METHYL-LITHIUM AS A CONVENIENT DEACYLATING AGENT OF ALKOXYCARBONYL AND BENZOYL PROTECTED SECONDARY HYDRAZIDES. APPLICATIONS IN THE FIELD OF AZETIDINO-DIAZEPINES AND OF THEIR PHOTOISOMERS

Théophile Tschamber and Jacques Streith*
Ecole Nationale Supérieure de Chimie
Université de Haute-Alsace F-68093 Mulhouse Cedex France

Abstract - Methyl-lithium proved to be a useful deacylating reagent for alkoxycarbonyl- and benzoyl-protected secondary hydrazides, leading thereby - after protonation - to the R-CO-NR'-NH-R" functionality. This methodology found some application with azetidinodiazepines 1, in which the N-Y group was cleaved selectively without destruction of the β-lactam moiety.

INTRODUCTION. - In a previous publication we showed that azetidinodiazepines **1** could easily be synthesized in a stereospecific way from the corresponding monocyclic 1,2-diazepines.[1] Furthermore direct irradiation of compounds **1** by uv light led stereospecifically to the tricyclic photoisomers **5**,[2] whereas triplet photosensitized irradiation of **1** gave the type **9** anti-Bredt photoisomers. [2]
Our next objective was the selective deprotection of the hydrazide moieties, i.e. replacement of Y by H of compounds **1** and **5**, the ultimate goal being the attachment of an anionic functionality to N(2) in order to arrive at some analogues of β-lactam antibiotics. Aiming in particular at the preparation of azadienes **3** (see below), we did obtain these latter ones by pyrolysis of the corresponding urea derivatives **2**.[3] Unfortunately the pyrolysis conditions proved to be rather harsh. Furthermore the synthesis of hydrazides **2** was cumbersome.[3] Therefore we investigated the deprotection of the urethane and benzamide type derivatives **1** and **5** by applying a methodology which had been introduced in 1983 by Sawyer.[4]
Sawyer showed that MeLi, when used in excess in the cold, clearly led to deacylation of secondary urethanes[4] which gave the corresponding secondary amines. He showed furthermore that these experimental conditions did not permit to cleave primary urethanes .[4]

DEACYLATION OF ALKOXYCARBONYL AND BENZOYL PROTECTED HYDRAZIDE DERIVATIVES WITH METHYL-LITHIUM. - When **1a** was treated with a two- to threefold excess of MeLi in THF/Et_2O at low temperature under argon, and thence with H_2O, azadiene **3a** was formed in moderate yield (63 %). Using the same methodology with **1b**, azadiene **3b** was obtained in poor yield only (17 %). Furthermore the benzamide functionality of **1c** was cleaved easily to give **3a** in good yield (89 %). The results which we obtained under

these experimental conditions with **1a** and **1c**, are of interest since the β-lactam moieties proved to be unexpectedly resistant.

We postulate the lithium salts of the bis-allylic azaanions **4a** and **4b** to be the most plausible intermediates in these cleavage reactions, as could be shown by the following experiment. Treatment of **1a** with MeLi as described above led to its disappearance. Addition of methyl chloroformate to this reaction mixture gave the urethane **1d** in good yield (75 %).

Similar results could also be obtained with the more severely strained tricyclic products **5a** and **5b**,[2] which are the photoisomers of **1a** and **1c** respectively. Consecutive treatment of **5a** and **5b** with MeLi and thence with H_2O gave **6** in moderate yields (63 % from **5a** ; 76 % from **5b**). Again we notice that the β-lactam moiety is unexpectedly stable under these experimental conditions.

The stability of the azetidinone ring of **1** and **5** we observed in the above described experiments with MeLi was puzzling. Nevertheless when the azetidinoazadiene **3a** was left to react with MeLi and thence with H_2O, it gave the methyl ketone **7** as the only isolable product (55 %). This result clearly shows that the urethane or the benzamide functionalities of **1** merely react with a faster rate than the β-lactame moieties. Once the anions **4** are formed, MeLi can no longer attack their β-lactam moieties since this leads to strong Coulombing repulsions. But as soon as the anions **4** are protonated to give **3a** and **3b**, these latter products which are neutral species do undergo nucleophilic attack at the β-lactam site.

That the azetidinone ring of **3** is prone to react with nucleophiles could also be shown by the following experiment. Reaction of **1a** with NaOMe **in MeOH** gave the ester **8** in good yield (87 %), a result which indicates that the postulated intermediate **4a** is protonated at once by the solvent to give **3a** which then undergoes ring-opening to give **8.**

Anion **4a** could even be regenerated from **3a** by using the sterically hindered base LICA (**L**ithium **I**sopropyl **C**yclohexyl **A**mide) at -70°C. Subsequent addition of methyl chloroformate to the anhydrous reaction mixture gave **1d**.

All these experimental data clearly indicate that the β-lactam rings of compounds **1** (and **5**) are sterically more hindered than the N(2)-carbonyl functionalities. They are also less reactive than the β-oriented H-C(6) atom of **3**, at least when bulky bases like LICA are used. If one considers compounds **1** as lying flat on a planar surface, the Me-C(8) group is oriented below (α-side), and the seven-membered ring above (β-side) this plane, so that both of these two moieties exert some steric repulsion upon the approaching MeLi reagent

Finally let us have a look at the behaviour of the so-called "anti-Bredt" photoisomer **9** in the presence of MeLi and of $NaBH_4$.* The structure of **9** had been ascertained by X-ray analysis which showed in particular that the imine double bond is twisted out of plane by about 20°C.[2] MeLi added to the C=N double bond of **9** leading to **10** (60 %), whereas the N-(3) urethane functionality did not seem to react at all. Similarly, **9** reacted with $NaBH_4$ to give the reduced product **11** in excellent yield (90 %). Here too the nucleophilic reagent (hydride) added to the imine double bond, leaving the urethane portion intact. In these latter two instances the reactivity we observed is somewhat reversed with respect to the one we had obtained with **1** and **5**, since the urethane functionalities were not attacked, neither by MeLi nor by $NaBH_4$. The fact that nucleophilic addition took place at the more hindered C(1) site is undoubtedly due to the twisted geometry of the imine double bond which confers to C(1) a stronger electrophilic character. Furthermore reaction products **10** and **11** are almost devoid of any ring strain and therefore more

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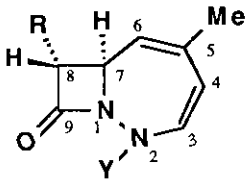
* Photoisomer **5** had been obtained by **direct** irradiation of **1c**, whereas **9** was formed during UV-irradiation of **1a** in the **presence of a triplet photosensitizer**[2].

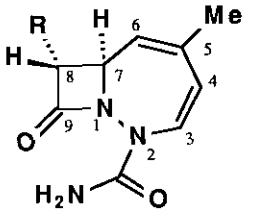
stable than educt **9**.

Scheme 1



1

a) R = Me; Y = CO_2Et
b) R = H ; Y = CO_2Et
c) R = Me ; Y = COPh
d) R = Me ; Y = CO_2Me



2

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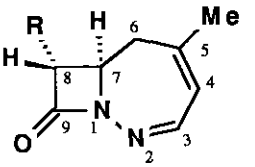
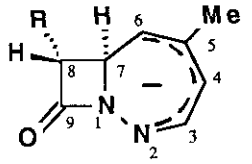
b) R = H



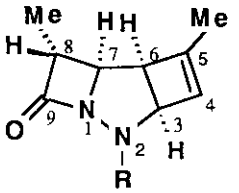
3

a) R = Me
b) R = H



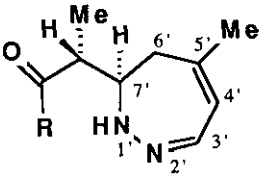
4

a) R = Me
b) R = H



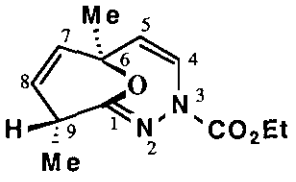
5 a) R = CO_2Et
b) R = COPh

6 R = H

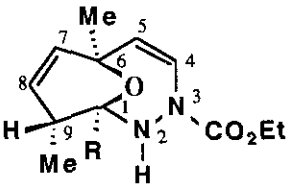


7 R = Me
8 R = OMe

Scheme 2



9



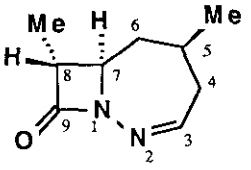
10 R = Me
11 R = H

SYNTHETIC UTILITY OF AZADIENES 3. - As stated above, our ultimate goal is the synthesis of analogues of β-lactam antibiotics. A first approach was as follows. Catalytic

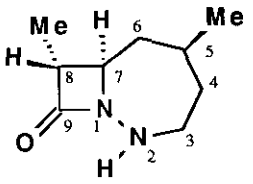
hydrogenation of **3a** over Pd/C led exclusively to the 4,5-dihydroproduct **12** (97 %) which could be hydrogenated further to **13a** (86 %) in the presence of Adam's catalyst (PtO_2). Hydrogenation of **3a** over Pt gave directly the tetrahydro product **13**.
Sulfonation of **13** *with the DMF/SO_3 complex, followed by treatment with nBu_4NHSO_4,* led to the ammonium salt **14** which by means of ion exchange gave the potassium salt **15** (racemic). A series of antibacterial tests (determination of MIC-values) with several Gram-positive and Gram-negative pathogenic bacterial strains, showed compound **15** to be devoid of any antibiotic activity.
Reaction of **13** with benzyl bromoacetate in the presence of NEt_3 and DMAP led to the formation of **16** (60 %) which by means of hydrogenolytic cleavage over Pd/C, gave the expected carboxylic acid **17** in quantitative yield. The potassium salt of (±)- **17** is awaiting antibacterial test determination.

STRUCTURAL ANALYSES.- The structures of type **1** and of type **2** products had been determined unambiguously by ^{1}H-nmr and by X-ray crystallographic analyses.[6] This was also the case for photoisomers **5**, **6** and **9**,[2] so that the structures of the newly formed derivatives of these basic structures could easily be ascertained (see **Experimental**). The only difficulty was to determine the conformation and the relative configuration of the dihydro compound **12**.

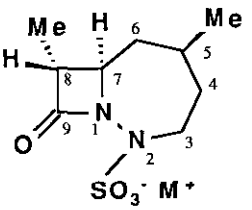
Scheme 3



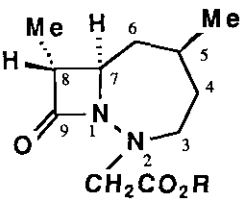
12



13



14 M = nBu_4N
15 M = K



16 R = CH_2Ph
17 R = H

According to a Dreiding model of **12** this compound may occur in two conformations : i) conformation **A** in which the boat shaped seven-membered ring has its convex side pointing toward the reader ; ii) conformation **B** in which the concave side of this seven-membered ring points toward the reader.

Hydrogen atom H-C(7) of **12** appears as a ddd with J=11.8, 3.2 and 2.7 Hz. This latter J value was identified as $J_{7,8}$. The two other coupling constants clearly indicate that **12** occurs in conformation **A** since only in this conformation the dihedral angle of H_α-C(6)-H-C(7) is about 90° (J=3.2 Hz) and the dihedral angle of H_β-C(6)-H-C(7) about 180° (J=11.8 Hz). In the hypothetical conformation **B** these two dihedral angles would appear with about the same magnitudes and therefore with similar J values.
H-C(5) can only be α-oriented in order to account for the magnitude of its J-values. In particular it is oriented quasi antiparallel with respect to H_β-C(6) ($J_{5,6\beta}$ = 11.6 Hz), whereas $J_{5,6\alpha}$ is much smaller (2.7 Hz). It follows that Me-C(5) is β-oriented, not only in the dihydrocompound **12**, but also in the tetrahydroproducts **13 - 17** (in all these products both $J_{5,6\beta}$ and $J_{6\beta,7}$ have magnitudes of about 11 Hz).

ACKNOWLEDGEMENTS
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EXPERIMENTAL

General. - Flash chromatography (FC)[7] : silica gel (Amicon 35-70). Tlc : aluminium roll (Merck 60 F254) . mp : Büchi SMP 20 apparatus ; not corrected. Ir spectra (cm^{-1}) : Perkin-Elmer 157-G. ^1H- and ^{13}C-nmr spectra : Bruker WP-80-DS WP-200, WP-400 apparatus ; TMS (^1H-nmr) and $CDCl_3$ (d($CDCl_3$) = 77.00 ppm with respect to TMS ; ^{13}C-nmr) as internal references ; δ in ppm and J in Hz. Ms were measured on a Varian MAT-311 spectrometer at the University of Rennes. Microanalyses were carried out by the Service Central de Microanalyses of the CNRS at Vernaison.

Starting materials. - Anhydrous THF was kept over 4 A molecular sieves. MeLi was purchased from FLUKA as a 1.6 molar solution in diethyl ether ; the amounts used in the following experiments are expressed in ml.

[7α, 8α]-5,8-Dimethyl-1,2-diazabicyclo[5.2.0]nona-2,4-dien-9-one (3a). -
a) To a stirred solution of **1a**[1] (5.00 g ; 21.2 mmol) in anhydrous THF (15 ml) at 0°C under Ar, was added the MeLi/Et_2O solution (14 ml). After 30 min H_2O (5 ml) was added, the reaction mixture was left to warm up to room temperature and then extracted with Et_2O. The organic phase was dried over $MgSO_4$, evaporated to dryness and the resulting residue was purified by fc (AcOEt/cyclohexane 6:4) giving **3a**[3] (2.20 g ; 63 %). A similar reaction performed at -70°C led to the same overall yield for **3a.**
b) To a stirred solution of **1c** (268 mg ; 1.00 mmol)[1] in anhydrous THF (3 ml) at -69°C under Ar, was added the MeLi/Et_2O solution (1 ml). After 15 min the reaction mixture was neutralized with a saturated aq. solution of NH_4Cl. Once at room temperatrure the mixture was extracted with Et_2O, the organic solutions were dried over $MgSO_4$ and evaporated to dryness. The reaction residue was separated and purified by fc (AcOEt/cyclohexane 7:3) leading to the crystalline **3a** (146 mg ; 89 %)[3].

5-Methyl-1,2-diazabicyclo[5.2.0]nona-2,4-dien-9-one (3b)[3].- To a stirred solution of **(1b)**[1] (1.03 g ; 4.63 mmol) in anhydrous THF (6 ml) at -66°C under Ar, was added the MeLi/Et_2O solution (3.5 ml) ; after 30 min some additional MeLi (1.5 ml) was added. After 30 min H_2O (5 ml) was added, the reaction mixture was left to warm up to room temperature and then extracted with Et_2O. The organic phase was dried over $MgSO_4$,

evaporated to dryness and the resulting residue separated by fc (AcOEt/cyclohexane 7:3) leading to two products : starting material **1b** (316 mg ; 31 %) and **3b**[3] (84 mg ; 17 %).

Methyl [7α, 8α]-5,8-dimethyl-9-oxo-1,2-diazabicyclo [5.2.0] nona-3,5-dien-2-carboxylate (1d). - a) To a stirred solution of **1a** (536 mg ; 2.27 mmol) in anhydrous THF (2 ml) at -67°C under Ar, was added the MeLi/Et_2O solution (2.0 ml). After 30 min a solution of methyl chloroformate (0.3 ml) in THF (0.5 ml) was added and the mixture left to react for another 30 min. Some H_2O was added and the reaction medium left to warm up to room temperature. Standard work-up (see above) followed by fc (AcOEt/cyclohexane 3:7) led to the colourless crystalline compound **1d** (370 mg ; 75 %). mp 75.5-76°C (ether/hexane). Ir(KBr) : 1798, 1782, 1722. Uv(MeOH) : 273 (8300). ^{1}H-Nmr ($CDCl_3$, 80 MHz) : 6.82 (d, J=9.5, H-C(3)) ; 5.78 (m ; H-C(6)) ; 4.99 (d, J=9.5, H-C(4)) ; 4.12 (m, H-C(7)) ; 3.91 (s, OMe) ; 2.68 (qd, J=7.5, 2, H-C(8)) ; 1.92 (m, Me-C(5)) ; 1.43 (d, J=7.5, Me-C(8)). Anal. Calcd for $C_{11}H_{14}N_2O_3$ (222.24) : C 59.45, H 6.35, N 12.60 ; Found : C 59.3, H 6.6, N 12.8.

b) To a stirred solution of cyclohexylisopropylamine (427 µl, 2.6 mmol) in THF (2 ml) at 0°C under Ar was added BuLi in hexane (1.6 ml ; 1.6 M solution). After 5 min the reaction mixture was cooled to -70°C and a solution of **3a** (328 mg ; 2.0 mmol) in THF (1.5 ml) was added dropwise. After 15 min a solution of methyl chloroformate (230 µl, ca. 3.0 mmol) in THF (0.8 ml) was added. After another 5 min H_2O (ca. 3 ml) was added. Standard work-up (see above) followed by fc (AcOEt/cyclohexane 4:6) led to crystalline **1d** (226 mg ; 51 %).

[3α,6α,7α,8α]-5,8-Dimethyl-9-oxo-1,2-diazatricyclo [5.2.0.0^{3,6}]nona-4-ene (6). -
a) To a stirred solution of **5a**[2] (472 mg ; 2.0 mmol) in anhydrous THF (4 ml) at -70°C under Ar, was added the MeLi/Et_2O solution (2.3 ml ; 3.7 mmol). After 30 min H_2O was added ; the standard work-up applied (see above), followed by fc (AcOEt/cyclohexane 6:4), led to the crystalline product **6**[5] (207 mg ; 63 %)
b) To a stirred solution of **5b**[2] (163 mg ; 0.607 mmol) in anhydrous THF (3 ml) at -65°C under Ar, was added the MeLi/Et_2O solution (1 ml). After 30 min the reaction mixture was neutralized with a saturated aq. NH_4Cl solution and left to warm up to room temperature. Standard work-up (see above) followed by fc (AcOEt/cyclohexane 7:3) led to the crystalline product **6**[5] (76 mg ; 76 %).

Threo 3-[6',7'-Dihydro-5'-methyl-1'H-1',2'-diazepine-7'-yl]butan-2-one (7). - To a stirred solution of **3a**[2] (820 mg ; 5.00 mmol) in anhydrous THF (5 ml) at -70°C under Ar, was added the MeLi/Et_2O solution (4.0 ml). After 5 min H_2O was added. Standard work-up (see above) followed by fc (AcOEt/cyclohexane 8:2) led to product **7** (496 mg ; 55 %) as a pale yellow oil. Ir($CHCl_3$) : 1758, 1708, 1640. Uv(MeOH) : 302 (3800), 237 (3700). ^{1}H-Nmr ($CDCl_3$, 80 MHz) : 6.62 (d, J=5.5, H-C(3')) ; 5.64 (dm, J=5.5, H-C(4')) ; 3.49 (dt, J=7.5, 5.0, H-C(7')) ; 2.94 (qd, J=7.5, 7.0, H-C(3)) ; 2.47 (d, J=5.0, 2H, H-C(6')) ; 2.19 (s, CO-Me) ; 1.90 (m, Me-C(5')) ; 1.12 (d, J=7.5, Me). Ms : m/z = 180 (M+, 30 %), 149 (17 %), 137 (9 %), 109 (100 %).
Threo Methyl 2-[6',7'-dihydro-5'-methyl-1H'-1',2'-diazepine-7'-yl]propanoate (8). - To a stirred solution of NaOMe (2 mg of Na) in MeOH (1.5 ml) at room temperature was added a solution of **1a** (549 mg ; 2.32 mmol) in MeOH (6 ml). After 20 min some NaOMe (5 mg of Na) in MeOH (5 ml) was added. After 1 d a few drops of H_2O were added and the reaction mixture was evaporated to dryness. Fc(AcOEt/cyclohexane 5:5) of the residue led to **8** (394 mg ; 87 %) as a colourless oil. Ir($CHCl_3$) : 1730. ^{1}H-Nmr ($CDCl_3$, 80 MHz) : 6.58 (d, J=5.5, H-C(3')) ; 5.85 (s broad, NH) ; 5.60 (dm, J=5.5, H-C(4')) ; 3.70 (s, OMe) ; 3.32 (td,

J=6.0, 4.5, H-C(7')), 2.85 (q, J=7.0, H-C(2)) ; 2.50 (m, 2 H-C(6')) ; 1.88 (m, Me-C(5')) ; 1.23 (d, J=7.0, Me). Hr-ms : 196.1221 ($C_{10}H_{16}N_2O_2$, M+, calc. 196.1212).

[1α,6α,9β]-1,6,9-Trimethyl-3-ethoxycarbonyl-10-oxa-2,3-diazabicyclo[4.3.1]-deca-4,7-diene (10). - To a stirred solution of **9**[2] (472 mg, 2 mmol) in anhydrous THF (5 ml) at -70°C under Ar, was added the MeLi/Et_2O solution (1.25 ml). After ca. 10 min H_2O (2 ml) was added and the reaction mixture left to warm up to room temperature. Standard work-up (see above) followed by fc(AcOEt/cyclohexane 1:9) led to **10** (302 mg ; 1.2 mmol ; 60 %) as colourless crystals. mp 50.6°C (pentane). Ir(KBr) : 1690, 1538, 1470. Uv(MeOH) : 235 (10200), 206 (8500). ^{1}H-Nmr ($CDCl_3$, 80 MHz) : 6.70 (d, J=8.5, H-C(4)) ; 5.90 (dd, J=10.0, 2.7, H-C(7)) ; 5.40 (dd, J=10.0, 1.6, H-C(8)), 4.73 (d, J=8.5, H-C(5)) ; 4.31 (dq, J=10.7, 7.0, CH_2-Me) ; 4.13 (dq, J=10.7, 7.0, CH_2-Me) ; 3.25 (s, N-H) ; 2.62 (qdd, J=7.6, 2.7, 1.6, H-C(9)) ; 1.42 (s, Me-C(1) or Me-C(6)) ; 1.31 (s, Me-C(6) or Me-C(1)) ; 1.29 (t, J=7.0, CH_2-CH_3) ; 1.10 (d, J=7.6, Me-C(9)). ^{13}C-Nmr ($CDCl_3$, 20.1 MHz) : 155.11 (S ; CO_2Et) ; 134.94 (Dquint, J=162, C(7)) ; 130.43 (Dd, J=179.5, C(4)) ; 125.69 (Dqd, J=162, C(8)) ; 116.76 (Dquint, J=160, C(5)) ; 88.93 (Sm, C(1)) ; 73.26 (Sm, C(6)) ; 62.1 (Tq, J=148, CH_2-Me) ; 37.37 (Dm, J=130, C(9)) ; 28.85 (Qlarge, J=129 ; Me-C(6)) ; 22.57 (Qt, J=127, Me-C(1)) ; 15.46 (Qt, J=127, Me-C(9)) ; 14.23 (Qt, J=127, CH_2-CH_3). Anal. Calcd for $C_{13}H_{20}N_2O_3$ (252.31) : C 61.88, H 7.99, N 11.10 ; Found : C 62.1, H 8.2, N 11.1.

[1α,6α,9β]-6,9-Dimethyl-3-ethoxycarbonyl-10-oxa-2,3-diazabicyclo[4.3.1]deca-4,7-diene (11). - To a stirred solution of **9**[2] (708 mg, 3.00 mmol) in anhydrous Et_2O (8 ml) under Ar was added $NaBH_4$ (138 mg) and thence dropwise anhydrous MeOH (1 ml). After ca. 1 h some brine was added. Standard work-up (see above) followed by fc(AcOEt/cyclohexane 2:8) gave **11** (645 mg, 90 %) as colourless crystals. mp 66°C (hexane). Ir(KBr) : 1730, 1642, 1520, 1478. Uv(MeOH) : 235 (10500), 205 (8800). ^{1}H-Nmr ($CDCl_3$, 80 MHz) : 6.69 (d, J=8.3, H-C(4)) ; 5.90 (dd, J=10.1, 2.7, H-C(7)) ; 5.44 (dm, J=10.1, H-C(8)) ; 4.98 (s ; N-H) ; 4.96 (d broad, J=5, H-C(1)) ; 4.78 (d, J=8.3, H-C(5)) ; 4.22 (qd, J=7.2, CH_2-Me) ; 4.23 (qd, J=7.2, CH_2-Me) ; 2.82 (m, H-C(9)) ; 1.34 (s, Me-C(6)) ; 1.30 (t, J=7.2, CH_2-CH_3) ; 1.07 (d, J=7.8, Me-C(9)). ^{13}C-Nmr ($CDCl_3$, 20.1 MHz) : 154.30 (Sm, CO_2Et) ; 134.48 (Dquint, J=160, C(7)) ; 130.79 (Dd, J=180, C(4)) ; 124.83 (Dm, J=160, C(8)) ; 117.58 (Dquint, J=160, C(5)) ; 85.43 (Dsext, J=168, C(1)) ; 72.63 (Sm, C(6)) ; 62.11 (Tq, J=148, CH_2-CH_3) ; 31.77 (Dsept, J=131.5, C(9)) ; 28.58 (Q, J=129, Me-C(6)) ; 15.01 (Qdd, J=127, Me-C(9)) ; 14.28 (Qt, J=127, CH_2-CH_3). Anal. Calcd for $C_{12}H_{18}N_2O_3$ (238.28) : C 60.48, H 7.61, N 11.76 ; Found : C 60.3, H 7.8, N 11.8.

[7α,8α]-5,8-Dimethyl-1,2-diazabicyclo[5.2.0]non-2-ene-9-one (12). - A stirred solution of **3a** (644 mg ; 3.92 mmol) in AcOEt (6 ml), containing 5 % Pd/C (12 mg), was put under H_2 (1 atm.) at room temperature for 3.5 h. After filtration the solution was evaporated to dryness, and the residue was purified by fc (AcOEt/cyclohexane 6:4) leading to **12** (633 mg ; 97 %) as colourless crystals. mp 45.5-46°C (Et_2O/hexane). Ir(KBr) : 1760-1745 (large), 1618, 1342. Uv(MeOH) : 255 (5300), 210 (7900). ^{1}H-Nmr $CDCl_3$, 200 MHz) : 7.06 (dd, J=6.2, 2.6, H-C(3)) ; 3.25 (ddd, J=11.8, 3.2, 2.7, H-C(7)) ; 2.90 (qd, J=7.3, 3.2, H-C(8)) ; 2.57 (ddt, J=15.6, 6.3, 2.0, H-C(4α)) ; 2.14 (dddd, J=13.1, 2.7, 2.7, 2.0 H-C(6α)) ; 1.96 (ddd, J=15.6, 10.8, 2.6, H-C(4β)) ; 1.65 (m, H-C(5)) ; 1.34 (d, J=7.3, CH_3-C(8)) ; 1.31 (dt, J=13.1, 11.6, H-C(6β)) ; 1.10 (d, J=6.6, CH_3-C(5)). Anal. Calcd for $C_9H_{14}N_2O$ (166.22) : C 65.03, H 8.49, N 16.85 ; Found : C 65.1, H 8.8, N 16.8.

[7α,8α]-5,8-Dimethyl-1,2-diazabicyclo[5.2.0]nonane-9-one (13). -
a) A stirred solution of **12** (135 mg, 0.812 mmol) in EtOH (3 ml) containing PtO_2 (4 mg) was put under H_2 (1 atm.) for 3 h. After filtration the solution was evaporated to dryness and the residue purified by fc (AcOEt) leading to **13** (117 mg, 86 %) as a colourless oil. Ir ($CHCl_3$) : 1745. ^{1}H-Nmr ($CDCl_3$, 80 MHz) : 4.04 (s broad, N-H) ; 3.43 (ddd, J=10.5, 2.5, 1.8, H-C(7)) ; 3.11 (ddd, J=14.0, 7.0, 4.0, H-C(3)) ; 3.00 (ddd, J=14.0, 7.0, 3.1, H-C(3)) ; 2.57 (qd, J=7.2, 1.8, H-C(8)) ; 2.23-1.25 (m, 2H-C(6), 2H-C(4), H-C(5)) ; 1.28 (d, J=7.2, CH_3-C(8)) ; 1.03 (d, J=6.O, CH_3-C(5)). ^{13}C-Nmr ($CDCl_3$; 20.1 MHz) : 166.23 (S, C(9)) ; 63.43 (Dm, J=148, C(7)) ; 46.57 (Dm, J=140, C(8)) ; 46.07 (T, J=136, C(3)) ; 40.70 (T, J=126 C(6)) ; 38.65 (T, J=126, C(4)) ; 32.32 (Dm, J=127, C(5)) ; 22.25 (Qm, J=125, CH_3-C(5)) ; 11.82 (Qt, J=128, CH_3-C(8)). Hr-ms : 168.1263 ($C_9H_{16}N_2O$, M+, Calcd 168.12626.)
b) A stirred solution of **3a** (500 mg, 3.05 mmol) in EtOH (8 ml) containing PtO_2 (25 mg) was put under H_2 (1 atm.) for 5 h. After filtration the solution was evaporated to dryness and the residue purified by fc as above leading to **13** (385 mg, 75 %).

Tetrabutylammonium[5β,7α,8α]-5,8-Dimethyl-9-oxo-1,2-diazabicyclo[5.2.0]nonane-2-sulfonate (14). - To a stirred solution of **13** (303 mg ; 1.80 mmol) in anhydrous CH_2Cl_2 (7 ml) at 0°C under Ar was added a 1M solution of the DMF/SO_3 complex in DMF (3.8 ml)[8]. After 20 min an aqueous 0.5 M solution of KH_2PO_4 (5 ml) was added . The reaction medium was washed with CH_2Cl_2, n-Bu_4NHSO_4 (601 mg) was added, and the reaction mixture was extracted with CH_2Cl_2. The organic solution was evaporated to dryness, DMF being eliminated i.vac. (10^{-2} Torr.), whereby **14** (685 mg, 78 %) was formed as a colourless oil. Ir($CHCl_3$) : 1745. ^{1}H-Nmr ($CDCl_3$, 400 MHz) : 4.00 (ddd, J=10.7, 4.2, 1.6, H-C(7)) ; 3.61 (ddd, J=12.9, 10.7, 3.4, H-C(3)) ; 3.40 (ddd, J=12.9, 5.5, 3.7, H-C(4)) ; 3.31 (m, CH_2N^+) ; 2.42 (qd, J=7.2, 1.6, H-C(8)) ; 2.07 (m, H-C(5)) ; 1.98 (ddd, J=13.1, 4.0, 2.5, H-C(6α)) ; 1.85 (dm, J=15.0, H-C(4)) ; 1.65 (m, $CH_2CH_2N^+$) ; 1.46 (m, H-C(4)) ; 1.46 (sext, J=7.4, $CH_2CH_2CH_2N^+$) ; 1.29 (d, J=7.2, Me-C(8) ; 1.16 (dt, J=13.1, 11.1, H-C(6β)) ; 1.00 (t, J=7.3, $CH_3CH_2CH_2CH_2N^+$)) ; 0.96 (d, J=6.9, Me-C(5)). ^{13}C-Nmr ($CDCl_3$, 20.1 MHz) : 169.55 (Sm, C(9)) ; 61.79 (Dm, J=148, C(7)) ; 57.82 (Tm, J=145, CH_2N^+) ; 49.35 (Tm, J=141, C(3)) ; 48.17 (Dm, J=141, C(8)) ; 41.70 (Tm, J=130, C(6)) ; 35.00 (Tm, J=127, C(4)) ; 32.04 (Dm, J=127, C(5)) ; 23.25 (Tm, J=130, $CH_2CH_2N^+$) ; 23.03 (Qm, J=126, Me-C(5)) ; 18.93 (Tm, J=130, $CH_2CH_2CH_2N^+$) ; 12.87 (Qm, J=128, $CH_3CH_2CH_2CH_2N^+$) ; 11.73 (Qm, J=130, Me-C(8)). MS-FABN : m/z = 247 (100 %) corresponding to the anion R-SO_3^-.

Potassium [5β,7α,8α]-5,8-Dimethyl-9-oxo-1,2-diazabicyclo[5.2.0]nonane-2-sulfonate (15). - A solution of salt **14** (3.59 g, 7.33 mmol) in MeOH/H_2O (1:2 ; 20 ml) was percolated over a K^+ doped DOWEX 50WX8 resin (1.7 meq/ml ; 33 ml), the elution being performed with H_2O. Part of H_2O was evaporated, the remaining solution was purified by percolation over an Amberlite XAD-2 column, and evaporated to dryness by lyophilisation. The residue (966 mg, 47 %) was recrystallized from MeOH. mp over 200°C dec.. Ir(KBr) : 1750, 1250, 1200, 1050. ^{1}H-Nmr ($CDCl_3$, DMSO-d_6, 400 MHz) : 3.64 (dt, J=11.3, 2.0, H-C(7)) ; 3.27 (ddd, J=14.1, 7.7, 2.0, H-C(3)) ; 3.10 (ddd, J=14.1, 9.5, 1.7, H-C(3)) ; 2.66 (qd, J=7.1, 1.7, H-C(8)) ; 2.15 (d large, J=13.5, H-C(6)) ; 1.96 (m, H-C(4)) ; 1.89 (m, H-C(5)) ; 1.57 (dtd, J=15.1, 9.2, 2.0, H-C(4)) ; 1.40 (dt, J=13.6, 11.1, H-C(6)) ; 1.31 (d, J=7.2, Me-C(8)) ; 1.07 (d, J=6.7, Me-C(5)). Anal. Calcd. for $C_9H_{15}N_2O_4SK$ (286.39) : C 37.74, H 5.28, N 9.78, S 11.20, K 13.65 : Found : C 37.5, H 5.4, N 9.7, S 11.7, K 13.0.

Benzyl [5β,7α,8α]-5,8-Dimethyl-9-oxo-1,2-diazabicyclo[5.2.0]nonane-2-acetate (16). - To a stirred solution of **13** (561 mg, 3.33 mmol) in anhydrous CH_2Cl_2 (5 ml) under Ar were added NEt_3 (1.5 ml), a small amount of DMAP and benzyl bromoacetate (0.75 ml). After 2 d at room temperature the reaction mixture was evaporated to dryness and purified by fc(AcOEt/cyclohexane 6:4) to give **16** (632 mg, 60 %) as a colourless oil. Ir($CHCl_3$) : 1733. ^{1}H-Nmr ($CDCl_3$, 80 MHz) : 7.33 (s, Ph) ; 5.13 (s, CH_2-Ph) ; 4.27 (d, J=17, CH_2-N) ; 3.70 (dm, J=11, H-C(7)) ; 3.55 (d, J=17, CH_2-N) ; 3.12 (m, 2H-C(3)) ; 2.41 (qd, J=7, 1.2, H-C(8)) ; 2.24-1.1 (m, 2H-C(4), 2H-C(6), H-C(5)) ; 1.16 (d, J=7, Me-C(8)) ; 0.98 (d, J=6, Me-C(5)). ^{13}C-Nmr ($CDCl_3$, 20.1 MHz) : 168.78 (S, CO_2Bn) ; 164.91 (S, C(9)) ; 134.98 (Sm, C_s-arom) ; 128.01 (D, J=162, C_o-arom) ; 127.83 (D, J=162, C_m-arom) ; 127.83 (D, J=162, C_p-arom) ; 65.75 (T, J=147, OCH_2Ph) ; 62.47 (D, J=152, C(7)) ; 54.50 (T, J=141, CH_2-N) ; 52.81 (T, J=136, C(3)) ; 47.12 (D, J=142, C(8)) ; 42.98 (T, J=127, C(6)) ; 35.19 (T, J=127, C(4)) ; 34.64 (D, J=126, C(5)) ; 22.57 (Qm, J=127, CH_3-C(5)) ; 12.18 (Qt, J=128, CH_3-C(8)). Hr-ms : 316.1779 ($C_{18}H_{24}N_2O_3$, Calcd 316.1787).

[5β,7α,8α]-5,8-Dimethyl-9-oxo-1,2-diazabicyclo[5.2.0]nonane-2-acetic acid (17). - To a stirred solution of **16** (218 mg, 0.69 mmol) in AcOEt (4ml) was added 5 % Pd/C (3 mg) under H_2 (1 atm.) at room temperature for 6 h. After filtration the solvent was evaporated and the residue was purified by fc(AcOEt) leading to crystalline **17** (155 mg ; 99 %). mp 121-122°C (AcOEt/hexane). Ir(KBr) : 1765 (large), 1705 (large). ^{1}H-Nmr ($CDCl_3$, 400 MHz) : 3.91 (d, J=17.2, CH_2-N) ; 3.71 (ddd, J=11.2, 3.0, 1.5, H-C(7)) ; 3.64 (d, J=17.2, CH_2-N) ; 3.20 (ddd, J=13.2, 8.2, 2.4, H-C(3)) ; 3.10 (ddd, J=13.2, 8.2, 2.4, H-C(3)) ; 2.55 (qd, J=7.2, 1.5, H-C(8)) ; 2.07 (dtd, J=13.7, 3.0, 1.3, H-C(6α)) ; 1.90 (m, H-C(4)) ; 1.81 (m, H-C(5)) ; 1.50 (dddd, J=15.0, 9.8, 8.2, 2.5, H-C(4)) ; 1.31 (dt, J=13.7, 11.2, H-C(6β)) ; 1.26 (d, J=7.2, CH_3-C(8)) ; 1.02 (d, J=6.8, CH_3-C(5)). ^{13}C-Nmr ($CDCl_3$, 20.1 MHz) : 171.38 (St, CO_2H) ; 166.41 (S sext., C(9)) ; 63.52 (Dm, J=154, C(7)) ; 54.91 (Ts, J=141, CH_2-N) ; 53.22 (Tm, J=136, C(3)) ; 47.26 (D, J=142, C(8)) ; 43.02 (Tm, J=127, C(6)) ; 35.37 (Tm, J=127, C(4)) ; 34.82 (Dm, J=127, C(5)) ; 22.93 (Qm, J=126, CH_3-C(5)) ; 12.50 (Qs, J=129, CH_3-C(8)). Anal. Calcd. for $C_{11}H_{18}N_2O_3$ (226.27) : C 58.39, H 8.02, N 12.38 ; Found : C 58.4, H 8.1, N 12.5.

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