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Oxazolidines as Intermediates in the Asymmetric Synthesis of 3-Substituted and 1,3-Disubstituted Tetrahydroisoquinolines

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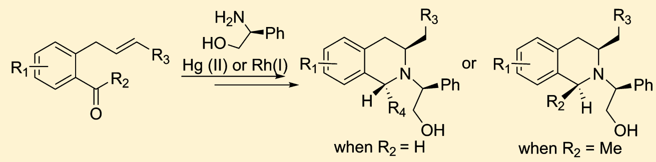
Supporting Information

ABSTRACT: A diastereoselective mercury(II)-promoted intramolecular cyclization of unsaturated aldehyde via an oxazolidine to prepare C-3-substituted tetrahydroisoquinoline is disclosed. The C-3 stereogenic center is subsequently exploited to create the C-1 stereocenter by coordination of the nucleophilic reagent to the oxygen atom of oxazolidine. Both *cis*- and *trans*-1,3-disubstituted tetrahydroisoquinolines can be readily prepared. In addition, when a cationic rhodium complex was used, intramolecular hydroamination was effected, thus avoiding mercury(II) salts and demercuration. The reaction is general and works well using aliphatic and aromatic aldehydes.



INTRODUCTION

1,2,3,4-Tetrahydroisoquinolines (THIQs; Figure 1) constitute a large class of natural and synthetic compounds with a wide diversity of biological properties.[1] The diverse pharmaceutical applications of THIQs have stimulated the development of several methodologies for the efficient preparation of these compounds. Much synthetic effort has been devoted to the synthesis of 1-substituted THIQs. The Pictet−Spengler,[2] Bischler−Napieralski cyclization/reduction,[3] noble transition metal catalyzed asymmetric hydrogenation of isoquinoline or dihydroisoquinoline derivatives,[4,5] and asymmetric nucleophilic addition to an iminium ion of the cyclic precursor[6] are popular methods for the synthesis of C-1-substituted THIQs. Few examples are known for the enantioselective synthesis of 1,3-disubstituted THIQs. Diastereoselective alkylation of C-3 substituted THIQs afforded chiral *trans*-1,3-disubstituted derivatives.[7] The Pictet−Spengler[8] and intramolecular Heck reactions,[9] electrophile-induced cyclization,[10] nucleophilic addition to 3-substituted isoquinolines followed by ionic hydrogenation,[11] and three-component reductive amination using an organocatalyst followed by intramolecular Michael addition[12] have been disclosed for the synthesis of 1,3-disubstituted THIQs. A key factor to be addressed in the synthesis of these molecules is the control of relative and absolute stereochemistries at C-1 and C-3. Although some elegant routes[13] have been disclosed, a generally applicable synthesis of 1,3-disubstituted THIQs is desirable.

We report herein a diastereoselective electrophile-induced intramolecular cyclization of an iminoalcohol/oxazolidine to prepare C-3-substituted THIQs (Scheme 1). The C-3 stereogenic center is subsequently exploited to create the C-1 stereocenter by nucleophilic addition to an iminium ion.

The key feature in this sequence is the use of a carbonyl group as a handle, which through the oxazolidine nitrogen functions as a nucleophile to create the C-3 stereocenter and subsequently through the iminium ion functions as an electrophile to create the C-1 stereocenter, both in an asymmetric fashion.

RESULTS AND DISCUSSION

3-Monosubstituted THIQ and *trans*-1,3-Disubstituted THIQ. The synthetic study commenced with the known aldehyde **1**,[14] which was prepared from 2-iodobenzoic acid. Aldehyde **1** on reaction with (*S*)-phenylglycinol in dichloromethane in the presence of anhydrous magnesium sulfate furnished an equilibrium mixture of imino alcohol **2** and oxazolidine **3** ,which was used without characterization in the next step. Reaction of the mixture of **2** and **3** in dichloromethane with a small excess of mercuric trifluoroacetate furnished the oxazolidine **4** as a single isomer, the structure of which was established by NOE (Scheme 2). Characteristically a NOE was observed between H_c and H_d; also, H_a showed no NOE. The most stable ground-state conformation of **3** would have the hydrogen in the same plane as the allyl residue ($A^{1,3}$ strain is avoided). *re*-Face attack of mercuric trifluoroacetate onto the double bond followed by *si*-face attack by the oxazolidine moiety involving a half-chair conformation would explain the formation of **4**.

Reductive demercuration using tributyltin hydride and triethylborane[15] cleanly afforded the C-3 methyl substituted THIQ derivative **5**. The next objective was the introduction of a C-1 substituent by nucleophilic addition. The reaction of **5** with methylmagnesium iodide, vinylmagnesium bromide, and 1-octynylmagnesium chloride cleanly afforded *trans*-1,3- disubstituted THIQ derivatives **6**−**8** (Scheme 3). The diastereoselective addition of organomagnesium compounds to oxazolidines has been described before.[8] Reduction of **4** with an excess of tributyltin hydride furnished the C-3-monosubstituted derivative **9**.

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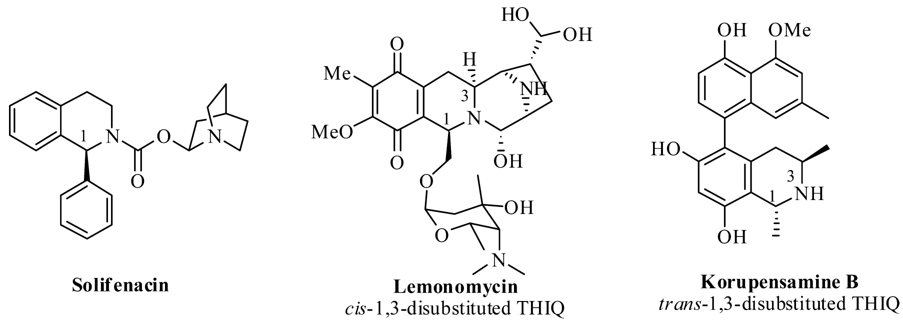
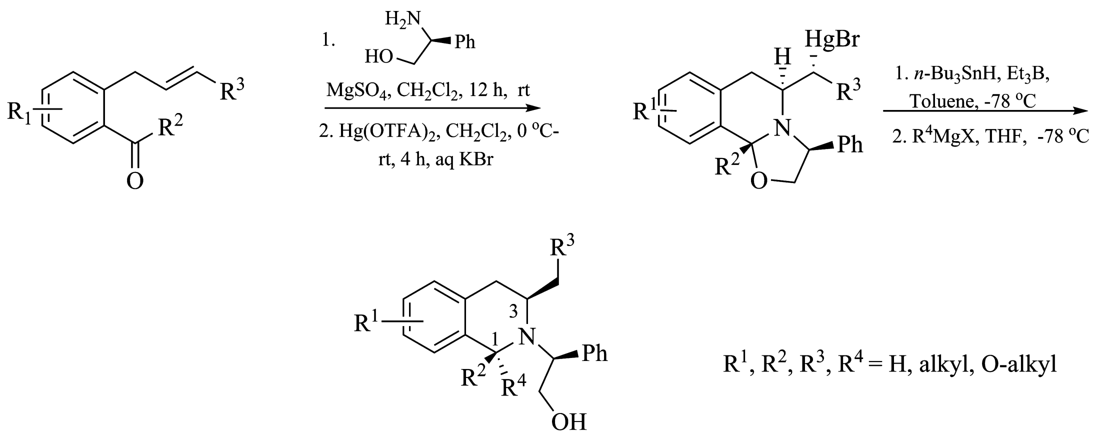
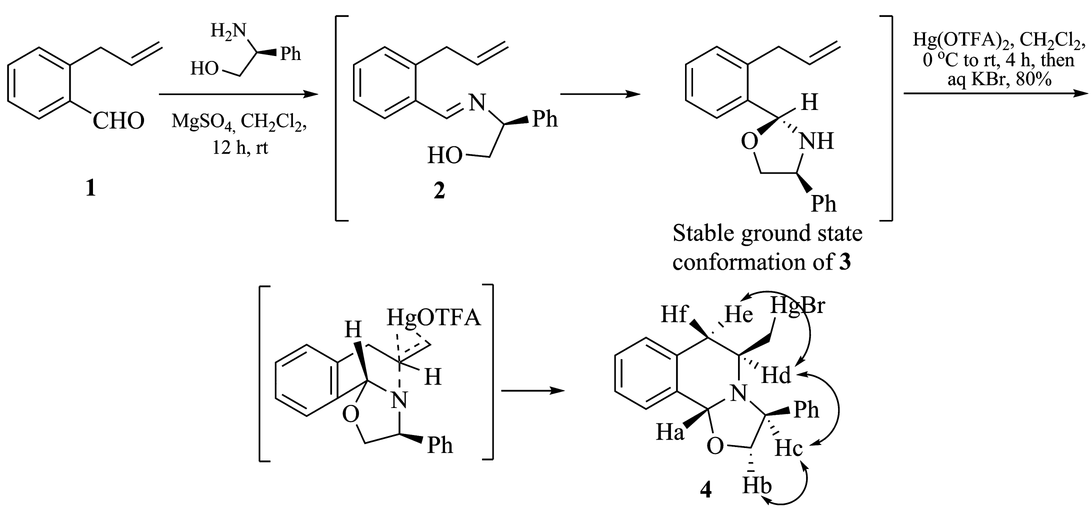


Figure 1. Naturally occurring biologically active tetrahydroisoquinolines.

Scheme 1. General Route to THIQs using Oxazolidine Intermediates



Scheme 2. Synthesis of Oxazolidine 4 by Hg(II)-Promoted Aminomercuration



Oxidative demercuration of **4** using $NaBH_4$ and TEMPO[16] cleanly furnished the oxygenated derivative **10**. Reduction of **10** using Zn/CH_3COOH furnished the C-3 hydroxymethyl derivative **11**. Compound **11** has been utilized in a diastereoselective alkylation to prepare *trans*-1,3-disubstituted THIQ.[17]

The structure of compound **6** was assigned by NOE studies. The presence of NOE between C-1 H and C-3 Me and the absence of NOE between C-1 H and C-3 H confirmed that both Me groups are *anti* to each other. The structures were assigned to compounds **7** and **8** on the basis of analogy. The stereochemical outcome can be rationalized by postulating transition state **I**, wherein the phenyl group of the amino alcohol would prevent nucleophilic attack to the *si* face of the iminium ion while the oxygen atom of the amino alcohol moiety would coordinate with the Grignard reagent and deliver it to the *re* face (Scheme 4).

The generality of the reaction was further explored using aldehydes **12**,[18] **14**, and **16**[19] (Scheme 5). The aminomercuration reaction proceeded in excellent yields with electron-rich aldehydes, and also ortho substitution relative to both carbonyl and allyl groups is well tolerated.

The reaction works well with the *trans*-disubstituted alkene **19** obtained by cross metathesis of aldehyde **1** and *cis*-1,4-butanediol. The structures were assigned to **13**, **15**, **17**, and **20** on the basis of analogy. These organomercurials can be transformed, as illustrated in Scheme 3 using compound **4**, into *trans*-1,3-disubstitued THIQs.

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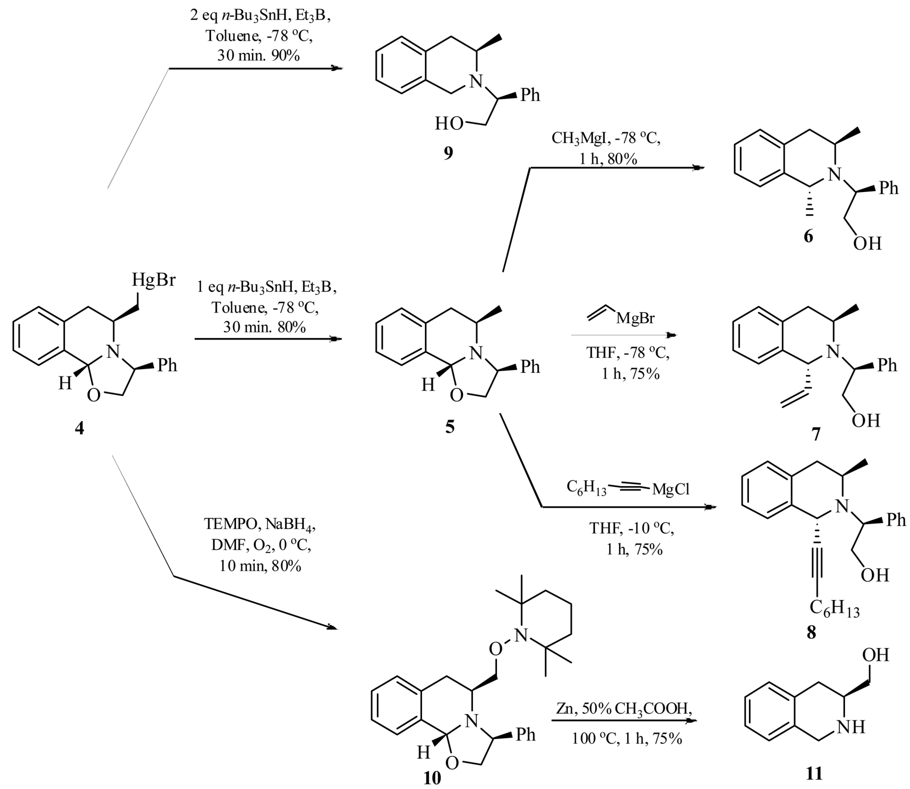
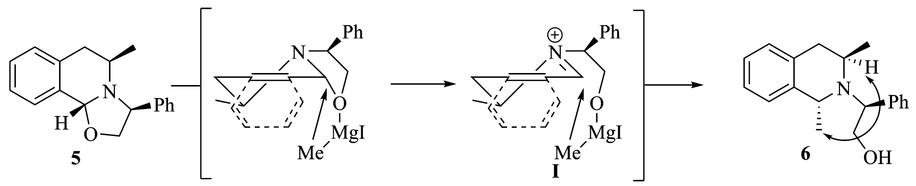
Scheme 3. Synthesis of *trans*-1,3-Disubstituted THIQs and 3-Substituted THIQs



Scheme 4. Model To Rationalize Stereoselective Formation of *trans*-1,3-THIQs



Racemic aliphatic aldehyde **21**[20] reacted under similar conditions to furnish a diastereomeric equimolar mixture of oxazolidines **22** and **23** (Scheme 6). The formation of only two isomers can be explained by efficient 1,2-asymmetric induction due to the phenyl group. Either **22** or **23** can be selectively obtained from optically pure **21**. Characteristic NOEs were observed between protons of H_a and H_b, H_b and H_c, and H_d and H_e in compound **22**, thus establishing its structure. The structure of compound **23** should be as depicted. 2,4,5-Trisubstituted pyrrolidine derivatives can be readily obtained by the reaction of bicyclic compound **22** or **23** with Grignard reagents following the disclosed methodology. In addition, with α-substituted and α,β-disubstituted, γ,δ-unsaturated aliphatic aldehydes as starting materials 2,3,5-trisubstituted and 2,3,4,5- tetrasubstituted pyrrolidines can be obtained.

***cis*-1,3-Disubstituted THIQs.** Since *cis*-1,3-disubstituted THIQs are more common in natural and synthetic compounds, we explored the stereoselective reduction of a THIQ tetrasubstituted at C-1 as a route to *cis*-1,3-disubstituted THIQs. Treatment of **24**[21] with (*S*)-phenylglycinol in the presence of titanium tetraethoxide furnished presumably an imine in equilibrium with the oxazolidine derivative, which without characterization was subsequently reacted with mercuric trifluoroacetate to yield oxazolidine **25** after treatment with aqueous potassium bromide (Scheme 7). Since compound **25** was not stable to column chromatography, the crude compound was taken ahead to demercuration. Demercuration using tributyltin hydride cleanly furnished compound **26**. Disappointingly, reduction of oxazolidine **26** with sodium borohydride in the presence of trifluoroacetic acid furnished the product **6**. Hydride transfer to the *si* face of the iminium ion would account for the formation of **6**. However, reduction with alane[22] furnished the *cis*-1,3-disubstituted THIQ **27**. With alane the hydride delivery probably takes place by coordination to the oxazolidine oxygen. The structure assigned to **27** was confirmed by NOE studies that revealed NOE between C-1 H and C-3 H. In a similar fashion, ketone **28**[23] was converted to mercuric compound **29**, and demercuration furnished oxazolidine **30**, which on reduction using alane afforded the *cis*-THIQ **31**. Thus, we have developed a route to selectively prepare *cis*- and *trans*-1,3-disubstituted THIQs.

Catalytic Hydroamination. A drawback of the methodology was the use of stoichiometric amounts of mercuric salt for aminomercuration and tributyltin hydride for demercuration. At this point in the research, the catalytic hydroamination reaction was envisaged as an alternate approach to prepare substituted THIQs. Catalytic hydroamination, if successful, would circumvent the use of both of these toxic reagents. Interestingly, the oxazolidine **32** could be obtained by subjecting the mixture of imino alcohol and oxazolidine, obtained from aldehyde **16** and

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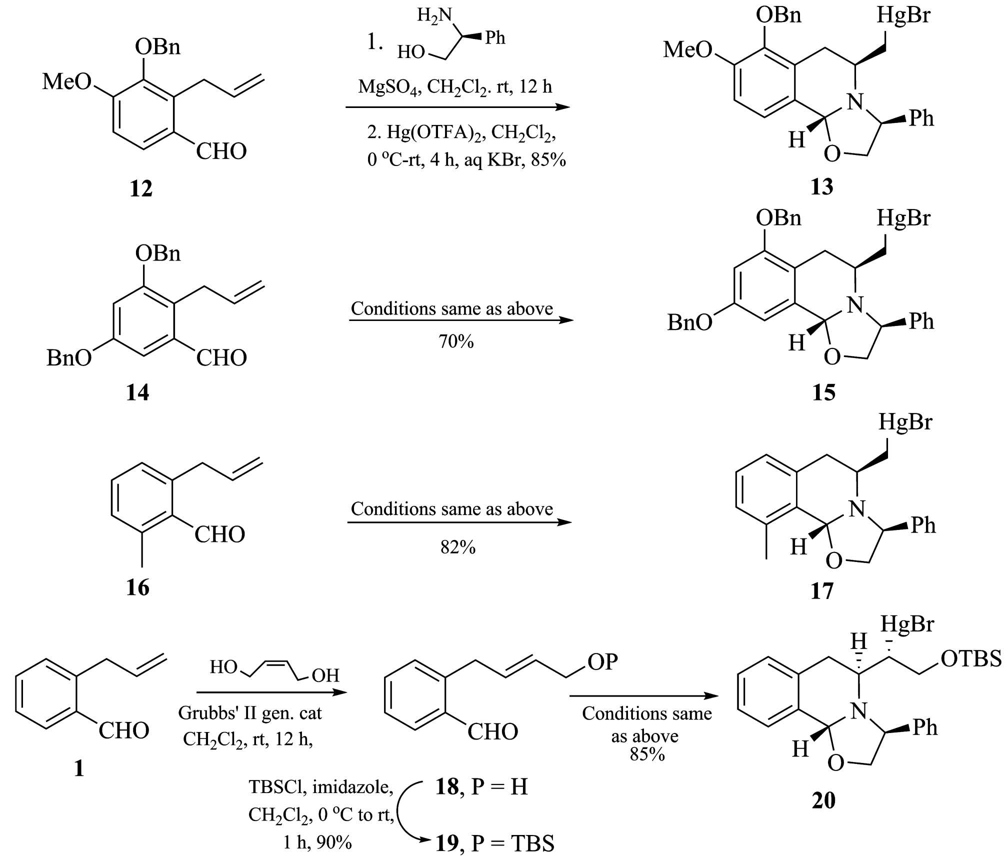
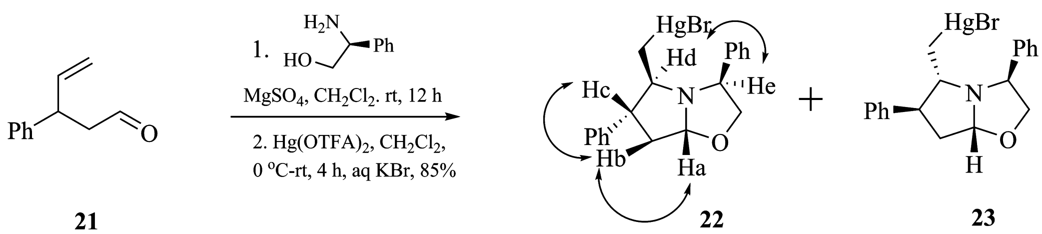
Scheme 5. Synthesis of a Variety of Organomercurials by Hg(II)-Promoted Cyclization



Scheme 6. Preparation of Pyrrolidine Derivatives from an Acyclic Aliphatic Aldehyde



(*S*)-phenylglycinol, to intramolecular hydroamination in the presence of $Rh(COD)BF_4$ and DPEphos in 1,4-dioxane[24] (Scheme 8). Compound **32** was identical with the product obtained by tributyltin hydride mediated demercuration of **17**. Aldehyde **12** likewise furnished oxazolidine **33**. Thus, catalytic hydroamination would be a valuable alternate route to C-3-substituted and *trans*-1,3-disubstituted THIQs, avoiding stoichiometric mercuric salts and tributyltin hydride.

■ CONCLUSION

Mercuric trifluoroacetate promoted diastereoselective preparation of 3-substituted THIQ from an *o*-allyl aldehyde is disclosed. The C-3 substituent serves to introduce the C-1 stereogenic center to access either 1,3-*trans* or 1,3-*cis* THIQs. The oxazolidine moiety functions as both a nucleophile and an electrophile in the creation of C-3 and C-1 stereocenters, respectively. The reaction can be conducted by using a catalytic amount of Rh(I) catalyst via hydroamination. Both *cis* and *trans* isomers of chiral 1,3-disubstituted 1,2,3,4-THIQs are found in biologically active alkaloids. The present work proposes a simple route to both the substitution patterns and compares favorably in terms of efficacy and scope to previous approaches. Substituted pyrrolidine and piperidine derivatives can be likewise be readily obtained. A simple readily available unsaturated aldehyde is converted to a complex target structure.

■ EXPERIMENTAL SECTION

Dry reactions were performed under an inert atmosphere using argon or nitrogen. All glassware apparatus used for reactions were thoroughly oven-dried. Anhydrous solvents were distilled prior to use: THF from Na and benzophenone; CH_2Cl_2 and toluene from CaH_2; MeOH from Mg cake; $CHCl_3$ from P_2O_5; acetone from $KMnO_4$ and K_2CO_3. Commercial reagents were used without purification. Column chromatography was carried out by using silica gel (100−200 mesh). Analytical thin-layer chromatography (TLC) was run on silica gel 60 F254 precoated plates (250 μm thickness). Optical rotations $[\alpha]_D$ were measured on a polarimeter and are given in units of 10^{-1} deg cm^2 g^{-1}. Infrared spectra were recorded neat or in KBr (as mentioned) and reported in wavenumbers (cm^{-1}). Mass spectral data were obtained using MS (EI) ESI and HRMS mass spectrometers. High-resolution mass spectra (HRMS; ESI+) were obtained using either a TOF or a double-focusing spectrometer. ^1H NMR spectra were recorded at 300, 400, or 500 MHz and ^{13}C NMR spectra at 75, 100, or 125 MHz in

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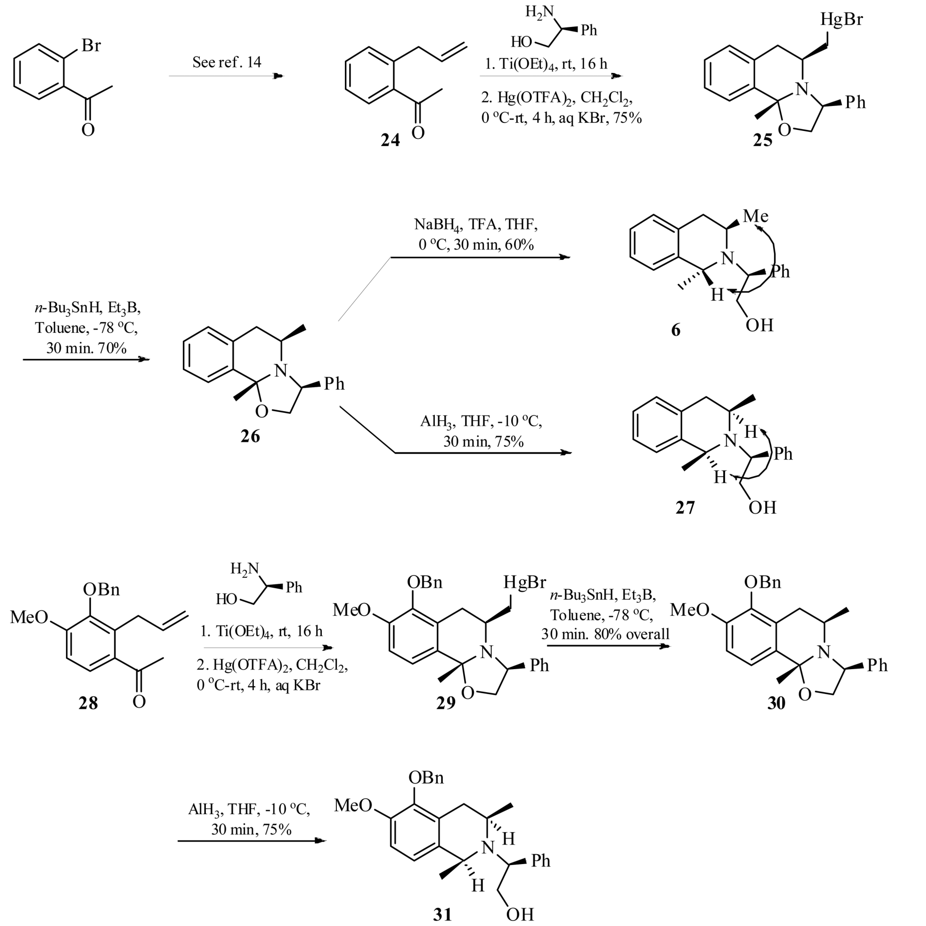
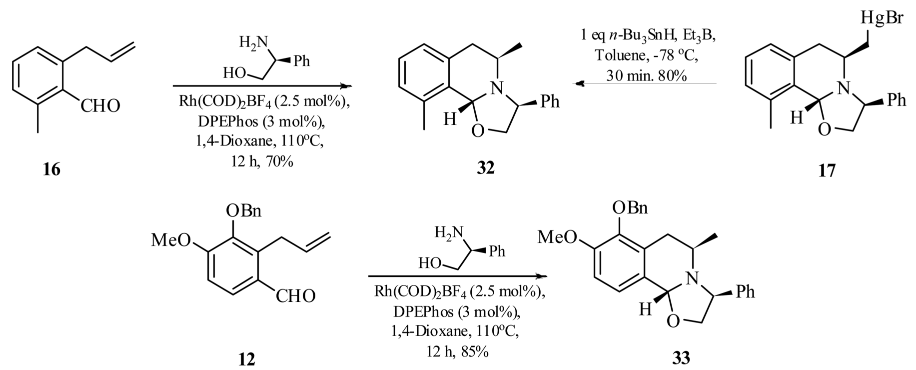
Scheme 7. Synthesis of *cis*-1,3-Disubstituted THIQs



Scheme 8. Preparation of THIQ Derivatives by Rh(I)-Catalyzed Hydroamination



$CDCl_3$ with the residual solvent signal as an internal standard unless mentioned otherwise; chemical shifts are in ppm downfield from tetramethylsilane, and coupling constants (J) are reported in hertz (Hz). The following abbreviations are used to designate signal multiplicity: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad.

General Procedure for the Preparation of Organomercurials. To a stirred solution of the aldehyde (1 equiv) in anhydrous dichloromethane (1 M) was added (S)-phenylglycinol (1.1 equiv) followed by anhydrous $MgSO_4$ (1 equiv). The reaction mixture was stirred at room temperature for 12 h. The reaction mixture was diluted with anhydrous dichloromethane (0.25 M) and cooled to 0 °C, and mercuric trifluoroacetate (1.2 equiv) was added. The reaction mixture was gradually warmed to room temperature and stirred further for a period of 4 h. The reaction mixture was cooled to 0 °C, quenched by adding saturated aqueous KBr solution, and stirred at room temperature for another 30 min. The resulting suspension was filtered through a pad of Celite, and the Celite pad was washed with dichloromethane (2 × 5 mL). The aqueous and organic layers were separated, and the aqueous layer was extracted with dichloromethane (2 × 5 mL). The combined organic layers were washed with saturated brine, dried, and evaporated to furnish the crude compound, which was purified by column chromatography using EtOAc/hexane (v/v) as the eluent to afford pure organomercurials.

*(((3S,5S,10bR)-3-Phenyl-3,5,6,10b-tetrahydro-2H-oxazolo[2,3-a]-isoquinolin-5-yl)methyl)mercury(II) Bromide (**4**).* Following the general procedure, the imine prepared from 2-allyl benzaldehyde **1** (146 mg, 1 mmol) and (S)-phenylglycinol (151 mg, 1.1 mmol) in the presence of anhydrous $MgSO_4$ was reacted with mercuric trifluoroacetate (479 mg, 1.1 mmol) to afford pure **4** (436 mg, 0.8 mmol) after aqueous KBr treatment as a pale white solid in 80% yield after column

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chromatography using 10% EtOAc/hexane (v/v) as the eluent. Mp: 79−81 °C. R_f = 0.2 (10% EtOAc/hexane, v/v). $[\alpha]_D^{25}$ = +1.9 (*c* 1, CH_2Cl_2). IR (neat): 2924, 2855, 1639, 1385, 1028, 755 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 7.43−7.01 (m, 9H), 5.53 (s, 1H), 4.38 (t, *J* = 8.1 Hz, 1H), 4.14 (dd, *J* = 8.3, 7.7 Hz, 1H), 3.63−3.53 (m, 2H), 2.80 (dd, *J* = 15.4, 2.8 Hz, 1H), 2.64 (dd, *J* = 15.4, 10.1 Hz, 1H), 2.2 (dd, *J* = 12.2, 4.3 Hz, 1H), 2.00 (dd, *J* = 12.2, 1.5 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 142.8, 133.6, 132.3, 129.6, 128.3, 128.0, 127.6, 127.3, 126.9, 126.8, 90.8, 73.5, 68.2, 56.3, 44.1, 40.0. MS (ESI): 545 $[M]^+$. HRMS (ESI): *m/z* $[M]^+$ calcd for $C_{18}H_{18}NOBrHg$ 545.0278, found 545.0269.

*(((3S,5S,10bR)-7-(Benzyloxy)-8-methoxy-3-phenyl-3,5,6,10b-tetrahydro-2H-oxazolo[2,3-a]isoquinolin-5-yl)methyl)mercury(II) Bromide (**13**).* Organomercurial **13** (578 mg, 0.85 mmol) was obtained, following the general procedure, from aldehyde **12** (282 mg, 1 mmol) as a white solid in 85% yield after column chromatography using 15% EtOAc/hexane (v/v) as the eluent. Mp: 143−145 °C. R_f = 0.2 (15% EtOAc/hexane, v/v). $[\alpha]_D^{25}$ = +69.2 (*c* 1, CH_2Cl_2). IR (neat): 2924, 2854, 1717, 1595, 1457, 1277, 1022, 751 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 7.5−7.3 (m, 10H), 7.2 (d, *J* = 8.3 Hz, 1H), 6.94 (d, *J* = 8.3 Hz, 1H), 5.54 (s, 1H), 5.01 (s, 2H), 4.43 (t, *J* = 8.3 Hz, 1H), 4.18 (dd, *J* = 8.3, 7.5 Hz, 1H), 3.92 (s, 3H), 3.63 (dd, *J* = 9.0, 8.3 Hz, 1H), 3.47−3.39 (m, 1H), 3.0 (dd, *J* = 15.8, 3.0 Hz, 1H), 2.2 (dd, *J* = 12.0, 4.5 Hz, 1H), 2.11 (dd, *J* = 15.8, 9.8 Hz, 1H), 1.94 (dd, *J* = 12.0, 1.5 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 152.3, 143.6, 142.7, 137.4, 129.6, 128.7, 128.4, 128.3, 127.9, 126.9, 125.4, 123.7, 111.1, 90.6, 74.7, 73.2, 68.0, 55.9, 55.8, 44.1, 33.7. MS (ESI): 682 $[M + H]^+$. HRMS (ESI): *m/z* $[M]^+$ calcd for $C_{26}H_{26}NO_3BrHg$ 681.0802, found 681.0792.

The aldehyde **14** was prepared from the known methyl 3-(benzyloxy)-5-hydroxybenzoate by employing a straightforward sequence of reactions.

*Methyl 3-(Allyloxy)-5-(benzyloxy)benzoate (**I**).* To a solution of methyl 3-(benzyloxy)-5-hydroxybenzoate (2 g, 8 mmol) in anhydrous acetone (16 mL) were added allyl bromide (0.8 mL, 9.6 mmol) and K_2CO_3 (1.1 g, 8 mmol). The mixture was refluxed for 3 h, inorganic salts were removed by filtration, and the solvent was evaporated to afford compound **I** (2 g, 7 mmol) as a red viscous liquid in 87% yield. R_f = 0.2 (10% EtOAc/hexane, v/v). IR (neat): 2948, 1722, 1597, 1442, 1237, 1162, 1050, 766 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 7.44−7.3 (m, 5H), 7.24 (s, 1H), 7.16 (s, 1H), 6.68 (s, 1H), 6.19−5.94 (m, 1H), 5.43−5.24 (m, 2H), 5.09 (s, 2H), 4.53 (d, *J* = 4.5 Hz, 2H), 3.8 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 166.3, 159.2, 159.1, 136.0, 132.3, 131.5, 128.1, 127.6, 127.0, 117.4, 107.79, 107.74, 106.7, 69.7, 68.5, 51.7. MS (ESI): 299 $[M + H]^+$. HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{18}H_{19}O_4$ 299.1277, found 299.1274.

*Methyl 2-Allyl-5-(benzyloxy)-3-hydroxybenzoate (**II**).* A solution of methyl benzoate **I** (2 g, 7 mmol) in dimethylacetamide (4 mL) was stirred at 180 °C for 10 h. The cold solution was washed with aqueous 2 N NaOH solution (2 × 10 mL). The aqueous layer was washed with Et_2O (10 mL), acidified with 2 N concentrated HCl, and extracted with ethyl acetate (2 × 20 mL). The combined organic layers were washed with brine, dried, and evaporated to afford compound **II** (1.4 g, 4.9 mmol) as a viscous liquid in 70% yield. R_f = 0.2 (10% EtOAc/hexane, v/v). IR (neat): 2949, 1705, 1608, 1340, 1202, 1033, 739 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 7.32−7.14 (m, 5H), 6.94 (d, *J* = 3 Hz, 1H), 6.49 (d, *J* = 3 Hz, 1H), 5.97−5.68 (m, 1H), 5.02−4.84 (m, 4H), 3.77 (s, 3H), 3.58 (d, *J* = 6.0 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 168.2, 157.5, 155.8, 136.6, 136.4, 131.9, 128.4, 128.1, 127.9, 127.3, 115.2, 108.7, 106.6, 70.0, 52.0, 30.4. MS (ESI): 299 $[M + H]^+$. HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{18}H_{19}O_4$ 299.1277, found 299.1275.

*Methyl 2-Allyl-3,5-bis(benzyloxy)benzoate (**III**).* To a suspension of sodium hydride (60% in Nujol, 240 mg, 6 mmol) in anhydrous THF (10 mL) cooled to 0 °C was added *n*-tetrabutylammonium iodide (185 mg, 0.5 mmol) followed by the dropwise addition of a solution of the phenol **II** (1.4 g, 4.9 mmol) in anhydrous THF (10 mL). The reaction mixture was stirred and warmed to room temperature gradually over a period of 30 min. The reaction mixture was recooled to 0 °C, and neat benzyl bromide (0.7 mL, 6 mmol) was added dropwise. The reaction mixture was stirred at room temperature for 6 h under an atmosphere of nitrogen and then quenched with saturated aqueous NH_4Cl solution (10 mL). The two layers were separated, and the aqueous layer was extracted with ethyl acetate (2 × 10 mL). The combined organic layers were washed successively with water and brine and dried over Na_2SO_4. The solvent was evaporated under reduced pressure, and the crude product was purified by column chromatography using 5% EtOAc/hexane (v/v) as the eluent to afford pure benzyl ether **III** (1.5 g, 3.9 mmol) in 80% yield as a viscous oil. R_f = 0.2 (5% EtOAc/hexane, v/v). IR (neat): 2927, 1719, 1600, 1454, 1234, 1054, 735 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 7.5−7.2 (m, 10H), 7.0 (d, *J* = 2.2 Hz, 1H), 6.7 (d, *J* = 2.2 Hz, 1H), 6.01−5.83 (m, 1H), 5.1−4.84 (m, 6H), 3.9 (s, 3H), 3.7 (d, *J* = 6.0 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 168.0, 157.7, 157.4, 137.1, 136.5, 136.4, 131.8, 128.4, 128.2, 127.9, 127.7, 127.5, 127.0, 122.9, 114.4, 106.6, 104.0, 70.2, 70.1, 51.9, 30.6. MS (ESI): 389 $[M + H]^+$. HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{25}H_{25}O_4$ 389.1748, found 389.1747.

*(2-Allyl-3,5-bis(benzyloxy)phenyl)methanol (**IV**).* To a stirred suspension of lithium aluminum hydride (174 mg, 4.6 mmol) in anhydrous THF (20 mL) cooled to 0 °C was added a solution of compound **III** (1.5 g, 3.9 mmol) in anhydrous THF (10 mL) dropwise under an N_2 atmosphere, and the mixture was warmed to room temperature over a period of 1 h. The reaction mixture was recooled to 0 °C and quenched by adding small ice pieces. The precipitated solids were filtered through Celite, and the solids were washed with hot EtOAc (2 × 10 mL). The combined filtrates were evaporated under reduced pressure, and the residue was purified by column chromatography using 10% EtOAc/hexane (v/v) as the eluent to afford the compound **IV** (1.1 g, 3.3 mmol) as a yellow liquid in 85% yield. R_f = 0.2 (10% EtOAc/hexane, v/v). IR (neat): 3302, 2924, 1600, 1433, 1151, 1041, 738 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 7.41−7.13 (m, 10H), 6.57 (d, *J* = 2.3 Hz, 1H), 6.43 (d, *J* = 2.3 Hz, 1H), 5.98−5.75 (m, 1H), 4.98−4.75 (m, 6H), 4.53 (s, 2H), 3.36 (d, *J* = 5.4 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 158.2, 157.4, 140.9, 137.5, 137.0, 136.9, 128.53, 128.5, 127.9, 127.7, 127.5, 127.0, 118.6, 114.4, 105.5, 99.9, 70.1, 70.0, 63.1, 29.3. MS (ESI): 361 $[M + H]^+$. HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{24}H_{25}O_3$ 361.1807, found 361.1803.

*2-Allyl-3,5-bis(benzyloxy)benzaldehyde (**14**).* To a solution of oxalyl chloride (0.4 mL, 4.9 mmol) in anhydrous dichloromethane (20 mL) cooled to −78 °C was added dropwise a solution of DMSO (0.5 mL, 6.6 mmol) in anhydrous dichloromethane (5 mL), and the mixture was stirred at the same temperature for 15 min. A solution of compound **IV** (1.1 g, 3.3 mmol) in anhydrous dichloromethane (5 mL) was added dropwise to the above mixture, and stirring continued at the same temperature for 45 min. Et_3N (2.3 mL, 17 mmol) was added, and the reaction mixture was warmed to −10 °C. Water (5 mL) was added, the two layers were separated, and the aqueous layer was extracted with dichloromethane (2 × 5 mL). The combined organic layers were washed with water and brine and dried over Na_2SO_4. The solvent was evaporated under reduced pressure, and the crude product was purified by column chromatography using 5% EtOAc/hexane (v/v) as the eluent to afford pure compound **14** (1 g, 2.9 mmol) as a red liquid in 88% yield. R_f = 0.2 (5% EtOAc/hexane, v/v). IR (neat): 2928, 1686, 1599, 1285, 1152, 1032, 739 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 10.2 (s, 1H), 7.47−7.25 (m, 10H), 7.03 (d, *J* = 2.2 Hz, 1H), 6.77 (d, *J* = 2.2 Hz, 1H), 6.08−5.9 (m, 1H), 5.16−4.82 (m, 4H), 3.8 (d, *J* = 5.2 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 191.4, 158.1, 157.8, 137.0, 136,4, 136.3, 135.2, 128.5, 128.0, 127.9, 127.5, 127.0, 124.9, 115.2, 106.5, 104.6, 70.5, 70.2, 27.6. MS (ESI): 359 $[M + H]^+$. HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{24}H_{23}O_3$ 359.1658, found 359.1647.

*(((3S,5S,10bR)-7,9-Bis(benzyloxy)-3-phenyl-3,5,6,10b-tetrahydro-2H-oxazolo[2,3-a]isoquinolin-5-yl)methyl)mercury(II) Bromide (**15**).* Organomercurial **15** (530 mg, 0.7 mmol) was obtained from aldehyde **14** (358 mg, 1 mmol) as a white solid in 70% yield after column chromatography using 15% EtOAc/hexane (v/v) as the eluent. Mp: 69−71 °C. R_f = 0.2 (10% EtOAc/hexane, v/v). $[\alpha]_D^{25}$ = +21.8 (*c* 1, CH_2Cl_2). IR (neat): 2924, 1718, 1600, 1453, 1262, 1028, 697 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 7.48−7.32 (m, 15H), 6.71 (d, *J* = 2.1 Hz, 1H), 6.58 (d, *J* = 2.1 Hz, 1H), 5.56 (s, 1H), 5.09−5.0 (m, 4H), 4.48 (dd, *J* = 8.2, 7.9 Hz, 1H), 4.24 (t, *J* = 8.0 Hz, 1H), 3.67 (t, *J* = 8.5 Hz, 1H), 3.62−3.57 (m, 1H), 3.14 (dd, *J* = 16.3, 3.2 Hz, 1H), 2.36 (dd, *J* = 16.3, 10.3 Hz, 1H), 2.3 (dd, *J* = 12.2, 4.4 Hz, 1H), 2.14 (dd, *J* = 12.2, 1.9 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 158.3, 155.8, 142.6, 136.7, 136.5, 135.7, 129.5, 128.4, 127.9, 127.5, 127.3, 127.2, 127.1, 126.8, 115.8, 103.5,

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100.5, 90.7, 73.2, 70.1, 70.0, 67.9, 56.0, 32.9, 29.5. MS (ESI): 758 [M + H]$^+$. HRMS (ESI): m/z [M + H]$^+$ calcd for $C_{32}H_{31}NO_3BrHg$ 758.1188, found 758.1162.

The aldehyde **16** was prepared from methyl 2-iodo-6-methylbenzoate **V** in a three-step sequence.

*Methyl 2-Allyl-6-methylbenzoate (**VI**).* To a solution of *i*-PrMgCl.LiCl (8.9 mL, 8.9 mmol, 1 M/THF) in anhydrous THF (9 mL) cooled to −10 °C was added a solution of compound **V** (2.1 g, 8.1 mmol) in THF (3 mL), and the mixture was stirred with the temperature allowed to rise to 0 °C over a period of 30 min. The reaction mixture was recooled to −10 °C, and CuCN·2LiCl (0.1 mL, 1 M/THF) was added. After 5 min, allyl bromide (0.5 mL, 9.7 mmol) was added to this mixture, and it was stirred at 0 °C for 1 h. The reaction mixture was quenched by adding saturated aqueous NH_4Cl (10 mL), and the mixture was stirred at room temperature for another 30 min. The reaction mixture was extracted with ethyl acetate (2 × 25 mL). The combined organic layers were washed with water and brine, dried over Na_2SO_4, and evaporated to furnish the crude compound, which was purified by column chromatography using 5% EtOAc/hexane (v/v) as the eluent to afford pure compound **VI** (1.1 g, 6 mmol) as a colorless liquid in 75% yield. R_f = 0.5 (10% EtOAc/hexane, v/v). IR (neat): 2952, 1729, 1437, 1271, 1115, 1071, 757 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.27−6.98 (m, 3H), 5.94−5.8 (m, 1H), 5.08−4.96 (m, 2H), 3.86 (s, 3H), 3.35 (d, *J* = 6.7 Hz, 2H), 2.3 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.1, 137.0, 136.6, 135.1, 133.5, 129.4, 128.0, 126.9, 115.9, 51.6, 38.0, 19.6. MS (ESI): 191 [M + H]$^+$. HRMS (ESI): m/z [M + H]$^+$ calcd for $C_{12}H_{15}O_2$ 191.1065, found 191.1068.

*(2-Allyl-6-methylphenyl)methanol (**VII**).* Following the procedure detailed for the preparation of **IV**, compound **VII** (777 mg, 4.8 mmol) was obtained from compound **VI** (1.1 g, 6 mmol) as a viscous liquid in 80% yield after column chromatography using 10% EtOAc/hexane (v/v) as the eluent. R_f = 0.2 (10% EtOAc/hexane, v/v). IR (neat): 3448, 2922, 1637, 1467, 1261, 914, 770, 665 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.1−6.88 (m, 3H), 6.07−5.88 (m, 1H), 5.02−4.82 (m, 2H), 4.57 (s, 2H), 3.42 (d, *J* = 6.0 Hz, 2H), 2.33 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 138.6, 137.9, 136.6, 129.0, 128.1, 128.0, 115.6, 58.8, 37.5, 19.4. MS (ESI): 163 [M + H]$^+$.

*2-Allyl-6-methylbenzaldehyde (**16**).* Following the procedure detailed for the preparation of **14**, compound **16** (640 mg, 4 mmol) was prepared from compound **VII** (777 mg, 4.8 mmol) as a colorless liquid in 85% yield after column chromatography using 10% EtOAc/hexane (v/v) as the eluent. R_f = 0.3 (10% EtOAc/hexane, v/v). IR (neat): 2926, 1692, 1592, 1467, 1189, 915, 734 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 10.43 (s, 1H), 7.23 (t, *J* = 7.7 Hz, 1H), 7.15 (d, *J* = 7.7 Hz, 2H), 5.97−5.81 (m, 1H), 5−4.81 (m, 2H), 3.61 (d, *J* = 6.0 Hz, 2H), 2.49 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 193.0, 142.3, 140.6, 136.9, 132.7, 131.9, 129.9, 128.7, 115.9, 36.9, 20.4. MS (ESI): 161 [M + H]$^+$.

*(((3S,5S,10bR)-10-Methyl-3-phenyl-3,5,6,10b-tetrahydro-2H-oxazolo[2,3-a]isoquinolin-5-yl)methyl)mercury(II) Bromide (**17**).* Organomercurial **17** (450 mg, 0.82 mmol) was obtained from aldehyde **16** (160 mg, 1 mmol) as a white solid in 82% yield after column chromatography using 10% EtOAc/hexane (v/v) as the eluent. Mp: 120−122 °C. R_f = 0.2 (10% EtOAc/hexane, v/v). $[\alpha]_D^{25}$ = −11.8 (*c* 1, CH_2Cl_2). IR (neat): 2927, 1731, 1636, 1454, 1255, 1033, 754 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.46−7.24 (m, 5H), 7.15 (t, *J* = 6.7 Hz, 1H), 7.05 (d, *J* = 6.7 Hz, 1H), 6.91 (d, *J* = 6.7 Hz, 1H), 5.46 (s, 1H), 4.45 (t, *J* = 8.3 Hz, 1H), 4.31 (t, *J* = 7.5 Hz, 1H), 3.82−3.74 (m, 1H), 3.61 (dd, *J* = 8.3, 7.5 Hz, 1H), 2.94 (dd, *J* = 15.8, 3.7 Hz, 1H), 2.73 (dd, *J* = 15.8, 10.5 Hz, 1H), 2.38 (s, 3H), 2.37 (dd, *J* = 12.0, 4.5 Hz, 1H), 2.1 (dd, *J* = 12.0, 2.2 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 142.7, 137.9, 133.8, 130.0, 129.7, 129.0, 128.4, 128.0, 126.7, 125.2, 89.8, 72.8, 66.9, 55.1, 40.3, 27.0, 19.4. MS (ESI): 560 [M + H]$^+$. HRMS (ESI): m/z [M + H]$^+$ calcd for $C_{19}H_{21}NOBrHg$ 560.0512, found 560.0523.

*(E)-2-(4-Hydroxybut-2-enyl)benzaldehyde (**18**).* To a stirred solution of *cis*-2-butene-1,4-diol (528 mg, 6 mmol) and aldehyde **1** (292 mg, 2 mmol) in anhydrous dichloromethane (10 mL) was added the Grubbs second-generation catalyst (42 mg, 0.05 mmol). The reaction mixture was stirred at room temperature under a nitrogen atmosphere for 12 h. The solvent was evaporated under reduced pressure, and the residue was purified by column chromatography using 20% EtOAc/hexanes (v/v) as the eluent to afford the pure allylic alcohol **18** (264 mg, 1.5 mmol) as a viscous oil in 75% yield. R_f = 0.2 (20% EtOAc/hexane, v/v). IR (neat): 3378, 2922, 1729, 1692, 1573, 1403, 1288, 1088, 974, 763 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 10.16 (s, 1H), 7.77 (dd, *J* = 7.5, 1.1 Hz, 1H), 7.46 (td, *J* = 7.5, 1.3 Hz, 1H), 7.34 (td, *J* = 7.5, 1.1 Hz, 1H), 7.22 (dd, *J* = 7.5, 1.3 Hz, 1H), 5.9−5.78 (m, 1H), 5.6−5.48 (m, 1H), 4.03 (d, *J* = 5.6 Hz, 2H), 3.75 (d, *J* = 6.0 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 192.5, 142.2, 133.9, 133.6, 131.9, 131.0, 130.8, 130.5, 126.8, 63.1, 35.0. MS (ESI): 199 [M + Na]$^+$. HRMS (ESI): m/z [M + Na]$^+$ calcd for $C_{11}H_{12}O_2Na$ 199.0734, found 199.0739.

*(E)-2-(4-(tert-Butyldimethylsilyloxy)but-2-enyl)benzaldehyde (**19**).* To a solution of alcohol **18** (265 mg, 1.5 mmol) in dry CH_2Cl_2 (10 mL) were added imidazole (204 mg, 3 mmol) and TBSCl (226 mg, 1.5 mmol) under N_2 atmosphere at 0 °C. The reaction mixture was gradually warmed to room temperature over a period of 1 h. Water was added to the reaction mixture, the two layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated to give a crude residue, which upon silica gel chromatography using 10% EtOAc/hexane (v/v) as the eluent afforded pure TBS ether **23** (377 mg, 1.3 mmol) as a viscous oil in 90% yield. R_f = 0.2 (10% EtOAc/hexane, v/v). IR (neat): 2954, 2730, 1698, 1464, 1253, 1046, 837, 776 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 10.42 (s, 1H), 8.01 (d, *J* = 7.5 Hz, 1H), 7.69 (t, *J* = 7.5 Hz, 1H), 7.55 (t, *J* = 7.5 Hz, 1H), 7.45 (d, *J* = 7.5 Hz, 1H), 6.1−5.97 (m, 1H), 5.73- 5.62 (m, 1H), 4.29 (t, *J* = 5.0, 1.3 Hz, 2H), 3.97 (d, *J* = 6.2 Hz, 2H), 1.04 (s, 9H), 0.2 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): 192.2, 142.6, 133.9, 133.7, 131.39, 131.3, 130.9, 128.8, 126.7, 63.5, 34.9, 25.8, 18.3, −3.6, −5.2. MS (ESI): 313 [M + Na]$^+$. HRMS (ESI): m/z [M + Na]$^+$ calcd for $C_{17}H_{26}O_2NaSi$ 313.1599, found 313.1607.

*((S)-2-(tert-Butyldimethylsilyloxy)-1-((3S,5S,10bR)-3-phenyl-3,5,6,10b-tetrahydro-2H-oxazolo[2,3-a]isoquinolin-5-yl)ethyl)-mercury(II) Bromide (**20**).* Organomercurial **20** (580 mg, 0.85 mmol) was obtained from aldehyde **19** (160 mg, 1 mmol) in 85% yield as a white solid after column chromatography using 5% EtOAc/hexane (v/v) as the eluent. Mp: 120−122 °C. R_f = 0.2 (5% EtOAc/hexane, v/v). $[\alpha]_D^{25}$ = −3.2 (*c* 1, CH_2Cl_2). IR (neat): 2928, 2858, 1387, 1032, 961, 776 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.6−7.14 (m, 9H), 5.72 (s, 1H), 4.53 (dd, *J* = 8.0, 7.3 Hz, 1H), 4.24 (t, *J* = 8.0 Hz, 1H), 4.02−3.85 (m, 2H), 3.79−3.62 (m, 2H), 3.3 (dd, *J* = 15.4, 2.9 Hz, 1H), 3.18−3.06 (m, 1H), 2.75 (dd, *J* = 15.4, 10.2 Hz, 1H), 0.98 (s, 9H), 0.15 (s, 3H), 0.12 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 142.8, 133.4, 132.4, 129.6, 128.4, 127.9, 127.5, 127.4, 127.0, 126.9, 90.7, 73.7, 68.6, 68.5, 62.5, 59.9, 37.4, 25.8, 18.0, −5.2, −5.3. MS (ESI): 690 [M + H]$^+$. HRMS (ESI): m/z [M + H]$^+$ calc for $C_{25}H_{35}NO_2SiBrHg$ 690.1326, found 690.1320.

*(((3S,5S,6R,7aR)-3,6-Diphenylhexahydropyrrolo[2,1-b]oxazol-5-yl)methyl)mercury(II) Bromide (**22**).* Organomercurials **22** and **23** were obtained in equimolar amounts from aldehyde **21** (160 mg, 1 mmol) in 85% yield as white solids after column chromatography using 10% EtOAc/hexane (v/v) as the eluent. Mp: 137−139 °C. R_f = 0.3 (10% EtOAc/hexane). $[\alpha]_D^{25}$ = +11.5 (*c* 1, CH_2Cl_2). IR (neat): 2923, 2814, 1486, 1377, 1144, 1024, 901, 696 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.33−7.14 (m, 10H), 5.1 (dd, *J* = 5.8, 3.7 Hz, 1H), 4.47 (dd, *J* = 8.8, 7.5 Hz, 1H), 4.04 (t, *J* = 7.5 Hz, 1H), 3.56 (dd, *J* = 8.8, 7.5 Hz, 1H), 3.5−3.43 (m, 1H), 2.9−2.76 (m, 1H), 2.66−2.55 (m, 1H), 2.13−1.18 (m, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 142.1, 139.6, 129.2, 129.0, 127.8, 127.7, 127.6, 126.6, 97.3, 75.8, 72.4, 67.8, 55.7, 39.2, 38.6. MS (ESI): 560 [M + H]$^+$. HRMS (ESI): m/z [M + H]$^+$ calcd for $C_{19}H_{21}BrNOHg$ 560.0512, found 560.0501.

*(((3S,5R,6S,7aR)-3,6-Diphenylhexahydropyrrolo[2,1-b]oxazol-5-yl)methyl)mercury(II) Bromide (**23**).* Mp: 135−137 °C. R_f = 0.2 (10% EtOAc/hexane). $[\alpha]_D^{25}$ = −41.2 (*c* 1, CH_2Cl_2). IR (neat): 2924, 2854, 1777, 1452, 1029, 755 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.46−7.1 (m, 10H), 5.46 (dd, *J* = 5.8, 3.7 Hz, 1H), 4.54 (dd, *J* = 8.4, 7.3 Hz, 1H), 4.08 (dd, *J* = 7.7, 7.3 Hz, 1H), 3.99 (t, *J* = 5.9 Hz, 1H), 3.65 (t, *J* = 8.4 Hz, 1H), 3.53 (t, *J* = 7.7 Hz, 1H), 2.58−2.53 (m, 1H), 2.49−2.43 (m, 1H), 2.05−1.91 (m, 1H), 1.7−1.55 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 141.9, 140.7, 129.5, 129.1, 128.4, 128.1, 127.6, 126.5, 99.1, 75.6, 67.9, 67.7, 50.8, 36.8, 31.8. MS (ESI): 560 [M + H]$^+$. HRMS (ESI): m/z [M + H]$^+$ calcd for $C_{19}H_{21}NOBrHg$ 560.0512, found 560.0500.

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General Procedure for Demercuration. To a stirred solution of the organomercurial (1 equiv) in dry toluene (0.25 M) cooled to −78 °C was added a solution of tributyltin hydride (1 equiv) in toluene (0.25 M) followed by triethylborane (0.6 equiv). The reaction mixture was stirred at −78 °C for 30 min and diluted with EtOAc (0.1 M) and saturated aqueous KF (0.5 M). The reaction mixture was stirred for another 30 min at room temperature. The precipitated tributyltin fluoride was removed by filtration and the solid washed with EtOAc. The combined filtrates were washed with brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The residual oil was purified by column chromatography using EtOAc/hexane (v/v) as the eluent to afford the pure demercuration product.

*(3S,5R,10bR)-5-Methyl-3-phenyl-3,5,6,10b-tetrahydro-2H-oxazolo[2,3-a]isoquinoline (**5**).* Following the general procedure for demercuration, compound **5** (210 mg, 0.8 mmol) was prepared from organomercurial **4** (545 mg, 1 mmol) as a colorless liquid in 80% yield after column chromatography using 10% EtOAc/hexane (v/v) as the eluent. R_f = 0.2 (10% EtOAc/hexane, v/v). $[\alpha]_D^{25}$ = +40 (*c* 1, $CHCl_3$). IR (neat): 2927, 2854, 1730, 1456, 1276, 952, 747 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ 7.42−7.0 (m, 9H), 5.41 (s, 1H), 4.38−4.28 (m, 2H), 3.65−3.55 (m, 1H), 3−2.88 (m, 1H), 2.76−2.59 (m, 2H), 1.08 (d, *J* = 6.0 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 142.7, 134.9, 132.6, 128.4, 127.9, 127.8, 127.4, 126.9, 126.5, 126.2, 90.5, 71.8, 66.3, 50.5, 37.3, 21.2. MS (ESI): 266 [M + H]$^+$. HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{18}H_{20}NO$ 266.1539, found 266.1536.

*(S)-2-((R)-3-Methyl-3,4-dihydroisoquinolin-2(1H)-yl)-2-phenylethanol (**9**).* Following the general procedure for demercuration, compound **9** (240 mg, 0.9 mmol) was prepared from organomercurial **4** (545 mg, 1 mmol) using excess tributyltin hydride (0.5 mL, 2 mmol) as a colorless liquid in 90% yield after column chromatography using 20% EtOAc/hexane (v/v) as the eluent. R_f = 0.2 (20% EtOAc/hexane). $[\alpha]_D^{25}$ = +10.4 (*c* 1, $CHCl_3$). IR (neat): 2957, 2863, 1457, 1219, 1075, 701 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ 7.42−6.88 (m, 9H), 3.89 (dd, *J* = 9.6, 5.7 Hz, 1H), 3.84 (dd, *J* = 11.4, 5.7 Hz, 1H), 3.81−3.63 (m, 3H), 3.55 (t, *J* = 5.7 Hz, 1H), 3.21 (dd, *J* = 15.4, 4.8 Hz, 1H), 3.17−2.97 (bs, 1H), 2.47 (d, *J* = 15.4 Hz, 1H), 0.99 (d, *J* = 6.7 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 139.1, 133.7, 133.1, 129.3, 128.7, 128.4, 127.8, 126.3, 126.1, 125.4, 68.0, 62.3, 50.5, 45.3, 35.6, 13.1. MS (ESI): 268 [M + H]$^+$. HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{18}H_{22}NO$ 268.1695, found 268.1694.

*(3S,5R,10bR)-5,10b-Dimethyl-3-phenyl-3,5,6,10b-tetrahydro-2H-oxazolo[2,3-a]isoquinoline (**26**).* To a solution of compound **24** (160 mg, 1 mmol) and (*S*)-phenylglycinol (151 mg, 1.1 mmol) in anhydrous dichloromethane (1 mL) was added $Ti(OEt)_4$ (0.5 mL, 2.2 mmol) and the mixture stirred at room temperature for 16 h to ensure imine formation. The reaction mixture was diluted with anhydrous dichloromethane (4 mL). Organomercurial **25** (420 mg, 0.75 mmol) was obtained following the general procedure in 75% yield after flash column chromatography using 10% EtOAc/hexane (v/v) as the eluent. R_f = 0.2 (10% EtOAc/hexane, v/v). Since **25** was found to be unstable, it was taken to the next step without characterization. Following the general procedure for demercuration, compound **26** (140 mg, 0.5 mmol) was obtained from organomercurial **25** (420 mg, 0.75 mmol) as a colorless liquid in 70% yield after column chromatography using 10% EtOAc/hexane (v/v) as the eluent. R_f = 0.2 (10% EtOAc/hexane). $[\alpha]_D^{25}$ = +16.4 (*c* 1, $CHCl_3$). IR (neat): 2925, 2866, 1755, 1455, 1251, 1073, 759 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 7.5−7.0 (m, 9H), 4.17 (dd *J* = 7.5, 3.7 Hz, 1H), 3.78 (t, *J* = 7.5 Hz, 1H), 3.65−3.5 (m, 2H), 2.94 (dd, *J* = 16.6, 11.3 Hz, 1H), 2.49 (dd, *J* = 16.6, 3.7 Hz, 1H), 1.76 (s, 3H), 1.36 (d, *J* = 6.7 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 146.4, 139.3, 135.3, 128.2, 128.1, 127.2, 126.9, 126.5, 95.9, 72.7, 58.6, 48.7, 29.9, 28.2, 21.6. MS (ESI): 280 [M + H]$^+$. HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{19}H_{22}NO$ 280.1695, found 280.1690.

*(S)-2-((1S,3R)-5-(Benzyloxy)-6-methoxy-1,3-dimethyl-3,4-dihydroisoquinolin-2(1H)-yl)-2-phenylethanol (**30**).* Following the procedure detailed above, ketone **28** (296 mg, 1 mmol) was subjected to an aminomercuration−demercuration sequence to furnish compound **30** (332 mg, 0.8 mmol) in 80% yield after column chromatography using 10% EtOAc/hexane (v/v) as the eluent. R_f = 0.3 (10% EtOAc/hexane). $[\alpha]_D^{25}$ = +42.7 (*c* 1, CH_2Cl_2). IR (neat): 2924, 2854, 1717, 1590, 1455, 1251, 1073, 759 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ 7.49−7.17 (m, 10H), 6.91−6.86 (m, 2H), 5.02−4.97 (m, 2H), 3.98 (dd, *J* = 8.0, 3.7 Hz, 1H), 3.89 (s, 3H), 3.69 (t, *J* = 8.0 Hz, 1H), 3.55 (dd, *J* = 8.1, 3.7 Hz, 1H), 2.88 (dd, *J* = 15.7, 3.4 Hz, 1H), 2.65−2.59 (m, 1H), 2.21 (dd, *J* = 15.7, 9.6 Hz, 1H), 1.76 (s, 3H), 0.86 (d, *J* = 6.8 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 151.3, 146.5, 143.2, 137.8, 128.54, 128.5, 128.3, 128.2, 128.1, 127.9, 126.8, 110.7, 95.7, 74.0, 72.5, 68.3, 58.4, 48.3, 31.7, 29.4, 21.7. MS (ESI): 416 [M + H]$^+$. HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{27}H_{29}NNaO_3$ 438.2040, found 438.2050.

*(3S,5R,10bR)-5,10-Dimethyl-3-phenyl-3,5,6,10b-tetrahydro-2H-oxazolo[2,3-a]isoquinoline (**32**).* Following the general procedure for demercuration, compound **32** (210 mg, 0.8 mmol) was prepared from organomercurial **17** (559 mg, 1 mmol) as a colorless liquid in 80% yield after column chromatography using 10% EtOAc/hexane (v/v) as the eluent. R_f = 0.2 (10% EtOAc/hexane). $[\alpha]_D^{25}$ = +58.9 (*c* 1, CH_2Cl_2). IR (neat): 2926, 2853, 1597, 1379, 1037, 700 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ 7.49−6.87 (m, 8H), 5.31 (s, 1H), 4.6- 4.41 (m, 2H), 3.7−3.63 (m, 1H), 3.11−2.99 (m, 1H), 2.85−2.67 (m, 2H), 2.35 (s, 3H), 1.2 (d, *J* = 6.0 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 143.0, 137.7, 135.1, 130.2, 128.5, 128.4, 128.0, 126.9, 126.5, 125.3, 89.1, 70.8, 64.8, 49.3, 38.0, 21.0, 19.0. MS (ESI): 280 [M + H]$^+$. HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{19}H_{22}NO$ 280.1691, found 280.1701.

*(3S,5S,10bR)-3-Phenyl-5-((2,2,6,6-tetramethylpiperidin-1-yloxy)-methyl)-3,5,6,10b-tetrahydro-2H-oxazolo[2,3-a]isoquinoline (**10**).* To a stirred solution of organomercurial **4** (545 mg, 1 mmol) in anhydrous DMF (10 mL) was added TEMPO (450 mg, 3 mmol). This solution was then added dropwise via cannula to an oxygen-saturated solution of $NaBH_4$ (150 mg, 4 mmol) in dry DMF (4 mL) cooled to 0 °C. After 10 min, the precipitated mercury was filtered through Celite and the solution was diluted with ether. The organic phase was washed with water and brine, dried over Na_2SO_4, and concentrated. The crude residue was purified by column chromatography using 5% EtOAc/hexane as the eluent to afford pure **10** (335 mg, 0.8 mmol) as a colorless liquid in 80% yield. R_f = 0.5 (10% EtOAc/hexane). $[\alpha]_D^{25}$ = +24.5 (*c* 1, $CHCl_3$). IR (neat): 2925, 2854, 1459, 1049, 956, 746 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 7.42−7.08 (m, 9H), 5.46 (s, 1H), 4.55 (t, *J* = 7.5 Hz, 1H), 4.32 (dd, *J* = 7.7, 7.5 Hz, 1H), 3.88−3.8 (m, 1H), 3.68−3.56 (m, 2H), 3.17−3.07 (m, 1H), 2.96 (dd, *J* = 16.0, 3.5 Hz, 1H), 2.69 (dd, *J* = 16.0, 9.0 Hz,1H), 1.6−0.8 (m, 18H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 141.7, 134.2, 132.7, 128.2, 127.8, 127.7, 127.5, 126.8, 126.4, 126.1, 89.9, 80.2, 71.6, 66.2, 59.4, 54.3, 39.2, 32.5, 31,7, 29.4, 19.9, 19.8, 16.7. MS (ESI): 421 [M + H]$^+$. HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{27}H_{37}N_2O_2$ 421.2858, found 421.2855.

*(S)-(1,2,3,4-Tetrahydroisoquinolin-3-yl)methanol (**11**).* To a stirred solution of **10** (335 mg, 0.8 mmol) in 50% aqueous CH_3COOH (8 mL) was added activated Zn dust (565 mg, 8.7 mmol). The mixture was submerged in an oil bath maintained at 100 °C and heated for 1 h. After it was cooled to room temperature, the mixture was diluted with H_2O (8 mL) and extracted with Et_2O (3 × 5 mL). The combined extracts were neutralized with saturated aqueous sodium bicarbonate solution, dried over Na_2SO_4, and evaporated. The residue was purified by column chromatography using 20% EtOAc/hexane (v/v) as the eluent to afford compound **11** (170 mg, 0.6 mmol) as a colorless liquid in 75% yield. R_f = 0.2 (10% EtOAc/hexane). $[\alpha]_D^{25}$ = +56.8 (*c* 1, $CHCl_3$). IR (neat): 3345, 2925, 2854, 1734, 1454, 1040, 754 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 7.22−6.98 (m, 4H), 4.85−4.71 (m, 2H), 3.89−3.76 (m, 2H), 3.69 (dd, *J* = 11.5, 7.1 Hz 1H), 2.82 (dd, *J* = 16.2, 11.5 Hz, 1H), 2.63 (dd, *J* = 16.2, 2.4 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 134.3, 132.4, 128.9, 126.4, 125.9, 124.1, 75.3, 68.0, 65.5, 29.4. MS (ESI): 164 [M + H]$^+$.

*(S)-2-((1R,3R)-1,3-Dimethyl-3,4-dihydroisoquinolin-2(1H)-yl)-2-phenylethanol (**6**).* To a stirred solution of compound **5** (265 mg, 1 mmol) in dry ether (4 mL) cooled to 0 °C was added methylmagnesium iodide (1.5 mL, 1.5 mmol, 1 M in ether) dropwise under an N_2 atmosphere. Stirring was continued for 1 h at 0 °C, and the reaction mixture was quenched with saturated aqueous NH_4Cl. The organic layer was separated from the aqueous layer, and the aqueous layer was extracted with ether (2 × 5 mL). The combined organic layers were washed with saturated brine, dried over anhydrous Na_2SO_4, and evaporated. The crude product was purified by column chromatography using 10% EtOAc/hexane (v/v) as the eluent to afford the pure product

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6 (220 mg, 0.8 mmol) in 80% yield as a colorless liquid. R_f = 0.3 (10% EtOAc/hexane, v/v). $[\alpha]_D^{25}$ = +46.9 (*c* 4, $CHCl_3$). IR (neat): 2923, 2854, 1739, 1376, 1032, 701 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 7.0 (d, *J* = 6.4 Hz, 2H), 6.92−6.75 (m, 6H), 6.55 (d, *J* = 7.3 Hz, 1H), 4.4 (dd, *J* = 13.5, 6.7 Hz, 1H), 4.17 (dd, *J* = 9.8, 5.6 Hz, 1H), 3.86 (t, *J* = 9.8 Hz, 1H), 3.72−3.6 (m, 1H), 3.5−3.4 (m, 1H), 2.48−2.2 (m, 2H), 1.48 (d, *J* = 6.4 Hz, 3H), 1.4 (d, *J* = 5.6 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 139.0, 138.5, 134.0, 128.9, 128.2, 127.5, 127.0, 126.8, 126.3, 125.4, 61.4, 60.3, 51.5, 47.3, 33.4, 24.5, 19.7. MS (ESI): 282 $[M + H]^+$. HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{19}H_{24}NO$ 282.1852, found 282.1851.

*(S)-2-((1R,3R)-3-Methyl-1-vinyl-3,4-dihydroisoquinolin-2(1H)-yl)-2-phenylethanol (**7**).* To a stirred solution of compound **5** (265 mg, 1 mmol) in dry THF (5 mL) cooled to −78 °C was added vinylmagnesium bromide (1.5 mL, 1.5 mmol, 1 M in THF) dropwise under an N_2 atmosphere, and the temperature was gradually allowed to rise to 0 °C over a period of 1 h. The reaction mixture was quenched with saturated aqueous NH_4Cl and the aqueous layer extracted with ethyl acetate (2 × 5 mL). The combined organic layers were washed with saturated brine and dried over anhydrous Na_2SO_4, and the solvent was removed in vacuo to afford pure **7** (220 mg, 0.75 mmol) as a colorless liquid in 75% yield after column chromatography using 5% EtOAc/hexane (v/v) as the eluent. R_f = 0.5 (10% EtOAc/hexane, v/v). $[\alpha]_D^{25}$ = +35.3 (*c* 1, $CHCl_3$). IR (neat): 2922, 2852, 1637, 1460, 1374, 1036, 757 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 7.5−6.6 (m, 9H), 6.03−5.88 (m, 1H), 5.15−4.85 (m, 2H), 4.73−4.70 (m, 1H), 4.23−4.2 (m, 1H), 3.89 (t, *J* = 8.7 Hz, 1H), 3.6−3.48 (m, 2H), 2.5−2.3 (m, 2H), 1.28 (d, *J* = 5.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 141.6, 137.4, 134.9, 129.9, 128.77, 128.71, 127.8, 127.7, 127.4, 125.9, 125.2, 116.5, 61.6, 60.9, 58.7, 47.8, 34.3, 19.3. MS (ESI): 294 $[M + H]^+$. HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{20}H_{24}NO$ 294.1853, found 294.1857.

*(S)-2-((1R,3R)-3-Methyl-1-(oct-1-ynyl)-3,4-dihydroisoquinolin-2(1H)-yl)-2-phenylethanol (**8**).* To a stirred solution of 1-octyne (330 mg, 3 mmol) in dry THF (1 mL) was added isopropylmagnesium chloride (3 mL, 3 mmol, 1 M in THF) dropwise under an N_2 atmosphere at −10 °C. The reaction mixture was gradually warmed to 0 °C and stirred further at the same temperature for 30 min. The reaction mixture was recooled to −10 °C, and compound **5** (265 mg, 1 mmol) in dry THF (4 mL) was added to it. Stirring was continued for 1 h at 0 °C, and the reaction mixture was quenched with saturated aqueous NH_4Cl. The layers were separated, and the aqueous layer was extracted with ether (2 × 5 mL). The combined organic layers were washed with saturated brine and dried over anhydrous Na_2SO_4, and the solvent was removed in vacuo. The crude product was purified through silica gel chromatography using 5% EtOAc/hexane (v/v) as the eluent to afford **8** (280 mg, 0.75 mmol) as a colorless liquid in 75% yield. R_f = 0.3 (10% EtOAc/hexane). $[\alpha]_D^{25}$ = +54.4 (*c* 1, $CHCl_3$). IR (neat): 2927, 2860, 1601, 1455, 1157, 1036, 747 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 7.25−6.76 (m, 9H), 4.8 (s, 1H), 4.28 (dd, *J* = 8.1, 5.6 Hz, 1H), 4.06 (dd, *J* = 11.1, 8.1 Hz, 1H), 3.87 (dd, *J* = 11.1, 5.6 Hz, 1H), 3.74−3.6 (m, 1H), 2.73 (dd, *J* = 16.0, 4.5 Hz, 1H), 2.39 (dd, *J* = 16.0, 8.3 Hz, 1H), 2.14 (t, *J* = 6.8 Hz, 2H), 1.5−0.77 (m, 14H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 139.6, 136.5, 134.2, 128.4, 128.0, 127.1, 126.5, 126.3, 125.6, 86.0, 80.7, 62.47, 62.4, 49.3, 49.2, 36.2, 31.2, 28.5, 22.4, 20.4, 18.8, 13.9, 13.5. MS (ESI): 376 $[M + H]^+$. HRMS (ESI): *m/z* $[M]^+$ calcd for $C_{26}H_{33}NO$ 375.2524, found 375.2556.

*(S)-2-((1R,3R)-1,3-dimethyl-3,4-dihydroisoquinolin-2(1H)-yl)-2-phenylethanol (**6**).* To a stirred solution of compound **26** (279 mg, 1 mmol) in anhydrous THF (4 mL) cooled to 0 °C was added sodium borohydride (185 mg, 5 mmol) followed by trifluoroacetic acid (0.8 mL, 10 mmol) under an N_2 atmosphere, and the mixture was warmed to room temperature gradually over a period of 30 min. The reaction mixture was quenched with aqueous $NaHCO_3$. The organic layer was separated from the aqueous layer, and the aqueous layer was extracted with ether (2 × 5 mL). The combined organic layers were washed with brine and dried over anhydrous Na_2SO_4, and the solvent was removed in vacuo. The crude product was purified through silica gel chromatography using 10% EtOAc/petroleum ether (v/v) to afford 1,3-*anti* alcohol **6** (168 mg, 0.6 mmol) in 60% yield.

*(S)-2-((1S,3R)-1,3-Dimethyl-3,4-dihydroisoquinolin-2(1H)-yl)-2-phenylethanol (**27**).* To a suspension of $LiAlH_4$ (410 mg, 10.3 mmol) in anhydrous ether (10 mL) cooled to −10 °C was added a solution of anhydrous $AlCl_3$ (500 mg, 3.5 mmol) dissolved in anhydrous ether (10 mL) under an argon atmosphere and the mixture stirred for 15 min. To the resulting alane was slowly added a solution of compound **26** (279 mg, 1 mmol) in dry THF (5 mL). The reaction mixture was stirred for another 30 min at −10 °C and quenched by adding small ice pieces. The precipitated solids were filtered through Celite, and the solids were washed with hot EtOAc (2 × 5 mL). The combined filtrates were evaporated under reduced pressure, and the residue was purified by column chromatography using 10% EtOAc/hexane (v/v) as the eluent to afford pure 1,3-*syn* alcohol **27** (210 mg, 0.75 mmol) as a viscous liquid in 75% yield. R_f = 0.3 (10% EtOAc/hexane, v/v). $[\alpha]_D^{25}$ = +121 (*c* 1, $CHCl_3$). IR (neat): 2960, 2925, 1453, 1374, 1031, 758 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 7.36−7.03 (m, 9H), 4.35 (dd, *J* = 9.7, 5.1 Hz, 1H), 4.33−4.28 (m, 1H), 4.1 (dd, *J* = 10.5, 9.7 Hz, 1H), 3.6 (dd, *J* = 10.5, 5.1 Hz, 1H), 3.65−3.58 (m, 1H), 3.05 (dd, *J* = 15.1, 4.5 Hz, 1H), 2.5 (dd, *J* = 15.5, 4.5 Hz, 1H), 1.51 (d, *J* = 6.4 Hz, 3H), 0.49 (d, *J* = 6.4 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 140.8, 139.6, 133.9, 128.5, 128.3, 127.7, 126.4, 125.8, 125.6, 60.2, 51.2, 44.8, 38.1, 23.0, 15.7. MS (ESI): 282 $[M + H]^+$. HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{19}H_{24}NO$ 282.1852, found 282.1846.

*(S)-2-((1S,3R)-5-(Benzyloxy)-6-methoxy-1,3-dimethyl-3,4-dihydroisoquinolin-2(1H)-yl)-2-phenylethanol (**31**).* Following the procedure detailed above, compound **30** (332 mg, 0.8 mmol) was subjected to alane reduction to furnish compound **31** (250 mg, 0.6 mmol) in 75% yield after column chromatography using 20% EtOAc/hexane (v/v) as the eluent. R_f = 0.2 (20% EtOAc/hexane). $[\alpha]_D^{25}$ = +86.7 (*c* 1, CH_2Cl_2). IR (neat): 2958, 2924, 2854, 1717, 1590, 1455, 1351, 1030, 759 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ 7.49−7.27 (m, 10H), 6.9−6.78 (m, 2H) 5.1−4.93 (m, 2H), 4.28 (dd, *J* = 10.5, 5.1 Hz, 1H), 4.24−4.17 (m, 1H), 4.03 (t, *J* = 10.1 Hz, 1H), 3.87 (s, 3H), 3.63 (dd, *J* = 10.5, 5.1 Hz, 1H), 3.54−3.46 (m, 1H), 2.7 (dd, *J* = 16.3, 4.7 Hz, 1H), 2.56 (dd, *J* = 16.3, 4.8 Hz, 1H), 1.46 (d, *J* = 6.4 Hz, 3H), 0.4 (d, *J* = 6.5 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 150.4, 145.3, 139.6, 134.2, 128.5, 128.3, 127.92, 127.9, 127.6, 121.9, 110.1, 74.2, 60.2, 60.1, 55.8, 50.6, 44.3, 32.3, 23.1. MS (ESI): 418 $[M + H]^+$. HRMS (ESI): *m/z* $[M + Na]^+$ calcd for $C_{27}H_{31}NNaO_3$ 440.2196, found 440.2218.

*(3S,5R,10bR)-5,10-dimethyl-3-phenyl-3,5,6,10b-tetrahydro-2H-oxazolo[2,3-a]isoquinoline (**32**).* To a stirred solution of compound **16** (160 mg, 1 mmol) and (*S*)-phenylglycinol (151 mg, 1.1 mmol) in 1,4-dioxane (5 mL) were added DPEphos (8 mg, 3 mol %) and $[Rh(COD)_2]BF_4$ (10 mg, 2.5 mol %) under an N_2 atmosphere, and the mixture was heated at 110 °C for 16 h. The reaction mixture was cooled to room temperature and filtered through Celite. The residue was washed with EtOAc (2 × 5 mL), and the combined filtrates were washed successively with water and brine, dried over anhydrous Na_2SO_4, and concentrated. The crude product was purified by silica gel chromatography using 10% EtOAc/petroleum ether (v/v) to give pure compound **32** (200 mg, 0.7 mmol) as a colorless liquid in 70% yield.

*(3S,5R,10bR)-7-(Benzyloxy)-8-methoxy-5-methyl-3-phenyl-3,5,6,10b-tetrahydro-2H-oxazolo[2,3-a]isoquinoline (**33**).* Following the procedure detailed above, aldehyde **12** (282 mg, 1 mmol) was subjected to catalytic hydroamination to furnish compound **33** (340 mg, 0.85 mmol) in 85% yield after column chromatography using 20% EtOAc/hexane (v/v) as the eluent. R_f = 0.2 (20% EtOAc/hexane). $[\alpha]_D^{25}$ = +79.5 (*c* 1, CH_2Cl_2). IR (neat): 2926, 2850, 1590, 1405, 1053, 752 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ 7.48−7.24 (m, 10H), 7.17 (d, *J* = 8.5 Hz, 1H), 6.9 (d, *J* = 8.5 Hz, 1H), 5.45 (s, 1H), 5.01 (d, *J* = 11.1 Hz, 1H), 4.97 (d, *J* = 11.1 Hz, 1H), 4.44−4.37 (m, 2H), 3.9 (s, 3H), 3.69 (dd, *J* = 11.1, 10.6 Hz, 1H), 2.94 (dd, *J* = 16.3, 3.2 Hz, 1H), 2.91−2.82 (m, 1H), 2.4 (dd, *J* = 16.3, 10.0 Hz, 1H), 1.11 (d, *J* = 6.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 152.1, 144.0, 142.8, 137.7, 132.4, 131.9, 130.8, 128.7, 128.6, 128.4, 128.3, 127.9, 127.5, 126.6, 126.4, 123.8, 110.7, 90.3, 74.5, 71.6, 66.1, 55.8, 50.1, 31.4, 21.3. MS (ESI): 402 $[M + H]^+$. HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{26}H_{28}NO_3$ 402.2064, found 402.2086.

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■ ASSOCIATED CONTENT

Supporting Information

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^{1}H and ^{13}C NMR spectra of new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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