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Enantioselective Production of Homochiral (+)-(1*R*,2*S*,3*S*,4*S*)- and (-)-(1*S*,2*R*,3*R*,4*R*)-Bicyclo(2.2.1)heptane-2,3-dicarboxylic Acid, 2-Methyl Esters. Formal Synthesis of the TXA_2 Antagonist S-1452.[&]

Ramon Casas and Rosa M. Ortuño*

Departament de Química, Universitat Autònoma de Barcelona, 08193 Bellaterra, Barcelona, Spain.

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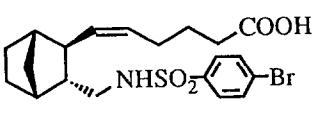
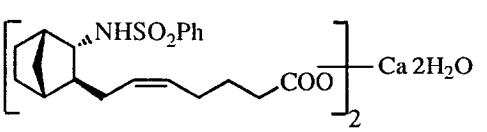
Abstract. Both enantiomers of the title half ester have been synthesized from D-mannitol as single chiral precursor. The dextro-enantiomer is the key intermediate in the synthesis of the TXA_2 antagonistic drug S-1452.

Homochiral compounds belonging to the bicyclo(2.2.1)heptane series are useful synthetic building blocks.[1] Several products with pharmaceutical properties possess structures related to this unit, among them carbocyclic analogues of prostaglandin endoperoxides,[2] and the recently discovered drugs which antagonize the action of thromboxane A_2 (TXA_2), such as **(I)** and **S-1452**.[3,4] Introduction of the α and β-side chains consists in performing well established chemical transformations from a carboxylic acid or from derived functions. Therefore, the practical synthetic interest lies on developing efficient and stereocontrolled methods to prepare suitable diastereomeric and enantiomeric norbornane half esters. Furthermore, biological activity of those compounds often depends on the absolute and relative configuration of the four chiral centers present in these molecules.[2,4]



(I)

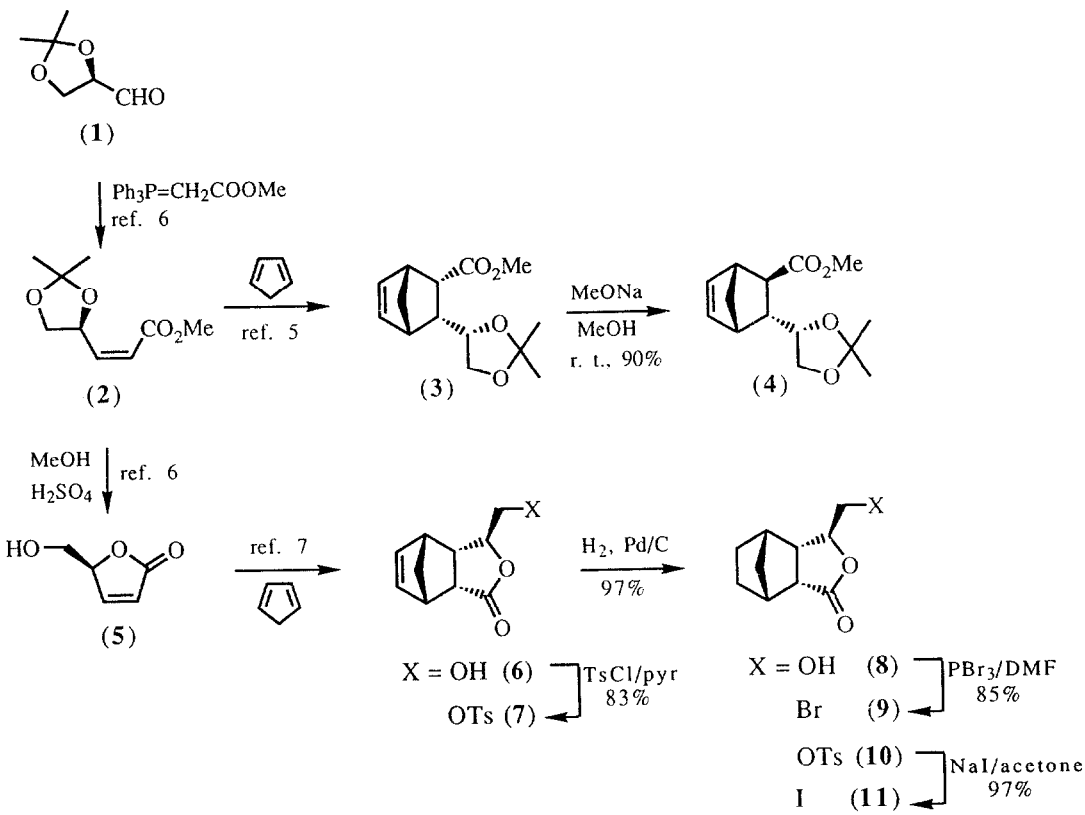


S-1452

We have recently reported[5] that (Z)-pentenoate **(2)**, easily synthesized from D-mannitol **(1)**,[6] adds to cyclopentadiene to give the optically pure (syn-endo)-adduct **(3)** in 85% yield. This is the converse syn/anti facial

diastereoselectivity respect to that observed in the Diels-Alder cycloadditions involving chiral butenolides such as (5),[7] that can be obtained through acid hydrolysis of ester (2).[6] (Scheme 1).

Thereby, alternative Diels-Alder reaction between cyclopentadiene and ester (2) or lactone (5) provides adducts (3) or (6), which are precursors, respectively, of the enantiomeric bicyclo(2.2.1)heptane half esters (15) and (19), according to the synthetic pathways that we describe in this paper.

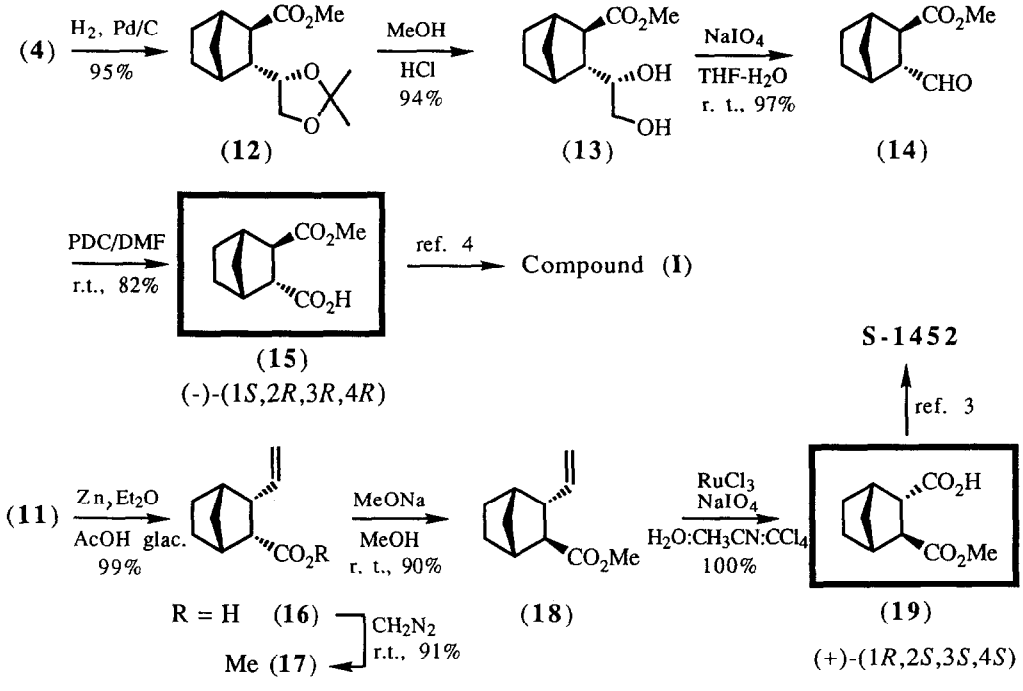


Scheme 1

Adduct (3) was cleanly epimerized with MeONa/MeOH at room temperature, giving the trans-norbornene derivative (4)[8] (Scheme 1), which was hydrogenated (Pd-C, 1 atm H_2, EtOAc) to afford the saturated compound (12) as a liquid $(\alpha)_D$ -9.2 , in 85% yield (two steps) (Scheme 2). Deprotection of the diol by using methanolic HCl, followed by oxidative cleavage by $NaIO_4$, led to the aldehyde (14). Further oxidation with PDC in DMF at room

temperature[8] furnished the (1S,2R,3R,4R)-(half-ester) **(15)**[4,10] as a solid, m.p. 53-54 °C, $(\alpha)_D$ -40.1 , in 65% overall yield from adduct **(3)**.

The dextro-enantiomer **(19)** was synthesized following the reaction sequence from adduct **(6)** depicted in Schemes 1 and 2. The unsaturated alcohol **(6)** was converted into the solid tosylate **(7)**, m.p. 97-98 °C, in 83% yield. Hydrogenation of the double bond of **(7)** in the same manner as described above for product **(4)**, followed by treatment with NaI in acetone, gave iodide **(11)** in 94% yield from **(7)**. Subsequent zinc-acetic acid reduction of **(11)** gave almost quantitatively the vinyl derivative **(16)** (Scheme 2). In an alternative shorter way, the saturated alcohol **(8)** was reacted with PBr_3 in DMF furnishing the bromide **(9)**, which was reduced with zinc in 9:1 isopropanol-water to afford **(16)** in 75% yield (two steps). Esterification with CH_2N_2, and epimerization (MeONa/MeOH) gave the trans-ester (18) as a liquid, $(\alpha)_D$ +43.3 . Finally, quantitative oxidation of the C-C double bond of **(18)** by using catalytic-$RuCl_3/NaIO_4$ in water-acetonitrile-carbon tetrachloride at room temperature[9] afforded the (1R,2S,3S,4S)-(half-ester) **(19)**,[3] m.p. 52-53 °C, $(\alpha)_D$ +39.1 , in 60% overall yield from adduct **(6)**.



Scheme 2

Compound **(19)** is the chiral key intermediate in the asymmetric synthesis of **S-1452**, a potent and orally active TXA_2 receptor antagonist, reported by Shionogi Company.[3] In turn, the enantiomer **(15)** is precursor of other drugs developed by ONO Pharmaceutical such as **(I)**, which is effective not only in inhibiting platelet aggregation, but also in inhibiting an increase in the pressor response caused by various stimulants related to TXA_2.[4]

Therefore, we have demonstrated that the control of syn/anti and endo/exo stereoselectivity in Diels-Alder reactions involving suitable cyclic or acyclic dienophiles, prepared from D-mannitol as single chiral precursor, offers a versatile and efficient synthetic entry to homochiral bicyclo(2.2.1)heptane-2,3-dicarboxylic acid half-esters with predictable absolute configuration and accessible in high yields.

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EXPERIMENTAL SECTION

Melting points were determined on a hot stage and are uncorrected. Distillation of small amounts was effected in a bulb-to-bulb distillation apparatus; only the oven temperatures (o.t.) are given. Electron-impact mass spectra were recorded at 70 eV.

(1R,2R,3R,4S)-3-[(4S)-4-(2,2-Dimethyl-1,3-dioxolo)]-2-methoxycarbonyl bicyclo(2.2.1)hept-5-ene (4). A solution of ester **(3)**[5a] (2.1 g, 8.2 mmol) and MeONa (1.1 g, 21.3 mmol) in anhydrous methanol (60 mL) was stirred at room temperature for 20 h. Then the solvent was removed and the residue was poured into dichloromethane (30 mL). The resultant suspension was washed successively with sat. aqueous NH_4Cl, dried, and evaporated. The residue was chromatographed through silica gel (9:1 hexane-ethyl acetate) to afford some starting material (7% recovery) and compound **(4)** (1.7 g, 82% yield) as a liquid, o.t. 65 °C (0.08 Torr); $(\alpha)_D$ -70.4 (c=3.61, $CHCl_3$); IR (film) 1733 cm^{-1}; MS, m/e 252 (M, 1), 237 (32), 194 (26), 129 (22), 117 (78), 97 (20), 91 (27), 66 (100), 59 (20), 43 (76); 400-MHz ^1H NMR ($CDCl_3$) δ 1.30 (3 H, s),1.40 (3 H, s), 1.46 (1 H, dd, J=8.7 Hz, J'=1.6 Hz), 1.61 (1 H, d, J=8.7 Hz), 1.64 (1 H, dd, J=5.0 Hz, J'=1.6 Hz), 2.39 (1 H, ddd, J=8.4 Hz, J'= 5.0 Hz, J''=3.4 Hz), 3.0 (1 H, m), 3.06 (1 H, m), 3.48 (1 H, ddd, J=10.1 Hz, J'=7.0 Hz, J''=5.8 Hz), 3.64 (1 H, dd, J=8.1 Hz, J'=7.0 Hz), 3.68 (3 H, s), 3.91 1H, dd, J=8.1 Hz, J'=5.8 Hz), 6.18 (2 H, complex abs.); 20-MHz ^{13}C NMR ($CDCl_3$) δ 25.68, 26.86, 44.43, 46.21, 46.91, 47.00, 48.12, 51.69, 68.41, 79.08, 108.72, 135.85, 136.33, 175.27. Anal. Calcd. for $C_{14}H_{20}O_4$: C, 66.65; H, 7.99. Found: C, 66.75; H, 7.96.

(1S,2R,5S,6S,7R)-5-p-Toluenesulfonyloxymethyl-4-oxatricyclo-(5.2.1.$0^{2,6}$)dec-8-en-3-one (7). A mixture of **(6)**[7b] (4.2 g, 23.4 mmol) and tosyl chloride (13.2 g, 69.3 mmol) in anhydrous pyridine (30 mL) was stirred at room temperature for 23 h. Dichloromethane (150 mL) was added and the solution was successively washed with 5% HCl, and dried. The residue was chromatographed on silica gel (2:1 hexane-ethyl acetate) to afford tosylate **(7)** (6.0 g, 77% yield) as a solid; m.p. 97-98 °C (dichloromethane-hexane); $(\alpha)_D$ +8.4 (c=1.27, $CHCl_3$); IR (KBr) 1758, 1590 cm^{-1}; MS, m/e 334 (M, 0.7), 97 (42), 66 (100); 400-MHz ^1H NMR ($CDCl_3$)

1.43 (1 H, d, J=8.6 Hz), 1.64 (1 H, m), 2.45 (3 H, s), 2.94 (1 H, m), 3.10 (1 H, broad s), 3.20-3.30 (2 H, complex abs.), 4.05 (3 H, complex abs.), 6.18 (1 H, dd, J=5.7 Hz, J'= 3.0 Hz), 6.25 (1 H, dd, J=5.7 Hz, J'=2.9 Hz), 7.34 (2 H, d, J=8.2 Hz), 7.75 (2 H, d, J=8.2 Hz); 20-MHz ^{13}C NMR ($CDCl_3$) δ 21.50, 42.98, 45.56, 45.77, 48.02, 51.63, 70.42, 78.36, 127.83, 129.93, 132.49, 134.21, 137.09, 145.21, 176.44. Anal. Calcd. for $C_{17}H_{18}O_5S$: C, 61.08; H, 5.39; S, 9.58. Found: C, 61.17; H, 5.40; S, 9.49.

(1R,2R,5S,6S,7S)-5-Hydroxymethyl-4-oxatricyclo(5.2.1.$0^{2,6}$)decan-3-one (8). A solution of unsaturated compound **(6)** (827 mg, 4.6 mmol) in ethyl acetate (25 mL) was hydrogenated at atmospheric pressure in the presence of 5% palladium on charcoal (98 mg). The catalyst was separated by filtration through celite and the solvent was removed to give a white solid that was purified by flash-chromatography on silica gel (1:1 hexane-ethyl acetate), affording pure saturated product **(8)** (818 mg, 97% yield); m.p. 72-73 °C (from ether-pentane); $(\alpha)_D$ -55.7 (c=1.88, $CHCl_3$); IR (KBr) 3600-3150 (broad), 1735 cm^{-1}; MS (CI, NH_3), m/e 217.15 (M+35, 10), 200.20 (M+18, 100), 183.10 (M+1, 8); 400-MHz ^1H NMR (acetone-d_6) δ 1.32-1.52 (6H, complex abs.), 2.34 (1 H, m), 2.47 (1 H, m), 2.69 (1 H, m), 2.90 (1 H, ddd, J=10.3 Hz, J'=5.8 Hz, J''=1.5 Hz), 3.55 (1H, ddd, J=11.9 Hz, J'= 5.5 Hz, J''=3.7 Hz), 3.67 (1 H, ddd, J=11.9 Hz, J'=5.5 Hz, J''=3.5 Hz), 4.14 (1 H, dd, J=J'=5.5 Hz), 4.36 (1 H, m); 100-MHz ^{13}C NMR ($CDCl_3$) δ 22.16, 25.24, 39.56, 40.04, 41.58, 44.56, 47.87, 65.11, 80.70, 179.08. Anal. Calcd. for $C_{10}H_{14}O_4$: C, 65.91; H, 7.74. Found: C, 65.88; H, 7.75.

(1R,2R,5S,6S,7S)-5-Bromomethyl-4-oxatricyclo(5.2.1.$0^{2,6}$)decan-3-one (9) A solution of PBr_3 (2.7 mL, 28.4 mmol) in anhydrous ether (25 mL) was added dropwise to stirred and ice-cooled anhydrous DMF (50 mL) under argon atmosphere. Then, a solution of alcohol **(8)** (1.3 g, 7.0 mmol) in DMF (18 mL) was subsequently added, the resultant mixture was stirred at 60 °C for 20 h, and then cooled to room temperature. Water (37 mL) was added dropwise and the mixture was extracted with ether (8 x 30 mL). The combined extracts were washed with water (3 x 15 mL) and dried. The solvent was removed and the oily residu was chromatographed on silica gel (4:1 hexane-ethyl acetate) to furnish bromide **(9)** (1.5 g, 86% yield) as a white solid, m.p. 99-100 °C (from $CHCl_3$-pentane); $(\alpha)_D$ -56.3 (c=1.35, $CHCl_3$); IR 1768 cm^{-1}; MS (CI, NH_3), m/e 279.10 and 281.10 (M+35, 18), 262.05 and 264.05 (M+18, 100); 400-MHz ^1H NMR ($CDCl_3$) δ 1.27-1.58 (6 H, complex abs.), 2.39 (1 H, m), 2.50 (1 H, m), 2.67 (1 H, m), 3.00 (1 H, ddd, J=11.6 Hz, J'=6.1 Hz, J''=1.8 Hz), 3.68 (1 H, dd, J=11.0 Hz, J'=4.3 Hz), 3.71 (1H, dd, J=11.0 Hz, J'=4.3 Hz), 4.65 (1 H, m); 20-MHz ^{13}C NMR ($CDCl_3$) δ 22.4, 25.12, 36.72, 39.61, 40.38, 41.69, 47.51, 47.78, 77.45, 177.34. Anal. Calcd. for $C_{10}H_{13}BrO_2$: C, 49.00; H, 5.35; Br, 32.60. Found: C, 48.97; H, 5.37; Br, 32.76.

(1R,2R,5S,6S,7S)-5-p-Toluenesulfonyloxymethyl-4-oxatricyclo-(5.2.1.$0^{2,6}$)decan-3-one (10). This compound was obtained through the same procedure than that described above for the preparation of product **(8)**. Yield: 4.0 g (97%); m.p. 160-161 °C (from $CHCl_3$-ether); $(\alpha)_D$ -3.6 (c=2.42, $CHCl_3$); IR (KBr) 1763 cm^{-1}; MS, m/e 151 (100), 85 (23), 83 (35), 67 (33); 400-MHz ^1H NMR ($CDCl_3$) δ 1.40-1.60 (6 H, complex abs.), 2.38 (1 H, m), 2.43 (3 H, s), 2.64 (1 H, m), 2.66 (1 H, m), 2.98 (1 H, dd, J=11.3 Hz, J'=5.3 Hz), 4.07 (1 H, dd, J=10.5 Hz, J'=3.0 Hz), 4.10 (1 H, dd, J=10.5 Hz, J'=3.0 Hz), 4.47 (1 H, m); 7.34 (2 H, d, J=8.2 Hz), 7.75 (2 H, d, J=8.2 Hz); 20-MHz ^{13}C NMR ($CDCl_3$) δ 21.53, 22.03, 25.17, 39.59, 40.05, 41.55, 44.77, 47.11, 71.07, 76.32, 127.82, 129.93, 132.38, 145.22, 177.09. Anal. Calcd. for $C_{17}H_{20}O_5S$: C, 60.70; H, 5.99; S, 9.53. Found: C, 60.52; H, 5.97; S, 9.47.

(1R,2R,5S,6S,7S)-5-Iodomethyl-4-oxatricyclo(5.2.1.$0^{2,6}$)decan-3-one (11) A solution of tosylate **(10)** (3.8 g, 11.4 mmol) and sodium iodide (25.8 g)

and the solid residue was poured into water (30 mL) and ethyl acetate (80 mL). The layers were separated and the organic phase was washed successively wit 5% aqueous $Na_2S_2O_3$ until colorless. The combined aqueous layers were extracted with ethyl acetate (30 mL) and the combined organic extracts were dried and the solvent was evaporated. Column chromatography of the residue on silica gel (hexane-ethyl acetate) furnished iodide **(11)** (3.1 g (97% yield) as a solid; m.p. 81-82 °C (from chloroform-ethyl acetate-hexane); $(\alpha)_D$ -54.3 (c=2.40, $CHCl_3$); IR (KBr) 1764 cm^{-1}; MS, m/e 293 (M, 2), 292 (18), 165 (58), 151 (100), 91 (30), 79 (42), 77 (27), 67 (79), 66 (32), 43 (21); 400-MHz ^1H NMR ($CDCl_3$) δ 1.30-1.70 (6 H, complex abs.), 2.41 (1 H, m), 2.56 (1 H, m), 2.66 (1 H, m), 3.07 (1 H, ddd, J=11.2 Hz, J'=5.6 Hz, J''=1.7 Hz), 3.30 (1 H, dd, J=11.4 Hz, J'=5.3 Hz), 3.35 (1 H, dd, J= 11.4 Hz, J'= 3.6 Hz), 4.38 (1 H, ddd, J=3.6 Hz, J'=6.2 Hz, J''=2.3 Hz); 100-MHz ^{13}C NMR ($CDCl_3$) δ 11.13; 22.58; 25.05; 39.56; 40.47; 41.74; 47.93; 49.14; 77.83; 177.47. Anal. Calcd. for $C_{10}H_{13}IO_2$: C, 41.12; H, 4.49: I, 43.45. Found: C, 41.10; H, 4.42; I, 43.08.

(1S,2R,3R,4R)-3-[(4S)-4-(2,2-Dimethyl-1,3-dioxolo)]2-methoxycarbonylbicyclo(2.2.1)heptane (12). This compound was synthesized following a similar procedure than that described above to prepare **(8)**. Yield: 2.2 g (100%). Product **(12)** is a liquid, o.t. 95 °C (0.1 Torr); $(\alpha)_D$ -9.2 (c=2.23, $CHCl_3$); IR (film) 1735 cm^{-1}; MS (CI, NH_3), m/e 272.25 (M+18, 89), 255.30 (M+1, 100); 400-MHz ^1H NMR ($CDCl_3$) δ 1.10 (1 H, m); 1.24 (1 H, m), 1.32 (3 H, s), 1.36 (3 H, s), 1.42 (1 H, m), 1.51-1.60 (3 H, complex abs.), 1.68 (1 H, d, J=5.8 Hz), 2.17 (1 H. m), 2.41-2.46 (2 H, complex abs.), 3.58 (1 H, dd, J=8.0 Hz, J'=7.2 Hz), 3.62 (3 H, s), 3.86 (1 H, ddd, J=10.2 Hz, J'=7.2 Hz, J''=5.7 Hz), 3.98 (1 H, dd, J=8.0 Hz, J'=5.7 Hz); 20-MHz ^{13}C NMR ($CDCl_3$) δ 22.30, 25.67, 26.74, 29.18, 37.48, 38.58, 41.28, 47.87, 49.99, 51.46, 68.70, 77.00, 108.69, 174.99. Anal. Calcd. for $C_{14}H_{22}O_4$: C, 66.12; H, 8.72. Found: C, 66.02; H, 8.72.

(1S,2R,3R,4R)-3-[(1S)-(1,2-Dihydroxyethyl)]-2-methoxycarbonylbicyclo-(2.2.1)heptane (13). A mixture containing ketal **(12)** (2.3 g, 8.6 mmol), HCl sat. methanol (5 mL), water (8 mL) and methanol (90 mL) was stirred at room temperature for 24 h. The solvent was removed to afford an oil that was chromatographed through silica gel (1:9 hexane-ethyl acetate) to give pure diol **(13)** (1.8 g, 98% yield), o.t. 160 °C (0.6 Torr), $(\alpha)_D$ -14.2 (c=5.21, $CHCl_3$); IR (film) 3690-3090 (broad), 1731 cm^{-1}; MS, m/e 183 (31), 156 (51), 151 (100), 124 (20), 95 (27), 67 (87), 55 (20); MS (CI, NH_3), m/e 232.30 (M+18, 100), 215.25 (M+1, 31); 400-MHz ^1H NMR ($CDCl_3$) δ 1.13 (1 H, m), 1,26 (1 H, m), 1.40-1.46 (2 H, complex abs.), 1.53-1.61 (2 H, complex abs.), 1.77 (1 H, d, J=5.2 Hz), 2.20 (1 H, m), 2.44 (1 H, broad s), 2.52 (1 H, m), 3.35 (OH, broad s), 3.43-3.58 (2 H, complex abs.), 3.65 (3 H, s), 3.69 (1 H, m); 20-MHz ^{13}C NMR ($CDCl_3$) δ 22.19, 29.40, 37.65, 38.00, 41.40, 46.65, 50.21, 51.81, 65.73, 73.15, 176.09. Anal. Calcd. for $C_{11}H_{18}O_4$: C, 61.66; H, 8.47. Found: C, 61.59,; H, 8.51.

(1S,2R,3R,4R)-3-Formyl-2-methoxycarbonylbicyclo(2.2.1)heptane (14). A suspension of sodium periodate (2.4 g, 11.2 mmol) in water (3 mL) was added dropwise to a stirred solution of diol **(13)** (1.5 g, 7.3 mmol) in THF (25 mL) and the mixture was stirred at room temperature for 5 h. Then, ether (50 mL) was added and the resultant suspension was filtered. The organic solvents were evaporated and the residue was extracted with dichloromethane (3 x 25 mL). The combined extracts were dried and the solvent was removed to afford an oil that was chromatographed on silica gel (1:1 hexane-ethyl acetate) giving aldehyde **(14)** (1.3 g, 97% yield); o.t. 60 °C (0.1 Torr); $(\alpha)_D$ +34.7 (c=2.02, $CHCl_3$); IR (film) 1737 cm^{-1}; MS, m/e 180 (30), 167 (20), 166 (24), 150 (38), 139 (33), 132 (45), 130 (53), 124 (42), 114 (47), 110 (30), 93 (50), 91 (43), 77 (48), 67 (100), 66 (77); MS (CI, NH_3), m/e 217.40 (M+35, 2), 200.25 (M+18, 100), 183.25 (M+1, 6); 400-MHz ^1H NMR ($CDCl_3$) δ 1.16-1.29 (2 H, complex abs.), 1.32 (1 H, dq, J=10 Hz, J'=1.6

Hz), 1.43 (1 H, m), 1.54-1.62 (2 H, complex abs.). 2.58 (1 H, d, J=4.0 Hz), 2.81 (1 H, m), 2.83 (1 H, dd, J=5.3 Hz, J'=1.6 Hz), 3.20 (1 H, m), 3.66 (3 H, s), 9.72 (1 H, s); 20-MHz ^{13}C NMR ($CDCl_3$) δ 24.04, 28.88, 38.02, 41.81, 45.33, 51.83, 57.60, 174.73, 201.82. Anal. Calcd. for $C_{10}H_{14}O_3$: C, 65.91; H, 7.74. Found: C, 65.90; H, 7.80.

(1S,2R,3R,4R)-3-Carboxy-2-methoxycarbonylbicyclo(2.2.1)heptane (15). Pyridinium dichromate (3.9 g, 10.4 mmol) was added to a solution of aldehyde **(14)** (0.8 g, 4.7 mmol) in DMF (35 mL), and the mixture was stirred at room temperature for 26 h. Then, water (80 mL) was added and the resultant aqueous solution was extracted with ether (5 x 30 mL). The combined organic extracts were dried and the solvents were evaporated, giving a residue that was chromatographed on silica gel (7:3 hexane-ethyl acetate) to afford the half-ester **(15)** (0.6 g, 65% yield), as a solid, m.p. 53-54 °C (from ether-hexane); $(\alpha)_D$ -54.2 (c=0.96, $CHCl_3$), and -40.1 (c=0.98, MeOH) (Lit.[10] m.p. 59-60 °C; $(\alpha)_D$ -38.3 (c=2.01 MeOH), 99.8% ee). Previously undescribed spectra follow. MS (CI, NH_3), m/e 233.25 (M+35, 2), 216.25 (M+18, 100), 199.25 (M+1, 9); 20-MHz ^{13}C NMR ($CDCl_3$) δ 24.22, 28.85, 38.18, 40.24, 41.74, 48.54, 49.48, 51.95, 174.92, 178.84.

(1R,2R,3S,4S)-2-Carboxy-3-vinylbicyclo(2.2.1)heptane (16). (a) From iodide **(11)**: Glacial acetic acid (10 mL) and zinc dust (3.0 g, 46.3 mmol) were added to a solution of **(11)** (2.0 g, 7.0 mmol) in ether (60 mL), and the mixture was heated to reflux for 9 h, then filtered through celite. The solvent was removed to give a residue that was chromatographed on silica gel (3:2 hexane-ethyl acetate) affording compound **(16)** (1.1 g, 99% yield). (b) From bromide **(9)**: A mixture of **(9)** (3.8 g, 15.6 mmol) and HCl activated zinc dust (60 g, 0.9 mol) in 9:1 n-propanol-water (100 mL) was heated with stirring at 80 °C for 3 h. The solvent was removed and the residue was poured into chloroform (30 mL) and washed with water (2 x 7 mL). The solution was dried and the solvent was evaporated. The residue was chromatographed on silica gel (1:4 hexane-ethyl acetate) to afford **(16)** (2.3 g, 88% yield). Compound **(16)** is an oil, o.t. 95 °C (0.6 Torr); $(\alpha)_D$ -61.1 (c=1.92, $CHCl_3$); IR (film) 3500-2400 (broad), 1705, 1638 cm^{-1}; MS, m/e 167 (M+1, 6), 166 (M, 45), 138 (28), 125 (58), 121 (46), 107 (20), 100 (93), 99 (51), 94 (32), 93 (56), 91 (45), 79 (80), 67 (100), 66 (50), 53 (44), 41 (86); 400-MHz ^1H NMR ($CDCl_3$) δ 1.18-1.51 (4 H, complex abs.), 1.61 (1 H, m), 1.82 (1 H, m), 2.15 (1 H, broad s), 2.25 (1 H, broad s), 2.68 (1 H, m), 2.96 (1 H, ddd, J=11.6 Hz, J'=4.2 Hz, J''=1.8 Hz), 4.95 (2 H, complex abs.), 6.00 (1 H, dt, J=16.9 Hz, J'=10.1 Hz), 8.89 (1 H, broad s); 100-MHz ^{13}C NMR ($CDCl_3$) δ 22.54, 23.62, 40.28, 41.12, 43.88, 45.88, 48.32, 115.93, 138.04, 179.11. Anal. Calcd. for $C_{10}H_{14}O_2$: C, 72.26; H, 8.99. Found: C, 72.33; H, 8.55.

(1R,2R,3S,4S)-2-Methoxycarbonyl-3-vinylbicyclo(2.2.1)heptane (17). An ethereal solution of diazomethane was added dropwise to a stirred solution of acid **(16)** (0.9 g, 5.7 mmol) in ether (40 mL) until persistent yellow colour. The solvent was evaporated and the residue was chromatographed on silica gel (9:1 hexane-ethyl acetate) to afford quantitatively ester **(17)** (0.9 g) as a liquid o.t. 40 °C (0.05 Torr); $(\alpha)_D$ -70.4 (c=1.42, $CHCl_3$); IR (film) 1737, 1637 cm^{-1}; MS, m/e 180.20 (M, 9), 140 (25), 120 (23), 114 (100), 113 (44), 93 (30), 91 (30), 81 (29), 79 (45), 67 (44); 400-MHz ^1H NMR (acetone-d_6) δ 1.29-1.41 (2 H, complex abs.), 1.41 (1 H, ddd, J=9.6 Hz, J'=J''=1.7 Hz), 1.51 (1 H, m), 1.67 (1 H, m), 1.97 (1 H, m), 2.19 (1 H, broad s), 2.44 (1 H, broad s), 2.74 (1 H, m), 2.90 (1 H, ddd, J=11.6 Hz, J'=3.9 Hz, J''=1.7 Hz), 3.55 (3 H, s), 4.94 (1 H, dd, J=10.0 Hz, J'=2.4 Hz), 4.99 (1 H, ddd, J=16.8 Hz, J'=2.4 Hz, J''=0.6 Hz), 6.05 (1 H, ddd, J=16.8 Hz, J'=J''=10.0 Hz); 20-MHz ^{13}C NMR ($CDCl_3$) δ 22.38, 23.36, 40.18, 40.96, 43.62, 45.86, 48.06, 50.46, 115.38, 137.96, 173.08. Anal. Calcd. for $C_{11}H_{16}O_2$: C, 73.30; H, 8.95. Found: C, 73.30; H, 9.04.

(1R,2S,3S,4S)-3-carboxy-2-methoxycarbonylbicyclo(2.2.1)heptane (19) through compound (18). (1R,2S,3S,4S)-2-Methoxycarbonyl-3-vinylbicyclo-(2.2.1)heptane **(18)** was obtained by epimerization of ester **(17)** following a similar method than that described above for the epimerization of **(3)**; yield: 390 mg (90%); b.p. 50 °C (0.2 Torr); $(\alpha)_D$ +43.3 (c=2.63, $CHCl_3$); IR (film) 1732, 1639 cm^{-1}; MS, m/e 180 (M, 6), 139 (27), 121 (44), 120 (51), 114 (21), 113 (100), 91 (37), 81 (43), 79 (50), 67 (41), 53 (32); 400-MHz ^1H NMR ($CDCl_3$) δ 1.14-1.28 (3 H, complex abs.), 1.46-1.58 (3 H, complex abs.), 2.02 (1 H, d, J=5.5 Hz), 2.19 (1 H, m), 2.41 (1 H, m), 2.72 (1 H, m), 3.58 (3 H, s), 4.99-5.04 (2 H, complex abs.), 5.77 (1 H, ddd, J=17.1 Hz, J'=10.4 Hz, J''=6.7 Hz); 20-MHz ^{13}C NMR ($CDCl_3$) δ 22.67, 29.83, 38.00, 41.61, 41.81, 48.62, 51.57, 115.33, 133.30, 175.79.

To a solution of **(18)** (96 mg, 0.53 mmol) in 4:3:3 water-acetonitrile-carbon tetrachloride (10 mL) sodium periodate (513 mg, 2.4 mmol) and ruthenium trichloride hydrate (13 mg) were successively added. The resultant black solution was stirred at room temperature for 6 h and then ether (20 mL) was added and the mixture was stirred for 10 minutes. The layers were separated and the aqueous phase was extracted with ether (2 x 20 mL); the combined extracts were washed with sat. aqueous NaCl (10 mL), dried, and the solvents were removed. The residue was chromatographed on silica gel (1:1 hexane-ethyl acetate) affording quantitatively half-ester **(19)** (108 mg); m.p. 52-53 °C (hexane); $(\alpha)_D$ +39.0 (c=0.87, MeOH) (Lit.[3] m.p. 59-60 °C; $(\alpha)_D$ 38.4 (c=2.00, MeOH) 97.4% ee).

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