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

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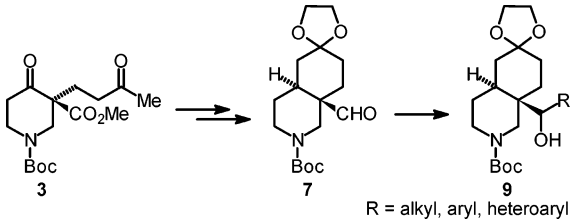
ABSTRACT



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.

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(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.

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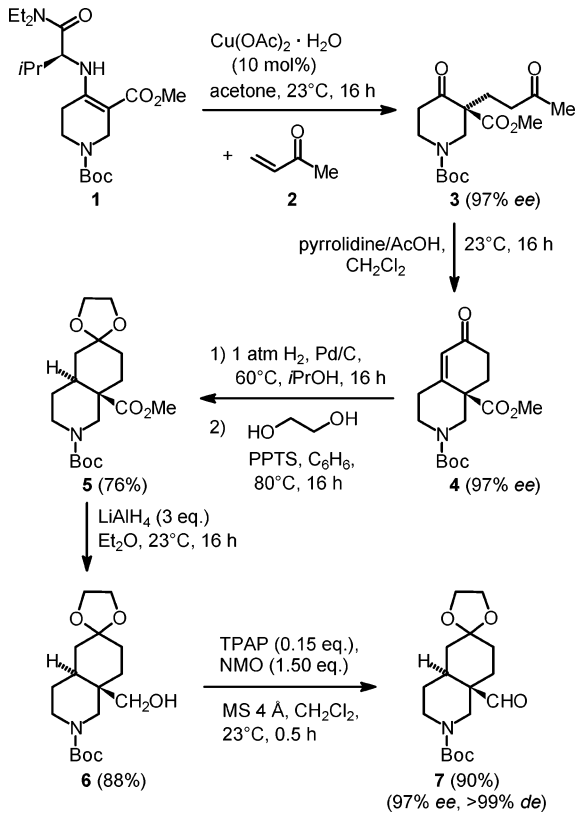
Scheme 1. Synthesis of the Decahydro-6-isoquinolone Scaffold 7



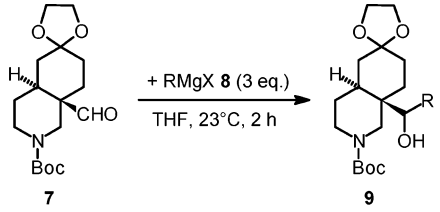
to give the octahydro-6-isoquinolone derivative **4**.[4c] Hydrogenation of the C−C double bond proceeded with high *trans*-selectivity (>95%) by applying Pd/C and 1 atm H_2 in 2-propanol as the solvent. With EtOH as the solvent, acetalization of the ketone moiety to afford the diethyl ketal was observed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

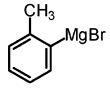
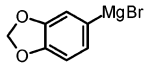
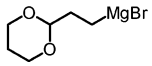
The minor *cis*-diastereomer was removed upon purification all along the subsequent operations. Protection of the ketone as 1,3-dioxolane derivative **5** was achieved with ethylene glycol using standard conditions. Reduction of the ester function with $LiAlH_4$ afforded isoquinolone derivative **6**. 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.

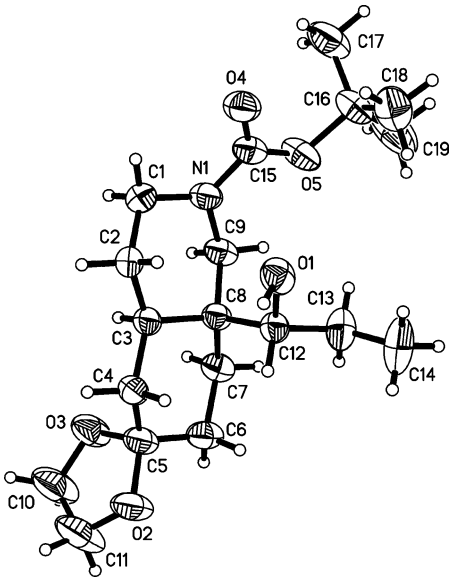
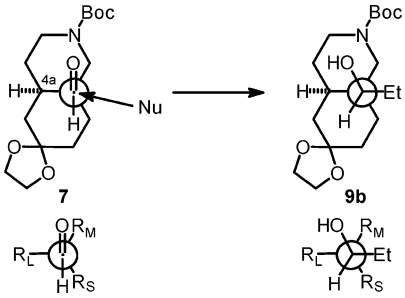


Figure 1. ORTEP view of Grignard addition product **9b**. The depicted enantiomer has a (4a*R*,8a*S*,9*R*)-configuration.

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 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.

Scheme 2. Diastereoselectivity of the Grignard Addition



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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.