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Dynamic thermodynamic resolution of *N*-methylpseudoephedrine α-bromo esters for asymmetric syntheses of α-hydroxy carboxylic acid derivatives

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Abstract—An example of dynamic thermodynamic resolution in the nucleophilic substitution reactions of α-bromo esters with an oxygen nucleophile is described. Temperature controlled epimerization–substitution sequence provides a practical protocol for the preparation of highly enantioenriched α-hydroxy carboxylic acid derivatives up to 72% yield with 99:1 er.

1. Introduction

Dynamic thermodynamic resolution has been recently recognized as an effective synthetic method for obtaining highly enantioenriched products from racemic substrates.[1] The difference in the thermodynamic stabilities of two epimeric species under the influence of a chiral reagent is the primary source of asymmetric induction. In addition to the induced thermodynamic resolution, the control of subsequent step for which either the major or the minor epimer is significantly more reactive could present additional opportunities for reinforcing the asymmetric induction. Though dynamic thermodynamic resolution is widely applicable to various kinds of chemical reactions, most of successful examples have been mainly in the area of electrophilic substitution reactions of organolithium nucleophiles.[2] Here we wish to report an example of dynamic thermodynamic resolution in the nucleophilic substitution reactions of α-bromo ester electrophiles for asymmetric syntheses of α-hydroxy carboxylic acid derivatives. Since optically active α-hydroxy carboxylic acids are central structural subunits in numerous biologically interesting natural and unnatural compounds, several efficient chemical and enzymatic methods have been developed for their preparations.[3] For example, asymmetric nucleophilic substitution of α-halo carboxylic acid derivative with oxygen nucleophiles has recently emerged as promising chemical approaches.[3f–h] Our successful results on dynamic resolution of *N*-methylpseudoephedrine α-halo esters in nucleophilic substitution reactions prompt us to extend the methodology to asymmetric syntheses of α-hydroxy carboxylic acid derivatives.[4]

2. Results and discussion

α-Bromo-α-alkyl esters **1**–**4** were prepared by the coupling of (*S*,*S*)-*N*-methylpseudoephedrine and corresponding racemic α-bromo carboxylic acids in 77–85% yields.[5] It was found that α-bromo-α-methyl ester **2** spontaneously epimerized at α-position in solution, while the α-bromo esters **1**, **3** and **4** were configurationally stable in various solvents. When α-bromo-α-methyl ester **2** (α*S*/α*R*=67:33) in CH_3CN was stirred for 1.5 h, spontaneous epimerization provided **2** with a ratio of 80:20 (α*S*/α*R*). In the presence of Et_3N, all α-bromo esters **1**, **2**, **3** and **4** were configurationally labile as shown in Table 1.[6] The treatment of α-bromo esters **1**–**4** with Et_3N in CH_3CN at room temperature induced the thermodynamic equilibrium of two epimers favoring the thermodynamically more stable (α*S*)-epimer.[7] Rate of epimerization and the thermodynamic ratio largely depend on the alkyl group at α-position of the α-bromo esters.[8] α-Bromo-α-ethyl ester **1** equilibrated to a thermodynamic ratio of 89:11 after 20 h. (Table 1, entry 1–4) In the case of α-bromo-α-methyl ester **2**, the equilibration was faster and the thermodynamic ratio was higher as shown in entry 11. α-Bromo esters **3** and **4** reached thermodynamic equilibrium after 24 and 7 h, respectively as shown in entries 14 and 17. The epimerizations were very sensitive to the solvent used as shown in entries 4–7 and 10. Highest ratios were observed with the most polar solvent CH_3CN, while the epimerization in DMF gave a mixture of decomposed α-bromo esters with comparably high ratios. When the epimerization of **1** was executed entirely at 50°C, the thermodynamic equilibrium with 82:18 dr was established

Keywords: dynamic thermodynamic resolution; asymmetric syntheses; α-hydroxy carboxylic acid; chiral auxiliaries; nucleophilic substitution.

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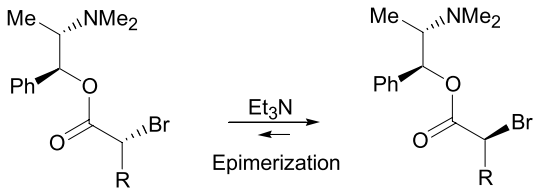
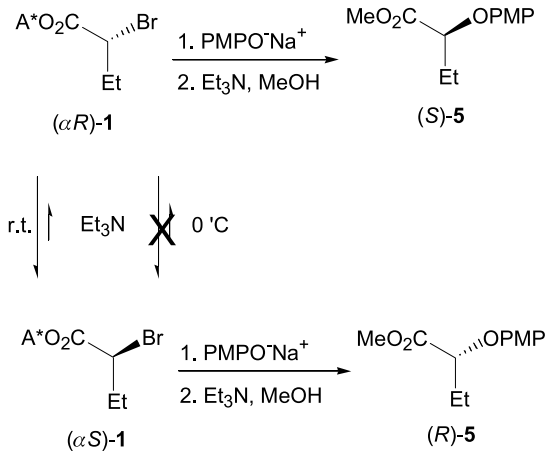
Table 1. Epimerizations of **1**–**4**



Entry	R[a]	Solvent	Temperature	Time (h)	Dr[b] (αS/αR)
1	CH_2CH_3 (**1**)	CH_3CN	Room temperature	2	64:36
2	CH_2CH_3 (**1**)	CH_3CN	Room temperature	4	70:30
3	CH_2CH_3 (**1**)	CH_3CN	Room temperature	20	89:11
4	CH_2CH_3 (**1**)	CH_2Cl_2	Room temperature	20	68:32
5	CH_2CH_3 (**1**)	THF	Room temperature	20	61:39
6	CH_2CH_3 (**1**)	Ether	Room temperature	20	60:40
7	CH_2CH_3 (**1**)	Toluene	Room temperature	20	62:38
8	CH_2CH_3 (**1**)	CH_3CN	50°C	0.5	82:18
9	CH_2CH_3 (**1**)	CH_3CN	0°C	24	51:49
10	CH_3 (**2**)	CH_2Cl_2	Room temperature	20	69:31
11	CH_3 (**2**)	CH_3CN	Room temperature	1	97:3
12	CH_3 (**2**)	CH_3CN	0°C	22	53:47
13	$(CH_2)_3CH_3$ (**3**)	CH_3CN	Room temperature	5	70:30
14	$(CH_2)_3CH_3$ (**3**)	CH_3CN	Room temperature	24	85:15
15	$(CH_2)_3CH_3$ (**3**)	CH_3CN	0°C	24	52:48
16	$(CH_2)_2Ph$ (**4**)	CH_3CN	Room temperature	3	75:25
17	$(CH_2)_2Ph$ (**4**)	CH_3CN	Room temperature	7	80:20
18	$(CH_2)_2Ph$ (**4**)	CH_3CN	0°C	22	50:50

[a] Diastereomeric ratios (Drs) of **1**–**4** before the epimerization are approximately 50:50.
[b] Drs are determined by ^1H NMR.

Table 2. Temperature effect on substitution



A* = (*S*,*S*)-*N*-methylpseudoephedrine
PMP = *p*-methoxyphenyl

Entry	Dr of **1**[a] (αS/αR)	Substitution[b]	% Yield (% conversion)[c]	Er[d] (*R*/*S*)
1	56:44	Room temperature, 3 h	73 (99)	75:25
2	89:11	Room temperature, 3 h	77 (99)	90:10
3	89:11	Room temperature, 0.3 h	21 (34)	89:11
4	82:18	50°C, 0.5 h	54 (99)	82:18
5	50:50	0°C, 1 h	22 (28)	80:20
6	89:11	0°C, 0.5 h	11 (20)	97:3
7	89:11	0°C, 4 h	31 (44)	97:3
8	89:11	0°C, 12 h	69 (89)	94:6
9	89:11	0°C, 20 h	75 (99)	90:10

[a] Diastereomeric ratio of **1** before the addition of $PMPO^-Na^+$.
[b] All reactions were carried in CH_3CN with 1.2 equiv. of nucleophile in the presence of Et_3N.
[c] % Conversions were determined by ^1H NMR of reaction mixture.
[d] The ers are determined by CSP-HPLC (Chiralcel-OD).

very fast (entry 8). The epimerizations of all α-bromo esters **1**, **2**, **3** and **4** are quite slow at 0°C as shown in Table 1, entries 9, 12, 15 and 18.

When α-bromo ester **1** (56:44 dr) was treated with sodium *p*-methoxyphenoxide ($PMPO^-Na^+$) in the presence of Et_3N for 3 h at room temperature, the S_N2 reaction and subsequent methanolysis gave the product **5** with 75:25 enantiomeric ratio (er). (Table 2, entry 1) When **1** was allowed to equilibrate before the addition of nucleophile, the epimerization provided the thermodynamically equilibrated mixture **1** with 89:11 dr (Table 1, entry 3). Following nucleophilic substitution with $PMPO^-Na^+$ provided (*R*)-**5** with 90:10 er after subsequent methanolysis.[9] (Table 2, entry 2) The er of the product **5** was dependent on the starting ratio of two epimers of **1**. If the epimerization is fast with respect to the rate of substitution with the nucleophile then the enantiomeric ratios observed in both entry 1 and entry 2 reactions will be the same, since the stereoselectivity is determined by the difference in the transition states energies of both nucleophilic substitution reactions. The results in entries 1 and 2 indicate that the epimerization of **1** is not fast with respect to their rate of substitution enough to get to thermodynamic equilibrium before the substitution. Almost same enantiomeric ratio (89:11 er) observed at a different conversion implies that no significant kinetic resolution occurs in the reaction with the nucleophile at room temperature.[10] (entry 3) The 75:25 er of **5** from α-bromo esters **1** with 56:44 er might be a consequence of the dynamic epimerization to favor (α*S*)-epimer being competitive with the rate of substitution.[11] At 50°C the substitution provided a product ratio (82:18 er) that reflected the thermodynamic populations of two epimers at 50°C (entry 4).

In an effort to improve the stereoselectivity, we examined the substitution at lower temperature. Since the α-bromo ester **1** is configurationally stable at 0°C (Table 1, entry 9), the product **5** with 89:11 er is necessarily obtained at complete conversion.[12] However, higher ers could be obtained if one diastereomer reacts considerably faster and the reaction is terminated before complete conversion. When **1** (50:50 dr) was treated with $PMPO^-Na^+$ at 0°C and quenched after 1 h (28% conversion), the methanolysis of the reaction mixture gave **5** in 22% yield with 80:20 er. (Table 2, entry 5) The ratio of reactivities of two epimers, selectivity factor ($s=k_R/k_S$), was estimated to be 5.0 at 0°C, which corresponds to a free energy difference of 0.9 kcal/mol at 0°C.[13] The observed kinetic resolution in the reaction with $PMPO^-Na^+$ nucleophile at 0°C may be coupled with the induced thermodynamic resolution to improve the stereoselectivity. When the substitutions of **1** (89:11 dr) were terminated at 20% conversion and at 44% conversion, both reactions gave significantly increased enantiomeric ratio of 97:3 (entries 6 and 7). At 89% conversion, the product **5** was obtained in 69% yield with 94:6 er which is still much higher than the thermodynamic ratio (entry 8). As

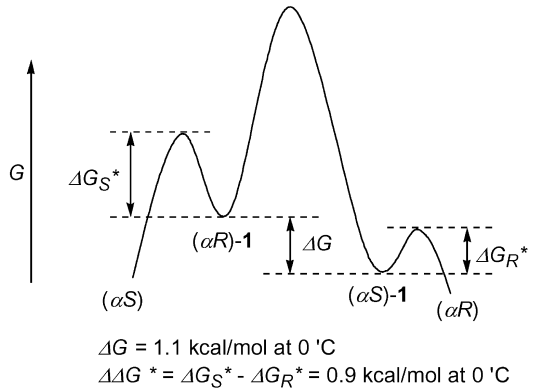
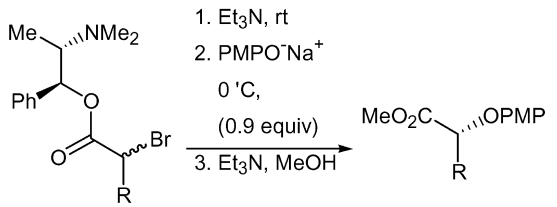


Figure 1. Energy diagram for the reaction of (α*S*)-**1** and (α*R*)-**1** with $PMPO^{-}Na^{+}$ at 0°C.



2 R = Me
3 R = *n*-Bu
4 R = $(CH_2)_2Ph$

(*R*)-**6** R = Me
72% yield, 99:1 er
(*R*)-**7** R = *n*-Bu
67% yield, 98:2 er
(*R*)-**8** R = $(CH_2)_2Ph$,
61% yield, 86:14 er
(at -30 'C,
50% yield, 96:4 er)

Scheme 1. Temperature controlled epimerization-substitution protocol for **2**–**4**.

expected, the product **5** with 90:10 er was obtained at complete conversion (entry 9). These results are summarized in the energy diagram shown in Figure 1.

The scope of the warm–cool methodology was investigated with other α-bromo esters **2**–**4**. Treatment of α-bromo ester **2** with Et_3N in CH_3CN at room temperature provided the thermodynamically equilibrated epimeric mixture with a ratio of 97:3 and subsequent reaction with $PMPO^{-}Na^{+}$ (0.9 equiv. for incomplete conversion) for 14 h at 0°C provided the product **6** with 99:1 er in 72% isolated yield after methanolysis as shown in Scheme 1. This temperature controlled epimerization-substitution protocol is also practical for the preparation of highly enantioenriched product **7** with 98:2 er in 67% yield. However, similar treatment of α-bromo ester **4** (80:20 dr) gave the product **8** in 61% yield with moderately increased er of 86:14. Highly enantioenriched product **8** (96:4 er) was obtained in 50% yield on the treatment of **4** with $PMPO^{-}Na^{+}$ (0.9 equiv.) for 24 h at −30°C.

3. Conclusion

We have described a successful example of a dynamic thermodynamic resolution in the nucleophilic substitution reactions of *N*-methylpseudoephedrine α-bromo esters with an oxygen nucleophile. Preparation of highly enantioenriched α-hydroxy carboxylic acid precursors was achieved using temperature controlled epimerization–substitution protocol. The thermodynamic equilibrium coupled with a kinetic resolution in separate controllable steps can provide for the formation of significantly enantioenriched products from the reaction which may seem to have a low level of stereoselectivity at first sight.

4. Experimental

4.1. General procedure for the preparation of (*S*,*S*)-*N*-methylpseudoephedrine α-bromo-α-alkyl esters 1–4

(*S*,*S*)-*N*-Methylpseudoephedrine (1.0 equiv.), racemic α-bromo carboxylic acid (1.1 equiv.), DCC (1.1 equiv.) and DMAP (0.1 equiv.) were dissolved in dry CH_2Cl_2 and stirred at room temperature for 3 h. The precipitate was filtered off and the organic phase was washed with water. The organic phase was dried over $MgSO_4$, filtered and concentrated to provide the crude product that was purified by column chromatography on silica gel.

4.1.1. *N*-Methylpseudoephedrine 2-bromobutanoate (1). A colorless oil was obtained in 81% yield. ^1H NMR ($CDCl_3$, 400 MHz, two diastereomers) 7.34–7.27 (m, 5H), 5.72, 5.71 (d, *J*=9.0, 9.3 Hz, 1H), 4.25–4.19 (m, 1H), 2.99 (m, 1H), 2.31, 2.30 (s, 6H), 2.17–1.92 (m, 2H), 1.01, 0.96 (t, *J*=7.4, 7.4 Hz, 3H), 0.72, 0.70 (d, *J*=7.3, 7.5 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) 169.1, 138.8, 128.8, 128.6, 127.9, 79.0, 63.1, 48.9, 41.3, 28.8, 12.1, 10.3. Anal. calcd for $C_{15}H_{22}BrNO_2$: C, 54.89; H, 6.76; N, 4.27. Found: C, 54.89; H, 6.89; N, 4.15.

4.1.2. *N*-Methylpseudoephedrine 2-bromopropanoate (2). A colorless oil was obtained in 85% yield. ^1H NMR ($CDCl_3$, 400 MHz, two diastereomers) 7.35–7.29 (m, 5H), 5.72, 5.68 (d, *J*=8.9, 9.2 Hz, 1H), 4.47–4.37 (m, 1H), 3.01 (m, 1H), 2.32, 2.31 (s, 6H), 1.81, 1.80 (d, *J*=5.8, 6.7 Hz, 3H), 0.73, 0.70 (d, *J*=6.8, 6.9 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) 169.6, 138.5, 128.8, 128.6, 127.9, 79.2, 63.2, 41.3, 41.2, 22.2, 10.0. Anal. calcd for $C_{14}H_{20}BrNO_2$: C, 53.51; H, 6.42; N, 4.46. Found: C, 53.44; H, 6.67; N, 4.31.

4.1.3. *N*-Methylpseudoephedrine 2-bromohexanoate (3). A colorless oil was obtained in 83% yield. ^1H NMR ($CDCl_3$, 400 MHz, two diastereomers) 7.35–7.26 (m, 5H), 5.72, 5.71 (d, *J*=9.0, 9.2 Hz, 1H), 4.29–4.23 (m, 1H), 3.00 (m, 1H), 2.31, 2.30 (s, 6H), 2.15–1.91 (m, 2H), 1.47–1.20 (m, 4H), 0.89, 0.85 (t, *J*=6.8, 7.0 Hz, 3H), 0.73, 0.71 (d, *J*=6.8, 6.8 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) 169.3, 138.6, 128.7, 128.6, 127.9, 79.0, 63.1, 47.1, 41.3, 35.2, 29.6, 22.5, 14.2, 10.2. Anal. calcd for $C_{17}H_{26}BrNO_2$: C, 57.31; H, 7.36; N, 3.93. Found: C, 57.31; H, 7.40; N, 3.99.

4.1.4. *N*-Methylpseudoephedrine 2-bromo-4-phenylbutanoate (4). A colorless oil was obtained in 77% yield. ^1H NMR ($CDCl_3$, 400 MHz, two diastereomers) 7.35–7.17 (m, 10H), 5.74, 5.73 (d, *J*=9.2, 9.3 Hz, 1H), 4.26–4.19 (m, 1H), 3.00 (m, 1H), 2.72 (m, 2H), 2.45–2.20 (m, 2H), 2.30, 2.29 (s, 6H), 0.72, 0.70 (d, *J*=7.4, 7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) 169.1, 140.6, 140.5, 138.7, 138.5, 129.0,

128.7, 128.0, 126.7, 79.1, 63.1, 46.2, 41.2, 37.0, 33.5, 9.7. Anal. calcd for $C_{21}H_{26}BrNO_2$: C, 62.38; H, 6.48; N, 3.46. Found: C, 62.25; H, 6.54; N, 3.74.

4.2. General procedure for asymmetric preparation of α-hydroxy carboxylic acid derivatives 5–8

To a solution of (α*RS*)-α-bromo esters in CH_3CN (ca. 0.1 M) at room temperature was added Et_3N (1.1 equiv.). The resulting reaction mixture was stirred at room temperature for an appropriate time, and then $PMPO^-Na^+$ (0.9 equiv.) in CH_3CN was slowly added at 0°C. ($PMPO^-Na^+$ was prepared by adding sodium hydride (1.2 equiv., 60% dispersion in mineral oil, An excess amount of NaH was used for the better yields in substitutions[12]) to a stirred solution of *p*-methoxyphenol (0.9 equiv.) in CH_3CN and stirring for 0.5 h under a nitrogen atmosphere). After 14 h stirring under a nitrogen atmosphere, the mixture was treated with extractive work up and the solvent was evaporated. The crude mixture and Et_3N (0.2 equiv.) in methanol were refluxed for 7 h. The solvent was evaporated and the crude material was purified by column chromatography.

4.2.1. (*R*)-Methyl-2-*p*-anisyloxybutanoate (5). A colorless oil was obtained in 61% yield. ^{1}H NMR ($CDCl_3$, 400 MHz) 6.85–6.79 (m, 4H), 4.48 (t, *J*=6.3 Hz, 1H), 3.76 (s, 3H), 3.74 (s, 3H), 1.96 (m, 2H), 1.07 (t, *J*=7.4 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) 172.9, 154.9, 152.5, 116.9, 115.1, 79.2, 56.1, 52.5, 26.7, 10.1. Anal. calcd for $C_{12}H_{16}O_4$: C, 64.27; H, 7.19. Found: C, 64.28; H, 7.17. The enantiomeric ratio of **5** was determined to be 96:4 in favor of the *R* enantiomer by CSP-HPLC using racemic material as a standard. (Chiralcel OD column; 10% 2-propanol in hexane; 0.5 mL/min; the *R*-enantiomer (major) had a retention time of 13.0 min, and the *S*-enantiomer (minor) had a retention time of 11.1 min.)

4.2.2. (*R*)-Methyl-2-*p*-anisyloxypropanoate (6). A colorless oil was obtained in 72% yield. ^{1}H NMR ($CDCl_3$, 400 MHz) 6.85–6.79 (m, 4H), 4.67 (q, *J*=6.8 Hz, 1H), 3.75 (s, 3H), 3.74 (s, 3H), 1.58 (d, *J*=6.8 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) 173.3, 154.9, 152.1, 116.9, 115.1, 74.0, 56.0, 52.6, 19.0. The spectral data of **6** were identical to those of the authentic material reported previously.[3i] The enantiomeric ratio of **6** was determined to be 99:1 in favor of the *R* enantiomer by CSP-HPLC using racemic material as a standard. (Chiralcel OD column; 10% 2-propanol in hexane; 0.9 mL/min; the *R*-enantiomer (major) had a retention time of 10.8 min, and the *S*-enantiomer (minor) had a retention time of 7.2 min.)

4.2.3. (*R*)-Methyl-2-*p*-anisyloxyhexanoate (7). A colorless oil was obtained in 67% yield. ^{1}H NMR ($CDCl_3$, 400 MHz) 6.84–6.79 (m, 4H), 4.48 (dd, *J*=5.3, 7.5 Hz, 1H), 3.75 (s, 3H), 3.74 (s, 3H), 1.92 (m, 2H), 1.49–1.34 (m, 4H), 0.92 (t, *J*=7.3 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) 173.1, 154.9, 152.5, 116.8, 115.1, 78.1, 56.0, 52.5, 33.1, 27.8, 22.7, 14.3. Anal. calcd for $C_{14}H_{20}O_4$: C, 66.65; H, 7.99. Found: C, 66.67; H, 7.98. The enantiomeric ratio of **7** was determined to be 98:2 in favor of the *R* enantiomer by CSP-HPLC using racemic material as a standard. (Chiralcel OD column; 10% 2-propanol in hexane; 0.5 mL/min; the *R*-enantiomer (major) had a retention time of 12.4 min, and the *S*-enantiomer (minor) had a retention time of 11.1 min.)

4.2.4. (*R*)-Methyl-2-*p*-anisyloxy-4-phenylbutanoate (8). A colorless oil was obtained in 61% yield. ^{1}H NMR ($CDCl_3$, 400 MHz) 7.29–7.18 (m, 5H), 6.83–6.80 (m, 4H), 4.52 (dd, *J*=4.5, 8.4 Hz, 1H), 3.76 (s, 3H), 3.72 (s, 3H), 2.83 (m, 2H), 2.24 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) 172.9, 154.9, 152.3, 141.1, 129.0, 128.9, 126.6, 116.8, 115.1, 76.7, 56.1, 52.7, 34.9, 31.7. The spectral data of **8** were identical to those of the authentic material reported previously.[3h] The enantiomeric ratio of **8** was determined to be 86:14 (96:4 at −30°C substitution) in favor of the *R* enantiomer by CSP-HPLC using racemic material as a standard. (Chiralcel OD column; 10% 2-propanol in hexane; 0.9 mL/min; the *R*-enantiomer (major) had a retention time of 9.2 min, and the *S*-enantiomer (minor) had a retention time of 8.2 min.) The absolute configuration of (*R*)-**8** was assigned by the conversion to methyl-2-hydroxy-4-phenylbutanoate using ceric ammonium nitrate (CAN) and comparison of the well established CSP-HPLC analysis data.[3e] (Chiralcel OD column; 10% 2-propanol in hexane; 1.0 mL/min; the *R*-enantiomer (major) had a retention time of 10.7 min, and the *S*-enantiomer (minor) had a retention time of 8.1 min.)

Acknowledgements

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5. Both (*S*,*S*)- and (*R*,*R*)-*N*-methylpseudoephedrine are commercially available and also can be easily prepared by *N*-methylation of pseudoephedrine with MeI and NaH.
6. It is speculated that the epimerization of α-bromo esters can be promoted by a base via keto–enol tautomerism and the spontaneous epimerization of **2** in the absence of Et_3N is attributed to the internal base on *N*-methylpseudoephedrine.
7. The absolute configurations at α-positions of (α*S*)-**1** and (α*S*)-**2** were assigned by comparison to the ^1H NMR of authentic epimers prepared from commercially available compounds. Those of (α*S*)-**3** and (α*S*)-**4** were assigned by analogy to the formation of (α*S*)-**1** and (α*S*)-**2**.
8. When (1*R*,2*S*)-*N*-methylephedrine was used as a chiral auxiliary, the treatment of the α-bromo-α-methyl ester with Et_3N in CH_3CN for 10 h at room temperature gave no detectable epimerization. Also, we have found that alteration of the alkyl group on the nitrogen of pseudoephedrine has a dramatic effect on the epimerization. Treatment of *N*-benzyl or *N*-allyl pseudoephedrine α-bromo-α-methyl ester with Et_3N in CH_3CN at room temperature gave no detectable epimerization.
9. (a) It has been confirmed that the dr of the precursor of **5** is retained during the methanolysis of the reaction mixture and isolation process to recover **5**. (b) The absolute configuration of (*R*)-**8** was assigned by comparison of CSP-HPLC retention time with the reported value in Ref. 3e. Those of (*R*)-**5**, (*R*)-**6** and (*R*)-**7** were assigned by analogy to the formation of (*R*)-**8**. In each case the minor (*S*)-enantiomer eluted more rapidly than the major (*R*)-enantiomer. See Section 4.
10. The maximum error on all er values, as derived from chiral stationary phase HPLC analysis, is ±1%.
11. Seeman, J. I. *Chem. Rev.* **1983**, *83*, 83.
12. We have found that the α-positions of **1** and the precursor of **5** are configurationally stable under the substitution reaction condition (0°C with Et_3N, $PMPO^-Na^+$ and an excess of NaH in CH_3CN).
13. The selectivity factor (*s*) was estimated using the equation, $s=k_R/k_S=\ln[1-C(1+ee)]/\ln[1-C(1-ee)]$, where ee is the enantiomeric excess of **5** and the conversion (*C*) determined by ^1H NMR of reaction mixture.