SYNTHESIS OF HOMOCHIRAL β-SULFINYL NITRONES AND THEIR APPLICATION FOR ENANTIOSELECTIVE SYNTHESIS OF (+)-EUPHOCOCCININE†

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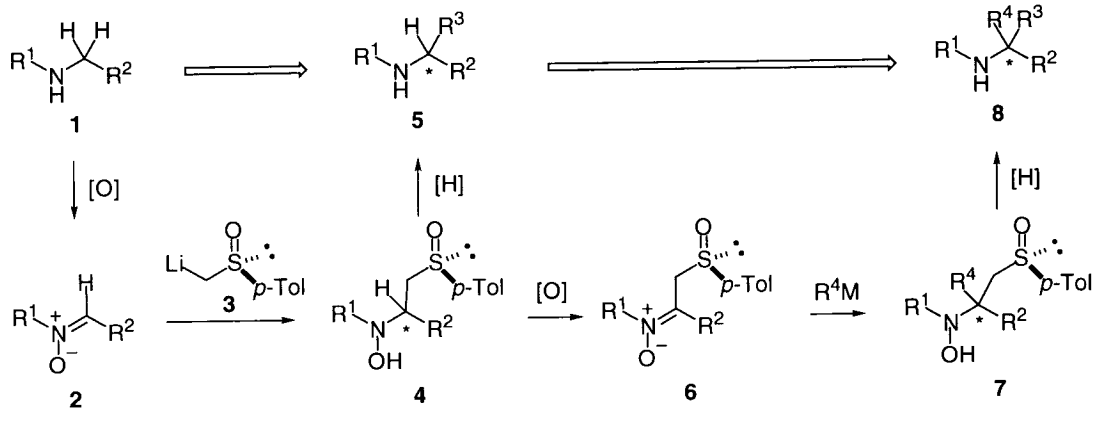
Abstract — Homochiral β-sulfinyl nitrones can be prepared from secondary amines in three steps. Enantioselective synthesis of defensive alkaloid (+)-euphococcinine (**9**) has been accomplished by means of diastereoselective allylation of homochiral β-sulfinyl nitrone (**13**) followed by intramolecular 1,3-dipolar cycloaddition reaction.

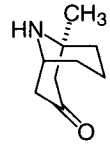
Optically active sulfoxides are versatile intermediates for asymmetric synthesis.[1] During the course of our study for introduction of substituents at the α-position of secondary amines *via* nitrones,[2] we have found that optically active α-substituted secondary amines (**5**) can be prepared from secondary amines (**1**) using optically active sulfoxides as chiral auxiliaries as shown in Scheme I (**1** → **2** → **4** → **5**).[3] Thus, diastereoselective addition of the homochiral α-sulfinyl carbanion (**3**) to nitrones (**2**), prepared readily by the catalytic oxidation of secondary amines (**1**) with H_2O_2,[2] gives optically active β-sulfinyl hydroxylamines (**4**), which are key intermediates for synthesis of optically active α-substituted secondary amines (**5**).

Scheme I

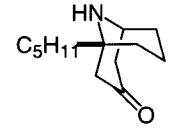


† This paper is dedicated to Prof. Teruaki Mukaiyama on the occasion in his 73rd birthday.

We wish to report here a convenient method for synthesis of homochiral β-sulfinyl nitrones (**6**) from secondary amines (**1**) and its application for synthesis of α,α-disubstituted hydroxylamines (**7**), which are precursors of α,α-disubstituted secondary amines (**8**) bearing quaternary carbon α to the nitrogen, by addition of nucleophiles to **6** as shown in Scheme I. Furthermore, we report the usefulness of these reactions for enantioselective synthesis of homotropane alkaloid, (+)-euphococcinine (**9**) and the precursor of (–)-adaline (**10**).

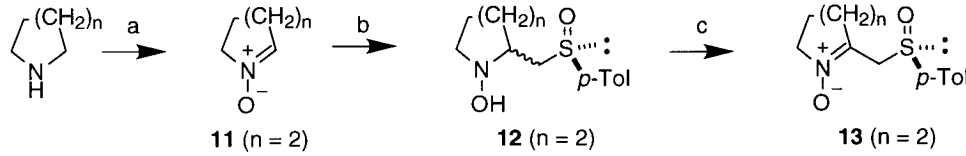


(+)-Euphococcinine (**9**)



(–)-Adaline (**10**)

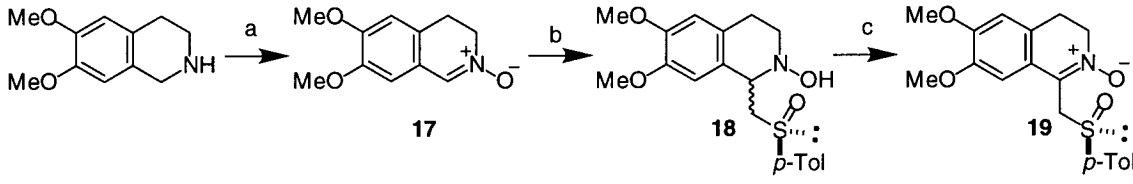
2,3,4,5-Tetrahydropyridine *N*-oxide (**11**) was prepared in 88% yield by the SeO_2-catalyzed oxidation of piperidine with H_2O_2.[2a] Addition of (*R*)-*p*-tolylsulfinylmethyllithium (**3**), prepared by the reaction of (*R*)-methyl *p*-tolyl sulfoxide[4] with LDA, to the nitrone (**11**) in THF at –78 °C gave a diastereomeric mixture of β-sulfinyl hydroxylamines (**12**) (67:33) in 52% yield. Selective oxidative transformation of **12** to the corresponding nitrone is very difficult, because competitive oxidation of the sulfinyl group would occur. We found that the biomimetic oxidation of **12** with a H_2O_2 solution in the presence of 3 mol % of 5-ethyllumiflavinium perchlorate ($FlEt^+ \bullet ClO_4^-$) as a catalyst in MeOH at 0 °C proceeded chemoselectively.[5] Short column chromatography gave (*SR*)-2-(*p*-tolylsulfinylmethyl)-2,3,4,5-tetrahydropyridine *N*-oxide (**13**) ($[\alpha]_D^{23}$ +89.4° (*c* 0.595, $CHCl_3$)) in 55% yield. Alternatively, the oxidative transformations were performed upon treatment of β-sulfinyl hydroxylamines with magnesium monoperoxyphthalate (MMPP)[6] in MeOH at –20 °C or Ni_2O_3 in $CHCl_3$ at room temperature. Homochiral β-sulfinyl nitrone (**16**) ($[\alpha]_D^{23}$ +55.8° (*c* 0.645, $CHCl_3$)) and isoquinoline derivative (**19**) ($[\alpha]_D^{23}$ +58.6° (*c* 1.90, $CHCl_3$)) were prepared from pyrrolidine and 1,2,3,4-tetrahydroisoquinoline in 44% and 50% overall yields, respectively, using similar procedure.



11 (n = 2) **12** (n = 2) **13** (n = 2)

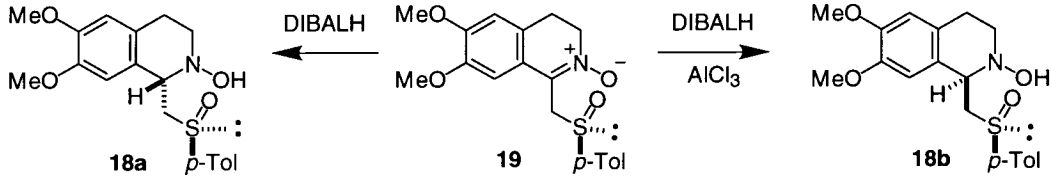
14 (n = 1) **15** (n = 1) **16** (n = 1)

(a) H_2O_2, SeO_2 (cat.), acetone, rt, (b) **3**, THF, -78°C, (c) H_2O_2, $FlEt^+ \bullet ClO_4^-$ (cat.), MeOH, 0 °C



(a) H_2O_2, Na_2WO_4 (cat.), MeOH, rt, (b) **3**, THF, -78°C, (c) Ni_2O_3, $CHCl_3$, rt

We investigated diastereoselective addition of nucleophiles to homochiral β-sulfinyl nitrones. First, we examined the diastereoselective addition of hydrides. The reaction of nitrone (**19**) with diisobutylaluminum hydride (DIBALH) at –78 °C gave a diastereomeric mixture of **18a** and **18b** with a 95:5 ratio in 59% yield. Noteworthy is that the reverse diastereoselectivity was observed, when the reaction of **19** with DIBALH was performed in the presence of $AlCl_3$, affording a mixture of **18a** and **18b** with a 10:90 ratio in 96% yield. The observed reverse diastereoselectivity can be rationalized by assuming the chelation of $AlCl_3$ to both the oxygen of the nitrone and the oxygen of the sulfinyl group. Each of the stereoisomers (**18a**) (mp 154.0–155.0 °C, $[\alpha]_D^{26}$ +106.6° (*c* 1.31, acetone)) and (**18b**) (mp 92.0 °C, $[\alpha]_D^{26}$ +56.5° (acetone)) was obtained as an enantiomerically pure crystalline after column chromatography and subsequent recrystallization.

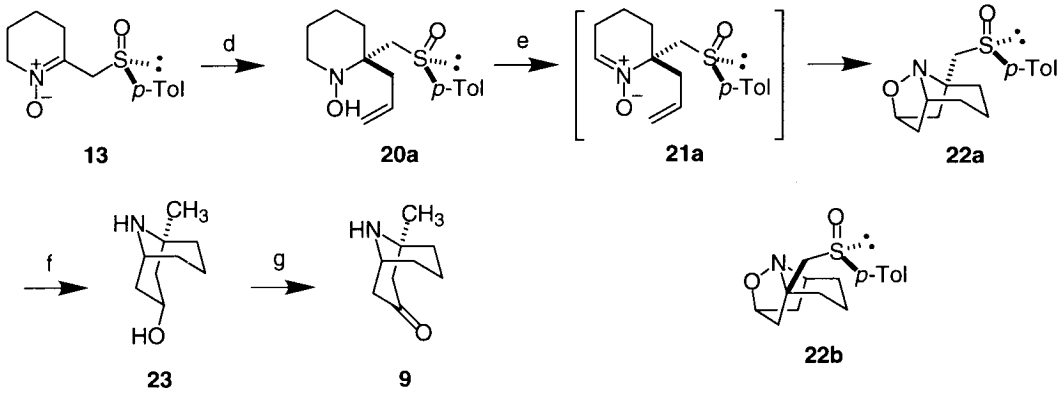


Next, we examined the diastereoselective addition of carbon nucleophiles to homochiral β-sulfinyl nitrones. Actually, this method is useful for synthesis of optically active α,α-disubstituted hydroxylamines and can be applied to the enantioselective synthesis of defensive alkaloid, (+)-euphococcinine (**9**), and the precursor of (–)-adaline (**10**). The compound (**9**) has been found as the part of the chemical defense system of both Australian mealybug ladybird (*Cryptolaemus montrouzieri*)[7] and Mexican bean beetle (*Epilachna varivestis*)[8] and are proven feeding deterrents to spiders and ants. The poor availability in nature (15 μg of **9** per specimen) and their interesting and potentially useful activity have prompted a number of approaches to the synthesis of these compounds.[9] Asymmetric syntheses of these alkaloids have been performed by two methods; i) diastereoselective double Michael addition of (+)-α-methylbenzylamine to 3-alkyl-2,7-

cyclooctadienones[10] and ii) diastereoselective formation of a quaternary carbon α to the piperidine nitrogen and subsequent intramolecular Mannich reaction.[11]

The reaction of β-sulfinyl nitrone (**13**) with allylmagnesium bromide in the presence of $AlCl_3$ afforded a mixture of (2*S*,S*R*)-2-allyl-*N*-hydroxy-2-(*p*-tolylsulfinylmethyl)piperidine (**20a**) and its 2*R*-isomer (**20b**) (83:17). Column chromatography of the mixture gave enantiomerically pure **20a** ($[\alpha]_D^{24}$ +74.8° (*c* 1.71, $CHCl_3$)) and **20b** ($[\alpha]_D^{24}$ +17.2° (*c* 0.79, $CHCl_3$)) in 54% and 6% yields, respectively. Treatment of the hydroxylamine (**20a**) with Ni_2O_3 and subsequent intramolecular 1,3-dipolar cycloaddition of the resulting nitrone (**21a**) gave (1*S*,3*R*,5*R*,S*R*)-1-(*p*-tolylsulfinylmethyl)-10-oxa-9-azatricyclo[3.3.1.$1^{3,9}$]decane (**22a**) ($[\alpha]_D^{22}$ +150.6° (*c* 0.840, $CHCl_3$)) in 54% isolated yield. Reductive cleavage of both the sulfinyl group and the N—O bond of **22a** upon treatment with Raney Ni (W-2) gave the bicyclic alcohol (**23**) in 95% yield. Oxidation of the alcohol (**23**) with pyridinium chlorochromate (PCC) gave (+)-euphococcinine (**9**) ($[\alpha]_D^{24}$ +7.43° (*c* 0.350, MeOH))[12] (lit.,[10] $[\alpha]_D$ +7.5° (*c* 2.0, MeOH)), of which spectral properties were identical with those reported.[10,11] Similarly, the oxidation of **20b** with Ni_2O_3 followed by 1,3-dipolar cycloaddition gave 1*R*,3*S*,5*S*,S*R*-tricyclic adduct (**22b**) ($[\alpha]_D^{21}$ +170.4° (*c* 0.365, $CHCl_3$)) in 51% yield, which is a potential precursor of (–)-adaline (**10**).

Scheme II



(d) $AlCl_3$, CH_2=$CHCH_2MgBr$, THF, –78 °C (54%), (e) Ni_2O_3, $CHCl_3$, rt (54%), (f) Raney Ni (W-2), H_2O, 30 °C (95%), (g) PCC, CH_2Cl_2, rt (30%)

In conclusion, we have established the method for synthesis of optically active β-sulfinyl nitrones and showed the usefulness of these nitrones for enantioselective synthesis of homotropane alkaloids. This strategy will be applied for synthesis of various nitrogen-containing heterocyclic compounds bearing asymmetric quaternary carbon α to the nitrogen.

ACKNOWLEDGMENT

This work was supported by "Research for the Future" Program, the Japan Society for the Promotion of Science, and a Grant-in-Aid for Scientific Research, the Ministry of Education, Science, Sports and Culture of Japan.

REFERENCES AND NOTES

1 For a recent review, see: M. C. Carreño, *Chem. Rev.*, 1995, **95**, 1717.

2 (a) S.-I. Murahashi and T. Shiota, *Tetrahedron Lett.*, 1987, **28**, 2383; (b) S.-I. Murahashi, H. Mitsui, T. Shiota, T. Tsuda, and S. Watanabe, *J. Org. Chem.*, 1990, **55**, 1736; (c) S.-I. Murahashi, T. Shiota, and Y. Imada, *Org. Syntheses*, 1992, **70**, 265; (d) S.-I. Murahashi, Y. Imada, and H. Ohtake, *J. Org. Chem.*, 1994, **59**, 6170.

3 S.-I. Murahashi, J. Sun, and T. Tsuda, *Tetrahedron Lett.*, 1993, **34**, 2645.

4 G. Soladie, *Synthesis*, 1981, 185.

5 S.-I. Murahashi, T. Oda, and Y. Masui, *J. Am. Chem. Soc.*, 1989, **111**, 5002.

6 H. Harry, *Aldrichimica Acta*, 1993, **26**, 35.

7 W. V. Brown and B. P. Moore, *Aust. J. Chem.*, 1982, **35**, 1255.

8 T. Eisner, M. Goetz, D. Aneshansley, G. Ferstandig-Arnold, and J. Meinwald, *Experientia*, 1986, **42**, 204.

9 Syntheses of racemic euphococcinine and adaline, for examples: (a) E. Gössinger and B. Witkop, *Monatsh. Chem.*, 1983, **111**, 803; (b) D. H. Gnecco-Medina, D. S. Grierson, and H.-P. Husson, *Tetrahedron Lett.*, 1983, **24**, 2099; (c) E. C. Davison, A. B. Holmes, and I. T. Forbes, *Tetrahedron Lett.*, 1995, **36**, 9047.

10 R. K. Hill and L. A. Renbaum, *Tetrahedron*, 1982, **38**, 1959.

11 C. Yue, J. Royer, and H.-P. Husson, *J. Org. Chem.*, 1992, **57**, 4211.

12 All compounds were characterized by ^{1}H (270 MHz) and ^{13}C NMR (68 MHz), IR, and HRMS. The ratios of diastereomers were determined by ^{1}H NMR spectroscopy of the crude and purified products. Data for (+)-euphococcinine (**9**) are as follows: ^{1}H NMR ($CDCl_3$) δ 1.18 (s, 3 H), 1.40–1.85 (m, 6 H), 2.23 (d, J = 16.0 Hz, 1 H), 2.39 (ddd, J = 16.5, 11.9, 1.8 Hz, 2 H), 2.56 (d, J = 16.0 Hz, 1 H), 3.60 (m, 1 H); ^{13}C NMR ($CDCl_3$) δ 17.9, 31.0, 31.4, 38.4, 46.0, 49.8, 52.5, 53.3, 210.4. HRMS (EI) *m/z* Found: 153.1154. Calcd for $C_9H_{15}NO$: 153.1154.

Received, 6th May, 1999