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Diastereospecific Synthesis of Tetrahydroisoquinolines via Radical Cyclization: Application in the Synthesis of ent-Tadalafil

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Abstract: An enantioselective synthesis of 1-substituted tetrahydroisoquinolines from L–Dopa methyl ester through intramolecular aryl radical cyclization is demonstrated. The strategy consists of bromination of (*S*)-2-amino-3-(2-bromo-4,5-dimethoxyphenyl)propanoate followed by condensation with various aldehydes to afford bromoimidate ester. Aryl radicals generated from bromoimidate ester under the radical generating conditions (^{n}Bu$_3$SnH/AIBN) cyclizes *via* 6-*endo* mode to afford *cis*-1-substituted tetrahydroisoquinolines exclusively in 99% ee. The utility of this synthetic protocol is demonstrated in the synthesis of (6*S*, 12a*S*) Tadalafil (5 steps, 21%, 99% ee).

Keywords: diastereospecific synthesis; isoquinolines; radical cyclization; Tadalafil; tetrahydroisoquinolines

Introduction

Tetrahydroisoquinolines, particularly 1-substituted tetrahydroisoquinolines exist in naturally occurring alkaloids and pharmaceutical agents. For example, Higenamine is an alkaloid isolated from the roots of the *aconitum japonicum* plant. It acts as a β_2 adrenoreceptor agonist and shows vasodilating activity.[1] Solifenacin, a M3 selective receptor blocker is used to treat urinary incontinence.[2] Naturally occurring alkaloid noscapine isolated from *papaver somniferum* plant is used as a cough-suppressing medicine.[3] The compound MY336-1 was isolated from *streptomyces gabonae* and utilized in the treatment of hypertension and cardiac arrhythmias.[4] Salsolidine acts as a human monoamine oxidase A inhibitor and displays antidepressant activity.[5] Emetine commonly found in the ground roots of *uragoga ipecacuanha* has been used in the therapy of amebiasis.[6] Isoquinoline-based alkaloid papaverine shows an antispasmodic activity and is useful in the treatment of smooth muscle spasm.[7] Commercial drug quinisocaine as a topical anesthetic utilized to reduce pruritus (Figure 1).[8]

Most of the tetrahydroisoquinolines present in plant alkaloids and pharmaceutical agents have a chiral center at the C-1 position. Traditionally, Pictet-

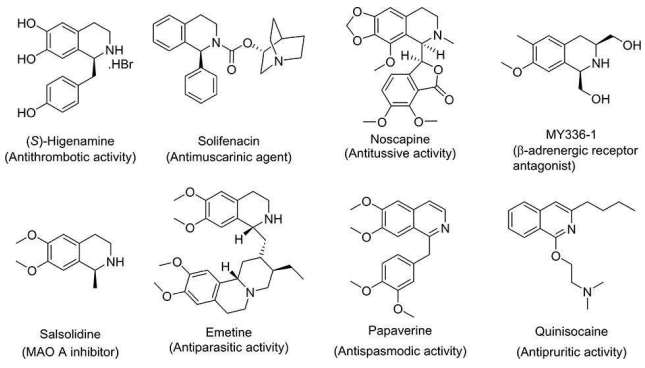


Figure 1. Biologically active 1-substituted tetrahydroiso quinolines and isoquinolines.

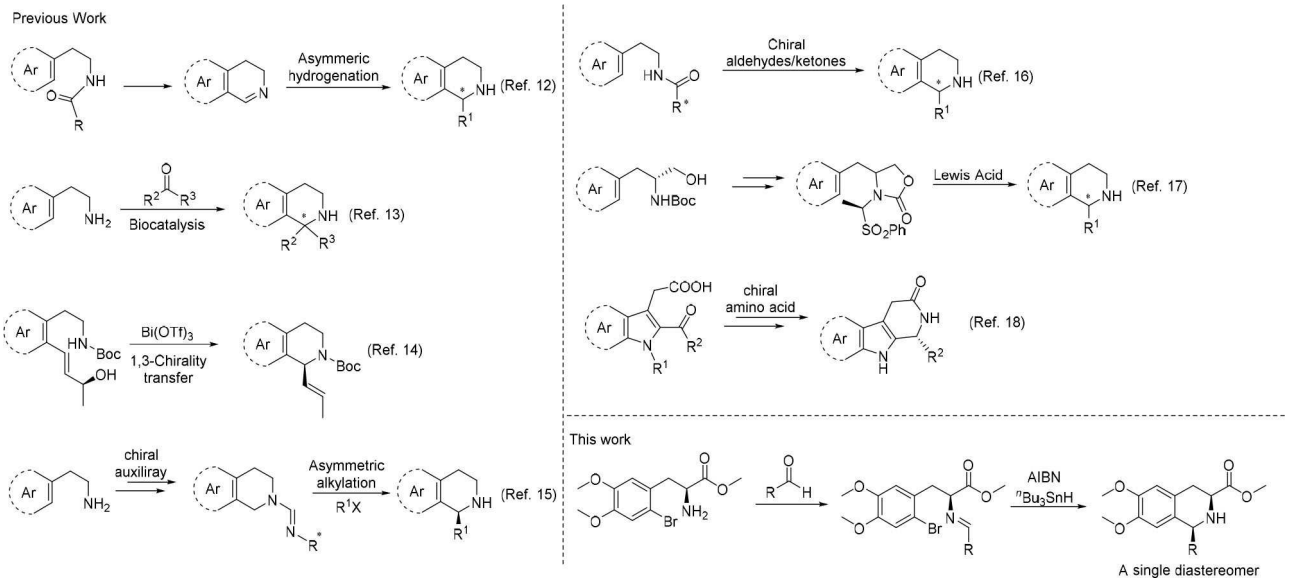
Spengler condensation and Bischler-Napieralski reaction of phenethylamines with aldehydes is an eminent strategy for the construction of a tetrahydroisoquinoline scaffold.[9,10] However, these methods are limited to the substrates containing electron-rich phenethyl aromatic rings. Moreover, the stereochemical outcome of the transformation ends up with a mixture of stereoisomers.[9,11] Hence, various synthetic strategies and modifications of the traditional methods aimed at the asymmetric synthesis of 1-substituted tetrahydroisoquinolines (Scheme 1). For example, Zhang's group reported iridium-catalysed asymmetric hydrogenation of 1-aryl-substituted dihydroisoquinolines to access chiral 1-aryl-substituted tetrahydroisoquinolines.[12] Ward found that enzyme norcoclaurine synthase can efficiently catalyze Pictet-Spengler reaction to afford chiral disubstituted tetrahydroisoquinolines.[13] Bismuth (III) trifluoromethanesulfonate catalyzed chiral synthesis of 1-substituted tetrahydroisoquinolines was documented by Uenishi and colleagues.[14] Meyers's group reported asymmetric alkylation of C-1 carbon of tetrahydroisoquinoline in the presence of oxazoline chiral auxiliary to give chiral tetrahydroisoquinoline derivatives.[15] Park developed asymmetric intramolecular cyclization of β-phenethylamine with chiral aldehydes or ketones.[16] Recently, Kallman's group described a stereoselective Pictet-Spengler cyclization of *N*-(phenylsulfonyl)alkyloxazolidinone in the presence of Lewis acid.[17] Dalpozzo reviewed an enantioselective synthesis of 1-substituted tetrahydro-*β*-carbolines by reacting 2-acyl-3-indoleacetic acid with chiral amino acid.[18]

Despite the synthetic strategies mentioned above being useful and elegant, they possess multiple limitations such as low to moderate enantioselectivity, low substrate scope and the necessity to use expensive chiral catalysts. Since the synthesis of chiral 1-substituted tetrahydroisoquinolines remains a challenge,[19] and in this regard, there is an utmost need to develop a synthetic protocol for the synthesis of 1-substituted tetrahydroisoquinolines (THIQs) which could be efficient and enantioselective. Herein we report the highly enantioselective synthesis of 1-substituted THIQs from L-Dopa through a radical intramolecular cyclization.

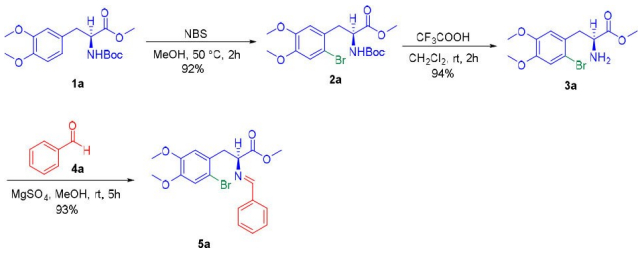
Results and Discussion

The requisite radical precursor bromoimidate ester **5a** was prepared from commercially available L-3,4-dihydroxyphenylalanine methyl ester *via* bromination followed by imination with various aldehydes. The Boc-protected methyl ester amine **1a** was obtained from L-Dopa through series of functional group transformations.[20] Esterification of L-Dopa and the subsequent protection of amino group gave Boc-protected L-Dopa methyl ester. Next, methylation and bromination of **1a** afforded **2a**.[21] Removal of the Boc group gave methyl (*S*)-2-amino-3-(2-bromo-4,5-dimethoxyphenyl) propanoate **3a**. The desired imine intermediate **5a** was obtained when **3a** was treated with an aldehyde (Scheme 2).

Our study began with syringe-pump addition of a mixture of AIBN and $^{n}Bu_3SnH$ to **5a** (0.01 M) in toluene under an argon atmosphere. The reaction afforded tetrahydroisoquinoline **6a-*cis*** regioselectively via 6-*endo* closure to the C-atom in only 54% yield along with isoquinoline **7a** (Table 1, entry 1). The



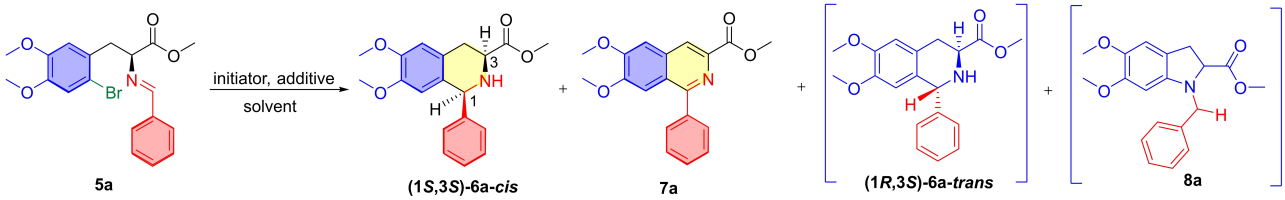
Scheme 1. Methods for the synthesis of chiral 1-substituted tetrahydroisoquinolines.



Scheme 2. Synthesis of methyl (*S*)-2-(benzylideneamino)-3-(2-bromo-4,5-dimethoxyphenyl)propanoate **5a**.

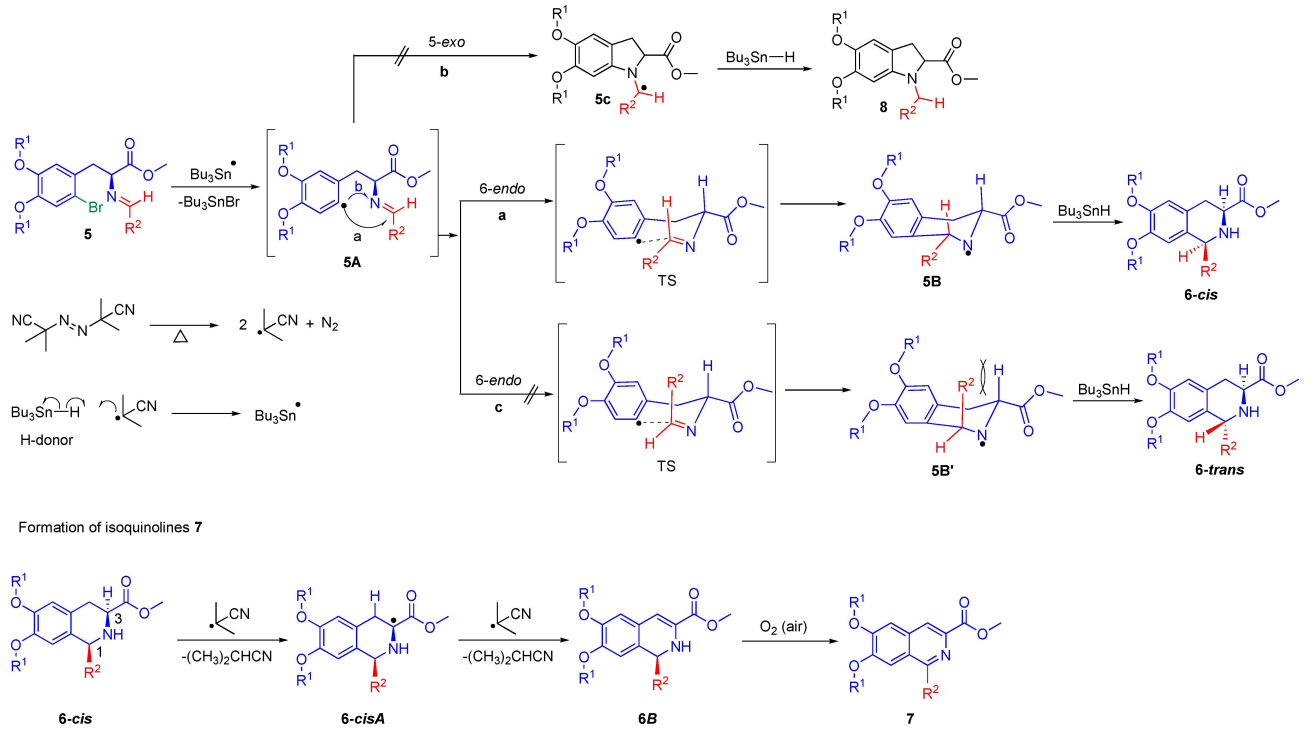
stereochemistry of **6a-*cis*** was assigned by ^{1}H NMR and NOE. A singlet at δ 5.09 ppm for C1-H proton appeared in proton NMR. Correlation between C1-H and C3-H protons was established through NOESY (See SI, S28). A highly competitive 1-phenylindoline **8a** formation through 4-*exo* ring closure to the *N*-atom was not observed in this case. The stereoselectivity in the cyclization could be reasoned on the basis of conformational[22] and molecular modeling analysis (Scheme 3). Accordingly, for *cis*-1,2,3-substituted tetrahydroisoquinolines, the bulky substituents at C1 and C3 and *N*-substitution prefer pseudoequatorial position which ultimately forces the newly formed tetrahydroisoquinoline ring in the most stable distorted half-chair conformation. Next, we attempted to improve the reaction yield. Accordingly, when the same reaction was carried out using 2.5 equivalents of ^{n}Bu$_3$SnH, the yield of **7a** did not improve (Table 1, entry 2). The yield of **7a** was decreased when the amount of ^{n}Bu$_3$SnH was increased up to 3 equivalents (Table 1, entry 3). Subsequently, we tried the reaction at a slightly higher reactant concentration and lower temperature. In view of that, radical cyclization at 0.05 M concentration of **5a** at 60 °C furnished **6a-*cis*** in a slightly lower yield, but the formation of **7a** was drastically suppressed (Table 1, entry 4). An increase in the reaction temperature to 70 °C significantly increased the reaction yield (Table 1, entry 5). To our delight, when the same reaction was carried out for 2 h, the tetrahydroisoquinoline **6a-*cis*** was obtained in good yield (70%) with 99% ee along with the oxidized

Table 1. Optimization of reaction conditions.[a]



Entry	Initiator (equiv)	Additive (equiv.)	Conc. (M)	Temp (°C)	Yield (%)[b] **6a-*cis***	**7a**	ee (%)
1	AIBN (1.5)	^{n}Bu$_3$SnH (2.2)	0.01	70	54	15	60
2	AIBN (1.5)	^{n}Bu$_3$SnH (2.5)	0.01	70	55	18	43
3	AIBN (1.5)	^{n}Bu$_3$SnH (3)	0.01	100	44	30	12
4	AIBN (1.5)	^{n}Bu$_3$SnH (2.2)	0.05	60	50	7	50
5	AIBN (1.5)	^{n}Bu$_3$SnH (2.2)	0.05	70	66	12	99
6[c]	AIBN (1.5)	^{n}Bu$_3$SnH (2.2)	0.05	70	**72**	10	**99**
7[d]	AIBN (1.5)	^{n}Bu$_3$SnH (2.2)	0.05	70	46	32	85
8	AIBN (1.5)	^{n}Bu$_3$SnH (2.2)	0.05	80	17	62	90
9	AIBN (1.5)	(TMS)$_3$SiH (2.2)	0.05	70	25	48	33
10	BPO (1.5)	^{n}Bu$_3$SnH (2.2)	0.05	90	–	50	–
11	DTBP (1.5)	^{n}Bu$_3$SnH (2.2)	0.05	25	–	55	–
12	Et$_3$B (2.5)	^{n}Bu$_3$SnH (2.2)	0.05	25	–	–	–
13[e]	–	Bis(tributyltin) (2.2)	0.05	25	30	10	20
14[f],[g]	–	Et$_3$N (10)	0.01	25	–	46	–
15[g]	AIBN (1.5)	^{n}Bu$_3$SnH (2.5)	0.01	25	–	42	–

[a] Reaction conditions: **5a** (1 equiv) 0.01 M, a radical initiator, additive, toluene (10 mL), syringe pump addition at a rate of 2 mL/h, under argon atmosphere for 5 h.
[b] Isolated yield.
[c] Reaction for 2 h.
[d] Benzene as a solvent was used.
[e] Benzene, UV irradiation (254 nm).
[f] CH$_3$CN as a solvent was used.
[g] UV irradiation (254 nm).

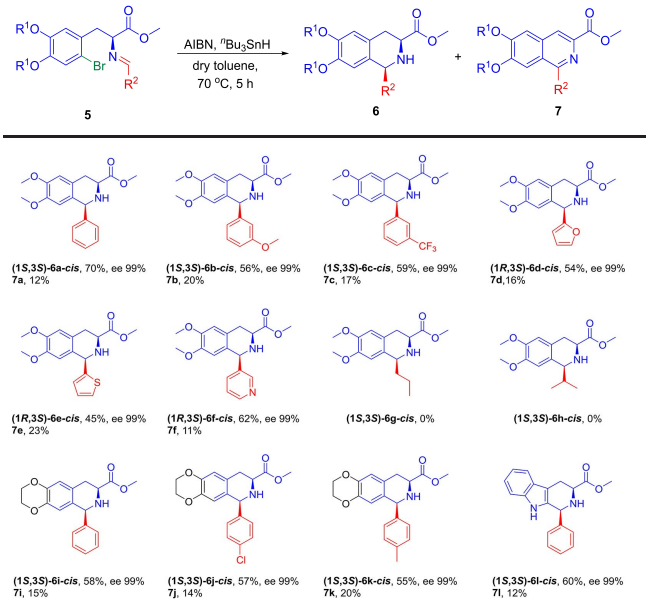


Scheme 3. A plausible radical mechanism for the formation of **6-*cis*** and isoquinoline **7**.

product **7a** (Table 1, entry 6). Changing the reaction solvent to benzene reduced the efficiency of intramolecular radical cyclization and increased the isoquinoline product **7a** (32%) (Table 1, entry 7). Elevation of the temperature to 80 °C did not improve the yield and the chiral HPLC analysis revealed partial racemization of the product (Table 1, entry 8). The use of $(TMS)_3SiH$ as a H-donor in the reaction instead of $^nBu_3SnH$ afforded **6a-*cis*** in poor yield (Table 1, entry 9). Incorporation of initiators like benzoyl peroxide (BPO), di-*tert*-butyl peroxide (DTBP) or triethylborane other than AIBN in the reaction yielded either only isoquinoline **7a** or no reaction at all (Table 1, entries 10–12). We also tried to drive this reaction by irradiating the reaction mixture with a UV lamp (254 nm) in the presence of bis(tributyltin) in benzene. The reaction afforded desired product in only 30% yield along with **7a** (10%) and the starting material (Table 1, entry 13). When the reaction was performed in the presence of triethylamine under UV irradiation, oxidized product **7a** was obtained exclusively (Table 1, entry 14). No desired product was observed when the reaction was conducted using 1.5 equiv. of AIBN and 2.5 equiv. of $^nBu_3SnH$ under the UV irradiation (Table 1, entry 15).

With the optimized conditions in hand, the scope and generality of the intramolecular radical cyclization reaction were investigated (Table 2). Accordingly, a variety of aromatic aldehydes bearing electron-donating and electron-withdrawing groups were subjected to the radical transformation. The substituent groups had little influence on the reaction and the corresponding

Table 2. The substrate scope for the synthesis of tetrahydroisoquinolines **6** and isoquinolines **7**.[a]



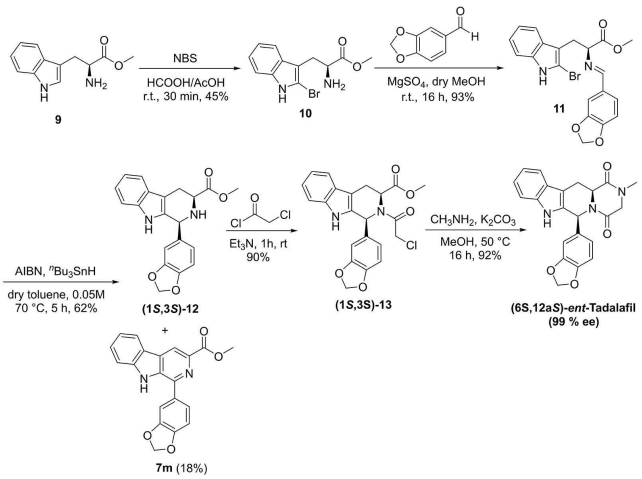
[a] Reaction conditions: **5** (1 equiv.), AIBN (1.5 equiv.), $^nBu_3SnH$ (2.2 equiv.), dry toluene, syringe pump addition, 70 °C, 5 h. All the reactions were carried out at 0.05 M reactant concentration.

products were obtained in good yield (**6b-*cis***, **6c-*cis***, **6j-*cis*** and **6k-*cis***). Besides, heteroaromatic aldehydes were also examined. The use of furan-2-carboxaldehyde and thiophene-2-carboxaldehyde furnished the desired products in moderate yield (**6d-*cis*** and **6e-*cis***). The impact on the yields could be attributed to the decomposition of the starting material owing to the instability of the aldimine group during the reaction. Pleasingly, aldimine generated from pyridine-2-carboxaldehyde was stable and in this case, **6f-*cis*** was obtained in good yield. However, when aliphatic aldehydes were employed in the reaction, the desired products (**6g-*cis*** and **6h-*cis***) did not obtain. When hydroxyl groups of substrates were protected by formation of ether, they needed a longer time for reaction completion (**6i-*cis***, **6j-*cis*** and **6k-*cis***). Notably, bromo aldimine obtained from tryptophan methyl ester underwent this transformation smoothly to afford **6l-*cis*** in good yield.

The possible mechanism for the formation of tetrahydroisoquinoline **6-*cis*** in a regio- and stereo selective manner has been proposed in Scheme 3. Initially, the decomposition of AIBN forms isobutyronitrile radicals which then react with $^{n}Bu_3SnH$ to generate tributyltin radicals. Removal of the Br atom of **5** by tributyltin radical in a chain-propagating step gives intermediate **5A**. Subsequent intramolecular addition of aryl radical through 6-*endo* closure to the C-atom furnishes intermediate **5B** having a chair-like six-membered transition state where C1 and C3 substituents possess pseudoequatorial positions (path a). This mode of cyclization proceeds in preference to either the formation of indoline **8** through intermediate **5c** by 5-*exo* closure to the *N*-atom (path b) or diastereomer **6-*trans*** via chair like intermediate **5B′** comprising 1,3-diaxial interactions. Lastly, tetrahydroisoquinoline **6-*cis*** is formed by the abstraction of H atom from $^{n}Bu_3SnH$.

Based on the literature reports[23] and experimental observations, the formation of isoquinoline **7** from tetrahydroisoquinoline **6-*cis*** is proposed. The isobutyronitrile radical abstracts C3-H hydrogen of **6-*cis*** to form tetrahydroisoquinolinyl radical **6-*cis*A**. Subsequent abstraction of the C4-H hydrogen of **6-*cis*A** by another isobutyronitrile radical generates dihydroisoquinoline **6B**. Lastly, aerobic oxidation of **6B** in the presence of air (O_2) as an oxidant yields isoquinoline **7**.

Finally, the synthetic utility was demonstrated in the stereoselective synthesis of the enantiomer of Tadalafil which is a cGMP specific type V phosphodiesterase (PDE 5) inhibitor (Scheme 4). Our initial efforts to brominate D-tryptophan methyl ester **9** by *N*-bromosuccinimide gave a mixture of 2-bromo tryptophan methyl ester **10** (45%), 2,5- and 2,6-dibromotryptophan methyl esters.[24] In the next step, condensation of **10** with piperonal in dehydrating condition



Scheme 4. A radical synthesis of *ent*-Tadalafil.

provided imine **11**. Next, the crude imine **11** was subjected to the optimized condition of intramolecular radical cyclization in toluene to deliver tetrahydro-1*H*-pyrido[3,4-*b*] indole-3- carboxylate **12** in 62% yield and methyl 1-(benzo[d][1,3]dioxol-5-yl)-9H-pyrido [3,4-b] indole-3-carboxylate **7m** in 18% yield. Acylation of **12** with chloroacetyl chloride under basic conditions yielded intermediate **13** in 90% yield. Lastly, the diketopiperazine ring was constructed via double nucleophilic substitution using methylamine to furnish *ent*-Tadalafil (5 steps, 21%) with 99% ee.

Conclusion

In conclusion, we have demonstrated a method for the synthesis of enantiomerically pure *cis*-1-substituted tetrahydroisoquinolines **6**. The sp^2 aryl radical of bromoimidate ester subsequently cyclized *via* intramolecular 6-*endo* attack. The conformational preference for a chair-like six-membered transition state where bulky substituents at C1 and C3 require pseudoequatorial positions rationalizes *cis* selectivity. Whereas, a conformer that could lead to *trans*-1-substituted tetrahydroisoquinolines possess 1,3-diaxial interactions between substituents at C1 and C3. This protocol also provides an alternative route towards a privileged scaffold-isoquinoline **7**. The practicality of this method was shown in the preparation of *ent*-Tadalafil in 21% (overall yield) with 99% ee.

Experimental Section

General Methods

^{1}H NMR (400 MHz) and ^{13}C NMR (101 MHz) spectra were recorded on 400-MR automated spectrometer. Chemical shifts are reported in parts per million (ppm) on the δ scale from an internal standard (TMS). Analytical thin-layer chromatography

(TLC) was performed using 0.25 mm silica gel-coated Kiselgel 60 F_{254} plates. Flash chromatography was performed using the indicated solvent and silica gel 60 (Merck, 230–400 mesh). High-resolution mass spectra (HRMS) were recorded in ESI mode using TOF mass spectrometer. All materials were purchased from commercial sources and used without further purification.

A Representative Procedure for the Synthesis of Methyl (1S,3S)-6,7-Dimethoxy-1-Phenyl-1,2,3,4-Tetrahydroisoquinoline-3-Carboxylate (6 a-*cis*)

To the stirred solution of methyl (*S*,*E*)-2-(benzylideneamino)-3-(2-bromo-4,5-dimethoxyphenyl) propanoate **5 a** (0.3 g, 0.6 mmol) in degassed toluene (5 mL) was added a mixture of AIBN (0.1 g, 0.7 mmol) and $^{n}Bu_3SnH$ (0.4 g, 1.4 mmol) in degassed toluene (10 mL) via syringe-pump (2 mL/h) under an argon atmosphere while heating at 80 °C for 2 h. After completion, toluene was evaporated under reduced pressure. The crude product was purified by flash column chromatography (35-40% ethyl acetate in hexanes) to obtain methyl (1*S*,3*S*)-6,7-dimethoxy-1-phenyl-1,2,3,4-tetrahydroisoquinoline-3-carboxylate **6 a-*cis*** as a white solid (0.14 g, 70%) and methyl 6,7-dimethoxy-1-phenylisoquinoline-3-carboxylate **7 a** as a yellow solid (0.024 g, 12%).

Methyl (1*S*,3*S*)-6,7-dimethoxy-1-phenyl-1,2, 3,4-tetrahydroisoquinoline-3-carboxylate **6 a-*cis***: ^{1}H NMR (400 MHz, acetone-d_6) δ 7.48–7.22 (m, 5H), 6.75 (s, 1H), 6.18 (s, 1H), 5.09 (d, J= 1.9 Hz, 1H), 3.85–3.81 (m, 1H), 3.78 (s, 3H), 3.73 (s, 3H), 3.49 (s, 3H), 3.01 (s, 1H), 2.99 (s, 1H); HRMS (ESI) *calcd.* for $C_{19}H_{22}NO_4$ 328.1549; found 328.1548; HPLC analysis: (25% *i*-PrOH/hexanes, 0.3 mL/min, 256 nm); 99% ee: t_R = 24.0 min.

Methyl 6,7-dimethoxy-1-phenylisoquinoline-3-carboxylate **7 a**: ^{1}H NMR (400 MHz, *acetone-d_6*) δ 8.45 (s, 1H), 7.78 (d, J= 7.6 Hz, 2H), 7.66–7.50 (m, 4H), 7.47 (s, 1H), 4.06 (s, 3H), 3.92 (s, 3H), 3.87 (s, 3H) ; ^{13}C NMR (101 MHz, C_3D_6O) δ 166.1, 157.8, 153.4, 152.1, 140.0, 139.7, 133.4, 129.7, 128.4, 128.2, 123.9, 121.5, 106.6, 105.2, 55.5, 55.1, 51.4. MS (ESI): *m/z* 324.2.

Acknowledgments

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