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Asymmetric synthesis of α,α-disubstituted α-amino alcohol derivatives

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Abstract—We herein report an asymmetric synthesis of α,α-disubstituted α-amino alcohol derivatives **3**, key intermediates of a novel immunomodulator, using enzymatic desymmetrization of 2-alkyl-2-*tert*-butoxycarbonylamino-1,3-propanediols **1a** and **1b**. This method makes it possible to prepare a chiral analogue of FTY720 **4**. These synthetic procedures allow for a broad structure variation in order to evaluate structure–activity relationships and the mechanism of action for sphingosine 1-phosphate-1 ($S1P_1$) receptor agonist.

1. Introduction

In recent years, a great deal of attention has been focused on the synthesis of α,α-disubstituted α-amino alcohol derivatives with a view to design and synthesise biologically active compounds.[1] In particular, α,α-disubstituted α-amino alcohols are recognized as significant components of novel immunomodulators, such as FTY720 and its chiral analogues.[2] Accordingly, the synthetic importance, as well as the biological interest for the construction of optically active quaternary carbon centers, has been recognized, as seen in the recent positive reviews.[3] In this context, and as a part of our $S1P_1$ receptor agonist research program, we have been interested in the study and development of a methodology for the synthesis of intermediate **3**. Preliminary studies indicated that the stereochemistry of the quaternary carbon center is closely associated with the biological activity, and that the (*R*)-configuration has been shown to be essential for $S1P_1$ agonistic activity. We have already reported on the practical synthetic method used for the preparation of (4*R*)-methyl-4-[2-(thiophen-2-yl)ethyl]oxazolidin-2-one **9a** via enzymatic desymmetrization of 2-*tert*-butoxycarbonylamino-2-methyl-1,3-propanediol **1a**.[4] Herein, we report the experimental details of a practical and versatile synthesis of a series of novel thiophene, furan and pyrrole-based amino alcohol analogues in the same manner. Additionally, the chiral analogue of FTY720 **4**,[1,5] which is an invaluable tool for the elucidation of FTY720's mechanism of action, was prepared using this methodology (Scheme 1).

Among a number of synthetic methods for the preparation of α,α-disubstituted α-amino alcohols, the enzymatic desymmetrization of achiral 2-alkyl-2-*tert*-butoxycarbonylamino-1,3-propanediol leading to an enantiomerically enriched monoester was considered attractive. Desymmetrization reactions have an advantage over conventional kinetic resolution reactions with regards to their potential ability to achieve high enantiomeric excess (ee) and also to obtain up to 100% conversion. Although many successful examples of similar desymmetrization of 2-monosubstituted-1,3-propanediols have already been reported,[6] to the best of our knowledge, there are only a few examples of such desymmetrization methods applied to prochiral compounds bearing a quaternary carbon center.[7] Therefore, our practical synthetic method used for the preparation of (4*R*)-methyl-4-[2-(thiophen-2-yl)ethyl]oxazolidin-2-one **9a** via enzymatic desymmetrization of 2-*tert*-butoxycarbonylamino-2-methyl-1,3-propanediol **1a** allows for a broad structural variation and delivers the essential tools for further elucidating the $S1P_1$ receptor agonist.

2. Results and discussion

At first, in order to examine the effects of the substituents at the 3-position on the thiophene ring, (2*R*)-amino-2-methyl-4-(3-substituted-thiophen-2-yl)butan-1-ol D-(−)-tartaric acid salts **10a**–**e**, key intermediates of the desired amino alcohol derivatives, were synthesized as is shown

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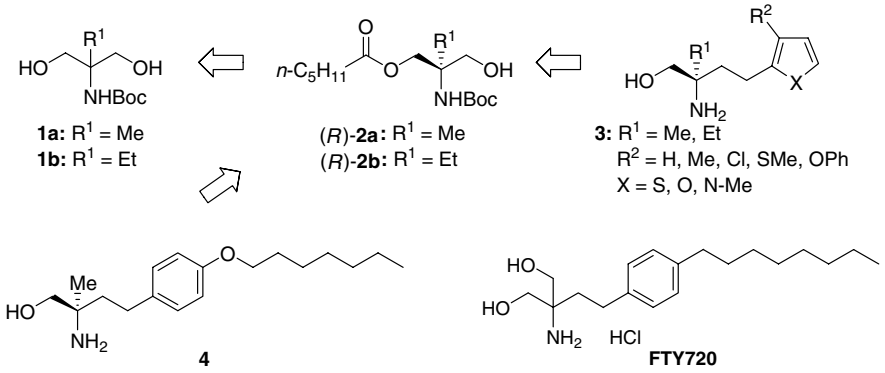
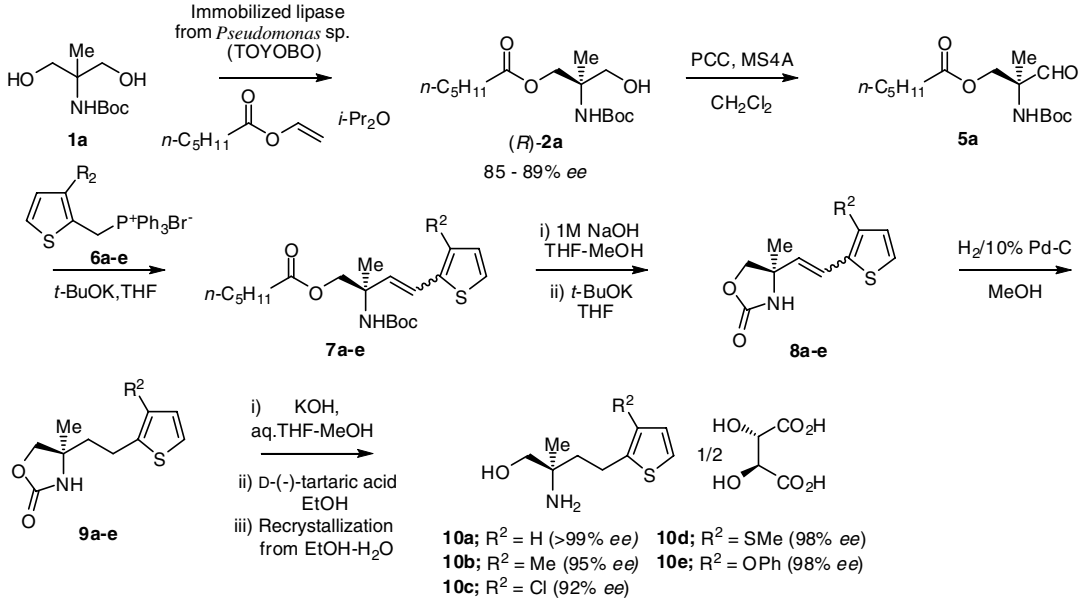


Scheme 1.

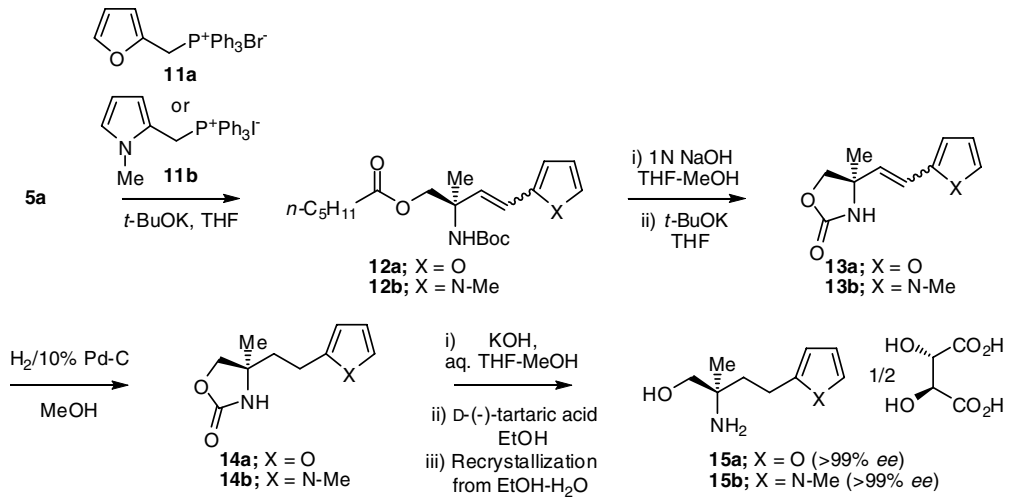
in Scheme 2. 2-*tert*-Butoxycarbonylamino-2-methyl-1,3-propanediol **1a** was treated with the immobilized lipase from *Pseudomonas* sp. (TOYOBO) and vinyl *n*-hexanoate in *i*-Pr_2O at room temperature to obtain optically active monoester (*R*)-**2a** (88% yield, 85–89% ee). After the oxidation of the primary alcohol with PCC in CH_2Cl_2, Wittig condensation of **5a** with various types of phosphonium salts **6a–e** was carried out in the presence of *t*-BuOK in THF at 0 °C. The subsequent deprotection of the ester group of **7a–e** followed by treatment with *t*-BuOK in THF provided **8a–e** in good yield. After formation of the oxazolidinone ring, olefin reduction with 10% Pd–C in MeOH under a hydrogen atmosphere provided **9a–e** in good yield. Compounds **9a–e** were then hydrolyzed and resolved with D-(−)-tartaric acid in EtOH to give salts **10a–e**. Recrystallization of the resulting salts from aqueous EtOH was accomplished to increase the ee to 92 to >99%.

These encouraging results obtained in the preparation of **10a–e** prompted us to apply this synthetic methodology to the preparation of (2*R*)-amino-2-methyl-4-(furan-2-yl)butan-1-ol 1/2 D-(−)-tartaric acid salt **15a** and (2*R*)-amino-2-methyl-4-(1-methylpyrrol-2-yl)butan-1-ol 1/2 D-(−)-tartaric acid salt **15b**, as shown in Scheme 3. In general, furan or pyrrole-based derivatives could also be synthesized along the same procedures described in Scheme 2. Wittig condensation of aldehyde **5a** with phosphonium salt **11a** or **11b** was carried out in the presence of *t*-BuOK in THF to yield **12a** and **12b** in good yield, respectively. After deprotection of the ester group of **12a** or **12b**, treatment with *t*-BuOK in THF provided **13a** or **13b** in good yield. Then, the reduction of olefin with 10% Pd–C in MeOH under a hydrogen atmosphere provided **14a** or **14b** in good yield. Finally, **14a** and **14b** were hydrolyzed and resolved with D-(−)-tartaric acid in EtOH to give salts **15a** and **15b**. Recrystallization of the resulting salts from aqueous EtOH was accomplished to increase the ee to >99%. Thus, by using common key intermediate **5a**, a practical and versatile synthetic method for the preparation of novel thiophene, furan and pyrrole-based amino alcohol analogues **10a–e** and **15a** and **15b** had been achieved.

On the other hand for the preparation of the ethyl-substituted oxazolidinones **18a–c**, better results were obtained



Scheme 2.

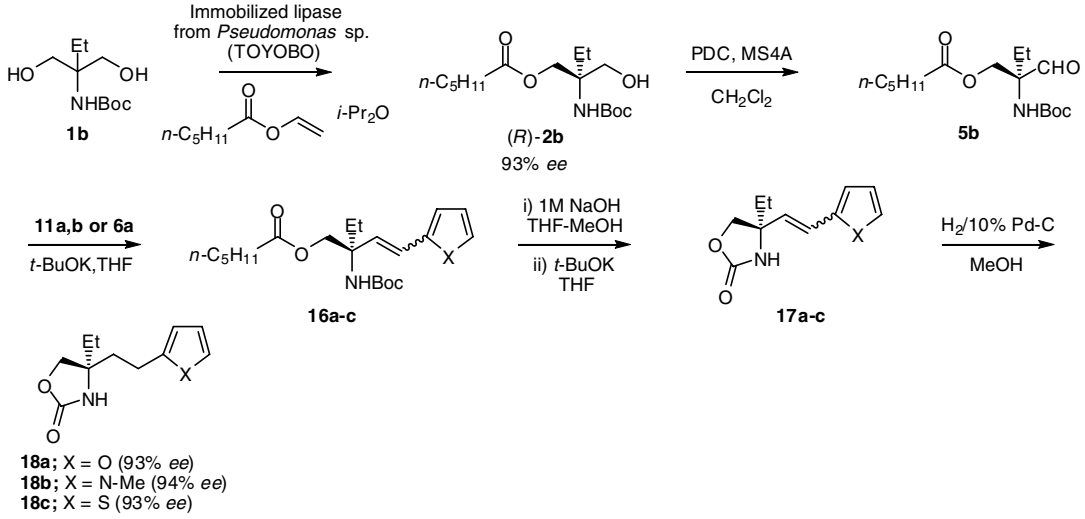


Scheme 3.

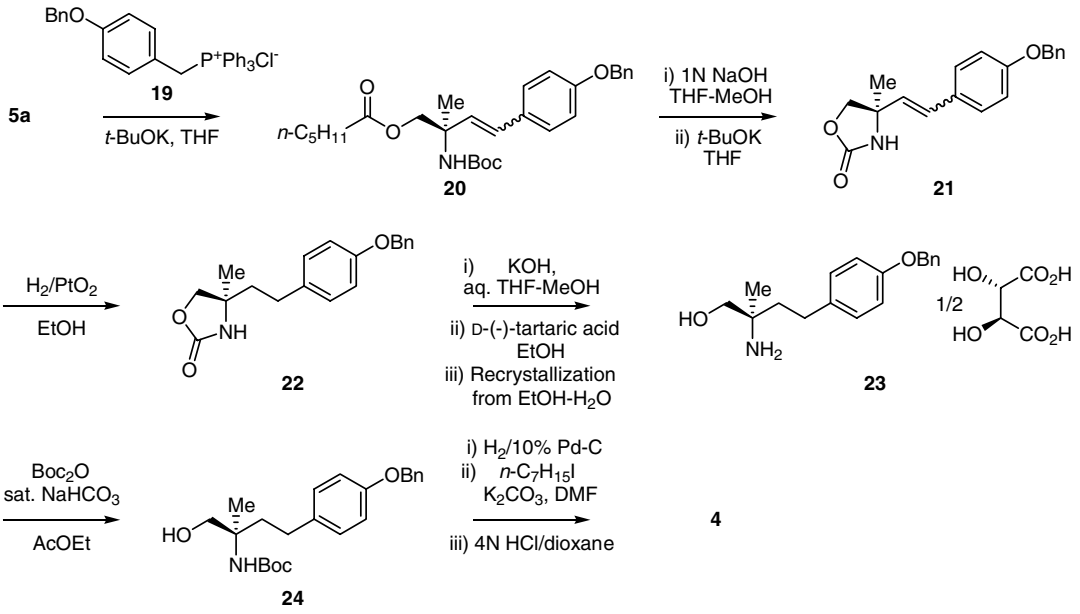
using 2-*tert*-butoxycarbonylamino-2-ethyl-1,3-propanediol **1b** for the lipase-catalyzed desymmetrization. The reaction was carried out in a similar manner using **1a** as a starting material to obtain the desired monoester (*R*)-**2b** in an 87% yield with an ee of 93%. As shown in Scheme 4, the desired **18a–c** could be obtained with the same procedure as described in Schemes 2 and 3.

Having determined the synthetic conditions for the preparation of the desired amino alcohol derivatives using lipase-catalyzed desymmetrization, we sought to apply this method to the synthesis of a chiral analogue of FTY720 **4**. FTY720, a synthetic analogue of ISP-1 (myriocin) derived from the fungus *Isaria sinclairii*, is an orally active immunomodulator under development by Mitsubishi Pharma Corporation and Novartis for potential use in organ transplantation and autoimmune diseases.[8] The active, phosphorylated form of FTY720 acts as a $S1P_1$ receptor agonist, and has recently been shown to induce internalization of the $S1P_1$ receptor, rendering lymphocytes unresponsive to S1P present in the blood, and thus depriving T and B cells of an obligatory signal to exit from lymphoid organs.[9] According to their information, using a chiral analogue of FTY720 **4** revealed that only the (*R*)-enantiomer is biologically active in vivo and only the phosphate of (*R*)-enantiomer has strong binding affinity on S1P receptors. Therefore, chiral analogues of FTY720, such as **4**, are invaluable tools to differentiate biological effects and to further elucidate FTY720's mechanism of action. In 2002, Hinterding et al. reported the first asymmetric synthesis of **4**[2a] using the Schöllkopf protocol,[10] and then they applied this methodology to the preparation of key intermediate **24** to allow for a broad structure variation of the lipophilic side chain.[1]

Finally, the synthetic route to the chiral analogue of FTY720 **4** is shown in Scheme 5. The Wittig condensation of aldehyde **5a** with phosphonium salt **19**[11] was carried out in the presence of *t*-BuOK in THF to provide **20** in good yield. After the formation of the oxazolidinone ring, reduction of the olefin with PtO_2 in EtOH under a hydrogen atmosphere provided **22** in good yield. Compound **22** was then hydrolyzed and resolved with D-(−)-tartaric acid in EtOH to give salts **23**, and recrystallization of the result-



Scheme 4.



Scheme 5.

ing salts from aqueous EtOH was accomplished to increase the ee to >99%. After protection of amino group with Boc_2O and $NaHCO_3$, the benzyl group was deprotected via hydrogenolysis. Then, incorporation of the lipophilic side chain via phenol alkylation using *n*-heptyl iodide in the presence of K_2CO_3 in THF, followed by deprotection of Boc group, gave **4** in good yield.

3. Conclusion

An efficient method for the preparation of **3**, a key intermediate of the $S1P_1$ agonist with high enantiomeric purity, through the use of lipase-catalyzed desymmetrization of **1a** and **1b** as the key step has been described. We successfully applied this method to the preparation of a chiral analogue of FTY720 **4**. Further work in this area is now in progress.

4. Experimental

4.1. General

All melting points were measured on a Yanaco MP-500D micro melting point apparatus and are uncorrected. Optical rotations were measured with a JASCO P-1030 digital polarimeter. The IR spectra were measured on a JASCO FT/IR 610, JASCO FT/IR 8300 or JASCO FT/IR 8900 spectrophotometer as KBr plates or $CHCl_3$ solution, and peaks are recorded in cm^{-1}. ^1H NMR spectra were recorded on a JEOL JNM-GSK 400, Varian Mercury-400 or Inova-500 spectrometer in $CDCl_3$, CD_3OD, DMSO-d_6, or D_2O. ^1H NMR chemical shifts are reported in parts per million downfield of internal tetramethylsilane. Mass spectra were recorded using a JEOL JMS-BU 20, JMS-700 or JMS-700QQ spectrometer. Elemental analysis was performed on a Yanaco MT-5 or MT-6. An analytical HPLC was performed on a HITACHI D-7000 interface equipped with a HITACHI L-7400 UV detector, a HITACHI L-7100 intelligent pump and a HITACHI L-7300 column oven. Thin layer chromatography (TLC) was used routinely to monitor the progress and purity of compounds and performed on Merck Kieselgel 60 F_{254} plates. For flash column chromatography, silica gel (Kieselgel 60, 230–400 mesh) was employed.

4.2. (2*R*)-*tert*-Butoxycarbonylamino-3-*n*-hexanoyloxy-2-methyl-1-propanol (*R*)-2a

2-*tert*-Butoxycarbonylamino-2-methyl-1,3-propanediol **1a** (20.0 g, 97.4 mmol) was suspended in diisopropyl ether (200 ml), and vinyl *n*-hexanoate (16.3 ml, 0.10 mol) and lipase [Immobilized lipase from *Pseudomonas* sp. (TOYOBO; 0.67 U/mg)] (0.8 g) were added thereto followed by vigorous stirring for 2 h at room temperature. The reaction solution was filtered, and the filtrate was evaporated under reduced pressure. The obtained residue was purified by chromatography on a silica gel column (eluent, *n*-hexane–AcOEt = 10:1–2:1) to afford the title compound (25.0 g, 85%) as a colorless oil in an enantiomeric excess of 85%. The obtained (2*R*)-*tert*-butoxycarbonylamino-3-*n*-hexanoyloxy-2-methyl-1-propanol was subjected to an optically active HPLC column for analytical separation [column, Chiralcel OF (4.6∅ × 250 mm); eluent, 70:30 *n*-hexane–2-propanol mixture; flow rate, 0.5 ml/min; t_R of (*S*)-isomer, 8.2 min; t_R of (*R*)-isomer, 10.5 min] to determine the enantiomeric excess. The absolute configuration of (*R*)-**2a** was determined by comparison of the specific rotation with that of the known compound, (2*R*)-*tert*-butoxycarbonylamino-2-methyl-3-buten-1-ol, which can be easily synthesized from (*R*)-**2a** as described in Ref. 12. $[\alpha]_D^{25} = -8.5$ (*c* 1.86, $CHCl_3$); IR (KBr): 3415, 3380, 2961, 2935, 2874, 1721, 1505, 1458, 1392, 1368, 1293, 1248, 1168, 1076 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 4.86 (s, 1H), 4.25 (d, 1H,

$J = 11.2$ Hz), 4.19 (d, 1H, $J = 11.2$ Hz), 3.86 (br s, 1H), 3.70–3.55 (m, 2H), 2.36 (t, 2H, $J = 7.4$ Hz), 1.68–1.58 (m, 2H), 1.44 (s, 9H), 1.40–1.30 (m, 4H), 1.25 (s, 3H), 0.90 (t, 3H, $J = 7.0$ Hz); MS (FAB) m/z: 304 $(M+H)^+$.

4.3. (2*S*)-*tert*-Butoxycarbonylamino-3-*n*-hexanoyloxy-2-methyl-1-propanal 5a

(2*R*)-*tert*-Butoxycarbonylamino-3-*n*-hexanoyloxy-2-methyl-1-propanol (*R*)-**2a** (30.7 g, 0.10 mol) was dissolved in CH_2Cl_2 (600 ml), and then molecular sieves 4 Å (220 g) and pyridinium chlorochromate (43.6 g, 0.20 mol) were added thereto in an ice bath followed by stirring for 2 h at room temperature. The reaction solution was diluted with Et_2O, and then the solution was filtered. The filtrate was evaporated in vacuo, and the residue purified by chromatography on a silica gel column (eluent, *n*-hexane–AcOEt = 10:1–5:1) to give the title compound (28.8 g, 95%) as a colorless oil. IR (liquid film): 3367, 2961, 2935, 2874, 1742, 1707, 1509, 1458, 1392, 1369, 1290, 1274, 1254, 1166, 1100, 1078 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 9.45 (s, 1H), 5.26 (br s, 1H), 4.44 (d, 1H, $J = 11.2$ Hz), 4.32 (d, 1H, $J = 11.2$ Hz), 2.32 (t, 2H, $J = 7.6$ Hz), 1.70–1.55 (m, 2H), 1.45 (s, 9H), 1.38 (s, 3H), 1.40–1.25 (m, 4H), 0.90 (t, 3H, $J = 7.0$ Hz); MS (FAB) m/z: 302 $(M+H)^+$.

4.4. (2*R*)-*tert*-Butoxycarbonylamino-1-*n*-hexanoyloxy-2-methyl-4-(thiophen-2-yl)-3-butene 7a

(Thiophen-2-yl)methyl triphenylphosphonium bromide **6a** (67.1 g, 0.15 mol) was suspended in THF (750 ml), and potassium *t*-butoxide (17.2 g, 0.15 mol) was added thereto followed by stirring under a nitrogen atmosphere for 20 min at room temperature. A THF (250 ml) solution of (2*S*)-*tert*-butoxycarbonylamino-3-*n*-hexanoyloxy-2-methyl-1-propanal **5a** (23.0 g, 76.4 mmol) was added dropwise to the reaction solution in an ice bath, and then the reaction mixture was stirred for 30 min in the ice bath. To the reaction solution was added water, and the resulting solution extracted with AcOEt, and then the organic layer washed with brine. The organic layer was dried over anhydrous Na_2SO_4, and the solvent was evaporated under reduced pressure. The residue was purified by chromatography on a silica gel column (eluent, *n*-hexane–AcOEt = 20:1) to afford the title compound (27.8 g, 96%) as a colorless oil. IR (liquid film): 3370, 2961, 2933, 1725, 1495, 1456, 1391, 1367, 1247, 1167, 1109, 1100, 1072, 697 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.32–7.26, 7.16–7.14 (m, total 1H), 7.04–7.01, 7.01–6.93 (m, total 2H), 6.63 (d, 0.5H, $J = 16.0$ Hz), 6.60 (d, 0.5H, $J = 13.6$ Hz), 6.10 (d, 0.5H, $J = 16.0$ Hz), 5.58 (d, 0.5H, $J = 13.6$ Hz), 4.94, 4.93 (br s, total 1H), 4.40–4.10 (m, 2H), 2.34 (t, 2H, $J = 7.4$ Hz), 1.70–1.55 (m, 2H), 1.57, 1.50, 1.44 (s, total 9H), 1.40–1.25 (m, 7H), 0.88 (t, 3H, $J = 7.0$ Hz); MS (FAB) m/z: 381 (M^+).

4.5. (4*R*)-Methyl-4-[2-(thiophen-2-yl)ethenyl]oxazolidin-2-one 8a

(2*R*)-*tert*-Butoxycarbonylamino-1-*n*-hexanoyloxy-2-methyl-4-(thiophen-2-yl)-3-butene **7a** (40.5 g, 0.11 mol) was dissolved in a mixture of THF (150 ml) and MeOH (150 ml), and a 1 M aqueous NaOH solution (530 ml) was added thereto in an ice bath followed by stirring for 30 min in the ice bath and subsequently for 1 h at room temperature. After the reaction solution was concentrated in vacuo, water was added thereto, and the solution extracted with CH_2Cl_2, and then the organic layer washed with brine. The organic layer was dried over anhydrous Na_2SO_4, and the solvent evaporated in vacuo to give a crude product (35.0 g). This crude product was dissolved in THF (300 ml), and potassium *t*-butoxide (17.8 g, 0.16 mol) was added thereto in an ice bath followed by stirring for 10 min in the ice bath and subsequently for 40 min at room temperature. To the reaction solution was added water, and the resulting solution extracted with AcOEt, and then the organic layer washed with brine. After the organic layer was dried over anhydrous Na_2SO_4, the solvent was evaporated under reduced pressure. The residue was purified by chromatography on a silica gel column (eluent, *n*-hexane–AcOEt = 3:1–1:1) to afford the title compound (18.0 g, 81%) as a white solid. IR (KBr): 3275, 3110, 2974, 1752, 1391, 1376, 1281, 1169, 1039, 960, 704 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.34 (d, 0.5H, $J = 5.1$ Hz), 7.19 (d, 0.5H, $J = 5.0$ Hz), 7.07–6.91 (m, 2H), 6.74 (d, 0.5H, $J = 16.0$ Hz), 6.59 (d, 0.5H, $J = 12.5$ Hz), 6.17 (br s, 1H), 6.06 (d, 0.5H, $J = 16.0$ Hz), 5.65 (d, 0.5H, $J = 12.5$ Hz), 4.41 (d, 0.5H, $J = 8.6$ Hz), 4.31–4.16 (m, 1.5H), 1.60 (s, 1.5H), 1.55 (s, 1.5H); MS (FAB) m/z: 209 (M^+).

4.6. (4*R*)-Methyl-4-[2-(thiophen-2-yl)ethyl]oxazolidin-2-one 9a

(4*R*)-Methyl-4-[2-(thiophen-2-yl)ethenyl]oxazolidin-2-one **8a** (18.0 g, 86.0 mmol) was dissolved in MeOH (150 ml), and 10% palladium–charcoal (4.5 g) was added thereto followed by stirring for 10 h at room temperature under a hydrogen atmosphere. The palladium–charcoal in the reaction solution was removed by filtration, and the filtrate was evaporated in vacuo. The solid obtained was washed with Et_2O, and dried to give the title compound (16.5 g, 91%) as a white solid. The obtained (4*R*)-methyl-4-[2-(thiophen-2-yl)ethyl]oxazolidin-2-one **9a** was subjected to an optically active HPLC column for analytical separation [column, Chiralcel OD-H (4.6∅ × 250 mm); eluent, 60:40 *n*-hexane–2-propanol mixture; flow rate, 0.5 ml/min; t_R of (*S*)-isomer, 16.8 min; t_R of (*R*)-isomer, 17.6 min] to determine the enantiomeric purity. The enantiomeric excess of this reaction product was confirmed to be 85% ee. $[\alpha]_D^{25} = +5.1$ (*c* 2.4, $CHCl_3$); IR (KBr): 3283, 1770, 1399, 1244, 1043, 941, 846, 775, 706, 691 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.15 (d, 1H, $J = 5.2$ Hz), 6.93 (dd, 1H, $J = 5.2$, 3.6 Hz), 6.81 (d, 1H, $J = 3.6$ Hz), 5.39 (br s, 1H), 4.19 (d, 1H, $J = 8.4$ Hz), 4.08 (d, 1H, $J = 8.4$ Hz), 3.00–2.84 (m, 2H), 2.08–1.92 (m, 2H), 1.42; MS (EI) m/z: 211 (M^+).

This optical purity 85% ee compound (11 g) was then dissolved in a mixture of AcOEt (25 ml) and *n*-hexane (5.0 ml) by heating, and the solution left at room temperature for 2 h. The precipitated white crystals were filtered off and dried to give the title compound (4.0 g, 99% ee). $[\alpha]_D^{25} = +7.8$ (*c* 2.0, $CHCl_3$).

4.7. (2*R*)-Amino-2-methyl-4-(thiophen-2-yl)butan-1-ol 1/2 D-(−)-tartrate 10a

(4*R*)-Methyl-4-[2-(thiophen-2-yl)]ethyl]oxazolidin-2-one **9a** (85% ee, 7.30 g, 34.6 mmol) was dissolved in a mixture of THF (35 ml) and MeOH (70 ml), and a 5 M aqueous KOH solution (70 ml) was added thereto in an ice bath followed by stirring for 2 days at 80 °C. To the reaction solution was added CH_2Cl_2, and the solution was washed with water. The organic layer was dried over anhydrous $MgSO_4$, and the solvent evaporated under reduced pressure. The obtained residue (6.20 g) was dissolved in EtOH (60 ml), and D-(−)-tartaric acid (5.19 g, 34.6 mmol) in EtOH (50 ml) was added thereto to give a precipitate. The precipitate was filtered off to afford the crude title compound (7.56 g). The crude compound (7.54 g) obtained was recrystallized from a mixture of EtOH (75 ml) and water (50 ml), and the title compound (5.89 g, 98% ee) was obtained. In addition, the obtained target compound (5.88 g) was recrystallized from EtOH (60 ml) and water (54 ml) to afford the title compound (5.11 g, 99.7% ee). Mp 234–235 °C; $[\alpha]_D^{24} = -14.0$ (*c* 1.0, H_2O); IR (KBr): 3400, 3218, 3126, 2937, 2596, 1599, 1530, 1400, 1124, 1077, 715 cm^{-1}. Anal. Calcd for $C_9H_{15}NOS{\cdot}0.5C_4H_6O_6$: C, 50.95; H, 6.61; N, 5.40; S, 12.36. Found: C, 50.68; H, 6.91; N, 5.38; S, 12.48.

4.8. (2*R*)-Amino-2-methyl-4-(3-methylthiophen-2-yl)butan-1-ol 1/2 D-(−)-tartrate 10b

According to a procedure similar to that described for the preparation of **10a**, **10b** was prepared from **5a** (95% ee). IR (KBr): 3406, 2952, 2927, 1631, 1569, 1390, 1296, 1067 cm^{-1}; ^1H NMR (400 MHz, D_2O): δ 7.22 (d, 1H, $J = 5.1$ Hz), 6.92 (d, 1H, $J = 5.1$ Hz), 4.32 (s, 1H), 3.72 (d, 1H, $J = 12.3$ Hz), 3.64 (d, 1H, $J = 12.3$ Hz), 2.94–2.80 (m, 2H), 2.18 (s, 3H), 2.07–1.87 (m, 2H), 1.39 (s, 3H); MS (FAB) *m*/*z*: 200 $(M+H)^+$ as free form of the title compound. Anal. Calcd for $C_{10}H_{17}NOS{\cdot}0.5C_4H_6O_6{\cdot}0.5H_2O$: C, 50.86; H, 7.47; N, 4.94; S, 11.31. Found: C, 51.30; H, 7.25; N, 5.11; S, 11.62.

4.9. (2*R*)-Amino-2-methyl-4-(3-chlorothiophen-2-yl)butan-1-ol 1/2 D-(−)-tartrate 10c

According to a procedure similar to that described for the preparation of **10a**, **10c** was prepared from **5a** (92% ee). IR (KBr): 3395, 3176, 2954, 1632, 1569, 1390, 1296, 1068, 863 cm^{-1}; ^1H NMR (400 MHz, D_2O): δ 7.34 (d, 1H, $J = 5.3$ Hz), 7.00 (d, 1H, $J = 5.3$ Hz), 4.32 (s, 1H), 3.72 (d, 1H, $J = 12.4$ Hz), 3.64 (d, 1H, $J = 12.4$ Hz), 2.97–2.87 (m, 2H), 2.11–1.94 (m, 2H), 1.39 (s, 3H); MS (FAB) *m*/*z*: 220 $(M+H)^+$ as free form of the title compound. Anal. Calcd for $C_9H_{14}ClNOS{\cdot}0.5C_4H_6O_6$: C, 44.82; H, 5.81; Cl, 12.03; N, 4.75; S, 10.88. Found: C, 44.73; H, 5.81; Cl, 11.97; N, 4.75; S, 10.88.

4.10. (2*R*)-Amino-2-methyl-4-(3-methylthiolthiophen-2-yl)butan-1-ol 1/2 D-(−)-tartrate 10d

According to a procedure similar to that described for the preparation of **10a**, **10d** was prepared from **5a** (98% ee). IR (KBr): 3408, 3054, 2921, 2589, 1620, 1581, 1395, 1341, 1318, 1121, 1074, 712 cm^{-1}; ^1H NMR (400 MHz, CD_3OD): δ 7.26 (d, 1H, $J = 5.2$ Hz), 7.02 (d, 1H, $J = 5.2$ Hz), 4.33 (s, 1H), 3.63 (d, 1H, $J = 11.7$ Hz), 3.55 (d, 1H, $J = 11.7$ Hz), 3.00–2.92 (m, 2H), 2.38 (s, 3H), 2.03–1.86 (m, 2H), 1.34 (s, 3H); MS (FAB) *m*/*z*: 232 $(M+H)^+$ as free form of the title compound. Anal. Calcd for $C_{10}H_{17}NOS_2{\cdot}0.5C_4H_6O_6$: C, 47.04; H, 6.58; N, 4.57; S, 20.93. Found: C, 47.12; H, 6.58; N, 4.57; S, 21.17.

4.11. (2*R*)-Amino-2-methyl-4-(3-phenoxythiophen-2-yl)-butan-1-ol 1/2 D-(−)-tartrate 10e

According to a procedure similar to that described for the preparation of **10a**, **10e** was prepared from **5a** (98% ee). IR (KBr): 3397, 3219, 2940, 2890, 1588, 1516, 1491, 1399, 1384, 1231, 1116 cm^{-1}; ^1H NMR (400 MHz, D_2O): δ 7.45–7.42 (m, 2H), 7.33 (d, 1H, $J = 5.5$ Hz), 7.15 (t, 1H, $J = 7.5$ Hz), 7.02 (d, 2H, $J = 8.4$ Hz), 6.84 (d, 1H, $J = 5.5$ Hz), 4.32 (s, 1H), 3.58 (d, 1H, $J = 12.3$ Hz), 3.53 (d, 1H, $J = 12.3$ Hz), 2.85–2.72 (m, 2H), 2.04–1.85 (m, 2H), 1.24 (s, 3H); MS (FAB) *m*/*z*: 278 $(M+H)^+$ as free form of the title compound. Anal. Calcd for $C_{15}H_{19}NOS{\cdot}0.5C_4H_6O_6$: C, 57.94; H, 6.29; N, 3.97; S, 9.10. Found: C, 57.63; H, 5.97; N, 4.03; S, 9.12.

4.12. (2*R*)-*tert*-Butoxycarbonylamino-1-*n*-hexanoyloxy-2-methyl-4-(furan-2-yl)-3-butene 12a

To a suspension of (furan-2-yl)methyl triphenylphosphonium bromide **11a** (33.65 g, 79.5 mmol) in THF (90 ml) was added a solution of potassium *t*-butoxide (8.94 g, 79.7 mmol) in THF (90 ml) with stirring under ice-cooling over a 10 min interval, and the resulting mixture stirred under ice-cooling for 15 min. Subsequently, to the reaction mixture was added a solution of (2*S*)-*tert*-butoxycarbonylamino-3-*n*-hexanoyloxy-2-methyl-1-propanal **5a** (16.2 g, 53.7 mmol) in THF (60 ml) with stirring under ice-cooling over a 15 min interval, and the resulting mixture was stirred under ice-cooling for 30 min. After stirring, to the reaction mixture was added a saturated aqueous NH_4Cl solution to quench the reaction, and then the reaction temperature raised to room temperature. After evaporation of the reaction mixture in vacuo, to the residue were added water and AcOEt and then the resulting mixture was extracted with AcOEt. The extract was washed successively with water and brine and dried over anhydrous Na_2SO_4. After filtration, the solvent was removed in vacuo, and the residue purified by chromatography on a silica gel (eluent, *n*-hexane–AcOEt = 10:1) to afford the title compound (19.32 g, 98%). IR (liquid film): 3445, 2962, 2933, 2873, 2250, 1720, 1497, 1457, 1391, 1368, 1249, 1165, 1075, 1015 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.45 (d, 1H, $J = 1.6$ Hz), 7.33 (d, 1H, $J = 1.5$ Hz), 6.41 (dd, 1H, $J = 2.9$, 1.6 Hz), 6.36–6.35 (m, total 2H), 6.33 (d, 1H, $J = 15.9$ Hz), 6.26–6.22 (m, total 2H), 6.20 (d, 1H, $J = 15.9$ Hz), 5.59 (d, 1H, $J = 12.7$ Hz), 5.22 (br s, 1H), 4.82 (br s, 1H), 4.43 (d, 1H, $J = 11.0$ Hz), 4.32 (d, 1H, $J = 11.0$ Hz), 4.25 (d, 1H, $J = 11.0$ Hz), 4.18 (d, 1H, $J = 11.0$ Hz), 2.36–2.32 (m, total 4H), 1.67–1.22 (m, total 40H), 0.92–0.87 (s, total 6H); MS (FAB) *m*/*z*: 366 $(M+H)^+$.

4.13. (2*R*)-*tert*-Butoxycarbonylamino-1-*n*-hexanoyloxy-2-methyl-4-(1-methylpyrrol-2-yl)-3-butene 12b

(1-Methylpyrrol-2-yl)methyl triphenylphosphonium iodide **11b** (58.0 g, 120 mmol) was suspended in THF (300 ml) and a solution of potassium *t*-butoxide (13.5 g, 120 mmol) in THF (180 ml) was added thereto under ice-cooling with stirring over 30 min, followed by further stirring of the mixture under ice-cooling for 80 min. A solution of (2*S*)-*tert*-butoxycarbonylamino-3-*n*-hexanoyloxy-2-methyl-1-propanal **5a** (30.3 g, 101 mmol) in THF (120 ml) was added to the reaction mixture over 30 min and the mixture stirred under ice-cooling for 30 min. A saturated aqueous NH_4Cl solution was added to the reaction mixture to stop the reaction and the temperature of the liquid was returned to room temperature. After evaporation of the reaction mixture in vacuo, to the residue were added water and AcOEt and then the resulting mixture was extracted with AcOEt. The extract was washed successively with water and brine and dried over anhydrous Na_2SO_4. After filtration, the solvent was removed in vacuo, and the residue purified by chromatography on a silica gel (eluent, *n*-hexane–AcOEt = 9:1) to afford the title compound (37.0 g, 97%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.60 (t, 1H, $J = 2.3$ Hz), 6.57 (t, 1H, $J = 2.3$ Hz), 6.38 (d, 1H, $J = 16.1$ Hz), 6.30–6.26 (m, 2H), 6.27 (d, 1H, $J = 12.5$ Hz), 6.11 (t, 1H, $J = 3.2$ Hz), 6.08 (t, 1H, $J = 3.2$ Hz), 5.99 (d, 1H, $J = 16.1$ Hz), 5.58 (d, 1H, $J = 12.5$ Hz) 5.04 (br s, 1H), 4.81 (br s, 1H), 4.34–4.16 (m, 4H), 3.60 (s, 3H), 3.54 (s, 3H), 2.36–2.30 (m, 4H), 1.67–1.22 (m, 36H), 0.92–0.87 (s, 6H); MS (EI) *m*/*z*: 280 (M^+).

4.14. (4*R*)-Methyl-4-[2-(furan-2-yl)ethenyl]-1,3-oxazolidin-2-one 13a

To a solution of (2*R*)-*tert*-butoxycarbonylamino-1-*n*-hexanoyloxy-2-methyl-4-(furan-2-yl)-3-butene **12a** (19.3 g, 52.9 mmol) in a mixed solvent of THF (53 ml) and MeOH (53 ml) was added a 2 M aqueous NaOH solution (53 ml), and the resulting mixture stirred at room temperature for 1 h. After stirring, to the reaction mixture were added water and CH_2Cl_2, and the resulting mixture was extracted with CH_2Cl_2. The extract was washed with brine and dried over anhydrous Na_2SO_4. After filtration, the solvent was removed in vacuo to afford the crude product (14.8 g, 100%). Subsequently, to a solution of the crude product in THF (150 ml) was added a solution of potassium *t*-butoxide (7.20 g, 64.2 mmol) in THF (50 ml) with stirring under ice-cooling over a 10 min interval, and the resulting mixture stirred at the same temperature for 1 h. After stirring, the reaction mixture was neutralized with acetic acid (3.65 ml, 63.8 mmol) and evaporated in vacuo. To the residue were added water and AcOEt, and the resulting mixture was extracted with AcOEt. The extract was washed with brine and dried over Na_2SO_4. After filtration, the solvent was removed in vacuo, and the residue was purified by chromatography on a silica gel (eluent, *n*-hexane–AcOEt = 1:1) to afford the title compound (10.0 g, 98%). IR ($CHCl_3$): 3451, 2252, 1757, 1396, 1374, 1281, 1165, 1044, 1016 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.49 (d, 1H, $J = 1.6$ Hz), 7.36 (d, 1H, $J = 1.6$ Hz), 6.46 (d, 1H, $J = 2.1$ Hz), 6.43 (d, 1H, $J = 16.1$ Hz), 6.04–6.37 (m, total 2H), 6.30 (br s, 1H), 6.30 (d, 1H, $J = 3.3$ Hz), 6.21 (d, 1H, $J = 12.7$ Hz), 6.18 (d, 1H, $J = 16.1$ Hz), 5.88 (br s, 1H), 5.62 (d, 1H, $J = 12.7$ Hz), 4.41 (d, 1H, $J = 8.5$ Hz), 4.37 (d, 1H, $J = 8.5$ Hz), 4.23 (d, 1H, $J = 8.3$ Hz), 4.17 (d, 1H, $J = 8.3$ Hz), 1.65 (s, 3H), 1.54 (s, 3H); MS (EI) *m*/*z*: 193 (M^+).

4.15. (4*R*)-Methyl-4-[2-(1-methylpyrrol-2-yl)ethenyl]-1,3-oxazolidin-2-one 13b

(2*R*)-*tert*-Butoxycarbonylamino-1-*n*-hexanoyloxy-2-methyl-4-(1-methylpyrrol-2-yl)-3-butene **12b** (37.0 g, 97.8 mmol) was dissolved in a mixture of THF (100 ml) and MeOH (100 ml) and a 2 M aqueous NaOH solution (100 ml) was added thereto, followed by stirring of the mixture at room temperature for 1 h. After stirring, to the reaction mixture were added water and CH_2Cl_2, and the resulting mixture was extracted with CH_2Cl_2. The extract was washed with brine and dried over anhydrous Na_2SO_4. After filtration, the solvent was removed in vacuo to afford the crude product (28.8 g, 100%). A solution of potassium *t*-butoxide (13.2 g, 117 mmol) in THF (80 ml) was added to a solution of the crude product in THF (320 ml) under ice-cooling over 10 min and the mixture was stirred at the same temperature for 20 min. After stirring, the reaction mixture was neutralized with acetic acid (6.7 ml, 117 mmol) and evaporated in vacuo. To the residue were added water and AcOEt, and the resulting mixture was extracted with AcOEt. The extract was washed with brine and dried over Na_2SO_4. After filtration, the solvent was removed in vacuo, and the residue purified by chromatography on a silica gel (eluent, *n*-hexane–AcOEt = 1:1–1:2) to afford the title compound (20.3 g, 100%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.67 (t, 1H, $J = 2.1$ Hz), 6.62 (t, 1H, $J = 1.5$ Hz), 6.48 (d, 1H, $J = 15.7$ Hz), 6.36 (dd, 1H, $J = 3.7$, 1.5 Hz), 6.31 (d, 1H, $J = 12.2$ Hz), 6.14–6.10 (m, 2H), 6.07 (br d, 1H, $J = 3.6$ Hz), 5.99 (d, 1H, $J = 15.7$ Hz), 5.65 (d, 1H, $J = 12.2$ Hz), 5.46 (br s, 1H), 5.11 (br s, 1H), 4.31 (d, 1H, $J = 8.2$ Hz), 4.22 (d, 1H, $J = 8.2$ Hz), 4.17 (d, 1H, $J = 8.2$ Hz), 4.16 (d, 1H, $J = 8.2$ Hz), 3.62 (s, 3H), 3.55 (s, 3H), 1.59 (s, 3H), 1.57 (s, 3H); MS (EI) *m*/*z*: 206 (M^+).

4.16. (4*R*)-Methyl-4-[2-(furan-2-yl)ethyl]-1,3-oxazolidin-2-one 14a

To a suspension of 10% palladium–charcoal (50% wet with water) (1.00 g) in MeOH (20 ml) was added a solution of (4*R*)-methyl-4-[2-(furan-2-yl)ethenyl]-1,3-oxazolidin-2-one **13a** (10.0 g, 52.0 mmol) in MeOH (180 ml) with stirring, and the resulting mixture stirred at room temperature under a hydrogen atmosphere for 40 min. After stirring, the palladium–charcoal in the reaction mixture was filtered off using Celite, and the filtrate was evaporated in vacuo. The residue obtained was purified by chromatography on a silica gel column (eluent, *n*-hexane–AcOEt = 3:2–1:1) to afford the title compound (7.95 g, 78%). Furthermore, the obtained (4*R*)-methyl-4-[2-(furan-2-yl)ethyl]-1,3-oxazolidin-2-one **14a** was subjected to an optically active HPLC column for analytical separation [column, Chiralpak AD (4.6∅ × 250 mm); eluent, 85:15 *n*-hexane–2-propanol mixture; flow rate, 1.0 ml/min; t_R of (*S*)-isomer, 13.1 min; t_R of (*R*)-isomer, 15.4 min] to determine the enantiomeric purity. The enantiomeric excess of this reaction product was

confirmed to be 84% ee. IR ($CHCl_3$): 3450, 2975, 2928, 2250, 1755, 1599, 1508, 1400, 1381, 1147, 1045, 1010 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.31 (br s, 1H,), 6.29 (br d, 1H, $J = 2.6$ Hz), 6.03 (d, 1H, $J = 2.6$ Hz), 5.92 (br s, 1H), 4.11 (d, 1H, $J = 8.4$ Hz), 4.04 (d, 1H, $J = 8.4$ Hz), 2.72 (t, 2H, $J = 8.0$ Hz), 1.98–1.94 (m, 2H), 1.68–1.61 (m, 2H), 1.38 (s, 3H); MS (EI) m/z: 195 (M^+).

4.17. (4*R*)-Methyl-4-[2-(1-methylpyrrol-2-yl)ethyl]-1,3-oxazolidin-2-one 14b

To a suspension of 10% palladium–charcoal (50% wet with water) (2.02 g) in MeOH (40 ml) was added a solution of (4*R*)-methyl-4-[2-(1-methylpyrrol-2-yl)ethenyl]-1,3-oxazolidin-2-one **13b** (20.3 g, 97.8 mmol) in MeOH (360 ml) with stirring, and the resulting mixture stirred at room temperature under a hydrogen atmosphere for 60 min. After stirring, palladium–charcoal in the reaction mixture was filtered off using Celite, and the filtrate was evaporated in vacuo. The residue was purified by chromatography on a silica gel column (eluent, *n*-hexane–AcOEt = 3:2) to afford the title compound (18.8 g, 88%). Furthermore, the obtained (4*R*)-methyl-4-[2-(1-methylpyrrol-2-yl)ethyl]-1,3-oxazolidin-2-one **14b** was subjected to an optically active HPLC column for analytical separation [column, Chiralcel OJ (4.6∅ × 250 mm); eluent, 70:30 *n*-hexane–2-propanol mixture; flow rate, 1.0 ml/min; t_R of (*S*)-isomer, 12.5 min; t_R of (*R*)-isomer, 15.5 min] to determine the enantiomeric purity. The enantiomeric excess of this reaction product was confirmed to be 75% ee. IR (KBr): 3289, 3103, 2977, 2938, 1759, 1713, 1495, 1397, 1381, 1309, 1281, 1231, 1032, 945, 928, 776, 718, 706, 656 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 6.58 (t, 1H, $J = 2.4$ Hz), 6.05 (dd, 1H, $J = 3.2$ Hz, 2.4 Hz), 5.88 (br d, 1H, $J = 3.2$ Hz), 5.15 (br s, 1H), 4.14 (d, 1H, $J = 8.3$ Hz), 4.07 (d, 1H, $J = 8.3$ Hz), 2.70–2.58 (m, 2H), 2.00–1.87 (m, 2H), 1.42 (s, 3H); MS (EI) m/z: 208 (M^+).

4.18. (2*R*)-Amino-2-methyl-4-(furan-2-yl)butan-1-ol 1/2 D-(−)-tartrate 15a

To a solution of (4*R*)-methyl-4-[2-(furan-2-yl)ethyl]-1,3-oxazolidin-2-one **14a** (29.9 g, 153.2 mmol) in a mixed solvent of THF (150 ml) and MeOH (150 ml) was added a 5 M aqueous KOH solution (150 ml) with stirring, and the resulting mixture was refluxed for 3 days. After cooling, to the reaction mixture was added water, and the resulting mixture was extracted with CH_2Cl_2. The extract was dried over anhydrous Na_2SO_4. After filtration, the filtrate was evaporated in vacuo. Subsequently, to a solution of the residue obtained in EtOH (250 ml) was added a solution of D-(−)-tartrate (11.5 g, 76.6 mmol) in EtOH (100 ml) with stirring, and the resulting mixture stirred for 10 min. The crude crystals precipitated were collected by filtration and then recrystallized from a mixed solvent of EtOH (300 ml) and water (75 ml) to afford the title compound (24.4 g, 99.3% ee) as colorless plate crystals. Mp 200–204 °C; $[\alpha]_D^{24} = -11.9$ (*c* 1.0, H_2O); IR (KBr): 3405, 3226, 3135, 2943, 2597, 1598, 1528, 1401, 1299, 1228, 1124, 1079, 1003, 740 cm^{-1}; MS (FAB) m/z: 170 $(M+H)^+$ as free form of title compound. Anal. Calcd for $C_9H_{15}NO_2 \cdot 0.5C_4H_6O_6$: C, 54.09; H, 7.43; N, 5.73. Found: C, 53.93; H, 7.30; N, 5.79.

4.19. (2*R*)-Amino-2-methyl-4-(1-methylpyrrol-2-yl)butan-1-ol 1/2 D-(−)-tartrate 15b

To a solution of (4*R*)-methyl-4-[2-(1-methylpyrrol-2-yl)ethyl]-1,3-oxazolidin-2-one **14b** (17.9 g, 86.0 mmol) in a mixed solvent of THF (250 ml) and MeOH (125 ml) was added a 5 M aqueous KOH solution (125 ml) with stirring, and the resulting mixture refluxed for 4 days. After cooling, to the reaction mixture was added water, and the resulting mixture extracted with CH_2Cl_2. The extract was dried over anhydrous Na_2SO_4. After filtration, the filtrate was evaporated in vacuo. Subsequently, to a solution of the residue obtained in EtOH (260 ml) was added D-(−)-tartrate (6.45 g, 43.0 mmol) with stirring for 2 h. The precipitated crystal was collected by filtration to obtain a crude crystal (20.7 g). The crude crystal (18.7 g) was recrystallized from a mixture of EtOH (370 ml) and water (37 ml) and the thus obtained crystal was recrystallized again from a mixture of EtOH (300 ml) and water (30 ml). Furthermore, the obtained crystal was recrystallized again from a mixture of ethanol (240 ml) and water (24 ml) to obtain the title compound (10.5 g, 99.7% ee) as a colorless scaly crystal. Mp 183–185 °C; $[\alpha]_D^{24} = -13.3$ (*c* 1.0, H_2O); IR (KBr): 3480, 3430, 2926, 2634, 2545, 1586, 1516, 1389, 1359, 1309, 1291, 1105, 1039, 710, 690 cm^{-1}; MS (FAB) m/z: 183 $(M+H)^+$ as free form of the title compound. Anal. Calcd for $C_{10}H_{18}N_2O \cdot 0.5C_4H_6O_6$: C, 56.01; H, 8.23; N, 10.89. Found: C, 55.81; H, 8.22; N, 10.89.

4.20. (2*R*)-*tert*-Butoxycarbonylamino-2-ethyl-3-*n*-hexanoyloxy-1-propanol (*R*)-2b

To a suspension of 2-*tert*-butoxycarbonylamino-2-ethyl-1,3-propanediol **1b** (52.9 g, 241 mmol) in diisopropyl ether (1.0 l) were added successively vinyl *n*-hexanoate (41 ml, 254 mmol) and lipase [Immobilized lipase from *Pseudomonas* sp. (TOYOBO; 0.67 U/mg)] (2.1 g) with stirring, and the resulting mixture was stirred at room temperature for 4 h. After stirring, the reaction mixture was filtered and evaporated in vacuo, and the residue purified by chromatography on a silica gel column (eluent, *n*-hexane–AcOEt = 7:1–2:1) to afford the title compound (66.8 g, 87%) as a colorless oil of 93% ee. The obtained (2*R*)-*tert*-butoxycarbonylamino-2-ethyl-3-*n*-hexanoyloxy-1-propanol was subjected to an optically active HPLC column for analytical separation [column, Chiralcel OF (4.6∅ × 250 mm); eluent, 80:20 *n*-hexane–2-propanol mixture; flow rate, 0.5 ml/min; t_R of (*S*)-isomer, 7.4 min; t_R of (*R*)-isomer, 7.9 min] to determine the enantiomeric excess. IR ($CHCl_3$): 3371, 2966, 2935, 1722, 1503, 1460, 1368, 1249, 1168, 1086, 1028, 866, 781 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 4.76 (br s, 1H), 4.24 (d, 1H, $J = 11.0$ Hz), 4.10 (d, 1H, $J = 11.0$ Hz), 3.65–3.62 (m, 2H), 2.35 (t, 2H, $J = 7.7$ Hz), 1.78–1.69 (m, 1H), 1.63–1.53 (m, 4H), 1.44 (s, 9H), 1.30–1.25 (m, 4H), 0.87–0.83 (m, 6H); MS (FAB) m/z: 318 $(M+H)^+$.

4.21. (2*S*)-*tert*-Butoxycarbonylamino-2-ethyl-3-*n*-hexanoyloxy-1-propanal 5b

To a solution of (2*R*)-*tert*-butoxycarbonylamino-3-*n*-hexanoyloxy-2-ethyl-1-propanol (*R*)-**2b** (66.7 g, 210 mmol) in CH_2Cl_2 (700 ml) were successively added 4 Å (117 g)

molecular sieve and pyridinium dichromate (117 g, 311 mmol) with stirring under ice-cooling, and then the resulting mixture was stirred at room temperature for 2 h. After stirring, to the reaction mixture was added Et_2O, and the resulting mixture was filtered. The filtrate was evaporated in vacuo, and the residue was purified by chromatography on a silica gel column (eluent, *n*-hexane–AcOEt = 10:1–5:1) to afford the title compound (45.9 g, 69%). IR ($CHCl_3$): 3418, 2979, 2934, 2873, 1737, 1710, 1496, 1369, 1251, 1160 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 9.34, (s, 1H), 5.30 (br s, 1H), 4.60 (d, 1H, $J = 11.4$ Hz), 4.40 (d, 1H, $J = 11.4$ Hz), 2.28 (t, 2H, $J = 7.3$ Hz), 2.18–2.06 (m, 1H), 1.79–1.69 (m, 1H), 1.62–1.55 (m, 2H), 1.44 (s, 9H), 1.34–1.22 (m, 4H), 0.90 (t, 3H, $J = 7.3$ Hz), 0.81 (t, 3H, $J = 7.3$ Hz); MS (FAB) *m*/*z*: 316 $(M+H)^+$.

4.22. (2*R*)-*tert*-Butoxycarbonylamino-2-ethyl-1-*n*-hexanoyloxy-4-(furan-2-yl)-3-butene 16a

To a suspension of (furan-2-yl)methyl triphenylphosphonium bromide **11a** (4.04 g, 9.54 mmol) in THF (32.4 ml) was added potassium *t*-butoxide (1.06 g, 9.45 mmol) with stirring under ice-cooling, and the resulting mixture stirred under ice-cooling for 15 min. After stirring, to the reaction mixture was added a solution of (2*S*)-*tert*-butoxycarbonylamino-2-ethyl-3-*n*-hexanoyloxy-1-propanal **5b** (2.01 g, 6.37 mmol) in THF (10 ml) with stirring under ice-cooling over a 5 min interval, and the resulting mixture stirred under ice-cooling for 30 min. After stirring, to the reaction mixture was added a saturated aqueous NH_4Cl solution to quench the reaction, and the reaction temperature was raised to room temperature. After evaporation of the reaction mixture in vacuo, to the residue were added water and AcOEt, and the resulting mixture was extracted with AcOEt. The extract was washed with brine and dried over anhydrous Na_2SO_4. After filtration, the solvent was removed in vacuo, and the residue purified by chromatography on a silica gel (eluent, *n*-hexane–AcOEt = 5:1) to afford the title compound (2.39 g, 99%). IR ($CHCl_3$): 3446, 2970, 2933, 2873, 1722, 1494, 1459, 1391, 1380, 1368, 1249, 1163 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.44 (br d, 1H, $J = 1.5$ Hz), 7.33 (br d, 1H, $J = 1.5$ Hz), 6.41 (dd, 1H, $J = 2.9$, 1.5 Hz), 6.38 (d, 1H, $J = 2.9$ Hz), 6.36 (dd, 1H, $J = 2.9$, 1.5 Hz), 6.29 (d, 1H, $J = 16.8$ Hz), 6.28 (d, 1H, $J = 12.5$ Hz), 6.22 (d, 1H, $J = 2.9$ Hz), 6.09 (d, 1H, $J = 16.8$ Hz), 5.47 (d, 1H, $J = 12.5$ Hz), 5.21 (br s, 1H), 4.66 (br s, 1H), 4.50 (d, 1H, $J = 11.7$ Hz), 4.41 (d, 1H, $J = 11.7$ Hz), 4.33 (br s, 2H), 2.31 (q, total 4H, $J = 7.7$ Hz), 2.08–1.88 (m, total 4H), 1.47–1.42 (m, total 10H), 1.32–1.26 (m, total 18H), 0.93–0.86 (m, total 12H); MS (FAB) *m*/*z*: 379 (M^+).

4.23. (2*R*)-*tert*-Butoxycarbonylamino-2-ethyl-1-*n*-hexanoyloxy-4-(1-methylpyrrol-2-yl)-3-butene 16b

The reaction was carried out in a manner similar to that described in Section 4.22 using **5b** and **11b** as starting materials to obtain the title compound (yield: 69%). IR (liquid film): 3379, 2966, 2934, 1726, 1489, 1367, 1245, 1167 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 6.61–6.54 (m, 1H), 6.39–6.21 (m, 2H), 6.13–6.05 (m, 1H), 5.89–5.37 (m, 1H), 4.39–4.20 (m, 2H), 3.65–3.52 (m, 3H), 2.31 (t, 2H, $J = 7.3$ Hz), 1.99–1.23 (m, 17H), 0.97–0.85 (t, 6H, $J = 7.3$ Hz); MS (FAB) *m*/*z*: 392 (M^+).

4.24. (2*R*)-*tert*-Butoxycarbonylamino-2-ethyl-1-*n*-hexanoyloxy-4-(thiophen-2-yl)-3-butene 16c

The reaction was carried out in a similar manner to that described in Section 4.22 using **5b** and **6a** as starting materials to obtain the title compound (yield: 100%). IR (liquid film): 3368, 2967, 2932, 2872, 1725, 1699, 1496, 1366, 1246, 1168, 1080, 958, 696 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.30–7.13 (m, 1H), 7.05–6.92 (m, 2H), 6.66–6.56 (m, 1H), 6.01–5.43 (m, 1H), 4.95–4.60 (m, 1H), 4.45–4.25 (m, 2H), 2.32 (t, 2H, $J = 7.3$ Hz), 2.10–1.23 (m, 17H), 0.97–0.83 (m, 6H); MS (FAB) *m*/*z*: 395 (M^+).

4.25. (4*R*)-Ethyl-4-[2-(furan-2-yl)ethenyl]-1,3-oxazolidin-2-one 17a

To a solution of (2*R*)-*tert*-butoxycarbonylamino-2-ethyl-1-*n*-hexanoyloxy-4-(furan-2-yl)-3-butene **16a** (2.33 g, 6.14 mmol) in a mixed solvent of THF (7 ml) and MeOH (7 ml) was added a 1.8 M aqueous NaOH solution (7 ml), and the resulting mixture stirred at room temperature for 3 h. After stirring, to the reaction mixture were added water and AcOEt, and the resulting mixture was extracted with AcOEt. The extract was washed with brine and dried over anhydrous Na_2SO_4. After filtration, the solvent was removed in vacuo to afford the crude product (1.68 g, yield: 97%). Subsequently, to a solution of the crude product obtained above in THF (30 ml) was added potassium *t*-butoxide (1.21 g, 10.8 mmol) with stirring, and the resulting mixture was at the same temperature for 3 h. After stirring, to the reaction mixture were added water and AcOEt, and the resulting mixture was extracted with AcOEt. The extract was washed with brine and dried over anhydrous Na_2SO_4. After filtration, the solvent was removed in vacuo, and the residue was purified by chromatography on a silica gel (eluent, *n*-hexane–AcOEt = 3:1–1:1) to afford the title compound (1.24 g, 100%). IR ($CHCl_3$): 3453, 2975, 1757, 1396, 1373, 1053, 1015 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.43 (d, 1H, $J = 1.5$ Hz), 7.32 (d, 1H, $J = 1.5$ Hz), 6.45 (dd, 1H, $J = 3.7$, 1.5 Hz), 6.44 (d, 1H, $J = 16.1$ Hz), 6.39 (dd, 1H, $J = 3.7$, 1.5 Hz), 6.37 (d, 1H, $J = 3.7$ Hz), 6.29 (d, 1H, $J = 3.7$ Hz), 6.25 (d, 1H, $J = 12.5$ Hz), 6.13 (d, 1H, $J = 16.1$ Hz), 5.62 (br s, total 2H), 5.53 (d, 1H, $J = 12.5$ Hz), 4.44 (d, 1H, $J = 8.8$ Hz), 4.36 (d, 1H, $J = 8.8$ Hz), 4.24 (d, 1H, $J = 8.8$ Hz), 4.22 (d, 1H, $J = 8.8$ Hz), 1.93 (q, 2H, $J = 7.3$ Hz), 1.85–1.76 (m, 2H), 0.99 (t, 3H, $J = 7.3$ Hz), 0.98 (t, 1H, $J = 7.3$ Hz); MS (EI) *m*/*z*: 207 (M^+).

4.26. (4*R*)-Ethyl-4-[2-(1-methylpyrrol-2-yl)ethenyl]-1,3-oxazolidin-2-one 17b

The reaction was carried out in a manner similar to that described in Section 4.25 using (2*R*)-*tert*-butoxycarbonylamino-2-ethyl-1-*n*-hexanoyloxy-4-(1-methylpyrrol-2-yl)-3-butene **16b** as a starting material to obtain the title compound (yield: 74%). IR (liquid film): 3268, 2971, 1749, 1482, 1397, 1380, 1271, 1056, 719 cm^{-1}; ^1H NMR

(400 MHz, $CDCl_3$): δ 6.66–6.57 (m, 1H), 6.48 (d, 1H, $J = 15.7$ Hz), 6.35–6.30 (m, 1H), 6.12–6.05 (m, 1H), 5.90 (d, 1H, $J = 15.7$ Hz), 4.30–4.15 (m, 2H,) 3.55–3.50 (m, total 3H), 1.90–1.72 (m, 2H), 0.95–1.05 (m, 3H); MS (EI) m/z: 220 (M^+).

4.27. (4*R*)-Ethyl-4-[2-(thiophen-2-yl)ethenyl]-1,3-oxazolidin-2-one 17c

The reaction was carried out in a manner similar to that described in Section 4.25 using (2*R*)-*tert*-butoxycarbonylamino-2-ethyl-1-*n*-hexanoyloxy-4-(thiophen-2-yl)-3-butene **16c** as a starting material to obtain the title compound (yield: 100%). IR (liquid film): 3263, 3112, 2970, 1748, 1395, 1381, 1270, 1044, 960, 702 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.36–7.16 (m, 1H), 7.05–6.93 (m, 2H), 6.79–6.63 (m, 1H), 6.02–5.57 (m, 2H), 4.42–4.23 (m, 2H), 1.91–1.76 (m, 2H), 1.04–0.97 (m, 3H); MS (EI) m/z: 223 (M^+).

4.28. (4*R*)-Ethyl-4-[2-(furan-2-yl)ethyl]-1,3-oxazolidin-2-one 18a

To a solution of (4*R*)-ethyl-4-[2-(furan-2-yl)ethenyl]-1,3-oxazolidin-2-one **17a** (1.24 g, 5.99 mmol) in MeOH (40 ml) was added 10% palladium–charcoal (50% wet with water) (124 mg), and the resulting mixture was stirred at room temperature under a hydrogen atmosphere for 2 h. After stirring, its inside atmosphere was replaced with nitrogen, and palladium–charcoal in the reaction mixture was filtered off using Celite, which was washed with AcOEt. The filtrate and the washing were combined and concentrated to dryness in vacuo, and the residue was purified by chromatography on a silica gel (eluent, *n*-hexane–AcOEt = 1:1–1:2) to afford the title compound (144 mg, 12%). Furthermore, the obtained (4*R*)-ethyl-4-[2-(furan-2-yl)ethyl]-1,3-oxazolidin-2-one **18a** was subjected to an optically active HPLC column for analytical separation [column, Chiralpak AD-H (4.6∅ × 250 mm); eluent, 90:10 *n*-hexane–2-propanol mixture; flow rate, 1.0 ml/min; t_R of (*S*)-isomer, 11.1 min; t_R of (*R*)-isomer, 12.8 min] to determine the enantiomeric excess (93% ee). $[\alpha]_D^{24} = +13.9$ (*c* 3.1, $CHCl_3$); IR ($CHCl_3$): 3453, 2973, 229, 1757, 1601, 1397, 1380, 1052 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.32 (br d, 1H, $J = 2.2$ Hz), 6.29 (t, 1H, $J = 2.2$ Hz), 6.03 (br d, 1H, $J = 2.2$ Hz), 5.40 (m, 1H), 4.11 (d, 1H, $J = 8.8$ Hz), 4.07 (d, 1H, $J = 8.8$ Hz), 2.74–2.67 (m, 2H), 1.97–1.93 (m, 2H), 1.72–1.64 (m, 2H), 0.96 (t, 3H, $J = 7.3$ Hz). MS (EI) m/z: 209 (M^+).

4.29. (4*R*)-Ethyl-4-[2-(1-methylpyrrol-2-yl)ethyl]-1,3-oxazolidin-2-one 18b

The reaction was carried out in a manner similar to that described in Section 4.28 using (4*R*)-ethyl-4-[2-(1-methylpyrrol-2-yl)ethenyl]-1,3-oxazolidin-2-one **17b** as a starting material to obtain the title compound (yield: 96%). The **18b** obtained was subjected to an optically active HPLC column for analytical separation [column, Chiralcel OJ-H (4.6∅ × 250 mm); eluent, 60:40 *n*-hexane–2-propanol mixture; flow rate, 1.0 ml/min; t_R of (*S*)-isomer, 8.5 min; t_R of (*R*)-isomer, 11.3 min] to determine the enantiomeric excess (94% ee). $[\alpha]_D^{24} = +10.3$ (*c* 1.0, $CHCl_3$); IR (liquid film): 3270, 2969, 2938, 1748, 1495, 1400, 1302, 1271, 1049, 709 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 6.58 (t, 1H, $J = 2.4$ Hz), 6.06 (dd, 1H, $J = 3.2$, 2.4 Hz), 5.88 (m, 1H), 4.15 (d, 1H, $J = 8.8$ Hz), 4.10 (d, 1H, $J = 8.8$ Hz), 3.54 (s, 3H), 2.63–2.59 (m, 2H), 1.96–1.91 (m, 2H), 1.75–1.56 (m, 2H), 0.98 (t, 3H, $J = 7.3$ Hz); MS (EI) m/z: 222 (M^+).

4.30. (4*R*)-Ethyl-4-[2-(thiophen-2-yl)ethyl]-1,3-oxazolidin-2-one 18c

The reaction was carried out in a manner similar to that described in Section 4.28 using (4*R*)-ethyl-4-[2-(thiophen-2-yl)ethenyl]-1,3-oxazolidin-2-one **17c** as a starting material to obtain the title compound (yield: 94%). The thus obtained **18c** was subjected to an optically active HPLC column for analytical separation [column, Chiralpak AD (4.6∅ × 250 mm); eluent, 85:15 *n*-hexane–2-propanol mixture; flow rate, 1.0 ml/min; t_R of (*S*)-isomer, 10.9 min; t_R of (*R*)-isomer, 13.5 min] to determine the enantiomeric excess (93% ee). $[\alpha]_D^{24} = +11.9$ (*c* 1.0, $CHCl_3$); IR (liquid film): 3264, 2969, 2933, 1749, 1399, 1269, 1042, 700 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.14 (d, 1H, $J = 5.1$ Hz), 6.92 (dd, 1H, $J = 5.1$, 2.9 Hz), 6.81 (d, 1H, $J = 2.9$ Hz), 6.05 (br s, 1H), 4.14 (s, 2H), 2.89 (q, 2H, $J = 7.3$ Hz), 2.04–1.91 (m, 2H), 1.75–1.62 (m, 2H), 0.98 (t, 3H, $J = 7.3$ Hz); MS (EI) m/z: 225 (M^+).

4.31. 4-(4-Benzyloxyphenyl)-(2*R*)-*tert*-butoxycarbonylamino-1-*n*-hexanoyloxy-2-methyl-3-butene 20

(4-Benzyloxyphenyl)methyl triphenylphosphonium chloride **19** (87.5 g, 177 mmol) was suspended in THF (500 ml) and a solution of potassium *t*-butoxide (19.8 g, 177 mmol) in THF (250 ml) was added thereto under ice-cooling with stirring over 30 min, followed by further stirring of the mixture under ice-cooling for 30 min. A solution of (2*S*)-*tert*-butoxycarbonylamino-3-*n*-hexanoyloxy-2-methyl-1-propanal **5a** (50.0 g, 166 mmol) in THF (250 ml) was added to the reaction mixture over 30 min and the mixture was stirred at ambient temperature for 30 min. A saturated aqueous NH_4Cl solution was added to the reaction mixture to stop the reaction. After evaporation of the reaction mixture in vacuo, to the residue were added water and AcOEt and then the resulting mixture was extracted with AcOEt. The extract was washed successively with water and brine and dried over anhydrous $MgSO_4$. After filtration, the solvent was removed in vacuo, and the residue was purified by chromatography on a silica gel (eluent, *n*-hexane–AcOEt = 6:1) to afford the title compound (78.2 g, 98%). ^1H NMR (400 MHz, $CDCl_3$): δ 7.45 (m, total 14H), 6.92 (d, total 4H, $J = 8.1$ Hz), 6.55 (t, 1H, $J = 12.5$ Hz), 6.44 (d, 1H, $J = 16.1$ Hz), 6.13 (t, 1H, $J = 16.1$ Hz), 5.61 (d, 1H, $J = 12.5$ Hz), 5.06 (s, total 4H), 4.82 (br s, 1H), 4.71 (br s, 1H), 4.30–4.13 (m, total 4H), 2.35–2.29 (m, total 4H), 1.67–1.24 (m, total 36H), 0.91–0.86 (m, total 6H); MS (EI) m/z: 481 (M^+).

4.32. (4*R*)-[2-(4-Benzyloxyphenyl)ethenyl]-4-methyl-1,3-oxazolidin-2-one 21

4-(4-Benzyloxyphenyl)-(2*R*)-*tert*-butoxycarbonylamino-1-*n*-hexanoyloxy-2-methyl-3-butene **20** (78.2 g, 162 mmol)

was dissolved in a mixture of THF (160 ml) and MeOH (160 ml) and a 2 M aqueous NaOH solution (160 ml) was added thereto, followed by stirring of the mixture at room temperature for 2 h. After stirring, to the reaction mixture were added water and CH_2Cl_2, and the resulting mixture was extracted with CH_2Cl_2. The extract was washed with brine and dried over anhydrous Na_2SO_4. After filtration, the solvent was removed in vacuo to afford the crude product (67.9 g, 100%). A solution of potassium *t*-butoxide (21.9 g, 195 mmol) in THF (200 ml) was added to a solution of the crude product in THF (300 ml) under ice-cooling over 15 min and the mixture was stirred at the same temperature for 1 h. After stirring, the reaction mixture was neutralized with acetic acid (11.2 ml, 195 mmol) and evaporated in vacuo. To the residue were added water and AcOEt, and the resulting mixture was extracted with AcOEt. The extract was washed with brine and dried over $MgSO_4$. After filtration, the solvent was removed in vacuo, and the residue was purified by chromatography on a silica gel (eluent, *n*-hexane–AcOEt = 1:1–1:2) to afford the title compound (45.21 g, 90%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.46–7.29 (m, total 12H), 7.09 (d, total 2H, $J = 8.1$ Hz), 6.98–9.93 (m, total 4H), 6.60 (d, 1H, $J = 11.7$ Hz), 6.55 (d, 1H, $J = 16.1$ Hz), 6.10 (d, 1H, $J = 16.1$ Hz), 5.63 (d, 1H, $J = 11.7$ Hz), 5.08 (s, 2H), 5.07 (s, 2H), 5.02 (br s, 1H), 4.88 (br s, 1H), 4.26 (d, 1H, $J = 8.1$ Hz), 4.24 (d, 1H, $J = 8.1$ Hz), 4.18 (d, 1H, $J = 8.1$ Hz), 4.07 (d, 1H, $J = 8.1$ Hz), 1.57 (s, 3H), 1.51 (s, 3H); MS (EI) *m*/*z*: 309 (M^+).

4.33. (4*R*)-[2-(4-Benzyloxyphenyl)ethyl]-4-methyl-1,3-oxazolidin-2-one 22

To a suspension of platinum(IV) oxide (1.3 g, 4.4 mmol) in EtOH (520 ml) was added a solution of (4*R*)-[2-(4-benzyloxyphenyl)ethenyl]-4-methyl-1,3-oxazolidin-2-one **21** (45.2 g, 146 mmol) in THF (260 ml) with stirring, and the resulting mixture stirred at 50 °C under a hydrogen atmosphere for 10 h. After stirring, platinum(IV) oxide in the reaction mixture was filtered off using a filter paper. The residue on the filter paper was washed with THF, the filtrate and the washings were combined and evaporated in vacuo. The residue was crystallized with diisopropyl ether and the precipitated crystal was collected by filtration to afford the title compound (43.8 g, 96%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.44–7.31 (m, 5H), 7.09 (d, 2H, $J = 8.1$ Hz), 6.92 (d, 2H, $J = 8.1$ Hz), 5.04 (s, 2H), 4.88 (br s, 1H), 4.17 (d, 1H, $J = 8.1$ Hz), 4.06 (d, 1H, $J = 8.1$ Hz), 2.69–2.56 (m, 2H), 1.95–1.83 (m, 2H), 1.41 (s, 3H); MS (EI) *m*/*z*: 311 (M^+).

4.34. (2*R*)-Amino-4-(4-benzyloxyphenyl)-2-methylbutan-1-ol 1/2 D-(−)-tartrate 23

To a solution of (4*R*)-[2-(4-benzyloxyphenyl)ethyl]-4-methyl-1,3-oxazolidin-2-one **22** (43.8 g, 141 mmol) in a mixed solvent of THF (560 ml) and MeOH (280 ml) was added a 5 N aqueous KOH solution (280 ml) with stirring, and the resulting mixture was refluxed for 4 days. After cooling, to the reaction mixture was added water, and the resulting mixture was extracted with CH_2Cl_2. The extract was dried over anhydrous Na_2SO_4. After filtration, the filtrate was evaporated in vacuo. The residue was recrystallized from AcOEt (165 ml) and *n*-hexane (600 ml) to afford (2*R*)-amino-4-(4-benzyloxyphenyl)-2-methylbutan-1-ol (35.8 g, 89%) as a colorless scaly crystal. Then, a small amount of the obtained (2*R*)-amino-4-(4-benzyloxyphenyl)-2-methylbutan-1-ol was converted to 1-acetoxy-(2*R*)-acetylamino-4-[4-benzyloxyphenyl]-2-methylbutan via acylation with acetic anhydride in the presence of triethylamine and 4-dimethylaminopyridine in CH_2Cl_2. The obtained product was subjected to an optically active HPLC column for analytical separation [column, Chiralcel OD-H (4.6∅ × 250 mm); eluent, 85:15 *n*-hexane–2-propanol mixture; flow rate, 1.0 ml/min; t_R of (*R*)-isomer, 21.1 min; t_R of (*S*)-isomer, 23.6 min] to determine the optical purity. The optical purity of this reaction product was confirmed to be 85% ee. Subsequently, to a solution of the obtained (2*R*)-amino-4-(4-benzyloxyphenyl)-2-methylbutan-1-ol (total 35.8 g, 125 mmol) in EtOH (total 3.2 l) and H_2O (total 2.6 l) was added a solution of D-(−)-tartrate (total 9.35 g, 62.3 mmol) in H_2O (total 600 ml) with stirring under hot water bath heating divided into five parts and the clear solution was left at ambient temperature overnight. The precipitated crystal was collected by filtration to obtain a crude crystal (total 36.5 g). The crude crystal was recrystallized from a mixture of EtOH (total 2.8 l) and water (total 2.8 l) and divided into four parts to obtain the title compound (total 32.6 g, 99.9% ee) as a colorless scaly crystal. IR (KBr): 3397, 3223, 3116, 3034, 2932, 1600, 1513, 1400, 1243, 1123, 1076, 1046, 736, 694 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.44–7.30 (m, 5H), 7.11 (d, 2H, $J = 8.6$ Hz), 6.92 (d, 2H, $J = 8.6$ Hz), 5.06 (s, 2H), 3.78 (s, 1H), 3.36 (d, 1H, $J = 11.2$ Hz), 3.32 (d, 1H, $J = 11.2$ Hz), 2.56–2.46 (m, 2H), 1.72–1.59 (m, 2H), 1.11 (s, 3H); MS (FAB) *m*/*z*: 286 $(M+H)^+$ as free form of the title compound. Anal. Calcd for $C_{18}H_{23}NO_2{\cdot}0.5C_4H_6O_6$: C, 66.65; H, 7.27; N, 3.89. Found: C, 66.25; H, 7.03; N, 3.90.

4.35. *tert*-Butyl [(1*R*)-3-[4-(benzyloxy)phenyl]-1-(hydroxymethyl)-1-methylpropyl]carbamate 24

To a slurry of compound **23** (15 mg, 0.042 mmol) in AcOEt (1 ml) were added satd $NaHCO_3$ (1 ml) and di-*tert*-butyl dicarbonate (14 mg, 0.063 mmol) at room temperature. After stirring for 6 h at 50 °C, the reaction mixture was cooled to room temperature and poured into water, and extracted with Et_2O. The combined organic layer was washed with brine, dried over $MgSO_4$ and filtered. The filtrate was evaporated in vacuo, and the residue was purified by chromatography on a silica gel column (eluent, *n*-hexane–AcOEt = 2:1–1:1) to afford the title compound (12 mg, 77%) as a white crystalline solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.45–7.28 (m, 5H), 7.11 (d, 2H, $J = 8.6$ Hz), 6.89 (d, 2H, $J = 8.6$ Hz), 5.04 (s, 2H), 4.63 (br s, 1H), 4.10 (br, 1H), 3.70 (dd, 1H, $J = 6.3$, 11.3 Hz), 3.63 (dd, 1H, $J = 4.3$, 11.3 Hz), 2.62 (dt, 1H, $J = 5.5$, 12.1 Hz), 2.52 (dt, 1H, $J = 12.1$, 5.1 Hz), 2.02 (dt, 1H, $J = 12.1$, 5.5 Hz), 1.84 (dt, 1H, $J = 12.1$, 5.1 Hz), 1.44 (s, 9H), 1.22 (s, 3H); MS (FAB) *m*/*z*: 386 $(M+H)^+$.

4.36. (2*R*)-Amino-4-[4-(heptyloxy)phenyl]-2-methylbutan-1-ol 4

To a solution of compound **24** (12 mg, 0.032 mmol) in MeOH (1 ml) was added 10% Pd–C (15 mg) and the air

was replaced with hydrogen. After stirring for 22 h at room temperature, the reaction mixture was filtered through Celite. The filtrate was evaporated in vacuo to give a white solid, which was dissolved in DMF (0.5 ml). To this solution were added 1-iodoheptane (11 μl, 0.064 mmol) and potassium carbonate (14 mg, 0.10 mmol). After stirring for 3 h at 60 °C, the reaction mixture was cooled to room temperature and poured into water, and extracted with Et_2O. The combined organic layer was washed with brine, dried over $MgSO_4$ and filtered. The filtrate was evaporated in vacuo, and the residue obtained was purified by chromatography on a silica gel column (eluent, *n*-hexane–AcOEt = 4:1–2:1) to afford *tert*-butyl [(1*R*)-3-[4-(heptyloxy)phenyl]-1-(hydroxymethyl)-1-methylpropyl]carbamate (8.2 mg, 65%) as a white crystalline solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.08 (d, 2H, $J = 8.6$ Hz), 6.81 (d, 2H, $J = 8.6$ Hz), 4.62 (br s, 1H), 4.08 (br, 1H), 3.92 (t, 2H, $J = 6.6$ Hz), 3.70 (dd, 1H, $J = 11.3$, 7.0 Hz), 3.63 (dd, 1H, $J = 11.3$, 5.1 Hz), 2.61 (dt, 1H, $J = 12.1$, 5.5 Hz), 2.52 (dt, 1H, $J = 13.7$, 5.5 Hz), 2.02 (dt, 1H, $J = 13.7$, 5.1 Hz), 1.84 (dt, 1H, $J = 13.7$, 5.5 Hz), 1.78 (quintet, 2H, $J = 7.8$ Hz), 1.49–1.22 (m, 17H), 1.22 (s, 3H), 0.89 (t, 3H, $J = 7.0$ Hz); MS (FAB) *m*/*z*: 394 $(M+H)^+$. To a solution of *tert*-butyl [(1*R*)-3-[4-(heptyloxy)phenyl]-1-(hydroxymethyl)-1-methylpropyl]carbamate (8.2 mg, 0.021 mmol) in MeOH (1 ml) was added 4 M solution of HCl in dioxane (0.5 ml) at room temperature. After stirring for 3 h at room temperature, the reaction mixture was evaporated in vacuo to give a white solid, which was dissolved in AcOEt (1 ml). To this solution was added satd $NaHCO_3$ (0.5 ml), and this mixture was stirred for 1 h at room temperature. The resulting mixture was poured into water, and extracted with AcOEt. The combined organic layer was washed with brine, dried over $MgSO_4$ and filtered. The filtrate was evaporated in vacuo to give compound **4** (3.5 mg, 56%) as a pale yellow solid. $[\alpha]_D^{24} = -5.6$ (*c* 0.21, $CHCl_3$); IR (KBr): 3235, 2925, 2856, 1566, 1513 cm^{-1}; ^{1}H NMR (400 MHz, CD_3OD): δ 7.11 (d, 2H, $J = 8.3$ Hz), 6.81 (d, 2H, $J = 8.3$ Hz), 3.93 (t, 2H, $J = 6.3$ Hz), 3.43 (d, 1H, $J = 10.7$ Hz), 3.38 (d, 1H, $J = 10.7$ Hz), 2.58 (t, 2H, $J = 8.8$ Hz), 1.78–1.64 (m, 4H), 1.50–1.43 (m, 2H), 1.42–1.29 (m, 6H), 1.14 (s, 3H), 0.92 (t, 3H, $J = 6.8$ Hz); MS (FAB) *m*/*z*: 294 $(M+H)^+$.

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