A Facile Synthesis of CD45 Protein Tyrosine Phosphatase Inhibitor Marine Natural Product Pulchellalactam[1]

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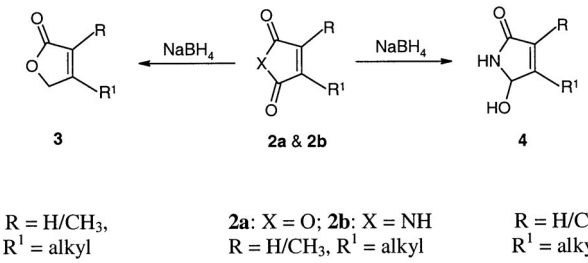
Received 17 February 2004; revised 29 March 2004

Abstract: A facile five-step route to the naturally occurring CD45 protein tyrosine phosphatase inhibitor, (*Z*)-pulchellalactam, with 64% overall yield has been demonstrated starting from citraconimide (**5**) via regioselective $NaBH_4$ reduction, catalytic hydrogenation, resin-catalyzed dehydration, *N*-BOC protection, and stereoselective condensation pathway.

Key words: CD45 PTP inhibitor, pulchellalactam, citraconimide, two reductions, resin-catalyzed dehydration, synthesis

Recently, a receptor-like transmembrane protein tyrosine phosphatase, CD45,[2] has been shown to play a crucial role in activation of both B and T cells.[3] CD45 therefore represents a therapeutic target for various autoimmune and chronic anti-inflammatory diseases.[4] As a part of efforts to find enzyme inhibitors from microbiological sources, Alvi et al.[5] identified the marine fungus *Corollospora pulchella* extract with very potent CD45 activity and a novel pulchellalactam (**1**) was isolated from the crude extract as an active component. Recently, Li et al.[6] reported the first total synthesis of **1** in six steps and 32% overall yield from BOC-glycine. Very recently, Parsons et al.[7] reported a second four-step synthesis of **1** with 10% overall yield starting from 2-methylhexan-3-one via a metal catalyzed radical cyclization pathway. Development of new efficient synthetic routes to **1** for the realistic supply of the natural product is a challenging task of current interest.[6,7] In our continuing interest[8] to provide new synthetic routes to bioactive natural products using cyclic anhydrides as potential precursors, we herein report a facile five-step synthesis of **1** starting from citraconimide (**5**) via a double reductive dehydration pathway.

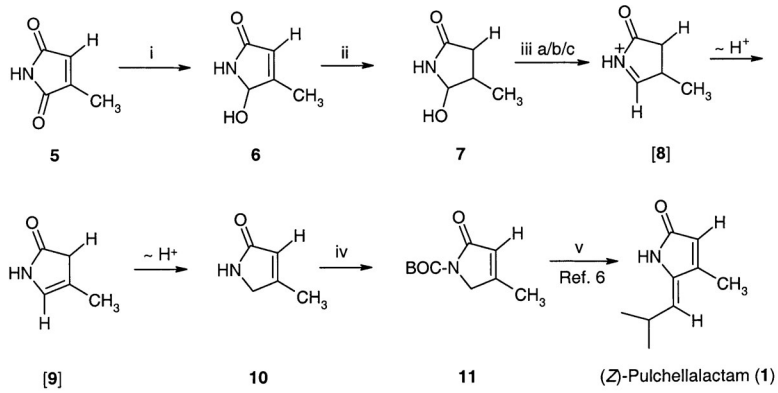
Alkyl and dialkyl substituted maleic anhydrides are known[9] to undergo highly regioselective $NaBH_4$-reductions at the hindered/relatively more hindered carbonyl group to directly form the corresponding γ-butyrolactones **3**. Similar regioselectivity has been also observed[10] during the $NaBH_4$-reductions of alkyl and dialkyl substituted maleimides, but these reactions stop with the formation of corresponding 5-hydroxy-γ-lactams **4** (Scheme 1). Such type of tight regiocontrol during the $NaBH_4$ reductions has not been observed[11] with the corresponding alkyl and vicinal dialkyl substituted succinimides. We planned to take the advantage of such type of regioselective reduction of maleimides for an efficient synthesis of **10** (Scheme 2). Citraconimide (**5**) underwent a highly regioselective $NaBH_4$-reduction to exclusively give the corresponding hydroxylactam **6** in ca 100% yield. The palladium on charcoal-catalyzed hydrogenation of **6** furnished a mixture of the two stereoisomers of **7** in ca 100% yield, in a 1:2 ratio (by ^1H NMR spectrum). Such type of hydroxylactams on treatment with *p*-toluenesulfonic acid (*p*-TSA) are known to undergo polymerization reactions.[12] We systematically studied the dehydration of **7** under acidic conditions. *p*-TSA in refluxing benzene gave the desired product **10** only in 25–30% yields. The lactam **7** on heating in glacial HOAc at 80 ºC for one hour furnished **10** with 50–55% yield. Finally, we could effect an efficient conversion of **7** to **10** using the strong acidic resin Amberlyst. The resin-catalyzed dehydration of **7** in refluxing CH_3CN gave the desired 4-methyl-3-pyrrolin-2-one (**10**)[13] in 92% yield. We surmise that the above dehydration process of **7** to **10** takes place via intermediate **9** and a very facile in situ prototopic shift.[14] The conversion of **9** to **10** could be because of conjugation of the carbon-carbon double bond with the carbonyl group. The lactam **10** on reaction with BOC-anhydride in CH_3CN at room temperature gave the BOC-protected lactam **11** in 85% yield. The lactam **11** under Li et al. conditions[6] exclusively furnished the bioactive natural product (*Z*)-pulchellalactam (**1**) in 82% yield. The analytical and spectral data obtained for **1** were in complete agreement with the reported data.[5–7] Starting from citraconimide (**5**), pulchellalactam (**1**) was obtained in five-steps with 64% overall yield.



Scheme 1

In summary, we have demonstrated an efficient approach to 4-methyl-3-pyrrolin-2-one and completed a facile synthesis of the bioactive natural product pulchellalactam us-

SYNTHESIS 2004, No. 10, pp 1560–1562
Advanced online publication: 16.06.2004
DOI: 10.1055/s-2004-822407; Art ID: Z03304SS



Scheme 2 *Reagents, conditions and yields*: (i) $NaBH_4$ (1 equiv), EtOH, –40 ºC, 1 h (ca 100%); (ii) Pd/C, H_2, MeOH, r.t., 2 h (ca 100%); (iii) (a) *p*-TSA (cat.), benzene, reflux, 3 h (25–30%), (b) HOAc, 80 ºC, 1 h (50–55%), (c) Amberlyst resin, CH_3CN, reflux, 2 h (92%); (iv) $(BOC)_2O$ (1.5 equiv), DMAP, CH_3CN, r.t., 3 h (85%); (v) NaH, THF, isobutyraldehyde, r.t., 5 min. (82%).

ing a new synthetic approach. We feel that the present approach is general and can be used to design a synthetic library of pulchellalactam analogues.

Melting points are uncorrected. ^{1}H NMR spectra were recorded on a Bruker AC 200 NMR spectrometer (200 MHz), Bruker MSL 300 NMR spectrometer, and Bruker DRX 500 NMR spectrometer with TMS as an internal standard. The ^{13}C NMR spectra were recorded on a Bruker AC 200 NMR spectrometer (50 MHz), Bruker MSL 300 NMR spectrometer (75 MHz), and Bruker DRX 500 NMR spectrometer (125 MHz). Mass spectra were recorded on a Finnigan Mat 1020 mass spectrometer at 70 eV. Column chromatographic separations were carried out on ACME silica gel (60–120 mesh). Petroleum ether with a bp range of 60–80 ºC was used. $NaBH_4$, palladium on carbon (10 wt%), *p*-toluenesulfonic acid, Amberlyst resin, di-*t*-butyl carbonate, NaH, dimethylaminopyridine, and isobutyraldehyde were obtained from Aldrich Chemical Co. Citraconimide (**5**) was prepared from citraconic anhydride by using the known procedure.[15]

5-Hydroxy-4-methyl-3-pyrrolin-2-one (6)

$NaBH_4$ (1.60 g, 40 mmol) was added at –30 ºC to a solution of citraconimide (**5**; 4.44 g, 40 mmol) in absolute EtOH (60 mL). After the reaction mixture was stirred at –30 °C to –40 ºC for 50 min, the excess $NaBH_4$ was quenched at –40 ºC by adding drop-wise 10% aqueous HOAc to pH 7. The solvent was evaporated under reduced pressure at r.t. and the residue was extracted with acetone (50 mL). Filtration and evaporation of the extract in vacuo afforded **6**; yield: 4.52 g (ca 100%); colorless crystalline solid; mp 163–164 °C (EtOAc).

IR (Nujol): 3202, 1711, 1665, 1645, 1460 cm^{-1}.

^{1}H NMR (500 MHz, CD_3OD): δ = 2.05 (s, 3 H), 5.36 (s, 1 H), 5.74 (s, 1 H).

^{13}C NMR (125 MHz, CD_3OD): δ = 13.5, 83.5, 122.4, 163.5, 175.5.

MS: *m*/*z* = 113, 98, 85, 69, 39.

Anal. Calcd for $C_5H_7NO_2$: C, 53.09; H, 6.24; N, 12.38. Found: C, 53.26; H, 6.33; N, 12.41.

5-Hydroxy-4-methyl-2-pyrrolidinone (7)

A mixture of hydroxylactam **6** (1.13 g, 10 mmol) and Pd/C catalyst (30 mg) in MeOH (15 mL) was subjected to hydrogenation at hydrogen balloon pressure for 2 h at r.t. The reaction mixture was filtered through celite and the filtrate was concentrated in vacuo to give saturated hydroxylactam **7**; yield:1.15 g (ca 100%); thick colorless oil.

IR ($CHCl_3$): 3261, 1672, 1460 cm^{-1}.

^{1}H NMR (200 MHz, CD_3OD): δ = 1.05 (d, *J* = 6 Hz, 2 H), 1.07 (d, *J* = 8 Hz, 1 H), 1.57–2.75 (complex m, 3 H), 4.77 (d, *J* = 2 Hz, 0.33 H), 5.01 (d, *J* = 6 Hz, 0.67 H).

MS: *m*/*z* = 115, 98, 70, 57, 46.

Anal. Calcd for $C_5H_9NO_2$: C, 52.16; H, 7.88; N, 12.17. Found: C, 51.97; H, 7.96; N, 12.28.

4-Methyl-3-pyrrolin-2-one (10)

To a solution of sat. hydroxylactam **7** (575 mg, 5 mmol) in anhyd CH_3CN was added Amberlyst resin (100 mg) and the reaction mixture was refluxed under Ar atmosphere for 2 h. The reaction mixture was allowed to reach r.t. and then it was filtered and concentrated under reduced pressure to give a residue. Silica gel column chromatographic purification of the residue using EtOAc and MeOH mixture (98:2) gave pure lactam **10**; yield: 446 mg (92%); colorless crystalline solid; mp 110–111 °C.

IR ($CHCl_3$): 3460, 1717, 1688, 1261, 1215 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.06 (s, 3 H), 3.90 (s, 2 H), 5.83 (s, 1 H), 6.35–6.50 (br s, 1 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 15.3, 51.7, 122.3, 158.5, 176.0.

Anal. Calcd for C_5H_7NO: C, 61.83; H, 7.27; N, 14.42. Found: C, 62.01; H, 7.13; N, 14.37.

***N*-*tert*-Butoxycarbonyl-4-methyl-3-pyrrolin-2-one (11)**

A solution of DMAP (31 mg, 0.25 mmol) in anhyd CH_3CN (3 mL) was added drop-wise to a mixed solution of lactam **10** (243 mg, 2.5 mmol) and di-*t*-butyl carbonate (818 mg, 3.75 mmol) in CH_3CN (12 mL) at r.t. under N_2 atmosphere and the mixture was stirred for 3 h. The reaction mixture was concentrated under vacuum at r.t. to give a residue. Silica gel column chromatographic purification of the residue using a petroleum ether and EtOAc mixture (7:3) gave thick colorless oil **11**; yield: 420 mg (85%).

IR ($CHCl_3$): 1774, 1724, 1643, 1445 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.51 (s, 9 H), 2.06 (d, *J* = 2 Hz, 3 H), 4.18 (s, 2 H), 5.82 (br s, 1 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 15.5, 28.0, 54.3, 82.6, 122.8, 149.4, 158.1, 169.7.

Anal. Calcd for $C_{10}H_{15}NO_3$: C, 60.89; H, 7.67; N, 7.10. Found: C, 61.02; H, 7.77; N, 7.23.

5-(*Z*)-Isobutylidene-4-methyl-1,5-dihydropyrrol-2-one (Pulchellalactam, 1)

A solution of *N*-BOC lactam **11** (197 mg, 1 mmol) in anhyd THF (5 mL) was treated with 60% NaH (62 mg, 1.52 mmol) at r.t. and stirred for 5 min. Isobutyraldehyde (0.28 mL, 3 mmol) was added to the mixture and stirred for 5 more min. The reaction mixture was concentrated in vacuo at r.t. to give a residue. The residue was dissolved in CH_2Cl_2 (30 mL), which was then washed with 5% HCl (10 mL), aq $NaHCO_3$ (10 mL), and brine (10 mL). The organic layer was dried over Na_2SO_4, filtered, and concentrated in vacuo. Silica gel column chromatographic purification of the residue using a petroleum ether and EtOAc mixture (7:3) afforded (*Z*)-pulchellalactam (**1**) as thick colorless oil; yield: 124 mg (82%).

IR ($CHCl_3$): 3209, 1682, 1464, 1215 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.11 (d, *J* = 6 Hz, 6 H), 2.08 (s, 3 H), 2.55–2.90 (m, 1 H), 5.12 (d, *J* = 8 Hz, 1 H), 5.86 (s, 1 H), 8.81 (br s, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 11.8, 22.9, 27.6, 120.0, 121.1, 137.5, 148.8, 171.5.

Anal. Calcd for $C_9H_{13}NO$: C, 71.49; H, 8.66; N, 9.27. Found: C, 71.55; H, 8.81; N, 9.15.

Acknowledgments

S. M. thanks CSIR, New Delhi, for the award of a research fellowship. N. P. A. thanks the Department of Science and Technology, New Delhi, for financial support.

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