DOI: 10.1002/adsc.200600482

Diastereoselective Synthesis of 2,6-*trans*-Disubstituted Piperidines *via* Sequential Cross-Metathesis–Cationic Cyclisation

Stefan Mix[a] and Siegfried Blechert[a,*]

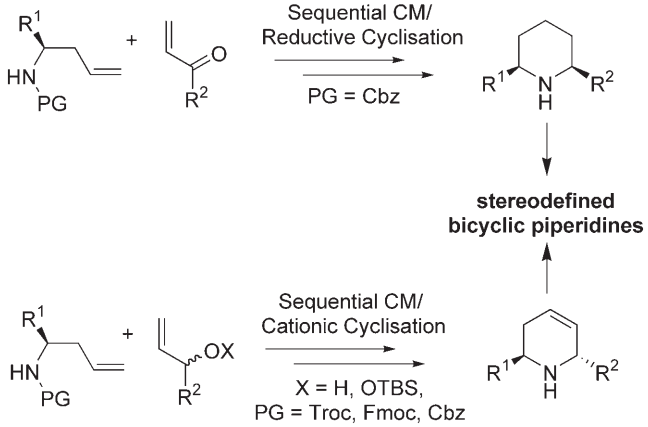
[a] Technische Universität Berlin, Institut für Chemie, Strasse des 17. Juni 135, 10623 Berlin, Germany
Fax: (+49)-30-3142-3619; e-mail: blechert@chem.tu-berlin.de

Received: September 19, 2006

Supporting information for this article is available on the WWW under http://asc.wiley-vch.de/home/.

Abstract: Ruthenium-catalysed cross-metathesis of protected homoallylamine derivatives with vinyl carbinols furnished allylic alcohols, which underwent stereoconvergent cyclisation to *trans*-tetrahydropyridines upon treatment with $BF_3{\cdot}OEt_2$. The new methodology was used for the preparation of enantiopure piperidine and indolizidine natural products.

Keywords: cationic cyclisation; cross-metathesis; 6-*endo-trig* cyclisation; 3,5-disubstituted indolizidines; 2,6-disubstituted piperidines; ruthenium



Scheme 1. CM cyclisation sequences (PG = protective group).

Piperidine alkaloids are widespread in nature and exhibit manifold biological activities. 2,6-Disubstituted piperidines represent an important class within this natural product family, to which belong also a number of substituted indolizidines.[1] Since many of these compounds possess interesting pharmacological properties, a number of stereoselective synthetic routes to the 2,6-disubstituted piperidine scaffold have been developed.[2]

A simple and flexible access to this class of compounds by the sequential combination of cross-metathesis (CM) and reductive cyclisation was developed in our laboratory. CM of chiral *N*-carboxybenzyl (Cbz)-protected homoallylamines with vinyl ketones gives δ-*N*-Cbz-amino ketones, which cyclise under hydrogenolytic conditions. 2,6-Disubstituted piperidines are obtained from this process with high *cis*-selectivity.[3] The combination of CM and reductive domino cyclisation was reported to yield 3,5-disubstituted indolizidines, e.g., the alkaloid (+)-monomorine 1.[4] In this paper, we present a new sequence of CM and stereocontrolled cyclisation to 2,6-*trans*-piperidines (Scheme 1).

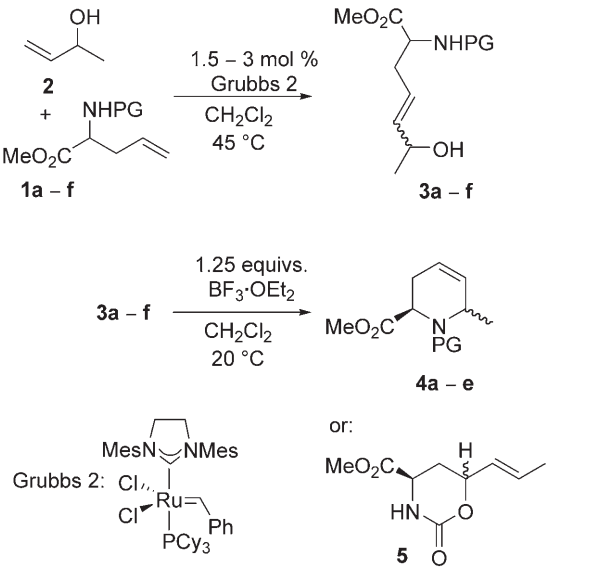
Cationic cyclisation provides an alternative cyclisation mode to reductive procedures. In this method, a precursor is needed which facilitates the formation of a carbocation. The piperidine ring is closed by subsequent reaction with a moiety containing a nucleophilic nitrogen. An example of this is the intramolecular Pd-catalysed amination of allyl alkyl carbonates, which gives 2-vinylpiperidines.[5] To the best of our knowledge, there is no example yet of a stereoselective cationic 6-*endo-trig* cyclisation to 2,6-disubstituted 1,2,5,6-tetrahydropyridines.

In order to develop this synthetic method, protected allylglycine esters were chosen as starting materials. The nature of the *N*-protecting group was expected to be important for the success of this strategy. Given the utility of the above-mentioned Pd-catalysed 6-*exo-trig* process, CM followed by analogous 6-*endo-trig* cyclisations of 1-methylallyl carbonates with various *N*-protected glycine esters were investigated initially. However, CM of 1-methylallyl carbonates was low yielding, requiring high catalyst loadings, and the following cyclisations gave low diastereoselectivities. This approach was therefore problematic. Conversely, the generation of allylic cations directly from crossed allylic alcohols was successful. Thus, CM of esters **1** with allylic alcohol **2** gave crossed products **3** in high

yields, using only 1.5–3 mol% of Grubbs 2 catalyst and two equivalents of the allylic alcohol cross-partner **2** (Table 1). With **3a–f** as substrates, suitable reaction conditions for their cationic cyclisation were investigated. The use of 1.25 equivalents of $BF_3{\cdot}OEt_2$ gave the smoothest reaction within 20 min at 20 °C in dichloromethane (0.05 M) independent of the substrate involved. Other Lewis acids, such as $MeAlCl_2$ and $SnCl_4$ gave the same major products, but mediated a less clean reaction. Polyphosphoric acid reacted only at elevated temperature to give complex product mixtures.

The $BF_3{\cdot}OEt_2$-mediated cationic 6-*endo-trig* cyclisation gave *trans*-2,6-disubstituted 1,2,5,6-tetrahydropyridines with 5:1 selectivity, when starting with the acid-stable carbamates **3a–c**. However, the tested sulfonamides **3d**,**e** gave a much lower stereoselectivity. Using the *N*-nosyl-protected allylic alcohol **3e** a moderate excess of the *cis*-product was obtained. Upon cyclisation, the *N*-Boc-derivative **3f** gave no tetrahydropyridine at all, but [1,3]oxazinan-2-one **5** instead.

Table 1. CM-cationic cyclisation with various protective groups.



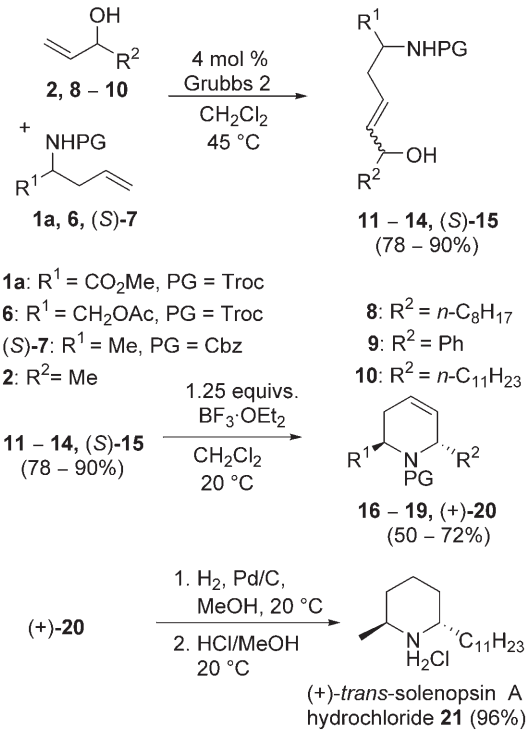
Starting ester	PG	CM (yield)	Cyclisation (yield)	*trans:cis* ratio
1a	Troc	**3a** (80%)[a]	**4a** (90%)[a]	5:1[c]
1b[6]	Cbz	**3b** (74%)[a]	**4b** (80%)[a]	5:1[d]
1c[7]	Fmoc	**3c** (72%)[a]	**4c** (81%)[a]	5:1[c]
1d[8]	Tos	**3d** (75%)[b]	**4d** (90%)[b]	1:1[c]
1e[9]	*p*-Nos	**3e** (78%)[b]	**4e** (90%)[a]	1:2.5[c]
1f[10]	Boc	**3f** (85%)[a]	**5** (71%)[a]	1.2:1

[a] Isolated yield.
[b] Yield determined by ^1H NMR.
[c] Assigned by conversion to *N*-benzyl analogue (Ref.[11]).
[d] Assigned by NOE analysis of derived *N*-methylpiperidinomethanol.

After suitable reaction conditions and protecting groups were identified, the scope of the reaction sequence of CM and cationic cyclisation was examined. By varying the substituents R^1 in the protected amine component and R^2 in the allylic alcohols we wished to investigate the relationship between substitution pattern and stereoselectivity (Table 2). Using 4 mol% of Grubbs 2 catalyst, the CM reactions proceeded as efficiently as seen with the model system. Moreover, the cationic cyclisations of the CM products to the piperidines **16–20** were much more *trans*-selective, bearing bulkier substituents than were attached to the model system, allthough in slightly lower yields.

In order to investigate if the cationic cyclisation proceeded free of racemisation, tetrahydropyridine (+)-**20** was synthesised starting with enantiopure homoallylamine derivative (*S*)-**7**.[4] Subsequent hydrogenation and hydrochloride formation gave the natural

Table 2. Variation of substitution pattern.



Substrates	CM (yield)[a]	Cyclisation (yield)[a]	*trans:cis* ratio
1a + 8	**11** (78%)	**16** (59%)	5:1[b]
1a + 9	**12** (88%)	**17** (66%)	*trans* only[b]
6 + 2	**13** (90%)	**18** (72%)	*trans* only[b]
6 + 8	**14** (82%)	**19** (50%)	*trans* only[b]
(*S*)-**7**[c] **+ 10**	**15** (75%)	**20** (58%)	*trans* only

[a] Isolated yields
[b] Assigned by LAH reduction to the corresponding *N*-methylpiperidinomethanol, on which NOE could be seen.
[c] Prepared according to Ref.[4]

product enantiomer (+)-*trans*-solenopsin A as the hydrochloride salt **21**. Spectroscopic, melting point and optical rotation measurements of **21** were in agreement with literature data.[12]

Apart from the protecting group dependence of chemo- and stereoselectivity of this new 6-*endo-trig* cyclisation, it is noteworthy that the reaction proceeds with apparent stereoconvergence. Whereas the CM products **3a–c** were formed as *E*/*Z*,*lk*/*ul*-mixtures of diastereoisomers in almost equal amounts (confirmed by NMR and GC/MS), their cyclisation gave one major diastereoisomer in high yield. The only explanation for this is that both *E*- and *Z*-CM products cyclised to the same diastereoisomer, probably after forming allyl cations of identic configuration. Minimised steric interactions between R^1 and the adjacent CH_2 group in the preferred ring closure transition state could explain the observed *trans*-selectivity, leading to nucleophilic attack on one face of the allyl cation. A *trans*-product would be formed, if R^2 was *exo*-oriented in the reactive allyl cation configuration.

After establishing the *trans*-selective synthetic sequence to 2,6-disubstituted piperidines, this method was utilised for the synthesis of the indolizidine natural product enantiomer (−)-**26** (Scheme 2). The TBS-protected γ-ketovinyl carbinol **23** was synthesised in 5 steps from γ-butyrolactone and subsequently reacted with enantiopure Cbz-protected homoallylamine (*S*)-**7** in a CM reaction. This required elevated temperature and the use of the more stable Grubbs–Hoveyda catalyst. A separate deprotection of the TBS group was unnecessary, because CM product **24** (formed as *E*,*Z*,*lk*,*ul*-mixture) cyclised smoothly to tetrahydropyridine **25** in excellent yield and with high *trans*-selectivity.

During the following reductive cyclisation, the endocyclic double bond in **25** was hydrogenated and indolizidine (−)-**26** was formed in 64% yield. Moreover, the *trans*-substituted 5-membered ring in the cyclised product was formed with 2.1:1 diastereoselectivity. The stereochemistry was assigned using spectroscopic data from a previous racemic synthesis of all four diastereoisomers, which had been conducted to ascertain which of the diastereoisomers is formed by *Solenopsis* fire ants.[13]

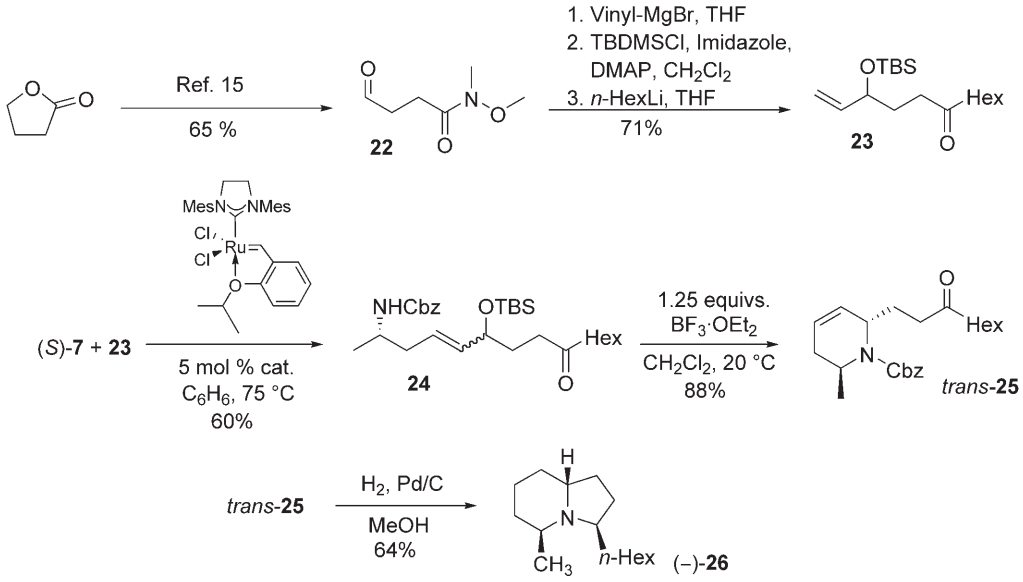
The observed stereoselectivity for the 5-membered ring closure is usually higher starting with *cis*-2,6-disubstituted piperidines, when the 5-membered ring would have *cis*-substitution.[14] However, given how difficult the diastereoselective synthesis of enantiopure indolizidine diastereomers of type **26** still is, the synthetic access presented here is simple and efficient.

In conclusion, 2,6-disubstituted 1,2,5,6-tetrahydropyridines can be obtained with high *trans*-selectivity by sequential CM and Lewis acid mediated stereoconvergent cyclisation. The method presented starts with carbamate-protected homoallylamines and vinyl carbinols, and tolerates ester and ketone functionalities. It is complementary to the *cis*-selective sequence of CM and reductive cyclisation. Furthermore, the endocyclic double bond of the cyclisation products may be useful for other synthetic transformations.

Experimental Section

Preparation of 6-Hydroxy-2-(2,2,2-trichloroethoxycarbonylamino)-hept-4-enyl Acetate (13)

In a 10-mL, round-bottom, 2-neck flask equipped with reflux condenser and magnetic stirrer, *N*-Troc-allylglycinol



Scheme 2. Total synthesis of indolizidine enantiomer (−)-**26.**

acetate **6** (128 mg, 0.4 mmol), buten-3-ol **2** (58 mg, 0.8 mmol) and Grubbs 2 catalyst (13.6 mg, 4 mol%) were dissolved in CH_2Cl_2 (4 mL) and refluxed for 18 h under an N_2 atmosphere. After removal of solvent and volatile components under reduced pressure, the residue was purified by flash chromatography (SiO_2, Hex:MtBE:MeOH, 5:1:0.1). Product **13** was obtained as mixture of *E/Z,lk/ul*-diastereoisomers as a light brown oil; yield: 130 mg (0.36 mmol, 90%); ^{1}H NMR (500 MHz; $CDCl_3$): $\delta = 1.18$–1.26 (br, 3H), 2.05 (s, 3H), 2.08–2.20 (br, 1H), 2.20–2.35 (m, 2H), 3.90–4.00 (m, 1H), 4.04–4.15 (m, 2H), 4.20–4.28 (br, 1H), 4.64–4.80 (br, 2H), 5.29–5.50 (br, 1H), 5.50–5.65 (m, 2H); ^{13}C NMR (125.8 MHz; $CDCl_3$): $\delta = 20.87$ (CH_3), 23.37 (CH_3), 34.41 (CH_2), 50.34 (CH), 50.36 (CH), 65.20 (CH_2), 68.25 (CH), 68.36 (CH), 74.54 (CH_2), 95.62 (C), 124.41 (CH), 124.47 (CH), 138.51 (CH), 138.58 (CH), 154.29 (C), 171.03 (C); IR: $\nu = 732$ (s), 818 (s), 971 (m), 1044 (s), 1100 (s), 1148 (m), 1227 (ss), 1367 (m), 1533 (s), 1717 (ss), 2968 (w), 3333 cm^{-1} (br); EI-MS (70 °C): $m/z = 364$ (M^+), 288 (20), 278 (35), 270 (40), 234 (100%), 218 (98), 86 (35); HR-MS: $m/z = 287.9960$ (calcd. for $C_9H_{13}O_3NCl_3$ [$M^+ - C_3H_5O_2$ α-cleavage]: 287.9961).

Conversion to 2,2,2-Trichloroethyl *trans*-2-Acetoxymethyl-6-methyl-3,6-dihydro-2*H*-pyridine-1-carboxylate (18)

In a 25-mL, round-bottom flask, cross-metathesis product **13** (105 mg, 0.301 mmol) and $BF_3{\cdot}OEt_2$ (54 mg, 0.38 mmol) were dissolved in CH_2Cl_2 (6 mL) and stirred for 30 min at 20 °C under air. The mixture was then quenched with saturated aqueous $NaHCO_3$ solution (12 mL), stirred vigorously for 15 min and extracted with MtBE (35 mL). The organic phase was washed with brine and dried with Na_2SO_4. After concentrating the mixture under reduced pressure, the residue was purified by flash chromatography (SiO_2, Hex:MtBE, 10:1). Product **18** was obtained as a colourless oil; yield: 72 mg (0.217 mmol, 72%, pure *trans*-diastereomer); ^{1}H NMR (500 MHz; $CDCl_3$): $\delta = 1.30$–1.41 (br, 3H), 2.02 (s, 3H), 2.20–2.30 (br, 1H), 2.36–2.45 (br, 1H), 4.05–4.14 (br, 2H), 4.18–4.45 (br, 2H), 4.69–4.85 (br, 2H), 5.74–5.80 (br, 1H), 5.81–5.88 (m, 1H); ^{13}C NMR (125.8 MHz; $CDCl_3$): $\delta = 20.93$ (CH_3), 22.47 (CH_3), 24.80 (CH_2), 48.77 (CH), 50.04 (CH), 50.57 (CH), 63.49 (CH_2), 63.95 (CH_2), 68.66 (CH), 75.19 (CH_2), 95.50 (C), 122.31 (CH), 131.14 (CH), 154.69 (C), 170.71 (C); IR: $\nu = 715$ (m), 1041 (m), 1108 (s), 1130 (m), 1227 (s), 1400 (s), 1712 (s), 1744 (s), 2956 cm^{-1} (w); EI-MS (25 °C): $m/z = 345$ (M^+), 272 (90), 270 (100%), 168 (15), 154 (25), 131 (20); HR-MS: $m/z = 343.0150$ (calcd. for $C_{12}H_{16}O_4NCl_3$ [M^+]: 343.0145); anal. calcd. for $C_{12}H_{16}O_4NCl_3$ (%): C 41.82, H 4.68, N 4.06; found: C 41.89, H 4.55, N 4.01.

Acknowledgements

The authors thank the Fonds der Chemischen Industrie and the Schering AG for supporting this work.

References

[1] a) E. A. Gerson, R. G. Kelsey, *Biochemical Systematics and Ecology*, **2004**, *32*, 63; b) D. O'Hagan, *Nat. Prod. Rep.* **2000**, *17*, 435; c) D. O'Hagan, *Nat. Prod. Rep.* **1997**, *14*, 637; d) M. Pan, T. J. Mabry, J. M. Beale, B. M. Mamiya, *Phytochemistry* **1997**, *45*, 517; e) S. Leclerq, J. C. Braekman, D. Daloze, J. M. Pasteels, R. K. Van der Meer, *Naturwissenschaften* **1996**, *83*, 222.

[2] Selected reviews: a) J. P. A. Harrity, O. Provoost, *Org. Biomol. Chem.* **2005**, *3*, 1349; b) M. G. P. Buffat, *Tetrahedron* **2004**, *60*, 1701; c) F.-X. Felpin, J. Lebreton, *Current Organic Synthesis* **2004**, *1*, 83–109; d) S. Laschat, T. Dickner, *Synthesis* **2000**, *13*, 1781–1813; e) A. Mitchison, A. Nadin, *J. Chem. Soc., Perkin Trans. 1* **1999**, 2553; f) A. Nadin, *J. Chem. Soc., Perkin Trans. 1* **1998**, 3493; g) M. Bols, *Acc. Chem. Res.* **1998**, *31*, 1; h) U. Kazmaier, *Recent Res. Dev. Org. Chem.* **1998**, *2*, 351; i) S. Leclercq, D. Daloze, J.-C. Braekman, *Org. Prep. Proced. Int.* **1996**, *28*, 501.

[3] a) P. Dewi-Wülfling, J. Gebauer, S. Blechert, *Synlett* **2006**, *3*, 487; b) J. Gebauer, S. Blechert, *Synlett* **2005**, *18*, 2826; c) J. Gebauer, P. Dewi, S. Blechert, *Tetrahedron Lett.* **2005**, *46*, 43; d) S. Randl, S. Blechert, *Tetrahedron Lett.* **2004**, *45*, 1167.

[4] a) S. Randl, S. Blechert, *J. Org. Chem.* **2003**, *68*, 8879.

[5] a) Y. Hirai, J. Watanabe, T. Nozaki, H. Yokoyama, S. Yamaguchi, *J. Org. Chem.* **1997**, *62*, 776; b) Y. Hirai, K. Shibuya, Y. Fukuda, H. Yokoyama, S. Yamaguchi, *Chem. Lett.* **1997**, 221; c) K. Takao, Y. Nigawara, E. Nishino, I. Takagi, K. Maeda, K. Tadano, S. Ogawa, *Tetrahedron* **1994**, *50*, 5681.

[6] Prepared according to: Q. B. Broxterman, B. Kaptein, J. Kamphuis, H. E. Schoemaker, *J. Org. Chem.* **1992**, *57*, 6286.

[7] Prepared according to: J. Pernerstorfer, M. Schuster, S. Blechert, *Chem. Commun.* **1997**, 1949.

[8] Prepared according to: N. J. Turner, G. M. Whitesides, *J. Am. Chem. Soc.* **1989**, *111*, 624.

[9] Prepared according to: C. J. Easton, S. C. Peters, *Tetrahedron Lett.* **1992**, *33*, 5581.

[10] Prepared according to: S. C. G. Biagini, S. E. Gibson, S. P. Keen, *J. Chem. Soc., Perkin Trans. 1* **1998**, *16*, 2485.

[11] NMR data for the *N*-benzyl analogue are given by: P. D. Bailey, G. R. Brown, F. Korber, A. Reed, R. D. Wilson, *Tetrahedron: Asymmetry* **1991**, *2*, 1263.

[12] a) T. J. Wilkinson, N. W. Stehle, P. Beak, *Org. Lett.* **2000**, *2*, 155; b) M. T. Reding, S. L. Buchwald, *J. Org. Chem.* **1998**, *63*, 6344.

[13] a) J. S. T. Gorman, T. H. Jones, T. F. Spande, R. R. Snelling, J. A. Torres *J. Chem. Ecol.* **1998**, *24*, 933; b) T. H. Jones, R. J. Highet, M. S. Blum, H. M. Fales, *J. Chem. Ecol.* **1984**, *10*, 1233.

[14] a) H. Takahata, H. Bandoh, T. Momose, *Tetrahedron* **1993**, *49*, 11205; b) P. E. Sonnet, D. A. Netzel, R. Mendoza, *J. Heterocyclic Chem.* **1979**, *16*, 1041; see also Refs.[4,][13a]

[15] K. Shishido, M. Shindo, Y. Fukuda, *Org. Lett.* **2003**, *5*, 749.

