

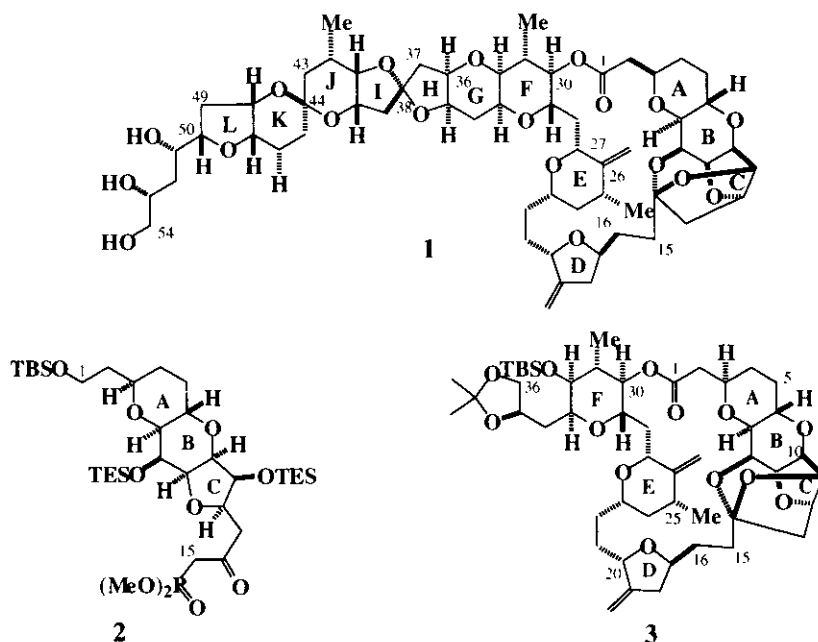
ON THE STEREOSELECTIVE CONSTRUCTION OF THE B AND A RINGS OF HALICHONDRIIN B. A PM3 STUDY

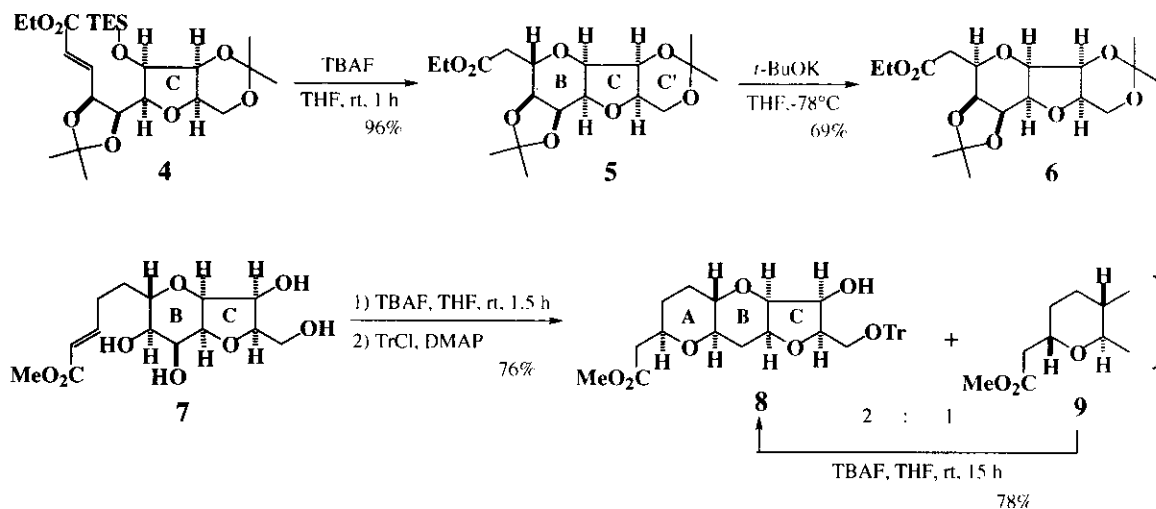
Osamu Yonemitsu,* Tatsuya Yamazaki, and Jun-ichi Uenishi

Department of Chemistry, Okayama University of Science, Okayama 700-0005, Japan

Abstract—PM3 calculations were carried out to study the origin of stereoselectivity in the intramolecular Michael reaction for a highly efficient construction of the B and A rings of halichondrin B.

Halichondrin B (**1**) is a marine polyether macrolide with a highly complex structure, possessing antitumor activity. It was isolated and its structure established by Uemura in 1985¹ and synthesized by Kishi in 1992.² As part of our synthetic studies of **1**, we reported a synthesis of the C1-C15 fragment (**2**)³ and its coupling with the C16-C36 fragment to give the C1-C36 lactone part (**3**).⁴ For the synthesis of **2**, the stereoselective construction of the A, B and C rings was, of course, most important, and we synthesized first the C ring starting from D-glucose and then built up two different type rings, 2,6-*trans*-substituted tetrahydro-2H-pyran (*trans*-THP) (B) and 2,6-*cis* compound (*cis*-THP) (A) in that order by means of the same cyclization

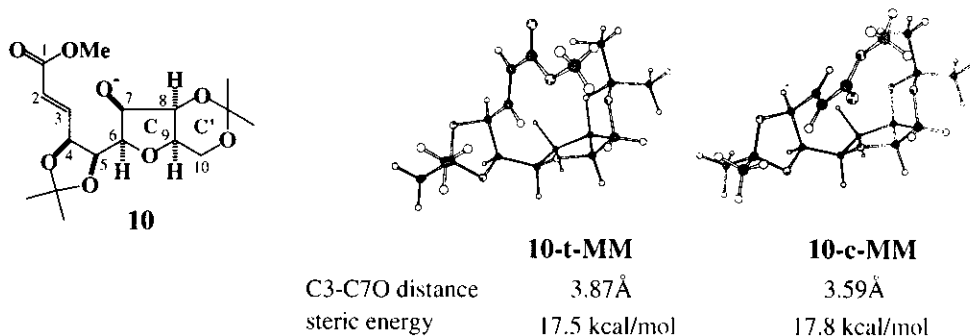




method, an intramolecular Michael reaction. A *cis*-THP in rather simple compounds is usually more stable than the corresponding *trans*-THP, and hence we constructed stereoselectively the B and A rings under kinetical and thermodynamical conditions, respectively. On treatment with tetra-*n*-butylammonium fluoride (TBAF) at room temperature for a short while, **4** gave only the expected *trans*-THP (**5**), which was isomerized with *t*-BuOK to the *cis*-THP (**6**). Under similar conditions **7** cyclized to a 2:1 mixture of the expected *cis*-THP (**8**) and its *trans* isomer (**9**) after tritylation, and **9** was isomerized to **8** by prolonged treatment with TBAF.

Molecular mechanics (MM2) calculations utilizing MacroModel⁵ and CONFLEX⁶ indicated that **5** is 2.0 and 2.48 kcal/mol, respectively, less stable than **6**. Therefore, **5** is evidently the kinetic product. In order to reveal the reason why **4** selectively gave **5** under the above Michael reaction conditions, dominant ground-state conformers of the expected anionic intermediate (**10**) were first searched by the MacroModel calculation.⁵ The energy difference between the most stable conformers **10t-MM** and **10c-MM**, which are expected to cyclize to *trans*-THP and *cis*-THP, respectively, was only 0.3 kcal/mol; hence, as it was presumed, the ground-state conformation of **10** should have no influence on the selective formation of **5**. This stereocontrol should be determined by the difference in energy between the diastereomeric transition structures⁷ leading to **5** and **6**. Semiempirical MO calculations using the PM3 Hamiltonian⁸ of MOPAC 9.3 (key words: CHARGE = -1, PRECISE, TS) were applied to search the transition structures.

The ground state structure of **10** was again calculated by PM3, using **10t-MM** as an input structure, to give only one broad energy minimum structure (Hf=-329.2 kcal/mol) with C2-3-4-5 torsion angle (TA) 217°.



which is almost on the cis-trans border. Two structures, **10t-MO** and **10c-MO**, were arbitrarily chosen as the initial structures, and several distances between C3 and C7-O⁻ were held constant (reaction coordinate: RC) and other geometric parameters were optimized by PM3 calculations. The results shown in Table 1 disclose the energy profile to each transition state; that is, as RC is shortened, **10t-MO** and **10c-MO** approach the

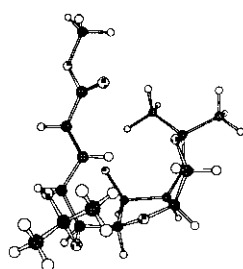
Table 1. Selected Heat of Formation and Geometric Parameters.

| RC ^a | Hf ^b | TA ^c | RC ^a | Hf ^b | TA ^c |
|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| Trans series | | | Cis series | | |
| 2.777 | -328 | 210 | 2.787 | -329 | 228 |
| (10t-MO) | | | (10c-MO) | | |
| 2.6 | -326 | 210 | 2.6 | -326 | 228 |
| 2.4 | -318 | 210 | 2.4 | -318 | 229 |
| 2.2 | -317 | 181 | 2.2 | -315 | 261 |
| 2.1 | -316 | 164 | 2.1 | -314 | 267 |
| 2.0 | -317 | 164 | 2.0 | -313 | 267 |
| 1.9 | -318 | 169 | 1.9 | -313 | 271 |
| 1.8 | -321 | 162 | 1.8 | -314 | 271 |
| 1.6 | -328 | 163 | 1.6 | -320 | 264 |

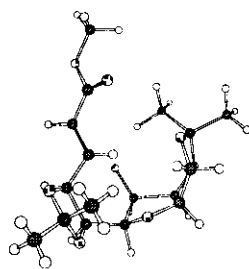
^a Distance (C3-C7O) (Å) ^b Heat of formation (kcal/mol) ^c Tortion angle (C2-3-4-5)

corresponding transition states, **TS-t** and **TS-c**, with TA rotating anticlockwise by about 55° and clockwise by about 44°, respectively.

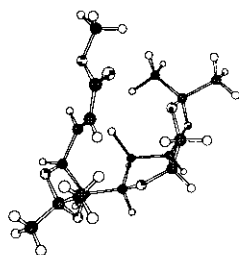
The resulting transition structures were subjected to vibrational analysis and only one imaginary frequency was found in each case. The energy difference between **TS-t** and **TS-c** was calculated to be 3.7 kcal/mol. As shown in their stereoviews, the structures of **TS-t** and **TS-c** are of great interest and probably explain the



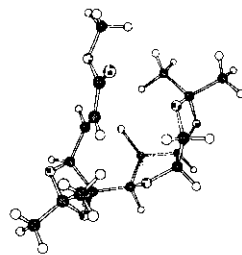
TS-t



Distance (C3-C7O) : 2.07 Å
Heat of formation : 317.0 kcal/mol
Tortion angle (C2-3-4-5) : 154.8 °
Angle (C2-3-C7O) : 101.6 °



TS-c



Distance (C3-C7O) : 1.96 Å
Heat of formation : 313.3 kcal/mol
Tortion angle (C2-3-4-5) : 272.1 °
Angle (C2-3-C7O) : 113.6 °

reason why **TS-t** is lower in energy than **TS-c**. In the transition states, C7-O⁻ approaches to C3 with a C2-3-C7O angle 101.6° in **TS-t** and 113.6° in **TS-c** according to the Burgi-Dunitz trajectory⁹ in order to form the *B* ring in a boat form (a boatlike transition state), not in a chair form.¹⁰ Therefore, the C1, 2 group in **TS-t** is situated in an equatorial position on the forming B ring, whereas that in **TS-c** is in an axial position. A difference in the interatomic distance between C3 and C7-O⁻, which in **TS-t** (2.07Å) is 0.11Å longer (an earlier transition state) than that in **TS-c** (1.96Å), may account for a main reason why **TS-t** is lower in energy than **TS-c**, and an additional reason is probably provided by the distance between repulsive C1-O (carbonyl) and C10-O in **TS-t** (3.59Å) which is 0.14Å longer than that in **TS-c** (3.45Å).

Finally, MM calculations using MacroModel of **8** and **9** revealed their steric energies in the most stable conformers to be 16.4 and 20.0 kcal/mol, respectively, showing clearly that **8** is thermodynamically more stable than **9**.

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10. The C' rings of **TS-t** and **TS-c** are both in a twist-boat form in order to avoid a steric effect by an axial methyl group in the acetonide when the C' rings present in a chair form.

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