Prochiral Recognition in the Reaction of 3-Substituted Glutaric Anhydrides with Chiral Secondary Alcohols

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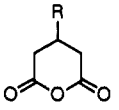
The scope of a previously-reported process for the desymmetrization 3-substituted glutaric anhydrides has been investigated. Thus, prochiral anhydrides **5–9** react with 1-(1′-naphthyl)ethanol (**2**) to give glutaric acid half-esters, which are esterified by treatment with diazomethane to obtain the corresponding diesters **16–20**. The degree of prochiral recognition is inversely related to the steric bulk of the stereodifferentiating group, with the series TBDMSO, Me, Et, Ph, *i*-Pr, and *t*-Bu giving ratios of 40:1, 16:1, 14:1, 8:1, 7:1, and 1:3, respectively. The absolute sense of the prochiral recognition was established by conversion of two of the diesters, **16a** and **18a**, into 3-substituted valerolactones (**22a**, **22c**) of known absolute configuration.

In connection with our synthetic approach to the mevinic acids,[1] we introduced a method for desymmetrization of ethers of 3-hydroxyglutaric anhydride. Thus, as shown in Scheme I, prochiral anhydride **1** reacts with (*S*)-1-(1′-naphthyl)ethanol (**2**) in the presence of 4-(*N*,*N*-dimethylamino)pyridine (DMAP) to give ester **3** with good diastereomeric surplus. With the enantiotopic carbonyl groups thus distinguished, compound **3** can be employed for a number of purposes. For example, the free carboxy group can be esterified and the benzylic bond cleaved by hydrogenolysis to obtain the chiral 3-hydroxyglutaric acid derivative **4** with an enantiomeric purity of 96–97% ee.[2]

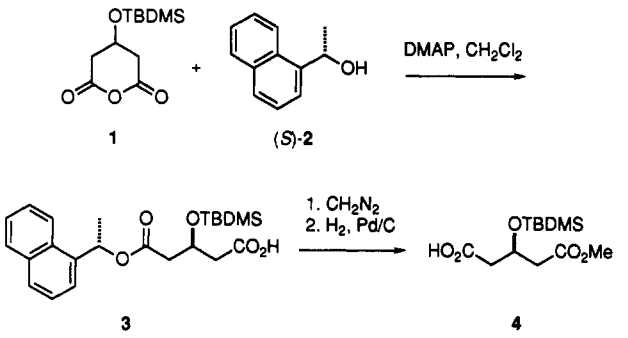
It was of interest to us to explore the generality of this phenomenon by examining other 3-substituted glutaric anhydrides. To this end, we have evaluated anhydrides **5–9**. Compound **5** is commercially available.[3] Compound



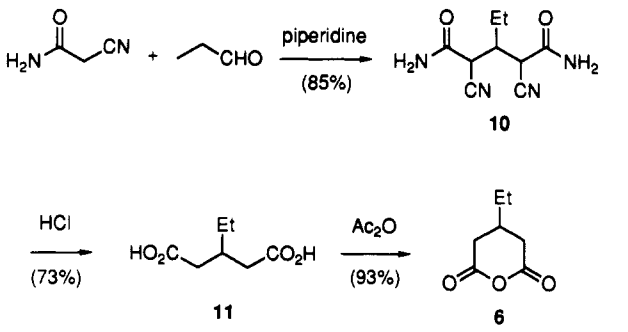
5: R = Me
6: R = Et
7: R = *i*-Pr
8: R = Ph
9: R = *t*-Bu

8 was prepared by dehydration of the commercially-available 3-phenylglutaric acid.[4] Compound **6** was prepared in 58% overall yield by modification of a published procedure for synthesis of **5** (Scheme II).[5] Attempts to prepare compounds **7** and **9** by this method failed. However, condensation of isobutryaldehyde or pivalaldehyde with ethyl cyanoacetate, followed by addition of dimethyl sodiomalonate afforded cyano triesters **12** and **13** in good yield. There is some transesterification of the ethyl ester to the methyl ester in this procedure. However, this is inconsequential, since the next step is hydrolysis of the triester. Surprisingly, treatment of **12** with concentrated HCl did not provide the desired diacid. However, decarboxylation and hydrolysis are accomplished by treatment of **12** with 48% aqueous HBr, which affords 3-isopropylglutaric acid (**14**) in 87% yield. The diacid is

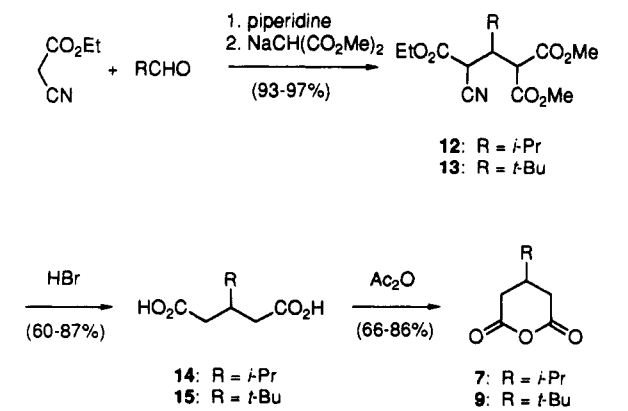
Scheme I



Scheme II



Scheme III



(1) (a) Rosen, T.; Heathcock, C. H. *J. Am. Chem. Soc.* **1985**, *107*, 3731. (b) Hecker, S. J.; Heathcock, C. H. *J. Am. Chem. Soc.* **1986**, *108*, 4586. (c) Heathcock, C. H.; Hadley, C. R.; Rosen, T.; Theisen, P. D.; Hecker, S. J. *J. Med. Chem.* **1987**, *30*, 1858.
(2) Theisen, P. D.; Heathcock, C. H. *J. Org. Chem.* **1988**, *53*, 2374.
(3) Aldrich, Chemical Co., catalog no. M4,780-9.
(4) Aldrich Chemical Co., catalog no. 19,126-4.
(5) (a) Kent, R. E.; McElvain, S. M. *Organic Syntheses*; Wiley: New York, 1955; Collect. Vol. III, p 591. (b) Cason, J. *Organic* Syntheses; Wiley: New York, 1961; Collect. Vol. IV, p 630.

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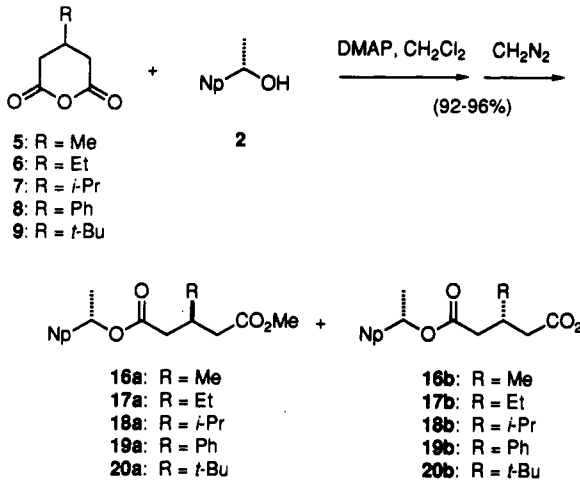
Scheme IV



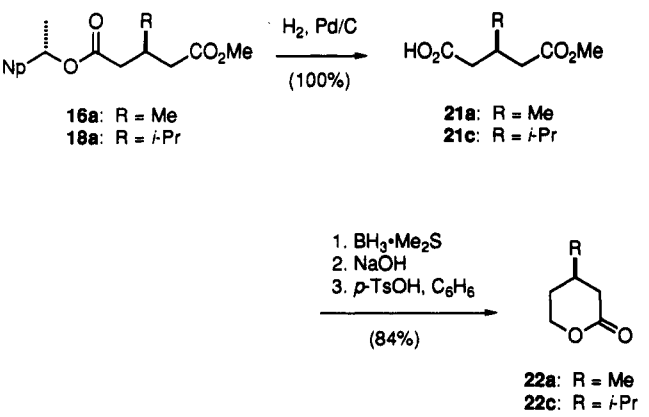
cyclized to 3-isopropylglutaric anhydride by treatment with acetic anhydride to obtain anhydride **7** in 86% yield (70% overall yield from isobutyraldehyde). The identical sequence of reactions converts pivalaldehyde to anhydride **9** in 38% overall yield.

Results

Anhydrides **5–9** were each allowed to react with 1-(1′-naphthyl)ethanol (**2**) under the optimal conditions[2] for prochiral recognition with anhydride **1** (Scheme IV).[6] The crude products were esterified by treatment with diazomethane and the diastereomeric ratios determined by integration of the methyl ester resonances in the ^1H NMR spectrum. The diastereomer ratios observed with anhydrides **5–9** were 16:1, 14:1, 7:1, 8:1, and 1:3, respectively.

The major products obtained from anhydrides **5** and **7** (**16a** and **16c**, respectively) were hydrogenolyzed and the resulting acids (**21a** and **21c**) reduced by borane.[7] Upon acidification, lactones **22a** and **22c** were obtained in overall yields of 80–82%.[8] The absolute configurations of **22a** and **22c** were elucidated by comparison of their observed optical rotations with those reported in the literature.[9] Thus, the sense of prochiral recognition in the reactions of **2** with **5** and **7** is the same as that previously observed in its reaction with ether **1**, which gives the two diastereomeric products in a ratio of 40:1 under the same conditions.[2] For the ethyl-, phenyl-, and *tert*-butyl-substituted anhydrides **6**, **8**, and **9** the corresponding valerolactones are not known, so the sense of prochiral recognition has to be assigned by circumstantial arguments. The configuration of the major product (**17b**) in the reaction of the ethyl-substituted anhydride **6** can be confidently assigned by analogy to that of the major isomers from reactions of the methyl- and isopropyl-substutuuted anhydrides **5** and **7**. The configuration of the major isomer derived from *tert*-butyl-substituted anhydride **9** is believed to be opposite that of the major isomer derived from the other four anhydrides on the basis of the following NMR arguments. First, the ^1H NMR chemical shifts of the methoxy resonances in the diesters follow a distinct pattern. For **16–19**, the CH_3O resonance of the major isomer is downfield from that of the minor isomer by 10–25 Hz. However, for diesters **20**, the CH_3O resonance of the major isomer is upfield from that of the minor isomer by 50 Hz. Second, the ^{13}C NMR spectra of diesters **18** and **20** also show a consistent pattern if one compares the chemical shifts of the major and minor isomer resonances, peak by peak. For every single resonance, the relative chemical shift of the minor isomer is reversed in the *tert*-butyl analog **20**, compared to the isopropyl analog **18**. Finally, the configurations of **19a** and **19b**, obtained from the phenyl-substituted anhydride **8**, are assigned on the basis of the aforementioned regular pattern of the CH_3O resonances, and by analogy with the proven configurations of **18a** and **18b**, given the similar steric properties of phenyl and isopropyl.

Scheme V



Discussion

The results of this investigation show clearly that the previously-reported desymmetrization of 3-substituted glutaric anhydrides by reaction with 1-(1′-naphthyl)-ethanol is a general process and that useful enantiomeric purities can be obtained in some cases. The results are also interesting in that the stereoselectivity appears to have an inverse dependence on the steric bulk of the stereodifferentiating group; as the size of this group increases, the degree of prochiral recognition actually decreases! That is, for the series TBDMSO, Me, Et, *i*-Pr, and *t*-Bu, the prochiral recognition ratios are 40:1,[2] 16:1, 14:1, 7:1, and 1:3, respectively.

The probable mechanism for the desymmetrization reaction is summarized in Scheme VI.[1c] For a given anhydride, the prochiral recognition results from differences in the rates of reaction of the chiral secondary alcohol with the enantiomeric *N*-acylpyridinium zwitterions. These rate differences presumably have their origin in different repulsive and attractive effects in the diastereomeric transition states. However, because the intermediates are conformationally flexible, with many degrees of rotational freedom, it is virtually impossible to model the transition states. Nevertheless, the observed substituent effect series is counterintuitive, as we normally assume that the stereoselectivity of a reaction should be proportional to the steric bulk of the stereodifferentiating group. In the present case, we observe just the opposite, at least over the range of groups studied; prochiral recognition increases when we decrease the size of the stereodiffer-

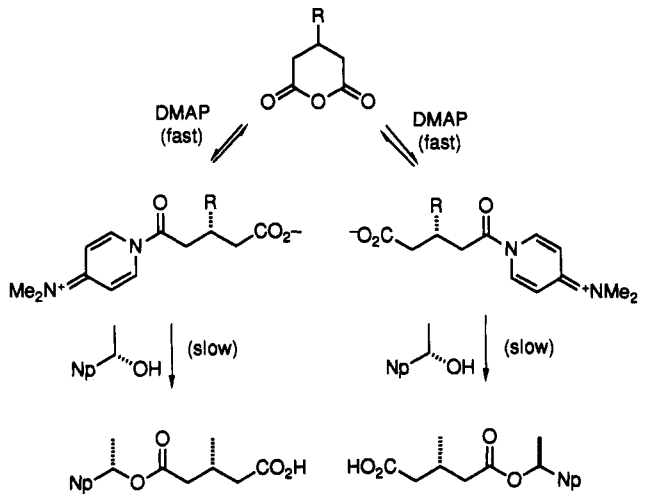
(6) All reactions were initially carried out with racemic **2**. Subsequently, some reactions were repeated with either (*R*)- or (*S*)-**2** in order to prepare scalemic 3-alkylglutaric acid half-esters. Full details are found in the Experimental Section.

(7) Yoon, N. M.; Pak, C. S.; Brown, H. C.; Krishnamurthy, S.; Stocky, T. P. *J. Org. Chem.* **1973**, *38*, 2786.

(8) This sequence was carried out with material derived from (*S*)-**2** for the methyl-substituted anhydride **5** and with material derived from (*R*)-**2** for the isopropyl-substituted anhydride **7**.

(9) Irwin, A. J.; Jones, J. B. *J. Am. Chem. Soc.* **1977**, *99*, 556.

Scheme VI



entiating ligand from isopropyl to ethyl to methyl to silyloxy. Note that it is highly unlikely that this trend would continue to even smaller stereodifferentiating groups, such as tritium or deuterium.

The relatively complex relationship that exists between the size of the C-3 stereodifferentiating group and the sense and magnitude of prochiral recognition probably means that there are two or more alternative transition-state conformations for each diastereomeric combination. For example, it is possible that one conformation is favored by increasing steric bulk of the C-3 substituent, but that this substituent also exerts a steric repulsive effect that tends to inhibit the rate of reaction from this conformation. The result of such an interplay of effects could be a trend such as that which we observe.

Experimental Section

General. Alcohol-free ethereal solutions of CH_2N_2 were prepared from the reaction of *N*-methyl-*N*-nitroso-*p*-toluenesulfonamide (Diazald) with KOH in the presence of 2-(2-ethoxyethoxy)ethanol and were stored at −20 °C over KOH pellets at least 24 h before use. Gravity column chromatography was done with Merck silica gel 60 (70–230 mesh ASTM), and flash chromatography[10] was done with MN silica gel 60 (230–400 mesh ASTM). TLC was performed with Analtech silica gel FG TLC plates (250 μm), and compound visualization was effected with a 5% solution of 12-molybdophosphoric acid in ethanol or a solution of 10% vanillin and 5% H_2SO_4 in 95% ethanol. Solvent removal was accomplished at aspirator pressure using a rotary evaporator. ^1H NMR and ^{13}C NMR spectra were measured as $CDCl_3$ solutions at 500 and 125 MHz, unless specified otherwise. *J* values are given in Hz.

3-Ethylglutaric Anhydride (6). A mixture of 15.60 g (0.186 mol) of cyanoacetamide (Kodak, recrystallized from 95% EtOH) and 102 mL of H_2O was swirled until the solid had gone into solution and then cooled to 10 °C. The flask was shaken vigorously while 5.40 g (0.093 mol, 6.71 mL) of freshly-distilled propionaldehyde and 0.60 mL (6 mmol) of piperidine were added successively. The solution was allowed to stand at rt for 2 h and then cooled to 0 °C with vigorous shaking. The mixture was held at 0 °C for 1 h and then allowed to warm to rt. After the ice had melted the precipitated solid was filtered from solution and washed with cold H_2O. The solid was dried overnight to obtain 16.40 g (85%) of 3-ethyl-2,4-dicyanoglutaramide (10) as a white powder, mp 136–139 °C. A mixture of 16.30 g (0.078 mol) of this material and 30 mL of concentrated aqueous HCl was warmed on a steam bath until the solid dissoved, diluted with 30 mL of H_2O, and heated at reflux overnight (12 h). The solution was cooled to rt, saturated with NaCl, and extracted with ether (5 × 100 mL). The ether portions were combined, dried over $MgSO_4$, and concentrated to obtain 9.10 g (73%) of 3-ethylglutaric acid (11) as an off-white solid, mp 63–65 °C. A mixture of 25 mL of acetic anhydride and 8.90 g (0.056 mol) of the crude diacid was refluxed for 4 h. The reaction mixture was then fractionally distilled, first at ambient pressure and then under vacuum, to obtain 7.36 g (93%, 58% overall from cyanoacetamide) of anhydride 6 as a clear colorless oil, bp 116–120 °C (0.5 torr). ^1H NMR: δ 0.99 (t, 3, *J* = 7.5), 1.46 (dt, 2, *J* = 7.3, 7.5), 2.09 (m, 1), 2.43 (dd, 2, *J* = 10.3, 17.3), 2.89 (dd, 2, *J* = 4.5, 17.3). ^{13}C NMR: δ 10.67, 27.32, 30.16, 35.61, 166.52. Anal. Calcd for $C_7H_{10}O_3$: C, 59.14; H, 7.09. Found: C, 59.24; H, 6.96.

3-Isopropylglutaric Anhydride (7). A mixture of 14.40 g (18.14 mL, 0.194 mol, Aldrich) of isobutyraldehyde, 22.60 g (21.26 mL, 0.20 mol) of ethyl cyanoacetate, 0.20 mL (0.002 mol) of piperidine, and 40 mL of benzene was refluxed under a Dean-Stark trap until the dehydration was complete (~3 h). The solvent was removed, and the residue was added to a solution of dimethyl sodiomalonate [from dimethyl malonate (26.20 g, 22.66 mL, 0.20 mol), and sodium (0.46 g, 0.022 mol)] in 20 mL of dry MeOH. The mixture was refluxed for 4 h, cooled to rt, acidified with 2 N HCl, and extracted with ether (3 × 100 mL). The combined ethereal fractions were washed with H_2O, dried ($MgSO_4$), and concentrated to obtain 54.28 g (93%) of methyl ethyl 2-carbomethoxy-4-cyano-3-isopropylglutarate (12) as an orange oil. A mixture of 54.0 g (0.180 mol) of this material and 70 mL of 48% aqueous HBr was refluxed for 24 h. The mixture was reduced in volume by 40 mL, and 40 mL of fresh 48% aqueous HBr was added. The mixture was refluxed for 24 h and then poured into 200 mL of ice-cold H_2O and extracted with ether (4 × 200 mL). The combined ethereal portions were washed with H_2O, dried over $MgSO_4$, and concentrated to obtain 27.42 g (87%) of 3-isopropylglutaric acid (14) as an off-white solid, mp 83–87 °C (lit.[11] mp 102 °C). The crude diacid (27.0 g, 0.155 mol) and 85 mL of acetic anhydride was refluxed for 5 h and then fractionally distilled to obtain 20.80 g (86%, 70% from isobutyraldehyde) of analytically-pure 3-isopropylglutaric anhydride (7) as a clear pale yellow oil, bp 138 °C (0.5 Torr). The material solidified upon standing in the refrigerator and could be recrystallized from hexanes to obtain a white solid, mp 25.5–26.5 °C. ^1H NMR: δ 0.97 (d, 6, *J* = 6.6), 1.62 (m, 1), 1.95 (m, 1), 2.42 (dd, 2, *J* = 11.5, 17.3), 2.88 (dd, 2, *J* = 4.3, 17.3). ^{13}C NMR: δ 19.00, 31.08, 33.74, 34.78, 166.87. Anal. Calcd for $C_8H_{12}O_3$: C, 61.52; H, 7.75. Found: C, 61.39; H, 7.73.

3-Phenylglutaric Anhydride (8). A mixture of 5.00 g (23.3 mmol) of 3-phenylglutaric acid (Aldrich, 97%) and 50 mL of $SOCl_2$ (0.686 mol, Alfa, 97%) was refluxed overnight (15 h). The $SOCl_2$ was removed, leaving ~5 g of a brown solid residue that was recrystallized from EtOAc/hexanes to obtain 4.22 g (95%) of anhydride 8 as a white solid, mp 104–105 °C. ^1H NMR: δ 2.87 (dd, 2, *J* = 11.5, 17.3), 3.10 (dd, 2 *J* = 4.3, 17.3), 3.43 (m, 1), 7.21 (d, 2, *J* = 7.5), 7.33 (t, 1, *J* = 7.4), 7.40 (t, 2, *J* = 7.5). ^{13}C NMR: δ 34.02, 37.06, 126.21, 128.10, 129.33, 139.05, 165.87. Anal. Calcd for $C_{11}H_{10}O_3$: C, 69.46; H, 5.30. Found: C, 69.20; H, 5.28.

3-*tert*-Butylglutaric Anhydride (9). A mixture of 17.20 g (21.69 mL, 0.199 mol) of pivalaldehyde, 22.60 g (21.26 mL, 0.20 mol) of ethyl cyanoacetate, 0.20 mL (0.002 mol) of piperidine, and 40 mL of benzene was refluxed until the dehydration was complete (~3 h). The solvent was removed, and the residue (36.2 g of an orange oil) was added to a solution of dimethyl sodiomalonate [from dimethyl malonate (26.20 g, 22.66 mL, 0.20 mol) and sodium (0.46 g, 0.022 g-atoms)] in 20 mL of dry MeOH. The mixture was refluxed for 6 h, cooled to rt, acidified with 2 N HCl, and extracted with ether (3 × 100 mL). The combined ethereal fractions were washed with H_2O, dried over $MgSO_4$, and concentrated to obtain 60.47 g (97%) of methyl ethyl 2-carbomethoxy-4-cyano-3-*tert*-butylglutarate (13) as an orange oil. A solution of the crude glutarate (60.0 g, 0.191 mol) in 70 mL of 48% aqueous HBr was refluxed for 24 h. The mixture was reduced in volume by 40 mL, an additional 40 mL of 48% aqueous HBr was added, and the resulting mixture was refluxed for another 24 h and then poured into 200 mL of ice-cold H_2O and extracted with ether (4 × 200 mL). The combined ethereal portions were

(10) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.

(11) Lister, K. P. L.; Hui, R. A. H. F.; Jones, J. B. *J. Org. Chem.* **1986**, *51*, 2047.

washed with H_2O, dried over $MgSO_4$, and concentrated to obtain 21.78 g (60%) of 3-*tert*-butylglutaric acid (**15**) as an off-white solid, mp 86–92 °C. A small sample of the acid was recrystallized from EtOAc/hexanes to obtain white mica-like plates, mp 144.5–145.5 °C.

A mixture of 21.0 g (0.112 mol) of the crude 3-*tert*-butylglutaric acid and 60 mL of acetic anhydride was refluxed for 5 h and then fractionally distilled to obtain 12.28 g (65%, 38% from pivalaldehyde) of analytically-pure 3-*tert*-butylglutaric anhydride (**9**) as a clear pale yellow oil, bp 146–148 °C (0.5 torr). The material solidified upon standing, was recrystallized from EtOAc/hexanes to obtain 9.40 g (50%, 31% from pivalaldehyde) of crystalline white flakes, mp 63.5–64.5 °C. ^{1}H NMR: δ 0.95 (s, 9), 1.93 (tt, 1, J = 4.1, 12.8), 2.37 (dd, 2, J = 12.8, 17.2), 2.87 (dd, 2, J = 4.1, 17.2). ^{13}C NMR: δ 26.38, 31.91, 32.24, 38.66, 167.11. Anal. Calcd for $C_9H_{14}O_3$: C, 63.51; H, 8.29. Found: C, 63.78; H, 8.34.

(1′*SR*,3*SR*)-1-(1′-Naphthyl)ethyl Methyl 3-Methylpentanedioate (16a). A mixture of 140 mg (0.81 mmol) of alcohol (±)-**2**,[2] 55 mg (0.45 mmol) of DMAP, and 2.5 mL of CH_2Cl_2 was cooled to −78 °C, and 58 mg (0.45 mmol, Aldrich) of 3-methylglutaric anhydride (±)-**5** was added. The resulting mixture was allowed to warm to −40 °C and stirred for 2 d. The reaction mixture was diluted with 25 mL of ether and washed with 10 mL of 1 M aqueous H_3PO_4 and 5 mL of saturated aqueous $NaHCO_3$. The combined aqueous washings were extracted with 10 mL of ether. The combined organic fractions were dried and concentrated to obtain 193 mg of acid as a clear colorless oil. The crude acid was taken up in minimal ether, added to ~3 mL of a 0.28 M solution of CH_2N_2 in ether, and allowed to stand overnight at rt. The solvent was removed to obtain 189 mg of a clear colorless oil. The material was purified by radial preparative layer chromatography (2-mm plate of silica gel with 9:1 hexanes/EtOAc as eluant) to obtain 132 mg (94%) of a clear oil that proved to be a 16:1 mixture of diastereomers by ^{1}H NMR analysis of the methyl ester peaks (**16a**: δ 3.66; C-3 diastereomer, **16b**: δ 3.64). ^{1}H NMR: δ 1.01 (d, 3, J = 6.6), 1.71 (d, 3, J = 6.6), 2.23 (dd, 1, J = 7.6, 15.2), 2.30 (dd, 1, J = 7.2, 15.2), 2.38 (dd, 1, J = 5.8, 14.8), 2.43 (dd, 1, J = 6.4, 14.8), 2.49 (m, 1), 3.66 (s, 3), 6.67 (q, 1, J = 6.6), 7.51 (m, 3), 7.60 (d, 1, J = 7.1), 7.80 (d, 1, J = 8.2), 7.87 (d, 1, J = 7.8), 8.08 (d, 1, J = 8.4). ^{13}C NMR: δ 19.79, 21.70, 27.47, 40.56, 41.09, 51.43, 69.36, 123.09, 123.19, 125.31, 125.63, 126.26, 128.41, 128.87, 130.20, 133.79, 137.38, 171.54, 172.70. Anal. Calcd for $C_{19}H_{22}O_4$: C, 72.59; H, 7.06. Found: C, 72.83; H, 7.22.

(1′*S*,3*S*)-(−)-1-(1′-Naphthyl)ethyl Methyl 3-Methylpentanedioate (16a). The foregoing procedure was repeated with 6.20 g (36.0 mmol) of (*S*)-1-(1′-naphthyl)ethanol (**2**),[2] 2.45 g (20 mmol) of DMAP, 2.56 g (20 mmol) of 3-methylglutaric anhydride (**5**), and 25 mL of CH_2Cl_2. This process provided 6.11 g (97%) of diester **16a** as a clear colorless oil. The spectral characteristics were identical to those of the racemic material, $[\alpha]^{22}_D$ = −14.0 (*c* = 1, EtOAc).

(1′*SR*,3*SR*)-1-(1′-Naphthyl)ethyl Methyl 3-Ethylpentanedioate (17a). A mixture of 140 mg (0.81 mmol) of alcohol (±)-**2**,[2] 55 mg (0.45 mmol) of DMAP, and 2.5 mL of CH_2Cl_2 was cooled to −78 °C, and 64 mg (0.45 mmol) of anhydride **6** was added. The reaction mixture was allowed to warm to −40 °C and stirred for 3 d and then was diluted with 25 mL of ether and washed with 10 mL of 1 M aqueous H_3PO_4 and 5 mL of saturated aqueous $NaHCO_3$. The combined aqueous washings were extracted with 10 mL of ether. The combined organic fractions were dried and concentrated to obtain 227 mg of a clear colorless oil. The crude acid was taken up in minimal ether, added to ~3 mL of a 0.28 M solution of CH_2N_2 in ether, and kept overnight at rt. The solvent was removed to obtain 227 mg of a clear pale yellow oil. The material was purified by radial preparative-layer chromatography (2-mm plate of silica gel with 3:1 hexanes/EtOAc as eluant) to obtain 140 mg (95%) of a clear colorless oil that proved to be a 14:1 mixture of diastereomers by ^{1}H NMR analysis of the methyl ester peaks (**17a**: δ 3.64; C-3 diastereomer, **17b**: δ 3.62). IR ($CHCl_3$): 2970, 1735, 1445, 1380, 1270, 1175, 1075, 915 cm^{-1}. ^{1}H NMR: δ 0.89 (t, 3, J = 7.4), 1.40 (dt, 2, J = 6.5, 7.4), 1.70 (d, 3, J = 6.6), 2.34 (m, 3), 2.43 (m, 2), 3.64 (s, 3), 6.67 (q, 1, J = 6.6), 7.47 (m, 3), 7.60 (d, 1, J = 7.1), 7.79 (d, 1, J = 8.2), 7.87 (d, 1, J = 7.95), 8.08 (d, 1, J = 8.4). ^{13}C NMR: δ 10.88, 21.74, 26.60, 33.58, 37.90, 38.39, 51.43, 69.37, 123.11, 123.20, 125.32, 125.63, 126.26, 128.40, 128.88, 130.21, 133.80, 137.44, 171.84, 173.00. Anal. Calcd for $C_{20}H_{24}O_4$: C, 73.14; H, 7.37. Found: C, 73.06; H, 7.21.

(1′*SR*,3*SR*)-1-(1′-Naphthyl)ethyl Methyl 3-Isopropylpentanedioate (18a). A mixture of 140 mg (0.81 mmol) of alcohol (±)-**2**,[2] 55 mg (0.45 mmol) of DMAP, and 2.5 mL of CH_2Cl_2 was cooled to −78 °C, and 70 mg (0.45 mmol) of anhydride **7** was added. The reaction mixture was allowed to warm to −40 °C and stirred for 4 d and then was diluted with 25 mL of ether and washed with 10 mL of 1 M aqueous H_3PO_4 and 5 mL of saturated aqueous $NaHCO_3$. The combined aqueous washings were extracted with 10 mL of ether. The combined organic fractions were dried and concentrated to obtain 233 mg of a clear colorless oil. The crude acid was taken up in minimal ether and added to ~3 mL of a 0.28 M solution of CH_2N_2 in ether. The mixture was allowed to stand overnight at rt. The solvent was removed to obtain 233 mg of a clear pale yellow oil. The material was purified by radial preparative-layer chromatography (2-mm plate of silica gel with 3:1 hexanes/EtOAc as eluant) to obtain 150 mg (97%) of a clear colorless oil that proved to be a 7:1 mixture of diastereomers by ^{1}H NMR analysis of the methyl ester peaks (**18a**: δ 3.64; C-3 diastereomer, **18b**: δ 3.59). ^{1}H NMR: δ 0.85 (d, 3, J = 6.8), 0.87 (d, 3, J = 6.8), 1.70 (d, 3, J = 6.6), 1.74 (m, 1), 2.28 (m, 1), 2.36 (m, 4), 3.64 (s, 3), 6.66 (q, 1, J = 6.6), 7.50 (m, 3), 7.60 (d, 1, J = 7.1), 7.79 (d, 1, J = 8.2), 7.87 (d, 1, J = 7.7), 8.08 (d, 1, J = 8.3). ^{13}C NMR: δ 18.90 (18.83, 18.96), 21.70 (21.67), 30.19 (29.64), 35.68 (35.64), 36.13 (36.26), 37.69 (37.73), 51.45 (51.41), 69.36 (69.38), 123.09 (123.12, 123.16 (123.19), 125.21, 125.59, 126.21, 128.35, 128.84, 130.19, 133.77, 137.44, 172.15, 173.31. Anal. Calcd for $C_{21}H_{26}O_4$: C, 73.66; H, 7.65. Found: C, 73.82; H, 7.67.

(1′*R*,3*R*)-(+)-1-(1′-Naphthyl)ethyl Methyl 3-Isopropylpentanedioate ((+)-18a). The foregoing procedure was carried out with 7.00 g (40.5 mmol) of (*R*)-(+)-1-(1′-naphthyl)ethanol, (*R*)-**2**,[2] 2.75 g (22.5 mmol) of DMAP, 25 mL of CH_2Cl_2, and 3.50 g (22.5 mmol) of anhydride **7** to obtain 7.06 g (96%) of the half-acid, half-ester as a clear colorless oil, $[\alpha]^{23}_D$ = +13.6 (*c* = 1, $CHCl_3$). ^{1}H NMR: δ 0.87 (d, 3, J = 6.8), 0.88 (d, 3, J = 6.7), 1.69 (d, 3, J = 6.6), 1.78 (m, 1), 2.39 (m, 6), 6.66 (q, 1, J = 6.6), 7.49 (m, 3), 7.59 (d, 1, J = 7.1), 7.79 (d, 1, J = 8.2), 7.86 (d, 1, J = 7.9), 8.07 (d, 1, J = 8.4). ^{13}C NMR: δ 18.91, 18.98, 21.70, 30.20, 35.64, 36.09, 36.19, 37.50, 69.55, 123.09, 123.19, 125.33, 126.64, 126.27, 128.41, 128.87, 130.19, 133.79, 137.37, 172.25, 179.03. Anal. Calcd for $C_{20}H_{24}O_4$: C, 73.14; H, 7.37. Found: C, 72.84; H, 7.60.

Treatment of 4.80 g (14.6 mmol) of this material in 30 mL of ether with 75 mL (17 mmol) of a 0.28 M solution of CH_2N_2 in ether afforded 4.94 g (99%) of analytically-pure diester **18a** as a clear pale yellow oil. The spectral characteristics were identical to those of the racemic material, $[\alpha]^{23}_D$ = +14.0 (*c* = 1, $CHCl_3$).

(1′*SR*,3*SR*)-1-(1′-Naphthyl)ethyl Methyl 3-Phenylpentanedioate (19a). A mixture of 140 mg (0.81 mmol) of alcohol (±)-**2**, 55 mg (0.45 mmol) of DMAP, and 5 mL of CH_2Cl_2 was cooled to −78 °C, and 86 mg (0.45 mmol) of anhydride **8** was added. The reaction mixture was allowed to warm to −40 °C and stirred for 3 d and then diluted with 25 mL of ether and washed with 10 mL of 1 M aqueous H_3PO_4 and 5 mL of saturated aqueous $NaHCO_3$. The combined aqueous washings were extracted with 10 mL of ether. The combined organic fractions were dried and concentrated to obtain 239 mg of a cloudy water-white liquid. The crude acid was taken up in minimal ether and added to ~3 mL of a 0.28 M solution of CH_2N_2 in ether. The mixture was allowed to stand overnight at rt. The solvent was removed to obtain 242 mg of a cloudy pale yellow oil. The material was purified by radial preparative layer chromatography (2-mm plate of silica gel with 9:1 hexanes/EtOAc as eluant) to obtain 156 mg (92%) of a clear colorless oil that proved to be an 8:1 mixture of diastereomers by ^{1}H NMR analysis of the methyl ester peaks (**19a**: δ 3.57; C-3 diastereomer, **19b**: δ 3.55). ^{1}H NMR: δ 1.58 (d, 3, J = 6.6), 2.66 (dd, 1, J = 8.0, 15.54), 2.69 (dd, 1, J = 7.0, 15.5), 2.75 (dd, 1, J = 8.3, 14.8), 2.81 (dd, 1, J = 6.9, 14.8), 3.57 (s, 3), 3.69 (m, 1), 6.56 (q, 1, J = 6.6), 7.22 (m, 5), 7.40 (m, 2), 7.47 (m, 2), 7.75 (m, 1), 7.84 (m, 1), 7.94 (m, 1). ^{13}C NMR: δ 21.50, 38.33, 40.59, 40.73, 51.56, 69.60, 123.05, 123.19, 125.32, 125.58, 126.25, 126.95, 127.25, 128.32, 128.57, 128.83, 130.14, 133.75, 137.15, 142.36, 170.79, 171.98. Anal. Calcd for $C_{24}H_{24}O_4$: C, 76.57; H, 6.43. Found: C, 76.38; H, 6.47.

(1′*SR*,3*RS*)-1-(1′-Naphthyl)ethyl Methyl 3-*tert*-Butylpentanedioate (20b). A mixture of 140 mg (0.81 mmol) of alcohol (±)-2,[2] 55 mg (0.45 mmol) of DMAP, and 2.5 mL of CH_2Cl_2 was cooled to −78 °C, and 77 mg (0.45 mmol) of anhydride **9** was added. The reaction mixture was allowed to warm to −40 °C and stirred for 16 d and then diluted with 25 mL of ether and washed with 10 mL of 1 M aqueous H_3PO_4 and 5 mL of saturated aqueous $NaHCO_3$. The combined aqueous washings were extracted with 10 mL of ether. The combined organic fractions were dried and concentrated to obtain 229 mg of a clear aquamarine-colored oil. The crude acid was taken up in minimal of ether and added to ~3 mL of a 0.28 M solution of CH_2N_2 in ether. After standing overnight at rt, the solvent was removed to obtain 225 mg of a clear pale yellow oil. The material was purified by radial preparative-layer chromatography (2-mm plate of silica gel with 3:1 hexanes/EtOAc as eluant) to obtain 145 mg (91%) of a clear colorless oil that proved to be a 3:1 mixture of diastereomers by ^1H NMR analysis of the methyl ester peaks (**20b**: δ 3.51; C-3 diastereomer, **20a**: δ 3.61). ^1H NMR: δ 0.89 (s, 9), 1.69 (d, 3, J = 6.6), 2.18 (dd, 1, J = 7.5, 15.5), 2.24 (dd, 1, J = 8.1, 15.5), 2.39 (m, 1), 2.46 (dd, 1, J = 4.9, 15.6), 2.58 (dd, 1, J = 4.4, 15.6), 3.51 (s, 3), 6.65 (q, 1, J = 6.6), 7.48 (m, 3), 7.62 (d, 1, J = 7.0), 7.79 (d, 1, J = 8.2), 7.86 (d, 1, J = 8.1), 8.09 (d, 1, J = 8.5). ^{13}C NMR: δ 21.60 (21.66), 27.11, 33.33 (33.29), 35.58 (35.68), 36.03 (35.93), 41.40 (41.33), 51.47 (51.56), 69.43 (69.36), 123.19 (123.14), 123.27, 125.31, 125.58, 126.20, 128.31, 128.81, 130.18, 133.73, 137.39, 172.64, 173.76. Anal. Calcd for $C_{22}H_{28}O_4$: C, 74.13; H, 7.92. Found: C, 74.30; H, 7.82.

(3*R*)-Methyl Hydrogen 3-Methylpentanedioate (21a). A mixture of 5.60 g (17.8 mmol) of diester **16a**, 50 mL of EtOAc, and 500 mg of 10% Pd/C was stirred at rt under 1 atm of H_2 for 4 d, diluted with EtOAc, and filtered through a Celite pad, which was rinsed well with EtOAc. The filtrate was concentrated to obtain 5.40 g of a clear pale yellow oil, which was taken up in ether and extracted with saturated aqueous $NaHCO_3$. The aqueous layer was acidified with 6 N HCl and extracted with ether. The ether portions were combined, dried over $MgSO_4$, and concentrated to obtain 2.63 g (99%) of monomethyl-3-methylglutaric acid (**21a**) as a water-white liquid. The spectral characteristics were in agreement with those reported in the literature.[12] ^1H NMR: δ 1.05 (d, 3, J = 6.5), 2.29 (m, 2), 2.44 (m, 3), 3.68 (s, 3). ^{13}C NMR: δ 19.82, 27.15, 40.44, 40.48, 51.56, 172.76, 178.52. Anal. Calcd for $C_7H_{12}O_4$: C, 52.49; H, 7.55. Found: C, 52.32; H, 7.49.

(*R*)-(+)-3-Methylvalerolactone ((+)-22a). A solution of 1.200 g (7.50 mmol) of **21a** and 20 mL of THF was cooled to 0 °C, and 760 μL (7.60 mmol, Aldrich) of a 10 M solution of BH_3·SMe_2 was added dropwise by syringe. The mixture was allowed to warm to rt and stirred for 2 h. The mixture was cooled to 0 °C, and 5 mL of H_2O was added. The mixture was concentrated, and the residue was taken up in EtOAc and dried over $MgSO_4$. The solvent was removed under reduced pressure to obtain 902 mg of a clear colorless oil, which was treated with 4 mL of 2 N NaOH. The mixture was stirred overnight at rt, acidified with 6 N HCl, and extracted with EtOAc (2 × 50 mL). The combined organic portions were dried and concentrated to obtain 875 mg of a clear colorless oil. A solution of the crude hydroxy acid and 10 mg of *p*-TsOH in 15 mL of benzene was refluxed for 4 h and then cooled to rt, washed with H_2O (2 × 15 mL), and concentrated to obtain 800 mg of pale yellow oil. This material was purified by flash chromatography (30 g of silica gel, 230–400 mesh, MN, with 2:1 hexanes/EtOAc as eluant) to obtain 701 mg (82%) of lactone **22a** as a clear colorless oil, $[\alpha]^{22}_D$ = +23.8 (c = 4.5, $CHCl_3$) [lit.[9] $[\alpha]^{25}_D$ = +27.6 (c = 5.6, $CHCl_3$)]. The observed specific rotation indicates that the lactone is 86% ee, assuming that the Irvin and Jones rotation is the maximum. The other spectral characteristics were in agreement with those reported.[9] ^1H NMR: δ 1.07 (d, 3, J = 6.0), 1.53 (m, 1), 1.93 (dd, 1, J = 3.8, 14.0), 2.11 (m, 1), 2.68 (dd, 1, J = 9.9, 15.5), 4.27 (ddd, 1, J = 3.8, 7.3, 15.2), 4.43 (ddd, 1, J = 4.7, 7.7, 15.2). ^{13}C NMR: δ 21.32, 26.42, 30.48, 38.09, 68.48, 171.16. Anal. Calcd for $C_6H_{10}O_2$: C, 63.13; H, 8.83. Found: C, 62.87; H, 8.91.

(3*S*)-Methyl Hydrogen 3-Isopropylpentanedioate (21c). A mixture of 4.80 g (14.02 mmol) of diester **18c**, 25 mL of EtOAc, and 300 mg of 10% Pd/C was stirred at rt under 1 atm of H_2 for 6 d and then diluted with EtOAc and filtered through a Celite pad. The Celite was rinsed well with EtOAc, and the filtrate was concentrated to obtain 4.98 g of a clear pale yellow oil. This material was taken up in EtOAc and extracted with 150 mL of 0.1 N NaOH. The aqueous layer was acidified with 6 N HCl and extracted with EtOAc (3 × 150 mL). The organic portions were combined, dried over $MgSO_4$, and concentrated to obtain 2.64 g (100%) of analytically-pure monomethyl 3-isopropylglutarate (**21c**) as a water-white liquid. ^1H NMR: δ 0.90 (d, 6, J = 6.9), 1.79 (m, 1), 2.32 (m, 3), 2.41 (m, 2), 3.67 (s, 3), 9.67 (bs, 1). ^{13}C NMR: δ 18.85, 18.87, 30.30, 35.67, 35.71, 37.44, 51.56, 173.45, 179.46. Anal. Calcd for $C_9H_{16}O_4$: C, 57.43; H, 8.57. Found: C, 57.37; H, 8.69.

(*S*)-(−)-3-Isopropylvalerolactone ((−)-22c). A mixture of 2.30 g (12.2 mmol) of acid/ester **21c** and 20 mL of THF was cooled to 0 °C, and 1.30 mL (13.0 mmol) of a 10 M solution of BH_3·SMe_2 was added dropwise by syringe. The mixture was allowed to warm to rt and stirred for 2 h. The mixture was cooled to 0 °C, and 15 mL of H_2O was added. The mixture was concentrated, and the residue was taken up in EtOAc, washed successively with 0.05 N aqueous HCl (2 × 25 mL) and saturated aqueous $NaHCO_3$ (2 × 20 mL), and dried. The solvent was removed to obtain 1.838 g of a clear pale yellow oil. A mixture of the crude hydroxy ester and 12 mL of 2 N NaOH was stirred overnight at rt, acidified with 6 N HCl, and extracted with EtOAc (3 × 100 mL). The combined organic portions were dried and concentrated to obtain 1.675 g of hydroxy acid as a clear, pale yellow oil. This material was dissolved in 20 mL of benzene, and 20 mg of *p*-TsOH was added. The mixture was refluxed for 4 h, cooled to rt, washed with H_2O (2 × 15 mL), and concentrated to obtain 1.455 g of a pale yellow oil. This material was purified by flash chromatography (50 g of silica gel, 230–400 mesh, MN, with 2:1 hexanes/EtOAc as eluant) to obtain 1.381 g (81%) of lactone **22c** as a clear colorless oil, $[\alpha]^{23}_D$ = −17.0 (c = 1, EtOH) [lit.[9] $[\alpha]^{25}_D$ = −22.67 (c = 1.0, EtOH)]. The observed specific rotation indicates that the lactone is 75% ee, assuming that the Irvin and Jones rotation is the maximum. The other spectral characteristics were in agreement with those found in the literature.[9] ^1H NMR: δ 0.92 (d, 3, J = 6.3), 0.94 (d, 3, J = 6.7), 1.55 (m, 2), 1.75 (m, 1), 1.93 (m, 1), 2.22 (dd, 1, J = 9.0, 17.3), 2.68 (ddd, 1, J = 1.4, 6.0, 17.3), 4.23 (ddd, 1, J = 3.7, 10.9, 14.8), 4.41 (ddd, 1, J = 3.9, 8.0, 14.8). ^{13}C NMR: δ 19.08, 19.18, 26.24, 32.22, 33.99, 37.77, 68.62, 171.93. Anal. Calcd for $C_8H_{14}O_2$: C, 67.57; H, 9.92. Found: C, 67.32; H, 9.81.

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Supplementary Material Available: Full listings of infrared absorptions of all compounds reported (2 pages). This material is contained in libraries on micorfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

(12) Adachi, K.; Kobayashi, S.; Ohno, M. *Chimia* **1986**, *40*, 311.