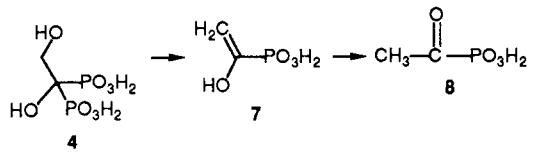
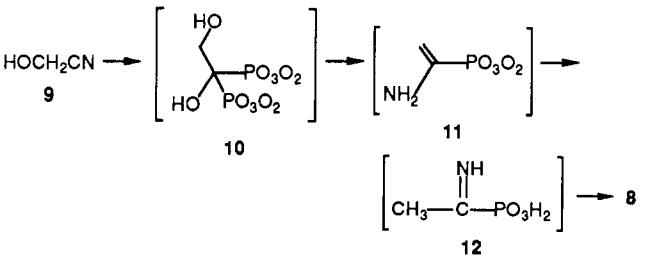
we may propose a potential pathway for the decomposition of DHEDPA (4). The formation of acetylphosphonate (8) can be accounted for by the loss of phosphoric acid generating enol-phosphonic acid 7, which is the tautomer of acetylphosphonate (8). The suggested pathway is cer-



tainly not unreasonable considering the Horner-Emmons reaction and the ease with which phosphorus forms P-O bonds. The observed pH dependency may be explained by the expected difficulty for an anionic center (PO_3H^- or PO_3^{2-}) to accept the additional electron density from the hydroxyl oxygen required to generate the P-O bond.

If the above mechanistic proposal has any validity, we should observe similar decomposition products for other β-hydroxyethane-1,1-diphosphonic acids. Fukuda[5] has reported that 2-hydroxy-1-aminoethane-1,1-diphosphonic acid (10) is stable in alkaline solution, which certainly carries the implication that it is not stable in acidic solutions. Although some of the ^1H NMR data reported by Fukuda for 10 was obtained in acidic media, no degradation products were mentioned. Therefore, we reexamined the properties of 10, especially the ^{31}P NMR data, by reacting hydroxyacetonitrile (9) and phosphorus acid. It should be noted that we did not attempt to isolate 10 or any salt of 10, but rather immediately acidified the solution to allow in situ decomposition to occur. The ^{31}P NMR data



indicated that the phosphorus-containing products are acetylphosphonic acid (8) and phosphoric acid.

We may presume that the reaction proceeds through the intermediacy of 2-hydroxy-1-aminoethane-1,1-diphosphonic acid (10), which, according to our proposed pathway, under the acidic conditions we utilized for workup would decompose through enamine 11 to the imine of acetylphosphonic acid (12) and phosphoric acid. The imine (12) would be expected to hydrolyze to the ketonic form and is not observed.

We are currently investigating the apparent pivotal role that a β-hydroxyl group performs in the facile decomposition of substituted alkyl diphosphonates by extending our study to longer alkyl groups. We will report the full details of our research in the near future.

Acknowledgment. This work was performed under the auspices of the Office of Basic Energy Sciences, Division of Chemical Sciences, U.S. Department of Energy under contract number W-31-109-ENG-38. I would like to thank Phil Horwitz for his advice and encouragement during this research. I would like to acknowledge the technical assistance of Paul Rickert and Carolyn Jacobs, an Argonne Department of Educational Programs Undergraduate Summer Research Participant.

(5) Fukuda, M.; Okamoto, Y.; Sakurai, H. *Chem. Lett.* **1977**, 529.

Stereoselective Cyclopropanation of the 10-Membered Enone. Total Synthesis of Bicyclohumulenone

Takashi Takahashi,* Yoshiro Yamashita, Takayuki Doi, and Jiro Tsuji

Department of Chemical Engineering, Tokyo Institute of Technology, Meguro, Tokyo 152, Japan

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Summary: The stereoselective synthesis of bicyclohumulenone and a discussion of the diastereoselectivity of the cyclopropanation based on MM2 calculations are presented.

Sir: Macrocyclic compounds have conformational properties which are quite useful for stereochemical control in the syntheses of natural products.[1] We have recently demonstrated that the transannular [2,3]-Wittig rearrangements[2] of macrocyclic ethers yield germacrane lactones and the transannular Diels-Alder reactions[3] of macrocyclic trienes provide steroid A, B, C rings with higher degree of efficiency and stereoselectivity. In these "endocyclic" cyclizations, the interior side of π orbitals oriented horizontally to the plane of the ring is used for the carbon-carbon bond formation (Figure 1, 1). In this paper we report the first total synthesis of bicyclohumulenone (5)[4] via the "exocyclic" cyclization of the macrocyclic enolate 2.

(1) (a) Still, W. C.; Galynker, I. *Tetrahedron* **1981**, *37*, 3981. (b) Paquette, L. A.; Reagan, J.; Schreiber, S. L.; Teleha, C. A. *J. Am. Chem. Soc.* **1989**, *111*, 2331.

(2) (a) Takahashi, T.; Nemoto, H.; Kanda, Y.; Tsuji, J.; Fujise, Y. *J. Org. Chem.* **1986**, *51*, 4315. (b) A related work: Marshall, J. A.; Jenson, T. M.; Delfoff, B. S. *Ibid.* **1986**, *51*, 4316.

(3) (a) Takahashi, T.; Shimizu, K.; Doi, T.; Tsuji, J.; Fukazawa, Y. *J. Am. Chem. Soc.* **1988**, *110*, 2674. (b) A related work: Baettig, K.; Dallaire, C.; Pitteloud, R.; Deslongchamps, P. *Tetrahedron Lett.* **1987**, *28*, 5249.

(4) Bicyclohumulenone was isolated from a species of liverworts, *Plagischila acanthophylla* subsp. *Japonica* (Matsuo, A.; Nozaki, H.; Nakayama, M.; Kushi, Y.; Hayashi, S.; Komori, T.; Kamijo, N. *J. Chem. Soc., Chem. Commun.* **1979**, *4*, 174), and it has an aroma reminiscent of a variety of odors based on the strong powdery, woody note, such as the odors of patchouli, vetiver, cedarwood, orris, moss, carnation, etc. Preparation of bicyclohumulenone by the transannular cyclization of humulene 9,10-epoxide was reported: Shirahama, H.; Hayano, Kanemoto, Y.; Misumi, S.; Ohtsuka, T.; Hashiba, N.; Furusaki, A.; Murata, S.; Noyori, R.; Matsumoto, T. *Tetrahedron Lett.* **1980**, *21*, 4385.

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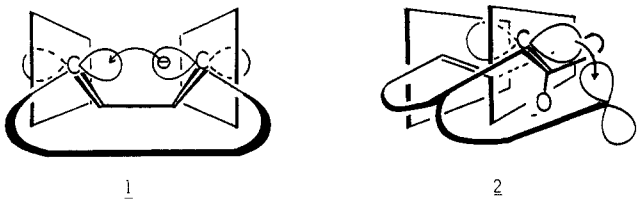
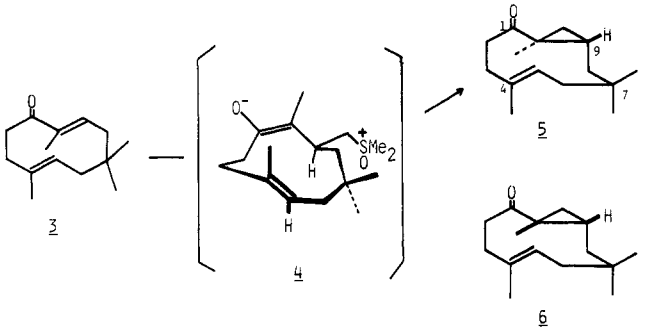


1 2

Figure 1.

Scheme I

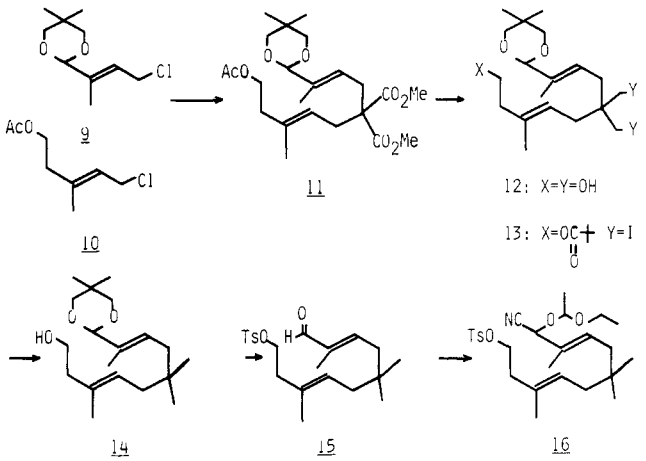


3 4 5 6

Stereochemical predictions (or analyses) in macrocyclic systems are quite difficult because of their various possible conformations. Molecular mechanics calculations[5] and MM2 transition structure models[6] have proven to be useful in predictions (or analyses) of the stereoselectivities in macrocyclic reactions. Molecular modeling based on these calculations can also be useful in designing the synthetic key intermediate.[7] As described below (Figure 2), MM2 calculations of the various possible conformations of the starting enone **3** and the likely *E*- and *Z*-enolate intermediates **7** and **8** suggest that the cyclopropanation[8] of **3** using oxysulfurane could provide a highly stereoselective trans cyclopropanation. Thus, in our synthetic plan (Scheme I), the enone **3** is the key intermediate and its 10-membered skeleton is constructed by the intramolecular alkylation[9] of the cyanohydrin ether **16**.

The cyclopropanation described here involves an initial reversible conjugated addition of the ylide to the enone **3** followed by an irreversible ring closure. The conformational analyses of **3** and its *E*-, *Z*-enolate intermediates **7b** and **8b** ($CH_2S(O)Me_2$ replaced by a methyl) were conducted with the ring making program[10] at 30° dihedral angle resolution and the MM2 calculations.[11] These analyses[12] showed (Figure 2) that the s-trans conformations **3A**, **3B**, and **3C** were lower in energy than its s-cis conformation **3D**,[13] and that conjugated addition would lead to the *E*- and *Z* enolate **7a** and **8a**, respectively. Shown below were the structures and the strain energies of the lowest *E*- and *Z*-enolate conformations **7E** and **8F** providing the trans cyclopropane **5**, while the lowest *E*- and *Z*-enolate conformations **7G** and **8H** leading the cis cyclopropane **6** were more strained than **7E** and **8F**. Based on the assumption of the early reactant-like transition state for the ring closure, it was clear that the lower energy enolates **7E** and **8F** could yield the preferential formation of the trans cyclopropane **5**.[14]

Scheme II



9 10 11 12: X=Y=OH 13: X=OC(=O)I, Y=I 14 15 16

The enone **3** was prepared in the following way (Scheme II). Alkylations of dimethyl malonate with allyl chlorides **9**[15] and **10** (K_2CO_3/acetone reflux, NaH/THF) were carried out stepwise to give the dialkylated product **11** in 60% overall yield. Complete reduction of **11** ($LiAlH_4$, 65% yield), selective protection of the homoallylic alcohol of **12** (mp 120–122 °C) with trimethylacetyl chloride, and tosylation of the remaining diol followed by iodonation gave the diiodide **13** in 60% overall yield. Simultaneous reduction of the pivaloyl and iodide groups in **13** with lithium triethylborohydride gave the alcohol **14** in 75% yield. Tosylation of **14** and hydrolysis of the acetal (*p*-TsOH/acetone, 25 °C) gave the aldehyde **15** in 66% overall yield. Protected cyanohydrin formation[9a] in three steps (Me_3SiCN/KCN/18-crown-6, 0.3 N HCl/THF, ethyl vinyl ether/H^+) gave **16** in 83% overall yield. Cyclization of **16** (5.2 mmol) with $LiN(TMS)_2$ (20 mmol) in dioxane (40 mL) at 80 °C and acid treatment (*p*-TsOH/MeOH, 0 °C) of the product followed by basic treatment (2% aqueous NaOH) of the cyanohydrin gave the enone **3**[16] in 87% overall yield from **16**. We could not detect the olefinic stereoisomer[17]

(5) (a) Allinger, N. L. *J. Am. Chem. Soc.* **1977**, *99*, 8127; QCPE 395. (b) Jamie, C.; Osawa, E. *Tetrahedron* **1983**, *39*, 2769.

(6) Houk, K. N.; Paddon-row, M. N.; Rondan, N. G.; Wu, Y.; Brown, F. K.; Spellmeyer, D. C.; Metz, J. T.; Li, Y.; Loncharich, R. J. *Science (Washington, D.C.)* **1986**, *231*, 1108.

(7) Takahashi, T.; Kanda, Y.; Nemoto, H.; Kitamura, K.; Tsuji, J.; Fukazawa, Y. *J. Org. Chem.* **1986**, *51*, 3393.

(8) Review; Trost, B. M.; Melvin, L. S. *Sulfur Ylids*; Academic Press: New York, 1975; pp 42.

(9) (a) Takahashi, T.; Kitamura, K.; Nemoto, H.; Tsuji, J. *Tetrahedron Lett.* **1983**, *24*, 3489. (b) The normal (3,4,5) ring formations by intramolecular alkylation of cyanohydrin ether: Stork, G.; Pepezay, J. C.; d'Angela, J. *Tetrahedron Lett.* **1975**, 389.

(10) (a) Still, W. C. In *Current Trends in Organic Synthesis*; Nozaki, H., Ed.; Pergamon Press: New York, 1983; pp 223–246. (b) Fukazawa, Y.; Usui, S.; Uchio, Y.; Shiobara, Y.; Kodama, M. *Tetrahedron Lett.* **1986**, *27*, 1825.

(11) The program MACROMODEL (Version 2.0) was employed for these calculations. We are grateful to Professor Clark Still for providing a copy of this program.

(12) Although the correspondance between calculated and experimental product ratio is semiquantitative, our modeling described here is quite crude. Modifications of parameters for the aggregated methyl enolate structures are necessary to obtain more exact calculation; however, these calculations would be sufficient to predict the stereoselectivity in organic synthetic studies (See ref 1a).

(13) More conformational informations are available in supplementary material.

(14) Assuming the cyclopropanations of the kinetically formed enolates **7E** and **8F** are faster than those conformational interconversions, a simpler expectation (or explanation) for the preferential formation of the trans cyclopropane is also possible.

(15) The acetal **9** was prepared in 60% overall from pyruvic aldehyde dimethyl acetal by the addition of vinylmagnesium chloride followed by acid treatment (concentrated HCl/NaCl/CuCl) and acetal formation (2,2-dimethyl-1,3-propanediol/*p*-TsOH).

(16) Satisfactory ^1H NMR, IR, and MS properties were obtained.

(17) Takahashi, T.; Nemoto, H.; Tsuji, J. *Tetrahedron Lett.* **1983**, *24*, 2005.

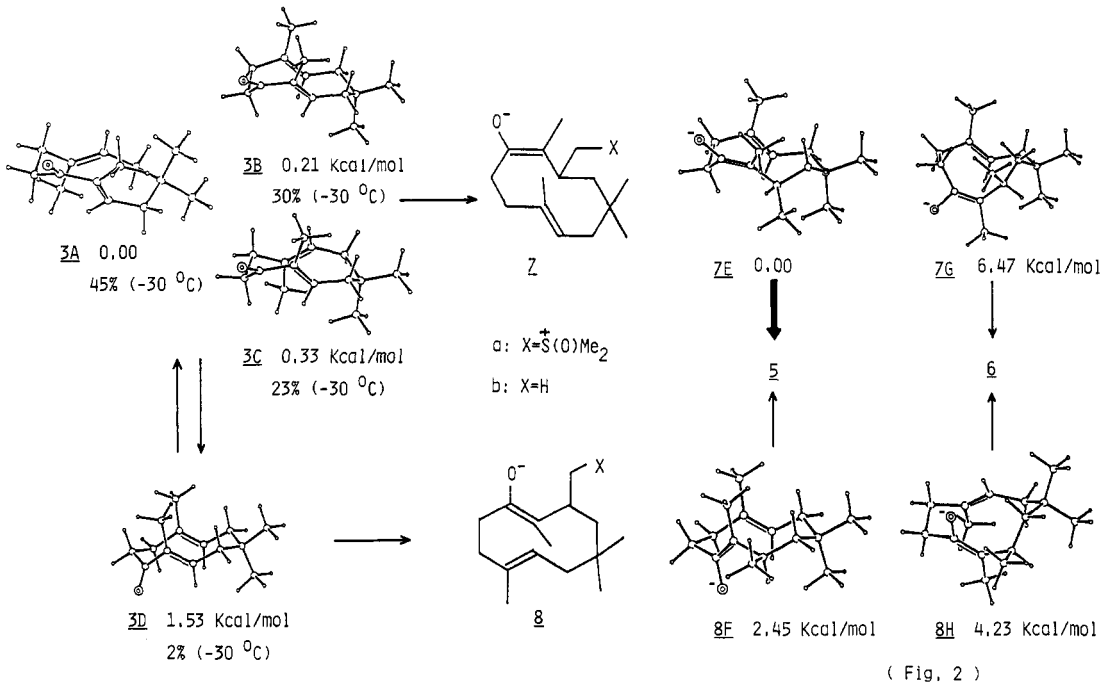


Figure 2.

and the β-elimination product of the tosylate, although this cyclization involved the alkylation of the homoallyl tosylate which was unstable to the strong basic condition.

The ^{1}H NMR spectrum of the enone **3** showed the broad olefinic peaks at 4.8–5.5 and 5.9–6.8 ppm in $CDCl_3$ at room temperature, while the each of the broad olefinic signals observed at room temperature separated into a pair of sharp peaks with an intensity ratio of about 56:44 in the same solvent at −30 °C. MM2 calculations and the Boltzmann distribution of conformers showed that the four conformers **3A**, **3B**, **3C**, and **3D** were equilibrated at −30 °C in a ratio 45:30:23:2. Assuming that two groups of conformers were constituted of **3B**, **3C**, and **3A**, conformational distribution ((**3B** + **3C**):**3A** = 53:45) based on calculations were consistent with those observed in NMR spectrum. Stereoselective cyclopropanation of **3** (Me_3S-(O)I–NaH/DMSO at 0 °C) gave the bicyclohumulenone (**5**)[18] in 90% yield; none of the cis stereoisomer **6** was detected in the crude product. Rationalization for this high trans stereoselectivity was available by MM2 calculations of the enone **3** and the model enolate **7E** as described above. They predict that the peripheral addition of oxysulfurane should proceed through the lower energy conformations **3B** (or **3A**, **3C**)[13] to lead the most likely enolate intermediate **4**, followed by ring closure gave the trans cyclopropane **5**. Thus conformational analyses of the enone (or enolates) are important to predict the stereoselectivity in macrocyclic reactions, and these considerations of stereochemical control based on MM2 calculations might have predictable value in organic syntheses.

Acknowledgment. We are grateful to Professor Y. Fukazawa (Hiroshima University) and Professor K. Yamamoto (Tokyo Institute of Technology) for helpful discussions on the MM2 calculations. We are indebted to Kuraray Co. for providing 5-acetoxy-3-methyl-(*E*)-2-pentenyl chloride.

Supplementary Material Available: Spectral data for new compounds, cyclization procedure, cyclopropanation procedure, and details of MM2 and NMR studies (8 pages). Ordering information is given on any current masthead page.

(18) The ^{1}H NMR, ^{13}C NMR, IR, and MS data of the synthetic (±)-bicyclohumulenone (mp 69–72 °C) were identical with those of natural product. We are indebted to Professor Asakawa for providing natural bicyclohumulenone.

Thermolysis of *N*-Benzyl-2,2-dichlorocyclopropanecarboxaldimines: A Novel Ring Enlargement to 2-Phenylpyridines

Shinzo Kagabu,* Shigemi Naruse, Yuko Tagami, and Yasuo Watanabe
Department of Chemistry, Faculty of Education, Gifu University, Yanagido 1-1, Gifu 501-11, Japan
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Summary: Schiff bases of 2,2-dichlorocyclopropanecarbaldehydes with arylmethylamines were pyrolyzed to 2-arylpyridines. Tungsten(VI) oxide promoted the transformation. The reaction pathway is discussed.

Sir: The thermal rearrangement of vinylcyclopropanes has been the subject of many mechanistic and theoretical studies and recently has received attention as a synthetic tool.[1-10] In general, the thermolysis of vinylcyclopropane

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