

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

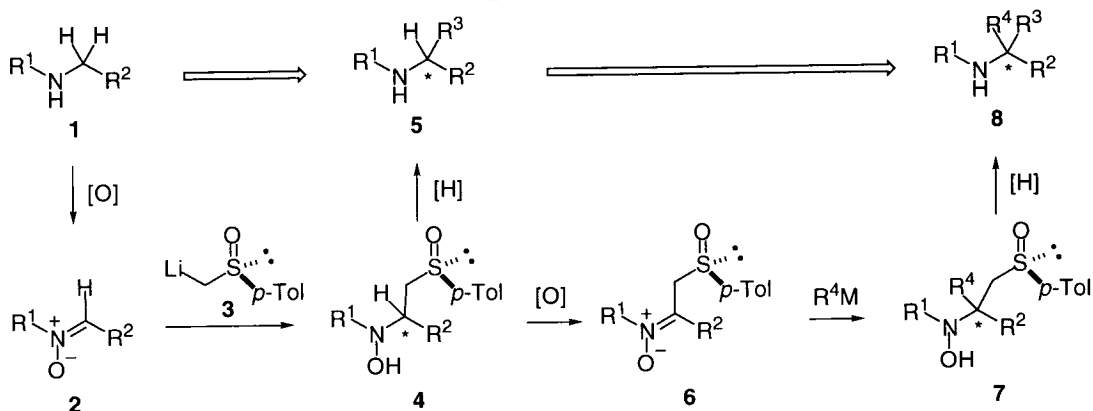
Shun-Ichi Murahashi,* Jun Sun, Hiroyuki Kurosawa, and Yasushi Imada

Department of Chemistry, Graduate School of Engineering Science,
Osaka University, Machikaneyama 1-3, Toyonaka, Osaka 560-8531, Japan

Abstract — Homochiral β -sulfinyl nitrones can be prepared from secondary amines in three steps. Enantioselective synthesis of defensive alkaloid (+)-euphoccocinine (**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** $\rightarrow$ **2** $\rightarrow$ **4** $\rightarrow$ **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

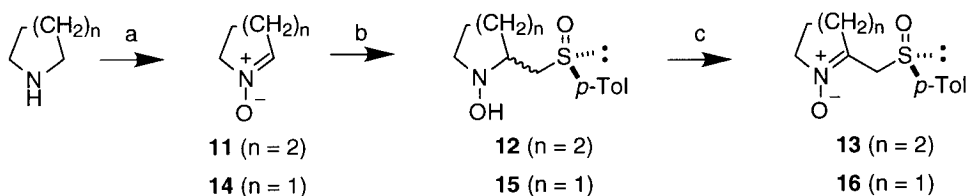


[†] This paper is dedicated to Prof. Teruaki Mukaiyama on the occasion in his 73rd birthday.

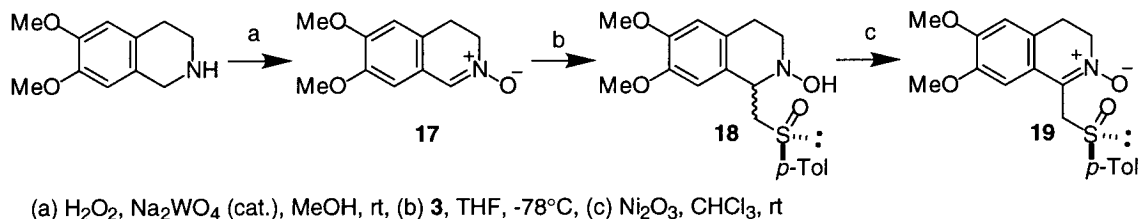
We wish to report here a convenient method for synthesis of homochiral β -sulfinyl nitrones (**6**) from secondary amines (**1**) and its application for synthesis of α,α -disubstituted hydroxylamines (**7**), which are precursors of α,α -disubstituted secondary amines (**8**) bearing quaternary carbon 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**).



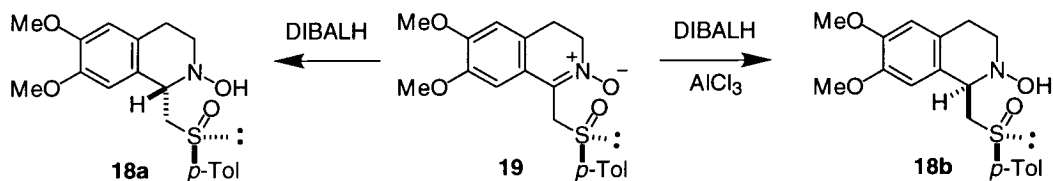
2,3,4,5-Tetrahydropyridine *N*-oxide (**11**) was prepared in 88% yield by the SeO_2 -catalyzed oxidation of piperidine with H_2O_2 .^{2a} Addition of (*R*)-*p*-tolylsulfinylmethyl lithium (**3**), prepared by the reaction of (*R*)-methyl *p*-tolyl sulfoxide⁴ with LDA, to the nitron (**11**) in THF at -78°C gave a diastereomeric mixture of β -sulfinyl hydroxylamines (**12**) (67:33) in 52% yield. Selective oxidative transformation of **12** to the corresponding nitron 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-ethylthiumflavinium perchlorate ($\text{FlEt}^+\cdot\text{ClO}_4^-$) 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**) ($[\alpha]_{\text{D}}^{23} +89.4^\circ$ (*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 nitron (**16**) ($[\alpha]_{\text{D}}^{23} +55.8^\circ$ (*c* 0.645, CHCl_3)) and isoquinoline derivative (**19**) ($[\alpha]_{\text{D}}^{23} +58.6^\circ$ (*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.



(a) H_2O_2 , SeO_2 (cat.), acetone, rt, (b) **3**, THF, -78°C , (c) H_2O_2 , $\text{FlEt}^+\cdot\text{ClO}_4^-$ (cat.), MeOH, 0°C



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 $154.0\text{--}155.0^\circ\text{C}$, $[\alpha]_{\text{D}}^{26} +106.6^\circ$ (c 1.31, acetone)) and (**18b**) (mp 92.0°C , $[\alpha]_{\text{D}}^{26} +56.5^\circ$ (acetone)) was obtained as an enantiomerically pure crystalline after column chromatography and subsequent recrystallization.

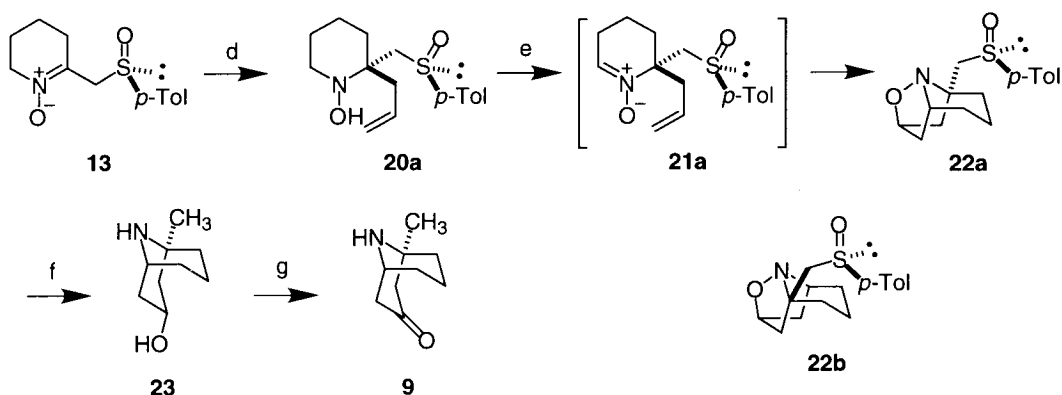


Next, we examined the diastereoselective addition of carbon nucleophiles to homochiral β -sulfinyl nitrones. Actually, this method is useful for synthesis of optically active α,α -disubstituted hydroxylamines and can be applied to the enantioselective synthesis of defensive alkaloid, (+)-euphococcinine (**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-

cyclooctadienones¹⁰ and ii) diastereoselective formation of a quaternary carbon α to the piperidine nitrogen and subsequent intramolecular Mannich reaction.¹¹

The reaction of β -sulfinyl nitron (13) with allylmagnesium bromide in the presence of AlCl_3 afforded a mixture of (2*S*,*SR*)-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 ($[\alpha]_{\text{D}}^{24} +74.8^\circ$ (*c* 1.71, CHCl_3)) and 20b ($[\alpha]_{\text{D}}^{24} +17.2^\circ$ (*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 nitron (21a) gave (1*S*,3*R*,5*R*,*SR*)-1-(*p*-tolylsulfinylmethyl)-10-oxa-9-azatricyclo[3.3.1.1^{3,9}]decane (22a) ($[\alpha]_{\text{D}}^{22} +150.6^\circ$ (*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) ($[\alpha]_{\text{D}}^{24} +7.43^\circ$ (*c* 0.350, MeOH))¹² (lit.,¹⁰ $[\alpha]_{\text{D}} +7.5^\circ$ (*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*,*SR*-tricyclic adduct (22b) ($[\alpha]_{\text{D}}^{21} +170.4^\circ$ (*c* 0.365, CHCl_3)) in 51% yield, which is a potential precursor of (–)-adaline (10).

Scheme II



(d) AlCl_3 , $\text{CH}_2=\text{CHCH}_2\text{MgBr}$, 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

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- 12 All compounds were characterized by ^1H (270 MHz) and ^{13}C NMR (68 MHz), IR, and HRMS. The ratios of diastereomers were determined by ^1H NMR spectroscopy of the crude and purified products. Data for (+)-euphococcinine (**9**) are as follows: ^1H 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 $\text{C}_9\text{H}_{15}\text{NO}$: 153.1154.

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