groups directed the course of the stereoselection. Compound **1a** gave the trans isomer as a single product. Cyclization of **1b** at −15 °C is an alternative method for the trans lactam. For the preparation of cis isomers, introduction of Cbz or Ts to the trichloroacetamides and subsequent cyclization at −70 °C are effective.

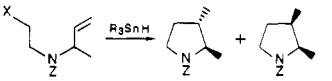
In typical examples, a benzene solution of **1a** was heated in a sealed tube at 140 °C for 1 h in the presence of $RuCl_2(PPh_3)_3$ (5 mol %) to give *trans*-**2a** in 82% yield. Alternatively, a carefully deaerated dichloromethane solution of **1c** was stirred below −70 °C in the presence of CuCl/bpy (1:1, 5 mol %) to give **2c** in 90% yield, in which a cis/trans ratio was 90:10.[8] We found another set of the selective cyclization to form either cis or trans isomers in the reactions of trichloroacetamides from 4-amino-2-heptene as shown in Table I. We are currently investigating the scope and mechanistic aspects to determine the stereochemical course.[9]

(8) This new process can be applied to the cyclization of a wide variety of trichloroacetamides bearing *N*-alkyl or *N*-Ts and *N*-Cbz groups. The reactions were generally completed within 1 h at room temperature to give the corresponding lactams in almost quantitative yields.

Acknowledgment. We are grateful to the Ministry of Education, Science, and Culture for Grant-in-Aid for Scientific Research (63470073) and Saneyoshi Foundation for financial support.

Supplementary Material Available: Experimental details for cyclization of **1a–d**, spectral data of the products **2a–d**, and procedures to determine the stereochemistry (4 pages). Ordering information is given on any current masthead page.

(9) In a typical example, a mixture of CuCl (0.005 mmol) and bipyridine (0.005 mmol) was placed in a Pyrex tube. Compound **1b** (0.1 mmol) dissolved in carefully deaerated dichloromethane (1.4 mL) was added, and the tube was sealed under vacuum. After stirring at −70 °C for 48 h, **2b** was obtained by chromatographic purification. We also found that stereochemical course was dependent on the nitrogen substituents in the β-amino radical cyclization described below. The stereoselectivities are similar to those observed in the copper- or ruthenium-catalyzed system. This result excludes the direct participation of any metallic species in the determining step of the stereochemistry.



X = Cl, Z = CH_2Ph, R = Ph; 110 °C, 5 h, 72% trans/cis = 79:21
X = Br, Z = Ts, R = Bu; 110 °C, 1h, 89% trans/cis = 35:65

Articles

Nonempirical Confirmations of the Absolute Configuration of (+)-α-Methoxy-α-(trifluoromethyl)phenylacetic Acid

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The absolute configuration of the widely used chiral derivatizing agent α-methoxy-α-(trifluoromethyl)phenylacetic (MTPA) acid has been unambiguously determined through the use of two independent, nonempirical methods as *R* and *S* for the (+)- and (−)-enantiomers, respectively. The first approach utilizes the exciton chirality CD method to nonempirically determine the absolute stereochemistry of the *p*-chlorobenzoate derivative of (+)-*trans*-1-hydroxy-2-bromo-1,2,3,4-tetrahydroanthracene. Since the relative stereochemistry of the (−)-MTPA ester of the same alcohol had been elucidated by X-ray crystallographic analysis, the absolute configuration of the (−)-MTPA acid has thus been determined. Alternatively, the single-crystal X-ray analysis of the (+)-MTPA ester derivative of (+)-*trans*-1-hydroxy-2-bromo-1,2,3,4-tetrahydronaphthalene has elucidated its relative stereochemistry. This ester has subsequently been correlated chemically with (+)-naphthalene 1,2-oxide whose absolute stereochemistry had previously been established, thus setting the absolute configuration of (+)-MTPA acid. These configuration proofs, taken together with the three previous empirical correlations and the X-ray structure determination and chemical correlation of Boyd and co-workers, leave no reasonable doubt concerning the absolute configuration of this important reagent.

Optically active α-methoxy-α-(trifluoromethyl)phenylacetic acid (MTPA acid), the Mosher reagent, was originally developed in 1969[1] for use in determination of the enantiomeric purity of chiral alcohols and amines by NMR spectroscopy. The use of this reagent was subsequently expanded to chromatographic resolution of chiral alcohols[2] and assigning the absolute configuration of its chiral esters based on empirical correlation between their NMR chemical shift and absolute stereochemistry of the alcohol.[3] Despite its general use in organic chemistry,[4,5] the un-

(1) Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.* **1969**, *34*, 2543.
(2) (a) van Tamelen, E. E.; Seiler, M. P.; Wierenga, W. *J. Am. Chem. Soc.* **1972**, *94*, 8229. (b) Judy, K. J.; Schooley, D. A.; Dunham, L. L.; Hall, M. S.; Bergot, B. J.; Siddall, J. B. *Proc. Natl. Acad. Sci. USA* **1973**, *70*, 1509. (c) Koreeda, M.; Weiss, G.; Nakanishi, K. *J. Am. Chem. Soc.* **1973**, *95*, 239.

(3) (a) Dale, J. A.; Mosher, H. S. *J. Am. Chem. Soc.* **1973**, *95*, 512. (b) Sullivan, G. R.; Dale, J. A.; Mosher, H. S. *J. Org. Chem.* **1973**, *38*, 2143.
(4) For recent applications, see: (a) Trost, B. M.; O'Krongly, D.; Belletire, J. L. *J. Am. Chem. Soc.* **1980**, *102*, 7595. (b) Trost, B. M.; Curran, D. P. *Tetrahedron Lett.* **1981**, *22*, 4929. (c) Brooks, D. W.; Mazdiyasni, H.; Sallay, P. *J. Org. Chem.* **1985**, *50*, 3411. Hull, W. H.; Seehholzer, K.; Baumeister, M.; Ugi, I. *Tetrahedron* **1986**, *42*, 547. (e) Findeis, M. A.; Whitesides, G. M. *J. Org. Chem.* **1987**, *52*, 2838. (f) Wang, Y.-F.; Wong, C.-H. *Ibid.* **1988**, *53*, 3127. (g) Dussault, P.; Porter, N. A. *J. Am. Chem. Soc.* **1988**, *110*, 6276.

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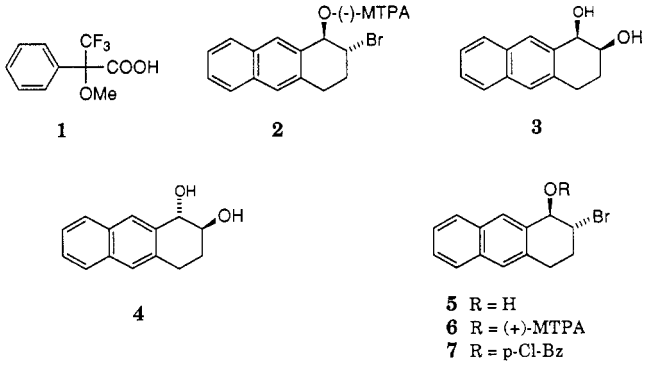
equivocal assignment of the absolute configuration of MTPA acid has remained elusive. The initial assignment of *R* configuration to (+)-MTPA acid (1) made by Mosher[1] was based on its chemical correlation to (−)-α-hydroxy-α-(trifluoromethyl)phenylacetic acid. The configuration of the latter had been postulated to be *R* through the comparison of the NMR chemical shifts of its methyl ester in a chiral solvent with those of (*R*)-(−)-methyl mandelate, (*R*)-(−)-methyl atrolactate, and (*R*)-(+)-methyl α-(trifluoromethyl)phenylacetate.[6] This configurational assignment of MTPA acid was further supported by the CD spectroscopic study of MTPA acid and other α-substituted phenylacetic acids[7] as well as the results on the asymmetric synthesis of (−)-MTPA acid,[8] based on the assumption of the Prelog generalization for asymmetric induction.[9] More recently, Boyd determined the relative stereostructure of (−)-MTPA ester **2** by X-ray analysis.[10] The ester **2** was, through a series of chemical reactions, transformed into both *cis*- and *trans*-diols, **3** and **4**, respectively. Both of these diols were converted into the configurationally established (*S*)-2-hydroxy-1,2,3,4-tetrahydrophenanthrene,[11] thus possibly confirming the absolute configuration of MTPA acid. Unfortunately, the chemical reactions employed in the key steps during the conversions of the ester **2** into both **3** and **4** leave some mechanistic ambiguities[12] that could have considerable bearing on the conclusion to be drawn.



1 **2** **3**

4

5 R = H
6 R = (+)-MTPA
7 R = p-Cl-Bz

In light of its widespread usage in organic and bioorganic chemistry, an independent, unequivocal assignment of the absolute stereochemistry of this highly versatile chiral MTPA acid is urgently required. Here we report that the absolute configuration of MTPA has been unambiguously confirmed by the use of the nonempirical exciton chirality CD method[13] and X-ray analysis.

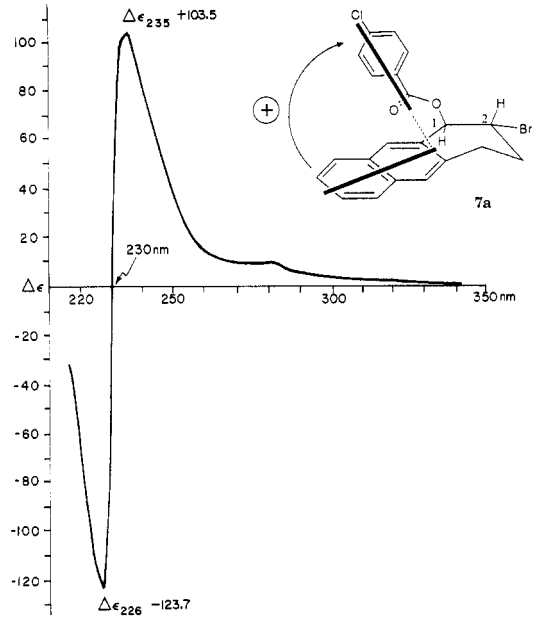


Figure 1. CD spectrum of (1*R*,2*R*)-(+)-*trans*-1-[(*p*-chlorobenzoyl)oxy]-2-bromo-1,2,3,4-tetrahydroanthracene [(+)-**7**] in MeOH/dioxane (9/1) at 25 °C; sample concentration 4.80×10^{-6} M.

Absolute Stereochemistry of (+)-*trans*-1-Hydroxy-2-bromo-1,2,3,4-tetrahydroanthracene [(+)-5]. Since the relative stereochemistry of (−)-MTPA ester **2**[14] is known by X-ray analysis,[10] the absolute configuration of the MTPA group could be determined if that of the *trans*-bromohydrin portion, i.e. (+)-**5**,[10] is unambiguously established. Thus, the direct assignment of the absolute stereochemistry of (+)-**5** based on exciton chirality CD method was undertaken. Racemic *trans*-1-hydroxy-2-bromo-1,2,3,4-tetrahydroanthracene was resolved through preparative TLC separation of the mixture of the two diastereomeric esters prepared from the racemic bromohydrin and (+)-MTPA chloride. The 360-MHz ^{1}H NMR analysis of each diastereomer, after one recrystallization from hexanes, revealed that it was virtually free of the other diastereomer (less than 1%). Treatment of the more polar, late-eluting diastereomer **6L**, mp 121 °C, $[\alpha]^{23}$ +55.0° (*c* 0.101, $CHCl_3$), with diisobutylaluminum hydride (DIBAL) in THF resulted in the formation of (+)-*trans*-bromohydrin (**5**)[10] (68% yield), mp 92–93 °C, $[\alpha]^{23}$ +68.1° (*c* 0.128, $CHCl_3$). Similarly, the (−)-enantiomer of **5**, mp 91–92 °C, $[\alpha]^{23}$ −62.2° (*c* 0.124, $CHCl_3$), was obtained in 53% yield from the less polar, early-eluting diastereomer **6E**, mp 123 °C, $[\alpha]^{24}$ +1.5° (*c* 0.102, $CHCl_3$).

The absolute stereochemistry of (+)-**5** was determined by the use of the exciton chirality CD method on its *p*-chlorobenzoate derivative (+)-**7**, mp 163–164 °C, $[\alpha]^{24}$ +62.1° (*c* 0.103, $CHCl_3$). The CD spectrum of (+)-**7** showed a pair of strong Cotton effects with opposite signs centering at 230 nm ($\Delta\epsilon_{235}$ +103.5, $\Delta\epsilon_{226}$ −123.7) (Figure 1). This typical exciton interaction pattern is clearly ascribable to the coupling between the ^1A–^1B_b transition dipole (long axis) of the naphthalene chromophore (220 nm)[15] and the intramolecular charge-transfer dipole of the *p*-chloro-

(5) For advantages of using MTPA over other chiral derivatizing reagents, see: (a) Yamaguchi, S. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press, New York, 1983; Vol. 1, Chapter 7. (b) Balani, S. K.; Boyd, D. R.; Cassidy, E. S.; Greene, R. M. E.; McCombe, K. M.; Sharma, N. D.; Jennings, W. B. *Tetrahedron Lett.* **1981**, *22*, 3277.

(6) Pirkle, W. H.; Beare, S. D. *Tetrahedron Lett.* **1968**, 2579. There is a typographical error in this paper: (*R*)-(+) symbol for compound **2** on p 2581 should read (*R*)-(−).

(7) Barth, G.; Voelter, W.; Mosher, H. S.; Bunnenberg, E.; Djerassi, C. *J. Am. Chem. Soc.* **1970**, *92*, 875.

(8) Hub, L.; Mosher, H. S. *J. Org. Chem.* **1970**, *35*, 3691.

(9) (a) Prelog, V. *Helv. Chim. Acta* **1953**, *36*, 308. (b) Prelog, V. *Bull. Soc. Chim. Fr.* **1956**, 987.

(10) Balani, S. K.; Boyd, D. R.; Cassidy, E. S.; Devine, G. L.; Malone, J. F.; McCombe, K. M.; Sharma, N. D.; Jennings, W. B. *J. Chem. Soc., Perkin Trans. 1* **1983**, 2751.

(11) Akhtar, M. N.; Boyd, D. R.; Thomson, N. J.; Koreeda, M.; Gibson, D. T.; Mahadevan, V.; Jerina, D. M. *J. Chem. Soc., Perkin Trans. 1* **1975**, 2506.

(12) (a) Winstein, S.; Roberts, R. M. *J. Am. Chem. Soc.* **1953**, *75*, 2297. (b) Ziffer, H.; Imuta, M. *J. Org. Chem.* **1978**, *43*, 4540. (c) Boyd, D. R.; Sharma, N. D.; Smith, A. E. *J. Chem. Soc., Perkin Trans. 1* **1982**, 2767. (d) Imuta, M.; Ziffer, H. *J. Am. Chem. Soc.* **1979**, *101*, 3990.

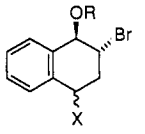
(13) (a) Harada, N.; Nakanishi, K. *Acc. Chem. Res.* **1972**, *5*, 257. (b) Harada, N.; Nakanishi, K. *Circular Dichroic Spectroscopy, Exciton Coupling in Organic Stereochemistry*; University Science Books: Mill Valley, CA, 1983.

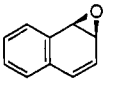
(14) The term (+)- or (−)-MTPA ester refers to an ester obtained using the acid chloride prepared from (+)- or (−)-MTPA acid, respectively.

(15) Harada, N.; Takuma, Y.; Uda, H. *J. Am. Chem. Soc.* **1976**, *98*, 5408.

benzoate chromophore (240 nm).[16] Furthermore, the positive, longer wavelength Cotton effect defines a positive chirality between these two electric transition dipoles as drawn in **7a**.[13] Therefore, the absolute stereochemistry of (+)-*trans*-1-hydroxy-2-bromo-1,2,3,4-tetrahydroanthracene [(+)-**5**] is now unambiguously elucidated as 1*R*,2*R* as shown in **5**. Accordingly, on the basis of the results on the X-ray analysis of **2** by Boyd,[10] the *R* and *S* configurations are assigned to (+)- and (−)-MTPA acids, respectively.

X-ray Crystallographic Analysis of the (+)-MTPA Ester of (1*R*,2*R*)-*trans*-1-Hydroxy-2-bromo-1,2,3,4-tetrahydronaphthalene (9L). The absolute stereochemistry of (+)-naphthalene 1,2-oxide has been established as 1*R*,2*S* as shown in **11**[17] through its chemical correlation with (*S*)-(−)-2-hydroxy-1,2,3,4-tetrahydronaphthalene.[18] In connection with our study on the enzymatic deactivation of optically active naphthalene 1,2-oxide, we had occasion to analyze the stereostructure of the intermediate (+)-MTPA ester **9**. Elucidation of the relative stereochemistry of **9** by X-ray crystallographic analysis and its chemical correlation with (+)- or (−)-naphthalene 1,2-oxide should lead to the direct assignment of the absolute configuration of (+)-MTPA acid.





11

8 R = X = H
9 R = (+)-MTPA, X = H
10 R = (+)-MTPA, X = Br

Racemic *trans*-bromohydrin **8**[19] was resolved as above through preparative TLC separation of the mixture of its two diastereomeric (+)-MTPA esters. The diastereomeric purity of the more polar, late-eluting isomer **9L**, mp 68 °C, $[\alpha]^{25}$ −49.1° (*c* 0.175, $CHCl_3$), reached over 99% after recrystallization from hexanes as judged from its 360-MHz proton NMR spectrum. Benzylic bromination of this diastereomerically pure **9L** with NBS in the presence of AIBN[20] afforded a ca. 20:1 epimeric mixture of bromides **10L** (58%), which was then treated, after chromatographic separation, with excess sodium methoxide in THF at −5 °C to give rise to (1*R*,2*S*)-(+)-naphthalene 1,2-oxide (**11**), $[\alpha]^{0}$ +138° (*c* 0.0247, $CHCl_3$), in 78% yield. Similarly, the less polar, early-eluting diastereomer **9E** was transformed into (1*S*,2*R*)-(−)-naphthalene 1,2-oxide, $[\alpha]^{0}$ −153° (*c* 0.0249, $CHCl_3$). This establishes the stereochemistry at C-1 and C-2 of the more polar diastereomer **9L** as being the 1*R*,2*R* configuration. The stereostructure of the same diastereomer **9L** determined by X-ray crystallographic analysis is shown in Figure 2. This clearly indicates the relative stereochemistry of three chiral centers, thus defining the *R* configuration for (+)-MTPA acid.

In conclusion, the two independent results delineated above utilizing the nonempirical exciton chirality CD method and the X-ray analysis have determined the absolute configuration of (+)-MTPA acid (**1**) as *R*. These two configuration proofs, taken together with the three previous empirical correlations and the X-ray structure

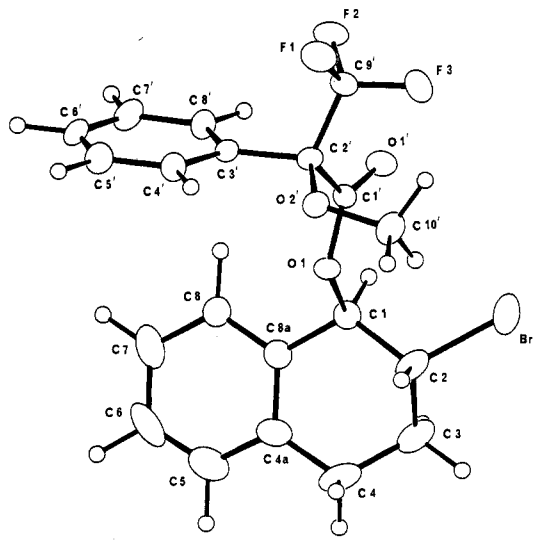


Figure 2. X-ray crystal structure of (1*R*,2*R*)-*trans*-1-[[(+)-2-methoxy-2-phenyl-2-(trifluoromethyl)acetyl]oxy]-2-bromo-1,2,3,4-tetrahydronaphthalene (**9L**).

determination and chemical correlation of Boyd and coworkers,[10] leave no reasonable doubt concerning the absolute configuration of this important reagent.

Experimental Section

General Methods. ^1H NMR and ^{13}C NMR spectra were recorded on either a Bruker WM360 or AM300 spectrometer in $CDCl_3$. Chemical shifts are reported in parts per million (δ units) relative to an internal standard, tetramethylsilane, and multiplicities are indicated by s (singlet), d (doublet), t (triplet), q (quadruplet), m (multiplet), and br (broadened). Data are given as follows: chemical shift (multiplicity, coupling constant, integrated intensity, and assignment). The multiplicity indicated for each ^{13}C NMR chemical shift represents the observed splitting pattern of the corresponding C-13 peak when run in an off-resonance decoupling mode. Note, however, that those multiplicities with asterisks indicate splitting patterns due to C–F couplings and were observed even when the C-13 spectrum was obtained in a broad-band decoupled mode. Optical rotations were measured on a Perkin-Elmer polarimeter 241 in a microcell (pathlength = 10 cm; volume = 1 mL) at the sodium-D line absorption and the temperature/solvent indicated. CD spectra were recorded on a JASCO Model J-40 automatic recording spectropolarimeter. Melting points were determined on a Thermolyne HP-12615 using Gold Seal cover glasses and are uncorrected. Elemental analyses were performed by Galbraith Laboratories, Inc., TN.

Flash column chromatography separations were performed after Still's procedure[21] using E. Merk 230–400 mesh silica gel (Kieselgel 60). Preparative TLC separations were performed on glass plates coated with silica gel (Analtech UNIPLATE, silica gel GF, 20 × 20 cm, 1000 μm). Benzene and tetrahydrofuran (THF) were freshly distilled over sodium metal and benzophenone. Pyridine was distilled over potassium hydroxide or calcium oxide prior to use. All other reagents employed in this study were commercially available and further purified when necessary prior to use. Reactions were run under the positive pressure of nitrogen (predried over anhydrous calcium sulfate), unless otherwise noted.

(+)-α-Methoxy-α-(trifluoromethyl)phenylacetyl chloride [(+)-MTPA chloride] was prepared by following the literature procedure;[1] $[\alpha]^{25}$ +130.0° (*c* 2.37, CCl_4) [lit.[1] $[\alpha]^{24}$ +129.0° (*c* 5.17, CCl_4)]. 1,2-Dihydroanthracene was readily obtainable from 1,2,3,4-tetrahydroanthracene[22] and 1,2-dihydronaphthalene (technical, 75%), purchased from Aldrich Chemical Co., was used without further purification. Racemic *trans*-bromohydrins **5** and **8** were prepared[19] from 1,2-dihydroanthracene and 1,2-dihydronaphthalene, respectively.

(16) Jaffe, H. H.; Orchin, M. *Theory and Application of Ultraviolet Spectroscopy*; Wiley: New York, 1962.
(17) (a) Boyd, D. R.; Jerina, D. M.; Daly, J. W. *J. Org. Chem.* **1970**, *35*, 3170. (b) Akhtar, M. N.; Boyd, D. R.; Hamilton, J. G. *J. Chem. Soc., Perkin Trans. 1* **1979**, 2437.
(18) Arakawa, H.; Torimoto, N.; Masui, T. *Tetrahedron Lett.* **1968**, 4115.
(19) Dalton, D. R.; Dutta, V. P.; Jones, D. C. *J. Am. Chem. Soc.* **1968**, *90*, 5498.
(20) Yagi, H.; Jerina, D. M. *J. Am. Chem. Soc.* **1975**, *97*, 3185.
(21) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.
(22) Fu, P. P.; Lee, H. M.; Harvey, R. G. *Tetrahedron Lett.* **1978**, 551.

Pure Diastereomers of *trans*-1-[[(+)-2-Methoxy-2-phenyl-2-(trifluoromethyl)acetyl]oxy]-2-bromo-1,2,3,4-tetrahydroanthracene [(1*S*,2*S*)-6E and (1*R*,2*R*)-6L]. Racemic bromohydrin **5** (568 mg, 2.0 mmol) was dissolved in a mixture of 0.81 mL of pyridine (8.0 mmol) and 40 mL of benzene in a 100-mL, round-bottomed flask and was treated with (+)-MTPA-Cl (758 mg, 3.0 mmol) at room temperature. The reaction mixture was refluxed for 27 h and cooled to room temperature, whereupon 50 mL of water was added. The mixture was extracted with diethyl ether (3 × 70 mL), and the combined organic layers were washed successively with 0.1 M aqueous HCl (20 mL), saturated aqueous sodium bicarbonate (20 mL), and water (30 mL) and dried over anhydrous magnesium sulfate. Rotary evaporation of the solvent afforded a yellow solid, which was purified by flash column chromatography (1:10 diethyl ether/*n*-pentane) to give rise to 931 mg (99% yield) of **6** as a ca. 1:1 mixture (judged by 300-MHz ^{1}H NMR) of two diastereomers. Separation of these two diastereomers was achieved by the use of preparative TLC (developed with 1:25 diethyl ether/hexanes; ca. 35 mg of the mixture was separated on one plate). Three to five successive developments resulted in clear separation of two UV-absorbing (254 nm) bands, from which two pure diastereomers were recovered (eluted from silica gel with ethyl acetate).

Early-eluting isomer **6E** (441 mg) (higher R_f): mp 123 °C (hexanes); $[\alpha]^{24}$ +1.5° (*c* 0.102, $CHCl_3$); ^{1}H NMR (300 MHz) δ 2.201 (dddd, *J* = 4.8, 5.4, 6.0, 14.4 Hz, 1 H, 3a-H), 2.379 (dddd, *J* = 3.0, 5.1, 9.9, 14.4 Hz, 1 H, 3b-H), 3.041 (ddd, *J* 4.8, 5.1, 17.3 Hz, 1 H, 4a-H), 3.252 (ddd, *J* = 6.0, 9.9, 17.3 Hz, 1 H, 4b-H), 3.474 (q, $^5J_{H-F}$ = 1.2 Hz, 3 H, OCH_3), 4.557 (ddd, *J* = 3.0, 4.2, 5.4 Hz, 1 H, 2-H), 6.551 (d, *J* = 4.2 Hz, 1 H, 1-H), 7.21–7.51 (m, 7 H, Ar Hs), 7.65–7.84 (m, 4 H, Ar Hs); ^{13}C NMR (75 MHz) δ 25.68 (t, 4-C), 27.31 (t, 3-C), 47.83 (d, 2-C), 55.46 (q, OCH_3), 75.65 (d, 1-C), 84.57 (q,* $^2J_{C-F}$ = 28.9 Hz, 2′-C), 123.34 (q,* $^1J_{C-F}$ = 288.5 Hz, CF_3), 125.71 (d), 126.93 (d), 127.10 (d), 127.23 (d, 2 C), 127.36 (d), 127.93 (d), 128.35 (d, 2 C), 128.95 (s), 129.57 (d), 130.25 (d), 132.09 (s), 132.21 (s), 133.15 (s), 133.79 (s), 165.56 (s, 1′-C). Anal. Calcd for $C_{24}H_{20}O_3BrF_3$: C, 58.43; H, 4.09. Found: C, 58.73; H, 4.31.

Late-eluting isomer **6L** (416 mg) (lower R_f): mp 121 °C (hexanes); $[\alpha]^{23}$ +55.0° (*c* 0.101, $CHCl_3$); ^{1}H NMR (300 MHz) δ 2.319 (dddd, *J* = 5.7, 5.7, 5.8, 14.1 Hz, 1 H, 3a-H), 2.528 (dddd, *J* = 3.2, 5.7, 8.9, 14.1 Hz, 1 H, 3b-H), 3.032 (ddd, *J* = 5.7, 5.7, 16.9 Hz, 1 H, 4a-H), 3.213 (ddd, *J* = 5.7, 8.9, 16.9 Hz; 1 H, 4b-H), 3.545 (q, $^5J_{H-F}$ = 1.1 Hz, 3 H, OCH_3), 4.593 (ddd, *J* = 3.2, 5.1, 5.8 Hz, 1 H, 2-H), 6.564 (d, *J* = 5.1 Hz, 1 H, 1-H), 7.31–7.47 (m, 5 H, Ar Hs), 7.53–7.64 (m, 5 H, Ar Hs), 7.710 (d, *J* = 7.7 Hz, 1 H, Ar Hs); ^{13}C NMR (75 MHz) δ 22.26 (t, 4-C), 28.38 (t, 3-C), 48.36 (d, 2-C), 55.63 (q, OCH_3), 75.97 (d, 1-C), 84.72 (q*, $^2J_{C-F}$ = 28.1 Hz, 2′-C), 123.21 (q,* $^1J_{C-F}$ = 288.4 Hz, CF_3), 125.60 (d), 126.79 (d), 126.99 (d), 127.07 (d), 127.40 (d, 2 C), 127.85 (d), 128.37 (d, 2 C), 129.13 (s), 129.53 (d), 129.63 (d), 131.85 (s), 131.95 (s), 132.97 (s), 133.51 (s), 165.76 (s, 1′-C). Anal. Found: C, 58.78; H, 4.14.

(1*R*,2*R*)-(+)-*trans*-1-Hydroxy-2-bromo-1,2,3,4-tetrahydroanthracene [(+)-5]. A solution of **6L** (395 mg, 0.8 mmol) in 20 mL of THF in a 50-mL, round-bottomed flask was treated with 8 mL of a 1 M DIBAL solution in THF (8 mmol) at −10 °C, and the mixture was stirred for 2 days at room temperature. After quenching the reaction with 40 mL of 10% aqueous HCl in an ice bath, most of THF was evaporated in vacuo, and the resulting two-phase mixture was diluted with 100 mL of water. The organic layer was extracted with diethyl ether (3 × 70 mL), and the combined extracts were washed with water (2 × 50 mL) and dried over anhydrous magnesium sulfate. Rotary evaporation of the solvent afforded a white crystalline residue, which was purified by flash column chromatography (2:1 dichloromethane/hexanes) to give 151 mg (68% yield) of (+)-**5** as colorless needles: mp 92–93 °C (hexanes); $[\alpha]^{23}$ +68.1° (*c* 0.128, $CHCl_3$); ^{1}H NMR (300 MHz) δ 2.316 (dddd, *J* = 6.0, 8.6, 9.5, 14.1 Hz, 1 H, 3_{ax}-H), 2.574 (dddd, *J* = 3.4, 5.6, 5.7, 14.1 Hz, 1 H, 3_{eq}-H), 2.724 (br s, 1 H, OH), 3.040 (ddd, *J* = 5.7, 8.6, 17.1 Hz, 1 H, 4_{ax}-H), 3.154 (ddd, *J* = 5.6, 6.0, 17.1 Hz, 1 H, 4_{eq}-H), 4.386 (ddd, *J* = 3.4, 7.4, 9.5 Hz, 1 H, 2_{ax}-H), 5.031 (d, *J* = 7.4 Hz, 1 H, 1_{ax}-H), 7.37–7.46 (m, 2 H, Ar Hs), 7.550 (s, 1 H, 5-H), 7.69–7.81 (m, 2 H, Ar Hs), 8.004 (s, 1 H, 10-H); ^{13}C NMR (75 MHz) δ 28.30 (t, 4-C), 30.17 (t, 3-C), 56.37 (d, 2-C), 74.50 (d, 1-C), 125.50 (d), 126.31 (d), 126.69 (d), 126.99 (d), 127.25 (d), 127.86 (d), 132.29 (s), 132.83 (s), 133.03 (s), 134.39 (s). Anal. Calcd for $C_{14}H_{13}OBr$: C, 60.67; H, 4.73. Found: C, 60.91; H, 4.74.

(1*S*,2*S*)-(−)-*trans*-1-Hydroxy-2-bromo-1,2,3,4-tetrahydroanthracene [(−)-5]. (−)-**5** was prepared from **6E** by the method used for the synthesis of (+)-**5** in 53% yield: mp 91–92 °C (hexanes); $[\alpha]^{23}$ −62.2° (*c* 0.124, $CHCl_3$) [lit.[10] mp 90–92 °C; $[\alpha]_D$ −61° ($CHCl_3$)]. Anal. Found: C, 60.88; H, 4.75.

(1*R*,2*R*)-(+)-*trans*-1-[(*p*-Chlorobenzoyl)oxy]-2-bromo-1,2,3,4-tetrahydroanthracene [(+)-7]. Bromohydrin (+)-**5** (139 mg, 0.50 mmol) and 0.2 mL of pyridine (2.5 mmol) were dissolved in 30 mL of benzene in a 100-mL, round-bottomed flask, and the solution was treated with 0.13 mL of *p*-chlorobenzoyl chloride (1.0 mmol) at room temperature. The mixture was heated at reflux for 48 h. Upon cooling to room temperature, 50 mL of water was added, and the resulting mixture was washed with 0.1 M aqueous HCl (20 mL) and brine (2 × 20 mL) and dried over anhydrous magnesium sulfate. Rotary evaporation of the solvent afforded a yellow crystalline residue, which was purified by flash column chromatography (1:2 dichloromethane/hexanes) to give 135 mg of (+)-**7** (65% yield; 87% yield based on recovered starting material): mp 163–164 °C (diethyl ether–hexanes); $[\alpha]^{24}$ +62.1° (*c* 0.102, $CHCl_3$); ^{1}H NMR (300 MHz) δ 2.356 (dddd, *J* = 5.3, 5.4, 6.2, 14.5 Hz, 1 H, 3a-H), 2.648 (dddd, *J* = 3.0, 5.7, 9.1, 14.5 Hz, 1 H, 3b-H), 3.155 (ddd, *J* = 5.4, 5.7, 17.2 Hz, 1 H, 4a-H), 3.332 (ddd, *J* = 5.3, 9.1, 17.2 Hz, 1 H, 4b-H), 4.690 (ddd, *J* = 3.0, 4.8, 6.2 Hz, 1 H, 2-H), 6.575 (d, *J* = 4.8 Hz, 1 H, 1-H), 7.36–7.47 (m, 4 H, Ar Hs), 7.67–7.85 (m, 4 H, Ar Hs), 7.94–7.99 (m, 2 H, Ar Hs); ^{13}C NMR (75 MHz) δ 26.33 (t, 4-C), 28.18 (t, 3-C), 49.00 (d, 2-C), 74.54 (d, 1-C), 125.61 (d), 126.69 (d), 127.05 (d), 127.11 (d), 127.92 (d), 128.34 (s), 128.78 (d, 2 C), 129.71 (d), 130.19 (s), 131.24 (d, 2 C), 132.16 (s), 133.21 (s), 133.56 (s), 139.83 (s), 164.80 (s, 1′-C). Anal. Calcd for $C_{21}H_{16}O_2BrCl$: C, 60.67; H, 3.88; Found: C, 60.59; H, 3.85.

Pure Diastereomers of *trans*-1-[[(+)-2-Methoxy-2-phenyl-2-(trifluoromethyl)acetyl]oxy]-2-bromo-1,2,3,4-tetrahydronaphthalene [(1*S*,2*S*)-9E and (1*R*,2*R*)-9L]. Racemic bromohydrin **8** (1.590 g, 7.0 mmol) and 5.7 mL of pyridine (10.4 mmol) were dissolved in 30 mL of benzene in a 100-mL, round-bottomed flask, and the solution was treated with 17 mg of 4-(dimethylamino)pyridine (0.14 mmol) and 2.122 g of (+)-MTPA chloride (8.4 mmol) at room temperature. The reaction mixture was then heated at reflux for 3.5 h. After cooling to room temperature, 100 mL of water was added. The resulting mixture was extracted with diethyl ether (3 × 100 mL). The combined organic layers were washed with 0.1 M aqueous HCl (2 × 30 mL), water (2 × 60 mL), and brine (2 × 50 mL) and dried over anhydrous magnesium sulfate. Rotary evaporation of the solvent afforded a yellow oil, which was purified by flash column chromatography (1:20 diethyl ether/hexanes) to give a mixture of two diastereomers **9** (3.101 g, 99% yield) as a colorless oil. Separation of the two diastereomers was achieved by preparative TLC (one to two developments with 1:25 diethyl ether/hexanes; sample size 50–60 mg of the mixture per plate). The diastereomeric purity of the late-eluting **9L**, after recrystallization from hexanes at −10 °C, reached over 99% as judged from its 360-MHz ^{1}H NMR analysis. However, the early-eluting diastereomer **9E** did not crystallize under various conditions, and its diastereomeric purity was determined to be 98%.

Early-eluting diastereomer **9E** (higher R_f) (1.507 g): $[\alpha]^{25}$ +91.7° (*c* 0.410, $CHCl_3$); ^{1}H NMR (360 MHz) δ 2.117 (dddd, *J* = 4.8, 5.4, 6.0, 14.7 Hz, 1 H, 3a-H), 2.237 (dddd, *J* = 2.9, 5.0, 10.2, 14.7 Hz, 1 H, 3b-H), 2.809 (ddd, *J* = 4.8, 5.0, 17.2 Hz, 1 H, 4a-H), 3.055 (ddd, *J* = 6.0, 10.2, 17.2 Hz, 1 H, 4b-H), 3.489 (q, $^5J_{H-F}$ = 1.1 Hz, 3 H, OCH_3), 4.463 (ddd, *J* = 2.9, 3.9, 5.4 Hz, 1 H, 2-H), 6.358 (d, *J* = 3.9 Hz, 1 H, 1-H), 7.14–7.23 (m, 2 H, Ar Hs), 7.27–7.37 (m, 5 H, Ar Hs), 7.43–7.46 (m, 2 H, Ar Hs); ^{13}C NMR (90.56 MHz) δ 25.56 (t, 4-C), 27.11 (t, 3-C), 47.66 (d, 2-C), 55.43 (q, OCH_3), 75.30 (d, 1-C), 84.90 (q,* $^2J_{C-F}$ = 28.8 Hz, 2′-C), 123.38 (q,* $^1J_{C-F}$ = 288.6 Hz, CF_3), 126.63 (d), 127.33 (d, 2 C), 128.36 (d, 2 C), 129.07 (d), 129.27 (d), 129.59 (d), 130.18 (s), 130.43 (d), 132.28 (s), 136.37 (s), 165.62 (s, 1′-C). Anal. Calcd for $C_{20}H_{18}O_3BrF_3$: C, 54.19; H, 4.09. Found: C, 54.12; H, 4.25.

Late-eluting diastereomer **9L** (lower R_f) (1.486 g): mp 68 °C (hexanes); $[\alpha]^{25}$ −49.1° (*c* 0.175, $CHCl_3$) ^{1}H NMR (360 MHz) δ 2.239 (dddd, *J* = 5.0, 5.7, 6.4, 14.3 Hz, 1 H, 3a-H), 2.412 (dddd, *J* = 3.0, 5.5, 9.1, 14.3 Hz, 1 H, 3b-H), 2.844 (ddd, *J* = 5.0, 5.5, 17.3 Hz, 1 H, 4a-H), 3.048 (ddd, *J* = 5.7, 9.1, 17.3 Hz, 1 H, 4b-H), 3.527 (q, $^5J_{H-F}$ = 1.2 Hz, 3 H, OCH_3), 4.532 (ddd, *J* = 3.0, 4.6, 6.4 Hz,

Table I. Summary of Crystal Data, Intensity Collection, and Structure Refinement Data for 9L

chemical formula	$C_{20}H_{18}O_3BrF_3$
mol wt, g/mol	443.3
space group	$P2_12_12_1$
lattice constants, Å	
a	19.206 (4)
b	11.491 (3)
c	8.638 (3)
unit cell vol, Å^3	1906.5 (9)
Z	4
D_{calcd}, g/mL	1.544
crystal dimensions, nm	0.322 × 0.563 × 0.646
μ (Mo Kα, cm^{-1})	21.26
no. of unique reflections	1865
no. of reflections with $I > 3\sigma(I)$	1387
no. of atoms/asymmetric unit	45
R	0.057
R_w	0.054
largest residuals (e/Å^3)	0.59
goodness of fit (GOF)	1.50

1 H, 2-H), 6.373 (d, J = 4.6 Hz, 1 H, 1-H), 7.09–7.13 (m, 3 H, Ar Hs), 7.20–7.26 (m, 1 H, Ar H), 7.34–7.41 (m, 3 H, Ar Hs), 7.52–7.55 (m, 2 H, Ar Hs); ^{13}C NMR (90.56 MHz) δ 25.98 (t, 4-C), 27.85 (t, 3-C), 48.13 (d, 2-C), 55.52 (q, OCH_3), 75.60 (d, 1-C), 84.75 (q,* $^2J_{C-F}$ = 28.2 Hz, 2′-C), 123.21 (q,* $^1J_{C-F}$ = 288.7 Hz, CF_3), 126.54 (d), 127.48 (d, 2 C), 128.40 (d, 2 C), 128.89 (d), 129.07 (d), 129.67 (d), 129.95 (d), 130.22 (s), 131.78 (s), 136.08 (s), 165.83 (s, 1′-C). Anal. Found: C, 54.46; H, 4.13.

X-ray Crystallographic Analysis of Diastereomer 9L. Single crystals of **9L** were grown from its hexane solution and mounted on a Syntex $P2_1$ diffractometer. Table I contains a summary of data collection conditions and results. Lattice parameters were determined from a least-squares refinement of 15 reflection settings obtained from an automatic centering routine. Intensity data were obtained using Mo Kα radiation monochromated from a graphite crystal whose diffraction vector was parallel to the diffraction vector of the sample. Three standard reflections were measured for every 50 reflections. The data were reduced by procedures previously described.[23] The data were corrected for absorption.[23]

The structure was solved using SHELXS86.[23] In the subsequent refinement the function $\Sigma w(|F_o| - |F_c|)^2$ was minimized where $|F_o|$ and $|F_c|$ are the observed and calculated structure factor amplitudes. The agreement indices $R_1 = \Sigma(|F_o| - |F_c|)/\Sigma|F_o|$ and $R_2 = [\Sigma w(|F_o| - |F_c|)^2/\Sigma w|F_o|^2]^{1/2}$ were used to evaluate the results. The atomic scattering factors are from *The International Tables for X-Ray Crystallography*.[24]

Least-squares refinement results using anisotropic thermal parameters for all non-hydrogen atoms are shown in Table I. Hydrogen atoms were located by difference Fourier and refined with fixed U values (isotropic temperature factors) of 0.10.

Figure 2 shows the structure of **9L**. The supplementary material includes final positional parameters with estimated standard deviations (Table A), anisotropic thermal parameters with their estimated standard deviations (Table B), and the crystallographically determined bond distances and angles (Table C).

Bromination of Diastereomers 9L and 9E. Diastereomerically pure **9L** (887 mg, 2.0 mmol) was dissolved in 30 mL of CCl_4 in a 100-mL, round-bottomed flask equipped with a reflux condenser. The solution was treated with 392 mg of *N*-bromosuccinimide (2.2 mmol) and 5.6 mg of α,α′-azoisobutyrodinitrile (AIBN) (0.04 mmol) at room temperature, and the resulting mixture was irradiated with a sun lamp (Cole-Parmer Dyna-Lume Model 3151-6) for 30 min. During the period of irradiation, the intensity of the light was controlled so that the reaction temperature was kept just below reflux. After cooling to room temperature, precipitates were removed by filtration. The filtrate was condensed to dryness in vacuo to afford a crystalline residue, which was purified by preparative TLC (developed 3–5 times with 1:30 diethyl ether–hexanes; sample size ca. 50 mg per plate) to give 609 mg of a ca. 20:1 epimeric mixture of bromides **10L** as a colorless oil (58% yield). Major epimer: ^{1}H NMR (360 MHz) δ 2.824 (ddd, J =4.5, 10.7, 14.8 Hz, 1 H, 3a-H), 2.958 (ddd, J = 3.4, 4.1, 14.8 Hz, 1 H, 3b-H), 3.687 (q, $^5J_{H-F}$ = 1.2 Hz, 3 H, OCH_3), 4.776 (ddd, 1 H, J = 3.4, 8.2, 10.7 Hz, 2-H), 5.480 (dd, J = 4.1, 4.5 Hz, 1 H, 4-H), 6.536 (d, J = 8.2 Hz, 1 H, 1-H), 6.835 (d, J = 8.0, 1 H, Ar H), 7.11–7.15 (m, 1 H, Ar H), 7.26–7.30 (m, 1 H, Ar H), 7.39–7.46 (m, 4 H, Ar Hs), 7.66–7.70 (m, 2 H, Ar Hs); ^{13}C NMR (90.56 MHz) δ 41.14 (t, 3-C), 45.48 (d, 2-C), 46.98 (d, 4-C), 55.98 (q, OCH_3), 76.30 (d, 1-C), 84.71 (q,* $^2J_{C-F}$ = 29.3 Hz, 2′-C), 123.25 (q,* $^1J_{C-F}$ = 289.0 Hz, CF_3), 127.54 (d, 2 C), 127.83 (d), 128.51 (d, 2 C), 129.16 (d), 129.31 (d), 129.83 (d), 130.42 (d), 131.50 (s), 131.70 (s), 136.10 (s), 166.52 (s, 1′-C). Anal. Calcd for $C_{20}H_{17}O_3Br_2F_3$: C, 46.00; H, 3.28. Found: C, 46.39; H, 3.79.

The same procedure was followed for the synthesis of an epimeric mixture of bromides **10E** starting from **9E** (66% yield; oil): ^{1}H NMR (360 MHz) δ 2.770 (ddd, J = 4.8, 9.6, 14.7 Hz, 1 H, 3a-H), 2.889 (ddd, J = 3.4, 5.2, 14.7 Hz, 1 H, 3b-H), 3.546 (q, $^5J_{F-H}$ = 0.9 Hz, 3 H, OCH_3), 4.701 (ddd, J = 3.4, 7.4, 9.6 Hz, 1 H, 2-H), 5.489 (dd, J = 4.8, 5.2 Hz, 1 H, 4-H), 6.483 (d, J = 7.4, 1 H, 1-H), 7.181 (d, J = 7.7, 1 H, Ar H), 7.27–7.42 (m, 5 H, Ar Hs), 7.489 (d, J = 7.7, 1 H, Ar H), 7.603 (m, 2 H, Ar Hs); ^{13}C NMR (90.56 MHz) δ 40.45 (t, 3-C), 45.36 (d, 2-C), 46.52 (d, 4-C), 55.65 (q, OCH_3), 76.31 (d, 1-C), 84.79 (q,* $^2J_{C-F}$ = 29.7 Hz, 2′-C), 123.30 (q,* $^1J_{C-F}$ = 288.9 Hz, CF_3), 127.65 (d), 128.49 (d), 128.66 (d), 129.26 (d), 129.61 (d), 129.82 (d), 130.64 (d), 131.24 (s), 131.57 (s), 136.37 (s), 166.32 (s, 1′-C). Anal. Found: C, 46.27; H, 3.62.

Pure Enantiomers of Naphthalene 1,2-Oxides [(1*R*,2*S*)-(+)-11 and (1*S*,2*R*)-(−)-11]. Bromides **10L** (22 mg, 42 μmol) and 13.6 mg of sodium methoxide (anhydrous powder; 0.25 mmol) were dissolved in 2 mL of anhydrous THF in a 25-mL, round-bottomed flask. The resulting pale yellow solution was stirred at −5 °C for 70 h. The reaction was stopped by vacuum filtering the reaction mixture using precooled filtration system, with anhydrous cold (below −5 °C) diethyl ether (10 mL). The filtrate was immediately washed with a mixture of ice and cold 1 M aqueous KOH (5 mL) and dried over anhydrous sodium carbonate at 0–5 °C. Rotary evaporation of the solvent at 0 °C afforded 4.7 mg of (+)-11 as colorless crystals (78% yield): mp 45–50 °C (decomposition); $[\alpha]^0$ +138° (*c* 0.0247, $CHCl_3$) {lit.[17b] $[\alpha]_D$ +149° ($CHCl_3$; concentration not given)}. The ^{1}H NMR data were identical with those reported by Vogel:[25] ^{13}C NMR (75 MHz) δ 53.44 (d, 2-C), 57.24 (d, 1-C), 124.81 (d, 3-C), 128.00 (d, 4-C), 128.85 (s, 1 C and d, 2 C), 129.92 (d), 131.67 (d), 132.21 (s). The conversion of **10E** to (−)-11 {mp 41–45 °C (decomposition); $[\alpha]^0$ −153° (*c* 0.0249, $CHCl_3$); lit.[10] $[\alpha]_D$ −128° ($CHCl_3$; concentration not given)} was also effected as above in 79% yield.

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Supplementary Material Available: Three tables of final atomic coordinates, bond distances and angles, and thermal parameters (4 pages). Ordering information is given on any current masthead page.

(23) Computations were carried out on an Amadahl 5860 computer. The structure was solved using the direct methods program SHELXS86 by George Sheldrick. Other programs used during the structural analysis were from the SHELX program package by George Sheldrick, Institute fur Anorganishe Chemie der Universitat Gottingen, Federal Republic of Germany, and ORTEP, a thermal ellipsoidal drawing program by C. K. Johnson.

(24) *The International Tables for X-ray Crystallography*; Ibers, J. A., Hamilton, W. C., Eds.; Kynoch Press: Birmingham, England, 1974; Vol. IV, Tables 2.2 and 2.3.1.

(25) Vogel, E.; Klarner, F.-G. *Angew. Chem., Int. Ed. Engl.* **1968**, *7*, 374.