by graphite-monochromated Mo K_α radiation (λ = 0.7114 Å) up to θ = 23° on a CAD-4 diffractometer with low-temperature setup (T = 83 K). Intensities were corrected for Lorentz and polarization factors, yielding 2331 independent reflections with $F_o > 3\sigma(F_o)$. The structure was solved by direct methods and refined to R = 0.0369 and R = 0.045 [$w = 3.0873/[\sigma^2(I_o) + 0.001F^2]$].

Acknowledgment. The authors thank Dr. M. Cojocaru for the determination of the mass spectra and the reviewer for suggesting an experiment to verify the mechanism. Support by the Israel Academy for Sciences and Humanities and the U.S-Israel Binational Science Foundation is also acknowledged.

Supplementary Material Available: ^1H and ^{13}C NMR data (Tables II and III, respectively) for all the compounds synthesized, X-ray data for both the dimer **3c** and the silver complex, atom coordinates (Table IV), anisotropic temperature factors (Table V), hydrogen atom coordinates (Table VI), bond distances (Table VII), bond angles (Table VIII), and bond distances and short contacts to silver (Table IX) (15 pages). Ordering information is given on any current masthead page.

Synthesis of Enantiomerically Pure γ-Amino-β-hydroxybutyric Acid Using Malic Acid as the Chiral Precursor

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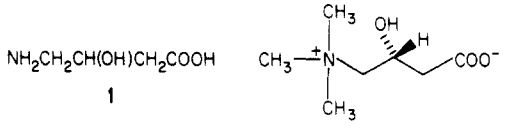
The synthesis of enantiomerically pure γ-amino-β-hydroxybutyric acid using malic acid as the chiral precursor is described. The key step involves the regioselective carboxamidation of the β-carboxyl group (adjacent to the hydroxyl) in malic acid. This was achieved by converting (*S*)-malic acid to its cyclic anhydride **8**, which was then treated with ammonia. Protection of the alcoholic group in the ester amide **9** as a *tert*-butyl ether followed by $LiAlH_4$ reduction gave 3-(*tert*-butyloxy)-4-aminobutanol (**11c**). The amino group in **11c** was protected as the *tert*-butyl carbamate to give (*S*)-3-(*tert*-butyloxy)-4-[((*tert*-butyloxy)carbonyl)amino]butanol (**12c**). The oxidation of the primary alcoholic group was successfully carried out with zinc permanganate to give the desired acid (*S*)-3-(*tert*-butyloxy)-4-[((*tert*-butyloxy)carbonyl)amino]butyric acid (**13c**). Removal of the protecting groups gave (*S*)-(+)-γ-amino-β-hydroxybutyric acid, the optical rotation measurements of which indicated no racemization during the six-step synthesis. The *R* isomer could be synthesized starting from (*R*)-malic acid. Thus a short and efficient route to chirally pure (*R*)- and (*S*)-γ-amino-β-hydroxybutyric acid is presented. Furthermore, this work also highlights zinc permanganate as a useful oxidant for the preparation of carboxylic acids.

γ-Amino-β-hydroxybutyric acid (**1**) is a compound of great pharmacological importance because of its biological function as a neuromodulator in the mammalian central nervous system.[1,2] Of particular interest is the *R*-(−)

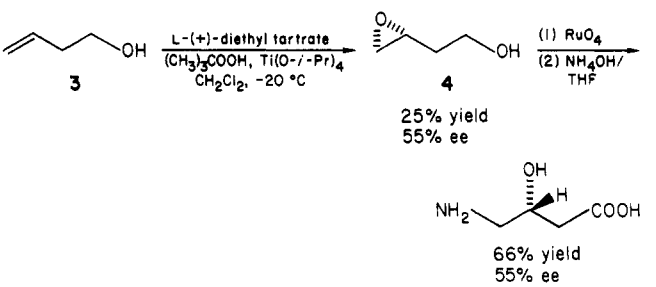


1 **2**

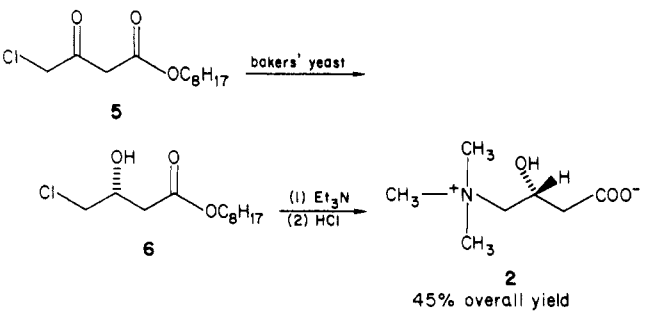
isomer, as it has been shown to have greater biological activity than the *S*-(+) isomer.[3] This γ-aminobutyric acid (GABA) derivative has also been used as a synthetic precursor for certain heterocyclic GABA-receptor agonists.[4] Furthermore, (*R*)-carnitine (**2**), again a compound of considerable biological significance,[5-7] is a derivative of **1**.

An efficient synthetic route leading to optically pure (**1**) is desirable to make the compound more available for biological studies. Our interest in this GABA derivative stems from its possible use in the design of a model of the peptide hormone β-endorphin. We have proposed that the β-endorphin molecule consists of three regions, a specific recognition site which corresponds to the Met-enkephalin sequence, a hydrophilic spacer from residues 6–12, and an

Scheme I



Scheme II



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(3) Kurano, Masayasu, Miyaruoto, Shigetoshi, Shigeoka, Satoshi, Mori, and Akitane. Japanese Patent, 1976; *Chem. Abstr.* **1977**, *86*, 89207*u*.
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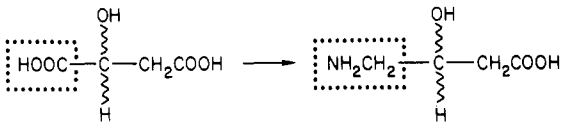
amphiphilic helix from residue 13 to the C terminus. We plan to incorporate an enantiomer of the GABA derivative **1** as the fundamental constituent of the spacer region.

The *R* isomer of **1** has generally been obtained by resolution of the racemate.[8a,b] Although an improved method for the optical resolution of **1** has been reported recently,[3] a simple, efficient synthetic pathway to the chirally pure compounds, designed to be less tedious and more economical, would be desirable. Jung et al.[8c] have reported the synthesis of the *R* isomer of **1** using L-ascorbic acid as the chiral precursor. Their nine-step synthesis gives an overall yield of ~10% and requires large quantities of solvents and reagents to prepare substantial amounts. Although the (*R*)- and (*S*)-glycerol acetonides, the intermediates in the above synthesis, are now commercially available, though expensive, the reported optical rotation values[9] for the final product indicate the poor optical purity of the (*R*)-GABA derivative. A much shorter route to (*R*)-**1** involves Sharpless asymmetric epoxidation of the homoallylic alcohol[10] (Scheme I). Unfortunately, both the chemical as well as the optical yields of the epoxide **4** are less than the usual high yields obtained with other asymmetric epoxidations.

The most efficient route to (*R*)-carnitine (**2**) appears to be that of Sih and co-workers.[11] The salient feature of this synthesis, shown in Scheme II, is the introduction of the chiral center via asymmetric reduction of the ketone functionality in **5** using Baker's yeast. By this method, the *R* isomer could be obtained in high optical purity when the alkyl residue of the ester grouping in **5** was C_8H_{17} but the *S* isomer, which was obtained by increasing the bulkiness of the ester grouping, was not of high optical purity. The method for the synthesis of the enantiomers of **1**, reported in the present paper, can be carried out on a large scale and leads to optically pure compound, and the stereochemistry of the final product is determined by that of the starting chiral precursor.

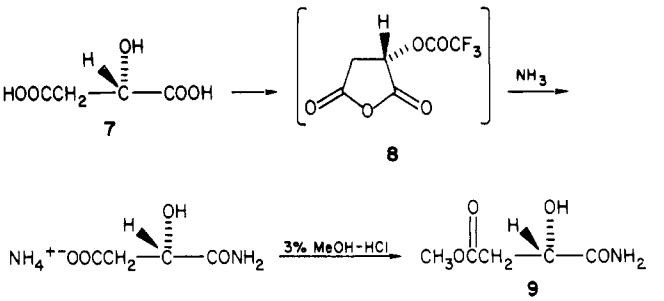
Results and Discussion

Malic acid (**7**), an inexpensive β-hydroxy acid, available commercially in both the *R* and *S* configurations, seemed to be good selection from the "chiral pool" of the organic substrates that might serve as starting materials. Reaction

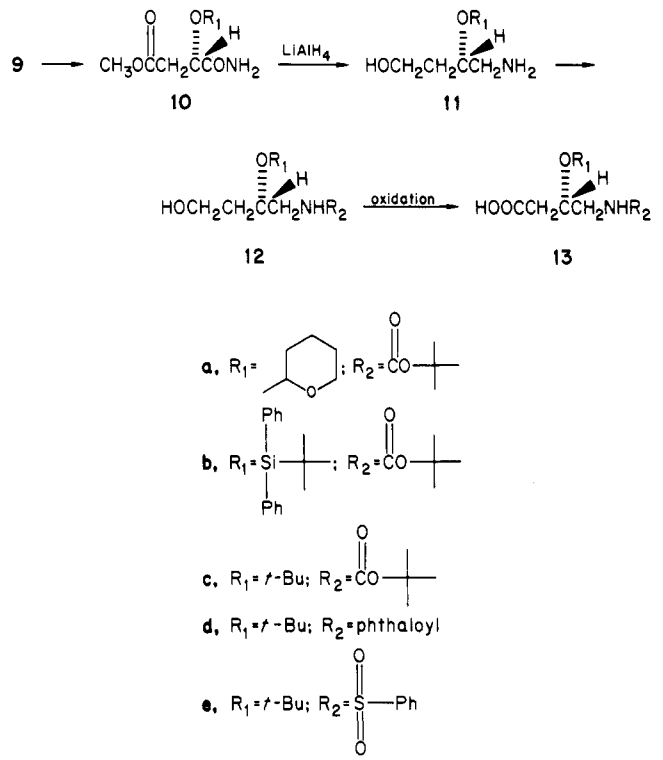


of L- or (*S*)-malic acid with trifluoroacetic anhydride at 0 °C, followed by removal of excess trifluoroacetic anhydride and trifluoroacetic acid, gave the cyclic anhydride **8**[12] (Scheme III). Treatment with gaseous ammonia and subsequently with 3% MeOH–HCl gave the ester amide **9** in 80% yield. The remaining material was the other isomer of the ester amide. This reaction could be carried out easily on a 10 mmol–0.5 mol scale without significant change in the yield.

Scheme III



Scheme IV



To avoid possible racemization during the subsequent reduction step, **9** was converted to the THP ether[13] **10a** in 80–100% yield after purification, depending on the scale of the reaction (Scheme IV). Reduction of **10a** with $LiAlH_4$[14] afforded a quantitative yield of the butanolamine derivative **11a** whose amino group was protected with the (*tert*-butyloxy)carbonyl function. However, oxidation of the product (**12a**) obtained in 90% yield with pyridinium dichromate[15] or ruthenium tetroxide[16] to acid **13a** proceeded at best in 10% yield (see Experimental Section). Protection of the hydroxyl of **9** by the diphenyl-*tert*-butylsilyl group[17] gave ether **10b** in almost quantitative yield. However, the protecting group was removed during the subsequent $LiAlH_4$ reduction, which is surprising in view of the reported stability of the related *tert*-butyldimethylsilyl group toward hydrogenation conditions.[18]

(8) (a) Lindstedt, S.; Lindstedt, G. *Arkiv. Kemi.* **1964**, *93*, 22. (b) Tomita, M.; Sendju, Y. *Z. Phys. Chem., Abt. B* **1927**, *169*, 263. (c) Jung, M. E.; Shaw, T. J. *J. Am. Chem. Soc.* **1980**, *102*, 6304 and references cited therein.

(9) Optical rotation reported by Jung et al., $[\alpha]^{25}_D$ −7.09 (*c* 3.5, H_2O) [lit.[8a,b] $[\alpha]^{20}_D$ −21.06° (in water), $[\alpha]^{27}_{589}$ −21.4° (*c* 1.18, H_2O)].

(10) Rossiter, B. E. Ph.D. Thesis, Stanford University, October, 1981.

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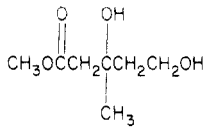
Since the *tert*-butyl ether group can be introduced and removed without any racemization of the chiral center bearing the hydroxyl group,[19] **9** was converted to the *tert*-butyl ether **10c**. The best conditions using liquid isobutylene in CH_2Cl_2 and catalytic amounts of concentrated H_2SO_4 afforded 65–75% yield of pure product. Compared with the literature, which reports yields of 90–95% by this procedure, the lower yields in the present instance are due to poor solubility of **9** in CH_2Cl_2. $LiAlH_4$ reduction of **10c** gave (**11c**), which was converted to **12c** in 90% yield, but ruthenium tetraoxide and Jones oxidation[20] of **12c** again gave only low yields (15 and 25%, respectively) of the desired acid (**13c**). The yields of the ruthenium tetraoxide oxidation did not improve when the amino group was protected as a benzene sulfonamide. When the phthaloyl protecting group was employed, oxidation of **12d** obtained from **11d** with *N*-(ethoxycarbonyl)phthalimide[21] in 70% yield and with ruthenium tetraoxide gave the desired acid **13d** in 50% yield, but purification was difficult. To overcome this problem use of zinc permanganate was investigated. Under mild conditions[22] this reagent selectively oxidizes the primary hydroxyl group of **14** to the carboxyl group, and unlike po-



14

tassium permanganate oxidations where the reaction medium becomes alkaline as the reaction proceeds, zinc permanganate oxidations tend to maintain neutral conditions.[23] This could be a significant factor if the side reaction reducing the yields during the oxidations with RuO_2 and Cr^{+6} are the result of proton removal from the NHR_2 grouping and the subsequent attack of the anion on the activated carboxyl group.

Indeed, oxidation of **12c** with zinc permanganate in acetone at 0 °C proceeded more cleanly than previously and gave 55% isolated yield of the required acid **13c**. The final hydrolysis of both protecting groups gave a material with mp and spectral characteristics identical with those of the authentic sample. The optical rotation $[\alpha]^{25}_D$ +20.1° (*c* 1.7, H_2O) [lit.[8a,b] $[\alpha]^{20}_D$ +18.3° (in water), $[\alpha]^{23}_{589}$ +20.4° (*c* 1.48, H_2O)] showed that the product was optically pure and that no racemization occurred during the synthesis.

The overall yield for the six-step synthesis we have developed is 25% and is actually greater than 30%, if one takes into account the amount of starting material recovered during formation of **10c**. All of the reactions described could be carried out on a larger scale and the *R*-(−) isomer is accessible by using (*R*)-malic acid as starting material.

Our results on oxidation reactions with different reagents also indicate that zinc permanganate is a simple and very useful oxidant for the preparation of carboxylic acids. Its synthetic utility could well be exploited in those instances where the compatibility of this versatile reagent with various functional groups may assume importance.

Experimental Section

^1H NMR spectra were recorded on samples dissolved in $CDCl_3$ unless otherwise stated, and the chemical shifts (δ) are given with respect to tetramethylsilane as the internal standard. All melting points were taken on a Thomas-Hoover melting point apparatus and are uncorrected.

THF was distilled from sodium/benzophenone immediately before use. Tetrahydropyran was distilled prior to use. Dioxane–HCl (4 N) was purchased from Pierce Chemical Co. Dowex 50W-X8 (200–400 mesh, H^+ form) cation-exchange resin was obtained from Bio-Rad. Boron trifluoride–phosphoric acid complex was purchased from Fluka. Thin-layer chromatography was performed on precoated silica gel 60F-254 plates (Merck, 0.25-mm layer thickness). Flash chromatography was performed by the method of Still[24] with 40–60-μm silica gel (E. Merck 9355).

(*S*)-2-Hydroxy-3-(methoxycarbonyl)propionamide (9). To L-malic acid (*S* configuration) (30 g, 0.224 mol) in a 500-mL round-bottomed flask cooled in an ice bath was added trifluoroacetic anhydride (75 mL). The viscous reaction mixture was stirred at 0 °C for 2 h; subsequently, excess trifluoroacetic anhydride and trifluoroacetic acid were removed by vacuum distillation at 0 °C. The residual solid residue was dried for an additional 30 min at room temperature. The white solid obtained was then dissolved in 300 mL of dry THF, and after the mixture was cooled in an ice bath, dry ammonia gas was slowly bubbled into the vigorously stirred solution for 3 h. Then the reaction mixture was allowed to warm up to room temperature and left overnight. After removal of THF, the resultant white gummy solid was dried in vacuum for 2 h and then treated with 3% methanolic hydrogen chloride. After 14 h, the precipitated ammonium chloride was removed by filtration and washed with 250 mL of methanol. The solvent was removed from the washings and combined with the filtrate, and the residue was washed with ethyl acetate (6 × 100 mL). The washings were combined and after the solvent was removed a light yellow-colored thick liquid was obtained.

The residue from the ethyl acetate washings was dried, treated with 200 mL of 3% MeOH–HCl for 12 h and worked up similarly. Combination of this material with that obtained earlier and evaporation of the solvent gave 40 g of crude material. This mixture as analyzed by TLC (9:1 CH_2Cl_2–MeOH; phosphomolybdic acid spray) contained a major fraction with R_f ~0.35, the right isomer, and a slightly more polar compound (R_f ~0.25) as a minor component, which was the other isomer. Trifluoroacetamide and a small amount of dimethyl malate were cleanly separated from the major component, which was purified by column chromatography (silica gel, 70–230 μm; 9:1 CH_2Cl_2–MeOH). This purification was repeated, and a colorless thick liquid which solidified on standing was obtained, **9**: 25 g (80%); mp 40–42 °C; $[\alpha]^{22}_D$ −46.5° (*c* 2.11, EtOH); IR ν_{max} 3450 (br), 3335 (br), 1740 (s), 1680 (br s) cm^{-1}; ^1H NMR δ 2.88 (AB q, J = 15, 4, 9 Hz, 2 H), 3.75 (s, 3 H), 4.2 (d, J = 6 Hz, 1 H), 4.5 (m, 1 H), 6 (br s, 1 H), 6.8 (br s, 1 H); mass spectrum, m/e 148 [$(M + 1)^+$]. Anal. Calcd for $C_5H_9NO_4$: C, 40.82; H, 6.12; N, 9.52. Found: C, 40.55; H, 6.37; N, 9.29.

(*S*)-2-(2-Tetrahydropyranyloxy)-3-(methoxycarbonyl)-propionamide (10a). The hydroxy compound **9** (0.5 g, 3.4 mmol) in a 100-mL flask was dissolved in boiling, anhydrous, freshly distilled methylene chloride. After the mixture cooled to room temperature freshly distilled dihydropyran (0.57 g, 0.62 mL, 6.8 mmol) followed by pyridinium *p*-toluenesulfonate (0.17 g, 0.68 mmol) was added. After 24 h of reaction and dilution with 30 mL of CH_2Cl_2, the mixture was passed through a 5-cm pad of Florisil under suction; subsequently, the Florisil was washed with an additional 25 mL of CH_2Cl_2. After solvent evaporation the crude product showed very little starting material by TLC (9:1 CH_2Cl_2–MeOH) and was purified by flash chromatography (same solvent system) to give a colorless thick oil that solidified on standing, **10a** (0.77 g, 98% yield): mp 52–53 °C; $[\alpha]^{22}_{589}$ +0.44° (*c* 4.1, MeOH); IR ν_{max} (neat) 3480, 3320, 3200 (br s) 1750 (s), 1690

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(br s) 1590 (br s), 1120–1140 (br s), 1070 (br s), 1035 (s), 1020 (s) cm^{-1}; ^1H NMR δ 1.3–2.0 (m, 6 H), 2.8 (AB q, J = 8, 4 Hz, 2 H), 3.2–3.9 (m, 2 H), 3.65 (s, 3 H), 4.4 (d t, J = 5, 10 Hz, 1 H), 4.7 (br s, 1 H), 5.75 (br s, 1 H), 6.8 (br s, 1 H); mass spectrum, m/e 232 [$(M + 1)^+$]. Anal. Calcd for $C_{10}H_{17}NO_5$: C, 57.95; H, 7.36; N, 6.06. Found: C, 52.05; H, 7.43; N, 5.92.

With larger amounts of **9** (30–50 mmol) longer reaction times (36 h) were employed, and the yields of isolated material were about 80%; however, in these instances the unreacted starting material could be recovered and reused.

(*S*)-3-(2-Tetrahydropyranyloxy)-4-aminobutanol (11a). To a stirred suspension of lithium aluminum hydride (0.68 g, 17.9 mmol) in 25 mL of dry THF was added dropwise a solution of **10a** (1.1 g, 4.76 mmol) in dry THF (15 mL), and the mixture was heated at reflux overnight. After the mixture cooled, water (0.68 mL), 15% NaOH (0.68 mL), and again water (3 × 0.68 mL) were added, and the reaction mixture was stirred for 45 min. After the addition of THF (25 mL), stirring was continued for an additional 30 min. The solid precipitate was removed by filtration and washed with 150 mL of THF. The combined filtrate was collected and the solvent removed to give a colorless thick liquid (0.89 g, 98% yield), which by TLC was a single compound, as determined with ninhydrin: IR ν_{max} (neat) 3440 (br s), 3360 (s), 3300 (s), 3200 (br s), 1600 (br s), 1140 (s), 1120 (s), 1080 (br s), 1020 (br s) cm^{-1}; mass spectrum, m/e 190 [$(M + 1)^+$]. This material was employed for the next synthetic step without further purification. Similar yields were obtained for reactions carried out on a larger scale (30 mmol).

(*S*)-3-(2-Tetrahydropyranyloxy)-4-[((*tert*-butyloxy)carbonyl)amino]butanol (12a). Di-*tert*-butyl dicarbonate (1.2 g, 5.3 mmol) in 5 mL of *tert*-butyl alcohol (or dioxane) was added to a stirred solution of **11a** (0.9 g, 4.76 mmol) in 10 mL of *tert*-butyl alcohol (or dioxane). After the mixture was stirred for 1 h, the solvent was removed on a rotary evaporator, and by flash chromatography (EtOAc) the product **12a**, a colorless thick liquid, with R_f 0.35 was collected (1.3 g, 90% yield): IR ν_{max} (neat) 3450, 3320 (br s), 1685–1720 (br s), 1520 (br s), 1390 (s), 1370 (s), 1270, 1250 (br s), 1170 (br s), 1140 (s), 1140 (s), 1075 (s), 1025 (s) cm^{-1}; ^1H NMR δ 1.3–2 (m, 17 H), 3–4.3 (m, 8 H), 4.6 (br s, 1 H), 4.75 and 5.6 (br s, 1 H); mass spectrum, m/e 290 [$(M + 1)^+$].

(*S*)-2-(*tert*-Butyldiphenylsiloxy)-3-(methoxycarbonyl)propionamide (10b). To a stirred solution of *tert*-butyldiphenylsilyl chloride (1.13 g) in 2 mL of dry THF were added 0.5 g (3.4 mmol) of **9**. and 0.58 g (8.5 mmol) of imidazole. The reaction mixture was stirred at 36 °C for 10 h, then poured into 50 mL of saturated brine solution, and extracted with ethyl acetate (3 × 50 mL). The combined extracts were washed with water (2 × 25 mL) and dried over anhydrous Na_2SO_4, and the solvent was removed to give a colorless thick liquid, which was purified by flash chromatography (3:2 CH_2Cl_2–EtOAc) to give 1.3 g (100% yield) of **10b** showing a single UV detectable spot on TLC: IR ν_{max} (neat) 3480 (s), 3350, 3200 (br s), 1960, 1900, 1830 (br s), 1740 (br s), 1700 (br s), 1590 (br s), 1475 (s), 1240 (br s), 1190, 1170 (br s), 1110 (br s), 940 (br s), 820 (s), 740 (s), 700 (s), 610 (s) cm^{-1}; ^1H NMR δ 1–1.2 (s, 9 H), 2.9 (AB q, J = 10 Hz, 2 H), 3.7 (s, 3 H), 4.1 (m, 1 H), 5.8 and 6.8 (br s, 2 H), 7.4–7.7 (m, 10 H); mass spectrum, m/e 386 [$(M + 1)^+$].

(*S*)-2-(*tert*-Butyloxy)-3-(methoxycarbonyl)propionamide (10c). To compound **9** (2.15 g, 14 mmol) placed in 30 mL of CH_2Cl_2 in a 150-mL pressure bottle cooled in an acetone–dry ice bath was added 30–40 mL of freshly distilled liquid isobutylene, followed by 0.3 mL of concentrated H_2SO_4. The suspension was shaken at room temperature for 48 h, giving a clear solution. After the solution was cooled in an ice bath, N_2 was blown through to remove all the isobutylene. After dilution with 50 mL of CH_2Cl_2, shaking with $NaHCO_3$ for 5–10 min, filtration, and solvent removal, a thick oil containing starting material (R_f 0.3, 9:1 CH_2Cl_2–MeOH) and the product (R_f 0.6) were obtained. Purification by flash chromatography (EtOAc) gave 2.1 g (70% yield) of **10c**, mp 79–82 °C, as a colorless thick oil which solidified slowly on standing: $[\alpha]^{22}_D$ −53.1° (*c* 2.13, MeOH); IR ν_{max} (neat) 3480, 3340, 3200 (br s), 1740, 1680 (br s), 1590 (br s), 1440 (s), 1395 (s), 1370, 1360 (br s), 1260, 1240 (br s), 1195, 1170 (br s), 1090 (br s), 1000 (s), 950 (s), 840 (s), 800 (br s), 700 (s) cm^{-1}; ^1H NMR δ 1.38 (s, 9 H), 2.7 (m, 2 H), 3.7 (s, 3 H), 4.3 (t, J = 6 Hz, 1 H), 5.7 and 6.7 (br s, 2 H); mass spectrum, m/e 204 [$(M + 1)^+$]. Anal. Calcd for $C_9H_{17}NO_4$: C, 53.20; H, 8.37; N, 6.90. Found: C, 53.41; H, 8.59; N, 6.62. The starting material could be recovered and reused in the above reaction. When dioxane was used as the solvent, the yields were somewhat higher (75%).

(*S*)-3-(*tert*-Butyloxy)-4-phthalimidobutanol (12d). The lithium aluminum hydride reduction of **10c** to **11c** was carried out in a manner similar to that described for **10a** (yield 90–95%). Addition of 1.5 g (9.32 mmol) of **11c** in 7 mL of dry THF to an ice-cooled solution of *N*-carbethoxyphthalimide (2.05 g, 9.35 mmol) in 25 mL of dry THF, stirring at 0 °C for 10 min and then at room temperature for 17 h, and solvent removal gave a compound with R_f 0.39 (9:1 CH_2Cl_2–MeOH) as the major fraction apart from ethyl carbamate (R_f 0.75). The product **12d** purified by repeated flash chromatography (EtOAc and 9:1 CH_2Cl_2–MeOH) was obtained in 1.9 g (70%) yield as a colorless thick liquid which solidified on standing: mp 72 °C; IR ν_{max} (KBr film) 3450–3200 (br s), 1720–1690 (br s) cm^{-1}; ^1H NMR δ 1.25 (s, 9 H), 1.75 (m, 2 H), 2.7 (br s, 1 H), 3.5 (d of m, 2 H), 4 (m, 1 H), 4.2 (q, J = 9 Hz, 2 H), 7.5 (m, 4 H); mass spectrum, m/e 292 [$(M + 1)^+$].

(*S*)-3-(*tert*-Butyloxy)-4-[((*tert*-butyloxy)carbonyl)amino]butanol (12c). About 0.9 g (5.6 mmol) of **11c** was dissolved in 10 mL of dioxane or *tert*-butyl alcohol, to which was added a solution of 1.34 g (6.2 mmol) of *tert*-butyl dicarbonate in 5 mL of dioxane (or *tert*-butyl alcohol). After the mixture was stirred at room temperature for 1 h, removal of the solvent, and purification by flash chromatography (EtOAc as the eluent, R_f 0.43), 1.4 g (90% yield) of **12c** was obtained: $[\alpha]^{22}_D$ −1.93 (*c* 2.28, MeOH); IV ν_{max} 3450–3300 (br s), 1700 (br s), 1530 (br s), 1390, 1370 (s), 1270, 1250 (br s), 1170 (br s), 1070 (br s), 1010 (s), 940 (br s), 870 (br s), 750 (s) cm^{-1}; ^1H NMR δ 1.25 (s, 9 H), 1.4 (s, 9 H), 1.8 (m, 2 H), 2.8 (br s, 1 H), 3.2 (m, 2 H), 3.8 (m, 2 H), 3.9 (m, 1 H), 4.9 (br s, 1 H); mass spectrum, m/e 262 [$(M + 1)^+$].

Oxidation Reactions. General Procedure for the Pyridinium Dichromate Oxidations of 12a and 12c. A solution of **12a** or **12c** in dry DMF (2 mL per g of pyridinium dichromate) was stirred with pyridinium dichromate (3–4 equiv) for 7–10 h. The reaction mixture was diluted with water (10-fold) and extracted with either ether or ethyl acetate. The identification of the acid product was carried out employing TLC and spectral characterization. Only when about 0.2 mL of water/mL of DMF was added in the oxidation mixtures was the desired acid obtained in 5–10% yield.

Ruthenium Tetraoxide Oxidation of 12d. To 0.29 g (1 mmol) of **12d** dissolved in 3 mL of CH_3CN and 3 mL of CCl_4 mixed with 4.5 mL of water was added 0.64 g (3 mmol) of sodium metaperiodate. After the mixture was stirred vigorously 5–6 mg (2.2 mol %) of ruthenium trichloride hydrate was added. After 75 min, 20 mL of CH_2Cl_2 was added, the organic phase was separated, and the aqueous phase was extracted with CH_2Cl_2 (3 × 30 mL). The combined extracts were dried over anhydrous Na_2SO_4, concentrated, diluted with ether, passed through a 5-cm pad of Celite, and washed with ether. The filtrate was concentrated, diluted with 50 mL of CH_2Cl_2, and washed with 1 N NaOH (3 × 25 mL). The washings were acidified to pH 2–3 with 1 N HCl and extracted with EtOAc (3 × 25 mL). The combined extracts were washed with water (2 × 25 mL) and dried over anhydrous Na_2SO_4, and the solvent was removed to give light yellow-colored oil **13d**, which solidified on standing, yielding 0.15 g (50%). This material seemed nearly pure by TLC: IV ν_{max} (KBr film) 3350–2500 (br s), 1720–1690 (br s), 1600 (s); ^1H NMR (acetone-d_6) 1.25 (s, 9 H), 2.5 (br d, 2 H), 3.9 (br d, 2 H), 4.1 (br s, 1 H), 7.3–7.8 (m, 4 H); mass spectrum, m/e 306 [$(M + 1)^+$] (positive ion chemical ionization), 304 [$(M - 1)^-$] (negative ion chemical ionization).

The yields of the desired acid starting from **12a** and **12c** were 10% and 15%, respectively.

Zinc Permanganate Oxidation of 12c. To a vigorously stirred solution of compound **12c** (0.62 g, 2.4 mmol) in 30 mL of acetone cooled to 0 °C in a 100-mL round-bottomed flask was added 0.64 g (1.56 mmol) of zinc permanganate hexahydrate in small portions over 20 min. After the mixture was stirred at 0 °C for an additional 20 min, the excess permanganate was destroyed by careful addition of 30% H_2O_2 solution. After evaporation of acetone, 25 mL of water was added, followed by acidification to pH 2–3 with 4 N H_2SO_4. Then H_2O_2 was carefully added (pH 2–3) so that all the MnO_2 dissolved completely to give

a clear solution. The mixture was extracted with ethyl acetate (3 × 30 mL), the extract concentrated to 30 mL, washed with 1 N NaOH (3 × 30 mL), cooled to 0 °C, acidified to pH 2–3 with 1 N HCl, and again extracted with EtOAc (3 × 30 mL), the extract washed with water and dried over anhydrous Na_2SO_4, and the solvent removed to give colorless thick oil **13c**: 0.34 g (55% yield); IR ν_{max} (neat) 3400–3500 (br s), 1720, 1590 (br s), 1395, 1370 (s), 1270 (br s), 1170 (br s), 1080 (br s), 760, 740 (s) cm^{-1}; ^1H NMR δ 1.2 (s, 9 H), 1.45 (s, 9 H), 2.6 (m, 2 H), 3.3 (m, 2 H), 4.1 (m, 1 H), 4.9 (br s, 1 H); mass spectrum, m/e 276 [$(M + 1)^+$].

(*S*)-3-Hydroxy-4-aminobutyric Acid. After compound **13c**, 0.13–0.14 g (0.5 mmol) stood in 2 mL of 4 N dioxane–HCl at room temperature for 16 h, dioxane was blown off with N_2, and the precipitated solid was dissolved in 3.5 mL of water. The mixture was charged on a Dowex 50 W-X8 cation-exchange resin column (200–400 mesh, H^+ form, 9 cm × 1 cm), which was washed with water until the effluent was neutral and then eluted with 25–30 mL of 2 N ammonium hydroxide. Removal of the water at room temperature gave a white solid. Ethanol was added, and after an hour the solvent was removed and the residue dried under vacuum overnight. A light yellow solid, 57 mg (95% yield), was obtained: mp 214 °C (lit. 212–214 °C); $[\alpha]^{22}_D$ +20.1 (*c* 1.7, H_2O) [lit.[8a,b] $[\alpha]^{20}_D$ +18.3° (H_2O), $[\alpha]^{23}_{589}$ +20.4° (*c* 1.48, H_2O)]; IR ν_{max} (KBr) 3450, 3100–2500, 2150, 1665 cm^{-1}; ^1H NMR (D_2O, Me_4Si external standard) δ 2.3 (br d, J = 6 Hz, 2 H), 3.0 (m, 2 H), 4.1 (m, 1 H). Anal. Calcd for $C_4H_9NO_3$: C, 40.34; H, 7.56; N, 11.77. Found: C, 40.34; H, 7.73; N, 11.47.

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Photoinduced Methanol-Incorporated Cyclization of *N*-(3-Phenylallyl)arenedicarboximides

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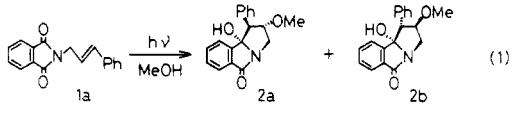
Irradiation of *trans-N*-(3-phenylallyl)arenedicarboximides **1b**, **1c**, and **1d** in methanol–acetonitrile (1/1 v/v) gave methanol-incorporated cyclization products **3a** + **3b**, **6a** + **6b**, and **7**, respectively. Chemical and spectroscopic evidence for the structure of the products is presented. The photocyclization of **1c** predominantly afforded the more sterically crowded product (**6a**). The suggested reaction mechanism, involving initial intramolecular electron transfer from the alkenyl moiety to the singlet excited state of the arenedicarboximide moiety, was supported by the examination of the fluorescence spectra, trans–cis isomerization during the cyclization, and the free-energy change associated with the electron transfer (ΔG_{et}). The calculated spin density of radical anion of naphthalene-1,2-dicarboximide rationalizes the photochemical result of **1c**.

Recently, photoreactions involving electron-transfer processes have received much attention with regards to both the synthetic and mechanistic aspects in organic photochemistry.[1] In the course of studies on the photochemistry of imides, we and other groups have found in the photoreactions of phthalimide–alkene systems a variety of alcohol (solvent)-incorporated intramolecular cyclization[2] and intermolecular addition products,[3] which seems to occur via electron-transfer processes. A typical example is shown in eq 1. However, the imide compounds em-



(1)

ployed in the previous investigations have been confined to phthalimides, and only little information has been reported on the effect of arene structure of arenedicarboximides (aromatic imides).[4] Our studies have been focused on elucidation of the effect of extended π-conjugation system in the arene structure.[5] Here we report the results of intramolecular photoreactions of three types of *trans-N*-(3-phenylallyl)arenedicarboximide in methanol–acetonitrile, indicating that the methanol-incorporated photocyclization is characteristic for the series of the *N*-alkenylarenedicarboximides.

Results and Discussion

Irradiation of *trans-N*-(3-phenylallyl)naphthalene-2,3-dicarboximide (**1b**) in N_2-purged methanol–acetonitrile (1/1 v/v) gave two methanol-incorporated cyclization products [**3a** (55%) and **3b** (16%)] (eq 2). Support for the structure of **3a** was furnished by dehydration of **3a** to give **4** and by acid degradation of **3a** and **4** to **5a** (eq 3). The stereochemistry of **3a** and **3b** was deduced from the similarity of the ^1H NMR spectra (coupling constants between H^a–H^d) of **3a** and **3b** to those of **1a** and **1b**.[2a]

Irradiation of *trans-N*-(3-phenylallyl)naphthalene-1,2-dicarboximide (**1c**) in methanol–acetonitrile (1/1 v/v) gave mainly two methanol-incorporated cyclization products [**6a** (57%) and **6b** (34%)] together with the minor stereoisomers (eq 4). Acid treatment of **6a** and **6b** gave different

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