Natural (−)-Vasicine as a Novel Source of Optically Pure 1-Benzylpyrrolidin-3-ol

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A facile and scalable methodology for the preparation of optically active (3*S*)-1-benzylpyrrolidin-3-ol (**3**), an important drug precursor, is reported. Starting from the naturally occurring alkaloid (−)-vasicine (**1**), a major alkaloid of the plant *Adhatoda vasica*, **3** was obtained in 84% overall yield (*Scheme 3*).

Introduction. – The pyrrolidin-3-ol moiety is present in a wide range of naturally occurring alkaloids and biologically active molecules [1] and commonly used as an intermediate for the preparation of a variety of drugs. Pharmaceuticals such as the antihypertensive barnidipine A [2], the quinolinone antibiotic clinafloxacin B [3], the muscarinic receptor antagonists darifenacine C [4], the anticoagulant DX-9065a [5], the carbapenem antibiotic RS-533 [6], and the natural product detoxin A_1-D [7], a detoxification agent, comprise a pyrrolidinol subunit or a derivative thereof (*Fig.*). Recently, several pyrrolidinols have been described as versatile chiral ligands and promoters in organocatalysis [8].

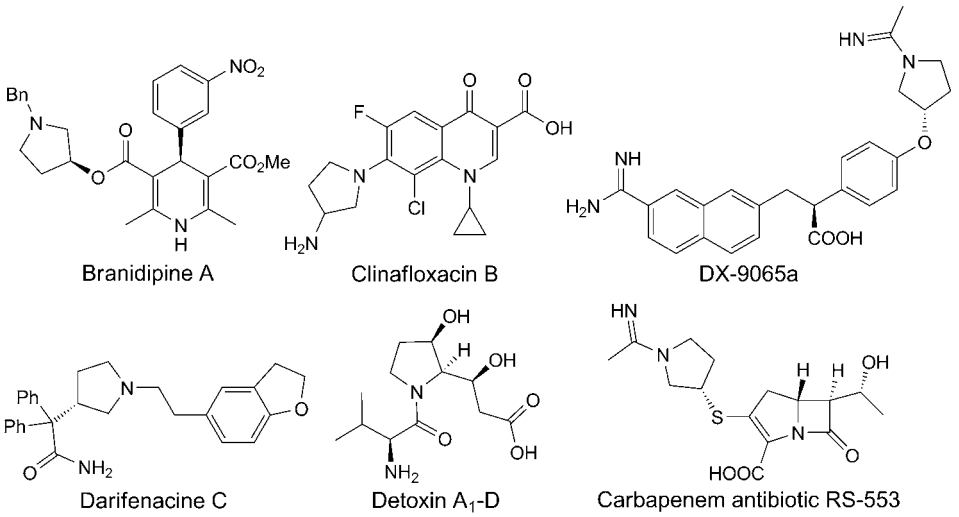


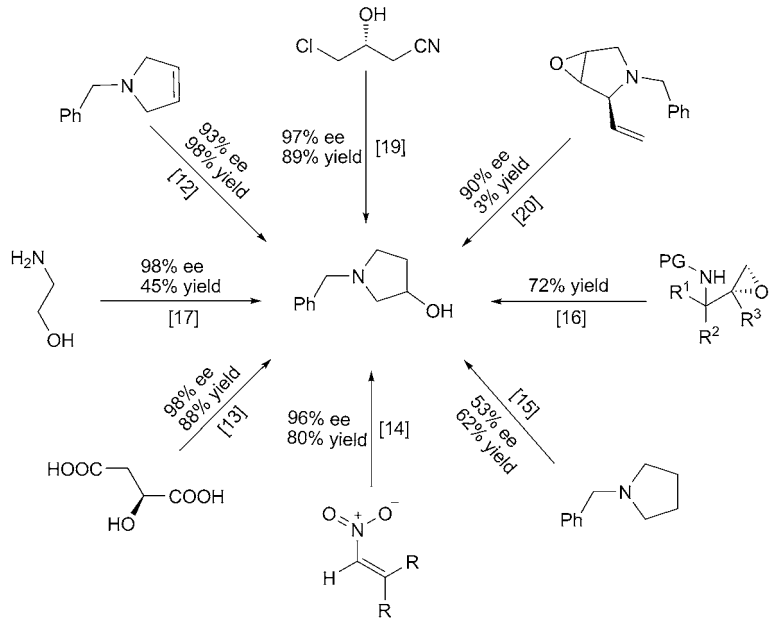
Fig. 1. *Drugs and natural products featuring a pyrrolidin-3-ol moiety or a derivative thereof*

Due to the growing interest and applications of the pyrrolidin-3-ol scaffold, a number of synthetic as well as biotransformation approaches for the stereoselective synthesis of its *N*-benzyl derivative have been attempted [9].

The reported synthetic strategies include intramolecular displacement of a leaving group by an amine [10], haloamidation reactions [11], asymmetric hydroboration of 2,5-dihydro-1*H*-pyrrole derivatives [12], reduction of lactams [13], nitroalkene [4 + 2] cycloadditions [14], enzymatic hydroxylation [15], reaction of epoxysulfonamides with sulfoxonium ylides [16], cyclization of α-lithio-carbamates [17], amino acids as chiral educts [18], from optically active precursors such as 1-halobutan-2-ols [19] or 4-halo-3-hydroxy butanenitriles [19], and regioselective oxirane ring opening [20]; some of these syntheses are roughly sketched in *Scheme 1*. Most of the chemical transformations required multi-step reaction strategies or involved expensive chemicals, which make the process uneconomical.

One of the commercial approaches is the biotransformation of *N*-benzylpyrrolidine *via* microbial oxidation, which directly provided the mono-oxygenated product at low concentrations and enatiomer purity (53% ee), requiring, however, further crystallization for enantiomer enrichment (*Scheme 1*) [15].

Scheme 1. *Existing Routes to Chiral Pyrrolidin-3-ol*



Evidently, though several methodologies for the preparation of enantiomer-enriched pyrrolidin-3-ol and its derivatives are documented in the literature, yet a simple and efficient process for the preparation of the enantiomerically pure product from an inexpensive, renewable, and easily available starting material remains one of the important challenges. The present communication describes a concise, scalable, and economical synthesis of optically pure 1-benzylpyrrolidin-3-ols from the naturally

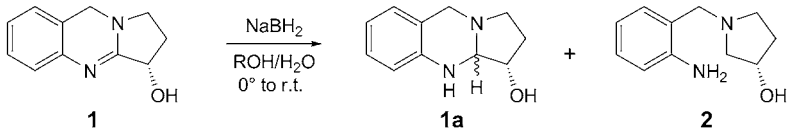
occurring alkaloid (−)-vasicine (**1**), isolated from the leaves of *Adhatoda vasica* [21], where **1** is present in good concentrations (*ca.* 1–2%) [22]. The results also reconfirm the absolute configuration (3*S*) of the natural alkaloid (−)-vasicine (**1**) [23]. In an early report, the absolute configuration was assigned as (3*R*) by *Szulzewsky et al.* [24], based on the anomalous crystallographic X-ray dispersion data of its hydrochloride. However, in 1996, *Joshi*, *Newton*, and co-workers [25] revised the previously assigned (3*R*) configuration of (−)-vasicine (**1**) to (3*S*) on the basis of the X-ray crystal-structure analyses of the (+)-vasicinone and (+)-vasicine hydrobromides derived from the natural alkaloids.

Results and Discussion. – The synthetic strategy towards the (3*S*)- and (3*R*)-pyrrolidinol essentially involves the elimination of the 'anilinic' N-atom from the quinazoline ring moiety of (−)-vasicine (**1**), thus requiring the cleavage of the C=N bond of **1** followed by hydrodeamination of the intermediate aromatic amine to give (3*S*)-1-benzylpyrrolin-3-ol (**3**) [21]. *Mitsunobu* [26] inversion would then allow the formation of the (3*R*)-enantiomer **4**.

Thus, the key steps in the elimination of the 'anilinic' N-atom required a suitable reduction methodology for the C=N amidine moiety of **1** and concomitant cleavage of a C–N bond. A simple hydride reduction strategy appeared to be the best option for the formation of the desired products.

In the initial experiment, $NaBH_4$ in commercial EtOH (95%) reduced (−)-vasicine (**1**) to a mixture of two products, **1a** and **2**, in a ratio of 75:15 (*Scheme 2*). In dry EtOH, the formation of only **1a** was observed, and no C–N bond cleavage to product **2** occurred (*Table*, *Entry 1*), whereas in H_2O, **1** was converted directly to **2** in 70% yield (*Entry 11*). These experiments suggested that H_2O played an important role in the cleavage of the amidine bond. Optimizing the reduction parameters (*Table*) established that in MeOH/H_2O 1:1, **1** was quantitatively converted to **2** within 2 h (*Entry 9*). Increasing the amount of H_2O beyond 50% impaired the substrate solubility, resulting in a decrease of the yield (*Entry 10*)

Scheme 2. *Cleavage of the Amidine Bond of (−)-Vasicine* (**1**)



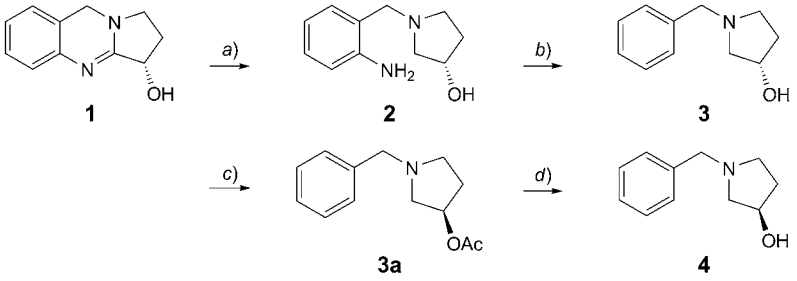
1 **1a** **2**

In the next step, hydrodeamination was efficiently achieved by treatment of **2** with isoamyl nitrite (= 3-methylbutyl nitrite) [27] in DMF at 65° to obtain (3*S*)-1-benzylpyrrolidin-3-ol (**3**) in 85% yield (84% based on **1**; *ca.* 99% ee) (*Scheme 3*). By comparison of the sign and value of the rotation with those of the commercial sample (*Sigma-Aldrich*, Mumbai), **3** was assigned as (3*S*)-1-benzylpyrrolidin-3-ol. In the final step, the inversion of the configuration at C(3) was smoothly and quantitatively effected by treatment of **3** with *Mitsunobu* reagent yielding the enantiomer (3*R*)-1-benzylpyrrolidin-3-ol (**4**) *via* **3a**.

Table. *Effect of Different Solvents on Cleavage of the Amidine Bond of (−)-Vasicine* (**1**)

Entry	Solvent	Yield after 2 h [%]	
		1a	**2**
1	EtOH	80	0
2	H_2O/EtOH (1 : 4)	35	60
3	H_2O/EtOH (1 : 1)	0	75
4	^{i}PrOH	50	0
5	H_2O/^{i}PrOH (1 : 4)	20	50
6	H_2O/^{i}PrOH (1 : 1)	10	60
7	MeOH	95	0
8	H_2O/MeOH (1 : 4)	10	80
9	H_2O/MeOH (1 : 1)	0	ca. 99
10	H_2O/MeOH (3 : 2)	0	75
11	H_2O	0	70

Scheme 3. *Synthesis of (3*S*)- and (3*R*)-1-Benzylpyrrolidin-3-ol* (**3** and **4**, resp.)

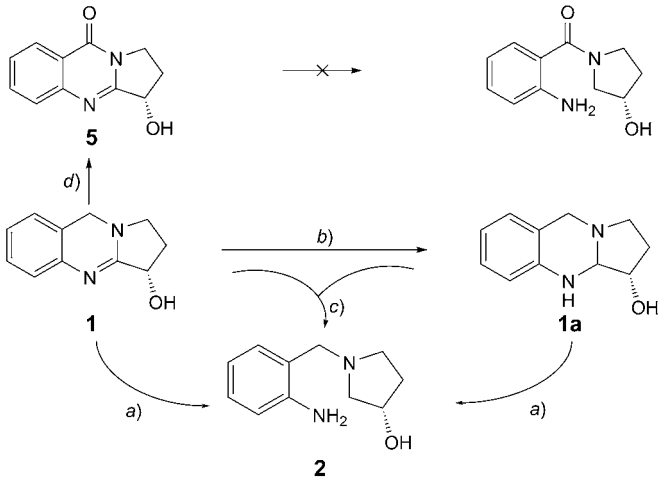


a) $NaBH_4$, MeOH/H_2O 1 : 1. *b*) Isoamyl nitrite, DMF, 65°. *c*) Ph_3P, EtOOCN=NCOOEt, AcOH, THF. *d*) LiOH, THF, H_2O, 0°.

To gain an insight into the mechanism and the role of H_2O in the amidine bond cleavage, we dracked if $NaBO_2$ was the tangible reactive species during C–N bond cleavage, since $NaBH_4$ is known to react with H_2O to form $NaBO_2$ [28]. Therefore, the reaction of **1** with $NaBH_4$/$NaBO_2$ 3 : 2 in the absence of H_2O (anh. MeOH) was performed at room temperature (*Scheme 4*). Gratifyingly, the reaction proceeded as expected, resulting in complete reduction of **1** to give only **2**. When the same reaction was carried out with vasicinone (**5**), no reduction/cleavage product was observed, indicating that the presence of a lone pair of electron at the tertiary N-atom was essential for the initial reduction. In vasicinone (**5**), this lone pair is unavailable due to conjugation with the C=O function.

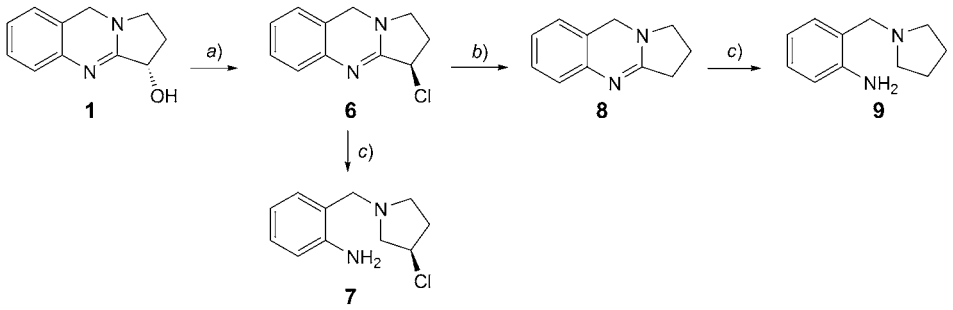
To ascertain that the 3-OH group was not playing any role during the amidine-bond cleavage, vasicine **1** was replaced by the derivatives 3-chloro-3-deoxyvasicine (**6**) [30] and 3-deoxyvasicine (**8**) [31] (*Scheme 5*). On treatment with $NaBH_4$ in MeOH/H_2O 1 : 1, the C=N bond of both **6** and **8** was cleaved to produce compound **7** and **9**, respectively. These experiments confirmed that $NaBO_2$ as well as the lone electron pair at the tertiary N-atom in the ring played vital roles in the amidine bond cleavage.

Scheme 4. *Reactions Conducted to Support the Proposed Mechanism*



a) $NaBH_4$, $MeOH/H_2O$ (1:1). *b*) $NaBH_4$, dry MeOH. *c*) $NaBH_4$ $NaBO_2$, dry MeOH. *d*) H_2O_2/acetone [29]

Scheme 5. *Cleavage of the Amidine Bond of 3-Deoxyvasicine* (**8**) *and 3-Chloro-3-deoxyvasicine* (**6**)

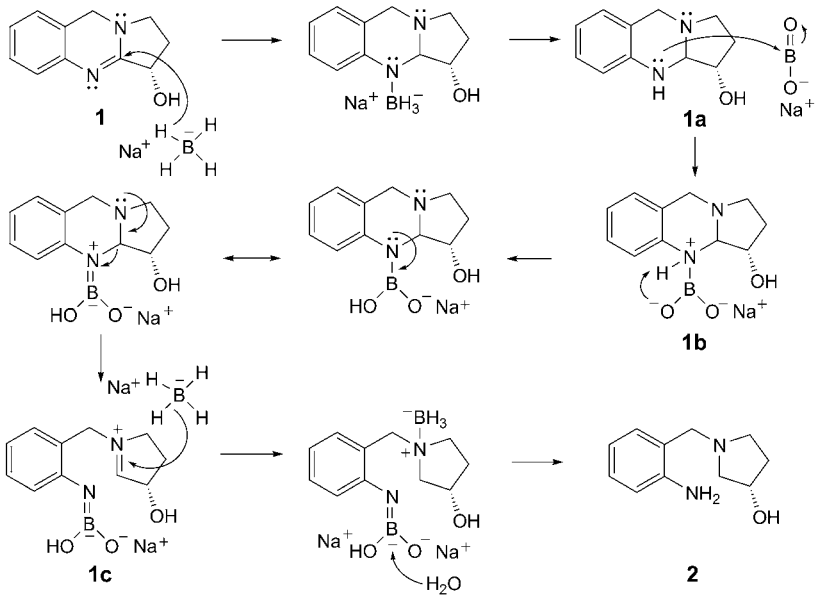


a) $POCl_3/PCl_5$. *b*) Zn/HCl. *c*) $NaBH_4$, $MeOH/H_2O$ 1:1.

On the basis of the above experiments a plausible mechanism for the amidine bond cleavage is proposed (*Scheme 6*). In the first step, the $NaBH_4$ acts as a hydride source in reducing the C=N bond to give dihydro derivative **1a**. The presence of H_2O in the reaction medium generates $NaBO_2$, which activates the ring N-atom in **1a** to create a borate complex **1b**. The activation is followed by the cleavage of the C–N bond generating the carbocation **1c** which is stabilized by the electron pair at the tertiary N-atom. The stabilized carbocation is finally reduced by $NaBH_4$ to produce **2** (*Scheme 6*).

Conclusions. – A concise methodology for the preparation of the enantiomers **3** and **4** of 1-benzylpyrrolidin-3-ol from naturally occurring alkaloid (−)-vasicine (**1**) as the starting material was developed. The methodology is not only facile but also scalable.

Scheme 6. *Plausible Mechanism for the Amidine-Bond Cleavage in (−)-Vasicine* (**1**)



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Experimental Part

General. Reagents and solvents used were mostly of LR grade. Dry solvents were from *Merck*. TLC: Silica-gel-coated aluminium plates. CC = Column chromatography. Optical rotation: *Perkin-Elmer-241* polarimeter; at 25°; with Na_D light. ^{1}H- and ^{13}C-NMR Spectra: *Bruker-Avance-400* and-*500* spectrometers; δ in ppm rel. to Me_4Si as internal standard, *J* in Hz. HR-ESI-MS: *Agilent Technology 6540 UHD*, *Acurrat Mass Q-TOF-LC-MS* instrument; in *m*/*z*.

Extraction of (−)-*Vasicine* (**1**) *from* Adhatoda vasica. Air-dried, powdered leaf of *A. vasica* (1 kg) was extracted with EtOH (5 × 3 l) at r.t. for 72 h. The combined EtOH extract was concentrated to 200 ml. The concentrate was treated with a 30% (*w*/*v*) aq. citric acid soln. (1.0 l) and stirred at r.t. for 3 h. The mixture was filtered and the filtrate extracted with $CHCl_3$ (3 × 1.0 l). The aq. layer was then separated and basified with aq. NH_3 soln. to pH 9.5 followed by the extraction with $CHCl_3$ (3 × 1 l). The combined $CHCl_3$ layers were concentrated to give an amorphous residue of **1**, which was then recrystallized in EtOH to give pure **1** (14 g), Crystalline white solid. M.p. 212°. $[\alpha]_D^{25} = -239$ (*c* = 2.6, $CHCl_3$) [32].

*(3*S*)-1-[(2-Aminophenyll)methyl]pyrrolidin-3-ol* (**2**) [21]. To a soln. of natural (−)-vasicine (**1**; 10 g, 53 mmol) in MeOH/H_2O 1 : 1 (100 ml), $NaBH_4$ (5.87 g, 158 mmol) was added in small amounts within 1 h under continuous stirring. The mixture was stirred for an additional hour and then extracted with CH_2Cl_2 (3 × 100 ml). The extract was dried (Na_2SO_4) and concentrated: **2** (99%). Light yellow semi-solid. $[\alpha]_D^{25} = -199$ (*c* = 3, $CHCl_3$). ^{1}H-NMR (500 MHz, $CDCl_3$): 1.63–1.79 (*m*, 1 H); 2.1–2.2 (*m*, 1 H); 2.24–2.30 (*m*, 1 H); 2.4–2.6 (*m*, 2 H); 2.73–2.84 (*m*, 1 H); 3.60 (*dd*, *J* = 12.1, 11.9, 2 H); 4.22–4.38 (*m*, 1 H); 6.6–6.74 (*m*, 2 H); 7.00 (*d*, *J* = 7.8, 1 H); 7.07 (*t*, *J* = 7.1, 1 H). ^{13}C-NMR (100 MHz, $CDCl_3$): 34.9; 52.4; 59.1; 62.6; 71.1; 115.6; 117.8; 123.5; 128.3; 129.8; 146.4. HR-ESI-MS: 193.1343 (M^+, $C_{11}H_{17}N_2O^+$; calc. 193.1341).

Pyrrolidinol of **2** *from* (−)-*Vasicine* (**1**) *in the Presence of Sodium Metaborate* ($NaBO_2$)*:* To a soln. of **1** (1 g, 5.291 mmol) in dry MeOH (10 ml), $NaBO_2$ (0.45 g, 7.125 mmol) was added at r.t. under continuous stirring followed by $NaBH_4$ (0.146 g, 3.96 mmol) in small portions at regular intervals within 2 h. After completion of the reaction, H_2O, 20 ml was added, the product extracted with $CHCl_3$ (3 × 25 ml), and the combined $CHCl_3$ layer dried (Na_2SO_4) and concentrated in a thin-film evaporator: **2** (99%). Light yellow semi-solid. $[\alpha]_D^{25} = -199$ ($c = 3$, $CHCl_3$); 99% ee.

*(3*S*)-1,2,3,3a,4,9-Hexahydropyrrolo[2,1-*b*]quinazolin-3-ol* (**1a**). To a soln. of **1** (1 g, 5.291 mmol) in dry MeOH (15 ml), $NaBH_4$ (0.10g, 2.70 mmol) was added at r.t. in small portions at regular intervals continuous within 1 h under continuous stirring. The mixture was quenched with AcOEt (5 ml) and extracted with $CHCl_3$ (3 × 25 ml), the extract concentrated, and the residue vacuum dried: **1a** (95%; inseparable mixture of diastereoisomers). Light yellow solid. M.p 123–125°. ^{1}H-NMR (500 MHz, $CDCl_3$): 1.70–1.89 (*m*, 1 H); 2.23–2.49 (*m*, 2 H); 2.81–2.97 (*m*, 1 H); 3.09–3.21 (*m*, 1 H); 3.71–3.82 (*dd*, *J* = 10.4, 11.1, 2 H); 4.18–4.25 (*m*, 1 H); 4.30–4.39 (*m*, 1 H); 6.67–6.83 (*m*, 2 H); 6.91–7.23 (*m*, 2 H). ^{13}C-NMR (125 MHz, $CDCl_3$): 26.40; 27.02; 43.44; 43.90; 47.63; 66.54; 69.45; 110.23; 113.23; 114.10; 114.89; 116.44; 123.34; 123.78; 137.45. HR-ESI-MS: 191.1172 (M^+, $C_{11}H_{15}N_2O^+$; calc. 191.1184).

Pyrrolidinol **2** *from* **1a** *in the Presence of Sodium Metaborate* ($NaBO_2$). To a soln. of **1a** (1 g, 5.26 mmol) in dry MeOH (20 ml), $NaBO_2$ (0.45 g, 7.125 mmol) was added, followed by $NaBH_4$ (0.10 g, 2.70 mmol) in small portions at regular intervals within 1 h under continuous stirring for. After completion of the reaction, H_2O (20 ml), was added and the product extracted with $CHCl_3$ (3 × 25 ml). The combined $CHCl_3$ layer was dried (Na_2SO_4) and concentrated: **2** (99%). Light yellow semi-solid $[\alpha]_D^{25} = -199$ ($c = 3$, $CHCl_3$); 99% ee.

*(3*S*)-1-(Phenylmethyl)pyrrolidin-3-ol* (**3**). A soln. of **2** (2 g, 10.4 mmol) in a minimum amount of DMF (5 ml) was added dropwise under stirring to a soln. of isoamyl nitrite (2.8 ml, 20.81 mmol) and DMF (2 ml) heated at 65°. After 30 min, the mixture was cooled to r.t., the pH adjusted to 8 by adding NH_3 soln., and the mixture extracted with $CHCl_3$ (3 × 50 ml). The extract was evaporated and the residue purified by CC (basic alumina, *ca.* 150 mesh): pure **3** (1.475 g 85%). Colorless liquid. $[\alpha]_D^{25} = -3.7$ ($c = 5$, MeOH); ee > 99%. ^{1}H-NMR (500 MHz, $CDCl_3$): 1.64–1.72 (*m*, 1 H); 2.1–2.6 (*m*, 1 H); 2.28–2.32 (*m*, 1 H); 2.52–2.62 (*m*, 2 H); 2.74–2.82 (*m*, 1 H); 2.91–2.93 (*m*, 1 H); 3.58 (*s*, 2 H); 4.24–4.31 (*m*, 1 H); 7.20–7.32 (*m*, 5 H). ^{13}C-NMR (125 MHz, $CDCl_3$): 34.8; 52.5; 60.2; 62.8; 70.8; 127.3; 128.4; 128.8; 138.4. HR-ESI-MS: 178.1235 (M^+, $C_{11}H_{16}NO^+$; calc. 178.1232).

*(3*R*)-1-(Phenylmethyl)pyrrolidin-3-ol Acetate* (**3a**). Diethyl diazene-1,2-dicarboxylate (6.92 ml, 35.17 mmol) was added dropwise to a stirred soln. of Ph_3P (41.78 mmol) in dry THF (300 ml) at 0° under N_2. After 30 min, **3** (6.71 g in 25 ml THF) was added dropwise and stirred for another 20 min at 0° prior to the addition of AcOH (4.1 ml, 70 mmol) at r.t. After 16 h at r.t., the mixture was acidified with dil. HCl soln. and extracted with $CHCl_3$ (3 × 50 ml). The pH of the aq. layer was adjusted to 8.0 by adding NH_3 soln., and the aq. phase was again extracted with $CHCl_3$ (3 × 50 ml). Drying (Na_2SO_4) and solvent removal afforded **3a** (6.89 g, 89%). Light yellow liquid. ^{1}H-NMR (500 MHz, $CDCl_3$): 1.80–1.90 (*m*, 1 H); 2.03 (*s*, 3 H); 2.20–2.30 (*m*, 1 H); 2.40–2.48 (*m*, 1 H); 2.63–2.68 (*m*, 1 H); 2.70–2.78 (*m*, 2 H); 3.64 (*dd*, *J* = 12.4, 12.2, 2 H); 5.12–5.21 (*m*, 1 H); 7.15–7.25 (*m*, 5 H). ^{13}C-NMR (125 MHz, $CDCl_3$): 21.1; 31.8; 52.6; 59.7; 60.1; 74.0; 127.1; 128.5; 128.8; 138.3; 170.8. HR-ESI-MS: 220.1336 (M^+, $C_{13}H_{18}N_2O^+$; calc. 220.1338).

*(3*R*)-1-(Phenylmethyl)pyrrolidin-3-ol* (**4**). To a soln. of **3a** (6.3 mmol; prepared above without further purification) in THF/MeOH 3:1 (10 ml), an aq. $LiOH \cdot H_2O$ soln. (0.5 mmol, 1 ml) was added and stirred for 2 h at 0°. The mixture was diluted with sat. aq. NH_4Cl soln. (20 ml) and extracted with $CHCl_3$ (3 × 60 ml), the extract dried (Na_2SO_4) and solvent concentrated, and the residue purified by CC (basic alumina, *ca.* 150 mesh): pure **4** (99%). Light yellow liquid. $[\alpha]_D^{25} = +3.68$ ($c = 5$, MeOH); 98% ee. ^{1}H-NMR (500 MHz, $CDCl_3$): 1.60–1.70 (*m*, 1 H); 2.0–2.4 (*m*, 1 H); 2.28–2.31 (*m*, 1 H); 2.50–2.64 (*m*, 2 H); 2.74–2.80 (*m*, 1 H); 2.89–2.93(*m*, 1 H); 3.60 (*s*, 2 H); 4.24–4.31 (*m*, 1 H); 7.20–7.32 (*m*, 5 H). ^{13}C-NMR (125 MHz, $CDCl_3$): 34.7; 52.4; 60.2; 62.8; 70.8; 127.2; 128.3; 128.7; 138.44. HR-ESI-MS: 178.1240 (M^+, $C_{11}H_{16}NO^+$; calc. 178.1232).

2-[(3-Chloropyrrolidin-1-yl)methyl]benzenamine (**7**). To a soln. of 3-chloro-3-deoxyvasicine (**6**; 1 g, 4.854 mmol; prepared as described in [30]) in MeOH/H_2O 1:1 (10 ml) was added $NaBH_4$ (0.58 g, 17 mmol) in small amounts within 1 h under continuous stirring. The mixture was stirred for an additional

hour and then extracted with CH_2Cl_2 (3×10 ml). The extract was dried (Na_2SO_4) and concenterated: **7** (99%). Light yellow semi-solid. ^{1}H-NMR (500 MHz, $CDCl_3$): 1.85–1.95 (*m*, 1 H); 2.30–2.44 (*m*, 1 H); 2.40–252 (*m*, 1 H); 2.68–2.80 (*m*, 2 H); 2.96–3.04 (*m*, 1 H); 3.60 (*dd*, *J* = 11.4, 10.2, 2 H); 4.28–4.34 (*m*, 1 H); 6.60–6.70 (*m*, 2 H); 7.00 (*d*, *J* = 8.4, 1 H); 7.10 (*t*, *J* = 7.0, 1 H). ^{13}C-NMR (125 MHz, $CDCl_3$): 37.0; 54.5; 54.1; 65.6; 73.4; 115.6; 117.8; 123.5; 128.3; 129.8; 146.4. HR-ESI-MS: 211.1008 (M^+, $C_{11}H_{16}ClN_2^+$; calc. 211.1002).

2-(Pyrrolidin-1-ylmethyl)benzenamine (**9**). As described for **7**; with 3-deoxyvasicine (**8**; 0.5 g, 2.9 mmol; prepared as described in [31]), MeOH/H_2O 1:1 (10 ml), and $NaBH_4$ (0.35 g , 10 mmol); **9** (99%). Light yellow semi-solid. ^{1}H-NMR (400 MHz, $CDCl_3$): 1.64–1.72 (*m*, 2 H); 1.73–1.78 (*m*, 2 H); 3.11 (*t*, *J* = 6.4, 2 H); 3.46 (*t*, *J* = 6.9, 2 H); 3.67 (*s*, 2 H); 6.61–1.69 (*m*, 2 H); 7.15–7.25 (*m*, 2 H). ^{13}C-NMR (100 MHz, $CDCl_3$): 36.8; 38.2; 52.1; 58.9; 62.1; 115.8; 117.6; 123.4; 128.4; 129.8; 146.3. HR-ESI-MS: 177.1396 (M^+, $C_{11}H_{17}N_2^+$; calc. 177.1392).

REFERENCES

[1] A. F. M. Rizk, 'Naturally Occurring Pyrrolizidine Alkaloids', Ed. A. F. M. Rizk, CRC Press, Boca Raton, 1991, p. 1; S. G. Pyne, M. Tang, *Curr. Org. Chem*. **2005**, *9*, 1393.

[2] K. Tamazawa, H. Arima, T. Kojima, Y. Isomura, M. Okada, S. Fujita, T. Furuya, T. Takenaka, O. Inagaki, M. Terai, *J. Med. Chem*. **1986**, *29*, 2504.

[3] E. Rubinstein, *Chemotherapy* **2001**, *47*, Suppl. 3, 3–8; discussion 44-8.

[4] A. Graul, J. Castaner, *Drugs Future* **1996**, *21*, 1105.

[5] T. Nagahara, Y. Yokoyama, K. Inamura, S. Katakura, S. Komoriya, H. Yamaguchi, T. Hara, M. Iwamoto, *J. Med. Chem.* **1994**, *37*, 1200.

[6] T. Miyadera, Y. Sugimura, T. Hashimoto, T. Tanaka, K. Iino, T. Shibata, S. Sugawara, *J. Antibiot.* **1983**, *36*, 1034.

[7] H. Yonehara, H. Seto, S. Aizawa, T. Hidaka, A. Shimazu, N. Otake, *J. Antibiot.* **1968**, *21*, 369; M. M. Joullié, W.-R. Li, S.-Y. Han, *Heterocycles* **1993**, *36*, 359.

[8] X. Xie, Y. Chen, D. Ma, *J. Am. Chem. Soc.* **2006**, *128*, 16050.

[9] D. M. Flanagan, M. M. Joullié, *Heterocycles* **1987**, *26*, 2247.

[10] H. Iida, N. Yamazaki, C. Kibayashi, *J. Org. Chem.* **1987**, *52*, 1956; L. J. Liotta, B. Ganem, *Synlett* **1990**, 503; C. S. Pak, G. H. Lee, *J. Org. Chem.* **1991**, *56*, 112; T. Shibata, K. Iino, Y. Sugimura, *Heterocycles* **1986**, *24*, 1331; D. K. Thompson, C. N. Hubert, R. H. Wightman, *Tetrahedron* **1993**, *49*, 3827.

[11] Y. Tamaru, S. Kawamura, T. Bando, I. C. Tanaka, M. Hojo, Z. Yoshida, *J. Org. Chem.* **1988**, *53*, 5491; D. R. Williams, M. H. Osterhout, J. M. McGill, *Tetrahedron Lett.* **1989**, *30*, 1327; H. Takahata, Y. Banba, M. Tajima, T. Momose, *J. Org. Chem.* **1991**, *56*, 240.

[12] H. C. Brown, J. V. N. VaraPrasad, A. K. Gupta, *J. Org. Chem.* **1986**, *51*, 4296.

[13] A. Naylor, D. B. Judd, D. I. C. Scopes, A. G. Hayes, P. J. Birch, *J. Med. Chem.* **1994**, *37*, 2138; K. L. Bhat, D. M. Flanagan, M. M. Joullié, *Synth. Commun.* **1985**, *15*, 587; B. D. Harris, K. L. Bhat, M. M. Joullié, *Synth. Commun.* **1986**, *16*, 181.

[14] S. E. Denmark, M. E. Schnute, *J. Org. Chem.* **1994**, *59*, 4576.

[15] Z. Li, H.-J. Feiten, D. Chang, W. A. Duetz, J. B. van Beilen, B. Witholt, *J. Org. Chem.* **2001**, *66*, 8424.

[16] D. M. Hodgson, M. J. Fleming, Z. Xu, C. Lin, S. J. Stanway, *Chem. Commun*. **2006**, 3226.

[17] G. Christoph, C. Stratmann, I. Coldham, D. Hoppe, *Org. Lett.* **2006**, *8*, 4469.

[18] T. Mathieu, C. Francois, E.Gwilherm, *Tetrahedron Lett.* **2008**, *49*, 1175.

[19] N. Seido, Y. Okeda, H. Kumobayashi, to *Takasago Perfumery Co. Ltd.*, EP 0452143, 16.10.1991; K. Inoue, H. Kutsuki, J. Hasegawa, S. Takahashi, to *Kanegafuchi Chemical Ind.*, EP 0347818, 27.12.1989.

[20] A. Rives, Y. Génisson, V. Faugeroux, C. Zedde, C. Lepetit, R. Chauvin, N. Saffon, N. A. Abadie, S. Colié, T. Levade, M. Baltas, *Eur. J. Org. Chem.* **2009**, *15*, 2474.

[21] S. C. Taneja, M. A. Aga, B. Kumar, V. K. Sethi, S. S. Andotra, G. N. Qazi, US Pat. 2012101285, 26.04.2012.

[22] K. Pandita, M. S. Bhatia, R. K. Thappa, S. G. Agarwal, K. H. Dhar, C. K. Atal, *Planta Med.* **1983**, *48*, 81, and refs. cit. therein.
[23] M. K. Choudhury, *Naturwissenschaften* **1979**, *66*, 205; H. L. Bhalla, J. L. D'Cruz, C. K. Kokate, *Indian Drugs* **1982**, *20*, 16.
[24] K. Szulzewsky, J. Hohne, S. Johne, D. Groger, *J. Prakt. Chem.* **1976**, *318*, 463.
[25] B. S. Joshi, M. G. Newton, D. W. Lee, A. D. Barber, S. W. Pelletier, *Tetrahedron: Asymmetry* **1996**, *7*, 25.
[26] O. Mitsunobu, M. Yamada, *Bull. Chem. Soc. Jpn.* **1967**, *40*, 2380; O. Mitsunobu, M. Yamada, *Bull. Chem. Soc. Jpn*. **1967**, *40*, 935.
[27] M. P. Doyle, J. F. Dellaria, Jr., B. Siegfried, S. W. Bishop, *J. Org. Chem.* **1977**, *42*, 3494.
[28] S. C. Amendola, P. Onnerud, M. Kelly, P. Petillo, S. L. Sharp-Goldman, M. Binder, *J. Power Sources* **1999**, *84*, 130.
[29] D. R. Metha, J. S. Naravane, R. M. Desai, *J. Org. Chem.* **1963**, *28*, 445.
[30] E. Späth, E. Nikawitz, *Ber. Dtsch. Chem. Ges.* **1934**, *67B*, 45.
[31] T. P. Ghose, *Q. J. Indian Chem. Soc.* **1927**, *4*, 1.
[32] S. K. Chattopadhyay, G. D. Bagchi, P. D. Dwivedi, S. Srivastava, WO 03 080618, 02.10.2003.

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