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Two Distinct Conformational Isomers of the 16-Membered Epoxyenone, the Key Synthetic Intermediate of Maridonolides. Conformational Analysis and Completely Stereoselective Reduction of the C9 Carbonyl Group[1)]

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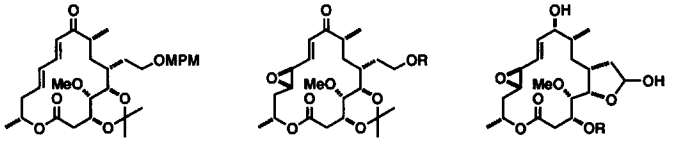
Summary The key synthetic intermediate of maridonolides (**2**) has two easily detectable conformational isomers in solution. The conformational analysis of the 16-membered epoxyenone ring and the effect of conformation on reactivity in the reduction of the C9 carbonyl group are described.

Recently, we have reported the total synthesis of aglycons of the typical 16-membered macrolide antibiotics via the dienone derivative (**1**) as a common intermediate, applying stereoselective epoxidation and reduction on macrolactone rings by virtue of a conformational analysis of **1**[2)] based on NMR measurements and MMP2-CONFLEX2[3)] calculations. In these studies, we found that interestingly the epoxyenone derivative (**2**), the key synthetic intermediate of maridonolides,[4)] exists as a mixture of two interconvertible conformational isomers easily detectable by TLC analysis and ^{1}H NMR spectroscopy. Usually macrolactones in solution have several major conformations, which can be detected only by NOE measurements because of their rapid interconversion. So far as we know, this is the first case that the conformers of such a macrolactone like **2** can be easily detected by the usual analyses as described.

We report here the conformational analysis of the appreciably stable isomers of **2**, and the relation between their conformation and reactivity in the reduction of the C9 carbonyl group.



1

2 : R = MPM
3 : R = TBDPS

Maridonolide I : R = COEt
Maridonolide II : R = COMe

Fig. 1

On a silica gel TLC [EtOAc-hexane (1 : 1)] **2** was detected as two separated spots corresponding to the conformational isomers A and B, whose ^{1}H NMR spectra differ from one another [A : B = 2 : 3], nevertheless, we failed to separate A and B by usual chromatographic techniques. ^{1}H NMR measurements[5)] and two dimensional TLC analyses[6)] at different temperature made it clear that an interconversion occurs between these two conformers at room temperature and stops below -35°C. Since the conformational control is sometimes crucial for the introduction of new chiral centers into macrocyclic systems,[2)] we next tried to determine both conformations by NMR studies.[7)]

Table. 1 Vicinal coupling constants (J;Hz) of conformers A and B of 3

J_{H-H}	A	B
2-3	4.0,10.0	3.0,4.5
3-4	1.0	1.5
4-5	0	0
5-6	6.5	6.5
6-7	2.0,8.5	3.0,4.0
7-8	6.5,7.0	2.0,10.0
10-11	15.5	15.0
11-12	6.0	3.0
12-13	2.0	0
13-14	6.0,6.5	0,9.5
14-15	3.0,9.5	2.0,11.5

^{1}HNOESY A : H7-H10, H4-H10, H10-H13, H11-H12, H13-H14
B : H8-H10, H10-H13, H11-H12, H13-H14

On the basis of J values (Table. 1) and NOESY data of the siloxy derivative (**3**)[8] by reference to the reported conformational analysis of **1**,[2b] both conformations of A and B are estimated as shown in Fig. 2.[9] The two isomers are the rotamers of the epoxyenone and C3,5 acetonide ring. A has 9,10-*s-cis*, 11,12-*s-trans* conformation of the epoxyenone lying nearly in the plane of the 16-membered ring, while the epoxyenone of B is 9,10-*s-cis*, 11,12-*s-cis* form and perpendicular to the plane of the 16-membered ring. Situation of the 6-membered C3,5 acetonide rings is also quite different between A and B. The chair form ring of A is situated in the plane of the 16-membered ring like the epoxyenone, and that of B has vertical location.

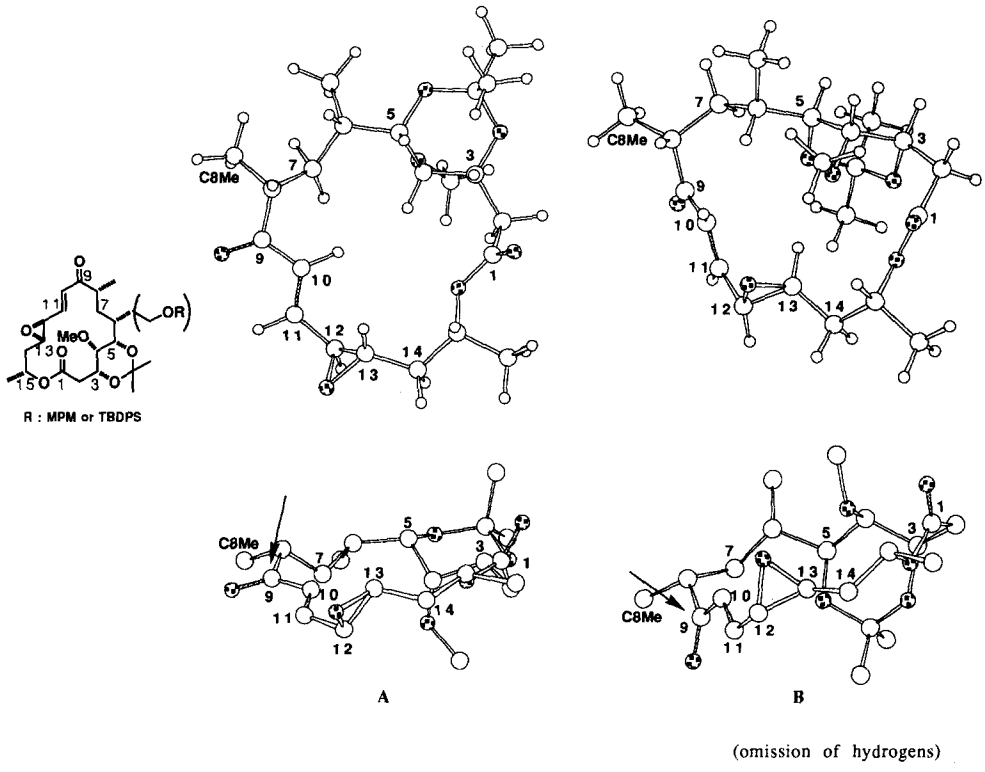


Fig. 2 Estimated conformations of A and B

Fortunately, B crystallized in MeOH and the conformation in the solid state was determined by X-ray diffraction (Fig. 3). From comparing Fig. 2 with Fig. 3, it is obvious that the solution

conformation estimated from the NMR data is almost identical with the crystal structure. Since the epoxy ring is fixed to the outside of the 16-membered ring to avoid the transannular stereoelectronic repulsion, the conformational change of **2** and **3** needs somewhat forced rotation of the acetonide ring as well as the epoxyenone, so the interconversion between A and B becomes to be slow.[10]

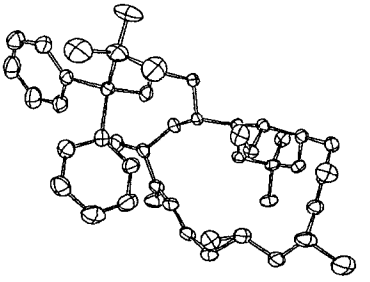
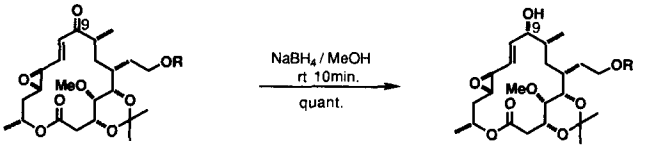


Fig. 3 ORTEP drawing of the crystal structure

The above conformational analysis also suggested that A and B played an important role in stereoselectivity of the reduction of the C9 carbonyl group, the key reaction in the synthesis of maridonolides. In A, to avoid steric hinderance by the C7 metylene group, the hydride would attack from upper side (arrow) to give the desired 9*R* alcohol, and also expected to afford the 9*R* alcohol by hydride's attack from outside of the macrolactone ring in B. In short, both A and B protected their C3,5 diol with an acetonide have advantageous conformations in the stereoselective reduction of the C9 carbonyl group. Actually, when **2** and **3** were treated with $NaBH_4$ in MeOH at room temperature, the reduction proceeded smoothly and the expected 9*R* alcohol derivatives (**4**, **5**) were obtained as a single product in quantitative yield (Scheme. 1).



2 : R=MPM
3 : R=TBDPS

4 : R=MPM
5 : R=TBDPS

Scheme. 1

As can be seen from Fig. 2, the above reduction was presumed to proceed more faster from A than B because the C9 carbonyl group of B is sterically hindered by the C8 methyl group. The following examination proved this assumption. The NMR measurement of the mixture after carefull treatment of **3** with 0.5 equivalent of $NaBH_4$ in CD_3OD at -40°C, at which the conformational interconversion stoped as described before, showed that the stereoselective reduction of A only occured and B remained unchanged.

Although the detailed conformation of A is not clear yet, the above successful results show our conformational analysis to be reliable.

Finally, the 9*R* alcohol derivative (**4**) was converted to maridonolides in several steps.[2b)]

References and Notes

1) Chiral synthesis of polyketide derived natural products. 36. For part 35 see : N. Nakajima, T. Matsushima, O. Yonemitsu, H. Goto, and E. Osawa, *Chem. Pharm. Bull.*, in press.

2) a) N. Nakajima, K. Uoto, O. Yonemitsu, *Heterocycles.*, **31**, 5 (1990) ; b) N. Nakajima, T. Matsushima, O. Yonemitsu, H. Goto, and E. Osawa, *J. Org. Chem.*, **55**, 1129 (1990) ; c) N. Nakajima, K. Uoto, and O. Yonemitsu, *Chem. Pharm. Bull.*, **39**, 64 (1991).

3) H. Goto, and E. Osawa, *J. Am. Chem. Soc.*, **111**, 8950 (1989).

4) Maridomycins : M. Muroi, M. Izawa, M. Asai, T. Kishi, K. Mizuno, *J. Antibiot.*, **26**, 199 (1973).

5) **2** gave broad unresolved peaks at 100°C (in DMSO-d_6).

6) At the first development at room temperature, **2** was detected as two spots. On standing for 15 minutes at room temperature after the first development, the interconversion between two conformers occured, and each spot appeared as two spots at the second development. On the other hand, at -35°C, the initial two spots remained unchanged at the second development after standing for 1 week.

7) Since reliable MM calculation for epoxyenones is still impossible, the NMR studies are very important. For the conformational studies of macrocyclic systems in solution, see : a) A. B. Smith III, J. L. Wood, C. J. Rizzo, G. T. Furst, P. J. Carroll, J. Donhue, and S. Omura, *J. Org. Chem.*, **55**, 1133 (1990) ; b) T. H. Keller, and L. Weiler, *J. Am. Chem. Soc.*, **112**, 450 (1990) ; c) *idem*, *Tetrahedron Lett.*, **31**, 6307 (1990) ; d) I. Paterson, and D. J. Rawson, *Tetrahedron Lett.*, **30**, 7463 (1989) ; e) T. H. Keller, E. G. Neeland, S. Rettig, J. Trotter, and L. Weiler, *J. Am. Chem. Soc.*, **110**, 7858 (1988) ; f) E. Neeland, J. P. Ounsworth, R. J. Sims, and L. Weiler, *Tetrahedron Lett.*, **28**, 35 (1987) ; g) J. R. Everrett, and J. W. Tyler, *J. Chem. Soc. Perkin Trans.* 2, 1659 (1987) ; h) E. Vedejs, W. H. Dent, III, D. M. Gapinski, C. K. McClure, *J. Am. Chem.Soc.*, **109**, 5437 (1987) ; i) S. K. Arora, and A. M. Kook, *J. Org. Chem.*, **52**, 1530 (1987) ; j) L. Cellai, S. Cerrini, A. Serge, M. Brufani, W. Fedli, and A. Vaciago, *J. Org. Chem.*, **47**, 2652 (1982) ; k) W. C. Still, and I. Galynker, *Tetrahedron*, **37**, 3981 (1981).

8) **3** was easily obtained from the degradation product of josamycin (leucomycin A_3) via several conventional reactions including epoxidation, and gave more clearly resolved ^1H NMR peaks. For the degradation of josamycin, see : K. C. Nicolaou, S. P. Seitz, M. R. Pavia, *J. Am. Chem. Soc.*, **103**, 1222, 1224 (1981).

9) The dihedral angles were estimated by reference to the Karplus equation, except for the angle of the olefin proton (H11) and epoxy ring proton (H12), which was determined in accordance with the following report. F. Jansen, and C. S. Foote, *J. Am. Chem. Soc.*, **109**, 6376 (1987).

10) **1** has several conformers in solution mainly caused by easy rotation of the dienone without unfavorable transannular interaction, and their interconversion occurs rapidly and can be detected only by NOE measurements. For the details, see ref. 2b.

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