HETEROCYCLES, Vol. 78, No. 9, 2009, pp. 2233 - 2244. © The Japan Institute of Heterocyclic Chemistry
Received, 9th March, 2009, Accepted, 11th May, 2009, Published online, 11th May, 2009.
DOI: 10.3987/COM-09-11700

(*S*)-MANDELATE-MEDIATED DYNAMIC KINETIC RESOLUTION OF α-BROMO ESTERS FOR ASYMMETRIC SYNTHESES OF AMINOFLAVONES, DIHYDROQUINOXALINONES AND DIHYDROBENZOXAZINONES

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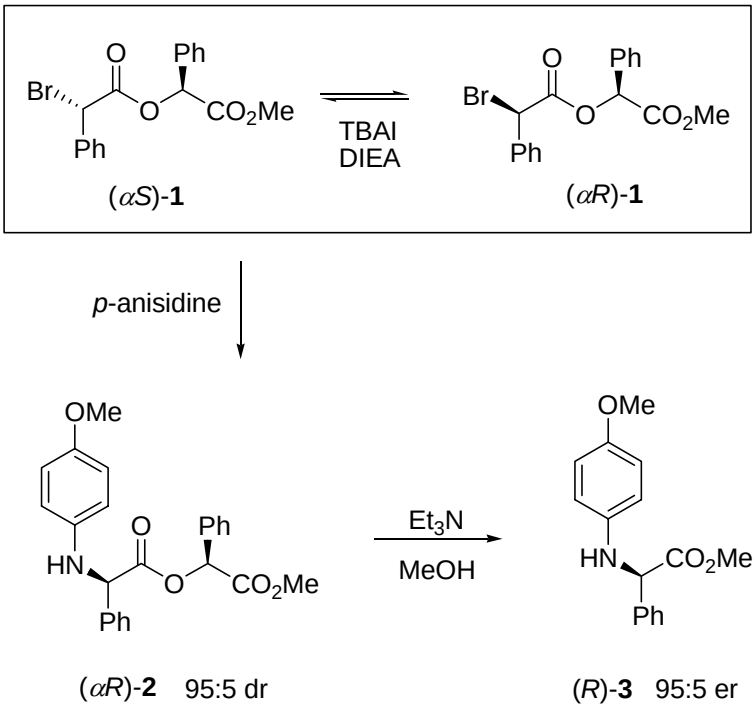
Abstract – (*S*)-Mandelate-mediated dynamic kinetic resolution of α-bromo esters in nucleophilic substitution reaction has been investigated. Reactions of various aryl amine nucleophiles in the presence of TBAI and DIEA can provide the substitution products **2** and **7-19** up to 95% yield and 96:4 dr. Also, the simple procedure with spontaneous removal of the chiral auxiliary provides a practical protocol for asymmetric syntheses of dihydroquinoxalinones **20**-**26** and dihydrobenzoxazinones **27-30** up to 97:3 er.

INTRODUCTION

Chiral auxiliary mediated dynamic resolution of α-haloacyl compounds has been recently developed as an effective synthetic method for asymmetric syntheses of α-substituted carboxylic acid derivatives.[1] Although a high level of stereoselectivity in the dynamic resolution is achieved by several chiral auxiliaries, it is still desirable to find effective chiral auxiliaries amenable to easily scalable processes under mild and simple reaction conditions. Herein we report the first successful example of (*S*)-mandelate-mediated dynamic kinetic resolution of α-bromo esters in nucleophilic substitution with various aryl amines.

RESULTS AND DISCUSSION

Treatment of methyl (*S*)-mandelate with racemic α-bromo-α-phenylacetic acid in the presence of DCC and DMAP provided α-bromo-α-phenyl ester (α*RS*)-**1** in 69% yield with 50:50 diastereomeric ratio (dr). When the two diastereomeric mixture of (α*RS*)-**1** was treated with *p*-anisidine (*p*-MeOPhNH$_2$, 1.5 equiv), tetrabutylammonium iodide (TBAI, 1.0 equiv) and diisopropylethylamine (DIEA, 1.0 equiv) in CH_2Cl_2 at



Scheme 1. (*S*)-Mandelate-mediated asymmetric nucleophilic substitution

room temperature for 12 h, the amino acid derivative **2** was produced in 86% yield with 95:5 dr as shown in Scheme 1. Subsequent removal of the chiral auxiliary with MeOH and Et_3N gave *N*-aryl phenylglycinate (*R*)-**3** in 88% yield with 95:5 enantiomeric ratio (er).[2] The results imply that α-bromo stereogenic center is configurationally labile with respect to the rate of substitution and (α*RS*)-**1** is dynamically resolved under the reaction condition.

In order to understand the reaction pathway and the origin of stereoselectivity, we carried out a series of reactions as shown in Table 1. When the mixture of two epimers of **1** (50:50 dr or 70:30 dr) was allowed to reach thermodynamic equilibrium in the presence of TBAI and DIEA, the epimeric ratio of recovered **1** was analyzed by ^{1}H NMR, and determined to be 51:49 in both cases. (entries 1 and 2) These results indicate that α-bromo ester **1** is configurationally labile under the reaction condition and the

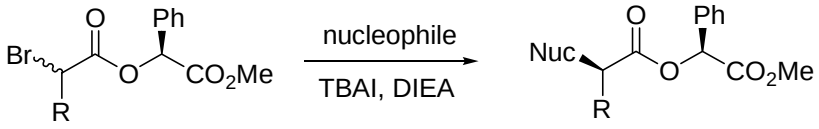
Table 1. Dynamic kinetic resolution of α-bromo ester **1**

Entry	Substrate (Dr)[a]	Condition[b]	Product (Dr)[a]
1	**1** (50:50)	DIEA, TBAI	**1** (51:49)
2	**1** (70:30)[c]	DIEA, TBAI	**1** (51:49)
3	**1** (71:29)[c]	DIEA, TBAI, *p*-anisidine	**2** (95:5)
4	**2** (83:17)[c]	DIEA, TBAI, *p*-anisidine	**2** (83:17)

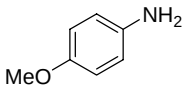
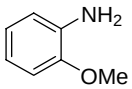
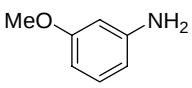
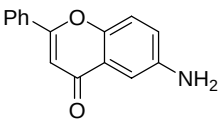
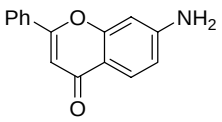
(a) The drs are determined by ^{1}H NMR. (b) The reactions were carried out in CH_2Cl_2. (c) The mixtures are prepared by column chromatography with fractional collection.

thermodynamic stabilities of two epimers are almost same, ruling out dynamic thermodynamic resolution (DTR) as a primary pathway.[3] In the reaction of **1** (71:29 dr) with *p*-anisidine, DIEA and TBAI as shown in entry 3, same dr of **2** (95:5 dr) was observed as in the reaction of **1** of 50:50 dr. Thus, the dr of product **2** is not dependent on the starting ratio of two epimers of **1**. When the configurational stability of **2** (83:17 dr) was examined by the treatment with *p*-anisidine (1.5 equiv), TBAI (1.0 equiv) and DIEA (1.0 equiv) in CH_2Cl_2 for 24 h, no epimerization was detected by ^{1}H-NMR, which can rule out the possibility of epimerization after the nucleophilic substitution reaction. (entry 4) These preliminary results indicate that the epimerization promoted by TBAI and DIEA is sufficiently fast with respect to the rate of substitution and the primary pathway of the asymmetric induction is a dynamic kinetic resolution (DKR).

Table 2. Reactions of **1** and **4-6** with various aryl amine nucleophiles



1, **4-6** **2**, **7-19**

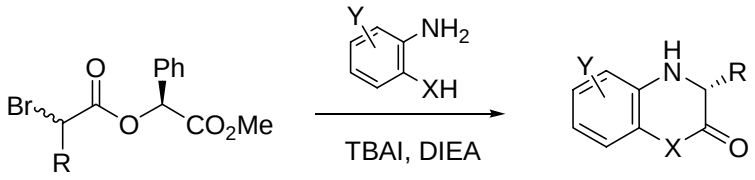
Entry[a]	R	Nucleophile	%Yield[b]	Dr[c]
1	Ph (**1**)		93 (**2**)	96:4
2	Me (**4**)		88 (**7**)	90:10
3	Et (**5**)		95 (**8**)	91:9
4	*n*-Bu (**6**)		82 (**9**)	90:10
5	Ph (**1**)		83 (**10**)	93:7
6	Me (**4**)		70 (**11**)	86:14
7	Ph (**1**)		80 (**12**)	96:4
8	Me (**4**)		73 (**13**)	88:12
9	Et (**5**)		78 (**14**)	90:10
10	*n*-Bu (**6**)		61 (**15**)	89:11
11	Ph (**1**)		53 (**16**)	94:6
12	Me (**4**)		42 (**17**)	85:15
13	Et (**5**)		51 (**18**)	85:15
14	Ph (**1**)		33 (**19**)	87:13

(a) The reactions were carried out in MeCN. (b) Isolated yields. (c) The drs are determined by ^{1}H NMR of reaction mixture.

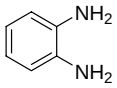
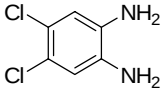
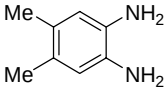
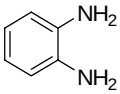
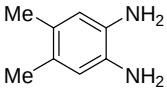
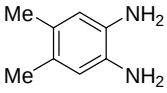
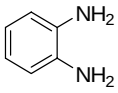
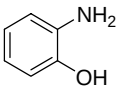
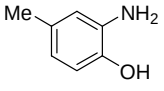
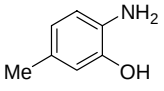
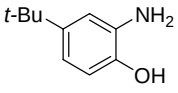
The scope of the dynamic kinetic resolution has been investigated with various aryl amines in MeCN as shown in Table 2. The treatment of **1** with *p*-anisidine (1.5 equiv) in MeCN for 24 h at room temperature gave **2** in 93% yield with 96:4 dr. (entry 1) Under the same reaction condition, the reactions of α-alkyl α-bromoacetates **4-6** gave amino esters **7-9** with slightly lower drs.[4] (entry 2-4) In the reactions with two different anisidines, similar stereoselectivities were obtained with *m*-anisidine (entries 7-10), whereas *o*-anisidine gave slightly lower stereoselectivities (entries 5-6). In our continuing investigation on the stereoselective preparation of flavonoid derivatives and their activity studies,[5] we have attempted to synthesize enantioenriched *N*-carboxyalkylated flavones **16-19** as shown in entries 11-14. When α-bromoacetate **1** was treated with 6-aminoflavone, DIEA and TBAI for 24 h, the substitution provided **16** in 53% yield with 94:6 dr. Analogous to the reactions with *p*-anisidine, the reaction of α-alkyl α-bromoacetates **4** and **5** with 6-aminoflavone gave lower selectivity of 85:15 dr. (entries 12 and 13) The substitution of **1** with 7-aminoflavone, however, was slower than the reaction with 6-aminoflavone under the same condition (entry 14) and the reactions of **4-6** with 7-aminoflavone did not provide the substituted products. Limited results indicate that the substituents of aryl amine nucleophile may have a little effect on stereoselectivity, but that it significantly affected the rate of substitution.

Encouraged by the high enantioselectivities in the reactions of α-bromo acetates **1** and **4-6** with various aryl amines, we set out to examine the DKR in substitutions with 1,2-diaminobenzene and 2-aminohydroxybenzene nucleophiles for asymmetric syntheses of dihydroquinoxalinones and dihydrobenzoxazinones as shown in Table 3. Dihydroquinoxalinone and dihydrobenzoxazinone structural cores are of interest as important pharmacophores in many biologically active compounds and there is growing interest in the asymmetric preparation of them.[6,7] When α-bromo-α-phenylacetate **1** was treated with 1,2-phenylenediamine, TBAI and DIEA in MeCN for 24 h at room temperature, the substitution and following spontaneous cyclization gave 3-phenyl dihydroquinoxalinone **20-22** in 92-87% yields with 97:3-94:6 ers. (entries 1-3) As with α-alkyl-α-bromoacetates **4-6**, the reactions in MeCN took place to afford 3-alkyl substituted dihydroquinoxalinones **23-26** with slightly lower stereoselectivities of 92:8-87:13 ers. (entries 4-7) In addition, we were very pleased to demonstrate that this methodology is also efficient for the asymmetric preparation of 3-phenyl dihydrobenzoxazinones **27-30** with high selectivities and good yields as shown in entries 8-11. For example, when α-bromo-α-phenylacetate **1** was treated with 2-aminophenol in CH_2Cl_2 for 6 h, dihydrobenzoxazinone **27** was obtained in 71% yield with 91:9 er. Also, the reactions of **1** with various substituted 2-aminophenols produced dihydrobenzoxazinones **28-30** with similar yields and enantioselectivities. Curiously, when the reactions were carried out in MeCN, **27-30** were obtained with lower yields (50-40%) and enantioselectivities (88:12-81:19 er) compared to the reaction in CH_2Cl_2.

Table 3. Asymmetric syntheses of dihydroquinoxalinones and dihydrobenzoxazinones

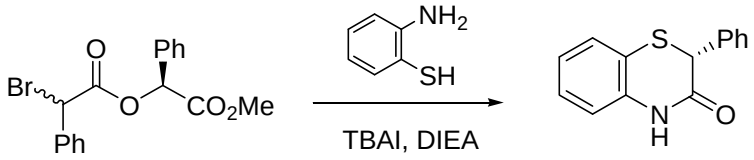


1, **4-6** X = NH, O **20-30**

Entry[a]	R	Nucleophile	%yield[b]	er (*R*:*S*)[c]
1	Ph		92 (**20**)	96:4
2	Ph		87 (**21**)	97:3
3	Ph		90 (**22**)	94:6
4	Me		79 (**23**)	89:11
5	Me		88 (**24**)	87:13
6	Et		81 (**25**)	92:8
7	*n*-Bu		71 (**26**)	90:10
8	Ph		71 (**27**)	91:9
9	Ph		79 (**28**)	90:10
10	Ph		68 (**29**)	90:10
11	Ph		80 (**30**)	91:9

(a) The reactions were carried out in MeCN for **20-26** and CH_2Cl_2 for **27-30**. (b) Isolated yields. (c) The ers are determined by CSP-HPLC (Chiralcel OJ-H column for **20-26** and OD column for **27-30**).

Next, we tested the stereocontrolling ability of mandelate in nucleophilic substitution with a 2-aminothiophenol. Treatment of α-bromo-α-phenylacetate **1** with 2-aminothiophenol in the presence of TBAI and DIEA gave no amino-substituted product and instead produced thio-substituted product, dihydrobenzothiazinone **31** in 85% yield with 69:31 dr as shown in Scheme 2. The low selectivity observed in the reaction of the thiol nucleophile might be attributed to their incapability for the hydrogen bonding interaction. It is well known that the origin of the high diastereoselectivity in the reactions of α-haloacyl compounds with amine nucleophiles is due essentially to the formation of an intermolecular hydrogen bond that facilitates delivery of the nucleophile.[1a,1h,1i]



1 **31** 69:31 er

Scheme 2. Synthesis of a dihydrobenzothiazinone

We conclude that (*S*)-mandelate is an effective and convenient chiral auxiliary for dynamic kinetic resolution of α-bromo esters in nucleophilic substitution with aryl amines. The methodology can provide a general procedure for asymmetric syntheses of (*R*)-dihydroquinoxalinones and (*R*)-dihydrobenzoxazinones. Since both enantiomers of mandelic acid are readily available, this method enables one to prepare (*S*)-products as well. Simple and easy procedure in obtaining optically active *N*-aryl amino acid derivatives suggests that this DKR approach should be further developed.

EXPERIMENTAL

(*S*)-Mandelic acid derived α-bromoacetates **1** and **4-6** were prepared by the coupling reaction of methyl mandelate and α-bromoacetic acid derivatives with DCC and DMAP.[1i] ^{1}H and ^{13}C NMR spectra were acquired on Bruker 400 (400MHz ^{1}H, 100.6MHz ^{13}C) spectrometer using chloroform-*d* or DMSO-d_6. The purities (>95%) of products were estimated by ^{13}C NMR. Analytical chiral stationary phase (CSP) HPLC was performed on pump system coupled to absorbance detector (215nm). Chiralcel OJ-H column (25cm×4.6mm i.d.) and Chiralcel OD column (25cm×4.6mm i.d.) with isopropanol/ hexane mobile phase were used to determine enantiomeric ratios.

General procedure for asymmetric nucleophilic substitution of α-bromo esters: To a solution of α-bromoacetate (1.0 mmol) in CH_2Cl_2 or MeCN (*ca.* 0.1 M) at rt were added DIEA (1.0 equiv), TBAI (1.0 equiv) and an aryl amine nucleophile (1.5 equiv). After the resulting reaction mixture

was stirred at rt for 6-24 h, the solvent was removed under reduced pressure and the crude material was purified by column chromatography to give a product.

2-Methoxy-2-oxo-(*S*)-1-phenylethyl 2-(*p*-methoxyanilino)-(*R*)-phenylacetate (2) A yellow oil was obtained in 86% yield. ^{1}H NMR ($CDCl_3$, 400 MHz, major diastereomer) 7.47 (m, 2H), 7.28 (m, 8H), 6.71 (d, J = 8.9 Hz, 2H), 6.56 (d, J = 8.9 Hz, 2H), 5.93 (s, 1H), 5.22 (d, J = 4.8 Hz, 1H), 4.60 (d, J = 4.8 Hz, 1H), 3.66 (s, 3H), 3.65 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz, major diastereomer) 171.9, 169.2, 153.1, 140.6, 137.6, 133.7, 129.6, 129.3, 129.1, 128.9, 127.9, 127.7, 115.3, 75.5, 62.1, 56.1, 53.2. For removal of chiral auxiliary, the mixture of 2 and Et3N (10 equiv) in MeOH (0.05 M) was stirred at rt for 1 day. The solvent was evaporated and the crude material was purified by column chromatography to give (*R*)-**3** in 88% yield. ^{1}H NMR ($CDCl_3$, 400 MHz) 7.48-7.25 (m, 5H), 6.69 (d, J = 8.9 Hz, 2H), 6.52 (d, J = 8.9 Hz, 2H), 5.00 (s, 1H), 4.67 (br, 1H), 3.72 (s, 3H), 3.67 (s, 3H). The spectral data of **3** were identical to those of the authentic material reported in ref. 1e. Chiral HPLC: 95:5 er, t_R (*S*)-minor enantiomer, 73.7 min; t_R (*R*)-major enantiomer, 65.9 min; (Chiralcel OJ-H column; 20% 2-propanol in hexane; 0.5 mL/min).

2-Methoxy-2-oxo-(*S*)-1-phenylethyl 2-(*p*-methoxyanilino)-(*R*)-propionate (7) A colorless oil was obtained in 88% yield. ^{1}H NMR ($CDCl_3$, 400 MHz, major diastereomer) 7.43-7.34 (m, 5H), 6.75 (d, J = 8.8 Hz, 2H), 6.60 (d, J = 8.8 Hz, 2H), 5.96 (s, 1H), 4.22 (q, J = 6.8 Hz, 1H), 3.93 (s, 1H), 3.69 (s, 3H), 3.64 (s, 3H), 1.47 (d, J = 7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz, major diastereomer) 174.6, 169.4, 153.2, 141.1, 134.1, 129.7, 129.3, 128.1, 115.5, 115.3, 75.1, 56.1, 53.4, 53.1, 19.3.

2-Methoxy-2-oxo-(*S*)-1-phenylethyl 2-(*p*-methoxyanilino)-(*R*)-butanoate (8) A colorless oil was obtained in 95% yield. ^{1}H NMR ($CDCl_3$, 400 MHz, major diastereomer) 7.42-7.32 (m, 5H), 6.75 (d, J = 8.8 Hz, 2H), 6.61 (d, J = 8.8 Hz, 2H), 5.96 (s, 1H), 4.09 (t, J = 6.3 Hz, 1H), 3.87 (br, 1H), 3.69 (s, 3H), 3.64 (s, 3H), 1.95-1.77 (m, 2H), 0.99 (t, J = 7.4 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz, major diastereomer) 174.0, 169.4, 153.2, 141.3, 134.1, 129.7, 129.2, 128.1, 115.5, 115.1, 75.0, 59.1, 56.1, 53.0, 26.7, 10.5.

2-Methoxy-2-oxo-(*S*)-1-phenylethyl 2-(*p*-methoxyanilino)-(*R*)-hexanoate (9) A colorless oil was obtained in 82% yield. ^{1}H NMR ($CDCl_3$, 400 MHz, major diastereomer) 7.36 (m, 5H), 6.76 (d, J = 8.9 Hz, 2H), 6.62 (d, J = 8.9 Hz, 2H), 5.96 (s, 1H), 4.13 (t, J = 6.5 Hz, 1H), 3.88 (br, 1H), 3.70 (s, 3H), 3.65 (s, 3H), 1.88-1.75 (m, 2H), 1.41-1.28 (m, 4H), 0.85 (t, J = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz, major diastereomer) 174.2, 169.3, 153.2, 141.3, 134.2, 129.8, 129.3, 127.9, 115.5, 115.3, 75.1, 58.0, 56.1, 53.0, 33.3, 28.1, 22.9, 14.3.

2-Methoxy-2-oxo-(*S*)-1-phenylethyl 2-(*o*-methoxyanilino)-(*R*)-phenylacetate (10) A yellow oil was obtained in 83% yield. ^{1}H NMR ($CDCl_3$, 400 MHz, major diastereomer) 7.52-7.26 (m, 10H), 6.75 (m, 2H), 6.67 (m, 1H), 6.47 (m, 1H), 5.94 (s, 1H), 5.40 (d, J = 6.0 Hz, 1H), 5.28 (d, J = 6.0 Hz, 1H), 3.83 (s,

3H), 3.68 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz, major diastereomer) 171.6, 169.2, 147.5, 137.5, 136.4, 133.7, 129.5, 129.3, 129.1, 128.8, 127.9, 127.6, 121.5, 118.0, 111.3, 110.0, 75.5, 61.2, 55.9, 53.1.

2-Methoxy-2-oxo-(*S*)-1-phenylethyl 2-(*o*-methoxyanilino)-(*R*)-propionate (11) A colorless oil was obtained in 70% yield. ^{1}H NMR ($CDCl_3$, 400 MHz, major diastereomer) 7.41-7.35 (m, 5H), 6.85-6.75 (m, 2H), 6.71 (d, J = 7.5 Hz, 1H), 6.63 (d, J = 7.6 Hz, 1H), 5.95 (s, 1H), 4.79 (d, J = 7.8 Hz, 1H), 4.22 (m, 1H), 3.81 (s, 3H), 3.68 (s, 3H), 1.55 (d, J = 7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz, major diastereomer) 174.3, 169.3, 147.5, 136.8, 133.9, 129.6, 129.3, 127.7, 121.5, 118.1, 111.1, 110.2, 75.0, 55.8, 53.1, 52.2, 19.2.

2-Methoxy-2-oxo-(*S*)-1-phenylethyl 2-(*m*-methoxyanilino)-(*R*)-phenylacetate (12) A yellow oil was obtained in 80% yield. ^{1}H NMR ($CDCl_3$, 400 MHz, major diastereomer) 7.48 (m, 2H), 7.27 (m, 8H), 7.00 (m, 1H), 6.28 (m, 1H), 6.22 (m, 1H), 6.16 (m, 1H), 5.93 (s, 1H), 5.27 (d, J = 5.8 Hz, 1H), 4.88 (d, J = 5.8 Hz, 1H), 3.68 (s, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz, major diastereomer) 171.6, 169.2, 161.2, 147.7, 137.4, 133.6, 130.5, 129.6, 129.4, 129.1, 128.9, 127.8, 127.6, 106.9, 104.1, 100.0, 75.6, 61.2, 55.4, 53.2.

2-Methoxy-2-oxo-(*S*)-1-phenylethyl 2-(*m*-methoxyanilino)-(*R*)-propionate (13) A colorless oil was obtained in 73% yield. ^{1}H NMR ($CDCl_3$, 400 MHz, major diastereomer) 7.41-7.33 (m, 5H), 7.08 (m, 1H), 6.31-6.20 (m, 3H), 5.97 (s, 1H), 4.29 (q, J = 6.8 Hz, 1H), 4.21 (s, 1H), 3.70 (s, 3H), 3.66 (s, 3H), 1.48 (d, J = 6.8 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz, major diastereomer) 174.3, 169.3, 161.3, 148.3, 133.9, 130.5, 129.7, 129.3, 127.9, 106.8, 104.2, 99.8, 75.2, 55.4, 53.1, 52.4, 19.1.

2-Methoxy-2-oxo-(*S*)-1-phenylethyl 2-(*m*-methoxyanilino)-(*R*)-butanoate (14) A colorless oil was obtained in 78% yield. ^{1}H NMR ($CDCl_3$, 400 MHz, major diastereomer) 7.41-7.35 (m, 5H), 7.07 (t, J = 8.0 Hz, 1H), 6.31-6.25 (m, 2H), 6.21 (s, 1H), 5.97 (s, 1H), 4.17 (m, 2H), 3.75 (s, 3H), 3.68 (s, 3H), 1.97-1.79 (m, 2H), 0.99 (t, J = 7.4 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz, major diastereomer) 173.6, 169.3, 161.3, 148.6, 133.9, 130.5, 129.7, 129.2, 128.0, 106.8, 104.3, 99.9, 75.1, 58.2, 55.4, 53.0, 26.4, 10.4.

2-Methoxy-2-oxo-(*S*)-1-phenylethyl 2-(*m*-methoxyanilino)-(*R*)-hexanoate (15) A colorless oil was obtained in 61% yield. ^{1}H NMR ($CDCl_3$, 400 MHz, major diastereomer) 7.38 (m, 5H), 7.07 (t, J = 8.1 Hz, 1H), 6.31-6.25 (m, 2H), 6.21 (m, 1H), 5.98 (s, 1H), 4.20 (m, 1H), 4.10 (m, 1H), 3.75 (s, 3H), 3.69 (s, 3H), 1.78 (m, 2H), 1.34 (m, 4H), 0.85 (t, J = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz, major diastereomer) 173.8, 169.3, 161.2, 148.6, 134.1, 130.5, 129.8, 129.2, 127.9, 106.8, 104.3, 99.8, 75.0, 56.9, 55.5, 53.0, 33.0, 28.0, 22.8, 14.3.

2-Methoxy-2-oxo-(*S*)-1-phenylethyl 2-[(4-oxo-2-phenyl-*4H*-chromen-6-yl)amino]-(*R*)-phenylacetate (16) A yellow oil was obtained in 53% yield. ^{1}H NMR ($CDCl_3$, 400 MHz, major diastereomer) 7.88 (m, 2H), 7.50 (m, 5H), 7.38-7.26 (m, 10H), 7.04 (m, 1H), 6.74 (s, 1H), 5.95 (s, 1H), 5.43 (d, J = 6.3 Hz, 1H), 5.13 (d, J = 6.3 Hz, 1H), 3.72 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz, major diastereomer) 178.1, 171.3,

169.1, 163.1, 150.2, 143.8, 136.7, 133.5, 132.5, 131.7, 129.6, 129.4, 129.3, 129.1, 129.0, 127.8, 127.6, 126.6, 125.1, 121.7, 119.5, 107.1, 106.0, 75.8, 61.0, 53.2.

2-Methoxy-2-oxo-(*S*)-1-phenylethyl 2-[(4-oxo-2-phenyl-*4H*-chromen-6-yl)amino]-(*R*)-propanoate (17) A yellow oil was obtained in 42% yield. ^{1}H NMR ($CDCl_3$, 400 MHz, major diastereomer) 7.91 (m, 2H), 7.53-7.34 (m, 10H), 7.05 (m, 1H), 6.78 (s, 1H), 5.98 (s, 1H), 4.46 (m, 1H), 4.38 (m, 1H), 3.70 (s, 3H), 1.56 (d, J = 6.7 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz, major diastereomer) 178.7, 174.0, 169.2, 163.2, 150.3, 144.5, 133.6, 132.5, 131.7, 129.9, 129.4, 129.2, 128.0, 126.6, 125.2, 121.9, 119.6, 107.1, 105.7, 75.4, 53.1, 52.3, 19.0.

2-Methoxy-2-oxo-(*S*)-1-phenylethyl 2-[(4-oxo-2-phenyl-*4H*-chromen-6-yl)amino]-(*R*)-butanoate (18) A yellow oil was obtained in 51% yield. ^{1}H NMR ($CDCl_3$, 400 MHz, major diastereomer) 7.90 (m, 2H), 7.51-7.35 (m, 10H), 7.07 (m, 1H), 6.77 (s, 1H), 5.99 (s, 1H), 4.45 (br, 1H), 4.36 (q, J = 5.9 Hz, 1H), 3.69 (s, 3H), 2.07-1.85 (m, 2H), 1.03 (t, J = 7.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz, major diastereomer) 178.7, 173.2, 169.2, 163.2, 150.3, 144.8, 133.9, 132.5, 131.7, 129.7, 129.3, 129.2, 128.0, 126.6, 125.2, 121.9, 119.5, 107.1, 105.8, 75.4, 58.1, 53.1, 26.3, 10.2.

2-Methoxy-2-oxo-(*S*)-1-phenylethyl 2-[(4-oxo-2-phenyl-*4H*-chromen-7-yl)amino]-(*R*)-phenylacetate (19) A yellow oil was obtained in 33% yield. ^{1}H NMR ($CDCl_3$, 400 MHz, major diastereomer) 8.06-7.26 (m, 15H), 6.69 (m, 3H), 6.53 (s, 1H), 6.00 (s, 1H), 5.52 (d, J = 5.6 Hz, 1H), 5.39 (d, J = 5.6 Hz, 1H), 3.74 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz, major diastereomer) 178.1, 170.7, 169.0, 162.8, 158.8, 150.9, 136.0, 133.3, 132.5, 131.5, 129.7, 129.6, 129.3, 129.0, 128.8, 127.7, 127.6, 127.3, 126.5, 116.1, 113.8, 107.8, 98.8, 75.8, 60.7, 53.3.

3-Phenyl-3,4-dihydro-1,4-quinoxalin-2-one (20) A white solid was obtained in 92% yield. m.p. 192-194 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) 7.95 (br, 1H), 7.43-6.70 (m, 9H), 5.08 (s, 1H), 4.28 (br, 1H). The spectral data were identical to those of the authentic material reported in ref. 8a. Chiral HPLC: 96:4 er, t_R (*S*)-minor enantiomer, 38.3 min; t_R (*R*)-major enantiomer, 35.7 min; (Chiralcel OJ-H column; 20% 2-propanol in hexane; 0.5 mL/min).

6,7-Dichloro-3-phenyl-3,4-dihydro-1,4-quinoxalin-2-one (21) A white solid was obtained in 87% yield. m.p. 230-231 °C; ^{1}H NMR (DMSO-d_6, 400 MHz) 10.1 (br, 1H), 7.88-7.75 (m, 5H), 7.50-7.48 (m, 2H), 6.77 (br, 1H), 5.55 (s, 1H)**;** ^{13}C NMR (DMSO-d_6, 100 MHz) 166.1, 140.6, 134.9, 129.3, 128.8, 127.7, 126.9, 125.9, 120.5, 116.7, 115.1, 60.5; Chiral HPLC: 97:3 er, t_R (*S*)-minor enantiomer, 40.6 min; t_R (*R*)-major enantiomer, 35.6 min; (Chiralcel OJ-H column; 20% 2-propanol in hexane; 0.5 mL/min).

6,7-Dimethyl-3-phenyl-3,4-dihydro-1,4-quinoxalin-2-one (22) A white solid was obtained in 90% yield. m.p. 203-204 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) 8.44 (br, 1H), 7.41-7.28 (m, 5H), 6.50 (s, 2H), 5.01 (s, 1H), 4.11 (br, 1H), 2.15 (s, 3H), 2.14 (s, 3H). The spectral data were identical to those of the authentic material reported in ref. 8a. Chiral HPLC: 94:6 er, t_R (*S*)-minor enantiomer, 43.3 min; t_R (*R*)-major enantiomer,

32.6 min; (Chiralcel OJ-H column; 20% 2-propanol in hexane; 0.5 mL/min).

3-Methyl-3,4-dihydro-1,4-quinoxalin-2-one (23) A white solid was obtained in 79% 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). The spectral data were identical to those of the authentic material reported in ref. 8a. Chiral HPLC: 89:11 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-1,4-quinoxalin-2-one (24) A white solid was obtained in 88% 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)**.** The spectral data were identical to those of the authentic material reported in ref. 8a. Chiral HPLC: 87:13 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).

6,7-Dimethyl-3-ethyl-3,4-dihydro-1,4-quinoxalin-2-one (25) A pale yellow oil was obtained in 81% 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)**.** The spectral data were identical to those of the authentic material reported in ref. 8a. Chiral HPLC: 92:8 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-Butyl-3,4-dihydro-1,4-quinoxalin-2-one (26) A colorless oil was obtained in 71% 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). The spectral data were identical to those of the authentic material reported in ref. 8a. Chiral HPLC: 90:10 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-Phenyl-3,4-dihydro-1,4-benzoxazin-2-one (27) A yellow oil was obtained in 71% yield. ^{1}H NMR ($CDCl_3$, 400 MHz) 7.40-6.80 (m, 9H), 5.07 (s, 1H), 4.24 (s, 1H); The spectral data were identical to those of the authentic material reported in ref. 7a. Chiral HPLC: 91:9 er, t_R (*R*)-major enantiomer, 16.2 min; t_R (*S*)-minor enantiomer, 20.0 min; (Chiralcel OD column; 20% 2-propanol in hexane; 0.5 mL/min).

6-Methyl-3-phenyl-3,4-dihydro-1,4-benzoxazin-2-one (28) A yellow oil was obtained in 79% yield. ^{1}H NMR ($CDCl_3$, 400 MHz) 7.38 (m, 5H), 6.92 (d, J = 8.2 Hz, 1H), 6.66 (d, J = 8.2 Hz, 1H), 6.62 (s, 1H), 5.04 (s, 1H), 4.17 (s, 1H), 2.29 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) 165.7, 139.3, 137.0, 135.5, 132.4, 129.4, 129.3, 127.7, 121.4, 117.1, 115.7, 59.7, 21.4; Chiral HPLC: 90:10 er, t_R (*R*)-major enantiomer, 18.8 min; t_R (*S*)-minor enantiomer, 25.9 min; (Chiralcel OD column; 20% 2-propanol in hexane; 0.5 mL/min).

7-Methyl-3-phenyl-3,4-dihydro-1,4-benzoxazin-2-one (29) A pale yellow oil was obtained in 68% yield. ^{1}H NMR ($CDCl_3$, 400 MHz) 7.38 (m, 5H), 6.85 (s, 1H), 6.82 (d, J = 7.9 Hz, 1H), 6.70 (d, J = 7.9

Hz, 1H), 5.01 (s, 1H), 4.14 (s, 1H), 2.28 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) 165.7, 141.3, 136.9, 130.8, 130.2, 129.4, 129.3, 127.9, 126.1, 117.8, 115.2, 59.9, 21.0; Chiral HPLC: 90:10 er, t_R (*R*)-major enantiomer, 21.3 min; t_R (*S*)-minor enantiomer, 35.1 min; (Chiralcel OD column; 20% 2-propanol in hexane; 0.5 mL/min).

6-*tert*-Butyl-3-phenyl-3,4-dihydro-1,4-benzoxazin-2-one (30) A brown oil was obtained in 80% yield. ^{1}H NMR ($CDCl_3$, 400 MHz) 7.38 (m, 5H), 6.92 (d, J = 8.5 Hz, 1H), 6.88 (m, 1H), 6.82 (s, 1H), 5.01 (s, 1H), 4.19 (s, 1H), 1.29 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz) 165.9, 149.0, 139.2, 136.9, 132.2, 129.4, 129.3, 128.1, 117.9, 116.8, 112.4, 60.0, 34.9, 31.8; Chiral HPLC: 91:9 er, t_R (*R*)-major enantiomer, 14.7 min; t_R (*S*)-minor enantiomer, 23.3 min; (Chiralcel OD column; 20% 2-propanol in hexane; 0.5 mL/min).

2-Phenyl-3,4-dihydro-1,4-benzothiazin-3-one (31) A yellow oil was obtained in 85% yield. ^{1}H NMR ($CDCl_3$, 400 MHz) 8.74 (s, 1H), 7.38-6.88 (m, 9H), 4.69 (s, 1H). The spectral data were identical to those of the authentic material reported in ref. 8b. Chiral HPLC: 69:31 er, t_R major enantiomer, 44.4 min; t_R minor enantiomer, 60.8 min; (Chiralcel OJ-H column; 20% 2-propanol in hexane; 0.5 mL/min).

ACKNOWLEDGEMENTS

This work was supported by grants from the Korea Research Foundation (KRF-2006-005-J03402) and Seoul R&BD Program (WR090671).

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