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CONVENIENT SYNTHESIS OF PULCHELLALACTAM, A CD45 PROTEIN TYROSINE PHOSPHATASE INHIBITOR FROM THE MARINE FUNGUS *COROLLOSPORA PULCHELLA*, AND ITS RELATED COMPOUNDS

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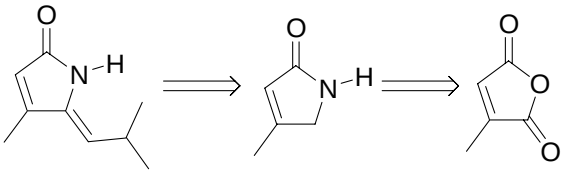
Abstract – Convenient synthesis of pulchellalactam (**1a**) and its related compounds was accomplished. Total yields of (*Z*)-pulchellalactam and (*E*)-pulchellalactam were 55% for 5 steps and 43% for 8 steps from commercially available and inexpensive citraconic anhydride, respectively.

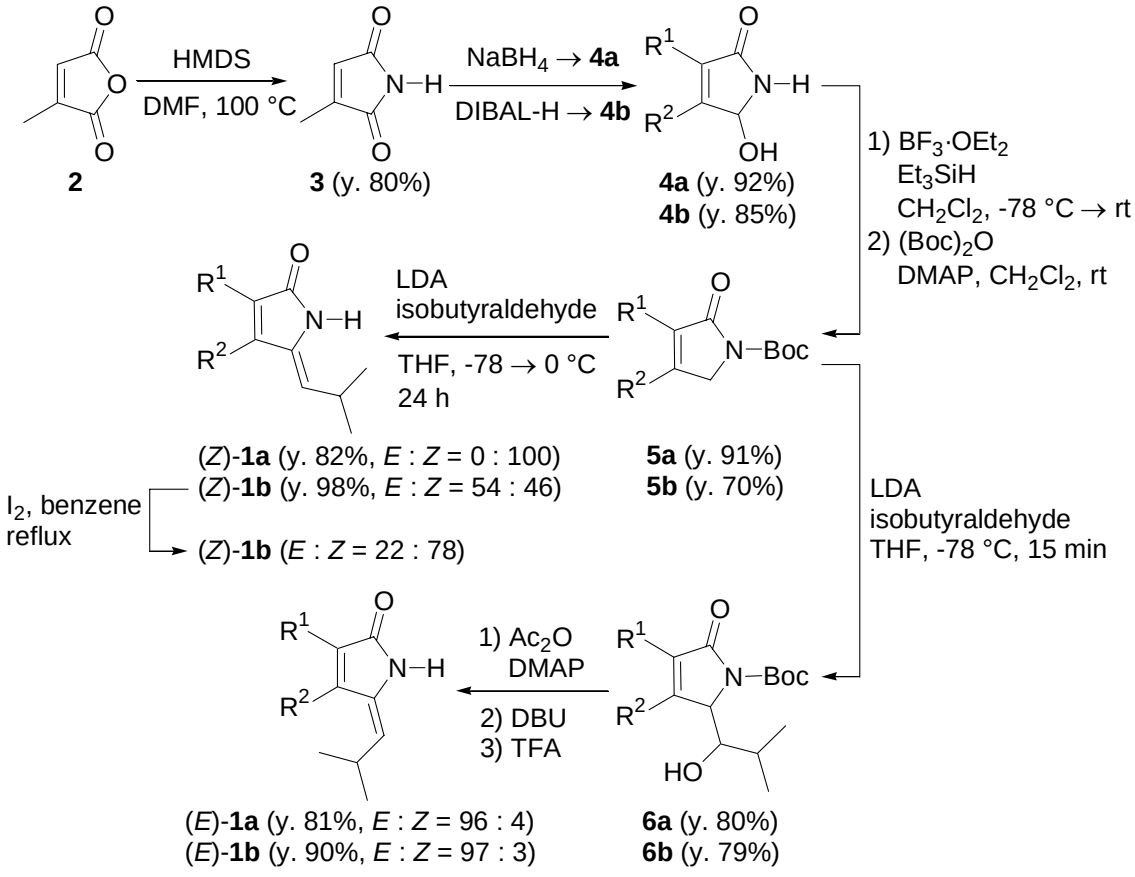
Pulchellalactam (**1a**), (5*Z*)-1,5-dihydro-4-methyl-5-(2-methylpropylidene)pyrrol-2(2*H*)-one, was isolated from the marine fungus *Corollospora pulchella* in 1998 by Alvi *et al.*[1] Its bioactivity is a dose-dependent inhibitor of CD45 protein tyrosine phosphatase with an IC_{50} of 124 μg/mL; interestingly, this inhibition is specific for CD45. Since CD45 participates in activation of both B and T cells *via* their antigen-specific receptors, pulchellalactam (**1a**) might be expected as a drug intervention in various auto-immune and/or inflammatory diseases.[1,2] Quite recently, the synthesis of **1a** has been reported by Li *et al.*[3] The key step of the sequence involves addition and elimination of an enolic lactam with an organocuprate reagent. Their total synthesis afforded (*Z*)-**1a** in 6 steps and 32% overall yield from Boc-glycine. Independently, we have recently accomplished convenient synthesis of **1a** and its related compounds (**1b**) from commercially available and quite inexpensive citraconic anhydride (**2**), employing regioselective reduction of citraconimide (**3**) (Scheme 1).



(*Z*)-Pulchellalactam (**1a**)

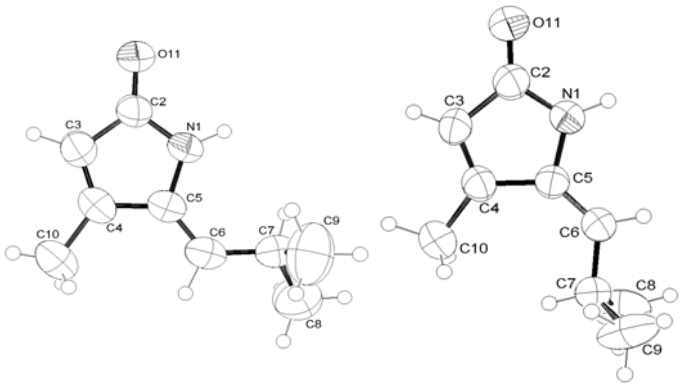
Scheme 1. Synthetic plan of (*Z*)-**1a** from citraconic anhydride.

A conventional method for the preparation of citraconimide (**3**) is heating the anhydride (**2**) under reflux in the presence of $NH_4OAc/AcOH$,[4] however, giving **3** in 41% yield. A higher yield was achieved by using 1,1,1,3,3,3-hexamethyldisilazane (HMDS) as ammonia equivalent in DMF at 100 °C as shown in Scheme 2. In 1999, we succeeded in synthesis of an antitumor alkaloid (jatropham) through regioselective reduction of **3**, in which $NaBH_4$ reduction afforded 1,5-dihydro-5-hydroxy-4-methyl-2*H*-pyrrol-2-one (**4a**), whereas $NaBH_4/CeCl_3$ or DIBAL-H reduction gave the regioisomer (**4b**) with extremely high regioselectivities.[5] We obtained **4a** as a single regioisomer by recrystallization. Reductive deoxygenation[6] of **4a** following Boc-protection[7] furnished *N*-*tert*-butoxycarbonyl-1,5-dihydro-4-methyl-pyrrol-2(2*H*)-one (**5a**)[8] in 91% yield. The pyrrol-2(2*H*)-one (**5a**) was treated with LDA at -78 °C, and the resulting anion was reacted with isobutyraldehyde. Interestingly, the product highly depended on the reaction time and temperature. Longer reaction time and higher reaction temperature gave the desirable (*Z*)-**1a** as a single geometrical isomer in a single step. On the other hand, the aldol reaction at -78 °C for 15 min gave the aldol product (**6a**) in 80% yield, which was easily transformed into (*E*)-**1a** in an *E*/*Z* ratio of 96/4 by elimination and deprotection.[9]



Scheme 2. Synthesis of pulchellalactam (**1a**) and its analogue (**1b**).

Structural determinations of both isomers, (*Z*)- and (*E*)-**1a**, were performed by X-Ray crystallographic analysis as shown in Figure 1.[10] We also tried to determine the structure of synthetic pulchellalactam (**1a**) by NMR spectral analyses compared with the reported value of the natural product. ^{1}H and ^{13}C NMR chemical shifts are given in Table 1. Most of the signals were in agreement with the reported values of (*E*)-pulchellalactam; however, unfortunately signals for H-6 proton and C-6 carbon were found to differ.



(*Z*)-Pulchellalactam (*E*)-Pulchellalactam

Figure 1. X-Ray structure of pulchellalactam.

Table 1. ^{1}H and ^{13}C NMR chemical shifts (ppm).

No.	Natural[a)]	(*Z*)-**1a**	(*E*)-**1a**
H-1	9.41 (br s)	7.65 (br s)	8.10 (br s)
H-3	5.94 (br s)	5.86 (br s)	5.91 (br s)
H-6	5.40 (d, 9.87 Hz)	5.11 (d, 9.80 Hz)	5.30 (d, 10.60 Hz)
H-7	2.60-2.67 (m)	2.51-2.64 (m)	2.89-3.10 (m)
H-8,9	1.12 (d, 6.63 Hz)	1.11 (d, 6.80 Hz)	1.08 (d, 6.60 Hz)
H-10	2.11 (d, 1.16 Hz)	2.08 (s)	2.28 (s)
C-2	173.1	173.0	171.7
C-3	119.7	120.7	125.7
C-4	150.2	148.5	146.9
C-5	137.0	137.7	136.6
C-6	125.5	120.7	124.5
C-7	28.0	27.3	26.6
C-8,9	22.7	22.8	23.4
C-10	11.9	11.7	16.1

a) Revised spectrum data provided by Dr. Khisal A. Alvi.

(*Z*)-Pulchellalactam is thermodynamically quite stable at least for a half-year, while the (*E*)-isomer is relatively unstable. An *E*/*Z* ratio of 99/1 of (*E*)-**1a** decreased to 70/30 after 1 week, then 24/76 after 3 months, even stored in a freezer at –20 °C. It took one week or more to isolate natural pulchellalactam from the marine fungus; therefore, it seemed reasonable to assume that the stereochemistry of **1a** was *E*.

One principal advantage of our synthetic method is a convenient approach to the related compounds, 1,5-dihydro-3-methyl-5-(2-methylpropylidene)pyrrol-2(2*H*)-one (**1b**). In a similar way to the synthesis of (*Z*)-**1a**, **1b** was obtained as a mixture of geometrical isomers in an *E*/*Z* ratio of 54/46 in 47% overall yield.

Refluxing in benzene with iodine afforded the thermodynamically more stable geometrical isomer ((*Z*)-**1b**) in an *E*/*Z* ratio of 22/78. Similarly, (*E*)-**1b** was obtained in an *E*/*Z* ratio of 97/3 in 34% overall yield, which was relatively unstable to show an *E*/*Z* ratio of 82/18 after being stored at –20 °C for 1 week. In conclusion, we have shown a synthesis of (*Z*)- and (*E*)-pulchellalactams (**1a**) from commercially available citraconic anhydride. Interestingly, the product ratio in the aldol reaction highly depended on the reaction time and temperature to give the (*E*)- and (*Z*)-isomers, regioselectively.

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9. The geometrical selectivity was determined by ^{1}H NMR spectrometry before deprotection of the Boc group due to instability of (*E*)-**1a**.
10. (*Z*)-**1a**: monoclinic ($P2_1/c$); a=11.9896(45)Å, b=6.9290(34)Å, c=12.5863(32)Å; β = 115.698(20)°, *Z*=4, R1(wR2)=0.0662(0.1679). (*E*)-**1a**: monoclinic ($P2_1/c$); a=9.6464(158)Å, b=8.4541(63)Å, c=11.7772(54)Å; β = 107.423(67)°, *Z*=4, R1(wR2)=0.0591(0.0809).