Pergamon

Tetrahedron, Vol. 53, No. 25, pp. 8519-8530, 1997

0040-4020/97 $17.00 + 0.00

PII: S0040-4020(97)00510-3

Unusual Reductive Cleavage of 7-Oxa-bicyclo[2,2,1]heptane System for the Synthesis of Tetrahydrofuran Derivatives

Giovanni Viti*, Enzo Perrotta, Danilo Giannotti, Rossano Nannicini

Chemical Research Department, Menarini Ricerche S.p.A., Via Sette Santi 3, 50131 Firenze (Italy)

Abstract: An unusual reductive cleavage of a C-C bond adjacent to the ethereal bridge in the 7-oxa-bicyclo[2,2,1]heptane system led to some valuable tetrahydrofuran derivatives and, in particular, to tetrahydrofuranyl glycine derivatives. © 1997 Elsevier Science Ltd.

Introduction

In the last two decades there has been an increasing demand on new, non-natural amino acids and of their corresponding amino aldehydes as building blocks for pharmacological agents. Few examples exist where 2-tetrahydrofuranyl is used as a side chain of an amino acid[1] and their synthetic pathways generally involve the reduction of the furan ring with the consequent formation of mixtures of stereoisomers.

7-Oxa-bicyclo[2,2,1]heptane derivatives have the tetrahydrofuranyl moiety included in their structure and can be easily prepared, sometimes with complete stereocontrol, by the well-known Diels Alder reaction. On principle 2-tetrahydrofuranyl derivatives could be generated out of the bicyclic system by the C-C cleavage of one of the bonds adjacent to the ethereal bridge without affecting the stereogenic centers not involved in the cleavage; but, in our knowledge, this procedure has not been described up to now.

In this paper we report the reductive cleavage of a C-C bond adjacent to the ethereal bridge in the 7-oxa-bicyclo[2,2,1]heptane system leading to some valuable tetrahydrofuran derivatives.

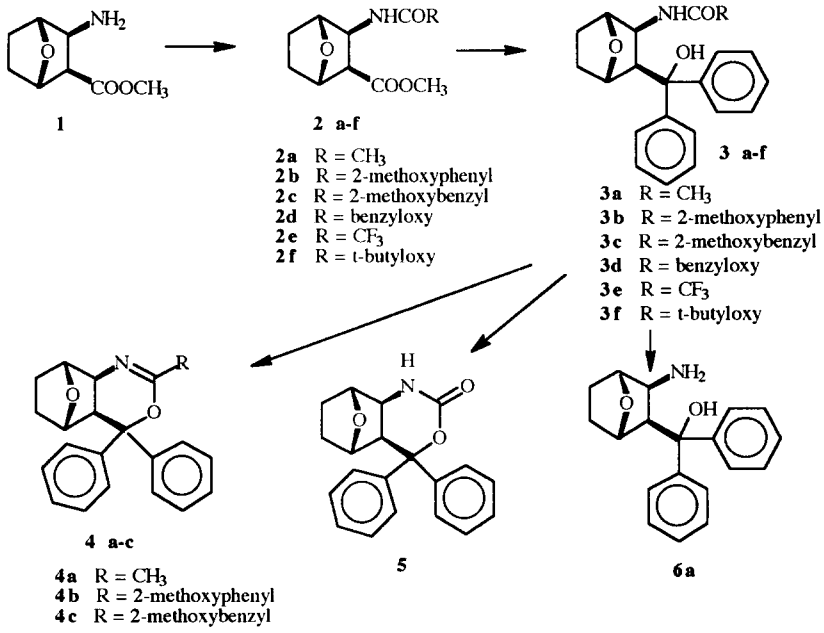
Results and Discussion

According to our research program we used methyl 3-*exo*-amino-7-oxabicyclo[2,2,1]heptane-2-*exo*-carboxylate **1**[2] as the starting material[3] for the synthesis of 2-*exo*-diphenylmethyl-3-*exo*-amino-7-oxabicyclo[2,2,1]heptane derivatives as new potential tachykinin antagonists.

Acylation reactions of compound **1** (Scheme 1) gave the N-protected derivatives **2a-f** which reacted with phenylmagnesium bromide giving the diphenylcarbinols **3a-f**. Tertiary alcohol can generally be reduced to the corresponding alkane according to the procedure described by Carey and Tremper with trifluoroacetic acid (TFA) and triethylsilane;[4] the presence of phenyl rings is highly recommended in this type of reaction in order to stabilize the carbocation and to minimize the elimination reaction.

When compounds **3a-c**, bearing acyl-protecting groups on the amino moiety, were treated according to this procedure, no reduction was detected and the formation of an oxazine ring (compounds **4a-c**) was observed. When the urethane-type benzyloxycarbonyl protecting group was used (compound **3d**), elimination of the benzyl moiety took place and oxazinone **5** was obtained. The formation of an oxazine ring was probably due to the TFA which acted as a dehydrating agent.[5]

Scheme 1

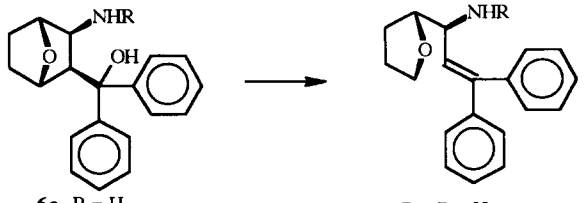


Thus, in acid dehydrating conditions, the presence of an acyl-type protecting group determined the formation of a cyclic oxazine, preventing the expected reduction by the triethylsilane. To avoid this undesired cyclization, we removed the amino protecting group before submitting our diphenyl carbinols to the reduction. Cleavage of the amide bond in compounds **3a-c** under basic condition was very difficult, while the trifluoroacetate **3e** was hydrolysed, with 0.25 M NaOH/ethanol 1:1, in 1 h at reflux temperature, to give the amine **6a**; compound **6a** was also obtained, without any cyclization, when the acid-labile protecting group t-butyloxycarbonyl in compound **3f** was removed with TFA in dichloromethane.

When the reduction of the diphenylcarbinol moiety of compound **6a** with triethylsilane/TFA[4] in dichloromethane was attempted, the unexpected reductive cleavage of a C-C bond and the formation in a good yield of the tetrahydrofuran derivative **7a** were observed. Similarly the secondary amines **6b** and **6c** (obtained by a $LiAlH_4$ reduction of **3b** and **3d**[6] respectively) gave the tetrahydrofurans **7b** and **7c**.

TFA could be conveniently replaced by the Lewis acid boron trifluoride diethyl etherate with a high increase in the yield.

The reaction was slow, taking up to 8 hours at reflux temperature to go to completion, and, in addition, no NMR evidence for the presence of the elimination product of type **8** could be detected.

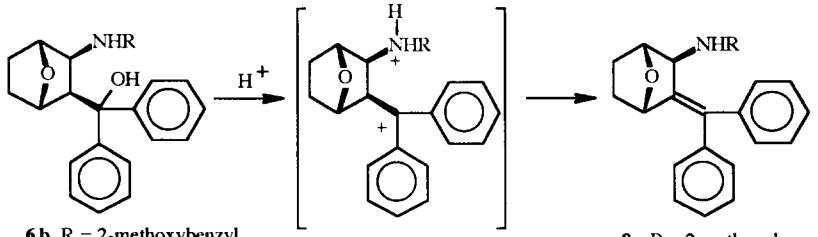


6a R = H
6b R = 2-methoxybenzyl
6c R = methyl

7a R = H
7b R = 2-methoxybenzyl
7c R = methyl

The use of TFA in dichloromethane in the absence of triethylsilane afford dehydration of **6b** to alkene **8**, but it took several days at reflux temperature[7] indicating that dehydration is much slower than the reductive cleavage and that the two reactions probably follow different pathways.

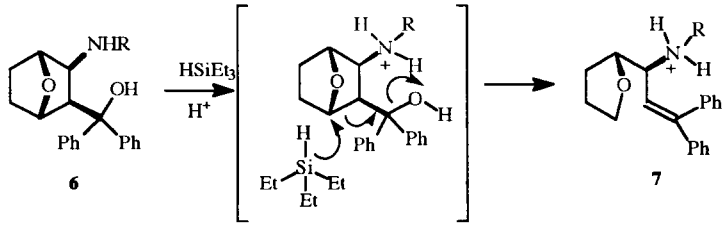
Dehydration was believed to be a consequence of the initial formation of a carbocation on the diphenylmethyl moiety, but probably the spatially close ammonium group, due to the salification of the amine in the acid medium, hindered its formation and made the entire dehydration process very difficult.



6b R = 2-methoxybenzyl

8 R = 2-methoxybenzyl

Since no reductive cleavage could be observed with triethylsilane without the addition of an acid, the formation of an ammonium ion was believed to play a fundamental role in the reaction pathway as tentatively depicted in the following scheme:

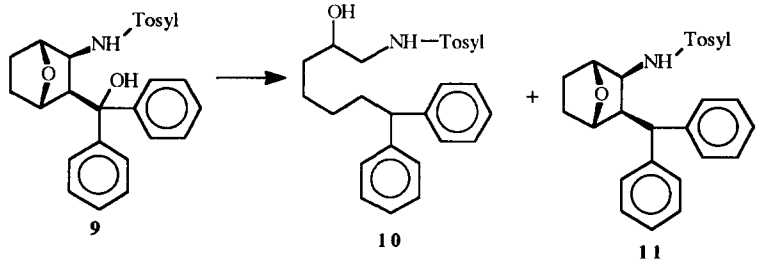


6

7

No diastereoisomers were detected in the NMR spectra, indicating that the two stereogenic centers of compounds **7** probably retained the original configuration of reactants **6**.

In order to evaluate the importance of the basic amine group in this peculiar reductive cleavage, the tosyl derivative **9** was prepared; **9** had no basic amine and, in addition, did not contain any carbonyl group which could induce a cyclization to an undesired oxazine of type **4**.

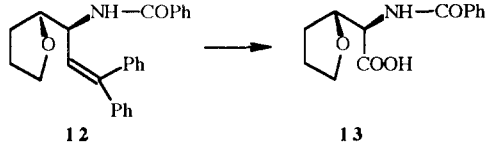


9 **10** **11**

Reaction of compound **9** with TFA or boron trifluoride diethyl etherate/triethylsilane gave as major products two compounds which were identified as compounds **10** and **11**; in any case no NMR evidence for the presence of compounds of type **7** could be detected in the reaction mixture.

Formation of compound **11** strongly supported our hypothesis on the importance of protonation of the amine in this peculiar reductive cleavage. In fact, formation of the carbocation on the diphenylcarbinol moiety in compound **9** would presumely not be hindered by any vicinal ammonium ion, making the subsequent reduction, by the hydride triethylsilane to the corresponding diphenylmethane derivative **11**, feasible.

Compounds **7** can be considered as 2-tetrahydrofuranylglycine derivatives with the carboxylic function masked with a diphenylmethylene group; therefore oxidation of the double bond was examined to generate the desired carboxy group.



12 **13**

As expected, the oxidation with ruthenium oxide[8] of the benzoyl protected amine **12** gave the 2-tetrahydrofuranylglycine derivative **13** in good yield.[9]

Experimental section

Melting points were determined by a Mettler FP81 apparatus. All the nmr spectra were measured on a Varian Gemini spectrometer operating at 200 MHz for proton and 50.3 MHz for carbon and were recorded in $CDCl_3$ solution unless otherwise stated. The resonances are expresssed in p.p.m. and coupling constants J in Hertz. Data were transferred to a Macintosh computer and processed using the SwaN-MR program.[10] Homonuclear and heteronuclear correlation spectra were recorded using the standard Varian software. Mass spectra were

taken with a Hewlett Packard 5988A spectrometer using the electrical ionization (EI) or the thermospray (TS) technique and are presented as m/z (% rel. int.).

Methyl 3-exo-acetylamino-7-oxabicyclo[2,2,1]heptane-2-exo-carboxylate **2a**. Acetic anhydride (2 ml, 22 mmol) was added to a solution of the hydrochloric salt of compound **1** (2 g, 9.6 mmol) in acetic acid (10 ml). After stirring for 2 h at room temperature, the solution was warmed at 80-100°C for half an hour, evaporated *in vacuo* and the residue crystallized with isopropyl ether. The solid material was purified by chromatography eluting with petroleum ether-EtOAc (3:1) to give compound **2a** ; yield 85%. MS (TS): 214 (100, M+1$^+$), 231 (84, M+18$^+$); ^{1}H NMR (D_2O): 1.5-1.9 (m, 4H), 1.91 (s, 3H, CH_3), 3.11 (d, 1H, J = 8.4), 3.6 (s, 3H, CH_3), 4.42 (m, 2H), 4.85 (d, 1H, J = 2.2), 8.07 (m, 1H, NH); ^{13}C NMR (D_2O): (CH_3) 26.0, 56.5 (CH_2) 30.0, 32.2, (CH) 58.6, 60.6, 82.6, 84.7, (C) 177.6, 177.7. Elem. Anal., found % (calcd for $C_{10}H_{15}NO_4$): C, 56.31 (56.33); H, 7.25 (7.09); N, 6.48 (6.57).

Similarly, using 1.2 eq. of acetic anhydride in a CH_3CN solution of the hydrochloric salt of compound **1**, in the presence of 2.5 eq. of NEt_3, the following acyl derivatives were obtained.

Methyl 3-exo-(2-methoxybenzoyl)amino-7-oxabicyclo[2,2,1]heptane-2-exo-carboxylate **2b**; yield 63%. MS (TS): 306 (100, M+1$^+$); ^{1}H NMR: 1.4-1.8 (m, 4H), 2.96 (d, 1H, J = 7.9), 3.47 (s, 3H, CH_3), 3.89 (s, 3H, CH_3), 4.34 (d, 1H, J = 4.0), 4.76 (m, 2H), 6.87 (d, 1H, J = 7.8), 6.96 (t, 1H, J = 7.8), 7.36 (dt, 1H, J = 2.0, 7.8), 8.06 (dd, 1H, J = 2.0, 7.8), 8.39 (d, 1H, NH, J = 9.8). Elem. Anal., found % (calcd for $C_{16}H_{19}NO_5$): C, 63.07 (62.94); H, 6.21 (6.27); N, 4.58 (4.59).

Methyl 3-exo-[(2-methoxyphenyl)acetyl]amino-7-oxabicyclo[2,2,1]heptane-2-exo-carboxylate **2c**; yield 78%. MS (TS): 320 (100, M+1$^+$); ^{1}H NMR 1.4-1.8 (m, 4H), 2.83 (d, 1H, J = 8.2), 3.19 (s, 3H, CH_3), 3.37 (d, 1H, J = 13.8), 3.60 (d, 1H, J = 13.8), 3.89 (s, 3H, CH_3), 4.22 (d, 1H, J = 5.2), 4.54 (dd, 1H, J = 8.2; 10.1), 4.70 (d, 1H, J = 4.2), 6.72 (d, 1H, NH, J = 10.1), 6.90 (m, 2H), 7.20 (m, 2H); ^{13}C NMR: (CH_3) 51.1, 55.1, (CH_2) 25.5, 28.9; 38.8, (CH) 53.0, 55.2, 77.7, 81.1, 110.5, 120.8, 128.6, 131.0, (C) 123.2, 157.8, 170.6, 170.9. Elem. Anal., found % (calcd for $C_{17}H_{21}NO_5$): C, 63.77 (63.94); H, 6.61 (6.63); N, 4.51 (4.39). CAUTION: the product was highly vesicant!

Methyl 3-exo-benzyloxycarbonylamino-7-oxabicyclo[2,2,1]heptane-2-exo-carboxylate **2d**;[11] yield 81%. MS (TS): 306 (100, M+1$^+$); ^{1}H NMR 1.4-1.8 (m, 4H), 2.97 (d, 1H, J = 8.1), 3.49 (s, 3H, CH_3), 4.35 (m, 2H), 4.75 (m, 2H), 4.92 (d, 1H, J = 12.6), 5.46 (d, 1H, NH, J = 10.6), 7.1-7.4 (m, 5H); ^{13}C NMR: (CH_3) 51.6, (CH_2) 25.7, 28.9, 66.7, (CH) 53.6, 57.9, 77.8, 81.1, 126.8, 128.1 (2C), 128.3 (2C), (C) 127.1, 155.8, 170.4. Elem. Anal., found % (calcd for $C_{16}H_{19}NO_5$): C, 62.87 (62.94); H, 6.41 (6.27); N, 4.42 (4.59).

Methyl 3-exo-trifluoroacetylamino-7-oxabicyclo[2,2,1]heptane-2-exo-carboxylate **2e**; yield 42%. MS (TS): 268 (100, M+1$^+$); ^{1}H NMR 1.4-1.8 (m, 4H), 2.95 (d, 1H, J = 7.9), 3.58 (s, 3H, CH_3), 4.41 (m, 2H), 4.73 (d, 1H, J = 3.3), 7.76 (d, 1H, NH, J = 8.8); ^{13}C NMR : (CH_3) 52.0 (CH_2) 25.9, 28.9, (CH) 52.8, 55.8, 78.5, 80.7, (C) 120.4 (q, $^2J_{CF}$ = 28.5), 158.5 (q, $^3J_{CF}$ = 3.7), 171.1. Elem. Anal., found % (calcd for $C_{10}H_{12}F_3NO_4$): C, 44.78 (44.95); H, 4.35 (4.53); N, 5.09 (5.24).

Methyl 3-exo-t-butyloxycarbonylamino-7-oxabicyclo[2,2,1]heptane-2-exo-carboxylate **2f**; yield 77%. MS (TS): 272 (100, M+1$^+$); ^{1}H NMR 1.2-1.4 (m, 9H), 1.4-1.8 (m, 4H), 2.90 (d, 1H, J = 8.2), 3.61 (s, 3H, CH_3), 4.2-4.3 (m, 2H), 4.71 (d, 1H, J = 2.1), 7.02 (d, 1H, NH, J = 8.3); ^{13}C NMR: (CH_3) 28.2 (3C), 51.4, (CH_2) 25.7, 29.0, (CH) 53.6, 57.5, 77.8, 81.1, (C) 79.4, 155.6, 170.1. Elem. Anal., found % (calcd for $C_{13}H_{21}NO_5$): C, 57.46 (57.55); H, 7.89 (7.80); N, 4.97 (5.16).

2-exo-Acetylamino-3-exo-(1,1-diphenyl-1-hydroxy)methyl-7-oxabicyclo[2,2,1] heptane **3a**. A solution of a Grignard reagent, obtained by reacting bromobenzene (2 ml, 18.8 mmol) and Mg (0.45 g, 18.8 mmol) in dry THF (80 ml), was added to compound **2a** (1 g, 4.7 mmol) suspended in 50 ml of THF in a ice-bath. When the addition was completed, the ice-bath was removed and the mixture was gently refluxed for 2 h. After cooling, solid ammonium chloride was added (0.5 g) and then water (10 ml) until the formation of a jelly material was apparently complete. The THF solution was decanted out, the jelly residue was washed with EtOAc (3 x 50 ml) and the organic solutions were collected all together. The solvent was evaporated *in vacuo* and the oily residue purified by chromatography eluting with mixtures of petroleum ether and EtOAc, starting with petroleum ether-EtOAc (8:1) and increasing the amount of EtOAc to petroleum ether-EtOAc (2:1), and finally EtOAc to give compound **3a**; yield 57%; m.p. 165°C (dec.). MS (TS): 338 (100, M+1$^+$); ^{1}H NMR: 1.28 (s, 3H, CH_3), 1.5-1.85 (m, 4H), 3.81 (d, 1H, J = 8.4), 4.37 (m, 2H), 4.49 (s, 1H, OH), 4.59 (dd, 1H, J = 8.4, 9.2), 7.01 (d, 1H, J = 9.2, NH), 7.1-7.6 (m, 10H); ^{13}C NMR: (CH_3) 22.2, (CH_2) 26.9, 29.0, (CH) 53.8, 55.2, 78.2, 84.0, 124.2 (2C), 124.8 (2C), 126.5, 126.6, 128.4 (2C), 128.5 (2C), (C) 79.5, 145.7, 147.6, 169.4. Elem. Anal., found % (calcd for $C_{21}H_{23}NO_3$): C, 74.78 (74.75); H, 6.69 (6.87); N, 4.01 (4.15).

Similarly the following diphenylcarbinol derivatives were obtained.

2-exo-(2-Methoxy-benzoyl)amino-3-exo-(1,1-diphenyl-1-hydroxy)methyl-7-oxabicyclo[2,2,1]heptane **3b**; yield 68%; m.p. 219-220°C (EtOH). MS (EI): 429 (3, M$^+$), 411 (4, M$^+$-18), 352 (3), 294 (5), 247 (50), 135 (100), 105 (43), 77 (21); ^{1}H NMR: 1.5-1.9 (m, 4H), 3.36 (d, 1H, J = 8.3), 3.86 (s, 3H, CH_3), 4.41 (m, 2H), 4.50 (d, 1H, J = 3.6), 4.92 (dd, 1H, J = 8.9, 8.3), 6.7-7.5 (m, 13H), 7.83 (dd, 1H, J = 7.7, 1.8), 9.10 (d, 1H, NH, J = 8.9); ^{13}C NMR: (CH_3) 54.4, (CH_2) 27.3, 29.1, (CH) 55.3, 55.8, 78.7, 84.8, 110.6, 120.3, 126.8 (2C), 125.1 (2C), 126.2, 126.5, 127.6 (2C), 128.5 (2C), 131.8, 132.2, (C) 79.4, 120.8, 145.3, 148.5, 157.6, 164.6. Elem. Anal., found % (calcd for $C_{27}H_{27}NO_4$): C, 75.68 (75.50); H, 6.50 (6.34); N, 3.33 (3.26).

2-exo-[(2-Methoxy-phenyl)acetyl]amino-3-exo-(1,1-diphenyl-1-hydroxy)methyl-7-oxabicyclo[2,2,1] heptane **3c**; yield 73%; m.p. 211-213°C (EtOH). MS (EI): 443 (4, M$^+$), 425 (3, M$^+$-18), 366 (4), 294 (3), 261 (100), 148 (18), 121 (47), 105 (45), 77 (20); ^{1}H NMR: 1.4-1.9 (m,4H), 2.77 (d, 1H, J = 15.0), 2.97 (d, 1H, J = 15.0), 3.26 (d, 1H, J = 8.1), 3.82 (s, 3H, CH_3), 4.07 (s, 1H), 4.23 (d, 1H, J = 2.1), 4.31 (d, 1H, J = 3.2), 4.60 (dd, 1H, J = 9.4, 8.1) 6.8-6.9 (m, 3H), 7.1-7.5 (m, 11H); ^{13}C NMR: (CH_3) 53.6, (CH_2) 26.9, 28.9, 37.9, (CH) 55.1, 55.3, 78.3, 84.3, 110.2, 120.5, 124.6 (2C), 125.0 (2C), 126.4, 126.5, 128.2 (2C), 128.3, 128.4 (2C), 132.1, (C) 79.3 123.3, 145.5, 148.0, 157.1, 170.5. Elem. Anal., found % (calcd for $C_{28}H_{29}NO_4$): C, 75.64 (75.82); H, 6.69 (6.59); N, 3.32 (3.16).

2-exo-Benzyloxycarbonylamino-3-exo-(1,1-diphenyl-1-hydroxy)methyl-7-oxabicyclo [2,2,1]heptane **3d**; yield 61%; m.p. 169-170°C (EtOH). MS (EI): 429 (1, M^+), 338 (3), 320 (3), 277 (8), 247 (10),183 (71), 156(38), 105 (63), 91 (100), 77 (41); ^{1}H NMR 1.5-1.8 (m, 4H), 3.37 (d, 1H, J = 8.3), 4.20 (s, 1H, OH), 4.37 (m, 3H), 4.55 (d, 1H, J = 12.4), 4.78 (d, 1H, J = 12.4), 6.25 (d, 1H, NH, J = 9.7), 7.0-7.6 (m, 15H) ; ^{13}C NMR: (CH_2) 27.0, 29.2, 66.2, (CH) 54.6, 58.0, 78.4, 84.3, 124.6 (2C), 125.1 (2C), 126.3, 126.6, 127.7 (2C), 128.3 (3C), 128.6 (2C), (C) 79.7 127.3, 145.9, 148.3, 155.5. Elem. Anal., found % (calcd for $C_{27}H_{27}NO_4$): C, 75.27 (75.50); H, 6.37 (6.34); N, 3.34 (3.26).

2-exo-Trifluoroacetylamino-3-exo-(1,1-diphenyl-1-hydroxy)methyl-7-oxabicyclo[2,2,1] heptane **3e**; yield 77%. MS (TS): 392 (100, M+1$^+$); ^{1}H NMR 1.5-1.9 (m, 4H), 3.42 (d, 1H, J = 8.2), 4.16 (s, 1H, OH), 4.4-4.6 (m, 3H), 7.1-7.5 (m, 10H), 8.38 (d, 1H, NH, J = 8.3); ^{13}C NMR: (CH_2) 26.6, 29.4, (CH) 53.5, 56.1, 78.3, 83.5, 124.0 (2C), 124.7 (2C), 127.0 (2C), 128.6 (2C), 128.8 (2C), (C) 79.8, 115.5 (q, $^2J_{CF}$ = 28.1), 144.5, 147.1, 156.1 (q, $^3J_{CF}$ = 3.7). Elem. Anal., found % (calcd for $C_{21}H_{20}F_3NO_3$): C, 64.64 (64.44); H, 5.27 (5.15); N, 3.45 (3.58).

2-exo-t-Butyloxycarbonylamino-3-exo-(1,1-diphenyl-1-hydroxy)methyl-7-oxabicyclo[2,2,1] heptane **3f**; yield 49%; m.p. 176-7°C (EtOH). MS (TS): 396 (100, M+1$^+$); ^{1}H NMR 1.1-1.3 (m, 9H), 1.4-1.8 (m, 4H), 3.38 (d, 1H, J = 8.2), 4.34 (m, 4H), 6.07 (brs, 1H, NH), 7.1-7.5 (m, 10H); ^{13}C NMR: (CH_3) 28.1, (CH_2) 26.9, 29.0, (CH) 54.2, 57.1, 78.3, 84.6, 124.4 (2C), 125.0 (2C), 126.3, 126.5, 128.3 (2C), 128.5 (2C), (C) 78.5, 79.6, 146.0, 148.3, 155.1. Elem. Anal., found % (calcd for $C_{24}H_{29}NO_4$): C, 72.68 (72.89); H, 7.51 (7.39); N, 3.74 (3.54).

2-Methyl-4,4-diphenyl-5,8-epoxy-4a,5,6,7,8,8a-hexahydro-4H-3,1-benzoxazine **4a**. In an attempt to reduce carbinol, compound **3a** (100 mg, 0.29 mmol) was dissolved in CH_2Cl_2 (10 ml) and heated, at reflux temperature, with TFA (3 ml) and triethylsilane (0.8 ml, 10 mmol), for 8 h. The solvent was removed and the solid material purified by chromatography eluting with petroleum ether-EtOAc (1:1); yield 82%. MS (TS): 320 (100, M+1$^+$); ^{1}H NMR 1.5-2.0 (m, 4H), 2.05 (s, 3H, CH_3), 3.11 (d,1H, J = 7.3), 3.83 (d, 1H, J = 7.3), 4.11 (d, 1H, J = 3.1), 4.49 (d, 1H, J = 5.5), 7.2-7.5 (m, 10H); ^{13}C NMR: (CH_3) 22.2, (CH_2) 25.6, 31.1, (CH) 49.7, 60.5, 77.2, 82.7, 124.7 (2C), 125.8 (2C), 127.0, 127.8, 128.4 (2C), 128.5 (2C), (C) 80.9, 143.8, 143.9, 161.8. Elem. Anal., found % (calcd for $C_{21}H_{21}NO_2$): C, 78.94 (78.96); H, 6.59 (6.62); N, 4.41 (4.38). Comparable results were obtained in the absence of triethylsilane.

Similarly the following oxazines were obtained.

2-Methoxyphenyl-4,4-diphenyl-5,8-epoxy-4a,5,6,7,8,8a-hexahydro-4H-3,1-benzoxazine **4b**; yield 73%; m.p. 163-5°C dec. MS (TS): 412 (100, M+1$^+$); ^{1}H NMR 1.5-2.0 (m, 4H), 3.36 (d,1H, J = 7.3), 3.80 (s, 3H, CH_3) 4.18 (m, 2H), 4.72 (d, 1H, J = 5.5), 6.9-7.0 (m, 2H), 7.2-7.6 (m, 12H); ^{13}C NMR: (CH_3) 55.8, (CH_2) 25.9, 31.2, (CH) 50.7, 61.9, 77.3, 83.1, 112.0, 120.0, 125.1 (2C), 126.8, 127.0 (2C), 127.5, 128.0 (2C), 128.4 (2C), 130.5, 130.9 (C) 80.6, 124.3, 144.2, 145.0, 156.5, 158.0. Elem. Anal., found % (calcd for $C_{27}H_{25}NO_3$): C, 78.80 (78.81); H, 6.21 (6.12); N, 3.52 (3.40).

2-Methoxybenzyl-4,4-diphenyl-5,8-epoxy-4a,5,6,7,8,8a-hexahydro-4H-3,1-benzoxazine **4c**; yield 67%; m.p. 122°C dec. MS (EI): 425 (13, M^+), 260 (100), 183(16), 121 (56), 91 (99); ^1H NMR 1.4-1.9 (m, 4H), 3.03 (d, 1H, J = 7.3), 3.59 (d, 2H, J = 6.6), 3.70 (s, 3H, CH_3), 3.91(d, 1H, J = 7.3), 4.07 (d, 1H, J = 3.2), 4.47 (d, 1H, J = 5.5), 6.7-6.9 (m, 2H), 7.1-7.4 (m, 12H); ^{13}C NMR: (CH_3) 55.1, (CH_2) 25.7, 31.2, 37.7 (CH) 51.9, 61.0, 77.2, 83.0, 110.2, 120.3, 124.9 (2C), 126.1 (2C), 126.7, 127.1, 127.8, 128.1 (2C), 128.3 (2C), 130.8 (C) 79.8, 124.2, 144.0, 144.7, 157.6, 160.0. Elem. Anal., found % (calcd for $C_{28}H_{27}NO_3$): C, 79.20 (79.03); H, 6.23 (6.40); N, 3.29 (3.29).

When treated under similar dehydrating conditions, compound **3d** gave *4,4-diphenyl-5,8-epoxy-4a,5,6,7,8,8a-hexahydro-4H-3,1-benzoxazin-2-one* **5**; yield 66%; m.p. 308°C dec. MS (EI): 321 (7, M^+), 277 (63), 220 (100), 165 (45), 105 (60), 91 (30). ^1H NMR 1.4-1.9 (m, 4H), 3.20 (d, 1H, J = 7.9), 3.70 (m, 1H), 4.26 (d, 1H, J = 3.5), 4.41 (d, 1H, J = 5.7), 5.87 (s, 1H, NH), 7.1-7.6 (m, 10H); ^{13}C NMR: (CH_2) 24.7, 30.8, (CH) 48.6, 58.4, 77.4, 83.4, 124.9 (2C), 125.0 (2C), 127.1, 127.6, 128.6 (2C), 128.8 (2C), (C) 84.2, 143.2, 143.9, 157.4. Elem. Anal., found % (calcd for $C_{20}H_{19}NO_3$): C, 74.67 (74.75); H, 6.09 (5.96); N, 4.43 (4.36).

2-exo-Amino-3-exo-(1,1-diphenyl-1-hydroxy)methyl-7-oxabicyclo[2,2,1]heptane **6a**. Compound **3e** (3.6 g, 9.2 mmol) was dissolved in ethanol-sodium hydroxide solution 10% (1:1) (100ml) and heated at reflux temperature for 1 h. The solution was concentrated under reduced pressure to remove most of the ethanol and then extracted with chloroform. The solvent was removed to afford a white solid; yield 93%; m.p. 192-3°C (EtOH). MS (EI): 295 (100, M^+), 277 (14), 183 (58), 105 (98), 77 (56). ^1H NMR 1.4-1.9 (m, 4H), 2.95 (d,1H, J = 6.7), 2.7-3.4 (v br s, 3H), 3.66 (d, 1H, J = 6.7), 4.32 (d, 1H, J = 5.7), 4.48 (d, 1H, J = 4.2), 7.1-7.7 (m, 10H); ^{13}C NMR: (CH_2) 26.4, 30.5, (CH) 55.0, 58.7, 78.3, 83.4, 125.3 (2C), 125.4 (2C), 126.0, 126.4, 128.1 (2C), 128.4 (2C), (C) 78.4, 147.6, 150.1. Elem. Anal., found % (calcd for $C_{19}H_{21}NO_2$): C, 77.11 (77.25); H, 7.34 (7.16); N, 4.59 (4.74).

The same product was obtained by treating compound **3f** with TFA 50% in CH_2Cl_2 for half an hour at room temperature with comparable yield.

2-exo-(2-Methoxybenzyl)amino-3-exo-(1,1-diphenyl-1-hydroxy)methyl-7-oxabicyclo [2,2,1]heptane **6b**. Compound **3b** (0.5 g, 1.24 mmol) was treated in THF (50 ml) with $LiAlH_4$ (0.2 g, 5 mmol) for 6h at room temperature followed by 1h under refluxing. The excess $LiAlH_4$ was carefully destroyed with water, the solution was decanted and the solid residue extracted with EtOAc. The collected organic solutions were evaporated under reduced pressure and the solid residue chromatographed with petroleum ether-EtOAc (5:1); yield 83%; m.p. 189-190°C. MS (EI): 415 (4, M^+), 397 (4, M^+-18), 294 (7), 232 (71), 121 (100), 105 (17), 91 (28), 77 (23). ^1H NMR 1.39 (m, 2H), 153 (m, 1H), 173 (m, 1H), 3.00 (d, 1H, J = 6.9), 3.19 (d, 1H, J = 6.8), 3.15-3.3 (m, 3H), 3.66 (s, 3H), 4.4 0 (m, 2H), 6.7-6.9 (m, 3H), 7.1-7.5 (m, 6H), 7.56 (dd, 2H, J = 8.5, 1.4), 7.67 (dd, 2H, J = 8.5, 1.4); ^{13}C NMR: (CH_3) 55.1, (CH_2) 26.1, 30.8, 47.7, (CH) 55.0, 64.5, 77.8, 80.2, 109.8, 120.1, 125.2 (2C), 125.5 (2C), 125.8, 126.2, 128.0 (2C), 128.3 (2C), 128.4 , 130.0, (C) 78.0, 126.8, 147.6, 150.0, 157.4. Elem. Anal., found % (calcd for $C_{27}H_{29}NO_3$): C, 78.08 (78.04); H, 6.85 (7.03); N, 3.32 (3.37).

2-exo-Methylamino-3-exo-(1,1-diphenyl-1-hydroxy)methyl-7-oxabicyclo[2,2,1] heptane **6c**. A solution of $LiAlH_4$ 1 M in THF (3.5 ml) was added to compound **3d** (1 g, 2.33 mmol) in THF (20 ml), under stirring, and heated in order to maintain a gentle reflux condition for a 3h period. The excess $LiAlH_4$ was carefully destroyed with water, the solution was decanted and the solid residue extracted with EtOAc. The collected organic solutions were evaporated under reduced pressure and the solid residue chromatographed with petroleum ether-EtOAc (1:3); yield 94%; m.p. 193-4°C (EtOH). MS (EI): 309 (6, M^+), 291 (4), 183 (7), 126 (100), 105 (31), 77 (30). ^1H NMR 1.4-1.9 (m, 4H), 1.99 (s, 3H, NCH_3), 3.04 (d, 1H, J = 6.8), 3.17 (d, 1H, J = 6.7), 3.3-3.6 (v br s, NH), 4.40 (d, 1H, J = 4.0), 4.51 (d, 1H, J = 5.8), 4.69 (s, 1H), 7.1-7.7 (m, 10H); ^{13}C NMR: (CH_3) 34.8, (CH_2) 26.4, 30.9, (CH) 55.5, 68.5, 78.1, 79.4, 125.3 (2C), 125.4 (2C), 126.0, 126.4, 128.1 (2C), 128.3 (2C), (C) 78.2, 147.9, 150.1. Elem. Anal., found % (calcd for $C_{20}H_{23}NO_2$): C, 77.75 (77.64); H, 7.65 (7.49); N, 4.39 (4.52).

(2'RS, 3SR)-1,1-diphenyl-3-(tetrahydrofuran-2'-yl)-3-amino-prop-1-ene **7a**.

Method A) A solution of compound **6a** (0.2 g, 0.68 mmol), triethylsilane (1 ml, 6.3 mmol) and TFA (2 ml, 24.7 mmol) in CH_2Cl_2 was heated under reflux for 8 h, the decrease of the reactant being monitored by tlc with petroleum ether-EtOAc (1:1). The solvent was removed under reduced pressure, the residue was dissolved in cold water (50 ml) and washed with diethyl ether (3x30ml). The water solution was made basic with sodium carbonate and extracted with CH_2Cl_2 (3x30ml). The solution was dried over $MgSO_4$. The solvent was removed under reduced pressure affording compound **7a** as an oil; yield 53%. A portion was purified by chromatography on silica gel with EtOAc as eluent.

Method B) A solution of compound **6a** (0.62 g, 2.1 mmol), triethylsilane (3 ml, 18.9 mmol) and boron trifluoride diethyl etherate (1.5 ml, 11.8 mmol) in CH_2Cl_2 was heated under reflux for 8 h. After the usual work up, a pale yellow oil was obtained; yield 84%. MS (TS): 280 (100, $M+1^+$); ^1H NMR; 1.89 (m, 4H), 2.23 (br s, 2H, NH_2), 3.59 (dd, 1H, J = 9.7, 4.1), 3.79 (m, 1H), 3.89 (m, 2H), 6.05 (d, 1H, J = 9.7), 7.1-7.5 (m, 10H); ^{13}C NMR: (CH_2) 26.1, 26.8, 68.4, (CH) 53.0, 82.2, 127.1, 127.2 (2C), 127.3, 128.0 (2C), 128.2 (2C), 129.4, 129.5 (2C), (C) 139.6, 142.0, 143.2. Elem. Anal., found % (calcd for $C_{19}H_{21}NO$): C, 81.53 (81.68); H, 7.75 (7.57); N, 5.62 (5.73).

Similarly the following tetrahydrofuranes were obtained.

(2'RS, 3SR)-1,1-Diphenyl-3-(tetrahydrofuran-2'-yl)-3-(2-methoxybenzyl)amino-prop-1-ene **7b**; method A), yield 37%. MS (TS) 400 (100, $M+1^+$); MS (E.I.) 328 (95), 206(8), 121(100). ^1H NMR; 1.88 (m, 4H), 2.2 (br s, 1H, NH), 3.46 (dd, 1H, J = 9.9, 4.4), 3.51 (d, 1H, J = 13.4), 3.81 (s, 3H, CH_3), 3.75-3.85 (m, 2H), 3.84 (d, 1H, J = 13.4), 3.96 (m, 1H), 6.05 (d, 1H, J = 9.9), 6.65-6.75 (m, 2H), 7.05-7.35 (m, 12H); ^{13}C NMR: (CH_3) 58.9, (CH_2) 26.1, 27.2, 46.6, 68.4, (CH) 55.1, 81.4, 110.0, 120.2, 126.8, 127.1, 127.2 (2C), 127.8, 128.1 (2C), 128.2 (2C), 128.7, 129.5, 129.7 (2C), (C) 128.5, 139.7, 143.1, 144.7, 157.4. Elem. Anal., found % (calcd for $C_{27}H_{29}NO_2$): C, 81.08 (81.17); H, 7.45 (7.32); N, 3.42 (3.51).

(2'RS, 3SR)-1,1-Diphenyl-3-(tetrahydrofuran-2'-yl)-3-methylamino-prop-1-ene **7c**; method B), yield 91%. MS (TS) 294 (100, $M+1^+$); ^1H NMR; 1.89 (m, 4H), 2.39 (s, 3H, CH_3), 3.43 (dd, 1H, J = 10.2, 3.7), 3.81 (m, 2H), 3.89 (m, 1H), 4.76 (br s, 1H, NH), 6.03 (d, 1H, J = 10.2), 7.1-7.5 (m, 10H); ^{13}C NMR: (CH_3) 32.5, (CH_2) 26.1, 27.3, 68.6, (CH) 61.4, 80.8, 126.0, 127.3 (2C), 127.4, 127.6, 128.2 (2C), 128.4(2C),

129.6 (2C), (C) 139.7, 141.8, 146.7. Elem. Anal., found % (calcd for $C_{20}H_{23}NO$): C, 81.71 (81.87); H, 8.03 (7.90); N, 4.62 (4.77).

2-exo-(2-Methoxybenzyl)amino-3-diphenylmethylen-7-oxabicyclo[2,2,1]heptane **8**. A solution of compound **6b** (0.2 g, 0.5 mmol) in 30 ml of a mixture of CH_2Cl_2 and TFA (1:1) was heated under reflux for 96 h, the decrease of the reactant being followed by tlc with petroleum ether-EtOAc (1:1). The solvent was removed under reduced pressure. The oily residue was washed with 10% sodium carbonate solution and extracted with CH_2Cl_2. Evaporation of the solvent gave an oil which was chromatographed with petroleum ether-EtOAc (7:1); yield 73%. MS (E.I.) 397 (47, M^+), 277 (10), 276 (73), 167 (24), 121 (100). ^1H NMR: 1.5-1.9 (m, 4H), 3.62 (s, 2H), 3.69 (s, 1H), 3.71-3.73 (4H, CH_3+ CH), 4.74 (d, 1H, J = 5.1), 5.06 (d, 1H, J = 4.4), 6.7-6.85 (m, 3H), 7.1-7.4 (m, 11H); ^{13}C NMR: (CH_3) 63.1, (CH_2) 25.8, 30.0, 46.2, (CH) 55.0, 78.0, 79.6, 110.0, 120.2, 126.8, 126.9, 127.8, 128.1 (2C), 128.3 (2C), 128.4 (2C), 128.8 (2C), 129.6, (C) 127.6, 134.4, 140.8, 142.0, 144.5, 157.3. Elem. Anal., found % (calcd for $C_{27}H_{27}NO_2$): C, 81.41 (81.58); H, 6.68 (6.85); N, 3.58 (3.52).

2-exo-Tosylamino-3-exo-(1,1-diphenyl-1-hydroxy)methyl-7-oxabicyclo[2,2,1]heptane **9**. A solution of compound **6a** (0.5 g, 1.7 mmol) in CH_2Cl_2 (50 ml) was treated with triethylamine (0.5 ml, 3.6 mmol) and with tosyl chloride (0.35 g, 1.8 mmol) in an ice bath, under stirring for 12 h. The mixture was washed with 10% HCl solution (3 x 20 ml) and brine (20 ml). The solvent was removed and the solid recrystallized from ethanol; yield 41%; m.p. 216-217°C. MS (TS) 450 (47, $M+1^+$); MS (E.I.) 294 (14), 183 (77), 155 (17), 112 (100), 105 (55), 91 (47), 77 25). ^1H NMR 1.4-1.8 (m, 4H), 2.40 (s, 3H, CH_3), 3.31 (d, 1H, J = 8.2), 3.67 (dd, 1H, J = 8.4, 8.2), 4.12 (s, 1H), 4.32 (m, 1H), 4.64 (d, 1H, J = 4.4), 6.28 (d, 1H, J = 8.4, NH), 7.1-7.5 (m, 14H); ^{13}C NMR: (CH_3) 21.4, (CH_2) 26.4, 29.2, (CH) 53.9, 60.0, 78.4, 84.1, 124.3 (2C), 124.8 (2C), 126.6, 126.7, 127.0 (2C), 128.7 (4C), 129.4 (2C) (C) 79.6, 137.4, 142.6, 145.5, 148.3. Elem. Anal., found % (calcd for $C_{26}H_{27}NO_4S$): C, 69.20 (69.46); H, 6.04 (6.05); N, 3.26 (3.12).

A solution of compound **9** (0.11 g, 0.25 mmol) in CH_2Cl_2 (5 ml) was treated with triethylsilane (0.5 ml, 3.1 mmol) and boron trifluoride diethyl etherate (0.34 ml, 0.27 mmol) at reflux for 5 h. The solvent was removed. The residue was resuspended in CH_2Cl_2 (50 ml) and washed with 10% sodium carbonate solution and brine (20 ml). Evaporation of the solvent gave mainly a single compound which, after a purification by chromatography with petroleum ether/EtOAc (1:4) (yield 63%), was tentatively interpretated as *1-tosylamino-2-hydroxy-7,7-diphenyl-heptane* **10**. MS (E.I.): 438 (37, $M+1^+$), 420 (18), 360 (5), 284 (19), 266 (9), 253 (5), 172 (25), 157 (100), 93 (45). ^1H NMR 1.2-1.5 (m, 6H, $3CH_2$), 2.01 (m, 2H, CH_2), 2.41 (s, 4H, CH_3 + OH), 2.73 + 3.01 (when resonance at 5.42 was decoupled: dd + dd, 2H, CH_2, J = 12.9, 8.1 + 12.9, 3.0), 3.64 (m, 1H, CH), 3.87 (t, 1H, CH, J = 7.7), 5.42 (br t, 1H, NH), 7.1-7.5 (m, 12H), 7.76 (d, 2H, J = 8.3); ^{13}C NMR: (CH_3) 21.4, (CH_2) 25.3, 27.9, 34.5, 35.5, 48.8, (CH) 51.3, 70.4, 126.0 (2C), 127.1 (2C), 127.7 (2C), 128.0, 128.2, 128.4 (4C), 129.7 (2C) (C) 137.6, 143.4, 145.1, 148.5.

When compound **9** (0.2 g, 0.49 mmol) was treated in CH_2Cl_2 (5 ml) with triethylsilane (1 ml, 6.2 mmol) and TFA (2 ml, 30 mmol) at reflux for 6 h a mixture of products was obtained; after chromatography with petroleum ether/EtOAc (1:4) as eluent, two compounds were isolated and tentatively interpretated as compound

10 (yield 32%) and *2-exo-tosylamino-3-exo-diphenylmethyl-7-oxabicyclo[2,2,1] heptane* **11** (yield 17%). MS (TS) 434 (100, M+1$^+$); MS (E.I.): 278 (26), 266 (12), 167 (100), 165 (25), 155 (32), 111 (10), 91 (70). ^{1}H NMR 1.4-1.8 (m, 4H), 2.40 (s, 3H, CH_3), 2.87 (dd, 1H, J = 12.9, 7.7), 3.53 (dd, 1H, J = 8.9, 7.7), 3.85 (d, 1H, J = 12.9), 4.08 (d, 1H, J = 3.7), 4.36 (d, 1H, J = 5.4), 4.67 (d, 1H, NH, J = 8.9), 7.1-7.5 (m, 14H); ^{13}C NMR: (CH_3) 21.4, (CH_2) 25.3, 32.3, (CH) 50.4, 51.7, 60.0, 78.5, 82.5, 126.3, 126.5, 127.1 (2C), 127.2 (2C), 128.0, 128.4, 128.9 (4C), 129.5 (2C) (C) 137.4, 142.9, 144.7, 148.3. Elem. Anal., found % (calcd for $C_{26}H_{27}NO_3S$): C, 71.94 (72.03); H, 6.35 (6.28); N, 3.32 (3.23).

(2'RS, 3SR)-1,1-Diphenyl-3-(tetrahydrofuran-2'-yl)-3-benzoylamino-prop-1-ene **12**. A solution of compound **7a** (1.1 g, 3.9 mmol) in $CHCl_3$ (50 ml) was treated with triethylamine (0.6 ml, 4.6 mmol) and with benzoyl chloride (0.33 g, 4.6 mmol) in an ice bath, under stirring for 8 h. The mixture was washed with 10% HCl solution (3 x 20 ml) and brine (20 ml). The solvent was removed and the oily residue was chromatographied with petroleum ether-EtOAc (2:1); yield 63%. MS (TS): 384 (100, M+1$^+$); ^{1}H NMR 1.6-2.1 (m, 4H), 3.85 (m, 1H), 3.97 (m, 1H), 4.12 (m, 1H), 4.95 (ddd, 1H, J = 9.8, 8.4, 3.1), 6.12 (d, 1H, J = 9.8), 6.85 (bd, 1H, NH J = 8.4), 7.3-7.7 (m, 10H), 7.7-7.8 (m, 1H), 8.0-8.2 (m, 4H); ^{13}C NMR: (CH_2) 26.2, 27.8, 68.8 (CH) 52.0, 81.3, 123.8, 127.2 (2C), 127.4(2C), 127.5, 127.6, 128.0(2C), 128.2(2C), 128.7(2C), 129.7(2C), 131.9 (C) 138.9, 139.0, 142.1, 145.5, 169.6. Elem. Anal., found % (calcd for $C_{26}H_{25}NO_2$): C, 81.39 (81.43); H, 6.42 (6.57); N, 3.59 (3.65).

(2'RS, 2SR)-2-(Tetrahydrofuran-2'-yl)-2-benzoylamino-acetic acid **13** .Compound **12** (180 mg, 0.48 mmol) was dissolved in CCl_4/CH_3CN (1/1 v/v, 8 ml), water (ml 6) and sodium metaperiodate (420 mg, 1.96 mmol) were added and the mixture was stirred for ten minutes. Ruthenium dioxide monohydrate (22 mg, 0.16 mmol) was added in one portion and the mixture was stirred vigorously for 1 h at room temperature. Then CH_2Cl_2 was added (20 ml), and the phases were separated. The upper aqueous phase was extracted with CH_2Cl_2 (4 x10 ml) and the combined organic extracts were dried over magnesium sulphate and concentrated. The resulting residue was diluted with ethyl ether (ml 4) and a solution of sodium carbonate 5% (ml 6) was added. After stirring (30 min.) the organic phase was separated and the aqueous phase was washed with ethyl ether (2 x 2ml). The aqueous phase was acidified with HCl 5N, extracted with CH_2Cl_2 (4 x 10 ml) and the combined organic extracts were dried over magnesium sulphate and concentrated. The residue was purified by column chromatography (90:5:5 ethyl acetate/methanol/acetic acid) to afford compound **13**; yield 52%. MS (TS) : 250 (100, M+1$^+$); MS (EI): 204 (5), 179 (22), 122 (15), 105 (75), 71 (100). ^{1}H NMR 1.8-2.3 (m, 4H), 3.84 (m, 1H), 3.95 (m, 1H), 4.25 (m, 1H), 4.89 (dd, 1H, J = 8.1, 5.5), 6.0-7.0 (vbs, 1H), 7.06 (bd, 1H, J = 8.1), 7.4-7.6 (m, 3H), 7.7-7.9 (m, 2H); ^{13}C NMR: (CH_2) 26.2, 29.3, 69.0, (CH) 60.6 , 80.3, 127.3 (2C), 128.6 (2C), 132.4, (C) 131.9, 168.1, 176.7. Elem. Anal., found % (calcd for $C_{13}H_{15}NO_4$): C, 62.49 (62.64); H, 5.98 (6.07); N, 5.58 (5.62).

Acknowledgment. We thank Dr. Antonio Triolo for ms data, Dr. Giuseppe Balacco for the interpretation of some NMR spectra and Dr. Antonio Guidi for the helpful discussions. This work was partially supported by M.U.R.S.T. (Ministero dell' Università e della Ricerca Scientifica e Tecnologica, Roma- Italy) (IMI grant n° 56665).

References and notes

1. (a) Sheha, M. M.; Nakata, S.; Enomoto, H.; Kimura, T.; Mimoto, T.; Hattori, N.; Mahfouz, N. M.; Hassan, H. Y.; Youssel, A. F.; et al. *Pept. Chem.* **1995**, 32, 349-352. - (b) Kohn, H.; Sawhney, K. N.; Bardel, P.; Robertson, D. W.; Leander, J. D. *J. Med. Chem.* **1993**, 36, 3350-3360.- (c) Janusz, *J.* M.; Young, P. A.; Blum, R. B.; Riley, C. M. *J. Med. Chem.* 1990, 33, 1676-1682. - (d) Williams, R. M.; Sinclair, P. *J.*; Zhai, D.; Chen, D. *J. Am. Chem. Soc.* **1988**, 110, 1547-57.- (e) Ben-Ishai, D.; Sataty, I.; Bernstein, Z. *Tetrahedron*, **1976**, 32, 1571-1573.- (f) Katagiri, K.; Tori, K.; Kimura, Y.; Yoshida, T.; Nagasaki, T.; Minato, H. *J. Med. Chem.* **1967**, 10, 1149-1154.
2. Zefirov, N.S.; Ivanova, R. A.; Filatova, R. S.; Yur'ev, Y. K. *J. Gen. Chem. USSR* **1965**, 35, 1794-1797.
3. Synthesis of compound **1** is somehow tricky. In fact compound **1** can be obtained by the Hofmann reaction on 3-exo-carboxamido-7-oxabicyclo [2,2,1]heptane-2-exo-carboxylic acid which is very unstable and must be used as soon as prepared. We got fairly good results bubbling NH_3 in the ethereal solution of exo-cis-7-oxabicyclo[2,2,1]heptane-2,3-dicarboxylic acid anhydride, collecting the solid by filtration, pouring it into water, treating, while cooling, with hydrochloric acid until pH 3 and using the collected solid material , still wet and without any purification, immediately in the Hofmann reaction.
4. (a) Carey, F. A.; Tremper, H. S. *J. Org. Chem.* **1971**, 36, 758-761 - (b) Carey, F. A.; Tremper, H. S. *J. Am. Chem. Soc.* **1968**, 90, 2578-2586.
5. Dehydratation of **3a** to the oxazine **4a** was easily achieved, in a shorter reaction time, with the more powerful dehydrating agent thionyl chloride.
6. (a) Mc Clure, D. E.; Arison, B. H.; Jones, J. H.; Baldwin, J. J. *J. Org. Chem.* **1981**, 46, 2431-2433 - (b) Maryanoff, B. E.; Almond Jr., H. R. *J. Org. Chem.* **1986**, 51, 3295-3302.
7. Dehydratation was accomplished in a more acceptable way using the much stronger dehydrating agent $SOCl_2$ on the hydrochloric salt of **6b**.
8. Carlsen, P.H.J.; Katsuki V.S.M.; Sharpless, K.B. *J. Org. Chem.* **1981**, 46, 3936-3938.
9. In an attempt to use the system $RuCl_3$ anhydrous/ RuO_2 monohydrate the corresponding N-benzoyl-amino aldehyde was obtained in good yield, but the reaction was not repeated. MS (TS): 234 (100, $M+1^+$), (EI): 204(12), 163(38), 105(100), 71(56); ^1H NMR 2.00 (m, 2H), 2.15 (m, 2H), 3.80 (m,1H), 3.96 (m, 1H), 4.18 (m,1H), 4.83 (dd, 1H, J = 8.1, 5.8), 6.95 (bs, 1H), 7.4-7.6 (m, 3H), 7.7-7.9 (m, 2H), 9.85 (s, 1H); ^{13}C NMR: (CH_2) 25.4, 28.9, 80.0, (CH) 61.4, 69.0, 127.2 (2C), 128.7 (2C), 131.9, 199.6 (C) 134.1, 169.4 .
10. G. Balacco , *J. Chem. Inf. Comput. Sci.*, 1994, **34**, 1235-1241.
11. (a) Hagishita, S. ; Seno, K. *Chem. Pharm. Bull.* **1989**, 37, 327-335. - (b) Eggelte, T. A.; deKonig, H.; Huisman, H. O. *Tetrahedron* **1973**, 29, 2445-2491

(*Received in UK* 17 *March* 1997; *revised* 1 *May* 1997; *accepted* 8 *May* 1997)