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Synthesis of the C1′−C11′ Oxazole-Containing Side Chain of Leucascandrolide A. Application of a Sonogashira Cross-Coupling

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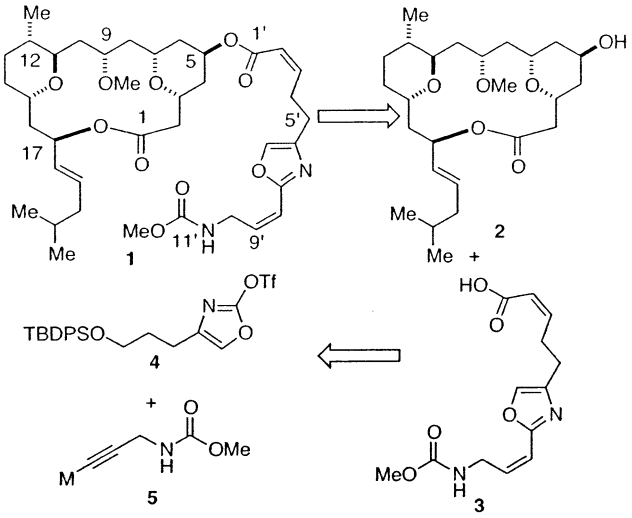
Abstract: An efficient, convergent synthesis of the C1′−C11′ side chain (**3**) of leucascandrolide A (**1**) has been achieved. The key bond connection is made through the use of a palladium(0)-catalyzed Sonogashira cross-coupling between trifloyl oxazole (**4**) and alkynylmetal species (**5**).

Leucascandrolide A (**1**) is a doubly O-bridged, 18-membered macrolide isolated from the calcareous sponge *Leucascandra caveolata* obtained from the northeastern coast of New Caledonia in the Coral Sea.[1] The relative stereochemistry of **1** was determined by extensive two-dimensional ^{1}H NMR experiments. The absolute stereochemistry was assigned through correlation of the C5 stereocenter by employing Mosher's method at the C5 hydroxyl. Leucascandrolide A exhibits high in vitro cytotoxicity against human KB and p388 tumor cell lines displaying low IC_{50}'s of 0.05 and 0.26 μg/mL, respectively. It also shows potent antifungal activity against *Candida albicans*, a pathogenic yeast that attacks AIDS patients and other immunocompromised individuals.[2]

Recent reports indicate that leucascandrolide A is no longer available from its original natural source. It has been postulated that **1** is not a metabolite of *L. caveolata*, but rather that of an opportunistic bacteria that colonized the sponge, as evidenced by the large amounts of dead tissue in the initial harvest of the marine sponge.[3] This fact, in addition to its structural complexity, has spurred many synthetic efforts toward leucascandrolide A,[4] including a report of its first total synthesis from the Leighton group.[5]

A brief retrosynthetic analysis of leucascandrolide A (**1**) reveals two principal fragments: the 18-membered macrolide **2** and the C1′−C11′ oxazole side chain **3** (Scheme 1). Motivation for pursuing a synthesis of **3** and structural analogues arises from our interest in leucascandrolide A's biological profile. At present, it is understood that macrolide **2** is responsible for cytotoxicity, whereas the side chain **3** is responsible for its antifungal properties.

SCHEME 1. Retrosynthesis of Leucascandrolide A



In a recent paper, we have documented a Pd(0)-mediated cross-coupling of trifloyloxazoles with vinylstannanes, which shows that **3** could be further divided into the appropriate coupling partners, trifloyloxazole **4** and alkynylmetal species **5**.[6] To alleviate difficulties associated with the synthesis of a potentially unstable alkynylmetal species, we examined the applicability of a Sonogashira coupling to these substrates.[7] In a recent communication, it was found that this indeed is a viable method for these types of sp−sp^2 bond constructions.[8]

To explore the applicability of this methodology toward the synthesis of **3**, it was first necessary to obtain the 4-alkyl-2-trifloyloxazole **4** (Scheme 2).

Synthesis of **4** began with the protection of commercially available 4-penten-1-ol **6** as its TBDPS ether and subsequent dihydroxylation of the resulting silyl ether with osmium tetraoxide to afford diol **7** in 95% yield. Selective oxidation of the *secondary* alcohol using the conditions described by Ishii, 1.6 mol % of peroxotungstophosphate (PCWP) and H_2O_2 gave hydroxy ketone **8** in 95% yield.[9] Cyclization of **8** to oxazolone **9** was accomplished using a three-step one-pot protocol. Treatment of **8** with a solution of phosgene in toluene, followed by exposure to aqueous NH_4OH, and then brief acidification (pH <3.5) with concentrated H_2SO_4 afforded ox-

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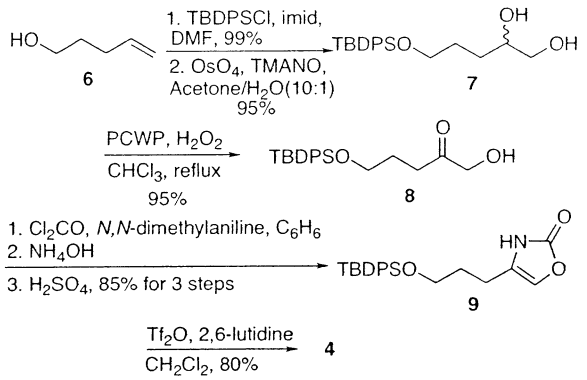
SCHEME 2. Synthesis of the Trifoyloxazole 4



SCHEME 3. Synthesis of the Alkyne Coupling Partner

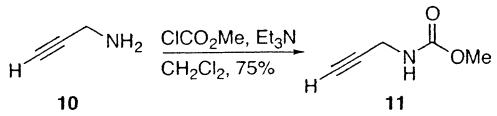
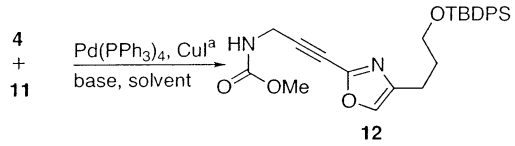


TABLE 1. Sonogashira Coupling under Various Conditions



entry	base	solvent	*T* (°C)	time (h)	yield (%)
1	Et_3N	DMF	65	12	trace
2	2,6-lutidine	DMF	65	12	55
3	2,6-lutidine	DMF	rt	12	trace
4	2,6-lutidine	dioxane	rt	4	84

[a] All reactions were run 0.3 M in dioxane using 10 mol % $Pd(PPh_3)_4$, 5 mol % CuI, 1.6 equiv of alkyne, and 5.0 equiv of amine base.

azolone **9** in 85% yield. Treatment of **9** with 2,6-lutidine in the presence of trifluoromethanesulfonic anhydride (Tf_2O) gave the desired trifloyloxazole **4** in 80% yield.

Our next objective was to synthesize the cross-coupling partner, alkyne **11** (Scheme 3). This was initiated by treatment of propargylamine **10** with methylchloroformate giving coupling partner **11** in 75% yield.

With trifloyloxazole **4** and alkyne **11** in hand it was then possible to explore the Sonogashira coupling to the synthesis of the C1′-C11′ fragment of leucascandrolide A (Table 1). Using our initial coupling conditions (DMF, Et_3N, 65 °C, entry 1), no desired product was obtained. The major products were oxazolone **9** and the alkyne homocoupling product of **11**. It is noteworthy this 2-trifloyloxazole is relatively chemically unstable and must be used immediately after preparation and purification.

The instability of triflate **4** prompted us to seek compatible coupling conditions. In initial model studies, the use of 2,6-lutidine promotes coupling with relatively unstable trifloyloxazoles.[8] Indeed, we were able to obtain a 55% yield of desired coupling product **12** albeit with significant amounts of triflate decomposition products

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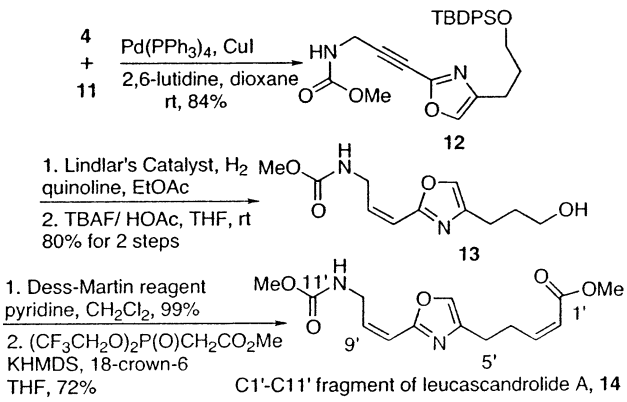
SCHEME 4. Completion of the C1′−C11′ Fragment



(Table 1, entry 2). In an effort to diminish decomposition of **4** we attempted to lower the reaction temperature. This unfortunately did not yield significant amounts of product (Table 1, entry 3). Empirically, it was determined that a solvent substitution of 1,4-dioxane for DMF greatly increased the efficiency of the Sonogashira coupling process. The coupling in 1,4-dioxane proceeded smoothly at ambient temperature utilizing 2,6-lutidine as the amine base providing desired product **12** in 84% yield (Table 1, entry 4).

With alkynyl oxazole **12** in hand, a straightforward sequence was used to complete the fragment of leucascandrolide A (Scheme 4). Installation of the (*Z*)-olefin using a Lindlar reduction, followed by removal of the silyl protecting group using TBAF buffered with HOAc gave oxazole **13** in 80% yield for the two steps. Completion of the fragment was accomplished by using a Dess−Martin oxidation[10] followed by a Still−Gennari olefination[11] to give the completed C1′-C11′ fragment **14**. This material possesses ^1H and ^{13}C NMR data in accord with those reported by others[4d,5] and correlates well with that of the natural product.[1]

In conclusion, an efficient synthesis of the C1′−C11′ fragment of leucascandrolide A has been completed in a nine-step sequence utilizing a convergent Sonogashira cross-coupling strategy. The approach highlights the use of underdeveloped 2-trifloyloxazoles as electrophilic reaction partners in Pd(0)-mediated cross-coupling reactions. The flexibility and convergence of the route could lend itself to the synthesis of useful amounts of a variety of side-chain analogues, thereby providing a greater understanding of leucascandrolide A's antifungal properties.

Experimental Section

General Methods. ^1H and ^{13}C NMR spectra were taken in $CDCl_3$ at 400 and 75 MHz, respectively, unless otherwise specified. Chemical shifts are reported in parts per million using the solvent internal standard (chloroform, 7.24 and 77.00 ppm, respectively). Infrared resonance spectra were recorded on a FTIR spectrometer. High-resolution mass spectra were obtained on a MAT-90 spectrometer. THF, C_6H_6, and CH_2Cl_2 were obtained from a dry solvent system (alumina) and used without further drying. DMF (anhydrous 99.8%) and $CHCl_3$ (ACS grade) were purchased directly from Aldrich and used without further purification. 1,4-Dioxane was distilled from sodium benzophenone ketal prior to use. Et_3N, pyridine, and 2,6-lutidine were

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distilled over KOH. CuI[12] was purified by known methods. Phosgene was purchased as a 1.93 M solution in toluene from Fluka Chemical Corp. and used as supplied. $Pd(PPh_3)_4$ was synthesized[13] by a known method. Peroxotungstophosphate (PCWP) was freshly prepared according to the known procedure.[14] All other reagents were used as supplied. All reactions were carried out in oven-dried glassware under argon pressure unless otherwise specified. Analytical thin-layer chromatography was performed on Sorbent Technologies 0.20 mm silica gel 60 Å plates. Flash chromatography was performed on Sorbent Technologies 32−63 μm 60 Å silica gel.[15]

***tert*-Butylpent-4-enyloxydiphenylsilane.** An oven-dried 100 mL flask was charged with 4-penten-1-ol **(6)** (1.00 g, 11.61 mmol) and a magnetic stir bar. The alcohol was dissolved in 30 mL of DMF. To the reaction mixture were then added imidazole (1.58 g, 23.22 mmol) and TBDPSCl (3.09 g, 11.26 mmol). The reaction mixture was stirred at rt for 12 h, diluted with water (50 mL), and extracted with Et_2O (3 × 50 mL). The combined organic extracts were washed with water (100 mL) and brine (100 mL), dried with $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified on SiO_2 (2% EtOAc/hexanes) to give 3.76 g (99%) of silyl ether as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66−7.63 (m, 4H), 7.42−7.32 (m, 6H), 5.78 (ddt, 1H, J = 7.2, 10.2, 15.6 Hz), 4.98 (dd, 1H, J = 1.4, 15.6 Hz), 4.90 (dd, 1H, J = 1.4, 10.2 Hz), 3.65 (t, 2H, J = 6.4 Hz), 2.13 (dt, 2H, J = 7.2, 7.6 Hz), 1.64 (tt, 2H, J = 6.4, 7.6 Hz), 1.03 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.5, 135.6, 134.1, 129.5, 127.6, 114.5, 63.3, 31.8, 30.0, 26.9, 19.2; IR (neat) ν_{max} 3071, 2956, 2932, 2858, 2361, 2383, 1640, 1472, 1428, 1109, 703; HRMS (CI, CH_4) m/z calcd for $C_{21}H_{29}OSi$ $[M + H]^+$ 325.1987, found 325.1968.

5-(*tert*-Butyldiphenylsilanyloxy)pentane-1,2-diol (7). A 250 mL round-bottom flask was charged with the silyl ether of **6** and a stir bar and diluted with 60 mL of acetone/water (10:1). Trimethylamine *N*-oxide (1.93 g, 17.42 mmol) was then added to the reaction mixture. A 0.2 M solution of OsO_4 in toluene was added (1.16 mL, 0.232 mmol), and the reaction mixture was stirred overnight at rt. The reaction was quenched by the addition of saturated sodium sulfite (100 mL) and extracted with EtOAc (3 × 150 mL). The combined organic layers were washed with brine, dried with $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified on SiO_2 (50% EtOAc/Hexanes) to give 3.86 g of **7** (95%) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66−7.63 (m, 4H), 7.42−7.32 (m, 6H), 3.77−3.71 (m, 1H), 3.68 (t, 2H, J = 5.6 Hz); 3.64 (dd, 1H, J = 3.2, 8.0 Hz); 3.45 (dd, 1H, J = 3.2, 7.6 Hz); 1.67−1.46 (m, 4H), 1.03 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 135.5, 133.5, 129.6, 127.6, 71.9, 66.7, 63.9, 29.9, 28.6, 26.8, 19.1; IR (neat) ν_{max} 3398, 3071, 2932, 2859, 1710, 1427, 1109, 735; HRMS(CI, NH_3) m/z calcd for $C_{22}H_{31}O_3Si$ $[M + H]^+$ 359.2042, found 359.2072.

5-(*tert*-Butyldiphenylsilanyloxy)-1-hydroxypentan-2-one (8). A 100 mL round-bottom flask was charged with diol **7**, a stir bar, and diluted with 15 mL of $CHCl_3$. PCWP (0.111 g, 0.053 mmol) and 30% H_2O_2 (1.64 mL, 16.02 mmol) were added to the reaction mixture. The flask was fitted with a reflux condenser and refluxed for 16 h with stirring before heating was discontinued. The reaction was quenched by the addition of saturated sodium sulfite (15 mL) and water (30 mL). The organic layer was separated, and the remaining aqueous layer was extracted with EtOAc (2 × 50 mL). The combined organic layers were dried with $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified on SiO_2 (30% EtOAc/hexanes) to give 0.903 g of **8** (95%) as a pale yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63−7.60 (m, 4H), 7.43−7.35 (m, 6H), 4.22 (d, 2H, J = 4.8 Hz), 3.66 (t, 2H, J = 6.0 Hz), 3.04 (t, 1H, J = 4.8 Hz), 2.51 (t, 2H, J = 7.6 Hz), 1.86 (tt, 2H, J = 6.0, 7.6), 1.02 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 209.4, 135.5, 133.4, 129.6, 127.6, 67.9, 62.7, 34.7, 26.7, 26.2, 19.0; IR (neat) ν_{max} 3485, 3072, 2932, 2859, 2252, 1719, 1428, 1109, 909; HRMS(CI, CH_4) m/z calcd for $C_{21}H_{29}O_3Si$ $[M + H]^+$ 357.1886, found 357.1930.

4-[3-(*tert*-Butyldiphenylsilanyloxy)propyl]-3*H*-oxazol-2-one (9). A 100 mL round-bottom flask was charged with ketone **8** (0.570 g, 1.60 mmol) and a stir bar. Benzene (3 mL) and *N*,*N*-dimethylaniline (0.50 mL) were added, and the reaction mixture was cooled to 0 °C. Phosgene (0.950 mL, 1.93 M in toluene, 1.83 mmol) was added, and the reaction mixture was stirred for 30 min. Concentrated NH_4OH (10 mL) was added carefully with a pipet, and the reaction mixture was stirred for an additional 30 min before concd H_2SO_4 was added to bring the reaction pH to approximately 3. The reaction mixture was diluted with water (100 mL) and extracted with EtOAc (3 × 50 mL). The combined organic layers were washed with brine, dried with $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified on SiO_2 (40% EtOAc/hexanes) to give 0.519 g of **9** (85%) as a yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.54 (bs, 1H), 7.64−7.61 (m, 4H), 7.43−7.37 (m, 6H), 6.42 (s, 1H), 3.69 (t, 2H, J = 5.6 Hz), 2.45 (t, 2H, J = 7.6 Hz), 1.74 (tt, 2H, J = 5.6, 7.6 Hz), 1.05 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.1, 135.4, 133.5, 129.6, 127.6, 127.1, 124.1, 62.3, 29.5, 26.8, 20.4, 19.1; IR (neat) ν_{max} 3163, 3071, 2932, 2858, 1746, 1472, 1109, 704; HRMS(CI, NH_3) m/z calcd for $C_{23}H_{28}NO_3Si$ $[M + H]^+$ 382.1838, found 382.1840.

Trifluoromethanesulfonic Acid 4-[3-(*tert*-Butyldiphenylsilanyloxy)propyl]oxazol-2-yl Ester (4). A 100 mL round-bottom flask was charged with oxazolone **9** (0.250 g, 0.655 mmol) and a stir bar. CH_2Cl_2 (3.5 mL) was added, and the reaction mixture was cooled to −78 °C. 2,6-Lutidine (0.140 g, 1.31 mmol) was then added via syringe followed by the addition of Tf_2O (0.277 g, 0.983 mmol). The reaction mixture was then allowed to warm to rt with stirring for 30 min. The reaction was diluted with water (50 mL) and extracted with CH_2Cl_2 (3 × 50 mL). The combined organic layers were washed with brine, dried with $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified on SiO_2 (10% Et_2O/pentane) to give 0.280 g of **4** (80%) as a colorless oil. Triflate **4** is chemically unstable and used immediately after preparation: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64−7.60 (m, 4H), 7.41−7.34 (m, 6H), 7.12 (s, 1H), 3.67 (t, 2H, J = 6.0 Hz), 2.61 (t, 2H, J = 7.6 Hz), 1.85 (tt, 2H, J = 6.0, 7.6 Hz), 1.03 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 149.5, 142.1, 135.5, 133.9, 133.7, 129.6, 127.7, 118.4 (q, CF_3, J = 319.7 Hz), 62.5, 30.3, 26.8, 22.9, 19.2; IR (neat) ν_{max} 2932, 2361, 1735, 1426, 1248, 1030, 702; HRMS (CI, CH_4) m/z calcd for $C_{23}H_{26}F_3NO_5SSi$ $[M]^+$ 513.1253, found 513.1282.

[3-[4-[3-(*tert*-Butyldiphenylsilanyloxy)propyl]oxazol-2-yl]prop-2-ynyl]carbamic Acid Methyl Ester (12). A 50 mL round-bottom flask was charged with triflate **4** (0.130 g, 0.253 mmol) and a stir bar. 1,4-Dioxane (1.2 mL) and 2,6-lutidine (0.136 g, 1.23 mmol) were added with stirring. Alkyne **11** (0.045 g, 0.405 mmol), $Pd(PPh_3)_4$ (30 mg, 0.025 mmol), and CuI (3 mg, 0.013 mmol) were added, and the reaction mixture was stirred at rt for 4−5 h. The reaction mixture was then diluted with EtOAc (~10 mL) and filtered through a thin pad of SiO_2 and concd in vacuo. The residue was purified on SiO_2 (30% EtOAc/hexanes) to give 0.101 g of **12** (84%) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64−7.62 (m, 4H), 7.41−7.32 (m, 6H), 7.21 (s, 1H), 4.90 (bs, 1H), 4.22−4.19 (m, 2H), 3.69 (bs, 3H), 3.66 (t, 2H, J = 6.4 Hz), 2.61 (t, 2H, J = 7.6 Hz), 1.87 (tt, 2H, J = 6.4, 7.6 Hz), 1.03 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.5, 145.5, 141.7, 135.5, 135.1, 133.7, 129.5, 127.6, 87.9, 71.3, 62.7, 52.5, 31.2, 30.8, 26.8, 22.4, 19.1; IR (neat) ν_{max} 3542, 3072, 2956, 2931, 2859, 2252, 1724, 1515, 1253, 1110, 734; HRMS (CI, CH_4) m/z calcd for $C_{28}H_{33}N_2O_4Si$ $[M + H]^+$ 477.2209, found 477.2208.

[3-[4-[3-(*tert*-Butyldiphenylsilanyloxy)propyl]oxazol-2-yl]prop-2-ynyl]carbamic Acid Methyl Ester (13). A 50 mL round-bottom flask was charged with oxazole **12** (0.101 g, 0.210 mmol) and a stir bar. EtOAc (23.0 mL) and quinoline (0.043 g, 0.336 mmol) were added with stirring. Lindlar's catalyst, 5 wt % Pd on $CaCO_3$ posioned w/lead (0.101 g, 100 wt %), was added, and the reaction was placed under H_2 and stirred for 3 h. The reaction was filtered through a pad of Celite and concentrated

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in vacuo. The crude compound was then redissolved in THF and cooled to 0 °C. A premixed solution of TBAF (0.420 mL, 0.420 mmol) and HOAc (0.025 g, 0.420 mmol) was then added via syringe. The reaction was allowed to warm to rt with stirring for 24 h. The reaction was then quenched with water (15 mL) and extracted with EtOAc (3 × 25 mL). The combined organic extracts were washed with brine, dried with $MgSO_4$, filtered, and concentrated in vacuo. The crude residue was purified on SiO_2 (90% EtOAc/hexanes) to give 0.041 g of **13** (80%) as a low melting yellow solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 (s, 1H), 6.28 (d, 1H, J = 11.6 Hz), 6.07 (dt, 1H, J = 5.2, 11.6 Hz), 5.45 (bs, 1H), 4.29 (t, 2H, J = 5.2 Hz), 3.71 (t, 2H, J = 6.0 Hz), 3.67 (bs, 3H), 2.65 (t, 2H, J = 7.2 Hz), 2.32 (bs, 1H), 1.89 (tt, 2H, J = 6.0, 7.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.0, 157.2, 141.4, 136.5, 133.8, 116.3, 62.0, 52.2, 39.5, 31.1, 22.8; IR (neat) ν_{max} 3320, 2924, 2850, 1700, 1522, 1262, 1055; HRMS (CI, CH_4) m/z calcd for $C_{11}H_{17}N_2O_4$ $[M + H]^+$ 241.1188, found 241.1195.

[3-[4-(3-Oxopropyl)oxazol-2-yl]allyl]carbamic Acid Methyl Ester. A 25 mL round-bottom flask was charged with alcohol **12** (0.035 g, 0.145 mmol) and a stir bar. CH_2Cl_2 (3.00 mL) and Dess−Martin reagent (0.154 g, 0.364 mmol) were added with stirring. Pyridine (0.029 g, 0.364 mmol) was added, and the reaction was stirred for 1 h at rt. The reaction was concentrated in vacuo crude and purified on SiO_2 (60% EtOAc/hexanes) to give 0.035 g of aldehyde (99%) as a colorless oil. This unstable aldehyde was used immediately without further purification.

5-[2-(3-Methoxycarbonylaminopropenyl)oxazol-4-yl]pent-2-enoic Acid Methyl Ester (14). A solution of 18-crown-6 (0.193 g, 0.730 mmol) and bis(2,2,2-trifluoroethyl)(methoxycarbonylmethyl) phosphonate (0.61 g, 0.191 mmol) in THF (4 mL) was cooled to −78 °C, treated with a solution of KHMDS (0.170 mL, 0.153 mmol, 0.91 M in THF), and stirred for 10 min. The reaction mixture was then treated with a solution of [3-[4-(3-oxopropyl)oxazol-2-yl]allyl]carbamic acid methyl ester (0.035 g, 0.146 mmol) in THF (4 mL) dropwise. The reaction was allowed to stir at −78 °C for 4 h before being quenched with satd NH_4Cl (10 mL) and allowed to stir to rt. The reaction was then extracted with CH_2Cl_2 (3 × 10 mL). The combined organic extracts were washed with brine, dried with $MgSO_4$, filtered, and concentrated in vacuo. The crude residue was purified on SiO_2 (40% EtOAc/hexanes) to give 0.031 g of **3** (73%) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 (s, 1H), 6.28 (d, 1H, J = 8.0 Hz), 6.25 (dt, 1H, J = 7.2, 8.0 Hz), 6.06 (dt, 1H, 5.6, 11.4 Hz), 5.81 (d, 1H, J = 11.4 Hz), 5.57 (bs, 1H), 4.29 (t, 2H, J = 5.6 Hz), 3.69 (s, 3H), 3.65 (s, 3H), 3.00 (dt, 2H, J = 7.2, 8.0 Hz), 2.68 (t, 2H, J = 7.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.7, 159.9, 157.1, 148.9, 141.1, 136.2, 133.9, 120.2, 116.7, 52.1, 51.1, 39.2, 27.5, 26.6; IR (neat) ν_{max} 3358, 2984, 2952, 2925, 1722, 1522, 1247, 1198, 1045; HRMS (CI, CH_4) m/z calcd for $C_{14}H_{19}N_2O_5$ $[M + H]^+$ 295.1294, found 295.1294.

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Supporting Information Available: Spectral data (^{1}H and ^{13}C NMR) of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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