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PHOTOCHEMICAL ROUTES FROM ARENES TO INOSITOL INTERMEDIATES: THE PHOTO-OXIDATION OF SUBSTITUTED cis-CYCLOHEXA-3,5-DIENE-1,2-DIOLS

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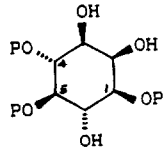
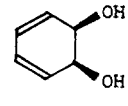
Summary: Endoperoxides such as (**6**), (**15**), (**16**) and (**20**) are available by microbial oxidation and photo-oxidation of arenes; u.v. photolysis of (**6**) yields mainly the $\beta\gamma$-epoxyketone (**9**), and further photolysis gives (**10**) via photoepimerisation.

There has been intense recent interest in the role of myo-inositol trisphosphate (IP_3, **1**) and its synthetic analogues as secondary cell messengers.[1,2] Nearly all the preparative routes to these compounds involve abundant myo-inositol (**2**) and depend on protection/deprotection steps to distinguish the hydroxyl groups and to generate the desired positional isomers.[3,4] In view of the limited natural occurrence of other cyclitol stereoisomers in plant material,[5] adaptable synthetic routes to such compounds are desirable.

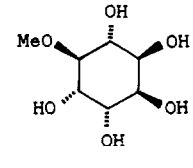
The stereospecific microbial oxidation of benzene to cis-cyclohexa-3,5-diene-1,2-diol (**3**) using Pseudomonas putida strains has made this a readily available material, of potential in synthesis.[6] In particular, Ley and his group have shown attractive syntheses both of pinitol (**4**)[7] and, very recently, of IP_3 from benzene.[8] We now report the use of photo-oxidation and endoperoxide photolysis to give specific stereoisomers of polyoxygenated cyclohexenes from arenes, thus generating what we believe to be worthwhile intermediates for inositol and inosose synthesis: starting from toluene, this route has provided enantiospecific syntheses.



(1) R = PO_3H_2
(2) R = H



(3)

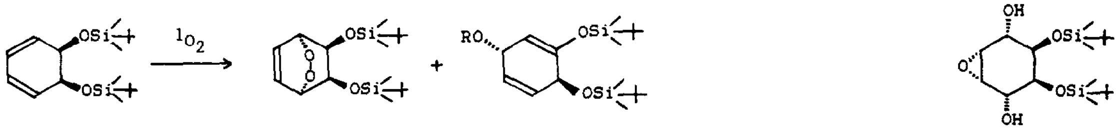


(4)

Photosensitised oxidation of the disilylated diene (**5**)[9] at -80°C, followed by low temperature chromatography, gave a single endoperoxide isomer (**6**, 32%) assigned the trans-stereochemistry shown, and a hydroperoxide (**7**, 45%)

which was stable in solution over several days at 20°C.[10] Attempted chromatography of the photo-oxidation products at room temperature led to the isolation of 1,2-di(t-butyldimethylsilyloxy)benzene, formed by aromatisation of (7),[11] as well as the endoperoxide (6). Reduction of the hydroperoxide (7) by triphenylphosphine in dichloromethane gave the arene 1,4-hydrate (7', 100%).

Synthetic application of the endoperoxide was shown by reduction of (6) to the diol (thiourea/methanol), followed by epoxidation (MCPBA) which gave (8) (95%); finally, treatment with acidified (CF_3CO_2H) methanol yielded pinitol (4) (60%), identical with an authentic sample.



(5) Si = $SiBu^tMe_2$ (6) (7) R = OH (7') R = H (8)

Photolysis of the endoperoxide (6) in benzene solution led to a 3:1:1 ratio of the βγ-epoxyketones (9) and (10) and the diepoxide (11). Unusually, the epoxyketones were sufficiently stable to be isolated by column chromatography.[12] Control experiments showed that prolonged photolysis of the individual isomers (9) and (10) led to a 2:3 photostationary state mixture; this represents one of a limited number of examples in which photoepimerisation can be attained in cycloalkanones, presumably via α-cleavage and reclosure, without dominant ring opening reactions.[13] The diepoxide (11) was independently produced as the major outcome of cobalt(II) tetraphenylporphyrin-catalysed endoperoxide rearrangement.[14] Treatment of the individual βγ-epoxyketones with a catalytic amount of triethylamine in benzene gave clean conversion to the stereoisomeric protected hydroxyenones (12) and (13), respectively.[15]

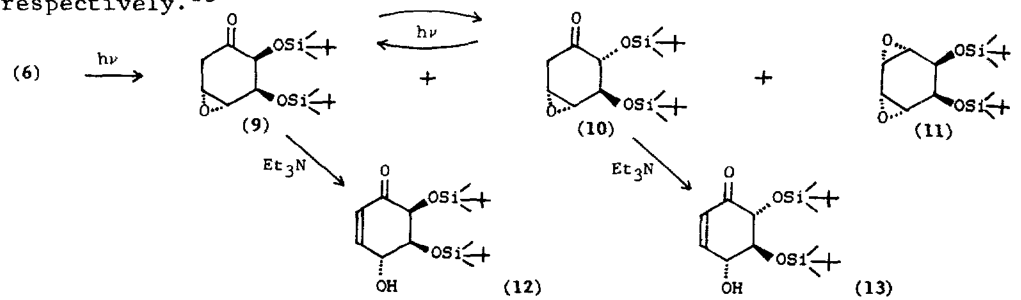
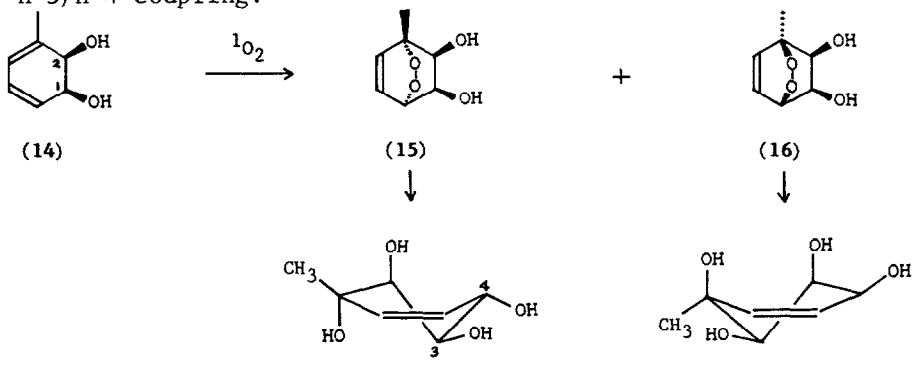


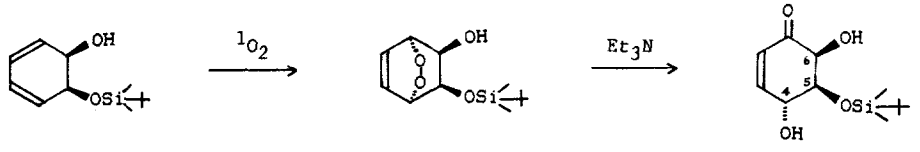
Photo-oxidation of the methyl substituted diol (14) (configuration 1S,2R; obtainable from toluene by microbial oxidation),[16] led to the two chiral endoperoxides (15) and (16), formed in the ratio 1.6:1 and separated by chromatography. Reduction of each isomer (thiourea/methanol)[17] led to the cyclohexene tetrols (17) and (18) in good yield (80-95%): the rapid assembly of the four chiral centres in (17) and (18) makes this a notable reaction

sequence. The conformation of the tetrols can be understood in terms of cyclohexene half-chairs, in which only (**17**) possesses the large (J=8 Hz) diaxial H-3/H-4 coupling.



(**14**) (**15**) (**16**) (**17**) (**18**)

Photosensitised oxidation of the monosilylated dienediol (**19**) led to endoperoxide (**20**), isolated by column chromatography as the major product (35%). An interesting and stereospecific rearrangement of (**20**) occurred on treatment with triethylamine in dichloromethane, to give the 5-silylated enone (**21**) (100%). The position of silylation in (**21**) was confirmed by acetylation (Ac_2O/pyridine) of the remaining hydroxyl groups, which gave firstly the 4-acetate (4 days, 20°C) and eventually under more forcing conditions (4 days, 60°C), the 4,6-diacetate: nmr spectra showed a characteristic low field shift of 1.1-1.3 ppm for the 4-H and 6-H protons on acetylation. We interpret the selectivity of the endoperoxide rearrangement as involving base-catalysed abstraction from the less hindered α-proton of (**20**).[18]



(**19**) (**20**) (**21**)

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