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A New Synthesis of α-Santalol

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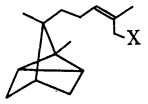
Synopsis. A new synthesis of α-santalol (**1**) is described. 1-Benzyloxy-4-bromo-2-methyl-2-butene (**6**) was converted by the reaction with nickel carbonyl to the π-allylic nickel bromide complex (**7**), which reacted with (−)-π-bromotricyclene (**8**) to afford benzyl ether (**2**). The benzyl ether (**2**) was led to (**1**) (cis: trans=40: 60) by reductive cleavage of the benzyloxy group.

α-Santalol (**1**), which is one of the main constituents of East Indian sandalwood oil, is highly prized in perfumery. Thus, many synthetic approaches have been studied.[1-7]



1, X=OH
2, X=OCH_2Ph
3, X=H

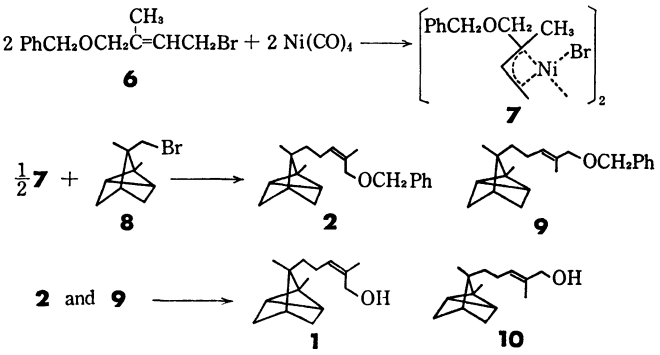
It is known that the π-allylnickel halide complex reacts with alkyl halides to afford allylalkanes.[8] Corey reported that α-santalene (**3**) was synthesized by the reaction of π-iodotricyclene with π-1,1-dimethylallylnickel bromide.[8] Sathe reported that the transformation of α-santalene to α-santalol was carried out by the selenium dioxide oxidation of (**3**), followed by reduction of the resulting aldehyde.[2] However, in the literature the stereochemistry of the product was not described. We reinvestigated Sathe's method and showed that the resulting alcohol was *trans*-α-santalol, isomeric to natural α-santalol, which has a *cis* configuration at the trisubstituted olefin moiety in the side chain.[9] We attempted to synthesize α-santalol by the crosscoupling reaction of a functionalized prenyl fragment with a tricyclene component.

$$PhCH_2OCH_2\overset{CH_3}{\overset{|}{C}}{=}O + (EtO)_2\overset{O}{\overset{\|}{P}}CH_2CO_2Et \longrightarrow PhCH_2OCH_2\overset{CH_3}{\overset{|}{C}}{=}CHCO_2Et \longrightarrow \mathbf{4}$$

$$\longrightarrow PhCH_2OCH_2\overset{CH_3}{\overset{|}{C}}{=}CHCH_2OH \longrightarrow \mathbf{5}$$

$$\longrightarrow PhCH_2OCH_2\overset{CH_3}{\overset{|}{C}}{=}CHCH_2Br \quad \mathbf{6}$$

(−)-π-Bromotricyclene (**8**) was prepared by the method of Corey.[10] Ethyl 4-benzyloxy-3-methyl-2-butenoate (**4**), which was prepared by the Wittig reaction of benzyloxyacetone with diethyl (ethoxycarbonylmethyl)phosphonate, was converted to 4-benzyloxy-3-methyl-2-buten-1-ol (**5**) by lithium aluminum hydride reduction. Bromination of alcohol (**5**) was carried out by the reaction with phosphorus tribromide and pyridine in petroleum ether to give 1-benzyloxy-4-bromo-2-methyl-2-butene (**6**). Bromide (**6**) was a *cis* and *trans* mixture (32: 68). The cross-coupling reaction of π-3-(benzyloxymethyl)-2-butenylnickel bromide (**7**), which was transformed from **6** (*cis*: *trans*=32: 68) and nickel carbonyl, with (−)-π-bromotricyclene (**8**) in hexamethylphosphoric triamide (HMPT) afforded benzyl ethers of α-santalol (**2**: **9**=40: 60). The *cis* (**2**) and *trans* (**9**) mixture of benzyl ethers was led to α-santalol (**1**: **10**=40: 60) by reductive cleavage of the benzyl ether function with lithium in ethylamine at −78 °C. Efforts to increase its selectivity in dimethylformamide or *N*-methylpyrolidone were unsuccessful. Stereoisomers of α-santalol were separated by means of column chromatography over silica gel (benzene–ethyl acetate). The isolated *cis*-α-santalol (**1**) was completely identical with natural α-santalol.



Experimental

All the boiling points are uncorrected. The IR spectra were recorded on a Hitachi Model 215 spectrophotometer. The NMR spectra were recorded on a JEOL Model C-60 spectrometer using tetramethylsilane as an internal standard.

Ethyl 4-Benzyloxy-3-methyl-2-butenoate (4). Diethyl (ethoxycarbonylmethyl)phosphonate (13.4 g) in tetrahydrofuran (THF) (20 ml) was added to sodium hydride (2.6 g) in THF (80 ml) at 22—35 °C and the mixture was stirred for 1.5 h at room temperature. Benzyloxyacetone (8.2 g) in THF (20 ml) was added dropwise to this mixture during 2.5 h at 22—35 °C with additional stirring for 1 h under reflux. After the usual work-up, distillation gave ethyl 4-benzyloxy-3-methyl-2-butenoate (**4**) (9.9 g; 74%), bp 120—129 °C/0.4 mmHg. *cis*: *trans*=37: 63. IR: 1700, 1650 cm^{-1}. NMR (CCl_4): δ 1.25 (t, 3H), 1.99 and 2.08 (*cis* and *trans* each s, 3H), 3.90 (s, 2H), 4.10 (q, 2H), 4.46 (s, 2H), 5.65 and 5.89 (*cis* and *trans* each t, 1H), 7.21 (s, 5H). Found: C, 71.80; H, 7.92%. Calcd for $C_{14}H_{18}O_3$: C, 71.77; H, 7.74%.

4-Benzyloxy-3-methyl-2-buten-1-ol (5). A solution of

ethyl 4-benzyloxy-3-methyl-2-butenoate (**4**) (18.7 g) in diethyl ether (50 ml) was added dropwise to a stirred slurry of lithium aluminum hydride (3.8 g) in diethyl ether (100 ml) for 1.5 h at 22—35 °C, and then stirred for 2 h. The mixture was neutralized with hydrochloric acid and extracted with ether. After drying over Na_2SO_4, distillation gave 4-benzyloxy-3-methyl-2-buten-1-ol(**5**) (15.3 g; quantitative), bp 125—134 °C/0.2 mmHg. *cis*: *trans*=37: 63. IR: 3350, 1070 cm^{-1}. NMR (CCl_4): δ 1.65 and 1.77 (*trans* and *cis* each s, 3H), 2.8 (br, 1H), 3.81 and 3.93 (*trans* and *cis* each s, 2H), 4.05 (d, 2H), 4.39 (s, 2H), 5.57 (t, 1H), 7.20 (s, 5H). Found: C, 74.49; H, 8.41%. Calcd for $C_{12}H_{16}O_2$: C, 74.97; H, 8.39%.

*1-Benzyloxy-4-bromo-2-methyl-2-butene (**6**).* To a solution of 4-benzyloxy-3-methyl-2-buten-1-ol (**5**) (7.0 g) and pyridine (1 ml) in petroleum ether (50 ml) was added phosphorus tribromide (4.3 g) in petroleum ether (10 ml) dropwise for 2.5 h at −15——5 °C. After the addition was complete, the reaction mixture was stirred for 1 h at −11——7 °C. After work-up, crude 1-benzyloxy-4-bromo-2-methyl-2-butene (**6**) (7.8 g; 84%) was obtained as a pale yellow oil. This bromide was used without further purification. *cis*: *trans*= 32: 68. n_D^{20} 1.5455. IR: 2850, 1660 cm^{-1}. NMR (CCl_4): δ 1.73 and 1.85 (*trans* and *cis* each s, 3H), 3.90 (s, 2H), 3.95 (d, 2H), 4.45 (s, 2H), 5.80 (s, 1H), 7.30 (s, 5H).

*Benzyl Ether of α-Santalol (**2** and **9**).* 1-Benzyloxy-4-bromo-2-methyl-2-butene (**6**) (*cis*: *trans*=32: 68, 14 g) in benzene (90 ml) was added dropwise to a solution of nickel carbonyl (14 g) in benzene (90 ml) for 1.5 h at 49—51 °C under an argon atmosphere. After the addition was complete, the reaction mixture was stirred for 3.5 h under the same conditions. Then the excess nickel carbonyl and the benzene were removed under reduced pressure, and to the residue HMPT (90 ml) was added. (−)-π-Bromotricyclene (**8**) (3.9 g) in HMPT (40 ml) was added dropwise to the solution of the nickel complex for 1 h at 40—45 °C, and stirred for 21 h. After work-up, the distillation gave benzyl ethers of α-santalol (**2** and **9**) (2.5 g; 45%), bp 138—142 °C/0.2 mmHg. *cis*: *trans*=40: 60. IR: 2920, 1080 cm^{-1}. NMR (CCl_4): δ 0.80 (s, 3H), 0.95 (s, 3H), 0.80—2.10 (m, 11H), 1.63 and 1.70 (*trans* and *cis* each s, 3H), 3.76 and 3.89 (*trans* and *cis* each s, 2H), 4.34 (d, 2H), 5.30 (m, 1H), 7.23 (s, 5H). Found: C, 85.00; H, 9.67%. Calcd for $C_{22}H_{30}O$: C, 85.11; H, 9.74%.

*α-Santalol (**1**).* Small pieces of lithium (0.3 g) were added to the stirred ethylamine (75 ml) at −10—0 °C until all the lithium was dissolved. After cooling to −78 °C, benzyl ethers of α-santalol (**2**: **9**=48: 52, 2.9 g) in petroleum ethers (10 ml) was added. After stirring for 2.5 h at −78 °C, ammonium chloride (2.0 g) was added and the ethylamine was distilled out. After work-up, the distillation gave α-santalol (**1** and **10**) (1.9 g; 90%), bp 98—102 °C/0.17 mmHg. *cis*: *trans*=48: 52. *cis*- and *trans*- α-Santalol were each isolated by means of column chromatography over silica gel (10: 1 benzene ethyl acetate as eluent). *cis*-α-Santalol (**1**): n_D^{20} 1.5018, $[\alpha]_D^{20}$ +17.20 (c=0.8, $CHCl_3$). IR: 3300, 2950, 1005 cm^{-1}. NMR ($CDCl_3$): δ 0.82 (s, 3H), 0.82—2.20 (m, 12H), 0.98 (s, 3H), 1.80 (s, 3H), 4.13 (s, 2H), 5.33 (t, 1H). *trans*-α-Santalol (**10**): n_D^{20} 1.5013, $[\alpha]_D^{20}$ +17.22 (c=1.5, $CHCl_3$). IR: 3300, 2940, 1005 cm^{-1}. NMR ($CDCl_3$): δ 0.85 (s, 3H), 0.85—2.20 (m, 12H), 1.00 (s, 3H), 1.68 (s, 3H), 3.99 (s, 2H), 5.40 (t, 1H).

References

1) J. Colonge, G. Descotes, Y. Bahurel, and A. Menet, *Bull. Soc. Chim. Fr.*, **1966**, 374.

2) V. M. Sathe, K. K. Chakravarti, M. V. Kadival, and S. C. Bhattacharyya, *Indian J. Chem.*, **4**, 393 (1966).

3) S. Y. Kamat, K. K. Chakravarti, and S. C. Bhattacharyya, *Tetrahedron*, **23**, 4487 (1967).

4) R. G. Lewis, D. H. Gustafson, and W. F. Erman, *Tetrahedron Lett.*, **1967**, 401.

5) E. J. Corey and H. Yamamoto, *J. Am. Chem. Soc.*, **92**, 226 (1970).

6) E. J. Corey, H. A. Kirst, and J. A. Katzenellenbogen, *J. Am. Chem. Soc.*, **92**, 6314 (1970).

7) M. Julia, Ger. Offen., 2341872 (1974).

8) E. J. Corey and M. F. Semmelhack, *J. Am. Chem. Soc.*, **89**, 2755 (1967).

9) We referred to Faulkner's publication in order to determine the stereochemistry by NMR data. And Bhalerao reported that the aldehyde obtained by the selenium dioxide oxidation had a *trans* configuration. D. J. Faulkner, *Synthesis*, **1971**, 175; Uday T. Bhalerao and Henry Rapoport, *J. Am. Chem. Soc.*, **93**, 4835 (1971).

10) E. J. Corey, S. W. Chow, and R. A. Scherrer, *J. Am. Chem. Soc.* **79**, 5773 (1957).