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Enantioselective synthesis of novel, highly conformationally constrained peptide surrogates

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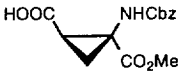
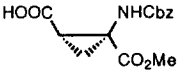
Abstract: Two new enantiomeric peptide surrogates as well as a tripeptide, all of them having highly conformationally constrained structures, have been synthesized. (*Z*)-cyclo-Aspartic acid and convenient α-substituted isoserine derivatives, in both antipodal forms, as well as methyl (*R*)-2-phenylglycinate, have been used as the monomeric units. © 1997 Elsevier Science Ltd

Introduction

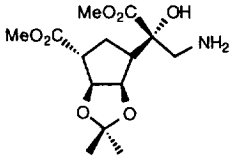
Peptide surrogates have received great attention during recent years for several reasons. For instance, the inclusion of urea units in peptidic sequences is being used in combinatorial chemistry to find compounds with interesting pharmacological properties and enhanced proteolytic stabilities relative to the corresponding peptides.[1] In addition, highly conformationally constrained peptidomimetics have been utilized both for the above mentioned purpose and to be used as biological probes. One of the most frequent modifications in this class of compounds consists of the inclusion of protein methanologs[2] and, with this aim, much synthetic effort has been devoted to achieving stereoselective and efficient syntheses of cyclopropane amino acids.[3] The substitution of a proteinogenic amino acid in a peptidic chain by a methanolog has resulted, for instance, in the study of the stereochemical features involved in receptor interactions related to the neurotransmission mechanisms.[4] Other structural modifications giving rise to constrained peptides have also been carried out and, very recently, the incorporation of cyclobutane amino acids in bioactive peptides has been published.[5]



1



ent-1



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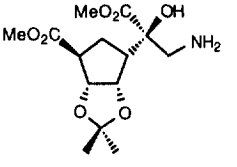
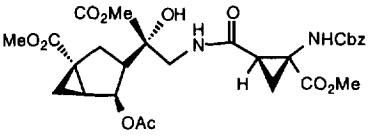


ent-2



3

As part of our research program on the asymmetric synthesis of carbocyclic amino acids and homologs, we have synthesized (2*S*,3*R*)-Cbz-cyclo-Asp-OMe, **1**,[6,7] as well as its enantiomer, **ent-1**[7] from D-glyceraldehyde as the only source of chirality. On the other hand, the enantiomeric α-substituted isoserine derivatives **2** and **ent-2** have also been synthesized.[8] Preparation of amino ester **2** involves a chemoenzymatic resolution of an appropriate intermediate, whereas D-glyceraldehyde has been used as a chiral precursor of **ent-2**. Other isoserine derivatives have also been obtained in our laboratory[9,10] and, in a recent publication, we have reported the incorporation of one of them in the dipeptide surrogate **3**.[10]

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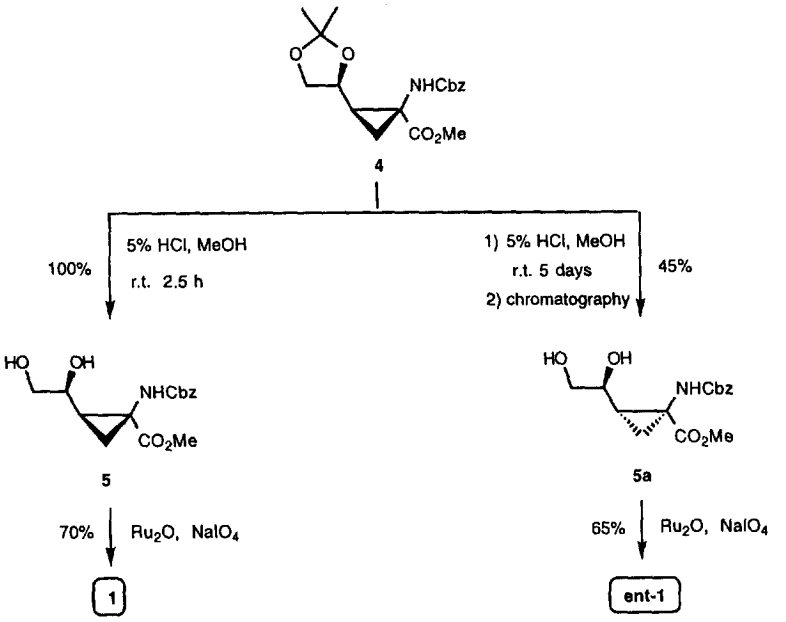
In this paper we describe the synthesis of two new enantiomeric pseudopeptides prepared from the pairs **1/2** and **ent-1/ent-2**, respectively, as well as a tripeptide obtained from the pair **1/2** and (*R*)-(2)-phenyl glycine. All of them present rigid structures and conveniently-protected additional functional groups.

Results and discussion

Scheme 1 summarizes the enantioselective stereodivergent synthesis of **1** and **ent-1** from the common intermediate **4**, obtained by cyclopropanation[11,12] of a homochiral aminopentenoate resulting, in turn, from Wittig–Horner condensation[7,13] of D-glyceraldehyde acetonide and a suitable phosphonate.[13]



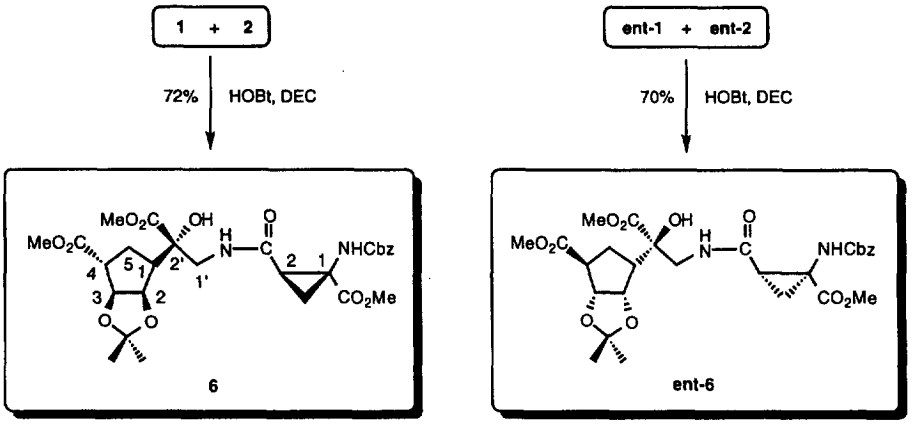
Scheme 1.

Hydrolysis of the acetonide **4** with 5% HCl in methanol, at room temperature for 2.5 hours, afforded quantitatively diol **5**. On the other hand, hydrolysis for longer time periods allowed epimerization of the cyclopropane-stereogenic centers. Thus, a 1:1 mixture of diols **5** and **5a** was obtained after treatment of **4** with acid for 5 days, pure diastereomer **5a** being isolated by column chromatography. Subsequent oxidative cleavage of diols **5** and **5a** with catalytic $Ru_2O \cdot xH_2O$ in the presence of sodium periodate provided the enantiomeric acids **1** and **ent-1**, respectively.[7] These compounds are suitably protected for the incorporation in the pseudopeptides **6** and **ent-6** (Scheme 2) by means of specific bonding to the free carboxyl group.

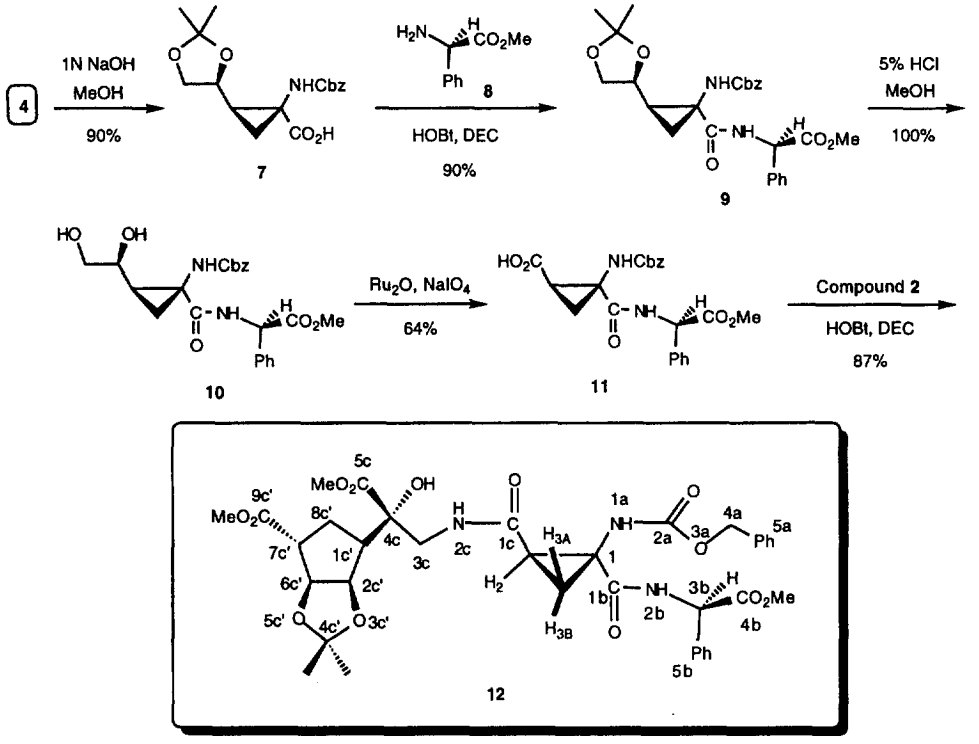
1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide (DEC) was chosen as a coupling reagent to form amide bonds,[14] due to the easy separation of the produced peptides from the resultant urea. The reaction was catalyzed by *N*-hydroxybenzotriazole (HOBt), an efficient additive used in racemization-free peptide couplings.[15]

Thus, reaction of acid **1** with amine **2** in the presence of 0.5 eq of HOBt and 3 eq of the carbodiimide hydrochloride in DMF as a solvent, at room temperature for 30 hours, provided the dipeptide **6** (72% yield) as a highly hygroscopic solid which, after lyophilization, showed m.p. 43–46°C, $[\alpha]_D$ −28.0 (c 0.5, chloroform). Similarly, coupling of **ent-1** to **ent-2** gave **ent-6** with 70% yield, as a solid, m.p. 43–46°C, $[\alpha]_D$ +28.2 (c 0.5, chloroform).

Synthesis of tripeptide **12** (Scheme 3) requires coupling of the carboxyl groups in amino acid **1** to the free amino groups of methyl (*R*)-2-phenylglycinate, **8**, and amino ester **2**, respectively. The



Scheme 2.



Scheme 3.

synthetic sequence starts from product **4** which, under saponification with methanolic 1 N NaOH, affords acid **7** in 90% yield. This compound is suitable for the specific creation of an amide bond involving *C-1*, and bears an additional carboxylic acid-function in a latent form. Coupling of acid **7** with **8**, under the same conditions as above, gave the new dipeptide **9** as a solid, m.p. 153–156°C, $[\alpha]_D$ −100.0 (c 1.0, chloroform) in 90% yield. The acetonide was cleaved by treatment of **9** with 5% HCl in methanol, at room temperature for 5 hours, giving quantitatively diol **10**. This compound was oxidized by the action of $Ru_2O \cdot xH_2O/NaIO_4$, at room temperature for 1.5 hours, obtaining acid **11** in 64% yield, as a solid, m.p. 171–174°C, $[\alpha]_D$ −140.0 (c 0.6, chloroform). Finally, coupling between

11 and amine **2**, under similar conditions than those described before, led to the tripeptide **12** in 87% yield (45% overall yield from **4**).

Unfortunately, these new peptide surrogates did not afford suitable crystals for their structural analysis by X-ray diffraction, which would have led to information about crystal packing. Nevertheless, high resolution NMR techniques provided evidence for the expected structures and suggested that, at least in solution, the side-chains of both cyclopentane and cyclopropane rings are in extended conformations, significant intramolecular hydrogen bonds were not observed either by ^{1}H NMR or by IR spectrophotometry. Proton assigments for product **12**, as the most representative example, are given in Table 1.

Experimental section

Flash column chromatography was carried out on silica gel (230–400 mesh). Melting points were determined on a hot stage and are uncorrected. Electron-impact mass spectra were recorded at 70 eV. Chemical shifts in NMR spectra are given in ppm relative to internal TMS (δ scale).

(1S,2R,4′S)-(−)-1-[N-(benzyloxycarbonyl)amino]-2-(2′,2′-dimethyl-1′,3′-dioxolan-4′-yl)cyclopropanecarboxylic acid ***7***

A solution of ester **4** (398 mg, 1.1 mmol) in methanol (8 mL) was stirred with 1 N NaOH (5.7 mL, 5.7 mmol) at room temperature for 16 h. The solution was acidified to pH 3–4 with 5% HCl and the produced precipitate was dissolved by adding ethyl acetate (15 mL). The two layers were separated and the aqueous phase was extracted with ethyl acetate (3×10 mL). The combined organic phases were dried and solvent was removed. The residue was chromatographed (1:1 ethyl acetate–hexane) to afford 345 mg of acid **7** (90% yield) as a white solid. Crystals, m.p. 112–116°C (from ethyl acetate–pentane); $[\alpha]_D$ −50.0 (c 1.0, chloroform); IR (KBr) 3500–2300 (br), 3357, 1730, 1694 cm^{-1}; 250-MHz ^{1}H NMR (acetone-d_6) 1.20 (m, 1 H), 1.22 (s, 3 H), 1.54 (dd, J=9.5 Hz, J'=5.1 Hz, 1 H), 1.94 (m, 1 H), 3.70–3.83 (complex abs, 2 H), 4.01 (dt, J=8.4 Hz, J'=5.7 Hz, 1 H), 5.04 and 5.14 (AB system, J=12.8 Hz, 2 H), 7.02 (br s, 1 H), 7.28–7.38 (complex abs, 5 H); 62.5-MHz ^{13}C NMR ($CDCl_3$) 20.68, 25.11, 26.45, 30.31, 37.70, 66.88, 69.41, 75.37, 108.67, 127.74, 127.94, 128.23, 135.85, 156.73, 176.22; MS, *m/z* (%) 320 (M−15, 1), 108 (35), 107 (29), 91 (100), 80 (27), 79 (45), 77 (26), 59 (65), 43 (48). Anal. Calcd. for $C_{17}H_{21}O_6N$: C, 60.89; H, 6.31; N, 4.18. Found: C, 60.79; H, 6.35; N, 4.12.

Methyl (1S,2R,1′S)-(−)-1-[N-(benzyloxycarbonyl)amino]-2-(1′,2′-dihydroxyethyl)cyclopropyl-1-carbonyl-N-[(R)-2-phenylglycinate] ***10***

A solution of acetonide **9** (271 mg, 0.6 mmol) and 5 drops of 5% HCl in methanol (12 mL) was stirred at room temperature for 3 h. The solvent was removed and the residue was chromatographed (3:1 ethyl acetate–hexane) to give quantitatively 246 mg of diol **10** as a white solid. Crystals, m.p. 137–142°C; $[\alpha]_D$ −58.67 (c 0.75, chloroform); IR (KBr) 3700–3000 (br), 1736, 1659, 1511 cm^{-1}; 250-MHz ^{1}H NMR (acetone-d_6) 1.10 (dd, J=7.1 Hz, J'=4.7 Hz, 1 H), 1.55 (dd, J=9.3 Hz, J'=4.7 Hz, 1 H), 1.72 (m, 1 H), 3.46 (m, 1 H), 3.64 (m, 1 H), 3.67 (s, 3 H), 3.99 (d, J=4.7 Hz, 1 H), 4.33 (s, 1 H), 5.05 and 5.15 (AB system, J=12.5 Hz, 2 H), 5.47 (d, J=6.7 Hz, 1 H), 7.11 (s, 1 H), 7.31 (complex absorption, 10 H), 7.75 (d, J=6.7 Hz, 1 H); 62.5-MHz ^{13}C NMR ($CDCl_3$) 20.4, 30.5, 39.3, 52.8, 56.9, 66.2, 67.2, 70.6, 127.0, 127.3, 127.9, 128.1, 128.4, 128.9, 135.8, 135.9, 156.6, 171.5, 171.5; MS, *m/z* (%) 442 (M, 1), 260 (7), 150 (8), 149 (16), 121 (15), 106 (25), 92 (8), 91 (100), 79 (13), 77 (13), 65 (6). Anal. Calcd. for $C_{23}H_{26}O7N_2$: C, 62.43; H, 5.92; N, 6.33. Found: C, 62.24; H, 6.00; N, 6.22.

Methyl (1S,2R)-(−)-1-[N-(benzyloxycarbonyl)amino]-2-carboxycyclopropyl-1-carbonyl-N-[(R)-2-phenyl-glycinate] ***11***

Sodium periodate (184 mg, 0.9 mmol) and Ru_2O hydrate (8 mg) were added to an ice-cooled solution of diol **10** (76 mg, 0.2 mmol), in 2:2:3 CCl_4–CH_3CN–H_2O (3.5 mL). The mixture was stirred at room temperature for 1.5 h. Then ether (5 mL) was added and the layers were separated. The aqueous layer was extracted with ethyl acetate (3×10 mL) and the combined organic phases were dried. The

solvent was removed and the residue was chromatographed (2:1 ethyl acetate–hexane) to afford acid **11** (46 mg, 64% yield). Crystals, m.p. 171–174°C (from ethyl acetate–pentane); $[\alpha]_D$ −140.0 (c 0.6, methanol); IR (KBr) 3600–2300 (br), 1736, 1694, 1695, 1518 cm^{-1}; 250-MHz ^1H NMR (methanol-d_4) 1.65 (m, 2H), 2,59 (t, J=8.0 Hz, 1 H), 3.69 (s, 3 H), 5.10 (s, coalescent AB system, 2 H), 5.45 (d, J=6.4 Hz, 1 H), 5.45 (br s, 1 H), 7.25–7.35 (complex abs, 10 H), 8.26 (d, J=6.4 Hz, 1 H); 62.5-MHz ^{13}C NMR (methanol-d_4) 22.1, 28.7, 42.7, 53.3, 58.36, 67.9, 128.4, 128.4, 128.7, 129.0, 129.5, 129.8, 137.6, 137.9, 159.0, 171.6, 172.1, 172.4; MS, *m/z* (%) 426 (M, 2), 215 (14), 132 (16), 121 (17), 108 (25), 107 (22), 106 (30), 91 (100), 79 (34), 77 (35). Anal. Calcd. for $C_{22}H_{22}O_7N_2$: C. 61.97; H, 5.20; N, 6.57. Found: C, 61.94; H, 5.19; N, 6.47.

Coupling of amino acids. General procedure

A typical experiment was run as follows for the synthesis of dipeptide **9**. 1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide chlorhydrate (381 mg, 2.0 mmol) was added to a stirred solution containing acid **7** (222 mg, 0.7 mmol), methyl (*R*)-2-phenyl glycinate, **8** (164 mg, 1.0 mmol), and *N*-hydroxybenzotriazole (45 mg, 0.3 mmol) in anhydrous DMF (3 mL). The light-protected mixture was stirred under nitrogen atmosphere at room temperature for 30 h. Progress of the reaction was monitored by TLC until starting materials disappeared. Then ethyl acetate (15 mL) was added and the resultant solution was washed with saturated aqueous sodium bicarbonate (3×8 mL). The organic phase was dried and solvents were removed at reduced pressure. The residue was chromatographed (mixtures of ethyl acetate–hexane as eluent) to afford compound **9**.

Compounds **6**, **ent-6**, and **12** were prepared in a similar way. All of them were characterized as follows.

Methyl (1S,2R,2'S)-(−)-1-[N-(benzyloxycarbonyl)amino]-2-[2'-hydroxy-2'-methoxycarbonyl-2'-([1S,2R,3S,4R]-2,3-isopropylidenedioxy-4-methoxycarbonylcyclopent-1-yl)ethylaminocarbonyl]-cyclopropane-1-carboxylate ***6***

Yield: 50 mg, 77%. Hygroscopic solid that, after lyophilization (H_2O–CH_3CN), showed m.p. 43–46°C; $[\alpha]_D$ −28.0 (c 0.5, chloroform). IR (KBr) 3374, 1737, 1527 cm^{-1}; 250-MHz ^1H NMR (acetone-d_6) 1,26 (s, 3 H), 1.44 (s, 3 H), 1.61 (dd, J=8.8 Hz, J'=4.7 Hz, 1 H), 1.74 (dd, J=7.5 Hz, J'=4.7 Hz, 1 H), 1.83–1.91 (complex abs, 2 H), 2.40 (m, 1 H), 2.63 (dd, J=8.8 Hz, 7.5 Hz, 1 H), 2.81 (m, 1 H), 3,43 (dd, J=13.9 Hz, J'=5.1 Hz, 1 H), 3.63 (s, 3 H), 3.64 (s, 3 H), 3.66 (s, 3 H), 3.73 (dd, J=13.9 Hz, J'=7.3 Hz, 1 H), 4.69–4.74 (complex abs, 2 H), 4.83 (br s, 1 H), 5.10 and 5.15 (AB system, J=12.6 Hz, 2 H), 6.78 (br s, 1 H), 7.29–7.38 (complex abs, 5 H), 7.70 (d, J=6.2 Hz); 62.5-MHz ^{13}C NMR ($CDCl_3$) 19.3, 24.3, 26.8, 29.6, 30.0, 39.3, 46.9, 49.4, 50.4, 51.0, 51.9, 52.0, 65.9, 76.4, 79.7, 82.5, 112.8, 127.1, 127.5, 128.1, 137.1, 156.8, 167.3, 171.2, 173.1, 174.1. Anal. Calcd. for $C_{28}H_{36}O_{12}N_2$: C, 56.75; H, 6.12; N, 4.73. Found: C, 56.68; H, 6.18; N, 4.68.

Methyl (1R,2S,2'R)-(+)-1-[N-(benzyloxycarbonyl)amino]-2-[2'-hydroxy-2'-methoxycarbonyl-2'-([1R,2S,3R,4S]-2,3-isopropylidenedioxy-4-methoxycarbonylcyclopent-1-yl)ethylaminocarbonyl]-cyclopropane-1-carboxylate ***ent-6***

Yield: 47 mg, 72%. Hygroscopic solid that, after lyophilization (H_2O–CH_3CN), showed m.p. 43–46°C; $[\alpha]_D$ +28.2 (c 0.5, chloroform).

Methyl (1S,2R,4'S)-(−)-1-[N-(benzyloxycarbonyl)amino]-2-(2',2'-dimethyl-1',3'-dioxolan-4'-yl)-cyclopropyl-1-carbonyl-N-[(R)-2-phenylglycinate] ***9***

Yield: 287 mg, 90%. Crystals, m.p. 153–156°C (from ethyl acetate–pentane); $[\alpha]_D$ −100.0 (c 1.0, chloroform); IR (KBr) 3447, 3272, 1733, 1648, 1526 cm^{-1}; 250-MHz ^1H NMR (acetone-d_6) 1.15 (dd, J=7.3, J'=4.9 Hz, 1 H), 1.27 (s, 3 H), 1.33 (s, 3 H), 1.40 (dd, J=9.5 Hz, J'=4.9 Hz, 1 H), 1.89 (m, 1 H), 3.68 (s, 3 H), 3.70–3.79 (complex abs, 2 H), 3.96 (m, 1 H), 5.10 and 5.17 (AB system, J=12.8 Hz, 2 H), 5.48 (d, J=7.3 Hz, 1 H), 7.21 (br s, 1 H), 7.28–7.40 (complex abs, 10 H), 7.76 (d, J=7.3 Hz, 1 H); 62.5-MHz ^{13}C NMR ($CDCl_3$) 20.2, 25.7, 27.1, 28.8, 40.0, 52.8, 57.5, 67.1, 70.5,

Table 1. ^{1}H NMR Chemical shifts (ppm), multiplicity, and coupling constants (Hz) for **12**[a,b]

H_2	H_{3A}	H_{3B}	H_{1a} (N*H*)	2 H_{4a}	H_{5a} (*Ph*)	O*H*
2.56, dd *J*= 8.9, *J'*= 7.1	1.60, dd *J*=7.1, *J'*=4.4	1.53, dd *J*=8.9, *J'*=4.4	6.83, br s	5.10 and 5.19 d, *J*= 12.8	7.32-7.38 complex abs	4.94, s
H_{2b} (N*H*)	H_{3b}	H_{5b} (*Ph*)	H_{2c} (N*H*)	2 H_{3c}	$H_{1c'}$	$H_{2c'}$
7.95, d *J*=7.3	5.50, d *J*=7.3	7.32-7.38 complex abs	7.79, t *J*=5.1	3.51, dd *J*=13.9, *J'*=5.1	2.42, dt *J*=7.6, *J'*=2.0	4.71, m
$H_{6c'}$	$H_{7c'}$	2 $H_{8c'}$	CH_3	CH_3	CH_3O	CH_3O	CH_3O
4.71, m	2.82, m	1.88, m	1.26, s	1.45, s	3.64, s	3.67, s	3.69, s

[a] In acetone-d_6. [b] Numeration is different from that used in nomenclature for compound **12**.

76.2, 109.0, 128.0, 128.5, 128.7, 128.8, 129.2, 129.4, 137.9, 138.0, 157.4, 171.4, 171.6; MS, *m/z* (%) 482 (M, 5), 149 (21), 132 (15), 121 (18), 106 (17), 91 (100), 79 (13), 77 (16), 43 (16). Anal. Calcd. for $C_{26}H_{30}O_7N_2$: C, 64.72; H, 6.27; N, 5.81. Found: C, 64.78; H, 6.22; N, 5.95.

*Methyl (1S,2R,2'S)-(−)-1-[N-(benzyloxycarbonyl)amino]-2-[2'-hydroxy-2'-methoxycarbonyl-2'-([1S,2R,3S,4R]-2,3-isopropylidenedioxy-4-methoxycarbonylcyclopent-1-yl)ethylaminocarbonyl]-cyclopropyl-1-carbonyl-*N*-[(R)-2-phenylglycinate] **12***

Yield: 104 mg, 87%. Crystals, m.p. 168–172°C (from ethyl acetate–pentane); $[\alpha]_D$ −66.6 (c 0.6, methanol); IR (KBr) 3502, 3396, 3253, 1736, 1653, 1519 cm^{-1}. See Table 1 for description of the ^{1}H NMR spectrum. 62.5-MHz ^{13}C NMR (acetone-d_6) 20.9, 25.3, 27.8, 30.3, 30.7, 41.9, 48.1, 50.3, 51.5, 51.7, 52.0, 52.9, 57.6, 67.1, 77.7, 80.7, 83.5, 113.8, 128.1, 128.5, 128.6, 129.0, 129.0, 129.2, 129.5, 137.8, 137.9, 157.7, 167.8, 170.5, 171.6, 174.1, 175.0; MS, *m/z* (%) 330 (1), 108 (84), 107 (57), 91 (16), 79 (100), 78 (12), 77 (58), 51 (24), 50 (20). Anal. Calcd. for $C_{36}H_{43}O_{13}N_3$: C, 59.58; H, 5.97; N, 5.79. Found: C, 59.63, H, 6.08; N, 5.77.

Acknowledgements

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