Preparation and Determination of Absolute Configurations and Rotations of 1,2-Dimethyl-5-norbornen-2-yl Derivatives[1]

Harlan L. Goering* and Chiu-Shan Chang

Department of Chemistry, University of Wisconsin, Madison, Wisconsin 53706

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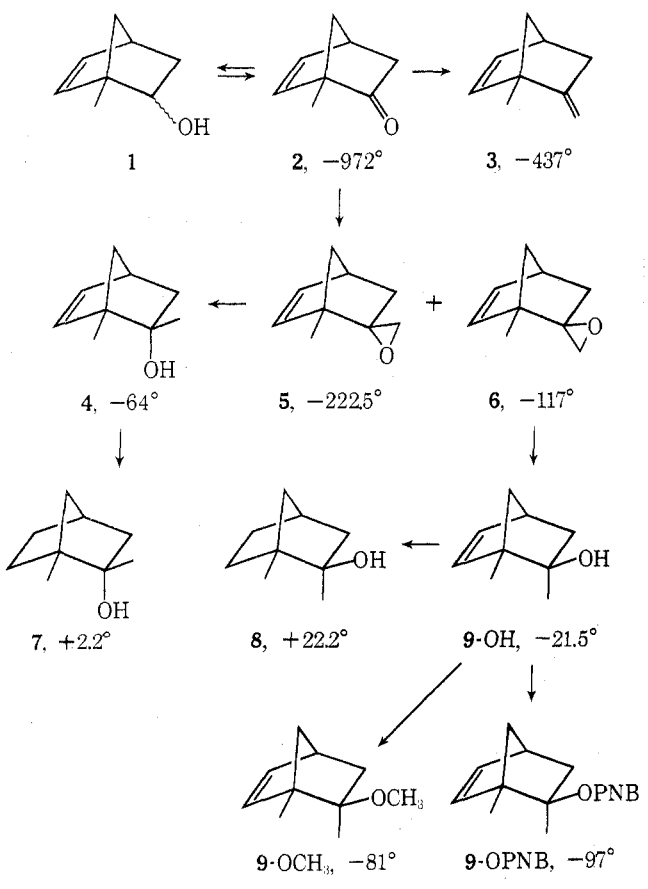
Racemic and optically active 1-methyl-5-norbornen-2-one (**2**) have been converted into 1,2-dimethyl-5-norbornen-*exo*-2-yl derivatives (**9**) and 1,2-dimethyl-5-norbornen-*endo*-2-ol (**4**). Absolute configurations have been established by correlation of optically active **9**-OH and **4** with the corresponding saturated analogs, 1,2-dimethyl-*exo*-2-norbornanol (**8**) and 1,2-dimethyl-*endo*-2-norbornanol (**7**). Enantiomeric compositions of active compounds were determined directly with an optically active NMR shift reagent, tris(3-heptafluorobutyryl-*d*-camphorato)europium(III).

We have recently investigated the symmetry properties of ionic intermediates involved in solvolytic reactions of 1,2-dimethyl-5-norbornen-*exo*-2-yl *p*-nitrobenzoate (**9**-OPNB).[2] This paper describes the preparation of the necessary compounds and the correlations of optical configurations and rotations required for that investigation.

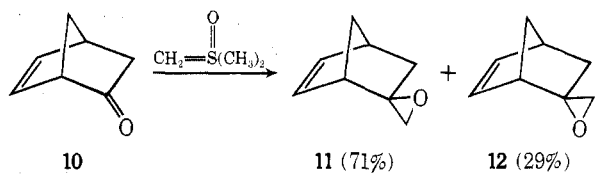
Racemic and optically active 1-methyl-5-norbornen-2-one (**2**) were converted into the 1,2-dimethyl-5-norbornen-*exo*-2-yl system (**9**) as outlined in Chart I. The ketone **2** was also converted to 2-methylene-1-methyl-5-norbornene (**3**) by the Wittig reaction. The latter was an expected solvolysis product for **9**-OPNB.

Optically active 1-methyl-5-norbornen-2-one (**2**) was obtained as follows. Lithium aluminum hydride reduction of racemic **2**[3] gave a 90:10 exo:endo mixture of 1-methyl-5-norbornen-2-ols (**1**). This mixture was converted into the acid phthalate derivative, which was resolved by recrystallization of the brucine salt. Saponification of the active acid phthalate gave (−)-**1** (96% endo isomer), which was converted into (−)-**2** by Oppenauer oxidation. The most active samples of (−)-**2** were shown to be about 90% optically pure (see below).

Chart I



The bicyclic ketone **2** was converted into the desired 1,2-dimethyl-5-norbornen-2-yl system by a method reported by Bly and coworkers[4] for similar transformations of dehydronorcamphor (**10**). These workers observed that dimethyloxosulfonium methylide attacks **10** primarily from the endo direction to give a 71:29 mixture of the exo (**11**) and endo (**12**) oxiranes.



10 **11** (71%) **12** (29%)

Similar results were obtained with **2**. In this case a 73:27 mixture of spiro[1-methyl-5-norbornen-*exo*-2,2′-oxacyclopropane] (**6**) and spiro[1-methyl-5-norbornen-*exo*-2,2′-oxacyclopropane] (**5**) was obtained. The isomeric oxiranes were separated by preparative GC and converted to the corresponding tertiary alcohols, **9**-OH and **4**, by reduction[4] with lithium aluminum hydride. The overall yield for the two-step conversion of **2** to the desired exo tertiary alcohol (**9**-OH) was about 50%. The endo tertiary alcohol (**4**) was also prepared directly from **2** by reaction with methylmagnesium bromide. As in the case of the parent dehydronorcamphor (**10**),[4] this reaction involves about 97% exo attack.

Absolute configurations are shown in Chart I. These were established by conversion of (−)-1,2-dimethyl-5-norbornen-*endo*-2-ol (**4**) to (+)-1,2-dimethyl-*endo*-2-norbornanol (**7**) by reduction with diimide. Similarly, (−)-1,2-dimethyl-5-norbornen-*exo*-2-ol (**9**-OH) was converted to (+)-1,2-dimethyl-*exo*-2-norbornanol (**8**). Absolute configurations of the saturated tertiary alcohols (**7** and **8**) are known;[5] thus, these correlations establish absolute configurations for all of the compounds in the chart.

Absolute rotations[6] are included in Chart I. These were determined from observed rotations of homogeneous samples of known enantiomeric composition. Except for the hydrocarbon **3** and the bicyclic methyl ether **9**-OCH_3, enantiomeric compositions were determined directly with an optically active NMR shift reagent, tris(3-heptafluorobutyryl-*d*-camphorato)europium(III) [Eu(hfbc)$_3$].[7] Observed shift differences for enantiotopic signals are tabulated in the Experimental Section. It is noteworthy that the absolute rotations determined in the present work for **7** and **8** are in excellent agreement with values obtained earlier[5] by other methods. The absolute rotation for 2-methylene-1-methyl-5-norbornene (**3**) was determined by correlation with the precursor (**2**).

1,2-Dimethyl-5-norbornen-*exo*-2-ol (9-OH) was converted into the *p*-nitrobenzoate derivative (9-OPNB) by a conventional method.[5] The most active sample was 91% optically pure. The tertiary alcohol 9-OH was also converted into the methyl ether 9-OCH_3 by the Williamson method. This was an expected methanolysis product for 9-OPNB. The absolute rotation of 9-OCH_3 was deduced by correlation with active 9-OH.

Experimental Section

A 100-ft SE-30 capillary column was used for analytical GC and a 5 ft × 0.25 in. column packed with 10% FFAP on Chromosorb W 60/80 was used for preparative GC. NMR spectra were determined with a JEOL MH-100 spectrometer. Melting points are not corrected.

(−)-1-Methyl-5-norbornen-2-ol (1). A solution of 20 g (0.164 mol) of 1-methyl-5-norbornen-2-one[3] in dry ether was added slowly to a solution of 7 g of lithium aluminum hydride in 220 ml of dry ether at a rate so that gentle reflux was maintained. The reaction mixture (under dry nitrogen) was refluxed for an additional 6 hr. Work-up in the usual manner gave 19 g (94%) of **1-methyl-5-norbornen-2-ol** (1) consisting of about 90% endo isomer and 10% exo isomer. A solution of 19 g (0.153 mol) of this mixture and 28.1 g (0.19 mol) of purified phthalic anhydride in 400 ml of anhydrous pyridine was heated on a steam bath for 4 hr. After cooling the mixture was poured onto a slurry of ice and 500 ml of 10% hydrochloric acid. The resulting mixture was extracted four times with chloroform. The extracts were combined, washed once with cold 5% hydrochloric acid and twice with water, and dried over magnesium sulfate. Removal of solvent gave 40 g (95%) of residual crude **1-methyl-5-norbornen-2-yl acid phthalate.** After recrystallization from a benzene–pentane mixture the acid phthalate had mp 96°; NMR (CCl_4) δ 9.6 (s, 1 H, acid), 7.5–7.96 (m, 4 H, aromatic), 6.3 (q, 1 H, olefin), 5.87 (d, 1 H, olefin), 5.3 (q, 1 H), 2.8 (s, 1 H), 2.3–2.56 (m, 1 H), 1.4 (s, 3 H), 1.0–1.48 (m, 3 H).

Anal. Calcd for $C_{16}H_{16}O_4$: C, 70.57; H, 5.92. Found: C, 70.71; H, 5.96.

The above acid phthalate was resolved as follows. In a typical resolution a solution of 40 g (0.147 mol) of the above crude acid phthalate and 58 g (0.147 mol) of brucine in a mixture of 500 ml of methanol and 300 ml of acetone was concentrated with a rotary evaporator to a volume of about 300 ml. The resulting solution was chilled in a refrigerator (−20°) for 2 days. Filtration gave a first crop of 71.4 g of brucine salt. Three additional recrystallizations of this crop from a 5:3 methanol–acetone mixture gave 40 g of brucine salt. The acid phthalate was regenerated from the brucine salt as follows. The above 40 g of salt was dissolved in 200 ml of methylene chloride and the solution was extracted with four 90-ml portions of cold 5% aqueous sodium hydroxide. The extracts were combined, shaken with methylene chloride, acidified with cold dilute hydrochloric acid, and extracted with chloroform. After drying ($MgSO_4$) and removal of the solvent, 11 g of colorless **(−)-1-methyl-5-norbornen-2-yl acid phthalate,** $[\alpha]^{25}D$ −22° (*c* 0.8, $CHCl_3$), was obtained.[8]

A solution of the above optically active acid phthalate in 45 ml of 20% aqueous sodium hydroxide was steam distilled until 250 ml of distillate was collected. The distillate was saturated with sodium chloride and extracted several times with pentane. The pentane extract was dried ($MgSO_4$) and removed under reduced pressure. Analytical GC (71°) showed that the residue consisted of 96% *endo*- and 4% **(−)-*exo*-1-methyl-5-norbornen-2-ol** (1). After purification by preparative GC (65°) this sample of (−)-1 had mp 53–55° (sublimation), $[\alpha]^{25}D$ −67.2° (*c* 0.53, $CHCl_3$).[8]

Anal. Calcd for $C_8H_{12}O$: C, 77.37; H, 9.74. Found: C, 77.26; H, 9.66.

(−)-1-Methyl-5-norbornen-2-one (2). Oxidation of a 4-g sample of the above (−)-1 with quinone and aluminum *tert*-butoxide in benzene by a procedure described earlier[9] gave 3.61 g (90%) of (−)-2 which was isolated by short-path distillation (54°, 12 mm). After purification by preparative GC (65°) this colorless liquid sample of (−)-2 had $[\alpha]^{25}D$ −884° (*c* 0.43, $CHCl_3$).[8] The NMR spectrum in the presence of Eu(hfbc)$_3$[7] showed that this sample was 91% optically pure.

Reaction of (−)-1-Methyl-5-norbornen-2-one (2) with Dimethyloxosulfonium Methylide. To a stirred suspension of 1.416 g (0.06 mol) of sodium hydride in 24 ml of dimethyl sulfoxide (Me_2SO) under dry nitrogen was added 6.5 g (0.03 mol) of trimethyloxosulfonium iodide.[10] After hydrogen evolution ceased a solution of 3.6 g (0.03 mol) of the above (−)-2 in 10 ml of Me_2SO was added dropwise with cooling. After addition of the (−)-2, which required about 15 min, the reaction mixture was stirred at room temperature for 2 hr and then at 60° for 1 hr. The solution was cooled, diluted with 100 ml of water, and extracted with pentane. The pentane extract was washed with water, dried ($MgSO_4$), and concentrated under reduced pressure. Analytical GC indicated that the residue consisted of 68% spiro[1-methyl-5-norbornen-*exo*-2,2′-oxacyclopropane] (6), 25% spiro[1-methyl-5-norbornen-*endo*-2,2′-oxacyclopropane] (5), and 7% of an unidentified product. Pure (−)-6 and (−)-5 were obtained by preparative GC (65°).

The (−)-6 had mp 44–46°; $[\alpha]^{25}D$ −106° (*c* 0.43, $CHCl_3$); NMR (CCl_4) δ 6.20 (q, 1 H), 5.7 (d, 1 H), 2.8 (s, 1 H), 2.59 (s, 2 H), 1.5–1.82 (m, 4 H), 1.0 (s, 3 H). The NMR spectrum in the presence of Eu(hfbc)$_3$ indicated that this sample was 91% optically pure.

Anal. Calcd for $C_9H_{12}O$: C, 79.37; H, 8.88. Found: C, 79.40; H, 8.85.

The colorless liquid sample of pure (−)-5 had $[\alpha]^{25}D$ −222.5° (*c* 0.73, $CHCl_3$); NMR (CCl_4) δ 6.28 (q, 1 H), 5.84 (d, 1 H), 2.76 (s, 1 H), 2.68 (q, 2 H), 1.2–2.1 (m, 4 H), 1.0 (s, 3 H).[8] The NMR spectrum in the presence of Eu(hfbc)$_3$ indicated that this sample was 91% optically pure.

Anal. Calcd for $C_9H_{12}O$: C, 79.37; H, 8.88. Found: C, 79.35; H, 8.90.

1,2-Dimethyl-5-norbornen-*exo*-2-ol (9-OH). Racemic and optically active 9-OH were obtained as described below for preparation of (−)-9-OH. A slurry of 1.743 g (13 mmol) of the above (−)-6 and 800 mg of lithium aluminum hydride in 40 ml of ether was refluxed for 6 hr, after which the mixture was cooled and hydrolyzed with 15% aqueous sodium hydroxide. The precipitated salts were removed by filtration and the dried ethereal solution ($MgSO_4$) concentrated to give 1.70 g (96%) of colorless needles, mp 65° (sublimation). An analytical sample of **(−)-1,2-dimethylnorbornen-*exo*-2-ol (9-OH)** was prepared by preparative GC (65°): $[\alpha]^{25}D$ −19.5° (*c* 0.38, $CHCl_3$); NMR δ 6.01 (q, 1 H), 5.66 (d, 1 H), 2.66 (s, 1 H), 1.0–1.9 (m, 5 H), 1.16 (s, 3 H), 1.1 (s, 3 H).[8] The NMR spectrum in the presence of Eu(hfbc)$_3$ indicated that this sample was 91% optically pure.

Anal. Calcd for $C_9H_{14}O$: C, 78.21; H, 10.21. Found: C, 78.00; H, 10.32.

Correlation of (−)-1,2-Dimethyl-5-norbornen-*exo*-2-ol (9-OH) with (+)-1,2-Dimethyl-*exo*-2-norbornanol (8). To a rapidly stirred solution of 200 mg (1.45 mmol) of the above (−)-9-OH and 20 g (103 mmol) of dipotassium azodicarboxylate[11] in 50 ml of methanol under nitrogen was added 12.5 ml of glacial acetic acid. The dropwise addition resulted in gas evolution and reflux was controlled by the rate of addition. The solution was stirred for an additional 5 hr and then cooled and diluted with 50 ml of water. The resulting mixture was extracted with several portions of pentane and after drying ($MgSO_4$), the pentane was removed under reduced pressure. The residual product was purified by preparative GC (65°). The resulting homogeneous (+)-8 had $[\alpha]^{25}D$ 21.1° (*c* 0.11, $CHCl_3$). The NMR spectrum was indistinguishable from that of an authentic sample of 8.[5,8] The NMR spectrum in the presence of Eu(hfbc)$_3$ indicated that this sample was 91% optically pure.

1,2-Dimethyl-5-norbornen-*exo*-2-yl *p*-Nitrobenzoate (9-OPNB). Racemic and optically active 9-OPNB were prepared as described below for the preparation of (−)-9-OPNB. A solution of 1.64 g (12 mmol) of the above (−)-9-OH in 20 ml of anhydrous tetrahydrofuran under nitrogen was refluxed over 601 mg (15 mmol) of potassium for 4 hr. The solution was chilled to −78° and slowly mixed with a similarly chilled solution of 2.78 g (15 mmol) of purified *p*-nitrobenzoyl chloride in 35 ml of tetrahydrofuran. After mixing, the resulting solution was stirred at −78° for an additional 5 hr and then warmed to room temperature and diluted with benzene. The resulting solution was shaken with water and the benzene solution dried ($MgSO_4$) and concentrated to a yellow residue. This material was purified by column chromatography (Al_2O_3 with benzene as eluent) followed by recrystallization from ether–pentane. The resulting (−)-9-OPNB was nearly colorless and had mp 133–133.5°; $[\alpha]^{25}D$ −88.3° (*c* 0.46, $CHCH_3$); NMR (CCl_4) δ 8.06–8.4 (m, 4 H), 6.26 (q, 1 H), 5.76 (d, 1 H), 2.76 (s, 1 H), 1.2–2.4 (m, 4 H), 1.52 (s, 3 H), 1.44 (s, 3 H).[8] The NMR spectrum in the presence of Eu(hfbc)$_3$ indicated that this sample was 91% optically pure.

Anal. Calcd for $C_{16}H_{17}NO_4$: C, 66.88; H, 5.96. Found: C, 66.96; H, 6.03.

1,2-Dimethyl-5-norbornen-*endo*-2-ol (4). A 335-mg (2.45 mmol) sample of the above (−)-5 was converted into (−)-4 by the procedure described above for conversion of 6 into 9-OH. After pu-

Table I
Data for Determination of Enantiomeric Compositions of Compounds in Chart I[a]

Compd	R/S	ΔΔδ (ppm)
2	0.79	0.18
4	0.38	0.14
5	0.64	0.18
6	0.56	0.22
7	0.62	0.12
8[b]	0.63	0.12
9-OH[b]	0.42	0.14
9-OPNB	0.68	0.20

[a] Enantiotopic methyl signals used for determinations. Downfield methyl signal used for dimethyl compounds. [b] Both methyl signals were isolated from other resonances and suitable for determination of enantiotopic compositions.

rification by preparative GC (65°) the homogeneous liquid sample of (−)-**4** had $[\alpha]^{25}D$ −5.77° (*c* 0.90, $CHCl_3$); NMR (CCl_4) δ 6.3 (q, 1 H), 5.82 (d, 1 H), 2.64 (s, 1 H), 1.04–1.92 (m, 5 H), 1.3 (s, 3 H), 1.22 (s, 3 H).[8] The NMR spectrum in the presence of Eu(hfbc)$_3$ indicated that this sample was 91% optically pure.

Anal. Calcd for $C_9H_{14}O$: C, 78.21; H, 10.21. Found: C, 78.19; H, 10.23.

This compound was also prepared directly from a sample of the above-described (−)-**2** by reaction with methylmagnesium bromide in the usual manner.[9] The sample of (−)-**4** obtained by this method was purified by preparative GC and had the same rotation and NMR spectrum as the sample described above.

Correlation of (−)-1,2-Dimethyl-5-norbornen-*endo*-2-ol (4) with (+)-1,2-Dimethyl-*endo*-2-norbornanol (7). Diimide reduction of a 200-mg sample of the above (−)-**4** by the method described above for reduction of **9**-OH gave (+)-**7**, $[\alpha]^{25}D$ 2.0° (*c* 0.6, $CHCl_3$). The NMR spectrum was indistinguishable from that of an authentic sample.[5,8] The NMR spectrum in the presence of Eu(hfbc)$_3$ indicated that this sample was 91% optically pure.

1-Methyl-2-methylene-5-norbornene (3). A sample of (+)-**2**, $[\alpha]^{25}D$ 627° (*c* 0.46, $CHCl_3$) (65% optically pure), was converted to (+)-**3** by the Wittig reaction using a general procedure described earlier.[5] The (+)-**3** was isolated and purified by preparative GC (50°) and had $[\alpha]^{25}D$ 282°; NMR (CCl_4) δ 6.04 (q, 1 H), 5.66 (d, 1 H), 4.74 (d, 2 H), 2.88 (s, 1 H), 1–2.5 (m, 4 H), 1.3 (s, 3 H). Since this sample should have the same optical purity as the (+)-**2** from which it was derived, the calculated absolute rotation for **3** is 437°.

1,2-Dimethyl-*exo*-2-methoxy-5-norbornene (9-OCH_3). A mixture of 343 mg (2.49 mmol) of (+)-**9**-OH, $[\alpha]^{25}D$ 13.3° (*c* 0.2, $CHCl_3$), and 97 mg (2.49 mmol) of potassium in 10 ml of tetrahydrofuran under dry nitrogen was refluxed for 5 hr, cooled to room temperature, and mixed with a solution of 353 mg (2.49 mmol) of iodomethane in 5 ml of tetrahydrofuran. The resulting mixture was stored at room temperature for 1 hr and then diluted with water and extracted with ether. The extract was dried ($MgSO_4$) and concentrated. The residual (+)-**9**-OCH_3 was isolated and purified by preparative GC. Homogeneous (+)-**9**-OCH_3 was obtained as a colorless liquid and had $[\alpha]^{25}D$ 49.8° (*c* 0.59, $CHCl_3$); NMR (CCl_4) δ 6.10 (q, 1 H), 5.75 (d, 1 H), 3.2 (s, 3 H), 2.7 (s, 1 H), 1.0–2.0 (m, 4 H), 1.1 (s, 3 H), 1.04 (s, 3 H). Assuming that there is no loss of optical configuration in this transformation the absolute rotation for **9**-OCH_3 is 81°.

Anal. Calcd for $C_{10}H_{16}O$: C, 78.89; H, 10.59. Found: C, 78.71; H, 10.47.

Determination of Enantiomeric Compositions. Enantiomeric compositions of active samples were determined directly with an NMR shift reagent, Eu(hfbc)$_3$, as outlined previously.[7] Isolated corresponding enantiotopic signals were expanded and relative peak areas determined with a planimeter. Pertinent data are summarized in Table I, which shows the Eu(hfbc)$_3$/substrate molar ratio (R/S) and the observed magnitudes of nonequivalence (ΔΔδ). Carbon tetrachloride was the solvent in all determinations. Enantiotopic methyl signals were used in each case. For dimethyl compounds the downfield signal was used.

Registry No.—(±)-*exo*-**1**, 56292-49-0; (±)-*endo*-**1**, 56292-50-3; (−)-*exo*-**1**, 56324-12-0; (−)-*endo*-**1**, 56324-13-1; (±)-**2**, 56292-51-4; (−)-**2**, 56324-14-2; (+)-**2**, 56324-15-3; (+)-**3**, 56292-52-5; (−)-*endo*-**4**, 56292-53-6; (−)-*endo*-**5**, 56292-54-7; (−)-*exo*-**6**, 56324-16-4; (+)-**7**, 18366-96-6; (+)-**8**, 56389-60-7; (−)-**9**-OH, 56324-17-5; (+)-**9**-OH, 56324-18-6; (−)-**9**-OPNB, 56292-55-8; (+)-**9**-OCH_3, 56292-56-9; phthalic anhydride, 85-44-9; (±)-*endo*-1-methyl-5-norbornen-2-yl acid phthalate, 56292-57-0; (±)-*exo*-1-methyl-5-norbornen-2-yl acid phthalate, 56292-58-1; brucine, 357-57-3; (−)-*endo*-1-methyl-5-norbornen-2-yl acid phthalate, 56324-19-7; (−)-*exo*-1-methyl-5-norbornen-2-yl acid phthalate, 56324-20-0; dimethyloxosulfonium methylate, 5367-24-8; tris(3-heptafluorobutyryl-*d*-camphorato)europium(III), 34788-82-4.

References and Notes

(1) This work was supported by the National Science Foundation (GP-6555X) and the Air Force Office of Scientific Research (AFOSR-71-1974).
(2) H. L. Goering and C.-S. Chang, unpublished work.
(3) H. L. Goering and C.-S. Chang, *J. Org. Chem.*, **40**, 2565 (1965).
(4) R. S. Bly, C. M. DuBose, Jr., and G. B. Konizer, *J. Org. Chem.*, **33**, 2188 (1968).
(5) H. L. Goering, C. Brown, S. Chang, J. V. Clevenger, and K. Humski, *J. Org. Chem.*, **34**, 624 (1969).
(6) Rotations are $[\alpha]^{25}D$ for chloroform solutions.
(7) H. L. Goering, J. N. Eikenberry, G. S. Koermer, and C. J. Lattimer, *J. Am. Chem. Soc.*, **96**, 1493 (1974).
(8) Except in the presence of optically active NMR shift reagents, NMR spectra of optically active samples were indistinguishable from those of the corresponding racemic compounds.
(9) H. L. Goering, A. C. Backus, C.-S. Chang, and D. Masilamani, *J. Org. Chem.*, **40**, 1533 (1975).
(10) R. Kuhn and H. Trischmann, *Justus Liebigs Ann. Chem.*, **611**, 117 (1958).
(11) J. A. Berson, M. S. Poonian, and W. J. Libbey, *J. Am. Chem. Soc.*, **91**, 5577 (1969).