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A novel and enantioselective synthesis of D-(+)-biotin via a Sharpless asymmetric dihydroxylation strategy

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ABSTRACT

A novel and enantioselective synthesis of D-(+)-biotin has been accomplished starting from commercially available cyclohexanone. The key steps in the sequence are the Sharpless asymmetric dihydroxylation of a (*E*)-ethyl 3-(2-chlorocyclohex-1-en-1-yl)acrylate derivative to establish the stereocenters of D-(+)-biotin, the carboxyalkyl side chain is introduced by unmasking the cyclohexene by ozonolysis and enzymatic hydrolysis of a thioacetate.

1. Introduction

D-(+)-Biotin (vitamin H)[1] is a water-soluble vitamin, involved in an essential part of the metabolic cycle causing catalytic fixation of carbon dioxide in the biosynthesis of fatty acids, sugars, and α-amino acids. It is used as a feed additive particularly in the poultry industry. In addition, it was recently found that biotin **1** enhances insulin secretion in animals, suggesting it to be a promising therapeutic candidate as an anti-diabetic drug.[2] Biotin has a remarkably strong affinity toward avidin[3] and streptavidin[1b] and their complexes are extensively used in the area of drug delivery, immunoassay, isolation, and localization. D-(+)-Biotin (Fig. 1) finds use for the clinical treatment of hair loss, brittle nails, and in tonic formulations for children.[3b] The lack of efficient fermentation methods for biotin has gained the attention of organic chemists toward its synthesis.

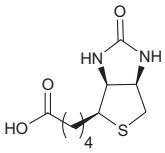

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Figure 1. Structure of D-(+)-biotin.

Over the past few decades, many efforts have been made toward the development of an efficient process for the total synthesis of D-(+)-biotin **1**. A number of new synthetic approaches involving different strategies for the control of three adjacent stereogenic centers are reported in the literature. To the best of our knowledge, very few syntheses of D-(+)-biotin that involve intermolecular asymmetric induction are reported in the literature.[1a] Many synthetic approaches, such as diastereoisomeric or enzymatic resolutions,[4] chiral pool methods involving carbohydrates,[5] cysteine,[6] and L-aspartic acid[7] have been described. Our research group has been actively involved in the stereoselective synthesis of D-(+)-biotin via chiral pool methods and has reported D-(+)-biotin syntheses starting from L-cysteine[8] and glucosamine.[9] Herein we report an asymmetric total synthesis of **1** starting from a commercially available achiral starting material viz. cyclohexanone.

The envisaged retrosynthetic strategy for biotin **1** is shown in Scheme 1. A linear synthetic strategy was used wherein olefin **2** was conceived as the direct precursor to **1**. Olefin **2** would then in turn be accessed from thioacetate **3** upon hydrolysis and intramolecular cyclization. The carboxyalkyl side chain of biotin **1** could be unmasked by ozonolysis of cyclohexene **5**. The vicinal diamine group can be introduced via sequences involving the opening of a cyclic sulfite, which could be prepared from diol **6** and S_N2 substitution of a leaving group by azide.

2. Results and discussion

Following a literature procedure,[10] cyclohexanone **7** was subjected to Vilsmeier–Haack reaction to furnish aldehyde **8**, which was homologated using a Wittig reaction to afford unsaturated ester **9** (Scheme 2).

This prochiral unsaturated ester **9** was deemed to be a suitable substrate for installation of the stereogenic centers. Compound **9** was subjected to Sharpless asymmetric dihydroxylation (SAD)[11] conditions with $(DHQD)_2PHAL$ as a chiral catalyst to yield chiral diol **6** in 84% yield with ⩾99% ee.[12] To install the azido functional-

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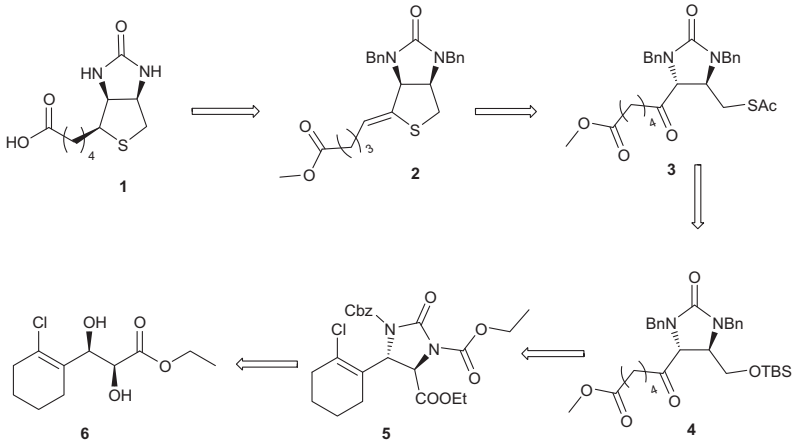
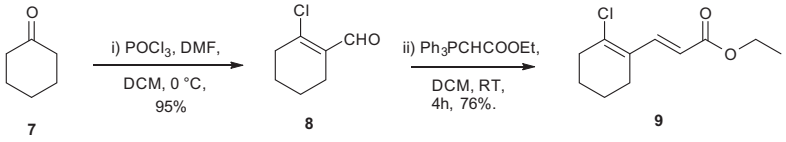


Scheme 1. Key retrosynthetic disconnections.

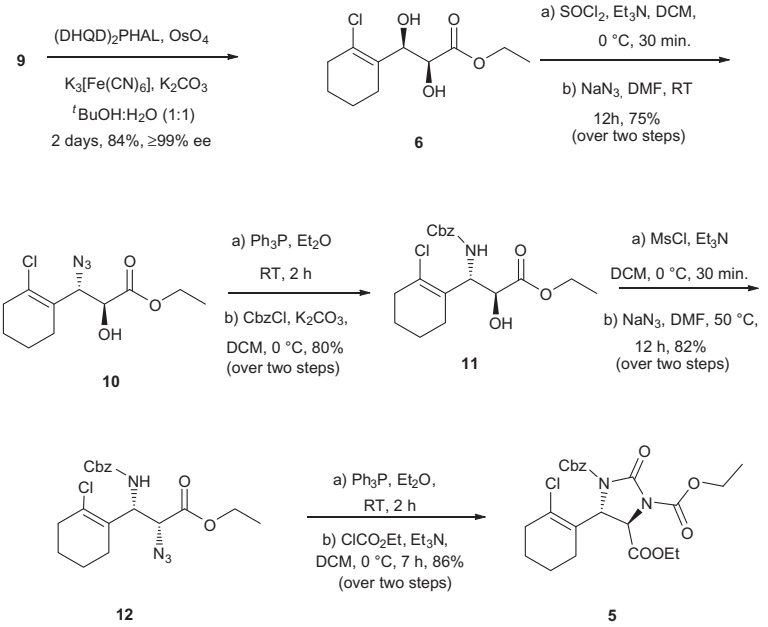


Scheme 2. Synthesis of unsaturated ester **9**.

ity, diol **6** was converted into a cyclic sulfite/sulfate. Direct conversion of the sulfite/sulfate into the corresponding diazide was unsuccessful in our hands. Hence it was decided to convert the sulfite into a diamine in a stepwise fashion. This was carried out by regioselective opening of the cyclic sulfite using NaN_3 in DMF to exclusively give β-azido ester **10** (Scheme 3).[13]

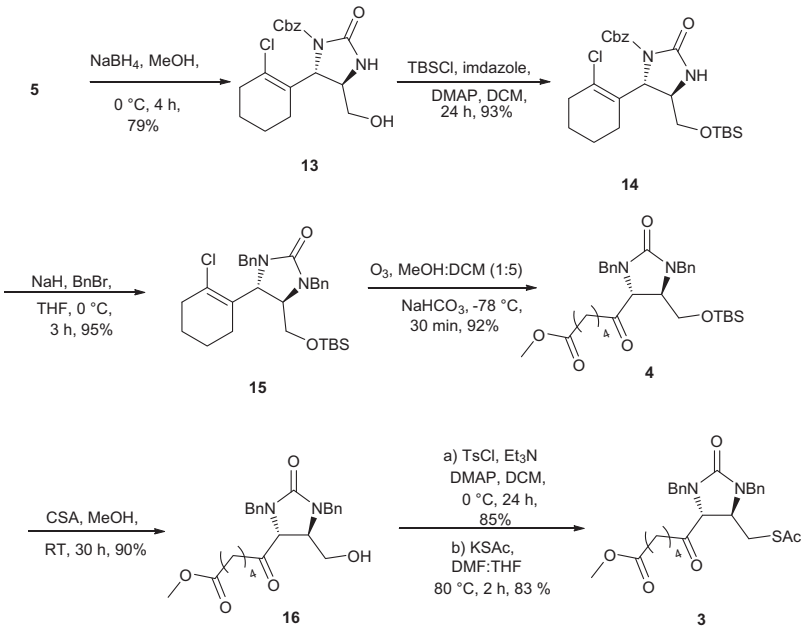
azidoamine **12**. Again the azide was reduced by using Staudinger reaction conditions to give the amine, which upon treatment with ethyl chloroformate in the presence of triethylamine, gave a cyclic protected urea **5** (Scheme 3).[15]

With compound **5** in hand, the ester was reduced using $NaBH_4$ in methanol at 0 °C, to furnish the hydroxyl compound



Scheme 3. Synthesis of urea **5**.

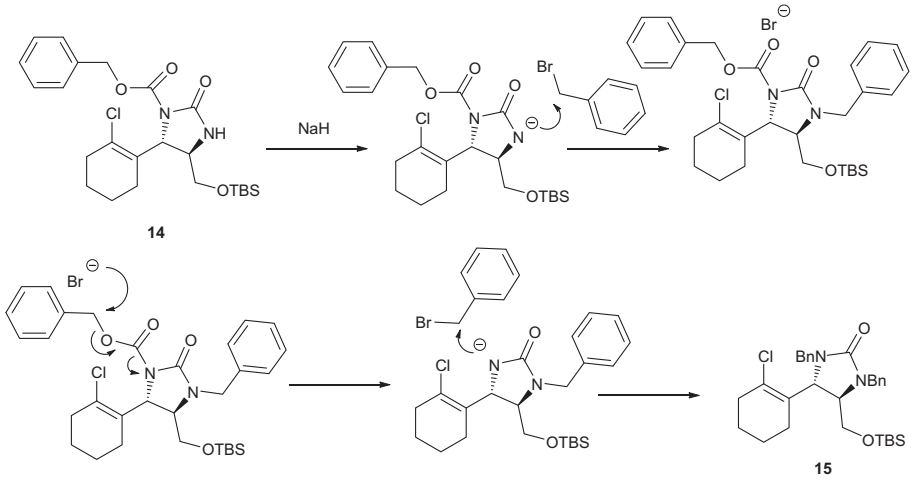
The azide was reduced under Staudinger reaction conditions[14] followed by protection using CbzCl to furnish carbamate **11**. The second amine was installed by converting the hydroxyl group into its mesylate using mesyl chloride and triethylamine, which was displaced by an azide using sodium azide in DMF to give **13**. The proximal carbamate was also selectively hydrolyzed during the reduction. The protection of primary hydroxyl group in **13** with *tert*-butylchlorodimethylsilane in the presence of imidazole in dichloromethane at room temperature gave TBS ether **14**.



Scheme 4. Synthesis of thioacetate **3**.

Upon treatment with sodium hydride, benzyl bromide **14** was converted into bisbenzyl imidazolidone **15**. A noteworthy feature of this transformation is the formation of a bis *N*-benzyl derivative, which involved the deprotection of the carbamate followed by alkylation in the same pot. We believe that the protection–deprotection proceeds via the reaction pathway illustrated in Scheme 5.

4 was carried out using camphorsulfonic acid to afford the corresponding alcohol **16**. We next set out to construct the tetrahydrothiophene ring. The introduction of sulfur was carried out by converting the primary hydroxyl group into a good leaving group. The hydroxyl group in compound **16** was converted into its tosylate after which it was displaced by potassium thioacetate in

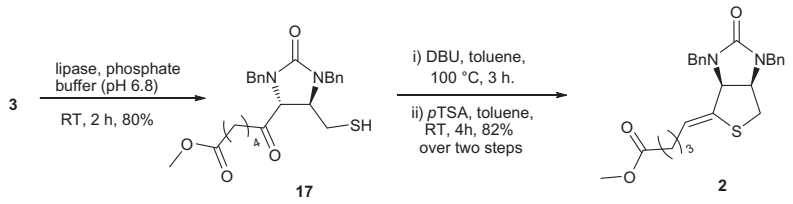


Scheme 5. Possible mechanism for conversion of **14** into **15**.

First, benzyl protection of the NH takes place under the basic reaction conditions. The bromide generated is possibly responsible for the nucleophilic deprotection of the carbamate. Finally, the anion formed attacked on the benzyl bromide resulting in **15**. The structure of **15** was determined by spectroscopic analysis. The IR spectrum of **15** showed the disappearance of a peak at 1775 cm^{-1}, which clearly indicated the loss of the Cbz group. The ^1H NMR spectrum of **15** revealed four upfield signals at 4.00, 4.08, 4.52, and 4.93 thus indicating the installation of benzyl groups. The HRMS peak at *m*/*z* 547.2523 further supported the formation of bis *N*-benzyl derivative **15**.

When performing the ozonolysis reaction, imidazolidone **15** was converted into ketoester **4**. Deprotection of the TBS ether of DMF:THF to furnish thioacetate **3** (Scheme 4).[16] With all of the structural constituents for biotin being present and in place in compound **3**, the only thing left to do was the acetate deprotection of **3**. Efforts toward this seemingly simple deprotection of acetate **3** to thiol **17** failed under a variety of reaction conditions.[17] Finally, hydrolysis under enzymatic condition using lipase (*Candida rugosa*)[18] gave thiol **17** in good yields. Subsequent cyclization of thiol **17** with a catalytic amount of DBU and elimination using *p*TSA gave olefin **2** (Scheme 6).

The spectroscopic data for olefin **2** were in agreement with the literature.[8] Since the conversion of olefin **2** to (+)-biotin **1** has been reported by us[8,9] and others,[1] this constitutes as a formal synthesis of (+)-biotin.



Scheme 6. Synthesis of D-(+)-biotin.

3. Conclusion

We have accomplished an asymmetric synthesis of D-(+)-biotin by employing Sharpless asymmetric dihydroxylation as the single source of chirality. The enantioselectivity was introduced by intermolecular asymmetric induction, which is the first report of its kind utilized in the synthesis of biotin. The carboxyalkyl side chain of D-(+)-biotin was introduced by unmasking of a cyclohexene, and is a novel strategy in our synthesis.

4. Experimental

4.1. General

Melting points are recorded using a Buchi B-540 or M-560 melting point apparatus in capillary tubes and are uncorrected; the temperatures are in °C. IR spectra were recorded on a Perkin–Elmer Infrared Spectrophotometer Model 68B or on a Perkin–Elmer 1615 FT Infrared spectrophotometer. ^{1}H (200, 400 and 500 MHz) and ^{13}C (50, 100 and 125 MHz) NMR spectra were recorded on a Bruker spectrometer, using a 2:1 mixture of $CDCl_3$ and CCl_4 as solvent. The chemical shifts (δ ppm) and coupling constants (Hertz) are reported in the standard fashion with reference to chloroform-d 7.26 (for ^{1}H) or the central line (77.0 ppm) of $CDCl_3$ (for ^{13}C). In the ^{13}C NMR spectra, the nature of the carbons (C, CH, CH_2, or CH_3) was determined by recording the DEPT-135 spectra. The enantiomeric excesses of the products were determined by HPLC employing a chiralcel OJ-H column (250 × 4.6 mm) or comparing the specific rotation of the known compounds. The reaction progress was monitored by TLC analysis using thin layer plates precoated with silica gel 60 F_{254} (Merck) and visualized by fluorescence quenching or iodine or by charring after treatment with *p*-anisaldehyde. Merck's flash silica gel (200–400 mesh) was used for column chromatography. All small scale dry reactions were carried out using standard syringe-septum techniques. Low temperature reactions were carried out using a bath made of sodium chloride and ice. Dry DCM was prepared by distillation over phosphorus pentoxide or calcium hydride. Dry DMF was prepared by distillation over calcium hydride. Dry toluene was prepared by distillation over calcium hydride. All other reagents and solvents were used as received from the manufacturer, unless otherwise specified. All air and water sensitive reactions were performed in flame dried flasks under a positive flow of argon and conducted under an argon atmosphere.

4.2. (*E*)-Ethyl 3-(2-chlorocyclohex-1-en-1-yl)acrylate 9

A mixture of anhydrous DCM (80 mL) and anhydrous DMF (15.7 mL, 204.08 mmol) was cooled to 0 °C using ice and to this was added $POCl_3$ (15.1 mL, 163.26 mmol) dropwise and stirred for 2 h at room temperature. Cyclohexanone **7** (10.0 g, 102.04 mmol) in DCM (20 mL) was then added dropwise at 0 °C and stirred for 4 h at room temperature. The reaction mixture was quenched first by using ice followed by the careful addition of satd. $NaHCO_3$ solution. The reaction mixture was allowed to separate in separating funnel, after which the organic layer was separated and the aqueous layer was again extracted twice using DCM (50 mL). The collected organics were dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo to furnish chloro aldehyde **8** (14.0 g, 95%) as a crude product.

The crude aldehyde (14.0 g, 97.22 mmol) was dissolved in DCM (150 mL) and to it was added Ph_3PCHCO_2Et (50.7 g, 145.83 mmol). The reaction mixture was stirred for 4 h. The crude residue was directly adsorbed on silica gel and purified using flash chromatography (4% EtOAc/pet ether) to furnish the α,β-unsaturated ester **9** (25.7 g, 76%) as a colorless liquid. R_f (10% EtOAc/pet ether) 0.6; IR ($CHCl_3$): 2938, 1713, 1622, 1292, 1175 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$+CCl_4): δ 1.30 (t, J = 7.1 Hz, 3H), 1.62–1.76 (m, 4H), 2.26 (br s, 2 H), 2.51 (br s, 2H), 4.21 (q, J = 7.1 Hz, 2 H), 5.85 (d, J = 15.9 Hz, 1 H), 7.91 (d, J = 15.9 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$+CCl_4): δ 14.2, 21.7, 23.3, 26.1, 35.1, 60.1, 118.1, 128.5, 139.0, 141.1, 166.7; HRMS ESI $[M+H]^+$ calcd for $C_{11}H_{16}O_2Cl$ 215.0833, found 215.0832.

4.3. (2*S*,3*R*)-Ethyl 3-(2-chlorocyclohex-1-en-1-yl)-2,3-dihydroxypropanoate 6

To a mixture of $K_3Fe(CN)_6$ (13.8 g, 42.03 mmol), K_2CO_3 (5.8 g, 42.03 mmol), and $(DHQD)_2PHAL$ (0.109 g, 0.14 mmol) in ^{t}BuOH-H_2O (1:1, 120 mL) cooled at 0 °C was added osmium tetroxide (1 mL, 0.1 M solution in toluene, 0.4 mol %) followed by methane sulfonamide (1.32 g, 14.01 mmol). After stirring for 5 min at 0 °C, olefin **9** (3.0 g, 14.01 mmol) was added in one portion. The reaction mixture was stirred at 0 °C for 2 days and then quenched with solid sodium sulfite (6 g). The stirring was continued for an additional 45 min and then the solution was extracted with EtOAc (3 × 30 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by flash column chromatography using silica gel (30% EtOAc/pet ether) to provide diol **6** (2.92 g, 84% yield) as a white solid. Melting point 65–67 °C. R_f (20% EtOAc/pet ether) 0.3; $[\alpha]_D^{25} = +5.2$ (*c* 1.92, $CHCl_3$); IR ($CHCl_3$): 3446 (broad), 2937, 1736, 1105 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$+-CCl_4): δ 1.31 (t, J = 7.1 Hz, 3H), 1.59–1.79 (m, 4 H), 2.12–2.43 (m, 4H), 2.82 (br s, 1H), 3.29 (br s, 1H), 4.20–4.34 (m, 3H), 4.95 (d, J = 4.2 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$+CCl_4): δ 14.2, 22.0, 23.7, 25.5, 34.1, 62.1, 72.1, 73.2, 128.5, 132.6, 172.8; HRMS ESI $[M+Na]^+$ calcd for $C_{11}H_{17}O_4ClNa$ 271.0708, found 271.0706.

4.4. (2*S*,3*S*)-Ethyl 3-azido-3-(2-chlorocyclohex-1-en-1-yl)-2-hydroxypropanoate 10

To a cooled (0 °C) solution of diol **6** (2.5 g, 10.08 mmol) in DCM (25 mL) was added Et_3N (2.82 mL, 20.16 mmol) followed by thionyl chloride (1.02 mL, 12.09 mmol) in a dropwise manner. The resulting reaction mixture was then stirred for 2 h at room temperature and concentrated under reduced pressure to obtain the sulfite as a thick oil. The crude sulfite was dissolved in DMF (30 mL) and to this solution was added sodium azide (1.3 g, 20 mmol) and stirred overnight. The reaction mixture was quenched using water (150 mL) and extracted in EtOAc (2 × 20 mL). The combined

organics were washed with water, dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo carefully. The crude product was purified on flash chromatography using silica gel (20% EtOAc/pet ether) to afford azidialcohol **10** (2.05 g, 75%) as a gummy liquid. R_f (20% EtOAc/pet ether) 0.5; $[\alpha]_D^{25} = -40.9$ (*c* 1.32, $CHCl_3$); IR ($CHCl_3$): 3448 (broad), 2938, 2104, 1736, 1603, 1267 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$+CCl_4): δ 1.34 (t, *J* = 7.1 Hz, 3H), 1.54–1.88 (m, 4H), 2.19 (br s, 2H), 2.40 (br s, 2H), 2.92 (br s, 1H), 4.19–4.36 (m, 3H), 5.01 (d, *J* = 5.9 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$+CCl_4): δ 14.1, 22.1, 23.6, 26.2, 34.2, 62.3, 65.1, 71.6, 128.6, 132.6, 172.4; HRMS ESI $[M+Na]^+$ calcd for $C_{11}H_{16}O_3N_3ClNa$ 296.0772, found 296.0770.

4.5. (2*S*,3*S*)-Ethyl 3-(((benzyloxy)carbonyl)amino)-3-(2-chloro cyclohex-1-en-1-yl)-2-hydroxypro panoate 11

To a solution of azidoalcohol **10** (2.0 g, 7.32 mmol) in diethyl ether (20 mL) were added PPh_3 (4.57 g, 18.31 mmol) and stirred until the evolution of nitrogen gas ceased (2 h). After completion of the reaction, the solvent was evaporated under reduced pressure to obtain the amine as a thick oil. The crude amine was dissolved in DCM (20 mL) and to this solution was added K_2CO_3 (2.51 g, 18.2 mmol), CbzCl (1.49 mL, 8.74 mmol) and stirred overnight (12 h). The reaction mixture was filtered and the filtrate was treated with water (30 mL) and was extracted in DCM (2 × 20 mL). The combined organics were washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo. The crude product was purified on flash chromatography using silica gel (20% EtOAc/pet ether) to afford carbamate **11** (2.2 g, 80%) as a gummy liquid. R_f (30% EtOAc/pet ether) 0.4; $[\alpha]_D^{25} = -17.9$ (*c* 1.59, $CHCl_3$); IR ($CHCl_3$): 3393 (broad), 2932, 1732, 1690, 1511, 1218 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$+CCl_4): δ 1.30 (t, *J* = 7.2 Hz, 3H), 1.57–1.69 (m, 4H), 2.10 (br s, 2H), 2.22–2.45 (m, 2H), 2.96 (br s, 1H), 4.07–4.19 (m, 1H), 4.20–4.31 (m, 1H), 4.39 (d, *J* = 4.3 Hz, 1H), 5.05–5.14 (m, 2H), 5.25–5.29 (m, 1H), 5.55 (d, *J* = 8.2 Hz, 1H), 7.27–7.40 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$+CCl_4): δ 14.0, 22.2, 23.6, 27.0, 34.3, 54.2, 62.3, 67.0, 72.4, 128.2, 128.3 (2C), 128.5 (2C), 129.4, 131.0, 136.4, 155.4, 172.5; HRMS ESI $[M+H]^+$ calcd for $C_{19}H_{25}O_5NCl$ 382.1416, found 382.1408.

4.6. (2*R*,3*S*)-Ethyl 2-azido-3-(((benzyloxy)carbonyl)amino)-3-(2-chlorocyclohex-1-en-1-yl) propanoate 12

To a stirred solution of carbamate **11** (2 g, 5.27 mmol) in dry DCM (20 mL) was added Et_3N (2.21 mL, 15.81 mmol) at 0 °C, followed by the dropwise addition of mesyl chloride (0.64 mL, 7.9 mmol) and the reaction mixture was stirred for 4 h under a nitrogen atmosphere. The reaction mixture was diluted with DCM (20 mL) and washed with a saturated solution of sodium bicarbonate (20 mL) and water (20 mL). The organic layer was separated, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to afford the *O*-mesyl compound.

To a solution of the crude *O*-mesyl compound in anhydrous DMF (25 mL) was added sodium azide (0.68 g, 10.44 mmol) and the reaction mixture was stirred at 50 °C for 12 h under nitrogen atmosphere. After completion of the reaction (monitored by TLC), the reaction mixture was cooled to room temperature, diluted with water (75 mL), and extracted with EtOAc (3 × 20 mL). The combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography using silica gel (7% EtOAc/pet ether) to afford azide **12** (2.12 g, 82%) as a gummy liquid. R_f (10% EtOAc/pet ether) 0.5; $[\alpha]_D^{25} = +11.6$ (*c* 1.73, $CHCl_3$); IR ($CHCl_3$): 2930, 2114, 1742, 1505, 1216 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$+CCl_4): δ 1.26 (t, *J* = 7.0 Hz, 3H), 1.60–1.73 (m, 4H), 1.98–2.19 (m, 2H), 2.39 (br s, 2H), 4.13–4.34 (m, 2H), 4.48 (br s, 1H), 4.99–5.15 (m, 2H), 5.21–5.38 (m, 2H), 7.27–7.44 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$+CCl_4): δ 14.1, 22.1, 23.4, 27.0, 34.0, 53.4, 62.3, 64.8, 67.1, 128.1, 128.2 (2C), 128.5 (2C), 130.0, 130.6, 136.3, 155.2, 167.7; HRMS ESI $[M+Na]^+$ calcd for $C_{19}H_{23}O_4N_4ClNa$ 429.1300, found 429.1295.

4.7. (4*R*,5*S*)-1-Benzyl 3,4-diethyl 5-(2-chlorocyclohex-1-en-1-yl)-2-oxoimidazolidine-1,3,4-tricar-boxylate 5

To a solution of azide **12** (2.1 g, 5.17 mmol) in diethyl ether (20 mL) was added PPh_3 (3.39 g, 12.92 mmol) and stirred until the evolution of nitrogen gas ceased (2.5 h). After completion of the reaction, the solvent was evaporated under reduced pressure to obtain the amine as a thick oil. The crude amine was dissolved in DCM (25 mL) and to this solution were added Et_3N (5.74 mL, 40.96 mmol) and ethyl chloroformate (3.88 mL, 40.96 mmol) at 0 °C and stirred (12 h). The reaction mixture was then quenched with water (30 mL) and extracted in DCM (2 × 20 mL). The combined organics were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. The crude product was purified on flash chromatography using silica gel (20% EtOAc/pet ether) to afford urea **5** (2.1 g, 86%) as a gummy liquid. R_f (30% EtOAc/pet ether) 0.4; $[\alpha]_D^{25} = -8.1$ (*c* 2.6, $CHCl_3$); IR ($CHCl_3$): 2929, 1818, 1750, 1726, 1694, 1437, 1250 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$+CCl_4): δ 1.25–1.38 (m, 6H), 1.53–1.71 (m, 4H), 1.89 (br s, 2H), 2.18–2.45 (m, 2H), 4.18–4.41 (m, 5H), 5.15 (d, *J* = 12.2 Hz, 1H), 5.29 (d, *J* = 2.9 Hz, 1H), 5.38 (d, *J* = 12.2 Hz, 1H), 7.27–7.44 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$+CCl_4): δ 14.07, 14.14, 21.6, 23.2, 24.1, 33.9, 55.4, 58.0, 62.4, 63.7, 68.4, 128.3 (2C), 128.47, 128.53 (2C), 129.5, 131.7, 134.9, 147.4, 150.3, 151.0, 168.6; HRMS ESI $[M+Na]^+$ calcd for $C_{23}H_{27}ClN_2O_7Na$ 501.1399, found 501.1400.

4.8. (4*R*,5*S*)-Benzyl 5-(2-chlorocyclohex-1-en-1-yl)-4-(hydroxy methyl)-2-oxoimidazolidine-1-carboxylate 13

To a solution of urea **5** (1.8 g, 3.76 mmol) in methanol (15 mL) was added $NaBH_4$ (0.57 g, 15.04 mmol) at 0 °C portionwise. The reaction mixture was allowed to stir for 4 h at room temperature. After completion of the reaction, the reaction mixture was concentrated under reduced pressure. The aq solution of NH_4Cl was added to the semisolid mass and allowed to stir for 30 min after which the reaction mixture was extracted with EtOAc (2 × 20 mL). The combined organic layer was dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified on flash chromatography using silica gel (90% EtOAc/pet ether) to afford alcohol **13** (0.9 g, 79%) as a white solid. Melting point 165–167 °C. R_f (EtOAc) 0.3 long tail; $[\alpha]_D^{25} = -65.5$ (*c* 2.0, $CHCl_3$); IR ($CHCl_3$): 3370 (broad), 2931, 2860, 1773, 1389, 1337, 1288, 1117 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$+CCl_4): δ 1.35–1.55 (m, 3H), 1.61–2.01 (m, 4H), 2.13–2.37 (m, 3H), 3.33 (br s, 1H), 3.54–3.65 (m, 1H), 3.73–3.76 (m, 1H), 4.99 (d, *J* = 12.1 Hz, 1H), 5.19 (d, *J* = 3.5 Hz, 1H), 5.33 (d, *J* = 12.1 Hz, 1H), 7.26–7.35 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$+CCl_4): δ 21.8, 23.4, 24.4, 33.9, 56.7, 57.9, 64.1, 67.5, 128.3 (3C), 128.4 (2C), 128.8, 131.6, 135.4, 151.1, 156.5; HRMS ESI $[M+Na]^+$ calcd for $C_{18}H_{21}O_4N_2ClNa$ 387.1082, found 387.1080.

4.9. (4*R*,5*S*)-Benzyl 4-(((*tert*-butyldimethylsilyl)oxy)methyl)-5-(2-chlorocyclohex-1-en-1-yl)-2-oxoimidazolidine-1-carboxyl ate 14

To a solution of alcohol **13** (800 mg, 2.65 mmol) in anhydrous DCM (10 mL) was added imidazole (360 mg, 5.3 mmol) followed by the addition of TBSCl (600 mg, 3.97 mmol) and DMAP (cat.) at 0 °C under a nitrogen atmosphere. The reaction was then allowed to stir at room temperature for 24 h. After completion of the reac-

tion (monitored by TLC), the reaction mixture was diluted with water (15 mL) and extracted with DCM (3 × 15 mL). The combined organic layer was dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified on flash chromatography using silica gel (50% EtOAc/pet ether) to afford TBS ether **14** (1.17 g, 93%) as a colorless liquid. R_f (50% EtOAc/pet ether) 0.5; $[\alpha]_D^{25} = -47.5$ (*c* 4.0, $CHCl_3$); IR ($CHCl_3$): 2923, 2857, 1775, 1390, 1333, 1108 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$+CCl_4): δ 0.02 (s, 6H), 0.83 (s, 9H), 1.48–1.63 (m, 4H), 1.85–2.03 (m, 2H), 2.18–2.26 (m, 2H), 3.28–3.31 (m, 1H), 3.63 (qd, *J* = 10.4, 4.4 Hz, 2H), 5.06 (d, *J* = 12.3 Hz, 1H), 5.17 (d, *J* = 2.5 Hz, 1H), 5.32 (d, *J* = 12.3 Hz, 1H), 6.70 (s, 1H), 7.25–7.38 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$+CCl_4): δ −5.5, −5.4, 18.1, 21.7, 23.4, 24.4, 25.7 (3C), 33.8, 56.3, 57.8, 65.2, 67.4, 128.1, 128.27 (2C), 128.34 (2C), 128.8, 131.8, 135.6, 150.9, 155.9; HRMS ESI $[M+Na]^+$ calcd for $C_{24}H_{35}O_4N_2ClNaSi$ 501.1947, found 501.1947.

4.10. (4*R*,5*S*)-1,3-Dibenzyl-4-(((*tert*-butyldimethylsilyl)oxy) methyl)-5-(2-chlorocyclohex-1-en-1-yl)imidazolidin-2-one 15

To a solution of 60% NaH (137 mg, 5.72 mmol, washed with dry petroleum ether by 2–3 times) in dry THF (10 mL) was added TBS ether **14** (1.1 g, 2.29 mmol) in anhydrous THF (5 mL) at 0 °C, stirred for 10 min. Benzyl bromide (0.72 mL, 5.72 mmol) was then added dropwise and the reaction was stirred for 3 h at room temperature. Upon completion of the reaction, it was quenched by the addition of satd. NH_4Cl solution and extracted with EtOAc (2 × 15 mL), washed with water then brine. The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified on flash chromatography using silica gel (10% EtOAc/pet ether) to afford benzyl protected cyclic urea **15** (1.14 g, 95%) as%) as a white solid. Melting point 87–89 °C. R_f (20% EtOAc/pet ether) 0.6; $[\alpha]_D^{25} = -33.1$ (*c* 2.9, $CHCl_3$); IR ($CHCl_3$): 2930, 2857, 1698, 1448, 1252, 1119 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$+CCl_4) δ −0.04 (s, 3H), -0.02 (s, 3H), 0.83 (s, 9H), 1.08–1.65 (m, 6H), 2.18–2.24 (m, 2H), 3.09 (dt, *J* = 6.1, 3.9 Hz, 1H), 3.40–3.67 (m, 2H), 4.00 (d, *J* = 12.3 Hz, 1H), 4.08 (d, *J* = 12.3 Hz, 1H), 4.52 (d, *J* = 15.0 Hz, 1H), 4.56–4.59 (m, 1H), 4.93 (d, *J* = 15.0 Hz, 1H), 7.24–7.32 (m, 10H). ^{13}C NMR (125 MHz, $CDCl_3$+CCl_4) δ −5.6, −5.5, 18.3, 21.7 (2C), 23.6, 25.9 (3C), 34.3, 46.2, 46.9, 56.6, 57.8, 62.6, 127.3, 127.4, 128.3 (2C), 128.4 (2C), 128.5 (2C), 128.8 (2C), 130.2, 131.1, 137.4, 137.4, 160.3; HRMS ESI $[M+Na]^+$ calcd for $C_{30}H_{41}O_2N_2ClNaSi$ 547.2518, found 547.2523.

4.11. Methyl 6-((4*R*,5*R*)-1,3-dibenzyl-5-(((*tert*-butyldimethyl silyl)oxy)methyl)-2-oxoimidazolidin-4-yl)-6-oxohexanoa- te 4

To a solution of benzyl protected cyclic urea **15** (1.1 g, 2.10 mmol) and sodium hydrogen carbonate (352 mg, 4.20 mmol) in dichloromethane (20 mL) and methanol (4 mL) at −78 °C, ozone was bubbled. The ozone addition was stopped when the solution turned blue (35 min) and dimethyl sulfide (1 mL, excess) was added at the same temperature. The solution was then allowed to warm to room temperature. All of the solvent was removed from the reaction mixture under reduced pressure, washed with water, and extracted with EtOAc (2 × 20 mL). The combined organic layer was dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified on flash chromatography using silica gel (20% EtOAc/pet ether) to afford methyl ester **4** (1.07 g, 92%) as a white solid. Melting point 62–64 °C. R_f (30% EtOAc/pet ether) 0.5; $[\alpha]_D^{25} = -12.2$ (*c* 2.0, $CHCl_3$); IR ($CHCl_3$): 2924, 1733, 1706, 1690, 1463, 1252 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$+CCl_4) δ −0.06 (s, 3H), -0.05 (s, 3H), 0.81 (s, 9H), 1.32–1.39 (m, 4H), 1.98–2.08 (m, 1H), 2.11–2.23 (m, 3H), 3.16 (q, *J* = 4.3 Hz, 1H), 3.39–3.55 (m, 2H), 3.66 (s, 3H), 3.70 (d, *J* = 4.3 Hz, 1H), 4.02–4.06 (m, 2H), 4.79–4.94 (m, 2H), 7.19–7.33 (m, 10H); ^{13}C NMR (100 MHz, $CDCl_3$+CCl_4) δ −5.6, -5.5, 22.5, 24.2, 25.9 (3 C), 29.8, 33.7, 37.4, 46.3, 47.2, 51.5, 56.4, 62.7, 63.5, 127.69, 127.75, 128.1 (2 C), 128.7 (2 C), 128.7 (2 C), 128.8 (2 C), 136.5, 137.0, 159.6, 173.4, 207.4; HRMS ESI $[M+Na]^+$ calcd for $C_{31}H_{44}O_5N_2NaSi$ 575.2912, found 575.2915.

4.12. Methyl 6-((4*R*,5*R*)-1,3-dibenzyl-5-(hydroxymethyl)-2-oxo imidazolidin-4-yl)-6-oxohexanoate 16

To a solution of ester **4** (1 g, 1.81 mmol) in MeOH (10 mL) was added camphorsulfonic acid (42 mg, 0.18 mmol) at 0 °C. The reaction was then allowed to stir at room temperature for 30 h. After completion of the reaction (as monitored by TLC), the reaction mixture was concentrated under reduced pressure. An aq. solution of $NaHCO_3$ was then added to the semisolid mass and extracted with EtOAc (2 × 20 mL). The combined organic layer was dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified on flash chromatography using silica gel (60% EtOAc/pet ether) to afford alcohol **16** (713 mg, 90%) as a white solid. Melting point 84–86 °C. R_f (60% EtOAc/pet ether) 0.3; $[\alpha]_D^{25} = -11.1$ (*c* 2.0, $CHCl_3$); IR ($CHCl_3$): 3409 (broad), 2928, 1726, 1682, 1451, 1238 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$+CCl_4) δ 1.36 (br s, 4H), 2.10–2.25 (m, 4H), 2.76 (br s, 1H), 3.20 (br s, 1H), 3.49 (d, *J* = 11.6 Hz, 1H), 3.62 (br s, 1H), 3.67 (s, 3H), 3.86 (s, 1H), 4.12–4.15 (m, 2H), 4.75–4.89 (m, 2H), 7.19–7.40 (m, 10H); ^{13}C NMR (125 MHz, $CDCl_3$+CCl_4) δ 22.4, 24.1, 33.6, 37.7, 46.2, 47.4, 51.5, 56.7, 61.5, 63.5, 127.78, 127.8, 128.0 (2 C), 128.5 (2 C), 128.8 (2 C), 128.8 (2 C), 136.2, 136.8, 160.0, 173.5, 207.6; HRMS ESI $[M+Na]^+$ calcd for $C_{25}H_{30}O_5N_2Na$ 461.2047, found 461.2045.

4.13. Methyl 6-((4*R*,5*R*)-5-((acetylthio)methyl)-1,3-dibenzyl-2-oxoimidazolidin-4-yl)-6-oxohexanoate 3

To a stirred solution of alcohol **16** (630 mg, 1.44 mmol) in dry DCM (10 mL) was added Et_3N (0.3 mL, 2.16 mmol) at 0 °C, followed by the addition of tosyl chloride (328 mg, 1.73 mmol) and DMAP (cat.). The reaction mixture was stirred for 24 h under a nitrogen atmosphere; after completion of the reaction (monitored by TLC), the reaction mixture was washed with a saturated solution of $NaHCO_3$ (10 mL), water (10 mL), and extracted with DCM (2 × 20 mL). The combined organic layer was dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to afford an *O*-tosyl compound, which was used as such for the next transformation.

To a solution of crude *O*-tosyl compound in anhydrous DMF (8 mL) and anhydrous THF (12 mL) was added sodium thioacetate (208 mg, 1.83 mmol) and the reaction mixture was stirred at 80 °C for 2 h under a nitrogen atmosphere. After completion of the reaction (as monitored by TLC), the reaction mixture was cooled to room temperature, diluted with water (50 mL), and extracted with EtOAc (3 × 20 mL). The combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography using silica gel (20% EtOAc/pet ether) to afford thioacetate **3** (502 mg, 83%) as a yellow liquid. R_f (20% EtOAc/pet ether) 0.4; $[\alpha]_D^{25} = +40.0$ (*c* 1.0, $CHCl_3$); IR ($CHCl_3$): 2923, 2851, 1728, 1710, 1695, 1451, 1215 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$+-CCl_4): δ 1.31–1.42 (m, 4H), 1.99–2.09 (m, 1H), 2.10–2.21 (m, 3H), 2.24 (s, 3H), 2.85 (dd, *J* = 14.2, 6.3 Hz, 1H), 3.15 (dd, *J* = 14.2, 2.7 Hz, 1H), 3.30–3.33 (m, 1H), 3.47 (d, *J* = 4.6 Hz, 1H), 3.65 (s, 3H), 3.95 (d, *J* = 15.1 Hz, 1H), 4.05 (d, *J* = 15.1 Hz, 1H), 4.87–4.90 (m, 2H), 7.21–7.41 (m, 10H); ^{13}C NMR (125 MHz, $CDCl_3$+CCl_4): δ 22.4, 24.1, 30.5, 31.4, 33.6, 37.8, 45.9, 47.0, 51.5, 54.2, 64.8, 127.82, 127.84, 128.3 (2 C), 128.72 (2 C), 128.76 (2 C), 128.8 (2

C), 136.2, 136.5, 159.0, 173.4, 194.2, 206.6; HRMS ESI $[M+Na]^+$ calcd for $C_{27}H_{32}O_5N_2NaS$ 519.1924, found 519.1918.

4.14. Methyl 6-((4*R*,5*R*)-1,3-dibenzyl-5-(mercaptomethyl)-2-oxoimidazolidin-4-yl)-6-oxohexanoate 17

A suspension of **3** (300 mg, 2.5 mM) in a phosphate buffer (pH 6.8, 50 mL) was purged with a stream of nitrogen for 5 min. Next, the lipase (150 mg) from *Candida rugosa* (706 units/ mg) was added and the contents were stirred vigorously. After 2 h, the reaction mixture was extracted with DCM (3 × 20 mL). The organic extracts were washed with brine, dried (Na_2SO_4), and then evaporated to give thiol **17**. The purification of thiol was effected by flash chromatography using silica gel (20% EtOAc/pet ether) to afford thiol **17** (219 mg, 80%) as a yellow liquid. R_f (20% EtOAc/pet ether) 0.4; $[\alpha]_D^{25} = +17.5$ (*c* 2.6, $CHCl_3$); IR ($CHCl_3$): 3016, 2923, 2851, 1725, 1695, 1451, 1215 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$+CCl_4): δ 1.11 (dd, *J* = 9.2, 7.8 Hz, 1H), 1.27–1.44 (m, 4H), 2.01–2.28 (m, 4H), 2.47–2.71 (m, 2H), 3.21–3.38 (m, 1H), 3.65 (s, 3H), 3.77 (d, *J* = 4.5 Hz, 1H), 4.02 (d, *J* = 15.2 Hz, 1H), 4.08 (d, *J* = 14.8 Hz, 1H), 4.85 (d, *J* = 14.8 Hz, 1H), 4.89 (d, *J* = 15.2 Hz, 1H), 7.19–7.36 (m, 10H); ^{13}C NMR (50 MHz, $CDCl_3$+CCl_4): δ 22.3, 24.0, 26.8, 33.5, 37.7, 45.7, 47.3, 51.4, 56.2, 64.5, 127.7 (2 C), 127.9 (2 C), 128.0, 128.4, 128.6 (2 C), 128.7 (2 C), 135.9, 136.3, 159.4, 173.4, 207.4; HRMS ESI $[M+H]^+$ calcd for $C_{25}H_{31}O_4N_2S$ 455.1999, found 455.1993.

4.15. (*Z*)-Methyl 5-((3a*S*,6a*R*)-1,3-dibenzyl-2-oxotetrahydro-1*H*-thieno[3,4-*d*]imidazol-4(2*H*)-ylidene)pentanoate 2

Thiol **17** (200 mg, 0.44 mmol) was dissolved in 5 mL of toluene, after which DBU (0.03 mmol) was slowly added dropwise at room temperature under a nitrogen atmosphere with continuous stirring. After the complete addition, the reaction mixture was heated at 100 °C for 3 h. After completion of the reaction (as monitored by TLC), toluene was removed under reduced pressure, diluted with EtOAc (10 mL), and washed with water (5 mL). The organic layer was separated and washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure after which it was subjected to elimination.

The crude hydroxyl compound (200 mg, 0.44 mmol) was dissolved in toluene (5 mL) and *p*TSA (0.025 mmol) was added at room temperature. The reaction mixture was then stirred continuously under a nitrogen atmosphere. The progress of the reaction was monitored by TLC, which indicated that no unreacted starting material remained after 4 h. Toluene was then removed under reduced pressure, after which was added EtOAc and neutralized with sodium bicarbonate solution and washed with water (5 mL). The organic layer was separated and washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. Purification was effected by flash chromatography using silica gel (20% EtOAc/pet ether) to afford olefin **2** (157 mg, 82%) as a yellow liquid. R_f (30% EtOAc/pet ether) 0.4; $[\alpha]_D^{25} = +192$ (*c* 1, $CHCl_3$) (lit. $[\alpha]_D^{25} = +194$ (*c* 1, $CHCl_3$)[8b]; IR ($CHCl_3$): 3032, 2928, 1743, 1634, 1440 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$+CCl_4) δ 1.65–1.75 (m, 2H), 2.03–2.11 (m, 2H), 2.27 (t, *J* = 7.5 Hz, 2H), 2.93–2.97 (m, 2H), 3.66 (s, 3H), 4.01 (d, *J* = 15.5 Hz, 1H), 4.10 (ddd, *J* = 9.0, 7.5, 4.0 Hz, 1H), 4.20 (d, *J* = 15.5 Hz, 1H), 4.73 (d, *J* = 10.1 Hz, 1H), 4.80 (d, *J* = 14.5 Hz, 1H), 4.95 (d, *J* = 15.6 Hz, 1H), 5.41 (t, *J* = 7.0 Hz, 1H), 7.29–7.37 (m, 10H); HRMS ESI $[M+Na]^+$ calcd for $C_{25}H_{28}O_3N_2NaS$ 459.1713, found 459.1707.

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