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Stereospecific Synthesis of *cis*- and *trans*-2,3-Epoxycycloheptanol

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cis- and *trans*-2,3-Epoxycycloheptanols were prepared stereospecifically from cyclohept-2-en-1-ol (**1**). Oxidation of **1** with *tert*-butyl hydroperoxide in the presence of a molybdenum catalyst gave the *cis* isomer (**2**) in high yield. The *trans* isomer (**3**) was obtained *via* the bromohydrin (**4**). The structure of **4** is discussed.

Keywords——*cis*-2,3-epoxycycloheptanol; *trans*-2,3-epoxycycloheptanol; stereospecific epoxidation; molybdenum hexacarbonyl; regiospecific bromohydrin formation; protection of hydroxyl group

Recently 2,3-epoxycycloalkanols have been recognized as versatile intermediates for syntheses of natural products. In contrast to many successful efforts with five-, six-, and eight-membered allylic alcohols,[2] stereospecific epoxidation of seven-membered allylic alcohols has never been achieved. For example, it is known that peracid oxidation of cyclohept-2-en-1-ol (**1**) gives a mixture of the *cis*- (**2**) and *trans*-epoxide (**3**), and separation is very difficult.[3] In connection with our synthetic studies on pseudoguaianolides, reasonable quantities of *cis*- and *trans*-2,3-epoxycycloheptanol derivatives were required in a stereochemically homogeneous state. This made it imperative to develop general methods for the stereospecific conversion of seven-membered allylic alcohols to *cis*- and *trans*-epoxides. We have achieved this with the simple compound **1**, as reported here.

Sharpless and co-workers have reported a highly efficient method for *cis* epoxidation of cyclic allylic alcohols with high stereospecificity.[4] Application of this method to our specific case proved successuful. Thus, the reaction of **1** with *tert*-butyl hydroperoxide yielded **2** stereospecifically in moderate (with vanadium oxyacetylacetonate) to high (with molybdenum hexacarbonyl) yield.[5]

The stereospecific synthesis of **3** proved to be difficult, but after many attempts it was achieved as follows. Treatment of **1** with N-bromosuccinimide in aqueous monoglyme gave the crude bromohydrin (**4**) which, without further purification, was treated with potassium carbonate in aqueous methanol. This sequence of reactions provided **3** stereospecifically in high yield.[6]

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[5] After the completion of this work, application of Sharpless' method to a number of cyclic allylic alcohols was reported elsewhere. See, T. Itoh, K. Jitsukawa, K. Kaneda and S. Teranishi, *J. Am. Chem. Soc.*, **101**, 159 (1979). In our case, the vanadium-catalyzed reaction was rather troublesome and the best yield was 32%. In contrast, the molybdenum-catalyzed reaction proceeded smoothly in high yield.

[6] Application of the same reaction sequence to cyclohex-2-en-1-ol, however, gave a mixture of *cis*- and *trans*-epoxides in equal amounts.

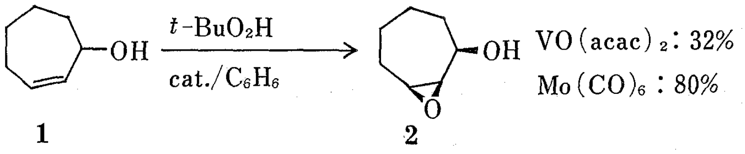

Chart 1

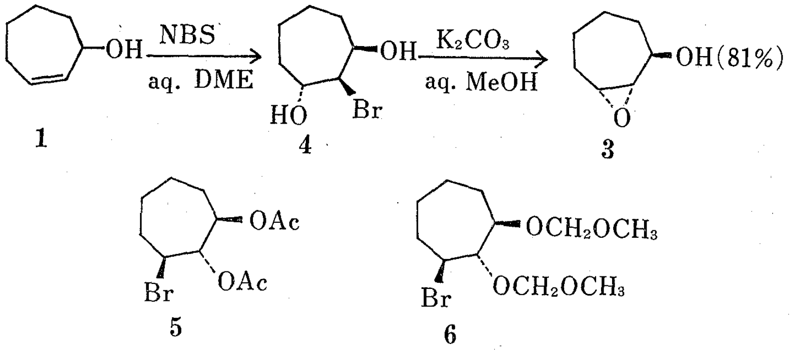

Chart 2

The structures of **2** and **3** were confirmed by comparison of the corresponding *cis*- and *trans*-cycloheptan-1,2-diols, obtained by lithium aluminum hydride reduction, with authentic samples. The structure of the intermediate bromohydrin was suggested to be **4**, based on the following evidence. (A) No acetonide formation was observed on treatment with acetone and anhydrous cupric sulfate. (B) In the proton nuclear magnetic resonance spectra of the diacetate and bis-methoxymethyl ether (*vide infra*) the proton on the bromine-bearing carbon was observed as a doublet of doublets at δ 4.33 and δ 4.45, respectively. The alternative structures (**5**) and (**6**) would have caused this proton to appear as a doublet of triplets.

Unambiguous proof of the structure, however, was obtained by its conversion to *trans*-cycloheptan-1,3-diol (**7**).

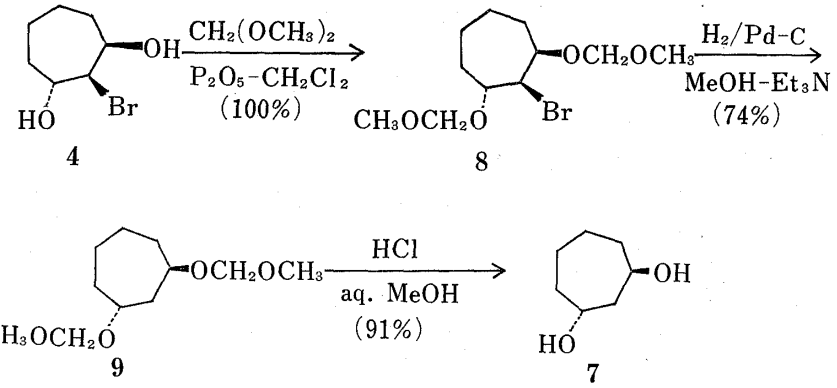

Chart 3

It was first protected as the bis-methoxymethyl ether (**8**) by treatment with methylal and phosphorus pentoxide in dichloromethane.[7] The debrominated product (**9**), obtained by hydrogenolysis of **8** in the presence of 5% palladium on carbon, was refluxed with hydrochloric acid in methanol to give the diol **7**, which was identical as regards physical and spectroscopic properties with an authentic sample.[3,8]

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Experimental

All melting points and boiling points are uncorrected. Infrared (IR) spectra were measured with a Hitachi 285 spectrophotometer. Nuclear magnetic resonance (NMR) spectra were measured with a JEOL PMX 60 spectrometer using TMS as an internal standard. Mass (MS) spectra were measured with a Shimadzu LKB-9000 spectrometer.

Cyclohept-2-en-1-ol (**1**)[9]——A solution of cyclohept-2-enyl bromide (55 g, 0.31 mol) in acetone (300 ml) was added to a stirred solution of $NaHCO_3$ (40 g, 0.48 mol) in H_2O (1.5—1) at room temperature during 2 hr and the mixture was stirred overnight. It was saturated with NaCl, extracted with AcOEt, and the combined organic extracts were washed with brine, and dried. After removing the solvent the residue was distilled to give **1** (32 g, 91%), bp 52—53° (3 mmHg).

***cis*-2,3-Epoxycycloheptan-1-ol** (**2**)——i) With Vanadium Catalyst: To a stirred solution of vanadium oxyacetylacetonate (5 mg) in C_6H_6 (5 ml) was added **1** (1.0 g, 8.9 mmol) in C_6H_6 (5 ml), followed by *tert*-butyl hydroperoxide (0.96 g, 10.7 mmol) in C_6H_6 (10 ml) at room temperature under argon. The mixture was heated at 50° overnight. It was washed with aqueous $NaHSO_3$ and brine, then dried. The solvent was removed to give the crude product (776 mg), which was chromatographed on silica gel, eluting with $CHCl_3$–MeOH, to give **2** (367 mg, 32%) as a colorless oil.

ii) With Molybdenum Catalyst: A solution of *tert*-butyl hydroperoxide (0.96 g. 10.7 mmol) in C_6H_6 (25 ml) was added at room temperature to a stirred solution of **1** (1.0 g, 8.9 mmol) and molybdenum hexacarbonyl (*ca.* 10 mg) in C_6H_6(25 ml). The mixture was refluxed for 3 hr, and worked up as in i) to give the crude product (1.089 g). This oil was either (a) distilled *in vacuo* to give **2** (687 mg, 60%), bp 69—71° (3 mmHg) (lit[3]; bp 78—78.5° (1.4 mmHg)), or (b) chromatographed on silica gel, eluting with $CHCl_3$–MeOH, to give **2** (916 mg, 80%). Its phenylurethane; mp 129—131° (lit[3]; mp 129.5—130°).

***trans*-2,3-Epoxycycloheptan-1-ol** (**3**)——A stirred solution of **1** (5g, 44.6 mmol) in monoglyme (300 ml) and H_2O (60 ml) was treated wth N-bromosuccinimide (9.5 g, 53.4 mmol) portionwise with ice-coling. After 30 min at 0°, stirring was continued for a further 3.5 hr at room temperature. The reaction was quenched with aqueous $NaHSO_3$, and monoglyme was removed *in vacuo*. The residue was saturated with NaCl, extracted with AcOEt, and the combined extracts were washed with 50% brine and brine, then dried. After removing the solvent, the residue was dissolved in MeOH (300 ml)–H_2O (60 ml), and solid K_2CO_3 (10 g, 72.5 mmol) was added in one portion. After stirring at ambient temperature overnight, MeOH was removed *in vacuo*, then the residue was saturated with NaCl, extracted with Et_2O, and dried. The residue, after removal of the solvent, was distilled to give **3** (4.16 g), bp 99—105° (7 mmHg) (lit[3] bp 88.0° (1.9 mmHg)). The forerun and the residue were combined and chromatographed on silica gel, eluting with $CHCl_3$–MeOH, to give a further crop of **3** (0.15 g); total yield, 4.67 g (81%). Its phenylurethane: mp 132—134° (lit[3]; mp 134—134.5°).

2β-Bromo-1α,3β-dihydroxycycloheptane (**4**)——The crude bromohydrin (1.76 g), obtained as above from **1** (1.0 g), was recrystallized from $CHCl_3$ to give **4** (910 mg) as colorless needles. The mother liquor (867 mg) was chromatographed repeatedly on silica gel, eluting with $CHCl_3$–MeOH, to give a further crop of **4** (0.4 g); total yield, 1.31 g (70%), mp 127.5—128.5°. IR $\nu_{\max}^{\mathrm{KBr}}$ $\mathrm{cm^{-1}}$: 3300, 1400, 1050, 680. NMR (CD_3OD) δ: 4.75 (2H, s), 4.40—3.88 (3H, m), 2.3—1.3 (8H, m). MS *m/e*: 209, 207 (M^+), 111, 93, 67, 57, 55. *Anal.* Calcd for $C_7H_{13}BrO_2$: C, 40.21; H, 6.27. Found: C, 40.19; H, 5.92. Its diacetate, obtained by reaction with acetic anhydride in pyridine, gave the following spectral data. IR $\nu_{\max}^{\mathrm{CHCl_3}}$ $\mathrm{cm^{-1}}$: 1725, 1365, 1210. NMR ($CDCl_3$) δ: 5.4—5.0 (2H, m), 4.33 (1H, d-d, $J=2$, 7 Hz), 2.1 (6H, s), 2.3—1.4 (8H, m).

2β-Bromo-1α,3β-bis(methoxymethoxy)-cycloheptane (**8**)——Pure **4** (1.0 g, 4.78 mmol) was converted into its bis-methoxymethyl ether **8** according to the published procedure[7] (1.47 g, 100%). IR $\nu_{\max}^{\mathrm{CHCl_3}}$ $\mathrm{cm^{-1}}$: 1145, 1090, 1040, 920. NMR ($CDCl_3$) δ: 4.7 (4H, s), 4.45 (1H, d-d, $J=2$, 6 Hz), 4.3—3.9 (2H, m), 3.4 (6H, s), 2.3—1.1 (8H, m). MS *m/e*: 123, 111, 95, 93, 45. An analytical sample was obtained by distillation *in vacuo*; bp 100° (0.17 mmHg). *Anal.* Calcd for $C_{11}H_{21}BrO_4$: C, 44.45; H, 7.12. Found: C, 44.46; H, 7.20.

1α,3β-Bis(methoxymethoxy)-cycloheptane (**9**)——A mixture of **8** (1.47 g, 4.78 mmol), Et_3N (3 ml), and 5% Pd-C (150 mg) in MeOH (10 ml) was hydrogenated overnight at room temperature under atmospheric pressure of H_2. The catalyst was filtered off, washed well with MeOH, and MeOH was removed. The residue was taken up in AcOEt, washed with 50% brine and brine, then dried. Removal of the solvent gave the crude product, which was chromatographed on silica gel, eluting with $CHCl_3$–MeOH, to give pure **9** (739 mg, 74%). IR $\nu_{\max}^{\mathrm{CHCl_3}}$ $\mathrm{cm^{-1}}$: 2940, 1450, 1140, 1090, 1040, 915. NMR ($CDCl_3$) δ: 4.63 (4H, s,) 4.2—3.6 (2H, m), 3.33 (6H, s,) 2.3—1.1 (10H, m, including a triplet at δ 2.0 ($J=7$ Hz)). MS *m/e*: 141, 111, 95, 45. An analytical sample was obtained by distillation *in vacuo*; bp 68° (0.17 mmHg). *Anal* Calcd for $C_{11}H_{22}O_4$: C, 60.52; H, 10.16. Found: C, 60.25; H, 9.89.

***trans*-Cycloheptan-1,3-diol** (**7**)——A solution of **9** (739 mg, 3.38 mmol) and 10% HCl (15 ml) in MeOH (20 ml) was refluxed for 5 hr. After neutralization with aqueous $NaHCO_3$, MeOH was removed. The residue was extracted with AcOEt after saturation with NaCl, and dried. Removal of the solvent gave a

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residue, which was purified by chromatography on silica gel, eluting with $CHCl_3$–MeOH, to give pure **7** (400 mg, 91%). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3350, 1460, 1040, 1015. NMR ($CDCl_3$) δ: 4.3—3.7 (2H, m), 3.0 (2H, s, disappeared on adding D_2O), 2.3—1.1 (10H, m, including a triplet at δ 2.0 (J=7 Hz)). Although our synthetic sample did not crystallize (its melting point was reported to be 53.0—54.0° in ref. 3), its identity as *trans*-1,3-diol was firmly established by the presence of a triplet at δ 2.0, which is seen only in this compound, and in no other isomers. This signal was assigned to the methylene protons between the two hydroxyl groups by a decoupling experiment.

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Quantitative Analysis of the Isomers of Hydroxyphenylalanine by High-Performance Liquid Chromatography using a Fluorimetric Detector

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A sensitive high-performance liquid chromatographic technique for the quantitative analysis of the isomers of hydroxyphenylalanine has been developed. The chromatographic conditions were as follows: stainless steel column (2.1 × 500 mm) packed with Hitachi ♯3011-C resin; mobile phase, a mixture of equal volumes of 0.025 M sodium acetate and 0.05 M acetic acid; flow rate, 0.8 ml/min; temperature, 45°; detection, fluorimetric detector.

This procedure was found to be suitable for the analysis of 3,4-dihydroxyphenylalanine, *p*-tyrosine, *m*-tyrosine, *o*-tyrosine, and phenylalanine.

Keywords——phenylalanine; *o*-tyrosine; *m*-tyrosine; *p*-tyrosine; 3,4-dihydroxyphenylalanine; fluorescence high-performance liquid chromatography; fluorimetry

In mammals, phenylalanine is in large part metabolized by conversion to tyrosine in the liver. In addition, in the brain and adrenals, phenylalanine is transformed into the catecholamines by way of tyrosine and 3,4-dihydroxyphenylalanine (DOPA).[2] Recently, Tong *et al.*,[3] reported that incubation of phenylalanine-^{14}C with bovine adrenal medulla homogenate in the presence of a pteridine co-factor and a DOPA decarboxylase inhibitor gave rise to three radioactive products which were identified with an amino acid analyzer as tyrosine, *m*-tyrosine and DOPA. However, the phenylalanine peak appears to overlap the *o*-tyrosine peak under their chromatographic conditions. The object of our study was to elucidate the nature of the enzymatic and nonenzymatic hydroxylation system for phenylalanine. In order to study these phenomena quantitatively it is necessary to establish a method for systematic quantitative analysis of hydroxylated phenylalanine compounds. Formerly, paper chromatography[4] and ion-exchange chromatography[5] had been used for this purpose, but a more sensitive method is desirable.

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