Enantiodivergent Route to Both Enantiomers of β-Santalene and *epi*-β-Santalene from a Single Chiral Template

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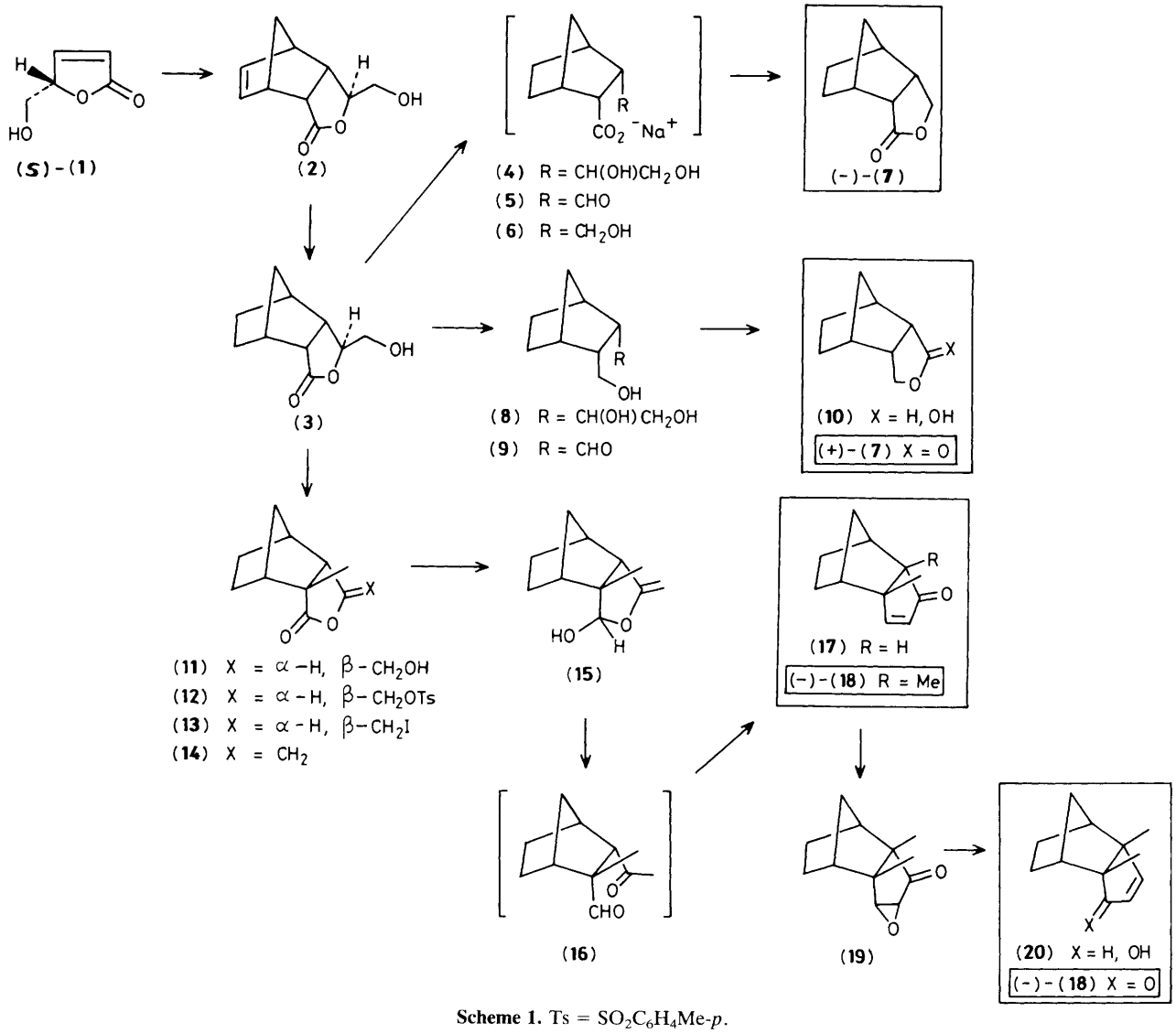
An enantiodivergent route to both enantiomers of β-santalene and *epi*-β-santalene, constituents of East Indian sandalwood oil, has been developed using a single chiral template.

An efficient synthesis of (*S*)-5-hydroxymethylbuten-2-olide (**1**) from D-mannitol has recently been developed by this laboratory.[1] In this context, we report here a stereocontrolled enantiodivergent route to both enantiomers of β-santalene[2] (**26**) and *epi*-β-santalene[3] (**31**), constituents of the prized essential oil of East Indian sandalwood, using (**1**) as common chiral template.

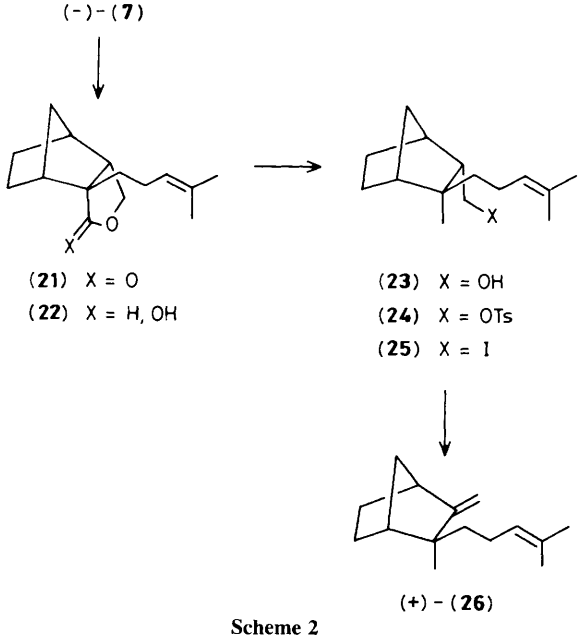
Heating (**1**) with excess of cyclopentadiene (10.0 equiv.) in a sealed tube (140 °C, 9 h) without solvent gave the crystalline *endo*-adduct† (**2**), m.p. 96—97 °C, $[\alpha]_D^{26}$ −49.77° (*c* 1.01, $CHCl_3$), in 60% yield after removal of a minor amount of isomeric adducts by recrystallization (hexane–ether). The adduct (**2**) was hydrogenated (H_2, 10% Pd–C, MeOH) to give the saturated lactone (**3**), m.p. 75—76 °C, $[\alpha]_D^{26}$ −54.95° (*c* 1.00, $CHCl_3$), in 98% yield. Saponification of (**3**) (20% aq. NaOH, 0 °C), followed by sequential treatment of the resulting carboxylate (**4**) with sodium periodate and sodium borohydride in the same flask (0 °C to room temp.) furnished the (−)-lactone (**7**), $[\alpha]_D^{26}$ −156.21° (*c* 0.81, $CHCl_3$), in 66% yield after acid work-up (10% aq. HCl). Alternatively, (**3**) was sequentially reduced [$LiAlH_4$, tetrahydrofuran (THF), 0 °C] and oxidized (aq. $NaIO_4$) to give the lactol (**10**) which was further oxidized (Ag_2CO_3–Celite,[4] benzene, reflux) to furnish the enantiomeric (+)-lactone (**7**), $[\alpha]_D^{26}$ +153.28° (*c* 1.01, $CHCl_3$), in 47% overall yield.

Alkylation of (**3**), without protecting the hydroxy group, [lithium di-isopropylamide (LDA) (2.1 equiv.), THF, −78 °C to room temp., then MeI, −78 °C] gave (**11**), m.p. 99—101 °C, $[\alpha]_D^{25}$ −49.54° (*c* 1.01, $CHCl_3$), in 82% yield. Tosylation [*p*-Me-$C_6H_4SO_2Cl$, Et_3N, 4-*N*,*N*-dimethylaminopyridine (DMAP), 0 °C to room temp.] of (**11**), followed by treatment of the resulting (**12**), m.p. 88 °C, $[\alpha]_D^{23}$ 0° (*c* 1.02, $CHCl_3$), with sodium iodide (methyl ethyl ketone, 70 °C, 24 h) gave the iodide (**13**), m.p. 81—82 °C, $[\alpha]_D^{24}$ −81.36° (*c* 1.02, $CHCl_3$), in 85% yield. Upon treatment with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) (1.5 equiv., benzene, 70 °C, 22 h) (**13**) gave the enol-lactone (**14**), $[\alpha]_D^{24}$ +32.86° (*c* 1.01, $CHCl_3$), in 95% yield. Partial reduction of (**14**) with di-isobutylaluminium hydride (1.0 equiv., CH_2Cl_2, −78 °C) gave the lactol (**15**) which was immediately treated with aqueous base (0.5 M aq. KOH, EtOH, room temp., 14 h) forming the enone (**17**), $[\alpha]_D^{25}$ +147.05° (*c* 1.02, $CHCl_3$), in 71% yield *via* the spontaneous aldolization of (**16**). Alkylation of (**17**) (LDA,

† Satisfactory spectral (i.r., ^1H n.m.r., mass) and (combustion and/or high resolution mass spectral) data were obtained for all new isolable compounds.



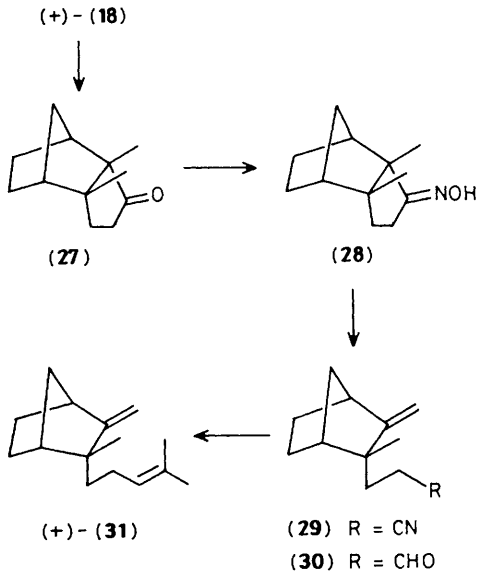
Scheme 1. Ts = $SO_2C_6H_4Me$-*p*.



Scheme 2

THF, −78 to −30 °C, then MeI, −78 °C) afforded the (+)-dimethylenone (**18**), m.p. 65—66 °C, $[\alpha]_D^{26}$ +37.33° (*c* 0.60, $CHCl_3$), in 85% yield. Chirality inversion of (+)-(**18**) was accomplished by 1,3-ketone transposition employing the Wharton reaction.[5] Thus, treatment of (+)-(**18**) with alkaline 30% hydrogen peroxide (0.5 M aq. NaOH, 0 °C to room temp.) gave the single epoxide (**19**), $[\alpha]_D^{24}$ +99.10° (*c* 1.03, $CHCl_3$), in 90% yield. Exposure of (**19**) to hydrazine hydrate (85%) in the presence of acetic acid in boiling methanol afforded the allylic alcohol (**20**), m.p. 80—81 °C, $[\alpha]_D^{28}$ +40.20° (*c* 0.80, $CHCl_3$), in 37% yield, which on oxidation under Swern conditions[6] afforded the enantiomeric (−)=enone (**18**), m.p. 65—66 °C, $[\alpha]_D^{28}$ −37.89° (*c* 0.80, $CHCl_3$), in 70% yield (Scheme 1).

Having obtained both enantiomers of (**7**) and (**18**), we synthesized the natural products using one enantiomer of each as representative. Thus, (−)-(**7**) was alkylated with 4-methylpent-3-enyl bromide[7] (LDA, THF, −78 °C) to give (**21**), $[\alpha]_D^{24}$ −78.67° (*c* 0.40, $CHCl_3$), in 61% yield. Reduction of (**21**) with di-isobutylaluminium hydride (2.0 equiv., THF, −78 °C), followed by treatment of the resulting lactol (**22**) with hydrazine hydrate (3.5 equiv.) and potassium hyroxide (3.5 equiv., diethylene glycol, 130 then 200 °C) gave the primary alcohol (**23**), $[\alpha]_D^{24}$ −79.34° (*c* 0.50, $CHCl_3$), in



Scheme 3

73% yield. Compound (**23**) was sequentially tosylated (*p*-$MeC_6H_4SO_2Cl$, Et_3N, DMAP, 0 °C to room temp.), substituted (NaI, methyl ethyl ketone, 70 °C), and dehydrohalogenated (DBU, benzene, 70 °C) to afford (+)-β-santalene (**26**), $[\alpha]_D^{25}$ +108.6° (*c* 0.51, $CHCl_3$) {lit.[3c] $[\alpha]_D^{28}$ −112° (*c* 5.01, $CHCl_3$)}, in 87% yield (Scheme 2).

Hydrogenation of (+)-(**18**) (H_2, 10% Pd–C, methanol) gave the ketone (**27**), m.p. 120—121 °C, $[\alpha]_D^{25}$ +211.34° (*c* 1.06, $CHCl_3$), in 95% yield. Oximation (hydroxylamine hydrochloride, pyridine) of (**27**), followed by treatment of the resulting single oxime (**28**) with phosphorus pentachloride allowed facile dehydrative cleavage[8] to give the unsaturated nitrile (**29**), $[\alpha]_D^{27}$ + 27.49° (*c* 0.24, $CHCl_3$), in 61% yield. Reduction of (**29**) with di-isobutylaluminium hydride (1.0 equiv., THF, −78 °C, followed by acid work-up) gave the aldehyde (**30**) which on Wittig condensation (Ph_3Pr^iPBr, Bu^nLi, THF, −78 °C) afforded (+)-*epi*-β-santalene (**31**), $[\alpha]_D^{25}$ +25.94° (*c* 0.39, $CHCl_3$) {lit.[3a] $[\alpha]_D^{29}$ +26.90° (*c* 0.40, $CHCl_3$)}, in 75% yield.

We thank the Ministry of Education, Science and Culture of Japan for financial support.

Received, 13th July 1987; Com. 1004

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