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Highly Diastereoselective Synthesis of (-)-Petasinecine via Ireland-Claisen-Type Rearrangement

Johann Mulzer* and Mazin Shanyoor

Institut für Organische Chemie der Freien Universität Berlin
Takustraße 3, D-14195 Berlin, FRG.

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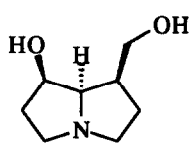
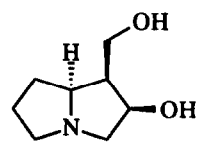
Abstract: A highly diastereoselective synthesis of petasinecine from L-proline via an Ireland-Claisen-type rearrangement (**5** -> **7**; Scheme 1) is described.

Necine bases such as hastanecine (**1**) have received much attention due to their widespread occurrence in the plant kingdom and their interesting physiological properties.[1a,b] The pyrrolizidine nucleus has repeatedly served as a testcase for novel synthetic methodology,[1c-f] e.g. free radical cyclization,[2] [4+1]-annulation,[3] Speckamp- [4,5] or Dieckmann[6] -cyclization to form the bicyclic ring system with the proper substitution pattern in an enantiomerically and diastereomerically controlled manner.



Hastanecine **1**



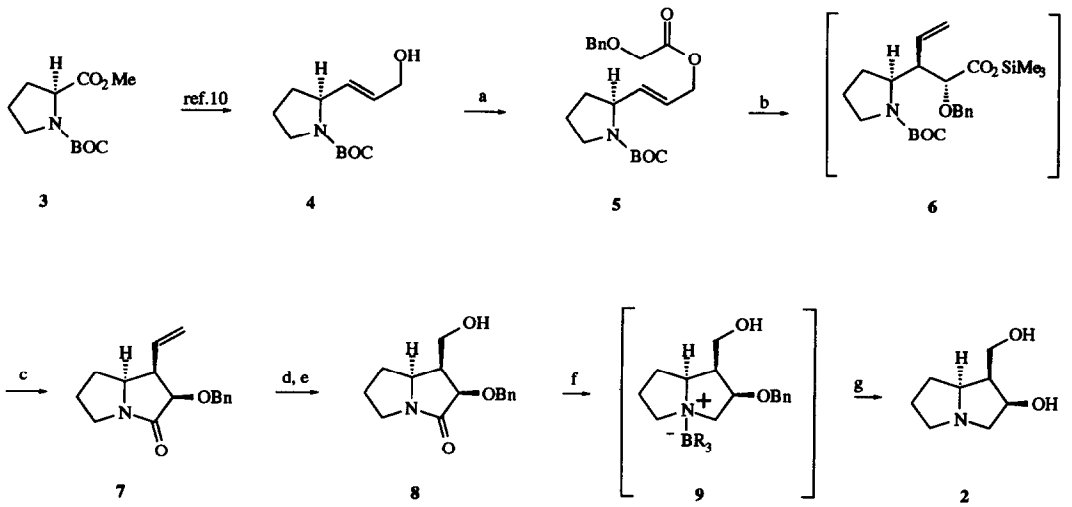
Petasinecine **2**

Petasinecine (**2**), the necine base of the two pyrrolizidine alkaloids petasinine and petasinoside, is a regioisomer of **1** and has been isolated from *Petasites japonicus* Maxim.[7] Astonishlingly, **2** has not been prepared on an enantio- and diastereo-controlled route yet. In continuation of our previous work[8] on necine bases we developed a synthesis of **2** wich is based on an Ireland-Claisen-type rearrangement[9] to annulate a second five-membered ring to L-proline in a highly efficient way (Scheme 1).

N-Boc-L-proline methylester **3** was transformed into the know allylic alcohol **4**,[10] wich was esterified to give the key intermediate **5**. Unter the conditions described by *Burke, Kallmerten* and *Fujisawa*[11] **5** was converted into **7** in one single operation. No other stereoisomer could be detected (500 MHz-^{1}H- and 125 MHz ^{13}C-spectra and HPLC). The stereochemistry of **7** was unambiguously determind by NOE-difference spectroscopy. The synthesis of **2** was

completed by conversion of the vinyl group to the alcohol **8**, reduction of the amide and removal of the benzyl protective group.[12] The compound thus obtained is identical in all respects with petasinecine[7] (mp, optical rotation and NMR spectra). The overall yield is 70% from **4** over 7 steps with 3 isolated intermediates (**5**, **7**, **8**).[13]

Scheme 1.



3 4 5 6

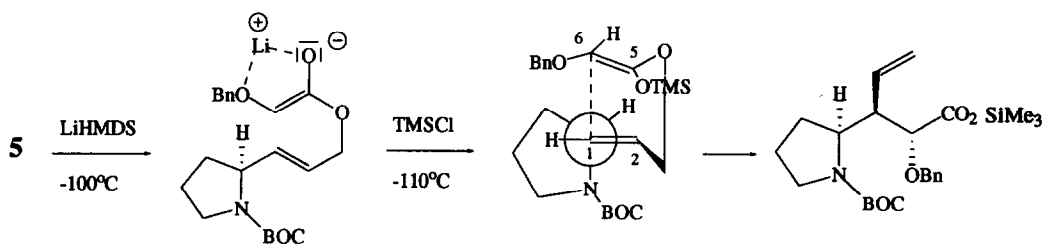
7 8 9 2

(a) $BnOCH_2COCl$ / Py, r.t., 98%, 5h; (b) LiHMDS / TMSCl / THF, -110°C, 2h, then 5h at 0°C; (c) F_3CCO_2H / BuOH, -20°C, 1h, r.t., 16h, +60°C, 48h, 82%; (d) O_3 / MeOH, -78°C, 10min; (e) $NaBH_4$ / MeOH, -78°C, 16h, 92%; (f) BH_3 · THF / THF/ +60°C, 48h; (g) 10% Pd-C / H_2 / MeOH, r.t.,1 bar; 48h, 98%.

The high diastereoselectivity of the Ireland-Claisen-type-rearrangement (Scheme 2) may be interpreted by the following assumptions:

a. the deprotonation of **5** leads to a chelated enolate **10**.
b. a chairlike transition state is adopted, as normal for acyclic substrates.[14]
c. with respect to the diastereofacial induction, *Houk's model*[15] is applicable, resulting in a minimum of *inside crowding*.
d. the N-Boc-moiety exerts a strong antiperiplanar effect.

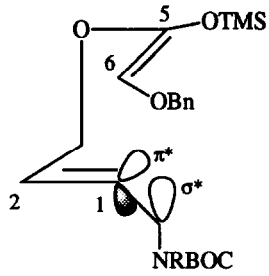
Scheme 2.



10 11 6

These assumptions are in agreement with reactive conformation **11**. According to the concept of Hehre and Kahn[16] the electron withdrawing Boc substituent lowers the energy of the 1,2 π^*-orbital via a σ^*-π^*- interaction (Figure 1). On the other hand the energy level of the 5,6-π-orbital is increased by the two electron donating residues (OBn and OTMS). This leads to a strong HOMO-LUMO interation lowering the activation barrier of the rearrangement,[16] which thus proceeds at low temperature (0°C) and with high stereoselectivity.

Figure 1.



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13. (a) : (**7**) : Compound **5** (2 g, 5.33 mmol) in THF (80 mL) was treated dropwise with a solution of LiHMDS (1.2 M in THF, 25 mL, 15.99 mmol) at -100°C. After 1h TMSCl (4.28 mL, 31.98 mmol) was added at -110°C. The solution was stirred for 1h and warmed to 0°C over 5h. The mixture was carefully treated with trifluoroacetic acid (20 mL) and butanol (40 mL) at -20°C. 1h later the mixture was warmed to r.t. and stirred for 16h. After this time the solution was warmed to +60°C and refluxed for 48h. Brine (30 mL) and Et_2O (100 mL) were added, the aqueous phase was separated, and extracted with Et_2O (3 x 100 mL). The combined organic layers were dried with $MgSO_4$, the solvent was removed and the residue was purified by flash column chromatography on silicagel (hexane / EtOAc, 1 : 3). **^{1}H-NMR** (250 MHz, $CDCl_3$, TMS): δ = 1.52-1.87 (m, 2H), 1.88-2.01 (m, 2H), 2.92-3.06 (m, 1H), 3.26 (ddd, 1H, J= 5,25 Hz, J= 6,25 Hz, J= 10 Hz), 3,58 (m_c, 1H), 3.72 (m, 1H), 4.36 (d, 1H, J= 5.25 Hz), 4.70 (s, 2H), 5.16 (dd, 1H, J=2 Hz, J=17.75 Hz), 5.24 (dd, 1H, J= 2 Hz, J= 10 Hz), 7.3 (m, 5H). **^{13}C-NMR** (63 MHz, $CDCl_3$, TMS): δ = 25.109, 25.405, 41.576, 48.976, 59.170, 71,463, 79.945, 119.609, 127.587, 127.896, 128.188, 131.599. $[\alpha]_D^{25}$: -1 (c = 1, $CHCl_3$).

    (b) : (**8**): Ozonolysis of **7** with $NaBH_4$-workup under standard conditions furnished **8**. **^{1}H-NMR** (250 MHz, $CDCl_3$, TMS): δ = 1.72-1.86 (m, 2H), 1.88-2.01 (m, 1H), 2.02-2.19 (m,1H), 2.34 (t, 1H, J = 7.5 Hz), 2.64-2.76 (m, 1H), 3.01-3.15 (m,1H), 3.44-3.56 (m, 1H), 3.68-3.86 (m, 3H), 4.50 (d, 1H, J = 7.63 Hz), AB-system: (δ = 4.51, δ = 5.16, 2H, J = 12.5 Hz), 5.20-5.4 (m, 5H). **^{13}C-NMR** (63 MHz, $CDCl_3$, TMS): δ = 25.259, 25.817, 41.041, 42.625, 59.140, 59.662, 79.861, 172.033. $[\alpha]_D^{25}$: +87 (c = 0.3, $CHCl_3$).

    (c) : (**2**) : Compound **8** (0.220 g, 0.84 mmol) in THF was treated dropwise with 5 ml BH_3-THF (1 M in THF, 5 mmol) at 0°C and stirred for 10 min at 0°C. After this time the solution was refluxed for 48h. The reaction was quenched with abs. MeOH (80 mL). The crude adduct **9** was hydrogenated in MeOH / THF with 10% Pd-C (100 mg) at r.t. and 1 bar for 48h. After filtration the solvent was evaporated and the product was isolated by flash column chromatography on silicagel (MeOH / NH_3 / CH_2Cl_2, 1 : 1 : 10).

    ^{1}H-NMR (250 MHz, MeOH-d_4, TMS): δ = 1,57-1,81 (m, 2H), 1.87-2.08 (m, 2H), 2.22-2.37 (m, 1H), 2.73-2.85 (ddd, 1H, J = 0.5 Hz, J = 1.25 Hz, J = 12.5 Hz), 2.86-2.95 (m. 1H), 3.05-3.15 (ddd, 1H, J = 4.5 Hz, J = 5 Hz, J = 12.5 Hz), 3.15-3.23 (m,1H), 3.46-3.62 (m, 1H), 3.76 (dd,1H, J = 7 Hz, J = 7.5 Hz), 3.92 (dd, 1H, J = 7.5 Hz, J = 8 Hz), 4.29.(m, 1H). **^{13}C-NMR** (63 MHz, MeOH-**d_4**, TMS): δ = 27.829, 28.541, 49,566, 57.740, 59.573, 63.274, 67.663, 74.319. $[\alpha]_D^{25}$: -21° (0.25, EtOH), mp : 135.°C (ref. 7 : $[\alpha]_D^{25}$: -20° (0.25, EtOH), mp. : 132-134°C).
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