Pergamon

Tetrahedron: *Asymmetry* 9 (1998) 3275–3282

TETRAHEDRON: *ASYMMETRY*

A practical synthesis of (*R*)-3-chlorostyrene oxide starting from 3-chloroethylbenzene

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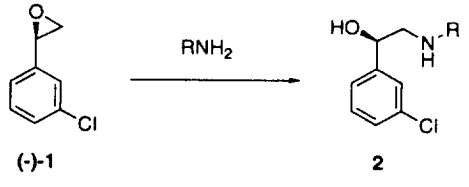
Received 24 July 1998; accepted 12 August 1998

Abstract

A novel and practical synthesis of (*R*)-3-chlorostyrene oxide (−)-**1** was achieved starting from commercially available 3-chloroethylbenzene **3**. Enantiopure (−)-3-chlorostyrene bromohydrin (−)-**5** was obtained by the treatment of racemic (±)-**5** with lipase QL in the presence of acylating reagents. 3-Chloro-α,β-dibromoethylbenzene **4**, a precursor of (±)-**5**, was synthesized via the expeditious bromination of **3** which was developed by these authors.

1. Introduction

Homochiral styrene oxides are important chiral starting materials for the pharmaceutical industry.[1] In particular, (*R*)-3-chlorostyrene oxide (−)-**1** is the common key intermediate for the preparation of several β-3-adrenergic compounds **2** that show antiobesity and antidiabetic activities (Scheme 1).[2]



(-)-1 2

Scheme 1.

To date, many kinds of synthetic methods for the preparation of (−)-**1** in enantiomerically pure or enriched form have been reported. Microbial reduction of α-bromo-3-chloroacetophenone and subsequent treatment with base afforded (−)-**1** in >99% *ee*.[3] Asymmetric reduction of α,3-dichloroacetophenone using an oxazaborolidine-based catalyst and subsequent treatment with base afforded (−)-**1** in 85% *ee*

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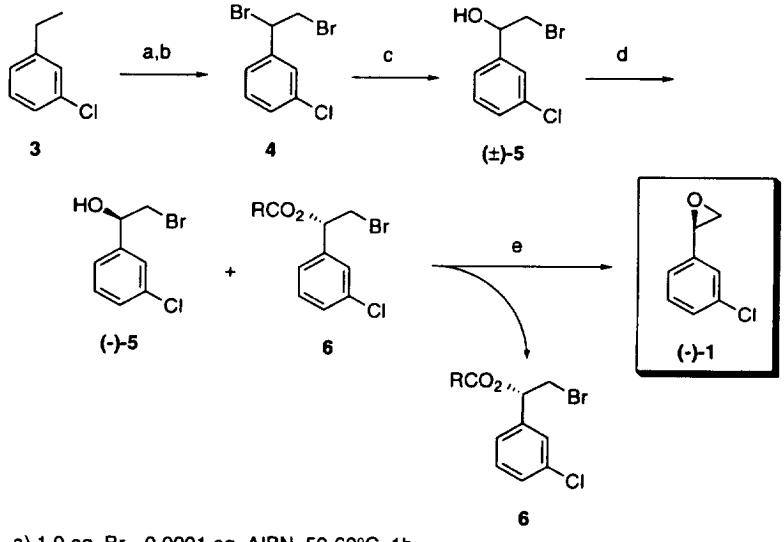
0957-4166/98/$ - see front matter
PII: S0957-4166(98)00337-1

and 36% overall yield from 3-chloroacetophenone.[2b] Asymmetric dihydroxylation of 3-chlorostyrene followed by a stereospecific ring closure afforded (−)-**1** in 98% *ee*.[4] Enzymatic resolution of racemic (−)-**1** has also yielded enantiopure (−)-**1** but in only 5% yield.[5] These syntheses suffer from the problem of using expensive materials and/or low productivity.

Recently we discovered an expeditious synthesis of 3-chloro-α,β-dibromoethylbenzene **4** via bromination of commercially available 3-chloroethylbenzene **3**.[6] This process was expected to present a highly attractive method for the preparation of 3-chlorostyrene bromohydrin (±)-**5**, a key intermediate of (−)-**1**. We describe here a new route to (−)-**1**, which employs readily available materials and is applicable to industrial scale preparation because of its high efficiency.

2. Result and discussion

The whole process is delineated in Scheme 2. The readily available 3-chloroethylbenzene **3** was brominated with 1.0 equiv. of Br_2 in the presence of 0.0001 equiv. of 2,2′-azobis(isobutyronitrile) (AIBN) at 50–60°C for 1 h and was successively brominated with 1.5 equiv. of Br_2 in the presence of 0.0025 equiv. of I_2 at 70°C for 2 h to afford **4** in 95% yield.[6]

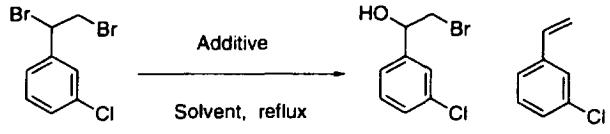


a) 1.0 eq. Br_2, 0.0001 eq. AIBN, 50-60°C, 1h
b) 1.5 eq. Br_2, 0.0025 eq. I_2, 70°C, 2h (95% from **3**, one-pot preparation)
c) H_2O, 0.05 eq. KI, reflux, 32h (74%); d) Lipase catalyzed transesterification (See Table 2-5)
e) Cyclization and separation (See scheme 3)

Scheme 2.

Hydrolysis of dibromide **4** with water was examined under various reaction conditions and the results are illustrated in Table 1. In our initial attempt (entry 1), the result was disappointing because of the low conversion of **4**. The use of DMF and NMP accelerated the conversion of **4**, but the yield of bromohydrin (±)-**5** was quite low (entry 2–5). The addition of KI in DMF–H_2O accelerated the reaction rate, but the predominant formation of 3-chlorostyrene **7** via dehydrobromination of (±)-**5** occurred (entry 6). When the reaction was carried out in only H_2O, the yield of (±)-**5** was increased to 84% (entry 7). Under these conditions, the addition of KI accelerated the reaction rate without the formation of **7**. The use of water as the reaction solvent allowed the easy separation of (±)-**5** without extraction with solvent.

Table 1
Hydrolysis of **4** with water in various reaction conditions



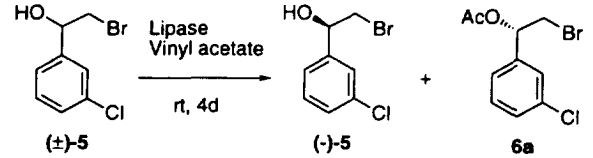
4 (±)-**5** **7**

Entry	Solvent	Additive	Time (h)	Conv. (%)	Yield[c] (±)-5 (%)	Yield[c] 7 (%)
1[a]	70% Acetone-H_2O	-	8	3	2	-
2[a]	50% NMP-H_2O	-	12	90	56	4
3[a]	50% DMF-H_2O	-	8	94	56	2
4[a]	75% NMP-H_2O	-	8	69	34	11
5[a]	25% DMF-H_2O	-	8	39	21	1
6[a]	25% DMF-H_2O	0.02 eq. KI	8	91	41	21
7[b]	H_2O	0.05 eq. KI	32	96	84	0.5

a) 1.0 g of **4** and 10 mL of solvent were used.
b) 1065 g of **4** and 10.5 L of solvent were used.
c) Yields were based on **4**.

Next, we examined the kinetic resolution of (±)-**5** by lipase catalyzed transesterification in organic media. We first explored the resolution of (±)-**5** using different lipases with vinyl acetate[7] at rt and the results are illustrated in Table 2. In this resolution, (+)-**5** was mainly acylated to give acetate **6a** and (−)-**5** remained in low to high enantiomeric purity. Among the lipases examined, lipase QL (*Alcaligenes* sp.) was effective for the resolution of (±)-**5** and (−)-**5** was obtained in 97% *ee* (entry 6).

Table 2
Resolution of (±)-**5** using various lipases with vinyl acetate[a]



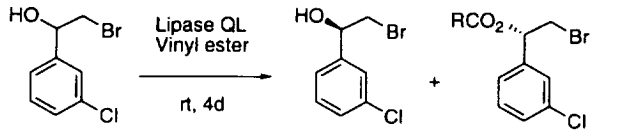
(±)-**5** (-)-**5** **6a**

Entry	Lipase	conv. (%)	(-)-5 ee (%)	E[b]
1	Lipase PS	46	60	11
2	Lipase D	3	2	5
3	Lipase G	3	2	5
4	Lipase AY	9	7	6
5	Nobozym 435	9	7	6
6	Lipase QL	60	97	17

a) 30 mg of (±)-**5**, 1.5 mL of vinyl acetate, and 30 mg of lipases were used.
b) E value[8] $E = \ln[(1-c)(1-ee(S))] / \ln[(1-c)(1+ee(S))]$

It is well known that the variation of acylating reagents may influence the reaction rate as well as enantiomer selectivity.[9] Therefore several vinyl esters[7] were examined to find a more suitable acylating reagent for this resolution with lipase QL. The results are illustrated in Table 3. Among vinyl esters

Table 3
Resolution of (±)-**5** using lipase QL with various vinyl esters[a]



(±)-**5** (-)-**5**

6a R = CH_3
6b R = CH_3CH_2
6c R = $CH_3(CH_2)_4$
6d R = $CH_3(CH_2)_{10}$

Entry	Acylating Reagent	ester **6**	conv. (%)	(-)-**5** ee (%)
1	Vinyl Acetate	**6a**	39	56
2	Vinyl Propionate	**6b**	30	30
3	Vinyl Caproate	**6c**	28	29
4	Vinyl Laurate	**6d**	31	34

a) 100 mg of (±)-**5**, 1.0 mL of vinyl esters, and 10 mg of lipase QL were used.

examined, the use of vinyl acetate exhibited a fast reaction rate in this resolution with lipase QL (entry 1).

The solvent effects were examined for this resolution with lipase QL in the presence of vinyl acetate at 35°C. The results are illustrated in Table 4. Among the solvents examined, the use of *i*-Pr_2O gave a good E value (E=43), but the reaction rate was not fast enough to apply to a practical resolution of (±)-**1** (entry 5).

Table 4
Solvent effect of resolution of (±)-**5** with vinyl acetate[a]

(±)-**5** —(Lipase QL, vinyl acetate, 35°C, 62h)→ (-)-**5** + **6a**

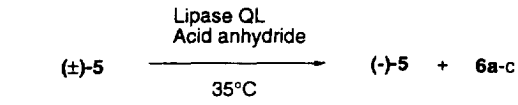
Entry	Solvent	conv. (%)	(-)-**5** ee (%)	E[b]
1	*n*-Heptane	59	88	12
2	Isooctane	58	89	13
3	Toluene	56	88	16
4	*t*-BuOMe	55	97	34
5	*i*-Pr_2O	53	95	43

a) 100 mg of (±)-**5**, 2.0 eq. of vinyl acetate, 10 mg of lipase QL, and 1.0 mL of solvents were used.
b) E value[8] $E = \ln[(1-c)(1-ee(S))] / \ln[(1-c)(1+ee(S))]$

Finally, several acid anhydrides[10] were examined and the results are illustrated in Table 5. Among the acid anhydrides examined, the use of propionic anhydride exhibited a fast reaction rate, especially with *t*-BuOMe as the reaction solvent which gave a high E value (E>116, entry 4).

The isolation method of (−)-**1** is shown in Scheme 3. The racemic alcohol (±)-**5** was reacted with propionic anhydride in the presence of 20% (W/W) lipase QL at 35°C for 24 h to give a mixture of alcohol (−)-**5** and propionate **6b**, and then the mixture was treated with aqueous NaOH to afford a mixture of epoxide (−)-**1** and ester **6b**. Under these reactions conditions, ester **6b** was not hydrolyzed

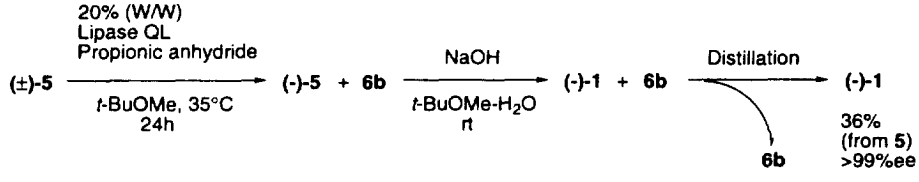
Table 5
Resolution of (±)-**5** using lipase QL with various acid anhydrides



Entry	Acylating Reagent	Solvent	Time (h)	ester **6**	conv. (%)	(-)-**5** ee (%)	E[c]
1[a]	Acetic Anhydride	*i*-Pr_2O	150	**6a**	48	76	23
2[a]	Propionic Anhydride	*i*-Pr_2O	45	**6b**	54	93	29
3[a]	Caproic Anhydride	*i*-Pr_2O	122	**6c**	51	84	25
4[a]	Propionic Anhydride	*t*-BuOMe	45	**6b**	52	>99	>116
5[b]	Propionic Anhydride	*t*-BuOMe	24	**6b**	54	>99	>61

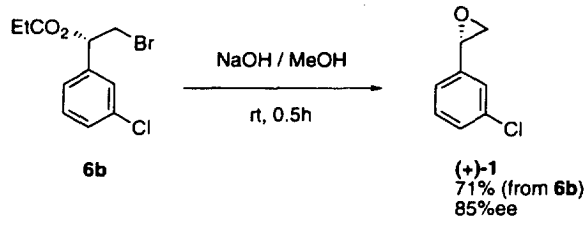
a) 100 mg of (±)-**5**, 0.7 eq. of acid anhydrides, 10 mg of lipase QL and 1.0 mL of solvents were used.
b) 53.8 g of (±)-**5**, 0.7 eq. of acid anhydrides, 10 g of lipase QL and 330 mL of solvents were used.
c) E value[8] E = ln[(1-c)(1-ee(S))] / ln[(1-c)(1+ee(S))]

and the racemization of (−)-**1** did not occur. The epoxide (−)-**1** was separated from the mixture by distillation in >99% *ee* and 36% isolated yield from racemate (±)-**5**.



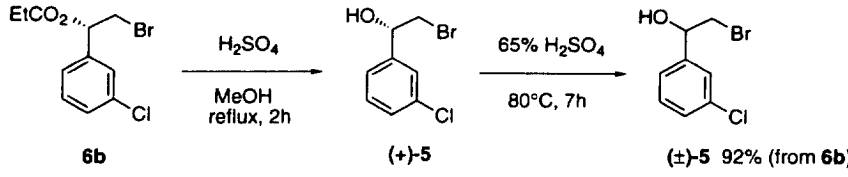
Scheme 3.

The propionate **6b** was treated with NaOH/MeOH at rt to give (+)-**1** in 85% *ee* and 71% isolated yield from **6b** (Scheme 4).



Scheme 4.

The utilization of the ester **6b** is also important for economical reasons. The ester **6b** is treated with MeOH in the presence of H_2SO_4 to give (+)-**5**. The racemization of (+)-**5** was examined in the presence of various acids such as H_2SO_4, CF_3CO_2H, $MeSO_3H$, and CF_3SO_3H. Of these, the use of 65% aqueous H_2SO_4 at 80°C was shown to be best, giving racemic (±)-**5** in high overall yield (92% from **6b**) and with a fast reaction rate (Scheme 5).



Scheme 5.

3. Conclusion

In conclusion, a novel and practical synthesis of (−)-**1** was accomplished starting from commercially available 3-chloroethylbenzene **3**. This method employs readily available materials and proceeds with high efficiency. Also, the overall process does not require restricted reaction conditions. These features make this process applicable to industrial scale preparation of (−)-**1**.

4. Experimental

4.1. General

^{1}H NMR (300 MHz) spectra were recorded on a Varian UNITY 300 spectrometer in $CDCl_3$ solutions, using tetramethylsilane as an internal standard. IR spectra were recorded on JASCO IR-810 spectrophotometer. Reactions and purities were checked by Shimadzu GC-14B gas chromatography using biphenyl as an internal standard (column: SE-30 10%, 4.0 mm×2.0 m; detector: FID; carrier gas: N_2). High performance liquid chromatography (HPLC) was used for the enantiomeric excess analyses of **1**, **5**, **6a** and **6b**. Chiralcel OJ (eluent: *n*-hexane:*i*-PrOH (90:10), 1.0 mL/min; detect: 220 nm) was used for determination of enantiomeric excess for **5**. Chiralcel OJ (eluent: *n*-hexane:*i*-PrOH (95:5), 1.0 mL/min; detect: 220 nm) was used for determination of enantiomeric excess for **6b**. Chiralcel OJ (eluent: *n*-hexane, 1.0 mL/min; detect: 220 nm) was used for determination of enantiomeric excess for **6a**. Chiralpak AD (eluent: *n*-hexane:*i*-PrOH (1000:0.4), 1.0 mL/min; detect: 220 nm) was used for determination of enantiomeric excess for **1**. Specific rotations were recorded on JASCO DIP-370 polarimeter in the indicated solvent.

4.2. Materials

Solvents and materials were industrial grade and used without further purification. Lipase QL was a gift from Meito Sangyo Co. Novozym 435 was a gift from Novo-Nordisk Co. Lipase PS, D, G, and AY were gifts from Amano Pharmaceutical Co.

4.3. 2-Bromo-1-(3-chlorophenyl)ethanol (±)-5

A mixture of **4** (1065 g, purity 88%, 3.14 mol),[6] KI (10.8 g, 65.1 mmol), and H_2O (10.5 L) was refluxed with stirring for 32 h. The reaction mixture was cooled to rt and washed with 5% aqueous $NaHCO_3$ and 10% aqueous NaCl. The lower organic layer was separated to give crude (±)-**5** (yellow oil, 714 g, purity 87%, 2.64 mol, 84% from **4**). The low boiling materials were distilled off from crude (±)-**5** (710 g) at rt to 115°C/0.5 mmHg to afford purified (±)-**5** (yellow oil, 593 g, purity 92%, 2.31 mol, 74% from **4**), which was used in the next step without further purification. The small portion of purified (±)-**5** was subjected to silica gel column chromatography to give pure (±)-**5**. Yellow oil; IR (neat) 3400, 1425, 1195, 1062,

782 cm^{-1}; ^1H NMR δ 2.66 (1H, d, *J*=3.3 Hz), 3.51 (1H, dd, *J*=8.7 and 10.5 Hz), 3.64 (1H, dd, *J*=3.3 and 10.5 Hz), 4.91 (1H, dt, *J*=3.3 and 8.7 Hz), 7.26–7.32 (3H, m), 7.41 (1H, s).

4.4. Lipase catalyzed resolution of bromohydrin (±)-5: typical procedure

Bromohydrin (±)-**5** (1.60 g, 6.79 mmol) was dissolved in vinyl acetate (8.0 mL). After the addition of lipase QL (320 mg), the mixture was stirred at rt for 7 days. The lipase was removed by filtration and the filtrate was concentrated under reduced pressure. The residue was subjected to silica gel column chromatography with *n*-hexane:ethyl acetate (20:1) to give pure (*R*)-2-bromo-1-(3-chlorophenyl)ethanol (−)-**5** (529 mg, 2.25 mmol, 97% ee, 33% from (±)-**5**) and (*S*)-2-bromo-1-(3-chlorophenyl)ethyl acetate **6a** (910 mg, 3.28 mmol, 75% *ee*, 48% from (±)-**5**). (−)-**5**: Yellow oil; $[\alpha]_D^{20}$ −24.3 (*c* 1.05; $CHCl_3$). **6a**: Yellow oil; $[\alpha]_D^{20}$ +34.1 (*c* 1.14; $CHCl_3$); IR (neat) 1755, 1375, 1240, 1210 cm^{-1}; ^1H NMR δ 2.16 (3H, s), 3.57 (1H, dd, *J*=5.1 and 10.8 Hz), 3.63 (1H, dd, *J*=7.5 and 10.8 Hz), 5.93 (1H, dd, *J*=5.1 and 7.5 Hz), 7.22–7.26 (1H, m), 7.31–7.35 (3H, m).

4.5. (R)-3-Chlorostyrene oxide (−)-1 and (S)-2-bromo-1-(3-chlorophenyl)ethyl propionate 6b

Purified (±)-**5** (53.8 g, purity 92%, 0.210 mol) and propionic anhydride (19.5 g, 0.150 mol) were dissolved in *t*-butyl methyl ether (330 mL). After the addition of lipase QL (10 g), the mixture was stirred at 35°C for 24 h. The lipase was removed by filtration and the filtrate was treated with 1N aqueous NaOH (260 g, 0.260 mol) at rt for 2 h. The organic layer was separated and washed with water and brine. The solvent was removed under reduced pressure and the residual oil was purified by bulb to bulb distillation at 60–90°C/0.5 mmHg to give the distillate (15.7 g), which was purified by fractional distillation to afford (−)-**1** boiling at 77–80°C/3.0 mmHg (11.8 g, 76.2 mmol, >99% *ee*, 36% from racemate (±)-**5**). Colorless liquid; $[\alpha]_D^{20}$ −11.1 (*c* 1.23; $CHCl_3$); IR (neat) 3057, 2994, 1600, 1576, 1478, 1198 cm^{-1}; ^1H NMR δ 2.76 (1H, dd, *J*=2.4 and 5.4 Hz), 3.14 (1H, dd, *J*=4.2 and 5.4 Hz), 3.83 (1H, dd, *J*=2.4 and 4.2 Hz), 7.15–7.19 (1H, m), 7.26–7.28 (3H, m).

The residue of the distillation was crude **6b** (32.4 g, purity 83%, 92.3 mmol, 85% *ee*, 44% from racemate **5**). The small portion was purified by silica gel column chromatography to give pure **6b**. Yellow oil; $[\alpha]_D^{20}$ +50.8 (*c* 1.00; $CHCl_3$); IR (neat) 1740, 1170, 1078, 1089 cm^{-1}; ^1H NMR δ 1.18 (3H, t, *J*=7.5 Hz), 2.34–2.54 (2H, m), 3.57 (1H, dd, *J*=5.1 and 10.8 Hz), 3.62 (1H, dd, *J*=7.5 and 10.8 Hz), 5.94 (1H, dd, *J*=5.1 and 7.5 Hz), 7.22–7.28 (1H, m), 7.30–7.35 (3H, m).

Found: C, 45.08; H, 4.16. Calcd for $C_{11}H_{12}BrClO_2$; C, 45.31; H, 4.15.

4.6. (S)-3-Chlorostyrene oxide (+)-1

To a solution of MeOH (100 mL) and NaOH (5.4 g, 135 mmol) was added crude **6b** (20.0 g, purity 81%, 55.8 mmol, 85% *ee*) and the resulting solution was stirred at rt for 0.5 h. The reaction mixture was diluted with water and extracted with ethyl ether. The organic layer was separated and washed with water and brine. The solvent was removed under reduced pressure, and the residue was purified by fractional distillation to afford (+)-**1** boiling at 77–80°C/3.0 mmHg (6.14 g, 39.7 mmol, 85% *ee*, 71% from **6b**). Colorless liquid; $[\alpha]_D^{20}$ +9.4 (*c* 1.07; $CHCl_3$).

4.7. Preparation of 2-bromo-1-(3-chlorophenyl)ethanol (±)-5: by acid catalyzed racemization

MeOH (31 mL) and conc. H_2SO_4 (2.0 mL) were added to **6b** (31.0 g, purity 83%, 88.4 mmol, 85% *ee*) and the resulting mixture was refluxed for 2 h. After cooling, the reaction mixture was quenched by saturated aqueous $NaHCO_3$ and extracted with toluene. The organic layer was separated, washed with brine, and concentrated under reduced pressure to afford the residue (27.0 g). To the residue (14.9 g) was added 65% aqueous H_2SO_4 (15 g) and the mixture was heated with stirring at 80°C for 7 h. After cooling, the reaction mixture was diluted with toluene, the organic layer was separated and washed with water, saturated aqueous $NaHCO_3$, and brine. The solvent was removed under reduced pressure to afford yellow oil (±)-**5** (13.1 g, purity 81%, 45.1 mmol, 0% *ee*, 92% from **6b**).

Acknowledgements

We are grateful to Professor T. Kitahara, The University of Tokyo, for his reviewing of this article. We are also grateful to the members of the Kurosaki Research Center and the Analytical Laboratory in the Yokohama Research Center of the Mitsubishi Chemical Corporation for their expert technical assistance.

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