Communications

[2,3]-Wittig Rearrangement of 13-Membered Diallylic Ethers, Six-Step Synthesis of Costunolide[1]

Summary: The stereoselective synthesis of costunolide using [2,3]-Wittig rearrangement of 13-membered diallylic ethers and discussion for the diastereoselectivity are presented.

Sir: Some previous attempts at stereocontrolled reactions by conformational restriction usually involved weak, noncovalent forces.[2] However, if two prochiral carbons are more rigidly locked at a short distance from each other with covalent bonds shown in **1**, the reaction involving two centers proceeds in a better yield and with higher stereoselectivity. Figure 1 suggests an intramolecular reaction in a medium ring.[3]

In this paper we wish to report the stereoselective [2,3]-Wittig rearrangement of a 13-membered diallylic ether and its application to the synthesis of costunolide (**5**), which is one member of an important group of natural products and possesses wide-ranging biological activities.[4] Success of this approach (Scheme I) to the synthesis of **5** required the following three selectivities in the [2,3]-Wittig rearrangement: (1) the periselectivity ([2,3]- vs. [1,2]- and [1,4]-shift), (2) the regioselectivity (α vs. α' lithiation) in ether **7**, and (3) the stereoselectivity (trans stereochemistry between the C(6) and C(7) as well as the *E* geometry of the C(4),C(5) olefin in the rearranged product **6**).

Extensive studies on the diastereoselectivity and enantioselectivity of *acyclic* [2,3]-Wittig rearrangements have recently been carried out.[5] However the rearrangement in *cyclic* systems, wherein all five atoms participating in the rearrangement are incorporated into a ring, has not been studied. The conformational nature, especially the horizontal π-orbital orientation of the olefin to the plane of the ring[6] (Figure 1), should give a different sense and degree of diastereoselectivity from acyclic systems, as described in following model reactions.

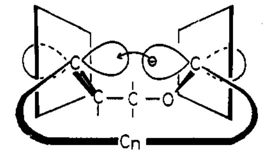

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Figure 1.

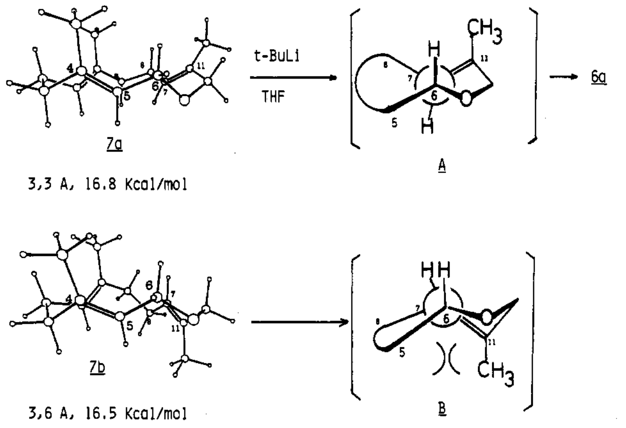
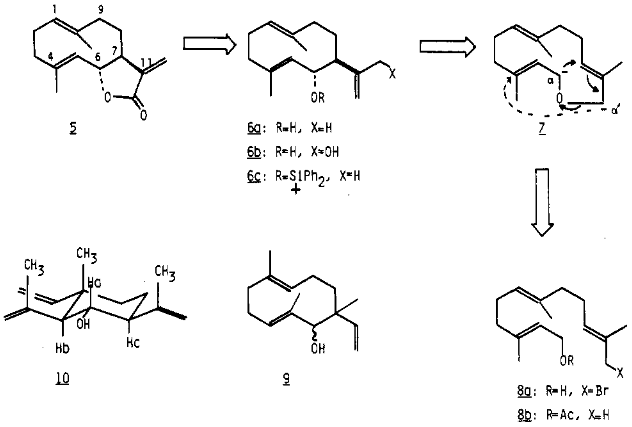
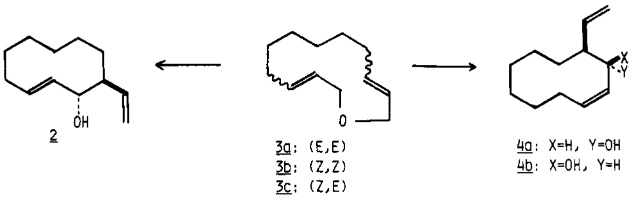


Figure 2. Conformations of 7 obtained from MM2 calculation and those steric energies and distances between those reactive centers [C(6),C(7)].

Scheme I



Scheme II



The [2,3]-Wittig rearrangement of (*E*,*E*)- and (*Z*,*Z*)-diallylic ethers[7] **3a** and **3b** (t-BuLi in THF, −78 °C, 6–10 h) proceeded with high peri- and stereoselectivities (>98%) to give (*E*)-*trans*-1-hydroxy-10-vinyl-2-cyclodecene (**2**)[7]

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[1] A partial account has been presented: Takahashi, T.; Nemoto, H.; Tsuji, J. Presented at the 50th Spring Meeting of Japan Chemical Society, 1985; Abstract p 904.

[2] Typical examples are observed in cross aldol condensation (metal-mediated chelation, steric interaction in six-membered ring transition-state model, etc.), Diels–Alder reactions (π–π overlap, etc.), and so on. (a) Evans, D. A.; Nelbson, J. V.; Taber, T. R. *Top. Stereochem.* **1982**, *13*, 1. (b) Paquette, L. A. *Asymmetric Synth.* **1983**, *3*, 455.

[3] Both inter- and intramolecular reactions in medium rings proceed with high stereoselectivity. Intermolecular reactions: (a) Still, W. C.; Novack, V. J. *J. Am. Chem. Soc.* **1984**, *106*, 1148. (b) Vedejs, E.; Gapinski, D. M. *Ibid.* **1983**, *105*, 5058. Intramolecular reactions: (c) Still, W. C.; Romero, A. G.; *Ibid.* **1986**, *108*, 2105. d) Schreiber, S. L.; Sammakia, T.; Hulin, B.; Shculte, G. *Ibid.* **1986**, *108*, 2106. Intramolecular reactions: (e) Abelman, M. M.; Funk, R. L.; Munger, J. D., Jr. *Ibid.* **1982**, *104*, 4030. (f) Begley, M. J.; Cameron, A. G.; Knight, D. W. *J. Chem. Soc., Chem. Commun.* **1984**, *827*. (g) Ohtsuka, Y.; Oishi, T. *Tetrahedron Lett.* **1986**, *27*, 203. (h) Kodama, M.; Yokoo, S.; Matsuki, Y.; Ito, S. *Ibid.* **1979**, 1687. (i) Takeda, K. *Tetrahedron* **1974**, *30*, 1525. (j) Niwa, M.; Nishiyama, A.; Iguchi, M.; Yamamura, S. *Bull. Chem. Soc. Jpn.* **1975**, *48*, 2930.

[4] (a) Fischer, N. H.; Oliver, E. J.; Fischer, H. D. *Fortschr. Chem. Org. Naturst.* **1979**, *38*, 47. (b) Cassady, J. M.; Matthew, S. *Anticancer Agents Based on Natural Product Models*; Academic: New York, 1980; p 201. (c) Hoffmann, H. M. R.; Jurgen, R. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 94.

[5] (a) Baldwin, J. E.; Patrick, J. E. *J. Am. Chem. Soc.* **1971**, *93*, 3556. (b) Nakai, T.; Mikami, K.; Taya, S. *Ibid.* **1981**, *103*, 6492. (c) Mikai, K.; Kimura, Y.; Kishi, Y.; Nakai, T. *J. Org. Chem.* **1983**, *48*, 279. (d) Tsai, D. J.; Midland, M. M. *Ibid.* **1984**, *49*, 1843. (e) Marshall, J. A.; Jenson, T. M. *Ibid.* **1984**, *49*, 1707.

[6] (a) Still, W. C. *J. Am. Chem. Soc.* **1979**, *101*, 2493. (b) Still, W. C.; Galynker, I. *Tetrahedron* **1981**, *23*, 3981.

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(94% yield) and its *Z* isomer **4a**[7] (96% yield), respectively, without isomerization of the olefin. In contrast to these results, the asymmetric *Z,E* ether **3c**[7] gave a mixture of **2**, **4b**, and **4a**[7] (9:41:50, total 95% yield) with high regioselectivity but with poor stereoselectivity[8] (Scheme II).

We then attempted the [2,3]-Wittig rearrangement of **7** for the synthesis of costunolide (**5**) (Scheme I). The bromo alcohol **8a** was prepared from easily available farnesyl acetate (**8b**) in three steps [(1) SeO_2/*t*-BuOOH, (2) CBr_4/PPh_3, (3) K_2CO_3/MeOH]. The macrocyclic ether **7** was synthesized from **8a** in 60% yield by using high dilution technique; a solution of **8a** (16.0 mmol) in dry benzene (100 mL) was added dropwise over 2 h to a suspension of NaH (30 mmol) and dicyclohexano-18-crown-6 (16.0 mmol) in benzene (200 mL) at 80 °C. The rearrangement of **7** in ether under the same condition described above gave a mixture of **6a**[9,10] and **9** in a 75:25 ratio (total isolated yield, 98%). None of diastereomer of **6a** could be detected by HPLC analysis.

The exclusive formation of the trans isomer **6a** can be understood by examining the possible transition states[11] for rearrangement of the allyllithiums A and B obtained upon lithiation of the comformers **7a** and **7b**[12] (Figure 2). The transition-state B developed from **7b** suffers from the 1,3-interaction between C(6–5) C–C bond and C(11)–Me and likewise the eclipsing 1,2-interaction between C(6–5) and C(7–8) C–C bonds. The transition-state A formed from **7a** does not experience these unfavorable interactions. Therefore, the rearrangement proceeds in such a way as to make two adjacent larger groups, C(6–5) and C(7–8) C–C bonds, becoming trans to each other in the five-membered cyclic transition states.

The isopropenyl moiety in **6a** was oxidized[14] with *sec*-BuLi/TMEDA/O_2[15] to give the diol **6b** in 60% yield. Moreover the diol **6b** was obtained directly from **7** with *sec*-BuLi in ether and then TMEDA/O_2 in 40% yield. The diol **6b** was converted to **5** with MnO_2 in ether at room temperature for 12 h. The synthetic (±)-costunolide (**5**) (mp 64–66 °C) was found by IR and ^1H NMR spectra and TLC analysis to be identical with a sample of natural product.[9]

This type of stereocontrol might have predictable value in organic synthesis. Development of this methodology combined with remote stereochemical control and cyanohydrin methodology[16] to the synthesis of natural products are in progress.[17]

Acknowledgment. We are grateful to Professor T. Nakai (Tokyo Institute of Technology) and Professor S. Ito (Tohoku University) for helpful discussions on the transition state of [2,3]-Wittig rearrangements. We also thank I. Miura (Otsuka Pharmaceutical Co.) and T. Nakata (The Institute of Physical and Chemical Research) for their help in the interpretation of the NMR spectra.

Registry No. (±)-**2**, 104423-38-3; **3a**, 104423-35-0; **3b**, 104423-36-1; **3c**, 104423-37-2; (±)-**4a**, 104486-18-2; (±)-**4b**, 104486-19-3; (±)-**5**, 104527-18-6; (±)-**6a**, 104423-07-6; (±)-**6b**, 104486-16-0; (±)-**6c**, 104423-08-7; (±)-**6c** (epoxide), 104423-42-9; **6c**-ol (isomer 1), 104438-53-1; **6c**-ol (isomer 2), 104423-43-0; **7**, 104423-09-8; **8a**, 104423-12-3; **8a** (acetate), 104423-44-1; **8b**, 4128-17-0; **8b**-ol, 93787-91-8; **9**, 104423-11-2; (±)-**10**, 104423-10-1; I, 629-09-4; II, 6089-04-9; IIIa, 104423-13-4; IIIb, 3516-38-9; IIIc, 104423-14-5; IV, 72312-54-0; V, 72312-58-4; VI, 104423-18-9; VIIa, 104423-15-6; VIIb, 104423-16-7; VIIIa, 72312-63-1; VIIIb, 104423-17-8; IX, 104423-19-0; IX (THP), 104423-45-2; X, 104423-20-3; X·XI (ester), 104423-40-7; XI, 104423-21-4; XII, 104423-22-5; XII-ol, 104423-41-8; XIII, 104423-23-6; XIII-ene, 104423-46-3; XIV, 104423-24-7; XIV (tosylate), 104423-47-4; XV, 104423-25-8; XV-diol (tosylate), 104423-48-5; XVI, 104423-26-9; (±)-XVII, 104423-27-0; (±)-XVII (acetate), 104423-28-1; XVII (ethoxyethylether), 104423-49-6; (±)-XVII (tetrahydro acetate), 104423-29-2; XVII (tetrahydro alcohol), 104423-30-5; XVII (tetrahydro tosylate), 104423-31-6; (±)-XVIII, 104423-32-7; (±)-XVIII-al, 104423-33-8; (±)-XIX, 104423-39-4; (±)-XX, 104486-17-1; (±)-XXI, 104486-20-6; XXII, 104423-34-9.

Supplementary Material Available: Preparation methods for **3a–c**, relative stereochemical determinations of **2** and **4a,b**, and NMR and IR spectra of **2**, **3a–c**, **4a,b**, **5**, **6a**, and **7** (27 pages). Ordering information is given on any current masthead page.

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[7] Comparison of our results with those of acyclic systems[5b] regarding stereoselectivity is outlined as follows: (1) higher degree with the same sense in the case of *E,E*, (2) higher degree with the opposite sense in the case of *Z,Z*. Preparations of **3a–c**, and determinations of relative stereochemistry of **2** and **4a,b** are available in the supplementary material.

[8] [2,3]-Wittig rearrangement of the corresponding *Z,E* acyclic system has not been examined.

[9] The structure of **6a** was confirmed by ^1H NMR and ^{13}C NMR. Moreover the stereoselective Cope rearrangement of **6a** gave **10** as a single product (refluxing in benzene for 6 h). The observed coupling constant ($J_{H_a,H_b} = J_{H_a,H_c} = 9.4$ Hz) of **10** suggest the trans stereochemistry between C(6) and C(7) and the (4*E*,10*E*)-olefin geometry in **6a** (see ref 3h).

[10] Recently I. Kitagawa and H. Shibuya have synthesized the same compound by macrocyclization of the aldehyde allylic bromide promoted by Cr(II) and completed the synthesis of costunolide (14 steps from farnesyl acetate). We are indebted to Professor Kitagawa for providing NMR spectra of this compound and natural costunolide. Shibuya, H.; Ohashi, K.; Kawashima, K.; Hori, K.; Murakami, N.; Kitagawa, I. *Chem. Lett.* **1986**, 85.

[11] Three types envelope transition-state models for the acyclic [2,3]-Wittig rearrangement have been proposed: (a) Trost, B. M.; Hammen, R. F. *J. Am. Chem. Soc.* **1973**, *95*, 962. (b) Still, W. C.; Mitra, A. *Ibid.* **1978**, *100*, 1928. See also ref 5c,d.

[12] Although the mechanism of the lithiation is not fully understood, the structure of the π orbital at C(7,11) and C(4,5) may play an important role in the lithiation at C(6). The transition state of this rearrangement would be very early (see ref 11b). Therefore, 32 conformers of the ground-state model **7** were created on the basis of the fact that all the sp^2 planes are perpendicular to the medium ring plane. The results of these MM2 calculations[13] indicated that conformers **7a** and **7b** had the shortest distance between C(6) and C(7) despite its lower energy.

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

[14] Epoxidation and hydroboration of silylated compound **6c** using mCPBA and disiamylborane also proceeded at the most reactive C(1),-C(10) olefin. Oxidation of **6c** with SeO_2 or with *sec*-BuLi/TMEDA/O_2 gave the C(10)-hydroxymethyl derivative.

[15] (a) Crawford, R. J.; Erman, W. F.; Broaduss, C. D. *J. Am. Chem. Soc.* **1972**, *94*, 4298. (b) Suemune, H.; Iwasaki, G.; Ueno, K.; Sakai, K. *Chem. Pharm. Bull.* **1984**, *32*, 4632.

[16] Takahashi, T.; Nemoto, H.; Tsuji, J. *Tetrahedron Lett.* **1983**, *24*, 3485.

[17] Professor J. A. Marshall (Marshall, J. A.; Jensen, T. M.; DeHoff, B. S. *J. Org. Chem.*, accompanying paper in this issue) reports his successful independent new route to the carbon skeleton of cembranoid using [2,3]-Wittig rearrangement of 17-membered diallylic ether. We thank him for communicating his results to us in advance of publication.

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[2,3]Wittig Ring Contraction. A New Route to Cembranoid Natural Products

Summary: A new route to the cembranoid skeleton is described wherein a 17-membered propargyl allyl ether is subjected to [2,3]Wittig rearrangement to afford a 14-membered carbocyclic with substituents appropriate for elaboration to cembrane natural products.

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