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THE FIRST STEREOSELECTIVE SYNTHESIS OF (+)-NUCIFEROL AND (+)-NUCIFERAL

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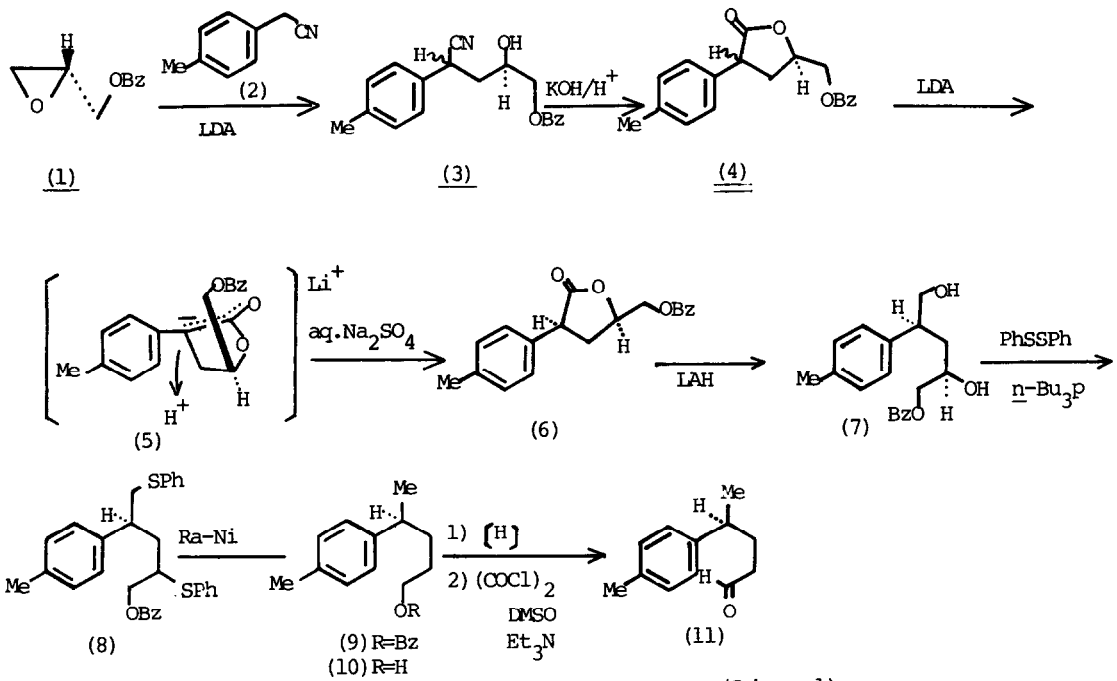
Summary: Using (S)-benzyl 2,3-epoxypropyl ether (1), the first stereoselective synthesis of (+)-nuciferol (14) and (+)-nuciferal (16) has been achieved. Employing the same methodology an enantioselective synthesis of (+)-α-curcumene (17) is also described.

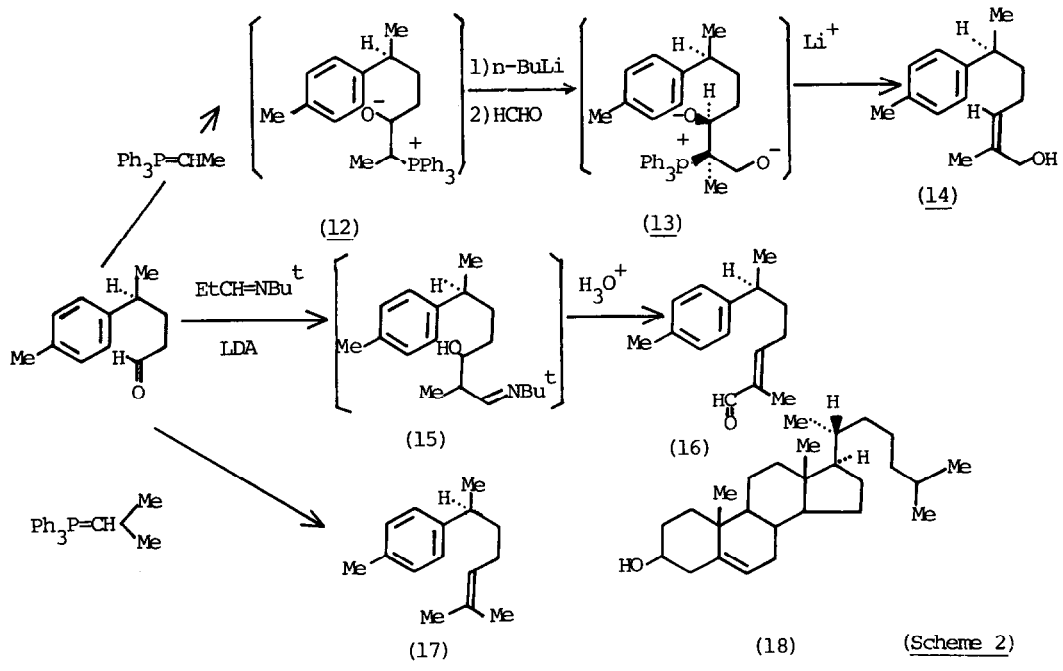
The monocyclic aromatic bisaborane type sesquiterpenes (+)-nuciferol (14) and (+)-nuciferal (16) were isolated from the wood oil of "Kaya" (Torreya nucifera Sieb. et Zucc.) by Sakai, Nishimura, and Hirose in 1965[1]. Although a number of racemic syntheses of the latter have been reported[2], but none of syntheses for the former in both racemic and natural forms as well as the latter in natural forms have been reported so far. We now describe the first enantioselective synthesis of both sesquiterpenes using (S)-benzyl 2,3-epoxypropyl ether (1)[3] which is readily available from a naturally abundant hexose D-mannitol.

The synthetic scheme is initiated by (S)-benzyl 2,3-epoxypropyl ether (1) which is condensed with 4-methylphenylacetonitrile (2) in the presence of lithium diisopropylamide at -78° to ambient temperature to give the cyano-alcohol (3) in a mixture of epimers. The mixture was then hydrolyzed with 10 % ethanolic potassium hydroxide at reflux temperature, followed by acid work-up to give the disubstituted γ-lactone (4) in 65 % overall yield from (3) as a 1 : 1 mixture of epimers[4]. The key stereocontrolling step was carried out by a one-portional addition of an excess of a saturated aqueous sodium sulfate at -78° to the enolate (5) generated in situ from the mixture (4) with lithium diisopropylamide in tetrahydrofuran to give rise the syn α/γ-isomer (6) in 74 % yield as a sole product.

Having controlled the stereochemistry by the kinetic protonation in a remarkable selectivity, the syn-lactone (6) was reduced with lithium aluminum hydride in tetrahydrofuran to give the diol



(Scheme 1)



(Scheme 2)

(7)[5] quantitatively. Treatment of the diol (7) with 4 equiv of diphenyl disulfide and tri-n-butylphosphine in pyridine[6] at 100° afforded the disulfide (8) which was then refluxed with Raney nickel catalyst (W-2) in ethanol to give the benzyl ether (9)[5] and the primary alcohol (10)[5] in yields of 68 and 21 % from the diol (7). Hydrogenolysis of (9) in the presence of 10 % palladized carbon yielded the primary alcohol (10) which was then converted into the key aldehyde (11)[5] in 85 % yield employing the Moffatt-Swern conditions[7].

Construction of the Z-trisubstituted olefin moiety of (+)-nuciferol (14) was simply accomplished by employing the modification of the Wittig reaction developed by Corey and Yamamoto[8]. Thus, the aldehyde (11)[2c] was treated with ethylidenetriphenylphospholane at -78° for 5 min to produce the betaine (12) which was then treated with one equiv of n-butyllithium, followed by two equiv of paraformaldehyde to furnish (+)-nuciferol (14), $[\alpha]_D$ + 37.6° (c = 0.94, $CHCl_3$) (natural[1], $[\alpha]_D$ + 41.06° ($CHCl_3$)), in 42 % yield identical in all respects with an authentic material[9].

Conversion of the aldehyde (11) into (+)-nuciferal (16) was simply carried out by employing the established method for the synthesis of racemic nuciferal developed by Büchi and Wüest[2c]. Thus, the aldehyde (11) was treated with propylidene-t-butylamine in the presence of lithium diisopropylamide, followed by acid hydrolysis to give (+)-nuciferal (16), $[\alpha]_D$ + 54.7° (c = 1.13, $CHCl_3$) (natural[1], $[\alpha]_D$ + 62.07° (c = 16.55, $CHCl_3$)), in 55 % yield identical in all respects with the literature data.

Using the aldehyde (11) an enantioselective synthesis of (+)-α-curcumene (17) was also achieved. Thus, upon treatment with isopropylidenetriphenylphospholane in a standard manner, (11) furnished the α-curcumene (17)[10], $[\alpha]_D$ + 42.8° (c = 1.18, $CHCl_3$) (natural[11], $[\alpha]_D$ + 45.1° (c = 0.75, $CHCl_3$)), in 44 % yield.

The present route may be applicable not only to other members of the bisabolane family, but also the construction of aliphatic side chains of steroids (e.g. (18)) as we already have established an efficient synthesis of (R)-benzyl 2,3-epoxypropyl ether from (D)-mannitol[12].

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4. Both epimers could be separated by a silica-gel column chromatography : The syn isomer, mp 66-67 C°, $[\alpha]_D$ -10.6° (c 1.15, EtOH), νmax (cm^{-1}) 1760; δ (ppm) 2.33 (s, 3H), 2.1-3.0 (m, 2H), 3.70 (d, 2H, J=4Hz), 3.85 (dd, 1H, J=9,12 Hz), 4.60 (s, 2H), 4.4-5.0 (m, 1H, 7.12 (s, 4H), 7.30 (s, 5H), and the anti isomer, oil, $[\alpha]_D$ - 39.9° (c 2.59, EtOH), ν max (cm^{-1}) 1760 ; δ (ppm) 2.33 (s, 3H), 2.3-2.6 (m, 2H), 3.6-3.8 (m, 2H), 4.00 (t, 1H, J=9Hz), 4.57 (s, 2H), 4.6-4.9 (m, 1H), 7.10 (s, 4H), 7.30 (s, 5H).

5. (7): oil, $[\alpha]_D$ + 7.92° (c 1.24, EtOH), νmax (cm^{-1}) 3300, δ (ppm) 1.5-1.9 (m, 2H), 2.33 (s, 3H), 2.3-2.8 (br, 2H, exchangeable), 2.8-3.2 (m, 1H), 3.2-4.0 (m, 5H), 4.50 (s, 2H), 7.10 (s, 4H), 7.30 (s, 5H).

(9): oil, $[\alpha]_D$ + 6.61° (c 1.42, EtOH), δ(ppm) 1.21 (d, 3H, J=7Hz), 1.3-1.8 (m, 4H), 2.30 (s, 3H), 2.4-2.9 (m, 1H), 3.25-3.6 (m, 2H), 4.43 (s, 2H), 7.03 (s, 4H), 7.27 (s, 5H).

(10): oil, $[\alpha]_D$ + 8.20° (c 1.42, $CHCl_3$), νmax (cm^{-1}) 3300, δ (ppm) 1.23 (d, 3H, J=7Hz), 1.2-1.9 (m, 7H), 2.30 (s, 3H), 2.4-2.9 (m, 1H), 3.55 (t, 2H, J=6Hz), 7.07 (s, 4H).

(11): oil, ν max (cm^{-1}) 2700, 1720 δ (ppm) 1.28 (d, 3H, J=7Hz), 1.5-2.2 (m, 4H), 2.33 (s, 3H, 2.5-3.0 (m, 1H), 7.07 (s, 4H), 9.64 (t, 1H, J=1Hz).

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9. We are greatly indebted to Dr. Tsutomu Sakai, Suntory Institute for Bioorganic Research, for this comparison.

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