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Graphical Abstract

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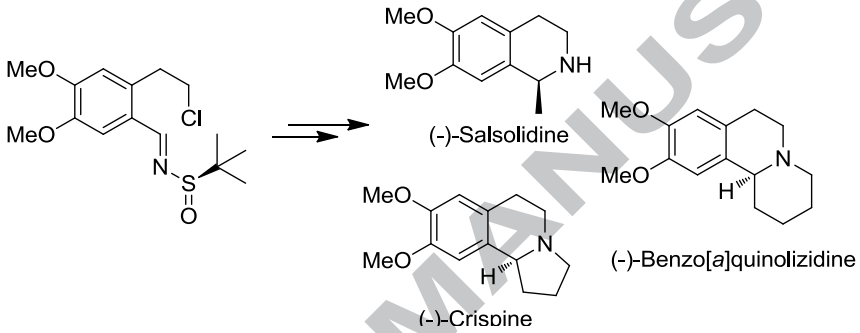

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TETRAHEDRON LETTERS

A convergent and stereoselective total synthesis of (-)-crispine A, (-)-benzo[*a*]quinolizidine and (-)-salsolidine

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Abstract: A novel strategy has been developed for the syntheses of (-)-crispine, (-)-benzo[*a*]quinolizidine and (-)-salsolidine using (*R*)-*tert*-butanesulfinamide as a source of chirality. The approach involves the stereoselective addition of Grignard reagent to chiral *N*-sulfinyl imine followed by cyclization of the secondary amide with a tethered halide as key steps.

Keywords: Asymmetric synthesis, (*R*)-*tert*-butanesulfinamide, allylation of *N*-sulfinyl imine, isoquinoline alkaloids

Crispine A was isolated from Carduus crispus plant along with crispine B and three other bicyclic isoquinoline alkaloids (Figure 1). It belongs to a family of pyrroloisoquinoline alkaloids and is used in folk medicine for the treatment of bronchitis, stenocardia, gastroenteritis and rheumatism. It also shows a promising biological activity against human cancer cell lines.[1] Therefore, crispine A has attracted many synthetic chemists to take up its total synthesis. As a result, various approaches have appeared in the literature for the synthesis of racemic crispine A.[2-4] Subsequently, stereoselective syntheses of (+)-crispine A have been reported using approaches such as asymmetric Strecker reaction,[5] asymmetric transfer hydrogenation,[6,7] asymmetric allylation of cyclic imines,[8] diastereoselective cyclization of *N*-acyliminium,[9] chemo-enzymatic deracemization,[10] α-amidoalkylation of tricyclic lactam with alkylmagnesium halide,[11] and Pictet−Spengler stereodirected cyclization.[12] Recently, an electrochemical approach has also been reported for the asymmetric synthesis of crispine A.[13] However, only a few methods have been reported for the synthesis of (-)-benzo[*a*]quinolizidine and (-)-salsolidine.[14]

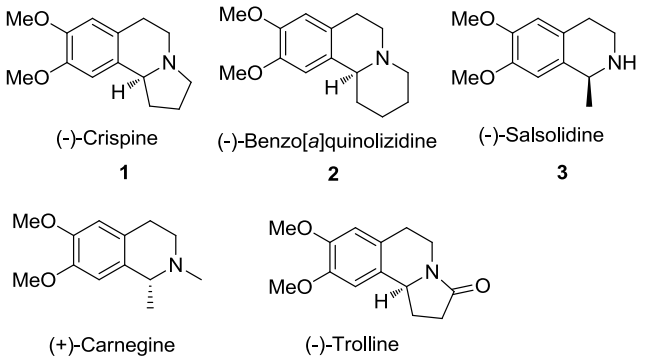
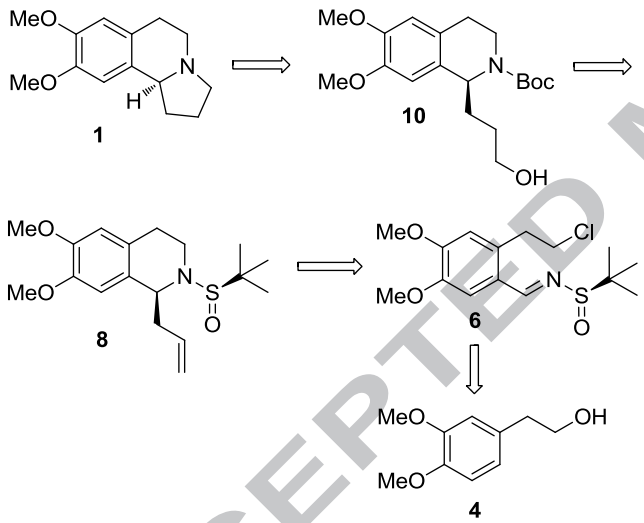


Figure 1. Examples of crispine, salsolidine and benzo[*a*]quinolizidine

N-*tert*-Butanesulfinamide is a versatile chiral auxiliary for the preparation of synthetically useful chiral amines.[15] Addition of an organometallic reagent onto enantiopure sulfinimine is one of the most elegant methods for the synthesis of chiral secondary amines. The sulfinyl group is highly stereodirecting and activates the C=N bond effectively in nucleophilic addition reactions and can easily be removed under mild conditions to afford the enantiopure amines.[16] However, the use of this useful chiral auxiliary to the total synthesis of isoquinoline alkaloids is still unexplored.

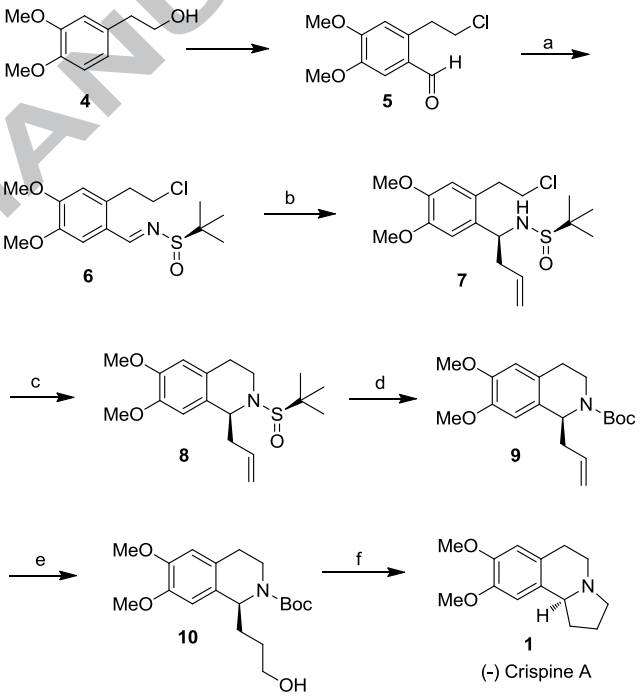
Inspired by its potential application in natural products synthesis,[16a] we wish to report the total syntheses of (-)-crispine, (-)-benzo[*a*]quinolizidine and (-)-salsolidine using *N*-*tert*-butanesulfinamide as a chiral source.

At the outset, we attempted the stereoselective total synthesis of (-)-crispine (**1**) *via* the addition of allylmagnesium bromide to enantiopure sulfinyl imine. Our retrosynthetic approach for the synthesis of (-)-crispine (**1**) is outlined in Scheme 1. Accordingly, we envisioned that (-)-crispine (**1**) could be accessed from primary alcohol **10** which in turn could be prepared by hydroboration of the olefin **9**. The key intermediate **9** was proposed to be obtained through allylation of enantiopure *N*-sulfinyl imine **6**. Aldimine **6** could be prepared by condensation of (*R*)-*tert*-butanesulfinamide with aldehyde **5** which could be derived from 2-(3,4-dimethoxyphenyl)ethanol **4**.



Scheme 1. Retrosynthetic approach of (-)-crispine

Accordingly, we began the synthesis of (-)-crispine (**1**) from commercially available 2-(3,4-dimethoxyphenyl)ethanol **4**, which was converted into the corresponding aldehyde **5** in 70% yield using a known procedure.[17] Treatment of the aldehyde **5** with (*R*)-*tert*-butanesulfinamide in the presence of anhydrous $CuSO_4$ afforded the corresponding *N*-sulfinyl imine **6** in 81% yield.[18] Addition of allylmagnesium bromide to aldimine **6** at -78 ˚C in CH_2Cl_2 gave the homoallylic sulfinamide **7** in 80% yield with 9:1 ratio of diastereomers.[19] The diastereomeric mixture could easily be separated by column chromatography. An intramolecular ring closure of a major isomer **7** in the presence of NaH in DMF at room temperature gave the cyclized product **8** in 76% yield.[20] Removal of the sulfinyl group with ethanolic HCl gave the tetrahydroisoquinoline in 85% yield.[21] The resulting free amine was then protected as a Boc derivative **9** in 80% yield by treatment with an excess of TEA in CH_2Cl_2 followed by addition of Boc anhydride.[18] Hydroboration of the terminal olefin **9** with BH_3.DMS in THF followed by oxidation with H_2O_2 in the presence of NaOH gave the primary alcohol **10** in 89% yield. Protection of **10** with mesyl chloride in the presence of Et_3N gave the mesylate which was subsequently converted into the target molecule, (-)-crispine A (**1**) in 69% yield over two steps using TMSOTf in CH_2Cl_2 (Scheme 2). The spectral data of synthetic (-)-crispine A (**1**) was in good agreement with the natural product.[1,24]

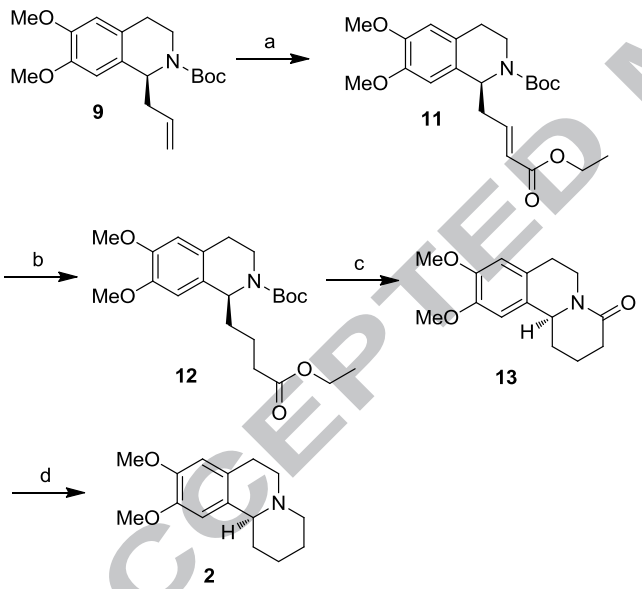


Scheme 2. Synthesis of crispine A (**1**)

Reagents and conditions: a) (*R*)-*tert*-Butanesulfinamide, $CuSO_4$, CH_2Cl_2, 25 °C, 24h, 81%; b) AllylMgBr, CH_2Cl_2, -78 °C, 1h, 80%; c) NaH, DMF, 0 °C to r.t., 6h, 76%; d) (i) EtOH-HCl, 1,4-dioxane, 0 °C to r.t., 5h; (ii) Boc_2O, Et_3N, CH_2Cl_2, r.t., 1h, 75% (over two steps); e) (i) BH_3.DMS, THF, 0 °C, 3h; (ii) H_2O_2, NaOH, r.t., 24h, 89%; (f) MsCl, Et_3N, CH_2Cl_2, r.t., 4h; (ii) TMSOTf, CH_2Cl_2, r.t., 4h, 69% (over two steps).

After successful synthesis of crispine A, we attempted the total synthesis of (-)-benzo[*a*]quinolizidine (**2**) following the above

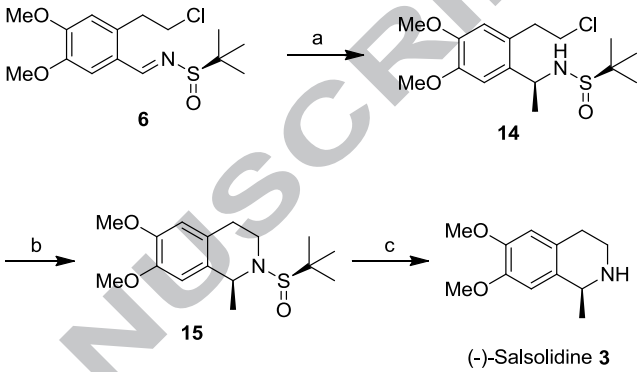
sequence of reactions to prepare the key fragment **9**. Oxidative cleavage of the terminal olefin of **9** using OsO_4, 2,6-lutidine and $NaIO_4$ gave the aldehyde in 78% yield which when subjected to Wittig olefination with a two carbon stable ylide gave the corresponding α,β-unsaturated ester **11** in 84% yield (Scheme 3).[22] Reduction of conjugated olefin **11** using $NiCl_2.6H_2O/NaBH_4$ afforded the saturated ester **12** in 81% yield. Removal of the Boc group from compound **12** with TMSOTf in CH_2Cl_2 followed by cyclization of the resulting secondary amine with a tethered ester in the presence of K_2CO_3 and 18-crown-6 in MeOH gave the lactam **13** in 79% yield (over two steps).[23] Reduction of the lactam **13** with lithium aluminum hydride (LAH) in THF afforded the (-)-benzo[*a*]quinolizidine (**2**) in 71% yield $[\alpha]_D$= -54.5, *c* = 0.6, MeOH] (Scheme 3).[6b] The optical rotation and spectral data of the (-)-benzo[*a*]quinolizidine (**2**) are in good agreement with the data reported in the literature.[14a,24]



Scheme 3. Synthesis of (-)-benzo[*a*]quinolizidine

Reagents and conditions: a) (i) OsO_4, 2,6-lutidine, $NaIO_4$, 1,4-dioxane, 2h, 78%; (ii) PPh_3CHCO_2Et, C_6H_6, 80 °C, 2h, 84%; b) $NiCl_2.6H_2O/NaBH_4$, MeOH, 0 °C to r.t., 2h, 81%; c) (i) TMSOTf, CH_2Cl_2, r.t., 5h, (ii) K_2CO_3, 18-crown-6, MeOH, r.t., 1d, 79%; (over two steps); d) LAH, THF, 70 °C, 2h, 71%.

Eventually, we extended this approach to the total synthesis of (-)-salsolidine. Accordingly, treatment of *N*-sulfinyl aldimine **6** with methylmagnesium bromide at -78 ˚C in CH_2Cl_2 gave the methyl sulfinamide **14** in 79% yield (95:5 ratio of diastereomers).[19] An intramolecular ring closure of **14** in the presence of NaH in DMF at room temperature gave the cyclized product **15** in 76% yield.[20] Removal of the sulfinyl group with ethanolic HCl gave the (-)-salsolidine **3** in 86% yield (Scheme 4). The optical rotation and spectral data of the (-)-salsolidine (**3**) are in good agreement with the data reported in literature.[14,24]



Scheme 4. Synthesis of (-)-salsolidine

Reagents and conditions: (a) MeMgBr, CH_2Cl_2, -78 °C, 2h, 79%; b) NaH, DMF, 0 °C to r.t., 6h, 76%; c) EtOH-HCl, 1,4-dioxane, 0 °C to r.t., 5h, 86%.

In summary, an efficient approach has been devised for the enantioselective syntheses of (-)-crispine, (-)-benzo[*a*]quinolizidine and (-)-salsolidine using (*R*)-*tert*-butanesulfinamide as a chiral source. The use of a readily available chiral auxilliary makes this synthesis simple, quite efficient and attractive.

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24. **Spectral data for selected compounds**

(-)-Crispine A (1):
$[\alpha]^{20}_{D}$ – 91 (*c* = 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.61 (1H, s), 6.57 (1H, s), 3.85 (6H, s), 3.53-3.44 (1H, m), 3.23-3.13 (1H, m), 3.12-2.94 (2H, m), 2.80-2.55 (3H, m), 2.40-2.27 (1H, m), 1.96-1.67 (3H, m); ^{13}C NMR (75 MHz, $CDCl_3$): δ 147.1, 130.5, 126.0, 111.2, 108.7, 62.6, 55.9, 55.7, 52.9, 48.0, 30.5, 27.7. IR (KBr): ν_{max} 3423, 2935, 1612, 1519, 1256, 1008, 755 cm^{-1}; MS (ESI): *m/z* 234 $[M+H]^+$.

(*S*)-9,10-Dimethoxy-2,3,4,6,7,11*b*-hexahydro-1*H*-pyrido[2,1-*a*]isoquinoline (2):
$[\alpha]^{20}_{D}$ – 62 (*c* = 0.5, MeOH); ^{1}H NMR (600 MHz, $CDCl_3$): δ 6.66 (1H, s), 6.58 (1H, s), 3.84 (3H, s), 3.84 (3H, s), 3.56-3.46 (1H, m), 3.31-3.10 (3H, m), 2.82-2.69 (1H, m), 2.66-2.52 (1H, m), 2.35-2.24 (1H, m), 2.08-1.50 (6H, m); ^{13}C NMR (75 MHz, $CDCl_3$): δ 148.0, 147.5, 126.3, 124.7, 111.2, 108.0, 61.7, 55.8, 55.7, 50.3, 29.5, 29.3, 26.6, 23.2. IR (KBr): ν_{max} 3415, 2927, 2855, 1608, 1516, 1259, 1028, 764 cm^{-1}; MS (ESI): *m/z* 248 $[M+H]^+$.

(-)-Salsolidine (3):
$[\alpha]^{20}_{D}$ – 54 (*c* = 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.62 (1H, s), 6.57 (1H, s), 4.06 (1H, q, *J* = 6.7 Hz), 3.85 (3H, s), 3.84 (3H, s), 3.31-3.20 (1H, m), 3.07-2.94 (1H, m), 2.87-2.73 (1H, m), 2.72-2.60 (2H, m), 1.45 (3H, d, *J* = 6.7 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 147.3, 147.2, 132.0, 126.4, 111.6, 109.0, 55.8, 55.7, 51.0, 41.4, 29.5, 22.5. IR (KBr): ν_{max} 3415, 2924, 2853, 1610, 1515, 1030, 759 cm^{-1}; MS (ESI): *m/z* 208 $[M+H]^+$.

(*R*,*E*)-*N*-(2-(2-Chloroethyl)-4,5-dimethoxybenzylidene)-2-methylpropane-2-sulfinamide (6):
$[\alpha]^{20}_{D}$ – 52 (*c* = 0.5, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.69 (1H, s), 7.41 (1H, s), 6.78 (1H, s), 3.96 (3H, s), 3.92 (3H, s), 3.76-3.65 (2H, m), 3.46-3.33 (2H, m), 1.27 (9H, s); ^{13}C NMR (75 MHz, $CDCl_3$): δ 160.4, 152.0, 148.0, 133.4, 124.6, 113.7, 112.6, 57.4, 56.0, 55.8, 44.7, 35.7, 22.4. IR (KBr): ν_{max} 3444, 2923, 2853, 1460, 1271, 770 cm^{-1}; MS (ESI): *m/z* 233 $(M+H)^+$.

(*R*,*N*)-((*S*)-1-(2-(2-Chloroethyl)-4,5-dimethoxyphenyl)but-3-enyl)-2-methylpropane-2-sulfinamide (7):
$[\alpha]^{28}_{D}$ –29 (*c* = 0.7, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.80 (1H, s), 6.61 (1H, s), 5.73-5.60 (1H, m), 5.19-5.06 (2H, m), 4.60-4.51 (1H, m), 3.81 (3H, s), 3.76 (3H, s), 3.73-3.66 (2H, m), 3.64-3.55 (1H, m), 3.10-2.99 (2H, m), 2.53-2.44 (1H, m), 2.43-2.32 (1H, m), 1.13 (9H, s); ^{13}C NMR (75 MHz, $CDCl_3$): δ 148.2, 148.1 134.1, 131.2, 128.7, 119.2, 112.9, 110.3, 55.8, 55.4, 51.8, 44.6, 43.1, 35.7, 22.5; IR (KBr): ν_{max} 3425, 2927, 1518, 1213, 1030 cm^{-1}; MS (ESI): *m/z* 374 $[M+H]^+$.

(*S*)-1-Allyl-2-((*R*)-*tert*-Butylsulfinyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (8):
$[\alpha]^{20}_{D}$ + 62 (*c* = 0.55, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.55 (1H, s), 6.52 (1H, s), 6.0-5.83 (1H, m),

5.15-5.04 (2H, m), 4.30 (1H, t, *J* = 6.7 Hz), 3.82-3.79 (6H, m), 3.50-2.91 (1H, dd, *J* = 6.7, 6.0 Hz), 3.33-3.20 (1H, m), 3.05-2.91 (1H, m), 2.77-2.46 (3H, m), 1.15 (9H, s); ^{13}C NMR (75 MHz, $CDCl_3$): δ 147.4, 146.7, 135.0, 129.3, 125.3, 117.7, 111.4, 109.7, 58.1, 55.6, 55.5, 41.1, 27.5, 22.7. IR (KBr): ν_{max} 3450, 2929, 1636, 1516, 1118, 763 cm^{-1}; MS (ESI): *m/z* 338 $[M+H]^+$.

(*S*)-*tert*-Butyl-1-allyl-6,7-dimethoxy-3,4-dihydroisoquinoline-2(1*H*)-carboxylate (9):
$[\alpha]^{20}_D$ + 109 (*c* = 0.3, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.63-6.55 (2H, m), 5.95-5.57 (1H, m), 5.21-4.94 (3H, m), 4.28-3.92 (1H, m), 3.85 (6H, s), 3.34-3.0 (1H, m), 2.97-2.73 (1H, m), 2.69-2.48 (3H, m), 1.48 (9H, s); ^{13}C NMR (75 MHz, $CDCl_3$): δ 154.6, 147.6, 147.2, 135.1, 128.9, 126.4, 117.1, 111.4, 109.8, 79.7, 55.9, 55.8. IR (KBr): ν_{max} 2972, 2926, 1691, 1517, 1166, 770 cm^{-1}; MS (ESI): *m/z* 334 $[M+H]^+$.

(*S*)-*tert*-Butyl-1-(3-hydroxypropyl)-6,7-dimethoxy-3,4-dihydroisoquinoline-2(1*H*)-carboxylate (10):
$[\alpha]^{20}_D$ + 84 (*c* = 0.25, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.63-6.56 (2H, m), 5.16 (1H, br.s), 4.22 (1H, br.s), 3.91-3.64 (8H, m), 3.31-3.05 (1H, m), 2.94-2.74 (1H, m), 2.69-2.56 (1H, m), 1.90-1.78 (2H, m), 1.74-1.58 (2H, m), 1.47 (9H, s); ^{13}C NMR (75 MHz, $CDCl_3$): δ 155.1, 147.3, 129.8, 126.0, 111.3, 110.1, 79.7, 62.7, 56.0, 55.8, 54.1, 42.6, 38.2, 33.3, 29.6, 28.4, 28.1, 22.6. IR (KBr): ν_{max} 3446, 2930, 2853, 1684, 1516, 1423, 1163, 935, 762 cm^{-1}; MS (ESI): *m/z* 374 $[M+Na]^+$.

(*S*,*E*)-*tert*-Butyl-1-(4-ethoxy-4-oxobut-2-enyl)-6,7-dimethoxy-3,4-dihydroisoquinoline-2(1*H*)-carboxylate (11):
$[\alpha]^{20}_D$ + 51.5 (*c* = 0.75, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.06-6.95 (1H, m), 6.62-6.56 (2H, m), 5.88-5.77 (1H, m), 5.12-5.06 (1H, m), 4.27-4.12 (2H, m), 3.85 (6H, s), 3.30-3.06 (2H, m), 2.92-2.76 (1H, m), 2.72-2.60 (3H, m), 1.47 (9H, s), 1.31-1.24 (3H, m); ^{13}C NMR (75 MHz, $CDCl_3$): δ 166.0, 154.2, 147.8, 147.4, 145.1, 128.0, 126.5, 123.4, 111.5, 109.5, 80.2, 60.2, 56.0, 55.8, 39.8, 36.6, 29.6, 28.2, 14.2. IR (KBr): ν_{max} 2974, 2931, 1716, 1690, 1517, 1416, 1164, 1099, 770 cm^{-1}; MS (ESI): *m/z* 428 $[M+Na]^+$.

(*S*)-*tert*-Butyl-1-(4-ethoxy-4-oxobutyl)-6,7-dimethoxy-3,4-dihydroisoquinoline-2(1*H*)-carboxylate (12):
$[\alpha]^{20}_D$ + 54 (*c* = 0.5, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.62-6.54 (2H, m), 5.01-4.91 (1H, m), 4.18-4.06 (2H, m), 3.89-3.83 (6H, m), 3.30-3.01 (2H, m), 2.97-2.74 (1H, m), 2.67-2.55 (1H, m), 2.48-2.28 (2H, m), 1.85-1.68 (4H, m), 1.48 (9H, s), 1.25 (3H, t, *J* = 6.7 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 173.2, 154.7, 147.5F, 147.2, 129.5, 126.2, 111.4, 109.7, 79.9, 60.2, 55.9, 55.8, 53.9, 38.0, 36.4, 34.0, 28.3, 27.8, 21.9, 14.1. IR (KBr): ν_{max} 2931, 1732, 1688, 1418, 1251, 1166, 1033, 769 cm^{-1}; MS (ESI): *m/z* 430 $[M+Na]^+$.

(*S*)-9,10-Dimethoxy-2,3,6,7-tetrahydro-1*H*-pyrido[2,1-*a*]isoquinolin-4-(11b*H*)-one (13):
$[\alpha]^{20}_D$ – 38.8 (*c* = 0.9, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.68 (1H, s), 6.62 (1H, s), 4.93-4.83 (1H, m), 4.66-4.57 (1H, m), 3.87 (6H, s), 2.99-2.75 (2H, m), 2.69-2.47 (3H, m), 2.46-2.31 (1H, m), 2.01-1.76 (2H, m), 1.75-1.59 (1H, m); ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.6, 147.6, 147.5, 128.8, 127.0, 111.3, 108.0, 56.5, 56.0, 55.7, 39.6, 32.0, 30.7, 28.2, 19.3. IR (KBr): ν_{max} 3422, 2931, 1612, 1514, 1260, 1222, 768 cm^{-1}; MS (ESI): *m/z* 262 $[M+H]^+$.

(*S*)-*N*-((*S*)-1-(2-(2-Chloroethyl)-4,5-dimethoxyphenyl)ethyl)-2-methylpropane-2-sulfinamide (14):
$[\alpha]^{20}_D$ – 10 (*c* = 0.3 $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.89 (1H, s), 6.62 (1H, s), 4.82-4.70 (1H, m), 3.86 (3H, s), 3.82 (3H, s), 3.78-3.58 (2H, m), 3.14-3.06 (2H, m), 1.48 (3H, d, *J* = 6.7 Hz), 1.19 (9H, s); ^{13}C NMR (75 MHz, $CDCl_3$): δ 148.8, 148.7, 133.0, 128.0, 112.8, 109.6, 55.8, 55.7, 49.0, 44.6, 35.6, 25.0, 22.5. IR (KBr): ν_{max} 3448, 2923, 2853, 1612, 1519, 1217, 1028, 692 cm^{-1}; MS (ESI): *m/z* 348 $[M+H]^+$.

(*S*)-2-((*S*)-*tert*-Butylsulfinyl)-6,7-dimethoxy-1-methyl-1,2,3,4-tetrahydroisoquinoline (15):
$[\alpha]^{20}_D$ + 28 (*c* = 0.3 $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.56 (1H, s), 6.50 (1H, s), 4.44 (1H, q, *J* = 7.5 Hz), 3.83 (6H, s), 3.50-3.38 (1H, m), 3.31-3.17 (1H, m), 3.08-2.92 (1H, m), 2.69-2.57 (1H, m), 1.54 (3H, d, *J* = 6.7 Hz), 1.19 (9H, s); ^{13}C NMR (75 MHz, $CDCl_3$): δ 147.4, 147.2, 131.0, 125.4, 111.4, 109.4, 58.0, 55.8, 55.7, 52.3, 38.0, 28.0, 23.0, 21.7. IR (KBr): ν_{max} 3449, 2927, 2855, 1613, 1517, 1122, 1029, 753 cm^{-1}; MS (ESI): *m/z* 312 $[M+H]^+$.