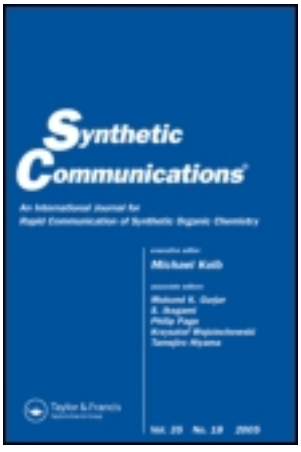

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Jean-Paul Hermet [a], Virginie Caubert [a] & Nicole Langlois [a]
[a] Institute of Organic Chemistry, National Center of Scientific Research, Gif-sur-Yvette, France
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Short Synthesis of Pulchellalactam

Jean-Paul Hermet, Virginie Caubert, and Nicole Langlois
Institute of Organic Chemistry, National Center of Scientific Research, Gif-sur-Yvette, France

Abstract: *tert*-Butyl 4-methyl-2-oxo-2,5-dihydro-1*H*-pyrrole-1-carboxylate **4** was synthesized by a short two-step procedure: regioselective 1,3-dipolar diazomethane cycloaddition to *N*-Boc-pyrrolinone **2** and thermolysis of the adduct. The compound **4** could be converted in one step into pulchellalactam.

Keywords: Diazomethane cycloaddition, marine metabolite, pyrazolines, unsaturated γ-lactams

Pulchellalactam **1** is a potent CD45 protein tyrosine phosphatase (PTP) inhibitor, which was isolated in 1998 from the marine fungus *Corollospora pulchella*, growing on driftwood from Peleliu.[1] PTP inhibitors are promising biochemical agents, and CD45 is a therapeutic target for several autoimmune and inflammatory diseases. Because of these biological activities and the restricted availability of the natural pulchellalactam, four syntheses of **1** have been achieved today.[2–5] Three of them involve the unsaturated γ-lactam **4** as a synthetic precursor of **1**.[2,4,5] The first synthesis of both isomers *E* and *Z* allowed the assignment of *Z* configuration to the chain double bond of pulchellalactam and described the conversion of **4** into **1** in one step and high yield.

We describe here a new and straightforward route to this direct precursor **4**, starting from *N*-Boc pyrrolinone **2**.

We anticipated that regioselective 1,3-dipolar diazomethane cycloaddition to **2**, followed by thermolysis of the adduct, would afford the desired compound **4**, as outlined in Scheme 1.

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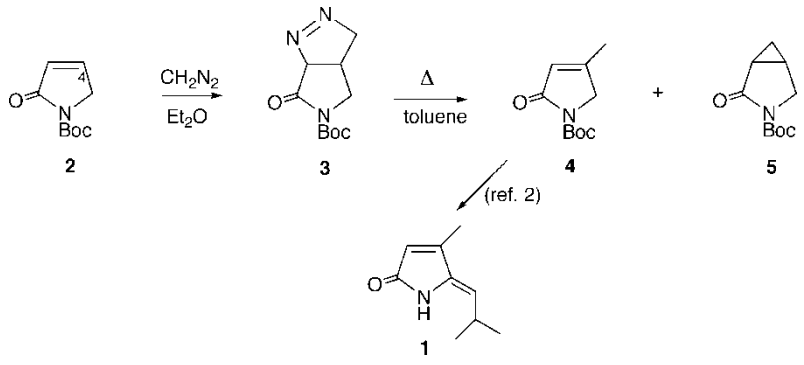
Address correspondence to Nicole Langlois, Institute of Organic Chemistry, National Center of Scientific Research, 91198, Gif-sur-Yvette, France. E-mail: nicole.langlois@icsn.cnrs-gif.fr



Scheme 1.

Diazomethane cycloadditions to electron-deficient double bonds have been known for a long time.[6] They occurred generally with high regioselectivity, explained by the magnitude of the orbital coefficients for the dipole HOMO and the dipolarophile LUMO.[7] Several types of α,β-unsaturated carbonyls have been studied as dipolarophiles: ketones,[8] esters[6,9] or lactones,[10] imides,[11] *N*-acyllactams,[12] and *N*-acylsultams.[13] To the best of our knowledge, few examples of dipolar cycloaddition of diazomethane to α,β-unsaturated lactams have been described today,[7] and acyclic unsaturated amides have not been used as dipolarophiles. The thermolysis of the resulting cycloadducts to prepare derivatives of β-methyl unsaturated lactams have been reported only in rare cases,[12] probably due, in part, to the possible isomerisation of initial Δ^1 into Δ^2-pyrazolines.

Accordingly, the *N*-Boc pyrrolinone **2** was prepared by oxidation of pyrrole with hydrogen peroxide as described,[14] followed by protection of the nitrogen as a *tert*-butylcarbamate,[15] a suitable and particularly inexpensive method for our purpose.[16] The cycloaddition was performed at room temperature by simple addition of a diazomethane solution in diethyl ether to the *N*-Boc-pyrrolinone **2**. The cycloaddition proceeded smoothly with complete regioselectivity. Varying the reaction time, we observed the initial formation of Δ^1-pyrazoline **3** as a single isomer. After 14 h, this cycloadduct was isolated in 68% yield (c.a. 100% based on the recovered starting material **2**). Thus, the reaction was stopped at this stage before completion to avoid by-product formation.

For the following thermolysis step, a solution of **3** in dry toluene was heated under reflux (oil bath at 125°C) for 8 h, giving rise to the target methylated pyrrolinone **4** (71%), together with small amounts of the known *N*-*tert*-butoxycarbonyl-3,4-methano-2-pyrrolidinone **5** (9%).[17] The compound **4**, by condensation of isobutyraldehyde in the presence of NaH with concomitant Boc *N*-*O* migration and elimination, led to pulchellalactam **1** in 86% yield.[2]

In conclusion, we developed a very short route to the direct synthetic precursor of natural pulchellalactam **1** by the regiospecific cycloaddition of diazomethane to the easily available unsaturated γ-lactam **2** and thermolysis of the cycloadduct in 48% overall yield.

EXPERIMENTAL

General

Melting points were determined with a Büchi B-540 apparatus and are uncorrected. Optical rotations were measured on a Jasco P-1010 polarimeter and concentrations are given in g/100 mL. IR spectra (film, $CHCl_3$) were recorded on a Perkin Elmer Spectrum BX (FT) instrument. ^{1}H NMR spectra were obtained ($CDCl_3$, $CHCl_3$ $\delta = 7.27$ ppm) from a Bruker AM 300 spectrometer (s, d, t, dd, and m indicate singlet, doublet, triplet, doublet of doublets, and multiplet, respectively). ^{13}C NMR spectra were recorded also with the AM 300 (75.0 MHz, $CDCl_3$ centered at 77.0 ppm). Mass spectra and high-resolution mass spectra were measured on a Navigator (ESI) or a Micromass LC-TOF spectrometer. Chromatography was performed on silica gel (SDS 230–400 mesh) and preparative thin-layer chromatography on silica gel (Merck HF 254 + 366).

tert-Butyl 6-oxo-3a,4,6,6a-tetrahydropyrrolo[3,4-*c*]pyrazole-5(3*H*)-carboxylate *3*

An excess of diazomethane (prepared in Et_2O from diazald just before the use)[18] was added, in three portions, to *tert*-butyl 2-oxo-2,5-dihydro-1*H*-pyrrole-1-carboxylate **2** (128 mg, 0.70 mmol), and the mixture was stirred at room temperature for 14 h. The colorless reaction mixture was evaporated to dryness under reduced pressure at rt. The residue was purified by preparative TLC (eluent– heptane-EtOAc 3:7) to afford **3** as white crystals (107 mg, 68%) and starting **2** (41 mg, 32%). Decomposition with release of gas at 142–3°C. IR: 2978, 2931, 1774, 1712, 1367 cm^{-1}. MS (ESI, MeOH): 248 (MNa^+, 100%). HRMS: calcd. for $C_{10}H_{15}N_3O_3Na$: 248.1011, found: 248.1030. ^{1}H NMR (300 MHz, $CDCl_3$): 5.49 (ddd, 1H, $J = 9$, $J' \sim J'' \sim 2$ Hz, H-6a), 4.83 (ddd, 1H, $J = 18.4$, $J' = 9$, $J'' \sim 2$ Hz, Ha-3), 4.72 (ddd, 1H, $J = 18.4$, $J' \sim 3$, $J'' \sim 2$ Hz, Hb-3), 3.97 (dd, 1H, $J = 11.7$, $J' = 9.2$ Hz, Ha-4), 3.27 (dd, 1H, $J = 11.7$, $J' = 4.3$ Hz, Hb-4), 2.81 (m, 1H, H-3a), 1.51 (s, 9H, CH_3, *t*-Bu) ppm. ^{13}C NMR (75.0 MHz, $CHCl_3$): 164.65 (CO), 149.53 (NCO_2), 96.95 (C-6a), 86.34 (C-3), 83.98 (qC, *t*-Bu), 51.05 (C-4), 27.92 (CH_3, *t*-Bu), 25.38 (C-3a) ppm.

tert-Butyl 4-methyl-2-oxo-2,5-dihydro-1*H*-pyrrole-1-carboxylate 4

A solution of pyrazoline **3** (94.5 mg, 0.42 mmol) in toluene (5 mL) was heated under reflux (oil bath thermostated at 125°C) for 8 h. After being cooled at room temperature, the solvent was eliminated by evaporation under reduced pressure to give the crude thermolysis product, which was purified by preparative TLC (eluent–heptane-Et_2O 1:2) affording **4** as colorless needles after crystallization in a Et_2O–pentane mixture (58.6 mg, 71%) and cyclopropane **5** (7.5 mg, 9%). **4**: mp: 72–73°C (lit.: oil).[2,5] IR: 2989, 2976, 2930, 1774, 1702, 1698, 1636, 1455 cm^{-1} (lit.: 1774, 1643, 1445 cm^{-1}).[5] MS (ESI, MeOH): 220 (MNa^+, 100%), HRMS: calcd. for $C_{10}H_{15}NO_3Na$ (MNa^+): 220.0950, found: 220.0952.^{1}H (300 MHz, $CDCl_3$): 5.82 (m, 1H, H-3), 4.18 (m, 1H, H_2-5), 2.07 (m, 3H, CH_3-4), 1.47 (s, 9H, CH_3 *t*-Bu) ppm (lit. δ: 5.82, 4.18, 2.06, 1.51 ppm).[5] ^{13}C NMR (75.0 MHz, $CHCl_3$): 169.57 (CO), 157.97 (NCO_2), 149.46 (C-4), 122.90 (C-3), 82.64 (qC, *t*-Bu), 54.32 (C-5), 28.01 (CH_3, *t*-Bu), 15.49 (CH_3-4) ppm (lit. δ: 169.7, 158.1, 149.4, 122.8, 82.6, 54.3, 28.0, 15.5 ppm).[5] Anal. calcd. for $C_{10}H_{15}NO_3$: C, 60.89; H, 7.67; N, 7.10. Found: C, 60.69; H, 7.75; N, 7.06.

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