Planar Chirality: Cycloaddition and Transannular Reactions of Optically Active Azoninones that Contain (*E*)-Olefins

Alexander Sudau,[a] Winfried Münch,[a] Jan W. Bats,[b] and Udo Nubbemeyer*[a]

Abstract: Unsaturated nine-membered ring lactams that contain (*E*)-olefins within the ring are characterized by planar chiral properties. Thus, selective conversions of the double bond allowed a complete transfer of the planar chiral information into new stereogenic centers. The basis of the transformations was the high activation barrier that prevented efficient flipping of the double bond at room temperature (epimerization $pR \Leftrightarrow pS$) with respect to the ring. Cycloadditions led diastereoselectively to cyclopropano, epimino, epoxy, and dihydroxy azonanones under mild conditions with moderately high yields. The epoxy azonanones were subjected to regio- and diastereoselective transannular epoxide opening/ring contraction sequences to give hydroxy indolizidinones. The regiochemical and stereochemical outcome strongly depends on the configuration of the oxirane and the chiral information of the lactam unit. The so-formed optically active bicycles with defined substitution patterns should serve as versatile building blocks in alkaloid synthesis.

Keywords: chirality · cycloaddition · hydroxylation · lactams · ring contraction

Introduction

"Planar chirality" is a controversial terminus technicus: on the one hand, such stereogenic information can be described as a chirality that originates from a helix. A sequence of three nonplanar vectors is characterized by a defined torsion angle with a topographic descriptor *P* (plus) or *M* (minus), depending on its sign.[1] By using the terms stereogenic center, axis, plane, and helix defined by Cahn, Ingold, and Prelog,[2] a stereogenic plane can be described as a planar arrangement of at least four centers (atoms) with a fifth center placed outside of this original plane. A ring that contains an *E* double bond corresponds to these requirements. Following the Schlögl nomenclature,[3] the descriptors *pS* (*M*) and *pR* (*P*) can be used to describe the topographic properties of the ring arrangement (p = planar).

The planar chiral properties of medium-sized rings that contain (*E*)-olefins can be investigated because they have a measurable half-life. While optically active, planar chiral, eight-membered rings are known to be stable, nine- and ten-membered rings suffer from a fast racemization because of the facile flipping of the double bond with respect to the ring.[4] In contrast, a range of unsaturated nine-membered ring lactams was found to maintain the planar chiral information of the (*E*)-olefin at room temperature.[5] Preliminary kinetic investigations and molecular mechanics calculations gave a half-life of $\approx$10 h at 40 °C and an epimerization activation energy of $>$23 kcal^{-1}, depending on the substitution pattern. The highly hindered rotation of the double bond with respect to the ring allows the planar diastereomers to undergo transannular reactions depending on the conformation: the addition of soft electrophiles, such as PhSeBr, Br_2, and I_2 at the double bond leads to a consecutive attack by the lactam nitrogen at the nascent onium ion. Subsequent debenzylation leads regioselectively and diastereoselectively to the corresponding indolizidinones with a defined substitution pattern. The planar chiral information is completely converted into new chiral centers. Here we report on cycloadditions of the unsaturated planar diastereomeric nine-membered ring lactams. The 5,6-unsaturated 3,8-disubstituted azoninones, *pS*-**3** and *pR*-**4**, serve as reactants in the syntheses of 3,5,6,8-tetrafunctionalized nine-membered ring lactams **5**–**18** and indolizidinones **19**–**21**.[6]

[a] Dr. U. Nubbemeyer, A. Sudau, W. Münch
Institut für Chemie, Organische Chemie
Freie Universität Berlin, Takustr. 3, 14195 Berlin (Germany)
Fax: (+49) 30-83855163
E-mail: udonubb@chemie.fu-berlin.de

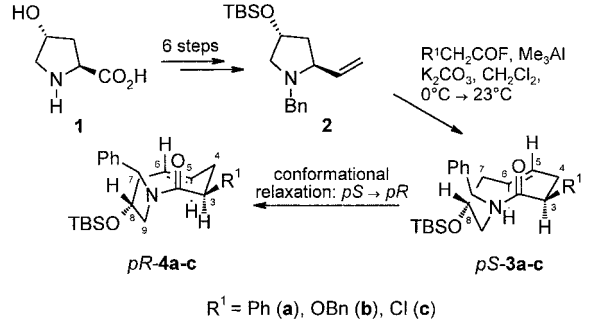
[b] Dr. J. W. Bats
Institut für Organische Chemie, J. W. Goethe Universität Frankfurt
Marie-Curie-Str. 11, 60439 Frankfurt/Main (Germany)

Supporting information (^{13}C NMR spectra, NOEDS data for all new compounds, modified preparation procedure for *p*TosN=IPh, spectral data of **19**, **22**, and **23**, crystallographic data for **5c**, **11c**, **12c**, **12b**, **20b**, and ORTEP plots for **5c**, **11c**, **12b** and **12c**; 44 pages overall) for this article is available on the WWW under http://www.wiley-vch.de/home/chemistry/ or from the author.

Results and Discussion

The 2-azoninones *pS*-**3** and *pR*-**4**, which contain 5,6-(*E*) double-bonds, were efficiently generated by a seven-step

sequence that started from *trans*-4-hydroxy-L-(−)-proline (**1**) with an overall yield of ≈50% (Scheme 1):[5] after esterification of **1**, the *N*-benzyl group was introduced by treatment of the secondary amine with benzyl chloride in the presence of triethylamine. The protection of the alcohol as a TBS ether (TBS = *tert*-butyldimethylsilyl) generated the proline ester.

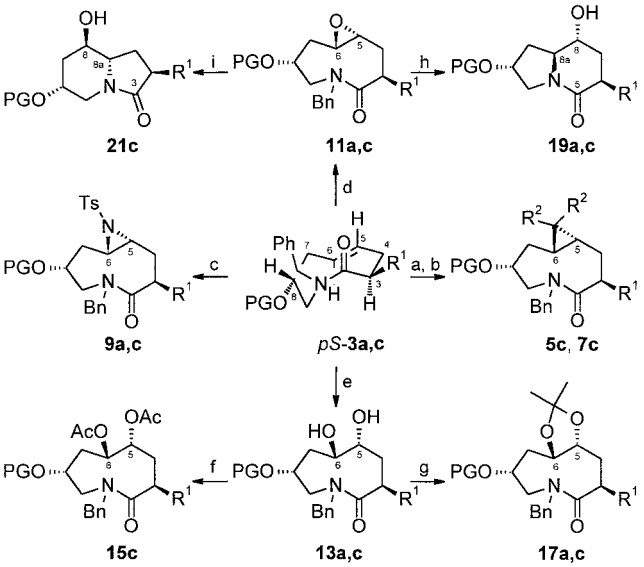


Scheme 1. Synthesis of the planar diastereomeric azoninones *pS*-**3** and *pR*-**4**.

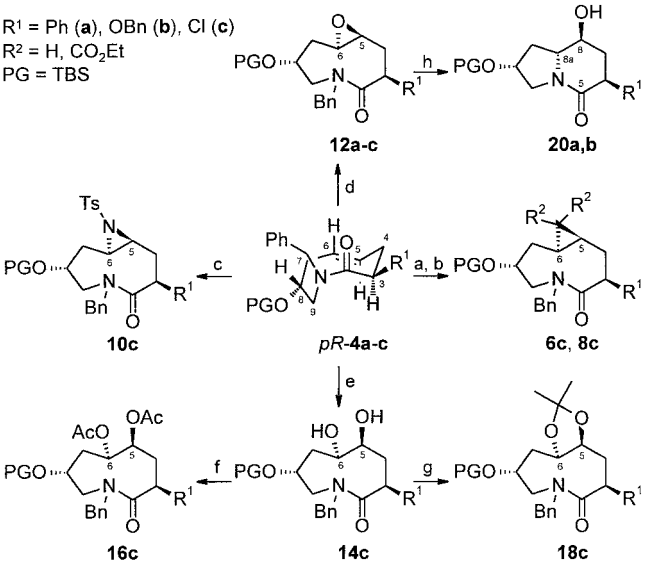
The reduction of the carboxyl function with diisobutyl aluminum hydride (DIBALH) yielded the primary carbinol. A subsequent Swern oxidation led to the corresponding aldehyde, which was immediately converted into the vinylpyrrolidine **2** by a Wittig olefination with methylenetriphenylphosphorane to avoid any epimerization to the 2,4-*cis* product. The zwitterionic aza-Claisen rearrangement of the *trans*-4-silyloxy-2-vinylpyrrolidine (**2**) to the γ,δ-unsaturated lactams *pS*-**3** proceeded with an almost complete 1,4-chirality transfer and the formation of an (*E*)-olefin in the medium-sized ring, which is characterized by additional planar chiral properties: immediately after the reaction, lactams **3a–c** were isolated which had conformations that contain a rigid *pS* conformation of the olefin and a fairly flexible arrangement of the lactam unit. The relaxation from the kinetically generated conformations into the thermodynamically stable forms **4a–c**, with almost rigid arrangements of lactam and olefin with respect to the ring, required a significantly high activation energy (Scheme 1).[7]

With the intention of testing some cycloaddition reactions at the *E* double-bonds of the azoninones, two potential problems should be considered. On the one hand, the nine-membered ring framework is maintained, even in the product. Several azoninones **3** and **4** have characteristic, fairly flexible amide groups that complicate the NMR spectra and the correct determination of the structural properties. On synthesizing azonanones, the probability of generating flexible compounds should increase.[8] On the other hand, the reactant olefin lacks substituents that determine the regioselectivity. Hence, the generation of regioisomers is avoided by employing exclusively symmetric reagents on investigating the first set of cycloadditions. The results starting from *pS*-**3a,c** are outlined in Scheme 2; the results starting from *pR*-**4a–c** are outlined in Scheme 3. Details of the results of the cycloaddition reactions are given in Table 1. For nomenclature see Table 2.

Initial cyclopropanations were carried out by subjecting the azoninones *pS*-**3a,c** and *pR*-**4a–c** to the conditions published



Scheme 2. Cycloadditions of azoninone *pS*-**3a,c** and oxirane opening-ring contraction of epoxy azonane **11**: a) CH_2N_2, [$Pd(OAc)_2$] cat., Et_2O, RT, 12 h; b) $N_2C(CO_2Et)_2$, [$Pd(OAc)_2$] cat., PhMe, 60 °C, 12 h; c) *p*TosN=I-Ph, [$Cu(OTf)_2$] cat., MeCN, 10 °C, 0.5–3 h; d) *m*CPBA, CH_2Cl_2, phosphate buffer (pH = 7), 0 °C or RT, 3–5 h; e) $RuCl_3$ cat., $NaIO_4$, H_2O, MeCN, EtOAc, 5 min, 0 °C; f) Ac_2O, Py, DMAP cat., CH_2Cl_2, RT, 3 h; g) $Me_2C(OMe)_2$, *p*TsOH cat., Me_2CO, RT, 3 h; h) TMSI, (LiI), $CHCl_3$, RT, 0.5–5 min; i) TMSI, LiI, $CHCl_3$, −10 °C, 3 min. Yields: see Tables 2 and 3.



Scheme 3. Cycloadditions of azoninone *pR*-**4a–c** and oxirane opening-ring contraction of epoxy azonane **12**. Reaction conditions: see legend of Scheme 2. Yields: see Tables 2 and 3.

by Vorbrüggen on the treatment of olefins with diazomethane in presence of catalytic amounts of palladium(II) acetate.[9] Low reaction temperatures of maximal 23 °C were recommended because of the long reaction time of more than 12 h. Epimerization (*pS*-**3c** ⇔ *pR*-**4c**) did not occur; for example, single diastereomers of **5c** or **6c** were isolated with high yield (Table 1, Entries a and b).[7] In contrast, the analogous cyclopropanation with diethyl diazomalonate as the carbenoid equivalent required significantly higher reaction temper-

© WILEY-VCH Verlag GmbH, D-69451 Weinheim, 2001
0947-6539/01/0703-0612 $ 17.50+.50/0 *Chem. Eur. J.* **2001**, *7*, No. 3

Table 1. Results of the cycloaddition reactions.

Entry	Azoninone	Reagent	Scale[a]	Yield [%]	Azonanones (ratio) from *pS*	from *pR*
a	*pS*-**3c**	CH_2N_2	p	92	**5c** (1)	**6c** (–)
b	*pR*-**4c**	CH_2N_2	p	96	**5c** (9)	**6c** (91)
c	*pR*-**4c**	$N_2C(CO_2Et)_2$	a	30	**7c** (2)	**8c** (3)
d	*pS*-**3a**	*p*TsN=IPh	a	58	**9a** (1)	**10a** (–)
e	*pS*-**3c**	*p*TsN=IPh	a	56	**9c** (1)	**10c** (–)
f	*pR*-**4c**	*p*TsN=IPh	p	52	**9c** (–)	**10c** (1)
g	*pS*-**3a**	*m*CPBA	p	100	**11a** (1)	**12a** (–)
h	*pR*-**4a**	*m*CPBA	p	95	**11a** (1)	**12a** (6)
i	*pR*-**4b**	*m*CPBA	p	91	**11b** (–)	**12b** (1)
j	*pS*-**3c**	*m*CPBA	p	92	**11c** (1)	**12c** (–)
k	*pR*-**4c**	*m*CPBA	a	86	**11c** (–)	**12c** (1)
l	*pS*-**3a**	$RuCl_3/NaIO_4$/DMP	p	95	**17a** (1)	**18a** (–)
m	*pS*-**3c**	$RuCl_3/NaIO_4/Ac_2O$	a	70	**15c** (1)	**16c** (–)
n	*pR*-**4c**	$RuCl_3/NaIO_4/Ac_2O$	a	98	**15c** (10)	**16c** (88)
o	*pS*-**3c**	$RuCl_3/NaIO_4$/DMP	a	71	**17c** (1)	**18c** (–)
p	*pR*-**4c**	$RuCl_3/NaIO_4$/DMP	a	72	**17c** (17)	**18c** (55)

[a] a = analytical scale, not optimized; p = preparative scale.

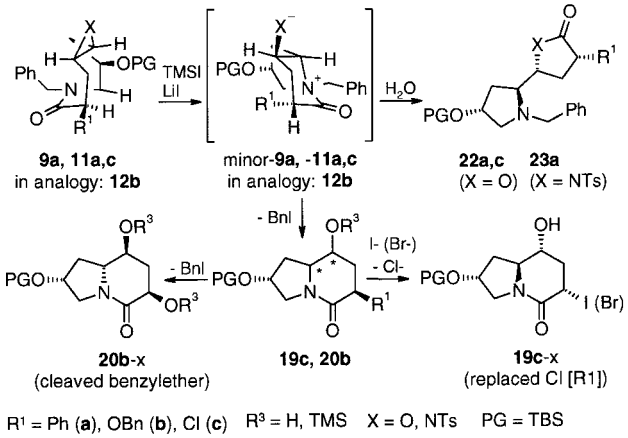
Table 2. Nomenclature of the azonanones.

R[1]\X	CH_2	$C(CO_2Et)_2$	NTos	O	$(OH)_2$	$(OAc)_2$	$OC(Me_2)O$
from *pS*-**3**	**5**	**7**	**9**	**11**	**13**	**15**	**17**
Ph/Cl	–/**c**	–/**c**	**a/c**	**a/c**	**a/c**	–/**c**	**a/c**
from *pR*-**4**	**6**	**8**	**10**	**12**	**14**	**16**	**18**
Ph/OBn/Cl	–/–/**c**	–/–/**c**	–/–/**c**	**a/b/c**	–/–/**c**	–/–/**c**	–/–/**c**

atures of 65 °C. Hence, the reaction of azoninone *pS*-**3c** led to the formation of a mixture of the diastereomeric 5,6-cyclopropano azonanones **7c** and **8c** in a 2:3 ratio. This indicated a partial epimerization of *pS*-**3c** into *pR*-**4c** during the course of the reaction (Table 1, Entry c).

The generation of 5,6-aziridino azonanones was somewhat tricky. The best reagent to introduce the nitrogen at low temperatures was found to be (*N*-(*p*-toluenesulfonyl)imino)-phenyl iodinane, as reported by Yamada.[10] The lactams *pS*-**3a,c** and *pR*-**4c** were treated with the reagent in presence of catalytic amounts of copper(II) triflate to give the aziridines **9a**, **9c**, and **10c**, respectively, as single diastereomers (Table 2, Entries d–f).[11] Although the reaction was found to be complete after 0.5–3 h according TLC analyses, the yields obtained were only moderate (50–60%) after aqueous work-up. The *N*-tosyl aziridines were found to be unstable: azonanone **9a** decomposed completely after being stored at room temperature overnight; the major product generated was the five-membered ring lactam **23** (Scheme 4) which indicated a reorganization of the bicyclic skeleton.[12]

The epoxidation of the azoninones *pS*-**3** and *pR*-**4** in a buffered *m*-chloroperbenzoic acid (*m*CPBA) solution proceeded with fairly high yields to give the 5,6-epoxy azonanones **11** and **12** (Table 2, Entries g–k).[13] The cycloaddition was always found to be diastereoselective because of an efficient and fast reaction, even at low temperatures (0–5 °C), that mostly prevented epimerization (*pS*-**3** ⇔ *pR*-**4**). In contrast to the epimino azonanones, the corresponding epoxides **11** were more stable: column chromatography and HPLC could be run under neutral conditions to avoid any skeletal rearrangement to give the corresponding lactones



Scheme 4. Competing reactions of epoxy azonanones **11** during the course of the transannular ring contractions.

22 (Scheme 4). The products could be stored for several months without decomposition.

The introduction of two adjacent OH groups was effected by a procedure published by Shing:[14] the azoninones *pS*-**3** and *pR*-**4** were treated with $NaIO_4$ in the presence of catalytic amounts of $RuCl_3$ to give diastereoselectively the dihydroxy-azonanes **13** and **14**, respectively (Table 2, Entries l–p). The purification of the polar diols and the consecutive proof of the stereochemical properties by spectral analyses was difficult. Hence, the crude diols **13** and **14** were immediately protected under standard basic conditions with Ac_2O to give the 5,6-bisacetates **15** and **16**,[15] or, alternatively, with dimethoxypropane in presence of catalytic amounts of *p*TsOH, to give the 5,6-acetonides **17** and **18**.[16] Both protective-group insertions proceeded with moderately high yields, the resulting products were easily to handle as regards isolation and purification. The ease of spectral analyses depended strongly on the substitution pattern of the materials: compounds **16** and **18** were characterized by the coexistence of at least two conformations at room temperature.

All cycloadditions led diastereoselectively to single azonanones **5**–**14**, with respect to the newly formed stereogenic centers.[7] The relative configuration of the protons of C5 and C6 was always found to be *trans*, as proved beyond doubt by NOE analyses.[17] These results were confirmed independently by X-ray analyses of some azonanones (Figures 1–3).[18] On

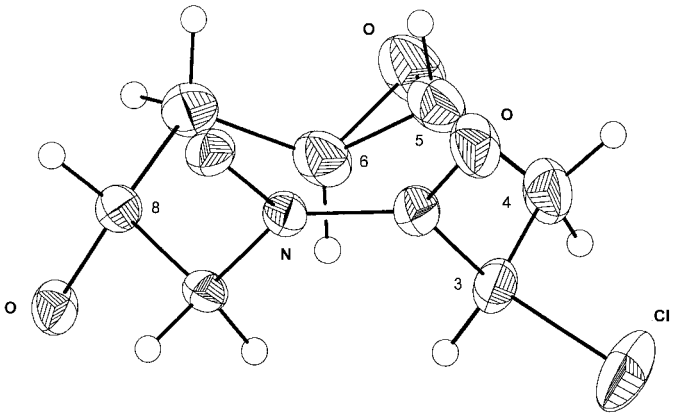


Figure 1. ORTEP plot of azonanone **11c** (without TBS and Ph).

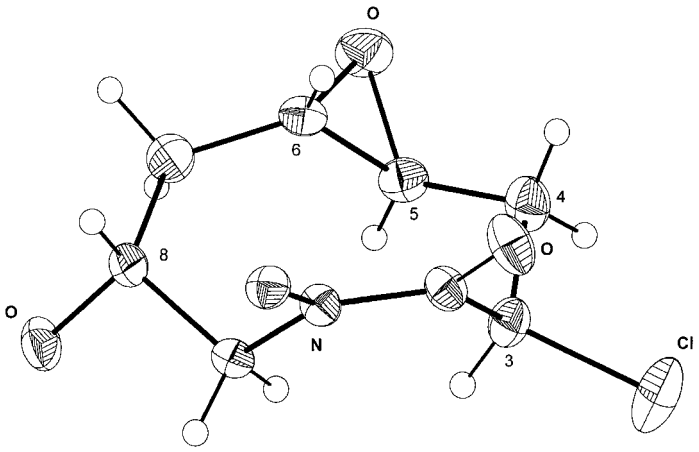


Figure 2. ORTEP plot of azonanone **12c** (without TBS and Ph)

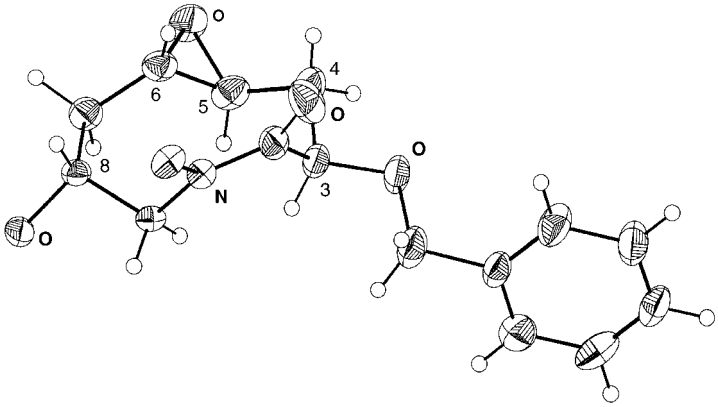


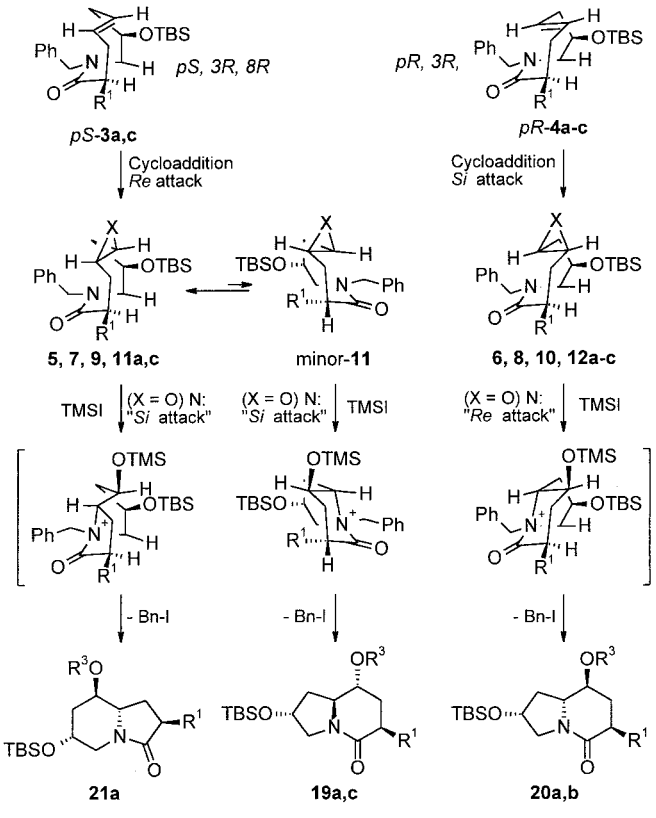
Figure 3. ORTEP plot of azonanone **12b** (without TBS and Ph)

generating the azonanones that contain an additional three-membered ring (**5**–**12**), the properties of the ^{1}H and ^{13}C NMR spectra were closely related to those of the unsaturated reactants: the cyclopropano, epimino, and epoxy azonanones **5**, **7**, **9**, and **11** that originated from *pS*-**3** were identified by the proximity of the H3, H6, and H9α protons. The lactam unit showed a *cis* arrangement of C3 and C9 (about 20% NOE amplification of H3 and H9α) with respect to its partial double-bond character and a *syn* arrangement of the carbonyl O atom and H5. In contrast to the reactant *pS*-azoninones **3**, no evidence of further species (conformers, equilibration of the lactam function) could be detected in the NMR spectra which implies almost rigid conformations.

The cyclopropano, epimino, and epoxy azonanones **6**, **8**, **10**, and **12** that originate from *pR*-**4**, were characterized by the proximity of the protons H3, H5, and H9α. Again, the lactam unit showed a *cis* arrangement of C3 and C9 (about 20% NOE amplification of H3 and H9α) with respect to its partial double bond. However, a *syn* arrangement between the carbonyl O atom and H6 was found. In several cases, two sets of peaks occurred in the NMR spectra. Furthermore, in the NOE spectra, the irradiation of several peaks induced negative peaks at different shift values. Evidently, a transfer of magnetization from the major compound to a minor diastereomer was found. Both types of results indicated a potential equilibrium of at least two conformations (planar diastereomers) of the lactam function (partial double bond). In contrast, the reactant azoninones *pR*-**4** showed no evidence of further species, an indication of almost rigid conformations.[5]

In the analysis of the dihydroxyazonanones **13** and **14** as well as the protected derivatives **15** to **18**, the determination of the configuration of the newly generated stereogenic centers was more complicated: at room temperature; all NMR spectra were characterized by a doubled set of signals or by very broad peaks which indicated conformational mobility. The lower temperature NMR spectra (10 to $-10\,^{\circ}$C) always contained two sets of sharp peaks which represents an equilibrium of two discrete conformations. The structural properties of at least one of these conformations was determined by NOE analysis to prove the complete diastereoselectivity of the dihydroxylation.[17]

Apparently, the stereochemical course of the reactions was quite reasonable, all reactions underwent well-known electrophilic [2+1] cycloaddition or *syn* dihydroxylation at the olefin (Scheme 5). In the case of the *pS*-lactams **3**, the reagent attacked the unshielded *Re* face of the double bond to give the 5*R*,6*R* azonanones **5**, **9**, **11**, and **13**. Because of the change in the planar chirality, the double bond of the *pR*-lactams **4** suffered from a attack on the *Si* face of the reagent to give the 5*S*,6*S* azonanones **6**, **10**, **12**, and **14**. As expected, no mixtures of the two series of azonanones were found if the reaction



Scheme 5. Cycloaddition and regio- and diastereoselective transannular ring contraction paths of the azoninones *pS*-**3** and *pR*-**4**.

© WILEY-VCH Verlag GmbH, D-69451 Weinheim, 2001
0947-6539/01/0703-0614 $ 17.50+.50/0 *Chem. Eur. J.* **2001**, *7*, No. 3

temperature was low enough and the time was sufficiently short to prevent the flipping of the double bond with respect to the ring (*pS*-**3** ⇔ *pR*-**4**). The activation energy of the epimerization of the planar chiral information was significantly higher than that of the addition reaction (*anti*-Curtin–Hammett). As a limitation, the cyclopropanation of *pS*-**3c** with diazodiethyl malonate gave a mixture of **7c** and **8c** (resulting from *pR*-**4c** formed during the course of the reaction) because of the high reaction temperature. Evidently, both azoninones *pS*-**3** and *pR*-**4** were characterized by related reactivities, no resolution (only one of the diastereomers underwent the cycloaddition) could be achieved by the use of the present conditions.

Transannular ring contractions: Recent investigations have shown that diastereoselective and regioselective transannular ring contractions could be achieved by the treatment of *pS*-**3** and *pR*-**4** azoninones with PhSeBr, Br_2, and I_2 to yield the corresponding 8-phenylselenyl, 8-bromo, and 8-iodo indolizidin-5-ones (of type **19** and **20**), respectively.[5, 6] With the intention of generating 8-hydroxy indolizidin-5-ones **19** and **20**, the epoxy azonanones **11** and **12** were chosen as suitable intermediates to investigate the transannular oxirane opening.

The epoxides **11** and **12** were treated with TMSBr, TMSI, or, alternatively, with TMSI/LiI in $CHCl_3$ at room temperature to induce a fast transannular reaction.[19] The contraction of the nine-membered rings in **11** and **12** was complete almost immediately after the reagent had been added. The products, 8-hydroxy indolizidin-5-ones **19** (from **11**) and **20** (from **12**), were diastereoselectively and regioselectively generated, respectively. In the absence of LiI, the resulting 8-OH function of **19** and **20** was still protected as a TMS ether.

Two aspects were found to be crucial: any water should be carefully excluded to avoid the formation of the competing **22** lactones that originate from an aqueous cleavage of the intermediate acylammonium salt (Scheme 4).[20, 21] Furthermore, the cyclizations of 3-benzyloxy azonanone **12b** and the 3-chloro analogue **11c** and **12c** were found to suffer from some side reactions. The *O*-benzyl group in **12b** was found to be partly removed by the use of excess TMSI or/and by an increase in the reaction time.[22] The chloride in **11c** and **12c** was found to be partly exchanged for bromide (TMSBr) or iodide in the presence of excess LiI or by an increase in the reaction time (Scheme 4).[23] Summing up these findings, a smooth reaction of the epoxy azonanones **11**/**12** required carefully optimized reaction conditions to achieve a maximal yield of the indolizidinones **19**/**20** (Schemes 2 and 3). If the reaction conditions were changed so that a solution of the nine-membered ring lactam **11a** was added to a solution of the reagent at $-10\,^{\circ}C$, the regioisomeric indolizidin-3-one **21a** was isolated as the major product (Scheme 2).[5]

The relative configuration of the new stereogenic centers and the position of the ring junction were proved by NOE analyses[17] and, in one attempt (**20b**), by X-ray analysis (Figure 4 and Table 3).[24]

Mechanistic conclusions: Apparently, the stereochemical course of the ring contractions was quite reasonable: all reactions underwent well-known *anti*-epoxide openings. The

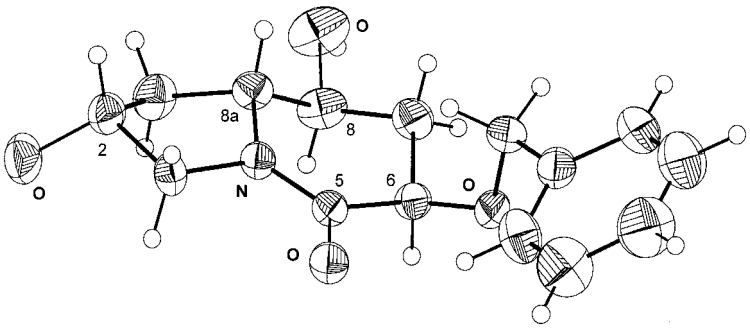


Figure 4. ORTEP plot of indolizidinone **20b**.

Table 3. Data of the transannular reactions.

Entry	Epoxide	Reagent	Scale[a]	Yield [%] of Lactam (R^3) **19**	**20**	**21**	Yield [%] lactone **22**
a	**11a**	TMSI	p	60 (H)	–	–	15
b	**11a**	TMSI/LiI	a	–	–	19 (H)	–
c	**12a**	TMSI	a		32 (H)		–
		TMSBr	a		n.d. (TMS)		
d	**12b**	TMSI/LiI	p		57 (H)		–
e	**11c**	TMSI	a	47 (TMS)	–	–	n.d.[b]
		TMSI/LiI	a	32 (H)	–		–

[a] a = analytical scale, not optimized; p = preparative scale. [b] n.d. = not detected.

electrophilic TMS halide activated the oxirane by attack on the oxygen. The nascent cation at C6 was trapped by an intramolecular attack of the nitrogen to generate the intermediate acylammonium salt. The benzyl group was finally removed by nucleophilic substitution with the halide anion to yield the indolizidinones **19a/c** and **20a/b**, respectively (Scheme 5). Recapitulating the sequence, the azoninone *pS*-**3a/c** underwent an *anti* addition of an electrophilic oxygen and a nucleophilic nitrogen. The initial *Re* attack of the electrophile (O) generated the 5*R*,6*R* epoxy azonanones **11a/c**, the final *Si* attack of the nitrogen led to the corresponding indolizidinones **19a/c**. Because of the inverted planar chiral information, *pR*-**4a/b** underwent a *Si* face addition of the electrophile (O) to give the 5*S*,6*S*-epoxy azonanones **12a/b**. Consequently, the final *Re* attack of the nitrogen at C6 formed the indolizidinones **20a/b**. As expected, no mixtures of the indolizidinones **19** or **20** were found.

The explanation of the regiochemical course of the reaction is still somewhat speculative; however, a preliminary hypothesis should be submitted. All planar diastereomeric arrangements of the azonanones **11** and **12** were characterized by defined transannular distances between the nitrogen and C5 or C6 of the olefin (Table 4). A potential fast equilibrium of at least two conformations (planar diastereomers) could be presupposed according to the NMR analyses, although one of these conformers might have been sparsely populated.[25] The central assumption is that the shortest distance between the nitrogen and C5 or C6 of the olefin, respectively, governs the regiochemical outcome of the transannular reactions that generate the indolizidinones **19** and **20** or **21**.

Determination of the transannular distances (Table 4, Figures 2 and 3) between the nitrogen and C5 or C6 in the 5*S*,6*S*-lactams **12** by X-ray analyses and some simple struc-

Table 4. Transannular distances in 5,6-epoxy azonanones.

5,6-Epoxy azonanone	Transannular distance [Å][a] N to C5 calcd	N to C5 found	N to C6 calcd	N to C6 found
11a	3.18		3.23	
minor-**11a**	3.29		2.88	
trans-**11a**	3.23		2.81	
11c	3.18	3.13	3.23	3.24
minor-**11c**	3.30		2.82	
trans-**11c**	3.24		2.77	
12a	3.39		3.01	
12b	3.35	3.38	2.92	3.05
12c	3.36	3.39	2.91	3.00

[a] Calcd: MM+ optimized structure; found: X-ray analysis.

tures optimized by force-field calculations[26] indicated that N1 was positioned somewhat closer to C6 than to C5. In spite of flexible conformations of these lactams (conformational mobility of the lactam group according NMR and NOE experiments), the ring contraction generated regioselectively the new bond between N1 and C6, as found in the indolizidinones **20** (Figure 4).

Apparently, the analogous argumentation failed to explain the formation of the indolizidinones **19** starting from the 5*R*,6*R*-epoxy lactams **11**: in the present case the transannular distances (Table 4, Figure 1) between the nitrogen and C5 were found to be somewhat shorter than that to C6, according to the X-ray analysis and some simple structures optimized by force-field calculations.[26] Considering the predominant conformation of these lactams, the ground state should have led to the indolizidinones **21**, as found in a single experiment: at $-10\,^{\circ}C$, the transannular ring contraction was significantly faster than a conformational relaxation of the lactam function. This resulted in the regioselective formation of the indolizidinone **21a** (*anti*-Curtin–Hammett). In contrast, the reaction led to the regioisomeric indolizidinones **19** at room temperature, even though no further predominant conformation **11** (planar diastereomer) could be detected (all spectral data of the lactams **11** measured at $-20\,^{\circ}C$, $0\,^{\circ}C$, and room temperature were almost identical). Actually, the dictates of the Curtin–Hammett principle seemed to be the crucial factor that concerns the relative arrangement of the lactam function with respect to the ring. A further conformation, minor-**11** (though sparsely populated), must have been much more reactive with respect to the transannular reaction than the predominant arrangement of **11**, although NOE and NMR data of the 5*R*,6*R*-lactams gave no cogent information concerning the conformational mobility. Simple structures optimized by force-field calculations resulted in short transannular distances between N1 and C6 (relative to that between N1 and C5) in a 5*S*,6*S*-epoxy azonanone that had a conformation of type minor-**11**; however, severe repulsive interactions (at low concentrations) might have circumvented the occurrence of adequate peaks in the spectral analyses. Scheme 5 and Table 4 should enlighten this argumentation. However, selective formation of two regioisomeric products starting from one and the same reactant presupposed the existence of at least two reactive conformations of the azonanones with (planar) diastereomeric properties of the lactam function. Nevertheless, the exact reaction path is still not proven.

Conclusions

The planar diastereomeric azoninones *pS*-**3** and *pR*-**4** were subjected to cycloadditions to synthesize the azonanones **5**–**18**. Low-temperature reactions allowed an almost complete conversion of the planar chiral information of the reactants into new chiral centers of the products. Cyclopropane-, aziridine-, and oxirane-annulated azonanones were synthesized as well as dihydroxylated (protected) nine-membered ring lactams.

The oxirane functions of the epoxy azonanones **11** and **12** underwent regioselective openings and consecutive transannular ring contraction sequences to generate the 8-hydroxy indolizidinones **19**–**21** with a complete stereoselectivity and a high regioselectivity. The exclusive formation of δ-valerolactams was always found when the reactions were carried out at room temperature, although the reactant azonanones were characterized by high conformational mobility of the amide function with diastereomeric properties. As expected, the conversions of the 5*S*,6*S*-azonanones **12** yielded, exclusively, bicycles **20** because of their short N–C6 distances, as determined by X-ray analyses and some force-field optimized calculations. In contrast, the 5*R*,6*R*-azonanones **11** used different reaction paths to generate the bicycles **19**. The direct conversion of the conformation, determined by X-ray and NOE analyses, indicated a slightly shorter N–C5 distance, which implied the formation of (some) γ-butyrolactam product **21**. Evidently, the lactam function of the azonanones **11** was characterized by some flexibility to generate at least one additional, significantly more reactive conformer, minor-**11**, with a shorter N–C6 distance to induce an efficient formation of δ-valerolactam **19**.

We are currently investigating the scope and limitations of the regioselective and diastereoseletive cycloaddition reactions and, if operative, a subsequent ring contraction to employ an appropriate sequence in a natural product synthesis.

Experimental Section

^{1}H NMR and ^{13}C NMR spectra, and NOE experiments were recorded on a Bruker AC250 or on a Bruker AC550 spectrometer at room temperature unless otherwise specified. Tetramethylsilane was used as the internal standard. IR spectra were obtained from a Perkin Elmer 257 or 580B spectrophotometer. Optical rotations were measured with a Perkin Elmer P241 polarimeter in a 1 dm cell. Mass spectra were recorded on a Varian MAT711 or 112S, The high-resolution mass spectra (HRMS) were obtained with a Varian MAT711 spectrometer. Polyfluro kerosene (PFK) was used as the reference and the results were determined by a peak-matching method, resolution: >10000. Ion source temperature: 250 °C; electron energy: 0.8 mA. The melting points (not corrected) were measured with a Büchi SMP20. For HPLC, Knaur pumps UV and RI detectors and Rheodyne injection systems were used. Preparative amounts of the lactams were separated with on a 32 mm × 120 mm column and 5 μm nucleosil 50–5 obtained from Macherey and Nagel, with a flow of about 80 mL min^{-1}. Column chromatography was carried out on Merck silica gel 0.063–0.2 μm, 70–230 mesh A. Progress of the reactions was monitored by

© WILEY-VCH Verlag GmbH, D-69451 Weinheim, 2001
0947-6539/01/0703-0616 $ 17.50+.50/0 *Chem. Eur. J.* **2001**, *7*, No. 3

thin-layer chromatography (TLC) performed on aluminum sheets precoated with silica gel 60 (thickness 0.25 mm). All solvents were dried before use by means of standard procedures. X-ray analyses were performed with $Mo_{K\alpha}$ radiation ($\lambda = 0.71073$ Å). The structures were determined by direct methods with the program SHELXS. The H atoms were taken from a difference Fourier synthesis and were refined with isotropic thermal parameters. The non-H atoms were refined with anisotropic thermal parameters. The structure was refined on F values with the following weighting scheme: $\omega(F) = 4F^2/[\sigma^2(F^2) + (0.03F^2)^2]$. The final difference density was between -0.29 and $+0.36$ e Å^{-3}.

Standard procedure for the cyclopropanation: The azoninone (1 mol equiv) was dissolved in Et_2O (10 mL) at room temperature. A saturated solution of freshly prepared diazomethane (in excess) in Et_2O and $[Pd(OAc)_2]$ (2.5–13 mol %) were added subsequently. The mixture was stirred overnight and then washed (aqueous $NaHCO_3$) and dried (Na_2SO_4). The solvent was removed and the crude product was purified by column chromatography or by re-crystallization.

(3*R*,5*R*,6*R*,8*R*)-1-Benzyl-8-(*tert*-butyldimethylsilyloxy)-3-chloro-5,6-methanoazonan-2-one (5c): Reaction with *pS*-**3c** (200 mg, 0.51 mmol) and $[Pd(OAc)_2]$ (13 mol %) followed the standard cyclopropanation procedure. Chromatography: *n*-hexane/EtOAc 3:1, $R_f = 0.42$; yield: 190 mg (0.47 mmol, 91.7 %) as colorless crystals; m.p. 133–134 °C; $[\alpha]_D^{20} = -96.1$ ($c = 1.6$ in $CHCl_3$); ^{1}H NMR (270 MHz, $CDCl_3$): $\delta = 7.50-7.20$ (m, 5H), 5.20 (d, $J = 14$ Hz, 1H), 5.20–5.10 (dd, $J = 10$, 10 Hz, 1H), 4.20–4.10 (m, 1H), 4.20–4.10 (m, 1H), 4.08–4.00 (d, $J = 14$ Hz, 1H), 3.88–3.78 (dd, $J =$ 15, 9.6, 0.5 Hz, 1H), 3.18–3.08 (dd, $J = 15$, 5 Hz, 1H), 2.60–2.50 (ddd, $J =$ 12.5, 10, 5 Hz, 1H), 2.02–1.95 (d, $J = 14$ Hz, 1H), 1.55–1.42 (ddd, $J = 12.5$, 11, 7 Hz, 1H), 0.8 (s, 9H), 0.75–0.40 (m, 4H), 0.30–0.10 (m, 1H), −0.01 (s, 3H), −0.10 (s, 3H); ^{13}C NMR (67.9 MHz, $CDCl_3$): $\delta = 170.1$ (s), 136.6 (s), 128.7 (d), 128.6 (d), 127.8 (d), 67.7 (d), 52.4 (d), 50.9 (t), 49.0 (t), 39.3 (t), 39.2 (t), 25.7 (q,), 20.4 (d), 17.9 (s), 11.7 (t), 9.9 (d), −4.9 (q), −5.0 (q); IR (KBr) $\tilde{\nu} = 3426$ (m), 2928 (s), 2855 (s), 1656 (s, C=O), 1449 (s), 1254 (m), 1197 cm^{-1} (s); MS (80 eV, EI, 80 °C): *m*/*z* (%): 407 (9) $[M]^+$, 392 (16) $[M - CH_3]^+$, 372 (44) $[M - Cl]^+$, 350 (94) $[M - C_4H_9]^+$; HRMS $C_{22}H_{34}ClNO_2Si$ $[M]^+$: calcd 407.20742; found 407.204736.

(3*R*,5*S*,6*S*,8*R*)-1-Benzyl-8-(*tert*-butyldimethylsilyloxy)-3-chloro-5,6-methanoazonan-2-one (6c): Before starting the cyclopropanation, the reactant azoninone *pS*-**3c** was heated for at least 3 h to 65 °C to achieve a high degree of conversion into azoninone *pR*-**4c** (**3c**:**4c** ≈ 1:4.3). Reaction of azoninone *pR*-**4c** (0.42 g, 1.06 mmol) and $[Pd(OAc)_2]$ (5 mg, 2 mol %) by the standard cyclopropanation procedure, followed by chromatography hexane/EtOAc 3:1, $R_f = 0.42$ gave a colorless oil as a mixture of **6c** and **5c** (4.3:1), yield: 0.41 g (1.02 mmol, 95.7 %). Fractional crystallization of **5c** (solid) from Et_2O/*n*-hexane gave **6c** (oil, purity 96 %). $[\alpha]_D^{20} = -20.1$ ($c = 2$ in $CHCl_3$); ^{1}H NMR (270 MHz, $CDCl_3$): $\delta =$ 7.50–7.20 (m, 5H), 5.40–5.30 (d, $J = 15$ Hz, 1H), 5.00 (dd, $J = 12$, 2 Hz, 1H), 4.20–4.00 (m, 3H), 4.20–4.00 (m, 3H), 3.18–3.10 (d, $J = 12$ Hz, 1H), 2.55–2.45 (ddd, $J = 13$, 3, 3 Hz, 1H), 2.40–2.30 (dd, $J = 14$, 6 Hz, 1H), 0.8 (s, 9H), 0.75–0.40 (m, 5H), −0.01 (s, 3H), −0.10 (s, 3H); ^{13}C NMR (67.9 MHz, $CDCl_3$): $\delta = 171.1$ (s), 136.6 (s), 128.6 (d), 127.9 (d), 127.5 (d), 67.4 (d), 55.7 (d), 53.5 (t), 49.2 (t), 41.9 (t), 39.6 (t), 25.5 (q, Si–C(CH_3)$_3$), 20.6 (d), 17.7 (s, Si–C(CH_3)$_3$), 12.5 (d), 9.3 (t), −4.4 (q, Si–CH_3), −4.9 (q, Si–CH_3); IR (KBr): $\tilde{\nu} = 2953$ (s), 2928 (s), 2857 (s), 1654 (s), 1447 (s), 1257 (m), 1197 (m), 1090 cm^{-1} (s); MS (80 eV, EI, 80 °C): *m*/*z* (%): 407 (13) $[M]^+$, 392 (7) $[M - CH_3]^+$, 372 (34) $[M - Cl]^+$, 350 (100) $[M - C_4H_9]^+$; HRMS (80 eV, 80 °C): $C_{22}H_{34}ClNO_2Si$ $[M]^+$: calcd 407.204736; found 407.20196.

(3*R*,5*R*,6*R*,8*R*)-1-Benzyl-8-(*tert*-butyldimethylsilyloxy)-5,6-bis-(ethyloxycarbonyl)-methano-3-chloroazonane-2-one (7c) and (3*R*,5*S*,6*S*,8*R*)-1-benzyl-8-(*tert*-butyldimethylsilyloxy)-5,6-bis-(ethyloxycarbonyl)-methano-3-chloroazonan-2-one (8c): Reaction of *pS*-**3c** (0.16 g, 0.414 mmol), diethyl diazomalonate (2 equiv) and $[Pd(OAc)_2]$ (10 mg, 10 mol %) in dry toluene (20 mL) at 60 °C, otherwise following the standard cyclopropanation procedure. Purification: filtration through a short silica gel column. Separation by HPLC: 8 % EtOAc/*n*-hexane. Yield: 28.5 mg (0.05 mmol, 12.4 %) **7c** and 40.4 mg (0.07 mmol, 17.7 %) of **8c** as colorless oils.

Minor diastereomer ***7c***: $[\alpha]_D^{20} = -46.1$ ($c = 1.4$ in $CHCl_3$); ^{1}H NMR (270 MHz, $CDCl_3$): $\delta =$ 7.50–7.20 (m, 5H), 5.25–5.15 (d, $J = 14$ Hz, 1H), 5.12–5.05 (dd, $J = 10$, 6 Hz, 1H), 4.30–4.10 (m, 5H), 4.05–3.95 (d, $J =$ 14 Hz, 1H), 3.80–3.75 (ddd, $J = 15$, 10, 0.5 Hz, 1H), 3.20–3.10 (dd, $J = 15$, 6 Hz, 1H), 2.50–2.40 (ddd, $J = 12$, 11, 6 Hz, 1H), 1.90–1.76 (m, 3H), 1.60–1.50 (ddd, $J = 11$, 8, 6 Hz, 1H), 1.30–1.20 (m, 6H), 1.02–0.90 (m, 1H), 0.8 (s, 9H), −0.01 (s, 3H), −0.10 (s, 3H); ^{13}C NMR (67.9 MHz, $CDCl_3$): $\delta =$ 168.3 (s), 167.7 (s), 167.2 (s), 136.2 (s), 128.7 (d), 128.6 (d), 127.9 (d), 66.9 (d, C8), 61.8 (t), 61.5 (t), 51.6 (d), 50.7 (t), 49.2 (t), 39.6 (s), 34.6 (t), 32.6 (t), 32.1 (d), 25.7 (q, Si–C(CH_3)$_3$), 23.7 (d), 17.9 (s, Si–C(CH_3)$_3$), 14.2 (q), 14.1(q), −4.9 (q, Si–CH_3), −5.0 (q, Si–CH_3); IR (KBr): $\tilde{\nu} = 3444$ (w), 2954 (s), 2935 (s), 2856 (s), 1726 (s, C=O), 1661 (s, C=O), 1443 (s), 1366 (s), 1292 (s), 1074 cm^{-1} (s); MS (80 eV, EI, 110 °C): *m*/*z* (%): 551 (23) $[M]^+$, 536 (4) $[M - CH_3]^+$, 516 (8) $[M - Cl]^+$, 506 (17) $[M - C_2H_5O]^+$, 494 (100) $[M - C_4H_9]^+$, 460 (8), 394 (10), 356 (8), 296 (28); HRMS (80 eV, 110 °C): $C_{28}H_{42}NO_6SiCl$ $[M]^+$: calcd 551.24700; found 551.24730.

Major diastereomer ***8c***: The NMR spectra of **8c** showed a second set of minor peaks that originated from a minor conformation (ratio 1:5, flexible amide geometry?). NOE experiments indicated a fast interconversion of minor-**8c** and major-**8c**. $[\alpha]_D^{20} = 16.4$ ($c = 1.3$ in $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 7.50-7.20$ (m, 5H), 5.16–5.12 (d, $J = 15$ Hz, 1H), 5.00–4.96 (dd, $J = 12$, 2 Hz, 1H), 4.34–4.28 (d, $J = 15$ Hz, 1H), 4.34–4.28 (d, $J = 15$ Hz, 1H), 4.25–4.10 (m, 5H), 4.10–4.00 (m, 1H), 3.80–3.75 (ddd, $J = 14.5$, 9 Hz, 1H), 3.20–3.15 (d, $J = 14.5$ Hz, 1H), 2.45–2.40 (d, $J =$ 13 Hz, 1H), 2.15–2.09 (dd, $J = 13$, 6 Hz, 1H), 1.93–1.85 (ddd, $J = 12$, 8, 4 Hz, 1H), 1.85–1.78 (ddd, $J = 12$, 12, 12 Hz, 1H), 1.62–1.58 (dd, $J = 11$, 8 Hz, 1H), 1.30–1.20 (m, 6H), 1.05–0.98 (ddd, $J = 13$, 10, 10 Hz, 1H), 0.8 (s, 9H), −0.01 (s, 3H), −0.10 (s, 3H); ^{13}C NMR (67.9 MHz, $CDCl_3$): $\delta =$ 169.8 (s), 167.4 (s), 166.9 (s), 136.6 (s), 128.7 (d), 128.0 (d), 127.6 (d), 67.3 (d), 61.8 (t), 61.7 (t), 54.6 (d), 54.4 (t), 49.9 (t), 37.6 (s), 36.4 (t), 34.1 (t), 32.3 (d), 25.7 (q, Si–C(CH_3)$_3$), 25.5 (d), 17.7 (s, Si–C(CH_3)$_3$), 14.2 (q), −4.4 (Si–CH_3), −4.8 (Si–CH_3); IR (KBr): $\tilde{\nu} = 3065$ (m), 3032 (m), 2932 (s), 2858 (s), 1727 (s, C=O), 1660 (s, C=O), 1449 (s), 1368 (s), 1213 (s), 1094 cm^{-1} (s); MS (80 eV, EI, 120 °C): *m*/*z* (%): 551 (7) $[M]^+$, 536 (2) $[M - CH_3]^+$, 516 (5) $[M - Cl]^+$, 506 (11) $[M^- C_2H_5O]^+$, 494 (100) $[M - C_4H_9]^+$, 460 (13), 394 (10), 356 (10), 296 (20); HRMS (80 eV, 120 °C): $C_{28}H_{42}NO_6SiCl$ $[M]^+$: calcd 551.24700; found 551.24762.

Standard procedure for the aziridination: The azoninone (1 mol equiv) in dry MeCN was treated with (*p*-toluenesulfonylimino)phenyliodinane (1.2–1.4 equiv) and $[Cu(OTf)_2]$ (1–5 mol %) at 10 °C. After complete conversion of the reactant (careful monitoring by TLC) the mixture was hydrolyzed with aqueous $NaHCO_3$. The aqueous layer was extracted with Et_2O and washed with brine. After drying (Na_2SO_4), the solvent was removed and the crude product was purified by column chromatography or by HPLC.

(3*S*,5*R*,6*R*,8*R*)-1-Benzyl-8-(*tert*-butyldimethylsilyloxy)-5,6-(*N*-tosyl)-epimino-3-phenylazonan-2-one (9a): Reaction with *pS*-**3a** (0.15 g, 0.34 mmol), PhI=NTos (1.4 equiv) and $[Cu(OTf)_2]$ (2 mg, 1.2 mol %) in dry MeCN (15 mL). Reaction time: 30 min. Purification: the crude oil was dissolved in Et_2O, most of the *p*-toluenesulfonylamide that originated from decomposed PhI=NTos precipitated after addition of excess hexane (→ Et_2O/hexane 1:5). After filtration, the crude oil was purified by means of HPLC (12 % EtOAc/*n*-hexane). Yield 0.12 g (0.2 mmol, 57.7 %) of **9a** as a colorless oil. Compound **9a** was found to be unstable, and converted to give **23** with some decomposition. $[\alpha]_D^{20} = -54.8$ ($c = 1.5$ in $CHCl_3$); ^{1}H NMR (270 MHz, $CDCl_3$): δ 7.90–7.80 (d, $J = 8$ Hz, 2H), 7.60–7.10 (m, 12H), 5.20–5.10 (d, $J = 14$ Hz, 1H), 4.55–4.45 (m, 1H), 4.30–4.20 (m, 1H), 4.28–4.10 (d, $J = 14$ Hz, 1H), 4.11–4.01 (dd, $J = 15$, 10 Hz, 1H), 3.36–3.26 (dd, $J =$ 15, 6 Hz, 1H), 3.00–2.90 (dd, $J = 10$, 4 Hz, 1H), 2.80–2.60 (m, 2H), 2.44 (s, 3H), 2.32–2.25 (d, $J = 14.6$ Hz, 1H), 2.10–1.95 (m, 1H), 1.65–1.50 (m, 1H), 0.8 (s, 9H), 0.01 (s, 3H), −0.01 (s, 3H); ^{13}C NMR (67.9 MHz, $CDCl_3$): $\delta = 173.3$ (s, C=O), 144.2 (s), 138.5 (s), 137.1 (s), 136.8 (s), 129.6 (d), 128.7 (d), 128.5 (d), 128.4 (d), 127.9 (d), 127.4 (d), 127.3 (d), 66.5 (d, C8), 51.0 (t), 49.0 (t), 48.9 (d), 43.7 (d), 41.8 (t), 35.1 (t), 31.8 (t), 25.7 (q, Si–C(CH_3)$_3$), 21.6 (q, *p*-Tos-CH_3), 17.9 (s, Si–C(CH_3)$_3$), −4.9 (q, Si–CH_3).

(3*R*,5*R*,6*R*,8*R*)-1-Benzyl-8-(*tert*-butyldimethylsilyloxy)-3-chloro-5,6-(*N*-tosyl)-epiminoazonan-2-one (9c): Reaction with *pS*-**3c** (0.15 g, 0.38 mmol), PhI=NTos (1.3 equiv) and $[Cu(OTf)_2]$ (6 mg, 5 mol %) in dry MeCN (15 mL). Reaction time: 3 h. Purification: The crude product was dissolved in EtOAc and passed through a short silica gel column to remove the *p*-$TosNH_2$. Chromatography by HPLC (12 % EtOAc/*n*-hexane). Yield: 0.12 g (0.21 mmol, 56.1 %) of **9c** as a colorless oil. $[\alpha]_D^{20} = -31.6$ ($c = 1.6$ in $CHCl_3$); ^{1}H NMR (270 MHz, $CDCl_3$): $\delta = 7.85-7.75$ (m, 2H), 7.50–7.10 (m, 7H), 5.20–5.15 (d, $J = 14$ Hz, 1H), 5.15–5.08 (dd, $J = 10$, 7 Hz, 1H), 4.30–4.19 (m, 1H), 4.15–4.05 (d, $J = 14$ Hz, 1H), 3.72–3.60 (dd, $J = 15$, 10 Hz, 1H), 3.38–3.28 (dd, $J = 15$, 6 Hz, 1H), 2.85–2.75 (dd, $J = 11$, 5 Hz, 1H),

2.65 – 2.50 (ddd, $J = 12, 12, 5$ Hz, 1H), 2.50 – 2.38 (m, 1H), 2.42 (s, 3H), 2.35 – 2.25 (m, 1H), 2.25 – 2.20 (d, $J = 14.6$ Hz, 1H), 1.58 – 1.45 (m, 1H), 0.83 (s, 9H), 0.00 (s, 3H), – 0.06 (s, 3H); ^{13}C NMR (67.9 MHz, $CDCl_3$):$\delta = 168.8$ (s, C=O), 144.5 (s), 136.6 (s), 135.9 (s), 129.7 (d), 128.9 (d), 128.6 (d), 128.2 (d), 127.3 (d), 66.1 (d, C8), 50.7 (t), 50.2 (d), 49.5 (t), 46.5 (d), 41.1 (d), 34.7 (t, 2 peaks?), 25.6 (q, Si–C(CH_3)$_3$), 21.5 (q), 17.8 (Si–C(CH_3)$_3$), – 5.0 (q, Si–CH_3), – 5.1 (q, Si–CH_3); IR (KBr): $\tilde{\nu} = 2954$ (s), 2929 (m), 2857 (m), 1747 (m, C=O), 1656 (s, C=O), 1598 (m), 1495 (m), 1471 (s), 1447 (s), 1325 (s), 1258 (s), 1161 (s), 1090 cm^{-1} (s); MS (80 eV, EI, 60 – 100 °C): m/z (%): 562 (0.6) $[M]^+$, 547 (2) $[M^-CH_3]^+$, 527 (0.7) $[M - Cl]^+$, 505 (2) $[M^-C_4H_9]^+$, 290 (100), 281 (8), 157 (4), 126 (3), 91 (42), 75 (9), 73 (4); HRMS (80 eV, 120 °C): $C_{27}H_{36}N_2O_{4SCl}Si$ $[M - CH_3]^+$: calcd 547.185361; found 547.18194.

(3*R*,5*S*,6*S*,8*R*)-1-Benzyl-8-(*tert*-butyldimethylsilyloxy)-3-chloro-5,6-(*N*-tosyl)-epiminoazonan-2-one (10c): Reaction with *pR*-**4c** (0.2 g, 0.51 mmol), PhI=NTos (1.2 equiv) and $[Cu(OTf)_2]$ (9 mg, 5 mol %) in dry MeCN (15 mL). Reaction time: 2 h. Purification: The crude product was dissolved in EtOAc and passed through a short silica gel column to remove the *p*-TosNH_2. Chromatography by HPLC (12 % EtOAc/*n*-hexane). Yield: 0.15 g (0.27 mmol, 52.5 %) of **10c** as a colorless oil. The NMR spectra of **10c** showed a second set of minor peaks that originated from a minor conformation (ratio 3:7, flexible amide geometry?). NOE experiments indicated a fast interconversion of minor-**10c** and major-**10c**. $[\alpha]_D^{20} = 5.3$ ($c = 1.6$ in $CHCl_3$); ^{1}H NMR (major conformation, 270 MHz, $CDCl_{3};\ \delta =$ 7.85 – 7.75 (m, 2H), 7.50 – 7.10 (m, 7H), 5.13 – 5.05 (d, $J = 14.6$ Hz, 1H), 5.00 – 4.90 (dd, $J = 12$, 1.5 Hz, 1H), 5.00 – 4.90 (dd, $J = 12$, 1.5 Hz, 1H), 4.35 – 4.30 (d, $J = 14.6$ Hz, 1H), 4.13 – 4.05 (m, 1H), 3.95 – 3.83 (dd, $J = 14.6$, 9 Hz, 1H), 3.35 – 3.25 (d, $J = 14.6$ Hz, 1H), 2.90 – 2.80 (ddd, $J = 11$, 4, 4 Hz, 1H), 2.70 – 2.45 (m, 3H), 2.43 (s, 3H), 2.25 – 2.10 (ddd, $J = 12$, 12, 12 Hz, 1H), 1.70 – 1.58 (ddd, $J = 12$, 12, 10 Hz, 1H), 0.8 (s, 9H), 0.01 (s, 6H); ^{13}C NMR (major conformation, 67.9 MHz, $CDCl_3$): $\delta = 169.4$ (s), 144.5 (s), 136.7 (s), 136.3 (s), 135.5 (s), 129.7 (d), 128.8 (d), 127.9 (d), 127.3 (d), 126.6 (d), 66.3 (d), 54.3 (t), 52.5 (d), 50.1 (t), 46.5 (d), 42.7 (d), 37.6 (t), 36.3 (t), 25.4 (q, Si–C(CH_3)$_3$), 21.5 (q), 17.6 (s, Si–C(CH_3)$_3$), – 4.5 (q, Si–CH_3), – 4.9 (q, Si–CH_3); ^{1}H NMR (minor conformation, 270 MHz, $CDCl_3$): $\delta = 7.85$ – 7.75 (m, 2H), 7.50 – 7.10 (m, 7H), 5.12 – 5.05 (d, $J = 15$ Hz, 1H), 5.05 – 5.00 (m, 1H), 4.68 – 4.52 (m, 1H), 4.45 – 4.35 (d, $J = 15$ Hz, 1H), 4.20 – 4.15 (m, 1H), 2.70 – 2.45 (m, 3H), 2.43 (s, 3H), 2.32 – 2.25 (m, 1H), 1.95 – 1.80 (m, 2H), 0.83 (s, 9H), 0.04 (s, 6H); IR (KBr): $\tilde{\nu} = 2954$ (s), 2929 (m), 2857 (m), 1656 (s, C=O), 1598 (m), 1495 (m), 1471 (s), 1449 (s), 1325 (s), 1260 (s), 1161 (s), 1090 (s), 1006 cm^{-1} (m); ^{MS}(80 eV, EI, 150 °C): m/z (%): 562 (0.8) $[M]^+$, 547 (3) $[M - CH_3]^+$, 527 (0.8) $[M - Cl]^+$, 505 (4) $[M - C_4H_9]^+$, 290 (100), 281 (88), 157 (14), 126 (27), 91 (93), 75 (34), 73 (11); HRMS (80 eV, 120 °C): $C_{27}H_{36}N_2O_{4SCl}Si$ $[M - CH_3]^+$: calcd 547.185361; found 547.18377.

Standard procedure for the epoxidation: The azoninone (1 mol equiv) was dissolved in a 1:1 mixture of CH_2Cl_2 and phosphate buffer (pH = 7). *m*-Chloroperbenzoic acid (1.2 mol equiv) was added and the mixture was stirred at 4 °C or room temperature. After 3 – 5 h, the reaction was found to be complete as monitored by TLC analysis. The reaction mixture was then poured into saturated aqueous $NaHCO_3$/$NaHSO_3$. The organic layer was washed (saturated aqueous $NaHCO_3$ and brine) and dried (Na_2SO_4). After evaporation of the solvent, the product was purified by recrystallization or by HPLC.

(3*S*,5*R*,6*R*,8*R*)-1-Benzyl-8-(*tert*-butyldimethylsilyloxy)-5,6-epoxy-3-phenylazonan-2-one (11a): Reaction with *pS*-**3a** (1.06 g, 2.4 mmol) followed the standard epoxidation procedure. Purification by crystallization from Et_2O/*n*-hexane. Yield: 1.19 g (2.4 mmol, 100 %) as colorless crystals. M.p. 111 – 114 °C; $[\alpha]_D^{20} = -128.7$ ($c = 1.8$ in $CHCl_3$); ^{1}H NMR (270 MHz, $CDCl_3$): $\delta = 7.5 - 7.2$ (m, 5H), 5.02 – 4.95 (d, $J = 14$ Hz, 1H), 4.52 – 4.45 (dd, $J = 12$, 7 Hz, 1H), 4.3 – 4.25 (d, $J = 14$ Hz, 1H), 4.25 – 4.2 (m, 1H), 4.2 – 4.05 (dd, $J = 14$, 11 Hz, 1H), 3.35 – 3.2 (dd, $J = 14$, 5 Hz, 1H), 3.03 – 2.95 (m, 1H), 2.85 – 2.75 (ddd, $J = 12$, 12, 5 Hz, 1H), 2.70 – 2.60 (ddd, $J = 8$, 5, 2 Hz, 1H), 2.25 – 2.15 (m, 1H), 1.60 – 1.50 (ddd, $J = 12$, 8, 7 Hz, 1H), 1.10 – 1.00 (ddd, $J = 14$, 11, 5 Hz; 1H), 0.80 (s, 9H), 0.05 (s, 3H), – 0.05 (s, 3H); ^{13}C NMR (67.9 MHz, $CDCl_3$): $\delta = 173.6$ (s, C=O), 138.8 (s), 137.1 (s), 128.7 (d), 128.5 (d), 128.3 (d), 127.8 (d), 127.3 (d), 66.2 (d), 59.7 (d), 52.4 (d), 51.8 (t), 49.2 (t), 43.8 (d), 37.0 (t), 34.3 (t), 25.7 (q, Si–C(CH_3)$_3$), 17.9 (s, Si–C(CH_3)$_3$), – 4.9 (q, Si–CH_3); IR (KBr): $\tilde{\nu} = 2929$ (s), 2950 (s), 2856 (s), 1646 (s, N–CO), 1446 (m), 1415 (m), 1252 (m), 1187 cm^{-1} (m); MS (80 eV, EI, 110 °C): m/z (%): 451 (100) $[M]^+$, 436 (10) $[M - CH_3]^+$, 394 (20) $[M^-C_4H_9]^+$, 360 (20), 290 (90), 91 (15), 73 (8); HRMS (80 eV, 110 °C): $C_{27}H_{37}NO_3Si$ $[M]^+$: calcd 451.25427; found 451.25439.

(3*S*,5*S*,6*S*,8*R*)-1-Benzyl-8-(*tert*-butyldimethylsilyloxy)-5,6-epoxy-3-phenylazonan-2-one (12a): Before starting the epoxidation, the reactant azoninone *pS*-**3a** was heated for at least 8 h to 60 °C to achieve a high degree of conversion into azoninone *pR*-**4a** (**3a**:**4a** ≈ 1:8). Reaction of *pR*-**4a** (170 mg, 0.39 mmol) followed the standard epoxidation procedure. Purification by HPLC (12 % EtOAc/*n*-hexane). Yield: 167.3 mg (0.37 mmol, 95 %) as an inseparable mixture of **12a** (81.5 %) and **11a** (13.5 %), colorless oil. Some **11a** could be separated by crystallization from Et_2O/*n*-hexane at – 20 °C. The resulting mixture contained ≈ 10 % of remaining **11a** in 90 % of **12a**. The NMR spectra of **12a** showed a second set of minor peaks originating from a minor conformation (< 5 %, flexible amide geometry?). NOE experiments indicated a fast interconversion of minor-**12a** and major-**12a**. $[\alpha]_D^{20} = -64.1$ ($c = 1.8$, $CHCl_3$); ^{1}H NMR (270 MHz, $CDCl_3$, major conformer): $\delta = 7.5 - 7.2$ (m, 5H), 5.02 – 5.10 (d, $J = 15$ Hz, 1H), 4.40 – 4.10 (m, 4H), 3.30 – 3.20 (d, $J = 14$ Hz, 1H), 3.03 – 2.95 (ddd, $J = 10$, 6, 4 Hz, 1H), 2.75 – 2.68 (ddd, $J = 11$, 2, 2 Hz, 1H), 2.70 – 2.60 (ddd, $J = 8$, 5, 2 Hz, 1H), 2.70 – 2.50 (m, 2H), 2.02 – 1.98 (ddd, $J = 13$, 13, 10 Hz, 1H), 1.40 – 1.20 (m, 1H), 0.80 (s, 9H), 0.05 (s, 3H), – 0.05 (s, 3H); ^{13}C NMR (62.9 MHz, $CDCl_3$): $\delta = 174.8$ (s), 140.4 (s), 137.2 (s), 129.1 (d), 128.6 (d), 128.4 (d), 127.8 (d), 127.5 (d), 127.2 (d), 126.6 (d), 66.1 (d), 59.7 (d), 54.1 (t), 53.3 (d), 49.4 (t), 44.4 (d), 40.7 (t), 34.9 (t), 25.6 (q), 14.0 (s), – 4.6 (Si–CH_3), – 4.9 (Si–CH_3); IR (KBr) $\tilde{\nu} = 2953$ (s), 2928 (s), 1641 (s, CO), 1265 cm^{-1} (m); MS (80 eV, EI, 100 – 120 °C): m/z (%): 451 (73) $[M]^+$, 436 (21) $[M - CH_3]^+$, 394 (76) $[M^-C_4H_9]^+$, 360 (34), 290 (100), 197 (20), 158 (65), 91 (90); HRMS (80 eV, 120 °C): $C_{27}H_{37}NO_3Si$ $[M]^+$: calcd 451.254273; found 451.25073.

(3*R*,5*S*,6*S*,8*R*)-1-Benzyl-3-benzyloxy-8-(*tert*-butyldimethylsilyloxy)-5,6-epoxyazonan-2-one (12b): Before starting the epoxidation, the reactant azoninone *pS*-**3b** was heated for at least 3 h to 60 °C to achieve a high degree of conversion into azoninone *pR*-**4b** (**3b**:**4b** ≈ 1:12). Reaction of *pR*-**4b** (1.86 g, 3.99 mmol) followed the standard epoxidation procedure. Purification by HPLC (12 % EtOAc/*n*-hexane) Yield: 1.75 g (3.36 mmol, 91 %) as colorless crystals. M.p. 119 – 121 °C; $[\alpha]_D^{20} = 76.3$ ($c = 1.6$ in $CHCl_3$); ^{1}H NMR (270 MHz, $CDCl_{3};\ \delta =$ 7.40 – 7.10 (m, 10H), 5.28 – 5.19 (d, $J =$ 14 Hz, 1H), 4.65 – 4.57 (d, $J = 12$ Hz, 1H), 4.45 – 4.38 (dd, $J = 12.5$, 2 Hz, 1H), 4.45 – 4.38 (dd, $J = 12.5$, 2 Hz, 1H), 4.38 – 4.21 (d, $J = 14$ Hz, 1H), 4.35 – 4.29 (d, $J = 12$ Hz, 1H), 4.28 – 4.10 (m, 1H), 3.83 – 3.70 (ddd, $J = 14.7$, 9.6, 2 Hz, 1H), 3.13 – 3.05 (d, $J = 14.7$ Hz, 1H), 2.80 – 2.70 (m, 1H), 2.60 – 2.50 (m, 3H), 1.70 – 1.53 (ddd, $J = 12.5$, 12.5, 12.5 Hz, 1H), 1.12 – 0.99 (ddd, $J = 15.5$, 12, 9 Hz, 1H), 0.8 (s, 9H), 0.01 (s, 6H); ^{13}C NMR (67.9 MHz, $CDCl_3$): $\delta = 172.2$ (s), 136.9 (s), 136.8 (s), 128.6 (d), 128.6 (d), 128.1 (d), 128.0 (d), 127.8 (d), 127.6 (d), 71.4 (d), 71.0 (t), 65.9 (d), 53.2 (d), 53.0 (t), 49.3 (t), 40.2 (t), 35.3 (t), 25.4 (q, Si–C(CH_3)$_3$), 17.6 (s, Si–C(CH_3)$_3$), – 4.6 (Si–CH_3), – 5.0 (Si–CH_3); IR (KBr): $\tilde{\nu} = 2950$ (s), 2933 (s), 2858 (m), 1652 (s, C=O), 1458 (m), 1441 (m), 1259 (m), 1110 (m), 1077 cm^{-1} (s); ^{MS}(80 eV, EI, 150 °C): m/z (%): 481 (6) $[M]^+$, 466 (1) $[M - CH_3]^+$, 424 (12) $[M^-C_4H_9]^+$, 390 (38), 375 (32), 290 (50), 91 (100), 73 (20); HRMS (80 eV, 130 °C): $C_{28}H_{39}NO_4Si$ $[M]^+$: calcd 481.264838; found 481.26187.

(3*R*,5*R*,6*R*,8*R*)-1-Benzyl-8-(*tert*-butyldimethylsilyloxy)-3-chloro-5,6-epoxyazonan-2-one (11c): Reaction of *pS*-**3c** (500 mg, 1.31 mmol) followed the standard epoxidation procedure. Purification by crystallization. Yield: 480 mg (1.2 mmol, 92 %) of **11c** as colorless crystals; m.p. = 148 – 152 °C; $[\alpha]_D^{20} = -100.3$ ($c = 1.6$ in $CHCl_3$); ^{1}H NMR (270 MHz, $CDCl_{3};\ \alpha =$ 7.5 – 7.2 (m, 5H), 5.02 – 4.95 (d, $J = 14$ Hz, 1H) 4.52 – 4.45 (dd, $J =$ 12, 7 Hz, 1H), 4.3 – 4.25 (d, $J = 14$ Hz, 1H), 4.25 – 4.2 (m, 1H), 4.2 – 4.05 (dd, $J = 14$, 11 Hz, 1H), 3.35 – 3.2 (dd, $J = 14$, 5 Hz, 1H), 3.03 – 2.95 (m, 1H), 2.85 – 2.75 (ddd, $J = 12$, 12, 5 Hz, 1H), 2.70 – 2.60 (ddd, $J = 8$, 5, 2 Hz, 1H), 2.25 – 2.15 (m, 1H), 1.60 – 1.50 (ddd, $J = 12$, 8, 7 Hz, 1H), 1.10 – 1.00 (ddd, $J = 14$, 11, 5 Hz, 1H), 0.80 (s, 9H), 0.05 (s, 3H), – 0.05 (s, 3H); ^{13}C NMR (67.9 MHz, $CDCl_3$): $\delta = 169.3$ (s), 136.2 (s), 128.8 (d), 128.7 (d), 65.9 (d), 57.4 (d), 52.0 (d), 51.5 (t), 50.2 (d), 49.9 (t), 37.6 (t), 36.7 (t), 25.6 (q), 17.9 (s), – 4.9 (q), – 5.06 (q); IR (KBr): $\tilde{\nu} = 2932$ (s), 2950 (s), 2889 (s), 2857 (m), 1650 (s, C=O), 1453 (s), 1427 (s), 1254 cm^{-1} (s); MS (80 eV, EI, 150 °C): m/z (%): 409 (15) $[M]^+$, 394 (3) $[M - CH_3]^+$, 374 (6) $[M - Cl]^+$, 352 (8) $[M^-C_4H_9]^+$, 290 (100) $[M - C_4H_4ClO_2]^+$, 91 (80); HRMS: $C_{21}H_{32}ClNO_3Si$ $[M]^+$: calcd 409.18400; found 409.18426.

(3*R*,5*S*,6*S*,8*R*)-1-Benzyl-8-(*tert*-butyldimethylsilyloxy)-3-chloro-5,6-epoxyazonan-2-one (12c): Reaction of *pR*-**4c** (150 mg, 0.39 mmol) followed the standard epoxidation procedure. Purification by crystallization. Yield: 134 mg (0.34 mmol, 86 %), colorless crystals of an inseparable mixture of **12c** (95 %) and **11c** (5 %). M.p. 152 – 154 °C; $[\alpha]_D^{20} = -14.0$ ($c = 1.9$, $CHCl_3$); ^{1}H NMR (270 MHz, $CDCl_{3};\ \delta = 7.50 - 7.20$ (m, 5H), 5.21 – 5.12 (d, $J =$

© WILEY-VCH Verlag GmbH, D-69451 Weinheim, 2001
0947-6539/01/0703-0618 $ 17.50+.50/0 *Chem. Eur. J.* **2001**, *7*, No. 3

15 Hz, 1H), 5.02–4.95 (dd, J = 12, 2 Hz, 1H), 4.30–4.20 (d, J = 15 Hz, 1H), 4.30–4.20 (d, J = 15 Hz, 1H), 4.20–4.10 (m, 1H), 3.93–3.83 (ddd, J = 14.5, 10, 0.5 Hz, 1H), 3.20–3.13 (dd, J = 14.5, 1.5 Hz, 1H), 2.90–2.82 (ddd, J = 10, 4, 2.5 Hz, 1H), 2.73–2.63 (ddd, J = 12, 4, 4 Hz, 1H), 2.60–2.50 (m, 2H), 1.95–1.80 (ddd, J = 12.5, 10, 10 Hz, 1H), 1.20–1.00 (ddd, J = 13, 11, 8 Hz, 1H), 0.8 (s, 9H), −0.01 (s, 3H); ^{13}C NMR (67.9 MHz, $CDCl_3$): δ = 170.0 (s, C=O), 136.3 (s), 128.8 (d), 128.0 (d), 127.8 (d), 65.9 (d, C8), 57.0 (d, C3), 53.9 (t), 53.0 (d), 51.9 (d), 50.1 (t), 40.2 (t), 38.9 (t), 25.5 (q, Si−C(CH_3)$_3$), 17.7 (s, Si−C(CH_3)$_3$), −4.5 (q, Si−CH_3), −4.9 (q, Si−CH_3); IR (KBr): $\tilde{\nu}$ = 3427 (w), 2948 (s), 2928 (s), 2883 (s), 2856 (m), 1651 cm^{-1} (s, C=O); MS (80 eV, EI, 150 °C): m/z (%): 409 (20) $[M]^+$, 374 (8) $[M-Cl]^+$, 352 (14) $[M-C_4H_9]^+$, 318 (6), 290 (33), 120 (23), 91 (100); HRMS (80 eV, 130 °C): $C_{21}H_{32}NO_3ClSi$ $[M]^+$: calcd 409.18400; found 409.18054.

Standard procedure for the dihydroxylation: The azoninone (1 mol equiv) in MeCN/EtOAc (1:1, 18 mL) was treated with a mixture of $NaIO_4$ (1.5 equiv) and $RuCl_3$ (5 mol%) in H_2O at 0 °C. After 5 min of vigorous stirring, the reaction was stopped by the addition of aqueous $NaHSO_3$. The aqueous layer was extracted twice with EtOAc, after drying (Na_2SO_4) and removal of the solvent the crude dihydroxyazonanone **13** or **14** was subjected to the protective group insertions without any further purification.

Protection as a bis-acetate ***15*** *or* ***16***: The crude diol in dry CH_2Cl_2 was treated with pyridine (4 equiv), a catalytic amount of DMAP, and Ac_2O (4 equiv), and the aqueous layer was extracted with CH_2Cl_2 (4 ×) and dried (Na_2SO_4). The crude product was purified by column chromatography.

Protection as an isopropylidene ketal ***17*** *or* ***18***: The crude diol in dry acetone was treated with 2,2-dimethoxypropane (4 equiv) and catalytic amounts of *p*-TsOH. After stirring at room temperature for 3 h, the mixture was quenched with aqueous $NaHCO_3$. The aqueous layer was extracted with EtOAc (2 ×) and dried (Na_2SO_4). The crude product was purified by column chromatography.

(3*R*,5*R*,6*R*,8*R*)-1-Benzyl-5,6-diacetoxy-8-(*tert*-butyldimethylsilyloxy)-3-chloroazonan-2-one (15c): Reaction with *pS*-**3c** (100 mg, 0.25 mmol), $NaIO_4$ (1.5 equiv), and $RuCl_3$ (7 mol%) followed the standard dihydroxylation/bisacetate protection procedure. Chromatography (EtOAc/*n*-hexane 1:4, R_f = 0.28). Yield 92 mg (0.18 mmol, 70.5%) of **15c** as a colorless oil. At room temperature, ^{1}H and ^{13}C and NMR spectra of **15c** were characterized by broad lines. At 10 °C, a second set of minor peaks that originated from a minor conformation appeared. $[\alpha]_D^{20}$ = −16.4 (c = 1.6 in $CHCl_3$); ^{1}H NMR (500 MHz, 287 K, C_6D_6, major conformation): δ = 7.40–7.10 (m, 5H), 5.13–5.05 (m, 2H), 4.80–4.75 (d, J = 15 Hz, 1H), 4.65–4.60 (dd, J = 10, 4 Hz, 1H), 4.15–4.05 (d, J = 15 Hz, 1H), 3.60–3.52 (m, 1H), 2.90–2.80 (dd, J = 15, 10 Hz, 1H), 2.75–2.68 (d, J = 15 Hz, 1H), 2.55–2.46 (dd, J = 12, 12 Hz, 1H), 2.15–2.08 (m, 1H), 1.85–1.78 (d, J = 16 Hz, 1H), 1.72 (s, 3H), 1.60 (s, 3H), 0.83 (s, 9H), −0.14 (s, 3H), −0.17 (s, 3H); ^{13}C NMR (67.9 MHz, 287 K, C_6D_6, major conformation): δ = 169.2 (s), 168.8 (s), 137.3 (d), 129.2 (d), 128.9 (d), 71.7 (d), 71.4 (d), 65.3 (d), 54.3 (t), 51.2 (t), 49.6 (d), 39.6 (t), 38.4 (t), 25.7 (q, Si−C(CH_3)$_3$), 20.6 (q, OCOCH_3), 20.4 (q, OCOCH_3), 17.9 (s, Si−C(CH_3)$_3$), −4.8 (q, Si−CH_3), −5.0 (q, Si−CH_3); IR (KBr): $\tilde{\nu}$ = 2954 (s), 2930 (s), 2886 (s), 2857 (s), 1745 (s, C=O), 1667 (s, C=O), 1471 (m), 1446 (m), 1368 (m), 1243 (s), 1082 (s), 1032 cm^{-1} (s); MS (80 eV, EI, 130 °C): m/z (%): 511 (0.7) $[M]^+$, 496 (0.3) $[M-CH_3]^+$, 476 (3) $[M-Cl]^+$, 468 (0.7) $[M-COCH_3]^+$, 454 (26) $[M-C_4H_9]^+$, 394 (10), 304 (47), 244 (15), 200 (25), 117 (6), 91 (100), 73 (12); HRMS (80 eV, 130 °C): $C_{25}H_{38}NO_6SiCl$ $[M]^+$: calcd 511.215694; found 511.21911.

(3*R*,5*S*,6*S*,8*R*)-1-Benzyl-5,6-diacetoxy-8-(*tert*-butyldimethylsilyloxy)-3-chloroazonan-2-one (16c): Reaction with *pR*-**4c** (150 mg, 0.38 mmol), $NaIO_4$ (1.5 equiv), and $RuCl_3$ (7 mol%) followed the standard dihydroxylation/bisacetate protection procedure. Chromatography (EtOAc/*n*-hexane 1:4, R_f = 0.28). Yield 172 mg (0.38 mmol, 88.2%) of **16c** as a colorless oil, ≈20 mg (0.04 mmol, 10%) of **15c** were separated in an additional fraction. (At room temperature, the ^{1}H and ^{13}C and NMR spectra of **16c** were characterized by broad lines. At −10 °C, a second set of minor peaks that originated from a minor conformation appeared. $[\alpha]_D^{20}$ = 6.9 (c = 1.5 in $CHCl_3$); ^{1}H NMR (500 MHz, 263 K, CD_2Cl_2, major conformation): δ = 7.40–7.20 (m, 5H), 5.50–5.40 (d, J = 15 Hz, 1H), 5.20–5.15 (m, 1H), 5.10–5.05 (m, 1H), 4.95–4.85 (m, 1H), 4.15–4.05 (m, 1H), 3.85–3.80 (d, J = 15 Hz, 1H), 3.65–3.59 (dd, J = 12, 5 Hz, 1H), 3.20–3.15 (m, 1H), 2.70–2.60 (m, 2H), 2.20–2.05 (m, 2H), 2.01 (s, 6H), 0.80 (s, 9H), 0.06 (s, 3H), 0.03 (s, 3H); ^{1}H NMR (500 MHz, 263 K, CD_2Cl_2, minor conformation): δ = 7.40–7.20 (m, 5H), 5.45–5.40 (d, J = 15 Hz, 1H), 5.00–4.80 (m, 2H), 4.47–4.43 (m, 1H), 4.25–4.15 (m, 2H), 4.05–4.00 (d, J = 15 Hz, 1H), 3.20–3.10 (m, 1H), 2.35–2.30 (m, 1H), 2.20–2.00 (m, 2H), 2.04 (s, 6H), 1.90–1.85 (m, 1H), 0.84 (s, 9H), 0.01 (s, 3H), 0.00 (s, 3H); ^{13}C NMR (125.8 MHz, 263 K, CD_2Cl_2 both conformers): δ = 169.7, 169.6, 167.3, 136.3, 136.2, 128.8, 128.6, 128.2, 127.9, 127.8, 127.4, 77.8, 71.6, 70.5, 70.2, 68.8, 65.3, 56.9, 54.4, 51.7, 50.4, 50.0, 49.6, 41.8, 40.6, 38.1, 37.6, 25.5, 25.4, 21.0, 17.8, −5.2, −5.3; IR (KBr): $\tilde{\nu}$ = 2954 (s), 2930 (s), 2857 (s), 1744 (s, C=O), 1646 (s, N−CO), 1657 (s, N−CO), 1462 (s), 1453 (s), 1366 (s), 1240 (s), 1218 cm^{-1} (s); MS (80 eV, EI, 135 °C): m/z (%): 511 (6) $[M]^+$, 496 (3) $[M-CH_3]^+$, 476 (6) $[M-Cl]^+$, 454 (38) $[M-C_4H_9]^+$, 394 (91), 304 (33), 200 (25), 117 (26), 91 (100); HRMS (80 eV, 130 °C): $C_{25}H_{38}NO_6SiCl$ $[M]^+$: calcd 511.215694; found 511.21415.

(3*S*,5*R*,6*R*,8*R*)-1-Benzyl-8-(*tert*-butyldimethylsilyloxy)-5,6-isopropylidendioxy-3-phenylazonan-2-one (17a): Reaction with *pS*-**3a** (350 mg, 0.80 mmol), $NaIO_4$ (1.3 equiv), and $RuCl_3$ (4.2 mol%) followed the standard dihydroxylation/isopropylidene acetal protection procedure. Chromatography (EtOAc/*n*-hexane 1:3, R_f = 0.48). Yield 0.39 g (0.77 mmol, 95.2%) of **17a** as a colorless oil. $[\alpha]_D^{20}$ = −85.2 (c = 1.3, $CHCl_3$); ^{1}H NMR (270 MHz, CD_2Cl_2; δ = 7.50–7.40 (m, 2H), 7.40–7.10 (m, 8H), 5.10–5.00 (d, J = 14 Hz, 1H), 4.35–4.25 (dd, J = 12.7, 5 Hz, 1H), 4.20–4.10 (m, 2H), 4.10–4.00 (d, J = 14 Hz, 1H), 3.81–3.72 (ddd, J = 11, 8, 5 Hz, 1H), 3.72–3.60 (dd, J = 15.6, 8 Hz, 1H), 3.42–3.35 (dd, J = 15.6, 6 Hz, 1H), 2.82–2.70 (ddd, J = 12.7, 12.7, 5 Hz, 1H), 2.25–2.15 (ddd, J = 16, 6, 2 Hz, 1H), 1.98–1.85 (m, 2H), 1.35 (s, 3H), 1.34 (s, 3H), 0.83 (s, 9H), 0.08 (s, 3H), 0.00 (s, 3H); ^{13}C NMR (67.9 MHz, CD_2Cl_2): δ = 174.2 (s), 140.4 (s), 137.7 (s), 129.2 (d), 128.9 (d), 128.8 (d), 128.6 (d), 128.2 (d), 127.7 (d), 107.8 (s), 81.1 (d), 75.7 (d), 68.0 (d, C8), 54.6 (t), 50.4 (t), 42.2 (d), 41.5 (t), 38.5 (t), 27.0 (q), 26.9 (q), 26.1 (q, Si−C(CH_3)$_3$), 18.5 (s, Si−C(CH_3)$_3$), −4.5 (q, Si−CH_3), −4.6 (q, Si−CH_3); IR (KBr): $\tilde{\nu}$ = 2984 (s), 2929 (s), 2885 (s), 2855 (s), 1649 (s, N−CO), 1253 (m), 1209 (s), 1096 cm^{-1} (s); MS (80 eV, EI, 120 °C): m/z (%): 509 (15) $[M]^+$, 494 (16) $[M-CH_3]^+$, 451 (38) $[M-C_3H_6O]^+$, 436 (8), 394 (100) $[M-C_4H_9-C_3H_6O]^+$, 319 (63), 252 (43); HRMS (80 eV, 120 °C): $C_{30}H_{43}NO_4Si$ $[M]^+$: calcd 509.296140; found 509.29627.

(3*R*,5*R*,6*R*,8*R*)-1-Benzyl-8-(*tert*-butyldimethylsilyloxy)-3-chloro-5,6-isopropylidendioxyazonan-2-one (17c): Reaction with *pS*-**3c** (150 mg, 0.38 mmol), $NaIO_4$ (1.5 equiv), and $RuCl_3$ (4.6 mol%) followed the standard dihydroxylation/isopropylidene acetal protection procedure. Chromatography (EtOAc/*n*-hexane 1:3, R_f = 0.48). Yield 0.128 g (0.27 mmol, 70.9%) of **17c** as a colorless oil. $[\alpha]_D^{20}$ = −42.8 (c = 1.6, $CHCl_3$). Though most of the signals appeared as sharp lines in the ^{1}H NMR spectrum, broad lines of some signal indicated the existence of a second (flexible amide geometry?). NOE experiments indicated a fast interconversion of both species. Furthermore, broad lines with a weak intensity were found in the ^{13}C NMR spectrum for C6/C5 and C7/C4. ^{1}H NMR (270 MHz, CD_2Cl_2; δ = 7.40–7.10 (m, 5H), 5.10–5.00 (m, 2H), 4.20–4.10 (m, 1H), 4.10–4.00 (m, 2H), 3.65–3.55 (m, 1H), 3.55–3.45 (dd, J = 15.6, 8 Hz, 1H), 3.45–3.30 (m, 1H), 2.75–2.65 (dd, J = 12, 12, 4 Hz, 1H), 2.28–2.15 (ddd, J = 12.6, 11, 6 Hz, 1H), 2.19–2.09 (ddd, J = 15.6, 6, 2 Hz, 1H), 1.80–1.68 (dd, J = 15.6, 6 Hz, 1H), 1.35 (s, 3H), 1.31 (s, 3H), 0.83 (s, 9H), 0.08 (s, 3H), −0.00 (s, 3H); ^{13}C NMR (67.9 MHz, CD_2Cl_2): δ = 169.8 (s), 136.8 (s), 129.4 (d), 129.0 (d), 128.5 (d), 108.1 (s, acetonide C), 79.8 (d), 75.2 (d), 67.4 (d, C8), 53.9 (t), 50.8 (t), 49.4 (d), 41.1 (t), 40.2 (t), 26.9 (q), 26.8 (q), 26.0 (q, Si−C(CH_3)$_3$), 18.3 (Si−C(CH_3)$_3$), −4.5 (q, Si−CH_3), −4.7 (q, Si−CH_3); IR (KBr): $\tilde{\nu}$ = 2985 (s), 2953 (s), 2930 (s), 2886 (s), 2857 (s), 1662 (s, N−CO), 1472 (s), 1450 (s), 1432 (m), 1380 (s), 1369 (s), 1259 (s), 1209 (s), 1169 (s), 1098 (s), 1061 (s), 1028 cm^{-1} (s); MS (80 eV, EI, 110 °C): m/z (%): 467 (3) $[M]^+$, 452 (8) $[M-CH_3]^+$, 431 (3) $[M-HCl]^+$, 410 (13) $[M-C_4H_9]^+$, 394 (2), 373 (7), 352 (60); HRMS (80 eV, 120 °C): $C_{24}H_{38}NO_4SiCl$ $[M]^+$: calcd 467.225865; found 467.22723.

(3*R*,5*S*,6*S*,8*R*)-1-Benzyl-8-(*tert*-butyldimethylsilyloxy)-3-chloro-5,6-isopropylidendioxyazonan-2-one (18c): Before starting the dihydroxylation, the reactant azoninone *pS*-**3c** was heated for at least 1 h to 65 °C to achieve a high degree of conversion into azoninone *pR*-**4c** (**3c**:**4c** ≈ 1:3.5). Reaction with *pS*-**3c** (150 mg, 0.38 mmol), $NaIO_4$ (1.5 equiv), and $RuCl_3$ (4.6 mol%) followed the standard dihydroxylation/isopropylidene acetal protection procedure. Chromatography (EtOAc/*n*-hexane 1:5, R_f = 0.56). Yield 98 mg (0.21 mmol, 55.5%) of **18c** as a colorless oil and 29 mg (6.3 mmol, 16.5%) of **17c**. $[\alpha]_D^{20}$ = 28.0 (c = 1.7, $CHCl_3$). The ^{1}H NMR spectrum of **18c** showed an unseparated mixture of at least two conformers at room temperature (very

broad lines only). At 233 K the two discrete conformers appeared. NOE experiments indicated a fast interconversion of both species (flexible amide geometry?). ^{1}H NMR (500 MHz, 233 K, CD_2Cl_2, major conformation): δ = 7.40–7.10 (m, 5H), 5.30–5.25 (d, J = 15 Hz, 1H), 4.85–4.78 (dd, J = 10.6, 10.6 Hz, 1H), 4.48–4.43 (d, J = 15 Hz, 1H), 4.06–4.00 (m, 1H), 3.90–3.85 (m, 1H), 3.55–3.48 (m, 2H), 3.29–3.24 (d, J = 16 Hz, 1H), 2.80–2.73 (dd, J = 16, 10 Hz, 1H), 2.18–2.08 (m, 2H), 2.05–1.95 (m, 1H), 1.32 (s, 3H), 1.28 (s, 3H), 0.79 (s, 9H), 0.04 (s, 3H), −0.08 (s, 3H); ^{1}H NMR (500 MHz, 233 K, CD_2Cl_2, minor conformation): δ = 7.40–7.10 (m, 5H), 5.28–5.22 (d, J = 15 Hz, 1H), 4.92–4.88 (d, J = 10.1 Hz, 1H), 3.98–3.93 (m, 1H), 3.93–3.85 (m, 2H), 3.72–3.67 (m, 1H), 3.62–3.55 (dd, J = 15.5, 10 Hz, 1H), 3.17–3.12 (d, J = 15.3 Hz, 1H), 2.65–2.55 (m, 2H), 2.25–2.18 (d, J = 15 Hz, 1H), 2.03–1.93 (m, 1H), 1.31 (s, 3H), 1.26 (s, 3H), 0.79 (s, 9H), 0.04 (s, 3H), 0.02 (s, 3H); ^{13}C NMR (125.76 MHz, 233 K, CD_2Cl_2, both conformers): δ = 171.9, 169.0, 137.4, 137.3, 130.0, 129.7, 129.2, 129.1, 128.2, 128.1, 109.2, 107.7, 81.0, 80.8, 79.1, 78.6, 75.1, 71.3, 67.5, 58.1, 56.1, 51.8, 51.3, 49.5, 48.5, 44.6, 41.9, 38.9, 36.5, 27.8, 27.7, 27.5, 26.6, 26.5, 19.0, 18.9, −3.9, −4.0, −4.1, −4.2; IR (KBr): $\tilde{\nu}$ = 2985 (s), 2953 (s), 2930 (s), 2857 (s), 1652 (s, N–CO), 1472 (s), 1452 (s), 1432 (m), 1379 (s), 1369 (s), 1254 cm^{-1} (s); MS (80 eV, EI, 130 °C): m/z (%): 467 (2) $[M]^+$, 452 (3) $[M^-CH_3]^+$, 431 (1) $[M-HCl]^+$, 410 (9) $[M-C_4H_9]^+$, 91 (100); HRMS (80 eV, 130 °C): $C_{24}H_{38}NO_4SiCl$ $[M]^+$: calcd 467.225865; found 467.22934.

Standard procedure for the transannular epoxide opening: The epoxy azonanone (1 mol equiv) in $CHCl_3$ (10 mL) was treated with anhydrous LiI (1 equiv) and TMSI (1.3 equiv) at room temperature. After max. 5 min of vigorous stirring the reaction was quenched by the addition of saturated aqueous $NaHCO_3$ and 10% aqueous $Na_2S_2O_3$ (3:1); after a few minutes, a clear colorless solution was obtained. The aqueous layer was extracted twice with Et_2O, after drying (Na_2SO_4) and removal of the solvent, the crude indolizidinones **19**–**21** and lactones **22** were purified by column chromatography or HPLC.

(2*R*,6*S*,8*R*,8a*S*)-2-(*tert*-Butyldimethylsilyloxy)-8-hydroxy-6-phenyl-5(8H)-indolizidinone (19a): Reaction with **11a** (1.1 g, 2.44 mmol), TMSI (1.1 equiv) without LiI followed the standard transannular epoxide opening procedure. Chromatography (gradient EtOAc/*n*-hexane 1:3 to EtOAc, R_f = 0.28). Yield 530 mg (1.47 mmol, 60%) of **19a** (crystallized from *n*-hexane/Et_2O 3:1, first fraction: 250 mg, 0.69 mmol, 28.3%) and 170 mg (0.38 mmol, 15.4%) of **22a** as a colorless oil.

Indolizidinone ***19a***: Colorless crystals; m.p. 143–145 °C; $[\alpha]_D^{20}$ = −60.8 (c = 2.0, $CHCl_3$); ^{1}H NMR (270 MHz, $CDCl_3$, δ = 7.30–7.15 (m, 3H), 7.10–7.00 (m, 2H), 4.45–4.40 (dd, J = 5, 5 Hz, 1H), 3.80–3.68 (dd, J = 13, 5 Hz, 1H), 3.70–3.55 (m, 3H), 3.42–3.35 (br s, 1H), 3.35–3.30 (d, J = 13 Hz, 1H), 2.25–2.15 (dd, J = 12.7, 4 Hz, 1H), 2.10–2.00 (m, 2H), 1.62–1.50 (ddd, J = 12.7, 10.7, 4 Hz, 1H), 0.89 (s, 9H), −0.09 (s, 6H); ^{13}C NMR (67.9 MHz, CD_2Cl_2): δ = 169.6 (s), 142.8 (s), 128.9 (d), 128.8 (d), 127.1 (d), 69.7 (d), 68.2 (d), 62.3 (d), 56.1 (t), 46.8 (d), 42.1 (t), 39.4 (t), 26.1 (Si–C(CH_3)$_3$), 18.5 (Si–C(CH_3)$_3$), −4.5 (Si–CH_3), −4.6 (Si–CH_3); IR (KBr): $\tilde{\nu}$ = 3307 (br s), 2955 (s), 2928 (s), 2885 (m), 2856 (s), 1613 (s, C=O), 1450 (s), 1278 (m), 1257 cm^{-1} (m); MS (70 eV, EI, 100 °C): m/z (%): 360 (0.1) $[M^{-H}]^+$, 346 (4) $[M-CH_3]^+$, 304 (100) $[M^-C_4H_9]^+$, 286 (13), 258 (29), 116 (11); HRMS (80 eV, 100 °C): $C_{25}H_{38}NO_6SiCl$ $[M-CH_3]^+$: calcd 346.183847; found 346.18722.

(2*R*,6*S*,8*S*,8a*R*)-2-(*tert*-Butyldimethylsilyloxy)-8-hydroxy-6-phenyl-5(8H)-indolizidinone (20a): Reaction with **12a** (160 mg, 0.35 mmol) followed the standard transannular epoxide opening procedure. Chromatography (EtOAc/*n*-hexane 1:1, R_f = 0.13). Yield 41 mg (0.11 mmol, 32%) of **20a** as colorless crystals. M.p. 170–178 °C. Data of **20a** (OH): $[\alpha]_D^{20}$ = +37.2 (c = 1.9, $CHCl_3$); ^{1}H NMR (270 MHz, $CDCl_3$, δ = 7.50–7.20 (m, 5H), 4.41–4.31 (m, 1H), 3.60–3.40 (m, 5H), 2.42–2.32 (ddd, J = 12, 6, 6 Hz, 1H), 2.22–2.12 (m, 1H), 1.85–1.75 (dd, J = 11, 11, 2 Hz, 1H), 1.71–1.61 (ddd, J = 12, 11, 8 Hz, 1H), 0.90 (s, 9H), 0.01 (s, 3H), 0.00 (s, 3H); ^{13}C NMR (67.9 MHz, $CDCl_3$): δ = 169.2 (s), 141.0 (s), 128.5 (d), 128.1 (d), 126.7 (d), 70.2 (d), 69.2 (d), 62.5 (d), 53.5 (t), 47.7 (d), 40.3 (t), 40.2 (t), 25.7 (q, Si–C(*C*H_3)$_3$), 17.9 (s, Si–*C*(CH_3)$_3$), −4.9 (q, Si–CH_3); IR (KBr): $\tilde{\nu}$ = 3442 (s), 2956 (s), 2929 (s), 2895 (m), 2857 (s), 1616 (s, C=O), 1465 (s), 1445 (s), 1260 cm^{-1} (s); MS (80 eV, EI, 140 °C): m/z (%): 361 (0.1) $[M]^+$, 346 (2) $[M-CH_3]^+$, 304 (100) $[M^-C_4H_9]^+$, 200 (3), 176 (5), 118 (5); HRMS (80 eV, 140 °C): $C_{19}H_{28}NO_3Si$ $[M-CH_3]^+$: calcd 346.183847; found 346.18634.

(2*R*,6*R*,8*S*,8a*R*)-6-Benzyloxy-2-(*tert*-butyldimethylsilyloxy)-8-hydroxy-5(8H)-indolizidinone (20b): Reaction with **12b** (2.8 g, 5.81 mmol) followed the standard transannular epoxide opening procedure. Reaction time < 2 min to avoid the cleavage of the benzylether. Chromatography (EtOAc/*n*-hexane 1:1, R_f = 0.13). Yield 1.3 g (3.32 mmol, 57%) as colorless crystals. M.p. 140–143 °C; $[\alpha]_D^{20}$ = 69.8 (c = 1.9 in $CHCl_3$); ^{1}H NMR (270 MHz, $CDCl_3$, δ = 7.40–7.20 (m, 5H), 4.85–4.80 (d, J = 12 Hz, 1H), 4.70–4.65 (d, J = 12 Hz, 1H), 4.40–4.30 (m, 1H), 4.00–3.95 (dd, J = 7, 5 Hz, 1H), 3.75–3.68 (ddd, J = 8, 8, 6 Hz, 1H), 3.60–3.50 (ddd, J = 8, 8, 8 Hz, 1H), 3.45–3.40 (m, 2H), 3.00–2.80 (br s, 1H), 2.45–2.35 (ddd, J = 12, 6, 6 Hz, 1H), 2.35–2.28 (ddd, J = 14, 6, 6 Hz, 1H), 2.00–1.90 (ddd, J = 14, 8, 8 Hz, 1H), 1.82–1.70 (ddd, J = 13, 8, 7 Hz, 1H), 0.85 (s, 9H), 0.05 (s, 6H); ^{13}C NMR (67.9 MHz, $CDCl_3$): δ = 168.2 (s), 137.6 (s), 128.3 (d), 127.9 (d), 127.7 (d), 74.7 (d), 72.5 (t), 69.6 (d), 69.2 (d), 61.8 (d), 52.9 (t), 40.1 (t), 37.4 (t), 25.7 (q, Si–C(*C*H_3)$_3$), 17.9 (s, Si–*C*(CH_3)$_3$), −4.9 (q, Si–CH_3); IR (KBr): $\tilde{\nu}$ = 3327 (br s), 2953 (s), 2928 (s), 2896 (s), 2856 (s), 1622 cm^{-1} (s, C=O); MS (80 eV, EI, 130 °C): C=O = 390 (0.2) $[M]^+$, 376 (2) $[M-CH_3]^+$, 334 (100) $[M-C_4H_9]^+$, 285 (97) $[M-CH_3-C_7H_7]^+$; HRMS (80 eV, 120 °C): $C_{17}H_{24}NO_4Si$ $[M-C_4H_9]^+$: calcd 334.147462; found 334.14364.

(2*R*,6*R*,8*R*,8a*S*)-2-(*tert*-Butyldimethylsilyloxy)-6-chloro-8-hydroxy-5(8H)-indolizidinone (19c): Reaction with **11c** (0.5 g, 1.22 mmol) and TMSI (1.2 equiv) followed the standard transannular epoxide opening procedure. Reaction time < 90 s to avoid most of the chlorine–iodine exchange (in some attempts up to 10% of 6-iodo compounds were detected by NMR spectroscopy and MS). Chromatography (EtOAc/*n*-hexane 1:1, R_f = 0.15). Yield 124 mg (0.39 mmol, 32%) of **19c** (OH) as colorless crystals. M.p. 152 °C; $[\alpha]_D^{20}$ = −62.0 (c = 1.9 in $CHCl_3$); ^{1}H NMR (270 MHz, $CDCl_3$, δ = 4.55–4.50 (dd, J = 5, 2 Hz, 1H), 4.48–4.42 (dd, J = 12.8, 12.8 Hz, 1H), 4.10–3.96 (ddd, J = 14, 8.8, 4 Hz, 1H), 3.81–3.72 (dd, J = 13.6, 5 Hz, 1H), 3.72–3.62 (m, 1H), 3.40–3.33 (d, J = 13.6 Hz, 1H), 3.10–3.05 (s, 1H), 2.51–2.42 (ddd, J = 14, 4, 2 Hz, 1H), 2.40–2.20 (m, 2H), 1.73–1.61 (ddd, J = 12, 12, 4 Hz, 1H), 0.90 (s, 9H), 0.01 (s, 6H); ^{13}C NMR (67.9 MHz, $CDCl_3$): δ = 164.4 (s, C=O), 68.6 (d), 66.9 (d), 62.2 (d), 56.3 (t), 53.7 (d), 41.3 (t), 40.2 (t), 25.7 (q, Si–C(*C*H_3)$_3$), 17.9 (s, Si–*C*(CH_3)$_3$), −4.8 (q, Si–CH_3), −4.9 (q, Si–CH_3); IR (KBr): $\tilde{\nu}$ = 3319 (br s), 2956 (s), 2929 (s), 2856 (s), 1629 (S, C=O), 1472 (s), 1274 cm^{-1} (s); MS (70 eV, EI, 140 °C): m/z (%): 304 (3) $[M^-CH_3]^+$, 262 (100) $[M-C_4H_9]^+$, 228 (10), 186 (5), 116 (5); HRMS (80 eV, 130 °C): $C_{13}H_{23}NO_3SiCl$ $[M-CH_3]^+$: calcd 304.113575; found 304.11690.

(2*S*,6*R*,8*R*,8a*S*)-6-(*tert*-Butyldimethylsilyloxy)-8-hydroxy-2-phenyl-3(8H)-indolizidinone (21a): Reaction with epoxy azonanone **11a** (190 mg, 0.42 mmol) and LiI (1.2 equiv), fast addition of TMSI (1.2 equiv) at −10 °C. Reaction time: 3 min, work-up following the standard transannular epoxide opening procedure. Chromatography (EtOAc/*n*-hexane 1:3, R_f = 0.1). Yield 29 mg (0.08 mmol, 19%) of **21a** (OH) as colorless crystals. M.p. 145 °C; $[\alpha]_D^{20}$ = −39.4 (c = 1.5 in $CHCl_3$); ^{1}H NMR (270 MHz, $CDCl_3$): δ = 7.50–7.20 (m, 5H), 4.10–4.08 (m, 1H), 4.03–3.98 (d, J = 13 Hz, 1H), 3.82–3.70 (ddd, J = 10, 10, 4 Hz, 1H), 3.70–3.60 (dd, J = 10, 8 Hz, 1H), 3.32–3.23 (ddd, J = 12, 8, 4 Hz, 1H), 2.78–2.72 (d, J = 13 Hz, 1H), 2.67–2.60 (s, 1H), 2.52–2.40 (ddd, J = 13.6, 10, 4 Hz, 1H), 2.30–2.20 (ddd, J = 13.6, 8, 8 Hz, 1H), 2.15–2.05 (m, 1H), 1.52–1.42 (ddd, J = 13, 12, 2 Hz, 1H), 0.90 (s, 9H), 0.01 (s, 3H), 0.00 (s, 3H); ^{13}C NMR (67.9 MHz, $CDCl_3$): δ = 174.4 (s), 140.3 (s), 128.6 (d), 127.8 (d), 126.8 (d), 67.4 (d), 66.3 (d), 61.3 (d), 46.9 (d), 46.4 (t), 40.8 (t), 31.4 (t), 25.7 (q, Si–C(*C*H_3)$_3$), 17.9 (s, Si–*C*(CH_3)$_3$), −4.98 (q, Si–CH_3), −5.13 (q, Si–CH_3); IR (KBr): $\tilde{\nu}$ = 3312 (s), 2954 (s), 2926 (s), 2852 (s), 1652 (s, C=O), 1473 (s), 1463 (s), 1255 (s), 1078 cm^{-1} (s); MS (80 eV, EI, 145 °C): m/z (%): 361 (0.1) $[M]^+$, 346 (2) $[M-CH_3]^+$, 304 (100) $[M^-C_4H_9]^+$; HRMS (80 eV, 140 °C): $C_{19}H_{28}NO_3Si_1$ $[M-CH_3]^+$: calcd 346.183847; found 346.18588.

Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Data Centre as supplementary publication nos. CCDC-145065 (**5c**), CCDC-145066 (**11c**), CCDC-145067 (**12c**), CCDC-145068 (**12b**), CCDC-145069 (**20b**). Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ.UK (fax: (+44) 1223 336–033, e-mail: deposit@ccdc.cam.ac.uk).

Acknowledgements

We thank the Deutsche Forschungsgemeinschaft, the Fonds der Chemischen Industrie, and the Schering Research Foundation for their support of this work.

 © WILEY-VCH Verlag GmbH, D-69451 Weinheim, 2001 0947-6539/01/0703-0620 $ 17.50+.50/0

[1] V. Prelog, G. Helmchen, *Angew. Chem*. **1982**, *94*, 614; *Angew. Chem. Int. Ed. Engl*. **1982**, *21*, 507.

[2] R. S. Cahn, C. K. Ingold, V. Prelog, *Angew. Chem*. **1966**, *78*, 413; *Angew. Chem. Int. Ed. Engl*. **1966**, *5*, 385.

[3] K. Schlögl, *Top. Curr. Chem*. **1984**, *125*, 27.

[4] a) A. C. Cope, B. A. Pawson, *J. Am. Chem. Soc*. **1965**, *87*, 3649; b) A. C. Cope, K. Banholzer, H. Keller, B. A. Pawson, J. J. Wang, H. J. S. Winkler, *J. Am. Chem. Soc*. **1965**, *87*, 3644; c) Binsch, *J. Am. Chem. Soc*. **1965**, *87*, 5157; d) D. M. Pawar, S. D. Miggins, S. V. Smith, E. A. Noe, *J. Org. Chem*. **1999**, *64*, 2418.

[5] a) A. Sudau, U. Nubbemeyer, *Angew. Chem.* **1998**, *110*, 1178; *Angew. Chem. Int. Ed.* **1998**, *37*, 1140; b) A. Sudau, W. Münch, J. W. Bats, U. Nubbemeyer, *J. Org. Chem*. **2000**, *65*, 1710.

[6] For further syntheses of unsaturated medium-sized ring lactams including some transannular reactions see: a) C. J. Deur , M. W. Miller, L. S. Hegedus, *J. Org. Chem*. **1996**, *61*, 2871; b) P. A. Evans, A. B. Holmes, R. P. McGeary, A. Nadin, K. Russell, P. J. O'Hanlon, N. D. Pearson, *J. Chem. Soc. Perkin Trans. I* **1996**, 123; c) P. A. Evans, A. B. Holmes, I. Collins, P. R. Raithby, K. Russell, *J. Chem. Soc. Chem. Commun*. **1995**, 2325; d) P. A. Evans, A. B. Holmes, K. Russell, *Tetrahedron Lett*. **1992**, *33*, 6857; e) P. A. Evans, I. Collins, P. Hamley, A. B. Holmes, P. R. Raithby, K. Russell, *Tetrahedron Lett*. **1992**, *33*, 6859; f) E. D. Edstrom, *J. Am. Chem. Soc*. **1991**, 113, 6690; g) E. D. Edstrom, *Tetrahedron Lett*. **1991**, 32, 5709; h) P. Wipf, W. Li, *J. Org. Chem*. **1999**, *64*, 4576.

[7] Ratio of **3**:**4** after heating to 60 °C: **3a**:**4a** = 5:95 (4 h), **3b**:**4b** = 1:13 (3 h), **3c**:**4c** = 1:4.3 (3 h). Separation of **3** and **4** by column chromatography or HPLC, if necessary. In some experiments starting from *pR*-**4**, some *pS*-**3** reamined as impurity. Usually, the reactant ratio (*pS*-**3**/*pR*-**4**) was completely transferred on generating the corresponding products (no epimerization).

[8] Conformational flexibility of azonanones: a) G. L. Olson, M. E. Voss, D. E. Hill, M. Kahn, V. S. Madison, C. M. Cook, *J. Am. Chem. Soc*. **1990**, *112*, 323; b) Terpenes: G. Guella, G. Chiasera, I. D'Diaye, F. Pietra, *Helv. Chim. Acta* **1994**, *77*, 1203; c) A. J. Minnaard, J. B. P. A. Wijnberg, A. de Groot, *J. Org. Chem*. **1997**, *62*, 7346; d) Indolizidines: W. H. Pearson, E. J. Hembre, *J. Org. Chem*. **1996**, *61*, 5546.

[9] a) U. Mende, B. Radüchel, W. Skuballa, H. Vorbrüggen, *Tetrahedron Lett*. **1975**, 629; b) J. Kottwitz, H. Vorbrüggen, *Synthesis* **1975**, 636; c) M. Suda, *Synthesis* **1981**, 714; Preparation of diazomethane: D. A. Evans, S. P. Tanis, D. J. Hart, *J. Am. Chem. Soc*. **1981**, *103*, 5813.

[10] a) Y. Yamada, T. Yamamoto, M. Okawara, *Chem. Lett*. **1975**, 361; b) M. J. Södergren, D. A. Alonso, A. V. Bedekar, P. G. Andersson, *Tetrahedron Lett*. **1997**, *38*, 6897; for a modified preparation procedure of the reagent see the Supporting Information.

[11] a) D. A. Evans, M. M. Faul, M. T. Bilodeau, *J. Org. Chem*. **1991**, *56*, 6744; b) D. A. Evans, M. M. Faul, M. T. Bilodeau, *J. Am. Chem. Soc*. **1994**, *116*, 2742; c) Z. Li, K. R. Conser, E. N. Jacobsen, *J. Am. Chem. Soc*. **1993**, *115*, 5326.

[12] For spectral data of γ-butyrolactam **23**, see the Supporting Information.

[13] a) M. Imuta, H. Ziffer, *J. Org. Chem*. **1979**, *44*, 1351; b) N. N. Schwartz, H. Blumbergs, *J. Org. Chem*. **1964**, *29*, 1976.

[14] a) T. K. M. Shing, E. K. W. Tam, V. W.-F. Tai, I. H. F. Chung, Q. Jiang, *Chem. Eur. J*. **1996**, *2*, 50; b) T. K. M. Shing, V. W.-F. Tai, E. K. W. Tam, *Angew. Chem*. **1994**, *106*, 2408; *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 2312; c) T. K. M. Shing, L. H. Wan, *J. Org. Chem.* **1996**, *61*, 8468; d) T. K. M. Shing, E. K. W. Tam, *J. Org. Chem.* **1998**, *63*, 1547.

[15] G. Höfle, W. Steglich, H. Vorbrüggen, *Angew. Chem.* **1978**, *90*, 602; *Angew. Chem. Int. Ed. Engl*. **1978**, *17*, 569.

[16] P. Garner, J. M. Park, *Org. Synth. Coll.* **1998**, *9*, 300.

[17] For detailed NOE data see the Supporting Information.

[18] X-ray analyses were obtained from azonanones **5c**, **11c**, **12b**, and **12c**. For detailed data including a complete structure plot see the Supporting Information and information deposited with the Cambridge Data Centre. X-ray data of **5c** (CCDC-145065): colorless, transparent prism crystallized from Et_2O/*n*-hexane at $-20\,^{\circ}C$, $C_{22}H_{34}NO_2Cl_1Si_1$ ($M_r = 408.06$); crystal dimensions $0.40 \times 0.45 \times 0.52\ mm^3$; monoclinic; space group $P2_1$. X-ray data of **11c** (CCDC-145066): colorless, transparent prism crystallized from Et_2O/*n*-hexane at room temperature, $C_{21}H_{32}N_1O_3Cl_1Si_1$ ($M_r = 410.02$); crystal dimensions $0.38 \times 0.52 \times 0.64\ mm^3$; orthorhombic; space group $P2_12_12_1$ (Figure 1). X-ray data of **12c** (CCDC-145067): colorless, transparent prism crystallized from Et_2O/*n*-hexane at room temperature, $C_{21}H_{32}N_1O_3Cl_1Si_1$ ($M_r = 410.02$); crystal dimensions $0.56 \times 0.56 \times 0.52\ mm^3$; orthorhombic; space group $P2_12_12_1$ (Figure 2). X-ray data of **12b** (CCDC-145068): colorless, transparent prism crystallized from Et_2O/*n*-hexane at room temperature, $C_{28}H_{39}N_1O_4Si_1$ ($M_r = 481.69$); crystal dimensions $0.65 \times 0.26 \times 0.22\ mm^3$; monoclinic; space group $P2_1$ (Figure 3).

[19] a) S. E. Denmark, P. A. Barsanti, K.-T. Wong, R. A. Stavenger, *J. Org. Chem*. **1998**, *63*, 2428; b) C. E. Garrett, C. G. Fu, *J. Org. Chem*. **1997**, *62*, 4534.

[20] For spectral data of γ-butyrolactones **22** see the Supporting Information.

[21] Generally, the lactones **22** can be used as intermediates to generate the desired indolizidinones **19**: after hydrogenolytic removal of the benzylamine, a subsequent lactone–lactam conversion should lead to the desired bicyclic products.

[22] a) R. S. Lott, V. S. Chauhan, C. H. Stammer, *J. Chem. Soc. Chem. Commun*. **1979**, 495; b) A. S. Kende, J. P. Rizzi, *J. Am. Chem. Soc*. **1981**, *103*, 4247.

[23] Finkelstein reaction: in analogy to H. B. Schurink, *Org. Synth. Coll. 2*, **1955**, 476.

[24] X-ray analysis was obtained from indolizidinone **20b**: colorless, transparent prism crystallized from Et_2O/*n*-hexane at room temperature, $C_{21}H_{33}N_1O_4Si_1$ ($M_r = 391.57$); crystal dimensions $0.76 \times 0.50 \times 0.34\ mm^3$; monoclinic; space group $P2_1$ (Figure 4).

[25] As a matter of principle, the lactam function can adopt four discrete arrangements: $2 \times Z$ (*pR* and *pS*) and $2 \times E$ (*pR* and *pS*) with respect to the oxygen and benzyl groups.

[26] Force-field calculations of cyclic 1,5-nonadienes were reported by D. N. J. White, M. J. Bowill, *J. Chem. Soc. Perkin Trans. II* **1977**, 1610 and A. Deiters, C. Mück-Lichtenfeld, R. Fröhlich, D. Hoppe, *Org. Lett*. **2000**, *2*, 2415 (including kinetic measurements); force-field MM+ calculations had been carried out with Hyperchem by arranging C3 and C9 in a *cis* configuration with respect to the double-bond character of the lactam unit. Structures **11** and minor-**11** as outlined in Scheme 5, data are given in Table 4. Potential *trans*-**11** with C3 and C9 *trans* with respect to the double bond character of the lactam unit not shown.

Received: July 20, 2000 [F2612]