STEREOSELECTIVE INTRAMOLECULAR MICHAEL REACTION OF THE 18-MEMBERED α,β-UNSATURATED MACROLACTAM: MM2 TRANSITION STRUCTURE MODELS

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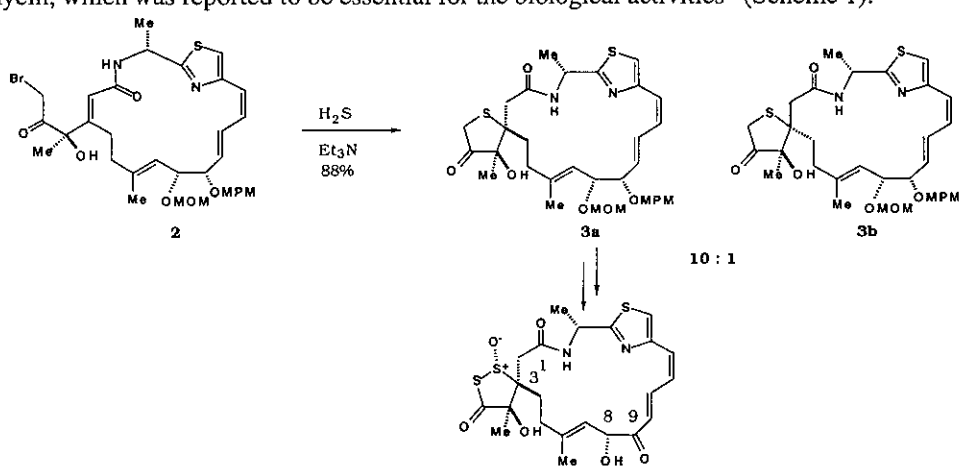
Abstract- Intramolecular Michael reaction of the 18-membered α,β-unsaturated lactam, a key reaction in the total synthesis of leinamycin (**1**), and a discussion of its high diastereoselectivity based on MM2 transition structure models are presented.

Leinamycin (**1**), a novel antitumor antibiotic with unusual spiro 1-oxo-1,2-dithiolan-3-one moiety, was isolated from a culture broth of *Streptomycets* sp. at Kyowa Hakko and showed potent antitumor activities against murine experimental tumors.[1,2] The unique structural features as well as interesting antitumor activities prompted us[3] and others[4] to undertake the total synthesis of this fascinating molecule. One of the key reactions in our recent first total synthesis of (+)-leinamycin (**1**)[5] was the stereoselective intramolecular Michael addition of the thiolate, which was derived from the bromoketone (**2**), to the C-3 position of 18-membered α, β–unsaturated lactam to give a 10 : 1 mixture of spiro sulfides (**3a**) and (**3b**). The desired isomer (**3a**) was the critical intermediate for the construction of the characteristic spiro dithiolanone moiety of leinamycin, which was reported to be essential for the biological activities[2] (Scheme 1).



Scheme 1

Few intramolecular Michael reactions to afford 5-membered sulfides,[6] especially in connection with the stereoselectivity, have been reported. While the extensive theoretical studies on the *intermolecular* Michael reactions have been reported,[7] *intramolecular* versions have received little attention.[8] Molecular mechanics calculations[9] and MM2 transition structure models[10] have proven useful for analysis and prediction of the stereoselectivities in macrocyclic reactions. In this paper, we describe the new transition-state model obtained by semi-empirical MO calculations to account for the stereoselectivities of the intramolecular Michael reaction of the sulfides.

Since the Michael reaction shown in Scheme 1 is considered to proceed under kinetic control, the analysis of the transition state structures could be crucial. The transition state structure for the intramolecular Michael addition of a simple model compound (**4**) was determined by PM3 calculations.[11] The preliminary MM2 calculations of amides (**4**) and (**6**) revealed that low energy conformers of **4** and **6** had *s-cis* conformations because *s-trans* conformations has the steric repulsion between vinyl methyl and amide methyl groups. Thus, only the *s-cis* conformation of amide (**4**) was taken into account for the PM3 calculations. The distance between the sulfur nucleophile and the β-carbon atom in **4** was used as the reaction coordinate (RC) for the Michael reaction. The RC was held constant at several values (1.974, 2.2, 2.4, 2.5, 2.6, 2.7, 2.8, 3.0, 3.2, 3.4 Å) and then all the remaining geometric parameters were optimized by PM3 to define the potential energy profile of the reaction. Transition state optimization of the stationary structure, which was energy maximum with respect to the forming bond length (RC = 2.6 Å), was carried out to locate the transition state (**5**) of the Michael reaction. The transition state (**5**) has been characterized by harmonic frequency analysis and possesses one imaginary vibrational frequency. The coordinates of the transition structure (**5**) thus obtained were used for the MM2 transition structure modeling studies of the Michael reaction.

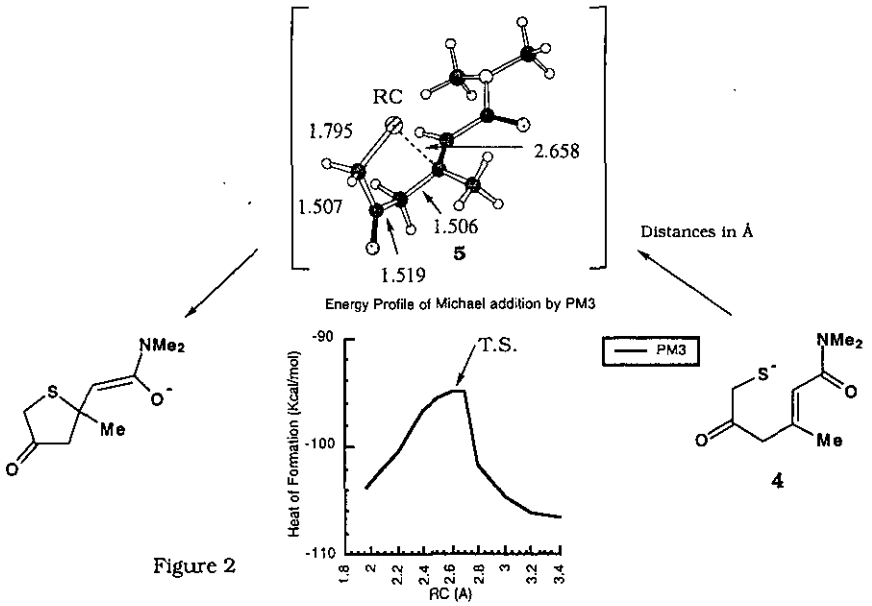


Figure 2

The stereoselectivity in the intramolecular Michael addition of **6** (the two secondary alkoxy groups at C-8 and C-9 in **2** were replaced with the methoxy groups for simplification of the MM2 calculations) was examined by the rigid MM2 transition model. The two transition states, **TS-a** (forming **7a** with R configuration at C-3) and **TS-b** (forming **7b** with S configuration at C-3), were calculated as follows. The positions of the core transition structure (denoted by * in **6**) were fixed at the PM3 geometry by FXAT option in MacroModel with the force constant 9999.0 kcal/mol Å**2. The conformational space of the rest of the molecule was explored by Monte Carlo conformational search[12] and the energy minimization was carried out with MM2* force field implemented in MacroModel.[13]

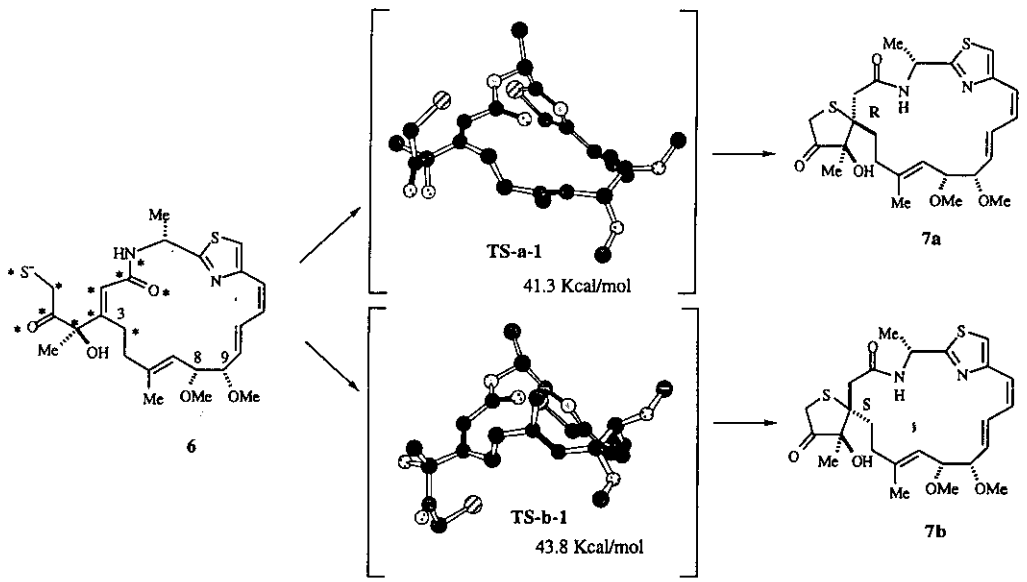
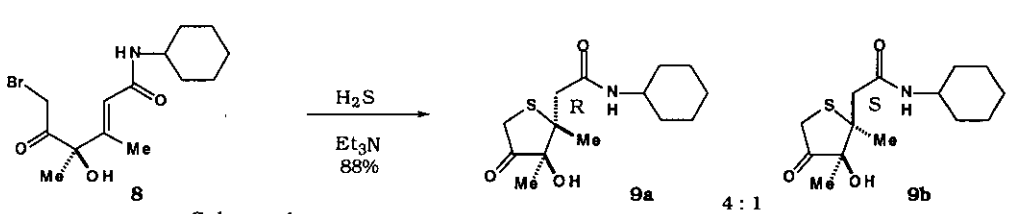


Figure 3 MM2 Transition Structure Model

The lowest energy conformations of **TS-a-1** to form **7a** and **TS-b-1** to form **7b** are shown in Figure 3. Boltzmann distribution of these conformers at 25 °C predicts the **7a/7b** ratio of 97 : 3. This could explain the stereoselective formation of **3a** in the intramolecular Michael reaction.

In our earlier studies on the construction of 1-oxo-1,2-dithiolan-3-one moiety of leinamycin,[3] a simpler compound (**8**) was used for the intramolecular Michael reaction. A relatively lower stereoselectivity (*ca.* 4 : 1) was observed in this case (Scheme 4). Application of the rigid MM2 transition model to this simpler system revealed that the energy of the most stable transition state structure to form **9a** was 40.0 kcal/mol, while the energy of the one to form **9b** was 40.7 kcal/mol. The difference of only 0.7 kcal/mol between them was consistent with the low stereoselectivity in this system.



Scheme 4

In summary, we have shown that the MM2 calculation of the transition structures is useful for the analysis (and possibly prediction) of the stereoselectivity of the intramolecular Michael reactions in the macrocyclic system. This method is also applicable for the discussion of the stereoselectivity of the Michael reaction in the simple acyclic system.

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