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Diastereoselective Protonation of Lactam Enolates Derived from (*R*)-Phenylglycinol. A Novel Asymmetric Route to 4-Phenyl-1,2,3,4-tetrahydroisoquinolines

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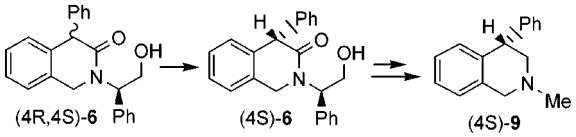
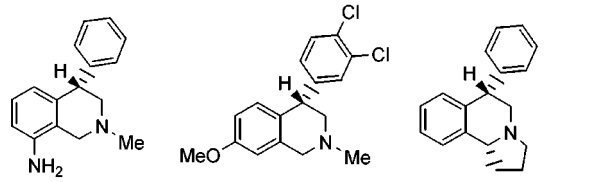
ABSTRACT



Highly diastereoselective protonation of chiral lactam enolates of 4-substituted-1,4-dihydroisoquinolin-3-ones is reported. Protonation and alkylation processes of these lactam enolates derived from phenylglycinol occur with opposite diastereofacial selectivity. This diastereoselective protonation has been applied to the asymmetric synthesis of (4*S*)-*N*-methyl-4-phenyl-1,2,3,4-tetrahydroisoquinoline 9 obtained in up to 97% ee.

While much effort has been devoted to the asymmetric synthesis of 1-substituted tetrahydroisoquinolines,[1] relatively little work has been done on the asymmetric synthesis of tetrahydroisoquinolines substituted at the 4-position.[2] This class of compounds is of considerable interest because of the important biological properties of 4-aryl tetrahydroisoquinolines that display central nervous system activity. This is illustrated by nomifensine,[3] dichlofensine,[4] or hexahydropyrrolo[2,1-*a*]isoquinolines,[5] which inhibit dopamine, noradrenaline, or serotonine (re)uptake mechanisms.



Although these compounds exhibit pronounced enantioselective activity, development of asymmetric approaches have been scarcely reported. In continuation of our investigation into the asymmetric synthesis of this class of compounds,[6] we herein wish to disclose a novel route to enantiomerically pure 4-aryl tetrahydroisoquinolines based

(1) For a review on asymmetric synthesis of 1-substituted tetrahydroisoquinolines, see: Rozwadowska, M. D. *Heterocycles* **1994**, *39*, 903.
(2) (a) Belvisi, L.; Gennari, C.; Poli, G.; Scolastico, C.; Salom, B. *Tetrahedron: Asymmetry* **1993**, *4*, 273.
(3) (a) Ulin, J.; Gee, A. D.; Malmborg, P.; Tedroff, J.; Långström, B. *Appl. Radiat. Isot.* **1989**, *40*, 171. (b) Kaczián, E. Z.; György, L.; Deák, G.; Seregi, A.; Dóda, M. *J. Med. Chem.* **1986**, *29*, 1189.
(4) (a) Omer, L. M. O. *Int. J. Clin. Pharmacol. Ther. Toxicol.* **1982**, *20*, 320. (b) Cherpillod, C.; Omer, L. M. O. *J. Int. Med. Res.* **1981**, *9*, 324.
(5) (a) Maryanoff, B. E.; Vaught, J. L.; Shank, R. P.; McComsey, D. F.; Costanzo, M. J.; Nortey, S. O. *J. Med. Chem.* **1990**, *33*, 2793. (b) Maryanoff, B. E.; McComsey, D. F.; Gardocki, J. F.; Shank, R. P.; Costanzo, M. J.; Nortey, S. O.; Schneider, C. R.; Setler, P. E. *J. Med. Chem.* **1987**, *30*, 1433.

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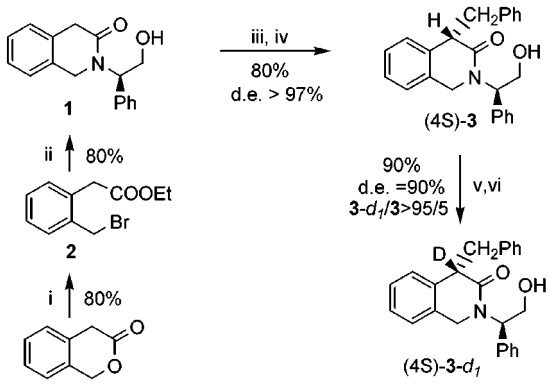
upon diastereoselective protonation of chiral lactam enolates derived from (*R*)-phenylglycinol.

We recently reported a diastereoselective alkylation of chiral 1,2,3,4-tetrahydroisoquinolin-3-ones derived from (*R*)-phenylglycinol.[7] The synthesis of lactam **1** starts from the readily available isochroman-3-one, which upon treatment with HBr in ethanol gave rise to **2**, which was subsequently condensed with (*R*)-phenylglycinol to provide the desired tetrahydroisoquinoline **1** in 62% overall yield. Excellent diastereoselectivities were observed during the alkylation of the corresponding lactam enolate under the conditions depicted in Scheme 1. The absolute configuration at C_4 of

Scheme 1[a]



[a] Reagents and conditions: i, HBr/EtOH, rt; ii, (*R*)-(−)-phenylglycinol/EtOH, rt → reflux; iii, LHMDS/THF/−78 °C; iv, $PhCH_2Br$/−78 °C; v, *n*-BuLi/−78 °C; vi, EtOD/−78 °C.

the major isomer was established as (*S*) by X-ray analysis. Attempts to apply that approach to the asymmetric synthesis of 4-aryl tetrahydroisoquinolines by electrophilic arylation of the lactam enolate with diphenyliodonium salts[8] were unsuccessful, leading in most cases to recovery of the starting material. However, it was observed that when pure (4*S*)-**3** was subjected to the deprotonation conditions described in Scheme 1 and subsequently treated with EtOD, a high degree of diastereoselectivity was retained, 90% de (Scheme 1).

Interestingly, the obtained major diastereoisomer (4*S*)-**3**-d_1 clearly indicates that protonation of the enolate intermediate occurred with diastereoselection opposite to that observed during alkylation processes. Only a few investigations have been reported with regard to the sense of the diastereoselection in both alkylation and protonation processes of chiral amide enolates.[9] In alkylation processes, a five-membered ring chelate between the lithium alkoxide and the lone pair of the pyramidalized nitrogen of the lactam enolate has been suggested to be responsible for the stereoselectivity. In that situation, the stereochemical outcome of the alkylation would arise from an attack of the electrophile *anti* to the nitrogen lone pair (Figure 1).[10] On this basis, opposite

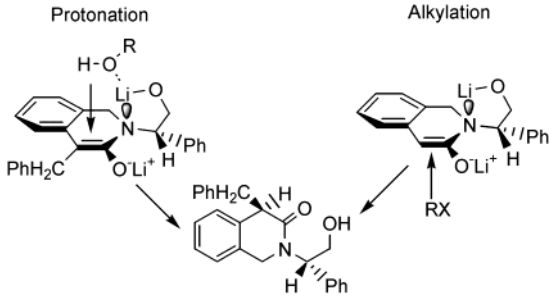


Figure 1. Proposed stereodirecting effect of the lithium alkoxide to account for the diastereofacial discrimination with alcohols (the absolute configuration of phenylglycinol lactam enolates in this figure is (*S*) for clarity).

diastereofacial selectivities observed in protonation reactions could rely on a complexation of the protonating agent with the lithium alkoxide to subsequently direct the protonation on the opposite face of the enolate (Figure 1).[11]

We then applied this diastereoselective protonation to the asymmetric synthesis of 4-phenyl-1,2,3,4-tetrahydroisoquinolines. The required 4-phenyl-1,2,3,4-tetrahydroisoquinolin-3-one (4*R*,4*S*)-**6** has been prepared in a manner similar to that described for the preparation of **1**. Treatment of the readily available 2-benzylphenylmethanol **4**[12] with *n*-BuLi in THF at room temperature for 24 h followed by quenching the reaction with methyl chloroformate afforded 4-phenyl isochroman-3-one **5**[13] in 54% yield. The isochroman-3-one **5** was then treated with HBr in ethanol and subsequently

(6) Prat, L.; Mojovic, L.; Levacher, V.; Dupas, G.; Quéguiner, G.; Bourguignon, J. *Tetrahydron: Asymmetry* **1998**, *9*, 2509.

(7) (a) Philippe, N.; Levacher, V.; Dupas, G.; Duflos, J.; Quéguiner, G.; Bourguignon, J. *Tetrahedron: Asymmetry* **1996**, *7*, 417. (b) This approach, based on Husson's methodology first developed in the piperazine series, has been applied afterwards in the tetrahydroisoquinoline series as well. Roussi, F.; Quirion, J. C.; Tomas, A.; Husson, H. P. *Tetrahedron* **1998**, *54*, 10363.

(8) For phenylation of enolates with diphenyliodonium salts, see: (a) Varvoglis, A. *Synthesis* **1984**, 709. (b) Gao, P.; Portoghese, P. S. *J. Org. Chem.* **1995**, *60*, 2276. (c) Chen, Z. C.; Jin, Y. Y.; Stang, P. J. *J. Org. Chem.* **1987**, *52*, 4115. (d) Ryan, J. H.; Stang, P. J. *Tetrahedron Lett.* **1997**, *38*, 5061.

(9) This comparison has been done by Davies and Seebach in the course of studies related to diastereoselective alkylation and protonation of lithium enolates derived from chiral imidazolidinones or diketopiperazines. In both examples, whether alkyl halides or various proton sources are used to quench the corresponding enolates, the same diastereofacial selectivity is observed, see: Bull, S. D.; Davies, S. G.; Epstein, S. W.; Ouzman, J. V. A. *Tetrahedron: Asymmetry* **1998**, *9*, 2795. Seebach, D.; Dziadulewicz, E.; Behrendt, L.; Cantoreggi, S.; Fitzi, R. *Liebigs Ann. Chem.* **1989**, 1215.

(10) Micouin, L.; Jullian, V.; Quirion, J. C.; Husson, H. P. *Tetrahedron: Asymmetry* **1996**, *7*, 2839.

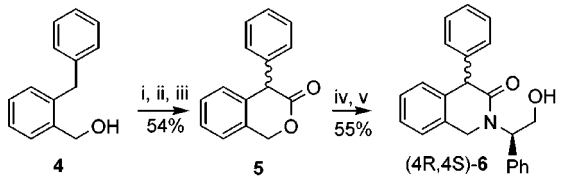
(11) (a) Our results, therefore, find analogy in the work of Askin. Indeed, alkylation of prolinol amide enolates with alkyl halides and epoxides takes place with opposite diastereoselectivity. This finding is interpreted by the author by an intermolecular chelation of the epoxide with the lithium alkoxide, see: Askin, D.; Volante, R. P.; Ryan, K. M. *Tetrahedron lett.* **1988**, *29*, 4245. (b) The same phenomenon has been observed with pseudoephedrine amide enolates. Myers, A. G.; McKinstry, L. *J. Org. Chem.* **1996**, *61*, 2428.

(12) For further preparation of 2-benzylphenylmethanol **4**, see: (a) Woo, Y. L.; Wonbo, S.; Kwang, D. C. *J. Chem. Soc., Perkin Trans. 1* **1992**, 881. (b) Hamon, M.; Gardent, J. *Bull. Soc. Chem. Fr.* **1966**, 556.

(13) For further preparation of 4-phenyl isochroman-3-one, see: Azzena, U.; Demartis, S.; Melloni, G. *J. Org. Chem.* **1996**, *61*, 4913. See ref 14b.

condensed with (*R*)-phenylglycinol to provide lactam **6** as an epimeric mixture at C-4 (50:50) in 55% yield (Scheme 2).

Scheme 2[a]

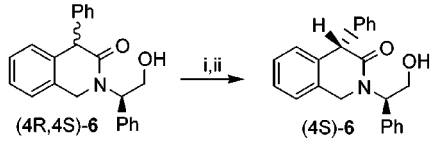


[a] Reagents and conditions: i, *n*-Buli/rt/24 h/THF; ii, ClCOOEt/−78 °C; iii, H_3O^+; iv, HBr/EtOH/rt/48 h; v, (*R*)-phenylglycinol/K_2CO_3/EtOH/rt → reflux.

Lactam (4*R*,4*S*)-**6** was then subjected to deprotonation by *n*-BuLi in THF at −78 °C followed by EtOD quench, affording lactam **6**-d_1 (**6**-d_1/**6**, 95:5) in up to 85% de (entry 1). With intend to optimize the diastereoselectivity, different proton sources were screened. As can be seen from Table 1, the stereoselectivity is highly dependent on the nature of protonating agent (entries 1−6). It seems that hindered protonating agents lead to lower diastereoselectivity (entries 4 and 6). The best result was attained with a saturated aqueous solution of ammonium chloride affording lactam **6** in up to 97% de (entry 5).

Reduction with diborane afforded tetrahydroisoquinoline **7** in 69% yield without epimerisation at C-4 (de > 97%). Debenzylation (65%) and reductive methylation (95%) led to the known *N*-methyl-4-phenyl-1,2,3,4-tetrahydroisoquinoline **9** in up to 97% ee (Scheme 3). As expected from the diastereoselection obtained with lactam **3**, the absolute configuration at C-4 was assigned as (*S*) by comparison of the sign of the optical rotation with the literature data.[14]

Table 1. Influence of the Proton Source on the Diastereoselectivity

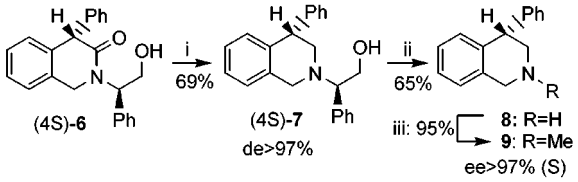


Reagents and conditions: i, *n*-BuLi (3eq)/THF/-78°C; ii, Proton sources/-78°C.

entry	proton source	yield (%)[a]	de (%)[c]
1	EtOH(D)[b]	85	85
2	MeOH	90	73
3	*t*-BuOH	90	76
4	Ph_3COH	86	33
5	H_2O/NH_4Cl	92	97
6	2,6-di-*tert*-butyl-4-methylphenol	80	49

[a] Yield analytically pure material. [b] Quenching the reaction with EtOD afforded **6**-d_1 with 95% deuterium incorporation at C-4. [c] Determined by HPLC analysis.

Scheme 3[a]



[a] Reagents and conditions: i, BH_3/THF/reflux; ii, H_2/$Pd(OH)_2$/EtOH; iii, $(CHO)_n$/$Pd(OH)_2$/H_2.

To conclude, the highly diastereoselective alkylation of lactam enolates derived from amino alcohols reported previously has been extended to diastereoselective protonation, broadening the synthetic usefulness of this class of amide enolates. This is well exemplified in this report by the asymmetric synthesis of 4-phenyl-1,2,3,4-tetrahydroisoquinolines, which are not easily accessible by direct asymmetric arylation.

Acknowledgment. We thank les régions de Haute et Basse Normandie for support of this work (Réseau Interrégional Normand de Chimie Organique Fine). We are grateful to Dr. Loic Toupet for providing X-ray analysis.

Supporting Information Available: Experimental procedures and full characterization for all compounds. X-ray ORTEP diagram of compound **3**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(14) Toome, V.; Blount, J. F.; Grethe, G.; Uskokovic, M. *Tetrahedron Lett.* **1970**, *11*, 49. Kihra, M.; Ikeuchi, M.; Adachi, S.; Nagao, Y.; Moritoki, H.; Yamaguchi, M.; Taira, Z. *Chem. Pharm. Bull.* **1995**, *43*, 1543.