tanone, 29577-67-1; *trans*-1,2-dimethylcycloheptane, 13151-50-3; *cis*-1,3-dimethylcycloheptane, 13151-53-6; *trans*-1,3-dimethylcycloheptane, 13151-52-5; bicyclo[3.2.2]nonane-2,2-dicarboxylic anhydride, 29577-71-7; bicyclo[3.2.2]non-2-ene, 7124-86-9; *cis*-1,4-bis(hydroxymethylene)cycloheptane, 29577-72-8, 29577-73-9 (bis-3,5-dinitrobenzoate); *cis*-1,4-bis(tosyloxymethylene)-cycloheptane, 29577-74-0; *cis*-1,4-dimethylcycloheptane, 14190-15-9; 5-hydroxymethylcycloheptene, 17328-87-9; *cis*-5-hydroxymethylcycloheptene oxide, 29577-76-2; 2-hydroxy-7-oxabicyclo[3.2.2]nonane, 17328-88-0, 29577-78-4 (3,5-dinitrobenzoate); *trans*-2-methyl-*cis*-5-hydroxymethylcycloheptanol, 17328-91-5; *trans*-1,4-dimethylcycloheptane, 13151-54-7.

The Synthesis and Stereochemistry of the Four Isomeric Pinane-2,3-diols

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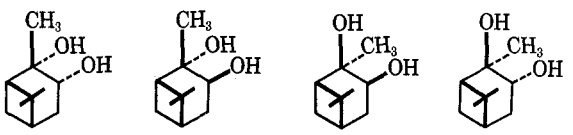
The synthesis of the four possible pinane-2,3-diols, **1–4**, is described and rigorous stereochemical assignments are made. Several anomalous reactions were observed in which an attacking species reacts preferentially on the pinane ring system from the same side as the *gem*-dimethyl bridge.

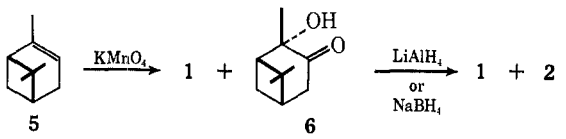
In connection with our study of the base-catalyzed rearrangement of 2,3-pinanediol monotosylates,[3] we required synthetic routes to the four possible pinane-2,3-diols **1–4**. At the time this study was initiated,



1 **2** **3** **4**

two of these diols (**1** and **2**) had been reported in the literature but there was confusion and disagreement as to the stereochemistry of these diols.[4–9] We have presented evidence which clarified the stereochemistry of these diols[10] and these assignments have been independently confirmed by other workers.[11–13]

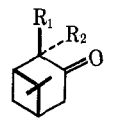
Diols 1 and 2.—Oxidation of α-pinene (**5**) with potassium permanganate under neutral conditions gives a modest yield of the ketol **6**, whereas oxidation



5 **6**

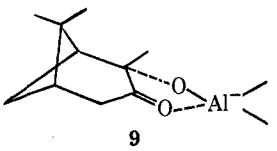
under basic conditions gives the diol **1** in low yield. None of the diol **3** can be detected by spectral methods or by thin layer chromatography (tlc) in the crude product from this reaction. Thus, the reaction of **5** with permanganate ion is highly stereoselective and the attack of the oxidant occurs from the side opposite the *gem*-dimethyl bridge. The expectation that attack of external reagents on the pinane skeleton should occur from this direction has been widely used in assigning stereochemistry to various pinane derivatives, but, as will be shown below, it is not an unfailing guide to stereochemical assignments in this system.

Because the metal hydride reduction of both isopinocamphone (**7**) and pinocamphone (**8**) have been



7, R_1 = Me; R_2 = H
8, R_1 = H; R_2 = Me

reported[14] to be highly stereoselective with attack of the reagent from the side opposite the *gem*-dimethyl bridge, it was expected that the reduction of ketol **6** with lithium aluminum hydride ($LiAlH_4$) would give mainly diol **2**. Surprisingly, this reduction produced the readily separable diols **1** and **2** in the ratio 54:46. Two previous reports of the reduction of ketol **6** with $LiAlH_4$ had claimed that only diol **2** was produced,[6,15] whereas Suga[8] reports that diols **1** and **2** are formed in the ratio 63:37 in reasonable agreement with our results. This seemingly anomalous stereochemical result might be rationalized by assuming that a complex of the type **9** is formed. In such a complex C-3 is pulled



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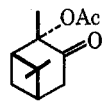
downward in order to obtain coplanarity in the five-membered complex ring and molecular models indicate that in such an arrangement attack of hydride from the top side would be favored. In order to determine

(1) Alfred P. Sloan Foundation Research Fellow, 1970–1972.
(2) Gulf Fellow, 1968–1969; NSF Summer Fellow, 1969; NSF Trainee, 1969–1970.
(3) R. G. Carlson and J. K. Pierce, *Tetrahedron Lett.*, 6213 (1968).
(4) T. Kuwata, *J. Amer. Chem. Soc.*, **59**, 2509 (1937).
(5) M. Delepine, A. Horeau, and M. Grandperrin-Haruspe, *Ann. Chim. (Paris)*, **18**, 250 (1943).
(6) H. Schmidt, *Chem. Ber.*, **93**, 2485 (1960).
(7) H. Schmidt, M. Muhlstädt, and P. Son, *ibid.*, **99**, 2736 (1966).
(8) T. Suga, T. Shishibori, T. Hirata, and T. Matsuura, *Bull. Chem. Soc. Jap.*, **41**, 1180 (1968).
(9) J. M. Coxon, E. Dansted, M. P. Hartshorn, and K. E. Richards, *Tetrahedron*, **24**, 1193 (1968).
(10) R. G. Carlson, J. K. Pierce, T. Suga, T. Hirata, and T. Matsuura, *Tetrahedron Lett.*, 5941 (1968).
(11) A. Zschunke, M. Muhlstädt, and C. Fleming, *Tetrahedron*, **24**, 6469 (1968).
(12) J. M. Coxon, E. Dansted, M. P. Hartshorn, and K. E. Richards, *Tetrahedron Lett.*, 1149 (1969).
(13) M. D. Brice, J. M. Coxon, E. Dansted, M. P. Hartshorn, and W. T. Robinson, *Chem. Commun.*, 356 (1969).
(14) (a) W. Huckel and D. Holzwarth, *Justus Liebigs Ann. Chem.*, **697**, 69 (1966); (b) G. Zweifel and H. C. Brown, *J. Amer. Chem. Soc.*, **86**, 393 (1964); (c) P. Teisseire, A. Galfre, M. Plattier, and B. Corbier, *Recherches*, **15**, 52 (1966); (d) P. Teisseire, A. Galfre, M. Plattier, and B. Corbier, *ibid.*, **16**, 59 (1967).
(15) H. Harispe and A. Bargeboer, *C. R. Acad. Sci., Ser. C*, **245**, 1550 (1957).

whether this was a tenable hypothesis, two further experiments were conducted. The ketol **6** was reduced with sodium borohydride in methanol with the expectation that because of the hydroxylic nature of the solvent, complexation similar to **9** would not occur and, indeed, this reduction gave the diols **1** and **2** in the ratio 17:83. The ketol was also converted to acetoxy ketone **10** and reduction of **10** with $LiAlH_4$ gave **1** and **2** in the



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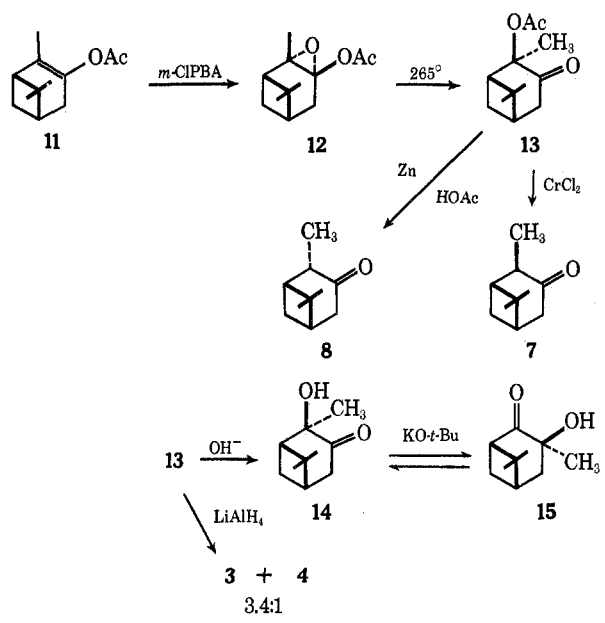
ratio 6:94. This result is also consistent with the above postulate because if ketone reduction precedes ester reduction a complex of the type **9** cannot be formed.

Diols 3 and 4.—The introduction of the oxygen substituent at C-2 on the same side as the *gem*-dimethyl bridge makes the synthesis of diols **3** and **4** somewhat more complicated than the preparation of **1** and **2** and requires a different synthetic strategy. One approach to systems with this stereochemistry is outlined in Scheme I. Conversion of the known[16] enol acetate **11**

SCHEME I



to the epoxy acetate **12** was easily accomplished with *m*-chloroperbenzoic acid, but the thermal rearrangement of **12** to the acetoxy ketone **13** proved to be surprisingly difficult. Such rearrangements usually occur very readily and epoxy acetates of this type are often difficult to isolate and purify. For example, 1-acetoxy-1,2-epoxycyclohexane undergoes rearrangement when heated for a few minutes at 100°.[17] In contrast, **12** could be heated at 150° for 5 min with no rearrangement and the use of higher temperatures and longer reaction times gave mainly decomposition products. Attempts to bring about the rearrangement by chromatography on silica gel[18] or by catalysis with boron trifluoride etherate[19] led to incomplete reaction and the formation of a large number of by-products. It was finally found that the rearrangement of **12** to **13** could be cleanly effected by passing **12** in a stream of nitrogen through a column of glass beads maintained at 265°. Although rearrangements of this type are known to proceed with clean inversion of configuration at the migration terminus,[20] the rather drastic conditions necessary for the rearrangement of **12** required proof that the pinane skeleton was still intact. Reduction of **13** with zinc and acetic acid gave pinocamphone (**8**), presumably arising by isomerization of **7** to **8**. In contrast, reduction of **13** with chromium(II) chloride[21] gave isopinocamphone **7** indicating that the conditions for this reduction are sufficiently mild to give the ketone produced by initial kinetically controlled protonation. The difficulty encountered in bringing about the rearrangement of **12** to **13** reflects the severe interaction between the acetoxy group and the C-9 methyl group in the transition state for the rearrangement.

Reduction of **13** with $LiAlH_4$ produced the noncrystalline *cis*-diol **3** and the crystalline *trans*-diol **4** in the ratio 3.4:1. The stereochemistry of these diols is unambiguously established by the experiments described below. Our initial plan for the synthesis of diol **4** was based on the assumption that Meerwein–Ponndorf–Verley (MPV) reduction of **13** or **14** would lead to the more stable diol **4** by analogy with the work of Schmidt[6] who showed that MPV reduction of ketol **6** gave exclusively diol **2**. When ketol **14** was subjected to reduction with aluminum isopropoxide in isopropyl alcohol, a diol was obtained which, by virtue of its nmr spectrum, was clearly neither of the diols **3** or **4**. The new diol showed an absorption in its nmr spectrum for a proton on a carbon bearing a hydroxyl group as a doublet at δ 3.85 (J = 5.0 Hz). This suggested that **14** had undergone a ketol rearrangement[22] to give **15** under the strongly basic conditions of the MPV reduction prior to reduction and that the new diol was derived from reduction of **15**. Indeed, when ketol **14** was treated with potassium *tert*-butoxide in *tert*-butyl alcohol it was gradually converted to the isomeric ketol **15** and an equilibrium was established which consisted of 58% **15** and 42% **14**. The new ketol **15** was identical with the ketol obtained by oxidation of the diol from the MPV reduction of **14**.

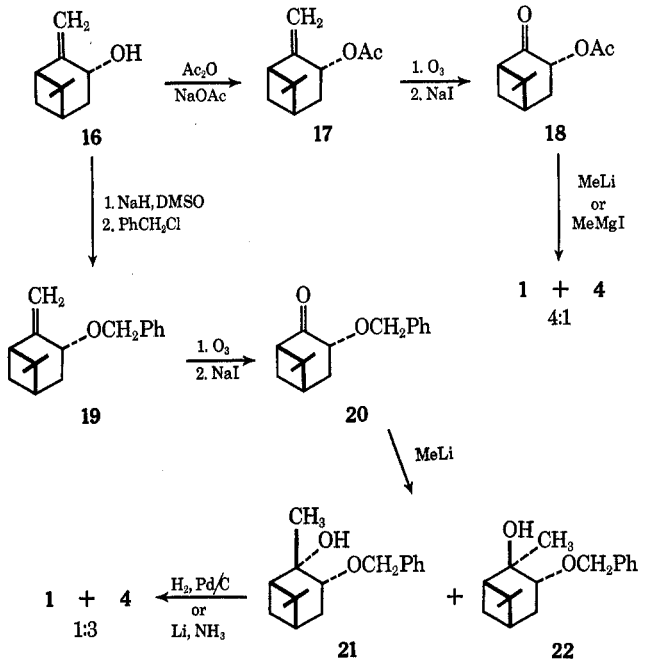
In contrast to the ready rearrangement of ketol **14**, the isomeric ketol **6** could be recovered unchanged after prolonged treatment with potassium *tert*-butoxide in refluxing *tert*-butyl alcohol. The stability of **6** reflects the fact that in the transition state for a similar ketol rearrangement the migrating methyl group would interact very severely with the C-9 methyl group. Such an interaction is not developed in the rearrangement of **14** to **15**.

Because of the failure of this route to cleanly produce *trans*-diol **4**, an alternative route to this compound was devised based upon the proposition that addition of methyllithium or methylmagnesium iodide to a suitably substituted nopinone would lead to diol **4**. For this

(16) M. P. Hartshorn and A. F. A. Wallis, *Tetrahedron*, **21**, 273 (1965).
(17) K. L. Williamson, J. I. Coburn, and M. F. Herr, *J. Org. Chem.*, **32**, 3934 (1967).
(18) N. S. Leeds, D. K. Fukushima, and T. F. Gallagher, *J. Amer. Chem. Soc.*, **76**, 2943 (1954).
(19) H. B. Henbest and T. I. Wrigley, *J. Chem. Soc.*, 4596 (1967).
(20) K. L. Williamson and W. S. Johnson, *J. Org. Chem.*, **26**, 4563 (1961).
(21) H. O. House and R. G. Carlson, *ibid.*, **29**, 74 (1964).
(22) N. L. Wendler, "Molecular Rearrangements," P. de Mayo, Ed., Interscience, New York, N. Y., 1964, pp 1114–1121.

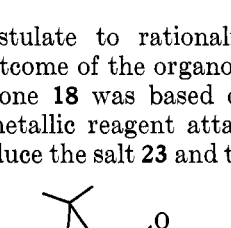
purpose the keto acetate **18** was prepared as outlined in Scheme II. Surprisingly, addition of methyllithium

SCHEME II



to **18** gave a mixture of the diols **1** and **4** in the ratio 4:1. Essentially the same product distribution was obtained when methylmagnesium iodide was used in place of methyllithium. Thus, the attack of the organometallic reagents occurs overwhelmingly from the same side as the *gem*-dimethyl bridge. Subsequent to our studies Schmidt[23] reported that inverse addition of methylmagnesium iodide to **18** followed by hydrolysis gave only *trans*-diol **4** in 28% yield. In our hands, this procedure gave the diol **4** in 24% yield as well as the *cis*-diol **1** in 20% yield.[24] Thus, the order of addition of the Grignard reagent also affects the stereochemical outcome of this reaction in a manner which remains unclear.

Our initial postulate to rationalize the "wrong" stereochemical outcome of the organometallic reactions with acetoxy ketone **18** was based on the possibility that the organometallic reagent attacked the acetoxy group first to produce the salt **23** and that attack on this



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salt occurred preferentially from the top side because of charge repulsion. This suggested that replacement of the acetoxy group by a benzyl group might reverse the stereochemical outcome. The corresponding benzyloxy ketone **20** was prepared as shown in Scheme II. Addition of methyllithium produced the hydroxy ethers **21** and **22** in the ratio 1:3. Hydrogenolysis of the benzyl protecting groups in a carefully base-washed apparatus or cleavage with lithium in liquid ammonia gave the diols **1** and **4** in the ratio 1:3. Thus, the change in protecting group reverses the stereochemical outcome of the addition to the C-2 carbonyl group.

(23) H. Schmidt, M. Muhlstadt, and H. C. Flemming, *Chem. Ber.*, **102**, 118 (1969).

(24) Diol **4** is highly crystalline and easily isolated from the crude products of these reactions. In contrast the *cis*-diol **1** is a very low-melting solid and is easily discarded with mother liquors from the crystallization of **4** unless great care is exercised.

Experimental Section[25]

Preparation of Ketol 6.—To a cold (ice bath) solution of 100 g (0.734 mol) of α-pinene {Aldrich, $[\alpha]^{25}D$ +37.32° (*c* 2.7, $CHCl_3$)} in 883 g of 90% aqueous acetone was added with stirring 200 g (1.265 mol) of pulverized potassium permanganate over a period of 10 hr. The reaction mixture was stirred at 0–5° for an additional 24 hr, filtered, evaporated to *ca.* 250 ml, and extracted with ether. The combined ethereal extracts were washed with water and saturated aqueous sodium bicarbonate, dried, and concentrated to give 64.07 g of an oil which was distilled to give 58.55 g (48%) of ketol **6**, bp 113–115° (17 mm). A small portion of the distillate was recrystallized from pentane to afford pure ketol **6**: mp 34–35°; $n^{28}D$ 1.4877; $[\alpha]^{25}D$ −27.50° (*c* 2.5, $CHCl_3$) {lit.[4,6] mp 35.5–36.6°; bp 96.5–96.7 (5 mm); $n^{20}D$ 1.490; $[\alpha]^{20}D$ −18.56° (*c* 14.44, EtOH)}; ir (CCl_4) 3610 (free OH), 3500 (bonded OH), and 1720 cm^{-1} (C=O); nmr (CCl_4) δ 2.60–1.65 (m, 7), 1.38 (s, 3, CH_3), 1.32 (s, 3, CH_3), and 0.88 (s, 3, CH_3).

Preparation of Diol 1.—A solution of 23.4 g (0.148 mol) of potassium permanganate and 5 g (0.125 mol) of sodium hydroxide in 800 ml of water cooled to 0° was added quickly with vigorous stirring to a cold (−5°) mixture of 1.0 l. of *tert*-butyl alcohol, 200 ml of water, and 500 g of cracked ice containing 13.27 (0.0974 mol) of α-pinene {$[\alpha]^{25}D$ −22.46° (*c* 3, $CHCl_3$)}. After 3.0 min of reaction, sulfur dioxide was bubbled through the solution to ensure complete reduction of the permanganate. The precipitated manganese dioxide was removed by filtration through a layer of Celite 512. The filtrate was evaporated under reduced pressure to *ca.* 250 ml and was continuously extracted with ether for 48 hr. Concentration of the ether layer afforded 7.27 g of a viscous yellow oil. This oil was chromatographed on 400 g of Silicar CC-7, 100–200 mesh silica gel. The early fractions eluted with ether–pentane mixtures gave 1.08 g (7%) of ketol **6** {$[\alpha]^{25}D$ +5.66 (*c* 2, $CHCl_3$)}. Later fractions yielded 5.73 g of a mixture of diol **1** and a carboxylic acid. The mixture was dissolved in 150 ml of ether, washed with five 50-ml portions of saturated aqueous sodium bicarbonate, dried, and concentrated to give 3.07 g (18%) of a clear oil. A small portion of this oil was recrystallized from hexane to afford the pure diol **1**: mp 55–56°; $[\alpha]^{25}D$ −0.71 (*c* 2, $CHCl_3$) (lit.[6,8] mp 55.5–56.0°); ir (CCl_4) 3610 (free OH) and 3420 cm^{-1} (bonded OH); nmr ($CDCl_3$) δ 3.96 (dd, 1, J = 9.0 and 5.0 Hz, CHOH), 2.65–1.33 (m, 6), 1.29 (s, 3, CH_3), 1.26 (s, 3, CH_3), and 0.93 (s, 3, CH_3).

Preparation of Keto Acetate 10.—To a solution of 5.00 g (28.8 mmol) of ketol **6** in 11.6 g (115 mmol) of anhydrous triethylamine and 20 ml of anhydrous ether cooled to 0° was added with stirring under nitrogen over a period of 0.5 hr a solution of 6.80 g (86.5 mmol) of acetyl chloride in 20 ml of ether. The mixture was stirred at 0° for 4 hr, allowed to warm to room temperature, and stirred for 20 hr. The reaction mixture was diluted with 200 ml of ice water and extracted with ether. The combined extracts were washed with cold 1 *N* hydrochloric acid, saturated sodium carbonate, and brine and dried. Removal of the solvent gave 5.38 g of an orange oil which was chromatographed on 425 g of silica gel (100–200 mesh). Elution with ether–hexane mixtures afforded in middle fractions 4.60 g (76%) of a viscous, colorless oil which was recrystallized from hexane to afford 2.68 g (45%) of **10** as colorless needles: mp 42–44°; $[\alpha]^{24}D$ +2.08° (*c* 2, $CHCl_3$); ir (CCl_4) 2950 (CH), 1740 (ester C=O), 1720 cm^{-1} (ketone C=O); nmr (CCl_4) δ 3.00–1.95 (m, 6), 1.91 (s, 3, CH_3COO), 1.51 (s, 3, CH_3), 1.36 (s, 3, CH_3), 0.86 (s, 3, CH_3).

Anal. Calcd for $C_{12}H_{18}O_3$: C, 68.54; H, 8.63. Found: C, 68.43; H, 8.92.

(25) All boiling points are uncorrected and all melting points are corrected. The infrared spectra were recorded on a Beckman IR-8 spectrophotometer and the nuclear magnetic resonance spectra were recorded on a Varian A-60, A-60A or HA-100 instrument using tetramethylsilane as an internal standard. Gas chromatography studies utilized an Aerograph A-90P or F & M Model 700 gas chromatograph and a Beckman 10-in. recorder equipped with a Disc Integrator. Unless otherwise stated, magnesium sulfate was employed as the drying agent.

Reduction of Ketol 6 with Sodium Borohydride.—A cold (0°) solution of 483.9 mg (2.88 mmol) of ketol **6** {mp 34–35°, $[\alpha]^{25}D$ −21.98° (*c* 2.5, ethanol)} and 146.1 mg (3.86 mmol) of sodium borohydride in 10 ml of dry methanol was stirred under nitrogen at 0° for 2 hr. The methanol was removed under reduced pressure and the residue partitioned between water and ether. The aqueous layer was extracted with several portions of ether and the combined extracts were dried and concentrated to give 287 mg (59%) of crude **2**, mp 147–153°. Several recrystallizations from diethyl ether afforded the pure *trans*-diol **2** as fine, colorless needles: mp 169–170° (lit.[6,8] mp 159–160°); ir (KBr) 3500–3100 (broad, bonded OH), 1160, 1080, and 1052 cm^{-1}; nmr ($CDCl_3$) δ 4.18 (dd, 1, *J* = 6.0 and 10.0 Hz, CHOH), 2.50–1.50 (m, 8), 1.35 (s, 3, CH_3), 1.25 (s, 3, CH_3), and 0.95 (s, 3, CH_3).

Reduction of 0.405 g (2.41 mmol) of ketol **6** in 10 ml of absolute methanol by 0.122 g (3.22 mmol) of sodium borohydride as described above afforded 0.240 g of a colorless solid which was chromatographed through 24 g of neutral silica gel (100–200 mesh) contained in a 30 cm × 15.5 mm glass column. Elution with ether–hexane mixtures afforded in the early fractions 0.113 g (28%) of unreacted ketol **6**. Middle fractions afforded 0.022 g (5%) of *cis*-diol **1**. The last fractions furnished 0.111 g (27%) of *trans*-diol **2**.

Lithium Aluminum Hydride Reduction of Ketol 6.[6]—To a solution of 0.122 g (3.22 mmol) of powdered lithium aluminum hydride in 7 ml of ether was added dropwise under nitrogen with stirring a solution of 0.405 g (2.41 mmol) of ketol **6** in 5 ml of ether at such a rate as to maintain a gentle reflux. After addition was complete the mixture was heated at reflux for 0.5 hr and allowed to cool. To the mixture was added 0.11 ml of water, 0.11 ml of aqueous 15% sodium hydroxide, and 0.33 ml of water and the mixture was stirred for 1 hr to ensure decomposition of the reduction complex. The mixture was filtered and the granular precipitate was washed with several portions of ether. The combined extracts were washed with water, dried, and concentrated to give 0.370 g of a colorless solid which was chromatographed through 24 g of neutral silica gel (100–200 mesh) contained in a 30 cm × 15.5 mm glass column. Elution with ether–petroleum ether mixtures afforded in the early fractions 0.033 g (8%) of ketol **6**. Middle fractions afforded 0.177 g (43.3%) of *cis*-diol **1**. The last fraction furnished 0.151 g (36.8%) of *trans*-diol **2**.

Lithium Aluminum Hydride Reduction of Keto Acetate 10.—Following the procedure described for lithium aluminum hydride reduction of ketol **6**, 0.506 g (2.41 mmol) of acetoxy ketone **10** was reduced with 0.200 g (5.27 mmol) of lithium aluminum hydride to a colorless solid, 0.277 g, which was chromatographed as previously described to give 0.015 g (4%) of *cis*-diol **1** and 0.249 g (61%) of *trans*-diol **2**.

Preparation of Epoxy Acetate 12.—In a 2-l. flask equipped with dropping funnel, Trubore stirrer, and condenser was placed 41.50 g (0.247 mol) of enol acetate **11**[26] {$[\alpha]^{25}D$ +31.49° (*c* 10, $CHCl_3$)} and 140 ml of methylene chloride. The flask and contents were cooled to 0° and a solution of 60.5 g (0.309 mol, 90% assay, FMC) of *m*-chloroperbenzoic acid in 975 ml of methylene chloride was added dropwise with stirring over a period of 1.0 hr. At intervals, 1-ml aliquots were removed from the reaction mixture and diluted with 10 ml of water and 10 ml of 10% potassium iodide solution; the iodine liberated was titrated to a starch indicator end point with 0.01 *N* sodium thiosulfate. After 13 hr of reaction at 0° 10% of the initial peracid remained. At this time the ice-cold reaction mixture was filtered and the filtrate was washed with 10% sodium bisulfite solution until neutral to starch–iodide paper, then with saturated sodium bicarbonate until neutral to litmus, and with one portion of brine. The methylene chloride solution was dried (Na_2SO_4), concentrated, and distilled giving 29.14 g of a colorless oil which contained[27] 60% of epoxy acetate **12**. Fractional distillation afforded a clear oil which solidified to a white solid, mp 30–51°. Recrystallization from hexane followed by sublimation afforded pure epoxy acetate **12**: mp 59–61°; bp 72–76° (0.15 mm); $[\alpha]^{25}D$ +48.64° (*c* 3.5, $CHCl_3$); ir (CCl_4) 1755 cm^{-1} (ester C=O); nmr (CCl_4) δ 2.04 (s, 3, $COCH_3$), 1.33 (s, 3, CH_3), 1.29 (s, 3, CH_3), and 0.95 (s, 3, CH_3).

Anal. Calcd for $C_{12}H_{18}O_3$: C, 68.55; H, 8.63. Found: C, 68.45; H, 8.57.

(26) M. P. Hartshorn and A. F. A. Wallis, *Tetrahedron*, **21**, 273 (1965).

(27) A vpc column packed with 10% SF-96 on 60–80 mesh Chromosorb W was employed for this analysis.

Pyrolysis of Epoxy Acetate 12.—Crude epoxy acetate **12** (29.14 g, containing 60% **12**) was passed through a 0.75 × 30 in. Pyrex tube filled with 0.25-in.-diameter glass beads at a rate of 1 drop per 5 sec. The tube was held vertically and heated to 265°. Nitrogen was passed through the tube simultaneously at a rate of 120 ml/min. The gaseous and liquid effluent from the bottom of the tube was collected in two successive traps cooled to 0°. The column was cooled after all the material had passed through and was rinsed with three 100-ml portions of ether and the material in the traps was dissolved in 200 ml of ether. The combined etheral solutions were washed with aqueous saturated sodium bicarbonate, dried, and concentrated. Vpc analysis[27] of the crude product demonstrated that approximately 10% of the original epoxy acetate **12** remained; therefore, the above procedure was repeated. The crude product (28.99 g) was distilled through a spinning band annular still giving a fraction [14.62 g, bp 76–78° (0.20 mm)] which crystallized when scratched with a glass rod. The crystals were recrystallized from pentane to afford 7.43 g (45%) of pure keto acetate **13**: mp 50–51°; $[\alpha]^{25}D$ −0.33° (*c* 12, chloroform); ir (CCl_4) 1740 (ester C=O), 1710 cm^{-1} (ketone CO); nmr (CCl_4) δ 3.17 (m, 1), 2.57 (m, 3), 2.08 (m, 1), 1.95 (s, 3, $COOCH_3$), 1.52 (s, 3, CH_3), 1.35 (s, 3, CH_3), 1.25–1.08 (m, 10), and 0.97 (s, 3, CH_3).

Anal. Calcd for $C_{12}H_{18}O_3$: C, 68.54; H, 8.63. Found: C, 68.55; H, 8.42.

Reductive Cleavage of Keto Acetate 13. A. With Chromous Chloride.—In a 50-ml flask was placed 10 g of zinc dust, 0.8 g of mercuric chloride, 0.5 ml of concentrated hydrochloric acid, and 10 ml of water. The mixture was shaken for 5 min, the supernatant liquid was decanted, and 20 ml of water and 5 ml of concentrated hydrochloric acid were added to the residue. Carbon dioxide was bubbled through the solution for 3 min and 5 g of chromic chloride hexahydrate was added. Of the resulting blue solution, 15 ml was added dropwise over a period of 10 min to 108 mg (0.5 mmol) of keto acetate **13** in 20 ml of acetone with stirring under CO_2 at room temperature. The mixture was stirred at room temperature for 1.0 hr, diluted with 50 ml of brine, and extracted with ether. The combined extracts were washed with saturated sodium bicarbonate solution, dried, and concentrated to give 80 mg of a clear oil which was composed[28] of 96% ketone **7** and 4% ketone **8**.

B. With Zinc and Acetic Acid.—In a 50-ml flask equipped with magnetic stirrer and reflux condenser was placed 105 mg (0.5 mmol) of keto acetate **13**, 10 g of zinc dust, and 35 ml of glacial acetic acid. The reaction mixture was refluxed for 24 hr, allowed to cool, and filtered. The zinc residue was washed with ether and the combined filtrate and washings were evaporated to a small volume and diluted with 50 ml of ether. The ether solution was washed with 5% sodium hydroxide solution and brine, dried, and concentrated to give 80 mg of a light brown oil which was composed[28] of 80% ketone **8** and 20% ketone **7**.

Lithium Aluminum Hydride Reduction of Keto Acetate 13.—Following the procedure described for lithium aluminum hydride reduction of ketol **6**, 4.29 g (20.4 mmol) of keto acetate **13** was reduced with 1.70 g (44.7 mmol) of lithium aluminum hydride. The crude product was a colorless semisolid (3.15 g, 91%) which was chromatographed through 200 g of neutral silica gel (100–200 mesh) contained in a 60 cm × 33 mm glass column. Elution with ether–hexane mixtures afforded in early fractions 2.33 g (67%) of *cis*-diol **3** as a viscous, colorless oil: $[\alpha]^{25}D$ +25.03° (*c* 1.5, $CHCl_3$); ir (CCl_4) 3670, (free OH), 3430 cm^{-1} (bonded OH); nmr ($CDCl_3$) δ 3.86 (dd, 1, *J* = 9.0 and 7.0 Hz, CHOH), 3.00–1.40 (m, 8), 1.23 (s, 6, $2CH_3$), and 1.06 (s, 3, CH_3).

Anal. Calcd for $C_{10}H_{18}O_2$: C, 70.55; H, 10.65. Found: C, 70.62; H, 10.94.

Later fractions afforded 0.70 g (20%) of a colorless, crystalline material which was recrystallized from ethyl acetate to afford pure *trans*-diol **4**: mp 152–153°; $[\alpha]^{30}D$ −29.10° (*c* 1, $CHCl_3$); ir ($CHCl_3$) 3600 (free OH), 3550–3100 cm^{-1} (bonded OH); nmr ($CDCl_3$) δ 4.28 (dd, 1, *J* = 4.5 and 9.5 Hz, CHOH), 3.20 (s, 1, broad, OH), 2.65 (s, 1, OH), 2.60–1.32 (m, 6), 1.28 (s, 3, CH_3), 1.25 (s, 3, CH_3), and 1.06 (s, 3, CH_3).

Anal. Calcd for $C_{10}H_{18}O_2$: C, 70.55; H, 10.66. Found: C, 70.33; H, 10.44.

Preparation of Ketol 14.—A solution of 0.72 g (3.43 mmol) of keto acetate **13** in 50 ml of water and 50 ml of methanol containing 5.0 mmol of sodium hydroxide was stirred at room temperature

(28) A vpc column packed with Carbowax 20M on 60–80 mesh Chromosorb W was employed for this analysis.

for 5.5 hr. The reaction mixture was diluted with 50 ml of water and extracted three 50-ml portions of ether. The combined ether extracts were washed with water, dried, and concentrated to give ketol **14** as a colorless oil, 0.48 g (84%), which was shown by vpc analysis[27] to consist of a single component: bp 53–55° (0.15 mm); $[\alpha]^{25}D$ +90.41° (*c* 5, $CHCl_3$); 3600 (free OH), 3500 (bonded OH), 1710 (ketone C=O), 1385 and 1370 cm^{-1} (gem-dimethyl); nmr (CCl_4) δ 3.10 (s, 1, OH), 2.55 (m, 3) 2.10 (m, 3), 1.33 (s, 3, CH_3), 1.21 (s, 3, CH_3), and 0.95 (s, 3, CH_3).

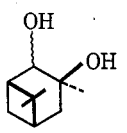
Anal. Calcd for $C_{10}H_{16}O_2$: C, 71.39; H, 9.59. Found: C, 71.67; H, 9.68.

In order to ensure that no rearrangement had occurred during this hydrolysis, a sample of ketol **14** was acetylated using acetyl chloride and triethylamine in ether to regenerate keto acetate **13**.

Aluminum Isoproxide Reduction of Ketol 14.—To 2.01 g (11.9 mmol) of ketol **14** was added 80 ml of absolute isopropyl alcohol, and 9.0 g (44 mmol) of freshly prepared, distilled aluminum isopropoxide.[29] The reaction mixture was stirred and distilled through a 2-in. fractionating Claisen head at the rate of 3 ml/hr. At the end of 12 hr there was a negative 2,4-dinitrophenylhydrazine test[29] for the distillate and the distillation was halted. The contents of the flask were allowed to cool and were stirred with 80 ml of 2% sodium hydroxide solution for 2 hr. The resultant sludge was filtered and the filtrate was extracted with three 100-ml portions of ether. The combined extracts were washed with water and brine, dried, and concentrated to give 1.35 g (66%) of a yellow oil which was shown by tlc analysis to contain unreacted ketol **14** and one other component. The crude product was eluted with ether–hexane solutions through 120 g of neutral silica gel (100–200 mesh) contained in a 60 cm × 25 mm glass column. Late fractions afforded a diol as a clear, homogeneous oil: 1.01 g (50%); $[\alpha]^{25}D$ −12.00° (*c* 3, $CHCl_3$); ir ($CHCl_3$) 3600 (free OH), 3400 cm^{-1} (broad, bonded OH); nmr ($CDCl_3$) δ 3.85 (d, 1, J = 5.0 Hz, CHOH), 3.42 (broad s, 2, 2 OH), 2.50–1.80 (m, 6), 1.43 (s, 3, CH_3), 1.21 (s, 3, CH_3), and 1.10 (s, 3, CH_3).

Anal. Calcd for $C_{10}H_{18}O_2$: C, 70.55; H, 10.66. Found: C, 70.78; H, 10.44.

Based on the above spectral data and its oxidation to ketol **15** this diol is one of the isomeric diols **24**.



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Oxidation of Diol 23.—A solution of 100 mg (0.588 mmol) of diol **23** and 1.0 ml of ether was cooled to 0° and stirred while a solution of 59 mg (0.196 mmol) of sodium dichromate dihydrate, 0.04 ml (0.783 mmol) of 96% sulfuric acid, and 1.0 ml of water was added dropwise over a period of 5 min. The reaction mixture was stirred at 0° for 0.5 hr, allowed to warm to room temperature, and stirred for 2.0 hr. The reaction mixture was diluted with 10 ml of water, saturated with sodium chloride, and extracted with ether. The combined ether extracts were washed with aqueous saturated sodium bicarbonate, water, and aqueous saturated sodium chloride, dried, and concentrated to give a pale green oil, 51 mg (51%), which had an ir spectrum and vpc retention time[27] identical with ketol **15**.

Equilibration of Ketols 14 and 15.—A solution of 0.91 g (5.40 mmol) of ketol **14** in 35 ml of dry *tert*-butyl alcohol was added under nitrogen with stirring to a solution of potassium *tert*-butoxide prepared from 0.30 g (7.78 mmol) of potassium and 30 ml of *tert*-butyl alcohol. The reaction mixture was heated at 65° for 9 hr and stirred and then concentrated under reduced pressure to near dryness, diluted with 250 ml of water, and extracted with ether. The combined extracts were washed with water and brine, dried, and concentrated to give a yellow oil, 0.74 g (84%), which contained 42.4% unreacted ketol **14** and 57.6% of a new ketol characterized as **15**. Further heating with base led to no change in the composition of the mixture. This mixture was separated into individual components by preparative vpc.[30] The minor component displayed ir and nmr spectra identical with the starting ketol **14**. Ketol **15**, the major component, was a clear viscous oil: ir (CCl_4) 3580 (free OH), 3450 (bonded OH), 1710 cm^{-1} (ketone C=O); nmr (CCl_4) δ 3.30–1.60 (m, 7), 1.40 (s, 3, CH_3), 1.38 (s, 3, CH_3), 0.91 (s, 3, CH_3).

Anal. Calcd for $C_{10}H_{16}O_2$: C, 71.39; H, 9.59. Found: C, 71.53; H, 9.78.

Treatment of Ketol 6 with Potassium *tert*-Butoxide.—A solution of 1.82 g (10.80 mmol) of ketol **6** in 60 ml of *tert*-butyl alcohol was added in one portion under nitrogen with stirring to a solution of potassium *tert*-butoxide in *tert*-butyl alcohol prepared from 0.60 g (16 g-atoms) of potassium and 70 ml of *tert*-butyl alcohol. The reaction was stirred at 65° for 10 hr during which time the solution became dark red. The reaction mixture was worked up as above to afford 1.62 g (84%) of a yellow oil which had ir, nmr, and vpc spectra identical with starting ketol **6**.

Preparation of Keto Acetate 18.—A solution of 9.01 g (47 mmol) of acetate **17**[31] {$[\alpha]^{25}D$ +7.78°, (*c* 2, $CHCl_3$)} in 100 ml of absolute methanol was exhaustively ozonized at −70°. The ozonized solution was added to a solution of 4 ml of absolute methanol, 12 ml of glacial acetic acid, and 24 g of sodium iodide, and the mixture was stirred at 25° for 7 hr and then added to 300 ml of water and 15 ml of saturated sodium bisulfite solution. The solution was made basic with solid sodium bicarbonate and extracted with ether. The combined extracts were washed with water and brine, dried, and concentrated to give 8.27 g (91%) of a light yellow oil. Distillation afforded pure **18**: bp 80.5–81° (0.22 mm); ir (CCl_4) 1750 (ester C=O), 1730 cm^{-1} (ketone C=O); nmr (CCl_4) δ 5.13 (dd, 1, J = 9 and 3 hz, CHOAc), 2.04 (s, 3, $COOCH_3$), 1.38 (s, 3, CH_3), and 0.94 (s, 3, CH_3).

Anal. Calcd for $C_{11}H_{16}O_3$: C, 67.32; H, 8.22. Found: C, 67.20; H, 8.41.

Addition of Methyllithium to Keto Acetate 18.—To 23 ml (15 mmol) of 0.67 *N* methyllithium in ether cooled to −70° was added in one portion a solution of 0.50 g (2.6 mmol) of keto acetate **18** in 5 ml of ether. The resulting solution was allowed to warm to room temperature and stirred under nitrogen for 24 hr. The reaction mixture was poured into 150 ml of water and extracted with two 50-ml portions of ether and one 50-ml portion of methylene chloride. The combined extracts were dried and concentrated to give a yellow oil, 0.42 g (96%), which was chromatographed over 24 g of neutral silica gel (100–200 mesh) contained in a 30 cm × 15.5 mm glass column. Elution with ether–hexane mixtures afforded in early fractions 0.28 g (65%) of viscous, colorless *cis*-diol **1**. Later fractions afforded 0.075 g (17%) of crystalline *trans*-diol **4**.

Addition of Methylmagnesium Iodide to Keto Acetate 18. A. Normal Addition.—To a solution of methylmagnesium iodide prepared from 0.37 g (15 mg-atoms) of magnesium turnings, and 2.19 g (15 mmol) of methyl iodide in 15 ml of absolute ether was added at 0° under nitrogen with stirring over a period of 5 min 0.50 g (2.6 mmol) of keto acetate **18** in 5 ml of anhydrous ether. The resulting solution was allowed to warm to room temperature and was stirred for 16 hr. The reaction mixture was heated at reflux for 3 hr, cooled, poured into 150 ml of water, and extracted with ether and methylene chloride. The combined extracts were washed with water and brine, dried, and concentrated to give 0.36 g (84%) of a clear, colorless oil which was chromatographed through 24 g of neutral silica gel (100–200 mesh) contained in a 30 cm × 15.5 mm glass column. Elution with ether–hexane mixtures afforded in early fractions 0.18 g (42%) *cis*-diol **1**. Later fractions afforded 0.04 g (10%) of *trans*-diol **4**.

B. Inverse Addition.—To a solution of 0.50 g (2 mmol) of keto acetate **18** in 2.5 ml of anhydrous ether cooled to 0° was added under nitrogen with stirring over a period of 2 hr a solution of methylmagnesium iodide prepared from 0.18 g (7.7 mg-atoms) of magnesium turnings, 1.08 g (7.7 mmol) of methyl iodide, and 2.5 ml of ether. The reaction mixture was refluxed for 2 hr and then the reaction was quenched by the addition of 5.0 g of ice. The precipitated magnesium hydroxide was dissolved in a minimum amount of saturated ammonium chloride solution, and the mixture was extracted with ether. The combined extracts were washed with water and brine, dried, and concentrated to afford 0.45 g of a viscous yellow oil which was stirred for 20 hr at room temperature with 25 ml of 1 *N* methanolic potassium hydroxide. The reaction mixture was diluted with 60 ml of water and extracted with chloroform. The combined chloroform extracts were washed with water and brine, dried, and concentrated to give 0.27 g (63%) of a semisolid which was chromatographed as

(29) A. L. Wilds, *Org. React.*, **2**, 178 (1944).

(30) A 10 ft × 3/8 in. vpc column packed with 30% DEGS on 30–60 mesh Chromosorb W was employed for this separation.

(31) H. Schmidt, *Chem. Ber.*, **77**, 167 (1944).

described above to give 0.08 g (20%) of *cis*-diol **1** and 0.10 g (24%) of *trans*-diol **4**.

Preparation of Benzyl Ether 19.—A dispersion of 53% sodium hydride in mineral oil (3.24 g of sodium hydride, 0.135 mol) was washed with three 50-ml portions of dry pentane under nitrogen. After the final wash the residual pentane was evaporated *in vacuo* and 60 ml of dimethyl sulfoxide was added dropwise under nitrogen. The resulting solution was stirred at room temperature for 0.5 hr. To this solution was added dropwise over a period of 5 min a solution of 13.70 g (0.090 mol) of **16**[32] {$[\alpha]^{25}D$ −26.26° (*c* 2, $CHCl_3$)} in 40 ml of dimethyl sulfoxide, and the mixture was stirred at room temperature for 10 hr. To this mixture was added 17.0 g (0.135 mol) of benzyl chloride with stirring over a period of 0.5 hr. The reaction mixture was stirred for 1.0 hr, diluted with 350 ml of ice water, and extracted with pentane. The combined extracts were washed with brine, dried, and concentrated to give 26.87 g of a pale yellow oil from which crystallized 0.46 g of *trans*-stilbene. The remaining material was distilled to give 14.55 g (67%) of **19**: bp 115–116° (0.25 mm); $[\alpha]^{25}D$ −21.79° (*c* 3.5, $CHCl_3$); ir (CCl_4) 3090 (C=CH), 3050 (aromatic CH), 1640 (C=C), 1380 and 1360 (*gem*-dimethyl), 1055 (CO), 897 (C=CH_2), and 692 cm^{-1} (aromatic); nmr (CCl_4) δ 7.23 (s, 5, C_6H_5), 4.86 (s, 2, C=CH_2), 4.62 (d, 1, J = 12.0 Hz), 4.35 (d, 1, J = 12.0 Hz) (AB system, OCH_2Ph), 3.97 (m, 1, $CHOCH_2Ph$), 2.60–1.50 (m, 6), 1.30 (s, 3, CH_3), and 0.82 (s, 3, CH_3).

Anal. Calcd for $C_{17}H_{22}O$: C, 84.25; H, 9.15. Found: C, 83.98; H, 9.31.

Preparation of Keto Benzyl Ether 20.—A solution of 14.31 g (59 mmol) of olefin **19** in 150 ml of absolute methanol was ozonized for 1.0 hr at −70°. The ozonized solution was stirred vigorously with a mixture of 55 ml of methanol, 15 ml glacial acetic acid, and 29.6 g, (0.198 mol) of sodium iodide under nitrogen at room temperature for 7.0 hr. The resultant iodine-colored solution was diluted with 450 ml of water and treated with 25 ml of saturated sodium bisulfite solution. The solution was made basic by addition of solid sodium bicarbonate and was extracted with ether. The combined ethereal extracts were washed with water and brine, dried, and concentrated to give 14.22 g of a pale yellow oil which was recrystallized from hexane to afford 5.64 g (39%) of colorless, crystalline keto ether **20**: mp 51–52°; $[\alpha]^{25}D$ +1.01° (*c* 3.5, $CHCl_3$); ir (CCl_4) 3040 (aromatic CH), 2950 (CH), 1715 (ketone C=O), 1385 and 1370 (*gem*-dimethyl), 1055 (CO), and 695 cm^{-1} (aromatic); nmr (CCl_4) δ 7.21 (s, 5, C_6H_5), 3.90 (d, 1, J = 12.0 Hz), 3.74 (d, 1, J = 12.0 Hz) (AB system, OCH_2Ph), 2.70–1.60 (m, 6), 1.35 (s, 3, CH_3), and 0.77 (s, 3, CH_3).

(32) J. K. Crandall and L. Chang, *J. Org. Chem.*, **32**, 435 (1967).

Anal. Calcd for $C_{16}H_{20}O_2$: C, 78.65; H, 8.25. Found: C, 78.87; H, 8.48.

Treatment of 20 with Methyllithium.—To 57 ml (38 mmol) of 0.67 *N* ethereal methyllithium cooled to −70° was added under nitrogen 4.20 g (17.2 mmol) of crystalline keto ether **20** in 30 ml of anhydrous ether. The solution was allowed to warm to room temperature and was stirred for 25 hr. The reaction mixture was poured into 300 ml of water and extracted with ether. The ethereal extracts were dried and concentrated to give 4.57 g of a mixture of alcohols **21** and **22** as a pale yellow oil. Without further purification the benzyl group was reductively cleaved as described below.

Hydrogenolysis of Alcohols 21 and 22. A. By Catalytic Hydrogenation.—In an alcoholic potassium hydroxide washed Paar hydrogenation bottle was placed 0.80 g (3.08 mmol) of the mixture of alcohols **21** and **22** contained above in 50 ml of absolute ethanol and 0.3 g of 5% palladium-on-charcoal catalyst. The mixture was shaken under a 60-psi atmosphere of hydrogen for 24 hr, filtered, and concentrated to give a 0.61 g of a colorless semisolid which was chromatographed through 24 g of neutral silica gel (100–200 mesh) contained in a 30 cm × 15.5 mm glass column. Elution with ether–hexane mixtures afforded in the earlier fractions 0.09 g (16.9%) of *cis*-diol **1**. Later fractions afforded 0.25 g (48.5%) of *trans*-diol **4**.

B. By Reduction with Sodium in Liquid Ammonia.—To 150 ml of liquid ammonia which had been distilled through a potassium hydroxide tower was added 1.00 g (3.9 mmol) of the mixture of alcohols **21** and **22** in 6 ml of absolute ethanol. To this solution was added 0.44 g (19 mg-atoms) of sodium in small pieces. When all of the sodium was added, the solution maintained a dark blue color for *ca.* 3 min and then spontaneously became colorless. The mixture was allowed to stir an additional 1 hr and the ammonia was allowed to evaporate. The residue was diluted with 150 ml of water and extracted with chloroform. The combined extracts were washed with water and brine, dried, and concentrated to give 0.41 g of a pale yellow semisolid which was chromatographed through 17 g of neutral silica gel (100–200 mesh) contained in a 38 cm × 11.5 mm glass column. Elution with petroleum ether–ether mixtures afforded in the early fractions 88 mg (13.5%) of *cis*-diol **1**. Later fractions afforded 150 mg (23%) of *trans*-diol **4**.

Registry No.—**1**, 18680-27-8; **2**, 21803-49-6; **3**, 29333-10-6; **4**, 20536-52-1; **6**, 1845-25-6; **10**, 29333-13-9; **12**, 29333-14-0; **13**, 29333-15-1; **14**, 22419-98-3; **15**, 29333-17-3; **18**, 22419-94-9; **19**, 29333-19-5; **20**, 29333-20-8; **23**, 29333-21-9.

An Efficacious Methyl-Labeled (±)-Camphor Synthesis[1]

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A nine-step (±)-camphor synthesis is reported which allows the individual labeling of each of the three methyl groups, all steps proceeding in high yield. Norcamphor is methylated, carboxylated, and then treated with methylmagnesium bromide, leading to 2-*endo*,3-*exo*-dimethyl-3-*endo*-hydroxy-2-*exo*-norbornanecarboxylic acid. This acid was rearranged in 85% sulfuric acid to 1,7-dimethylnorbornane-7-carbo-2-lactone, which was reduced with lithium aluminum hydride and monotosylated with tosyl chloride to give 8-tosyloxyisoborneol. Chromic acid–pyridine oxidation to 8-tosyloxycamphor, followed by tosyl group displacement with iodide ion and catalytic hydrogenolysis, led to (±)-camphor.

We wish to report a convenient synthesis of (±)-camphor which allows the specific labeling of each of the three methyl groups. The sequence approximates one reported earlier by Finch and Vaughan[3] with, however, some important variances (Chart I) and all steps proceeding in good yield.

The procedure commences from norcamphor (**1**), which was methylated essentially by the method described by Corey and coworkers,[4] yielding the exo methyl ketone **2**. This ketone was converted to the corresponding enolate anion using triphenylmethylsodium,

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(2) Recipient of a National Science Foundation Traineeship, 1967–1971.

(3) A. M. T. Finch and W. R. Vaughan, *J. Amer. Chem. Soc.*, **87**, 5520 (1965); **91**, 1416 (1969).

(4) E. J. Corey, R. Hartmann, and P. A. Vatakencherry, *ibid.*, **84**, 2611 (1962); J. Wolinsky, D. R. Dimmel, and T. W. Gibson, *J. Org. Chem.*, **32**, 2087 (1967).