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Graphical Abstract.

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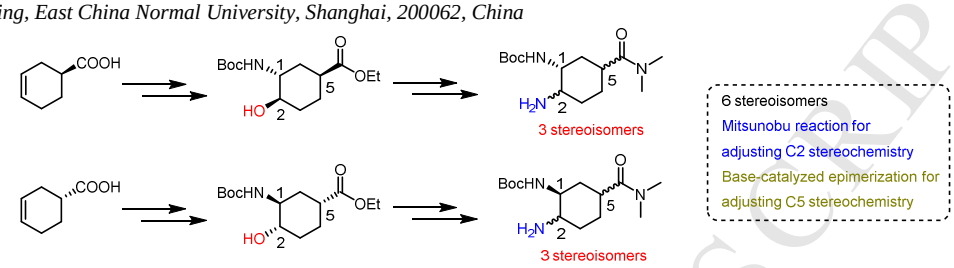

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ABSTRACT

An efficient stereoselective route for the preparation of six stereoisomers of tert-butyl ((1*R*, 2*S*, 5*S*)-2-amino-5-(dimethylcarbamoyl)cyclohexyl)carbamate **1** starting from simple 3-cyclohexene-1-carboxylic acid has been described. Stereochemistry of the title compounds was controlled at C2 center by Mitsunobu reaction and at C5 via a base-catalyzed epimerization. Only a limited usage of column chromatography has provided a direct and scalable route for the six stereoisomers.

1. Introduction

Factor Xa (fXa), a serine protease, plays an important role in the coagulation pathway and forms the prothrombinase complex via binding to factor Va on activated platelet surface. The prothrombinase complex converts prothrombin to another serine protease, thrombin.[1] Thrombin is responsible for the conversion of soluble fibrinogen into insoluble strands of fibrin and also the formation of blood clots.[2] Thus, factor Xa has become an attractive target for anticoagulant treatment.[3] Edoxaban is known to be an orally and direct factor Xa inhibitor for the prevention and treatment of venous thromboembolisms, and also anticipated to exhibit superior oral absorption and a lower risk of bleeding when compared to other available anticoagulants.[4-6]

Tert-butyl ((1*R*,2*S*,5*S*)-2-amino-5-(dimethylcarbamoyl)cyclohexyl) carbamate **1** has been reported as a key intermediate in the synthesis of edoxaban (Fig. 1).[7] Similar cycloalkanediamine derivatives have gained much interest due to their potential as therapeutic drugs for thrombotic diseases.[8] The *cis*-1, 2-diaminocyclohexane and a carboxamide substituent on the C5 of cyclohexane ring which exist in compound **1** makes 7 possible stereoisomers. Hence, the stereochemistry of the three substituents on the cyclohexane ring can greatly affect the anti-fXa activity of edoxaban.[8b] Nagata and coworkers have reported the synthesis of four stereoisomers of 3, 4-diaminocyclohexane carboxylic acid derivatives in order to elucidate the significance of each substituent stereochemistry for anti-fXa activity.[8b] However, all four compounds they synthesized were only in racemic form. Meanwhile, the control and detection of impurities is very important for industrial production of pharmaceutical drugs. Some stereoisomers of compound **1** may be useful intermediates for the synthesis of impurities of edoxaban, which are generated in the industrial production process.[9] Additionally, the derivatives of 3, 4-diaminocyclo-hexane carboxylic acid can be used as chiral organocatalysts for asymmetric direct aldol reaction with high enantioselectivity.[10]

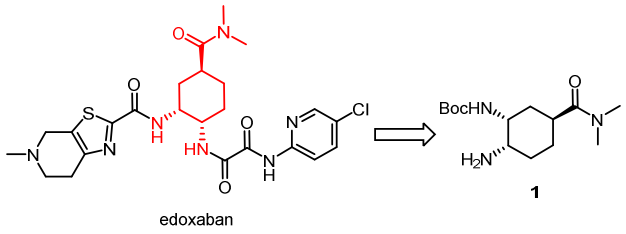

Fig. 1. Structures of edoxaban and its key intermediate.

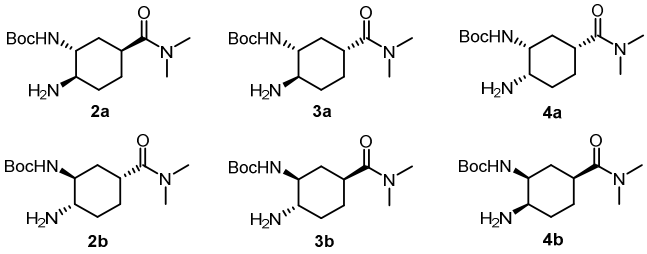

Fig. 2. Structures of six stereoisomers of compound **1**.

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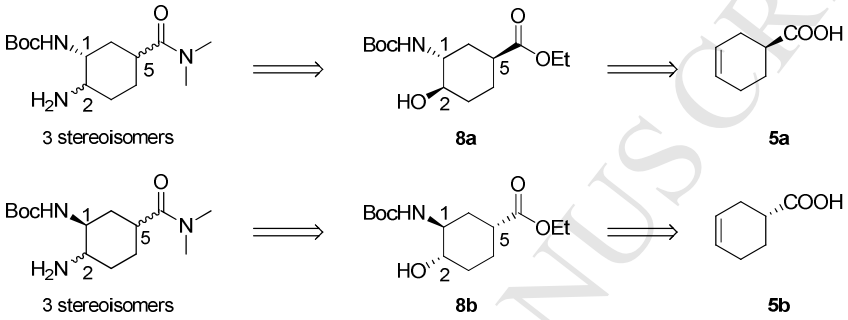
Due to these significant biological activities and structural importance, several processes have been reported for the preparation of compound **1**,[8d,11] and its enantiomer, which could also be easily achieved following the same route from enantiomeric precursor. However, there were only a few reports about the synthesis of diastereoisomers of **1**.[9] Herein we report our results of stereoselective synthesis of six stereoisomers of compound **1** starting from 3-cyclohexene-carboxylic acid (Fig. 2) by using Mitsunobu reaction and a base-catalyzed epimerization as key steps of the strategy.

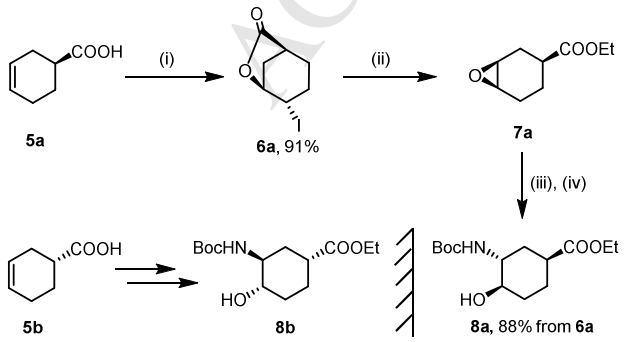
2. Results and discussion

The designed strategy for the synthesis of the six stereoisomers starting from cyclohexene carboxylic acid **5** is shown in scheme 1. One of the targeted stereoisomers of compound **1** could be achieved from **8a** by the installation of amino group via the displacement of tosylated/mesylated alcoholic group of **8a** by azide (N_3) followed by reduction. On the other hand, the other isomer could be resulted from **8a** via the inversion of C2 hydroxyl group under Mitsunobu reaction conditions[12] using a carboxylic acid nucleophile, subsequent hydrolysis, mesylation or tosylation to form a leaving group followed by azide substitution and further reduction. The key intermediate compound **8a** which in turn could be obtained by a literature reported four-step sequence from **5a**[8b,11a] The stereochemistry at C5 can also be adjusted by racemization of the ester group of **8a**.[13] Inversion of amino stereochemistry at C1 is difficult to achieve by our synthetic route, however, identical sequences starting from (*R*)-3-cyclohexene-carboxylic acid **5b** allow access to epimers at C1.



Scheme 1. Retro synthetic approach for the synthesis of 6 stereoisomers.

Keeping our synthetic strategy in mind, we have commenced with (*S*)-3-cyclohexene-1-carboxylic acid **5a** which has been prepared from commercially available racemic 3-cyclohexene-1-carboxylic acid.[14] Thus treatment of **5a** with KI and I_2,[15] resulted 4-iodo-6-oxabicyclo[3.2.1]octan-7-one **6a** in excellent yield followed by ethanolysis in the presence of NaOH afforded the *cis*-epoxide **7a**. Without further purification, the epoxide **7a** has been allowed to react with an excess amount of ammonia in the next step. Nucleophilic opening of the substituted *cis*-epoxide **7a** with ammonia gave *trans*-amino alcohol as a single isomer with high regio- and stereoselectivity in accordance with Fürst-Plattner rule.[16] Furthermore, the chemo selective protection of the amino group with Boc_2O afforded the key intermediate **8a** in almost quantitative yield with an overall yield of 80% (Scheme 2). The same protocol was applied on (*R*)-3-cyclohexene-1-carboxylic acid **5b** in order to accomplish the other enantiomer **8b** and successfully achieved **8b** in comparable yields to that of **8a**.



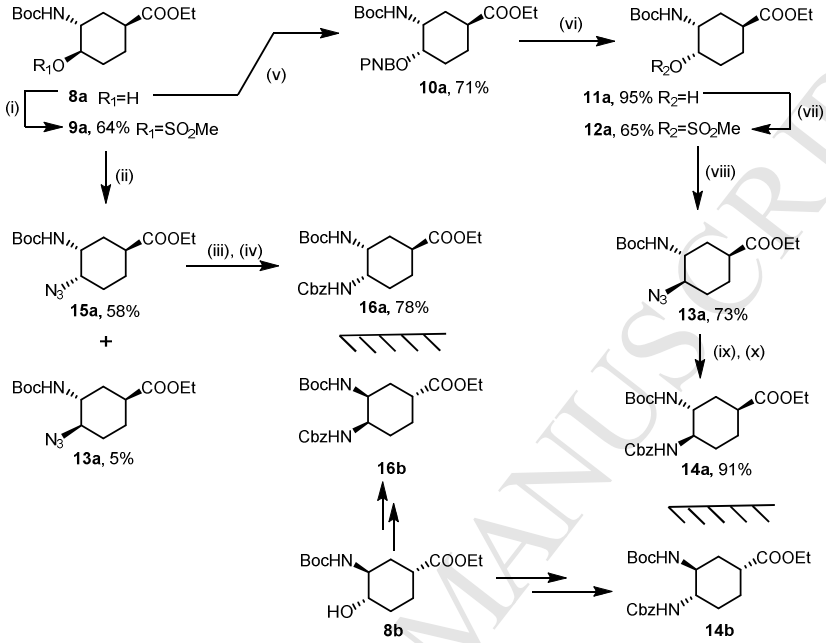
Sheme 2. *Reagents and conditions:* (i) KI, I_2, $NaHCO_3$,H_2O, rt; (ii) 2 N NaOH, EtOH, rt; (iii) 28% ammonia, EtOH, 45 ^oC; (iv) Boc_2O, EtOH, 0 ^oC to rt.

Succeeding the achievement of key intermediates **8a** and **8b**, we have turned our interest towards the title compounds. We have envisioned that, the C2 amino can be introduced by the conversion of C2 hydroxyl to mesylate followed by nucleophilic displacement with sodium azide and subsequent hydrogenation. Hence mesylation of alcohol **8a** with MsCl in the presence of Et_3N in dichloromethane gave mesylate **9a**. The mesylate **9a** upon treatment with NaN_3 in DMF in the presence of catalytic amount of 15-crown-5 at 75 ^oC for 48 h furnished the nucleophilic substitution product **15a** in 58% yield with inversion of configuration at C2. It's worth mentioning that the epimer **13a** with retention of configuration at C2 was also obtained in 5% yield, which is due to the neighboring-group participation.[17] Advancement of azide **15a** to **16a** was achieved in a two-step sequence, i.e., Pd/C catalyzed hydrogenation followed by protection of amino group with Cbz resulted the *cis*-diaminocyclohexane **16a** with two different protecting groups (Scheme 3).

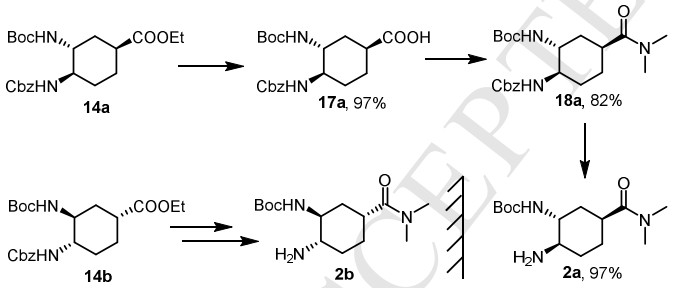
Although a small amount of epimer **13a** with retention of configuration at C2 can be obtained by the above mentioned method, however, a multigram scale synthesis was hard to achieve because of low yield. Therefore, the inversion of configuration at C2 hydroxyl was required before the mesylation. We have tried initially the Mitsunobu reaction of **8a** with PPh_3 and DIAD in THF in the presence of $(TsO)_2Zn$, by anticipating that formation of leaving group -OTs as well as inversion of configuration of hydroxyl can be achieved in one-step procedure,[18] however, no reaction occurred. We next shifted to the conventional Mitsunobu condition, the desired alcohol **11a** with inversion of configuration at C2 was achieved in two steps. Treatment of **8a** with DEAD, PPh_3 and *p*-nitrobenzoic acid in THF, to afford benzoate **10a** in 71% yield. Selective hydrolysis of benzoate **10a** was achieved by treatment with K_2CO_3 in EtOH to afford the alcohol **11a** (Scheme 3).

Following the same procedures for the synthesis of **16a** from **8a** as described above, **11a** was converted into *trans*-diaminocyclohexane **14a** in a four-step sequence. Compound **14a** is a common intermediate for the synthesis of both targets **2a** and **3a**. It is noteworthy that mesylate **12a** was treated with NaN_3 to afford **13a** with inversion of configuration at C2 as the sole product in 73% yield without neighboring-group participation due to the Boc protected amino group and the leaving group being on the same side. The enantiomers **14b** and **16b** were obtained by identical sequences from **8b**.

In the final stages of the synthesis of **2a** (Scheme 4), hydrolysis of ethyl ester **14a** with $LiOH \cdot H_2O$ in aqueous EtOH afforded the carboxylic acid **17a** in a quantitative yield. Amide **18a** was prepared by a conventional condensation of carboxylic acid **17a** with dimethylamine in the presence of EDCI and HOBt in DMF. The amide **18a** was then subjected to Pd-catalyzed hydrogenation to produce the required monoprotection target compound *trans*-diaminocyclohexane carboxamide **2a**. Whereas, the enantiopure **2b** was prepared by the application of identical sequences from **14b**.

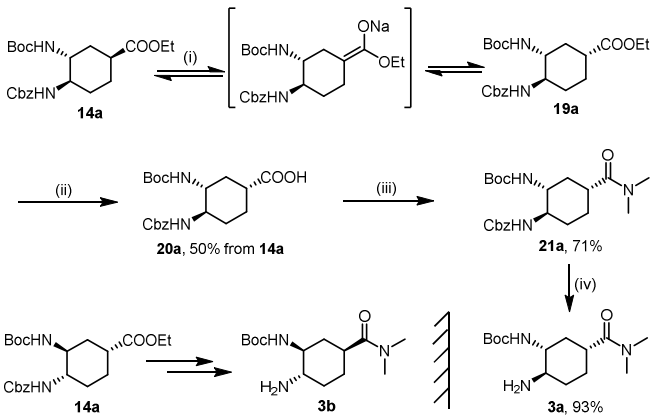


Sheme 3. *Reagents and conditions*: (i) CH_3SO_2Cl, Et_3N, CH_2Cl_2, 0 °C; (ii) NaN_3, 15-crown-5, DMF, 75 °C; (iii) 10% Pd/C, H_2, EtOH, rt; (iv) CbzCl, $NaHCO_3$, ethyl acetate/H_2O, 0 °C to rt; (v) PPh_3, DEAD, *p*-nitrobenzoic acid, THF, 0 °C to rt; (vi) K_2CO_3, EtOH, rt; (vii) CH_3SO_2Cl, Et_3N, CH_2Cl_2, 0 °C; (viii) NaN_3, 15-crown-5, DMF, 75 °C; (ix) 10% Pd/C, H_2, EtOH, rt; (x) CbzCl, $NaHCO_3$, ethyl acetate/H_2O, 0 °C to rt.



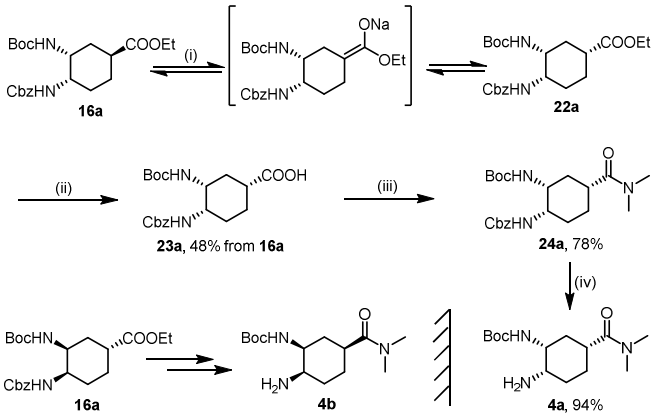
Sheme 4. *Reagents and conditions*: (i) $LiOH \cdot H_2O$, EtOH, rt; (ii) EDCI, HOBt, $Me_2NH \cdot HCl$, Et_3N, DMF, 0 °C to rt; (iii) 10% Pd/C, H_2, MeOH, rt.

The inversion of stereochemistry at C5 was achieved by a base-catalyzed epimerization of the ethyl ester **16a** via an enolate intermediate.[13] We initially employed LDA or LiHMDS as bases in THF for deprotonation of the chiral center C5 and subsequent quenched by water, however, resulted a complex mixture. When we have treated **14a** with a slightly excess amount of sodium ethoxide[9] in anhydrous EtOH at 50 °C for overnight, formation of a mixture of **14a** and **19a** was observed with both retention and inversion of configuration at C5 (Scheme 5). ^1H NMR showed that the ratio of two diastereomers with retention (**14a**) and inversion (**19a**) of configuration at C5 was 36:64. However, we were unable to separate the diastereomeric mixtures by column chromatography even on a small scale because of closed Rf values. The diastereomeric mixtures were then hydrolyzed to corresponding carboxylic acid in one-pot by addition of water to the reaction mixtures. Even the diastereomeric mixtures of carboxylic acid also can't be separated by column chromatography.



Sheme 5. *Reagents and conditions*: (i) NaOEt, EtOH, 50 °C; (ii) NaOH, EtOH/H_2O, rt; (iii) EDCI, HOBt, $Me_2NH \cdot HCl$, Et_3N, DMF, 0 °C to rt; (iv) 10% Pd/C, H_2, MeOH, rt.

Much to our delight, the required optically pure **20a** can be easily separated out in 50% yield by simply recrystallization using EtOH/H_2O 10:1 as recrystallization solvents. The using of column chromatography can be avoided which makes it possible to prepare the optically pure **20a** on a large scale. Subsequent amidation and deprotection in a good yield to give the required monoprotection target compound *trans*-diaminocyclohexane carboxamide **3a**. The enantiomeric **3b** was prepared by identical sequences from **14b.**



Sheme 6. *Reagents and conditions*: (i) NaOEt, EtOH, 50 °C; (ii) NaOH, EtOH/H_2O, rt; (iii) EDCI, HOBt, Me_2NH•HCl, Et_3N, DMF, 0 °C to rt; (iv) 10% Pd/C, H_2, MeOH, rt.

A similar strategy was used for the synthesis of *cis*-diaminocyclohexane **4a** (Scheme 6). Epimerization of **16a** was performed in anhydrous EtOH with sodium ethoxide at 50 °C for overnight, subsequent hydrolysis of ethyl ester in one-pot gave the carboxylic acid as a mixture of two diastereoisomers. It is noteworthy that the required enantiomerically pure carboxylic acid **23a** with inversion of configuration at C5 was separated out in 48% yield by simple recrystallization using a mixture of hexane/ethyl acetate in 5:1 ratio as recrystallization solvents. Subsequent amidation and deprotection lead to the required monoprotection target compound *cis*-diaminocyclohexane carboxamide **4a** in good yield. The enantiomeric **4b** was also obtained in identical sequences from **16b**.

3. Conclusions

In conclusion, a highly efficient and stereoselective synthetic route for the six stereoisomers of tert-butyl ((1*R*,2*S*,5*S*)-2-amino-5-(dimethylcarbamoyl)cyclo-hexyl)carbamate **1** from 3-cyclo-hexene-1-carboxylic acid have been accomplished. The efficiency of our approach derived from Mitsunobu reaction for fine-tuning of C2 stereochemistry and a base-catalyzed epimerization for amending C5 stereochemistry. Other features of our synthesis include separation of the diastereomeric mixtures by simple recrystallization which allows for multigram scale synthesis of target compounds. Each isomer may be considered a valuable intermediate for the synthesis of potential fXa inhibitors for further biological evaluation. The strategy might also be useful for synthesis of other analogues of trisubstituted cyclohexane.

4. Experimental section

4.1. General experimental

All chemicals were of reagent grade quality purchased from commercial sources and used without further purification. Anhydrous THF was distilled over sodium. HRMS (ESI) Mass spectra were recorded on Bruker microTOF-Q 10198 mass spectrometer. ^{1}H NMR, ^{13}C NMR and 2D NMR (^{1}H-^{13}C HSQC, ^{1}H-^{1}H COSY, and ^{1}H-^{1}H NOESY) spectra were recorded on a Brucker Ascend-400 MHz spectrometer, 400 MHz for ^{1}H and 100 MHz for ^{13}C. Optical rotations were recorded on an Autopol VI polarimeter.

*4.2. (S)-3-cyclohexene-1-carboxylic acid (**5a**)*

Optically pure **5a** was prepared by resolution of racemic cyclohex-3-enylcarboxylic acid following the method disclosed by Schwartz *et al.*[14] Racemic cyclohex-3-enylcarboxylic acid (100 g, 0.79 mol) was added to acetone (500 mL) and heated to 55 °C, to the solution, (*R*)-(+)-α-phenethylamine (95.6 g, 0.79 mol) in acetone (200 mL) was added dropwise over 30 min. After 1 h, the mixture was cooled to room temperature and (*R*)-(+)-α-phenethylamine salt of cyclohex-3-enylcarboxylic acid was formed. The precipitate obtained was filtered off and washed with acetone. The salt was recrystallized with acetone as solvent. Recrystallization of the salt was repeated until a required optical rotation $[\alpha]^{25}_D < -40°$ was achieved.

(*R*)-(+)-α-phenethylamine salt of (*S*)-3-cyclohexene-1-carboxylic (57.6 g, 233 mmol) was dissolved in ethyl acetate (900 mL) and 2 N HCl (900 mL). The phases were separated, and the aqueous layer was extracted with ethyl acetate (300 mL). The organic fractions were combined, washed with water (200 mL) and saturated brine (200 mL), and dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo to give optically pure **5a** (28.8 g , 29%) as a colorless oil; $[\alpha]^{25}_D$ -82.6° (c 1.0, MeOH).

For the enantiomer **5b;** a colorless oil $[\alpha]^{25}_D$ +85.2° (c 1.0, MeOH).

*4.3. (1S,4S,5S)-4-iodo-6-oxabicyclo [3.2.1] octan-7-one (**6a**)*

Sodium bicarbonate (56 g, 0.67 mol) was added to a solution of **5a** (28 g, 0.22 mol) in water (450 mL). To the solution, iodine (59.8 g, 0.24 mol) and potassium iodide (220 g, 1.33 mol) were added successively, followed by stirring at room temperature for 5 h. The reaction mixture was quenched with sodium thiosulfate, and extracted with ethyl acetate (2 × 200 mL). The combined organic layers were washed with water (100 mL) and saturated brine (100 mL), and then dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure. The obtained pale yellow solid was added hexane (150 mL) and stirred at room temperature for 1 h, the solid was collected by filtration and dried to give **6a** (50.9 g , 91%) as a white solid; $[\alpha]^{25}_D$ -20.4° (c 1.0, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.97 – 4.74 (m, 1H), 4.51 (t, *J* = 4.4 Hz, 1H), 2.79 (d, *J* = 12.3 Hz, 1H), 2.67 (t, *J* = 3.9 Hz, 1H), 2.52 – 2.34 (m, 2H), 2.12 (dd, J = 16.5, 5.2 Hz, 1H), 1.98 – 1.77 (m, 2H); 13C NMR (100 MHz, $CDCl_3$) δ 177.74, 80.21, 38.60, 34.51, 29.72, 23.81, 23.12; HRMS (ESI; m/z) $[M+Na]^+$ calcd for $C_7H_9O_2INa$ 274.9545, found 274.9555.

For the enantiomer **6b**; a white solid ; 93% yield; $[\alpha]^{25}_D$ +26.5° (c 1.0, MeOH); HRMS (ESI; m/z) $[M+Na]^+$ calcd for $C_7H_9O_2INa$ 274.9545, found 274.9549.

*4.4. Ethyl (1S,3R,4R)-3-((tert-butoxycarbonyl)amino)-4-hydroxycyclohexane-1-carboxylate (**8a**)*

2 N aqueous sodium hydroxide (116 mL, 0.23 mol) was added to a solution of **6a** (48.3 g, 0.193 mol) in EtOH (70 mL) and the reaction was stirred at room temperature for 3 h. EtOH was removed under reduced pressure, and the residue was extracted with dichloromethane (180 mL). The organic layer was washed with water (35 mL) and saturated brine (35 mL), and then dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure to give crude **7a** as a yellow oil. The compound

was used for next step without further purification. 28% aqueous ammonia (315 mL) was added to a solution of crude **7a** in EtOH (150 mL), the reaction was stirred at 45 °C overnight. The reaction was cooled to room temperature and concentrated in vacuo to afford the crude amino alcohol as a pale yellow oil. The oil was dissolved in EtOH (300 mL) and Boc_2O (41.3 g, 0.19 mol) was then added in ice-water bath. After 15 min, the reaction was allowed to warm to room temperature. After 2 h, the solvent was removed under reduced pressure to give **8a** (48.3 g, 88%) as a colorless oil. The crude **8a** was used for next step without further purification; $[\alpha]^{25}_D$ +4.1° (c 1.0, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.73 (br s, 1H), 4.16 (ddd, *J* = 10.3, 7.1, 3.5 Hz, 2H), 3.70 – 3.24 (m, 3H), 2.63 (dd, *J* = 8.8, 4.3 Hz, 1H), 2.41 – 2.25 (m, 1H), 2.16 – 2.07 (m, 1H), 1.95 – 1.79 (m, 1H), 1.52 (dd, *J* = 11.0, 8.9 Hz, 2H), 1.45 (s, 10H), 1.27 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, CDCl3) δ 174.14, 156.75, 79.96, 73.26, 60.61, 52.79, 38.71, 31.20, 29.87, 28.35, 24.64, 14.22; HRMS (ESI; m/z) $[M+Na]^+$ calcd for $C_{14}H_{25}NO_5Na$ 310.1630, found 310.1620.

For the enantiomer **8b**; a colorless oil; 83% yield; $[\alpha]^{25}_D$ -2.1° (c 1.0, MeOH); HRMS (ESI; m/z) $[M+Na]^+$ calcd for $C_{14}H_{25}NO_5Na$ 310.1630, found 310.1618.

*4.5. Ethyl (1S,3R,4R)-3-((tert-butoxycarbonyl)amino)-4-((methylsulfonyl)oxy) cyclohexane-1-carboxylate (**9a**)*

Methanesulfonyl chloride (8.5 mL, 0.11 mol) was added dropwise to a solution of **8a** (21.2 g, 0.074 mol) and triethylamine (20.5 mL, 0.148 mol) in dichloromethane (200 mL) at 0 °C over 30 min under argon atmosphere. The reaction was stirred at the same temperature for 2 h, water (100 mL) was then added. The mixture was separated and the organic layer was washed with saturated aqueous solution of sodium bicarbonate (60 mL) and saturated brine (60 mL) and dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure, isopropyl ether (45 mL) and isopropanol (22 mL) were added to the resultant residue, and the mixture was at room temperature for 1 h, the solid was collected by filtration and dried to give **9a** (17.3 g , 64%) as a white solid; $[\alpha]^{25}_D$ +1.8° (c 1.0, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.78 (br s, 1H), 4.65 (m, 1H), 4.16 (q, *J* = 7.1 Hz, 2H), 3.83 (qd, *J* = 7.5, 4.6 Hz, 1H), 3.06 (s, 3H), 2.58 (s, 1H), 2.35 – 2.22 (m, 1H), 1.82 – 1.64 (m, 2H), 1.45 (s, 9H), 1.27 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.80, 155.09, 80.00, 79.38, 60.79, 49.51, 38.25, 37.90, 30.28, 28.34, 27.52, 23.76, 14.20; HRMS (ESI; m/z) $[M+Na]^+$ calcd for $C_{15}H_{27}NO_7SNa$ 388.1406, found 388.1409.

For the enantiomer **9b**; a colorless oil; 76% yield; $[\alpha]^{25}_D$ -0.9° (c 1.0, MeOH); HRMS (ESI; m/z) $[M+Na]^+$ calcd for $C_{15}H_{27}NO_7SNa$ 388.1406, found 388.1410.

*4.6. Ethyl (1S,3R,4S)-4-azido-3-((tert-butoxycarbonyl)amino) cyclohexane-1-carboxylate (**15a**)*

To a solution of **9a** (17 g, 0.0465 mol) in DMF (100 mL) was added sodium azide (6 g, 0.093 mol) and 15-crown-5 (five drops) sequentially, and the mixture was stirred at 75 °C for 48 h. The reaction was allowed to cool to room temperature, then water (50 mL) and ethyl acetate (125 mL) were added to the reaction mixture. The phases were separated, and the aqueous layer was extracted with ethyl acetate (75 mL). The organic fractions were combined, washed with water (50 mL) and saturated brine (50 mL), and dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo and purified by silica gel column chromatography (with 1/6 EtOAc/hexane as eluent) to give **15a** (8.4 g, 58%) as a white solid and the epimer **13a** (0.75 g, 5%) as a white solid; $[\alpha]^{25}_D$ +55.3° (c 1.0, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.66 (d, *J* = 7.7 Hz, 1H), 4.15 (q, *J* = 7.1 Hz, 2H), 3.89 (d, *J* = 12.9 Hz, 2H), 2.73 – 2.55 (m, 1H), 1.98 – 1.88 (m, 1H), 1.89 – 1.72 (m, 5H), 1.45 (s, 9H), 1.26 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.19, 154.97, 79.73, 60.92, 60.66, 48.21, 38.13, 29.36, 28.35, 25.55, 22.41, 14.21; HRMS (ESI; m/z) $[M+Na]^+$ calcd for $C_{14}H_{24}N_4O_4Na$ 335.1695, found 335.1706.

For the enantiomer **15b**; a white solid; 47% yield; $[\alpha]^{25}_D$ -47.0° (c 1.0, MeOH); HRMS (ESI; m/z) $[M+Na]^+$ calcd for $C_{14}H_{24}N_4O_4Na$ 335.1695, found 335.1691.

*4.7. Ethyl(1S,3R,4S)-4-(((benzyloxy)carbonyl)amino)-3-((tert-butoxy- carbonyl)amino)cyclohexane-1-carboxylate (**16a**)*

10% palladium on carbon (0.75 g) was added to a solution of **15a** (7.54 g, 0.024 mol) in ethanol (50 mL), followed by stirring at room temperature for 4 h under hydrogen atmosphere. The reaction mixture was filtered, concentrated in vacuo. The obtained residue was suspended in a mixture of ethyl acetate (150 mL) and water (30 mL), followed by addition of sodium bicarbonate (4.04 g, 0.048 mol). Benzyl chloroformate (3.8 mL, 0.026 mol) was added to the reaction mixture at 0 °C over 10 min, and then the reaction was warmed to room temperature. After 1 h, the mixture was separated and the aqueous layer was extracted with ethyl acetate (50 mL). The organic fractions were combined, washed with water (50 mL) and saturated brine (50 mL), and dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo. The obtained solid was recrystallized (with 1/5 EtOAc/hexane as solvents) to give **16a** (7.9 g, 78%) as a white solid; $[\alpha]^{25}_D$ -33.6° (c 1.0, MeOH); ^{1}H NMR (400 MHz, DMSO) δ 7.43 – 7.24 (m, 5H), 6.97 (s, 1H), 6.55 (d, *J* = 5.2 Hz, 1H), 5.01 (q, *J* = 11.7 Hz, 2H), 4.04 (q, *J* = 7.1 Hz, 2H), 3.91 (d, *J* = 3.6 Hz, 1H), 3.50 (m, 1H), 2.62 (m, 1H), 1.85 (dd, *J* = 29.9, 12.2 Hz, 2H), 1.56 (dd, *J* = 26.1, 12.1 Hz, 3H), 1.46 – 1.30 (m, 10H), 1.17 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, DMSO) δ 174.68, 155.47, 155.27, 137.16, 128.24, 127.64, 127.55, 77.83, 65.07, 59.75, 50.48, 47.77, 36.13, 31.68, 28.19, 26.17, 25.20, 14.04; HRMS (ESI; m/z) $[M+Na]^+$ calcd for $C_{22}H_{32}N_2O_6Na$ 443.2158, found 443.2154.

For the enantiomer **16b**; a white solid; 87% yield; $[\alpha]^{25}_D$ +32.0° (c 1.0, MeOH); HRMS (ESI; m/z) $[M+Na]^+$ calcd for $C_{22}H_{32}N_2O_6Na$ 443.2158, found 443.2157.

*4.8. (1S,2R,4S)-2-((tert-butoxycarbonyl)amino)-4-(ethoxy-carbonyl)cyclohexyl 4-nitrobenzoate (**10a**)*

To a stirred solution of **8a** (23 g, 0.08 mol) in anhydrous THF (350 mL) was added triphenylphosphine (31.4 g, 0.12 mol) and *p*-nitrobenzoic acid (16 g, 0.096 mol) sequentially. DEAD (20.9 g, 0.12 mol) in anhydrous THF (50 mL) was added dropwise to the reaction mixture at 0 °C under an argon atmosphere over 30 min. After stirring at 0 °C for another 30 min, the reaction was allowed to warm to room temperature. After 12 h, the reaction mixture was concentrated in vacuo and the residue was dissolved in ethyl acetate (500 mL). The organic layer was washed with saturated aqueous solution of sodium bicarbonate (150 mL) and saturated brine (100 mL) and dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure and the residue was purified by silica gel column chromatography (with 1/10 EtOAc/hexane as eluent) to give **10a** (27.9 g, 71%) as a white solid; $[\alpha]^{25}_D$ +26.4° (c 1.0, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.27 (d, *J* = 8.6 Hz, 2H), 8.20 (d, *J* = 8.6 Hz, 2H), 5.20 (d, *J* = 6.9 Hz, 1H), 4.79 (s, 1H), 4.27 (s, 1H), 4.18 (q, *J* = 7.1 Hz, 2H), 2.61 (s, 1H), 2.04 (dt, *J* = 26.7, 11.3 Hz, 4H), 1.92 – 1.71 (m, 2H), 1.39 (s, 9H), 1.28 (t, *J* = 7.1 Hz, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.12, 163.85, 155.16, 150.52, 135.80, 130.79, 123.45, 79.77, 73.46, 60.77, 47.34, 37.79, 30.89, 29.66, 28.28, 25.40, 24.36, 14.20; HRMS (ESI; m/z) $[M+Na]^+$ calcd for $C_{21}H_{28}N_2O_8Na$ 459.1743, found 459.1745.

For the enantiomer **10b**; a white solid; 69% yield; $[\alpha]^{25}_D$ -31.5° (c 1.0, MeOH); HRMS (ESI; m/z) $[M+Na]^+$ calcd for $C_{21}H_{28}N_2O_8Na$ 459.1743, found 459.1747.

*4.9. Ethyl(1S,3R,4S)-3-((tert-butoxycarbonyl)amino)-4-hydroxy-cyclohexane-1-carboxylate (**11a**)*

Potassium carbonate (9.1 g, 0.066 mol) was added to a solution of **10a** (26.2 g, 0.06 mol) in ethanol (250 mL). The reaction was stirred at room temperature overnight. The reaction mixture was concentrated in vacuo and the residue was dissolved in ethyl acetate (400 mL). The organic layer was washed with water (150 mL) and saturated brine (100 mL) and dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure and the residue was purified by silica gel column chromatography (with 1/6 to 1/3 EtOAc/hexane as eluent) to give **11a** (16.4 g, 95%) as a colorless oil; $[\alpha]^{25}_D$ +12.2° (c 1.0, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.93 (s, 1H), 4.14 (q, J = 7.1 Hz, 2H), 3.91 (s, 1H), 3.84 (s, 1H), 3.06 (s, 1H), 2.51 (m, 1H), 2.06 – 1.98 (m, 1H), 1.97 – 1.88 (m, 1H), 1.87 – 1.75 (m, 2H), 1.69 – 1.52 (m, 2H), 1.45 (s, 9H), 1.26 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.87, 156.47, 79.83, 77.38, 77.06, 76.74, 69.51, 60.52, 50.16, 37.86, 30.16, 29.65, 28.36, 24.19, 14.18; HRMS (ESI; m/z) $[M+Na]^+$ calcd for $C_{14}H_{25}NO_5Na$ 310.1630, found 310.1635.

For the enantiomer **11b**; a white solid; 92% yield; $[\alpha]^{25}_D$ -15.7° (c 1.0, MeOH); HRMS (ESI; m/z) $[M+Na]^+$ calcd for $C_{14}H_{25}NO_5Na$ 310.1630, found 310.1636.

*4.10. Ethyl (1S,3R,4S)-3-((tert-butoxycarbonyl)amino)-4-((methylsulfonyl)oxy)cyclohexane-1-carboxylate (**12a**)*

Methanesulfonyl chloride (6 mL, 0.078 mol) was added dropwise to a solution of **11a** (15 g, 0.052 mol) and triethylamine (14.5 mL, 0.104 mol) in dichloromethane (150 mL) at 0 °C over 15 min under argon atmosphere. The reaction was stirred at the same temperature for 2 h, water (75 mL) was then added. The mixture was separated and the organic layer was washed with saturated aqueous solution of sodium bicarbonate (50 mL) and saturated brine (50 mL) and dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure, isopropyl ether (30 mL) and isopropanol (15 mL) were added to the resultant residue, and the mixture was at room temperature for 1 h, the solid was collected by filtration and dried to give **12a** (12.3 g , 65%) as a white solid; $[\alpha]^{25}_D$ +40.4° (c 1.0, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.94 (s, 1H), 4.71 (d, J = 7.6 Hz, 1H), 4.17 (tt, J = 7.2, 3.6 Hz, 2H), 3.96 (s, 1H), 3.03 (s, 3H), 2.71 (d, J = 4.0 Hz, 1H), 2.11 – 1.95 (m, 2H), 1.95 – 1.68 (m, 4H), 1.44 (s, 9H), 1.27 (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.91, 154.97, 79.96, 79.72, 60.82, 48.02, 38.10, 37.99, 28.52, 28.34, 26.87, 21.49, 14.21; HRMS (ESI; m/z) $[M+Na]^+$ calcd for $C_{15}H_{27}NO_7SNa$ 388.1406, found 388.1402.

For the enantiomer **12b**; a white solid; 77% yield; $[\alpha]^{25}_D$ -45.2° (c 1.0, MeOH); HRMS (ESI; m/z) $[M+Na]^+$ calcd for $C_{15}H_{27}NO_7SNa$ 388.1406, found 388.1404.

*4.11. Ethyl(1S,3R,4R)-4-azido-3-((tert-butoxycarbonyl)amino) cyclohexane-1-carboxylate (**13a**)*

To a solution of **12a** (11 g, 0.03 mol) in DMF (100 mL) was added sodium azide (3.9 g, 0.06 mol) and 15-crown-5 (five drops) sequentially, and the mixture was stirred at 75 °C for 24 h. The reaction was allowed to cool to room temperature, then water (50 mL) and ethyl acetate (200 mL) were added to the reaction mixture. The phases were separated, and the aqueous layer was extracted with ethyl acetate (50 mL). The organic fractions were combined, washed with water (80 mL) and saturated brine (80 mL), and dried over anhydrous sodium sulfate, the solvent was removed under reduced pressure. The obtained pale yellow solid was added hexane (60 mL) and stirred at room temperature for 1 h, the solid was collected by filtration and dried to give **13a** (6.9 g , 73%) as a white solid; $[\alpha]^{25}_D$ +21.7° (c 1.0, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.70 (s, 1H), 4.16 (q, J = 7.1 Hz, 2H), 3.66 (ddd, J = 11.9, 7.7, 3.8 Hz, 1H), 3.54 (s, 1H), 2.59 (s, 1H), 2.30 – 2.18 (m, 1H), 2.06 – 1.93 (m, 1H), 1.92 – 1.80 (m, 1H), 1.77 – 1.59 (m, 3H), 1.46 (s, 9H), 1.27 (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.03, 155.06, 79.83, 61.33, 60.68, 50.13, 38.22, 30.65, 28.35, 26.14, 24.21, 14.20; HRMS (ESI; m/z) $[M+Na]^+$ calcd for $C_{14}H_{24}N_4O_4Na$ 335.1695, found 335.1694.

For the enantiomer **13b**; a white solid; 68% yield; $[\alpha]^{25}_D$ -25.9° (c 1.0, MeOH); HRMS (ESI; m/z) $[M+Na]^+$ calcd for $C_{14}H_{24}N_4O_4Na$ 335.1695, found 335.1686.

*4.12. Ethyl(1S,3R,4R)-4-(((benzyloxy)carbonyl)amino)-3-((tert-butoxycarbonyl)amino)cyclohexane-1-carboxylate (**14a**)*

10% palladium on carbon (0.68 g) was added to a solution of **13a** (6.8 g, 0.021 mol) in ethanol, followed by stirring at room temperature for 4 h under hydrogen atmosphere. The reaction mixture was filtered, concentrated in vacuo. The obtained residue was suspended in a mixture of ethyl acetate (60 mL) and water (10 mL), followed by addition of sodium bicarbonate (3.67 g, 0.044 mol). Benzyl chloroformate (3.44 mL, 0.024 mol) was added to the reaction mixture at 0 °C over 10 min, and then the reaction was warmed to room temperature. After 1 h, the mixture was separated and the aqueous layer was extracted with ethyl acetate (30 mL). The organic fractions were combined, washed with water (450 mL) and saturated brine (45 mL), and dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo. The obtained solid was recrystallized (with 1/5 EtOAc/hexane as solvents) to give **14a** (8.36 g, 91%) as a white solid; $[\alpha]^{25}_D$ +23.9° (c 1.0, MeOH); ^{1}H NMR (400 MHz, DMSO) δ 7.43 – 7.21 (m, 5H), 7.03 (d, J = 6.9 Hz, 1H), 6.67 (d, J = 8.1 Hz, 1H), 5.12 – 4.90 (m, 2H), 4.07 (p, J = 7.2 Hz, 2H), 3.46 (d, J = 5.7 Hz, 1H), 3.32 – 3.24 (m, 1H), 2.77 – 2.65 (m, 1H), 2.03 (d, J = 12.6 Hz, 1H), 1.95 – 1.82 (m, 1H), 1.77 – 1.63 (m, 1H), 1.57 – 1.38 (m, 3H), 1.36 (s, 9H), 1.19 (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, DMSO) δ 173.82, 155.74, 155.36, 137.21, 128.23, 127.63, 127.54, 77.50, 65.03, 59.80, 53.15, 49.64, 37.79, 31.36, 28.17, 27.62, 24.83, 14.08; HRMS (ESI; m/z) $[M+Na]^+$ calcd for $C_{22}H_{32}N_2O_6Na$ 443.2158, found 443.2136.

For the enantiomer **14b**; a white solid; 83% yield; $[\alpha]^{25}_D$ -29.3° (c 1.0, MeOH); HRMS (ESI; m/z) $[M+Na]^+$ calcd for $C_{22}H_{32}N_2O_6Na$ 443.2158, found 443.2152.

*4.13. (1S,3R,4R)-4-(((benzyloxy)carbonyl)amino)-3-((tert-butoxy-carbonyl)amino)cyclohexane-1-carboxylic acid (**17a**)*

$LiOH\cdot H_2O$ (0.84 g, 19.9 mmol) was added to a solution of **14a** (2.8 g, 6.64 mmol) in ethanol (30 mL) and water (5 mL) at room temperature. The reaction was stirred for 6 h, concentrated in vacuo and the residue was dissolved in water (20 mL). The reaction mixture was acidified to pH=4-5 by addition of 1 N HCl and a white precipitate was formed. The solid was collected and dried to give **17a** (2.56 g, 97%) as a white solid; $[\alpha]^{25}_D$ +26.7° (c 1.0, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.57 (br s, 1H), 7.40 – 7.24 (m, 5H), 6.41 (d, J = 9.4 Hz, 1H), 5.13 (d, J = 12.4 Hz, 1H), 5.02 (d, J = 12.5 Hz, 1H), 4.85 (d, J = 9.6 Hz, 1H), 3.58 – 3.31 (m, 2H), 2.78 (s, 1H), 2.52 (d, J = 11.2 Hz, 1H), 2.22 (d, J = 13.3 Hz, 1H), 1.95 – 1.79 (m, 1H), 1.57 (dt, J = 8.4, 7.9 Hz, 1H), 1.37 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.95, 157.07, 156.90, 136.96, 128.37, 127.98, 127.83, 80.62, 66.38, 55.72, 51.48, 38.82, 33.86, 29.70, 28.89, 28.27, 25.24; HRMS (ESI; m/z) $[M+Na]^+$ calcd for $C_{20}H_{28}N_2O_6Na$ 415.1845, found 415.1841.

For the enantiomer **17b**; a white solid; 99% yield; $[\alpha]^{25}_{D}$ -24.5° (c 1.0, MeOH); HRMS (ESI; m/z) $[M+Na]^+$ calcd for $C_{20}H_{28}N_2O_6Na$ 415.1845, found 415.1840.

*4.14. Benzyl tert-butyl ((1R,2R,4S)-4-(dimethylcarbamoyl) cyclohexane-1,2-diyl)dicarbamate (**18a**)*

To a solution of **17a** (2.36 g, 6 mmol) in DMF (30 mL) was added triethylamine (4.12 mL, 30 mmol), HOBt (1.62 g, 12 mmol) and dimethylamine hydrochloride (1.47 g, 18 mmol) sequentially, the mixture was stirred at 0 °C under argon atmosphere for 10 min, followed by addition of EDCI (2.3 g, 16 mmol). After 30 min, the reaction was allowed to warm to room temperature and stirred for 2 h. Water (30 mL) and ethyl acetate (80 mL) were added to the reaction mixture. The phases were separated, and the aqueous layer was extracted with ethyl acetate (50 mL). The organic fractions were combined, washed with saturated aqueous solution of sodium bicarbonate (50 mL) and saturated brine (50 mL), and dried over anhydrous sodium sulfate, the solvent was removed under reduced pressure. The crude residue was purified by silica gel column chromatography (with 1/30 MeOH/CH_2Cl_2 as eluent) to give **18a** (2.1 g, 82%) as a white solid; $[\alpha]^{25}_{D}$ +2.2° (c 1.0, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 (dt, J = 6.0, 3.9 Hz, 5H), 5.47 (s, 1H), 5.07 (s, 2H), 4.69 (d, J = 8.0 Hz, 1H), 4.03 (s, 1H), 3.43 (d, J = 6.7 Hz, 1H), 3.01 (d, J = 10.5 Hz, 3H), 2.91 (s, 3H), 2.16 – 2.05 (m, 1H), 1.95 – 1.69 (m, 3H), 1.57 (ddd, J = 17.4, 12.5, 5.5 Hz, 1H), 1.40 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.44, 156.53, 155.93, 136.68, 128.42, 127.90, 79.29, 66.46, 54.94, 50.13, 37.42, 35.65, 34.61, 32.80, 31.57, 28.33, 27.98, 25.64, 22.64, 14.11; HRMS (ESI; m/z) $[M+Na]^+$ calcd for $C_{22}H_{33}N_3O_5Na$ 442.2318, found 442.2311.

For the enantiomer **18b**; a white solid; 73% yield; $[\alpha]^{25}_{D}$ -1.3° (c 1.0, MeOH); HRMS (ESI; m/z) $[M+Na]^+$ calcd for $C_{22}H_{33}N_3O_5Na$ 442.2318, found 442.2319.

*4.15. tert-Butyl((1R,2R,5S)-2-amino-5-(dimethylcarbamoyl) cyclohexyl)carbamate (**2a**)*

10% palladium on carbon (0.24 g) was added to a solution of **18a** (1.68 g, 4.01 mmol) in ethanol (20 mL), followed by stirring at room temperature for 6 h under hydrogen atmosphere. The reaction mixture was filtered, concentrated in vacuo to give **2a** (1.11 g, 97%) as a white solid; $[\alpha]^{25}_{D}$ -10.0° (c 1.0, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.78 (d, J = 7.4 Hz, 1H), 3.73 (s, 1H), 3.03 (s, 3H), 2.93 (s, 3H), 2.88 – 2.80 (m, 1H), 2.70 (s, 1H), 2.17 – 2.07 (m, 1H), 1.87 – 1.80 (m, 1H), 1.79 – 1.64 (m, 2H), 1.61 – 1.49 (m, 2H), 1.44 (s, 9H), 1.26 (s, 2H).; ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.78, 155.55, 79.25, 77.40, 77.09, 76.77, 53.17, 52.25, 37.30, 35.62, 34.97, 29.64, 29.30, 28.38, 24.59; HRMS (ESI; m/z) $[M+H]^+$ calcd for $C_{14}H_{28}N_3O_3$ 286.2131, found 286.2121.

For the enantiomer **2b**; a white solid; 93% yield; $[\alpha]^{25}_{D}$ +13.2° (c 1.0, MeOH); HRMS (ESI; m/z) $[M+H]^+$ calcd for $C_{14}H_{28}N_3O_3$ 286.2131, found 286.2130.

*4.16. (1R,3R,4R)-4-(((benzyloxy)carbonyl)amino)-3-((tert-butoxycarbonyl)amino)cyclohexane-1-carboxylic acid (**20a**)*

Sodium ethoxide (1.22 g, 24.0 mmol) was added to a solution of **14a** (5.46 g, 15.0 mmol) in aqueous ethanol (60 mL), and the mixture was stirred at 45 °C under argon atmosphere. After 12 h, the reaction was allowed to cool to room temperature. To the reaction mixture was added water (15 mL) and stirred at room temperature for 3 h. The reaction mixture was concentrated in vacuo and the residue was dissolved in water (30 mL). The reaction mixture was acidified to pH=4-5 by addition of 1 N HCl and a white precipitate was formed. The solid was collected and dried to give an offwhite solid. The obtained solid was recrystallized (with 1/5 EtOAc/hexane as solvents) to give **20a** (2.94 g, 50%) as a white solid; $[\alpha]^{25}_{D}$ -9.8° (c 1.0, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 (s, 5H), 5.35 (d, J = 7.9 Hz, 1H), 5.07 (s, 2H), 4.86 (d, J = 8.5 Hz, 1H), 3.51 – 3.28 (m, 2H), 2.49 – 2.33 (m, 1H), 2.28 (dd, J = 12.8, 2.0 Hz, 1H), 2.15 (d, J = 10.3 Hz, 1H), 2.10 – 1.97 (m, 1H), 1.49 (d, J = 13.1 Hz, 1H), 1.39 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.78, 156.74, 156.53, 136.48, 128.47, 128.05, 127.96, 79.91, 66.68, 55.30, 53.15, 41.62, 34.38, 31.63, 29.69, 28.30, 27.38; HRMS (ESI; m/z) $[M+Na]^+$ calcd for $C_{20}H_{28}N_2O_6Na$ 415.1845, found 415.1829.

For the enantiomer **20b**; a white solid; 43% yield; $[\alpha]^{25}_{D}$ +7.4° (c 1.0, MeOH); HRMS (ESI; m/z) $[M+Na]^+$ calcd for $C_{20}H_{28}N_2O_6Na$ 415.1845, found 415.1834.

*4.17. Benzyl tert-butyl((1R,2R,4R)-4-(dimethylcarbamoyl) cyclohexane-1,2-diyl)dicarbamate (**21a**)*

To a solution of **20a** (2.68 g, 6.7 mmol) in DMF (35 mL) was added triethylamine (4.7 mL, 34.2 mmol), HOBt (1.84 g, 13.7 mmol) and dimethylamine hydrochloride (1.67 g, 20.5 mmol) sequentially, the mixture was stirred at 0 °C under argon atmosphere for 10 min, followed by addition of EDCI (2.62 g, 13.65 mmol). After 30 min, the reaction was allowed to warm to room temperature and stirred for 2 h. Water (35 mL) and ethyl acetate (90 mL) were added to the reaction mixture. The phases were separated, and the aqueous layer was extracted with ethyl acetate (50 mL). The organic fractions were combined, washed with saturated aqueous solution of sodium bicarbonate (50 mL) and saturated brine (50 mL), and dried over anhydrous sodium sulfate, the solvent was removed under reduced pressure. The crude residue was purified by silica gel column chromatography (with 1/30 MeOH/CH_2Cl_2 as eluent) to give **21a** (2.0 g, 71%) as a white solid; $[\alpha]^{25}_{D}$ -3.4° (c 1.0, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 (s, 5H), 5.33 (d, J = 7.0 Hz, 1H), 5.08 (s, 2H), 4.98 (d, J = 7.8 Hz, 1H), 3.42 (ddd, J = 18.4, 11.2, 3.3 Hz, 2H), 3.03 (s, 3H), 2.93 (s, 3H), 2.62 (ddd, J = 11.9, 8.7, 3.3 Hz, 1H), 2.20 (dd, J = 12.9, 3.0 Hz, 1H), 2.06 – 1.96 (m, 1H), 1.77 (d, J = 13.6 Hz, 1H), 1.68 – 1.52 (m, 2H), 1.39 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.87, 156.63, 156.56, 136.60, 128.44, 127.97, 79.64, 66.55, 55.62, 53.36, 39.16, 37.14, 35.67, 34.73, 31.89, 28.30, 27.51; HRMS (ESI; m/z) $[M+Na]^+$ calcd for $C_{22}H_{33}N_3O_5Na$ 442.2318, found 442.2305.

For the enantiomer **21b**; a white solid; 78% yield; $[\alpha]^{25}_{D}$ +2.6° (c 1.0, MeOH); HRMS (ESI; m/z) $[M+Na]^+$ calcd for $C_{22}H_{33}N_3O_5Na$ 442.2318, found 442.2326.

*4.18. tert-Butyl((1R,2R,5R)-2-amino-5-(dimethylcarbamoyl) cyclohexyl)carbamate (**3a**)*

10% palladium on carbon (0.19 g) was added to a solution of **21a** (1.9 g, 4.53 mmol) in ethanol, followed by stirring at room temperature for 6 h under hydrogen atmosphere. The reaction mixture was filtered, concentrated in vacuo to give **3a** (1.2 g, 93%) as a white solid; $[\alpha]^{25}_{D}$ -47.1° (c 1.0, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.07 (d, J = 9.0 Hz, 1H), 3.31 (d, J = 9.0 Hz, 1H), 3.05 (s, 3H), 2.93 (s, 3H), 2.68 (t, J = 11.7 Hz, 1H), 2.52 (s, 3H), 2.13 – 2.05 (m, 1H), 2.03 – 1.94 (m, 1H), 1.80 – 1.71 (m, 1H), 1.64 – 1.48 (m, 2H), 1.44 (s, 9H), 1.27 (d, J = 12.1 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.35, 156.23, 79.37, 56.15, 54.66, 39.23, 37.18, 35.66, 34.91, 29.65, 28.39, 27.72; HRMS (ESI; m/z) $[M+Na]^+$ calcd for $C_{14}H_{27}N_3O_3Na$ 308.1950, found 308.1941.

For the enantiomer **3b**; a white solid; 96% yield; $[\alpha]^{25}_{D}$ +41.9° (c 1.0, MeOH); HRMS (ESI; m/z) $[M+H]^+$ calcd for $C_{14}H_{28}N_3O_3$ 286.2131, found 286.2134.

*4.19. (1R,3R,4S)-4-(((benzyloxy)carbonyl)amino)-3-((tert-butoxycarbonyl)amino)cyclohexane-1-carboxylic acid (**23a**)*

Sodium ethoxide (1.42 g, 20.9 mmol) was added to a solution of **16a** (7.3 g, 17.4 mmol) in aqueous ethanol (70 mL), and the mixture was stirred at 45 °C under argon atmosphere. After 12 h, the reaction was allowed to cool to room temperature. To the reaction mixture was added water (20 mL) and stirred at room temperature for 3 h. The reaction mixture was concentrated in vacuo and the residue was dissolved in water (40 mL). The reaction mixture was acidified to pH=4-5 by addition of 1 N HCl and a white precipitate was formed. The solid was collected and dried to give an offwhite solid. The obtained solid was recrystallized (with 1/10 H_2O/EtOH as solvents) to give **23a** (3.3g, 48%) as a white solid; $[\alpha]^{25}_D$ +41.8° (c 1.0, MeOH); ^{1}H NMR (400 MHz, DMSO) δ 12.05 (s, 1H), 7.48 – 7.25 (m, 5H), 6.89 (d, *J* = 5.9 Hz, 1H), 6.43 (d, *J* = 7.5 Hz, 1H), 5.13 – 4.94 (m, 2H), 3.80 (s, 1H), 3.51 (s, 1H), 2.30 (s, 1H), 1.84 (d, *J* = 7.2 Hz, 1H), 1.72 – 1.51 (m, 3H), 1.47 (t, *J* = 10.0 Hz, 2H), 1.37 (s, 9H); ^{13}C NMR (100 MHz, DMSO) δ 175.66, 156.11, 154.57, 137.06, 128.28, 127.77, 127.73, 77.85, 65.27, 49.84, 48.81, 40.98, 28.66, 28.16, 21.82; HRMS (ESI; m/z) $[M+Na]^+$ calcd for $C_{20}H_{28}N_2O_6Na$ 415.1845, found 415.1845.

For the enantiomer **23b**; a white solid; 46% yield; $[\alpha]^{25}_D$ -40.6° (c 1.0, MeOH); HRMS (ESI; m/z) $[M+Na]^+$ calcd for $C_{20}H_{28}N_2O_6Na$ 415.1845, found 415.1848.

*4.20. Benzyl tert-Butyl((1S,2R,4R)-4-(dimethylcarbamoyl) cyclohexane-1,2-diyl)dicarbamate (**24a**)*

To a solution of **23a** (3.14 g, 8 mmol) in DMF (30 mL) was added triethylamine (5.5 mL, 40 mmol), HOBt (2.16 g, 16 mmol) and dimethylamine hydrochloride (1.96 g, 24 mmol) sequentially, the mixture was stirred at 0 °C under argon atmosphere for 10 min, followed by addition of EDCI (3.07 g, 16 mmol). After 30 min, the reaction was allowed to warm to room temperature and stirred for 2 h. Water (30 mL) and ethyl acetate (80 mL) were added to the reaction mixture. The phases were separated, and the aqueous layer was extracted with ethyl acetate (50 mL). The organic fractions were combined, washed with saturated aqueous solution of sodium bicarbonate (50 mL) and saturated brine (50 mL), and dried over anhydrous sodium sulfate, the solvent was removed under reduced pressure. The crude residue was purified by silica gel column chromatography (with 1/30 MeOH/CH_2Cl_2 as eluent) to give **24a** (2.6 g, 78%) as a white solid; $[\alpha]^{25}_D$ +39.4° (c 1.0, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 – 7.27 (m, 5H), 5.91 – 5.71 (m, 2H), 5.08 (s, 2H), 4.10 – 3.97 (m, 1H), 3.74 (s, 1H), 2.99 (s, 3H), 2.89 (s, 3H), 2.68 (t, *J* = 12.5 Hz, 1H), 1.90 (s, 2H), 1.78 (dd, *J* = 13.7, 7.3 Hz, 2H), 1.59 (dd, *J* = 18.5, 9.8 Hz, 2H), 1.42 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.87, 156.71, 155.58, 136.56, 128.47, 128.15, 128.05, 79.23, 66.70, 50.02, 49.71, 38.24, 37.28, 35.87, 29.69, 28.40, 22.69, 14.11; HRMS (ESI; m/z) $[M+Na]^+$ calcd for $C_{22}H_{33}N_3O_5Na$ 442.2318, found 442.2298.

For the enantiomer **24b**; a white solid; 71% yield; $[\alpha]^{25}_D$ -44.2° (c 1.0, MeOH); HRMS (ESI; m/z) $[M+Na]^+$ calcd for $C_{22}H_{33}N_3O_5Na$ 442.2318, found 442.2318.

*4.21. tert-Butyl((1R,2S,5R)-2-amino-5-(dimethylcarbamoyl) cyclohexyl)carbamate (**4a**)*

10% palladium on carbon (0.22 g) was added to a solution of **21a** (2.2 g, 5.25 mmol) in ethanol, followed by stirring at room temperature for 6 h under hydrogen atmosphere. The reaction mixture was filtered, concentrated in vacuo to give **4a** (1.41 g, 94%) as a white solid; $[\alpha]^{25}_D$ +4.4° (c 1.0, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.59 (d, *J* = 7.6 Hz, 1H), 3.59 (s, 1H), 3.09 (d, *J* = 2.1 Hz, 1H), 3.06 (s, 3H), 2.94 (s, 3H), 2.63 (s, 1H), 1.68 (tt, *J* = 12.3, 7.3 Hz, 5H), 1.50 (d, *J* = 12.7 Hz, 2H), 1.43 (s, 10H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.67, 155.49, 78.93, 51.06, 48.43, 38.86, 37.18, 35.64, 32.17, 29.06, 28.40, 21.68; HRMS (ESI; m/z) $[M+H]^+$ calcd for $C_{14}H_{28}N_3O_3$ 286.2131, found 286.2144.

For the enantiomer **24b**; a white solid; 90% yield; $[\alpha]^{25}_D$ -2.9° (c 1.0, MeOH); HRMS (ESI; m/z) $[M+Na]^+$ calcd for $C_{14}H_{27}N_3O_3Na$ 308.1950, found 308.1962.

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References and notes

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Supplementary Material

Supplementary data include ^{1}H, ^{13}C NMR spectra of all the products. Supplementary data associated with this article can be found in the online version, at http://