CH_3O), 28688-23-5; I (R_1 = Cl, R_2 = R_3 = H), 28688-27-9; I (R_1 = R_3 = H, R_2 = Cl), 23586-58-5; II (R_1 = R_2 = R_3 = H), 122-57-6; II (R_1 = R_3 = H, R_2 = CH_3), 3160-38-1; II (R_1 = R_2 = R_3 = CH_3), 53389-56-3; II (R_1 = CH_3O, R_2 = R_3 = H), 10542-87-7; II (R_1 = R_3 = H, R_2 = CH_3O), 943-88-4; II (R_1 = Cl, R_2 = R_3 = H), 20766-37-4; II (R_1 = R_3 = H, R_2 = Cl), 3160-40-5; H_2C=CHCO-CH_3, 78-94-4; Li_2PdCl_4, 15525-45-8.

Asymmetric Epoxidation of Allyl Alcohol: Efficient Routes to Homochiral β-Adrenergic Blocking Agents

Janice M. Klunder, Soo Y. Ko, and K. Barry Sharpless*

Department of Chemistry, Massachusetts Institute of Technology, Cambridge, Massachusetts 02139

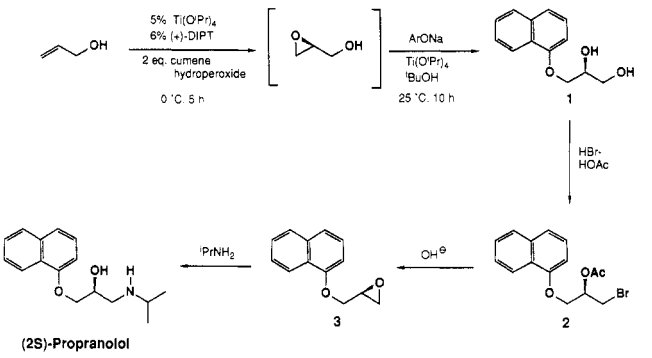
Received April 15, 1986

Since the discovery of the titanium-catalyzed asymmetric epoxidation of allylic alcohols in 1980,[1] ongoing efforts in these laboratories have been directed toward expanding the scope and synthetic utility of the reaction. A serious limitation of the original procedure has been its failure when applied to substrates with a strong propensity for undergoing ring-opening reactions. Of the many reaction modifications which have been explored, the recent development of an effective catalytic procedure[2] has offered the most general solution to this important problem and has allowed even allyl alcohol to be included for the first time on the roster of successful substrates. Although a full description of this new development will be reported shortly, the practical importance of homochiral glycidol in the synthesis of β-adrenergic blocking agents (β-blockers) prompts us to disclose here two very efficient routes to (2*S*)-propranolol, each utilizing the asymmetric epoxidation of allyl alcohol.[3-5]

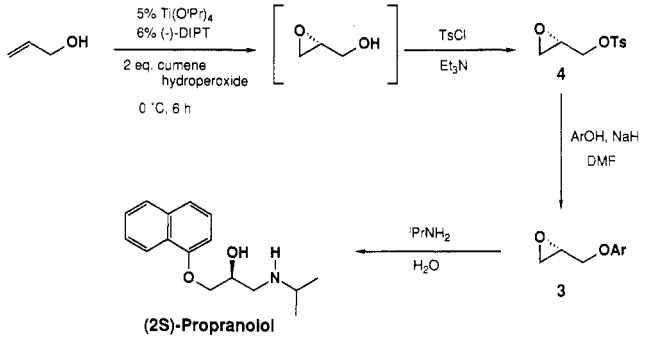
A common strategy used in the two procedures is the in situ derivatization of glycidol: after completion of the asymmetric epoxidation reaction, the unstable glycidol is derivatized rather than isolated directly from the reaction mixture. These derivatives are not only easier to handle, but are also more advanced synthetic intermediates than is the parent glycidol.

In the first procedure, glycidol is opened in situ by 1-naphthoxide (Scheme I). Thus, after asymmetric epoxidation is complete, the excess hydroperoxide is reduced with trimethyl phosphite, and the reaction mixture is treated with sodium 1-naphthoxide in *tert*-butyl alcohol in the presence of 1 equiv $Ti(O\text{-}i\text{-}Pr)_4$.[6] The opening

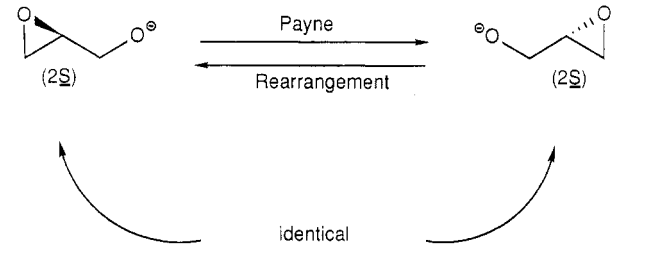
Scheme I



Scheme II



Scheme III



product, diol **1**, is then converted to the epoxide **3** by a known procedure.[7] Ring opening of **3** with isopropylamine gives (2*S*)-propranolol. Recrystallization of the hydrochloride salt yields enantiomerically pure (2*S*)-(−)-propranolol hydrochloride in 48% overall yield from allyl alcohol.

In the alternative procedure (Scheme II), catalytic asymmetric epoxidation of allyl alcohol is followed, again after reduction of excess hydroperoxide with trimethyl phosphite, by in situ tosylation of the intermediate glycidol. The isolated glycidyl tosylate (**4**) is crystalline, of high (≥90%) enantiomeric purity, and indefinitely stable to handling and storage at room temperature. A convenient, one-pot procedure is then employed to convert (2*S*)-glycidyl tosylate into the β-blocker (2*S*)-propranolol. Thus, treatment of **4** with sodium 1-naphthoxide in DMF results in selective displacement of the tosylate moiety to afford epoxy ether **3**. Epoxide opening is effected by refluxing the entire reaction mixture with isopropylamine and water to give (2*S*)-propranolol. Recrystallization of the hydrochloride salt as above provides (2*S*)-(−)-propranolol hydrochloride in 70% yield from **4**.

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(2) (a) Hanson, R. M.; Sharpless, K. B. *J. Org. Chem.* **1985**, *51*, 1922. (b) Hanson, R. M.; Ko, S. Y.; Gao, Y.; Masamune, H.; Klunder, J. M.; Sharpless, K. B., submitted for publication.

(3) For previously reported preparations of (2*S*)-propranolol and related compounds by nonenzymatic asymmetric synthesis, see: (a) Miyano, S.; Lu, L. D.-L.; Viti, S. M.; Sharpless, K. B. *J. Org. Chem.* **1985**, *50*, 4350. (b) Katsuki, T. *Tetrahedron Lett.* **1984**, *25*, 2821. (c) Bäckvall, J. E.; Björkman, E. E.; Byström, S. E. *Tetrahedron Lett.* **1982**, *23*, 943.

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(5) Numerous preparations of homochiral β-blockers which rely on the elaboration of chiral building blocks derived from D-mannitol have been reported. For examples, see: (a) Jurczak, J.; Pikul, S.; Bauer, T. *Tetrahedron* **1986**, *42*, 447 and references cited therein. (b) Bouzoubaa, M.; Leclerc, G.; Rakhit, S.; Andermann, G. *J. Med. Chem.* **1985**, *28*, 896. (c) Nakano, J.; Mimura, M.; Hayashida, M.; Kimura, K.; Nakanishi, T. *Heterocycles* **1983**, *20*, 1975.

(6) The additional $Ti(O\text{-}i\text{-}Pr)_4$ is required to mediate the opening of the glycidol by the aryloxide, see: Caron, M.; Sharpless, K. B. *J. Org. Chem.* **1985**, *50*, 1557.

(7) (a) Golding, B. T.; Hall, D. R.; Sakrikar, S. *J. Chem. Soc., Perkin Trans. 1* **1973**, 1214. (b) Ellis, M. K.; Golding, B. T. *Org. Synth.* **1984**, *63*, 140.

0022-3263/86/1951-3710$01.50/0

Although the two procedures appear very similar, there are significant differences which bear mention. The in situ opening reaction (Scheme I) takes place at the C-3 center of glycidol, while reaction of glycidyl tosylate with sodium naphthoxide (Scheme II) occurs highly selectively at C-1.[8] Therefore, while L-(+)-diisopropyl tartrate (DIPT) produces the active 2S enantiomer of propranolol in Scheme I, D-(−)-DIPT is used in Scheme II to produce the same enantiomer.

Both glycidol and glycidyl tosylate possess two potential sites of electrophilic reactivity, the latent reactivity of the carbinol carbon of glycidol being revealed by Payne rearrangement (Scheme III). It is important to recognize, however, that due to felicitous symmetry properties, *this rearrangement does not change the absolute configuration of the glycidol molecule.* Full retention of stereochemical integrity in any ring-opening process involving glycidol (including that depicted in Scheme I) is thus ensured. In reactions of glycidyl tosylate, on the other hand, competitive C-3 epoxide opening, followed by internal tosylate displacement, affords a product of opposite configuration from that produced by direct tosylate displacement. Fortunately, the selectivity of the reaction depicted in Scheme II is quite high (97:3),[8a] and the slight deterioration of enantiomeric excess has not proved troublesome in the preparation of propranolol, for which optical purity is readily increased by recrystallization. The use of homochiral epichlorohydrin or glycidyl mesylate in this reaction sequence should be avoided, since a substantial loss in optical purity is expected to result from their lower selectivities in aryloxide displacements.[8b]

The two synthetic schemes presented here are generally applicable to other β-blockers of similar structure, by choosing appropriate aromatic alcohols and amines as the nucleophiles. The 2R enantiomers of the β-blockers, the clinical effects of which have attracted attention recently,[9] are also as easily accessible by simply using the opposite tartrate enantiomer at the asymmetric epoxidation step. We feel that the two procedures described here are of complementary synthetic utility and that each will find application in the preparation of β-blockers and related compounds. The approach outlined in Scheme II suffers from the moderate yields of glycidyl tosylate obtained thus far. When a large quantity of a single compound is desired, therefore, the route of choice will probably be that outlined in Scheme I. On the other hand, the convenience and flexibility of the one-pot procedure in Scheme II, as well as the ready availability of the stable intermediate **4** of high enantiomeric excess, render the glycidyl tosylate approach particularly suited for the preparation of lesser quantities of several analogues.

Experimental Section

General. Molecular sieves (3 Å, Aldrich Chemical Co.) were activated by heating in a vacuum oven at 160 °C and 0.05 mmHg for at least 8 h. Diisopropyl tartrate [76 °C (0.1 mm)] and titanium(IV) isopropoxide [72–73 °C (0.8 mm)] (Aldrich) were distilled under vacuum and were stored under an inert atmosphere. Allyl alcohol and cumene hydroperoxide (technical grade, 80%, Aldrich) were dried prior to use over 3-Å molecular sieves (pellet form), but otherwise used as received. Dichloromethane (EM Reagent) was not distilled but was also dried over 3-Å molecular sieves (pellet form). 1-Naphthol (Aldrich) was sublimed prior to use.

Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. GC analysis was performed with a Perkin-Elmer 3920 gas chromatograph equipped with a Carbowax 20 M capillary column. IR spectra were recorded on a Perkin-Elmer 597 spectrophotometer. ^{1}H NMR spectra were recorded on a Bruker WM-250 (250 MHz) spectrometer with tetramethylsilane or deuterated solvents as internal standards. Optical rotations were measured on a Perkin-Elmer 241 polarimeter, using a 1-cm^3 capacity (1-dm path length) quartz cell. Microanalyses were performed by Robertson Laboratory, Florham Park, NJ.

Synthesis of (2*S*)-Propranolol via in Situ Opening Procedure. An oven-dried 500-mL three-necked round-bottomed flask fitted with septum and stir-bar was charged with 3-Å molecular sieves (3.5 g, powder form) and dichloromethane (190 mL). Under a nitrogen atmosphere, L-(+)-diisopropyl tartrate (1.25 mL, 1.39 g, 5.95 mmol) and allyl alcohol (6.8 mL, 5.81 g, 0.1 mol) were added, and the solution was cooled to −5 °C. Titanium(IV) isopropoxide (1.5 mL, 1.4 g, 5.0 mmol) was added, and the mixture was stirred at −5 °C for 10–30 min. Cumene hydroperoxide (36 mL, ca. 0.2 mol) was added slowly over a period of 30 min. The mixture was stirred under nitrogen at −3 to 0 °C until GC analysis indicated >95% reaction (5 h).[10]

The reaction mixture was cooled to −25 ± 5 °C and $(MeO)_3P$ (16 mL, 16.8 g, 0.135 mol) was added over a period of 30 min. The mixture was warmed to room temperature and then poured into a 1-L three-necked flask containing a ArO^-Na^+ solution [prepared from 1-naphthol (14.5 g, 0.10 mol) and NaH (oil free, 2.4 g, 0.10 mol) in *t*-BuOH (400 mL, dried over 3-Å powdered sieves) under nitrogen] and a stir bar. Titanium(IV) isopropoxide (36 mL, 34.4 g, 0.12 mol) was added, and the mixture was stirred overnight at 25 °C under nitrogen.

The reaction mixture was filtered through a pad of Celite and the pad washed with EtOAc (300 mL). The filtrate was concentrated to ca. $^1/_4$ of its volume, 10% H_2SO_4 (200 mL) was added, and the mixture was stirred vigorously for 1 h. Phase separation, extraction (Et_2O), and concentration at 60 °C (first at 5–10 mm and then at 0.5 mm) were followed by hydrolysis of the tartrate ester (150 mL of ether and 100 mL of 1 N NaOH, stirred for 45 min at room temperature). The phases were separated, the aqueous layer was extracted with portions of ether, the combined ether layers were washed with saturated NH_4Cl and brine, dried (Na_2SO_4), and concentrated to provide crude (2*S*)-3-(1-naphthoxy)-1,2-propanediol (**1**). This diol could be purified by recrystallization (CCl_4) but was generally used directly in the next step.

The crude diol **1** was dissolved in 30% HBr–AcOH (Aldrich, 110 mL) at 0 °C, and then the solution was stirred at 35 ± 5 °C (water bath) for 30 min. It was diluted with cold water (250 mL), and the aqueous solution was extracted with portions of ether. The combined organic phases were washed with 1 N NaOH (until the aqueous phase became neutral) and then concentrated to yield crude bromoacetate **2**.

This was dissolved in methanol (100 mL) and 3 N NaOH in methanol (40 mL, 0.12 mol OH^-) was added at 0 °C. After being stirred for 10 min at that temperature, the mixture was diluted with ether (500 mL) and washed with water. Drying (Na_2SO_4) and concentration afforded crude (2*S*)-3-(1-naphthyloxy)-1,2-epoxypropane (**3**), which was dissolved in isopropylamine (100 mL). Water (5 mL) was added and the solution heated to reflux for 2.5 h and then concentrated to give crude (2*S*)-propranolol as a solid, which was then dissolved in ether and treated with gaseous HCl to afford a white solid (21.63 g, 73.2% from allyl alcohol). This solid was recrystallized from methanol–ether to afford 15.00 g of (2*S*)-propranolol hydrochloride (50.8%). A second recrystallization from methanol–ether provided white crystals of (2*S*)-propranolol hydrochloride 14.18 g (48%): mp

(8) (a) Detailed investigations of the selectivity of these reactions will be reported at a later date. (b) McClure, D. E.; Arison, B. H.; Baldwin, J. J. *J. Am. Chem. Soc.* **1979**, *101*, 3666.

(9) (a) Ariëns, E. J. *Eur. J. Clin. Pharmacol.* **1984**, *26*, 663. (b) Nelson, W. L.; Wennerstrom, J. E.; Sankar, S. R. *J. Org. Chem.* **1977**, *42*, 1006.

(10) The crude reaction mixture was injected directly onto the column. Retention times varied, depending on the age and condition of the column, but were on the order 1.5–2.5 min for allyl alcohol and 5.5–6.5 min for glycidol (70 °C for 4 min, rate 32 °C per min) and were determined by comparison to authentic samples. The reaction has been followed by observing the appearance of product relative to an internal standard (squalane). More generally and in the experiments reported here, the extent of conversion has been determined by measuring the ratio of product to starting material, with correction for the relative response factors.

192.5–193.5 °C; $[\alpha]^{21}_D$ –25.7° (*c* 1.18, EtOH) [lit.[4c] $[\alpha]^{21}_D$ –25.5° (*c* 1.01, EtOH)]; IR (KBr) 3340, 2980, 2800, 2535 (w), 2495 (w), 2395 (w), 1580, 1508, 1458, 1395, 1376, 1274, 1245, 1158, 1105, 1078, 1030, 1018, 994, 960, 911, 797, 776, 739 cm^{-1}; NMR (D_2O) δ 8.07 (m, 1 H), 7.70–7.75 (m, 1 H), 7.26–7.42 (m, 4 H), 6.77 (d, *J* = 7.5 Hz, 1 H), 4.18–4.27 (m, 1 H), 4.08 (dd, *J* = 4, 10.5 Hz, 1 H), 4.01 (dd, *J* = 5, 10.5 Hz, 1 H), 3.28 (quintet, *J* = 6.6 Hz, 1 H), 3.15 (dd, *J* = 4, 13 Hz, 1 H), 3.08 (dd, *J* = 8.5, 13 Hz, 1 H), 1.15 (d, *J* = 6.6 Hz, 3 H), 1. 14 (d, *J* = 6.5 Hz, 3 H).[9b] Anal. Calcd for $C_{16}H_{22}ClNO_2$: C, 64.96; H, 7.50; Cl, 11.99; N, 4.74. Found: C, 64.91; H, 7.50; Cl, 12.27; N, 4.75. A small amount of the (2*S*)-propranolol hydrochloride was treated with base (1 N NaOH–CH_2Cl_2) to regenerate the free amine, which was then protected as the benzylamine (1 equiv of BnBr, aqueous K_2CO_3–THF, reflux, 20 h). ^1H NMR analysis of the Mosher ester ((+)-MTPACl,[11] 4-DMAP, Et_3N, CH_2Cl_2) showed only one diastereomer.

Preparation of (2*S*)-Glycidyl Tosylate (4). An oven-dried 4-L three-necked flask equipped with a mechanical stirrer, low-temperature thermometer, Claisen adapter, nitrogen inlet, and rubber septum was charged with activated 3-Å powdered sieves (35 g) and 1.9 L of dichloromethane. D-(–)-Diisopropyl tartrate (14.0 g, 0.06 mol) was added via cannula as a solution in 15 mL of CH_2Cl_2, washing with an additional 10 mL of CH_2Cl_2. Allyl alcohol (68.0 mL, 58.1 g, 1.0 mol) was then added, the mixture cooled to –5 °C under nitrogen, and Ti(O-*i*-Pr)$_4$ (15.0 mL, 14.3 g, 0.05 mol) added via syringe. After the mixture was stirred for 30 min, precooled (ice bath) cumene hydroperoxide (80%, 350 mL, ca. 2 mol) was added via cannula over a period of 1 h with an internal temperature maintained at ≤–2 °C. The reaction mixture was stirred vigorously under nitrogen at –5 to 0 °C for 6 h. After the mixture was cooled to –20 °C, trimethyl phosphite was added very slowly via cannula, with the temperature not allowed to rise above –10 °C and the reduction of hydroperoxide carefully monitored [TLC in 40% EtOAc/hexane; tetramethylphenylenediamine spray indicator (1.5 g in 128:25:1 mL MeOH/H_2O/HOAc); ca. 141 mL (148.9 g, 1.2 mol) of $P(OMe)_3$ were required for complete reduction; further excess should be avoided]. The reaction is quite exothermic and addition took 1 h. Triethylamine (175 mL, 127 g, 1.26 mol) was then added, followed by addition of *p*-toluenesulfonyl chloride (200.4 g, 1.05 mol) as a solution in 250 mL of dichloromethane. The flask was stoppered and transferred to a freezer at –20 °C.

After 10 h the reaction mixture was allowed to warm gradually to room temperature and then filtered through a pad of Celite, with additional dichloromethane washing. The resultant yellow solution was washed with 10% tartaric acid, followed by saturated brine, dried ($MgSO_4$), and concentrated to afford an oil, from which volatile components (e.g., cumene, 2-phenyl-2-propanol, $P(OMe)_3$, $OP(OMe)_3$, etc.) were removed under high vacuum (ca. 0.5 mm) at 65 °C on a rotary evaporator equipped with a dry ice condenser. The residue was filtered through a short pad of silica gel (ca. 1 g per g of crude oil), by eluting with dichloromethane under nitrogen pressure. Concentration gave a lemon yellow oil (193.5 g), which was dissolved in ca. 175 mL of warm Et_2O and crystallized by addition of petroleum ether and cooling, seeding with pure material.[12] The resulting off-white solid was recrystallized twice (Et_2O–petroleum ether), by seeding each time with pure material. (2*S*)-Glycidyl tosylate[13] was obtained as large white prisms (91.7 g, 40%); mp 46–48.5 °C: $[\alpha]^{25}_D$ +17.5° (*c* 2.13, $CHCl_3$); 94% ee;[14,15] IR (KBr) 3075, 3000, 2935, 1598, 1362, 1195, 1180, 965, 915, 815, 775, 666, 558 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.81 (d, *J* = 8 Hz, 2 H), 7.36 (d, *J* = 8 Hz, 2 H), 4.26 (dd, *J* = 3, 11.4 Hz, 1 H), 3.95 (dd, *J* = 6.0, 11.4 Hz, 1 H), 3.16–3.23 (m, 1 H), 2.82 (t, *J* = 5 Hz, 1 H), 2.60 (dd, *J* = 3, 5 Hz, 1 H), 2.46 (s, 3 H). Anal. Calcd for $C_{10}H_{12}O_4S$: C, 52.62; H, 5.30. Found: C, 52.75; H, 5.29.

Preparation of (2*S*)-Propranolol from (2*S*)-Glycidyl Tosylate. In a 250-mL round-bottomed flask equipped with a rubber septum was suspended sodium hydride (oil free, 1.15 g, 0.048 mol) in DMF (40 mL, Mallinkrodt, used as received but stored over 3-Å sieves) at room temperature under a nitrogen atmosphere. 1-Naphthol (6.06 g, 0.042 mol) was added via cannula as a solution in DMF (20 mL) to produce a foamy green sludge. After 15–30 min, a solution of (2*S*)-glycidyl tosylate (94% ee, from above, 9.138 g, 0.040 mol) in DMF (20 mL) was added via cannula. A clear green-brown solution resulted.

After 4 h the reaction was judged to be complete by TLC (40% EtOAc/hexane). Isopropylamine (34 mL, 0.4 mol) and water (3.4 mL, 0.19 mol) were added, the septum was replaced with a cold water condenser, and the reaction was heated to reflux (bath temperature was about 90 °C). The reaction was followed by TLC (50% CH_2Cl_2/hexane). After 4 h the heat was removed, the reaction mixture diluted with water (100 mL) and extracted with ether (3 × 100 mL). The combined organic extracts were washed with 1 N NaOH and saturated brine, dried over Na_2SO_4, and concentrated under reduced pressure. Overnight drying in vacuo afforded a yellow solid (9.75 g).

This solid was dissolved in ether (100 mL), treated with gaseous HCl and the resulting white solid (10.62 g) collected by suction filtration. Recrystallization from methanol–ether afforded 7.11 g (60%) of (2*S*)-(–)-propranolol hydrochloride as white crystals, mp 192–193.5 °C, $[\alpha]^{21}_D$ –25.7° (*c* 1.23, EtOH). Anal. Calcd for $C_{16}H_{22}ClNO_2$: C, 64.96; H, 7.50; N, 4.74. Found: C, 64.76; H, 7.61; N, 4.66. Slightly off-white crystals (1.5 g) were obtained as a second crop. Recrystallization afforded an additional 1.18 g (10%) of (2*S*)-(–)-propranolol hydrochloride, mp 191.5–194 °C, $[\alpha]^{21}_D$ –26° (*c* 0.94, EtOH).

Acknowledgment. We are grateful to the National Institutes of Health (GM28384) and to Eli Lilly and Company for financial support.

Registry No. **1**, 56715-19-6; **2**, 103728-77-4; **3**, 61249-00-1; **4**, 70987-78-9; (+)-MTPACl, 20445-33-4; (L)-(+)-$Me_2CHOCOCH(OH)CH(OH)CO_2CHMe_2$, 2217-15-4; $H_2C{=}CHCH_2OH$, 107-18-6; $Ti(OCHMe_2)_4$, 546-68-9; Me_2CHNH_2, 75-31-0; (D)-(–)-$Me_2CHOCOCH(OH)CH(OH)CO_2CHMe_2$, 62961-64-2; 4-$MeC_6H_4SO_2Cl$, 98-59-9; $C_6H_5CHMe_2$, 98-82-8; $MeC(OH)(C_6H_5)CH_3$, 617-94-7; BnBr, 100-39-0; (2*S*)-propranolol, 4199-09-1; (2*S*)-propranolol hydrochloride, 4199-10-4; 1-naphthol sodium salt, 3019-88-3; 1-naphthol, 90-15-3; (*S*)-1-((phenylmethyl)amino)-3-(1-naphthalenyloxy)-2-propanol, 103617-36-3.

(11) (+)-α-Methoxy-α-(trifluoromethyl)phenylacetyl chloride.

(12) In our experience, seeding greatly facilitates crystallization in this case. Seed crystals may be obtained by purifying a small portion of the crude oil by column chromatography (silica gel, EtOAc/hexane).

(13) This compound has previously been reported as the racemate: (a) Pierre, J.-L.; Arnaud, P. *Bull. Soc. Chim. Fr.* **1969**, 2868. (b) Chautemps, P.; Pierre, J.-L.; Arnaud, P. *C.R. Seances Acad. Sci., Ser. 3* **1968**, *266*, 622. (c) Nakabayashi, N.; Masuhara, E; Iwakura, Y. *Bull. Chem. Soc. Jpn.* **1966**, *39*, 413. (d) Ichikawa, K. *Yuki Gosei Kagaku Kyokaishi* **1964**, *22*, 553.

(14) Enantiomeric excess was determined by Mosher ester analysis of the iodohydrin derived from glycidyl tosylate. See ref 2b for experimental details.

(15) *Note Added in Proof*: In a recent experiment, following the same procedure, material of 98% ee was obtained. We have also found that stirring during crystallization leads to higher chemical purity earlier in the recrystallization sequence.

Consequences of Hydrophobic Association in Photoreactions: Photodimerization of Stilbenes in Water

M. S. Syamala and V. Ramamurthy*

Department of Organic Chemistry, Indian Institute of Science, Bangalore-506 012, India

Received November 12, 1985

Hydrophobic interactions are of considerable importance in maintaining the structure of biological membranes, proteins, and nucleic acids. The same interaction is also responsible for the association of organic solutes in water, a well-substantiated phenomenon.[1] Such an association could play a significant role during cycloaddition reactions

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