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CYCLOPROPANES AS CONFORMATIONALLY RESTRICTED PEPTIDE ISOSTERES. DESIGN AND SYNTHESIS OF NOVEL COLLAGENASE INHIBITORS

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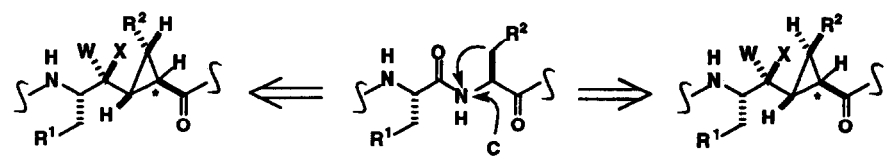
Abstract. The 1,2,3-trisubstituted cyclopropane derivatives **9** and **10** were prepared as conformationally constrained analogues of the known collagenase inhibitor **8**. The syntheses of **9** and **10** featured the highly enantioselective Rh_2[*S*-MEPY]$_4$ catalyzed cyclization of the allylic diazo ester **11** to give the lactone **13**. Opening of the lactone ring of **13** with *N,O*-di-(*p*-methoxybenzyl)hydroxylamine under Weinreb conditions followed by refunctionalization, coupling of the intermediate acid **16** with **17** and deprotection led to the dipeptide analogue **9**. Alternatively, the lactone ring of **13** could be opened with the protected tyrosine **21** by a novel variant of the Weinreb protocol to give directly the dipeptide analogue **22** which was then converted into **10**.

INTRODUCTION. The invention and synthesis of peptide mimics[1] coupled with their incorporation in pseudopeptide ligands that will bind to macromolecular receptors and enzyme active sites is one of the most exciting areas in contemporary bioorganic chemistry. Since most of the conformationally restricted replacements of peptide secondary structure reported to date are designed to imitate a turn or helix,[2] we were attracted to the significant challenge of creating novel isosteric replacements that would enforce an extended (β-strand) conformation on the backbone of oligopeptides while projecting the amino acid side chains in a specific orientation. Based upon a series of molecular modeling studies, we reasoned that 1,2,3-trisubstituted cyclopropanes of the general types **2** and **3** would constitute rigid, isosteric replacements of the dipeptide array **1**.[3-5] Operationally, **2** and **3** are derived from **1** by replacing the amide nitrogen with a carbon and forming a single bond between this atom and C(β) on the



2: W, X = H, OH, O

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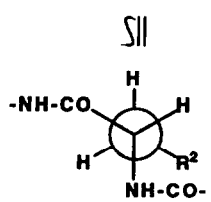
3: W, X = H, OH, O



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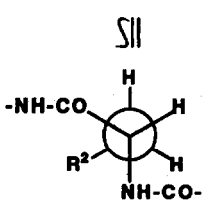

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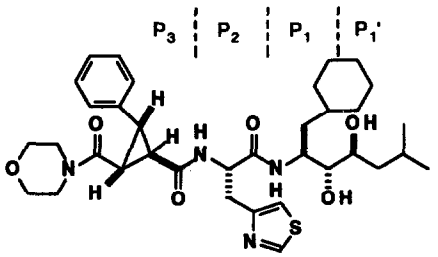
amino acid side chain. There are several design features of these dipeptide surrogates that merit comment. For example, both **2** and **3** endow the peptide backbone with structural rigidity closely mimicking a β-strand by locking the ϕ-angle. In the isostere **2**, the amino acid side chain is cis to the *N*-terminus of the oligopeptide, and the R^2 group in **2** is oriented so that it occupies approximately the same region of space relative to the backbone that it would if the χ_1-angle at the corresponding amino acid residue in **1** were fixed at -60°. The trisubstituted cyclopropane subunit in **2** thus is a rigid isosteric replacement for the *gauche*(-) conformer of an amino acid residue, as shown in **4**. Similarly, in the cyclopropane **3**, the R^2 group is cis to the *C*-terminus, and the R^2 group of the side chain is so positioned that **3** is a conformationally restricted mimic of the *gauche*(+) conformer **5** in which the χ_1-angle is +60°. The ability to restrict conformational space available to the side chain residues is highly significant since these appendages provide the crucial sites for recognition, binding and consequent transduction. Finally, the absolute stereochemistry at C* in both **2** and **3** corresponds to the configuration at the alpha carbon in natural L-amino acids, and, if desired, it would be possible to invert this stereocenter to prepare peptide mimics of D-amino acids. It should be noted that the backbone side chains on cyclopropanes related to **2** and **3** could also be cis to each other thereby initiating a turn in the backbone.

Although our modeling studies suggested that trisubstituted cyclopropanes related to **2** and **3** should serve as rigid mimics of localized β-strand structure, it was necessary to verify this hypothesis by demonstrating the efficacy of such replacements in biologically active pseudopeptides. Toward this end, we incorporated truncated analogues of **2** and **3** as combined *N*-terminal and P_3 replacements in the design of a unique series of potent renin inhibitors.[4] For example, the pseudopeptide **6**, which bears a cyclopropyl Phe at the P_3 position of the inhibitor, exhibited an IC_{50} = 0.7 nM against purified human renin (pH 6.0).[4a] This compound was more potent than any of the other three possible diastereomers of the corresponding cyclopropyl Phe replacement in which carbonyl groups were trans by a factor of greater than 200. In the same assay, the flexible analogue **7** had an IC_{50} = 0.36 nM.[4a] The comparable potencies of **6** and **7** strongly suggests that the preorganized spatial arrangement of the substituents on the rigid cyclopropane replacement at the P_3 inhibitor subsite in **6** closely approximates the three dimensional orientation of these groups in the biologically active conformation of **7**. Similar results have been obtained with related renin inhibitors bearing a sulfone moiety in place of the morpholine amide function.[4b]



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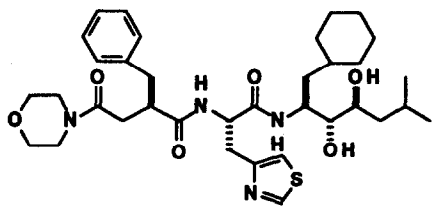

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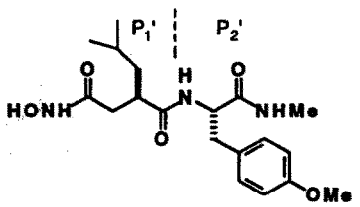
Based upon these results, we were excited by the possibility that cyclopropane derived isosteres of natural amino acids might be exploited in a general way to help define the biologically active conformation of oligopeptide or pseudopeptide ligands. Once the conformation of the bound ligand had been determined, it would then be possible to exploit such conformationally restricted ligands to map the three dimensional features of its respective

receptor or enzyme active site. Thus, we envisioned that stereochemically-defined cyclopropane surrogates of the general type **2** and **3** could be implemented as invaluable tools in the effort to develop a better understanding of the complex ligand-receptor interactions in biological systems.

RESULTS AND DISCUSSION. Since there are no X-ray crystallographic structural data for complexes of collagenase with a bound inhibitor, we queried whether the pseudopeptides **9** and **10** might be used to gain insights regarding the biologically active conformation of the known collagenase inhibitor **8**.[6,7] These compounds were designed to address the specific question of whether the leucine replacement at the P_1' site of **8** bound to collagenase in an extended, β-strand conformation with the isopropyl group oriented in either the *gauche*(-) or the *gauche*(+) conformation, as in **9** and **10**, respectively. If the potency of **9** or **10** as inhibitors of collagenase was comparable to that of **8**, this investigation would further establish the viability of cyclopropanes derived from **2** and **3** as isosteric replacements of dipeptide subunits, *and* it would support the exciting hypothesis that these surrogates could be employed as stereochemical and conformational probes of enzyme active sites. Another objective of this study was to develop improved synthetic methods for coupling the substituted cyclopropane subunits with amino acids, thereby facilitating access to the targeted inhibitor candidates.



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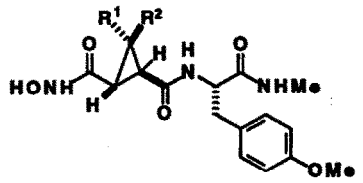
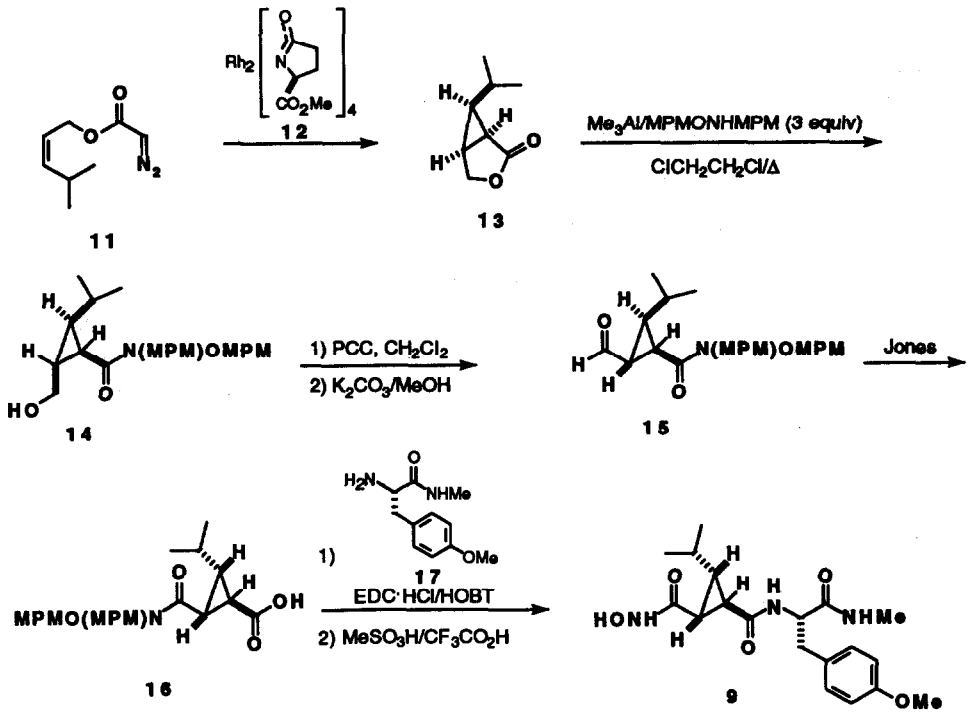


9: R^1 = *i*-Pr; R^2 = H
10: R^1 = H; R^2 = *i*-Pr

In analogy with our earlier work,[4a] the absolute stereochemistry at the cyclopropane carbons of the dipeptide replacement was established by the highly enantioselective intramolecular cyclopropanation of the allylic diazo ester **11** with Rh_2[*S*-MEPY]$_4$ (**12**) catalyst[8] to give **13** (≥94% ee).[9] The lactone moiety was opened using *N*-(*p*-methoxybenzyl)-*O*-(*p*-methoxybenzyl) hydroxylamine, which was prepared in 49% overall yield from hydroxylamine by simple modification of known procedures,[10] according to the standard Weinreb protocol[11] to give the protected hydroxamic acid **14** in 70% yield. Oxidation of the primary alcohol of **14** using PCC followed by base induced epimerization of the intermediate aldehyde gave **15** which was then subjected to Jones oxidation to deliver the acid **16** in 70% overall yield. Coupling of **16** with the tyrosine derivative **17**[12] using standard methods for peptide bond formation followed by removal of the *p*-methoxybenzyl (MPM) protecting groups[13] by acid-catalyzed solvolysis gave **9**, which is the conformationally restricted *gauche*(-) mimic of **8**. We initially examined simple benzyl protecting groups for the hydroxamic acid moiety, but although the *O*-benzyl group could be readily removed by hydrogenolysis, we were unable to effect hydrogenolysis of the *N*-benzyl group under conditions that did not concomitantly lead to significant reductive cleavage of the N-O bond.

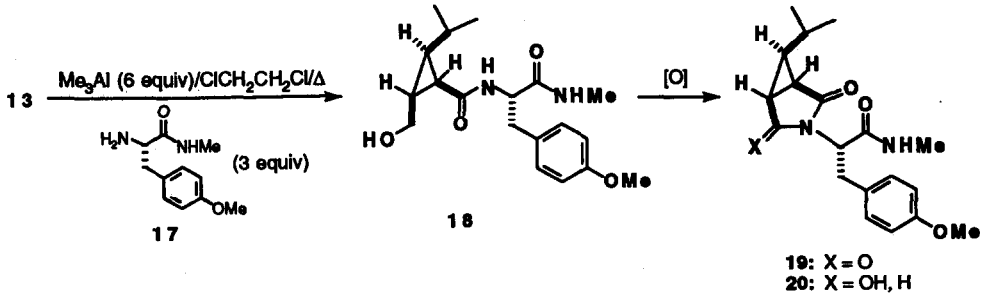
Having secured the requisite *gauche*(-) mimic **9**, it remained to prepare the corresponding *gauche*(+) mimic **10**. Since one of our goals was to make the route to **10** as concise as possible, we decided to explore the possibility of using a suitable derivative of L-tyrosine as the nucleophile to open the lactone ring of **13** with *direct formation of an amide bond*. Exploitation of the lactone moiety of cyclopropyl lactones related to **13** as the activated carboxyl group for the formation of the critical peptide linkage would greatly facilitate the synthesis of

Scheme 1



pseudopeptide ligands containing the cyclopropane surrogates. Toward this end, we developed a novel variant of the Weinreb protocol in which the reagents obtained upon combination of *unprotected* amino acids with trimethylaluminum were employed as nucleophiles to open lactones related to **13** to give dipeptide derivatives in a single step; at least one equivalent of trimethylaluminum must be used for each acidic proton in the amino acid subunit.[14] Thus, reaction of **13** with an excess of the reagent obtained upon treating tyrosine *N*-methyl amide **17** with two equivalents of trimethylaluminum gave the dipeptide analogue **18** in 75% yield (Scheme 2). The next step in the conversion of **18** into **10** involved oxidation of the primary alcohol function to an aldehyde to set the stage

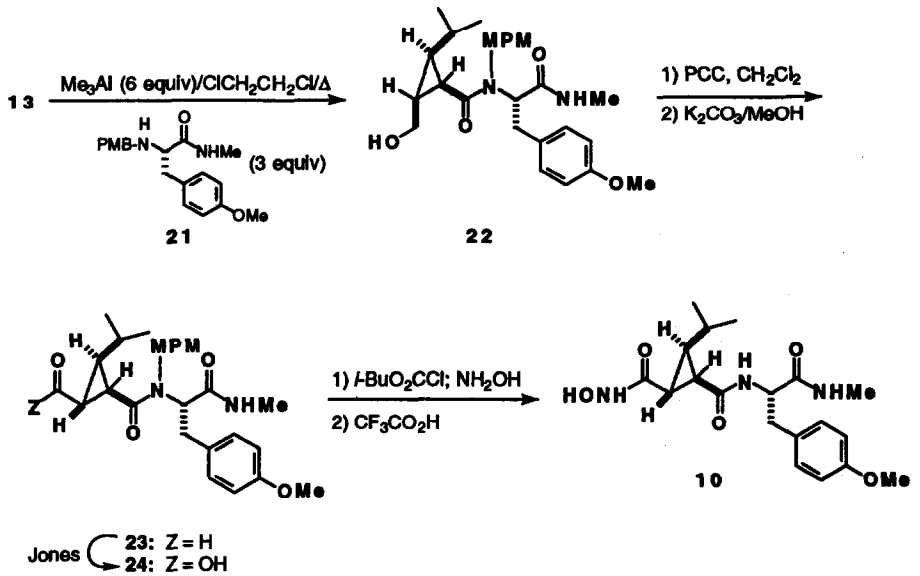
Scheme 2



for epimerization and eventual hydroxamic acid formation. However, oxidation of **18** with PCC gave the imide **19** as the exclusive product, presumably by oxidation of the hemi aminal **20** that formed *in situ* by cyclization of the intermediate aldehyde. Swern oxidation of **18** delivered **20**, but all attempts to effect the requisite inversion alpha to the latent aldehyde group of **20** via epimerization of the open chain form were unsuccessful. Based upon these results, it was apparent that protection of the amino group of tyrosine would be necessary.

Cognizant of the potential problems associated with removing various protecting groups from amide nitrogens, we reasoned that the *p*-methoxybenzyl group (MPM) would again be well suited to the task at hand. In the event, tyrosine *N*-methyl amide **17** was converted into **21** by reductive amination with *p*-anisaldehyde ($NaBH_4$, MeOH, 3Å molecular sieves; 81%). The reaction of **13** with an excess of the reagent obtained upon treating the *N*-protected tyrosine *N*-methyl amide derivative **21** with two equivalents of trimethylaluminum gave the dipeptide analogue **22** in 55% yield (Scheme 3). The oxidation of **22** to the corresponding aldehyde now proceeded in a straightforward fashion, and subsequent epimerization of the intermediate aldehyde gave **23** in 68%

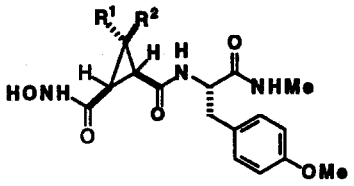
Scheme 3



overall yield in analogy with the related conversion of **14** → **15**. Oxidation of the aldehyde function in **23** gave the carboxylic acid **24**, which was coupled with hydroxylamine via a mixed anhydride protocol. Final removal of the *N*-(*p*-methoxybenzyl) group was achieved by acid-catalyzed solvolysis to give **10** in good overall yield from **24**.

With the conformationally restricted hydroxamic acid derivatives **9** and **10** in hand, it remained to compare their efficacy against that of the flexible collagenase inhibitor **8** to determine whether the three dimensional spatial orientations enforced by either pseudopeptide closely mimicked that of the bound conformation of **8**. Toward this end, compounds **8** -**10** were evaluated as inhibitors of the 92-kDa type IV collagenase[15] using a ^{14}C gelatin degradation assay.[16] Compound **10** had no observable activity against the activated enzyme at concentrations up to 100 μM. On the other hand, compound **9** was an inhibitor and exhibited an IC_{50} of approximately 50 μM,

although it was less potent than **8** ($IC_{50} \approx 1$ μM). Based upon these preliminary results, it is apparent that **9** more closely approximates the biologically active conformation of **8** at the P_1' subsite than **10**. However, it is also clear that the orientation of the backbone atoms and the side chain of **9** does not accurately represent the bound conformation of **8** at P_1'. Consequently, we are in the process of preparing other stereochemical probes such as **25** and **26**, and the biological evaluation of these pseudopeptide ligands will provide additional insights into this issue. Related experiments to extend these studies to establishing the topographical requirements at the P_2' subsite of **8** are also in progress, and these results will be reported in due course.



25: $R^1 = i\text{-Pr}$; $R^2 = H$
26: $R^1 = H$; $R^2 = i\text{-Pr}$

EXPERIMENTAL SECTION

General. Unless otherwise noted, solvents and reagents were reagent grade and used without purification. Tetrahydrofuran (THF) was distilled from potassium/benzophenone ketyl under nitrogen, and dichloromethane (CH_2Cl_2) was distilled from calcium hydride prior to use. Reactions involving air or moisture sensitive reagents or intermediates were performed under an inert atmosphere of argon in glassware that had been oven or flame dried. Melting points are uncorrected. Infrared (IR) spectra were recorded either neat on sodium chloride plates or as solutions in $CHCl_3$ as indicated and are reported in wavenumbers (cm^{-1}) referenced to the 1601.8 cm^{-1} absorption of a polystyrene film. ^1H (300 MHz) and ^{13}C (75 MHz) NMR spectra were obtained as solutions in $CDCl_3$ unless otherwise indicated, and chemical shifts are reported in parts per million (ppm, δ) downfield from internal standard Me_4Si (TMS). Coupling constants are reported in hertz (Hz). Spectral splitting patterns are designated as s, singlet; br, broad; d, doublet; t, triplet; q, quartet; m, multiplet; and comp, complex multiplet. Flash chromatography was performed using Merck silica gel 60 (230-400 mesh ASTM). Percent yields are given for compounds that were ≥95% pure as judged by NMR.

4-Methyl-2-(Z)-pentenyl diazoacetate (11). The *p*-toluenesulfonylhydrazone of glyoxylic acid chloride[17] (3.19 g, 12.3 mmol) was added to a solution of 4-methyl-2-(*Z*)-penten-1-ol[18](1.12 g, 11.2 mmol) in dry CH_2Cl_2 (70 mL) at 0 °C, whereupon *N,N*-dimethylaniline (1.69 g, 14.0 mmol) was added. After stirring at 0 °C for 15 min, Et_3N (5.80 g, 57.5 mmol) was added slowly. The resulting dark suspension was stirred for 15 min at 0 °C and then for 30 min at room temperature, whereupon an equal volume of water was added. The reaction mixture was extracted with Et_2O (3 x 100 mL), and the combined organic fractions were dried ($MgSO_4$) and concentrated *in vacuo*. The crude **11** thus obtained was purified by flash chromatography using pentane/Et_2O (25:1) to furnish 14.3 g (76%) of pure **11** as a yellow oil: ^1H NMR δ 5.51-5.30 (comp, 2 H), 4.76 (s, 1 H), 4.72 (d, J = 6.1 Hz, 2 H), 2.70-2.62 (m, 1H), 0.99 (s, 3 H), 0.97 (s, 3 H); ^{13}C NMR δ 166.6, 142.8, 120.8, 60.6,

46.1, 37.4, 26.9, 22.9; IR ($CHCl_3$) ν 2114, 1687 cm^{-1}; mass spectrum, *m/z* 169.0988 (base) ($C_8H_{12}N_2O_2$+H requires 169.0977), 167, 149, 85.

[1*R*-(1α,5α,6α)]-6-(2-Propyl)-3-oxabicyclo[3.1.0]hexan-2-one (13). A solution of the diazoester **11** (0.80 g, 4.76 mmol) in dry CH_2Cl_2 (50 mL) was added *via* syringe pump to a refluxing solution of the chiral rhodium catalyst **12** (0.04 g, 0.05 mmol) in CH_2Cl_2 (188 mL) over a period of 12-18 h. The reaction was cooled to room temperature, and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography eluting with pentane/Et_2O (5:1) to give 0.59 g (85%) of **13** as a colorless oil in ≥94% enantiomeric excess.[9] ^1H NMR δ 4.42 (dd, *J* = 9.9, 5.6 Hz, 1 H), 4.14 (d, *J* = 9.9 Hz, 1 H), 2.36-2.29 (m, 1 H), 2.18 (dd, *J* = 8.7,6.9 Hz, 1H), 1.35-1.16 (comp, 2 H), 1.07 (d, *J* = 6.6 Hz, 3 H), 1.05 (d, *J* = 6.6 Hz, 3 H); ^{13}C NMR δ 174.6, 65.7, 29.7, 22.7, 22.4, 22.3, 21.6, 21.5; IR ($CHCl_3$) ν 1762 cm^{-1}; mass spectrum, *m/z* 141.0918 (base) ($C_8H_{12}O_2$+H requires 141.0916), 129, 123.

[1*R*-(1α,2α,3α)]-2-(Hydroxymethyl)-1-{*N*-[*O*-(*p*-methoxybenzyl)]-*N*-(*p*-methoxybenzyl)hydroxycarboxamido}-3-(2-propyl)cyclopropane (14). A solution of Me_3Al (0.68 mL of 2.0 M in hexane, 1.36 mmol) was slowly added to a solution of *N*-(*p*-methoxybenzyl)-*O*-(*p*-methoxybenzyl)-hydroxylamine[10] (0.37 g, 1.36 mmol) in dry $ClCH_2CH_2Cl$ (4 mL) at room temperature. After stirring at room temperature for 1 h, a solution of the lactone **13** (0.63 g, 0.45 mmol) in $ClCH_2CH_2Cl$ (2 mL) was added dropwise. The reaction was heated at 83 °C for 4 h, cooled to 0 °C, and carefully quenched with 1 N HCl (3 mL). The aqueous mixture was extracted with CH_2Cl_2 (3 x 10 mL), and the combined extracts were dried ($MgSO_4$) and concentrated under reduced pressure. The crude **14** was purified by flash chromatography using a hexanes/EtOAc (1:1) as eluent to give 0.13 g (70%) of pure **14** as a colorless oil: ^1H NMR δ 7.22 (d, *J* = 8.4 Hz, 2 H), 7.17 (d, *J* = 8.4 Hz, 2 H), 6.84 (d, *J* = 8.4 Hz, 2 H), 6.81 (d, *J* = 8.4 Hz, 2 H), 4.81 (d, *J* = 15.0 Hz, 1 H), 4.75 (d, *J* = 10.2 Hz, 1 H), 4.64 (d, *J* = 10.2 Hz, 1 H), 4.53 (d, *J* = 15.0 Hz, 1 H), 4.07-3.98 (m, 2 H), 3.74 (s, 3 H), 3.66 (s, 3 H), 2.77 (br s, 1 H), 2.19-2.17 (m, 1 H), 1.98-1.90 (m, 1 H), 1.63-1.57 (m, 1 H), 1.22-1.20 (m, 1 H), 0.91 (d, *J* = 6.6 Hz, 3 H), 0.78 (d, *J* = 6.6 Hz, 3 H); ^{13}C NMR δ 173.4, 159.8, 158.9, 130.5, 129.8, 128.5, 126.6, 113.8, 113.6, 76.6, 58.1, 55.0, 49.6, 49.4, 33.8, 26.2, 22.6, 22.5, 19.1; IR ν 3499, 1731, 1634 cm^{-1}; mass spectrum, *m/z* 414.2282 ($C_{24}H_{31}NO_5$+H requires 414.2280), 396, 274, 154, 121 (base).

[1*R*-(1α,2α,3α)]-1-{*N*-[*O*-(*p*-Methoxybenzyl)]-*N*-(*p*-methoxybenzyl)hydroxycarboxamido}-3-(2-propyl)cyclopropane-2-carboxaldehyde. To a solution of pyridinium chlorochromate (0.13 g, 0.62 mmol) in dry CH_2Cl_2 (2 mL) at room temperature was added a solution of the hydroxy amide **14** (0.13 g, 0.31 mmol) in CH_2Cl_2 (2 mL), and the reaction mixture was stirred for 12 h. The reaction was diluted with Et_2O (15 mL), the dark mixture was filtered through Celite, and the filtrate was concentrated under reduced pressure. The crude aldehyde was purified by flash chromatography using hexane/EtOAc (3:1) as eluant to give 0.11 g (87%) of the all cis aldehyde as viscous colorless oil: ^1H NMR δ 9.83 (d, *J* = 7.3 Hz, 1 H), 7.23 (d, *J* = 8.5 Hz, 2 H), 7.16 (d, *J* = 8.5 Hz, 2 H), 6.88-6.80 (comp, 4 H), 4.84 (d, *J* = 15.0 Hz, 1 H), 4.76 (d, *J* = 10.5 Hz, 1 H), 4.66 (d, *J* = 10.5 Hz, 1 H), 4.56 (d, *J* = 15.0 Hz, 1 H), 3.81 (s, 3 H), 3.78 (s, 3 H), 2.75-2.65 (m, 1 H), 2.52-2.38 (m, 1 H), 1.95-1.87 (m, 1 H), 1.56-1.48 (m, 1 H), 1.00 (d, *J* = 6.6 Hz, 3 H), 0.80 (d, *J* = 6.6 Hz, 3 H); ^{13}C NMR δ 201.1, 171.8, 160.1, 159.1, 130.8, 130.2, 128.4, 126.4, 114.1, 113.9, 77.1, 55.3, 49.8, 36.8, 33.3, 28.0, 22.8, 22.6, 22.3; IR ν 1692, 1647 cm^{-1}; mass spectrum, *m/z* 412.2128 (base) ($C_{24}H_{29}NO_5$+H requires 412.2124), 154, 121.

[1*R*-(1α,2β,3α)]-1-{*N*-[*O*-(*p*-Methoxybenzyl)]-*N*-(*p*-methoxybenzyl)hydroxycarboxamido}-3-(2-propyl)cyclopropane-2-carboxaldehyde (15). A solution of the cis-aldehyde from the preceeding experiment (0.11 g, 0.26 mmol) in degassed, anhydrous MeOH (10 mL) containing K_2CO_3 (0.18 g, 1.3 mmol), and the mixture was stirred at room temperature for 12 h. The mixture was diluted with H_2O (5 mL) and extracted with CH_2Cl_2 (3 x 15 mL); the combined extracts were dried ($MgSO_4$) and concentrated under reduced pressure to yield 0.10 g (94%) of **15** as a thick oil. The crude **15** was used in the next step without further purification ^1H NMR δ 9.35 (d, *J* = 3.3 Hz, 1 H), 7.24-7.18 (comp, 4 H), 6.87-6.81 (comp, 4 H), 4.82-4.75 (comp, 2 H), 4.68 (d, *J* = 10.4 Hz, 1 H), 4.57 (d, *J* = 15.0 Hz, 1 H), 3.78 (s, 3 H), 3.76 (s, 3 H), 2.81-2.77 (m, 1 H), 2.52-2.14 (m, 1 H), 1.76-1.71 (m, 1 H), 1.61-1.54 (m, 1 H), 0.96 (d, *J* = 6.6 Hz, 3 H), 0.76 (d, *J* = 6.6 Hz, 3 H); ^{13}C NMR δ 199.1, 170.1, 160.1, 159.2, 130.9, 130.1, 129.3, 126.3, 114.0, 113.7, 76.6, 55.1, 49.9, 38.6, 35.4, 26.9, 25.3, 21.5, 21.4; IR ν 1710, 1649 cm^{-1}; mass spectrum, *m/z* 412.2121 (base) ($C_{24}H_{29}NO_5$+H requires 412.2124), 154, 121.

[1*R*-(1α,2β,3α)]-1-{*N*-[*O*-(*p*-methoxybenzyl)]-*N*-(*p*-methoxybenzyl)hydroxycarboxamido}-3-(2-propyl)cyclopropane-2-carboxylic acid (16). To an ice cooled solution of **15** (0.11 g, 0.26 mmol) in acetone (8 mL) was added 8 N Jones reagent (0.45 mL, 3.6 mmol), and the reaction was stirred for 2 h at 0-5 °C. The mixture was diluted with H_2O (10 mL), extracted with CH_2Cl_2 (3 x 15 mL), and the combined extracts were dried ($MgSO_4$) and concentrated under reduced pressure. The crude acid was purified by flash chromatography using hexane/EtOAc (1:3) containing 2% AcOH as eluent to give 0.094 g (85%) of **16** as a yellow oil: ^1H NMR δ 7.22 (d, *J* = 8.6 Hz, 2 H), 7.19 (d, *J* = 8.7 Hz, 2 H), 6.86 (d, *J* = 8.6 Hz, 2 H),6.82 (d, *J* = 8.7 Hz, 2 H), 4.81-4.75 (comp, 2 H), 4.67 (d, *J* = 10.3 Hz, 1 H), 4.57 (d, *J* = 15 Hz, 1 H), 3.77 (s, 3 H), 3.76 (s, 3 H), 2.78-2.74 (m, 1 H), 2.24 (dd, J = 5.0, 4.9 Hz, 1 H), 1.71-1.65 (m, 1 H), 1.60-1.53 (m, 1 H), 0.99 (d, *J* = 6.5 Hz, 3 H), 0.75 (d, *J* = 6.5 Hz, 3 H); ^{13}C NMR δ 177.4, 170.3, 160.1, 159.1, 131.0, 130.2, 128.4, 126.3, 114.0, 113.8, 77.5, 55.2, 49.9, 38.7, 27.1, 26.2, 25.4, 22.3, 22.0; IR ν 2963, 1698, 1650 cm^{-1}; mass spectrum, *m/z* 428.2068 ($C_{24}H_{29}NO_6$+H requires 428.2073), 394, 320, 272, 153, 121(base).

***N*-[(1*R*-(1α,2β,3α))-1-{*N'*-[*O*-(*p*-methoxybenzyl)]-*N'*-(*p*-methoxybenzyl)hydroxycarboxamido}-3-(2-propyl)-2-cyclopropanoyl]-*O*-methyl-L-tyrosine-*N*-methylamide.** A solution of the cyclopropane carboxylic acid **16** (90 mg, 0.21 mmol), 1-hydroxybenzotriazole (HOBT) (90 mg, 0.67 mmol), and **17** (53 mg, 0.25 mmol) in dry DMF (3 mL) was cooled in a carbon tetrachloride-dry ice bath, and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC·HCl) (48 mg, 0.25 mmol) was added. The solution was allowed to warm to room temperature and stirred for 24 h. The resulting solution was partitioned between EtOAc (20 mL) and brine (3 x 10mL), and the organic layer was dried ($MgSO_4$) and evaporated to give a thick yellow oil. The crude product was purified by flash chromatography hexane/EtOAc (1:4) to give 96 mg (74%) of **9**: ^1H NMR δ ^1H NMR δ 7.15-7.04 (comp, 4 H), 7.00-6.97 (comp, 3 H), 6.78 (d, *J* = 5.7 Hz, 2 H), 6.75 (d, *J* = 5.9 Hz, 2 H), 6.66 (d, 8.5 Hz, 2 H), 6.11-6.10 (br s, 1 H), 4.75-4.69 (comp, 2 H), 4.59-4.46 (comp, 3 H), 3.70 (s, 6 H), 3.60 (s, 3 H), 2.91-2.87 (comp, 2 H), 2.71-2.68 (m, 1 H), 2.58 (d, *J* = 4.7 Hz, 3 H), 2.16-2.13 (m, 1 H), 1.58-1.49 (m, 2 H), 0.86 (d, *J* = 6.1 Hz, 3 H), 0.70 (d, *J* = 6.1 Hz, 3 H); ^{13}C NMR δ 171.6, 171.5, 171.1, 160.0, 159.1, 158.4, 130.9, 130.2, 128.6, 126.7, 126.4, 126.1, 114.0, 113.9, 113.8, 77.2, 55.5, 55.2, 55.0, 50.1, 37.8, 37.3, 28.1, 26.1, 25.5, 22.1, 21.9; IR ν 3450, 1651, 1645, 1612 cm^{-1}; mass spectrum, *m/z* 618.3176 ($C_{35}H_{43}N_3O_7$+H requires 618.3179), 587, 343, 271, 176,136 (base), 121.

***N*-[(1*R*-(1α,2β,3α))-1-(Hydroxycarboxamido)-3-(2-propyl)-2-cyclopropanoyl]-*O*-methyl-L-tyrosine-*N*-methylamide (9).** To a solution of the protected dipeptide from the preceeding experiment (20 mg, 0.032 mmol) in trifluoroacetic acid (1 mL) was added methanesulfonic acid (58 mg, 0.6 mmol), and the reaction mixture was stirred at room temperature for 24 h. The trifluoroacetic acid was removed *in vacuo* and the resulting adduct was dissolved in EtOAc (10 mL). Saturated aqueous $NaHCO_3$ (4 mL) was added to the solution and the organic layer was removed. The aqueous layer was saturated with NaCl and it was extracted with EtOAc (3x 10 mL). The combined extracts were dried ($MgSO_4$) and removed under vacuum. The crude product was recrystallized from EtOAc to yield **9** (9 mg, 75%) as a white solid: m.p. 254 °C (dec.); ^{1}H NMR (C_5D_5N) δ 9.72 (d, *J* = 8.5 Hz, 1 H), 8.85 (br s, 1 H), 7.21 (d, *J* = 8.5 Hz, 2 H), 6.79 (d, *J* = 8.5 Hz, 2 H), 5.25-5.20 (m, 1 H), 3.56 (s, 3 H), 3.31 (dd, *J* = 13.4, 7.6 Hz, 1 H), 3.09 (dd, *J* = 13.4, 8.0 Hz, 1 H), 2.93 (dd, *J* = 5.1, 5.0 Hz, 1 H), 2.73 (d, *J* = 4.5 Hz, 3 H), 2.65 (dd, *J* = 9.4, 5.0 Hz, 1 H), 2.06-2.00 (m, 1 H), 1.73-1.69 (m, 1 H), 0.89 (d, *J* = 6.5 Hz, 3 H), 0.79 (d, *J* = 6.5 Hz, 3 H); ^{13}C NMR (C_5D_5N) δ 172.5, 171.8, 168.0, 158.7, 130.8, 130.4, 114.1, 56.1, 54.9, 38.7, 35.8, 27.6, 26.7, 26.0, 22.6, 22.4; IR (C_5D_5N) ν 3403, 1670, 1667, 1538 cm^{-1}; mass spectrum, *m/z* 378.2027($C_{19}H_{27}N_3O_5$+H requires 378.2028), 321, 277, 207, 185 (base), 149.

***N*-[(1*R*-(1α,2α,3α))-2-(Hydroxymethyl)-3-(2-propyl)-cyclopropanoyl]-*N'*-(*p*-methoxybenzyl)-*O*-methyl-L-tyrosine-*N*-methylamide (22).** A solution of Me_3Al (4.29 mL of 2.0 M in hexanes, 8.58 mmol) was slowly added to a solution of the L-tyrosine derivative **21** (1.40 g, 4.29 mmol) in dry $ClCH_2CH_2Cl$ (10 mL) at room temperature. After stirring at room temperature for 1 h, a solution of the lactone **13** (0.20 g, 1.43 mmol) in $ClCH_2CH_2Cl$ (5 mL) was added dropwise. The reaction was heated at 83 °C for 36 h, whereupon it was cooled to 0 °C and carefully quenched with 2 N HCl (40 mL). The aqueous mixture was extracted with CH_2Cl_2 (3 x 25 mL), and the combined extracts were dried ($MgSO_4$) and concentrated under reduced pressure. The unreacted tyrosine amide could be recovered after neutralization of the aqueous layer with saturated aq. K_2CO_3 and extraction of the aqueous solution with CH_2Cl_2 (3 x 25 mL). The crude **22** was purified by flash chromatography using hexane/EtOAc (2:1) as eluent to give 0.37 g (55%) of pure **22** as a viscous oil: ^{1}H NMR δ 7.13 (d, *J* = 8.6 Hz, H), 7.02 (d, *J* = 8.6 Hz, 2 H), 6.85 (d, *J* = 8.5 Hz, 2 H), 6.75 (d, *J* = 8.5, 2 H), 6.14-6.12 (br q, 1 H), 5.09 (dd, *J* = 10.1, 5.2 Hz, 1 H), 4.82 (d, *J* = 17.7 Hz, 1 H), 4.72 (d, *J* = 17.7 Hz, 1 H), 4.05-4.02 (comp, 2 H), 3.79 (s, 3 H), 3.76 (s, 3 H), 3.15 (dd, *J* = 13.6, 10.1 Hz, 1 H), 2.71-2.64 (comp, 4 H), 1.85-1.73 (comp, 2 H), 1.65-1.57 (comp, 2 H), 1.26-1.13 (m, 1 H), 0.94 (d, *J* = 6.6 Hz, 3 H), 0.88 (d, *J* = 6.6 Hz, 3 H); ^{13}C NMR δ 174.3, 170.3, 158.8, 158.1, 130.1, 129.3, 129.2, 127.1, 114.1, 113.7, 59.0, 58.5, 55.3, 55.1, 48.9, 33.6, 26.2, 25.8, 23.3, 22.7, 22.5, 21.4; IR ($CHCl_3$) ν 3433, 2954, 1676, 1611 cm^{-1}; mass spectrum, *m/z* 469.2712 ($C_{27}H_{36}N_2O_5$+H requires 469.2702), 451, 438 (base), 277, 154, 121.

***N*-[(1*R*-(1α,2α,3α))-2-Formyl-3-(2-propyl)cyclopropanoyl]-*N'*-(*p*-methoxybenzyl)-*O*-methyl-L-tyrosine-*N*-methylamide.** Alcohol **22** (0.41 g, 0.88 mmol) was oxidized with PCC according to the procedure outlined for the oxidation of **14** to give 0.31 g (75%) of the corresponding cis aldehyde as a colorless glass: ^{1}H NMR δ 9.88 (d, *J* = 5.8 Hz, 1 H), 7.15 (d, *J* = 8.6 Hz, 2 H), 7.01 (d, *J* = 8.4 Hz, 2 H), 6.86 (d, *J* = 8.6 Hz, 2 H), 6.74 (d, *J* = 8.4 Hz, 2 H), 6.16 (br q, 1 H), 5.14 (dd, *J* = 10.4, 5.2 Hz, 1 H), 4.85 (d, *J* = 18.0 Hz, 1 H), 4.77 (d, *J* = 18.0 Hz, 1 H), 3.79 (s, 3 H), 3.75 (s, 3 H), 3.12 (dd, *J* = 13.3, 10.4 Hz, 1 H), 2.68-2.63 (comp, 4 H), 2.36 (dd, *J* = 8.8, 8.7 Hz, 1 H), 2.31-2.18 (m, 1 H), 1.95-1.87 (m, 1 H), 1.55-1.45 (m, 1 H), 1.07 (d, *J* = 6.6 Hz, 3 H), 0.97 (d, *J* = 6.6 Hz, 3 H); ^{13}C NMR δ 200.1, 171.3, 170.1, 158.8, 158.2, 130.1, 128.9, 126.9, 114.2, 113.7, 58.8, 55.2, 55.1, 48.6, 36.0, 33.6, 32.8, 30.7, 25.8, 22.7, 22.6, 22.4; IR ν 3422, 1681,

1616 cm^{-1}; mass spectrum, *m/z* 467.2549 (base) ($C_{27}H_{34}N_2O_5$+H requires 467.2545), 436, 329, 191, 165,121.

***N*-[(1*R*-(1α,2β,3α))-2-Formyl-3-(2-propyl)cyclopropanoyl]-*N'*-(*p*-methoxyphenyl methyl)-*O*-methyl-L-tyrosine-*N*-methylamide (23).** Prepared as a colorless glass in 91% yield from the cis aldehyde (0.10 g, 0.21 mmol) above in accordance with the procedure described for the preparation of **15**. ^1H NMR δ 9.37 (d, *J* = 3.7 Hz, 1 H), 7.13 (d, *J* = 8.5 Hz, 2 H), 7.02 (d, *J* = 8.5 Hz, 2 H), 6.84 (d, *J* = 8.6 Hz, 2 H), 6.74 (d, *J* = 8.6 Hz, 2 H), 6.12 (br q, 1 H), 5.16 (dd, *J* = 10.3, 5.1 Hz, 1 H), 4.86 (d, *J* = 17.8 Hz, 1 H), 4.74 (d, *J* = 17.8 Hz, 1 H), 3.79 (s, 3 H), 3.75 (s, 3 H), 3.14 (dd, *J* = 13.5, 10.3 Hz, 1 H), 2.72-2.60 (comp, 5 H), 2.44 (dd, *J* = 9.0, 4.4 Hz, 1 H), 1.60-1.57 (comp, 2 H), 1.01 (d, *J* = 5.9 Hz, 3 H), 0.83 (d, *J* = 5.9 Hz, 3 H); ^{13}C NMR δ 198.8, 170.2, 170.1, 158.8, 158.2, 130.1, 129.0,127.0, 114.3, 113.8, 58.9, 55.2, 55.1, 47.9, 38.3, 35.4, 33.6, 28.7, 25.9, 22.4, 21.7; IR ν 3422, 1681, 1616 cm^{-1}; mass spectrum, *m/z* 467.2536 (base) ($C_{27}H_{34}N_2O_5$+H requires 467.2545), 436, 359, 191, 121.

***N*-[(1*R*-(1α,2β,3α))-2-Carboxyl-3-(2-propyl)cyclopropanoyl]-*N'*-(*p*-methoxyphenyl methyl)-*O*-methyl-L-tyrosine-*N*-methylamide (24).** Prepared as a viscous oil in 76% yield by Jones oxidation of **23** (0.33 g, 0.71 mmol) according to the procedure outline above for the preparation of **16**. ^1H NMR δ 9.55 (br s, 1 H), 7.13 (d, *J* = 8.5 Hz, 2 H), 7.01 (d, *J* = 8.5 Hz, 2 H), 6.83 (d, *J* = 8.6 Hz, 2 H), 6.73 (d, *J* = 8.6 Hz, 2 H), 6.20 (br q, 1 H), 5.14 (dd, *J* = 10.3, 5.1 Hz, 1 H), 4.86 (d, *J* = 17.8 Hz, 1 H), 4.71 (d, *J* = 17.8 Hz, 1 H), 3.78 (s, 3 H), 3.74 (s, 3 H), 3.12 (dd, *J* = 13.6, 10.3 Hz, 1 H), 2.63-2.57 (comp, 4 H), 2.38-2.07 (comp, 2 H), 1.53-1.49 (comp, 2 H), 1.02 (d, *J* = 5.9 Hz, 3 H), 0.79 (d, *J* = 5.9 Hz, 3 H); ^{13}C NMR δ 176.9, 170.6, 170.2, 158.7, 158.1, 130.0, 129.0, 128.9, 127.1, 114.2,113.7, 58.9, 55.2, 55.0, 48.0, 38.3, 33.7, 28.7, 26.3, 26.0, 25.8, 22.3, 21.6; IR ν 3423, 2961, 1699, 1664, 1636 cm^{-1}; mass spectrum, *m/z* 483.2480 (base) ($C_{27}H_{34}N_2O_6$+H requires 483.2495), 452, 375, 191, 121.

***N*-[(1*R*-(1α,2β,3α))-2-(Hydroxycarboxamido)-3-(2-propyl)cyclopropanoyl]-*N'*-(*p*-methoxyphenyl methyl)-*O*-methyl-L-tyrosine-*N*-methylamide.** To a solution of the acid **24** (120 mg, 0.25 mmol) in THF (2 mL), at 0 °C, was added triethylamine (30 mg, 0.30 mmol) followed by isobutyl chloroformate (40 mg, 0.30 mmol). The solution was allowed to warm to room temperature and stirred for 1 h. The solution was then cooled to 0 °C, and hydroxylamine hydrochloride (90 mg, 1.24 mmol) and triethylamine (150 mg, 1.48 mmol) were added. The solution was allowed to warm to room temperature and stirred for 12 h, whereupon the solvent was removed under reduced pressure. The resultant solid was taken up in EtOAc (40 mL), washed with dilute citric acid (2 x 30 mL), dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by flash chromatography using hexane/EtOAc (1:3) containing 2% AcOH as eluent to provide 80 mg (65%) of pure hydroxamic acid as a white solid: m.p. 220 °C (dec); ^1H NMR (CD_3OD) δ 9.70 (br s, 2 H), 7.64 (br q, 1 H), 7.12 (d, *J* = 8.5 Hz, 2 H), 6.98-6.96 (d, *J* = 8.5 Hz, 2 H), 6.82 (d, *J* = 8.6 Hz, 2 H), 6.71 (d, *J* = 8.6 Hz, 2 H), 5.12-4.91 (comp, 2 H), 4.77 (d, *J* = 17.6 Hz, 1 H), 3.74 (s, 3 H), 3.72 (s, 3 H), 3.05 (dd, *J* = 13.6, 9.3 Hz, 1 H), 2.75 (dd, *J* = 13.6, 6.5 Hz, 1 H), 2.57 (d, *J* = 3.5 Hz, 3 H), 2.36 (dd, *J* = 9.3, 4.8 Hz, 1 H), 2.11 (dd, *J* = 5.0, 4.8 Hz, 1 H), 1.54-1.39 (comp, 2 H), 0.97 (d, *J* = 6.4 Hz, 3 H), 0.81 (d, *J* = 6.4 Hz, 3 H); ^{13}C NMR (C_5D_5N) δ ; IR (C_5D_5N) ν 3401, 1675, 1666, 1538 cm^{-1}; mass spectrum, *m/z* 498 (base), 497.2521 ($C_{27}H_{35}N_3O_6$ requires 497.2525), 467, 451, 175, 154, 121.

***N*-[(1*R*-(1α,2β,3α))-2-(Hydroxycarboxamido)-3-(2-propyl)cyclopropanoyl]-*O*-methyl-L-tyrosine-*N*-methylamide (10).** A solution of the protected amide (60 mg, 0.12 mmol) from the preceeding experiment in trifluoroacetic acid (15 mL) was stirred in a glass stoppered flask for 16 h. The trifluoroacetic acid

was removed by azeotropic distillation with benzene under reduced pressure to yield the crude product as a yellow solid which was recrystallized from $CHCl_3$/MeOH (15:1) to yield 30 mg (73%) of **10** as a white solid: m.p. 261-262 °C; ^1H NMR (C_5D_5N) δ 9.65 (d, J = 8.4 Hz, 1 H), 8.67 (br s, 1 H), 7.24 (d, J = 8.4 Hz, 2 H), 6.81 (d, J = 8.4 Hz, 2 H), 5.23-5.16 (m, 1 H), 3.56 (s, 3 H), 3.37 (dd, J = 13.5, 7.6 Hz, 1 H), 3.16 (dd, J = 13.5,7.0 Hz, 1 H), 3.04 (dd, J = 9.3, 4.7 Hz, 1 H), 2.81 (d, J = 4.5 Hz, 3 H), 2.68 (dd, J = 4.9, 4.8 Hz, 1 H), 2.13-2.06 (m, 1 H), 1.85-1.77 (m, 1 H), 0.95 (d, J = 6.5 Hz, 3 H), 0.87 (d, J = 6.4 Hz, 3 H); ^{13}C NMR (C_5D_5N) δ 172.4, 169.9, 169.7, 158.7, 130.7, 130.4, 114.1, 56.0, 54.0, 44.6, 38.2, 35.7, 28.3, 26.0, 25.9, 22.5, 22.3; IR (C_5D_5N) ν 3401, 1675, 1666, 1538 cm^{-1}; mass spectrum, *m/z* 378.2017 ($C_{19}H_{27}N_3O_5$+H requires 378.2029), 347, 188, 154, 115 (base), 113.

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