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SYNTHESIS OF (±)-NITRAMINE, (±)-ISONITRAMINE AND (±)-SIBIRINE VIA DIELS-ALDER REACTIONS

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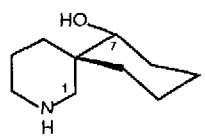
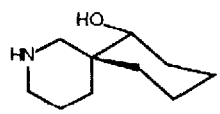
Abstract: *Diels-Alder reactions with N-protected methyleneglutarimides are used to construct the spiro-framework during the synthesis of the title alkaloids.*

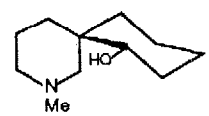
Three related piperidine alkaloids nitramine **1**, isonitramine **2** and sibirine **3** have been isolated[1] from plants of the Nitraria species. X-ray analysis[1] showed that nitramine and isonitramine are diastereomers, while sibirine is the enantiomer of N-methylisonitramine[2]. Their interesting 2-azaspiro-[5.5]-undecane skeleton has stimulated several syntheses[3,4]. Two of these syntheses are asymmetric[4], and confirm the absolute configurations of these alkaloids. In most cases the diastereomeric ratio (which is the final nitramine/isonitramine ratio) was obtained during spirocyclization, or during reduction of the carbonyl group at C-7. In our synthesis, the carbonskeleton was constructed in one single step from easily available starting materials.



nitramine **1**

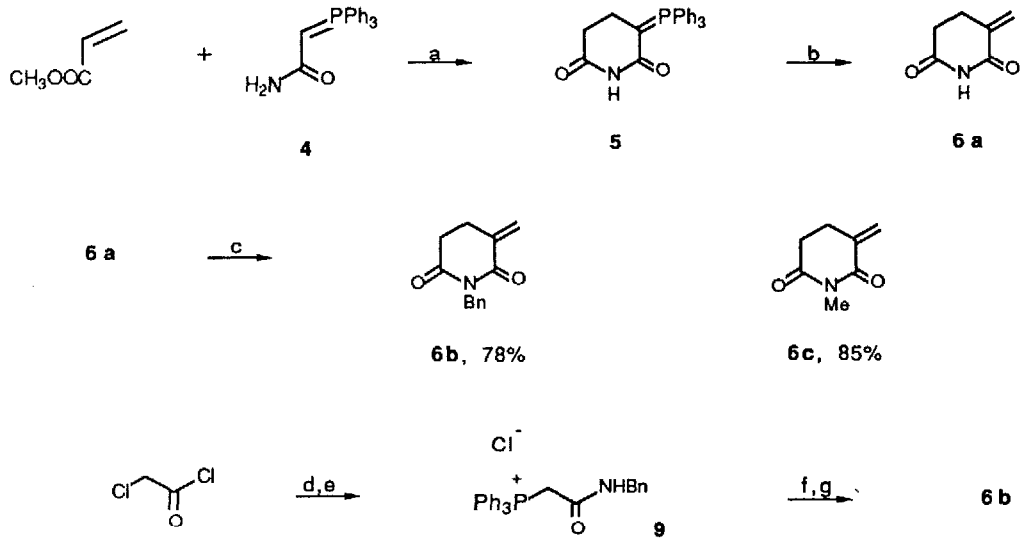


isonitramine **2**



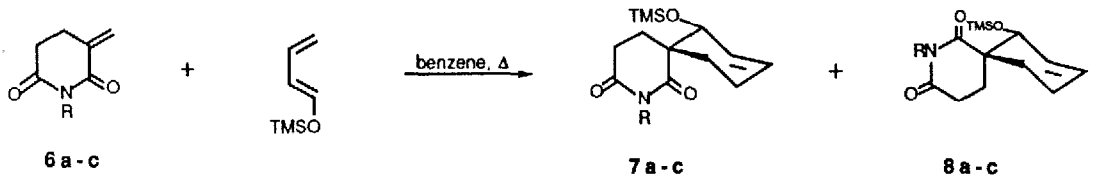
sibirine **3**

The 2-methyleneglutarimides we have described before[5], were expected to be good dienophiles in a Diels-Alder reaction. Michael addition of stabilized ylid **4**[6] with methyl acrylate in methanol yielded 79% of the glutarimide ylid **5** which was converted to methylene glutarimide **6a** (86%) via a Wittig reaction with paraformaldehyde. In an attempted thermal condensation with trimethylsilyloxybutadiene, this unsubstituted glutarimide only produced polymerization products, so the reaction was repeated with glutarimides in which the N-H group was protected. Mitsunobu coupling of **6a** with benzyl alcohol and methyl alcohol afforded **6b** and **6c** in respectively 78% and 85% yield. N-benzyl-2-methyleneglutarimide **6b** was also obtained from benzylamine and chloroacetylchloride.



a) methanol, RT, 20h, 79%; **b**) $(CH_2O)_n$, $CHCl_3$, reflux, 2h, 86%; **c**) triphenylphosphine, diethyl azodicarboxylate, benzylalcohol (**6b**) or methanol (**6c**), THF, 0°C to RT; **d**) benzylamine, THF, 0°; **e**) triphenylphosphine, acetonitril, reflux, 1h, 64% over two steps; **f**) methyl acrylate, NaOMe/methanol, RT, 20h; **g**) $(CH_2O)_n$, toluene, reflux, 2h, 60% over two steps.

Heating **6b** with trimethylsilyloxybutadiene (2.5eq) in benzene at 105° during 40 hours yielded a 1 : 4.3 mixture of **7b** and **8b** (64%)[7]. The diastereomers could be easily separated via chromatography on silica. Improving the yield and diastereoselectivity by using Lewis acids at lower temperatures was not possible, since rapid decomposition of the diene took place. With acetoxybutadiene instead of trimethylsilyloxybutadiene the reaction was considerable slower and more polymerization of the dienophile occurred. The configurations of **7b** and **8b** were established by converting them into (±)-nitramine and (±)-isonitramine respectively, in two reduction steps. The lithium aluminiumhydride reduction in THF led to the formation of substantial amounts of ring opened products. Repeating the reaction, using diethylether as a solvent (OH^-/H^+workup) produced the piperidines in high yield. The final hydrogenation/debenzylation step was not succesfull with Pd/C; the use of $Pd(OH)_2$ on carbon (Pearlmans catalyst) however gave quantitative yields of the desired alkaloids.



6a-c **7a-c** **8a-c**

	7	8
a. R= H	0 %	0 %
b. R= Bn	12 %	52 %
c. R= Me	13 %	52 %

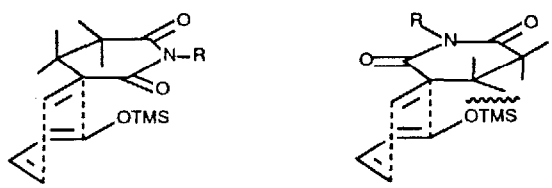
7b 1. LAH, ether, 72% / 2. H_2, $Pd(OH)_2$, 98% → (±) nitramine **1**

8b 1. LAH, ether, 95% / 2. H_2, $Pd(OH)_2$, 98% → (±) isonitramine **2**

8c 1. LAH, ether, 80% / 2. H_2, $Pd(OH)_2$, 98% → (±) sibirine **3**

Since the main isomer of the Diels-Alder reaction posessed the stereostructure of isonitramine, the reaction was repeated with N-methyl-2-methyleneglutarimide **6c**, which gave **7c** and **8c** in almost the same yield and diastereomeric ratio as with the N-benzyl derivative. LAH reduction of **8b** (OH^-/H^+workup) and hydrogenation gave (±)-sibirine **3** in 78% yield.

The stereochemistry of the cycloaddition can be explained by steric interactions of the glutarimide 3- and 4-protons with the trimethylsilyloxy-substituent in the diene. The trimethylsilyloxybutadiene used (Aldrich) was a 85/15- mixture of E- and Z-isomers[9]. Pure Z-diene was prepared via literature procedures[9,10] and was shown to be unreactive under these reaction conditions. Since the E-diene is responsible for both cycloadducts, the main isomer has to be produced via an "exo"-transition state, with the trimethylsilyloxy-substituent placed under the almost planar imide-function. From models it could be concluded, that steric interaction of the trimethylsilylether with the glutarimide methylene groups disfavours endo approach.



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7. Compound **7b**: IR($CHCl_3$): 1720, 1670 cm^{-1}; ^{1}H-NMR($CDCl_3$, 200 MHz): δ 0.03 (s, 9H, OTMS), 1.4 - 2.4 (m, 6H), 2.7 (m, 2H, H_4), 4.19 (m, 1H, H_7), 4.83 (d, 1H, $J_{a,b}$= 13.8, CH_2N), 5.0 (d, 1H, $J_{a,b}$= 13.8, CH_2N), 5.60 (m, 1H, H_8), 5.82 (m, 1H, H_9), 7.1 - 7.4 (m, 5H, Ar), ^{13}C-NMR($CDCl_3$, 62.9 MHz): δ 0.0 (TMS); 22.3 - 27.12 (4x CH_2), 43.37 (CH_2N), 45.22 (spiro-C), 70.12 (C_7), 126.9 - 130.45 (C_8, C_9, C-Ar), 137.65 (C-Ar), 171.95, 173.64 (2x C=O).
   Compound **8b**: IR($CHCl_3$): 1720, 1670 cm^{-1}; ^{1}H-NMR($CDCl_3$, 200 MHz): δ 0.00 (s, 9H, OTMS), 1.60 - 2.35 (m, 6H), 2.57 (m, 1H, H_{4a}), 2.93 (m, 1H, H_{4b}), 4.88 (d, J = 2.1, H_7), 4.92 (d, 1H, $J_{a,b}$= 14.0, CH_2N), 4.99 (d, 1H, $J_{a,b}$= 14.0, CH_2N), 5.45 (dd, J = 1.8 and 10.2, H_8), 5.67 (m, 1H, H_9), 7.1 - 7.4 (m, 5H, Ar), ^{13}C-NMR($CDCl_3$, 62.9 MHz): δ 0.02 (TMS); 188.85, 21.69 (2x CH_2, C_5 and C_{11}), 29.19, 29.85 (2x CH_2, C_4 and C_{10}), 42.25 (CH_2N), 46.17 (spiro-C), 71.80 (C_7), 126.26 - 130.5 (C_8, C_9, C-Ar), 137.54 (C-Ar), 172.54 - 177.06 (2x C=O).
8. The spectral data of the alkaloids were in agreement with the literature values.
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