Negishi, *J. Am. Chem. Soc.*, **89**, 5285 (1967); (b) C. F. Lane and H. C. Brown, *J. Organomet. Chem.*, **34**, C29 (1972); (c) M. M. Rogic, *Intra-Sci. Chem. Rep.*, **7**, 155 (1973).
(19) D. S. Matteson and R. W. H. Mah, *J. Org. Chem.*, **28**, 2171 (1963); D. S. Matteson and R. W. H. Mah, *J. Am. Chem. Soc.*, **85**, 2599 (1963).
(20) D. A. Evans, R. C. Thomas, and J. A. Walker, *Tetrahedron Lett.*, 1427 (1976). Matteson has reported a cross coupling process similar to the one described here in a review of the chemistry of methanetriborinic and methanetetraboronic esters; cf. *Synthesis*, 147 (1975).
(21) E. J. Corey and D. J. Beames, *J. Am. Chem. Soc.*, **94**, 7210 (1972).
(22) A. F. Kluge, K. G. Untch, and J. H. Fried, *J. Am. Chem. Soc.*, **94**, 9256 (1972).
(23) (a) H. C. Brown, T. Hamaoka, and N. Ravindran, *J. Am. Chem. Soc.*, **95**, 5786 (1973); (b) *ibid.*, **95**, 6456 (1973).
(24) The minor loss in stereospecificity in this process may be due to competitive cis elimination of the β haloborane.
(25) We have found **38b** to the unstable in THF solutions.
(26) M. F. Lappert in "The Chemistry of Boron and Its Compounds", E. L. Muetterties, Ed., Wiley, New York, N.Y., 1967, pp 529–535.
(27) H. C. Brown and M. Ravindran, *J. Am. Chem. Soc.*, **95**, 2396 (1973); H. C. Brown and S. K. Gupta, *ibid.*, **97**, 5249 (1975).
(28) H. Gilman and F. K. Cartledge, *J. Organomet Chem.*, **2**, 447 (1964).

Total Synthesis of (±)-*cis*-Sativenediol

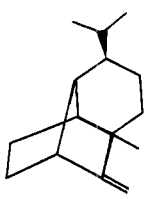
John E. McMurry* and Michael G. Silvestri

Thimann Laboratories, University of California, Santa Cruz, California 95064

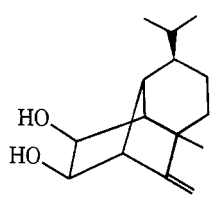
Received June 17, 1976

A total synthesis of the plant growth promoter *cis*-sativenediol (**2**) is reported. The key step involves internal alkylation to cyclopropane **7** followed by thermal rearrangement to tricyclic enone **6**. Cis hydroxylation of the double bond, followed by transformation of the carbonyl into a methylene group, completes the synthesis.

Some years ago we reported[1] a stereospecific total synthesis of the tricyclic sesquiterpene hydrocarbon sativene (**1**). More recently, our continuing interest in this skeletal class has also led to syntheses of copacamphene[2] and of longifolene.[3] When, therefore, Marumo[4] and Arigoni[5] independently assigned the *cis*-sativenediol structure (**2**) to a metabolite isolated from the fungus *Helminthosporium sativum*, we were drawn to attempt a synthesis of the molecule.[6] The Marumo report is particularly interesting because it appears that *cis*-sativenediol posesses gibberellin-like plant growth promoter activity.



1

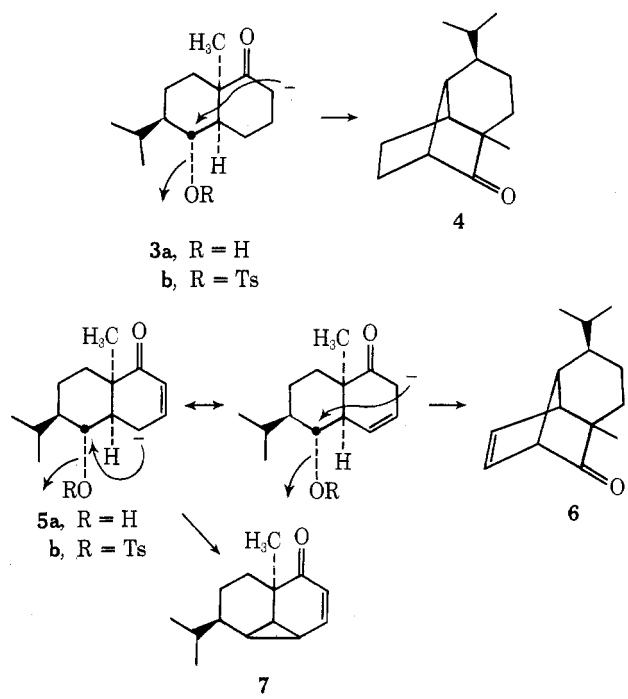


2

The key step in our sativene synthesis was the intramolecular alkylation of bicyclic keto tosylate **3b** to tricyclic ketone **4**. If one imagines that the cis diol functionality in the target **2** arises by less hindered exo hydroxylation of the proper olefinic ketone **6**, then this requires that we synthesize and cyclize the enone tosylate **5b**. One conceivable difficulty with this route is that **5b** might choose an alternate mode of cyclization leading to cyclopropane **7**, but only experiment can show which cyclization path is more favorable.

Enone **5b** was therefore synthesized in straightforward manner from **3a** whose synthesis we have previously reported[1] (Scheme I). One modification made in the present work, however, is the use of aqueous titanous ion[7] to cleave 2,4-DNP **14** to the corresponding ketone **3a**. The transformation occurred in 97% yield vs. the 70% reported earlier when ozonolytic cleavage was used. Ketone **3a** was readily transformed into enone **5a** in 82% yield by the Reich–Sharpless procedure,[8] and, after tosylation, we were ready to attempt intramolecular alkylation.

Treatment of keto tosylate **5b** with 1.2 equiv of dimsyl sodium in Me_2SO for 5 min at room temperature led to a 96% yield of pure cyclization product. Ir and NMR spectroscopy clearly showed, however, that the product was exclusively the undesired cyclopropane, **7** (ir 1670 cm^{-1}).

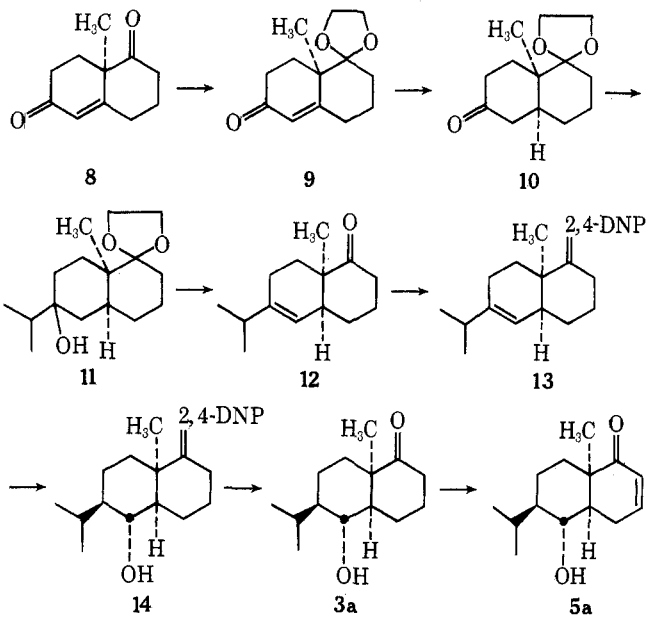


We had hoped, from inspection of molecular models, that geometric constraints imposed by the decalin system would hinder the development of orbital overlap necessary for three-membered ring formation, but this was clearly not the case.

Since the cause of the problem is the extended enolate system in **5b** one can devise potential solutions based on carrying out the cyclization with enone equivalents to **5** in which the double bond is somehow masked. The actual resolution of the problem turns out to be much simpler, however, when one realizes that the undesired product **7** and the desired product **6** are formally interconvertible by a vinylcyclopropane → cyclopentene rearrangement. Thus they should be in a thermal equilibrium, and one would expect the relatively unstrained **6** to predominate rather than cyclopropane **7**. When, in fact, **7** was heated to 450 °C in a nitrogen swept quartz pyrolysis system, **6** was isolated as the sole product in nearly quantitative yield.

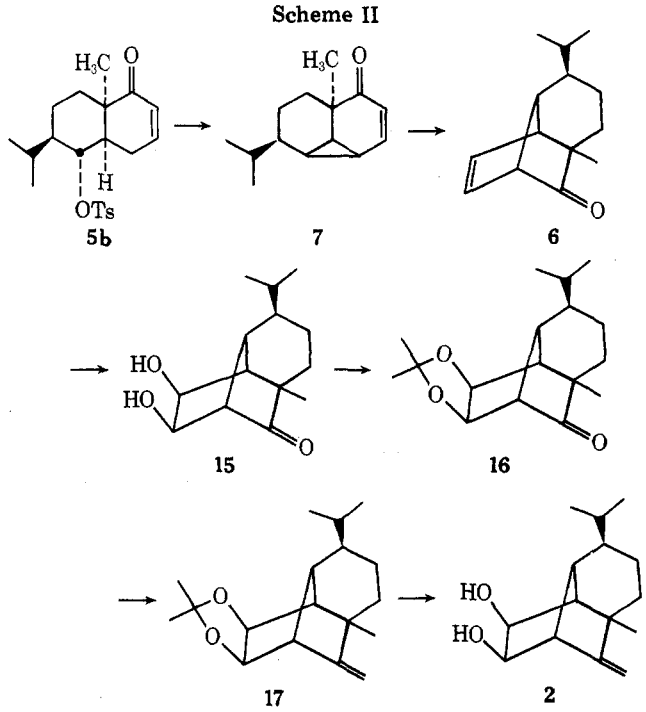
With this key rearrangement completed, **6** was then

Scheme I

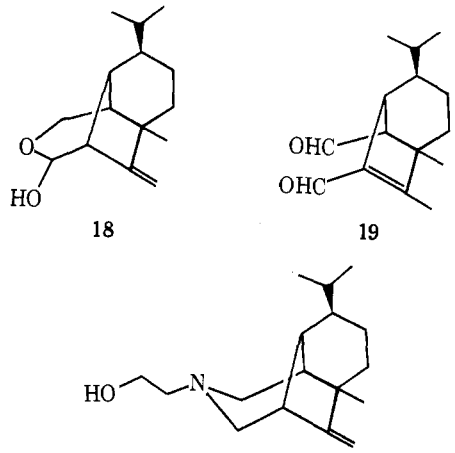


transformed into *cis*-sativenediol. Hydroxylation of **7** with OsO_4 took place exclusively from the less hindered exo direction to afford a keto diol (**15**) which was protected as the acetonide **16**. Addition of methyllithium to the carbonyl, followed by dehydration of the resultant alcohol with thionyl chloride in pyridine, led to (±)-*cis*-sativenediol acetonide (**17**). Removal of the protective group by treatment with dilute acid in methanolic THF gave synthetic **2**, identical in its ir and NMR characteristics with the natural product.[9] An alternative sequence, designed to avoid the two steps involved in diol protection and deprotection, might be to transform keto olefin **6** into a diolefin which could be selectively hydroxylated at the endocyclic double bond. This scheme failed, however, when **6** failed to react with methylenetriphenylphosphorane and when the tertiary alcohol from addition of methyllithium to **6** gave a mixture of rearrangement products on attempted dehydration with thionyl chloride in pyridine. The transformations leading to *cis*-sativenediol are summarized in Scheme II.

Scheme II



This synthesis of *cis*-sativenediol proceeds in an overall yield of nearly 17% for 16 steps from the Wieland–Miescher ketone (**8**) and should serve to make sufficient quantities available for biological testing. One further point is that since Marumo has reported[4] the periodate oxidation of **2** to prehelminthosporal[10] (**18**), this work constitutes a total synthesis of that material, of helminthosporal (**19**), and of the related



phytotoxin, victoxinine[11] (**20**). The entire class of sativene metabolites is therefore made available by synthesis.[12]

Experimental Section

NMR spectra were obtained in $CDCl_3$ solution (Me_4Si internal standard), except where indicated, on Varian A-56/60A and JEOL PS 100 instruments. Ir spectra were obtained on a Perkin-Elmer 337. Mass spectra were taken on a Hitachi Perkin-Elmer RMU6E and high-resolution mass spectra were obtained at the University of California, Berkeley. Melting points were determined on a Hoover-Thomas apparatus and are uncorrected.

1α-Hydroxy-2β-isopropyl-4aα-methyl-1,2,3,4,4a,7,8,8aα-octahydronaphthalen-5(6*H*)-one (3a). A buffered solution of titanium trichloride was prepared by the addition of NH_4OAc (25.7 g, 0.334 mmol) in nitrogen-purged water (100 ml) to an aqueous titanium trichloride solution (35 ml, 1.6 M) under N_2. The 2,4-DNP alcohol **14**[1] (1.5 g, 3.71 mmol) in dimethoxyethane (150 ml) was added and the resulting solution warmed to 85 °C for 10 min. The reaction mixture was cooled, diluted with H_2O, and extracted three times with ether. The combined ether extracts were washed with saturated $NaHCO_3$, H_2O, and saturated NaCl. The ether solution was dried ($MgSO_4$), filtered, and concentrated. The crude oil was chromatographed on alumina (ether eluent) to give 0.80 g (97%) of the desired keto alcohol **3a** which crystallized on standing in the refrigerator: mp 66–67 °C; ir (neat) 3450 (OH) and 1705 cm^{-1} (C=O); NMR (CCl_4) δ 1.31 (s, 3 H) and 0.95 and 0.80 (two doublets, 6 H, J = 7 Hz).

1α-Hydroxy-2β-isopropyl-4aα-methyl-1,2,3,4,4a,8aα-hexahydronaphthal-6-en-5(8*H*)-one (5a). Keto alcohol **3a** (0.50 g, 2.23 mmol) in THF (25 ml) was added dropwise to a 0.2 M solution of lithium isopropylcyclohexylamide (25 ml) cooled at −78 °C under N_2. After 20 min, phenylselenyl chloride (0.51 g, 2.68 mmol) in THF (25 ml) was added dropwise to the cooled solution. The solution was stirred at −78 °C for 1 h and warmed to room temperature. The solution was quenched with cold saturated NH_4Cl solution and extracted three times with ether. The combined extracts were washed with 1 N HCl, $NaHCO_3$, H_2O, and saturated NaCl. The ether was dried ($MgSO_4$), filtered, and concentrated. The crude concentrate was dissolved in THF (50 ml), 30% H_2O_2 (0.70 ml) added, and the solution stirred for 1 h. Water was added and the mixture was extracted with ether. The ether extract was washed with saturated Na_2CO_3, H_2O, and saturated NaCl. The extract was dried ($MgSO_4$), filtered, and concentrated. Chromatography on neutral alumina (ether eluent) gave 0.41 g (82%) of the desired enone alcohol **5a** as a colorless oil: ir (neat) 3445 (OH) and 1675 cm^{-1} (C=O); NMR ($CDCl_3$) δ 0.70 and 0.88 (two doublets, 6 H, J = 7 Hz), 1.15 (s, 3 H), 5.88 (d of m, 1 H, J = 10 Hz), and 6.75 (m, 1 H).

Anal. Calcd for $C_{14}H_{22}O_2$: m/e 222.1620. Found: m/e 222.1629.

2β-Isopropyl-4aα-methyl-1α-toluenesulfonyloxy-1,2,3,4,4a,-8aα-hexahydronaphthal-6-en-5(8*H*)-one (5b). The enone alcohol **5a** (0.30 g, 1.35 mmol) was dissolved in dry pyridine (6 ml) under N_2.

p-Toluenesulfonyl chloride (0.65 g, 3.26 mmol) was added and the solution allowed to stand for 3 days at room temperature. Water (10 ml) was added, and the solution was placed in the refrigerator for crystallization; 0.36 g (70%) of the desired keto tosylate **5b**, mp 142.5–143.5 °C, was collected.

9-Isopropyl-6-methyltricyclo[4.4.0.0^{2,10}]dec-3-en-5-one (7). A solution of dimethyl sulfinyl carbanion in Me_2SO (3.8 ml, 0.50 M) was added dropwise to a solution of keto tosylate **5b** (0.60 g, 1.59 mmol) in 9 ml of Me_2SO under N_2. After 5 min at room temperature the reaction mixture was quenched with water, saturated with NaCl, and extracted twice with ether. The ether extracts were washed with H_2O and with saturated NaCl, then dried ($MgSO_4$), filtered, and concentrated. The crude oil was chromatographed on Florisil (8% ethyl acetate–92% pentane eluent) to give 0.31 g (96%) of the cyclopropyl compound **7** as a colorless oil: ir (neat) 1670 cm^{-1} (C=O); NMR ($CDCl_3$) δ 0.96 and 1.15 (two doublets, 6 H, J = 6 Hz), 1.40 (s, 3 H), 5.76 (d, 1 H, $J_{3,4}$ = 10 Hz), 7.00 (d of d, 1 H, $J_{3,4}$ = 10 and $J_{2,3}$ = 4 Hz); mass psectrum M$^+$ *m/e* 204.

3-Isopropyl-6-methyltricyclo[4.4.0.0^{2,8}]dec-9-en-7-one (6). A quartz tube with quartz chip packing, which had been neutralized with bis(trimethylsilyl)acetamide, was heated to 450 °C with a N_2 flow rate of 50 ml/min passing through. Cyclopropyl compound **7** (0.60 g, 2.94 mmol) was dissolved in hexanes and added dropwise to the column over a period of 1 h. The pyrolysate was trapped in a dry ice cooled receiver and then concentrated. The crude oil was chromatographed on silica gel (5% ethyl acetate–95% pentane eluent) to give 0.54 g (90%) of the desired tricyclic ketone **6** as a colorless oil: ir (neat) 1745 cm^{-1} (C=O); NMR ($CDCl_3$) δ 0.87 and 0.91 (two doublets, 6 H, J = 6 Hz), 1.02 (s, 3 H), 2.37 (m, 1 H), 2.72 (m, 1 H), 2.98 (m, 1 H), 6.05 (broadened d of d, 1 H, $J_{9,10}$ = 6, $J_{1,10}$ = 3 Hz), 6.59 (d of d, 1 H, $J_{9,10}$ = 6, $J_{8,9}$ = 3 Hz).

Anal. Calcd for $C_{14}H_{20}O$: *m/e* 204.1514. Found: *m/e* 204.1528.

9,10-Dihydroxy-3-isopropyl-6-methyltricyclo[4.4.0.0^{2,8}]-decan-7-one (15). Tricyclic ketone **6** (0.35 g, 1.71 mmol) was dissolved in pyridine (4.5 ml), and added to a solution of OsO_4 (4.6 ml, 0.39 M) in benzene. The resulting solution was stirred under N_2 for 18 h. After this time a solution consisting of $NaHSO_3$ (0.84 g), H_2O (14 ml), and pyridine (9 ml) was added and stirred for 40 min. The resulting orange solution was extracted with $CHCl_3$, washed with H_2O and saturated NaCl, and dried (Na_2SO_4). Filtration and concentration under vacuum gave 0.36 g (87%) of the desired diol **15** as a crystalline material: mp 119–120 °C; ir ($CHCl_3$) 3410 and 3325 (OH), 1745 cm^{-1} (C=O); NMR ($CDCl_3$) δ 3.81 and 4.11 (two doublets, 2 H, J = 6 Hz); mass spectrum M$^+$ *m/e* 238.

9,10-Dihydroxy-3-isopropyl-6-methyltricyclo[4.4.0.0^{2,8}]-decan-7-one Acetonide (16). Diol **15** (0.34 g, 1.43 mmol) was dissolved in acetone (20 ml) and CH_2Cl_2 (60 ml). Toluenesulfonic acid H_2O (0.04 g) was added and the solution warmed to 75 °C under N_2. Water was removed using a Soxhlet extractor containing 4 Å molecular sieves. After 24 h, the reaction mixture was cooled, neutralized with saturated $NaHCO_3$, and extracted with ether. The ether was washed with H_2O, dried (Na_2SO_4), filtered, and concentrated. The crude oil was chromatographed on Florisil (10% ethyl acetate–90% pentane eluent) to give 0.35 g (89%) of the desired acetonide **16**, which crystallized on standing in the refrigerator: mp 64–65 °C; ir ($CHCl_3$) 1750 cm^{-1} (C=O); NMR ($CDCl_3$) δ 1.30 (s, 3 H), 1.49 (s, 3 H), 4.13 and 4.48 (two doublets, 6 H, J = 6 Hz).

Anal. Calcd for $C_{17}H_{26}O_3$: *m/e* 278.1882. Found: *m/e* 278.1870.

(±)-*cis*-Sativenediol Acetonide (17). Acetonide **16** (0.23 g, 0.827 mmol) was dissolved in ether (10 ml) and added to a solution of methyllithium (29 ml, 1.45 M) under N_2. The solution was warmed to reflux for 12 h and cooled. The mixture was poured into ice, extracted with ether, and washed with saturated NaCl. The ether was dried ($MgSO_4$), filtered, and concentrated. Ir showed complete absence of carbonyl absorption, and the presence of hydroxyl absorption at 3620 and 3480 cm^{-1}. This crude alcohol was dissolved in pyridine (13 ml) and cooled to 0 °C. Thionyl chloride (0.3 ml) was added and the reaction mixture stirred at 0 ° for 30 min. Water was added and the mixture extracted with ether. The ether extracts were washed with cold 6 N HCl and with saturated $NaHCO_3$, dried ($MgSO_4$), filtered, and concentrated. The crude oil was chromatographed on silica gel (5% ethyl acetate–95% pentane eluent) to give 0.22 g (94%) of the desired exocyclic methylene compound **17** as a colorless oil which crystallized on standing in the refrigerator: mp 28–29 °C; ir (neat) 1670 and 885 cm^{-1} (C=CH$_2$); NMR ($CDCl_3$) δ 4.64 and 4.90 (two doublets, 2 H); mass spectrum M$^+$ *m/e* 276.

(±)-*cis*-Sativenediol (2). Acetonide **17** (51 mg, 0.186 mmol) was dissolved in THF (4 ml) and methanol (20 ml) with stirring under N_2. Hydrochloric acid (2 ml, 2 N) was added and the solution stirred at room temperature for 3 days. An excess of solid $NaHCO_3$ was added, and stirring continued for 1 h. The solution was filtered and concentrated. Ether was added, and the solution washed with saturated NaCl, dried ($MgSO_4$), filtered, and concentrated. The crude reaction mixture was chromatographed on silica gel (5% ethyl acetate–95% pentane eluent) to give 18 mg of starting material **17**, and 28 mg (65%, 100% based on recovered starting material) of (±)-*cis*-sativenediol as a colorless oil which solidified on standing in the refrigerator. The diol was recrystallized from acetonitrile, mp 56–57 °C. The synthetic product was identical with the natural product by spectral comparison: ir (CCl_4) 3640, 3365, 885 cm^{-1}; NMR ($CDCl_3$) δ 0.88 and 0.94 (two doublets, 6 H, J = 7 Hz), 1.04 (s, 1 H), 1.57 (m, 1 H), 2.42 (m, 1 H), 2.65 (m, 1 H), 3.64 and 4.03 (two doublets, 2 H, J = 6 Hz), 4.60 and 4.91 (two doublets, 2 H).

Anal. Calcd for $C_{15}H_{24}O_2$: *m/e* 236.1776. Found: *m/e* 236.1773.

Registry No.—**2**, 60426-94-0; **3a**, 60410-80-2; **5a**, 60410-81-3; **5b**, 60410-82-4; **6**, 60410-83-5; **7**, 60410-84-6; **14**, 60410-85-7; **15**, 60410-86-8; **16**, 60410-87-9; **17**, 60410-88-0; *p*-toluenesulfonyl chloride, 98-59-9.

References and Notes

(1) J. E. McMurry, *J. Am. Chem. Soc.*, **90**, 6821 (1968).
(2) J. E. McMurry, *J. Org. Chem.*, **36**, 2826 (1971).
(3) J. E. McMurry and S. J. Isser, *J. Am. Chem. Soc.*, **94**, 7132 (1972).
(4) M. Nukina, H. Hattori, and S. Marumo, *J. Am. Chem. Soc.*, **97**, 2542 (1975).
(5) (a) F. Dorn and D. Arigoni, *Experientia*, **31**, 753 (1975); (b) F. Dorn, P. Bernasconi, and D. Arigoni, *Chimia*, **29**, 24 (1975).
(6) Marumo (ref 4) also reported isolation of an isomeric material to which he assigned a *trans*-sativenediol structure. Arigoni, however (ref 5a), has shown that this assignment is incorrect and that the molecule in question possesses an isosativene skeleton.
(7) J. E. McMurry and M. Silvestri, *J. Org. Chem.*, **40**, 1502 (1975).
(8) (a) H. J. Reich, I. L. Reich, and J. M. Renga, *J. Am. Chem. Soc.*, **95**, 5813 (1973); (b) K. B. Sharpless, R. F. Lauer, and A. Y. Teranishi, *J. Am. Chem. Soc.*, **95**, 6137 (1973).
(9) We thank Professor S. Marumo for sending copies of the ir and NMR spectra of *cis*-sativenediol.
(10) P. de Mayo, R. E. Williams, and Y. E. Spencer, *Can. J. Chem.*, **43**, 1357 (1965).
(11) F. Dorn and D. Arigoni, *J. Chem. Soc., Chem. Commun.*, 1342 (1972).
(12) After the completion of this work, an alternative synthesis of (+)-*cis*-sativenediol appeared: E. Piers and H. P. Isenring, *Synth. Commun.*, **6**, 221 (1976).