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Enantioselective Syntheses of Tussilagine and Isotussilagine

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Abstract: Tussilagine and isotussilagine are synthesized through the coupling reactions of *N,N*-disubstituted β-amino-esters with methyl pyruvate and Mitsunobu reactions as key steps.

Keywords: tussilagine, isotussilagine, enantioselective synthesis.

Pyrrolizidine alkaloids have stimulated a great deal of interest because of their diverse biological activities and their wide distribution in nature.[1,2] Among hundreds of isolated pyrrolizidines, tussilagine and its C-2 epimer isotussilagine are atypical and non-toxic pyrrolizidines bearing a methyl group at the C-2 position.[1] They have been found to exist in *Tussilago farara*, *Echinacea purpurea*, *Arnica* and *E. angustifolia*.[3] Although a synthetic route for these compounds has been reported,[4] neither compound has been prepared *via* an enantio- and diastereo-controlled route. In continuation of our previous work on the synthesis of polyfunctionalized pyrrolidinones,[5] we have developed an enantioselective protocol for synthesizing tussilagine and isotussilagine. Herein we detail our results.

As outlined in Scheme I, the α,β-unsaturated ester **1** was prepared by the following three steps: 1) mono-protection of 1,4-butanediol with a benzyl group; 2) oxidation of the unprotected hydroxyl group to an aldehyde using PCC; 3) a Wittig reaction using Ph_3PCHCO_2Me. Addition of lithium (*S*)-*N*-benzyl-*N*-α-methylbenzylamide[6] to **1** gave **2** as a single isomer in 83% yield. Next, treatment of **2** with LDA followed by trapping the generated anion with methyl pyruvate afforded two separable isomers **3** and **4**.[5a] Both compounds were hydrogenated under Pd/C catalysis to provide pyrrolidinones **5** and **8**, respectively and their structures were assigned from their NOESY spectra. Significant NOEs were observed between the 3-Me and 4-H, 3-Me and 5-H, and 4-H and 5-H in the spectrum of **5** and we therefore assigned the (3*R*,4*R*,5*S*)-stereochemistry of **5**. In the spectrum of **8** an NOE was observed only between 4-H and 5-H, which implied the (3*S*,4*R*,5*S*)-stereochemistry of **8**. With pyrrolidinone **5** in hand, the next step was to form another five-membered ring to finish the synthesis of isotussilagine. After some experimentation, we found that a Mitsunobu reaction was suitable for this step. Thus, treatment of **5** with PBu_3/ADDP[7] produced the ring-closure product **6** in a 91% yield. The amide **6** could be reduced selectively to the amine **7** using $BH_3{\cdot}Me_2S$; **7** is the 1-epimer of isotussilagine. We considered that **7** was not as thermodynamically stable as isotussilagine and that it should be possible to convert it into the target molecule by treatment with base. Accordingly, after stirring a mixture of **7** and K_2CO_3 in methanol at room temperature for 1 day, we found that **7** was converted completely to isotussilagine **11**.[8] The product had spectra[3,4] identical with those of

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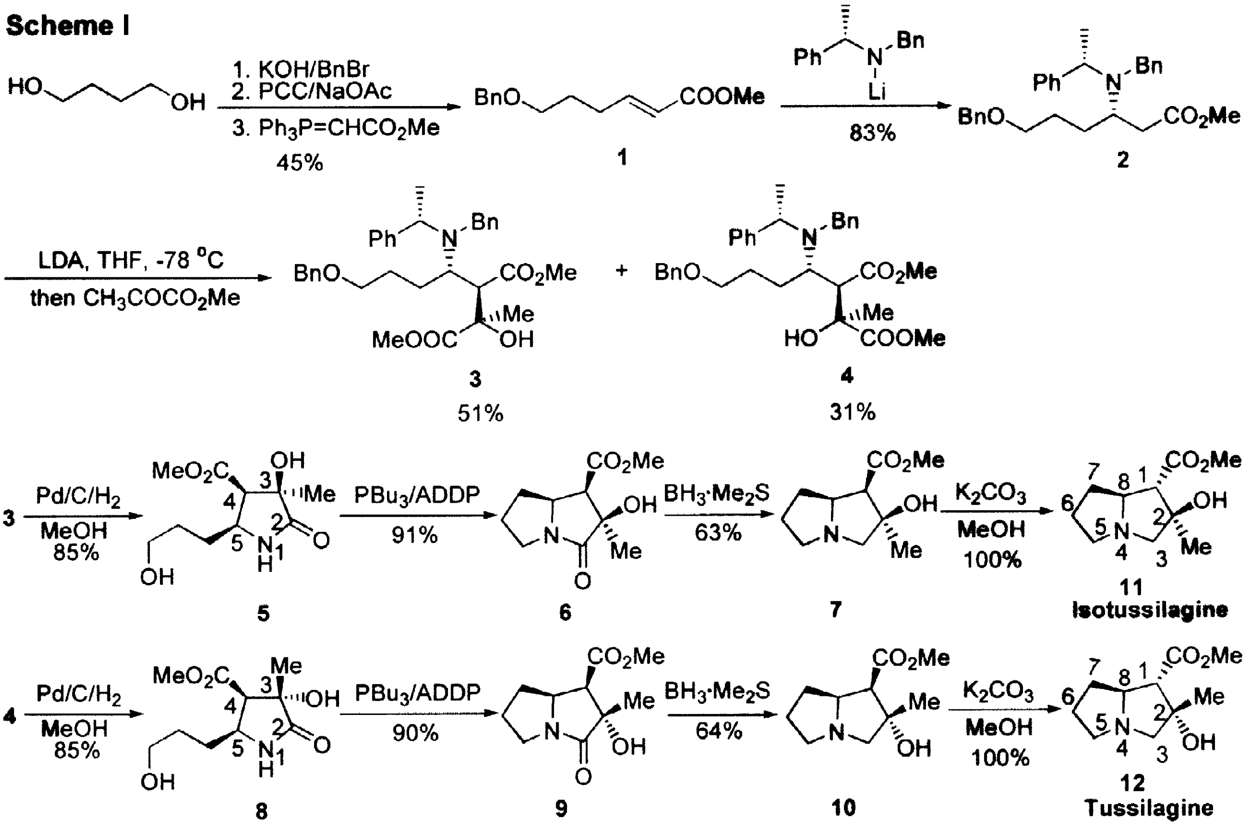
isotussilagine and its structure was further confirmed by its NOESY spectrum, in which an NOE signal between the 2-Me and 8-H, but no NOE signal between the 2-Me and 1-H, was observed. Therefore, we have developed a stereoselective route for synthesizing isotussilagine, with a 9.3% overall yield, from 1,4-butandiol. In a similar manner, we synthesized tussilagine 12[8] from pyrrolidinone 4 in a 5.6% overall yield. Its spectral data were the same as those reported.[3]

Scheme I



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8. Selected data for **11**: $[\alpha]^{25}_{D}$ = +129 (*c* 0.17 $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.44 (dt, *J* = 10.1, 1.8 Hz, 1H), 4.00 (s, 1H), 3.77 (s, 3H), 3.58 (d, *J* = 12.2 Hz, 1H), 3.15 (dt, *J* = 11.6, 5.8 Hz, 1H), 3.03 (m, 1H), 2.95 (d, *J* = 12.2 Hz, 1H), 2.63 (d, *J* = 10.5 Hz, 1H), 2.31-1.58 (m, 4H), 1.48 (s, 3H). **12**: $[\alpha]^{25}_{D}$ = -2.7 (*c* 0.15, EtOH) (lit[3c] $[\alpha]^{25}_{D}$ = -2.7 (*c* 0.15, EtOH)); ^{1}H NMR (300 MHz, CD_3SOCD_3) δ 3.84 (dt, *J* = 10.3, 4.8 Hz, 1H), 3.65 (s, 3H), 3.18 (s, 2H), 3.08 (dt, *J* = 10.8, 6.8 Hz, 1H), 2.92 (d, *J* = 8.6 Hz, 1H), 2.68 (m, 1H), 2.10 (m, 1H), 1.98 (m, 2H), 1.80 (m, 1H), 1.20 (s, 3H).