Enantioselective Total Syntheses of the Nitraria Alkaloids (−)-Nitramine and (+)-Isonitramine

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Introduction

The 2-azaspiro[5.5]undecane alkaloids sibirine (**1**), nitramine (**2**), and isonitramine (**3**) have received considerable synthetic attention[1,2] since their isolation from the plant genus Nitraria.[3] This interest originates from the peculiar structure of these azaspiroalkaloids and their structural resemblance to neurotoxic histrionicotoxines **4**, that possess a 1-azaspiro[5.5]undecan-8-ol skeleton (Figure 1).[4]

Although a considerable number of synthetic routes toward the Nitraria alkaloids can be found in the literature,[1,2] only a small number of them deal with enantioselective or enantiospecific syntheses.[2] Several alkaloids are present in plants in the form of racemic mixtures suggesting a nonenzymatic formation of these molecules. In fact, most of the many different alkaloids that have been isolated from Nitraria species are racemates, such as (±)-nitramine (**2**), nitraramine, nitramidine, and schoberine.[5] In spite of the generally racemic nature of Nitraria alkaloids, it has unequivocally been established that (+)-nitramine (**2**) was isolated from *Nitraria schoberi* L., while (−)-sibirine (**1**) and (+)-isonitramine (**3**) (as well as racemic nitramine) were found in *Nitraria sibirica* Pall.[1a,2a] This finding makes enantioselective synthetic routes toward these particular alkaloids rather attractive.

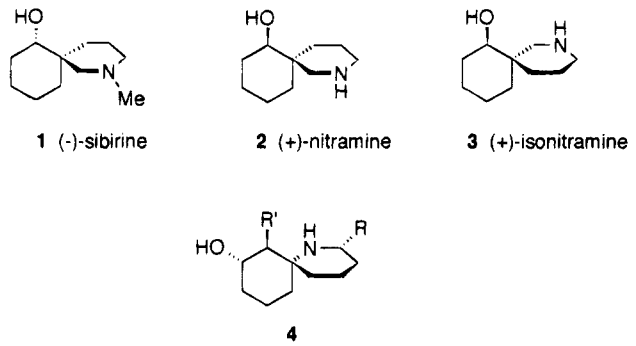

Figure 1.

Results and Discussion

The readily available (1R,2S)-β-OH-ester **5**[6] (95% ee) was stereospecifically converted into the β-OH-lactam **8** *via* a sequence of reactions involving double deprotonation with LDA and a subsequent enantioselective alkylation with the N,N-disilylated 3-bromopropylamine **6** (Scheme 1).[7] The resulting functionalized ester **7** was converted to (6*S*,7*S*)-7-OH-lactam **8** *via* N-deprotection with potassium carbonate in methanol under reflux during which a spontaneous cyclization occurred.

The melting point of (6*S*,7*S*)-spirolactam **8** was 119.6–120.3 °C, as mentioned in an earlier literature report concerning racemic **8** (lit.[1d] mp 118–121 °C). However, this result was in sharp contrast with another literature report, where it was stated that the melting point of the enantiomer (6*R*,7*R*)-**8** was 108–109 °C, which is significantly different from our measured value. After repeated syntheses of (6*S*,7*S*)-**8** from **5**, the melting point of our synthetic (6*S*,7*S*)-**8** consistently remained 119–121 °C. Also the α_D-value of (6*S*,7*S*)-**8** (-40.6°, *c* 0.20, $CHCl_3$) differed from the reported value of (6*R*,7*R*)-**8** (+37.2°, *c* 0.20, $CHCl_3$).[2a] As the present synthetic scheme leading from β-hydroxy ester **5** to β-hydroxy spirolactam **8** was repeated five times and gave rise to a measured α_D-value in the range of −40.6° to −42.1° (*c* 0.20, $CHCl_3$), it was concluded that a reliable high optical purity of spirolactam **8** was obtained. Indeed, the high resolution ^{13}C-NMR spectrum of (6*S*,7*S*)-**8** showed no traces of any impurities or diastereomers of **8** present in the sample.

Lithium aluminum hydride reduction of lactam (6*S*,7*S*)-**8** afforded (−)-nitramine **9** in an overall yield of 40% from β-OH-ester **5** after flash chromatography. In earlier literature reports, 2 mol equiv of lithium aluminum hydride and 15 h of stirring at room temperature were sufficient to obtain a complete reduction of stereoisomers of lactam **8** (i.e., the racemate[1d] and the (6*R*,7*R*)-[2a,c] and (6*R*,7*S*)-[2c] enantiomers). Contrary to these results, reduction of lactam **8** under these conditions led to only 10–20% conversion. After several attempts to ameliorate the conversion ratio (larger excess of the hydride reagent, increased reaction temperature, longer reaction time), a complete reduction of spirolactam **8** could be accomplished with 20 mol equiv of lithium aluminum hydride after three days at room temperature. An increase in temperature resulted in several side reactions. The cause of this rather unexpectedly laborious reduction step is still under investigation.

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(1) (a) Snider, B. B.; Cartaya-Marin, C. P. *J. Org. Chem.* **1984**, *49*, 1688. (b) Mieczkowski, J. B. *Bull. Pol. Acad. Sci. Chem.* **1985**, *33*, 13. (c) Kozikowski, A. P., Yuen, P.-W. *J. Chem. Soc., Chem. Commun.* **1985**, 847. (d) Hellberg, L. H.; Beeson, C. *Tetrahedron Lett.* **1986**, *27*, 3955. (e) Carruthers, W.; Moses, R. C. *J. Chem. Soc., Chem. Commun.* **1987**, 509. (f) Carruthers, W.; Moses, R. C. *J. Chem. Soc., Perkin Trans 1* **1988**, 1625. (g) Tanner, D.; He, H. M.; Bergdahl, M. *Tetrahedron Lett.* **1988**, *29*, 6493. (h) Wanner, M. J.; Koomen, G.-J. *Tetrahedron Lett.* **1989**, *30*, 2301. (i) Kim, D.; Kim, H. S.; Yoo, J. Y. *Tetrahedron Lett.* **1991**, *32*, 1577. (j) Fujii, M.; Kawaguchi, K.; Nakamura, K.; Ohno, A. *Chem. Lett.* **1992**, 1493. (k) Wanner, M. J.; Koomen, G.-J. *Tetrahedron* **1992**, *48*, 3935. (l) Keppens, M.; De Kimpe, N. *Synlett* **1994**, 285.

(2) (a) McCloskey, P. J.; Schultz, A. G. *Heterocycles* **1987**, *25*, 437. (b) Quirion, J.-C.; Grierson, D. S.; Royer, J.; Husson, H.-P. *Tetrahedron Lett.* **1988**, *29*, 3311. (c) Tanner, D.; He, H. M. *Tetrahedron* **1989**, *45*, 4309. (d) Imanishi, T.; Kurumada, T.; Maezaki, N.; Sugiyama, K.; Iwata, C. *J. Chem. Soc., Chem. Commun.* **1991**, 1409. (e) Westermann, B.; Scharmann, G.; Kortmann, J. *Tetrahedron Asymm.* **1993**, *4*, 2119.

(3) (a) Novgorodova, N. Y.; Maekh, S. K.; Yunusov, S. Y. *Chem. Nat. Prod.* **1973**, *9*, 191. (b) Osmanov, Z.; Ibragimov, A. A.; Yunusov, S. Y. *Chem. Nat. Prod.* **1977**, *13*, 607. (c) Osmanov, Z.; Ibragimov, A. A.; Yunusov, S. Y. *Chem. Nat. Prod.* **1982**, *18*, 121.

(4) Daly, J. W. In *Progress in the Chemistry of Organic Natural Products*; Herz, W., Grisebach, H., Kirby, G. W., Eds.; Springer Verlag: New York, **1982**; Vol. 41, p 205.

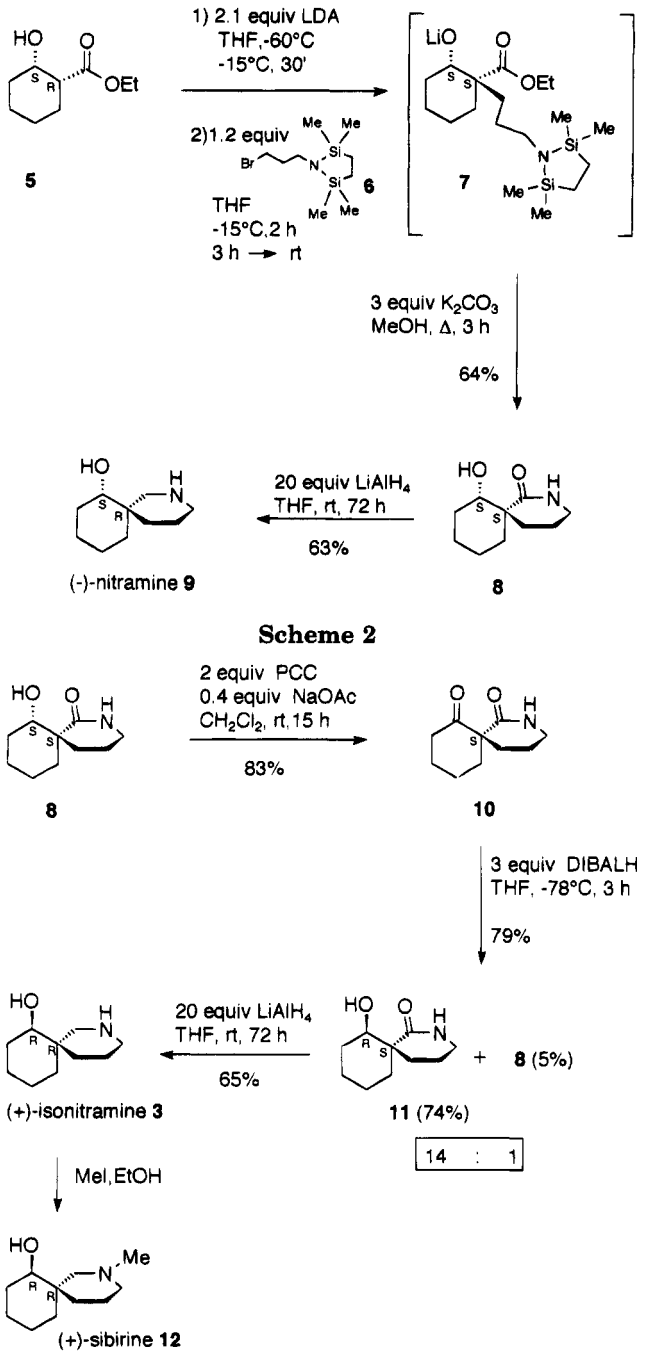
(5) Wanner, M. J.; Koomen, G. J. In *Studies in Natural Products Chemistry*; Atta-ur-Rahman, Ed., Elsevier: Amsterdam, 1994; Vol. 14, p 731.

(6) Fráter, G. *Helv. Chim. Acta* **1980**, *63*, 1383.

(7) De Kimpe, N.; Keppens, M.; Stevens, C. *Tetrahedron Lett.* **1993**, *34*, 4693.

0022-3263/95/1960-3916$09.00/0

Scheme 1



Scheme 2

Oxidation of (6*S*,7*S*)-7-OH-lactam **8** with pyridinium chlorochromate (PCC) in dichloromethane in the presence of sodium acetate afforded (S)-β-ketolactam **10** in good yield (Scheme 2). In accordance with an analogous reaction for the conversion of **10** to **11**, described in the literature,[2a] this spirolactam **10** was reduced enantioselectively to (6*S*,7*R*)-β-OH-lactam **11** and its diastereomer (6*S*,7*S*)-**8** in a 14:1 ratio, respectively, using DIBALH in THF as reducing agent. Recrystallization of this reaction mixture containing **11** and **8** afforded the pure (6*S*,7*R*)-spirolactam **11**, which was reduced with $LiAlH_4$ as described above to afford (+)-isonitramine (**3**) in an overall yield of 40% from lactam **8**. As shown in the experimental section, all spectral data, melting points, and optical rotations of **10**, **11** and **3** are consistent with data reported in the literature.[2a,b] This synthetic pathway toward (+)-isonitramine also constitutes a formal synthesis of (+)-sibirine (**12**), since this only requires reaction of **3** with MeI in ethanol, as described several times in the literature.[2a,b]

In conclusion, a straightforward enantioselective synthesis of (−)-nitramine and (+)-isonitramine has been presented. In addition, a formal synthesis of (+)-sibirine is reported. This short entry into various Nitraria alkaloids contrasts dramatically with other lengthy, multistep syntheses of Nitraria alkaloids reported so far.

Experimental Section

General Methods.[8] NMR spectra were obtained on a 270 MHz instrument. Mass spectra were recorded using the GC-MS technique.

(6*S*,7*S*)-7-Hydroxy-1-oxo-2-azaspiro[5.5]undecane (8). To a stirred, cooled (0 °C) solution of diisopropylamine (0.667 g, 6.6 mmol) in dry THF (7 mL) was added n-BuLi (2.5 M solution in hexane; 2.52 mL, 6.3 mmol) under a nitrogen atmosphere. This solution was cooled to −60 °C, upon which (1*R*,2*S*)-ethyl 2-hydroxycyclohexane carboxylic ester (**5**)[6] (0.516 g, 3.0 mmol) in THF (2 mL) was slowly added *via* a syringe. The reaction mixture was subsequently stirred at −15 °C for 30 min. A solution of 1-(3-bromopropyl)-2,2,5,5-tetramethyl-1-aza-2,5-disilacyclopentane (**6**)[9] (1.01 g, 3.6 mmol) in THF (5 mL) was then added at −15 °C, after which the resulting mixture was stirred at this temperature for 2 h. Stirring was continued for an additional period of 3 h without cooling. The solution was poured into a 0.5 N aqueous solution of NaOH (50 mL) and extracted with ether (3 × 15 mL). The combined ethereal layers were dried (K_2CO_3). After evaporation of the solvent, the residue was dissolved in methanol (15 mL), and after addition of K_2CO_3 (1.24 g, 9.0 mmol), the resulting suspension was stirred under gentle reflux for 3 h. The reaction mixture was poured into water (50 mL) and extracted with CH_2Cl_2 (3 × 15 mL), after which the organic layers were dried (K_2CO_3). The residue was suspended in pentane (20 mL), upon which a viscous oil separated from the pentane solution. The supernatant was decanted, and the remaining sticky residue was washed with pentane (2 × 20 mL). This residue solidified after complete evaporation of the solvent. The combined decanted pentane phases were concentrated and kept at −20 °C for 24 h, after which some additional solid was formed. This crystallization procedure was repeated until no further solid could be recovered. The solid materials were combined and consisted of nearly pure (>92%) spirolactam **8** (0.430 g, 64%). This solid can be used as such for further elaboration. Flash chromatography of the crude solid (CH_2Cl_2/MeOH 98/2; R_f = 0.15) yielded pure lactam **8** (0.198 g, 36%): mp 119.6−120.4 °C (lit.[1d] mp 118−121 °C); $[\alpha]^{23}_D$ −40.6° (*c* 0.20, $CHCl_3$) [lit.[2a] $[\alpha]^{23}_D$ of the (6*R*,7*R*)-enantiomer +37.2° (*c* 0.20, $CHCl_3$)]; IR (KBr) 3100−3360, 1610−1620 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 1.4−2.2 (12H, m); 3.2−3.4 (2H, m); 3.73 (1H, br s); 5.88 and 7.29 (each 1H, each br s); ^{13}C-NMR ($CDCl_3$) δ 18.5, 18.9, 19.7, 27.2, 27.9, 42.1, 43.3, 71.5, 179.6; MS (70 eV) *m*/*z* (%) 183 (M^+, 2), 165(13), 155(19), 136(8), 128(7), 112(100), 99(7), 98(6), 84(3), 81(3), 79(4), 69(15), 67(5), 56(5), 55(8), 53(4), 44(11), 43(6), 42(4), 41(17). Anal. Calcd for $C_{10}H_{17}O_2N$: C, 65.54; H, 9.35. Found: C, 65.66; H, 9.20.

(−)-Nitramine (9). To a stirred, cooled (0 °C) suspension of $LiAlH_4$ (1.90 g, 50 mmol) in dry THF (20 mL) was added dropwise lactam **8** (0.458 g, 2.5 mmol) in THF (5 mL) under a nitrogen atmosphere. The suspension was stirred at rt for 72 h, after which it was cooled to 0 °C. A saturated aqueous NH_4Cl solution and a 50% aqueous NaOH solution were then added alternately (each time a portion of 3 drops) and very slowly under vigorous stirring until no hydride was left (**CAUTION**). The suspension was filtered, the precipitate thoroughly washed with CH_2Cl_2 (4 × 20 mL), and the filtrate dried (K_2CO_3). After evaporation of the solvents, the resulting light yellow viscous oil (0.403 g) was purified by flash chromatography ($CHCl_3$/MeOH/NH_4OH_{aq}, 25% 46/50/4; R_f = 0.25), which afforded pure (−)-nitramine (**9**) (0.267 g, 63%). $[\alpha]^{23}_D$ −19.9° (*c* 1.34, CH_2Cl_2) [lit.[2c] $[\alpha]^{22}_D$ of (+)-nitramine +21.3° (*c* 1.52, CH_2Cl_2)]; IR (NaCl)

(8) De Kimpe, N.; Boelens, M.; Baele, J. *J. Org. Chem.* **1994**, *59*, 5485.
(9) Djuric, S.; Venit, J.; Magnus, P. *Tetrahedron Lett.* **1981**, *22*, 1787.

3100–3500 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 1.0–2.2 (12H, m); 2.44 (1H, d, J = 11.9 Hz); 2.64 (1H, txd, J_1= 10.9 Hz, J_2 = 3.30 Hz); 2.93 (1H, dxt, J_1 = 10.9 Hz, J_2 = 4.28 Hz); 3.37 (1H, d, J = 11.9 Hz); 3.52 (1H, dxd, J_1= 9.90 Hz, J_2 = 3.96 Hz); 3.85 (2H, br s); ^{13}C-NMR ($CDCl_3$) δ 21.1, 23.5, 24.0, 32.1, 36.0, 36.3, 37.7, 46.9, 52.2, 77.7; MS (70 eV) m/z (%) 169 (M^+, 12), 151(12), 123(13), 122-(15), 84(26), 57(30), 56(26), 55(11), 44(59), 43(100), 41(16). Anal. Calcd for $C_{10}H_{19}ON$: N, 8.27. Found: N, 8.18.

(6*S*)-1,7-Dioxo-2-azaspiro[5.5]undecane (10). To a stirred suspension of PCC (0.431 g, 2.0 mmol) and NaOAc (0.033 g, 0.4 mmol) in dry CH_2Cl_2 (3 mL) was added lactam **8** (0.183 g, 1.0 mmol) in CH_2Cl_2 (2 mL), upon which the mixture was stirred for 15 h. The dark suspension was poured into an aqueous 1 N solution of NaOH (50 mL) and extracted with CH_2Cl_2 (3 × 30 mL). The combined organic layers were washed with 1 N NaOH and with brine (each 50 mL) and dried (K_2CO_3). The resulting off-white crystals of **10** (0.150 g, 83%) were pure enough (>96%) to be used as such in the following reaction step. Flash chromatography (CH_2Cl_2/MeOH 98/2; R_f = 0.09) afforded the pure spiro compound **10** (0.120 g, 66%): mp 184.4–184.6 °C (lit.[2a] mp 184–185 °C); $[\alpha]^{23}_D$ +53.1° (*c* 1.05, $CHCl_3$) [lit.[2a] $[\alpha]^{23}_D$ of the (6*R*)-enantiomer −50.8° (*c* 1.16, $CHCl_3$)]; IR (KBr) 3050–3200, 1695, 1660 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 1.6–2.0 and 2.2–2.7 (12H, m); 3.2–3.4 (2H, m); 6.73 (1H, br s); ^{13}C-NMR ($CDCl_3$) δ 18.8, 20.5, 26.4, 30.8, 36.6, 39.0, 41.9, 57.1, 172.2, 210.4; MS (70 eV) m/z (%) 181 (M^+, 29), 153(31), 126(16), 125(30), 112(100), 69(18), 67(14), 55(17), 43(16), 41(27). Anal. Calcd for $C_{10}H_{15}O_2N$: N, 7.73. Found: N, 7.87.

(6*S*,7*R*)-7-Hydroxy-1-oxo-2-azaspiro[5.5]undecane (11). 7-OH-Lactam **11** was synthesized from spiro compound **10** *via* a procedure that was described in the literature.[2a] Instead of 2.1 equiv of DIBALH, as mentioned in the literature, 3 equiv of DIBALH were necessary to accomplish complete reduction of **10** to **11**. Starting from 0.181 g (1.0 mmol) of **10**, 0.140 g of reaction mixture (**11**+**8**) was obtained (79% yield) in a diastereomeric ratio of 14:1, respectively. Recrystallization from ethyl acetate/pentane (4:1) yielded the pure β-OH-lactam **11**. This spiro compound could also be purified through flash chromatography (CH_2Cl_2/MeOH 95/5; R_f = 0.05): mp 147.9–149.2 °C (lit.[2a] mp 148–149 °C); $[\alpha]^{23}_D$ −73.7° (*c* 0.32, $CHCl_3$) [lit.[2a] $[\alpha]^{23}_D$ of the (6*R*,7*S*)-enantiomer +73.9° (*c* 0.50, $CHCl_3$)]; IR (KBr) 3100–3460, 1640, 1608 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 1.2–2.0 (12H, m); 2.60–2.61 (1H, m); 3.2–3.4 (2H, m); 4.2–4.3 (1H, m); 6.24 (1H, br s); ^{13}C-NMR ($CDCl_3$) δ 19.3, 19.7, 21.4, 24.5, 28.8, 32.5, 42.1, 48.1, 72.7, 178.0; MS (70 eV) m/z (%) 183 (M^+, 12), 165-(28), 155(18), 112(100), 99(10), 69(18), 55(14), 43(11), 41(20). Anal. Calcd for $C_{10}H_{17}O_2N$: N, 7.64. Found: N, 7.73.

(+)-Isonitramine (3). (+)-Isonitramine (**3**) was synthesized from **11** in a similar way as (−)-nitramine **9** was synthesized from **8**. Yield after flash chromatography: 65% (scale: 1.0 mmol **12**; $CHCl_3$/MeOH/NH_4OH_{aq}, 25% 46/50/4; R_f = 0.23). (+)-Isonitramine (**3**) was recrystallized from ethyl acetate/pentane (3:1): mp 101.9–102.8 °C (lit.[2a] mp 103–104 °C); $[\alpha]^{23}_D$ +5.8° (*c* 1.4, $CHCl_3$) [lit.[2b] $[\alpha]^{23}_D$ +5° (*c* 1.2, $CHCl_3$)]; IR (KBr) 3278, 3000–3500 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 0.9–1.8 and 1.95–2.3 (12H, m); 2.52 (1H, d, J = 11.2 Hz); 2.60 (1H, txd, J_1 = 11.1 Hz, J_2 = 3.63 Hz); 2.93 (1H, br d, J = 11.2 Hz); 3.03 (1H, dxm, J = 11.1 Hz); 2.7–3.3 (2H, broad); 3.66 (1H, dxd, J_1 = 11.2 Hz, J_2 = 3.63 Hz); ^{13}C-NMR ($CDCl_3$) δ 20.3, 23.1, 24.3, 28.8, 29.7, 36.2, 36.7, 47.3, 60.8, 80.5; MS (70 eV) m/z (%) 169 (M^+, 16), 151(15), 123(18), 122(19), 96(16), 84(35), 81(14), 67(15), 57(35), 56(32), 55(18), 44-(58), 43(100), 42(15), 41(24). Anal. Calcd for $C_{10}H_{19}ON$: N, 8.27. Found: 8.11.

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