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TETRAHEDRON: *ASYMMETRY*

Synthesis of novel and enantiomerically pure epoxypropylamine: a divergent route to the chiral β-adrenergic blocking agents

Xue-Long Hou,* Bin-Feng Li and Li-Xin Dai

Laboratory of Organometallic Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 354 Fenglin Road, Shanghai 200032, China

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Abstract

The chiral building block (*S*)-*N*-benzyl-*N*-isopropyl-2,3-epoxypropylamine is obtained by means of chlorohydroxylation of allylamine, followed by Jacobsen's hydrolytic kinetic resolution with water. A concise, divergent five-step synthesis of three β-adrenergic blocking agents in high enantiomeric excess using (*S*)-*N*-benzyl-*N*-isopropyl-2,3-epoxypropylamine as the key intermediate is described.

1. Introduction

The enantiomers of chiral drugs often show different pharmacological and metabolic characteristics. The synthesis of homochiral drugs has become a key issue not only in academic research but also in the pharmaceutical industry.[1] β-Adrenergic blocking agents of the 3-(aryloxy)-2-hydroxy-*N*-isopropylpropylamine, type **1** (Scheme 1), are such a group of drugs whose biological activity resides almost exclusively in the *S* enantiomer. For instance, as a β-blocker with longer plasma half-life, the *S* isomer of propranolol **1a** is 100-fold more potent than the *R* form.[2]

Many syntheses of the homochiral β-adrenergic blocking agents **1** have been published, mainly using two strategies through the disconnection of bonds a or b (Scheme 2).[3–8] The disconnection mode a of **1** gives the (*S*)-3-(aryloxy)-2-hydroxypropylamine **2**, which can be obtained from the enzymatic resolution of intermediate compounds,[3] asymmetric ring-opening of aryl glycidyl ethers with $TMSN_3$ catalysed by Salen (Cr),[4] or nitroaldol reaction.[5] With the disconnection mode b, (*S*)-arylglycidyl ether **3** is obtained. Many methods have been adopted to prepare this chiral aryl glycidyl ether **3**, for example, Sharpless asymmetric epoxidation,[6] and asymmetric dihydroxylation[7] or from enantiomerically pure natural products.[8]

* Corresponding author. E-mail: xlhou@pub.sioc.ac.cn

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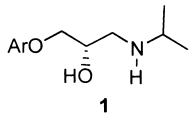
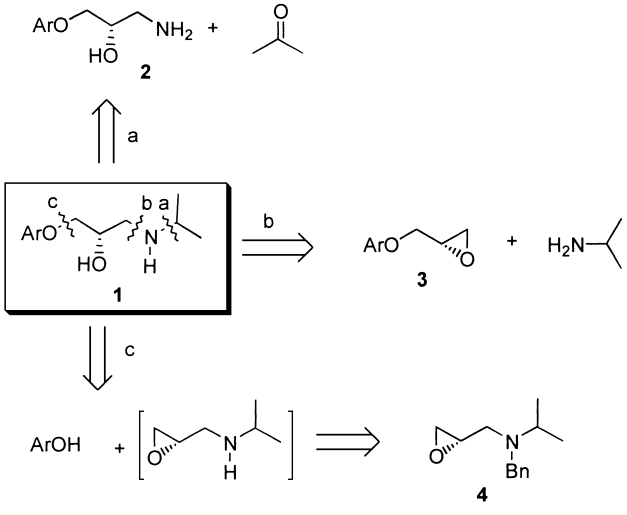


1

ArOH	β-Blocker
1a: α-Naphthol	Propranolol
1b: Guaiacol (2-Methoxyphenol)	Moprolol
1c: *m*-Cresol (3-Methylphenol)	Toliprolol

Scheme 1.

By retrosynthetic analysis, we envisaged that the disconnection mode c is an alternative and convenient strategy, which gives the (*S*)-*N*-benzyl-*N*-isopropyl-2,3-epoxypropylamine **4** and phenols. According to the *Dictionary of Drugs*,[9] there are more than 30 kinds of β-adrenergic blocking agents, which have a similar structure. The substituent on the nitrogen atom is always the isopropyl group and they only differ in the aryloxy group, such as propranolol **1a**, moprolol **1b**, toliprolol **1c**. Gowther et al. have synthesised 54 kinds of compounds of type **1**, varying with different substituted phenoxy groups, to scan the physiological activity.[10] To synthesise this series of β-blockers, we think the third strategy is a more convenient and effective one, because we can open the epoxide ring of the general intermediate, (*S*)-*N*-benzyl-*N*-isopropyl-2,3-epoxypropylamine **4** by using different phenols, to give a series of the corresponding products.



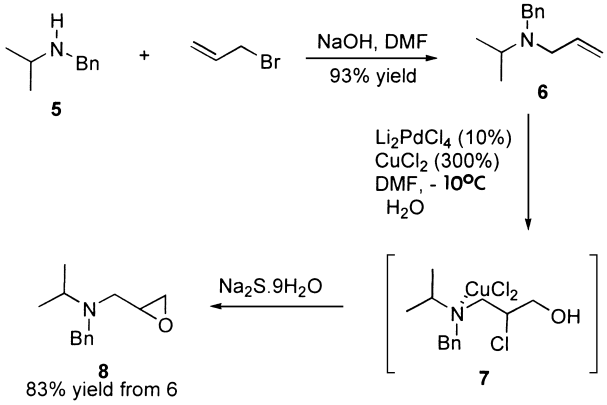
Scheme 2.

Obviously, the key step of the third strategy is how to synthesise the optically active epoxypropylamine **4**. To the best of our knowledge, few methods have been reported in the literature that afford this three-carbon chiral intermediate or its derivatives.[11] Our group reported the Pd-catalysed chlorohydroxylation of allylamine and found that the products were easily converted into 2,3-epoxypropylamines,[12] but the asymmetric induction of an attempted asymmetric chlorohydroxylation from a chiral allylamine was not very satisfactory. Recently, Jacobsen et al.[13a,b] reported a convenient method to obtain optically active terminal epoxides by an efficient hydrolytic kinetic resolution. Afterwards, this procedure was adopted by other authors to synthesise chiral terminal epoxides.[13c–f] To date there has been no report about the kinetic resolution of aminomethyl substituted epoxide. Herein we would like to disclose the synthesis of the chiral (*S*)-*N*-benzyl-*N*-isopropyl-2,3-epoxypropylamine **4** through the Pd-catalysed

chlorohydroxylation of allylamine **6** and the kinetic resolution of the reaction product with water catalysed by (*S*,*S*)-(Salen)Co(III)OAc,[13] and provide an example of its application as a chiral building block in divergent protocol to prepare β-adrenergic blocking agents. The syntheses of (*S*)-propranolol **1a**, (*S*)-moprolol **1b**, (*S*)-toliprolol **1c** can serve as the examples.

2. Results and discussion

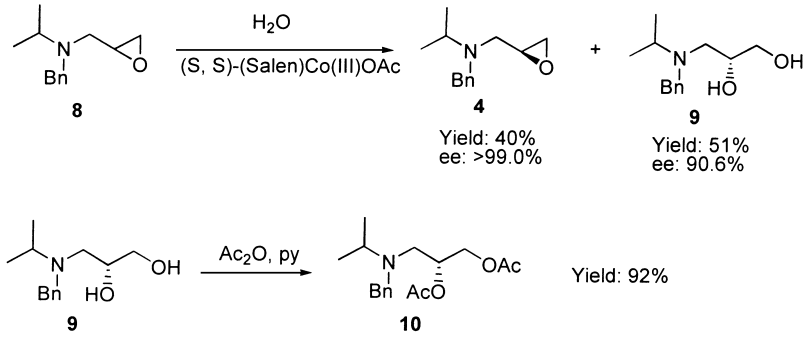
By treatment of *N*-benzyl-*N*-isopropylallylamine **6** with water in the presence of $Li_2PdCl_4/CuCl_2$ at −10°C in DMF, followed by decomplexation of the $CuCl_2$ from the chlorohydroxylation product with excess $Na_2S\cdot 9H_2O$,[12] *N*-benzyl-*N*-isopropyl-2,3-epoxypropylamine **8** was obtained directly with high yield (Scheme 3). In this step, the reaction temperature was the most important factor. If the reaction was operated at a higher temperature, for example, 40°C, only 30% yield of the *N*-benzyl-*N*-isopropyl-2,3-epoxypropylamine **8** was obtained. At the same time, 65% yield of benzylisopropylamine **5** was isolated as a product by deallylation of allylamine **6**.[14]



Scheme 3.

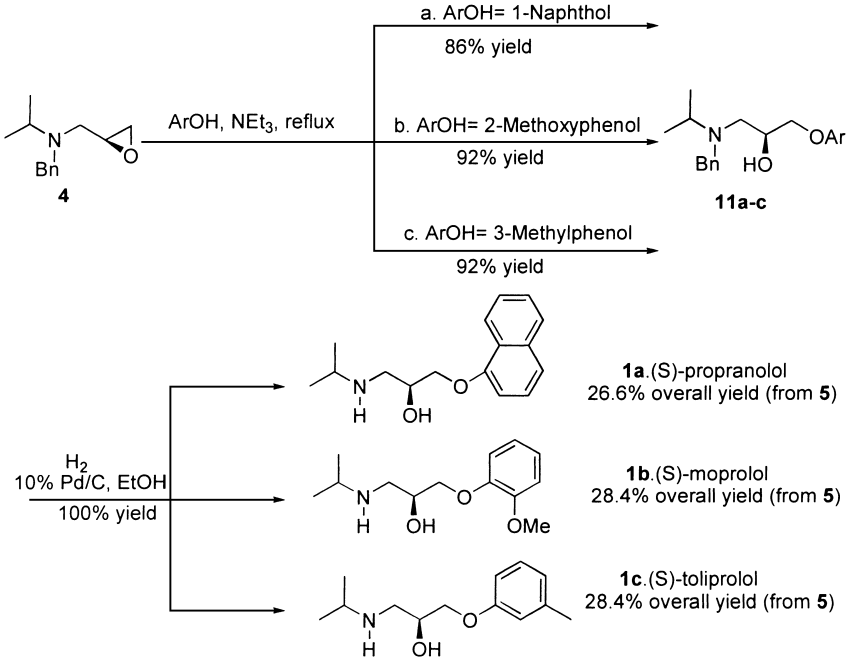
The hydrolytic kinetic resolution of epoxypropylamine **8** was very efficient (Scheme 4). *N*-Benzyl-*N*-isopropyl-2,3-epoxypropylamine **8** was treated with 0.55 equivalents of water catalysed by 0.01 equivalents of (*S*,*S*)-(Salen)Co(III)OAc to provide (*S*)-*N*-benzyl-*N*-isopropyl-2,3-epoxypropylamine **4** with 40% yield (>99% ee) and the diol **9** with 51% yield (90.6% ee).[13] The absolute configuration of the diol **9** was determined as (*R*) by transforming the ring-opened product to the known compound **10**[15] and thus the configuration of the epoxypropylamine **4** must be (*S*). We noted that if the benzylcarbonate protective group (Cbz, $COOCH_2C_6H_5$) replaced the benzyl group (substituent of the nitrogen atom), the hydrolytic kinetic resolution was not so good and only 45% yield of epoxypropylamine **4** was afforded with 47.3% ee. This result means the amino group may play a role in this reaction.

The epoxide ring of the (*S*)-*N*-benzyl-*N*-isopropyl-2,3-epoxypropylamine **4** could not be opened by the aryloxide mediated with $Ti(OPr^i)_4$.[16] We then mixed the epoxypropyl amine **4** and phenol in refluxing NEt_3; (*S*)-3-(aryloxy)-2-hydroxy-1-(*N*-benzyl-*N*-isopropyl)propylamines **11a–c** were obtained with high yield (Scheme 5), and no regioisomers were detected. The enantiomeric excess of the ring-opened products, for example **11c**, were equal to that of the epoxypropylamine **4** (determined by HPLC), which showed that no racemisation had occurred in this step. Debenzylations of the (*S*)-3-(aryloxy)-2-hydroxy-1-(*N*-benzyl-*N*-isopropyl)propylamines **11a–c** were performed by hydrogenolysis catalysed by 10% Pd/C in ethanol with quantitative yield.[17]



Scheme 4.

Thus, β-adrenergic blocking agents **1a–c** were provided in 26.6%, 28.4% and 28.4% overall yields and >99.0% ee, respectively, from benzylisopropylamine **5** in five steps. It should be pointed out that the diol **9** obtained in the kinetic resolution procedure is also an important intermediate. It can be easily transformed by simple manipulation[13e] to the (*R*)-epoxypropylamine **4**, which could be used to prepare other molecules of interest, for example, practolol,[18] another β-adrenergic blocking agent with biological activity residing in the *R* enantiomer.



Scheme 5.

In summary, we have developed a novel and facile method for the synthesis of the enantioenriched (*S*)-β-adrenergic blocking agents. It is noteworthy that water was the reagent used in the second and third steps. This methodology is comparable, if not superior, to the existing repertoire and is attractive on several accounts: it involves a short synthetic sequence, produces uniformly good overall yields, high enantiomeric excess and all the reaction conditions are mild and convenient. No moisture-free, oxygen-free manipulations and hazardous peroxide are involved. Moreover, the synthetic route described here is a general, divergent procedure to a series of β-adrenergic blocking agents.

3. Experimental

3.1. General method

The commercially available reagents were used without further purification. Li_2PdCl_4 and (Salen)-Co(II) were prepared according to the literature procedure.[19,20] ^{1}H NMR spectra were recorded on a Bruker AMX-300 (300 MHz) spectrometer in $CDCl_3$ at room temperature and chemical shifts were expressed in ppm from internal TMS. Mass spectra and high-resolution mass spectra were determined on HP5989A and Finnigan MAT mass spectrometers, respectively. Elemental analyses were performed on a Foss–Heraeus Vario EL instrument. Optical rotations were measured using a Perkin–Elmer 341 polarimeter (concentration c given as g/100 mL). The enantiomeric excess of (*S*)-*N*-benzyl-*N*-isopropyl-2,3-epoxypropylamine **4**, the (*R*)-diol **9** and (*S*)-1-(*N*-benzyl-*N*-isopropylamino)-3-(3-methylphenoxy)-2-propanol **11c** were determined by chiral HPLC on a Chiralcel OJ column. Melting points were uncorrected.

3.2. N-*Benzyl*-N-*isopropylallylamine* ***6***

To a solution of NaOH (2.4 g, 60 mmol) in DMF (10 mL), benzylisopropylamine **5** (4.51 g, 30 mmol) was added, and the mixture was cooled in an ice-water bath. Allyl bromide (3.3 mL, 3.1 g, 40 mmol) in DMF (5 mL) was added over 10 min. The mixture was warmed to room temperature and stirred for 1 h. It was then diluted with ether (100 mL), washed with brine (3×20 mL) and the organic layer was dried (Na_2SO_4), concentrated under reduced pressure and purified by column chromatography over silica gel to give *N*-benzyl-*N*-isopropylallylamine **6** (5.28 g, 93% yield). ^{1}H NMR ($CDCl_3$/TMS, 300 MHz) δ (ppm) 1.10 (d, 6.7 Hz, 6H), 3.02–3.15 (m, 3H), 3.63 (s, 2H), 5.11–5.29 (m, 2H), 5.86–5.95 (m, 1H), 7.26–7.45 (m, 5H). EI-MS *m/z* (%) 189 (M^+, 5.1), 174 (71), 91(100). Anal. calcd for $C_{13}H_{19}N$: C, 82.48; H, 10.12; N, 7.40. Found: C, 82.46; H, 10.47; N, 7.30.

3.3. N-*Benzyl*-N-*isopropyl-2,3-epoxypropylamine* ***8***

To a solution of Li_2PdCl_4 (524 mg, 2 mmol) and $CuCl_2$ (8.07 g, 60 mmol) in DMF (100 mL), the allylamine **6** (3.78 g, 20 mmol) was added at room temperature. After stirring for 15 min, the mixture was cooled to −10°C and water (10 mL) was added in one portion, then CF_3COOH was added to adjust the reaction mixture to pH 4. After the reaction was complete as monitored by TLC, an excess of $Na_2S\cdot 9H_2O$ was added. The mixture was stirred at room temperature overnight, filtered through a pad of Celite and the Celite pad was washed with ether (300 mL). The combined filtrate was washed with brine (100 mL×3), dried over anhydrous Na_2SO_4, and concentrated under vacuum. Purification by flash chromatography provided the *N*-benzyl-*N*-isopropyl-2,3-epoxypropylamine **8** (3.42 g, 83% yield). ^{1}H NMR ($CDCl_3$/TMS, 300 MHz): δ (ppm) 1.05 (d, 6.6 Hz, 3H), 1.09 (d, 6.6 Hz, 3H), 2.41–2.43 (m, 1H), 2.54–2.69 (m, 3H), 2.94–2.99 (m, 1H), 3.09 (m, 6.6 Hz, 1H), 3.56, 3.77 (AB, J_{AB}=14.1 Hz, 2H), 7.24–7.27 (m, 5H). EI-MS *m/z* (%) 205 (M+1, 5.3), 190 (52), 162 (37), 91 (100). Anal. calcd for $C_{13}H_{19}NO$: C, 76.04; H, 9.33; N, 6.83. Found: C, 75.81; H, 9.46; N, 6.87.

3.4. Kinetic resolution

A mixture of (*S*,*S*)-(Salen)Co(II)[20] (60.2 mg, 0.1 mmol) and acetic acid (12 mg, 0.2 mmol) in toluene (2 mL) was stirred under air for 2 hours at room temperature. The solvent was removed under reduced

pressure. The *N*-benzyl-*N*-isopropyl-2,3-epoxypropylamine **8** (2.05 g, 10 mmol) was added in one portion, and to the stirred mixture cooled in an ice-water bath, water (99 mg, 5.5 mmol) was slowly added over 0.5 hour. Then the reaction was stirred at room temperature for 36 hours. The reaction mixture was diluted with ethyl acetate (50 mL), dried over anhydrous Na_2SO_4, and filtered through a pad of activated carbon to remove the colour. The filtrate was concentrated and purified by flash chromatography to give the (*S*)-*N*-benzyl-*N*-isopropyl-2,3-epoxypropylamine **4** (0.826 g, 40% yield) and the (*R*)-diol **9** (1.142 g, 51% yield). Compound **4**: $[\alpha]_D^{20}$=+20.8 (c, 1.0, $CHCl_3$), >99.0% ee (HPLC). Compound **9**:[15] $[\alpha]_D^{20}$=+54.8 (c, 1.45, $CHCl_3$), 90.6% ee (HPLC). ^{1}H NMR ($CDCl_3$/TMS, 300 MHz): δ (ppm) 1.01 (d, 6.6 Hz, 3H), 1.05 (d, 6.7 Hz, 3H), 2.43 (dd, 13.0 Hz, 4.3 Hz, 1H), 2.62 (dd, 13.0 Hz, 8.2 Hz, 1H), 2.92–3.01 (m, 1H), 3.41 (dd, 11.1 Hz, 4.1 Hz, 1H), 3.51–3.70 (m, 4H), 7.22–7.34 (m, 5H). EI-MS *m/z* (%) 223 (M^+, 31), 162 (100), 91 (60).

*3.5. Amino diol diacetate **10**[15]*

To a solution of amino diol **9** (213 mg, 1 mmol) in pyridine (1 mL), Ac_2O (245 mg, 2.4 mmol) was added, and the mixture was stirred for 30 minutes at 60°C. The reaction was diluted with ether (30 mL), washed with 10% NaOH (10 mL), water (10 mL) and brine (10 mL), dried (Na_2SO_4) and concentrated. Flash chromatography afforded **10** (283 mg, 92% yield). $[\alpha]_D^{20}$=−39.5 (c, 1.248, EtOH) (lit. $[\alpha]_D^{20}$=−39.8 (c, 1.25, EtOH, ≅90% ee). ^{1}H NMR ($CDCl_3$/TMS, 300 MHz): δ (ppm) 0.96 (d, 6.6 Hz, 3H), 0.99 (d, 6.6 Hz, 3H), 1.97 (s, 3H), 2.01 (s, 3H), 2.51 (dd, 5.6 Hz, 13.4 Hz, 1H), 2.61 (dd, 7.8 Hz, 13.4 Hz, 1H), 3.54 (d, 14.1 Hz, 1H), 3.65 (d, 14.1 Hz, 1H), 4.06 (dd, 6.0 Hz, 11.9 Hz, 1H), 4.28 (dd, 3.0 Hz, 11.9 Hz, 1H), 7.20–7.28 (m, 5H). EI-MS *m/z* (%) 308 (M+1, 11), 162 (100), 91 (55).

*3.6. General procedure for ring-opening of (*S*)-*N*-benzyl-*N*-isopropyl-2,3-epoxypropylamine **4** with phenols*

To a solution of (*S*)-*N*-benzyl-*N*-isopropyl-2,3-epoxypropylamine **4** (205 mg, 1 mmol) in NEt_3 (5 mL), phenol (1 mmol) was added, and the mixture was refluxed overnight. The solvent was removed under reduced pressure and the residue was purified by flash column chromatography to furnish the corresponding products **11a–c**. Compound **11a**:[21] (86% yield) $[\alpha]_D^{20}$=+28.8 (c, 3.24, EtOH) (lit. $[\alpha]_D^{20}$=+9.2 (c, 3.13, EtOH, about 32% ee). ^{1}H NMR ($CDCl_3$/TMS, 300 MHz): δ (ppm) 1.08 (d, 6.6 Hz, 3H), 1.16 (d, 6.7 Hz, 3H), 2.78 (d, 6.4 Hz, 2H), 3.06–3.10 (m, 1H), 3.62, 3.82 (AB, J_{AB}=13.6 Hz, 2H), 4.08–4.16 (m, 3H), 6.79 (dd, 0.9 Hz, 7.5 Hz, 1H), 7.26–7.51 (m, 9H), 7.80 (d, 7.0 Hz, 1H), 8.19 (d, 9.7 Hz, 1H). EI-MS *m/z* (%) 350 (M+1, 3.3), 162 (100), 91 (69).

Compound **11b**: (92% yield) $[\alpha]_D^{20}$=+35.7 (c, 2.12, EtOH). ^{1}H NMR ($CDCl_3$/TMS, 300 MHz): δ (ppm) 1.04 (d, 6.6 Hz, 3H), 1.09 (d, 6.7 Hz, 3H), 2.66–2.68 (m, 2H), 2.96–3.05 (m, 1H), 3.59, 3.73 (AB, J_{AB}=13.7 Hz, 2H), 3.84 (s, 4H), 3.99 (s, 2H), 6.89–6.94 (m, 4H), 7.25–7.33 (m, 5H). EI-MS *m/z* (%) 330 (M+1, 16.2), 162 (100), 91 (34). EI-HRMS calcd for $C_{20}H_{27}NO_3$: 329.1991; found: 329.1992.

Compound **11c**: (92% yield) $[\alpha]_D^{20}$=+28.7 (c, 1.2, EtOH). ^{1}H NMR ($CDCl_3$/TMS, 300 MHz): δ (ppm) 1.02 (d, 6.6 Hz, 3H), 1.07 (d, 6.7 Hz, 3H), 2.30 (s, 3H), 2.56–2.63 (m, 2H), 2.96–3.00 (m, 1H), 3.55, 3.70 (AB, J_{AB}=13.7 Hz, 2H), 3.86–3.92 (m, 3H), 6.66–6.75 (m, 3H), 7.10–7.31 (m, 6H). EI-MS *m/z* (%) 313 (M^+, 10.0), 162 (100), 91 (85). EI-HRMS calcd for $C_{20}H_{27}NO_2$: 313.2042; found: 313.2024.

3.7. General procedure for debenzylation

A solution of (*S*)-3-(aryloxy)-2-hydroxy-1-(*N*-benzyl-*N*-isopropyl)propylamine **11a**–**c** (1 mmol) and 10% Pd/C catalyst (40 mg) in ethanol (10 mL) was shaken in a Parr series 3900 hydrogenation apparatus at 4 kg/cm^2 hydrogen pressure and 25°C for 24 h. The mixture was filtered through a pad of Celite and concentrated under reduced pressure to provide the corresponding product **1a**–**c** (100% yield).

Compound **1a**:[22] $[\alpha]_D^{20}$=−9.9 (c, 0.5, EtOH) (lit. $[\alpha]_D^{20}$=−10.2 (c, EtOH)); mp: 72–73°C (lit. 72–73°C); ^{1}H NMR ($CDCl_3$/TMS, 300 MHz): δ (ppm) 1.07 (d, 6.0 Hz, 6H), 2.82–2.94 (m, 4H), 4.10–4.18 (m, 3H), 6.80 (d, 7.4 Hz, 1H), 7.34–7.48 (m, 4H), 7.77–7.80 (m, 1H), 8.23–8.26 (m, 1H). EI-MS *m/z* (%) 260 (M+1, 48.7), 72 (100).

Compound **1b**:[23] $[\alpha]_D^{20}$=−5.6 (c, 4.5, EtOH) (lit. $[\alpha]_D^{20}$=−5.3–5.7 (c, 5.0, EtOH)); mp: 80–81°C (lit. 82–83°C); ^{1}H NMR ($CDCl_3$/TMS, 300 MHz): δ (ppm) 1.06 (d, 1.1 Hz, 3H), 1.09 (d, 1.1 Hz, 3H), 1.80–2.87 (m, 5H), 3.85 (s, 3H), 3.98–4.07 (m, 3H), 6.89–6.98 (m, 4H). EI-MS *m/z* (%) 240 (M+1, 100), 72 (77.7).

Compound **1c**:[24] $[\alpha]_D^{20}$=−9.9 (c, 0.83, EtOH) (lit. $[\alpha]_D^{20}$=−9.9 (c, 0.99, EtOH); mp: 76–78°C (lit. 76–77°C); ^{1}H NMR ($CDCl_3$/TMS, 300 MHz): δ (ppm) 1.09 (d, 6.3 Hz, 6H), 2.32 (s, 3H), 2.68–3.20 (m, 5H), 3.90–4.03 (m, 3H), 6.71–6.79 (m, 3H), 7.13–7.18 (m, 1H). EI-MS *m/z* (%) 223 (M^+, 31), 72 (100).

Acknowledgements

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References

1. Stinson, S. C. *C and EN* **1998**, *77 (September 21)*, 83.
2. Silber, B.; Holford, N. H. C.; Riegelman, S. *J. Pharm. Sci*. **1982**, *71*, 699.
3. For example: (a) Matsuo, N.; Ohno, N. *Tetrahedron Lett*. **1985**, *26*, 5533; (b) Wang, Y. F.; Chen, S. T.; Liu, K. K. C.; Wong, C. H. *Tetrahedron Lett*. **1989**, *30*, 1917; (c) Terao, Y.; Murata, M.; Nishino, T.; Kamimura, M. *Tetrahedron Lett*. **1988**, *29*, 5173; (d) Bevinakatti, H. S.; Banerji, A. A. *J. Org. Chem*. **1991**, *56*, 5372; (e) Landner, W. E.; Whitesides, G. M. *J. Am. Chem. Soc*. **1984**, *106*, 7250; (f) Whitesides, G. M.; Lander, W. E. US Patent 4,732,853, 1988; *Chem. Abstr*. **1989**, *110*, 55991e.
4. Larrow, J. F.; Schaus, S. E.; Jacobsen, E. N. *J. Am. Chem. Soc*. **1996**, *118*, 7420.
5. Sasai, H.; Itoh, N.; Suzuki, T.; Shibasaki, M. *Tetrahedron Lett*. **1993**, *34*, 855.
6. For example: (a) Katsuki, T. *Tetrahedron Lett*. **1984**, *25*, 2821; (b) Klunder, J. M.; Ko, S. Y.; Sharpless, K. B. *J. Org. Chem*. **1986**, *51*, 3710; (c) Hanson, R. M.; Ko, S. Y.; Sharpless, K. B. US Patent 4,900,847, 1900; Eur. Patent Appl. EP 197,766, 1986; *Chem. Abstr*. **1987**, *106*, 66494e; (d) Sharpless, K. B.; Onami, J. H. Int. Patent Appl. WO 88 00, 1990, **1988**; *Chem. Abstr*. **1988**, *109*, 54646c.
7. Wang, Z. M.; Zhang, X. L.; Sharpless, K. B. *Tetrahedron Lett*. **1993**, *34*, 2267.
8. For example: Jung, M. E.; Shaw, T. J. *J. Am. Chem. Soc*. **1980**, *102*, 6304; (b) Veloo, R. A.; Koomen, G. J. *Tetrahedron: Asymmetry* **1993**, *4*, 2401; (c) Nakano, J.; Mimura, M.; Hayashida, M.; Kimura, K.; Nakaishi, T. *Heterocycles* **1983**, *20*, 1975.
9. Elks, J.; Ganellin, C. R. *Dictionary of Drugs*; Chapman and Hall: London, 1990.
10. Gowther, A. F.; Gilman, D. J.; Mcloughlin, B. J.; Smith, L. H.; Turner, R. W.; Wood, T. M. *J. Med. Chem*. **1969**, *12*, 638.
11. Kitchin, J.; Bethell, R. C.; Cammack, N.; Dolan, S.; Evans, D. N.; Holman, S.; Holmes, D. S.; McMeekin, P.; Mo, C. L.; Nieland, N.; Orr, D. C.; Saunders, J.; Shenoy, B. E. N.; Starkey, J. D.; Storer, R. *J. Med. Chem*. **1994**, *37*, 3707.
12. Lai, J. Y.; Wang, F. S.; Guo, G. Zh.; Dai, L. X. *J. Org. Chem*. **1993**, *58*, 6944.
13. (a) Tokunaga, M.; Lorrow, J. F.; Kakiuchi, F.; Jacobsen, E. N. *Science* **1997**, *277*, 936; (b) Furrow, M. E.; Schaus, S. E.; Jacobsen, E. N. *J. Org. Chem*. **1998**, *63*, 6776; (c) Savle, P. S.; Lamoreaux, M. J.; Berry, J. F.; Gandour, R. D. *Tetrahedron:*

Asymmetry **1998**, *9*, 1843; (d) Gurjar, M. K.; Sadalapure, K.; Adhikari, S.; Sarma, B.; Talukdar, A.; Chorghads, M. *Heterocycles* **1998**, *48*, 1471; (e) Gurjar, M. K.; Sarma, B.; Sadalapure, K.; Adhikari, S. *Synthesis* **1998**, 1424; (f) Yu, Q.; Wu, Y.; Xia, L. J.; Tang, M. H.; Wu, Y. L. *Chem. Commun.* **1999**, 129.

14. (a) Guibe, F. *Tetrahedron* **1997**, *53*, 13509; (b) Guibe, F. *Tetrahedron* **1998**, *54*, 2967.
15. Ko, S. Y.; Sharpless, K. B. *J. Org. Chem*. **1986**, *51*, 5413.
16. Caron, M.; Sharpless, K. B. *J. Org. Chem*. **1985**, *50*, 1557.
17. Hartung, W. H.; Simonott, R. *Org. React.* **1953**, *VII*, 263.
18. *The Merck Index*, 12th ed.; Budavari, S.; O'Neil, M. J.; Smith, A.; Heckelman, P. E.; Kinneary, J. F., Eds.; Merck: Rahway, NJ, 1321.
19. Cope, A. C.; Friedrich, E. C. *J. Am. Chem. Soc.* **1968**, *90*, 909.
20. Leung, W. H.; Chan, E. Y. Y.; Chow, E. K. F.; Williams, I. D.; Peng, S. M. *J. Chem. Soc., Dalton Trans*. **1996**, 1229.
21. Miyano, S. E.; Lu, L. D. L.; Viti, S. M.; Sharpless, K. B. *J. Org. Chem*. **1985**, *50*, 4350.
22. (a) Howe, R.; Shanks, R. G. *Nature* **1966**, 1336; (b) *The Merck Index*, 12th ed.; Budavari, S.; O'Neil, M. J.; Smith, A.; Heckelman, P. E.; Kinneary, J. F., Eds.; Merck: Rahway, NJ, 1347.
23. (a) Kan, K.; Miyama, A.; Hamoguchi, S.; Ohashi, T.; Watanabe, K. *Agr. Biol. Chem*. **1985**, *49*, 207; (b) *The Merck Index*, 12th ed.; Budavari, S.; O'Neil, M. J.; Smith, A.; Heckelman, P. E.; Kinneary, J. F., Eds.; Merck: Rahway, NJ, 1623.
24. (a) Howe, R.; Rao, B. S. *J. Med. Chem*. **1968**, *11*, 1118; (b) *The Merck Index*, 12th ed.; Budavari, S.; O'Neil, M. J.; Smith, A.; Heckelman, P. E.; Kinneary, J. F., Eds.; Merck: Rahway, NJ, 1071.