following flash chromatography and sublimation: mp 60–62 °C (lit. mp 61–63 °C);[45] ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.08–2.06 (m, 1 H), 1.80–1.18 (m, 12 H), 0.80 (d, J = 6.8 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 79.01, 42.69, 40.57, 38.05, 37.51, 32.87, 30.67, 19.68, 18.48; IR (CCl_4) 3401, 2931, 2860, 1455, 1120 cm^{-1}; LRMS (EI) m/e 140 (1), 97 (100), 70 (6). Anal. Calcd for $C_9H_{16}O$: C, 77.09; H, 11.50. Found: C, 77.31; H, 11.34.

7,7-Dimethylbicyclo[3.2.1]octan-1-ol (4m): 3m (0.249 g, 0.892 mmol); yield 0.078 g (57%); mp 62–64 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.09–2.06 (m, 2 H), 1.74–1.50 (m, 5 H), 1.35–1.17 (m, 5 H), 0.97 (s, 3 H), 0.95 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 79.78, 44.06, 42.57, 39.92, 36.48, 31.36, 30.96, 28.47, 20.86, 19.55; IR (CCl_4) 3613, 3448, 2931, 1454, 1079 cm^{-1}; LRMS (EI) m/e 154 (5), 111 (73), 97 (100), 70 (47). Anal. Calcd for $C_{10}H_{18}O$: C, 77.87; H, 11.76. Found: C, 78.01; H, 11.50.

(1′*S*,5′*R*)-6′-Methylspiro[cyclopropane-1,2′-bicyclo-[3.2.1]octan]-1′-ol (4n): 3n (0.075 g, 0.26 mmol); yield 0.032 g (75%) as an inseparable 3:1 mixture of C-6 epimers; bp 65 °C (1.0 mmHg); ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.45–2.29 (m, 1 H), 2.15 (ddd, J = 12.7, 8.7, 1.9 Hz, 1 H), 2.01–1.80 (m, 8 H), 1.62–1.40 (m, 6 H), 1.18–1.12 (m, 2 H), 1.02 (d, J = 7.1 Hz, 3 H), 0.99 (d, J = 7.3 Hz, 3 H), 0.88–0.80 (m, 2 H), 0.68–0.55 (m, 4 H), 0.17–0.02 (m, 4 H); ^{13}C NMR (75 MHz, $CDCl_3$) (major) δ 79.29, 46.37, 43.20, 42.40, 35.02, 31.57, 31.15, 27.11, 23.79, 9.74, 7.25; (minor) 78.70, 47.05, 44.16, 40.53, 34.92, 32.01, 27.73, 26.14, 15.22, 10.10, 7.28; IR (CCl_4) 3378, 3072, 3002, 2931, 2849, 1449, 1296, 1108 cm^{-1}; HRMS calcd for $C_{11}H_{18}O$ 166.1358, found 166.1372; LRMS (EI) m/e major 166 (4), 122 (100), 109 (47), 95 (93), 93 (80), 67 (49), minor 166 (3), 122 (100), 109 (38), 95 (89), 93 (67), 67 (44).

Acknowledgment. We thank the National Institutes of Health for their generous support of our program.

Supplementary Material Available: ^{1}H and ^{13}C NMR data for all bridgehead bicyclic alcohols for which elemental analyses are not reported; spectra are also included for the synthetic intermediates along the pathway to the iodo ketone substrates (111 pages). Ordering information is given on any current masthead page.

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Highly Effective and Practical Enantioselective Synthesis of Half-Esters of Bicyclo[2.2.1]heptanedicarboxylic Acid

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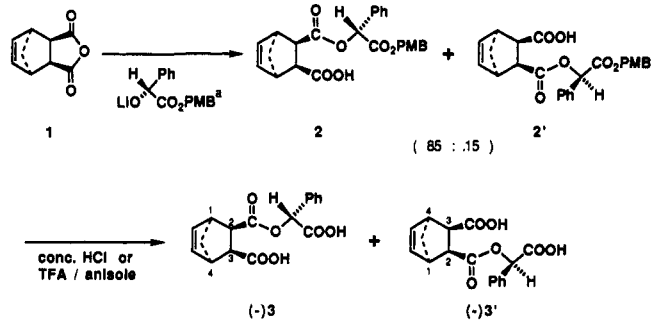
An effective and practical enantioselective synthesis of half-esters of bicyclo[2.2.1]heptane-2,3-dicarboxylic acid was developed by enantioselective fission of σ-symmetrical cyclic anhydrides with chiral mandelic acid derivatives, followed by deprotection of the mandelate moiety, crystallization, and further modification. These half-esters are very attractive chiral building blocks for numerous natural products, and this new method makes possible their synthesis via common intermediates with high optical purity.

Compounds possessing the bicyclo[2.2.1[heptane skeleton are very important compounds because they occur as natural products and serve as versatile building blocks for the synthesis of numerous compounds. They have been employed, for example in the synthesis of prostanoids,[1] alkaloids,[2] terpenes,[3] insecticides,[4] and nucleosides.[5]

Although enzymatic hydrolysis and the Diels–Alder reaction are very attractive for the asymmetric synthesis of half-esters of bicyclo[2.2.1]heptane-2,3-dicarboxylic acid, enzymatic methods have inevitable limitations[6] and the effective Diels–Alder reactions have mostly been limited to *trans*-2,3-dicarboxylic acid derivatives.[7] Moreover, some of these reactions do not offer the convenience of a simple procedure for large-scale synthesis.

Scheme I



Described herein is an enantioseletive synthesis yielding optically pure cis and trans half-esters of bicyclo[2.2.1]-heptane-2,3-dicarboxylic acid from a common intermedi-

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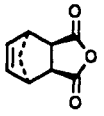
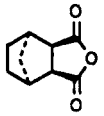
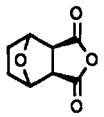
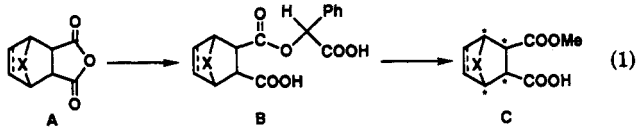
Table I. Conversion of Anhydride A to Dicarboxylic Acid B (See Scheme I)

anhydride	mandelate	temp (°C)	ratio of diastereomer	deprotection	product	overall yield (%)	purity[a] (% de)
 1	*R*, PMB[b]	−35	85:15	A[e]	(−)-3 (2*R*,3*S*)	50.2	100.0
	S, Bh[c]	−78	74:26	B[f]	(+)-3 (2*S*,3*R*)	47.0	100.0
 1′	*R*, Bz[d]	−65	87:13	C[g]	(−)-4 (2*R*,3*S*)	66.0	100.0
	S, PMB	−35	86:14	A	(+)-4 (2*S*,3*R*)	65.5	100.0
 1″	*R*, Bz	−65	73:27	C	(−)-5 (2*S*,3*R*)	35.8	97.0
	S, Bz	−65	74:26	C	(+)-5 (2*R*,3*S*)	36.0	97.0

[a] After crystallization, determined by HPLC. [b] *p*-Methoxybenzyl. [c] Benzhydryl. [d] Benzyl. [e] A: concd HCl in CH_3CN. [f] B: trifluoroacetic acid in anisole. [g] C: H_2/Pd–C in MeOH.

ate. Our enantioselective synthesis of the half-esters was accomplished by enantioselective fission of σ-symmetrical five-membered anhydride A with chiral mandelic acid derivatives and subsequent deprotection of the mandelate moiety, followed by simple crystallization for purification, giving stereochemically pure dicarboxylic acids B, which were transformed into stereoisomers of half-esters C in high optical purity (eq 1).



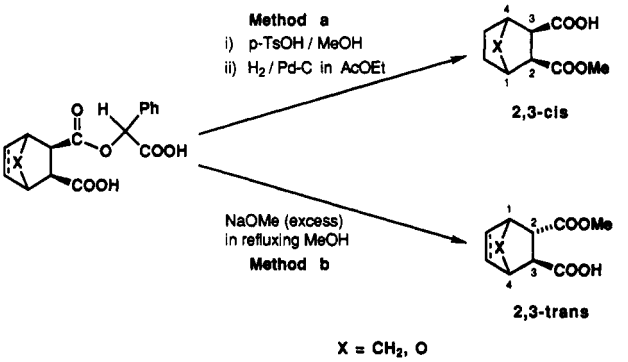
(1)

Results and Discussion

Enantioselective Fission of Cyclic meso Anhydride. Mandelic acid derivatives were employed as the chiral controller because they allow easy purification of the dicarboxylic acids by simple crystallization after deprotection of the mandelate moiety. Enantioselective fission of anhydride 1 with the lithium *p*-methoxybenzyl (*R*)-(−)-mandelate was conducted at −35 °C in THF, giving a mixture of half-ester 2 (2*R*,3*S*) and its diastereomer 2′ (85:15). Without purification, the crude product was transformed into a mixture of (−)-3 and its diastereomer (−)-3′ by hydrolytic deprotection of the *p*-methoxybenzyl ester using concd HCl in CH_3CN or trifluoroacetic acid/anisole in CH_2Cl_2, followed by crystallization from ethyl acetate to obtain stereochemically pure crystalline product (−)-3 in 50.2% yield (100.0% de) from the anhydride 1 (Scheme I). Several trials were done using other esters in an attempt to improve the ratio of enantioselectivity (Table I). Dicarboxylic acid (+)-3, the enantiomer of (−)-3, was also obtained by employing benzhydryl (*S*)-(+)-mandelate, in place of *p*-methoxybenzyl (*R*)-(−)-mandelate, in the same manner (Table I, Scheme I). It is not clear why the benzhydryl ester gave lower enantioselectivity.

In the case of 1′ having a saturated nucleus, the benzyl or *p*-methoxybenzyl esters were selected because the deprotection could be easily accomplished without any side reactions by hydrogenolysis using 10% Pd–C in MeOH,[8] and we obtained dicarboxylic acid (−)-4.[9]

Scheme II



The best result for enantioselective fission of cyclic anhydrides was attained when benzyl (*R*)-(−)-mandelate was used in the reaction with 1′ and gave dicarboxylic acid (−)-4 in 66% yield.

The stereochemistry of saturated dicarboxylic acid (−)-4 was determined by X-ray crystallographic analysis (see the supplementary material).

This reaction was extended to the 7-oxabicyclo[2.2.1]-heptane compounds, which are very important starting materials for the synthesis of natural products. In the oxa series, exo meso anhydride 1″ was chosen as the starting material to extend the limitations of this reaction. Although the yield was not as high as in the endo series of 7-carba derivatives and lower than that of the enzyme-catalyzed hydrolysis, almost pure dicarboxylic acids were obtained (97.0% de) as shown in Table I.

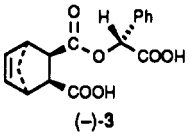
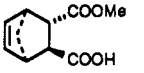
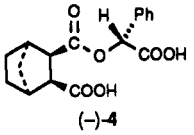
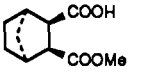
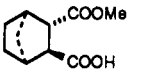
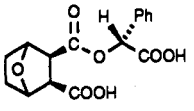
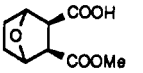
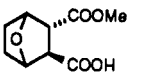
Transformation of Dicarboxylic Acids B into Half-Esters C. Transformation of these dicarboxylic acids into the desired half-esters was attained by two independent procedures: (a) methylation with MeOH and *p*-toluenesulfonic acid, followed by catalytic hydrogenolysis in ethyl acetate giving cis half-esters, and (b) epimerization and methanolysis reaction, using a large excess of NaOMe in refluxing MeOH to obtain trans half-esters (Scheme II, Table II).

Note that addition of the diacids to a large excess (10 equiv) of NaOMe in refluxing MeOH (high concentration

(8) The use of other solvents, such as ethyl acetate, at a higher pressure of hydrogen caused excessive reduction of the product, giving meso dicarboxylic acid.

(9) (a) Ohtani, M.; Matsuura, T. EP-A-373949, 1988, Dec. 14. (b) Ohtani, M.; Matsuura, T.; Watanabe, F.; Narisada, M. *J. Org. Chem.* 1991, *56*, 2122.

Table II. Transformation of Dicarboxylic Acid B into Half-Ester C[a]

di-acid	method[a]	half-ester	compd no.	$[\alpha]^{28}_D$[b] (deg)	% yield	% ee[c]
 (−)-3	b		(+)-6	+138.1	93	99.8
(+)-3	b		(−)-6	−140.0	93.8	99.8
	a		(+)-7	+17.1	80	>99.9
(−)-4	b		(+)-8	+38.4	94	97.4
(+)-4	a		(−)-7	−17.4	88	>99.9
(+)-4	b		(−)-8	−38.3	95	99.8
	a		(−)-9	−4.9	82	97.0
(−)-5	b		(+)-10	+73.3	50	96.0
(+)-5	a		(+)-9	+4.4	78	97.0
(+)-5	b		(−)-10	−74.5	50	95.2

[a] See Scheme II. [b] Rotations measured in MeOH (c = 2). [c] Determined by HPLC analysis of the corresponding (*S*)-α-methylbenzyl amide.

is recommended) is required to promote rapid epimerization of the mandelate esters. Insufficient NaOMe led to cyclization to meso anhydrides which gave racemic half-esters.[9]

The enantiomeric purity (% ee) of these half-esters was satisfactorily high when measured by HPLC from the ratio of the diastereomeric amides derived from the half-esters and (*S*)-(−)-α-methylbenzylamine.

Compounds (−)-6,[10] (+)-8,[9] and (−)-9[6] are known in the literature, and (−)-6 and (+)-8 were used as key intermediates for the synthesis of thromboxane A_2 receptor antagonists, ONO-8809 and S-1452, respectively.

We were able to obtain four stereoisomers of the half-esters from a cyclic meso anhydride. When exo or endo meso anhydrides having the same structure are used, it should be possible to synthesize eight stereoisomers of the half-esters via two common intermediates by the above simple reactions with high optical purity and on a large scale. The new route described above for the synthesis of half-esters of bicyclo[2.2.1]heptane-2,3-dicarboxylic acid offers the major advantages of applicability to all possible stereoisomers, conciseness, simplicity of the reactions, and the possibility of large-scale preparation.

Experimental Section

Reactions using anhydrous solvents (dried over type 4A molecular sieves) were carried out in a nitrogen atmosphere. Melting points are not corrected. Organic extracts were dried over anhydrous $MgSO_4$.

(1*S*,2*R*,3*S*,4*R*)-2-[(*R*)-Mandeloxycarbonyl]bicyclo-[2.2.1]hept-5-ene-3-carboxylic Acid ((−)-3). Representative Procedure for Preparation of Dicarboxylic Acids B. A solution of *p*-methoxybenzyl (*R*)-mandelate[9] (20.97 g, 70 mmol × 1.1) in 175 mL of THF was cooled to −78 °C, and then 43.75 mL (70 mmol) of 1.6 M *n*-BuLi in hexane was added dropwise over 30 min and the mixture was stirred for 30 min at −78 °C. A solution of 11.5 g (70 mmol) of meso anhydride 1 in 50 mL of THF at −35 °C was added, and the resulting mixture was stirred for 1 h at −35 °C. The reaction mixture was acidified with 2 N HCl, and the product was extracted with ethyl acetate. The organic layer was washed with water, dried, and concentrated to obtain 30.6 g (quantitative) of the crude ester 2. To a solution of the crude 2 in 160 mL of CH_3CN was added 35.9 mL of concd HCl, and the miture was stirred for 16 h at rt. The reaction mixture was adjusted to pH 4 with 4 N NaOH, made alkaline with an aqueous $NaHCO_3$ at 0 °C, and washed with ethyl acetate. The aqueous solution was acidified with concd HCl and extracted with ethyl acetate. The organic solution was washed with water, dried, and concentrated in vacuo to give a crystalline residue ((−)-3/(−)-3′ = 85/15). Recrystallization from ethyl acetate gave 11.2 g (50%) of the pure diacid (−)-3 (100.0% de) as colorless plates: mp 169–171 °C. The enantiomeric purity was determined by HPLC using Nucleosil 5C.[18] Mobile phase $CH_3CN/MeOH/H_2O/AcOH$ (200/200/450/1); flow rate 1.0 mL/min; detection 225 nm. IR ($CHCl_3$): 3500–2400, 1734 cm^{-1}. ^1H NMR ($CDCl_3$–TMS): δ 1.36 (AB q, A part, J = 7.2 Hz, 1 H), 1.51 (AB q, B part, J = 7.2 Hz, 1 H), 3.15 (br s, 2 H), 3.43 (d AB q, A part, J = 2.9, 10.4 Hz, 1 H), 3.53 (d AB q, B part, J = 3.1, 10.4 Hz, 1 H), 5.86 (s, 2 H), 6.14–6.33 (m, 2 H), 7.32–7.62 (m, 5 H). $[\alpha]_D$: −159.5 ± 1.0° (MeOH, c 1.99, 24 °C). Anal. Calcd for $C_{17}H_{16}O_6$: C, 64.55; H, 5.10. Found: C, 64.46; H, 5.12.

(1*R*,2*S*,3*R*,4*S*)-2-[(*S*)-Mandeloxycarbonyl]bicyclo-[2.2.1]hept-5-ene-3-carboxylic Acid ((+)-3). The benzhydryl ester of (+)-3 was prepared by using benzhydryl (*S*)-(+)-mandelate, in place of *p*-methoxybenzyl (*R*)-(−)-mandelate, in the same manner as 2. Benzhydryl (*S*)-(+)-mandelate was obtained as follows: To a solution of (*S*)-(+)-mandelic acid (10.0 g, 65.7 mmol) in AcOEt (100 mL), was added diphenyldiazomethane (12.76 g, 65.7 mmol) at 0 °C, and the mixture was stirred for 1 h at 20 °C. Concentration of the solution in vacuo and crystallization of the residue from ether–petroleum ether gave 20.9 g (100%) of benzhydryl (*S*)-(+)-mandelate as colorless plates: mp 87–88 °C.

Deprotection of benzhydryl ester of (+)-3 was done as follows: To a solution of benzhydryl ester of (+)-3 (43 g, 89 mmol) in CH_2Cl_2 (60 mL) were added anisole (18 mL) and trifluoroacetic acid (50 mL) at 0 °C, and the mixture was stirred for 1 h at 0 °C. The reaction mixture was partitioned between AcOEt and aqueous $NaHCO_3$. The aqueous solution was acidified with concd HCl and extracted with AcOEt. The organic solution was washed with water, dried, and concentrated in vacuo to give a crystalline residue. Recrystallization from AcOEt gave 13.4 g (47%) of (+)-3: mp 168–170 °C; $[\alpha]_D$ +160.5 ● 1.0° (MeOH, c 2.00, 23.5 °C). Anal. Calcd for $C_{17}H_{16}O_6 \cdot 0.25H_2O$: C, 63.64; H, 5.19. Found: C, 63.64; H, 5.01.

(1*R*,2*R*,3*S*,4*S*)-2-[(*R*)-Mandeloxycarbonyl]bicyclo-[2.2.1]heptane-3-carboxylic Acid ((−)-4). A mixture of 1 (82

(10) Hamanaka, N.; Seko, T.; Miyazaki, T.; Naka, M.; Furuta, K.; Yamamoto, H. *Tetrahedron Lett.* **1989**, *30*, 2399.

g, 0.5 mol) and 10% Pd–C (4.5 g) in dioxane (300 mL) was stirred for 6 h at 1 atm of H_2. The solid was removed by filtration, and the filtrate was concentrated in vacuo. Recrystallization of the residue gave 81.7 g (98%) of 1′ as colorless plates, mp 169–171 °C (in a sealed tube) (lit.[11] mp 167 °C). Deprotection of the benzyl ester (80 g, 0.2 mol) was conducted in methanol (600 mL) using 10% Pd–C (8 g) as usual at 1 atm of H_2. Yield: 41 g (66%). MP: 164–166 °C. IR (KBr): 3400, 3240, 1742, 1710 cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.46 (br s, 4 H), 1.57–1.75 (m, 1 H), 1.84–2.08 (m, 1 H), 2.40–2.62 (m, 2 H), 3.02 (d AB q, A part, J = 3.6, 11.6 Hz, 1 H), 3.29 (d AB q, B part, J = 4.4, 11.6 Hz, 1 H), 5.86 (s, 1 H), 7.33–7.65 (m, 5 H). $[\alpha]_D$: −117.1 ± 0.8° (MeOH, c 1.93, 25 °C). Anal. Calcd for $C_{17}H_{18}O_6$: C, 64.13; H, 5.71. Found: C, 63.83; H, 5.73.

(1*S*,2*S*,3*R*,4*R*)-2-[(*S*)-Mandeloxycarbonyl]bicyclo-[2.2.1]heptane-3-carboxylic Acid ((+)-4). Yield: 40 g (66%). MP: 163–165 °C. $[\alpha]_D$: +116.3 ± 0.8° (MeOH, c 2.00, 24 °C). Anal. Calcd for $C_{17}H_{18}O_6$: C, 64.13; H, 5.71. Found: C, 64.11, H, 5.66.

(1*R*,2*S*,3*R*,4*S*)-2-[(*R*)-Mandeloxycarbonyl]-7-oxabicyclo[2.2.1]heptane-3-carboxylic Acid ((−)-5). Yield: 7.1 g (36%). Mp: 175–177 °C; IR (Nujol) 3480–2200, 1733, 1712, 1659 cm^{-1}. ^1H NMR (CD_3OD): δ 1.55–1.88 (m, 4 H), 3.13 (AB q, A part, J = 9.6 Hz, 1 H), 3.19 (AB q, B part, J = 9.6 Hz, 1 H), 4.83–4.90 (m, 2 H), 5.85 (s, 1 H), 7.35–7.65 (m, 5 H). $[\alpha]_D$: −111.9 ± 1.5° (MeOH, c 1.01, 23 °C). Anal. Calcd for $C_{16}H_{16}O_7$: C, 59.99; H, 5.04. Found: C, 59.85; H, 5.04.

(1*S*,2*R*,3*S*,4*R*)-2-[(*S*)-Mandeloxycarbonyl]-7-oxabicyclo[2.2.1]heptane-3-carboxylic Acid ((+)-5). Yield: 5 g (36%). Mp: 175–177 °C. $[\alpha]_D$: +110.0 ± 1.5° (MeOH, c 1.00, 24 °C). Anal. Calcd for $C_{16}H_{16}O_7 \cdot 0.5H_2O$: C, 58.35; H, 5.21. Found: C, 58.33; H, 5.48.

(1*S*,2*S*,3*S*,4*R*)-2-(Methoxycarbonyl)bicyclo[2.2.1]hept-5-ene-3-carboxylic Acid ((+)-6). Representative Procedure for Preparation of Trans Half-Esters of Bicyclo[2.2.1]heptane Derivatives. To a refluxing solution of NaOMe (278 g, 28% solution in MeOH, 1.44 mol) was added a solution of diacid **3** (45.7 g, 144 mmol) in 200 mL of MeOH over 2 h. The reaction mixture was refluxed for 1 h, concentrated in vacuo, and partitioned between CH_2Cl_2 and 2 N HCl. The organic solution was washed with water, dried over Na_2SO_4, and concentrated in vacuo, giving the crude product, recrystallization of which from n-hexane gave 26.3 g (93%) of the title compound (99.8% ee) as colorless plates, mp 78–79 °C. IR ($CHCl_3$): 3400–2400, 1729, 1708, cm^{-1}. ^1H NMR ($CDCl_3$) δ 1.48 (AB q, A part, J = 8.0 Hz, 1 H), 1.63 (AB q, B part, J = 8.0 Hz, 1 H), 2.66 (dd, J = 1.6, 4.6 Hz, 1 H), 3.14 (br s, 1 H), 3.30 (br s, 1 H), 3.43 (dd, J = 3.6, 4.6 Hz, 1 H), 3.73 (s, 3 H), 6.14 (d AB q, A part, J = 2.9, 5.5 Hz, 1 H), 6.29 (d AB q, B part, J = 3.1, 5.5 Hz, 1 H). $[\alpha]_D$: +138.1 ± 0.9° (MeOH, c 2.01, 24 °C). Anal. Calcd for $C_{10}H_{12}O_4$: C, 61.21; H, 6.17. Found: C, 60.89; H, 6.13. The enantiomeric purity of the half esters was determined by HPLC analysis of the corresponding (*S*)-α-methylbenzyl amide (Table II) using Nucleosil 5C.[18] Mobile phase CH_3CN/H_2O (1:1); flow rate 0.5 mL/min; detection 225 nm.

(1*R*,2*R*,3*R*,4*S*)-2-(Methoxycarbonyl)bicyclo[2.2.1]hept-5-ene-3-carboxylic Acid ((−)-6). Yield: 0.4 g (93%). Mp: 78–79 °C. $[\alpha]_D$: −140.8 ± 0.9° (MeOH, c 2.02, 23 °C). Mp and $[\alpha]_D$ values are not recorded in the literature.[10] Anal. Calcd for $C_{10}H_{12}O_4$: C, 61.21; H, 6.17. Found: C, 61.00; H, 6.09.

(1*R*,2*S*,3*S*,4*S*)-2-(Methoxycarbonyl)bicyclo[2.2.1]heptane-3-carboxylic Acid ((+)-8). Yield: 700 g (94%). Mp: 59–60 °C (lit.[9] mp 59–60 °C). IR (KBr): 3720–2400, 1728, 1705, 1690 cm^{-1}. ^1H NMR ($CDCl_3$) δ 1.20–1.74 (m, 6 H), 2.59 (br s, 1 H), 2.69 (br s, 1 H), 2.79 (d, J = 5.4 Hz, 1 H), 3.27 (dd, J = 3.8, 5.4 Hz, 1 H), 3.69 (s, 3 H). $[\alpha]_D$: +38.4 ± 0.4° (MeOH, c 2.00, 25 °C) (lit.[9] $[\alpha]_D$ +38.4° (MeOH, c 2, 25 °C)). Anal. Calcd for $C_{10}H_{14}O_4$: C, 60.59; H, 7.12. Found: C, 60.66; H, 7.08.

(1*S*,2*R*,3*R*,4*R*)-2-(Methoxycarbonyl)bicyclo[2.2.1]heptane-3-carboxylic Acid ((−)-8). Yield: 200 g (95%). Mp: 59–60 °C. $[\alpha]_D$: −38.3 ± 0.4° (MeOH, c 2.01, 25 °C). Anal. Calcd for $C_{10}H_{14}O_4$: C, 60.59; H, 7.12. Found: C, 60.47; H, 7.08.

(1*R*,2*R*,3*R*,4*S*)-2-(Methoxycarbonyl)-7-oxabicyclo-[2.2.1]heptane-3-carboxylic Acid ((+)-10). Yield: 1.2 g (50%). Mp: 134–135 °C; IR (Nujol) 3400–2480, 1736, 1725 cm^{-1}. ^1H NMR ($CDCl_3$) δ 1.45–1.95 (m, 4 H), 3.14 (d, J = 5.1 Hz, 1 H), 3.50 (td, J = 5.5, 1.5 Hz, 1 H), 3.74 (s, 3 H), 4.84 (t, J = 5.0 Hz, 1 H), 4.92 (d, J = 5.0 Hz, 1 H). $[\alpha]_D$: +73.3 ± 0.6° (MeOH, c 2.01, 24 °C). Anal. Calcd for $C_9H_{12}O_5$: C, 54.00; H, 6.05. Found: C, 53.98; H, 5.97.

(1*S*,2*S*,3*S*,4*R*)-2-(Methoxycarbonyl)-7-oxabicyclo[2.2.1]-heptane-3-carboxylic Acid ((−)-10). Yield: 0.4 g (50%). Mp: 133–134 °C. $[\alpha]_D$: −73.5 ± 0.6° (MeOH, c 2.01, 23 °C). Anal. Calcd for $C_9H_{12}O_5$: C, 54.00; H, 6.05. Found: C, 54.03; H, 6.06.

(1*S*,2*S*,3*R*,4*R*)-2-(Methoxycarbonyl)bicyclo[2.2.1]heptane-3-carboxylic Acid ((+)-7). Representative Procedure for Preparation of Cis Half-Esters of Bicyclo[2.2.1]heptane Derivatives. A solution of (1*R*,2*R*,3*S*,4*S*)-2-(mandeloxycarbonyl)-3-(methoxycarbonyl)bicyclo[2.2.1]heptane (22.72 g, 71.3 mmol) and *p*-TsOH (2.73 g, 14.3 mmol) in 400 mL of MeOH was refluxed for 24 h. The reaction mixture was concentrated and partitioned between ethyl acetate and 5% aqueous $NaHCO_3$. The organic solution was washed with water, dried, and concentrated in vacuo, giving the crude dimethyl ester. Hydrogenolysis of the crude product in ethyl acetate using 10% Pd–C as usual gave the crude cis half-ester, which was partitioned between toluene and 5% aqueous $NaHCO_3$. The aqueous solution was washed with toluene, acidified with 2 N HCl, and extracted with ethyl acetate. The organic solution was washed with water, dried, and concentrated in vacuo to give 11.3 g (80%) of the title compound (>99.9% ee) as a colorless oil. IR (KBr): 3400–2400, 1735, 1708 cm^{-1}. ^1H NMR ($CDCl_3$) δ 1.35–1.53 (m, 4 H), 1.65–1.88 (m, 2 H), 2.48–2.64 (br m, 2 H), 2.96 (d AB q, A part, J = 3.4, 11.7 Hz, 1 H), 3.03 (d AB q, B part, J = 4.4, 11.7 Hz, 1 H), 3.64 (s, 3 H). $[\alpha]_D$: +17.1 ± 0.3° (MeOH, c 2.06, 23 °C). Anal. Calcd for $C_{10}H_{14}O_4$: C, 60.59; H, 7.12. Found: C, 60.42; H, 7.05.

(1*R*,2*R*,3*S*,4*S*)-2-(Methoxycarbonyl)bicyclo[2.2.1]heptane-3-carboxylic Acid ((−)-7). Yield: 23 g (88%). Colorless oil. $[\alpha]_D$: −17.4 ± 0.3° (MeOH, c 2.05, 24 °C). Anal. Calcd for $C_{10}H_{14}O_4$: C, 60.59; H, 7.12. Found: C, 60.48; H, 7.12.

(1*S*,2*R*,3*S*,4*R*)-2-(Methoxycarbonyl)-7-oxabicyclo[2.2.1]-heptane-3-carboxylic Acid ((−)-9). Yield: 2.4 g (82%). Mp: 104–106 °C (lit.[6a] mp 104 °C). IR (Nujol): 3400–2480, 1736, 1731 cm^{-1}. ^1H NMR ($CDCl_3$) δ 1.45–1.60 (m, 2 H), 1.73–1.93 (m, 2 H), 3.01 (AB q, A part, J = 9.6 Hz, 1 H), 3.03 (AB q, B part, J = 9.6 Hz, 1 H), 3.66 (s, 3 H), 4.87–5.03 (m, 2 H), 6.56 (br s, 1 H). $[\alpha]_D$: −4.9 ± 0.2° (MeOH, c 2.01, 24 °C) (lit.[6a] $[\alpha]_D$ −3.9° (MeOH, c 2, 20 °C)). Anal. Calcd for $C_9H_{12}O_5$: C, 54.00; H, 6.05. Found: C, 53.83; H, 6.04.

(1*R*,2*S*,3*R*,4*S*)-2-(Methoxycarbonyl)-7-oxabicyclo[2.2.1]-heptane-3-carboxylic Acid ((+)-9). Yield: 0.3 g (78%). Mp: 103–105 °C. $[\alpha]_D$: +4.4 ± 0.2° (MeOH, c 2.01, 24 °C). Anal. Calcd for $C_9H_{12}O_5$: C, 54.00; H, 6.05. Found: C, 53.67; H, 5.90.

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Supplementary Material Available: X-ray crystallographic data of (−)-4 (5 pages). Ordering information is given on any current masthead page.

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