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Asymmetric addition of nucleophiles to C-1 position of isoquinolines using (*S*)-alanine derivatives as chiral auxiliaries

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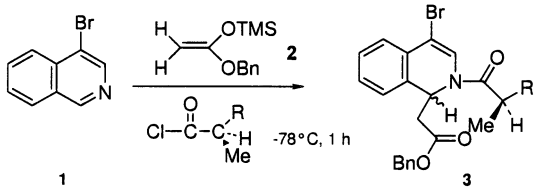
Abstract—5,8-Dibromoisoquinoline derivatives were allowed to react with a nucleophile (silyl enol ether or allyltributyltin) in the presence of an acyl chloride derived from (*S*)-alanine to afford the 1,2-addition products in good chemical yields and high stereoselectivity. The bromo groups were readily removed by a reduction process in which the double bond at C3–C4 was also reduced. Thus the reaction system provided a general method to synthesize asymmetric 1-substituted tetrahydroisoquinolines. In order to determine the absolute configuration of the reaction product, (−)-homolaudanosine was synthesized in an enantiopure form. The stereoselectivity was rationally understood from the conformation of intermediary N-acylated isoquinolinium salts.

Tetrahydroisoquinoline alkaloids are among major constituents of natural products, and there have been many reports concerning the total syntheses of these compounds.[1] Most of these have a chiral center at their C-1 position, and various enantioselective techniques have been applied to the syntheses. General procedures for obtaining tetrahydroisoquinoline ring systems involve asymmetric Pictet–Spengler ring-closing reaction,[2] and Bischler–Napieralski reaction followed by enantioselective reduction,[3] both of which often require electron-donating group(s) on benzene ring for the ring-closing processes. Recently, 1-substituted (and 5,6,7,8-unsubstituted) tetrahydroisoquinolines have been found to be relevant to pathogenesis of Parkinson's disease[4] and have received attention from the field of medicinal chemistry,[5] thus the modification of these methods would be necessary. On the other hand, direct introduction of substituents on the isoquinoline ring in a stereoselective manner was seldom reported. A standard procedure has been developed by Meyers et al.[6] in which a 2-substituted 1,2,3,4-tetrahydroisoquinoline was used as a starting material. A similar procedure has been reported by Gawley et al.[7] Other possible substrates are 1-unsubstituted 3,4-dihydro and aromatic isoquinolines. Since catalytic asymmetric addition to imines have been developed recently using various catalysts,[8] 3,4-dihydroisoquinoline derivatives, which have an imine moiety, seem to be good starting materials. These catalytic methods were, however, mostly applied to imines having an aromatic substituent on nitrogen, thus these methods would not be applicable to 3,4-dihydroisoquinolines. Thus, there is an only study that reported the asymmetric addition to the compounds using a stoichiometric amount of allylzinc reagent.[9] In the cases of isoquinoline rings, Comins et al. showed that 6,7-dimethoxyisoquinoline was attacked by methylmagnesium iodide in the presence of (−)-8-phenylmenthyl chloroformate, and the reaction product was converted by several steps to (+)-carnegine in 62% ee.[10] Although this system was carried out by simple procedures, the obtained ee was insufficient.

In the course of our study for the reactivity of *N*-acylazolium and azinium salts,[11] we reported the asymmetric addition of allyltributyltin to 4-bromoisoquinoline using MTPA chloride as an acylating agent.[12] To make the reaction system useful for practical asymmetric synthesis, we investigated the reaction using naturally occurring carboxylic acids as chiral auxiliaries, and found that simple ones derived from amino acids were good auxiliaries for the asymmetric induction. And it was also revealed that introduction of bromo group(s) to isoquinoline ring improved both chemical yields and diastereoselectivity considerably. This paper describes these results.[13]

Amino acids were adopted as chiral auxiliaries because they are inexpensive, readily available, and have various types of substituents. Fortunately, (*S*)-alanine, the simplest and most inexpensive chiral amino acid, was found to give moderate to high diastereoselectivity (Eq. (1)).[14]



(1)

Keywords: isoquinoline; asymmetric addition; 5,8-dibromoisoquinoline; allyltributyltin; silyl enol ether; chiral auxiliary; alanine; homolaudanosine.

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Table 1. Asymmetric addition reaction of 4-bromoisoquinoline (**1**) with benzyl trimethylsilyl ketene acetal (**2**) in the presence of an acyl chloride derived from (*S*)-alanine

Entry	R	Solvent	Product	Yield of **3** (%)	de (%)[a]
1	Benzyloxycarbonylamino	CH_2Cl_2	–	0	–
2	Benzoylamino	CH_2Cl_2	–	0	–
3	Phenylsulfonylamino	CH_2Cl_2	**3a**	67	61
4	Phenylsulfonylamino	Toluene	**3a**	88	30
5	Phenylsulfonylamino	DMF	**3a**	Quant.	9
6	1-Naphthylsulfonylamino	CH_2Cl_2	**3b**	70	7
7	*p*-Nitophenylsulfonylamino	toluene	**3c**	70	51
8	*p*-Nitophenylsulfonylamino	CH_2Cl_2	**3c**	56	82
9	Phthalimido[b]	CH_2Cl_2	**3d**	68	86

[a] The diastereomeric excess was determined by ^{1}H NMR.
[b] (*RS*)-*N*-Phthaloylalanyl chloride was used.

Table 1 shows the results of the reaction using 4-bromoisoquinoline (**1**), benzyltrimethylsilyl ketene acetal (**2**), and acyl chloride derived from (*S*)-alanine. All the reactions were carried out at −78°C for 1 h to compare the data under the same conditions, thus the yields are not optimized. Several protecting groups were used for the amino group of alanine. Although the reaction did not proceed by use of a standard protecting group such as benzyloxycarbonyl or benzoyl group (entries 1 and 2), the use of more electron-withdrawing phenylsulfonyl group resulted in a moderate chemical yield and de in dichloromethane (entry 3). Other solvents gave lower selectivity despite high chemical yields (entries 4 and 5). Further experiments showed that *p*-nitrophenylsulfonyl and phthaloyl groups were better protecting groups (entries 8 and 9).

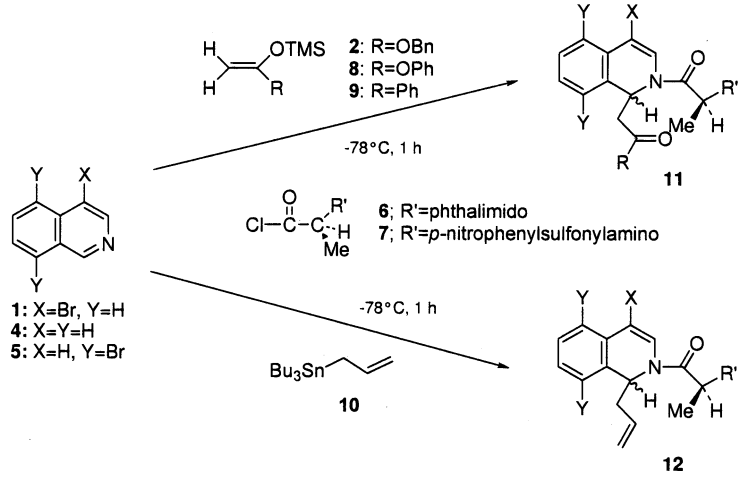
Next, other nucleophiles were applied to the reaction using parent isoquinoline (**4**), **1**, and 5,8-dibromoisoquinoline (**5**),[15] and the results are summarized in Table 2 (Scheme 1).

Isoquinoline (**4**) afforded moderate chemical and stereochemical yields using *N*-phthaloylalanyl chloride (**6**) (entries 1 and 8), but the selectivity did not reach a practical level. Introduction of a bromo group slightly improved the diastereoselectivity (entry 7 and Table 1), and 5,8-dibromo isoquinoline (**5**) gave the best results in every case (entries

Table 2. Asymmetric addition of isoquinoline derivatives with silyl enol ethers or allyltributyltin in the presence of the acyl chloride **6** or **7**

Entry	Substrate	Acyl chloride[a]	Nucleophile	Product	Yield (%)	de[b] (%)
1	**4**	**6**	**2**	**11a**	89	77
2	**4**	**7**	**2**	**11b**	57	59
3	**5**	**6**	**2**	**11c**	77	92
4	**5**	**7**	**2**	**11d**	75	72
5	**5**	**6**	**8**	**11e**	98	86
6	**5**	**6**	**9**	**11f**	99	81
7	**1**	**6**	**10**	**12a**	69	59
8	**4**	**6**	**10**	**12b**	67	76
9	**5**	**6**	**10**	**12c**	75	95

[a] The acyl chloride **6** was used as a racemic form except entry 6.
[b] The diastereomeric excess was determined by ^{1}H NMR.



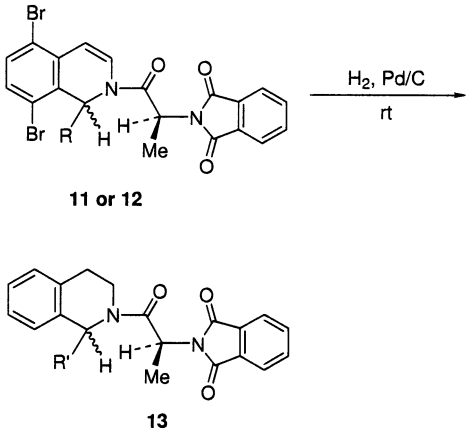
Scheme 1.

Table 3. Reduction of bromo groups and a double bond of compound **11** or **12**

Entry	Compound	R	Solvent	Product	R′	Yield (%)
1	**11c**	CH_2COOBn	MeOH/AcOEt	**13a**	CH_2COOMe	76
2	**12c**	$CH_2CH{=}CH_2$	MeOH	**13b**	$CH_2CH_2CH_3$	91
3	**11f**	CH_2COPh	MeOH/AcOEt	**13c**	CH_2CH_2Ph	82

3–6 and 9). For acyl chlorides, the phthaloyl derivative 6 showed good reactivity and selectivity, although *N*-(*p*-nitrophenylsulfonyl)alanyl chloride (**7**) had similar selectivity in some cases.

The above results indicated that parent isoquinoline itself was not a suitable substrate for the asymmetric addition, and introduction of bromo group(s) was crucial for the good diastereoselectivity. Compound **5** was readily synthesized from **4**, bromine and $AlCl_3$ in a good yield,[15] and the bromo groups of **5** were found to be eliminated by reduction by which the C3–C4 double bond was hydrogenated concurrently (Eq. (2) and Table 3).



(2)

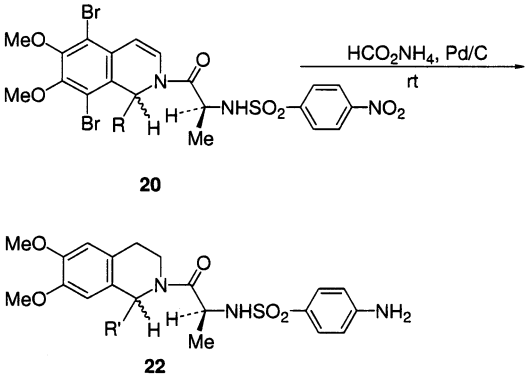
Thus, the double bond and bromo groups at C-5 and C-8 were reduced simultaneously to give tetrahydro derivatives **13** under catalytic hydrogenation conditions. Since other reducible functional groups were also converted under the conditions, suitable transformation or protection of these groups is needed before the reduction. It was suggested, however, that 5,8-dibromo derivative **5** is a potential substitute for parent **4** in our reaction system.

Compound **13c** thus obtained was recrystallized once to give an optically pure form, and readily transformed by reduction with $LiAlH_4$ to give an optically pure tetrahydro compound **14**,[16] whose configuration was supposed to be *R* by derivatization to **15** using MTPA chloride (modified Mosher method)[17] (Scheme 2).

With these precedents in hand, we next investigated reaction using 6,7-dimethoxyisoquinoline (**16**), which is the most ubiquitous nucleus in isoquinoline alkaloids, and the results are shown in Table 4 (Scheme 3).

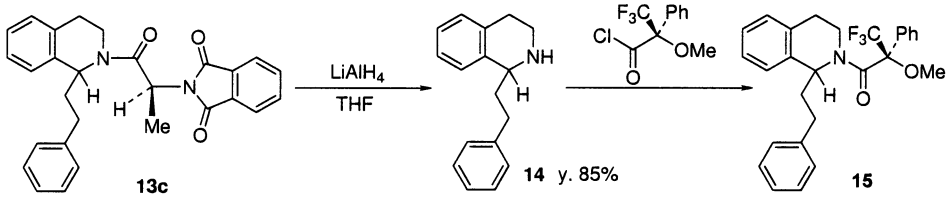
Although the compound **16** itself afforded low chemical yields (entries 1 and 2), corresponding 5,8-dibromo derivative **17**, which was readily obtained from **16**, was found to give high chemical yields and stereoselectivities. In these cases, the chiral auxiliaries **6** and **7** afforded comparable results, and **7** was superior to **6** in the addition of silyl enol ethers (entries 3 and 4), whereas **6** showed better selectivity in the case of allyltributyltin (entries 8 and 9). The diastereoselectivity was seldom altered by the bulkiness of nucleophiles (entries 6 vs 7), thus it was suggested that a stable conformation of *N*-acyl quaternary salts formed in situ controlled the selectivity without influence of the nucleophile.

The obtained products **20** were converted to corresponding tetrahydro derivatives **22** by the reduction with Pd/C–HCO_2NH_4 (Eq. (3) and Table 5). In these cases, the use of Pd/C–H_2 afforded a mixture of some reduced products.



(3)

Thus the process was proved to be a good alternative for the direct addition to 6,7-dimethoxyisoquinoline (**16**). Therefore, the data shown above revealed that brominated isoquinoline derivatives are good substrates for asymmetric 1,2-addition, and subsequent transformation completes a versatile method for chiral tetrahydroisoquinoline synthesis.

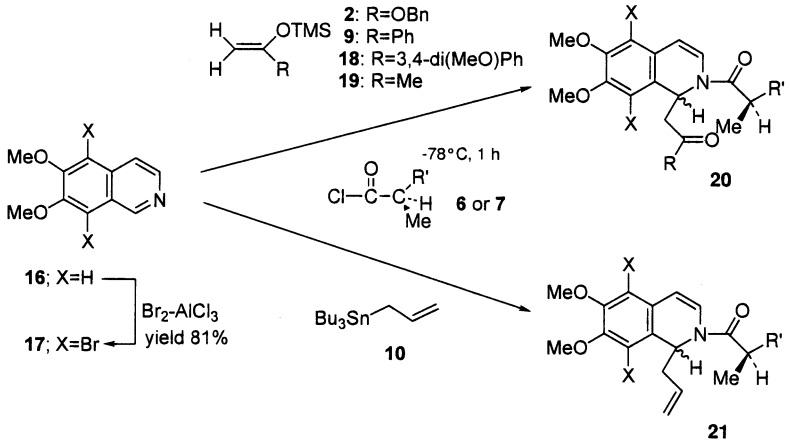


Scheme 2.

Table 4. Asymmetric addition of 6,7-dimethoxyisoquinoline (**16**) or 5,8-dibromo derivative (**17**) with silyl enol ether or allyltributyltin in the presence of the acyl chloride derive from (*S*)-alanine

Entry	Substrate	Acyl chloride[a]	Nucleophile	Product	Yield (%)	de[b] (%)
1	**16**	**6**	**2**	**20a**	38	74
2	**16**	**7**	**2**	**20b**	20	67
3	**17**	**6**	**2**	**20c**	100	84
4	**17**	**7**	**2**	**20d**	86	96
5	**17**	**7**	**18**	**20e**	93	93
6	**17**	**7**	**9**	**20f**	85	83
7	**17**	**7**	**19**	**20g**	65	94
8	**17**	**6**	**10**	**21a**	83	91
9	**17**	**7**	**10**	**21b**	73	69

[a] Compound **6** was used as a racemic form.
[b] The diastereomeric excess was determined by ^{1}H NMR.

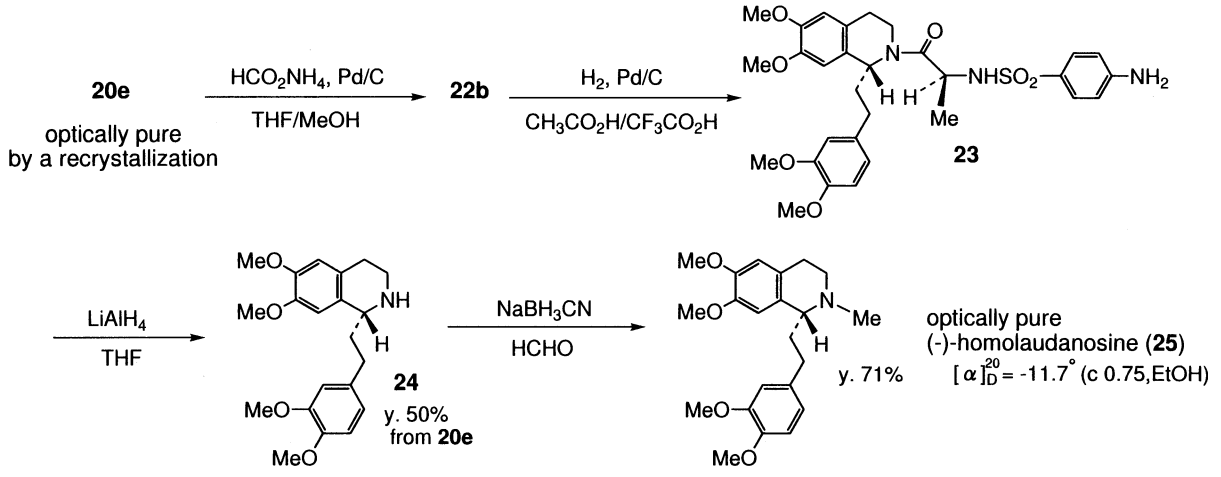


Scheme 3.

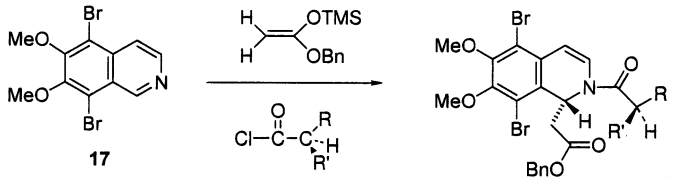
Table 5. Reduction of **20** with HCO_2NH_4–Pd/C

Entry	Compound	R	Solvent	Product	R′	Yield (%)
1	**20d**	CH_2COOBn	MeOH/THF	**22a**	CH_2COOH	98
2	**20e**	CH_2CO-3,4-di(MeO)Ph	MeOH/THF	**22b**	CH_2CO-3,4-di(MeO)Ph	65
3	**20f**	CH_2COPh	MeOH	**22c**	$CH_2CH(OH)$–Ph	62[a]

[a] The reaction was run at 70°C.



Scheme 4.



20d: R=*p*-nitrophenylsulfonylamino, R'=Me: 96%de (y 86%)
26: R=*p*-nitrophenylsulfonylamino, R'=*i*-Pr: 19%de (y 68%)

20c: R=phthalimido, R'=Me: 84%de (y 100%)
27: R=phthalimido, R'=*i*-Pr: 95%de (y 98%)

Scheme 5.

We next carried out the confirmation of the absolute configuration using the synthesis of (−)-homolaudanosine,[18] and the procedure is shown in Scheme 4. Compound **20e** obtained in 93% de was recrystallized from hexane/AcOEt to give a single diastereomer, and converted to **22b** by the reduction with Pd/C–HCO_2NH_4. Compound **22b** was treated with H_2–Pd/C in TFA/AcOH to reduce the keto carbonyl group to give **23**. Reduction of **23** with $LiAlH_4$ eliminated the chiral auxiliary to give compound **24**, which was methylated by HCHO–$NaBH_3CN$ to form homolaudanosine (**25**) in an optically pure form. The measurement of the specific rotation indicated that the absolute configuration of **25** was *R*. The overall yield from **17** was 32% with a single enantiomer.

The data shown in Tables 2 and 4 suggested that the stereoselectivity was regulated by a conformation of the quaternary salts of isoquinolines without the participation of nucleophiles, and the results shown in Schemes 2 and 4 indicated that *p*-nitrophenylsulfonyl and phthaloyl groups on (*S*)-alanyl moiety both showed the *R* selectivity. In order to obtain further information for the selectivity, chiral auxiliaries derived from (*S*)-valine were synthesized and used for the reaction of compound **17** and *O*-benzyl trimethylsilyl ketene acetal (**2**) (Scheme 5).

Isopropyl group affected the de in a negative manner in the case of *p*-nitrophenylsulfonyl group (19% de), but in a positive manner for phthalimide group (95% de). Thus, stable conformations of N-acylated isoquinolinium salts were calculated by the PM3 method, and the results are shown in Figs. 1 and 2.

As shown in Fig. 1, the isopropyl group rendered the *p*-nitrophenylsulfonyl group lower toward the *Re* side because of the steric repulsion between these two groups. That results in the block of both sides of the reaction site, and the stereoselectivity might be lowered accompanied by decrease of the chemical yield. On the contrary, exchange of methyl group to isopropyl group had no influence on conformation of the quaternary salts in the cases of phthalimido groups (Fig. 2). This is probably due to the rather restricted conformation of phthaloyl group than that of *p*-nitrophenylsulfonyl group. Thus the bulkiness of the alkyl group effectively shielded the *Si* face of the reaction site to afford the high selectivity, especially in the case of isopropyl group.

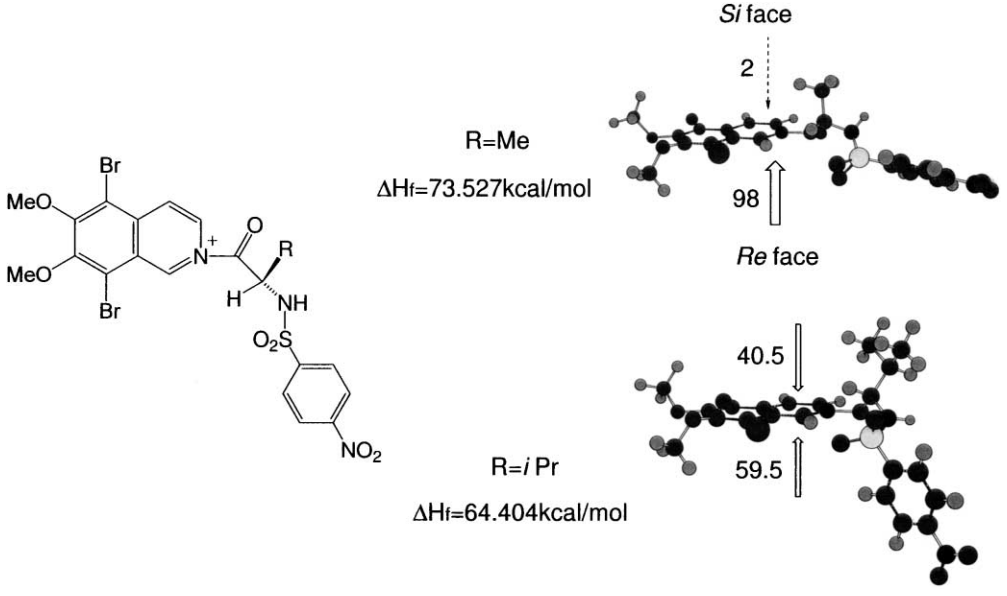


Figure 1. Calculated PM3 structures of *N*-(*p*-nitrophenylsulfonly)alanyl- and *N*-(*p*-nitrophenylsulfonyl) valinyl-5,8-dibromo-6,7-dimethoxyisoquinolinium salts.

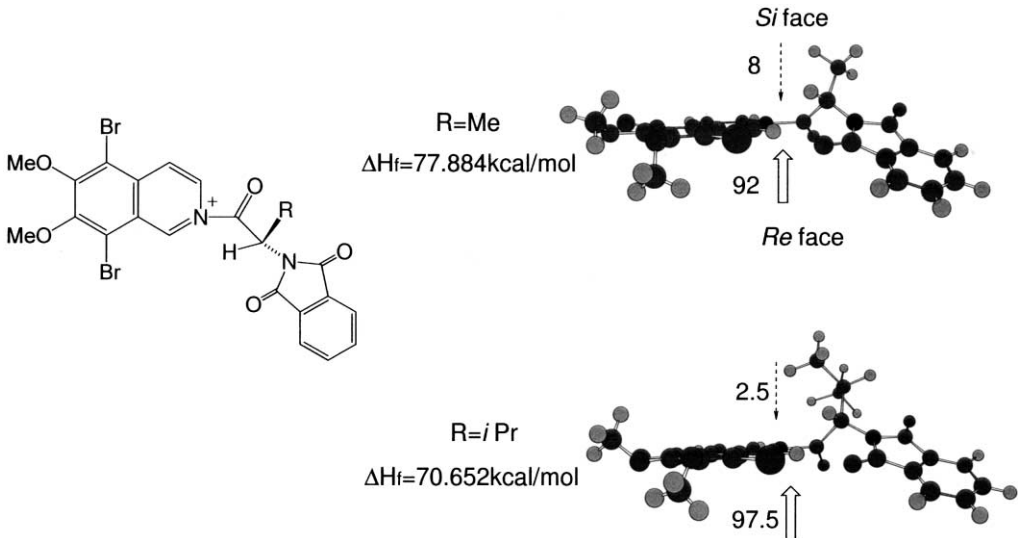


Figure 2. Calculated PM3 structures of *N*-phthaloylalanyl- and *N*-phthaloylvalinyl-5,8-dibromo-6,7-dimethoxyisoquinolinium salts.

In this paper, we disclosed a general method by which asymmetric 1-substituted tetrahydroisoquinolines was synthesized from corresponding aromatics. Introduction of bromo groups on the substrate effectively increased both chemical yields and stereoselectivity to give a practical level of asymmetric adducts. Application of the reaction system toward synthesis of isoquinoline alkaloids such as emetine and pronuciferine,[19] and other derivatives that might have bioactivity towards Parkinson's disease is now under investigation.[20]

1. Experimental

1.1. General remarks

Melting points are uncorrected. ^{1}H- and ^{13}C NMR spectra of $CDCl_3$ and CD_3OD solutions were recorded at 500 and 125 MHz, respectively, with tetramethylsilane (TMS) as an internal standard. High-resolution mass spectra (FAB-HRMS) were measured using *p*-nitrobenzyl alcohol as a matrix.

1.2. Preparation of substrates

5,8-Dibromoisoquinoline (**5**)[15] and 6,7-dimethoxyisoquinoline (**16**)[21] were prepared according to the literatures. 5,8-Dibromo-6,7-dimethoxyisoquinoline (**17**) was synthesized using the same method as **5**.

1.2.1. 5,8-Dibromo-6,7-dimethoxyisoquinoline (17). y 81%; Pale yellow needles from ethanol; mp 124.0–124.6°C. ^{1}H NMR ($CDCl_3$) δ 4.02 (3H, s), 4.05 (3H, s), 7.97 (1H, d, J=5.4 Hz), 8.64 (1H, d, J=5.4 Hz), 9.56 (1H, s). ^{13}C NMR ($CDCl_3$) δ 61.2, 61.3, 114.5, 118.7, 124.8, 133.8, 144.1, 149.9, 151.2, 154.0. HRMS (FAB): Calcd for $C_{11}H_9Br_2NO_2$ $(M+H)^+$: 345.9078. Found 345.9102.

1.3. Preparation of chiral auxiliaries

Chiral acids derived from (*S*)-alanine and (*S*)-valine were synthesized according to the literatures shown below: *N*-phenylsulfonyl-(*S*)-alanine;[22] *N*-(*p*-nitrophenylsulfonyl)-(*S*)-alanine;[22] *N*-phthaloyl-(*S*)-alanine;[23] *N*-(1-naphthylsulfonyl)-(*S*)-alanine;[24] *N*-(*p*-nitrophenylsulfonyl)-(*S*)-valine;[25] *N*-phthaloyl-(*S*)-valine.[26] Since racemic *N*-phthaloylalanine is commercially available (Tokyo Chemical Industry Co.), it was used for the estimation of diastereoselectivity of the addition reaction.

1.4. Preparation of silyl enol ethers

Two silyl enol ethers which are not commercially available were synthesized according to the reported methods: benzyl trimethylsilyl ketene acetal;[27] 1-(3,4-dimethoxyphenyl)-1-(trimethylsilyloxy)ethylene.[18b]

1.5. Reaction of 4-bromoisoquinoline with silyl enol ethers in the presence of an acyl chloride derived from (*S*)-alanine

To a benzene solution (3 ml) of *N*-protected (*S*)-alanine (or racemic *N*-phthaloylalanine) (0.23 mmol) was added thionyl chloride ($SOCl_2$) (0.3 ml), and the mixture was allowed to react at 60°C for 1 h. Then the solvent and excess $SOCl_2$ were evaporated off in vacuo to leave viscous oil. Methylene chloride (2 ml) and 4-bromoisoquinoline were successively added to the oil and the mixture was cooled to −78°C under Ar. To the solution was added a cooled CH_2Cl_2 solution (1 ml) of benzyl trimethylsilyl ketene acetal (0.23 mmol). The mixture was allowed to react for 1 h at −78°C under Ar, then brought to room temperature. The solvent was evaporated off to leave a residue, which was chromatographed on silica gel (CH_2Cl_2/Et_2O=10:1) to give the product. The de was estimated from ^{1}H NMR data of the crude sample before the column chromatography. The melting points and spectral data were obtained from the samples after purification.

1.5.1. Benzyl 4-bromo-1,2-dihydro-2-[*N*-phenylsulfonyl-(*S*)-alanyl]isoquinolin-1-ylacetate (3a). y 67%; Yellow powder from hexane; mp 110.6–112.1°C (55% de). The

NMR spectra of the major isomer are shown; ^{1}H NMR ($CDCl_3$) δ 1.33 (3H, d, J=6.8 Hz), 2.43 (1H, dd, J=14.0, 6.0 Hz), 2.51 (1H, dd, J=13.6, 8.0 Hz), 4.23 (1H, dq, J=10.0, 7.2 Hz), 4.92 (1H, d, J=12.0 Hz), 4.99 (1H, d, J=12.0 Hz), 5.55 (1H, t, J=7.2 Hz), 5.65 (1H, d, J=9.6 Hz), 6.72 (1H, d, J=1.2 Hz), 6.83–7.90 (14H, m). ^{13}C NMR ($CDCl_3$) δ 19.3, 39.1, 48.6, 50.1, 66.8, 108.7, 122.3, 125.5, 126.2, 126.9, 128.3, 128.40, 128.43, 128.46, 128.6, 129.0, 129.2, 131.9, 132.5, 135.2, 138.5, 169.1, 169.5. Anal. Calcd for $C_{27}H_{25}BrN_2O_5S$: C, 56.95; H, 4.42; N, 4.92. Found C, 57.20; H, 4.24; N, 4.75.

1.5.2. Benzyl 4-bromo-1,2-dihydro-2-{*N*-[1-naphthylsulfonyl-(*S*)-alanyl]}isoquinolin-1-ylacetate (3b). y 70%; Yellow powder from CH_2Cl_2/Et_2O; mp 70–71°C (31% de). The NMR spectra of the major isomer are shown; ^{1}H NMR ($CDCl_3$) δ 1.28 (3H, d, J=6.8 Hz), 2.28 (1H, dd, J=13.6, 6.4 Hz), 2.32 (1H, dd, J=12.0, 8.8 Hz), 4.15 (1H, dq, J=10.0, 6.8 Hz), 4.85 (1H, d, J=12.0 Hz), 4.90 (1H, d, J=12.0 Hz), 5.73–5.79 (2H, m), 6.52 (1H, s), 6.73–8.67 (16H, m). ^{13}C NMR ($CDCl_3$) δ 19.4, 39.2, 48.6, 49.9, 66.8, 107.7, 108.1, 122.3, 123.5, 124.1, 124.4, 125.5, 126.3, 126.7, 128.4, 128.5, 128.6, 128.7, 129.0, 129.1, 129.6, 131.6, 133.2, 133.6, 134.3, 134.6, 135.2, 169.0, 169.1. Anal. Calcd for $C_{31}H_{27}BrN_2O_5S$: C, 60.07; H, 4.40; N, 4.52. Found C, 60.35; H, 4.35; N, 4.41.

1.5.3. Benzyl 4-bromo-1,2-dihydro-2-[*N*-(*p*-nitrophenyl)-sulfonyl-(*S*)-alanyl]isoquinolin-1-ylacetate (3c). y 56%; Yellow needles from hexane; mp 77.7–78.1°C (77% de). The NMR spectra of the major isomer are shown; ^{1}H NMR ($CDCl_3$) δ 1.39 (3H, d, J=7.0 Hz), 2.41 (1H, dd, J=13.8, 5.8 Hz), 2.51 (1H, dd, J=13.8, 8.4 Hz), 4.28 (1H, dq, J=10.1, 7.0 Hz), 4.92 (1H, d, J=12.1 Hz), 5.00 (1H, d, J=12.1 Hz), 5.54 (1H, dd, J=8.4, 5.8 Hz), 5.61 (1H, d, J=10.1 Hz), 6.72 (1H, d, J=1.5 Hz), 6.90 (1H, d, J=7.0 Hz), 7.26–7.31 (3H, m), 7.32–7.37 (3H, m), 7.41 (1H, td, J=7.7, 1.3 Hz), 7.54 (1H, dd, J=7.7, 1.1 Hz), 7.76 (4H, s). ^{13}C NMR ($CDCl_3$) δ 19.2, 38.9, 48.6, 50.0, 66.8, 109.4, 121.6, 123.5, 124.2, 125.4, 127.6, 127.7, 128.0, 128.2, 128.3, 128.9, 129.9, 131.3, 134.9, 144.4, 149.3, 168.7, 168.8. Anal. Calcd for $C_{27}H_{24}BrN_3O_7S$: C, 52.78; H, 3.94; N, 6.84. Found: C, 53.11; H, 3,90; N, 6.84.

1.5.4. Benzyl 4-bromo-1,2-dihydro-2-[*N*-phthaloyl-alanyl]isoquinolin-1-ylacetate (3d). y 68%; Colorless powder; mp 65–66°C (100% de, a racemic mixture). ^{1}H NMR ($CDCl_3$) δ 1.62 (3H, d, J=7.2 Hz), 2.63 (1H, dd, J=13.6, 6.8 Hz), 2.69 (1H, dd, J=13.6, 6.8 Hz), 5.00–5.12 (3H, m), 6.05 (1H, t, J=7.2 Hz), 6.78 (1H, s), 7.08–7.22 (4H, m), 7.33–7.37 (5H, m), 7.69 (2H, dd, J=5.6, 3.2 Hz), 7.76 (2H, dd, J=5.6, 3.2 Hz). ^{13}C NMR ($CDCl_3$) δ 15.4, 39.6, 46.7, 51.7, 66.8, 106.5, 123.3, 123.5, 124.1, 125.0, 126.2, 128.2, 128.3, 128.5, 129.0, 131.3, 132.5, 134.1, 134.3, 135.5, 166.6, 166.7, 169.4. Anal. Calcd for $C_{29}H_{23}N_2O_5Br$: C, 62.24; H, 4.15; N, 5.01. Found C, 62.22; H, 4.25; N, 4.87.

1.6. Reaction of isoquinolines (1, 4 and 5) with various silyl enol ethers or allyltributyltin in the presence of an acyl chloride derived from (*S*)-alanine

The same reaction procedure mentioned above was applied to these reactions. In the case of the reactions using allyltributyltin, sat. KF solution (4 ml) was added to the mixture after the reaction went to completion, and the mixture was allowed to stand for 1 h with stirring. Then Et_2O (15 ml) was added, and the precipitate thus formed was filtered. The filtrate was evaporated off to leave a residue, which was chromatographed on silica gel to give the product. The de was estimated from ^{1}H NMR data of the crude sample before the column chromatography. The melting points and spectral data were obtained from the samples after purification.

1.6.1. Benzyl 1,2-dihydro-2-[*N*-phthaloylalanyl]isoquinolin-1-ylacetate(11a). y 89%; Colorless needles from CH_2Cl_2/hexane; mp 183.4–184.8°C (100% de, a racemic mixture). ^{1}H NMR ($CDCl_3$) δ 1.63 (3H, d, J=7.0 Hz), 2.61 (1H, dd, J=13.4, 6.9 Hz), 2.68 (1H, dd, J=13.4, 6.9 Hz), 5.01 (1H, d, J=12.3 Hz), 5.12 (1H, q, J=7.0 Hz), 5.75 (1H, d, J=7.6 Hz), 6.06 (1H, t, J=6.9 Hz), 6.42 (1H, d, J=7.6 Hz), 6.88 (1H, d, J=6.8 Hz), 7.09–7.14 (3H, m), 7.30–7.38 (5H, m), 7.68 (2H, dd, J=5.5, 3.1 Hz), 7.77 (2H, dd, J=5.5, 3.1 Hz). ^{13}C NMR ($CDCl_3$) δ 15.4, 39.4, 46.6, 51.6, 66.7, 110.8, 122.8, 123.5, 124.8, 126.4, 127.6, 127.9, 128.2, 128.5, 129.1, 131.4, 132,1, 134.2, 135.6, 166.8, 166.9, 169.7. Anal. Calcd for $C_{29}H_{24}N_2O_5$: C, 72.49; H, 5.03; N, 5.83. Found: C, 72.45; H, 4.77; N, 5.81.

1.6.2. Benzyl 1,2-dihydro-2-[*N*-(*p*-nitrophenyl)sulfonyl-(*S*)-alanyl]isoquinolin-1-ylacetate (11b). y 57%; Yellow needles from hexane; mp 68.1–70.5°C (64% de). The NMR spectra of the major isomer are shown; ^{1}H NMR ($CDCl_3$) δ 1.39 (3H, d, J=7.0 Hz), 2.38 (1H, dd, J=13.7, 5.9 Hz), 2.48 (1H, dd, J=13.7, 8.6 Hz), 4.32 (1H, dq, J=10.1, 7.0 Hz), 4.91 (1H, d, J=12.1 Hz), 5.00 (1H, d, J=12.1 Hz), 5.50 (1H, dd, J=8.6, 5.9 Hz), 5.65 (1H, d, J=10.1 Hz), 6.14 (1H, d, J=7.7 Hz), 6.37 (1H, d, J=7.7 Hz), 6.89 (1H, d, J=7.7 Hz), 7.08–7.24 (3H, m), 7.26–7.38 (5H, m), 7.73 (2H, d, J=9.3 Hz), 7.76 (2H, d, J=9.3 Hz). ^{13}C NMR ($CDCl_3$) δ 19.2, 38.9, 48.7, 50.0, 66.8, 114.3, 121.2, 123.8, 125.4, 125.8, 128.2, 128.3, 128.39, 128.46, 128.53, 128.8, 128.9, 131.4, 135.3, 144.5, 149.7, 169.3, 169.7. Anal. Calcd for $C_{27}H_{25}N_3O_7S$: C, 60.55; H, 4.70; N, 7.85. Found: C, 60.44; H, 4.61; N, 7.50.

1.6.3. Benzyl 5,8-dibromo-1,2-dihydro-2-[*N*-phthaloyl-alanyl]isoquinolin-1-ylacetate (11c). y 77%; Colorless needles from CH_2Cl_2/hexane; mp 152.6–152.9°C (100% de, a racemic mixture). ^{1}H NMR ($CDCl_3$) δ 1.62 (3H, d, J=7.0 Hz), 2.55 (1H, dd, J=12.7, 3.8 Hz), 2.63 (1H, dd, J=12.7, 9.2 Hz), 5.03–5.10 (3H, m), 6.05 (1H, d, J=7.6 Hz), 6.41 (1H, dd, J=9.2, 3.8 Hz), 6.55 (1H, d, J=7.6 Hz), 7.21 (1H, d, J=8.7 Hz), 7.23 (1H, d, J=8.7 Hz), 7.33–7.39 (5H, m), 7.70 (2H, dd, J=5.3, 3.1 Hz), 7.78 (2H, dd, J=5.3, 3.8 Hz). ^{13}C NMR ($CDCl_3$) δ 15.4, 36.5, 46.8, 51.8, 67.1, 109.4, 119.4, 120.5, 123.6, 125.9, 128.2, 128.4, 128.5, 131.2, 131.3, 133.0, 133.1, 134.3, 135.6, 166.9, 167.3, 169.5. Anal. Calcd for $C_{29}H_{22}Br_2N_2O_5$: C, 54.57; H, 3.47; N, 4.39. Found: C, 54.27; H, 3.13; N, 4.31.

1.6.4. Benzyl 5,8-dibromo-1,2-dihydro-2-[*N*-(*p*-nitrophenyl)sulfonyl-(*S*)-alanyl]isoquinolin-1-ylacetate (11d). y 75%; Pale yellow needles from CH_2Cl_2/hexane; mp

165.6–167.8°C (100% de); $[\alpha]^{25}_{D}=-303.9$ (100% ee) (*c* 1.02, $CHCl_3$). ^1H NMR ($CDCl_3$) δ 1.38 (3H, d, *J*=7.0 Hz), 2.34 (1H, dd, *J*=13.2, 3.8 Hz), 2.46 (1H, dd, *J*=13.2, 10.3 Hz), 4.28–4.35 (1H, m), 4.91 (1H, d, *J*=12.3 Hz), 5.00 (1H, d, *J*=12.3 Hz), 5.75 (1H, d, *J*=10.3 Hz), 5.86–5.89 (1H, m), 6.44 (1H, dd, *J*=7.7, 2.0 Hz), 6.50–6.54 (1H, m), 7.26–7.38 (6H, m), 7.42 (1H, dd, *J*=8.6, 1.8 Hz), 7.79 (2H, d, *J*=8.8 Hz), 7.85 (2H, d, *J*=8.8 Hz). ^{13}C NMR ($CDCl_3$) δ 19.1, 35.8, 48.7, 49.9, 67.0, 112.4, 119.8, 120.1, 123.5, 124.0, 128.1, 128.2, 128.3, 128.4, 130.2, 132.0, 133.1, 133.6, 135.1, 144.3, 149.3, 168.7, 169.7. Anal. Calcd for $C_{27}H_{23}Br_2N_3O_7S$: C, 46.77; H, 3.34; N, 6.06. Found: C, 46.63; H, 3.01; N, 6.04.

1.6.5. Phenyl 5,8-dibromo-1,2-dihydro-2-[*N*-phthaloyl-alanyl]isoquinolin-1-ylacetate (11e). y 98%; Colorless needles from $CHCl_3$/hexane; mp 190°C (100% de, a racemic mixture). ^1H NMR ($CDCl_3$) δ 1.66 (3H, d, *J*=7.2 Hz), 2.72 (1H, dd, *J*=12.4, 8.8 Hz), 2.80 (1H, dd, *J*=12.4, 8.8 Hz), 5.20(1H, q, *J*=8.0 Hz), 6.16 (1H, d, *J*=8.0 Hz), 6.56(1H, dd, *J*=8.0, 4.0 Hz), 6.66 (1H, d, *J*=8.0 Hz), 7.18–7.28 (5H, m), 7.39 (1H, d, *J*=8.4 Hz), 7.41 (1H, d, *J*=7.6 Hz), 7.72 (2H, dd, *J*=5.6, 3.2 Hz), 7.80 (2H, dd, *J*=5.6, 3.2 Hz). ^{13}C NMR ($CDCl_3$) δ 15.5, 36.8, 46.8, 51.7, 109.6, 119.4, 120.5, 121.5, 123.5, 125.7, 125.8, 129.2, 131.1, 131.2, 132.3, 132.9, 133.1, 134.2, 150.5, 166.7, 167.4, 167.9. Anal. Calcd for $C_{28}H_{20}Br_2N_2O_5$: C, 53.84; H, 3.24; N, 4.49. Found: C, 53.55; H, 2.95; N, 4.54.

1.6.6. 5,8-Dibromo-1,2-dihydro-1-phenacyl-2-[*N*-phthaloyl-(*S*)-alanyl]isoquinoline (11f). y 99%; Colorless powder from AcOEt/hexane; mp 193–194°C (100% de); $[\alpha]^{25}_{D}=-513.3$ (100% ee) (*c* 1.02, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.57 (3H, d, *J*=6.8 Hz), 3.02 (1H, dd, *J*=12.4, 9.6 Hz), 3.29 (1H, dd, *J*=12.4, 4.4 Hz), 5.08 (1H, q, *J*=6.8 Hz), 6.09 (1H, d, *J*=7.6 Hz), 6.44 (1H, dd, *J*=8.8, 3.6 Hz), 6.58 (1H, d, *J*=8.4 Hz), 7.25 (2H, s), 7.46 (2H, t, *J*=7.6 Hz), 7.57 (1H, t, *J*=7.2 Hz), 7.69 (2H, dd, *J*=5.2, 2.8 Hz), 7.77 (2H, dd, *J*=5.2, 3.2 Hz), 7.98 (2H, d, *J*=7.2 Hz). ^{13}C NMR ($CDCl_3$) δ 15.4, 39.7, 46.7, 52.4, 109.5, 119.6, 120.5, 123.6, 126.1, 128.5, 128.6, 131.4, 131.5, 132.2, 133.0, 133.2, 133.4, 134.3, 137.2, 166.9, 167.1, 196.9. Anal. Calcd for $C_{28}H_{20}Br_2N_2O_4$: C, 55.29; H, 3.31; N, 4.61. Found: C, 54.87; H, 2.88; N, 4.50.

1.6.7. 1-Allyl-4-bromo-1,2-dihydro-2-[*N*-phthaloylalanyl]-isoquinoline (12a). y 69%; Colorless powder from hexane; mp 61.6–63.3°C (56% de, a racemic mixture). The NMR spectra of the major isomer are shown; ^1H NMR ($CDCl_3$) δ 1.68 (3H, d, *J*=6.9 Hz), 2.39 (2H, t, *J*=7.3 Hz), 4.95 (1H, d, *J*=17.0 Hz), 5.00 (1H, d, *J*=10.0 Hz), 5.15 (1H, q, *J*=6.9 Hz), 5.65 (1H, t, *J*=7.3 Hz), 5.72 (1H, ddt, *J*=17.0, 10.0, 7.3 Hz), 6.80 (1H, d, *J*=0.7 Hz), 7.03–7.09 (1H, m), 7.68 (2H, dd, *J*=5.5, 3.0 Hz), 7.75 (2H, dd, *J*=5.5, 3.0 Hz). ^{13}C NMR ($CDCl_3$) δ 15.6, 39.7, 46.8, 54.5, 106.6, 118.0, 123.3, 124.0, 124.6, 126.2, 127.5, 128.2, 128.3, 131.1, 133.2, 133.4, 134.0, 166.3, 166.5. Anal. Calcd for $C_{23}H_{19}BrN_2O_3$: C, 61.21; H, 4.24; N, 6.21. Found: C, 61.43; H, 4.17; N, 5.94.

1.6.8. 1-Allyl-1,2-dihydro-2-[*N*-phthaloylalanyl]isoquinoline (12b). y 67%; Yellow powder from CH_2Cl_2/hexane; mp 166.0–167.8°C (83% de, racemic mixture). The NMR spectra of the major isomer are shown; ^1H NMR ($CDCl_3$) δ 1.68 (3H, d, *J*=7.0 Hz), 2.40 (2H, t, *J*=7.1 Hz), 4.92 (1H, dd, *J*=17.0, 1.9 Hz), 4.98 (1H, dd, *J*=10.0, 1.9 Hz), 5.19 (1H, q, *J*=7.0 Hz), 5.66 (1H, t, *J*=7.1 Hz), 5.73 (1H, d, *J*=7.7 Hz), 5.75 (1H, ddt, *J*=17.0, 10.0, 7.1 Hz), 6.43 (1H, dd, *J*=7.7, 1.0 Hz), 6.87–6.90 (1H, m), 7.03–7.06 (1H, m), 7.09–7.16 (2H, m), 7.68 (2H, dd, *J*=5.5, 3.1 Hz), 7.78 (2H, dd, *J*=5.5, 3.1 Hz). ^{13}C NMR ($CDCl_3$) δ 15.5, 39.7, 46.7, 54.3, 111.0, 117.7, 123.1, 123.5, 124.7, 126.4, 127.1, 127.4, 129.3, 131.4, 133.3, 134.0, 134.1, 166.8, 167.0. Anal. Calcd for $C_{23}H_{20}N_2O_3$: C, 74.18; H, 5.41; N, 7.52. Found: C, 74.06; H, 5.42; N, 7.58.

1.6.9. 1-Allyl-5,8-dibromo-1,2-dihydro-2-[*N*-phthaloyl-alanyl]isoquinoline (12c). y 75%; Colorless powder from CH_2Cl_2/hexane; mp 170.9–171.5°C (100% de, a racemic mixture). ^1H NMR ($CDCl_3$) δ 1.71 (3H, d, *J*=7.0 Hz), 2.40 (2H, t, *J*=7.2 Hz), 4.96 (1H, d, *J*=17.2 Hz), 5.01 (H, d, *J*=10.0 Hz), 5.20 (1H, q, *J*=7.0 Hz), 5.84 (2H, ddt, *J*=17.2, 10.0, 7.2 Hz), 6.08 (1H, d, *J*=7.8 Hz), 6.12 (1H, t, *J*=7.2 Hz), 6.59 (1H, d, *J*=7.8 Hz), 7.19 (1H, d, *J*=8.5 Hz), 7.21 (1H, d, *J*=8.5 Hz), 7.70 (2H, dd, *J*=5.3, 2.9 Hz), 7.78 (2H, dd, *J*=5.3, 2.9 Hz). ^{13}C NMR ($CDCl_3$) δ 15.5, 37.0, 46.8, 53.3, 109.7, 117.7, 119.2, 120.4, 123.4, 125.7, 131.0, 131.2, 132.1, 132.4, 133.6, 134.1, 134.4, 166.9, 167.1. Anal. Calcd for $C_{23}H_{18}Br_2N_2O_3$: C, 52.10; H, 3.42; N, 5.28. Found: C, 51.97; H, 3.07; N, 5.24.

1.7. Reduction of bromo groups and a double bond at C3–C4 of compound 11 or 12

To a solution of compound **11c** (0.32 mmol) in MeOH (25 ml)/AcOEt (10 ml), 10% Pd/C (200 mg) was added and the mixture was allowed to react under H_2 atmosphere at room temperature for 3 h. Then the mixture was filtered through a plug of Celite, and the filtrate was evaporated to dryness under reduced pressure. The residue was purified by silica gel chromatography (AcOEt) to give the product.

1.7.1. Methyl 1,2,3,4-tetrahydro-2-[*N*-phthaloylalanyl]-isoquinolin-1-ylacetate (13a). y 76%; Colorless needles from Et_2O/hexane; mp 143.5–144.5°C (100% de, a racemic mixture). The product was obtained as a mixture of two conformational isomers (2:1). The NMR spectra of the major isomer are shown; ^1H NMR ($CDCl_3$) δ 1.77 (3H, d, *J*=6.0 Hz), 2.72–2.93 (6H, m), 3.61–3,77 (2H, m), 3.69 (3H, s), 5.23 (1H, q, *J*=5.9 Hz), 5.93 (1H, dd, *J*=6.6, 4.4 Hz), 7.04 (1H, d, *J*=5.9 Hz), 7.13–7.18 (3H, m), 7.71 (2H, dd, *J*=4.4, 2.4 Hz), 7.82 (2H, dd, *J*=4.4, 2.4 Hz). ^{13}C NMR ($CDCl_3$) δ 15.4, 29.1, 40.2, 41.2, 47.4, 50.9, 52.0, 123.5, 126.8, 127.1, 127.2, 128.6, 131.7, 133.3, 134.2, 135.8, 167.7, 168.3, 170.9. Anal. Calcd for $C_{23}H_{22}N_2O_5$: C, 67.97; H, 5.46; N, 6.89. Found: C, 68.03; H, 5.37; N, 6.89.

1.7.2. 1,2,3,4-Tetrahydro-2-[*N*-phthaloylalanyl]-1-propylisoquinoline (13b). y 91%; Colorless powder from AcOEt/hexane; mp 114.4–115.3°C (100% de, a racemic mixture). The product was obtained as a mixture of two conformational isomers (2.5:1). The NMR spectra of the major isomer are shown; ^1H NMR ($CDCl_3$) δ 0.95 (3H, t, *J*=7.2 Hz), 1.31–1.51 (2H, m), 1.66–1.89 (2H, m), 1.83

(3H, d, J=7.2 Hz), 2.75–2.89 (2H, m), 3.60 (1H, ddd, J=13.6, 9.6, 5.2 Hz), 3.75 (1H, dt, J=13.6, 4.4 Hz), 5.27 (1H, q, J=7.2 Hz), 5.55 (1H, dd, J=8.8, 5.6 Hz), 7.00–7.21 (4H, m), 7.68 (2H, dd, J=5.6, 3.2 Hz), 7.80 (2H, dd, J=5.6, 3.2 Hz). ^{13}C NMR ($CDCl_3$) δ 13.9, 15.5, 19.5, 29.0, 38.9, 39.8, 47.5, 53.2, 123.3, 126.1, 126.3, 127.4, 128.3, 131.6, 132.9, 134.0, 137.6, 167.7, 168.1. Anal. Calcd for $C_{23}H_4N_2O_3$: C, 73.38; H, 6.43; N, 7.44. Found: C, 73.18; H, 6.66; N, 7.41.

1.7.3. 1,2,3,4-Tetrahydro-1-phenethyl-2-[*N*-phthaloyl-(*S*)-alanyl]isoquinoline (13c). y 82%; Colorless powder from CH_2Cl_2/AcOEt; mp 140–141°C (100% de); $[\alpha]^{25}_D$=−64.9 (100% ee) (c 1.02, $CHCl_3$). The product was obtained as a mixture of two conformational isomers (2.5:1). The NMR spectra of the major isomer are shown; ^{1}H NMR ($CDCl_3$) δ 1.83 (3H, d, J=6.0 Hz), 2.02–2.93 (2H, m), 2.61–2.86 (4H, m), 3.61 (1H, ddd, J=10.4, 7.2, 4.2 Hz), 3.77 (1H, dt, J=11.0, 3.7 Hz), 5.24 (1H, q, J=5.9 Hz), 5.67 (1H, dd, J=4.4, 2.9 Hz), 7.01–7.27 (9H, m), 7.69 (2H, dd, J=4.4, 2.4 Hz), 7.81 (2H, dd, J=4.4, 2.4 Hz). ^{13}C NMR ($CDCl_3$) δ 15.6, 29.1, 32.7, 38.3, 40.0, 47.5, 53.5, 123.4, 125.8, 126.4, 126.6, 127.5, 128.27, 128.34, 128.5, 131.7, 134.0, 134.1, 137.3, 141.7, 167.8, 168.7. Anal. Calcd for $C_{28}H_{26}N_2O_3$: C, 76.69; H, 5.98; N, 6.39. Found: C, 76.34; H, 6.05; N, 6.36.

1.8. Synthesis of 1,2,3,4-tetrahydro-1-phenethylisoquinoline (14)

To a THF solution (14 ml) of compound **13c** (1.0 mmol), $LiAlH_4$ (2.5 mmol) was added and the mixture was allowed to react for 1 h at room temperature. Then water was added and the mixture was extracted with AcOEt. The organic layer was dried over $MgSO_4$, and evaporated off to leave a residue, which was chromatographed on silica gel ($CHCl_3$/MeOH=20) to give the product.

1.8.1. 1,2,3,4-Tetrahydro-1-(2-phenethyl)isoquinoline (14). y 85%; Pale brown oil; $[\alpha]^{25}_D$=+23.2 (100% ee) (c 1.02, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.99–2.18 (3H, m), 2.68–2.86 (4H, m), 2.99 (1H, ddd, J=12.4, 7.6, 5.2 Hz), 3.23 (1H, dt, J=12.4, 5.6 Hz), 3.99 (1H, dd, J=9.2, 3.6 Hz), 7.05–7.29 (9H, m). ^{13}C NMR ($CDCl_3$) δ 29.9, 32.4, 38.1, 40.9, 55.3, 125.8, 125.9, 126.1, 128.4, 129.3, 135.2, 139.3, 142.3. HRMS (FAB): Calcd for $C_{17}H_{20}N$ $(M+H)^+$: 238.1595. Found 238.1619.

1.9. Conversion of compound 14 to the MTPA derivative 15

Triethylamine (0.3 ml) and a THF solution (2 ml) of (*R*)-methoxy(trifluoromethyl)phenylacetyl chloride ((*R*)-MTPA chloride) (0.4 mmol) were successively added to a CH_2Cl_2 solution (2 ml) of compound **14** (0.11 mmol), and the mixture was allowed to react for 8 h at room temperature. After addition of AcOEt (15 ml), the mixture was washed with sat. $NaHCO_3$ (10 ml×3), and the organic layer was dried over $MgSO_4$, and evaporated. The residue was purified with alumina column chromatography (CH_2Cl_2/hexane=1) to give the product.

1.9.1. 1,2,3,4-tetrahydro-2-[methoxy(trifluoromethyl)-phenylacetyl]-1-(2-phenethyl)isoquinoline (15). y 56%; Colorless oil. The product was obtained as a mixture of two conformers (4:1). In the ^{1}H NMR, the existence of two conformers was shown only at the peak of OMe group (δ 3.84 and 3.23); ^{1}H NMR ($CDCl_3$) δ 1.49 (1H, ddd, J=16.5, 11.0, 5.5 Hz), 2.12–2.18 (3H, m), 2.71–2.88 (2H, m), 3.39 (1H, ddd, J=14.1, 11.7, 4.6 Hz), 3.84 (3.23 for the minor isomer) (3H, q, J=1.5 Hz), 4.11 (1H, ddd, J=13.9, 5.2, 1.3 Hz), 5.82 (1H, dd, J=8.4, 5.0 Hz), 6.84 (1H, d, J=7.5 Hz), 7.06–7.54 (13H, m). In the ^{13}C NMR, almost all the peaks showed the existence of the isomers, thus the NMR spectra of the major isomer are shown; ^{13}C NMR ($CDCl_3$) δ 26.7, 33.2, 38.2, 38.9, 40.6, 53.1, 55.8, 126.0, 126.1, 126.6, 126.7, 127.1, 127.5, 128.2, 128.3, 128.4, 128.5, 129.3, 132.9, 133.9, 136.5, 141.5, 164.6. HRMS (FAB): Calcd for $C_{27}H_{27}F_3NO_2$ $(M+H)^+$: 454.1994. Found 454.1963.

The proton on C-1 position of **15** showed a double doublet signal at δ 5.82. A corresponding diastereomeric mixture was synthesized using racemic **14** and (*R*)-MTPA chloride, and the mixture showed the signal of C-1 proton at 5.71 (t, J=7.2 Hz) and 5.82 (dd, J=8.4, 5.0 Hz) at a ratio of 1 to 1. In Ref. 17b, Hoye and Renner extended modified Mosher method to secondary amines which have a chiral center at α-position. They suggested that positive $\Delta\delta$ ((the δ value of (*S*)-MTPA amide)−(the δ value of (*R*)-MTPA amide)) indicates the absolute configuration as (*R*). Thus the configuration of compound **14** was indicated as (*R*) using the above data ($\Delta\delta$=+0.11).

1.10. Reaction of 6,7-dimethoxyisoquinolines (16 or 17) with silyl enol ethers or allyltributyltin in the presence of an acyl chloride derived from (*S*)-alanine

The same procedure as in the case of isoquinoline (**1**, **4** and **5**) was applied to these reactions.

1.10.1. Benzyl 1,2-dihydro-6,7-dimethoxy-2-[*N*-phthaloyl-(*S*)-alanyl]isoquinolin-1-yl-acetate (20a). y 38%; Pale yellow powder from AcOEt/Hexane; mp 173.5–174.2°C (83% de). The NMR spectra of the major isomer are shown; ^{1}H NMR ($CDCl_3$) δ 1.62 (3H, d, J=7.2 Hz), 2.62 (1H, dd, J=13.6, 7.0 Hz), 2.68 (1H, dd, J=13.6, 6.8 Hz), 3.75 (3H, s), 3.77 (3H, s), 5.03 (1H, d, J=12.4 Hz), 5.10 (1H, d, J=12.4 Hz), 5.11 (1H, q, J=6.4 Hz), 5.69 (1H, d, J=8.0 Hz), 6.02 (1H, t, J=6.8 Hz), 6.34 (1H, d, J=8.0 Hz), 6.40 (1H, s), 6.69 (1H, s), 7.31–7.38 (5H, m), 7.69 (2H, dd, J=5.6, 3.2 Hz), 7.78 (2H, dd, J=5.6, 3.2 Hz). ^{13}C NMR ($CDCl_3$) δ 15.5, 39.3, 46.5, 51.2, 55.7, 55.8, 66.5, 107.9, 109.7, 110.7, 120.9, 121.8, 123.3, 124.7, 127.9, 128.0, 128.3, 131.1, 133.9, 135.4, 148.06, 148.10, 166.5, 166.6, 169.6. Anal. Calcd for $C_{31}H_{28}N_2O_7$: C, 68.88; H, 5.22; N, 5.18. Found C, 68.67; H, 5.11; N, 5.18.

1.10.2. Benzyl 1,2-dihydro-6,7-dimethoxy-2-[*N*-(*p*-nitrophenyl)sulfonyl-(*S*)-alanyl]isoquinolin-1-ylacetate (20b). y 20%; Yellow needles from hexane; mp 77.9–79.0°C (61% de). The NMR spectra of the major isomer are shown; ^{1}H NMR ($CDCl_3$) δ 1.37 (3H, d, J=7.0 Hz), 2.39 (1H, dd, J=13.7, 6.0 Hz), 2.45 (1H, dd, J=13.7, 8.1 Hz), 3.82 (3H, s), 3.93 (3H, s), 4.35 (1H, bs), 4.91 (1H, d, J=12.2 Hz), 4.98 (1H, d, J=12.2 Hz), 5.43 (1H, dd, J=8.1, 6.0 Hz), 5.85–5.88 (1H, m), 6.06 (1H, d, J=7.5 Hz), 6.30 (1H, d,

J=7.5 Hz), 6.47 (1H, s), 6.65 (1H, s), 7.24–7.28 (2H, m), 7.30–7.36 (3H, m), 7.79 (2H, d, J=9.3 Hz), 7.82 (2H, d, J=9.3 Hz). ^{13}C NMR ($CDCl_3$) δ 19.2, 39.1, 48.7, 49.8, 55.9, 56.1, 66.7, 108.5, 108.6, 114.0, 119.0, 120.9, 123.6, 123.9, 128.10, 128.12, 128.17, 128.3, 135.1, 144.2, 148.8, 149.2, 149.3, 169.2, 169.3. HRMS (FAB): Calcd for $C_{29}H_{30}N_3O_9S$ $(M+H)^+$: 596.1703. Found 596.1702.

1.10.3. Benzyl 5,8-dibromo-1,2-dihydro-6,7-dimethoxy-2-[*N*-phthaloylalanyl]isoquinolin-1-ylacetate (20c). y 100%; Colorless powder from AcOEt/hexane; mp 68.5–69.8°C (100% de, a racemic mixture). ^{1}H NMR ($CDCl_3$) δ 1.62 (3H, d, J=7.2 Hz), 2.55 (1H, dd, J=12.8, 4.0 Hz), 2.62 (1H, dd, J=12.8, 9.2 Hz), 3.83 (3H, s), 3.86 (3H, s), 5.02–5.11 (1H, m), 6.10 (1H, d, J=7.6 Hz), 6.44 (1H, dd, J=8.4, 3.2 Hz), 6.51 (1H, d, J=7.6 Hz), 7.28–7.39 (5H, m), 7.71 (2H, dd, J=5.6, 2.8 Hz), 7.78 (2H, dd, J=5.2, 3.2 Hz). ^{13}C NMR ($CDCl_3$) δ 15.4, 36.5, 46.8, 51.6, 60.7, 60.9, 67.1, 109.6, 115.5, 116.8, 123.5, 124.8, 127.2, 128.2, 128.4, 128.5, 128.9, 131.4, 134.2, 134.3, 135.7, 150.3, 167.0, 167.3, 169.7. HRMS (FAB): Calcd for $C_{31}H_{27}Br_2N_2O_7$ $(M+H)^+$: 697.0185. Found 697.0253.

1.10.4. Benzyl 5,8-dibromo-1,2-dihydro-6,7-dimethoxy-2-[*N*-(*p*-nitrophenyl)sulfonyl-(*S*)-alanyl]isoquinolin-1-ylacetate (20d). y 86%; Colorless powder from AcOEt/hexane; mp 139°C (100% de); $[\alpha]^{25}_D$=−209.3 (100% ee) (c 1.09, $CHCl_3$). ^{1}H NMR ($CDCl_3$) δ 1.38 (3H, d, J=7.0 Hz), 2.35 (1H, dd, J=13.0, 3.7 Hz), 2.42 (1H, dd, J=13.0, 9.0 Hz), 3.98 (3H, s), 3.99 (3H, s), 4.27(1H, dq, J=10.1, 7.0 Hz), 5.75 (1H, d, J=10.1 Hz), 5.87 (1H, dd, J=9.5, 3.7 Hz), 6.44 (2H, s), 7.29–7.36 (5H, m), 7.83 (2H, d, J=8.8 Hz), 7.90 (2H, d, J=8.8 Hz). ^{13}C NMR ($CDCl_3$) δ 19.1, 36.2, 48.8, 50.1, 60.8, 61.0, 67.0, 112.2, 116.3, 116.4, 122.7, 123.6, 126.1, 127.7, 128.2, 128.3, 128.5, 128.6, 135.3, 144.3, 149.5, 151.0, 151.2, 169.0, 169.8. Anal. Calcd. for $C_{29}H_{27}Br_2N_3O_9S$: C, 46.20; H, 3.62; N, 5.58. Found: C, 46.47; H, 3.37; N, 5.58.

1.10.5. 5,8-Dibromo-1-(3,4-dimethoxyphenacyl)-1,2-dihydro-6,7-dimethoxy-2-[*N*-(*p*-nitrophenyl)sulfonyl-(*S*)-alanyl]isoquinoline (20e). y 93%; Colorless powder from AcOEt/Hexane; mp 213–214°C (100% de); $[\alpha]^{25}_D$=−284.9 (100% ee) (c 0.46, $CHCl_3$). ^{1}H NMR ($CDCl_3$) δ 1.40 (3H, d, J=7.0 Hz), 2.63 (1H, dd, J=12.3, 11.2 Hz), 3.13 (1H, dd, J=12.6, 3.7 Hz), 3.90 (3H, s), 3.94 (3H, s), 4.01 (3H, s), 4.04 (3H, s), 4.23 (2H, dq, J=10.3, 7.0 Hz), 5.54 (1H, d, J=10.3 Hz), 5.87 (1H, dd, J=10.7, 3.3 Hz), 6.50 (2H, s), 6.88 (1H, d, J=8.4 Hz), 7.36 (1H, d, J=1.8 Hz), 7.62 (1H, dd, J=8.4, 1.8 Hz), 7.77 (2H, d, J=9.0 Hz), 7.85 (2H, d, J=8.8 Hz). ^{13} C NMR ($CDCl_3$) δ 19.1, 29.7, 39.0, 48.8, 50.6, 56.0, 56.1, 60.8, 61.1, 110.0, 110.6, 112.1, 116.1, 116.6, 122.9, 123.3, 123.6, 126.2, 128.3, 128.7, 129.7, 144.2, 149.1, 149.4, 150.9, 151.1, 153.7, 169.8, 194.4. Anal. Calcd for $C_{30}H_{29}$ $Br_2N_3O_{10}S$: C, 45.99; H, 3.73; N, 5.36. Found: C, 46.19; H, 3.50; N, 5.38.

1.10.6. 5,8-Dibromo-1,2-dihydro-6,7-dimethoxy-2-[*N*-(*p*-nitrophenyl)sulfonyl-(*S*)-alanyl]-1-phenacylisoquinoline (20f). y 85%; Yellow prisms from AcOEt/hexane; mp 219–220°C (100% de); $[\alpha]^{25}_D$=−222.4 (100% ee) (c 0.41, $CHCl_3$). ^{1}H NMR ($CDCl_3$) δ 1.37 (3H, d, J=6.8 Hz), 2.69 (1H, dd, J=12.4, 10.8 Hz), 3.17 (1H, dd, J=12.8, 3.6 Hz), 4.01 (3H, s), 4.04 (3H, s), 4.22 (1H, dq, J=10.4, 7.0 Hz), 5.57 (1H, d, J=10.4 Hz), 5.87 (1H, dd, J=10.8, 3.6 Hz), 6.48 (1H, d, J=1.2 Hz), 6.49 (1H, d, J=1.2 Hz), 7.44 (2H, t, J=7.2 Hz), 7.57 (1H, t, J=7.6 Hz), 7.77 (2H, d, J=9.2 Hz), 7.85 (2H, d, J=9.2 Hz), 7.89 (2H, d, J=8.0 Hz). ^{13}C NMR ($CDCl_3$) δ 19.3, 39.6, 49.0, 50.6, 61.2, 61.4, 112.5, 116.4, 116.8, 123.8, 124.3, 126.5, 128.6, 128.9, 129.0, 133.8, 136.6, 144.5, 149.7, 151.2, 151.4, 170.1, 196.3. Anal. Calcd for $C_{28}H_{25}Br_2N_3O_8S$: C, 46.49; H, 3.48; N, 5.81. Found: C, 46.78; H, 3.19; N, 5.75.

1.10.7. 1-Acetonyl-5,8-dibromo-1,2-dihydro-6,7-dimethoxy-2-[*N*-(*p*-nitrophenyl)sulfonyl-(*S*)-alanyl]isoquinoline (20g). y 65%; Colorless powder from AcOEt/hexane; mp 207–209°C (100% de); $[\alpha]^{25}_D$=−276.8 (100% ee) (c 0.21, $CHCl_3$). ^{1}H NMR ($CDCl_3$) δ 1.43 (3H, d, J=8.0 Hz), 2.21 (3H, s), 2.31 (1H, t, J=11.2 Hz), 2.46 (1H, dd, J=12.0, 2.8 Hz), 4.00 (3H, s), 4.02 (3H, s), 4.26 (1H, dq, J=10.4, 6.8 Hz), 5.60 (1H, d, J=8.0 Hz), 5.82 (1H, ddd, J=11.6, 2.4, 1.2 Hz), 6.44 (1H, dd, J=7.6, 0.8 Hz), 6.49 (1H, d, J=7.6 Hz), 7.82 (2H, d, J=9.2 Hz), 7.90 (2H, d, J=8.8 Hz). ^{13}C NMR ($CDCl_3$) δ 19.1, 29.7, 44.7, 48.8, 49.7, 60.9, 61.1, 112.3, 116.1, 116.6, 122.4, 123.7, 126.0, 128.0, 128.7, 144.4, 149.5, 151.1, 151.2, 170.2, 204.8. Anal. Calcd for $C_{23}H_{23}Br_2N_3O_8S$: C, 41.77; H, 3.51; N, 6.35. Found: C, 42.02; H, 3.23; N, 6.32.

1.10.8. 1-Allyl-5,8-dibromo-1,2-dihydro-6,7-dimethoxy-2-[*N*-phthaloylalanyl]isoquinoline (21a). y 83%; Yellow powder from AcOEt/hexane; mp 125–126°C (100% de, a racemic mixture). ^{1}H NMR ($CDCl_3$) δ 1.70 (3H, d, J=6.8 Hz), 2.38 (2H, t, J=6.8 Hz), 3.85 (3H, s), 3.88 (3H, s), 4.96 (1H, dd, J=16.8, 1.6 Hz), 5.01 (1H, dd, J=10.4, 1.6 Hz), 5.16 (1H, q, J=6.8 Hz), 5.79–5.90 (1H, m), 6.09–6.16 (2H, m), 6.50 (1H, dd, J=6.8, 1.6 Hz), 7.71 (2H, dd, J=5.6, 3.2 Hz), 7.79 (2H, dd, J=5.6, 3.2 Hz). ^{13}C NMR ($CDCl_3$) δ 15.5, 37.1, 53.3, 60.7, 60.9, 110.1, 116.0, 116.8, 117.7, 123.5, 124.6, 127.1, 130.6, 131.4, 133.9, 134.2, 150.1, 150.3, 167.1, 167.2. HRMS (FAB): Calcd for $C_{25}H_{23}N_2O_5Br_2$ $(M+H)^+$: 588.9973. Found 588.9968.

1.10.9. 1-Allyl-5,8-dibromo-1,2-dihydro-6,7-dimethoxy-2-[*N*-(*p*-nitrophenyl)sulfonyl-(*S*)-alanyl]isoquinoline (21b). y 73%; Yellow granules from AcOEt/hexane; mp 176–177°C (75% de). The NMR spectra of the major isomer are shown; ^{1}H NMR ($CDCl_3$) δ 1.40 (3H, d, J=6.8 Hz), 2.13–2.26 (2H, m), 4.00 (6H, s), 4.30 (1H, dq, J=10.0, 6.8 Hz), 4.86 (1H, dd, J=16.8, 1.6 Hz), 4.91 (1H, dd, J=10.4, 1.6 Hz), 5.53–5.65 (2H, m), 5.80 (1H, d, J=8.4 Hz), 6.39 (1H, dd, J=7.6, 1.2 Hz), 6.44 (1H, d, J=7.6 Hz), 7.84 (2H, d, J=8.8 Hz), 7.90 (2H, d, J=9.2 Hz). ^{13}C NMR ($CDCl_3$) δ 19.6, 37.1, 48.7, 51.8, 60.8, 61.0, 112.4, 116.1, 116.3, 118.0, 122.5, 123.6, 125.9, 128.6, 129.4, 133.4, 144.3, 149.5, 150.7, 150.8, 169.8. HRMS (FAB): Calcd for $C_{23}H_{24}Br_2N_3O_7S$ $(M+H)^+$: 643.9701. Found 643.9750.

1.11. Reduction of compounds 20 to tetrahydro derivatives 22

To a MeOH solution (2 ml) of compound **20** (0.2 mmol) were added sat. HCO_2NH_4 (2 ml) and 10% Pd/C(0.4 equiv.), and the mixture was allowed to react for 6 h

at room temperature. Then the mixture was filtered through a plug of Celite, and the filtrate was evaporated in vacuo. To the residue was added AcOEt (60 ml), and the solution was washed with two portions of water (10 ml) and brine (5 ml). The organic layer was dried over $MgSO_4$, and evaporated to leave a residue, which was chromatographed on silica gel to give compound **22**.

1.11.1. 2-[*N*-(*p*-Aminophenyl)sulfonyl-(*S*)-alanyl]-1,2,3,4-tetrahydro-6,7-dimethoxyisoquinolin-1-ylacetic acid (22a). y 98%; Colorless powder from AcOEt/hexane; mp 128–130°C (100% de); $[\alpha]^{25}_D$=+17.8 (100% ee) (*c* 0.087, $CHCl_3$). ^{1}H NMR (CD_3OD) δ 1.28 (3H, d, *J*=7.1 Hz), 2.55–2.83 (4H, m), 3.47 (1H, m), 3.75 (1H, m), 3.85 (3H, s), 3.88 (3H, s), 4.25 (1H, dq, *J*=10.1, 7.1 Hz), 5.57 (1H, d, *J*=10.1 Hz), 6.22 (2H, d, *J*=8.6 Hz), 6.63 (1H, s), 6.65 (1H, m), 7.42 (2H, d, *J*=8.6 Hz). ^{13}C NMR (CD_3OD) δ 19.3, 28.1, 39.1, 41.4, 49.2, 50.3, 56.0, 56.2, 109.8, 111.2, 113.7, 119.1, 124.8, 127.0, 129.0, 147.9, 148.3, 150.5, 171.6, 173.9. Anal. Calcd for $C_{22}H_{29}N_3O_8S$ (monohydrate): C, 53.32; H, 5.90; N, 8.48. Found: C, 53.36; H, 5.48; N, 8.01.

1.11.2. 2-[*N*-(*p*-Aminophenyl)sulfonyl-(*S*)-alanyl]1,2,3,4-tetrahydro-6,7-dimethoxy-1-(3,4-dimethoxyphenacyl)-isoquinoline (22b). y 65%; Colorless powder (isolated with preparative TLC); mp 135–137°C (100% de); $[\alpha]^{25}_D$=−36.2 (100% ee) (*c* 0.31, $CHCl_3$). ^{1}H NMR ($CDCl_3$) δ 1.21 (3H, d, *J*=6.8 Hz), 2.56–2.77 (2H, m), 3.16 (1H, dd, *J*=14.0, 6.8 Hz), 3.29 (1H, dd, *J*=14.0, 6.8 Hz), 3.53–3.56 (2H, m), 3.78 (3H, s), 3.87 (3H, s), 3.92 (3H, s), 3.94 (3H, s), 4.09 (1H, dq, *J*=9.2, 7.2 Hz), 5.62 (1H, d, *J*=8.8 Hz), 5.64 (1H, d, *J*=6.8 Hz), 6.26 (2H, d, *J*=8.8 Hz), 6.54 (1H, s), 6.60 (1H, s), 7.43 (2H, d, *J*=8.8 Hz), 7.52 (1H, s), 7.55 (1H, s), 7.57 (1H, s). ^{13} C NMR ($CDCl_3$) δ 19.9, 28.2, 40.2, 44.7, 49.1, 50.5, 56.0, 56.08, 56.12, 56.2, 110.0, 110.1, 110.2, 111.1, 113.5, 122.9, 124.9, 127.6, 127.8, 129.0, 130.0, 147.4, 147.9, 149.0, 150.2, 153.3, 170.4, 195.4. HRMS (FAB): Calcd for $C_{30}H_{36}N_3O_8S$ $(M+H)^+$: 598.2223. Found 598.2272.

1.11.3. 2-[*N*-(*p*-Aminophenyl)sulfonyl-(*S*)-alanyl]-1,2,3,4-tetrahydro-1-(2-hydroxyphenethyl)isoquinoline (22c). y 62%; Colorless powder (isolated with preparative TLC); mp 164–166°C. The product was obtained as a mixture of diastereomers and conformers (ratio unknown). The NMR spectra of a major isomer are shown; ^{1}H NMR ($CDCl_3$) δ 1.48 (3H, d, *J*=6.8 Hz), 1.97–2.01 (2H, m), 2.61–3.06 (3H, m), 3.71–3.75 (2H, m), 3.90 (3H, s), 3.92 (3H, m), 4.42 (1H, dq, *J*=10.4, 6.8 Hz), 5.44 (1H, d, *J*=10.4 Hz), 5.59 (1H, d, *J*=10.0 Hz), 6.00 (2H, d, *J*=8.4 Hz), 6.63 (1H, s), 6.69 (1H, s), 7.12–7.33 (5H, m), 7.37 (2H, d, *J*=8.8 Hz). ^{13}C NMR ($CDCl_3$) δ 20.2, 28.0, 39.1, 45.9, 49.2, 50.1, 53.4, 56.0, 69.4, 109.7, 111.0, 113.6, 113.9, 125.4, 127.2, 128.3, 128.4, 129.0, 129.1, 129.2, 142.9, 147.7, 147.8, 150.5. Anal. Calcd for $C_{28}H_{35}N_3O_7S$ (monohydrate): C, 60.31; H, 6.33; N, 7.54. Found: C, 60.22; H, 5.88; N, 7.18.

1.12. Transformation of compound 20e to 24 via three steps of reduction

Compound **20e** (493 mg), which was purified to optically pure form by recrystallization, was dissolved in MeOH (30 ml)/THF (12 ml) solvent. Then sat. HCO_2NH_4 (10 ml) and 10% Pd/C (325 mg) was added to the solution, and the mixture was allowed to react for 17 h at room temperature. The mixture was filtered through a plug of Celite, and the filtrate was concentrated in vacuo. To the residue was added 10 ml of water, and the mixture was extracted with three portions of AcOEt (20 ml). The organic layer was washed with brine (5 ml), dried over $MgSO_4$, and evaporated to give compound **22b** (426 mg). The compound **22b** (387 mg) was dissolved in a mixed solvent of AcOH (20 ml) and trifluoroacetic acid (2 ml), and 10% Pd/C (510 mg) was added successively. The mixture was allowed to stir for 21 h under H_2 atmosphere at room temperature, then was filtered to give a filtrate, to which AcOEt (100 ml) was added. The mixture was washed with aq. 20% K_2CO_3 (20 ml×3), and the aqueous layer was extracted with AcOEt (20 ml×2). The organic layers were combined, washed with brine (15 ml), dried over $MgSO_4$, and evaporated off to leave **23** (278 mg) as colorless oil. Compound **23** was used for the next procedure without further purification. To a THF solution (10 ml) of compound **23** (182 mg) was added $LiAlH_4$ (60 mg), and the mixture was allowed to react at 0°C for 1 h. After addition of 20 ml of water, the mixture was extracted with AcOEt (20 ml×4). The organic layer was washed with brine, dried over $MgSO_4$, and evaporated off. The residue was purified by silica gel chromatography (AcOEt) to give compound **24** (65 mg).

1.12.1. 2-[*N*-(*p*-Aminophenyl)sulfonyl-(*S*)-alanyl]-6,7-dimethoxy-1,2,3,4-tetrahydro-1-(3,4-dimethoxyphenethyl)-isoquinoline (23). The product was obtained as a mixture of two conformers (7:1). The NMR spectra of the major isomer are shown; ^{1}H NMR ($CDCl_3$) δ 1.38 (3H, d, *J*=7.0 Hz), 1.90–2.05 (2H, m), 2.40–2.45 (1H, m), 2.55–2.66 (4H, m), 3.43–3.50 (1H, m), 3.834 (3H, s), 3.836 (3H, s), 3.85 (3H, s), 3.88 (3H, s), 4.18 (1H, dq, *J*=9.2, 7.0 Hz), 5.24 (1H, dd, *J*=9.9, 5.3 Hz), 5.74 (1H, d, *J*=9.2 Hz), 6.23 (2H, d, *J*=8.8 Hz), 6.48 (1H, s), 6.58 (1H, s), 6.65–6.67 (2H, m), 6.77 (1H, d, *J*=8.8 Hz), 7.44 (2H, d, *J*=8.8 Hz). ^{13}C NMR ($CDCl_3$) δ 20.4, 28.1, 32.0, 37.9, 38.9, 49.1, 52.3, 55.85, 55.91, 55.98, 56.02, 56.2, 110.1, 111.2, 111.6, 113.7, 119.9, 124.5, 127.4, 129.02, 129.08, 129.14, 133.9, 147.3, 147.4, 147.8, 148.8, 150.3, 170.8.

1.12.2. 1,2,3,4-Tetrahydro-6,7-dimethoxy-1-(3,4-dimethoxyphenethyl)isoquinoline (24). y 50% from **20e**. Colorless oil; $[\alpha]^{25}_D$=+4.3 (100% ee) (*c* 0.32, EtOH). ^{1}H NMR ($CDCl_3$) δ 1.26 (1H, brs), 2.04–2.14 (2H, m), 2.67–2.73 (2H, m), 2.78–2.85(2H, m), 3.04 (1H, ddd, *J*=10.0, 5.9, 4.2 Hz), 3.29 (1H, dt, *J*=10.0, 4.4 Hz), 3.83 (3H, s), 3.852 (3H, s), 3.856 (3H, s), 3.862 (3H, s), 4.04 (1H, dd, *J*=7.0, 2.4 Hz), 6.57 (1H, s), 6.58 (1H, s), 6.76–6.81 (3H, m). ^{13}C NMR ($CDCl_3$) δ 28.8, 29.7, 31.9, 38.2, 40.9, 55.0, 55.8, 55.9, 56.1, 109.2, 111.3, 111.7, 111.8, 120.2, 126.8, 130.1, 134.6, 147.3, 147.4, 147.6, 148.9. HRMS (FAB): Calcd for $C_{21}H_{27}NO_4$ $(M+H)^+$: 358.2019. Found 358.2060.

1.12.3. Synthesis of homolaudanosine (25). To a CH_3CN solution (0.3 ml) of compound **24** (0.07 mmol) was added 37% aq. HCHO solution (30 mg) and $NaBH_3CN$ (8 mg), and the mixture was allowed to react for 40 min at room temperature. After quenching with AcOH, 10% aq. NaOH (4 ml) was added and the mixture was extracted with AcOEt

(6 ml×3). The organic layer was extracted with 10% aq. HCl (4 ml×3), which was made basic with 20% aq. NaOH. The basic aqueous layer was extracted with AcOEt (8 ml×3), and the organic layers thus obtained were combined, dried over $MgSO_4$ and evaporated off to leave crude homolaudanosine (**25**). Preparative TLC (silica gel 5717, $CHCl_3$/MeOH=20) was employed for further purification. y 71%. Colorless oil. $[\alpha]^{20}_D$=+11.7 (100% ee) (*c* 0.75, EtOH). ^{1}H NMR ($CDCl_3$) δ 2.01–2.07 (2H, m), 2.48 (3H, s), 2.50–2.56 (1H, m), 2.66–2.81 (4H, m), 3.12–3.18 (1H, m), 3.43 (1H, t, *J*=5.4 Hz), 3.83 (3H, s), 3.85 (3H, s), 3.856 (3H, s), 3.858 (3H, s), 6.54 (1H, s), 6.58 (1H, s), 6.71–6.74 (2H, m), 6.79 (1H, d, *J*=8.1 Hz). These data are identical with the reported ones.[18]

1.13. Molecular orbital calculations

The molecular orbital calculations were carried out using the PM3 procedure[28] with the standard parameters, as implemented in the MOPAC2000 program.

1.14. Synthesis of the 1,2-addition products using chiral auxiliaries derived from (*S*)-valine

The same procedure as in the case of **16** or **17** was applied to these reactions. The de was estimated from ^{1}H NMR data of the crude sample before the column chromatography. The melting points and spectral data were obtained from the samples after purification.

1.14.1. Benzyl 5,8-dibromo-1,2-dihydro-6,7-dimethoxy-2-[*N*-(*p*-nitrophenyl)sulfonyl-(*S*)-valinyl]isoquinolin-1-ylacetate (26). y 68%; Colorless powder from $CHCl_3$/hexane; mp 205–208°C (100% de); $[\alpha]^{25}_D$=−217.5 (100% ee) (*c* 0.30, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 0.94 (3H, d, *J*=6.7 Hz), 1.13 (3H, d, *J*=6.7 Hz), 1.96–2.02 (1H, m), 2.33 (1H, dd, *J*=13.4, 3.7 Hz), 2.42 (1H, dd, *J*=13.1, 9.5 Hz), 3.95 (1H, dd, *J*=10.4, 4.0 Hz), 3.98 (3H, s), 4.00 (3H, s), 4.90 (1H, d, *J*=12.2 Hz), 4.98 (1H, d, *J*=12.2 Hz), 5.55 (1H, d, *J*=10.4 Hz), 5.85 (1H, dd, *J*=9.5, 3.4 Hz), 6.39 (1H, d, *J*=7.9 Hz), 6.41 (1H, d, *J*=7.6 Hz), 7.23–7.38 (5H, m), 7.81 (2H, d, *J*=8.9 Hz), 7.85 (2H, d, *J*=8.9 Hz). ^{1}H NMR ($CDCl_3$) (for the minor isomer) δ 0.72 (3H, d, *J*=6.7 Hz), 1.05 (3H, d, *J*=6.7 Hz), 1.96–2.02 (1H, m), 2.19 (1H, dd, *J*=12.8, 4.0 Hz), 2.44 (1H, dd, *J*=12.8, 7.6 Hz), 3.85 (3H, s), 3.86 (3H, s), 4.29 (1H, dd, *J*=9.2, 3.4 Hz), 4.80 (1H, d, *J*=12.2 Hz), 4.83 (1H, d, *J*=12.2 Hz), 5.66 (1H, d, *J*=8.9 Hz), 6.17 (1H, dd, *J*=7.6, 4.0 Hz), 6.34 (1H, d, *J*=7.6 Hz), 6.51 (1H, d, *J*=7.9 Hz), 7.23–7.38 (5H, m), 8.03 (2H, d, *J*=8.9 Hz), 8.33 (2H, d, *J*=8.5 Hz). ^{13}C NMR ($CDCl_3$) (for the major isomer) δ 16.1, 19.8, 30.5, 36.7, 50.2, 57.7, 60.8, 61.0, 66.9, 112.1, 116.3, 116.4, 122.8, 123.5, 126.0, 127.7, 128.2, 128.3, 128.5, 128.6, 135.4, 144.3, 149.4, 151.0, 151.2, 168.7, 169.0. Anal. Calcd for $C_{31}H_{31}Br_2N_3O_9S$ (for the major isomer): C, 47.65; H, 4.00; N, 5.38. Found: C, 47.95; H, 3.73; N, 5.35.

1.14.2. Benzyl 5,8-dibromo-1,2-dihydro-6,7-dimethoxy-2-[*N*-phthaloyl-(*S*)-valinyl]isoquinolin-1-ylacetate (27). y 98%. Colorless oil (95% de). ^{1}H NMR ($CDCl_3$) δ 0.84 (3H, d, *J*=7.0 Hz), 1.11 (3H, d, *J*=6.7 Hz), 2.54 (1H, dd, *J*=12.5, 4.3 Hz), 2.58 (1H, dd, *J*=12.5, 9.2 Hz), 2.88–2.93 (1H, m), 3.82 (3H, s), 3.85 (3H, s), 4.67 (1H, d, *J*=9.2 Hz), 5.05 (1H, d, *J*=12.5 Hz), 5.09 (1H, d, *J*=11.9 Hz), 6.07 (1H, d, *J*=7.9 Hz), 6.48 (1H, dd, *J*=8.6, 4.0 Hz), 6.66 (1H, d, *J*=7.9 Hz), 7.32–7.42 (5H, m), 7.71 (2H, dd, *J*=5.5, 3.1 Hz), 7.79 (2H, dd, *J*=5.5, 3.1 Hz). ^{13}C NMR ($CDCl_3$) δ 18.6, 20.7, 27.9, 36.6, 51.7, 56.2, 60.7, 61.0, 67.1, 109.2, 115.5, 116.9, 123.7, 125.1, 127.4, 128.2, 128.4, 128.5, 128.9, 131.1, 134.4, 135.7, 150.2, 150.8, 165.9, 167.3, 169.7. HRMS (FAB): Calcd for $C_{33}H_{31}Br_2N_2O_7$ $(M+H)^+$: 725.0498. Found 725.0553.

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