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Synthesis of enantiopure 2-azabicyclo[3.3.1]nonanes by a radical ring closure

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Abstract

The first synthesis of enantiomerically pure 2-azabicyclo[3.3.1]nonanes by an intramolecular radical reaction of the trichloroacetamido group bearing an (*S*)-*N*-1-phenylethyl substituent with the silyl enol ether moiety in compounds **7** is described. The procedure allows the two enantiomers of the 2-azabicyclo[3.3.1]nonane-3,6-dione, **3** and *ent*-**3**, to be prepared separately. β-Lactam **8** and normorphan **9** are also formed from **7** through an initial radical translocation process in the cyclization step. © 1999 Elsevier Science Ltd. All rights reserved.

1. Introduction

We have recently reported the synthesis of 2-azabicyclo[3.3.1]nonanes by radical cyclization of 1-(carbamoyl)dichloromethyl radicals with simple,[1] as well as electron poor[2] or electron rich alkenes.[3] As part of our continuing interest in radical cyclizations leading to morphan compounds,[4–8] we have initiated a study of the synthesis of enantiopure 2-azabicyclo[3.3.1]nonanes, for which there is no precedent in the literature.[9]

In this paper we describe the application of our procedure for the cyclization of trichloroacetamides with silyl enol ethers, reported in the racemic series (**I** → *rac*-**II**),[3] using a trichloroacetamide carrying the *N*-[(*S*)-1-phenylethyl] substituent to obtain a diastereomeric mixture of morphans **1** and **2** (Scheme 1). The aim of this work was the preparation of two enantiomers of 2-azabicyclo[3.3.1]nonane-3,6-dione (**3** and *ent*-**3**) by a synthetic route involving diastereomeric precursors that could be easily separated and thus allow the determination of their absolute configuration by NMR techniques, taking advantage of the chiral substituent with a known configuration upon the nitrogen atom. These two enantiomers, **3** and *ent*-**3**, could be useful as models in polarimetry determination in other asymmetric synthesis of morphans. Unexpectedly, studying the course of radical cyclization became a second goal because it diverges from that observed in the racemic series, as commented on below.

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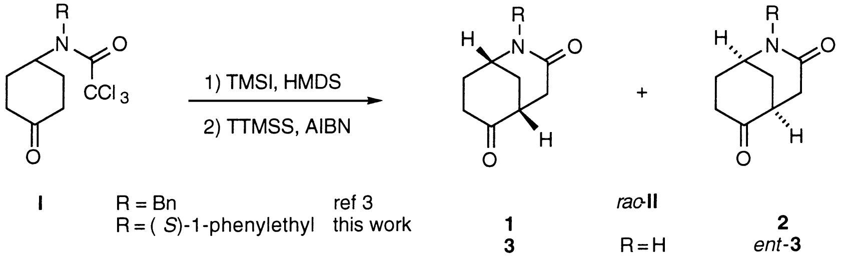
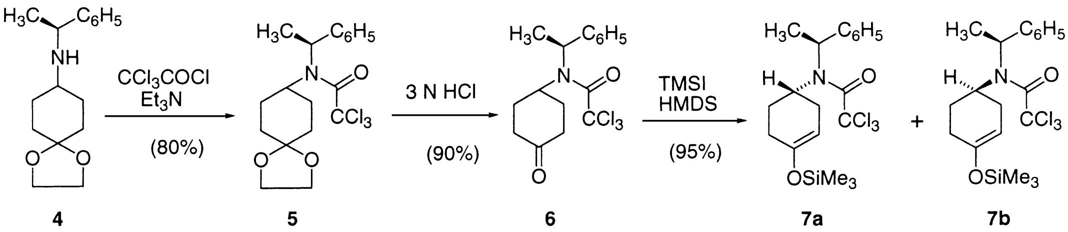


Scheme 1.

2. Results and discussion

2.1. Radical cyclization of trichloroacetamides **7** by the hydride method

The preparation of enantiopure trimethylsilylenol ethers **7** was carried out following the same reaction sequence we had previously performed for the preparation of the racemic *N*-benzyl analogue **I**.[3] Reductive amination of 1,4-cyclohexanedione monoethylene acetal with (*S*)-1-phenylethylamine (i, molecular sieves; ii, $NaBH_4$) gave **4** in excellent yield. Formation of the trichloroacetamide **5** requires more vigorous conditions (CH_2Cl_2, reflux) than those used in the benzyl series. Hydrolysis of the acetal in **5** (3N HCl, reflux), followed by treatment of the resulting ketone **6** with HMDS and TMSI afforded a non-separated mixture of the two diastereomers **7a** and **7b** in almost quantitative yield (Scheme 2).

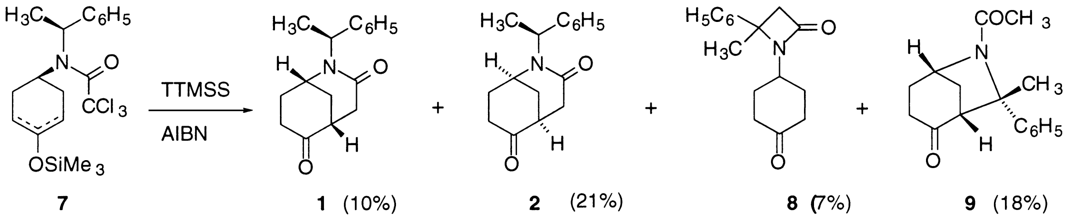


Scheme 2.

Trimethylsilylenol ethers **7a** and **7b** were obtained in an equimolecular ratio (determined by ^1H NMR) as the chiral inductor was too far from the two diastereotopic methylene groups to the carbonyl group to promote an enantioselective discrimination. The NMR analysis of trichloroacetamides **7** showed that each diastereomer appears with a different preferred conformation around the amide bond.[10] We assigned the structure **7a** to the compound with an *E* preferred conformation and the structure **7b** to the compound with a *Z* preferred conformation, taking into account their behaviour in the following cyclization step.

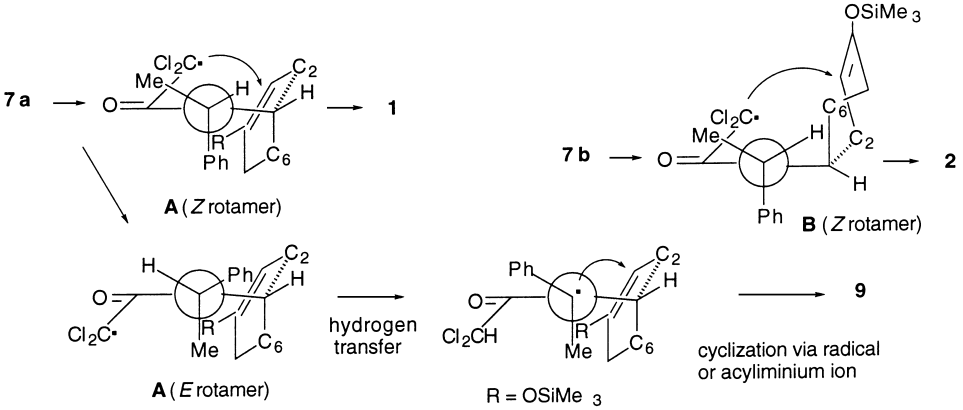
Surprisingly, when we submitted the trimethylsilylenol ether mixture **7a** and **7b** to the same reaction conditions described for cyclization of the *N*-benzyl analogue **I** (TTMSS 3.5 equiv., AIBN 1 equiv. in benzene, reflux 3 h), four compounds were isolated after careful chromatographic separation of the reaction mixture. Together with the expected diastereomers **1** and **2** in 10% and 21% yield, respectively, the β-lactam **8** (7%) and normorphan **9** (18%) were also isolated (Scheme 3).

One possible explanation for the observed different course in the radical cyclization of **7a** and **7b** is based on the consideration of the Felkin–Anh model for the radical intermediates (Scheme 4). The two Felkin–Anh conformers **A** and **B**, where the N–C bond of the amide is regarded as a double bond, can be considered for the radical intermediates generated from **7a** and **7b**. In conformer **A** steric repulsion between the phenyl group and the cyclohexane backbone becomes evident. We assumed, therefore, that the cyclization might proceed more quickly by way of the sterically favoured radical intermediate **B**.



Scheme 3.

Intermediate **A**, meanwhile, suffers preferentially competitive pathways leading to **8** and **9**. Additionally, as we have noted, **7a** (the precursor of **A**) has an *E* conformation around the amide bond which is unfavourable for the cyclization purpose.[11]



Scheme 4. Reaction pathway of radicals derived from **7a** and **7b**

Isolation of β-lactam **8** and normorphan **9** could be explained on the basis of a radical translocation from the initially formed 1-(carbamoyl)dichloromethyl radical to a 1-amido-1-phenylethyl radical, which directly or indirectly gives rise to these two products. The mechanism of the reaction is currently under study in our laboratory. Interestingly, normorphan **9** is an enantioenriched product (see below) even though the stereogenic centre at the benzylic position had been converted into a radical intermediate during its formation. This fact implies that **9** arises preferentially from one of the silyl enol ethers, in fact from **7a**. The formation of **9** could be derived from an oxidation[12] of the translocated amidoyl radical to an acyliminium ion which can undergo the cyclization upon the silyl enol ether group. We suggest that **7a** evolves preferentially by this pathway, not only because the transition state reflected in Scheme 4 leading to **1** is sterically demanding but also because its *E* rotamer evolves easier by an initial hydrogen transfer. On the other hand, β-lactam **8** is a quasi-racemic compound considering the NMR analysis of its acetal with a chiral diol (see below). A review of processes involving *N*-(1-phenylethyl)carbamoylmethyl radicals,[13,14] which lacks two additional chloro atoms present in our initial radical species from **7**, did not show any by-product related to those isolated by us.

When we used experimental conditions for the radical cyclization different to those described above, the results did not improve. The cyclization of trichloroacetamides **7a** and **7b** at higher temperatures (TTMSS 3.5 equiv., AIBN 1 equiv. in refluxing toluene) gave, along with normorphan **9** (8%), a separable 1:2 mixture of the monochlorinated bicyclo ketones **10a** and **10b** in 33% yield (Fig. 1).

These two compounds, upon reduction with Zn/NH_4Cl afforded the previously obtained ketones **1** and **2**. On the other hand, when the reaction was carried out with 4.5 equiv. of TTMSS (AIBN 1 equiv. in refluxing benzene) the bicyclic alcohols **11a** and **11b** were obtained in addition to compounds **1**, **2**, **8** and

10a **10b** **11a** R = H **12a** R = Cl **11b** **12b**

Figure 1.

9. Using Bu_3SnH instead of TTMSS the resulting crude material showed even more complexity. After laborious column chromatography, monochloro bicyclo alcohols **12a** and **12b** in a 2:3 ratio and 26% combined yield were isolated. These compounds were converted into the bicyclic alcohols **11a** and **11b** by reduction with Zn/NH_4Cl.

We noted that in all cases, compounds of series **a** (configuration 1*S*) were formed in lower yield than those of series **b** (configuration 1*R*) as was observed for compound **1** with respect to **2** (Scheme 5).

3 ***ent*-3**

Scheme 5.

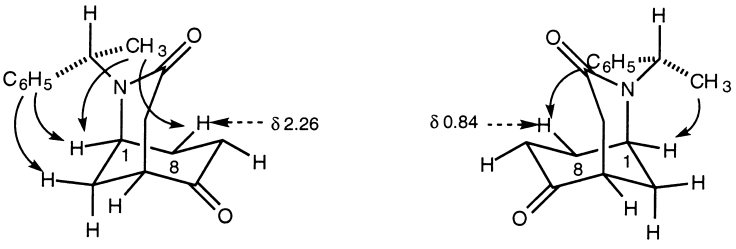
Treatment of **1** and **2** separately with sodium in liquid ammonia gave the corresponding two enantiomers of the 2-azabicyclo[3.3.1]nonane-3,6-dione, **3** and *ent*-**3**, in 45 and 54% yield, respectively. No reduction of the ketone carbonyl group was observed in any case. The specific rotation for the (1*S*,5*R*) enantiomer **3** was $[\alpha]_D^{22}$ +33 (*c* 1.0, MeOH), whereas for the (1*R*,5*S*) enantiomer *ent*-**3** was $[\alpha]_D^{22}$ −36 (*c* 1.0, MeOH).

2.2. Spectroscopic analysis of azabicyclic compounds isolated

The structural assignment for the target compounds **1**, **2** and **3**, the unexpected compounds **8** and **9**, and morphans **10**–**12** (**a**,**b**) were carried out by 2D NMR analysis (COSY, HMQC, NOESY and HMBC).

Positive diagnostic evidence for the (1*S*,5*R*) configuration for **1** and (1*R*,5*S*) configuration for **2** came from NOESY experiments on these compounds (Fig. 2). The resulting 2D spectrum for **1** showed off-diagonal cross-peaks connecting H-1 and H-8_{eq} with methyl protons, thus indicating their spacial proximity. Strong correlations were also observed between aromatic protons and H-1 and H-9, whereas the methine proton of the side chain did not show any signal. On the other hand, for compound **2** a good correlation between the methyl group and the H-1 proton was observed. Moreover, in its ^{1}H NMR spectrum, the signal for H-8_{eq} appears shielded (δ 0.84) with regard to that of isomer **1** (δ 2.26). The high-field shift of H-8_{eq} in **2** indicates that this proton is held directly below the benzene ring.

NMR spectra of compound **8** indicate a 4-substituted cyclohexanone pattern and the IR spectrum shows a diagnostic absorption for the β-lactam carbonyl group (1741 cm^{-1}). In the ^{13}C NMR spectrum there are signals for a quaternary aliphatic carbon (δ 59.0) and a single aliphatic methine carbon (δ 51.2). The methyl group appears as a singlet (δ 1.83) and the enantiotopic protons at the 3-position appear as two doublets (*J*=15 Hz) in the ^{1}H NMR spectrum.



1 **2**

Figure 2.

13

14 R = $COCH_3$
15 R = CH_2CH_3

Figure 3.

For compound **9**, most of the signals in the ^1H and ^{13}C NMR spectra are duplicated due to the presence of two rotamers in a 1:1 ratio. In the ^{13}C NMR spectrum the acetamide methyl group appears at δ 23.8 and 24.1 for each rotamer. On the other hand, the methyl group bonded to the quaternary carbon resonates at δ 23.0 and 24.9 for each rotamer.

The enantiomeric purity of **8** and **9**, both containing a ketone group, was determined by analysis of the NMR spectra of their enantiomeric pure cyclic acetals, which were obtained by condensation (benzene reflux, TsOH) with (−)-(2*R*,3*R*)-butane-2,3-diol.[15] The resulting acetal **13** showed to be a quasi-equimolecular mixture of two compounds reflecting the quasi-racemic character of **8** (Fig. 3). NMR spectra of **14** were complex due to the presence of rotamers and we decided to reduce the amide carbonyl group ($LiAlH_4$, THF) to give the amino derivative **15**, whose ^{13}C NMR spectrum showed two sets of signals that correspond to a mixture of diastereomers in a 5:1 ratio (determined by the singlet of the methyl groups in the ^1H NMR spectrum). As a consequence, compound **9** is a scalemic mixture, in which the enantiomer depicted in Scheme 3 is the predominant one.

The absolute configuration for **9** at C-1, which in turn implies the configuration at C-5, was deduced from the ^{13}C NMR[16] of compound **15**.[17] The configuration at the quaternary centre at C-7 was established by analysis of NOESY spectra of **15**. In this compound a contact between H-8 and CH_3 at C-7 was observed implying that CH_3 has a *cis* location with respect to the bridgehead protons and thus allowing the 7*S* configuration to be established.

The spectroscopic data of morphans **10** are very similar to those of the dechlorinated ones **1** and **2**. Hence, the isomer which shows a shielded H-8_{eq} was assigned to the absolute configuration depicted for compound **10b**. The same diagnostic criteria were applied for alcohols **11** and **12**. When the H-8_{eq} was shielded, for example **11b** shows this proton at δ 0.54, the compound was considered to belong to the 1*R*,5*S* series. The stereochemistry at C-4 in compounds **10a** and **12a** (*R*) and **10b** and **12b** (*S*) was deduced from the coupling constant of H-4_{ax}, $J\sim7$ Hz, which indicates an equatorial disposition for the chlorine atom at C-4. The preferred formation of these stereoisomers indicates that the hydrogen atom transfer from the hydride reagent to the monochlorinated radical intermediate centred at C-4 occurs in an axial fashion.[18] The equatorial disposition of the hydroxyl group at C-6 for compounds **11** and **12** was deduced from the multiplicity of H-6_{ax}.

3. Conclusions

The first synthesis of enantiomerically pure 2-azabicyclo[3.3.1]nonanes is described. Although the yield in the radical cyclization of *N*-(α-methylbenzyl) substituted trichloroacetamides **7** was low, diastereomers **1** and **2** have allowed the preparation of enantiopure 2-azabicyclo[3.3.1]nonane-3,6-diones **3** and *ent*-**3**, which can be used as pattern compounds in other asymmetric approaches to the synthesis of morphans. Furthermore, the radical process from **7** has followed an unexpected course, resulting in the formation, by a radical translocation, of interesting structures, such as β-lactam **8** and normorphan **9**.

4. Experimental

4.1. General

^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ solution at 300 MHz, or at 500 MHz when noted, and 75.4 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. Infrared spectra were recorded on a Nicolet 205 FT-IR spectrophotometer. HRMS were determined on an Autospec-VG apparatus. Optical rotations were taken on a Perkin–Elmer 241 polarimeter with a 1 ml (L=1 dm) cell. TLC was performed on SiO_2 (silica gel 60 F_{254}, Merck). The spots were located by UV light, a 1% $KMnO_4$ solution or hexachloroplatinate or anisaldehyde reagents. 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 atmosphere with dry, freshly distilled solvents under anhydrous conditions. 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. Microanalyses were performed by the ‘Centro de Investigación y Desarrollo’ (CSIC), Barcelona. As a chiral starting material (*S*)-α-methylbenzylamine (98% ee) was used.

4.2. 4-[(S)-1-Phenylethylamino]cyclohexan-1-one ethylene acetal **4**

A mixture of (*S*)-(−)-α-methylbenzylamine (2.76 ml, 21.5 mmol) and 1,4-cyclohexanedione monoethylene acetal (3 g, 19.2 mmol) 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 concentrated. To the residue dissolved in MeOH (40 ml) and cooled at 0°C was added $NaBH_4$ (1.3 g, 34.4 mmol) and the mixture stirred for an additional 4 h. Water (10 ml) was added to the reaction mixture and MeOH was evaporated. The residue was dissolved in CH_2Cl_2 and washed with brine. Concentration of the dried organic extracts afforded **4** (4.8 g, 96%) as an orange oil, which was used in the next step without further purification. An analytical sample was obtained by chromatography (EtOAc:CH_2Cl_2, 1:1): $[\alpha]_D^{22}$ −50.5 (*c* 1.6, MeOH); IR (NaCl): 3450; ^1H NMR: 1.32 (d, *J*=7 Hz, 3H, CH_3), 1.37–1.99 (m, 8H), 2.38 (m, 1H, H-4_{ax}), 3.91 (s, 4H, OCH_2), 3.88–3.96 (m, 1H, CH), 7.20–7.35 (m, 5H, ArH); ^{13}C NMR: 25.0 (CH_3), 29.6 and 31.1 (C-3 and C-5), 32.7 and 32.9 (C-2 and C-6), 51.9 (C-4), 54.7 (CH), 64.0 and 64.1 (CH_2O), 108.6 (C-1), 126.3, 126.6 and 128.3 (Ar), 146.1 (C-*ipso*); HRMS calcd for $C_{16}H_{23}NO_2$: 261.1728; found: 261.1723.

4.3. *2,2,2-Trichloro-*N*-[(*S*)-1-phenylethyl]-*N*-(4-ethylenedioxycyclohex-1-yl)acetamide* **5**

To a solution of **4** (5 g, 19.1 mmol) in CH_2Cl_2 (54 ml) containing triethylamine (5.5 ml, 38.4 mmol) trichloroacetyl chloride (4.3 ml, 38.3 mmol) in CH_2Cl_2 (10 ml) was added dropwise. The mixture was heated at reflux for 24 h, concentrated and the resulting residue was dissolved in CH_2Cl_2, washed with 1N aqueous HCl, saturated aqueous K_2CO_3, and brine. The organic layer was dried and concentrated to leave a solid which was triturated with ether to give, as a brown crystalline material, trichloroacetamide **5** (5.75 g, 80%) as a 1:3 mixture (estimated by ^{1}H NMR) of rotamers *Z* and *E*: mp 147–148°C (CH_2Cl_2); $[\alpha]_D^{22}$ −49.5 (*c* 1, MeOH); IR (NaCl): 1681; ^{1}H NMR: 1.50–2.20 (m, 8H), 1.83 (d, *J*=7 Hz, 3H, CH_3), 3.81–4.00 (m, 4H, CH_2O and 0.25H, rotamer *Z*, H-1$_{ax}$), 4.52–4.65 (m, 1.6H, rotamer *E*, H-1$_{ax}$ and CH), 5.84 (q, *J*=6.5 Hz, 0.2H, rotamer *Z*, CH), 7.18–7.55 (m, 5H, ArH); ^{13}C NMR: 64.3 and 64.5 (CH_2O), 94.2 (CCl_3), 125.7, 126.5, 127.4, 127.9, 128.1 and 128.3 (Ar); rotamer *Z*: 17.0 (CH_3), 25.3 and 25.9 (C-2 and C-6), 33.9 and 34.0 (C-3 and C-5), 56.7 (CH), 58.4 (C-1), 107.3 (C-4), 140.5 (C-*ipso*), 158.2 (CO); rotamer *E:* 17.8 (CH_3), 27.2 and 27.7 (C-2 and C-6), 33.6 and 33.9 (C-3 and C-5), 54.7 (C-1), 58.2 (CH), 107.0 (C-4), 138.0 (C-*ipso*), 159.5 (CO). Anal. calcd for $C_{18}H_{22}Cl_3NO_3$: C, 53.15; H, 5.45; N, 3.44; Cl, 26.15; found: C, 52.96; H, 5.34; N, 3.66; Cl, 26.28.

4.4. *2,2,2-Trichloro-*N*-[(*S*)-1-phenylethyl]-*N*-(4-oxocyclohex-1-yl)acetamide* **6**

A solution of **5** (2.5 g, 6.15 mmol) in THF (10 ml) and 3N aqueous HCl (10 ml) was heated at reflux for 10 h. The THF was evaporated and the mixture was basified with 2.5N aqueous NaOH, and extracted with CH_2Cl_2. Concentration of the dried extracts gave a residue which was chromatographed (CH_2Cl_2) to give, as a white solid, ketone **6** (2 g, 90%) as a 7:3 mixture (estimated by ^{1}H NMR) of rotamers *Z* and *E*: mp 127–128°C (CH_2Cl_2); $[\alpha]_D^{22}$ −54.0 (*c* 1, MeOH); IR (NaCl): 1717, 1689; ^{1}H NMR: 2.17–2.59 (m, 6H), 2.69 and 2.83 (2 qd, *J*=12 and 5 Hz, 2H, H-3$_{ax}$ and H-5$_{ax}$), 7.30–7.57 (m, 5H, ArH); rotamer *Z*: 1.81 (d, *J*=7 Hz, 2.1H, CH_3), 3.20 (tt, *J*=11 and 5 Hz, 0.7H, H-1$_{ax}$), 5.91 (q, *J*=7 Hz, 0.7H, CH); rotamer *E*: 1.85 (d, *J*=7 Hz, 0.9H, CH_3), 4.55 (q, *J*=7 Hz, 0.3H, CH), 5.07 (tm, *J*=11 Hz, 0.3H, H-1$_{ax}$); ^{13}C NMR: 94.1 (CCl_3), 125.6, 126.8, 127.3, 128.2, 128.3 and 128.5 (Ar); rotamer *Z:* 17.1 (CH_3), 26.2 and 26.7 (C-2 and C-6), 39.1 and 39.2 (C-3 and C-5), 56.2 (C-1), 56.9 (CH), 138.0 (C-*ipso*), 159.1 (CON), 209.9 (CO); rotamer *E*: 18.0 (CH_3), 29.1 and 29.7 (C-2 and C-6), 39.4 and 39.7 (C-3 and C-5), 55.0 (C-1), 57.3 (CH), 140.0 (C-*ipso*), 158.2 (CON), 207.7 (CO). Anal. calcd for $C_{16}H_{17}Cl_3NO_2$: C, 53.14; H, 4.74; N, 3.87; Cl, 29.41; found: C, 53.27; H, 4.72; N, 3.83; Cl, 29.31.

4.5. *2,2,2-Trichloro-*N*-[(*S*)-1-phenylethyl]-*N*-(4-trimethylsilyloxycyclohex-3-en-1-yl)acetamides* ***7a*** *and* ***7b***

To a cooled (−20°C) solution of ketone **6** (2 g, 5.54 mmol) in 1:1 pentane:CH_2Cl_2 (140 ml) were added hexamethyldisilazane (3.1 ml, 14.7 mmol) and trimethylsilyl iodide (1.6 ml, 11.1 mmol). The resulting solution was stirred at −20°C for 2 h and quenched by the addition of saturated aqueous $NaHCO_3$ (70 ml). The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2. The combined organic extracts were washed with 10% aqueous sodium thiosulfate, dried, and concentrated to give a nearly 1:1 mixture of diastereomeric silyl enol ethers **7** (2.38 g, quantitative) as a yellow oil, which was used without further purification in the next step. An analytical sample of **7** was obtained after chromatography (CH_2Cl_2) as a colourless oil; IR (NaCl): 1685; ^{1}H NMR: 0.11 and 0.20 (2 s, 9H, CH_3Si), 1.75 and 1.84 (2 d, *J*=7 Hz, 3H, CH_3), 1.84–2.70 (m, 6H), 2.90–3.11 and 4.78 (2 m, 1H, H-1$_{ax}$), 4.53 and 5.85 (2 q, *J*=6.5 Hz, 1H, CH), 4.73 and 4.83 (2 m, $W_{1/2}$=11 Hz, 1H, H-3), 7.20–7.60 (m, 5H, ArH);

^{13}C NMR: **7a** (*E* conformer): 0.2 (CH_3Si), 18.2 (CH_3), 25.6, 26.9 and 30.0 (C-2, C-5 and C-6), 55.0 (C-4), 56.2 (CH), 94.5 (CCl_3), 102.2 (C-3), 125.3, 125.9, 126.7, 127.4, 127.9, 128.2, 128.3 and 128.4 (Ar), 140.5 (C-*ipso*), 149.6 (C-4), 158.7 (CO); **7b** (*Z* conformer): 0.2 (CH_3Si), 17.1 (CH_3), 25.8, 27.3 and 29.6 (C-2, C-5 and C-6), 56.2 (CH), 56.9 (C-4), 94.3 (CCl_3), 101.2 (C-3), 126.7, 128.0 and 128.4 (Ar), 138.5 (C-*ipso*), 149.7 (C-4), 158.9 (CO). Minor signals for other rotamers were observed. HRMS calcd for $C_{19}H_{26}Cl_3NO_2Si$: 433.0798; found: 433.0790.

*4.6. Radical cyclization of trichloroacetamides **7**. General procedure. With 3.5 equiv. of TTMSS in benzene*

A suspension of **7** (500 mg, 1.15 mmol) and AIBN (200 mg, 1.22 mmol) in benzene (10 ml) was heated to reflux. Then, TTMSS (1.24 ml, 4.02 mmol) was added dropwise and the reaction mixture was stirred at this temperature for 3 h. After evaporation of the solvent the residue was chromatographed (cyclohexane to EtOAc). TLC (2% MeOH in EtOAc, anisaldehyde reagent).

The first eluate gave 4-methyl-4-phenyl-1-(4-oxo-1-cyclohexyl)-2-azetidinone (**8**, 20 mg, 7%): $[\alpha]_D^{22}$ −4.4 (*c* 1.0, MeOH); R_f 0.34 (purple); IR (NaCl): 1741, 1721; ^{1}H NMR (500 MHz, COSY, NOESY): 1.83 (s, 3H, CH_3), 1.95–2.01 (m, 2H, H-2 and H-6), 2.08–2.22 (m, 4H), 2.30–2.38 (m, 2H, H-3 and H-5), 2.93 (2 d, *J*=15 Hz, 2H, CH_2), 3.54 (m, 1H, H-1_{ax}), 7.20–7.40 (m, 5H, ArH); ^{13}C NMR (HMQC, HMBC): 23.7 (CH_3), 30.2 and 30.3 (C-2 and C-6), 39.2 and 39.4 (C-3 and C-5), 51.2 (C-1), 53.8 (CH_2), 59.0 (C), 125.5, 127.8, 128.0, 128.6 and 128.8 (Ar), 141.9 (C-*ipso*), 167.2 (CON), 209.1 (CO). HRMS calcd for $C_{16}H_{19}NO_2$: 257.1415; found: 257.1414.

The second eluate gave (1*S*,5*R*)-*N*-[(*S*)-1-phenylethyl]-2-azabicyclo[3.3.1]nonane-3,6-dione (**1**, 30 mg, 10%): mp 138–139°C; $[\alpha]_D^{22}$ −7.8 (*c* 1.0, MeOH); R_f 0.26 (dark green); IR (NaCl): 1715, 1635; ^{1}H NMR (500 MHz, COSY, NOESY): 1.64 (d, *J*=7 Hz, 3H, CH_3), 1.82 (tdd, *J*=14.5, 5 and 2.5 Hz, 1H, H-8_{ax}), 1.85–1.93 (m, 2H, H-9), 2.26 (dm, *J*=14 Hz, 1H, H-8_{eq}), 2.36 (dd, *J*=15.5 and 5 Hz, 1H, H-7_{eq}), 2.52 (dd, *J*=18 and 2 Hz, 1H, H-4_{eq}), 2.58 (td, *J*=15.5 and 6.5 Hz, 1H, H-7_{ax}), 2.77 (m, 1H, H-5_{eq}), 2.80 (dd, *J*=18 and 8 Hz, 1H, H-4_{ax}), 3.43 (m, 1H, H-1_{eq}), 6.17 (q, *J*=7.5 Hz, 1H, CH), 7.20–7.40 (m, 5H, ArH); ^{13}C NMR (HMQC): 17.2 (CH_3), 33.3 (C-8), 33.5 (C-9), 33.9 (C-7), 35.0 (C-4), 43.9 (C-5), 46.6 (C-1), 51.7 (CH), 127.3, 127.7 and 128.6 (Ar), 140.0 (C-*ipso*), 168.3 (C-3), 211.0 (C-6). Anal. calcd for $C_{16}H_{19}NO_2$.1/3 H_2O: C, 72.99; H, 7.53; N, 5.32; found: C, 72.78; H, 7.60; N, 5.30.

The third eluate gave (1*R*,5*S*)-*N*-[(*S*)-1-phenylethyl]-2-azabicyclo[3.3.1]nonane-3,6-dione (**2**, 61 mg, 21%): $[\alpha]_D^{22}$ −196 (*c* 1.0, MeOH); R_f 0.25 (dark green); IR (NaCl): 1714, 1631; ^{1}H NMR (500 MHz, COSY, NOESY): 0.84 (dm, *J*=14 Hz, 1H, H-8_{eq}), 1.36 (tdd, *J*=14.5, 5 and 2.5 Hz, 1H, H-8_{ax}), 1.58 (d, *J*=7 Hz, 3H, CH_3), 2.01 (dd, *J*=15.5 and 5 Hz, 1H, H-7_{eq}), 2.04–2.07 (m, 2H, H-9), 2.29 (td, *J*=15.5 and 6.5 Hz, 1H, H-7_{ax}), 2.49 (ddd, *J*=21.5, 3.5 and 1 Hz, 1H, H-4_{eq}), 2.75 (dd, *J*=22 and 8 Hz, 1H, H-4_{ax}), 2.75 (m, 1H, H-5_{eq}), 3.79 (m, 1H, H-1_{eq}), 6.17 (q, *J*=7 Hz, 1H, CH), 7.20–7.43 (m, 5H, ArH); ^{13}C NMR (HMQC): 15.7 (CH_3), 31.8 (C-8), 33.7 (C-7 and C-9), 35.0 (C-4), 43.8 (C-5), 46.5 (C-1), 51.0 (CH), 127.8, 128.0 and 128.6 (Ar), 140.2 (C-*ipso*), 167.9 (C-3), 211.3 (C-6). Anal. calcd for $C_{16}H_{19}NO_2$: C, 74.68; H, 7.44; N, 5.44; found: C, 74.86; H, 7.52; N, 5.39.

The fourth eluate gave (1*R*,5*S*,7*S*)-6-acetyl-7-methyl-7-phenyl-6-azabicyclo[3.2.1]octan-2-one (**9**, 53 mg, 18%). The following data correspond to a scalemic mixture of **9** and its enantiomer in a 5:1 ratio:[18] $[\alpha]_D^{22}$ −66.4 (*c* 1.0, MeOH); R_f 0.22 (orange); IR (NaCl): 1708, 1649; ^{1}H NMR (500 MHz, COSY): 1.58 (d, *J*=12.5 Hz, 0.5H, rotamer *E*, H-8_{syn}), 1.64 (d, *J*=12.5 Hz, 0.5H, rotamer *Z*, H-8_{syn}), 1.75 (dtd, *J*=13.5, 10 and 2.5 Hz, 0.5H, H-4), 1.85 (s, 1.5H, rotamer *E*, CH_3), 1.87 (s, 1.5H, rotamer *E*, CH_3CON), 1.89 (s, 1.5H, rotamer *Z*, CH_3), 1.85–1.90 (m masked, 0.5H, H-4), 1.90–2.10 (m, 0.5H, H-3), 2.10–2.16 (m, 0.5H, rotamer *E*, H-8_{anti}), 2.17–2.23 (m, 0.5H, rotamer *Z*, H-8_{anti}), 2.29 (s, 1.5H, rotamer *Z* CH_3CON), 2.28–2.35 (m, 0.5H, H-3 and 0.5H, H-4), 2.42–2.60 (m, 0.5H, H-3 and 0.5H, H-4), 2.70–2.74 (m, 1H, H-1), 4.39 (m, $W_{1/2}$=13 Hz, 0.5H, rotamer *Z*, H-5), 4.89 (m, $W_{1/2}$=13 Hz, 0.5H, rotamer *E*, H-5), 7.15–7.40 (m, 5H, ArH); ^{13}C NMR (HMQC, HMBC): 27.5 and 29.7 (C-4), 34.8 and 35.1 (C-3), 125.0, 125.7, 126.8, 127.5, 128.2 and 128.6 (Ar); rotamer *Z*: 23.0 (CH_3), 23.8 (CH_3CON), 30.8 (C-8), 56.6 (C-5), 63.6 (C-1), 69.2 (C-7), 142.8 (C-*ipso*), 168.6 (CON), 208.9 (C-2); rotamer *E*: 24.1 (CH_3CON), 24.9 (CH_3), 29.4 (C-8), 56.1 (C-5), 65.7 (C-1), 67.1 (C-7), 143.8 (C-*ipso*), 170.5 (CON), 209.8 (C-2). HRMS calcd for $C_{16}H_{19}NO_2$: 257.1416; found: 257.1415.

4.7. *Radical cyclization of trichloroacetamides* **7**. *With 3.5 equiv. of TTMSS in toluene*

Following the general procedure trimethylsilyl enol ethers **7** (350 mg, 0.8 mmol) in toluene (7 ml) were treated with AIBN (139 mg, 0.85 mmol) and 3.5 equiv. of TTMSS (0.86 ml, 2.8 mmol) and the crude material was chromatographed (1% MeOH in CH_2Cl_2). The first eluate gave the monochloro bicyclo ketones **10a** and **10b** (77 mg, 33% combined yield) as a mixture of diastereomers in a 1:2 ratio. The second eluate gave normorphan **9** (16 mg, 8%). Separation of the diastereomeric mixture was accomplished by a second column chromatography (EtOAc in hexane from 50% to 70%). The first eluate gave (1*S*,4*R*,5*S*)-4-chloro-[(*S*)-1-phenylethyl]-2-azabicyclo[3.3.1]nonane-3,6-dione **10a**: IR (NaCl): 1717, 1652; ^{1}H NMR (500 MHz, COSY): 1.66 (d, *J*=7.5 Hz, 3H, CH_3), 1.82 (tdd, *J*=15, 5 and 2.5 Hz, 1H, H-8_{ax}), 1.99 (m, 2H, H-9), 2.25 (dm, *J*=14 Hz, 1H, H-8_{eq}), 2.46 (dm, *J*=14 Hz, 1H, H-7_{eq}), 2.66 (td, *J*=15 and 7 Hz, 1H, H-7_{ax}), 3.11 (m, $W_{1/2}$=14 Hz, 1H, H-5_{eq}), 3.46 (br s, 1H, H-1_{eq}), 4.70 (d, *J*=7 Hz, 1H, H-4_{ax}), 6.10 (q, *J*=7 Hz, 1H, CH), 7.28–7.50 (m, 5H, ArH); ^{13}C NMR (HMQC): 17.1 (CH_3), 33.1 (C-8), 34.2 (C-9), 34.8 (C-7), 47.2 (C-5), 52.0 (C-1), 53.2 (CH), 55.5 (C-4), 127.4, 128.1 and 128.9 (Ar), 139.4 (C-*ipso*), 165.7 (C-3), 206.9 (C-6). Anal. calcd for $C_{16}H_{18}NO_2Cl.1/4\ H_2O$: C, 64.86; H, 6.29; N, 4.73; found: C, 64.55; H, 6.29; N, 4.97. The second eluate gave (1*R*,4*S*,5*R*)-4-chloro-2-[(*S*)-1-phenylethyl]-2-azabicyclo[3.3.1]nonane-3,6-dione **10b**: IR (NaCl): 1721, 1650; ^{1}H NMR (500 MHz, COSY): 0.85–0.95 (m, 1H, H-8_{eq}), 1.41 (tdd, *J*=14, 4.5 and 2.5 Hz, 1H, H-8_{ax}), 1.63 (d, *J*=7 Hz, 3H, CH_3), 2.16 (dm, *J*=14 Hz, 2H, H-7_{eq} and H-9_{anti}), 2.26 (ddd, *J*=14, 6.5 and 2.5 Hz, 1H, H-9_{syn}), 2.40 (td, *J*=14.5 and 7 Hz, 1H, H-7_{ax}), 3.15 (m, $W_{1/2}$=14 Hz, 1H, H-5_{eq}), 3.81 (br s, 1H, H-1_{eq}), 4.67 (d, *J*=7.5 Hz, 1H, H-4_{ax}), 6.16 (q, *J*=7 Hz, 1H, CH), 7.25–7.50 (m, 5H, ArH); ^{13}C NMR (HMQC): 15.8 (CH_3), 31.4 (C-8), 34.5 (C-9), 34.6 (C-7), 47.2 (C-5), 51.6 (C-1), 52.3 (CH), 55.2 (C-4), 127.7, 128.3 and 128.8 (Ar), 139.5 (C-*ipso*), 165.3 (C-3), 207.0 (C-6).

4.8. *Radical cyclization of trichloroacetamides* **7**. *With 4.5 equiv. of TTMSS in benzene*

Following the general procedure, trichloroacetamides **7** (1 g, 2.3 mmol) in benzene (20 ml) were treated with AIBN (377 mg, 2.3 mmol) and 4.5 equiv. of TTMSS (3.2 ml, 10.35 mmol), and the crude material was chromatographed (EtOAc in hexane from 50% to 70%). The first fraction gave the β-lactam **8** (34 mg, 6%), the second fraction gave the ketone **1** (42 mg, 7%), the third fraction afforded the ketone **2** (70 mg, 12%), the fourth fraction gave the normorphan **9** (110 mg, 19%), and the last fraction gave a diastereomeric mixture of alcohols **11a** and **11b** (80 mg, 13% combined yield) in a 1:3 ratio. (1*S*,5*R*,6*R*)-6-Hydroxy-2-[(*S*)-1-phenylethyl]-2-azabicyclo[3.3.1]nonan-3-one **11a**: IR (NaCl): 3600, 1608; ^{1}H NMR: 1.56 (d, *J*=7.5 Hz, CH_3), 2.13 (m, H-5), 2.48 (dd, *J*=19 and 7.5 Hz, H-4_{ax}), 2.83 (d, *J*=19 Hz, H-4_{eq}), 3.59 (m, $W_{1/2}$=9 Hz, H-1), 3.72 (m, H-6_{ax}), 6.07 (q, *J*=7.5 Hz, CH), 7.20–7.40 (m, ArH); ^{13}C NMR: 17.2 (CH_3), 25.8 (C-7), 29.7 (C-8), 31.2 (C-9), 31.7 (C-4), 33.9 (C-5), 46.5 (C-1), 51.2 (CH), 71.4 (C-6), 127.8, 128.4 and 128.5 (Ar), 140.7 (C-*ipso*), 171.1 (C-3). (1*R*,5*S*,6*S*)-6-Hydroxy-2-[(*S*)-1-phenylethyl]-2-azabicyclo[3.3.1]nonan-3-one **11b**: IR (NaCl): 3600, 1608; ^{1}H NMR: 0.54 (dm, *J*=13.7 Hz, 1H, H-8_{eq}), 0.99 (tdd, *J*=13.5, 4 and 2.5 Hz, 1H, H-8_{ax}), 1.21 (qd, *J*=13.5 and 4 Hz, 1H, H-7_{ax}), 1.35 (dm, *J*=14 Hz, 1H, H-7_{eq}), 1.52 (d, *J*=7 Hz, 3H, CH_3), 1.82–1.94 (m, 2H, H-9), 2.22 (m, 1H, H-5), 2.43 (dd, *J*=19 and 7.5 Hz, 1H, H-4_{ax}), 2.80 (dd, *J*=19 and 0.75 Hz, 1H, H-4_{eq}), 3.52 (m, $W_{1/2}$=9 Hz, 1H, H-1), 3.65 (dt, *J*=11 and 4.5 Hz, 1H, H-6_{ax}), 6.05 (q, *J*=7.5 Hz, 1H, CH), 7.20–7.40 (m, 5H, ArH); ^{13}C NMR: 15.7 (CH_3), 25.6 (C-7), 29.3 (C-8), 31.0 (C-9), 32.1 (C-4), 33.7 (C-5), 46.5 (C-1), 50.9 (CH), 71.3 (C-6), 127.2, 127.3 and 127.6 (Ar), 140.6 (C-*ipso*), 170.6 (C-3). HRMS calcd for $C_{16}H_{21}NO_2$ 259.1572; found: 259.1579.

4.9. *Radical cyclization of trichloroacetamides **7**. With 3.5 equiv. of Bu_3SnH in benzene*

Following the general procedure, trichloroacetamides **7** (200 mg, 0.46 mmol) in benzene (4 ml) were treated with AIBN (80 mg, 0.49 mmol) and 3.5 equiv. of Bu_3SnH (0.43 ml, 1.61 mmol), and the crude material was chromatographed (1% MeOH in CH_2Cl_2) to give a diastereomeric mixture of monochloro bicyclo alcohols **12a** and **12b** (36 mg, 27% combined yield) in a 1:2 ratio. (1*S*,4*R*,5*S*,6*R*)-4-Chloro-6-hydroxy-2-[(*S*)-1-phenylethyl]-2-azabicyclo[3.3.1]nonan-3-one **12a**: IR (NaCl): 3450, 1648; ^{1}H NMR: 1.20–2.10 (m, 6H), 1.62 (d, *J*=7 Hz, 3H, CH_3), 3.23 (m, 1H, H-5_{eq}), 3.70 (m, 1H, H-6_{ax}), 3.91 (m, 1H, H-1_{eq}), 4.88 (d, *J*=6.5 Hz, 1H, H-4), 5.99 (q, *J*=7.5 Hz, 1H, CH), 7.20–7.50 (m, 5H, ArH); ^{13}C NMR: 15.9 (CH_3), 26.6 (C-7), 31.1 (C-8), 34.2 (C-9), 40.1 (C-5), 47.1 (C-1), 53.1 (CH), 59.5 (C-4), 74.7 (C-6), 127.3 and 127.9 (ArH), 139.8 (C-*ipso*), 166.2 (C-3). (1*R*,4*S*,5*R*,6*S*)-4-Chloro-6-hydroxy-2-[(*S*)-1-phenylethyl]-2-azabicyclo[3.3.1]nonan-3-one **12b**: IR (NaCl): 3450, 1648; ^{1}H NMR: 0.71 (dm, *J*=13 Hz, 1H, H-8_{eq}), 1.10 (tm, *J*=13 Hz, 1H, H-8_{ax}), 1.57 (d, *J*=7 Hz, 3H, CH_3), 1.25–2.10 (m, 4H), 2.82 (m, $W_{1/2}$=12 Hz, 1H, H-5_{eq}), 3.57 (m, 1H, H-1_{eq}), 3.70 (m, 1H, H-6_{ax}), 4.82 (d, *J*=6.5 Hz, 1H, H-4), 5.94 (q, *J*=7.5 Hz, 1H, CH), 7.20–7.50 (m, 5H, ArH); ^{13}C NMR: 17.1 (CH_3), 26.8 (C-7), 29.3 (C-8), 34.4 (C-9), 39.8 (C-5), 47.5 (C-1), 52.7 (CH), 59.4 (C-4), 74.7 (C-6), 127.7 and 128.5 (ArH), 139.8 (C-*ipso*), 166.2 (C-3).

4.10. *Reduction of monochloro ketones **10a** and **10b***

To a solution of monochlorinated bicyclo ketones **10a** and **10b** (55 mg, 0.19 mmol) in MeOH (4 ml) were added ammonium chloride (61 mg, 1.14 mmol) and, after cooling to 0°C, powdered zinc (120 mg, 1.9 mmol). Stirring was continued at room temperature for 24 h and the reaction mixture was filtered through Celite and the filtrate concentrated to give ketones **1** and **2** (43 mg, 89% combined yield).

4.11. *Reduction of monochloro alcohols **12a** and **12b***

Operating as above, **12a** and **12b** (35 mg, 0.12 mmol) in CH_3OH (4 ml) were treated with powdered zinc (76 mg, 1.2 mmol) and ammonium chloride (38 mg, 0.12 mmol) to give alcohols **11a** and **11b** (26 mg, 85% combined yield).

4.12. *(1*S*,5*R*)-2-Azabicyclo[3.3.1]nonane-3,6-dione **3***

To a solution of amide **1** (30 mg, 0.12 mmol) in THF (6 ml) at −78°C was added liquid ammonia (25 ml) and sodium (22 mg, 0.95 mmol) in small portions, and the mixture was stirred at this temperature for 1 h. The reaction was quenched by the addition of ammonium chloride, and the mixture was allowed to warm to room temperature to remove any excess ammonia. To the reaction mixture was added successively saturated ammonium chloride solution (3 ml), EtOAc (100 ml) and, after stirring for 2 h, Na_2SO_4, and the dried organic extracts concentrated. Purification by chromatography (EtOAc:MeOH, 90:10) of the residue afforded morphan **3** (8 mg, 45%) as a white solid: mp 107–108°C; $[\alpha]_D^{22}$ +33 (*c* 1.0, MeOH); IR (NaCl): 3200, 1706, 1648; ^{1}H NMR (500 MHz, COSY, HMQC): 1.97 (tdd, *J*=13.5, 5.5 and 2.5, 1H, H-8$_{ax}$), 2.09 (dm, *J*=13.5 Hz, 1H, H-9), 2.15 (m, 1H, H-8$_{eq}$), 2.21 (ddd, *J*=13.5, 6.5 and 3 Hz, 1H, H-9), 2.45 (m, 2H, H-4$_{eq}$ and H-7$_{eq}$), 2.60 (ddd, *J*=16.5, 13 and 7 Hz, 1H, H-7$_{ax}$), 2.70 (dd, *J*=18.5, 7 Hz, 1H, H-4$_{ax}$), 2.84 (m, $W_{1/2}$=13 Hz, 1H, H-5$_{eq}$), 3.84 (m, $W_{1/2}$=11 Hz, 1H, H-1$_{eq}$), 6.20 (br s, 1H, H-1$_{eq}$); ^{13}C NMR (HMQC): 31.1 (C-9), 33.4 (C-8), 33.7 (C-7), 34.5 (C-4), 43.5 (C-1), 46.2 (C-5), 170.5 (C-3), 210.7 (C-6). Anal. calcd for $C_8H_{11}NO_2.H_2O$: C, 56.13; H, 7.65; N, 8.18; found: C, 56.39; H, 7.68; N, 8.14.

*4.13. (1*R*,5*S*)-2-Azabicyclo[3.3.1]nonane-3,6-dione* ent-***3***

Operating as above, from amide **2** (40 mg, 0.12 mmol), liquid ammonia (25 ml) and sodium (30 mg, 1.3 mmol) in THF (6 ml), after chromatography (EtOAc:MeOH, 90:10), *ent*-**3** (13 mg, 54%) was isolated as a white solid; $[\alpha]_D^{22}$ −36 (*c* 1.0, MeOH). The mp, IR, ^{1}H and ^{13}C NMR spectra were coincident with those of **3**. MS (CI) *m/z* 154 ($[M+H]^+$, 100), 149 (6), 85 (10), 83 (15).

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17. (1*R*,5*S*,7*S*)-6-Ethyl-2-[4′*R*,5′*R*-4′,5′-dimethyl-spiro-1′3′-dioxolane]-7-methyl-7-phenyl-6-azabicyclo[3.2.1]octane (**15**): ^{13}C NMR: 15.5 (CH_3), 17.3 and 18.1 (CH_3 acetal), 21.8 (7-CH_3), 25.9 (C-4), 32.0 and 32.7 (C-3 and C-8), 38.4 (NCH_2), 54.2 (C-5), 55.9 (C-1), 67.1 (C-7), 77.6 and 78.9 (CH acetal), 110.6 (C-2), 125.3, 126.1, 127.4, 152.8 (Ar). The minor signals corresponding to the (1*S*,5*R*,7*R*) isomer are the following: 14.0, 16.8, 17.0, 21.7, 26.2, 29.7, 31.4, 38.4, 53.9, 55.3, 68.1, 77.2, 77.9, 110.2, 124.9, 126.0, 127.4 and 152.8.
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