Synthesis of the $C_{1'}$−$C_{11'}$ Segment of Leucascandrolide A

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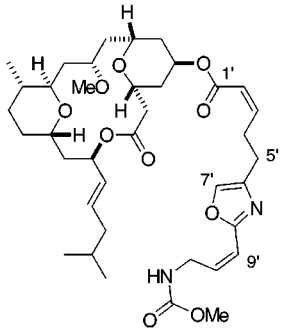
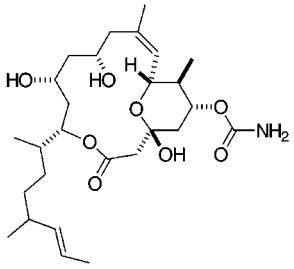
Introduction

Leucascandrolide A is a doubly bridged 18-membered macrolide of a new structural type isolated in 1996 from a calcareous sponge *Leucascandra caveolata* collected along the east coast of New Caledonia, Coral Sea.[1] It is quite likely that the actual biosynthetic origin of this compound as well as of leucascandrolide B is microbial.[2] While leucascandrolides were isolated in significant quantities (70 mg from 240 g, 0.03% yield, for leucascandrolide A) from largely necrotic and therefore possibly extensively colonized sponge, a subsequent expedition collecting intact sponge did not provide any trace of product.[2] The structure of leucascandrolide was determined by HRMS and MS−MS as well as by 2D NMR, and its absolute configuration was derived from degradation and Mosher ester studies.[1] The functional group and ring array of leucascandrolide A is vaguely reminiscent of the mycalolide class of macrolides.[3]



Leucascandrolide A



Leucascandrolide B

Leucascandrolide B differs from A by a smaller (i.e., 16- vs 18-membered), not uniformly 1,3-dioxygenated lactone ring, the lack of an oxazole in the side chain, and more extensive methyl branching. The biological profile of leucascandrolide A is quite powerful. The compound showed strong cytotoxic activity in vitro on KB and P388 cells (IC_{50}'s of 50 and 250 ng/mL), as well as very strong inhibition of *Candida albicans* (inhibition diameter of 26/40, 23/20, and 20/10 mm/μg per disk). The latter is interesting in view of the growing concern among AIDS patients about this pathogenic yeast. The Pietra group was able to remove the side chain from the macrolide and determine that the latter is essential for cytotoxic activity, whereas the former contributes mainly to the antifungal properties of leucascandrolide A. Leucascandrolide B lacks significant cytotoxic and antifungal activity.

Leucascandrolide A has an attractive range of cytotoxic and antifungal activities, but further investigations of its pharmacological and clinical potential are limited due to the lack of success in retrieving additional natural compound from sponge.[2] As part of our program on the synthesis of bioactive marine natural products,[4] we are interested in developing a total synthesis approach that can address the supply problem and provide crucial insights into structure−activity relationships. We now report the preparation of the $C_{1'}$−$C_{11'}$ side chain segment of the natural product.[5,6]

Results and Discussion

In consideration of the sensitivity of the two (*Z*)-alkenes in the oxazole side chain of leucascandrolide A, we decided to use an alkyne as a surrogate of the $C_{9'}$−$C_{10'}$ alkene and install the alkene moiety via Lindlar hydrogenation followed by a Still−Wittig reaction for the chain extension at the $C_{2'}$−$C_{3'}$ (*Z*)-alkene. A segment condensation of the readily available acid **3** and amino alcohol **4** would provide the precursor for the oxazole segment (Figure 1).

N-Acylation of propargylamine (**5**) with methylchloroformate followed by deprotonation with lithium hexamethyldisilazide and carboxylation of the anion with solid carbon dioxide provide alkynoate **3** in 55% overall yield (Scheme 1). After activation with PyBrOP,[7] condensation of acid **3** with amino alcohol **4** led to the unstable diamide **2** in 82% yield. The silyl ether **4** was obtained in a surprisingly selective monosilylation from known aminodiol **6**.[8]

Among other side reactions, hydroxy amide **2** readily rearranged to an amino ester derivative upon storage and was therefore immediately used for the next step. In preparation for a modified Robinson−Gabriel synthesis of the oxazole,[9] the primary alcohol function in **2** was

(1) D'Ambrosio, M.; Guerriero, A.; Debitus, C.; Pietra, F. *Helv. Chim. Acta* **1996**, *79*, 51.

(2) (a) D'Ambrosio, M.; Tato, M.; Pocsfalvi, G.; Debitus, C.; Pietra, F. *Helv. Chim. Acta* **1999**, *82*, 347. (b) D'Ambrosio, M.; Tato, M.; Pocsfalvi, G.; Debitus, C.; Pietra, F. *Helv. Chim. Acta* **1999**, *82*, 1135.

(3) See, for example: Matsunaga, S.; Liu, P.; Celatka, C. A.; Panek, J. S.; Fusetani, N. *J. Am. Chem. Soc.* **1999**, *121*, 5605−5606.

(4) (a) Wipf, P. *Chem. Rev.* **1995**, *95*, 2115. (b) Wipf, P.; Lim, S. *Chimia* **1996**, *50*, 157. (c) Wipf, P.; Xu, W. *J. Org. Chem.* **1996**, *61*, 6556. (d) Wipf, P.; Venkatraman, S. *J. Org. Chem.* **1996**, *61*, 6517. (e) Wipf, P.; Fritch, P. C. *J. Am. Chem. Soc.* **1996**, *118*, 12358. (f) Wipf, P. In *Alkaloids: Chemical and biological perspectives*; Pelletier, S. W., Ed.; Pergamon: New York, 1998; pp 187−228. (g) Wipf, P.; Yokokawa, F. *Tetrahedron Lett.* **1998**, *39*, 2223. (h) Wipf, P.; Uto, Y. *J. Org. Chem.* **2000**, *65*, 1037. (i) Wipf, P.; Reeves, J. T.; Balachandran, R.; Guiliano, K. A.; Hamel, E.; Day, B. W. *J. Am. Chem. Soc.* **2000**, *122*, 9391. (j) Wipf, P.; Miller, C. P.; Grant, C. M. *Tetrahedron* **2000**, *56*, 9143.

(5) For the preparation of the C_1−C_{13} fragment of leucascandrolide A, see: Crimmins, M. T.; Carroll, C. A.; King, B. W. *Org. Lett.* **2000**, *2*, 597.

(6) After the completion of our work, the first total synthesis of leucascandrolide A was disclosed: Hornberger, K. R.; Hamblett, C. L.; Leighton, J. L. *J. Am. Chem. Soc.* **2000**, *122*, 12894.

(7) (a) Frerot, E.; Coste, J.; Pantaloni, A.; Dufour, M.-N.; Jouin, P. *Tetrahedron* **1991**, *47*, 259. (b) Andrus, M. B.; Lepore, S. D.; Turner, T. M. *J. Am. Chem. Soc.* **1997**, *119*, 12159.

(8) (a) Houston, D. M.; Dolence, E. K.; Keller, B. T.; Patel-Thombre, U.; Borchardt, R. T. *J. Med. Chem.* **1985**, *28*, 467. (b) Herbrandson, H. F.; Wood, R. H. *J. Med. Chem.* **1969**, *12*, 620.

(9) (a) Wipf, P.; Miller, C. P. *J. Org. Chem.* **1993**, *58*, 3604. (b) Wipf, P.; Lim, S. *J. Am. Chem. Soc.* **1995**, *117*, 558. (c) Wipf, P.; Lim, S. *Chimia* **1996**, *50*, 157.

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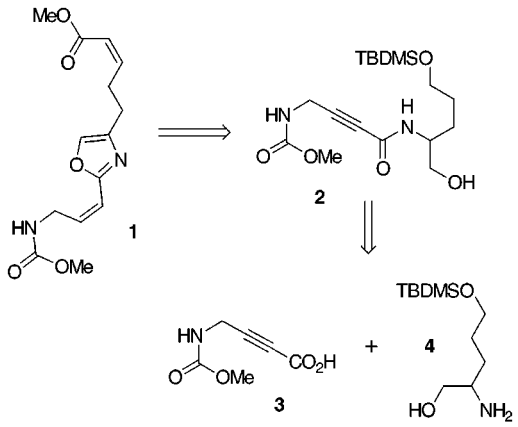
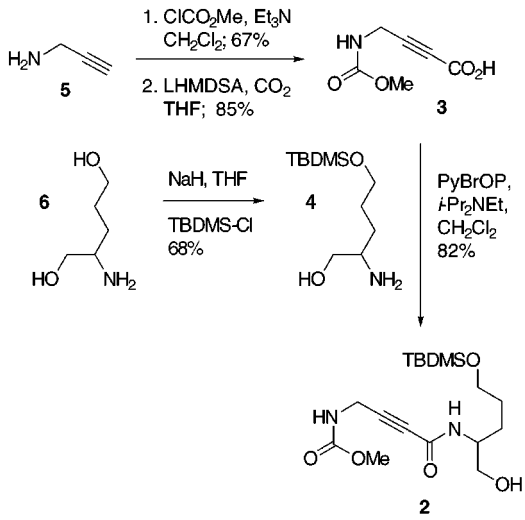


Figure 1. Retrosynthetic approach.

Scheme 1

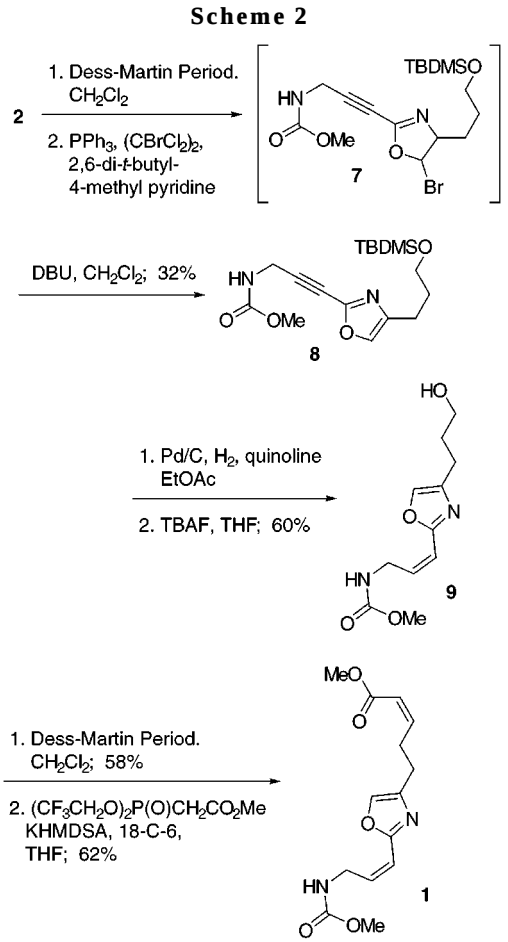


oxidized with Dess−Martin reagent (Scheme 2).[10] Cyclodehydration of the resulting aldehyde with triphenylphosphine in the presence of 2,6-di-*tert*-butyl-4-methylpyridine provided the intermediate bromooxazoline **7**,[9b,c] which readily eliminated hydrogen bromide upon treatment with DBU to give the chemically relatively stable oxazole **8** in 32% overall yield. At this point, the alkyne was converted to the (*Z*)-alkene under Lindlar conditions,[11] and primary alcohol **9** was obtained in 60% yield after removal of the silyl ether with TBAF in THF. A second Dess−Martin oxidation followed by a Still−Wittig condensation[12] provided the desired leucascandrolide side-chain methyl ester **1** as a single stereoisomer in 62% yield in addition to 16% of recovered aldehyde. All spectroscopic data, in particular, the ^{1}H and ^{13}C NMR resonances of **1**, were in close agreement with the corresponding shifts reported for the natural product.[1]

Conclusions

An efficient convergent pathway provided the $C_{1'}$−$C_{11'}$ side chain of the antifungal antitumor agent leucascandrolide A in nine steps and in 3.2% overall yield for the longest linear sequence. Highlights of the synthetic strategy are the preparation of the oxazole moiety by a mild three-stage process involving oxidation−cyclodehydration−dehydrohalogenation of the unstable alcohol **2** and the semihydrogenation of the alkyne moiety at the stage of the relatively stable oxazole **8** to give the novel *cis*-alkenyl oxazole derivative that is a unique structural feature of leucascandrolide A. Further progress toward the macrolide portion of this natural product will be reported in due course.

Scheme 2



Experimental Section

General Methods. All reactions with moisture-sensitive compounds were conducted in oven-dried glassware under an atmosphere of dry nitrogen. Solvents were dried by distillation from sodium benzophenone (THF) or from CaH_2 (CH_2Cl_2). Starting materials that were commercially available were used without purification. Melting points are uncorrected and were determined using crystallized samples. NMR spectra were obtained at 300 MHz/75 MHz (^{1}H/^{13}C) in $CDCl_3$ unless otherwise noted. 2-Aminopentane-1,5-diol (**6**) was prepared from L-glutamic acid according to literature procedures.[8]

Prop-2-ynylcarbamic Acid Methyl Ester. A solution of propargylamine (1.0 g, 18 mmol) and triethylamine (3.5 mL, 25 mmol) in CH_2Cl_2 (30 mL) was cooled to 0 °C and treated dropwise with methyl chloroformate (1.50 mL, 19.5 mmol). The reaction mixture was allowed to warm to room temperature, stirred overnight, and quenched with 6 N HCl (3 mL) and water (20 mL). The aqueous layer was extracted with ethyl acetate, and the combined organic layers were washed with brine, dried

(10) (a) Dess, D. B.; Martin, J. C. *J. Am. Chem. Soc.* **1991**, *113*, 7277. (b) Ireland, R. E.; Liu, L. *J. Org. Chem.* **1993**, *58*, 2899.
(11) Marvell, E. N.; Li, T. *Synthesis* **1973**, 457.
(12) Still, W. C.; Gennari, C. *Tetrahedron Lett.* **1983**, *24*, 4405.

(Na_2SO_4), and filtered. The solution was evaporated onto SiO_2 and purified by chromatography on SiO_2 (ethyl acetate/hexanes, 3:7 to 6:4) to yield 1.36 g (67%) of prop-2-ynylcarbamic acid methyl ester as a colorless oil: R_f 0.5 (ethyl acetate/hexanes, 2:3); IR (neat) 3296, 2955, 2123, 1712, 1530, 1256 cm^{-1}; ^1H NMR δ 5.3−5.1 (b, 1 H), 3.92 (bs, 2 H), 3.64 (s, 3 H), 2.21 (s, 1 H); ^{13}C NMR δ 156.8, 80.0, 71.5, 52.5, 30.9; MS(EI) *m/z* (rel intensity) 113 (M^+, 49), 98 (100), 82 (18); HRMS *m/z* calcd for $C_5H_7N_1O_2$ 113.0477, found 113.0479.

4-Methoxycarbonylaminobut-2-ynoic Acid (3). A solution of lithium hexamethyldisilazide (1.06 M, 11.5 mL, 12.2 mmol) in THF (120 mL) was cooled to −78 °C and treated dropwise with a solution of prop-2-ynylcarbamic acid methyl ester (649 mg, 5.74 mmol) in THF (10 mL). The reaction mixture was stirred for 1 h at −78 °C. Subsequently, carbon dioxide (from dry ice) was bubbled through the solution for 2 h. The reaction mixture was quenched at −78 °C by aqueous, saturated $NaHCO_3$ (5 mL). After being warmed to room temperature, the solution was acidified with 6 N HCl and extracted with ethyl acetate. The combined organic layers were concentrated, and the residue was dissolved in aqueous $NaHCO_3$ and washed with CH_2Cl_2. The aqueous layer was acidified by slow addition of concentrated HCl and extracted with ethyl acetate. The combined organic extracts were dried (Na_2SO_4) and concentrated to yield 770 mg (85%) of **3** as a slightly yellow oil that crystallized to a white solid upon standing: R_f 0.4 (ethyl acetate/hexanes/TFA, 40:60:1): mp 95−96 °C; IR (neat) 3337, 2959, 2244, 1708, 1532, 1255 cm^{-1}; ^1H NMR (CD_3OD) δ 4.04 (s, 2 H), 3.68 (s, 3 H); ^{13}C NMR (CD_3OD) δ 159.3, 156.1, 85.2, 75.8, 53.0, 31.2; MS(EI) *m/z* (rel intensity), 157 (M^+, 54), 139 (38), 113 (7), 98 (100), 82 (15), 81(15), 59 (20); HRMS *m/z* calcd for $C_6H_7N_1O_4$ 157.0375, found 157.0380.

2-Amino-5-(*tert*-butyldimethylsilanyloxy)pentan-1-ol (4). To a suspension of freshly washed (hexanes) sodium hydride (60% dispersion in mineral oil, 41 mg, 1.03 mmol) in THF (40 mL) was added a solution of 2-amino-1,5-pentanediol (122 mg, 1.03 mmol) in hot THF (10 mL). The reaction mixture was stirred for 8 h at room temperature and then treated dropwise with *tert*-butyldimethylsilyl chloride (1 M in THF, 1 mL, 1 mmol). After 20 min, the reaction mixture was evaporated onto SiO_2, and chromatography on SiO_2 (CH_2Cl_2/methanol/NH_4OH, 95:5:0 to 90:10:0 to 90:10:1) yielded 160 mg (68%) of **4** as a pale yellow oil: R_f = 0.3−0.4 (CH_2Cl_2/MeOH, 9:1, 3-fold developed); IR (neat) 3345, 2929, 2858, 1635, 1521, 1471, 1388, 1361, 1255, 1098, 836, 776 cm^{-1}; ^1H NMR δ 4.05−3.95 (b, 4 H), 3.69 (t, 1 H, J = 9.4 Hz), 3.63 (t, 3 H, J = 5.7 Hz), 3.45 (t, 1 H, J = 9.4), 3.07 (bs, 1 H), 1.65−1.49 (m, 4 H), 0.88 (s, 9 H), 0.05 (s, 6 H); ^{13}C NMR δ 65.0, 63.1, 53.4, 29.3, 26.2, 18.6, −5.1; MS(EI) *m/z* (rel intensity) 202 ([M − CH_2OH]$^+$, 27), 176 (4), 159 (34), 141 (10), 129 (7), 101(12), 84 (47), 75 (84), 70 (100), 56 (20); HRMS *m/z* calcd for $C_{10}H_{24}NOSi$ (M − CH_2OH) 202.1627, found 202.1629.

[3-[4-(*tert*-Butyldimethylsilanyloxy)-1-hydroxymethylbutylcarbamoyl]prop-2-ynyl]carbamic Acid Methyl Ester (2). To a solution of **4** (149 mg, 0.639 mmol) and **3** (84 mg, 0.54 mmol) in CH_2Cl_2 (2 mL) was added diisopropylamine (186 μL, 1.07 mmol). The reaction mixture was cooled to −10 °C, treated with PyBrOP (350 mg, 0.751 mmol), and allowed to warm to room temperature. After 6 h, the reaction was quenched with aqueous $NaHCO_3$. The organic layer was diluted with CH_2Cl_2 (8 mL), sequentially washed with 0.1 N HCl, water, and brine, and dried (Na_2SO_4). The solvent was removed under vacuum to yield an orange viscous oil. Purification by chromatography on SiO_2 (ethyl acetate) gave 163 mg (82%) of **2** as a slightly yellow oil: R_f 0.5 (ethyl acetate). This compound proved to be very unstable and was therefore used immediately after preparation.

[3-[4-[3-(*tert*-Butyldimethylsilanyloxy)propyl]-oxazol-2-yl]prop-2-ynyl]carbamic Acid Methyl Ester (8). To a solution of **2** (75 mg, 0.20 mmol) in CH_2Cl_2 (5 mL) was added Dess−Martin periodinane (171 mg, 0.404 mmol). The reaction mixture was stirred for 1 h and purified by chromatography on SiO_2 (ethyl acetate/hexanes, 3:2). The resulting clear oil was immediately dissolved in CH_2Cl_2 (10 mL) and treated with triphenylphosphine (165 mg, 0.629 mmol), 2,6-di-*tert*-butyl-4-methylpyridine (332 mg, 1.617 mmol), and 1,2-dibromo-1,1,2,2-tetrachloroethane (204 mg, 0.626 mmol). The reaction mixture was stirred for 10 h, treated with DBU (266 μL, 1.78 mmol), and stirred for an additional 6 h. Purification by chromatography on SiO_2 (ethyl acetate/hexanes, 3:7) gave 23 mg (32%) of **8** as a slightly yellow oil: R_f 0.5 (ethyl acetate/hexanes, 2:3); IR (neat) 2954, 2929, 2857, 2250, 1729, 1587, 1534, 1472, 1255, 1102, 837, 777 cm^{-1}; ^1H NMR δ 7.33 (s, 1 H), 5.11 (bs, 1 H), 4.22 (d, 2 H, J = 5.5 Hz), 3.70 (bs, 3 H), 3.62 (t, 2 H, J = 6.1 Hz), 2.57 (t, 2 H, J = 7.6 Hz), 1.82 (tt, 2 H, J = 7.2, 6.6 Hz), 0.87 (s, 9 H), 0.02 (s, 6 H); ^{13}C NMR δ 156.7, 145.8, 142.1, 135.4, 87.9, 71.7, 62.2, 52.8, 31.5, 31.3, 26.1, 22.7, 18.5, −5.1; MS(EI) *m/z* (rel intensity) 337 ([M − CH_3]$^+$, 68), 295 (100), 263 (45), 238 (31), 98 (14), 89 (11), 75 (19), 73 (15), 59 (12); HRMS *m/z* calcd for $C_{13}H_{19}N_2O_4Si$ (M − $C(CH_3)_3$) 295.1114, found 295.1116.

[3-[4-(3-Hydroxypropyl)oxazol-2-yl]allyl]carbamic Acid Methyl Ester (9). To a solution of **8** (90 mg, 0.26 mmol) in ethyl acetate (30 mL) were added quinoline (50 μL, 0.42 mmol) and Lindlar's catalyst (90 mg). The reaction mixture was stirred for 3 h at room temperature under hydrogen (1 atm) and filtered through Celite, and the resulting yellow-orange residue was dissolved in THF (20 mL). Tetrabutylammonium fluoride (150 mg, 0.57 mmol) was added, and the reaction mixture was stirred at room temperature for 14 h. The solvent was removed under vacuum, and purification of the resulting red, oily residue by chromatography on SiO_2 (ethyl acetate) gave **9** as a slightly yellow oil (36.4 mg, 60%): R_f 0.2 (EtOAc); IR (neat) 3327, 2925, 2851, 1704, 1523, 1264, 1055 cm^{-1}; ^1H NMR δ 7.37 (s, 1 H), 6.29 (d, 1 H, J = 11.8 Hz), 6.08 (dt, 1 H, J = 11.7, 6.4 Hz), 5.50 (bs, 1 H), 4.35−4.25 (m, 2 H), 3.72 (t, 2 H, J = 6.1 Hz), 3.68 (s, 3 H), 2.66 (t, 2 H, J = 7.1 Hz), 2.25 (bs, 1 H), 1.90 (tt, 2 H, J = 6.8, 6.4 Hz); ^{13}C NMR δ 160.2, 157.4, 141.7, 136.7, 134.0, 116.7, 62.3, 52.4, 39.7, 31.4, 23.0; MS(EI) *m/z* (rel intensity) 240 (M^+, 100), 222 (7), 208 (40), 195 (29), 181 (23), 163 (25), 151 (29), 136 (31), 47 (125), 81 (57), 66 (45), 54 (33); HRMS *m/z* calcd for $C_{11}H_{16}N_2O_4$ 240.1110, found 240.1119.

[3-[4-(3-Oxopropyl)oxazol-2-yl]allyl]carbamic Acid Methyl Ester. To a solution of **9** (7 mg, 0.03 mmol) in CH_2Cl_2 (10 mL) was added Dess−Martin periodinane (24 mg, 0.057 mmol). The reaction mixture was stirred for 1 h, concentrated, and purified by chromatography on SiO_2 (ethyl acetate/hexanes, 4:1−1:0) to yield 4 mg (58%) of [3-[4-(3-oxopropyl)oxazol-2-yl]allyl]carbamic acid methyl ester as a clear, colorless oil: R_f 0.4, ethyl acetate/

hexanes, 4:1). This compound proved to be unstable and was therefore used immediately after preparation.

5-[2-(3-Methoxycarbonylaminopropenyl)oxazol-4-yl]pent-2-enoic Acid Methyl Ester (1). A solution of 18-crown-6 (104 mg, 0.393 mmol) and bis(2,2,2-trifluoroethyl)(methoxycarbonylmethyl) phosphonate (20 μL, 0.10 mmol) in THF (2 mL) was cooled to −78 °C and treated with a solution of potassium hexamethyldisilazide (16 mg, 0.080 mmol) in THF (1 mL). The reaction mixture was stirred for 5 min, and then a solution of [3-[4-(3-oxopropyl)oxazol-2-yl]allyl]carbamic acid methyl ester (18.3 mg, 0.0770 mmol) in THF (5 mL) was added dropwise with stirring. After 3 h at −78 °C, the mixture was quenched with saturated aqueous NH_4Cl. Upon warming to room temperature, the aqueous layer was diluted with water and extracted with CH_2Cl_2, and the combined organic layers were dried (Na_2SO_4) and filtered. The solvent was removed under vacuum to give a slightly yellow oil that was purified by chromatography on SiO_2 (ethyl acetate/CH_2Cl_2, 1:4 to 2:3) to yield 3 mg (16%) of recovered aldehyde and 14 mg (62%) of **1** as a clear, colorless oil: R_f 0.4 (ethyl acetate/CH_2Cl_2, 1:4); IR (neat) 3348, 3136, 2993, 2951, 2923, 2852, 1721, 1521, 1252, 1198, 1003 cm^{-1}; ^{1}H NMR δ 7.37 (s, 1 H); 6.23−6.31 (m, 2 H), 6.10 (dt, 1 H, J = 11.6, 6.4 Hz), 5.82 (dt, 1 H, J = 11.5, 1.6 Hz), 5.57 (bs, 1 H), 4.35−4.25 (m, 2 H), 3.71 (s, 3 H), 3.68 (s, 3 H), 3.01 (ddt, 2 H, J = 1.5, 7.3, 7.3 Hz), 2.70 (t, 2 H, J = 7.2 Hz); ^{1}H NMR (C_5D_5N) δ 8.44 (bs, 1 H), 7.61 (s, 1 H); 6.38 (d, 1 H, J = 11.9 Hz), 6.32−6.22 (m, 2 H), 5.92 (d, 1 H, J = 11.5 Hz), 4.80 (bt, 2 H, J = 5.4 Hz), 3.74 (s, 3 H), 3.63 (s, 3 H), 3.14 (dt, 2 H, J = 7.3, 7.3 Hz), 2.69 (t, 2 H, J = 7.4 Hz); ^{13}C NMR δ 166.9, 160.2, 157.4, 149.1, 141.4, 136.4, 134.1, 120.4, 116.9, 52.4, 51.3, 39.5, 27.7, 25.8; ^{13}C NMR (C_5D_5N) δ 166.6, 160.5, 158.1, 141.7, 138.6, 134.5, 120.4, 115.5, 51.9, 51.0, 40.8, 28.0, 25.9; MS(EI) m/z (rel intensity) 294 (M^+, 100), 263 (28), 233 (63), 206 (40), 195 (48), 160 (31), 114 (41), 91 (41); HRMS m/z calcd for $C_{14}H_{18}N_2O_5$ 294.1216, found 294.1220.

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Supporting Information Available: ^{1}H and ^{13}C 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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