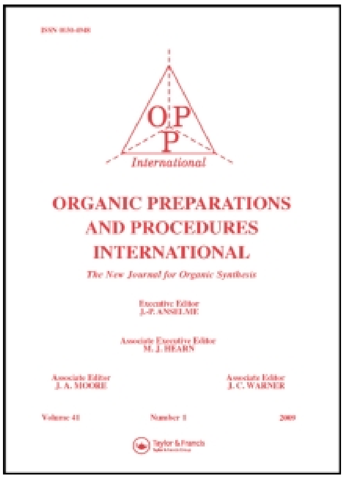

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Grant R. Krow[a]; Richard Carmosin[a]; Anthony Mancuso[a]
[a] Temple University, Philadelphia, Pennsylvania

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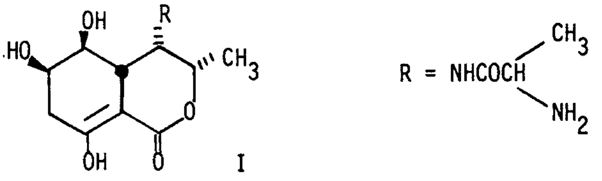
A SIMPLE SYNTHESIS OF 4-CYCLOHEXENE-1,2-cis-DIOL AND ITS USE AS THE PRECURSOR OF A FUNCTIONALIZED CYCLOHEXENONE SYNTHON

Grant R. Krow,* Richard Carmosin, and Anthony Mancuso
Temple University, Philadelphia, Pennsylvania 19122

In connection with studies directed toward the synthesis of the anti-leukemic agent actinobolin[1] (I), we have synthesized the polyfunctional acid sensitive cyclohexenone, 4,5-cis-dihydroxycyclohex-2-en-1-one (VII).



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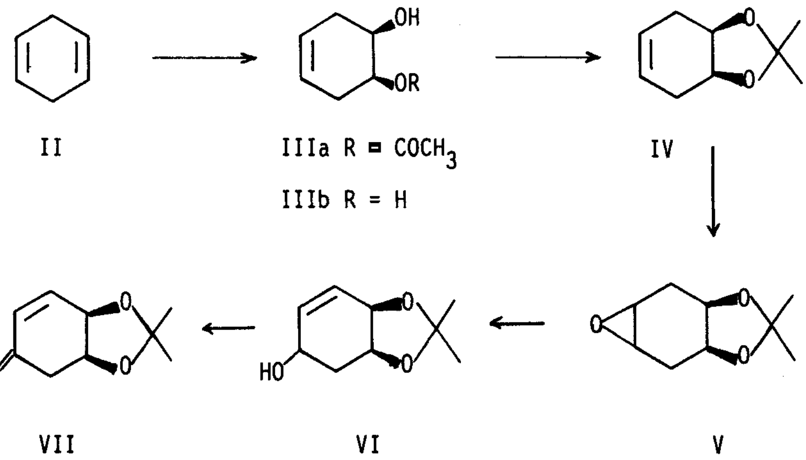

A procedure[2] avoiding the use of silver salts for cis-hydroxylation of olefins was applied to cyclohexa-1,4-diene (II). Thus reaction of II with potassium iodate and iodine in glacial acetic acid followed by treatment with potassium acetate afforded the cis-monoacetate (IIIa) Alcoholysis with potassium methoxide led to cyclohex-4-ene-cis-1,2-diol[3,4] (IIIb) in 71% overall yield. The diol IIIb was ketalized using 2,2-dimethoxypropane in the presence of p-toluenesulfonic acid[5] to afford IV, which was epoxidized[6] with m-chloroperbenzoic acid in chloroform to give epoxyketal V of undetermined configuration. Treatment of V with lithium diethylamide[7] yielded the unsaturated alcohol VI in 85% yield. Oxidation of the alcohol VI with freshly prepared manganese dioxide[8] in chloroform gave desired cyclohexenone VII in 56% yield; however, the yield was not reproducible on scale-up. An appreciable amount of hydroquinone, formed by β-elimination and tautomerization of VII, was formed, presumably *via* catalysis by the water of hydration in the active manganese dioxide. The problem of aromatization of VII was circumvented using pyridinium chlorochromate[9] to effect the oxidation of alcohol VI to crystalline ketone VII in 85% yield.

EXPERIMENTAL

All melting points are uncorrected, IR spectra were obtained on a Perkin-Elmer Infracord Spectrometer Model 137B; NMR specrta were determined in $CDCl_3$ on a Varian XL-100-15 instrument; UV spectra were recorded on a Cary-14 UV Spectrometer. Microanalyses were performed by Micro Analysis, Wilmington, Delaware. Magnesium sulfate was used as drying agent.

Cyclohex-4-ene-cis-1,2-diol (IIIb).- 1,4-Cyclohexadiene (20 g, 0.25 mol), potassium iodate (13.5 g, 0.62 mol), and iodine (31.5 g, 0.125 mol) in acetic acid (400 ml) were stirred at 60° for 3 hrs.[2] After cooling, potassium acetate (25 g, 0.25 mol) was added and the mixture was refluxed an additional 3 hrs. After cooling, water (4 ml) was added and the solvent was removed *in vacuo*. The residue taken up in ether (250 ml) was washed with saturated aqueous sodium thiosulfate solution (20 ml) to remove the brown color. After drying, solvent was removed *in vacuo* and cyclohex-4-ene-*cis*-1,2-diol monoacetate (IIIa), 29.25 g (75%), was distilled, bp 83-92° (1.4 mm), lit[3] bp 94° (2 mm). The *cis*-monoacetate IIIa (5.3 g, 0.034 mol), and sodium methoxide (1 g) in dry methanol (60 ml) were heated to reflux for 1 hr, cooled, and carbon dioxide (2.5 g) was bubbled into the solution. The solvent was removed *in vacuo*, and saturated aqueous sodium chloride (4 ml) was added to the residue. Ether extraction, drying, and removal of solvent afforded 3.7 g (95%) of crystalline diol IIIb mp 80-82°; lit[3] mp 80-81° (ether/pet ether); NMR δ 2.3 (m, 4H), 3.5 (s, 2H), 3.9 (t, 2H), 5.55 (s, 2H).

1,2-Isopropylidenedioxycyclohex-4-ene (IV).- *cis*-Diol IIIb (10.0 g, 0.88 mol) was dissolved in 2,2-dimethoxypropane (200 ml) and *p*-toluenesulfonic acid (0.5 g) was added.[5] After stirring for 48 hrs at 30°, chloroform (400 ml) was added. The organic layer was washed with saturated aqueous sodium bicarbonate (2 x 50 ml), dried, filtered, and solvent removed *in vacuo*. Distillation afforded 10.5 g (78%) of ketal IV, bp 67-69° (22 mm); NMR δ 1.33 (s, 3H), 1.46 (s, 3H), 2.28 (m, 4H), 4.38 (m, 2H), 5.82 (t, 2H).

Anal. Calcd for $C_9H_{14}O_2$: C, 70.10; H, 9.15
Found: C, 69.92; H, 8.93

1,2-Isopropylidenedioxycyclohexane-4,5-epoxide (V).- To an ice-cooled solution of 1,2-isopropylidenecyclohex-4-ene (IV) (50.0 g, 0.325 mol) in chloroform (300 ml) was added dropwise a solution of 85% *m*-chloroperbenzoic acid (65.8 g, 0.325 mol) in chloroform (300 ml).[6] The reaction was stirred for 3 hrs at 0°, then 16 hrs at 30°. Sodium sulfite solution (20% aqueous, 150 ml) was added and the mixture was stirred for 1 hr. The organic phase was separated, washed with 10% sodium hydroxide (50 ml), dried, filtered, and solvent was removed *in vacuo* to afford upon distillation at 53-55° (0.2 mm), epoxide V, 45.3 g (82%); NMR δ 1.25 (s, 3H), 1.42 (s, 3H), 2.18 (m, 4H), 3.16 (m, 2H), 4.24 (m, 2H).

Anal. Calcd for $C_9H_{14}O_3$: C, 63.51; H, 8.29
Found: C, 63.61; H, 8.12

4,5-Isopropylidenedioxycyclohex-2-en-1-ol (VI).- A solution of lithium diethylamide[7] was prepared by dissolving diethylamine (12.3 g, 0.25 mol) in ether under a nitrogen atmosphere at 0°, adding *n*-butyllithium (104 ml of a 2.4 molar solution in hexane, 0.25 mol), and stirring for 25 min at 0°. The 1,2-isopropylidenedioxycyclohexane-4,5-epoxide V (17 g, 0.1 mol) dissolved in ether (50 ml) was added dropwise at 0° over 0.5 hr and the reaction was stirred an additional 2 hrs at 0° and 15 hrs at 30°. Water (50 ml) was added, the organic layer was separated, and the water layer extracted with ether (2 x 50 ml). The combined ethereal layers were dried, filtered, and solvent was removed *in vacuo* to give allylic alcohol VI, 14.5 g (85%), as white crystals, mp 58-59°, sublimed at 40° (0.5 mm); NMR δ 1.28 (s, 6H), 2.32 (m, 2H), 3.75 (m, 1H), 4.38 (m, 2H), 5.78 (m, 2H).

Anal. Calcd for $C_9H_{14}O_3$: C, 63.50; H, 8.29
Found: C, 63.44; H, 8.04

4,5-Isopropylidenedioxycyclohex-2-en-1-one (VII).- (Method A) Pyridinium chlorochromate[9] (23.25 g, 0.11 mol) was dissolved in dry methylene chloride (150 ml) and 4,5-isopropylidenedioxycyclohex-2-en-1-ol (VI) (14.5 g, 0.085 mol) in methylene chloride (50 ml) was added to the stirred solution rapidly at room temperature. The reaction was stirred under a nitrogen atmosphere for 1.5 hrs at 30°, then filtered through florisil. Removal of solvent *in vacuo* afforded 12.1 g (85%) of conjugated ketone VII, mp 70.5-71° (chloroform); NMR δ 1.40 (s, 6H), 2.82 (m, 2H), 4.72 (m, 2H), 6.07 (d, 1H), 6.65 (dt, 1H), IR ($CHCl_3$) 1680 cm^{-1}, UV (cyclohexane) λ_{max} 218 nm, ε 2750. (Method B) Activated manganese dioxide[8] (47 g) was added to allylic alcohol VI (1.4 g, 0.008 mol) in chloroform (500 ml) and the mixture was stirred 4 days at 30°. Catalyst was filtered, washed with chloroform and the combined washings were concentrated to afford conjugated ketone VII, 770 mg (56%), mp 70-71° (hexane).

Anal. Calcd for $C_9H_{12}O_3$: C, 64. 28; H, 7.19
Found: C, 64.01; H, 7.19

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