CHEMISTRY LETTERS, pp. 1153-1156, 1993.

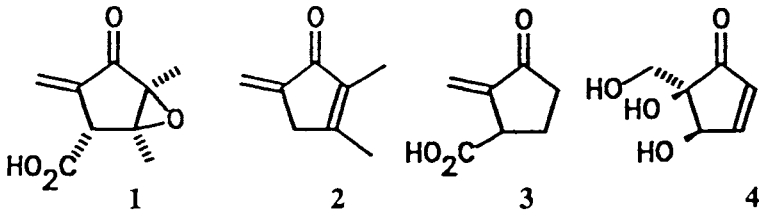
Stereospecific Epoxidation of 4-Hydroxycyclopent-2-enones

Maurizio D'AURIA* and Giovanni PIANCATELLI†

Dipartimento di Chimica, Università della Basilicata, Via N. Sauro 85, 85100 Potenza, Italy
†Centro CNR di Studio per la Chimica delle Sostanze Organiche Naturali, Dipartimento di Chimica, Università di Roma "La Sapienza", P.le A. Moro 2, 00185 Roma, Italy

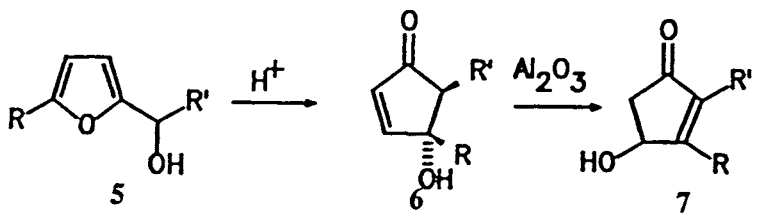
The treatment of 4,5-dialkyl-4-hydroxy-6-cyclopent-2-en-1-ones with H_2O_2 and KOH gave in high yields 2,3-epoxy-2,3-dialkyl-4-hydroxycyclopentanones. Furthermore, only one stereoisomer, characterized by *trans* relationship between the hydroxy group and the epoxide was obtained. This behaviour can be explained considering that epoxidation occurs during a base catalyzed transposition of the starting cyclopentenone.

Methylenomycin A (**1**) and B (**2**),[1] Sarkomycin (**3**),[2] and Pentenomycin (**4**)[3] are the most representative members of cyclopentanoid antibiotics; these compounds show a methylene group in α-position to a carbonyl group as main structural feature. Cyclopentanoid antibiotics have attracted considerable attention of synthetic organic chemists with regard to their interesting biological properties: for example, Sarkomycin (**3**) is an active in vivo antitumor agent.[4]



1 **2** **3** **4**

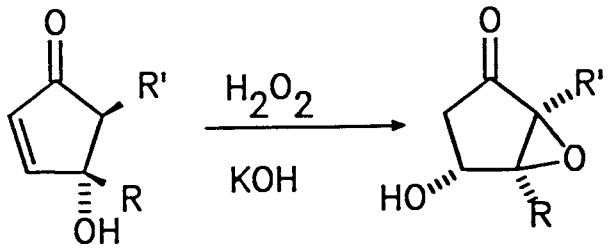
Some years ago, our group described a simple and useful procedure for the synthesis of cyclopentenones **6** and **7** from furyl carbinols **5** (Scheme 1).[5] Furyl carbinols **5** were turned into the corresponding cyclopentanone **6** through a molecular rearrangement catalyzed by acid or zinc chloride. The reaction proceeds in a stereospecific manner yielding only one enantiomeric pair, characterized by *trans* relationship of the OH group and the side chain. Then, **6** can be directly converted into **7** via isomerization on alumina surface. The synthetic route outlined in scheme 1 could furnish a useful starting material for the synthesis of modified derivatives of Methylenomycin A bearing a hydroxyl group and this was the object of our work.



5 **6** **7**

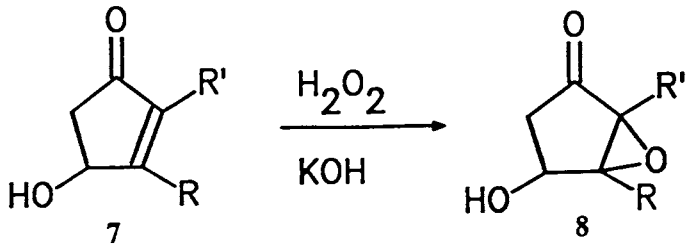
Scheme 1.

In order to the test this possibility we have studied the epoxidation of cyclopentenone ring. Unexpectedly, the epoxidation (hydrogen peroxide and 1 M KOH) of cyclopentenones **6** gave compounds **8** in high yields (Table 1). In a typical experiment 1 g of cyclopentenone was dissolved in MeOH (60 ml). At room temperature 30% H_2O_2 (7.2 ml) was added, and then, dropwise 1 M KOH (3.3 ml). After 30 min, the mixture was neutralized by 2 M HCl. The mixture was then poured in brine and extracted many times with Et_2O. The neutral combined organic extracts were dried over Na_2SO_4 and the solvent removed under reduced pressure to give pure **8**.



6 **8**

The reaction was stereospecific (only one stereoisomer was observed). In fact, ^{1}H NMR spectrum of **8a** showed a doublet at δ 2.60 (J = 7 Hz) and a doublet at δ 2.55 (J = 7 Hz) for the methylene group and a doublet of doublet at δ 4.33 ($J_1 = J_2$ = 7 hz) for the proton at C-4. If the epoxidation was carried out on the compound 7 (R' = C_6H_5, R = CH_3) we obtained, on the contrary, a mixture of stereoisomeric compounds **8** (overall yield 71%). In this case, the ^{1}H NMR spectra of each isomeric product confirmed our interpretation: in fact, one product showed ^{1}H NMR spectrum consistent with that described above; the other compound showed ^{1}H NMR spectrum completely different: the methylene group appeared to be a doublet at δ 2.16 with J = 18 Hz and a



7 **8**

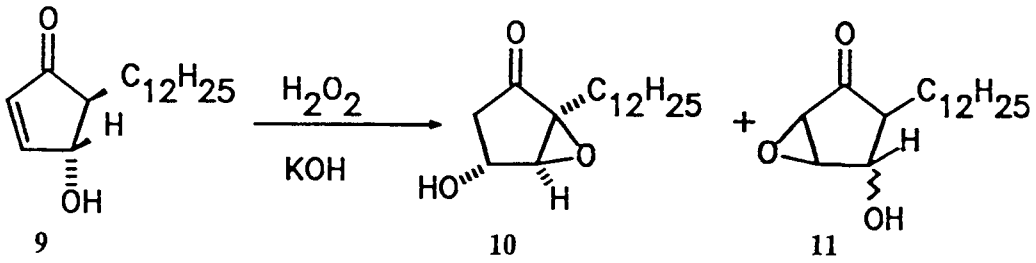
doublet of doublet at δ 2.93 with J_1 = 6 and J_2 = 18 Hz, while the proton at C-4 was a doublet at δ 4.53 with J = 6 Hz. The *trans*-relationship of OH group at C-4 and the oxirane ring was determined via ^{1}H NMR spectrum of **8b** where the methyl group at C-3 was replaced by a hydrogen: in this case the proton at C-3 appeared to be a doublet at δ 4.00 with J = 2 Hz consistent with *trans*-relationship of proton at C-3 and one at C-4.[6)]

Table 1. Epoxidation of 4-hydroxycyclopentenones

Starting compound	R'	R	Product	Yields/% a)
6a	C_6H_5	CH_3	**8a**	98
6b	C_6H_5	H	**8b**	40
6c	p-$CH_3C_6H_4$	CH_3	**8c**	96
6d	p-$CH_3OC_6H_4$	CH_3	**8d**	100

a) All the yields refer to isolated pure products.

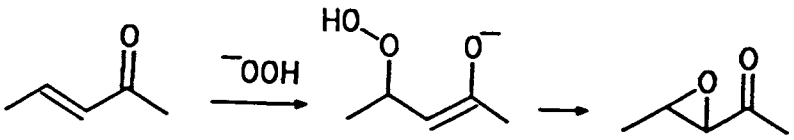
All the data reported in table 1 demonstrate that the reaction **6** → **8** needs the presence of both aryl groups and the methyl group. In fact, several attempts to obtain the conversion **6** → **8** were unsuccesful when there is an alkyl side chain C-5 compound **9**, treated with H_2O_2 and KOH, furnished a 3:1 mixture of two products **10** and **11** in the overall yield of 55%.



9 **10** **11**

Therefore, the described procedure furnishes an useful synthetic method to obtain modified cyclopentanoid antibiotics with an aryl group and an OH group: in fact, compound **8** can be easily transformed in α-methylene derivatives via a known procedure:[7] treatment of **8** with LDA and formaldehyde followed by elimination reaction carried out with dimethylformamide dineopentyl acetal can furnish the target compounds.

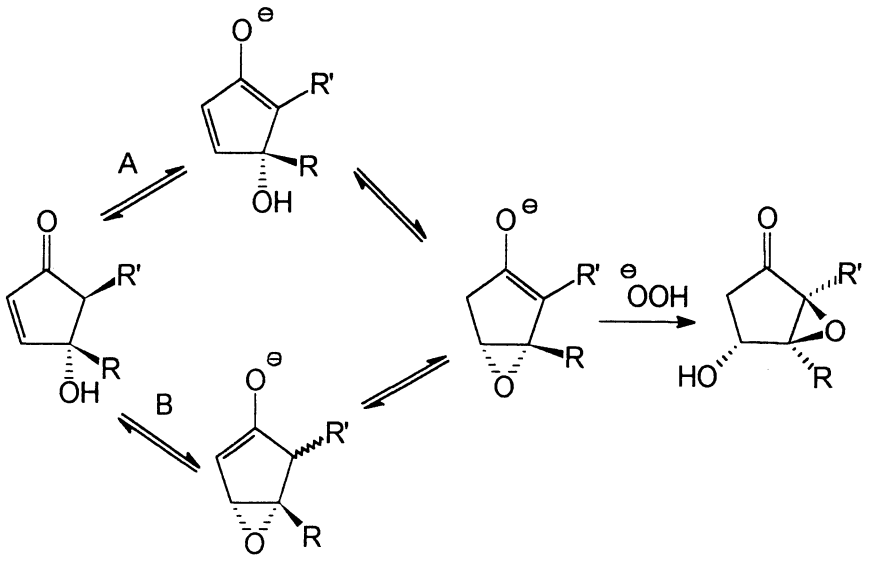
The action of hydrogen peroxide in alkaline medium on α,β-unsaturated carbonyl compounds is well



known and this mechanism is able to explain the reactions **7** → **8** and **9** → **11**; however it can not account of the product obtained in the other cases.

In this case we can propose a mechanism reported in the following scheme. Our hypothesis involves the formation of an epoxide intermediate that can be trapped by a nucleoplile ⁻OOH to give the product. Two possibilities can be formulated in order to explain the formation of this intermediate. In the path A, enolization and transposition gave the intermediate, while, in path B, the epoxide was obtained via internal addition of hydroxy group isomerization.

The path A is very similar to the proposed mechanism for the reaction **6** →**7**,[5] and our experimental results could show the presence of an intermediate never proposed before.[8]



References

1) T. Haneishi, N. Kitahara, Y. Takiguchi, M. Arai, and S. Sugawara, *J. Antibiot.*, **27**, 386 (1974).

2) H. Umezawa, T. Takeuchi, K. Nitta, T. Yamamoto, and S. Yamaoka, *J. Antibiot.A*, **6**, 101 (1953); H. Umezawa, T. Takeuchi, K. Nitta, Y. Okami, T. Yamamoto, and S. Yamaoka, *ibid.*, **6**, 153 (1953).

3) K. Umino, T. Furumai, N. Matsuzawa, Y. Awataguchi, Y. Ito, and T. Okuda, *J. Antibiot.*, **26**, 506 (1973); K. Hatano, T. Hasegawa, M. Izawa, M. Asai, and H. Iwasaki, Japan Kokai 7570597 (1975), *Chem. Abstr.*, **84**, 3287n (1976).

4) U. Hornemann and D.A. Hopwood, Antibiotics, ed by J. W. Corcoran, Springer-Verlag, Berlin, (1981), Vol. 4; A. Terahara, T. Haneishi, and M. Arai, *Heterocycles*, **13**, 353 (1979); T. Haneishi, A. Terahara, K. Hamano, and M. Arai, *J. Antibiot.*, **27**, 3555 (1976).

5) G. Piancatelli, *Heterocycles*, **19**, 1735 (1982) and references cited therein.

6) K. Ogura, M. Yamashita, and G. Tsuchihashi, *Tetrahedron Lett.*, **1976**, 759; G. Piancatelli, A. Scettri, and S. Barbadoro, *ibid.*, **1976**, 3555.

7) J. Jernow, W. Tautz, P. Rosen, and J. F. Blount, *J. Org. Chem.*, **44**, 4210 (1979).

8) L. Novak, P. Kolonits, C. Szantay, J. Aszodi, and M. Kajtar, *Tetrahedron*, **38**, 153 (1982).

(Received November 17, 1992)