Highly *Z* Selective Synthesis of Functionalized Monoterpenoids *via* *N*-Ylide [2,3]Sigmatropic Rearrangement and Its Application to 13-*cis*-Retinol

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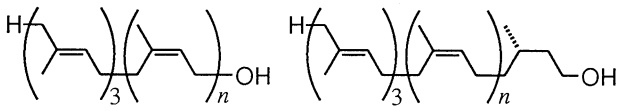
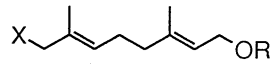
Highly stereoselective elongation of a functionalized *E* isoprene unit on the *Z* terminal methyl of prenol was achieved by the *N*-ylide rearrangement of *N*-tiglyl-β-methallyldimethylammonium salt. (*E*,*Z*)-Rearrangement product was converted into 13-*cis*-retinol *via* useful conjugated triene isoprenoid synthon.

In recent years several kinds of polyprenols such as betulaprenols (**1**),[1] bacteriaprenols (**2**),[2] dolichols (**3**),[3] and others[4] have been isolated from plant and animal tissues and microorganisms. As natural sources of polyprenols are extremely rare, an efficient method of synthesis of these compounds is desired. Several syntheses of all-*trans*-polyprenyl compounds have been reported utilizing such bifunctional (*E*,*E*)-monoterpenoid synthons as **4a**[5] and **4b**,[6] whereas the syntheses of polyprenols with specifically positioned *Z*-trisubstituted olefinic bonds as described above have scarcely been reported because of difficult availability of cisoid isoprenoid synthons. Only one synthesis of (*Z*,*Z*)-synthon **5** has been reported.[7]

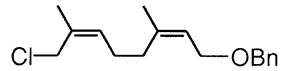


1, *n* = 3–6; **2**, *n* = 7–9

3, *n* = 10–17



4a, X = Cl, R = Bn
4b, X = Br, R = Ac



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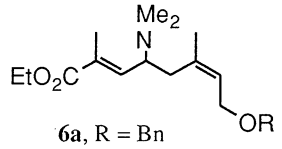
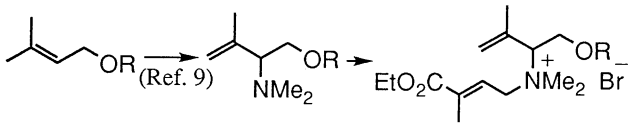


6a, R = Bn
6b, R = Si^{t}BuMe$_2$

We have reported stereocontrolled or stereoselective synthesis of trisubstituted (*E*)- and/or (*Z*)-olefins using an *N*-ylide [2,3]sigmatropic rearrangement of ammonium salts.[8] Reported herein is highly (*Z*)-stereoselective [2,3]sigmatropic rearrangement which provides trisubstituted (*E*,*Z*)-synthons **6a** and **6b** starting from *N*-tiglyl-β-methallyldimethylammonium salts and its application to conjugated triene synthons by oxidative removal of the dimethylamino group. Further application of the key triene synthon to the stereoselective synthesis of 13-*cis*-retinol (**7**) is also reported.

Prenyl benzyl ether was converted *via* ene-type chlorination followed by amination into internal allylamine, which was reacted with ethyl γ-bromotiglate in MeCN to give quaternary salt **8a**.[9] Treatment of **8a** either with potassium *tert*-butoxide in THF-HMPA or with alkali metal ethoxide in ethanol resulted in the



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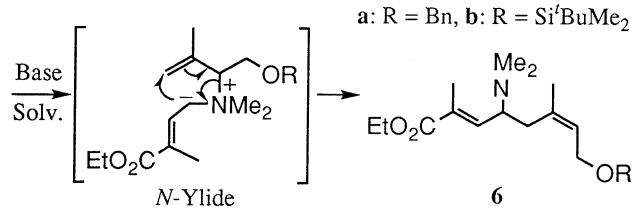
a: R = Bn, **b**: R = Si^{t}BuMe$_2$



N-Ylide **6**

Table 1. Reaction of *N*-Tiglyl-*N*-β-methallyldimethylammonium Salts **8a** and **8b**

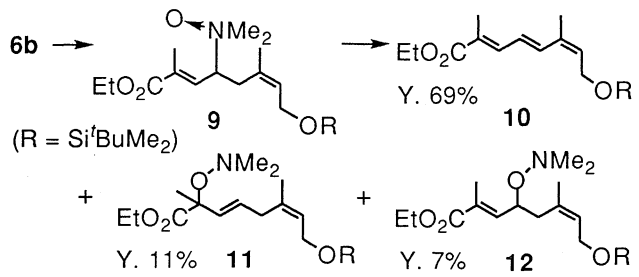
Run	Salt	Base	Solvent	Conditions(°C / h)	Yield(%)	*Z* : *E*
1	**8a**	KO^{t}Bu	THF-HMPA[b]	−70 / 2	41	**100** : 0[c]
2	**8a**	LiOEt	EtOH	−70 / 2	37	**100** : 0[c]
3	**8a**	NaOEt	EtOH	−70 / 2	32	**100** : 0[c]
4	**8a**	KOEt	EtOH	−70 / 4	43	**100** : 0[c]
5	**8b**	KOEt	EtOH	−78 / 5	71[d]	**95** : 5[e]

[a] Isolated yield. [b] HMPA content was 20 vol%. [c] An examination by the chemical shifts of olefinic methyl protons for ^{1}H NMR and those of olefinic methyl carbons for ^{13}C NMR ($CDCl_3$) [δ 1.84(3H, s); 24.1] suggested that single stereoisomer (*Z*)-**6a** is produced. [d] Besides [2,3]sigmatropic rearrangement product **6b**, [1,2] and [3,3] rearrangement products were obtained in 10% and 7% yields, respectively. And each of these including *Z*- and *E*-[2,3] products was easily separated by silica gel column chromatography. [e] Each stereochemistry of the isolated stereoisomers was analyzed by ^{1}H and ^{13}C NMR ($CDCl_3$) spectroscopy as follows: (*Z*)-**6b**: δ 1.73(3H, s); 23.8, (*E*)-**6b**: δ 1.62(3H, s); 15.9.

formation of an *N*-ylide, which underwent [2,3]sigmatropic rearrangement to give diene **6a** which possessed a newly formed *Z* and tiglyl-origin *E* stereochemistry (Table 1, runs 1–4). Similarly, the reaction of **8b** with potassium ethoxide in ethanol afforded (*Z*)-olefin **6b** highly stereoselectively (run 5). It should be noted that the high *Z*-selective character of the present system is in sharp contrast to our previous system which affords (*E*,*E*)- or (*E*,*Z*)-sesquiterpenoid synthons according to the reaction conditions.[10]

This *Z*-selectivity of the rearrangement was applied to a stereoselective synthesis of 13-*cis*-retinol (**7**), of which only a few syntheses were reported.[11]

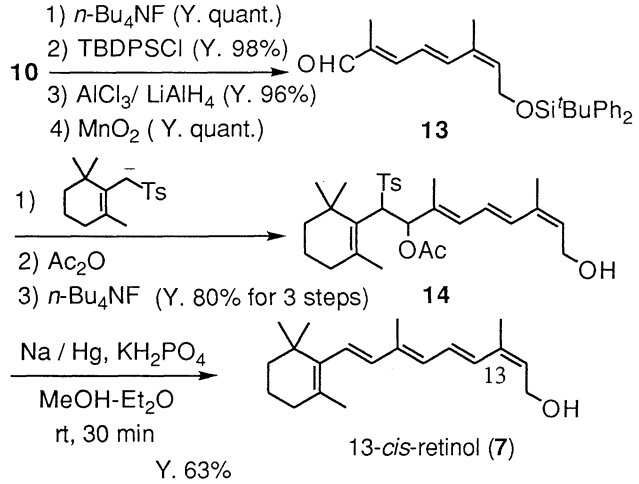
Treatment of **6b** with peracetic acid in dichloromethane at −60 °C in the presence of sodium carbonate resulted in the formation of the *N*-oxide intermediate **9**, which was followed by a Cope elimination during warming up to 0 °C for 30 min to give triene **10**.[12] The *E* stereochemistry of the newly formed double bonds was confirmed by the ^{1}H-NMR spectrum {δ 6.85



Scheme 1.

(d, 1H, J = 15 Hz)}. Besides this Cope elimination, [2,3]sigmatropic rearrangement product **11**[12] and [1,2] rearrangement product **12**[12] were obtained in 11% and 7% yield, respectively. Furthermore **11** was gradually transformed into triene **10** *via* *N*-oxide **9** in MeOH. This unique transformation was completed within 3 d in MeOH at ambient temperature (Scheme 1).

Because of labile property against $AlCl_3$, *tert*-butyldimethylsilyl protecting group was then replaced by *tert*-butyldiphenylsilyl group (Scheme 2). Transformation of ester group to formyl group was carried out by treatment of AlH_3,[13] followed by active manganese (IV) oxide. β-Cyclogeranyl *p*-tolyl sulfone[14] was converted with *n*-BuLi into its carbanion, which reacted with the triene aldehyde **13**[12] and quenched with acetic anhydride[15] followed by desilylation to give β-acetoxysulfone **14**,[12] which underwent smooth reductive cleavage with sodium amalgam to furnish the desired 13-*cis*-retinol (**7**). The structure of the synthetic 13-*cis*-retinol was confirmed by a comparison of its spectral data with those in the literature.[11]



Scheme 2.

As summary, highly stereoselective elongation of a functionalized isoprene unit on the Z terminal methyl of prenol was achieved by the *N*-ylide rearrangement of *N*-tiglyl-β-methallyldimethylammonium salt. And conjugated triene skeleton can be obtained by oxidative removal of the amino group of the rearrangement product. The present method is useful for the construction of (*E*,*Z*)-1,5-diene or conjugated (*E*,*E*,*Z*)-triene monoterpenoid synthons.

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10 We recently reported that 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. Treatment of a salt with base in an aprotic solvent gave (*E*)-isomer predominantly and (*Z*)-isomer was formed predominantly when the salt was treated with an alkoxide base in a protic solvent. And a functionalized sesquiterpenoid synthon can be obtained by reductive removal of the amino group of the rearrangement product, see: K. Honda, M. Tabuchi, and S. Inoue, *Chem. Lett.*, **1996**, 385.

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12 Spectral data for the selected compounds are as follows. **10**: ^{1}H-NMR ($CDCl_3$) δ 0.09(s, 6H), 0.91(s, 9H), 1.32(t, J = 7 Hz, 3H), 1.92(s, 3H), 1.99(s, 3H), 4.22(q, J = 7 Hz, 2H), 4.39(d, J = 6.3 Hz, 2H), 5.63(t, J = 6.3 Hz, 1H), 6.50(dd, J = 11, 15 Hz, 1H), 6.85(d, J = 15 Hz, 1H), 7.26(d, J = 11 Hz, 1H). **11**: ^{1}H-NMR ($CDCl_3$) δ 0.06(s, 6H), 0.90(s, 9H), 1.28(t, J = 7.3 Hz, 3H), 1.54(s, 3H), 1.67(s, 3H), 2.61(s, 6H), 4.16(d, J = 6.6 Hz, 2H), 4.20(q, J = 7.3 Hz, 2H), 5.39(t, J = 6.6 Hz, 1H), 5.5-5.7(m, 2H). **12**: ^{1}H-NMR ($CDCl_3$) δ 0.06(s, 6H), 0.90(s, 9H), 1.29(t, J = 7.3 Hz, 3H), 1.77(s, 3H), 1.87(s, 3H), 2.0-2.5(m, 2H), 2.54(s, 6H), 4.16(d, J = 6.3 Hz, 2H), 4.19(q, J = 7.3 Hz, 2H), 4.51(q, J = 6.9 Hz, 1H), 5.39(t, J = 6.3 Hz, 1H), 6.66(d, J = 6.9 Hz, 1H). **13**: ^{1}H-NMR ($CDCl_3$) δ 1.06(s, 9H), 1.86(s, 3H), 1.92(s, 3H), 4.42(d, J = 6.3 Hz, 2H), 5.81(t, J = 6.3 Hz, 1H), 6.57(dd, J = 12, 15 Hz, 1H), 6.73(d, J = 15 Hz, 1H), 6.75(d, J = 12 Hz, 1H), 7.3-7.7(m, 10H), 9.42(s, 1H). **14**: ^{1}H-NMR ($CDCl_3$) δ 0.72(s, 3H), 1.11(s, 3H), 1.3-1.7(m, 4H), 1.64(bs, 1H), 1.71(s, 3H), 1.86(s, 3H), 2.01(s, 3H), 2.0-2.2(m, 2H), 2.11(s, 3H), 2.47(s, 3H), 4.19(d, J = 10.6 Hz, 1H), 4.27(d, J = 7 Hz, 2H), 5.58(t, J = 7 Hz, 1H), 5.99(d, J = 11 Hz, 1H), 6.02(d, J = 10.6 Hz, 1H), 6.33(dd, J = 11, 15 Hz, 1H), 6.51(d, J = 15 Hz, 1H), 7.35(d, J = 8.6 Hz, 2H), 7.83(d, J = 8.6 Hz, 2H).

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