Pergamon

SCIENCE DIRECT®

Tetrahedron 59 (2003) 3359–3368

TETRAHEDRON

Asymmetric synthesis of a tricyclic core structure of the securinega alkaloids virosecurinine and allosecurinine

Rainer Kammler,[a] Kurt Polborn[b] and Klaus Th. Wanner[c,*]

[a]*Verla-Pharm Arzneimittel, Bernrieder-Str. 1, 82327 Tutzing, Germany*
[b]*Department of Chemistry, Ludwig-Maximilians-University of Munich, Butenandtstr. 5-13, 81377 Munich, Germany*
[c]*Department of Pharmacy, Ludwig-Maximilians-University of Munich, Butenandtstr. 5-13, 81377 Munich, Germany*

Received 31 January 2003; revised 25 February 2003; accepted 10 March 2003

Abstract—A concise asymmetric synthesis of tricyclic core structures of virosecurinine [(+)-**1**] and allosecurinine [(−)-**2**] is presented. An asymmetric electrophilic α-amidoalkylation reaction employing a chiral enamide gave access to enantiopure (*S*)-2-anisylpiperidine with the diastereoselectivity (d.s.) of 93/7. The latter was transformed into the target compounds, with the main steps involving a Birch-reduction followed by an ozonolysis of the resulting 1,4-cylohexadiene and a final spirocyclization reaction.

1. Introduction

The securinega alkaloids comprise a small group of about 20 tetracyclic compounds produced by plants of the genera *Securinega*, *Phyllantus*, *Margaritaria* and *Breynia*, which belong to the family Euphorbiaceae. They exhibit a unique ring skeleton composed of a 6-azabicyclo[3.2.1]octane moiety as a core structure [B/C in (−)-**1**], which in addition to an α,β-unsaturated-γ-lactone unit [see D in (−)-**1**][1] is either fused with a piperidine (securinine-type alkaloids; ring A in (−)-**1**) or with a pyrrolidine ring (for nor-securinine-type alkaloids). Securinine [(−)-**1**], the most abundant alkaloid of this group, was isolated first in 1956[2] and was structurally elucidated in the early 1960s.[3] Later on also the three stereoisomers of securinine [(−)-**1**]-virosecurinine [(+)-**1**] (enantiomer of securinine), allosecurinine [(−)-**2**] and viroallosecurinine [(+)-**2**]-were found in plants of the family Euphorbiaceae (Fig. 1).

The *Securinega* alkaloids show a great scope referring to their biological activity. In Russia, for example, securinine [(−)-**1**] has been used since 1968 as a CNS stimulating drug.[4] However, the mode of action of (−)-**1** as a drug was not uncovered before 1985, when it was found that securinine [(−)-**1**] acts as a competitive antagonist at the GABA binding site of the $GABA_A$-receptor complex.[5] Besides, also antibacterial[6] and antimalarial activity have been reported for this compound (−)-**1**.[7]

Despite the wide scope of biological activities of (−)-**1** no enantioselective synthesis has been described so far for this alkaloid, though a few total syntheses for the racemate of (−)-**1** are known.[8,9] This is surprising, as the securinine alkaloids (−)-**1**, (+)-**1**, (−)-**2** and (+)-**2** display distinct differences with respect to their pharmacological activity, with securinine [(−)-**1**] being the most potent isomer especially as a ligand of the GABA binding site of the $GABA_A$ receptor complex.

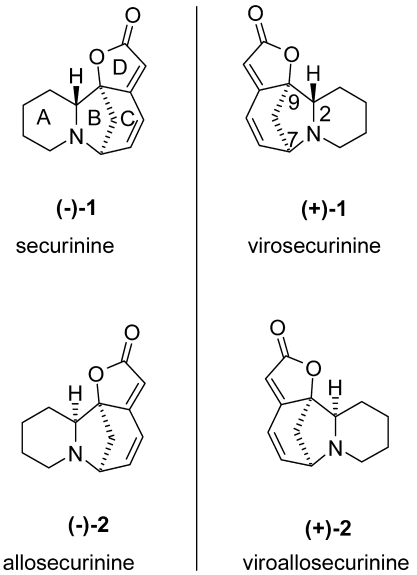


Figure 1.

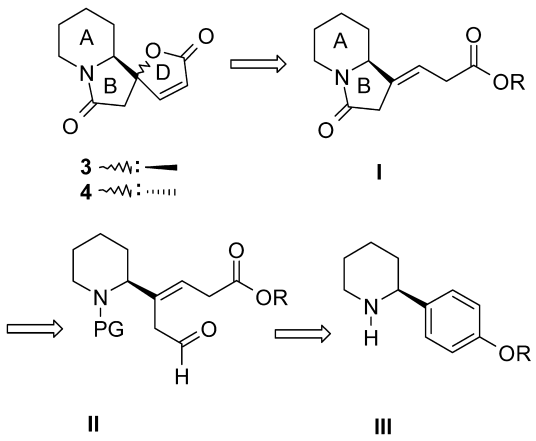
2. Synthetic strategy

The goal of this study was the development of an

Keywords: virosecurinine; allosecurinine; α-amidoalkylation.

* Corresponding author. Tel.: +49-89-2180-77249/77248; fax: +49-89-2180-77247; e-mail: klaus.wanner@cup.uni-muenchen.de

0040–4020/03/$ - see front matter
doi:10.1016/S0040-4020(03)00406-X



Scheme 1.

asymmetric synthesis giving access to compounds like **3** and **4** as substructures of the securinine alkaloids (−)-**1**, (+)-**1**, (−)-**2** and (+)-**2** comprising rings A, B and D of the aforementioned compounds. As a reasonable approach a strategy was envisaged where at first the stereocenter at C-2 of the piperidine ring is established, whereas the adjacent spirocyclic stereocenter is set up in an independent later step. In accord with the above concept and as outlined in Scheme 1 compounds like **III** appeared to be a suitable starting point for the synthesis of the desired compounds, e.g. **3** and **4**. Thus, the preparation of an enantiomerically pure piperidine derivative **III** appeared to be a key step in the overall synthesis. To this end the methyl derivative (*S*)-2-anisylpiperidine (**III**, R=Me) was selected.

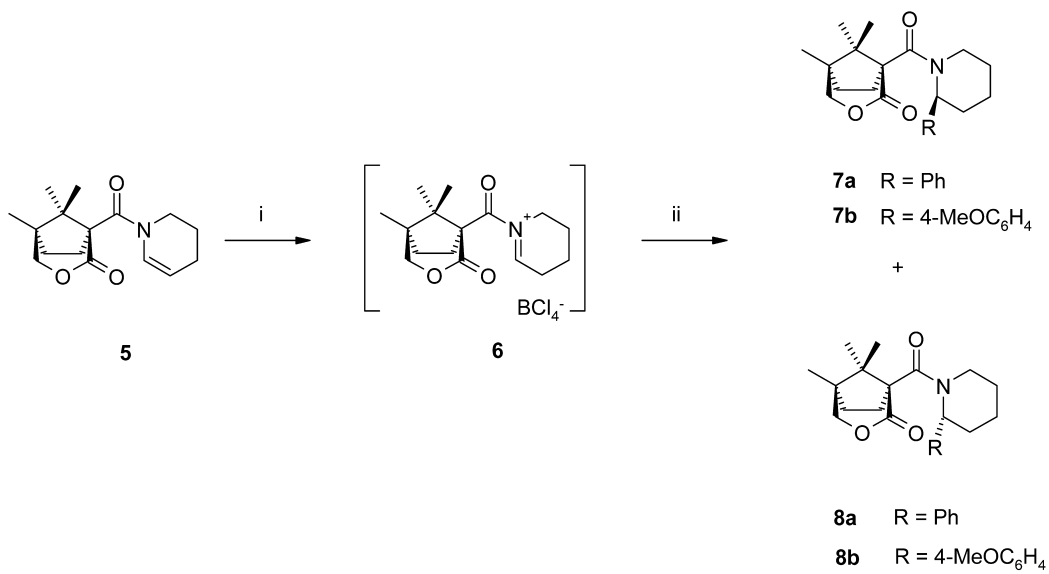
3. Results and discussion

3.1. Preparation of the (*S*)-2-anisylpiperidine [(*S*)-9b]

Among the methods currently available for the asymmetric synthesis of C-2 substituted piperidines the most intriguing with regard to simplicity and flexibility, are those which allow the introduction of the C-2-substituent in a stereocontrolled manner. Some time ago we reported on a cationic type of asymmetric synthesis involving chiral *N*-acyliminium ions provided with an *N*-acyl group as chiral auxiliary which we have termed Asymmetric Electrophilic α-Amidoalkylation (AEαA).[10] Enamide **5** shown in Scheme 2 represents an optimized reagent that we developed for the asymmetric synthesis of chiral piperidines by asymmetric electrophilic α-amidoalkylation reactions.[11] Especially, organomagnesium, organozinc and organoaluminum derivatives proved to be useful as trapping reagents for the *N*-acyliminium ions (e.g. **6**) derived from **5** which are formed during the course of the amidoalkylation reactions. The asymmetric induction is assumed to be the result of a coordination complex that might form from **6** by addition of the organometallic reagent to the lactone function of the chiral auxiliary.[11c]

In continuation of our interest in the exploration of **5** as an amidoalkylation reagent, we decided to employ enamide **5** also in this study, which seemed, of course, also well suited for a rapid and efficient access to the required 2-substituted piperidine derivative (*S*)-**9b**. Thus, for the synthesis of (*S*)-**9b** amidoalkylation reactions of **5** with organomagnesium and organozinc compounds derived from 4-bromoanisole were performed. For comparison purposes, in addition, also the synthesis of the basic phenyl derivative (*S*)-**9a** was studied. To accomplish the amidoalkylation reaction enamide **5** was first treated with HCl (in CH_2Cl_2 at −78°C). The reactive intermediate thus formed—most likely the corresponding α-chloroamide—was then trapped by addition of the appropriate organometallic reagent (see Table 1, entries 1, 2, 4 and 5). In a second set of experiments one equivalent of BCl_3[12] was added to the reaction mixture prior to the addition of the organometallic reagent, as it was speculated that this might improve the yields of the trapping reaction. The results obtained for these reactions are summarized in Table 1.

The reactions with the organomagnesium compounds proceeded with reasonable diastereoselectivities and



Scheme 2. *Reagents and conditions*: (i) (1) HCl/CH_2Cl_2, (2) BCl_3/*n*-heptane/−78°C; (ii) MR_n.

Table 1. Preparation of **7a/b** and **8a/b** by amidoalkylation reactions with **5**

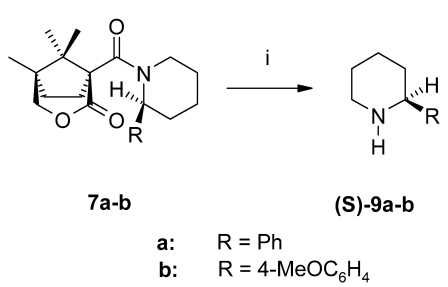
Entry	Product **7**+**8**	Reagent	Equiv.	Additive	d.s.[a] **7/8**	Yield (%) **7**+**8**
1	**a**	$PhMgBr$[b] (Et_2O)	1.1	–	88/12	47
2	**a**	$ZnCl_2$[c]/$PhMgBr$[b] (1.0/1.7 equiv.; Et_2O)	1.1	–	94/6	47
3	**a**	$ZnCl_2$[d]/$PhMgBr$[e] (1.0/1.7 equiv.; Et_2O/THF)	3.0	1.1 equiv. BCl_3	91/9	91
4	**b**	4-$MeOC_6H_4MgBr$[e] (THF)	3.0	–	85/15	74
5	**b**	$ZnCl_2$[c]/4-$MeOC_6H_4MgBr$[e] (1.0/2.0 equiv.; Et_2O/THF)	3.0	–	93/7	56
6	**b**	$ZnCl_2$[d]/4-$MeOC_6H_4MgBr$[e] (1.0/1.6 equiv.; Et_2O/THF)	2.5	1.1 equiv. BCl_3	93/7	99

[a] Determined by HPLC from the crude reaction product.
[b] 3.0 M in Et_2O.
[c] 1.0 M in Et_2O.
[d] 0.7 M in Et_2O.
[e] 1.0 M in THF.

mediocre to good yields (see Table 1, entries 1 and 4). With the organozinc species the diastereoselectivity could be significantly improved, whereas the yield remained unchanged or dropped (see Table 1 entry 2 and 5). The best results were finally seen for those reactions where in addition to the organozinc compound one equivalent of BCl_3 had been applied. Though in case of the phenylation reaction the diastereoselectivity slightly dropped (from 94/6 to 91/9), the yield rose to 91% (see Table 1, entry 3). The result obtained for the introduction of the 4-methoxyphenyl substituent was even more pleasing. In this case, the diastereoselectivity remained unchanged (**7b/8b**=93/7), whereas the yield became almost quantitative (99%, see Table 1 entry 6). We assume that with BCl_3 as an additive the α-chloroamide present in the reaction mixture is completely transformed to the corresponding *N*-acyliminium ion, thus giving rise to a highly efficient trapping reaction. In the absence of an extra Lewis acid the *N*-acyliminium ions most likely are formed by the organometallic reagent, which, however, seems to be less effective.

The mixture of diastereomers **7a/8a** and **7b/8b** resulting from the amidoalkylation reactions were finally separated by either preparative HPLC (**7a/8a**) or by flash chromatography (**7b/8b**) to give the single diastereomers in pure form. From these for the subsequent reactions only the major diastereomers **7a** and **7b** were used.

The next step involved the removal of the chiral auxiliary, which was accomplished by a reductive cleavage procedure. When $Na[AlH_2(OMe)_2]$ was employed, which turned out to be best suited for this purpose {2.0 equiv. $Na[AlH_2(OMe)_2]$, THF, −25°C}, the amines (*S*)-**9a** and (*S*)-**9b** were obtained in good to excellent yields of 65 and 92%, respectively (Scheme 3). In contrast, reagents like Red-Al®, $Na[AlH_4]$, $Na[AlH_2Et_2]$ and $Li[AlH_2(OMe)_2]$ gave far lower yields.

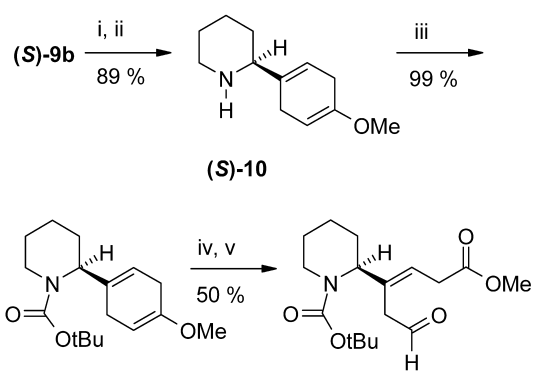


Scheme 3. *Reagents and conditions*: (i) $Na[AlH_2(OMe)_2]$, THF, −25°C, 24 h.

The stereochemistry of compound (*S*)-**9a** was established by comparison of the optical rotation of the hydrochloride of (*S*)-**9a** with the literature value reported for an authentic sample. For the hydrochloride of (*S*)-**9a** an optical rotation of $[\alpha]_D^{23}=+9.5°$ was found, indicating that this compound and consequently also the free amine (*S*)-**9a** must be of (*S*)-configuration {lit. value[13] for (*R*): $[\alpha]_D=-9.6°$}. The ^1H NMR spectra of the major diastereomer **7a** and the minor diastereomer **8a** of the phenyl adduct where found to be quite similar to those of the major diastereomer **7b** and minor diastereomer **8b** with a 4-methoxyphenyl substituent. Thus, the relative stereochemistry of **7a** and **7b** and **8a** and **8b**, respectively, should be the same. Accordingly and by taking into account that **7a** is the precursor of **9a** [with (*S*)-configuration] and **7b** the precursor of **9b**, the piperidine derivative **9b** must be of (*S*)-configuration as well.

3.2. Birch-reduction and ozonisation of (*S*)-9b

The next steps of our synthesis were directed towards the preparation of aldehyde (*S*)-**12** utilizing the anisylpiperidine (*S*)-**9b** as starting material, which had become available in enantiomerically pure form by the amidoalkylation reaction described above. The strategy we used was analogous to the one Corey et al. had applied as key steps in the synthesis of a juvenile hormone.[14] Thus, in the first step (*S*)-**9b** was subjected to a Birch-reduction whereupon the piperidine derivate (*S*)-**10** provided with a cyclohexadiene moiety was obtained (yield 89%). Protection of the amino function of (*S*)-**10** with a Boc-group lead to the carbamate (*S*)-**11**, which

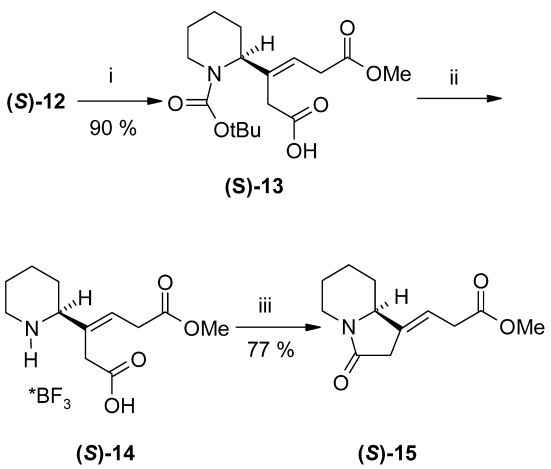


Scheme 4. *Reagents and conditions*: (i) Li, NH_3, Et_2O, −40°C; (ii) EtOH; (iii) MeCN, NE*t*iPr_2, $(Boc)_2O$, 25°C, 3 days; (iv) O_3, MeOH, −78°C, 2 h; (v) Me_2S.

finally upon ozonisation provided the desired aldehyde (*S*)-**12** in a reasonable yield (50%) (see Scheme 4).

3.3. Formation of lactam (*S*)-15

At next, according to our synthetic plan, (*S*)-**12** had to be transformed to the bicyclic lactam (*S*)-**15**. To this end (*S*)-**12** was subjected to an oxidation reaction with $NaClO_2$ (in *t*BuOH/phosphate-buffer) in the presence of 2-methyl-2-butene as chlorine-scavenger,[15] which provided the carboxylic acid (*S*)-**13** in 90% yield. Deprotection with $BF_3{\cdot}Et_2O$ in CH_2Cl_2[16] led to the γ-amino acid (*S*)-**14** as a BF_3 adduct. For convenience this was used for the subsequent cyclization reaction without further purification. Activation of the carboxylic acid function of (*S*)-**14** with Mukaiyama's reagent (2-chloro-1-methylpyridinium iodide)[17] finally initiated a clean cyclization reaction affording (*S*)-**15** in 77% yield (Scheme 5).

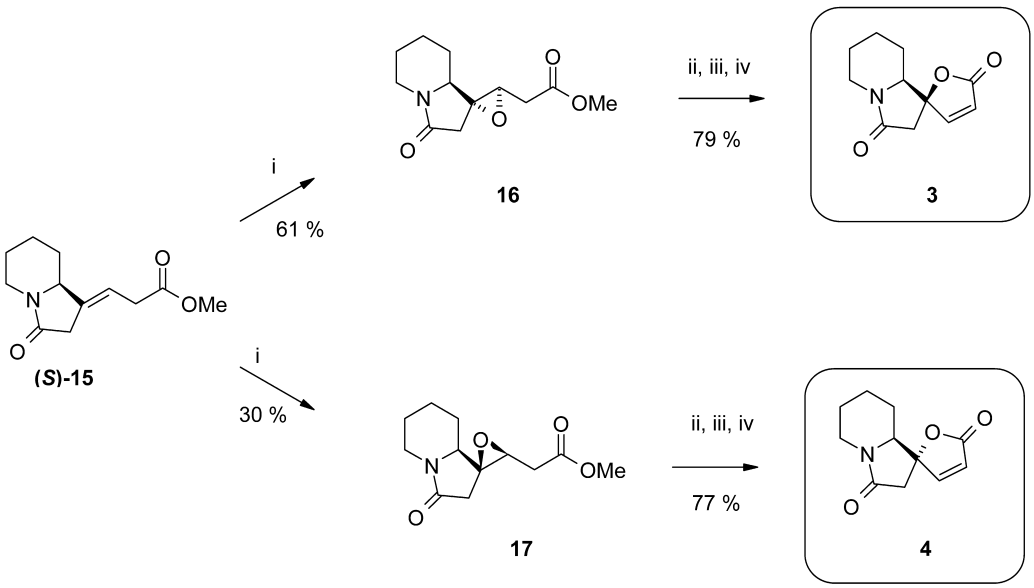


Scheme 5. *Reagents and conditions*: (i) $NaClO_2$, 2-methyl-2-butene, PO_4^{3-}-buffer (pH 7), *t*BuOH, 3 h; (ii) $BF_3{\cdot}Et_2O$, CH_2Cl_2, 30 min; (iii) 2-chloro-1-methylpyridinium iodide, $NEt{i}Pr_2$, CH_2Cl_2, 16 h.

3.4. Cyclization to the target-lactones 3 and 4

To establish the furan ring, the synthetic task still left to complete the synthesis of our target compounds, we followed a procedure put forth by Cory et al.[18] According to this procedure the bicyclic lactam (*S*)-**15** was first subjected to an epoxidation reaction with MCPBA in CH_2Cl_2 which resulted in the formation of the two diastereomeric epoxy derivatives **16** and **17**. Though the total yield was quite pleasing (91%) the diastereoselectivity amounted only to 2/1. Separation by flash chromatography provided the pure diastereomers for the final lactonization reaction. This cyclization was accomplished by first treating the diastereomers with TFA in CH_2Cl_2 (for 6 h at room temperature) and subsequently after removal of the solvent with TFAA and NEt_3. According to ^1H NMR spectroscopy with TFA only hydroxy lactones were formed, which then had to be treated with TFAA/NEt_3 to provide the unsaturated compounds. Presumably, the acid catalyzed ring opening of the oxirane moiety is facilitated by a neighboring-group effect arising from the ester function. This may finally lead to a stereocontrolled formation of the γ-lactone ring via inversion at the stereocenter being affected.[19] In support of this assumption from **16** only the diastereomer **3** and from **17** only diastereomer **4** was obtained, both in high yields (**3** 79%; **4** 77%; see Scheme 6).

The relative stereochemistry of the major cyclization product **3** was established by an X-ray analysis (Fig. 2). According to the result of this analysis and by taking into account that (*S*)-**9b** as a precursor to **3** was found to be of (*S*)-configuration the spirocyclic compound **3** must possess (1′*R*,8′a*S*)-stereochemistry. Hence compound **4** as a stereoisomer of **3** differing from the latter in the chirality of the spirocyclic carbon must be of (1′*S*,8′a*S*)-configuration. Thus, with the synthesis of **3** and **4** tricyclic substructures of the securinine-type alkaloids have been established with their stereochemistry corresponding to virosecurinine [(+)-**1**] and allosecurinine [(−)-**2**], respectively. From the above



Scheme 6. *Reagents and conditions*: (i) MCPBA, CH_2Cl_2, 24 h; (ii) TFA, CH_2Cl_2, 6 h; (iii) TFAA, 5 h; (iv) NEt_3, 1 h.

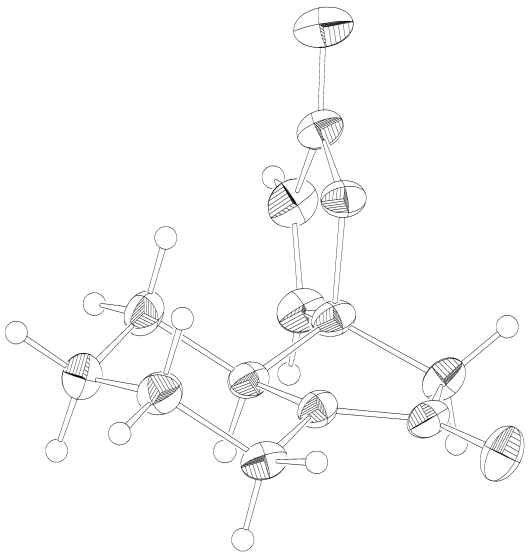


Figure 2. X-Ray structure of **3**.

assignment also the stereochemistry of the epoxy derivatives **16** and **17** may be deduced. As both cyclization reactions gave single but different stereoisomers it is reasonable to assume, that the cyclization—as a result of a neighboring-group effect arising from the ester moiety—proceeded with inversion at the spirocyclic stereocenter. Consequently the epoxides **16** and **17** should display the stereochemistry shown.

4. Conclusion

In summary, we have developed an enantioselective synthesis of the tricyclic compounds **3** and **4** representing substructures of virosecurinine [(+)-**1**] and allosecurinine [(−)-**2**]. Starting from the enamide **5** the synthesis of the substructures **3** and **4** has been accomplished in ten overall chemical steps with a total yield of 12 and 6%, respectively.

The synthesis commenced with asymmetric electrophilic α-amidoalkylation reactions employing the chiral enamide **5** providing (*S*)-**7b** as a key compound with the diastereoselectivity (d.s.) of 93/7. From the latter enantiopure (*S*)-2-anisylpiperidine [(*S*)-**9b**] was obtained. Birch-reduction of (*S*)-**9b** followed by an ozonolysis of the resulting 1,4-cylohexadiene (*S*)-**10** and a spirocyclization reaction, as main transformations, led finally to **3** and **4**. Work directed towards the synthesis of securinine-type alkaloids based on a related strategy is in progress.

5. Experimental

5.1. General

Melting points (uncorrected): Dr Tottoli (Büchi Nr. 510) apparatus. ^{1}H NMR-spectra and ^{13}C NMR-spectra: Jeol JNMR-GX 400, δ-scale (ppm), TMS int. stand., in several cases coalescence occurred and the signals were broadened and unresolved (unr.) and as a consequence thereof no exact integrals could be obtained. Mass spectra: Hewlett Packard 5989 A with 59980 B particle beam LC/MS interface HRMS: Jeol GCmateII GC-MS-System with direct inlet. IR-Spectra: Spectral photometer 1600 (Perkin–Elmer) and Paragon 1000 (Perkin–Elmer), liquids were run as films, solids as KBr pellets. Optical rotation: Polarimeter 241 MC (Perkin–Elmer). Combustion analysis: CHN Rapid (Heraeus). Solvents were dried and kept under nitrogen and were freshly distilled before use. Unless otherwise indicated, all reactions were carried out under a nitrogen atmosphere. Column chromatography (CC): Flash chromatography on silicagel (Merck 60 F-254, 0.040–0.063 mm). Analytical HPLC: L-6200 pump (Merck–Hitachi), L-4000 UV–Vis detector, 254 nm (Merck–Hitachi), D-2500 and D-7500 Chromato Integrator (Merck–Hitachi), column LiChroCART® with LiChrospher® Si 60 cartridge (5 μm, 250×4 mm with precolumn 4×4 mm) (Merck). Preparative HPLC: L-6000 pump, L-4000 UV–Vis dedector, 254 nm (Merck–Hitachi), D-2000 Chromato Integrator (Merck–Hitachi), column Hibar RT LiChrosorb® Si 60 (7 μm, 250×25 mm) (Merck).

5.2. Electrophilic α-amidoalkylation—general procedure (GP1)

At −78°C by means of a gas-tight syringe first 3–10 equiv. of HCl gas were passed into CH_2Cl_2 (4 ml per 1 mmol enamide **5**) before a solution of the enamide **5** in CH_2Cl_2 (4 ml per 1 mmol **5**) was added dropwise under vigorous stirring. Excess HCl was stripped off in vacuo at −60 to −78°C (60 min) and then a solution of the organometallic reagent (1.1–3.0 equiv. referring to enamide **5**) was added dropwise. The reaction mixture was stirred for 90 min at −78°C and finally quenched with saturated $NaHCO_3$-solution. The aqueous layer was extracted several times with CH_2Cl_2 and the combined organic layers were dried ($MgSO_4$) and concentrated. The d.s. of the reaction was determined by HPLC from the resulting residue. The crude products were purified by CC to yield a mixture of the diastereomeres **7a**,**b**/**8a**,**b**. Pure diastereomeres were obtained by prep. HPLC.

5.2.1. (1*S*,5*R*)-1-[(*S*)-2-Phenylpiperidin-1-ylcarbonyl]-5,8,8-trimethyl-3-oxabicyclo[3.2.1]octan-2-one ((*S*)-7a) and (1*S*,5*R*)-1-[(*R*)-2-Phenylpiperidin-1-ylcarbonyl]-5,8,8-trimethyl-3-oxabicyclo[3.2.1]octan-2-one ((*R*)-8a). (A) According to GP1 from 100 mg (0.361 mmol) of **5** and 132 μl (0.396 mmol, 1.1 equiv.) of PhMgBr (3.0 M in Et_2O). CC (petrolether/EtOAc=6/4) afforded 77 mg (60%) of a mixture of **7a** and **8a**. The d.s. was determined by analytical HPLC (*n*-heptane/*iso*-propanole=98/2, 1.0 ml/min): (*S*)-**7a** (26.2 min)/(*R*)-**8a** (20.6 min)=88/12.). Separation of the diastereomers by prep. HPLC (*n*-heptane/EtOAc=85/15, 15 ml/min) yielded 60 mg (47%) of **7a** and 7 mg (5%) of **8a**.

Compound (*S*)-**7a**. Colorless crystals, mp 162°C. $[\alpha]_D^{20}=-28.6$ (c=0.50, CH_2Cl_2). TLC: R_f=0.42 (petrolether/EtOAc=6/4). ^{1}H NMR ([D$_2$] 1,1,2,2-tetrachloroethane, 120°C): δ=0.89 (s, 3H, CH_3), 1.00 (s, 3H, CH_3), 1.27 (s, 3H, CH_3), 1.44–2.02 (m, 7H, CH_2), 2.22–2.37 (m, 2H, CH_2), 2.43–2.83 (m, 1H, CH_2), 2.94–3.08 (m, 1H, NCH_{2ax}), 3.54–3.68 (m, 1H, NCH_{2eq}), 3.89 (d, J=10.6 Hz, 1H, CH_2OCO), 4.13 (d, J=10.6 Hz, 1H, CH_2OCO), 5.82–5.88 (m, 1H, NCH), 7.18–7.22 (m, 1H, C_6H_5), 7.23–7.35

(m, 4H, C_6H_5). IR: $\tilde{\nu}$=1729 cm^{-1}, 1629. MS (CH_4, CI); *m/z* (%): 356 (100) [M+H$^+$]. $C_{22}H_{29}NO_3$ (355.5): calcd C 74.34, H 8.22, N 3.94; found C 74.46, H 7.97, N 4.06.

Compound (*R*)-**8a**. Colorless oil. TLC: R_f=0.42 (petrolether/EtOAc=6/4). ^{1}H NMR ([D_2] 1,1,2,2-tetrachloroethane, 120°C): δ=0.88 (s, 3H, CH_3), 1.06 (s, 3H, CH_3), 1.31 (s, 3H, CH_3), 1.42–2.07 (m, 7H, CH_2), 2.22–2.37 (m, 2H, CH_2), 2.35–2.55 (m, unr., 1H, CH_2), 2.90–3.04 (m, 1H, NCH_{2ax}), 3.73–3.90 (m, 1H, NCH_{2eq}), 3.86 (d, *J*=10.7 Hz, 1H, CH_2OCO), 4.11 (d, *J*=10.7 Hz, 1H, CH_2OCO), 5.56–5.69 (m, unr., 1H, NCRH), 7.17–7.21 (m, 1H, C_6H_5), 7.26–7.38 (m, 4H, C_6H_5). MS (CH_4, CI); *m/z* (%): 356 (100) [M+H$^+$].

(B) According to GP1 from 52 mg (0.187 mmol) of **5** and 1.4 ml (0.21 mmol, 1.1 equiv.) of an organozinc reagent generated by treating 0.5 ml (1.5 mmol) of PhMgBr (3 M in Et_2O) in 5.5 ml THF with 0.9 ml (0.9 mmol of $ZnCl_2$ 1 M in Et_2O). CC (petrolether/EtOAc=6/4) afforded 31 mg (47%) of a mixture of **7a** and **8a**.

Analytical HPLC. (*S*)-**7a**/(*R*)-**8a**=94/6.

(C) According to GP1 from 299 mg (1.078 mmol) of **5**. After removal of excess HCl 1.0 ml (1.0 mmol, 0.93 equiv.) of BCl_3 (1 M in *n*-heptane) was added at −78°C followed by 10.0 ml (3.21 mmol, 3.0 equiv.) of an organozinc reagent generated by treating 10.0 ml (10.0 mmol) of PhMgBr (1 M in THF) with 8.4 ml (5.9 mmol) of $ZnCl_2$ (0.7 M in Et_2O) after 3 h. CC (petrolether/EtOAc=6/4) afforded 347 mg (91%) of a mixture of **7a** and **8a**.

Analytical HPLC (*n*-heptane/*iso*-propanole=98/2, 1.0 ml/min): (*S*)-**7a** (26.2 min)/(*R*)-**8a** (20.6 min)=91/9.

5.2.2. (1*S*,5*R*)-1-[(*S*)-2-(4-Methoxyphenyl)piperidin-1-ylcarbonyl]-5,8,8-trimethyl-3-oxabicyclo[3.2.1]octan-2-one ((*S*)-7b) and (1*S*,5*R*)-1-[(*R*)-2-(4-methoxyphenyl)-piperidin-1-ylcarbonyl]-5,8,8-trimethyl-3-oxabicyclo-[3.2.1]octan-2-one ((*R*)-8b). (A) According to GP1 from 92 mg (0.33 mmol) of **5** and 1.0 ml (1.0 mmol, 3.0 equiv.) of 4-$CH_3OC_6H_4MgBr$ (1.0 M in THF). CC (petrolether/EtOAc=6/4) afforded 93 mg (74%) of a mixture of **7b** and **8b**. Prep. HPLC (*n*-heptane/1,4-dioxane=88/12, 9 ml/min) yielded 78 mg (61%) of **7b** and 12 mg (8%) of **8b**. Analytical HPLC (*n*-heptane/1,4-dioxane=88/12, 1.0 ml/min): (*S*)-**7b** (28.4 min)/(*R*)-**8b** (24.8 min)=85/15.

Compound (*S*)-**7b**. Colorless crystals, mp 121°C. $[\alpha]_D^{20}$=−39.4 (*c*=0.96, CH_2Cl_2). TLC: R_f=0.38 (petrolether/EtOAc=60/40). ^{1}H NMR ($C_2D_2Cl_4$, 130°C): δ=0.94 (s, 3H, CH_3), 1.05 (s, 3H, CH_3), 1.34 (s, 3H, CH_3), 1.52–1.78 (m, 5H, CH_2), 1.78–1.89 (m, 1H, CH_2), 1.91–2.02 (m, 2H, CH_2), 2.33 (d, *J*=14.0 Hz, 2H, CH_2), 3.04 (t, *J*=12.6 Hz, 1H, NCH_{2ax}), 3.60–3.68 (m, 1H, NCH_{2eq}), 3.83 (s, 3H, OCH_3), 3.94 (d, *J*=11.1 Hz, 1H, CH_2OCO), 4.18 (d, *J*=11.1 Hz, 1H, CH_2OCO), 5.83–5.90 (m, 1H, NCHR), 6.92 (d, *J*=8.2 Hz, 2H, C_6H_4), 7.24 (d, *J*=8.2 Hz, 2H, C_6H_4). IR: $\tilde{\nu}$=2933 cm^{-1}, 1733, 1617. MS (CH_4, CI); *m/z* (%): 386 [M+H$^+$] (2), 83 (100). $C_{23}H_{31}NO_3$ (385.5): calcd C 71.66, H 8.11, N 3.63; found C 71.63, H 8.22, N 3.55.

Compound (*R*)-**8b**. Colorless oil. TLC: R_f=0.43 (petrolether/EtOAc=60/40). ^{1}H NMR ($C_2D_2Cl_4$, 130°C): δ=0.93 (s, 3H, CH_3), 1.10 (s, 3H, CH_3), 1.35 (s, 3H, CH_3), 1.45–1.73 (m, 4H, CH_2), 1.76–1.87 (m, 1H, CH_2), 1.88–2.08 (m, 2H, CH_2), 2.33 (d, *J*=13.6 Hz, 2H, CH_2), 2.36–2.61 (m, unr., 1H, CH_2,) 2.99 (t, *J*=12.9 Hz, 1H, NCH_{2ax}), 3.73–3.83 (m, 1H, NCH_{2eq}), 3.83 (s, 3H, OCH_3), 3.92 (d, *J*=10.8 Hz, 1H, CH_2OCO), 4.16 (d, *J*=10.8 Hz, 1H, CH_2OCO), 5.52–5.74 (m, 1H, NCHR), 6.93 (d, *J*=8.2 Hz, 2H, C_6H_4), 7.28 (d, *J*=8.2 Hz, 2H, C_6H_4). MS (CH_4, CI); *m/z* (%): 386 [M+H$^+$] (11), 83 (100).

(B) According to GP1 from 96 mg (0.35 mmol) of **5** and 3.0 ml (0.99 mmol, 3.0 equiv.) of an organozinc reagent generated by treating 2.0 ml (2.0 mmol) of 4-$MeOC_6H_4$-MgBr (1 M in THF) with 1.0 ml (1.0 mmol) of $ZnCl_2$ (1 M in Et_2O). CC (petrolether/EtOAc=6/4) afforded 75 mg (56%) of a mixture of **7b** and **8b**.

Analytical HPLC: (*S*)-**7b**/(*R*)-**8b**=93/7.

(C) According to GP1 from 3.850 g (13.88 mmol) of **5**. After removal of excess HCl 13.8 ml (13.8 mmol, 0.99 equiv.) of BCl_3 (1 M in *n*-heptane) was added at −78°C followed by 105 ml (35.0 mmol, 2.5 equiv.) of an organozinc reagent generated by treating 55.0 ml (55.0 mmol) of 4-$MeOC_6H_4MgBr$ (1 M in THF) with 50.0 ml (35.0 mmol) of $ZnCl_2$ (0.7 M in Et_2O). CC (petrolether/EtOAc=6/4) afforded 5.320 mg (99%) of a mixture of **7b** and **8b**.

Analytical HPLC: (*S*)-**7b**/(*R*)-**8b**=93/7.

5.3. Reductive cleavage of the amide bond—general procedure (GP2)

To a solution of 1.0 mmol of **7a**,**b** in 5 ml of THF 2 equiv. of $Na[AlH_2(OMe)]_2$ (0.925 M in THF) was added dropwise at −25°C. The reducing agent has been generated by treating 1 equiv. of $NaAlH_4$ (1.0 M in THF) with 2 equiv. of MeOH. After stirring for 24 h at −25°C the reaction mixture was quenched by addition of MeOH, acidified with dilute HCl and extracted several times with Et_2O. Then 2 M NaOH was added and the alkaline aqueous layer was extracted several times with Et_2O. The combined organic layers were dried ($MgSO_4$) and concentrated. The crude product was purified by CC.

5.3.1. (*S*)-2-Phenylpiperidinium chloride ((*S*)-9a). According to GP2 from 195 mg (0.549 mmol) of **7a**. CC (Et_2O/$NEtMe_2$=98/2) afforded the pure amine which was redissolved in 15 ml of Et_2O. Addition of 12 M HCl at 0°C under vigorous stirring and subsequent removal of the solvent in vacuo yielded 70 mg (65%) of (*S*)-**9a**.

Colorless crystals, mp 193–195°C (lit.[13]: 194–195°C). $[\alpha]_D^{23}$=+9.5 (*c*=1.30, MeOH) {lit.[13]: (*R*)-**9a**: $[\alpha]_D$=−9.6 (MeOH)}.

5.3.2. (*S*)-2-(4-Methoxyphenyl)piperidine ((*S*)-9b). According to GP2 from 3.30 g (8.65 mmol) of **7b**. The crude product was purified by CC (Et_2O/$NEtMe_2$=98.5/1.5) to yield 1.501 g (92%) of (*S*)-**9b**.

Colorless oil. $[\alpha]_D^{22}=-21.1$ (c=0.54, MeOH). TLC: R_f=0.31 (Et_2O/$NEtMe_2$=98.5/1.5). ^1H NMR ($CDCl_3$): δ=1.41–1.69 (m, 5H, 2×CH_2, NH), 1.73–1.80 (m, 1H, CH_2), 1.84–1.91 (m, 1H, CH_2), 2.79 (td, J=11.4/2.6 Hz, 1H, NHCH_{2ax}), 3.18 (d, J=11.4 Hz, 1H, NHCH_{2eq}), 3.53 (dd, J=10.0/2.5 Hz, 1H, NHCR), 3.80 (s, 3H, OCH_3), 6.86 (d, J=8.6 Hz, 2H, $H_{aromat.}$), 7.29 (dt, J=8.6/2.1 Hz, 2H, $H_{aromat.}$). IR: $\tilde{\nu}$=3322 cm^{-1}, 2997, 2932, 2851, 2785, 1611, 1584, 1513. MS (70 eV); m/z (%): 191 [M^+] (1), 83 (100). $C_{12}H_{17}NO$ (191.3): calcd C 75.35, H 8.96, N 7.32; found C 75.46, H 8.92 N 7.26.

5.3.3. (*S*)-2-(4-Methoxycyclohexa-1,4-dienyl)piperidine ((*S*)-10). To a solution of 1.400 g (7.319 mmol) of (*S*)-**9b** in 39 ml of Et_2O at −78°C ~155 ml of liquid NH_3 was added. The resulting mixture was warmed to −40°C before 1.072 g (154.4 mmol, 21.1 equiv.) of Lithium as small pieces was added. The resulting blue colored solution was kept at −40°C for 30 min before it was quenched by addition of distilled EtOH and allowed to slowly warm to room temperature (~16 h) in order to remove the solvent (attention gaseous NH_3). Then 100 ml of H_2O was added and the aqueous layer was extracted several times with CH_2Cl_2. The combined organic layers were dried ($MgSO_4$) and concentrated in vacuo and the crude product was purified by CC (Et_2O/$NEtMe_2$=98.5/1.5) to yield 1.250 g (89%) of (*S*)-**10**.

Colorless crystals, mp 37°C. $[\alpha]_D^{22}=-19.9$ (c=1.07, MeOH). TLC: R_f=0.48 (Et_2O/$NEtMe_2$=95/5). ^1H NMR ($CDCl_3$): δ=1.25–1.49 (m, 3H, CH_2), 1.49–1.63 (m, 2H, NCH_2CH_{2eq} and NH), 1.67 (d_{broad}, J=11.4 Hz, 1H, NCHRCH_{2eq}), 1.83 (d_{broad}, J=8.7 Hz, 1H, NCH_2CH_2-CH_{2eq}), 2.67 (td, J=12/2.6 Hz, 1H, NHCH_{2ax}), 2.74 (s_{broad}, 2H, =CHCH_2), 2.76–2.94 (m, 2H, =CHCH_2), 2.97 (d_{broad}, J=10.3 Hz, 1H, NHCRH), 3.12 (d, J=12 Hz, 1H, NHCH_{2eq}), 3.55 (s, 3H, OCH_3), 4.63–4.67 (m, 1H, CH_3OC=CH), 5.59–5.64 (m, 1H, HNCHCR=CH). IR: $\tilde{\nu}$=1695 cm^{-1}, 1663. MS (CH_4, CI); m/z (%): 194 (100) [M+H^+]. $C_{12}H_{19}NO$ (193.3): calcd C 74.57, H 9.91, N 7.25; found C 74.44, H 10.20, N 7.09.

5.3.4. *tert*-Butyl (*S*)-2-(4-methoxycyclohexa-1,4-dienyl)-piperidine-1-carboxylate ((*S*)-11). To a solution of 338 mg (1.75 mmol) of (*S*)-**10** and 499 mg (2.29 mmol, 1.3 equiv.) of $(Boc)_2O$ in 17.5 ml of MeCN 326 μl of $NEt{i}Pr_2$ was added dropwise at room temperature. After three days of stirring the reaction mixture was concentrated and purified by CC (petrolether/EtOAc=6/4) to yield 510 mg (99%) of (*S*)-**11**.

Colorless crystals, mp 56–58°C. $[\alpha]_D^{25}=-83.6$ (c=1.00, MeOH). TLC: R_f=0.65 (petrolether/EtOAc=6/4). ^1H NMR ($CDCl_3$): δ=1.46 (s, 9H, $C(CH_3)_3$), 1.50–1.67 (m, 5H, CH_2), 2.00 (d_{broad}, J=13.6 Hz, 1H, NCHRCH_{2eq}), 2.55–2.83 (m, 5H, 2x=CHCH_2, NCH_{2ax}), 3.56 (s, 3H, OCH_3), 3.96 (d_{broad}, J=14.0 Hz, 1H, NCH_{2eq}), 4.64 (t, J=3.5 Hz, 1H, NCRH), 4.62–4.69 (m, 1H, MeOC=CH), 5.45–5.50 (m, 1H, HNCHCR=CH). IR: $\tilde{\nu}$=2936 cm^{-1}, 1690. MS (CH_4, CI); m/z (%): 294 (9) [M+H^+], 266 (3), 238 (100). $C_{17}H_{27}NO_3$ (293.4): calcd C 69.59, H 9.28, N 4.77; found C 69.46, H 9.41, N 4.79.

5.3.5. *tert*-Butyl (*S*)-(*E*)-2-(1-methoxycarbonyl-5-oxo-pent-2-en-3-yl)piperidine-1-carboxylate ((*S*)-12). Into a solution of 250 mg (0.852 mmol) of (*S*)-**11** in 8.5 ml of MeOH at −78°C 1 equiv. of ozone was passed. After stirring at −78°C for 2 h 233 μl (3.17 mmol, 3.7 equiv.) of Me_2S was added dropwise. The reaction mixture was allowed to warm to room temperature within 19 h. Then it was concentrated and the crude product was purified by CC (*i*-hexane/EtOAc=6/4) to yield 140 mg (50%) of (*S*)-**12**.

Colorless oil. $[\alpha]_D^{25}=-79.0$ (c=1.25, CH_2Cl_2). TLC: R_f=0.35 (*i*-hexane/EtOAc=6/4). ^1H NMR ($CDCl_3$): δ=1.44 (s, 9H, $C(CH_3)_3$), 1.53–1.73 (m, 5H, CH_2), 2.01 (d_{broad}, J=14.0 Hz, 1H, NCHRCH_{2eq}), 2.65 (td, J=13.3/2.8 Hz, 1H, NCH_{2ax}), 3.07–3.14 (m, 4H, MeO_2-CCH_2 and CHOCH_2), 3.69 (s, 3H, OCH_3), 3.92 (d_{broad}, J=13.3 Hz, 1H, NCH_{2eq}), 4.70–4.75 (m, 1H, NCHR), 5.80 (td, J=7.2/2.1 Hz, =CH), 9.57 (t, J=2.0 Hz, 1H, COH). IR: $\tilde{\nu}$=2939 cm^{-1}, 2867, 1740, 1723, 1690. MS (CH_4, CI); m/z (%): 326 (5) [M+H^+], 208 (100). $C_{17}H_{27}NO_5$ (325.4): calcd C 62.75, H 8.36, N 4.30; found C 62.52, H 8.33, N 4.57.

5.3.6. (*S*)-(*E*)-3-(1-*tert*-Butyloxycarbonylpiperidin-2-yl)-5-methoxycarbonyl-pent-3-enoic acid ((*S*)-13). To 165 mg (0.507 mmol) of *S*-(**12**) in 11.0 ml of *t*BuOH and 2.5 ml of 2-methyl-2-butene within 10 min 73.3 mg (0.648 mmol, 1.28 equiv.) of $NaClO_2$ (80%) in 1.8 ml of phosphate buffer ((pH=7, c=1.0 M) and 2.2 ml H_2O was added at room temperature. After 3 h of stirring the reaction mixture was concentrated and the resulting residue was extracted several times with 10 ml of Et_2O. The combined organic layers were dried (Na_2SO_4) and concentrated. The crude product was purified by CC (EtOAc/HOAc=98/2) to yield 156 mg (90%) of (*S*)-**13**.

Colorless oil. $[\alpha]_D^{23}=-123.3$ (c=0.60, CH_2Cl_2). TLC: R_f=0.50 (EtOAc/HOAc=98/2). ^1H NMR ($CDCl_3$): δ=1.46 (s, 9H, $C(CH_3)_3$), 1.55–1.76 (m, 5H, CH_2), 2.05 (d_{broad}, J=13.3 Hz, 1H, NCHRCH_{2eq}), 2.70 (t_{broad}, J=13.4 Hz, 1H, NCH_{2ax}), 2.98 (d, J=15.3 Hz, 1H, HOOCCH_2), 3.12 (d, J=15.3 Hz, 1H, HOOCCH_2), 3.18–3.32 (m, 2H, MeOOCCH_2), 3.70 (s, 3H, OCH_3), 3.92 (d_{broad}, J=13.4 Hz, 1H, NCH_{2eq}), 4.71–4.76 (m, 1H, NCHR), 5.78 (t, J=7.0 Hz, 1H, =CH). IR: $\tilde{\nu}$=3170 cm^{-1}, 2940, 2958, 2604, 1738, 1694, 1644. MS (CH_4, CI); m/z (%): 342 (1) [M+H^+], 242 (100). $C_{17}H_{27}NO_6$ (341.4): calcd C 59.81, H 7.97, N 4.10; found C 59.39, H 8.24, N 3.94.

5.3.7. (*S*)-(*E*)-3-Piperidin-2-yl-5-methoxycarbonylpent-3-enoic acid ((*S*)-14). (A) ((*S*)-**14**·CF_3CO_2H): To 73 mg (0.21 mmol) of (*S*)-**13** in 200 μl of CH_2Cl_2 1.0 ml of CF_3CO_2H was added dropwise and the reaction mixture was stirred for 5 h at room temperature. Removal of the solvent in vacuo yielded 76 mg (~100%) of (*S*)-**14**·CF_3CO_2H.

Yellowish oil. $[\alpha]_D^{23}=-13.0$ (c=0.67, H_2O). ^1H NMR (D_2O): δ=1.33–1.55 (m, 3H, CH_2), 1.66–1.84 (m, 3H, CH_2), 2.86 (td, J=13/3.0 Hz, 1H, HNCH_{2ax}), 3.07 (d, J=7.6 Hz, 2H, MeOOCCH_2), 3.11–3.15 (m, 2H, HOOCCH_2), 3.26 (d_{broad}, J=13 Hz, 1H, HNCH_{2eq}), 3.50 (s, 3H, OCH_3), 3.54 (d_{broad}, J=11.0 Hz, 1H, HNCHR), 5.83 (t, J=7.6 Hz, 1H, =CH). IR: $\tilde{\nu}$=3446 cm^{-1}, 2958, 2865, 2526, 1731, 1672. MS (CH_4; CI); m/z (%): 242 (13)

[M+H$^+$], 224 (100). $C_{14}H_{20}F_3NO_6$ (355.3): calcd C 47.32, H 5.67, N 3.94; found C 46.82, H 5.50, N 3.78.

(B) ((*S*)-**14**·BF_3): To 173 mg (0.507 mmol) of (*S*)-**14** in 7.0 ml CH_2Cl_2 at room temperature within 5 min 195 μl (1.55 mmol, 3.06 equiv.) of BF_3·OEt_2 was added. Removal of the solvent (in vacuo) after 30 min yielded 205 mg (~98%) of (*S*)-**14**·2.5BF_3. The formula was delineated from the results of the combustion analysis, but no attempts were made to determine the nature of the formed complex.

Colorless oil. ^{1}H NMR (D_2O): δ=1.37–1.60 (m, 3H, CH_2), 1.72–1.90 (m, 3H, CH_2), 2.92 (td, *J*=12.7/3.0 Hz, 1H, HNCH_{2ax}), 3.12 (d, *J*=7.4 Hz, 2H, MeOOCCH_2), 3.17–3.19 (m, 2H, HOOCCH_2), 3.31 (d_{broad}, *J*=12.7 Hz, 1H, HNCH_{2eq}), 3.56 (s, 3H, OCH_3), 3.59 (d_{broad}, *J*=12.1 Hz, 1H, HNC*H*R), 5.88 (t, *J*=7.4 Hz, 1H, =CH). IR: $\tilde{\nu}$=3208 cm^{-1}, 2953, 2859, 2500, 1732, 1715, 1652. MS (CH_4, CI); *m*/*z* (%): 242 (1) [M+H$^+$], 224 (100). $C_{12}H_{19}NO_4$·2.5BF_3 (410.8): calcd C 35.09, H 4.66, N 3.41; found C 35.19, H 5.21, N 3.50.

5.3.8. Methyl (*S*)-(*E*)-3-(3-oxoindolizidin-1-ylidene) propionate ((*S*)-15). To 95 mg (0.23 mmol) of (*S*)-**14**·BF_3 (method B) in 4.8 ml of CH_2Cl_2 66 mg (0.26 mmol, 1.1 equiv.) of 2-chloro-1-methylpyridinium iodide was added at room temperature followed by the dropwise addition of 162 μl (0.932 mmol, 3.61 equiv.) of N*i*Pr_2Et. The reaction mixture was stirred for 16 h at room temperature, concentrated and purified by CC (EtOAc/HOAc=98/2). The crude product was dissolved in 3.0 ml of saturated $NaHCO_3$-solution and extracted several times with CH_2Cl_2. The combined organic layers were dried (Na_2SO_4) and concentrated in vacuo to yield 40 mg (77%) of (*S*)-**15**.

Colorless crystals, mp 50°C. $[\alpha]_D^{23}$=−15.7 (*c*=1.05, CH_2Cl_2). TLC: R_f=0.23 (EtOAc/HOAc=98/2). ^{1}H NMR (CD_2Cl_2): δ=1.20 (tdd, *J*=13/11/3.3 Hz, 1H, NCHRCH_{2ax}), 1.30 (qdd, *J*=13/5/3.5 Hz, 1H, NCH_2CH_{2ax}), 1.48 (qt, *J*=13/3.5 Hz, 1H, $NCH_2CH_2CH_{2ax}$), 1.61–1.69 (m, 1H, NCH_2CH_{2eq}), 1.85–1.92 (m, 1H, $NCH_2CH_2CH_{2eq}$), 1.93–2.00 (m, 1H, NCHRCH_{2eq}), 2.61 (td_{broad}, *J*=13/3.5 Hz, 1H, NCH_{2ax}), 2.94–2.98 (m, 2H, $NCOCH_2$), 3.02 (dq, *J*=7/1.5 Hz, 2H, MeOOCCH_2), 3.65 (s, 3H, OCH_3), 3.92 (d_{broad}, *J*=11 Hz, 1H, NCHR), 4.12 (ddt, *J*=13/5/1.5 Hz, 1H, NCH_{2eq}), 5.52–5.60 (m, 1H, =CH). IR: $\tilde{\nu}$=3460 cm^{-1}, 2940, 2858, 1738, 1694, 1682. MS (70 eV); *m*/*z* (%): 223 (9) [M$^+$], 150 (100). $C_{12}H_{17}NO_3$·0.25H_2O (227.8): calcd C 63.28, H 7.74, N 6.15; found C 63.08, H 7.37, N 6.08.

5.3.9. Methyl (1*R*,3′*R*,8a*S*)-3-oxo-spiro[indolizidin-1,2′-oxiran]-3′-ylacetate ((16)) and methyl (1*S*,3′*S*,8a*S*)-3-oxo-spiro[indolizidin-1,2′-oxiran]-3′-ylacetate ((17)). To 40 mg (0.179 mmol) of (*S*)-**15** in 1.5 ml of CH_2Cl_2 85 mg (~0.27 mmol, ~1.5 equiv.) MCPBA was added and the reaction mixture was stirred for 24 h at room temperature The solvent was evaporated and the residue was purified by CC (EtOAc/HOAc=98/2) to yield 26 mg (61%) of **16** and 13 mg (30%) of **17**.

Compound **16**. Colorless oil. $[\alpha]_D^{23}$=−19.7 (*c*=1.13, CH_2Cl_2). TLC: R_f=0.25 (EtOAc/HOAc=98/2). ^{1}H NMR (CD_2Cl_2): δ=1.20–1.38 (m, 2H, NCHRCH_{2ax}, NCH_2CH_{2ax}), 1.42 (qt, *J*=13/3 Hz, 1H, $NCH_2CH_2CH_{2ax}$), 1.60–1.68 (m, 1H, NCH_2CH_{2eq}), 1.68–1.74 (m, 1H, NCHRCH_{2eq}), 1.84–1.94 (m, 1H, $NCH_2CH_2CH_{2eq}$), 2.36 (dd, *J*=18.2/1.7 Hz, 1H, $NCOCH_2$), 2.45 (dd, *J*=17.0/6.1 Hz, 1H, $MeOCOCH_2$), 2.59 (dd, *J*=17.0/6.1 Hz, 1H, $MeOCOCH_2$), 2.63 (d, *J*=18.2 Hz, 1H, $NCOCH_2$), 2.62–2.69 (m, 1H, NCH_{2ax}), 3.36 (dd, *J*=12.0/3.5 Hz, 1H, NCHR), 3.41 (t, *J*=6.1 Hz, 1H, CO*H*R), 3.69 (s, 3H, OCH_3), 4.17 (ddt, *J*=13/5/1.7 Hz, 1H, NCH_{2eq}). 100 MHz ^{13}C NMR (CD_2Cl_2): δ=23.48 ($NCH_2CH_2CH_2$), 24.43 (NCH_2CH_2), 29.03 (NCHRCH_2), 33.92 ($NCOCH_2$), 35.37 (MeO_2CCCH_2), 39.82 (NCH_2), 51.97 (OCH_3), 54.46 (CHOR), 61.64 (NCR_2H), 63.37 (CR_3OR), 168.60 (NCO), 170.25 (OCO). IR: $\tilde{\nu}$=3456 cm^{-1}, 2940, 2858, 1738, 1694. MS (CH_4, CI); *m*/*z* (%): 240 (100) [M+H$^+$]. HRMS (200°C, EI 70 eV): calcd for $C_{12}H_{17}NO_4$: 239.11576. Found: 239.1126.

Compound **17**. Colorless oil. $[\alpha]_D^{23}$=−16.7 (*c*=0.30, CH_2Cl_2). TLC: R_f=0.19 (EtOAc/HOAc=98/2). ^{1}H NMR (CD_2Cl_2): δ=1.20–1.42 (m, 3H, NCHRCH_{2ax}, NCH_2CH_{2ax}, $NCH_2CH_2CH_{2ax}$), 1.44–1.52 (m, 1H, NCHRCH_{2eq}), 1.63–1.71 (m, 1H, NCH_2CH_{2eq}) 1.88–1.96 (m, 1H, $NCH_2CH_2CH_{2eq}$), 2.27 (d, *J*=18.2 Hz, 1H, $NCOCH_2$), 2.52 (dd, *J*=16/6 Hz, 1H, $MeOCOCH_2$), 2.57 (dd, *J*=16/6 Hz, 1H, $MeOCOCH_2$), 2.56–2.65 (m, 1H, NCH_{2ax}), 2.71 (dd, *J*=18.2/1.7 Hz, 1H, $NCOCH_2$), 3.28 (t, *J*=6.0 Hz, 1H, COHR), 3.60 (dd, *J*=11.5/3.5 Hz, 1H, NCHR), 3.69 (s, 3H, OCH_3), 4.11–4.18 (m, 1H, NCH_{2eq}). 100 MHz ^{13}C NMR (CD_2Cl_2): δ=23.10 ($NCH_2CH_2CH_2$), 24.24 (NCH_2CH_2), 25.54 (NCHRCH_2), 34.57 ($NCOCH_2$), 35.34 (MeO_2CCCH_2), 39.92 (NCH_2), 52.01 (OCH_3), 54.49 (CHOR), 58.93 (NCR_2H), 62.15 (CR_3OR), 168.99 (NCO), 170.38 (OCO). IR: $\tilde{\nu}$=3446 cm^{-1}, 2948, 2854, 1738, 1694. MS (CH_4, CI); *m*/*z* (%): 240 (100) [M+H$^+$]. $C_{12}H_{17}NO_4$ (239.3): calcd C 60.24, H 7.16, N 5.85; found C 59.77, H 7.02, N 5.71.

5.3.10. (1′*R*,8′a*S*) Spiro[furan-2,1′-indolizidine]-3′,5(2*H*)-dione (3). 22 mg (0.092 mmol) of **16** in 200 μl of CH_2Cl_2 were treated with 1.0 ml of TFA for 6 h at room temperature The solvent was removed in vacuo and to the resulting residue 200 μl of CH_2Cl_2 and 1.0 ml of TFAA were added. Then the reaction mixture was stirred for 5 h at room temperature before it was concentrated in vacuo. The residue was redissolved in 1.0 ml of CH_2Cl_2, 250 μl of NEt_3 was added and the mixture was stirred for an additional 1 h at room temperature. The crude product that was obtained after removal of the solvent was purified by CC (EtOAc/HOAc=90/10) to yield 15 mg (79%) of **3**.

Colorless crystals, mp 137–138°C. $[\alpha]_D^{23}$=+56.8 (*c*=0.37, CH_2Cl_2). TLC: R_f=0.14 (EtOAc/HOAc=90/10). ^{1}H NMR (CD_2Cl_2): δ=1.30–1.40 (m, 2H, NCHRCH_{2ax} and NCH_2CH_{2ax}), 1.40–1.50 (m, 2H, $NCH_2CH_2CH_{2ax}$ and NCHRCH_{2eq}) 1.66–1.75 (m, 1H, NCH_2CH_{2eq}), 1.88–1.96 (m, 1H, $NCH_2CH_2CH_{2eq}$), 2.52 (d, *J*=17.6 Hz, 1H, $NCOCH_2$), 2.59–2.68 (m, 1H, NCH_{2ax}), 2.77 (dd, *J*=17.6/1.8 Hz, 1H, $NCOCH_2$), 3.52–3.57 (m, 1H, NCHR), 4.05–4.12 (m, 1H, NCH_{2eq}), 6.12 (d, *J*=5.5 Hz, 1H, OCOCH=), 7.36 (d, *J*=5.5 Hz, 1H, OCOCH=C*H*). 100 MHz ^{13}C NMR (CD_2Cl_2): δ=23.36 ($NCH_2CH_2CH_2$), 23.75 (NCH_2CH_2), 24.00 (NCRHCH_2), 40.90 (NCH_2 and

NCOCH_2), 62.09 (NCHR), 88.36 (CR_3OR), 122.78 (O_2CC=), 155.16 (O_2CCH=CH), 169.53 (NCO), 171.43 (O_2C). IR: $\tilde{\nu}$=3446 cm^{-1}, 3109, 2951, 2862, 1780, 1693. MS (CH_4, CI); *m/z* (%): 208 (100) [M+H^+]. $C_{11}H_{13}NO_3$ (207.2): calcd C 63.76, H 6.32, N 6.76; found C 63.43, H 6.31, N 6.59.

5.3.11. (1′*S*,8′a*S*)-Spiro[furan-2,1′-indolizidine]-3′,5(2*H*)-dione (4). 6 mg (0.025 mmol) of **17** in 200 μl of CH_2Cl_2 were treated with 0.5 ml of TFA for 6 h at room temperature. The solvent was removed in vacuo and to the resulting residue 100 μl of CH_2Cl_2 and 0.5 ml of TFAA were added. Then the reaction mixture was stirred for 5 h at room temperature before it was concentrated in vacuo. The residue was redissolved in 0.5 ml of CH_2Cl_2, 100 μl of NEt_3 was added and the mixture was stirred for an additional h at room temperature. The crude product, that was obtained after removal of the solvent, was purified by CC (EtOAc/HOAc=90/10) to yield 4 mg (77%) of **4**.

Colorless crystals, mp 145–147°C. $[\alpha]_D^{23}$=−71.4 (*c*=0.28 in CH_2Cl_2). TLC: R_f=0.22 (EtOAc/glacial acetic acid=90/10). ^{1}H NMR (CD_2Cl_2): δ=1.21 (qd, *J*=12.5/3.3 Hz, 1H, NCHRCH_{2ax}), 1.24–1.40 (m, 1H, NCH_2CH_{2ax}), 1.44 (qt, *J*=13.0/3.2 Hz, 1H, NCH_2CH_2-CH_{2ax}), 1.62–1.70 (m, 2H, NCHRCH_{2eq} and NCH_2CH_{2eq}), 1.88–1.96 (m, 1H, $NCH_2CH_2CH_{2eq}$), 2.66 (dd, *J*=17.6/1.5 Hz, 1H, $NCOCH_2$), 2.725 (d, *J*=17.6 Hz, 1H, $NCOCH_2$), 2.73 (td_{broad}, *J*=13/3 Hz, 1H, NCH_{2ax}), 3.61 (dd, *J*=12.5/3.3 Hz, 1H, NCHR), 4.13 (dd_{broad}, *J*=13/4 Hz, 1H, NCH_{2eq}), 6.14 (d, *J*=5.7 Hz, 1H, OCOCH=), 7.42 (d, *J*=5.7 Hz, 1H, OCOCH=CH). 100 MHz ^{13}C NMR (CD_2Cl_2): δ=23.90 ($NCH_2CH_2CH_2$), 24.54 (NCH_2CH_2), 28.77 (NCRHCH_2), 39.96 (NCOCH_2), 40.81 (NCH_2), 64.87 (NCHR), 89.06 (CR_3OR), 122.78 (O_2CC=), 154.61 (O_2-CCH=CH), 168.55 (NCO), 171.18 (O_2C). IR: $\tilde{\nu}$=3445 cm^{-1}, 3080, 2939, 2853, 1760, 1683. MS (CH_4, CI); *m/z* (%): 208 (100) [M+H^+]. $C_{11}H_{13}NO_3$ (207.2): calcd C 63.76, H 6.32, N 6.76; found C 63.48, H 6.37, N 6.60.

6. X-Ray analyses

Crystal data for **3**. $C_{11}H_{13}NO_3$, *M*=207.22, monoclinic, space group *C*2, *a*=15.792 (3), *b*=5.4734(8), *c*=12.599 (3) Å, β=109.83 (2), volume=1024.5 (3) $Å^3$, *Z*=4, D_c=1.343 mg m^{-3}, *m*=0.098 mm^{-1}, crystal dimensions. 13×30×53 mm^3, *F*(000)=440, *T*=295(2) K, θ=2.70–23.96°. 1879 reflections measured, unique reflections 1601 [R_{int}=0.0118], min. and max. transmission 0.9372 and 0.9979, *R*1=0.0346, *wR*2=0.0849 for all 1522 reflections with $I>2\sigma(I)$ and *R*1=0.0371, *wR*2=0.0883 for all reflections and 136 refined parameters and 1 restraint. Final electron density 0.164 and −0.178 e $Å^{-3}$, *S*=1.129, absolute structure parameter—0.3 (13).

The data set was collected on a Nonius MACH3 Kappa diffractometer with Mo Kα radiation (λ=0.71073 Å). The structure was solved by direct methods using SHELXS-86[20] and refined by full matrix least squares on F^2 by SHELXL-93.[21] The molecular views were realized by ZORTEP.[22]

Crystal and data collections parameters were deposited with the Cambridge Crystallographic Data Center. The data will be sent on quoting the CCDC-200973 number (e-mail: deposit@ccdc.cam.ac.uk).

Acknowledgements

Financial support of this work by the Deutsche Forschungsgemeinschaft, the Fonds der Chemischen Industrie and the BMBF is gratefully acknowledged.

References

1. (a) Snieckus, V. In *The Alkaloids. The Securinega Alkaloids*; Manske, R. H. F., Ed.; Academic: New York, 1973; Vol. 14, pp 425–506. (b) Beutler, J. A.; Brubaker, A. N. *Drugs Future* **1987**, *12*, 957–976.
2. Murav'eva, V. I.; Ban'kovskii, A. I. *Chem. Abstr.* **1957**, *51*, 8121a.
3. Sito, S.; Kodera, K.; Shigematsu, N.; Ide, A.; Sugimoto, N.; Horii, Z.; Hanaoaka, M.; Yamawaki, Y.; Tamura, Y. *Tetrahedron* **1963**, *19*, 2085. and references cited.
4. *Russian Pharmacopeia*; 10th ed., 1968; pp 612–614.
5. Beutler, J. A.; Karbon, E. W.; Brubaker, A. N.; Malik, R.; Curtis, D. R.; Enna, S. J. *Brain Res.* **1985**, *330*, 135–140.
6. Mensah, J. L.; Lagarde, I.; Ceschin, C.; Michel, G.; Gleye, J.; Fouraste, I. *J. Ethnopharmacol.* **1990**, *28*, 129–131.
7. Weenen, H.; Nkunya, M. H. H.; Bray, D. H.; Mwasumbi, L. B.; Kinabo, L. S.; Kilimali, V. A. E. B.; Wijnberg, J. B. P. A. *Planta Med.* **1990**, *56*, 371–373.
8. (a) Horii, Z.; Hanaoka, M.; Yamawaki, Y.; Tamura, Y.; Saito, S.; Shigematsu, N.; Kotera, K.; Yoshikawa, H.; Sato, Y.; Nakai, H.; Sugimoto, N. *Tetrahedron* **1967**, *23*, 1165–1174. (b) Liras, S.; Davoren, J. E.; Bordner, J. *Org. Lett.* **2001**, *3*, 703–706.
9. (a) Honda, T.; Namiki, H.; Kudoh, M.; Watanabe, N.; Nagase, H.; Mizutani, H. *Tetrahedron Lett.* **2000**, *41*, 5927–5930. (b) Honda, T.; Namiki, H.; Kudoh, M.; Nagase, H.; Mizutani, H. *Heterocycles* **2003**, *59*, 169–187.
10. (a) Wanner, K. Th.; Wadenstorfer, E.; Kärtner, A. *Synlett* **1991**, 797–799. (b) For an excellent review of *N*-acyliminium ion chemistry see: Speckamp, W. N.; Moolenaar, M. J. *Tetrahedron* **2000**, *56*, 3817–3856.
11. (a) Paintner, F. PhD Thesis, LMU München, 1995. (b) Wanner, K. Th.; Paintner, F. *Tetrahedron* **1994**, *50*, 3113–3122. (c) Wanner, K. Th.; Paintner, F. *Justus Liebigs Ann. Chem.* **1996**, 1941–1948. (d) Kammler, R. PhD Thesis, LMU München, 2000.
12. (a) Mayr, H. In *Fundamentals of the Reactions of Carbocations with Nucleophiles*; *Plastics Engineering*, Matyjaszewski, M., Ed.; Marcel Dekker: New York, 1996; Vol. 35, pp 51–136. (b) Paquette, L. A. *Encyclopedia of Reagents for Organic Synthesis*; Wiley: New York, 1995; pp 648–651.
13. Vetuschi, C.; Ottolino, A.; Tortorella, V. *Gazz. Chim. Ital.* **1975**, *105*, 935–938.
14. (a) Corey, E. J.; Katzenellenbogen, J. A.; Gilman, N. W.; Roman, S. A.; Erickson, B. W. J. *J. Am. Chem. Soc.* **1968**, *90*, 5618–5620. (b) Corey, E. J.; Yamamoto, H. J. *J. Am. Chem. Soc.* **1970**, *92*, 6636–6637. (c) Corey, E. J.; Yamamoto, H. *J. Am. Chem. Soc.* **1970**, *92*, 6637–6638.

15. (a) Kraus, G. A.; Roth, B. *J. Org. Chem.* **1980**, *45*, 4825–4830. (b) Bal, B. S.; Childers, W. E.; Pinnick, H. P. *Tetrahedron* **1981**, *37*, 2091–2096.
16. Wassermann, H. H.; Robinson, R. P.; Carter, C. G. *J. Am. Chem. Soc.* **1983**, *105*, 1697–1698.
17. (a) Mukaiyama, T.; Bald, E.; Saigo, K. *Chem. Lett.* **1975**, 1163–1167. (b) Huang, H.; Iwasawa, N.; Mukaiyama, T. *Chem. Lett.* **1984**, 1465–1466.
18. Cory, R. M.; Ritchie, B. M.; Shrier, A. M. *Tetrahedron Lett.* **1990**, *31*, 6789–6792.
19. Bardili, B.; Marschall-Weyerstahl, H.; Weyerstahl, P. *Liebigs Ann. Chem.* **1985**, 275–300.
20. Sheldrick, G. M. *SHELXS-86, Program for Crystal Structure Solution*; University of Göttingen, 1986.
21. Sheldrick, G. M. *SHELXL-93, Program for Crystal Structure Refinement*; University of Göttingen, 1993.
22. Zsolnai, L.; Huttner, G. *ZORTEP*; University of Heidelberg, 1994.