Keywords: diketopiperazines · 2-oxindoles · spirotryprostatin A · spiro compounds · total synthesis

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[9] Relevant NOE enhancements in ^{1}H NMR spectra of **12**: irradiated signal (enhancements), H4 (H8β, H19), H8α (H8β, H9, H18), H8β (H4, H8α, H19), H9 (H8α, H8β, H18), H18 (H8α, H9), H19 (H4, H5, H18).

[10] **12**: ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 8.54$ (s, 1H), 7.40 (d, $J = 2.3$ Hz, 1H), 7.31 – 7.16 (m, 5H), 6.54 (dd, $J = 8.3$, 2.3 Hz, 1H), 6.47 (d, $J =$ 2.3 Hz, 1H), 4.18 (dd, $J = 10.6$, 5.6 Hz, 1H), 3.78 (s, 3H), 3.78 (s, 3H), 3.64 (d, $J = 9.5$ Hz, 1H), 2.83 (dd, $J = 13.7$, 10.6 Hz, 1H), 2.68 (br s, 1H), 2.11 (dd, $J = 13.7$, 5.6 Hz, 1H), 1.27 – 1.09 (m, 2H), 1.21 (s, 3H), 1.18 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 180.8$, 174.4, 159.9, 141.2, 137.6 (2C), 131.7, 128.7, 128.3 (2C), 125.1, 124.2, 107.4, 97.2, 66.2, 59.1, 58.6, 55.5, 52.3, 48.0, 43.3, 41.3, 29.2, 29.1.

[11] Yields based on recovered starting material. Actual yields are 57% for **9** and 31% for **11**.

[12] S. A. Boyd, W. J. Thompson *J. Org. Chem.* **1987**, *52*, 1790.

[13] **14**: ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 9.02$ (s, 1H), 7.41 – 7.30 (m, 5H), 6.53 (d, $J = 8.4$ Hz, 1H), 6.36 (d, $J = 2.3$ Hz, 1H), 6.08 (dd, $J = 8.4$, 2.3 Hz, 1H), 4.84 (dd, $J = 10.7$, 5.7 Hz, 1H), 4.25 (dd, $J = 8.0$, 8.0 Hz, 1H), 4.09 (dd, $J = 6.7$, 6.3 Hz, 1H), 3.72 (s, 3H), 3.55 (m, 1H), 2.49 (dd, $J = 13.4$, 11.1 Hz, 1H), 2.36 – 1.92 (m, 8H),1.31 (s, 3H), 0.45 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 181.7$, 167.5, 166.8, 160.4, 142.4, 138.1 (2C), 131.7, 128.7, 128.5 (2C), 126.5, 119.2, 106.6, 97.6, 61.3, 58.7, 58.0, 55.4, 55.1, 48.3, 45.0, 42.8, 34.5, 27.9, 27.7, 26.5, 23.6.

[14] For an example of racemization of phenylalanine derivatives under these conditions, see: R. D. Larsen, R. A. Reamer, E. G. Corely, P. Davis, E. J. J. Grabowski, P. J. Reider, I. Shinkai *J. Org. Chem.* **1991**, *56*, 6034.

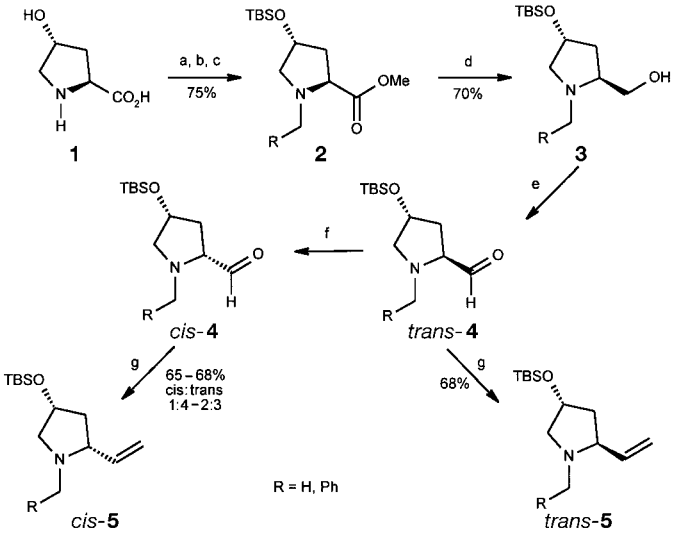
Unusual Diastereoselection in the Synthesis of Nine-Membered Ring Lactams and Conformation-Controlled Transannular Reactions to Generate Optically Active Indolizidinones**

Alexander Sudau and Udo Nubbemeyer*

Nine-membered ring lactams ("azoninones") of defined constitutions and configurations had been synthesized from vinylpyrrolidines by a zwitterionic aza-Claisen rearrangement.[1, 2] The highly ordered chairlike transition state[3] of the [3,3] sigmatopic rearrangement always induced the complete 1,3-chirality transfer from an (*E*)-allylamine to the corresponding γ,δ-unsaturated lactam.[1, 3] Furthermore an almost complete simple diastereoselection was operative[2, 3] resulting from a defined (*Z*)-enolate geometry in the hypothetical zwitterionic intermediate. A diastereoselective transannular reaction then converted the azoninones into indolizidinones.[2]

Here we report on the 1,4-chirality[3] transfer of the zwitterionic rearrangement induced by the defined enolate geometry, which had been sparsely investigated up to now. Terminally unsubstituted allylamines served as reactants, and the azoninones so formed were used as the key intermediates in the synthesis of chiral indolizidinones.

As starting compounds we chose the optically active *N*-benzyl- and *N*-methylvinylpyrrolidines *trans*-**5** and *cis*-**5**, which were generated from 4-*trans*-hydroxy-L-proline (**1**) in six steps (Scheme 1).



Scheme 1. Synthesis of the vinylpyrrolidines. a) $SOCl_2$, MeOH, reflux, 6 h; b) 98% HCO_2H, 37% CH_2O, reflux, 7h or PhCHO, $NaBH_3CN$, MeOH, 60°C, 2 d; c) TBSCl, imidazole, CH_2Cl_2, 20°C, 12 h; d) DIBAH, Et_2O, 0°C, 5 h; e) $C_2O_2Cl_2$, DMSO, Et_3N, CH_2Cl_2, −60°C, 2 h; f) cat. base, CH_2Cl_2, 20°C, 1 d;[12] g) $[Ph_3PCH_3]^+I^-$, *n*-BuLi, THF, −78°C to 20°C, 16 h.

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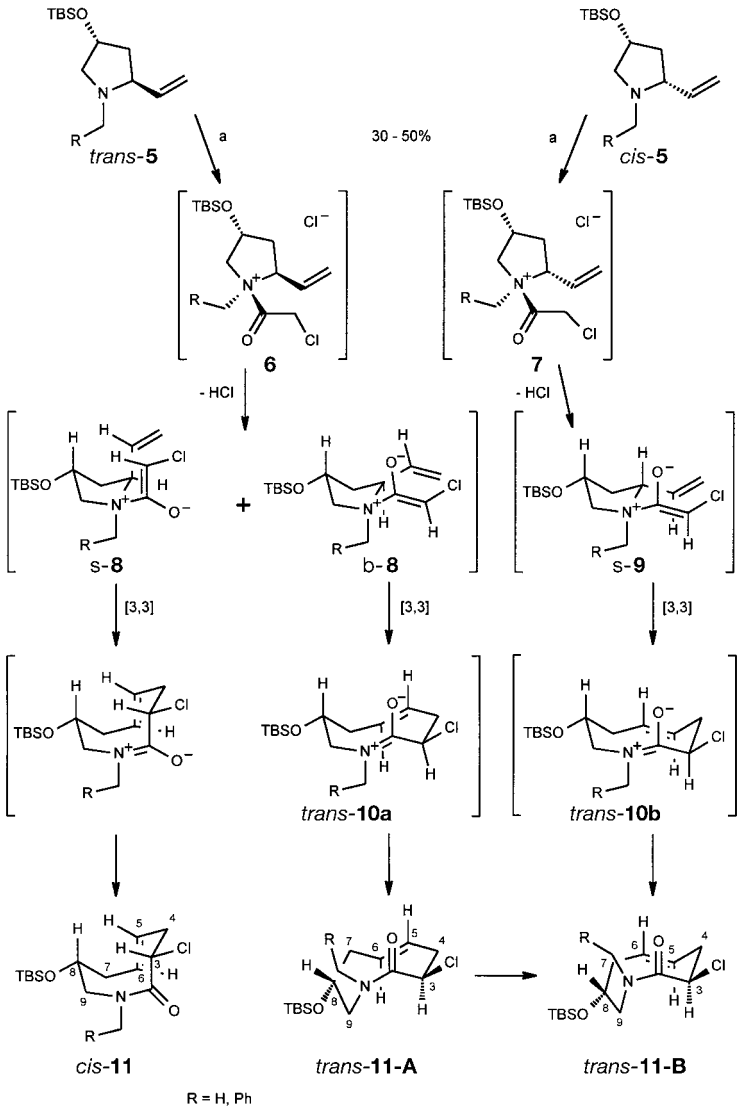
After esterification,[4] **1** was subjected to a reductive amination either with formaldehyde (Clarke – Eschweiler)[5] or with benzaldehyde.[6] The hydroxyl group was then protected as a silyl ether[7] with *tert*-butyldimethylsilyl chloride (TBSCl) to generate the *N*-methyl- or the *N*-benzylaminoesters **2**, respectively. Reduction[8] with DIBAH to the alcohols **3** and subsequent Swern oxidation[9] led to the aldehydes *trans*-**4**, which were converted by a Wittig olefination with methylenetriphenylphosphorane[10, 11] into vinylpyrrolidines *trans*-**5**. Leaving the aldehyde *trans*-**4** as it was at room temperature led to a partial epimerization of the C-2 formyl groups; this method thus afforded *cis*-vinylpyrrolidines *cis*-**5** after separation of the diastereomers.[12]

Under standard conditions[1, 2] the vinylpyrrolidines **5** were treated with chloroacetyl chloride in chloroform in presence of trimethylaluminium (Scheme 2). The reactions of both *trans*- and *cis*-vinylpyrrolidines **5** gave good yields of the corresponding azoninones (*trans*-**11**) configured *trans* with respect to positions 3 and 8. Only the rearrangement of the *N*-benzylpyrrolidine *trans*-**5** led to the formation of a small amount of the 3,8-*cis* diastereomer *cis*-**11** as a by-product (*cis*-**11**:*trans*-**11** 1:5).[13] The diastereomers were separated by preparative HPLC, and the relative configurations of the stereogenic centers were proved beyond doubt by NOE analysis.[13, 14]

The formation of the 3,8-disubstituted lactam *trans*-**11** from vinylpyrrolidine *trans*-**5** was characterized by a conspicuous change of its conformation: right after the isolation of the product a 3,8-*trans*-configured azoninone with the defined conformation *trans*-**11**-**A** was identified. The NOE analysis indicated the proximity of protons H-3, H-6, and H-9α. If the product was kept neat or in solution ($CDCl_3$, MeCN, etc.) at room temperature for 3 – 5 days, a complete change of the conformation to *trans*-**11**-**B** was observed. Now the NOE analysis proved the proximity of protons H-3, H-5, and H-9α:[14] the 3,8-*trans* configuration was maintained. The rearrangement of the vinylpyrrolidine *cis*-**5**, however, directly afforded the lactam with the stable conformation *trans*-**11**-**B**; no molecular relaxation could be detected.[14] The *N*-methyl and *N*-benzyl compounds behaved quite similarly. The **A** and **B** conformations of the major lactam *trans*-**11** (R = Ph) differed unequivocally from the minor diastereomer *cis*-**11** (R = Ph) isolated from this reaction (the spectroscopic data are summarized in Table 1).



Scheme 2. Zwitterionic aza-Claisen rearrangement. a) $ClCH_2COCl$, Me_3Al, $CHCl_3$, K_2CO_3, 0°C, 1 d.

Fundamentally the reaction of the two diastereomeric allylamines **5** to the same product **11** might have been caused by passing a common transition state. On the other hand ^1H and ^{13}C spectroscopic analyses gave evidence of two defined diastereomorphic transition states **8** and **9**.[15] Another explanation for the observations could be as follows: In the first step of the reaction two acylammonium salts **6** and **7** were diastereoselectively generated bearing the acyl group in *anti* position to the bulky silyl substituent. Such primary active species were investigated in the *N*-methyl series (R = H).[16] After deprotonation to form the hypothetical zwitterions **8** and **9** the enolates should be *Z*-configured as all amide enolates.[17] The arrangement in a chairlike transition state[18] conformation s-**9** with minimized 1,3-diaxial repulsions led, after rearrangement, to *trans*-**10b** and isomerization of the amide bond directly to lactam *trans*-**11**-**B**. The generation of a chair-like conformation from zwitterion s-**8** was apparently hindered by severe repulsive interactions (1,3-strain). Therefore the system rearranged preferentially via the alternative boat-conformation b-**8**,[19] which is normally known to be disfavored in acyclic reactions. After sigmatropic rearrangement to *trans*-**10a** and isomerization of the amide bond, lactam *trans*-**11** with the less stable conformation *trans*-**11**-**A** was formed as the primary isolated product. The change towards the more stable lactam with the conformation *trans*-**11**-**B** was caused by molecular relaxation.[20]

Recent investigations[2] have shown that defined configured 3,4-difunctionalized azoninones under-

Table 1. Spectroscopic data of **11** (R = Ph), and **12** – **14**.[a]

cis-**11**: IR: $\tilde{\nu}$ = 1645 (C=O), 1451, 1421, 1260 cm^{-1}; MS (60°C): *m*/*z*: 393 [*M*$^+$], 378, 358, 336, 302, 246, 91, 73; ^{1}H NMR: δ = 7.25 – 7.35 (m, 5H; Ar), 6.04 (ddd, ^3J = 16, 10, 5, 1H; H-6), 5.44 (ddd, ^3J = 16, 12, 4, 1H; H-5), 5.14 (d, ^2J = 15, 1H; CH_2Ar), 5.02 (dd, ^3J = 4, 2, 1H; H-3), 4.64 (ddd, ^2J = 15, ^3J = 9, ^4J = 1, 1H; H-9α), 4.08 (d, ^2J = 15, 1H; CH_2Ar), 3.91 (m, 1H, H-8), 2.97 (d, ^2J = 15, 1H; H-9β), 2.80 – 2.65 (m, 3H; H-7β, CH_2-4), 2.12 (ddd, ^2J = 12, ^3J = 12, 9, 1H, H-7α), 0.83 (s, 9H, *t*BuSi), 0.04 (s, 3H; MeSi), 0.02 (s, 3H; MeSi); ^{13}C NMR: δ = 169.8 (s), 137.4, 131.9 (d), 131.0 (d), 129.1, 127.7, 127.6, 71.6 (d), 65.1 (d), 56.2 (t), 51.3 (t), 43.6 (t), 36.8 (t), 26.3 (q), 18.3 (s), – 4.4 (q)

trans-**11-A**: ^{1}H NMR: δ = 7.25 (m, 5H; Ar), 5.76 (ddd, ^3J = 15, 11, 3, 1H; H-6), 5.44 (ddd, ^3J = 16, 9, 6, 1H; H-5), 5.05 (d, ^2J = 14, 1H; CH_2Ph), 4.84 (dd, ^3J = 10, 8, 1H; H-3), 4.17 (d, ^2J = 15, 1H; CH_2Ph), 4.05 (m, 1H; H-8), 3.55 (dd, ^2J = 16, 10, 1H; H-9α), 3.01 (dd, ^2J = 15, ^3J = 4, 1H; H-9β), 2.90 (m, 1H; H-4α), 2.54 (ddd, ^2J = 17, ^3J = 10, 6, 1H; H-4β), 2.28 (m, 1H; H-7α), 2.09 (ddd, ^2J = 17, ^3J = 11, 5, 1H; H-7β), 0.81 (s, 9H; *t*BuSi), – 0.01 (s, 3H; MeSi), – 0.07 (s, 3H; MeSi); ^{13}C NMR: δ = 169.8 (s), 136.8, 131.2 (d), 130.8 (d), 128.7, 128.0, 127.9, 66.5 (d), 55.3 (d), 51.8 (t), 49.4 (t), 39.2 (t), 37.12 (t), 25.7 (q), 17.9 (s), – 4.8 (q), – 5.0 (q)

trans-**11-B**: IR: $\tilde{\nu}$ = 1644 (C=O), 1451, 1421, 1260 cm^{-1}; MS (60°C): *m*/*z* = 393 [*M*$^+$], 378, 358, 336, 302, 246, 91, 73; ^{1}H NMR: δ = 7.2 – 7.3 (m, 5H; Ar), 5.67 (ddd, ^3J = 16, 10, 6, 1H; H-5), 5.34 (ddd, ^3J = 15, 11, 3, 1H; H-6), 5.22 (d, ^2J = 15 Hz, 1H; CH_2Ar), 4.50 (dd, ^3J = 12, 3, 1H; H-3), 4.09 (d, ^2J = 15, 1H; CH_2-Ar), 4.01 (m, 1H; H-8), 3.62 (dd, ^2J = 14, ^3J = 9, 1H; H-9α), 2.97 (d, ^2J = 14, 1H; H-9β), 2.60 – 2.80 (m, 3H; H-7β, CH_2-4), 2.02 (ddd, ^2J = 12, ^3J = 12, 9, 1H; H-7α), 0.81 (s, 9H; *t*BuSi), 0.02 (s, 3H; MeSi), 0.00 (s, 3H; MeSi); ^{13}C NMR: δ = 169.6 (s), 136.8 (s), 131.2 (d), 130.1 (d), 128.6 (d), 127.9 (d), 127.6 (d), 69.5 (d), 56.2 (d), 54.3 (t), 49.7 (t), 42.8 (t), 40.1 (t), 25.6 (q), 17.8 (s), – 4.5 (q), – 4.9 (q)

12: IR: $\tilde{\nu}$ = 1644 (C=O), 1578, 1458, 1434, 1388, 1280, 1249 cm^{-1}; MS (150°C): *m*/*z*: 459 [*M*$^+$], 444, 402, 302, 244, 210, 170; ^{1}H NMR: δ = 7.40 (m, 2H; *o*-Ar), 7.00 – 6.90 (m, 3H; *m*-, *p*-Ar), 4.00 (dd, ^3J = 9, 6, 1H; H-6), 3.84 (dddd, ^3J = 6, 6, 6, 6, 1H; H-2), 3.55 (dd, ^2J = 12, ^3J = 6, 1H; H-3α), 3.37 (dd, ^2J = 12, ^3J = 7, 1H; H-3β), 3.05 (ddd, ^3J = 10, 10, 5, 1H; H-8a), 2.53 – 2.4 (m, 2H; H-7α, H-8), 2.20 – 2.05 (m, 2H; H-1β, H-7β), 1.47 (ddd, ^2J = 13, ^3J = 10, 8, 1H; H-1α), 0.92 (s, 9H, *t*BuSi), – 0.02 (s, 3H; MeSi), – 0.03 (s, 3H; MeSi); ^{13}C NMR: δ = 164.2 (s), 136.3 (d), 129.5 (d), 125.8 (d), 125.9 (s), 68.8 (d), 61.8 (d), 54.1 (d), 53.9 (t), 42.0 (t), 40.7 (t), 40.7 (d), 22.7 (q), 17.9 (s), – 4.9 (q), – 5.0 (q)

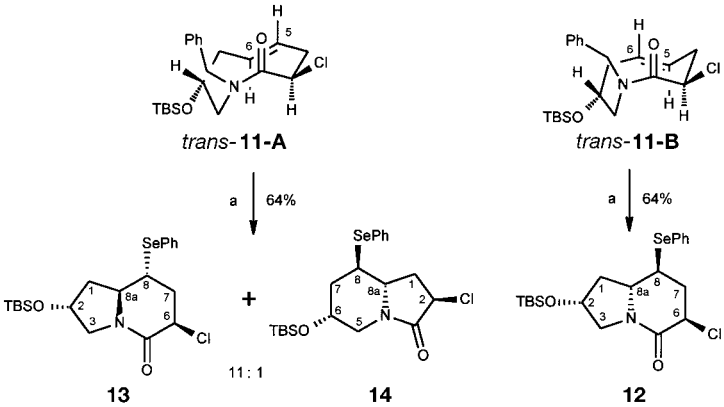
13: IR: $\tilde{\nu}$ = 1663 (C=O), 1578, 1448, 1364, 1253 cm^{-1}; MS (150°C): *m*/*z*: 459 [M$^+$], 444, 402, 302, 244, 210, 170, 134, 73; ^{1}H NMR: δ = 7.50 – 7.45 (m, 2H; *o*-Ar), 7.05 – 7.00 (m, 3H; *m*-, *p*-Ar), 4.03 (dd, ^3J = 4, 1.5, 1H; H-6), 3.86 (dd, ^3J = 5, 5, 1H; H-2), 3.72 (dd, ^2J = 13, ^3J = 5, 1H; H-3β), 3.62 (ddd, ^3J = 11, 11, 5, 1H; H-8a), 3.42 (d, ^2J = 14, 1H; H-3α), 3.25 (ddd, ^3J = 11, 11, 3, 1H; H-8), 2.23 (ddd, ^2J = 15, ^3J = 2, 2, 1H; H-7β), 2.11 (dd, ^2J = 13, ^3J = 4, 1H, H-1α), 1.48 (ddd, ^2J = 15, ^3J = 13, 5, 1H; H-7α), 1.07 (ddd, ^2J = 12, ^3J = 12, 4, 1H; H-1β), 0.91 (s, 9H; *t*BuSi), – 0.03 (s, 3H; MeSi), – 0.06 (s, 3H; MeSi); ^{13}C NMR: δ = 162.9 (s), 136.4, 129.4, 128.7, 126.1, 68.4 (d), 61.7 (d), 56.5 (d), 55.0 (t), 42.9, 39.9, 36.5, 25.8 (q), 18.0 (s), – 4.9 (q)

14: IR: $\tilde{\nu}$ = 1714 (CO) 1578, 1472, 1435, 1257 cm^{-1}; MS (150°C): *m*/*z*: 459 [*M*$^+$], 444, 402, 244, 210, 73; ^{1}H NMR: δ = 7.56 – 7.50 (m, 2H; *o*-Ar), 7.35 – 7.26 (m, 3H; *m*-, *p*-Ar), 4.34 (dd, ^3J = 8, 3, 1H; H-2), 4.03 – 3.93 (m, 2H; H-5α, H-6), 3.60 – 3.50 (ddd, ^3J = 11, 7, 7, 1H; H-8a), 3.22 – 3.10 (m, 1H; H-8), 2.75 (d, ^2J = 12, 1H; H-5β), 2.23 (ddd, ^2J = 15, ^3J = 6, 2, 1H; H-1β), 2.32 – 2.25 (m, 1H; H-1α), 2.25 – 2.15 (m, 1H; H-7α), 1.68 (m, 1H; H-7β), 0.81 (s, 9H; *t*BuSi), 0.02 (s; MeSi), – 0.03 (s; MeSi); ^{13}C NMR: δ = 135.7, 129.1, 128.4, 65.1 (d), 58.9 (d), 53.8 (d), 46.5 (t), 40.6, 39.6, 36.7, 25.5 (q)

[a] IR: (KBr/film). MS: EI, 70 eV. ^{1}H NMR: 270 MHz, $CDCl_3$, 20°C, TMS, *J* in Hz. ^{13}C NMR: 67.9 MHz, $CDCl_3$, 20°C. Experimental details: Ref. [2]; other spectroscopic data: Refs. [14, 22, 24].

went regio- and diastereoselective ring contractions to indolizinones. Apparently, the rigid conformation of the lactams involved caused the formation of a single product in high yield. Since the 3,8-disubstituted lactam (R = Ph) exists either in the relatively long-lived conformation *trans*-**11-A** immediately after the rearrangement of lactam *trans*-**5** or in the stable conformation *trans*-**11-B**, we could study the selectivity of the ring contraction.

Under standard conditions[2, 21], the treatment of the stable conformation *trans*-**11-B** of 3-chlorolactam (R = Ph) with phenylselanyl chloride in acetonitrile at room temperature led to the formation of the single regio- and diastereomerically pure indolizidinone **12** (Scheme 3, Table 1). The relative



Scheme 3. Transannular reaction. a) PhSeCl, MeCN, 20°C, 3 h.

configurations of the new stereogenic centers were proved by NOE analysis, and the position of the phenylselanyl substituent was determined by HETCOR (heteronuclear correlation).[22] The analogous reaction of conformation *trans*-**11-A** (R = Ph) took an alternative regio- and stereochemical course: Instead of the generation of the known indolizidinone **12**, two further bicycles, **13** and **14**, were formed in an 11:1 ratio (see Table 1). The structural analysis was again achieved by HETCOR and NOE analyses.[22]

The results indicated that the particular conformation of lactam *trans*-**11** directed the regio- and the diastereoselectivity of the transannular reaction. In contrast to processes following the Curtin – Hammett Principle,[23] the activation energy for the conformational relaxation appeared to be much higher than that of the reaction! The different relative arrangement of the π-systems (amide and olefin) caused a relatively stable facial chirality: the electrophile ($PhSe^+$) always attacked the free face of the olefin (that is, the face unhindered by the ring).

The zwitterionic aza-claisen rearrangement of 2-vinylpyrrolidines to the γ,δ-unsaturated lactams proceeded with a high 1,4-chirality transfer. Relative to well-known acyclic Claisen rearrangements an unusual diastereoselectivity in the reaction of amine *trans*-**5** and the usual stereochemistry in the reaction of *cis*-**5** both led to azoinone *trans*-**11** with identical olefin and amide geometries. However, the initial conformations (**A** and **B**) differed with respect to the relative orientation of the π-systems. The relaxation from the kinetically generated conformation *trans*-**11-A** into the thermodynamically stable *trans*-**11-B** required a significantly higher activation energy than the transannular reactions. In contrast to the dictates of the Curtin – Hammett Principle, lactam *trans*-**11** allowed defined reactions depending on the predominant conformation. The facial chiralality of the nine-membered ring could be used to generate defined stereogenic

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centers in the indolizidinones by means of the ring contraction. Further investigations into the scope and limitations of the diastereoselective transannular reaction are in progress.

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Keywords: chirality · heterocycles · lactams · rearrangements · ring contractions

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[14] All previously isolated lactams displayed an *E*-olefin and an "*E*"-amide geometry. Structural proof: *cis*-**11**: Olefin (*E*): ^3J(H-5,H-6) = 16 Hz (^{1}H-NMR); NOE analysis (irradiation of H-*x* ⇒ enhancement at H-*y* [%]): H-4α ⇒ H-6 (7); H-6 ⇒ H-4α (4); H-5 ⇒ H-7β (8); H-7β ⇒ H-5 (10). Amide ("*E*"): H-3 ⇒ H-9β (2); H-9β ⇒ H-3 (3). Relative configuration of C-3 and C-8 (*cis*): H-3 ⇒ H-5 (3), H-9β (2); H-5 ⇒ H-3 (2), H-8 (3), H-9β (1); H-8 ⇒ H-5 (5), H-9β (3); H-9β ⇒ H-3 (2), H-5 (1), H-8 (4). *trans*-**11**-**A**: Olefin (*E*): ^3J(H-5,H-6) = 16 Hz (^{1}H-NMR); NOE analysis: H-4α ⇒ H-6 (7); H-6 ⇒ H-4α (4); H-5 ⇒ H-7β (6); H-7β ⇒ H-5 (8). Amide ("*E*"): H-3 ⇒ H-9α (17); H-9α ⇒ H-3 (28). Relative configuration of C-3 and C-8 (*trans*): H-3 ⇒ H-6 (4), H-9α (17); H-6 ⇒ H-3 (3), H-9α (3); H-9α ⇒ H-3 (27), H-6 (6); H-8 ⇒ H-9β (4); H-9β ⇒ H-8 (6). *trans*-**11**-**B**: Olefin (*E*): ^3J(H-5,H-6) = 16 Hz (^{1}H-NMR); NOE analysis: H-4β ⇒ H-6 (6); H-6 ⇒ H-4β (5); H-5 ⇒ H-7α (10); H-7α ⇒ H-5 (13). Amide ("*E*"): H-3 ⇒ H-9α (15); H-9α ⇒ H-3 (28). Relative configuration of C-3 and C-8 (⇒ *trans*): H-3 ⇒ H-5 (4), H-9α (15); H-5 ⇒ H-3 (3), H-9α (3); H-9α ⇒ H-3 (28), H-5 (5); H-8 ⇒ H-6 (3), H-9β (2); H-9β ⇒ H-8 (3).
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[22] Structural proof: a) Position bridgehead C-8a and PhSe-substituent by ^{1}H/^{13}C HETCOR analysis for **12**, **13**, and **14**: in each case coupling C-1 (Ar) with H-8; C-8 (d, $\delta \approx 40$) with H-8 ⇒ substituent Se; C-8a (d, $\delta \approx 60$) with H-8a ⇒ substituent N. **12**: NOE analysis: Relative configuration of C-2, C-6, C-8 and C-8a (⇒ β: H-2, H-8a; α: H-6, H-8): H-2 ⇒ H-8a (9); H-8a ⇒ H-2 (6), H-7β (8); H-6 ⇒ H-8 (7), H-7α (7); H-8 ⇒ H-6 (7), H-1α (4); H-1α ⇒ H-8 (8). **13**: NOE analysis: Relative configuration of C-2, C-6, C-8, and C-8a (⇒ β: H-2, H-8; α: H-6, H-8a): H-1β ⇒ H-2 (9), H-8 (10), H-2 ⇒ H-1β (6), H-3β (5); H-8 ⇒ H-1β (5), H-7β (4); H-6 ⇒ H-7α (4), H-7α ⇒ H-6 (11); H-8a ⇒ H-7α (10), H-1α (5); H-7α ⇒ H-6 (11), H-8a (5); H-1α ⇒ H-8a (5). **14**: NOE analysis: (irradiation of H-*x* ⇒ enhancement at H-*y* [%]) relative configuration of C-2, C-6, C-8, and C-8a (⇒ β: H-6, H-8a; α: H-2, H-8): H-1β ⇒ H-8a (10); H-5β ⇒ H-7β (3), H-8a (3); H-7β ⇒ H-5β (3), H-8a (2); H-8a ⇒ H-1β (8), H-5β (7), H-7β (7); H-6 ⇒ H-7β (4); H-2 ⇒ H-1α (8), H-1α ⇒ H-2 (4), H-8 (11); H-8 ⇒ H-1α (11), H-7α (8). For IR data see Table 1.
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An Enzyme-Labile Linker Group for Organic Syntheses on Solid Supports**

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Combinatorial chemistry has proven to be a new and valuable method for the rapid identification and further development of compounds with a predetermined profile of properties, not only for drug discovery but also for asymmetric catalysis.[1] In the majority of the cases combinatorial syntheses are carried out on solid supports. Once the desired compounds are constructed they have to be released from the supports selectively and without attack on the synthesized structures through cleavage of a suitable anchor group (linker). Combinatorial synthesis gives access to a multitude of different classes of compounds with a wide range of stability under the conditions of the releasing reactions. Therefore the development of broadly applicable linkers

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