N-Methyl Pseudoephedrine-mediated Asymmetric Syntheses of Dihydroquinoxalinones for the Preparation of Flavane Analogues

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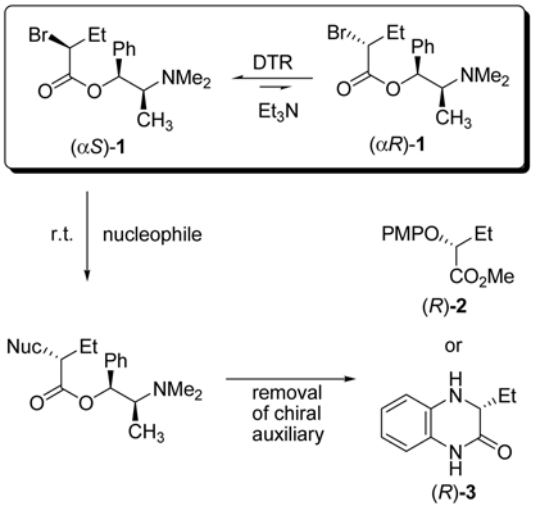
N-Methyl pseudoephedrine mediated asymmetric nucleophilic substitution of α-bromo esters has recently been developed in our laboratory for stereoselective preparation of α-amino, α-mercapto and α-hydroxy carboxylic acids.[1,2] The successful results on dynamic resolution of *N*-methyl pseudoephedrine α-bromo esters prompt us to extend the methodology to asymmetric syntheses of 3-substituted dihydroquinoxalinone derivatives. Since dihydroquinoxalinone core is of interest as an important pharmacophore in many biologically active compounds,[3] substantial progress has been made toward the development of asymmetric synthetic methods for these compounds.[4] Most strategies of previous reports are based on nucleophilic aromatic substitution of *o*-fluoronitrobenzene derivatives with optically pure amino acid derivatives and they are, consequently, limited by the diversity of available optically pure amino acids. Herein we report a novel asymmetric synthetic method for 3-substituted dihydroquinoxalinones *via* dynamic resolution of *N*-methyl pseudoephedrine α-bromo esters in nucleophilic substitution with various symmetric and non-symmetric 1,2-phenylenediamine nucleophiles.

We have previously reported highly stereoselective reactions of (*S,S*)-*N*-methyl pseudoephedrine α-bromo esters with various nitrogen, sufur and oxygen nucleophiles and the primary pathway of the asymmetric induction is a dynamic thermodynamic resolution (DTR) in which the product ratio is determined by the ratio of two epimeric species that is established before the substitution.[5] As shown in Table 1, the reactions of *N*-methyl pseudoephedrine α-bromo-α-ethyl ester (α*RS*)-**1** (56:44 dr) with sodium *p*-methoxyphenoxide ($PMPO^-Na^+$) produced (*R*)-**2** after methanolysis with 75:25 er.[1a] (entry 1) In contrast, when **1** was allowed to equilibrate before the addition of $PMPO^-Na^+$, the epimerization with Et_3N gave the thermodynamically equilibrated mixture (89:11 dr) of **1** and the following substitution provided (*R*)-**2** with 90:10 er after methanolysis (entry 2). The dependency of product ratios on the dr of α-bromo ester implied that the epimerization of **1** is not fast with respect to their rate of substitution enough to get to thermodynamic equilibrium before the substitution. When we used 1,2-phenylenediamine as a nucleophile for asymmetric syntheses of dihydroquinoxalinones, the slow substitution of the weak nucleophile was completed within 3 days (>95% conversion) and spontaneous intramolecular amide formation of the second amino group furnished 3-ethyl dihydroquinoxalinone **3** in 71% yield with 91:9 er (*R:S*).[6] (entry 3) Slower reaction of 1,2-phenylenediamine compared to the reaction of $PMPO^-Na^+$ could provide α-bromo ester **1** more time for epimerization before the substitution and the improved stereoselectivity. The stepwise epimerization-substitution protocol shown in entry 4 provided **3** in 63% yield with an increased er of 98:2. The significant enhancement of product ratio compared to thermodynamic ratio (89:11 dr) of **1** suggest an additional asymmetric induction by dynamic kinetic resolution.[1b,1c]

As shown in Table 2, preliminary studies on solvent effect showed that the substitutions in toluene and diethyl ether proceeded very slowly and gave lower stereoselectivities than in CH_3CN (entries 1 and 2). In *n*-hexane, no detectable amount of product **3** was produced. The substitutions in

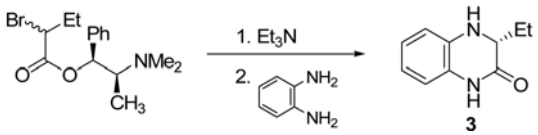
Table 1. Dynamic resolution of α-bromo ester **1**



Entry	Dr of **1**[a]	Nucleophile	Yield (%)[b]	Er[c]
1	56:44	$PMPO^-Na^+$	73 (**2**)	75:25
2	89:11	$PMPO^-Na^+$	77 (**2**)	90:10
3	60:40	1,2-phenylenediamine	71 (**3**)	91:9
4	89:11	1,2-phenylenediamine	63 (**3**)	98:2

[a]Drs were determined by ^{1}H-NMR. [b]Isolated yields. [c]The ers were determined by CSP-HPLC.

Table 2. Asymmetric syntheses of dihydroquinoxalinone **3**



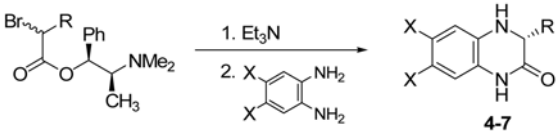
Entry[a]	Substitution Condition[b]	Yield (%)[c]	Er (*R*:*S*)[d]
1	Toluene, Et_3N	21	89:11
2	ether, Et_3N	19	92:8
3	THF, Et_3N	69	97:3
4	$CHCl_3$, Et_3N	72	97:3
5	CH_2Cl_2, Et_3N	70	97:3
6	CH_3CN, Et_3N, TBAI	68	98:2
7	CH_2Cl_2, Et_3N, TBAI	64	96:4

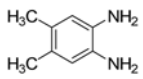
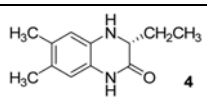
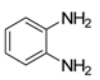
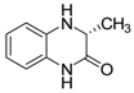
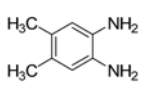
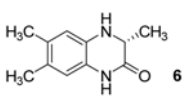
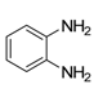
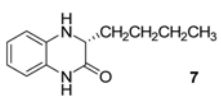
[a]The epimerization was carried out for 20 h in CH_3CN. [b]The substitutions were carried out for 3 days. [c]Isolated yields. [d]The ers were determined by CSP-HPLC (Chiralcel OJ-H).

THF, $CHCl_3$ and CH_2Cl_2 proceeded at about the same rate and stereoselectivity as in CH_3CN (entries 3, 4 and 5). The results seem to indicate that a limiting polarity of the solvent medium exists, beyond which increasing polarity will result in neither improved reaction rate nor improved enantioselectivity. In the presence of tetrabutylammonium iodide (TBAI), no significant differences in reaction rate and enantioselectivity were observed in CH_2Cl_2 and CH_3CN, as shown in entries 6 and 7.[7]

Next, we examined the scope of the epimerization-substitution protocol with various phenylenediamine nucleophiles and α-bromo esters as shown in Table 3. Treatment of thermodynamically equilibrated mixture **1** with 4,5-dimethyl-1,2-phenylenediamine for 72 h at room temperature gave 3-ethyl dihydroquinoxalinone **4** in 72% yield with 95:5

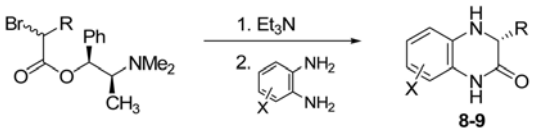
Table 3. Asymmetric syntheses of dihydroquinoxalinones **4-7**

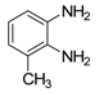
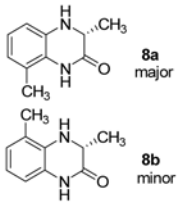
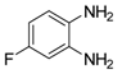
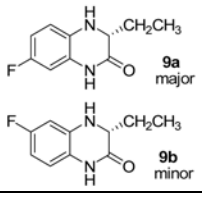


Entry[a]	Nucleophile	R	Product	Yield (%)[b]	Er (*R*:*S*)[c]
1		Et	 **4**	72	95:5
2		Me	 **5**	68	99:1
3		Me	 **6**	67	85:15
4		*n*-Bu	 **7**	76	99:1

[a]All substitutions were carried out in CH_3CN for 3 days. [b]Isolated yields. [c]The ers were determined by CSP-HPLC (Chiralcel OJ-H).

Table 4. Regioselective asymmetric syntheses of dihydroquinoxalinones **8** and **9**



Entry[a]	Nucleophile	R	Products	Yield (%)[b] (major: minor)[c]	Er (*R*:*S*)[d] major: minor
1		Me	 **8a** major **8b** minor	52 (85:15)	94:6, 87:13
2		Et	 **9a** major **9b** minor	66 (87:13)	99:1, 99:1

[a]All reactions were carried out in CH_3CN. [b]Isolated yields. [c]The regioisomeric ratios were determined by ^{1}H-NMR and confirmed by HPLC. [d]The ers were determined by CSP-HPLC (Chiralcel OJ-H for **8** and Chiralcel OB-H for **9**).

er (entry 1). Furthermore, when the equilibrated mixture of α-bromo-α-methyl acetate with a thermodynamic ratio of 98:2 was treated with phenylenediamine, the reaction afforded the 3-methyl dihydroquinoxalinone **5** with higher stereoselectivity (99:1 er, entry 2). As with 4,5-dimethyl-1,2-phenylenediamine nucleophile, however, the reaction in CH_3CN took place to afford dihydroquinoxalinone **6** in 67% yield with much lower stereoselectivity of 85:15 er (entry 3). This methodology is also efficient for the asymmetric preparation of 3-butyl dihydroquinoxalinone **7** with 99:1 er (entry 4).

As shown in Table 4, substitutions of α-bromo esters with non-symmetric phenylenediamine nucleophiles can produce two regioisomeric dihydroquinoxalinones. We initially examined 2,3-diaminotoluene as a nucleophile to understand the effect of *ortho*-substituent of 1,2-phenylenediamine. (entry 1) When the equilibrated mixture of α-bromo-α-methyl ester was treated with the nucleophile, the reaction for 72 h at room temperature gave 3-methyl-8-methyl dihydroquinoxalinone **8a** as a major product with 94:6 er and 3-methyl-5-methyl dihydroquinoxalinone **8b** as a minor product with 87:13 er. The regioselectivity of 85:15 suggests significantly different reactivities of two amino groups. The sterically less hindered amino group of the nucleophile is more reactive than amino group with *ortho*-methyl group. The regioisomer **8a** was assigned as a major isomer by comparison to the ^{1}H-NMR of authentic material individually prepared.[8] Furthermore, we attempted the substitution reaction with 4-fluoro-1,2-phenylenediamine nucleophile and comparable regioselectivity was observed (entry 2). When

the equilibrated mixture of α-bromo-α-ethyl ester was treated with the nucleophile, the reaction for 72 h at room temperature gave 3-ethyl-7-fluoro-dihydroquinoxalinone **9a** as a major product with 99:1 er and 3-ethyl-6-fluoro-dihydroquinoxalinone **9b** as a minor product with 99:1 er. The amino group *para* to the fluorine reacted faster than the amino group *meta* to the fluorine. The regiochemistry of **9** was assigned by comparison to the ^{1}H NMR of authentic material reported previously.[3a] The regiochemical aspects of the preliminary results showed that regioselectivity depends critically on the steric effect of *ortho*- and *meta*-substituents of 1,2-phenylenediamine.

In summary, we have developed *N*-methyl pseudoephedrine mediated asymmetric syntheses of dihydroquinoxalinone derivatives *via* dynamic resolution of α-bromo-α-alkyl esters. The process with mild condition is quite simple and does not rely on the availability of optically pure amino acid derivatives. Further applications of this methodology to the asymmetric syntheses of various kinds of heterocyclic compounds are underway.

Experimental

N-Methyl pseudoehedrine α-bromo acetates were prepared by previously reported methods.[1] ^{1}H and ^{13}C NMR spectra were acquired on Bruker 400 (400 MHz ^{1}H, 100.6 MHz ^{13}C) spectrometer using chloroform-*d* or DMSO-d_6 as the internal standard. Analytical chiral stationary phase HPLC was performed on pump system coupled to absorbance detector (215 nm). Chiralcel OJ-H column (25 cm × 4.6 mm i.d.) and Chiralcel OB-H column (25 cm × 4.6 mm i.d.) with isopropanol/hexane mobile phase were used to determine enantiomeric ratios. The purities (> 95%) of products were estimated by NMR.

General procedure for the preparation of 3-9. To a solution of *N*-methyl pseudoephedrine α-bromo ester in CH_3CN (*ca.* 0.1 M) at room temperature were added Et_3N (1.0 equiv). The resulting reaction mixture was stirred at room temperature for 20 h, and then a 1,2-phenylenediamine (1.5 equiv) was added. After the resulting reaction mixture was stirred at room temperature for 72-96 h, the mixture was quenched with *aq*. 5%-HCl solution. The resulting mixture was extracted with methylene chloride and the combined extracts were washed with brine. The solvent was removed under reduced pressure and the crude material was purified by column chromatography to give a 3-substituted dihydroquinoxalinone.

3-Ethyl-3,4-dihydro-2(*1H*)-quinoxalinone (3). A pale yellow oil was obtained in 63% yield. ^{1}H NMR ($CDCl_3$, 400 MHz) 9.11 (br, 1H), 6.90-6.66 (m, 5H), 3.98 (br, 1H), 3.86 (m, 1H), 1.83 (m, 2H), 1.04 (t, J = 7.4 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) 169.6, 133.5, 125.7, 124.2, 119.6, 115.8, 114.4, 58.0, 25.5, 10.0. Chiral HPLC: 98:2 er, t_R (*R*)-major enantiomer, 30.3 min; t_R (*S*)-minor enantiomer, 31.9 min; (Chiralcel OJ-H column; 10% 2-propanol in hexane; 0.5 mL/min).

6,7-Dimethyl-3-ethyl-3,4-dihydro-2(*1H*)-quinoxalinone (4). A pale yellow oil was obtained in 72% yield. ^{1}H NMR ($CDCl_3$, 400 MHz) 8.44 (br, 1H), 6.51 (s, 1H), 6.49 (s, 1H), 3.80 (m, 2H), 2.15 (s, 6H), 1.79 (m, 2H), 1.02 (t, J = 7.4 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) 169.4, 132.3, 131.1, 127.8, 123.5, 116.9, 116.1, 58.2, 25.2, 19.7, 19.3, 10.1. Chiral HPLC: 95:5 er, t_R (*R*)-major enantiomer, 24.1 min; t_R (*S*)-minor enantiomer, 33.2 min (Chiralcel OJ-H column; 15% 2-propanol in hexane; 0.5 mL/min).

3-Methyl-3,4-dihydro-2(*1H*)-quinoxalinone (5). A white solid was obtained in 68% yield. m.p. 150-151 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) 8.81 (br, 1H), 6.91-6.67 (m, 4H), 4.02 (q, J = 6.6 Hz, 1H), 3.85 (br, 1H), 1.46 (d, J = 6.6 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) 170.1, 133.9, 126.1, 124.2, 120.0, 115.9, 114.5, 52.3, 18.3. The spectral data of **5** were identical to those of the authentic material reported previously.[9a] Chiral HPLC: 99:1 er, t_R (*R*)-major enantiomer, 36.9 min; t_R (*S*)-minor enantiomer, 39.0 min; (Chiralcel OJ-H column; 10% 2-propanol in hexane; 0.5 mL/min).

6,7-Dimethyl-3-methyl-3,4-dihydro-2(*1H*)-quinoxalinone (6). A white solid was obtained in 67% yield. m.p. 195-196 °C; ^{1}H NMR (DMSO-d_6, 400 MHz) 10.02 (br, 1H), 6.51 (s, 1H), 6.48 (s, 1H), 5.69 (br, 1H), 4.11 (br, 1H), 3.68 (m, 1H), 2.06 (s, 3H), 2.05 (s, 3H), 1.23 (d, J = 6.6 Hz, 3H); ^{13}C NMR (DMSO-d_6, 100 MHz) 169.3, 133.1, 130.6, 125.9, 125.0, 116.7, 115.8, 52.0, 19.8, 19.5, 18.1. The spectral data of **6** were identical to those of the authentic material reported previously.[9b] Chiral HPLC: 85:15 er, t_R (*R*)-major enantiomer, 23.3 min; t_R (*S*)-minor enantiomer, 21.6 min; (Chiralcel OJ-H column; 20% 2-propanol in hexane; 0.5 mL/min).

3-Butyl-3,4-dihydro-2(*1H*)-quinoxalinone (7). A colorless oil was obtained in 76% yield. ^{1}H NMR ($CDCl_3$, 400 MHz) 8.84 (br, 1H), 6.90-6.66 (m, 4H), 3.95 (br, 1H), 3.90 (m, 1H), 1.80 (m, 2H), 1.37 (m, 4H), 0.91 (t, J = 7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) 169.6, 133.4, 125.7, 124.2, 119.7, 115.8, 114.5, 56.8, 32.0, 27.9, 22.9, 14.4. The spectral data of **7** were identical to those of the authentic material reported previously.[9c] Chiral HPLC: 99:1 er, t_R (*R*)-major enantiomer, 21.5 min; t_R (*S*)-minor enantiomer, 25.4 min; (Chiralcel OJ-H column; 10% 2-propanol in hexane; 0.5 mL/min).

3-Methyl-8(5)-methyl-3,4-dihydro-2(*1H*)-quinoxalinone (8) The 85:15 mixture of **8a** and **8b** was obtained as a white solid in 52% yield. ^{1}H NMR ($CDCl_3$, 400 MHz) **8a**, 8.11 (br, 1H), 6.80-6.56 (m, 3H), 3.98 (q, J = 6.6 Hz, 1H), 3.83 (br, 1H), 2.25 (s, 3H), 1.46 (d, J = 7.2 Hz, 3H); **8b**, 8.69 (br, 1H), 6.80-6.56 (m, 3H), 4.04 (q, J = 6.6 Hz, 1H), 3,71 (br, 1H), 2.17 (s, 3H), 1.49 (d, J = 6.8 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) **8a**, 169.5, 132.0, 125.7, 125.5, 122.4, 119.4, 113.8, 52.3, 18.5, 17.1. Chiral HPLC: **8a**, 94:6 er, t_R (*R*)-major enantiomer, 65.0 min; t_R (*S*)-minor enantiomer, 69.9 min; **8b**, 87:13 er, t_R (*R*)-major enantiomer; 74.2 min t_R (*S*)-minor enantiomer, 54.6 min (Chiralcel OJ-H column; 5% 2-propanol in hexane; 0.5 mL/min).

3-Ethyl-6(7)-fluoro-3,4-dihydro-2(*1H*)-quinoxalinone (9). The 87:13 mixture of **9a** and **9b** was obtained as a brown oil in 66% yield. ^{1}H NMR (DMSO-d_6, 400 MHz) **9a**, 10.26 (br, 1H), 6.70-6.51 (m, 3H), 5.95 (s, 1H), 3.63 (m,

1H), 1.61 (m, 2H), 0.92 (m, 3H); **9b**, 10.20 (br, 1H), 6.70-6.51 (m, 3H), 6.30 (s, 1H), 3.75 (m, 1H), 1.61 (m, 2H), 0.92 (m, 3H). The spectral data of **9a** and **9b** were identical to those of the authentic material reported previously.[3a] Chiral HPLC: **9a**, 99:1 er, t_R (*R*)-major enantiomer, 29.0 min; t_R (*S*)-minor enantiomer, 40.5 min; **9b**, 99:1 er, t_R (*R*)-major enantiomer, 36.2 min; t_R (*S*)-minor enantiomer, 32.1 min (Chiralcel OB-H column; 10% 2-propanol in hexane; 0.5 mL/min).

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References and Notes

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