Diels–Alder Reactions involving *cis*-1,2-Isopropylidenedioxycyclohexa-3,5-diene and Enzymatic Resolution of One of the Adducts

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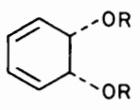
cis-1,2-Isopropylidenedioxycyclohexa-3,5-diene undergoes Diels–Alder [4 + 2] cycloaddition reactions with a variety of dienophiles including dimethyl acetylenedicarboxylate; the adduct formed with the latter dienophile was hydrolysed stereoselectively by pig liver esterase.

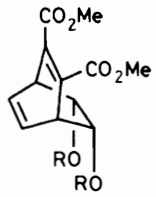
A biotransformation that is difficult to emulate using presently available chemical reagents is the conversion of benzene into *cis*-cyclohexa-3,5-diene-1,2-diol (**1**) using *Pseudomonas putida*.[1] The diol (**1**) is readily converted into the dibenzoate (**2**) and the diester has been used to prepare the natural product pinitol in racemic form.[2]

All our attempts to react the dibenzoate (**2**) with dienophiles were unsuccessful. For example, no reaction occurred on treatment of (**2**) with nitrosobenzene and dimethyl acetylenedicarboxylate (DMAD) at ambient temperature, while heating solutions containing compound (**2**) simply gave rise to phenylbenzoate.

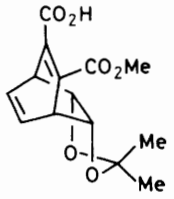
Reaction of the diol (**1**) with acetone under carefully defined conditions (0—5 °C, 3 h, acetone, toluene-*p*-sulphonic acid catalyst) gave the acetal (**3**) (50%); a more convenient method involved reaction of the diol (**1**) with 2,2-dimethoxy-



(1) R = H
(2) R = COPh
(3) R,R = CMe_2



(4) R,R = CMe_2
(5) R = H
(6) R = COPh



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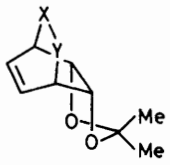
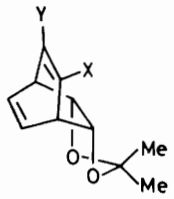
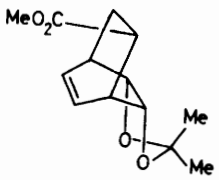


(8) X = PhN, Y = O
(9) X = Y = $CHCO_2Me$
(10) X = Y = CHCN
(11) X = Y = $C(CN)_2$
(13) X = Y = NCO_2Et



(12) X = CO_2Me, Y = H



(14)

propane under acid catalysis which furnished the acetal (**3**) in 72% yield. Phenol was formed as a side-product but was readily removed by washing a solution of the products with aqueous NaOH.

The acetal (**3**) reacted smoothly with DMAD in hot benzene over 16 h to give the adduct (**4**) [m.p. 90 °C, δ ($CDCl_3$) 6.38 (2H, dd, 2 × CH alkene), 4.38 (2H, t, 2 × CHO) 4.22 (2H, m, 2 × CH), 3.78 (6H, s, 2 × CO_2Me), 1.34 (3H, s, Me), 1.26 (3H, s, Me)] in 70% yield after chromatography.[3]

The same product was formed in equally high yield by stirring an aqueous suspension of the acetal (**3**) and DMAD in water at room temperature. The acetal group was removed from compound (**4**) using Amberlyst 15 resin in hot methanol to afford the diol (**5**) (73%), which was subsequently esterified to furnish the diester (**6**) (74%). The prochiral diester (**4**) was hydrolysed by pig liver esterase over 4 h to produce optically active mono-ester (**7**) in 88% yield ($[\alpha]_D^{25}$ −34°; *c* 5.7, CH_2Cl_2). The absolute configuration of the carboxylic acid (**7**) is tentatively assigned as shown on the basis of Ohno's earlier work on closely related systems.[5]

The diene (**3**) reacted with a wide range of dienophiles. For example nitrosobenzene gave the tricyclic compound (**8**) (70% yield after chromatography) while dimethyl fumarate, fumaronitrile, tetracyanoethylene, and methyl propynoate gave the corresponding adducts (**9**) (70%), (**10**) (52%), (**11**) (71%), and (**12**) (85.5%). Diethyl azodicarboxylate gave a quantitative (crude) yield of the adduct (**13**). Reaction of the diene (**3**) with excess of methyl acrylate in benzene at reflux for two days gave the ester (**14**) (80%). The *endo*-configuration of the adduct was conclusively proved by n.m.r. nuclear Overhauser experiments.

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