, 4 and 2 Hz, 1 H, H-8_{ax}), 1.61 (qd, J = 14 and 4 Hz, 1H, H-7_{ax}), 1.66 (dm, J = 13 Hz, 1H, H-9*S*), 1.80 (dm, J = 13 Hz, 2H, H-7_{eq} and H-8_{eq}), 1.87 (dm, J = 13 Hz, 1H, H-9*R*), 2.38 (dm, J =18 Hz, 1H, H-4_{eq}), 2.48 (dt, J =13.5 and 3.5 Hz, 1H, H-6_{ax}), 2.52-2.60 (m, 2H, H-4_{ax} and H-5_{eq}), 3.41 (br s, 1H, H-1_{eq}), 3.62 (s, 3H, OCH_3), 3.88 and 5.18 (2d, J = 15 Hz, 2H, CH_2Ph), 7.15-7.27 (m, 5H, ArH); ^{13}C NMR, Table 2. Anal. Calcd. for $C_{17}H_{21}NO_3.1/2H_2O$: C, 68.90; H, 7.48; N 4.73. Found: C, 69.26; H, 7.42; N, 4.70.

4-(*N*-Benzylchloroacetamido)-1-cyclohexenecarbonitrile (19a). To a solution of amine **8** (1.5 g, 7.1 mmol) in CH_2Cl_2 (3.2 ml) was added triethylamine (1 ml, 7.4 mmol). The mixture was cooled to 0 °C and a solution of chloroacetyl chloride (0.73 ml, 9.15 mmol) in CH_2Cl_2 (1.2 ml) was added dropwise. After 2 h of stirring at room temperature the reaction mixture was concentrated. The resultant residue was taken up with EtOAc and washed with saturated aqueous K_2CO_3 and brine. After evaporation of the dried extracts the residue was chromatographed (CH_2Cl_2) to afford, as an oil, chloroacetamide **19a** (1.7 g, 86%) as a 7:3 mixture (estimated by ^1H-NMR) of rotamers *Z* and *E*: IR (NaCl) 1654; ^1H NMR 1.85 (m, 2H), 2.38 (m, 4H), 4.00 (s, 1.4H, rotamer *Z*, CH_2Cl), 4.05 (m, 0.3H, rotamer *E*, H-4_{ax}), 4.20 (s, 0.6H, rotamer *E*, CH_2Cl), 4.48 (m, 0.7H, rotamer *Z*, H-4_{ax}), 4.57 (s, 2H, CH_2Ph), 6.51 (m, $W_{1/2}$ = 10 Hz, H-2), 7.19 (d, J = 7 Hz, 2H, ArH), 7.30-7.45 (m, 3H, ArH); ^{13}C NMRrotamer *Z* 25.2 (C-6), 27.1 (C-5), 29.0 (C-3), 41.9 (CH_2Cl), 48.0 (NCH_2), 50.7 (C-4), 112.0 (C-1), 118.8 (CN), 125.7, 128.0, 129.2, and 136.7 (Ar), 142.9 (C-2), 167.5 (CO); rotamer *E* 25.2 (C-6), 27.3 (C-5), 30.7 (C-3), 41.3 (CH_2Cl), 44.8 (NCH_2), 53.2 (C-4), 112.0 (C-1), 118.8 (CN), 126.6, 127.2, 128.6, and 136.7 (Ar), 142.2 (C-2), 167.5 (CO). HRMS calcd for $C_{16}H_{17}ClN_2O$ 288.1024, found 288.1029.

Methyl 4-(*N*-Benzylchloroacetamido)-1-cyclohexenecarboxylate (20a). Operating as above, from **9** (652 mg, 3.1 mmol), Et_3N (0.45 ml, 3.3 mmol), chloroacetyl chloride (0.31 ml, 4 mmol) and CH_2Cl_2 (1.4 ml) an oil was obtained, which after chromatography (CH_2Cl_2) gave chloroacetamide **20a** (852 mg, 96%) as a 6:4 mixture (estimate by ^1H-NMR) of rotamers *Z* and *E*: IR (NaCl) 1711, 1648; ^1H NMR 1.75 (qd, J = 12 and 5.5 Hz, 1H, H-5_{ax}), 1.8-6.24 (m, 5H), 3.71 (s, 3H, OCH_3), 3.97 (s, 1.2H, rotamer *Z*, CH_2Cl), 4.05 (m, 0.4H, rotamer *E*, H-4_{ax}), 4.20 (s, 0.8H, rotamer *E*, CH_2Cl), 4.58 (m, 0.6H, rotamer *Z*, H-4_{ax}), 4.58 (s, 2H, CH_2Ph), 6.85 (m, $W_{1/2}$ = 9 Hz, 1H, H-2), 7.21 (d, J = 7.5 Hz, 2H, ArH), 7.31 and 7.39 (2t, J = 7 Hz, 3H, ArH); ^{13}C NMR rotamer *Z* 24.4 (C-6), 25.7 (C-5), 28.8 (C-3), 42.0 (CH_2Cl), 47.4 (NCH_2), 51.2 (C-4), 51.6 (OCH_3), 125.5, 127.7, 129.0, and 138.0 (Ar), 130.0 (C-1), 137.2 (C-2), 167.0 and 167.4 (CO); rotamer *E* 24.7 (C-6), 27.5 (C-5), 30.5 (C-3), 41.4 (CH_2Cl), 44.7 (NCH_2), 51.6 (OCH_3), 54.1 (C-4), 126.5, 126.9, 128.4, and 138.0 (Ar), 130.0 (C-1), 136.5 (C-2), 167.0 (CO). HRMS calcd for $C_{17}H_{20}ClNO_3$ 321.1132, found 321.1145.

4-(*N*-Benzyliodoacetamido)-1-ciclohexenecarbonitrile (19b). To a solution of chloroacetamide **19a** (1 g, 3.1 mmol) in acetonitrile (50 ml) was added NaI (831 mg, 5.54 mmol). The reaction mixture was stirred at room temperature for 9 h, filtered and the filtrate evaporated to dryness. The obtained residue was dissolved in CH_2Cl_2 and washed with 0.1 M aqueous $Na_2S_2O_3$ solution. The organic phase was dried and evaporated to leave a residue which was purified by chromatography (CH_2Cl_2) providing **19b** (849 mg, 71%) as a 7:3 mixture (estimate by ^1H-NMR) of rotamers *Z* and *E*: yellow solid, mp 121-122 °C (EtOAc); IR (KBr) 2215, 1637; ^1H NMR 1.84-2.00 (m, 2H), 2.20-2.50 (m, 4H), 3.62 (s, 1.4H, rotamer *Z*, CH_2I), 3.85 (s, 0.6 H, rotamer *E*, CH_2I), 3,96 (m, 0.3H, rotamer E, H-4_{ax}), 4.52 (s, 2H, CH_2Ph), 4.50 (m, 0.7H, rotamer Z, H-4_{ax}), 6,52 (m, $W_{1/2}$ = 12 Hz, 1H, H-2), 7.20 (d, J = 7 Hz, 2H, ArH), 7.30 and 7.39 (2t, J = 7 Hz, 3H, ArH); ^{13}C NMR rotamer *Z* -2.0 (CH_2I), 24.8 (C-6), 26.9 (C-5), 28.6 (C-3), 48.7 (NCH_2), 50.1 (C-4), 111.9 (C-1), 118.7 (CN), 125.3, 127.8, 129.0, and

136.7 (Ar), 142.8 (C-2), 169.0 (CO); rotamer *E* -3.3 (CH_2I), 26.5 (C-6), 27.3 (C-5), 30.2 (C-3), 44.5 (NCH_2), 53.9 (C-4), 112.1 (C-1), 118.5 (CN), 126.3, 126.9, 128.5, and 138.2 (Ar), 142.2 (C-2), 168.1 (CO). Anal. Calcd for $C_{16}H_{15}IN_2O$: C, 50.54; H, 4.21; I, 33.38; N, 7.37. Found: C, 50.44; H, 4.56; I, 33.39; N, 7.01.

Methyl 4-(*N*-Benzyliodoacetamido)-1-cyclohexenecarboxylate (20b). Operating as above, from chloroacetamide **20a** (134 mg, 0.4 mmol), sodium iodide (102 mg, 0.67 mmol) and acetonitrile (6.7 ml) an oil was obtained, which after chromatography gave iodoacetamide **20b** (138 mg, 80%) as a 7:3 mixture (estimate by ^{1}H-NMR) of rotamers *Z* and *E*: IR (NaCl) 1712, 1643; ^{1}H NMR 1.70 (qd, J = 12 and 5 Hz, 1H, H-5_{ax}) 1.68-2.65 (m, 5H), 3.61 (s, 1.4H, rotamer Z, ICH_2), 3.71 (s, 2.1H, rotamer Z, OCH_3), 3.73 (s, 0.9 H, rotamer *E*, OCH_3), 3.86 (s, 0.6H, rotamer *E*, ICH_2), 3.95 (m, 0.3H, rotamer *E*, H-4_{ax}), 4.53 (s, 1.4 H, rotamer Z, CH_2Ph), 4.56 (s, 0.6H, rotamer E, CH_2Ph), 4.63 (m, 0.7H, rotamer Z, H-4_{ax}), 6.82 (m, $W_{1/2}$ = 10 Hz, 1H, H-2), 7.21 (d, J = 7.5 Hz, 2H, ArH), 7.30 and 7.39 (2t, J = 7 Hz, 3 H, ArH); ^{13}C NMR rotamer *Z* -1.7 (CH_2I), 24.3 (C-6), 25.4 (C-5), 28.4 (C-3), 48.2 (NCH_2), 50.7 (C-4), 51.5 (OCH_3), 125.3, 127.5, 128.9, and 138.5 (Ar), 129.6 (C-1), 136.5 (C-2), 166.9 (CO), 169.0 (NCO); rotamer *E* -3.2 (CH_2I), 24.7 (C-6), 27.1 (C-5), 30.1 (C-3), 44.5 (NCH_2), 51.6 (OCH_3), 54.9 (C-4), 126.4, 126.7, 128.3, and 138.5 (Ar), 129.7 (C-1), 137.1 (C-2), 168.0 (NCO). HRMS calcd for $C_{17}H_{20}INO_3$ 413.0488, found 413.0490.

Attempt of TTMSS radical cyclization of iodoacetamide 19b. A solution of α,β-unsaturated nitrile **19b** (200 mg, 0.5 mmol) in deoxygenated benzene (16 ml) was heated at reflux. Then, a mixture of TTMSS (0.2 ml, 0.6 mmol) in benzene (20 ml) was added dropwise at a rate of 4.1 ml/h by means of a syringe pump. After completion of addition the reaction mixture was kept at reflux overnight. After evaporation of the solvent, the residue was chromatographed (1% MeOH in CH_2Cl_2) to give, as an oil, **4-(*N*-benzylacetamido)-1-cyclohexenecarbonitrile (21**, 91mg, 68%) as a 7:3 mixture (estimated by ^{1}H-NMR) of *Z* and *E* rotamers: IR (NaCl) 2214, 1642; ^{1}H NMR 1.60-1.80 (m, 2H, H-5), 2.15-2.40 (m, 4 H), 2.04 (s, 2.1H, rotamer Z, CH_3), 2.21 (s, 0.9H, rotamer *E*, CH_3), 3.93 (m, 0.3H, rotamer *E*, H-4_{ax}), 4.44 (s, 1.4H, rotamer Z, CH_2Ph), 4.52 (s, 0.6H, rotamer *E*, CH_2Ph), 4.54 (m, 0.7H, rotamer Z, H-4_{ax}), 6.45 (m, $W_{1/2}$ = 10 Hz, H-2), 7.14 (d, J = 7.5 Hz, 2H, ArH), 7.24 and 7.32 (2t, J = 7.5 Hz, 3 H, ArH); ^{13}C NMR rotamer *Z* 22.5 (CH_3), 25.5 (C-6), 27.2 (C-5), 29.3 (C-3), 48.3 (NCH_2), 49.3 (C-4), 111.8 (C-1), 118.9 (CN), 125.7, 127.5, 128.5, and 137.5 (Ar), 143.3 (C-2), 171.7 (CO); rotamer *E* 22.0 (CH_3), 27.1 (C-6), 27.4 (C-5), 30.6 (C-3), 44.3 (NCH_2), 53.0 (C-4), 126.7, 126.9, 128.9, and 138.8 (Ar), 142.5 (C-2), 170.7 (NCO). HRMS calcd for $C_{16}H_{18}N_2O$ 254.1419, found 254.1417.

Radical cyclization of iodoacetamide 20b. Following the general procedure, α,β-unsaturated ester **20b** (138 mg, 0.33 mmol) in benzene (2.7 ml) was treated with TTMSS (0.11 ml, 0.36 mmol) and AIBN (23 mg, 0.14 mmol), and the crude material was chromatographed (1% MeOH in CH_2Cl_2). The first eluate gave azabicyclo **15** (5 mg, 5%). The second eluate gave **methyl 4-(*N*-benzylacetamido)-1-cyclohexenecarboxylate (22**, 65 mg, 68 %) as an oil, whose ^{1}H NMR spectrum showed the presence of two rotamers in a ratio *ca.* 7:3: IR (NaCl) 1713, 1646; ^{1}H NMR 1.69 (qd, J = 12 and 5.5 Hz, 1H, H-5_{ax}), 1.80 (m, 1H, H-5_{eq}), 2.07 (s, 2.1H, rotamer Z, CH_3), 2.14-2.62 (m, 4H), 2.26 (s, 0.9H, rotamer *E*, CH_3), 3.70 (s, 2.1 H, rotamer Z, OCH_3), 3.72 (s, 0.9 H, rotamer *E*, OCH_3), 3.95 (m, 0.3H, rotamer *E*, H-4_{ax}), 4.50 (s, 1.4 H, rotamer Z, CH_2Ph), 4.59 (s, 0.6 H, rotamer E, CH_2Ph), 4.70 (m, 0.7H, rotamer Z, H-4_{ax}), 6.85 (m, $W_{1/2}$ = 10 Hz, H-2), 7.22 (d, J = 7 Hz, 2H, ArH), 7.28 and 7.36 (2 t, J = 7 Hz, 3H, ArH); ^{13}C NMR rotamer *Z* 22.5 (CH_3), 24.6 (C-6), 26.1 (C-5), 29.2 (C-3), 47.9 (NCH_2), 49.9 (C-4), 51.5 (OCH_3), 125.7, 127.3, 128.8, and 138.0 (Ar), 129.6 (C-1), 137.7 (C-2), 167.2 (CO), 171.6 (NCO); rotamer *E* 22.0 (CH_3), 24.9 (C-6), 27.6 (C-5), 30.5 (C-3), 44.3 (NCH_2), 51.7 (C-4), 54.1 (OCH_3), 126.7, 126.8, 128.3, and 139.2 (Ar), 129.8 (C-1), 136.9 (C-2), 167.0 (CO), 170.7 (NCO). Anal. Calcd for $C_{17}H_{21}NO_3$: C, 71.04; H, 7.37; N, 4.88. Found: C, 70.96; H, 7.39; N, 4.98.

ACKNOWLEDGMENT

Support for this research was provided by DGICYT (Spain) through Grant PB94-0858. Thanks are also due to the "Comissionat per a Universitats i Recerca" (CIRIT, Catalonia) for a fellowship to one of us (C. E.).

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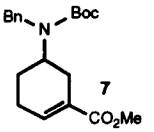

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(*Received in UK* 23 *September* 1996; *revised* 12 *November* 1996; *accepted* 14 *November* 1996)