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Transformation of an Optically Active Decahydro-6-isoquinolone Scaffold: Perfect Felkin–Anh Diastereoselectivity

Jens Christoffers,* Heiko Scharl, Wolfgang Frey, and Angelika Baro

Institut für Organische Chemie, Universität Stuttgart, Pfaffenwaldring 55, 70569 Stuttgart, Germany

jchr@po.uni-stuttgart.de

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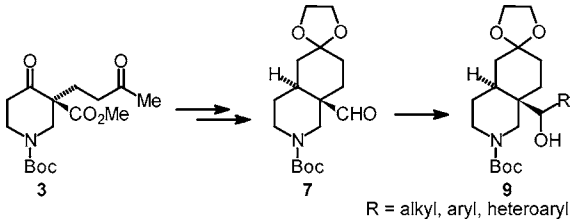
ABSTRACT



Diastereomerically and enantiomerically pure decahydro-6-isoquinolone derivative 7 (>99% de, 97% ee) was obtained from the Michael addition product 3. Interestingly, aldehyde 7 reacted with a number of different Grignard reagents to give the secondary alcohols 9 in good yields as single diastereomers. This result can be explained by taking the Felkin–Anh model into account.

Piperidines and 4-piperidones are very important structural motifs in medicinal chemistry.[1,2] The *trans*-decahydro-6-isoquinolone scaffold, as is present in compound **7** (Scheme 1), may be regarded as an extended 4-piperidone derivative with enhanced conformational rigidity due to the *trans*-fusion of two six-membered rings. This type of bicyclic system is rarely reported and, moreover, known only in racemic form so far.[3] Herein we report on the first optically active decahydro-6-isoquinolone derivative with a quaternary stereocenter.

The synthesis of aldehyde **7** is based on the copper-catalyzed Michael reaction of chiral enamine **1** with methyl vinyl ketone **2** as the key step.[4] The chiral auxiliary L-valine diethylamide thereby guarantees near-quantitative enantioselectivity in the construction of the quaternary stereocenter.[5] Piperidone carboxylate **3** with (*S*)-configuration at the stereogenic center[6] was cyclized by Robinson annulation

(1) Review: Weintraub, P. M.; Sabol, J. S.; Kane, J. M.; Borcherding, D. R. *Tetrahedron* **2003**, *59*, 2953−2989.

(2) (a) Egle, I.; MacLean, N.; Demchyshyn, L.; Edwards, L.; Slassi, A.; Tehim, A. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 3419−3421. (b) Dimmock, J. R.; Jha, A.; Zello, G. A.; Quail, J. W.; Oloo, E. O.; Nienaber, K. H.; Kowalczyk, E. S.; Allen, T. M.; Santos, C. L.; De Clercq, E.; Balzarini, J.; Manavathu, E. K.; Stables, J. P. *Eur. J. Med. Chem.* **2002**, *37*, 961−972. (c) Cicchi, S.; Revuelta, J.; Zanobini, A.; Betti, M.; Brandi, A. *Synlett* **2003**, 2305−2308. (d) Novelli, F.; Sparatore, F. *Farmaco* **2002**, *57*, 871−882. (e) Bleicher, K. H.; Wüthrich, Y.; De Boni, M.; Kolczewski, S.; Hoffmann, T.; Sleight, A. J. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 2519−2522.

(3) (a) MaGee, D. I.; Lee, M. L.; Decken, A. *J. Org. Chem.* **1999**, *64*, 2549−2554. (b) Simon, C.; Peyronel, J.-F.; Rodriguez, J. *Org. Lett.* **2001**, *3*, 2145−2148. (c) Simon, C.; Lieby-Muller, F.; Peyronel, J.-F.; Constantieux, T.; Rodriguez, J. *Synlett* **2003**, 2301−2304.

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(5) Reviews: (a) Denissova, I.; Barriault, L. *Tetrahedron* **2003**, *59*, 10105−10146. (b) Christoffers, J.; Baro, A. *Angew. Chem.* **2003**, *115*, 1726−1728; *Angew. Chem., Int. Ed.* **2003**, *42*, 1688−1690. (c) Christoffers, J.; Mann, A. *Angew. Chem.* **2001**, *113*, 4725−4732; *Angew. Chem., Int. Ed.* **2001**, *40*, 4591−4597. (d) Corey, E. J.; Guzman-Perez, A. *Angew. Chem.* **1998**, *110*, 402−415; *Angew. Chem., Int. Ed.* **1998**, *37*, 388−401. (e) Fuji, K. *Chem. Rev.* **1993**, *93*, 2037−2066. (f) Martin, S. F. *Tetrahedron* **1980**, *36*, 419−460.

(6) Christoffers, J.; Frey, W.; Scharl, H.; Baro, A. *Z. Naturforsch.* **2004**, *59b*, in press.

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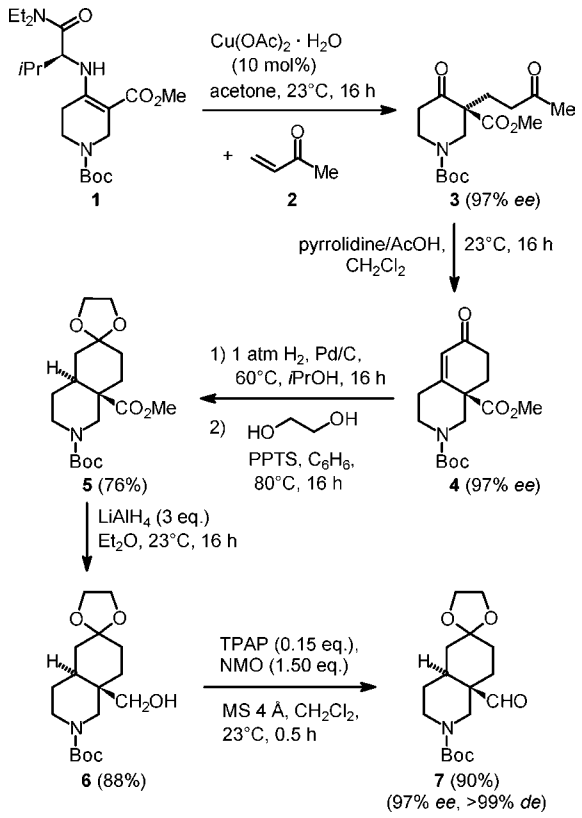
Scheme 1. Synthesis of the Decahydro-6-isoquinolone Scaffold 7



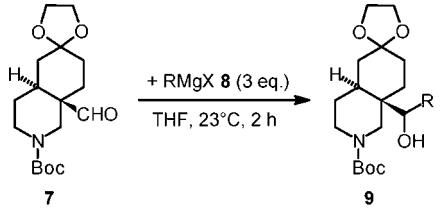
to give the octahydro-6-isoquinolone derivative **4**.[4c] Hydrogenation of the C−C double bond proceeded with high *trans*-selectivity (>95%) by applying Pd/C and 1 atm H_2 in 2-propanol as the solvent. With EtOH as the solvent, acetalization of the ketone moiety to afford the diethyl ketal was observed as a side reaction.

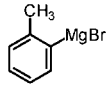
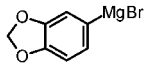
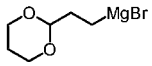
The minor *cis*-diastereomer was removed upon purification all along the subsequent operations. Protection of the ketone as 1,3-dioxolane derivative **5** was achieved with ethylene glycol using standard conditions. Reduction of the ester function with $LiAlH_4$ afforded isoquinolone derivative **6**. Finally, the aldehyde moiety was installed by selective reoxidation of the primary alcohol following the Ley procedure.[7] The (*R*)-configured compound **7** was obtained as a diastereomerically pure material (>99% de) with an optical purity of 97% ee. Analogously, racemic **7** was isolated in diastereomerically pure form.

During our project to utilize scaffold **7** as an optically active building block which allows for transformations at the ketone, the piperidine NH and the aldehyde functions, we first envisioned the Grignard reaction with the carbaldehyde group resulting in a number of secondary alcohols **9** as the addition products (Table 1).

(7) Ley, S. V.; Norman, J.; Griffith, W. P.; Marsden, S. P. *Synthesis* **1994**, 639−666.

Table 1. Grignard Addition Reaction of Scaffold 7



	RMgX	product	yield (%)
8a	MeMgBr	**9a**	83
8b	EtMgBr	**9b**	71
8c	PhMgBr	**9c**	70
8d	allylMgBr	**9d**	39
8e	*i*PrMgBr	**9e**	37[a]
8f		**9f**	72
8g	2-thienylMgBr	**9g**	73
8h		**9h**	62
8i		**9i**	76
8j		**9j**	84

[a] With 26% of alcohol **6** as byproduct.

A series of various Grignard reagents **8a**−**j** was converted with racemic aldehyde **7** at 23 °C.[8] Apart from allylmagnesium bromide (**8d**) and isopropylmagnesium bromide (**8e**), the yields of Grignard addition are generally in the range of 70−84%. More interestingly, in all cases only a single diastereomer of alcohol **9** is observed in the NMR spectra. We would like to point out that Grignard addition to aldehydes in a neopentyl environment has been reported so far without any stereoselectivity at all.[9]

We succeeded to obtain single crystals of alcohol **9b** which are suitable for X-ray single-crystal analysis (Figure 1).[10] As can be seen in Figure 1, the relative configuration of the racemic material **9b** is 4a*R**,8a*S**,9*R**.

According to the Felkin−Anh model[11] we assume the most reactive conformation with the bridging C4a−C8a bond as the largest group (R_L), which is perpendicular to the aldehyde moiety as shown in Scheme 2.

(8) For details, see the Supporting Information.

(9) (a) Vishnumurthy, K.; Cheung, E.; Scheffer, J. R.; Scott, C. *Org. Lett.* **2002**, *4*, 1071−1074. (b) Schwede, W.; Cleve, A.; Ottow, E.; Wiechert, R. *Tetrahedron Lett.* **1993**, *34*, 5257−5260. (c) Appendino, G.; Hoflack, J.; De Clercq, P. J.; Chiari, G.; Calleri, M. *Tetrahedron* **1988**, *44*, 4605−4618.

(10) Crystallographic data for the structure of **9b** have been deposited with the Cambridge Crystallographic Data Center (CCDC-229856). Copies of the data can be obtained free of charge on application to the Director, CCDC, 12 Union Road, Cambridge CB2 1EZ, U.K.; fax: (int.) +44-1223/336-033; E-mail: deposit@ccdc.cam.ac.uk.

(11) (a) Anh, N. T. *Top. Curr. Chem.* **1980**, *88*, 145−162. (b) Mulzer, J. *Nachr. Chem. Technol. Lab.* **1984**, *32*, 16−18. (c) Wu, Y.-D.; Houk, K. N. *J. Am. Chem. Soc.* **1987**, *109*, 908−910.

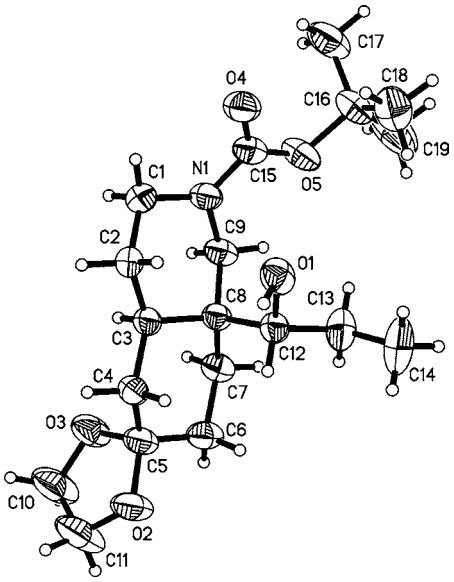
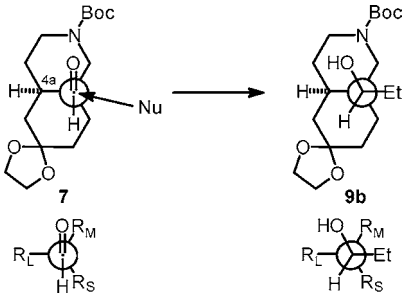


Figure 1. ORTEP view of Grignard addition product **9b**. The depicted enantiomer has a (4a*R*,8a*S*,9*R*)-configuration.

Due to the shielding effect of the Boc protecting group, the piperidine ring defines the medium-sized residue (R_M). From the crystal structure in Figure 1 it becomes apparent that the dioxolane moiety does not have a significant influence on the Grignard addition to the carbaldehyde function. Thus, as shown in Scheme 2, the nucleophilic Grignard reagent reacts preferentially along the Bürgi−Dunitz trajectory[12] from the *Re* face of the aldehyde. Consequently, a single diastereomer is formed, as is presented

Scheme 2. Diastereoselectivity of the Grignard Addition



by the relative configuration in Figure 1. As already mentioned, high diastereoselectivity for the addition of nucleophiles to carbaldehyde groups in a neopentyl environment has not been reported so far.

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Note Added after ASAP Posting. In the left column of the last page, the *Re* face was incorrectly named *Si* in the version posted ASAP March 2, 2004; the corrected version was posted March 3, 2004.

Supporting Information Available: Experimental procedure and characterization of compound **9b**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL049831Q

(12) See the thematic issue of *Chemical Reviews* devoted to diastereoaddition, for example: Mengel, A.; Reiser, O. *Chem. Rev.* **1999**, *99*, 1191−1223.