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Stereocontrolled Synthetic Entries to Homochiral Hydroxylated Norbornene Derivatives. Formal Synthesis of Some Carbocyclic Nucleosides.

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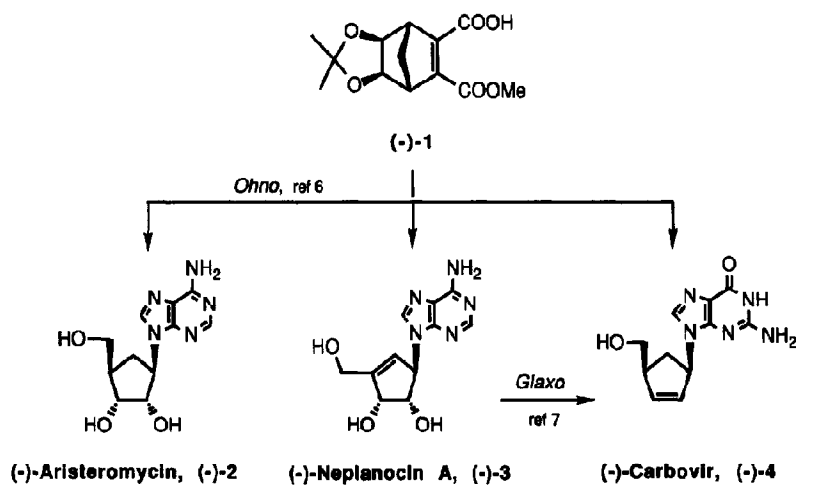
Abstract: *Several homochiral hydroxylated norbornene derivatives have been synthesized from D-mannitol. Stereocontrolled Diels-Alder cycloadditions and stereospecific hydroxylations are key processes for the creation of the stereogenic centers in the target molecules. These compounds are real or potential precursors in the synthesis of carbocyclic nucleosides and related products.*

INTRODUCTION

The so called carbocyclic nucleoside family includes important compounds such as the naturally occurring antineoplasic antibiotics (-)-aristeromycin, (-)-**2**, isolated from *Streptomyces citricolor*,[1] and (-)-neplanocin A, (-)-**3**, produced by *Actinoplacea ampulariella* sp.,[2] and the antiviral agent (-)-carbovir, (-)-**4**, which is a



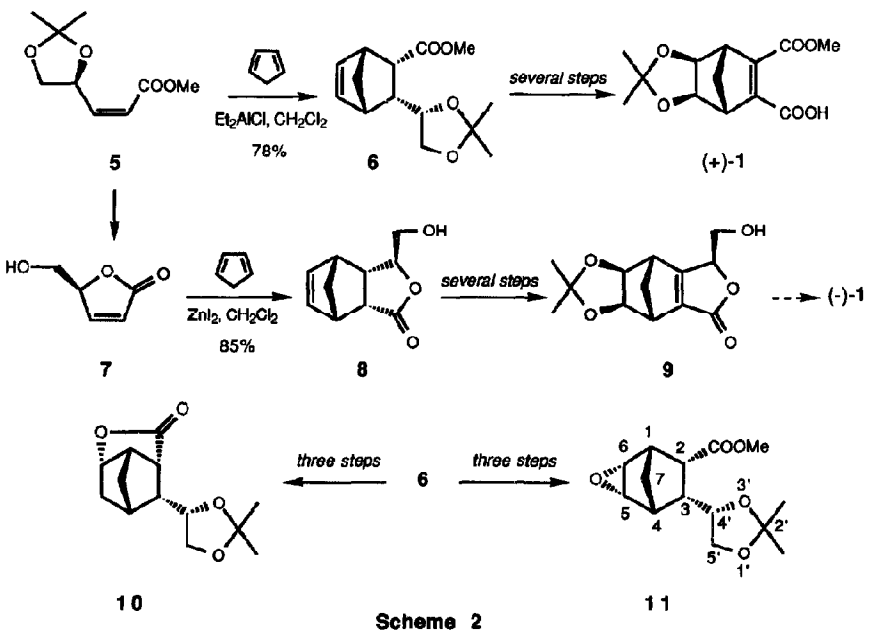
Scheme 1

selective inhibitor of human immunodeficiency virus (HIV-1) in vitro.[3] These products and other structurally related molecules are receiving much attention by several research groups owing to their therapeutic properties, and many synthetic methods for the preparation of racemic or homochiral compounds have recently been reported.[4,5] Among them, Ohno and coworkers described the first synthesis of (-)-**2** and (-)-**3** using the hemiester (-)-**1** (Scheme 1) as a key intermediate, which was obtained in homochiral form by means of chimio-enzymatic asymmetric induction on a suitable precursor. Ozonolysis of the C-C double bond afforded the cyclopentanic structure containing all the stereogenic centers of the target molecules.[4] The Glaxo Company has transformed (-)-aristeromycin into (-)-carbovir,[6] the Ohno's hemiester is also a formal precursor of this product.

Currently, investigations are focused on the influence the absolute configuration and functionalization of the cyclopentane ring moiety exert on the biological activity of such molecules. With this aim, we have synthesized several hydroxylated norbornene derivatives which, according to Ohno's protocol, are potential precursors of carbocyclic nucleosides and related compounds. The preparation of the antipodal hemiester (+)-**1** starting from D-mannitol is also described, this product being a formal precursor of (+)-**4** and of the unnatural enantiomers (+)-**2** and (+)-**3** (*dextro* series).

RESULTS AND DISCUSSION

The strategy lies in the use of compounds **6** and **8** as starting materials in the synthesis of hemiester (+)-**1** and tetracyclic lactone **9** (Scheme 2), respectively, which are obtained through the Diels-Alder cycloadditions of



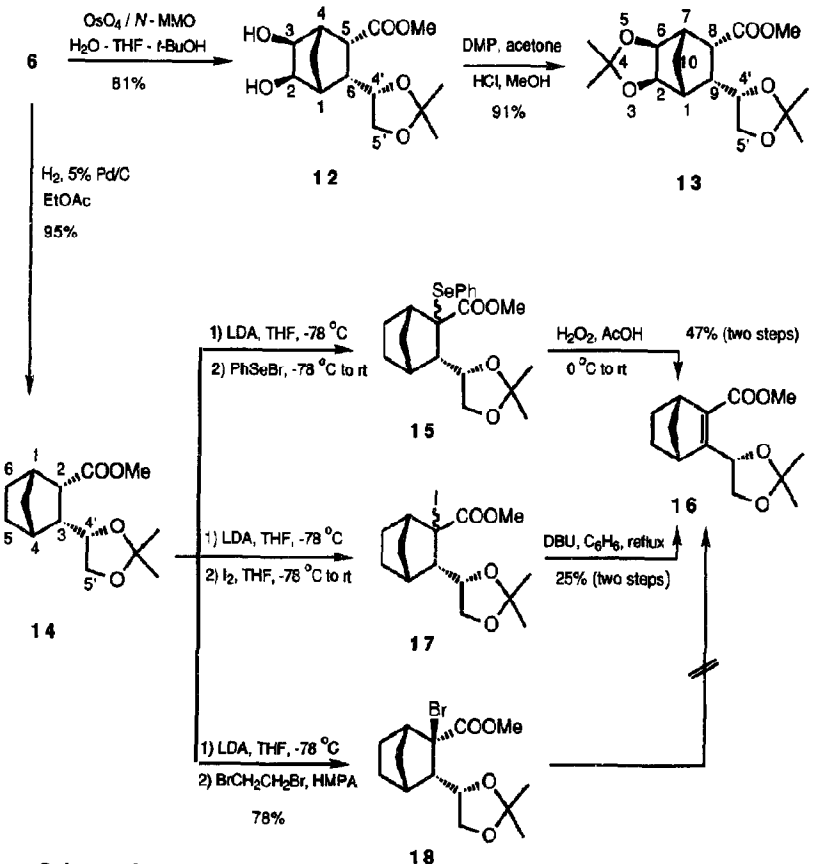
Scheme 2

cyclopentadiene to dienophiles **5**[7,8] and **7**[9,10] prepared, in turn, from D-mannitol as the only chiral precursor.[11] Ester **6** has been converted into hemiester (+)-**1** whereas lactone **8** could lead to the antipode (-)-**1** through the key intermediate **9**. Therefore, synthetic routes to both pairs of enantiomers corresponding to compounds **2-4** (*dextro* and *levo* series) could be accomplished. On the other hand, oxygenated derivatives such as **10** and **11** (Scheme 2) have been synthesized. These compounds could also be precursors of other carbocyclic compounds.

Hemiester (+)-1 (Schemes 3 and 4).

This compound has recently been synthesized by García-Ruano and coworkers in 77% ee, also starting from a Diels-Alder adduct. In this case, asymmetry was induced by means of an auxiliary chiral sulfoxide, attached to the dienophile moiety.[12]

Two features are noteworthy in our synthesis of (+)-**1** from **6**: the dihydroxylation of the C-C double bond in **6** in order to produce unambiguously two new stereogenic centers and the subsequent creation



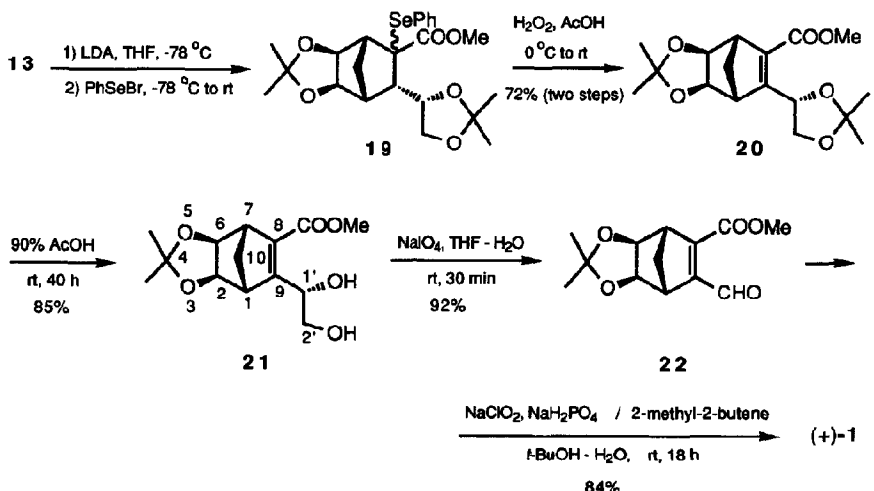
Scheme 3

of the C-C double bond which must afford cyclopentane derivatives through oxidative cleavage. The first objective was accomplished by means of a completely stereospecific dihydroxylation using catalytic osmium tetroxide /*N*-methylmorpholine *N*-oxide that furnished product **12** in 81% yield as a single isomer. The diol **12** was protected through conversion into the acetonide **13** following standard methods (Scheme 3). The second objective, introduction of the C-C double bond, required further studies which are described below.

Several methods based on β-elimination processes were tried using compound **14** as an easily accessible model (Scheme 3). Some previous experiments were performed on adduct **6** but the double bond was not compatible with the reagents and conditions required. The saturated ester **14** was obtained in 95% yield by catalytic hydrogenation of **6** and submitted to treatment with LDA at -78 °C. The resulting lithium enolate was reacted with PhSeBr to afford the mixture of epimers **15** which was subsequently treated with hydrogen peroxide and glacial acetic acid, from 0 °C to room temperature, to give the unsaturated ester **16** in 47% overall yield. This low yield was attributed to the stereoelectronic requirements of the pyrolytic elimination of phenylselenenic acid that involves only one of the epimeric selenides **15**. Therefore, we decided to try the elimination of hydrogen halides according to other mechanistic pathways. The first step was the introduction of an halogen atom, such as iodine or bromine, at the α-carbonyl position.

Reaction between the lithium enolate of **14** and iodine in THF from -78 °C to room temperature furnished a mixture of iodides **17** which, without further purification, was treated with DBU in refluxing benzene for 6 hours, affording **16** in 25% yield for the two steps. On the other hand, bromination of **14** was accomplished by using 1,2-dibromoethane as brominating agent, at 0 °C, giving compound **18** in 78% yield.[13] Nevertheless, all attempts to eliminate hydrogen bromide from **18** were unsuccessful.

The first method tried on **14** (pyrolysis of a selenoxide) was then applied to molecule **13** obtaining the unsaturated ester **20** in 72% yield (Scheme 4). Gratifyingly this yield is much higher than that corresponding to the model.

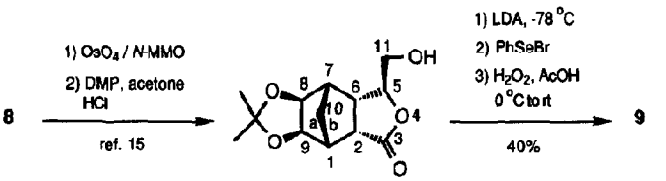


Scheme 4

The primary alcohol-acetonide in **20** was selectively hydrolysed with 90% acetic acid at room temperature for 40 h, affording the diol **21** which was oxidatively cleaved under treatment with aqueous sodium periodate to produce **22** (Scheme 4). The last step was the oxidation of the unsaturated aldehyde **22** to carboxylic acid. Among other methods described in the literature for this purpose, the use of sodium chlorite in *tert*-butanol-water in the presence of 2-methyl-2-butene as chlorine trapping agent[14] afforded excellent results in our case, allowing the hemiester (+)-**1** to be obtained in 84% yield. This product is a solid, m.p. 115-117 °C, $[\alpha]_D$ +28.6 (Lit, ref 12: $[\alpha]_D$ +22.0, 77% ee; ref 4 : mp 115-118 °C, $[\alpha]_D$ -23.8, 80% ee, for the enantiomer (-)-**1**).

Unsaturated lactone 9 *(Scheme 5).*

Lactone **8**[9,10] was dihydroxylated to give **23**,[15] according to the procedure described above for ester **6**. The creation of the C-C double bond was achieved by introduction of a phenylseleno group at the α-carbonyl position followed by oxidation and concomitant elimination of phenylselenenic acid, affording the rigid tetracyclic lactone **9** in 40% yield. This product was characterized as a solid, m.p. 138-140 °C, $[\alpha]_D$ -37.5.



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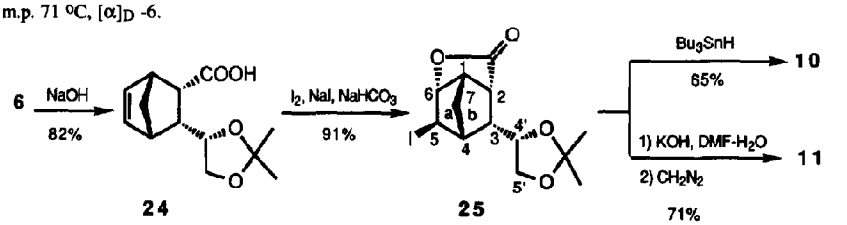
Scheme 5

Lactone 10 and ester 11 *(Scheme 6).*

The stereocontrolled functionalization involving formal hydroxylation of the C-C double bond in **6**,[7,8] in order to synthesize the target molecules **10** and **11**, passes through a iodolactonizaton process. Ester **6** was thereby treated with aqueous sodium hydroxide giving acid **24** which under reaction with iodine and sodium iodide in the presence of sodium bicarbonate afforded iodolactone **25** in 91% yield. This compound is an intermediate for obtaining either lactone **10** or epoxyester **11**. Thus, in the first pathway the halogen atom was removed in compound **24** by reduction with Bu_3SnH to provide lactone **10** as a solid, m.p. 78 °C, $[\alpha]_D$ -48.9. In a second pathway, iodolactone **25** underwent lactone ring-opening and subsequent epoxidation via internal displacement of iodide, induced by potassium hydroxide in aqueous DMF. The resultant crude carboxylic acid was then reacted with diazomethane to furnish the *endo*-epoxyester **11** in 71% yield as a solid, m.p. 71 °C, $[\alpha]_D$ -6.



24 **25**

Scheme 6

These transformations allowed therefore the stereospecific functionalization of the C-C double bond from the precursor **6**. Molecules **10** and **11** present, respectively, six and seven stereogenic centers with unambiguous absolute configuration. It is noteworthy that the chirality at C_5 in **11**, and at C_6 in **10** and **11** (see Schemes 2 and 6 for numeration of the carbon atoms) is converse with respect to that induced by direct dihydroxylation of **6** in the synthetic route leading to hemiester (+)-**1**.

CONCLUSION

Efficient and convenient synthetic methods have been developed in order to prepare homochiral oxygenated norbornene derivatives which posses functional groups that make them suitable to be converted into carbocyclic nucleosides and related products. D-mannitol is the only chiral precursor from which divergent synthetic routes have been derived towards the target molecules. The absolute configuration of the stereogenic centers in these compounds has been determined by the synergic combination of the stereocontrol in the Diels-Alder cycloadditions involved in the production of **6** and **8**, and the stereospecificity in the hydroxylation of the C-C double bond from these precursors.

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).

Methyl (1*S*,2*S*,3*R*,4*R*)-3-[(4*S*)-4-(2,2-dimethyl-1,3-dioxolo)]bicyclo[2.2.1]heptan-2-ylcarboxylate, 14. A solution of unsaturated ester **6** (1.0 g, 3.9 mol) in ethyl acetate (50 mL) containing 5% Pd/C (100 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 (9:1 hexane ethyl acetate) to afford the saturated ester **14** (0.9 g, 94% yield); o.t. 110 °C (0.06 Torr); $[\alpha]_D$ +42.6 (c=0.75, $CHCl_3$); IR (film) 1735 cm^{-1}; MS, m/e 239 (M-15, 26), 165 (63), 130 (54), 98 (100), 72(44), 43(99); 400-MHz ^{1}H-NMR ($CDCl_3$) 1.20-1.50 (complex absorption, 5H), 1.30 (s, 3 H, C*H*$_3$), 1.40 (s, 3 H, C*H*$_3$), 1.71-1.76 (complex absorption, 1H), 2.01 (m, H_3), 2.42-2.50 (complex absorption, H_1 and H_4), 2.79 (dd, $J_{2,3}$=11.6 Hz, $J_{2,1}$=4.3 Hz, H_2), 3.49 (dd, $J_{5b',5a'}$= 8.2 Hz, $J_{5b',4'}$= 4.9 Hz, $H_{5b'}$), 3.60 (s, 3 H, OC*H*$_3$), 4.03 (dd, $J_{5a',5b'}$= 8.2 Hz, $J_{5a',4'}$= 4.9 Hz, $H_{5a'}$), 4.63 (m, $H_{4'}$); 100-MHz ^{13}C NMR ($CDCl_3$) 22.04, 24.14, 24.92, 27.13, 39.62, 39.82, 41.87, 45.73, 46.46, 51.15, 69.24, 74.31, 108.22, 173.80 (*C*O$_2$CH$_3$). Anal. Calcd. for $C_{14}H_{22}O_4$: C, 66.20; H, 8.73. Found: C, 66.31; H, 8.69.

Methyl (1*S*,2*S*,3*S*,4*R*)-2-bromo-3-[(4S)-(2,2-dimethyl-1,3-dioxolo)]bicyclo[2.2.1]heptan-2-ylcarboxylate, 18. A 1.6 M solution of BuLi in hexane (0.9 ml, 1.6 mmol) was added dropwise to a solution of diisopropylamine (220 µl, 1.6 mmol) in anhydrous THF (10 ml) cooled at -78 °C and the mixture was stirred for 30 min. Then a solution of ester **14** (200 mg, 0.8 mmol) in THF (6 ml) and HMPA (0.9 ml, 5.6 mmol) was subsequently added. The mixture was stirred for two hours to reach 0 °C. Then 1,2-dibromoethane (102 µl, 1.2 mmol) was added and the resultant solution was stirred at 0 °C for 3 hours. The solution was diluted with ethyl acetate, washing twice with saturated aqueous ammonium chloride and satured aqueous NaCl. The organic solvents were removed and the residue was chromatographed (mixtures of hexane-

ethyl acetate) to afford compound **18** (177 mg, 74% yield); o.t. 130 °C (0.2 Torr); $[\alpha]_D$ +33.4 (c=5.39, $CHCl_3$); IR (film) 1736 cm^{-1}; MS, m/e 317-319 (M-15), 259-257 (58), 177 (46), 101 (50), 72 (60), 43 (100); 250-MHz ^{1}H-NMR ($CDCl_3$) 1.23-1.50 (complex absorption, 3H), 1.29 (s, 3 H, CH_3), 1.38 (s, 3 H, CH_3), 1.54-1.68 (complex absorption, 2H), 1.87 (m, 1H), 2.36-2.40 (complex absorption, H_3 and H_4), 2.90 (m, H_1), 3.73 (s, 3 H, OCH_3), 3.93 (dd, $J_{5b',5a'}$= 8.0 Hz, $J_{5b',4'}$= 4.7 Hz, $H_{5b'}$), 4.10 (m, $H_{4'}$), 4.18 (dd, $J_{5a',5b'}$= 8.0 Hz, $J_{5a',4'}$= 5.8 Hz, $H_{5a'}$); 62.5-MHz ^{13}C NMR ($CDCl_3$) 21.40, 25.20, 25.81, 26.92, 37.20, 39.61, 47.66, 49.21, 53.21, 68.71, 69.32, 76.70, 108.51, 172.16 (CO_2CH_3). HRMS m/e Calcd. for $C_{14}H_{21}O_4Br$: 317.0388 (M-CH_3). Found: 317.0416.

Methyl (1*S*,4*R*)-3-[(4*S*)-4-(2,2-dimethyl-1,3-dioxolo)]bicyclo[2.2.1]hept-2-en-2-ylcarboxylate, 16.

(a) Through selenides 15: A 1.6M solution of BuLi in hexane (1.2 mL, 1.9 mmol) was added dropwise to a solution of diisopropylamine (270 µL, 1.9 mmol) in anhydrous THF (6 mL) cooled at -78 °C and the mixture was stirred for 30 min. Then a solution of ester **14** (325 mg, 1.3 mol) in THF (6 mL) was added. After stirring at -78 °C for 90 min phenylselenyl bromide was added in one portion (0.8 mmol prepared from diphenyl diselenide (265 mg) and 40 µL of bromine). The resultant solution was stirred at -78 °C for 5 h, then the reaction mixture was neutralized with saturated aqueous ammonium chloride and the layers were separated. The organic phase was dried and the solvent evaporated to afford a residue that was chromatographed (9:1 hexane-ethyl acetate) to afford a mixture of the epimeric selenides **15**. Subsequently, to an ice-cooled solution of this mixture in THF (6 mL) 30% hydrogen peroxide (0.9 mL) and glacial acetic acid (five drops) were added and the resultant solution was stirred for 1 h, then neutralized with saturated aqueous sodium bicarbonate and extracted with dichloromethane. The organic solvents were removed and the residue was chromatographed (9:1 hexane-ethyl acetate) to give the conjugated ester **16** (154 mg, 47% yield).

(b) Through iodides 17: Starting from **14** (250 mg, 1.0 mmol), the corresponding lithium enolate was produced as described above. Then 3.5 mL of a solution containing iodine (299 mg, 1.2 mmol) in THF (4 mL) was added dropwise at -78 °C until no decoloration was observed. The mixture was stirred for 30 min to reach room temperature. The solution was neutralized with saturated aqueous ammonium chloride and the layers were separated. The organic solvent was removed affording 382 mg of a residue that without purification was dissolved in anhydrous benzene (10 mL), DBU (0.2 mL) was added, and the solution was heated to reflux for 6 h. The reaction mixture was poured into ice-water (30 mL) and extracted with ethyl acetate (3x15 mL). The combined organic extracts were washed with diluted HCl until neutral pH, dried, and the solvent was evaporated to furnish a dark oil which was chromatographed (9:1 hexane-ethyl acetate) giving ester **16** (66 mg, 26% yield).

Physical and spectroscopic data for **16** follow: $[\alpha]_D$ +67.1 (c=1.40, $CHCl_3$); IR (film) 1707, 1630 cm^{-1}; MS, m/e 237 (M-15, 9), 194 (62), 166 (54), 163 (54), 162 (30), 135 (23), 134 (30), 92 (21), 79 (22), 77 (20), 73 (99), 72 (100), 43 (70), 42 (27); 400-MHz ^{1}H-NMR ($CDCl_3$) 1.10-1.27 (m, 4H), 1.30 (s, 3 H, CH_3), 1.40 (s, 3 H, CH_3), 1.67-1.81 (m, 2H), 3.18-3.22 (complex absorption, H_1 and H_4), 3.65 (dd, $J_{5b',5a'}$= 7.9 Hz, $J_{5b',4'}$= 7.3 Hz, $H_{5b'}$), 3.68 (s, 3 H, OCH_3), 4.25 (dd, $J_{5a',5b'}$= 7.9 Hz, $J_{5a',4'}$= 7.3 Hz, $H_{5a'}$), 5.35 (dd, $J_{4',5a'}$= $J_{4',5b'}$= 7.3 Hz, $H_{4'}$); 100-MHz ^{13}C NMR ($CDCl_3$) 25.20, 25.40, 25.48, 26.36, 43.95, 44.61, 47.47, 51.40, 69.29, 72.46, 110.36, 135.13, 161.63, 166.23 (CO_2CH_3). Anal. Calcd. for $C_{14}H_{20}O_4$: C, 66.73; H, 8.00. Found: C, 66.74; H, 8.00.

Methyl (1*S*,2*R*,3*S*,4*R*,5*S*,6*R*)-2,3-dihydroxy-6-[(4*S*)-4-(2,2-dimethyl-1,3-dioxolo)]bicyclo-[2.2.1]hept-5-ylcarboxylate, 12. Compound **6** (4.0 g, 15.9 mmol) in THF (5 mL) was added dropwise to a stirred and ice-cooled solution of *N*-methylmorpholine *N*-oxide (1.9 g, 16.3 mmol) and a crystal of osmium tetroxide in a 10:3:1 mixture of *t*-butanol-tetrahydrofuran-water (43 mL).The resultant mixture was stirred at room temperature for 24 h, filtered trough celite and the solvents were evaporated affording a viscous oil which was dissolved in ethyl acetate (20 mL) and washed with saturated aqueous ammonium chloride (3x5 mL). The solvent was removed and the residue was chromatographed (1:1 hexane-ethyl acetate) to afford 3.6 g of diol **12** (81% yield) as a solid; crystals, m.p. 117-119 °C (from ethyl acetate/pentane); $[\alpha]_D$ +23.9 (c=0.92, $CHCl_3$); IR (film) 3416 (OH), 3282 (OH), 1728 (C=O) cm^{-1}; MS, m/e 271 (M-15, 23), 179 (21), 97 (24), 72 (34), 43 (100); 400-MHz ^{1}H-NMR ($CDCl_3$) 1.19 (d, $J_{7b,7a}$= 10.9 Hz, H_{7b}), 1.30 (s, 3 H, CH_3), 1.40 (s, 3 H, CH_3), 1.95 (d, $J_{7a,7b}$= 10.9 Hz, H_{7a}), 2.09 (ddd, $J_{6,5}$=$J_{6,8}$= 11.6 Hz, $J_{6,1}$= 4.3 Hz, H_6), 2.38-2.45 (complex absorption, H_1 and H_4), 2.80 (dd, $J_{5,6}$=11.6 Hz, $J_{5,4}$=4.3 Hz, H_5), 3.21 (m, O*H*), 3.29 (m,O*H*), 3.49 (dd, $J_{5b',5a'}$= 8.5 Hz, $J_{5b',4'}$= 5.5 Hz, $H_{5b'}$), 3.60 (s, 3 H, OCH_3), 3.98 (dd, $J_{5a',5b'}$= 8.5 Hz, $J_{5a',4'}$= 6.1 Hz, $H_{5a'}$), 4.05 (m, H_2 or H_3); 4,27 (m, H_3 or H_2), 4.46 (m, $H_{4'}$); 100-MHz ^{13}C NMR (acetone-d_6) 25.37, 27.43, 33.20, 43.90, 45.26, 47.89, 48.88, 51.70, 69.17, 69.99, 70.33, 74.27, 108.78, 173.69 (CO_2CH_3). Anal. Calcd. for $C_{14}H_{22}O_6$: C, 58.80; H, 7.75. Found: C, 58.73; H, 7.76.

Methyl (1*S*,2*R*,6*S*,7*R*,8*S*,9*S*)-4,4-dimethyl-9-[(4*S*)-4-(2,2-dimethyl-1,3-dioxolo)]-3,5-dioxatricyclo[5.2.1.0^{2,6}]dec-8-ylcarboxylate, 13. A mixture of diol **12** (3.6 g, 12.7 mmol), HCl saturated methanol (0.5 mL), freshly distilled 2,2-dimethoxypropane (24 mL), and acetone (64 mL) was stirred at room temperature for 3 h, then neutralized with solid sodium bicarbonate, filtered, and the solvent was removed. The residue was chromatographed (2:1 hexane-ether) to afford compound **13** (3.7 g, 91% yield) as an oil, o.t. 160 °C (0.1Torr); $[\alpha]_D$ +13.8 (c=2.03, $CHCl_3$); IR (film) 1735 (C=O) cm^{-1}; MS, m/e 311 (M-15, 30), 253 (78), 193 (34), 151 (22), 79 (25), 72 (28), 43 (100); 400-MHz ^{1}H-NMR ($CDCl_3$) 1.10 (d,$J_{10b,10a}$= 10.4 Hz, H_{10b}), 1.24 (s, 3 H, CH_3), 1.27 (s, 3 H, CH_3), 1.36 (s, 3 H, CH_3), 1.40 (s, 3 H, CH_3), 1.84 (d,$J_{10a,10b}$= 10.4 Hz, H_{10a}), 2.16 (ddd, $J_{9,8}$=$J_{9,4'}$= 10.9 Hz, $J_{9,1}$= 4.8 Hz, H_9), 2.37-2.57 (complex absorption, H_1 and H_7), 2.83 (dd, $J_{8,9}$=10.9 Hz, $J_{8,7}$=4.3 Hz, H_8), 3.49 (dd, $J_{5b',5a'}$= 8.5 Hz, $J_{5b',4'}$= 4.8 Hz, $H_{5b'}$), 3.60 (s, 3 H, OCH_3), 3.98 (dd, $J_{5a',5b'}$= 8.5 Hz, $J_{5a',4'}$= 6.1 Hz, $H_{5a'}$), 4.37-4.42 (complex absorption, H_2 and H_6), 4.54 (m, $H_{4'}$); 100-MHz ^{13}C NMR ($CDCl_3$) 23.76, 24.66, 24.98, 26.83, 32.11, 42.20, 43.29, 43.47, 44.47, 51.28, 69.28, 72.89, 76.85, 77.29, 107.88, 108.24, 172.44 (CO_2CH_3). Anal. Calcd. for $C_{17}H_{26}O_6$: C, 62.63; H, 8.04. Found: C, 62.69; H, 8.12.

Methyl (1*S*,2*R*,6*S*,7*R*)-4,4-dimethyl-9-[(4*S*)-4-(2,2-dimethyl-1,3-dioxolo)]-3,5-dioxatricyclo[5.2.1.0^{2,6}]dec-8-en-8-ylcarboxylate, 20. Starting from **13** (2.0 g, 6.1 mmol) and following the procedure described above for the preparation of **15**, the epimeric mixture of selenides **19** (2.6 g, 87% yield) was obtained.

Oxidation of 2.0 g of this mixture with 30% hydrogen peroxide (3.5 mL) and drops of glacial acetic acid in THF (35 mL) at 0 °C for 1 h and further stirring for 20 min to reach room temperature followed by the standard work-up, afforded a crude that was chromatographed (4:1 hexane-ether) to give unsaturated ester **20** (1.1 g, 72% for the two steps). Oil, o.t. 155 °C (0.09 Torr); $[\alpha]_D$ +15.6 (c=1.12, $CHCl_3$); IR (film) 1714 (C=O), 1630 (C=C) cm^{-1}; MS, m/e 324 (M, 1), 309 (M-15, 2), 147 (21), 101 (25), 100 (100), 43 (23); 400-MHz ^{1}H-NMR ($CDCl_3$) 1.31 (s, 3 H, CH_3), 1.35 (s, 3 H, CH_3), 1.45 (s, 3 H, CH_3), 1.46 (s, 3 H, CH_3),

1.67 (d, $J_{10b,10a}$= 9.3 Hz, H_{10b}), 1.98 (d, $J_{10a,10b}$= 9.3 Hz, H_{10a}), 3.11-3.13 (complex absorption, H_1-H_7), 3.61 (dd, $J_{5b',5a'}$= $J_{5b',4'}$= 7.9 Hz, $H_{5b'}$), 3.69 (s, 3 H, OCH_3), 4.21 (dd, $J_{5a',5b'}$= $J_{5a',4'}$= 7.9 Hz, $H_{5a'}$), 4.33-4.39 (complex absorption, H_2-H_6), 5.35 (t, $J_{4',5a'}$=$J_{4',5b'}$= 6.7 Hz, $H_{4'}$); 100-MHz ^{13}C NMR ($CDCl_3$) 24.27, 25.21, 25.75, 26.12, 41.21, 47.27, 48.13, 51.35, 68.27, 71.39, 80.21, 80.22, 110.07, 113.59, 134.88, 160.72,164.35 (CO_2CH_3). Anal. Calcd. for $C_{17}H_{24}O_6$: C, 63.02; H, 7.47. Found: C, 62.90; H, 7.48.

Methyl (1*S*,2*R*,6*S*,7*R*)-4,4-dimethyl-9-[(1*S*)-1,2-dihydroxy]-3,5-dioxatricyclo[5.2.1.0^{2,6}]-dec-8-en-8-ylcarboxylate, 21. A solution containing acetonide **20** (1.2 g, 3.7 mmol) in 90% acetic acid (35 mL) was stirred at room temperature for 40 h. The reaction mixture was evaporated to dryness. The residue was dissolved in absolute ethanol (10 mL) and the solvent removed, repeting this process twice. Crude diol **21** was chromatographed (mixtures of hexane-ethyl acetate) to afford 175 mg of recovered **20** and pure **21** (898 mg, 85% yield) as an oil, o.t. 200 °C (0.2 Torr); $[\alpha]_D$ +11.3 (c=1.37, $CHCl_3$); IR (film) 3550-3078 (broad, OH), 1707 (C=O), 1630 (C=C) cm^{-1}; MS, m/e 284 (M, 1), 269 (M-15, 3), 195 (22), 163 (44), 135 (35), 100 (100), 85 (34), 43 (38); 400- MHz ^{1}H-NMR ($CDCl_3$) 1.25 (s, 3 H, CH_3), 1.40 (s, 3 H, CH_3), 1.74 (d, $J_{10b,10a}$= 9.5 Hz, H_{10b}), 1.96 (d, $J_{10a,10b}$= 9.5 Hz, H_{10a}), 3.00 (broad s, H_1 or H_7), 3.12 (broad s, H_7 or H_1), 3.54 (dd, $J_{2b',2a'}$= 10.9 Hz, $J_{2b',1}$= 6.7 Hz, $H_{2b'}$), 3.69 (dd, $J_{2a',2b'}$= 10.9 Hz, $J_{2a',1}$= 6.7 Hz, $H_{2a'}$), 3.70 (s, 3 H, OCH_3), 4.31-4.35 (complex absorption, H_2 and H_6), 4.82 (m, $H_{2'}$); 100-MHz ^{13}C NMR ($CDCl_3$) 24.26, 25.71, 25.71, 41.47, 47.37, 49.55, 51.82, 64.84, 70.40, 79.80, 80.05, 113.64, 133.84, 164.14, 165.50 (CO_2CH_3). Anal. Calcd. for $C_{14}H_{20}O_6$: C, 59.21; H, 7.10. Found: C, 59.17; H, 7.18.

Methyl (1*S*,2*R*,6*S*,7*R*)-4,4-dimethyl-9-formyl-3,5-dioxatricyclo[5.2.1.0^{2,6}]dec-8-en-8-yl carboxylate, 22. A suspension of sodium periodate (1.0 mg, 4.7 mmol) in THF (7 mL) and water (3 mL) was added dropwise to a stirred solution of diol **21** (920 mg, 3.2 mmol) in THF (15 mL). After additional stirring at room temperature for 30 min the produced solid was filtered out and successively washed with ether. The solvent was removed and the residue was extracted with dichloromethane. After evaporation, the reaction crude was chromatographed (2:1 hexane-ether) to afford aldehyde **22** as a viscous yellow oil (750 mg, 92% yield); o.t. 140 °C (0.3 Torr); $[\alpha]_D$ -12.6 (c=0.99, $CHCl_3$); IR (film) 1721 (C=O), 1672 (CHO), 1609 (C=C) cm^{-1}; MS, m/e 252 (M, 4), 237 (M-15, 17), 194 (72), 162 (40), 133 (100), 105 (63), 100 (87), 77 (61), 43 (54); 400-MHz ^{1}H-NMR ($CDCl_3$) 1.23 (s, 3 H, CH_3), 1.40 (s, 3 H, CH_3), 1.75 (d, $J_{10b,10a}$= 9.8 Hz, H_{10b}), 1.99 (d, $J_{10a,10b}$= 9.8 Hz, H_{10a}), 3.24 (broad s, H_1 or H_7), 3.32 (broad s, H_7 or H_1), 3.75 (s, 3 H, OCH_3), 4.13 (d, $J_{2,6}$= 5.3 Hz, H_2 or H_6), 4.27 (d, $J_{6,2}$= 5.3 Hz, H_6 or H_2), 10.2 (s, CHO); 100-MHz ^{13}C NMR ($CDCl_3$) 24.23, 25.65, 41.09, 45.47, 49.10, 52.27, 79.47, 79.79, 114.26, 149.32, 153.66, 163.06 (CO_2CH_3), 187.94 (CHO). Anal. Calcd. for $C_{13}H_{16}O_5$: C, 61.96; H, 6.40. Found: C, 61.78; H, 6.45.

Methyl (1*S*,2*R*,6*S*,7*R*)-9-carboxyl-4,4-dimethyl-3,5-dioxatricyclo[5.2.1.0^{2,6}]dec-8-en-8-yl carboxylate, (+)-1. A solution containing sodium chlorite (2.4 g, 26.5 mmol) and sodium dihydrogenphosphate (2.5 g, 20.8 mmol) in water (10 mL) was added dropwise to a stirred solution containing aldehyde **22** (750 mg, 3 mmol) and 2-methyl-2-butene (14.3 mL, 135 mmol) in *t*-butanol (50 mL). The mixture was stirred at room temperature for 18 h and the solvents and volatile components were evaporated. The residue was poured into water (10 mL) and washed with hexane. The aqueous phase was acidified with 10% HCl and then extracted with dichloromethane. These combined organic extracts were, in turn, extracted with saturated aqueous sodium carbonate. Subsequently, the combined basic aqueous phases were acidified

with HCl and then extracted with dichloromethane. After evaporation of the solvent, hemiester (+)-**1** was obtained as a solid (673 mg, 84% yield); crystals, m.p. 115-117 °C (from ethyl acetate-pentane); $[\alpha]_D$ +28.6 (c=1.10, $CHCl_3$); IR (KBr) 3550-3444 (broad, OH), 1728 (C=O), 1644 (C=O), 1602 (C=C) cm^{-1}; MS, m/e 268 (M, 1), 253 (M-15, 13), 210 (51), 163 (39), 151 (44), 149 (52), 105 (39), 100 (100), 59 (25), 43 (35); 250-MHz ^{1}H-NMR ($CDCl_3$) 1.31 (s, 3 H, C*H*$_3$), 1.46 (s, 3 H, C*H*$_3$), 1.85 (d, $J_{10b,10a}$= 10.2 Hz, H_{10b}), 2.02 (d, $J_{10a,10b}$= 10.2 Hz, H_{10a}), 3.33 (broad s, H_1 or H_7), 3.48 (broad s, H_7 or H_1), 3.90 (s, 3 H, OC*H*$_3$), 4.35 (broad s, H_2 and H_6); 62.5-MHz ^{13}C NMR ($CDCl_3$) 24.31, 25.71, 41.08, 49.27, 50.30, 53.90, 79.37, 79.55, 114.62, 142.85, 153.19, 161.56, 167.40. Anal. Calcd. for $C_{13}H_{16}O_6$: C, 58.26; H, 6.02. Found: C, 58.23; H, 6.06.

(1*R*,5*S*,7*S*,8*S*,9*R*)-5-Hydroxymethyl-8,9-isopropilydenedioxy-4-oxatricyclo[5.2.1.0^{2,6}]dec-en-3-one, 9. Unsaturated lactone **9** was synthesized from saturated **23**,[10] in 40% overall yield, following a similar procedure than that described above for esters **16** and **20**. Crystals, m.p. 138-140 °C (from ethyl acetate-pentane); $[\alpha]_D$ -37.5 (c=0.95, $CHCl_3$); IR (KBr) 3600-3100 (broad, OH), 1745, 1720 (C=O), 1626 (C=C) cm^{-1}; MS, m/e 237 (M-15, 9), 147 (33), 119 (72), 100 (100), 91(33), 85 (27), 82 (42), 77 (38), 43 (46); 250-MHz ^{1}H-NMR (acetone-d_6) 1.27 (s, 3 H, C*H*$_3$), 1.40 (s, 3 H, C*H*$_3$), 2.15 (ddddd, $J_{10b,10a}$= 9.5 Hz, $J_{10b,1}$= $J_{10b,7}$= $J_{10b,8}$= $J_{10b,9}$= 1.5 Hz, H_{10b}), 2.33 (ddd, $J_{10a,10b}$= 9.5 Hz, $J_{10a,1}$= $J_{10a,7}$= 1.5 Hz, H_{10a}), 2.99 (broad s, H_7), 3.18 (broad s, H_1), 3.77-3.91 (complex absorption, 2 H, H_{11a} and H_{11b}), 4.22 (dd, J= J'= 5.4 Hz, O*H*), 4.32 (dd, $J_{9,8}$= 5.5 Hz, H_9), 4.46 (d, $J_{8,9}$= 5.5 Hz, H_8), 5.04 (t, $J_{5,11a}$= $J_{5,11b}$= 4.4 Hz, H_5) ; 62.5-MHz ^{13}C NMR (acetone-d_6) 24.46, 26.14, 43.07, 46.80, 47.09, 62.19, 80.98, 81.54, 82.39, 115.32, 142.25, 168.18, 180.72 (*C*=O). Anal. Calcd. for $C_{13}H_{16}O_5$: C, 61.90; H, 6.39. Found: C, 61.96; H, 6.38.

(1*S*,2*S*,3*R*,4*R*)-3-[(4*S*)-4-(2,2-dimethyl-1,3-dioxolo)]-bicyclo[2.2.1]hept-5-en-2-ylcarboxylic acid, 24. Adduct **6** was dissolved in a 5% NaOH solution (670 µL, 0.837 mmol) and the mixture was stirred at room temperature for 20 h. The solution was acidified (pH = 4-5) with a saturated solution of NH_4Cl and extracted with Et_2O (6x10 mL). After drying with Na_2SO_4, the solvent was removed and the residue was chromatographed (1:2 ethyl acetate-hexane) to afford acid **24** (60 mg, 82 % yield) as a solid m.p. 44-46°C (from ethyl acetate-pentane); $[\alpha]_D$ +22.1 (c=1.00, $CHCl_3$); IR (KBr) 3300-2400 (broad, -OH), 1699 (CO), 1601 (C=C) cm^{-1}; MS, m/e 223 (M-15, 17), 117 (14), 115 (20), 97 (65), 72 (17), 66 (C_5H_6, 100), 65 (24), 43 ($C_3H_6^+$, 59); 250-MHz ^{1}H-RMN ($CDCl_3$) 1.23 (s, 3 H, C*H*$_3$), 1.30 (d, $J_{7b,7a}$= 10.0 Hz, H_{7b}), 1.42 (s, 3H, C*H*$_3$), 1.47 (ddd, $J_{7a,7b}$= 10.0 Hz, $J_{7a,1}$= $J_{7a,4}$= 1.9 Hz, H_{7a}), 2.50 (ddd, $J_{3,2}$= $J_{3,4'}$= 10.4 Hz, $J_{3,4}$= 3.1 Hz, H_3), 3.03 (dd, $J_{2,3}$= 10.4 Hz, $J_{2,1}$= 3.2 Hz, H_2), 3.13 (broad s, 2 H, H_1 and H_4), 3.66 (dd, $J_{5a',5b'}$= 8.3 Hz, $J_{5a',4}$= 4.9 Hz, $H_{5a'}$), 3.83 (m, $H_{4'}$), 3.99 (dd, $J_{5b',5a'}$= 8.3 Hz, $J_{5b',4}$= 6.0 Hz, $H_{5b'}$), 6.22 (dd, J= 5.7 Hz, J'= 2.9 Hz, H_5 or H_6), 6.27 (dd, J= 5.7 Hz, J'= 2.9 Hz) ; 62.5 MHz ^{13}C-RMN ($CDCl_3$) 25.10, 27.18, 45.92, 46.15, 47.06, 48.53, 49.24, 69.41, 77.06, 108.20, 135.49, 135.69, 178.63 (*C*=O). Anal. Calcd. for $C_{13}H_{18}O_4$: C, 65.53; H, 7.61. Found: C, 65.66; H, 7.68.

(1*S*, 2*R*, 3*S*, 4*R*, 5*R*, 6*R*)-3-[(4*S*)-4-(2,2-dimethyl-1,3-dioxolo)]-6-hydroxy-5-iodobicyclo [2.2.1]heptan-2-ylcarboxylic acid lactone, 25. A mixture of acid **24** (23 mg), 5% aqueous $NaHCO_3$ (0.2 mL), I_2 (49 mg), and NaI (145 mg) was stirred at room temperature for 10 h. The aqueous emulsion was decolourized with a 5% aqueous $Na_2S_2O_5$ and extracted with Et_2O (4x5 mL), the combined extracts were dried

on Na_2SO_4 and concentrated to give 31 mg (91 % yield) of iodolactone **24** prior to recrystallization from ethyl acetate-hexane. Crystals, m.p. 132-142°C (decomposed) (from ethyl acetate-hexane); $[\alpha]_D$ -48.9 (c=1.11, $CHCl_3$); IR (KBr) 1765 (C=O) cm^{-1}; MS, m/e 348 (M-15, 36), 118 (26), 117 (28), 91 (23), 43 ($C_3H_6^+$, 100), 41 (21) ; 250-MHz ^{1}H-NMR ($CDCl_3$) 1.31 (s, 3 H, CH_3), 1.39 (s, 3 H, CH_3), 1.84 (d, $J_{7b,7a}$= 11.7 Hz, H_{7b}), 2.22 (ddd, $J_{3,4}$= 11.0 Hz, $J_{3,2}$= 10.7 Hz, $J_{3,4}$= 3.3 Hz, H_3), 2.42 (ddd, $J_{7a,7b}$= 11.7 Hz, $J_{7a,1}$= $J_{7a,4}$= 1.5 Hz, H_{7a}), 2.51 (dd, $J_{2,3}$= 10.7 Hz, $J_{2,1}$= 4.9 Hz, H_2), 2.88 (broad s, H_4), 3.23 (dddd, $J_{1,2}$= $J_{1,6}$= 4.9 Hz, $J_{1,7a}$= $J_{1,7b}$= 1.5 Hz, H_1), 3.68 (dd, $J_{5a',5b'}$= 8.6 Hz. $J_{5a',4}$= 5.3 Hz, $H_{5a'}$), 3.99 (m, $H_{4'}$), 4.17 (dd, $J_{5b',5a'}$= 8.6 Hz, $J_{5b',4}$=6.0 Hz, $H_{5b'}$), 4.24 (d, $J_{5,6}$= 2.5 Hz, H_5), 5.16 (d, $J_{6,1}$= 4.9 Hz, H_6) ; 62.5-MHz ^{13}C NMR ($CDCl_3$) 25.07, 25.39, 27.00, 37.61, 39.45, 47.91, 49.01, 49.04, 68.17, 73.30, 89.33, 109.47, 177.43 (*C*=O). Anal. Calc. for $C_{13}H_{17}O_4I$: C, 42.88; H, 4.71. Found: C, 43.02; H, 4.69.

(1*S*,2*R*,3*R*,4*R*,6*S*)-3-[4(*S*)-4-(2,2-dimethyl-1,3-dioxolo)]-6-hydroxybicyclo[2.2.1]heptane-2-carboxylic acid lactone, 10. A solution of Bu_3SnH (105 µL, 0.390 mmol) in absolute ethanol (2 mL) was added dropwise to a solution of iodolactone **25** (70 mg, 0.192 mmol) in absolute ethanol (6 mL) at 10 °C under argon. The mixture was stirred a room temperature for 1 h. Ethanol was removed, the residue was poured into chloroform and washed with saturated aqueous $NaHCO_3$. The combined organic extracts were dried with Na_2SO_4 and concetrated. The residual oil was chromatographed (1:3 ethyl acetate-hexane) giving lactone **10** (30 mg, 66 % yield). Crystals, m.p. 77-78 °C (from ethyl acetate-hexane). $[\alpha]_D$ +41.9 (c=0.96, $CHCl_3$); IR (KBr) 1764 (C=O) cm^{-1}; MS, m/e 222 (M-15, 98), 181 (31), 119 (57), 101 (27), 91 (59), 79 (21), 72 (40), 43 ($C_3H_6^+$, 100), 41 ; 250-MHz ^{1}H-NMR ($CDCl_3$) 1.31 (s, 3 H, CH_3), 1.40 (s, 3 H, CH_3), 1.62-1.74 (complex absorption, 3H, H_{7a}, H_{7b}, H_{5exo}), 1.87 (dd, $J_{5endo,5exo}$= 14.6 Hz, $J_{5endo,4}$= 1.8 Hz), 2.15 (dddd, $J_{3,2}$=$J_{3,4'}$= 10.8 Hz, $J_{3,4}$= 3.1 Hz, $J_{3,5exo}$= 1.8 Hz, H_3), 2.47 (dd, $J_{2,3}$= 10.8 Hz, $J_{2,1}$= 4.9 Hz, H_2), 2.57 (broad s, H_4), 3.22 (dddd, $J_{1,2}$= $J_{1,6}$= 4.9 Hz, $J_{1,7a}$= $J_{1,7b}$= 1.5 Hz, H_1), 3.71 (dd, $J_{5a',5b'}$= 8.5 Hz, $J_{5a',4}$= 4.5 Hz, $H_{5a'}$), 4.02 (m, $H_{4'}$), 4.17 (dd, $J_{5b',5a'}$= 8.5 Hz, $J_{5b',4}$= 6.0 Hz, $H_{5b'}$), 4.78 (d, $J_{6,5exo}$= 7.7 Hz, $J_{6,1}$= 4.9 Hz, H_6) ; 62.5-MHz ^{13}C NMR ($CDCl_3$) 25.13, 27.01, 32.54, 37.66, 38.73, 41.05, 47.76, 48.35, 68.46, 74.20, 81.08, 109.02, 179.17 (*C*=O). Anal. Calc. for $C_{13}H_{18}O_4$: C, 65.79; H, 7.23. Found: C, 65.77, H, 7.37.

Methyl (1*S*,2*S*,3*R*,4*R*,5*S*,6*R*)-3-[(4*S*)-4-(2,2-dimethyl-1,3-dioxolo)]-5,6-epoxybicyclo-[2.2.1]heptane-2-ylcarboxylate, 11. Iodolactone **25** (79 mg, 0.217 mmol) was added to a solution of 10% KOH in aqueous DMF (5 mL). After stirring for 20 h, the solvent was evaporated. The residue obtained was diluted in 5 mL of water, acidified (pH=5) with aqueous HCl (5%) and extracted with Et_2O (4x10 mL). After drying with Na_2SO_4, the organic solution was treated with an ethereal solution of diazomethane until completion (monitoring by TLC). The solvent was eliminated and the residue was chromatographed (2:1 ethyl acetate-hexane) obtaining *endo*-epoxy **11** (41 mg, 71% yield). Crystals, m.p. 69-71 °C (from ethyl acetate-hexane). $[\alpha]_D$ -6.0 (c=1.00, $CHCl_3$); IR (KBr) 3054 (oxirane H-C), 1728 (C=O), 1268 (C-O) cm^{-1}; MS, m/e 149 (16), 95 (18), 81 (50), 69 (100), 60 (28), 55 (34), 43 (44), 41 (59); 250-MHz ^{1}H-NMR ($CDCl_3$) 1.29 (s, 3 H, CH_3), 1.40 (s, 3H, CH_3), 1.61 (d, $J_{7b,7a}$= 9.9 Hz, H_{7b}), 2.04 (ddd, $J_{7a,7b}$= 9.9 Hz, $J_{7a,1}$= $J_{7a,4}$= 2.1 Hz, H_{7a}), 2.14 (ddd, $J_{3,2}$= $J_{3,4'}$= 10.7 Hz, $J_{3,4}$= 3.7 Hz, H_3), 2.55 (broad s, H_4), 2.70-2.76 (complex absorption, 2 H, H_1 and H_2), 3.62 (broad s, 3 H, OCH_3), 3.69 (dd, $J_{5,6}$= $J_{5,4}$= 3.7 Hz, H_5), 3.74 (dd, $J_{6,5}$= $J_{6,1}$= 3.7 Hz, H_6), 3.85 (dd, $J_{5a',5b'}$= 9.0 Hz, $J_{5a',4}$= 3.6 Hz, $H_{5a'}$), 4.27 (dd, $J_{5b',5a'}$= 9.0 Hz, $J_{5b',4}$= 6.2 Hz, $H_{5b'}$), 4.69 (ddd, $J_{4',3}$= 10.7 Hz, $J_{4,5b'}$= 6.2 Hz, $J_{4,5a'}$= 3.6 Hz, $H_{4'}$) ; 62.5-MHz ^{13}C NMR ($CDCl_3$)

24.73, 27.38, 39.89, 42.32, 44.52, 48.32, 48.38, 51.36, 61.84, 62.38, 70.96, 74.71, 108.06, 172.58 (*C*=O). Anal. Calc. for $C_{14}H_{20}O_5$: C, 62.67; H, 7.51. Found: C, 62.89, H, 7.55.

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