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MICROBIAL OXIDATION IN SYNTHESIS: A SIX STEP PREPARATION OF (±)-PINITOL FROM BENZENE

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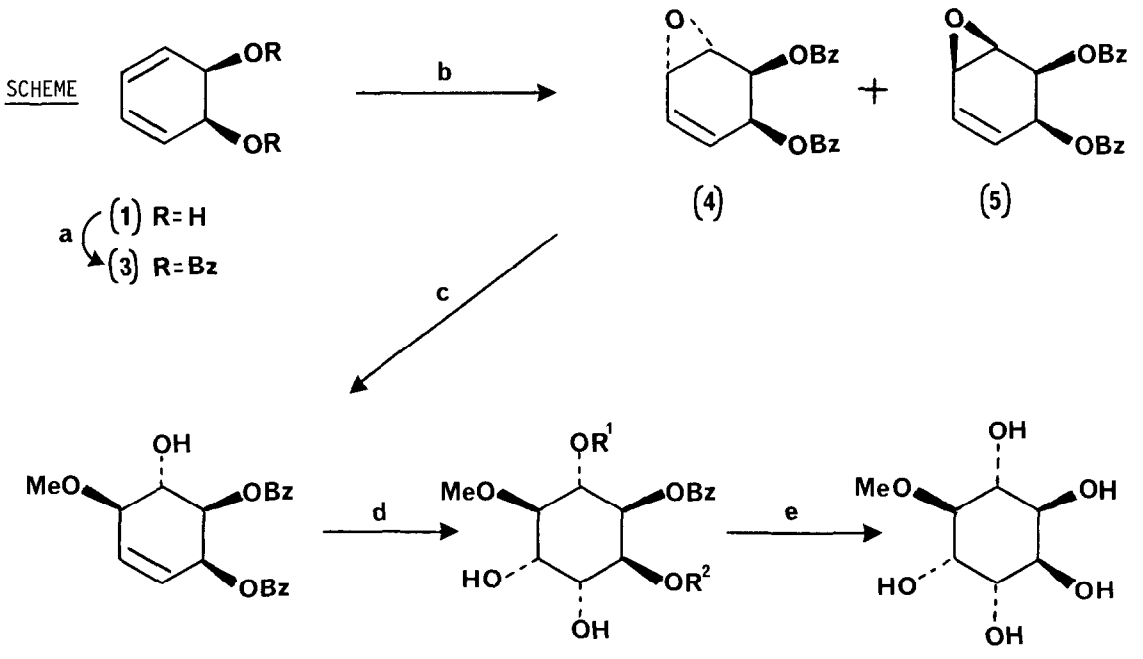
Summary: Synthesis of (±)-pinitol in 35% overall yield from benzene has been achieved where the key step involved microbial oxidation of benzene to cis-1,2-dihydroxycyclohexa-3,5-diene.

Traditionally the conversion of aromatic substrates to non-aromatic compounds relies almost entirely on the use of the Birch reduction, or other reduction processes, to disrupt the inherent stability of the aromatic sextet. There is no single chemical process to date which permits the direct oxidation of benzene or very simple aromatic systems to synthetically useful substances[1].

However, recent developments with microbial oxidants now makes cis-1,2-dihydroxycyclohexa-3,5-diene (1) readily available from benzene in large quantities using Pseudomonas putida[2]. This diene is well-suited for chemical elaboration. Here we illustrate an application to the efficient synthesis of a polyhydroxylated cyclohexane derivative, (±)-pinitol (2) (scheme). There is currently considerable interest in the synthesis of these cyclitol compounds and particularly in systems related to the cellular secondary messenger inositol-1,4,5-triphosphate[3].

SCHEME



a) 2.2 PhCOCl, pyridine, DMAP, 0°C 2hrs, RT 2½hrs.; b) 1.1 m-CPBA, $ClCH_2CH_2Cl$, pH 8 phosphate buffer, RT, 71hrs.; c) MeOH, (±)-camphorsulphonic acid, RT, 13hrs.;[2] d) 0.1% OsO_4, NMO, t-BuOH/THF/H_2O 10: 3 : 1, RT, 84hrs.; e) Et_3N/MeOH/H_2O 1 : 5 : 1, RT, 3hrs.

Dibenzoate (3) was prepared from (1) by standard procedures (84% yield)†. Epoxidation (m-CPBA, 1.1 eq, pH 8) of (3) afforded the vinyl epoxides (4) and (5) in 73% and 14% yields, respectively. These structures were confirmed by x-ray crystallographic methods††. No diepoxide was isolated in this reaction, even under more vigorous reaction conditions. Ring-opening of (4) using methanol and a trace of camphorsulphonic acid occurred solely at C-4, as expected, to provide (6) (88% yield), δ (400MHz) 8.00 (4H, m, Ph), 7.50 (6H, m, Ph), 6.13 (1H, dd, J = 10, 2 Hz, H_5), 6.02 (1H, ddd, J = 10, 5, 2 Hz, H_6) 5.94 (1H, dd, J = 5, 4.5 Hz, H_1), 5.35 (1H, dd, J = 11, 4.5 Hz, H_2), 4.40 (1H, dd, J = 11, 7.5 Hz, H_3), 3.99 (1H, ddt, J = 7.5, 2.0, 0.75 Hz, H_4), 3.60 (3H, s, Me), 2.55 (1H, br s, OH).

The alkenol (6) was converted into a 5:1 mixture (65%) of (7a) and (7b) by hydroxyl-directed[4] catalytic osmylation (0.1% OsO_4, NMO). Hydrolysis of (7a and 7b) ($Et_3N/MeOH/H_2O$)[5] and chromatography (silica, i-PrOH/$CHCl_3$ 2:1) of the water-soluble material provided (2), which was identical (TLC, high field NMR, IR, mass spectroscopy) with a natural sample of pinitol. This approach constitutes the first total synthesis of pinitol.

Pinitol has been shown to be a feeding stimulant for the larvae of the yellow butterfly, Eurema hecabe mandarina[6a], and also inhibits Heliothis zea larvae growth in soybeans[6b].

Acknowledgements

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Footnotes

† All new compounds gave satisfactory spectral, microanalytical and/or accurate mass data.

†† We thank Dr. D.J. Williams, Imperial College for these results.

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