Pergamon

Tetrahedron Vol. 51, No. 43, pp. 11841-11854, 1995

0040-4020/95 \$9.50+0.00

0040-4020(95)00745-8

Enantioselective Synthesis of Chiral Polyfunctional Cyclopentane Derivatives: Epoxy Esters, Hydroxy Esters, and Hydroxy Amino Esters

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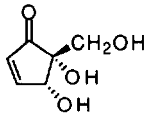
Abstract. *Enantiomeric epoxides have been synthetized in efficient and diastereoselective manner through the respective cycloadditions of diazomethane to the carbonyl group of antipodal cyclopentyl ketones. These epoxy derivatives are potent synthetic building blocks which have been used as versatile precursors to several enantiopure title compounds, these being molecules with a high functional density that bear, at least, four stereogenic centers in the cyclopentane ring and a quaternary stereocenter in the side-chain.*

INTRODUCTION

Structures containing a cyclopentane moiety bearing several chemical functions attached to stereogenic centers are widespread and often correspond to compounds displaying interesting biological properties, such as the following examples. The cyclopentenoid sarkomycin **1**,[1] is an important and well known antibiotic. The glycoprotein processing enzime inhibitor (+)-mannostatin A **2**, which inhibits Golgi processing mannosidase II of both plant and animal origins,[2] was recently isolated from the microorganism



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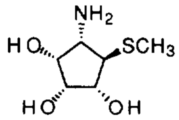

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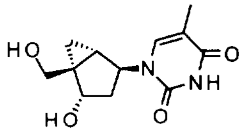

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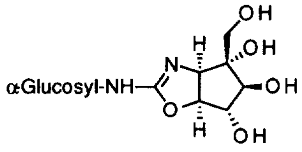

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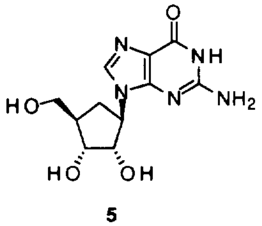

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Streptoverticillium verticillus var. *quintum* ME3-AG3.[3] (-)-Aristeromycin **5** is an antineoplasic antibiotic produced by *Streptomyces citricolor*[4] and is one of the most representative members belonging to the so-called carbocyclic nucleoside family, as also do the conformationally constrained thymidine analog **3**.[5]. As a last instance, trehazolin **4**, obtained from the culture broth of *Micromonospora* sp. SANK 62390,[6] is a potent inhibitor of trehalase which is a relevant enzime in control of insects and certain fungi.

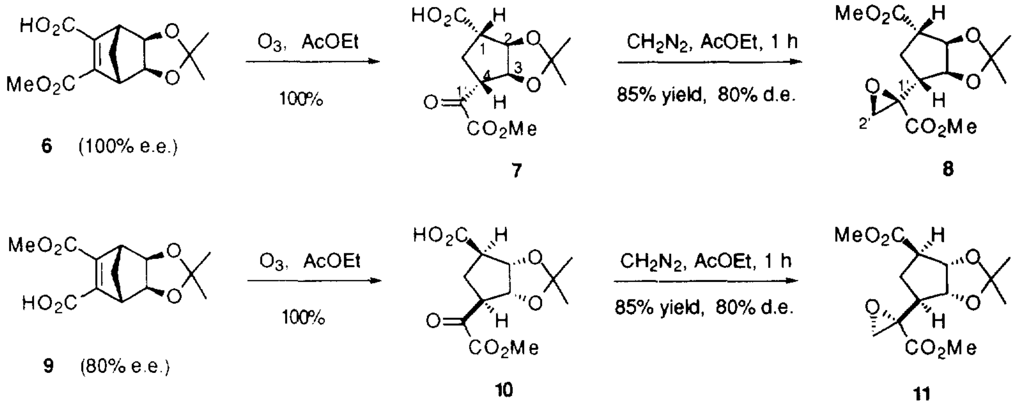
In a previous communication we reported the stereoselective synthesis of epoxide **8**[7] in two steps from enantiopure half-ester **6**[8] (Scheme 1). Absolute configuration of the stereogenic center at the oxirane ring was unequivocally established by X-ray structural analysis.[7] This epoxide is susceptible to react with several nucleophiles leading to the enantio and diastereocontrolled synthesis of a variety of cyclopentanoid derivatives. Since half-ester **9** is also available through the Ohno's strategy,[9] the obtention of both enantiomeric series becomes feasible.

In this article we describe the syntheses of the antipodal epoxides **8** and **11** and of enantiopure cyclopentyl hydroxy ester and hydroxy amino acid derivatives which result from oxirane-ring opening. Factors influencing the remarkable stereoselectivity in the formation of such epoxides are considered.

RESULTS AND DISCUSSION

1. Synthesis of compounds 8 and 11 and other related epoxides

Half-ester **6** was previously synthetized in our laboratory from D-mannitol as a chiral precursor, the key steps involving a stereoselective Diels-Alder cycloaddition followed by stereospecific dihydroxylation of the major adduct.[8] Ozonolysis of the double bond and concomitant reductive decarboxylation,[9] performed in ethyl acetate at -78 °C, led quantitatively to the keto half-ester **7** which was isolated and characterized (Scheme 1). Subsequent reaction of **7** with excess diazomethane in ethyl acetate at room temperature for 1 hour afforded epoxide **8** in 85% yield and 80% d.e. The minor diastereoisomer could be detected (GC, NMR) when working on a gramme or multigramme scale. Diastereomerically pure compound **8** is a solid, m.p. 72-74 °C, $[\alpha]_D$ +1.3, that could be purified by flash chromatography, and results from both methylation of the carboxy group and addition to the ketone in **7**.

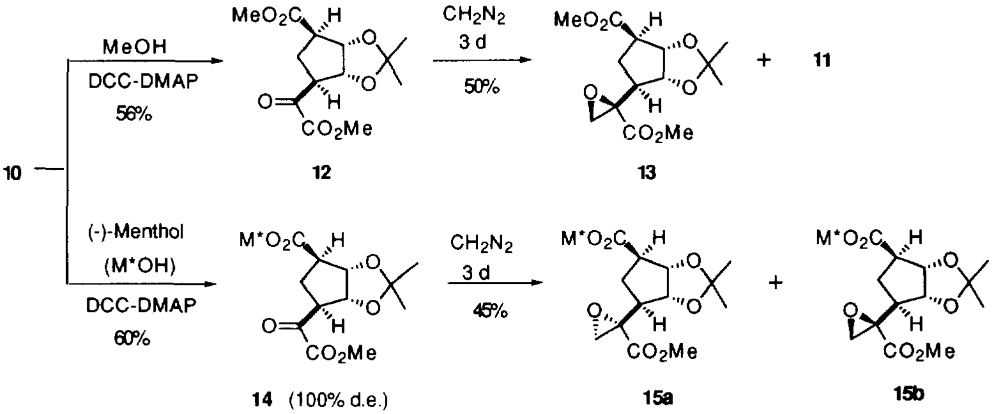


Scheme 1

On the other hand, according to Ohno's protocol,[9] the Diels-Alder adduct of dimethyl acetylenedicarboxylate and cyclopentadiene was diastereospecifically dihydroxylated and the produced *vic*-diol was protected as an acetonide. Subsequently, enantioselective hydrolysis by using pig liver esterase afforded the half-ester **9** in 80% e.e and on multigramme scale. Then, similarly to described above, epoxide **11** was prepared from **9**, by ozonolysis and subsequent reaction of the resulting keto ester **10** with diazomethane.

As mentioned before, two chemical transformations are involved in the respective formations of the epoxyesters **8** and **11**: methyl ester formation and addition of diazomethane to produce the oxirane ring. The sequential order in which these reactions occur could be important for the outcome.

In order to investigate the process, the dimethyl diester **12** was synthetized from **10** by reaction with methanol in the presence of DCC-DMAP (Scheme 2). Classical esterification conditions, involving the use of a strong mineral acid, were avoided in order to prevent a possible enolization that could allow the epimerization of any stereogenic center. Treatment of diester **12** with excess diazomethane for 5 days afforded a 1:1 diastereoisomeric mixture of epoxides **11** and **13** (80% e.e. each) in only 50% yield, along with starting material. This result clearly contrasts with that from reaction between keto-acid **10** and diazomethane, which was fast and stereoselective.



Scheme 2

The two diastereoisomers **11** and **13** could be easily differentiated by ^1H NMR, since oxirane methylene protons in **11** gave two doublets centered at 2.93 and 3.02 ppm with $J = 5.5$ Hz, while related protons in **13** absorbed at 2.59 and 2.75 ppm as doublets, $J = 5.9$ Hz.

In order to produce enantiopure epoxy derivatives from half-ester **10** the menthyl ester **14** was prepared in 100% d.e. (after removing the minor diastereoisomer) and 60% chemical yield (Scheme 2). Reaction between **14** and excess diazomethane afforded a 1:1 mixture of diastereoisomers **15** and **16** in 45% yield in a similar manner to that described above for dimethyl diester **12**.

These results suggest that epoxidation of the keto-half-esters **7** and **10** is assisted by the carboxy group, thus accounting for the enhanced reactivity and stereospecifity of these systems with respect to keto-diesters **12** and **14**. A simple explanation could be given assuming a conformational bias for half-esters **7** and **10**, in such a way that stereoelectronic factors would determine a preferred conformation in which one of the diastereotopic carbonyl faces should be more accessible to the attack of diazomethane, leading diastereoselectively to epoxide **8** from **7**, or **11** from **10**. This kind of conformation would not exist for diesters **12** and **14**.

To verify the feasibility of this hypothesis, conformational energy profiles corresponding to consider the rotation around the $C_{1'}$-C_4 bond in half-esters **7** (or **10**) and diester **12** were calculated by the AM1 method.[10] The energy has been computed for several values of the $OC_{1'}C_4C_1$ dihedral angle, in the range between 0 and 360 degrees, and the molecular geometry has been optimized with respect to the remaining degrees of freedom. Absolute energy minima correspond to dihedral angles of 14 degrees for **7** and 30 degrees for **12**. These structures are represented in Fig. 1.

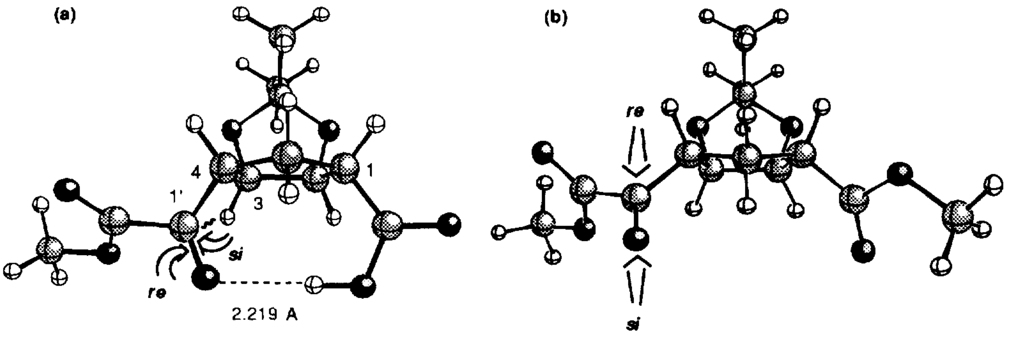
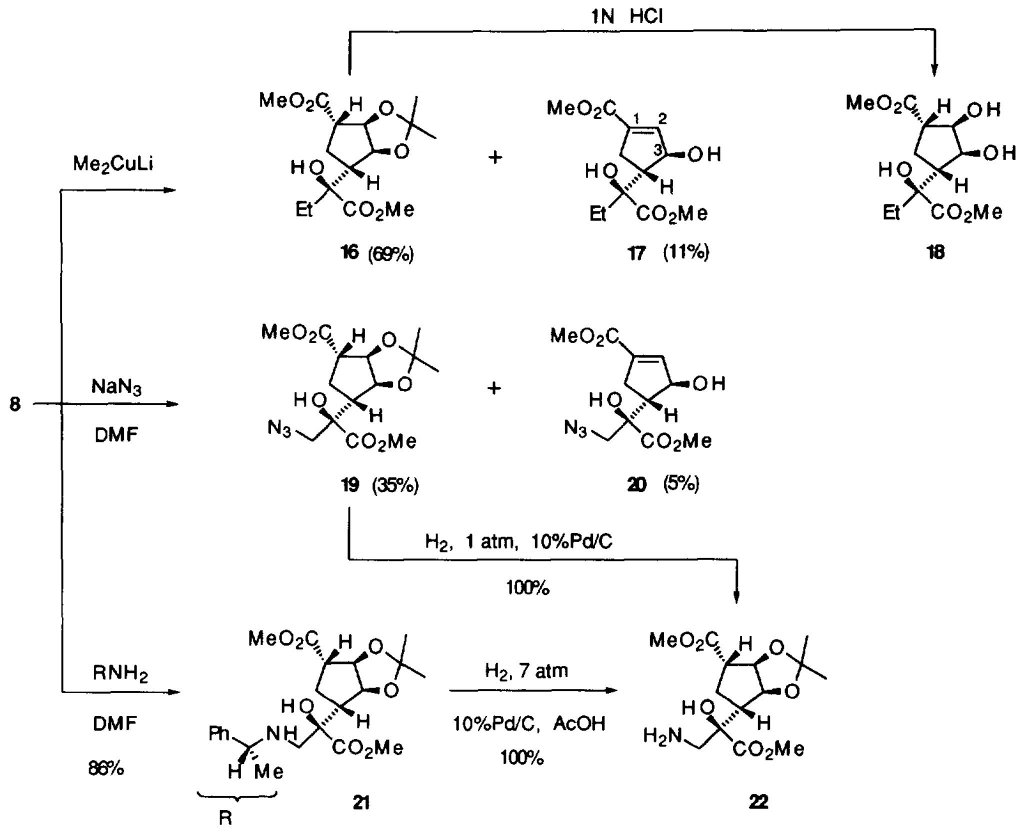


Figure 1. AM1 Calculated most stable conformations for : (a) Half-ester 7. (b) Diester 9.

In the case of half-ester **7**, Fig 1 (a) shows the conformation corresponding to the energy minimum in which the ketone oxygen and the proton of the carboxyl group are disposed at a distance of 2.219 A thus allowing a favourable interaction between both groups.[11] In such a conformation the preferential attack of diazomethane must take place on the *re* -face, whereas the attack to the opposite *si*-face is hindered by the close hydrogen atom attached to C_3. The most stable extended conformation for the corresponding dimethyl ester is represented in Fig 1 (b). In this case, the absence of a hydrogen bond allows a disposition of the carbonyl group in such a way that the attack to both faces is equally favoured. Therefore, the presence of a hydrogen bond could direct the attack of diazomethane to the activated carbonyl group, thus explaining the observed diastereoselectivity in the reactions of half-esters **7** and **10**, contrary to the reactions of the diesters **12** and **14**, and justifying the different reactivity of these substrates.

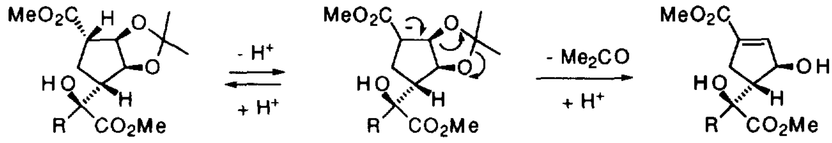
2. Reactions of epoxides 8 and 11 with Me_2CuLi and nitrogen-nucleophiles: synthesis of hydroxy diesters and hydroxy amino diesters.

Reaction of **8** with nucleophiles was first explored by using lithium dimethyl cuprate at -15 °C for 1 h to give hydroxy diester **16** in 69% yield, accompanied by unsaturated **17** (11% yield) (Scheme 3).



Scheme 3

This latter compound results from base-promoted β-elimination (Scheme 4). This hypothesis was verified when **17** was produced by treatment of **8** with DBU or, more efficiently, with LDA.

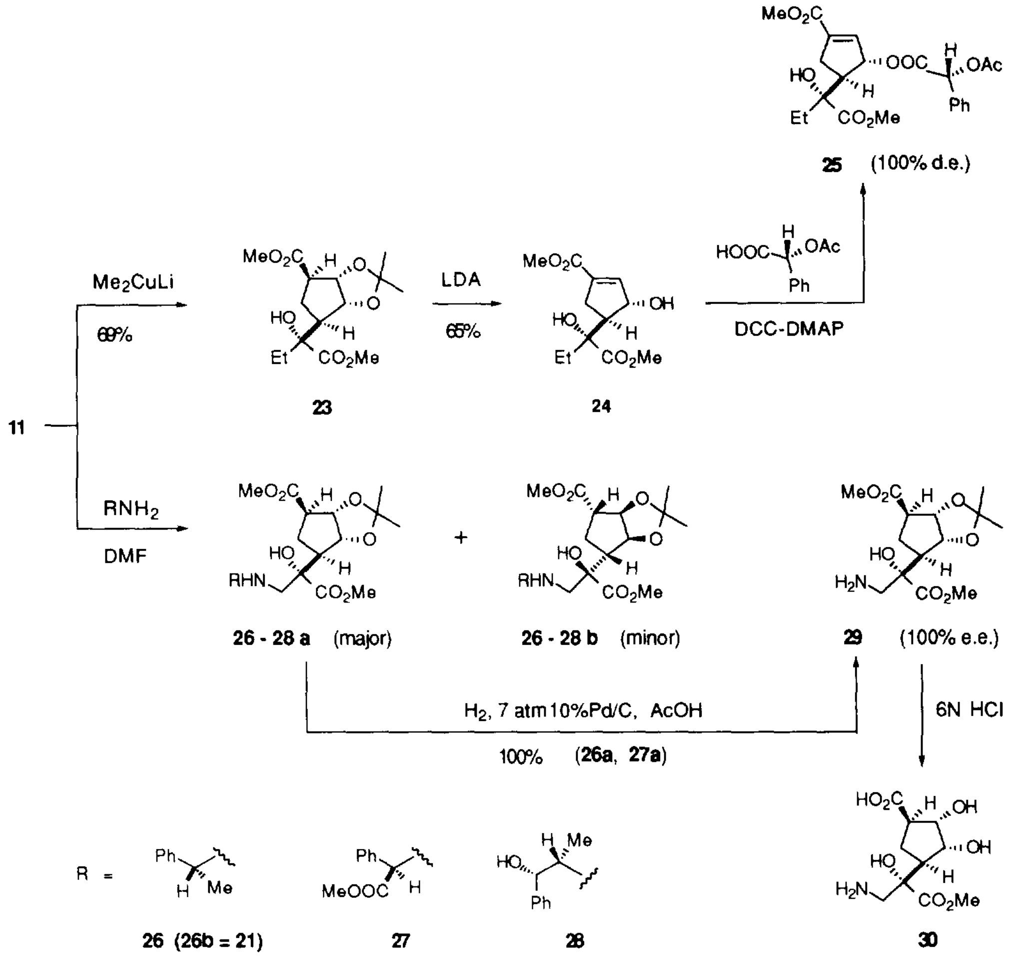


Scheme 4

Treatment of **16** with 1N HCl afforded triol **18** but **17** was not detected in these conditions, this result showing that formation of **17** is not acid-promoted (Scheme 3). Related elimination processes had previously been observed in lactonic carbohydrate derivatives and allowed the obtention of different interesting products.[12]

Epoxide **8** reacted slowly with sodium azide in anhydrous DMF at room temperature for 4 days to afford a mixture of **19** (35% yield) and **20** (5% yield). This last product was not detected when the reaction was carried out in aqueous DMF to provide **19** in 30% yield as the only defined product, as an oil $[\alpha]_D$ +46.2. Starting epoxide was not recovered in any case. Azide **19** was converted into the amino alcohol **22** by catalytic hydrogenation (10% Pd/C) at atmospheric pressure. Compound **22** is a solid, m.p. 122-124 °C, $[\alpha]_D$ +22.2, that was also prepared in higher overall yield through an alternative route. Thus, reaction between **8** and (+)-(*R*)-α-methylbenzylamine in DMF at 20 °C for 2 days furnished diastereoselectively **21** (86% yield) which, in turn, afforded quantitatively hydroxy amino diester **22** by catalytic hydrogenation (10% Pd/C) in acetic acid under 7 atmospheres pressure.

Diastereo- and enantiopure derivatives were also synthesized from epoxide **11** in the following way (Scheme 5). Reaction of **11** with lithium dimethylcuprate gave alcohol **23** in 70% yield and 80% e.e.



Scheme 5

Attempts to obtain the enantiomerically pure alcohol by using a chiral auxiliary failed since treatment with (*R*)-acetyl mandelic acid or camphor sulfonyl chloride in different reaction conditions was fruitless due to the lack of reactivity of the tertiary hydroxyl group. The allylic secondary alcohol **24** was obtained in 65% yield, along with 11% unreacted starting material, by treatment of **23** with LDA at 0 °C for 4 h. Preparation of an enantiomerically pure derivative was achieved in this case by reaction between **24** and (*R*)-*O*-acetyl mandelic acid in the presence of DCC and DMAP to yield, after purification, tetra-ester **25** as a single diastereoisomer which was fully charaterized as a solid of m.p. 90 °C (dec), $[\alpha]_D$ +50.4.

Optically pure products resulted from the reaction of **11** with several chiral amines leading to the creation of a β-amino-α-hydroxyester function in the side-chain. Thus, the diastereoisomeric mixtures of **26a** (major) and **26b**, and of **27a** (major) and **27b** were obtained in 86 and 70% yield, respectively, by reaction with (*R*)-(+)-α-methylbenzylamine in the former case and with methyl (-)-phenylglycine in the latter. Diastereoisomers **a** and **b** could be isolated in each case by flash column chromatography and fully characterized. Both compounds **26a** and **27a** were hydrogenated in catalytic conditions yielding quantitatively amine **29**, as a solid of m.p. 121-123 °C, $[\alpha]_D$ -22.1, which is the enantiomer of amine **22** (Scheme 3). Moreover, epoxide **11** was reacted with (1*R*,2*S*)-(-)-norephedrine in DMF to afford highly functionalized **28a** in 60% yield.

Furthermore, hydrolysis of **29** by using 6N HCl at room temperature for 16 hours afforded regioselectively half-ester **30**. Its structure was determined on the basis of NMR data, mainly from the HMBC (Heteronuclear Multiple Bond Connectivities) spectrum. Thus, the carboxyl carbon, at 178.4 ppm, correlates with H_1 (see Scheme 1 for numbering), at 2.5 ppm, while the methylene protons $H_{2'}$ (3.15 and 3.22 ppm) correlate with the ester-carbonyl carbon and with the methoxy-group carbon (174.0 and 54.3 ppm, respectively).

CONCLUSIONS

Efficient methods to prepare antipodal epoxides **8** and **11** have been accomplished. These products are versatile intermediates in the production of powerful chiral synthetic building blocks densely functionalized. For instance, compound **28a** contains seven asymmetric carbons, whose absolute and relative configuration is unambigously determined, as well as two ester, three alcohol and one amino groups.

These type of structures can be useful in the synthesis of *C*-glycosides and branched carbasugars bearing additional functionalities. On the other hand, amino acids or amino esters such as **29** and **30** are suitable to be incorporated into conformationally restricted peptidomimetics.

In conclusion, these products show promising structural features for the synthesis of molecules with biological properties. Active investigation in this field is carried out in our laboratory.

EXPERIMENTAL SECTION

All calculations have been done using the AM1 method[10] implemented in the AMPAC program.[13] 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*S*, 2*R*, 3*S*, 4*R*)-(-)-2,3-Isopropylidenedioxy-4-(1'-methoxycarbonyl-1'-oxomethyl)cyclopentane-1-carboxylic acid, 7. To a solution of **6**[8] (200 mg, 0.7 mmol) in ethyl acetate (20 mL) was bubbled through ozone at -78 °C for 10 minutes and then argon for 20 minutes allowing the mixture to reach r.t. The solvent was removed at reduced pressure to afford quantitatively compound **7** as a colorless oil (200 mg), $[\alpha]_D$ -12.5° (c= 1.6, $CHCl_3$); IR (film) 3700-3000 (broad), 1824, 1736 cm^{-1}; MS m/z 257 (M-15, 18), 97 (25), 86 (78), 84 (100), 71 (27); 250-MHz ^1H-NMR ($CDCl_3$) 1.28 (s, 3 H), 1.45 (s, 3 H), 2.29 (ddd, J = 10.8 Hz, J' =J'' = 5.3 Hz, 1 H), 2.47 (ddd, J = 16.1 Hz, J' = J'' = 8.0 Hz, 1 H), 2.98 (ddd, J = 7.6 Hz, J' = 5.3Hz, J'' = 2.4 Hz, 1 H), 3.64 (ddd, J = 7.8 Hz, J' = 5.3 Hz, J'' = 2.6 Hz, 1 H), 3.85 (s, 3 H), 4.87 (dd, J = 6.0 Hz, J' = 2.2 Hz, 1 H), 4.92 (dd, J = 6.0 Hz, J' = 2.2 Hz, 1 H), 9.25 (broad, 1 H); 62.5-MHz ^{13}C-NMR ($CDCl_3$) 192.8, 177.6, 160.6, 111.8, 82.6, 80.8, 53.7, 53.0, 49.6, 29.2, 26.6, 24.3. HRMS (EI) m/z: Calcd. for $C_{12}H_{16}O_7$: 257.066128 (M-15). Found: 257.068786.

(1*S*, 2*R*, 3*S*, 4*R*, 1'*R*)-(+)-2,3-Isopropylidenedioxy-4-(1',2'-epoxyethyl-1'-methoxycarbonyl)cyclopentane-1-carboxylic acid methyl ester, 8. A stirred solution of **7** (200mg, 0.74 mmol) in ethyl acetate (20 mL) was treated with excess diazomethane (0.35 g) at r.t. for 1 h. Removal of the solvent in vacuo yielded a 8:1 mixture of diastereomeric epoxyesters (80% d.e., GC). The major isomer **8** was isolated by column chromatography (3:1 hexane-ethyl acetate) as a solid (187 mg, 85% yield). Crystals, m.p. 72-74 °C (from ether-pentane); $[\alpha]_D$ +1.3° (c= 2.8, $CHCl_3$); IR (KBr) 1757, 1729 cm^{-1}; MS m/z 285 (M-15, 100), 211 (22), 193 (33), 165 (31), 59 (31), 55 (23), 43 (73); 400-MHz ^1H-NMR ($CDCl_3$) 1.23 (s, 3 H), 1.44 (s, 3 H), 1.82 (ddd, J =J' =J'' =12.4 Hz, 1 H), 2.36 (ddd, J =13.2 Hz, J' =J'' =7.3 Hz, 1 H), 2.87 (complex abs, 2 H), 2.93 (d, J = 5.5 Hz, 1 H), 3.02 (d, J = 5.5 Hz, 1 H), 3.65 (s, 3 H), 3.72 (s, 3 H), 4.05 (dd, J =J' = 7.3 Hz, 1 H), 4.71 (dd, J = 7.3 Hz, J' = 5.1 Hz, 1 H); 100-MHz ^{13}C-NMR ($CDCl_3$) 173.2 , 170.1 , 113.5, 81.8, 78.8, 55.7, 52.6, 52.0, 51.1, 49.2, 44.9, 31.2, 27.3, 24.9. Anal Calcd. for $C_{14}H_{20}O_7$: C, 55.99; H, 6.71. Found: C, 55.93; H, 6.96.

(1*R*, 2*S*, 3*R*, 4*S*)-(+)-2,3-Isopropylidenedioxy-4-(1'-methoxycarbonyl-1'-oxomethyl)-cyclopentane-1-carboxylic acid methyl ester, 12. DMAP (23 mg, 0.2 mmol) in anhydrous THF (2 mL) and anhydrous methanol (82 µL, 2.0 mmol) were subsequently added to a stirred and ice-cooled solution of **10** (507 mg, 1.9 mmol) in anhydrous THF (5 mL). Then, a solution of DCC (423 mg) in 5 mL of THF was added dropwise and the mixture was stirred at room temperature for 24 h and filtered. Solid DCU was washed with dichloromethane and the combined organic phases were washed with 0.5 N HCl (2x5 mL) and with saturated aqueous $NaHCO_3$ (2x5 mL), and dried. The solvents were evaporated at reduced pressure and the residue was chromatographed (3:1 hexane-ethyl acetate) affording diester **12** (300 mg, 56% yield). Colorless oil, o.t. 160-165°C (0.5 mm Hg); $[\alpha]_D$ +8.6° (c= 5.61, $CHCl_3$, 80% e.e.); IR (film) 1764, 1736 cm^{-1}; MS m/z 271 (M-15, 100), 227 (89), 197 (41), 169 (44), 151 (40), 141 (18), 125 (31), 109 (27); 250-MHz ^1H-NMR ($CDCl_3$) 1.19 (s, 3 H), 1.26 (s, 3 H), 1.95 (dd, J = 13.7 Hz, J' = 6.7 Hz, 1 H)), 2.42 (ddd, J = 13.7 Hz, J' = 11.8 Hz, J'' = 7.6 Hz, 1 H), 3.01 (d, J = 7.5 Hz, 1 H), 3.33 (d, J = 6.6 Hz, 1 H), 3.64 (s, 3.83, 3H), 4.80 (d, J = 5.5 Hz, 1 H), 5.14 (dd, J =J' = 5.8 Hz, 1 H); 62.5 MHz ^{13}C-NMR ($CDCl_3$) 190.3, 173.4, 160.9, 111.3, 82.7, 81.1, 53.0, 52.0, 47.9, 26.3, 25.6, 24.1. HRMS (EI) m/z: Calcd. for $C_{13}H_{18}O_7$: 271.081778 (M-15). Found: 271.080904.

(1*R*, 2*S*, 3*R*, 4*S*)-(-)-3-Isopropylidenedioxy-4-(1'-methoxycarbonyl-1'-oxomethyl)cyclopentane-1-carboxylic acid (1*R*,2*S*,5*R*)-menthyl ester, 14. Following the same procedure than that described above for the preparation of diester **12**, menthyl ester **14** (0.8 g, 60% yield) was obtained in 100% d.e. from acid **10** (1 g, 3.7 mmol) and (1*R*,2*S*,5*R*)-(-)-menthol (0.6 g, 4.0 mmol). Crystals, m.p. 50-52 °C (from ethyl acetate-pentane); $[\alpha]_D$ -39.5° (c= 1.5, CHCl$_3$); IR (KBr) 1757, 1736, 1680 cm^{-1}; MS m/z 395 (M-15, 2), 256 (M-CH$_3$-Menthyl, 23), 213 (28), 139 (Menthyl$^+$, 54), 83 (100), 81 (34), 69 (27), 59 (32), 57 (29), 55 (65), 43 (78), 41 (29); 400-MHz ^{1}H-NMR (CDCl$_3$) 0.72 (d, *J* = 7.0 Hz, 3 H), 0.87 (d, *J* = 5.8 Hz, 3 H), 0.88 (d, *J* = 7.0 Hz, 3 H), 0.90-1.10 (complex abs, 2 H), 1.23 (s, 3 H), 1.30 (s, 3 H), 1.30-1.50 (complex abs, 2 H), 1.65 (m, 2 H), 1.79 (dd, *J* = 7.0 Hz, *J'* = 2.8 Hz, 1 H), 1.88 (m, 1 H), 1.90 (ddd, *J* = 13.6 Hz, *J'* = 6.9 Hz, *J''*= 0.9 Hz, 1 H), 1.95 (m, 1 H), 2.48 (ddd, *J* = 13.4 Hz, *J'* = 11.9 Hz, *J''* = 7.6 Hz, 1 H), 3.00 (d, *J* = 7.3 Hz, 1 H), 3.61 (ddd, *J* = 12.8 Hz, *J'* = *J''* = 6.5 Hz, 1 H), 3.87 (s, 3 H), 4.64 (ddd, *J* = *J'* = 11.0 Hz, *J''* = 4.6 Hz, 1 H), 4.83 (d, *J* = 5.5 Hz, 1 H), 5.12 (dd, *J* = *J'* = 5.80 Hz, 1 H); 100-MHz ^{13}C-NMR (CDCl$_3$) 190.3, 172.6, 160.9, 111.1, 82.5, 81.3, 74.7, 52.9, 52.0, 48.2, 46.7, 40.6, 34.0, 31.2, 26.6, 26.2, 25.6, 24.1, 23.2, 21.8, 20.6, 16.1. Anal. Calcd. for C$_{22}$H$_{34}$O$_7$: C, 64.37; H, 8.35. Found: C, 64.50; H, 8.37.

(1*R*, 2*S*, 3*R*, 4*S*, 1′*S*)-(-)- and (-)-(1*R*, 2*S*, 3*R*, 4*S*, 1′*R*)-(-)-2,3-Isopropylidenedioxy-4-(1′,2′-epoxyethyl-1'-methoxycarbonyl)cyclopentane-1-carboxylic acid (1*R*,2*S*,5*R*)-menthyl ester, 15a and 15b. A stirred solution of **14** (350 mg, 0.8 mmol) in ethyl acetate (10 mL) was treated with excess diazomethane for 3 days. Removal of the unreacted diazomethane and the solvent gave a residue containing a 1:1 mixture of epoxides **15a** and **15b** and some starting material (determined by ^{1}H NMR). Column chromatography (4:1 hexane-ether) of this crude allowed the isolation of **15** (78 mg) and **15b** (57) along with 28 mg of a mixture of both diastereomers (45% total yield) and 21 mg of recovered **14**.

Epoxide 15a: Oil, $[\alpha]_D$ -38.0° (c= 4.5, CHCl$_3$); IR (film) 1729 cm^{-1}; MS m/z 409 (M-15, 15), 270 (M-CH$_3$-Ment, 90), 139 (Menthyl$^+$, 40), 83 (100), 80 (30), 69 (31), 57 (27), 55 (54), 43 (50); 250-MHz ^{1}H-NMR (CDCl$_3$) 0.71 (d, *J* = 6.9 Hz, 3 H), 0.85 (d, *J* = 3.7 Hz, 3 H), 0.88 (d, *J* = 3.3 Hz, 3 H), 0.80-1.10 (complex abs, 3 H), 1.20-1.50 (complex abs, 2 H), 1.28 (s, 3 H), 1.38 (s, 3 H), 1.57-1.68 (complex abs, 3 H), 1.70-1.94 (complex abs, 3 H), 2.71 (ddd, *J* = 12.1 Hz, *J'* = 7.9 Hz, *J''* = 4.4 Hz, 1 H), 2.86 (m, 1 H), 3.02 (d, *J* = 5.7 Hz, 1 H), 3.11 (d, *J* = 5.5 Hz, 1 H), 3.74 (s, 3 H), 4.63 (ddd, *J* = 15.4 Hz, *J'* = 10.8 Hz, *J''* = 4.4 Hz, 1 H), 4.90 (m, 2 H); 62.5-MHz ^{13}C-NMR (CDCl$_3$) 172.7, 170.7, 110.1, 82.5, 81.0, 74.6, 55.2, 52.5, 49.5, 48.4, 46.8, 42.4, 40.6, 34.1, 31.3, 26.9, 26.2, 25.8, 23.8, 23.2, 21.9, 20.7, 16.2. HRMS (EI) m/z: Calcd. para C$_{23}$H$_{36}$O$_7$: 424.246104. Found: 424.247086.

Epoxide 15b: Oil, $[\alpha]_D$ -24.9° (c= 3.05, CHCl$_3$); IR (film) 1764, 1729 cm^{-1}; MS m/z 409 (M-15, 11), 408 (47), 270 (M-CH$_3$-Ment, 84), 139 (Menthyl$^+$, 42), 83 (100), 81 (28), 69 (27), 57 (26), 55 (51), 43 (42); 250-MHz ^{1}H-NMR (CDCl$_3$) 0.71 (d, *J* = 6.9 Hz, 3 H), 0.80-1.10 (complex abs, 3 H), 0.88 (d, *J* =6.1 Hz, 2 CH$_3$), 1.20-1.50 (complex abs, 2 H), 1.24 (s, 3 H), 1.43 (s, 3 H), 1.60-1.70 (complex abs, 3 H), 1.80 (m, 1 H), 1.85-2.00 (complex abs, 2 H), 2.64 (d, *J* = 5.8 Hz, 1 H), 2.80 (d, *J* = 5.8 Hz, 1 H), 3.00 (m, 2 H), 3.73 (s, 3H), 4.62 (ddd, *J* = *J'* = 11.0 Hz, *J''* = 4.4 Hz, 1 H), 4.78 (d, *J* = 5.5 Hz, 1 H), 4.86 (dd, *J* =*J'* = 5.5 Hz, 1 H); 62.5-MHz ^{13}C-NMR (CDCl$_3$) 172.8, 170.9, 110.6, 82.0, 80.6, 74.6, 65.2, 52.4, 48.1, 48.0, 46.8, 41.5, 40.6, 34.1, 31.3, 26.2, 25.9, 25.8, 24.4, 23.2, 21.9, 20.7, 16.1. HRMS (EI) m/z: Calcd. for C$_{23}$H$_{36}$O$_7$: 424.246104. Found: 424.243500.

(1*S*, 2*R*, 3*S*, 4*R*,1′*R*)-(+)-2,3-Isopropylidenedioxy-4-(1'-ethyl-1'-hydroxy-1'-methoxycarbonylmethyl)-cyclopentane-1-carboxylic acid methyl ester, 16. A 1.6 M ethereal solution of MeLi (3.7 mL, 6.0 mmol) was added to a stirred suspension of CuI (570 mg, 3.0 mmol) in anhydrous ether, at -15 °C under argon atmosphere. After stirring for 30 minutes, a solution of epoxide **8** (300 mg, 1.0 mmol) in anhydrous ether (5 mL) was added and the mixture was stirred at -15 °C for 1 h. Then, saturated aqueous ammonium chloride

(10 mL) was added and the resulting mixture was stirred at r.t. for 20 minutes. The layers were separated and the aqueous phase was extracted with ethyl acetate (3x10 mL). The combined organic phases were dried and the solvents were removed to afford an oil that was chromatographed (2:1 hexane-ethyl acetate) to give alcohol **16** (215 mg, 69% yield) and **(3*S*, 4*R*,1′*R*)-3-hydroxy-4-(1'-ethyl-1'-hydroxy-1'-methoxycarbonylmethyl)cyclopent-1-ene-1-carboxylic acid methyl ester, 17,** (30 mg, 12% yield).

Compound 16: Crystals, m.p. 52-53°C (from ether-pentane); $[\alpha]_D$ +35.6° (c= 1.5, $CHCl_3$); IR (KBr) 3600-3300 (broad), 1736 cm^{-1}; MS m/e 301 (M-15, 12), 241 (43), 209 (26), 199 (25), 167 (47), 149 (22), 125 (57), 93 (30), 59 (32), 57 (100), 55 (39), 43 (48); 400-MHz ^{1}H-NMR ($CDCl_3$) 0.78 (t, J= 7.3 Hz, 3 H), 1.27 (s, 3 H), 1.47 (s, 3 H), 1.72-1.90 (complex abs, 4 H), 2.35 (ddd, $J = J'$ = 9.5 Hz, J'' = 5.1 Hz, 1 H), 2.82 (ddd, $J = J'$ = 9.5 Hz, J'' = 5.8 Hz, 1 H), 3.65 (s, 3 H), 3.75 (s, 3 H), 4.60 (dd, J = 7.3 Hz, J' = 5.1 Hz, 1 H), 4.68 (dd, J = 7.3 Hz, J' = 5.8 Hz, 1 H); 100-MHz ^{13}C-NMR ($CDCl_3$) 176.2, 173.7, 113.2 , 82.4, 80.3, 77.5, 52.9, 52.1, 52.0, 49.8, 30.8, 29.7, 27.4, 24.9, 7.8. Anal. Calcd. for $C_{15}H_{24}O_7$: C, 56.95; H, 7.65. Found: C, 56.91; H, 7.69.

Compound 17: Oil. IR (film) 3600-3100 (broad), 1722, 1638 cm^{-1}; MS m/z 258 (M, 2), 141 (35), 125 (44), 118 (48), 109 (38), 93 (25), 59 (21), 57 (100), 43 (20); 400-MHz ^{1}H-NMR ($CDCl_3$) 0.84 (t, J = 7.5 Hz, 3 H), 1.60 (broad s, 1 H), 1.87 (m, 2 H), 2.34-2.62 (complex abs, 3 H), 3.37 (broad s, 1 H), 3.74 (s, 3 H), 3.78 (s, 3 H), 4.90 (m, 1 H), 6.55 (m, 1 H); 100-MHz ^{13}C NMR ($CDCl_3$) 176.2, 165.1, 142.8, 136.0, 78.3, 78.1, 55.2, 53.0, 51.7, 31.6, 30.6, 7.9. HMRS (EI) m/z: Calcd. for $C_{12}H_{18}O_6$: 258.110339. Found: 258.112045.

(1*S*, 2*R*, 3*S*, 4*R*,1′*R*)-(+)-2,3-Dihydroxy-4-(1'-ethyl-1'-hydroxy-1'-methoxycarbonylmethyl)cyclopentane-1-carboxylic acid methyl ester, 18. A mixture of **16** (80 mg, 0.2 mmol), 1 N HCl (4 mL), and THF (8 mL) was stirred at r.t. for 2 days. The organic solvent was removed in vacuo and the aqueous solution was neutralized with $NaHCO_3$ and then extracted with ethyl acetate (3x10 mL). The combined organic extracts were dried and the solvent was evaporated . The residue was chromatographed (1:1 hexane-ethyl acetate) to give triol **18** as a thick colorless oil (30 mg, 43% yield); $[\alpha]_D$ +14.8° (c= 0.7, $CHCl_3$); IR (film) 3700-3100 (broad), 1729 cm^{-1}; 400-MHz ^{1}H-NMR ($CDCl_3$) 0.87 (t, J= 7.3 Hz, 3 H), 1.23 (m, 1 H), 1.53 (m, 1 H), 1.70 (broad s, 1 H), 1.83 (complex abs, 3 H), 2.30 (ddd, $J = J'$ = 10.2 Hz, J'' = 3.7 Hz, 1 H), 2.80 (ddd, J = 11.0 Hz, J' = 7.3 Hz, J'' = 3.7 Hz, 1 H), 2.90 (broad s, 1 H), 3.38 (broad s, 1 H), 3.69 (s, 3 H,), 3.75 (s, 3 H), 4.10 (m, 2 H); 100-MHz ^{13}C-NMR ($CDCl_3$) 176.1, 174.6, 78.3 75.0, 72.1, 52.9, 52.0, 51.3, 47.9, 30.6, 25.4, 7.9.

(1*S*, 2*R*, 3*S*, 4*R*,1′*R*)-(+)-2,3-Isopropylidenedioxy-4-(1′-azidomethyl-1'-hydroxy-1′-methoxycarbonylmethyl)cyclopentane-1-carboxylic acid methyl ester, 19, and (+)-(3*S*,4*R*,1′*R*)-3-hydroxy-4-(1′-azidomethyl-1'-hydroxy-1′-methoxy-carbonylmethyl)cyclopent-1-ene-1-carboxylic acid methyl ester, 20. A mixture of epoxide **8** (100 mg, 0.3 mmol), sodium azide (65 mg, 1 mmol) and anhydrous DMF (5 mL) was stirred at r.t. for 4 days under argon atmosphere. The solvent was removed at reduced pressure and the residue was poured into water (5 mL) and extracted with ethyl acetate (3x10 mL). The combined extracts were dried and the solvent was eliminated. The residue was chromatographed on Florisil (1:1 hexane-ethyl acetate) to yield compound **19** (40 mg, 35% yield) and conjugated **20** (5 mg, 5% yield). Both products are unstable oils.

Compound 19: $[\alpha]_D$ +46.2° (c= 1.0, $CHCl_3$); IR (film) 3700-3100 (broad), 2109, 1736 cm^{-1}; MS m/z 328 (M-15, 3), 300 (M-43, 3), 229 (25), 197 (31), 180 (26), 176 (28), 169 (40), 109 (37), 93 (29), 83 (25), 81

(28), 59 (77), 55 (100), 53 (34), 43 (98), 41 (28); 400-MHz ^{1}H-NMR ($CDCl_3$) 1.30 (s, 3 H), 1.48 (s, 3 H), 1.78-1.95 (complex abs, 2 H), 2.28 (ddd, J = 7.3 Hz, J' = 5.8 Hz, J'' = 1.5 Hz, 1H), 2.87 (ddd, J = 11.7 Hz, J' = 8.0 Hz, J'' = 5.8 Hz, 1 H), 3.43 (d, J = 13.2 Hz, 1 H), 3.57 (broad s, 1 H), 3.68 (s, 3 H), 3.70 (d, J = 13.2 Hz, 1 H), 3.82 (s, 3 H), 4.65 (dd, J = 7.3 Hz, J' = 5.8 Hz, 1 H), 4.75 (dd, J = 7.3 Hz, J' = 5.1 Hz, 1 H); 100-MHz ^{13}C-NMR ($CDCl_3$) 173.9, 173.3, 113.7, 82.3, 79.7, 57.0, 53.5, 52.2, 50.3, 49.2, 29.3, 27.4, 27.0, 24.9. HMRS (EI) m/z: Calcd. for $C_{14}H_{21}N_3O_7$: 328.114475 (M-15). Found: 328.115038.

Compound 20: $[\alpha]_D$ +10.4° (c= 1.8, $CHCl_3$); IR (film) 3700-3100 (broad), 2109, 1729, 1638 cm^{-1}; MS m/z 286 (M+1, 7), 285 (M, 49), 211 (21), 165 (36), 137 (24), 109 (25), 59 (59), 55 (47), 53 (22), 45 (32), 43 (100), 41 (29); 400-MHz ^{1}H-NMR ($CDCl_3$) 1.70 (broad s, 1 H), 2.32-2.52 (complex abs, 3 H), 3.52 (d, J =12.5 Hz, 1 H), 3.68 (broad s, 1 H), 3.71 (s, 3 H), 3.74 (d, J = 12.5 Hz, 1 H) , 3.83 (s, 3 H), 5.08 (m, 1 H), 6.55 (m, 1 H); 100-MHz ^{13}C-NMR ($CDCl_3$) 174.0, 164.9, 142.9, 135.4, 77.9, 77.2, 57.1, 53.5, 53.4, 51.8, 30.9. HMRS (EI) m/z: Calcd. for $C_{14}H_{21}N_3O_7$: 285.096085. Found: 285.095197.

(1*S*, 2*R*, 3*S*, 4*R*,1′*R*)-(+)-2,3-Isopropylidenedioxy-4-(1′-aminomethyl-1'-hydroxy-1′-methoxycarbonylmethyl)cyclopentane-1-carboxylic acid methyl ester, 22. *(a) From azide 19.* Azide **19** (28 mg, 0.1 mmol) in 1:1 ethyl acetate-96% ethanol (8 mL) was hydrogenated at atmospheric pressure in the presence of 10% palladium on charcoal (10 mg), for 3 h. The mixture was filtered through celite and the solvent was removed to afford quantitatively solid amine **22** (26 mg). *(b) From Benzylamine 21.* Compound **21** (**26b**, see below) (90 mg, 0.2 mmol) in glacial AcOH (10 mL) was hydrogenated at 7 atm pressure in the presence of 10% palladium on charcoal (45 mg) overnight. Then, ethyl acetate (10 mL) was added and the catalyst was removed by filtration through celite. The filtered solution was evaporated to dryness at reduced pressure and the residue was partitioned among dichloromethane and water, and neutralized with $NaHCO_3$. The phases were separated and the aqueous phase was extracted with dichloromethane. The combined organic layers were dried and the solvent was removed to afford **22** (65 mg, 96% yield). Crystals, m.p. 122-124 °C (from dichloromethane-hexane); $[\alpha]_D$ +22.2° (c= 0.9, $CHCl_3$); IR (KBr) 3374, 3300-3030 (broad), 1729 cm^{-1}; MS m/z 318 (M+1, 100), 302 (M-15, 1), 112 (72), 103 (17), 100 (33), 86 (56); 400-MHz ^{1}H-NMR ($CDCl_3$) 1.26 (s, 3 H), 1.45 (s, 3 H), 1.85 (complex abs, 2 H), 2.33 (ddd, J = 10.8 Hz, J' = 8.4 Hz, J'' = 5.7 Hz, 1 H), 2.45 (broad s, 2 H), 2.81 (ddd, J = 10.8 Hz, J' = 8.6 Hz, J'' = 5.8 Hz, 1 H), 2.99 (broad s, 1 H), 3.66 (s, 3H), 3.68 (d, J = 11.9 Hz, 1 H), 3.75 (d, J =12.0 Hz, 1 H), 3.78 (s, 3 H), 4.62 (dd, J = 7.5 Hz, J' = 5.7 Hz, 1 H), 4.72 (dd, J = 7.5 Hz, J' = 5.8 Hz, 1 H); 100-MHz ^{13}C NMR ($CDCl_3$) 175.4, 173.5, 113.3, 82.3, 79.9, 52.9, 52.0, 50.2, 49.4, 48.2, 29.8 27.3, 24.9. Anal. Calcd. for $C_{14}H_{23}NO_7$: C, 52.99; H, 7.31; N 4.41. Found: C, 53.08; H, 7.04; N, 4.32.

(3*R*,4*S*,1′*S*)-(+)-3-[1-Methoxycarbonyl-4-(1'-ethyl-1'-hydroxy-1'-methoxycarbonylmethyl)cyclopent-1-enyl] (*R*)-*O*-acetylmandelate, 25 *via* alcohol 24. A 1.6 M solution of BuLi in hexane (1.3 mL, 2.0 mmol) was added dropwise to a stirred solution of diisopropylamine (288 μL, 2.0 mmol) in anhydrous THF (2 mL) at -78 °C under nitrogen atmosphere. After stirring for 30 minutes, a solution of **23** (215 mg, 0.7 mmol) in THF (2 mL) were added at -78 °C and the mixture was stirred at -20 °C for 4 hours, then diluted with dichloromethane (10 mL) and neutralized with saturated aqueous ammonium chloride (5 mL). The aqueous phase was extracted with dichloromethane (2x5 mL) and dried. After removal of solvents the residue was chromatographed (1:1 hexane-ethyl acetate) to afford unsaturated **24** (114 mg, 65% yield) and 32 mg of recovered **23**.

To a stirred an ice-cooled solution of *O*-acetyl-(*R*)-(-)-mandelic acid (100 mg, 0.5 mmol) in anhydrous dichloromethane (3 mL) solutions of alcohol **24** (120 mg, 0.5 mmol) in 3 mL of dichloromethane and DMAP (7 mg, 0.05 mmol) in 1 mL of dichloromethane were subsequently added dropwise under nitrogen atmosphere. After stirring at r.t. for 3 days, the mixture was filtered. The solid was washed with dichloromethane and the filtrate was washed with 0.5 N HCl (2x5 mL) and saturated aqueous sodium bicarbonate (2x5 mL), and dried. The solvent was evaporated at reduced pressure and the residue was chromatographed (mixtures of hexane-ethyl acetate), affording 30 mg (15% yield) of **25**. Crystals, m.p. 90 °C (dec) (from ethyl acetate-pentane); $[\alpha]_D$ +50.4° (c= 1.3, $CHCl_3$); IR (KBr)1743, 1736, 1715, 1638 cm^{-1}; MS m/z 242 (M-192, 7), 149 (36), 125 (100), 124 (26), 118 (27), 107 (54), 93 (60), 79 (27), 65 (37), 59 (31), 57 (97), 43 (57); 400-MHz ^{1}H-NMR ($CDCl_3$) 0.77 (t, *J* = 7.3 Hz, 3 H), 1.66 (m, 2 H), 2.17 (s, 3 H), 2.34 (ddt, *J* = 16.5 Hz, *J'* = 7.3 Hz, *J''* = 1.8 Hz, 1 H), 2.55 (ddt, *J* = 16.5 Hz, *J'* = 9.2 Hz, *J''* = 1.8 Hz, 1 H), 2.78 (m, 1 H), 3.25 (s, 1 H), 3.68 (s, 3 H), 3.78 (s, 3 H), 5.84 (s, 1 H), 6.00 (m, 1 H), 6.34 (m, 1 H), 7.40 (complex abs, 5 H); 100-MHz ^{13}C-NMR ($CDCl_3$) 175.9, 170.3, 168.1, 164.5, 138.5, 137.9, 133.3, 129.3, 128.8, 127.5, 81.0, 77.6, 74.6, 52.9, 51.7, 50.6, 31.5, 30.3, 20.6, 7.9. Anal. Calcd. for $C_{22}H_{26}O_9$: C, 60.82; H, 6.03. Found: C, 60.68; H, 6.03.

(1*R*,2*S*,3*R*,4*S*,1´*S*)-(+)- and (1*S*,2*R*,3*S*,4*R*1´*R*)-(+)-2,3-Isopropylidenedioxy-4-(1'-hydroxy-1'-methoxycarbonylmethyl-1'-[(R)-α-methylbenzylaminomethyl])cyclopentane-1-carboxylic acid methyl ester, 26a and 26b. (*R*)-(+)-α-Methylbenzylamine (1.5 mL, 11.6 mmol) was added to a solution of epoxide **11** (1.2 g, 3.9 mmol) in 5 mL of DMF, and the light-protected mixture was stirred at r.t. for 2 days, then diluted with ethyl acetate (10 mL) and washed with water (3x10 mL). The organic phase was dried and the solvent was removed to afford a residue containing a 15: 1 mixture of amines **26a** and **26b** (determined by ^{1}H NMR). Column chromatography of this crude (mixtures of hexane-ethyl acetate as eluents) furnished 1.1 g of major **26a**, 56 mg of minor **26b** (**21**), and 180 mg of a mixture of both diastereomers (86% yield).

Amine 26a: Crystals, m.p. 92-94°C (from ether-pentane); $[\alpha]_D$ +4.0° (c= 5.0, $CHCl_3$); IR (KBr) 3508, 3030, 1743, 1722 cm^{-1}; MS m/z 422 (M+1, 0.2), 406 (M-15, 0.6), 135 (7), 134 (63), 120 (6), 118 (3), 106 (14), 105 (100); 400-MHz ^{1}H-NMR ($CDCl_3$) 1.17 (s, 3 H), 1.23 (d, *J* = 6.7 Hz, 3 H), 1.40 (s, 3 H), 1.60 (broad s, 1 H), 1.82 (m, 2 H), 2.10 (s, 1 H), 2.27 (ddd, *J* =*J'* = 9.8 Hz, *J''* = 5.5 Hz, 1 H), 2.74 (ddd, *J* = 12.8 Hz, *J'* = 8.6 Hz, *J''* = 4.9 Hz, 1 H), 2.76 (d, *J* = 12.8 Hz, 1 H), 2.85 (d, *J* = 12.8 Hz, 1 H), 3.63 (m, 1 H), 3.62 (s, 3 H), 3.71 (s, 3 H), 4.43 (dd, *J* = 7.3 Hz, *J'* = 4.9 Hz, 1 H), 4.63 (dd, *J* =*J'* = 7.3 Hz, 1 H); 100-MHz ^{13}C-NMR ($CDCl_3$) 175.5, 173.5, 145.2, 128.3, 126.9, 126.3, 113.1, 82.3, 80.0, 76.6, 57.6, 52.7, 52.6, 51.9, 50.3, 49.6, 29.7, 27.3, 24.8, 23.8. Anal. Calcd. for $C_{22}H_{31}NO_7$: C, 62.69; H, 7.41; N, 3.32. Found: C, 62.73; H, 7.54; N, 3.32.

Amine 26b: Crystals, m.p. 83-85°C (from ether-pentane); $[\alpha]_D$ +54.0° (c= 2.0, $CHCl_3$); IR (KBr) 3501, 3339, 3030, 1736 cm^{-1}; MS m/z 406 (M-15, 1), 135 (8), 134 (72), 106 (13), 105 (100); 400-MHz ^{1}H-NMR ($CDCl_3$) 1.21 (d, *J* = 5.5 Hz, 3 H), 1.23 (s, 3H), 1.38 (s, 3H,), 1.42 (broad s, 1H), 1.77 (m, 2H), 2.17 (ddd, *J* = 10.4 Hz, *J'* = 8.5 Hz, *J''* = 4.9 Hz, 1 H), 2.64 (d, *J* = 12.2 Hz, 1 H), 2.73 (ddd, *J* = 10.4 Hz, *J'* = 8.5 Hz, *J''* = 6.1 Hz, 1H), 2.88 (d, *J* = 11.6 Hz, 1 H), 3.62 (s, 3H), 3.68 (m, 1H), 3.67 (s, 3H), 4.56 (dd, *J* = 7.3 Hz, *J'* = 4.9 Hz, 1 H), 4.65 (dd, *J* =*J'* = 7.3 Hz, 1 H); 100-MHz ^{13}C-NMR ($CDCl_3$) 175.7, 173.6, 145.6, 128.1, 126.9, 126.7, 113.2, 82.5, 80.3, 77.4, 58.0, 53.0, 52.7, 52.0, 50.2, 49.7, 29.6, 27.4, 25.1, 24.9. Anal. Calcd. for $C_{22}H_{31}NO_7$: C, 62.69; H, 7.41; N, 3.32. Found: C, 62.61; H, 7.14; N, 3.25.

(1*R*,2*S*,3*R*,4*S*,1′*S*)-(-)- and (1*S*,2*R*3*S*,4*R*1′*R*)-(+)-2,3-Isopropylidenedioxy-4-(1'-hydroxy-1'-[(R)-α-methoxycarbonylbenzylaminomethyl]-1'-methoxycarbonyl-methyl)cyclopentane-1-carboxylic acid methyl ester, 27a and 27b. (*R*)-(-)-Phenylglycine methyl ester (331 mg, 2.0 mmol) in 2 mL of DMF was added to a solution of epoxide **11** (200 mg, 0.67 mmol) in 2 mL of DMF and the light-protected mixture was stirred at r.t. for 4 days, then diluted with ethyl acetate (10 mL), washed with water (3x10 mL), and dried. Removal of solvent at reduced pressure gave a residue that was chromatographed (mixtures of hexane-ethyl acetate as eluents) to provide 70 mg of major **27a** and 5 mg of minor **27b** (24% yield), along with 127 mg of unaltered **11** (64% recovery).

Amine 27a: Crystals , m.p. 132-133°C (from ethyl acetate-hexane); $[\alpha]_D$ -84.5° (c= 1.4, $CHCl_3$); IR (KBr) 3501, 1736, 1729, cm^{-1}; MS m/z 466 (M+1, 100), 318 (6), 178 (3), 168 (5), 166 (3), 112 (10), 100 (4); 400-MHz ^{1}H-NMR ($CDCl_3$) 1.23 (s, 3 H), 1.40 (s, 3 H), 1.73-1.86 (complex abs, 2 H), 2.21 (ddd, J = 11.6 Hz, J' = 6.7 Hz, J'' = 5.5 Hz, 1 H), 2.38 (broad s, 1 H), 2.74 (m, 1 H), 2.76 (d, J = 11.6 Hz, 1 H), 2.97 (d, J =12.2 Hz, 1 H), 3.60 (s, 3 H), 3.63 (s, 3 H), 3.65 (s, 3 H), 3.71 (s, 1 H), 4.27 (s, 1 H), 4.57 (dd, J = 7.3 Hz, J' = 5.5 Hz, 1 H), 4.66 (dd, $J = J'$ = 6.7 Hz, 1 H), 7.20-7.30 (complex abs, 5 H); 100-MHz ^{13}C-NMR ($CDCl_3$) 175.3, 173.5, 173.0, 138.1, 128.4, 128.0, 127.6, 113.3, 82.4, 80.1, 77.5, 65.2, 53.2, 52.7, 52.3, 52.0, 50.3, 49.6, 29.6, 27.4, 25.0. Anal. Calcd. for $C_{23}H_{31}NO_9$: C, 59.35; H, 6.71; N 3.01. Found: C, 59.20; H, 6.77; N, 3.00.

Amine 27b: Crystals, m.p. 95°C (dec) (from ethyl acetate-hexane); $[\alpha]_D$ +23.7° (c= 0.8, $CHCl_3$); IR (KBr) 3515, 1743, 1732, 1725 cm^{-1}; MS m/z 466 (M+1, 100), 318 (6), 178 (3), 168 (5), 166 (3), 112 (10), 100 (4); 400-MHz ^{1}H-NMR ($CDCl_3$) 1.25 (s, 3 H), 1.45 (s, 3 H), 1.85-1.90 (complex abs, 2 H), 2.32 (ddd, $J = J'$ = 9.7 Hz, J'' = 5.5 Hz, 1 H), 2.80 (m, 1 H), 2.84 (d, J = 12.2 Hz, 1 H), 2.97 (d, J = 12.8 Hz, 1 H), 3.65 (s, 3 H), 3.67 (s, 3 H), 3.78 (s, 3 H), 4.36 (s, 1 H), 4.56 (dd, J= 7.6 Hz, J' = 5.5 Hz, 1 H), 4.70 (dd, $J = J'$ = 7.1 Hz, 1 H), 7.26-7.31 (complex abs, 5 H); 100-MHz ^{13}C-NMR ($CDCl_3$) 175.2, 173.5, 173.0, 137.8, 128.7, 128.2, 127.4, 113.3, 82.4, 80.0, 77.0, 65.4, 53.1, 52.9, 52.2, 52.0, 50.3, 49.6, 29.8, 27.4, 24.9. Anal. Calcd. for $C_{23}H_{31}NO_9$: C, 59.35; H, 6.71; N, 3.01. Found: C, 59.37; H, 6.69; N, 3.02.

(1*R*,2*S*,3*R*,4*S*,1′*S*)-(-)-2,3-Isopropylidenedioxy-4-(1'-hydroxy-1'[(1S,2R)-(2-hydroxy-1-methyl-2-phenyl)ethylaminomethyl]-1'-methoxycarbonylmethyl)-cyclopentane-1-carboxylic acid methyl ester, 28a. (1*R*,2*S*)-(-)-Norephedrine (150 mg, 1.0 mmol) in DMF (2mL) was added to a solution of epoxide **11** (100 mg, 0.33 mmol) in DMF (2 mL) and the light-protected mixture was stirred at r.t. for 1 day, then diluted with ethyl acetate (10 mL), washed with water (3x10 mL), and dried. Removal of solvent afforded a crude that was chromatographed (mixtures of hexane-ethyl acetate as eluents) to provide 8 mg of a mixture of both diastereomers **28a/b** and 83 mg of major **28a** (60% yield). Crystals, m.p. 42°C (dec) (from ethyl acetate-hexane); $[\alpha]_D$-32.4° (c= 0.9, $CHCl_3$); IR (KBr) 3700-3200 (broad), 3030, 1736, cm^{-1}; MS m/z 452 (M+1, 17), 344 (10), 318 (24), 212 (38), 210 (40), 112 (100); 400-MHz ^{1}H-NMR ($CDCl_3$) 0.74 (d, J = 6.7 Hz, 3 H), 1.29 (s, 3 H), 1.49 (s, 3 H), 1.82-1.87 (complex abs, 2 H), 2.37 (ddd, $J = J'$ = 9.8 Hz, J'' = 5.5 Hz, 1 H), 2.85 (m, 2 H), 3.01 (d, J = 11.6 Hz, 1 H), 3.15 (d, J = 12.2 Hz, 1 H), 3.67 (s, 3 H), 3.80 (s, 3 H), 4.62-4.67 (complex abs, 3 H), 4.72 (dd, $J = J'$ = 6.7 Hz, 1 H), 7.18-7.30 (complex abs, 5 H); 100-MHz ^{13}C-NMR ($CDCl_3$) 175.5, 173.5, 140.9, 128.0, 126.9, 125.9, 113.4, 82.5, 80.2, 77.5, 72.3, 58.3, 53.2, 52.7, 52.0, 50.5, 49.5, 29.6, 27.4, 25.0, 14.7. Anal. Calcd. for $C_{23}H_{33}NO_8$: C, 61.18; H, 7.37; N 3.10. Found: C, 61.09; H, 7.35; N, 3.09.

(-)-(1*R*, 2*S*, 3*R*, 4*S*,1′*S*)-2,3-Isopropylidenedioxy-4-(1′-aminomethyl-1′-hydroxy-1′-methoxycarbonylmethyl)cyclopentane-1-carboxylic acid methyl ester, 29, and its hydrolysis to half-ester 30. A mixture of **26a** (200 mg, 0.47 mmol), glacial acetic acid (10 mL) and 10%Pd/C (90 mg) was hydrogenated under 7 atmospheres pressure, overnight. Then, 10 mL of ethyl acetate were added and the catalyst was removed by filtration. The solvents were evaporated at reduced pressure and the residue was poured into dichloromethane-water and neutralized with sodium bicarbonate. The layers were separated and the aqueous layer was extracted with dichloromethane. The combined organic phases were dried and the solvent was removed to afford quantitatively 148 mg of solid amine **29**. Crystals, m.p. 121-123 °C (from dichloromethane-hexane); $[\alpha]_D$ -22.1° (c= 1.4, $CHCl_3$); IR (KBr) 3374, 3300-3030, 3002, 1729 cm^{-1}; MS m/z 318 (M+1, 100), 302(M-15, 1), 112 (72), 103 (17), 100 (33), 86 (56); 400-MHz ^1H-NMR ($CDCl_3$) 1.26 (s, 3H), 1.45 (s, 3 H), 1.85 (complex abs, 2 H), 2.33 (ddd, J = 10.8 Hz, J' = 8.4 Hz, J'' = 5.7 Hz, 1 H), 2.45 (broad s, 2 H), 2.81 (ddd, J = 10.8 Hz, J' = 8.6 Hz, J'' = 5.8 Hz, 1 H), 2.99 (broad s, 1 H), 3.66 (s, 3 H), 3.68 (d, J = 11.9 Hz, 1 H), 3.75 (d, J =12.0 Hz, 1 H), 3.78 (s, 3 H), 4.62 (dd, J = 7.5 Hz, J' = 5.7 Hz, 1 H), 4.72 (dd, J = 7.5 Hz, J' = 5.8 Hz, 1 H); 100-MHz ^{13}C-NMR ($CDCl_3$) 175.4, 173.5, 113.3, 82.3, 79.9, 52.9, 52.0, 50.2, 49.4, 48.2, 29.8, 27.3, 24.9. Anal. Calcd. for $C_{14}H_{23}NO_7$: C, 52.99; H, 7.31; N 4.41. Found: C, 53.07; H, 7.00; N, 4.31. Compound **29** (100 mg, 0.3 mmol) and 6N HCl (4 mL) were stirred at room temperature for 16 h. Then water was removed and the residue was dissolved in EtOH (2 mL) and some drops of propylene oxide. After 15 min stirring the solution was evaporated and the residue was dissolved in 2 mL of water and eluted through a C_{18}-reverse phase cartridge to afford quantitatively a very insoluble yellowish solid that was identified as **half-ester 30**. IR (KBr) 3700-2300 (broad), 1736, 1616 cm-1; MS, m/z 248 (M-15, 2), 234 (M-29, 4), 58 (25), 44 (100); 250-MHz ^1H-NMR (D_2O) 1.34 (m, 1 H), 1.70 (m, 1 H), 2.13 (m, 1 H), 2.56 (m, 1 H), 3.15 (d, J = 13.6 Hz, 1 H), 3.22 (d, J = 13.6 Hz, 1 H), 3.56 (s, 3 H), 3.81 (m, 2 H); 62.5-MHz ^{13}C-NMR (D_2O) 178.4, 174.0, 76.0, 75.3, 71.9, 54.3, 49.9, 48.6, 44.7, 25.2.

Acknowledgements. M. D. Thanks the Ministerio de Educación y Ciencia for a fellowship. Financial support from DGICYT through the project PB91-0502 is gratefully acknowledged. The authors thank Dr. T. Parella (NMR Service, UAB) for performance of the NMR experiments.

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(*Received in UK* 17 *July* 1995; *revised* 1 *September* 1995; *accepted* 8 *September* 1995)