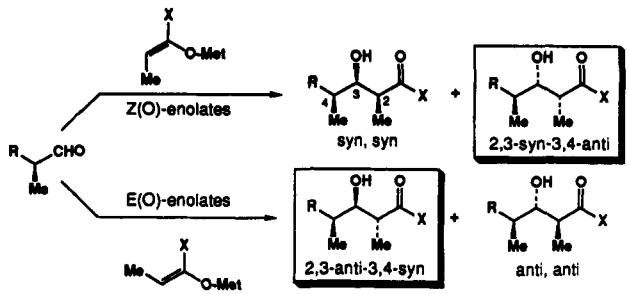
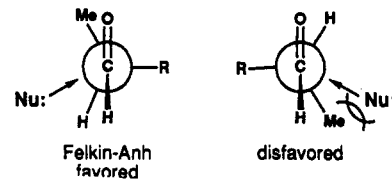
Scheme I[a]



[a] The two 2,4-anti methyl diastereomers are intrinsically favored as long as the steric requirements of R are greater than Me. Further, the intrinsic diastereofacial selectivity is expected to increase as the steric requirements of R increase relative to Me. Finally, as long as the first condition is met, the two 2,4-anti diastereomers will correspond to the products of "matched" double asymmetric reactions when appropriate chiral enolates are utilized.

targets is greatly simplified.[36,37]

In closing we wish to stress that the transition-state model discussed herein does not contradict the major precepts of the Felkin–Anh paradigm, specifically the stereoelectronic requirement that the developing C–C bond must overlap with and be stabilized by the σ^* orbital of one of the substituents α to the carbonyl.[8,29] The influence of steric effects was recognized early on by Anh and Eisenstein,[8f] who noted that if nucleophilic addition proceeds according to the Bürgi–Dunitz trajectory,[38] then the stereodifferentiation that occurs in the carbonyl addition step may be rationalized by the differential interactions of the nucleophile and the small (H) and medium sized groups (Me) in the two transition structures reproduced below. The present transition-state model simply expands the notion that steric interactions involving the nucleophile must be considered carefully, since, as is apparent by inspection of the three-dimensional transition structure **33**, interactions may indeed occur between the methyl substituent of propionate enolate and the carbonyl α-methyl group; the "normal" Felkin–Anh transition state thus may not necessarily be the lowest energy one. The lowest energy transition state will most certainly be the one that maximizes stereoelectronic stabilization, in the form of σ_{C-C}/σ^* interactions, and minimizes all nonbonded interactions, including the syn or gauche pentane interactions highlighted in this paper. When these effects are dissonant, as in the aldol reactions of *Z*(O)-enolates or the reactions of (*Z*)-crotylboronates and α-methyl chiral aldehydes, it appears that stereoelectronic stabilization plays a lesser role than the minimization of syn and gauche pentane interactions. Finally, we close by noting that other carbonyl addition reactions are known in which the usual stereochemical course is altered as a result of remote steric effects.[9b]



Acknowledgment. The author gratefully acknowledges support provided by the National Institute of General Medical Sciences (GM 38436), and fruitful discussions with Professor Evans during the final revisions of the manuscript.

(36) This point has been discussed in detail in connection with the reactions of α-methyl chiral aldehydes and crotylboronates (ref 6e).

(37) These considerations are also relevant to the analysis of fragment assembly steps involving aldol reactions of chiral enolates and chiral aldehydes. For two illustative examples: (a) Masamune, S.; Hirama, M.; Mori, S.; Ali, S. A.; Garvey, D. S. *J. Am. Chem. Soc.* **1981**, *103*, 1568 (conversion of **5** + **6** → **4**). (b) Evans, D. A.; Sheppard, G. S. *J. Org. Chem.* **1990**, *55*, 5192 (conversion of **4** + **7** → **8**).

(38) (a) Bürgi, H. B.; Dunitz, J. D.; Shefter, E. *J. Am. Chem. Soc.* **1973**, *95*, 5065. (b) Bürgi, H. B.; Lehn, J. M.; Wipff, G. *Ibid*, **1974**, *96*, 1956. (c) Bürgi, H. B.; Dunitz, J. D.; Lehn, J. M.; Wipff, G. *Tetrahedron* **1974**, *30*, 1563.

On the Maximum Rotation and the Solvobromination and -mercuration of Enantioenriched 1,3-Dimethylallene

Daniel J. Pasto* and Kiyoaki D. Sugi

Department of Chemistry and Biochemistry, University of Notre Dame, Notre Dame, Indiana 46556

Received January 23, 1991

The prior assignments of the maximum rotation of enantiomerically pure 1,3-dimethylallene (13DMA) based on the methoxybromination and -mercuration of enantioenriched 13DMA are shown to be drastically in error. A value of $[\alpha]_{589}$ of 81.0 ± 0.2° (25 °C in diethyl ether) has been determined directly on enantioenriched samples of 13DMA by the use of a chiral NMR shift reagent. The methoxybromination and -mercuration reactions, which were previously suggested to be completely stereospecific, are shown to occur with substantial losses in ee, suggesting that the intermediate onium ion intermediates undergo competitive ring opening to achiral substituted allyl cations thus resulting in loss of ee.

Introduction

Current studies in our laboratories investigating the stereochemical details of the (2 + 2) cycloaddition reactions of chiral allenes have initially focused on the cycloaddition reactions of enantioenriched (scalemic) 1,3-dimethylallene (13DMA), a reasonably readily available, simple chiral allene. Enantioenriched (*S*)-(+)-13DMA has been prepared by the partial asymmetric hydroboration of racemic 13DMA with diisopinocampheylborane prepared from (+)-α-pinene following the procedure of Waters and Caserio,[1] Waters, Linn, and Caserio,[2] and Rossi and Diversi[3] and modified by Brown and Singaram.[4] The enantiomeric

(1) Waters, W. L.; Caserio, M. C. *Tetrahedron Lett.* **1968**, 5233.

(2) Waters, W. L.; Linn, W. S.; Caserio, M. C. *J. Am. Chem. Soc.* **1968**, *90*, 6741.

(3) Rossi, R.; Diversi, P. *Synthesis* **1973**, 25.

0022-3263/91/1956-4157$02.50/0

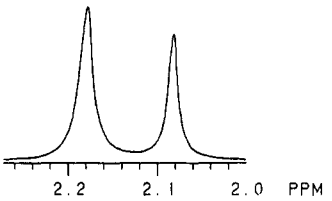


Figure 1. Methyl region of the 300-MHz ^1H NMR spectrum of 13DMA in the presence of a 3:1 mixture of Ag(fod) and Yb(hfc)$_3$ chiral NMR chemical shift reagents with double resonance of the vinyl proton.

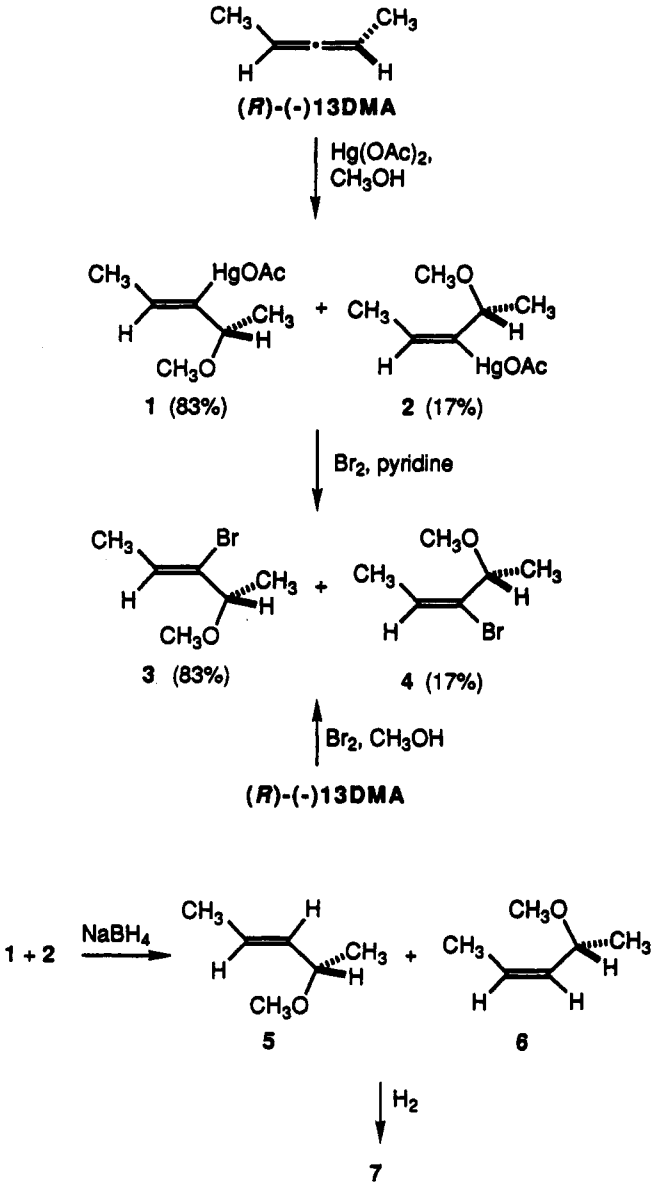
excess (ee) of the derived (*S*)-(+)-13DMA was initially assigned on the basis of the maximum reported value for $[\alpha]_D$ for enantiomerically pure 13DMA of 227°.[1] It became obvious that this value for $[\alpha]_D$ of enantiomerically pure 13DMA was seriously in error when (2 + 2) cycloadducts derived from enantioenriched samples of 13DMA with certain radicophiles possessed ee's almost *double* that of the starting 13DMA![5]

A review of the literature indicates values for the maximum rotation of enantiomerically pure 13DMA ranging from 78° to 227°. (*R*)-(−)-13DMA having $[\alpha]_D$ −78.8° was obtained after four successive asymmetric hydroborations with diisopinocampheylborane derived from (−)-α-pinene, which did not increase significantly on further treatments with diisopinocampheylborane,[6] leading to the assumption that the 13DMA was "almost optically pure".[7] Methoxymercuration of (*R*)-(−)-13DMA possessing $[\alpha]_D$ −14.5° followed by NMR analysis using (*R*)-(−)-2,2,2-trifluoro-1-(9-anthryl)ethanol as a chiral solvating agent indicated an ee of 9.2%, resulting in a calculated maximum rotation for enantiomerically pure 13DMA of 158°.[8]

In a study of the stereochemistry of electrophilic addition reactions of enantioenriched 13DMA, Waters, Linn, and Caserio[2] subjected (*R*)-(−)-13DMA to methoxymercuration followed by brominative electrophilic substitution to produce (*E*)- and (*Z*)-3-bromo-2-methoxy-3-pentene having the same optical rotation ($[\alpha]_D$ −5.7 ± 0.5°) as the products derived by the direct methoxybromination of (*R*)-(−)-13DMA ($[\alpha]_D$ −5.7 ± 0.2°). The methoxymercuration products were reduced to a mixture of (*E*)- and (*Z*)-2-methoxy-3-pentene with sodium borohydride and subjected to hydrogenation to produce 2-methoxypentane (7). The comparison of the optical rotation of the 2-methoxypentane with that of supposedly enantiomerically pure material[9] resulted in a calculated maximum rotation for 13DMA of 227°.[1] These results led us to suggest that both methoxybromination and -mercuration addition reactions proceeded with complete stereospecificity via onium-type intermediates.

Empirical methods have been also employed to calculate the maximum rotation of enantiomerically pure 13DMA. Brewster[10] has calculated a maximum rotation of 174°. Runge[11] has calculated a maximum rotation of between 92.7 and 96.7° (depending on the solvent) using the empirical algebraic method of Ruch.[12]

As it was critical to know the correct maximum rotation of enantiomerically pure 13DMA in order to interpret the stereochemical details of the cycloaddition reactions of enantioenriched 13DMA, we have undertaken a search for a more direct way in which to measure the ee of the samples of enantioenriched 13DMA, which has in turn led to a reinvestigation of the methoxybromination and -mercuration reactions of 13DMA.



Results

In 1986, Mannschreck and co-workers reported that a 1:1 mixture of the NMR shift reagents Ag(fod) and tris-[3-(heptafluoropropylhydroxymethylene)-(+)-camphorato]ytterbium(III) [Yb(hfbc)$_3$] was useful for the chiral recognition of allenic hydrocarbons by ^1H NMR.[13] Similar use of the reagent mixture on our samples of enantioenriched 13DMA derived by the partial asymmetric hydroboration of racemic 13DMA has allowed for the direct determination of the ee's of the samples. In the presence of the 3:1 mixture[14] of Ag(fod) and Yb(hfbc)$_3$, essentially

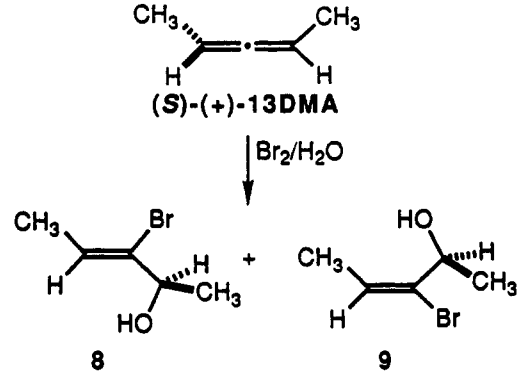
(4) Brown, H. C.; Singaram, B. *J. Org. Chem.* **1984**, *49*, 945.
(5) Pasto, D. J.; Sugi, K. D. Unpublished observations.
(6) Porri, L.; Rossi, R.; Ingrosso, G. *Tetrahedron Lett.* **1971**, 1083.
(7) Runge, W.; Kresze, G. *J. Am. Chem. Soc.* **1977**, *99*, 5597.
(8) Pirkle, W. H.; Boeder, C. W. *J. Org. Chem.* **1977**, *42*, 3697.
(9) Goering, H. L.; Pombo, M. M.; McMichael, K. D. *J. Am. Chem. Soc.* **1963**, *85*, 965.
(10) Brewster, J. H. *Topics in Stereochemistry*; Allinger, N. L., Eliel, E. L., Eds.; Wiley: New York, 1967; Vol. 2, p 35.
(11) Runge, W. "Stereochemistry of Allenes." In *The Chemistry of Allenes*; Landor, S. R., Ed.; Academic Press: New York, 1982; p 644.
(12) Ruch, E. *Acc. Chem. Res.* **1972**, *5*, 49.
(13) Mannschreck, A.; Munninger, W.; Burgemeister, T.; Gore, J.; Cazes, B. *Tetrahedron* **1986**, *42*, 399.
(14) In our experience, extreme line broadening results with the use of a 1:1 ratio of the shift reagents without achieving acceptable resolution of the diastereomeric peaks. The use of a 3:1 ratio results in better resolution of the diastereomerically related peaks with less line broadening.

Table I. ee's of the Enantioenriched 13DMA and the Percent Yields and ee's of the Hydroxybromination and -mercuration Products

13DMA % ee	product	% yield	% ee
25.8	8	72	21.8
	9	28	19.3
47.9	8	73	40.5
	9	27	30.4
25.8	10	75	11.8
	11	25	10.4

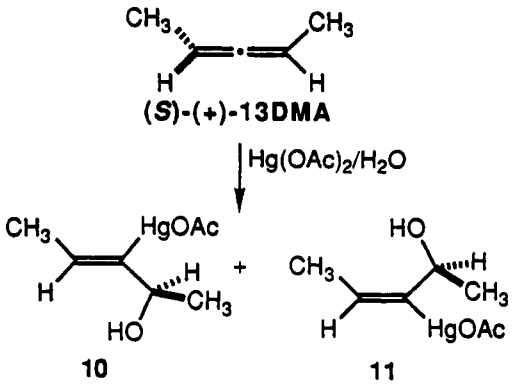
base line resolution of the methyl resonances of the diastereomeric complexes is achieved on double resonance of the vinyl protons (see Figure 1). From the rotations of the samples and the NMR-derived ee's, a maximum rotation of enantiomerically pure 13DMA is calculated to be 81.0 ± 0.2° (ether).

The ee's of the methoxybromination and -mercuration products derived from 13DMA reported earlier[1,2] could not be determined directly by the use of chiral NMR shift reagents. However, the hydroxybromination and hydroxymercuration of enantioenriched 13DMA produced mixtures of stereoisomeric products whose ee's could be readily and easily determined directly by the use of chiral NMR chemical shift reagents. The hydroxybromination of enantioenriched (*S*)-(+)-13DMA produces a mixture of the (*Z*)- and (*E*)-3-bromo-2-hydroxy-3-pentenes (**8** and **9**).[15] Direct ee analysis of the crude reaction mixture by NMR using an europium chiral shift reagent allowed for the measurement of the ee of each stereoisomer. The ee's of the starting 13DMA and the relative yields and ee's of **8** and **9** are given in Table I.



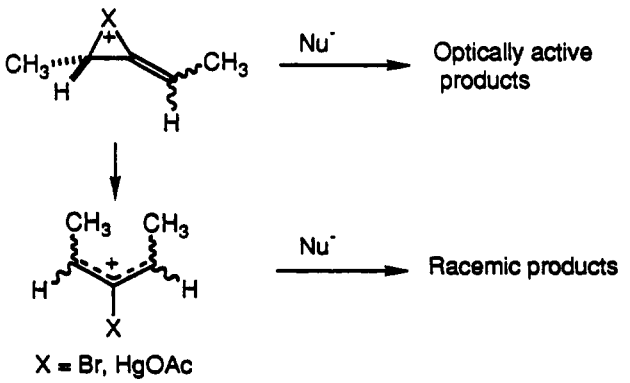
The hydroxymercuration of enantioenriched 13DMA produces a mixture of the (*Z*)- and (*E*)-3-(acetoxymercurio)-2-hydroxy-3-pentenes (**10** and **11**) whose ee's were easily measured directly by the use of a chiral europium NMR chemical shift reagent. The ee of the starting 13DMA and the relative yields and the ee's of **10** and **11** are given in Table I.

There are significant, and different, losses in ee in the formation of the stereoisomeric hydroxybromination products. For example, starting with 13DMA of 25.8% ee, there is an overall loss of 15.5% of the ee of the 13DMA encountered in the formation of the major isomer **8** and a 25.2% loss of the ee in the formation of **9**. Starting with 13DMA of 47.9% ee, there is a 15.4% loss in the ee in the formation of **8**, which is very similar to that encountered when starting with 13DMA of 25.8% ee; however, there is a significantly greater loss in the ee of 36.5% during the formation of **9**. It would appear that the relative extents of the loss of the ee of the 13DMA in the formation of the addition products are sensitive to the reaction conditions.



In the formation of the hydroxymercuration products **10** and **11**, starting with 13DMA of 25.8% ee there is a 54.3% loss of ee during the formation of **10**, while there is a 59.7% loss of ee during the formation of **11**. These losses in ee are significantly greater than those encountered in the hydroxybromination reaction, which undoubtedly reflects the weaker bonding in the mercuronium ion intermediates relative to that in the bromonium ion intermediates, which results in more extensive ring opening of the onium ion intermediates (see later discussion). Although we have carried out this reaction only once, the two vastly different estimates for the maximum rotation of enantiomerically pure 13DMA of 158° by Pirkle and co-workers[8] and 227° by Waters and co-workers,[1,2] both of which were derived from data obtained from the methoxymercuration reactions of enantioenriched 13DMA, suggests that the extent of ring opening of the mercuronium ion intermediates is an even more sensitive function of the reaction conditions.

The significant losses in ee during the formation of **8** and **9**, and **10** and **11**, from enantioenriched 13DMA indicate that these reactions do not occur with complete stereospecifically as originally suggested.[2] Open, achiral cationic intermediates, i.e., substituted allyl cations, must be formed either competitively with chiral onium ion formation or by the partial opening of the initially formed onium ion intermediates. The differences in the loss of ee in the formation of **8** and **9**, and also in the formation of **10** and **11**, suggest that the substituted allyl cations are not formed directly, but are formed by different extents of ring opening of the corresponding onium ion intemediates. This ring opening is not unexpected in view of the known propensity for allene oxides to undergo ring opening and rearrangement to cyclopropanones.[16]



(15) The stereochemistry of the major and minor isomers as being that shown in **8** and **9** is consistent with the relative magnitudes of the long-range coupling constants between the vinyl and carbinol protons, being larger (0.70 Hz) in the *Z* isomer **8** relative to that (0.47 Hz) in the *E* isomer **9**.

(16) Crandall, J. K.; Rambo, E. *J. Org. Chem.* **1990**, *55*, 5929. Crandall, J. K.; Batal, D. J. *J. Org. Chem.* **1988**, *53*, 1338 and references cited therein.

Experimental Section

Kinetic Resolution of 13DMA. The preparation of (*S*)-(+)-13DMA was carried out by the asymmetric hydroboration procedures of Waters and Caserio,[1] Waters, Linn, and Caserio,[2] and Rossi and Diversi,[3] as modified by Brown and Singaram.[4] Boron trifluoride dimethyl etherate (11.67 g, 102 mmol) was added slowly to 15.7 g (115 mmol) of (+)-α-pinene (+47.1°,[17] distilled from lithium aluminum hydride) and 2.9 g (76.8 mmol) of sodium borohydride in 70 mL of diglyme (freshly distilled from lithium aluminum hydride) at 0 °C under a nitrogen atmosphere. After being stirred for 8 h at 0 °C, another 15.7 g of (+)-α-pinene was added and the reaction mixture was allowed to stand for another 8 h. Racemic 13DMA (14 g, 205 mmol) was rapidly added, and the reaction mixture was stirred for 4 h at 0 °C, after which time the volatiles were removed at 50 °C under a slight reduced pressure. The resulting mixture of 13DMA and ether was separated by preparative GLC using a 12 ft × $^1/_4$ in. 20% SE-30 on Chromosorb P column at 60 °C, giving 4.2 g (30%) of (*S*)-(+)-13DMA.

Direct Determination of the ee of Optically Active Samples of Enantioenriched 13DMA. In NMR tubes were prepared three solutions of 3.5 mg of 13DMA (α = 0°; α = 0.261 ± 0.001°, *c* = 1.250; α = 0.355 ± 0.001°, *c* = 0.915 in ether) in 495 μL of $CDCl_3$ (0.117 M solutions). Microliter aliquots of a solution of 50 mg of Ag(fod)[17] and 50 mg of tris[3-heptafluoropropylhydroxymethylene)-(+)-camphorato]ytterbium(III) [Yb(hfc)$_3$][17] (3:1 molar ratio) in 500 μL of $CDCl_3$ were added, and the NMR spectra were recorded employing double resonance of the vinyl hydrogen region. The vinyl methyl region provided base line resolution of the vinyl methyl resonances, and the regions were integrated electronically. The ratios of the diastereomerically related methyl resonances gave ee's of 0.0, 25.9, and 47.9%, respectively, for the three samples of 13DMA.

Hydroxybromination of (*S*)-(+)-13DMA. In a 25-mL, septum-capped vial were placed 16 mg (0.1 mmol) of bromine, 20 g of ice–water and 8.2 mg (0.12 mmol) of (*S*)-(+)-13DMA (1st run α = 0.355 ± 0.001°, *c* = 0.915 in ether, 47.9% ee; 2nd run α = 0.262 ± 0.001°, *c* = 1.250 in ether, 25.8% ee). The vial was shaken until the color of the bromine disappeared (within 1 min). The reaction mixture was extracted with 10 1.5-mL portions of methylene chloride. The combined extracts were dried ($MgSO_4$), and the solvent was carefully evaporated under reduced pressure. The residue was dissolved in $CDCl_3$, and NMR spectra were recorded, indicating the presence of 72:28 (1st run) and 73:27 (2nd run) ratios of 8:9: HR EIMS (on mixture) *m/e* calcd for C_5H_9BrO 163.9837, found 163.9837.

8: 300-MHz ^{1}H NMR ($CDCl_3$) δ 1.37 (d, *J* = 6.33 Hz, 3 H), 1.68 (dd, *J* = 6.52, 0.41 Hz, 3 H), 4.32 (qdd, *J* = 6.33, 0.70, 0.41 Hz, 1 H), 6.06 (qd, *J* = 6.52, 0.70 Hz, 1 H).

9: 300-MHz ^{1}H NMR ($CDCl_3$) δ 1.32 (d, *J* = 6.28 Hz, 3 H), 1.73 (br d, *J* = 7.82 Hz, 3 H), 4.65 (qd, *J* = 6.28, 0.47 Hz, 1 H), 5.97 (qd, *J* = 7.82, 0.47 Hz, 1 H).

Determination of the ee's of the Hydroxybromination Products of (*S*)-(+)-13DMA. To the NMR solutions of 8 and 9 were added incremental amounts of a solution of tris[3-(trifluoromethylhydroxymethylene)-(+)-camphorato]europium(III)[17] dissolved in $CDCl_3$. The addition of aliquots of the shift reagent was continued until base line resolution of the vinyl methyl resonances was achieved while the vinyl hydrogen was irradiated. The resulting NMR spectra were electronically integrated, and the ee's of the two stereoisomeric hydroxybromination products was calculated from the relative integrals. The results are given in Table I.

Hydroxymercuration of (*S*)-(+)-13DMA. In a 15-mL, septum-sealed vial were placed 31.8 mg (0.1 mmol) of mercuric acetate, 10 g of ice–water, and 7.7 mg (0.11 mmol) of 13DMA (α = 0.120 ± 0.001°, *c* = 1.250, ether, 25.8% ee). The sealed vial was shaken until the solution became homogeneous. The aqueous solution was extracted with 10 1.5-mL portions of ether. The combined extracts were dried ($MgSO_4$), and the ether was removed under reduced pressure. The residue was dissolved in $CDCl_3$, and the 300-MHz ^{1}H NMR spectrum was recorded, indicating the presence of 10 and 11 in a 75:25 ratio.

10: 300-MHz ^{1}H NMR ($CDCl_3$) δ 1.27 (d, *J* = 6.18 Hz, 3 H), 1.89 (d, *J* = 6.42 Hz, 3 H), 3.38 (s, 3 H), 4.43 (br q, *J* = 6.18 Hz, 1 H), 6.20 (qd, *J* = 6.42, 0.81 Hz, 1 H). (^{1}H–^{199}Hg coupling of ~530 Hz was evident between the vinyl proton and the mercury atom. Other ^{1}H–^{199}Hg coupling constants could not be unambiguously assigned.)

11: 300-MHz ^{1}H NMR ($CDCl_3$) δ 1.24 (d, *J* = 6.18 Hz, 3 H), 1.79 (d, *J* = 6.90 Hz, 3 H), 3.38 (s, 3 H), 4.87 (qd, *J* = 6.18, 1.5 Hz, 1 H), 5.48 (qd, *J* = 6.90, 1.5 Hz, 1 H). (^{1}H–^{199}Hg coupling of ~320 Hz was evident between the vinyl proton and the mercury atom. Other ^{1}H–^{199}Hg coupling constants could not be unambiguously assigned.)

Determination of the ee's of the Hydroxymercuration Products of (*S*)-(+)-13DMA. To the NMR solution of the mixture of the hydroxymercuration products derived from (*S*)-(+)-13DMA were added aliquots of a solution of tris[3-(trifluoromethylhydroxymethylene)-(+)-camphorato]europium(III)[17] dissolved in $CDCl_3$ until base line resolution of the vinyl methyl resonances was achieved on double resonance of the vinyl proton. The ee's of the stereoisomeric addition products were determined directly from the NMR integral and are given in Table I.

Acknowledgment. We acknowledge support of this research by a grant from the National Science Foundation (CHE8709725).

(17) Aldrich Chemical Co., Milwaukee, WI.