

THE SYNTHESIS OF RACEMIC AZACARBAPENAMS

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Abstract — Ozonation of the tricyclic compounds 2, followed by photolysis of the secondary ozonides 6, led to a mixture of the rather unstable 2-azacarbapenems 7 and 8. Hydrogenation of 7 led to the expected 2-azacarbapenam derivatives 9.

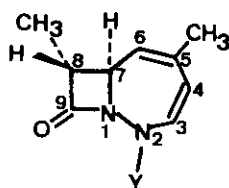
INTRODUCTION. In a recent publication we described the photoinduced electrocyclic isomerisation of some azetidinodiazepines 1 which led stereospecifically to the corresponding tricyclic compounds 2. Irradiation of educts 1 in the presence of a triplet-sensitizer (fluorenone) led in good chemical yield to the anti-Bredt isomers 3 which were also formed, albeit in low yields only, during the above cited direct photoirradiation experiments.¹ The structure analyses of these two types of photoisomers could be solved unambiguously, in particular through NOE measurements for compounds 2, and by means of an X-ray diagram for the anti-Bredt compound 3a.¹

Our next goal was the fragmentation - along the C₃-C₄ and C₅-C₆ bonds - of the cyclobutene ring of compounds 2, in order to arrive at the target azacarbapenam molecules 9. An additional challenge of our synthetic endeavour was the introduction at nitrogen atom N-2 of an anionic group (SO₃⁻), in order to confer to the target molecule 9 a "biological handle", without which no antibiotic activity could be expected.² We report herein the experimental results which we have obtained so far along these two lines of thought.

SYNTHESIS OF THE N-SULFONATED AMMONIUM SALT 2e

To begin with we investigated the possibility of obtaining the N-2 deprotected

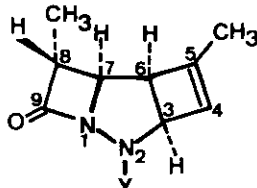
tricyclic compound 2d. Since we were not able to take off the ethoxycarbonyl group from the known product 2a, we had to synthesize its analogue 2b, starting from the N-iminopyridinium ylide 4b which was easily obtained from 4-picoline. Ultra-violet irradiation of 4b gave the corresponding 1,2-diazepine 5b (92 %) to which methylketene was added stereospecifically according to a known procedure,³ whereby the expected azetidinodiazepine 1b was obtained in high yield (94 %). Ultra-violet irradiation of 1b led in 91 % overall yield to the expected tricyclic isomer 2b (73 %) and to the bicyclic anti-Bredt isomer 3b (18 %). A similar reaction sequence led from 4-picoline to the N-iminopyridinium ylide 4c, to diazepine 5c (74 %), thence to the azetidinodiazepine 1c (98 %) and eventually to the corresponding tricyclic isomer 2c (40 %). It should be noted however that during this latter photoreaction the expected anti-Bredt isomer was not isolated. Treatment of 2b with tetra-n-butylammonium fluoride (TBAF)⁴ gave the expected product 2d (87 %) in a crystalline form which could be transformed into its N-sulfonated ammonium salt 2e (86 %) using successively the SO₃/DMF complex and tetra-n-butylammonium dihydrogenophosphate. Microbial tests (MIC-values) of 2e were measured with a series of pathogenic microorganisms and showed that this product had no antibacterial activity.



1a Y=CO₂Et

1b Y=CO₂CH₂CH₂SiMe₃

1c Y=CO₂CH₂pC₆H₄NO₂



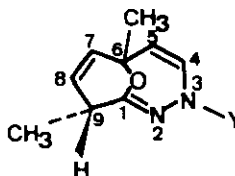
2a Y=CO₂Et

2b Y=CO₂CH₂CH₂SiMe₃

2c Y=CO₂CH₂pC₆H₄NO₂

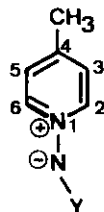
2d Y=H

2e Y=SO₃⁻nBu₄N⁺



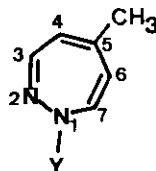
3a Y=CO₂Et

3b Y=CO₂CH₂CH₂SiMe₃



4b Y=CO₂CH₂CH₂SiMe₃

4c Y=CO₂CH₂pC₆H₄NO₂



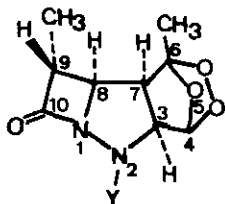
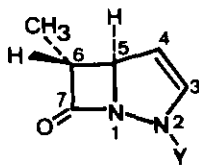
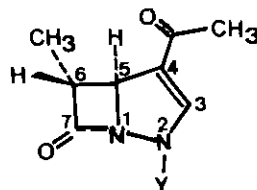
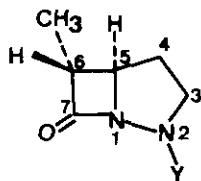
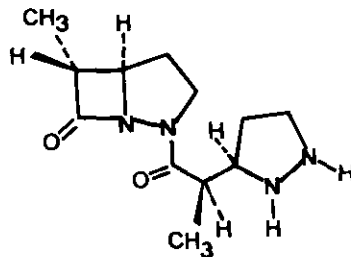
5b Y=CO₂CH₂CH₂SiMe₃

5c Y=CO₂CH₂pC₆H₄NO₂

SYNTHESES OF 2-AZACARBAPENAM DERIVATIVES 9a and 9b

Next we turned our attention to the fragmentation of the cyclobutene ring of compound 2a, according to the scheme we have outlined in general terms in the introduction (see above). Formation of a cis-glycol from 2a could not be achieved with OsO_4 . Therefore we tried a fragmentation methodology which is seldom used: ozonation of 2a led to the crystalline secondary ozonide 6a (60 %; mp 127°C without any noticeable decomposition) which could be cleaved photolytically with UV-light,⁵ giving way to the azacarbapenam derivatives 7a (32 %) and 8a (12 %). Similarly ozonation of 2b - without isolation of the corresponding ozonide -, followed by photolytic fragmentation, led to the azacarbapenam derivatives 7b (34 %) and 8b (13 %). Ozonation of 2c led to the expected ozonide 6c (60 %) whose photolytic fragmentation led to a mixture of products which could neither be isolated nor characterized.

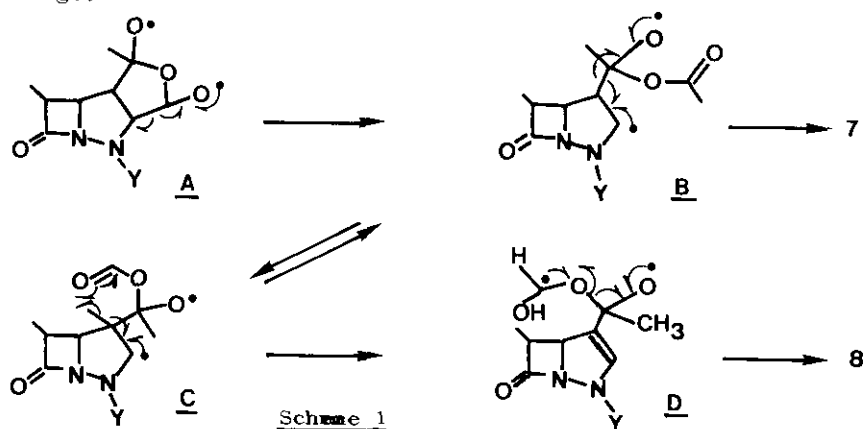
None of the two azacarbapenam derivatives 7a and 7b being stable entities, their catalytic hydrogenation led to the corresponding azacarbapenam compounds 9a and 9b which could be isolated as stable products.

6a Y=CO₂Et7a Y=CO₂Et8a Y=CO₂Et6c Y=CO₂CH₂CH₂PC₆H₄NO₂7b Y=CO₂CH₂CH₂SiMe₃8b Y=CO₂CH₂CH₂SiMe₃9a Y=CO₂Et9b Y=CO₂CH₂CH₂SiMe₃10

Simultaneous formation of the azacarbapenem derivatives 7 and 8, during photolytic fragmentation of the corresponding ozonides 6, deserves some mechanistic comments. We assume that the photoexcited ozonides 6 undergo homolytic O-O bond cleavage to give the diradical A which collapses via diradical B to the azacarbapenems 7 (Scheme 1). Diradical B may also be in a conformational equilibrium with C in which, by means of a six-membered transition state, an intramolecular hydrogen transfer would occur leading to diradical D. Fragmentation of diradical D eventually leads to the acetylazacarbapenems 8.

Treatment of 9b with TBAF led to the removal of the protective group, but instead of the expected N_2 -H azacarbapenam derivative, a dimer was isolated to which we assign tentatively structure 10. The IR spectrum of 10 shows in particular an azetidino-carbonyl ν ($C=O$) band at 1770 cm^{-1} and an amide band at 1620 cm^{-1} . It would seem therefore that the N_2 azacarbapenam nitrogen atom is nucleophilic enough to open up the azetidinone ring. Deprotection of 9b followed by sulfonation using the high dilution technique did not lead to the expected amino-sulfonate 9 ($Y = \text{SO}_3^- \text{nBu}_4\text{N}^+$).

Structural elucidation of the newly described compounds proved to be unequivocal, except for the dimer 10. It should be noted though that the ^{13}C -NMR spectra of all azetidinone derivatives described herein exhibit exceptionally high down field chemical shifts for the β -lactam carbonyl carbon atoms : 180.06 ppm for 2a,¹ 179.58 for 2e, 178.44 for 2c, 184.27 for 7a and 182.49 ppm for 9b. Penicillin and cephalosporin β -lactam carbonyl groups appear at higher fields.⁶ We believe therefore that the annelated β -lactams herein described show very little conjugation between the carbonyls and the associated nitrogen atoms of the azetidinone rings.



EXPERIMENTAL

Microanalyses were carried out by the Service Central de Microanalyse of the C.N.R.S. Melting points were taken with Büchi SMP-2 and Mettler FP5 apparatus and are not corrected. The uv spectra (λ_{max} nm (ϵ)) were recorded on a Varian Techtron 635 spectrophotometer. The ir spectra (cm^{-1}) were determined on a Perkin-Elmer 157 G spectrophotometer. The ^1H and ^{13}C nmr spectra were obtained with Varian T-60 (60 MHz), Bruker WP 80 (80 MHz) and Bruker WP 200 (200 MHz) instruments, with Me_4Si as an internal reference (δ ppm, J Hz). Normal ms as well as high resolution ms were measured with a MAT 311 mass spectrometer by the Centre de Mesures Physiques of the University of Rennes. Flash chromatographies were carried out with silica gel (Merck 60; 230-400 mesh) and thin-layer chromatographies on aluminium roll (Merck 60 F₂₅₄). The photochemical experiments were carried out under argon atmosphere in a Pyrex glass vessel using a water-cooled Hanovia immersion well (Corex glass) equipped with a Philips HPK 125 medium pressure mercury vapour lamp.

4-Methylpyridinium-N-trimethylsilylethoxycarbamide 4b : To a stirred solution of hydroxylamin-O-sulfonic acid at 0°C (51 g; 0.45 mol) in water (100 ml) are successively added over 15 min potassium hydroxide (35 g; 0.62 mol) in water (40 ml) and 4-picoline (70 g; 0.75 mol). After 2 days of continuous stirring at room temperature, potassium carbonate (32 g; 0.23 mol) is slowly added. After 2 h the precipitated solids are filtered off; ethanol (90 ml) is added to the solution, leading to additional precipitates which are filtered. The resulting solution is concentrated in vacuo and then diluted with ethanol (900 ml). After filtration the resulting solution is stirred at 10°C and potassium carbonate (90 g; 0.65 mol) and 2-trimethylsilylethyl-chloroformate⁷ (52.06 g; 0.29 mol) are added, the latter dropwise, and the reaction mixture is kept at room temperature for 24 h and then filtered over sinter glass. The solution is evaporated to dryness in vacuo and the crude pyridinium ylide 4b recrystallized from ethyl acetate/hexane (34.5 g; 47 %) as yellow crystals, mp 153°C. IR (KBr) : 1638, 1618, 1282 cm^{-1} . UV (MeOH) λ_{max} (ϵ) 309 nm (4800). ^1H -NMR (CDCl_3 at 60 MHz) δ : 8.69 (d; $J=6.5$ Hz; H-2 and H-6), 7.40 (d; $J=6.5$ Hz; H-3 and H-5), 4.21 (m; OCH_2), 2.53 (s; CH_3 -4), 1.08 (m; CH_2Si), 0.06 (s; SiMe_3). MS : m/z 252 (M^+ ; 10 %), 135 (71 %), 94 (100 %). Anal. calc. for $\text{C}_{12}\text{H}_{20}\text{N}_2\text{O}_2\text{Si}$ (252.39) : C, 57.11; H 7.99; N, 11.10; found : C, 57.4; H, 8.1; N, 11.3.

4-Methylpyridinium-N-p-nitrobenzyloxycarbamide 4c: By similar conditions and yields as above ylide 4c appears as colourless crystals, mp 187.5-188°C (CHCl₃/Ether). IR (KBr) : 1655 cm⁻¹. UV (MeOH) λ_{max} (ε) : 266 (10800). ¹H-NMR (CDCl₃ at 60 MHz) δ : 8.67 (d; J=7 Hz; H-2 and H-6), 8.21 (d; J=9 Hz; H-3' and H-5'), 7.62 (d; J=9 Hz; H-2' and H-6'), 7.43 (d; J=7 Hz; H-3 and H-5), 5.26 (s; OCH₂), 2.53 (s; Me-4). Anal. calc. for C₁₄H₁₃N₃O₄ (287.27): C, 58.53; H, 4.56; N, 14.63; found : C, 58.6; H, 4.5; N, 14.6.

5-Methyl-(2'-trimethylsilyl)ethoxycarbonyl-[1H]-1,2-diazepine 5b : A solution of pyridinium ylide 4b (23.3 g; 92 mmol) in toluene (10 ml) is irradiated for 9 h under nitrogen in a "falling film" type photoreactor⁸ equipped with two 1000 W medium pressure mercury vapour lamps, the reaction being followed by UV spectroscopy and by TLC until complete disappearance of the pyridinium ylide. After evaporation of the solvent in vacuo and flash-chromatography (AcOEt/cyclohexane 3/7) of the crude reaction mixture, diazepine 5b is obtained as yellow crystals (21.5 g; 92 %), mp 59.5-60.5°C (hexane). IR (KBr) : 1692 cm⁻¹. UV (MeOH) λ_{max} (ε) 350 (300), 222 (10000). ¹H-NMR (CDCl₃ at 60 MHz) δ : 7.32 (d; J=3.5 Hz; H-3), 6.25 (d; J=7.5 Hz; H-7), 6.09 (m; H-4), 5.61 (dd; J=7.5 and 1.5 Hz; H-6), 4.40 (m; OCH₂), 1.93 (s; Me-5), 1.12 (m; CH₂Si), 0.05 (s; SiMe₃). Anal. Calc. for C₁₂H₂₀N₂O₂Si (252.39) : C, 57.11; H, 7.99; N, 11.10; found : C, 57.4; H, 8.1; N, 11.0.

5-Methyl-1-p-nitrobenzyloxycarbonyl-[1H]-1,2-diazepine 5c : Similar procedure as above starting from pyridinium ylide 4c (9.0 g; 31 mmol) yields diazepine 5c (6.67 g; 74 %) as yellow crystals (hexane), mp 92-92.5°C. IR (KBr) : 1700 cm⁻¹. UV (MeOH) λ_{max} (ε) : 330 (550, shoulder), 260 (13300) and 214 (20100). ¹H-NMR (CDCl₃ at 60 MHz) δ : 8.24 (d; J=8.5 Hz; mH-arom), 7.58 (d; J=8.5 Hz; oH-arom), 7.34 (d; J=3.5 Hz; H-3), 6.23 (d; J=7.5 Hz; H-7), 6.07 (m; H-4), 5.65 (dd; J=7.5 and 1.5 Hz; H-6), 5.39 (s; OCH₂), 1.92 (s; Me-5). Anal. calc. for C₁₄H₁₃N₃O₄ (287.27) : C, 58.53; H, 4.56; N, 22.28; found : C, 58.5; H, 4.3; N, 22.5.

[7α,8α]-5,8-Dimethyl-9-oxo-2-(2'-trimethylsilyl)ethoxycarbonyl-1,2-diazabicyclo[5.2.0]-nona-3,5-diene 1b : Through a solution of diazepine 5b (8.0 g; 31.7 mmol) in toluene (600 ml) which is kept at room temperature is passed the pyrolysis gas of butanone produced in a ketene lamp³, until disappearance of 5b as shown by TLC. After evaporation of the solvent in vacuo and flash chromatography (AcOEt/cyclohexane 1/9) of the crude reaction mixture, the β-lactam 1b (9.19 g; 94 %)

is obtained as a colourless oil. IR (CHCl₃) : 1773, 1722 cm⁻¹. UV (MeOH) λ_{max} (ε) : 270 (2400). ¹H-NMR (CDCl₃ at 60 MHz) δ : 6.82 (d; J=9.5 Hz; H-3), 5.78 (m; H-6), 4.97 (d; J=9.5 Hz; H-4), 4.35 (m; OCH₂), 4.15 (m; H-7), 2.64 (qd; J=7.5 and 2 Hz; H-8), 1.88 (t; J=2 Hz; Me-5), 1.41 (d; J=7.5 Hz; Me-8), 1.08 (m; CH₂Si), 0.05 (s; SiMe₃). MS : m/z = 308 (M⁺, 1 %), 73 (100 %). Exact Mass calc. for C₁₅H₂₄N₂O₃Si (MS) : 308.1556; found : 308.1542.

[7α,8α]-5,8-Dimethyl-2-p-nitrobenzyloxycarbonyl-9-oxo-1,2-diazabicyclo[5.2.0]-nona-3,5-diene 1c : A similar procedure as above starting from diazepine 5c (6.26 g; 21.8 mmol) yields the azetidinodiazepine 1c (7.35 g; 98 %) after flash chromatography (ethyl acetate/cyclohexane 3/7) as colourless crystals, mp 108.5-109°C (ether). IR (KBr) : 1785, 1735 cm⁻¹. UV (MeOH) λ_{max} (ε) : 269 nm (17200). ¹H-NMR (CDCl₃ at 60 MHz) δ : 8.18 (d; J=8.5 Hz; H-3' and H-5'), 7.50 (d; J=8.5 Hz; H-2' and H-6'), 6.74 (d; J=9.5 Hz; H-3), 5.75 (m; H-6), 5.31 (s; OCH₂), 5.00 (d; J=9.5 Hz; H-4), 4.07 (m; H-7), 2.67 (qd; J=7.5 and 2 Hz; H-8), 1.88 (t; J=2 Hz; Me-5), 1.37 (d; J=7.5 Hz; Me-8). Anal. calc. for C₁₇H₁₇N₃O₅ (343.33) : C, 59.47; H, 4.99; N, 12.24; found : C, 59.5; H, 5.0; N, 12.2.

[3α,6α,7α,8α]-5,8-Dimethyl-9-oxo-2-(2'-trimethylsilyl)-ethoxycarbonyl-1,2-diazatricyclo[5.2.0.0^{3,6}]-non-4-ene 2b and [1α,6α,9β]-6,9-dimethyl-3-(2'-trimethylsilyl)-ethoxycarbonyl-10-oxa-2,3-diazabicyclo[4.3.1]-deca-1,4,7-triene 3b :

A solution of the azetidinodiazepine 1b (8.33 g; 27.0 mmol) in methylene chloride (1 l) is irradiated by UV-light for 5 h until complete consumption of the starting material, the reaction medium being monitored by TLC. After evaporation of the solvent in vacuo, the crude reaction mixture is separated into its components by flash chromatography (AcOEt/cyclohexane 2/8), whereby the two isomers 3b (1.50 g; 18 %) and 2b (6.11 g; 73 %) appear in that order.

Photoisomer 2b : colourless crystals, mp 83.5-84°C (ether/petrol-ether). IR (KBr) : 1780, 1770, 1705 cm⁻¹. UV (MeOH) λ_{max} (ε) : 238 (770, shoulder). ¹H-NMR (CDCl₃ at 60 MHz) δ : 5.86 (m; H-4), 5.30 (m; H-3), 4.27 (m; CH₂O), 3.70 (dm; 6.5 Hz; H-6), 3.40 (dd; J=6.5 and 1.5 Hz; H-7), 3.02 (qd; J=7.5 and 1.5 Hz; H-8), 1.80 (m; Me-5), 1.47 (d; J=7.5 Hz; Me-8), 1.03 (m; CH₂Si), 0.05 (s; SiMe₃). MS : m/z = 308 (M⁺, 1 %), 73 (100 %). Anal. calc. for C₁₅H₂₄N₂O₃Si (308.45) : C, 58.41; H, 7.84; N, 9.08; found C, 58.2; H, 7.7; N, 9.1.

Photoisomer 3b : colourless oil. IR (CHCl₃) : 1712, 1645 cm⁻¹. UV (MeOH) λ_{max}

(ϵ) : 240 (8800). $^1\text{H-NMR}$ (CDCl_3 at 60 MHz) δ : 6.93 (d; $J=10$ Hz; H-4), 5.77 (s; H-7 and H-8), 4.93 (d; $J=10$ Hz; H-5), 4.37 (m; OCH_2), 3.30 (q; $J=7$ Hz; H-9), 1.50 (s; Me-6), 1.25 (d; $J=7$ Hz; Me-9), 1.08 (CH_2Si), 0.05 (s; SiMe_3). MS : m/z = 308 (M^+ ; 3 %), 73 (100 %). Exact Mass calc. for $\text{C}_{15}\text{H}_{24}\text{N}_2\text{O}_3\text{Si}$ (MS) : 308.1556; found 308.1552.

[3 α ,6 α ,7 α ,8 α]-5,8-Dimethyl-2-p-nitrobenzyloxycarbonyl-9-oxo-1,2-diazatricyclo[5.2.0.0^{3,6}]-non-4-ene 2c : A solution of the azetidinodiazepine 1c (6.44 g; 18.7 mmol) in methylene chloride (800 ml) is irradiated by UV-light through Vycor-glass as above. After evaporation of the solvent in vacuo and flash-chromatography (ethyl-acetate/cyclohexane 3/7) of the crude reaction mixture, only photoisomer 2c could be isolated (2.5 g; 40 %) as colourless crystals, mp : 177-177.5°C (ethanol). IR (KBr) 1785, 1715 cm^{-1} . UV (MeOH) λ_{max} (ϵ) : 265 nm (10600). $^1\text{H-NMR}$ (CDCl_3 at 60 MHz) δ : 8.20 (d; $J=9$ Hz; H-3' and H-5'), 7.50 (d; $J=9$ Hz; H-2' and H-6'), 5.82 (m; H-4), 5.25 (s; OCH_2), 3.73 (dm; $J=6.5$ Hz; H-6), 3.45 (dd; $J=6.5$ and 1.8 Hz; H-7), 3.05 (qd, $J=7.3$ and 1.5 Hz; H-8), 1.81 (m; Me-5), 1.48 (d; $J=7.3$ Hz; Me-8). Anal. calc. for $\text{C}_{17}\text{H}_{17}\text{N}_3\text{O}_5$ (343.33) : C, 59.47; H, 4.99; N, 12.24; found : C, 59.3; H, 5.0; N, 12.0.

[3 α ,6 α ,7 α ,8 α]-5,8-Dimethyl-9-oxo-1,2-diazatricyclo[5.2.0.0^{3,6}]-non-4-ene 2d : To a stirred solution of 2b (2.10 g; 6.81 mmol) in anhydrous THF (20 ml) under argon at room temperature, TBAF (about 2 equivalents) is added in small portions until disappearance of the starting material. Water (10 ml) is added to the reaction medium which is then extracted several times with methylene chloride. The organic phase is filtered over Whatman 1 PS siliconated paper, the solvent evaporated in vacuo and the crude reaction mixture purified by flash-chromatography (ethyl acetate/cyclohexane 5/5). Compound 2d (972 mg; 87 %) is isolated as colourless crystals (CH_2Cl_2 /petrol-ether), mp 124-124.5°C. IR (KBr) 3260, 1732 cm^{-1} . UV (MeOH) λ_{max} (ϵ) : 235 (1000, shoulder). $^1\text{H-NMR}$ (CDCl_3 at 60 MHz) δ : 5.81 (m; H-4), 4.56 (m; H-3), 3.56 (dm; $J=6.5$ Hz; H-6), 3.3 (broad s; disappears in the presence of D_2O ; N-H), 3.22 (dd; $J=6.5$ and 2 Hz; H-7), 2.92 (q; $J=7.5$ Hz; H-8), 1.77 (m; Me-5), 1.42 (d; $J=7.5$ Hz; Me-8). $^{13}\text{C-NMR}$ (CDCl_3 at 20.1 MHz) δ ($^1J_{\text{C-H}}$) : 179.58 (S; C-9), 146.73 (S; C-5), 132.52 (Dqd; 172 Hz; C-4), 70.03 (Ds; 154 Hz; C-3), 59.87 (Dq; 157 Hz; C-7), 53.09 (Ddm; 147 Hz; C-6), 43.39 (Dq; 140 Hz; C-8), 15.92 (Qs; 127 Hz; Me-5), 14.51 (Qt; 128 Hz; Me-8). MS : m/z 164 (M^+ ; 6 %), 108 (100 %). Anal. calc. for $\text{C}_9\text{H}_{12}\text{N}_2\text{O}$ (164.20) : C, 65.83;

H, 7.37; N, 17.06; found : C, 66.1; H, 7.5; N, 17.1.

Tetra-n-butylammonium[3 α ,6 α ,7 α ,8 α]-5,8-dimethyl-9-oxo-1,2-diazatricyclo-[5.2.0.0^{3,6}]-non-4-ene-2-sulfonate 2e : To a stirred solution of 2d (972 mg; 5.90 mmol) in anhydrous methylene chloride (40 ml) at 0°C under argon, was rapidly added the SO₃/DMF-complex⁹ (15 ml; about 15 mmol). After 30 min at 0°C the starting material had disappeared and the reaction mixture is added to a 0.5 M potassium dihydrogenophosphate water solution (120 ml). The aqueous phase is separated, washed several times with methylene chloride, and tetra-n-butylammonium dihydrogenophosphate (2.00 g; 5.90 mmol) is added to it. Extraction of this water solution is performed with methylene chloride, the organic phase is dried and the solvent evaporated in vacuo (45°C/0.05 Torr) until complete disappearance of DMF. Compound 2e is obtained as a colourless oil (2.48 g; 86 %). IR (CHCl₃) : 1755 cm⁻¹. UV (MeOH) λ_{max} (ϵ) 232 (900; shoulder). ¹H-NMR (CDCl₃ at 60 MHz) δ : 5.72 (m; H-4), 5.15 (m; H-3), 3.70 (s; H-7 and H-6), 2.83 (q; J=7.5 Hz; H-8), 1.73 (s; Me-5), 1.38 (d; J=7.5 Hz; Me-8), 3.5-3.1, 1.8-1.2, 1.2-0.8 (several multiplets; n-butyl). ¹³C-NMR (CDCl₃ at 20.1 MHz) δ (¹J_{C-H}) : 178.44 (Sq; C-9), 146.32 (S quint.d, C-5), 131.70 (Dm; 172 Hz; C-4), 71.31 (Dm; 157 Hz; C-3), 58.69 (Dm; 159 Hz; C-7), 57.55 (Tm; 145 Hz; N-CH₂), 52.95 (Dm; 145 Hz; C-6), 43.79 (Dm; 140 Hz; C-8), 23.02 (Tm; 128 Hz; NCH₂CH₂), 18.79 (Tm; 127 Hz; NCH₂CH₂CH₂), 15.51 (Qs; 126 Hz; Me-5), 13.64 (Qm; 127 Hz; Me-8), 12.82 (Qm; 126 Hz; N(CH₂)₃CH₃).

Treatment of isomer 2a with osmium tetroxide : To a stirred solution of compound 2a (500 mg; 2.20 mmol) in acetone (2.5 ml) is successively added a solution of N-methylmorpholine-N-oxide (300 mg; 2.50 mmol) in water (1 ml) and acetone (1 ml), and thence a solution of OsO₄ (5mg; catalytic amount) in t-butanol (1.1 ml). This mixture is stirred at room temperature for 2 days. A sodium disulfite solution is then added, along with some celite, and the suspension is filtered over sinter-glass. The resulting solution is acidified to pH 2 and extracted several times with methylene chloride. The combined organic extracts are dried and evaporated to dryness in vacuo and the residue separated by flash-chromatography which leads to the recovery of starting material 2a only. No glycol could be isolated. The same procedure at 50°C led to the same negative result.

[3 α ,7 α ,8 α ,9 α]-6,9-Dimethyl-2-ethoxycarbonyl-10-oxo-1,2-diaza-5-oxatricyclo-[6.2.0.0^{1,8}]-4,6-epidioxy-decane 6a : To silicic acid (Merck, 70-230 mesh; 25 g)

which had been hydrated with water (1.25 ml) is added a solution of compound 2a (250 mg; 1.06 mmol) in ether (75 ml) and the resulting suspension is stirred and thence evaporated to dryness. A stream of ozone and oxygen is passed through the powdery residue at -78°C for 2 h. The reaction mixture is then eluted with methylene chloride at room temperature and evaporated to dryness leading thereby to ozonide 6a as colourless crystals (pentane/CH₂Cl₂), mp 127-128°C. IR (KBr) 1780, 1730, 1120, 1000 cm⁻¹. UV (CH₃CN) λ_{max} (ε) : 256 nm (800). ¹H-NMR (CDCl₃ at 80 MHz) δ : 5.95 (s; H-4), 4.98 (d; J=7 Hz; H-3), 4.24 (q; J=7 Hz; OCH₂), 3.66 (dd; J=8.5 and 2.8 Hz; H-8), 3.41 (qd; J=7.5 and 2.8 Hz; H-9), 3.23 (dd; J=8.5 and 7.0 Hz; H-7), 1.80 (s; Me-6), 1.48 (d; J=7.5 Hz; Me-9), 1.31 (t; J=7 Hz; OCH₂CH₃). MS : m/z = 284 (M⁺; 1 %), 141 (100 %). Anal. calc. for C₁₂H₁₆N₂O₆ (284.10) : C, 50.70; H, 5.67; N, 9.85; found : C, 50.3; H, 5.7; N, 10.0.

[3α,7α,8α,9α]-6,9-Dimethyl-2-p-nitrobenzyloxycarbonyl-10-oxo-1,2-diaza-5-oxatricyclo[6.2.0.0^{1,8}]-4,6-epidioxycane 6c : A solution of 2c (202 mg; 0.59 mmol) in acetonitrile (35 ml) kept at -40°C is bubbled with a mixture of oxygen and ozone. After the elimination of excess ozone with a stream of nitrogen the solvent is evaporated in vacuo and the residue recrystallized in acetonitrile/ether leading to ozonide 6c (138 mg; 60 %) as colourless crystals, mp 152°C. IR (KBr) 1780, 1660 cm⁻¹. UV (CH₃CN) λ_{max} : 263 nm. ¹H-NMR (CDCl₃ at 200 MHz) δ : 8.25 (d; J=9 Hz; H-3' and H-5'), 7.57 (d; J=9 Hz; H-2' and H-6'), 5.97 (s; H-4), 5.38 (d; J=13.4 Hz; OCH), 5.24 (d; J=13.4 Hz; OCH), 5.00 (d; J=6.8 Hz; H-3), 3.73 (dd; J=8.8 and 3 Hz; H=7), 3.47 (qd; J=7.5 and 3 Hz; H-8), 3.33 (dd; J=8.8 and 6.8 Hz; H-6), 1.83 (s; Me-5), 1.52 (d; J=7.5 Hz; Me-8). Anal. calc. for C₁₇H₁₇N₃O₈ (391.33) : C, 52.17; H, 4.38; N, 10.74; found : C, 51.5; H, 4.3; N, 10.4.

[5α,6α]-2-Ethoxycarbonyl-6-methyl-7-oxo-1,2-diazabicyclo[3.2.0]-hept-3-ene 7a and [5α,6α]-4-acetyl-2-ethoxycarbonyl-6-methyl-7-oxo-1,2-diazabicyclo[3.2.0]-hept-3-ene 8a : Into a solution of 2a (500 mg; 2.12 mmol) in acetonitrile (50 ml) which is kept at -40°C a mixture of oxygen and ozone is bubbled until complete disappearance of the starting material (TLC). After elimination of excess ozone with a stream of nitrogen the solution is transferred at room temperature into a photoreactor (Pyrex-glass), some fluorenone (80 mg) is added, and the resulting solution is irradiated with UV-light under nitrogen atmosphere for 30 min. After evaporation of solvent in vacuo the residue is separated by

flash-chromatography (ethyl acetate/cyclohexane 1/9 to 3/7) leading to compounds 7a (149 mg; 32 %) and 8a (61 mg; 12 %).

Compound 7a : yellow oil, bp 130°C / 0.1 Torr. IR (CCl₄) 1800, 1730, 1715 and 1590 cm⁻¹. ¹H-NMR (CDCl₃ at 80 MHz) δ : 6.88 (ddd; J=4.2, 2 and 0.9 Hz; H-3), 5.48 (dd; J=4.2 and 1.5 Hz; H-4), 4.55 (m; H-5), 4.33 (q; J=7 Hz; OCH₂), 3.35 (qd; J=7.5 and 2.8 Hz; H-6), 1.53 (d; J=7.5 and 2.8 Hz; Me-6), 1.34 (t; J=7 Hz; OCH₂CH₃). ¹³C-NMR (CDCl₃ at 20.1 MHz) δ (¹J_{C-H}) : 184.27 (Sm; C-7), 152.88 (St; CO₂Et), 132.52 (Ddd; 193 Hz; C-3), 109.48 (Ddd; 179 Hz; C-4), 66.07 (Dm; 160 Hz; C-5), 62.61 (Tq; 149 Hz; CO₂CH₂), 55.64 (Dq; 140 Hz; C-6), 14.05 (Qt; 128 Hz; CO₂CH₂CH₃), 13.87 (Qt; 130 Hz; Me-6). MS : m/z 196 (M⁺, 19 %), 95 (100 %). Exact Mass calc. for C₉H₁₂N₂O₃ (MS) : 196.0847; found : 196.0843.

Compound 8a : unstable oil. IR (CHCl₃) 1810, 1725, 1655 cm⁻¹. ¹H-NMR (CDCl₃ at 80 MHz) δ : 7.64 (m; H-3), 4.66 (dd; J=3 and 1.3 Hz; H-5), 4.36 (q; J=7 Hz; OCH₂), 3.48 (Qd; J=7.8 and 3 Hz; H-6), 2.35 (s; COCH₃), 1.55 (d; J=7.8 Hz; Me-6), 1.28 (t; J=7 Hz; OCH₂CH₃).

[5α,6α]-6-Methyl-7-oxo-2(2'-trimethylsilyl)-ethoxycarbonyl-1,2-diazabicyclo[3.2.0]-hept-3-ene 7b and [5α,6α]-4-acetyl-6-methyl-7-oxo-2-(2'-trimethylsilyl)-ethoxycarbonyl-1,2-diazabicyclo[3.2.0]-hept-3-ene 8b : Into a solution of 2b (3.00 g; 9.7 mmol) in acetonitrile (300 ml) which is kept at -40°C a mixture of oxygen and ozone is bubbled for 2 h until complete disappearance of the starting material (TLC). After elimination of excess ozone with a stream of nitrogen the solution is transferred at room temperature into a photoreactor (Pyrex-glass), some fluorenone (500 mg) is added, and the resulting solution is irradiated with UV-light under nitrogen atmosphere for 2.5 h. After evaporation of the solvent in vacuo the residue is separated by flash-chromatography (ethyl acetate/cyclohexane 2/8) leading to compounds 7b (885 mg; 34 %) and 8b (403 mg; 13 %).

Compound 7b : unstable yellow oil. IR (CCl₄) : 1815, 1720, 1140 cm⁻¹. ¹H-NMR (CDCl₃ at 60 MHz) δ : 6.87 (m; H-3), 5.47 (dd; J=4 and 2 Hz; H-4), 4.47 (m; H-5), 4.33 (m; OCH₂), 3.03 (qd; J=7.5 and 2 Hz; H-6), 1.47 (d; J=7.5, Me-6), 1.06 (m; CH₂Si), 0.06 (s; SiMe₃).

Compound 8b : unstable yellow oil. ¹H-NMR (CDCl₃ at 60 MHz) δ : 7.57 (m; H-3), 4.60 (m; H-5); 4.36 (m; OCH₂), 3.43 (qd; J=7.5 and 2.5 Hz; H-6); 2.33 (s; COCH₃), 1.54 (d; J=7.5 Hz; Me-6), 1.10 (m; CH₂Si), 0.08 (s; SiMe₃).

[5 α ,6 α]-2-Ethoxycarbonyl-6-methyl-7-oxo-1,2-diazabicyclo[3.2.0]-heptane 9a :

A solution of 7a (407 mg; 2.10 mmol) in ethyl-acetate (8 ml) is hydrogenated over 5 % Pd/C (34 mg) at atmospheric pressure for 1 h until complete consumption of the starting material (TLC). The reaction mixture is filtered over silicic acid and the solution evaporated to dryness in vacuo whereby compound 9a is obtained as a colourless compound (371 mg; 90 %). IR (CCl₄) : 1812, 1725 cm⁻¹. ¹H-NMR (CDCl₃ at 60 MHz) δ : 4.23 (q; J=7 Hz; H-5), 4.1 (m; OCH₂), 3.97-3.20(m; H-4), 2.90 (dq; J=7.5 and 2.5 Hz; H-6), 1.75-2.60 (m; H-3), 1.43 (d; J=7.5 Hz; Me-6), 1.30 (t; J=7 Hz; OCH₂CH₃). ¹³C-NMR(CDCl₃ at 20.1 MHz) δ (¹J_{C-H}) : 182.49 (Sm; C-7), 156.25 (Sm; CO₂Et), 62.29 (Tq; 148 Hz; OCH₂), 59.19 (Dm; 159 Hz; C-5), 50.99 (D sext; 139 Hz; C-6), 50.35 (T; 146 Hz; C-3), 30.13 (T; 133 Hz; C-4), 14.10 (Qt; 127 Hz; OCH₂CH₃), 13.60 (Qt; 129 Hz; Me-6). MS : m/z 198 (M⁺; 7 %), 142 (100 %). Exact Mass calc. for C₉H₁₄N₂O₃ : 198.1004; found 198.1008.

[5 α ,6 α]-6-Methyl-7-oxo-2-(2'-trimethylsilyl)-ethoxycarbonyl-1,2-diazabicyclo[3.2.0]-heptane 9b :

A solution of 7b (400 mg; 1.50 mmol) in ethyl acetate (30 ml) is hydrogenated over 5 % Pd/C (50 mg) at atmospheric pressure for 2 h, until complete consumption of the starting material (TLC). The reaction mixture is filtered over silicic acid and the solution evaporated to dryness in vacuo whereby compound 9b (272 mg; 57 %) is obtained as colourless crystals, mp 45-47°C. IR (CCl₄) 1805, 1712 cm⁻¹. ¹H-NMR (CDCl₃ at 60 MHz) δ : 4.23 (m; H-5 and O-CH₂), 3.83-3.17 (m; H-4), 2.90 (qd; J=7.5 and 2.5 Hz; H-6), 2.60-1.63 (m; H-3), 1.43 (d; J=7.5 Hz; Me-6), 1.03 (m; CH₂Si), 0.06 (s; SiMe₃). ¹³C-NMR (CDCl₃) δ (¹J_{C-H}) : 182.22 (Sm; C-7), 156.39 (Sm; CO₂), 64.61 (Tt; 149 Hz; CO₂CH₂), 59.14 (Dm; 159 Hz; C-5), 50.95 (D-sext, 140 Hz; C-6), 50.31 (Ts; 146 Hz; C-3), 30.13 (Ts; 134 Hz; C-4), 17.24 (Ts; 122 Hz; CH₂Si), 13.64 (Qt; 130 Hz; Me-6), -1.89 (Qs; 119 Hz; Si Me₃). MS : m/z 270 (M⁺; 2 %), 73 (100 %). Exact Mass calc. for C₁₂H₂₂N₂O₃Si (MS) : 270.1399; found : 270.1398.

Deprotection of 9b with TBAF : reaction of 9b with TBAF in THF led to a dimer ; tentative structure 10. MS : m/z 252 (M⁺).

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