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STEREOSPECIFIC SYNTHESIS OF (±)-β-SANTALOL

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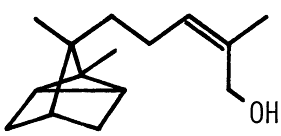
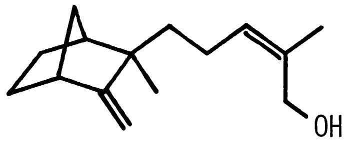
A stereospecific synthesis of 1-acetoxy-5-bromo-2-methyl-2-*cis*-pentene in 4 steps starting from 3-formyl-5,6-dihydro-2*H*-pyran, dimer of acrolein, followed by alkylation of 2-ethoxycarbonyl-3-methylbicyclo[2.2.1]hept-2-ene with the bromide furnished a facile synthesis of (±)-β-santalol.

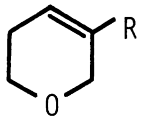
East Indian sandalwood oil is a prized essential oil of sweet woody fragrance. α-Santalol (1) and β-santalol (2) account for about 90% of the oil and are generally considered to be responsible for the basic sandalwood note. Although many papers have been reported on the synthesis of β-santalol,[1-4] those methods do not permit the accumulation of large amounts of material owing to low or unspecified stereoselectivity or low overall yields. Here we report a new method of the stereospecific synthesis of 2, which features the novel use of a dihydropyran as the key precursor of the side-chain unit with *cis*-trisubstituted olefinic linkage and involves a bicyclic α,β-unsaturated ester as the other synthetic component.



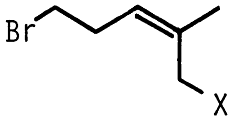
1



2



3, R = CHO
4, R = CH_2OH
5, R = CH_3

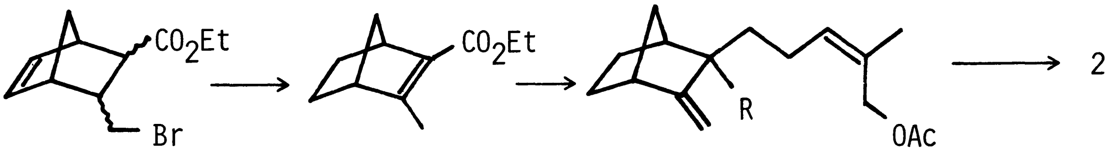


6, X = Br
7, X = OAc

Reaction of 3-formyl-5,6-dihydro-2*H*-pyran (3)[5] with sodium borohydride in ethanol at room temperature gave 3-hydroxymethyl-5,6-dihydro-2*H*-pyran (4) in 76% yield, which was subjected to Birch reduction with sodium (large excess) and ethanol (1 equiv) in liquid ammonia at −50 °C to afford 3-methyl-5,6-dihydro-2*H*-pyran (5) in 80% yield. Reaction of 5 with triphenylphosphine dibromide in acetonitrile–chlorobenzene (3:1) at reflux for 20 h gave 1,5-dibromo-2-methyl-2-*cis*-pentene (6) in 69% yield, which was treated with sodium acetate in DMF at room temperature for 12 h to effect selective displacement of the allylic position yielding 1-acetoxy-5-bromo-2-methyl-2-*cis*-pentene (7) in 64% yield, homogeneous on g.l.c., b.p. 70-72 °C at 0.4 mmHg; δ 1.19 (3H, s), 2.00 (3H, s), 2.60

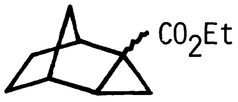
(2H, m), 3.40 (2H, t), 4.60 (2H, s), and 5.60 (1H, m).

The Diels-Alder adduct (8)[6] of cyclopentadiene and ethyl γ-bromocrotonate was catalytically hydrogenated to give the saturated ester 9 in 90% yield, which was converted into 2-ethoxycarbonyl-3-methylbicyclo[2.2.1]hept-2-ene (10) in 40% yield with DBU (1 equiv) in DMSO at 80 °C for 6 h, whereas the treatment of 9 with sodium ethoxide in DMSO at 80 °C for 12 h yielded a tricyclic ester 11 in 60% yield.



8 10

12, R = CO_2Et
13, R = CH_2OH
14, R = CH_2Br



11

Treatment of the ester 10 with lithium diisopropylamide in THF-HMPA (4:1) at −78 °C followed by addition of 7 yielded 12 in 76% yield after purification by column chromatography on silica gel. The exclusive α and *exo* alkylation was confirmed by satisfactory n.m.r. spectrum [δ 2.50 and 2.60 (1H each, s, C-1-H and C-4-H), 4.83 and 4.96 (1H each, s, $=CH_2$)].[7] When 12 was treated with diisobuthylaluminum hydride (2 equiv) in toluene at −78 °C for 1 h, 2-*endo*-methylol compound 13 was obtained in 86% yield with the terminal acetate group completely retained. The alcohol 13 was converted with phosphorus tribromide to 14 which was treated with lithium aluminum hydride in THF at reflux for 30 h to afford β-santalol (2) in 72% yield. The structure was confirmed by the comparison of i.r. and n.m.r. spectra and the retention time on g.l.c. with those of a sample from natural sources.

References

1) G. Buchbauer, Chem. Ztg., 100, 225, (1976); C. H. Heathcock in "The Total Synthesis of Natural Products," ed. by J. ApSimon, Vol. 2, Wiley Interscience, New York, N. Y. (1973), pp 481-491.
2) P. A. Christenson and B. J. Willis, J. Org. Chem., 44, 2012, (1979).
3) M. Baumann and W. Hoffmann, Liebigs Ann. Chem., 1979, 743.
4) C. Sreekumar, K. P. Darst, and W. C. Still, J. Org. Chem., 45, 4260, (1980).
5) B. P. Geyer and R. H. Mortimer, U. S. Patent 2514156 (1950); Chem. Abstr., 44, 8377i (1950).
6) H. Shimomura, Agr. Biol. Chem., 39, 657, (1975).
7) A stereoselective synthesis of (±)-β-santalene was reported by French chemists. They found stereoselective reaction of 2-methoxycarbonyl-3-methylenebicyclo-[2.2.1]heptane with 5-iodo-2-methyl-2-pentene affording an *exo*-alkylated product which was converted to (±)-β-santalene. (M. Bertrand, H. Monti, and K. C. Houng, Tetrahedron Letters, 1979, 15).

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