Tetrahedron Letters No. 14, pp 1155 - 1158, 1973. Pergamon Press. Printed in Great Britain.

STEREOCHEMICAL FACTORS IN A CATIONIC CYCLIZATION REACTION. THE SYNTHESIS OF 10-EPI-β-VETIVONE

Patrick M. McCurry, Jr.*, Rajendra K. Singh

and in part Steven Link

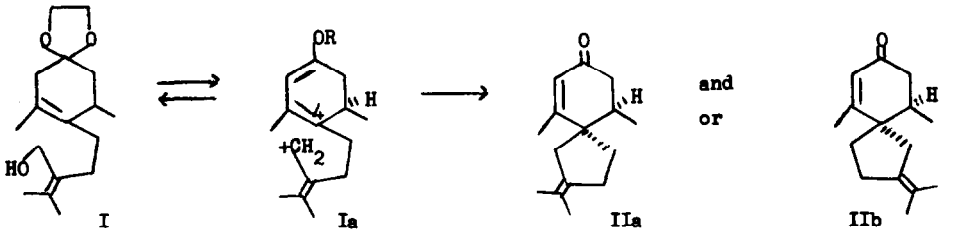
Department of Chemistry, Carnegie-Mellon University

Pittsburgh, Pennsylvania 15213 U.S.A.

(Received in USA 16 October 1972; received in UK for publication 22 February 1973)

The biogenic-like cyclization of unsaturated allylic alcohols is becoming an increasingly important route to natural products[1,2]. As a result of our continuing interest in the stereochemistry of addition reactions in substituted cyclohexene derivatives[3,4] and in order to gain insight into the steric requirements for such processes, we chose to examine the intramolecular alkylation of compound I.

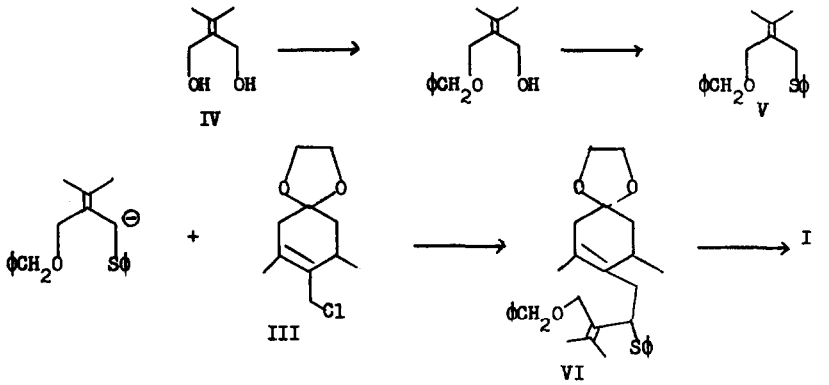
This particular reaction was selected in order to address two questions: (i) could the 1-alkoxybutadiene moiety in Ia exhibit enough nucleophilicity at the 4-position to parallel the Winstein Ar 1,5[5] cyclization, thereby favoring spiro[5.4]decenone over the usual preference for decalin formation in cationic cyclization reactions: (ii) if spiro alkylation occurs, what would



I Ia IIa IIb

be its stereochemical pathway? One of the possible diastereomers, IIa, is ± β-vetivone[6].

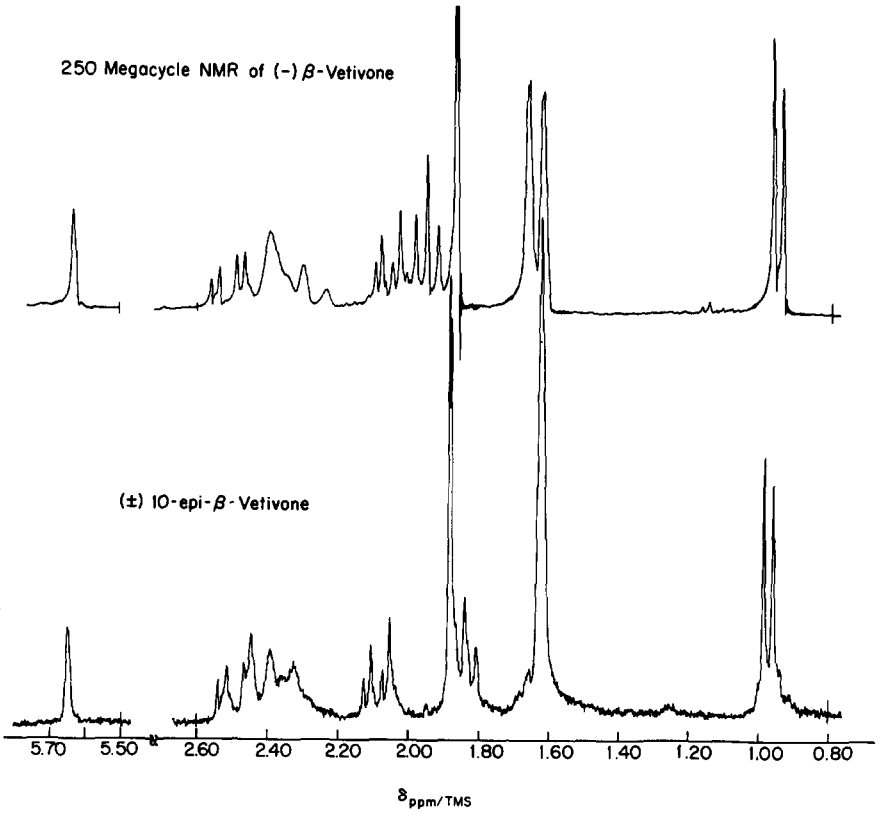
The basic skeleton of the desired substrate I was assembled by a Biellman coupling of the known[4] allylic chloride III and the thioether V. The known diol IV[8] was monoalkylated with benzyl chloride using sodium hydride in DMF/benzene. The hydroxy ether so produced was transformed via its derived (MeLi, HMPA, ether, TsCl)[9] chloride, into the thioether V by the action of lithium thiophenoxide[10].



Compound V (bp 160° at 0.1 mm), obtained in 50% yield from IV, exhibited the following spectral characteristics: IR (film), 6.30, 9.23, 9.39, 9.79, 13.59, and 14.42 μ; NMR (CCl_4) δ = 1.58 and 1.67, $>C=C(\underline{CH_3})_2$; δ = 3.70, $-\underline{CH_2}-S$; δ = 4.15, $-\underline{CH_2}OCH_2\varphi$; δ = 4.43, $-O\underline{CH_2}\varphi$; δ = 7.1-7.5, 10 H, aromatic; High Resolution Mass Spec., calc. m/e = 298.1391, measured m/e = 298.1378.

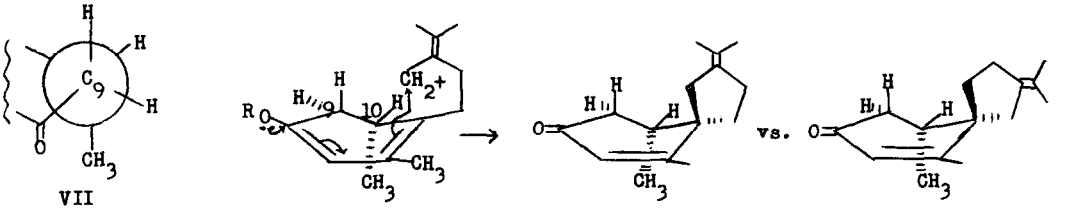
Normal workup after coupling allowed isolation of highly air-sensitive VI, which, without further purification, was reduced with excess lithium in anhydrous ethyl amine at -78°, under Argon[10]. This resulted in concurrent desulfurization and debenzylation[11] producing the desired substrate I, isolated in 35% yield by chromatography on Florisil (benzene-chloroform, 7:3). This compound exhibited the following spectroscopic properties: IR (film) 2.78, 6.03, 7.95, 9.30, 9.81 and 12.41 μ; NMR (CCl_4) δ = 1.09, doub., J = 7.0 Hz, $>CH\underline{CH_3}$; δ = 1.64 (3H) and 1.76 (6H), $>C=<\underline{CH_3}$; δ = 3.93, sing., $-O-\underline{CH_2}\underline{CH_2}-O-$; δ = 4.03, broad sing., $>C=<\underline{CH_2}OH$. High Resolution Mass Spec., calc. m/e = 280.2038, measured m/e = 280.2076.

Compound I (100 mg) was dissolved in 4.5 ml of aqueous formic acid (70% HCO_2H) and the solution maintained at room temperature for six hrs. Chromatography on silica gel afforded 47 mg (60%) of a mixture[12] containing 70% of a bicyclic ketone which was purified by preparative GLC (220°C, 10'20% Craig on 60/80 Chrom W, retention time, 23.6 min; retention time of natural IIa[13], 22.6 min.). This substance was obtained in crystalline form (mp 53-54.5°; reported[6] for ± IIa, 43.5-46°; High Resolution Mass Spec., calc. m/e for IIa = 218.1671, measured m/e = 218.1668). Comparison of the IR, 60 MHz NMR, and Mass Spectra of IIa[13] and our cyclization product revealed differences whose subtleties did not allow definitive differentiation. However, examination of the 250 MHz NMR spectra (CCl_4) of the two compounds, shown in the accom-



panying figure, clearly establishes their non-identity, thereby allowing for the assignment of structure IIb to our spiro-alkylated product[15].

The differences in the NMR of spectra of IIa and IIb arise from the chemical shifts of protons of the cyclopentane ring (as shown by double resonance experiments). The similarity of the vicinal coupling constants of the C_9 methylene group (multiplets at ~ 2.1 and 2.5 ppm) for IIa and IIb prompts us to assign conformation VII to the molecules.

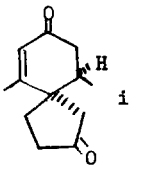


The stereoselectivity of this novel spiro-alkylation reaction is probably a result of "axial" alkylation in which the allylic cation approaches the face of the molecule opposite the "pseudo axial" C_{10} methyl group[14], i.e., I'a. We plan to further investigate this potentially useful method in greater detail.

Acknowledgment.- Financial support from Carnegie-Mellon University and the Petroleum Research Fund administered by the American Chemical Society is gratefully acknowledged. We wish to thank all persons connected with the NIH Facility for Biomedical Studies (Grant #RR00292) for the use of the 250 Mc NMR machine, especially Dr. P. Balaram for carrying out pertinent double resonance experiments.

REFERENCES

1. See W. S. Johnson et al., J. Am. Chem. Soc., 93, 4332 (1971) for the synthesis of progesterone.
2. See P. Naegeli and R. Kaiser, Tetrahedron Letters, 2013 (1972) for the synthesis of β-acoratriene.
3. P. M. McCurry, Jr., ibid., 1841 (1971).
4. P. M. McCurry, Jr., ibid., 1845 (1971).
5. A. Ogiso et al., Chem. Pharm. Bull., 18, 1283 (1970).
6. J. A. Marshall and P. C. Johnson, J. Org. Chem., 35, 192 (1970).
7. J. F. Biellman and J. B. Ducep, Tetrahedron Letters, 3707 (1969).
8. J. A. Marshall, H. Faubl and T. M. Warne, Jr., Chem. Comm., 753 (1967).
9. G. Stork, P. A. Grieco and M. Gregson, Tetrahedron Letters, 1393 (1969).
10. E. E. van Tamelen, P. M. McCurry and U. Huber, Proc. Nat. Acad. Sci. U.S.A., 68, 1294 (1971).
11. See reference 10 for a similar application in the Synthesis of Cecropia Juvenile Hormone.
12. The major by-product is tentatively assigned the structure 4,9-dimethyl-7-isopropylidine-$\Delta^{4,10}$-2-octalone on the basis of its IR and 60 Mc NMR spectra, and we conclude that spiro[5.4]decenone is the preferred product of cyclization in this particular reaction.
13. A general sample of (-)β-vetivone was kindly supplied by Professor J. A. Marshall.
14. This is probably due to i) the lack of 1,3 axial-axial interactions and ii) the minimization of Johnson-Mahlotra allylic 1,3 strain.
15. As a chemical proof of structure, we have selectively ozonized IIb and obtained the known spiro-enedine i, the structure of which has been rigorously established[4].



i