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TETRAHEDRON: *ASYMMETRY*

A facile asymmetric synthesis of 1-substituted tetrahydroisoquinoline based on a chiral ligand-mediated addition of organolithium to imine

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Abstract

A two-step methodology involving an asymmetric addition of organolithium to an imine and subsequent Moffat oxidation as the key steps provided a new synthetic way to the optically and biologically active 1-substituted tetrahydroisoquinolines.

Tetrahydroisoquinolines are a class of biologically potent compounds. The existence of 1,2,3,4-tetrahydroisoquinoline (TIQ) and 1-methyl-TIQ (1MeTIQ, **1a**) in the human brain is now in no doubt.[1] The complete prevention of MPTP induced parkinsonism by pretreatment with **1a**[2] and the inhibition of monoamine oxidase[3] have renewed interest related to the pathogenesis of Parkinson's disease. 1-Phenyl-TIQ **1b**, originally developed as a general anesthetic agent, shows phencyclidine-like stereotyped behavior and ataxia.[4] Since the enantiomers were observed to vary in affinity,[4b] the synthesis of chiral 1-substituted TIQ is the current focus in medicinal organic chemistry.[5]

The diastereoselective Pictet–Spengler reaction is well established, but requires tedious methodology for the construction of the chiral TIQ.[6] The asymmetric alkylation of TIQ has also been developed.[7] The asymmetric reduction[8] and alkylation[9] of the dihydroisoquinoline derivatives are the most recently explored technology. Although the two-step process of construction of the chirality and subsequent cyclization to the target TIQ has been developed,[10] enantioselective construction of the secondary amine by the electrophilic alkylation of the imine and followed by cyclization to the chiral TIQ have not yet been explored. We describe herein that the chiral ligand-mediated asymmetric addition of organolithiums to the acyclic imine **3**[11,12] and subsequent cyclization of the secondary amine **5** under Moffat oxidation conditions provide the new route to the chiral 1-substituted TIQ **1** (Fig. 1).

The reaction of 2 equiv. of methyllithium with **3a**,**b**, prepared by the condensation of **2**[13] with anisidine or 2-methylanisidine, in the presence of 2.6 equiv. of the chiral ligand **6** in toluene at −95°C afforded **4a**,**b** (R=Me, Ar=PMP, MePMP) in 71 and 84% ee, respectively (Table 1, entries 1, 3).[14] The catalytic

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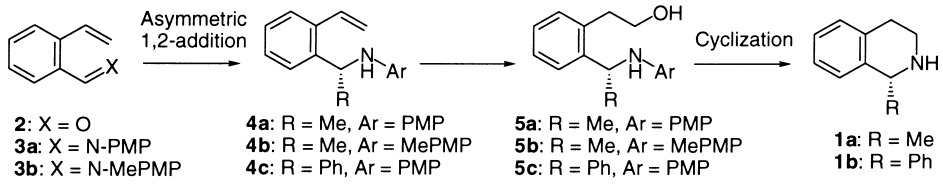

Figure 1. The synthesis of **1** by asymmetric addition and cyclization

asymmetric reaction was possible by using 0.3 equiv. of **6** at −42°C to afford **4b** in 62% ee (entries 5, 6).

The reaction of phenyllithium with **3a** under the control of **6** gave, however, **4c** in only 9% ee (entry 7). After examination of the ligands **7**–**9** (Fig. 2), the ligand **9**[15] was found to give **4c** in 50% ee (entry 10).[16] The enantioenrichment of **4c**-hydrochloride was possible by recrystallization from hexane–chloroform to give **4c** of 71% ee in 62% yield.

Table 1
The ligand-mediated asymmetric reaction of methyl- and phenyllithium with the imine **3**[a]

Entry	**4**	R	Ar	**6-9**	eq	temp (°C)	yield (%)	ee (%)	*R/S*
1	**4a**	Me	PMP	**6**	2.6	–95	76	71	*R*
2				**9**	2.6	–95	92	60	*R*
3	**4b**		MePMP	**6**	2.6	–95	99	84	*R*
4				**9**	2.6	–95	99	73	*R*
5				**6**	2.6	–42	93	78	*R*
6				**6**	0.3	–42	99	62	*R*
7	**4c**	Ph	PMP	**6**	2.6	–78	95	9	*R*
8				**7**	2.6	–78	87	36	*S*
9				**8**	2.6	–78	94	41	*R*
10				**9**	2.6	–78	93	50	*R*

a) The 2 equiv of organolithium was used in the toluene solvent.

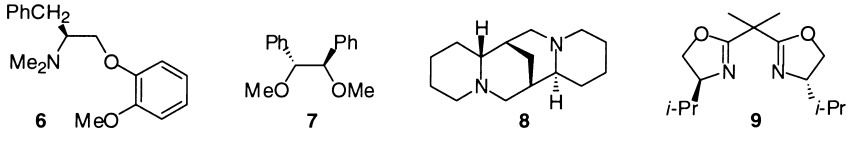

Figure 2. The chiral ligands **6**–**9**

Hydroboration with disiamylborane and oxidative work-up of **4a** of 71% ee afforded **5a** quantitatively. Treatment of **5a** with DMSO-DCC under Moffat oxidation conditions directly afforded **10a** in 71% yield. Removal of the PMP group of **10a** with ammonium cerium(IV) nitrate (CAN) completed the synthesis of *R*-**1a**[17] without racemization in 50% overall yield from **4a** (Fig. 3). The MePMP-amine **4b** of 84% ee was also successfully converted by the same method, to *R*-**1a** in 20% overall yield.

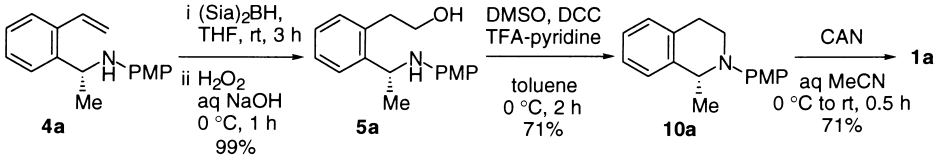

Figure 3. The asymmetric synthesis of **1a**

The same reaction sequence for **1a** was applicable to the synthesis of *R*-**1b**[18] of 52% ee in 57% overall yield from **4c** of 50% ee (Fig. 4).

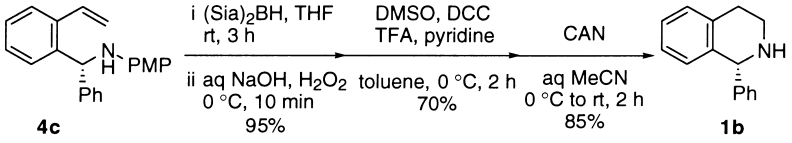

Figure 4. The asymmetric synthesis of **1b**

The presented two-step procedure for the asymmetric synthesis of 1-substituted TIQ is facile and will be applicable to other biologically potent TIQ. Further studies directed toward more efficient asymmetric alkylation of the imine are in progress in our laboratories.

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References

1. Kohno, M.; Ohta, S.; Hirobe, M. *Biochem. Biophys. Res. Commun*. **1986**, *140*, 448–454.
2. Yamakawa, T.; Ohta, S. *Biochem. Biophys. Res. Commun*. **1997**, *236*, 676–681.
3. Thull, U.; Kneubühler, S.; Gaillar, D. P.; Carrupt, P.-A.; Testa, B.; Altomare, C.; Carotti, A.; Jenner, P.; McNaught, K. St. P. *Biochem. Pharmacology* **1995**, *50*, 869–877.
4. (a) Gray, N. M.; Cheng, B. K.; Mick, S. J.; Lair, C. M.; Contreras, P. C. *J. Med. Chem*. **1989**, *32*, 1242–1248. (b) Minor, D. L.; Wyrick, S. D.; Charifson, P. S.; Watts, V. J.; Nichols, D. E.; Mailman, R. B. *J. Med. Chem*. **1988**, *31*, 1941–1946.
5. Rozwadowska, M. D. *Heterocycles* **1994**, *39*, 903–931.
6. For example, see: Tomioka, K.; Koga, K.; Yamada, S. *Chem. Pharm. Bull*. **1977**, *25*, 2689–2691. Enantioselective Pictet–Spengler reaction of β-carboline has been reported. Kawate, T.; Yamada, H.; Soe, T.; Nakagawa, M. *Tetrahedron: Asymmetry* **1996**, *7*, 1249–1252.
7. Meyers, A. I. *Tetrahedron* **1992**, *48*, 2589–2612.
8. (a) Morimoto, T.; Ohta, M.; Suzuki, N.; Achiwa, K. *Tetrahedron: Asymmetry* **1998**, *9*, 183–187. (b) Kitamura, M.; Hsiao, Y.; Tsukamoto, M.; Ohta, T.; Takaya, H.; Noyori, R. *J. Org. Chem*. **1994**, *59*, 297–310. (c) Murahashi, S.-I.; Watanabe, S.; Shiota, T. *J. Chem. Soc., Chem. Commun*. **1994**, 725–726. (d) Willoghby, C. A.; Buchwald, S. L. *J. Org. Chem*. **1993**, *58*, 7627–7629. (e) Yamada, K.; Takeda, M.; Iwakuma, T. *J. Chem. Soc., Perkin Trans. 1* **1983**, 265–270.
9. (a) Wünsch, B.; Nerdinger, S. *Chem. Lett*. **1998**, 799–800. (b) Ukaji, Y.; Shimizu, Y.; Kenmoku, Y.; Ahmed, A.; Inomata, K. *Chem. Lett*. **1997**, 59–60. (c) Warrener, R. N.; Liu, L.; Russell, R. A. *Chem. Commun*. **1997**, 2173–2174. (d) Nakamura, M.; Hirai, A., Nakamura, E. *J. Am. Chem. Soc*. **1996**, *118*, 8489–8490.
10. Ponzo, V. L.; Kaufman, T. S. *Tetrahedron Lett*. **1995**, *36*, 9105–9108.
11. Taniyama, D.; Kanai, M.; Iida, A.; Tomioka, K. *Chem. Pharm. Bull*. **1997**, *45*, 1705–1707.
12. (a) Enders, D.; Reinhold, U. *Tetrahedron: Asymmetry* **1997**, *8*, 1895–1946. (b) Denmark, S. E.; Nicaise, O. J.-C. *Chem. Commun*. **1996**, 999–1004.
13. Dale, W. J.; Starr, L.; Strobel, C. W. *J. Org. Chem*. **1961**, *26*, 2225–2227.
14. The new compounds described herein gave the satisfactory analytical and spectroscopic data. The ee was determined by the chiral stationary phase HPLC (Daicel Chiralcel OD-H, *i*-PrOH:hexane, 1:100).
15. Corey, E. J.; Imai, N.; Zhang, H.-U. *J. Am. Chem. Soc*. **1991**, *113*, 728–729.
16. The ee was determined by NMR of the 1-methoxyphenylacetamide derivative.
17. (a) Craig, J. C.; Lee, S.-Y. C.; Chan, R. P. K.; Wang, I. Y.-F. *J. Am. Chem. Soc*. **1977**, *99*, 7996–8002. (b) Leith, W. *Monatsch Chem*. **1929**, *53*, 956–962.
18. Ludwig, M.; Beer, H.; Lotter, H.; Wanner, K. Th. *Tetrahedron: Asymmetry* **1997**, *8*, 2693–2695.