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Stereospecific Course of a Transannular C-H Insertion Process

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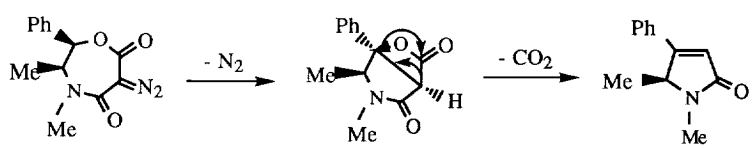
Abstract: The steric course of the catalytic decomposition of the chiral diazoxazepanedione **1** to 2-pyrrolone **3** was clarified by the X-ray diffraction study of the enantiomerically pure pyrrolidine **5**, obtained by reductive cleavage of the unisolated intermediate bicyclic compound **2**.

Following our studies in the field of stabilized carbenes or carbenoids generated by decomposition of α–diazocarbonyl compounds[1], we have recently reported the synthesis of the enantiopure unsaturated lactam **3** by catalytic decomposition of the chiral diazoxazepanedione **1**, readily obtained from ephedrine.[2] The global reaction involves an intramolecular carbenic CH insertion followed by a ring contraction-decarboxylation step. (Scheme 1). The process suggested a mechanism involving the formation of the bicyclic lactone-lactam **2** as the key intermediate.

Scheme 1



1 **2** **3**

This work has been aimed not only at defining the stereochemical course of the carbenic attack by investigating the hypothesized intermediate **2** but also at determining the possibility of transforming **2** into interesting homochiral pyrrolidinones and pyrrolidines.

Initially, we attempted to confirm the presence of **2** in the reaction mixture. The reaction, carried out in $CDCl_3$, was therefore monitored by ^1H NMR analysis: it was possible to single out some signals attributable to a compound having the structure **2**, in the ^1H NMR spectra, recorded at different reaction times. Subsequently, it was possible to establish that after 3h, the reaction time required for the disappearance of the starting material, the reaction mixture contained **2** and its compound of decomposition **3** in a proportion of 85% and 15%, respectively. Next, it was attempted to isolate **2** but all efforts were ineffective because of the very fast decomposition occurring during the removal of the solvent.

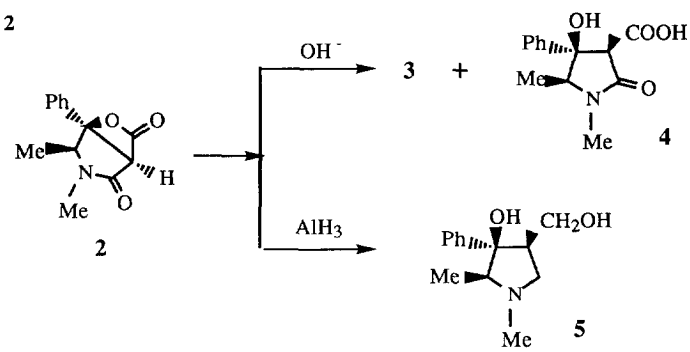
The transformation of **2**, without its isolation, was therefore planned with the aim of obtaining an isolable compound having no change at the preformed stereogenic centres.

For this purpose, the hydrolytic opening of the lactonic moiety of **2** was performed. Hydrolysis was carried out in basic conditions when the maximum concentration of **2** was reached in the reaction mixture. The desired

3-carboxy-4-hydroxy-4-phenyl-5-methyl-2-pyrrolidinone **4** was obtained in mixture with the unsaturated lactam **3** (the ratio **3/4** was about 1/1) (Scheme 2). Compound **4** was then separated as a white powder and its ^1H NMR analysis showed it to be a single diastereoisomer; unfortunately, all attempts to obtain crystals suitable for X-ray analysis failed.

An alternative reaction involving the reductive lactonic ring opening of **2** was then performed. Thus, the reduction carried out with alane afforded exclusively the 1,2-dimethyl-3-hydroxy-3-phenyl-4-hydroxy methyl-pyrrolidine **5** as a white solid in 81% yield. Its crystals were submitted to an X-ray diffraction study.

Scheme 2



This analysis confirmed the presence of a single diastereomer in the crystals of **5**, resulting from the space chiral group P21 ascertained for that structure, and, since the C2 stereocentre is unaffected in the process, allowed to assign , as shown in Figure 1, to the other C3 and C4 stereocentres, the 3S and 4R configurations, respectively.

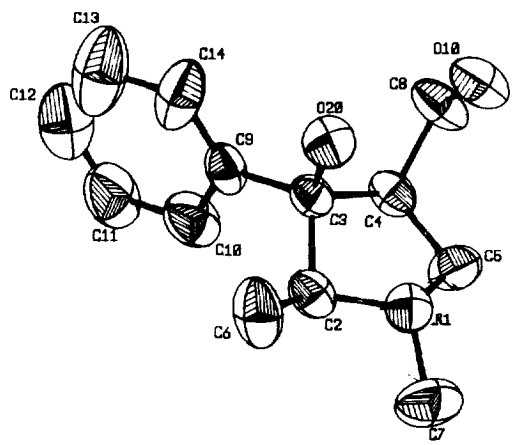


Fig 1. ORTEP view of (2S,3S,4R)-**5**.

These conclusions led also to establish the absolute configuration of **4** as 3R,4S,5S. Consequently, also the absolute configurations at the C3 and C4 stereocenters of bicyclic intermediate **2**, could be assigned as 3S, 4S.

These results show that the regiospecific intramolecular insertion on the asymmetric phenyl-substituted C-H bond of the diazoxazepanedione **1** proceeds with retention of configuration[3] giving the bicycle **2** bearing a *cis*-fusion,[4] as depicted in Scheme 1.

Finally, it is noteworthy that lactam **4** and pyrrolidine **5**, both bearing a quaternary asymmetric carbon, are enantiopure building blocks of potential synthetic utility concerning two classes of important bioactive and therapeutic compounds: γ-aminobutyric acid (GABA) precursors[5] and potential analgetic agents[6], respectively.

Experimental.

Melting points are uncorrected. ^1H (300 MHz) and ^{13}C NMR spectra were performed on a Varian VXR-300 spectrometer with TMS as the internal standard. The optical rotations were measured by a Perkin-Elmer 142 automatic polarimeter in a 1 dm tube. All reactions were carried out under argon atmosphere: all reagents and solvents employed were reagent grade materials purified by standard methods and redistilled before use. (2R,3S)-(-)-6-Diazo-3,4-dimethyl-2-phenyloxazepane-5,5-dione (**1**) and (R)-(+)-1,5-dimethyl-4-phebyl-1,5-dihydro-2H-pyrrol-2-one (**3**) were prepared according to Saba *et al.* [2]

Catalytic decomposition of 1: Rh(II)acetate dimer (10 mg) was added under argon to a solution of diazo compound **1** (100 mg, 0.39 mmol) in $CDCl_3$ (3 ml) and the mixture stirred at room temperature. After 3h the ^1H NMR spectra showed that the reaction mixture contained **2** and its compound of decomposition **3** in a proportion of 85% and 15%, respectively. ^1H NMR for **2**: ($CDCl_3$) δ: 7.47-7.37 (5H, m), 4.27 (1H, s), 3.92 (1H, q, J = 6.6 Hz), 2.93 (3H, s), 1.38 (3H, d, J = 6.6 Hz).

(-)-(3S,4S,5S)-3-Carboxy-4-hydroxy-4-phenyl-5-methyl-2-pyrrolidinone (4): Rh(II)acetate dimer (26 mg) was added under argon to a solution of diazo compound **1** (259 mg, 1 mmol) in CH_2Cl_2 (10 ml), and the mixture stirred at room temperature for 3h. A solution of KOH (56 mg in 15 ml H_2O) was then added and the mixture stirred for 3 h. The separated organic layer was dried over $MgSO_4$ and concentrated *in vacuo* to give a white solid identified as the unsaturated lactam **3** (84 mg, 45%). The aqueous solution was acidified with 1M HCl , extracted with EtOAc (3X10 ml), the combined organic phases dried over $MgSO_4$, and the solvent removed to give **4** as a white powder: 122 mg (49%); m.p. 120° C (dec.) ; $[\alpha]^{25}_D$ -32 (*c* 0.5, $CHCl_3$). ^1H NMR ($CDCl_3$) δ: 7.50-7.26 (5H, m), 3.97 (1H, s), 3.72 (1H, q, J = 6.6 Hz), 2.93 (3H, s), 1.21 (3H, d, J = 6.6 Hz). ^{13}C NMR ($CDCl_3$) δ: 170.1, 168.4, 140.6, 128.7, 128,1, 125.1, 65.6, 56.3, 27.5, 9.6. IR (Nujol): 2935, 2930, 2840, 2142, 1660, 1605, 1302, 1140, 735 cm^{-1}. *Elem. anal.*, found % (calcd. for $C_{13}H_{15}NO_4$): C, 62.43 (62.64) H, 6.03 (6.07); N, 5.78 (5.62)

(+)-(2S,3S,4R)-1,2-dimethyl-3-hydroxy-3-phenyl-4-hydroxymethylpyrrolidine (5): Anhydrous THF (12 ml) was added under argon at 0°C to $AlCl_3$ (0.4 g, 3.0 mmol). Then a 1M solution of $LiAlH_4$ in THF (9 ml, 9 mmol) was added dropwise (H_2 evolution!). The reaction mixture was stirred at room temperature for 20 min., cooled at -78°C and the decomposition solution of diazo compound **1** (200 mg, 0.77 mmol), performed as above, was slowly added. After 1h stirring at -78°C, the reaction mixture was cautiously quenched with 1M HCl, diluted with H_2O and extracted with CH_2Cl_2 (4X10 ml). The combined organic phases were washed with brine, dried ($MgSO_4$) and after removal of the solvent *in vacuo*, the pyrrolidine **5** was obtained as white crystals: 136 mg (81.4%); m.p.119-120 °C (dec) ; $[\alpha]^{25}_D$ +75 (*c* 1, $CHCl_3$); ^1H NMR ($CDCl_3$) δ: 7.49-7.21 (5H, m), 3.74 (2H, d, J = 4.5 Hz), 3.63-3.34 (1H, m), 3.13 (1H, AB system), 2.84-2.69 (IH, m), 2.66-2.57

(2H, m), 2.47 (1H, q, J = 6.6 Hz), 2.34 (3H, s), 0.85 (3H, d, J = 6.6 Hz). ^{13}C NMR ($CDCl_3$) δ: 142.9, 128.5, 126.7, 125.1, 83.3, 72.1, 62.2, 56.9, 49.9, 39.7, 10.2. IR (Nujol): 2935, 2930, 2840, 2142, 1660, 1605, 1302, 1140, 735 cm^{-1}. *Elem. anal.*, found % (calcd. for $C_{13}H_{19}NO_2$): C, 70.23 (70.56) H, 8.53 (8.65); N, 6.50 (6.33)

Structure determination of **5**. *Crystal data*: $C_{13}H_{19}NO_2$, monoclinic, space group P21, a = 13.281(2), b = 7.694(1), c = 6.391(1) Å, V = 634 (6) $Å^3$, Z = 2, D_c = 1.16 gr cm^{-3}, μ = 0.72 mm^{-1} (Mo-Kα, λ = 0.7107 Å). Data were collected at 293 K on a Philips PW 2100 diffractometer using *θ/2θ* scan mode. The data were not corrected for absorption. 1781 reflections with θ in the range 2-28° were measured; 1651 of them were independent, observed reflexions: 651 (F>3σ (F). The structure was solved by the direct method program SIR 92[7] using direct methods and refined to R = 0.051 using SHELX76[8] by a weigthting scheme based on measured e.s.d.'s; $w = 1/[\sigma^2(F) + 0.0055F^2]$[8]. The hydrogen atoms were refined isotropically. For the molecular drawing, ORTEP program was used.

Additional material is available from the Cambridge Crystallographic Data Centre[9].

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9. Tables for atomic coordinates, comprises H-atom coordinates, displacement parameters, selected bond distances, selected bond angles, and observed and calculated structure factors are available from the Director of the Cambridge Crystallographic Data Centre, University Chemical Laboratory, Lensfield road, CambridgeCB2 I EW, UK. Any request should be accompained by the full literature citation for this paper.

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