A RADICAL ROUTE TO MORPHANS. SYNTHESIS AND SPECTROSCOPIC DATA OF THE 2-AZABICYCLO[3.3.1]NONANE

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Abstract - The synthesis of 1-benzyl-2-azabicyclo[3.3.1]nonan-3-one (**8**) through radical cyclization, involving an intramolecular addition of a carbamoyldichloromethyl radical upon an alkene, is described. Conversion of **8** to the morphan itself, and the spectroscopic analysis of some derivatives of this series are reported.

INTRODUCTION

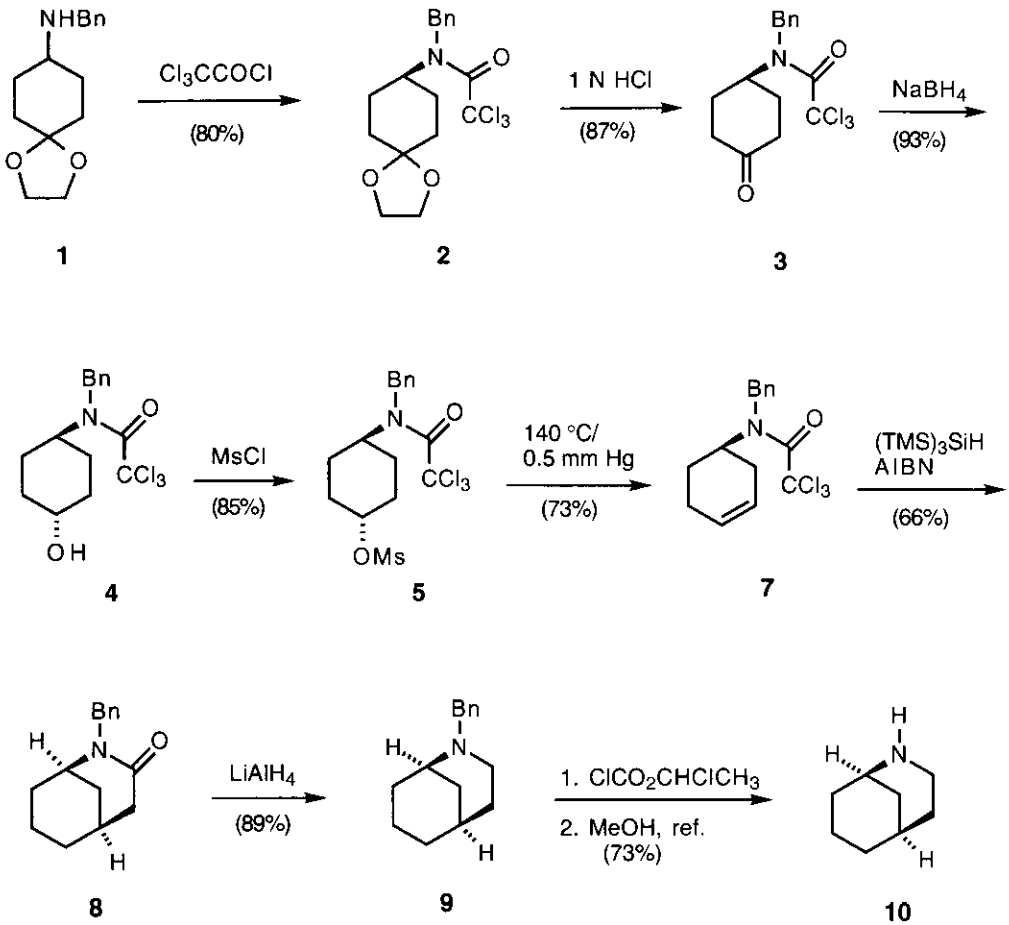
The 2-azabicyclo[3.3.1]nonane (morphan)[1] framework constitutes a structural subunit of several types of alkaloids, as well as other recently isolated natural products, with significant pharmacological activities.[2] As a consequence, methods inducing the ring closure of this heterocyclic system are of great interest for the development of synthetic approaches to compounds that embody this nucleus.[3]

We have recently described a new synthetic entry to 2-azabicyclo[3.3.1]nonanes by means of radical cyclization of a trichloroacetamide group upon alkenes possessing withdrawing groups such as cyano or ester.[4,5] Now we report that morphan compounds can also be achieved using the cyclization of 1-(carbamoyl)dichloromethyl radicals when acting upon an alkene lacking a deactivating group.[6] Trichloroacetamides have been used to prepare 5-membered lactams by means of a radical cyclization upon simple alkenes, either by the hydride method[7] or by metal-mediated processes,[8] but there are not any precedents for the preparation of 6-membered rings using a non-activated alkene as acceptor.[9]

The only two syntheses of the 2-azabicyclo[3.3.1]nonane itself were reported in the 50's by Cronyn[10a] and Ginsburg[10b] and so no NMR data are available. In this paper we report a new synthesis of morphan and also the conformational analysis of this azabicyclic system taking into account the NMR data obtained from 2D NMR experiments.

RESULTS

The preparation of trichloroacetamide (**5**), the required substrate for the study of the radical cyclization, was achieved starting from amino acetal (**1**).[4] Trichloroacetylation of **1** and further chemo-



Scheme 1. Synthesis of 2-azabicyclo[3.3.1]nonane derivatives

selective hydrolysis of **2** gives ketone (**3**) in 70% overall yield. A slightly lower yield was obtained when we effected the two-step sequence in reverse involving an initial hydrolysis followed by the formation of the amide bond. The transformation of **3** to the desired alkene (**7**)[11] was carried out by means of $NaBH_4$ reduction, followed by dehydration of the alcohol (**4**)[12] through mesylate (**5**), which was heated at reduced pressure to undergo a pyrolytic β-elimination in a *Ei* process.[13]

The radical cyclization of **7** was carried out with tris(trimethylsilyl)silane (TTMSS) as the radical mediator. When trichloroacetamide (**7**) was treated with TTMSS (3.3 equiv) and AIBN in refluxing benzene (0.12 M) over a period of 3 h, the expected cyclization to the 2-azabicyclo[3.3.1]nonane ring system took place with a concomitant reduction of the two additional chloro atoms (66% yield). The carboradical cyclization of 4-(trichloroacetamido)cyclohexene (**7**) to give **8** constitutes a new example of the scarce 6-*exo*-*trig* cyclizations from 3-aza-6-heptenyl radicals. Reduction of lactam (**8**) with $LiAlH_4$ gives the *N*-benzylmorphan (**9**) which was debenzylated by means of treatment with α-chloroethyl chloroformate followed by methanolysis of the carbamate intermediate to give the morphan itself (**10**).[10]

CONFORMATIONAL ANALYSIS

The potential conformational mobility of the morphan rings makes it an interesting system to study.[14] As occurs in the carbocyclic analogue bicyclo[3.3.1]nonane and related azabicyclic compounds,[15] the *endo* 3,7-hydrogen-hydrogen transannular interaction appears in morphan (**10**) in the chair-chair conformation. If the cyclohexane ring of **10** was in a boat conformation, the equatorial protons at C-6 and C-8 would eclipse or nearly eclipse the protons of the adjacent ring junction C-atoms. This relationship would be expected to result in large values of $^3J_{HH}$, a situation clearly not consistent with the observed multiplicities of either ring junction proton in any of the compounds of our series (**8**-**10**). From the morphan (**10**), the most significant NOESY correlation appeared between the axially located protons at C-3 (δ 3.36) and C-7 (δ 1.92), which agrees with the suggested chair-chair conformation, as depicted in Figure 1. The ^{1}H NMR data corroborates this feature, the aforementioned protons of both **10** and **9** appearing relatively downfield due to their steric compression. In compound (**10**), the chemical shift of H-3_{ax}, the most deshielded aliphatic proton, suggests that it is not antiperiplanar regarding the lone pair of the nitrogen atom, which consequently adopts an equatorial disposition.[16]

The most significant data in the ^{13}C NMR spectra for **9** and **10** corroborate that these compounds have the same ring conformation. For example, the difference in the chemical shifts of *C*-8 (δ 25.6 for **9** and δ 29.7 for **10**) arises from the disappearance of the 1,3-diaxial relationship, present in a chair-chair conformation, between the *N*-benzyl group and the axial hydrogen at C-8, which explains the downfield shift observed for this methylene carbon in **10**.

Also noteworthy is the anisotropic influence of carbonyl amide at C-3 upon the chemical shift of *C*-7 in azabicyclo **8**. The proximity of the 3 *endo* substituent and the carbon 7 induces a large change in the chemical shift of that carbon. With respect to a hydrogen atom, the effect of a carbonyl oxygen atom at carbon 3 is a displacement of carbon 7 resonance *ca.* 5 ppm upfield[17] (compare **8** with **9**). The same effect was observed (see Figure 1) when the carbonyl group is located at C-7 with respect to the methylene at C-3.[18]

In summary, irrespectively of the lactam, tertiary or secondary amine character of the nitrogen atom, azabicyclo compounds (**8**, **9** and **10**) show the chair-chair as the preferred conformation.

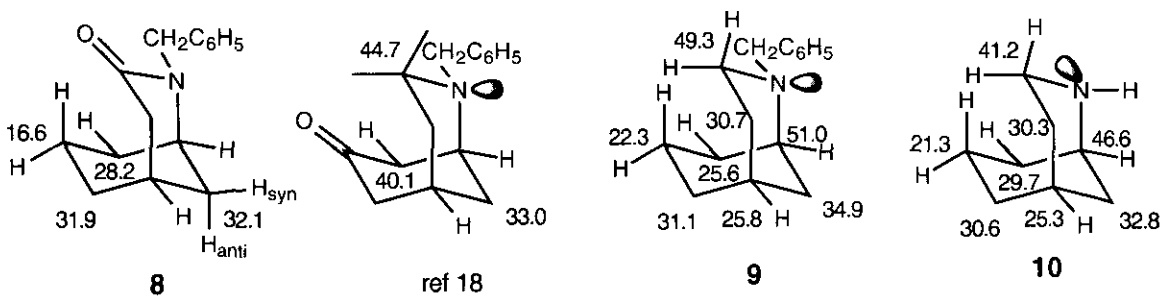


Figure 1. Selected ^{13}C NMR data of 8-10 and their preferred conformations

EXPERIMENTAL

Unless otherwise noted, ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ solution at 300 and 75 MHz respectively, using TMS as an internal standard. In addition, 2D NMR COSY and HMQC experiments were performed on a Varian XL-500 instrument. Chemical shifts are reported in ppm downfield (δ) from TMS. IR spectra were recorded on a Nicolet 205 FT infrared spectrophotometer and the only noteworthy absorptions are listed (cm^{-1}). MS spectra were determined on a Hewlett-Packard 5988 A mass spectrometer or an Autospec-VG (HRMS). TLC was performed on SiO_2 (silica gel 60 F_{254}, Merck), and the spots were located by UV light and a 1% $KMnO_4$ solution or with iodoplatinate reagent. Chromatography refers to flash chromatography and was carried out on SiO_2 (silica gel 60, SDS, 230-400 mesh ASTM). All reactions were carried out under an argon or nitrogen atmosphere. Solvents were dried and purified prior to use when deemed necessary. 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 and HRMS were performed by the Centro de Investigación y Desarrollo (CSIC), Barcelona.

4-(*N*-Benzyltrichloroacetamido)-1-cyclohexanone (3). Method A: To a solution of **1** (4 g, 16.2 mmol) in CH_2Cl_2 (48 mL) were added pyridine (2.75 mL, 34 mmol) and, slowly, a solution of trichloroacetyl chloride (2.7 mL, 24.3 mmol) in CH_2Cl_2 (12 mL). After stirring overnight at rt, 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, concentrated, and chromatographed (CH_2Cl_2) to give **4-(*N*-benzyltrichloroacetamido)-1-cyclohexanone ethylene acetal** (**2**, 5.08 g, 80%) as a white solid: mp 139-143 °C (*i*-PrOH); IR (KBr) 1677; ^1H NMR 1.5-2.0 (m, 8H), 3.8 (s, 4H, OCH_2), 4.55 (m, 1H, H-4_{ax}), 4.60 (s, 2H, CH_2Ar), 7.15-7.35 (m, 5H, ArH); ^{13}C NMR 27.3 (C-3 and C-5), 33.6 (C-2 and C-6), 47.6 (CH_2Ar), 57.8 (C-4), 64.1 and 64.3 (OCH_2), 93.5 (CCl_3), 106.9 (C-1), 126.0, 126.7, and 128.3 (Ar), 137.2 (C-*ipso*), 160.4 (CO). *Anal.* Calcd for $C_{17}H_{20}NO_3Cl_3$: C, 52.17; H, 5.15; N, 3.58; Cl, 26.83. Found: C, 52.05; H, 5.17; N, 3.59; Cl, 27.06.

A solution of the above acetal (5 g, 12.8 mmol) in THF (20 mL) and 1 N aqueous HCl (20 mL) was heated at reflux temperature for 15 h. The THF was rotatory evaporated and the mixture was extracted with CH_2Cl_2. The organic extracts were washed with brine, dried and concentrated to give a solid, which was recrystallized from ether to give **3** (3.9 g, 87%) as a white solid: mp 109-113 °C (Et_2O); IR (KBr) 1717, 1661; ^1H NMR 1.85-2.55 (m, 8H), 4.63 (br s, 2H, CH_2Ar), 5.00 (m, 1H, H-4_{ax}), 7.10-7.45 (m, 5H, ArH); ^{13}C NMR 29.4 (C-3 and C-5), 39.5 (C-2 and C-6), 47.7 (CH_2Ar), 57.0 (C-4), 93.5 (CCl_3), 126.1, 127.2, and 128.6 (Ar), 136.9 (C-*ipso*), 160.5 (NCO), 207.8 (CO). *Anal.* Calcd for $C_{15}H_{16}NO_2Cl_3$: C, 51.67; H, 4.63; N, 4.02. Found: C, 51.52; H, 4.73; N, 3.96.

Method B: Acetal (**1**) was hydrolyzed on a 0.2 mol scale in 88% yield, as we have previously described.[4] To a solution of the resulting ketone (35 g, 172 mmol) in CH_2Cl_2 (490 mL) were added pyridine (29 mL, 360 mmol) and a solution of trichloroacetyl chloride (0.84 mL, 7.52 mmol) in CH_2Cl_2 (2 mL). Operating as above, amide (**3**, 36 g, 60%) was obtained. Operating on a 10 mmol scale the yield increased to 78%.

***trans*-4-(*N*-Benzyltrichloroacetamido)-1-cyclohexanol (4).** To a solution of ketone (**3**) (5.4 g, 15.5 mmol) in MeOH (324 mL) cooled to -20 °C was added $NaBH_4$ (876 mg, 23.15 mmol) and the reaction mixture was stirred at this temperature for 5 h. Then water (10 mL) was added, MeOH was rotatory evaporated, and the aqueous phase was extracted with EtOAc. The organic extracts were washed with brine, dried and concentrated to give a solid, which was chromatographed (1:99 MeOH-CH_2Cl_2) to give **4** (5 g, 93%) as a white solid: mp 70-71 °C (Et_2O); IR (KBr) 3400, 1656; ^{1}H NMR 1.30-2.10 (m, 8H), 3.53 (m, 1H, H-4_{ax}), 4.50 (m, 1H, H-1_{ax}), 4.58 (s, 2H, CH_2Ar), 7.10-7.40 (m, 5H, ArH); ^{13}C NMR 28.0 (C-3 and C-5), 33.8 (C-2 and C-6), 47.5 (CH_2Ar), 58.2 (C-4), 68.7 (C-1), 93.3 (CCl_3), 125.8, 126.7, and 128.3 (Ar), 136.9 (C-*ipso*), 160.4 (CO). *Anal.* Calcd for $C_{15}H_{18}NO_2Cl_3$: C, 51.38; H, 5.17; N, 3.99; Cl, 30.33. Found: C, 51.64; H, 5.24; N, 4.00; Cl, 29.99.

4-(*N*-Benzyltrichloroacetamido)-1-cyclohexyl methanesulfonate (5). To a solution of alcohol (**4**) (2.5 g, 7.13 mmol) in CH_2Cl_2 (136 mL) cooled to -10 °C were added Et_3N (2 mL, 14.34 mmol), methanesulfonyl chloride (1.36 mL, 17.5 mmol), and DMAP (496 mg, 4.05 mmol). After stirring the reaction mixture at this temperature for 3 h, water was added and the organic phase was washed with 1 N aqueous HCl, saturated aqueous $NaHCO_3$, and water. Concentration of the dried organic extracts afforded a solid which was recrystallized from 1:1 Et_2O/CH_2Cl_2 to give mesylate (**5**) (2.6 g, 85%) as a white solid: mp 148-149 °C; IR (KBr) 1672; ^{1}H NMR 1.57-2.30 (m, 8H), 2.99 (s, 3H, CH_3), 4.40-4.70 (m, 3H, CH_2Ar and H-1_{ax}), 7.10-7.40 (m, 5H, ArH); ^{13}C NMR 28.1 (C-3 and C-5), 31.6 (C-2 and C-6), 38.6 (CH_3), 47.6 (CH_2Ar), 57.4 (C-4), 78.6 (C-1), 93.5 (CCl_3), 126.1, 127.1, and 128.6 (Ar), 137.0 (C-*ipso*), 160.5 (CO). *Anal.* Calcd for $C_{16}H_{20}NO_4Cl_3S$: C, 44.82; H, 4.70; N, 3.27; Cl, 24.81. Found: C, 44.61; H, 4.75; N, 3.25; Cl, 24.98.

4-(*N*-Benzyltrichloroacetamido)-1-cyclohexene (7). Mesylate (**5**) (1 g, 2.33 mmol)) was heated at 0.5 mm Hg and at 145 °C it began to liquefy. These conditions were maintained until all the solid had become liquid (*ca.* 30 min). The obtained violet oil was dissolved in CH_2Cl_2 and washed with 2 N aqueous NaOH. Concentration of the dried extracts followed by chromatography (CH_2Cl_2) gave **7** as a transparent oil (560 mg, 73%; 87% based on recovered starting material) along with 168 mg of unreacted **5**. For **7**: IR (KBr) 1673; ^{1}H NMR 1.70-2.40 (m, 6H), 4.54 and 4.70 (2 d, J = 15.5 Hz, 2H, CH_2Ar), 4.78 (m, 1H, H-4_{ax}), 5.50-5.70 (m, 2H, H-1 and H-2), 7.15-7.40 (m, 5H, ArH); ^{13}C NMR 25.4 (C-6), 27.1 (C-5), 29.2 (C-3), 47.7 (CH_2Ar), 55.9 (C-4), 93.6 (CCl_3), 124.5, 126.1, 126.6, 126.9, and 128.5 (C-1, C-2, and Ar), 137.4 (C-*ipso*), 160.7 (CO). HRMS Calcd for $C_{15}H_{16}NOCl_3$ 331.0306, found 331.0297.

2-Benzyl-2-azabicyclo[3.3.1]nonan-3-one (8). To a boiling solution of **7** (518 mg, 1.56 mmol) and AIBN (271 mg, 1.65 mmol) in benzene (13 mL) was added TTMSS (1.68 mL, 5.46 mmol) dropwise, and the mixture was heated under reflux for 3 h. After the solvent had been evaporated off, the residue was chromatographed (3:97 MeOH-CH_2Cl_2) to give **8** (237 mg, 66%) as a yellow oil: IR (KBr) 1637; ^{1}H NMR (500 MHz, COSY) 1.34 (ddd, J = 13.5, 8.5, and 2 Hz, 1H, H-8_{ax}), 1.48-1.54 (m, 2H, H-7), 1.58 (m, 1H, H-6_{ax}), 1.64 (dm partially masked, J = 12 Hz, 1H, H-6_{eq}), 1.67 (ddd, J = 13, 5, 3 Hz, 1H, H-9_{anti}), 1.76

(dm, J = 13 Hz, 1H, H-8_{eq}), 1.79 (dm, J = 13 Hz, 1H, H-9_{syn}), 2.21 (m, $W_{1/2}$ = 15 Hz, 1H, H-5_{eq}), 2.34 (dt, J = 18.5, 1 Hz, 1H, H-4_{eq}), 2.71 (dd, J = 18.5, 7 Hz, 1H, H-4_{ax}), 3.44 (m, $W_{1/2}$ = 9 Hz, 1H, H-1_{eq}), 3.85 and 5.30 (2 d, J = 15 Hz, 2H, CH_2Ar), 7.21-7.31 (m, 5H, ArH); ^{13}C NMR (HMQC) 16.6 (C-7), 27.0 (C-5), 28.2 (C-8), 31.9 (C-6), 32.1 (C-9), 37.7 (C-4), 48.0 (CH_2Ar), 51.2 (C-1), 127.1, 127.7, and 128.4 (Ar), 137.7 (C-*ipso*), 171.4 (CO). HRMS Calcd for $C_{15}H_{19}NO$ 229.1466, found 229.1468. *Anal.* Calcd for $C_{15}H_{19}NO.2/3\ H_2O$: C, 74.64; H, 8.49, N, 5.80. Found: C, 74.30; H, 8.21; N, 6.01.

2-Benzyl-2-azabicyclo[3.3.1]nonane (9). To a suspension of $LiAlH_4$ (31 mg, 0.81 mmol) in THF (1 mL) was added **8** (63 mg, 0.27 mmol) in THF (1 mL), and the reaction mixture was stirred for 24 h at rt. Water (2 mL) was added, the resulting suspension was filtered through a short pad of Celite, and the filtrate extracted with Et_2O and concentrated. The residue was dissolved in EtOAc and extracted with 1 N aqueous HCl. The aqueous phase was neutralized with 2 N aqueous NaOH and extracted with EtOAc. Concentration of the dried organic extracts gave **9** (52 mg, 89%) as a yellow oil: IR (NaCl) 2925; ^1H NMR (500 MHz, COSY) 1.32 (dddd, J = 14, 13, 7, 3.5 Hz, 1H, H-8_{ax}), 1.54 (ddd, J = 12, 6, 3.5 Hz, 1H, H-9_{anti}), 1.57 (m, 1H, H-7), 1.62 (ddt, J = 13.5, 7, 2 Hz, 1H, H-4_{eq}), 1.66-1.71 (m, 2H, H-6), 1.76-1.85 (m, 2H, H-9_{syn} and H-7), 1.90 (m, $W_{1/2}$ = 12 Hz, 1H, H-5_{eq}), 1.98 (tt, J = 12.5, 6 Hz, 1H, H-4_{ax}), 2.11 (dm, J = 14.5 Hz, 1H, H-8_{eq}), 2.71 (m, 1H, H-3_{eq}), 2.80 (m, $W_{1/2}$ = 9 Hz, 1H, H-1_{eq}), 2.86 (td, J = 12, 5 Hz, 1H, H-3_{ax}), 3.62 and 3.70 (2 d, J = 13.5 Hz, 2H, CH_2Ar), 7.18-7.36 (m, 5H, ArH); ^{13}C NMR (HMQC) 22.3 (C-7), 25.6 (C-8), 25.8 (C-5), 30.7 (C-4), 31.1 (C-6), 34.9 (C-9), 49.3 (C-3), 51.0 (C-1), 60.5 (CH_2Ar), 126.6, 128.1, and 128.8 (Ar), 138.8 (C-*ipso*). HRMS Calcd for $C_{15}H_{21}N$ 215.1674, found 215.1665.

A similar result was obtained operating on a 1 mmol scale at reflux temperature for 2 h.

2-Azabicyclo[3.3.1]nonane (10). To a solution of **9** (30 mg, 0.14 mmol) in 1,2-dichloroethane (3 mL) was added 1-chloroethyl chloroformate (0.04 mL, 0.4 mmol) and the reaction mixture was heated at reflux for 3 h. The reaction mixture was concentrated, MeOH (2 mL) was added, and heated at reflux for 1 h to give **10.HCl** (17 mg, 73%) as a solid: IR (NaCl) 3416; ^1H NMR (500 MHz, COSY) 1.55 (m, 1H, H-9_{anti}), 1.65-1.74 (m, 6H, H-4_{ax}, H-6, H-7 and H-8_{ax}), 1.98 (br s, 1H, H-5_{eq}), 2.12 (m, 2H, H-4_{eq} and H-9_{syn}), 2.28 (m, 1H, H-8_{eq}), 3.20 (m, 1H, H-3_{eq}), 3.36 (m, 1H, H-3_{ax}), 3.50 (br s, 1H, H-1); ^{13}C NMR (HMQC) 20.2 (C-7), 23.7 (C-5), 26.6 (C-8), 27.1 (C-4), 29.6 (C-6), 30.1 (C-9), 39.8 (C-3), 47.0 (C-1).

Morphan (**10.HCl**) was dissolved in CH_2Cl_2 and washed with saturated aqueous Na_2CO_3 solution. After drying and concentration, free amine base (**10**) was isolated. It can be purified by chromatography (Al_2O_3, 5:95 MeOH-CH_2Cl_2). ^1H NMR (500 MHz, COSY) 1.58 (ddd, J = 13, 2.5, 2.5, 1H, 9-H_{anti}), 1.69 (m, 3H, H-4, H-7 and H-8), 1.74 (m, 2H, H-6), 1.92 (m, 2H, H-7 and H-9_{syn}), 2.00 (m, 2H, H-5 and H-8), 2.04 (m, 1H, H-4), 3.04 (ddd, J = 12.5, 5.5, 1.5, 1H, H-3_{eq}), 3.33 (br s, 1H, H-1), 3.39 (td, J = 12.5, 5.5, 1H, H-3_{ax}). ^{13}C NMR (HMQC) 21.3 (C-7), 25.3 (C-5), 29.7 (C-8), 30.3 (C-4), 30.6 (C-6), 32.8 (C-9), 41.2 (C-3), 46.6 (C-1).

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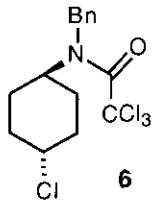
11. Trichloroacetamide (**7**) was also available by trichloroacetylation (80%) of *N*-benzyl-*N*-(3-cyclohexenyl)amine, previously described by us: J. Quirante, C. Escolano, and J. Bonjoch, *Synlett*, 1997, 179.
12. Attempts to dehydrate **4** ($POCl_3$, pyridine, benzene, rt) gave chloride (**6**) as the major compound (60%), whereas alkene (**7**) was formed in only 21% yield. Chloride (**6**): IR (KBr) 1673; ^1H NMR

(200 MHz) 1.50-2.35 (m, 8 H), 4.15-4.60 (m, 2 H, H-1_{eq} and H-4_{ax}), 4.66 (s, 2 H, CH_2Ar), 7.10-7.40 (m, 5 H, ArH); ^{13}C NMR 24.1 (C-3 and C-5), 33.0 (C-2 and C-6), 48.0 (CH_2Ar), 57.3 (C-4), 58.1 (C-1), 93.6 (CCl_3), 126.3, 127.0, and 128.5 (Ar), 137.4 (C-*ipso*), 160.5 (CO). *Anal.* Calcd for $C_{15}H_{16}NOCl_3$: C, 48.81; H, 4.64; N, 3.79; Cl, 38.42. Found: C, 49.08; H, 4.66; N, 3.81; Cl, 38.42.



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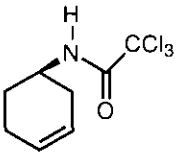
13. The pyrolytic process requires careful experimental conditions in order to avoid additional debenzylation of the alkene formed. This latter process can take place in *N*-benzylamides in the presence of methanesulfonic acid [B. Loev, M. A. Haas, and F. Dowalo, *Chem. Ind.* (*London*), 1968, 973], which in our case was generated i*n situ* from **5** in the β-elimination reaction.
Thus, working at temperatures higher than 150 °C at 0.5 mm Hg, after the workup, trichloroacetamide (**11**) was isolated as the major product. ^1H NMR 1.68-1.83 (m, 1H), 1.86-2.09 (m, 2H), 2.12-2.24 (m, 2H), 2.49 (dm, J = 17, 1H, H-3), 4.13 (m, 1H, H-4), 5.64 and 5.76 (2 dddd. J = 10, 3.6, 1.9, 1.7, 1H each. H-1 and H-2), 6.68 (br s, 1H, NH); ^{13}C NMR: 22.9 (C-6), 26.8 (C-5), 30.6 (C-3), 46.7 (C-4), 92.7 (CCl_3), 123.5 and 127.1 (C-1 and C-2), 161.1 (CO)



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