



A facile and efficient asymmetric synthesis of (+)-salsolidine

Daisuke Taniyama, Masayoshi Hasegawa and Kiyoshi Tomioka*

Graduate School of Pharmaceutical Sciences, Kyoto University, Yoshida, Sakyo-ku, Kyoto 606-8501, Japan

Received 21 April 2000; accepted 19 May 2000

Abstract

A three-key step methodology involving a highly selective asymmetric addition of an organolithium reagent to an *N*-naphthalenylimine, cyclization and oxidative removal of the *N*-naphthalenyl group provided a facile and efficient synthetic way to (+)-salsolidine. © 2000 Elsevier Science Ltd. All rights reserved.

Biological activity, especially that related to the pathogenesis of Parkinson's disease, has recently renewed interest in tetrahydroisoquinolines (TIQs) and related natural isoquinoline alkaloids.^{1,2} Since the enantiomers were observed to vary in activity,³ the synthesis of chiral 1-substituted TIQ is the current focus in medicinal organic chemistry.⁴ We have previously reported an approach to asymmetric synthesis of chiral 1-methyl and 1-phenyl TIQs based on a chiral external ligand-mediated asymmetric 1,2-addition reaction of organolithium reagents with the corresponding *N*-*p*-methoxyphenyl (PMP) imines.⁵ Extension of the method to an alkaloid natural product, salsolidine **1**, incurred several crucial problems such as moderate enantioselectivity and poor efficiency in oxidative removal of the *N*-PMP group.⁶ We describe herein a facile asymmetric synthesis of (+)-salsolidine **1** by employing highly efficient asymmetric addition of an organolithium reagent to *N*-1-naphthalenylimine and a new procedure for oxidative removal of the *N*-aryl group.^{7,8}

At first, we examined asymmetric addition reaction of methyllithium with imines **2** bearing substituted phenyl and naphthalenyl groups as an *N*-substituent, Ar (Fig. 1). The reaction was conducted in the presence of a stoichiometric amount of **3** in toluene at -95°C for 0.5 h to give the corresponding amines **4** in reasonably high chemical yields (Table 1). The enantioselectivity was not very high for **2a,b** bearing substituted phenyl groups as Ar (entries 1 and 2). We were very pleased to find that **2d–f** bearing substituted 1-naphthalenyl groups were converted to the amines **4d–f** (R = Me) in quite high ees, 97–94% (entries 4–6). It is interesting to note that enantioselectivity rises from 73 to 97% in the reverse order of electronegativity of the 4-substituent on the naphthalene, Cl, H, NMe₂ and OMe. This indicates that loss of electrophilicity of the imine gives rise to higher enantioselectivity, probably due to formation of a tight, three-component

* Corresponding author. E-mail: tomioka@pharm.kyoto-u.ac.jp

complex between imine **2**, MeLi, and the chiral ligand **3** (entries 3–6). Enantioenrichment was possible by recrystallizing **4** to afford optically pure amines in high overall yield (entries 4 and 5). The imine **2f** bearing a 4-methoxynaphthalenyl group is also a suitable substrate for addition of butyl- and phenyllithiums to afford the corresponding amines **4f** (R = Bu, Ph) in 86 and 92% ees, respectively (entries 7–8).

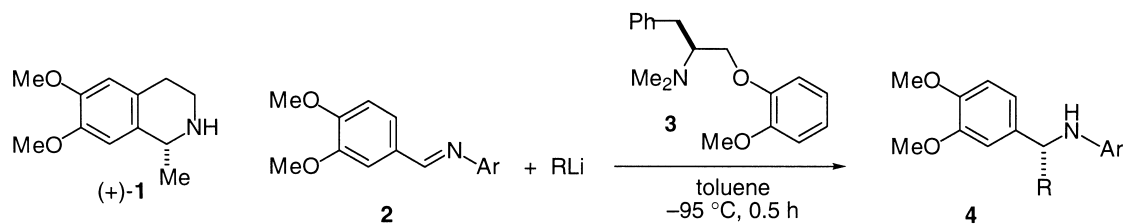


Figure 1. Asymmetric addition of organolithium reagents to **2** in the presence of **3**

Table 1
Asymmetric addition of RLi to **2** in the presence of **3** producing **4**

Entry	2	Ar	RLi	yield/% ^a	ee/% ^a	confign
1	a	<i>p</i> -MeOPh	Me	99	78	<i>R</i>
2	b	<i>p</i> -Me ₂ NPh	Me	99	88	<i>R</i> ^b)
3	c	4-ClNaph	Me	95	73	<i>R</i> ^b)
4	d	1-Naph	Me	99 (71)	94 (>99)	<i>R</i> ^b)
5	e	4-Me ₂ NNaph	Me	99 (74)	97 (>99)	<i>R</i>
6	f	4-MeONaph	Me	97	97	<i>R</i>
7	f	4-MeONaph	Bu ^c)	97	86	<i>R</i> ^b)
8	f	4-MeONaph	Ph	99	92	<i>R</i> ^b)

a) Numbers in parentheses are yield and ee for recrystallized compounds. Ee was determined by HPLC using a chiral stationary phase column (Daicel Chiralpak AD and OD-H) eluted with *i*-PrOH/hexane. b) Configurations were predicted by analogy. c) The reaction was conducted in a mixture of ether-toluene (2/1).

The next problem to be solved was oxidative removal of the *N*-aryl group. Treatment of **4f** (Ar = 4-MeONaph, R = Me) with ammonium cerium(IV) nitrate (CAN) in aqueous acetonitrile under standard conditions⁵ failed to provide the corresponding primary amine **5** in a detectable yield (Fig. 2). To avoid further Michael-type addition reaction of the primary amine **5** with naphtho-1,4-quinone **6** produced, sodium borohydride was added to the mixture to reduce **6** to naphthalene-1,4-diol **7**. To our delight, under these conditions the primary amine **5** was isolated in 47% yield. Substantial improvement in yield was realized by further treatment with acetic anhydride to afford a mixture of the primary amine **5** and its acetoamide **8** in 75% combined yield.

This new procedure for CAN oxidation is applicable to **4a** (Ar = PMP, R = Me) to afford a mixture of the amine **5** and amide **8** in 89% combined yield. Isolation of diacetate of benzene-1,4-diol **9** in 67% yield indicates that treatment with sodium borohydride reduces benzoquinone to

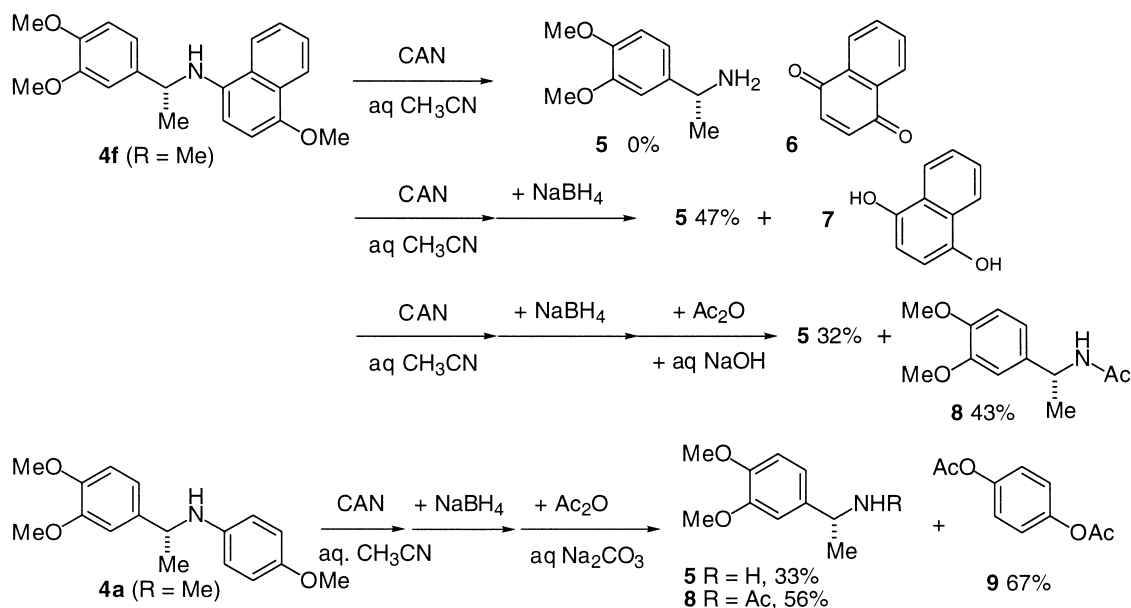


Figure 2. Successful treatment of **4** with CAN–NaBH₄–Ac₂O for oxidative removal of *N*-aryl group

benzene-1,4-diol, and further treatment with acetic anhydride acetylates diol to diacetate **9**, which process avoids back-oxidation to benzoquinone (Fig. 2).

Having established a new procedure for asymmetric alkylation and oxidative removal of the *N*-aryl group, we then focused on asymmetric synthesis of (+)-salsolidine **1**. Condensation of **10** and **11**⁹ gave an imine **12**, which was subjected asymmetric alkylation with MeLi in the presence of a stoichiometric amount of **3** to give an amine **13** in 93% ee and quantitative yield (Fig. 3).

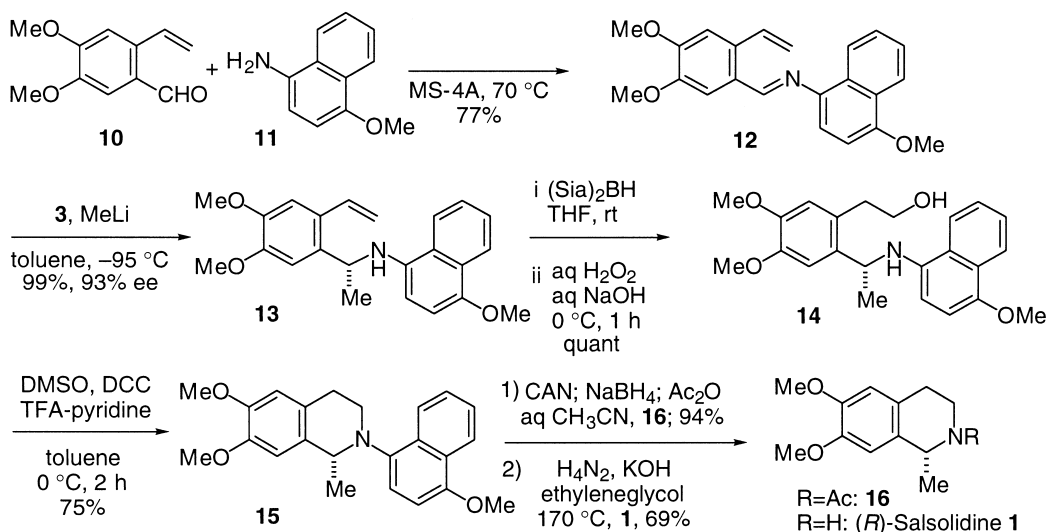


Figure 3. Asymmetric synthesis of (+)-salsolidine **1** from **10**

Hydroboration and subsequent oxidation gave an alcohol **14**, which was then subjected to cyclization to afford **15** in 75% overall yield from **13**. New CAN procedure gave **16** in 94% yield. Hydrolysis of **16** afforded the target (+)-**1** in 69% yield. Specific rotation of synthetic (+)-*R*-**1** ($[\alpha]_D^{25} +54.0$ (c 0.63, EtOH)) is indistinguishable from that of the reported (–)-*S*-**1** ($[\alpha]_D -59.5$ (c 4.39, EtOH)).¹⁰

The presented three-step procedure for the highly selective asymmetric synthesis of salsolidine is applicable to other biologically potent TIQ and related natural alkaloids. Further studies directed toward more efficient asymmetric alkylation of imines are in progress in our laboratories.

Acknowledgements

We acknowledge financial support from the Japan Society for Promotion of Science (RFTF-96P00302) and the Ministry of Education, Science, Sports and Culture, Japan.

References

1. (a) Nagatsu, T. *Neurosci. Res.* **1997**, *29*, 99–111. (b) Sano, T. *J. Synth. Org. Chem. Jpn.* **1999**, *57*, 136–140.
2. Tetrahydroisoquinoline (TIQ) and 1-methyl TIQ: (a) Yamakawa, T.; Ohta, S. *Biochem. Biophys. Res. Commun.* **1997**, *236*, 676–681. (b) Thull, U.; Kneubühler, S.; Gaillard, P.; Carrupt, P.-A.; Testa, B.; Altomare, C.; Carotti, A.; Jenner, P.; McNaught, K. St. P. *Biochem. Pharmacol.* **1995**, *50*, 869–877. (c) Kohno, M.; Ohta, S.; Hirobe, M. *Biochem. Biophys. Res. Commun.* **1986**, *140*, 448–454. 1-Phenyl TIQ: (d) Gray, N. M.; Cheng, B. K.; Mick, S. J.; Lair, C. M.; Contreras, P. C. *J. Med. Chem.* **1989**, *32*, 1242–1248. (e) Charifson, P. S.; Wyrick, S. D.; Hoffman, A. J.; Simmons, R. M. A.; Bowen, J. P.; McDougald, D. L.; Mailman, R. B. *J. Med. Chem.* **1988**, *31*, 1941–1946.
3. (a) Maruyama, W.; Naoi, M.; Kasamatsu, T.; Hashizume, Y.; Takahashi, T.; Kohda, K.; Dostert, P. *J. Neurochem.* **1997**, *69*, 322–329. (b) Tatton, W. G.; Ju, W. Y. L.; Holland, D. P.; Tai, C.; Kwan, M. *J. Neurochem.* **1994**, *63*, 1572–1575.
4. (a) Rozwadowska, M. D. *Heterocycles* **1994**, *39*, 903–931. (b) Shinohara, T.; Takeda, A.; Toda, J.; Sano, T. *Chem. Pharm. Bull.* **1998**, *46*, 430–433.
5. Taniyama, D.; Hasegawa, M.; Tomioka, K. *Tetrahedron: Asymmetry* **1999**, *10*, 221–223.
6. Gittins (née Jones), C. A.; North, M. *Tetrahedron: Asymmetry* **1997**, *8*, 3789–3799.
7. Enantioselective Pictet–Spengler reaction of β -carboline has been reported. (a) Kawate, T.; Yamada, H.; Soe, T.; Nakagawa, M. *Tetrahedron: Asymmetry* **1996**, *7*, 1249–1252. Asymmetric alkylation of an amine: (b) Meyers, A. I. *Tetrahedron* **1992**, *48*, 2589–2612. Asymmetric reduction: (c) Morimoto, T.; Suzuki, N.; Achiwa, K. *Tetrahedron: Asymmetry* **1998**, *9*, 183–187. (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. Asymmetric alkylation of an imine: (f) Wünsch, B.; Nerdinger, S. *Chem. Lett.* **1998**, 799–800. (g) Ukaji, Y.; Shimizu, Y.; Kenmoku, Y.; Ahmed, A.; Inomata, K. *Chem. Lett.* **1997**, 59–60. (h) Warrenner, R. N.; Liu, L.; Russell, R. A. *Chem. Commun.* **1997**, 2173–2174. (i) Nakamura, M.; Hirai, A.; Nakamura, E. *J. Am. Chem. Soc.* **1996**, *118*, 8489–8490.
8. For recent asymmetric synthesis of **1**, see: (a) Hajipour, A. R.; Hantehzadeh, M. *J. Org. Chem.* **1999**, *64*, 8475–8478. (b) Ukaji, Y.; Kenmoku, Y.; Inomata, K. *Tetrahedron: Asymmetry* **1996**, *7*, 53–56. (c) Munchhof, M. J.; Meyers, A. I. *J. Org. Chem.* **1995**, *60*, 7086–7087. (d) Ponzo, V. L.; Kaufman, T. S. *Tetrahedron Lett.* **1995**, *36*, 9105–9108. (e) Suzuki, H.; Aoyagi, S.; Kibayashi, C. *Tetrahedron Lett.* **1995**, *36*, 6709–6712. (f) Kitamura, M.; Hsiao, Y.; Ohta, M.; Tsukamoto, M.; Ohta, T.; Takaya, H.; Noyori, R. *J. Org. Chem.* **1994**, *59*, 297–310. (g) Murahashi, S.; Watanabe, S.; Shiota, T. *J. Chem. Soc., Chem. Commun.* **1994**, 725–726. (h) Willoughby, C. A.; Buchwald, S. L. *J. Am. Chem. Soc.* **1994**, *116*, 11703–11714. (i) Yamato, M.; Hashigaki, K.; Qais, N.; Ishikawa, S. *Tetrahedron* **1990**, *46*, 5909–5920.
9. Karuso, P.; Taylor, W. C. *Aust. J. Chem.* **1984**, *37*, 1271–1282.
10. Battersby, A. R.; Edwards, T. P. *J. Chem. Soc.* **1960**, 1214–1221.