Stereoselective Synthesis of Oxygenated Trisubstituted Olefins Using N-Ylides [2,3]Rearrangement

Kiyoshi Honda,* Daisuke Igarashi, Masatoshi Asami, Seiichi Inoue*

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

Fax +81-45-339-3970; E-mail: inoue@syn.synchem.bsk.ynu.ac.jp

Received 12 March 1998

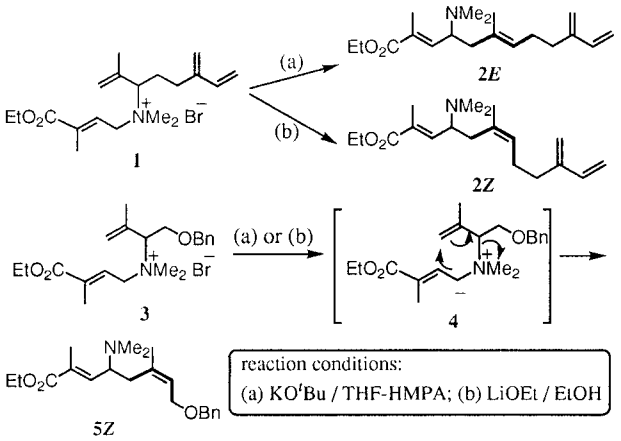
Abstract: [2,3]Sigmatropic rearrangement of *N*-(ethoxycarbonyl)-methyl-β-methallylammonium ylide with an oxygen functionality at the β–position or γ'-position forms trisubstituted *trans*-olefins with high stereoselectivity. On the other hand, the rearrangement of salts having a tiglyl ester moiety instead of a carbethoxy group affords *cis*-olefins. The present method was applied to the synthesis of plaunotol.

We have reported stereoselective or stereocontrolled synthesis of trisubstituted olefins using an *N*-ylide [2,3]sigmatropic rearrangement of β-methallylammonium salts.[1]

Recently, 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 *N*-tiglyl-β-methallyldimethylammonium salts under the selected reaction conditions.[2]

Treatment of **1** with potassium *tert*-butoxide in a mixture of THF-HMPA resulted in a 71 : 29 mixture of **2*E*** and **2*Z*** in a 69% combined yield. On the contrary, the stereoselectivity of the [2,3]sigmatropic rearrangement was reversed under the following reaction conditions: treatment of **1** with lithium ethoxide in ethanol resulted in a 13 : 87 mixture of **2*E*** and **2*Z*** in a 65% combined yield. Notably, isolation of each rearrangement product was easily achieved by column chromatography on silica gel.

Interestingly, treatment of **3** either with potassium *tert*-butoxide in THF-HMPA or with alkali metal ethoxide in ethanol resulted in the formation of an *N*-ylide **4**, which underwent [2,3]sigmatropic rearrangement to give exclusively diene **5*Z*** which was composed of a newly formed *Z* and tiglyl-origin *E* olefinic moiety.[3] It should be noted that the high *Z*-selective character of this system is in sharp contrast to our previous system[2] as shown in Scheme 1.

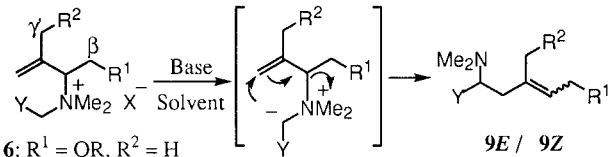


Scheme 1

Therefore, we suggested that this dramatical inversion of stereoselectivity came from presence or absence of an oxygen functionality in the β-position.

This observation prompted us to investigate the reactions of some oxygenated ammonium salts with bases.

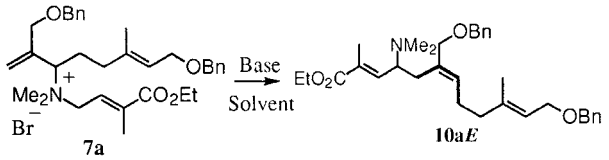
Reported herein is highly *Z*- and *E*-stereoselective [2,3]sigmatropic rearrangement which provides trisubstituted allylic alcohol derivatives **9, 10** and **11** from ammonium salts **6, 7** and **8** oxygenated at the β- or γ'-position.



6: R^1 = OR, R^2 = H
7: R^1 = alkyl, R^2 = OR
8: R^1 = H, R^2 = OBn
X = halogen; Y = (a): -CH=C(Me)CO_2Et, (b): CO_2Et, (c): CN

First, we examined the rearrangement of salt **7a** oxygenated at the γ'-position as shown in Table 1. Treatment of **7a** with potassium *tert*-butoxide in a mixture of THF-DMPU resulted in a 78 : 22 mixture of **10a*E*** and the corresponding (*Z*)-isomer in a 43% combined yield and treatment with lithium ethoxide in ethanol gave **10a*E*** predominantly (91% *E*) in a 41% combined yield. Determination of *Z*/*E* was established by NMR and NOE analysis. This strong *E*-selective character (*cis* relationship between long carbon chains around the carbon-carbon double bond) is similar to that of the rearrangement of salt **3** which shows highly *cis*-selectivity.

Table 1. Reaction of γ'-Oxygenated *N*-Tiglyldimethylammonium Salts **7a**



Run	Base	Solvent	Conditions (°C / h)	Yield (%)[a]	*E* :*Z*[b]
1	KO*t*Bu	THF-DMPU	–70 / 3	43	**78** : 22[c]
2	LiOEt	EtOH	0 / 3	41	**91** : 9[c]

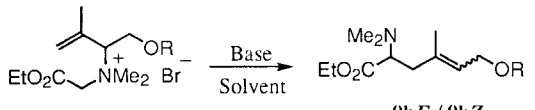
[a]Combined yield. [b]NMR analysis. [c]Each sterochemistry of the isolated stereosisomers was analyzed by ^{1}H and ^{13}C NMR ($CDCl_3$) spectroscopy

We next examined the rearrangement of **6b** as shown in Table 2. All reactions were highly *E*-selective (run 1~4) as well as the rearrangement of the corresponding salts having no oxygen functionality at the β-position.[2b] And higher basicity increased the *E*-selectivity of the rearrangement (run 3).

Next, we examined the rearrangement of the corresponding salts with carbonitrile as an electron-withdrawing group. Interestingly, no stereoselectivity was obtained except for the case of R = H which is strongly *E*-selective (run 4~6) as shown in Table 3.

Finally, we examined the rearrangement of salt **8b** oxygenated at the γ'-position. The stereoselectivity of this rearrangement was the same as that of salt **6b**, which leads to a highly *trans* relationship between long

Table 2. Reaction of β-Oxygenated *N*-(Ethoxycarbonyl)methyldimethylammonium Salts **6b**

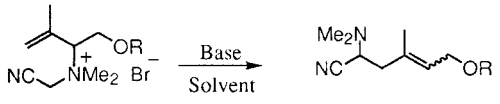


6b R = TBS, THP, Bn **9b*E* / 9b*Z***

Run	R	Base	Solvent	Conditions (°C / h)	Yield[a] (%)	*E* :*Z*[b]
1	TBS	KO*t*Bu	DMF	–40 / 24	73	**96** : 4[c]
2	TBS	NaOEt	EtOH	0 / 3.5	71	**93** : 7[c]
3	THP	LDA	THF	–70 / 1	67	**100** : 0[c,d]
4	Bn	LHMDS	DMF	–50 / 10	68	**95**: 5[c]

[a] Isolated yield. [b] GC analysis. [c] Each stereochemistry of the isolated stereoisomers was analyzed by ^{1}H and ^{13}C NMR ($CDCl_3$) spectroscopy as follows: **9b*E*** (R = TBS): δ 1.60(3H, s); 16.5, **9b*Z*** (R = TBS): δ 1.68(3H, s); 23.8, **9b*E*** (R = THP): δ 1.71(3H, s); 16.2, **9b*E*** (R = Bn): δ 1.67(3H, s); 16.3, **9b*Z*** (R = Bn): δ 1.78(3H, s); 23.4. [d] This stereoisomer was confirmed by NOE analysis

Table 3. Reaction of β-Oxygenated *N*-Cyanomethyldimethylammonium Salts **6c**

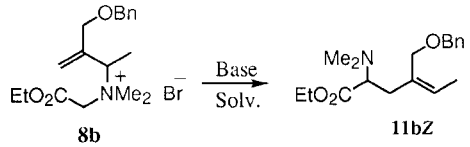


6c R = Bn, H **9c*E* / 9c*Z***

Run	R	Base	Solvent	Conditions (°C / h)	Yield[a] (%)	*E* :*Z*[b]
1	Bn	KO*t*Bu	THF	–70 / 3	67	34 : **66**[c]
2	Bn	LDA	THF	–70 / 0.5	58	34 : **66**[c]
3	Bn	LiOEt	EtOH	0 / 5	67	**60** : 40[c]
4	H	KO*t*Bu	DMF	–50 / 0.5	29	**95** : 5[c]
5	H	LDA	THF	–70 / 3	13	**95** : 5[c]
6	H	NaOMe	MeOH	–70 / 2	65	**90** : 10[c]

[a] Isolated yield. [b] GC analysis. [c] Each stereochemistry of the isolated stereoisomers was analyzed by ^{1}H and ^{13}C NMR ($CDCl_3$) spectroscopy as follows: **9c*E*** (R = Bn): δ 1.62(3H, s); 16.2, **9c*Z*** (R = Bn): δ 1.83(3H, s); 23.4, **9c*E*** (R = H): δ 1.73(3H, s); 15.9, **9c*Z*** (R = H): δ 1.83(3H, s); 23.8

Table 4. Reaction of γ-Oxygenated Ammonium Salts **8b**



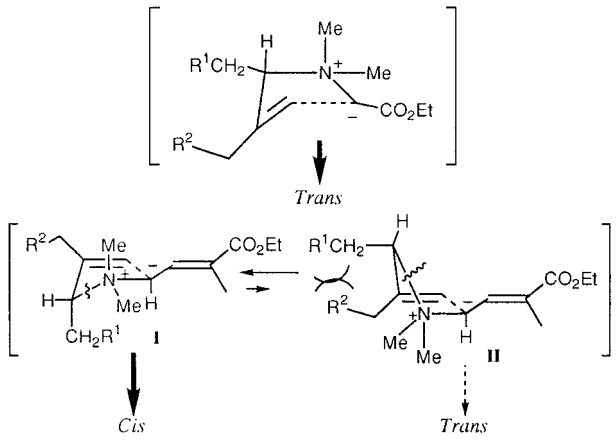
8b **11b*Z***

Run	Base	Solvent	Conditions(°C / h)	Yield(%)[a]	*E* :*Z*
1	KO*t*Bu	THF	–70 / 2	88	0 : **100**
2	NaOEt	EtOH	0 / 2	88	0 : **100**

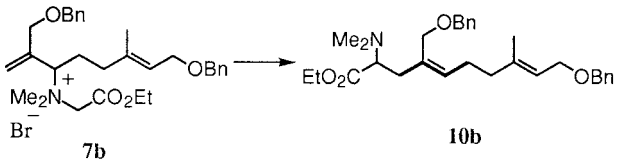
[a] Isolated yield

carbon chains around the carbon-carbon double bond under two basic rearrangement conditions as shown in Table 4.

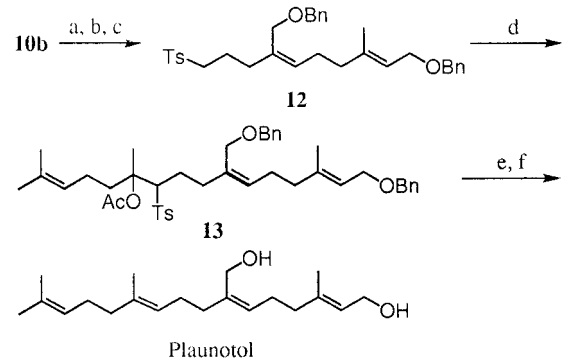
[2,3]Sigmatropic rearrangement of salts **6b**, **8b** and **6c** (R = H) having an electron-withdrawing group directly on the ylide carbon may have the usual concerted transition state of a doubly suprafacial mode[4] exerting no vicinal repulsion between R^1CH_2 and the vinyl R^2CH_2 group, which leads to a *trans* olefin as shown in Scheme 2. On the other hand, the [2,3]sigmatropic rearrangement of salts **3** and **7a** seems to have an earlier (*i.e.*, reactant-like) transition state than that of the above-mentioned stable ylides. Thus another envelope conformation can be postulated as a plausible transition state leading to the *cis* olefin. The conformational preference of **I** over **II** may result from vicinal repulsion between R^1CH_2 and the vinyl R^2CH_2 group, which has been used for the ylide [2,3] processes.[5]



Scheme 2



The present method was applied with the synthesis of plaunotol[6] as shown in Scheme 3.



a, MeI (98%); b, (i) 5% Na/Hg (ii) $LiAlH_4$ (99%, 2 steps); c, (i) TsCl, (ii) NaI, (iii), TsNa (83%, 3 steps); d, (i) nBuLi, methylheptenone, (ii) Ac_2O (88%); e, 5% Na/Hg (68%); f, Na/NH_3 (95%)

Scheme 3

Treatment of **7b** with potassium *tert*-butoxide in THF at –70 °C afforded (*Z*)-ester **10b** exclusively in 96% yield.

A reductive removal of the dimethylamino group was achieved by quaternization of **10b**, followed by treatment of sodium amalgam in a buffer solution. The subsequent reduction of ester was carried out with lithium aluminum hydride to give the corresponding alcohol. *p*-Tolylsulfone **12** was then obtained in 83% yield by the conventional method from alcohol via the corresponding tosylate and iodide. Tolylsulfone **12** was converted with n-BuLi into carbanion, which reacted with methylheptenone and quenched with acetic anhydride to give C_{20} product **13**, which was subjected to Na/Hg and Na/NH_3 reduction succesively to furnish the desired plaunotol.

In summary, [2,3]sigmatropic rearrangement of β- or γ-oxygenated *N*-(ethoxycarbonyl)methyl-β-methallylammonium ylides form trisubstituted *trans*-olefins with high stereoselectivity. On the other hand, the rearrangement of salts having a tiglyl ester moiety instead of a carbethoxy group affords *cis*-olefins. These reactions will find application to the synthesis of functionalized terpenoid and other natural products having defined olefin stereochemistry.

References and Notes

(1) a) Honda, K.; Inoue, S.; Sato, K. *J. Am. Chem. Soc*., **1990**, *112*, 1999 ; b) Honda, K.; Inoue, S.; Sato, K. *J. Org. Chem*., **1992**, *57*, 428 ; c) Honda, K.; Inoue, S. *Synlett*, **1994**, 739.

(2) Honda, K.; Tabuchi, M.; Inoue, S. *Chem. Lett.*, **1996**, 385.

(3) Honda, K.; Yoshii, I.; Inoue, S. *Chem. Lett.*, **1996**, 671.

(4) Yamamoto, Y.; Oda, J.; Inouye, Y. *J. Org. Chem*., **1976**, *41*, 303; Inoue, S.; Iwase, N.; Miyamoto, O.; Sato, K. *Chem. Lett.*, **1986**, 2035.

(5) Trost, B. M.; Mervin, L. S. Jr., *Sulfer Ylides*; Blomquist, A. T.; Wasserman, H. H., Eds.; Academic Press: New York, **1979**, 108–127

(6) For synthesis of plaunotol, see: Ogiso, A.; Kitazawa, E.; Kurabayashi, M.; Sato, A.; Takahashi, S.; Noguchi, H.; Kuwano, H.; Kobayashi, S.; Mishima, H. *Chem. Pharm. Bull*., **1978**, *26*, 3117 ; Sato, K.; Inoue, S.; Iwase, N.; Honda, K. *Bull. Chem. Soc. Jpn*., **1990**, *63*, 1328 ; Inoue, S.; Honda, K.; Iwase, N.; Sato, K. *Bull. Chem. Soc. Jpn*., **1990**, *63*, 1629.