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Straightforward Stereoselective Access to Cyclic Peptidomimetics

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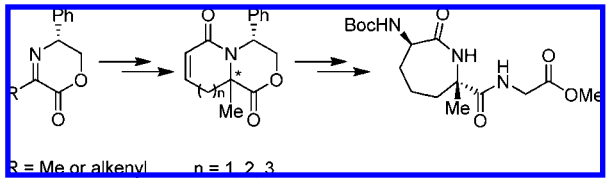

The preparation of cyclic dipeptide mimetics from chiral imino lactones derived from (*R*)-phenylglycinol is described. Key steps of the synthetic route included the fully stereoselective construction of a quaternary center, the formation of six-, seven-, or eight-membered lactams by means of an RCM cyclization, and the introduction of a new amino group within the lactam ring. The synthesis of a tripeptide mimetic is also reported.

The search for new peptidomimetic structures is a common approach to obtain drug-like compounds derived from biologically active peptides.[1] One of the most pursued strategies consists of the preparation of cyclic analogues in order to reduce the conformational freedom of the parent peptides.[2] In this context, many conformationally constrained mimics of reverse turns have been designed and synthesized, considering that turns are ubiquitous structural motifs in peptides and proteins and are also essential for folding and molecular recognition events.[3]

Among all types of reverse turns, β-turns are the most frequent and extensively studied. They involve four amino acid residues and are usually stabilized by an intramolecular hydrogen bond that forms a 10-membered ring (Figure 1). In fact,

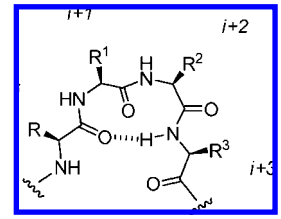

FIGURE 1. Structure of a β-turn.

evidence of this hydrogen bond typically serves to verify the β-turn pattern.[4] A large number of cyclic or bicyclic β-turn mimics have been described,[5] some of which exhibit biological activities.[6] Among them, Freidinger lactams are the most emblematic example.[7]

We report herein a new synthetic route for preparing potential β-turn mimics. The target compounds would consist of a cyclic dipeptide framework **1** of varying ring sizes, also containing a quaternary center that infers an additional element of constraint[8] (Scheme 1). This scaffold would be constructed with the aid of a ring-closing metathesis (RCM) reaction[9] from a suitable diene precursor **2** followed by the stereoselective introduction of a new amino group within the ring. We used chiral imino lactones **3** as starting materials, which can be easily prepared from the

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(8) For previous synthetic approaches to molecules related to **1**, see:(a) Westermann, B.; Diedrichs, N.; Krelaus, R.; Walter, A.; Gedrath, I. *Tetrahedron Lett.* **2004**, *45*, 5983–5986. (b) Cordero, F. M.; Pisaneschi, F.; Meschini Batista, K.; Valenza, S.; Machetti, F.; Brandi, A. *J. Org. Chem.* **2005**, *70*, 856–867. (c) Verbist, B. M. P.; De Borggraeve, W. M.; Toppet, S.; Compernolle, F.; Hoornaert, G. J. *Eur. J. Org. Chem.* **2005**, 2941–2950.

(9) The use of metathesis reactions in peptidomimetic synthesis has been recently reviewed; see: (a) Brik, A. *Adv. Synth. Catal.* **2008**, *350*, 1661–1675. For selected examples, see: (b) Fink, B. E.; Kym, P. R.; Katzenellenbogen, J. A. *J. Am. Chem. Soc.* **1998**, *120*, 4334–4344. (c) Hoffmann, T.; Lanig, H.; Waibel, R.; Gmeiner, P. *Angew. Chem., Int. Ed.* **2001**, *40*, 3361–3364. (d) Creighton, C. J.; Leo, G. C.; Du, Y.; Reitz, A. B. *Bioorg. Med. Chem.* **2004**, *12*, 4375–4385.

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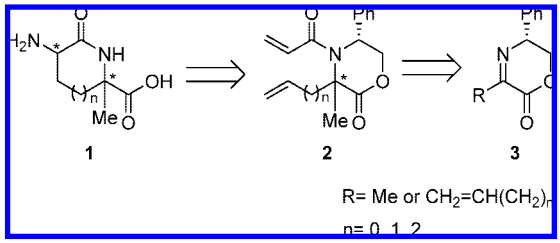
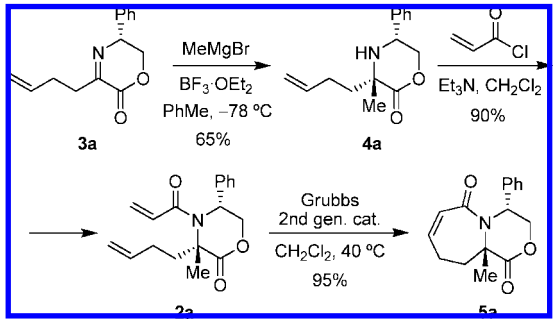
SCHEME 1. Synthetic Plan



SCHEME 2. Synthesis of Bicyclic Lactam 5a

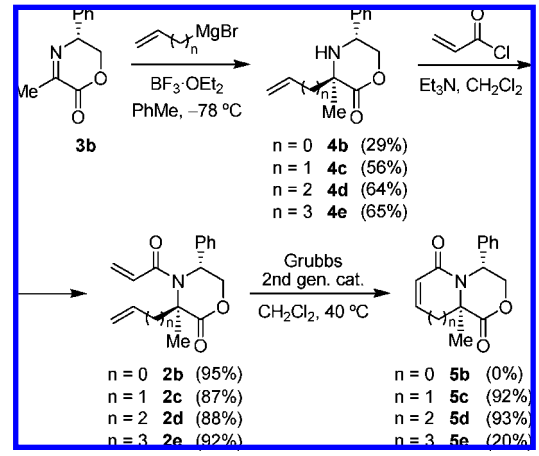


condensation of the corresponding α-keto esters with (*R*)-phenylglycinol.[10−12] These dipeptide mimetics **1** are suitable for further elongations at both C- and N-termini in order to complete the *β*-turn arrangement.

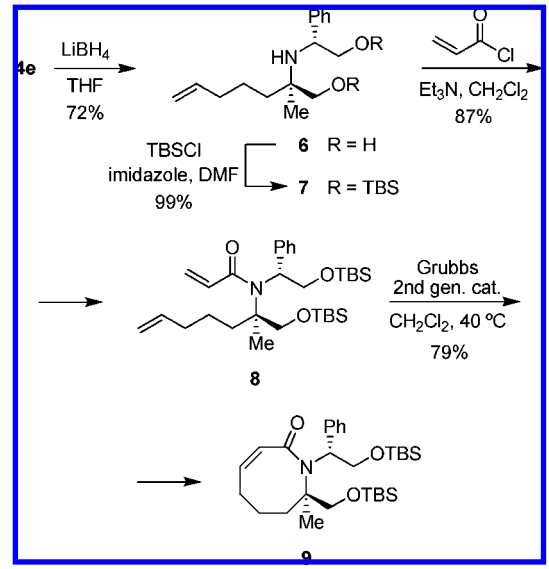
To test the feasibility of our strategy, we first employed unsaturated imine **3a**, available from ethyl 2-oxohex-5-enoate[13] and (*R*)-phenylglycinol (Scheme 2). Thus, chemo- and stereoselective addition[10] of MeMgBr mediated by $BF_3 \cdot OEt_2$ afforded morpholinone **4a** as a single isomer, having the phenyl and methyl groups in *trans* relationship.[14,15] Next, reaction of **4a** with acryloyl chloride led to diene **2a**, which in turn easily cyclized in the presence of second generation Grubbs catalyst to produce the corresponding RCM compound **5a**.

We next explored the possibility of accessing other ring sizes and stereochemical arrangements. Since imino lactones related to **3a** containing allyl or vinyl groups are difficult to obtain, we decided to develop a common synthetic route starting from the previously reported methyl imine **3b**[10] (Scheme 3). Thus, addition of vinyl-, allyl-, but-3-enyl-, and pent-4-enylmagnesium bromides afforded compounds **4b**−**e**,[16] which were then converted into acrylamides **2b**−**e**. However, the subsequent RCM reaction (second generation Grubbs catalyst, refluxing CH_2Cl_2)

SCHEME 3. Synthesis of Bicyclic Lactams 5c−e



SCHEME 4. Synthesis of Eight-Membered Lactam 9



only proceeded satisfactorily in the case of six- and seven-membered rings to give compounds **5c** and **5d**, respectively. The corresponding five-membered compound **5b** was not detected,[17] most probably due to the highly congested structure of the diene precursor[18] and the presence of the quaternary center, whereas eight-membered product **5e** was obtained in low yield using refluxing toluene.

An alternative approach to the five- and eight-membered rings would be the prior opening of the lactone before the RCM process in order to eliminate any element of constraint that might preclude the cyclization step. Thus, reduction of lactone **4e** with $LiBH_4$ followed by TBS protection of the resulting diol **6** afforded bis-silyl ether **7** (Scheme 4). In this case, the derived acrylamide **8** smoothly cyclized to produce eight-membered lactam **9**. In contrast, the preparation of the corresponding five-membered compound using a similar sequence was yet again ineffective.

(10) Harwood, L. M.; Vines, K. J.; Drew, M. G. B. *Synlett* **1996**, 1051–1053.

(11) We have recently used imines **3** in the preparation of optically pure *β*-amino-α-trifluoromethyl alcohols by means of the addition of $TMSCF_3$ to the lactone moiety. See: Fustero, S.; Albert, L.; Aceña, J. L.; Sanz-Cervera, J. F.; Asensio, A. *Org. Lett.* **2008**, *10*, 605–608.

(12) Related chiral templates such as Williams' diphenyloxazinones have also been used in the synthesis of quaternary amino acids; see: Williams, R. M.; Zhai, W. *Tetrahedron* **1988**, *44*, 5425–5430.

(13) Macritchie, J. A.; Silcock, A.; Willis, C. L. *Tetrahedron: Asymmetry* **1997**, *8*, 3895–3902.

(14) The configuration of the new stereogenic center was assumed as depicted according to previous results (see ref 10) and confirmed in subsequent transformations carried out. Moreover, the stereochemical integrity was preserved in the Grignard addition step as determined by chiral HPLC analysis of compounds **4**.

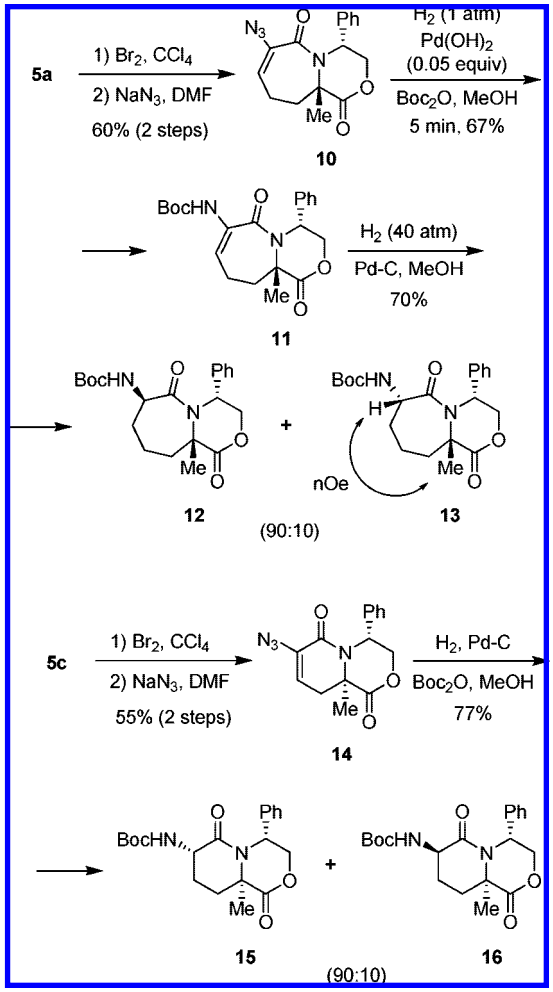
(15) A diastereoselective radical addition of alkyl groups to iminolactones **3** was also reported; see: Miyabe, H.; Yamaoka, Y.; Takemoto, Y. *J. Org. Chem.* **2005**, *70*, 3324–3327.

(16) For the synthesis of a trifluoromethyl analogue of **4c**, see: Chaume, G.; Van Severen, M.-C.; Marinkovic, S.; Brigaud, T. *Org. Lett.* **2006**, *8*, 6123–6126.

(17) Other conditions tested included the use of Grubbs second generation catalyst in the presence of $Ti(O\text{-}i\text{-}Pr)_4$, Grubbs-Hoveyda catalyst, or heating under microwave irradiation. In all cases the starting material was recovered unchanged.

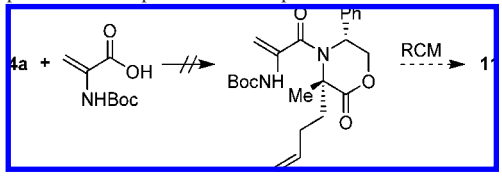
(18) Preparation of five-membered lactams fused with other rings by means of RCM are very scarce in the literature; see: (a) Lim, S. H.; Ma, S.; Beak, P. *J. Org. Chem.* **2001**, *66*, 9056–9062. (b) Muroni, D.; Mucedda, M.; Saba, A. *Tetrahedron Lett.* **2008**, *49*, 2373–2376.

SCHEME 5. Functionalizations of Lactams 5a and 5c

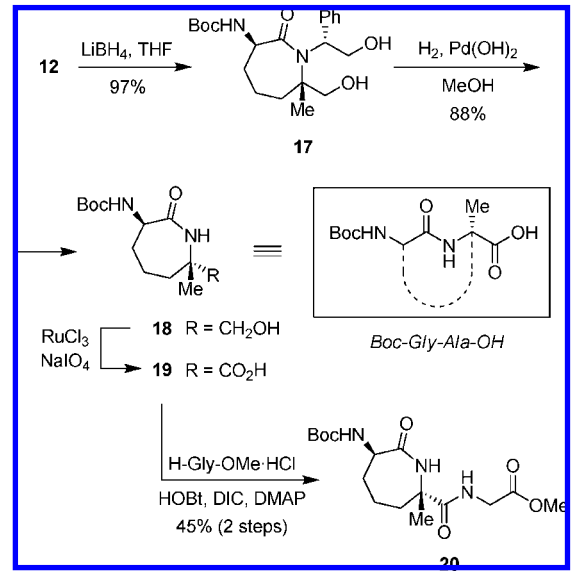


The following step was to locate an amino group next to the lactam carbonyl in compounds **5** or **9**.[19] After much experimentation, functionalization of the double bond in compound **5a** was most efficiently carried out by reaction with Br_2, thus producing a mixture of diastereoisomeric dibromides that were then converted into vinyl azide **10** (Scheme 5). At this point, hydrogenation of the double bond and the azide functionality in the presence of Boc_2O furnished an equimolecular mixture of epimers **12** and **13**, regardless of the different reaction conditions examined (catalyst, solvent, and hydrogen pressure). However, a much more selective result was achieved in a two-step process through the partial reduction of the azide to the corresponding *N*-Boc-amine **11** (5 mol % $Pd(OH)_2$, 5 min) followed by the further hydrogenation of the double bond at high pressure to give **12** as the major product with 90:10 selectivity. Both epimers were easily separated by column chromatography, and the configuration of the newly created stereogenic center was deduced by NOE correlations carried out in both **12** and **13** (see Supporting Information). A similar sequence or reactions from six-membered lactam **5c** led to *N*-Boc-protected amines **15** and **16**, also with good selectivity. In this case, the configuration of the amino group was deduced by coupling constant measurements.

(19) Direct coupling of amine **4a** with a *N*-Boc-protected dehydroalanine failed to provide a RCM precursor of compound **11**.



SCHEME 6. Synthesis of Tripeptide 20



The observed selectivity in the hydrogenation of lactams **11** and **14** may be rationalized by the blocking effect of the methyl group, which hinders one of the faces of the double bond. Thus, the methyl and BocNH groups are displayed in *cis* relationship in the resulting major diastereoisomers **12** and **15**, respectively. Conversely, the different behavior toward hydrogenation of vinyl azide **10** and *N*-Boc amine **11** could possibly originate from the much larger steric size of the BocNH group in the latter compound.

Finally, we carried out the removal of the chiral auxiliary by reduction of bicyclic lactam **12** to diol **17**,[20] followed by hydrogenation to monocyclic lactam **18** and reoxidation to obtain carboxylic acid **19** (Scheme 6). This compound constitutes a cyclic analogue of dipeptide Boc-Gly-Ala-OH, and the Boc protecting group may act as a surrogate of the amino acid *i* of a β-turn structure. To complete the β-turn pattern, the introduction of a new amino acid residue ($i + 3$) took place through the condensation of **19** with glycine methyl ester to finally obtain tripeptide mimetic **20**.[21]

In summary, an efficient access to cyclic dipeptide structures from simple, chiral templates derived from (*R*)-phenylglycinol has been developed. These compounds could represent the central segment of prospective cyclic β-turn scaffolds. Further synthetic work and conformational analysis of the target peptidomimetics are in progress.

Experimental Section

(4*R*,10a*S*)-10a-Methyl-4-phenyl-3,4,10,10a-tetrahydro-1*H*-[1,4]oxazino[4,3-*a*]azepine-1,6(9*H*)-dione (5a). Grubbs second generation

(20) Base-mediated transesterification or hydrogenolysis at high pressure of the lactone ring in **12** failed to give the corresponding hydroxy ester or hydroxy acid.

(21) Related seven-membered lactams were prepared by Holmes and co-workers, although lacking the quaternary center. In their work, the *cis* diastereoisomer had an extended conformation, whereas the *trans* isomer formed a β-turn structure. See: Nadin, A.; Derrer, S.; McGeary, R. P.; Goodman, J. M.; Raithby, P. R.; Holmes, A. B.; O'Hanlon, P. J.; Pearson, N. D. *J. Am. Chem. Soc.* **1995**, *117*, 9768–9769.

catalyst (107 mg, 0.13 mmol) was added to a solution of **2a** (754 mg, 2.52 mmol) in CH_2Cl_2 (60 mL). The mixture was heated at reflux for 2 h, allowed to cool to room temperature, and concentrated at reduced pressure. The product was purified by column chromatography on silica to afford 648 mg of **5a** as a white solid (95% yield). R_f 0.16 (hexane/EtOAc, 2:1). Mp: 208−209 °C. $[\alpha]^{25}_D$ −30.7 (*c* 0.9, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.70 (s, 3H), 2.07 (ddd, J = 15.5, 11.3, 5.9 Hz, 1H), 2.44−2.69 (m, 2H), 3.11 (dddd, J = 14.9, 6.0, 3.2, 1.2 Hz, 1H), 4.84 (dd, J = 12.0, 2.6 Hz, 1H),4.89 (dd, J = 12.0, 2.6 Hz, 1H), 5.93 (br, 1H), 6.13 (dq, J = 12.5, 1.3 Hz, 1H), 6.34 (dtd, J = 12.5, 3.9, 0.9 Hz,1H), 7.24−7.37 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.5, 27.2, 34.7, 53.7, 61.5, 69.3, 126.7, 126.7, 128.0, 128.9, 136.9, 140.9, 165.9, 171.5. HRMS (FAB) calcd for $C_{16}H_{18}NO_3$ $[M + 1]^+$ 272.1287; found 272.1292.

(4*R*,7*R*,10a*S*)-7-(*tert*-Butoxycarbonylamino)-10a-methyl-4-phenylhexahydro-1*H*-[1,4]oxazino[4,3-*a*]azepine-1,6(7*H*)-dione (12) and (4*R*,7*S*,10a*S*)-7-(*tert*-Butoxycarbonylamino)-10a-methyl-4-phenylhexahydro-1*H*-[1,4]oxazino[4,3-*a*]azepine-1,6(7*H*)-dione (13). Pd−C (10 wt %, 68 mg, 0.64 mmol) was added to a solution of **11** (200 mg, 0.64 mmol) in MeOH (12.8 mL). The mixture was stirred under H_2 atmosphere (40 atm) for 18 h, filtered, and concentrated at reduced pressure. The product was purified by column chromatography on silica to afford 157 mg of **12** (63% yield) and 17 mg of **13** (7% yield), both as white solids. Data for **12**: R_f 0.22 (hexane/EtOAc, 2:1). Mp: 106−107 °C. $[\alpha]^{25}_D$ −77.2 (*c* 1.2, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.41 (s, 9H), 1.82 (s, 3H), 1.87−2.04 (m, 2H), 2.05−2.22 (m, 1H), 2.22−2.46 (m, 2H), 3.07 (dd, J = 16.3, 5.2 Hz, 1H), 4.19 (d, J = 9.0 Hz, 1H), 4.49 (dd, J = 12.0, 1.3 Hz, 1H), 5.08 (dd, J = 12.4, 3.4 Hz, 1H), 5.54 (d, J = 2.0 Hz, 1H), 5.83 (br, 1H), 7.08 (d, J = 6.9 Hz, 2H), 7.26−7.42 (m, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 18.6, 25.1, 28.0, 28.3, 32.2, 54.1, 57.2, 63.4, 68.9, 79.6, 125.2, 127.8, 129.0, 139.8, 155.4, 170.7, 172.0. HRMS (EI) calcd for $C_{21}H_{28}N_2O_5$ $[M]^+$ 388.1998; found 388.1990. Data for **13**: R_f 0.34 (hexane/EtOAc, 2:1). Mp: 123−124 °C. $[\alpha]^{25}_D$ −86.5 (*c* 1.1, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.34−1.60 (m, 1H), 1.44 (s, 9H), 1.64−2.19 (m, 4H), 1.86 (s, 3H), 2.55 (d, J = 13.9 Hz, 1H), 4.60 (ddd, J = 12.1, 6.8, 2.6 Hz, 1H), 4.80 (dd, J = 12.1, 2.7 Hz, 1H), 4.89 (dd, J = 12.1, 1.8 Hz, 1H), 5.88 (d, J = 6.8 Hz, 1H), 6.02 (br, 1H), 7.22−7.40 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.5, 24.8, 28.3, 31.9, 36.0, 53.0, 54.6, 63.5, 68.2, 79.6, 127.2, 128.2, 129.0, 135.9, 155.2, 171.4, 172.7. HRMS (EI) calcd for $C_{21}H_{28}N_2O_5$ $[M]^+$ 388.1998; found 388.2003.

Methyl 2-((2*S*,6*R*)-6-(*tert*-Butoxycarbonylamino)-2-methyl-7-oxoazepane-2-carboxamido)acetate (20). $NaIO_4$ (706 mg, 3.30 mmol) and $RuCl_3 \cdot 2H_2O$ (2 mg, 0.01 mmol) were added to a solution of **18** (90 mg, 0.33 mmol) in 2:1:1.5 $MeCN/CH_2Cl_2/H_2O$ (3.3 mL) at 0 °C. The mixture was stirred at 0 °C for 3 h, and then H_2O was added. The aqueous layer was extracted with CH_2Cl_2, and the combined organic layers were dried over Na_2SO_4, filtered, and concentrated at reduced pressure. The crude acid **19** was dissolved in DMF (2.4 mL) and DIC (0.07 mL, 0.48 mmol), HOBt (65 mg, 0.48 mmol), H-Gly-OMe·HCl (60 mg, 0.48 mmol), and DMAP (15 mg, 0.12 mmol) were added. The mixture was stirred at room temperature for 12 h and then H_2O was added. The aqueous layer was extracted with EtOAc, and the combined organic layers were dried over Na_2SO_4, filtered, and concentrated at reduced pressure. The product was purified by column chromatography on silica to afford 54 mg of **20** as a white solid (45% yield). R_f 0.23 (hexane/EtOAc, 1:10). Mp: 151−152 °C. $[\alpha]^{25}_D$ −13.7 (*c* 1.0, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.39 (s, 9H), 1.33−1.46 (m, 2H), 1.50 (s, 3H), 1.72−2.09 (m, 3H), 2.46 (dt, J = 14.3, 3.3 Hz, 1H), 3.69 (s, 3H), 3.92−4.19 (m, 3H), 5.62 (d, J = 5.8 Hz, 1H), 6.75 (s, 1H), 7.23 (t, J = 5.5 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.7, 28.3, 30.3, 30.5, 37.9, 41.4, 52.2, 54.5, 60.2, 79.4, 154.8, 170.2, 173.1, 175.8. HRMS (FAB) calcd for $C_{16}H_{28}N_3O_6$ $[M + 1]^+$ 358.1978; found 358.1961.

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Supporting Information Available: Experimental procedures and characterization data and NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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