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Application of Unusual Grignard Reaction for the Stereoselective Synthesis of Antidepressant Drug (*R*)-(–)-Venlafaxine

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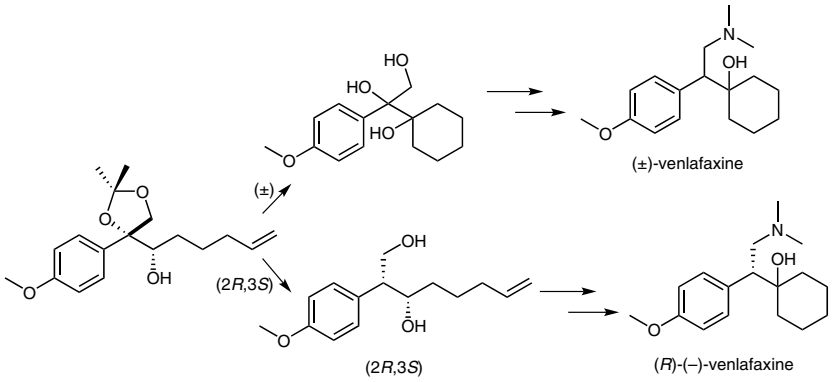

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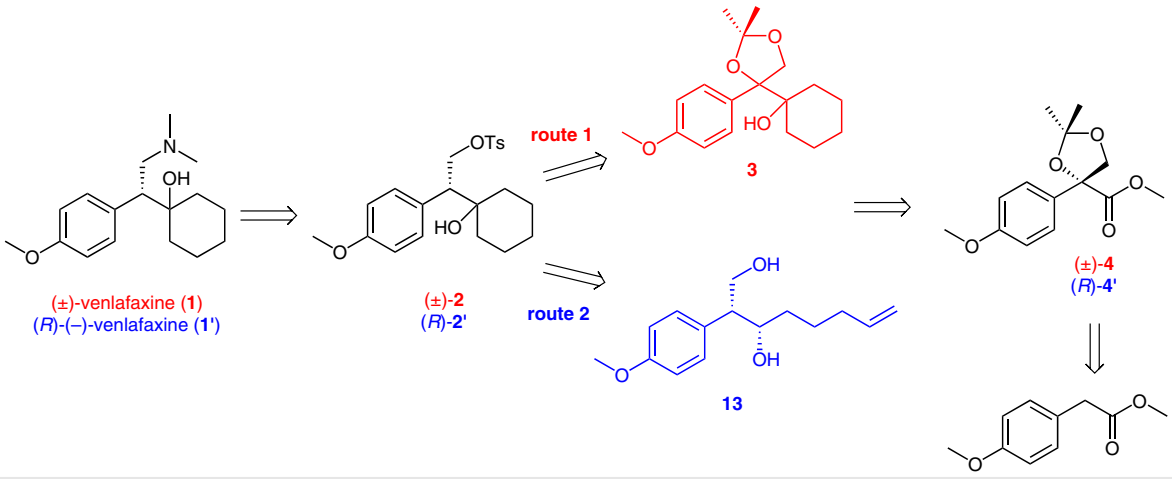
Abstract An enantioselective synthesis of antidepressant drug (*R*)-(–)-venlafaxine is accomplished as an application of recently explored unusual Grignard reaction. An innovative method for the generation of chirality at extremely reactive benzylic center along with determination of absolute stereochemistry has been discussed. The key steps involved in the synthesis include Sharpless asymmetric dihydroxylation for the induction of chirality and an unusual Grignard reaction.

Key words antidepressant drug, unusual Grignard reaction, Sharpless asymmetric dihydroxylation, reductive dehydroxylation

WHO reported that in the year 2002 among all diseases, depression was the third leading cause of burden, which is expected to show a rising trend during the next 20 years.[1] Venlafaxine (**1**) is a modern age 'in practice' antidepressant drug. It is licensed for the treatment of depression, panic disorder, social phobia, anxiety, and vasomotor symptoms as it works by altering unbalanced chemicals in brain. It is marketed in the racemic form under trade names Effexor or Effexor XR – XR for the extended release dosing property. It shows minimum protein binding property as compared to other antidepressants, hence is activity-specific and demonstrates significantly minimum risk of side effects.[2] It inhibits reuptake of biogenic amines like serotonin and norepinephrine, hence called as serotonin norepinephrine reuptake inhibitor (SNRI). (*S*)-Venlafaxine is a selective serotonin reuptake inhibitor whereas (*R*)-venlafaxine is more selective towards the norepinephrine transporter.[3] Under placebo-controlled clinical trials, the efficacy of venlafaxine was shown to be significantly superior to placebo on the Hamilton depression rating scale and clinical global impression. Venlafaxine was among the best-sold antidepressants in the world during the period ranging from 2008 to 2010.[4]

Venlafaxine possesses a chiral center at the benzylic position, a tertiary amine, and a tertiary hydroxy group, hence is a representative of phenylethylamine class of antidepressants, which have a distinctive structure. Since past few years our lab is one of the most active group in the synthesis of venlafaxine[5] although over period of time many total syntheses of this drug featuring racemic as well as chiral synthesis were reported in the literature.[6] The synthesis of (*S*)-venlafaxine was reported by Davies et al. employing Rh-catalyzed intermolecular C–H activation reaction. Later Nanda et al. reported the synthesis of both the enantiomers by employing lipase-catalyzed enzymatic kinetic resolution.[7] Recently, two asymmetric syntheses using organocatalytic Michael addition reaction by using L-proline based organocatalyst and Sharpless asymmetric epoxidation reaction approach were reported by our group.[8] We report here the synthesis of (*R*)-(–)-venlafaxine as an application of diastereoselective unusual Grignard reaction.[9]

In continuation of the ongoing research towards the enantioselective synthesis of venlafaxine, chirality induction was planned by means of Sharpless asymmetric dihydroxylation (Scheme 1, route 1). As per our reterosynthetic analysis, (*R*)-(–)-venlafaxine (**1′**) can be accessed from compound **2** by displacing the tosyl group with dimethylamine. The tosylate can be easily prepared from compound **3** by hydrogenolysis at the benzylic center. The tricyclic compound **3** can be synthesized from the acetonide protected ester **4** by means of Grignard reaction with 1,5-(dibromomagnesio)pentane.[5d] The optically active ester **4** in turn can be obtained by exomethylenation followed by Sharpless asymmetric dihydroxylation of the methyl ester of *p*-methoxyphenylacetic acid.



Scheme 1 Retrosynthetic analysis of venlafaxine

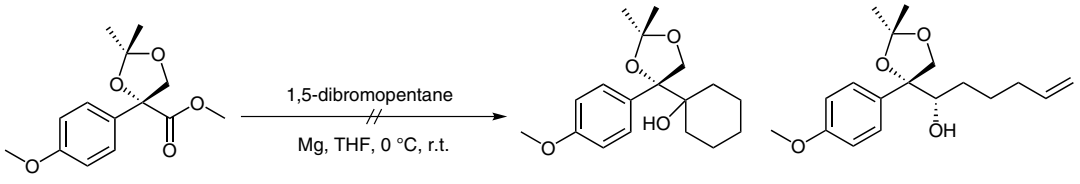
Before undertaking the asymmetric synthesis and to optimize the proposed sequence of reactions, we first executed the racemic synthesis of venlafaxine. When the acetonide **4** was treated with the Grignard reagent prepared from 1,5-dibromopentane, surprisingly it did not furnish the desired addition product **3**, instead formation of compound **7** was observed in excellent yield and diastereoselectivity (Scheme 2).[9]

With this secondary alcohol **7** in hand it was decided to proceed towards synthesis of target molecule. IBX oxidation of **7** gave the desired ketone **8** in 89% yield. Compound **8** on treatment with vinylmagnesium bromide furnished alcohol **9** in 85% yield and not completely separable diastereomeric mixture. As there is need to destroy the newly generated chiral center in the next step of the synthesis, no attempt was made to separate the diastereomers. The compound **9** was subjected to ring-closing metathesis in the presence of the Grubbs' first-generation catalyst to furnish cyclohexene **10**, which was reduced under hydrogenation conditions to afford the reduced product **3** in 95% yield (Scheme 3).

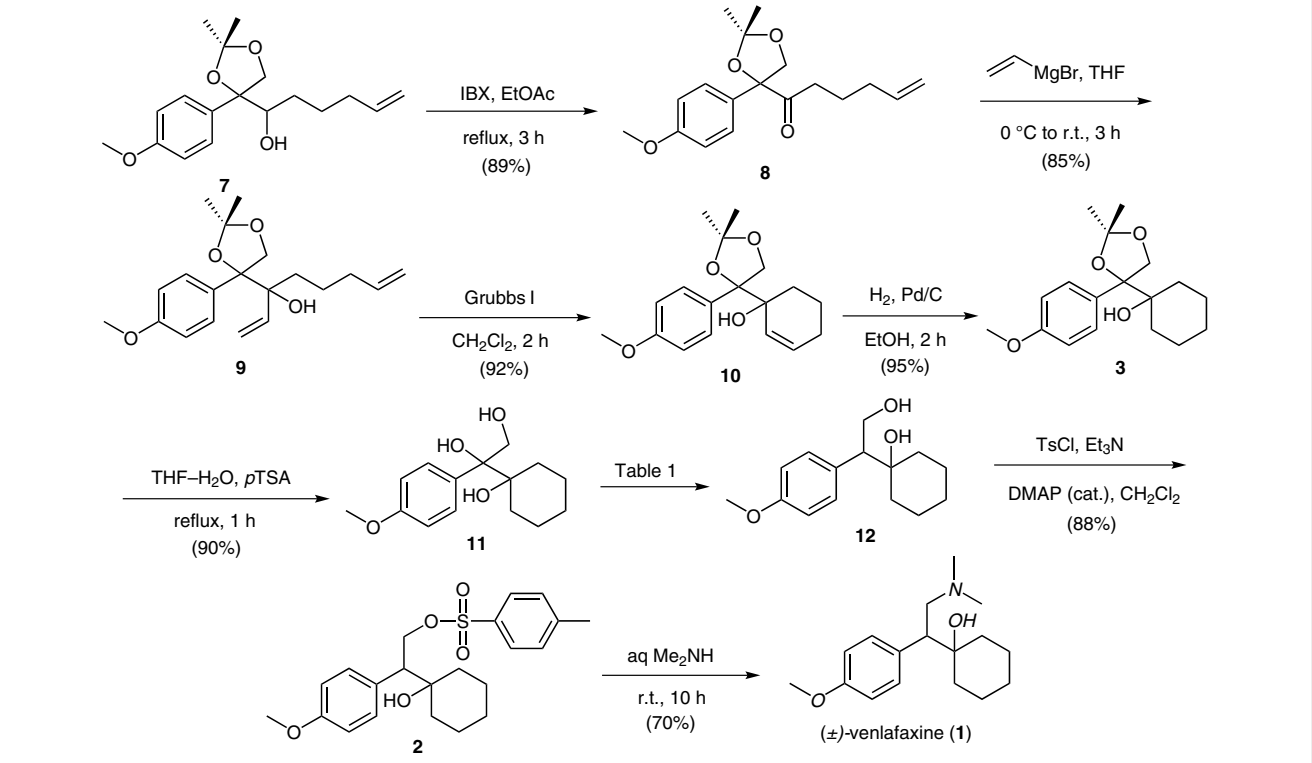
Compound **3** when refluxed in the presence of catalytic *p*-TSA in THF as a solvent for one hour gave the acetonide deprotected triol **11**. Encouraged by our previous results obtained in the case of enantioselective hydrogenolysis[10] at benzylic center in the total synthesis of optically active *ar*-himachalene, this triol **11** was subjected to hydrogenation reaction. Different hydrogenating reagents were tried for conversion of compound **11** into compound **12** (Table 1). It was found that by using Raney Ni, Pd/C, and Pearlman's catalyst, etc. the starting material (SM) was recovered unchanged. Then, ionic hydrogenation employing triethylsilane in the presence of catalytic $BF_3{\cdot}OEt_2$ was performed to furnish the product **12**. Since ionic conditions lead to the formation of carbocation, the expected product was predicted to be racemic.[10] The primary hydroxy group in compound **12** was selectively protected as its tosylate on treatment with tosyl chloride in the presence of Et_3N to furnish

Table 1 Conversion of Compound **11** into Compound **12**

Entry	Reagent	Hydrogenation conditions	Time (h)	Yield (%)
1	Raney Ni	EtOH, reflux	3	SM
2	Pd/C	H_2, EtOH	10	SM
3	Pd/C	H_2, EtOH, reflux	12	SM
4	$Pd(OH)_2$	H_2, EtOH	6–8	SM
5	$Pd(OH)_2$	H_2, EtOH, reflux	4	SM
7	cat. $BF_3{\cdot}OEt_2$	Et_3SiH, r.t./0 °C	3/5	62/55



Scheme 2 Observation of unusual Grignard reaction[9]



Scheme 3 Synthesis of (±)-venlafaxine

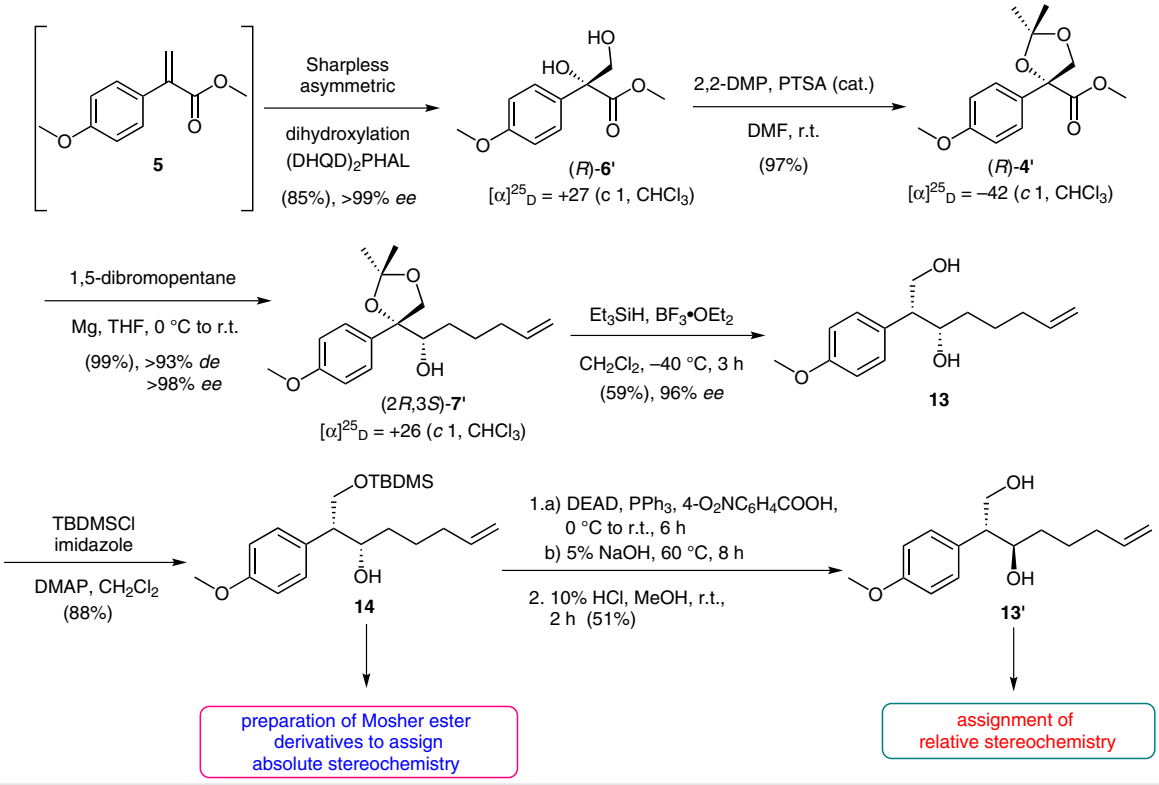
the corresponding tosyl alcohol **2**, which on displacement with aqueous dimethylamine at room temperature for 10 hours afforded (±)-venlafaxine (**1**) (Scheme 3).

The disappointment in achieving asymmetric hydrogenolysis for the synthesis of venlafaxine along with the motivating observation of diastereoselective unusual Grignard reaction, prompted us to revise the retrosynthetic analysis (Scheme 1, route 2). As the steric crowding around benzylic hydroxy in compound **11** was the suspected reason for the failure of enantioselective hydrogenolysis reaction, it was planned to reduce benzylic hydroxy functionality at an earlier stage of the synthesis of (*R*)-(–)-venlafaxine (**1′**). Accordingly, diol **13** could be obtained by unusual Grignard reaction with the acetonide protected ester (*R*)-**4′** followed by reductive dehydroxylation at benzylic position. The chiral ester (*R*)-**6′** could be obtained by Sharpless asymmetric dihydroxylation.

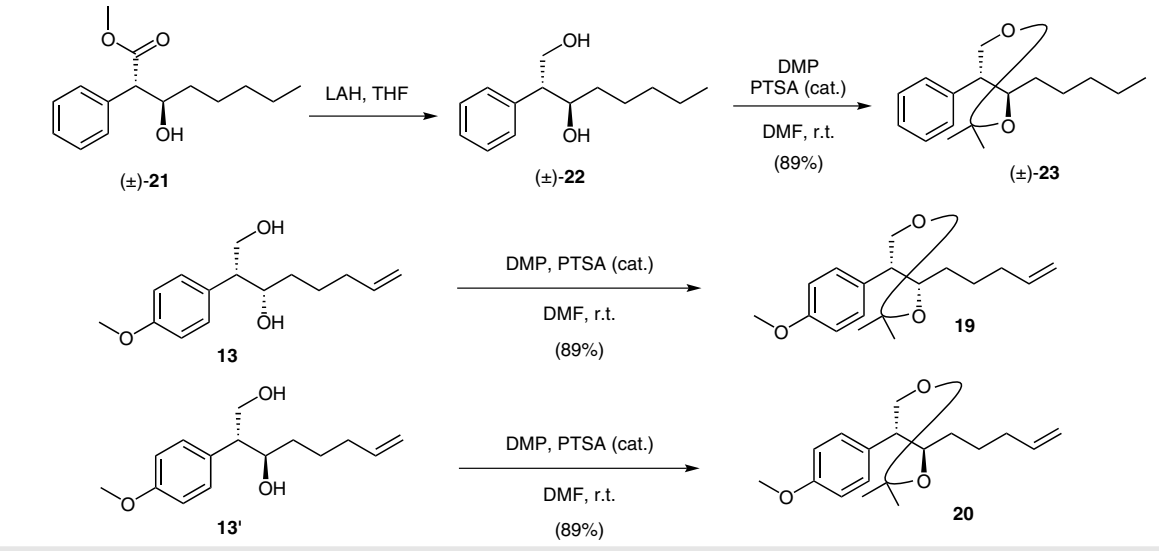
Accordingly, the exomethylene compound **5** was then subjected to Sharpless asymmetric dihydroxylation by employing $(DHQD)_2PHAL$ as the chiral catalyst to furnish diol (*R*)-**6′** in 85% yield and in 99% *ee* (Scheme 4). The diol (*R*)-**6′** was protected as its acetonide and then subjected to the unusual Grignard reaction to furnish (*R*)-**7′** with >98% *ee*, which proves that the Grignard reaction was highly diastereoselective as well as enantioselective. Deoxygenation of tertiary alcohol in (*R*)-**7′** using triethylsilane and catalytic $BF_3{\cdot}OEt_2$ was carried out at –40 °C. Although this transformation involved formation of benzylic carbocation, deoxygenated product **13** was obtained with excellent diastereoselectivity and enantioselectivity (96% *ee*).[11] The primary alcohol in **13** was selectively protected as its TBDMS ether to furnish compound **14**.

The *syn* relative configuration in compound **14** was determined by inverting the free secondary hydroxyl chiral center by treatment under Mitsunobu reaction conditions[12] as well as by preparation of acetonide compounds **19** and **20**, furthermore comparing reported literature for similar compounds (Scheme 5,Table 2).[13] The absolute stereochemistry at benzylic position was established based on the relative stereochemistry with respect to the secondary alcohol, after careful ^1H NMR analysis of both the enantiomers of Mosher's esters prepared from compound **14**, which was assigned to be '*R*'.[14] This established that the transformation of compound (*R*)-**7** to compound (2*R*,3*S*)-**13** took place as a result of inversion of configuration at the benzylic carbon.

Having established the relative and absolute stereochemistry, attention was focused towards completion of (*R*)-(–)-venlafaxine (**1′**). Accordingly, oxidation of secondary hydroxy group in compound (2*R*,3*S*)-**14** with Dess–Martin periodinane was carried out to obtain ketone (*R*)-**15** with >92% *ee*.[11] This protected ketone (*R*)-**15** was subjected to the Grignard reaction with vinylmagnesium bromide to furnish the alcohol **16** in 85% yield. The alcohol **16** was treated under ring-closing metathesis conditions in the

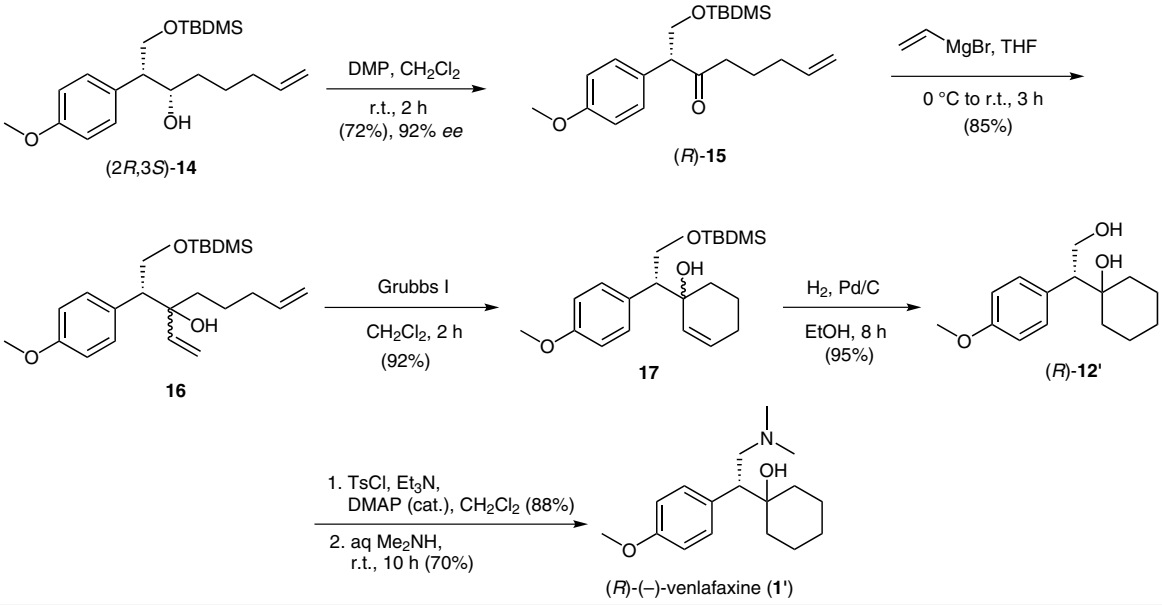


Scheme 4 Synthesis of chiral diol



Scheme 5 Determination of relative configuration

presence of Grubbs' first-generation catalyst to obtain cyclohexene **17** in 92% yield. Subjecting compound **17** to hydrogenation for eight hours led to the double bond reduction along with TBDMS deprotection to furnish diol (*R*)-**12'**.[15] Following the same sequence of reactions as in the racemic synthesis, compound (*R*)-**12'** was converted into (*R*)-(–)-venlafaxine (**1'**) with 97% *ee* after recrystallization (Scheme 6).[11,16] The venlafaxine thus obtained matched well with the reported spectroscopic data in the literature.[8] By employing $(DHQ)_2PHAL$ as the chiral catalyst in



Scheme 6 Completion of synthesis of (*R*)-(–)-venlafaxine

Table 2 Comparison of Data to Assign Relative Configuration

Compound	Diol[a]	Its acetonide[a]
Known compound	13.2, **8.4**, 4.5 [(±)-**22**]	16.3, **10.4**, 5.4 [(±)-**23**]
Before Mitsunobu reaction	11.1, **6.8**, 4.5 [(2*R*,3*S*)-**13**]	11.2, **6.8**, 4.6 (**19**)
After Mitsunobu reaction	13.1, **8.2**, 4.8 [(2*R*,3*R*)-**13'**]	16.4, **10.8**, 5.5 (**20**)

[a] *J* (coupling constant) values at benzylic CH (in Hz).

Sharpless asymmetric dihydroxylation reaction the '*S*' enantiomer also could be prepared following the above reaction sequence.

In conclusion, we have accomplished the synthesis of (±)-venlafaxine (**1**) along with the enantioselective synthesis of (*R*)-(–)-venlafaxine (**1'**) as an application of diastereoselective and enantioselective unusual Grignard reaction. The synthetic sequence involved Sharpless asymmetric dihydroxylation reaction for chirality induction and unusual diastereoselective Grignard reaction for the installation of secondary alcohol followed by stereoselective dehydroxylation.

The ^{1}H NMR spectra were recorded on 200, 400, and 500 MHz NMR spectrometer using TMS as the internal standard. The ^{13}C NMR spectra were recorded on 200 NMR spectrometer (50 MHz), 400 NMR spectrometer (100 MHz), and 500 NMR spectrometer (125 MHz). Mass spectra were recorded on a MS-TOF mass spectrometer. The IR spectra were recorded on a PerkinElmer 1760 FT IR spectrometer. Mg metal turnings were activated, washed, and dried before use. Commercially available *p*-methoxyphenylacetic acid, 1,5-dibromopentane, OsO_4, *N*-methylmorpholine *N*-oxide (NMO), AD-mix-β, and Grubbs' first-generation catalyst were used as received.

1-[4-(4-Methoxyphenyl)-2,2-dimethyl-1,3-dioxolan-4-yl]hex-5-en-1-one (8)

Compound **7** (1.50 g, 1.00 mmol) was dissolved in EtOAc (8 mL), and IBX (3.75 g, 2.50 mmol) was added in one portion. The resulting suspension was refluxed at 80 °C and stirred vigorously. After 3 h, the reaction mixture was cooled to r.t., filtered, and washed with EtOAc (3 × 10 mL), and the combined filtrates were concentrated to furnish **8** (1.32 g, 89%) as a colorless oil.

IR ($CHCl_3$): 2948, 1710, 1660, 1558, 1492 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.29 (d, *J* = 8.85 Hz, 2 H), 6.84 (d, *J* = 8.85 Hz, 2 H), 5.75–5.55 (m, 1 H), 4.90–4.81 (m, 2 H), 3.78 (s, 3 H), 2.76–2.60 (m, 1 H), 2.48–2.32 (m, 1 H), 1.96–1.84 (m, 2 H), 1.62–1.51 (m, 2 H), 1.48 (s, 3 H), 1.42 (s, 3 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 209.8, 159.4, 137.9, 130.7, 126.0, 115.1, 114.0, 111.0, 89.8, 71.9, 55.1, 35.7, 32.9, 26.7, 25.8, 22.5.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{18}H_{24}O_4Na$: 327.3231; found: 327.3228.

3-[4-(4-Methoxyphenyl)-2,2-dimethyl-1,3-dioxolan-4-yl]octa-1,7-dien-3-ol (9)

A solution of **8** (3.00 g, 20 mmol) in anhyd THF (15 mL) was added dropwise to a solution of vinylmagnesium bromide (12.0 mL of a 1.7 M solution in THF, 22 mmol) at 0 °C. After 30 min, the reaction was quenched with sat. aq NH_4Cl (10 mL). The organic phase was then extracted with Et_2O, the combined extracts were washed with H_2O and brine, dried (anhyd Na_2SO_4), filtered, and concentrated under reduced pressure. The crude residue obtained was purified by column chromatography using 200–400 mesh silica gel (8% EtOAc–PE) to furnish **9** (2.77 g, 85%) as a colorless oil.

IR ($CHCl_3$): 3435, 2968, 1610, 1525, 1393, 1272 cm^{-1}.

Data for pure diastereomer

^1H NMR (200 MHz, $CDCl_3$): δ = 7.28 (d, *J* = 8.85 Hz, 2 H), 6.81 (d, *J* = 8.85 Hz, 2 H), 5.76–5.62 (m, 2 H), 5.29–5.15 (m, 2 H), 4.94–4.83 (m, 2 H), 4.45 (d, *J* = 8.34 Hz, 1 H), 4.15 (d, *J* = 8.34 Hz, 1 H), 3.78 (s, 3 H), 1.96–1.85 (m, 2 H), 1.59–1.50 (m, 1 H), 1.47 (s, 3 H), 1.41–1.19 (m, 3 H), 1.15 (s, 3 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 158.8, 139.3, 138.6, 134.3, 128.5, 114.6, 114.5, 112.8, 110.0, 88.7, 77.9, 71.7, 55.0, 34.4, 34.0, 26.4, 26.0, 22.4.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{20}H_{28}O_4Na$: 355.4828; found: 355.4825.

1-[4-(4-Methoxyphenyl)-2,2-dimethyl-1,3-dioxolan-4-yl]cyclohex-2-en-1-ol (10)

In a round-bottomed flask, Grubbs I catalyst (0.720 g, 1.2 mmol, 0.2 equiv) was dissolved in anhyd CH_2Cl_2 (8 mL). To this solution was added **9** (2.00 g, 6 mmol, 1 equiv) and stirred for 2 h. After complete consumption of the starting material, the reaction mixture was filtered and washed with CH_2Cl_2 (3 × 3 mL). The solvent extracts were combined and evaporated under reduced pressure. The crude residue was purified by silica gel column chromatograpy using PE–EtOAc (3:1) to afford **10** (1.68 g, 92%) as a colorless oil.

IR ($CHCl_3$): 3466, 2931, 1393 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ (*dr* 6:**4**) = 7.30 (d, *J* = 8.34 Hz, 2 H), 6.80 (d, *J* = 8.34 Hz, 2 H), 6.01–5.63 (m, 2 H), 4.61 (d, *J* = 8.59 Hz, 0.63 H), **4.47** (d, *J* = 8.21 Hz, 0.37 H), 4.24–4.05 (m, 1 H), 3.78 (s, 3 H), 2.15–1.80 (m, 3 H), 1.72–1.56 (m, 2 H), 1.53 and 1.48 (s, 3 H), 1.42–1.28 (m, 1 H), 1.23 and 1.16 (s, 3 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ (*dr* 6:**4**) = **158.6**, 158.5, 134.7, **134.4**, 133.7, 131.3, 128.9, 128.27, **128.21**, 127.5, 112.6, 110.0, **88.9**, 88.3, **72.3**, 72.1, **71.6**, 70.9, 54.9, **31.8**, 31.1, 26.3, **26.0**, 25.6, **25.0**, 24.9, 18.2, **18.1**.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{18}H_{24}O_4Na$: 327.6936; found: 327.6935.

1-[4-(4-Methoxyphenyl)-2,2-dimethyl-1,3-dioxolan-4-yl]cyclohexan-1-ol (3)

To a stirred solution of **10** (1.5 g, 4.9 mmol) in anhyd EtOH (5 mL) was added a catalytic amount of 10% Pd/C and the resulting reaction mixture was vigorously stirred at r.t. for 2 h under H_2 atmosphere (1–2 psi). After complete consumption of the starting material, as monitored by TLC, the reaction mixture was filtered through a short pad of Celite and washed carefully with EtOH. The EtOH extracts were combined and evaporated under reduced pressure. The crude product thus obtained was subjected to column chromatography using 60–120 mesh silica gel with EtOAc–PE (15%) as an eluent to furnish **3** (1.43 g, 95%) as a colorless oil.

IR ($CHCl_3$): 3475, 2930, 1608, 1293 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 7.30 (d, *J* = 8.85 Hz, 2 H), 6.83 (d, *J* = 8.85 Hz, 2 H), 4.53 (d, *J* = 8.47 Hz, 1 H), 4.20 (d, *J* = 8.47 Hz, 1 H), 3.81 (s, 3 H), 1.83 (br s, 1 H), 1.62–1.55 (m, 4 H), 1.50 (s, 3 H), 1.38–1.24 (m, 4 H), 1.30 (s, 3 H), 1.12–0.91 (m, 2 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 158.6, 134.6, 128.3, 112.7, 109.7, 89.7, 73.8, 70.8, 55.1, 32.1, 31.6, 26.4, 26.1, 25.5, 21.5, 21.3.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{18}H_{26}O_4Na$: 329.4020; found: 329.4022.

1-(1-Hydroxycyclohexyl)-1-(4-methoxyphenyl)ethane-1,2-diol (11)

To a stirred solution of **3** (1.0 g, 1.1 mmol) in THF–H_2O (1:1, 12 mL) was added a catalytic amount of *p*-TSA. The resulting reaction mixture was heated at 65 °C for 1 h. After completion of the reaction, the mixture was cooled to r.t., extracted with EtOAc (3 × 20 mL), followed by subsequent washings with aq $NaHCO_3$ (3 × 25 mL). The organic extracts were dried (anhyd Na_2SO_4), and filtered. The solvent was removed under reduced pressure to afford **11** (0.869 g, 90%) as a white semisolid.

IR ($CHCl_3$): 3435, 3075, 2932, 1620, 1560, 1219 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 7.37 (d, *J* = 8.84 Hz, 2 H), 6.85 (d, *J* = 8.84 Hz, 2 H), 4.16–3.96 (m, 2 H), 4.24 (d, *J* = 11.50 Hz, 1 H), 3.89 (d, *J* = 11.50 Hz, 1 H), 3.80 (s, 3 H), 1.89–1.65 (m, 4 H), 1.59–1.38 (m, 6 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 158.7, 132.8, 128.0, 113.2, 79.7, 76.3, 66.3, 55.1, 31.6, 31.4, 25.5, 21.6, 21.0.

HRMS (ESI): *m*/*z* [M + 1]$^+$ calcd for $C_{15}H_{23}O_4$: 267.5621; found: 267.5618.

1-[2-Hydroxy-1-(4-methoxyphenyl)ethyl]cyclohexanol (12)

To a stirred solution of **11** (0.8 g, 3 mmol, 1 equiv) in anhyd CH_2Cl_2 (6 mL) at 0 °C was added Et_3SiH (0.693 mL, 6 mmol, 2 equiv) followed by $BF_3{\cdot}OEt_2$ (0.20 mL, 0.5 equiv). The reaction mixture was warmed to r.t. over 30 min and stirred for 3 h. After completion of the reaction, mixture was quenched by the addition of sat. aq $NaHCO_3$ (5 mL) and extracted with CH_2Cl_2 (3 × 15 mL). The combined organic layers were washed with brine (10 mL), dried (anhyd Na_2SO_4), and filtered. Evaporation of solvent and purification of the residue by chromatography on a 60–120 mesh silica gel column (eluent: 40% EtOAc–PE) furnished **12** (0.46 g, 62%) as a colorless oil.

IR ($CHCl_3$): 3461, 3002, 2936, 2589, 1612 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 7.19 (d, *J* = 8.59 Hz, 2 H), 6.84 (d, *J* = 8.72 Hz, 2 H), 4.16–3.96 (m, 2 H), 3.79 (s, 3 H), 2.80 (t, *J* = 6.44 Hz, 1 H), 2.25 (br s, 2 H), 1.74–1.25 (m, 10 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 158.6, 131.3, 130.5, 113.8, 74.0, 63.3, 56.2, 55.1, 36.7, 34.7, 25.6, 21.7, 21.6.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{15}H_{22}O_3Na$: 273.3329; found: 273.3332.

2-(1-Hydroxycyclohexyl)-2-(4-methoxyphenyl)ethyl 4-Methylbenzenesulfonate (2)

A round-bottomed flask was charged with **12** (0.250 g, 1 mmol, 1.00 equiv) and anhyd CH_2Cl_2 (10 mL). To the resulting solution were added DMAP (0.087 g, 0.6 mmol, 0.6 equiv), TsCl (0.339 g, 1.5 mmol, 1.5 equiv), and Et_3N (0.16 mL, 1 mmol, 1.00 equiv) and the mixture was stirred for 5 h at 0 °C. The suspension was diluted with Et_2O (20 mL) and stirred for an additional 30 min. The solution was then washed sequentially with 10% aq $NaHCO_3$ (2 × 10 mL) and brine (20 mL). The combined organic layers were dried (anhyd Na_2SO_4), filtered, and concentrated under reduced pressure. The crude residue was purified by chromatography on a 200–400 mesh silica gel column using 8% EtOAc–PE as an eluent to furnish pure **2** (0.355 g, 88%) as a pale yellow solid; mp 108 °C.

IR ($CHCl_3$): 3056, 2952, 1611, 1312, 1132, 725 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 7.57 (d, *J* = 8.24 Hz, 2 H), 7.25 (d, *J* = 7.93 Hz, 2 H), 6.97 (d, *J* = 8.54 Hz, 2 H), 6.74 (d, *J* = 8.55 Hz, 2 H), 4.61 (dd, *J* = 9.76, 4.88 Hz, 1 H), 4.30 (t, *J* = 9.46 Hz, 1 H), 3.78 (s, 3 H), 2.91 (dd, *J* = 8.85, 5.19 Hz, 1 H), 2.44 (s, 3 H), 1.68–1.64 (m, 2 H), 1.67 (br s, 1 H), 1.54–1.50 (m, 3 H), 1.42–1.37 (m, 3 H), 1.22–1.16 (m, 2 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 158.6, 144.2, 133.1, 130.2, 129.6, 127.9, 113.6, 72.6, 70.6, 55.0, 53.7, 36.2, 36.1, 25.4, 21.8, 21.6.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{22}H_{28}O_5SNa$: 427.1690; found: 427.1692.

1-[2-(Dimethylamino)-1-(4-methoxyphenyl)ethyl]cyclohexan-1-ol [1, (±)-Venlafaxine]

To a stirred solution of **2** (0.220 g, 0.5 mmol, 1.0 equiv) was added 40% aq Me_2NH (3 mL). The resultant reaction mixture was stirred at r.t. for 10 h. After completion of the reaction, the mixture was concentrated under reduced pressure at 60 °C to furnish a crude residue. The crude residue was subjected to further purification by chromatography on a 60–120 mesh silica gel column to give **1** (0.105 g, 70%), and after recrystallization from EtOAc (64%) as a white solid; mp 286 °C.[8]

IR ($CHCl_3$): 3164, 2982, 2938, 2860, 1610 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.03 (d, *J* = 8.84 Hz, 2 H), 6.79 (d, *J* = 8.84 Hz, 2 H), 3.78 (s, 3 H), 3.32 (t, *J* = 12.30 Hz, 1 H), 2.95 (dd, *J* = 12.30, 3.29 Hz, 1 H), 2.35 (s, 3 H), 2.31–2.28 (m, 1 H), 1.78–1.26 (m, 8 H), 1.03–0.88 (m, 2 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 158.3, 132.6, 130.3, 130.1, 113.4, 74.1, 61.2, 55.1, 51.7, 45.4, 38.0, 31.2, 26.0, 21.6, 21.3.

MS (ESI): *m*/*z* = 278 [M + 1]$^+$.

(2*R*,3*S*)-2-(4-Methoxyphenyl)oct-7-ene-1,3-diol [(2*R*,3*S*)-13]

To a solution of (2*R*,3*S*)-**7′** (1.5 g, 1 mmol, 1 equiv) in anhyd CH_2Cl_2 (3 mL) was added Et_3SiH (1.38 mL, 2 mmol, 2 equiv) followed by $BF_3{\cdot}OEt_2$ (0.39 mL, 0.5 mmol, 0.5 equiv) and the resulting suspension was stirred at –40 °C over 3 h. After completion of the reaction, the mixture was quenched by careful addition of sat. aq NH_4Cl (0.5 mL), warmed to r.t., and extracted with CH_2Cl_2 (3 × 15 mL). The combined organic layers were washed with brine (10 mL) and dried (anhyd Na_2SO_4). Evaporation of solvent and purification of the residue by chromatography on a 200–400 mesh silica gel column (20% EtOAc–PE) furnished (2*R*,3*S*)-**13** (0.385 g, 59%) as a white solid; mp 64 °C; $[\alpha]_D^{25}$ +30 (*c* 1, $CHCl_3$).

IR ($CHCl_3$): 3482, 2925, 2860, 1616, 1435, 1069 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.22 (d, *J* = 8.59 Hz, 2 H), 6.89 (d, *J* = 8.59 Hz, 2 H), 5.78 (ddt, *J* = 16.93, 11.11, 6.57 Hz, 1 H), 5.03–4.88 (m, 2 H), 4.08–3.84 (m, 3 H), 3.80 (s, 3 H), 2.84 (ddd, *J* = 11.11, 6.57, 4,55 Hz, 1 H), 2.08–1.99 (m, 2 H), 1.83 (br s, 2 H), 1.59–1.32 (m, 4 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 158.7, 138.5, 130.22, 130.21, 114.5, 113.9, 72.3, 64.5, 55.1, 52.2, 34.3, 33.5, 25.1.

MS (ESI): *m*/*z* = 273 [M + Na]$^+$.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{15}H_{22}O_3Na$: 273.0659; found: 273.0655.

(2*R*,3*S*)-1-[(*tert*-Butyldimethylsilyl)oxy]-2-(4-methoxyphenyl)oct-7-en-3-ol [(2*R*,3*S*)-14]

To a stirred solution of (2*R*,3*S*)-**13** (1.20 g, 4.8 mmol, 1.0 equiv) in anhyd CH_2Cl_2 (10 mL) waas added TBDMSCl (0.705 g, 4.8 mmol, 1.0 equiv) followed by the addition of imidazole (0.480 g, 7.2 mmol, 1.5 equiv) and DMAP (0.058 g, 0.48 mmol, 0.1 equiv). The reaction mixture was stirred at r.t. for 3 h and then diluted with CH_2Cl_2 (10 mL). The CH_2Cl_2 layer was washed with aq NH_4Cl (10 mL) and the aqueous layer was extracted with CH_2Cl_2 (3 × 15 mL). The combined organic layers were dried (anhyd Na_2SO_4), filtered, and concentrated under reduced pressure. The crude residue was purified by chromatography on a 200–400 mesh silica gel column using 10% EtOAc–PE ether to furnish (2*R*,3*S*)-**14** (1.53 g, 88%) as a pale yellow viscous oil; $[\alpha]_D^{25}$ –28 (*c* 1, $CHCl_3$).

IR ($CHCl_3$): 3438, 2936, 2861, 1614, 1461, 1269 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.18 (d, *J* = 8.55 Hz, 2 H), 6.82 (d, *J* = 8.54 Hz, 2 H), 5.77 (ddt, *J* = 17.09, 10.38, 6.72 Hz, 1 H), 4.98–4.90 (m, 2 H), 4.03–3.98 (m, 2 H), 3.87 (dd, *J* = 9.76, 4.88 Hz, 1 H), 3.79 (s, 3 H), 2.76–2.73 (m, 1 H), 2.06–2.01 (m, 2 H), 1.62–1.55 (m, 2 H), 1.45–1.39 (m, 2 H), 0.89 (s, 9 H), 0.02 (s, 6 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 158.3, 138.7, 131.3, 130.2, 114.4, 113.5, 72.7, 65.6, 55.1, 51.4, 34.0, 33.6, 25.8, 25.3, 18.1, –5.6.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{21}H_{36}O_3SiNa$: 387.2326; found: 387.2324.

(*R*)-1-[(*tert*-Butyldimethylsilyl)oxy]-2-(4-methoxyphenyl)oct-7-en-3-one [(*R*)-15]

The alcohol (2*R*,3*S*)-**14** (0.8 g, 2.2 mmol, 1.0 equiv) was dissolved in anhyd CH_2Cl_2 (35 mL) and stirred at 0 °C in an ice bath. To this solution was added Dess–Martin periodinane (1.12 g, 3.3 mmol, 1.5 equiv) in one portion and the reaction mixture allowed to stir at r.t. for 1 h. The reaction was quenched at 0 °C by stirring with sat. aq $Na_2S_2O_3$ and $NaHCO_3$ (1:1, 20 mL) for 10 min to destroy any unreacted Dess–Martin reagent. The mixture was poured into a separatory funnel and extracted with CH_2Cl_2 (3 × 20 mL). The organic layers were combined and washed with brine, dried (anhyd Na_2SO_4), filtered, and concentrated under reduced pressure to furnish (*R*)-**15** (0.572 g, 72%) as almost pure product, which was isolated as a colorless oil; $[\alpha]_D^{25}$ –32 (*c* 1, $CHCl_3$).

IR ($CHCl_3$): 2967, 1713, 1611, 1510 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.15 (d, *J* = 8.71 Hz, 2 H), 6.85 (d, *J* = 8.71 Hz, 2 H), 5.80–5.60 (m, 1 H), 4.19 (dd, *J* = 9.35, 8.84 Hz, 1 H), 3.88 (dd, *J* = 8.84, 5.24 Hz, 1 H), 3.78 (s, 3 H), 3.65 (dd, *J* = 9.35, 5.24 Hz, 1 H), 2.47–2.29 (m, 2 H), 2.03–1.91 (m, 2 H), 1.69–1.58 (m, 2 H), 0.84 (s, 9 H), –0.01 (s, 3 H), –0.02 (s, 3 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 209.7, 158.9, 137.9, 129.4, 128.0, 115.0, 114.0, 65.0, 59.9, 55.2, 42.3, 32.9, 25.8, 22.5, 18.2, –5.58.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{21}H_{34}O_3SiNa$: 385.2168; found: 385.2165.

3-{2-[(*tert*-Butyldimethylsilyl)oxy]-1-(4-methoxyphenyl)ethyl}octa-1,7-dien-3-ol (16)

Compound **16** was prepared as per the previously mentioned experimental procedure for compound **9**; yield: 2.38 g from 2.50 g (88%); colorless oil.

Data for pure diastereomer

IR ($CHCl_3$): 3449, 2941, 1611, 1252, 1090 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.30 (d, *J* = 8.84 Hz, 2 H), 6.83 (d, *J* = 8.84 Hz, 2 H), 5.87–5.61 (m, 2 H), 5.41 (dd, *J* = 17.05, 2.03 Hz, 1 H), 5.21 (dd, *J* = 10.49, 2.03 Hz, 1 H), 4.97–4.32 (m, 2 H), 4.15 (dd, *J* = 9.86, 4.17 Hz, 1 H), 4.08 (br s, 1 H), 3.88 (dd, *J* = 9.86, 4.17 Hz, 1 H), 3.80 (s, 3 H), 2.63 (t, *J* = 4.17 Hz, 1 H), 1.96–1.85 (m, 2 H), 1.43–1.37 (m, 2 H), 1.34–1.28 (m, 2 H), 0.89 (s, 9 H), –0.03 (s, 6 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 158.4, 143.6, 138.8, 132.1, 130.9, 114.3, 113.7, 113.3, 78.4, 66.3, 55.0, 53.4, 38.1, 34.1, 25.8, 22.6, 18.1, –5.7.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{23}H_{38}O_3SiNa$: 413.2482; found: 413.2480.

1-{2-[(*tert*-Butyldimethylsilyl)oxy]-1-(4-methoxyphenyl)ethyl}cyclohex-2-enol (17)

Compound **17** was prepared as per the previously mentioned experimental procedure for compound **10**; yield: 0.620 g from 0.690 g (92%); colorless oil; $[\alpha]_D^{25}$ +15 (*c* 1, $CHCl_3$).

IR ($CHCl_3$): 3460, 2931, 2868, 1611, 1350, 1096 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.23 (d, *J* = 8.80 Hz, 2 H), 6.82 (d, *J* = 8.80 Hz, 2 H), 5.85 (d, *J* = 10.27 Hz, 1 H), 5.74–5.69 (m, 1 H), 4.17–4.09 (m, 2 H), 3.78 (s, 3 H), 2.90 (t, *J* = 5.38 Hz, 1 H), 2.02–1.97 (m, 1 H), 1.88–1.80 (m, 1 H), 1.77–1.69 (m, 1 H), 1.66–1.57 (m, 1 H), 0.91 (s, 9 H), 0.05 (s, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 158.2, 132.5, 132.4, 130.4, 128.8, 113.2, 72.5, 65.4, 55.1, 53.8, 33.0, 25.7, 25.0, 18.7, 18.0, –5.7.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{21}H_{34}O_3SiNa$: 385.5432; found: 385.5437.

(*R*)-1-[2-Hydroxy-1-(4-methoxyphenyl)ethyl]cyclohexanol [(*R*)-12′]

To a stirred solution of **17** (0.5 g, 1.38 mmol) in anhyd EtOH (5 mL) was added 10% Pd/C (0.2 mg) in a single portion and the resulting reaction mixture was vigorously stirred at r.t. for 8 h under H_2 atmosphere (1–2 psi). After complete consumption of the starting material, the reaction mixture was filtered and washed carefully with EtOH. The EtOH extracts were combined and evaporated under reduced pressure. The crude product thus obtained was subjected to column chromatography using 60–120 mesh silica gel with EtOAc–PE (15%) as an eluent to furnish pure (*R*)-**12′** (0.328 g, 95%) as a colorless oil; $[\alpha]_D^{25}$ +12.4 (*c* 1, $CHCl_3$).

(*R*)-2-(1-Hydroxycyclohexyl)-2-(4-methoxyphenyl)ethyl 4-Methylbenzenesulfonate [(*R*)-2′]

Compound (*R*)-**2′** was prepared as per the previously mentioned experimental procedure for compound **2**; yield: 0.355 g from 0.250 g (88%); pale yellow solid; mp 109 °C; $[\alpha]_D^{25}$ –18.8 (*c* 1, $CHCl_3$).

(*R*)-1-[2-(Dimethylamino)-1-(4-methoxyphenyl)ethyl]cyclohexan-1-ol [(*R*)-1′, (*R*)-Venlafaxine]

Compound (*R*)-**1′** was prepared as per the previously mentioned experimental procedure for compound **1**; yield: 0.105 g from 0.220 g (70%); white solid; mp 286 °C; $[\alpha]_D^{25}$ –24.5 (*c* 1, EtOH) {Lit.[3,16] $[\alpha]_D^{25}$ –27.1 (*c* 1.04, EtOH)}.

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Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0036-1588911.

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Hz, 2 H), 6.85 (d, *J* = 8.54 Hz, 2 H), 5.72 (ddt, *J* = 17.09, 10.38, 6.72 Hz, 1 H), 4.95–4.88 (m, 2 H), 4.05–3.97 (m, 2 H), 3.90–3.86 (m, 1 H), 3.79 (s, 3 H), 2.78 (ddd, *J* = 13.12, 8.24, 4.88 Hz, 1 H), 2.02–1.90 [m, 3 H (contains two br s for 2-OH)], 1.56–1.51 (m, 1 H), 1.41–1.30 (m, 4 H). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 158.5, 138.5, 132.0, 129.1, 114.6, 114.1, 76.2, 67.1, 55.2, 52.7, 35.1, 33.4, 24.4.

(13) (a) **19**: IR ($CHCl_3$): 1610, 1556, 1412, 1226 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ (*dr*: 9:**1**) = 7.40 (d, *J* = 8.53 Hz, 2 H), 7.08 (d, *J* = 7.63 Hz, 0.30 H), 6.82 (d, *J* = 8.53 Hz, 1.70 H), 5.71 (ddt, *J* = 17.06, 10.29, 6.77 Hz, 1 H), 4.95–4.86 (m, 2 H), 4.31 (dd, *J* = 11.55, 3.77 Hz, 1 H), 4.13 (ddd, *J* = 9.29, 6.53, 3.26 Hz, 1 H), 3.97–3.87 (m, 1 H), 3.80 (s, 3 H), **2.68** (ddd, *J* = 16.17, 10.68, 5.19 Hz, 0.10 H), 2.46–2.40 (m, 0.90 H), 1.97–1.92 (m, 2 H), 1.53 (s, 3 H), 1.52 (s, 3 H), 1.42–1.31 (m, 1 H), 1.34–1.30 (m, 1 H), 1.20–1.14 (m, 2 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = **158.6**, 158.3, **138.7**, 138.6, **132.7**, **131.1**, 130.5, 129.0, 114.5, **114.4**, **114.1**, 113.4, 96.8, **96.2**, **73.3**, 71.2, 65.7, **55.1**, 55.0, **46.5**, 43.1, **33.6**, 33.5, 33.0, **32.9**, **29.4**, 24.7, **24.4**, **19.4**, 19.1. HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{18}H_{26}O_3Na$: 313.2103; found: 313.2108. (b) **20**: ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.10 (d, *J* = 8.55 Hz, 2 H), 6.86 (d, *J* = 8.55 Hz, 2 H), 5.72 (ddt, *J* = 16.79, 10.07, 6.41 Hz, 1 H), 4.94–4.86 (m, 2 H), 3.97 (ddd, *J* = 10.38, 6.43, 3.36 Hz, 1 H), 3.91 (t, *J* = 11.29 Hz, 1 H), 3.82–3.77 (m, 1 H), 3.79 (s, 3 H), 2.70 (ddd, *J* = 16.17, 10.38, 6.43 Hz, 1 H), 2.33–2.29 (m, 1 H), 2.06–1.98 (m, 1 H), 1.96–1.90 (m, 1 H), 1.57 (s, 3 H), 1.54–1.48 (m, 1 H), 1.45 (s, 3 H), 1.34–1.30 (m, 2 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 158.5, 138.8, 131.0, 129.0, 114.2, 114.1, 98.3, 73.2, 65.8, 55.2, 46.5, 33.5, 32.8, 29.6, 24.3, 19.3.

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