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An improved asymmetric synthetic route to a novel triple uptake inhibitor antidepressant (2*S*,4*R*,5*R*)-2-benzhydryl-5-((4-methoxybenzyl)amino)tetrahydro-2*H*-pyran-4-ol (D-142)

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Abstract

Triple monoamine reuptake inhibitors have been implicated in the development of a new generation of antidepressants with higher efficacy than the currently existing therapies. In this paper, we have developed an alternative efficient synthetic route for triple monoamine reuptake inhibitor D-142 in 18.5% overall yield in 11 steps starting from diphenylmethane. D-142 was developed by us recently. The key step of the present synthetic strategy is the preferential formation of a bromohydrin from olefin *via* a *cis*-bromonium intermediate, which introduced significant efficiency in the overall synthesis. Furthermore, we have developed an efficient way to recycle the optically active intermediate diol back to the desired chiral epoxide.

1. Introduction

Depression is a common psychiatric disorder that is characterized by sadness, loss of interest in activities and decreased energy. After cardiovascular disease, depression is considered as the second most debilitating disease in the world and it is believed that at least 20% of all individuals suffer from a depressive episode at least once in their lifetime. The causes of depression are complex and differ widely among individuals, however they are thought to involve brain biochemistry, inherited genes, social environment, and upbringing. It is widely believed that the dysfunction of the dopamine, serotonin, and norepinephrine neurotransmitter systems results in precipitation of depression.^{1,2}

A large number of chemical structures have been developed for targeting monoamine transporter systems to treat diseases such as depression. Similarly, various structurally different molecules have been developed for the inhibition of the serotonin transporter, known as selective serotonin reuptake inhibitors (e.g. fluoxetine, Figure 1).^{3–5} Selective serotonin reuptake inhibitors are known to possess pharmacological activity against depression and are used extensively as antidepressant agents. The highly selective norepinephrine blocker known as norepinephrine reuptake inhibitors (e.g. reboxetine, Figure 1) has been advanced for its strong antidepressant effect.^{6,7} Compounds, which are potent at being both serotonin transporters and NET (norepinephrine transporter), are known as serotonin and norepinephrine reuptake inhibitors (e.g. duloxetine and venlafaxine, Figure 1).^{8,9} However, neither selective serotonin reuptake inhibitors nor norepinephrine reuptake inhibitors are fully satisfactory due to a delayed onset of action, low rate of response and side effects that can affect compliance. Ironically, none of the current pharmacotherapies for depression includes dopaminergic activity even though dopamine has been strongly linked to depression. In recent drug development work, an approach towards the development of

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triple reuptake inhibitors as new generation of a broad spectrum antidepressants has been undertaken,^{10,11} (e.g. DOV 21,947 and PCR-050, Figure 1). Triple monoamine reuptake inhibitors inhibit the uptake of all three neurotransmitters. Preclinical studies indicate that a drug inhibiting the uptake of all three of these neurotransmitters could produce a more rapid onset of action and should possess greater efficacy than traditional antidepressants due to additional dopaminergic activity. In our recent reports,^{12–14} we have demonstrated the development of asymmetric 3,6-disubstituted¹⁴ and 2,4,5-trisubstituted pyran derivatives targeting monoamine transporter systems. Herein we report an efficient and improved asymmetric synthesis of our lead antidepressant trisubstituted pyran compound D-142.

2. Result and discussion

Scheme 1 outlines the synthesis of key intermediate epoxide **7**. The commercially available diphenylmethane **1** was treated with 2-dimethylaminoethylchloride hydrochloride **2** in the presence of *n*-butyl lithium to give amine **3**, which was oxidized to amine oxide **4** by reaction with 30% hydrogen peroxide solution. Pyrolysis of compound **4** at 80–180 °C under reduced pressure produced olefin **5**. In comparison to our earlier synthesis,¹² in the present synthesis, we could herein synthesize olefin **5** on a large scale (42 g, 87% overall yield, 3 steps) without the requirement of column chromatography purification. On the other hand, in our earlier synthesis we synthesized olefin **5** in 46% yield by a Wittig reaction of diphenylacetaldehyde. Even though the present synthesis might require more steps, it is a more efficient practical synthetic route. Next, olefin **5** was treated with *m*-chloroperbenzoic acid to give racemic epoxide **6**. The racemate **6** was resolved by hydrolytic kinetic resolution¹⁵ using Jacobsen's catalyst to give (*R*)-2-benzhydryloxirane **7** (99% ee) and (*S*)-3,3-diphenylpropane-1,2-diol **8** (99% ee) in high enantiomeric excess.

Scheme 2 describes the synthesis of (*R*)-2-benzhydryloxirane **7** from (*S*)-3,3-diphenylpropane-1,2-diol **8**, which was obtained from resolution of racemic epoxide **6** as shown in Scheme 1. The primary hydroxy functionality in diol **8** was selectively protected with TBDMS-Cl in the presence of imidazole to give compound **9**, which was then mesylated to furnish compound **10**. Deprotection of the TBDMS group in compound **10** produced alcohol **11** which was converted to epoxide **7** in good yield by reaction with K₂CO₃ in methanol.

Scheme 3 describes the synthesis of target compound **18** (D-142) starting from epoxide **7**. The epoxide ring opening of **7** with vinyl magnesium bromide was achieved in the presence of copper(I) iodide to obtain alcohol **12** regioselectively. *O*-Alkylation of **12** with allyl bromide in the presence of NaH produced compound **13**, which was converted into pyran derivative **14** by a ring-closing metathesis reaction in the presence of 1st generation Grubbs catalyst.¹⁶ The reaction of olefin **14** with *N*-bromoacetamide in aqueous dioxane produced bromohydrin **16**. It is perceivable that both diastereoisomers of the intermediate bromonium ion might exist in a very rapid equilibrium with each other. Irreversible ring opening of a *cis*-bromonium ion would be expected to proceed in a *trans*-diaxial manner^{12,13,17,18} via a chair like transition state to provide compound **16** as a major product. This kinetically controlled ring opening was preceded via attack of the nucleophile at the site remote from the endocyclic oxygen atom where carbocationic character is better tolerated.^{19,20} However, such a ring opening in a *trans*-bromonium ion is not favored energetically as it will involve a high energy twist boat like transition state. The relative stereochemistry of bromohydrin **16** was confirmed by NMR experiments. We have studied these NMR studies in C₆D₆, as the –OCH₂ and –CHBr protons appeared at the same chemical shift values in CDCl₃. The assignment of protons was carried out by ¹H NMR and ¹H-¹H COSY NMR experiments (Figure 2A). The splitting of H-2 is a doublet of doublet of doublet (4.40 ppm, ddd, *J* = 2.4, 8.8, 11.2 Hz), this is possible only when H-2 is in an axial position because the small

coupling (2.4 Hz) is from the interaction with H-3eq, while 8.8 Hz represents a coupling with Ph₂CH, and 11.2 Hz corresponds to an axial-axial coupling with the H-3 axial proton. This confirms the equatorial position of the benzhydryl moiety. The coupling widths for both protons H-4 (m, 3.59 ppm) and H-5 (m, 3.24 ppm) are 6.8 Hz, and this can only be possible if they are in equatorial positions as they produce only eq-eq and ax-eq vicinal couplings with the adjacent protons. The splitting of H-3ax at 2.04 ppm is ddd with 3.2, 10.8, 14.0 Hz coupling constants; the coupling constants 10.8 Hz is with vicinal H-2ax, 14.0 Hz corresponds to geminal coupling with the H-3eq, small coupling constant of 3.2 Hz is from an interaction with H-4; this small coupling constant of 3.2 Hz can only be possible if H-4 is in an equatorial position. Furthermore, the H-6 axial proton appears at 3.85 ppm as a doublet of doublet ($J = 2.4, 13.2$ Hz); the big doublet is from the geminal coupling with H-6 eq, and the small doublet is from vicinal coupling with H-5. This can only be possible if H-5 is in an equatorial position. Hence, we have demonstrated that the hydroxyl group at the 4-position is in an axial position and the bromine at the 5-position is also in an axial position.

This stereochemistry of bromohydrin **16** was further confirmed by NOE experiments (Figure 2B): i) Irradiation of the OH at 0.86 ppm resulted in an NOE enhancement at 3.24 and 3.59 ppm. The enhancement for H-5 at 3.24 indicates that it is in a *cis*-relationship to OH. Therefore, H-5 is in an equatorial position. The enhancement at 3.59 was attributed to the H-4eq geminal proton. ii) Irradiation of the signal at 2.04 ppm for H-3ax resulted in an NOE enhancement at 1.22, 3.59, and 3.89 ppm. The enhancement at 3.59 implies that H-4 is in a *cis* relationship to H-3ax. Therefore, H-4 is in an equatorial position. iii) Irradiation of the signal at 3.85 ppm for H-6ax resulted in an NOE enhancement at 3.24, 3.62, and 4.40 ppm. The enhancement for H-5 at 3.24 indicates that it is in a *cis*-relationship to H-6ax. Therefore, H-5 is in an equatorial position.

The *trans*-diaxial bromohydrin **16** was treated with a base to give *trans*-epoxide **17** in 89% yield, whose spectroscopic data and specific rotation were in agreement with the reported values.¹² In our previous synthesis, the direct epoxidation of olefin **14** with *m*CPBA gave low stereoselectivity resulting in formation of *trans*-epoxide **17** in 50% yield along with 41% of the *cis*-epoxide.¹² Finally, the *trans*-diaxial opening of epoxide **16** was achieved by reaction with 4-methoxybenzylamine in refluxing ethanol to give target compound **18** (D-142), whose spectroscopic data¹² was in agreement with the reported values. In the current synthetic strategy, the target compound D-142 was obtained in 18.5% overall yield, whereas in our previous synthetic route, it was obtained in 3.4% overall yield. Hence, this is a more efficient synthetic strategy in terms of overall yield also.

3. Conclusion

Herein we have developed an improved synthesis of a new generation of antidepressant compounds; triple monoamine uptake inhibitor **18** (D-142). Triple monoamine reuptake inhibitors have recently been implicated in the production of a potent antidepressant effect and are considered as new generation of antidepressants. Compared to our previously published synthesis of this compound, the current synthesis is more efficient. The preferential formation of *trans*-epoxide **17** via intermediate bromohydrin **16** introduced significant improvement in the overall synthesis efficiency. Furthermore, we have developed an efficient way to recycle the optically active intermediate diol **8** back to the desired epoxide **7**.

4. Experimental

Reagents and solvents were obtained from commercial suppliers and used as received unless otherwise indicated. Dry solvents were obtained according to the standard procedures. All

reactions were performed under an inert atmosphere (N₂) unless otherwise noted. Analytical silica gel-coated TLC plates (Si 254F) were purchased from Baker, Inc and were visualized with UV light or by treatment with phosphomolybdic acid (PMA). Column chromatography was performed on Silica Gel (230–400 mesh) using ethyl acetate and hexanes mixture as eluent. ¹H NMR and ¹³C spectra were recorded on Varian 400 MHz FT NMR spectrometer with tetramethylsilane as the internal standard.

4.1. *N,N*-Dimethyl-3,3-diphenylpropan-1-amine **3**

To an ice-cooled stirred solution of diphenylmethane **1** (42 g, 250 mmol) in anhydrous THF (500 mL) was added *n*-butyl lithium (300 mL, 2.5 M solution in THF, 750 mmol) slowly under a nitrogen atmosphere. After stirring for 1 h, 2-dimethylaminoethylchloride hydrochloride **2** (37.45 g, 260 mmol) was added in small portions. The reaction mixture was allowed to reach room temperature and stirred overnight. The reaction mixture was quenched by the addition of water (400 mL) at 0 °C and extracted with diethyl ether (3 × 150 mL). The combined organic layer was washed with water (150 mL), brine (150 mL), dried over Na₂SO₄, and the solvent was removed under reduced pressure to give compound **3** (59.2 g, quantitative yield) as a thick syrup. ¹H NMR (400 MHz, CDCl₃): δ 2.13–2.26 (m, 10H), 3.96–4.00 (m, 1H), 7.14–7.35 (m, 10H). ¹³C NMR (100 MHz, CDCl₃): δ 33.87, 45.81, 49.24, 58.31, 126.37, 128.06, 128.68, 145.12.

4.2. *N,N*-Dimethyl-3,3-diphenylpropan-1-amine *N*-oxide **4**

To crude compound **3** (59.2 g, 247 mmol), 30% hydrogen peroxide (60 mL) was added. After stirring overnight at room temperature, the excess hydrogen peroxide was decomposed with manganese (IV) oxide powder at 0 °C. The reaction mixture was filtered, the residue was washed with 2-propanol, and the filtrate was concentrated under reduced pressure to give compound **4** (62.5 g, quantitative yield) as a brown liquid. ¹H NMR (400 MHz, CDCl₃): δ 2.63–2.71 (m, 2H), 3.05–3.20 (m, 8H), 3.90–4.00 (m, 1H), 7.15–7.32 (m, 10H). ¹³C NMR (100 MHz, CDCl₃): δ 29.56, 49.07, 58.93, 70.45, 126.95, 127.81, 129.00, 143.53.

4.3. Prop-2-ene-1,1-diylidibenzene **5**

Crude compound **4** (62.5 g, 245 mmol) was heated up to 180 °C under vacuum at 2 mm Hg. The pyrolysate, which was collected in a flask cooled in an ice bath, was taken up in ether (600 mL) and washed several times with 10% hydrochloric acid (300 mL), water (300 mL), brine (300 mL), dried over Na₂SO₄, and the solvent was removed under reduced pressure. It was finally purified by vacuum distillation at 120 °C under 0.3 mm Hg vacuum to give compound **5** (41.5 g, 87 %) as a colorless liquid. ¹H NMR (400 MHz, CDCl₃): δ 4.74, (d, *J* = 7.2 Hz, 1H), 5.00 (d, *J* = 17.2 Hz, 1H), 5.23 (d, *J* = 10.0 Hz, 1H), 6.27–6.36 (m, 1H), 7.16–7.36 (m, 10H).

4.4. 2-Benzhydryloxirane **6**

To an ice-cooled stirred solution of olefin **5** (40 g, 206 mmol) in dichloromethane (500 mL) was added *m*-chloroperbenzoic acid (76.4 g, 70% purity, 310 mmol) portion wise. The reaction mixture was allowed to reach room temperature and stirred overnight. The reaction mixture was filtered to remove solid *m*-chlorobenzoic acid, after which the filtrate was quenched with 1 M Na₂SO₃ (250 mL) solution at 0 °C, and extracted with dichloromethane (3 × 150 mL). The combined organic layer was washed with saturated NaHCO₃ (2 × 300 mL) solution, water (300 mL), brine (200 mL), dried over Na₂SO₄, and the solvent was removed under reduced pressure. The residue was purified by both column chromatography using 10% ethyl acetate in hexanes and followed by vacuum distillation at 140 °C under 0.3 mm Hg vacuum to give compound **6** (36.3 g, 84 %) as a colorless liquid. ¹H NMR (400

MHz, CDCl₃): δ 2.53, (dd, J = 2.4, 4.8 Hz, 1H), 2.85 (dd, J = 4.0, 4.8 Hz, 1H), 3.50–3.56 (m, 1H), 3.82 (d, J = 7.2 Hz, 1H), 7.22–7.36 (m, 10H). ¹³C NMR (100 MHz, CDCl₃): δ 47.15, 53.97, 55.54, 127.45, 127.53, 129.09, 129.21, 129.25, 141.70.

4.5. (R)-2-Benzhydryloxirane 7 and (S)-3,3-diphenylpropane-1,2-diol 8

A mixture of (*R,R*)-(–)-*N,N'*-bis(3,5-di-*tert*-butylsalicylidene)-1,2-cyclohexane diaminocobalt (II) (0.43 g, 0.65 mmol), dichloromethane (15 mL), and acetic acid (75 μ L, 1.3 mmol) was stirred for 1 h at room temperature. The solvent was removed under reduced pressure and the residue was dried. To this residue, racemic epoxide **6** (27.5 g, 130.78 mmol) was added and the reaction mixture was cooled down in an ice bath. Next, H₂O (1.65 mL, 91.54 mmol) was added dropwise and the reaction mixture was allowed to reach room temperature. After stirring for 72 h, the residue was purified by column chromatography to give compound **7** (13.2 g, 48%) as a yellow liquid and compound **8** (13.3 g, 48%) as a yellow solid. Enantiomerically pure epoxide **7** was again purified by vacuum distillation at 140 °C under 0.3 mm Hg vacuum. The enantiomeric excess of the epoxide **7** was determined to be 99% by chiral HPLC analysis [(*R,R*)-Whelk O-1, 99.8:0.2 hexanes:2-propanol, 1 mL/min, 254 nm, t_R (minor) = 18.31 min, t_R^{21} = 19.55]. Data for compound **7**: $[\alpha]_D^{25}$ = +10.1 (*c* 1.0, CH₃OH). ¹H NMR (400 MHz, CDCl₃): δ 2.53, (dd, J = 2.4, 4.8 Hz, 1H), 2.85 (dd, J = 4.0, 4.8 Hz, 1H), 3.50–3.56 (m, 1H), 3.82 (d, J = 7.2 Hz, 1H), 7.22–7.36 (m, 10H). ¹³C NMR (100 MHz, CDCl₃): δ 47.15, 53.97, 55.54, 127.45, 127.53, 129.09, 129.21, 129.25, 141.70. Data for compound **8**: The ee of diol **8** was determined to be 99% by chiral HPLC analysis on the basis of recycled epoxide **7**. Mp = 81–83°C. $[\alpha]_D^{25}$ = +48.0 (*c* 1.0, CH₃OH). ¹H NMR (400 MHz, CDCl₃): δ 2.02, (t, J = 6.0 Hz, 1H), 2.10 (d, J = 3.2 Hz, 1H), 3.44–3.52 (m, 1H), 3.62–3.68 (m, 1H), 4.05 (d, J = 9.6 Hz, 1H), 4.44–4.50 (m, 1H), 7.10–7.25 (m, 10H). ¹³C NMR (100 MHz, CDCl₃): δ 55.05, 64.99, 74.27, 127.05, 127.16, 128.40, 128.89, 129.01, 129.09, 141.44, 141.76.

4.6. (S)-3-((*tert*-Butyldimethylsilyl)oxy)-1,1-diphenylpropan-2-ol 9

Into a stirred solution of alcohol **8** (6.0 g, 26.28 mmol) in dichloromethane (40 mL), *tert*-butyldimethyl silyl chloride (3.96 g, 26.28 mmol) and imidazole (3.58 g, 52.56 mmol) were added at 0 °C. Then the reaction mixture was stirred for 1 hour allowing the temperature to return to room temperature. The product was extracted from the reaction mixture with CH₂Cl₂ (3 $\times$ 100 mL), washed with water, dried over Na₂SO₄, filtered, and concentrated. The crude material was purified by column chromatography over silica gel (Hexane/EtOAc, 4:1) to give 8.28 g (92%) of **9** as colorless oil. $[\alpha]_D^{25}$ = +31.6 (*c* 1.0, CH₃OH). ¹H NMR (CDCl₃, 400 MHz): δ 0.02 (s, 6H), 0.89 (s, 9H), 2.51 (d, J = 4.8 Hz, 1H), 3.43 (dd, J = 10 Hz, 6 Hz, 1H), 3.57 (dd, J = 10, 3.6 Hz, 1H), 4.03 (d, J = 8.8 Hz, 1H), 4.36–4.45 (m, 1H), 7.15–7.34 (m, 8H), 7.36–7.42 (m, 2H). ¹³C NMR (CDCl₃, 100 MHz): δ –4.75, 26.5, 55.1, 65.9, 74.1, 127.2, 127.3, 128.9, 129.1, 129.3, 129.4, 142.4, 142.8.

4.7. (S)-3-((*tert*-Butyldimethylsilyl)oxy)-1,1-diphenylpropan-2-yl methanesulfonate 10

Into a stirred solution of alcohol **9** (8.0 g, 23.35 mmol) in DCM (40.0 mL), methanesulfonyl chloride (1.09 mL, 23.35 mmol) and Et₃N (6.47 mL, 46.71 mmol) were added at 0 °C. The reaction mixture was then stirred for 2 hours allowing the temperature to return to room temperature. The reaction mixture was extracted with CH₂Cl₂ (3 $\times$ 100 mL), washed with water, dried over Na₂SO₄, filtered, and concentrated. The crude material was purified by column chromatography over silica gel (Hexane/EtOAc, 4:1) to give 9.33 g (95%) of **10** as a colorless oil. $[\alpha]_D^{25}$ = –40.4 (*c* 0.5, CH₃OH). ¹H NMR (CDCl₃, 400 MHz): δ –0.03 (s, 6H), 0.88 (s, 9H), 2.34 (d, J = 1.6 Hz, 3H), 3.70 (dd, J = 11.2 Hz, 4.4 Hz, 1H), 3.84 (dd, J = 11.6 Hz, 3.6 Hz, 1H), 4.42 (d, J = 9.2 Hz, 1H), 5.29–5.36 (m, 1H), 7.19–7.37 (m, 8H), 7.38–7.43 (m, 2H). ¹³C NMR (CDCl₃, 100 MHz): δ –2.3, 26.4, 38.5, 53.2, 64.3, 86.9, 128.0, 128.2, 128.9, 129.4, 129.5, 129.8, 140.2, 141.0.

4.8. (S)-3-Hydroxy-1,1-diphenylpropan-2-yl methanesulfonate **11**

Into a stirred solution of **10** (9.0 g, 21.40 mmol) in THF (60.0 mL), TBAF (23.5 mL, 1 M solution in THF, 23.50 mmol) was added slowly at 0 °C and stirring was continued for 1 hour at the same temperature. Next, the THF was removed *in vacuo* and the crude product was extracted with dichloromethane (3 × 100 mL), washed with water, dried over Na₂SO₄, filtered, and concentrated. The crude material was purified by silica gel column chromatography (Hexane/EtOAc, 3:2) to give 5.83 g (89%) of **11** as a white solid. Mp = 106–108 °C. $[\alpha]_D^{25} = -38.8$ (c 0.5, CH₃OH). ¹H NMR (400 MHz, CDCl₃): δ 2.36 (s, 3H), 3.60–3.78 (m, 1H), 3.82–3.90 (m, 1H), 4.33 (d, *J* = 10.4 Hz, 1H), 5.42–5.50 (m, 1H), 7.10–7.58 (m, 10H). ¹³C NMR (CDCl₃, 100 MHz): δ 38.1, 52.7, 63.8, 86.4, 127.5, 127.7, 128.4, 128.9, 129.0, 129.3, 139.8, 140.5.

4.9. (R)-2-Benzhydryloxirane **7**

Into a stirred solution of alcohol **11** (5.5 g, 17.95 mmol) in anhydrous CH₃OH (20 mL), K₂CO₃ (2.97 g, 21.54 mmol) was added slowly at room temperature. The reaction mixture was stirred for 5 hours at the same temperature. Next, CH₃OH was removed *in vacuo* and the crude product was purified by silica gel column chromatography (Hexane/EtOAc, 4:1) to give 3.32 g (88%) of **7** as a colorless oil. $[\alpha]_D^{25} = +10.9$ (c 1.0, CH₃OH).

4.10. (S)-1,1-Diphenylpent-4-en-2-ol **12**

Into a stirred solution of epoxide **7** (2.75 g, 13.08 mmol) in anhydrous THF (50 mL) was added copper (I) iodide (0.25 g, 1.31 mmol) and vinyl magnesium bromide (32.70 mL, 1 M solution in tetrahydrofuran, 32.69 mmol) at –78 °C. After stirring overnight at room temperature under a nitrogen atmosphere, the reaction mixture was quenched by the addition of saturated NH₄Cl solution (50 mL) at 0 °C, and extracted with ethyl acetate (3 × 75 mL). The combined organic layer was washed with water (50 mL), brine (50 mL), dried over Na₂SO₄, and the solvent was removed under reduced pressure. The residue was purified by column chromatography using 10% ethyl acetate in hexanes to give compound **12** (2.45 g, 79%) as a thick syrup. $[\alpha]_D^{25} = -36.6$ (c 0.5, CH₃OH). $\{[\alpha]_D^{25} = -36.6$ (c 0.5, MeOH)}. ¹H NMR (400 MHz, CDCl₃): δ 1.73 (d, *J* = 3.2 Hz, 1H), 2.08–2.18 (m, 1H), 2.28–2.36 (m, 1H), 3.92 (d, *J* = 8.8 Hz, 1H), 4.40–4.46 (m, 1H), 5.04–5.14 (m, 2H), 5.84–5.95 (m, 1H), 7.14–7.41 (m, 10H). ¹³C NMR (100 MHz, CDCl₃): δ 39.77, 58.22, 73.09, 118.22, 126.88, 127.09, 128.55, 128.94, 129.01, 129.04, 135.06, 141.59, 142.51.

4.11. (S)-(2-(Allyloxy)pent-4-ene-1,1-diyl)dibenzene **13**

Into an ice-cooled stirred solution of alcohol **12** (2.45 g, 10.28 mmol) in anhydrous DMF (40 mL) was added sodium hydride (0.82 g, 60% in mineral oil, 20.56 mmol) under a nitrogen atmosphere and was stirred for 1 h followed by the addition of allyl bromide (2.61 mL, 30.84 mmol). The reaction mixture was allowed to reach room temperature and was further stirred overnight. The reaction mixture was then quenched by the addition of saturated NH₄Cl solution (50 mL) at 0 °C and extracted with ether (3 × 75 mL). The combined organic layer was washed with water (50 mL), brine (50 mL), dried over Na₂SO₄, and the solvent was removed under reduced pressure. The residue was purified by column chromatography using 5% ethyl acetate in hexanes to give compound **13** (2.4 g, 84%) as a thick syrup. $[\alpha]_D^{25} = +23.6$ (c 1.0, CH₃OH). ¹H NMR (400 MHz, CDCl₃): δ 2.16–2.24 (m, 1H), 2.30–2.38 (m, 1H), 3.69 (dd, *J* = 5.6, 12.4 Hz, 1H), 3.92 (dd, *J* = 5.6, 12.4 Hz, 1H), 4.00–4.10 (m, 2H), 4.95–5.10 (m, 4H), 5.62–5.73 (m, 1H), 5.82–5.94 (m, 1H), 7.16–7.42 (m, 10H). ¹³C NMR (100 MHz, CDCl₃): δ 37.32, 56.27, 71.73, 81.87, 116.66, 117.59, 126.49, 126.63, 128.39, 128.70, 128.86, 129.41, 134.92, 135.25, 142.28, 142.91.

4.12. (S)-2-Benzhydryl-3,6-dihydro-2H-pyran 14

To a stirred solution of compound **13** (2.0 g, 7.18 mmol) in anhydrous benzene (75 mL) was added a 1st generation Grubbs catalyst (0.12 g, 0.14 mmol) under a nitrogen atmosphere. The reaction mixture was slowly heated at reflux and the reflux was continued for 2 h. After cooling to room temperature, the solvent was removed under reduced pressure. The residue was purified by column chromatography using 5% ethyl acetate in hexanes to give compound **14** (1.5 g, 83%) as a white solid. Mp = 74–76°C. $[\alpha]_D^{25} = -94.6$ (c 0.5, CH₃OH). ¹H NMR (400 MHz, CDCl₃): δ 1.88–1.96 (m, 1H), 2.12–2.24 (m, 1H), 4.10 (d, *J* = 9.2 Hz, 1H), 4.26–4.38 (m, 2H), 4.41 (dt, *J* = 2.8, 9.6 Hz, 1H), 5.80–5.90 (m, 2H), 7.26–7.50 (m, 10H). ¹³C NMR (100 MHz, CDCl₃): δ 30.33, 57.58, 66.53, 75.59, 124.70, 126.52, 126.64, 126.88, 128.71, 128.74, 128.88, 128.91, 142.59, 142.76.

4.13. (2S,4R,5R)-2-Benzhydryl-5-bromotetrahydro-2H-pyran-4-ol 16

Into a stirred solution of compound **14** (1.38 g, 5.51 mmol) in 1:1 mixture of H₂O/dioxane (30 mL) was added *N*-bromoacetamide (1.14 g, 8.27 mmol) portion wise. After stirring for 4 h at room temperature, the reaction mixture was diluted with ether (75 mL), and the organic layer was washed with saturated NaHCO₃ (50 mL) solution. The aqueous layer was extracted additionally with ether (2 × 50 mL). The combined organic layer was washed with water (40 mL), brine (40 mL), dried over Na₂SO₄, and the solvent was removed under reduced pressure. The residue was purified by column chromatography using 15% ethyl acetate in hexanes to give compound **16** (1.61 g, 84%) as a white solid. Mp = 54–56°C. $[\alpha]_D^{25} = -114.4$ (c 0.5, CH₃OH). ¹H NMR (400 MHz, C₆D₆): δ 0.86 (d, *J* = 3.2 Hz, 1H, OH), 1.22 (dt, *J* = 2.0, 14 Hz, 1H, H-3eq), 2.04 (ddd, *J* = 3.2, 10.8, 14 Hz, 1H, H-3ax), 3.24 (m, 1H, H-5eq), 3.59 (m, 1H, H-4eq), 3.62 (d from dt, *J* = 13.2 Hz, 1H, H-6eq), 3.85 (dd, *J* = 2.4, 13.2 Hz, 1H, H-6ax), 3.89 (d, *J* = 8.8 Hz, 1H, Ph₂CH), 4.40 (ddd, *J* = 2.4, 8.8, 11.2 Hz, 1H, H-2ax), 6.92–7.14 (m, 8H, aromatic), 7.30 (d, *J* = 7.2 Hz, 2H, aromatic). ¹³C NMR (100 MHz, CDCl₃): δ 32.71, 50.76, 56.20, 67.12, 68.86, 74.21, 126.65, 126.91, 128.62, 128.97, 141.95, 142.08.

4.14. (1S,4S,6R)-4-Benzhydryl-3,7-dioxabicyclo[4.1.0]heptane 17

Into an-ice cooled stirred solution of compound **16** (1.6 g, 4.61 mmol) in dioxane (15 mL) was added 20% NaOH solution (15 mL). After stirring for 30 min at room temperature, the reaction mixture was diluted with water and then extracted with ethyl acetate (3 × 75 mL). The combined organic layer was washed with water (40 mL), brine (40 mL), dried over Na₂SO₄, and the solvent was removed under reduced pressure. The residue was purified by column chromatography using 15–20% ethyl acetate in hexanes to give *trans*-compound **17** (1.1 g, 89%) as a white solid. Mp = 99–101°C. $[\alpha]_D^{25} = -58.6$ (c 0.5, CH₃OH). ¹H NMR (400 MHz, CDCl₃): δ 1.66–1.74 (m, 1H), 1.86–1.92 (m, 1H), 3.28 (t, *J* = 4.0 Hz, 1H), 3.34 (m, 1H), 3.82 (d, *J* = 9.2 Hz, 1H), 3.95 (d, *J* = 13.6 Hz, 1H), 4.14 (dt, *J* = 2.4, 10.0 Hz, 1H), 4.22 (dd, *J* = 4.0, 13.6 Hz, 1H), 7.16–7.36 (m, 10H). ¹³C NMR (100 MHz, CDCl₃): δ 30.53, 51.48, 57.37, 66.27, 71.86, 126.66, 126.93, 128.53, 128.65, 128.90, 141.85, 142.35.

4.15. (2S,4R,5R)-2-Benzhydryl-5-((4-methoxybenzyl)amino)tetrahydro-2H-pyran-4-ol 18 (D-142)

A mixture of epoxide **17** (0.5 g, 1.88 mmol) and 4-methoxy benzylamine (4.90 mL, 37.57 mmol) in ethanol (20 mL) was refluxed overnight under a nitrogen atmosphere. The solvent was removed under reduced pressure and the residue was purified by column chromatography using 5% methanol in ethyl acetate to give compound **18** (D-142) (0.58 g, 76%) as a white solid. $[\alpha]_D^{25} = -72.6$ (c 0.5, CH₃OH). ¹H NMR (400 MHz, CDCl₃): δ 1.43 (dt, *J* = 3.6, 13.6 Hz, 1H), 1.60 (br s, 2H), 1.73 (dt, *J* = 3.2, 13.6 Hz, 1H), 2.44 (d, *J* = 2.4 Hz, 1H), 3.66 (d, *J* = 12.8 Hz, 2H), 3.74–3.84 (m, 5H), 3.90 (dd, *J* = 2.8, 12.4 Hz, 1H),

3.93–3.98 (m, 2H), 4.50 (dt, $J = 2.4, 10.4$ Hz, 1H), 6.85 (d, $J = 8.8$ Hz, 2H), 7.12–7.38 (m, 12H). ^{13}C NMR (100 MHz, CDCl_3): δ 33.37, 50.71, 55.21, 56.41, 56.51, 64.75, 67.30, 73.53, 113.77, 126.25, 126.45, 128.32, 128.35, 128.37, 128.57, 129.22, 132.21, 142.01, 142.11, 158.62. The product was converted into the corresponding mesylate salt; mp: 162–164°C. Anal. calcd for $\text{C}_{27}\text{H}_{33}\text{NO}_6\text{S} \cdot 0.4\text{H}_2\text{O}$: C, 63.98; H, 6.72; N, 2.76. Found: C, 64.02; H, 6.59; N, 2.79.

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Figure 1.
Molecular structures of selected dopamine, serotonin and norepinephrine transporters blockers

Figure 2.

A) Important correlations in COSY spectrum of bromohydrin **16**. $J_{3ax,3eq} = 14.0$ Hz, $J_{3ax,2ax} = 10.8$ Hz, $J_{3ax,4eq} = 3.2$ Hz, $J_{6ax,6eq} = 13.2$ Hz, and $J_{6ax,5eq} = 2.4$ Hz, **B)** NOE enhancements in bromohydrin **16**

Scheme 1.

Reagents and Conditions: (a) *n*-BuLi, THF, 0 °C-rt, overnight, quantitative; (b) H₂O₂, overnight, quantitative; (c) 80–180 °C, vacuum distillation, 87%; (d) *m*-CPBA, DCM, rt, overnight, 84%; (e) (*R,R*)-(-)-*N,N'*-bis(3,5-di-*tert*-butylsalicylidene)-1,2-cyclohexanediaminocobalt (Jacobsen's catalyst), H₂O, 72 h, 48% yield and 99% ee for both 7 and 8.

Scheme 2.

Reagents and conditions: a) TBDMSCl, imidazole, DCM, 0°C-rt, 1 h, 92%; (b) CH₃SO₂Cl, Et₃N, DCM, 0°C-rt, 12 h, 95%; (c) TBAF, THF, 0°C, 1 h, 89%; (d) K₂CO₃, CH₃OH, rt, 5 h, 88%.

Scheme 3.

Reagents and Conditions: (a) Vinylmagnesium bromide, CuI, THF, room temperature, overnight, 79%; (b) NaH, allyl bromide, DMF, 0°C-rt, overnight, 84%; (c) 1st generation Grubbs catalyst, benzene, reflux, 2 h, 83%; (d) *N*-bromoacetamide, dioxane-H₂O, rt, 4 h, 84%; (e) 20% NaOH, dioxane, 0 °C-rt, 30 min, 89%; (f) 4-methoxy benzylamine, EtOH, reflux, overnight, 76%.