Enantio- and Diastereoselective Synthesis of a 3,4-Divinylpyrrolidine via Asymmetric Deprotonation and Cyclization of a 9-Chloro-5-aza-2,7-nonadiene

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Dedicated to Professor B. Franck on the occasion of his 75th birthday

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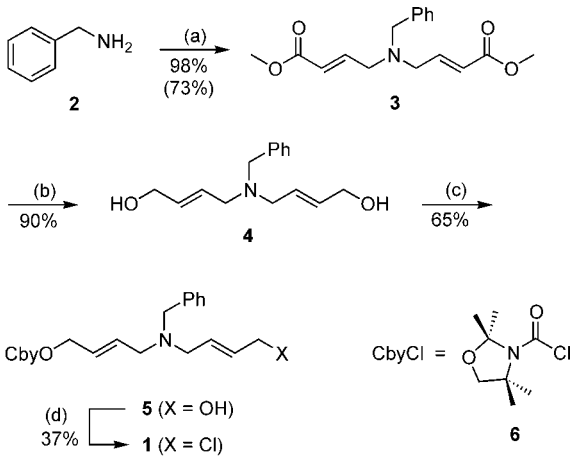
Chiral pyrrolidines are common structural subunits found in a variety of biological active compounds such as natural products and pharmaceuticals.[1] Enantiomerically pure pyrrolidines have also been used as auxiliaries in stereoselective transformations.[2] Hence, there is a demand for new stereoselective methods to construct the pyrrolidine skeleton.[3]

Although in most of the pyrrolidine syntheses a carbon-nitrogen bond formation takes place, there are also some carbanion-induced ring-closing reactions.[4] Herein we want to report an asymmetric carbanionic cyclization reaction which allows the stereochemical control of two new stereocenters in the formed pyrrolidine.

We applied our previously developed procedure for carbocyclization[5,6] to the 4-aza-2,7-diene **1**. The diene **1** has been synthesized starting from benzylamine **2**. Bis-allylation of **2** with commercially available 4-bromobut-2-enoic acid methyl ester (*E*/*Z* = 80:20) furnished **3** nearly quantitatively as an *E*/*Z*-mixture of 80:20. After column chromatography pure (2*E*,7*E*)-**3** was obtained in 73% yield. A subsequent reduction with DIBAH provided the diol **4** (90%), which has been used in the following step without further purification. A mono-carbamoylation of **4** using the carbamoyl chloride **6** (CbyCl)[7] furnished **5** in 65% yield.[8] The reaction sequence was completed by a chlorination of **5**. The low yield of 37% in the last step resulted from the instability of the chloride **1** (Scheme 1).[9]

The cyclization reaction (Scheme 2) starts with an enantioselective deprotonation of **1** by means of the chiral base *n*-BuLi/(–)-sparteine (*n*-BuLi/**7**).[10] The allyllithium species (*S*)-**8**[11] reacts from the *endo*-conformation[12] via the transition state **A** under regioselective C–C-bond formation between both γ-positions and simultaneous elimination of lithium chloride. In **A** the two allylic moieties are in a coplanar orientation which allows a favorable π/π*-interaction and the reaction proceeds exclusively to the *cis*-configured pyrrolidine **9** (*dr* = 100:0).[13] The cyclization takes place in an *anti*-S_E' fashion at the lithium-bearing allyl moiety, which leads to the (3*R*,4*R*)-configuration of the newly formed stereocenters.[14] The enantiomeric ratio (*er*) of **9** has been determined to 95:5 (90% *ee*) by ^{1}H NMR-spectroscopy of a 1:1 mixture of Mosher's acid and **9**.[15] The high *er* of **9** results from the high rate of the cyclization step, which is much faster than the epimerization of the configuratively labile allyllithium species (*S*)-**8**.



Scheme 1. Synthesis of the cyclization precursor **1**. (a) 4-Bromobut-2-enoic acid methyl ester (2.2 equiv., *E*/*Z* = 80:20), K_2CO_3 (1.5 equiv.), 80 °C; (b) DIBAH (1.5 equiv.), hexane/THF, –78 °C; (c) NaH (0.25 equiv.), **6** (0.25 equiv.), THF, 60 °C; (d) LiCl (4.0 equiv.), *n*-BuLi (1.3 equiv.), CH_3SO_2Cl (2.0 equiv.), THF, –78 °C → rt

[a] X-ray analysis

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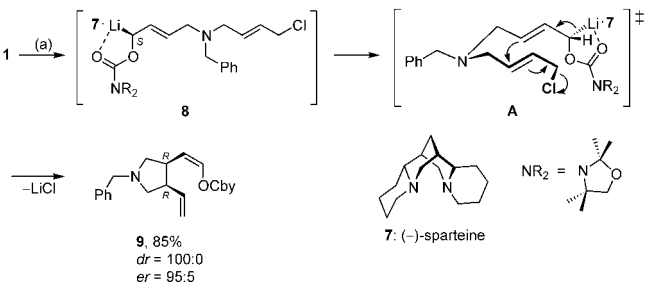
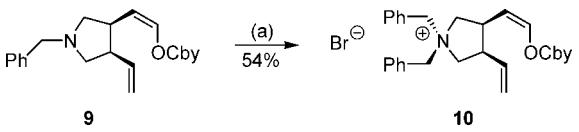
This high cyclization rate is also the reason why the δ-elimination of a lithium amide,[16a] a possible side-reaction, does not occur.[16b]



Scheme 2. Cyclization of **1**. (a) *n*-BuLi (2.2 equiv.), **7** (2.2 equiv.), toluene, –90 °C, 2 h.

In a similar cyclization reaction, when using the achiral ligand *N*,*N*,*N*′,*N*′-tetramethylethylenediamine instead of (–)-sparteine, diastereomerically pure *rac*-**9** has been obtained with 72% yield.

Reaction of (3*R*,4*R*)-**9** with benzyl bromide at elevated temperature furnished the pyrrolidinium bromide (3*R*,4*R*)-**10** as a colorless solid (Scheme 3).[17]



Scheme 3. Synthesis of the pyrrolidinium bromide **10**. (a) Benzyl bromide (2.0 equiv.), $CHCl_3$, 50 °C, 20 h.

Crystals suitable for anomalous X-ray diffraction analysis were grown by vapor diffusion of pentane into a solution of **10** in CH_2Cl_2. The crystal structure analysis[18] of **10** clearly shows an envelope conformation of the five-membered ring, the *cis*-configuration of the vinyl-substituents and the (3*R*,4*R*)-configured stereocenters (Figure 1).

The carbamoyloxyvinyl group in **9** represents a masked 2-oxoethyl group. Several methods have been developed for its transformation into further functional groups.[10a,19]

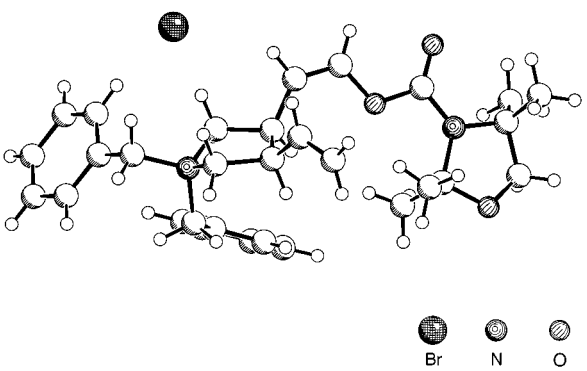


Figure 1. X-ray crystal structure analysis of **10**.[18]

In summary, we have developed a new method for the construction of diastereomerically pure and highly enantioenriched 3,4-disubstituted pyrrolidines in high yield. The reaction consists of an enantioselective (–)-sparteine-mediated lithiation and a subsequent intramolecular *anti*-$S_E'S_N'$-cycloalkylation. The application of this reaction in the synthesis of natural products is under investigation.

Experimental Section

The diene **1** (100 mg, 0.25 mmol) and (–)-sparteine (141 mg, 0.60 mmol) were dissolved in toluene (5 mL) under argon. After the solution had been cooled to –90 °C, a 1.6 M hexane solution of *n*-butyllithium (0.34 mL, 0.54 mmol) was added slowly, and the solution was stirred at this temperature for 2 h. Methanol (1 mL) and saturated NH_4Cl solution (1 mL) were then added, and the reaction mixture was warmed to room temperature. After a standard work-up procedure, the crude product was purified by column chromatography with diethyl ether on silica gel to yield **9** as colorless liquid; yield: 78 mg (85%, 90% *ee*).

Acknowledgements

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References and Notes

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[5] A. Deiters, D. Hoppe, *Angew. Chem.* **1999**, *111*, 529–532; *Angew. Chem. Int. Ed.* **1999**, *38*, 546–548.

[6] We already applied this reaction in the synthesis of divinylcyclopentanes (see ref. [5]), but here we report a revised cyclization mechanism. We now have some evidence that the previously proposed lithium-ene reaction is in fact an *anti*-$S_E'S_N'$-cycloalkylation.

[7] F. Hintze, D. Hoppe, *Synthesis* **1992**, 1216–1218.

[8] The yield of **5** is based on the amount of CbyCl (**6**).

[9] **1**: $R_f = 0.63$ (DE); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.35$, 1.41 [s, 6H, CH_3(Cby)]; 1.51, 1.55 [s, 6H, CH_3(Cby)]; 3.02–3.16 (m, 4H, CH_2); 3.57 (s, 2H, CH_2Ph); 3.71 [s, 2H, CH_2(Cby)]; 4.03 (d, 2H, CH_2Cl, $^3J = 5.9$ Hz); 4.55–4.58 (m, 2H, CH_2O); 5.72–5.87 (m, 4H, CH); 7.20–7.37 (m, 5H, H_{phenyl}); anal. calcd. for $C_{23}H_{33}ClN_2O_3$ (420.97): C 65.62, H 7.90, N 6.65; found: C 65.48, H 7.92, N 6.80.

[10] Reviews: (a) D. Hoppe, T. Hense, *Angew. Chem.* **1997**, *109*, 2376–2410; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 2282–2316; (b) P. Beak, A. Basu, D. J. Gallagher, Y. S. Park, S. Thayumanavan, *Acc. Chem. Res.* **1996**, *29*, 552–560.

[11] The *S* configuration of the lithiated intermediate **8** has been determined for the corresponding 5-carba cyclization precursor (see ref. [5]).

[12] Review: M. Schlosser, O. Desponds, R. Lehmann, E. Moret, G. Rauchschwalbe, *Tetrahedron* **1993**, *49*, 10175–10203.

[13] **9**: $R_f = 0.25$ (DE/PE = 1 : 1); $[\alpha]_D^{20} = +37.0$ ($c = 1.52$, $CHCl_3$) for 90% *ee*; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.33$–1.39 [m, 6H, CH_3(Cby)]; 1.49–1.52 [m, 6H, CH_3(Cby)]; 2.24 (t, 1H, CH_2, $^2J = 8.3$ Hz); 2.29–2.38 (m, 1H, CH_2); 2.90–3.07 (m, 3H, CH_2); 3.28–3.46 (m, 1H, CH); 3.63 (s, 2H, CH_2Ph); 3.70 [s, 2H, CH_2(Cby)]; 4.68 (dd, 1H, CH, $^3J = 5.9$ Hz, $^3J = 10.0$ Hz); 4.88–4.96 (m, 2H, CH_2); 5.64–5.76 (m, 1H, CH); 6.95 (d, 1H, CH, $^3J = 5.9$ Hz); 7.17–7.31 (m, 5H, H_{phenyl}); anal. calcd. for $C_{23}H_{32}N_2O_3$ (384.51): C 71.84, H 8.39, N 7.29; found: C 71.77, H 8.50, N 7.74.

[14] The stereochemical course of the allyl chloride substitution is assumed to be also anti-stereospecific; for a review about S_N-reactions, see: R. M. Magid, *Tetrahedron* **1980**, *36*, 1901–1930.

[15] F. J. Villani, Jr., M. J. Costanzo, R. R. Inners, M. M. Mutter, D. E. McClure, *J. Org. Chem.* **1986**, *51*, 3715–3720.

[16] (a) F. F. Huerta, C. Gómez, M. Yus, *Tetrahedron* **1996**, *52*, 13243–13254; (b) For allylic *O*-carbamates with an oxy-group in 5-position only elimination reactions occur at –78 °C: A. Deiters, *PhD Thesis*, Universität Münster, **2000**; P. H. Mason, N. D. Emslie, *Tetrahedron* **1995**, *51*, 2673–2678.

[17] **10**: mp 125 °C (CH_2Cl_2); $[\alpha]_D^{20} = +8.8$ ($c = 0.38$, $CHCl_3$) for 90% *ee*; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.36$–1.61 [m, 12H, CH_3(Cby)]; 3.06–3.17 (m, 1H, CH); 3.41–3.57 (m, 2H, CH_2); 3.58–3.73 (m, 1H, CH); 3.76 [s, 2H, CH_2(Cby)]; 4.12–4.29 (m, 3H, CH, CH_2); 4.92–5.26 (m, 6H, CH_2, CH_2Ph); 5.32–5.45 (m, 1H, CH); 6.98 (d, 1H, CH, $^3J = 6.9$ Hz); 7.42–7.54, 7.63–7.72 (each m, 10H, H_{phenyl}); $C_{30}H_{39}BrN_2O_3$ (555.56), ESI-HRMS calcd. 475.2961 (M–Br), found 475.2955 (M–Br).

[18] X-ray crystal structure analysis of **10:** formula $C_{30}H_{39}N_2O_3Br$, M = 555.54, colorless crystal 0.25 × 0.10 × 0.05 mm, a = 10.640(3), b = 8.210(1), c = 16.740(4) Å, β = 91.24(2)°, V = 1462.0(6) Å^3, $\rho_{calc} = 1.262$ g · cm^{-3}, $\mu = 21.59$ cm^{-1}, empirical absorption correction via ψ scan data ($0.614 \le T \le 0.900$), Z = 2, monoclinic, space group P21 (No. 4), λ = 1.54178 Å, T = 223 K, ω/2θ scans, 5038 reflections collected (±h, –k, ±l), [(sinθ)/λ] = 0.62 Å^{-1}, 2521 independent ($R_{int} = 0.195$) and 1891 observed reflections [$I \ge 2\sigma(I)$], 330 refined parameters, R = 0.067, $wR_2 = 0.0126$, max. residual electron density 0.87 (–1.38) e Å^{-3}, Flack parameter 0.00(4), hydrogens calculated and refined as riding atoms. Data set was collected with an Enraf-Nonius CAD4 diffractometer. Programs used: data collection EXPRESS (Nonius B. V., 1994), data reduction MolEN (K. Fair, Enraf-Nonius B. V., 1990), structure solution SHELXS-97 (G. M. Sheldrick, *Acta Cryst.* **1990**, *A46*, 467–473), structure refinement SHELXL-97 (G.M. Sheldrick, Universität Göttingen, 1997), graphics SCHAKAL (E. Keller, Universität Freiburg, 1997). Crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-151975. Copies of the data can be obtained free of charge on application to The Director, CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: int. code +44(1223)336–033, e-mail: deposit@ccdc.cam.ac.uk].

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