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A STEREOSELECTIVE SYNTHESIS OF β,γ-DISUBSTITUTED ALLYLIC ALCOHOLS OF Z-CONFIGURATION

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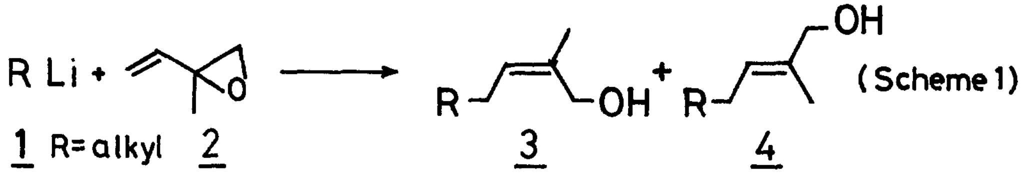
Summary: Reaction of alkyllithiums 1 with isoprene epoxide 2 gives β,γ-disubstituted allylic alcohols 3 of Z-configuration. The reaction of π-lithiotricyclene as alkyllithium gives α-santalol 5, which is one of the main constituents in East Indian sandalwood oil.

The reaction of vinyl epoxides with Grignard reagents and methyllithium was reported to give the mixtures of 1,2-and 1,4-adducts and with organocopper reagents to give 1,4-adducts of E-configuration[1]. Although it was claimed that the reaction of phenyllithium with isoprene epoxide gave a 1,4-adduct of Z-configuration as major product[2], there appears no general method to prepare 1,4-adducts (β,γ-disubstituted allylic alcohols) of Z-configuration from isoprene epoxide.

It was found that the reaction of alkyllithiums 1 with isoprene epoxide 2 gives the isomeric mixtures of β,γ-disubstituted allylic alcohols 3 and 4 in moderate to good yields[3]. (Scheme 1)



The major product was shown to have Z-configuration on the basis of ^{1}H-NOE (ref.4), ^{13}C-and ^{1}H-NMR spectra (ref.5 and 6). No products other than 1,4-adducts were found. The predominancy of Z-isomer was improved when the

Table 1. Synthesis of β,γ-disubstituted allylic alcohols

R	Base[a]	Temp(°C)	Solvent	Yield(%)[b]	Z/E[c]
n-C_4H_9	none	0	Hexane	76	88/12
"	TMEDA	"	"	68	96/4
"	Et_3N	"	"	79	94/6
"	n-C_4H_9OLi	"	"	73	97/3
sec-C_4H_9	none	"	"	63	86/14
"	TMEDA[d]	"	"	74	89/11
"	n-C_4H_9OLi	"	"	51	98/2
n-C_8H_{17}	TMEDA	-20	"	55	96/4
"	n-C_4H_9OLi	0	"	75	93/7
cyclo-C_3H_5	none	-30	Et_2O	77[e]	82/18
cyclo-C_6H_{11}	"	"	"	55	89/11
$PhCH_2CH_2$	"	"	"	70	79/21
"	TMEDA	-20	"	59	98/2

a. Molar ratios of amine, lithium butoxide and isoprene epoxide to alkyllithium were 2.0, 1.0 and 1.1∿1.3, respectively.

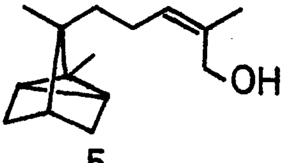
b. Isolated yields either by distillation (Kugelrohr) or preparative TLC.

c. Determined by gas chromatography (Golay column, PEG 20M, 45m, 140°) and/or ^{1}H-NMR.

d. Molar ratio of TMEDA to sec-butyllithium was 1.0.

e. Crude yield.

reaction was conducted in the presence of a base such as tertiary amine or lithium alkoxide. The effect of these additives may be attributed to the dissociation of alkyllithiums[8]. The results are summarised in Table 1.



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The present method was successfully applied to a stereoselective synthesis of α-santalol 5, which is one of the main costituents in East indian sandalwood oil.

Thus, π-bromotricyclene (224.5 mg, 1.0 mmol,

$[\alpha]_D$-9.81°)[9] was lithiated with lithium dispersion (containing 2% Na, 115 mg, 5.0 mmol) at 0° under argon atmosphere. Triethylamine (206.5 mg, 2.0 mmol) in pentane (1 ml) was added dropwise to the reaction mixture. Then, isoprene epoxide (85.1 mg, 1.0 mmol) in pentane (1 ml) was added dropwise and the resulting mixture was stirred for 50 min at 0° and for 30 min at room temperature, respectively. After usual work up, α-santalol was obtained in 58% yield (Z/E=88/12). The pure Z-isomer[10] was obtained by silica gelcolumn gel column chromatography (elution with ether-hexane mixture, 1:1), which gave $[\alpha]_D$+17.6° (c=1.0, $CHCl_3$)[11].

We are indebted to Dr. S. Nakamura for his valuable suggestion, Mr. K. Moriguchi for the measurements of ^{13}C-NMR, ^{1}H-NOE spectra and Mr. K. Hirose for his technical assistance.

References and Notes

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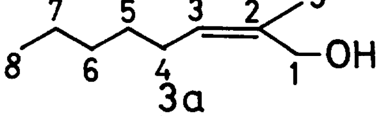
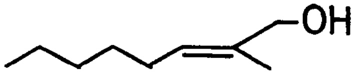
2. (a) J. A. Miller and G. C. Aithie, Tetrahedron Lett., 4419 (1975);
   (b) The reaction of phenyllithium with isoprene epoxide was conducted in our laboratory to give a mixture of 1,2-and 1,4-adduct in 27% and 56% yield, respectively. The Z/E ratio of 1,4-adduct was 50/50.
3. A similar selectivity was observed in the reaction of alkyllithiums with butadiene monoepoxide.
4. The irradiation of H-4 proton in the major component 3a of reaction mixture (Z/E=95/5) increased the intensity of H-1 (30%) and the irradiation of H-3 proton in the minor component 4a increased the intensity of H-1 (21%). Thus, 3a and 4a were assigned to Z-and E-configuration, respectively.



3a



4a

5. The stereochemistry of 3a was also confirmed by the steric shift of ^{13}C-NMR

(ref.7). The signal of C-1 in 3a appeared at δ 61.5 which was 7.5 ppm higher compared to that of E-isomer (δ 69.0 ppm). The ^{13}C-NMR data of 3a was as follows ($CDCl_3$/TMS). δ 61.5 (C-1) 134.3 (C-2) 128.7 (C-3) 27.6 (C-4) 29.8 (C-5) 31.6 (C-6) 22.6 (C-7) 14.0 (C-8) 21.2 (C-9).

6. ^{1}H-NMR data of Z-isomers ($CDCl_3$/TMS); 3a (CCl_4), R=n-C_4H_9: δ 5.23 (t,1H) 4.03 (s,2H) 3.33 (s,1H,-OH) 1.75 (s,3H) 2.25∿0.6 (m,11H), 3b R=sec-C_4H_9: 5.30 (t,1H) 4.10 (s,2H) 2.1∿0.6 (m,15H), 3c R=cyclo-C_6H_{11}: 5.42 (t,1H) 4.17 (s,2H) 2.3∿0.6 (m,17H), 3d R=cyclo-C_3H_5: 5.42 (t,1H) 4.12 (s,2H) 2.2∿1.6 (m,6H) 0.9∿0.0 (m,5H), 3e R=$PhCH_2CH_2$: 7.22 (s,5H) 5.32 (t,1H) 4.06 (s,2H) 2.70 (t,2H) 2.2∿1.1 (m,8H), 3f R=n-C_8H_{17}: 5.22 (t,1H) 4.05 (s,2H) 1.78 (t,3H) 2.3∿0.7 (m,20H).
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10. NMR spectrum was identical with the reported one, which was kindly gifted from Prof. H. Nozaki, Kyoto University.
11. Synthetic; $[\alpha]_D^{25}$+17.5°(ref.12a), $[\alpha]_D^{25}$+16.1°(ref.12b) and $[\alpha]_D^{25}$+17.2° (ref.12c). Natural; $[\alpha]_D^{25}$+17.0°(ref.12d).
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