650.1258. Anal. Calcd for $C_{35}H_{27}N_3O_4S_3$: C, 64.69; H, 4.19; N, 6.47; S, 14.80. Found: C, 64.09; H, 4.15; N, 6.31; S, 14.95.

With Sodium 5-Mercapto-1-methyltetrazole. Triflate **10b** (1.170 g, 2.00 mmol) and sodium 5-mercapto-1-methyltetrazole hydrate (330 mg, 2.40 mmol) were dissolved in dry tetrahydrofuran (100 mL), and the solution was stirred at room temperature overnight. The solution was then evaporated in vacuo, and the residue was taken up in ethyl acetate and washed with water. The organics were dried over magnesium sulfate and evaporated. The crude product was recrystallized from hot methanol (ca. 125 mL). White small needles of **15** were obtained. Yield: 0.940 g (85%) of material having the following properties. NMR ($CDCl_3$, 300 MHz): δ 7.35–7.20 (m, 7 H), 6.84 (d, J = 8.5 Hz, 2 H), 6.11 (d, J = 9.2 Hz, 1 H exch), 5.84 (dd, J = 9.2 Hz, J' = 5.0 Hz, 1 H), 5.19 (m, 2 H), 4.97 (d, J = 5.0 Hz, 1 H), 3.93 (s, 3 H), 3.77 (s, 3 H), 3.76 (d, J = 18.0 Hz, 1 H), 3.61 (m, 2 H), 3.34 (d, J = 18.0 Hz). Accurate mass determination (M + 1): calcd for $C_{24}H_{25}N_6O_5S_2$ 553.1328, found 553.1338. Anal. Calcd for $C_{24}H_{24}N_6O_5S_2$: C, 54.33; H, 4.38; N, 15.21; S, 11.61. Found: C, 54.03; H, 4.28; N, 15.20; S, 11.61.

With Sodium Phenyl Selenide–Borane Adduct. To a solution of diphenyl diselenide (230 mg, 0.736 mmol) in dry, degassed tetrahydrofuran (5 mL) was added dropwise a stock solution of sodium borohydride in dry diglyme (0.5 M, 2.65 mL, 1.325 mmol) at room temperature over 10 min. The solution decolorized completely and became slightly warm, with evolution of hydrogen. After 15 min at room temperature, this solution was cooled to −78 °C, and a solution of triflate **10c** (810 mg, 1.310 mmol) in dry THF (4 mL, plus two 0.5-mL rinses) was added by syringe over 1–2 min. The solution was allowed to reach −20 °C over 3 h and then kept at this temperature overnight (freezer). Sodium hydrogen carbonate (5%, 100 mL) was then added, followed by ethyl acetate. The organics were further washed with water and brine and dried over magnesium sulfate. The crude was purified by flash chromatography (10% ethyl acetate in hexane to elute traces of yellow diphenyl diselenide, followed by 25% ethyl acetate to elute **16**). Yield: 743 mg (90%) of a white foam, having the following properties. NMR ($CDCl_3$, 300 MHz): δ 7.70–7.20 (m, 15 H), 6.95 (s, 1 H), 5.57 (dd, J = 9.6 Hz, J' = 4.7 Hz, 1 H), 5.23 (d, J = 9.6 Hz, 1 H exch), 4.94 (d, J = 4.7 Hz, 1 H), 3.21 (m, 2 H), 1.44 (s, 9 H). Accurate mass determination (M + 1): calcd for $C_{31}H_{31}N_2O_5SSe$ 623.1119, found 623.1122. Anal. Calcd for $C_{31}H_{30}N_2O_5SSe$: C, 59.89; H, 4.86; N, 4.51. Found: C, 59.81; H, 5.13; N, 4.41.

With Pyrrolidine. Triflate **10c** (389 mg, 0.633 mmol) was dissolved in dry tetrahydrofuran (7 mL) and cooled to −78 °C. Neat pyrrolidine (0.105 mL, 1.253 mmol) was added dropwise by syringe, and the pale orange solution was stirred at this temperature for 30 min. Ice-cold water (20 mL) was then added, followed by ethyl acetate. The organic phase was washed repeatedly with ice-cold water and then dried over sodium sulfate. The crude enamine (339 mg, 100%) was triturated with hexane (ca. 25 mL), filtered, and washed with cold hexane. After drying in vacuo the purified **17** weighed 254 mg (75%) and had the following properties. NMR ($CDCl_3$, 300 MHz): δ 7.55–7.15 (m, 10 H), 6.64 (s, 1 H), 6.24 (br d, J = 8.4 Hz, 1 H exch), 5.28 (dd, J = 8.4 Hz, J' = ca. 4 Hz, 1 H), 5.00 (d, J = ca. 4 Hz, 1 H), 3.44 (m, 2 H), 3.14–3.08 (m, 3 H), 2.62 (d, J = 13.8 Hz, 1 H), 2.0–1.5 (m, 4 H), 1.48 (s, 9 H). Accurate mass determination (M + 1): calcd for $C_{29}H_{34}N_3O_5S$ 536.2219, found 536.2205.

With Pyridine. Triflate **10c** (271 mg, 0.44 mmol) was dissolved in dry dichloromethane (2 mL), neat pyridine (0.035 mL, 0.44 mmol) was then added, and the solution was stirred at room temperature for 16 h. The solvent was evaporated in vacuo, and the crude pyridinium salt was triturated twice with ether. Yield: 299 mg (98%) of **18** having the following properties. NMR ($CDCl_3$, 300 MHz): δ 8.67 (br d, 2 H), 8.20 (m, 1 H), 7.71 (m, 2 H), 7.3–7.0 (m, 11 H), 6.72 (s, 1 H), 6.28 (br d, 1 H exch), 5.89 (s, 1 H), 5.47 (br dd, 1 H), 5.13 (d, J = 4 Hz, 1 H), 1.45 (s, 9 H). Accurate mass determination (M + 1): calcd for $C_{30}H_{31}N_3O_5S$ 544.1906, found 544.1894. Anal. Calcd for $C_{31}H_{30}N_3O_8S_2F_3$: C, 53.60; H, 4.36; N, 6.06; F, 8.22. Found: C, 53.55; H, 4.31; N, 5.72; F, 8.43.

With *N*-Methylmorpholine. Triflate **10c** (704 mg, 1.14 mmol) was dissolved in dry THF (10 mL), cooled to −78 °C, and treated with neat *N*-methylmorpholine (0.120 mL, 1.09 mmol). The solution was allowed to reach room temperature over 4 h, the solvent was then evaporated, and the crude product was triturated with ether (10 mL), filtered, and washed with more ether (2 × 5 mL). Yield: 616 mg (95%) of **19** after drying in vacuo. NMR ($CDCl_3$, 300 MHz): δ 7.4–7.2 (m, 11 H), 6.90 (s, 1 H), 6.60 (d, J = 9.3 Hz, 1 H exch), 5.85 (s, 1 H), 5.31 (br dd, 1 H), 4.95 (br d, J = ca. 4 Hz, 1 H), 4.0–3.2 (m, 8 H), 1.40 (s, 9 H). Accurate mass determination (M + 1): calcd for $C_{30}H_{37}N_3O_6S$ 567.2403, found 567.2390. Anal. Calcd for $C_{31}H_{36}N_3O_9S_2F_3$: C, 52.02; H, 5.07; N, 5.87; S, 8.96. Found: C, 52.06; H, 5.27; N, 5.72; S. 8.52.

Acknowledgment. We thank J. Lajeunesse of Bristol-Myers Candiac, Canada, for supplies of triflate **10c**. We are also grateful to Dr. K. Singleton and Dr. S. Klohr of the Analytical Department of Bristol-Myers in Wallingford for recording the mass spectra.

Preparation of (1*R*,2*S*)- and (1*S*,2*R*)-2-Chloro-1,2-diphenylethanol and Other β-Halohydrins in Enantiomerically Pure Form[1]

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Received December 27, 1988

Recently we began a program exploring the chemistry of enantiomerically pure ketene acetals of type A.[3] Our retrosynthetic analysis (Scheme I) led us to consider their preparation from chiral, nonracemic halohydrins of type B, which would arise from the corresponding diols C. Herein we report methods for the efficient synthesis of a variety of enantiomerically pure β-halohydrins B, including both enantiomers of *erythro*-2-chloro-1,2-diphenylethanol (B, R = C_6H_5, X = Cl), which to our knowledge has not previously been described in enantiomerically pure form.[4]

Enantiomerically pure ketals and acetals have enjoyed great success in diastereoselective reactions as removable chiral auxiliaries.[5] Our need to have access to a wide range of chiral, nonracemic diols for initial screening purposes prompted our choice of tartaric acid, a prominent member of the pool of chiral carbon compounds[6] and, in certain derivative forms, an important auxiliary for asymmetric syntheses,[7] as our starting point. Our task was made easier by the extensive array of tartrate-derived compounds documented in the literature.[8] Indeed, several previously synthesized diols appeared particularly attractive for our project. These included the protected hydroxymethyl

(1) A preliminary account of these results has been reported at the 196th National Meeting of the American Chemical Society, Los Angeles, CA, Sept 1988; paper ORGN 231.

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(3) Konopelski, J. P.; Boehler, M. A. *J. Am. Chem. Soc.* **1989**, *111*, 4515–7.

(4) *threo*-2-Chloro-1,2-diphenylethanol has been described in optically active form. See: (a) Berti, G.; Bottari, F.; Ferrarini, P. L.; Macchia, B. *J. Org. Chem.* **1965**, *30*, 4291–6. (b) Imuta, M.; Ziffer, H. *Ibid.* **1979**, *44*, 2505–9.

(5) Takacs, J. M.; Anderson, L. G.; Newsome, P. W. *J. Am. Chem. Soc.* **1987**, *109*, 2542–4 and references therein.

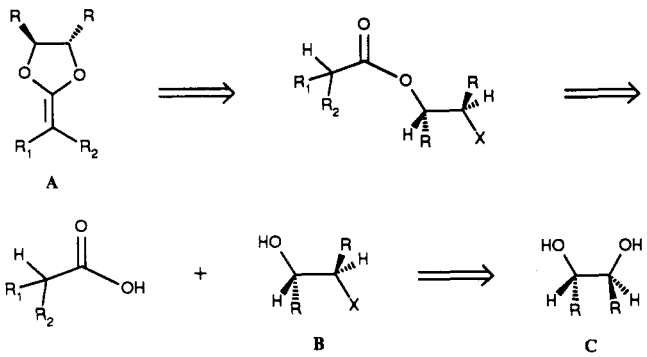
(6) Scott, J. W. In *Asymmetric Synthesis*; Morrison, J. D., Scott, J. W., Eds.; Academic Press: New York, 1984; Vol. 4, pp 1–226.

(7) For two recent examples, see: (a) Gao, Y.; Hanson, R. M.; Klunder, J. M.; Ko, S. Y.; Masamune, H.; Sharpless, K. B. *J. Am. Chem. Soc.* **1987**, *109*, 5765–80. (b) Roush, W. R.; Banfi, L. *Ibid.* **1988**, *110*, 3979–82.

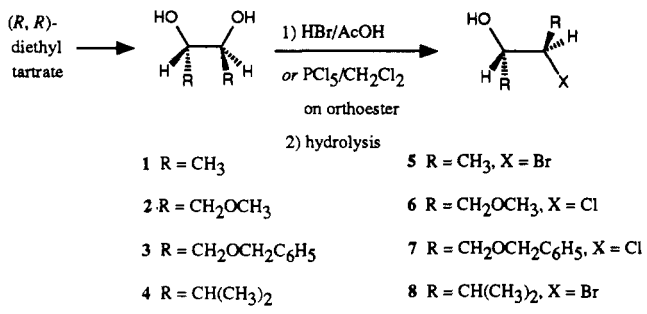
(8) Seebach, D.; Hungerbühler, E. In *Modern Synthetic Methods*; Scheffold, R., Ed.; Salle + Sauerländer: Frankfurt, 1980: pp 91–172.

0022-3263/89/1954-4966$01.50/0

Scheme I



Scheme II



1 R = CH_3 5 R = CH_3, X = Br

2 R = CH_2OCH_3 6 R = CH_2OCH_3, X = Cl

3 R = $CH_2OCH_2C_6H_5$ 7 R = $CH_2OCH_2C_6H_5$, X = Cl

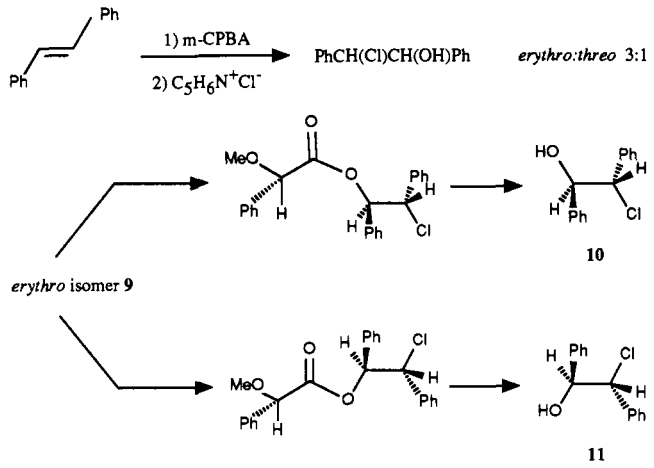
4 R = $CH(CH_3)_2$ 8 R = $CH(CH_3)_2$, X = Br

derivatives **2**[9] and **3**,[10] in which the R groups bear an electronegative atom but have approximately the same steric presence as a methyl group (i.e., butanediol **1**[11]), as well as the more sterically demanding (*S*,*S*)-2,5-dimethyl-3,4-hexanediol (**4**).[12]

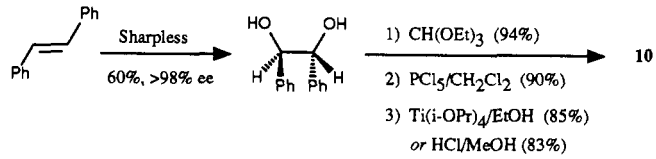
Two methods for the transformation of diols C to halohydrins B have been employed (Scheme II). Treatment of the diols directly with HBr/AcOH affords bromoacetates, which upon hydrolysis yield the desired bromohydrins.[13] This procedure works well for compounds **1** and **4** and diethyl tartrate itself,[14] but, not unexpectedly, fails for diols **2** and **3**, as the ether linkages are cleaved during the process. Fortunately, an alternative method recently employed by Nicolaou has proven to be quite useful.[15] Formation of the orthoester functionality by treatment of the diol with triethyl orthoformate proceeds in excellent yield (>90%). Addition of freshly sublimed PCl_5 to a solution of the orthoester in CH_2Cl_2 affords the corresponding β-chloroformates, in which a single inversion has occurred, in very good yield. Removal of the formate functionality yields the desired erythro chlorohydrin. This procedure, although involving an extra step as compared with HBr/AcOH treatment, appears to be quite general and occurs in good yield overall.

In addition to the halohydrins discussed above, we were interested in synthesizing both enantiomers of *erythro*-2-chloro-1,2-diphenylethanol, as the steric demands of the phenyl group are similar to those of the isopropyl group[16] (in **8**) while the electronic characteristics are quite different. At the start of this work, there appeared to be no method for the synthesis of these compounds in high enantiomeric purity and in sufficient quantities for our purposes. As it seemed cumbersome to transform the COOR group of a dialkyl tartrate to the desired C_6H_5 group, we opted for a different approach, and two independent syntheses of the desired β-halohydrin have been developed.

Scheme III



Scheme IV



Our initial idea was to form racemic *erythro*-2-bromo-1,2-diphenylethanol and resolve the enantiomers through the formation of esters of (*S*)-*O*-methylmandelic acid.[17] As both the β-halo esters and β-halo alcohols would be sensitive to base (formation of epoxide), acid hydrolysis would be employed for ester cleavage. However, while we were able to prepare the desired erythro bromohydrin in good yield from *trans*-stilbene (NBS, aqueous DMSO) and separate the derived *O*-methylmandelate esters by MPLC, we were unable to hydrolyze the ester bond without concomitant benzyl bromide solvolysis. Even the mild Ti(*i*-OPr)$_4$ transesterification method of Seebach[18] led to poor yields of the desired product.

Fortunately, the same problems did not arise when chlorine was employed in the place of bromine. Thus, as shown in Scheme III, treatment of *trans*-stilbene under standard conditions (*m*-CPBA) affords the corresponding epoxide in good yield. However, stereospecific opening of the oxirane was no trivial matter![19] Numerous reaction conditions were tried without success; undesired threo material was consistently obtained in large quantity. Our best method to date involves treatment of *trans*-stilbene oxide with pyridine hydrochloride in $CHCl_3$ at reflux,[20] which affords a 90% yield of a 3:1 mixture of the desired

(9) Tamura, Y.; Annoura, H.; Fuji, M.; Yoshida, R.; Takeuchi, R.; Fujioka, H. *Chem. Pharm. Bull.* **1987**, *35*, 4736–46.
(10) Ando, N.; Yamamoto, Y.; Oda, J.; Inouye, Y. *Synthesis* **1978**, 688–90.
(11) Mori, K.; Tamada, S. *Tetrahedron* **1979**, *35*, 1279.
(12) (a) Matteson, D. S.; Kandil, A. A. *Tetrahedron Lett.* **1986**, *27*, 3831–4. (b) Matteson, D. S.; Beedle, E. C.; Kandil, A. A. *J. Org. Chem.* **1987**, *52*, 5034–6.
(13) Golding, B. T.; Hall, D. R.; Sakrikar, S. *J. Chem. Soc., Perkin Trans 1* **1973**, 1214.
(14) Mori, K.; Iwasawa, H. *Tetrahedron* **1980**, *36*, 87–90.
(15) Nicolaou, K. C.; Papahatjis, D. P.; Claremon, D. A.; Magolda, R. L.; Dolle, R. E., III *J. Org. Chem.* **1985**, *50*, 1440–56. We employed natural diethyl tartrate, thus producing the enantiomer of the compounds described in this paper.
(16) Hirsch, J. A. *Top. Stereochem.* **1967**, *1*, 199–222.
(17) Whitesell, J. K.; Reynolds, D. *J. Org. Chem.* **1983**, *48*, 3548.
(18) Seebach, D.; Hungerbuhler, E.; Naef, R.; Schnurrenberger, P.; Weidmann, B.; Zuger, M. *Synthesis* **1982**, 138–41.
(19) The problems associated with stereospecific transformations of *trans*-stilbene oxide are well documented. See: Bhat, K. S.; Joshi, P. L.; Rao, A. S. *Synthesis* **1984**, 142–5.
(20) Loreto, M. A.; Pellacani, L.; Tardella, P. A. *Synth. Commun.* **1981**, 287.

erythro β-chlorohydrin (**9**) together with the corresponding threo isomer. Isolation of crystalline **9** is accomplished by MPLC in an overall 55% yield from stilbene. Coupling of **9** with (*S*)-*O*-methylmandelic acid (DCC, DMAP) followed by MPLC and recrystallization effectively separates the diastereomers, as evidenced by monitoring the proton on the mandelate ester chiral carbon by ^{1}H NMR (δ 6.18 and 6.24). Removal of the mandelic acid fragment is achieved with Ti(*i*-OPr)$_4$ in ethanol; the ethyl mandelate produced can be saponified back to mandelic acid without racemization. Optical purity of the enantiomers **10**/**11** is ascertained by transformation to stilbene oxide (K_2CO_3/MeOH) and comparison of the optical rotation with that reported.[21a]

While this approach was adequate for initial quantities of **10**/**11**, the above synthesis was not efficient for the production of larger amounts of material needed for more extensive studies. To this end, we were eager to ascertain if enantiomerically pure hydrobenzoin, as obtained from the recently published asymmetric dihydroxylation method of Sharpless,[22] would be amenable to halohydrin formation without racemization. In the event (Scheme IV), this second synthesis of **10**/**11** affords enantiomerically pure material[21b] in good yield and in multigram quantities without the need for chromatographic separations.[23]

Compounds **10** and **11**, along with halohydrins **5**–**8**, join the growing number of small, highly functionalized members of the pool of chiral compounds.[24] The procedures outlined herein should also be amenable to the production of other enantiomerically pure β-halohydrins. Continued studies on the use of these halohydrins for the formation of ketene acetals of type A and the use of type A molecules as novel enantiomerically pure reagents in diastereoselective reactions will be reported in due course.

Experimental Section

General. All reaction solvents used were reagent grade and were distilled prior to use. All reactions were performed in oven- or flame-dried flasks under a positive pressure of nitrogen and were monitored by TLC on precoated silica gel 60F-254 plates (250 μm) obtained from EM products.

^{1}H and ^{13}C NMR spectra were recorded on a General Electric GN-300 NMR spectrometer. ^{1}H NMR spectra were collected in deuteriochloroform and are reported in δ (parts per million) shifts from tetramethylsilane (0.0) or internal chloroform (7.26) standards, followed by multiplicity, proton count, and coupling constant (hertz). ^{13}C NMR spectra were collected in deuteriochloroform and referenced to the center line of the deuteriochloroform triplet (77.09). Infrared (IR) spectra were recorded either neat or in chloroform on a Nicolet 5MX Fourier transform spectrophotometer. Low-resolution mass spectra were obtained by using a Finnigan 4000 instrument with a 6100 data station. High-resolution mass spectra were obtained at the UC, Riverside Analytical Chemistry Instrumentation Facility. Microanalyses were performed by Atlantic Microlab, Inc., Atlanta, GA.

Melting points were obtained by using a Thomas-Hoover instrument and are uncorrected.

Synthesis of β-Bromohydrin from Diol Using HBr/AcOH. (3*R*,4*R*)-4-Bromo-2,5-dimethyl-3-hexanol (8). (3*S*,4*S*)-2,5-Dimethyl-3,4-hexanediol (**4**, *S*-DIPED,[12] 0.400 g, 2.74 mmol) was stirred at room temperature for 14 h with 30% HBr/AcOH (3.0 mL), followed by quenching with ice water (12 mL). The aqueous solution was extracted with Et_2O (3 × 25 mL), and the combined organic layers were washed with water and brine, dried ($MgSO_4$), and concentrated to yield 0.650 g of a pale yellow oil. Without further purification, the oil was added to a solution of methanol (25 mL) contaiing 30% HBr/AcOH (0.25 mL), refluxed for 48 h, cooled, and treated with water (50 mL). The aqueous solution was subjected to continuous extraction with pentanes for 72 h. Evaporation of the resultant pentane solution afforded **8** (0.250 g, 41%) as a white crystalline solid: mp 69–70 °C; $[\alpha]^{25}_D$ = +8.0° (*c* = 2.3, toluene); ^{1}H NMR (300 MHz) δ 4.20 (dd, 1 H, *J* = 3.3, 7.5 Hz), 3.35 (dd, 1 H, *J* = 3.3, 7.5 Hz), 2.06 (m, 1 H), 1.59 (m, 1 H), 0.85–1.00 (br s, 12 H); ^{13}C NMR (75.47 MHz) δ 76.81, 62.25, 31.09, 19.40, 18.29, 18.08; IR ($CDCl_3$) 3420 cm^{-1}; mass spectrum (70 eV), *m*/*z* 192,190 (1, M$^+$ − 18), 180, 178 (1), 151, 149 (5), 137, 135 (100); HRMS (EI) calcd for $C_8H_{16}Br$ 191.0435, found 191.0449 (M$^+$ − OH). Anal. Calcd for $C_8H_{16}Br$: C, 45.92; H, 8.20. Found: C, 46.12; H, 8.27.

(2*S*,3*R*)-3-Bromo-2-butanol (5). (2*S*,3*S*)-(+)-2,3-Butanediol (**1**, 2.0 g, 0.022 mol) was treated with HBr/AcOH as described above to afford **5** (1.51 g, 45%) as a clear oil: bp 146–148 °C; $[\alpha]^{25}_D$ = −13.2° (*c* = 10.1, Et_2O); ^{1}H NMR (300 MHz) δ 4.27 (dq, 1 H, *J* = 7.2, 3.6 Hz), 3.84 (dq, 1 H, *J* = 7.2, 3.6 Hz), 2.30 (br s, 1 H), 1.62 (d, 3 H, *J* = 7.2 Hz), 1.21 (d, 3 H, *J* = 7.2 Hz); ^{13}C NMR (75.47 MHz) δ 71.21, 58.25, 20.44, 18.95; IR (neat) 3364, 2982, 2932 cm^{-1}; mass spectrum (25 eV), *m*/*z* 154 (13, M$^+$), 152 (25, M$^+$ and M$^+$ − 2), 150 (13, M$^+$ − 2), 134 (14), 135 (12), 109 (4), 107 (4), 55 (100).

(2*S*,3*S*)-1,4-Dimethoxy-2,3-butanediol Cyclic Ethyl Orthoester. (2*S*,3*S*)-1,4-Dihydroxy-2,3-butanediol 2,3-cyclic ethyl orthoester[15] (11.55 g, 64.9 mmol) was dissolved in dry THF (30 mL) and added to a stirred suspension of NaH (3.89 g, 162.2 mmol) in THF (200 mL) at 0 °C. The mixture was stirred at room temperature for 0.5 h before being cooled to 0 °C and treated with iodomethane (10.17 mL, 162.2 mmol). The reaction was allowed to proceed at room temperature for 1 h and then at 65 °C for 8 h. After cooling, the reaction mixture was treated with saturated NH_4Cl (70 mL) and the aqueous phase extracted with ether (4 × 30 mL). The combined organic solution was washed with saturated NaCl (1 × 40 mL) and dried over $MgSO_4$. Evaporation and purification by flash column chromatography (silica, 1:1 hexane/ether) afforded the desired orthoester (11.20 g, 84%) as a clear oil: $[\alpha]^{25}_D$ = −17.4° (*c* = 4.15, $CHCl_3$); ^{1}H NMR (300 MHz) δ 5.85 (s, 1 H), 4.16–4.12 (m, 1 H), 4.05 (q, *J* = 6.3 Hz, 1 H), 3.65–3.46 (m, 6 H), 3.39 (s, 6 H), 1.21 (t, *J* = 7.5 Hz, 3 H); ^{13}C NMR (75.47 MHz) δ 115.80 (d), 77.02 (d), 76.81 (d), 74.03 (t), 72.63 (t), 60.51 (t), 59.48 (q), 59.44 (q), 15.12 (q); IR (neat) 2980, 2930, 2870, 1454, 1376, 1197, 1136, 1069 cm^{-1}; mass spectrum, *m*/*z* 206 (M$^+$, 3), 205 (18), 161 (80), 115 (55), 119 (100).

(2*S*,3*R*)-1,4-Dimethoxy-3-chloro-2-butanol (6). To a cooled (0 °C) solution of (2*S*,3*S*)-1,4-dimethoxy-2,3-butanediol cyclic ethyl orthoester (11.19 g, 54.3 mmol) in dry CH_2Cl_2 (250 mL) was added PCl_5 (14.7 g, 70.6 mmol). The reaction mixture was allowed to warm to room temperature and stirred for an additional 8 h. After cooling to 0 °C, the reaction was quenched with saturated aqueous $NaHCO_3$ (250 mL) and stirred for 3 h. The organic layer was removed and the remaining aqueous solution further extracted with CH_2Cl_2 (2 × 40 mL). The combined organic extracts were washed with H_2O (1 × 40 mL), dried over $MgSO_4$, and concentrated to give the desired chloroformate (9.91 g, 93%) in sufficiently pure form for the next step. This material was dissolved in methanol (100 mL), and the resulting solution was cooled to 0 °C. Concentrated HCl (2 mL), dissolved in MeOH (10 mL), was added, and the resulting solution was warmed to 50 °C for 1 h. The reaction solution was cooled to room temperature and quenched with solid $NaHCO_3$ (0.5 g). Solvent was removed under high vacuum to give an oil, to which was added H_2O (10 mL). The resulting solution was extracted with ether (5 × 30 mL), and the extracts were dried ($MgSO_4$) and concentrated to give **6** (7.47 g, 78%) as an oil. Further purification of **6** could be accomplished by Kugelrohr distillation at reduced pressure: $[\alpha]^{25}_D$ = −0.7° (*c*

(21) (a) Mason, S. F.; Gottarelli, G.; Torre, G. *J. Chem. Soc. B* **1970**, 1349. The reported optical rotation of (*R*)-(+)-*trans*-stilbene oxide is $[\alpha]_D$ = 365°. An optical rotation of $[\alpha]_D$ = 354° was obtained for a sample of *trans*-stilbene oxide obtained from the (−)-chlorohydrin ($[\alpha]_D$ = −4.4°, $CHCl_3$) derived from (+)-chloromandelate ($[\alpha]_D$ = 21.4°, $CHCl_3$). (b) Material obtained from the Sharpless approach was, within the levels of detection, enantiomerically pure by the analysis presented above.

(22) Jacobsen, E. N.; Markó, I.; Mungall, W. S.; Schröder, G.; Sharpless, K. B. *J. Am. Chem. Soc.* **1988**, *110*, 1968–70.

(23) Replacing PBr_5 for PCl_5 in this sequence of steps results in the efficient synthesis of the corresponding β-haloformate. However, we were once again unable to hydrolyze the ester functionality without concomitant benzyl halide solvolysis.

(24) (a) Recently Sharpless has introduced the use of vicinal diol cyclic sulfates as a method for performing the same type of transformation as depicted herein. See: Gao, Y.; Sharpless, K. B. *J. Am. Chem. Soc.* **1988**, *110*, 7538–9. (b) See also: Joshi, N. N.; Srebnik, M.; Brown, H. C. *J. Am. Chem. Soc.* **1988**, *110*, 6246–8.

= 4.19, $CHCl_3$), 2.3° (c = 2.10, MeOH); ^1H NMR (300 MHz) δ 4.08–4.03 (m, 1 H), 3.98–3.91 (m, 1 H), 3.76 (d, J = 4.8 Hz, 2 H), 3.60 (d, J = 4.5 Hz, 2 H), 3.42 (s, 3 H), 3.40 (s, 3 H); ^{13}C NMR (75.47 MHz) δ 73.93 (t), 73.25 (t), 71.71 (d), 59.36 (q), 59.31 (q), 59.16 (d); IR (neat) 3442, 2986, 2982, 2896, 2829, 1456, 1194, 1123, 450 cm^{-1}; mass spectrum, m/z 171 (M^+ + 1, 20), 169 (M^+ + 1, 59), 139 (23), 137 (66), 125 (19), 123 (57), 115 (42), 105 (44), 88 (100). Anal. Calcd for $C_6H_{13}O_3Cl$: C, 42.74; H, 7.77. Found: C, 42.84; H, 7.82.

(2S,3R)-1,4-Bis(benzyloxy)-3-chloro-2-butanol (7). (2S,3R)-1,4-Bis(benzyloxy)-3-chloro-2-butanol formate[15] (0.725 g, 2.0 mmol) was treated with HCl/MeOH as described above to afford **7** (0.625 mg, 93%) as a clear oil: $[\alpha]^{25}_D$ = −2.2 (c = 9.0, $CHCl_3$); ^1H NMR (300 MHz) δ 7.34 (s, 10 H), 4.59 (d, 4 H, J = 10 Hz), 4.16 (m, 1 H), 4.04 (m, 1 H), 3.85 (m, 2 H), 3.71 (m, 2 H), 2.92 (br d, 1 H); ^{13}C NMR (75.47 MHz) δ 137.81, 137.70, 128.57, 127.97, 127.82, 73.58, 71.88, 71.35, 70.90, 59.57; IR (neat) 3445, 2867, 1667, 1112 cm^{-1}. Anal. Calcd for $C_{18}H_{21}O_3Cl$: C, 67.39; H, 6.60. Found: C, 67.17; H, 6.65. Confirmation of the absolute configuration of **7** was obtained by conversion to the corresponding epoxide by treatment with base. The epoxide obtained was identical, except for the sign of rotation, with that described by Nicolaou.[15]

(±)-*erythro*-2-Chloro-1,2-diphenylethanol (9). To a solution of pyridine hydrochloride (5.92 g, 51 mmol) in $CHCl_3$ (51 mL) at room temperature was added *trans*-stilbene oxide (5.01 g, 25.5 mmol). The mixture was heated to reflux for 9 h, cooled to ambient temperature, and poured into ice water (100 mL). The organic layer was dried (Na_2SO_4) and concentrated to yield 5.30 g (90%) of a pale yellow oil. The oil was shown to be a mixture of erythro and threo isomers of the desired β-chlorohydrin by direct integration of the ^1H NMR resonances of the corresponding epoxides.[21]

Separation of the isomers was effected by medium-pressure liquid chromatography (MPLC) utilizing 8% Et_2O in hexanes. The more polar erythro isomer (3.80 g) was isolated as a white solid. Recrystallization from hexanes afforded white crystals: mp 78.5–79.5 °C; ^1H NMR (300 MHz) δ 7.41–7.13 (m, 10 H), 5.04 (d, 1 H, J = 8.1 Hz), 4.97 (d, 1 H, J = 8.1 Hz), 3.17 (br s, 1 H); ^{13}C NMR (75.47 MHz) δ 139.60, 137.36, 128.82, 128.59, 128.46, 128.27, 127.20, 78.26, 67.01; IR ($CDCl_3$) 3410 cm^{-1}; mass spectrum (70 eV), m/z 217 (31, M^+ − 17), 215 (100), 197 (25), 107 (95); HRMS (EI) calcd for $C_{14}H_{13}OCl$ 232.0655, found 232.0646 (M).

Diastereomeric Esters of *erythro*-2-Chloro-1,2-diphenylethanol and (*S*)-*O*-Methylmandelic Acid. To a solution of erythro chlorohydrin **9** (3.80 g, 16.4 mmol), (S)-O-methylmandelic acid (2.48 g, 14.9 mmol), and 4-(dimethylamino)pyridine (DMAP, 0.20 g) in CH_2Cl_2 (40 mL) at 0 °C was added dropwise a solution of 1,3-dicyclohexylcarbodiimide (DCC, 5.0 g, 24.3 mmol) in CH_2Cl_2 (20 mL). A precipitate appeared upon completion of the DCC addition. The solution was allowed to warm to ambient temperature, and stirring was maintained for 24 h. Vacuum filtration of the precipitate was followed by successive washes of the filtrate of 50 mL each of 10% HCl, H_2O, saturated Na_2CO_3 solution, and brine. The organic solution was dried ($MgSO_4$) and concentrated to yield 6.0 g of oil.

The ester diastereomers were separated by MPLC by utilizing 5% Et_2O in hexanes. The less polar diastereomer, which was later shown to be the mandelate ester of (1S,2R)-2-chloro-1,2-diphenylethanol,[21] was further purified via recrystallization from 2% aqueous methanol at −33 °C. This compound was obtained as a poorly defined white precipitate (2.45 g, 82%), which became an oil upon standing at room temperature. The mandelate ester of the 1R,2S isomer was obtained as a white crystalline solid. Hexane recrystallization afforded 2.6 g of this material (88%). Mandelate ester of (1S,2R)-2-chloro-1,2-diphenylethanol: $[\alpha]^{25}_D$ = +15.8° (c = 2.7, $CHCl_3$); ^1H NMR (300 MHz) δ 7.35–7.02 (m, 15 H), 6.24 (d, 1 H, J = 6.9 Hz), 5.01 (d, 1 H, J = 6.9 Hz); ^{13}C NMR (75.47 MHz) δ 169.25, 136.71, 136.33, 135.74, 128.84, 128.66, 128.25, 127.66, 127.25, 82.67, 78.50, 63.84, 57.44; IR ($CDCl_3$) 1755 cm^{-1}. Mandelate ester of (1R,2S)-2-chloro-1,2-diphenylethanol: mp 84–85 °C; $[\alpha]^{25}_D$ = +21.4° (c = 2.1, $CHCl_3$); ^1H NMR (300 MHz) δ 7.35–7.13 (m, 13 H), 6.98 (br s, 1 H), 6.96 (t, 1 H, J = 1.2 Hz), 6.18 (d, 1 H, J = 6.9 Hz), 5.08 (d, 1 H, J = 6.9 Hz), 4.67 (s, 1 H), 3.26 (s, 3 H); ^{13}C NMR (75.47 MHz) δ 169.06, 136.97, 136.73, 128.78, 128.71, 128.65, 128.61, 128.38, 128.34, 128.07, 127.43, 127.28, 82.51, 78.67, 64.03, 57.49; IR ($CDCl_3$) 1755 cm^{-1}.

(1R,2S)- and (1S,2R)-2-Chloro-1,2-diphenylethanol (10 and 11). To the above isomer melting at 84–85 °C (0.42 g, 1.1 mmol) in anhydrous ethanol (10 mL) was added $Ti(i\text{-}OPr)_4$ (30 mg, 10 mol %). The resulting solution was refluxed for 8 h, cooled to 0 °C, quenched with 10% HCl solution (5.0 mL), and after 10 min, diluted further with water (10 mL). The aqueous solution was extracted with $CHCl_3$ (3 × 25 mL), dried ($MgSO_4$), and concentrated to give 0.43 g of crude oil.

Separation of ethyl mandelate from the desired β-chloro alcohol was accomplished via flash chromatography on silica gel utilizing 6% ether in hexanes. Ethyl mandelate was recovered in 88% yield. The more polar β-chloro ethanol, which is identified as (1R,2S)-2-chloro-1,2-diphenylethanol (**10**) by the procedure below, was obtained in 78% yield after recrystallization from hexanes: mp 80–81 °C; $[\alpha]^{25}_D$ = −4.4° (c = 2.4, $CHCl_3$).

Confirmation of absolute configuration and optical purity was determined by conversion of the β-halohydrin to stilbene oxide by treatment with base. The epoxide obtained was determined to be (R)-stilbene oxide, $[\alpha]^{25}_D$ = 354°, corresponding to an enantiomeric excess of 96%.

The other mandelate ester was treated with $Ti(i\text{-}OPr)_4$ in absolute ethanol as described above, affording a 75% yield of (1S,2R)-2-chloro-1,2-diphenylethanol (**11**) of 95% enantiomeric excess: mp 79.5–81 °C; $[\alpha]^{25}_D$ = 4.3° (c = 2.2, $CHCl_3$).

Mixed Ethyl Orthoester of (*R*,*R*)-Hydrobenzoin. Triethyl orthoformate (20.8 mL, 125 mmol) and glacial acetic acid (0.05 mL) were added to a solution of (R,R)-hydrobenzoin[22] (10.0 g, 45.7 mmol) dissolved in 50 mL of toluene. The reaction mixture was heated, and the ethanol/toluene azeotrope (76 °C) was removed via distillation, which was continued until the distillate temperature reached the boiling point of toluene (110 °C). Analysis by TLC showed no starting material present. The solution was cooled to room temperature and was neutralized with saturated aqueous NH_4OH. The organic layer was collected, dried (Na_2SO_4), and concentrated to afford 12.5 g of slightly yellow liquid, which was employed in the next step without further purification: ^1H NMR (300 MHz) δ 7.40–7.25 (m, 10 H), 6.21 (s, 1 H), 5.01 (d, 1 H, J = 7.2 Hz), 4.82 (d, 1 H, J = 7.2 Hz), 3.82 (q, 2 H, J = 7.2 Hz), 1.36 (t, 3 H, J = 7.2 Hz); ^{13}C NMR (75.47 MHz) δ 137.11, 136.36, 128.61, 128.50, 127.05, 126.76, 115.63, 86.52, 83.85, 60.75, 15.30; mass spectrum (CI, isobutane), m/z 271 (1, M^+ + 1), 225 (63), 197 (100).

(1R,2S)-2-Chloro-1,2-diphenylethanol Formate. The mixed ethyl orthoester of (R,R)-hydrobenzoin (12.5 g, 46.3 mmol) was treated with PCl_5 as described above for the synthesis of **6** to afford a light yellow solid (10.8 g, 90%). Recrystallization from hexanes afforded white crystals: mp 102.5–103.5 °C; $[\alpha]^{25}_D$ = −15.6° (c = 2.1, $CHCl_3$); ^1H NMR (300 MHz) δ 7.94 (s, 1 H), 7.34–7.12 (m, 10 H), 6.27 (d, 1 H, J = 7.2 Hz), 5.15 (d, 1 H, J = 7.2 Hz); ^{13}C NMR (75.47 MHz) δ 159.31, 136.87, 135.97, 129.02, 128.54, 128.37, 127.88, 127.04, 77.74, 63.82; IR ($CDCl_3$) 1730 cm^{-1}; mass spectrum (70 eV), m/z 262, 260 (1, M^+), 178 (8), 135 (100), 107 (83); HRMS (EI) calcd for $C_{15}H_{13}O_2Cl$ 260.0604, found 260.0616 (M).

(1R,2S)- and (1S,2R)-2-Chloro-1,2-diphenylethanol (10 and 11). (a) (1R,2S)-2-Chloro-1,2-diphenylethyl chloroformate (0.42 g, 1.1 mmol) was treated with $Ti(i\text{-}OPr)_4$ as described in the previous synthesis of **10** to give 0.43 g of crude oil. Flash chromatography on silica gel, utilizing 6% ether in hexanes, afforded (1R,2S)-2-chloro-1,2-diphenylethanol (**10**) in 85% isolated yield: mp 80–81 °C; $[\alpha]^{25}_D$ = 23.6° (c = 3.4, ethanol), $[\alpha]^{25}_D$ = −4.5° (c = 2.2, $CHCl_3$), $[\alpha]^{25}_D$ = −3.8° (c = 3.4, benzene). Anal. Calcd for $C_{14}H_{13}OCl$: C, 72.25; H, 5.63. Found: C, 72.35; H, 5.67. This material was shown to be >99% enantiomerically pure by conversion to stilbene oxide upon treatment with base. The epoxide obtained was determined to be (R)-stilbene oxide ($[\alpha]^{25}_D$ = 364° (c = 0.5, benzene)).

(b) (1S,2R)-2-Chloro-1,2-diphenylethanol formate (3.08 g, 11.8 mmol) (prepared as described above from (S,S)-hydrobenzoin[22]) was treated with HCl/MeOH as described above for the synthesis of **6** to afford 2.74 g of solid material. Recrystallization from hexanes afforded 2.3 g (83%) of **11** as white needles: mp 84.5–85.5 °C; $[\alpha]^{25}_D$ = −24.1° (c = 3.4, ethanol).

Acknowledgment. Research support by the UC Santa Cruz Committee on Research and the American Cancer

Society is gratefully acknowledged. We also thank Professor D. S. Matteson (Washington State University) for his generous gift of diol 4 prior to publication of the paper on its preparation, and Clark Eid for characterization of 6.

Supplementary Material Available: ^{13}C NMR spectra of 5, 11, the *O*-methylmandelate ester of 10, and (2*S*,3*S*)-1,4-dimethoxy-2,3-butanediol cyclic ethyl orthoester (4 pages). Ordering information is given on any current masthead page.

Alkylation and Rearrangement of Lithiated 3-Methyl-1,2-benzisoxazoles

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Received April 17, 1989

Setal exudates of lace bugs of the genus *Stephanitis* contain acetogenins that can be considered derivatives of 2,6-dihydroxyacetophenone elaborated, often with a 10-carbon unit, at the 2′-position.[1a,b] While considering synthetic pathways to certain of these compounds, including 2,6-dihydroxyalkanophenones, we became curious about possible reactions of deprotonated 3-methyl-1,2-benzisoxazoles with electrophiles. Their monocyclic counterparts, 3,5-dialkylisoxazoles, have been widely used as protected 1,3-dicarbonyl compounds.[2a-d] 3,5-Dimethylisoxazole, for example, can be selectively deprotonated at the 5-methyl group; after reaction with an appropriate electrophile, the functionalized isoxazole can be disassembled by reductive cleavage of the N–O bond. The resulting enamino ketone can be employed as such, or hydrolyzed to an elaborated 1,3-dicarbonyl compound.[2a-d] Similar reduction and hydrolysis of a 3-alkyl-1,2-benzisoxazole can be expected to provide an *o*-hydroxyalkanophenone.[2e]

The 3-position of a 1,2-benzisoxazole is analogous to the 3- and not the 5-position of an isoxazole. However, Brunelle[3] has reported that although 3,5-dimethylisoxazole was indeed first deprotonated and alkylated at the 5-methyl group, further reaction with *sec*-butyllithium followed by R–X led to alkylation at the 3-methyl group, whereby 3,5-dialkylisoxazoles could be obtained. Indeed, we found that if deprotonation of 3-methyl-1,2-benzisoxazole (**1a**) was effected with lithium diisopropylamide (LDA) at −75 °C *in the presence of* 1-bromodecane, a satisfactory (52%) yield of 3-undecyl-1,2-benzisoxazole (**1c**) could be obtained. Similarly, the 5-TBDMS ether **1d** was obtained (>70%) from **1b**.

In contrast to the considerable literature on isoxazole deprotonations, we found only one report of attempted deprotonation of 3-methyl-1,2-benzisoxazole (**1a**). Ranganathan et al.[4] treated **1a** with lithium dibutylamide at 0 °C and later added styrene. The only product isolated was a yellow solid (5%), mw 264, to which they assigned structure **2**; they did not comment on the mechanism or oxidation state change but suggested that the formation of this product established that deprotonation had occurred. Consistent with these results, we found that *sequential* treatment of **1a**[5] with *sec*-butyllithium (or LDA) and 1-bromodecane at −75 °C gave products resulting from a self-condensation of **1a** and little or no consumption of alkyl bromide. Flash chromatography afforded two yellow solids, **3a** and **4a**. The molecular weight (264) and melting point (218–219 °C) of **4a** indicated that it was probably the yellow solid described by Ranganathan et al.[4]

It soon became apparent that solutions of **3a** were unstable and that **3a** was rather rapidly converted to **4a**.[6] Aged solutions of **3a**, or even freshly prepared **3a** slowly desorbed from the probe, gave mass spectra identical with those of **4a** (mw 264). Rapidly desorbed **3a**, however, provided satisfactory spectra of a different compound whose molecular weight was 266. Molecular ions constituted the most abundant ions in the electron impact mass spectra (EIMS) of both **3a** and **4a**, both, but especially that of 4a, being surprisingly free of fragment ions. Chemical ionization mass spectra (CIMS) confirmed the molecular weights, and ammonia/deuterioammonia CI comparisons established three and two exchangeable hydrogens for **3a** and **4a**, respectively. These results indicated that **3a** was an easily oxidizable dihydro derivative of **4a**.

The chemical stability of **4a** paralleled its resistance to fragmentation. It was poorly soluble in nonpolar solvents and was stable to KOH in refluxing aqueous methanol and to H_2SO_4 in refluxing aqueous acetic acid. With Ac_2O/pyridine, **4a** gave a colorless diacetate **4c**; in contrast, **3a** was not cleanly acetylated, giving a mixture from which only **4c** was identified. In the presence of excess CH_2N_2 (3 h, room temperature) **4a** gave a red solution from which the monomethyl ether **4d** was the major product.

The TBDMS ether **1b** of 4-hydroxy-3-methyl-1,2-benzisoxazole[7] behaved in a somewhat similar fashion to **1a**, but in this case the initial dihydro analogue **3b** was more stable toward air oxidation than **3a** had been. Either silver oxide or activated manganese dioxide converted **3b** to **4b**; the latter reaction was rapid and preferred, since Ag_2O tended to promote some scrambling of the TBDMS groups.

Selected ^1H NMR spectral data for **4a**, **4b**, and several derivatives are included in Table I and the Experimental Section. Noteworthy features are the absence of either methyl or methylene absorptions, and two different phenolic O–H's for both **4a** and **4b** (best observed with C_5D_5N as solvent). Also evident in each spectrum is a pair of deshielded doublets (J = 1.8–2.1) coupled only to each other. The collective data suggest a six-membered heteroaromatic ring containing two nitrogens and substituted with two nonidentical hydrogens and two *o*-hydroxyaryl groups, which are also in nonidentical environments. Of the possibilities, it is seen that one of the possible pyri-

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(1) (a) Oliver, J. E.; Neal, J. W., Jr.; Lusby, W. R.; Aldrich, J. R.; Kochansky, J. P. *J. Chem. Ecol.* **1985**, *11*, 1223. (b) Oliver, J. E.; Neal, J. W., Jr.; Lusby, W. R. *Ibid.* **1987**, *13*, 763.

(2) (a) Kashima, C.; Yamamoto, Y.; Tsuda, Y. *Heterocycles* **1977**, *6*, 805. (b) Baraldi, P. G.; Barco, A.; Benetti, S.; Pollini, G. P.; Simoni, D. *Synthesis* **1987**, 857. (c) Wakefield, B. J.; Wright, D. J. *Adv. Heterocycl. Chem.* **1979**, *25*, 148 (d) Kochetkov, N. K.; Sokolov, S. D. *Adv. Heterocycl. Chem.* **1963**, *2*. (e) Smalley, R. K. *Adv. Heterocycl. Chem.* **1981**, *29*, 1.

(3) Brunelle, D. J. *Tetrahedron Lett.* **1981**, *22*, 3699.

(4) Ranganathan, S.; Ranganathan, P. V.; Ramachandran, P. V.; Mahanty, M. K.; Bamezai, S. *Tetrahedron* **1981**, *24*, 4171.

(5) Thakar, K. A.; Goswami, D. D.; Bhawal, B. M. *Ind. J. Chem.* **1977**, *15B*, 1058.

(6) The **3a** → **4a** transformation also occurred in the solid state, but much more slowly (substantial quantities of **3a** remained after 2–3 months). The infrared spectral data reported by Ranganathan et al. contained bands from both **3a** and **4a**, and it is likely that they were working with a mixture of the two.

(7) Crabbe, P.; Villarino, A.; Muchowski, J. M. *J. Chem. Soc., Perkin Trans. 1* **1973**, 2220.