# Stereoselective Synthesis of Trisubstituted *Z*- or *E*-Olefins Employing N-Substituted β-Methallyldimethylammonium Ylides

Kiyoshi Honda, Seiichi Inoue,* and Kikumasa Sato†

*Department of Synthetic Chemistry, Faculty of Engineering, Yokohama National University, Tokiwadai, Hodogayaku, Yokohama 240, Japan*

*Received August 22, 1991*

*Summary:* [2,3] Sigmatropic rearrangement of N-substituted β-methallyldimethylammonium ylides forms trisubstituted olefins with high stereoselectivity. Ylides with a powerful electron-withdrawing substituent (–$COCH_3$ or –$CO_2Et$) in the α-position and those with a vinyl group carrying an ester moiety at the β-position afford exclusively *E*- and *Z*-olefins, respectively.

Examination of the five-membered envelope conformation of transition state for the concerted [2,3] sigmatropic rearrangement suggests that an $R^1$ substituent on the α-carbon atom should prefer the equatorial position, leading almost exclusively to the *E* configuration of the newly created double bond (Scheme I). Many examples are found in Wittig,[1] Büchi,[2] sulfoxide,[3] sulfinate,[4] sulfenate,[5] sulfide,[6] sulfonium ylide,[7] phosphite,[8] and Meisenheimer[9] rearrangements.

One of the rare exceptions to this generalization was reported by Still in the Wittig rearrangement of anions derived from stannylmethyl ethers, which afforded *Z*-homoallyl alcohols as the major products.[10]

We recently reported a [2,3] sigmatropic rearrangement of nitrogen ylides that provided *Z*- or *E*-homoallylic dimethylamines with high stereoselectivity.[11] In the formation of β-methallyltrimethylammonium salts, two types of ylides are possible, one by removing a proton from a methyl group and the other by deprotonation at the allylic position. The ylide generated by the latter process leads to a *Z*-olefin after rearrangement, whereas the methylene ylide leads to an *E*-olefin.[11]

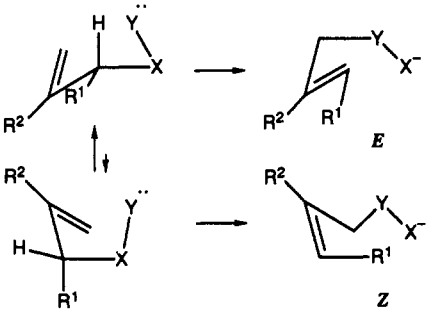
We wish to report another new stereoselective synthesis of *Z*- or *E*-trisubstituted olefins employing N-substituted β-methallyldimethylammonium ylides (Scheme II).

Table I shows the reaction of ammonium salts **1a–1f**. Treatment of **1a** (1 mmol) with potassium *tert*-butoxide (2 mmol) in DMF resulted in the presumed formation of ammonium ylide intermediate **2a** followed by spontaneous [2,3] sigmatropic rearrangement (2 h, –50 °C) to give *E*-ester **3a** in 84% yield with 100% stereoselectivity (run 2). Similarly, the reaction of **1b** with potassium *tert*-butoxide in DMF at –10 °C afforded *E*-ester **3b** exclusively in 81% yield (run 3).

Interestingly, treatment of **1c** (1 mmol) with potassium *tert*-butoxide (2 mmol) in DMF at –50 °C resulted in a 90:10 mixture of (*Z*)-**3c** and (*E*)-**3c**, without isomerization of the parent crotyl *E* double bond. Furthermore, higher solvent polarity and lower temperature increased the *Z* selectivity of the rearrangement (run 6). Similar results were obtained in the reaction of salts **1d–1f** (runs 7–9).

In the rearrangement of (ethoxycarbonyl)methyl- or acetonyl-substituted ammonium salts **1a,b,d,e**, stable ylides **2** may undergo [2,3] sigmatropic rearrangement to *E*-olefins via the usual concerted transition state of a doubly suprafacial mode,[9,13] in which $RCH_2$ on the allyl moiety takes a pseudoequatorial conformation.

**Scheme I**




**Scheme II**

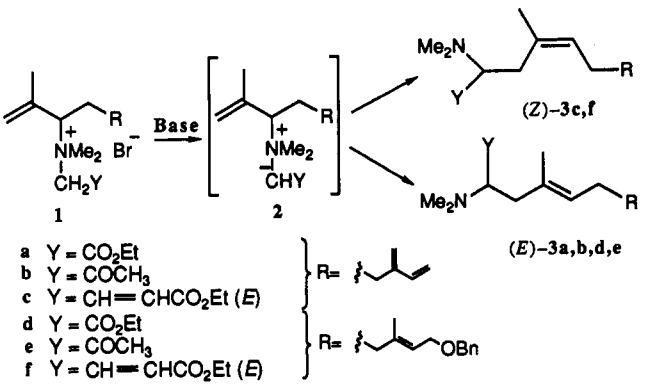



**Table I. Reaction of N-Substituted β-Methallyldimethylammonium Salts**

| run | substrate | base | solvent | temp[a] (°C) | yield (%) | *Z*:*E*[b,c] |
|---|---|---|---|---|---|---|
| 1 | **1a** | KO$^t$Bu | THF | –10 | 80 | 5:95 |
| 2 | **1a** | KO$^t$Bu | DMF | –50 | 84 | 0:100 |
| 3 | **1b** | KO$^t$Bu | DMF | –10 | 81 | 0:100 |
| 4 | **1b** | $K_2CO_3$ | DMF | 0[d] | 71 | 0:100 |
| 5 | **1c** | KO$^t$Bu | DMF | –50 | 72 | 90:10 |
| 6 | **1c** | KO$^t$Bu | THF–HMPA[e] | –70 | 76 | 100:0 |
| 7 | **1d** | KO$^t$Bu | DMF | –50 | 73 | 0:100 |
| 8 | **1e** | KO$^t$Bu | DMF | –10 | 72 | 0:100 |
| 9 | **1f** | KO$^t$Bu | THF–HMPA[e] | –70 | 64 | 95:5 |

[a] Unless otherwise noted, the reaction time was 2 h. [b] The ratio of *Z*/*E* was determined by capillary GC analysis. [c] Each of these compounds was separated carefully by column chromatography on silica gel and analyzed by NMR spectroscopy.[12] [d] The reaction time was 6 h. [e] HMPA content was 20 vol %.

In order to establish which of the alternative routes (Scheme III) is followed in the *Z*-selective rearrangement

† Professor Emeritus, Yokohama National University. Present address: President, Tokyo Technical College, Higashi 1-chome, Kunitachi, Tokyo 186.

(1) (a) Nakai, T.; Mikami, K.; Taya, S.; Kimura, Y.; Mimura, T. *Tetrahedron Lett.* **1981**, *22*, 69. (b) Nakai, T.; Mikami, K.; Taya, S.; Fujita, Y. *J. Am. Chem. Soc.* **1981**, *103*, 6492. (c) Rautenstrauch, V. *J. Chem. Soc. D* **1970**, 4, (d) Scholkopf, U.; Fellenberger, K. *Liebigs Ann. Chem.* **1966**, *698*, 80.

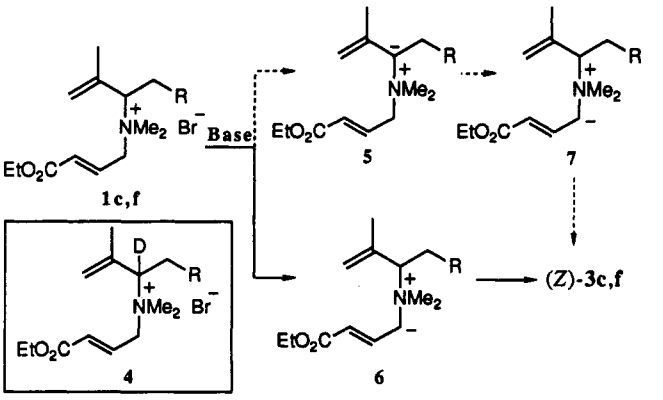
(2) (a) Büchi, G.; Cushman, M.; Wüest, H. *J. Am. Chem. Soc.* **1974**, *96*, 5563. (b) Chen, K.-K.; Saucy, G. *J. Org. Chem.* **1977**, *42*, 3828.

0022-3263/92/1957-0428$03.00/0 © 1992 American Chemical Society

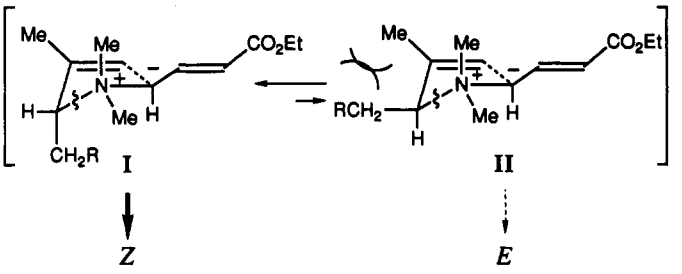
of bisallylic systems **1c** and **1f**, deuterio ammonium salt **4c** (96 ± 4% D) was synthesized and treated with potassium *tert*-butoxide in THF-HMPA at −70 °C. The deuterium content of *Z*-ester **3c** was determined to be 96 ± 4% D by $^1$H NMR after purification by column chromatography. This result rules out allylide **5** as an intermediate and establishes the direct formation of methylide **6**. Therefore the *Z*-selective character of the present system is in marked contrast to our previous system[11] from a mechanistic standpoint.

The [2,3] sigmatropic rearrangement of **1c,f** seems to have an earlier (i.e., reactant-like) transition state than that of the stable ylides **2a,b,d,e**. Thus another envelope conformation can be postulated as a plausible transition state leading to *Z*-olefins (Scheme IV).

**Scheme III**




**Scheme IV**




The conformational preference of I over II may result from vicinal repulsion between $RCH_2$ and the vinyl methyl group, which Still postulated to be an important factor in the *Z*-selective Wittig rearrangement.[10,14]

(3) (a) Blackburn, G. M.; Ollis, W. D.; Plackett, J. D.; Smith, C.; Sutherland, I. O. *J. Chem. Soc., Chem. Commun.* **1968**, 186. (b) Baldwin, J. E.; Hackler, R. E.; Kelly, D. P. Ibid. **1968**, 537, 538. (c) Evans, D. A.; Andrews, G. C.; Sims, C. L. *J. Am. Chem. Soc.* **1971**, *93*, 4956. (d) Evans, D. A.; Andrews, G. C.; Fujimoto, T. T.; Wells, D. *Tetrahedron Lett.* **1973**, 1385, 1389. (e) Grieco, P. A. *J. Chem. Soc., Chem. Commun.* **1972**, 702. (f) Grieco, P. A.; Finkelforn, R. S. *J. Org. Chem.* **1973**, *38*, 2245.

(4) Cope, A. C.; Morrison, D. E.; Field, L. *J. Am. Chem. Soc.* **1950**, *72*, 59.

(5) Bickart, P.; Carson, F. W.; Jacobus, J.; Miller, E. G.; Mislow, K. *J. Am. Chem. Soc.* **1968**, *90*, 4869.

(6) Snider, B. B.; Hrib, N. J.; Fuzesi, L. *J. Am. Chem. Soc.* **1976**, *98*, 7115.

(7) Grieco, P. A.; Boxler, D.; Hiroi, K. *J. Org. Chem.* **1973**, *38*, 2572.

(8) Macomber, R. S. *J. Am. Chem. Soc.* **1977**, *99*, 3072.

(9) (a) Yamamoto, Y.; Oda, J.; Inouye, Y. *J. Org. Chem.* **1976**, *41*, 303; *J. Chem. Soc., Chem. Commun.* **1973**, 848. (b) Inoue, S.; Iwase, N.; Miyamoto, O.; Sato, K. *Chem. Lett.* **1986**, 2035. Sato, K.; Miyamoto, O.; Inoue, S.; Iwase, N.; Honda, K. *Bull. Chem. Soc. Jpn.* **1990**, *63*, 1328.

(10) Still, W. C.; Mitra, A. *J. Am. Chem. Soc.* **1978**, *100*, 1927.

(11) Honda, K.; Inoue, S.; Sato, K. *J. Am. Chem. Soc.* **1990**, *112*, 1999.

(12) The stereochemistry of the rearrangement products was confirmed by $^1$H and $^{13}$C NMR ($CDCl_3$) as follows: (*E*)-**3a**, δ 1.64 ($CH_3$, s), 15.9; (*Z*)-**3a**, δ 1.72 ($CH_3$, s), 23.0; (*E*)-**3b**, δ 1.62 ($CH_3$, s), 16.0; (*Z*)-**3c**, δ 1.69 ($CH_3$, s), 23.8; (*E*)-**3c**, δ 1.59 ($CH_3$, s), 15.8; (*E*)-**3d**, δ 1.63 ($CH_3$, s), 15.9; (*E*)-**3e**, δ 1.61 ($CH_3$, s), 15.9; (*Z*)-**3f**, δ 1.67 ($CH_3$, s), 23.8; (*E*)-**3f**, δ 1.58 ($CH_3$, s), 16.1.

(13) (a) Baldwin, J. E.; Patrick, J. E. *J. Am. Chem. Soc.* **1971**, *93*, 3556. (b) Evans, D. A.; Andrews, G. C. *J. Am. Chem. Soc.* **1972**, *94*, 3672.

(14) Hoffmann, R. W. *Angew. Chem., Int. Ed. Engl.* **1979**, *18*, 563.

## Antineoplastic Agents. 214. Isolation and Structure of Cephalostatins 7-9[1a]

George R. Pettit,* Yoshiaki Kamano, Masuo Inoue, Claude Dufresne, Michael R. Boyd,[1b] Cherry L. Herald, Jean M. Schmidt, Dennis L. Doubek, and Nigel D. Christie

*Cancer Research Institute and Department of Chemistry, Arizona State University, Tempe, Arizona 85287-1604*

*Received June 27, 1991*

*Summary:* The Southern Indian Ocean marine worm *Cephalodiscus gilchristi* has been found to yield new cephalostatins 7-9.

Tube-inhabiting marine animals of the genus *Cephalodiscus* (one of two divisions in the class Pterobranchia, Hemichordata Phylum) are rarely encountered. Only some 18 species are presently known[2,3] and confined primarily to Antarctica.[4] One Southern Hemisphere temperate region species *Cephalodiscus gilchristi* was recorded[5] off the coast of South Africa in 1906 and described in more detail in 1915-17.[6] In 1988 we summarized results from the first chemical study of this genus and isolation of the powerful (P388 $ED_{50}$ $10^{-7}$-$10^{-9}$ μg/mL) cell growth inhibitor cephalostatin 1 (**1**)[7] from *C. gilchristi*. Subsequently we described cephalostatins 2-4[8] and 5-6[9] where introduction of an aromatic C′-ring (cf. **2** corresponding to cephalostatin 6) was found to greatly reduce (P388 $ED_{50}$ $\sim 10^{-2}$ μg/mL) the cytostatic activity. We now report that further detailed investigation of *C. gilchristi* antineoplastic

(1) (a) For series part 213 refer to: Bai, R.; Pettit, G. R.; Hamel, E. *J. Biol. Chem.* **1990**, 265, 17141. (b) NCI Frederick Cancer Research and Development Center, Frederick, MD 21702.

(2) Bayer, F. M. *Bull. Inst. Mar. Sci. Gulf Caribbean* **1962**, *12*(2), 306-312.

(3) Markham, J. C. *Antarctic Research Services*; Llano, G. A., Wallen, E., Eds.; University of Miami: Miami, FL, 1971; Vol. 17, p 83.

(4) The first recognized species (*C. nigrescens*) of this genus was collected during expeditions of the *Erebus* and *Terror* in 1841-2: Ridewood, W. C. *Ann. Mag. Nat. Hist.* **1912**, *10*(8) (Art. 45), 550-555.

(5) *C. gilchristi* was recognized as a new species by: Ridewood, W. C. *Mar. Invest.* **1906**, 4, 173-192.

(6) (a) Gilchrist, J. D. F. *Ann. Mag. Nat. Hist.* **1915**, *16*(8) (Art. 30), 233-243. (b) Gilchrist, J. D. F. *Q. Jl. Microsc. Sci.* **1917**, *62*, 189-211.

(7) Pettit, G. R.; Inoue, M.; Kamano, Y.; Herald, D. L.; Arm, C.; Dufresne, C.; Christie, N. D.; Schmidt, J. M.; Doubek, D. L.; Krupa, T. S. *J. Am. Chem. Soc.* **1988**, *110*, 2006.

(8) Pettit, G. R.; Inoue, M.; Kamano, Y.; Dufresne, C.; Christie, N.; Niven, M. L.; Herald, D. L. *J. Chem. Soc., Chem. Commun.* **1988**, 865.

(9) Pettit, G. R.; Kamano, Y.; Dufresne, C.; Inoue, M.; Christie, N.; Schmidt, J. M.; Doubek, D. L. *Can. J. Chem.* **1989**, 1509.

0022-3263/92/1957-0429$03.00/0 © 1992 American Chemical Society