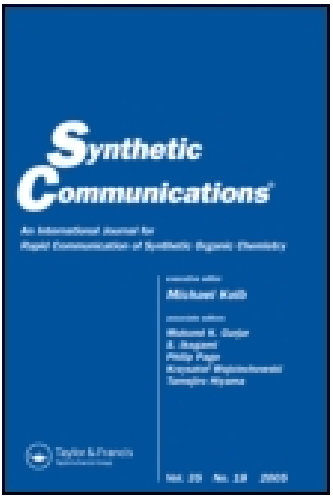

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# Synthesis of 4-(R)-Naphthalene-2-yloxy-1-(1-Ph and 4-(S)-Naphthalen-2-yloxy-1-(1-Phe Versatile Chiral Intermediates for Synthesis

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# Synthesis of 4-(*R*)-Naphthalene-2-yloxy-1-(1-Phenyl-(*S*)-Ethyl)-Pyrrolidin-3-(*R*)-ol and 4-(*S*)-Naphthalen-2-yloxy-1-(1-Phenyl-(*S*)-Ethyl)-Pyrrolidin-3-(*S*)-ol: Versatile Chiral Intermediates for Synthesis

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## ABSTRACT

A convenient and rapid synthesis of 4-(*R*)-(naphthalen-2-yloxy)-1-(1-phenyl-(*S*)-ethyl)-pyrrolidin-3-(*R*)-ol and 4-(*S*)-(naphthalen-2-yloxy)-1-(1-phenyl-(*S*)-ethyl)-pyrrolidin-3-(*S*)-ol is disclosed. The reaction

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scheme is highlighted by the *meso*-epoxidation of 1-(1-phenyl-(*S*)-ethyl)-2,5-dihydro-1*H*-pyrrole followed by addition of 2-naphthol alkoxide to provide both expected diastereoisomers. Separation of the diastereoisomers by crystallization provided access to both diastereoisomers in modest yield without the employment of expensive chiral catalysts. X-ray analysis of one of the diastereoisomers led to the unambiguous assignment of each diastereoisomer. These chiral pyrrolidine analogues should be useful as intermediates in natural product, combinatorial/parallel synthesis, and medicinal chemistry.

*Key Words:* Chiral 3,4-disubstituted pyrrolidines; Meso-epoxide ring opening; Pyrrolidine analogs.



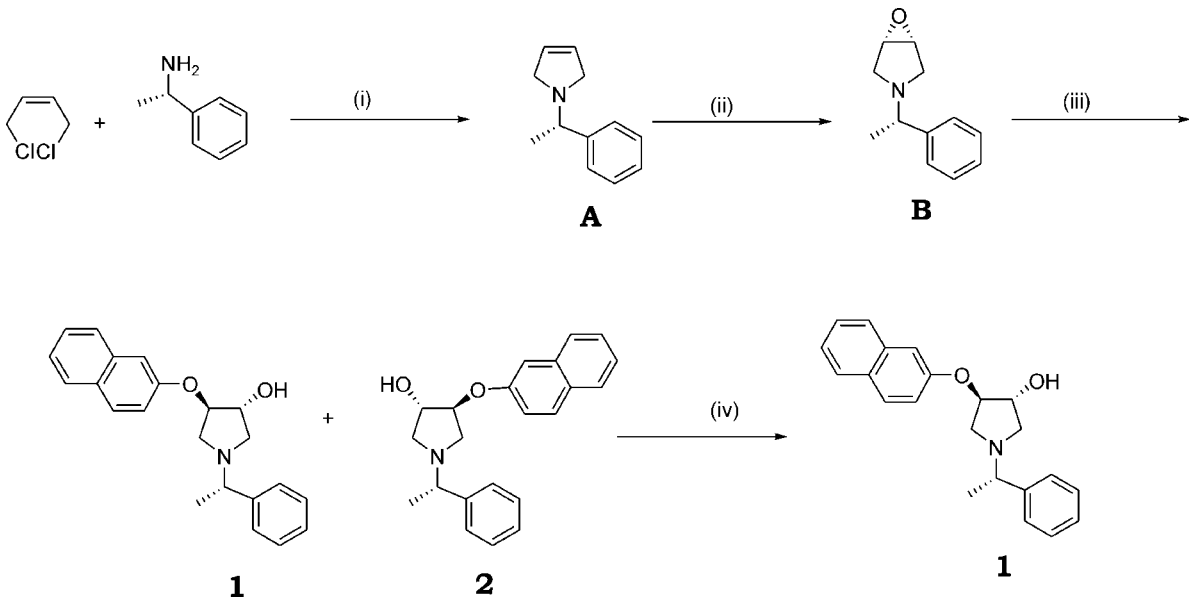
## INTRODUCTION

The presentation of substituents in both the 3- and 4-positions of the pyrrolidine scaffold combined with the stereochemical configuration present in molecules **1** and **2**, provide useful intermediates for natural product synthesis, combinatorial/parallel synthesis, and medicinal chemistry.[1] However, protocols for the preparation of chiral 3,4-disubstituted pyrrolidines are relatively sparse.[1c] Methods have involved chiral starting materials, such as hydroxycitric acid lactones,[1d] D- and L-tetronic acids,[1g] tartaric acid,[1h] and chiral oxazolidinones (used for 1,3-dipolar cycloadditions).[2a,2b] Disclosed herein, we wish to report a convenient and rapid synthesis of 4-(*R*)-(naphthalen-2-yloxy)-1-(1-phenyl-(*S*)-ethyl)-pyrrolidin-3-(*R*)-ol (**1**) and 4-(*S*)-(naphthalen-2-yloxy)-1-(1-phenyl-(*S*)-ethyl)-pyrrolidin-3-(*S*)-ol (**2**) from inexpensive racemic starting materials (Scheme 1).

Construction of the pyrrolidine core (**A**) began with a condensation reaction between *cis*-1,4-dichloro-2-butene and *S*-(-)-$\alpha$-methylbenzylamine, an amine that served as a chiral auxillary for the generation of diastereoisomers. Epoxidation of **A** with meta-chloroperoxybenzoic acid produced compound **B** in good yield.[a]

Epoxide ring opening with 2-naphthol in the presence of cesium carbonate gave two diastereoisomers (**1** and **2**) in 41% yield in approximately a 1 : 1 ratio. The products were crystallized from a mixture of dichloromethane and hexanes to provide compound **1** (56% from mixture/12% overall yield) as a single diastereoisomer. The stereochemistry of compound **1** was

[a]Compound **B** was characterized by $^1$H NMR, COSY, HSQC, and NOESY (data not shown).




***Scheme 1.*** Synthetic route to diastereomerically pure pyrrolidine intermediates **1** and **2**. Reagents and conditions: (i) $NEt_3$/AcOEt, rt, 18 h; (ii) *m*-CPBA/$H_2SO_4$/$CH_3COCH_3$, 0°C − rt, 18 h; (iii) 2-naphthol/$Cs_2CO_3$/18-crown-6/EtOH, reflux, 18 h; (iv) $CH_2Cl_2$/hexanes.

unambiguously assigned by x-ray[3],b and by high-resolution NMR techniques ($^1$H NMR, COSY, HSQC, NOESY) (Fig. 1). Compound **2** remained in the mother liquor and was accessed by evaporation of solvent *in vacuo*, followed

[b]Crystallographic Experimental Details:

| | |
|---|---|
| *A. Crystal Data* | |
| Formula | $C_{22}H_{23}NO_2$ |
| Formula weight | 333.41 |
| Crystal dimensions (mm) | 0.46 × 0.36 × 0.23 |
| Crystal system | Monoclinic |
| Space group | *I*2 (an alternate setting of *C*2 [No. 5]) |
| Unit cell parameters[1] | |
| *a*(Å) | 18.3026 (18) |
| *b*(Å) | 6.8814 (7) |
| *c*(Å) | 14.7614 (15) |
| $\beta$(deg) | 103.926 (2) |
| *V*(Å$^3$) | 1804.5 (3) |
| *Z* | 4 |
| $\rho$ calcd. (g cm$^{-3}$) | 1.227 |
| $\mu$ (mm$^{-1}$) | 0.078 |
| *B. Data Collection and Refinement Conditions* | |
| Diffractometer | Bruker PLATFORM/SMART 1000 CCD[2] |
| Radiation ($\lambda$[Å]) | Graphite-monochromated Mo K$\alpha$ (0.71073) |
| Temperature (°C) | −80 |
| Scan type | $\omega$ scans (0.2°) (25 s exposures) |
| Data collection 2$\theta$ limit (deg) | 52.76 |
| Total data collected | 4609 ($-20 \le h \le 22$, $-8 \le k \le 8$, $-12 \le l \le 18$) |
| Independent reflections | 3481 ($R_{int} = 0.0241$) |
| Number of observed reflections (*NO*) | 3140 [$F_o^2 \ge 2\sigma(F_o^2)$] |
| Structure solution method | Direct methods (*SHELXS-86*[3a]) |
| Refinement method | Full-matrix least-squares on $F^2$ (*SHELXL-93*[3b],[3]) |
| Absorption correction method | Multi-scan (*SADABS*) |
| Range of transmission factors | 0.9823–0.9650 |
| Data/restraints/parameters | 3481 [$F_o^2 \ge -3\sigma(F_o^2)$]/0/227 |
| Flack absolute structure parameter[3c],[4] | 0.3 (11) |
| Goodness-of-fit (*S*)[5] | 1.038 [$F_o^2 \ge -3\sigma(F_o^2)$] |
| Final *R* indices[6] | |
| $R_1$ [$F_o^2 \ge 2\sigma(F_o^2)$] | 0.0356 |
| $wR_2$[$F_o^2 \ge -3\sigma(F_o^2)$] | 0.0878 |
| Largest difference peak and hole | 0.189 and −0.123 e Å$^{-3}$ |

by flash column chromatography. Compound **2** was isolated in 50% yield from the mixture and in 11% overall yield.

In summary, a practical synthesis of 4-(*R*)-(naphthalen-2-yloxy)-1-(1-phenyl-(*S*)-ethyl)-pyrrolidin-3-(*R*)-ol (**1**) and 4-(*S*)-(naphthalen-2-yloxy)-1-(1-phenyl-(*S*)-ethyl)-pyrrolidin-3-(*S*)-ol (**2**) from inexpensive racemic starting materials is described. Separation of diastereoisomers by crystallization provided access to both diastereoisomers in good yield without the employment of expensive chiral catalysts.[4] Compounds **1** and **2** can serve as useful chiral intermediates in natural product, combinatorial/parallel synthesis, and medicinal chemistry.



## EXPERIMENTAL

All reagents were purchased from Aldrich and used without further purification. Solvents used were of high-performance liquid chromatography (HPLC) grade and used without further purification. Nuclear magnetic resonance (NMR) spectra were recorded on a Varian 400 MHz spectrometer and referenced to solvent. Melting point values are uncorrected.

### 1-(1-Phenyl-(*S*)-Ethyl)-2,5-Dihydro-1*H*-pyrrole (A)

To a solution of *cis*-1,4-dichloro-2-butene (5.0 g, 40 mmol) in ethyl acetate (200 mL) was added a mixture of *S*-(-)-$\alpha$-methylbenzylamine (4.85 g,

---

[1]Obtained from least-squares refinement of 3039 reflections with $5.69^\circ < 2\theta < 52.52^\circ$.

[2]Programs for diffractometer operation, data collection, data reduction, and absorption correction were those supplied by Bruker.

[3]Refinement on $F_o^2$ for all reflections [all of these having $F_o^2 \geq -3\sigma(F_o^2)$]. Weighted *R*-factors $wR_2$ and all goodnesses of fit *S* are based on $F_o^2$; conventional *R*-factors $R_1$ are based on $F_o$, with $F_o$ set to zero for negative $F_o^2$. The observed criterion of $F_o^2 > 2\sigma(F_o^2)$ is used only for calculating $R_1$, and is not relevant to the choice of reflections for refinement. *R*-factors based on $F_o^2$ are statistically about twice as large as those based on $F_o$, and *R*-factors based on all data will be even larger.

[4]The Flack parameter will refine to a value near zero if the structure is in the correct configuration and will refine to a value near one for the inverted configuration. In this case, the absolute structure cannot be reliably determined from the x-ray data, but can be assigned based upon the known stereochemistry of the precursor pyrrolidin-3,4-diol.

[5]$S = [\Sigma w(F_o^2 - F_c^2)^2/(n-p)]^{1/2}$ ($n$ = number of data; $p$ = number of parameters varied; $w = [\sigma^2(F_o^2) + (0.0387P)^2 + 0.4245P]^{-1}$, where $P = [\mathrm{Max}(F_o^2, 0) + 2F_c^2]/3$).

[6]$R_1 = \Sigma \| F_o| - |F_c \| / \Sigma |F_o|$; $wR_2 = [\Sigma w(F_o^2 - F_c^2)^2 / \Sigma w(F_o^4)]^{1/2}$.

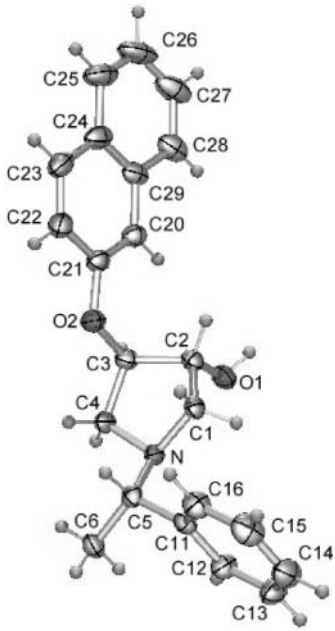



***Figure 1.*** X-ray of compound **1**.

40 mmol) and triethylamine (12 g, 120 mmol) in ethyl acetate (50 mL) at room temperature. The resulting mixture was stirred at room temperature overnight, and the crystallized solid was removed by filtration. After the solvent was evaporated *in vacuo*, the residue was subjected to flash column chromatography on silica gel eluting with ethyl acetate and hexanes (1 : 2) to give 4.0 g of 1-(1-phenyl-(*S*)-ethyl)-2,5-dihydro-1*H*-pyrrole (**A**) in 58% yield. $^{1}$H NMR (400 MHz, $CDCl_3$) $\delta$: 7.38–7.22 (*m*, 5H), 5.80 (*s*, 2H), 3.58–3.32 (*m*, 5H), 1.43–1.41 (*d*, $J = 6.0$ Hz, 3H). $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$: 145.90, 128.62, 128.04, 127.44, 127.13, 65.40, 58.77, 23.84. MS: $m/z$ 173.9 [M + 1].

### 3-(1-Phenyl-(*S*)-Ethyl)-6-oxa-3-aza-Bicyclo[3.1.0]Hexane (B)

To a solution of compound **A** (4.0 g, 23 mmol) in a mixture of $H_2SO_4$ (2.5 g, 27.8 mmol), $H_2O$ (3 mL), and acetone (50 mL) was added *m*-CPBA portion-wise at 0°C with stirring. After addition, the resulting mixture was stirred at room temperature overnight, and then the solvent was removed under reduced pressure. The residue was treated with 1N NaOH and extracted with dichloromethane. The organic layer was dried over $Na_2SO_4$

and evaporated *in vacuo*. The residue was subjected to flash column chromatography on silica gel eluting with ethyl acetate and hexanes (1 : 3) to give 2.5 g of 3-(1-phenyl-(*S*)-ethyl)-6-oxa-3-aza-bicyclo[3.1.0]hexane (**B**) in 57% yield. HPLC: 90.2%. $^1$H NMR (400 MHz, $CDCl_3$) $\delta$: 7.32–7.20 (*m*, 5H), 3.60–3.59 (*m*, 1H), 3.50–3.49 (*m*, 1H), 3.41–3.35 (*m*, 2H), 2.98 (*d*, $J = 11.7$ Hz, 1H), 2.46 (*dd*, $J = 1.0$ Hz, $J = 11.2$ Hz, 1H), 2.21 (*dd*, $J = 1.5$ Hz, $J = 11.7$ Hz, 1H), 1.37–1.36 (*d*, $J = 6.0$ Hz, 3H). $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$: 144.74, 128.57, 127.52, 127.33, 64.92, 55.83, 52.73, 22.96. MS: $m/z$ 190.1 [M + 1]. $[\alpha]^{24.7} = -22.7^\circ$ ($c = 0.5$, $CH_3OH$).



### 4-(*R*)-(Naphthalen-2-yloxy)-1-(1-Phenyl-(*S*)-Ethyl)-Pyrrolidin-3-(*R*)-ol (1) and 4-(*S*)-(Naphthalen-2-yloxy)-1-(1-Phenyl-(*S*)-Ethyl)-Pyrrolidin-3-(*S*)-ol (2)

A mixture of compound **B** (2.5 g, 13 mmol), 2-naphthol (3.8 g, 26 mmol), $Cs_2CO_3$ (10.8 g, 33 mmol), and 18-crown-6 (25 mg) in ethanol were refluxed overnight. The solvent was removed under reduced pressure. The residue was dissolved in ethyl acetate, washed with 1N NaOH, brine, and $H_2O$. The organic layer was dried over $Na_2SO_4$ and concentrated *in vacuo*. The residue was subjected to flash column chromatography on silica gel eluting with ethyl acetate and hexanes (1 : 3) to give 1.8 g of compounds **1** (Chiral HPLC: 44.89%, $R_t = 7.291$ min) and **2** (Chiral HPLC: 54.84%, $R_t = 6.8$ min) as a mixture in 41% yield. HPLC: 99.93%. (Chiral HPLC method: isopropyl alcohol/hexanes (20 : 80): Chiral PAK AD 0.46 cm $\theta \times$ 25 cm).

### 4-(*R*)-(Naphthalen-2-yloxy)-1-(1-Phenyl-(*S*)-Ethyl)-Pyrrolidin-3-(*R*)-ol (1)

1.8 g of compounds **1** and **2** were dissolved in dichloromethane ($\sim$2 mL) and added to hexanes (200 mL). The resulting solution was allowed to stand at room temperature for 2 days. Compound **1** (0.45 g) crystallized out preferentially [56% of 0.81 g (calcd.)]. (Chiral HPLC: 93%, $R_t = 7.326$ min) Mp = 157–158°C; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.77–7.73 (*m*, 3H), 7.46–7.12 (*m*, 9H), 4.79–4.76 (*m*, 1H), 4.28 (br *s*, 1H), 3.58 (*dd*, $J = 6.8$ Hz, $J = 10.7$ Hz, 1H), 3.39 (*q*, $J = 6.8$ Hz, 1H), 2.72 (*dd*, $J = 4.9$ Hz, $J = 10.2$ Hz, 1H), 2.70–2.59 (*m*, 1H), 2.53 (*dd*, $J = 3.9$ Hz, $J = 10.7$ Hz, 1H), 2.35 (*s*, 1H), 1.43–1.42 (*d*, $J = 6.3$ Hz, 3H). $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 155.65, 144.60, 134.67, 129.81, 129.22, 128.74, 127.82, 127.43, 127.35, 127.14, 126.64, 124.01, 119.36, 108.19, 83.33, 75.59, 65.05, 59.35, 57.37, 22.79. MS: $m/z$ 334.1 [M + 1]. $[\alpha]^{20.1} = -68.5^\circ$ ($c = 0.1$, $CH_3OH$). Anal.

calcd. for $C_{22}H_{23}NO_2$ (%): C, 79.25; H, 6.95; N, 4.20. Found: C, 78.58; H, 6.82; N, 4.13.

### 4-(*S*)-(Naphthalen-2-yloxy)-1-(1-Phenyl-(*S*)-Ethyl)-Pyrrolidin-3-(*S*)-ol (2)

The mother liquor was evaporated *in vacuo* and subjected to flash column chromatography [ethyl acetate/hexanes (1 : 10 to 1 : 5)] to afford 0.5 g of compound **2** [50% of 1 g (calcd.)]. Mp = 111–112°C; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.74–7.70 (*m*, 3H), 7.43–7.25 (*m*, 7H), 7.14–7.09 (*m*, 2H), 4.69 (*t*, $J = 4.9$ Hz, 1H), 4.33 (br s, 1H), 3.38 (*q*, $J = 7.2$ Hz, 1H), 3.20 (*dd*, $J = 6.8$ Hz, $J = 10.7$ Hz, 1H), 2.91 (*d*, $J = 9.6$ Hz, 1H), 2.77 (*dd*, $J = 4.9$ Hz, J = 9.8 Hz, 2H), 2.52 (*dd*, $J = 3.9$ Hz, $J = 10.7$ Hz, 1H), 1.40 (*d*, $J = 7.2$ Hz, 3H). $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 155.65, 144.50, 134.68, 129.79, 129.23, 128.67, 127.80, 127.47, 127.39, 127.13, 126.62, 124.00, 119.32, 108.26, 83.23, 75.74, 65.06, 58.86, 57.89, 22.72. MS: $m/z$ 334.1 [M + 1]. $[\alpha]^{25.1} = +21.2^\circ$ ($c = 0.5$, $CH_3OH$). Anal. calcd. for $C_{22}H_{23}NO_2$ (%): C, 79.25; H, 6.95; N, 4.20. Found: C, 78.77; H, 7.06; N, 4.18.

## REFERENCES

1. (a) Numata, A.; Ibrika, T. In *The Alkaloids*; Brossi, A., Ed.; Academic Press: New York, 1987; Vol. 31, Chap. 6; (b) Denmark, S.E.; Marcin, L.R. Asymmetric nitroalkene [4 + 2] cycloadditions: Enantioselective synthesis of 3-substituted and 3,4-disubstituted pyrrolidines. J. Org. Chem. **1995**, *60*, 3221–3235; (c) Bachi, M.D.; Bar-Ner, N.; Melman, A. Stereoselctive synthesis of (±)-$\alpha$-kainic acid using free radical key reactions. J. Org. Chem. **1996**, *61*, 7116–7124; (d) Ibnusaud, I.; Thomas, G. Biologically interesting chiral 3,4-disubstituted pyrrolidines from optically active hydroxycitric acid lactones. Tetrahedron Lett. **2003**, *44*, 1247–1249; (e) Willoughby, C.A.; Rosauer, K.G.; Hale, J.L.; Budhu, R.J.; Mills, S.G.; Chapman, K.T.; MacCoss, M.; Malkowitz, L.; Springer, M.S.; Gould, S.L.; DeMartino, J.A.; Siciliano, S.J.; Cascieri, M.A.; Carella, A.; Carver, G.; Holmes, K.; Schleif, W.A.; Danzeisen, R.; Hazuda, D.; Kessler, J.; Lineberger, J.; Miller, M.; Emini, E.A. 1,3,4-trisubstituted pyrrolidine CCR5 receptor antagonists bearing 4-aminoheterocycle substituted piperidine side chains. BioOrganic Med. Chem. Lett. **2003**, *13*, 427–431; (f) Lynch, C.L.; Hale, J.J.; Budhu, R.J.; Gentry, A.L.; Finke, P.E.; Caldwell, C.G.; Mills, S.G.; MacCross, M.; Shen, D.-M.; Chapman, K.T.; Malkowitz, L.; Springer, M.S.; Gould, S.L.; DeMartino, J.A.; Siciliano, S.J.;

Cascieri, M.A.; Carella, A.; Carver, G.; Holmes, K.; Schleif, W.A.; Danzeisen, R.; Hazuda, D.; Kessler, J.; Lineberger, J.; Miller, M.; Emini, E. CCR5 antagonists: 3-(Pyrrolidin-1yl)propionic acid analogues with potent anti-HIV activity. Organic Lett. **2003**, *5*, 2473–2475; (g) Limberg, G.; Lundt, I.; Zavilla, J. Deoxyiminoalditols from aldonic acids VI. Preparation of the four stereoisomeric 4-amino-3-hydroxypyrrolidines from bromodeoxytetronic acids. Discovery of a new $\alpha$-mannosidase inhibitor. Synthesis **1999**, 178–183; (h) Brandi, A.; Cicchi, S.; Paschette, V.; Pardo, D.G.; Cossy, J. A new nitrone from $C_2$ symmetric piperidine for the synthesis of hydroxylated indolizinone. Tetrahedron Lett. **2002**, *43*, 9357–9359; (i) Walsh, D.A.; Welstead, W.J. *Trans*-4-(2-chlorophenoxy)-1-Ethyl-3-Pyrrolidinol and Anti-depressant Use Thereof. U.S. 4,452,809, June 5, 1984; (j) Walsh, D.A.; Welstead, W.J. *Cis* and *Trans*-3-Aryloxy-4-Hydroxypyrrolidines Used as Anti-arrhythmics. U.S. 4,585,785, March 10, 1980; (k) Paioni, R. Derivatives of Perhydro-aza-Heterocycles. U.S. 4,160,837, July 10, 1979; (l) Enyedy, I.J.; Zaman, W.A.; Sakamuri, S.; Kozikowski, A.P.; Johnson, K.M.; Wang, S. Pharmacophore-based discovery of 3,4-disubstituted pyrrolidines as a novel class of monoamine transporter inhibitors. BioOrganic Med. Chem. Lett. **2001**, *11*, 1113–1118; (m) Dubuffet, T.; Muller, O.; Simont, S.S.; Descombes, J.-J.; Laubie, M.; Verbeuren, T.J.; Lavielle, G. Synthesis of new 3,4-Disubstituted pyrrolidines as thromboxane $A_2$/prostaglandin $H_2$ (TP) receptor antagonists. BioOrganic Med. Chem. Lett. **1996**, *6*, 349–352.

2. (a) Karlsson, S.; Han, F.; Hogberg, H.-E.; Caldirola, P. *trans*-3,4-Disubstituted pyrrolidines by 1,3-dipolar cycloaddition: enantioselective approaches and their limitations. Tetrahedron: Asymmetry **1999**, *10*, 2605–2616; (b) Ma, Z.; Wang, S.; Cooper, C.S.; Kung, A.K.C.; Lynch, J.K.; Plagge, F.; Chu, D.T.W. Asymmetric dipolar cycloaddition reactions: a practicle, convergent synthesis of chiral pyrrolidines. Tetrahedron: Asymmetry **1997**, *8*, 883–887.
3. (a) Sheldrick, G.M. Phase annealing in SHELX-90: direct methods for larger structures. Acta Crystallogr. **1990**, *A46*, 467–473; (b) Sheldrick, G.M. In Program for Crystal Structure Determination. SHELXL-93; University of Göttingen, Germany, 1993; (c) Flack, H.D. On enantiomorph-polarity estimation. Acta Crystallogr. **1983**, *A39*, 876–881; (d) Flack, H.D.; Bernardinelli, G. Absolute structure and absolute configuration. Acta Crystallogr. **1999**, *A55*, 908–915.
4. (a) Matsunaga, S.; Das, J.; Roels, J.; Vogel, E.M.; Yamamoto, N.; Iida, T.; Yamaguchi, K.; Shibasaki, M. Catalytic enantioselective *meso*-epoxide ring opening reaaction with phenolic oxygen nucleophilic promoted by gallium heterobimetallic multifunctional complexes. J. Am. Chem. Soc.

**2000**, *122*, 2252–2260; (b) Iida, T.; Yamamoto, N.; Matsunaga, S.; Woo, H.-G.; Shibasaki, M. Enantioselective ring opening of expoxides with 4-methoxyphenol catalyzed by gallium heterobimetallic complexes: An efficient method for the synthesis of optically active 1,2-diol monoethers. Angew. Chem. Int. Ed. **1998**, *37*, 2223–2226; (c) Schauss, S.E.; Larrow, J.F.; Jacobsen, E.N. Practical synthesis of enantiopure cyclic 1,2-amino alcohols via catalytic asymmetric ring opening of *meso*-epoxides. J. Org. Chem. **1997**, *62*, 4197–4199.

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