An Efficient Enantioselective Entry to the Piperidino-Quinolizidine Ring System of Lupine Alkaloids by Means of *N*-Acyliminium Ion Initiated Cyclization Reactions

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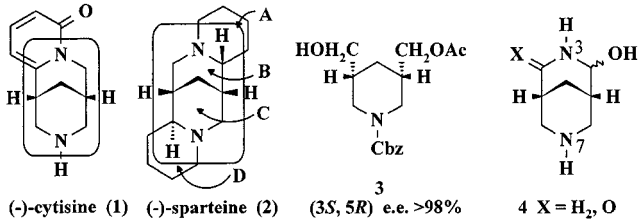
An efficient methodology for the enantioselective synthesis of the decahydro-1,5-methano-pyrido[1,2-*a*][1,5]diazocine skeleton found in tricyclic lupine alkaloids is described, starting from 3,5-disubstituted piperidines as chiral building blocks. Alkyne- or vinylsilane-terminated *N*-acyliminium ion cyclizations performed on appropriate 3,7-diazabicyclo[3.3.1]nonane derivatives allow for the highly stereoselective construction of piperidino-quinolizidine ring systems. A preliminary application of this methodology results in the synthesis of the quinolizidine alkaloid virgilidone.

Introduction

Lupine alkaloids, also called quinolizidines, constitute a large class of naturally occurring compounds widely distributed among various plant families,[1] such as the Leguminosae. As examples of their intriguing biological properties, we mention the activity of the tricyclic (−)-cytisine (**1**) as an agonist at the nicotinic receptor[2] and of some of its analogues as promising agents for the treatment of neurodegenerative deseases.[3] On the other hand, some of these structures have been attracting growing attention as chiral chelating bases, as can be seen by the broad use of the tetracyclic (−)-sparteine (**2**) in asymmetric deprotonations with alkyllithium agents.[4,5] As a consequence of these various possible applications, a considerable amount of attention has been focused on the syntheses of lupine alkaloids during the last few years, but, to the best of our knowledge, no enantioselective routes to tricyclic and tetracyclic systems have been published.[6]



(-)-cytisine (1) (-)-sparteine (2) **3** (3*S*, 5*R*) e.e. >98% 4 X = H_2, O

As part of our ongoing program concenring the enantioselective synthesis of natural nitrogen-containing compounds, we were interested in elaborating a short, efficient approach to the tricyclic core of quinolizidine alkaloids, in the optically active form, starting from the chiral *cis*-piperidine-3,5-dimethanol monoacetate (**3**). This compound, together with its enantiomer, is readily available by means of biocatalytic asymmetrization of the corresponding C_S-symmetric forms.[7] From a synthetic point of view, lupine alkaloids are usually regarded as quinolizidine-based structures, but, in our synthetic project, we preferred to single out another common feature, namely the presence of a chiral 3,7-diazabicyclo[3.3.1]nonane core, the so-called bispidine nucleus, on which one or two additional rings are fused. Recently,[8] we succeeded in developing a convenient enantioselective route to the highly functionalized 3,7-diazabicyclo[3.3.1]nonane derivatives **4**, as efficient precursors of chiral N^7-substituted-2-oxobispidines, representing the heterocyclic motif of a number of new pharmacologically active compounds that have been claimed to be cholinergic agents for the prevention and treatment of Alzheimer's disease.[9]

As an extension of our studies, we planned to apply an *N*-acyliminium ion initiated intramolecular cyclization to a suitable 3,7-diazabicyclo[3.3.1]nonane derivative, functionalized at N^3 with an appropriate tethered carbon π-nucleophile, as the key step to arrive at the piperidino-quinolizidine ring system. In this paper, we report an efficient elaboration of the C_1-symmetric piperidine **3** into the bicyclic N^3-substituted α-(hydroxy)lactams **5** and **6** (Scheme 1), and their conversion into the optically active piperidino-quinolizidines **7** and **8**, which represent the first advanced intermediates in the stereocontrolled synthesis of tricyclic lupine alkaloids.

The stereoselective cationic π-heterocyclization via *N*-acyliminium ions has been proven to be one of the most important methods for preparing nitrogen heterocycles.[10] In particular, the observed high versatility, also in the case of hindered substrates,[10a,11] together with the mild experimental conditions, made this procedure the method of choice in the synthesis of complex piperidine derivatives. At the onset of our studies, we selected the N^3-substituted chiral 3,7-diazabicyclo[3.3.1]nonanes **5** and **6**, as candidate sub-

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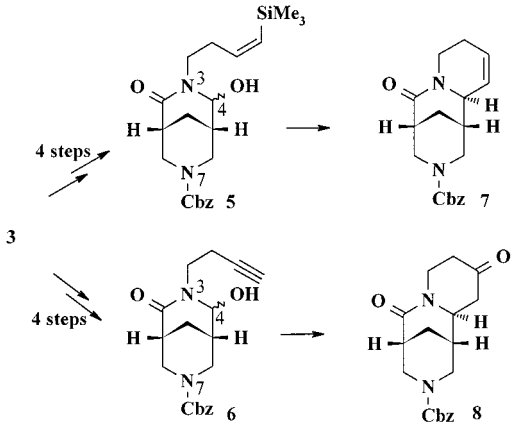


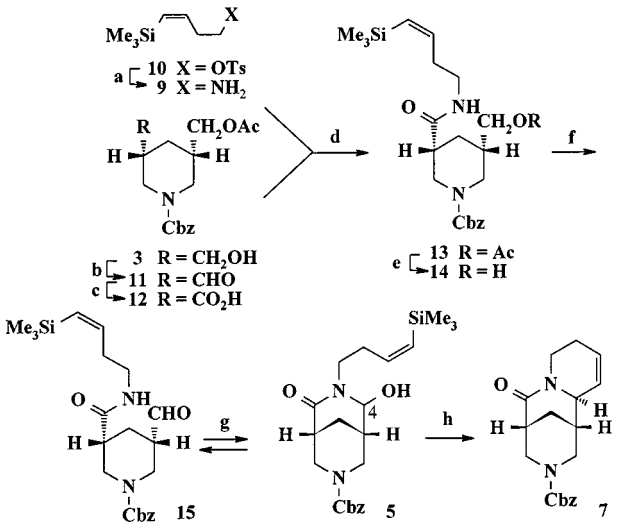
Scheme 1

strates, in which a tethered (*Z*)-vinylsilane and a terminal triple bond, respectively, were introduced as π-nucleophiles. The choice to use these alkenyl and alkynyl systems was prompted by the expectation that only the 6-*endo* type of cyclization would occur,[10b,10c,12,13] to give the azacyclic derivatives **7** and **8** regioselectively. Furthermore, although it was proposed[10b,10c,12] that the stereochemistry of the vinylsilane terminator would not be critical, in certain cases only the (*Z*)-vinyl isomer (as indicated in **5**) and not the (*E*)-vinyl isomer is described to undergo *N*-acyliminium-initiated cyclizations. A more important consideration which drove our strategy was that the bridgehead nature of **5** and **6** would prevent the formation of enamides from the intermediate *N*-acyliminium ions by the loss of a proton. This important side-reaction was reported[10a] to occur frequently in the case of intramolecular reactions of sterically hindered substrates to give dimeric structures. The question about the stereochemical outcome of the cyclization reactions (of **5** and **6**) remained to be addressed, although it was expected to occur predominantly from the less-hindered, convex, methylene bridgehead face of the bispidine nucleus to give ultimately a (6*S*) configuration (lupine alkaloids numbering) as indicated in structures **7** and **8**.

Results and Discussion

We began our investigation into the regio- and stereoselectivity of the cyclization reaction of compound **5** whose preparation is depicted in Scheme 2. The required (*Z*)-4-(trimethylsilyl)-3-buten-1-ylamine (**9**) was obtained in good yield, and 95% stereoisomeric purity, by aminolysis [excess NH_3(l)/THF, room temp.] of the readily available corresponding tosylate **10** in a sealed tube.[14]

Oxidation of the diol monoacetate **3** (98% *ee*) afforded the unstable aldehyde **11**, which instead of being purified, was used directly in the next step in order to preserve the stereochemical integrity at the C-3 carbon atom. Treatment with $KMnO_4$ in aqueous *t*BuOH in the presence of NaH_2PO_4 [15] provided the carboxylic acid **12** as a single stereoisomer (as shown by ^{1}H NMR spectroscopy) in 90% overall yield. Condensation of acid **12** with amine **9** using



Scheme 2. a) Excess NH_3(l)/THF, room temp. 63%; b) DMSO, $(COCl)_2$, NEt_3; then c) $KMnO_4$, *t*BuOH, NaH_2PO_4, 90%; d) HOBt, DCC, MeCN, 85%; e) NaOH, MeOH, 98%; f) Dess−Martin periodinane, CH_2Cl_2; then g) K_2CO_3, MeOH, 76%; h) TFA, 0 °C, 72%

DCC and HOBt (1-hydroxybenzotriazole) in MeCN gave 85% of amide **13**. Quantitative deacetylation of **13** with NaOH/MeOH was followed by oxidation of the resulting alcohol **14** with Dess−Martin periodinane to afford a separable 2.3:1 mixture of the aldehyde **15** and of the required cyclic tautomer **5**. The α-hydroxylactam **5** was obtained as a single stereoisomer.[16] Remarkably, when the above unseparated mixture was treated with K_2CO_3/MeOH,[17] **5** was isolated as the sole product in 76% yield from **14**.

With the desired (*Z*)-vinylsilane in hand, its *N*-acyliminium ion initiated cyclization was studied. This process proceeded smoothly by treatment of **5** in TFA for 2 h at 0 °C to provide the piperidino-quinolizidine **7** as the only isolated product in 72% yield. The structure of **7** was established by NMR spectroscopic analysis which demonstrated, to the limits of detection by 300-MHz ^{1}H NMR, that only a single (6*S*) stereoisomer was formed; the protons were assigned by COSY experiments. The stereochemistry of **7** was supported by NOE interactions between 6-H at δ = 4.02, 13e-H at δ = 4.16, and 2a-H at δ = 2.56 (Figure 1), and was confirmed by the negligible $J_{6,7}$ value which is indicative of an orthogonal nature of the C-6 (*S*) and C-7 (*S*) protons.

The formation of **7** as a single stereoisomer is consistent with *N*-acyliminium ion **16** undergoing cyclization only from the convex, sterically less hindered face of this bicyclo-[3.3.1]nonane intermediate, through a chair-like transition state, obeying the Stork−Eschenmoser hypothesis on olefin cyclization (Figure 1).[18] Apart from other conformational factors that could likely be involved,[19] this stereochemical outcome is presumably also due to the presence of the sterically demanding Cbz group, which is thought to block the *re* face of iminium group from attack by the π-nucleophile.

The synthesis of **6** followed a sequence similar to that described for **5** (Scheme 3). The amine **17**, prepared by means of a known procedure,[20] was treated with acid **12** in

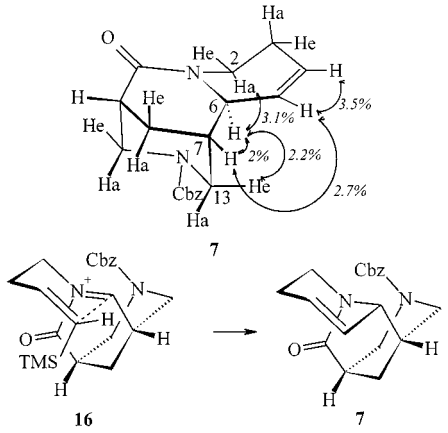
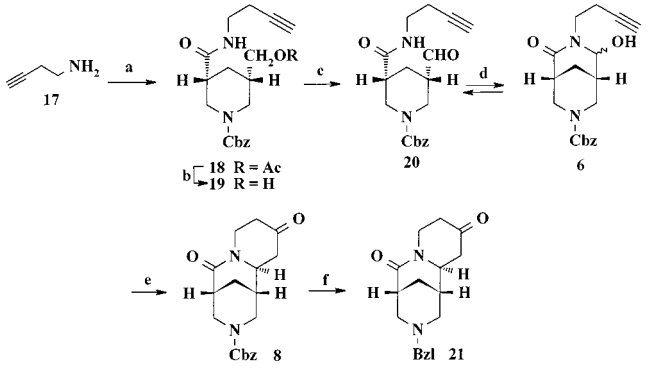


Figure 1. Selected NOE interactions detected by NOE difference studies (300 MHz, [D_6]DMSO, 50 °C) of **7** and proposed transition structure of *N*-acyliminium ion **16** for cyclization to **7**

the presence of DCC and HOBt in MeCN to give 80% of amide **18**. Quantitative deprotection of the acetate function of **18** with NaOH/MeOH followed by Dess−Martin periodinane oxidation of the alcohol **19** gave a separable 2:1 mixture of the aldehyde **20** and of the required bicyclic α-hydroxylactam **6**. Again, treatment of the above unseparated mixture with K_2CO_3/MeOH, yielded **6** in 78% from **19**.



Scheme 3. a) HOBt, DCC, MeCN, 80%; b) NaOH, MeOH, 98%; c) Dess−Martin periodinane, CH_2Cl_2; then d) K_2CO_3, MeOH, 78%; e) HCO_2H, 85 °C, 65%; f) H_2, Pd/C; then BzlBr, K_2CO_3, 70%

Iminium ion−acetylene cyclization was cleanly accomplished by treatment of amide **6** with formic acid[21] at 85 °C for 10 h, followed by hydrolysis, to provide tricyclic **8** in 65% yield. As was observed in the cyclization of **5**, only a single stereoisomeric cyclization product **8**, having the same 6,7-*trans* relative configuration, was produced from the precursor **6**.

No extraneous signals were detected in the NMR spectra of **8**. However, its stereochemistry could not be unambiguously determined from the ^{1}H NMR coupling constants and NOE experiments owing to the relative complexity of the spectrum in which broadening of most of the signals and some severe overlapping were observed. Straightforward conversion of **8** into the *N*-benzyl analogue **21** resulted in a more easily explainable ^{1}H NMR spectrum. Therefore, the stereochemistry of tricyclic **21** (and thus of **8**) was deduced from the observation of an almost negligible coupling (ca. 0.5 Hz) between 6-H (at δ = 3.39) and 7-H (at δ = 1.74). It was then confirmed by NOE interactions between 6-H and 2a-H (at δ = 2.84) and 13e-H (at δ = 2.77), and by the long-range (W) coupling between 6-H and 8a-H, observed in the COSY spectrum (Figure 2).

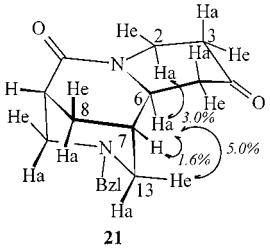
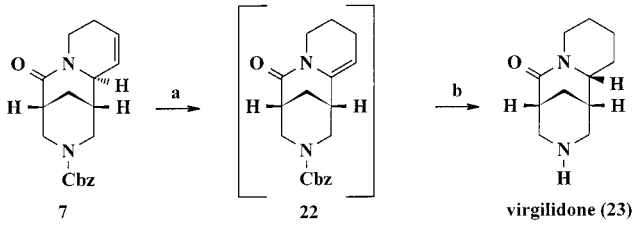


Figure 2. Selected NOE interactions detected by NOE difference studies (300 MHz, $CDCl_3$, 50 °C) of **21**

It is interesting to note here that reactions of **5** (and its 4-acetate) in the presence of Lewis acids (e.g. $BF_3{\cdot}Et_2O$, $ZnCl_2$, $TiCl_4$) were found to be capricious and inefficient, usually giving low yields of tricyclic **7**, accompanied by large amounts of unchanged material. A possible explanation of these unexpected results is that the presence of a Lewis acid promoter might drive the substrate to form a 1:1 complex in which the metal cation of the Lewis acid would prefer bidentate binding through N^3 and N^7 of the diazabicycle, thus preventing the formation of the planar *N*-acyliminium ion **16**. This point was not further examined, and the validity of our hypothesis remains to be established.

The azacycles **7** and **8** represent the first entry to chiral, nonracemic functionalized piperidino-quinolizidine platforms, which are substructures found in a number of biologically active quinolizidine alkaloids such as in the southern tricyclic part (BCD rings) of (−)-sparteine (**2**) or in aromatized piperidino-quinolizidine alkaloids such as (−)-cytisine (**1**). In addition, these adducts incorporate diverse functionalities which can be selectively manipulated. In order to expand the versatility of our approach, a particularly noteworthy transformation was effected, namely the complete inversion of configuration at the C-6 stereogenic centre, which allowed for the same 6,7-*cis* relationship found in natural tricyclic, nonaromatized, lupine alkaloids and in the northern tricyclic part (ABC rings) of (−)-sparteine (Scheme 4) to be set up.



Scheme 4. a) Pd/C, THF/NEt_3, 120 °C; then b) Pd/C, H_2, EtOH, 65%

Heating of **7** with Pd/C and NEt_3/THF[22] in a sealed tube resulted in the almost quantitative migration of the double bond to give the unstable enamide **22**, which rapidly became coloured when opened to air. Thus, this enamide

was not isolated but immediately hydrogenated in the presence of Pd on carbon to give the dihydro derivative **23**, with the (6*R*) configuration, as a single diastereoisomer in 65% overall yield. The expected stereoselective reduction of the C-5−C-6 double bond, with the concomitant deprotection of the amino group, allowed us to achieve an enantioselective synthesis of virgilidone **23**,[23] a quinolizidine alkaloid recently isolated from genus *Virgilia*, within the family Leguminosae.

Conclusions

In summary, an efficient route to chiral, nonracemic functionalized piperidino-quinolizidine platforms is detailed, involving an alkyne- or vinylsilane-terminated *N*-acyliminium ion cyclization as the key step. A first application of this methodology to the enantioselective synthesis of a lupine alkaloid is also described. The obtained results lay the groundwork for exploring the preparation of tricyclic structural analogues of sparteine, which could be envisaged as potential chiral ligands, with either the possible 6,7-*cis* or -*trans* relationships. It should be noted that the availability of both the enantiomeric forms (**3** and *ent*-**3**) of the chiral building block *cis*-piperidine-3,5-dimethanol monoacetate[7b] would allow for an access these systems as both antipodes, giving the possibility of overcoming the synthetic limitation of sparteine, which is readily available only as its (−) enantiomer. Further work is in progress in order to expand the utility of our approach.

Experimental Section

General: All solvents were distilled and thoroughly dried, when necessary, prior to use. − During usual workup, all organic extracts were dried (Na_2SO_4 or $MgSO_4$) and concentrated. − All reactions were monitored by thin-layer chromatography (TLC) on precoated silica gel 60 F_{254} (Merck); spots were visualized with UV light or by treatment with 1% aqueous $KMnO_4$ solution. Products were purified by flash chromatography (FC) on Merck silica gel 60 (230−400 mesh). − IR spectra of $CHCl_3$ solutions were recorded with a Perkin−Elmer 681 instrument. − ^1H and ^{13}C NMR spectra were recorded with Bruker AC 200 (^{1} H, 200 MHz; ^{13}C, 50.2 MHz) or AC 300 (^{1} H, 300 MHz; ^{13}C, 75.4 MHz) spectrometers in $CDCl_3$ solutions (unless otherwise stated) with TMS as internal standard. − Optical rotations were measured with a Perkin−Elmer 241 polarimeter. − HR, EI (70 eV) and FAB mass spectra in the positive mode, were measured with a VG 70-70 EQ-HF instrument, equipped with its standard sources.

(*Z*)-4-(Trimethylsilyl)-3-buten-1-ylamine (9): Liquid ammonia (12 mL) was added to a cooled (−50 °C) solution of **10**[14] (3.08 g, 10.33 mmol) in THF (16 mL) and the resulting mixture was kept at room temperature in a sealed tube for 24 h. The solvent was evaporated, and the crude oil was distilled under reduced pressure to provide the desired (*Z*)-4-trimethylsilyl-3-buten-1-ylamine (**9**) (928 mg, 63%). − ^1H NMR (300 MHz): δ = 6.28 (dt, 1 H, *J* = 14.1 Hz, 7.5 Hz, 2-CH), 5.62 (d, 1 H, *J* = 14.1 Hz, 1-CH), 2.78 (br. d, 2 H, *J* = 6.7 Hz, 4-CH_2), 2.28 (br. dt, 2 H, *J* = 7.5, 6.7 Hz, 3-CH_2), 1.41 (br. m, 2 H, NH_2), 0.15 (s, 9 H, −SiCH). − HRMS; *m*/*z*: calcd. for $C_7H_{17}NSi$ 143.1130, found 143.1115.

(3*R*,5*S*)-5-(Acetoxymethyl)-1-(benzyloxycarbonyl)piperidine-3-carboxylic Acid (12): Dimethyl sulfoxide (1.27 mL, 18 mmol) in CH_2Cl_2 (50 mL) was added to a stirred solution of oxalyl chloride (1.01 mL, 11.8 mmol) in CH_2Cl_2 (150 mL) at −65 °C, and the solution was stirred for 15 min. After the addition of a solution of **3**[7b] (2.89 g, 9 mmol) in CH_2Cl_2 (15 mL) at −60 °C within 5 min, the mixture was stirred for 15 min. After the addition of triethylamine (6.26 mL, 45 mmol), the mixture was stirred at the same temperature for 15 min, and then allowed to warm to room temperature. After being quenched with water, the mixture was extracted with CH_2Cl_2. The extract was washed with water, dried and concentrated to give aldehyde **11** as an oil (2.70 g).[7b] − To a solution of the above crude aldehyde **11** in *t*BuOH/phosphate buffer (pH = 7.2) (1.9:1, 102 mL) was added dropwise an aqueous solution of $KMnO_4$ (1 M, 51.3 mL, 51.3 mmol). The mixture was stirred at room temperature for 1 h, aqueous $NaHSO_3$ (5%) was added, and the resulting solution was poured into cold HCl (1 N). After extraction with EtOAc (3 × 60 mL), workup and chromatographic purification by FC (AcOEt) gave the acid **12** as an amorphous solid in 90% overall yield. − $[\alpha]_D^{20} = -7.5$ (*c* = 1, $CHCl_3$). − IR ($CHCl_3$): $\tilde{\nu}$ = 1780, 1725 cm^{-1}. − ^1H NMR (300 MHz, $CDCl_3$, 50 °C): δ = 7.35 (m, 5 H, arom.), 5.12 (s, 2 H, benzyl-H_2), 4.46 (br. d, 1 H, *J* = 12.7 Hz, 2-CH_{eq}), 4.28 (br. d, 1 H, *J* = 12.7 Hz, 6-CH_{eq}), 3.98 (dd, 1 H, *J* = 12.0, 5.5 Hz, CHOAc), 3.90 (dd, 1 H, *J* = 12.0, 6.7 Hz, CHOAc), 2.79 (t, 1 H, *J* = 12.7 Hz, 2-CH_{ax}), 2.46 (t, 1 H, *J* = 12.7 Hz, 6-CH_{ax}), 2.18 (br. d, 1 H, *J* = 12.4 Hz, 4-CH_{eq}), 2.03 (s, 3 H, OAc), 1.91 (m, 2 H, 3-CH/5-CH), 1.37 (q, 1 H, *J* = 12.4 Hz, 4-CH_{ax}). − ^{13}C NMR ($CDCl_3$, 75.4 MHz): δ = 177.5, 170.9, 155.1, 136.4, 128.5, 128.1, 127.9, 67.5, 65.9, 46.7, 45.4, 40.9, 35.0, 30.3, 20.7. − EI-MS; *m*/*z*: (relative intensity): 335 (28) $[M]^+$, 275 (54), 232 (100). − $C_{17}H_{21}N_1O_6$ (335.1): calcd. C 60.88, H 6.32, N 4.18; found C 60.95, H 6.47, N 4.05.

Benzyl (3*R*,5*S*)-5-Acetoxymethyl-3-{[(*Z*)-1-trimethylsilyl-1-buten-4-yl]carbamoyl}piperidine-1-carboxylate (13): A mixture of **9** (69 mg, 0.48 mmol), **12** (161 mg, 0.48 mmol), DCC (109 mg, 0.53 mmol), and HOBt (65 mg, 0.48 mmol) in CH_3CN (5 mL) was stirred at 25 °C for 12 h. The mixture was filtered, and the filtrate was concentrated to dryness. The residue was purified by FC (50% EtOAc/hexane) to give **13** (187 mg, 85%) as an oil. − $[\alpha]_D^{20} = -7.3$ (*c* = 1, $CHCl_3$). − IR ($CHCl_3$): $\tilde{\nu}$ = 1730, 1684 cm^{-1}. − ^1H NMR (300 MHz, $CDCl_3$, 50 °C): δ = 7.34 (m, 5 H, arom.), 6.23 (dt, 1 H, *J* = 13.5, 7.2 Hz, $Me_3SiCH{=}CH$), 5.66 (d, 1 H, *J* = 13.5 Hz, Me_3SiCH), 5.48 (m, 1 H, NH), 5.18 and 5.09 (AB system, 2 H, *J* = 12.5 Hz, benzyl-H_2), 4.27 (m, 2 H, 2-CH_{eq}/6-CH_{eq}), 3.98 (dd, 1 H, *J* = 11.4, 5.7 Hz, CHOAc), 3.89 (dd, 1 H, *J* = 11.4, 6.6 Hz, CHOAc), 3.30 (m, 2 H, $-CONHCH_2$), 2.87 (br. t, 1 H, *J* = 12.5 Hz, 2-CH_{ax}), 2.51 (br. t, 1 H, *J* = 12.5 Hz, 6-CH_{ax}), 2.33 (m, 2 H, $-CONHCH_2CH_2$), 2.20 (m, 1 H, 3-CH), 2.03 (s, 3 H, OAc), 1.92 (br. d, 1 H, *J* = 13.0 Hz, 4-CH_{eq}), 1.85 (m, 1 H, 5-CH), 0.14 (s, 9 H, −SiCH). − ^{13}C NMR ($CDCl_3$, 75.4 MHz): δ = 172.0, 170.8, 155.1, 144.4, 136.4, 132.6, 128.5, 128.1, 127.9, 67.2, 67.5, 65.9, 46.7, 46.4, 43.3, 38.9, 38.0, 34.9, 33.2, 20.7, 0.13. − FAB^+MS; *m*/*z*: 461 $[MH^+]$. − $C_{24}H_{36}N_2O_5Si$ (460.2): calcd. C 62.64, H 7.89, N 6.09; found C 62.78, H 7.80, N 6.21.

Benzyl (3*R*,5*S*)-5-Hydroxymethyl-3-{[(*Z*)-1-trimethylsilyl-1-buten-4-yl]carbamoyl}piperidine-1-carboxylate (14): To a solution of the acetate **13** (161 mg, 0.35 mmol) in MeOH (8 mL), a solution of NaOH (1.0 M, 0.7 mL) was added, and the mixture was stirred at room temperature until TLC (70% EtOAc/hexane) indicated that no substrate **13** remained (24 h). The reaction mixture was

quenched by the addition of saturated aqueous NH_4Cl (10 mL). A standard workup with EtOAc extraction and brine washing gave **14** (143 mg, 98%) as a colorless thick oil. − $[\alpha]_D^{20}$= + 11.9 (*c* = 1, $CHCl_3$). − IR ($CHCl_3$): $\tilde{\nu}$ = 1725, 1680 cm^{-1}. − ^1H NMR (300 MHz, $CDCl_3$, 50 °C): δ = 7.35 (m, 5 H, arom.), 6.20 (dt, 1 H, *J* = 13.7, 7.5 Hz, $Me_3SiCH{=}CH$), 5.64 (d, 1 H, *J* = 13.7 Hz, Me_3SiCH), 5.59 (m, 1 H, NH), 5.12 (s, 2 H, benzyl-H_2), 4.21 (m, 2 H, 2-CH_{eq}/6-CH_{eq}), 3.51 (d, 2 H, *J* = 6.3 Hz, CH_2OH), 3.29 (m, 2 H, $CONHCH_2$), 2.97 (br. t, 1 H, *J* = 12.5 Hz, 2-CH_{ax}), 2.51 (m, 1 H, 6-CH_{ax}), 2.30 (m, 2 H, $CONHCH_2CH_2$), 2.25 (m, 1 H, 3-CH), 1.94 (br. d, 1 H, *J* = 12.8 Hz, 4-CH_{eq}), 1.74 (m, 1 H, 5-CH), 0.13 (s, 9 H, SiCH). − ^{13}C NMR ($CDCl_3$, 75.4 MHz): δ = 172.8, 155.0, 144.5, 136.6, 132.4, 128.5, 128.0, 127.7, 67.2, 64.8, 46.9, 46.6, 43.1, 39.1, 38.3, 38.1, 33.2, 0.17. − FAB^+MS; *m*/*z*: 419 [MH^+]. − EI-HRMS for $C_{22}H_{34}N_2O_4Si$: calcd. 418.2288; found 418.2302. − $C_{24}H_{36}N_2O_5Si$ (418.2): calcd. C 68.93, H 8.68, N 6.70; found C 68.82, H 8.78, N 6.73.

(1*R*,4ξ,5*S*)-7-Benzyloxycarbonyl-4-hydroxy-3-[(*Z*)-1-trimethylsilyl-1-buten-4-yl]-3,7-diazabicyclo[3.3.1]nonan-2-one (5) and Benzyl (3*R*,5*S*)-5-Formyl-3-{[(*Z*)-1-trimethylsilyl-1-buten-4-yl]carbamoyl} piperidine-1-carboxylate (15): To a solution of **14** (150 mg, 0.36 mmol) in dry dichloromethane (3 mL) was added Dess−Martin reagent (183 mg, 0.43 mmol). The reaction mixture was stirred at room temperature for 20 h. After dilution with EtOAc (20 mL), water (10 mL) was added. The organic layer was separated, washed with aqueous $NaHCO_3$ and brine, dried and concentrated. The residue was purified by FC (60% EtOAc/hexane) to give the aldehyde **15** (92 mg, 62%) and **5** (40 mg, 26%), both as an oil. − **15:** IR ($CHCl_3$): $\tilde{\nu}$ = 2720, 1725, 1670 cm^{-1}. − ^1H NMR (300 MHz, $CDCl_3$, 50 °C): δ = 9.70 (s, 1 H, CHO), 7.37 (m, 5 H, arom.), 6.19 (dt, 1 H, *J* = 14.5, 7.5 Hz, $Me_3SiCH{=}CH$), 5.65 (d, 1 H, *J* = 14.5 Hz, Me_3SiCH), 5.13 (s, 2 H, benzyl-H_2), 4.15 (m, 2 H, 2-CH_{eq}/6-CH_{eq}), 3.29 (m, 2 H, $-CONHCH_2$), 2.98 (m, 2 H, 2-CH_{ax}/6-CH_{ax}), 2.42 (m, 1 H, 5-CH), 2.28 (m, 4 H, $CONHCH_2CH_2$/3-CH/4-CH_{eq}), 0.13 (s, 9 H, SiCH). − ^{13}C NMR ($CDCl_3$, 75.4 MHz): δ = 200.6, 171.5, 155.1, 144.3, 142.6, 136.3, 132.7, 128.5, 128.2, 128.0, 67.6, 47.7, 46.3, 43.4, 42.5, 39.0, 36.3, 33.2, 0.17. − FAB^+MS; *m*/*z*: 417 [MH^+]. − EI-HRMS for $C_{22}H_{32}N_2O_4Si$: calcd. 416.2131; found 416.2124. − **5:** − IR ($CHCl_3$): $\tilde{\nu}$ = 1725, 1660 cm^{-1}. − ^1H NMR (300 MHz, $CDCl_3$, 50 °C): δ = 7.35 (m, 5 H, arom.), 6.25 (dt, 1 H, *J* = 14.7, 7.5 Hz, $Me_3SiCH{=}CH$), 5.57 (d, 1 H, *J* = 14.7 Hz, Me_3SiCH), 5.14 and 5.00 (AB system, 2 H, *J* = 12.5 Hz, benzyl-H_2), 4.98 (m, 1 H, 4-CH), 4.50 (br. d, 1 H, *J* = 13.5 Hz, 8-CH_{eq}), 4.41 (br. d, 1 H, *J* = 13.3 Hz, 6-CH_{eq}), 3.41 (m, 2 H, $CONHCH_2$), 3.10 (br. d, 1 H, *J* = 13.5 Hz, 8-CH_{ax}), 2.92 (br. d, 1 H, *J* = 13.3 Hz, 6-CH_{ax}), 2.55 (m, 1 H, 1-CH), 2.30 (m, 2 H, $CONHCH_2CH_2$), 2.23 (m, 1 H, 5-CH), 2.12 (br. d, 1 H, *J* = 12.5 Hz, 9-CH), 1.92 (br. d, 1 H, *J* = 12.5 Hz, 9-CH), 0.17 (s, 9 H, SiCH). − FAB^+MS; *m*/*z*: 417 [MH^+]. − $C_{22}H_{32}N_2O_4Si$ (416.2): calcd. C 63.49, H 7.75, N 6.73; found C 63.55, H 7.81, N 6.76. − In a separate experiment, anhydrous K_2CO_3 (26 mg) was added to a solution of the above unseparated 2.3:1 mixture of compounds **15** and **5** (80 mg, 0.19 mmol) in methanol (4 mL). The resulting solution was heated at refluxed for 1 h, by which time all starting material had been consumed (TLC control, EtOAc). Evaporation of the solvent and FC (EtOAc) of the residue, gave **5** (69 mg, 76% yield from **14**) as the only isolated product.

Piperidino-Quinolizidine 7: Compound **5** (150 mg, 0.36 mmol) was dissolved in trifluoroacetic acid (5 mL) at 0 °C, and the reaction mixture was stirred at the same temperature for 6 h. The solvent was removed in a rotary evaporator, and the residue was poured carefully into a saturated aqueous solution of sodium hydrogen carbonate (10 mL) and the product was extracted into EtOAc (2 × 5 mL). After usual workup, the residue was purified by FC (EtOAc) to give the title compound **7** (85 mg, 72%) as a foam. − $[\alpha]_D^{20}$ = + 13.0 (*c* = 1.5, $CHCl_3$). − IR ($CHCl_3$): $\tilde{\nu}$ = 1725, 1660 cm^{-1}. − ^1H NMR (300 MHz, [D_6]DMSO, 80 °C): δ = 7.35 (m, 5 H, arom.), 5.86 (m, 1 H, 4-CH), 5.59 (br. d, 1 H, *J* = 10.2 Hz, 5-CH), 5.08 (m, 2 H, benzyl-H_2), 4.51 (dd, 1 H, *J* = 12.5, 6.0 Hz, 2-CH_{eq}), 4.22 (br. d, 1 H, *J* = 12.5 Hz, 11-CH_{eq}), 4.16 (br. d, 1 H, *J* = 12.5 Hz, 13-CH_{eq}), 4.02 (m, 1 H, 6-CH), 3.08 (dd, 1 H, *J* = 12.5, 2.4 Hz, 11-CH_{ax}), 3.04 (dd, 1 H, *J* = 12.5, 3.0 Hz, 13-CH_{ax}), 2.56 (dt, 1 H, *J* = 12.5, 4.4 Hz, 2-CH_{ax}), 2.45 (m, 1 H, 9-CH), 2.18 (m, 1 H, 3-CH), 2.08 (m, 1 H, 7-CH), 1.96 (m, 1 H, 3-CH), 1.86 (dm, 1 H, *J* = 13.0 Hz, 8-CH), 1.77 (dt, 1 H, *J* = 13.0, 3.0 Hz, 8-CH). − ^{13}C NMR ($CDCl_3$, 75.4 MHz): δ = 130.0, 128.2, 127.6, 66.6, 59.4, 49.8, 45.8, 40.4, 38.2, 33.3, 29.2, 25.1. − FAB^+MS; *m*/*z*: 327 [MH^+]. − EI-HRMS for $C_{19}H_{22}N_2O_3$: calcd. 326.1630; found 326.1651. − $C_{19}H_{22}N_2O_3$ (326.2): calcd. C 69.96, H 6.80, N 8.59; found C 70.02, H 6.70, N 8.45.

Benzyl (3*R*,5*S*)-5-Acetoxymethyl-3-[(3-butynyl)carbamoyl]piperidine-1-carboxylate (18): The reaction of **12** (330 mg, 0.98 mmol) with 3-butynamine (**17**) (68 mg, 0.98 mmol) in the presence of DCC (222 mg, 1.08 mmol), and HOBt (133 mg, 0.98 mmol), led to the formation of compound **18** (302 mg, 80%) as an oil, applying the procedure described above for compound **13**. − $[\alpha]_D^{20}$ = −9.7 (*c* = 1, $CHCl_3$). − IR ($CHCl_3$): $\tilde{\nu}$ = 3340, 3277, 1730, 1697 cm^{-1}. − ^1H NMR (300 MHz, $CDCl_3$, 50 °C): δ = 7.34 (m, 5 H, arom.), 5.85 (m, 1 H, NH), 5.15 and 5.10 (AB system, 2 H, *J* = 12.5 Hz, benzyl-H_2), 4.28 (m, 2 H, 2-CH_{eq}/6-CH_{eq}), 3.99 (dd, 1 H, *J* = 11.3, 5.0 Hz, CHOAc), 3.89 (dd, 1 H, *J* = 11.3, 6.8 Hz, CHOAc), 3.38 (q, 2 H, *J* = 5.8 Hz, $CONHCH_2$), 2.88 (dd, 1 H, *J* = 13.3, 11.7 Hz, 2-CH_{ax}), 2.52 (br. t, 1 H, *J* = 12.5 Hz, 6-CH_{ax}), 2.38 (dt, 2 H, *J* = 3.2, 5.8 Hz, $CONHCH_2CH_2$), 2.27 (br. t, *J* = 12.5 Hz, 1 H, 3-CH), 2.03 (s, 3 H, OAc), 1.95 (m, 2 H, 4-CH_{eq}/C≡CH), 1.86 (m, 1 H, 5-CH), 1.52 (q, 1 H, *J* = 12.5 Hz, 4-CH_{ax}). − EI MS; *m*/*z*: 386 (9) [M^+], 344 (17), 333 (28), 290 (44), 279 (32), 251 (100). − $C_{21}H_{26}N_2O_5$ (386.2): calcd. C 65.31, H 6.79, N 7.25; found C 65.27, H 6.68, N 7.32.

Benzyl (3*R*,5*S*)-3-(3-Butynylcarbamoyl)-5-(hydroxymethyl)piperidine-1-carboxylate (19): This compound was prepared from acetate **18** (190 mg, 0.49 mmol) in 98% yield (165 mg) according to a procedure identical to that described above for **14**. − Colorless thick oil. − $[\alpha]_D^{20}$ = −14.0 (*c* = 1, $CHCl_3$). − IR ($CHCl_3$): $\tilde{\nu}$ = 1715, 1680 cm^{-1}. − ^1H NMR (300 MHz, $CDCl_3$, 50 °C): δ = 7.34 (m, 5 H, arom.), 6.25 (m, 1 H, NH), 6.00 (br. s, 1 H, OH), 5.13 (s, 2 H, benzyl-H_2), 4.21 (m, 2 H, 2-CH_{eq}/6-CH_{eq}), 3.48 (d, 2 H, *J* = 6.3 Hz, CH_2OH), 3.35 (q, 2 H, *J* = 6.2 Hz, $CONHCH_2$), 2.90 (dd, 1 H, *J* = 13.8, 10.5 Hz, 2-CH_{ax}), 2.56 (m, 1 H, 6-CH_{ax}), 2.36 (dt, 2 H, *J* = 3.0, 6.2 Hz, $CONHCH_2CH_2$), 2.29 (br. t, *J* = 12.5 Hz, 1 H, 3-CH), 1.97 (m, 2 H, 4-CH_{eq}/C≡CH), 1.72 (m, 1 H, 5-CH), 1.52 (q, 1 H, *J* = 12.5 Hz, 4-CH_{ax}). − ^{13}C NMR ($CDCl_3$, 75.4 MHz): δ = 170.8, 155.4, 136.3, 128.7, 128.5, 128.1, 83.5, 69.9, 68.1, 67.3, 47.5, 46.4, 44.3, 38.0, 35.0, 23.7, 19.3. − FAB^+MS; *m*/*z*: 345 [MH^+]. − $C_{19}H_{24}N_2O_4$ (344.2): calcd. C 66.30, H 7.03, N 8.14; found C 66.44, H 7.15, N 8.08.

(1*R*,4ξ,5*S*)-7-Benzyloxycarbonyl-3-(3-butyn-1-yl)-4-hydroxy-3,7-diazabicyclo[3.3.1]nonan-2-one (6) and Benzyl (3*R*,5*S*)-3-[(3-Butynyl)carbamoyl]-5-formylpiperidine-1-carboxylate (20): Dess−Martin reagent (272 mg, 0.64 mmol) was added to a solution of **19** (170 mg, 0.49 mmol) in dry dichloromethane (4 mL). The reaction mixture was stirred at room temperature for 20 h. After dilution with EtOAc (25 mL), water (13 mL) was added. The organic layer

was separated, washed with aqueous $NaHCO_3$ and brine, dried and concentrated. The residue was purified by FC (EtOAc) to give the aldehyde **20** (91 mg, 54%) as a thick oil and **6** (46 mg, 27%) as a white foam. − **20:** IR ($CHCl_3$): $\tilde{\nu}$ = 2728, 1725, 1670 cm^{-1}. − ^1H NMR (300 MHz, $CDCl_3$, 50 °C): δ = 9.62 (s, 1 H, CHO), 7.36 (m, 5 H, arom.), 6.01 (m, 1 H, NH), 5.14 (s, 2 H, benzyl-H_2), 4.37 (m, 1 H, 6-CH_{eq}), 4.24 (br. d, 1 H, *J* = 12.7 Hz, 2-CH_{eq}), 3.38 (q, 1 H, *J* = 6.3 Hz, $CONHCH_2$), 2.95 (dd, 1 H, *J* = 13.9, 10.2 Hz, 2-CH_{ax}), 2.89 (m, 1 H, 6-CH_{ax}), 2.43 (m, 1 H, 3-CH), 2.37 (dt, 2 H, *J* = 3.0, 6.2 Hz, $CONHCH_2CH_2$), 2.32 (m, 2 H, 5-CH/C≡CH), 2.24 (br. d, 1 H, *J* = 12.5 Hz, 4-CH_{eq}), 1.82 (q, 1 H, *J* = 12.5 Hz, 4-CH_{ax}). − ^{13}C NMR ($CDCl_3$, 75.4 MHz): δ = 200.6, 171.8, 155.1, 136.3, 128.5, 128.2, 128.0, 70.2, 67.6, 47.3, 46.3, 43.4, 42.4, 37.9, 27.7, 19.2. − FAB^+MS; *m/z*: 343 [MH^+]. − EI-HRMS for $C_{19}H_{22}N_2O_4$: calcd. 342.1580; found 342.1592. − **6:** IR ($CHCl_3$): $\tilde{\nu}$ = 1715, 1660 cm^{-1}. − ^1H NMR (300 MHz, $CDCl_3$, 50 °C): δ = 7.32 (m, 5 H, arom.), 5.12 and 5.02 (AB system, 2 H, *J* = 12.5 Hz, benzyl-H_2), 5.04 (m, 1 H, 4-CH), 4.51 (br. d, 1 H, *J* = 13.5 Hz, 8-CH_{eq}), 4.42 (br. d, 1 H, *J* = 13.3 Hz, 6-CH_{eq}), 4.39 (br. s, 1 H, OH), 3.59 (ddd, 1 H, *J* = 13.5, 8.7, 6.3 Hz, CONHCH), 3.41 (ddd, 1 H, *J* = 13.5, 9.0, 5.7 Hz, CONHCH), 3.11 (br. d, 1 H, *J* = 13.3 Hz, 6-CH_{ax}), 2.93 (dd, 1 H, *J* = 13.5, 2.5 Hz, 8-CH_{ax}), 2.57 (m, 1 H, 1-CH), 2.48 (m, 1 H, $CONHCH_2CH$), 2.38 (m, 1 H, $CONHCH_2CH$), 2.31 (t, 1 H, *J* = 1.8 Hz, C≡CH), 2.26 (m, 1 H, 5-CH), 2.13 (br. d, 1 H, *J* = 12.5 Hz, 9-CH), 1.93 (br. d, 1 H, *J* = 12.5 Hz, 9-CH). − FAB^+MS *m/z*: 343 [MH^+]. − $C_{19}H_{22}N_2O_4$ (342.2): calcd. C 66.69, H 6.48, N 8.19; found C 66.81, H 6.57, N 8.14. − In a separate experiment, anhydrous K_2CO_3 (52 mg) was added to a solution of the above unseparated 2:1 mixture of compounds **20** and **6** (130 mg, 0.38 mmol) in methanol (8 mL). The resulting solution was heated at reflux for 1 h, by which time all starting material had been consumed (TLC control, EtOAc). Evaporation of the solvent and FC (EtOAc) of the residue, gave **6** (125 mg, 78% yield from **19**) as the only isolated product.

Piperidino-Quinolizidine 8: Compound **6** (150 mg, 0.44 mmol) was dissolved in formic acid (2.2 mL), and the reaction mixture was stirred at 85 °C under a nitrogen for 36 h. The solvent was removed in a rotary evaporator, and the residue was poured carefully into a saturated aqueous solution of sodium hydrogen carbonate (20 mL) and the product was extracted into EtOAc (2 × 10 mL). After the usual workup, the residue was purified by FC (EtOAc) to give compound **8** (98 mg, 65%) as a foam. − $[\alpha]_D^{20}$ = − 4.2 (*c* = 1, $CHCl_3$). − IR ($CHCl_3$): $\tilde{\nu}$ = 1702, 1643 cm^{-1}. − ^1H NMR (300 MHz, [D_6]DMSO, 80 °C): δ = 7.32 (m, 5 H, arom.), 5.07 (s, 2 H, benzyl-H_2), 4.82 (dd, 1 H, *J* = 9.0, 4.3 Hz, 2-CH_{eq}), 4.43 (br. d, 1 H, *J* = 13.4 Hz, 11-CH_{eq}), 4.34 (br. d, 1 H, *J* = 13.4 Hz, 13-CH_{eq}), 3.60 (br. s, 1 H, 6-CH), 3.01 (br. d, 2 H, *J* = 13.8 Hz, 11-CH_{ax} and 13-CH_{ax}), 2.63 (br. s, 1 H, 9-CH), 2.37 (m, 5 H, 2-CH_{ax}, 3-CH_2, 5-CH_2), 2.23 (br. d, *J* = 13.6 Hz, 8-CH_{eq}), 1.84 (br. d, *J* = 13.6 Hz, 8-CH_{ax}), 1.77 (br. s, 7-CH). − ^{13}C NMR ($CDCl_3$, 75.4 MHz): δ = 205.7, 169.1, 136.5, 128.4, 128.0, 67.3, 58.8, 49.9, 47.8, 47.3, 40.7, 40.5, 38.1, 33.2, 25.1. − FAB^+MS; *m/z*: 343 [MH^+]. − EI-HRMS for $C_{19}H_{22}N_2O_4$: calcd. 342.1580; found 342.1565. − $C_{19}H_{22}N_2O_4$ (342.2): calcd. C 66.69, H 6.48, N 8.19; found C 66.80, H 6.31, N 8.14.

Piperidino-Quinolizidine 21: A solution of **8** (50 mg, 0.15 mmol) in EtOAc (2 mL) including Pd on carbon (10%, 5 mg) was shaken under hydrogen for 12 h. The catalyst was filtered off, and the solution was concentrated to dryness. The residue was dissolved in dioxane (2 mL), and K_2CO_3 (13 mg, 0.09 mmol) followed by BzlBr (27 mg, 0.16 mmol) were added. After being stirred at room temperature for 15 h, the reaction mixture was concentrated, the residue was poured into water and extracted with EtOAc, and the combined organic fractions were dried and concentrated. Flash chromatography of the residue gave **21** (31 mg, 70% yield) as a foam. − $[\alpha]_D^{20}$ = −5.3 (*c* = 1, $CHCl_3$). − IR ($CHCl_3$): $\tilde{\nu}$ = 1705, 1640 cm^{-1}. − ^1H NMR (300 MHz, $CDCl_3$, 50 °C): δ = 7.22 (m, 5 H, arom), 5.10 (ddd, 1 H, *J* = 13.0, 6.3, 2.7 Hz, 2-CH_{eq}), 3.39 (dd, 1 H, *J* = 12.5, 3.3 Hz, 6-CH), 3.59 and 3.30 (AB system, 2 H, *J* = 13.2 Hz, benzyl-H_2), 3.20 (br. dt, 1 H, *J* = 10.5, 1.5 Hz, 11-CH_{eq}), 2.84 (ddd, 1 H, *J* = 13.0, 11.2, 5.1 Hz, 2-CH_{ax}), 2.77 (br. d, 1 H, *J* = 10.2 Hz, 13-CH_{eq}), 2.64 (m, 1 H, 9-CH), 2.47 (m, 2 H, 3-CH_2), 2.29 (dd, 1 H, *J* = 10.5, 2.5 Hz, 11-CH_{ax}), 2.28 (m, 2 H, 5-CH_2), 2.18 (dd, 1 H, *J* = 10.2, 1.7 Hz, 13-CH_{ax}), 2.10 (br. d, 1 H, *J* = 12.9 Hz, 8-CH_{eq}), 1.74 (m, 1 H, 7-CH), 1.67 (dt, 1 H, *J* = 12.9, 2.8 Hz, 8-CH_{ax}). − ^{13}C NMR ($CDCl_3$, 75.4 MHz): δ = 207.1, 172.1, 138.2, 128.5, 128.4, 127.1, 62.1, 59.5, 58.7, 56.9, 48.1, 40.9, 40.5, 39.0, 34.0, 25.2. − FAB^+MS; *m/z*: 299 [MH^+]. − EI-HRMS for $C_{18}H_{22}N_2O_2$: calcd. 298.1681; found 298.1672.

Virgilidone (23): A mixture of **7** (50 mg, 0.15 mmol), Pd/C (10%, 5 mg) and THF/NEt_3 (8:2, 2 mL) was heated at 120 °C for 8 h in a sealed tube. After filtration, the solvent was evaporated under reduced pressure and the residue was dissolved in EtOH and hydrogenated in the presence of Pd/C (10%, 5 mg). After 12 h, the catalyst was filtered off and the solvent evaporated. Purification of the residue by FC (10% MeOH/CH_2Cl_2) gave **23** (20 mg, 65%) as a foam. − $[\alpha]_D^{20}$ = −4.1 (*c* = 1, $CHCl_3$). − IR ($CHCl_3$): $\tilde{\nu}$ = 1648 cm^{-1}. − ^1H NMR (300 MHz, $CDCl_3$, 50 °C): δ = 4.83 (dm, 1 H, *J* = 13.5 Hz, 2-CH_{eq}), 3.36 (ddd, 1 H, *J* = 11.4, 5.3, 2.5 Hz, 6-CH), 3.27 (br. d, 1 H, *J* = 13.5 Hz, 11-CH_{eq}), 3.20 (br. d, 1 H, *J* = 13.0 Hz, 13-CH_{eq}), 2.89 (dd, 1 H, *J* = 12.7, 2.7 Hz, 13-CH_{ax}), 2.78 (dd, 1 H, *J* = 13.4, 2.5 Hz, 11-CH_{ax}), 2.55 (br. s, 1 H, 9-CH), 2.44 (dt, 1 H, *J* = 12.9, 3.1 Hz, 2-CH_{ax}), 1.99 (br. d, 1 H, *J* = 5.5 Hz, 8-CH_{eq}), 1.93 (m, 1 H, 4-CH), 1.91 (dt, 1 H, *J* = 12.8, 2.6 Hz, 8-CH), 1.78 (m, 1 H, 7-CH), 1.76 (dm, 1 H, *J* = 10.1 Hz, 3-CH), 1.69 (dm, 1 H, *J* = 12.5 Hz, 5-CH_{eq}), 1.54 (dq, 1 H, *J* = 12.0, 3.5 Hz, 5-CH_{ax}), 1.49−1.40 (m, 2 H, 3-CH and 4-CH). − ^{13}C NMR ($CDCl_3$, 75.4 MHz): δ = 171.6, 59.8, 49.1, 47.3, 42.6, 39.8, 32.4, 30.3, 29.2, 25.5, 24.7. − FAB^+MS; *m/z*: 195 [MH^+]. − EI-HRMS for $C_{11}H_{18}N_2O$: calcd. 194.2888; found 194.2902.

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[1] For reviews on quinolizidine alkaloids, see: [1a] *The Alkaloids* (Ed.: G. A. Cordell), Academic Press Inc, **1995**, vol. 47, pp. 1−114. − [1b]J. P. Michael, *Nat. Prod. Rep* . **1997**, *14*, 21−41, and earlier references in this series.

[2] T. Schmeller, M. Sauerwein, F. Sporer, M. Wink, W. E. Muller, *J. Natural Products* **1994**, *57*, 1316−1319.

[3] B. T. O'Neill, PCT Int. Appl. WO98 18,798, **1998** [*Chem. Abstr.* **1998**, *119*, 4774k].

[4] For reviews, see: [4a] D. Hoppe, T. Hense, *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 2282−2316. − [4b] P. Beak, A. Basu, D. J. Gallagher, Y. S. Park, S. Thayumanavan, *Acc. Chem. Res.* **1996**, *29*, 552−560.

[5] For examples, see: [5a] J. Schwerdtfeger, D. Hoppe, *Angew. Chem. Int. Ed. Engl.* **1992**, *31*, 1505−1507. − [5b] A. R. Muci, K. R. Campos, D. A. Evans, *J. Am. Chem. Soc.* **1995**, *117*, 9075−9076. − [5c] M. D. Curtis, P. Beak, *J. Org. Chem.* **1999**, *64*, 2996−2997.

[6] [6a] N. Takatsu, M. Mocuchi, S. Ohmiya, H. Otomasu, *Chem. Pharm. Bull.* **1987**, *35*, 4991−4992. − [6b] H. Oynuma, S. Dan, H. Kakisawa, *J. Chem. Soc., Perkin Trans. 1* **1990**, 2593−2597. − [6c] H. Kubo, S. Ohmiya, I. Murakoshi, *Can. J. Chem.* **1994**, *72*, 214−217. − [6d] S. Fazylov, A. M. Gazaliev, L. M. Vlasova,

R. Z. Kasenov, *Zh. Obshch. Khim.* **1995**, *65*, 877 [*Chem. Abstr.* **1995**, *123*, 228605v]. – [6e] E. Marrière, J. Rouden, V. Tadino, M.-C. Lasne, *Org. Lett.* **2000**, *2*, 1121–1124.

[7] [7a] B. Danieli, G. Lesma, D. Passarella, A. Silvani, *Tetrahedron: Asymmetry* **1996**, *7*, 345–348. – [7b] B. Danieli, G. Lesma, D. Passarella, A. Silvani, *J. Org. Chem.* **1998**, *63*, 3492–3496.

[8] B. Danieli, G. Lesma, D. Passarella, A. Silvani, N. Viviani, *Tetrahedron* **1999**, *55*, 11871–11878.

[9] [9a] K. Kobayashi, K. Orita, A. Hamada, T. Inaba, H. Abe, S. Miyazaki, PCT Int. Appl. WO 96 30,372 [*Chem. Abstr.***1997**, *126*, 8107f]. – [9b] T. Inaba, H. Abe, S. Miyazaki, *Jpn. Kokai Tokkio Koho* JP 09, 255,679 [*Chem. Abstr.***1997**, *127*, 293136q].

[10] [10a] W. N. Speckamp, H. Hiemstra, *Tetrahedron* **1985**, *41*, 4367–4416. – [10b] T. A. Blumenkopf, L. E. Overman, *Chem Rev.* **1986**, *86*, 857–873. – [10c] C. Flann, T. C. Malone, L. E. Overman, *J. Am. Chem. Soc.* **1987**, *109*, 6097–6107. – [10d] D. J. Hart, in *Alkaloids: Chemical and Biological Perspectives* (Ed.: S. W. Pelletier), Wiley, New York, **1988**, vol. 6, chapter 3. – [10e]H. Hiemstra, W. N. Speckamp, *Alkaloids (N. Y.)* **1988**, *32*, 271. – [10f] W. N. Speckamp, M. J. Moolenaar, *Tetrahedron* **2000**, *24*, 3817–3856.

[11] B. P. Wijnberg, W. N. Speckamp, A. R. C. Oostveen, *Tetrahedron* **1982**, *38*, 209–217.

[12] L. E. Overman, T. C. Malone, G. P. Meier, *J. Am. Chem. Soc.* **1983**, *105*, 6993–6994.

[13] [13a] H. E. Schoemaker, Tj. Boer-Terpstra, J. Dijkink, W. N. Speckamp, *Tetrahedron* **1980**, *36*, 143–148. – [13b] H. Hiemstra, M. H. A. Sno, R. Vijn, W. N. Speckamp, *J. Org. Chem.* **1985**, *50*, 4014–4020.

[14] [14a] M. J. Brown, S. F. McCaan, L. E. Overman, *Org. Synth.* **1990**, *68*, 182–186. – [14b] C. J. Flann, T. C. Malone, L. E. Overman, *Org. Synth.* **1990**, *68*, 188–194.

[15] A. Abko, J. C. Robert, T. Takemasa, S. Masamune, *Tetrahedron Lett.* **1986**, *27*, 4537–4540.

[16] It was not possible to determine the configuration of the C-4 stereogenic centre of **5**, neither from the ^{1}H NMR coupling constants, nor from NOE experiments, due to the severe overlapping between the signals for 4-H and for the benzylic methylene proton signals at $\delta = 5.1–5.2$.

[17] Z. Sheikh, R. Stell, A. S. Tasker, P. Johnson, *J. Chem. Soc., Chem. Commun.* **1994**, 763–764.

[18] [18a] G. Stork, A. W. Burgstahler, *J. Am. Chem. Soc.* **1955**, *77*, 5068–5077 – [18b] A. Eschenmoser, L. Ruzicka, O. Jeger, D. Arigoni, *Helv. Chim. Acta* **1955**, *38*, 1890–1904 .

[19] T. Brukwicki, A. Przybyl, W. Wysocka, J. Sosnicki, *Tetrahedron* **1999**, *55*, 14501–14512.

[20] D. Perez, G. Burés, E. Guitian, L. Castedo, *J. Org. Chem.* **1996**, *61*, 1650–1654.

[21] W. G. Beyersbergen van Henegouwen, H. Hiemstra, *J. Org. Chem.* **1997**, *62*, 8862–8867.

[22] K. Th. Wanner, F. F. Paintner, *Tetrahedron* **1994**, *50*, 3113–3122.

[23] G. Veen, R. Greinwald, L. Witte, V. Wray, F.-C. Czygan, *Phytochemistry* **1991**, *30*, 1891–1895.

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