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The first simple and efficient synthesis of the unusual dipeptide part of Phomopsin A☆

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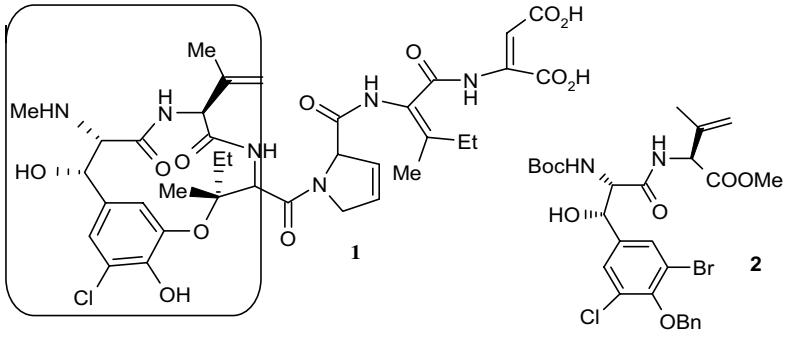
Abstract—A practical high yielding synthesis of the key halogenated dipeptide part of Phomopsin A **2** is reported. The key steps are a selective Heck coupling, a Sharpless asymmetric dihydroxylation in PEG and a benzoyl isocyanate mediated synthesis of dehydrovaline.

1. Introduction

The synthesis of unnatural amino acids especially those that are part structures of bioactive molecules, continues to attract the attention of synthetic organic chemists. Phomopsin A **1**[1] is one such 13-membered macrocycle with six amino acid residues, which shows cytotoxic activity by interfering with microtubule function through binding to tubulin. This natural product is the main cytotoxin isolated from cultures of *Phomospsis leptostromiformis*. Biological studies[2] have shown that this natural product causes similar mycotoxicosis and strongly inhibits polymerizatation of brain tubulin, similar to the activity of spindle poisons such as colchicine, podophyllotoxin, ustiloxin[3] and maytansinoids.[4] Phomopsin A consists of the unusual amino acid moieties, 2-amino-3-methylbut-3-enoic acid [(*S*)-3,4-didehydrovaline, H-L-3-ΔVal-OH], (2*S*,3*S*)-hydroxy isoleucine, (2*S*,3*S*)-3-hydroxy-2-(*N*-methyl)-tyrosine, (*E*)-2,3-didehydroaspartic acid, (*E*)-2,3-didehydroisoleucine (ΔIle) and 3,4-didehydroproline (ΔPro).

The presence of the 'unusual amino acids' and its novel biological properties,[5] and relatively scarce availability have prompted researchers to undertake its total synthesis. Surprisingly, no total synthesis of **1** has been achieved to date, although the synthesis of unusual amino acid parts[6] has been described. The most recent synthesis of the β-hydroxy phenyl alanine portion was achieved by Joullie et al.,[7] involving a Sharpless asymmetric amino hydroxylation strategy which lacks regiocontrol during the amino hydroxylation while the aryl



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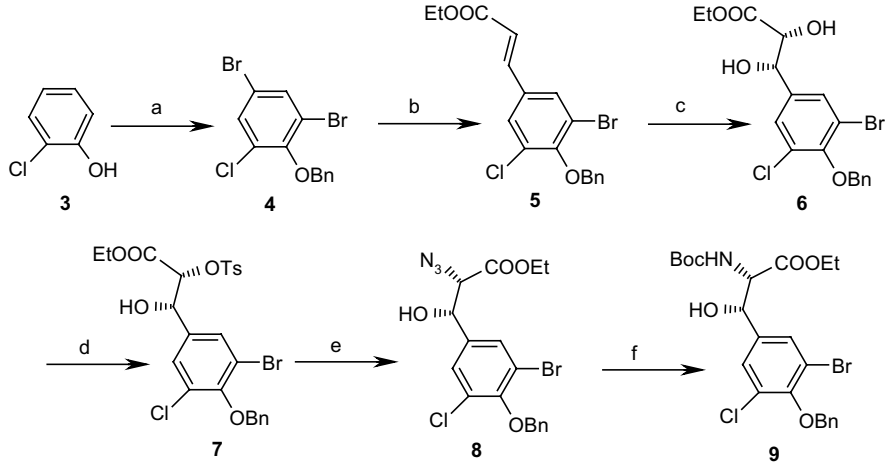
group is also not fully functionalized. The synthesis of other unusual amino acid dehydrovaline[8] is reasonably well addressed albeit in a greater number of steps.

Our studies have involved the total synthesis of bioactive natural products[9] especially compounds which have an unusual amino acid part structure. Herein, we report a new and flexible strategy for the unusual dipeptide part of Phomopsin A **2**.

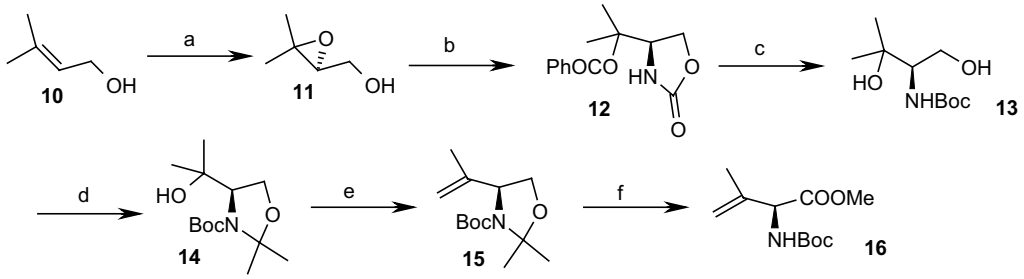
2. Results and discussion

The retrosynthetic analysis of β-hydroxy phenyl alanine derivative revealed that cinnamate ester **5** would be an ideal precursor, which in turn was realized from *ortho*-chlorophenol **3** via dibromination and selective Heck coupling with ethylacrylate. Accordingly, the commercially available *ortho*-chlorophenol **3** was treated with *N*-bromosuccinimide[10] in THF at 0 °C to yield the 2,4-dibromo-6-chloro phenol in 95% yield, which was subjected to benzylation (BnBr, K_2CO_3, acetone, reflux). The resultant benzyl ether **4** was subjected to a selective Heck reaction with ethyl acrylate in the presence of $Pd(OAc)_2$, PPh_3 and Et_3N at 100 °C to give ethyl cinnamate derivative **5** in over 90% yield. We anticipated that the bromo group C-4 of the benzene ring was the least hindered and would provide the required selectivity, which turned out to be correct. To confirm the structure of **5**, the other possible regioisomer was prepared by a slightly circuitous route[11]. The critical step of introducing chirality was achieved by using a modified Sharpless asymmetric dihydroxylation condition[12] [$(DHQ)_2PHAL$, OSO_4, NMO, PEG (400), 3 h] to realize diol **6** in 95% yield and over 98% ee (measured by chiral HPLC using chiralcel 10% isopropanol in hexane). Incidentally this substrate gave poor results under the conventional protocol conditions. The selective amination of the α-hydroxy group of **6** was effected in three steps via tosylation[13] (TsCl, Et_3N), azidation (NaN_3, DMF, 60 °C) and reductive protection carried out [TPP, EtOH, followed by exposure to $(Boc)_2O$] (Scheme 1, 42% overall yield).

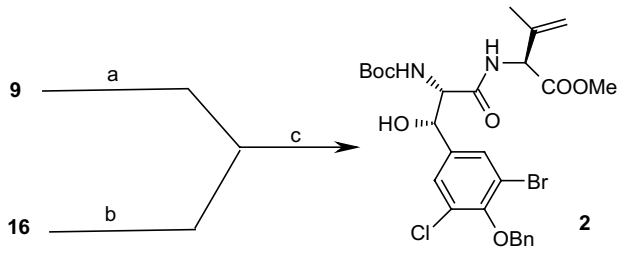
The required dehydrovaline methyl ester **16** was synthesized from prenol **10** via Sharpless asymmetric epoxidation[14] [(+)-DIPT, Ti(O-*i*-Pr)$_4$, cumene hydroperoxide] to obtain epoxide **11** in 95% ee and 90% yield. This, upon treatment with benzoyl isocyanate[15] in THF, $K^{+t}BuO^-$, furnished oxazolidinone **12**. Oxazolidinone **12** in the presence of 2 M KOH at 80 °C followed by protection



Scheme 1. Reagents and conditions: (a) (i) NBS, THF, 0 °C, 0.5 h; (ii) BnBr, K_2CO_3, acetone, reflux, 92.2% (two steps); (b) CH_2=CHCOOEt, $Pd(OAc)_2$, TPP, Et_3N, 100 °C, 90%; (c) $(DHQ)_2PHAL$, OsO_4, NMO·H_2O, PEG (400), 3 h, 95%; (d) TsCl, Et_3N, CH_2Cl_2, 0 °C, 12 h, 81%; (e) NaN_3, DMF, 60 °C, 72%; (f) TPP, EtOH, $(Boc)_2O$, 91%.



Scheme 2. Reagents and conditions: (a) (+)DIPT, Ti(O-*i*-Pr)$_4$, cumene hydroperoxide, 4 Å molecular sieves, CH_2Cl_2, −20 °C, 90%; (b) PhCONCO, THF, 0 °C, 0.5 h then $K^{+t}BuO^-$, 0 °C, 1 h, 88%; (c) 2 M KOH(aq), 80 °C, $(Boc)_2O$, THF, 93%; (d) 2,2-DMP, Cat PTSA, CH_2Cl_2, 0 °C, 86%; (e) MsCl, Et_3N, CH_2Cl_2, 76%; (f) (i) Jones' oxidation, (ii) CH_2N_2, dry other, 70% (two steps).



Scheme 3. Reagents and conditions: (a) $LiOH{\cdot}H_2O$, $THF–H_2O$; (b) 60% TFA, CH_2Cl_2; (c) EDC, HOBt, CH_2Cl_2, 0 °C to rt, over 5 h, 83%.

with $(Boc)_2O$ in THF yielded the 1° and 3° diol **13**. Acetonation (DMP, Cat PTSA, CH_2Cl_2) and elimination of the 3° alcohol (MsCl, Et_3N, CH_2Cl_2) were rather straightforward. The Jones' oxidation concomitantly cleaved the isopropylidene group and also oxidized the 1° alcohol group to the acid, which was characterized as its methyl ester **16** (Scheme 2, 33% overall yield).

After carrying out ester **9** hydrolysis and Boc deprotection of compound **16** to afford the corresponding free amine, both the acid and amine were coupled using EDC, HOBt to realize the dipeptide part of Phomopsin A **2** in 83% yield (Scheme 3).

3. Conclusion

In conclusion, we have developed a novel procedure for the synthesis of the fully functionalized dipeptide part of Phomopsin A in high yields. Incidentally, this is the first synthesis of the halogenated dipeptide portion of Phomopsin A. The construction of a 13-membered macrocycle with various unnatural pharmacophores towards understanding SAR is currently under progress.

4. Experimental

4.1. General

All solvents and reagents were purified by standard techniques. Crude products were purified by column chromatography on silica gel of 60–120 mesh. IR spectra were recorded on a Perkin–Elmer 683 spectrometer. Optical rotations were obtained on Jasco Dip 360 digital polarimeter. Melting points (uncorrected) were obtained using a Buchi 535 melting point apparatus. ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ solution on a Varian Gemini 200, Bruker Avance 300 or Varian Unity 400 NMR spectrometers. Chemical shifts were reported in ppm with respect to internal TMS. Coupling constants (J) are quoted in hertz. Mass spectra were obtained on a Agilent Technologies LC/MSD Trap SL.

4.1.1. 2-(Benzyloxy)-1,5-dibromo-3-chlorobenzene 4. To a stirred solution of 2-chlorophenol **3** (5 g, 40 mmol) in THF (50 mL) was added a solution of NBS (15.2 g, 85 mmol) in THF (30 mL) over 30 min at 0 °C. When the addition was complete, the reaction mixture was diluted with water and extracted with ethyl acetate (2×100 mL). The combined organic layers were washed with water and aqueous $Na_2S_2O_3$, followed by brine and dried over anhydrous Na_2SO_4. The solvent was removed in vacuo to afford the dibromo compound as pale yellow solid (10.51 g).

To a stirred solution of the above dibromo phenol (10.51 g, 36 mmol) in dry acetone (100 mL) was added K_2CO_3 (10.1 g, 73 mmol) followed by benzyl bromide (6.9 g, 40 mmol). The reaction mixture was refluxed for 3 h. After completion of the reaction, it was filtered and washed with acetone. The filtrate was concentrated under vacuo and purified by column chromatography to afford compound **4** (13.4 g, 92.2%) as a white solid: mp: 52–53 °C; IR (KBr): 1455, 1360, 1250, 1142 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.62 (d, $J = 2.2$ Hz, 1H), 7.51 (d, $J = 2.3$ Hz, 3H), 7.38–7.26 (m, 3H), 4.98 (s, 2H); MS (ESI): m/z 377 (M^++1), 375.

4.1.2. Ethyl (2*E*)-3-[4-(benzyloxy)-3-bromo-5-chlorophenyl]acrylate 5. A mixture of compound **4** (2 g, 5.3 mmol), ethyl acrylate (0.8 g, 7.9 mmol), TPP (0.056 g, 0.2 mmol), palladium acetate (0.024 g, 0.1 mmol) and triethyl amine (0.8 g, 7.9 mmol) in DMF (20 mL) was heated at 100 °C for 12 h under nitrogen atmosphere. The reaction mixture was diluted with ethyl acetate (100 mL), washed with water, brine, dried over anhydrous Na_2SO_4 and concentrated in vacuo. The crude residue was purified by column chromatography to afford the unsaturated ester **5** (1.9 g, 90%) as a white solid: mp: 78–80 °C; IR (KBr): 1710, 1645, 1120 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.64 (d, $J = 2.26$ Hz, 1H), 7.53–7.51 (m, 3H), 7.46 (d, $J = 15.1$ Hz, 1H), 7.44–7.30 (m, 3H), 6.36 (d, $J = 15.8$ Hz), 5.04 (s, 2H), 4.2 (q, $J = 7.5$ Hz, 2H), 1.34 (t, $J = 7.5$ Hz); MS (ESI): m/z 397 (M^++1), 395, 351, 349 and 189.

4.1.3. Ethyl (2*R*,3*S*)-3-[4-(benzyloxy)-3-bromo-5-chlorophenyl]-2,3-dihydroxypropanoate 6. To the unsaturated ester **5** (2 g, 5 mmol) in polyethylene glycol (400 MW, 5 g) was added OsO_4 (6.5 mg, 0.025 mmol), $NMO{\cdot}H_2O$ (0.89 g, 6.6 mmol) and $(DHQ)_2PHAL$ (79 mg, 0.1 mmol) under an inert atmosphere and stirred at room temperature for 3 h. The reaction mixture was diluted with the ether (20 mL) and stirred for 5 min. The ether layer was decanted and the procedure repeated (4×20 mL). The combined ether layers were washed with water and brine and dried over Na_2SO_4. The solvent was removed and the crude product purified by column chromatography to afford diol **6** (2.0 g, 95%) as a white solid. Diol **6** was formed in over 98% ee, measured by chiral HPLC using chiralcel 10% isopropanol in hexane: mp: 96 °C; $[\alpha]_D^{25} = +9.8$ (c 1.0, MeOH); IR (KBr): 3411, 2929, 1718, 1462, 1259 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.54–7.50 (m, 3H), 7.41–7.29 (m, 4H), 5.0 (s, 2H), 4.84 (dd, $J = 3.0$, 7.5 Hz, 1H), 4.34–4.23 (m, 3H), 3.13 (d, $J = 7.5$ Hz, OH), 2.74 (d, $J = 7.5$ Hz, OH), 1.32 (t, $J = 7.5$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 172.1, 151.2, 138.3, 135.9, 129.8, 129.2, 128.4 (2C), 128.3 (3C), 127.6, 118.6, 74.7, 74.2, 72.9, 62.3, 13.9; MS (ESI): m/z 453 (M^++23), 451 and 269.

4.1.4. Ethyl (2*R*,3*S*)-3-[4-(benzyloxy)-3-bromo-5-chlorophenyl]-3-hydroxy-2-{[(4-methylphenyl)sulfonyl]oxy}propanoate 7. To a stirred solution of diol ester **6** (2.15 g, 5 mmol) in CH_2Cl_2 (25 mL) at 0 °C under nitrogen was added triethyl amine (1.3 g, 12.5 mmol), followed by *p*-toluene sulfonyl chloride (1.15 g, 6 mmol). After stirring for 12 h at room temperature, the reaction mixture was diluted with water and extracted with CH_2Cl_2 (30 mL). The combined organic extracts were washed with water and brine and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure and the crude product purified by column chromatography to give the tosylated product **7** (2.36 g, 81%) as a viscous liquid: $[\alpha]_D^{25} = +36.8$ (*c* 2.5, MeOH); IR ($CHCl_3$): 3516, 1748, 1372, 1182, 1032 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.52–7.47 (m, 4H), 7.40–7.33 (m, 3H), 7.27 (d, $J = 2.3$ Hz, 1H), 7.20–7.16 (m, 3H), 5.04 (d, $J = 3.8$ Hz, 1H), 4.94 (s, 2H), 4.72 (d, $J = 3.8$ Hz, 1H), 4.25 (q, $J = 7.3$ Hz, 2H), 2.92 (d, $J = 6.8$ Hz, OH), 2.39 (s, 3H), 1.28 (t, $J = 7.3$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 166.7, 151.7, 145.4, 136.1, 132.2, 129.6 (3C), 129.3, 128.4 (3C), 128.3 (3C), 127.5 (3C), 118.8, 80.6, 74.7, 72.0, 62.4, 21.6, 13.8; MS (ESI): *m*/*z* 607 (M^++23), 605.

4.1.5. Ethyl (2*S*,3*S*)-2-azido-3-[4-(benzyloxy)-3-bromo-5-chlorophenyl]-3-hydroxypropanoate 8. To a stirred solution of tosylate **7** (1 g, 1.72 mmol) in DMF (10 mL) was added NaN_3 (0.9 g, 13.8 mmol) as a solid in one portion. The temperature was raised to 65 °C for 10 h, then cooled to room temperature and the reaction mixture diluted with water and extracted with ethyl acetate (2×20 mL). The combined organic layers were washed with water and brine and dried over anhydrous Na_2SO_4. The solvent was removed and the crude product purified by column chromatography to yield azide **8** (0.56 g, 72%) as a highly viscous liquid: $[\alpha]_D^{25} = +65.2$ (*c* 1.0, MeOH); IR ($CHCl_3$): 3486, 2115, 1737, 1259 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.52 (d, $J = 7.4$ Hz, 2H), 7.49 (d, $J = 1.6$ Hz, 1H), 7.40–7.32 (m, 4H), 5.07 (t, $J = 4.1$ Hz, 1H), 5.02 (s, 2H), 4.27 (q, $J = 7.5$ Hz, 2H), 3.92 (d, $J = 4.1$ Hz, 1H), 2.92 (d, $J = 4.2$ Hz, OH), 1.31 (t, $J = 7.5$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 168.1, 151.7, 137.6, 136.0, 129.8, 129.5, 128.5 (2C), 128.4 (3C), 127.6, 118.9, 74.9, 72.8, 67.1, 62.4, 14.0; MS (ESI): *m*/*z* 477 (M^++23), 475, 434, 282 and 191.

4.1.6. Ethyl (2*S*,3*S*)-3-[4-(benzyloxy)-3-bromo-5-chlorophenyl]-2-[(*tert*-butoxycarbonyl)amino]-3-hydroxypropanoate 9. To a stirred solution of azide compound **8** (0.6 g, 1.32 mmol) in ethanol (10 mL) was added TPP (0.51 g, 1.98 mmol) as a solid in one portion at room temperature. After stirring for 3 h, the azide was reduced into the corresponding amine. To this reaction mixture was added $(Boc)_2O$ (0.34 g, 1.58 mmol) and stirred for 5 h. Ethanol was removed and extracted with ethyl acetate (2×20 mL). The combined organic extracts were washed with water and brine and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure and the crude residue purified by column chromatography to afford compound **9** (0.63 g, 91%) as a viscous liquid: $[\alpha]_D^{25} = +2.5$ (*c* 1.0, MeOH); IR ($CHCl_3$): 3424, 2979, 1693, 1371, 1256, 1163 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.51–7.48 (m, 3H), 7.37–7.31 (m, 4H), 5.21 (d, $J = 9.5$ Hz, BocNH), 5.16 (t, $J = 3.8$ Hz, 1H), 5.00–4.94 (m, 2H), 4.42 (dd, $J = 9.5$, 3.8 Hz, 1H), 4.22 (q, $J = 7.2$ Hz, 2H), 3.03 (d, $J = 3.8$ Hz, OH), 1.37 (s, 9H), 1.29 (t, $J = 7.2$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.2, 155.6, 151.2, 138.5, 136.0, 129.6, 129.1, 128.4 (5C), 127.5, 118.5, 80.2, 74.8, 72.4, 61.8, 59.1, 28.0 (3C), 14.0; MS (ESI): *m*/*z* 552 (M^++23), 550, 455 and 412.

4.1.7. [(2*S*)-3,3-Dimethyloxiran-2-yl]methanol 11. In a 250 mL, round-bottomed two neck flask were flame-dried under vacuum 4 g of powdered 4 Å molecular sieves. Dry CH_2Cl_2 (100 mL), 3-methyl-2-butene-1-ol **10** (10 mL, 0.1 mol) and (+)-diisopropyl tartrate (1.6 mL, 7.35 mmol) were added and the reaction mixture cooled to −20 °C. After the introduction of Ti(O-*i*-Pr)$_4$ (1.5 mL, 4.9 mmol), the mixture was stirred for 30 min. Cumene hydroperoxide (80%, 31 mL, 0.162 mol) was then added over 2 h and the mixture stirred for an additional hour. Following the addition of citric acid monohydrate (1.14 g, 5.4 mmol) and diethyl ether (50 mL), the reaction mixture was warmed to room temperature and stirred overnight. Filtration through a pad of Celite and concentration in vacuo furnished an oil, which was purified by column chromatography to afford epoxide **11** (9.1 g, 90%) as colorless oil: $[\alpha]_D^{25} = -18.0$ (*c* 2.0, $CHCl_3$); IR (neat): 3430, 3000, 2970, 2930, 1382, 1227, 1126, 1032 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 3.93 (br s 1H), 3.83–3.75 (m, 1H), 3.68–3.59 (m, 1H), 2.97 (dd, $J = 4.2$, 6.4 Hz), 1.34 (s, 3H), 1.31 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 63.8, 60.9, 58.5, 24.4, 18.4; MS (ESI): *m*/*z* 125 (M^++23).

4.1.8. 1-Methyl-1-[(4*R*)-2-oxo-1,3-oxazolidin-4-yl]ethyl benzoate 12. To a stirred solution of epoxy alcohol **11** (1 g, 0.01 mol) in dry THF (10 mL) was added a solution of benzoyl isocyanate (1.45 g, 0.01 mol) in THF (10 mL) at 0 °C under a nitrogen atmosphere. After stirring for 0.5 h at 0 °C, the epoxy alcohol was converted into corresponding carbamate. To this reaction mixture at 0 °C was added $K^+{}^tBuO^-$ (2.2 g, 0.02 mol). After stirring for 1 h at room temperature, the reaction mixture was diluted with water and extracted with ethyl acetate (2×20 mL). The combined organic layers were washed with brine and dried over anhydrous Na_2SO_4. Concentration in vacuo and purification by column chromatography led to oxazolidinone **12** (2.15 g, 88%) as a viscous liquid: $[\alpha]_D^{25} = +12.3$ (*c* 1.0, MeOH); IR ($CHCl_3$): 2943, 1745, 1720, 1436, 1277, 1073 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.85 (d, $J = 7.4$ Hz, 2H), 7.69 (br s, NH), 7.48 (t, $J = 7.4$ Hz, 1H), 7.35 (d, $J = 7.4$ Hz, 2H), 4.48–4.39 (m, 2H), 4.06-4.03 (m, 1H), 1.56 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 165.3, 160.4, 133.0, 130.7, 129.44 (2C), 128.41 (2C), 82.0, 66.0, 60.3, 21.4 (2C); MS (ESI): *m*/*z* M^+ 250 (M^++1), 206, 189, 128 and 105.

4.1.9. *tert*-Butyl [(1*R*)-2-hydroxy-1-(hydroxymethyl)-2-methylpropyl]carbamate 13. Oxazolidinone **12** (1 g, 4 mmol) was taken in 2 M aqueous KOH (10 mL) and the temperature raised to 80 °C for 3 h the reaction mixture was cooled to room temperature and diluted with THF (20 mL). To this reaction mixture was added a

solution of $(Boc)_2O$ (1.0 g, 4.4 mmol) in THF (10 mL) at 0 °C, and stirred for 6 h at room temperature. The reaction mixture was diluted with water and extracted with ethyl acetate (2 × 30 mL). The combined organic layers were washed with water and brine and then dried over anhydrous Na_2SO_4. The solvent was removed and the residue was purified by column chromatography to afford 1° and 3° diol **13** (0.82 g, 93%) as a syrup: $[\alpha]_D^{25} = +2.7$ (*c* 1.0, MeOH); IR (neat): 3443, 2960, 2942, 1692, 1675, 1436 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 5.37 (d, *J* = 8.3 Hz, NH), 3.97 (dd, *J* = 3.0, 11.3 Hz, 1H), 3.75 (dd, *J* = 2.2, 10.5 Hz, 1H), 3.40 (d, *J* = 8.3 Hz, 1H), 2.93 (br s, OH), 1.45 (s, 9H), 1.34 (s, 3H), 1.22 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 156.4, 79.2, 73.6, 63.3, 57.9, 28.3 (3C), 27.5, 27.3; MS (ESI): *m*/*z* 242 (M^++23), 162 and 118.

4.1.10. *tert*-Butyl (4*R*)-4-(1-hydroxy-1-methylethyl)-2,2-dimethyl-1,3-oxazolidine-3-carboxylate 14. To a stirred solution of diol compound **13** (0.5 g, 2.3 mmol) in dry CH_2Cl_2 (15 mL) was added *p*-toluenesulfonic acid monohydrate (0.044 g, 0.23 mmol), 2,2-DMP (0.36 g, 3.4 mmol) at 0 °C and the reaction mixture stirred for 2 h at 0 °C. The reaction mixture was quenched with aqueous saturated $NaHCO_3$ solution and the organic layer washed with water and brine and dried over anhydrous Na_2SO_4. After concentration and purification by column chromatography 3° alcohol **14** (0.51 g, 86%) was obtained as a white solid: mp 36–37 °C; $[\alpha]_D^{25} = +22.9$ (*c* 1.0, MeOH); IR (KBr): 3412, 2970, 2925, 2878, 1696, 1670 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.13 (s, 3H), 1.16 (s, 3H), 1.50 (s, 12H), 1.57 (s, 3H), 3.76 (m, 1H), 3.97 (m, 2H), 5.1 (br s, OH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 155.5, 95.9, 81.1, 72.6, 66.2, 64.9, 28.1 (3C), 27.5, 27.1, 26.0, 24.4; MS (ESI): *m*/*z* 282 (M^++23), 213 and 182.

4.1.11. *tert*-Butyl (4*S*)-4-isopropenyl-2,2-dimethyl-1,3-oxazolidine-3-carboxylate 15. To a stirred solution of 3° alcohol compound **14** (0.98 g, 3.7 mmol) in CH_2Cl_2 (15 mL) was added methane sulfonyl chloride (1.4 mL, 18.3 mmol) and triethyl amine (5.1 mL, 36.6 mmol) at −10 °C. After stirring at room temperature for 1 h, the reaction mixture was poured into ether (50 mL) and water (30 mL). The organic layer was washed with aqueous 1 M 10% citric acid, aqueous saturated $NaHCO_3$ solution, brine and then dried over anhydrous Na_2SO_4. Concentration in vacuo gave a residue, which was purified by column chromatography to afford compound **15** (0.68 g, 76%) as a colorless syrup: $[\alpha]_D^{25} = +16.9$ (*c* 1.2, MeOH); IR ($CHCl_3$): 2982, 2928, 2875, 1703, 1663 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 4.83 (br s, 2H), 4.02 (dd, *J* = 7.2, 8.2 Hz, 1H), 3.70 (dd, *J* = 2.4, 8.8 Hz, 1H), 1.72 (s, 3H), 1.64 (s, 3H), 1.49 (s, 9H), 1.39 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 151.8, 144.1, 110.9, 79.6, 67.2, 62.1, 59.9, 27.9 (3C), 27.5, 26.9, 18.1; MS (ESI): *m*/*z* 242 (M^++1), 184, 140 and 102.

4.1.12. Methyl (2*S*)-2-[(*tert*-butoxycarbonyl)amino]-3-methylbut-3-enoate 16. To a solution of compound **15** (0.3 g, 1.2 mmol) in dry acetone (10 mL) at 0 °C, freshly prepared Jones' reagent (1 mL, 2.5 mmol) was added dropwise. After stirring for 12 h at room temperature, excess of Jones' reagent was quenched with isopropanol. Acetone was removed and extracted with ethyl acetate (2 × 10 mL). The combined organic extracts were washed with water and brine, dried over anhydrous Na_2SO_4 and concentrated to furnish the acid (0.24 g).

The above acid (0.24 g) was immediately dissolved in dry ether at 0 °C and treated with ethereal diazomethane. After 0.5 h, the ether was removed and the residue on purification by column chromatography afforded amino acid ester **16** (0.2 g, 70%) as a syrup: $[\alpha]_D^{25} = +37.5$ (*c* 1.0, MeOH); IR (neat): 3378, 2978, 1745, 1713 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 5.22 (br s, NH), 5.00 (d, *J* = 15.8 Hz, 2H), 4.68 (d, *J* = 7.5 Hz, 1H), 3.75 (s, 3H), 1.78 (s, 3H), 1.44 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.1, 154.7, 140.3, 114.6, 79.8, 58.8, 52.3, 28.1 (3C), 19.2; MS (ESI): *m*/*z* 252 (M^+ + 23), 195 and 151.

4.1.13. Methyl (2*S*)-2-{[(2*S*,3*S*)-3-[4-(benzyloxy)-3-bromo-5-chlorophenyl]-3-hydroxy-2-[(*tert*-butoxycarbonyl)amino]-propanoyl]amino}-3-methylbut-3-enoate 2. A mixture of ester **9** (0.15 g, 0.28 mmol) and $LiOH{\cdot}H_2O$ (36 mg, 0.86 mmol) in THF–H_2O (8:2, 5 mL) were stirred at room temperature for 2 h. The reaction mixture was acidified with aqueous sodium bisulfite and extracted with ethyl acetate. The organic layer was washed with water and brine, dried over anhydrous Na_2SO_4 and evaporated to furnish the acid (0.143 g), which was used further without any purification.

Compound **16** (70 mg, 0.31 mmol) was taken in 60% TFA in CH_2Cl_2 (2 mL) at 0 °C under an inert atmosphere. The reaction mixture was stirred for 1 h and concentrated under reduced pressure. The reaction mixture was basified by adding excess of Na_2CO_3 in CH_2Cl_2, the reaction mixture was filtered and the filtrate concentrated under reduced pressure to afford the amine (39 mg), which was used further without purification.

To a stirred solution of the above acid (0.143 g, 0.29 mmol), amine (39 mg, 0.29 mmol) and HOBt (40 mg, 0.29 mmol) in dry CH_2Cl_2 was added EDC (55 mg, 0.29 mmol) at 0 °C under an inert atmosphere and stirred for 1 h at 0 °C. The reaction mixture was warmed to room temperature and stirred for 4 h the reaction mixture was then diluted with water and extracted into CH_2Cl_2. The organic layer was washed with 5% aqueous citric acid, aqueous saturated $NaHCO_3$ solution, brine and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure and the crude product purified by column chromatography to afford dipeptide **2** (0.14 g, 83%) as a highly viscous liquid: $[\alpha]_D^{25} = +16.9$ (*c* 1.75, MeOH); IR ($CHCl_3$): 3419, 1654 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.54–7.52 (m, 3H), 7.39–7.30 (m, 4H and amideNH), 5.42 (d, *J* = 8.1 Hz, BocNH), 5.29 (s, 1H), 5.07 (s, 2H), 4.99 (s, 2H), 4.93 (d, *J* = 7.4 Hz, 1H), 4.41 (d, *J* = 8.1 Hz, 1H), 4.11 (d, *J* = 7.4 Hz, OH), 3.78 (s,3H), 1.81 (s, 3H), 1.39 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.8, 170.0, 156.0, 151.2, 139.1, 138.1, 136.2, 129.6, 129.2, 128.4 (5C), 127.4, 118.6, 115.9, 80.9, 74.7, 70.8, 59.3, 57.9, 52.7, 28.0 (3C), 19.6; MS (ESI): *m*/*z* 635 (M^++23), 633, 513 and 511.

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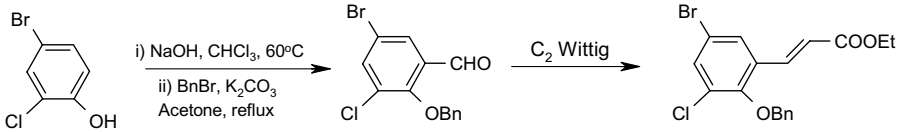
11. The other regioisomer was synthesized for reference following the scheme shown below.



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