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

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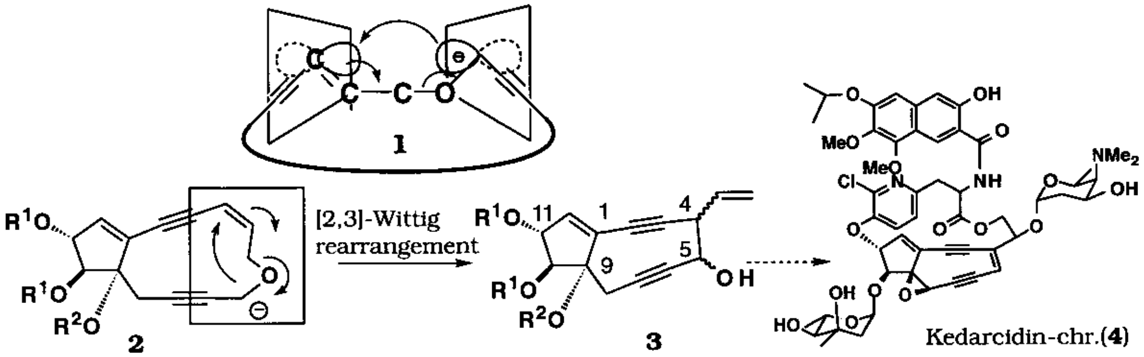
Abstract - Transannular [2,3]-Wittig rearrangement of the 12-membered cyclic ether, a key reaction to construct the 9-membered masked enediyne of kedarcidin chromophore, and a discussion of its diastereoselectivity based on a rigid MM2 transition state model are described.

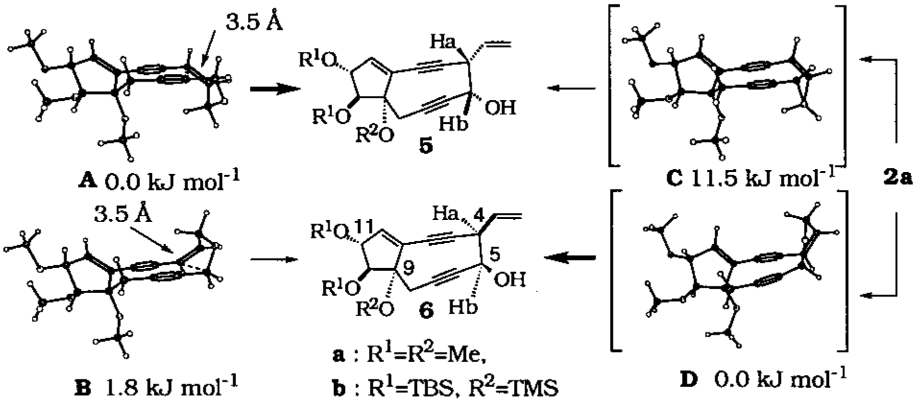
Stereochemical controls with predictable capabilities are essential in natural product syntheses. In macrocyclic system, the π-orbitals of olefins are oriented in the plane of the ring to minimize transannular nonbonded repulsions[1] (see **1** in Scheme 1). Therefore the inter- and intramolecular reactions 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 calculation[3] and/or transition state modeling[4] 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 rearrangement[5] 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).



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 model[8]) of **2** were examined. At first, conformational analysis of the 12-membered ether (**2a** ; $R^1 = R^2$ = 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) method[9] 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 (~3.5 Å) 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 conformers[11] 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.



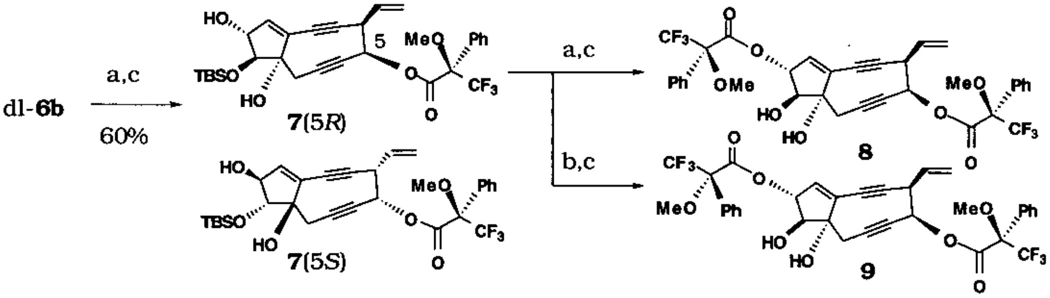
Calculation at ground state	**5a** : **6a**	=	77 : 23
Calculation at transition state	**5a** : **6a**	=	>1 : <99
Experiment	**5b** : **6b**	=	22 : 78

Figure 1

Moreover, to examine the stereoselectivity in the [2,3]-Wittig rearrangement of **2a** ($R^1 = R^2$ = methyl), MM2 transition state models (rigid transition state model[12]) 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 rearrangement[13] 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 products[15] (**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 method[16] (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**(5*R*) and **7**(5*S*) 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**(5*R*) and **7**(5*S*) (Figure 2). Treatment of the isolated **7**(5*R*) 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./CH_3CN

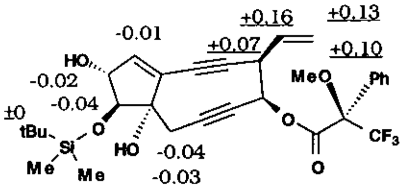


Figure 2 $\Delta\delta_H$ = **7**(5*S*) - **7**(5*R*)

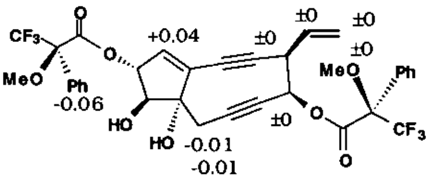


Figure 3 $\Delta\delta_H$ = **9** - **8**

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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., Elisevier 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**: ^{1}H 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: ^{1}H 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 $C_{29}H_{50}O_4KSi_3$ 585.2654, found 585.2614.
16 I. Ohtani, T. Kusumi, Y. Kashman, and H. Kakisawa, *J. Am. Chem. Soc.*, 1991, **113**, 4092.

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