oretical, 74%) of **2** as a dark red solid: mp >250 °C (CH_2Cl_2:hexane = 1:1); ^1H NMR ($CDCl_3$ + 1 drop of AcOH, 500 MHz) δ 13.18 (1 H, s, C-9 OH), 12.54 (1 H, s, C-4 OH), 7.10 (1 H, m, C-5′ H), 6.91 (1 H, d, J = 7.6 Hz, C-4′ H), 6.45 (1 H, d, J = 7.9 Hz, C-6′ H), 6.29 (1 H, s, C-7 H), 4.02 (3 H, s, OCH_3), 3.26 (2 H, t, J = 7.3 Hz, C-3′ H), 2.51 (2 H, t, J = 7.3 Hz, C-2′ H); ^{13}C NMR ($CDCl_3$ + 1 drop of CF_3CO_2D, 150 MHz) δ 201.31 (CO, C-1), 200.79 (CO, C-3), 189.02 (CO, C-8), 183.59 (CO, C-5), 161.55, 153.34, 150.99, 150.95, 149.07, 136.79, 135.13, 131.21, 131.11, 126.77, 118.58, 117.99, 113.49, 111.23, 65.72 (spiro carbon), 57.73 (OCH_3), 35.81 (CH_2), 32.63 (CH_2): IR (KBr) ν_{max} 3442, 2950, 1748, 1714, 1612, 1420, 1294 cm^{-1}; UV (H_2O) λ_{max}, nm (ε) (pH 11.9) 732 (7480), 250 (33 120), (pH 6.9) 630 (5670), 246 (20 980, sh), (pH 2.1) 504 (7540), 296 (7960 sh), 250 (27 780), 234 (28 820); EIMS, m/e (relative intensity) 406 (M^+, 38), 390 (7, $M^+ - CH_4$), 375 (4, $M^+ - OCH_3$), 363 (7), 275 (6), 247 (5), 91 (base), 77 (40), 57 (68); CIMS (2-methylpropane), m/e 409 ($M^+ + H + 2$ H, base, hydroquinone form); FABHRMS (glycerol, $M^+ + H + 2H$), m/e calcd for $C_{22}H_{16}O_8$ 409.0923, found 409.0922.

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Supplementary Material Available: Table summarizing the results of a study of the benzannulation of **10** and **11** and ^1H NMR spectra of **12**, **13**, **15–17**, and **2** (7 pages). Ordering information is given on any current masthead page.

Enantioselective Synthesis of S-1452, an Orally Active Potent Thromboxane A_2 Receptor Antagonist

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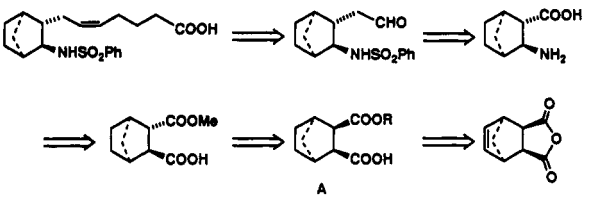
An efficient and extremely practical enantioselective fission of pro-chiral bicyclo[2.2.1]heptane-2,3-dicarboxylic anhydride was applied to the asymmetric synthesis of the potent and orally active thromboxane A_2 (TXA_2) receptor antagonist, S-1452. The lithium salt of (*R*)-(−)-benzylmandelate was employed as a chiral ligand, giving a crystalline key intermediate **3** of which the chemical purity was 100.0% after crystallization. Epimerization and the methanolysis process of **3** afforded the half ester **4**, which was transformed into S-1452.

Introduction

TXA_2 is a very potent inducer of human platelet aggregation and vascular smooth muscle contraction and has been considered to be an important endogenous mediator of circulatory disorders including angina pectoris, thrombosis, and asthma. Therefore, TXA_2 receptor antagonists may be very important compounds for the treatment of such diseases.[1] Among the number of TXA_2 receptor antagonists, S-145, *dl*-(5*Z*)-7-(3-*endo*-(phenylsulfonyl)amino)bicyclo[2.2.1]hept-2-*exo*-yl)heptenoic acid, has proved to be a very potent and novel therapeutic agent having long lasting biological activity.[2] Initially, S-145 had been developed as a racemate, and later the difference of biological activity and binding affinity to TXA_2/PGH_2 receptor between the *d* isomer and *l* isomer has been studied extensively.[3] The *d* isomer was found to be several to 20 times more potent than the *l* isomer, exhibiting higher binding affinity to the receptor. Although the potent *d* isomer can be synthesized by the use of the classical optical resolution method,[4] a practical large-scale synthesis of the *d* isomer became necessary for further development.

Chart I. Retrosynthesis of S-1452



Recently, S-1452, calcium (1*R*,2*S*,3*S*,4*S*)-(5*Z*)-7-(((phenylsulfonyl)amino)bicyclo[2.2.1]hept-2-yl)hept-5-enoate, has been established as being suitable as a chemically stable and orally active compound.[5] We therefore tried to develop a new method to produce S-1452 with high optical purity on a large scale. As shown in Figure 1, S-1452 has a structure analogous to prostaglandin H_2[6] except that the ω-side chain is modified to the (phenylsulfonyl)amino group and the nuclear oxygens to carbons. Thus, it would be desirable to obtain optically active

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(2) (a) Liao, P.; Johnson, G., III; Siegfried, M.; Lefer, A. M. *Eicosanoids* **1989**, *2*, 33. (b) Dube, G. P.; Brune, K. A.; Uchida, K.; Jakubowski, J. A. *Circulation* **1989**, *80*, Suppl. 524.

(3) (a) Hanasaki, K.; Arita, H. *Thromb. Res.* **1988**, *50*, 365. (b) Hanasaki, K.; Nagasaki, T.; Arita, H. *Biochem. Pharmacol.* **1989**, *38*, 2007. (c) Dube, G. P.; Kurz, W. L.; Mais, D. E.; Brune, K. A.; Rinkema, L. E.; Jakubowski, J. A. *Circulation* **1989**, *80*, Suppl. 439.

(4) Irwin, A. J.; Jones, J. B. *J. Am. Chem. Soc.* **1976**, *98*, 8476.

(5) Unpublished data. S-1452 is a physicochemically stable and nonhygroscopic crystal.

(6) It is well known that TXA_2 and PGH_2 share a common receptor: Hall, S. E.; Han, W.-C.; Harris, D. N.; Hedberg, A.; Ogletree, M. L. *J. Med. Chem.* **1989**, *32*, 974 and references cited therein. Recently, the TXA_2/PGH_2 receptor was purified from human blood platelets: Ushikubi, F.; Nakajima, M.; Hirata, M.; Okuma, M.; Fujiwara, M.; Narumiya, S. *J. Biol. Chem.* **1989**, *264*, 16496.

0022-3263/91/1956-2122$02.50/0

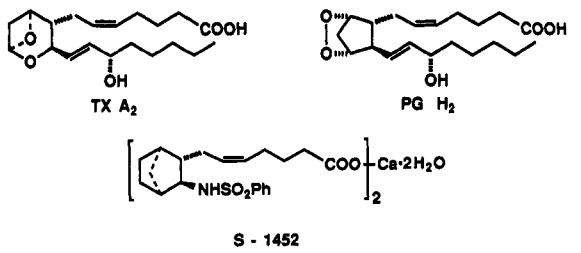


Figure 1.

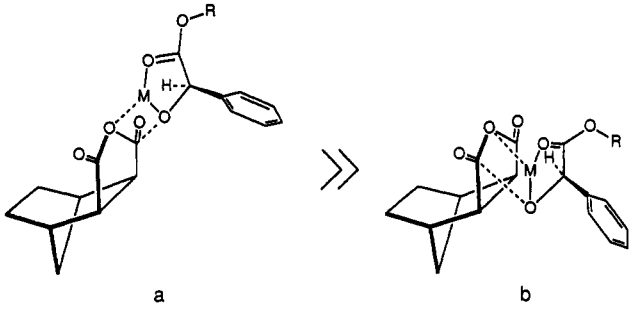


Figure 2. Possible transition states in enantioselective fission.

substituted bicyclo[2.2.1]heptane intermediates which could be functionalized to S-1452. Our asymmetric synthesis of S-1452 consisted of enantioselective synthesis of bicyclo[2.2.1]heptane cis half esters A as depicted by retrosynthetic analysis (Chart I).

Recently, a number of reports have described the asymmetric synthesis of bicyclo[2.2.1]heptane series using Diels–Alder reaction[7] or enzymatic hydrolysis[8]. Nonetheless, it remained difficult to practically obtain these compounds in high enantiomeric purity on a large scale. In this study, we discovered a very attractive method for synthesizing bicyclo[2.2.1]heptane half esters 4 by which all stereoisomers containing carboxyl substituents were stereoselectively and easily synthesized in an extremely high optical yield.[9] The feature of this asymmetric synthesis consists of enantioselective fission of σ-symmetrical cyclic anhydride with chiral controllers which can be recovered easily without racemization. To generalize this reaction to other pro-chiral cyclic anhydrides, several synthetic trials were done.[9] This method may offer practical routes for the synthesis of useful building blocks for prostanoids and other natural products.[10]

Scheme I. Enantioselective Cleavage of Meso Anhydride

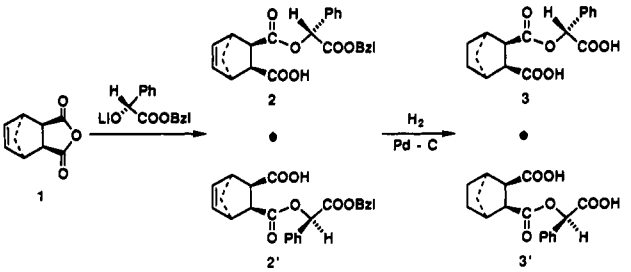
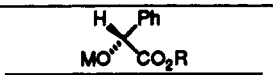


Table I. Effect of Metals and Esters on the Enantioselective Cleavage



M	R	ratio (2:2′)[a]	% yield (2 + 2′)
Li	Li	50:50	81
Li	Me	82:18	96
Li	CH_2Ph	86:14	99
Li	$CHPh_2$	73:27	96
Li	$CH_2C_6H_4OMe$	86:14	98
$^1/_2$Zn	CH_2Ph	85:15	71
$^1/_2$Mg	CH_2Ph	50:50	70
Na	CH_2Ph	59:41	64

[a] Determined by HPLC after conversion to 3 and 3′.

Results and Discussion

Enantioselective Fission of Cyclic Meso Anhydride. Among the many chiral nucleophiles, common mandelic acid derivatives are rarely employed so far as effective inducers of chirality.[11] However, the metal salt of optically active mandelate such as lithium (*R*)-mandelate was expected to be effective for the enantioselective fission of σ-symmetrical five-membered anhydrides, attacking *pro-R* carbonyl predominantly due to steric preference (a ≫ b) in the presumed transition states as depicted in Figure 2.

The lithium-chelating five-membered ring structure of benzyl (*R*)-mandelate, in which the steric difference between the phenyl ring and hydrogen might contribute to the enantioselection, was considered to have the possibility to be used for producing the key intermediate **3**. This could then be converted to the desired bicyclo[2.2.1]heptane half ester **4**. The absolute configuration of the key intermediate seemed to be predictable from the above point of view. Another important aspect for the use of optically active mandelates as chiral auxiliaries consisted of a simple purification process (crystallization) of intermediate **3**, which was derived from the ester **2** by deprotection (Scheme I).

Enantioselective fission of commercially available meso anhydride **1** with lithium (*R*)-benzylmandelate at −78 °C in THF gave a mixture of half ester **2** and **2′** in the ratio of 86:14. Without purification, treatment of the crude product with hydrogen using Pd–C in methanol, followed by a single crystallization from ethyl acetate gave the fine crystalline product **3** in 65% overall yield from anhydride **1** with 100.0% de (HPLC analysis). Improvement of the ratio of enantioselectivity was examined using other metals and several esters. The results are summarized in Table I. The best result was obtained when lithium was used in the reaction of benzyl or *p*-methoxybenzyl mandelate with the anhydride. The zinc salt of mandelate, prepared from the lithium salt and zinc chloride, exhibited a result

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(9) Submitted for publication.

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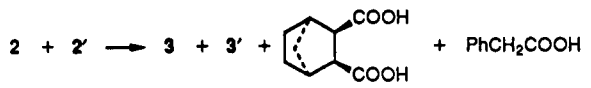
Table II. Deprotection of 2 by Catalytic Hydrogenolysis or Acidic Hydrolysis



catalyst	solvent	H_2 (atm)	ratio (3:3': $PhCH_2CO_2H$)	% yield of 3[a]
10% Pd-C	MeOH	1	86:14:0	65
10% Pd-C	MeOH	2	85:15:nd[b]	42
5% Pd-C	AcOEt	1	5:11:84	-
HCl	CH_3CN-H_2O	-	86:14:-	66[c]

[a] Isolated yield from anhydride 1 by crystallization: 100% de. [b] Not determined. [c] In this case, the lithium *p*-methoxybenzyl or benzhydryl (*R*)-mandelate was reacted with saturated cyclic anhydride, and the crude product was deprotected.

comparable with that of the lithium salt itself. The magnesium salt, prepared from the lithium salt and magnesium bromide (ethylene dibromide and magnesium) reacted only at a higher temperature (greater than room temperature) and did not show any enantioselectivity. The sodium salt, due to its inability of multicoordination with other heteroatoms such as oxygen, did not yield good results. Mandelic acid and esters other than benzyl or *p*-methoxybenzyl did not give better results than that obtained with the benzyl ester.

Deprotection of the crude benzyl ester of the mandelate moiety was achieved by catalytic hydrogenolysis. Lower pressure of hydrogen and the use of methanol as a solvent are recommended because the use of other solvents at a higher pressure of hydrogen causes excessive reduction of the products, giving meso dicarboxylic acid and phenylacetic acid. In the case of acid-sensitive esters, such as *p*-methoxybenzyl or benzhydryl, acid hydrolysis also gave the desired dicarboxylic acid derivative 3 (Table II).

The absolute stereochemistry and enantiopreference of this reaction can be easily determined by X-ray analysis of the diacid 3.[9]

Epimerization and Methanolysis of the Diacid 3. As shown in Figure 1, S-1452 has trans side chains which is similar to those of natural prostaglandins. We have already reported that trans configuration of the side chains and, moreover, cis configuration between bicyclic methylene bridge and α-side chain (the hexenoic acid moiety) were important factors for the biological potency as a TXA_2 receptor antagonist having the phenylsulfonyl side chain.[12] Considered in this light, transformation of the cis diacid 3 into bicyclo[2.2.1]heptane trans half ester 4 by the stereospecific epimerization–alcoholysis process is a very significant step for the construction of S-1452. Thus, the epimerization reaction was performed by gradually adding 2.5 equiv of sodium methoxide to 3 in refluxing methanol and THF, but afforded, unfortunately, racemic half ester 4 in quantitative yield (Table III, entry 2). As this result seemed to have arisen from the easy intramolecular cyclization reaction to meso anhydride 1', the optimum conditions for epimerization were examined carefully. A deficiency of methoxide caused total racemization and gave the *d*-cis half ester (entry 5). To promote epimerization of the ester without intramolecular cyclization, diacid 3 was added to a large excess (10 equiv) of concentrated sodium methoxide in methanol under reflux, and the optically active half ester 4 was obtained in 94% yield and 97.4% ee (entry 4) Chart II. Moreover, (*R*)-mandelic acid,

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Chart II. Determination of ee of Compound 4

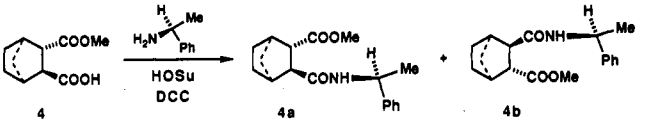
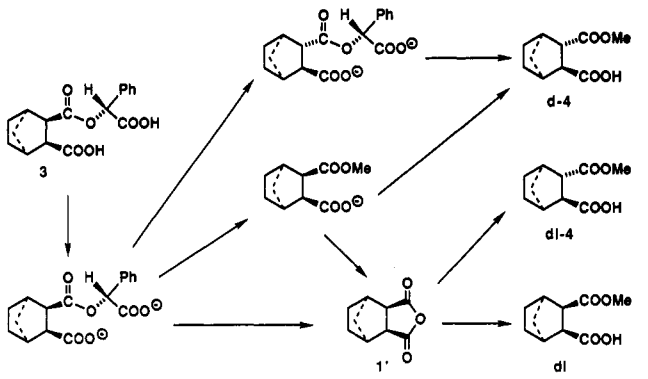
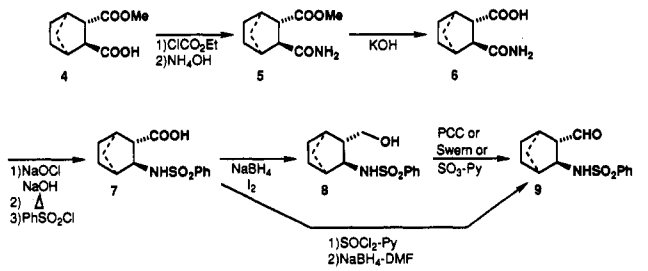


Chart III. Possible Mechanism of Racemization



Scheme II

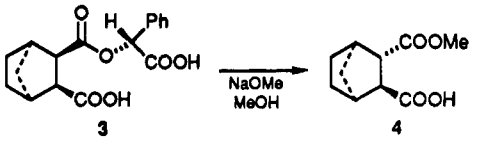


used as a chiral controller, was recovered without any racemization. The mechanism of racemization may be as follows. The presence of a large excess of sodium methoxide in the concentrated reaction mixture gives rise to rapid epimerization of the ester group, and then methanolysis gives the desired optically active *d*-trans half ester 4. However, an insufficient amount of sodium methoxide for epimerization causes the intramolecular cyclization of the dicarboxylate of 3 to the meso anhydride 1', followed by methanolysis to give *dl*-cis half ester or epimerization to give *dl*-trans half ester (Chart III, Table III). The present method indicates the practical value of a general synthetic method for bicyclo[2.2.1]heptane half esters which consist of eight stereoisomers.[9]

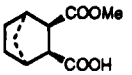
Transformation into S-1452. One general method for the conversion of carboxylic acids to nitrogen functions convertible to phenylsulfonylamides is the Curtius rearrangement. However, hazardous azide reagents and acyl azide compounds are not suitable for large-scale preparation. Also the Curtius route would require protection and deprotection of the amino group in our case. Hofmann rearrangement, on the other hand, is a very practical reaction for the conversion of a carboxylic acid to a phenylsulfonylamide, and we examined it intensively for the primary amide 6, which was obtained from the half ester 4 in three steps in 82% yield. Half amide 6 was treated with 1 equiv of aqueous sodium hypochlorite in aqueous sodium hydroxide solution. Heating to reflux for 30 min followed by phenylsulfonylation with phenylsulfonyl chloride at 0 °C gave sulfonamide 7 in 87% yield. This one-pot sulfonamide formation could be accomplished even on a multikilogram scale (Scheme II).

Although the direct conversion of the methyl ester of 7 to aldehyde 9 was attempted with DIBALH, only a mixture of primary alcohol 8 and starting material was

Table III. Epimerization and Methanolysis



3 4

entry	diacid (conc, %)	solvent	NaOMe (equiv)	procedure	time (h)	temp	4a:4b	others
1	5	MeOH–THF (1:1)	3.0	A[a]	2	reflux	96:4	
2	5	MeOH–THF (2:1)	2.5	B[b]	6	reflux	1:1	
3	10	MeOH	3.0	C[c]	5	reflux	97:3	
4	10	MeOH	10.0	C	2.2	reflux	98:2[d]	
5	5	MeOH–THF (2:1)	1.8	B	2	reflux	–	 dl

[a] A: Na salt of diacid was suspeded and dissolved gradually. [b] B: NaOMe was added slowly to a solution of di-acid (solution). [c] C: Diacid was added slowly to a hot solution of NaOMe (solution). [d] Recrystallization raised the ratio to 98.7:1.3.

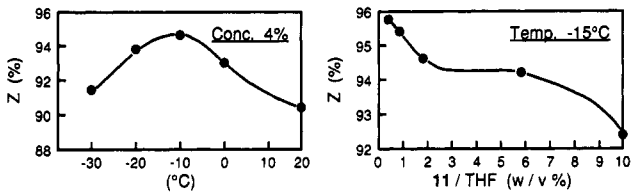


Figure 3. Improvement of Z/E ratio.

obtained. A small-scale reduction of the acid chloride derived from **7** using $NaBH_4$–DMF complex gave a promising result.[13] However, the acid chloride was extremely unstable and the scale up experiment was unsuccessful.

Thus, another two-step conversion was tried via primary alcohol **8**. Diborane reduction of acid **7** using $NaBH_4$–iodine[14] afforded primary alcohol **8**. Recrystallization of the crude product gave the pure alcohol in 95% yield, and the optical purity was found to be satisfactory (100% ee) by an HPLC method using a chiral column. Oxidation of alcohol **8** was tried by using oxalyl chloride–DMSO (Swern oxidation) giving aldehyde **9** in quantitative yield.

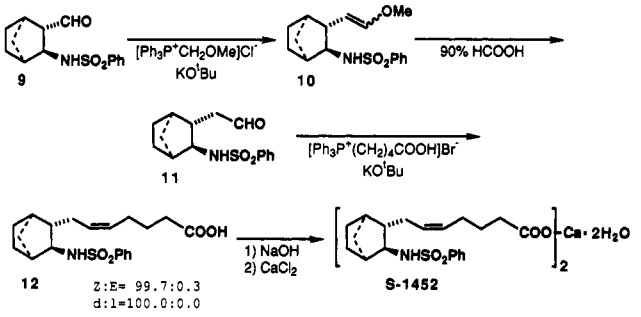
Double Wittig reaction of secondary aldehyde **9** provided (5*Z*)-hexenoic acid **12** via three steps in 86% yield. To diminish the production of *E* isomer, the second Wittig reaction using (4-carboxybutyl)triphenylphosphonium bromide and potassium *tert*-butoxide was examined.[15] A high-dilution reaction at −15 °C in THF was found to be the optimum condition to increase the *Z* isomer (Figure 3). The ratio of *Z* to *E* was raised to 95:5.

Purification of the *p*-methoxyphenethylamine salt of **12** by recrystallization gave almost pure acid after acidification (Z/E = 99.7/0.3, d/l = 100.0/0.0). The optical purity of the acid was determined by HPLC using a chiral column. Free acid **12** exhibited very potent inhibitory activity against biological responses induced by TXA_2-related inducers[1,3] (Scheme III).

This compound, however, proved to be unsuitable for development as a drug because of its relative instability. After several trials, the calcium salt was found to exhibit biological activity comparable to the free acid and have higher stability. Thus, S-1452, the calcium salt of **12**, was prepared by neutralization with aqueous sodium hydroxide (1 equiv), followed by cation exchange with an excess of calcium chloride.

(13) Babler, J. H.; Invergo, B. J. *Tetrahedron Lett.* **1981**, *22*, 11.
(14) Freeguard, G. F.; Long, L. H. *Chem. Ind.* **1965**, 471.
(15) See a review: Maryanoff, B.; Reitz, A. B. *Chem. Rev.* **1989**, *89*, 863.

Scheme III



Conclusion

The asymmetric synthesis of S-1452, a very potent TXA_2 receptor antagonist, was accomplished by enantioselective fission of a σ-symmetrical cyclic anhydride with (*R*)-benzylmandelate, followed by simple purification procedure to give the key diacid **3**. The diacid was transformed into S-1452 via bicyclo[2.2.1]heptane half ester **4** with extremely high purity on a multikilogram scale without any chromatographic separation. This method has excellent practical potential because of its ready availability, applicability to many bicyclo[2.2.1]heptane half esters, recoverability of the chiral controllers, and the high purity of the products with predictable absolute configurations.

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 solutions extractions were dried with anhydrous magnesium sulfate.

(1*S*,2*R*,3*S*,4*R*)-Bicyclo[2.2.1]hept-5-ene-2,3-dicarboxylic Acid, 2-(Benzyl (*R*)-mandelate) (2). A solution of benzyl (*R*)-mandelate (5.33 g, 22.0 mmol) in 50 mL of THF was cooled to −78 °C, 13.13 mL (21.0 mmol) of a 1.6-mol solution of *n*-butyllithium in hexane was added dropwise, and the mixture was stirred for 15 min. To the reaction mixture was added a solution of 3.32 g (20.0 mmol) of bicyclo[2.2.1]hept-5-ene-2,3-*endo*-dicarboxylic anhydride **1** in 20 mL of THF, and the resulting mixture was stirred for 1 h at −78 °C. The reaction mixture was acidified with 2 N HCl, and the product was extracted with ethyl acetate (EtOAc). The organic layer was washed with water and an aqueous solution of sodium chloride and then concentrated to obtain 9.33 g (99%) of a mixture of **2** and **2'**. The ratio was determined by HPLC after conversion to a mixture of **3** and **3'**. Compound **2** was purified by chromatography on silica gel for characterization: IR (film) 3600–2400, 1748, 1710, 1498, 1456, 1342, 1257, 1208, 1165, 1084, 1072, 912, 696 cm^{-1}; ^1H NMR δ 1.33 (AB q, A part, J = 8.9 Hz, 1 H), 1.48 (AB q, B part, J = 8.9 Hz, 1 H), 3.16 (br s, 1 H), 3.21 (br s, 1 H), 3.30 (d AB q, A part, J = 3.2,

10.2 Hz, 1 H), 3.47 (d AB q, B part, J = 3.4, 10.2 Hz, 1 H), 5.13 (s, 2 H), 5.97 (s, 1 H), 6.11 (d AB q, A part, J = 2.9, 5.9 Hz, 1 H), 6.28 (d AB q, B part, J = 2.8, 5.9 Hz, 1 H), 7.13–7.52 (m, 10 H).

The other metal salts of (*R*)-benzyl mandelate were made to react with 1 and ester 2 was obtained as shown in Table I. In the case of magnesium salt, the reaction proceeded only at room temperature. Several esters of mandelic acid were also examined, and the results are also shown in Table I.

(1*R*,2*R*,3*S*,4*S*)-Bicyclo[2.2.1]heptane-2,3-dicarboxylic Acid, 2-[(*R*)-Mandelic acid] Ester (3) and (1*S*,2*S*,3*R*,4*R*)-Bicyclo[2.2.1]heptane-2,3-dicarboxylic Acid, 2-[(*R*)-Mandelic acid] Ester (3′). To a solution of 4.06 g (10 mmol) of the crude mixture of 2 and 2′ in 30 mL of methanol was added 0.4 g of 10% palladium on carbon, and the mixture was stirred in a hydrogen atmosphere under ordinary pressure at room temperature for 1.5 h. The reaction mixture was filtered to remove the catalyst, and the filtrate was concentrated. The residue was partitioned between EtOAc and 5% aqueous $NaHCO_3$, and the aqueous layer was washed with EtOAc. After acidification with 2 N HCl, the mixture was extracted with EtOAc. The organic solution was dried and concentrated in vacuo, yielding 3.14 g (quantitative) of the crude diacid 3 (3/3′ = 86/14) HPLC. Recrystallization from EtOAc gave 2.05 g (65%) of the pure diacid (100.0% de) as colorless pillars: mp 164–166 °C. The diastereomeric excess 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 (KBr) 3400, 3240, 2960, 1742, 1710, 1428, 1242, 1222, 1215, 1185, 1170, 1050 cm^{-1}; ^1H NMR 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 1.934, 25 °C). Anal. Calcd for $C_{17}H_{18}O_6$: C, 64.13, H, 5.71. Found: C, 63.83; H, 5.73. From the mother liquor, the diastereomer 3′ was isolated as colorless pillars: mp 157–158 °C; IR (KBr) 3420, 3040, 2965, 1742, 1712, 1428, 1242, 1222, 1215, 1170, 1052 cm^{-1}; ^1H NMR δ 1.30–1.66 (m, 4 H), 1.69–1.87 (m, 1 H), 1.96–2.13 (m, 1 H), 2.60 (br s, 2 H), 3.04 (d AB q, A part, J = 2.8, 12.1 Hz, 1 H), 3.13 (d AB q, B part, J = 3.8, 12.1 Hz, 1 H), 5.84 (s, 1 H), 7.33–7.58 (m, 5 H); $[\alpha]_D$ −81.8 ± 0.6° (MeOH, c 2.005, 25 °C). Anal. Calcd for $C_{17}H_{18}O_6$: C, 64.13; H, 5.71. Found: C, 64.02; H, 5.57. Treatment of the saturated 2 (*p*-methoxybenzyl ester or benzhydryl ester) derived from the cyclic anhydride with concentrated HCl in CH_3CN also gave pure diacid 3 in 66% yield.

(1*R*,2*S*,3*S*,4*S*)-3-Carboxy-2-(methoxycarbonyl)bicyclo[2.2.1]heptane (4). To a refluxing solution of NaOMe (4 N in MeOH, 78.5 mL, 314 mmol) was added a solution of diacid 3 (10 g, 31.4 mmol) in 35 mL of MeOH over 2 h. The reaction mixture was refluxed for 12 min, concentrated in vacuo, and partitioned between CH_2Cl_2 and 2 N HCl. The organic solution was washed with water, dried, and concentrated in vacuo, giving the crude product, which on crystallization from petroleum ether gave 5.89 g (94%) of 4 (97.4% ee) as colorless pillars. The enantiomeric excess of the half ester 4 was determined by transforming it into the diastereomeric mixture (4a + 4b) using optically active phenethylamine, *N*-hydroxysuccinimide, and DCC and then measuring the diastereomer ratio by HPLC (Chart II):[16] mp 59–60 °C; IR (KBr) 3720–2400, 3438, 2970, 2880, 1728, 1705, 1690, 1438, 1374, 1312, 1238, 1195, 1177, 1121, 1052 cm^{-1}; ^1H NMR 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 2.002, 25 °C). Anal. Calcd for $C_{10}H_{14}O_4$: C, 60.58; H, 7.13. Found: C, 60.66; H, 7.08.

(1*R*,2*S*,3*S*,4*S*)-3-Carbamoyl-2-(methoxycarbonyl)bicyclo[2.2.1]heptane (5). To a solution of 4 (30 g, 151 mmol) in 300 mL of THF, triethylamine (23.2 mL, 151 mmol × 1.1), and ethyl chloroformate (15.9 mL, 151 mmol × 1.1) were added at 0 °C, and the mixture was stirred for 30 min at the same temperature. Next, 30.58 mL (151 mmol × 3) of 28% aqueous ammonia was added, and the mixture was stirred for 30 min and then partitioned between EtOAc and water. The organic solution was washed with water, dried, and concentrated in vacuo. The residue was recrystallized from ether and petroleum ether to give 25.19 g (84.3%) of amide 5 as colorless prisms: mp 110–112 °C; IR (KBr) 3435, 3300, 3190, 2960, 1722, 1676, 1658, 1618, 1436, 1415, 1312, 1225, 1201, 1182, 1156, 1115 cm^{-1}; ^1H NMR δ 1.26–1.70 (m, 6 H), 2.51 (br s, 1 H), 2.55–2.61 (br m, 1 H), 2.85 (dd, J = 5.5, 1.5 Hz, 1 H), 3.02–3.12 (m, 1 H), 3.68 (s, 3 H), 5.63 (br s 1 H); $[\alpha]_D$ +42.4 ± 0.8° (MeOH, c 1.000, 23 °C). Anal. Calcd for $C_{10}H_{15}O_3N$: C, 60.90; H, 7.67; N, 7.10. Found: C, 60.97; H, 7.68; N, 7.07.

(1*R*,2*S*,3*S*,4*S*)-3-Carbamoyl-2-carboxybicyclo[2.2.1]heptane (6). Ester amide 5 was hydrolyzed in the usual manner using 1 N KOH, and acid 6 was obtained in 96.9% yield as colorless plates: mp 197–200 °C; IR (KBr) 3442, 3358, 2960, 3650–2400, 1734, 1722, 1648, 1620, 1393, 1315, 1237, 1190 cm^{-1}; ^1H NMR (CD_3OD) δ 1.20–1.75 (m, 6 H), 2.56 (br s, 1 H), 2.78 (d, J = 5.2 Hz, 1 H), 3.09 (t, J = 5.2 Hz, 1 H), 3.05–3.19 (m, 1 H); $[\alpha]_D$ +42.6 ± 0.8° (MeOH, c 1.014, 24 °C). Anal. Calcd for $C_9H_{13}NO_3$: C, 58.99, H, 7.17; N, 7.65. Found: C, 59.11; H, 7.18; N, 7.79.

(1*S*,2*S*,3*S*,4*R*)-3-Carboxy-2-((phenylsulfonyl)amino)bicyclo[2.2.1]heptane (7). To a solution of aqueous sodium hypochlorite (14.7% solution, 141.6 g, 275 mmol), 206 mL of 2 N NaOH and a solution of 6 (50.39 g, 275 mmol) in 138 mL of 2 N NaOH were added at room temperature. The mixture was stirred for 1 h and heated to 100 °C over 30 min and refluxed for 15 min. After cooling immediately to room temperature, the reaction mixture was adjusted to pH 3–4 at 0 °C with 1 N HCl and washed with ethyl acetate and then with CH_2Cl_2. To this reaction mixture, 52.6 mL (275 mmol × 1.5) of phenylsulfonyl chloride was added at pH 11 (adjusted with 5 N NaOH) at room temperature, and stirring was continued for 30 min. Next, 55 mL of 5 N NaOH and 17.5 mL of phenylsulfonyl chloride were added with stirring for an additional 40 min. The reaction mixture was partitioned between EtOAc and water. The aqueous solution was acidified with 5 N HCl and extracted with EtOAc. The organic solution was washed with water, dried, and concentrated in vacuo. The residue was crystallized from toluene–ethyl acetate and gave 66.4 g (81.8%) of sulfonamide 7 as colorless pillars: mp 157–159 °C; IR (KBr) 3290, 3650–2400, 1705, 1461, 1448, 1424, 1307, 1294, 1260, 1251, 1226, 1155, 1096 cm^{-1}; ^1H NMR δ 1.18–1.77 (m, 6 H), 2.08 (dd, J = 4.8, 1.6 Hz, 1 H), 2.28 (br s, 1 H), 2.40–2.50 (br s, 1 H), 3.77–3.93 (m, 1 H), 5.24 (d, J = 7.0 Hz, 1 H), 7.45–7.67 (m, 3 H), 7.81–7.95 (m, 2 H); $[\alpha]_D$ +14.7 ± 0.5° (MeOH, c 1.004, 23 °C). Anal. Calcd for $C_{14}H_{17}NO_4S$: C, 56.93; H, 5.80; N, 4.74; S, 10.85. Found: C, 56.75; H, 5.73; N, 4.73; S, 10.81.

(1*S*,2*S*,3*S*,4*R*)-3-(Hydroxymethyl)-2-((phenylsulfonyl)amino)bicyclo[2.2.1]heptane (8). To a suspension of $NaBH_4$ (16.93 g, 179 mmol × 2.5) in 520 mL of dimethoxyethane was added 56.77 g (179 mmol × 1.25) of iodine slowly at 0 °C. To the mixture was added 52.86 g (179 mmol) of 7 at the same temperature, and the reaction mixture was stirred for 30 min at 10 °C. To the mixture were added 500 mL of ice water and EtOAc (1 L) carefully. The organic solution was washed successively with 1 N HCl (300 mL), 5% aqueous $NaHCO_3$ (400 mL), and water (400 mL), dried, and concentrated in vacuo. The residue was crystallized from ethyl acetate–toluene and gave 48.0 g (95.4%) of 8 as colorless prisms: mp 121–122 °C; IR (KBr) 3495, 3125, 2960, 1479, 1446, 1322, 1182, 1169, 1163, 1096, 1034 cm^{-1}; ^1H NMR δ 1.12–1.68 (m, 7 H), 1.78 (br s, 1 H), 2.05 (d, J = 2.8 Hz, 1 H), 2.10 (br s, 1 H), 3.05–3.18 (m, 1 H), 3.34 (d AB q, A part, J = 7.3, 10.8 Hz, 1 H), 3.42 (d AB q, B part, J = 7.6, 10.8 Hz, 1 H), 5.11 (d, J = 10.0 Hz, 1 H), 7.45–7.55 (m, 3 H), 7.86–7.96 (m, 2 H); $[\alpha]_D$ +7.8 ± 0.5° ($CHCl_3$, c 1.014, 25 °C). Anal. Calcd for $C_{14}H_{19}NO_3S$: C, 59.75; H, 6.82; N, 4.98; S, 11.39. Found: C, 59.83; H, 6.91; N, 5.02; S, 11.33. The enantiomeric purity of this compound was 100.0% ee (chiral HPLC: column, ULTRON ES-OVM (Shinwakako, Japan); solvent, MeOH/20 mmol KH_2PO_4 buffer solution (25/75); flow rate, 1.0 mL/min; detection, 230 nm).

(1*S*,2*S*,3*S*,4*R*)-3-(Formylmethyl)-2-((phenylsulfonyl)amino)bicyclo[2.2.1]heptane (11). To a solution of oxalyl chloride (22.3 mL, 213 mmol × 1.2) in CH_2Cl_2 (300 mL) and DMSO (40 mL) was added a solution of alcohol 8 (60.03 g, 213 mmol) in 440 mL of CH_2Cl_2 at −55 °C. After 15 min, triethylamine (89.2 mL, 213 mmol × 3) was added at −55 °C, and the reaction mixture was warmed to room temperature over 45 min and then poured into ice water. The organic solution was washed with water, dried, and concentrated in vacuo, giving 59.5 g (100%) of 9 as colorless pillars: mp 101–103 °C; ^1H NMR δ 1.12–1.84 (m,

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6 H), 2.16–2.34 (m, 2 H), 2.40–2.51 (br m, 1 H), 3.78–3.95 (m, 1 H), 4.90–5.10 (br m, 1 H), 7.45–7.70 (m, 3 H), 7.82–7.97 (m, 2 H), 9.57 (s, 1 H). Oxidation of 8 with PCC or pyridine–SO_3[17] gave the comparable results. This compound was unstable and used for the next reaction without purification.

To a suspension of methoxymethylphosphonium chloride (110 g, 213 mmol × 1.5) in 380 mL of THF, was added KO-*t*-Bu (35.8 g, 213 mmol × 1.5) at 0 °C, and the mixture was stirred for 30 min at 0 °C. Aldehyde **9** (59.5 g) in 240 mL of THF was added to the mixture at −20 °C. The mixture was stirred for 30 min at 0 °C and partitioned between toluene and water. The organic solution was washed with water, dried, and concentrated in vacuo, giving crude methyl vinyl ether **10**, which was dissolved in 70 mL of formic acid at room temperature. The mixture was stirred for 1 h and partitioned between EtOAc and aqueous $NaHCO_3$ (140 g). The organic solution was washed with water, dried, and concentrated in vacuo. The residue was recrystallized from ether–CH_2Cl_2 and gave 56.46 g (90%) of primary aldehyde **11** as colorless prisms: mp 100–103 °C; IR (KBr) 3420, 3260, 2970, 2875, 2820, 2720, 1722, 1449, 1320, 1165, 1092, 1070, 1062 cm^{-1}; ^1H NMR δ 1.15–1.80 (m, 7 H), 1.85 (br s, 1 H), 2.26–2.56 (m, 3 H), 2.74–2.83 (m, 1 H), 5.21 (d, J = 8.0 Hz, 1 H), 7.44–7.63 (m, 3 H), 7.75–7.98 (m, 2 H), 9.57 (s, 1 H); $[\alpha]_D$ 36.5 ± 0.8° ($CHCl_3$, c 0.994, 25 °C). Anal. Calcd for $C_{15}H_{19}NO_3S$: C, 61.40; H, 6.54; N, 4.77; S, 10.93. Found: C, 61.39; H, 6.51; N, 4.90; S, 11.02.

(1*R*,2*S*,3*S*,4*S*)-(5*Z*)-7-(3-((Phenylsulfonyl)amino)bicyclo[2.2.1]hept-2-yl)hept-5-enoic Acid (12). To a suspension of (4-carboxybutyl)triphenylphosphonium bromide (272 g, 185 mmol × 3.3) in 4 L of THF was added 125 g (185 mmol × 6) of KO-*t*-Bu at 0 °C, and the mixture was stirred for 1 h at the same temperature. To the mixture was added a solution of **11** (54.37 g, 185 mmol) in 350 mL of THF at −15 °C, and the reaction mixture was stirred for 2 h at the same temperature and then partitioned between toluene and aqueous NaOH. The aqueous solution was washed with toluene, acidified with 6 N HCl, and extracted with EtOAc. The EtOAc solution was washed with water, dried, and concentrated in vacuo, giving the crude acid **12** (66.0 g, 94.6%). The ratio of *Z* to *E* was 95:5, which was determined by HPLC (column, Nucleosil $5C_{18}$; mobile phase, $CH_3CN/MeOH/H_2O/AcOH$ = 300/200/350/1; flow rate, 2 mL/min; detection, 225 nm). The crude acid was treated with an equimolar amount of *p*-methoxyphenethylamine in CH_2Cl_2, and the resulting salt was recrystallized from CH_2Cl_2–ether (1:1), giving 64.3 g of the purified salt, which was partitioned between ethyl acetate and 2 N HCl. The usual procedure gave the purified acid **12** (45.9 g, 65.7%). The ratio of *Z* to *E* was 99.7:0.3, and the enantiomeric purity was determined (100.0% ee) by HPLC using a chiral column (column, Sumipax OA-4000, Sumitomo Chemical Co., Ltd., Japan; mobile phase, *n*-hexane/*i*PrOH/AcOH = 190/10/0.5; flow rate, 1.0 mL/min; detection, 240 nm): colorless plates; mp 60–61 °C; IR (Nujol) 3282, 3260, 3300, 2400, 1708, 1268, 1248, 1202, 1162, 1153, 1095, 1076 cm^{-1}; ^1H NMR δ 0.88–2.10 (m, 14 H), 2.14 (br s, 1H), 2.34 (t, J = 7.2 Hz, 2 H), 2.95–3.07 (m, 1 H), 5.13–5.35 (m, 3 H), 7.45–7.64 (m, 3 H), 7.85–7.94 (m, 2 H), 9.52 (br s, 1 H); $[\alpha]_D$ +27.1 ± 0.7° (MeOH, c 1.015, 24 °C). Anal. Calcd for $C_{20}H_{27}NO_4S$: C, 63.63; H, 7.21; N, 3.72; S, 8.49. Found: C, 63.56; H, 7.21; N, 3.83; S, 8.43.

Calcium (1*R*,2*S*,3*S*,4*S*)-(5*Z*)-7-(3-((Phenylsulfonyl)amino)bicyclo[2.2.1]hept-2-yl)hept-5-enoate Dihydrate (S-1452). To a solution of **12** (4.49 g, 11.9 mmol) in 11.9 mL of 1 N NaOH and 25 mL of water, was added a solution of $CaCl_2$ (1.32 g, 11.9 mmol) in 50 mL of water at room temperature. The reaction mixture was stirred for 6 h, and the resulting crystals were collected by filtration and washed with water, giving 4.68 g (94.9%) of S-1452 as colorless pillars: mp >300 °C dec; IR (Nujol) 3275, 1548, 1160, 1094, 758, 719, 689, 591 cm^{-1}; ^1H NMR δ 0.93–2.55 (m, 34 H), 3.02 (m, 2 H), 5.24 (m, 4 H), 6.48 (m, 2 H), 7.35–7.60 (m, 6 H), 7.85–8.00 (m, 4 H); $[\alpha]_D$ +19.0 ± 0.6° (MeOH, c 1.010, 26 °C). Anal. Calcd for $C_{40}H_{52}CaN_2O_8S_2 \cdot 2H_2O$: C, 57.94; H, 6.82; Ca, 4.83; N, 3.38, H_2O (Karl-Fischer), 4.35. Found: C, 57.80; H, 6.68; Ca, 5.06; N, 3.68, H_2O, 4.50.

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