Tetrahedron Vol 47, No 2, pp 229-238, 1991
Printed in Great Britain

0040-4020/91 $3 00+ 00

MECHANISM OF THE REARRANGEMENT OF THE BICYCLO [4.2.0] OCTAN SYSTEM TO THE BICYCLO [3.2.1] OCTAN SYSTEM

Josette BASTARD, Duc DO KHAC*, Marcel FETIZON
and Chantal PREVOST
Laboratoire de Synthèse Organique - Ecole Polytechnique
91128 PALAISEAU Cedex - France
Jean-Claude BELOEIL,
Institut de Chimie des Substances Naturelles, C.N.R.S.,
91190 GIF-sur-YVETTE - France

(*Received in Belgium* 24 *September* 1990)

Abstract : A concerted mechanism has been demonstrated for the rearrangement of a tetracyclic ion including a bicyclo [4.2.0] octan system to hibaol, using a selective deuteration on the migrating bond.

The stereochemistry of the selectively introduced deuterium was determined by three routes :
I) comparison of the high field ^{1}H NMR spectra of the deuterated and undeuterated compounds, using double irradiation;
II) high field ^{1}H NMR, coupled with molecular mechanics calculations;
III) two dimensional homo and heteronuclear NMR.

INTRODUCTION

The mechanism of cyclisation of manool 1 to hibaol 2 was elucidated twenty years ago by Edwards (1,2), Wenkert (3,4) and Hall (5). The use of labelled compounds derived from manool 1 established that the formation of hibaol 2 occured via an intermediate tetracyclic carbocation A (figure 1).

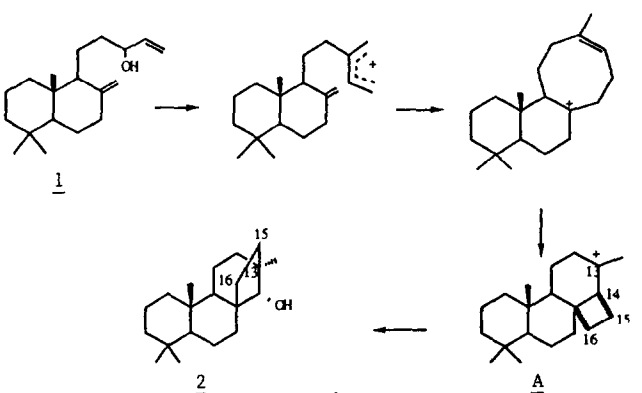


Figure 1

During the synthesis of hibaene 6, performed in our laboratory (figure 2), a conservation of the stereochemistry of the hydroxylic group in C_{16} was noticed during the solvolysis of the diols 4a and 4b. This fact led us to examine the mechanism of the migration of bond C_{14}-C_{15} to bond C_{13}-C_{15}.

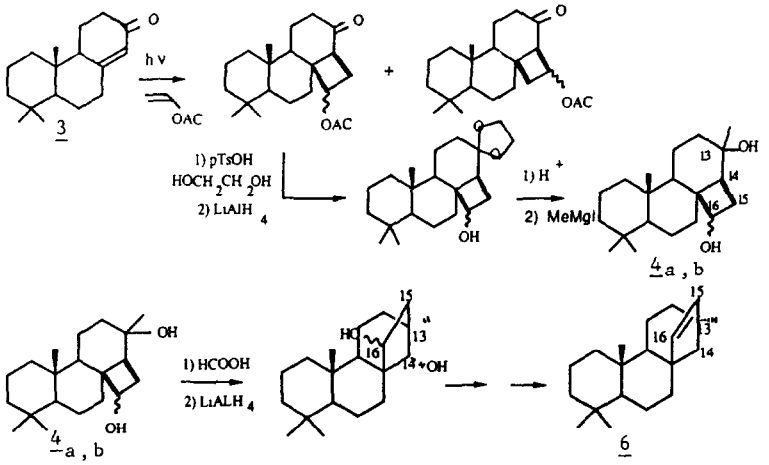


Figure 2

In order to avoid any interference in the mechanism due to solvatation effects, the study was performed on the compounds 9a* and 9b*, stereoselectively deuterated on the carbons C_{15} and C_{16} (figure 3) :

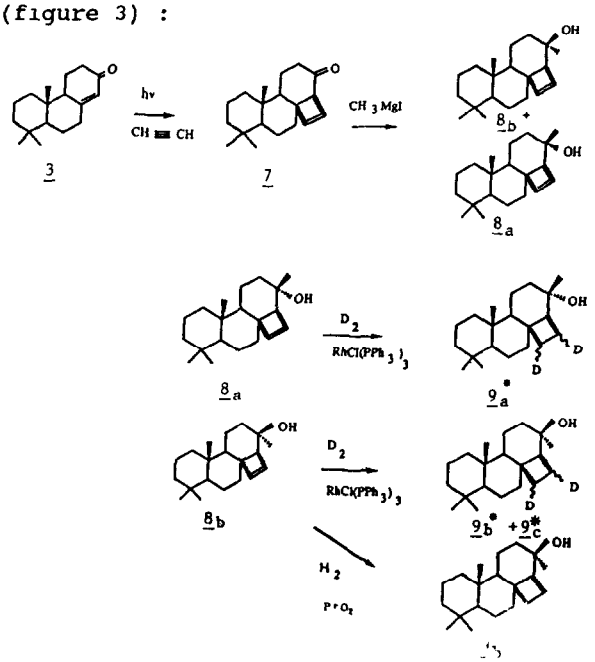


Figure 3

RESULTS AND DISCUSSION

The synthesis of the deuterated tertiary alcohols 9a* and 9b* was carried out according to scheme 3, from $\Delta^{8(14)}$ podocarpenone-13, 3 (7). The first step, a photochemically induced cycloaddition of acetylene to the α,β-unsaturated ketone 3 led to the ketone 7. As shown previously in our laboratory (6,7), the addition occurred specifically on the β side of 3.

Ketone 7 was then subjected to the action of methyl magnesium iodide, yielding a mixture of the alcohols 8a and 8b, which was easy to separate. With methyl lithium as a reagent, isomer 8b was obtained as a major product (80% of the mixture).

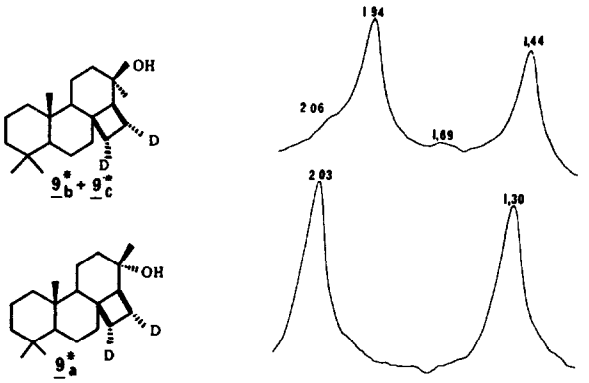
The addition of deuterium was performed independently on 8a and 8b, in the presence of Wilkinson's catalyst $RhCl(PPh_3)_3$ which is known to give exclusively cis additions (8,9).

Selectivity of the addition of deuterium on 8a and 8b

The selectivity of addition was demonstrated by studying the deuteration products of 8a and 8b by ^2H NMR (figure 4) :

- only two resonance signals were observed on the ^2H NMR spectrum of the 8a deuteration product (respectively at 1.39 and 2.03 ppm) ; this indicates that the deuterium addition occured with a total stereoselectivity, leading to a single compound 9a* ;

- the 8b deuteration product spectrum presents two main resonance signals, at 1.44 and 1.94 ppm, accompanied by two minor ones, in a 95/5 ratio ; the minor isomeric compound 9c* could not be detected in the ^1H NMR or the ^{13}C NMR spectra. It can be concluded that the deuterium addition occured preferentially on one side, giving way to a major compound 9b* and a minor one 9c*.



^2H NMR spectra of $\underline{9}^*_a$ and ($\underline{9}^*_b$+$\underline{9}^*_c$)

Figure 4

A stereochemistry α for the two deuterium was established by a high resolution ^1H NMR study performed on $\underline{9b}^*$ (14) ($\underline{9c}^*$ could not be detected on the spectrum). This study included a comparison with the non deuterated analog spectrum, the use of the double irradiation technique, and a bidimensional NMR study (16).

Mechanism of rearrangement of the tetracyclic carbocation A

The preliminary formation of the carbocation A in C_{13} was demonstrated previously in our laboratory (7) (figure 5) :

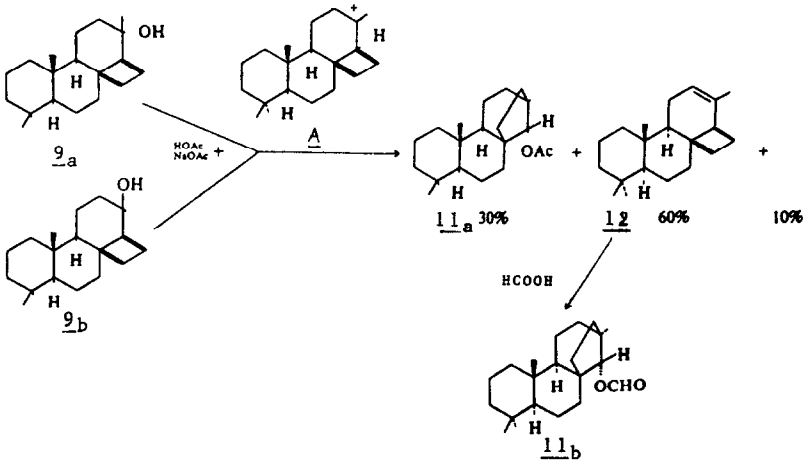


Figure 5

Formolysis of 9a* and (9b* + 9c*) might involve, after this first step, a concerted or a non-concerted mechanism : the second hypothesis implies that each of the alcohols 9a* and (9b* + 9c*) could lead to a mixture of four stereoisomeric compounds (as far as deuterium is concerned) (figure 6a) ; while the first hypothesis presumes a conservation of the deuterium stereochemistry (figure 6b).

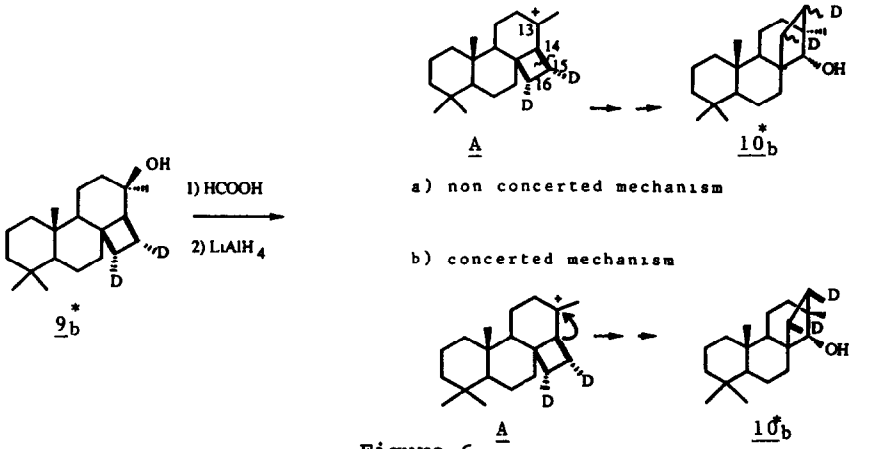
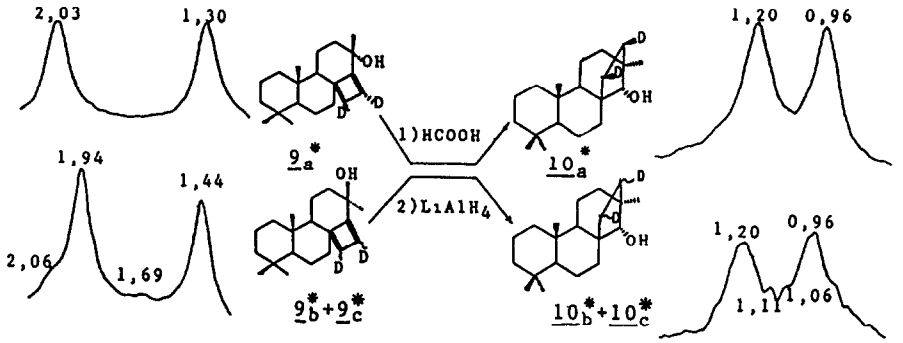


Figure 6

The rearrangement reaction was performed on 9a* and (9b* + 9c*) respectively. A ^{2}H NMR analysis showed that the precursors characteristics had been preserved : the (9b* + 9c*) rearrangement product spectrum presents two main signals at 1.20 and 0.96 ppm and two secondary ones, respectively attributed to compounds 10b* (product of 9b*) and 10c* (product of 9c*) ; whereas only two signals are visible on the spectrum of 10a*, the single rearrangement product of 9a* (figure 7).

Moreover, the ^{2}H NMR signals of 10a* coincide remarkably well with those of 10b*. A comparison of the ^{1}H NMR and ^{13}C NMR spectra of 10a* and (10b* + 10c*) clearly demonstrates the identity of 10a* and 10b* (the two spectra present a perfect superposition, and 10c* could not be detected in either case).



^2H NMR of $\underline{9}_a^*$, ($\underline{9}_b^*$+$\underline{9}_c^*$), ($\underline{10}_b^*$+$\underline{10}_c^*$), $\underline{10}_a^*$

Figure 7

Since isomerism did not occur during the migration of the C_{14}-C_{15} to C_{13}-C_{15} bond, it was concluded that the mechanism of ion A rearrangement is concerted.

In addition, the identity of $\underline{10a}^*$ and $\underline{10b}^*$ confirmed that the previous deuterium addition on 8a and 8b had occurred principally on the same side of the cyclobutane ring.

CONCLUSIONS

Using a selective deuteration on the cyclobutenic moiety of the alcohols 8a and 8b, it was established that the mechanism of rearrangement of the bicyclo [4.2.0] octan system of carbocation A to a bicyclo [3.2.1] octan system, is concerted.

A stereochemistry α was evidenced for the selective attack of the deuterium on each of the alcohols 8a and 8b.

This stereochemistry had been hoped for, considering the characteristics of action of the Wilkinson's catalyst : in addition to the fact that only cis additions are permitted, a great sensibility to steric interactions have been described in the literature. We therefore performed the addition on the methyl-16,hydroxyl-16 derivative 8, instead of its ketonic procursor 7, in order to increase the difficulty of approach by the β-side.

The experimental results thus confirmed our suppositions. The presence of a minor isomer in 9b*, deuterated on the β side, can be attributed to the possibility of a partial adsorption of the β hydroxy-16 on the complex $RhCl(PPh_3)_3$ (9).

EXPERIMENTAL PART

The infrared spectra (CCl_4) were measured on a PERKIN-ELMER 399 spectrometer. Proton nuclear magnetic resonance spectra were obtained at 400 MHz (Dr KAN's prototype - ORSAY - Université Paris-Sud, France). ^{13}C NMR spectra were recorded at 25.2 MHz using a VARIAN CFT.20 or a VARIAN XL.100 spectrometer operating in the Fourier transform mode. The bidimensional NMR spectra were carried out with a BRUKER WM.400. Chemical shifts are reported in parts per million (δ) downfield from tetramethylsilane as the internal standard. Coupling constants (J) are given in Hertz (Hz) with the following abreviations for splitting patterns : s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet. Melting points were determined on a BUCHI melting point apparatus and are uncorrected. Column chromatography was performed on 230-400 Mesh MERCK silica gel 60. Irradiations were carried out in acetone as the solvent under argon by using 150 W HANAU lamp and a pyrex filter (λ > 290 nm). The reaction was followed by U.V. absorption of the starting material (TLC silica gel 60 PF 254 MERCK) ; spots were detected by spraying with 50% H_2SO_4, followed by heating. Acetone was purified by distillation from $KMnO_4$. The force field computations were performed on a NAS 9080 computer. The program used is based on Allinger's MM_2 version interfaced with graphic software.

- Ketone 7 (photocycloaddition of acetylene to α,β-unsaturated ketone 3)

A solution of 3 (500 mg) in purified acetone (250 ml) was purged with argon for 0.5 hours in a photoreaction vessel. Acetylene was dissolved in the acetone solution of 3 at -15°C (≃15 ml) and then irradiated with a TQ 150 HANAU high pressure Hg lamp through a pyrex filter for 15 hours at -15°C. Concentration to dryness gave 600 mg of a crude product which

was purified by flash column chromatography using a mixture of pentane/ether : 4/1 v/v as eluent to give ketone 7 (7) (310 mg), (62% yield), m.p. = 76-77°C ; IR (KBr) : 3050, 1695, 815, 790, 735 and 725 cm^{-1} ; ^1H NMR ($CDCl_3$) : δ 6.59 (d, J 2.5, 1H, H-16) ; 6.04 (q, J 2.5 and 1.5, 1H, H-15) ; 2.95 (broad s 1/2 W : 4.5 Hz, 1H, H-14) ; 0.89 (s, 9H, 2 Me-4 and Me-10). Anal. Calc. for $C_{19}H_{28}O$: C, 83.77 ; H, 10.36. Found : C, 83.70 ; H, 10.40.

- Alcohols 8a and 8b

A solution of ketone 7 (520 mg) in 20 ml of dry diethylether) was added dropwise at 0°C to a solution of CH_3MgI in 40 ml dry diethylether (prepared from Mg (1.35 mg) and CH_3I (5 ml), with stirring overnight at room temperature. Then a saturated NH_4Cl aq. (5ml) was added at 0°C to destroy the reagent. The solvent was extracted with diethylether. The combined ether extracts were washed with a saturated NaCl aq., dried and evaporated. The crude mixture (500 mg) whose constituents were separated by TLC on silica gel +4% $AgNO_3$ with pentane/ether : 6/4 v/v mixture as eluent affording 8a (13-OHα) 250 mg, 8b (13-OHβ) 180 mg.

8a m.p. = 170-172°C, Rf : 0.4 (pentane/ether 7/3). IR (CCl_4) : 3610, 3040 cm^{-1} ; ^1H NMR ($CDCl_3$) : δ 6.38 (d, J 2.5, 1H, H-16) ; 6.09 (q, J 2.5 and 1.5, 1H, H-15) ; 2.25 (broad s 1/2 W : 4 Hz, 1H, H-14) ; 1.27 (s, 3H, Me-13) and 0.85 (s, 9H, 2 Me-4 and Me-10). Mass spectra (CI/isobutane) : MH^+ (m/z 289, 22.5%) ; $[MH-H_2O]^+$ (m/z 271, 70%) (18). Anal. Calc. for $C_{20}H_{32}O$: C, 83.86 ; H, 10.56. Found : C, 83.15 ; H, 11.03.

8b m.p. = 87-89°C, Rf : 0.6 (pentane/ether 1/1). IR (CCl_4) : 3610, 3040 cm^{-1} ; ^1H NMR ($CDCl_3$) : δ 6.29 (d, J 2.5, 1H, H-16) ; 5.84 (q, J 2.5 and 1.5, 1H, H-15) ; 2.18 (broad s 1/2 W : 4 Hz, 1H, H-14) ; 1.12 (s, 3H, Me-13) and 0.84 and 0.85 (s, 9H, 2 Me-4 and Me-10). Mass spectra (CI/isobutane) : MH^+ (m/z 289, 4.3%) ; $[MH-H_2O]^+$ (m/z 271, 88%) (18). Anal. Calc. for $C_{20}H_{32}O$: C, 83.86 ; H, 10.56. Found : C, 83.07 ; H, 11.09.

- Alcohols 9a* and 9b*

8b (165 mg) was deuterated ($2H_2$ gas) in benzene (10 ml) with RhCl $(PPh_3)_3$ (cat.). The mixture solution was evaporated and chromatographed on a column of silica gel (pentane/ether : 7/3 v/v) to give 145 mg of 9b (90% yield).

9b* m.p. = 93-95°C, Rf : 0.5 (pentane/ether 7/3). IR (CCl_4) : ν_{OH} : 3580, 3400, ν_{C-D} : 2180 cm^{-1} ; ^1H NMR ($CDCl_3$) : δ 2.15 (broad d, J 9, 1H, H-16) ; 1.90 (m, 1H, H-7) ; 1.77 (d, J 9, 1H, H-15) ; 1.67 (broad s, 1H, H-14) ; 1.08 (s, 3H, Me-13) ; 0.73 and 0.84 (2s, 9H, 2 Me-4 and Me-10). Mass spectra (CI/isobutane) : MH^+ (m/z 292, 5%) ; $[MH-H_2O]^+$ (m/z 275, 85%). ^{13}C NMR ($CDCl_3$) : C-1 38.5, C-2 18.4, C-3 42.3, C-4 33.2, C-5 56.8, C-6 19.3, C-7 42.6, C-8 42.3, C-9 50.5, C-10 38.5, C-11 18.0, C-12 34.7, C-13 70.3, C-14 50.9, C-15-D 17.2, C-16-D 28.4, C-17 31.2, C-18 33.6, C-19 21.7, C-20 14.3.

The same procedure was applied to 8a to produce 9a* (yield 90%)

9a* m.p. = 135-137°C, Rf : 0.4 (pentane/ether 7/3). IR (CCl_4) : ν_{OH} : 3580, 3400, ν_{C-D} : 2180 cm^{-1} ; ^1H NMR ($CDCl_3$) : δ 1.20 (s, 3H, Me-13) ; 0.73 and 0.84 (2s, 9H, 2 Me-4 and Me-10). Mass spectra (CI/isobutane) : MH^+ (m/z 292, 5%) ; $[MH-H_2O]^+$ (m/z 275, 85%). ^{13}C NMR ($CDCl_3$) : C-1 38.4, C-2 18.3, C-3 42.2, C-4 33.2, C-5 56.8, C-6 18.9, C-7 43.3, C-8 40.8, C-9 52.2, C-10 38.5, C-11 18.1, C-12 30.7, C-13 73.0, C-14 48.1, C-15-D 16.9, C-16-D 27.0, C-17 27.7, C-18 33.5, C-19 21.5, C-20 13.8.

- Rearranged alcohols 10a* and 10b*

A solution of 9a* or 9b* (130 mg) in 14 ml of formic acid was stirred at room temperature under an inert atmosphere overnight. Evaporation of the formic acid gave 134 mg of a formate compound which was reduced by $LiAlH_4$ (160 mg) in dry ether (5 ml) at room temperature (1 hour). The mixture solution was, then, hydrolysed at 0°C with successively, water (0.2 ml), aq. NaOH (15%) (0.2 ml) and water (0.3 ml). The mixture was treated with ether. After filtration ($MgSO_4$) and evaporation of

ether, a cristalline alcohol 10a* (or a mixture of 10a* + 10b*) was obtained (115 mg, 88% yield).

- 10a* m.p. : 113-115°C ; mixture of 10a* + 10b* m.p. : 106-109°C. $(\alpha)_D$ = -6° (C=0.74). IR (CCL_4) : 3605, 3470, 2180 cm^{-1}. ^1H NMR ($CDCl_3$) : δ 2.89 (s, 1H, H-14) ; 0.92 (s, 6H, Me-17 and Me-20) ; 0.83 (s, 3H, Me-18) ; 0.78 (s, 3H, Me-19). ^2H NMR ($CHCl_3$) 10a* : δ 1.20 and 0.96 (broad 2s, 2D). 10a* + 10b* : major signals : δ 1.20 and 0.96 (broad 2s, 2D), minor signals, <5% : δ 1.11 and 1.06 (broad 2s, 2D).
^{13}C NMR of 10a* ($CDCl_3$) : C-1 39.7, C-2 18.4, C-3 41.9, C-4 33.2, C-5 55.8, C-6 19.2, C-7 39.4, C-8 45.2, C-9 46.7, C-10 37.3, C-11 19.8, C-12 31.8, C-13 40.0, C-14 83.7, C-15-D 32.0, C-16-D 29.3, C-17 24.9, C-18 33.6, C-19 21.9, C-20 15.4.

REFERENCES

1. Edwards, O.E.; Rosich, R.S., *Can. J. Chem.* **1968**, *46*, 1113.
2. Edwards, O.E.; Mootoo, B.S., *Can. J. Chem.* **1969**, *47*, 1191.
3. Wenkert, E.; Kumazawa, Z., *Chem. Com.* **1968**, 140.
4. Fourrey, J.L.; Polonsky, J.; Wenkert, E., *J. Chem. Soc.* D **1969**, 714.
5. Hall, S.F.; Oehlschlager, A.C., *J. Chem. Soc.* D **1969**, 1157.
6. Lazare, S., *These ès-Sciences Physiques, Universite Paris-Sud, Orsay*, **Avril 1977**.
7. Do Khac Manh, D.; Fetizon, M.; Flament, J.P., *Tetrahedron* **1975**, *31*, 1297.
8. Khan, M.M.T.; Martell, A.E., "Homogeneous Catalysis by Metal Complexe", *vol. 1*, Academic Press, New York and London **1974**, p. 46.
9. Osborn, J.A.; Jardine, F.H.; Young, J.F.; Wilkinson, G., *J. Chem. Soc. A* **1966**, 1711.
10. Allinger, N.L., *J. Am. Chem. Soc.* **1977**, *99*, 8127.
11. Allinger, N.L.; Yuh, Y., *Q.C.P.E.* **1980**, *12*, 395.
12. Karplus, M., *J. Am. Chem. Soc.* **1963**, *85*, 2870.
13. Karplus, M., *J. Chem. Phys.* **1959**, *30*, 11.
14. Prevost, C., Thèse es Sciences Physiques, Universite Paris-Sud, Orsay, Juin 1987.
15. Sternhell, S., *Quartely Review (London)* **1969**, *23*, 236.
16. Bax, A., "Two dimensional Nuclear Magnetic Resonance in Liquids", Delft University Press, R. Reidel Publishing Company **1982**.
17. Bernassau, J.M., Personal communication.
18. Bastard, J.; Do Khac Manh, D.; Fetizon, M.; Tabet, J.C., ; Fraisse D., *J.C.S. Perkin II* **1981**, 1591.
19. Do Khac, M.; Fetizon, M.; Lazare, S.; Grant, P.K.; Nicholls, M.J.; Liau, M.T.L.; Francis, M.J.; Poisson, J.; Bernassau, J.M.; Roque, N.F.; Wovkulich, P.M.; Wenkert, E., *Tetrahedron* **1981**, *37*, 2371-2374.