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Efficient Total Synthesis of Pulchellalactam, a CD45 Protein Tyrosine Phosphatase Inhibitor

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A new approach to a CD45 protein tyrosine phosphatase inhibitor, pulchellalactam, is described. The key step of the sequence involves addition and elimination of an enolic lactam in a single step and 70% yield, employing an organocuprate reagent. The resulting α,β-unsaturated lactam could be condensed with isobutyraldehyde to produce *Z*-pulchellalactam or converted into siloxypyrrole, which was subjected to the BF_3·Et_2O-promoted coupling reaction with isobutyraldehyde to afford *E*-pulchellalactam after E1-cB elimination and TFA deprotection. This first total synthesis afforded *Z*-pulchellalactam in six steps and 32% overall yield from Boc-glycine. The same sequence of reactions could also be applied to the liquid- or solid-phase synthesis of trifunctionalized pulchellalactam derivatives.

Introduction

Covalent modification by protein tyrosine phosphorylation is a major mechanism for regulating cellular processes such as proliferation, differentiation, cell growth, cell−cell interactions, metabolism, T-cell activation, and the antigen-specific receptor signaling in B cells.[1] The state of tyrosine phosphorylation on the target protein is reversibly controlled through the dynamic actions of protein tyrosine kinases (PTKs), enzymes that catalyze the transfer of phosphate from adenosine triphosphate to tyrosine residues in specific protein substrates,[2] and phosphatases (PTPs) that remove the phosphate groups from phosphotyrosine residues.[3−5] Numerous specific inhibitors of PTKs have been discovered and tested as therapeutic agents against human diseases.[6−10] The large diversity of the PTP family and the demonstrated roles of certain PTPs as positive regulators of cellular signaling pathways and in a number of disease states indicate that PTP inhibitors are promising biochemical and therapeutic agents.[1,11−13]

Recently, a receptor-like transmembrane protein tyrosine phosphatase, CD45,[14] has been shown to play a crucial role in activation of both B and T cells.[15−18] CD45 therefore represents a therapeutic target for various autoimmune and chronic anti-inflammatory diseases.[12,19−22] Currently, there are few readily available potent inhibitors of CD45 protein tyrosine phosphatase other than vanadate. Thus, a great need remains for the discovery of selective and potent CD45 inhibitors. The key to discovering a selective CD45 inhibitor may lie in the chemical modification of existing nonselective inhibitors.

As part of our ongoing studies toward the discovery of protein tyrosine kinase[23,24] and phosphatase inhibitors, we have begun to adapt a parallel combinatorial-based approach and devise strategies to generate selective, small-molecule, active-site inhibitors of CD45. To shorten the time from initial discovery to clinic, we purposefully focused on readily available natural product scaffolds and excluded phosphates in our design to enhance the likelihood that the resulting compounds would enter cells. In 1996, Gunasekera and Clardy isolated dysidiolide, a novel protein phosphatase inhibitor from a Caribbean sponge, and suggested that in dysidiolide[25] the γ-hydroxybutenolide residue likely serves as a surrogate phosphate, while the long side chain occupies a hydro-

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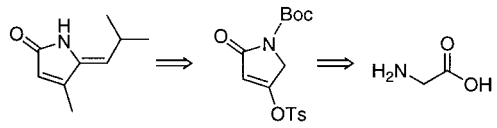
SCHEME 1



phobic binding pocket associated with the normal substrate. Alvi and his collegues later discovered a potent CD45 inhibitor, pulchellalactam,[26] with a 3-pyrrol-2-one core moiety from the marine fungus *Corollospora pulchella*. Based on these two reports, we envisioned a pyrrol-2-one moiety providing the scaffold for construction of a CD45 inhibitor, with the C4 side chain mimicking the hydrophobic unit of dysidiolide.

Despite its potential utility, sufficient amounts of pulchellalactam are difficult to obtain from the natural source, and the stereochemistry of its double bond was not assigned. Therefore, the total synthesis of pulchellalactam represents the only realistic supply of the natural product necessary for further biological evaluation and allows the preparation of analogues for structure−activity relationship studies. Herein, we report a general approach to the synthesis of *Z*- and *E*-pulchellalactam in solution. This strategy was also successfully applied to the liquid-phase organic synthesis of *Z*-pulchellalactam.

Results and Discussion

Recent synthetic studies toward lactam-containing heterocycles for use in biological discovery efforts have been intense,[27−30] but no general synthetic method that is applicable to the liquid- or solid-phase synthesis of 3-pyrrolin-2-ones substituted at the 4-position has yet been reported. In this total synthesis, the key steps of our approach were focused on the formation of the 3-pyrrolin-2-one ring and its condensation with an aldehyde. Fortunately, a method for the synthesis of a substituted pyrrolidinone from D-serine was reported by Joullié et al.,[31−34] and condensation of a γ-substituted siloxypyrrole with isobutyraldehyde and benzaldehyde was also described by Baldwin and Bermejo, respectively.[35] This background led us to outline the retrosynthetic route as shown in Scheme 1.

The synthesis of pulchellalactam began with the coupling of Boc-glycine with 2,2-dimethyl-1,3-dioxane-4,6-dione (Meldrum's acid) to afford the acylated Meldrum acid, followed by intramolecular cyclization and then decarboxylation to provide compound **2** (Scheme 2). Although acylation of Meldrum's acid has been performed by using different carboxyl activating reagents,[31] we found isopropyl chloroformate to be a more affordable reagent than isopropenyl chloroformate, and this compound was the best agent for our system. It gave a satisfactory yield and a clean crude product for the next step cyclization to afford lactam **2**. Introduction of the side chain at the 4-position proved to be nontrivial. NMR data revealed that compound **2** existed as the enol form in DMSO-d_6, while the keto form was observed under dilution in the less polar solvent, deuteriochloroform. The enolized lactams generated under both acidic and basic conditions are inert toward nucleophilic attack. To overcome such an intrinsic difficulty, the basicity of the incoming organometallic reagent has to be carefully balanced to avoid the competing, facile enolization process.[36,37] However, carbonyl alkylation of compound **2** in different solvents by organoaluminum[36,38] and Grignard reagents gave only recovered starting materials.

In light of this result with compound **2**, we next prepared enolized tosylate **3** in the hope that the α,β-unsaturated carbonyl compound would undergo Michael reaction with an organocopper reagent. To our delight, Michael addition and elimination of tosylate proceeded nicely in one step at 0 °C, delivering 4-methyl-3-pyrrolin-2-one **4** in 70% yield. With the *N*-Boc lactam **4** in hand, we then sought to synthesize *E*-pulchellalactam using a steric control approach. Treatment of compound **4** with *tert*-butyldimethylsilyl triflate (TBDMSOTf) in the presence of diisopropylethylamine (DIPEA) gave siloxypyrrole **5** in quantitative crude yield. Compound **5** was unstable on silica gel. Initially, condensation of isobutyraldehyde with the siloxypyrrole **5** was carried out using the synthetic protocol of Baldwin and co-workers,[35] since this procedure afforded the unsaturated γ,γ-disubstituted lactam of lactacystin in 55% yield. However, in the present situation, the reaction with $SnCl_4$ gave only a trace amount of the product.[35,39] Consequently, we performed the above reaction at −78 °C, with various Lewis acids such as $ZnBr_2$ and $TiCl_4$. When boron trifluoride etherate was used,[40,41] the expected γ-adduct **6** was obtained predominantly in 87% yield from compound **4**. Acetylation was then carried out by adding excess amounts of acetic anhydride and DMAP to the reaction mixture. Base-catalyzed elimination of the erythro and threo acetates **7** with DBU gave an inseparable mixture of two alkenes (**8**) in 88% yield. The ratio of these two geometrical isomers were found to be 10:1 (*E*/*Z*) by NMR analysis. Deprotection of the mixture (**8**) with trifluoroacetic acid (TFA) in dichloromethane afforded a 90% yield of pure *E*-pulchellalactam **1** after flash column chromatography purification of the two regioisomers. After the

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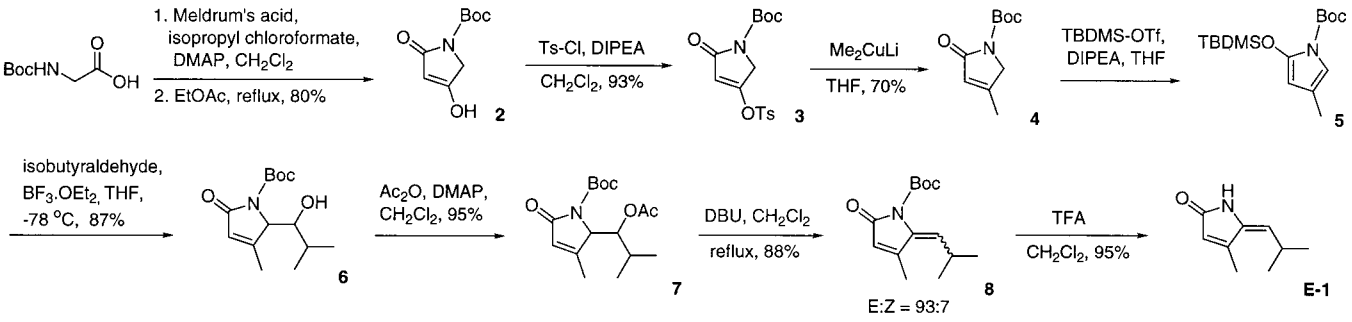
SCHEME 2



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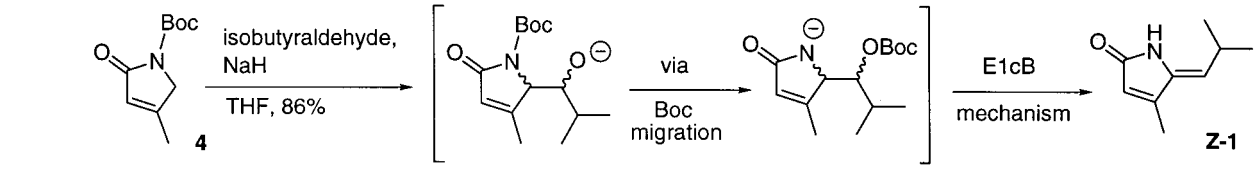

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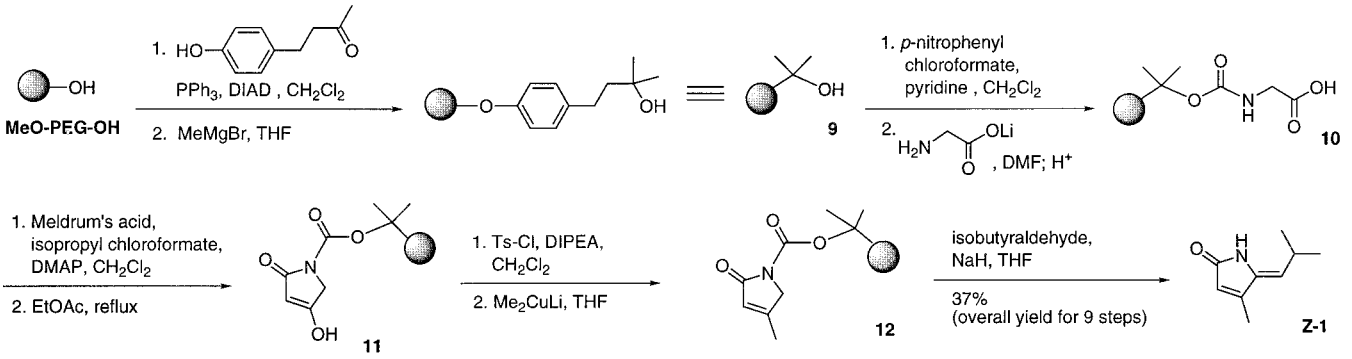

reaction time was increased and the reaction mixtures were allowed to heat at reflux in order to eliminate the acetates, the *E*/*Z* ratio of pulchellalactam was dramatically decreased. The highest *E*/*Z* ratio was found to be approximately 93:7, and an excellent yield of compound **8** was achieved. The elimination of the acetate group of compound **7** leading to *E*-Boc-pulchellalactam **8** with high *E* selectivity proceeded presumably via the E1cB mechanism[42−46] with the help of a steric factor from the *N*-Boc moiety.

Next, we turned our attention to investigate the methodology, which might produce *Z*-pulchellalactam exclusively (Scheme 3). After several trials using acid-, fluoride-, or base-promoted condensation, it was found that the treatment of the compound **4** with NaH in dichloromethane at 0 °C followed by the addition of isobutyraldehyde led to the exclusive formation of the *Z*-pulchellalactam **1** in 86% yield. To the best of our knowledge, little is known about this type of reaction. We assume that allylic deprotonation of compound **4** and condensation with aldehyde led to *Z*-pulchellalactam **1** also through an E1cB mechanism[42−46] via *tert*-butoxycarbonyl group (Boc) migration (Scheme 3).

Synthetic *E*- and *Z*-pulchellalactam were characterized using spectroscopic techniques. The structure of synthetic *Z*-pulchellalactam was verified not only by the COSY and NOSY spectra but also by X-ray crystallography. The spectroscopic data obtained for synthetic *Z*-pulchellalactam were in agreement with those reported for the natural product with two exceptions.[47] The signal for H-7 in the published report was erroneously given as 2.26, whereas we found the signal at 2.62, and the signal for H-6 was found at 5.12.[47]

Because of the success of the solution method, we extended and modified this protocol to a synthesis on soluble polymer support as shown in Scheme 4. The soluble polymer support—poly(ethylene glycol)monomethyl ether—of MW 5000 (MeO-PEG-OH) was first treated with 4-(4-hydroxyphenyl)-2-butanone, triphenylphosphine, and diisopropyl azodicarboxylate (DIAD) in CH_2Cl_2 followed by a Grignard reaction to afford tertiary alcohol **9**.[24] The resulting soluble polymer **9** was converted to an activated carbamate[48] and treated with glycine lithium salt to afford polymer **10**.[24] *Z*-Pulchella-

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lactam was then obtained in 37% overall yield using a strategy similar to that employed for the above solution method. This new, traceless liquid-phase strategy described herein will permit combinatorial synthesis of the novel pyrrol-2-one-containing heterocycles.

Conclusions

In summary, we have completed the first synthesis of *Z*-pulchellalactam (**Z-1**) and *E*-pulchellalactam (**E-1**) by sequential two-stage grafting of side chains to the central pyrrol-2-one ring with tight control of regioselectivity. This synthesis can be carried out in large scale and is suited for the production of quantities of these lead compounds for further biological studies. The synthesis of *Z*-pulchellalactam was carried out in five steps and an overall yield of 45%, which also provides a feasible combinatorial route to prepare analogues of pulchellalactam for structure−activity relationship studies. Three sites of functional diversities can be introduced on the pyrrol-2-one ring in the combinatorial synthesis, thus providing corresponding sites of hydrophilic, hydrophobic, and other interactions with protein tyrosine phosphatases. Therefore, this approach can be expected to develop more selective and potent CD45 inhibitors based on the pyrrol-2-one structure. The preparation of a library containing structurally diversified analogues of pulchellalactam is currently underway in our laboratory. The biological results and the comparison with pulchellalactam and dysidiolide will be reported in due course.

Experimental Section

General Methods. All solvents were reagent grade and distilled before use. Analytical thin-layer chromatography (TLC) was performed on Merck silica gel (60 F 254) plates (0.25 mm). Visualization was effected with ultraviolet light or any of the following reagents: ninhydrin, phosphomolybdic acid, and anisaldehyde. Chromatography was carried out on Merck silica gel 60 (particle size 240−400 mesh). Chemical shifts were measured in parts per million (δ) relative to tetramethylsilane (TMS), dimethyl sulfoxide-d_6 (DMSO-d_6), or chloroform ($CDCl_3$) as the internal standard. Coupling constants (J values) are reported in hertz (Hz). IR absorptions are reported in wavenumbers (cm^{-1}). The spectra taken were referenced to the 1601 cm^{-1} band of polystyrene, and only the most prominent or characteristic absorptions are noted. High-resolution mass spectra (HRMS) were obtained using either ammonia chemical ionization (CI) or electron impact (EI).

4-Hydroxy-2-oxo-2,5-dihydropyrrole-1-carboxylic Acid *tert*-Butyl Ester (2). To a stirred solution of Boc-Gly-OH (3.00 g, 17.14 mmol) in dry methylene chloride (36 mL) at 0 °C under argon were added Meldrum's acid (2.972 g, 20.55 mmol) and (dimethylamino)pyridine (5.243 g, 42.83 mmol). A solution of isopropyl chloroformate in toluene (25.73 mL, 25.73 mmol) was added dropwise, and the reaction mixture was stirred for 3 h at 0 °C. The mixture was washed twice with 15% $KHSO_4$ (30 mL), the organic layer was dried over $MgSO_4$, and the solution was concentrated to afford the crude acylated Meldrum's acid. This material was then refluxed in ethyl acetate (340 mL) for 1 h to afford crude compound **2**. The crude product was recrystallized from ethyl acetate to give a crystalline solid of compound **2** (2.73 g) in 80% yield: IR (KBr) 2982, 2686, 1759, 1603, 1434, 1417, 1366, 1306, 1154, 1080, 849, 805, 753 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 1.53 (s, 9H), 4.23 (s, 2H), 4.97 (s, 1H) 12.25 (br s, 1H); ^{13}C NMR ($CDCl_3$) δ 27.71, 49.34, 80.74, 94.29, 148.89, 169.17, 174.34; HRMS calcd for $C_9H_{13}O_4N$ (M^+) 199.0845, found 199.0847.

2-Oxo-4-(toluene-4-sulfonyloxy)-2,5-dihydropyrrole-1-carboxylic Acid *tert*-Butyl Ester (3). Under an argon atmosphere, compound **2** (1.00 g, 5.02 mmol) was dissolved in CH_2Cl_2 (50 mL). *p*-Toluenesulfonyl chloride (0.958 g, 5.02 mmol) and DIPEA (1.75 mL, 10.04 mmol) were added to this solution, and the resulting mixture was stirred for 6 h at ambient temperature. The reaction mixture was washed with 5% HCl (5 mL), 5% $NaHCO_3$ (10 mL), and saturated sodium chloride (10 mL) solutions, dried over $MgSO_4$, and filtered. The solvent was removed in vacuo, and the residue was chromatographed on silica gel using ethyl acetate/hexane (2:8) as eluants to give 1.65 g (93% yield) of compound **3** as a white solid: IR (KBr) 2971, 1739, 1715, 1628, 1398, 1356, 1164, 935, 786, 749 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.43 (s, 9H), 2.40 (s, 3H), 4.13 (s, 2H), 5.65 (s, 1H), 7.34 (d, 2H, J = 8.0 Hz), 7.76 (d, 2H, J = 8.2 Hz); ^{13}C NMR ($CDCl_3$) δ 21.22, 27.40, 48.87, 82.62, 106.65, 127.95, 129.94, 130.30, 146.68, 148.05, 162.36, 166.37; HRMS calcd for $C_{16}H_{19}NO_6S$ (M + H) 354.1011, found 354.1019. Anal. Calcd for $C_{16}H_{19}NO_6S$: C, 54.38; H, 5.42; N, 3.96. Found: C, 54.11; H, 5.42; N, 3.79.

4-Methyl-2-oxo-2,5-dihydropyrrole-1-carboxylic Acid *tert*-Butyl Ester (4). CuI (0.593 g, 3.11 mmol) was placed in a 25 mL round-bottomed flask equipped with a stir bar and sealed with a septum. The flask was evacuated and purged with Ar; the process was repeated three times. THF (15 mL) was injected, and the mixture was cooled to 0 °C. The reaction mixture was then treated with 1 M MeLi (6.22 mL, 6.22 mmol) in cumene/THF, and the stirring was continued for about 10 min. After the orange-yellow mixture was decolorized, compound **3** (0.500 g, 1.42 mmol) was added to this solution. After 2 h at 0 °C, the mixture was poured into a solution of 25% NH_4OH (4 mL) and 37% HCl (2 mL) and vigorously stirred for 1 h at ambient temperature before being extracted with ethyl acetate (3 × 25 mL). The organic layer was dried (Na_2SO_4), filtered, and concentrated. The residue was chromatographed on silica gel using ethyl acetate/hexane (3:7) as eluants to give 0.196 g (70% yield) of compound **4** as an oil: IR (KBr) 3000, 2932, 1717, 1638, 1456, 1342, 1210, 1144, 860, 779, 640 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.42 (s, 9H), 1.98 (s, 3H), 4.09 (s, 2H), 5.72 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 15.10, 27.61, 53.94, 82.03, 122.20, 148.84, 158.07, 169.39; HRMS calcd for $C_{10}H_{15}NO_3$ (M + H) 197.1052, found 197.1059. Anal. Calcd for $C_{10}H_{15}NO_3$: C, 60.90; H, 7.67; N, 7.10. Found: C, 60.83; H, 7.69; N, 7.06.

2-(1-Hydroxy-2-methylpropyl)-3-methyl-5-oxo-2,5-dihydropyrrole-1-carboxylic Acid *tert*-Butyl Ester (6). To a solution containing compound **4** (0.13 g, 0.662 mmol) and THF (1.44 mL) at room temperature were added DIPEA (0.31 mL, 1.32 mmol) and *tert*-butyldimethylsilyl trifluoromethanesulfonate (0.24 mL, 1.32 mmol). Stirring at room temperature was continued for 2 h, and isobutyraldehyde (0.30 mL, 3.31 mmol) was added to the reaction mixture. The solution was cooled to −78 °C, and 0.25 mL of $BF_3{\cdot}OEt_2$ (1.99 mmol) was added dropwise. The reaction mixture was kept at −78 °C for 40 min and then poured into 15 mL of 5% $NaHCO_3$. The reaction mixture was then concentrated under reduced pressure. The resulting crude material was dissolved in CH_2Cl_2 (80 mL) and washed with 5% HCl (5 mL), 5% $NaHCO_3$ (10 mL), and saturated sodium chloride (10 mL) solutions. The organic layer was dried (Na_2SO_4), filtered, and concentrated. The resulting crude oil was purified by column chromatography eluting with ethyl acetate/hexane (3:7). Compound **6** (0.155 g, 87% yield) was obtained as a white solid: IR (KBr) 3468, 2970, 1766, 1682, 1343, 1293, 1146, 1080, 847, 764 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.97 (t, 6H, J = 6.6 Hz), 1.53 (s, 9H), 1.67−1.72 (m, 1H), 2.12 (s, 3H), 3.72−3.82 (m, 1H), 4.56−4.67 (m, 1H), 5.81 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 15.35, 16.49, 18.98, 20.23, 27.92, 30.19, 54.21, 67.08, 75.39, 82.49, 82.84, 122.65, 122.97, 149.98, 158.11, 162.85, 169.73; HRMS calcd for $C_{14}H_{23}NO_4$ (M + H) 270.1705, found 270.1710.

2-(1-Acetoxy-2-methylpropyl)-3-methyl-5-oxo-2,5-dihydropyrrole-1-carboxylic Acid *tert*-Butyl Ester (7). Compound **6** (50 mg, 0.186 mmol) was dissolved in CH_2Cl_2 (10 mL) and treated with DMAP (68 mg, 0.557 mmol) and acetic

anhydride (0.041 mL, 0.56 mmol). The reaction mixture was stirred at room temperature for 24 h. The reaction mixture was then diluted with ethyl acetate (100 mL) and washed with 10% HCl (40 mL), 5% $NaHCO_3$ (30 mL), and saturated NaCl (30 mL) solutions. The organic phase was dried (Na_2SO_4), filtered, and concentrated. The crude oil was purified by column chromatography eluting with ethyl acetate/hexane (3:7) to give an oil (55 mg, 95%): IR (KBr) 2979, 1781, 1743, 1715, 1371, 1313, 1231, 1164, 1027, 848 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.79 (d, 3H, $J = 6.7$ Hz), 0.90 (d, 3H, $J = 6.6$ Hz), 1.50 (s, 9H), 1.81−1.88 (m, 1H), 2.02 (s, 3H), 2.34 (s, 3H), 4.59 (d, 1H, $J = 3.0$ Hz), 5.18 (dd, 1H, $J = 7.9$ Hz, $J = 3.2$ Hz), 5.79 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 16.36, 18.94, 20.14, 20.53, 27.94, 28.49, 64.64, 75.49, 83.22, 123.95, 149.13, 161.08, 169.38, 169.78; HRMS calcd for $C_{16}H_{25}NO_5$ (M + H) 311.1733, found 311.1726.

2-Isobutylidene-3-methyl-5-oxo-2,5-dihydropyrrole-1-carboxylic Acid *tert*-Butyl Ester (8). To a solution of compound **7** (0.100 g, 0.321 mmol) in dry CH_2Cl_2 (15 mL) was added DBU (0.14 mL, 0.963 mmol). The solution was refluxed under an argon atmosphere for 24 h. The reaction mixture was cooled and then concentrated under reduced pressure. The resulting crude product was purified by column chromatography eluting with ethyl acetate/hexane (1:9). Pure product **8** (0.071 g, 88% yield) was obtained as a white solid: IR (KBr) 2976, 2872, 1780, 1643, 1388, 1369, 1311, 1287, 1164, 1120, 833 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.07 (*E*) and 1.02 (*Z*) (each d, 6H, $J = 5.96$, 6.06 Hz), 1.52 (s, 9H), 2.04 (*Z*) and 2.26 (*E*) (each s, 3H), 2.62−2.74 (*Z*) and 2.97−3.09 (*E*) (each m, 1H), 5.16 (*Z*) and 6.47 (*E*) (each d, 1H, $J = 10.0$, 11.7 Hz), 5.70 (*Z*) and 5.78 (*E*) (each s, 1H). Anal. Calcd for $C_{14}H_{21}NO_3$: C, 66.91; H, 8.42; N, 5.57. Found: C, 66.99; H, 8.45; N, 5.57.

***E*-5-Isobutylidene-4-methyl-1,5-dihydropyrrole-2-one (E-1).** To a stirred solution of compound **8** (0.10 g, 0.398 mmol) in dry CH_2Cl_2 (1 mL) at 0 °C, and under a nitrogen atmosphere, was added anhydrous trifluoroacetic acid (1.5 mL) in CH_2Cl_2 (0.5 mL). The cooling bath was removed, and the stirring was continued for 0.5 h, after which time the solvent was removed under reduced pressure. The residual TFA was removed with dry toluene (3 × 10 mL) and hexane (2 × 10 mL). The organic layer was washed with 5% $NaHCO_3$ (5 mL) and saturated NaCl (5 mL) solutions. The organic layer was dried (Na_2SO_4), filtered, and concentrated. The resulting crude product was purified by column chromatography, eluting with ethyl acetate/hexane (2:8) to afford pure compound **E-1** (0.052 g) in 86% yield: IR (KBr) 3199, 2963, 2926, 1680, 1508, 1385, 1361, 1258, 1143, 974, 840, 757 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.03 (d, 6H, $J = 6.6$ Hz), 2.23 (s, 3H), 2.85−3.03 (m, 1H), 5.35 (d, 1H, $J = 10.8$ Hz), 5.87 (s, 1H), 9.44 (br s, 1H); ^{13}C NMR ($CDCl_3$) δ 16.11, 23.44, 26.63, 124.44, 125.78, 136.53, 146.96, 171.66; HRMS calcd for $C_9H_{13}NO$ (M^+) 151.0997, found 151.0994. Anal. Calcd for $C_9H_{13}NO$: C, 71.49; H, 8.67; N, 9.26. Found: C, 71.69; H, 8.60; N, 9.12.

***Z*-5-Isobutylidene-4-methyl-1,5-dihydropyrrol-2-one (Z-1).** Compound **4** (0.10 g, 0.51 mmol) was dissolved in THF (5 mL) and treated with 60% NaH (0.031 g, 0.761 mmol). Stirring at ambient temperature was continued for 5 min, and isobutyraldehyde (0.14 mL, 1.52 mmol) was added to the mixture. The solution was concentrated in vacuo, and the residue was dissolved in dichloromethane (30 mL). The dichloromethane solution was then washed with 5% HCl (5 mL), $NaHCO_3$ (5 mL), and saturated NaCl (5 mL) solutions. The organic layer was dried (Na_2SO_4), filtered, and concentrated. The resulting crude oil was purified by column chromatography, eluting with ethyl acetate/hexane (2:8) to afford compound **Z-1** (66 mg) in 86% yield: IR (KBr) 3164, 3033, 2954, 1700, 1674, 1459, 1348, 1330, 1101, 966, 844, 762, 677 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.07 (d, 6H, $J = 6.6$ Hz), 2.03 (s, 3H), 2.62 (m, 1H), 5.12 (d, 1H, $J = 9.8$ Hz), 5.83 (s, 1H), 9.43 (br s, 1H); ^{13}C NMR ($CDCl_3$) δ 11.81, 22.84, 27.36, 120.59, 120.68, 137.63, 148.53, 172.88; HRMS calcd for $C_9H_{13}NO$ (M^+) 151.0997, found 151.1002. Anal. Calcd for $C_9H_{13}NO$: C, 71.49; H, 8.67; N, 9.26; Found: C, 71.50; H, 8.68; N, 9.29.

Liquid-Phase Synthesis of *Z*-Pulchellalactam (Z-1). To a cold (0 °C) solution of soluble polymer support (MeO-PEG-OH, 3.0 g, 0.60 mmol), 4-(4-hydroxyphenyl)-2-butanone (0.985 g, 6.0 mmol), and triphenylphosphine (0.787 g, 3.0 mmol) in dry CH_2Cl_2 (15 mL) was added dropwise a solution of 95% diisopropyl azodicarboxylate (DIAD) (0.623 mL, 3.0 mmol) in dry CH_2Cl_2 (15 mL). After 1 h at 0 °C, the reaction mixture was warmed to ambient temperature and stirred for 30 h. After the reaction was complete, the solution was concentrated by rotary evaporation and the reaction mixture was precipitated twice with CH_2Cl_2 (15 mL) and ether (100 mL). Polymer-bound product was then collected under aspirator pressure using a fritted funnel to give a white solid (2.95 g). The resulting ketone (2.7 g, 0.525 mmol) was placed in a 50 mL round-bottomed flask equipped with a stir bar and sealed with a septum. The flask was evacuated and purged with Ar; the process was repeated twice. THF (20 mL) was injected, and the mixture was then treated with 1 M MeMgBr (5.25 mL, 5.25 mmol) in THF. The reaction mixture was stirred at room temperature for 24 h. After the reaction was complete, the reaction mixture was precipitated with ether (50 mL). The crude product was dissolved in dichloromethane (120 mL) and stirred with 1 N NaOH (20 mL) for 1 h. The aqueous layer was separated, and the organic layer was then washed with 5% HCl (15 mL), 5% $NaHCO_3$ (15 mL), and saturated NaCl (5 mL) solutions. The organic layer was dried ($MgSO_4$), filtered, and concentrated. The residue was dissolved in dichloromethane (20 mL) and precipitated with ether (100 mL). Polymer-bound product **9** was then collected under aspirator pressure using a fritted funnel to give a white solid (2.86 g). The tertiary alcohol **9** (2.28 g, 0.422 mmol) was dissolved in dry CH_2Cl_2 (15 mL) at 0 °C and treated with *p*-nitrophenyl chloroformate (0.534 g, 2.65 mmol) and pyridine (0.178 mL, 2.208 mmol) under an argon atmosphere. After 2 h at 0 °C, the reaction mixture was warmed to ambient temperature and stirred for 24 h. After the reaction was complete, dichloromethane (120 mL) was added to the solution, and the organic layer was then washed with saturated NaCl (20 mL) solution. The organic layer was dried ($MgSO_4$), filtered, and concentrated by rotary evaporation. The residue was dissolved in dichloromethane (15 mL) and precipitated with ether (75 mL). Polymer-bound carbonate was then collected under aspirator pressure using a fritted funnel. The crude PEG carbonate was redissolved in dichloromethane (15 mL), precipitated with ether (75 mL), and dried in vacuo for the next sequence. The resulting polymer bound carbonate (2 g, 0.375 mmol) was then treated with freshly prepared glycine lithium salt[24] (0.0456 g, 0.563 mmol) in DMF (9.4 mL). The mixture was stirred for 48 h at room temperature. The solution was evaporated in vacuo to remove DMF, and the residue was dissolved in dichloromethane (60 mL). The dichloromethane solution was then washed with 5% HCl (10 mL), 5% $NaHCO_3$ (10 mL), and saturated NaCl (10 mL) solutions. The organic layer was concentrated, and ether (75 mL) was added to the reaction mixture. Polymer-bound acid **10** was then collected under aspirator pressure using a fritted funnel. The crude PEG acid **10** (1.95 g) was redissolved in dichloromethane (15 mL), precipitated with ether (75 mL), and dried in vacuo for the next sequence. The synthesis was completed according to the above experimental procedure used for the synthesis of *Z*-pulchellalactam (**Z-1**), except for column chromatography, as the purification was changed to precipitation.

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Supporting Information Available: ^1H and ^{13}C NMR spectra for compounds **2**−**4**, *Z*-**1**, **6**−**8**, and *E*-**1**; single-crystal X-ray data for *Z*-pulchellalactam. This material is available free of charge via the Internet at http://pubs.acs.org.

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