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Asymmetric synthesis of six tetrahydroisoquinoline natural products through α-amination of an aldehyde

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ABSTRACT

An enantioselective route towards the synthesis of C-1 substituted tetrahydroisoquinoline natural products is reported. Six different natural products are synthesized from a single aldehyde using proline-catalyzed asymmetric α-hydrazination reaction as the key step. The highly enantioselective introduction of an amino group is exploited to synthesize (−)-calycotomine, (−)-salsolidine, (−)-carnegine, (+)-homolaudanosine, (+)-homoprotoberberine and (+)-crispine A.

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1. Introduction

The tetrahydroisoquinoline (THIQ) scaffold is an important structural unit, found in many naturally occurring alkaloids, biologically active molecules, and pharmaceuticals (Fig. 1) [1]. Among this class of compounds, C1-substituted THIQ are the most common and they have gained significant attention due to their high bioactivity as SK channel ligands [2] and because they act as receptor antagonists for the treatment of insomnia [3a-d]. Various enantioselective methods available for the synthesis of these compounds include the transformations at C1 position like cyano addition [4], metal catalyzed addition of terminal alkynes [5], allylsilanes [6], asymmetric hydrogenation [7] in the presence of chiral ligands, photoredox catalysis [8], Pictet-Spengler [9], 1,3-dipolar cycloaddition [10] and oxidative cross-coupling [11]. Additionally, various racemic approaches using metal-catalyzed C−H alkylation/allylation [12], metal-free coupling with different nucleophiles such as allylsilanes, coumarins, nitroalkanes, Grignard reagents [13] and through photocatalysis [14] are also available. In the recent years, the groups of Opatz [15], and Lumb [16] have contributed significantly to the synthesis of compounds containing THIQ units. Menéndez and co-authors have summarized the research activities towards the synthesis of tetrahydroisoquinolines during the last two decades in two reviews [17]. We observed that organocatalytic pathways for the asymmetric synthesis of C1-substituted THIQs are rare. First among a few notable ones is the chiral Pictet Spengler reaction by Hiemstra and co-workers where moderate ee was achieved, which was further enhanced by crystallizing the chiral products [18]. Itoh and co-workers reported a method involving an asymmetric Strecker reaction using Jacobsen's thiourea catalyst, which resulted in high yields and enantioselectivity [4a,b].

2. Results and discussion

Our group is actively involved in the use of proline-catalyzed asymmetric amination [19] and hydroxylation of aldehydes for the synthesis of natural products [20]. The stereochemical outcome of the reaction is governed by proline via the enamine intermediate (Fig. 2.). The proposed model is based on Houk's transition state calculation on Hajos–Parrish–Eder–Sauer–Wiechert reaction [21].

We envisaged that a divergent route for the synthesis of C1-substituted THIQs (**1**–**6**) can be achieved from the aldehyde **7**. A retrosynthetic route is outlined in (Scheme 1).

Our synthetic efforts started from 3,4-dimethoxyphenethyl methanesulfonate **8**, which was synthesized from commercially

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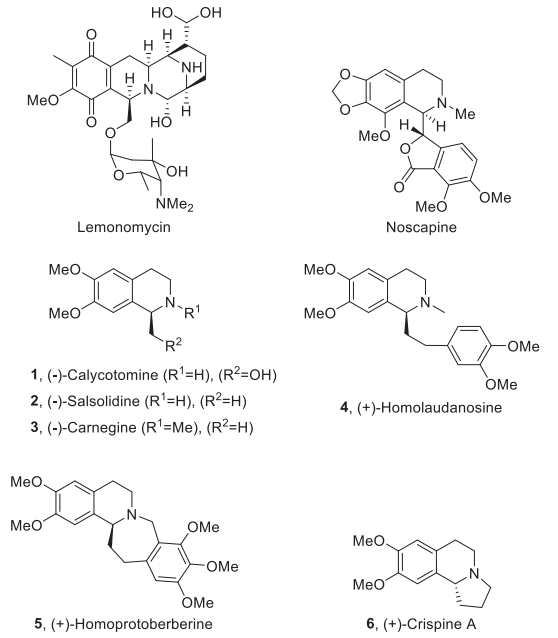


Fig. 1. Representative tetrahydroisoquinoline containing alkaloids.

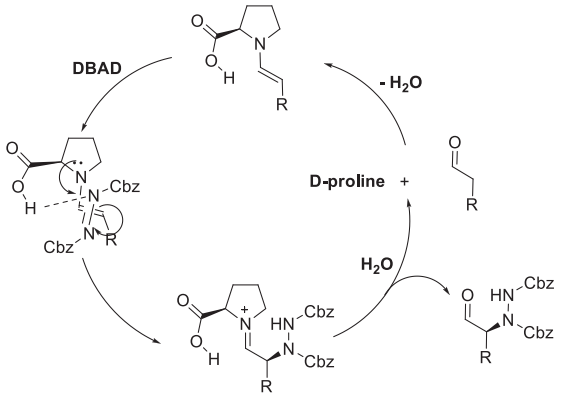
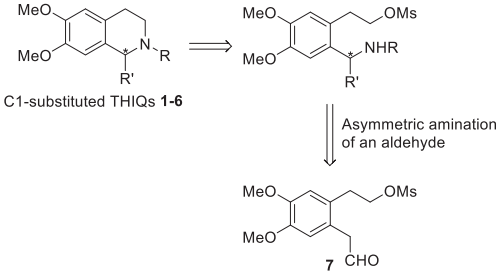
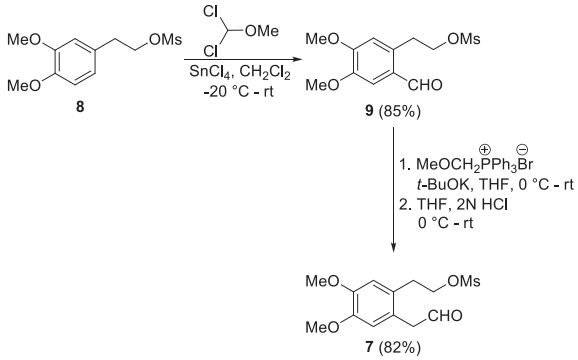


Fig. 2. General mechanism for the proline catalyzed α-amination of aldehydes.



Scheme 1. Retrosynthetic route for THIQs **1**–**6** from the aldehyde **7**.

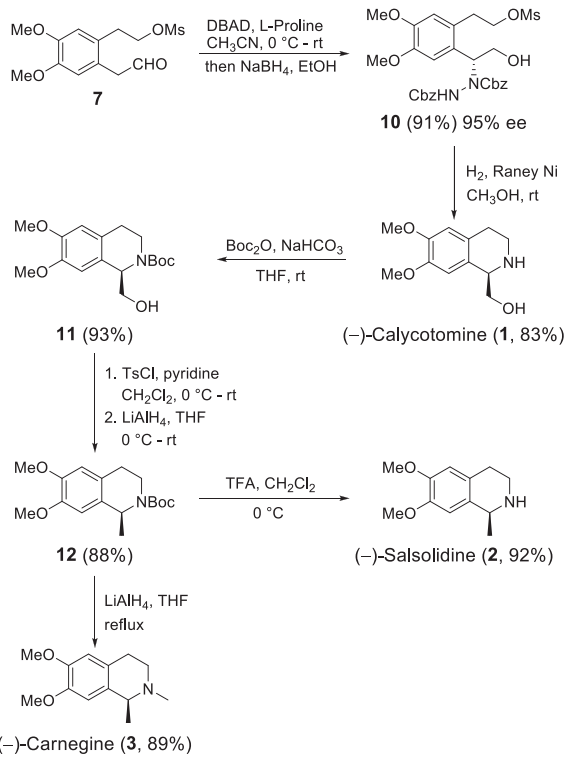
available 2-(3,4-dimethoxyphenyl)ethan-1-ol using a reported procedure [22]. Formylation of **8** was carried out in the presence of $SnCl_4$ using dichloromethyl methyl ether in CH_2Cl_2 to get the aldehyde **9** in 85% yield (Scheme 2). Wittig reaction of **9** with (methoxymethyl)triphenylphosphonium bromide followed by hydrolysis in acidic medium gave the aldehyde **7** in 82% yield over two steps.



Scheme 2. Synthesis of aldehyde **7**.

With the desired aldehyde **7** in our hand, the synthesis of (−)-calycotomine (**1**), (−)-salsolidine (**2**) and (−)-carnegine (**3**) were carried out. The aldehyde **7** was subjected to asymmetric α-hydrazination using dibenzyl azodicarboxylate (DBAD) in the presence of L-proline (0 °C − rt, 4 h, CH_3CN). After 4 h, the crude product was reduced using $NaBH_4$ to get the β-hydrazino alcohol **10** in 91% yield and with 95% ee (Scheme 3). The enantiomeric purity was calculated using chiral HPLC by comparing the chromatogram of **10** with the racemic mixture obtained from the reaction catalyzed by DL-proline. The alcohol **10** was subjected to hydrogenation with Raney-Ni (CH_3OH, rt) resulting in the cleavage of the benzyloxycarbonyl groups and the *N*–*N* bond. The primary amine cyclized in situ displacing the mesylate group to give (−)-calycotomine (**1**) in 83% yield (Scheme 3).

THIQs **2** and **3** were then prepared from **1**. The secondary amino group in **1** was protected as the Boc derivative (Boc_2O, $NaHCO_3$, THF, rt) to get **11** in 93% yield. The hydroxyl group in **11** was transformed into an unstable tosyl derivative (TsCl, pyridine,



Scheme 3. Synthesis of (−)-Calycotomine (**1**), (−)-Salsolidine (**2**), (−)-Carnegine (**3**).

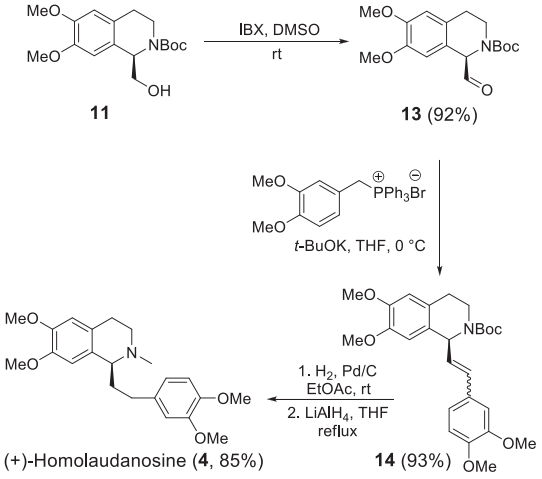
CH_2Cl_2, 0 °C - rt), which was immediately reduced with $LiAlH_4$ to **12** (88% over two steps). Removal of the *N*-Boc group in **12** with trifluoroacetic acid (50%, CH_2Cl_2, 0 °C) gave (−)-salsolidine (**2**) in 92% yield (Scheme 3). Reduction of the *N*-Boc group in **12** using $LiAlH_4$ (THF, reflux) gave (−)-carnegine (**3**) in 89% yield (Scheme 3).

Our next target was (+)-homolaudanosine (4). A limited number of syntheses are available in the literature. Szarek and co-workers achieved its synthesis by functionalization of tartaric acid [23], and few reports are using nucleophilic addition on imines at C1 position in the presence of metal catalysts [5b,6b,24]. We started the synthesis from the alcohol **11** by oxidizing it into the aldehyde **13** (92%, IBX, DMSO, rt, Scheme 4). Aldehyde **13** was immediately subjected to a Wittig reaction with (3,4-dimethoxybenzyl)triphenylphosphonium bromide (*t*-BuOK, THF, 0 °C - rt) leading to the olefin **14** as a mixture of isomers (93% yield). Hydrogenation of the double bond in **14** (H_2, Pd/C, EtOAc, rt) followed by the reduction of the *N*-Boc group ($LiAlH_4$, THF, reflux) provided (+)-homolaudanosine (**4**) (85% over two steps, Scheme 4). The optical rotation of our synthetic sample of **4** {$[\alpha]_D^{25}$ + 5.1 (c 0.2, CH_2Cl_2)} was in close agreement with that reported in the literature {$[\alpha]_D^{25}$ + 3.0 (c 1.3, $CHCl_3$)} [5b].

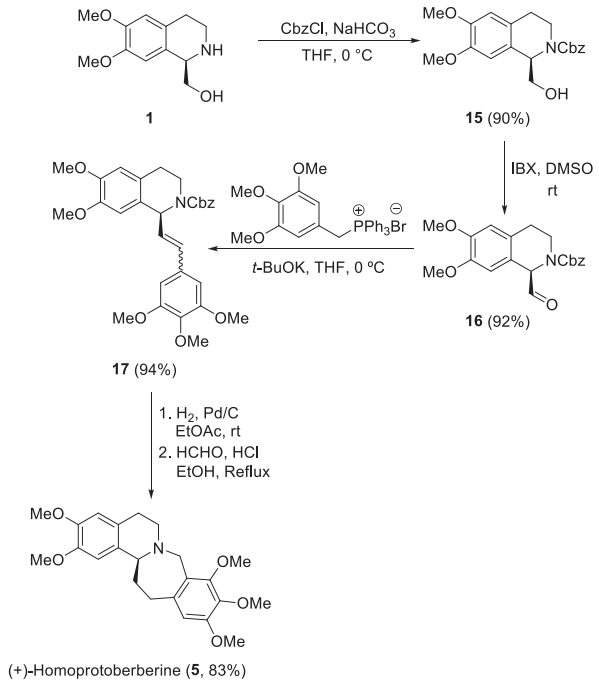
With the optimized technique in our hand, we attempted the synthesis of the more complex molecule, (+)-homoprotoberberine (**5**). The racemic homoprotoberberine framework has been constructed with metal-mediated [25] and with metal free synthetic pathways [26]. Three chiral syntheses have been reported so far. Other than the synthesis by Szarek and co-workers using tartaric acid [23], nucleophilic addition on isoquinoline ring by Ohsawa and co-workers [27] and copper catalyzed C—C coupling of terminal alkynes by Liu and co-workers [5d] are the methods available. We began our synthesis of **5** by carrying out Cbz protection of **1** (benzyl chloroformate, $NaHCO_3$, 0 °C - rt) to get the tertiary benzyl carbamate **15** in 90% yield (Scheme 5).

The hydroxyl group in **15** was oxidized to an aldehyde function to get **16** (92%, IBX, DMSO, rt). The aldehyde **16** was subjected to a Wittig reaction with (3,4,5-trimethoxybenzyl)triphenylphosphonium bromide (*t*-BuOK, THF, 0 °C - rt) to get the olefin **17** as a mixture of isomers (94%). Hydrogenation of **17** followed by Pictet-Spengler reaction of the resulting amine (HCHO, HCl, EtOH, reflux) yielded (+)-homoprotoberberine (**5**) in 85% yield (Scheme 5). The optical rotation of our sample of **5** {$[\alpha]_D^{25}$ – 101 (c 0.6, CH_2Cl_2)} was consistent with that reported in literature {$[\alpha]_D^{25}$ – 98.5 (c 0.12, CH_3OH)} [5d].

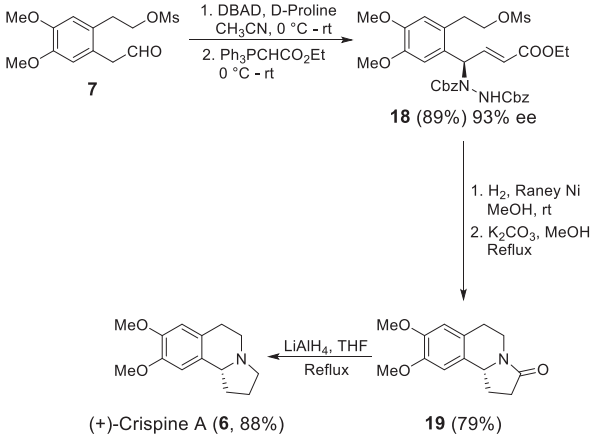
Crispine A has remained as an attractive choice for synthetic chemists and several interesting syntheses are available. Methods such as lithiation [28], C—H allylation [13d] at C-1 position and Lewis acid catalyzed lactamization [12c] have been employed. A number of enantioselective synthesis of (+)-crispine A (**6**) are reported. Several strategies have been used such as functionalization of the C-1 position through nucleophilic addition using chiral auxiliaries [4b,5c,6b], through asymmetric Pictet-Spengler reactions [15,29,30], with the help of chiral metal complexes [31] and a few metal-free synthesis are also available [4c]. In contrast to the previously reported methods, our strategy offers an alternative synthetic route for (+)-crispine A (**6**) in four steps from the aldehyde **7** (Scheme 6). In order to produce the opposite stereochemistry to that of compounds (**1**–**5**) at the C1 position, D-proline was used as the catalyst for the asymmetric α-functionalization. Aldehyde **7** was treated with dibenzyl azodicarboxylate in the presence of D-proline and after the complete disappearance of the yellow color, Wittig reaction was carried out on the aldehyde function by adding (carbethoxymethylene)triphenylphosphorane (Ph_3P=



Scheme 4. Synthesis of (+)-Homolaudanosine (**4**).



Scheme 5. Synthesis of (+)-Homoprotoberberine (**5**).



Scheme 6. Synthesis of (+)-Crispine A (**6**).

$CHCO_2Et$) to get the unsaturated ester **18** in 89% yield and 93% ee (Scheme 6).

The reduction of the γ-hydrazino α,β-unsaturated ester **18** was performed using Raney-Ni, which resulted in a mixture of products as observed on TLC. To our delight, when the mixture was treated with K_2CO_3 (CH_3OH, reflux), a tricyclic lactam **19** could be isolated as the major product in 79% yield. The lactam **19** was reduced using $LiAlH_4$ (THF, reflux) to get **6** in 88% yield (Scheme 6). The measured optical rotation for (+)-crispine A (**6**) {$[\alpha]_D^{25}$ + 90.4 (c 0.36, CH_2Cl_2)} matched with that reported in literature {$[\alpha]_D^{25}$ + 90 (c 1.0, $CHCl_3$)}.[29]

Thus, the syntheses of six THIQs (**1**–**6**) were achieved from a single aldehyde **7** using proline-catalyzed asymmetric α-amination as the key step.

3. Conclusions

We have demonstrated an application of proline-catalyzed α-amination reaction of aldehydes for the synthesis of C1-substituted tetrahydroisoquinolines. This organocatalytic pathway has led to the synthesis of all the six target molecules with high enantioselectivity. Syntheses of six different natural products from a common aldehyde exemplify the synthetic utility of this methodology where all the reactions performed are simple and high yielding. The current method is complimentary to existing methods, which rely on a late cyclization reaction through aromatic electrophilic substitution reactions such as Pictet-Spengler or Bischler-Napieralski reactions. However, the current method requires a suitable aldehyde as the starting material, the preparation of which need not be always trivial with high selectivity as in the case reported here.

4. Experimental section

4.1. General information

All of the chemicals were purchased from commercial sources. The ^{1}H NMR spectra of compounds containing the hydrazino group were complex at r.t. due to the presence of rotamers. They were therefore recorded at 80 °C in DMSO-d_6. Column chromatography was done with silica gel (particle size 60–120 and 100–200 mesh) purchased from Merck. The enantiomeric ratios were determined by chiral HPLC analysis using Daicel chiralpak IC and Phenomenex Cellulose-1 columns with a mixture of hexane and isopropanol as an eluent at 25 °C. Optical rotation was measured using a 5.0 mL cell with a 10 dm path length and is reported as $[\alpha]_D^{25}$(*c* in g per 100 mL solvent).

4.2. 2-formyl-4,5-dimethoxyphenethyl methanesulfonate (9)

To a stirred solution of **8** (1.10 g, 4.23 mmol) at −20 °C in dry CH_2Cl_2 (20 mL) was added dichloromethyl methyl ether (0.57 mL, 6.34 mmol) and stirred for 30 min $SnCl_4$ (1 M solution in CH_2Cl_2, 7.19 mL, 7.19 mmol) was added dropwise over a period of 30 min at the same temperature. The reaction mixture was warmed to r.t. and stirred for an additional 12 h. The reaction was monitored through TLC, and after the complete disappearance of starting material on TLC, the reaction mixture was quenched with a saturated solution of $NaHCO_3$ (10 mL) and the product was extracted with CH_2Cl_2 (3 × 25 mL), and dried over Na_2SO_4. The solvents were removed under reduced pressure and the crude product was purified through column chromatography (75:25 petroleum ether/EtOAc) to get **9** as an oil which solidified on cooling, m.p. 74–76 °C (1.03 g, 85%); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 10.03 (s, 1H), 7.29 (s, 1H), 6.78 (s, 1H), 4.41 (t, *J* = 6.7 Hz, 2H), 3.95 (s, 3H), 3.92 (s, 3H), 3.41 (t, *J* = 6.7 Hz, 2H), 2.92 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 190.9, 153.5, 148.3, 133.2, 127.1, 115.0, 114.5, 70.0, 56.3, 56.2, 37.4, 32.4 ppm; FTIR (thin film): 3011, 2935, 2852, 1711, 1678, 1600, 1570, 1516, 1465 cm^{-1}. HRMS (ESI-TOF) *m*/*z*: [M + Na]$^+$ calcd. for $C_{12}H_{16}NaO_6S$ 311.0565, found 311.0565.

4.3. 4,5-dimethoxy-2-(2-oxoethyl)phenethylmethanesulfonate (7)

Potassium *t*-butoxide (0.59 g, 5.27 mmol) was added to a stirred solution of methoxymethyltriphenylphosphonium bromide (2.13 g, 6.25 mmol) in dry THF (15 mL) at 0 °C under nitrogen atmosphere and the stirring was continued at this temperature for 20 min, after which the aldehyde **9** (0.95 g, 3.29 mmol) in dry THF (12 mL) was added to the reaction mixture dropwise and further stirring was continued at room temperature for 2 h. After the complete disappearance of starting material on TLC, the reaction mixture was quenched with saturated NH_4Cl solution (10 mL). The product was extracted with EtOAc (3 × 15 mL), and dried over anhydrous Na_2SO_4. The solvents were removed under reduced pressure, and the crude product was purified through column chromatography (85:15 petroleum ether/EtOAc) to get enol ether as a colorless oil (0.93 g, 90%). The enol ether was dissolved in THF (15 mL) and 2 N HCl (5 mL) was added dropwise to the reaction mixture and stirred for 6 h. The product was extracted with EtOAc (3 × 15 mL), and dried over anhydrous Na_2SO_4. The solvents were removed under reduced pressure and the crude product was purified through column chromatography (75:25 petroleum ether/EtOAc) to get an aldehyde **7** as a colorless oil (0.81 g, 82%); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.72 (t, *J* = 1.9 Hz, 1H), 6.74 (s, 1H), 6.64 (s, 1H), 4.30 (t, *J* = 7.1 Hz, 2H), 3.86 (s, 3H), 3.85 (s, 3H), 3.70 (d, *J* = 1.9 Hz, 2H), 2.96 (t, *J* = 7.1 Hz, 2H), 2.90 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 199.0, 148.7, 148.4, 127.5, 122.7, 114.0, 113.4, 69.7, 56.1, 56.0, 47.9, 37.4, 32.5 ppm; FTIR (thin film): 2938, 2836, 2728, 1720, 1609, 1519, 1466 cm^{-1}. HRMS (ESI-TOF) *m*/*z* [M + Na]$^+$ calcd. for $C_{13}H_{18}NaO_6S$ 325.0722, found 325.0726.

4.4. Dibenzyl (R)-1-(1-(4,5-dimethoxy-2-(2-((methylsulfonyl)oxy) ethyl)phenyl)-2-hydroxyethyl)hydrazine-1,2-dicarboxylate (10)

To a stirred solution of the aldehyde **7** (1.00 g, 3.31 mmol) in CH_3CN (20 mL) were added dibenzylazodicarboxylate (DBAD), (1.08 g, 3.64 mmol) and L-proline (0.04 g, 0.33 mmol) at 0 °C under nitrogen atmosphere and the mixture was stirred for 2 h. The stirring was continued at room temperature until the solution turned colorless from yellow. The reaction mixture was again cooled to 0 °C, $NaBH_4$ (0.18 g, 4.96 mmol) and ethanol (5 mL) were added to the reaction mixture. The stirring was continued for additional 15 min and the reaction was quenched with saturated NH_4Cl solution (5 mL). The product was extracted with ethyl acetate (3 × 30 mL), dried over anhydrous Na_2SO_4. The solvents were removed under reduced pressure, and the product was purified through column chromatography (40:60 petroleum ether/EtOAc) to get an alcohol **10** as a syrup (1.81 g, 91%); $[\alpha]_D^{25}$ = +1.5 (c 0.26, CH_2Cl_2); ^{1}H NMR (400 MHz, DMSO-d_6, 80 °C) δ = 9.26 (s, 1H), 7.28 (s, 10H), 6.87 (s, 1H), 6.81 (s, 1H), 5.37 (s, 1H), 5.08 (s, 4H), 4.54 (s, 1H), 4.33 (s, 2H), 3.91–3.82 (m, 1H), 3.72 (s, 4H), 3.63 (s, 4H), 3.01 (s, 3H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6, rotamers) δ = 158.4, 156.3, 148.5, 147.9, 147.5, 136.9, 136.8, 136.7, 114.3, 114.1, 112.2, 111.8, 70.9, 67.5, 67.0, 66.2, 61.2, 56.1, 56.0, 55.9, 55.8, 37.0, 31.8 ppm; FTIR (thin film): 3453, 3302, 2931, 2854, 1712, 1519, 1455 cm^{-1}. HRMS (ESI-TOF) *m*/*z*: [M + NH_4]$^+$ calcd. for $C_{29}H_{38}N_3O_{10}S$ 620.2278, found 620.2279; HPLC (Diacel IC column, hexane: IPA = 80:20, flow rate: 1 mL/min, λ = 282 nm), t_R major = 68.0, t_R minor = 79.3, 95% ee.

4.5. (R)-(6,7-dimethoxy-1,2,3,4-tetrahydroisoquinolin-1-yl) methanol (1)

To a solution of **10** (1.10 g, 1.82 mmol) in CH_3OH (20 mL), was added Raney-Ni (0.90 g, prewashed with absolute ethanol) followed by 0.10 mL of acetic acid, and the mixture was stirred for 16 h at r.t. under a hydrogen atmosphere. The reaction mixture was then filtered through a celite pad, and the solution was concentrated under reduced pressure. The crude product was purified by column chromatography (92:08 CH_2Cl_2/CH_3OH) to get **1** as a white solid, m.p. 139 °C (0.33 g, 83%); $[\alpha]_D^{25} = -31.4$ (c 0.40, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 6.58 (s, 1H), 6.57 (s, 1H), 3.96 (dd, J = 9.2, 4.3 Hz, 1H), 3.84 (s, 3H), 3.84 (s, 3H), 3.74 (dd, J = 10.6, 3.9 Hz, 1H), 3.64–3.58 (m, 1H), 3.08–3.01 (m, 3H), 2.75–2.59 (m, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 147.9, 147.6, 127.4, 126.6, 112.0, 109.2, 64.0, 56.1, 55.96, 38.8, 28.9 ppm; FTIR (thin film): 3300 cm^{-1}. HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd. for $C_{12}H_{18}NO_3$224.1287, found 224.1294.

4.6. Tert-butyl (R)-1-(hydroxymethyl)-6,7-dimethoxy-3,4-dihydroisoquinoline-2(1H)-carboxylate (11)

To a stirred solution of **1** (0.56 g, 2.51 mmol) in THF (15 mL) were added $NaHCO_3$ (0.52 g, 6.27 mmol) and $(Boc)_2O$ (1.15 mL, 5.02 mmol) and the reaction mixture was stirred for 8 h. After the complete disappearance of starting material the reaction mixture was filtered, concentrated and purified by column chromatography (60:40 petroleum ether/EtOAc) to get **11** as a colorless oil (0.75 g, 93%); $[\alpha]_D^{25} = +53.0$ (c 0.46, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 6.66 (s, 1H), 6.60 (s, 1H), 5.12 (d, J = 56.2 Hz, 1H), 3.82 (t, J = 10.1 Hz, 9H), 3.31 (d, J = 62.0 Hz, 1H), 2.79 (bs, 1H), 2.66 (d, J = 15.1 Hz, 1H), 1.47 (s, 9H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 157.0, 148.1, 147.6, 127.2, 125.3, 111.4, 110.2, 80.5, 67.5, 56.5, 56.1, 55.9, 39.7, 28.5, 28.2 ppm; FTIR (thin film): 3451, 2929, 1688, 1611, 1519, 1464, 1454 cm^{-1}. HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd. for $C_{17}H_{26}NO_5$ 324.1811, found 324.1817.

4.7. Tert-butyl (S)-6,7-dimethoxy-1-methyl-3,4-dihydroisoquinoline-2(1H)-carboxylate (12)

To a stirred solution of **11** (0.74 g, 2.29 mmol) in dry CH_2Cl_2(20 mL) at 0 °C were added pyridine (0.46 mL, 5.72 mmol) and *p*-toluenesulfonyl chloride (0.87 g, 4.58 mmol) and the stirring was continued for 3 h. The reaction was monitored through TLC and after the complete disappearance of alcohol on it, the reaction mixture was quenched with saturated citric acid solution (5 mL) and the product was extracted with CH_2Cl_2 (3 × 15 mL), dried over anhydrous Na_2SO_4. The solvents were removed under reduced pressure, and the product was purified through column chromatography (70:30 petroleum ether/EtOAc) to get the unstable tosylated product (1.04 g, 96%). To a stirred solution of $LiAlH_4$ (0.16 g, 4.38 mmol) in dry THF (5 mL) at 0 °C was added the tosylated product obtained as above (1.04 g, 2.18 mmol) and the reaction mixture was stirred for 2 h at room temperature. After the complete disappearance of starting material on TLC, the reaction mixture was quenched carefully with saturated NH_4Cl solution (5 mL) and filtered on celite pad. The solvents were removed under reduced pressure, and the product was purified by column chromatography (80:20 petroleum ether/EtOAc) to get the desired product **12** as a colorless oil (0.61 g, 88%); $[\alpha]_D^{25} = +49.5$ (c 0.40, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 6.56 (d, J = 9.3 Hz, 2H), 5.08 (d, J = 53.4 Hz, 1H), 4.08 (d, J = 66.4 Hz, 1H), 3.82 (m, 6H), 3.15 (d, J = 29.6 Hz, 1H), 2.82 (bs, 1H), 2.60 (d, J = 15.7 Hz, 1H), 1.47 (s, 9H), 1.40 (d, J = 6.7 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 154.5, 147.6, 131.0, 130.4, 126.3, 125.9, 111.4, 109.8, 79.6, 56.1, 55.9, 50.2, 49.5, 38.0, 36.6, 28.6, 28.6, 21.9 ppm; FTIR (thin film): 2972, 2929, 2855, 1691, 1612, 1518, 1465, 1454 cm^{-1}. HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd. for $C_{17}H_{26}NO_4$ 308.1862, found 308.1866.

4.8. (S)-6,7-dimethoxy-1-methyl-1,2,3,4-tetrahydroisoquinoline (2)

To a stirred solution of **12** (0.25 g, 0.81 mmol) in dry CH_2Cl_2 (5 mL) was added trifluoroacetic acid (0.5 mL) at 0 °C. The reaction was monitored on TLC and after the complete disappearance of starting material, the solvents were removed under reduced pressure and the crude mixture was dissolved in EtOAc (4 mL) and $NaHCO_3$ (0.20 g, 2.43 mmol) was added. The mixture was stirred for 10 min to neutralize any residual acids present. The solids were filtered off, and the solution was concentrated and purified by column chromatography (93:07 CH_2Cl_2/CH_3OH) to get **2** as an oil(0.33 g, 92%); $[\alpha]_D^{25} = -45.4$ (c 0.60, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 6.61 (s, 1H), 6.55 (s, 1H), 4.04 (dd, J = 13.4, 6.8 Hz, 1H), 3.84 (s, 3H), 3.83 (s, 3H), 3.24 (m, 1H), 2.99 (m, 1H), 2.84–2.73 (m, 1H), 2.64 (m, 1H), 2.03 (s, 1H), 1.43 (d, J = 6.7 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 147.4, 147.3, 132.3, 126.8, 111.8, 109.1, 56.0, 55.9, 51.2, 41.8, 29.5, 22.8 ppm; FTIR (thin film): 2926, 2854, 1512, 1463 cm^{-1}. HRMS (ESI-TOF) m/z: $[M + H]^+$calcd. for $C_{12}H_{18}NO_2$ 208.1338, found 208.1338.

4.9. (S)-6,7-dimethoxy-1,2-dimethyl-1,2,3,4-tetrahydroisoquinoline (3)

To a stirred solution of $LiAlH_4$ (0.12 g, 3.25 mmol) in dry THF (4 mL) was added **12** (0.25 g, 0.81 mmol) dissolved in dry THF (5 mL) at 0 °C under nitrogen atmosphere. The reaction mixture was stirred for 30 min at same temperature and further it was refluxed for 8 h. After the complete disappearance of starting material on TLC, the reaction was quenched carefully with 2 N KOH solution (2 mL) and filtered through a celite pad. The solvents were removed under reduced pressure and the crude product obtained was purified by column chromatography (95:05 CH_2Cl_2/CH_3OH) to get **3** as an oil (0.16 g, 89%); $[\alpha]_D^{25} = -27.5$ (c 0.20, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 6.56 (s, 1H), 6.55 (s, 1H), 3.83 (s, 6H), 3.62 (dd, J = 13.3, 6.7 Hz, 1H), 3.12–3.03 (m, 1H), 2.79 (dd, J = 11.0, 5.3 Hz, 2H), 2.75–2.65 (m, 1H), 2.50 (s, 3H), 1.40 (d, J = 6.6 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 147.5, 147.4, 130.8, 125.4, 111.2, 109.9, 58.7, 56.0, 55.2, 48.5, 42.5, 27.0, 19.8 ppm; FTIR (thin film): 2924, 2852, 1514, 1463 cm^{-1}. HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd. for $C_{13}H_{20}NO_2$ 222.1494, found 222.1497.

4.10. Tert-butyl (R)-1-formyl-6,7-dimethoxy-3,4-dihydroisoquinoline-2(1H)-carboxylate (13)

To a stirred solution of an alcohol **11** (0.47 g, 1.47 mmol) in DMSO (10 mL) was added IBX (0.61 g, 2.20 mmol) and the reaction mixture was stirred for 3 h. After the complete disappearance of starting material on TLC, saturated $NaHCO_3$ solution (10 mL) was added and the product was extracted with EtOAc (3 × 15 mL), dried over anhydrous Na_2SO_4. The solvents were removed under reduced pressure and the product was purified by column chromatography (80:20 petroleum ether/EtOAc) to get **13** as an oil (0.43 g, 92%); $[\alpha]_D^{25} = +9.0$ (c 0.44, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 9.41 (d, J = 28.6 Hz, 1H), 6.80 (d, J = 9.7 Hz, 1H), 6.64 (s, 1H), 5.30, 5.10 (s, 1H), 3.85 (d, J = 5.2 Hz, 6H), 3.79–3.60 (m, 2H), 2.78 (bs, 2H), 1.47 (d, J = 11.5 Hz, 9H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 197.0, 196.9, 154.8, 148.8, 148.1, 128.2, 127.8, 119.1, 111.5, 110.6, 110.3, 81.4, 80.9, 64.6, 63.9, 56.1, 56.0, 41.0, 39.9, 28.7, 28.3 ppm; FTIR (thin film): 2926, 2851, 1735, 1694, 1610, 1519, 1464 cm^{-1}. HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd. for $C_{17}H_{24}NO_5$ 322.1654, found 322.1656.

4.11. Tert-butyl (S)-1-(3,4-dimethoxystyryl)-6,7-dimethoxy-3,4-dihydroisoquinoline-2(1H)-carboxylate (14)

Potassium *t*-butoxide (0.30 g, 2.74 mmol) was added to a stirring solution of (3,4-dimethoxybenzyl)triphenylphosphonium bromide (1.80 g, 3.66 mmol) in dry THF (15 mL) at 0 °C under nitrogen atmosphere and the stirring was continued at this temperature for 20 min. The aldehyde **13** (0.59 g, 1.83 mmol) in dry THF (12 mL) was added dropwise to the reaction mixture at the same temperature and the stirring was continued for next 2 h. After the complete disappearance of starting material on TLC, the reaction mixture was quenched with saturated NH_4Cl solution (10 mL). The product was extracted with EtOAc (3 × 15 mL), and dried over anhydrous Na_2SO_4. The solvents were removed under reduced pressure and the crude product was purified through column chromatography (80:20 petroleum ether/EtOAc) to get the olefin **14** as a syrup (0.77 g, 93%); $[\alpha]_D^{25} = +13.3$ (c 0.80, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ = 6.90–6.85 (m, 2H), 6.79 (d, J = 8.0 Hz, 1H), 6.64 (d, J = 2.4 Hz, 2H), 6.33 (d, J = 14.9 Hz, 1H), 6.19 (s, 1H), 5.65 (d, J = 87.8 Hz, 1H), 4.16 (s, 1H), 3.86 (s, 6H), 3.85 (s, 3H), 3.82 (s, 3H), 3.22 (s, 1H), 2.88 (t, J = 13.0 Hz, 1H), 2.65 (d, J = 15.8 Hz, 1H), 1.49 (s, 9H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ = 154.7, 149.1, 148.9, 148.0, 147.5, 131.3, 129.8, 127.4, 127.1, 127.0, 119.8, 111.4, 111.1, 110.9, 108.9, 79.9, 56.1, 56.0, 55.9, 55.9, 38.3, 28.6, 28.4 ppm; FTIR (thin film): 2932, 2835, 1689, 1603, 1583, 1515, 1463 cm^{-1}. HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd. for $C_{26}H_{34}NO_6$ 456.2386, found 456.2381.

4.12. (S)-1-(3,4-dimethoxyphenethyl)-6,7-dimethoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline (4)

To a stirred solution of **14** (0.32 g, 0.70 mmol) in EtOAc (5 mL) was added Pd/C (0.02 g) and the reaction mixture was stirred for 2 h at r.t. under hydrogen atmosphere. The reaction mixture was filtered on a celite pad and the solvents were removed under reduced pressure. The crude product obtained was transferred to a stirring solution of $LiAlH_4$ (0.10 g, 2.80 mmol) in dry THF (5 mL) at 0 °C under nitrogen atmosphere. The reaction mixture was stirred for 30 min at same temperature and further it was refluxed for 8 h. After the complete disappearance of starting material on TLC, the reaction was quenched carefully with 2 N KOH solution (2 mL) and filtered through a celite pad. The solvents were removed under reduced pressure and the crude product obtained was purified by column chromatography (95:05 CH_2Cl_2/CH_3OH) to get **4** as an oil (0.22 g, 85%); $[\alpha]_D^{25} = +5.1$ (c 0.20, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 6.73 (dd, J = 24.6, 7.4 Hz, 3H), 6.54 (d, J = 13.6 Hz, 2H), 3.83 (s, 10H), 3.81 (s, 2H), 3.41 (s, 1H), 3.15 (d, J = 7.5 Hz, 1H), 2.71 (m, 4H), 2.49 (d, J = 22.3 Hz, 4H), 2.03 (s, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 148.8, 147.3, 147.0, 135.5, 129.8, 126.7, 120.2, 111.9, 111.3, 111.3, 110.1, 62.7, 56.0, 56.0, 55.8, 48.0, 42.7, 37.1, 31.3, 25.3 ppm; FTIR (thin film): 2925, 28523, 1514, 1463 cm^{-1}. HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd. for $C_{20}H_{30}NO_4$ 372.2175, found 372.2171.

4.13. Benzyl (R)-1-(hydroxymethyl)-6,7-dimethoxy-3,4-dihydroisoquinoline-2(1H)-carboxylate (15)

To a stirred solution of **1** (0.35 g, 1.56 mmol) in THF (5 mL) at 0 °C were added $NaHCO_3$ (0.26 g, 3.12 mmol) and benzyl chloroformate (50% solution in toluene 0.66 mL, 2.34 mmol) and the reaction mixture was stirred for 4 h and then filtered, concentrated and purified by column chromatography (60:40 petroleum ether/EtOAc) to get **15** as a colorless oil (0.49 g, 90%); $[\alpha]_D^{25} = +69.6$ (c 0.26, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.44–7.26 (m, 5H), 6.67 (s, 1H), 6.60 (s, 1H), 5.19 (t, J = 19.1 Hz, 3H), 4.00 (d, J = 13.8 Hz, 1H), 3.83 (s, 6H), 3.80 (s, 1H), 3.41 (d, J = 57.1 Hz, 1H), 2.92–2.50 (m, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 157.2, 155.8, 148.2, 147.7, 136.5, 128.6, 128.2, 128.0, 124.9, 111.7, 111.4, 110.1, 109.9, 67.6, 67.1, 56.9, 56.1, 55.9, 39.5, 28.2 ppm; FTIR (thin film): 3440, 2925, 2854, 1689, 1611, 1518, 1433 cm^{-1}. HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd. for $C_{20}H_{24}NO_5$ 358.1654, found 358.1658.

4.14. Benzyl (R)-1-formyl-6,7-dimethoxy-3,4-dihydroisoquinoline-2(1H)-carboxylate (16)

Same procedure was used as **11** was converted to **13**; column chromatography (80:20 petroleum ether/EtOAc) to get **16** as a clear oil (0.48 g, 92%); $[\alpha]_D^{25} = -8.2$ (c 0.61, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 9.49 (d, J = 17.7 Hz, 1H), 7.43–7.28 (m, 5H), 6.80 (d, J = 22.8 Hz, 1H), 6.64 (s, 1H), 5.41, 5.29 (s, 1H), 5.19 (d, J = 14.1 Hz, 2H), 3.91 (m, 1H), 3.86 (d, J = 10.4 Hz, 6H), 3.72–3.57 (m, 1H), 2.78 (m, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 196.5, 156.2, 155.5, 148.9, 148.1, 136.3, 128.6, 128.2, 127.6, 119.4, 118.8, 111.5, 110.5, 110.2, 67.8, 64.3, 56.1, 56.0, 40.9, 28.4 ppm; FTIR (thin film): 2925, 2853, 1698, 1610, 1519, 1464 cm^{-1}. HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd. for $C_{20}H_{22}NO_5$ 356.1498, found 356.1498.

4.15. Benzyl (S)-6,7-dimethoxy-1-(3,4,5-trimethoxystyryl)-3,4-dihydroisoquinoline-2(1H)-carboxylate (17)

Potassium *t*-butoxide (0.17 g, 1.51 mmol) was added to a stirring solution of triphenyl(3,4,5-trimethoxybenzyl)phosphonium bromide (1.054 g, 2.02 mmol) in dry THF (10 mL) at 0 °C under nitrogen atmosphere and the stirring was continued at this temperature for 20 min. The aldehyde **16** (0.36 g, 1.01 mmol) in dry THF (8 mL) was added dropwise to the reaction mixture at the same temperature and the stirring was continued for next 2 h. After the complete disappearance of starting material on TLC, the reaction mixture was quenched with saturated NH_4Cl solution (10 mL). The product was extracted with EtOAc (3 × 15 mL), and dried over anhydrous Na_2SO_4. The solvents were removed under reduced pressure and the crude product was purified through column chromatography (80:20 petroleum ether/EtOAc)to get the olefin **17** as a syrup (0.77 g, 93%); $[\alpha]_D^{25} = -15.7$ (c 0.46, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.34 (m, 5H), 6.63 (d, J = 7.7 Hz, 2H), 6.52 (s, 2H), 6.27 (s, 2H), 5.75 (d, J = 49.2 Hz, 1H), 5.23 (s, 1H), 5.15 (d, J = 12.3 Hz, 1H), 4.18 (d, J = 33.8 Hz, 1H), 3.87 (s, 4H), 3.83 (s, 6H), 3.82 (s, 5H), 3.31 (bs, 1H), 2.91 (bs, 1H), 2.68 (d, J = 15.9 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 155.3, 153.3, 148.1, 147.6, 137.9, 136.7, 132.2, 128.6, 128.1, 126.7, 126.6, 126.4, 111.4, 110.8, 103.6, 67.4, 61.0, 56.1, 55.9, 38.5, 28.3 ppm; FTIR (thin film): 2997, 2926, 2853, 1697, 1610, 1582, 1509, 1463, 1454 cm^{-1}. HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd. for $C_{30}H_{34}NO_7$ 520.2335, found 520.2338.

4.16. (S)-2,3,9,10,11-pentamethoxy-5,6,8,13,14,14a hexahydrobenzo [5,6]azepino[2,1-a]isoquinoline (5)

To a stirred solution of **17** (0.25 g, 0.48 mmol) in EtOAc (5 mL) was added Pd/C (0.02 g) and the reaction mixture was stirred for 5 h at r.t. under hydrogen atmosphere. After the complete disappearance of starting material on TLC, the reaction mixture was filtered on a celite pad and the solvents were removed under reduced pressure. The crude product was dissolved in EtOH (7 mL) followed by addition of HCHO (37% w/w, 4.00 mL) and HCl (12 mol/L, 1.00 mL) under nitrogen atmosphere and the reaction mixture was refluxed in the dark for 12 h. After the complete disappearance of starting material on TLC, the solvents were evaporated and saturated $NaHCO_3$ solution (10 mL) was added to the residue and the product was extracted with CH_2Cl_2 (3 × 10 mL). The solvents were removed under reduced pressure and the crude product was purified through column chromatography (98:02 CH_2Cl_2/CH_3OH) to

get **5** as a clear oil (0.16 g, 83%); $[\alpha]_D^{25} = -101.0$ (c 0.60, CH_2Cl_2); ^1H NMR (400 MHz, $CDCl_3$) δ = 6.54 (s, 1H), 6.53 (s, 1H), 6.47 (s, 1H), 4.52 (d, J = 14.9 Hz, 1H), 4.13 (dd, J = 9.3, 4.4 Hz, 1H), 3.94 (d, J = 14.9 Hz, 1H), 3.86 (s, 3H), 3.85 (s, 3H), 3.83 (d, J = 1.5 Hz, 6H), 3.80 (s, 3H), 3.13 (t, J = 13.7 Hz, 1H), 2.99–2.89 (m, 1H), 2.79–2.67 (m, 2H), 2.62 (dd, J = 19.8, 8.7 Hz, 2H), 1.90 (dd, J = 13.9, 8.0 Hz, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 152.3, 151.8, 147.5, 147.0, 140.2, 138.8, 132.0, 126.1, 123.8, 111.4, 109.9, 108.1, 65.3, 61.4, 60.8, 56.0, 56.0, 55.8, 50.8, 42.7, 35.4, 31.5, 29.0 ppm; FTIR (thin film): 2925, 2853, 1597, 1518, 1493, 1462 cm^{-1}. HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd. for $C_{23}H_{30}NO_5$ 400.2124, found 400.2128.

4.17. Dibenzyl (R,E)-1-(1-(4,5-dimethoxy-2-(2-((methylsulfonyl) oxy)ethyl)phenyl)-4-ethoxy-4-oxobut-2-en-1-yl)hydrazine-1,2-dicarboxylate (18)

To a stirred solution of an aldehyde **7** (0.40 g, 1.32 mmol) in CH_3CN (12 mL) at 0 °C were added dibenzyl azodicarboxylate (DBAD), (0.43 g, 1.45 mmol) and D-proline (0.02 g, 0.13 mmol). The reaction mixture was stirred for 2 h at 0 °C and then at room temperature for next 2 h. The reaction mixture was again cooled to 0 °C and the Wittig salt $Ph_3P{=}CHCO_2Et$ (1.14 g, 3.30 mmol) in CH_2Cl_2 (7 mL) was added and stirred for additional 3 h at room temperature. The solvents were removed under reduced pressure and the product was isolated by column chromatography (60:40 petroleum ether/EtOAc) to get **18** as a syrup (0.78g, 89%); $[\alpha]_D^{25} = +16.8$ (c 0.26, CH_2Cl_2); ^1H NMR (400 MHz, DMSO-d_6, 80 °C) δ = 9.55 (s, 1H), 7.26 (s, 10H), 7.10–6.99 (m, 1H), 6.83 (s, 2H), 6.06 (s, 1H), 5.89 (s, 1H), 5.04 (d, J = 42.8 Hz, 4H), 4.31 (d, J = 30.9 Hz, 2H), 4.16–4.01 (m, 2H), 3.72 (d, J = 17.2 Hz, 3H), 3.63 (s, 3H), 3.03 (s, 1H), 3.02–2.88 (m, 4H), 1.22–1.09 (m, 3H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6, rotamers) δ = 165.9, 165.7, 157.3, 156.3, 155.5, 155.2, 149.1, 148.8, 148.4, 148.3, 147.5, 146.1, 146.0, 144.9, 136.9, 136.8, 136.7, 136.6, 129.6, 129.3, 128.9, 128.8, 128.4, 128.1, 127.8, 127.6, 123.6, 122.2, 114.2, 113.9, 111.6, 71.0, 70.8, 70.5, 67.7, 66.8, 66.1, 60.6, 56.3, 56.2, 56.1, 56.0, 55.9, 37.0, 37.0, 31.7, 31.4, 14.6 ppm; FTIR (thin film): 3311, 3063, 2958, 2935, 1713, 1519 cm^{-1}. HRMS (ESI-TOF) m/z: $[M + NH_4]^+$ calcd. for $C_{33}H_{42}N_3O_{11}S$ 688.2540, found 688.2540; HPLC (Cellulose-1 column, hexane: IPA = 90:10, flow rate: 1 mL/min, λ = 254 nm), t_R major = 59.1, t_R minor = 70.6, 93% ee.

4.18. (R)-8,9-dimethoxy-1,5,6,10b-tetrahydropyrrolo[2,1-a] isoquinolin-3(2H)-one (19)

To a stirred solution of **18** (0.60 g, 0.89 mmol) in CH_3OH (20 mL), was added Raney Ni (0.80 g, prewashed with absolute ethanol) followed by 0.05 mL of acetic acid, and the mixture was stirred for 16 h at room temperature under a hydrogen atmosphere. The reaction mixture was then filtered through a celite pad, and the solution was concentrated under reduced pressure. The crude product was dissolved in CH_3OH (10 mL) and K_2CO_3 (0.24 g, 1.78 mmol) was added and the reaction mixture was refluxed for 10 h. The reaction mixture was filtered through celite pad and the solvents were removed under reduced pressure and purified by column chromatography (92:08 CH_2Cl_2/CH_3OH) to get **19** as an oil (0.17 g, 79%); $[\alpha]_D^{25} = +171.9$ (c 0.32, CH_2Cl_2); ^1H NMR (400 MHz, $CDCl_3$) δ = 6.59 (s, 1H), 6.55 (s, 1H), 4.70 (t, J = 7.8 Hz, 1H), 4.28 (m, 1H), 3.84 (s, 3H), 3.84 (s, 3H), 2.99 (m, 1H), 2.93–2.80 (m, 1H), 2.69–2.40 (m, 4H), 1.88–1.76 (m, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 173.2, 148.1, 147.9, 129.4, 125.6, 111.7, 107.7, 56.6, 56.1, 56.0, 37.1, 31.8, 28.1, 27.8 ppm; FTIR (thin film): 2927, 2853, 1680, 1610, 1515, 1462 cm^{-1}. HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd. for $C_{14}H_{18}NO_3$ 248.1287, found 248.1281.

4.19. (R)-8,9-dimethoxy-1,2,3,5,6,10b-hexahydropyrrolo[2,1-a] isoquinoline (6)

To a stirred solution of $LiAlH_4$ (0.09 g, 2.26 mmol) in dry THF (3 mL) was added **19** (0.14 g, 0.56 mmol) dissolved in dry THF (4 mL) at 0 °C under nitrogen atmosphere. The reaction mixture was stirred for 30 min at same temperature and further it was refluxed for 8 h. After the complete disappearance of starting material on TLC, the reaction was quenched carefully with 2 N KOH solution (2 mL) and filtered through a celite pad. The solvents were removed under reduced pressure and the crude product obtained was purified by column chromatography (87:13 CH_2Cl_2/CH_3OH) to get **6** as an oil which solidified on cooling, m.p. 81 °C (0.11 g, 88%); $[\alpha]_D^{25} = +90.4$ (c 0.36, CH_2Cl_2); ^1H NMR (400 MHz, $CDCl_3$) δ = 6.58 (s, 1H), 6.54 (s, 1H), 3.82 (s, 6H), 3.53 (t, J = 7.3 Hz, 1H), 3.14 (d, J = 11.3 Hz, 1H), 3.08–2.92 (m, 2H), 2.68 (m, 3H), 2.38–2.26 (m, 1H), 1.98–1.82 (m, 2H), 1.72 (m, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 147.5, 147.4, 130.4, 126.0, 111.3, 108.9, 62.7, 56.0, 55.9, 53.1, 48.1, 30.7, 27.7, 22.3 ppm; FTIR (thin film): 2925, 2854, 2791, 1737, 1611, 1512, 1464 cm^{-1}. HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd. for $C_{14}H_{20}NO_2$ 234.1494, found 234.1490.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tet.2021.132121.

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