Stereocontrolled Elongation of a Functionalized Isoprene Unit on the *E* or *Z* Terminal Methyl of Terpenoids *via* *N*-Ylide Rearrangement of the Common Ammonium Salts

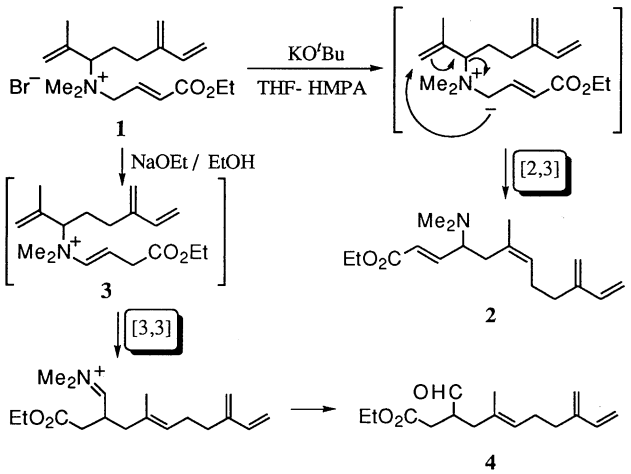
Kiyoshi Honda,* Masayuki Tabuchi, and Seiichi Inoue*
Department of Synthetic Chemistry, Faculty of Engineering, Yokohama National University, Tokiwadai 156, Hodogaya-ku, Yokohama 240

(Received February 1, 1996)

Stereocontrolled elongation of a functionalized isoprene unit on the *E* or *Z* terminal methyl of terpenoids was achieved by the *N*-ylide rearrangement of the common ammonium salts under the selected reaction conditions. One of rearrangement products, all-(*E*)-sesquiterpene carboxylate was converted into β-sinensal, a component of the essential oil of Chinese orange. General aspects of these transformations were described.

The [2,3] and [3,3]sigmatropic rearrangements are often used for the stereoselective preparation of di- and trisubstituted olefins.[1] Treatment of a quaternary ammonium salt with a base may bring about the formation of an ammonium ylide species followed by spontaneous [2,3]sigmatropic rearrangement to give a homoallylic tertiary amine.[2] [2,3]Sigmatropic rearrangement is occasionally accompanied by Hofmann elimination and other side reactions. Therefore reaction selectivity as well as stereoselectivity must be attained for the synthetic application.

We have reported a [2,3]sigmatropic *N*-ylide rearrangement that provides (*Z*)- or (*E*)-homoallylic dimethylamines with high stereoselectivity in good yields,[3] and [2,3]sigmatropic rearrangement of ylides with a powerful electron-withdrawing substituent (e.g. CO_2Et or Ac) at the ylide carbon affords exclusively (*E*)-olefin.[4] Furthermore, the vinylogous ylide derived from quaternary salt **1** affords (*Z*)-olefin **2**, whereas treatment of **1** with an alkoxide base in a protic solvent gives, after hydrolytic work-up, trisubstituted (*E*)-olefinic aldehyde **4** with complete stereoselectivity (Scheme 1).[4,5]



Scheme 1.

Herein we report a unique [2,3]sigmatropic *N*-ylide rearrangement which provides predominantly (*Z*)- or (*E*)-trisubstituted olefins according to the reaction conditions from the common ammonium salts.

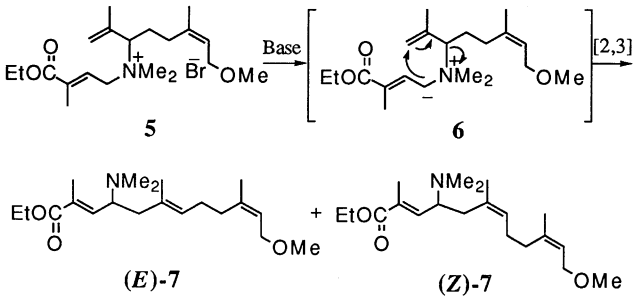


Table 1. Reaction of *N*-Tiglyl-*N*-β-Methallyldimethylammonium Salt **5**

Run	Base	Solvent	Conditions(°C / h)	Yield(%)[a]	*Z*:*E*[b]
1	KO^{t}Bu	THF-HMPA[c]	−70 / 2	41	27:**73**
2	KO^{t}Bu	THF-DMPU[d]	−70 / 2	46	28:**72**
3	KO^{t}Bu	THF	−70 / 2	45	30:**70**
4	KO^{t}Bu	DME	−70 / 2	55	39:**61**
5	KO^{t}Bu	CH_2Cl_2	−70 ~ rt / 3	52	42:**58**
6	LDA	THF	−70 / 2	45	43:**57**
7	DBU[e]	THF	−70 ~ rt / 12	66	40:**60**
8	DBU	EtOH	0 / 2	60	**72**:28
9	$NaNH_2$	NH_3	−65 / 4	36	**73**:27
10	LHMDS[f]	NH_3	−65 / 4	46	**72**:28
11	KOEt	EtOH	0 / 1	68	**80**:20
12	NaOEt	EtOH	0 / 1	56	**81**:19
13	LiOEt	EtOH	0 / 1	41	**87**:13

[a] Isolated yield [b] The stereochemistry of the products was confirmed by ^1H and ^{13}C NMR ($CDCl_3$) as follows (only the chemical shifts of olefinic methyl protons for ^1H NMR and those of olefinic methyl carbons for ^{13}C NMR are shown): (*E*)-7: δ 1.61 (3H, s); 15.9, (*Z*)-7: δ 1.69 (3H, s); 23.8. [c] HMPA content was 20 vol%. [d] 1,3-Dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone [e] 1,8-Diazabicyclo[5,4,0]undec-7-ene [f] Lithium hexamethyldisilazide

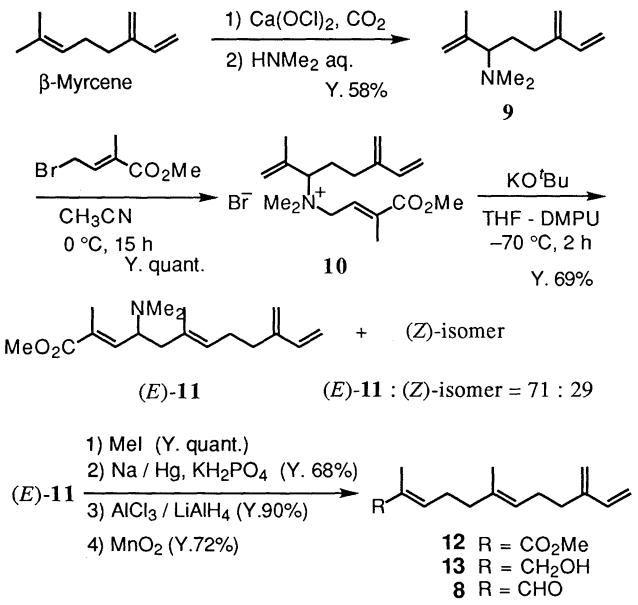
Quaternary ammonium salt **5** was treated with various bases under a variety of reaction conditions. The product mixture was analyzed by GLC and the stereoisomers (*E*)-**7** and (*Z*)-**7** were separated and characterized by ^1H- and ^{13}C-NMR spectra. The results are summarized in Table 1.

Treatment of **5** with potassium *tert*-butoxide in a mixture of either THF-HMPA or THF-DMPU gave (*E*)-**7** predominantly (runs 1 and 2). This result is in a sharp contrast to that of the rearrangement of salt **1** shown previously. Similarly, the reaction of **5** with a base, especially potassium *tert*-butoxide in an aprotic solvent such as THF, DME or CH_2Cl_2 afforded (*E*)-**7** predominantly (runs 3~5). And higher polarity of solvent seems

to increase the *E*-selectivity of the rearrangement.

On the contrary, the stereoselectivity of the [2,3]rearrangement was dramatically reversed and (*Z*)-**7** was formed predominantly when the salt **5** was treated with a base in a protic solvent, without isomerization of the parent *E* double bond in the tiglate moiety (runs 8~13). Presumably the formed ammonium ylide intermediate **6** rapidly underwent the [2,3]sigmatropic rearrangement without isomerization to a sort of enammonium salt **3** as observed in the case of **1**. Furthermore, lower basicity increased the *Z*-selectivity of the rearrangement (runs 8~13).

This new stereoselective reaction will play an important role in natural product synthesis, especially in the terpenoid field. *E*-Selectivity of the rearrangement was applied to a stereoselective synthesis of β-sinensal (**8**), a characteristic component of the essential oil of Chinese orange (Scheme 2).



Scheme 2.

β-Myrcene was converted *via* ene-type chlorination[6] followed by amination[7] into internal allylamine **9**, which was reacted with methyl γ-bromotiglate[8] in MeCN to give quaternary salt **10**. Treatment of **10** with potassium *tert*-butoxide in a mixture of THF-DMPU resulted in a 71 : 29 mixture of (*E*)-**11** and (*Z*)-isomer in a 69% combined yield. Notably, isolation of (*E*)-**11**[9] was easily achieved by column chromatography on silica gel.

The dimethylamino group in (*E*)-**11** was removed *via* quaternization with MeI, followed by treatment with sodium amalgam in a buffer solution without any conjugate reduction to give α,β-unsaturated ester **12**[9], which was reduced to the corresponding unsaturated alcohol **13**[9] in 90% yield with AlH_3[10] prepared *in situ* from aluminum chloride and lithium aluminum hydride.

Treatment of **13** with active manganese (IV) oxide in hexane at 0 °C for 3 h furnished the desired β-sinensal (**8**) in 72% yield.

As summary, stereocontrolled elongation of a functionalized *E* isoprene unit on the *E* or *Z* terminal methyl of terpenoids was achieved by the *N*-ylide rearrangement of the common ammonium salts under the selected reaction conditions. The present method is useful for the construction of both (*E*, *E*) and (*E*, *Z*) terpenoids.

References and Notes

1 D. J. Faulkner, *Synthesis*, **1971**, 175; S. Inoue and K. Honda, *J. Syn. Org. Chem., Jpn.*, **51**, 894 (1993). For reviews of [2,3]rearrangement, see: R. W. Hoffmann, *Angew. Chem. Int. Ed. Engl.*, **18**, 563 (1979); T. Nakai and K. Mikami, *Chem. Rev.*, **86**, 885 (1986); K. Mikami and T. Nakai, *Synthesis* , **1991**, 594; T. Nakai and K. Mikami, *Org. React.*, **46**, 105 (1995). For reviews of [3,3]rearrangement, see: F. E. Ziegler, *Chem. Rev.*, **88**, 1423 (1988); G. B. Bennett, *Synthesis*, **1977**, 589.

2 S. H. Pine, *Org. React.*, **18**, 403 (1970); A. R. Lepley and A. Giumanini, In "Mechanisms of Molecular Migrations," ed by B. S. Thyagarajan, Interscience, New York (1971), Vol. 3, p297; T. S. Stevens and W. E. Watts, "Selected Molecular Rearrangements," van Nostrand-Reinhold, London (1973), p81.

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

4 K. Honda, S. Inoue, and K. Sato, *J. Org. Chem.*, **57**, 428 (1992).

5 K. Honda and S. Inoue, *Synlett*, **1994**, 739.

6 S. G. Hegde, M. K. Vogel, J. Saddler, T. Hrinyo, N. Rockwell, R. Haynes, M. Oliver, and J. Wolinsky, *Tetrahedron Lett.*, **21**, 441 (1980).

7 S. Inoue, N. Iwase, O. Miyamoto, and K. Sato, *Chem. Lett.*, **1986**, 2035.

8 A. Loeffler, R. J. Pratt, H. P. Ruesch, and A. S. Dreiding, *Helv. Chim. Acta*, **53**, 383 (1970). A 2 : 1 mixture of γ-bromotiglate and β'-bromo isomer was used for the reaction. The latter was recovered unchanged after the reaction by extraction with ether.

9 Spectral data for the selected compounds are as follows. (*E*)-**11**: ^{1}H-NMR ($CDCl_3$) δ 1.60(s, 3H), 1.82(s, 3H), 2.0-2.4(m, 6H), 2.29(s, 6H), 3.3-3.4(m, 1H), 3.73(s, 3H), 4.9-5.0(m, 2H), 5.04(d, *J* = 10.9 Hz, 1H), 5.1-5.3(m, 1H), 5.20(d, *J* = 17.8 Hz, 1H), 6.36(dd, *J* = 10.9, 17.8 Hz, 1H), and 6.67(d, *J* = 10.2 Hz, 1H). **12**: ^{1}H-NMR ($CDCl_3$) δ 1.62(s, 3H), 1.84(s, 3H), 2.0-2.7(m, 8H), 3.73(s 3H), 5.01(m, 2H), 5.06(d, *J* = 10.9 Hz, 1H), 5.1-5.3(m, 1H), 5.24(d, *J* = 17.8 Hz, 1H), 6.38(dd, *J* = 10.9, 17.8 Hz, 1H), and 6.75(t, *J* = 10 Hz, 1H). **13**: IR(neat) 3350, 1040, 990, and 900 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 1.61(s, 3H), 1.67(s, 3H), 2.0-2.7(m, 8H), 3.99(s 2H), 5.01(m, 2H), 5.06(d, *J* = 10.9 Hz, 1H), 5.1-5.3(m, 1H), 5.24(d, *J* = 17.8 Hz, 1H), 5.40(t, *J* = 8 Hz, 1H), and 6.38(dd, *J* = 10.9, 17.8 Hz, 1H).

10 M. J. Jorgenson, *Tetrahedron Lett.*, **1962**, 559.