Oxidative Deamination of Tetrahydroanabasine with *o*-Quinones: An Easy Entry to Lupinine, Sparteine, and Anabasine

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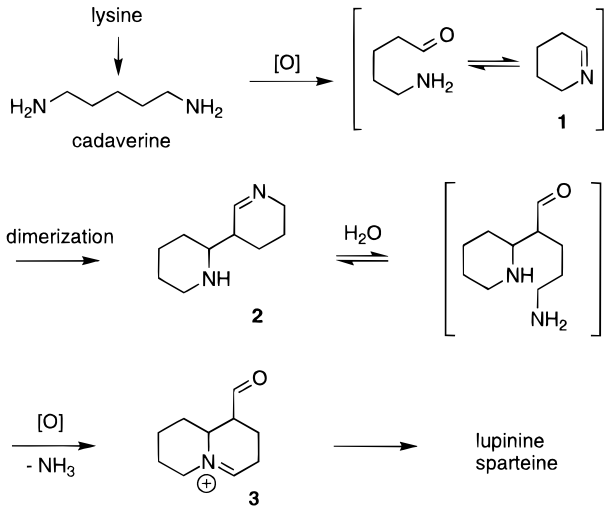
A mild oxidative deamination reaction of tetrahydroanabasine *O*-methyloxime **17** is described, making use of an *o*-quinone that is based on topaquinone (TPQ, **11**), the cofactor that is present in copper-containing amine oxidases. In situ ring closure of the oxidation product produced double-functionalized quinolizidine **5**, containing an enamine functionality with excellent reactivity. From this quinolizidine **5** a variety of biogenetically related lupin alkaloids were prepared: lupinine (**7**) and aminolupinane (**8**) via reductive sequences and sparteine (**9**) via a condensation reaction with dehydropiperidine **1**. The configurationally more favorable trans isomers epilupinine (**25**) and *β*-isosparteine (**10**) were formed when more drastic reaction conditions were used for oxime hydrolysis. Anabasine (**4**) and a new 5-piperidylanabasine derivative **6** were formed by an unexpected acid catalyzed ring transformation reaction, whereby the pyridine ring was formed via oxime-induced aromatization. The stereochemistry of the reaction products and the biogenetic implications are discussed.

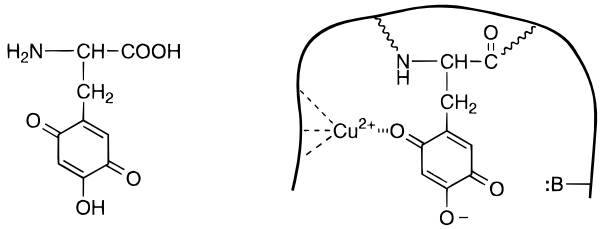
The lupin alkaloids have been an attractive synthetic target for several decades. During this period an increasing number of lupin alkaloids were identified from several lupin species,[1] and attention was given to their biogenesis.[1−3] Numerous labelling experiments have been performed, leading to the conclusion that cadaverine, and thus lysine, is the source of the carbon and nitrogen atoms present in these alkaloids. Schöpf studied the chemistry of dehydropiperidine (**1**), the expected product of the oxidative deamination of cadaverine *in vivo* (Scheme 1). This imine is extremely reactive and dimerizes spontaneously in water at neutral pH to form tetrahydroanabasine (**2**),[4] which can be isolated as its crystalline di-HBr salt.[5] Solutions of both dehydropiperidine and tetrahydroanabasine are too unstable to be obtained as such from plant material, which leaves the exact intermediates of the biosynthesis unclear. Diamine oxidase (DAO) catalyzed oxidative deamination of tetrahydroanabasine probably proceeds via the ring-opened, primary amino compound and transforms the dipiperidine ring system in **2** into quinolizidine **3**, which contains a characteristic structural unit of the lupin alkaloids. This hypothetical, difunctionalized intermediate in the biosynthesis of sparteine-, ormosanine-, and matrine-type alkaloids is obtained from plants in its stable reduced form: lupinine (**7**) and its isomer epilupinine (**25**).

This suggested bioroute seems plausible and emphasizes the possibilities of difunctionalized quinolizidine **5** as a useful synthetic intermediate for the laboratory synthesis of the lupin alkaloids. We will describe here the conversion of tetrahydroanabasine (**2**) into this reactive quinolizidine **5** via a mild, *o*-quinone-catalyzed oxidative deamination reaction that is related to the biosynthetic process catalyzed by the topaquinone (TPQ)-containing amine oxidases, the deaminating enzymes for, e.g., cadaverine and putrescine in plants (eq 1).

Scheme 1



$$\text{R-CH}_2\text{-NH}_2 + \text{H}_2\text{O} + \text{O}_2 \longrightarrow \text{R-CH=O} + \text{H}_2\text{O}_2 + \text{NH}_3 \qquad (1)$$



Topaquinone **11** enzyme-Cu^{2+}-cofactor complex **12**

Conversion of this intermediate (**5**) into the natural products anabasine, lupinine, sparteine, and *β*-isosparteine will be described (Scheme 2). In addition to

[⊗] Abstract published in *Advance ACS Abstracts,* July 15, 1996.

(1) For a recent review see: Saito, K.; Murakoshi, I. Chemistry, Biochemistry and Chemotaxonomy of Lupine Alkaloids in the Leguminosae. In Studies in Natural Products Chemistry 15; Atta-ur-Rahman, Ed.; Elsevier: Amsterdam, 1995; p 519.

(2) (a) Golebiewski, W. M.; Spenser, I. D. *Can. J. Chem.* **1985**, *63*, 2707. (b) Brown, A. M.; Rycroft, D. S.; Robins, D. J. *J. Chem. Soc., Perkin Trans. 1* **1991**, 2353. (c) Gavin, S. S.; Equi, A. M., Robins, D. J. *Can. J. Chem.* **1994**, *72*, 31.

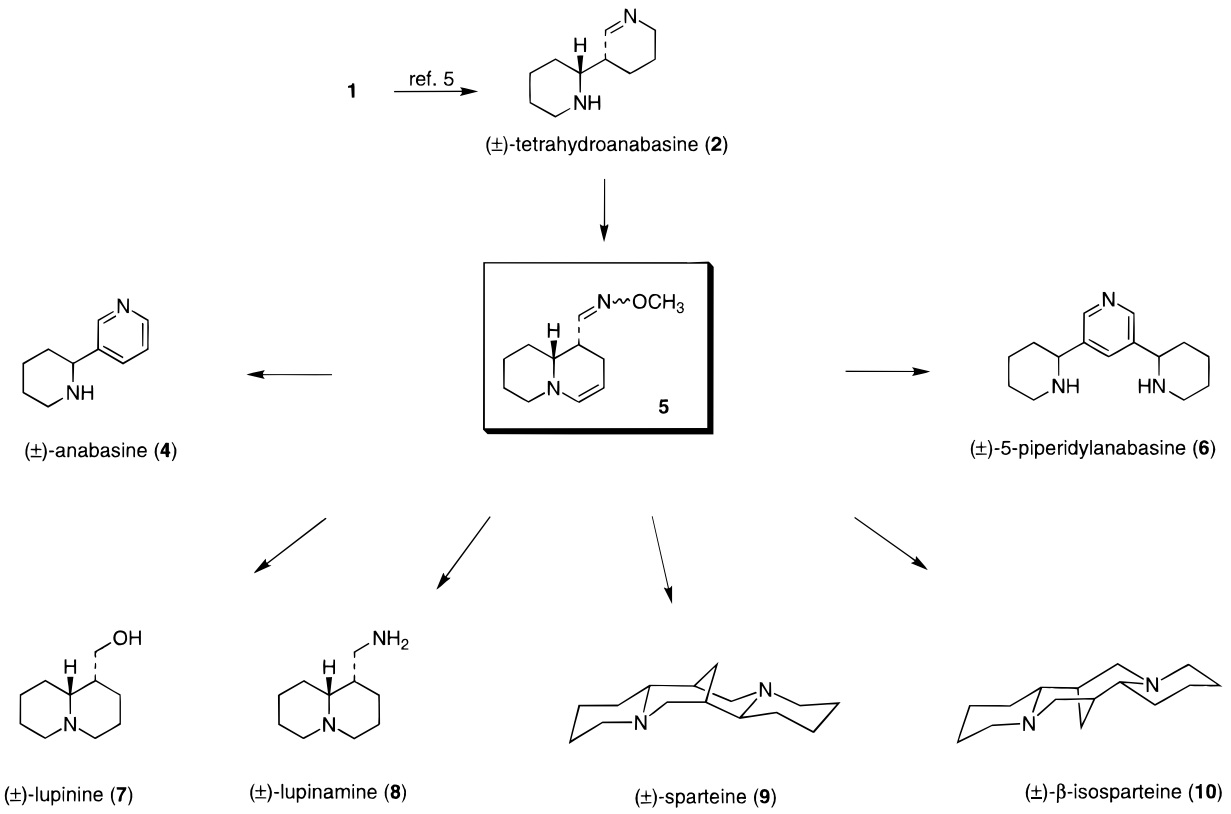
(3) Golebiewski, W. M.; Spenser, I. D. *Can. J. Chem.* **1988**, *66*, 1734.

(4) Schütte, H. R. *Arch. Pharm. (Weinheim)* **1960**, *293*, 1006.

(5) Tetrahydroanabasine **2** can be prepared from both α- and isotripiperidine: Schöpf, C.; Braun, F.; Koop, H.; Werner, G. *Liebigs Ann. Chem.* **1962**, *658*, 156.

S0022-3263(96)00213-7 CCC: $12.00

Scheme 2

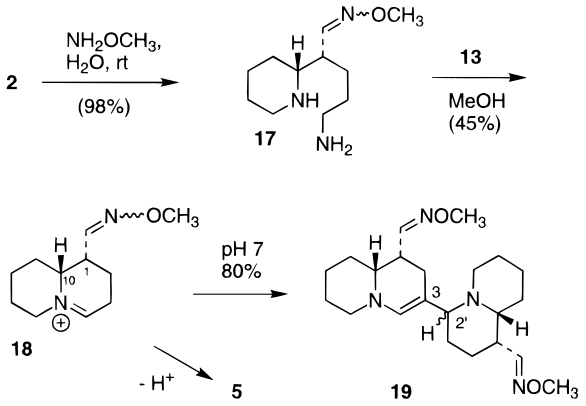


these alkaloids, lupinamine and a new, 3-piperidyl-substituted anabasine derivative are prepared from **5**. Since we use racemic tetrahydroanabasine, all of the synthetic products are obtained as racemates; it should be noted that often both antipodes and sometimes racemates of the natural alkaloids are isolated from different plants. Non enzymic biosynthesis of these compounds can explain this observation.[6] In a later stage of development, enzyme-catalyzed metabolism of one of the enantiomers might lead to optically active secondary metabolites.

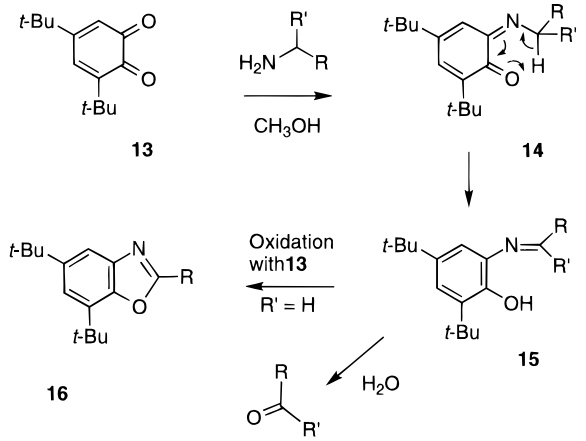
Chemistry

Our synthetic approach starts with tetrahydroanabasine (**2**), which can easily be prepared as its stable trans isomer starting from dehydropiperidine trimer as described by Schöpf.[5] To obtain a free amino group, which is required for oxidative deamination, the cyclic imine in **2** was converted into an *O*-methyloxime (**17**, Scheme 3). Although the oxime was isolated as a syn/anti mixture, the stereochemistry around the C−C bond was still preserved. In view of the limited stability of the deaminated product **5**, a mild oxidative procedure for this primary amine was required, and only the commercially available *o*-quinone **13** seemed suitable for this purpose (Scheme 4). Two *tert*-butyl substituents in **13** prevent conjugate addition reactions of nucleophiles to the reactive double bonds. It should be noted that this reagent was used for deamination reactions by Corey and

Scheme 3



Scheme 4



Achiwa[7] in 1969, several years before the comparable TPQ (**11**, eq 1) was found as the active cofactor in copper-containing amine oxidases.[8] Recently, several TPQ

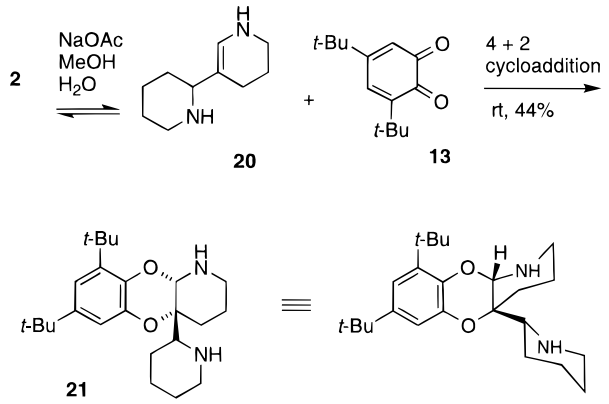
(6) McLean, S.; Misra, R.; Kumar, V.; Lamberton, J. A. *Can. J. Chem.* **1981**, *59*, 34.

(7) Corey E. J.; Achiwa, K. *J. Am. Chem. Soc.* **1969**, *91*, 1429. For further studies with quinone **13**, see: Klein, R. F. X.; Bargas, L. M.; Horak, V. *J. Org. Chem.* **1988**, *53*, 5994. Vander Zwan, M. C.; Hartner, F. W.; Reamer, R. A.; Tull, R. *J. Org. Chem.* **1978**, *43*, 509.

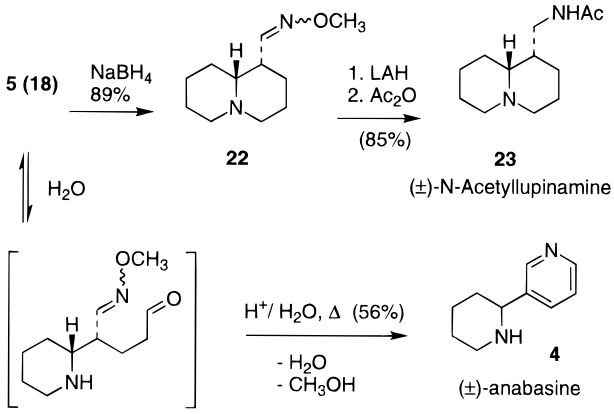
models were developed[9] for the oxidized form of the 2,4,5-trihydroxyphenylalanine (TOPA) cofactor, allowing studies toward the enzyme reaction. Until now, a synthetically useful catalyst that is based on TPQ has not been available since numerous side reactions occur in this complicated redox system. The mechanism of oxidation is shown in Scheme 4, where aromatization of **14** to **15** is the driving force of the reaction. According to Corey and Achiwa[7] ketones are obtained in high yield from **13** with primary, α-branched amines such as cyclohexylamine. Primary amines containing an α-unbranched substituent (e.g., benzylamine) are not suitable as substrate in the oxidative deamination with **13** since via a second quinone-catalyzed oxidation step benzoxazoles (**16**) are formed instead of aldehydes. In our substrate (**17**) overoxidation to the corresponding benzoxazole is prevented by the presence of a second amino group, which takes over the imino carbon atom initially formed and leads to a 6-membered cyclic iminium salt (**18**, Scheme 3). Thus, alkaline workup of the reaction of **17** with **13** provides quinolizidine **5** (45%), a reactive enamine that is our central precursor for the synthesis of several lupin alkaloids. Again, the stereochemistry was preserved, providing a cis relationship around the quinolizidine C1−C10 bond. **5** is stable for longer periods at −20 °C or as its hydrochloride in solution at room temperature. In contrast, enzymic oxidative deamination of **17** using commercially available porcine kidney diamine oxidase was not successful due to slow conversion of the substrate. Especially at neutral pH, which is required for this enzymic process, undesired reactions with the product **5** take place easily. The instability of **5** is demonstrated by stirring a solution of **5** overnight in aqueous methanol at pH 7, yielding 80% of dimer **19** as a result of enamine/imine equilibration followed by an iminoaldol condensation between **18** and **5** (Scheme 3). This dimer was present as a complex mixture of isomers at C4′, whereby each isomer consisted of four syn/anti isomers of the oximes.

Direct oxidation of tetrahydroanabasine **2** was attempted with quinone **13** in the presence of water, assuming that in an equilibrium the imine in **2** is hydrolyzed to its ring-opened amino aldehyde form (Scheme 1). Reaction of **2** with *o*-quinone **13** in a sodium acetate-buffered solution produced a crystalline 1:1 addition product, according to HRMS and NMR data. X-ray analysis[10] was required to establish its structure as **21**: the 4 + 2 cycloaddition product derived from the enamine **20** of tetrahydroanabasine (Scheme 5). Comparable examples of cycloaddition reactions between less substituted enamines and *o*-quinones have been described in the literature.[11]

Scheme 5



Scheme 6



Lupinamine.[12] Reduction of **5** with $NaBH_4$ in methanol gave a stable quinolizidine **22**, which was further reduced with $LiAlH_4$ to give lupinamine **8**, characterized as its *N*-acetyl derivative **23** (Scheme 6).

Anabasine.[13] Several methods for cleaving *O*-alkyl oximes are available.[14] Simple hydrochloric acid-catalyzed hydrolysis of **5** in acetone/water mixtures, however, gave an unexpected rearrangement, whereby oxime-induced aromatization of the piperidine ring gave racemic anabasine (**4**) in one step (Scheme 6). It should be noted that anabasine obtained from *Nicotiana* species is biogenetically derived from dehydropiperidine and nicotinic acid[13] and not from two molecules of dehydropiperidine. Although in vitro formation of anabasine is demonstrated with pea and lupine extracts[15] this has not been confirmed by *in vivo* labelling experiments.

Lupinine.[16] Milder hydrolytic conditions for oxime hydrolysis are based on reduction of the N−O bond, resulting in the formation of an imine, which is vulnerable to hydrolytic conditions. Aqueous sodium hydrogen sulfite, sodium dithionite, or $TiCl_3$/HCl indeed hydrolyzed the oxime at elevated temperatures; however, as a result of enolization of the intermediate aldehyde **24** (Scheme 7) the alcohols that were obtained in low yields after $NaBH_4$ workup consisted of mixtures of lupinine (**7**) and

(8) (a) Janes, S. M.; Mu, S.; Wemmer, D., Smith, A. J.; Kaur, S.; Maltby, D.; Burlingame, A. L.; Klinman, J. P. Science **1990**, *248*, 981. (b) Janes, S. M.; Palcic, M. M.; Scaman, C. H., Smith, A. J.; Brown, D. E.; Dooley, D. M.; Mure, M.; Klinman, J. P. *Biochemistry* **1992**, *31*, 12147. (c) Dooley, D. M.; McGuirl, M. A.; Brown, D. E.; Turowski, P. N.; McIntire, W. S.; Knowles, P. F. *Nature* **1991**, *349*, 262.

(9) Mure, M.; Klinman, J. P. *J. Am. Chem. Soc.* **1995**, *117*, 8698 and 8707. Lee, Y.; Sayre, L. M. *J. Am. Chem. Soc.* **1995**, *117*, 11823.

(10) The author has deposited atomic coordinates for this structure with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK. We wish to thank J. Fraanje, K. Goubitz, and H. Schenk of the Department of Crystallography of this University for the X-ray crystal structure determination of compound **21**.

(11) Ried, W.; Torok, E. *Liebigs Ann. Chem.* **1965**, *687*, 187.

(12) Recent syntheses of lupinamine: (a) Wanner, M. J.; Koomen G.-J. *Tetrahedron* **1991**, *47*, 8431. (b) Michael, J. P.; Jungmann, C. M. *Tetrahedron* **1992**, *48*, 10211.

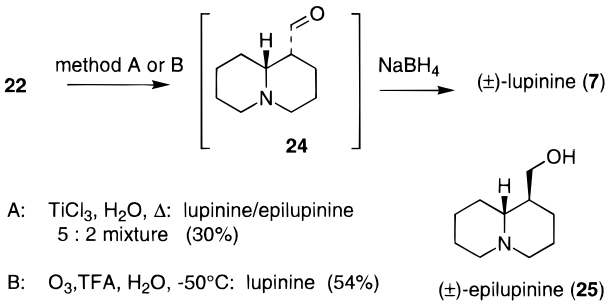
(13) (a) Watson, A. B.; Brown, A. M.; Colquhoun, I. J.; Walton, N. J.; Robins, D. J. *J. Chem. Soc., Perkin Trans. 1* **1990**, 2607. (b) Gross, D. In *Biochemistry of Alkaloids*; Mothes, K., Schütte, H. R., Luckner, M., Eds.; VCH publishers: Deerfield Beach, 1985; p 163.

(14) Weitz, D. J.; Bednarski, M. D. *J. Org. Chem.* **1989**, *54*, 4957 and references cited therein.

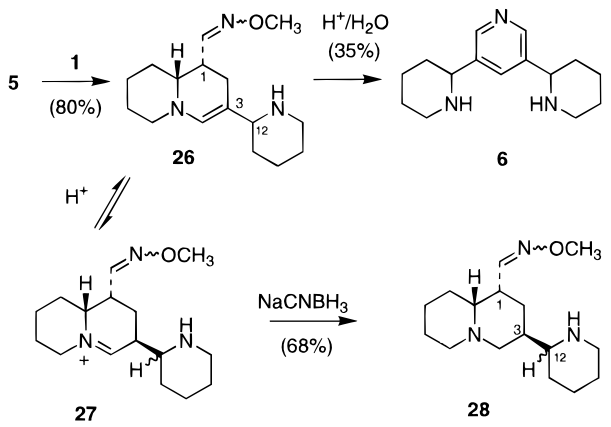
(15) Mothes, K.; Schütte, H. R.; Simon, H.; Weygand, F. *Z. Naturforsch., Teil B* **1959**, *14*, 49.

(16) For a recent synthesis of lupinine and epilupinine, see: Hua, D. H.; Miao, S. W.; Bravo, A. A.; Takemoto, D. J. *Synthesis* **1991**, 970.

Scheme 7



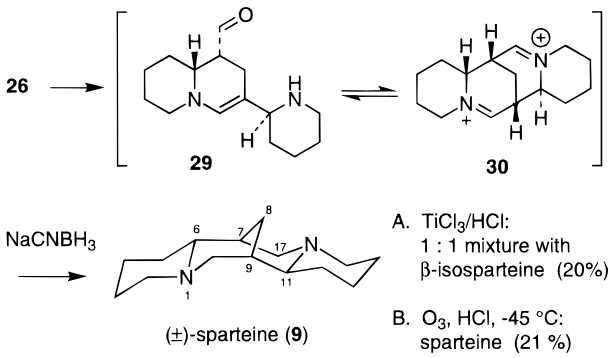
Scheme 8



the thermodynamically more stable epilupinine (**25**). An efficient oxidative removal of *O*-methyl oximes consists of treatment with ozone in methanol.[14] Trifluoroacetic acid was used to protonate the tertiary amine and to protect it from oxidation. Ozonolysis at −50 °C followed by the addition of $NaBH_4$ at low temperature yielded crystalline lupinine (**7**) as one isomer.

5-Piperidylanabasine. Sparteine and isomers are built up from three dehydropiperidine equivalents. Efficient condensation of **5** with dehydropiperidine (**1**) took place when optimized conditions were used (Scheme 8). Without precautions dimerization of both starting materials occurred to form **19** and tetrahydroanabasine (**2**). In situ monomerized α-tripiperidine[17] in HOAc/NaOAc buffered methanol gave 80% 3-piperidylquinolizidine **26** after a few hours at room temperature. This product was present as a mixture of isomers at C12 (each isomer as a syn/anti mixture of oximes), which was difficult to identify because in the ^1H and ^{13}C NMR spectra only small chemical shift differences were observed. During the condensation reaction the stereochemistry at C1 and C10 was not affected. Enamine **26** should be directly suitable for cyclization to sparteine after hydrolysis of the oxime. Heating **26** in aqueous HCl again gave the same rearrangement/aromatization process as observed for anabasine (**4**, Scheme 6) resulting in the formation of 5-piperidylanabasine (**6**) in moderate yield. The stereochemical relationship between the two piperidine rings could not be established because of the large distance between the asymmetric centers. Although NMR spectra

Scheme 9



indicate the presence of only one diastereoisomer[18] the possibility that **6** consists of two diastereoisomers cannot be excluded.

Sparteine[19] **and *β*-Isosparteine.**[20] Removal of the enamine double bond in **26** should prevent the aforementioned rearrangement into 5-piperidylanabasine during acid-catalyzed oxime hydrolysis. Acid free hydrogenation with H_2/Pd was not suitable, however, since reduction of the oxime was faster then reduction of the enamine. Reduction with $NaCNBH_3$ and acetic acid (Scheme 8) established the stereochemistry at C3 via protonation of the enamine, providing **27**. After reduction **28** was obtained with a trans relationship between C1 and C3, which is unsuitable for cyclization. We returned to compound **26**, which was subjected to oxidative removal of the oxime (Scheme 9) using ozone and acid, as described for the synthesis of lupinine in Scheme 7. The reaction proceeded very slowly and incomplete this time, probably because ozone has to react with a species that is protonated at two nitrogen atoms. Long reaction times and higher temperatures can give rise to several side reactions, according to a recent publication describing the ozonolysis of *O*-methyl oximes at 0 °C.[21] During the ring closure of **29** to **30** with NaOAc/HOAc an imine/enamine equilibrium takes place, enabling the formation of an intermediate with the substituents at C1 and C3 in a 1,3 diaxial position, which is required for cyclization. After $NaCNBH_3$ reduction of the 1,10;16,-17-didehydrosparteinium ion **30**, formed in a NaOAc/HOAc buffer, sparteine was obtained as the only isomer (21%). Reductive hydrolysis of the oxime functionality in **26** with $TiCl_3$/HCl at high temperatures (80−90 °C) was also attempted. Reduction of the intermediate iminium salts **30** with $NaCNBH_3$ followed by chromatography yielded *β*-isosparteine (**10**, 11%) and sparteine (**9**, 9%).

In view of the low yields, mechanistic statements concerning the stereochemical course of these reactions cannot be made. Considering the mildness of the ozonolysis with respect to isomerization, it is acceptable that during the synthesis of sparteine itself, the original stereocenters remain intact. The fourth, newly formed asymmetric carbon atom 9 will always adopt a cis relation with the other bridgehead carbon atom 7. The more symmetric isomer *β*-isosparteine is thermodynamically favorable and is formed as a result of one or more isomerization processes. The third possible isomer, α-isosparteine, was not observed in these reactions.

(17) The corresponding symmetric trimer of **1** is an easy to handle, crystalline substance. Dissolving this trimer in dilute HCl results in a rapid hydrolysis to the protonated monomeric form of **1**: (a) Schöpf, C.; Braun, F.; Komzak, A. *Chem. Ber.* **1956**, *89*, 1821. (b) Wanner, M. J.; Velzel, A. W.; Koomen, G.-J. *J. Chem. Soc., Chem. Commun.* **1993**, 174.

(18) In ^{13}C NMR only C3 of the piperidine ring was double ($\Delta\delta$ = 0.08 ppm).

(19) Bohlmann, F.; Zeisberg, R. *Chem. Ber.* **1975**, *108*, 1043.

(20) Bohlmann, F.; Schumann, D.; Arndt, C. *Tetrahedron Lett.* **1965**, 2703.

(21) Griesbaum, K.; Ovez, B.; Sung Huh, T.; Dong, Y. *Liebigs Ann. Chem.* **1995**, 1571.

Further improvement of the oxime hydrolysis procedures is necessary to study the stereochemical processes during sparteine formation.

Experimental Section[22]

Tetrahydroanabasine Oxime (17). Crystalline **2** (di-HBr salt, hydrate) was prepared from dehydropiperidine trimer **1** as described by Schöpf et al.[5] **2** (di-HBr salt, hydrate, 3.46 g, 10 mmol) was stirred overnight at rt with methoxyamine (4.5 mL of a 35% solution in water, 30 mmol) in methanol (35 mL). Water (ca. 5 mL) was added, followed by an excess amount of solid K_2CO_3. After the solution was stirred for 5 min, ether was added followed by enough Na_2SO_4 to bind the water that was present. The mixture was stirred for 1 h and filtrated, and the salts were washed several times with dry ether. The solvents were removed, and the resulting liquid was kept on the evaporator (45 °C, 20 mbar) for 2 h, yielding almost pure **17** (2.08 g, 98.5%) as an oil: syn:anti = 1:4; ^{1}H NMR ($CDCl_3$) δ 7.23 (d, J = 8.6 Hz, 1H, anti oxime), 6.52 (d, J = 8.4 Hz, 1H, syn oxime), 3.80 (s, 3H), 3.79 (s, 3H), 3.03 (m, 1H), 2.75−2.5 (m, 4H), 2.15 (m, 1H), 1.9−1.1 (m, 10 H); ^{13}C NMR ($CDCl_3$) δ 153.1 (syn oxime), 152.2 (anti oxime), 61.2, 58.6, 47.1, 45.3, 41.9, 31.2, 30.3, 26.4, 26.2, 24.7; IR ($CHCl_3$) 1585 cm^{-1}; HRMS obsd mass 214.1929, calcd for $C_{11}H_{24}N_3O$ (M + 1) 214.1883.

Quinolizidine 5. A solution of quinone **13** (1.10 g, 5 mmol) in THF (10 mL) was added dropwise to a stirred solution of oxime **17** (0.852 g, 4 mmol) in MeOH (35 mL) at 0 °C in 5 min. After 10 min at 0 °C, the dark reaction mixture was stirred at rt for 15 min and quickly concentrated to a small volume in vacuum (bath T < 30 °C). The residue was diluted with 5% HCl solution (100 mL) and ether (100 mL). The organic layer was washed twice with 5% HCl solution, and the combined aqueous layers were washed with ether. Solid K_2CO_3 was added, and enamine **5** was extracted with ether. In general, better yields were obtained when **5** was not purified but immediately used for further reactions. Flash chromatography (CH_2Cl_2/MeOH/concd NH_4OH 90/10/1) gave **5** (0.35 g, 45%) as a syrup: syn:anti = 1:2; ^{1}H NMR ($CDCl_3$) δ 7.47 (d, J = 8.5 Hz, 1H), 6.85 (d, J = 7.8 Hz, 1H), 5.72 (dd, J = 8 Hz, 1.8 Hz, 1H), 4.42 (m, 1H), 3.85 (s, 3H), 3.82 (s, 3H), 3.0−3.05 (m, 1H), 2.9−1.1 (m, 11H); ^{13}C NMR ($CDCl_3$) δ 152.7, 152.6, 137.5, 137.3, 96.3, 95.7, 61.4, 61.1, 58.0, 57.6, 53.0, 38.4, 31.6, 29.5, 29.0, 26.1, 25.9, 25.7, 25.6, 24.4.

Quinolizidine Dimer 19. A solution of **5** (0.049 g, 0.25 mmol) and acetic acid (15 μL, 0.025 mmol) in MeOH (1 mL) was stirred at rt for 20 h. Workup with aqueous K_2CO_3 and ether yielded after chromatography (CH_2Cl_2/MeOH/concd NH_4OH 95/5/0.5) dimer **19** (39 mg, 80%) as a mixture of isomers: ^{1}H NMR ($CDCl_3$) δ 7.9−6.5 (m, 10 different CH=N signals), 5.67 (broad, 1H, NCH=C), 3.86−3.80 (10 CH_3 signals); IR ($CHCl_3$) 1585 cm^{-1}; HRMS obsd mass 388.2847, calcd for $C_{22}H_{36}N_4O_2$ 388.2835.

Cycloaddition of Tetrahydroanabasine to 3,5-Di-*tert*-butyl-1,2-benzoquinone (21). Crystalline **2** (di-HBr salt, hydrate, 0.178 g, 0.5 mmol) was dissolved in MeOH (6 mL) together with NaOAc (0.082 g, 1 mmol). A solution of **13** (0.121 g, 0.55 mmol) in THF (1 mL) was added in one portion. The dark reaction mixture was stirred overnight and filtrated, yielding **21**[10] (0.085 g, 44%) as a white solid. When no crystallization takes place, alkaline workup (K_2CO_3, H_2O, ether) and trituration with MeOH gives comparable results. The filtrate contained small amounts of an isomer that could not be obtained in pure form. **21:** mp 214−218 °C (from MeOH) and 225−228 °C (from CH_2Cl_2/PE); IR ($CHCl_3$) 1586, 1482 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 6.83 (d, J = 2.3 Hz, 1H), 6.74 (d, J = 2.3 Hz, 1H), 5.19 (d, J = 0.5 Hz, 1H), 3.28 (m, J = 11.1, 2.7 Hz, 1H), 3.18 (ddd, J = 10.8, 10.8, 4.1 Hz, 1H), 3.10 (m, J = 13 Hz, 1H), 2.76 (m, J = 11.1, 4.1, 4.1 Hz, 1H), 2.62 (ddd, J = 13, 12.5, 2.8 Hz, 1H), 1.96 (m, 1H), 1.90−1.2 (m, 9H), 1.39 (s, 9H), 1.28 (m, 9H); ^{13}C NMR ($CDCl_3$) δ 142.6, 141.0, 138.2, 137.3, 115.2, 112.0, 81.4, 75.3, 57.1, 46.9, 39.2, 35.0, 34.3, 31.6, 29.8, 27.6, 25.6, 25.3, 25.1, 22.2; IR ($CHCl_3$) 1586, 1482 cm^{-1}; HRMS obsd mass 387.3012, calcd for $C_{24}H_{39}N_2O_2$ (M + 1) 387.3011.

Quinolizidine 22. Quinolizidine **5** (0.194 g, 1 mmol) was dissolved in MeOH (5 mL) and immediately reduced with $NaBH_4$ (0.076 g, 2 mmol) for 3 h at rt. The reaction mixture was concentrated in vacuum, quenched with 1 M HCl, and extracted with ether after addition of aqueous K_2CO_3. After chromatography (CH_2Cl_2/MeOH/concd NH_4OH 90/10/1) **22** (0.174 g, 89%) was obtained as a syrup: syn:anti = 1:4; ^{1}H NMR ($CDCl_3$) δ 7.78 (d, J = 8.8 Hz, 1H), 7.10 (d, J = 7.5 Hz, 1H), 3.84 (s, 3H), 3.81 (s, 3H), 3.0−1.15 (m, 16H); ^{13}C NMR ($CDCl_3$) δ 153.3 (syn), 152.8 (anti), 64.1, 63.8, 61.4, 61.2, 57.0, 56.9, 39.9, 36.0, 30.9, 30.6, 20.0, 25.7, 25.6, 24.6, 24.6, 22.4, 21.6; IR ($CHCl_3$) 2800, 2760, 1650 cm^{-1}. HRMS obsd mass 196.1578, calcd for $C_{24}H_{39}N_2O_2$ 196.1565.

***N*-Acetyllupinamine (8).** Oxime **22** (0.050 g, 0.25 mmol) was reduced with LAH (0.076 g, 2 mmol) in refluxing THF (2 mL) for 7 h. Workup with NaOH and ether gave the free amine as an oil, which was acetylated with a mixture of ethyl acetate and acetic anhydride (reflux, 1 h). The solvents were evaporated, and the residue was treated with aqueous ammonia. Ether extraction and recrystallization of the crude product (PE/EtOAc) gave **8**[12] (45 mg, 85%): mp 121−122 °C (needles); ^{1}H NMR ($CDCl_3$) δ 7.45 (br, 1H), 3.49 (dddd, J = 3.0, 5.7, 8.7, 13.9 Hz, 1H), 3.38 (dddd, J = 3.5, 6.7, 10.3, 13.9 Hz, 1H), 2.84 (m, 2H), 1.96 (s, 3H), 2.1−1.45 (m, 13H), 1.2−1.25 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 169.7, 64.8, 57.3, 57.1, 41.4, 36.0, 30.0, 29.8, 25.7, 24.8, 23.5, 22.0; IR ($CHCl_3$) 3460, 2800, 2760, 1650, 1520 cm^{-1}; HRMS obsd mass 211.1790, calcd for $C_{12}H_{23}N_2O$ (M + 1) 211.1884.

(±)-Anabasine (4). Quinolizidine **5** (0.039 g, 0.2 mmol) in aqueous HCl (5%, 0.5 mL) was kept at 90 °C for 24 h. The reaction mixture was made alkaline with excess solid K_2CO_3, and the product was extracted with ether. Chromatography (CH_2Cl_2/MeOH/concd NH_4OH 90/10/1) gave **4**[13] (0.018 g, 56%) as an oil: ^{1}H NMR ($CDCl_3$) δ 8.56 (d, J = 1.7 Hz, 1H), 8.46 (dd, J = 4.7, 1.4 Hz, 1H), 7.70 (ddd, J = 7.9, 1.8, 1.7 Hz, 1H), 7.22 (dd, J = 4.7, 7.9 Hz, 1H), 3.61 (dd, J = 10.5, 2.6 Hz, 1H), 3.18 (bd, J = 11.4 Hz, 1H), 2.78 (m, 1H), 2.0−1.4 (m, 6H); ^{13}C NMR ($CDCl_3$) δ 148.7, 148.6, 140.6, 134.1, 123.4, 59.8, 47.6, 34.8, 25.7, 25.2; IR ($CHCl_3$) 1590, 1500 cm^{-1}; HRMS obsd mass 162.1161, calcd for $C_{10}H_{14}N_2$ 162.1138.

Ozonolysis of 22: (±)-Lupinine (7). TFA (23 μL, 0.3 mmol) was added to a solution of oxime **22** (0.047 g, 0.24 mmol) in MeOH (3 mL). The solution was cooled to −60 °C and treated with ozone in portions. The bath temperature was kept between −50 and −60 °C, and after 90 min the solution was purged with nitrogen followed by the addition of $NaBH_4$ (0.038 g, 1 mmol). The reaction mixture was stirred at rt for 1 h, the solvent was evaporated, and the residue was treated with NaOH solution (1M, 5 mL). Addition of solid K_2CO_3 and ether extraction yielded pure lupinine[16] (**7**) (0.022 g, 54%): mp 58−59 °C (ether/hexane); ^{1}H NMR ($CDCl_3$) δ 4.14 (ddd, J = 10.7, 5.6, 1.2 Hz, 1H), 3.68 (d, J = 10.8 Hz, 1H), 2.81 (m, 2H), 2.15 (m, 2H), 2.01 (m, 1H), 1.9−1.45 (m, 10H), 11.25 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 66.0, 65.1, 57.1, 57.0, 38.1, 31.4, 29.7, 25.6, 24.6, 22.9; IR ($CHCl_3$) 3000−3500, 2810, 2770 cm^{-1}; HRMS obsd mass 169.1460, calcd for $C_{10}H_{19}NO$ 169.1501.

$TiCl_3$ Reduction of 22: (±)-Lupinine (7) and (±)-Epilupinine (25). A solution of **22** (0.047 g, 0.24 mmol) in aqueous $TiCl_3$ (10% solution in 25% HCl, 1 mL) was adjusted to pH 3−4 by the addition of Na_2CO_3. The resulting suspension was heated at 50 °C for one night, and the products were extracted with ether after basification with K_2CO_3. According to ^{1}H NMR the obtained product (12 mg, 30%) consisted of a 5:2 mixture of lupinine and epilupinine.[16] Epilupinine: ^{1}H NMR ($CDCl_3$) δ 3.64 (dd, J = 3.7, 10.8 Hz, 1H), 3.55 (dd, J = 10.8, 5.6 Hz, 1H).

3-Piperidylquinolizidine 26. α-Tripiperidine[5,15] (**1**) (0.332 g, 4 mmol) was stirred with aqueous HCl (30%, 1 mL) until a clear solution of **2** (hydrochloride) was obtained (ca. 1 h). Quinolizidine **5** (0.582 g, 3 mmol) was dissolved in MeOH (15 mL) and immediately mixed with the α-tripiperidine monomer (**1**) and sodium acetate (0.82 g, 10 mmol). After the mixture was stirred at rt for 3 h the MeOH was evaporated and the

(22) For general information, see: Wanner, M. J.; Koomen G.-J. *J. Org. Chem.* **1994**, *59*, 7479.

residue was diluted with K_2CO_3 solution and extracted three times with ether. Additional solid K_2CO_3 may be added to the water layer to improve the extraction. Chromatography (CH_2Cl_2/MeOH/concd NH_4OH 90/10/1) gave **26** (0.664 g, 80%) as a 1:1 mixture of isomers, each as a 1:2 mixture of syn and anti oximes: ^{1}H NMR ($CDCl_3$) δ 7.370 (d, J = 8.4 Hz, 1H), 7.366 (d, J = 8.4 Hz, 1H), 6.751 (d, J = 7.8 Hz, 1H), 6.749 (d, J = 7.8 Hz, 1H), 3.84, 3.83, 3.81, 3.79 (4 × CH_3), 3.3−1.2 (m, 23H); ^{13}C NMR ($CDCl_3$) δ 152.4, 152.4, 152.3, 152.2 (4 × CH=NO) 133.1, 132.8, 132.7, 132.5, (4 × NCH=), 112.1, 111.9, 11.6, 111.4 (4 × C-quart.); IR ($CHCl_3$) 1585 cm^{-1}; HRMS obsd mass 277.2172, calcd for $C_{16}H_{27}N_3O$ 277.2108.

(±)-5-Piperidylanabasine (6). A solution of **26** (0.028 g, 0.1 mmol) in aqueous HCl (5%, 2 mL) was kept at 80 °C for 5 h. The reaction mixture was cooled, made alkaline with K_2CO_3, and extracted with ether. Chromatography (CH_2Cl_2/MeOH/concd NH_4OH 85/15/1.5) gave **5** (0.008 g, 35%) as a glass: ^{1}H NMR ($CDCl_3$) δ 8.45 (d, J = 1.9 Hz, 2H), 7.72 (bs, 1H), 3.62 (dd, J = 10.2, 2.4 Hz, 2H), 3.18 (bd, J = 11.5 Hz, 2 H), 2.78 (ddd, J = 11.5, 11.5, 2.7 Hz, 2H),1.95−1.4 (m, 12H); ^{13}C NMR ($CDCl_3$) δ 147.4, 140.4, 132.4, 59.9, 47.7, 34.9, 34.8, 25.8, 25.3; IR ($CHCl_3$) 1595 cm^{-1}; HRMS obsd mass 245.1879, calcd for $C_{15}H_{23}N_3$ 245.1825.

Reduction of 26 to 28. Enamine **26** (0.277 g, 1 mmol) was stirred with $NaCNBH_3$ (0.094 g, 1.5 mmol) in a mixture of acetonitrile (8 mL) and acetic acid (2 mL) for 20 h at rt. Concd HCl (2 mL) was added, and after being stirred for 15 min the reaction mixture was concentrated in vacuum, made alkaline with K_2CO_3, and extracted with ether. Chromatography (CH_2Cl_2/MeOH/concd NH_4OH 85/15/1.5) gave **28** (0.190 g, 68%) as a syrup: ^{1}H NMR ($CDCl_3$) δ 7.72 (d, J = 8.8 Hz, 1H), 7.71 (d, J = 8.9 Hz, 1H), 7.05 (d, J = 7.3 Hz, 1H), 7.03 (d, J = 7.3 Hz, 1H), 3.82, 3.81, 3.80, 3.78 (4 × CH_3), 3.05−1.0 (m, 25H); IR ($CHCl_3$) 1585 cm^{-1}.

(±)-Sparteine[19,20] (9). Concd HCl (0.25 mL) was added dropwise to a solution of oxime **26** (0.139 g, 0.5 mmol) in MeOH (6 mL). The solution was cooled to −50 °C and treated with ozone at 30 min intervals. The bath temperature was kept between −45 and −55 °C, and after 7 h the solution was purged with nitrogen followed by the addition of dimethyl sulfide (0.19 mL, 2.5 mmol). After the solution was stirred at rt for 10 min, sodium acetate (0.492 g, 6 mmol) and acetic acid (2 mL) were added and stirring was continued for 1 h. Reduction was performed by adding $NaCNBH_3$ (0.126 g, 2 mmol) and stirring overnight. Concd HCl (2 mL) was added, and after being stirred for 15 min the reaction mixture was concentrated in vacuum, diluted with water, and made alkaline with excess K_2CO_3. Ether extraction and chromatography (CH_2Cl_2/MeOH/concd NH_4OH 85/15/1.5) gave sparteine (**9**) (0.025 g, 21%) as an oil: ^{1}H NMR ($CDCl_3$) δ 2.84 (bd, J = 11.4 Hz, 1H), 2.78 (dd, J = 10.9, 10.8 Hz, 1H), 2.69 (bd, J = 10.8 Hz, 1H), 2.54 (bd, J = 10.9 Hz, 1H), 2.38 (dd, J = 11.3, 3.5 Hz, 1H), 2.10 (m, 2H), 2.00 (dd, J = 11.0, 2.6 Hz, 1H), 1.95 (m, 1H), 1.85 (m, 1H), 1.75−1.15 (m, 15H), 1.08 (ddd, J = 12.1, 2.5, 2.5 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 66.4, 64.4, 61.8, 56.2, 55.3, 53.2, 35.9, 34.0, 30.0, 29.3, 27.5, 25.8, 25.4, 24.7, 24.6; HRMS obsd mass 234.2079, calcd for $C_{15}H_{26}N_2$ 234.2096.

(±)-β-Isosparteine[20] (10). $TiCl_3$ (0.308 g, 2 mmol) was added to a solution of oxime **26** (0.100 g, 0.36 mmol) in 5% HCl (4 mL), and the resulting mixture was heated at 80 °C overnight. After the mixture was cooled to rt, water (5 mL) was added and the HCl was neutralized with NaOAc until the mixture was slightly acidic. Additional acetic acid (1 mL) and $NaCNBH_3$ (0.032 g, 0.5 mmol) were added, and the suspension was stirred at rt for 20 h. Concd HCl (2 mL) was added, and after being stirred for 15 min the reaction mixture was made alkaline with excess solid K_2CO_3. Solids were removed by filtration and washed several times with ether. The combined filtrates were separated, and the aqueous layer was extracted with ether. Chromatography (CH_2Cl_2/MeOH/concd NH_4OH 85/15/1.5 → 75/25/2.5) gave first sparteine (**9**, 7.5 mg, 9%) and second β-isosparteine (**10**, 9.0 mg, 11%). **10**: ^{1}H NMR ($CDCl_3$) δ 23.02 (dd, J = 10.8, 6.6 Hz, 2H), 2.79 (ddd, J = 12.6, 2.0, 2.0 Hz, 2H), 2.45 (ddd, J = 12.6, 12.6, 2.5 Hz, 2H), 2.28 (bd, J = 11.8 Hz, 2H), 2.17 (dd, J = 10.8, 2.7 Hz, 2H), 1.75 (m, 2H), 1.65 (m, 2H), 1.6 (m, 4H), 1.52 (dd, J = 3.3, 3.3 Hz, 2H), 1.35 (m, 4H), 1.24 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 62.8, 55.1, 54.9, 34.4, 28.6, 25.4, 22.6, 19.8; HRMS obsd mass 234.2106, calcd for $C_{15}H_{26}N_2$ 234.2096.

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