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Chiral aziridine-2-carboxylates: versatile precursors for functionalized tetrahydroisoquinoline (THIQ) containing heterocycles

Kyu Myung Lee [a], Jong Chan Kim [a], Philjun Kang [a], Won Koo Lee [a,*], Heesung Eum [b], Hyun-Joon Ha [b,*]

[a] Department of Chemistry, Sogang University, Shinsu-dong 1, Mapo-gu, Seoul 121-742, Republic of Korea
[b] Department of Chemistry, Hankuk University of Foreign Studies, Yongin, Kyunggi-Do 449-719, Republic of Korea

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ABSTRACT

Preparation of functionalized 3,4-dihydroisoquinolines **17a**–**j** from (*S*)-*N*-methoxy-*N*-methyl-1-[(*R*)-1-phenylethyl]aziridine-2-carboxamide **4** is an effective route for the synthesis of 3-(hydroxymethyl)-1,2,3,4-tetrahydroisoquinolin-4-ols. Stereoselective reduction of the cyclic imines **17a**–**j** resulted in (1*S*,3*S*,4*R*)-4-(*tert*-butyldimethylsilyl-oxy)-3-[(*tert*-butyldimethylsilyloxy)methyl]-6,7-dimethoxy-1,2-disubstituted-1,2,3,4-tetrahydroisoquinolines and the desilylation of the TBS groups afforded (1*S*,3*S*,4*R*)-3-(hydroxymethyl)-6,7-dimethoxy-1,2-disubstituted-1,2,3,4-tetrahydroisoquinolin-4-ols **19a**–**i** in good yields. Also, an asymmetric synthesis of novel tetracyclic 3-(hydroxymethyl)-1,2,3,4-tetrahydroisoquinolin-4-ols **23** and **25** was successfully achieved via Pd-catalyzed N-arylation and C–C coupling reaction.

1. Introduction

Many tetrahydroisoquinoline (THIQ) derivatives, including several alkaloids, show pharmacologically important properties.[1] Also, some natural products containing THIQ moiety have been used as antitumor antibiotics,[2] antimalarial,[3] and ionotropic glutamate receptor antagonist[4] for central nervous system (CNS). Recently, (+)-tetrabenazine[5] (TBZ) **1** and (+)-dihydrotetrabenazine[6] (DTBZ) **2** were reported as therapeutic agents for imagining VMAT-2 in brain. Therefore, the synthesis of tetrahydroquinoline (THIQ) containing molecules has attracted much attention due to the importance of the compounds as pharmacophore.[7] The syntheses of functionalized tetrahydroisoquinolines, which have substituents at C-1, C-3, C-4 positions have been reported previously and the asymmetric synthesis of 1-substituted tetrahydroisoquinolines takes most of the cases.[8] Moreover, the introduction of substituents at 1-position provides variously substituted (aryl and aliphatic group) tetrahydroisoquinolines.[9] Though substitution at C-3, C-1, 3,[8f,10] as well as C-1 has been reported, there has not been many examples for the preparation of chiral 1,3,4-trisubstituted tetrahydroisoquinolines. Therefore, the synthesis of 1-substituted-3-hydroxymethyl-4-hydroxy-1,2,3,4-tetrahydroisoquinolines is a rare case except for some examples.[11] Koga et al. reported the asymmetric synthesis of 2-azapo-dophyllotoxins **3**[12] containing 3-(hydroxymethyl)-1-substituted-1,2,3,4-tetrahydroisoquinolin-4-ol structure, as a potent anticancer agent (Fig. 1). Therefore, we were interested in the synthesis of enantiomerically pure substituted 1,2,3,4-tetrahydroisoquinolines starting from chiral aziridines and we report herein an efficient synthesis of enantiopure 3-(hydroxylmethyl)-1-substituted-1,2,3,4-tetrahydroisoquinolin-4-ols and also THIQ containing heterocycles from the readily available chiral aziridine-2-carboxamide **4**.

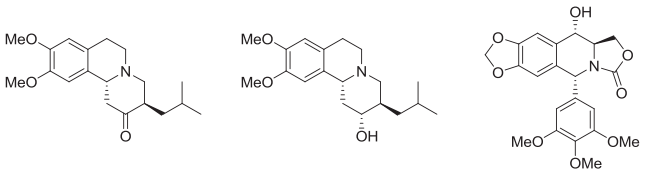

Fig. 1. Some examples of biologically active THIQs.

Chiral aziridines have been used as important chiral building blocks for the synthesis of various natural and unnatural amino acid derivatives,[13] and also biologically active heterocycles in asymmetric manners. Starting from chiral aziridines, we recently reported the synthesis of enantiomerically pure functionalized oxazolidinones,[14] imidazolidinones,[15] piperidines,[16] bicyclic triazoles,[17] and also phytosphingosine derivatives.[18] Furthermore, the synthesis of enantiomerically pure benzofused bicyclic heterocycles, such as 2-hydroxymethyl-1,2,3,4-tetrahydroquinolines, 3,4-dihydro-2*H*-

* Corresponding authors. Tel.: +82 2 705 8449; fax: +82 2 701 0967; e-mail addresses: wonkoo@sogang.ac.kr, wonkoo62@gmail.com (W.K. Lee), hjha@hufs.ac.kr (H.-J. Ha).

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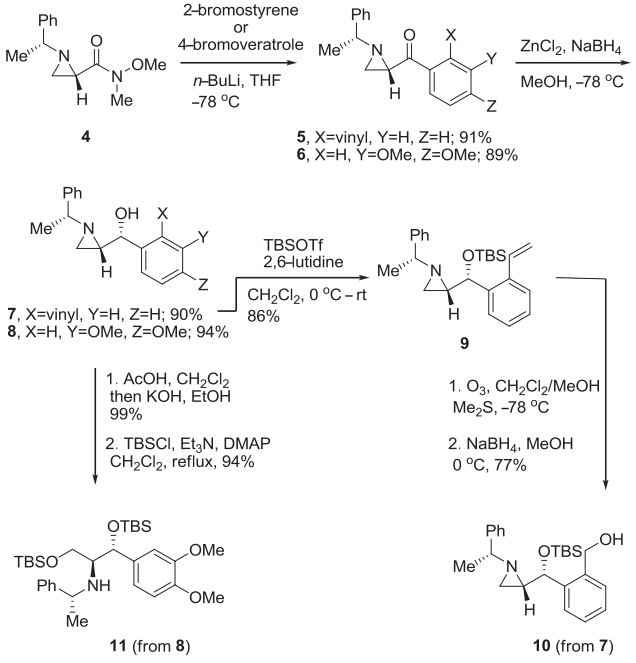
benzo[*b*][1,4]-oxazine, and 1,2,3,4-tetrahydroquinoxalines from chiral aziridine-2-methanol was reported.[19] The above results show that a variety of nitrogen containing heterocycles can be prepared from chiral aziridines stereoselectively using functional group elaboration and simple organic transformations.

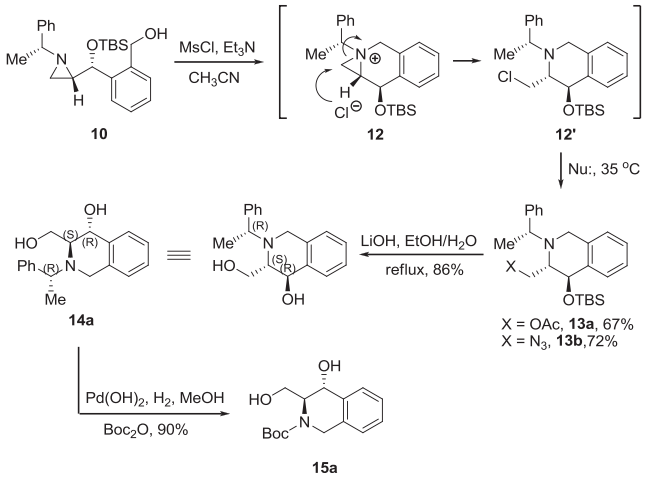
2. Results and discussion

The chiral aziridine-2-carboxamide can be converted to various acylaziridines via organometallic additions. (*S*)-*N*-Methoxy-*N*-methyl-1-[(*R*)-1-phenylethyl]aziridine-2-carboxamide **4** was reacted with *ortho*-lithiated styrene to provide the corresponding acylaziridine **5** in 91% yield. The reduction of the ketone by chelation-controlled reaction provided benzyl alcohol **7** in 90% yield (dr >99/1). The secondary benzylic alcohol of **7** was protected using TBSOTf and 2,6-lutidine at 0 °C to give 86% yield of the silyl ether **9**. Ozonolysis[20] of the styrene **9** in CH_2Cl_2/MeOH (1/1) at −78 °C provided the corresponding aldehyde and in situ reduction of the aldehyde with $NaBH_4$ at −78 °C provided the benzylic alcohol **10** in 77% yield (two steps). The aziridine-2-carboxamide **4**, obtained from the corresponding carboxylate and Weinreb's amine, and the lithiated 4-bromoveratrole were reacted to provide the corresponding ketone **6** in 89%. Tetrahydroisoquinolines have been prepared from phenylethanamine derivatives using the Bischler–Napieralski cyclization.[21] Therefore, we prepared the phenylethanamine derivative **11** via stereoselective reduction of the ketone, regioselective aziridine ring-opening followed by alcohol protection with TBS group for further ring cyclization reactions (Scheme 1).



Scheme 1. Preparation of substrate **10**, **11** for the synthesis of THIQ.

The reaction of the primary benzyl alcohol **10** with MsCl forms the corresponding mesylate and the nucleophilic aziridine nitrogen initiates the intramolecular cyclization reaction to form the aziridinium ion intermediate **12**.[22] Regioselective aziridine ring-opening reaction by the chloride liberated from the MsCl provided the corresponding chloride **12′**, which was isolated and confirmed using HRMS and ^{1}H NMR. Therefore, the reaction mixture was directly treated with an additional nucleophile, acetate or azide, to provide the acetate **13a** (when the nucleophile was acetate) and the azidomethyl compound **13b** (when the nucleophile was azide) in reasonable yields (Scheme 2). The TBS group of **13a** was deprotected

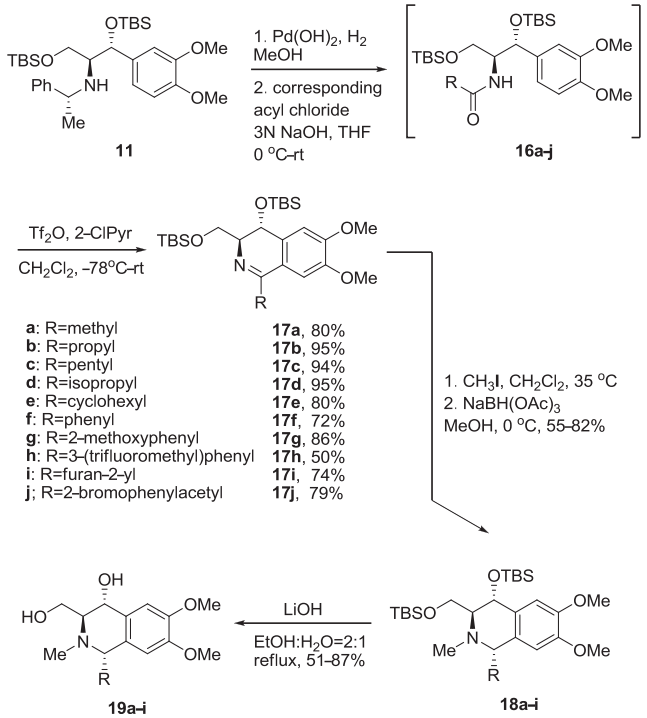


Scheme 2. Synthesis of 3-(hydroxymethyl)-3,4-dihydroisoquinolin-4-ol **15a** via formation and regioselective ring-opening of the aziridinium salt **12**.

and the acetate was hydrolyzed with LiOH·H_2O in aqueous EtOH (EtOH/H_2O=2/1, v/v) under refluxing for 8 h to provide the diol **14a** in 86% yield. The nitrogen protecting group of **14a** was also removed by successive catalytic hydrogenation with atmospheric pressure of H_2 in MeOH in the presence of Boc_2O to provide the *N*-Boc protected 3-(hydroxymethyl)-1,2,3,4-tetrahydroisoquinolin-4-ol **15a** in 90% yield, which is a novel method for the synthesis of enantiomerically pure 3-(hydroxymethyl)-1,2,3,4-tetrahydroisoquinolin-4-ol.[23]

The 1-α-methylbenzyl group of the chiral phenylethanamine **11** was removed by catalytic hydrogenation with $Pd(OH)_2$ to give the free amine and the following reaction with various acyl chlorides provided *N*-acylated products **16a–j** under basic aqueous THF in 72–99% yields.

Each of the *N*-acylated product **16a–j** underwent dehydrative cyclization[24] using a modified Bischler–Napieralski cyclization with Tf_2O and 2-ClPyr in CH_2Cl_2 to provide (3*S*,4*R*)-1-substituted-3,4-dihydroisoquinolines **17a–j** in 50–95% yields (Scheme 3).

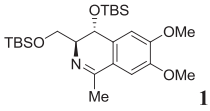
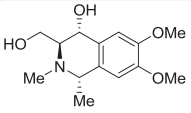
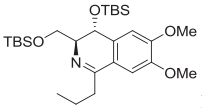
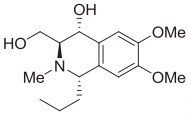
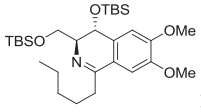
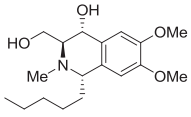
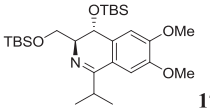
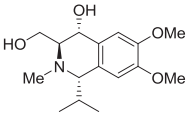
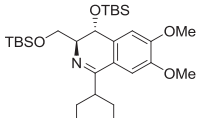
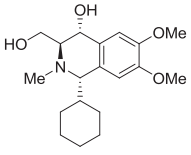
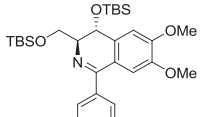
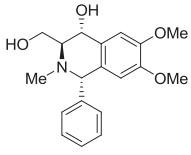
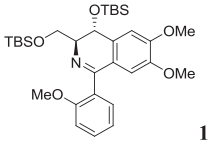
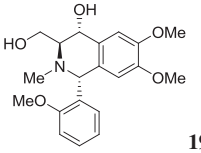


Scheme 3. The preparation of 1,2,3,4-substituted THIQs **19a–i** by a modified Bischler–Napieralski cyclization and the following reduction.

N-Methyl-1-substituted-3,4-dihydroisoquinolinium iodide intermediates were formed from the reaction of **17** and CH_3I in CH_2Cl_2 at 35 °C. The reduction of the iminium salt using $NaBH(OAc)_3$ in MeOH at 0 °C provided 1-substituted-*N*-methyl-1,2,3,4-tetrahydroisoquinolines **18a**–**i** in 55–82% yields (Table 1). While 1-aryl substituted-3,4-dihydroisoquinolines **17f**–**i** formed 3,4-dihydroisoquinolinium intermediate rapidly, 1-alkyl substituted-3,4-dihydroisoquinolines **17a**–**e** were not as reactive as 1-aryl substituted compounds. After stereoselective reduction of the 1-substituted-3,4-dihydroiso quinolinium iodide, the alcohol protecting groups of **18a**–**i** were cleaved by LiOH in aqueous EtOH ($EtOH/H_2O$=2/1, v/v) under reflux to give the corresponding diols **19a**–**i** in 51–87% yields (Table 1). The absolute configurations of C-1 of the corresponding desilylated products **19** were determined by ^1H–^1H NOE experiments, suggesting that (1*R*)-1-substituted 2-methyl-1,2,3,4-tetrahydroisoquinoline was the major product (Fig. 2).

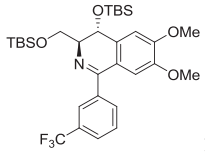
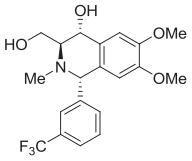
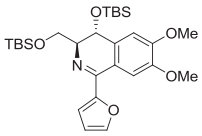
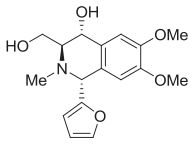
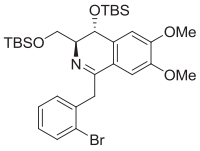
We also synthesized tetracyclic structures **23** and **25** containing 3-hydroxymethyl-4-hydroxy tetrahydroisoquinoline moiety using Pd-catalyzed intramolecular C–N and C–C bond formation. Indolo [2,1-*a*]isoquinolines[26] have been known for their biological activities[27] and the synthesis was accomplished by an intramolecular coupling of the aryl bromide with an amine nitrogen of 1-(2-bromobenzyl)-1,2,3,4-tetrahydroisoquinoline **20**, which was prepared by the stereoselective reduction of the imine obtained from

Table 1
Synthesis of 3-(hydroxymethyl)-1-substituted-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-ols **19a**–**i**

Entry	Substrate **17**	Product **18**		Product **19**
		Time[b] (h)	Yield[c] (%)	Yield (%)
1	 **17a**; 80[a]	40	55	 **19a**; 80
2	 **17b**; 95[a]	34	63	 **19b**; 70
3	 **17c**; 94[a]	36	73	 **19c**; 87
4	 **17d**; 95[a]	72	68	 **19d**; 70
5	 **17e**; 80[a]	40	62	 **19e**; 76
6	 **17f**; 72[a]	4.5	61	 **19f**; 82
7	 **17g**; 86[a]	4	78	 **19g**; 76

(*continued on next page*)

Table 1 (*continued*)

Entry	Substrate **17**	Product **18**		Product **19**
		Time[b] (h)	Yield[c] (%)	Yield (%)
8	 **17h**; 50[a]	3.5	82	 **19h**; 77
9	 **17i**; 74[a]	7	69	 **19i**; 51
10	 **17j**; 79[a]	ND[d]	ND[d]	ND[d]

[a] Isolated three steps yield. The cyclization reaction was carried out in the presence of Tf_2O (1.1 equiv) and 2-ClPyr (1.1 equiv) in anhydrous CH_2Cl_2 at −78 °C to rt.
[b] Reaction time of *N*-methylation step.
[c] Isolated yield. The stereoselective reduction was carried out in the presence of $NaBH(OAc)_3$ (2.0 equiv) in MeOH at 0 °C via *N*-methyl-tetrahydroisoquinolinium iodide intermediate.
[d] The reactions of the corresponding substrate were not carried out. No Data.

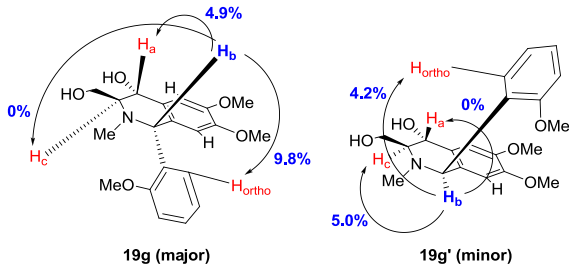
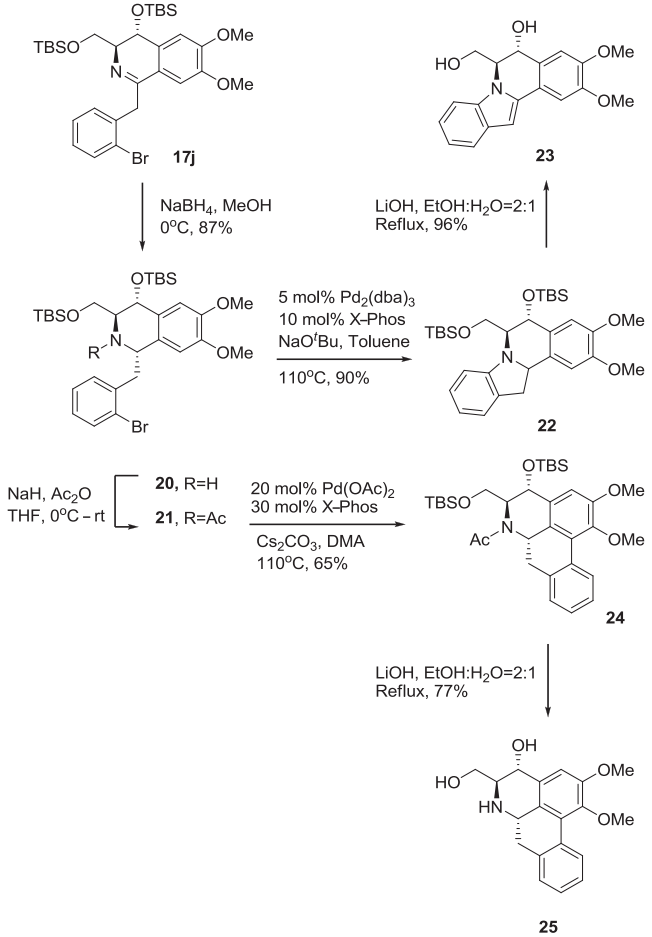


Fig. 2. NOE experiment for the determination of the absolute stereochemistry at C-1 position of **19g**, **19g′**.[25]

the intramolecular dehydrative cyclization product **17j** with $NaBH_4$ in MeOH at 0 °C in 87% yield (dr >9/1). The major diastereomer of the reduction product **20** was easily separated by flash column chromatography in high purity and Pd-catalyzed *N*-arylation[28] of **20** with 5 mol % $Pd_2(dba)_3$, 10 mol % X-Phos ligand, and NaO^tBu in toluene at 110 °C was completed within 1.5 h to give the tetracyclic 5,6-dihydroindoloisoquinolinol **22** in 90% yield. During the desilylation of the TBS group, the oxidation of the C(12)–C(12a) bond was also proceeded to provide 6-(hydroxymethyl)-5,6-dihydroindoloisoquinolin-5-ol **23** in 96% yield (Scheme 4). The synthesis and application of nuciferine alkaloid[29] containing tetrahydroisoquinoline (THIQ) motif are well known. Especially, direct C–H arylation[30] of unactivated substrates is an important key protocol for the synthesis of tetrahydro-4*H*-dibenzo[*de*,*g*]-quinoline. Following the recently reported method, substrate **21** protected by *N*-acetyl group was reacted with 20 mol % $Pd(OAc)_2$, 30 mol % X-Phos ligand, and Cs_2CO_3 in refluxing DMA to yield the cyclized product **24** in 65% yield (two steps).[31] The TBS groups of the cyclized product **24** were removed by LiOH in aqueous EtOH (EtOH/H_2O=2/1, v/v) to yield 5-(hydroxymethyl)-5,6,6a,7-tetrahydro-4*H*-dibenzo-[*de*,*g*]-quinolin-4-ol **25** in 77% yield (Scheme 4) (Fig. 3).



Scheme 4. Synthesis of tetracyclic 3-(hydroxymethyl)-1,2,3,4-tetrahydroisoquinolin-4-ols **23** and **25**.

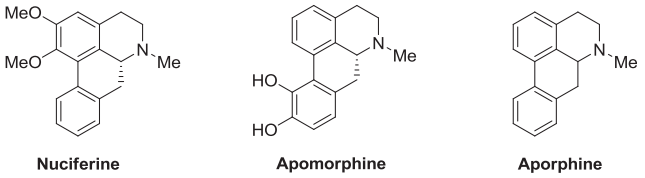


Fig. 3. Some examples of nuciferine alkaloids.

3. Conclusion

In conclusion, enantiomerically pure functionalized tetrahydroisoquinolines (THIQs) were efficiently prepared starting from chiral aziridines using simple organic transformations. Enantiopure 3-(hydroxymethyl)-1-functionalized-1,2,3,4-tetrahydroisoquinolin-4-ols were synthesized from chiral phenylethanamine **11** derived from chiral aziridine-2-carboxaimde **4** via modified Bischler–Napieralski cyclization and stereoselective reduction of the corresponding cyclized imines in moderate yields. Also, asymmetric synthesis of novel tetracyclic 3-(hydroxymethyl)-1,2,3,4-tetrahydroisoquinolin-4-ols was successfully achieved via Pd-catalyzed *N*-arylation and also C–C coupling reaction.

4. Experimental section

4.1. Remarks

All reactions were carried out under an atmosphere of nitrogen in oven-dried glasswares with magnetic stirring. Air sensitive reagents and solutions were transferred via syringe and were introduced to the apparatus through rubber septa. Tetrahydrofuran (THF) and diethyl ether (Et_2O) were distilled from sodium/benzophenone ketyl. Dichloro-methane (CH_2Cl_2) was distilled from calcium hydride. Reactions were monitored by thin layer chromatography (TLC) with 0.25 mm E. Merck pre-coated silica gel plates (60 F_{254}). Visualization was accomplished with either UV light, or by immersion in solutions of ninhydrin, *p*-anisaldehyde, or phosphomolybdic acid (PMA) followed by heating on a hot plate for about 10 s. Purification of reaction products was carried out by flash chromatography using Kieselgel 60 Art 9385 (230–400 mesh). ^{1}H NMR and ^{13}C NMR spectra were obtained using a Varian Gemini-300 (300 MHz for ^{1}H, and 75 MHz for ^{13}C), or a Varian 400 (400 MHz for ^{1}H, and 100 MHz for ^{13}C), or a Varian Inova-500 (500 MHz for ^{1}H, and 125 MHz for ^{13}C) spectrometers. Chemical shifts are reported relative to chloroform (δ=7.26) for ^{1}H NMR and chloroform (δ=77.2) for ^{13}C NMR. Data are reported as (br=broad, s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet). Coupling constants are given in hertz. Ambiguous assignments were resolved on the basis of standard one dimensional proton decoupling experiments. Optical rotations were obtained using a Rudolph Autopol III digital polarimeter and optical rotation data were reported as follows: $[\alpha]_D^{24}$ (concentration *c*=g/100 mL, solvent). Elemental analyses were performed by the Organic Chemistry Research Center at Sogang University using a Carlo Erba EA 1180 elemental analyzer. High resolution mass spectra were recorded on a 4.7 T IonSpec ESI-FTMS or a Micromass LCT ESI-TOF mass spectrometer. IR spectra were recorded neat on Nicolet Avatar 330 FT-IR. Melting points were recorded on an Electrothermal-9100 and are uncorrected. All commercially available compounds were used as received unless stated otherwise.

*4.1.1. ((S)-1-((R)-1-phenylethyl)aziridin-2-yl)(2-vinylphenyl)methanone (**5**).* To a 0.30 M solution of 2-bromostyrene (2.31 mL, 17.93 mmol) in anhydrous THF (42.70 mL) was added *n*-BuLi (8.32 mL, 2.00 M in hexane) in dropwise at −78 °C under nitrogen atmosphere. The reaction mixture was stirred for 1 h at −78 °C and (*S*)-*N*-methoxy-*N*-methyl-1-[(*R*)-1-phenylethyl]-aziridine-2-carboxamide **4** (3.00 g, 12.81 mmol) in anhydrous THF was slowly added to the resulting solution at −78 °C. The reaction mixture was continuously stirred for 30 min, and allowed to warm to room temperature. The reaction mixture was diluted with EtOAc and treated with aqueous NH_4Cl solution. The aqueous layer was extracted with CH_2Cl_2. The combined extracts were dried over anhydrous $MgSO_4$ and filtered then the solvent was removed in vacuo. The crude product was purified by silica gel flash column chromatography using EtOAc/hexane (15/85) to give 3.23 g of product **5** as a colorless oil (91%); $[\alpha]_D^{24}$ −55.3 (*c* 0.70, CH_3OH); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.50–7.13 (m, 9H), 6.79 (dd, 1H, *J*=10.8, 17.4 Hz), 5.56 (d, 1H, *J*=17.4 Hz), 5.10 (d, 1H, *J*=10.8 Hz), 2.70–2.67 (m, 1H), 2.67 (q, 1H, *J*=6.6 Hz) 2.53–2.51 (m, 1H), 1.92 (d, 1H, *J*=4.8 Hz), 1.50 (d, 3H, *J*=6.6 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 201.2, 144.3, 137.7, 137.0, 134.8, 131.3, 128.7, 128.3, 127.5, 127.4, 127.0, 126.7, 117.2, 70.7, 43.3, 38.2, 23.7; HRMS *m*/*z* calcd for $C_{19}H_{19}NO$ $[M+Na]^+$ 300.1365, found 300.1362.

*4.1.2. (3,4-Dimethoxyphenyl)[(S)-1-(R)-1-phenylethylaziridin-2-yl]methanone (**6**).* Colorless oil (89%); $[\alpha]_D^{24}$ −0.7 (*c* 1.14, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.42–7.38 (m, 3H), 7.32–7.20 (m, 4H), 6.71 (d, 1H, *J*=8.4 Hz), 3.90 (s, 3H), 3.82 (s, 3H), 2.87 (q, 1H, *J*=3.0 Hz), 2.72 (q, 1H, *J*=6.3 Hz), 2.56 (dd, 1H, *J*=1.5, 3.0 Hz), 1.92 (dd, 1H, *J*=1.5, 6.3 Hz), 1.52 (d, 3H, *J*=6.3 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 194.7, 153.5, 149.1, 144.3, 130.3, 128.7, 127.3, 126.8, 123.2, 110.5, 110.0, 70.9, 56.2, 56.1, 40.2, 36.9, 23.8; HRMS *m*/*z* calcd for $C_{19}H_{21}NO_3$ $[M+Na]^+$ 334.1419, found 334.1419.

*4.1.3. (R)-(S)-1-[(R)-1-Phenylethylaziridin-2-yl](2-vinylphenyl)methanol (**7**).* To a 0.20 M solution of **5** (3.00 g, 10.82 mmol) in MeOH (54.0 mL) was added $ZnCl_2$ (2.21 g, 16.22 mmol) at −78 °C. After stirring for an additional 30 min, $NaBH_4$ (0.82 g, 21.63 mmol) was added to the resulting solution at −78 °C. Stirring was continued for 3 h at −78 °C and the reaction mixture was allowed to warm to room temperature. The solvent was concentrated under reduced pressure and the resulting white sticky residue was diluted with CH_2Cl_2, then quenched with H_2O. The aqueous layer was extracted with CH_2Cl_2. The combined extracts were dried over anhydrous $MgSO_4$, filtered, and then the solvent was removed in vacuo. The crude product was purified by silica gel flash column chromatography using EtOAc/hexane (30/70) to give 2.72 g of product **7** as a colorless oil (90%); $[\alpha]_D^{24}$ +40.5 (*c* 0.96, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.42–7.22 (m, 9H), 6.83 (dd, 1H, *J*=10.8, 17.1 Hz), 5.55 (d, 1H, *J*=17.1 Hz), 5.20 (d, 1H, *J*=10.8 Hz), 5.00–4.98 (m, 1H), 3.01 (br, 1H), 2.66 (q, 1H, *J*=6.6 Hz), 2.08–2.07 (m, 1H), 1.88–1.85 (m, 1H), 1.43 (d, 3H, *J*=6.6 Hz), 1.41–1.39 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 144.4, 138.8, 136.0, 134.2, 128.6, 128.0, 127.6, 127.4, 126.7, 126.0, 125.8, 116.5, 69.2, 66.3, 42.0, 29.8, 23.2; FT-IR: *v* 3354 cm^{-1} (br, OH); HRMS *m*/*z* calcd for $C_{19}H_{21}NO$ $[M+Na]^+$ 302.1521, found 302.1524.

*4.1.4. (R)-(3,4-Dimethoxyphenyl)[(S)-1-(R)-1-phenylethylaziridin-2-yl]methanol (**8**).* White solid (94%); $[\alpha]_D^{24}$ +41.7 (*c* 0.77, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.31–7.25 (m, 5H), 6.81–6.75 (m, 3H), 4.58 (d, 1H, *J*=3.6 Hz), 3.85 (s, 3H), 3.83 (s, 3H), 2.96 (br, 1H), 2.66 (q, 1H, *J*=6.6 Hz), 2.13 (d, 1H, *J*=3.6 Hz), 1.83–1.79 (m, 1H), 1.63 (s, 1H), 1.43 (d, 3H, *J*=6.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.7, 148.3, 144.2, 134.3, 128.4, 127.1, 126.5, 118.4, 110.7, 109.2, 70.3, 69.1, 55.9, 55.7, 43.1, 29.8, 23.4; FT-IR: *v* 3363 cm^{-1} (br, OH); mp 131–133 °C; HRMS *m*/*z* calcd for $C_{19}H_{23}NO_3$ $[M+Na]^+$ 336.1576, found 336.1577.

*4.1.5. (S)-2-[(R)-(tert-Butyldimethylsilyloxy)(2-vinylphenyl)methyl]-1-[(R)-1-phenylethyl]aziridine (**9**).* To a 0.20 M solution of **7** (0.64 g, 2.29 mmol) in CH_2Cl_2 (11.50 mL) was added 2,6-lutidine (0.53 mL, 4.58 mmol) at 0 °C. To the reaction mixture was added TBSOTf (0.58 mL, 2.52 mmol) at 0 °C. After stirring for additional 15 min, the reaction mixture was allowed to warm to room temperature and diluted with CH_2Cl_2, treated with aqueous NH_4Cl solution. The

aqueous layer was extracted with CH_2Cl_2. The combined extracts were dried over anhydrous $MgSO_4$, filtered, and then the solvent was removed in vacuo. The crude product was purified by silica gel flash column chromatography using EtOAc/hexane (5/95) to give 773 mg of product **9** as a colorless oil (86%); $[\alpha]_D^{24}$ −47.6 (*c* 0.44, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.26–7.23 (m, 2H), 7.12–7.09 (m, 2H), 7.06 (s, 5H), 6.99 (dd, 1H, *J*=11.0, 17.5 Hz), 5.38 (d, 1H, *J*=17.5 Hz), 5.13 (d, 1H, *J*=11.0 Hz), 4.47 (d, 1H, *J*=6.5 Hz), 2.37 (q, 1H, *J*=6.5 Hz), 1.98 (d, 1H, *J*=3.5 Hz), 1.82–1.79 (m, 1H), 1.43 (d, 1H, *J*=6.5 Hz), 1.36 (d, 3H, *J*=6.5 Hz), 0.84 (s, 9H), 0.01 (s, 3H), −0.16 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 143.9, 140.5, 135.7, 135.3, 127.9, 127.4, 127.3, 127.2, 126.9, 126.7, 125.9, 115.5, 74.3 70.2, 44.7, 32.8, 25.9, 22.8, 18.3, −4.7, −4.8; HRMS *m*/*z* calcd for $C_{25}H_{35}NOSi$ $[M+Na]^+$ 416.2386, found 416.2383.

*4.1.6. (2-((R)-(tert-butyldimethylsilyloxy)((S)-1-((R)-1-phenylethyl) aziridin-2-yl)methyl)phenyl)methanol (**10**).* To a 0.20 M solution of **9** (675 mg, 1.72 mmol) in MeOH/CH_2Cl_2 (1/1) (8.60 mL) was added O_3 (g) at −78 °C using ozone gas generator. Stirring was continued 30 min under O_3 (g) at −78 °C. To the reaction mixture was added Me_2S and stirred for 1 h and then the solvent was removed under reduced pressure. To a 0.20 M solution of the crude product in MeOH (8.60 mL) was added $NaBH_4$ (130 mg, 3.43 mmol) at 0 °C and the reaction mixture was stirred for 1 h. The mixture was diluted with CH_2Cl_2 and treated with H_2O. The aqueous layer was extracted with CH_2Cl_2 and the combined extracts were dried over anhydrous $MgSO_4$, filtered, and then the solvent was removed in vacuo. The crude product was purified by silica gel flash column chromatography using EtOAc/hexane (10/90) to give 526 mg of the product **10** as a colorless oil (77%); $[\alpha]_D^{24}$ +6.9 (*c* 0.08, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.16–7.12 (m, 2H), 7.03 (t, 1H, *J*=7.5 Hz), 6.99–6.96 (m, 1H), 6.94 (t, 1H, *J*=6.0 Hz), 6.89 (t, 2H, *J*=7.5 Hz), 6.76 (d, 2H, *J*=7.5 Hz), 4.60 (d, 1H, *J*=12.0 Hz), 4.33 (d, 1H, *J*=12.0 Hz), 4.28 (d, 1H, *J*=8.0 Hz), 2.41 (q, 1H, *J*=6.5 Hz), 2.09 (d, 1H, *J*=3.5 Hz), 1.88–1.84 (m, 1H), 1.73 (d, 1H, *J*=6.5 Hz), 1.28 (d, 3H, *J*=6.5 Hz), 0.82 (s, 9H), −0.03 (s, 3H), −0.17 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 141.9, 141.3, 137.0, 129.9, 128.5, 128.1, 127.5, 127.0, 126.8, 126.1, 73.1, 69.9, 63.3, 44.1, 37.3, 25.8, 22.0, 18.2, −4.6, −4.7; FT-IR: *v* 3349 cm^{-1} (br, OH); HRMS *m*/*z* calcd for $C_{24}H_{35}NO_2Si$ $[M+Na]^+$ 420.2335, found 420.2333.

*4.1.7. (5R,6S)-5-(3,4-Dimethoxyphenyl)-2,2,3,3,9,9,10,10-octamethyl-N-[(R)-1-phenylethyl]-4,8-dioxa-3,9-disilaundecan-6-amine (**11**).* To a 0.20 M solution of **8** (6.26 g, 19.97 mmol) in CH_2Cl_2 (99.80 mL) was added AcOH (6.85 mL, 0.12 mol) at room temperature. After additional stirring for 8 h, the reaction was quenched with aqueous $NaHCO_3$ solution at 0 °C, and the aqueous layer was extracted with CH_2Cl_2, dried over anhydrous $MgSO_4$, concentrated under reduced pressure. The crude product was dissolved in EtOH (66.50 mL, 0.30 M) and KOH (3.36 g, 59.91 mmol) was added at room temperature. After additional stirring for 20 min, the solvent was removed under reduced pressure to give the 1,3-diol. The crude product was diluted with CH_2Cl_2, and treated with H_2O. The aqueous layer was extracted with CH_2Cl_2, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was dissolved in CH_2Cl_2 (99.80 mL) and added TBSCl (6.62 g, 43.93 mmol) at 0 °C. To the reaction mixture were added Et_3N (9.74 mL, 69.89 mmol) and DMAP (732 mg, 5.99 mmol) and stirred for 20 h at refluxing temperature. The reaction was quenched with H_2O and the aqueous layer was extracted with CH_2Cl_2. The combined extracts were dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. The crude product was purified by silica gel flash column chromatography using EtOAc/hexane (3/97) to give 10.41 g of **11** as a white solid (93%); [α]D24 −5.2 (*c* 1.10, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.15–7.12 (m, 3H), 6.87–6.86 (m, 2H), 6.55 (q, 2H, *J*=8.0 Hz), 6.64 (s, 1H), 4.48 (d, 1H, *J*=8.0 Hz), 3.91 (s, 3H), 3.81 (q, 1H, *J*=7.0 Hz), 3.78 (dd, 1H, *J*=4.0, 10.0 Hz), 3.71–3.69 (m, 1H), 3.68 (s, 3H), 2.55–2.52 (m, 1H), 1.44 (br, 1H), 1.17 (d, 3H, *J*=7.0 Hz), 0.95 (s, 9H), 0.81 (s, 9H), 0.10 (s, 3H), 0.08 (s, 3H), −0.02 (s, 3H), −0.26 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 148.6, 148.1, 146.0, 135.9, 128.1, 126.9, 126.6, 120.2, 110.2, 110.0, 75.1, 62.2, 61.2, 56.0, 55.8, 55.6, 26.2, 25.9, 25.1, 18.5, 18.3, −4.5, −4.9, −5.1, −5.3; mp 68–69 °C; HRMS *m*/*z* calcd for $C_{31}H_{53}NO_4Si_2$ $[M+Na]^+$ 582.3411, found 582.3410.

*4.1.8. [(3S,4R)-4-(tert-Butyldimethylsilyloxy)-2-(R)-1-phenylethyl-1,2,3,4-tetrahydroisoquinolin-3-yl]methyl acetate (**13a**).* To a 0.10 M solution of **10** (186 mg, 0.47 mmol) in CH_3CN (4.70 mL) was treated with MsCl (0.043 mL, 0.56 mmol) and Et_3N (0.13 mL, 0.94 mmol) at room temperature. After stirring for 5 min at room temperature, KOAc (92 mg, 0.94 mmol) was added to the reaction mixture. The resulting reaction mixture was stirred for 4 h at 45 °C and cooled to room temperature. The mixture was diluted with CH_2Cl_2 and treated with H_2O. The aqueous layer was extracted with CH_2Cl_2. The combined organic layer was dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. The crude product was purified by silica gel flash column chromatography using EtOAc/hexane (10/90) to give 139 mg of product **13a** as a colorless oil (67%); $[\alpha]_D^{24}$ +9.2 (*c* 0.13, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66 (d, 2H, *J*=7.2 Hz), 7.58 (t, 2H, *J*=7.2 Hz), 7.53–7.44 (m, 4H), 7.30–7.28 (m, 1H), 4.91 (d, 1H, *J*=2.0 Hz), 4.48 (dd, 1H, *J*=4.4, 11.2 Hz), 4.29 (d, 1H, *J*=15.2 Hz), 4.21 (q, 1H, 6.8 Hz), 3.92 (d, 1H, *J*=15.2 Hz), 3.87 (t, 1H, *J*=11.2 Hz), 3.59–3.57 (m, 1H), 2.24 (s, 3H), 1.74 (d, 3H, *J*=6.8 Hz), 1.12 (s, 9H), 0.26 (s, 3H), 0.21 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.9, 144.8, 136.0, 135.2, 129.4, 128.6, 127.9, 127.7, 127.1, 126.8, 126.7, 69.6, 62.4, 62.0, 59.7, 48.0, 26.1, 22.0, 21.0, 18.4, −4.3, −4.5; HRMS *m*/*z* calcd for $C_{26}H_{37}NO_3Si$ $[M+Na]^+$ 462.2441, found 462.2443.

*4.1.9. (3S,4R)-3-(Azidomethyl)-4-(tert-butyldimethylsilyloxy)-2-[(R)-1-phenylethyl]-1,2,3,4-tetrahydroisoquinoline (**13b**).* Colorless oil (72%); $[\alpha]_D^{24}$ −13.8 (*c* 0.32, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40–7.32 (m, 4H), 7.31–7.26 (m, 2H), 7.24–7.22 (m, 2H), 7.02–7.00 (m, 1H), 4.66 (d, 1H, *J*=2.8 Hz), 3.96 (d, 1H, *J*=14.8 Hz), 3.84 (q, 1H, *J*=6.4 Hz), 3.63 (d, 1H, *J*=14.8 Hz), 3.28 (dd, 1H, *J*=4.4, 12.0 Hz), 3.23–3.20 (m, 1H), 2.83 (dd, 1H, *J*=8.0, 12.0 Hz), 1.46 (d, 3H, *J*=6.4 Hz), 0.90 (s, 9H), 0.07 (s, 3H), −0.01 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.7, 135.8, 135.8, 128.7, 128.4, 127.8, 127.6, 127.3, 126.8, 126.7, 69.5, 62.4, 60.7, 50.7, 48.4, 26.1, 21.3, 18.3, −4.4, −4.4; FT-IR: *v* 2097 cm^{-1} (N_3); HRMS *m*/*z* calcd for $C_{24}H_{34}N_4OSi$ $[M+Na]^+$ 423.2581, found 423.2577.

*4.1.10. (3S,4R)-3-(Hydroxymethyl)-2-[(R)-1-phenylethyl]-1,2,3,4-tetrahydroisoquinolin-4-ol (**14a**).* Compound **13a** (119 mg, 0.27 mmol) was dissolved in EtOH/H_2O (2/1) (2.70 mL, 0.10 M) and lithium hydroxide monohydrate (114 mg, 2.71 mmol) was added at room temperature. The reaction mixture was heated to refluxing temperature and stirred for 8 h. The mixture was cooled to room temperature, and the solvent was removed under reduced pressure to give a crude sticky product. The crude product was diluted with CH_2Cl_2, and treated with H_2O. The aqueous layer was extracted with CH_2Cl_2 and dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by silica gel flash column chromatography using EtOAc/hexane (50/50) to give 66 mg of product **14a** as a yellow oil (86%); $[\alpha]_D^{24}$ +26.2 (*c* 0.25, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36–7.33 (m, 5H), 7.29–7.27 (m, 1H), 7.25–7.23 (m, 2H), 7.07–7.05 (m, 1H), 4.43 (s, 1H), 4.08 (d, 1H, *J*=16.0 Hz), 4.07–4.04 (m, 1H), 3.77 (d, 1H, *J*=16.0 Hz), 3.72–3.70 (m, 1H), 3.40–3.36 (m, 1H), 3.22–3.21 (m, 1H), 1.48 (d, 3H, *J*=6.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.7, 135.9, 134.3, 129.7, 128.9, 127.8, 127.6, 127.5, 127.1, 126.6, 67.8, 61.5, 60.8, 58.7, 47.4, 22.1; FT-IR: *v* 3389 cm^{-1} (br, OH); HRMS *m*/*z* calcd for $C_{18}H_{21}NO_2$ $[M+Na]^+$ 306.1470, found 306.1472.

*4.1.11. (3S,4R)-tert-Butyl-4-hydroxy-3-(hydroxymethyl)-3,4-dihydroisoquinoline-2(1H)-carboxylate (**15a**).* Compound **14a**

(29 mg, 0.10 mmol) was dissolved in MeOH (0.50 mL) and 10 wt % $Pd(OH)_2$ (2.5 mg) and $(Boc)_2O$ (22 mg, 0.10 mmol) were added. Then, the reaction mixture was stirred for 4 h under atmospheric pressure of H_2 (g). The reaction mixture was filtered to remove Pd catalyst and the solvent was removed under reduced pressure. The residue was purified by silica gel flash column chromatography using EtOAc/hexane (40/60) to give 23 mg of product **15a** as a colorless oil (90%); $[\alpha]_D^{24}$ +0.10 (*c* 0.17, CH_3OH); ^1H NMR (400 MHz, CD_3OD) δ 7.35 (d, 1H, *J*=6.8 Hz), 7.33–7.24 (m, 2H), 7.20–7.18 (m, 1H), 4.85–4.75 (m, 2H), 4.50–4.49 (m, 1H), 4.29 (dd, 1H, *J*=12.0, 16.8 Hz), 3.44–3.39 (m, 1H), 3.26–3.19 (m, 1H), 1.52 (s, 9H); ^{13}C NMR (100 MHz, CD_3OD) δ 157.7, 135.0, 134.0, 130.9, 129.4, 128.0, 127.2, 81.4, 68.0, 61.5, 60.2, 59.0, 44.8, 43.8, 28.7; FT-IR: *v* 3378 cm^{-1} (br, OH); HRMS *m*/*z* calcd for $C_{15}H_{21}NO_4$ $[M+Na]^+$ 302.1369, found 302.1365.

*4.1.12. (3S,4R)-4-(tert-Butyldimethylsilyloxy)-3-[(tert-butyldimethylsilyloxy)methyl]-6,7-dimethoxy-1-methyl-3,4-dihydroisoquinoline (**17a**).* To a 0.20 M solution of **11** (740 mg, 1.32 mmol) in MeOH (6.60 mL) was added 10 wt % $Pd(OH)_2$ (74 mg) and the mixture was stirred for 3 h under atmospheric pressure of H_2 (g). The mixture was filtered and the solvent was removed under reduced pressure. The crude product was dissolved in THF (4.40 mL, 0.30 M) and added aqueous 3 N NaOH solution (0.66 mL) at 0 °C. Then, acetic anhydride (0.15 mL, 1.59 mmol) was slowly added to the reaction mixture. The reaction mixture was stirred for 5 min and warmed to room temperature, neutralized with aqueous $NaHCO_3$ solution. The reaction mixture was diluted with EtOAc and the aqueous layer was extracted with EtOAc and dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. The crude product **16a** was dissolved in anhydrous CH_2Cl_2 (6.60 mL, 0.20 M) and added 2-ClPyr (0.14 mL, 1.45 mmol) and Tf_2O (0.24 mL, 1.45 mmol) at −78 °C. After 5 min, the reaction mixture was placed in an ice-water bath and warmed to 0 °C. After 5 min, the resulting solution was allowed to room temperature and then aqueous 3 N NaOH solution (0.66 mL) was added to neutralize the trifluoromethanesulfonate salts. The aqueous layer was extracted with CH_2Cl_2 and dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. The crude product was purified by silica gel flash column chromatography using EtOAc/hexane (40/60) to give 507 mg of **17a** as a brown oil (80%); $[\alpha]_D^{24}$ −52.2 (*c* 0.34, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 6.98 (s, 1H), 6.87 (s, 1H), 4.82 (d, 1H, *J*=6.0 Hz), 3.91 (s, 6H), 3.88–3.79 (m, 2H), 3.23 (dd, 1H, *J*=6.0, 9.9 Hz), 2.38 (s, 3H), 0.89 (s, 9H), 0.85 (s, 9H), 0.15 (s, 3H), 0.08 (s, 3H), 0.03 (s, 3H), −0.01 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 162.4, 151.1, 148.4, 131.3, 121.2, 110.6, 108.7, 66.4, 65.7, 62.2, 56.3, 56.1, 26.1, 26.0, 23.4, 18.5, 18.4, −4.1, −4.1, −5.1, −5.1; HRMS *m*/*z* calcd for $C_{25}H_{45}NO_4Si_2$ $[M+Na]^+$ 502.2785, found 502.2783.

*4.1.13. (3S,4R)-4-(tert-Butyldimethylsilyloxy)-3-[(tert-butyldimethylsilyloxy)-methyl]-6,7-dimethoxy-1-propyl-3,4-dihydroisoquinoline (**17b**).* Yellow solid (95%); $[\alpha]_D^{24}$ −58.1 (*c* 0.52, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 6.99 (s, 1H), 6.85 (s, 1H), 4.79 (d, 1H, *J*=3.0 Hz), 3.98–3.96 (m, 1H), 3.92 (s, 6H), 3.79 (dd, 1H, *J*=3.0, 6.0 Hz), 3.13 (t, 1H, *J*=9.5 Hz), 2.82–2.77 (m, 1H), 2.64–2.58 (m, 1H), 1.71–1.69 (m, 2H), 0.97 (t, 3H, *J*=6.0 Hz), 0.88 (s, 9H), 0.86 (s, 9H), 0.16 (s, 3H), 0.07 (s, 3H), 0.03 (s, 3H), −0.01 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.6, 150.9, 148.5, 131.6, 120.7, 111.0, 108.6, 66.6, 65.6, 61.8, 56.3, 56.1, 38.0, 26.1, 26.0, 20.7, 18.5, 18.3, 13.9, −4.1, −4.2, −5.1, −5.2; mp 62–64 °C; HRMS *m*/*z* calcd for $C_{27}H_{49}NO_4Si_2$ $[M+Na]^+$ 530.3098, found 530.3099.

*4.1.14. (3S,4R)-4-(tert-Butyldimethylsilyloxy)-3-[(tert-butyldimethylsilyloxy)methyl]-6,7-dimethoxy-1-pentyl-3,4-dihydroisoquinoline (**17c**).* Yellow oil, (94%); $[\alpha]_D^{24}$ −76.2 (*c* 0.72, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 7.00 (s, 1H), 6.85 (s, 1H), 4.79 (d, 1H, *J*=4.5 Hz), 3.99–3.96 (m, 1H), 3.93 (s, 3H), 3.92 (s, 3H), 3.80 (dd, 1H, *J*=4.5, 10.0 Hz), 3.13 (t, 1H, *J*=8.5 Hz), 2.82–2.76 (m, 1H), 2.66–2.60 (m, 1H), 1.69–1.64 (m, 2H), 1.36–1.32 (m, 4H), 0.90 (t, 3H, *J*=10.0 Hz), 0.88 (s, 9H), 0.86 (s, 9H), 0.16 (s, 3H), 0.07 (s, 3H), 0.03 (s, 3H), −0.01 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.9, 150.9, 148.5, 131.6, 120.6, 110.1, 108.6, 66.5, 65.5, 61.9, 56.3, 56.1, 36.1, 31.6, 27.2, 26.1, 26.0, 22.7, 18.5, 18.3, 14.2, −4.1, −4.2, −5.1, −5.2; HRMS *m*/*z* calcd for $C_{29}H_{53}NO_4Si_2$ $[M+Na]^+$ 558.3411, found 558.3411.

*4.1.15. (3S,4R)-4-(tert-Butyldimethylsilyloxy)-3-[(tert-butyldimethylsilyloxy)methyl]-1-isopropyl-6,7-dimethoxy-3,4-dihydroisoquinoline (**17d**).* Yellow oil, (95%); $[\alpha]_D^{24}$ −94.4 (*c* 0.75, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.03 (s, 1H), 6.89 (s, 1H), 4.77 (d, 1H, *J*=4.8 Hz), 3.92 (s, 3H), 3.91 (s, 3H), 3.89–3.85 (m, 1H), 3.82 (dd, 1H, *J*=4.8, 10.0 Hz), 3.26–3.22 (m, 1H), 3.20–3.18 (m, 1H), 1.21 (d, 3H, *J*=2.8 Hz), 1.20 (d, 3H, *J*=2.8 Hz), 0.88 (s, 9H), 0.86 (s, 9H), 0.16 (s, 3H), 0.06 (s, 3H), 0.04 (s, 3H), 0.00 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.4, 150.6, 148.3, 132.5, 120.6, 110.5, 108.2, 66.5, 65.0, 62.0, 56.3, 56.1, 31.8, 26.0, 26.0, 21.0, 20.9, 18.4, 18.3, −4.1, −4.3, −5.1, −5.2; HRMS *m*/*z* calcd for $C_{27}H_{49}NO_4Si_2$ $[M+Na]^+$ 530.3098, found 530.3094.

*4.1.16. (3S,4R)-4-(tert-Butyldimethylsilyloxy)-3-[(tert-butyldimethylsilyloxy)methyl]-1-cyclohexyl-6,7-dimethoxy-3,4-dihydroisoquinoline (**17e**).* Colorless oil, (80%); $[\alpha]_D^{24}$ −74.8 (*c* 0.70, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.02 (s, 1H), 6.87 (s, 1H), 4.75 (d, 1H, *J*=5.2 Hz), 3.92 (s, 6H), 3.90–3.87 (m, 1H), 3.80 (dd, 1H, *J*=5.2, 10.0 Hz), 3.19 (dd, 1H, *J*=7.2, 10.0 Hz), 2.84 (t, 1H, *J*=10.0 Hz), 1.89–1.83 (m, 3H), 1.75–1.67 (m, 2H), 1.52–1.14 (m, 4H), 1.28–1.22 (m, 1H), 0.88 (s, 9H), 0.86 (s, 9H), 0.16 (s, 3H), 0.06 (s, 3H), 0.04 (s, 3H), 0.00 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.8, 150.6, 148.3, 132.4, 120.6, 110.7, 108.3, 65.2, 62.0, 56.4, 56.1, 42.2, 31.4, 26.8, 26.5, 26.1, 26.0, 25.8, 18.5, 18.3, −4.1, −4.2, −5.1, −5.1; HRMS *m*/*z* calcd for $C_{30}H_{53}NO_4Si_2$ $[M+Na]^+$ 570.3411, found 570.3410.

*4.1.17. (3S,4R)-4-(tert-Butyldimethylsilyloxy)-3-[(tert-butyldimethylsilyloxy)methyl]-6,7-dimethoxy-1-phenyl-3,4-dihydroisoquinoline (**17f**).* White solid, (72%); $[\alpha]_D^{24}$ −36.8 (*c* 0.27, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 7.64–7.62 (m, 2H), 7.44–7.42 (m, 3H), 6.96 (s, 1H), 6.81 (s, 1H), 4.87 (d, 1H, *J*=5.0 Hz), 4.10–4.07 (m, 1H), 3.95 (s, 3H), 3.92 (dd, 1H, *J*=5.0, 10.5 Hz), 3.73 (s, 3H), 3.38 (dd, 1H, *J*=7.0, 10.5 Hz), 0.92 (s, 9H), 0.86 (s, 9H), 0.18 (s, 3H), 0.12 (s, 3H), 0.05 (s, 3H), −0.03 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.5, 150.1, 148.0, 139.1, 132.9, 129.3, 128.9, 128.2, 120.5, 111.3, 110.3, 66.7, 66.1, 62.0, 56.2, 56.2, 26.1, 26.0, 18.5, 18.4, −4.0, −4.2, −5.1, −5.1; mp 114–116 °C; HRMS *m*/*z* calcd for $C_{30}H_{47}NO_4Si_2$ $[M+Na]^+$ 564.2942, found 564.2941.

*4.1.18. (3S,4R)-4-(tert-Butyldimethylsilyloxy)-3-[(tert-butyldimethylsilyloxy)methyl]-6,7-dimethoxy-1-(2-methoxyphenyl)-3,4-dihydroisoquinoline (**17g**).* White solid, (86%); $[\alpha]_D^{24}$ −54.7 (*c* 0.40, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.38 (t, 1H, *J*=8.0 Hz), 7.32 (d, 1H, *J*=8.0 Hz), 7.03 (t, 1H, *J*=8.0 Hz), 6.95 (d, 1H, *J*=8.0 Hz), 6.87 (br, 1H), 6.52 (s, 1H), 4.93 (d, 1H, *J*=4.0 Hz), 4.23 (br, 1H), 3.93 (s, 3H), 3.91–3.89 (m, 1H), 3.68 (br, 3H), 3.67 (s, 1H), 3.66 (s, 3H), 0.89 (br, 9H), 0.87 (s, 9H), 0.17 (s, 3H), 0.09 (br, 3H), 0.04 (s, 3H), 0.00 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 157.4, 150.9, 150.0, 148.3, 138.8, 130.4, 130.1, 129.1, 124.6, 122.4, 121.5, 121.1, 110.9, 66.6, 66.5, 56.1, 56.1, 55.9, 26.1, 26.0, 25.8, 18.4, 18.3, −4.0, −4.1, −5.1, −5.1; mp 77–78 °C; HRMS *m*/*z* calcd for $C_{31}H_{49}NO_5Si_2$ $[M+Na]^+$ 594.3047, found 594.3047.

*4.1.19. (3S,4R)-4-(tert-Butyldimethylsilyloxy)-3-[(tert-butyldimethylsilyloxy)methyl]-6,7-dimethoxy-1-(3-(trifluoromethyl)phenyl)-3,4-dihydroisoquinoline (**17h**).* Pale yellow oil, (50%); $[\alpha]_D^{24}$ −25.8 (*c* 0.39, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 7.94 (s, 1H), 7.83 (d, 1H, *J*=8.0 Hz), 7.71 (d, 1H, *J*=8.0 Hz), 7.56 (t, 1H, *J*=8.0 Hz), 6.99 (s, 1H), 6.72 (s, 1H), 4.88 (d, 1H, *J*=6.4 Hz), 4.08–4.03 (m, 1H), 3.96 (s, 3H),

3.94–3.91 (m, 1H), 3.73 (s, 3H), 3.45 (dd, 1H, *J*=6.4, 10.0 Hz), 0.93 (s, 9H), 0.85 (s, 9H), 0.19 (s, 3H), 0.13 (s, 3H), 0.05 (s, 3H), −0.03 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.3, 151.3, 148.1, 139.7, 133.4, 132.2, 128.7, 126.1, 126.0, 125.9, 125.9, 119.8, 110.7, 110.3, 66.6, 66.3, 62.0, 56.2, 56.2, 26.1, 26.0, 18.5, 18.4, −4.0, −4.2, −5.1, −5.1; HRMS *m*/*z* calcd for $C_{31}H_{46}F_3NO_4Si_2$ $[M+Na]^+$ 632.2815, found 632.2813.

*4.1.20. (3S,4R)-4-(tert-Butyldimethylsilyloxy)-3-[(tert-butyldimethylsilyloxy)methyl]-1-(furan-2-yl)-6,7-dimethoxy-3,4-dihydroisoquinoline (**17i**).* Dark brown oil, (74%); $[\alpha]_D^{24}$ −10.5 (*c* 0.27, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.58 (s, 1H),7.34 (s, 1H), 6.96 (s, 1H), 6.91 (d, 1H, *J*=2.1 Hz), 6.53 (q, 1H, *J*=2.1 Hz), 4.86 (d, 1H, *J*=6.3 Hz), 4.06–4.02 (m, 1H), 3.95 (s, 3H), 3.92–3.91 (m, 1H), 3.89 (s, 3H), 3.38 (dd, 1H, *J*=6.3, 10.2 Hz), 0.92 (s, 9H), 0.86 (s, 9H), 0.18 (s, 3H), 0.10 (s, 3H), 0.06 (s, 3H), −0.02 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.2, 152.0, 151.2, 148.1, 143.8, 133.1, 119.3, 112.9, 111.4, 110.6, 110.3, 66.3, 65.5, 62.0, 56.3, 56.2, 26.1, 26.1, 18.5, 18.4, −4.1, −4.2, −5.0, −5.1; HRMS *m*/*z* calcd for $C_{28}H_{45}NO_5Si_2$ $[M+Na]^+$ 554.2734, found 554.2733.

*4.1.21. (3S,4R)-1-(2-Bromobenzyl)-4-(tert-butyldimethylsilyloxy)-3-[(tert-butyldimethylsilyloxy)methyl]-6,7-dimethoxy-3,4-dihydroisoquinoline (**17j**).* Brown oil, (79%); $[\alpha]_D^{24}$ −22.2 (*c* 0.17, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.55 (d, 1H, *J*=8.0 Hz), 7.27 (d, 1H, *J*=8.0 Hz), 7.09 (t, 1H, *J*=8.0 Hz), 7.02 (t, 1H, *J*=8.0 Hz), 6.87 (s, 1H), 6.76 (s, 1H), 4.83 (d, 1H, *J*=3.5 Hz), 4.45 (d, 1H, *J*=16.0 Hz), 4.22–4.19 (m, 1H), 4.00 (d, 1H, *J*=16.0 Hz), 3.88 (s, 3H), 3.84 (dd, 1H, *J*=3.5, 10.0 Hz), 3.79 (s, 3H), 3.13–3.09 (m, 1H), 0.90 (s, 9H), 0.88 (s, 9H), 0.20 (s, 3H), 0.06 (s, 3H), 0.03 (s, 3H), −0.01 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.2, 150.8, 148.6, 137.6, 132.7, 131.1, 130.4, 128.3, 127.8, 124.5, 120.0, 111.1, 109.0, 66.6, 66.2, 61.4, 56.3, 56.1, 42.7, 26.0, 26.0, 18.4, 18.3, −4.1, −4.2, −5.1, −5.2; HRMS *m*/*z* calcd for $C_{31}H_{48}BrNO_4Si_2$ $[M+H]^+$ 634.2384, found 634.2385.

*4.1.22. (1S,3S,4R)-4-(tert-Butyldimethylsilyloxy)-3-[(tert-butyldimethylsilyloxy)methyl]-6,7-dimethoxy-1,2-dimethyl-1,2,3,4-tetrahydroisoquinoline (**18a**).* To a 0.50 M solution of **17a** (520 mg, 1.08 mmol) in CH_2Cl_2 (2.20 mL) was treated with MeI (0.67 mL, 10.84 mmol) at room temperature and the mixture was stirred for 40 h at 35 °C. The reaction mixture was concentrated under reduced pressure, dissolved in MeOH (5.40 mL, 0.20 M). After the reaction mixture was cooled to 0 °C, $NaBH(OAc)_3$ (459 mg, 2.17 mmol) was added. After stirring for 30 min at 0 °C, the reaction mixture was warmed to room temperature and concentrated under reduced pressure. The sticky crude product was diluted in CH_2Cl_2 and neutralized with aqueous $NaHCO_3$ solution. The aqueous layer was extracted with CH_2Cl_2 and the combined extracts were dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. The crude product was purified by silica gel flash column chromatography using EtOAc/hexane (20/80) to give 295 mg of product **18a** as a yellow oil, (55%); $[\alpha]_D^{24}$ −9.4 (*c* 0.14, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.82 (s, 1H), 6.58 (s, 1H), 4.71 (d, 1H, *J*=4.0 Hz), 3.86 (s, 6H), 3.80–3.76 (m, 2H), 3.51–3.48 (m, 1H), 2.93–2.91 (m, 1H), 2.50 (s, 3H), 1.41 (d, 3H, *J*=6.5 Hz), 0.91 (s, 9H), 0.89 (s, 9H), 0.11 (s, 3H), 0.10 (s, 3H), 0.04 (s, 3H), 0.03 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 148.2, 147.5, 132.9, 128.4, 111.9, 109.1, 68.3, 66.2, 62.0, 56.2, 56.0, 55.9, 39.8, 26.1, 26.0, 18.6, 18.4, 18.3, −3.5, −3.7, −5.1, −5.2; HRMS *m*/*z* calcd for $C_{26}H_{49}NO_4Si_2$ $[M+Na]^+$ 518.3098, found 518.3099.

*4.1.23. (1S,3S,4R)-4-(tert-Butyldimethylsilyloxy)-3-[(tert-butyldimethylsilyloxy)methyl]-6,7-dimethoxy-2-methyl-1-propyl-1,2,3,4-tetrahydroisoquinoline (**18b**).* Yellow oil. See Table 1, (63%); $[\alpha]_D^{24}$ −4.9 (*c* 0.31, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.78 (s, 1H), 6.58 (s, 1H), 4.69 (d, 1H, *J*=4.8 Hz), 3.86 (s, 6H), 3.74 (q, 1H, *J*=5.4 Hz), 3.55 (t, 1H, *J*=5.4 Hz), 3.40–3.35 (m, 1H), 2.96–2.90 (m, 2H), 2.46 (s, 3H), 1.90–1.69 (m, 3H), 1.45–1.21 (m, 3H), 0.90 (s, 9H), 0.89 (s, 9H), 0.86 (s, 3H), 0.13 (s, 3H), 0.11 (s, 3H), 0.03 (s, 3H), 0.01 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.0, 147.3, 132.2, 128.7, 111.8, 109.6, 67.7, 66.1, 61.8, 61.2, 56.0, 55.9, 39.4, 35.0, 26.1, 26.0, 19.0, 18.4, 18.2, 14.5, −3.7, −4.0, −5.2, −5.3; HRMS *m*/*z* calcd for $C_{28}H_{53}NO_4Si_2$ $[M+Na]^+$ 546.3411, found 546.3410.

*4.1.24. (1S,3S,4R)-4-(tert-Butyldimethylsilyloxy)-3-[(tert-butyldimethylsilyloxy)methyl]-6,7-dimethoxy-2-methyl-1-pentyl-1,2,3,4-tetrahydroisoquinoline (**18c**).* Yellow oil. See Table 1 (73%); $[\alpha]_D^{24}$ −13.7 (*c* 0.26, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.78 (s, 1H), 6.58 (s, 1H), 4.68 (d, 1H, *J*=5.0 Hz), 3.86 (s, 6H), 3.74 (q, 1H, *J*=5.0 Hz), 3.54 (t, 1H, *J*=5.0 Hz), 3.39–3.36 (m, 1H), 2.95–2.91 (m, 1H), 2.45 (s, 3H), 1.89–1.84 (m, 1H), 1.79–1.74 (m, 1H), 1.42–1.39 (m, 1H), 1.30–1.25 (m, 5H), 0.90 (s, 9H), 0.89 (s, 9H), 0.85 (t, 3H, *J*=6.5 Hz), 0.13 (s, 3H), 0.11 (s, 3H), 0.03 (s, 3H), 0.01 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 148.0, 147.3, 132.0, 128.8, 111.8, 109.5, 67.7, 66.1, 61.7, 61.2, 56.0, 55.9, 39.4, 32.8, 32.4, 26.1, 26.0, 25.3, 22.9, 18.4, 18.2, 14.3, −3.7, −3.9, −5.2, −5.3; HRMS *m*/*z* calcd for $C_{30}H_{57}NO_4Si_2$ $[M+Na]^+$ 574.3724, found 574.3723.

*4.1.25. (1S,3S,4R)-4-(tert-Butyldimethylsilyloxy)-3-[(tert-butyldimethylsilyloxy)methyl]-1-isopropyl-6,7-dimethoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline (**18d**).* Yellow oil. See Table 1 (68%); $[\alpha]_D^{24}$ −27.7 (*c* 0.46, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.85 (s, 1H), 6.58 (s, 1H), 4.70 (d, 1H, *J*=7.0 Hz), 3.86 (s, 6H), 3.79 (q, 1H, *J*=5.5 Hz), 3.53 (q, 1H, *J*=5.5 Hz), 3.10 (d, 1H, *J*=7.0 Hz), 2.95–2.92 (m, 1H), 2.32 (s, 3H), 2.13–2.08 (m, 1H), 1.09 (d, 3H, *J*=6.5 Hz), 0.92 (s, 9H), 0.89 (s, 9H), 0.86 (d, 3H, *J*=6.5 Hz), 0.15 (s, 3H), 0.12 (s, 3H), 0.04 (s, 3H), 0.03 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 147.3, 147.1, 130.6, 129.8, 111.2, 110.9, 68.8, 66.8, 64.5, 61.6, 56.0, 55.9, 39.2, 31.7, 26.1, 26.0, 20.9, 20.7, 18.3, −3.4, −3.8, −5.2, −5.3; HRMS *m*/*z* calcd for $C_{28}H_{53}NO_4Si_2$ $[M+Na]^+$ 546.3411, found 546.3410.

*4.1.26. (1S,3S,4R)-4-(tert-Butyldimethylsilyloxy)-3-[(tert-butyldimethylsilyloxy)methyl]-1-cyclohexyl-6,7-dimethoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline (**18e**).* Colorless oil. See Table 1 (62%); $[\alpha]_D^{24}$ −9.4 (*c* 0.16, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.84 (s, 1H), 6.54 (s, 1H), 4.70 (d, 1H, *J*=7.0 Hz), 3.86 (s, 3H), 3.85 (s, 3H), 3.79 (dd, 1H, *J*=6.5, 10.5 Hz), 3.58 (dd, 1H, *J*=5.0, 10.5 Hz), 3.10 (d, 1H, *J*=7.0 Hz), 3.01 (q, 1H, *J*=6.5 Hz), 2.33 (s, 3H), 2.14 (d, 1H, *J*=12.5 Hz), 1.84 (d, 1H, *J*=12.5 Hz), 1.77–1.72 (m, 2H), 1.71–1.68 (m, 1H), 1.65–1.63 (m, 1H), 1.25–1.01 (m, 5H), 0.92 (s, 9H), 0.89 (s, 9H), 0.14 (s, 3H), 0.11 (s, 3H), 0.05 (s, 3H), 0.04 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 147.3, 147.1, 130.7, 129.7, 111.4, 105.1, 68.6, 66.7, 63.5, 61.7, 56.1, 55.9, 41.9, 38.8, 31.2, 27.0, 26.9, 26.8, 26.1, 26.1, 18.4, −3.3, −3.7, −5.2, −5.2; HRMS *m*/*z* calcd for $C_{31}H_{57}NO_4Si_2$ $[M+Na]^+$ 586.3724, found 586.3723.

*4.1.27. (1S,3S,4R)-4-(tert-Butyldimethylsilyloxy)-3-[(tert-butyldimethylsilyloxy)methyl]-6,7-dimethoxy-2-methyl-1-phenyl-1,2,3,4-tetrahydroisoquinoline (**18f**).* Colorless oil. See Table 1 (61%); $[\alpha]_D^{24}$+9.6 (*c* 0.16, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38 (d, 2H, *J* = 6.6 Hz), 7.24–7.12 (m, 3H), 6.63 (s, 1H), 6.15 (s, 1H), 4.75 (d, 1H, *J* = 2.1 Hz), 4.40 (s, 1H), 3.86 (dd, 1H, *J* = 3.6, 9.0 Hz), 3.80 (s, 3H), 3.56 (s, 3H), 3.26–3.20 (m, 1H), 3.13 (td, 1H, *J* = 3.6, 9.0 Hz), 2.33 (s, 3H), 0.90 (s, 9H), 0.82 (s, 9H), 0.15 (s, 3H), 0.13 (s, 3H), −0.06 (s, 3H), −0.10 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 148.3, 147.4, 145.6, 131.2, 129.1, 128.2, 127.1, 126.6, 112.5, 110.6, 68.6, 67.0, 65.9, 58.3, 55.9, 55.7, 40.8, 26.1, 26.0, 18.3, 18.3, −3.8, −4.1, −5.2, −5.4; HRMS *m*/*z* calcd for $C_{31}H_{51}NO_4Si_2$ $[M+Na]^+$ 580.3255, found 580.3253.

*4.1.28. (1R,3S,4R)-4-(tert-butyldimethylsilyloxy)-3-[(tert-butyldimethylsilyloxy)methyl]-6,7-dimethoxy-1-(2-methoxyphenyl)-2-methyl-1,2,3,4-tetrahydroisoquinoline (**18g**).* Colorless oil. See Table 1 (78%); $[\alpha]_D^{24}$+108.0 (c 0.96, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64 (d, 1H, *J* = 8.0 Hz), 7.16 (t, 1H, *J* = 8.0 Hz), 6.91–6.85 (m, 2H), 6.65 (s, 1H),

6.45 (s, 1H), 5.17 (s, 1H), 4.81 (d, 1H, J = 2.4 Hz), 3.96–3.95 (m, 1H), 3.93 (s, 3H), 3.84 (s, 3H), 3.65 (s, 3H), 3.30-3.25 (m, 1H), 3.21 (td, 1H, J = 2.4, 8.0 Hz), 2.38 (s, 3H), 0.96 (s, 9H), 0.88 (s, 9H), 0.22 (s, 3H), 0.18 (s, 3H), −0.01 (s, 3H), −0.05 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 157.4, 148.4, 147.2, 134.2, 132.1, 130.5, 127.5, 126.4, 121.5, 112.4, 110.4, 110.0, 68.8, 67.0, 58.4, 56.2, 55.8, 55.7, 55.6, 40.3, 26.1, 26.0, 18.3, 18.3, −3.8, −4.1, −5.2, −5.4; HRMS m/z calcd for $C_{32}H_{53}NO_5Si_2$ $[M+Na]^+$ 610.3360, found 610.3463.

*4.1.29. (1S,3S,4R)-4-(tert-Butyldimethylsilyloxy)-3-[(tert-butyldimethylsilyloxy)methyl]-6,7-dimethoxy-2-methyl-1-(3-(trifluoromethyl) phenyl)-1,2,3,4-tetrahydroisoquinoline (**18h**).* Yellow oil. See Table 1 (82%); $[\alpha]_D^{24}$ +43.9 (c 0.86, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71 (s, 1H), 7.65 (d, 1H, J=7.6 Hz), 7.47 (d, 1H, J=7.6 Hz), 7.37 (t, 1H, J=7.6 Hz), 6.67 (s, 1H), 6.17 (s, 1H), 4.80 (d, 1H, J=2.8 Hz), 4.53 (s, 1H), 3.90–3.87 (m, 1H), 3.85 (s, 3H), 3.63 (s, 3H), 3.28–3.23 (m, 1H), 3.19 (td, 1H, J=2.8, 8.8 Hz), 2.38 (s, 3H), 0.95 (s, 9H), 0.87 (s, 9H), 0.20 (s, 3H), 0.17 (s, 3H), −0.02 (s, 3H), −0.06 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.5, 147.7, 147.1, 132.5, 130.1, 128.7, 126.6, 125.6, 124.1, 124.0, 115.4, 112.6, 110.4, 68.6, 67.0, 65.7, 58.4, 55.9, 55.8, 40.7, 26.1, 26.0, 18.3, 18.3, −3.9, −4.2, −5.3, −5.4; HRMS m/z calcd for $C_{32}H_{50}F_3NO_4Si_2$ $[M+Na]^+$ 648.3128, found 648.3125.

*4.1.30. (1R,3S,4R)-4-(tert-Butyldimethylsilyloxy)-3-[(tert-butyldimethylsilyloxy)methyl]-1-(furan-2-yl)-6,7-dimethoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline (**18i**).* Brown oil. See Table 1 (69%); $[\alpha]_D^{24}$ +8.7 (c 0.66, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 (d, 1H, J=3.2 Hz), 6.85 (s, 1H), 6.42 (s, 1H), 6.31 (t, 1H, J=3.2 Hz), 6.14 (d, 1H, J=3.2 Hz), 4.81 (d, 1H, J=5.2 Hz), 4.77 (s, 1H), 3.89 (dd, 1H, J=5.2, 10.4 Hz), 3.86 (s, 3H), 3.74 (s, 3H), 3.62 (dd, 1H, J=5.2, 10.4 Hz), 3.07–3.03 (m, 1H), 2.49 (s, 3H), 0.93 (s, 9H), 0.86 (s, 9H), 0.15 (s, 3H), 0.07 (s, 3H), 0.02 (s, 3H), 0.01 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.8, 148.2, 148.0, 141.9, 128.8, 127.9, 111.8, 110.1, 109.6, 109.0, 68.1, 64.7, 60.5, 60.0, 55.9, 55.9, 40.2, 26.1, 26.0, 18.4, 18.3, −3.2, −3.6, −5.2, −5.3; HRMS m/z calcd for $C_{29}H_{49}NO_5Si_2$ $[M+Na]^+$ 570.3047, found 570.3045.

*4.1.31. (1S,3S,4R)-3-(hydroxymethyl)-6,7-dimethoxy-1,2-dimethyl-1,2,3,4-tetrahydroisoquinolin-4-ol (**19a**).* Substrate **18a** (172 mg, 0.35 mmol) was dissolved in EtOH/H_2O (2/1) (3.50 mL, 0.10 M) and lithium hydroxide monohydrate (145 mg, 3.46 mmol) was added at room temperature. The reaction mixture was heated to refluxing temperature and stirred for 5 h. The solution was cooled to room temperature and the solvent was removed under reduced pressure to give a crude sticky product. The crude product was diluted with CH_2Cl_2, and treated with H_2O. The aqueous layer was extracted with CH_2Cl_2 and the combined organic extracts were dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by silica gel flash column chromatography using MeOH/CH_2Cl_2 (10/90) to give 74 mg of product **19a** as a colorless oil, (80%); $[\alpha]_D^{24}$+10.0 (c 0.22, $CHCl_3$); ^{1}H NMR (400 MHz, CD_3OD) δ 7.03 (s, 1H), 6.67 (s, 1H), 4.57 (d, 1H, J = 8.0 Hz), 3.89 (dd, 1H, J = 5.2, 11.6 Hz), 3.83 (dd, 1H, J = 5.2, 11.6 Hz), 3.82 (s, 3H), 3.80 (s, 3H), 3.29–3.31 (m, 1H), 2.95–2.91 (m, 1H), 2.51 (s, 3H), 1.38 (d, 3H, J = 6.8 Hz) ; ^{13}C NMR (100 MHz, CD_3OD) δ 149.9, 149.4, 133.3, 129.7, 112.1, 110.6, 66.8, 62.7, 60.1, 59.8, 56.4, 56.4, 38.8, 18.4; FT–IR: ν 3378 cm^{-1} (br, OH); HRMS m/z calcd for $C_{14}H_{21}NO_4$ $[M+Na]^+$ 290.1369, found 290.1367.

*4.1.32. (1S,3S,4R)-3-(Hydroxymethyl)-6,7-dimethoxy-2-methyl-1-propyl-1,2,3,4-tetrahydroisoquinolin-4-ol (**19b**).* Yellow oil, (70%); $[\alpha]_D^{24}$ +2.0 (c 0.20, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.97 (s, 1H), 6.57 (s, 1H), 4.50 (d, 1H, J=8.0 Hz), 3.88 (s, 3H), 3.87 (s, 3H), 3.83–3.75 (m, 2H), 3.57 (t, 1H, J=5.6 Hz), 3.12 (q, 1H, J=7.2 Hz), 2.43 (s, 3H), 1.85–1.60 (m, 2H), 1.51–1.33 (m, 2H), 0.93 (t, 3H, J=7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.8, 148.1, 130.6, 128.7, 110.2, 109.6, 66.1, 62.4, 61.8, 60.0, 56.1, 56.0, 37.5, 36.9, 19.2, 14.2; FT-IR: ν 3383 cm^{-1} (br, OH); HRMS m/z calcd for $C_{16}H_{25}NO_4$ $[M+Na]^+$ 318.1682, found 318.1682.

*4.1.33. (1S,3S,4R)-3-(Hydroxymethyl)-6,7-dimethoxy-2-methyl-1-pentyl-1,2,3,4-tetrahydroisoquinolin-4-ol (**19c**).* Colorless oil, (87%); $[\alpha]_D^{24}$ +15.8 (c 0.54, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.95 (s, 1H), 6.56 (s, 1H), 4.47 (d, 1H, J=7.6 Hz), 3.86 (s, 6H), 3.77–3.74 (m, 2H), 3.54 (dd, 1H, J=5.2, 7.6 Hz), 3.09 (q, 1H, J=7.6 Hz), 2.81 (br, 2H), 2.41 (s, 3H), 1.83–1.68 (m, 2H), 1.44–1.37 (m, 1H), 1.33–1.22 (m, 5H), 0.87 (t, 3H, J=6.4 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 148.7, 147.9, 130.6, 128.7, 110.2, 109.4, 66.1, 62.4, 61.7, 60.0, 56.0, 55.9, 37.6, 34.5, 31.9, 25.4, 22.7, 14.1; FT-IR: ν 3388 cm^{-1} (br, OH); HRMS m/z calcd for $C_{18}H_{29}NO_4$ $[M+Na]^+$ 346.1995, found 346.1994.

*4.1.34. (1S,3S,4R)-3-(Hydroxymethyl)-1-isopropyl-6,7-dimethoxy-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-ol (**19d**).* Yellow oil, (70%); $[\alpha]_D^{24}$ +35.1 (c 0.54, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.02 (s, 1H), 6.58 (s, 1H), 4.45 (d, 1H, J=9.2 Hz), 3.94 (q, 1H, J=6.4 Hz), 3.88 (s, 3H), 3.86 (s, 3H), 3.72 (t, 1H, J=8.8 Hz), 3.21–3.15 (m, 1H), 3.08 (d, 1H, J=8.8 Hz), 2.60 (br, 2H), 2.30 (s, 3H), 2.06–1.97 (m, 1H), 1.08 (d, 3H, J=6.4 Hz), 1.00 (d, 3H, J=6.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.2, 147.8, 129.3, 129.0, 111.8, 110.1, 70.3, 66.0, 61.0, 60.4, 56.0, 56.0, 36.6, 32.4, 21.1; FT-IR: ν 3359 cm^{-1} (br, OH); HRMS m/z calcd for $C_{16}H_{25}NO_4$ $[M+Na]^+$ 318.1682, found 318.1680.

*4.1.35. (1S,3S,4R)-1-Cyclohexyl-3-(hydroxymethyl)-6,7-dimethoxy-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-ol (**19e**).* Colorless oil, (76%); $[\alpha]_D^{24}$ +15.0 (c 0.21, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.02 (s, 1H), 6.54 (s, 1H), 4.46 (d, 1H, J=6.0 Hz), 4.99 (dd, 1H, J=6.0, 10.0 Hz), 3.88 (s, 3H), 3.87 (s, 3H), 3.75 (t, 1H, J=10.0 Hz), 3.25–3.19 (m, 1H), 3.15 (d, 1H, J=8.4 Hz), 2.80 (br, 2H), 2.30 (s, 3H), 2.10 (d, 1H, J=12.4 Hz), 1.78–1.70 (m, 3H), 1.67–1.63 (m, 2H), 1.20–1.12 (m, 3H), 1.12–1.03 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.3, 147.8, 129.0, 128.9, 112.1, 110.2, 69.7, 66.1, 61.1, 60.1, 56.1, 56.0, 41.9, 36.4, 31.6, 31.4, 26.6; FT-IR: ν 3337 cm^{-1} (br, OH); HRMS m/z calcd for $C_{19}H_{29}NO_4$ $[M+H]^+$ 336.2176, found 336.2175.

*4.1.36. (1S,3S,4R)-3-(Hydroxymethyl)-6,7-dimethoxy-2-methyl-1-phenyl-1,2,3,4-tetrahydroisoquinolin-4-ol (**19f**).* Colorless oil, (82%); $[\alpha]_D^{24}$ +57.8 (c 0.45, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.31–7.23 (m, 3H), 7.21–7.20 (m, 2H), 6.89 (s, 1H), 6.18 (s, 1H), 4.65 (d, 1H, J=4.0 Hz), 4.55 (s, 1H), 3.93 (dd, 1H, J=5.5, 10.5 Hz), 3.85 (s, 3H), 3.61 (s, 3H), 3.53 (dd, 1H, J=7.5, 10.5 Hz), 3.22–3.18 (m, 1H), 2.40 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 148.7, 148.2, 143.0, 129.6, 129.2, 128.5, 127.9, 127.6, 111.5, 110.8, 67.5, 66.3, 65.5, 58.5, 55.9, 55.8, 40.4; FT-IR: ν 3349 cm^{-1} (br, OH); HRMS m/z calcd for $C_{19}H_{23}NO_4$ $[M+Na]^+$ 352.1525, found 352.1526.

*4.1.37. (1R,3S,4R)-3-(Hydroxymethyl)-6,7-dimethoxy-1-(2-methoxyphenyl)-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-ol (**19g**).* Pale yellow oil, (76%); $[\alpha]_D^{24}$ +27.4 (c 0.17, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.28–7.24 (m, 1H), 7.12 (d, 1H, J=7.0 Hz), 6.92–6.89 (m, 2H), 6.88 (s, 1H), 6.23 (s, 1H), 4.95 (s, 1H), 4.64 (d, 1H, J=4.0 Hz), 3.97 (dd, 1H, J=4.0, 11.0 Hz), 3.88 (s, 3H), 3.71 (s, 3H), 3.63 (s, 3H), 3.55 (dd, 1H, J=7.0, 11.0 Hz), 3.30–3.27 (m, 1H), 3.01 (br, 2H), 2.45 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 157.8, 148.7, 147.9, 131.1, 131.0, 129.8, 128.9, 127.6, 120.9, 111.9, 111.3, 110.0, 67.8, 65.8, 61.2, 58.6, 55.9, 55.8, 55.8, 40.4; FT-IR: ν 3352 cm^{-1} (br, OH); HRMS m/z calcd for $C_{20}H_{25}NO_5$ $[M+H]^+$ 360.1812, found 360.1812.

*4.1.38. (1S,3S,4R)-3-(Hydroxymethyl)-6,7-dimethoxy-1-(2-methoxyphenyl)-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-ol (**19g′**).* To a 0.50 M solution of **19g** (388 mg, 0.68 mmol) in CH_2Cl_2 (1.40 mL) was treated with MeI (0.21 mL, 3.40 mmol) at room temperature and stirred for 4 h at 35 °C. The reaction mixture was

concentrated under reduced pressure, dissolved in MeOH (3.40 mL, 0.30 M). After the reaction mixture was cooled to 0 °C, $NaBH_4$ (51 mg, 1.36 mmol) was added. After stirring for 30 min at 0 °C, the reaction mixture was warmed to room temperature and concentrated under reduced pressure. The sticky crude product was diluted in CH_2Cl_2 and aqueous $NaHCO_3$ solution. The aqueous layer was extracted with CH_2Cl_2 and the combined extract was dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. The mixture of two diastereomers[†] (dr 2/1) was purified by silica gel flash column chromatography using EtOAc/hexane (5/95) to give 51 mg of the reduced product. The desilylation of the reduced product gave **19g′** as a yellow oil (21%);[‡] $[\alpha]_D^{24}$ −6.2 (*c* 0.12, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ7.25 (t, 1H, *J*=10.0 Hz), 7.17 (d, 1H, *J*=7.6 Hz), 7.05 (s, 1H), 6.95–6.87 (m, 2H), 6.17 (s, 1H), 5.07 (s, 1H), 4.96 (d, 1H, *J*=7.6 Hz), 3.94–3.90 (m, 2H), 3.86 (s, 6H), 3.59 (s, 3H), 3.05 (br, 2H), 2.58–2.56 (m, 1H), 2.31 (s, 3H); ^{13}C NMR (MHz, $CDCl_3$) δ 157.9, 148.4, 148.0, 132.9, 130.2, 130.1, 129.7, 128.6, 121.4, 111.0, 110.4, 108.5, 67.9, 67.8, 62.2, 60.6, 56.1, 55.9, 55.8, 40.5; FT-IR: *v* 3358 cm^{-1} (br, OH); HRMS *m*/*z* calcd for $C_{20}H_{25}NO_5$ $[M+H]^+$ 360.1812, found 360.1812.

*4.1.39. (1S,3S,4R)-3-(Hydroxymethyl)-6,7-dimethoxy-2-methyl-1-(3-(trifluoromethyl)phenyl)-1,2,3,4-tetrahydroisoquinolin-4-ol (**19h**).* Pale yellow oil, (77%); $[\alpha]_D^{24}$ +37.5 (*c* 0.32, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.56–7.53 (m, 2H), 7.43 (t, 1H, *J*=7.5 Hz), 7.39 (d, 1H, *J*=7.5 Hz), 6.92 (s, 1H), 6.14 (s, 1H), 4.66–4.65 (m, 2H), 3.96 (dd, 1H, *J*=5.5, 10.5 Hz), 3.89 (s, 3H), 3.63 (s, 3H), 3.62–3.58 (m, 1H), 3.24–3.21 (m, 1H), 2.43 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 148.9, 148.5, 144.4, 132.5, 129.2, 128.5, 128.0, 125.9, 125.9, 124.7, 124.7, 111.7, 110.7, 67.5, 66.1, 65.6, 58.8, 56.0, 55.9, 40.5; FT-IR: *v* 3361 cm^{-1} (br, OH); HRMS *m*/*z* calcd for $C_{20}H_{22}F_3NO_4$ $[M+Na]^+$ 420.1399, found 420.1396.

*4.1.40. (1R,3S,4R)-1-(Furan-2-yl)-3-(hydroxymethyl)-6,7-dimethoxy-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-ol (**19i**).* Colorless oil, (51%); $[\alpha]_D^{24}$ +30.5 (*c* 0.21, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 (d, 1H, *J*=0.8 Hz), 6.96 (s, 1H), 6.42 (s, 1H), 6.29 (dd, 1H, *J*=0.8, 3.2 Hz), 6.10 (d, 1H, *J*=3.2 Hz), 4.77 (s, 1H), 4.66 (d, 1H, *J*=6.0 Hz), 3.91 (dd, 1H, *J*=6.0, 10.8 Hz), 3.87 (s, 3H), 3.74 (s, 3H), 3.69 (dd, 1H, *J*=6.0, 10.8 Hz), 3.09 (q, 1H, 6.0 Hz), 2.46 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.7, 148.8, 148.6, 142.6, 128.7, 126.6, 110.7, 110.1, 109.9, 109.6, 67.3, 63.6, 60.6, 59.9, 56.0, 55.9, 39.3; FT-IR: *v* 3345 cm^{-1} (br, OH); HRMS *m*/*z* calcd for $C_{17}H_{21}NO_5$ $[M+Na]^+$ 342.1318, found 342.1317.

*4.1.41. (1S,3S,4R)-1-(2-Bromobenzyl)-4-(tert-butyldimethylsilyloxy)-3[(tert-butyldimethylsilyloxy)methyl]-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (**20**).* To a 0.20 M solution of **17j** (1.33 g, 2.10 mmol) in MeOH (10.48 mL) was added $NaBH_4$ (159 mg, 4.19 mmol) at 0 °C. After stirring for 1 h, the reaction mixture was allowed to warm to room temperature. The reaction solvent was concentrated under reduced pressure and the resulting white sticky residue was diluted with CH_2Cl_2, quenched with H_2O. The aqueous layer was extracted with CH_2Cl_2. The combined extracts were dried over anhydrous $MgSO_4$, filtered, and then the solvent was removed in vacuo. The crude product was purified by silica gel flash column chromatography using EtOAc/hexane (15/85) to give 1.16 g of product **20** as a colorless oil, (87%); $[\alpha]_D^{24}$ +14.9 (*c* 1.10, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.62 (d, 1H, *J*=7.5 Hz), 7.32 (d, 1H, *J*=7.5 Hz), 7.27 (*t*, 1H, *J*=7.5 Hz), 7.14 (t, 1H, *J*=7.5 Hz), 6.95 (s, 1H), 6.80 (s, 1H), 4.51 (d, 1H, *J*=9.0 Hz), 4.26 (dd, 1H, *J*=3.0, 9.0 Hz), 4.08 (dd, 1H, *J*=3.0, 9.0 Hz), 3.90 (s, 3H), 3.87 (s, 3H), 3.57 (t, 1H, *J*=9.0 Hz), 3.29 (td, 1H, *J*=3.0, 9.0 Hz), 3.24 (dd, 1H, *J*=3.0, 13.5 Hz), 3.15 (dd, 1H, *J*=9.0, 13.5 Hz), 2.31 (br, 1H), 1.03 (s, 9H), 0.93 (s, 9H), 0.27 (s, 3H), 0.18 (s, 3H), 0.11 (s, 3H), 0.10 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 147.9, 147.7, 139.0, 133.1, 132.1, 131.1, 130.5, 128.2, 127.6, 125.1, 109.6, 109.5, 69.9, 65.4, 55.9, 55.9, 55.9, 54.8, 43.1, 26.2, 26.1, 18.6, 18.3, −3.3, −3.6, −5.2, −5.2; HRMS *m*/*z* calcd for $C_{31}H_{50}BrNO_4Si_2$ $[M+Na]^+$ 658.2360, found 658.2362.

*4.1.42. (5R,6S)-6-(Hydroxymethyl)-2,3-dimethoxy-5,6-dihydro-indolo[2,1-a]isoquinolin-5-ol (**23**).* To a 0.10 M solution of **20** (552 mg, 0.82 mmol) in anhydrous toluene (8.20 mL) was added $NaOBu^t$ (197 mg, 2.05 mmol) at room temperature under nitrogen atmosphere. The reaction mixture was degassed for 5 min and were added 5 mol % $Pd_2(dba)_3$ (28 mg) and 10 mol % X-Phos (55 mg). The reaction mixture was refluxed at 110 °C and stirred for 1.5 h under nitrogen atmosphere. After the reaction was completed, the reaction mixture was cooled to room temperature, filtered with a glass filter on a pad of Celite. The residue was concentrated in vacuo to give a crude product. The crude product was purified by silica gel flash column chromatography using EtOAc/hexane (5/95) to give 410 mg of product **22** (90%). The substrate **22** was dissolved in EtOH/H_2O (2/1) (7.40 mL, 0.10 M) and lithium hydroxide monohydrate (306 mg, 7.38 mmol) was added at room temperature. The mixture was heated to refluxing temperature and stirred for 24 h. The solution was cooled to room temperature and the solvent was removed under reduced pressure to give a crude sticky product. The crude product was diluted with CH_2Cl_2 and treated with H_2O. The aqueous layer was extracted with CH_2Cl_2, dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by silica gel flash column chromatography using MeOH/CH_2Cl_2 (5/95) to give 232 mg of product **23** as a yellowish brown solid, (96%); $[\alpha]_D^{24}$ −40.2 (*c* 0.28, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60 (d, 1H, *J*=8.0 Hz), 7.37 (d, 1H, *J*=8.0 Hz), 7.21 (s, 1H), 7.18 (td, 1H, *J*=1.2, 7.2 Hz), 7.10 (td, 1H, *J*=1.2, 7.2 Hz), 6.87 (s, 1H), 6.78 (s, 1H), 4.84 (d, 1H, *J*=6.0 Hz), 4.76 (td, 1H, *J*=2.0, 6.0 Hz), 3.97 (s, 3H), 3.89 (s, 3H), 3.56–3.52 (m, 1H), 3.43–3.37 (m, 1H), 2.31 (br, 1H), 1.85 (br, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.2, 149.4, 137.5, 133.3, 129.2, 124.5, 122.2, 120.8, 120.6, 120.4, 112.6, 109.4, 107.1, 96.6, 68.5, 63.0, 59.8, 56.2, 26.2; FT-IR: *v* 3382 cm^{-1} (br, OH); mp 102–104 °C; HRMS *m*/*z* calcd for $C_{19}H_{19}NO_4$ $[M+Na]^+$ 348.1212, found 348.1216.

*4.1.43. 1-((4R,5S,6aS)-4-(tert-butyldimethylsilyloxy)-5-((tert-butyldimethylsilyloxy)methyl)-1,2-dimethoxy-6a,7-dihydro-4H-dibenzo[de,g]quinolin-6(5H)-yl)ethanone (**24**).* To a 0.20 M solution of **20** (463 mg, 0.73 mmol) in DMF (3.60 mL) was added NaH (44 mg, 1.82 mmol) at 0 °C. After stirring for an additional 20 min, acetic anhydride (0.10 mL, 1.09 mmol) was slowly added to the reaction mixture at room temperature. Stirring was continued for 1 h and the reaction mixture was diluted with EtOAc and treated with H_2O. The aqueous layer was extracted with EtOAc and the combined extracts were dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. The *N*-acetyl protected product **21** was dissolved in DMA (14.5 mL, 0.05 M) and 20 mol % Pd(OAc) (33 mg), 30 mol % X-Phos (104 mg), and Cs_2CO_3 (710 mg, 2.18 mmol) were added at room temperature. The reaction mixture was heated to 110 °C for 5 h in preheated oil bath. And the reaction mixture was concentrated in vacuo to give a crude product. The crude product was purified by silica gel flash column chromatography using EtOAc/hexane (10/90) to give 282 mg of product **24** as a yellow solid, (65%); $[\alpha]_D^{24}$ −6.6 (*c* 0.12, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.33 (d, 1H, *J*=7.6 Hz), 7.34 (d, 1H, *J*=7.6 Hz), 7.31 (d, 1H, *J*=7.6 Hz), 7.27–7.23 (m, 1H), 6.69 (s, 1H), 4.77 (d, 1H, *J*=2.4 Hz), 4.30 (dd, 1H, *J*=2.4, 12.8 Hz), 4.25–4.22 (m, 1H), 4.13–4.08 (m, 1H), 3.90 (s, 3H), 3.67 (s, 3H), 3.46–3.42 (m, 1H), 3.39–3.36 (m, 1H), 2.47 (t, 1H, *J*=12.8 Hz), 2.28 (s, 3H), 0.86 (s, 9H), 0.84 (s, 9H), 0.19 (s, 3H), 0.10 (s,

[†] The ratio of each diastereomers was determined by ^{1}H NMR of the crude reduction product.

[‡] Yield was not optimized.

3H), -0.07 (s, 3H), −0.07 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.2, 147.0, 138.8, 131.5, 129.9, 128.6, 128.3, 128.0, 127.5, 126.9, 126.5, 120.6, 111.9, 67.8, 62.7, 60.1, 56.1, 51.7, 34.9, 25.9, 25.8, 24.3, 23.9, 18.2, 18.1, −4.1, −4.3, −5.4, −5.6; mp 117–119 °C; HRMS *m*/*z* calcd for $C_{33}H_{51}NO_5Si_2$ $[M+Na]^+$ 620.3204, found 620.3202.

*4.1.44. (4R,5S,6aS)-5-(Hydroxymethyl)-1,2-dimethoxy-5,6,6a,7-tetrahydro-4H-dibenzo[de,g]quinolin-4-ol (**25**).* Substrate **24** (49 mg, 0.082 mmol) was dissolved in EtOH/H_2O (2/1) (0.80 mL, 0.10 M) and lithium hydroxide monohydrate (34 mg, 0.82 mmol) was added at room temperature. The reaction mixture was heated to refluxing temperature and stirred for 1.5 h. The solution was cooled to room temperature and the solvent was removed under reduced pressure to give a crude sticky product. The crude product was diluted with CH_2Cl_2 and treated with H_2O. The aqueous layer was extracted with CH_2Cl_2 and dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by silica gel flash column chromatography using MeOH/CH_2Cl_2 (10/90) to give 21 mg of product **25** as a light brown oil, (77%); $[\alpha]_D^{24}$ +2.4 (*c* 0.14, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.36 (d, 1H, *J*=8.0 Hz), 7.30 (t, 1H, *J*=8.0 Hz), 7.23–7.19 (m, 2H), 6.94 (s, 1H), 4.43 (s, 1H), 3.93 (br, 2H), 3.91 (s, 3H), 3.66 (dd, 1H, *J*=4.5, 10.0 Hz), 3.62 (s, 3H), 3.59–3.57 (m, 1H), 3.56–3.54 (m, 1H), 2.81 (dd, 1H, *J*=4.5, 13.5 Hz), 2.73 (t, 1H, *J*=13.5 Hz), 2.04–2.00 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.2, 147.1, 135.8, 131.9, 129.4, 128.6, 128.1, 127.9, 127.5, 126.8, 126.6, 112.5, 66.3, 60.3, 59.7, 56.1, 47.5, 36.6, 29.8; FT-IR: ν 3400 cm^{-1} (br, OH); HRMS *m*/*z* calcd for $C_{19}H_{21}NO_4$ $[M+Na]^+$ 350.1369, found 350.1367.

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