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Synthesis of racemic nitramine, isonitramine and sibirine

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Abstract—Condensation of enol ether **6** with methyl vinyl ketone led easily to ketoaldehyde **7** whose cyclisation afforded the azaspiranic enone **8**, a key intermediate for the synthesis of the title alkaloids.

The synthesis of azaspiranic alkaloids such as nitramine **1**, isonitramine **2** and sibirine **3** has received much attention[1] since their isolation in 1973 (Fig. 1).[1a]

We have previously reported an easy access to 1,5-dicarbonyl compounds using Michael-type addition between an enol ether and methyl vinyl ketone (MVK), in the presence of an alcohol such as isopropanol, catalysed by boron trifluoride diethyl etherate (Scheme 1).[2]

We have now used this methodology to prepare amino 1,5-ketoaldehyde **7** from amino silyl enol ether **6**, which in turn served as the key intermediate for the synthesis of racemic **1**, **2** and **3** (Scheme 2).

Aldehyde **5** was obtained in two steps from commercially available 3-hydroxymethyl-piperidine **4** by selective protection of the secondary amine and oxidation

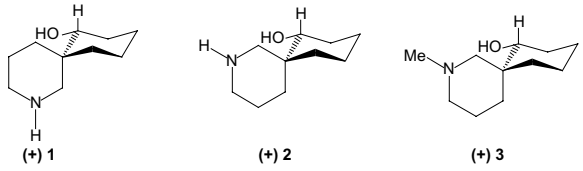
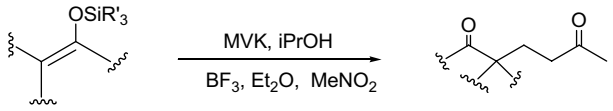


Figure 1.



Scheme 1.

of the primary alcohol with PCC. Compound **5** was transformed into silyl enol ether **6** by reaction with *tert*-butyldimethylsilyl chloride in the presence of triethylamine in DMF.[3] Reaction of **6** with MVK using our conditions then gave ketoaldehyde **7** in 73% yield.[4] The cyclisation of **7** into enone **8** was performed in an acidic medium.[5] Functional adjustment of **8** using a Wharton rearrangement[6] allowed access to (±)**1**, **2** and **3**. Thus, epoxyketone **9**, obtained by oxidation of enone **8** with alkaline hydrogen peroxide,[7] was transformed into allylic alcohol **11** without isolation of epoxyhydrazone **10**.[8] Hydrogenation of **11** led to diastereoisomeric alcohols **12** and **13** isolated by flash chromatography in 28% and 43% yield, respectively. Deprotection of the amino group of **12** and **13**, afforded racemic nitramine **1** and isonitramine **2**, whereas reduction of the carbamate group of **13** by LAH led to racemic sibirine **3** (Scheme 2).[9]

The synthesis described is efficient and easy to perform. Moreover, it is noteworthy that the azaspiro backbone is obtained by formation of the C7–C8 bond (Fig. 2), in contrast to previous syntheses, which are based on the formation of N1–C2[1e,f,h,n,u] C2–C3[1b,g,j,m,v] C3–C4[1d] or C3–C11[1l] bonds for ring closure. A procedure using the simultaneous formation of both rings has also been described using the CN(*R*,*S*) method.[1c,i,t]

Keywords: Azaspiranic alkaloids; Silyl enol ether; MVC.
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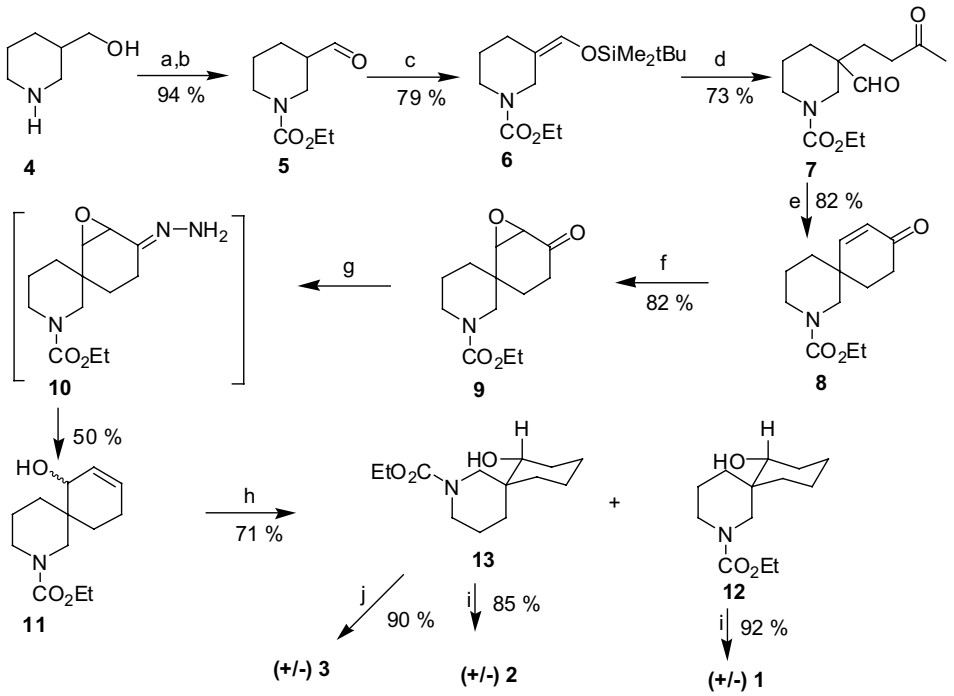

Scheme 2. Reagents and conditions: (a) $ClCO_2Et$, NEt_3, H_2O/acetone; (b) PCC, CH_2Cl_2; (c) NEt_3, TBDMSCl, DMF, 80 °C; (d) MVK, *i*-PrOH, $BF_3{\cdot}ET_2O$, $MeNO_2$, −20 °C; (e) HCl, 3 N, Δ; (f) H_2O_2, NaOH; (g) NH_2–NH_2, 2HCl, NEt_3, CH_3CN; (h) H_2, Pd–C, 10%; (i) NaOH, Δ; (j) LAH, THF, Δ.

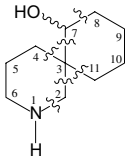

Figure 2.

Acknowledgments

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4. To a solution of **6** (4 mmol, 1.20 g) in nitromethane (3 mL) was added, at −20 °C, MVK (0.21 g, 3 mmol) in nitromethane (3 mL), followed by a solution of $BF_3{\cdot}Et_2O$ (1.08 mmol, 145 μL, 0.36 equiv vs MVK) in *i*-PrOH

(3 mmol, 230 μL) at −25 °C. The mixture was kept at −20 °C until disappearance of **6** (TLC, 5 h), then saturated $NaHCO_3$ (3 mL) was added at 0 °C. After returning to room temperature, the mixture was extracted with CH_2Cl_2 and the extract was dried over $MgSO_4$, filtered and evaporated. Purification was performed by flash chromatography (eluent: Et_2O–light petroleum ether = 20:100 to 50:100), providing ketoaldehyde **7** (0.56 g, 73%). IR: 1730; 1700. ^{1}HNMR: 9.4 (s, 1H); 4.1 (q, 2H, J = 6.7); 3.6 (m, 2H); 2.3 (m, 2H); 2.0 (s, 3H); 1.7 (m, 6H); 1.2 (t, 3H, J = 6.7). ^{13}CNMR: 207.1; 204.2; 155.1; 61.2; 48.9; 47.9; 43.7; 36.9; 29.7; 28.8; 26.0; 21.4; 14.4. Anal. Calcd for $C_{13}H_{21}NO_4$: C, 61.16; H, 8.29; N, 5.49. Found: C, 60.96; H, 8.40; N, 5.31.

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9. The spectroscopic data of compounds **1**, **2** and **3** were in agreement with those of the lit.[1h]