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Stereoselective Synthesis of (-)-Hydroxyclemastine as a Versatile Intermediate for the H_1 Receptor Antagonist Clemastine

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Hydroxyclemastine was targeted as a versatile analogue of clemastine with H_1 receptor antagonist activity. Stereoselective synthesis of (-)-hydroxyclemastine was performed in which the key step was chelation-controlled diastereoselective 1,2-addition of Grignard reagent to α-alkoxyketone.

Key words: Hydroxyclemastine, Clemastine, H_1 receptor antagonist, Chelation, Stereoselective

INTRODUCTION

Clemastine (**1**) is an H_1-receptor antagonist with excellent antihistaminic activity (Nelson, 2002). Clemastine has two chiral centers, and is marketed as the *R,R*-enantiomer (Fig. 1). The chiral center at benzhydryl carbon has a significant influence on potency, while the chiral center in the pyrrolidine ring is of lesser importance (Ebnoether *et al.*, 1976).

This *R,R*-eutomer of clemastine was prepared by the conventional optical resolution method (Nikiforov *et al.*, 1990; Takaoka, 1978). However, asymmetric synthesis of clemastine has not been reported to date. Presumably, the main obstacle to the asymmetric synthesis of clemastine originates from the structural similarity of phenyl and 4-chlorophenyl groups on benzhydryl carbon in clemasine. On the other hand, hydroxyclemastine is not only a precursor of clemastine, but it also provides an important scaffold for the versatile analogues of clemastine with H_1 receptor antagonist activity. Thus, hydroxyclemastine is a better synthetic target than clemastine. In this paper, we report an asymmetric synthesis of (-)-hydroxyclemastine using the chelation-controlled diastereoselective 1,2-addition reaction.

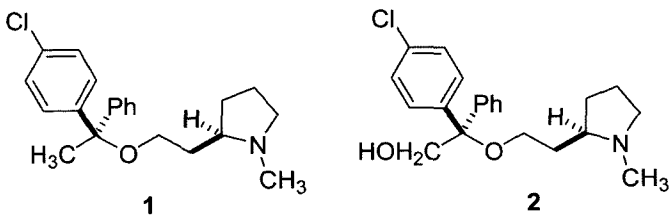

Fig. 1. Structure of clemastine (**1**) and hydroxyclemastine (**2**)

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MATERIALS AND METHODS

The melting points were obtained using MEL-TEMP® and were uncorrected. Optical rotations were measured on a JASCO DIP 1000 digital polarimeter. ^{1}H-NMR and ^{13}C-NMR spectra were obtained on a Varian 400 spectrometer and the chemical shifts are reported as values in parts per million (δ) relative to tetramethylsilane (TMS) as an internal standard. The infrared spectra (IR) were recorded on a JASCO FT/IR-430 spectrophotometer. Thin layer chromatography (TLC) was carried out on 0.25 mm E. Merck precoated silica gel glass plates ($60F_{254}$). Column chromatography was performed using the forced flow of indicated solvent on Merck Kieselgel 60 (230-400 mesh). Unless otherwise noted, the materials were obtained from commercially available sources and were used without further purification. Tetrahydrofuran (THF) was freshly distilled from sodium benzophenone ketyl under an argon atmosphere. Methylene chloride, benzene, dimethylformamide (DMF), triethylamine (TEA) and toluene were freshly distilled under a nitrogen atmosphere with calcium hydride.

(1*S*)-[(4*R*)-2,2-Dimethyl-[1,3]-dioxolan-4-yl]-(4-methoxyphenyl)methanol (4)

4-Methoxyphenylmagnesium bromide (1.0 M solution in

THF, 46 mL, 46.1 mmol) was added to a stirred solution of CuI (10.2 g, 53.8 mmol) in THF-DMS mixed solution (5:1, 230 mL) at -78°C under argon atmosphere. After being stirred for 20 min at -78°C, 2,3-*O*-isopropylidene-D-glyceraldehyde (**3**) (5 g, 38.4 mmol) was added dropwise to the reaction mixture. The reaction mixture was allowed to warm to room temperature over a 2 h period, and then quenched by the addition of a mixture of aq. NH_4Cl and conc. NH_4OH solution adjusted to pH 9. The resulting mixture was diluted with ethyl acetate. The organic layer was washed successively with the mixture of aq. NH_4Cl and conc. NH_4OH solution adjusted to pH 9, water and brine. After the conventional workup process, purification by column chromatography (17% ethyl acetate in hexane), followed by recrystallization (ethyl acetate/hexane) gave **4** as a white solid (6.6 g, 72 %): mp 41-42°C; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.29 (d, 2H, J = 4.8 Hz), 6.89 (d, 2H, J = 4.8 Hz), 4.51(dd, 1H, J = 8.0, 2.0 Hz), 4.22 (q , 1H, J = 6.4 Hz), 3.81 (s, 3H), 3.78 (dd, 1H, J = 8.4, 6.0 Hz), 3.68 (dd, 1H, J = 8.4, 6.0 Hz), 2.73 (s, 1H), 1.50 (s, 3H), 1.38 (s, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 159.58, 131.73, 128.13, 113.95, 110.07, 80.25, 75.59, 66.00, 55.21, 26.93, 25.37; IR (KBr pellet) cm^{-1} 3490, 3011, 2988, 1612, 1514, 1469, 1253; $[\alpha]_D^{22}$ -37.2 (*c* 0.4, $CHCl_3$); LRMS (EI, 70 eV) m/e (relative intensity) 238(M+, 3); Anal. calcd for $C_{13}H_{18}O_4$: C, 65.5; H, 7.6, found: C, 65.61; H, 7.44.

4-[(*S*)-(4-Methoxyphenyl)-(2-phenylallyloxy)methyl]-(4*R*)-2,2-dimethyl-[1,3]dioxolane (5)

The alcohol **4** (0.16 g, 0.68 mmol) was added to a suspension of NaH (0.06 g, 1.43 mmol, 60% disp.oil) in dimethoxyethane. After being stirred at 55°C for 30 min, 3-bromo-2-phenylpropene (0.20 mL, 1.02 mmol) was added at 0°C and the mixture was gradually heated to refluxing temperature for 5 h. The reaction mixture was quenched with aq. NH_4Cl (10 mL) and diluted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered, and then concentrated. The resulting crude residue was purified by column chromatograpy on silica gel (10% ethyl acetate in hexane) to give the title compound **5** as an oil (0.2 g, 83%): ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.34 (d, 2H, J = 8.7 Hz), 7.19 (m, 5H), 6.81 (d, 2H, J = 8.7 Hz), 5.42 (d, 1H, J = 1.3 Hz), 5.28 (d, 1H, J = 1.3 Hz), 4.33-4.24 (m, 3H), 4.10 (d, 1H, J = 10.3 Hz), 3.74 (s, 3H), 3.60-3.42 (m, 2H), 1.29 (s, 3H), 1.26 (s, 3H); IR (NaCl, neat) cm^{-1} 3073, 2985, 2935, 1655, 1611, 1585, 1511, 1456, 1371; LRMS (EI, 70 eV) m/e (relative intensity) 354 (M$^+$, 4); $[\alpha]_D^{25}$ -5.33 (*c* 0.12, $CHCl_3$).

2-[(4*R*)-(2,2-Dimethyl-[1,3]dioxolan-4-yl)-(*S*)-(4-methoxyphenyl)methoxy]-1-phenylethanone (6)

A gentle stream of dry ozone was passed through the stirred solution of the alkene **5** (0.18 g, 0.52 mmol) in MeOH-CH_2Cl_2 at -78°C. Ozonolysis was continued until the distinctive blue color of excess ozone was observed; ozonolysis was then terminated and the excess ozone was removed by purging with a stream of oxygen for 5-10 min. Dimethyl sulfide (0.5 mL) was then added. The resulting mixture was allowed to warm to room temperature over 2 h, and then it was concentrated. The residual solid was purified by silica gel chromatography (hexane/AcOEt = 5:1) to yield 0.17 g (89%) of the title compound **6** as a solid: mp 59-60°C (recrystallization from the mixture of *n*-hexane and EtOAc); ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.80 (d, 2H, J = 8.0 Hz), 7.78 (d, 2H, J = 8.0 Hz), 7.34 (t, 2H, J = 7.6 Hz), 7.19-7.17 (m, 1H), 6.47 (t, 1H, J = 7.6 Hz), 4.63 (d, 1H, J = 16.4 Hz), 4.57 (d, 1H, J = 16.4 Hz), 4.43-4.36 (m, 2H), 3.73 (s, 3H), 3.60 (dd, 1H, J = 8.4, 6.4 Hz), 3.51 (dd, 1H, J = 8.4, 6.4 Hz), 1.35 (s, 3H), 1.30 (s, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 196.11, 159.79, 134.92, 133.51, 128.94, 128.69, 128.38, 127.78, 113.93, 109.98, 83.29, 78.84, 770.99, 65.91, 55.07, 26.45, 25.45; IR (KBr pellet) cm^{-1} 2980, 2927, 1698, 1610, 1584, 1513, 1450, 1240; $[\alpha]_D^{23}$ -86.6 (*c* 0.51, $CHCl_3$); HRMS (FAB) calcd. for $C_{21}H_{24}O_5Na$ (M+Na)$^+$ 379.1521, found 379.1515.

(1*R*)-1-(4-Chlorophenyl)-2-{(1*S*)-[(4*R*)-(2,2-dimethyl-[1,3]-dioxolan-4-yl)]-(4-methoxyphenyl)methoxy}-1-phenylethanol (7)

Diphenylzinc (73.9 mg, 0.337 mmol) was added to a solution of ketone **6** (30 mg, 0.084 mmol) in CH_2Cl_2 (5 mL) at room temperature. The mixture was sonicated for 5 min in an ultrasonic water bath, and then stirred at room temperature for additional 30 min. To this mixture was added 1.0 M solution of 4-chlorophenylmagnesium bromide in diethyl ether (252 μL, 0.252 mmol) at -78°C, and the whole was stirred at -78°C for 2 h and allowed to warm to room temperature. The reaction mixture was quenched with aqueous $NaHCO_3$ (1 mL) and diluted with methylene chloride (30 mL). The organic layer was stirred with aqueous NH_4Cl (10 mL) for 10 min. The layers were separated, and the aqueous layer was extracted twice with methylene chloride (15 mL). The combined organic layer were washed with brine, dried over anhydrous Na_2SO_4, filtered, and then concentrated *in vacuo*. The resulting crude residue was purified by column chromatography on silica gel (a 1:6 mixture of ethyl acetate and hexane) to give the title compound **7** as pale yellow oil (34.1 mg, 87%): ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.27-7.25 (m, 4H), 7.20-7.17 (m, 4H), 7.14-7.12 (m, 1H), 7.08 (d, 2H, J = 8.8 Hz), 6.80 (d, 2H, J = 8.8 Hz), 4.31 (bs, 1H), 4.20-4.13 (m, 2H), 4.03 (d, 1H, J = 10.2 Hz), 3.74 (s, 3H), 3.60 (d, 1H, J = 10.2 Hz), 3.56 (dd, 1H, J = 8.8, 6.4 Hz), 3.44 (dd, 1H, J = 8.8, 6.4 Hz), 1.36 (s, 3H), 1.26 (s, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 160.15, 144.31, 143.48, 132.92, 129.91, 128.44, 128.66, 128.35, 128.29, 127.48, 126.40, 114.33, 110.38, 85.82,

79.39, 77.86, 76.11, 66.23, 55.47, 26.97, 25.75; IR (NaCl, neat) cm^{-1} 3446, 3032, 2986, 1512, 1490, 1448, 1243.; $[\alpha]_D^{23}$ +13.9 (*c* 0.93, $CHCl_3$, 90% de).

(2*R*)-2-{2-[(1*R*)-1-(4-Chlorophenyl)-2-{(1*S*)-[(4*R*)-(2,2-dimethyl-[1,3]-dioxolan-4-yl)]-(4-methoxyphenyl) methoxy}-1-phenylethoxy]ethyl}-1-methylpyrrolidine (8)

A solution of alcohol **7** (352.2 mg, 0.751 mmol, 82% de) in xylene (2 mL) was added to a suspenson of sodium hydride (60% dispersion in mineral oil, 90.1 mg, 5.8 mmol) in xylene (20 mL) at room temperature, followed by stirring for 10 min. Then a solution of (*R*)-2-(2-chloroethyl)-1-methylpyrrolidine (140 mg, 0.948 mmol) in xylene (3 mL) was added and the mixture was refluxed at 140°C for 4 h. The reaction mixture was quenched with water (10 mL) and diluted with ethyl acetate (50 mL). The layers were separated, and the aqueous layer was extracted twice with ethyl acetate (10 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered, and then concentrated *in vacuo*. The resulting crude residue was purified by column chromatograpy on silica gel (a 1:1 mixture of ethyl acetate and methanol) to give the title compound **8** as a pale yellow oil (339 mg, 78%): ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.19-7.14 (m, 9H), 6.85 (dd, 2H, *J* = 8.0, 8.0 Hz), 6.69 (dd, 2H, *J* = 8.8, 3.2 Hz), 4.12-4.06 (m, 2H), 3.95 (d, 1H, *J* = 10.0 Hz), 3.82(dd, 1H, *J* = 10.0, 4.0 Hz), 3.72 (s, 3H), 3.55-3.49 (m, 1H), 3.44-3.24 (m, 4H), 3.11-3.09 (m, 1H), 2.37 (s, 3H), 2.15 (quint, 1H, *J*=8.8 Hz), 2.03-1.36 (m, 6H), 1.23 (s, 3H), 1.22 (s, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 159.38, 143.03, 142.54, 132.49, 129.41, 1129.08, 128.69, 127.78, 127.74, 127.62, 127.59, 127.44, 127.36, 127.16, 113.54, 109.54, 83.47, 81.62, 78.62, 72.78, 65.58, 63.85, 61.47, 56.08, 40.30, 34.34, 30.84, 26.48, 25.56, 21.78; IR (NaCl, neat) cm^{-1} 3059, 2935, 1371, 1249, 1090; $[\alpha]_D^{26}$ -46.2 (*c* 0.61, $CHCl_3$).

(*R*)-1-(4-Chlorophenyl)-1-phenylethane-1,2-diol (9)

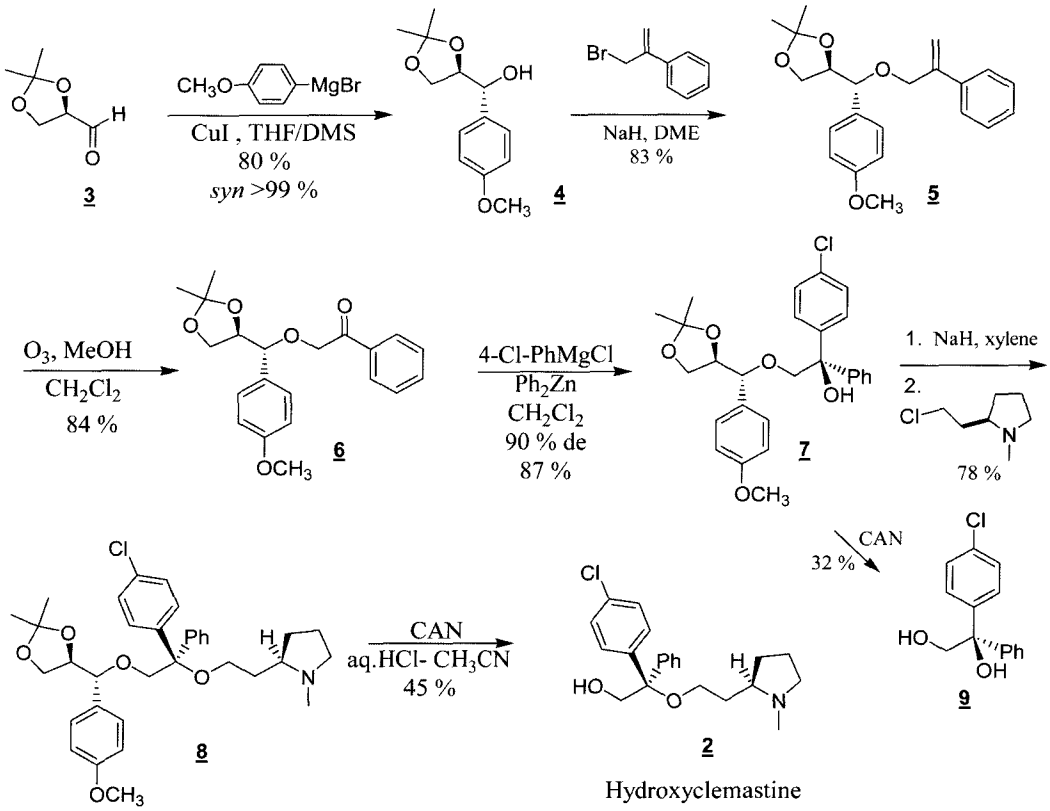
Ceric (IV) ammonium nitrate (173.5 mg, 0.32 mmol) was added to a stirred solution of 1-(4-chlorophenyl)-2-[(2,2-dimethyl-[1,3]dioxolan-4-yl)-(4-methoxyphenyl)methoxy]-1-phenylethanol (**7**, 74.2 mg, 0.158 mmol) in aq. acetonitrle (5 mL, CH_3CN:H_2O = 9:1) at 0°C. The reaction mixture was stirred at 0°C for 4 h before it was diluted with ethyl acetate (30 mL). The layers were separated, and the organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered, and then concentrated *in vacuo*. The resulting crude residue was purified by column chromatography on silica gel (20 % ethyl acetate in hexane) to give the title compound **9** as a white solid (10.6 mg, 32%): mp 90-91; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.38-7.19 (m, 9H), 4.09 (d, 1H, *J* = 11.4 Hz), 4.02 (d, 1H, *J* = 11.4 Hz), 3.16 (bs, 1H), 1.84 (bs, 1H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 143.35, 142.38, 133.19, 128.44, 128.38, 127.88, 127.56, 126.25, 78.17, 68.89; IR (KBr pellet,) cm^{-1} 3371, 3295, 3057, 2925, 1489, 1210; HPLC analysis: CHIRALCEL OD column, eluent = 5% isopropanol in hexane, flow rate = 0.5 mL/min, minor (*S* form) t_R = 49.7 min, major (*R* form) t_R = 57.1 min, minor/major = 1.0/19.2 (90.1 % ee); $[\alpha]_D^{26}$ -6.8 (*c* 1.63, $CHCl_3$); LRMS (FAB) m/e (relative intensity) 213 [$(M-OH)^+$, 31].

(2*R*)-2-(4-Chlorophenyl)-2-{2-[(2*R*)-(1-methylpyrrolidin-2-yl)]ethoxy}-2-phenylethanol (2)

5% HCl was added dropwise to a stirred solution of **8** (23.5 mg, 0.041 mmol, 82% de) in acetonitrile (10 mL) at 0°C until the solution became a clear. Then ceric (IV) ammonium nitrate (44.4 mg, 0.08 mmol) was added and the mixture was stirred for 3 h. The reaction mixture was quenched with saturated aqueous sodium sulfite (1 mL), basified with 1N-NaOH at 0°C, and diluted with methylene chloride (30 mL). The layers were separated, and the aqueous layer was extracted twice with methylene chloride (10 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered, and then concentrated *in vacuo*. The resulting crude residue was purified by column chromatography on silica gel (a 1:1 mixture of ethyl acetate and methanol) to give the title compound **2** as a pale yellow oil (6.7 mg, 45.4%): ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.27-7.13 (m, 9H), 4.43 (d, 7/10H, *J* = 12.0 Hz), 6.32 (d, 3/10H, *J* = 12.0 Hz), 4.14 (d, *J* = 12.0 Hz, 3/10H), 4.07 (d, 7/10H, *J* = 12.0 Hz), 3.38-3.34 (m, 1H), 3.29-3.13 (m, 1H), 3.07-3.01 (m, 1H), 2.35 (s, 3H), 2.11(quint, 1H, *J* = 8.0 Hz), 2.04-1.87 (m, 2H), 1.84-1.69 (m, 2H), 1.68-1.53 (m, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 143.58, 142.19, 132.36, 128.29, 128.00, 127.92, 127.19, 126.60, 82.01, 64.47, 64.39, 58.46, 57.04, 40.30, 29.73, 29.16, 21.56; IR (NaCl, neat) cm^{-1} 3406, 3060, 2947, 1644, 1489, 1251, 1091; $[\alpha]_D^{22}$ -35.3 (*c* 0.5, $CHCl_3$).

RESULTS AND DISCUSSION

Our synthetic strategy for (-)-hydroxyclemastine (**2**) was based on the approach outlined in Scheme 1, which involves 1,4-asymmetric induction by diastereoselective 1,2-addition reaction as a key step. From our previous work (Jung *et al.* 2000; Rhee *et al.* 2004), we envisioned that the chiral auxiliary **4** could play a dual role as a chiral inducer as well as a protecting group. We began our synthesis starting from 2,3-*O*-isopropylidene-D-glyceraldehyde (**3**). The aldehyde **3**, commercially or readily available from (*D*)-mannitol, reacted with 4-methoxyphenyl magnesium bromide and CuI in DMS-THF at -78°C to give the *syn* alcohol **4** in high diastereoselectivity (>99:1) (Sato *et al.*, 1985). Treatment of the alcohol **4** with NaH in



Scheme 1. Synthetic route to hydroxyclemastine

DME, followed by *O*-alkylation with 3-bromo-2-phenylpropene afforded the ether **5** in 83% yield. Subsequent exposure of the alkene **5** to O_3 in MeOH-CH_2Cl_2 at -78°C produced the corresponding ketone **6** in 89% yield. Then, we explored the optimal reaction condition for the stereoselective 1,2-addition of 4-chlorophenyl magnesium halide to **6**, testing the effect of different parameters such as solvent, temperature, and the presence of a Lewis acid. It was found that CH_2Cl_2 is the best solvent and Ph_2Zn is the best Lewis acid for the reaction. Thus, the coordination of **6** with Ph_2Zn in CH_2Cl_2, followed by addition of 4-chlorophenyl magnesium chloride at -78°C produced the desired alcohol **7** with 90% optical purity in 87% chemical yield. *O*-Alkylation of **7** with (*R*)-2-(2-chloroethyl)-1-methylpyrrolidine (Vernier *et al.* 1999) was effected by NaH in refluxing xylene to afford the amine **8** in 78% yield. Finally, deprotection of chiral auxiliary in **8** with ceric ammonium nitrate in aqueous acetonitrile gave the desired hydroxyclemastine in 45% yield. To determine the absolute configuration of the newly created chiral center, the alcohol **7** was converted to the corresponding diol **9** by treating with ceric ammonium nitrate. At this stage, the optical purity of the **7** was reconfirmed by analyzing the diol **9** by chiral HPLC (Chiralcel OD column). We also prepared this chiral diol **9** from the corresponding alkene by Sharpless asymmetric dihydroxylation (Vanhessche *et al.*, 1996). As expected, the enantiomeric excess was very low, not exceeding 29%. Before transforming this diol **9** to a known chiral compound by the chemical correlation method, we found several reports on chiral compounds having phenyl and 4-chlorophenyl groups on the same carbon (Forrat *et al.*, 2006; Goeber *et al.*, 1988). The absolute configurations of these compounds, however, were not described in any of the reports. Thus, the absolute configuration of **9** could not be rigorously established at the present stage, but was assigned tentatively as *R* on the basis of our proposed transition state model as shown in Fig. 2 (Jung *et al.*, 2000).

In summary, we have shown that (-)-hydroxyclemastine can be prepared efficiently from our chiral auxiliary *via* the chelation-controlled diastereoselective 1,2-addition reac-

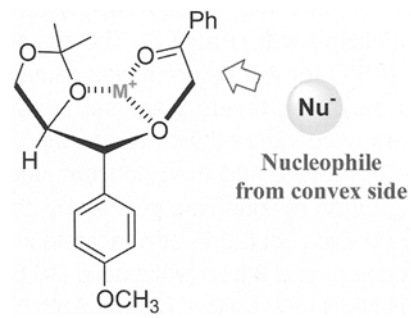


Fig. 2. Possible transition state for asymmetric 1,2-addition

tion. A high degree of 1,4-asymmetric induction has been achieved using this reaction system. The method described here is applicable to the preparation of a wide variety of clemastine analogues and chiral diols having two aryl groups on the same carbon.

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