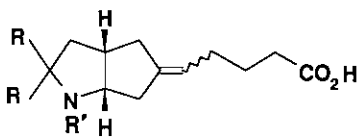
CYCLIZATION OF ALLYL SILANES - A NOVEL APPROACH TO 2-AZABICYCLO[3.3.0]OCTANES

Jean-Claude Gramain and Roland Remuson*
Laboratoire de Chimie des Substances Naturelles, U.A. CNRS 485,
Université Blaise Pascal (Clermont II) 63177 Aubière Cedex, France

Abstract - The methodology which consists in the electrophilic substitution of α-acyl and N-acyl iminium ions on allyl silanes has been used to accede to 2-azabicyclo[3.3.0] octane derivatives and realizes a formal total synthesis of azacarboprostacyclin analogs.

Since the discovery of prostacyclins PGI_2[1], a number of prostacyclin analogs have been reported such as carboprostacyclins and various aza analogs[2]. The preparation of this class of compounds and its congeners is of considerable interest due to their potentially usefulness in the treatment of thrombotic disease, hypertension, inhibition of platelet aggregation and all forms of vascular disease[3].
The common structure of azacarboprostacyclins consists in a functionalized 2-azabicyclo[3.3.0]octane framework. (cf. Scheme 1).

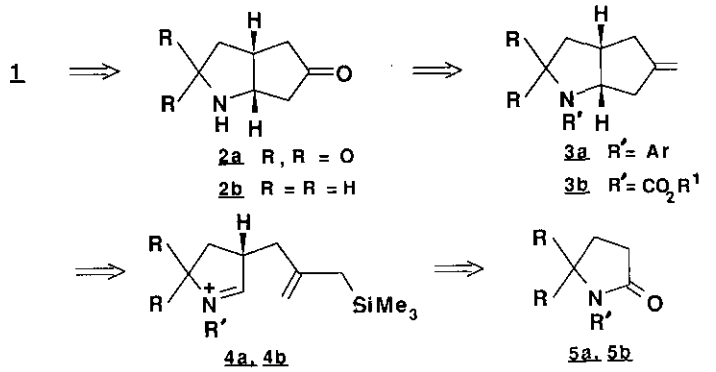
Scheme 1



1 R, R = O
R = R = H
R'=-CH_2-CH_2-CH(OH)-$(CH_2)_4$-CH_3

Several methods were used to synthesize these azabicyclic compounds[2] ; in our approach[7] the second ring is created by the intramolecular electrophilic substitution of an α-acyl or N-carboxyiminium ion on an allylsilane derivative (cf. Scheme 2).
Allylsilanes constitute a class of nucleophiles which were largely used in organic synthetic field[4]. These compounds exhibit an excellent reactivity towards electrophiles such as carbonyl derivatives[5] and more recently α-acyl iminium ions[6].
In recent papers, we related intramolecular reactions of cyclic α-acyl iminium ions with allylic silanes ; this strategy was employed with success to accede to indolizidine and quinolizidine bicyclic systems[7] and to realize, in four steps, a formal total synthesis of (±)-mesembrine in a stereospecific manner[8].
We wish to report here a new method for the preparation of 2-azabicyclo[3.3.0]octanes based on the electrophilic substitution of α-acyl iminium ions on an allylsilane derivative. Moreover, the formal total synthesis of 2-azacarboprostacyclin analogs was realized by the intramolecular cyclization of an allylsilane on a N-carboxy iminium ion.

Scheme 2.



Retrosynthetically, 1 might be derived from 2 by alkylation at the nitrogen position then a Wittig reaction. Intermediates 2a and 2b should easily be obtained by ozonolysis then deprotection of 3a and 3b ; which in turn might be derived from the cyclization of the iminium ions 4a and 4b which resulted from alkylation in 3-position with appropriate allylsilane moiety of corresponding imides 5a and 5b (cf. Scheme 2).

RESULTS AND DISCUSSION

The key step of this strategy consists in a nucleophilic substitution of the allylsilane moiety either on the α-acyl iminium ion 4a (R, R = O ; R' = Ar) or on the N-carboxy iminium ion 4b (R = R = H ; R' = CO_2R^1).

a) Cyclization on α-acyl iminium ion :

The starting materials required for our study are 3-substituted imides 6a[15], 6b[16], 6c and 6d (cf. Scheme 3). Direct alkylation in the α-position of carbonyl groups of imide is indeed not easy[10] because of the low acidity of the protons in this position. The presence of aryl or phenylsulfonyl[a] substituents might facilitate the abstraction of geminated hydrogens and allow the introduction of the allylsilane side chain.

The allylic silylated derivative was branched, in a first step, by alkylation of the corresponding imide. Direct alkylation of N-methyl-3-phenylsuccinimide 6a using NaH/ DMSO as base, then condensation of TMS-CH_2 C(= CH_2) CH_2 I in DME, led to imide 7a in 80 % yield (Scheme 3). Structure of 7a was elucidated by classic spectroscopic methods. Ir spectrum showed absorption bands at 1700 and 1780 cm^{-1} due to the carbonyl groups of a five membered ring imide. ^{1}H-Nmr spectrum of 7a exhibited a broad singlet around 5 ppm, attributed to the two methylenic protons and a singlet at 0.0 ppm corresponding to the protons of the trimethylsilyl group.

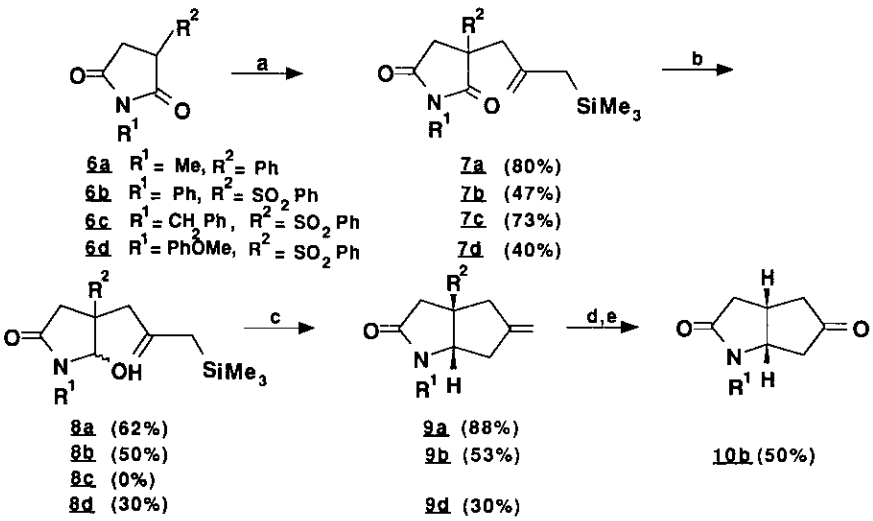
In the same way, alkylation of imides 6b, 6c and 6d led respectively to 7b, 7c and 7d in a range of 40-70 % yield.

Reduction of 7a using sodium borohydride in methanol at 0°C led to the hydroxylactam 8a as a mixture of two diastereoisomers in 62 % yield. Ir spectra showed absorption bands at 1700 cm^{-1} and 3450 cm^{-1} respectively due to the carbonyl group of a five membered ring lactam and the hydroxyl group. The structure of 8a was, moreover, confirmed by its ^{1}H-nmr spectrum data ; in particular we noted the appearance of a multiplet around 4 ppm attributed to the hydrogen α to the nitrogen atom of a lactam.

[a] Phenylsulfonyl groups might easily be removed at the end of the sequence of reactions to liberate azabicyclic compounds having no substituents at the ring junction. (cf. azacarboprostacyclin structure, Scheme 1).

The reduction of 3-substituted imides is regioselective as demonstrated by Speckamp[9] ; the hydride ion approaches *via* the less hindered CO (C_5-position) and adds to the C atom of the more hindered one (C_2-position). In our case, we obtained effectively as the major product, the hydroxy lactam coming from a reduction in C_2-position according to Speckamp's results.

Scheme 3



6a R^1 = Me, R^2 = Ph
6b R^1 = Ph, R^2 = SO_2Ph
6c R^1 = CH_2Ph, R^2 = SO_2Ph
6d R^1 = PhOMe, R^2 = SO_2Ph

7a (80%)
7b (47%)
7c (73%)
7d (40%)

8a (62%)
8b (50%)
8c (0%)
8d (30%)

9a (88%)
9b (53%)
9d (30%)

10b (50%)

a) NaH/DMSO, DME then $TMSCH_2C(=CH_2)CH_2I$; b) $NaBH_4$, MeOH, 0°C ; c) CF_3CO_2H, CH_2Cl_2, 0°C ; d) Na(Hg), Na_2HPO_4, MeOH, 0°C ; e) O_3, CH_2Cl_2-MeOH(1-1), Me_2S.

Treatment, in similar conditions, of the imide 7c did not lead to the expected hydroxy lactam 8c ; the only isolated products came from debenzylation and desulfonylation of the starting material. These surprising results (sulfones and N-benzyl lactams derivatives are recognized to be stable in presence of sodium borohydride) have not received a satisfying explanation by ourselves.

Treatment of hydroxylactam 8a with trifluoroacetic acid in methylene chloride at 0°C led to the expected bicyclic compound 9a in 88 % yield ; this product results from an intramolecular nucleophilic substitution of the allylsilane moiety on the α-acyl iminium ion which was generated in acidic medium. Structure of 9a was elucidated by spectroscopic methods. Ir spectra showed an absorption band at 1700 cm^{-1} characteristic of the carbonyl group of a five membered ring lactam : ^{1}H-Nmr spectrum showed a broad singlet at 5.0 ppm attributed to the methylenic protons and a doublet of doublet at 4.2 ppm attributed to the hydrogen α to the nitrogen of the lactam.

Desulfonylation of 9b (Na(Hg), Na_2HPO_4), then ozonolysis led to 10b in 50 % global yield.

Access to 2-azabicyclo[3.3.0]octanes was realized with a correct overall yield from readily available imides type 6. This methodology presents however some limitations :

- activation in the 3-position of the starting imide is necessary because of the low acidity of the corresponding protons.
- protection of nitrogen atom is necessary to avoid N-alkylation ; moreover protective groups such as benzyl or paramethoxyphenyl groups do not give good results in the sodium borohydride reduction step.

b) **Cyclization on N-carboxy iminium ions :**

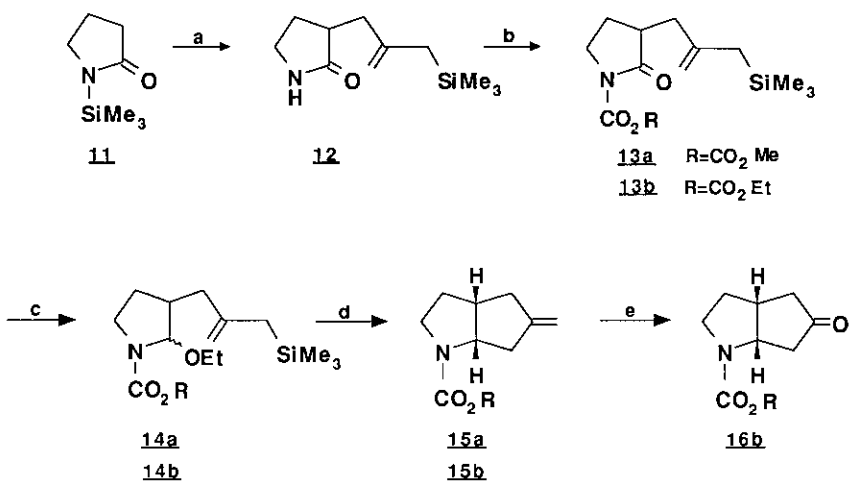
Access to 2-azacarboprostacyclin analogs using the previous route does not seem to be easy because of the difficulty to remove protective groups at the end of the synthese and the poor yields of the reduction step (*vide supra*). So, an another route based on the cyclization of N-carboxy iminium ion type 15 was tested. In this sequence, allylsilane side chain was introduced in a first step by alkylation of trimethylsilyl lactam 11 ; the imide function being created in a second step by N-carboxylation of lactam 12.

The precursor of the iminium ion was ethoxy lactam 14 (cf. Scheme 4) which derivated from imide 13. This way led to product 16b which is a key intermediate in the total synthesis of azacarboprostacyclin analogs[14].

Alkylation with 1-iodo-2-(trimethylsilylmethyl)propene at -78°C in THF of N-trimethylsilyl-2-pyrrolidone[11] using LDA as base led to lactam 12 in 67 % yield. Structure of 12 was elucidated by classic spectroscopic methods. Ir spectrum showed absorption band at 1700 which is characteristic of a carbonyl of five membered ring secondary lactam. ^{1}H-Nmr spectrum of 12 exhibited a singlet at 0.0 ppm due to the trimethylsilyl group and a broad singlet, exchanged with D_2O, at 7.8 ppm due to the proton on the nitrogen atom.

The N-carboxylation of 12 using LDA as base and Mander's reagent[12] ($CNCO_2Me$) as alkylating reagent led to N-carboxy lactams 13a and 13b in a 70-90 % range yield. Their ir spectra showed absorption bands around 1710 and 1790 cm^{-1} characteristic of the vibrations of carbonyl groups of N-carboxy-2-pyrrolidone. Their structure was morever confirmed by the ^{1}H-nmr spectra.

Scheme 4.



a) LDA, THF, -78°C, 1 h then $TMSCH_2C(=CH_2)CH_2I$; b) LDA, THF, 1 h then $CNCO_2R$; c) $NaBH_4$, H_2SO_4 then excess H_2SO_4 ; d) CF_3CO_2H, CH_2Cl_2, 0°C, 4 h ; e) O_3, CH_2Cl_2-MeOH (1-1), then Me_2S.

Reduction of 13a and 13b using Speckamp's method[13] ($NaBH_4$, little H_2SO_4, EtOH, -20°C then excess H_2SO_4, -20°C -> 20°C) gave ethoxyurethane[b] 14a and 14b in 60-80 % range yield as a mixture of two diastereoisomers. Ir spectra showed a band at 1700 cm^{-1} due to the vibration of the carbonyl group of urethane. ^{1}H-Nmr exhibited a multiplet at 5.0 ppm due to the hydrogen α to the nitrogen of urethane.

[b] Also many attempts of cyclization were realized on α-hydroxyurethanes using various reagents (Lewis acid, trifuoroacetic acid, ...), no positive results were obtained.

Morever, ^{1}H-nmr spectra of substrates 12, 13 and 14 showed singlets at 1.5 ppm typical of the methylenic protons α to trimethylsilyl group and spectra run without TMS showed a singlet around 0.0 ppm charactristic of the protons of trimethylsilyl group. Then, cyclization of the ethoxy carbamates 14a and 14b was envisaged ; treatment of compounds 14 at 0°C with fluoroacetic acid in methylene chloride led to bicyclic compounds 15a and 15b. Ir spectra showed a band at 1700 cm^{-1} typical of carbonyl group of a five membered ring urethane ; ^{1}H-nmr showed a multiplet at 3.5 ppm due to the proton at the ring junction in the α position to the nitrogen atom of urethane and a doublet at 4.9-4.7 ppm typical of an exo methylen group.
Ozonolysis (O_3 then Me_2S) of the bicyclic compound 15b gave the expected product 16b. Ir spectrum showed bands at 1700 and 1750 cm^{-1} respectively due to the vibrations of the carbonyl groups of a five membered ring lactam and a cyclopentanone; ^{1}H-nmr exhibited a quadruplet at 4.1 ppm and a triplet at 1.2 ppm due to the ethyl group. These spectroscopic data are in agreement with literature data[14].
16b constitutes a known intermediate in the total synthesis of azacarboprostacyclin analog type 1 (R = H).
The ultimate steps in the synthesis of 1 consist in :
1- Deprotection of the nitrogen atom then fixation of the appropriate side chain in this position.
2- Fixation of the side chain in 7-position using a Wittig reaction.
These two last steps are described in good yields in literature[14].
In conclusion, a novel formal total synthesis of 2-azacarboprostacyclin analogs was realized in correct overall yield from the readily available starting imide type 12.

EXPERIMENTAL

Melting points were determined using a Reichert hot stage apparatus and are uncorrected. Proton nuclear magnetic resonance spectra were recorded on Jeol C 60 H and Bruker MSL 300 spectrometers. Carbon 13 nuclear magnetic resonance spectra were run on Jeol FX 60 and Bruker MSL 300 spectrometers. Chemical shifts are recorded as δ-values (parts per million) relative to tetramethylsilane as the internal reference standard. A Perkin-Elmer 377 instrument was used to determine ir spectra. Mass spectra were recorded on a Varian CH 5 spectrometer. Merck Kieselgel 60 PF_{254} coated on glass plates was used for analytical chromatography. Products are purified by flash chromatography using silica gel Amicon (35-70 mesh).

1-Methyl-3-phenylsuccinimide (6a) and 1-phenyl-3-phenylsulfonylsuccinimide (6b) were prepared according to literature procedures[15, 16].

1-Aryl-3-phenylsulfonylsuccinimides (6c) and (6d) were prepared according to literature proce-dure[16].

1-Benzyl-3-phenylsulfonylsuccinimide (6c)
60 % yield, mp 117°C (ether) ; ir (cm^{-1}) 1720 and 1780 ; ^{1}H-nmr ($CDCl_3$) d 7.6 (5H, m, arom.), 7.2 (5H, m, arom.), 4.6 (2H, s, CH_2Ph), 4.3 (1H, dd, J_1 = 9 Hz, J_2 = 4.5 Hz), 3.2 (2H, m). Anal. calcd for $C_{17}H_{15}NO_4S$: C , 61.99 ; H, 4.59 ; N, 4.25. Found : C, 62.01 ; H, 4.61 ; N, 4.28.

1-p-Methoxyphenyl-3-phenylsulfonylsuccinimide (6d)
61 % yield, mp 193-194°C (ether), Lit.[16] mp 194-196°C ; ir (cm^{-1}) 1720 and 1790 ; ^{1}H-nmr ($CDCl_3$) d 7.9 (5H, m, arom.), 7.0 (4H, s, arom.), 4.5 (1H, dd), 3.9 (3H, s, OCH_3), 3.2 (2H, m).

1-Methyl-3-phenyl-3-[2-(trimethylsilylmethyl)allyl]succinimide (7a)

To a suspension of NaH (0.2 g, 7.8 mmol) in DME (7 ml) stirred at 0°C under nitrogen was added a solution of imide 6a (0.6 g, 3.2 mmol) in DME (7 ml). To this solution was added quickly DMSO (8 ml) and the resulting solution was stirred for 15 min at 0°C then a solution of 1-iodo-2-(trimethyl-silylmethyl)propene (0.3 g, 1.2 mmol) in DME (8 ml) was added dropwise for 5 min. Then, the solution was allowed to warm at 60°C and stirred at this temperature for 1 h. The mixture was poured into water (70 ml) and extracted with ether (3 x 20 ml), washed with brine (30 ml) and dried ($MgSO_4$). Purification by flash chromatography (Hexane-AcOEt 7:3) afforded 7a as an oil (0.8 g ; 80 %) ; ir (cm^{-1}) 1700 and 1780 ; ^{1}H-nmr ($CDCl_3$) δ 7.5 (5H, m, arom.), 4.8 (2H, d), 3.2 (2H, m), 3.0 (3H, s, N-CH_3), 2.9 (2H, m), 1.4 (2H, s, CH_2-$SiMe_3$), 0.0 (9H, s, $SiMe_3$) ; ^{13}C-nmr ($CDCl_3$) δ 181.5, 176.9, 147.5, 141.7, 130.3, 129.0, 127.5, 108.9, 53.0, 42.9, 34.3, 28.3, 26.4, 0.0. Exact mass calcd for $C_{18}H_{25}NO_2Si$ 315.1648 ; found 315.1647.

1-Phenyl-3-phenylsulfonyl-3-[2-(trimethylsilylmethyl)allyl]succinimide (7b)

To a suspension of NaH (0.05 g, 2 mmol) in anhydrous DME (2 ml) stirred at 0°C under nitrogen was added a solution of imide 6b (0.5 g, 1.6 mmol) in DME (20 ml). To this solution was quickly added DMSO (4 ml) and the resulting mixture was stirred at 0°C for 15 min, then added very slowly to a solution of 1-iodo-2(trimethylsilylmethyl)propene (0.6 g, 2.4 mmol) in DME (1 ml). The resulting solution was stirred at room temperature for 4 h. The mixture was poured into water (20 ml) and extracted with ether (3 x 5 ml), the organic layers were washed with brine and dried ($MgSO_4$). Purification by flash chromatography (Hexane-AcOEt 8:2) afforded 7b as an oil (0.3 g, 47 %) ; ir (cm^{-1}) 1720 and 1790 ; ^{1}H-nmr ($CDCl_3$) δ 7-8 (10H, m, arom.), 4.8 (2H, d, J = 6 Hz), 3.6 (2H, AB spectra, J_{AB} = 18 Hz), 2.8 (2H, AB spectra, J_{AB} = 13.5 Hz), 1.5 (2H, s), 0.0 (9H, s, $SiMe_3$). Ms (m/z) 441 (10), 426 (20), 300 (80), 226 (50), 147 (100), 73 (80). Exact mass calcd for $C_{23}H_{27}NO_4SSi$ 441.1423 ; found 441.1424.

1-Benzyl-3-phenylsulfonyl-3-[2-(trimethylsilylmethyl)allyl]succinimide (7c)

According to a similar procedure we got 7c as an oil in a 73 % yield after purification by flash chromatography (Hexane-AcOEt 8:2) ; ir (cm^{-1}) 1710 and 1780 ; ^{1}H-nmr ($CDCl_3$) δ7.8 (5H, m, arom.), 7.5 (5H, s, arom.), 4.6-4.8 (4H, m, CH_2Ph and CH_2CON), 3.45 (AB spectra, J_{AB} = 15 Hz), 2.8 (AB spectra, J_{AB} = 13 Hz), 1.2 (2H, m, CH_2-$SiMe_3$), 0.0 (9H, s, $SiMe_3$) ; ^{13}C-nmr ($CDCl_3$) δ 174.1, 173.6, 141.1, 136.05, 135.9, 135.2, 132.1, 130.2, 130.05, 129.85, 129.3, 118.8, 115.95, 72.4, 44.3, 39.3, 34.1, 28.4, 0.0. Exact mass calcd for $C_{24}H_{29}NO_4SSi$ 455.1579 ; found 455.1570.

1-(p-Methoxyphenyl)-3-phenylsulfonyl-3-[2-(trimethylsilylmethyl)allyl]succinimide (7d)

According to the previous procedure we got 7d as oil in a 40 % yield after purification by flash chromatography (Hexane-AcOEt 7:3) ; ir (cm^{-1}) 1720 and 1790; ^{1}H-nmr ($CDCl_3$) δ 7.7-8.2 (5H, m, arom.), 7.1 (4H, m, arom.), 4.8 (2H, m), 3.9 (3H, s, OCH_3), 3.5 (AB spectra, J_{AB} = 8 Hz), 2.9 (AB spectra, J_{AB} = 12 Hz), 1.5 (2H, s, CH_2SiMe_3), 0.0 (9H, s, $SiMe_3$) ; ^{13}C-nmr ($CDCl_3$) δ174.1, 174.0, 161.6, 141.55, 136.55, 135.6, 132.5, 130.6, 129.1, 128.9, 116.1, 72.9, 57.0, 39.5, 34.3, 29.3, 0.0. Exact mass calcd for $C_{24}H_{29}NO_5SSi$ 471.1555 ; found 471.1550.

1-Methyl-4-phenyl-4-[2-(trimethylsilylmethyl)allyl]-5-hydroxy-2-pyrrolidone (8a)

To a solution of imide 7a (0.8 g, 2.5 mmol) and sodium borohydride (0.6 g, 17 mmol) in absolute ethanol (46 ml) was added 2N HCl (five drops each 15 min). The resulting mixture was stirred at 0°C for 4 h, then

poured into ice-water and extracted with $CHCl_3$ (3 x 20 ml), washed with brine and dried ($MgSO_4$) to afford 8a as an oil which was purified by flash chromatography (Hexane-AcOEt 6:4) (0.5 g, 62 %) ; ir (cm^{-1}) 1700 and 3450 ; ^{1}H-nmr ($CDCl_3$) δ 7.5 (5H, s, arom.), 5.3 (1H, broad s, CH - N), 4.6 (2H, d), 3.0 (3H, s, CH_3), 2.9 (1H, broad s, OH, exch. with D_2O), 2.8 (2H, broad s), 2.5 (2H, broad s), 1.5 (2H, s, $C\underline{H}_2SiMe_3$), 0.0 (9H, s, $SiMe_3$) ; ^{13}C-nmr ($CDCl_3$) δ 188.4, 140.9, 131.1, 129.5, 127.8, 108.5, 53.5, 43.0, 39.4, 34.4, 28.9, 26.9, 0.0. Exact mass calcd for $C_{18}H_{27}NO_2Si$ 317.1804 ; found 317.1802.

1-Phenyl-4-phenylsulfonyl-4-[2-(trimethylsilylmethyl)allyl]-5-hydroxy-2-pyrrolidone (8b)

The previous procedure was used on the imide 7b to afford 8b as an oil in a 50 % yield after purification by flash chromatography (Hexane - AcOEt (6-4)), mp 134°C (ether) ; ir (cm^{-1}) 1710 and 3450 ; ^{1}H-nmr ($CDCl_3$) δ 7.4-8.1 (10H, m, arom.), 5.5 (1H, broad s), 4.9 (2H, d), 3.0 (1H, broad s, OH, exch. with D_2O), 2.9 (2H, broad s), 2.6 (2H, s), 1.5 (s, 2H, $C\underline{H}_2$-$SiMe_3$), 0.0 (9H, s, $SiMe_3$). Anal. calcd for $C_{23}H_{29}NO_4SSi$: C, 62.28 ; H, 6.59 ; N, 3.16. Found : C, 62.31; H, 6.62; N, 3.14.

Treatment of imide 7c with $NaBH_4$ in MeOH

To a solution of imide 7c (1.6 g, 3.5 mmol) in absolute methanol (85 ml) was added $NaBH_4$ (0.8 g, 21 mmol) ; the resulting mixture was stirred at 0°C for 5 h, then poured into ice-water, extracted with $CHCl_3$ (3 x 20 ml) and dried ($MgSO_4$). Purification by flash chromatography (Hexane-AcOEt (6-4)) afforded 1-benzyl-2,5-dioxo-3-[2-(trimethylsilylmethyl)allyl]pyrroline (0.5 g, 1.6 mmol) ; ir (cm^{-1}) 1710 and 1770 ; ^{1}H-nmr ($CDCl_3$) δ 7.3 (5H, s, arom.), 6.4 (1H, m), 4.6 (4H, m), 3.1 (2H, m), 1.5 (2H, s, CH_2-$SiMe_3$), 0.0 (9H, s, $SiMe_3$) ; ^{13}C-nmr ($CDCl_3$) δ 175.0, 171.85, 138.3, 137.15, 130.1, 121.6, 129.1, 124.3, 120.7, 43.5, 35.0, 26.8, 0.0. Exact mass calcd for $C_{18}H_{23}NO_2Si$ 313.1492 ; found 313.1491, and 3-phenylsulfonyl-3-[2-(trimethylsilylmethyl)allyl)succinimide (0.8 g, 2.2 mmol) ; ir (cm^{-1}) 1710, 1770 and 3440 ; ^{1}H-nmr ($CDCl_3$) δ 7.1-7.4 (6H, m, arom.) ; 5.1 (2H, broad s) ; 4.7 (2H, s) ; 3.4 (2H, m) ; 1.7 (2H, s, $C\underline{H}_2SiMe_3$) ; 0.0 (9H, s, $SiMe_3$) ; ^{13}C-nmr ($CDCl_3$) δ 181.3, 176.8, 147.3, 141.2, 130.5, 128.7, 127.2, 108.7, 43.1, 34.7, 28.9, 26.2, 0.0. Exact mass calcd for $C_{17}H_{23}N0_4SSi$ 365.1111, found 365.1110.

1-(p-Methoxyphenyl)-4-phenylsulfonyl-4-[2-(trimethylsilylmethyl)allyl]-5-hydroxy-2-pyrrolidone (8d)

To a solution of imide 7d (0.3 g, 0.6 mmol) in absolute methanol (15 ml) was added $NaBH_4$ (0.15 g, 4 mmol) the resulting solution was stirred at 0°C for 5 h, then poured into ice-water, extracted with $CHCl_3$ (3 x 10 ml) and dried ($MgSO_4$). Purification by flash chromatography (Hexane-ACOEt(6-4)) afforded 8d as oil (0.08 g, 30 %) ; ir (cm^{-1}) 1690 and 3400 ; ^{1}H-nmr ($CDCl_3$) δ 7.5 (5H, m, arom.), 6.9 (4H, m, arom.), 5.9 (1H, s, CH - OH), 5.6 (2H, d,J=6Hz), 4.8 (1H, broad s, OH, exch. with D_2O), 3.8 (3H, s, OCH_3), 3.0 (2H, s), 1.5 (2H, s, $C\underline{H}_2$ $SiMe_3$), 0.0 (9H, s, $SiMe_3$); ^{13}C-nmr ($CDCl_3$) δ 187.9, 140.9, 136.7, 135.4, 133.4, -131.5, 130.6, 129.8, 129.6, 128.2, 110.1, 62.1, 54.2, 38.2, 35.3, 28.2, 26.1, 0.0. Exact mass calcd for $C_{24}H_{31}NO_5SSi$ 473.1684 ; found 473.1683.

2-Aza-2-methyl-3-oxo-5-phenyl-7-methylenebicyclo[3.3.0]octane (9a)

To a solution of lactam 8a (0.2 g, 0.6 mmol) in anhydrous CH_2Cl_2 (1.5 ml) was added dropwise CF_3CO_2H (0.28 g, 2.5 mmol) at 0°C ; the resulting solution was stirred at 40°C for 20 h then washed with saturated $NaHCO_3$, water and dried ($MgSO_4$) to afford 9a as oil after purification by flash chromatography(Hexane-

AcOEt(1-9)),(0.15 g, 88 %) ; ir (cm^{-1}) 1700 ; ^{1}H-nmr ($CDCl_3$) δ 7.3 (5H, m, arom.), 4.9 (2H, broad s), 4.1 (1H, m, CH - N), 2.9 (3H, s, CH_3), 2.8-2.5 (6H, m) ; ^{13}C-nmr ($CDCl_3$) δ 173.4, 147.6, 128.8, 128.7, 126.7, 125.8, 125.4, 108.9, 70.9, 50.2, 46.5, 45.6, 36.7, 28.1. Exact mass calcd for $C_{15}H_{17}NO$ 227.1306 ; found 227.1308.

2-Aza-2-phenyl-3-oxo-5-phenylsulfonyl-7-methylenebicyclo[3.3.0]octane (9b)

To a solution of lactam 8b (0.09 g, 0.2 mmol) in anhydrous CH_2Cl_2 (0.6 ml) was added dropwise CF_3CO_2H (0.09 g, 0.8 mmol) at 0°C ; the resulting mixture was stirred at 0°C for 2 h then washed with saturated $NaHCO_3$, water and dried ($MgSO_4$). Purification by flash chromatography (Hexane-AcOEt (1-9)) afforded 9b as oil (0.04 g, 53 %) ; ir (cm^{-1}) 1710 ; ^{1}H-nmr ($CDCl_3$) δ 7.5 (5H, m, arom.), 6.8 (5H, m, arom.), 5.0 (2H, d), 4.3 (1H, m, CH - N), 2.7-2.4 (6H, m) ; ^{13}C-nmr ($CDCl_3$) δ 174.2, 145.4, 129.2, 128.7, 127.9, 126.8, 126.2, 125.9, 125.5, 125.2, 125.0, 108.7, 71.0, 51.3, 47.2, 44.3, 36.4. Exact mass calcd for $C_{20}H_{19}NO_3S$ 353.1081 ; found 353.1080.

2-Aza-2-(p-methoxyphenyl)-3-oxo-5-phenylsulfonyl-7-methylenebicyclo[3.3.0]octane (9d)

To a solution of hydroxylactam 8d (0.07 g, 0.15 mmol) in anhydrous CH_2Cl_2 (0.5 ml) was added dropwise CF_3CO_2H (0.07 g, 0.6 mmol) at 0°C, the resulting mixture was stirred at 0°C for 2 h then washed with saturated $NaHCO_3$, water and dried ($MgSO_4$). Purification by flash chromatography (Hexane-AcOEt (1-9)) afforded 9d as oil (0.015 g, 30 %) ; ir (cm^{-1}) 1710 ; ^{1}H-nmr ($CDCl_3$) δ 7.5 (5H, m, arom.), 7.0 (4H, m, arom.), 5.6 (1H, m, CH -N), 5.0 (2H, m), 3.8 (5H, m), 3.15 (2H, broad s), 1.9 (2H, m) ; ^{13}C-nmr ($CDCl_3$) δ 173.1, 148.1, 136.5, 135.4, 133.1, 129.6, 128.2, 128.0, 116.2, 72.3, 52.1, 46.9, 43.2, 35.9. Exact mass calcd for $C_{21}H_{21}NO_4S$ 383.1186 ; found 383.1187.

2-Aza-2-phenyl-3-oxo-7-methylenebicyclo[3.3.0]octane

To a solution of sulfone 9b (0.02 g, 0.055 mmol) and K_2HPO_4 (0.06 g, 0.23 mmol) in anhydrous methanol (0.7 ml) cooled at 0°C was added sodium amalgam Na(Hg) (0.1 g, 0.22 mmol). The resulting mixture was stirred at 50°C for 3 h, poured into a saturated solution of sodium bicarbonate, extracted with CH_2Cl_2 (3 ml) dried ($MgSO_4$) and purified by flash chromatography (Hexane-AcoEt (1-9)) to afford product as oil (0.01 g, 60 %) ; ir (cm^{-1}) 1710 ; ^{1}H-nmr ($CDCl_3$) δ 7.3-7.6 (5H, m), 5.1 (2H, d,J=6Hz), 4.4 (1H, m, CH-N), 2.5-2.8 (6H, m) ; ^{13}C-nmr ($CDCl_3$) δ 174.1, 148.2, 129.8, 128.6, 128.0, 127.5, 116.4, 72.4, 53.0, 46.8, 43.2, 33.1. Exact mass calcd for $C_{14}H_{15}NO$ 213.1150 ; found 213.1147.

2-Aza-2-phenyl-3,7-dioxobicyclo[3.3.0]octane (10b)

A solution of the previous lactam (0.10 g, 0.5 mmol) in CH_2Cl_2-MeOH (1-1) (10 ml) was cooled at - 78°C and ozonized for 30 min. Then, the solution was rapidly purged with N_2 for 10 min, treated with dimethyl sulfide (0.5 ml) and allowed to warm to room temperature. The solution was washed twice with water and once with brine then organic layers were dried ($MgSO_4$) and purified by flash chromatography (Hexane-AcOEt (1-9)) to afford 10b as oil (0.09 g, 80 %) ; ir (cm^{-1}) 1740 and 1710 ; ^{1}H-nmr ($CDCl_3$) δ 7.4-7.6 (5H, m, arom.), 4.6 (1H, m, CH-N), 3.2-1.5 (7H, m) ; ^{13}C-nmr ($CDCl_3$) δ 216.2, 175.4, 129.4, 128.7, 128.2, 127.9, 75.2, 51.4, 47.1, 44.1, 32.8. Exact mass calcd. for $C_{13}H_{13}NO_2$ 215.0943 ; found 215.0941.

1-Trimethylsilyl-2-pyrrolidone (11)

According to literature procedure[11], the desired product was got in 68 % yield after distillation *in vacuo* as a liquid bp_{12} = 88°C, Lit[17]. bp_{12}= 90°C ; ir (cm^{-1}) 1700 ; ^{1}H-nmr ($CDCl_3$) δ 3.1 (2H, t, CH_2-N), 2.0 (4H, m), 0.1 (9H, s, $SiMe_3$).

3-[2-(Trimethylsilylmethyl)allyl]-2-pyrrolidone (12)

To a solution of LDA obtained from $(iPr)_2NH$ (0.37g, 3.67 mmol) and nBuLi (2.3 ml, c = 1.6 M) (3.67 mmol) in anhydrous THF (4.5 ml) was added dropwise at - 78°C a solution of 11 (0.5 g, 3.2 mmol) in THF (2 ml), the mixture was stirred at - 78°C for 45 min. A solution of 1-iodo-2-(trimethylsilylmethyl)propene (0.84g, 3.3 mmol) in THF (2 ml) was then added dropwise and the resulting mixture was stirred at - 78°C overnight and allowed to warm at room temperature for 2 h. The mixture was poured into water and extracted with CH_2Cl_2, the combined organic layers were washed with aqueous sodium hydroxide 5 %, then water and dried ($MgSO_4$). After purification by flash chromatography (AcOEt) we afforded 12 (0.45 g, 67 %) as oil ; ir (cm^{-1}) 1700 and 3450 ; ^{1}H-nmr ($CDCl_3$) δ 7.8 (1H, broad s, exch. with D_2O, NH), 4.6 (2H, broad s), 3.3 (2H, dd, J_1=5Hz, J_2=9Hz CH-N), 1.8-2.6 (5H, m), 1.5 (2H, s, CH_2-$SiMe_3$), 0.0 (9H, s, $SiMe_3$) ; ^{13}C-nmr ($CDCl_3$) δ182.4, 146.4, 109.9, 41.8, 28.7, 27.5, 0.07. Exact mass calcd for $C_{11}H_{21}NOSi$ 211.1392 ; found 211.1390.

1-Carbomethoxy-3-[2-(trimethylsilylmethyl)allyl]-2-pyrrolidone (13a)

To a solution of LDA (1.02 mmol) in anhydrous THF (2 ml) was added dropwise at - 78°C a solution of 12 (0.18 g, 0.85 mmol) in THF (1 ml) ; the mixture was stirred at - 78°C for 45 min then neat methyl cyanoformate (0.1 g, 1.02 mmol) was added dropwise. The resulting mixture was stirred at - 78°C overnight and allowed to warm to room temperature for 2 h ; it was poured into water (4 ml), extracted with $CHCl_3$ (3 x 4 ml) and organic layers were dried ($MgSO_4$). Purification by flash chromatography (AcOEt) afforded 13a as oil (0.2 g, 90 %) ; ir (cm^{-1}) 1710 and 1790 ; ^{1}H-nmr ($CDCl_3$) δ 4.7 (2H, broad s), 3.9 (3H, s, CO_2CH_3), 3.7 (2H, m, CH_2-N), 2.0-2.8 (5H, m), 1.5 (2H, s, CH_2-$SiMe_3$), 0.0 (9H, s, $SiMe_3$) ; ^{13}C-nmr ($CDCl_3$) δ 175.3, 152.2, 144.2, 109.0, 53.2, 44.3, 42.0, 39.1, 26.0, 24.1, 0.0. Exact mass calcd for $C_{13}H_{23}NO_3Si$ 269.1446 ; found 269.1445.

1-Carboethoxy-3-[2-(trimethylsilylmethyl)allyl]-2-pyrrolidone (13b)

According to a similar procedure 13b was got as oil in 71 % yield after purification by flash chromatography (AcOEt) ; ir (cm^{-1}) 1720, 1750 and 1795 ; ^{1}H-nmr ($CDCl_3$) δ 4.7 (2H, broad s), 4.3 (2H, q, J=7 Hz, CO_2CH_2), 3.7 (2H, m, CH_2-N), 2.1-2.9 (5H, m), 1.5 (2H, s, CH_2-$SiMe_3$), 1.4 (3H, t, J=7Hz, CH_3CH_2), 0.0 (9H, s, $SiMe_3$) ; ^{13}C-nmr ($CDCl_3$) δ 177.0, 172.2, 153.3, 145.7, 140.4, 119.3, 110.45, 63.9, 45.7, 45.1, 43.5, 40.5, 31.5, 27.7, 27.4, 25.7, 20.7, 15.6, 0.05. Exact mass calcd for $C_{14}H_{25}NO_3Si$ 283.1597 ; found 283.1596.

1-Carbomethoxy-2-ethoxy-3-[2-(trimethylsilylmethyl)allyl]pyrrolidine (14a)

To a solution of imide 13a (0.25 g, 0.9 mmol) in absolute ethanol (7 ml) cooled at - 20°C, sodium borohydride (0.25 g, 6.5 mmol) was added. Then, each 5 min 2M H_2SO_4 (six drops) was added ; after completion of the reaction (1 h), the mixture was treated by 6M H_2SO_4 until the pH reached 2. The mixture was poured into a saturated solution of sodium bicarbonate and extracted with $CHCl_3$; the combined organic layers were washed with brine and dried (K_2CO_3). Purification by flash chromatography (AcOEt) afforded

14a as oil (0.2 g, 80 %) ; ir (cm^{-1}) 1710 ; ^{1}H-nmr ($CDCl_3$) δ 5.1 (1H, m, C<u>H</u>-OC_2H_5), 4.7 (2H, broad s), 3.9 (3H, s, CO_2CH_3), 3.4-3.7 (4H, m), 1.6-2.5 (5H, m), 1.5 (2H, s, CH_2-$SiMe_3$), 1.2 (3H, t, J=7Hz, CH_3CH_2), 0.0 (9H, s, $SiMe_3$) ; ^{13}C-nmr ($CDCl_3$) δ 157.75, 147.3, 146.1, 110.7, 109.4, 89.3, 89.2, 65.6, 53.7, 46.4, 45.6, 43.8, 41.1, 38.2, 28.5, 27.8, 16.7, 0.0. Exact mass calcd for $C_{15}H_{29}NO_3Si$ 299.1909 ; found 299.1909.

1-Carboethoxy-2-ethoxy-3-[2-(trimethylsilylmethyl)allyl]pyrrolidine (14b)

According to the previous procedure 14b was got in 60% yield as an oil after purification by flash chromatography (AcOEt) ; ir (cm^{-1}) 1700 ; ^{1}H-nmr ($CDCl_3$) δ 5.0 (1H, m, C<u>H</u>-OC_2H_5), 4.6 (2H, broad s), 4.15 (2H, q, J = 7Hz, CH_2CH_3), 3.5 (4H, m), 1.7-2.4 (4H, m), 1.5 (2H, s, CH_2-$SiMe_3$), 1.2 (3H, t, J =7 Hz, CH_3CH_2), 0.0 (9H, s, $SiMe_3$) ; ^{13}C-nmr ($CDCl_3$) δ 158.1, 147.2, 146.3, 110.9, 109.2, 89.4, 89.1, 65.4, 60.2, 54.1, 46.2, 45.8, 43.7, 41.2, 25.4, 24.8, 16.5, 16.1, 0.0. Exact mass calcd for $C_{16}H_{31}NO_3Si$ 313.2065 ; found 313.2066.

2-Aza-2-carbomethoxy-7-methylenebicyclo[3.3.0]octane (15a)

To a solution of urethane 14a (0.46 g, 1.5 mmol) in anhydrous CH_2Cl_2 (5 ml) was added dropwise CF_3CO_2H (0.7 g, 6.1 mmol) at 0°C ; the resulting mixture was stirred at this temperature for 4 h then washed with saturated $NaHCO_3$, water and dried ($MgSO_4$). Purification by flash chromatography (AcOEt) afforded 15a as oil (0.16 g, 60 %) ; ir (cm^{-1}) 1700 ; ^{1}H-nmr ($CDCl_3$) δ 4.9 (2H, d, J = 6Hz), 3.8 (3H, s, CO_2CH_3), 3.4 (1H, m, CH-N), 1.6-2.5 (10H, m) ; ^{13}C-nmr ($CDCl_3$) δ 158.2, 146.2, 109.8, 62.3, 51.8, 44.3, 42.5, 32.1, 28.2, 22.4. Exact mass calcd for $C_{10}H_{15}NO_2$ 181.1099 ; found 181.1098.

2-Aza-2-carboethoxy-7-methylenebicyclo[3.3.0]octane (15b)

According to the previous procedure 15b was got in 62 % yield as oil after purification by flash chromatography (AcOEt) ; ir (cm^{-1}) 1700 ; ^{1}H-nmr ($CDCl_3$) δ 4.7 (2H, d, J = 6Hz), 4.1 (2H, q, J=7Hz, CH_2CH_3), 3.5 (3H, m, CH-N and CH_2-N), 1.9-2.9 (8H, m), 1.2 (3H, t, J = 7Hz, CH_3-CH_2) ; ^{13}C-nmr ($CDCl_3$) δ 155.4, 143.4, 127.2, 112.6, 60.9, 45.5, 44.6, 41.9, 40.5, 22.15, 14.8. Exact mass calcd for $C_{11}H_{17}NO_2$ 195.1255 ; found 195.1254.

1-Carbomethoxy-2-hydroxy-3-[2-(trimethylsilylmethyl)allyl]pyrrolidine

To a solution of imide 13a (0.1 g, 0.37 mmol) in absolute ethanol (3 ml) cooled at 0°C, sodium borohydride (0.1 g, 2.6 mmol) was added once. The mixture was stirred at 0°C while six drops of 2M H_2SO_4 were added each 15 min. After completion of the reaction, the mixture was poured into saturated $NaHCO_3$ and extracted with $CHCl_3$; the combined organic layers were washed with brine and dried (K_2CO_3). Purification by flash chromatography (AcOEt) afforded product as oil (0.08 g, 75 %) ; ir (cm^{-1}) 1700 and 3600 ; ^{1}H-nmr ($CDCl_3$) δ 5.1 (1H, broad s, exch. with D_2O, OH), 4.6 (2H, broad s), 3.9 (3H, s, CO_2CH_3), 3.5 (1H, m, C<u>H</u>-OH), 1.9-2.6 (7H, m), 1.5 (2H, s, CH_2-$SiMe_3$), 0.0 (9H, s, $SiMe_3$).

2-Carboethoxy-2-aza-7-oxobicyclo[3.3.0]octane (16b)

A solution of urethane 15b (0.2 g, 1 mmol) in CH_2Cl_2-MeOH (1-1) (10 ml) was cooled at - 78°C and ozonized for 5 min. Then, the solution was rapidly purged with N_2 for 10 min, treated with dimethyl sulfide (5 ml) and allowed to warm to room temperature. The mixture was washed twice with water and once with brine ; organic layers were then dried ($MgSO_4$) and purified by flash chromatography (AcOEt) to afford 16b

as an oil (0.15 g, 80 %) ; ir (cm^{-1}) 1750 and 1700 ; ^{1}H-nmr ($CDCl_3$) δ 4.09 (2H, q, J = 7Hz, CH_2-CH_3), 1.2 (3H, t, J = 7Hz, CH_3-CH_2) according with literature data[14].

ACKNOWLEDGMENTS

We thank Doctor G. Dauphin for high field nmr measurements.

REFERENCES

1 . S. Moncada, R. Gryglewski, S. Bunting, and J.R. Vane, Nature, 1976, 263, 663.
2 . F. Cassidy, R.W. Moore, and G. Wootton, Tetrahedron Lett., 1981, 22, 253 ; C.L.J. Wang, Tetrahedron Lett., 1983, 24, 477 ; and references cited therein.
3 . J.R. Vane and S.Bergstrom, ed., "Prostacyclin", New-York, Raven Press, 1979.
4 . T.H. Chan and I. Fleming, Synthesis, 1979, 761 ; I. Fleming, Chem. Soc. Rev., 1981, 10, 83.
5 . E. Colvin, "Silicon in Organic Synthesis", Butterworths and Co Ltd, 1981 ; W.P. Weber, "Silicon Reagents for Organic Synthesis", Springer Verlag, Berlin, 1983.
6 . G.A. Kraus and K. Neuenschwander, J. Chem. Soc., Chem. Comm., 1982, 134 ; H. Hiemstra, M.H.A.M. Sno, R.J. Vijn, and W.N. Speckamp, J. Org. Chem., 1985, 50, 4014.
7 . J.C. Gramain and R. Remuson, Tetrahedron Lett., 1985, 26, 327.
8 . J.C. Gramain and R. Remuson, Tetrahedron Lett., 1985, 26, 4083.
9 . J.C. Hubert, J.B.P.A. Wijnberg, and W.N. Speckamp, Tetrahedron, 1978, 34, 179.
10 . R. Schlecker and D. Seebach, Helv. Chim. Acta, 1977, 60, 1459 ; C.R. Hauser and D.R. Bryant, J. Am. Chem. Soc., 1961, 83, 3468 ; H. Hiemstra, W.J. Klaver, and W.N. Speckamp, J. Org. Chem., 1984, 49, 1149.
11 . T. Nagasaka, S. Esumi, N. Ozawa, Y. Kosugi,and F. Hamaguchi, Heterocycles, 1981, 16, 1987.
12 . L.N. Mander and S.P. Sethi, Tetrahedron Lett., 1983, 24, 5425.
13 . K.H. Melching, H. Hiemstra, W.J. Klaver, and W.N. Speckamp, Tetrahedron Lett., 1986, 27, 4799.
14 . C.L.J. Wang, Tetrahedron Lett., 1983, 24, 477.
15 . C.A. Miller and L.M. Long, J. Am. Chem. Soc., 1951, 73, 4895.
16 . I. Matsuda, K. Akiyama, T. Toyoshima, S. Kato, and M. Mizuta, Bull. Chem. Soc. Japan, 1975, 48, 3675.
17. M. Rothe and T. Toth, Chem. Ber., 1966, 99, 3820.

Received, 9th January, 1989