Radical promoted cyclisations of trichloroacetamides with silyl enol ethers and enol acetates: the role of the hydride reagent [tris(trimethylsilyl)silane *vs.* tributylstannane]

Josefina Quirante, Carmen Escolano, Faïza Diaba and Josep Bonjoch*

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

Received (in Cambridge) 3rd February 1999, Accepted 11th March 1999

Reactions between 1-(carbamoyl)dichloromethyl radicals and electron-rich alkenes acting as radical acceptors are reported for the first time. The intramolecular reaction of trichloroacetamides with silyl enol ethers gives ketones using $(TMS)_3SiH$ as the mediator, and alcohols when using Bu_3SnH. The reaction with enol acetates gives acetates using either of the above hydride reagents. These radical processes have been applied to the synthesis of 2-azabicyclo-[3.3.1]nonanes.

Introduction

In the last decade, carbocyclisation of 3-azacarbo radicals and alkenes, with or without electron withdrawing groups, acting as radical acceptors has emerged as a powerful tool in the building of pyrrolidine or piperidine rings,[1] the most usual way to conduct this reaction being the hydride method, working with Bu_3SnH (TBTH) or $(Me_3Si)_3SiH$ (TTMSS) and a radical precursor.[2] In contrast, the use of alkenes with electron releasing groups in the construction of azacyclic derivatives has so far received almost no attention.[3] Moreover, although it is known that electrophilic radicals react with silyl enol ethers,[4–6] to our knowledge[7] there are only a few examples of radical cyclisations promoted by hydride reagents and silyl enol ethers,[8] or related alkyl enol ethers[9] or enol acetates.[10]

In this paper we report for the first time that trichloroacetamides as precursors of 1-(carbamoyl)dichloromethyl radicals[11–13] react with electron rich alkenes (Fig. 1) such as silyl enol ethers and enol acetates, resulting in carbocyclisations that lead to piperidine rings.[14] We also study the different behaviour of TTMSS and TBTH in these reactions.

From a synthetic standpoint, the radical cyclisation reported here constitutes a new general approach to the synthesis of 2-azabicyclo[3.3.1]nonanes which allows the functionalization at C-6, as occurs in many natural products that embody this subunit, for example, the recently isolated marine alkaloids sarains[15] and mandangamines,[16] or the novel immunosuppressant FR-901483.[17]

Results and discussion

We have studied the radical cyclization of trichloroacetamides with silyl enol ethers and enol acetates using trichloroacetamide **1** as the starting material, which is available in three steps from the monoethylene acetal of cyclohexane-1,4-dione.[12b] We first examined the behaviour of silyl enol ether **2**, prepared in 87% yield from cyclohexanone **1** by treatment with trimethylsilyl iodide and hexamethyldisilazane[18] (Scheme 1). When a solution

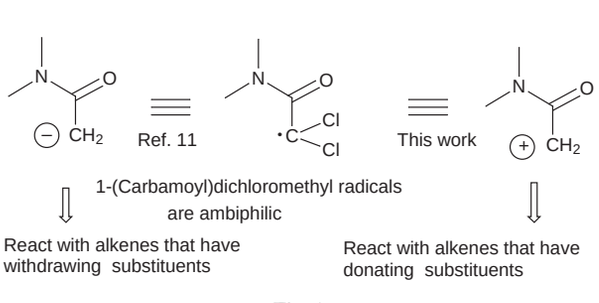
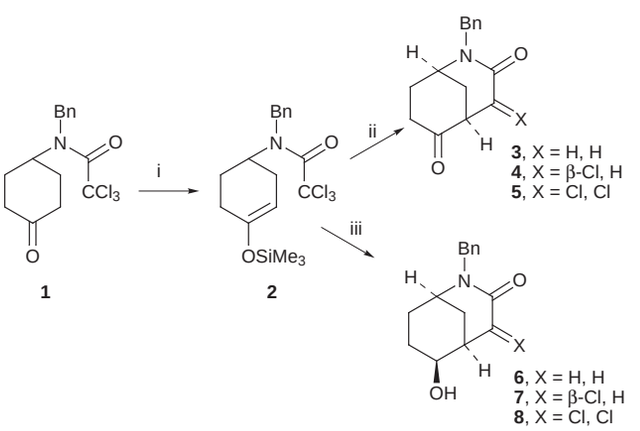


Fig. 1



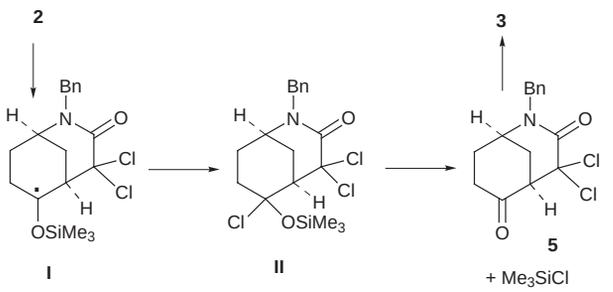
Scheme 1 *Reagents and conditions*: i, TMSI, HMDS, −20 °C (87%); ii, $(TMS)_3SiH$, AIBN, benzene, reflux (69% for **3**); iii, Bu_3SnH, AIBN, benzene, reflux (70% for **6**).

of **2** in benzene was treated with TTMSS and AIBN at reflux temperature, after work-up and chromatography, azabicyclic dione **3** was isolated in 69% yield. The formation of 2-azabicyclo[3.3.1]nonane-3,6-dione **3** directly from **2** is noteworthy, since it constitutes an example of a new synthetic method for the preparation of 1,4-dicarbonyl compounds (*i.e.* γ-ketoamides). We suggest that the ketone carbonyl group comes from the radical arising from the cyclization process, centered at C-6, which may capture a chlorine atom (inter- or intramolecularly) generating the α-chloro silyl ether followed by elimination of trimethylchlorosilane (Scheme 2). If this is true, the reaction should proceed with sub-stoichiometric amounts of TTMSS since an atom transfer process occurs. Effectively, when the trichloroacetamide was treated with only 0.25 equiv. of the hydride reagent, cyclization still takes place (65% yield), the isolated products being dichloro derivative **5** (43%) and monochloro derivative **4** (22%). The results of other experiments involving different quantities of TTMSS are depicted in Table 1.

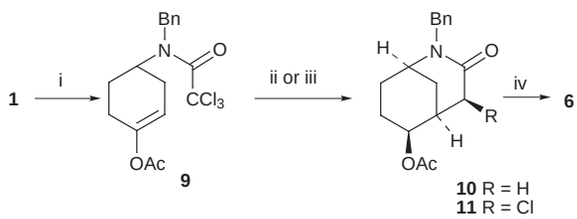
The course of this radical cyclization can be explained by the fact that the radical acceptor has a radical stabilizing substituent ($OSiMe_3$) that enables the radical **I** generated after

Table 1 Radical cyclization of trichloroacetamide **2**

Entry	Hydride	(Equiv.)	Overall yield	Yield of individual compounds (%)						
				3	**4**	**5**	**6**	**7**	**8**	**1**
1	TTMSS	3.5	69%	69				—		—
2	TTMSS	0.5	73%		36	37				
3	TTMSS	0.25	65%		22	43				3
4	TTMSS	0.15	15%			15				50
5	TBTH	4.5	70%	—	—	—	70	—	—	—
6	TBTH	3.5	77%			—	24	32	21	—
7	TBTH	1.2	77%		14	10	—	25	28	



Scheme 2



Scheme 3 *Reagents and conditions*: i, propen-2-yl acetate, TsOH, reflux (85%); ii, $(TMS)_3SiH$, AlBN, benzene, reflux (68% for **10**); iii, Bu_3SnH, AlBN, benzene, reflux (56% for **10**); iv, aqueous 2 M NaOH, EtOH, reflux (92% from **10**).

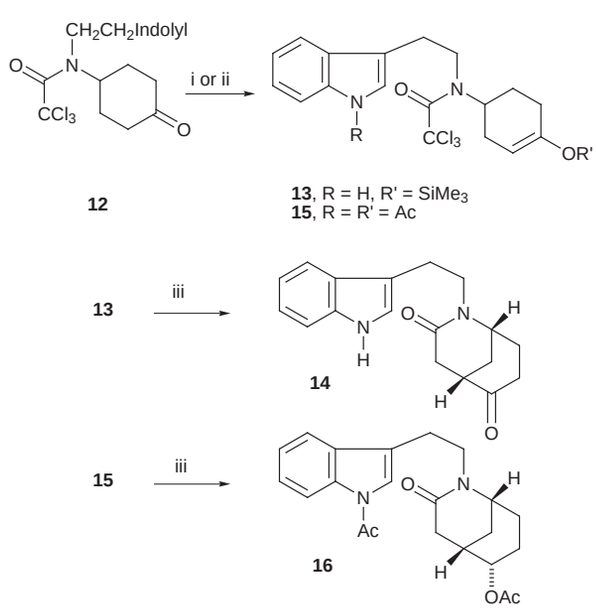
the cyclization to survive and participate in an atom transfer process. A plausible pathway for the formation of the ketone carbonyl group in compounds **3**–**5** from the radical intermediate **I** is depicted in Scheme 2. This process implies that abstraction of a chlorine atom by the carbon radical occurs, either from the starting material **2** or from $(TMS)_3SiCl$, to give α-chloro silyl ether **II**. Adduct **II** rapidly degrades to the ketone carbonyl and trimethylchlorosilane, probably *via* a four-centre type reaction,[19] and as the affinity between silicon and chlorine is strong, the reaction occurs very easily.[20] An alternative pathway for the formation of **5** without the intermediate **II** should not be discarded.

When we used TBTH instead of TTMSS as the hydride reagent to promote the radical cyclisation of **2** the end-products differed. Thus, independent of the quantity of TBTH used (from 4.5 to 0.25 equiv.) azabicyclic compounds containing a hydroxy group were isolated in all cases, the synthetic conditions using 4.5 equiv. being the best because they furnished azabicyclo **6** as the sole compound in 70% overall yield after cyclization and reduction. The equatorial disposition of the hydroxy group at C-6 was easily deduced from the multiplicity of H-6 (dt, *J* 11 and 5 Hz) in the ^1H NMR spectrum of **6**.

Use of TBTH in the above radical processes produced different results probably because it is a better hydrogen atom donor than TTMSS.[21] The reaction course does not seem to proceed through the azabicyclic ketone **5,** because in separate experiments **5** was not reduced to alcohol **8** when treated with TBTH, either in radical or ionic conditions. In both cases, the monochloro ketone **4** was isolated instead.[22] The formation of alcohols **6**–**8** when using TBTH can be explained, taking into account their stereochemistry (only equatorial isomers were isolated), by the reduction of the radical intermediate **I** which generates a silyl ether[23] that later undergoes an assisted cleavage in the reaction medium.[24]

We also studied the radical cyclization of enol acetate **9**, which was obtained by treatment of cyclohexanone **1** with toluene-*p*-sulfonic acid and prop-2-enyl acetate. The treatment of enol acetate **9** with TTMSS (3.5 equiv.) and AIBN under reaction conditions identical to those used for **2**, provided morphan **10**, as a single diastereoisomer in 68% yield (Scheme 3). Thus, the reaction involves direct reduction of the acetoxy radical intermediate. When operating with TBTH the same result was observed, although a small percentage of the monochloro derivative **11** was isolated. The relative configuration at C-6 in compound **10** (equatorial acetoxy group) was deduced from the multiplicity (dt, *J* 11 and 4.5 Hz) of H-6_{ax}. Additionally, the ^{13}C NMR data are in agreement with this assignment. Furthermore, saponification of **10** produces the alcohol **6**. The preferred formation of this stereoisomer indicates that hydrogen atom transfer from the hydride reagent to the α-acetoxy radical intermediate occurs in an axial fashion, the kinetic mode for such processes in cyclohexyl radicals.[25]

In order to explore the scope of this cyclization-type reaction in the preparation of more complex compounds (*e.g.* indole alkaloids), we examined the behaviour of the trichloroacetamides **13** and **15**, which incorporate a tryptamine unit. These radical precursors were obtained from **12**[1a] following the procedures used to obtain **2** and **9**, respectively, from **1** in the *N*-benzyl series. Under the reaction conditions used for the formation of enol acetate from indole ketone **12**, acetylation of NH-indole also took place, giving the acetylated indole derivative **15** (Scheme 4). After radical cyclisation and the



Scheme 4 *Reagents and conditions*: i, trimethylsilyl iodide, HMDS, −20 °C (85%); ii, propen-2-yl acetate, TsOH, reflux (56%); iii, $(TMS)_3SiH$, AlBN, benzene, reflux (58% for **14** and 60% for **16**).

subsequent reductive process, using TTMSS under the same reaction conditions as described above for the *N*-benzyl series, azabicyclic systems **14** (60%) and **16** (58%) were isolated.

In conclusion, the results reported here not only expand the usefulness of trichloroacetamides as starting materials for radical cyclisations but also enlarge the synthetic potential of silyl enol ethers[26] and enol acetates. The work outlined in this paper allows 1-(carbamoyl)dichloromethyl radicals, derived from the easily accessible trichloroacetamides, to be considered as umpoled reagents,[27] equivalent to α-carbonyl carbocations that can react with electron-rich alkenes. This is therefore an excellent method for conveniently synthesising 1,4-dicarbonyl compounds (*i.e.* **3** and **14**).

Experimental

^{1}H and ^{13}C NMR spectra were recorded at 300 and 50.3 MHz, respectively, in chloroform-d_1, unless otherwise stated. In addition, 2D nuclear magnetic resonance COSY and HMQC experiments were performed on a Varian XL-500 instrument. Chemical shifts are reported as δ values (ppm) relative to internal tetramethylsilane, and J values are given in Hz. Infrared spectra were recorded on a Nicolet 205 FT-IR spectrometer as either an evaporated film or liquid film on sodium chloride plates unless otherwise stated. Mass spectra were determined on a Hewlett-Packard 5988 A mass spectrometer or on an 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. Microanalyses were performed by the "Centro de Investigación y Desarrollo" (CSIC), Barcelona.

N-Benzyl-2,2,2-trichloro-*N*-[4-(trimethylsilyloxy)cyclohex-3-enyl]acetamide 2

To a solution of ketone **1** (3.87 g, 10.7 mmol) in dichloromethane–pentane 1:1 (135 cm^3) cooled at −20 °C, hexamethyldisilazane (6 cm^3, 21.4 mmol) and iodotrimethylsilane (3.1 cm^3, 21.4 mmol) were added dropwise. After stirring the reaction mixture at −20 °C for 2 h, saturated aqueous sodium hydrogen carbonate (135 cm^3) was added and the mixture stirred for 10 min. The dried organic phase was concentrated. The residue was dissolved in dichloromethane and washed with saturated aqueous sodium thiosulfate. The dried organic extracts were concentrated to give **2** (4.66 g, 87%) as a yellow oil, which was used without further purification in the next step (Found: C, 51.4; H, 5.7; N, 3.3; Cl, 25.7. $C_{18}H_{24}Cl_3NO_2Si$ requires C, 51.4; H, 5.75; N, 3.3; Cl, 25.3%); ν_{max}/cm^{-1} 1677; δ_H 0.2 (9 H, s, CH_3), 1.85–2.40 (6 H, m), 4.56 and 4.69 (each 1 H, 2 d, J 15.5, CH_2Ph), 4.76 (2 H, m, H-1$_{ax}$ and H-3), 7.15–7.40 (5 H, m, ArH); δ_C 0.2 (CH_3), 27.2, 27.2 and 29.6 (C-2, C-5 and C-6), 47.8 (CH_2Ph), 55.8 (C-1), 93.6 (CCl_3), 101.0 (C-3), 126.0, 126.9 and 128.5 (Ar), 137.3 (C-*ipso*), 149.6 (C-4), 160.8 (CO).

2-Benzyl-2-azabicyclo[3.3.1]nonane-3,6-dione 3

A suspension of silyl enol ether **2** (300 mg, 0.71 mmol) and AIBN (123 mg, 0.75 mmol) in benzene (6 cm^3) was heated to reflux. Then, TTMSS (0.76 cm^3, 2.48 mmol) was added dropwise and the reaction mixture was stirred at this temperature for 3 h. Evaporation of the solvent and chromatography of the residue [dichloromethane–MeOH (99:1)] gave **3** (120 mg, 69%) as a colourless oil (Found: M$^+$, 243.1249. $C_{15}H_{17}NO_2$ requires M, 243.1250); ν_{max}/cm^{-1} 1713, 1641; δ_H (COSY) 1.71 (1 H, tdd, J 13.5, 5.5, 2.5, H-8$_{ax}$), 1.99 (1 H, dm, J 13.5, H-9$_{anti}$), 2.06 (1 H, ddd, J 13, 6, 3, H-9$_{syn}$), 2.13 (1 H, m, H-8$_{eq}$), 2.28 (1 H, dd, J 15.5, 5, H-7$_{eq}$), 2.41 (1 H, ddd, J 16, 13, 7, H-7$_{ax}$), 2.47 (1 H, dd, J 17, 1.5, H-4$_{eq}$), 2.74 (1 H, dd, J 17, 7.5, H-4$_{ax}$), 2.76 (1 H, m, H-5$_{eq}$), 3.59 (1 H, m, $W_{1/2}$ 7,† H-1$_{eq}$), 4.03 and 5.25 (each 1H, 2 d, J 15, CH_2Ph), 7.20–7.30 (5 H, m, ArH); δ_C (HMQC) 29.9 (C-8), 32.3 (C-9), 34.0 (C-7), 35.0 (C-4), 44.2 (C-5), 48.4 (CH_2Ph), 50.0 (C-1), 127.7, 127.9 and 128.8 (Ar), 137.1 (C-*ipso*), 168.3 (C-3), 210.7 (C-6).

Cyclisation of 2 with 0.5 equiv. of TTMSS

Operating as above, silyl enol ether **2** (250 mg, 0.57 mmol) in benzene (5 cm^3) was treated with AIBN (99 mg, 0.57 mmol) and TTMSS (0.09 cm^3, 0.28 mmol). The crude material was chromatographed [hexane–AcOEt (1:1)]. The first eluate gave 2-*benzyl*-4,4-*dichloro*-2-*azabicyclo*[3.3.1]*nonane*-3,6-*dione* **5**, (67 mg, 37%) as a white solid; mp 102–103 °C (from dichloromethane) (Found: M$^+$, 311.0468. $C_{15}H_{15}Cl_2NO_2$ requires M, 311.0479); ν_{max}/cm^{-1} 1720, 1660; δ_H 1.82 (1 H, m, H-8$_{ax}$), 2.08 (1 H, ddd, J 14.5, 3.5, 2.5, H-9), 2.25 (1 H, dm, J 13, H-8$_{eq}$), 2.44–2.56 (2 H, m, H-7), 2.76 (1 H, ddd, J 14.5, 6.5, 3.5, H-9), 3.57 (1 H, m, W$_{1/2}$ 7, H-5$_{eq}$), 3.71 (1 H, m, $W_{1/2}$ 8, H-1$_{eq}$), 4.10 and 5.37 (each 1 H, 2 d, J 15, CH_2Ph), 7.20–7.40 (5 H, m, ArH); δ_C 30.1 (C-8), 31.0 (C-9), 34.9 (C-7), 49.6 (CH_2Ph), 51.1 (C-1), 62.9 (C-5), 81.2 (C-4), 127.8, 128.2 and 129.0 (Ar), 135.8 (C-*ipso*), 163.8 (C-3), 203.5 (C-6).

The second eluate gave (1*RS*,4*SR*,5*RS*)-2-*benzyl*-4-*chloro*-2-*azabicyclo*[3.3.1]*nonane*-3,6-*dione* **4**, (58 mg, 36%) as a white solid; mp 129–130 °C (from dichloromethane) (Found: M$^+$, 277.0862. $C_{15}H_{16}ClNO_2$ requires M, 277.0869); ν_{max}/cm^{-1} 1720, 1660; δ_H 1.79 (1 H, tdd, J 13.5, 5.5, 2.5, H-8$_{ax}$), 2.10-2.21 (1 H, m, H-9), 2.30 (1 H, ddd, J 13.5, 5.5, 2.5, H-8$_{eq}$), 2.43 (1 H, dm, J 15, H-7$_{eq}$), 2.52 (1 H, ddd, J 15.5, 13.5, 6.5, H-7$_{ax}$), 3.18 (1 H, m, $W_{1/2}$ 13, H-5$_{eq}$), 3.68 (1 H, m, $W_{1/2}$ 9, H-1$_{eq}$), 4.18 and 5.26 (1 H each, 2 d, J 15, CH_2Ph), 4.72 (1 H, d, J 7, H-4$_{ax}$), 7.20–7.40 (5 H, m, ArH); δ_C 29.7 (C-8), 33.1 (C-9), 34.7 (C-7), 49.4 (CH_2Ph), 50.8 (C-1), 52.1 (C-5), 55.1 (C-4), 128.0, 128.1 and 128.9 (Ar), 136.4 (C-*ipso*), 165.7 (C-3), 206.4 (C-6).

Cyclisation of 2 with 0.25 equiv. of TTMSS

Operating as above, silyl enol ether **2** (250 mg, 0.57 mmol) in benzene (5 cm^3) was treated with AIBN (93 mg, 0.57 mmol) and TTMSS (0.05 cm^3, 0.15 mmol), and the crude material was chromatographed [dichloromethane–MeOH (99.5:0.5)]. The first fraction gave ketone **1** (7 mg, 3%), the second gave **5** (77 mg, 43%) and the third gave **4** (35 mg, 22%).

(1*RS*,5*SR*,6*SR*)-2-Benzyl-6-hydroxy-2-azabicyclo[3.3.1] nonan-3-one 6

A suspension of silyl enol ether **2** (500 mg, 1.19 mmol) and AIBN (207 mg, 1.26 mmol) in benzene (10 cm^3) was heated to reflux. Then, TBTH (1.44 cm^3, 5.35 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 [dichloromethane–MeOH (96:4)] to give **6** (200 mg, 70%) as a white solid (Found: M$^+$, 245.1415. $C_{15}H_{19}NO_2$ requires M, 245.1420); ν_{max}/cm^{-1} 1616; δ_H 1.47–1.57 (5 H, m), 1.90 (1 H, dm, J 13, H-9), 2.27 (1 H, m, $W_{1/2}$ 13, H-5$_{eq}$), 2.46 (1 H, dd, J 18.5, 7, H-4$_{ax}$), 2.82 (1 H, d, J 18.5, H-4$_{eq}$), 3.38 (1 H, m, $W_{1/2}$ 8, H-1$_{eq}$), 3.75 (1 H, dt, J 11, 5, H-6$_{ax}$), 3.89 and 5.24 (each 1 H, 2 d, J 15, CH_2Ph), 7.20–7.40 (5 H, m, ArH); δ_C 25.2 (C-7), 27.4 (C-8), 30.3 and 30.4 (C-9 and C-4), 33.5 (C-5), 47.8 (CH_2Ph), 49.9 (C-1), 70.3 (C-6), 126.9, 127.3 and 128.2 (Ar), 137.1 (C-*ipso*), 171.2 (C-3).

† $W_{1/2}$ is the width at half maximum height of the signal.

Cyclisation of 2 with 3.5 equiv. of TBTH

Operating as above, silyl enol ether **2** (500 mg, 1.19 mmol) in benzene (10 cm^3) was treated with AIBN (207 mg, 1.26 mmol) and TBTH (1.12 cm^3, 4.16 mmol), and the crude material was chromatographed [dichloromethane–MeOH (96:4)]. The first fraction gave (1*RS*,5*RS*,6*SR*)-2-*benzyl*-4,4-*dichloro*-6-*hydroxy*-2-*azabicyclo*[3.3.1]*nonan*-3-*one* **8** (80 mg, 21%) as a white solid, mp 121–123 °C (from dichloromethane) (Found: C, 57.3; H, 5.6; N, 4.4. $C_{15}H_{17}Cl_2NO_2$ requires C, 57.3; H, 5.45; N, 4.45%); ν_{max}(KBr)/cm^{-1} 3598, 1671; δ_H 1.45–1.65 (2 H, m), 1.72 (1 H, dm, 1H), 1.85–2.05 (2 H, m), 2.64 (1 H, ddd, *J* 14, 6, 3, H-9), 3.17 (1 H, m, $W_{1/2}$ 8, H-5_{eq}), 3.46 (1 H, br s, H-1_{eq}), 3.86–3.93 (1 H, m, H-6_{ax}), 3.90 and 5.33 (each 1 H, 2 d, *J* 15, CH_2Ph), 7.20–7.40 (5 H, m, ArH); δ_C 26.4 (C-7), 28.0 (C-8), 31.0 (C-9), 49.2 (CH_2Ph), 50.9 (C-1), 51.4 (C-5), 73.7 (C-6), 86.1 (C-4), 127.6, 127.8 and 128.8 (Ar), 136.0 (C-*ipso*), 164.6 (C-3).

The second fraction gave (1*RS*,4*SR*,5*RS*,6*SR*)-2-*benzyl*-4-*chloro*-6-*hydroxy*-2-*azabicyclo*[3.3.1]*nonan*-3-*one* **7** (108 mg, 32%) as an oil (Found: C, 60.8; H, 6.55; N, 4.55. $C_{15}H_{18}ClNO_2 \cdot H_2O$ requires: C, 60.5; H, 6.75; N, 4.7%); ν_{max}/cm^{-1} 3700, 1653; δ_H 1.48 (1 H, m, H-8_{ax}), 1.60–2.12 (5 H, m), 2.89 (1 H, m, $W_{1/2}$ 11, H-5_{eq}), 3.43 (1 H, m, $W_{1/2}$ 8, H-1_{eq}), 3.83 (1 H, dt, *J* 12, 3.5, H-6_{ax}), 4.88 (1 H, d, *J* 6.5, H-4_{ax}), 3.96 and 5.27 (each 1 H, 2 d, *J* 15, CH_2Ph), 7.24–7.37 (5 H, m, ArH); δ_C 26.7 (C-7), 27.6 (C-8), 33.1 (C-9), 40.1 (C-5), 49.0 (CH_2Ph), 50.6 (C-1), 58.9 (C-4), 74.5 (C-6), 127.6, 127.9 and 128.6 (Ar), 136.6 (C-*ipso*), 166.7 (C-3).

The third fraction gave **6** (68 mg, 24%).

Cyclization of 2 with 1.2 equiv. of TBTH

Operating as above, silyl enol ether **2** (500 mg, 1.19 mmol) in benzene (10 cm^3) was treated with AIBN (207 mg, 1.26 mmol) and TBTH (0.38 cm^3, 1.43 mmol), and the crude material was chromatographed [hexane–AcOEt (30:70)]. The initial elution gave **5** (38 mg, 10%). Further elution gave **4** (45 mg, 14%), **8** (100 mg, 28%) and **7** (90 mg, 25%).

N-(4-Acetoxycyclohex-3-enyl)-*N*-benzyl-2,2,2-trichloroacetamide 9

A solution of ketone **1** (3 g, 8.6 mmol) and toluene-*p*-sulfonic acid (205 mg, 1.08 mmol) in prop-2-enyl acetate (30.7 cm^3, 278 mmol) was heated at reflux for 24 h. The mixture was cooled and sodium hydrogen carbonate was added. After filtration of the solid, the solvent was evaporated and the residue was chromatographed on alumina (dichloromethane) to give **9** (2.86 g, 85%) as a clear oil; ν_{max}/cm^{-1} 1756, 1676; δ_H 1.80–2.50 (6 H, m), 2.10 (3 H, s, CH_3), 4.55 and 4.73 (each 1 H, 2 d, *J* 16, CH_2Ar), 4.82 (1 H, m, H-1_{ax}), 5.30 (1 H, br s H-3), 7.10–7.45 (5 H, m, ArH); δ_C 20.8 (CH_3), 26.5 and 26.8 (C-2, C-5 and C-6), 47.6 (CH_2Ph), 55.0 (C-1), 93.4 (CCl_3), 111.5 (C-3), 125.9, 126.9 and 128.4 (Ar), 137.0 (C-*ipso*), 147.1 (C-4), 160.6 (NCO), 169.0 (CO).

(1*RS*,5*SR*,6*SR*)-6-Acetoxy-2-benzyl-2-azabicyclo[3.3.1] nonan-3-one 10

A suspension of enol acetate **9** (2.23 g, 5.71 mmol) and AIBN (975 mg, 5.93 mmol) in benzene (46 cm^3) was heated to reflux. Then, TTMSS (6.13 cm^3, 19.8 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 [dichloromethane–MeOH (98:2)] to give **10** (1.11 g, 68%) as a white solid, mp 146–147 °C (from ether) (Found: C, 71.0; H, 7.4; N, 4.9. $C_{17}H_{21}NO_3$ requires C, 71.05; H, 7.4; N, 4.9%); ν_{max} (KBr)/cm^{-1} 1731, 1639; δ_H (500 MHz, COSY) 1.46 (1 H, tdd, *J* 13, 3.5, 2, H-8_{ax}), 1.53 (1 H, qd, *J* 13.5, 4.5, H-7_{ax}), 1.74 (1 H, ddd, *J* 13.5, 5, 3, H-9_{anti}), 1.83 (1 H, dm, *J* 12, H-7_{eq}), 1.86 (1 H, dm, *J* 12, H-8_{eq}), 1.95 (1 H, ddd, *J* 13.5, 7, 3.5, H-9_{syn}), 2.05 (3 H, s, CH_3), 2.39 (1 H, m, $W_{1/2}$ 13, H-5_{eq}), 2.54 (1 H, dd, *J* 18.5, 7, H-4_{ax}), 2.75 (1 H, dt, *J* 19, 1, H-4_{eq}), 3.44 (1 H, br s, H-1_{eq}), 4.85 (1 H, dt, *J* 11, 4.5, H-6_{ax}), 3.93 and 5.26 (each 1 H, 2 d, *J* 15, CH_2Ph), 7.24–7.34 (5 H, m, ArH); δ_C (HMQC) 21.2 (CH_3), 22.3 (C-7), 27.6 (C-8), 30.8 (C-9), 31.3 (C-5), 31.5 (C-4), 48.1 (CH_2Ph), 49.9 (C-1), 73.3 (C-6), 127.3, 127.7 and 128,5 (Ar), 137.4 (C-*ipso*), 170.3 and 170.4 (C-3 and CO).

Conversion of 10 to 6

Aqueous sodium hydroxide (2 M, 25 cm^3) was added to the acetate **10** (500 mg, 1.74 mmol) in ethanol (25 cm^3) and the reaction mixture was heated at reflux temperature for 16 h. The ethanol was evaporated and the resulting aqueous phase was extracted with dichloromethane. Concentration of the dried organic extracts gave the alcohol **6** (392 mg, 92%).

Cyclisation of 9 using TBTH

Following the procedure outlined for the cyclisation of **2**, the enol acetate **9** (230 mg, 0.64 mmol) was treated with TBTH (0.59 cm^3, 2.24 mmol) and AIBN. After work-up, the crude material was chromatographed [hexane–AcOEt (1:9)]. The first fraction gave (1*RS*,4*SR*,5*RS*,6*SR*)-6-*acetoxy*-2-*benzyl*-4-*chloro*-2-*azabicyclo*[3.3.1]*nonan*-3-*one* **11** (27 mg, 13%) as an oil (Found: M^+, 321.0865. $C_{17}H_{20}ClNO_3$ requires *M*, 321.0871); ν_{max}/cm^{-1} 1729, 1656; δ_H 1.53 (1 H, m, H-8_{ax}), 1.8–2.2 (5 H, m), 2.07 (3 H, s, CH_3), 3.03 (1 H, m, $W_{1/2}$ 10, H-5_{eq}), 3.47 (1 H, br s, H-1_{eq}), 4.74 (1 H, d, *J* 5, H-4_{ax}), 4.94 (1 H, m, H-6_{ax}), 3.97 and 5.27 (each 1 H, 2 d, *J* 15, CH_2Ph), 7.23–7.36 (5 H, m, ArH); δ_C 21.3 (CH_3), 22.5 (C-7), 27.3 (C-8), 32.4 (C-9), 37.4 (C-5), 48.9 (CH_2Ph), 50.6 (C-1), 57.1 (C-4), 74.0 (C-6), 127.6, 127.9 and 128.6 (Ar), 136.7 (C-*ipso*), 167.1 (C-3), 170.6 (CO).

The second fraction gave the acetate **10** (104 mg, 56%).

2,2,2-Trichloro-*N*-[2-(indol-3-yl)ethyl]-*N*-[4-(trimethylsilyloxy)-cyclohex-3-enyl]acetamide 13

Following the procedure outlined for the synthesis of the silyl enol ether **2**, ketone **12** (500 mg, 1.23 mmol) gave the *title compound* **13** (500 mg, 85%) as a yellow solid which was used without purification in the next step (Found: C, 52.8; H, 5.8; Cl, 23.3; N, 5.9. $C_{21}H_{27}Cl_3NO_2Si$ requires: C, 53.2; H, 5.9; Cl, 23.45; N, 5.9%); ν_{max}/cm^{-1} 1670; δ_H 0.24 (9 H, s, CH_3), 1.85–2.45 (6 H, m), 3.11 and 3.55 (each 2 H, 2 m, AA′BB′ system, $InCH_2$-CH_2N), 4.64 (1 H, m, H-1′$_{ax}$), 4.82 (1 H, m, $W_{1/2}$ 10, H-3′), 7.0 (1 H, s, H-2), 7.15 (1 H, t, *J* 7, H-5), 7.20 (1 H, t, *J* 7, H-6), 7.35 (1 H, d, *J* 8, H-7), 7.78 (1 H, d, *J* 7.5, H-4), 8.31 (1 H, br s, NH); δ_C 0.2 (CH_3), 23.8 ($InCH_2$), 26.7 and 29.5 (C-2′, C-5′ and C-6′), 46.1 (CH_2N), 55.3 (C-1′), 93.7 (CCl_3), 101.0 (C-3′), 111.1 (C-7), 112.3 (C-3), 118.8 (C-4), 119.2 (C-5), 121.8 (C-6), 122.1 (C-2), 127.1 (C-3a), 136.1 (C-7a), 149.5 (C-4′), 160.1 (CO).

2-[2-(Indol-3-yl)]ethyl]-2-azabicyclo[3.3.1]nonane-3,6-dione 14

A suspension of silyl enol ether **13** (200 mg, 0.42 mmol) and AIBN (73 mg, 0.44 mmol) in benzene (3.5 cm^3) was heated to reflux. Then TTMSS (0.45 cm^3, 1.47 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 [dichloromethane–MeOH (99:1)] to give **14** (72 mg, 58%) as a white solid (Found: C, 69.7; H, 6.9; N, 9.0. $C_{18}H_{20}N_2O_2 \cdot 3/4\ H_2O$ requires C, 69.8; H, 7.0; N, 9.05%); ν_{max} (KBr)/cm^{-1} 3404, 1712, 1620; δ_H (COSY) 1.72 (1 H, tdd, *J* 13.5, 5.5, 2, H-8_{ax}), 1.86–1.87 (2 H, each apparent s, H-9), 2.16 (1 H, dm, *J* 13, H-8_{eq}), 2.31 (1 H, dd, *J* 16, 5, H-7_{eq}), 2.41 (1 H, ddd, *J* 16, 13, 7, H-7_{ax}), 2.44 (1 H, d, *J* 17.5, H-4_{eq}), 2.70 (1 H, dd, *J* 18, 8, H-4_{ax}), 2.73 (1 H, br s, H-5_{eq}), 3.06–3.23 (m, 3 H, NCH and $InCH_2$), 3.39 (1 H, m, $W_{1/2}$ 8, H-1_{eq}), 4.25 (1 H, m, NCH), 7.07 (1 H, d, *J* 2, H-2′), 7.13 (1 H, td, *J* 8, 1, H-5′), 7.20 (1 H, td, *J* 8, 1, H-6′), 7.37 (1 H, d, *J* 8, H-7′), 7.66 (1 H, d, *J* 8, H-4′), 8.08 (1 H, br s, NH); δ_C (HMQC) 23.6 ($InCH_2$), 30.4 (C-8), 31.9

(C-9), 33.9 (C-7), 35.1 (C-4), 44.1 (C-5), 47.8 (CH_2N), 52.0 (C-1), 111.2 (C-7′), 113.0 (C-3′), 118.7 (C-4′), 119.4 (C-5′), 121.9 (C-6′), 122.1 (C-2′), 127.4 (C-3a), 136.2 (C-7a), 168.1 (C-3), 211.1 (C-6).

N-(4-Acetoxycyclohex-3-enyl)-*N*-[2-(1-acetylindol-3-yl)ethyl]-2,2,2-trichloroacetamide 15

Following the procedure outlined above for the synthesis of the enol acetate **9**, the ketone **12** (3 g, 7.3 mmol) gave, after chromatography on alumina (dichloromethane), the *title compound* **15** (3.5 g, 56%) as an oil, which solidified on standing: mp 178.5–179 °C (in ether) (Found: M^+, 484.0723. $C_{22}H_{23}Cl_3N_2O_4$ requires *M*, 484.0730) (Found: C, 53.05; H, 4.6; N, 5.5. $C_{22}H_{23}Cl_3N_2O_4 \cdot 1/2H_2O$ requires C, 53.4; H, 4.9; N, 5.65%); ν_{max}/cm^{-1} 1754, 1704, 1681; δ_H (COSY): 2.00 (1 H, m, H-6′$_{eq}$), 2.03 (1 H, qd, *J* 12.5, 6, H-6′$_{ax}$), 2.14 (3 H, s, CH_3), 2.26 (1 H, dm, *J* 13.5, H-5′$_{eq}$), 2.32–2.51 (3 H, m, H-2′ and H-5′$_{ax}$), 2.63 (3 H, s, CH_3CON), 3.06 and 3.56 (each 2 H, 2 m, AA′BB′ system, $InCH_2CH_2N$), 4.70 (1 H, m, H-1′$_{ax}$), 5.34 (1 H, m, $W_{1/2}$10.5, H-3′), 7.27 (1 H, br s, H-2), 7.33 (1 H, td, *J* 7.5, 0.5, H-5), 7.38 (1 H, t, *J* 7.5, H-6), 7.73 (1 H, d, *J* 8, H-4), 8.43 (1 H, br d, *J* 8, H-7); δ_C (HMQC) 21.0 (CH_3), 23.6 ($InCH_2$), 24.0 (CH_3CON), 26.4 and 26.5 (C-2′, C-5′ and C-6′), 45.3 (CH_2N), 54.7 (C-1′), 93.5 (CCl_3), 111.7 (C-3′), 116.6 (C-7), 119.1 (C-4 and C-3), 122.7 (C-2), 123.7 (C-5), 125.4 (C-6), 130.1 (C-3a), 135.8 (C-7a), 147.3 (C-4′), 160.3 (NCO), 168.3 and 169.3 (CO).

(1*RS*,5*SR*,6*SR*)-6-Acetoxy-2-[2-(1-acetylindol-3-yl)ethyl]-2-azabicyclo[3.3.1]nonan-3-one 16

A suspension of enol acetate **15** (1.5 g, 3.08 mmol) and AIBN (537 mg, 3.57 mmol) in benzene (27 cm^3) was heated to reflux. Then, TTMSS (3.6 cm^3, 10.8 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 [dichloromethane–MeOH (98 : 2)] to give **16** (690 mg, 60%) as a white solid: mp 113–113.5 °C (from ether) (Found, M^+, 382.1892. $C_{22}H_{26}N_2O_4$ requires *M*, 382.1882) (Found: C, 67.6; H, 7.1; N, 7.1. $C_{22}H_{26}N_2O_4 \cdot 1/2H_2O$ requires C, 67.5; H, 6.95; N, 7.15%); ν_{max}/cm^{-1} 1731, 1704, 1633; δ_H (COSY) 1.46 (1 H, qd, *J* 13.5, 3.5, H-7$_{ax}$), 1.48 (1 H, tm, *J* 13.5, H-8$_{ax}$), 1.66 (1 H, ddd, *J* 13.5, 3.5, 2.5, H-9$_{anti}$), 1.76–1.89 (3 H, m, H-9$_{syn}$, H-7$_{eq}$ and H-8$_{eq}$), 1.93 (3 H, s, CH_3), 2.27 (1 H, m, $W_{1/2}$ 13.5, H-5$_{eq}$), 2.37 (1 H, dd, *J* 18.5, 7, H-4$_{ax}$), 2.50 (3 H, s, $NCOCH_3$), 2.61 (1 H, dd, *J* 19, 1.5, H-4$_{eq}$), 2.88–3.05 (3 H, m, NCH and $InCH_2$), 3.27 (1 H, br s, H-1$_{eq}$), 4.09–4.17 (1 H, m, NCH), 4.80 (1 H, dt, *J* 11.5, 5, H-6$_{ax}$), 7.29 (1 H, td, *J* 7.5, 1, H-5′), 7.32 (1 H, s, H-2′), 7.34 (1 H, td, *J* 7.5, 1, H-6′), 7.59 (1 H, d, *J* 7.5, H-4′), 8.40 (1 H, d, *J* 6.5, H-7′); δ_C (HMQC) 21.2 (CH_3), 22.1 (C-7), 23.4 ($InCH_2$), 24.0 (CH_3CON), 28.2 (C-8), 30.6 (C-9), 31.1 (C-5), 31.6 (C-4), 46.5 (CH_2N), 51.9 (C-1), 73.2 (C-6), 116.6 (C-7′), 118.8 (C-4′), 119.7 (C-3′), 122.5 (C-2′), 123.5 (C-5′), 125.3 (C-6′), 130.3 (C-3a), 135.7 (C-7a), 168.3 (NCO), 170.3 and 170.4 (C-3 and CO).

Acknowledgements

Support for this research was provided by DGES, Spain (project PB97-0877). Thanks are also due to "Comissionat per a Universitats i Recerca" (Catalonia) for Grant 1997SGR-00166 and for a fellowship to C. E.

Notes and references

1 For recent examples in natural product synthesis, see: (*a*) J. Quirante, C. Escolano, A. Merino and J. Bonjoch, *J. Org. Chem.*, 1998, **63**, 968; (*b*) L. Boiteau, J. Boivin, A. Liard, B. Quiclet-Sire and S. Z. Zard, *Angew. Chem., Int. Ed.*, 1998, **37**, 1128; (*c*) M. Ikeda, M. Hamada, T. Yamashita, F. Ikegami, T. Sato and H. Ishibashi, *Synlett*, 1998, 1246; (*d*) M. Ikeda, T. Sato and H. Ishibashi, *Rev. Heteroatom Chem.*, 1998, **18**, 169.

2 For some starting materials leading to a radical centre at the β-position to a nitrogen atom (3-azacarbon radicals) using the hydride method, see *inter alia*: S. J. Danishefsky and J. S. Panek, *J. Am. Chem. Soc.*, 1987, **109**, 917; Y. Watanabe, Y. Ueno, C. Tanaka, M. Okawara and T. Endo, *Tetrahedron Lett.*, 1987, **28**, 3953; G. Stork and R. Mah, *Heterocycles*, 1989, **28**, 723; H. Ishibashi, T. S. So, K. Okochi, T. Sato, N. Nakamura, H. Nakatani and M. Ikeda, *J. Org. Chem.*, 1991, **56**, 95; P. F. Keusenkothen and M. B. Smith, *Tetrahedron*, 1992, **48**, 2977; M. Ishizaki, K. Kurihara, E. Tanazawa and O. Hoshino, *J. Chem. Soc., Perkin Trans. 1*, 1993, 101; E. W. Della and A. M. Knill, *J. Org. Chem.*, 1996, **61**, 7529; A. F. Parsons and R. M. Pettifer, *Tetrahedron Lett.*, 1997, **38**, 5907; V. Gupta, M. Besev and L. Engman, *Tetrahedron Lett.*, 1998, **39**, 2429.

3 For examples of the use of (alkoxy)methoxyalkenes as radical acceptors of 3-azaradicals, see: S. Knapp and F. S. Gibson, *J. Org. Chem.*, 1992, **57**, 4802.

4 (*a*) For this intermolecular process mediated by a tin hydride, see: B. Giese, H. Horler and M. Leising, *Chem. Ber.*, 1986, **119**, 444; P. Renaud, *Tetrahedron Lett.*, 1990, **31**, 4601; (*b*) for addition of acyl radicals to silyl enol ethers, see: D. L. Boger and R. J. Mathvink, *J. Org. Chem.*, 1992, **57**, 1429.

5 For procedures to promote additions of electrophilic radicals to silyl enol ethers other than the hydride method, see: (*a*) an oxidative process, E. Baciocchi, A. Casu and R. Ruzziconi, *Synlett*, 1990, 679; Y. Kohno and K. Narasaka, *Chem. Lett.*, 1993, 1689; (*b*) the atom transfer method, K. Miura, Y. Takeyama, K. Oshima and K. Utimoto, *Bull. Chem. Soc. Jpn.*, 1991, **64**, 1542; (*c*) thiol-catalysed addition of aldehydes, H.-S. Dang and B. P. Roberts, *Chem. Commun.*, 1996, 2201; (*d*) photo-irradation, M. Mitani and H. Sakata, *Chem. Commun.*, 1998, 1877.

6 It has been noted that nucleophilic alkyl radicals do not react with silyl enol ethers: H. Urabe and I. Kuwajima, *Tetrahedron Lett.*, 1986, **27**, 1355.

7 For a review on radical cyclisation reactions, see: B. Giese, B. Kopping, T. Göbel, J. Dickhaut, G. Thoma, K. J. Kulicke and F. Trach, *Org. React.*, 1996, **48**, 301.

8 For references on (*a*) carbocyclic series, see ref. 6; (*b*) 1-oxa-2-silacyclohexanes, see R. D. Walkup, R. R. Kane and N. U. Obeyesekere, *Tetrahedron Lett.*, 1990, **31**, 1531; for related heterocyclic compounds: J. H. Hutchinson, T. S. Daynard and J. W. Gillard, *Tetrahedron Lett.*, 1991, **32**, 573; A. G. Myers, D. Y. Gin and D. H. Rogers, *J. Am. Chem. Soc.*, 1993, **115**, 2036.

9 (*a*) For cyclisations of alkyl radicals with enol ethers, see: A. L. J. Beckwith and D. H. Roberts, *J. Am. Chem. Soc.*, 1986, **108**, 5893; T. V. RajanBabu, T. Fukunaga and G. S. Reddy, *J. Am. Chem. Soc.*, 1989, **111**, 1759; J.-C. Lopez and B. Fraser-Reid, *J. Am. Chem. Soc.*, 1989, **111**, 3450; J. Marco-Contelles and B. Sánchez, *J. Org. Chem.*, 1993, **58**, 4293; C. Imboden, T. Bourquard, O. Corminboeuf, P. Renaud, K. Schenk and M. Zahouily, *Tetrahedron Lett.*, 1999, **40**, 495; (*b*) for cyclisations with aryl radicals, see: S. Atarashi, J.-K. Choi, D.-C. Ha, D. J. Hart, D. Kuzmich, C.-S. Lee, S. Ramesh and S. C. Wu, *J. Am. Chem. Soc.*, 1997, **119**, 6226; (*c*) for cyclisations with acyl radicals, see ref. 4*b*.

10 (*a*) For cyclisations of stabilized radicals with enol acetates, see: F. Barth and C. O-Yang, *Tetrahedron Lett.*, 1991, **32**, 5873; (*b*) for cyclisations from aryl radicals, see: S. A. Ahmad-Junan and D. A. Whiting, *J. Chem. Soc., Chem. Commun.*, 1988, 1160.

11 For hydride reagent promoted radical cyclisations of trichloroacetamides with alkenes with an electron-withdrawing substituent, see: (*a*) Y. Hirai, A. Hagiwara, T. Terada and T. Yamazaki, *Chem. Lett.*, 1987, 2417; (*b*) A. F. Parsons and R. J. K. Taylor, *J. Chem. Soc., Perkin Trans. 1*, 1994, 1945; (*c*) K. Goodall and A. F. Parsons, *Tetrahedron*, 1996, **52**, 6739; (*d*) J. Quirante, C. Escolano, M. Massot and J. Bonjoch, *Tetrahedron*, 1997, **53**, 1391.

12 For hydride reagent promoted radical cyclisations of trichloroacetamides with non-activated alkenes, see: (*a*) H. Nagashima, N. Ozaki, M. Ishii, K. Seki, M. Washiyama and K. Itoh, *J. Org. Chem.*, 1993, **58**, 464; (*b*) J. Quirante, C. Escolano, F. Diaba and J. Bonjoch, *Heterocycles*, 1999, **50**, in the press.

13 For hydride reagent promoted radical cyclisations of *N*-vinylic trichloroacetamides, see: H. Ishibashi, M. Higuchi, M. Ohba and M. Ikeda, *Tetrahedron Lett.*, 1998, **39**, 75; M. Ikeda, S. Ohtani, T. Yamamoto, T. Sato and H. Ishibashi, *J. Chem. Soc., Perkin Trans 1*, 1998, 1763.

14 For a preliminary report of part of this work, see: J. Quirante, C. Escolano, L. Costejà and J. Bonjoch, *Tetrahedron Lett.*, 1997, **38**, 6901.

15 (*a*) Y.-W. Guo, A. Madaio, G. Scognamiglio and E. Trivellone, *Tetrahedron*, 1996, **52**, 8341; (*b*) R. Downham, F. W. Ng and L. E. Overman, *J. Org. Chem.*, 1998, **63**, 8096.

16 (*a*) F. Kong, R. J. Andersen and T. M. Allen, *J. Am. Chem. Soc.*, 1994, **116**, 6007; (*b*) N. Matzanke, R. J. Gregg and S. M. Weinreb, *J. Org. Chem.*, 1997, **62**, 1920.
17 K. Sakamoto, E. Tsujii, F. Abe, T. Nakanishi, M. Yamashita, N. Shigematsu, S. Izumi and M. Okuhara, *J. Antibiot.*, 1996, **49**, 37.
18 R. D. Miller and D. R. McKean, *Synthesis*, 1979, 730.
19 For a related process catalysed by a ruthenium(II) phosphine complex, see: N. Kamigata, K. Udodaira and T. Shimizu, *J. Chem. Soc., Perkin Trans. 1*, 1997, 783.
20 The great strength of the Si–Cl bond in Me_3SiCl (112 kcal mol^{-1}) can drive the process.
21 C. Chatgilialoglu, J. Dickhaut and B. Giese, *J. Org. Chem.*, 1991, **56**, 6399.
22 Attempts to reduce ketone **3** were also unsuccessful when working with TBTH–AIBN, alone, with tributylchlorostannane or with trimethylchlorosilane in the reaction medium.
23 When the ratio of TBTH is low (see Table 1) a significant percentatge of ketones **4** and **5** are isolated, suggesting that a competitive mechanism, similar to that depicted in Scheme 2, is also operating.
24 (*a*) The direct formation of alcohols in reactions promoted by TBTH and silyl enol ethers has not previously been noted, see refs. 4 and 8; (*b*) for a simple reduction of α-silyloxyl radicals by TBTH, see: S.-Y. Chang, W.-T. Jiaang, C.-D. Cherng, K.-H. Tang, C.-H. Huang and Y.-M. Tsai, *J. Org. Chem.*, 1997, **62**, 9089.
25 D. P. Curran, N. A. Porte and B. Giese, *Stereochemistry of Radical Reactions*, VCH, Weinheim, 1996; W. Damm, B. Giese, J. Hartung, T. Hasskerl, K. N. Houk, O. Hüter and H. Zipse, *J. Am. Chem. Soc.*, 1992, **114**, 4067.
26 J. Burfeindt, M. Patz, M. Müller and H. Mayr, *J. Am. Chem. Soc.*, 1998, **120**, 3629 and refs. therein.
27 D. P. Curran, *Synlett*, 1991, 63.

Paper 9/00952C