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A Versatile and Highly Stereocontrolled Synthetic Approach to Homochiral Polyfunctional Norbornene and Norbornane Derivatives

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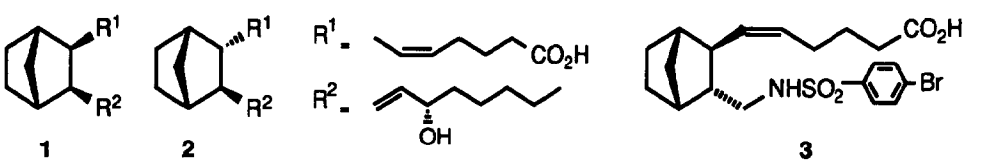
Abstract: *Several title compounds have been synthesized from D-mannitol as the unique chiral precursor. The target molecules include pairs of enantiomers and their configuration has mainly been assured by controlling the facial and the endo/exo diastereoselectivity in the Diels-Alder reactions of chiral cyclic or acyclic dienophiles. Some of the products obtained are key intermediates in the synthesis of biologically active compounds.*

INTRODUCTION

The stereocontrolled production of homochiral norbornene and norbornane derivatives, containing two or more functional groups, is of growing interest since such molecules are synthetic precursors of compounds with biological activity, such as prostanoids,[1] thromboxane antagonists,[2] or carbocyclic nucleosides with antibiotic properties,[3] several of them used as drugs. Some selected examples are the prostaglandin endoperoxide analogues **1** and **2**, which are effective inhibitors of blood platelet aggregation,[1b] and the TXA_2 antagonist ONO-8809, **3**,[2b] also a potent inhibitor of PGE_2 synthesis.[1b]



1 **2** **3**

Preparation of the title or related compounds has often been accomplished by employing chiral auxiliaries or chemoenzymatic approaches.[4] In both cases, obtaining high enantiomeric excesses depends on the efficiency in the asymmetric induction step. On the other hand, selective synthesis of the target products in each enantiomeric form also depends on the availability either of both antipodes of the auxiliary, or on the appropriate enzyme or microorganism.

The use of starting materials from the chiral pool offers a convenient solution to the former problem. Nevertheless, carbohydrates, hydroxy acids, and amino acids, which are the most common classes of chiral precursors,[5] are available from natural sources as one determined enantiomer, in most cases. Unnatural enantiomers are usually much more expensive and sometimes they can not be easily prepared.

In this paper we present a versatile and efficient synthetic approach to several title compounds in pure enantiomeric and diastereomeric form, starting from a unique chiral precursor. Control of the absolute configuration is mainly assured by the high facial and *endo/exo* diastereoselectivity in the thermal and in the catalyzed[6] asymmetric Diels-Alder reactions between cyclopentadiene and either *(Z)*-pentenoate **4**,[7] or butenolide **9**[8] (Scheme 1). Both dienophiles are commercially available; however, they can be prepared in large scale from *D*-glyceraldehyde, obtained in turn from commercial and cheap *D*-mannitol.[9]

RESULTS AND DISCUSSION

Scheme 1 shows, in addition to dienophiles **4** and **9**, the adducts **5** and **10** and some key intermediates related to the target molecules, which are represented at the right-side.

Adduct **5** was obtained in 85% yield, in multigramme scale, as a result of the excellent *syn-endo* diastereoselectivity in the Et_2AlCl catalyzed Diels-Alder reaction between pentenoate **4** and cyclopentadiene.[6] Compound **5** is the precursor of the half-esters **7** and **8**.

Alternatively, dienophile **9**, which can be obtained by acid hydrolysis of **4**,[9] afforded the *anti-endo* adduct **10** in 70% yield through thermal addition to cyclopentadiene.[8] The facial diastereoselectivity in this case is the converse of that found in the reactions of the open chain-dienophile **4**. This fact makes feasible the synthesis of homochiral stereoisomeric compounds. It is worthy of remark that the unsaturated half-ester **7** is the enantiomer of **13** and that the pair **8** and **17** also correspond to enantiomeric compounds.

Thereby, chirality of *C-4* in pentenoate **4** and of *C-5* in furanone **9**, which are the respective stereogenic centers, and epimerization at the α-position in **5**, **11**, and **14**, can be used to induce in most cases the absolute configuration of compounds **7**, **8**, **13**, **15**, and **17**. Furthermore, totally stereospecific hydroxylation of the C-C double bond in tricyclic lactone **10** develops the two additional stereogenic centers of **20**, in which *all six membered-ring carbon-atoms are stereogenic.*

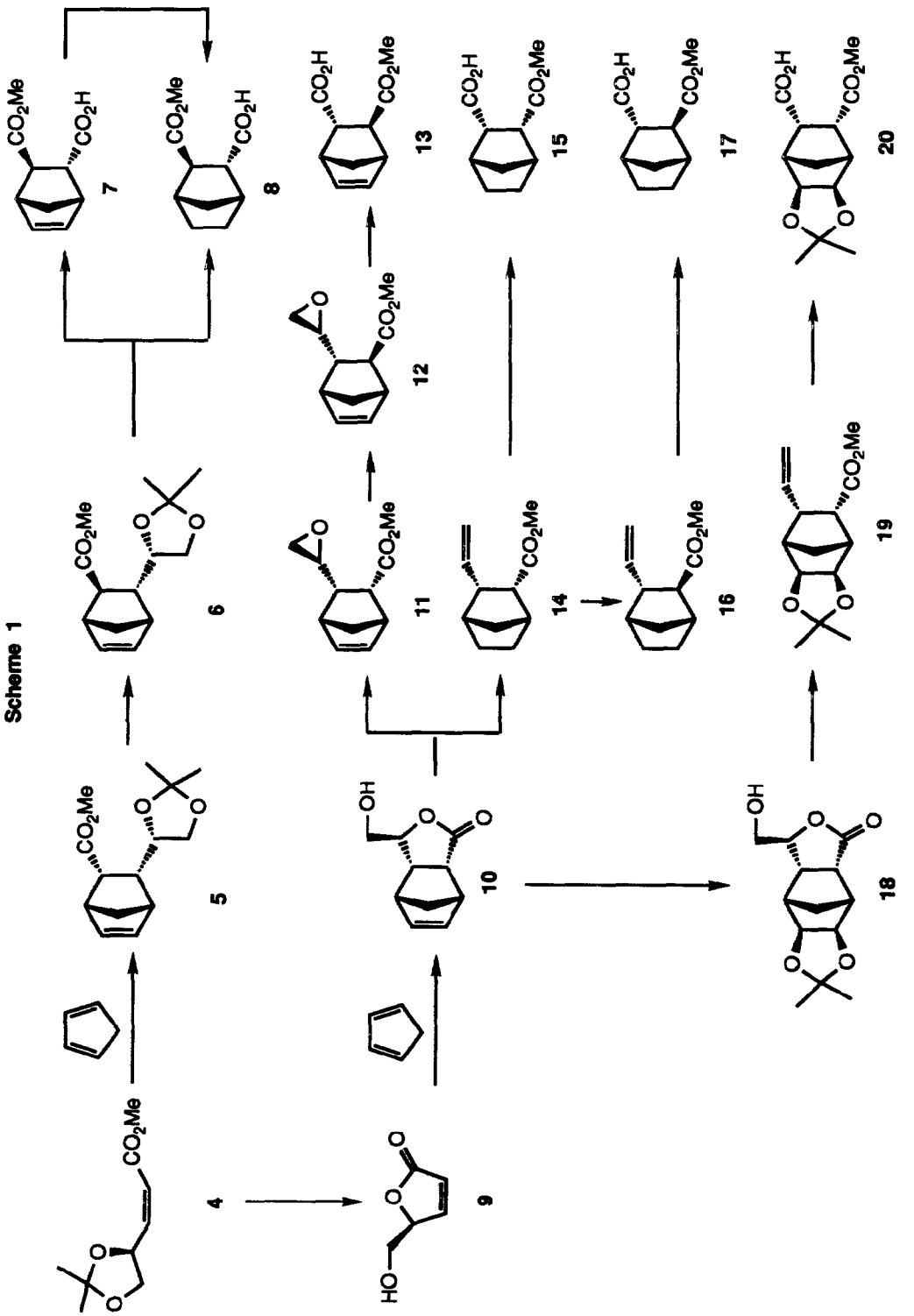
Half-esters **8** and **17** were used as key intermediates for the respective synthesis of thromboxane A_2 receptor antagonists ONO-8809[2b] and S-1452[2a] and we have described their preparation from **6** and **16** respectively in a recent publication.[10] Discussion of the synthetic pathways leading to the other half-esters follows.

Norbornene Derivative 7 (Scheme 2).

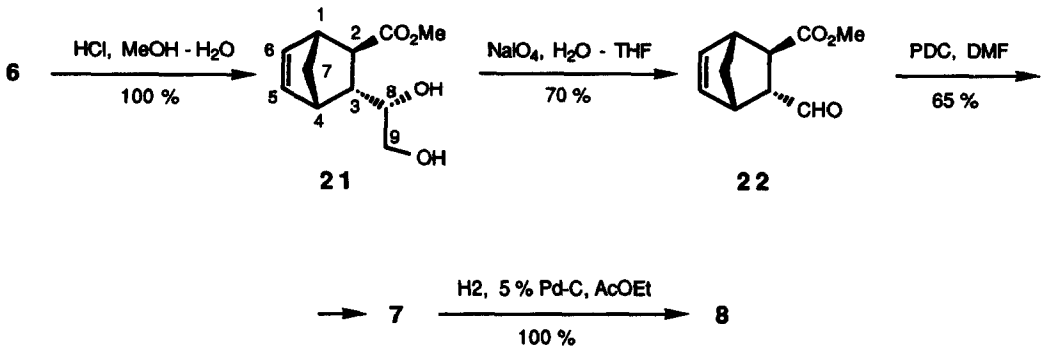
Compound **6**[10] was reacted with methanol saturated with HCl giving diol **21** in quantitative yield. Oxidative cleavage using $NaIO_4$ and subsequent oxidation of aldehyde **22** with pyridinium dichromate in dimethylformamide afforded the norbornene half-ester derivative **7**, as a solid m. p. 78-80 °C, $[\alpha]_D$ -164.8.

In turn, hydrogenation of **7** (5% Pd-C, 1 atm, ethyl acetate) yielded quantitatively the saturated product **8**, providing thus an alternative synthetic entry to this compound with respect to that described in reference 10.

Scheme 1



Scheme 2



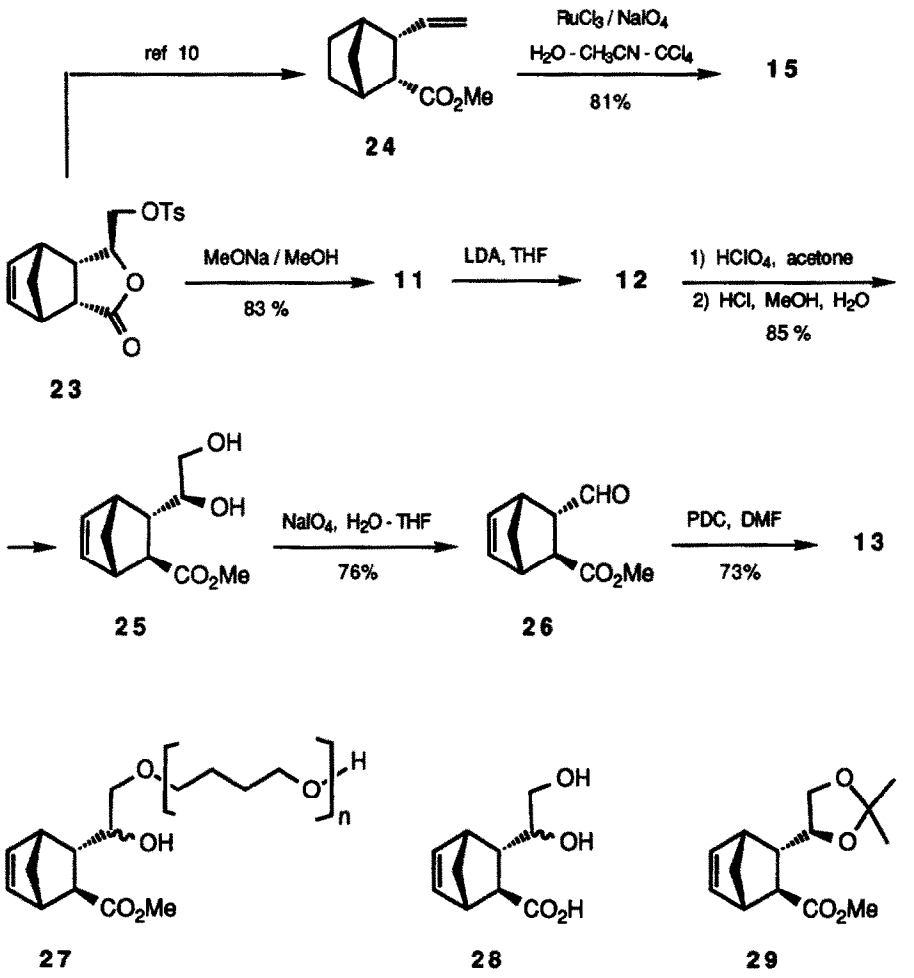
Unsaturated Half-Ester 13 and Saturated Half-Ester 15 (Scheme 3).

Tosylate **23,** obtained from **10**, was converted into the *cis* vinyl ester **24** as previously reported.[10] Oxidation of the C-C double bond by using catalytic-$RuCl_3$ / $NaIO_4$ in water-acetonitrile-carbon tetrachloride at room temperature[11] afforded, in 80 % yield, the *cis* half-ester **15**, $[\alpha]_D$ -19.4, which is diastereomeric with respect to **8** and **17.**

Tosylate **23** is also precursor of the unsaturated *trans* half-ester **13** through epoxide **12.** Reaction between **23** and sodium methoxide (1.3 eq) in anhydrous methanol at room temperature gave the *cis* epoxide **11** in 83% yield, along with the *trans* isomer **12** (5% yield). Epimerization of **11** to give **12** was attempted by using sodium methoxide, but products derived from oxirane ring-opening were obtained, either when catalytic or equimolecular base was added. Starting material **11** was quantitatively recovered when DBU was employed as a non-nucleophilic base, even in refluxing toluene for several hours. Finally, partial epimerization was accomplished by treatment of **11** with LDA (2 eq) at -78 °C followed by hydrolysis, thus giving a 1.2 : 1.0 mixture of *cis/trans* isomers **11** and **12.** This ratio did not vary from five minutes after the addition of LDA to 2.5 hours later. Compound **12** was isolated by column chromatography as a liquid $[\alpha]_D$ +98.1.

In the next step, acid promoted oxirane ring-opening was undertaken by using perchloric acid. Choice of the solvent was crucial in this process. The polyether **27** was identified (^1H NMR) as the major product when THF was employed. The reaction was very slow in dioxane, affording the desired compound **25** but also acid **28** and many unidentified by-products. The best result corresponded to the use of acetone at room temperature. In this case, diol **25** accompanied by its epimer at C-1' (enantiomer of **21**,5%) and acetonide **29** (major product) were obtained. This mixture afforded **25** by treatment with HCl in methanol-water, which was purified by crystallization giving a solid m.p. 70-71 °C, $[\alpha]_D$ +48.8. Oxidation with $NaIO_4$ was very fast, affording aldehyde **26** in less than five minutes. This compound was oxidized with pyridinium dichromate in dimethylformamide to furnish unsaturated half-ester **13**, which is the enantiomer of **7.** This product is a solid, m.p. 78-80°C, $[\alpha]_D$ +162.3.

Scheme 3

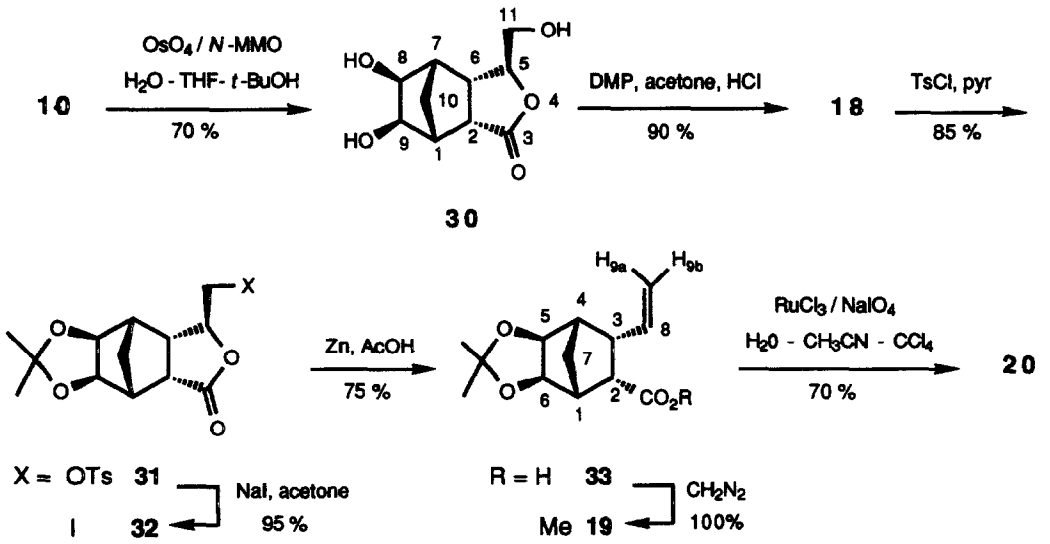


Tricyclic Half-Ester 20 (Scheme 4).

Dihydroxylation of **10** by using catalytic osmium tetroxide and *N*-methylmorpholine *N*-oxide (*N*-MMO)[12] occurred in an excellent stereospecific manner to afford diol **30**, m.p. 171-172 °C, $[\alpha]_D$ -40, in 70% yield. This product contains *seven* highly controlled stereogenic centers. Protection of the *vic*-diol function, through an acetonide formation performed in the usual manner, afforded the tetracyclic lactone derivative **18** which was converted into the tosylate **31**. Treatment of **31** with sodium iodide in acetone gave iodide **32**, from which reductive β–elimination (Zn, AcOH) led to the *cis* vinyl substituted acid **33** (75% yield). Methylation of **33** with diazomethane afforded ester **19** in quantitative yield, $[\alpha]_D$ -68.7, and subsequent oxidation of the

vinyl group by catalytic-$RuCl_3$ / $NaIO_4$ furnished the *cis* half-ester **20** in 70% yield, as a solid m.p. 142-145 °C, $[\alpha]_D$ -5.4.

Scheme 4



CONCLUSION

An efficient and versatile strategy has been developed in order to synthesize the target molecules in a highly stereocontrolled manner and in good overall yields. These compounds are important homochiral synthetic building blocks, which present several stereogenic centers and functional groups convenient for the introduction of other functionalities or alkyl chains. All these features should make them suitable for the preparation of biologically active products.

EXPERIMENTAL SECTION

Flash column chromatography was carried out on silica gel (240-400 mesh). Melting points were determined on a hot stage and are uncorrected. Distillation of small amounts of material was effected in a bulb-to-bulb distillation apparatus, with oven temperatures (o.t.) being reported. Electron-impact mass spectra were recorded at 70 eV. Chemical shifts in NMR spectra are given in ppm relative to internal TMS (δ scale).

(1*R*,2*R*,3*R*,4*S*)-3-[(1*S*)-1,2-Dihydroxyethyl]-2-methoxycarbonylbicyclo[2.2.1]hept-5-ene, 21. Water (9 mL) and HCl saturated methanol (8 mL) were added to a solution of acetonide **6** (1.7 g, 6.7 mmol) in methanol (50 mL). The mixture was stirred at room temperature for 48 h, the solvent evaporated and the residue was chromatographed (1:9 hexane-ethyl acetate) to afford 1.4 g of diol **21** (quant.) as an oil; o.t.

150 °C; $[\alpha]_D$ -50.5 (c=2.37, $CHCl_3$); IR 3700-3000 (broad), 1730 cm^{-1}; MS, m/e 182 (M-30, 2), 181 (M-31, 2), 151 (17), 115 (20), 97 (19), 91 (16), 66 (100); 400-MHz ^1H NMR ($CDCl_3$) 1.50 (broad s, 2H), 1.76 (d, J=4.9 Hz, 1H), 2.40 (m, 1H), 3.03-3.10 (complex absorption, 3H), 3.56 (m, 1H), 3.67 (m, 1 H), 3.67 (s, 3H), 6.19 (broad s, 2H); 20-MHz ^{13}C NMR ($CDCl_3$) 43.77, 46.83, 46.89, 47.04, 51.85, 65.47, 75.29, 135.65, 136.36, 175.91. Anal. Calcd. for $C_{11}H_{16}O_4$: C, 62.23; H, 7.60. Found: C, 61.81; H, 7.73.

(1*R*,2*R*,3*R*,4*S*)-3-Carboxy-2-methoxycarbonylbicyclo[2.2.1hept-5-ene, 7. A suspension of sodium periodate (2.1 g, 9.7 mmol) in 5:3 THF-H_2O (8 mL) was added dropwise to a stirred solution of diol **21** (1.4 g, 6.5 mmol) in THF (20 mL). The mixture was stirred at room temperature for 75 min, then ether (50 mL) was added, and the precipitate formed was filtered off and washed with ether (15 mL). The organic solvents were removed from the combined solutions and the residue was extracted with dichloromethane. The combined extracts were dried and the solvent was evaporated affording an oil which was chromatographed (7:3 hexane-ethyl acetate) to give **(1*R*,2*R*,3*R*,4*S*)-3-Formyl-2-methoxycarbonylbicyclo[2.2.1]hept-5-ene, 22** (0.8 g, 70% yield); o.t. 55 °C; $[\alpha]_D$ -108.9 (c=2.30, $CHCl_3$); IR (film) 1723 cm^{-1} (two carbonyl groups); MS, m/e 180 (M, 2), 121 (15), 91 (19), 83 (18), 66 (100); 400-MHz ^1H NMR (acetone-d_6) 1.42 (dddd, $J_{7b,7a}$=8.5 Hz, $J_{7b,2}$=$J_{7b,1}$=$J_{7b,4}$=1.7 Hz, H_{7b}), 1.63 (dddd, $J_{7a,7b}$=8.5 Hz, $J_{7a,1}$=$J_{7a,4}$=1.5 Hz, $J_{7a,2}$=0.6 Hz, H_{7a}), 2.66 (ddd, $J_{2,3}$=4.6 Hz, $J_{2,7b}$=1.7 Hz, $J_{2,7a}$=0.6 Hz, H_2), 3.12 (m, H_1), 3.31 (ddd, $J_{2,3}$=$J_{3,4}$=4.0 Hz, $J_{3,9}$=1.2 Hz, H_3), 3.37 (m, H_4), 3.66 (s, 3H, OCH_3), 6.09 (dd, $J_{5,6}$=5.7 Hz, $J_{5,4}$=3.0 Hz, H_5), 6.24 (dd, $J_{6,5}$=5.7 Hz, $J_{6,1}$=3.0 Hz, H_6), 9.52 (d, $J_{9,3}$=1.2 Hz, H_9); 20-MHz ^{13}C NMR ($CDCl_3$) 43.48 (C_4), 44.14 (C_2), 46.79 (C_7), 47.21 (C_1), 51.16 (OCH_3), 56.49 (C_3), 134.32 (C_5), 137.07 (C_6), 173.75 (CO_2CH_3), 200.53 (CHO).

Acid **7** is a solid which was obtained following the procedure described below for its enantiomer **13** (455 mg, 65% yield); m.p. 78-80 °C (from hexane-ethyl acetate), $[\alpha]_D$ -184.2 (c=1.52, $CHCl_3$) and -164.8 (c=0.82, MeOH) (lit.[13] m.p.78-79 °C, $[\alpha]_D$ -140.8 (c=2.02, MeOH), 99.8% ee); IR (KBr) 3500-2800 (broad), 1740, 1727, 1692 cm^{-1}; MS, m/e 196 (M, 1), 131 (40), 113 (14), 99 (17), 91 (30), 66 (100); 400-MHz ^1H NMR (acetone-d_6) 1.39 (dddd, $J_{7b,7a}$=8.5 Hz, $J_{7b,6}$=$J_{7b,3}$=$J_{7b,1}$=1.8 Hz, H_{7b}), 1.59 (d, $J_{7a,7b}$=8.5 Hz, H_{7a}), 2.59 (dd, $J_{1,2}$=4.6 Hz, $J_{1,7b}$=1.8 Hz, H_1), 3.06 (m, H_6), 3.23 (m, H_3), 3.31 (dd, $J_{2,1}$=4.6 Hz, $J_{2,3}$=3.7 Hz, H_2), 3.66 (s, 3H, OCH_3), 6.08 (dd, $J_{4,5}$=5.5 Hz, $J_{4,3}$=2.7 Hz, H_4), 6.26 (dd, $J_{5,4}$=5.5 Hz, $J_{5,6}$=3.0 Hz, H_5); 100-MHz ^{13}C NMR 46.21 (C_3), 47.55 (C_1), 47.89 (C_7), 48.29 (C_6), 48.31 (C_2), 52.15 (OCH_3), 135.88 (C_4), 138.12 (C_5), 174.34 (CO_2H), 175.20 (CO_2CH_3). Anal. Calcd. for $C_{10}H_{12}O_4$: C, 61.22; H, 6.16. Found: C, 61.15; H, 6.17.

(1*S*,2*R*,3*R*,4*R*)-3-Carboxy-2-methoxycarbonylbicyclo[2.2.1]heptane, 8. A solution of unsaturated half-ester **13** (175 mg, 0.90 mmol) in ethyl acetate (12 mL) containing 5% Pd-C (22 mg) was hydrogenated at atmospheric pressure and at room temperature. The suspension was filtered through celite and the solvent was removed. The residue was chromatographed (3:2 hexane-ethyl acetate) to afford saturated half-ester **8** (180 mg, quant.); $[\alpha]_D$ -39.3 (c=0.98, MeOH) (lit.[10] $[\alpha]_D$ -40.1 (c=0.97, MeOH); lit.[13] $[\alpha]_D$ -38.3 (c=2.01, MeOH), 99.8% ee).

(1*R*,2*R*,3*S*,4*S*)-3-Carboxy-2-methoxycarbonylbicyclo[2.2.1]heptane, 15. Sodium periodate (2.1 g, (10.1 mmol) and ruthenium trichloride hydrate (20 mg) were added to a solution of vinyl compound **24**[10]

(457 mg, 2.54 mmol) in 3:2:2 water-acetonitrile-carbon tetrachloride (21 mL). The mixture was stirred at room temperature for 90 minutes and then filtered. The filtrate was diluted with ether (30 mL) and, after stirring for five minutes the two phases were separated. The aqueous phase was extracted with ether (3x30 mL), and the combined organic layers were washed with brine and dried. The solvent was evaporated and the residue was chromatographed (3:2 hexane-ethyl acetate) to afford 215 mg (81% yield) of hemiester **15** as a colorless oil; o.t. 130 °C (0.07 Torr); $[\alpha]_D$ -19.4 (c=1.44, MeOH) (lit.[13] $[\alpha]_D$ -17.4 (c=2.05, MeOH), >99.9 ee); IR (film) 3700-2600 (broad), 1741, 1707 cm^{-1}; 400-MHz ^1H NMR (acetone-d_6) 1.33-1.45 (complex absorption, H_7, H_{5endo}, and H_{6endo}), 1.51 (m, H_8), 1.71 (m, H_{5exo}), 1.88 (m, H_{6exo}), 2.45 (broad s, H_4), 2.51 (broad s, H_1), 2.95 (ddd, $J_{3,2}$=10.7 Hz, $J_{3,4}$=4.0 Hz, $J_{3,5exo}$=1.6 Hz, H_3), 3.07 (ddd, $J_{2,3}$=10.7 Hz, $J_{2,1}$=4.5 Hz, $J_{2,6exo}$=1.5 Hz, H_2), 3.58 (s, 3H, OCH_3); 100-MHz ^{13}C NMR ($CDCl_3$) 22.17, 24.94, 40.11, 40.78, 41.34, 47.02, 47.16, 51.06, 173.16, 173.90; MS (CI, NH_3), m/e 216 (M+18, 100), 199 (M+1, 37), 198 (M, 2).

(1*S*,2*R*,3*S*,4*R*)-3-[(1*S*)-Epoxyethyl]-2-methoxycarbonylbicyclo[2.2.1]hex-5-ene, 11. A 2.2M solution of sodium methoxide in methanol (1.1 mL, 2.4 mmol)) was added to a solution of tosylate **23** (612 mg, 1.83 mmol) in anhydrous methanol, and the mixture was stirred at room temperature for 18 h. The solvent was removed and the residue was dissolved in ether (20 mL). The solution was washed with water until neutral pH, the organic phase was dried and the solvent was evaporated giving a liquid which was chromatographed (2:1 hexane-ethyl acetate) to afford pure **11** as a colorless liquid (295 mg, 83% yield), and the *trans* isomer **12** as a minor product (18 mg, 5% yield). Physical and spectral data for **11** follow: o.t. 70 °C (0.2 Torr); $[\alpha]_D$ -101.1 (c=0.91, $CHCl_3$); IR (film) 1741 cm^{-1}; MS, m/e 176 (M-15, 1), 163 (M-31, 1), 66 (100); 400-MHz ^1H NMR (acetone-d_6) 1.43 (complex absorption, H_{7a} and H_{7b}), 2.08 (ddd, $J_{3,2}$=9.8 Hz, $J_{3,8}$=8.9 Hz, $J_{3,4}$=3.5 Hz, H_3), 2.44 (dd, $J_{9a,9b}$=5.2 Hz, $J_{9a,8}$=2.6 Hz, H_{9a}), 2.48 (ddd, $J_{8,3}$=8.9 Hz, $J_{8,9b}$=4.0 Hz, $J_{8,9a}$=2.6 Hz, H_8), 2.57 (dd, $J_{9b,9a}$=5.2 Hz, $J_{9b,8}$=4.0 Hz, H_{9b}), 2.91 (m, H_4 or H_1), 3.09 (m, H_1 or H_4), 3.18 (dd, $J_{2,3}$=9.8 Hz, $J_{2,1}$=3.3 Hz, H_2), 3.60 (s, 3H, OCH_3), 6.17 (dd, J=5.7 Hz, J'=3.0 Hz, H_5 or H_6), 6.27 (ddd, J=5.7 Hz, J'=3.0 Hz, J"=0.7 Hz, H_6 or H_5); 100 MHz ^{13}C NMR (acetone-d_6) 46.29, 47.31, 47.37, 47.69, 49.64, 49.92, 51.33, 52.89, 134.41, 137.13, 173.96. Anal. Calcd. for $C_{11}H_{14}O_3$: C, 68.02; H, 7.27. Found: C, 67.74; H, 7.25.

(1*S*,2*S*,3*S*,4*R*)-3-[(1*S*)-Epoxyethyl]-2-methoxycarbonylbicyclo[2.2.1]hex-5-ene, 12. A 1.6M solution of BuLi in hexane (8.5 mL, 13.6 mmol) was added to an ice-cooled solution of diisopropylamine (2.0 mL, 14.2 mmol) in anhydrous THF and the mixture was stirred for 30 min, then cooled to -78 °C and a solution of *cis* epoxy ester **11** (1.3 g, 7.0 mmol) in anhydrous THF (50 mL) was added dropwise. The mixture was stirred at -78 °C for 30 min. Then ether (30 mL) and saturated aqueous NH_4Cl (30 mL) were subsequently added. The mixture was allowed to reach room temperature and the layers were separated. The aqueous layer was extracted with ether (2x20 mL) and the combined organic phases were washed with water (10 mL) and dried. The solvent was removed and the residue was chromatographed (7:3 hexane-ethyl acetate) to afford *trans* epoxy ester **12** (0.5 g, 37% yield) and *cis* epoxy ester **11** (0.6 g, 46% recovery). Compound **12** is a liquid, o.t. 80 °C; $[\alpha]_D$ +98.1 (c=0.89, $CHCl_3$); IR (film) 1731 cm^{-1}; MS, m/e 176 (M-15, 1), 163 (M-31, 3), 66 (100); 400 MHz ^1H NMR ($CDCl_3$) 1.43 (m, H_7), 1.63 (m, H_8), 2.14 (dd, $J_{2,3}$=4.7 Hz, $J_{2,7}$=1.6 Hz, H_2), 2.31 (ddd, $J_{3,9}$=6.5 Hz, $J_{3,2}$=4.7 Hz, $J_{3,4}$=3.5 Hz, H_3), 2.50 (dd, $J_{11,10}$=4.8 Hz, $J_{11,9}$=2.9 Hz, H_{11}), 2.59 (ddd, $J_{9,3}$=6.5 Hz, $J_{9,10}$=3.9 Hz, $J_{9,11}$=2.9 Hz, H_9), 2.68 (dd, $J_{10,11}$=4.8 Hz, $J_{10,9}$=3.9 Hz, H_{10}), 2.93 (m,

H_1), 3.02 (m, H_4), 3.69 (s, 3H, OCH_3), 6.18 (dd, J=5.7 Hz, J'=2.9 Hz, H_5 or H_6), 6.25 (dd, J=5.7 Hz, J'=3.1 Hz, H_6 or H_5); 20 MHz ^{13}C NMR ($CDCl_3$) 45.30, 45.59, 46.32, 46.59, 47.34, 47.42, 51.59, 53.77, 134.88, 136.81, 175.29. Anal. Calcd. for $C_{11}H_{14}O_3$: C, 68.02; H, 7.27. Found: C, 67.75; H, 7.34.

(1*S*,2*S*,3*S*,4*R*)-3-[(1*S*)-1,2-Dihydroxyethyl]-2-methoxycarbonylbicyclo[2.2.1]hept-5-ene, 25. A 60% aqueous perchloric acid solution (3 drops) and water (5 drops) were added to a solution of epoxide **12** (541 mg, 2.8 mmol) in acetone (25 mL). After stirring at room temperature for 20 h the solvent was evaporated, the residue was poured into methanol (20 mL), and then water (3 mL) and HCl saturated methanol (3 mL) were added. The resulting solution was stirred at room temperature for 20 h, then methanol was removed and the residue was taken into dichloromethane (20 mL). The layers were separated and the organic phase was washed with saturated aqueous sodium bicarbonate. The combined aqueous phases were extracted with dichloromethane (10x5 mL), the organic solution was dried, and the solvent was removed. The resultant oil was chroamtographed (ethyl acetate) to afford 500 mg (85% yield) of a 95:5 mixture (^1H NMR) of diol **25** and its epimer. The major product **25** was isolated by recrystallization from ether-pentane; m.p. 70-71 °C; $[\alpha]_D$ +48.8 (c=0.76, $CHCl_3$); IR (film) 3700-3000 (broad), 1729 cm^{-1}; MS, m/e 194 (M-18, 1), 147 (14), 115 (27), 97 (18), 67 (22), 66 (100); 250-MHz ^1H NMR ($CDCl_3$) 1.44 (dddd, $J_{7b,7a}$=8.8 Hz, $J_{7b,4}$=$J_{7b,1}$=$J_{7b,2}$=1.7 Hz, H_{7b}), 1.55 (d, $J_{7a,7b}$=8.8 Hz, H_{7a}), 2.12 (dd, $J_{2,3}$=4.7 Hz, $J_{2,7b}$=1.7 Hz, H_2), 2.38 (ddd, $J_{3,8}$=8.4 Hz, $J_{3,2}$=4.7 Hz, $J_{3,4}$=3.2 Hz, H_3), 2.77 (broad s, H_4 or H_1), 2.94-3.09 (complex absorption, H_{9a} and H_1 or H_4), 3.46 (d, $J_{9b,9a}$=11.5 Hz, $J_{9b,8}$=6.6 Hz, H_{9b}), 3.67 (m, H_8), 3.67 (s, 3H, OCH_3), 6.02 (d, J=5.5 Hz, J'=2.6 Hz, H_5 or H_6), 6.19 (d, J=5.5 Hz, J'=3.3 Hz, H_6 or H_5); 62.5-MHz ^{13}C NMR ($CDCl_3$) 43.98, 46.30, 47.81, 47.92 (2 C), 52.12, 65.30, 75.88, 134.37, 137.19, 176.47. Anal. Calcd. for $C_{11}H_{16}O_4$: C, 62.23; H, 7.60. Found: C, 62.29; H, 7.60.

(1*S*,2*S*,3*S*,4*R*)-3-Carboxy-2-methoxycarbonylbicyclo[2.2.1]hept-5-ene, 13. Aldehyde **26** was obtained in a similar way that those described above for its enantiomer **22** (251 mg, 76% yield); $[\alpha]_D$ +110.8 (c=2.65, $CHCl_3$).

Pyridinium dichromate (1.1 g, 2.8 mmol) was added to a solution of aldehyde **26** (0.2 g, 1.2 mmol) in anhydrous dimethylformamide (10 mL) and the mixture was stirred at room temperature for 40 h. The suspension was filtered through celite and the solvent was removed. The residue was poured into dichloromethane (15 mL) and the acid was extracted from the solution by washings with saturated aqueous carbonate (2x10 mL). The combined aqueous phases were acidified with 10% HCl and then extracted with dichloromethane (2x10 mL). The combined organic extracts were dried and the solvent was evaporated to give crude acid **13**, which was purified by column chromatography (4:1 hexane-ethyl acetate) to afford 172 mg (73% yield) of pure **13**; crystals, m.p. 78-80 °C (from hexane); $[\alpha]_D$ +162.3 (c=1.23, MeOH) (lit.[13] m.p. 78-79 °C; $[\alpha]_D$ +138.1 (c=2.02, MeOH) 99.8% ee).

(1*R*,2*R*,5*S*,6*S*,7*S*,8*S*,9*R*)-8,9-Dihydroxy-5-hydroxymethyl-4-oxatricyclo[5.2.1.$0^{2,6}$]decan-3-one, 30. Adduct **10** (1.2 g, 6.7 mmol) was added to a stirred and ice-cooled solution of *N*-methylmorpholine *N*-oxide (1.0 g, 8.5 mmol) and a crystal of osmium tetroxide in a 10:3:1 mixture of *t*-butanol-tetrahydrofuran-water (28 mL). The resultant mixture was stirred at room temperature for 24 h, filtered trough celite and 5% HCl was added to the filtrate to lower the pH to 6-7. The solution was continously extracted with

ethyl acetate and the layers were separated. The solvents were removed from the organic phase and the residue was chromatographed (9:1 ethyl acetate-methanol) to give triol **30** (1.0 g, 70% yield) as a solid; m.p. 171-172 °C; $[\alpha]_D$ -40 (c=1.40, methanol); IR (KBr) 3600-3000 (broad), 1783 cm^{-1}; MS, m/e 215 (M+1, 3), 214 (M, 12), 183 (M-CH_2OH, 100), 165 (45), 137 (36), 99 (30), 98 (42), 97 (37), 93 (40), 91 (52), 81 (52), 79 (78), 71 (82), 67 (58), 55 (38), 41 (56); 400-MHz ^1H NMR ($CDCl_3$) 1.34 (ddd, $J_{10b,10a}$=10.4 Hz, $J_{10b,8}$=$J_{10b,9}$=1.5 Hz, H_{10b}), 2.01 (ddd, $J_{10a,10b}$=10.4 Hz, $J_{10a,8}$=$J_{10a,9}$=1.5 Hz, H_{10a}), 2.21 (dd, J=4.9 Hz, J'=1.4 Hz, H_7), 2.41 (dd, $J_{1,2}$=6.0 Hz, J'=1 Hz, H_1), 2.66 (ddd, $J_{6,2}$=11.1 Hz, $J_{6,5}$=5.0 Hz, J'=2.2 Hz, H_6), 3.01 (dd, $J_{2,6}$=11.1 Hz, $J_{2,1}$=6.0 Hz, H_2), 3.51 (dd, J=12.1 Hz, J'=3.2 Hz, H_{11a} or H_{11b}), 3.66 (dd, J=12.0 Hz, J'=3.0 Hz, H_{11b} or H_{11a}), 3.70 (dd, J=6.0 Hz, J'=1.5 Hz, H_8 or H_9), 3.86 (dd, J=6 Hz, J'=1.7 Hz, H_9 or H_8), 3.86 (dd, J=6.0 Hz, J'=1.7 Hz, H_2 or H_1), 4.48 (dd, $J_{9,7}$=5.3 Hz, J'=3.0 Hz, H_9); 62.5-MHz ^{13}C NMR ($CDCl_3$) 35.94, 43.88, 46.88, 47.62, 48.06, 65.29, 70.32, 71.65, 81.79, 180.05. Anal. Calcd. for $C_{10}H_{14}O_5$: C, 56.07; H, 6.54. Found: C, 56.16, H, 6.55.

(1*R*,2*R*,6*S*,7*S*,8*S*,9*R*)-5-Hydroxymethyl-8,9-*O*-isopropylidenedioxy-4-oxatricyclo-[5.2.1.$0^{2,6}$]decan-3-one, 18. A mixture of triol **30** (3.2 g, 14.9 mmol), 35% HCl (1.5 mL), 2,2-dimethoxypropane (36 mL, 224 mmol), and acetone (275 mL) was heated to reflux for 22 h. The solvents were evaporated and the residue was chromatographed (1:1 ethyl acetate-hexane) to afford ketal **18** (3.4 g, 90% yield) as a solid; m.p. 137-138 °C (from ethyl acetate-hexane); $[\alpha]_D$ -40 (c=1.15, $CHCl_3$); IR (KBr) 3600-3000 (broad), 1769 cm^{-1}; MS, m/e 255 (M+1, 6), 239 (M-15, 100), 105 (27), 91 (41), 81 (26), 79 (62), 77 (34), 43 (83), 41 (26); 400-MHz ^1H NMR ($CDCl_3$) 1.26 (s, 3H, CH_3), 1.30 (d, $J_{10b,10a}$=11.6 Hz, H_{10b}), 1.43 (s, 3H, CH_3), 1.95 (d, $J_{10a,10b}$=11.6 Hz, H_{10a}), 2.44 (d, J=4.9 Hz, H_7), 2.70-2.75 (complex absorption, H_1 and H_6), 3.08 (dd, J=10.9 Hz, J'=6.0 Hz, H_2), 3.60 (dd, J=12.0 Hz, J'=3.2 Hz, H_{11a} or H_{11b}), 3.86 (dd, J=12.0 Hz, J'=2.3 Hz, H_{11b} or H_{11a}), 4.20 (d, $J_{8,9}$=5.2 Hz, H_8 or H_9), 4.27 (d, $J_{9,8}$=5.2 Hz, H_9 or H_8), 4.51 (m, H_5); 20-MHz ^{13}C NMR ($CDCl_3$) 23.83, 25.12, 34.91, 41.07, 42.93, 43.30, 44.15, 64.76, 76.99, 78.08, 79.41, 108.96, 177.21. Anal. Calcd. for $C_{13}H_{18}O_5$: C, 61.41; H, 7.09. Found: C, 61.45; H, 7.18.

(1*R*,2*R*,5*S*,6*S*,7*S*,8*S*,9*R*)-8,9-Isopropylidenedioxy-5-*p*-toluenesulfonyloxymethyl-4-oxatri-cyclo[5.2.1.$0^{2,6}$]decan-3-one, 31. Tosyl chloride (4.6 g, 24.2 mmol) was added to a stirred an ice-cooled solution of alcohol **18** (2.5 g, 9.8 mmol) and anhydrous pyridine (30 mL) in dry dichloromethane (70 mL). The mixture was stirred at room temperature for 23 h, and then it was extracted for several times with 5% HCl. The organic phase was dried and the solvent was removed. The residue was chromatographed (1:20 ether-dichloromethane) to afford tosylate **31** (3.4 g, 84% yield) as a solid; m.p. 118-120 °C (from ethyl acetate-hexane); $[\alpha]_D$ -10.6 (c=1.00, $CHCl_3$); IR (KBr) 1758 cm^{-1}; MS, m/e 409 (M+1, 2), 408 (M, 1), 393 (M-15, 72), 179 (18), 155 (34), 105 (20), 91 (100), 79 (32), 65 (32), 43 (39); 400-MHz ^1H NMR ($CDCl_3$) 1.22 (s, 3 H, CH_3), 1.31 (ddd, $J_{10b,10a}$=10.6 Hz, J=J'=1.4 Hz, H_{10b}), 1.41 (s, 3H, CH_3), 1.94 (d, $J_{10a,10b}$=10.6 Hz, H_{10a}), 2.43 (complex absorption, 4 H, Ar-CH_3 and H_7), 2.69 (d, $J_{1,2}$=6.1 Hz, H_1), 2.73 (ddd, $J_{6,2}$=10.8 Hz, $J_{6,5}$=5.1 Hz, J'=2.1 Hz, H_6), 3.04 (dd, $J_{2,6}$=10.8 Hz, $J_{2,1}$=6.1 Hz, H_2), 4.05-4.17 (complex absorption, H_{11a}, H_{11b}, H_8, and H_9), 4.54 (dd, $J_{5,6}$=5.1 Hz, J'=2.8 Hz, H_5), 7.33 (complex absorption 2 arylic H), 7.73 (complex absorption, 2 arylic H); 20-MHz ^{13}C NMR ($CDCl_3$) 21.25, 23.56, 24.88, 34.72, 40.99, 42.71, 43.08, 43.16, 70.46, 75.08, 76.67, 78.25, 108.84, 127.54 (2 C), 129.69 (2 C), 131.96, 145.10, 175.04. Anal. Calcd. for $C_{20}H_{24}O_7S$: C, 58.81; H, 5.92; S, 7.85. Found: C, 58.82; H, 5.94; S, 7.68.

(1*R*,2*R*,5*S*,6*S*,7*S*,8*S*,9*R*)-5-Iodomethyl-8,9-isopropylidenedioxy-4-oxatricyclo-[5.2.1.0^{2,6}]decan-3-one, 32. A mixture of tosylate **7** (3.1 g, 7.7 mmol) and sodium iodide (17.3 g, 115 mmol) in dry acetone (230 mL) was stirred at room temperature for 18 h, then heated to reflux for 5 h. The solvent was evaporated and the residue was poured into ethyl acetate (115 mL) and water (25 mL). The layers were separated and the organic phase was washed with 5% aqueous $Na_2S_2O_3$ (3x7 mL). The combined aqueous phases were extracted with ethyl acetate and the combined organic extracts were dried and the solvent was removed. The residue was cromatographed (1:1 ethyl acetate-hexane) to give iodide **32** (2.7 g, 96 % yield) as a solid; m.p. 114-118 °C (from ethyl acetate); $[\alpha]_D$ -29.9 (c=1.05, $CHCl_3$); IR (KBr) 1758 cm^{-1}; MS, m/e 349 (M-15, 100), 43 (25); 400-MHz ^{1}H NMR ($CDCl_3$) 1.26 (s, 3 H, C*H*$_3$), 1.33 (d, $J_{10b,10a}$=10.6 Hz, H_{10b}), 1.43 (s, 3 H, C*H*$_3$), 1.97 (d, $J_{10a,10b}$=10.6 Hz, H_{10a}), 2.47 (d, J=5 Hz, H_7), 2.61 (ddd, $J_{6,2}$=11.0 Hz, J=5.0 Hz, J'=2.1 Hz, H_6), 2.74 (d, $J_{1,2}$=5.8 Hz, H_1), 3.16 (dd, $J_{2,6}$=11.0 Hz, $J_{2,1}$=5.8 Hz, H_2), 3.31 (dd, J= 10.6 Hz, J'=6.0 Hz, H_{11a} or H_{11b}), 3.36 (dd, J=10.6 Hz, J'=3.6 Hz, H_{11b} or H_{11a}), 4.19 (d, $J_{8,9}$=5.4 Hz, H_8 or H_9), 4.28 (d, $J_{9,8}$=5.4 Hz, H_9 or H_8), 4.46 (m, H_5); 62.5-MHz ^{13}C NMR ($CDCl_3$) 10.86, 23.88, 25.18, 35.15, 42.85, 43.68, 44.15, 45.56, 76.62, 77.21, 77.85, 109.15, 175.64. Anal. Calcd. for $C_{13}H_{17}IO_4$: C, 42.87; H, 4.70; I, 33.84. Found: C, 43.31; H, 4.75: I, 34.28.

(1*R*,2*S*,3*S*,4*S*,5*S*,6*R*)-2-Carboxy-5,6-isopropylidenedioxy-3-vinylbicyclo[2.2.1]heptane, 33. A mixture of iodide **32** (1.8 g (4.9 mmol), zinc dust (2.1 g, 31 mmol), and glacial AcOH (10 mL) in dry ether (115 mL) was heated to reflux for 14 h. Then the mixture was filtered through celite and the solvent was removed. The residue was chromatographed (2:1 ethyl acetate-hexane) to furnish acid **33** (0.9 g, 75% yield) as a solid; m.p. 88-92 °C (from ethyl acetate-pentane); $[\alpha]_D$ -22.9 (c=1.40, $CHCl_3$); IR (KBr) 3600-2800 (broad), 1730 cm-1; MS, m/e 238 (M, 1), 223 (M-15, 100), 133 (21), 105 (21), 91 (28), 83 (23), 79 (23), 67 (22), 59 (21), 45 (58), 43 (50); 400-MHz ^{1}H NMR (CDCl3) 1.16 (d, $J_{7b,7a}$=10.4 Hz, H_{7b}), 1.28 (s, 3 H, C*H*$_3$), 1.43 (s, 3 H, C*H*$_3$), 1.88 (d, $J_{7a,7b}$=10.4 Hz, H_{7a}), 2.37 (d, $J_{1,2}$=4.3 Hz, H_1), 2.59 (d, J=2.4 Hz, H_4), 2.89 (ddd, $J_{3,2}$=11.6 Hz, $J_{3,8}$=9.8 Hz, J=4.3 Hz, H_3), 2.97 (dd, $J_{2,3}$=11.6 Hz, $J_{2,1}$=4.3 Hz, H_2), 4.44 (d, $J_{5,6}$=5.5 Hz, H_5 or H_6), 4.77 (d, $J_{6,5}$=5.5 Hz, H_6 or H_5), 5.07 (dd, $J_{9b,8}$=9.8 Hz, $J_{9b,9a}$=1.8 Hz, H_{9b}), 5.13 (dd, $J_{9a,8}$=16.4 Hz, $J_{9a,9b}$=1.8 Hz, H_{9a}), 5.87 (ddd, $J_{8,9a}$=16.4 Hz, $J_{8,9b}$=$J_{8,3}$=9.8 Hz, H_8); 62.5-MHz 13C NMR (CDCl3) 24.13, 25.27, 33.15, 43.18, 44.21, 44.95, 47.53, 76.47, 77.00, 108.29, 117.58, 135.08, 177.98. Anal. Calcd. for $C_{13}H_{18}O_4$: C, 65.52; H, 7.61. Found: C, 65.60; H, 7.70.

(1*R*,2*S*,3*S*,4*S*,5*S*,6*R*)-5,6-Isopropylidenedioxy-2-methoxycarbonyl-3-vinylbicyclo[2.2.1]-heptane, 19. An ethereal solution of diazomethane was added dropwise to a solution of acid **33** (0.7 g, 3.2 mmol) in ether (60 mL) until total consumption of the starting material, monitored by TLC. Then the excess diazomethane and the solvent were removed and the residue was purified by chromatography (1:1 ethyl acetate-hexane) to afford quantitatively ester **19** (0.8 g) as a solid; m.p. 44-47 °C (from ethyl acetate-pentane); $[\alpha]_D$ -68.7 (c=0.65, $CHCl_3$); MS, m/e 253 (M+1, 4), 252 (M, 1), 237 (M-15, 100), 195 (25), 163 (39), 117 (33), 105 (26), 91 (26), 91 (38), 79 (37), 77 (26), 67 (30), 59 (28), 53 (22), 43 (88), 41 (39). 400-MHz ^{1}H NMR ($CDCl_3$) 1.15 (d, $J_{7b,7a}$=10.5 Hz, H_{7b}), 1.28 (s, 3 H, C*H*$_3$), 1.43 (s, 3 H, C*H*$_3$), 1.87 (d, $J_{7a,7b}$=10.5 Hz, H_{7a}), 2.35 (d, $J_{4,3}$=3.9 Hz, H_4), 2.55 (d, J=3 Hz, H_1), 2.85 (ddd, $J_{3,2}$=11.7 Hz, $J_{3,8}$=9.6 Hz, $J_{3,4}$=3.9 Hz, H_3), 2.95 (dd, $J_{2,3}$=11.7 Hz, J'=4.2 Hz, H_2), 3.60 (s, 3 H, OC*H*$_3$), 4.45 (d, $J_{5,6}$=5.2 Hz, H_5 or H_6), 4.78

(d, $J_{6,5}$=5.2 Hz, H_6 or H_5), 5.04 (dd, $J_{9b,8}$=9.8 Hz, J'=1.8 Hz, H_{9b}), 5.10 (d, $J_{9a,8}$=16.8 Hz, H_{9a}), 5.85 (ddd, $J_{8,9a}$=16.8 Hz, $J_{8,9b}$=9.8 Hz, $J_{8,3}$=9.6 Hz,H_8); 62.5-MHz ^{13}C NMR ($CDCl_3$) 24.12, 25.33, 33.24, 43.30, 44.27, 44.94, 47.53, 51.30, 76.50, 77.06, 108.17, 117.26, 135.44, 172.61. Anal. Calcd. for $C_{14}H_{20}O_4$: C, 66.6; H, 7.99. Found: C, 66.5; H, 8.00.

(1*R*,2*S*,3*S*,4*S*,5*S*,6*R*)-3-Carboxy-5,6-isopropylidenedioxy-2-methoxycarbonylbicyclo-[2.2.1]heptane, 20. This product was prepared following a similar procedure than that described above for the synthesis of hemiester **15**. Product **20** was obtained (0.2 g, 70% yield) as a solid; m.p.142-145 °C (from ethyl acetate-pentane); $[\alpha]_D$ -5.4 (c=1.11, $CHCl_3$); IR (KBr) 3400-2600 (broad), 1739, 1709 cm^{-1}; MS, m/e 255 (M-15, 100), 239 (20), 223 (24), 195 (71), 79 (40), 59 (21), 43 (49); 250-MHz ^1H NMR ($CDCl_3$) 1.15 (ddd, $J_{7b,7a}$=11.0 Hz, $J=_{7b,6}=J_{7b,5}$=1.5 Hz, H_{7b}), 1.26 (s, 3 H, CH_3), 1.42 (s, 3 H, CH_3), 1.93 (ddd, $J_{7a,7b}$=11.0 Hz, J'=J"=1.4 Hz, H_{7a}), 2.60 (d, J=2.2 Hz, H_1 or H_4), 2.62 (d, J= 2.2 Hz, H_4 or H_1), 3.07 (dd, J=2.2 Hz, H_2 and H_3), 3.63 (s, 3 H, OCH_3), 4.52 (dd, J=5.9 Hz, J'= 1.5 Hz, H_5 or H_6), 4.57 (dd, J=5.9 Hz, J'= 1.5 Hz, H_6 or H_5); 62.5-MHz ^{13}C NMR ($CDCl_3$) 24.14, 25.29, 32.86, 43.58, 43.61, 43.68 (2 C), 51.66, 77.40, 77.50, 108.51; 171.69 (CO_2CH_3), 176.77 (CO_2H). Anal. Calcd. for $C_{13}H_{18}O_6$: C, 57.78; H, 6.71. Found: C, 57.71; H, 6.71.

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