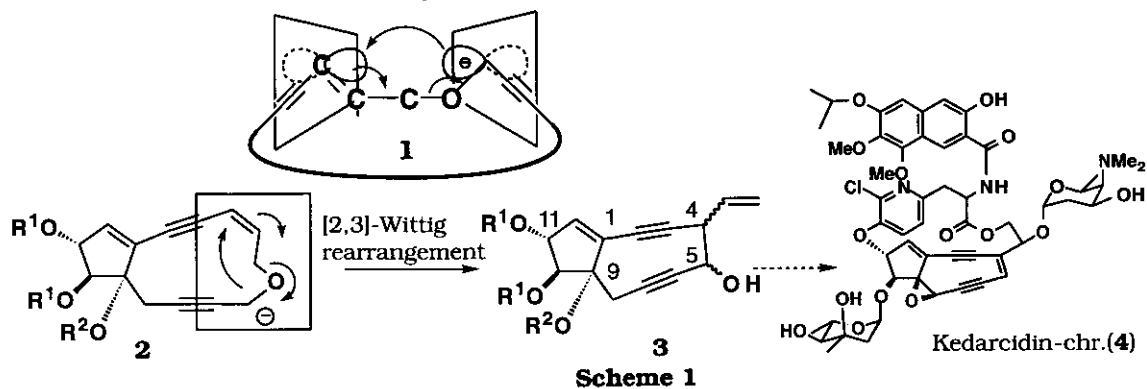


STEREOCHEMICAL ANALYSIS OF TRANSANNULAR [2,3]-WITTIG
REARRANGEMENT OF 12-MEMBERED CYCLIC ETHER BASED ON
RIGID MM2 TRANSITION STATE MODEL

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Abstract - Transannular [2,3]-Wittig rearrangement of the 12-membered cyclic ether, a key reaction to construct the 9-membered masked enediyne of kedarcidin chromophore, and a discussion of its diastereoselectivity based on a rigid MM2 transition state model are described.

Stereochemical controls with predictable capabilities are essential in natural product syntheses. In macrocyclic system, the π -orbitals of olefins are oriented in the plane of the ring to minimize transannular nonbonded repulsions¹ (see **1** in Scheme 1). Therefore the inter- and intramolecular reactions should proceed exclusively from one side of the olefins.² Although macrocycles are capable of being in a number of stable conformations, only a few of these conformations are appreciably populated at normal temperature. Thus, if molecular mechanics calculation³ and/or transition state modeling⁴ could provide the information about conformational properties of the macrocycles, the macrocyclic reactions should follow a predictable course in organic synthesis. Transannular [2,3]-Wittig rearrangement⁵ of the n -membered ether (**1**) offers a powerful method for constructing the $(n-3)$ -membered macrocycle with a high reactivity and stereoselectivity. In this paper, we describe transannular [2,3]-Wittig rearrangement of the 12-membered ether (**2**) to construct the 9-membered masked enediyne (**3**) which would be a potential synthetic key intermediate for the kedarcidin chromophore (**4**)^{6,7} (Scheme 1).



The relative stereochemistries among C(4)-vinyl and C(5), C(9), C(10), C(11)-hydroxyl groups in diyne (**3**) are essential in designing a DNA cleaving molecule. The "trans" relative stereochemistry between C(4)-

hydrogen and C(5)-alcohol in the rearrangement product (3) would facilitate β -elimination of the C(5)-alcohol to generate the highly reactive enediyne. The hydroxyl groups at C(10) and C(11) could be used to attach the chloroazatyrosyl naphthoamide and sugar moieties in kedarcidin-chr (4). It would be an important advance if asymmetric induction in the [2,3]-Wittig rearrangement of **2** could be estimated quantitatively. Thus, a conformational analysis (MM2 calculation) and a transition state modeling (rigid MM2 transition state model⁸) of **2** were examined. At first, conformational analysis of the 12-membered ether (**2a**; $R^1 = R^2 = \text{methyl}$) at a ground state was conducted to examine whether the transannular [2,3]-Wittig rearrangement of **2a** would be likely to proceed or not. All possible conformations of **2a** were generated by using Monte Carlo (MC) method⁹ and the resulting initial structures were energy-minimized by using MM2* force field in MacroModel.¹⁰ Thirty two unique lower energy conformers were found within 10 kJ mol⁻¹ of the global minimum. Figure 1 depicted the two lower energy conformers (A) and (B). These structures showed that both conformers (A) and (B) have a short distance ($\sim 3.5 \text{ \AA}$) between the two reactive sites with a good overlap of the π -orbital of olefin. Assuming an early reactant-like transition state for this rearrangement, these calculations and a Boltzmann distribution based on the energy differences among 32 conformers¹¹ predict that the reaction of **2a** should proceed smoothly to give **5a** and **6a**, having "cis/cis" and "cis/trans" relative stereochemistries among C(4)-vinyl, C(5)-OH and C(9)-OMe, respectively, in a ratio of 77 : 23.

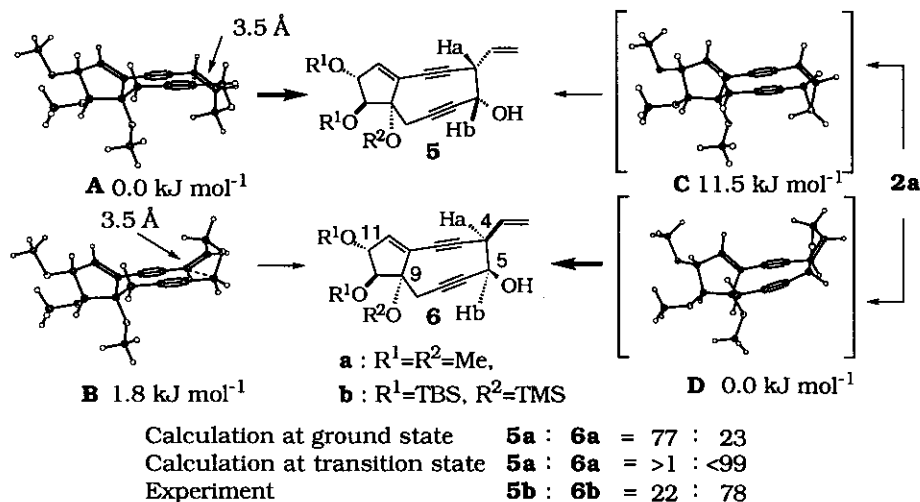


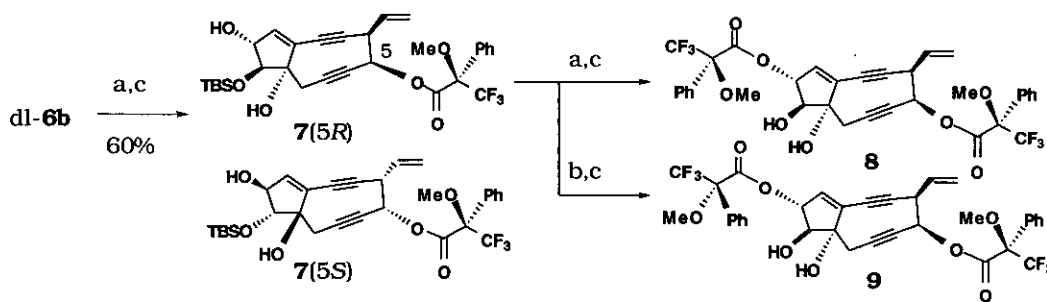
Figure 1

Moreover, to examine the stereoselectivity in the [2,3]-Wittig rearrangement of **2a** ($R^1 = R^2 = \text{methyl}$), MM2 transition state models (rigid transition state model¹²) were constructed. The geometry of a reactive site in **2a**, shown with open box (see Scheme 1), was fixed to the Houk's transition structure of [2,3]-Wittig rearrangement¹³ obtained by 3-21G *ab initio* calculation, and rest of the molecule was constructed by MC method. Resulting initial structures were energy minimized by the MM2* force field and two optimized transition state structures (C) and (D) were found. Results of the calculation, considering Boltzmann distribution, suggest that the transannular [2,3]-Wittig reaction of **2a** should lead to **5a** and **6a** in a ratio of <1 : >99. Thus, both calculations at a ground state and transition state predict that [2,3]-Wittig rearrangement of the 13-membered ether (**2a**) should lead to a "cis" relative stereochemistry between the

newly formed vinyl and hydroxyl groups in **5a** and **6a**. However, the major product predicted by MM2 calculations at a ground state is **5a** having a "cis" (C(5)-OH / C(9)-OMe)-relative stereochemistry and the dominant product proposed by a rigid MM2 transition state model is **6a** having a "trans" (C(5)-OH / C(9)-OMe)-relative stereochemistry.

[2,3]-Wittig rearrangement of **2b**¹⁴ ($R^1 = t$ -butyldimethylsilyl (TBS), $R^2 =$ trimethylsilyl (TMS)) was carried out as follows (Figure 1). Metallation of **2b** with t -butyllithium at -110 °C in THF over 20 min, followed by stirring of the resulting reaction mixture at -100 °C for another 5 min. gave a 22 : 78 mixture of the rearrangement products¹⁵ (**5b**) and (**6b**) in 65% combined yield.

The relative stereochemistry of the rearrangement products was determined as follows. The *cis* relative stereochemistry between (C(4)-vinyl / C(5)-OH) in **5b** and **6b** was confirmed by nOe experiments (19%; Ha, Hb; see Figure 1). The *trans* relative stereochemistry (C(5)-OH / C(9)-OTMS) in the major product(**6b**) was established by using a modified Mosher's method¹⁶ (Scheme 2). Treatment of the *dl*-**6b** with (*R*)- α -methoxy- α -(trifluoromethyl)phenylacetyl chloride (MTPA chloride), followed by selective removal of the C(11)-TBS group (40% aq. HF at 25 °C) gave a diastereomixtures of **7(5R)** and **7(5S)** in 60% overall yield. After separation of these isomers, the absolute configuration at C(5) in **7** was determined by the $\Delta\delta_H$ values for **7(5R)** and **7(5S)** (Figure 2). Treatment of the isolated **7(5R)** with (*R*)- and (*S*)-MTPA chloride and removal of the C(10)-TBS group with acid gave the di-MTPA esters (**8**) and (**9**), respectively. Based on the measured $\Delta\delta_H$ values for **8** and **9** (Figure 3), the absolute configuration at C(11) was determined as *R*-form. Since both the *cis* relative stereochemistry (C(4)-vinyl / C(5)-OH) in the rearrangement products (**5b**) and (**6b**) and the all *trans* relative stereochemistry (C(9), C(10) and C(11)-trisilyloxy groups) in the starting ether (**2b**) have been established, the relative stereochemistry between the C(5)-OH and C(9)-OMe in the rearrangement product (**6b**) should be a *trans* stereochemistry. Thus the relative stereochemistries among C(4), C(5) and C(9) in the major product (**6b**) agree with that predicted by a rigid MM2 transition state model. These results demonstrate that a rigid MM2 transition state model is applicable to the macrocyclic system and useful in designing synthetic intermediates.



Scheme 2 a : (*R*)-MTPACl, b : (*S*)-MTPACl, c : HF aq./CH₃CN

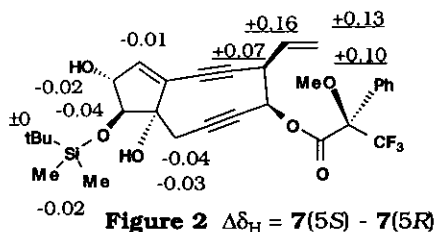


Figure 2 $\Delta\delta_H = 7(5S) - 7(5R)$

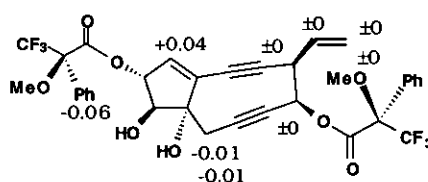


Figure 3 $\Delta\delta_H = 9 - 8$

ACKNOWLEDGMENT

This work was supported by Grant-in-Aids for Scientific Research on Priority Area No. 06240104 from the Ministry of Education, Science and Culture, Japan. We are grateful to Professor W. C. Still for providing a copy of MacroModel (ver. 4.5).

REFERENCES AND NOTES

- 1 a) W. C. Still and I. Galynker, *Tetrahedron*, 1981, **37**, 3981. b) W. C. Still, L. J. MacPherson, T. Harada, J. F. Callahan, and A. L. Rheingold, *Tetrahedron*, 1984, **40**, 2275.
- 2 Review: T. Takahashi, In *Studies in Natural Products Chemistry*, Vol. 8, Stereoselective Synthesis (Part E); A.-U. Rahman, Ed., Elsevier Science Publishers B. V., Amsterdam, 1991, p. 175.
- 3 U. Burkert and N. L. Allinger, *Molecular Mechanics*, ACS: Washington, DC, 1982.
- 4 a) K. N. Houk, M. N. Paddon-Row, N. G. Rondan, Y.-D. Wu, F. K. Brown, D. C. Spellmeyer, J. T. Metz, Y. Li, and R. J. Loncharich, *Science*, 1986, **231**, 1108. b) J. E. Eksterowicz and K. N. Houk, *Chem. Rev.*, 1993, **93**, 1533.
- 5 a) T. Takahashi, H. Nemoto, Y. Kanda, J. Tsuji, and Y. Fujise, *J. Org. Chem.*, 1986, **51**, 4315. b) J. A. Marshall, T. M. Jensojn, and B. S. DeHoff, *ibid.*, 1986, **51**, 4316. c) T. Takahashi, H. Nemoto, Y. Kanda, and J. Tsuji, *Heterocycles*, 1987, **25**, 139. d) T. Doi and T. Takahashi, *J. Org. Chem.*, 1991, **56**, 3465.
- 6 a) J. E. Leet, D. R. Schroeder, S. J. Hofstend, J. Golik, K. L. Colson, S. Huang, S. E. Klohr, T. W. Doyle, and J. A. Matsone, *J. Am. Chem. Soc.*, 1992, **114**, 7946. b) N. Zein, K. L. Colson, J. E. Leet, D. R. Schroeder, W. Solomon, T. W. Doyle, and A. M. Casazza, *Proc. Natl. Acad. Sci. U.S.A.*, 1993, **90**, 2822.
- 7 K. C. Nicolaou and W.-M. Dai, *Angew. Chem., Int. Ed. Engl.*, 1991, **30**, 1387.
- 8 a) T. Takahashi, H. Nemoto, Y. Kanda, J. Tsuji, Y. Fukazawa, Y. Okajima, and Y. Fujise, *Tetrahedron*, 1987, **43**, 5499.
- 9 G. Chang, W. C. Guida, and W. C. Still, *J. Am. Chem. Soc.*, 1989, **111**, 4379.
- 10 In these calculations, we used MM2* force field in MacroModel (ver. 4.5); F. Mohamadi, N. G. J. Richards, W. C. Guida, R. Liskamp, M. Lipton, C. Caufield, G. Chang, T. Hendrickson, and W. C. Still, *J. Comput. Chem.*, 1990, **11**, 440.
- 11 The population of the conformers that have no overlap of π -orbital of olefin is less than 3%.
- 12 a) K. N. Houk, S. R. Moses, Y.-D. Wu, N. G. Rondan, V. Jager, R. Schohe, and F. R. Fronczek, *J. Am. Chem. Soc.*, 1984, **106**, 3880. b) T. Takahashi, K. Shimizu, T. Doi, J. Tsuji, and Y. Fukazawa, *ibid.*, 1988, **110**, 2674. c) T. Takahashi, K. Shimizu, T. Doi, J. Tsuji, and K. Yamamoto, *Tetrahedron Lett.*, 1989, **30**, 4999. d) H. Yamada, K. Shimizu, M. Nisar, T. Takahashi, and J. Tsuji, *ibid.*, 1990, **31**, 2407. e) T. Doi, K. Shimizu, T. Takahashi, J. Tsuji, and K. Yamamoto, *ibid.*, 1990, **31**, 3313. f) T. Takahashi, Y. Sakamoto, and T. Doi, *ibid.*, 1992, **33**, 3519. g) T. Takahashi, M. Miyazawa, Y. Sakamoto, and H. Yamada, *Synlett*, 1994, 902.
- 13 Y.-D. Wu, K. N. Houk, and J. A. Marshall, *J. Org. Chem.*, 1990, **55**, 1421.
- 14 Preparation of the 13-membered ether(**2b**) will be submitted for publication from our laboratory.
- 15 **5b**: ^1H Nmr (270 MHz, CDCl_3) δ 5.85 (ddd, 1H, $J = 6.3, 10.0, 16.8$ Hz), 5.79 (d, 1H, $J = 2.0$ Hz), 5.41 (ddd, 1H, $J = 1.3, 1.3, 16.8$ Hz), 5.30 (ddd, 1H, $J = 1.3, 1.3, 10.0$ Hz), 4.51 (ddd, 1H, $J = 1.0, 1.6, 5.0$ Hz), 4.33 (dd, 1H, $J = 2.0, 4.3$ Hz), 4.20 (d, 1H, $J = 4.3$ Hz), 3.73 (dddd, 1H, $J = 1.3, 1.3, 5.0, 6.3$ Hz), 2.60 (dd, 1H, $J = 1.0, 17.5$ Hz), 2.26 (dd, 1H, $J = 1.6, 17.5$ Hz), 0.90 (s, 9H), 0.89 (s, 9H), 0.21 (s, 9H), 0.14 (s, 3H), 0.12 (s, 3H), 0.08 (s, 6H); ^{13}C nmr (67.8 MHz, CDCl_3) δ 133.7, 132.2, 131.3, 119.3, 98.9, 95.8, 89.7, 89.6, 88.4, 86.0, 80.8, 67.6, 48.7, 29.7, 25.9, 25.9, 18.1, 18.0, 2.5, -3.9, -4.4; ir(neat) 3430, 2950, 2926, 2854, 2206, 1631, 1470, 1251, 1113, 1069, 838, 778, 680 cm^{-1} .
6b: ^1H Nmr (270 MHz, CDCl_3) δ 5.82 (ddd, 1H, $J = 16.8, 9.9, 6.3$ Hz), 5.81 (d, 1H, $J = 2.3$ Hz), 5.44 (ddd, 1H, $J = 16.8, 1.7, 1.7$ Hz), 5.32 (ddd, 1H, $J = 9.9, 1.7, 1.7$ Hz), 4.58-4.48 (m, 1H), 4.32 (br dd, 1H, $J = 4.3, 2.3$ Hz), 4.12 (d, 1H, $J = 4.3$ Hz), 3.79 (m, 1H), 2.55 (dd, 1H, $J = 17.5, 2.3$ Hz), 2.36 (dd, 1H, $J = 17.5, 1.3$ Hz), 0.902 (s, 9H), 0.896 (s, 9H), 0.178 (s, 9H), 0.13 (s, 3H), 0.12 (s, 3H), 0.09 (s, 3H), 0.08 (s, 3H); ir(neat) 3402, 2950, 2924, 2890, 2852, 1713, 1630, 1460, 1250, 113, 1071, 838, 778 cm^{-1} ; ms(FAB) m/z 723 [M+DTDE+H], 569 [M+Na]; HRms (FAB) calcd for $\text{C}_{29}\text{H}_{50}\text{O}_4\text{KS}_3$ 585.2654, found 585.2614.
- 16 I. Ohtani, T. Kusumi, Y. Kashman, and H. Kakisawa, *J. Am. Chem. Soc.*, 1991, **113**, 4092.

Received, 8th February, 1996