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Regioselective monochloro substitution in carbohydrates and non-sugar alcohols *via* Mitsunobu reaction: applications in the synthesis of reboxetine†

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A regioselective high yielding monochloro substitution (chlorohydrin formation) *via* Mitsunobu reaction is reported. In carbohydrates and sterically hindered non-sugars, only the primary hydroxyl group is chlorinated, whereas in the non-sugar 1,2- and 1,3-alcohols, predominantly the secondary chloride substitution occurs. The versatile methodology provides indirect access to epoxides with the retention of configuration, as against conventional Mitsunobu reaction which generates epoxides with inversion. The methodology was successfully used as a key step in the synthesis of optically active diastereoisomers of the antidepressant drug reboxetine from (*R*)-2,3-*O*-cyclohexylidene-D-glyceraldehyde in ~43% overall yields.

Introduction

The Mitsunobu reaction[1] is a preferred reaction in synthetic[2] and medicinal chemistry fields to introduce various functional groups due to its efficacy, stereoselectivity, mild reaction conditions and wide applicability.[3] Compared to the extensive use of Mitsunobu reactions on the molecules containing mono hydroxyl groups,[4] there have been only a few reports on its applications in the molecules comprising multiple hydroxyls, especially vicinal hydroxyl groups.[5]

The halo alcohols such as chiral 1,2- and 1,3-chlorohydrins have attracted the interest of organic chemists both for their usefulness as versatile building blocks,[6] key intermediates[7] and synthons[8] for natural products[9] and a diversity of important bioactive molecules[10] as well as in asymmetric synthesis.[11] The chlorodeoxy sugars are of interest as precursors[6,12] for the synthesis of deoxy, amino-deoxy and unsaturated sugars. Despite their importance, the synthesis of chlorohydrins is not straightforward. Although various synthetic methods have been reported, most of them have limitations, such as harsh reaction conditions, low regioselectivities and moderate yields.[13] The most common methods for the synthesis of 1,2-halohydrins are halohydroxylation of alkenes[14] or ring opening of 1,2-epoxides,[15] which use silylhalides in the presence of different promoters,[16] elemental halogens with various catalysts,[17] borane halogenides[18] and metal halides with Lewis acid systems[19] or by using ionic liquids[20] and also from diols.[21] In carbohydrates, halogenation is usually achieved by Appel reaction[22] or by using other halogenating reagents.[23] Earlier work on the formation of chlorohydrins under Mitsunobu conditions, mainly for the purpose of mechanistic study using Ph_3P and Me_3SiX nucleophiles, was performed at −78 °C for longer periods (1–18 h) with low selectivities by Evans *et al.*[24] Therefore, an efficient method for halohydrin formation in multihydroxy molecules in a 'single step' would be highly advantageous for a host of useful synthetic transformations.[25]

As a part of our ongoing interest in the carbohydrate chemistry,[26] and further development of our recent interesting observations on regioselective azidation at the primary hydroxyl group in carbohydrates,[27] we report herein the results of our investigations of monochloro substitution in sugars (chlorohydrin formation), irrespective of the presence of other free hydroxyls in the carbohydrate ring as well as in non-sugars under Mitsunobu conditions using Me_3SiCl as a nucleophile. The indirect access to epoxides with the retention of configuration as against inversion in the normal Mitsunobu reaction is an important application of the present methodology. Besides, we also report the application of this reaction for an efficient synthesis of (2*R*,3*S*)-reboxetine **19** (an antidepressant drug) and (*R*)-hydroxymethylmorpholine **22**, an intermediate of (2*R*,3*S*)-reboxetine and other biologically active molecules.[28]

Results and discussion

The one-pot conversion to chlorohydrins was achieved by adding DIAD to a suspension of the substrate and Ph_3P in

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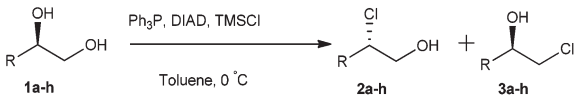
toluene at 0 °C. Trimethylsilyl chloride (Me_3SiCl) was injected after 15 minutes and the reaction mixture was stirred for 2 h. Initially, a series of solvents were screened to optimize the reaction conditions in 1,2-diols, wherein toluene emerged as the solvent of choice (ESI†).

In the case of 1,2-diols (entries 1 and 2, Table 1) both the chloro regioisomers were obtained in the ratio of 3 : 1, while in 1,3-diols (entries 4 and 5, Table 1), the 4 : 1 ratio was observed. In sterically hindered non-sugars high regioselectivity was observed, as chloro substitution occurred exclusively at the primary hydroxyl position (entries 6–8, Table 1). In the partially protected carbohydrates, it was observed that only the primary hydroxyl was regioselectively substituted by chlorine, furnishing chlorohydrins in high yields (Table 1).

Two possible mechanisms of regioselective chloro-substitution have been proposed to explain the product formation. The first possible mechanism *via* Mitsunobu reaction is based on the work by Evans *et al.*,[24] who claimed to have isolated the dioxaphospholane intermediate. The intermediate was prepared by bis(*trans*-oxyphosphoranylation) of 1,2-propanediol with diethoxytriphenylphosphorane (DTPP) and the structure was established by a ^{31}P NMR spectrum, indicating the presence of 1,3,2λ^5-dioxaphospholane (δ −37.5) and Ph_3PO (δ 27.0 ppm). After the reaction of the dioxaphospholane intermediate with trimethylsilyl reagents (Me_3SiX) at −78 °C for 18 h, the regioisomeric (silyloxy)phosphonium ions were observed at δ 62.0 and 63.5 ppm respectively (as monitored by ^{31}P NMR spectroscopy). Though the mechanism proposed by Evans *et al.* was related to a different substrate, on the basis of those studies we presume the formation of two conformational isomeric dioxaphospholanes **5a** and **5b** from 1,2- and 1,3-diols with Ph_3P and DIAD, which undergo a rapid interconversion through pseudorotation. The silylation at the more basic P–O apical oxygen leads to the formation of (silyloxy)phosphonium ions **7a** and **7b** and subsequent S_N2 displacement of Ph_3PO by a chloride ion affords the formation of a thermodynamically less stable C-2 chlorinated regioisomer as the major product, followed by *in situ* silyl group deprotection, possibly due to low pH (acidic pH) of the reaction medium during the stipulated reaction conditions, *i.e.* the addition of 1.3 equiv. of Me_3SiCl (Scheme 1).

Table 1 Mitsunobu reaction in non-sugars and sugar alcohols



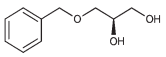
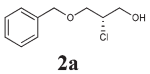
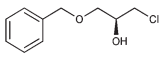
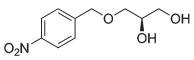
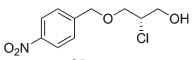
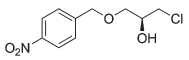
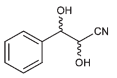
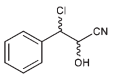
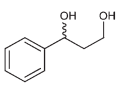
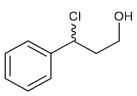
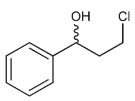
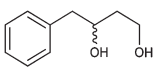
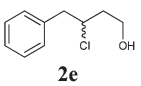
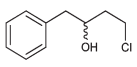
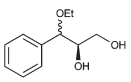
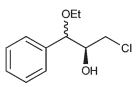
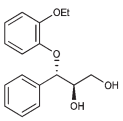
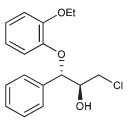
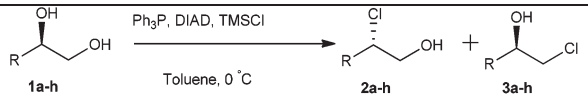
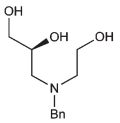
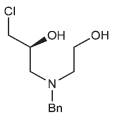
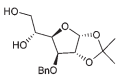
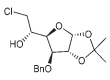
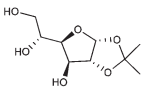
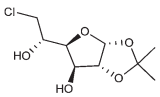
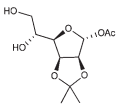
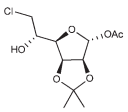
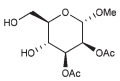
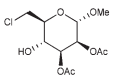
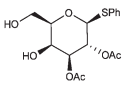
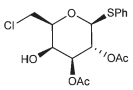
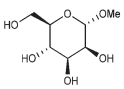
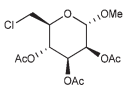
Entry	Diol	Time (h)	Product		Product ratio (2/3)	Total isolated yield (%)
1	 **1a**	2	 **2a**	 **3a**	3 : 1	92
2	 **1b**	2	 **2b**	 **3b**	3 : 1	90
3	 **1c**	2	 **2c**			94
4	 **1d**	2	 **2d**	 **3d**	4 : 1	82
5	 **1e**	2	 **2e**	 **3e**	4 : 1	80
6	 **1fa**	2		 **3fa**		97
7	 **1g**	2		 **3g**		98

Table 1 *(Contd.)*



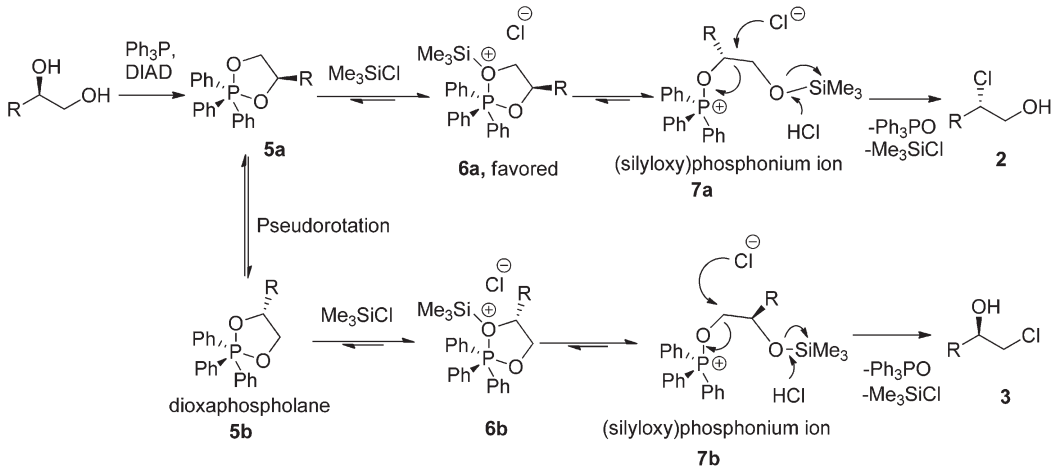
Entry	Diol	Time (h)	Product	Product ratio (2/3)	Total isolated yield (%)
8	 **1h**	2	 **3h**		90
9	 **1i**	2	 **3i**		95
10	 **1j**	2	 **3j**		85
11	 **1k**	2	 **3k**		95
12	 **1l**	2	 **3l**		94
13	 **1m**	2	 **3m**		94
14	 **1n**	6	 **3n**		90[b]

[a] Diastereomeric ratio 46 : 54. [b] Isolated as an acetylated product.

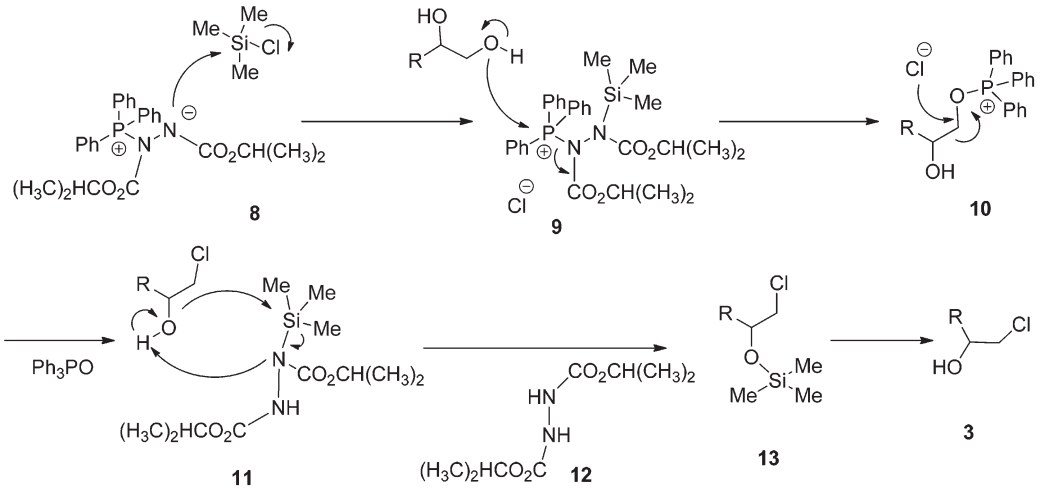
The *in situ* deprotection of the silyl group was verified by isolating the silyl protected intermediate, when the same reaction was effected using less than a molar equivalent, *i.e.* 0.8 equiv. of Me_3SiCl (ESI†). In conventional silyl protection procedures,[29] the chloride ion is trapped by adding a base, while in the present methodology, the reaction is carried out with 1.3 equiv. of Me_3SiCl in the absence of a base, indicating the possible role of pH during the silyl deprotection. The use of 1.3 molar equivalents of Me_3SiCl makes the reaction mixture acidic, thereby facilitating the *in situ* desilylation.

In another proposed mechanism, the chloro-substitution in sugars and sterically hindered non-sugars may also probably proceed *via* the formation of an adduct at the primary carbon through an imino-*O*-phosphorane intermediate[30] followed by the silyl attack at the imino-nitrogen, causing the formation of oxo-phosphonium salt **8**. This intermediate salt then undergoes a facile substitution by the chloride ion with concomitant silylation at secondary hydroxyl, followed by fast desilylation under the stipulated experimental conditions to form the desired chlorohydrins (Scheme 2). According to another literature report in *trans* cyclic 1,2-diols, the reaction occurs through an epoxide intermediate.[31]

The 1,2-diols have been reported to form epoxides under Mitsunobu conditions with low to moderate yields with the inversion of configuration, when no additional nucleophiles are used.[25] However, the present methodology has the advantage of providing indirect access to epoxides *via* chlorohydrin intermediates in high yields with the retention of configuration (Scheme 3). The epoxide formed can be easily transformed into a diversity of functionalities like amino alcohols, haloalcohols and other important moieties which can be highly useful in organic synthesis. The following scheme depicts the formation of epoxides in high yields (92–98%) using DBU as a base in dichloromethane, from the



Scheme 1 Probable mechanism of Mitsunobu chloride substitution in 1,2-diols.



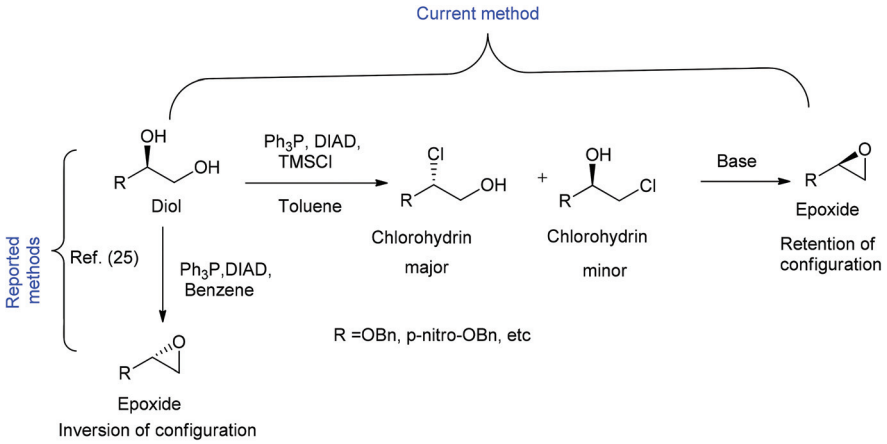
Scheme 2 Probable mechanism of Mitsunobu chloride substitution in sugars and sterically hindered non-sugars.

corresponding chlorohydrins with the retention of the configuration (Table 2, entries 1–3).

To further explore its scope and versatility, we successfully utilized this methodology in the synthesis of optically active diastereoisomers, *i.e.* (2*R*,3*S*)- and (2*S*,3*S*)-reboxetine **19** and (*R*)-hydroxymethylmorpholine **22**, an intermediate of (2*R*,3*S*)-reboxetine **19**, using the synthon (*R*)-2,3-*O*-cyclohexylidene-D-glyceraldehyde **14**. The process is high yielding and facile. Reboxetine is an antidepressant drug used in the treatment of clinical depression, panic disorders[32] and attention-deficit hyperactivity disorder (ADHD), as well as in neurodegenerative disorders including Alzheimer's and Parkinson's disease.[33] Among the reboxetine diastereomers, the (*S*,*S*)-reboxetine exhibits the best affinity and selectivity for the norepinephrine transporter (NET).[34] Jobson *et al.*[35] in 2008 reported that iodinated (2*R*,3*S*)-reboxetine has high affinity for the noradrenaline transporter (NAT), while its enantiomer (2*S*,3*S*) was much less potent in the same binding assay. These observations suggest that (2*R*,3*S*)-**19** diastereomer could also possess interesting inhibitory properties.

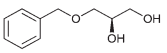
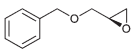
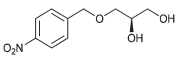
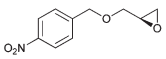
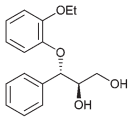
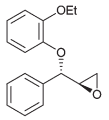
There are several reported syntheses of the reboxetine in both racemic and enantioenriched forms, which involve the separation of reboxetine enantiomers by optical resolution,[36] capillary electrophoresis,[37] or chiral HPLC[38] and other synthetic approaches.[39]

The present approach utilizes the synthon (*R*)-2,3-*O*-cyclohexylidene-D-glyceraldehyde **14**, which can be easily obtained from D-mannitol.[40] Grignard reaction of aldehyde (*R*)-**14** with bromobenzene afforded both *syn*- and *anti*-**15** diastereomers in a 1 : 1 ratio, which are easily separable by column chromatography. Thus, (2*R*,3*R*)-**15** can be easily converted to (2*R*,3*S*)-**15** and *vice versa* under the first Mitsunobu inversion *via* acetate (**16**) formation. The (2*R*,3*R*)-**15** undergoes a second Mitsunobu transformation with 2-ethoxyphenol to form (2*R*,3*S*)-**17**. The (2*R*,3*S*)-diol **1g** obtained by deprotection of the (2*R*,3*S*)-**17** was directly converted to chlorohydrin intermediate (2*S*,3*S*)-**3g** by Mitsunobu chloride substitution with Me_3SiCl as a



Scheme 3 Epoxide formation with retention of configuration in the present method.

Table 2 Epoxidation through chlorohydrin intermediate

Entry	Substrate	Time (h)	Product	Yield (%)
1	 (*R*)-**1a**	8	 (*R*)-**4a**	97
2	 (*R*)-**1b**	8	 (*R*)-**4b**	92
3	 (2*R*,3*S*)-**1g**	8	 (2*R*,3*S*)-**4g**	98

nucleophile and subsequently converted to (2*R*,3*S*)-epoxide **4g** in 98% yield with the retention of configuration. The synthesis of (2*R*,3*S*)-reboxetine **19** was finally accomplished *via* epoxide ring opening with 2-aminoethyl hydrogen sulphate (2-AEHS), followed by cyclization[39b] (~43% overall yield, Scheme 4). The (2*R*,3*S*)-**15** isomer was also similarly converted to (2*R*,3*S*)-reboxetine *via* Mitsunobu reaction. By this process both the isomers were successfully utilized for the synthesis of (2*R*,3*S*)-reboxetine. Though not included here, theoretically the (2*R*,3*S*)-**15** can also be easily used for the preparation of (2*R*,3*R*)-reboxetine, by following a similar synthetic pathway. For the preparation of (2*S*,3*S*)-reboxetine **19**, the diol (2*R*,3*S*)-**1g** was converted to (2*S*,3*S*)-epoxide **4g** under conventional Mitsunobu conditions and finally to enantiomerically pure (2*S*,3*S*)-reboxetine **19** by epoxide opening with 2-aminoethyl hydrogen sulphate (2-AEHS) and cyclization under basic conditions in good yields (Scheme 4).

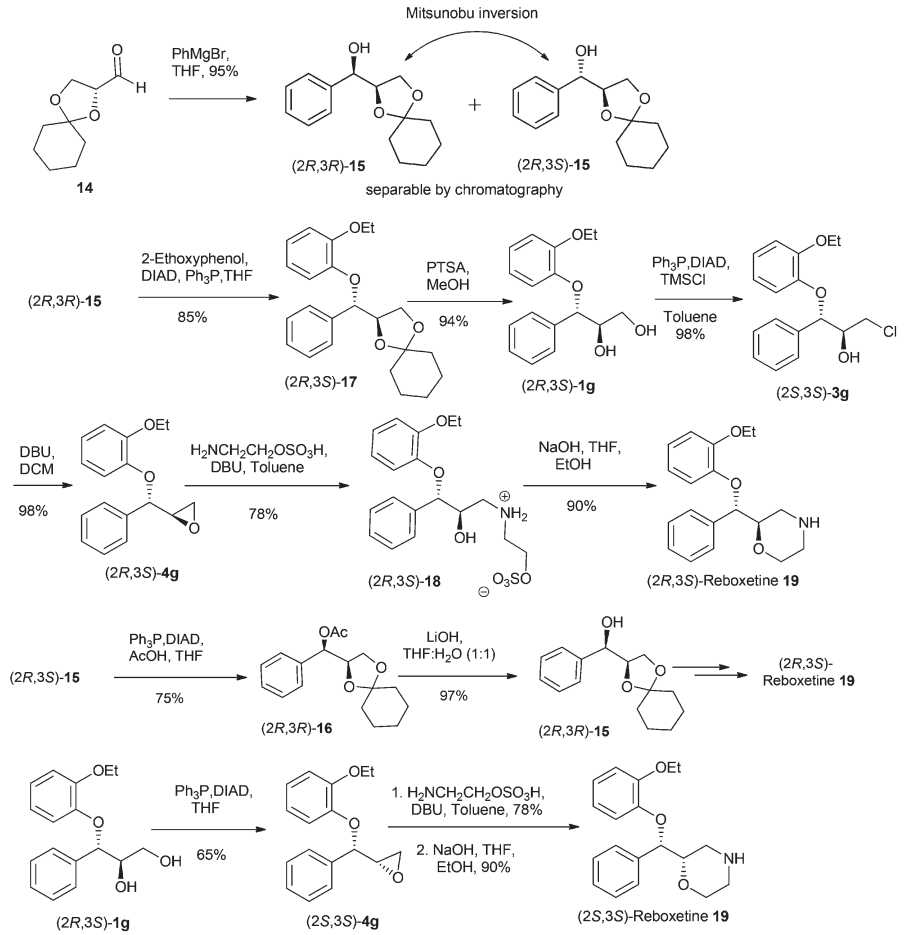
An alternate strategy was also devised for the synthesis of (2*R*,3*S*)-**19** by way of synthesizing (*R*)-*N*-benzyl-2-hydroxymethylmorpholine **22** intermediate, again using the aldehyde (*R*)-**14** as a starting material. There have been only a few literature reports related to the synthesis of racemic or a single enantiomer of **22**.[41] Herein, we report a novel and facile synthesis of chiral intermediate (*S*)-chlorohydrin **3h** under Mitsunobu conditions. Thus, the reductive amination of aldehyde (*R*)-**14** by 2-aminoethanol in presence of $NaBH_4$ afforded amino alcohol **20**, followed by *N*-benzylation to give (*S*)-**21**, which on cyclohexyl deprotection furnished (*S*)-**1h** in 90% yield. The (*S*)-**1h** was transformed into chlorohydrin (*S*)-**3h** in high yield (~73% overall yield) by utilizing the present Mitsunobu chloride substitution methodology. The chlorohydrin may easily be converted to (*R*)-morpholine **22** *via* an epoxide intermediate[41,42] and then to (2*R*,3*S*)-reboxetine **19** by methods reported in the literature (Scheme 5).[39f]

Conclusions

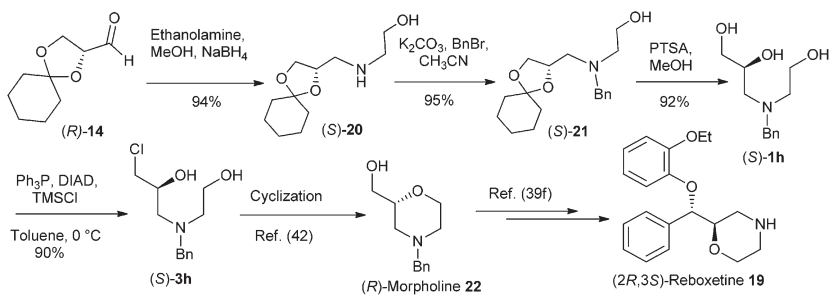
In conclusion an efficient regioselective monochloride substitution *via* Mitsunobu reaction is reported. In sugars and sterically hindered non-sugars, only the primary hydroxyl group is replaced by chlorine, while in non-sugar 1,2 and 1,3-diols, the secondary hydroxyl group gets preferably chlorinated. The methodology is successfully applied in the novel synthesis of (2*R*,3*S*)- and (2*S*,3*S*)-reboxetine (antidepressant), as well as the synthesis of a chiral hydroxymethyl morpholine derivative (also an intermediate of (2*R*,3*S*)-reboxetine). The methodology of chlorohydrin formation may also be used for the preparation of epoxides in high yields with the retention of configuration.

General experimental procedure

NMR experiments were performed using Bruker 200, 400 and 500 MHz spectrometers with TMS as the internal standard. Chemical shifts are expressed in parts per million (δ ppm). Reagents and solvents used were mostly of LR grade. Silica gel coated aluminum plates from M/s Merck were used for TLC. MS was performed using a High Resolution Mass Spectrometer MS Q-TOF LC/MS, Agilent Technologies 6540. Optical rotations were measured on a Perkin-Elmer 241 polarimeter at 25 °C using sodium D light. Melting points were determined using the Buchi B-542 apparatus by an open capillary method and are uncorrected. Chemicals were purchased from M/s Aldrich



Scheme 4 Synthesis of (2*R*,3*S*)- and (2*S*,3*S*)-reboxetine.



Scheme 5 Alternate synthesis of (2*R*,3*S*)-reboxetine.

Chemicals, Mumbai. All anhydrous reactions were carried out under a nitrogen atmosphere using freshly dried solvents. The organic extracts were dried over anhydrous Na_2SO_4.

General procedure of Mitsunobu chloride substitution for 1a–1m

Diisopropyl azodicarboxylate (DIAD) (3.0 mmol, 1.5 equiv.) was injected into a solution of an alcohol (2.0 mmol, 1.0 equiv.) and triphenylphosphine (Ph_3P) (2.6 mmol, 1.3 equiv.) in 15 mL anhydrous toluene at 0 °C. After stirring for 15 minutes at this temperature, trimethylsilyl chloride (Me_3SiCl) (2.6 mmol, 1.3 equiv.) under nitrogen was added. The reaction mixture was stirred at room temperature for 2 h. After the completion of the reaction as indicated by TLC, the reaction was quenched with ethyl acetate (3 × 25 mL). The combined organic extract was washed with water (2 × 10 mL) and brine solution (1 × 5 mL), dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue was subjected to column chromatography (silica gel, 0–30% EtOAc–hexane) to obtain the pure chlorohydrin product.

(*R*)-3-(Benzyloxy)propane-1,2-diol (1a).[43] Colorless liquid; $[\alpha]_D^{25}$ = +5.5 (*c* 1.0, $CHCl_3$); [lit.[43] $[\alpha]_D^{25}$ = +5.9 (*c* 1.0, $CHCl_3$)]; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.39–7.19 (m, 5H), 4.53 (s, 2H), 3.94–3.84 (m, 1H, CH_2OH), 3.67 (dd, *J* = 11.2, 3.6 Hz, 1H), 3.60 (dd, *J* = 11.5, 5.6 Hz, 1H), 3.55–3.47 (m, 2H), 3.02 (s, OH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 137.67, 128.41, 127.80, 127.73, 73.47, 71.62, 70.73 (*CH*OH), 63.96 (CH_2OH); HRMS (ESI) Calc. for $C_{10}H_{14}NaO_3$ $[M + Na]^+$ 205.0841, found 205.0834.

(*S*)-3-(Benzyloxy)-2-chloropropan-1-ol (2a). Prepared by the general procedure of Mitsunobu chloride substitution; yield 69%; colorless liquid; $[\alpha]_D^{25}$ = −6.5 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.38–7.28 (m, 5H), 4.56 (s, 2H), 4.16–4.10 (m, 1H, CH_2OH), 3.91–3.81 (m, 2H), 3.74–3.69 (m, 2H), 1.38 (s, OH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 137.49, 128.54, 127.97, 127.77, 73.56, 71.25, 64.69 (CH_2OH), 60.09 (*CH*Cl); HRMS (ESI) Calc. for $C_{10}H_{13}ClNaO_2$ $[M + Na]^+$ 223.0502, found 223.0486.

(*S*)-1-Chloro-3-benzyloxy-2-propanol (3a). Prepared by the general procedure of Mitsunobu chloride substitution; yield 23%; colorless oil; $[\alpha]_D^{25}$ = −5.5 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.30–7.20 (m, 5H), 4.50 (s, 2H), 3.95–3.90 (m, 1H, *CH*OH), 3.60–3.50 (m, 4H), 2.50 (s, OH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 137.66, 128.35, 127.96, 127.76, 73.60, 70.82, 70.36 (CH_2OH), 46.07 (CH_2Cl); HRMS (ESI) Calc. for $C_{10}H_{13}ClNaO_2$ $[M + Na]^+$ 223.0502, found 223.0484.

(*R*)-2-((Benzyloxy)methyl)oxirane (4a). 1,8-Diazabicyclo-[5,4,0]-7-undecene (DBU) (212 mg, 1.4 mmol) was added to a mixture of chlorohydrins **2a** and **3a** [800 mg (400 mg each **2a** and **3a**), 4.0 mmol] dissolved in anhydrous dichloromethane (15 mL) at 0 °C and stirred for 6 h until the consumption of the starting material. The reaction mixture was extracted with dichloromethane (3 × 20 mL). The organic layer was dried over anhydrous Na_2SO_4 and the residue was purified by column chromatography (silica gel, 0–5% EtOAc–hexane) to yield the pure (*R*)-epoxide **4a** in 97% yield (636 mg) as a colorless liquid; $[\alpha]_D^{25}$ = −6.8 (*c* 1.0, $CHCl_3$); [lit.[44] $[\alpha]_D^{20}$ = −5.3 (*c* 4.5, toluene)]; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.32–7.24 (m, 5H), 4.62–4.53 (q, *J* = 23.6, 12.0 Hz, 2H), 3.77–3.74 (dd, *J* = 11.6, 2.8 Hz, 1H), 3.45–3.41 (dd, *J* = 11.6, 6.0 Hz, 1H), 3.20–3.16 (m, 1H, $CHOCH_2$), 2.85–2.80 (q, *J* = 9.2, 4.8 Hz, 1H, CH_2OCH), 2.61–2.60 (q, *J* = 4.8, 2.8 Hz, 1H, CH_2OCH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 137.73, 128.22, 127.71, 127.55, 73.12, 70.62, 50.65 ($CHOCH_2$), 44.07 (CH_2OCH); HRMS (ESI) Calc. for $C_{10}H_{12}NaO_2$ $[M + Na]^+$ 187.0735, found 187.0730.

(*S*)-((1-(Benzyloxy)-3-chloropropan-2-yl)oxy)trimethylsilane (23). Diisopropyl azodicarboxylate (DIAD) (606 mg, 3.0 mmol) was injected into a solution of (*R*)-3-(benzyloxy)propane-1,2-diol **1a** (364 mg, 2.0 mmol) and triphenylphosphine (Ph_3P) (681 mg, 2.6 mmol) in 15 mL anhydrous toluene at 0 °C. After stirring for 15 minutes at this temperature, trimethylsilyl chloride (Me_3SiCl) (172 mg, 1.6 mmol) under nitrogen was added. The reaction mixture was stirred at room temperature for 2 h. After the completion of the reaction as indicated by TLC, the reaction was quenched with ethyl acetate (3 × 25 mL). The combined organic extract was washed with water (2 × 10 mL) and brine solution (1 × 5 mL), dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue was subjected to column chromatography (silica gel, 0–5% EtOAc–hexane) to obtain the pure silyl protected product **23** as a colorless liquid in yield 23% (125 mg); $[\alpha]_D^{25}$ = −4.1 (*c* 1.3, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.25–7.07 (m, 5H), 4.40 (s, 2H), 3.89–3.80 (m, 1H), 3.54–3.46 (dd, *J* = 4.8, 4.0 Hz, 1H), 3.42–3.26 (m, 3H), 0.10 (m, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 137.84, 128.22, 127.50, 74.18, 73.27, 71.47, 46.35 (CH_2Cl), 0.00 (3C); HRMS (ESI) Calc. for $C_{13}H_{21}ClNaO_2Si$ $[M + Na]^+$ 295.0897, found 295.0887.

Synthesis of (*R*)-3-((4-nitrobenzyl)oxy)propane-1,2-diol (1b). Compound **1a** (764 mg, 4.2 mmol) was slowly added dropwise for 10 minutes to a solution of concentrated nitric acid (3 vol., 6 mL) and sulfuric acid (1 vol., 2 mL) at 0 °C and stirred for 2 h. After the completion of the reaction, the extraction was done with dichloromethane (3 × 15 mL), dried over anhydrous $Na_2SO_4$and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel, 0–9% EtOAc–hexane) to obtain the product **1b** as a yellow solid in 83% yield (790 mg); mp. 101–103 °C; $[\alpha]_D^{25}$ = +3.3 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.17 (m, 2H), 7.62 (m, 2H), 4.55 (s, 2H), 3.95 (m, 1H), 3.80–3.50 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 148.66, 143.88, 128.54, 124.45, 74.78, 72.34, 69.08 (*CH*OH), 64.32 (CH_2OH); HRMS (ESI) Calc. for $C_{10}H_{13}NNaO_5$ $[M + Na]^+$ 250.0691, found 250.0684.

(*S*)-2-Chloro-3-((4-nitrobenzyl)oxy)propan-1-ol (2b). Prepared by the general procedure of Mitsunobu chloride substitution; yield 67%; yellow solid; mp. 45–48 °C; $[\alpha]_D^{25}$ = −1.6 (*c* 1.7, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.21 (m, 2H), 7.62 (m, 2H), 4.64 (s, 2H), 3.78–3.62 (m, 4H), 3.54 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 148.98, 142.75, 129.09, 122.65, 74.91, 72.54, 65.09 (CH_2OH), 60.64 (*CH*Cl); HRMS (ESI) Calc. for $C_{10}H_{12}ClNNaO_4$ $[M + Na]^+$ 268.0353, found 268.0346.

(*S*)-1-Chloro-3-((4-nitrobenzyl)oxy)propan-2-ol (3b). Prepared by the general procedure of Mitsunobu chloride substitution; yield 22%; yellow solid; mp. 40–42 °C; $[\alpha]_D^{25}$ = −3.1 (*c* 1.3, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.17 (m, 2H), 7.50 (m, 2H), 4.52 (s, 2H), 3.75 (m, 1H, *CH*OH), 3.49–3.30 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 149.96, 144.78, 129.49, 124.55, 74.01, 71.64, 70.29 (*CH*OH), 46.42 (CH_2Cl); HRMS (ESI) Calc. for $C_{10}H_{12}ClNNaO_4$ $[M + Na]^+$ 268.0353, found. 268.0350.

Synthesis of (*R*)-2-(((4-nitrobenzyl)oxy)methyl)oxirane (4b). Compound **4b** was prepared from **2b** and **3b** [980 mg (490 mg each **2b** and **3b**)] by the same procedure described for **4a**, as a yellowish semi-solid in 92% yield (769 mg); $[\alpha]_D^{25}$ = −2.3 (*c* 1.4, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.13 (m, 2H), 7.59 (m, 2H), 4.61 (s, 2H), 3.70 (q, *J* = 12.1, 2.6 Hz, 1H), 3.47–3.40 (m, 1H), 3.02 (m, 1H, $CHOCH_2$), 2.66 (dd, *J* = 9.1, 4.8 Hz, 1H, CH_2OCH), 2.58 (dd, *J* = 4.9, 2.5 Hz, 1H, CH_2OCH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 148.28, 143.65, 129.59, 121.65, 74.41, 73.94, 51.49 ($CHOCH_2$), 44.54 (CH_2OCH); HRMS (ESI) Calc. for $C_{10}H_{11}NNaO_4$: $[M + Na]^+$ 232.0586, found 232.0588.

2,3-Dihydroxy-3-phenylpropanenitrile (1c).[45] Colorless liquid: ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.34 (m, 5H), 4.77–4.75 (d, *J* = 6.4 Hz, 1H), 4.41–4.40 (d, *J* = 6.4 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 136.79, 129.14, 128.71, 126.82, 118.11,

74.54 (*C*HOH), 66.00 (*C*HOHCN); HRMS (ESI) Calc. for $C_9H_9NaNO_2$ $[M + Na]^+$ 186.0531, found 186.0524.

3-Chloro-2-hydroxy-3-phenylpropanenitrile (2c). Prepared by the general procedure of Mitsunobu chloride substitution; yield 94%; transparent liquid; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.49–7.38 (m, 5H), 5.08–5.02 (dd, J = 18.0, 6.0 Hz, 1H, *C*HOH), 4.73 (s, 1H, *C*HCl), 3.46 (s, OH); ^{13}C NMR (125 MHz, $CDCl_3$): δ 134.48, 129.84, 129.07, 127.85, 116.91, 67.35 (*C*HOHCN), 63.02 (*C*HCl); HRMS (ESI) Calc. for $C_9H_8ClNaNO$ $[M + Na]^+$ 204.0192, found 204.0184.

1-Phenylpropane-1,3-diol (1d).[46] Transparent liquid; ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.43–7.25 (m, 5H), 4.94–4.91 (q, J = 8.8, 3.6 Hz, 1H), 3.83–3.81 (t, J = 6.4, 5.6 Hz, 2H), 2.02–1.88 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 144.22, 128.35, 127.36, 125.58, 73.56 (*C*HOH), 60.83 (CH_2OH), 40.32; HRMS (ESI) Calc. for $C_9H_{12}NaO_2$ $[M + Na]^+$ 175.0735, found 175.0730.

3-Chloro-3-phenylpropan-1-ol (2d). Prepared by the general procedure of Mitsunobu chloride substitution; yield 65%; colorless semi-solid; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.41–7.25 (m, 5H), 5.14–5.11 (q, J = 9.2, 5.6 Hz, 1H, *C*HCl), 3.88–3.83 (m, 1H), 3.74–3.70 (m, 1H), 2.34–2.23 (m, 2H), 1.85 (bs, OH); ^{13}C NMR (125 MHz, $CDCl_3$): δ 141.59, 128.75, 128.47, 127.06, 60.43 (*C*HCl), 59.78 (*C*HOH), 42.35 (CH2); HRMS (ESI) Calc. for $C_9H_{11}ClNaO$ $[M + Na]^+$ 193.0396, found 193.0387.

3-Chloro-1-phenylpropan-1-ol (3d). Prepared by the general procedure of Mitsunobu chloride substitution; yield 16%; colorless semi-solid; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.36–7.24 (m, 5H), 4.94–4.90 (m, 1H, *C*HOH), 3.75–3.69 (m, 1H), 3.57–3.51 (m, 1H), 2.24–2.04 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 143.72, 128.68, 127.93, 125.79, 71.35 (*C*HOH), 41.71, 41.46 (CH_2Cl); HRMS (ESI) Calc. for $C_9H_{11}ClNaO$ $[M + Na]^+$ 193.0396, found 193.0390.

4-Phenylbutane-1,3-diol (1e).[47] Colorless semi-solid; ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.30–7.19 (m, 5H), 4.03–4.00 (d, J = 5.5 Hz, 1H, CH_2OH), 3.84–3.73 (m, 2H), 3.06 (s, OH), 2.77–2.71 (m, 2H), 1.69–1.66 (d, J = 4.7 Hz, 2H), 1.25 (s, OH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 138.40, 129.57, 128.63, 126.58, 72.59 (*C*HOH), 61.25 (CH_2OH), 44.39, 37.89; HRMS (ESI) Calc. for $C_{10}H_{14}NaO_2$ $[M + Na]^+$ 189.0891, found 189.0886.

3-Chloro-4-phenylbutan-1-ol (2e). Prepared by the general procedure of Mitsunobu chloride substitution; yield 64%; semi-solid; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.32–7.21 (m, 5H), 4.33–4.30 (m, 1H, *C*HCl), 3.84–3.81 (m, 2H), 3.09–3.06 (q, J = 7.2, 4.4 Hz, 2H), 2.08–2.02 (m, 1H), 1.89–1.81 (m, 1H), 1.66 (s, OH); ^{13}C NMR (125 MHz, $CDCl_3$): δ 137.64, 129.64, 128.47, 126.88, 60.48 (CH_2OH), 59.74 (*C*HCl), 45.21, 39.97; HRMS (ESI) Calc. for $C_{10}H_{13}ClNaO$ $[M + Na]^+$ 207.0553, found 207.0548.

4-Chloro-1-phenylbutan-2-ol (3e). Prepared by the general procedure of Mitsunobu chloride substitution; yield 16%; semi-solid; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.33–7.29 (m, 2H), 7.25–7.19 (m, 3H), 4.06–4.00 (m, 1H), 3.73–3.63 (m, 2H), 2.84–2.79 (dd, J = 13.6, 4.4 Hz, 1H), 2.70–2.64 (dd, J = 13.6, 8.8 Hz, 1H), 1.96–1.87 (m, 2H), 1.78 (s, OH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 137.91, 129.47, 128.71, 126.74, 69.56 (*C*HOH), 44.08 (CH_2), 41.86 (CH_2), 39.28 (CH_2Cl); HRMS (ESI) Calc. for $C_{10}H_{13}ClNaO$ $[M + Na]^+$ 207.0553, found 207.0550.

(2*R*)-3-Ethoxy-3-phenylpropane-1,2-diol (1f). Sodium hydride (NaH) (552 mg, 24 mmol) was slowly added to diastereomer (2*R*,3*R*/*S*)-**15** (496 mg, 2.0 mmol) dissolved in anhydrous THF (15 mL) at 0 °C. After 20 minutes ethyl iodide (403 mg, 2.6 mmol) was added and the reaction mixture was stirred for about 8–9 h. After the consumption of the starting material (TLC), the reaction was quenched with ethyl acetate (1 × 10 mL). After extracting with ethyl acetate (3 × 25 mL), the organic layer was dried over anhydrous Na_2SO_4, concentrated *in vacuo* and purified by column chromatography (silica gel, 0–7% EtOAc–hexane) to get a mixture of (2*R*,3*R*/*S*)-diastereomer as a colorless liquid in 85% yield (445 mg). This compound was transformed to diol (2*R*,3*R*/*S*)-**1f** according to the procedure described for **1g** in 90% yield (299 mg) as a colorless liquid in a *syn* : *anti* ratio of 46 : 54; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.47–7.21 (m, 10H), 4.33 (d, J = 6.1 Hz, 1H), 4.29 (d, J = 7.7 Hz, 1H), 3.81–3.59 (m, 4H), 3.53–3.26 (m, 6H), 1.18 (dt, J = 7.0, 1.8 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 141.87, 141.53, 131.00, 130.69, 130.67, 85.42, 85.32, 78.66, 78.06, 67.92, 67.79, 66.78 (CH_2), 65.78 (*C*HOH), 65.22 (CH_2OH), 17.79; HRMS (ESI) Calc. for $C_{11}H_{16}NaO_3$ $[M + Na]^+$ 219.0997, found 219.0988.

(2*S*)-1-Chloro-3-ethoxy-3-phenylpropan-2-ol (3f). Prepared by the general procedure of Mitsunobu chloride substitution; yield 97%; transparent liquid; *syn* : *anti* 46 : 54; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.48–7.27 (m, 10H), 4.41 (d, J = 7.1 Hz, 1H), 4.35 (d, J = 6.6 Hz, 1H), 3.93–3.88 (dd, J = 6.4, 4.1 Hz, 2H), 3.74–3.69 (m, 2H), 3.61–3.58 (dd, J = 4.0, 2.4 Hz, 1H), 3.47–3.34 (m, 4H), 3.29–3.27 (dd, J = 4.6, 2.4 Hz, 1H), 1.19 (td, J = 7.0, 5.7 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 138.23, 128.52, 127.44, 82.06, 74.76, 74.57 (*C*HOH), 64.71 (CH_2), 46.69 (CH_2OH), 45.26 (CH_2Cl), 15.25; HRMS (ESI) Calc. for $C_{11}H_{16}ClO_2$ $[M + H]^+$ 215.0839, found 215.0832.

(2*S*,3*S*)-1-Chloro-3-(2-ethoxyphenoxy)-3-phenylpropan-2-ol (3g). Prepared by the general procedure of Mitsunobu chloride substitution; yield 98%; colorless oil; $[\alpha]_D^{25}$ = −44.2 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.49–4.47 (m, 2H), 7.40–7.37 (m, 3H), 6.96 (m, 1H), 6.88 (m, 1H), 6.69 (m, 1H), 6.64 (m, 1H), 4.92 (d, J = 8.0 Hz, 1H), 4.42 (m, 1H), 4.15–4.11 (m, 2H), 3.69–3.65 (dd, J = 11.6, 3.6 Hz, 1H), 3.28–3.24 (dd, J = 11.6, 4.0 Hz, 1H), 1.65 (s, OH) 1.51 (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 150.16, 147.86, 138.00, 128.71, 127.26, 123.84, 120.89, 120.10, 112.90, 86.64, 74.90 (*C*HOH), 64.28 (CH_2), 45.15 (CH_2Cl), 14.79; HRMS (ESI) Calc. for $C_{17}H_{19}ClNaO_3$ $[M + Na]^+$ 329.0920, found 329.0915.

(*S*)-1-(Benzyl(2-hydroxyethyl)amino)-3-chloropropan-2-ol (3h). Prepared by the general procedure of Mitsunobu chloride substitution; yield 90%; light yellow oil; $[\alpha]_D^{25}$ = −15.5 (*c* 1.2, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.35–7.26 (m, 5H), 3.81–3.78 (m, 1H), 3.69–3.63 (m, 4H), 3.53–3.50 (q, J = 7.1, 5.5 Hz, 2H), 2.72–2.67 (m, 4H), 1.25 (bs, OH); ^{13}C NMR (125 MHz, $CDCl_3$): δ 138.78, 129.14, 129.00, 128.56, 127.54, 68.67 (*C*HOH), 59.76, 57.52, 56.72, 47.35 (CH_2Cl); HRMS (ESI) Calc. for $C_{12}H_{19}ClNO_2$ $[M + H]^+$ 244.1104, found 244.1112.

6-Chloro-6-deoxy-3-*O*-benzyl-L,2-*O*-(L-methylethylidene)-α-D-glucofuranose (3i). Prepared by the general procedure of Mitsunobu chloride substitution; yield 95%; semi-solid;

$[\alpha]_D^{25}$ = −23 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.39–7.33 (m, 5H), 5.92–5.91 (d, *J* = 3.6 Hz, 1H), 4.73–4.70 (m, 1H), 4.62–4.56 (m, 2H), 4.18–4.14 (m, 2H), 4.12–4.11 (d, *J* = 2.4 Hz, 1H), 3.85–3.82 (m, 1H), 3.72–3.68 (dd, *J* = 11.2, 5.6 Hz, 1H), 2.42 (s, OH), 1.42 (s, 3H), 1.30 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 154.92, 137.25, 129.88, 128.49, 128.03, 112.03, 105.22, 82.28, 81.61, 80.06, 72.34, 68.52, 48.36 (CH_2Cl), 26.85, 26.34, 21.70; HRMS (ESI) Calc. for $C_{16}H_{22}ClO_5$ $[M + H]^+$ 329.1156, found 329.1113.

6-Chloro-6-deoxy-l,2-*O*-(l-methylethylidene)-α-D-glucofuranose (3j). Prepared by the general procedure of Mitsunobu chloride substitution; yield 85%; semi-solid; $[\alpha]_D^{25}$ = +3.8 (*c* 1.5, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.90–5.86 (dd, *J* = 14.4, 3.6 Hz, 1H), 4.48–4.47 (q, *J* = 5.2, 4.0 Hz, 1H), 4.32–4.25 (m, 2H), 4.13–4.05 (m, 1H), 3.98–3.90 (dd, *J* = 11.6, 4.7 Hz, 1H), 3.92–3.85 (dd, *J* = 20.0, 4.6 Hz, 1H), 3.15 (s, OH), 1.63 (s, 3H), 1.50 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 111.59, 105.30, 85.19, 81.44, 74.37, 68.60, 47.99 (CH_2Cl), 26.93, 26.36; HRMS (ESI) Calc. for $C_9H_{16}ClO_5$ $[M + H]^+$ 239.0686, found 239.0680.

6-Chloro-6-deoxy-2,3-*O*-(l-methylethylidene)-1-*O*-acetyl-α-D-mannofuranose (3k). Prepared by the general procedure of Mitsunobu chloride substitution; yield 95%; white solid; mp. 83–85 °C; $[\alpha]_D^{25}$ = +13.5 (*c* 1.4, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.42 (bs, OH), 6.19 (s, 1H), 4.99–4.92 (m, 1H), 4.72 (dd, *J* = 5.8, 3.5 Hz, 1H), 4.17–4.08 (m, 2H), 3.87–3.84 (dd, *J* = 11.4, 3.1 Hz, 1H), 3.72–3.69 (dd, *J* = 11.4, 5.9 Hz, 1H), 2.06 (s, 3H), 1.68 (s, OH), 1.47 (s, 3H), 1.34 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 169.40, 113.45, 100.60, 84.88, 81.41, 79.53, 69.15, 47.78 (CH_2Cl), 26.01, 24.75, 21.02; HRMS (ESI) Calc. for $C_{11}H_{18}ClO_6$ $[M + H]^+$ 281.0792, found 281.0789.

Methyl 6-chloro-6-deoxy-2,3-di-*O*-acetyl-α-D-mannopyranoside (3l). Prepared by the general procedure of Mitsunobu chloride substitution; yield 94%; colorless semi-solid; $[\alpha]_D^{25}$ = +89.6 (*c* 0.5, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.31–5.28 (t, *J* = 19.20, 9.18 Hz, 1H), 4.94–4.93 (d, *J* = 3.62 Hz, 1H), 4.86–4.84 (m, 1H), 3.91–3.87 (m, 1H), 3.81–3.77 (dd, *J* = 11.9, 5.7 Hz, 1H), 3.68–3.62 (m, 2H), 3.43 (s, 3H), 2.10–2.06 (m, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 171.43, 170.27, 96.55, 72.72, 70.53, 69.76, 55.08, 44.00 (CH_2Cl), 20.63, 20.50; HRMS (ESI) Calc. for $C_{11}H_{18}ClO_7$ $[M + H]^+$ 297.0741, found 297.0738.

Thiophenyl 6-chloro-6-deoxy-2,3-di-*O*-acetyl-β-D-galactopyranoside (3m). Prepared by the general procedure of Mitsunobu chloride substitution; yield 94%; colorless viscous liquid; $[\alpha]_D^{25}$ = +4.5 (*c* 1.3, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.51–7.47 (m, 3H), 7.28–7.26 (m, 2H), 5.26 (d, *J* = 4.0 Hz, 1H), 4.99–4.96 (dd, *J* = 11.2, 5.7 Hz, 1H), 4.77–4.71 (d, *J* = 9.3 Hz, 1H), 4.35–4.28 (m, 1H), 3.96 (m, 1H), 3.92–3.81 (m, 1H), 3.71–3.68 (m, 1H), 2.09 (m, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.32, 170.28, 134.45, 132.09, 131.70, 128.54, 127.42, 126.23, 86.18, 78.04, 76.23, 73.16, 68.86, 45.68 (CH_2Cl), 20.30, 20.08; HRMS (ESI) Calc. for $C_{16}H_{20}ClO_6S$ $[M + H]^+$ 375.0669, found 375.0661.

Methyl 6-chloro-6-deoxy-2,3,4-tri-*O*-acetyl-α-D-mannopyranoside (3n). A mixture of methyl-α-D-mannopyranoside (776 mg, 4.0 mmol) and Ph_3P (1.36 g, 5.2 mmol) in toluene (20 mL) was partially dissolved on warming and DIAD (1.19 g, 5.9 mmol) was slowly added at 0 °C. After stirring for 15 minutes at this temperature, Me_3SiCl (550 mg, 5.1 mmol) under nitrogen was added using a syringe. The reaction mixture was stirred at room temperature for 3 h. After the completion of the reaction as indicated by TLC, pyridine (63 μL, 0.8 mmol) and acetic anhydride (1.65 μL, 16.2 mmol) were added to the reaction mixture. After the acetylation (6 h), the reaction was quenched with ethyl acetate (3 × 25 mL). The combined organic extracts were washed with water (2 × 10 mL) and brine solution (1 × 5 mL), dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue was subjected to column chromatography (silica gel, 0–15% EtOAc–hexane) to obtain pure product **3n** as a viscous liquid in 90% yield (1.216 g); $[\alpha]_D^{25}$ = +30.6 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.27–5.24 (m, 1H), 5.21 (d, *J* = 9.4 Hz, 1H), 5.19–5.15 (m, 1H), 4.65 (d, *J* = 1.7 Hz, 1H), 3.96–3.81 (m, 1H), 3.78–3.67 (dd, *J* = 5.2, 1.7 Hz, 1H), 3.63–3.52 (dd, *J* = 5.3, 1.7 Hz, 1H), 3.35 (s, 3H), 2.12–1.96 (3 × s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.43, 169.21, 98.39, 69.99, 69.70, 68.82, 65.95, 55.09, 44.45 (CH_2Cl), 22.15; HRMS (ESI) Calc. for $C_{13}H_{20}ClO_8$ $[M + H]^+$ 339.0847, found 339.0842.

(*S*)-2-((1,4-Dioxaspiro[4.5]decan-2-ylmethyl)amino)ethanol (20). In a solution comprising 2,3-*O*-cyclohexylideneglyceraldehyde **14** (850 mg, 5 mmol) and ethanol amine (366 mg, 6 mmol) dissolved in methanol (30 mL) was slowly added $NaBH_4$ (95 mg, 2.5 mmol), and the mixture was stirred overnight at room temperature. After the completion of the reaction (TLC), the methanol was evaporated and the residue was extracted with ethyl acetate (3 × 25 mL) and washed with brine solution (1 × 5 mL) and the organic layer was dried over anhydrous Na_2SO_4 to obtain the crude product **20**, which was purified by column chromatography (silica gel, 0–20% EtOAc–hexane) in 94% yield (1.01 g) as a colorless oil; $[\alpha]_D^{25}$ = −9.1 (*c* 1.0 $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ 4.26–4.24 (t, *J* = 11.8, 5.9 Hz, 1H), 4.06–4.03 (q, *J* = 7.9, 6.7 Hz, 1H), 3.68–3.64 (m, 3H), 2.82–2.79 (q, *J* = 9.65, 4.71 Hz, 1H), 2.78–2.75 (q, *J* = 11.87, 5.52 Hz, 3H), 1.62–1.55 (m, 8H), 1.42–1.37 (m, 2H); ^{13}C NMR (125 MHz, CDCl3): δ 109.72, 74.70, 67.01, 60.67, 52.22, 51.21, 36.33, 34.80, 24.86, 23.87, 23.75; HRMS (ESI) Calc. for $C_{11}H_{21}NNaO_3$ [M + Na]+ 238.1419, found 238.1411.

(*S*)-2-((1,4-Dioxaspiro[4.5]decan-2-ylmethyl)(benzyl)amino)-ethanol (21). K_2CO_3 (137 mg, 3.6 mmol) was added to the amino alcohol (*S*)-**20** (262 mg, 1.2 mmol) dissolved in acetonitrile (20 mL), followed by the addition of benzyl bromide (209 mg, 1.2 mmol) after 20 minutes. The reaction mixture was stirred at room temperature for 8 h. After the consumption of the starting material, the reaction mixture was concentrated under reduced pressure and the residue was dissolved in water (1 × 20 mL) and extracted with EtOAc (3 × 20 mL). The organic layer was dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. Purification of the residue by column chromatography (silica gel, 0–10% EtOAc–hexane) afforded (*S*)-**21** in 95% yield (353 mg) as a colorless liquid; $[\alpha]_D^{25}$ = +11.5 (*c* 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.36–7.26 (m, 5H), 4.22 (m, 1H), 3.99 (m, 1H), 3.77–3.57 (m, 4H), 3.48–3.43 (m, 1H), 2.75–2.64 (m, 4H), 1.56 (m, 8H), 1.28 (s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 138.87, 128.45, 128.05, 127.33, 109.72, 76.67, 69.34, 65.45, 62.69, 56.98, 55.67, 36.67, 34.77, 24.56,

23.67, 23.22; HRMS (ESI) Calc. for $C_{18}H_{28}NO_3$ $[M + H]^+$ 306.2069, found 306.2057.

(*S*)-3-(Benzyl(2-hydroxyethyl)amino)propane-1,2-diol (1h). A mixture of (*S*)-**21** (389 mg, 1.27 mmol) and PTSA (44 mg, 20 mol%) in MeOH (20 mL) was stirred at 50 °C until the starting material disappeared (as monitored by TLC, 8 h). The mixture was concentrated *in vacuo*, treated with water (1 × 20 mL) and extracted with EtOAc (3 × 20 mL). A $NaHCO_3$ solution (10%, 20 mL) was added to remove the excess PTSA. The combined organic extracts were washed with brine solution (1 × 10 mL), dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue was subjected to column chromatography (silica gel, 0–30% EtOAc–hexane) to obtain pure product (*S*)-**1h** in 92% yield (264 mg) as a colorless oil; $[\alpha]_D^{25}$ = −20.5 (*c* 1.1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.34–7.24 (m, 5H), 3.80–3.72 (m, 2H), 3.65–3.57 (m, 4H), 3.54–3.42 (dd, *J* = 11.5, 5.4 Hz, 1H), 3.24 (bs, OH), 2.81–2.54 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 138.14, 129.13, 128.50, 127.44, 69.01, 64.74, 59.68, 56.57, 56.24; HRMS (ESI) Calc. for $C_{12}H_{20}NO_3$ $[M + H]^+$ 226.1443, found 226.1438.

2,3-*O*-Cyclohexylidene-D-glyceraldehyde (14). To sodium metaperiodate ($NaIO_4$) (7.3 g, 34 mmol) and tetrabutylammonium bromide (PTC) (200 mg, 0.62 mmol) in water (60 mL) was added a solution of 1,2,5,6-di-*O*-cyclohexylidene-D-mannitol (10.0 g, 29.3 mmol) in THF (100 mL), and the mixture was stirred for 3 h at room temperature. After the completion of the reaction, the organic layer was separated and the aqueous layer was extracted with diethyl ether (3 × 35 mL). The combined diethyl ether solution was washed with water (1 × 35 mL) and dried over anhydrous sodium sulfate. The solvent was dried *in vacuo* to yield the title compound (*R*)-**14** in 90% yield (8.94 g) as a colorless viscous liquid; bp. 90–94 °C (2 mmHg) [lit.[48] 90–93 °C (2 mmHg)] $[\alpha]_D^{25}$ = +61.2 (*c* 3.4, benzene); ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.7 (s, 1H), 4.40 (m, 1H), 4.22–3.90 (m, 2H), 1.80–1.43 (m, 10H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 202.15 (*CH*O), 110.65, 98.39, 65.70, 36.15, 34.72, 25.00, 23.80; HRMS (ESI) Calc. for $C_9H_{15}O_3$ $[M + H]^+$ 171.1021, found 171.1019.

(2*R*,3*R*/*S*)-1,2-*O*-Cyclohexylidene-3-phenylpropane-3-ol (15). Bromobenzene (452 mg, 2.92 mmol) was added dropwise over 45 minutes at room temperature under nitrogen in the presence of a crystal of I_2 to magnesium turnings (75 mg, 2.92 mmol) placed in a reaction vessel comprising 60 mL anhydrous THF. After the generation of the Grignard reagent, the solution was cooled to −10 °C and cyclohexylideneglyceraldehyde (124 mg, 0.73 mmol) in THF (20 mL) was added dropwise to the reaction mixture. The reaction mixture was stirred at room temperature for 18 h and then cooled at 0 °C before the addition of saturated aqueous NH_4Cl. The mixture was extracted three times with EtOAc (3 × 40 mL). The extracts were combined and dried over anhydrous Na_2SO_4 and the solvent was evaporated under reduced pressure to get a mixture of *syn*- and *anti*-diastereomers in 95% total yield (687 mg). The crude products were purified by column chromatography (silica gel, 0–15% EtOAc–hexane) to provide (2*R*,3*R*)-**15** (46%) and (2*R*,3*S*)-**15** (46%) as colourless oils.

(2*R*,3*R*)-1,2-*O*-Cyclohexylidene-3-phenylpropane-3-ol (15). Yield 47%; colorless oil; $[\alpha]_D^{25}$ = +7.8 (*c* 1.0, $CHCl_3$); {lit.[49] for the (2*R*,3*R*/*S*) mixture, $[\alpha]_D^{22}$ = +11.0 (*c* 0.6, $CHCl_3$)}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.49–7.43 (m, 5H), 5.05 (d, *J* = 4.4 Hz, 1H), 4.45–4.41 (m, 1H), 4.08–4.04 (m, 1H), 3.85–3.81 (m, 1H), 2.6 (s, OH), 1.80–1.65 (m, 10H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 138.77, 127.53, 127.19, 126.69, 125.99, 124.98, 109.06, 78.08, 71.61, 63.12, 35.18, 33.66, 24.13, 23.03, 22.82; HRMS (ESI) Calc. for $C_{15}H_{20}NaO_3$ $[M + Na]^+$ 271.1310, found 271.1306.

(2*R*,3*S*)-1,2-*O*-Cyclohexylidene-3-phenylpropane-3-ol (15). Yield 47%; colorless oil; $[\alpha]_D^{25}$ = −5.6 (*c* 1.5, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.41–7.31 (m, 5H), 4.90 (d, *J* = 8.4 Hz, 1H), 3.89–3.85 (m, 2H), 3.64–3.61 (m, 1H), 2.06 (s, OH), 1.74–1.63 (m, 8H), 1.54–1.40 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 137.98, 128.52, 128.15, 126.47, 109.76, 83.19, 78.22, 60.33, 36.67, 36.54, 25.01, 23.74; HRMS (ESI) Calc. for $C_{15}H_{20}NaO_3$ $[M + Na]^+$ 271.1310, found 271.1302.

(2*R*,3*R*)-1,2-*O*-Cyclohexylidene-3-acetoxy-3-phenylpropane (16). Diisopropyl azodicarboxylate (DIAD) (1.22 g, 6.0 mmol) at 0 °C was injected into a mixture of (2*R*,3*S*)-1,2-*O*-cyclohexylidene-3-phenylpropane-3-ol **15** (992 mg, 4.0 mmol), Ph_3P (1.32 g, 5.2 mmol) and acetic acid (368 μL, 6.0 mmol) in anhydrous THF (20 mL) for 10 minutes under a nitrogen atmosphere. The reaction mixture was stirred at room temperature for 14 h. After the completion of the reaction as indicated by TLC, it was extracted with ethyl acetate (3 × 20 mL). The combined organic extracts were washed with water (2 × 10 mL) and brine solution (1 × 5 mL), dried with anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue was subjected to column chromatography (silica gel, 0–7% EtOAc–hexane) to obtain pure acetate (2*R*,3*R*)-**16** in 75% yield (870 mg), as a colorless oil; $[\alpha]_D^{25}$ = +11.5 (*c* 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.36–7.30 (m, 5H), 5.87 (d, *J* = 5.6 Hz, 1H), 4.35–4.31 (q, *J* = 12.0, 6.1 Hz, 1H), 3.99–3.92 (m, 2H), 2.11 (s, 3H), 1.65–1.52 (m, 10H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.67, 136.92, 128.56, 127.52, 126.65, 110.48, 77.47, 74.95, 65.36, 36.07, 35.04, 25.09, 23.77, 21.06; HRMS (ESI) Calc. for $C_{17}H_{22}NaO_4$ $[M + Na]^+$ 313.1416, found 313.1411.

Synthesis of (2*R*,3*R*)-1,2-*O*-cyclohexylidene-3-phenylpropane-3-ol (15) from (2*R*,3*R*)-16. The compound (2*R*,3*R*)-**16** (580 mg, 2 mmol) was dissolved in THF–H_2O (1 : 1 ratio), and lithium hydroxide (144 mg, 6 mmol) was added. The reaction mixture was stirred for 3 h until the hydrolysis was complete. The reaction was extracted with ethyl acetate (3 × 20 mL). The combined organic extracts were washed with brine solution (1 × 5 mL), dried with anhydrous Na_2SO_4 and concentrated *in vacuo* to get the pure (2*R*,3*R*)-**15** in 97% yield (481 mg) as a colorless liquid; HRMS (ESI) Calc. for $C_{15}H_{20}NaO_3$ $[M + Na]^+$ 271.1310, found 271.1303.

(2*R*,3*S*)-3-(2-Ethoxyphenoxy)-1,2-*O*-cyclohexylidene-3-phenylpropane (17). Diisopropyl azodicarboxylate (DIAD) (490 mg, 2.43 mmol) was added to a mixture of (2*R*,3*R*)-**15** (300 mg, 1.21 mmol), triphenylphosphine (636 mg, 2.43 mmol) and 2-ethoxyphenol (335 mg, 2.43 mmol) in anhydrous THF (15 mL) at 0 °C. The reaction mixture was allowed to reach room temperature and stirred for 24 h. After the completion of

the reaction (TLC), the extraction was done with ethyl acetate (3 × 30 mL). The organic layer was washed with water, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure and the crude product was purified by column chromatography (silica gel, 0–8% EtOAc–hexane) to provide (2*R*,3*S*)-**17** in 85% yield (378 mg) as a colorless oil; $[\alpha]_D^{25}$ = −12.2 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.34 (m, 2H), 7.32–7.27 (m, 3H), 6.85–6.81 (m, 2H), 6.78–6.65 (m, 2H), 5.17 (d, *J* = 6.2 Hz, 1H), 4.57 (q, *J* = 6.6 Hz, 1H), 4.08–4.04 (m, 2H), 3.84–3.78 (dd, *J* = 16.4, 8.5 Hz, 2H), 1.61–1.54 (m, 10H), 1.45–1.38 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 150.01, 147.90, 137.67, 128.15, 127.53, 127.12, 122.27, 120.90, 118.40, 114.51, 110.52, 82.65, 78.23, 65.40, 64.73, 35.90, 35.27, 25.16, 23.86, 14.95; HRMS (ESI) Calc. for $C_{23}H_{28}NaO_4$ $[M + Na]^+$ 391.1885, found 391.1891.

(2*R*,3*S*)-3-(2-Ethoxyphenoxy)-2-hydroxy-3-phenyl-1-propanol (1g). A mixture of (2*R*,3*S*)-**17** (467 mg, 1.27 mmol) and PTSA (44 mg, 20 mol%) in MeOH (30 mL) was stirred at 50 °C until the starting material disappeared (as monitored by TLC, 8 h). The mixture was concentrated *in vacuo* and extracted with EtOAc (3 × 25 mL). A $NaHCO_3$ solution (20%, 20 mL) was added to remove the excess PTSA, and the solvent was dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue was subjected to column chromatography (silica gel, 0–30% EtOAc–hexane) to obtain pure **1g** in 94% yield (343 mg) as a white crystalline solid; mp. 73–75 °C; $[\alpha]_D^{25}$ = +6.4 (*c* 1.0, ethanol); {lit.;[50] mp. 78–79 °C; $[\alpha]_D^{25}$ = +7.8 (*c* 1.0, ethanol)}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.46 (m, 1H); 7.41–7.33 (m, 4H), 6.96 (m, 1H), 6.89 (m, 1H), 6.74 (m, 1H), 6.63 (m, 1H), 4.87 (d, *J* = 8.0 Hz, 1H), 4.14 (m, 2H), 4.01 (m, 1H), 3.65 (m, 1H), 3.42 (m, 1H), 1.51 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 149.61, 147.80, 138.27, 129.56, 128.20, 127.09, 123.10, 120.81, 119.05, 112.66, 86.21, 75.51, 64.14, 62.03, 14.01; HRMS (ESI) Calc. for $C_{17}H_{20}NaO_4$ $[M + Na]^+$ 311.1259, found 311.1262.

(2*R*,3*S*)-3-(2-Ethoxyphenoxy)-3-phenylpropene-1,2-epoxide ((2*R*,3*S*)-4g). DBU (148 mg, 0.98 mmol) at 0 °C was added to the solution of chlorohydrin (2*S*,3*S*)-**3g** (100 mg, 3.3 mmol) in DCM (15 mL) and the reaction was stirred at room temperature. After the consumption of the starting material as indicated by TLC (6–7 h), the reaction was extracted with DCM (3 × 20 mL). The organic layer was dried over anhydrous Na_2SO_4 and concentrated *in vacuo* to obtain the pure epoxide (2*R*,3*S*)-**4g** in 98% yield (86 mg) as a colorless oil; $[\alpha]_D^{25}$ = −10.8 (*c* 0.5, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.44 (m, 2H), 7.37–7.30 (m, 3H), 6.89–6.86 (m, 3H), 6.78–6.75 (m, 1H), 4.91 (d, *J* = 6.0 Hz, 1H), 4.11–4.06 (q, *J* = 14.0, 7.2 Hz, 2H), 3.46 (m, 1H), 2.82–2.80 (t, *J* = 8.8, 4.4 Hz, 1H), 2.72–2.71 (q, *J* = 4.8, 2.8 Hz, 1H), 1.42 (t, *J* = 6.7 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 149.96, 147.80, 137.73, 130.03, 128.10, 126.83, 122.80, 120.98, 118.35, 114.24, 83.30, 64.77, 55.10, 44.65, 14.96; HRMS (ESI) Calc. for $C_{17}H_{18}NaO_3$ $[M + Na]^+$ 293.1156, found 293.1148.

(2*S*,3*S*)-3-(2-Ethoxyphenoxy)-3-phenylpropene-1,2-epoxide ((2*S*,3*S*)-4g). Diisopropyl azodicarboxylate (DIAD) (490 mg, 2.43 mmol) was added to a mixture of (2*R*,3S)-**1g** (348 mg, 1.21 mmol) and triphenylphosphine (636 mg, 2.43 mmol) in anhydrous THF (15 mL) at 0 °C. The reaction mixture was stirred for 24 h at room temperature. After the completion of the reaction (TLC), the extraction was done with ethyl acetate (3 × 30 mL) and the solvent was dried over anhydrous Na_2SO_4. The crude product was concentrated under reduced pressure and purified by column chromatography (silica gel, 0–6% EtOAc–hexane) to provide (2*S*,3*S*)-**4g** in 65% yield (212 mg) as a colorless oil; the spectral data are the same as reported in ref. 50. HRMS (ESI) Calc. for $C_{17}H_{18}NaO_3$ $[M + Na]^+$ 293.1156, found 293.1151.

{[(2*R*,3*S*)-3-(2-Ethoxyphenoxy)-2-hydroxy-3-phenyl-propyl]-amino}ethyl hydrogen sulfate-((2*R*,3*S*)-18). Compound **18** was prepared by following the procedure reported in ref. 39*b* in 78% yield. The spectral data are the same as reported in ref. 39*b*. HRMS (ESI) Calc. for $C_{19}H_{25}NNaO_6S$ $[M + H]^+$ 418.1300, found 418.1285.

{[(2*S*,3*S*)-3-(2-Ethoxyphenoxy)-2-hydroxy-3-phenyl-propyl]-amino}ethyl hydrogen sulfate-((2*S*,3*S*)-18). Compound **18** was prepared by following the procedure reported in ref. 39*b* in 78% yield. The spectral data are the same as reported in the literature. HRMS (ESI) Calc. for $C_{19}H_{25}NNaO_6S$ $[M + H]^+$ 418.1300, found 418.1291.

(2*R*,3*S*)-2-[α-(2-Ethoxyphenoxy)phenylmethyl]morpholine ((2*R*,3*S*)-19). NaOH (117 mg, 3 mmol) was added to a solution of (2*R*,3*S*)-**18** (417 mg, 1 mmol) in THF (17 mL) and EtOH (1.21 mL) at room temperature. The reaction mixture was heated to reflux for 3 h and cooled to room temperature. The reaction was quenched with water (1 × 20 mL) and extracted with ethyl acetate (3 × 25 mL). The organic layer was dried over anhydrous Na_2SO_4, concentrated *in vacuo*, and purified by column chromatography (silica gel, 0–20% EtOAc–hexane) to provide (2*R*,3*S*)-reboxetine **19** in 90% yield (281 mg) as a colorless oil; $[\alpha]_D^{25}$ = +11.6 (*c* 1.0, $CHCl_3$); [lit.[39a] $[\alpha]_D^{25}$ = +16.0 (*c* 0.68, CH_2Cl_2)]; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.48 (m, 2H), 7.45–7.30 (m, 3H), 6.87 (m, 1H), 6.81 (m, 2H), 6.60 (m, 1H), 5.23 (d, *J* = 6.4 Hz, 1H), 4.15 (m, 2H), 3.65 (m, 1H), 3.34 (m, 1H), 2.90–2.83 (m, 3H), 2.65 (m, 2H), 1.45 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 150.92, 148.71, 138.64, 129.32, 128.63, 124.52, 121.92, 118.92, 114.51, 84.41, 79.82, 67.02, 65.73, 47.81, 46.50, 15.36; HRMS (ESI) Calc. for $C_{19}H_{23}NNaO_3$ $[M + Na]^+$ 336.1576, found 336.1572.

(2*S*,3*S*)-2-[α-(2-Ethoxyphenoxy)phenylmethyl]morpholine ((2*S*,3*S*)-19). The compound (2*S*,3*S*)-**19** was prepared by following the procedure described for (2*R*,3*S*)-**19** in 90% yield (281 mg) as a colorless oil; the spectral data are the same as reported in ref. 39*f*. HRMS (ESI) Calc. for $C_{19}H_{23}NNaO_3$ $[M + Na]^+$ 336.1576, found 336.1568.

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