Organic Process Research & Development

COMMUNICATION

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Concise Synthesis of Two β-Adrenergic Blocking Agents in High Stereoselectivity Using the Readily Available Chiral Building Block (2*S*,2′*S*,2″*S*)-Tris-(2,3-epoxypropyl)-isocyanurate

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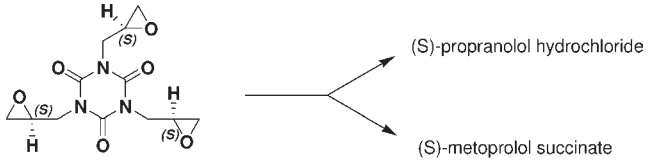
Supporting Information

ABSTRACT: A concise synthesis of (*S*)-propranolol and (*S*)-metoprolol in high stereoselectivity using the readily available chiral building block (2*S*,2′*S*,2″*S*)-tris-(2,3-epoxypropyl)-isocyanurate (**S-TGT**) as the key intermediate is described.

INTRODUCTION



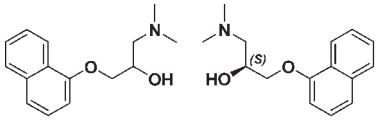
(2S, 2'S, 2"S)-tris-(2,3-epoxypropyl)-isocyanurate (**S-TGT**)

β-Adrenergic blocking agents (β-blockers) are important drugs used for the treatment of hypertension and angina pectoris.[1,2] Beta blockers are a common class of prescription drugs that counteract the stimulatory effects of adrenaline (epinephrine) on what are called the beta receptors. There are three known types of beta receptor, designated β_1, β_2, and β_3.

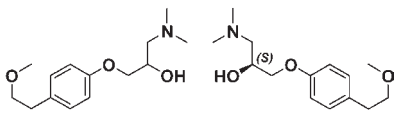
β_1-Adrenergic receptors are located mainly in the heart and in the kidneys. β_2-Adrenergic receptors are located mainly in the lungs, gastrointestinal tract, liver, uterus, vascular smooth muscle, and skeletal muscle. β_3-receptors are located in fat cells.

Propranolol is a known β-adrenergic blocking agent commonly used for the treatment of arterial hypertension (AHT) and some cardiovascular disorders. However, its use has been passed over by other beta-blocking agents, and side effects have been found, mainly in asthma patients.

Metoprolol is a widely used cardio-selective beta-blocker. However, like the rest of the other beta-blockers, it is also a racemic mixture of *R*- and *S*-isomers. The β_1 blocking activity (cardio selectivity) of metoprolol resides in the *S*-isomer, while the *R*-isomer exhibits β_2 blocking activity.



Propranolol **S-Propranolol (1)**



Metoprolol **(S)-Metoprolol (2)**

Most of the β-blockers possess a general structure Ar−O−$CH_2CH(OH)CH_2NHCH(CH_3)_2$ and have been used in the form of racemic mixtures.[3] There is certainly a strong need to replace approved racemic drugs with the single enantiomers.[4] There are several methods to obtain enantiomerically pure materials, which include classical resolution via diastereomers, chromatographic separation of enantiomers, enzymatic resolution, chiral kinetic resolution, and asymmetric synthesis.

Methods reported for the synthesis of (*S*)-propranolol involved the use of enzymes for resolution,[5] asymmetric hydrogenation using chiral metal complexes,[6] asymmetric epoxidation,[7] and synthesis from sorbitol[8] and also employed a polymer-supported reagent.[9]

Initially, Howe et al.[10] synthesized (*S*)-propranolol (**1**) by resolution of their racemates. Thus, 1-(dimethylamino)-3-(naphthalen-5-yloxy)propan-2-ol was resolved using (−)-O,O-di-*p*-toluoyl-tartaric acid. Later, Smith et al.[11] reported the synthesis of (*R*)-(+)-propranolol and confirmed its configuration by correlation with (*S*)-(+)-lactic acid. The compound **3** was prepared from (*S*)-(+)-lactic acid in three steps. The key intermediate (*R*)-(+)-**4** was prepared starting from epichlorohydrin in four steps (Scheme 1). After resolution, the (±)-chloroaminoalcohol afforded the (*R*)-(+)-chloroaminoalcohol **4**. The intermediate **4** was treated with LAH to give **3** which was also prepared from (*S*)-(+)-lactic acid, thereby confirming the configuration of the final product. This synthesis is tedious and necessarily involves resolution, in which ∼50% of another isomer is being wasted.

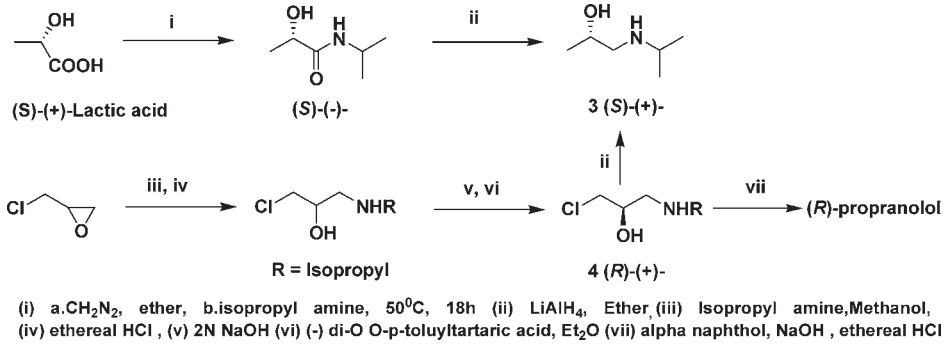
Similarly, synthetic strategies developed by Tsuda et al.,[12] Kojima et al.,[13] Katsuki et al.,[14] Kazunori et al.,[15] Sharpless et al.,[16] Wang et al.,[17] Cardillo et al.,[18] Yoshiyasu et al.,[19] Rama Rao et al.,[20] Shibasaki et al.,[21] Sinisterra et al.,[22] Kazuhiro et al.,[23] Hou et al.,[24] Salunkhe et al.,[25] Baeckwall et al.,[26] Kamal et al.,[27] Gurjar et al.,[28] and Joshi et al.[29] to harvest the single enantiomers of adrenergic blockers revolve around either the use of asymmetric catalysis, kinetic hydrolytic resolution, enzymatic resolution using lipase, or the use of *R*-epichlorohydrin. On a preparative scale, the enantiomers of propranolol have also been separated by multiple recrystallizations of the di(*p*-toluoyl)tartaric acid salts.[30]

Although a number of approaches have been described in the literature for the asymmetric synthesis of (*S*)-metoprolol and

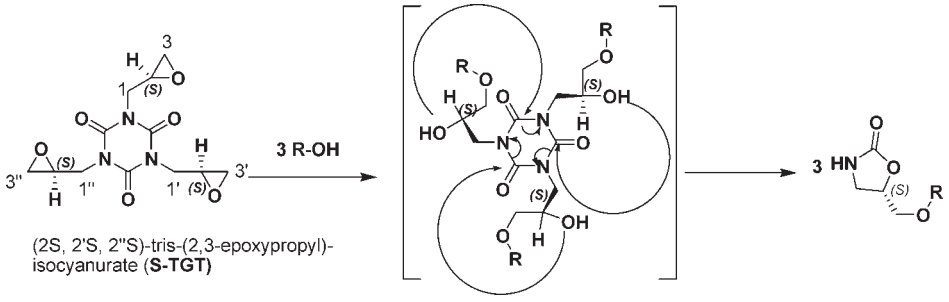
Received: May 9, 2011
Published: August 24, 2011

dx.doi.org/10.1021/op2001518 | *Org. Process Res. Dev.* 2011, 15, 1365–1370

Scheme 1



Scheme 2



(*S*)-propranolol, most of the methods require lengthy reaction sequences coupled with low yield and enantioselectivity. Synthetic efforts now need to be directed at short, practical routes that are amenable to scale-up for API preparation. In this context, the use of readily available chirally pure **S-TGT** provided a powerful tool for the generation of enantioenriched (*S*)-metoprolol and (*S*)-propranolol. The other salient features of this method include extraordinarily high levels of selectivity, easy availability of chirally pure glycidyl derivative **S-TGT**,[31] use of class-3 solvents, which makes it extremely simple to work with compared to other approaches, and excellent yields.

RESULTS AND DISCUSSION

On the basis of the proposed mechanism (Scheme 2), we envisaged that (2*S*,2′*S*,2″*S*)-tris-(2,3-epoxypropyl)-isocyanurate (**S-TGT**) is a substrate of special interest, as it serves as a common intermediate for (*S*)-metoprolol and (*S*)-propranolol and can be easily converted to compounds **6** and **9** by a simple reaction sequence in high enantiopurity and good yields (Scheme 3).

Thus, during the course of the reaction, the phenol derivative (**5** and **8**, respectively) attacks the C-3, C-3′, and C-3″ carbon of **S-TGT** and opens the epoxide ring. Subsequently, the free hydroxyl groups attack the carbonyl functionality to form the oxazolidinone **6** and **9**, respectively, with overall retention of stereochemistry.

As per the process disclosed by Ikeda et al.,[31] **S-TGT** can be obtained by alkylation of cyanuric acid with (*S*)-epichlorohydrin in the presence of a phase transfer catalyst and NaOH in 75−85% yield.

The general synthetic route we have employed for the synthesis of (*S*)-propranolol and (*S*)-metoprolol is presented in Scheme 3.

S-TGT was subjected to nucleophilic displacement with phenol nucleophiles **5** and **8**, respectively, to give chirally pure oxazolidines **6** and **9** followed by the N-alkylation of **6** and **9** with isopropyl bromide in the presence of sodium hydride to give the enantiomerically enriched N-alkylated oxazolidines **7** and **10** . Finally, the alkaline hydrolysis of **7** and **10** furnishes the stereoselective synthesis of β-blocker (*S*)-propranolol and (*S*)-metoprolol in high yield. The present method differs from the prior art methods[32,33] particularly in its use of different starting materials and different molar ratios of the reactants.

Typically, the ^{1}H NMR spectrum of **6** and **9** showed peaks at δ 5.1 and δ 4.98, respectively, due to a characteristic proton at the chiral center and a broad signal due to amide protons at δ 5.56 and δ 5.67. The ^{1}H NMR spectrum of **7** and **10** showed multiplicity at δ 1.23 and δ 1.21, respectively, due to the isopropyl group.

The structure of (*S*)-propranolol and (*S*)-metoprolol was confirmed using ^{1}H NMR, ^{13}C NMR, and HPLC, whereas chiral purity was confirmed by chiral HPLC.

To optimize reaction conditions, the reaction between **5** and **S-TGT** was taken as a model reaction. These optimized conditions were later employed for reacting corresponding phenol (**8**) with **S-TGT**. Different solvents were screened, and the results are reported in Table 1.

It was found that this reaction gave encouraging results in MIBK. As shown in Table 1 when **S-TGT** was reacted with the corresponding phenol **5** in acetonitrile and diethyl carbonate, ~20% conversion was observed (Table 1, entries 3 and 9), whereas only 10% conversion was noticed in propylene glycol (Table 1, entry 6).

dx.doi.org/10.1021/op2001518 |*Org. Process Res. Dev.* 2011, 15, 1365–1370

Scheme 3

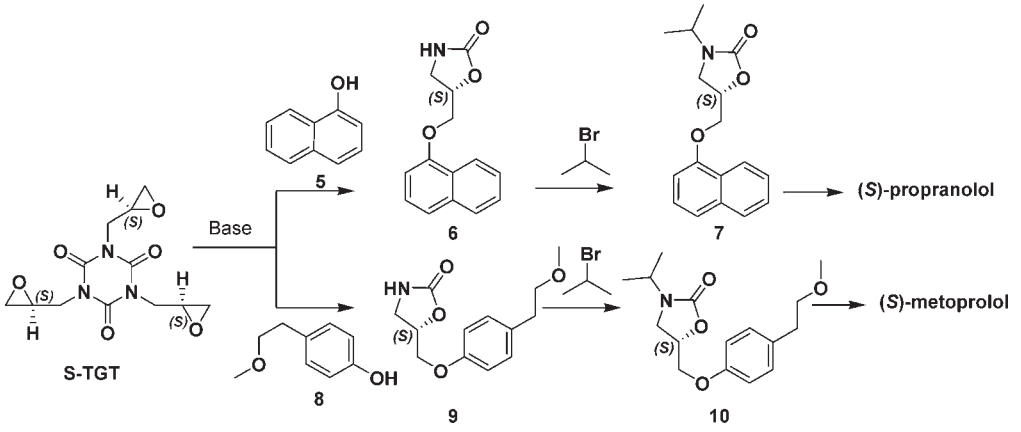
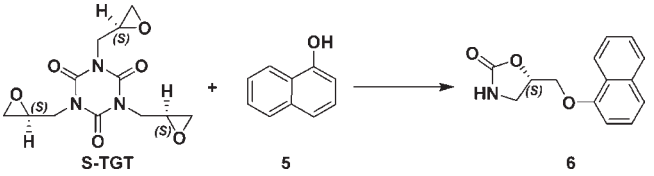


Table 1. Solvent Screening[a]



entry	solvent	base (equiv)	temp (°C)	time (h)	6 %[b]
1	MIBK	KOH (1.0)	65	5	<40
2	toluene	KOH (1.0)	65	7	--[c]
3	ACN	KOH (1.0)	65	5	<20
4	DMF	KOH (1.0)	65	7	--[c]
5	DMSO	KOH (1.0)	65	7	--[c]
6	propylene glycol	KOH (1.0)	65	5	<10
7	NMP	KOH (1.0)	65	7	--[c]
8	MTBE	KOH (1.0)	65	5	--[d]
9	diethyl carbonate	KOH (1.0)	65	5	<20

[a] Reaction performed on a 10 mmol scale with respect to (WRT) **S-TGT**. [b] By ^{1}H NMR, [c] No reaction. [d] Starting material insoluble.

Among all the solvents tried, only MIBK showed some promising result in which ~40% formation of **6** was observed. For a commercial process, this conversion seems to be very poor and may not be acceptable for larger-scale production, hence we decided to study other parameters such as molar ratios of reagents, temperature, and dilution. Eventually we found that ~0.3 equiv of base is sufficient for transformation. This reaction provided greater than 75% yield with greater than 98% chiral purity, and byproduct formation due to excessive hydrolysis of oxazolidinones was minimized. The results are summarized in Table 2.

Using 3 equiv of KOH we could isolate only 30% desired product (Table 2, entry 1), whereas 0.25 equiv of KOH showed a significant increase in yield (Table 2, entry 6). Reactions were also attempted using 0.15, 0.3, 0.6, 1.25, and 1.5 equiv of base, but satisfactory results were obtained only using 0.25 equiv of base (Table 2, entry 6). An amount of 0.15 equiv of base showed 45−50% unreacted TGT (Table 2, entry 7) and after 3 h reaction was found to be stagnant and degenerative, whereas 1.5 equiv of

Table 2. Optimization of Equivalents of Base Using MIBK Solvent[a]

entry	KOH (equiv)[b]	time (h)	yield **6** (%)[c]
1	3	3	30
2	1.5	2	45
3	1.25	5	50
4	0.6	3	60
5	0.3	2	75
6	**0.25**	**2**	**80**
7	0.15	5	55

[a] Reaction performed on a 10 mmol scale WRT **S-TGT**. [b] Powdered KOH having moisture content below 10% was used. [c] By column chromatography.

KOH showed comparatively less degradation than 3.0 equiv. Ultimately, entry 6 of Table 2 was found to be satisfactory in terms of yield and quality.

After optimizing the reaction conditions for **6**, we focused on alkylation of **6** using isopropyl bromide and sodium hydride. Indeed, sodium hydride is a commonly used base for deprotonation of amides, oxazolidinones, and other functional groups for the promotion of their nucleophilic substitution, typically in polar aprotic solvents such as DMSO, DMF, or acetonitrile. We decided to attempt this transformation using different bases in DMSO, and results are summarized in Table 3.

In an initial attempt, reaction of **6** with isopropyl bromide in the presence of potassium carbonate in DMSO showed only 25−30% conversion, hence various bases such as potassium *tert*-butoxide, sodium methoxide, sodium hydride, triethyl amine, etc. were tested.

Among the bases explored, NaH (Table 3, entry 5) was found to be satisfactory. Although DMSO is a good solvent for such reactions, a practical disadvantage in certain important situations is that DMSO and DMF cannot conveniently be used in combination with NaH due to formation of an explosive mixture above 45 °C. Attempts to try THF, CPME, 2-methyl THF, and sulfolane as solvent were also unsuccessful. Finally, we tested another good polar aprotic solvent *N*-methylpyrrolidone (NMP) to perform this reaction at 65 °C. To our delight, the reaction proceeded smoothly in NMP at 65 °C with superior yield and quality, and this reaction gave 90% yield of (*S*)-propranolol

dx.doi.org/10.1021/op2001518 |*Org. Process Res. Dev.* 2011, 15, 1365–1370

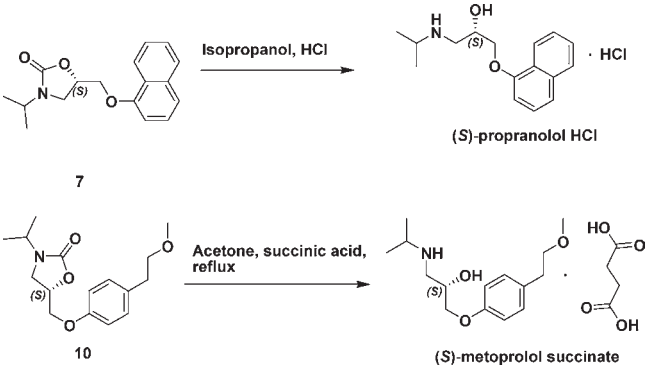
Table 3. Study of Base for Alkylation[a]

6 7

entry	base	temp (°C)	time (h)	yield 7 (%)[b]
1	KO^{t}Bu	0−10	3	10−15
2	KO^{t}Bu	45−55	3	10−15
3	K_2CO_3	45−55	5	10−15
4	NaH	0−10	3	50−55
5	**NaH**	**45−55**	**3**	**80−85**
6	TEA	45−55	5	no reaction
7	DBU	45−55	5	5−10

[a] Reaction performed on a 10 mmol scale WRT **6** in DMSO. [b] Isolated yield.

Scheme 4



precursor **7**. This reaction was also tested using 1.0 and 1.5 equiv of NaH, respectively, but satisfactory yields were obtained with 2.3 equiv of NaH. These optimized conditions were later used for the synthesis of (*S*)-metoprolol precursor **10**.

Finally, alkaline hydrolysis of N-alkylated oxazolidinones **7** and **10** complete the synthesis of (*S*)-propranolol and (*S*)-metoprolol in high overall yield and high chiral purity. These free bases were later converted to their pharmaceutically active salts to provide an active pharmaceutical ingredient using known methods (Scheme 4).

■ CONCLUSION

In summary, a concise synthesis of (*S*)-propranolol and (*S*)-metoprolol in high stereoselectivity has been achieved using the readily available chiral synthon **S-TGT** as the key step and source of chirality. The extension of the synthetic strategy described here employing the versatile intermediate **S-TGT** is being investigated for other chiral β-blockers.

■ EXPERIMENTAL SECTION

All materials were purchased from commercial suppliers. Unless specified otherwise, all reagents and solvents were used as supplied by manufacturers. Melting points were determined by an open air capillary with an X-6 melting point apparatus Beijing Tech Instrument Co Ltd. and are uncorrected. Varian ^{1}H NMR spectra (400 MHz) and ^{13}CNMR spectra (100 MHz) were recorded in $CDCl_3$ and DMSO-d_6, and mass spectra were determined on an API-2000LCMS mass spectrometer (Applied Biosciences).

Synthesis of (*S*)-5-((Naphthalen-4-yloxy)methyl)oxazolidin-2-one (6). (2*S*,2′*S*,2″*S*)-Tris-(2,3-epoxypropyl)-isocyanurate (5 kg, 16.8 mol) was added to mixture of α-naphthol (1.453 kg, 10.08 mol) and powdered potassium hydroxide (250 g) containing moisture less than 6% in methyl isobutyl ketone (25 L). The resulting reaction mass was heated to 110−115 °C for 2−3 h. After TLC ($CHCl_3$:CH_3OH; 9.5:0.5) showed disappearance of **S-TGT**, it was cooled and maintained under stirring at 5−10 °C for 2 h. The precipitated solid was filtered and dissolved in DCM (250 L). The organic layer was washed with 10% aqueous sodium hydroxide solution. The DCM layer was washed with sodium chloride followed by dilute hydrochloric acid and concentrated under vacuum, and the solid was crystallized from MIBK (25 L) to give 9.8 kg of (*S*)-5-((naphthalen-4-yloxy)methyl)oxazolidin-2-one (**6**) as an off-white solid in 80% yield and greater than 97% HPLC purity and greater than 99% chiral purity.

MP = 159 °C, $[\alpha]_D^{20}$ = −25.54 (c = 0.5, $CHCl_3$). MS(CI): calcd for $C_{14}H_{13}NO_3$ (M-H)/z, 242.26; found (M-H)/z, 242.2. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.73−3.76 (m, 1H), 3.84−3.88 (m, 1H), 4.29−4.37 (m, 2H), 5.08−5.13 (m, 1H), 5.56 (br s, 1H), 6.79−6.81 (d, 1H, J = 7.55 Hz), 7.34−7.38 (t, 1H), 7.44−7.78 (m, 3H), 7.8 (d, 1H), 8.18 (d, 1H). Anal. calcd for $C_{14}H_{13}NO_3$: C, 69.12; H, 5.39; N, 5.76. Found: C, 69.21; H, 5.32; N, 5.69.

[Chiral HPLC analysis; Chiral Technologies CHIRALCEL ADH column; eluent, *n*-hexane:ethanol:diethyl amine; flow rate, 1 mL/min; detector, 254 nm (t_R = 10.6 min) (t_S = 20.47 min).]

Synthesis of (*S*)-3-Isopropyl-5-((naphthalen-4-yloxy)methyl)oxazolidin-2-one (7). (*S*)-5-((Naphthalen-4-yloxy)methyl)oxazolidin-2-one (**6**) (3 kg, 12.33 mol) was added to a mixture of sodium hydride 60% dispersion in mineral oil (1.152 kg, 47.9 mol), in NMP (30 L) at 0−5 °C under an inert atmosphere. 2-Bromopropane (4.92 kg, 40 mol) was added in four equal lots over 20 min, and the reaction mass was gradually heated to 60−65 °C for 4−6 h. After TLC ($CHCl_3$:CH_3OH; 9.5:0.5) showed disappearance of **6**, it was cooled to 5−10 °C, and methanol (3 L) was added and poured on ice cold water (10 L). The product was filtered and washed with water (2 × 5 L). The solid was dried under reduced pressure to give 3.16 kg of (*S*)-3-isopropyl-5-((naphthalen-4-yloxy)methyl)oxazolidin-2-one (**7**) as an off-white solid in 90% yield with greater than 95% HPLC purity and greater than 99% chiral purity.

MP = 95 °C, $[\alpha]_D^{20}$ = 5.07 (c = 0.8, $CHCl_3$). MS(CI): calcd for $C_{17}H_{19}NO_3$ (M+H)/z, 286.34; found (M+H)/z, 286. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.73−3.76 (m, 1H), 3.84−3.88 (m, 1H), 4.29−4.37 (m, 2H), 5.08−5.13 (m, 1H), 5.56 (br s, 1H), 6.79−6.81 (d, 1H, J = 7.55 Hz), 7.34−7.38 (t, 1H), 7.44−7.78 (m, 3H), 7.8 (d, 1H), 8.18 (d, 1H). Anal. calcd for $C_{14}H_{13}NO_3$: C, 69.12; H, 5.39; N, 5.76. Found: C, 69.21; H, 5.32; N, 5.69.

[Chiral HPLC analysis; Chiral Technologies CHIRALCEL ADH column; eluent, *n*-hexane:ethanol:diethyl amine; flow rate, 1 mL/min; detector, 254 nm (t_R = 7 min) (t_S = 8.14 min).]

Synthesis of (*S*)-Propranolol (1). 85% potassium hydroxide flakes (9.55 kg, 170.3 mol) were added to a solution of 1:1 aqueous ethanol (54 L). The solution was stirred for 10 min, and (*S*)-3-isopropyl-5-((naphthalen-4-yloxy)methyl)oxazolidin-2-one (**7**) (2.7 kg, 9.46 mol) was added. The resulting reaction

mass was refluxed for 8−10 h. After completion of the reaction (monitored by TLC, $CHCl_3$:CH_3OH; 9.5:0.5), the excess alkali was neutralized by acetic acid (9 L), and product was extracted in DCM (2 × 5 L). The organic layer was concentrated under vacuum and flash chromatographed to give 1.44 kg of (*S*)-propranolol in 73% yield and greater than 98% HPLC purity.

The compound was purified using The Reveleris Flash system on 1.5 kg pf prepacked 40 μ silicagel cartridge supplied by Grace-USA, and the mobile phase was ethyl acetate:cyclohexane (9:1).

MP = 92 °C,[34] $[\alpha]_D^{20}$ = −21.6 (*c* = 1.02, EtOH). MS(CI) calcd for $C_{16}H_{21}NO_2$ (M+H)/*z*, 260.34; found (M+H)/*z*, 260.1. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.32 (d, 6H), 3.07−3.25 (m, 3H), 4.09−4.23 (m, 2H), 4.49 (m, 1H), 5.52 (br s, 2H), 6.78 (d, *J* = 7.5 Hz, 1H), 7.25−7.50 (m, 4H), 7.77−7.81 (m, 1H), 8.20−8.26 (m, 1H). Anal. calcd for $C_{16}H_{21}NO_2$: C, 74.1; H, 8.16; N, 5.4. Found: C, 74.2; H, 8.19; N, 5.51.

[Chiral HPLC analysis; Chiral Technologies CHIRALCEL OD-R column; eluent, 0.1 M sodium perchlorate/acetonitrile = 60/40; flow rate, 0.5 mL/min; detector, 254 nm (t_S = 14.1 min) (t_R = 15.27 min), Chiral purity: 99.88%.]

Synthesis of (*S*)-Propranolol Hydrochloride. To a solution of (*S*)-propranolol (**1**) (1.3 kg, 5.01 mol) in isopropanol (8 L) was bubbled dry HCl gas at 0−5 °C for 30 min, and the resulting solid was filtered and dried under vacuum to give 1.23 kg of (*S*)-propranolol hydrochloride in 84% yield and greater than 99.7% HPLC purity.

MP = 194−195 °C, $[\alpha]_D^{20}$ = −25.6 (*c* = 1.05, EtOH); lit. MP[6,7] 194−196 °C, $[\alpha]_D^{20}$ = −25.6 (*c* = 1.05, EtOH). MS(CI) calcd for $C_{16}H_{21}NO_2$ (M+H)/*z*, 260.34; found (M+H)/*z*, 260.1. ^{1}H NMR (400 MHz, D_2O): δ = 1.40−1.42 (d, 6H), 3.34−3.59 (m, 3H), 4.27−4.36 (m, 2H), 4.48−4.8 (m, 1H), 7.03−7.05 (d, 1H), 7.51−7.55 (t, 1H), 7.61−7.96 (m, 3H), 7.98−7.99 (d, 1H), 8.30−8.32 (m, 1H). Anal. calcd for $C_{16}H_{22}ClNO_2$: C, 64.97; H, 7.50; N, 4.74. Found: C, 64.88; H, 7.44; N, 4.71.

[Chiral HPLC analysis; Chiral Technologies CHIRALCEL OD-R column; eluent, 0.1 M sodium perchlorate/acetonitrile = 60/40; flow rate, 0.5 mL/min; detector, 254 nm (t_S = 14.1 min) (t_R = 15.27 min); chiral purity, 99.88%.]

Synthesis of (*S*)-5-((4-(2-Methoxyethyl)phenoxy)methyl)-oxazolidin-2-one (9). S-TGT (5 kg, 16.8 mol) was added to a mixture of 4-(2-methoxyethyl) phenol (**8**) (7.65 kg, 50.4 mol) and powdered potassium hydroxide (250 g) containing moisture less than 6% in methyl isobutyl ketone (25 L). The resulting reaction mass was heated to 110−115 °C for 2−3 h. After TLC ($CHCl_3$:CH_3OH; 9.5:0.5) showed disappearance of **S-TGT**, it was cooled and maintained under stirring at 0−10 °C for 2 h. The precipitated solid was filtered and washed with cold MIBK (20 L), and the wet cake was dissolved in DCM (30 L). The organic layer was washed with 10% aqueous sodium hydroxide solution to remove unreacted phenol. The DCM layer was washed with sodium chloride followed by dilute hydrochloric acid and concentrated under vacuum, and the solid was crystallized from methanol (6 L) to give 9.5 kg of (*S*)-5-((4-(2-methoxyethyl)phenoxy)methyl) oxazolidin-2-one (**9**) as an off-white solid in 75% yield in greater than 97% HPLC purity and greater than 99% chiral purity.

MP = 107 °C, $[\alpha]_D^{20}$ = 8.45 (*c* = 0.5, $CHCl_3$). MS(CI) calcd for $C_{13}H_{17}NO_4$ (M+Na)/*z*, 274.28; found (M+Na)/*z*, 274.1. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.8−2.84 (t, 2H), 3.34 (s, 3H), 3.52−3.62 (m, 3H), 3.73−3.78 (t, 1H), 4.08−4.16 (m, 2H), 4.92−4.98 (m, 1H), 5.66 (br s, 1H), 6.74−6.84 (d, 2H), 7.13−7.26 (d, 2H). Anal. calcd for $C_{13}H_{17}NO_4$: C, 62.14; H, 6.82; N, 5.57. Found: C, 62.1; H, 6.81; N, 5.61.

[Chiral HPLC analysis; Chiral Technologies CHIRALCEL ADH column; eluent, *n*-hexane:ethanol:diethyl amine; flow rate, 0.8 mL/min; detector, 254 nm (t_R = 17.09 min) (t_S = 18.71 min).]

Synthesis of (*S*)-5-((4-(2-Methoxyethyl)phenoxy)methyl)-3-isopropyloxazolidin-2-one (10). (*S*)-5-((4-(2-Methoxyethyl)phenoxy)methyl)oxazolidin-2-one (**9**) (9 kg, 35.8 mol) was added to a mixture of sodium hydride 60% dispersion in mineral oil (3.15 kg, 78.76 mol), in NMP (45 L) at 0−5 °C under inert atmosphere. 2-Bromopropane (14.94 kg, 121.45 mol) was added in four equal lots over 20 min, and the reaction mass was gradually heated to 60−65 °C for 5−6 h. After TLC ($CHCl_3$:CH_3OH; 9.5:0.5) showed disappearance of **9**, it was cooled to 5−10 °C, and methanol (6.5 L) was added and poured on ice cold water (180 L). The product was filtered and washed with water (2 × 15 L). The solid was dried under reduced pressure to give 7.88 kg of ((*S*)-5-((4-(2-methoxyethyl)phenoxy)methyl)-3-isopropyloxazolidin-2-one (**10**) as an off-white solid in 75% yield and greater than 96% HPLC purity and greater than 99% chiral purity.

$[\alpha]_D^{20}$ = 31.2 (*c* = 0.8, $CHCl_3$) MS(CI) calcd for $C_{16}H_{23}NO_4$ (M+H)/*z*, 294.36; found (M+H)/*z*, 294.1. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.19−1.21 (d, 2H), 2.80−2.84 (t, 2H), 3.34 (s, 3H), 3.46−3.49 (m, 1H), 3.54−3.58 (t, 2H), 3.62−3.66 (t, 1H), 4.04−4.17 (m, 1H), 4.77−4.83 (m, 1H), 6.81−6.83 (d, 2H), 7.13−7.26 (d, 2H). Anal. calcd for $C_{16}H_{23}NO_4$: C, 65.51; H, 7.9; N, 4.77. Found: C, 65.41; H, 7.72; N, 4.71.

[Chiral HPLC analysis; Chiral Technologies CHIRALCEL ADH column; eluent: *n*-hexane:ethanol:diethyl amine; flow rate, 0.8 mL/min; detector, 254 nm (t_R = 9.5 min) (t_S = 10.69 min).]

Synthesis of (*S*)-Metoprolol (2). Potassium hydroxide flakes (85%, 25.23 kg, 449.74 mol) were added to a solution of 1:1 aqueous ethanol (143 L). The solution was stirred for 10 min, and (*S*)-5-((4-(2-methoxyethyl)phenoxy)methyl)-3-isopropyloxazolidin-2-one (**10**) (7 kg, 23.86 mol) was added. The resulting reaction mass was refluxed for 8−10 h. After TLC ($CHCl_3$:CH_3OH; 9.5:0.5) showed completion of reaction, excess alkali was neutralized by acetic acid (~22 L), and product was extracted in DCM (2 × 30 L). The organic layer was concentrated under reduced pressure to give 5.36 kg of (*S*)-metoprolol in 83% yield and greater than 95% HPLC purity as a semisolid mass and greater than 99% chiral purity.

$[\alpha]_D^{20}$ = −8.72 (*c* = 10, $CHCl_3$).[29] MS(CI) calcd for $C_{15}H_{25}NO_3$ (M+H)/*z*, 268.36; found (M+H)/*z*, 268.1. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.08−1.09 (d, 6H), 2.62 (br s, 2H), 2.69−2.85 (m, 5H), 3.34 (s, 3H), 3.54 (t, 2H), 3.92−3.99 (m, 2H), 4.01−4.03 (m, 1H), 6.83−6.85 (d, 2H), 7.11−7.26 (d, 2H). Anal. calcd for $C_{15}H_{25}NO_3$: C, 67.38; H, 9.42; N, 5.24. Found: C, 67.41; H, 9.72; N, 5.71.

[Chiral HPLC analysis; DAICEL CHIRALCEL OD (4.6 × 25 cm) column; eluent, hexane/ethylalcohol/diethylamine = 70/30/0.1; flow rate, 0.5 mL/min; detector, 254 nm (t_R = 9.7 min) (t_S = 11.77 min); chiral purity: 99.8%.]

Synthesis of (*S*)-Metoprolol Succinate. (*S*)-Metoprolol (**2**) (1.45 kg, 5.423 mol) was dissolved in acetone (4.35 L) and stirred for 10 min. Succinic acid (667 g, 6.6 mol) was added, and the resulting reaction mass was refluxed for 1 h. The clear reaction mass was gradually cooled to 5−10 °C and stirred for 30−60 min. The precipitated (*S*)-metoprolol succinate was filtered and washed with cold acetone (500 mL), and the resulting

solid was dried under vacuum to give 1.8 kg of (*S*)-metoprolol succinate in 85% yield and greater than 99.7% HPLC purity as a white solid.

$[\alpha]_D^{20} = -16.2$ ($c = 1$, MeOH), MP = 107−108 °C. MS(CI): calcd for $C_{15}H_{25}NO_3$ (M+H)/*z*, 268.36; found (M+H)/*z*, 268.1. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 1.09−1.12 (d, 6H), 2.23 (s, 2H), 2.49−2.92 (m, 4H), 3.03−3.06 (m, 1H), 3.18 (s, 3H), 3.43−3.46 (t, 2H), 3.92−3.99 (m, 2H), 4.01−4.03 (m, 1H), 6.83−6.81 (d, 2H), 7.08−7.11 (d, 2H). Anal. calcd for $C_{15}H_{25}NO_3C_4H_6O_4$: C, 59.20.38; H, 8.11; N, 3.63. Found: C, 59.18; H, 8.32; N, 3.71.

[Chiral HPLC analysis; DAICEL CHIRALCEL OD (4.6 × 25 cm) column; eluent, hexane/ethylalcohol/diethylamine = 70/30/0.1; flow rate, 0.5 mL/min; detector, 254 nm (t_R = 9.7 min) (t_S = 11.77 min); chiral purity, 99.8%.]

■ ASSOCIATED CONTENT

Supporting Information. Additional characterization data of all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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■ ACKNOWLEDGMENT

The authors wish to thank Mr. Samit S. Mehta, Emcure Pharmaceuticals Ltd., for generous support and constant encouragement. The authors also wish to thank Dr. Milind M. Gharpure for the chemistry inputs and Mr. Satyajeet Biswas for analytical support. Finally, it is a pleasure to acknowledge the reviewers and Editor for valuable suggestions.

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