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 (+)-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 H2O2,2 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 \( \beta \)-sulfinyl nitrones (6) from secondary amines (1) and its application for synthesis of \( \alpha,\alpha \)-disubstituted hydroxylamines (7), which are precursors of \( \alpha,\alpha \)-disubstituted secondary amines (8) bearing quaternary carbon \( \alpha \) 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).

\[ \text{(+)-Euphococcinine (9)} \quad \text{(-)-Adaline (10)} \]

2,3,4,5-Tetrahydroxyridine N-oxide (11) was prepared in 88\% yield by the SeO\(_2\)-catalyzed oxidation of piperidine with H\(_2\)O\(_2\).\(^{2a}\) Addition of (R)-p-tolylsulfinylmethyl lithium (3), prepared by the reaction of (R)-methyl p-tolyl sulfoxide\(^4\) with LDA, to the nitro (11) in THF at \(-78^\circ\text{C}\) gave a diastereomeric mixture of \( \beta \)-sulfinyl hydroxylamines (12) (67:33) in 52\% yield. Selective oxidative transformation of 12 to the corresponding nitro is very difficult, because competitive oxidation of the sulfinyl group would occur.

We found that the biomimetic oxidation of 12 with a H\(_2\)O\(_2\) solution in the presence of 3 mol % of 5-ethylumiflavinium perchlorate (FeEt\(^{+}\)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-tetrahydroxyridine N-oxide (13) ([\(\alpha\)]\(_D\)\(^{23}+89.4^\circ\) (c 0.595, CHCl\(_3\))) in 55\% yield. Alternatively, the oxidative transformations were performed upon treatment of \( \beta \)-sulfinyl hydroxylamines with magnesium monoperxyphthalate (MMPP)\(^6\) in MeOH at -20\°C or Ni\(_2\)O\(_3\) in CHCl\(_3\) at room temperature. Homochiral \( \beta \)-sulfinyl nitro (16) ([\(\alpha\)]\(_D\)\(^{23}+55.8^\circ\) (c 0.645, CHCl\(_3\))) and isooquinoline derivative (19) ([\(\alpha\)]\(_D\)\(^{23}+58.6^\circ\) (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.

\begin{align*}
\text{(a) H}_2\text{O}_2, \text{SeO}_2 \text{ (cat.), acetone, rt, (b) 3, THF, -78^\circ\text{C}, (c) H}_2\text{O}_2, \text{FeEt}^{+}\text{ClO}_4^{-} \text{ (cat.), MeOH, 0^\circ \text{C}}
\end{align*}

\[ \text{(CH}_2)_n \text{N} \quad \text{a} \quad \text{(CH}_2)_n \text{N-O}^{-} \quad \text{b} \quad \text{(CH}_2)_n \text{N-} \quad \text{c} \quad \text{(CH}_2)_n \text{N-O}^{-} \quad \text{(a) H}_2\text{O}_2, \text{SeO}_2 \text{ (cat.), acetone, rt, (b) 3, THF, -78^\circ\text{C, (c) H}_2\text{O}_2, \text{FeEt}^{+}\text{ClO}_4^{-} \text{ (cat.), MeOH, 0^\circ \text{C}}}
\]
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 AlCl₃, 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 AlCl₃ 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, [α]D₂₆ +106.6° (c 1.31, acetone)) and (18b) (mp 92.0 °C, [α]D₂₆ +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\textsuperscript{10} and ii) diastereoselective formation of a quaternary carbon $\alpha$ to the piperidine nitrogen and subsequent intramolecular Mannich reaction.\textsuperscript{11}

The reaction of $\beta$-sulfinyl nitrene (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 ([$\alpha$]$_D^{24}$ +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$_2$O$_3$ and subsequent intramolecular 1,3-dipolar cycloaddition of the resulting nitrene (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$]$_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))\textsuperscript{12} (lit.,\textsuperscript{10} [$\alpha$]$_D$ +7.5° (c 2.0, MeOH)), of which spectral properties were identical with those reported.\textsuperscript{10,11} Similarly, the oxidation of 20b with Ni$_2$O$_3$ followed by 1,3-dipolar cycloaddition gave 1$R$,3$S$,5$S$,SR-tricyclic adduct (22b) ([$\alpha$]$_D^{21}$ +170.4° (c 0.365, CHCl$_3$)) in 51% yield, which is a potential precursor of (+)-adaline (10).

\begin{scheme}
\begin{center}
\includegraphics[width=\textwidth]{scheme.png}
\end{center}
\end{scheme}

(d) AlCl$_3$, CH$_2$=CHCH$_2$MgBr, THF, $-78$ °C (54%), (e) Ni$_2$O$_3$, CHCl$_3$, rt (54%), (f) Raney Ni (W-2), H$_2$O, 30 °C (95%), (g) PCC, CH$_2$Cl$_2$, rt (30%)

In conclusion, we have established the method for synthesis of optically active $\beta$-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 $\alpha$ 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.


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$_9$H$_{15}$NO: 153.1154.

Received, 6th May, 1999