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Enantioselective Synthesis of Novel Homochiral α-Substituted (*S*)-Isoserine Derivatives. Incorporation of this Amino Acid in a Highly Conformationally Constrained Dipeptide Surrogate

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Abstract. Optically pure isoserine derivatives with a chiral polyfunctional bicyclo[3.1.0]hexyl substituent at the α-carboxyl position were synthesized from a common cyclopentene precursor bearing an α-epoxy ester function in a side-chain. Cyclopropanation of the double bond and nucleophilic oxirane-ring opening by using a homochiral amine were the key steps. One of the synthesized derivatives was condensed with Cbz-cyclo-Asp-OMe affording a highly conformationally constrained dipeptide surrogate.
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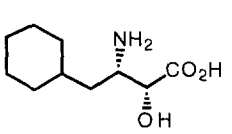
INTRODUCTION

The 3-amino-2-hydroxyacid (isoserine) structural moiety is present in several kinds of molecules with interesting biological properties. Such is the case of cyclohexylnorstatine **1**,[1] a constituent of dipeptide **4**, an active renin inhibitor developed by a Japanese company as an antihypertensive agent,[2] and (2*R*,3*S*)-3-amino-2-hydroxy-3-phenylpropionic acid, **2**, the side-chain amino acid of taxol which is a potent antileukemic and antitumor agent.[3]



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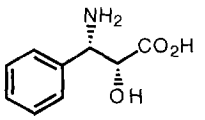

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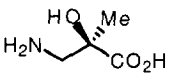

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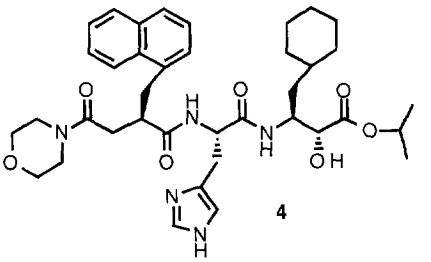

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Attention has also been devoted to α,α-disubstituted amino acids due to their verified or potential activity. For instance, 3-amino-2-hydroxy-2-phenylpropionic acid derivatives have been used as intermediates for cardiovascular agents and analgesics.[4] Moreover, the synthesis of (2*R*)-3-amino-2-hydroxy-2-methylpropionic acid (α-methylisoserine), **3**, has recently been reported.[5]

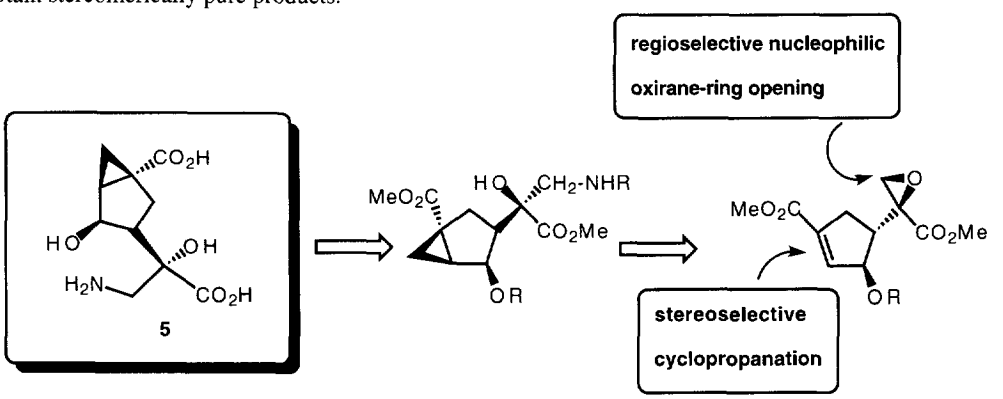
Furthermore, those polyfunctional amino acids with conformationally constrained structures are useful for incorporation in peptidomimetics employed as biological probes in mechanistic studies.[6] These molecules also present a great interest in the development of new pharmaceuticals able to interact with the receptors in a more specific manner.[7]

We reported in recent publications the synthetic potential of a homochiral polyfunctional cyclopentene containing an oxirane ring in a side-chain,[8] and the first results on the cyclopropanation of such a compound providing enantiomerically pure bicyclo[3.1.0]hexane derivatives.[9] This type of products are also useful to prepare rigid carbocycle-based potential drugs such as conformationally locked nucleoside analogs[10] and antisense nucleotides.[11]

We present in this article the efficient synthesis of the novel α-substituted isoserine analog **5** (Scheme 1) and a diastereomer, as well as some functional derivatives. These molecules bear two quaternary carbons, one in the ring-fusion and another in the side-chain, and three additional stereogenic centers, all of them with controlled absolute configuration. Condensation of a conveniently protected derivative of amino acid **5** with methyl (2*S*,3*R*)-*N*-benzyloxycarbonyl-2,3-methanoaspartate (Cbz-cyclo-Asp-OMe) to afford a fully protected and highly rigid dipeptide surrogate is also described.

RESULTS AND DISCUSSION

Scheme 1 shows the retrosynthetic pathway relating hydroxy amino acid **5** to a bicyclic intermediate already bearing the main chemical functions of the target. Such an intermediate should result from stereoselective cyclopropanation of a conjugated double bond and from regioselective nucleophilic oxirane-ring opening in a cyclopentene derivative used as a suitable precursor. At the beginning, the order in the performance of these key transformations seemed irrelevant. Nevertheless, it was revealed to be crucial to obtain stereomerically pure products.

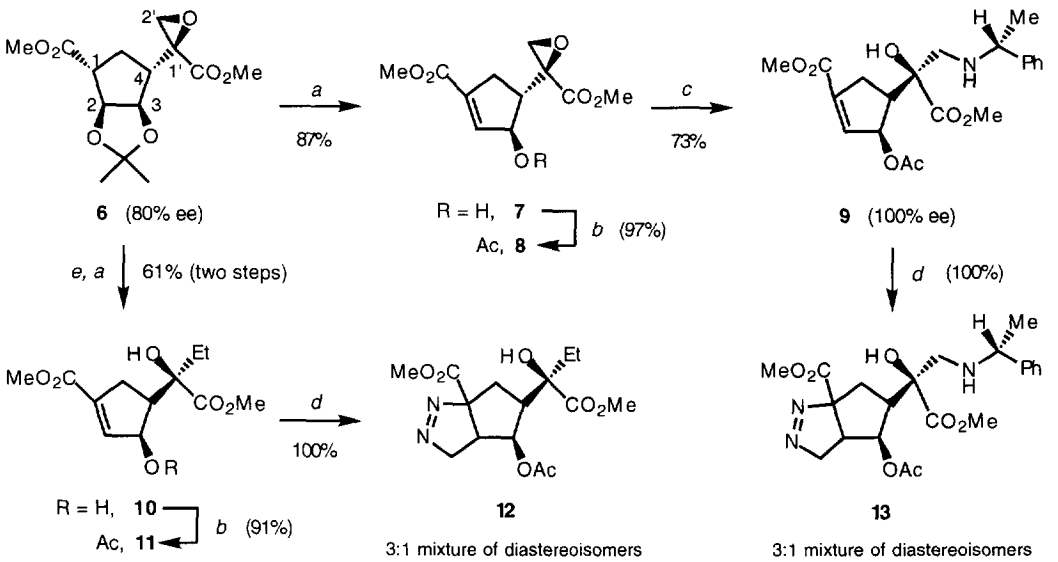


Scheme 1

We had previously described the preparation of compound **6** (Scheme 2) in 80% ee through a synthetic sequence involving the chemoenzymatic hydrolysis of an intermediate *meso* diester.[8] Base-promoted elimination of acetone from **6**, by using LDA at -78 °C for 4 hours afforded the new cyclopentenol **7** which was acetylated with acetic anhydride and pyridine in a dichloromethane solution to give acetate **8** in 90% yield. Subsequently, oxirane-ring opening was accomplished by reaction with (*R*)-α-methylbenzylamine in DMF at 60 °C for one day. This was a convenient homochiral reagent that allowed not only the introduction of the amino function but also the resolution of cyclopentene **9.** Major stereoisomer **9** was indeed isolated in 70% yield after column chromatography of the produced diastereomeric mixture. Products from 1,4-conjugate addition of the amine to the double bond were not detected.

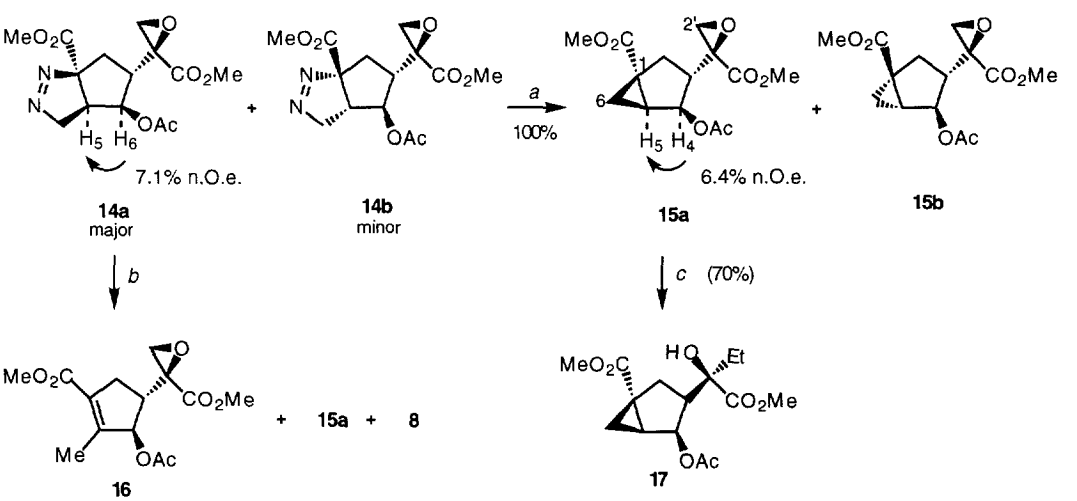
Cyclopropanation was then achieved through the 1,3-dipolar cycloaddition of diazomethane to the conjugated double bond in **9**. Thus, treatment of unsaturated ester **9** with an ether solution of this reagent, at room temperature for 3 hours furnished quantitatively pyrazoline **13** as a 3:1 mixture of diastereomers that could not been separated by crystallization or chromatographic techniques. To realize if the nature of the substituent at *C-1'* influenced the stereoselectivity of the cycloaddition, cyclopentene **11**[8] was prepared from **6**, in 55% overall yield. For this purpose, epoxide **6** was reacted with lithium dimethyl cuprate at -15 °C for

one hour followed by eliminaton of acetone and subsequent acetylation of the resultant secondary alcohol, as described above. Cyclopentene **11** was then reacted with diazomethane, in the same conditions as described for **9**, giving a mixture of pyrazolines **12** also in a 3:1 ratio of diastereomers.



Scheme 2: ***Reagents.*** *a: LDA b: Ac_2O, pyr c: (R)-α-methylbenzylamine d: CH_2N_2 e: Me_2CuLi*

Then, we tried an alternative route in which cyclopropanation and introduction of the amine followed the reverse order. Thus, epoxy cyclopentene **8** underwent reaction with diazomethane affording a 3:1 mixture of pyrazolines also in this case but, actually, column chromatography followed by crystallization gave pure **14a** as the major product and a minor **14b** enriched fraction (Scheme 3).



Scheme 3: ***Reagents.*** *a: hv, benzophenone, CH_2Cl_2 b: hv, toluene c: Me_2CuLi*

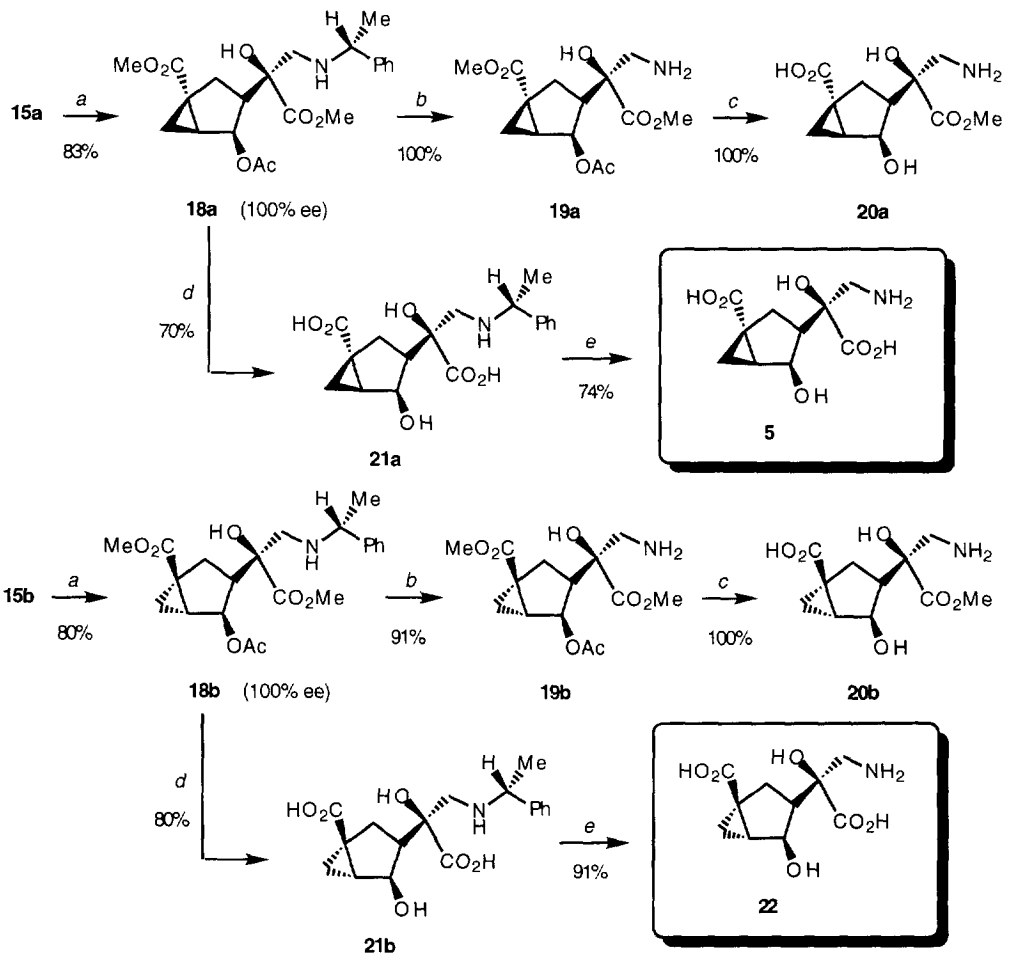
Stereochemistry was assigned on the basis of n.O.e. difference experiments, by considering the high significant enhancement (7.1%) obtained on H_5 when H_6 was selectively irradiated in **14a**. Since separation of the two diastereomers **14a** and **14b** was now feasible, we decide to explore the influence of the solvent used in the cycloaddition on the stereoselectivity. Therefore, cyclopentene **8** underwent reaction with diazomethane in different solvents, at room temperature for 3.5 hours. A 3:1 mixture of **14a/b** was quantitatively provided in either methanol, acetone, ethyl acetate, dichloromethane or ether. In chlorinated solvents, selectivity was increased with the number of chlorine atoms. Thus, a 5:1 mixture of **14a/b** was produced in 96% yield in chloroform, and these pyrazolines were obtained in a 6:1 ratio when carbon tetrachloride was used although in this case yield was lowered to 76%.

Photochemically promoted decomposition of **14a** was realized for the first time as a toluene solution contained in a Pyrex reactor, by irradiation with a 125 W medium-pressure mercury-lamp, at -78 °C for 70 minutes, affording the corresponding cyclopropane **15a** along with the insertion olefin **16** and enoate **8** (Scheme 3), this last compound proceding from cycloreversion of pyrazoline **14a**. The use of benzophenone as a photosensitizer as well as the solvent used was crucial to avoid the production of by-products and to improve the reaction yield. Thus, irradiation of a dichloromethane solution containing the mixture **14a/b**, in the presence of 0.5 equivalents of benzophenone, at -20 °C for 15 minutes, provided quantitatively a diastereomeric mixture of bicyclic compounds **15a** and **15b**, from which both isomers could be isolated by column chromatography. Minor isomer **15b**, although contaminated by some **15a** (both 80% ee), was also identified and characterized by its ^1H and ^{13}C-NMR spectral data. Stereochemistry of these compounds was also confirmed by NMR by considering the observed 6.4% n.O.e. on H_5 when H_4 was selectively irradiated in **15a** (Scheme 3).

Once the carbobicyclic framework had been assembled and the produced isomers had been separated and identified, we proceeded with the functionalization at the side-chain. Previously to this transformation, however, we used the reaction of major isomer **15a** with nucleophilic lithium dimethylcuprate to verify that the presence of the cyclopropane ring did not interfere in th S_N2-type process involved in the oxirane-ring opening. Tertiary alcohol **17** (Scheme 3) was obtained in 70% yield as in the case of treatment of epoxide **16** with this reagent, prior to the creation of the three-memberd ring (Scheme 1).

Then, the synthetic goals were achieved through the reaction of epoxides **15a** and **15b** with (*R*)-α-methylbenzylamine affording the enantio and diastereomerically pure amino hydroxy triesters **18a** and **18b** which were transformed to the target molecules **5** and **22**, respectively (Scheme 4). Epoxide **15a** was reacted with the homochiral amine to furnish enantiomerically pure **18a** (83% yield) as a dense oil that, once distilled, became a solid m.p. 40 °C (Scheme 4). Subsequently, a methanolic solution of benzylamine **18a** was hydrogenated under 3 atmospheres pressure in the presence of 10% palladium on charcoal as a catalyst, at room temperature for 4 hours, to yield quantitatively primary amine **19a** as a solid m.p. 119 °C, $[\alpha]_D$ +118.7. Treatment of this compound with 6N HCl and some drops of glacial acetic acid at room temperature overnight afforded chemoselectively compound **20a** (100% yield) showing that the α-hydroxy methyl ester was inert under these strongly acid hydrolysis conditions. The two methyl esters and acetate were hydrolyzed, however, by saponification of compound **18a** with 1N NaOH in methanol at 60°C for 1 hour affording diacid **21a** in 70% yield. Later hydrogenation in 1:1 methanol-water gave fully deprotected isoserine derivative **5** which was purified by elution through a C_{18}-reverse phase cartridge providing pure **5**, in 74% yield, as a solid m.p. 160 °C (dec), $[\alpha]_D$ +80.0.

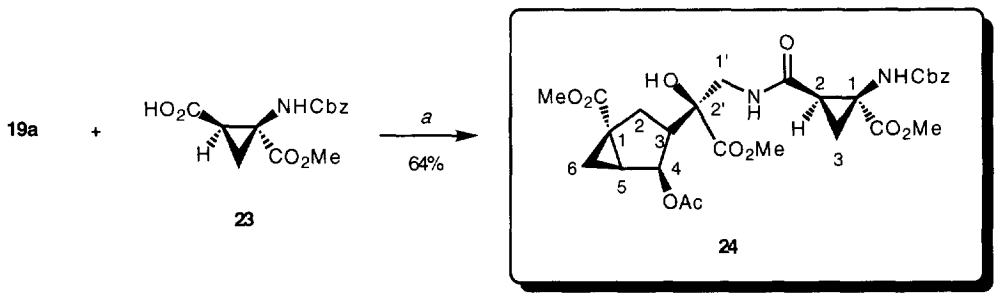
The same synthetic sequence was followed from diastereomeric epoxide **15b** to furnish dihydroxy amino diacid **22** (Scheme 4). Thus, enantiomerically pure **18b** was prepared by reaction of a diastereomeric mixture **15a/b** with (*R*)-α-methylbenzylamine. After separation of isomers by column chromatography, compound **18b** was obtained. Subsequent hydrogenation and acid hydrolysis provided methyl ester **20b** in 91% yield for the two steps. Alternatively, saponification of the three esters in **18b** gave **21b** which was hydrogenated to afford compound **22** (72% yield from **18b**). Purification as described above for **5** gave pure **22** as a solid m.p. 120 °C (dec), $[\alpha]_D$ -52.5.



Scheme 4: ***Reagents.*** *a: (R)-α-methylbenzylamine b: H_2, 3 atm, 10%Pd/C, MeOH c: 6N HCl, AcOH, d:1N NaOH, MeOH e: H_2, 3 atm, 10% Pd/C, 1:1 MeOH-H_2O*

The intermediate amines **19a** and **19b** are molecules suitably protected for incorporation in peptidomimetics, as also is the protein amino acid surrogate **23** (Scheme 5). Consequently, amine **19a** was condensed with Cbz-cyclo-Asp-OMe, **23**,[12] by using excess 1-(3-dimethylaminopropyl)-3-ethyl-carbodiimide as a dehydratation agent and 1 equivalent of 1-hydroxybenzotriazole (HOBT) as a catalyst, in anhydrous

DMF at room temperature for 2 days. After column chromatography of the crude, dipeptide **24** was obtained (64% yield) as a highly hygroscopic white solid which, after lyophilization, showed m.p. 87-88 °C and $[\alpha]_D$ +57.3.



Scheme 5: ***Reagents***. *a: 1-hydroxybenzotriazole, 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide*

CONCLUSIONS

Two diastereomeric conformationally constrained isoserine derivatives bearing a bulky bicyclic substituent at *C-2* position have been synthesized in enantiomerically pure form. These compounds contain several stereogenic centers and are densely functionalized, presenting interest due to their virtual biological properties, by themselves or incorporated in more complex structures. As a representative instance, condensation of one of these diastereomers with the protein methanolog Cbz-cyclo-Asp-OMe have efficiently been achieved to afford a highly rigid dipeptide surrogate. Biological evaluation of these molecules is in course.

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).

(3*S*,4*S*,1'*S*)-(+)-4-(1',2'-Epoxyethyl-1'-methoxycarbonyl)-3-hydroxycyclopent-1-ene-1-carboxylic acid methyl ester, 7. A 1.6 M solution of BuLi in hexane (921 mL, 2.2 eq) was added dropwise to a stirred solution of diisopropylamine (208 mL, 2.2 eq) in anhydrous THF (2 mL) at -78 °C under nitrogen atmosphere. After stirring for 10 min, a solution of **6** (200 mg, 0.67 mmol) in THF (3 mL) was added and the mixture was stirred at -78 °C for 4 h, then neutralized with saturated aqueous ammonium chloride (5 mL) and extracted with ethyl acetate (3x10 mL). The combined organic extracts were dried and the solvents were removed to afford a crude that was chromatographed (1:3 to 1:1 ethyl acetate-hexane) to afford allylic alcohol **7** (140 mg, 87% yield) and 10 mg of recovered **6**. Crystals, m.p. 70 °C dec. (from ether-pentane); $[\alpha]_D$ +75.5 (c=1.51, $CHCl_3$); IR (KBr) 3529 (broad), 1735, 1728, 1712, 1638 cm^{-1}; MS, m/e 242 (3, M), 227 (5, CH_3), 192 (29), 164 (40), 151 (41), 137 (61), 105 (42), 95 (31), 65 (31), 59 (100), 53 (40), 41 (30); 250-MHz ^1H NMR ($CDCl_3$) 1.77 (broad, 1H), 2.29 (ddt, J=16.3 Hz, J'=7.5 Hz, J''=J'''=2.2 Hz, 1H, H_5), 2.79-3.02 (complex abs., 2H, H_5 and H_4), 2.94 (d, J=5.5 Hz, 1H, $H_{2'}$), 3.09 (d, J=5.5 Hz, 1H, $H_{2'}$), 3.71 (s, 3H), 3.76 (s, 3H), 4.67 (ddd, J=8.4 Hz, J'=6.2 Hz, J''=2.2 Hz, 1H, H_3), 6.57 (dd, J=6.2 Hz, J'=2.2 Hz, 1H, H_2); 62.5-MHz ^{13}C NMR ($CDCl_3$) 32.3 (CH_2, C-5), 47.9 (CH, C-4), 50.1 (CH_2, C-2'), 51.7 (CH_3, OCH_3), 52.7 (CH_3, OCH_3), 56.3

(quaternary C-1'), 77.5 (CH, C-3), 135.4 (quaternary C-1), 142.5 (CH, C-2), 164.9 (C=O), 171.1 (C=O). Anal Calcd.for $C_{11}H_{14}O_6$: C, 54.54; H, 5.83. Found: C, 54.47; H, 5.86.

(3*S*,4*S*,1'*S*)-(+)-3-Acetyloxy-4-(1',2'-epoxyethyl-1'-methoxycarbonyl)cyclopent-1-ene-1-carboxylic acid methyl ester, 8. A mixture of alcohol **7** (1.47 g, 6.07 mmol), acetic anhydride (1.72 mL, 18.2 mmol), anhydrous pyridine (1.47 mL, 18.2 mmol) and dichloromethane (15 mL) was stirred at room temperature overnight. The solution was diluted with ethyl acetate (15 mL), 5% HCl was added (5 mL) and the layers were separated. The organic phase was successively washed with 5% HCl until acid pH. The aqueous layers were extracted with ethyl acetate (10 mL) and the combined organic phases were dried. After removal of solvents the residue was chromatographed (mixtures of ethyl acetate-hexane as eluent) to afford acetate **8** (1.67 g, 97% yield). Colorless oil, o.t. 170-175 °C (0.3 Torr); $[\alpha]_D$ +151.7 (c=3.23, $CHCl_3$); IR (film) 1736, 1645 cm^{-1}; MS, m/e 253 (3, M-31,-OCH_3), 242 (35, M-41, -$COCH_3$), 192 (61), 164 (50), 151 (40), 137 (40), 59 (28), 43 (100); 250-MHz ^1H NMR ($CDCl_3$) 1.92 (s, 3H), 2.39 (ddt, J=16.5 Hz, J'=6.9 Hz, J"=J'"=2.0 Hz, 1H, H_5), 2.76 (d, J=5.2 Hz, 1H, $H_{2'}$), 2.86 (ddt, J=16.5 Hz, J'=9.0 Hz, J"=J'"=2.0 Hz, 1H, H_5), 3.00 (m, 1H, H_4), 2.99 (d, J=5.2 Hz, 1H, $H_{2'}$), 3.61 (s, 3H), 3.64 (s, 3H), 5.45 (dt, J=4.0 Hz, J'=J"=2.0 Hz, 1H, H_3), 6.42 (dd, J=4.0 Hz, J'=2.0 Hz, 1H, H_2); 62.5-MHz ^{13}C NMR ($CDCl_3$) 20.6 (CH_3, $OCOCH_3$), 32.8 (CH_2, C-5), 44.1 (CH, C-4), 50.2 (CH_2, C-2'), 51.5 (CH_3, OCH_3), 52.4 (CH_3, OCH_3), 56.0 (quaternary C-1'), 78.4 (CH, C-3), 137.8 (quaternary C-1), 138.1 (CH, C-2), 164.1 (C=O), 169.6 (C=O), 170.1 (C=O). Anal. Calcd. for $C_{13}H_{16}O_7$: C, 54.93; H, 5.67. Found: C, 54.84; H, 5.70.

(3*S*,4*S*,1'*S*)-(+)-3-Acetyloxy-4-(1'-hydroxy-1'-methoxycarbonyl-1'-[(*R*)-α-methylbenzylaminomethyl]-methyl)cyclopent-1-ene-1-carboxylic acid methyl ester, 9. (*R*)-(+)-α-Methylbenzylamine (823 mL, 6.48 mmol) was added to a solution of epoxide **8** (306 mg, 1.08 mmol) in anhydrous DMF (3 mL) and the mixture was stirred at 60 °C for 24 h. The reaction mixture was partitioned between ethyl acetate (5 mL) and water (5 mL), the layers were separated and the organic phase were washed with water (3x5 mL). The combined aqueous washing layers were extracted with ethyl acetate (2x5 mL) and the combined organic phases were dried. Solvents were removed at reduced pressure and the crude was chromatographed (mixtures of ethyl acetate-hexane as eluent) to give amine **9** (321 mg, 73% yield) and 20 mg of recovered **8.** Compound **9** is a colorless oil that decomposed when distilled; $[\alpha]_D$ +133.8 (c=1.39, $CHCl_3$); IR (film) 3700-3200, 1743, 1736, 1721 cm^{-1}; MS, m/e 346 (2, M-59), 330 (100, M-164), 280 (9), 257 (7), 240 (5), 182 (5), 151 (9), 118 (9), 105 (71), 91 (12), 79 (17), 77 (13), 59 (9); 250-MHz ^1H NMR ($CDCl_3$) 1.23 (d, J=6.6 Hz, 3H), 1.82 (s, 3H, $OCOCH_3$), 2.35 (ddt, J=8.0 Hz, J'=4.1 Hz, J"=J'"=2.0 Hz, 1H, H_5), 2.50 (ddt, J=8.0 Hz, J'=4.9 Hz, J"=J'"=2.0 Hz, 1H, H_5), 2.52 (d, J=12.3 Hz, 1H, $H_{2'}$), 2.64 (m, 1H, H_4), 2.74 (d, J=12.3 Hz, $H_{2'}$), 3.61 (q, J=J'=J"=6.6 Hz, 1H), 3.65 (s, 3H), 3.73 (s, 3H), 5.60 (ddd, J=6.0 Hz, J'=4.1 Hz, J"=2.0 Hz, 1H, H_3), 6.46 (dd, J=4.1 Hz, J'=2.0 Hz, 1H, H_2), 7.20 (complex abs., 5H); 62.5-MHz ^{13}C NMR ($CDCl_3$) 20.6 (CH_3, $OCOCH_3$), 23.7 (CH_3), 31.0 (CH_2, C-5), 49.0 (CH, C-4), 51.6 (CH), 52.2 (CH_2, C-2'), 52.7 (CH_3, OCH_3), 57.8 (CH_3, OCH_3), 77.2 (quaternary C-1'), 79.4 (CH, C-3), 126.2 (aromatic CH), 126.9 (aromatic CH), 128.4 (aromatic CH), 137.9 (aromatic C_{ipso}), 138.7 (CH, C-2), 144.9 (quaternary C-1), 164.5 (C=O), 170.0 (C=O), 175.2 (C=O). Anal. Calcd. for $C_{21}H_{27}NO_7$: C, 62.21; H, 6.71; N, 3.45. Found: C, 62.21; H, 6.80; N, 3.24.

(3*S*,4*S*,1'*R*)-(+)-3-Acetyloxy-4-(1'-ethyl-1'-hydroxy-1'-methoxycarbonylmethyl)cyclopent-1-ene-1-carboxylic acid methyl ester, 11. The previously known alcohol **10**[8b] was reacted as described above for acetylation of **7** giving acetate **11** (180 mg, 91% yield). Colorless oil, o.t. 180-185 °C (0.5 Torr); $[\alpha]_D$ +132.2 (c=1.77, $CHCl_3$); IR (film) 3700-3300 (broad band), 1736, 1642 cm^{-1}; MS, m/e 269 (2, M-31), 241 (2, M-59), 181 (21), 149 (22), 141 (37), 125 (69), 124 (80), 118 (40), 93 (49), 65 (41), 59 (31), 57 (100), 43 (37);

250-MHz ^{1}H NMR ($CDCl_3$) 0.78 (t, J=7.3 Hz, 3H, H3'), 1.70 (complex absorption, 2H, H_2'), 2.01 (s, 3H), 2.36 (ddt, J=16.3 Hz, J'=7.0 Hz, J"=J'"=2.0 Hz, 1H, H_5), 2.57 (ddt, J=16.3 Hz, J'=8.9 Hz, J"=J'"=2.0 Hz, 1H, H_5), 2.75 (m, 1H, H_4), 3.69 (s, 3H), 3.75 (s, 3H), 5.90 (ddd, J=7.8 Hz, J'=4.0 Hz, J"=2.0 Hz, 1H, H_3), 6.53 (dd, J=4.0 Hz, J'=2.0 Hz, 1H, H_2); 62.5-MHz ^{13}C NMR ($CDCl_3$) 7.9 (CH_3, C-3'), 21.0 (CH_3, $OCOCH_3$), 30.2 (CH_2, C-2'), 31.4 (CH_2, C-5), 50.6 (CH_3, OCH_3), 51.7 (CH, C-4), 52.9 (CH_3, OCH_3), 77.8 (quaternary C-1'), 79.7 (CH, C-3), 138.2 (CH, C-2), 138.7 (quaternary C-1), 164.6 (C=O), 170.2 (C=O), 175.8 (C=O). Anal. Calcd. for $C_{14}H_{20}O_7$: C, 55.99; H, 6.71. Found: C, 56.01; H, 6.83

Reactions of cyclopentenes 9 and 11, respectively, with diazomethane. A typical experiment was run as follows. To a stirred and ice-cooled solution of cyclopentene **9** (100 mg, 0.25 mmol) in ether (10 mL) a freshly distilled ethereal solution of excess diazomethane (generated from *N*-methyl-*N*-nitroso-*p*-toluenesulphonamide (2.1 g, 10.0 mmol) and KOH (0.4 g, 7.1 mmol) was added. The mixture was stirred at r. t. for 3 h. Then, excess reagent and solvent were removed and the residue was chromatographed (1:1 ethyl acetate-hexane) to afford quantitatively 108 mg of solid pyrazoline **13** as a 3:1 mixture of diastereomers, ratio being determined by ^{1}H-NMR by integration of the signals at 5.17 and 5.35 ppm corresponding to H_4 in the major and the minor diastereomer, respectively. Neither chromatography nor recrystallization allowed the separation of both diastereomers.

In a similar manner, cyclopentene **11** was reacted with diazomethane to afford a 3:1 diastereomeric mixture of pyrazolines **12**.

Reaction of cyclopentene 8 with diazomethane: Pyrazolines 14a and 14b. Cyclopentene **8** was reacted with diazomethane as described above for **9** and **11**, giving quantitatively a 3:1 solid mixture of diastereomers **14a** and **14b** (1.25 g). Column chromatography allowed the obtention of pure **14a** (860 mg, 70% yield) and 600 mg of **14b** enriched fractions.

(1*S*,5*S*,6*S*,7*S*,1'*S*)-(+)-6-Acetyloxy-2,3-diaza-7-(1',2'-epoxyethyl-1'-methoxycarbonyl)-1-methoxycarbonylbicyclo[3.3.0]oct-2-ene, 14a: Crystals, m.p. 115 °C dec. (from ethyl acetate-pentane); $[\alpha]_D$ +229.5 (c=1.54, $CHCl_3$); IR (KBr) 1754, 1733 cm^{-1}; MS, m/e 327 (2, M+1), 267 (1, M-59), 206 (22), 178 (27), 165 (24), 119 (21), 91 (23), 59 (27), 43 (100); 250-MHz ^{1}H NMR (acetone d_6) 2.00 (s, 3H), 2.06 (m, 1H, H_7), 2.29 (dd, J=J'=13.7 Hz, 1H, H_8), 2.54 (dd, J=13.7 Hz, J'=6.8 Hz, 1H, H_8), 2.78 (d, J=5.3 Hz, 1H, H_2'), 2.94 (d, J=5.3 Hz, 1H, H_2'), 3.04 (ddd, J=J'=9.3 Hz, J"=3.1 Hz, 1H, H_5), 3.64 (s, 3H), 3.65 (s, 3H), 4.44 (dd, J=18.8 Hz, J'=9.3 Hz, 1H, H_4), 4.60 (dd, J=10.5 Hz, J'=9.3 Hz, 1H, H_6), 4.78 (dd, J=18.8 Hz, J'=3.1 Hz, 1H, H_4); 62.5-MHz ^{13}C NMR (acetone d_6) 20.7 (CH_3, $OCOCH_3$), 32.0 (CH_2, C-8), 40.8 (CH), 40.9 (CH), 51.7 (CH_2, C-2'), 52.8 (CH_3, OCH_3), 53.1 (CH_3, OCH_3), 55.9 (quaternary C-1'), 73.7 (CH, C-6), 80.5 (CH_2, C-4), 103.6 (quaternary C-1), 169.5 (C=O), 170.4 (C=O), 170.4 (C=O). Anal. Calcd. for $C_{14}H_{18}N_2O_7$: C, 51.53; H, 5.56; N, 8.58. Found: C, 51.60; H, 5.57; N, 8.54.

Photochemical decomposition of pyrazoline 14a: (1*R*,3*S*,4*S*,5*S*,1'*S*)-(+)-4-Acetyloxy-3-(1',2'-epoxy-ethyl-1'-methoxycarbonyl)-1-methoxycarbonylbicyclo[3.1.0]hexane, 15a, and (3*S*,4*S*,1'*S*)-(+)-3-acetyloxy-4-(1',2'-epoxyethyl-1'-methoxycarbonyl)-2-methylcyclopent-1-ene-1-carboxylic acid methyl ester, 16.

Method A. A stirred solution of pyrazoline **14a** (100 mg, 0.1 mmol) and benzophenone (28 mg, 0.15 mmol) in dry dichloromethane (25 mL) contained in a Pyrex reactor under nitrogen atmosphere, cooled at -20 °C, was irradiated with a 125 W medium pressure mercury-lamp for 15 min. Solvent was removed and the residue was chromatographed (mixtures of ethyl-acetate-hexane as eluent) to give quantitatively bicyclic compound **15a** (92 mg). Colorless oil, o.t. 175-180°C (0.4 Torr); $[\alpha]_D$ +135.4 (c=1.30, $CHCl_3$); IR (film) 1736 cm^{-1}; MS, m/e 267 (1, M-31), 239 (1, M-59), 189 (14), 178 (10), 137 (15), 119 (12), 105 (12), 91 (21),

79 (11), 77 (16), 59 (22), 43 (100); 250-MHz ^{1}H NMR ($CDCl_3$) 1.15 (dd, J=J'=5.1 Hz, 1H, H_{6a}), 1.35 (dd, J=8.4 Hz, J'=5,1 Hz, 1H, H_{6b}), 2.01 (s, 3H, $OCOCH_3$), 2.22 (complex absorption, 2H, H_{2a} and H_{2b}), 2.28 (ddd, J=8.6 Hz, J'=8.4 Hz, J''=5.1 Hz, 1H, H_5), 2.55 (m, H_3), 2.67 (d, J=5.3 Hz, 1H, $H_{2'a}$), 3.01 (d, J=5.3 Hz, 1H, $H_{2'b}$), 3.62 (s, 3H), 3.72 (s, 3H, OCH_3), 4.86 (dd, J=8.6 Hz, J'=4.6 Hz, 1H, H_4); 62.5-MHz ^{13}C NMR ($CDCl_3$) 14.8 (CH_2, C-6), 20.9 (CH_3, $OCOCH_3$), 27.9 (CH_2, C-2), 28.5 (quaternary C-1), 29.6 (CH), 38.7 (CH), 51.1 (CH_2, C-2'), 51.8 (CH_3, OCH_3), 52.6 (CH_3, OCH_3), 56.0 (quaternary C-1'), 73.4 (CH, C-4), 170.0 (C=O), 170.5 (C=O), 173.0 (C=O). Anal. Calcd. for $C_{14}H_{18}O_7$: C, 56.37; H, 6.08. Found: C, 56.09; H, 6.17.

Method B. A stirred solution of pyrazoline **14a** (140 mg, 0.43 mmol) in anhydrous toluene (40 mL) contained in a Pyrex reactor under nitrogen atmosphere, cooled at -78°C, was irradiated with a 125 W medium-pressure mercury-lamp for 70 min until complete disappearance of starting **14a** as monitored by UV (322 nm) and TLC. Solvent was removed and the residue was chromatographed (mixtures of ethyl acetate-hexane as eluyent) to afford, in order of elution, the methylene-insertion cyclopentene **16** (9 mg), a 1:1:2 mixture (50 mg) containing **16**, the cycloreversion product **8**, and bicyclic **15a** (determined by ^{1}H-NMR), and a 1:4 mixture (70 mg) of **8** and **15a**. Compound **16** is a pale yellow oil, $[\alpha]_D$ +143.3 (c=0.34, $CHCl_3$); IR (film) 1736, 1721, 1659 cm^{-1}; MS, m/e 267 (3, M-31), 238 (2, M-59), 224 (16), 206 (79), 179 (25), 178 (52), 165 (41), 163 (20), 147 (18), 135 (16), 119 (24), 91 (25), 79 (21), 77 (25), 59 (30), 43 (100); 250-MHz ^{1}H NMR ($CDCl_3$) 1.95 (s, 3H), 2.09 (s, 3H), 2.52 (ddt, J=12.4 Hz, J'=4.8 Hz, J''=J'''=2.4 Hz, 1H, H_5), 2.91 (d, J=5.2 Hz, 1H, $H_{2'}$), 2.99 (complex absorption, 2H, H_5 and H_4), 3.06 (d, J=5.2 Hz, 1H, $H_{2'}$), 3.73 (s, 3H), 3.76 (s, 3H), 5.63 (dd, J=J'=2.4 Hz, 1H, H_3); 62.5-MHz ^{13}C NMR ($CDCl_3$) 13.0 (CH_3), 20.9 (CH_3, -$OCOCH_3$), 33.7 (CH_2, C-5), 43.0 (CH, C-4), 50.6 (CH_2, C-2'), 51.3 (CH_3, OCH_3), 52.7 (CH_3, OCH_3), 56.4 (quaternary C-1'), 81.0 (CH, C-3), 126.7 (quaternary C-1), 149.9 (quaternary C-2), 165.3 (C=O), 170.1 (C=O), 170.5 (C=O) Anal. Calcd. for $C_{14}H_{18}O_7$: C, 56.37; H, 6.08. Found: C, 56.47; H, 6.21.

(1*R*,3*S*,4*S*,5*S*,1'*R*)-4-Acetyloxy-3-(1'-ethyl-1'-hydroxy-1'-methoxycarbonylmethyl)-1-methoxycarbonylbicyclo[3.1.0]-hexane, 17. A 1.6 M solution of MeLi (1.75 mL, 2.8 mmol) was added to a stirred suspension of CuI (267 mg, 1.4 mmol) in anhydrous ether (5 mL), at -15 °C under argon atmosphere. After stirring for 20 min, a solution of epoxide **15a** (210 mg, 0.7 mmol) in anhydrous ether (5 mL) was added dropwise and the mixture was stirred at -15 °C for 10 min. Then, saturated aqueous ammonium chloride (5 mL) was added and the resulting mixture was stirred at r.t. for 15 min. The layers were separated and the aqueous phase was extracted with ethyl acetate (3x5 mL). The combined organic phases were dried, the solvents were removed, and the residue was chromatographed (mixtures of ethyl acetate-hexane as eluent) to afford alcohol **17** (170 mg, 77% yield) as a colorless oil that became solid on distillation at o.t. 150-155°C (0.3 Torr); m.p. 50°C dec; $[\alpha]_D$ +129.5 (c=1.80, $CHCl_3$); IR (film) 3600-3300 (broad), 1736 cm^{-1}; MS, m/e 283 (2, M-31), 255 (8, M-59), 254 (24), 195 (31), 163 (22), 139 (43), 137 (36), 118 (32), 105 (36), 79 (26), 57 (100), 43 (60); 250-MHz ^{1}H NMR ($CDCl_3$) 0.74 (t, J=J'=7.4 Hz, 1H, $H_{3'}$), 1.04 (dd, J=J'=4.9 Hz, 1H, H_{6a}), 1.30 (dd, J=8.4 Hz, J'=4.9 Hz, 1H, H_{6b}), 1.60 (m, 2H), 1.68 (m, 1H), 2.03 (s, 3H, $OCOCH_3$), 2.14 (m, 1H), 2.39 (ddd, J=9.7 Hz, J'=8.4 Hz, J''=4.9 Hz, 1H), 3.28 (s, 1H), 3.62 (s, 3H), 3.76 (s, 3H), 5.34 (dd, J=7.3 Hz, J'=5.3 Hz, 1H, H_4); 62.5-MHz ^{13}C NMR ($CDCl_3$) 8.0 (CH_3, C-3'), 15.2 (CH_2, C-6), 21.1 (CH_3, $OCOCH_3$), 26.4 (CH_2, C-2), 28.9 (quaternary C-1), 29.9 (CH_2, C-2'), 30.7 (CH), 45.9 (CH), 51.8 (CH_3, OCH_3), 52.8 (CH_3, OCH_3), 75.0 (CH, C-4), 77.2 (quaternary C-1'), 170.4 (C=O), 173.4 (C=O), 175.8 (C=O). Anal. Calcd. for $C_{15}H_{22}O_7$: C, 57.32; H, 7.05. Found: C, 57.07; H, 7.04.

(1*R*,3*S*,4*S*,5*S*,1'*S*)-(+)-4-Acetyloxy-3-(1'-hydroxy-1'-methoxycarbonyl-1'-[(*R*)-α-methylbenzylamino-methyl]methyl)-1-methoxycarbonylbicyclo[3.1.0]hexane, 18a. A solution of epoxide **15a** (80% ee) (570 mg, 1.91 mmol) and (*R*)-α-methylbenzylamine (1.48 mL, 11.5 mmol) in anhydrous DMF was stirred at 60 °C for 24 h. Ethyl acetate (10 mL) and water (10 mL) were added and the layers were separated. The organic phase was washed with water (3x10 mL) and the combined aqueous phases were extracted with ethyl acetate (2x5 mL). The combined organic extracts were dried and solvents were removed at reduced pressure. The residue was chromatographed (mixtures of ethyl acetate-hexane as eluent) to afford enantio and diastereomerically pure amine **18a** (662 mg, 83% yield) and 94 mg of mixture of diastereomers. Compound **18a** is a colorless oil that became solid on distillation at o.t. 210-215°C (0.05 Torr); m.p. 40°C dec; $[\alpha]_D$ +126.0 (c=1.23, $CHCl_3$); IR (KBr) 3650-3370, 1736 cm^{-1}; MS, m/e 239 (3, M-180, -NHR-$OCOCH_3$), 189 (9), 178 (6), 137 (8), 119 (7), 105 (10), 91 (13), 77 (11), 59 (20), 43 (100); 250-MHz ^1H NMR ($CDCl_3$) 0.99 (dd, J=J'=5.0 Hz, 1H, H_{6a}), 1.22 (dd, J=7.5 Hz, J'=5.0 Hz, 1H, H_{6b}), 1.25 (d, J=6.6 Hz, 3H, CH_3), 1.67 (dd, J=12.2 Hz, J'=7.5 Hz, 1H, H_2), 1.72 (s, 3H, $OCOCH_3$), 2.01 (ddd, J=J'=10.8 Hz, J"=8.0 Hz, 1H, H_5), 2.18 (m, 1H), 2.30 (ddd, J=7.5 Hz, J'=5.0 Hz, J"=3.5 Hz, 1H, H_3), 2.48 (d, J=12.3 Hz, 1H, $H_{2'}$), 2.60 (d, J=12.3 Hz, $H_{2'}$), 3.59 (s, 3H), 3.61 (q, J=J'=J"=6.6 Hz, 1H), 3.77 (s, 3H), 5.16 (dd, J=8.0 Hz, J'=5.0 Hz, 1H, H_4), 7.13-7.30 (complex absorption, 5H); 62.5-MHz ^{13}C NMR ($CDCl_3$) 15.0 (CH_2, C-6), 20.8 (CH_3, $OCOCH_3$), 23.9 (CH_3), 25.9 (CH_2, C-2), 28.9 (quaternary C-1), 30.4 (CH, C-5), 44.1 (CH, C-3), 51.9 (CH_3, OCH_3), 52.1 (CH_2, C-2'), 52.9 (CH_3, OCH_3), 58.1 (CH), 74.7 (quaternary C-4), 77.1 (quaternary C-1'), 126.3 (aromatic CH), 127.0 (aromatic CH), 128.5 (aromatic CH), 145.0 (aromatic C_{ipso}), 170.2 (C=O), 173.4 (C=O), 175.5 (C=O). Anal. Calcd. for $C_{22}H_{29}NO_7$: C, 62.99; H, 6.97; N, 3.34. Found: C, 62.97; H, 7.05; N, 3.36

(1*S*,3*S*,4*S*,5*R*,1'*S*)-(+)-4-Acetyloxy-3-(1'-hydroxy-1'-methoxycarbonyl-1'-[(*R*)-α-methylbenzylamino-methyl]methyl)-1-methoxycarbonylbicyclo[3.1.0]hexane, 18b, through epoxide 15b. A mixture of pyrazolines **14a/b** (245 mg, 0.75 mmol) were decomposed photochemically as described above (*Method A*) affording quantitatively 202 mg of diastereomers **15a/b**. Column chromatography (mixtures of ethyl acetate-hexane as eluent) allowed the obtention of a **15b** enriched fraction, which was identified by its NMR spectral data. 250-MHz ^1H NMR ($CDCl_3$) 1.04 (dd, J=J'=5.1 Hz, 1H, H_6), 1.47 (ddd, J=9.6 Hz, J'=5.1 Hz, J"= 1.7 Hz, 1H, H_6), 1.69 (dd, J=14.1 Hz, J'=5.1 Hz, 1H, H_{2b}), 1.92 (dd, J=9.6 Hz, J'=5.1 Hz, 1H, H_5), 1.98 (s, 3H, $OCOCH_3$), 2.86 (d, J=5.1 Hz, 1H, $H_{2'}$), 2.97 (ddd, J=14.1 Hz, J'=11.5 Hz, J"=1.7 Hz, 1H, H_{2a}), 3.13 (d, J=5.1 Hz, 1H, $H_{2'}$), 3.24 (ddd, J=11.5 Hz, J'=5.1 Hz, J"=2.9 Hz, 1H, H_3), 3.61 (s, 3H), 3.68 (s, 3H), 4.56 (d, J=2.9 Hz, 1H, H_4); 62.5-MHz ^{13}C NMR ($CDCl_3$) 18.9 (CH_2, C-6), 21.0 (CH_3, -$OCOCH_3$), 31.5 (CH_2, C-2), 31.8 (quaternary C-1), 34.8 (CH), 47.4 (CH), 50.1 (CH_2, C-2'), 51.8 (CH_3, OCH_3), 52.9 (CH_3, OCH_3), 57.5 (quaternary C-1'), 75.9 (CH, C-4), 169.9 (C=O), 170.3 (C=O), 173.4 (C=O).

The mixture of epoxides **15a/b** was reacted with (*R*)-α-methylbenzylamine as described above for pure **15a**. Column chromatography afforded pure **18b** (62 mg) and 178 mg of a mixture containing all possible diastereomers (80% total yield). Compound **18b** is a colorless il, o.t. 140-145°C (0.1 Torr); $[\alpha]_D$ +24.0 (c=1.00, $CHCl_3$); IR (film) 3700-3300, 1729 cm^{-1}; MS, m/e 388 (1, M-31), 360 (1, M-59), 344 (3), 256 (2), 205 (13), 199 (13), 134 (58), 106 (12), 105 (100), 79 (12), 77 (11), 57 (12), 43 (36); 250-MHz ^1H NMR ($CDCl_3$) 1.17 (dd, J=J'=5.1 Hz, 1H, H_6), 1.24 (m, 1H, H_{2b}), 1.26 (d, J=6.6 Hz, 3H, CH_3), 1.47 (ddd, J=13.1 Hz, J'=6.9 Hz, J"=3.3 Hz, 1H, H_6), 1.54 (broad s., 1H), 1.87 (dd, J=5.0 Hz, J'=3.3 Hz, 1H, H_5), 1.92 (s, 3H), 2.51 (d, J=12.4 Hz, 1H, $H_{2'}$), 2.61 (ddd, J=13.1 Hz, J'=11.6 Hz, J"=3.3 Hz, 1H, H_{2a}), 2.70 (d, J=12.4 Hz, 1H, $H_{2'}$), 2.81 (ddd, J=11.6 Hz, J'=6.9 Hz, J"=5.0 Hz, 1H, H_3), 3.60 (s, 3H), 3.74 (q, J=J'=J"=6.6 Hz, 1H),

3.76 (s, 3H), 4.92 (d, J=5.0 Hz, 1H, H4), 7.10-7.30 (complex absorption, 5H); 62.5-MHz ^{13}C NMR ($CDCl_3$) 20.1 (CH_2, C-6), 20.9 (CH_3, $OCOCH_3$), 23.7 (CH_3), 28.9 (CH_2, C-2), 32.5 (quaternary C-1), 36.2 (CH), 51.7 (CH_3, OCH_3), 52.6 (CH_2, C-2'), 54.6 (CH_3, OCH_3), 57.7 (CH), 77.1 (quaternary C-1'), 77.6 (CH, C-4), 126.2 (aromatic CH), 127.0 (aromatic CH), 128.4 aromatic CH), 144.8 (aromatic C_{ipso}), 170.0 (C=O), 173.8 (C=O), 175.4 (C=O). Anal. Calcd. for $C_{22}H_{29}NO_7$: C, 62.99; H, 6.97; N, 3.34. Found: C, 62.87; H, 7.00; N, 3.40.

Hydrogenation of benzylamines 18a and 18b: (1*R*,3*S*,4*S*,5*S*,1'*S*)-(+)- and (1*S*,3*S*,4*S*,5*R*,1'*S*)-(-)-4-Acetyloxy-3-[1'-aminomethyl-1'-hydroxy-1'-methoxycarbonylmethyl]-1-methoxycarbonylbicyclo-[3.1.0]hexane, 19a and 19b, respectively. A solution of benzylamine **18a** (130 mg, 0.31 mmol) in MeOH (10 mL) was hydrogenated, at 3 atmospheres pressure, in the presence of 10% Pd/C (58 mg) at r.t. for 4 h. Catalyst was removed by filtration through celite and washed with methanol. Solvent was removed from the filtrate to afford quantitatively solid **19a** (97 mg). In the same way, diastereomeric primary amine **19b** was obtained (55 mg, 91% yield) from **18b** (80 mg, 019 mmol).

Amine 19a: Crystals, m.p. 178°C dec (from MeOH-ether); $[\alpha]_D$ +118.7 (c=1.55, MeOH); IR (KBr) 3450, 1736, 1729 cm^{-1}; MS, m/e 316 (8, M+1), 315 (1, M), 226 (67, M-89), 196 (26), 194 (39), 166 (26), 134 (28), 107 (30), 106 (22), 79 (48), 77 (27), 59 (30), 43 (100); 250-MHz ^{1}H NMR (methanol d4) 1.28 (dd, J=J'=5.2 Hz, 1H, H_{6a}), 1.39 (dd, J=8.4 Hz, J'=5.3 Hz, 1H, H_{6b}), 1.89 (ddd, J=14.0 Hz, J'=11.8 Hz, J''=8.4 Hz, 1H, H_2), 2.15 (s, 3H, $OCOCH_3$), 2.36 (complex absorption, 2H, H_2 and H_3), 2.43 (ddd, J=9.8 Hz, J'=J''=4.9 Hz, 1H, H_5), 3.15 (d, J=13.2 Hz, 1H, $H_{2'}$), 3.37 (d, J= 13.2 Hz, 1H, $H_{2'}$), 3.74 (s, 3H), 3.92 (s, 3H), 5.38 (dd, J=8.4 Hz, J'=4.9 Hz, 1H, H4); 62.5-MHz ^{13}C NMR (methanol d4) 15.5 (CH_2, C-6), 21.1 (CH_3, -$OCOCH_3$), 26.9 (CH_2, C-2), 29.9 (quaternary C-1), 31.4 (CH, C-5), 45.2 (CH_2, C-2'), 45.9 (CH, C-3), 52.6 (CH_3, OCH_3), 53.9 (CH_3, OCH_3), 75.8 (CH, C-4), 75.8 (quaternary C-1'), 172.2 (C=O), 173.4 (C=O), 174.8 (C=O). Anal. Calcd. for $C_{14}H_{21}NO_7$: C, 53.33; H, 6.71; N, 4.44. Found: C, 53.11; H, 6.87; N, 4.28.

Compound 19b: Crystals, m.p. 83°C dec (from MeOH-ether); $[\alpha]_D$ -22.9 (c=1.40, MeOH); IR (KBr) 3700-3300 (broad), 1736 cm^{-1}; MS, m/e 316 (8, M+1), 256 (13, M-59), 227 (11), 226 (73, M-89), 196 (24), 194 (55), 166 (32), 134 (33), 127 (24), 107 (34), 106 (22), 79 (42), 77 (24), 59 (27), 44 (27), 43 (100); 250-MHz ^{1}H NMR (methanol d4) 1.22 (dd, J=J'=5.1 Hz, 1H, H_{6a}), 1.65 (complex absorption, 2H, H_{6b} and H_{2b}), 2.06 (dd, J=9.7 Hz, J'=5.1 Hz, 1H, H5), 2.16 (s, 3H, $OCOCH_3$), 2.79 (ddd, J=13.5 Hz, J'=11.9 Hz, J''=1.7 Hz, 1H, H_{2a}), 3.05 (ddd, J=11.9 Hz, J'=7.5 Hz, J''=4.6 Hz 1H, H_3), 3.16 (d, J= 13.4 Hz, 1H, $H_{2'}$), 3.37 (d, J= 13.4 Hz, 1H, $H_{2'}$), 3.40 (s, 3H), 3.73 (s, 3H), 3.92 (s, 3H), 5.14 (d, J=4.6 Hz, 1H, H4); 62.5-MHz ^{13}C NMR (methanol d4) 20.7 (CH_2, C-6), 21.0 (CH_3, -$OCOCH_3$), 29.7 (CH_2, C-2), 33.6 (quaternary C-1), 37.3 (CH, C-5/C-3), 47.8 (CH_2, C-2'), 52.5 (CH, C-3/C-5), 53.4 (CH_3, OCH_3), 56.5 (CH_3, OCH_3), 78.4 (quaternary C-1'), 78.5 (CH, C-4), 172.0 (C=O), 174.8 (C=O), 175.1 (C=O). Anal. Calcd. for $C_{14}H_{21}NO_7$: C, 53.33; H, 6.71; N, 4.44. Found: C, 53.18; H, 6.80; N, 4.21.

Acid hydrolysis of triesters 19a and 19b: (1*R*,3*S*,4*S*,5*S*,1'*S*)-(+)- and (1*S*,3*S*,4*S*,5*R*,1'*S*)-(-)-4-Hydroxy-3-(1'-aminomethyl-1'-hydroxy-1'-methoxycarbonylmethyl)bicyclo[3.1.0]hexane-1-carboxylic acid, 20a and 20b, respectively. A mixture containing triester **19a** (80 mg, 0.25 mmol), 6 N HCl (3 mL), and some drops of glacial acetic acid was stirred at r.t. overnight. The mixture was evaporated to dryness and the obtained residue was poured into ethanol (1 mL) and then propylene oxide (some drops) was added. The white solid produced underwent the same repeated treatment to assure the total elimination of acid and then

was eluted with water through a C_{18}-reverse phase cartridge to afford quantitatively **20a** (65 mg) . Following the same procedure from **19b** (75 mg, 0.24 mmol), diastereomeric **20b** was quantitatively obtained (61 mg).

Compound 20a: Solid unable to be crystallized, m.p. 120°C dec.; $[\alpha]_D$ +78.5 (c=1.35, H_2O); IR (KBr) 3700-2350 (broad), 1739, 1706, 1623 cm^{-1}; MS, m/e 259 (1, M), 226 (58), 212 (83, -CH_2NH_2-OH), 194 (98), 166 (51), 134 (55), 127 (52), 107 (54), 106 (47), 79 (100), 77 (46), 59 (44), 55 (46), 50 (84), 45 (59), 44 (70), 43 (50); 250-MHz ^1H NMR (D_2O) 1.12 (m, 1H, H_{6a}), 1.20 (m, 1H, H_{6b}), 1.66 (m, 1H, H_2), 1.83-1.99 (complex absorption, 2H, H_2 and H_3), 2.03 (m, 1H, H_5), 3.26 (d, J=13.5 Hz, 1H, $H_{2'}$), 3.37 (d, J= 13.5 Hz, 1H, $H_{2'}$), 3.70 (s, 3H), 4.39 (m, 1H, H_4); 62.5-MHz ^{13}C NMR (D_2O) 15.1 (CH_2, C-6), 26.8 (CH_2, C-2), 28.4 (quaternary C-1), 33.0 (CH, C-5), 44.6 (CH_2, C-2'), 47.3 (CH, C-3), 54.3 (CH_3, OCH_3), 71.5 (CH, C-4), 75.5 (quaternary C-1'), 174.2 (C=O ester), 177.1 (C=O acid).

Compound 20b: Amorphous solid, m.p. 165°C dec; $[\alpha]_D$ -50.0 (c=0.56, H_2O); IR (KBr) 3700-3200 (broad), 1736, 1701, 1609 cm^{-1}; MS, m/e 259 (1, M), 226 (46), 212 (78, -CH_2NH_2-OH), 196 (86), 166 (50), 134 (51), 107 (45), 106 (40), 79 (100), 77 (45), 59 (43), 44 (86), 43 (50); 250-MHz ^1H NMR (D_2O) 0.74 (dd, J=J'=4.8 Hz, 1H, H_6), 1.30 (dd, J=13.4 Hz, J'=9.5 Hz, 1H, H_{2b}), 1.47 (dd, J=9.5 Hz, J'=4.8 Hz, 1H, H_6), 1.86 (dd, J=9.2 Hz, J'=5.4 Hz, 1H, H_5), 2.40 (dd, J=J'=13.4 Hz, 1H, H_{2a}), 2.61 (ddd, J=13.4 Hz, J'=9.5 Hz, J"=5.8 Hz, 1H, H_3), 3.11 (d, J=13.3 Hz, 1H, $H_{2'}$), 3.25 (d, J= 13.3 Hz, 1H, $H_{2'}$), 3.66 (s, 3H), 3.97 (d, J=5.8 Hz, 1H, H_4); 62.5-MHz ^{13}C NMR (D_2O) 24.0 (CH_2, C-6), 29.3 (CH_2, C-2), 33.4 (quaternary C-1), 39.3 (CH, C-5/C-3), 45.3 (CH_2, C-2'), 54.7 (CH_3, OCH_3), 60.0 (CH, C-3/C-5), 75.7 (CH, C-4), 76.2 (quaternary C-1'), 174.4 (C=O ester), 179.8 (C=O acid).

Saponification of triesters 18a and 18b: (1*R*,3*S*,4*S*,5*S*,1'*S*)-(+)- and (1*S*,3*S*,4*S*,5*R*,1'*S*)-(-)-3-(1'-Carboxy-1'-hydroxy-1'-[(*R*)-α-methylbenzylaminomethyl]methyl)-4-hydroxybiciclo[3.1.0]hexane-1-carboxylic acid, 21a and 21b, respectively. A mixture containing triester **18a** (145 mg, 0.35 mol), 1N NaOH (3.5 mL, 3.5 mmol), and methanol (2 mL) was stirred at 60 °C for 1 h. The solution was concentrated at reduced pressure, acidified with 5% HCl and extracted many times with ethyl acetate. The combined organic extracts were dried and solvent was removed to afford solid **21a** (85 mg, 70% yield). In a similar manner, diastereomeric triester **18b** (120 mg, 0.29 mmol) underwent saponification giving dihydroxy diacid **21b** (80 mg, 80% yield).

Compound 21a: Crystals, m.p 225°C dec (from 5% HCl-EtOH); $[\alpha]_D$ +61.8 (c=0.55, 1N HCl); IR (KBr) 3700-2300 (broad), 1704, 1648, 1616 cm^{-1}; MS, m/e 351 (1, M+2), 316 (2), 260 (5), 233 (5), 223 (5), 184 (4), 141 (7), 105 (18), 77 (15), 57 (100), 55 (9), 45 (25), 43 (19); 250-MHz ^1H NMR (D_2O) 1.01 (dd, J=J'=5.4 Hz, 1H, H_{6a}), 1.12 (dd, J=8.4 Hz, J'=5.4 Hz, 1H, H_{6b}), 1.50 (d, J=6.8 Hz, 3H, CH_3), 1.51-1.69 (complex absorption, 2H), 1.83 (m, 1H), 1.92 (ddd, J=8.4 Hz, J'=J"=5.1 Hz, 1H, H_5), 3.03 (d, J=13.3 Hz, 1H, $H_{2'}$), 3.09 (d, J=13.3 Hz, $H_{2'}$), 4.14 (dd, J=7.5 Hz, J"=5.1 Hz, 1H, H_4), 4.26 (q, J=J'=J"=6.8 Hz, 1H), 7.29 (complex absorption, 5H); 62.5-MHz ^{13}C NMR (D_2O) 15.3 (CH_2, C-6), 19.5 (CH_3), 27.7 (CH_2, C-2), 28.9 (quaternary C-1), 33.7 (CH, C-5), 47.5 (CH, C-3), 52.6 (CH_2, C-2'), 60.0 (CH), 72.5 (CH, C-4), 74.3 (quaternary C-1'), 128.7 (arom CH), 130.5 (arom CH), 130.6 (arom CH), 137.3 (arom C_{ipso}), 177.8 (C=O). Anal. Calcd. for $C_{18}H_{23}NO_6$: C, 61.86; H, 6.64; N, 4.01. Found: C, 61.87; H, 6.49; N, 3.84.

Compound 21b: Crystals, m.p. 135°C dec (from 5% HCl-EtOH); $[\alpha]_D$ -38.0 (c=1.00, 1N HCl); IR (KBr) 3700-2350 (broad), 1708, 1701, 1616 cm^{-1}; MS, m/e 332 (1), 316 (10), 134 (40), 120 (5), 106 (24), 105 (100), 91 (7), 79 (18), 77 (16), 51 (5), 44 (6); 250-MHz ^1H NMR (D_2O) 0.58 (dd, J=J'=5.1 Hz, 1H, H_6), 1.11 (dd, J=13.2 Hz, J'=9.0 Hz, 1H, H_{2b}), 1.30 (dd, J=9.6 Hz, J'=5.1 Hz, 1H, H_6), 1.39 (d, J=6.9 Hz, 3H, CH_3), 1.68 (dd, J=9.5 Hz, J'=5.3 Hz, 1H, H_5), 2.24 (m, 1H, H_{2a}), 2.34 (ddd, J=13.2 Hz, J'=9.5 Hz, J"=5.1 Hz,

1H, H_3), 2.78 (d, J=13.3 Hz, 1H, $H_{2'}$), 3.07 (d, J=13.3 Hz, $H_{2'}$), 3.56 (d, J=5.1 Hz, 1H, H_4), 4.19 (q, J=J'=J"=6.9 Hz, 1H), 7.20 (complex absorption, aromatic 5H); 62.5-MHz ^{13}C NMR (methanol d_4) 19.7 (CH_3), 24.1 (CH_2, C-6), 29.7 (quaternary C-1), 33.3 (CH_2, C-2), 39.6 (CH, C-5/C-3), 52.0 (CH_2, C-2'), 60.4 (CH, C-3/C-5), 60.9 (CH), 76.1 (quaternary C-1'), 76.1 (CH, C-4), 128.8 (aromatic CH), 130.5 (aromatic CH), 130.7 (aromatic CH), 137.3 (aromatic C_{ipso}), 173.0 (C=O, ester), 177.5 (C=O, acid). Anal. Calcd. for $C_{18}H_{23}NO_6$: C, 61.86; H, 6.64; N, 4.01. Found: C, 61.83; H, 6.76; N, 3.92.

Hydrogenation of benzylamines 21a and 21b: (1*R*,3*S*,4*S*,5*S*,1'*S*)-(+)- and (1*S*,3*S*,4*S*,5*R*,1'*S*)-(-)-3-(1'-Aminomethyl-1'-carboxy-1'-hydroxymethyl)-4-hydroxybicyclo[3.1.0]hexane-1-carboxylic acid, 5 and 22, respectively. A solution of **21a** (100 mg, 0.29 mmol) in 1:1 MeOH-water (10 mL) was hydrogenated at 3 atmospheres pressure in the presence of 10% Pd/C (45 mg). Catalyst was filtered off through celite, washed, and solvents were removed at reduced pressure. The residue was poured into water (2 mL) and eluted through a C_{18}-reverse phase cartridge by using, successively, water, 1:1 MeOH-water, and water, to afford amino acid **5** (52 mg, 74% yield) as a hygroscopic white solid. Similarly, benzylamine **21b** (70 mg, 0.20 mmol) furnished diastereomeric amino acid **22** (45 mg, 91% yield).

Amino acid 5: Crystals, m.p. 160°C dec (from MeOH-ether); $[\alpha]_D$ +80.0 (c=0.80, H_2O); IR (KBr) 3700-2650 (broad), 1722, 1701 cm^{-1}; MS, m/e 228 (1), 198 (6), 166 (5), 107 (5), 106 (5), 81 (8), 79 (14), 77 (11), 44 (100); 250-MHz ^1H NMR (D_2O) 1.11 (dd, J=J'=5.4 Hz, 1H, H_{6a}), 1.19 (dd, J=8.4 Hz, J'=5.4 Hz, 1H, H_{6b}), 1.67 (m, 1H, H_{2b}), 1.80 (m, 1H, H_3), 1.94 (m, 1H, H_{2a}), 2.03 (ddd, J=8.4 Hz, J=J'=5.4 Hz, 1H, H_5), 3.13 (d, J=13.4 Hz, 1H, $H_{2'}$), 3.27 (d, J= 13.4 Hz, 1H, $H_{2'}$), 4.34 (dd, J=8.4 Hz, J'=5.4 Hz, 1H, H_4); 62.5-MHz ^{13}C NMR (D_2O) 15.7 (CH_2, C-6), 27.1 (CH_2, C-2), 28.6 (quaternary C-1), 33.7 (CH, C-5), 45.3 (CH_2, C-2'), 47.2 (CH, C-3), 72.0 (CH, C-4), 75.4 (quaternary C-1'), 176.2 (C=O), 179.1 (C=O).

Amino acid 22: Crystals, m.p. 120°C dec (from MeOH-ether); $[\alpha]_D$ -52.5 (c=0.80, H_2O); IR (KBr) 3700-2300 (broad), 1708, 1701 cm^{-1}; MS, m/e 226 (1), 198 (2), 134 (4), 105 (6), 79 (8), 77 (5), 44 (100); 250-MHz ^1H NMR (D_2O) 0.80 (dd, J=J'=5.1 Hz, 1H, H_6), 1.34 (dd, J=13.4 Hz, J'=8.8 Hz, 1H, H_{2b}), 1.46 (dd, J=9.7 Hz, J'=5.1 Hz, 1H, H_6), 1.88 (dd, J=9.7 Hz, J'=5.8 Hz, 1H, H_5), 2.44 (dd, J=J'=13.4 Hz, 1H, H_{2a}), 2.60 (ddd, J=13.4 Hz, J'=8.8 Hz, J"=5.8 Hz, 1H, H_3), 3.10 (d, J=13.4 Hz, 1H, $H_{2'}$), 3.21 (d, J=13.4 Hz, $H_{2'}$), 3.97 (d, J=5.8 Hz, 1H, H_4); 62.5-MHz ^{13}C NMR (D_2O) 23.9 (CH_2, C-6), 29.2 (CH_2, C-2), 33.1 (quaternary C-1), 39.7 (CH, C-5/C-3), 45.5 (CH_2, C-2'), 59.6 (CH, C-3/C-5), 75.7 (CH, C-4), 75.8 (quaternary C-1'), 175.7 (C=O), 179.3 (C=O).

Condensation of amine 19a with Cbz-cyclo-Asp-OMe, 24: Synthesis of (1*S*,2*R*,2'*S*)-(+)-1-(*N*-benzyloxycarbonylamino)-2-[2'-hydroxy-2'-methoxycarbonyl-2'-([1*R*,3*S*,4*S*,5*S*]-4-acetyloxy-1-methoxycarbonylbicyclo[3.1.0]-hexan-3-yl)ethylaminocarbonyl]cyclopropane-1-carboxylic acid methyl ester, 24. A light-protected mixture containing amine **19** (80 mg, 0.25 mmol), acid **24** (67.4 mg, 0.23 mmol) prepared according to ref. 12, HOBT (31.0 mg, 0.23 mmol), and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide (132.3 mg, 0.69 mmol) was stirred under nitrogen atmosphere, at r.t. for 2 days. Then ethyl acetate was added (5 mL) and the solution was washed with water (3x5 mL) and dried. Solvent was removed at reduced pressure and the residue was chromatographed (mixtures of ethyl acetate-hexane as eluent) to afford dipeptide **24** (85 mg, 64% yield) as a highly hygroscopic solid that, after lyophilization (H_2O-CH_3CN), showed m.p. 87-89 °C; $[\alpha]_D$ +57.3 (c= 1.5, $CHCl_3$); IR (KBr) 3700-3150, 1736, 1686 cm^{-1}; MS, m/e 420 (M-170, 1), 229 (4), 199 (8), 185 (9), 169 (19), 134 (52), 106 (13), 105 (100), 91 (65), 79 (18), 77 (14), 55 (15), 46 (13), 43 (20); 250-MHz ^1H-NMR ($CDCl_3$) 1.06 (dd, J=J'=5.1 Hz, 1H), 1.32 (dd, J=8.4 Hz,

J'=5.1 Hz, 1H), 1.62 (s. broad, 1H), 1.77 (complex absorption, 3H), 2.03 (s, 3H), 2.19 (complex absorption, 2H), 2.42 (ddd, J=J'=8.5 Hz, J''=5.1 Hz, 1H), 2.46 (m, 1H), 3.02 (dd, J=14.0 Hz, J'=4.1 Hz, 1H), 3.60 (s., 3H, OCH_3), 3.61 (s, 3H, OCH_3), 3.70 (s, 3H, OCH_3), 3.83 (m, 1H), 5.08 (d, J=12.3 Hz, 1H), 5.18 (d, J=12.3 Hz, 1H), 5.35 (dd, J= 7.2 Hz, J=5.1 Hz, 1H, H_4), 5.50 (broad s, 1H), 6.20 (broad s, 1H), 7.28-7.33 (complex absorption, 5H); 62.5-MHz ^{13}C NMR ($CDCl_3$) 15.2 (CH_2, C-6), 20.3 (CH_2, cyclopropane C-3), 21.0 (CH_3, $OCOCH_3$), 27.0 (CH_2, C-5), 29.4 (quaternary bicyclo C-1), 30.9 (CH, cyclopropane C-2), 31.2 (CH), 40.2 (CH), 44.7 (quaternary cyclopropane C-1), 47.1 (CH_2,.C-1'), 52.0 (OCH_3), 52.9 (OCH_3), 53.0 (OCH_3), 66.8 (CH_2, CH_2Ph), 75.3 (CH, C-4), 77.4 (quaternary C-2'), 128.5 (aromatic CH), 128.5 (aromatic CH), 129.1 (aromatic CH), 138.0 (aromatic C_{ipso}), 157.6 (C=O, carbamate), 168.0 (C=O, amide), 170.9 (C=O), 172.2 (C=O), 173.5 (C=O), 174.9 (C=O). Anal. Calcd. for $C_{28}H_{34}N_2O_{12}$: C, 56.94; H, 5.80; N, 4.74. Found: C, 56.95; H, 5.98; N, 4.54.

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