Electronic Supplementary Material (ESI) for Organic & Biomolecular Chemistry.

SUPPORTING MATERIALS

Design Criteria For Minimalist Mimics Of Protein-protein Interface Segments

Jaru Taechalertpaisarn,[a] Rui-Liang Lyu,[a] Maritess Arancillo,[a] Chen-Ming Lin,[a] Zhengyang Jiang,[a] Lisa M. Perez,[b] Thomas R. Ioerger,[c] and Kevin Burgess[a]*

[a]Department of Chemistry and [b]Laboratory For Molecular Simulation, Texas A & M University, Box 30012, College Station, TX 77842-3012, USA. [c]Department of Computer Science, Texas A & M University, College Station, TX 77843-3112.

E-mail: burgess@tamu.edu

Contents

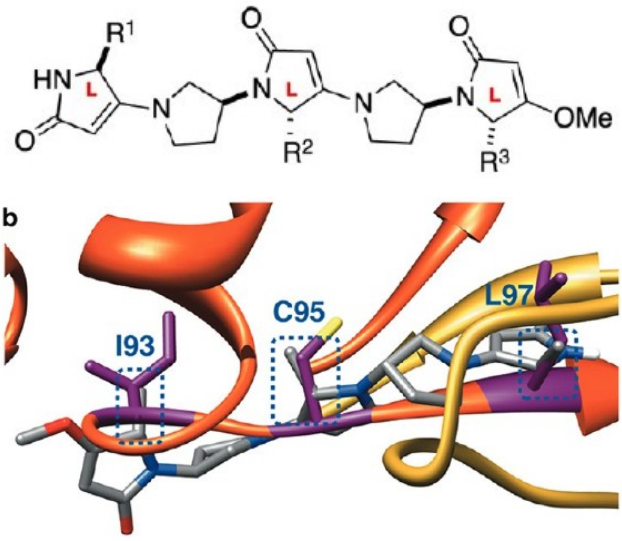
A. EKO Procedures **3**
B. Applications of EKO to Biological Targets **4**
Inhibition of HIV-1 protease dimer[3] 4
Modulation of antithrombin oligomerization[4] 4
Inhibition of PCSK9·LDLR interaction[5] 5
C. Synthesis Procedures **6**
Synthesis of Mimic 1 7
General Procedure for the Preparation of Dipeptide 9 8
General Procedure of Boc Deprotection 8
General Procedure for the Preparation of *C*-protected Hydantoin 16 8
General Procedure for the Preparation of Scaffold 17 8
Synthesis of Mimic 5 10
General Preparation of Ethyl-*N*-Boc-Dipeptide Thioester 18 11
General Preparation of *N*-Boc Oxazole 20 11
General Procedure for the Preparation of Scaffold 5 12
D. Characterization Data **13**
E. References **46**

A. EKO Procedures

The QMD was performed according to the procedure described before.[1, 2] After energy minimization in the QMD process, all conformers within 3.0 kcal/mol of the lowest energy conformer were clustered into families with similar RMSDs (< 0.5 Å) based on Cα – Cβ coordinates. The conformer having lowest energy in each family was selected as a representative. These representatives were systematically aligned on the Cα – Cβ coordinates of interface residues on > 240,000 protein-protein complexes recorded in the PDB, and the results were sorted based on RMSDs of Cα – Cβ coordinates.[1]

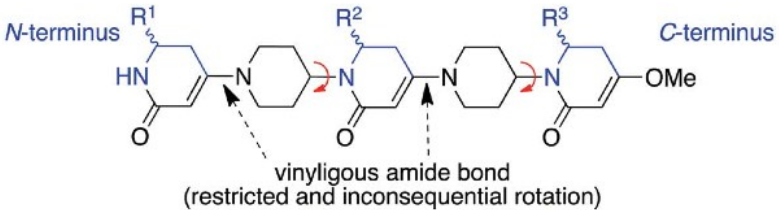
B. Applications of EKO to Biological Targets

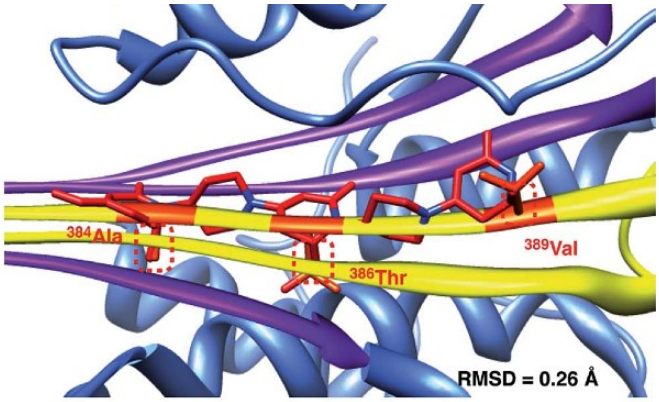
Inhibition of HIV-1 protease dimer[3]



HIV-1 protease is an enzyme involved in the synthesis of protein components of the HIV virion, which is essential to the life cycle of HIV. The mature form of HIV-1 protease is a homodimer. The active site lies on the interface of the two monomers, indicating that disruption of dimerization may lead to inhibition of its catalytic activity. Using EKO, we discovered our mimic shown above aligns on several locations on the dimer interface, with one example shown. Compound with corresponding side-chains were synthesized and assayed against HIV-1 protease, and achieved an IC_{50} of 3.7 μM.

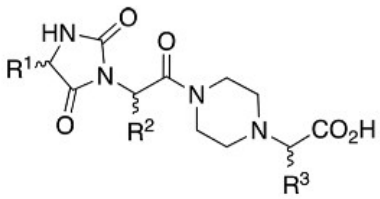
Modulation of antithrombin oligomerization[4]





α-antithrombin is a SERPIN that specifically inhibits thrombin. SERPINs are known to form homodimers and oligomers, which may lead to disease states known as serpinopathies. Mechanisms of SERPIN oligomerization is still much underexplored, thus any molecule that can modulate the oligomerization process may be valuable for understanding its mechanism. One putative model states that antithrombin oligomerization happens via the disruption of a metastable, self-folded monomer and a "domain swapping" process across multiple monomers. Thus, molecules that perturb the metastable antithrombin monomer and promote "domain swapping" may increase of level of its oligomerization. Using EKO, we discovered our oligopiperidine-piperidinone mimic shown above aligns on several locations in the self-folded monomer. Several candidate compounds based on this mimic were synthesized and assayed, and many showed the ability to disrupt monomer self-folding and significantly increase antithrombin oligomerization.

Inhibition of PCSK9·LDLR interaction[5]



LDLR is a cell surface receptor involved in the absorption of low-density lipoprotein (LDL) into hepatocytes. The PCSK9 protein downregulates LDLR, thereby increases blood LDL level, leading to hypercholesterolemia. Monoclonal antibodies that binds to PCSK9 have shown promising results in treating the said disease, but there has been no report of small molecules that directly inhibits the PCSK9·LDLR interaction. Using EKO, we discovered the hydantoin-piperazine mimic shown above overlays on several locations on the LDLR side of the PPI. Through extensive synthesis, assays, and structure-based modification, we arrived at the first small molecule inhibitor of PCSK9·LDLR interaction with an K_d of 24.8 μM.

C. Synthesis Procedures

All reactions were carried out under an inert atmosphere (nitrogen, or argon where stated) with dry solvents under anhydrous conditions. Glassware for anhydrous reactions was dried in an oven at 140ºC for minimum 6 h prior to use. Dry solvents were obtained by passing the previously degassed solvents through activated alumina columns. Reagents were purchased at a high commercial quality (typically 97 % or higher) and used without further purification, unless otherwise stated. High field NMR spectra were recorded at 400 MHz for ^{1}H, and 100 MHz for ^{13}C and were calibrated using residual non-deuterated solvent as an internal reference ($CDCl_3$: ^{1}H NMR = 7.24, ^{13}C NMR = 77.0). Flash chromatography was performed using silica gel (230-600 mesh). Analytical thin layer chromatography (TLC) was carried out on Merck silica gel plates with QF 254 indicator and visualized by UV, ceric ammonium molybdate, ninhydrin, *para*-methoxybenzaldehyde and/or potassium permanganate stains. The following abbreviations were used to explain the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, quint = quintet, dd = double doublet, dt = double triplet, dq = double quartet, m = multiplet, br = broad. Electrospray ionization mass spectrometry (ESI-MS) data were collected on triple-stage quadrupole instrument in a positive mode.

Synthesis of Mimic 1

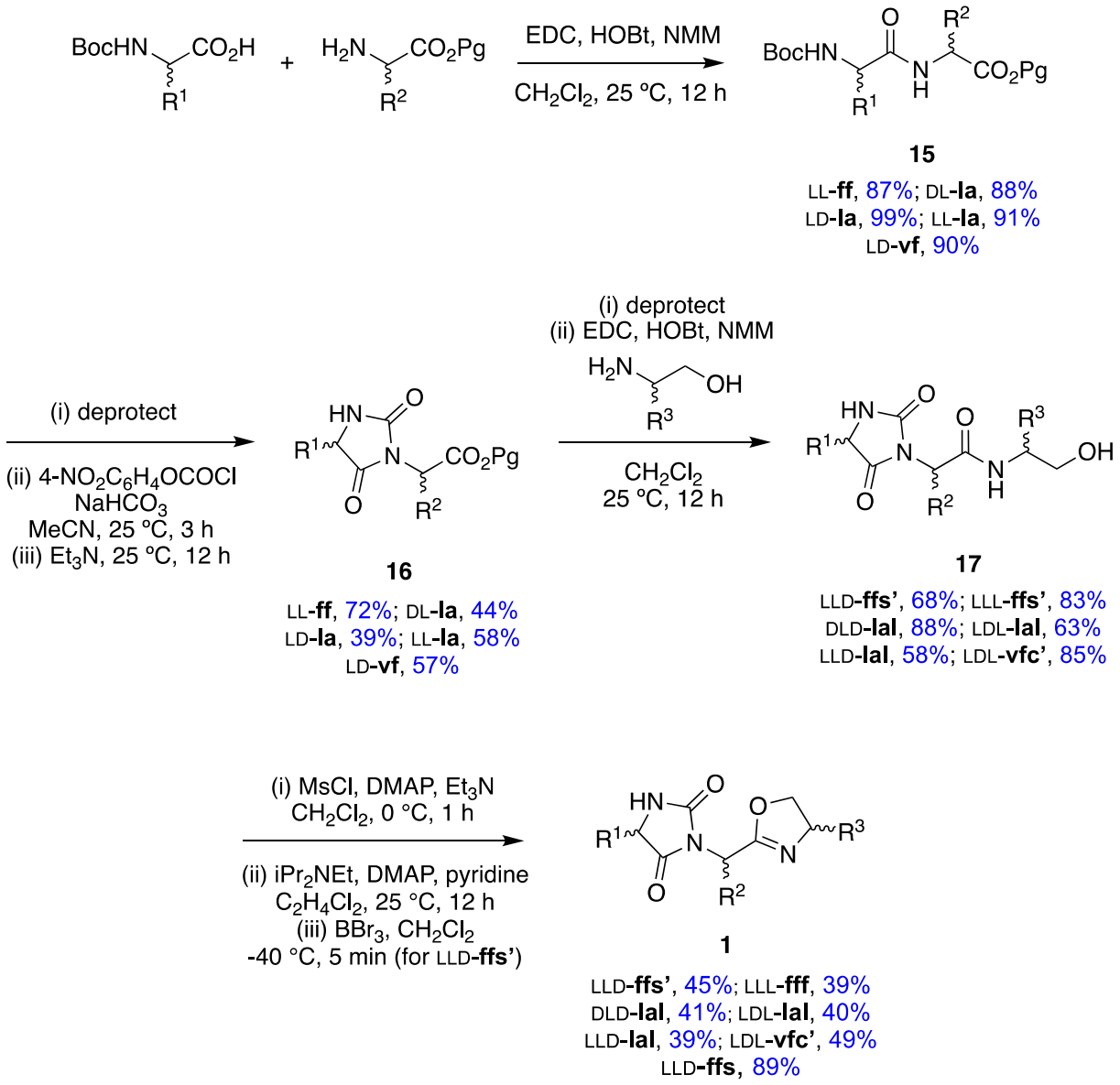


Figure S1. Syntheses of mimic **1**; lower case one-letter codes delineate the amino acid side-chains R^1 – R^3, and apostrophes (') denotes protecting groups, *eg* **s'** for the -CH_2OBn and **s** for -CH_2OH of Ser; **c'** for -CH_2SBn of Cys.

General Procedure for the Preparation of Dipeptide 9

A representative synthesis of the LD-**15la** is described as follows: Boc-L-leucine (2.47 g, 9.9 mmol) and HOBt (1.47 g, 10.9 mmol) were dissolved in dichloromethane (100 mL) at 0 ºC. EDC (2.09 g, 10.9 mmol) was added subsequently and the solution was stirred at 0 ºC for 30 min. *N*-methyl morpholine (3.27 mL, 29.7 mmol) and D-alanine benzyl ester (1.77 g, 9.9 mmol) were added. The reaction was stirred at ambient temperature for 12 h under Ar. The resulting solution was washed with 10 % citric acid, saturated $NaHCO_3$ solution and brine. The organic layer was dried over $MgSO_4$ and filtered. The solvent was removed under vacuum to obtain 3.80 g (98 %) of white solid, which was used in next step without further purification.

General Procedure of Boc Deprotection

Method A: This method was used for LL-**15ff** and LD-**15vf**. The solution of 4 M HCl in dioxane (10 mL) was cooled down to 0 ºC in ice bath under Ar. Then, this solution was transferred to pre-cool flask containing Boc-dipeptide (0.50 mmol). The solution was stirred at ambient temperature for additional 30 min until starting material was disappeared as monitored by TLC. The solvent was removed under vacuum. The crude oil was triturated with ether and filtered to obtain the product as a salt.

Method B: This method was used for DL-**15la**, LD-**15la** and LL-**15la**. Boc-dipeptide (1 mmol) was dissolved in 3 mL of dichloromethane, then TFA (1 mL) was added and the solution was stirred for 1 h. The solution was completely evaporated by rotavap, redissolved in dichloromethane and evaporated for at least 3 times to remove excess TFA. The crude oil was used in the next step without further purification.

General Procedure for the Preparation of *C*-protected Hydantoin 16

Hydantoin synthesis was performed as described in literature.[6, 7] A representative synthesis of the LL-**16ff** is described as follows: Boc-deprotected LL-**15ff** (1.35 g, 3 mmol), $NaHCO_3$ (1.26 g, 15 mmol) were dissolved in acetonitrile (48 mL). Then, *p*-nitrophenyl chloroformate (0.79 g, 3.9 mmol) was added. The cloudy solution was stirred at room temperature for 3 h under Ar. Et_3N (0.54 mL) was added, and the yellow solution was stirred for additional 12 h. After removal of acetonitrile under vacuum, the crude was dissolved in ethyl acetate, washed 5 times with 5% K_2CO_3, brine and dried over $MgSO_4$. The organic solution was removed to obtain the crude oil. The residue was purified by column chromatography on silica gel with hexanes-ethyl acetate (3:1) to afford the product (0.85 g, 72%) as pale yellow solid.

General Procedure for the Preparation of Scaffold 17

Method A: (*tert*-butyl ester protecting group): A representative synthesis of the LLL-**17fff** is described as follows: Compound LL-**16ff** (0.2 g, 0.51 mmol) was dissolved in dichloromethane (4 mL). TFA (1.3 mL) was

added and the solution was stirred at room temperature for 3 h. The solvent was removed under vacuum, and then repeated dissolve/evaporate cycles with dichloromethane several times to remove excess TFA. The crude oil was used for the next step without further purification.

The deprotected hydantoin, HOBt (76 mg, 0.56 mmol) were dissolved in dichloromethane (5 mL) in an ice bath. EDC (108 mg, 0.56 mmol) was added and the solution was stirred for 30 min at 0 ºC. *N*-methyl morpholine (0.17 mL, 1.53 mmol) and L-phenylalaninol (77 mg, 0.51 mmol) were added subsequently. The solution was stirred at ambient temperature for 12 h under Ar. Organic layer was washed with 1 N HCl solution, saturated $NaHCO_3$, brine and dried over $MgSO_4$ successively. The solution was removed under reduced pressure to obtain the product as white solid (199 mg, 83 %).

Method B: (benzyl ester protecting group): A representative synthesis of the LLD-**17lal** is described as follows: Compound LL-**16la** (0.47 g, 1.49 mmol) and 10 % Pd/C (0.15 g, 0.15 mmol) were dissolved in dried methanol (20 mL) under Ar. Then, H_2 was purged into the flask for 5 min and the solution was stirred under H_2 atmosphere for 12 h. The solution was filtered through celite. The clear solution was removed under vacuum to obtain the oil product (0.34 g, 100 %), which was used in the next step without further purification.

The deprotected hydantoin (0.34 g, 1.48 mmol), HOBt (0.26 g, 1.93 mmol) were dissolved in dichloromethane (20 mL) in an ice bath. EDC (0.37 g, 1.93 mmol) was added and the solution was stirred for 30 min at 0 ºC. *N*-methyl morpholine (0.49 mL, 4.45 mmol) and D-leucinol (0.22 g, 1.93 mmol) were added subsequently. The solution was stirred at ambient temperature for 12 h under Ar. Organic layer was washed with 1 N HCl solution, saturated $NaHCO_3$, brine and dried over $MgSO_4$ successively. The solution was removed under reduced pressure to obtain white solid (0.28 g, 58 %).

Synthesis of Mimic 5

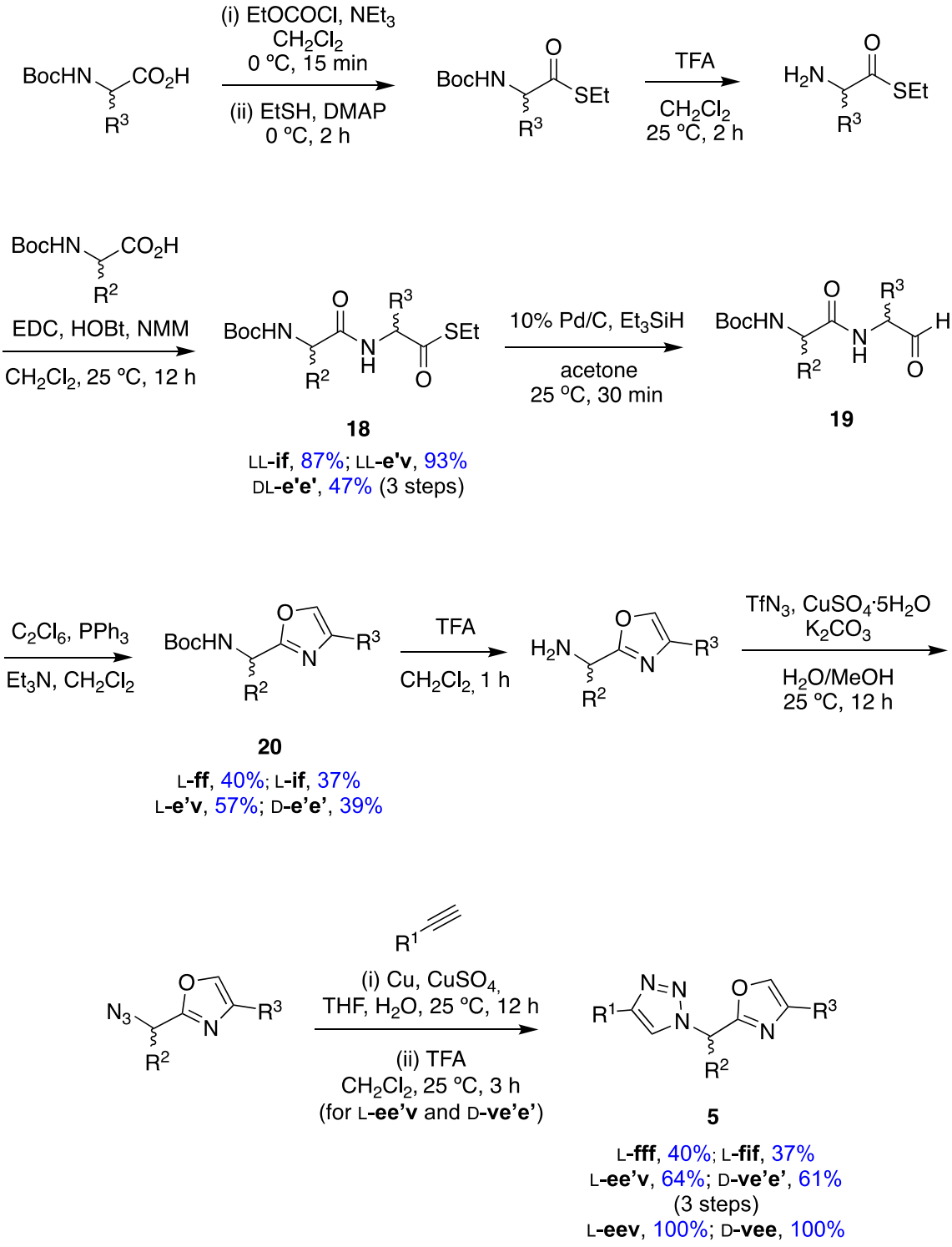


Figure S2. Syntheses of mimic **5**; notation follows the same rule as in Scheme S1.

General Preparation of Ethyl-*N*-Boc-Dipeptide Thioester 18

A representative synthesis of compound LL-**18e'v** is described as follows: Boc-valine (1.52 g, 7 mmol) was dissolved in dichloromethane (40 mL) at 0 ºC under Ar. Et_3N (6.83 mL, 49 mmol) was added in one portion followed by ethyl chloroformate (2.40 mL, 25 mmol) over 15 min. DMAP (0.09 g, 0.7 mmol) and EtSH (2.59 mL, 35 mmol) were added subsequently and the reaction was stirred for additional 2 h at 0 ºC. The reaction was quenched using 2.0 mL of glacial acetic acid. The mixture was then evaporated under reduced pressure and redissolved in dichloromethane. The solution was washed 3 times with 10 % citric acid, 3 times with saturated $NaHCO_3$, brine and dried over $MgSO_4$. Solvent was removed to obtain crystalline solid, which was used for the next step without further purification.

Boc deprotection of the Boc-valine-SEt (1.02 g, 3.89 mmol) was performed according to the method B of the General Procedure of Boc Deprotection as described above.

The solution of Boc-L-glutamic acid 5-benzyl ester (1.31 g, 3.89 mmol) and HOBt (0.58 g, 4.28 mmol) were dissolved in dichloromethane (50 mL) at 0 ºC. EDC (0.82 g, 4.28 mmol) was added and the solution was stirred for 30 min. *N*-methyl morpholine (1.28 mL, 11.7 mmol) and the NH_2-valine-SEt from the previous step dissolved in dichloromethane (20 mL) were added and the reaction was stirred at ambient temperature for 12 h under Ar. The solution was washed with 10 % citric acid, saturated $NaHCO_3$, brine and dried over $MgSO_4$. The solvent was removed under reduced pressure to obtain compound **18** (1.74 g, 93 %) as solid.

General Preparation of *N*-Boc Oxazole 20

Synthesis of aldehyde **19** and oxazole **20** was performed as described by Fukuyama & Tokuyama[8] and Morwick *et al*,[9] respectively. A representative synthesis of L-**20e'v** is described as follows: The dipeptide **18** (1.16 g, 2.41 mmol) was added with 10 % Pd/C (0.12 g, 0.02 mmol) and small amount of $MgSO_4$ in round-bottom flask and flushed with Ar. Acetone (5 mL) was added into, then Et_3SiH (1.15 mL, 7.23 mmol) was added dropwise over 10 min. The solution was stirred for 30 min and monitored the reaction by TLC until starting material disappeared. Once the reaction completed, the solution was filtered through celite and evaporated under reduced pressure to obtain crude aldehyde **19** as oil.

In the round-bottom flask, C_2Cl_6 (1.71 g, 7.23 mmol) and PPh_3 (1.90 g, 7.23 mmol) were dissolved in acetonitrile (19 mL) in an ice bath. Aldehyde **19** in 7 mL acetonitrile was added dropwise and the solution was stirred for 10 min at 0 ºC. Et_3N (2.02 mL, 14.5 mmol) was added to the solution and the reaction was stirred at ambient temperature for 12 h. The solution was removed under reduced pressure, and then redissolved in ethyl acetate. The organic solution was washed with water 3 times, brine and dried over $MgSO_4$. The organic layer was dried completely and the crude was purified by silica gel column chromatography using hexanes : ethyl acetate to obtain oxazole **20** (0.49 g, 57 %) as solid.

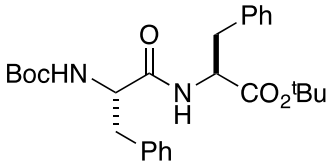
General Procedure for the Preparation of Scaffold 5

Azide synthesis and Cu(I)-catalyzed click reaction was performed as described in literature.[10, 11] A representative synthesis of L-**5ee'v** is described as follows: Boc-deprotection of L-**20e'v** (218 mg, 0.54 mmol) was performed same as method B of the general procedure of Boc deprotection as described above. The crude oxazole was dissolved in methanol (3.5 mL), then $CuSO_4.5H_2O$ (1.25 mg, 0.005 mmol) and K_2CO_3 (112 mg, 0.81 mmol) dissolved in water (1.75 mL) was added into the reaction. Then, fresh TfN_3 (3 mmol) in dichloromethane was added directly to the reaction. The solution was stirred for 12 h at room temperature. The organic solvent was removed under vacuum at room temperature. The remaining liquid was diluted with water and pH was adjusted to 2 with concentrated HCl. The aqueous layer was extracted 4 times with ethyl acetate. The combined organic layer was washed with brine and dried over $MgSO_4$. The solvent was removed under reduced pressure to afford azido-oxazole, which was used in the next step without further purification.

The azido-oxazole and 4-pentynoic acid (55.9 mg, 0.57 mmol) were dissolved in THF (1.7 mL) and water (0.3 mL). Subsequently, copper powder (34 mg, 0.54 mmol) and 1 M solution of $CuSO_4$ (0.05 mL, 0.05 mmol) were added. The solution was stirred for 12 h. After the reaction was complete, the pH was adjusted to 2 using concentrated HCl, then aqueous layer was extracted 4 times with ethyl acetate. The organic layer was combined, dried over $MgSO_4$ and removed under reduced pressure. The crude product was purified by silica gel column chromatography using hexanes : ethyl acetate (1:2) to obtain product L-**5ee'v** (148 mg, 64%) as solid. The deprotection of L-**5ee'v** and D-**5ve'e'** was performed as same as method B in the general procedure for the preparation of scaffold **17** to obtain L-**5eev** and D-**5vee** as an oil.

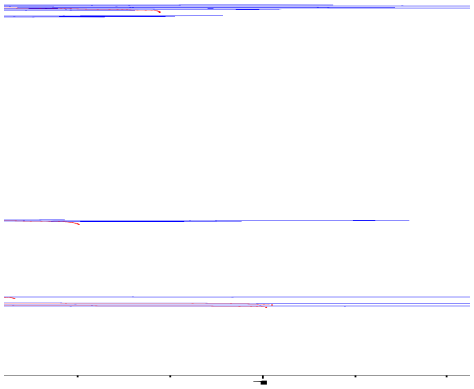
D. Characterization Data

***tert*-Butyl (*tert*-butoxycarbonyl)-*L*-phenylalanyl-*L*-phenylalaninate (LL-15ff)**

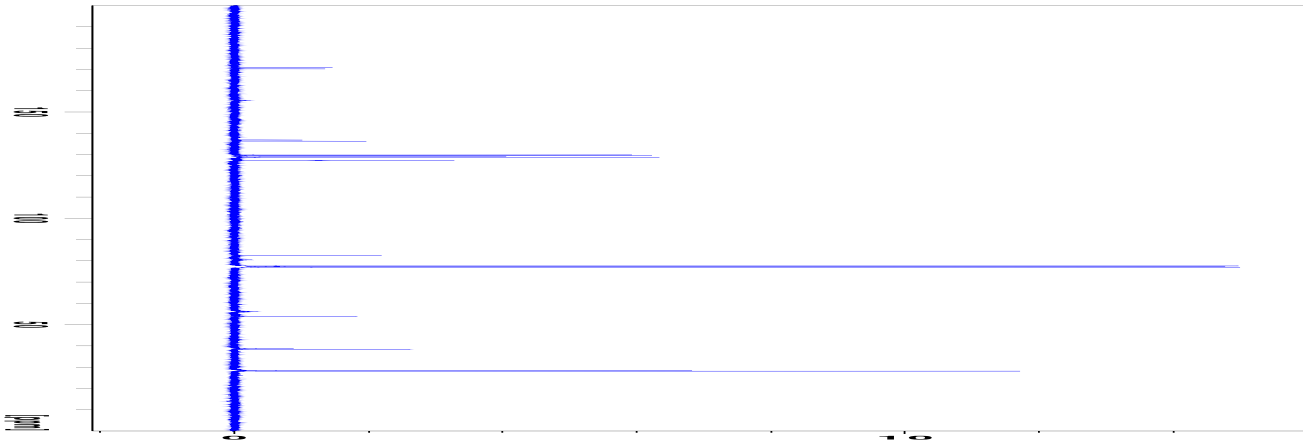


White solid, 87 % yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31-7.05 (m, 8H), 7.06 (m, 2H), 6.30 (br, 1H), 4.92 (br, 1H), 4.65 (q, *J* = 6.4 Hz, 1H), 4.33 (br, 1H), 3.05 (m, 4H), 1.41 (s, 9H), 1.37 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.8, 170.2, 136.8, 136.3, 129.7, 129.6, 128.9, 128.5, 127.2, 127.1, 82.5, 53.9, 38.4, 28.5, 28.1; HRMS (ESI) m/z calcd for $C_{27}H_{36}N_2O_5$ 468.2624; found 491.2537 $(M+Na)^+$

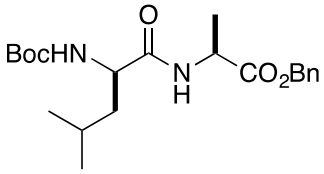
^{1}H NMR spectrum:



^{13}C NMR spectrum:

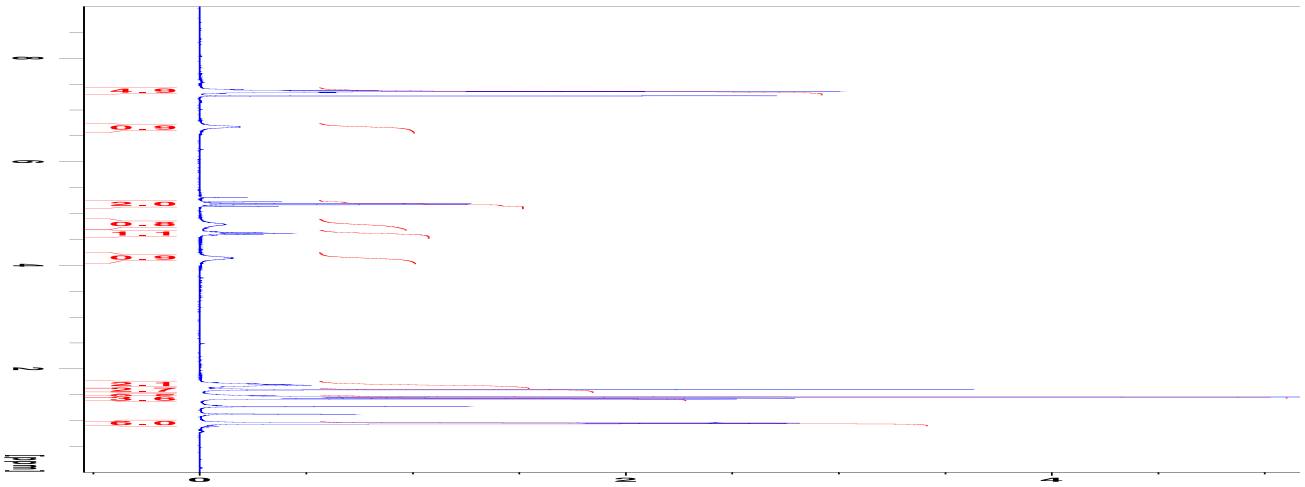


Benzyl (*tert*-butoxycarbonyl)-*D*-leucyl-*L*-alaninate (DL-15la)

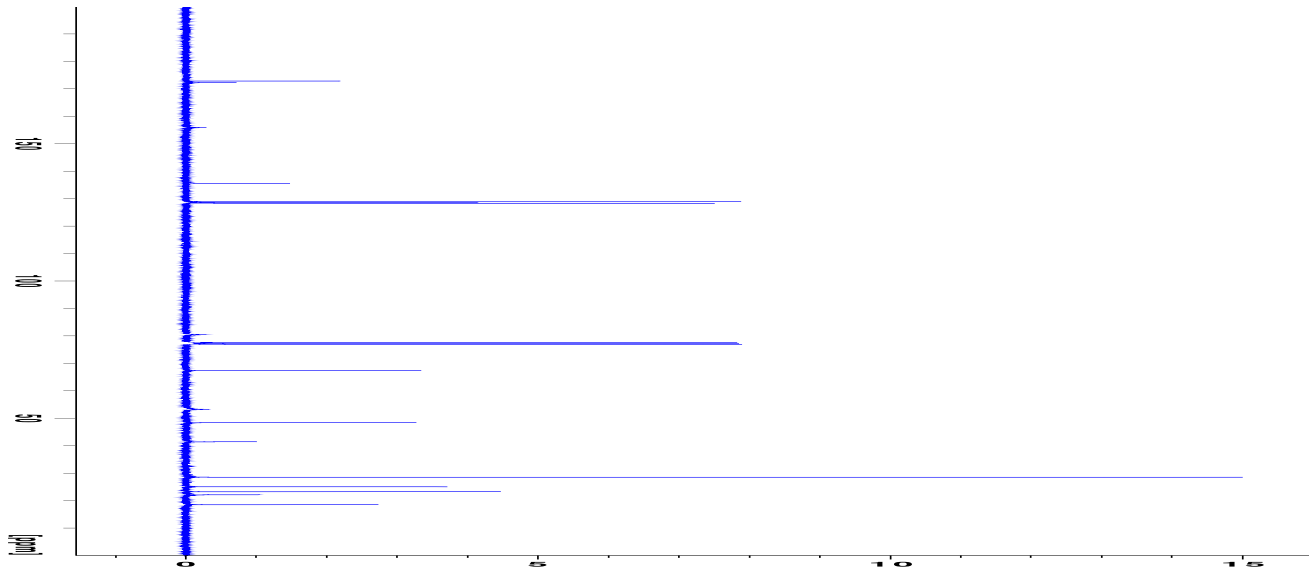


White solid, 88 % yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 (m, 5H), 6.67 (br, 1H), 5.18 (dd, *J* = 22.2, 12.3 Hz, 2H), 4.79 (br, 1H), 4.61 (quint, *J* = 7.1 Hz, 1H), 4.13 (br, 1H), 1.70 (m, 2H), 1.45 (s, 9H), 1.44 (m, 1H), 1.42 (d, *J* = 7.1 Hz, 3H), 0.95 (d, *J* = 4.2 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.8, 172.3, 156.0, 135.6, 128.8, 128.6, 128.3, 80.4, 67.3, 53.2, 48.3, 41.4, 28.5, 25.0, 23.2, 22.1, 18.4; HRMS (ESI) m/z calcd for $C_{21}H_{32}N_2O_5$ 392.2311; found 393.2372 $(M+H)^+$, 415.2178 $(M+Na)^+$

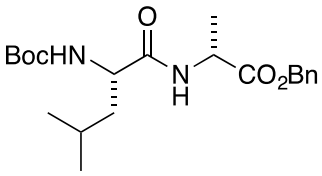
^{1}H NMR spectrum:



^{13}C NMR spectrum:

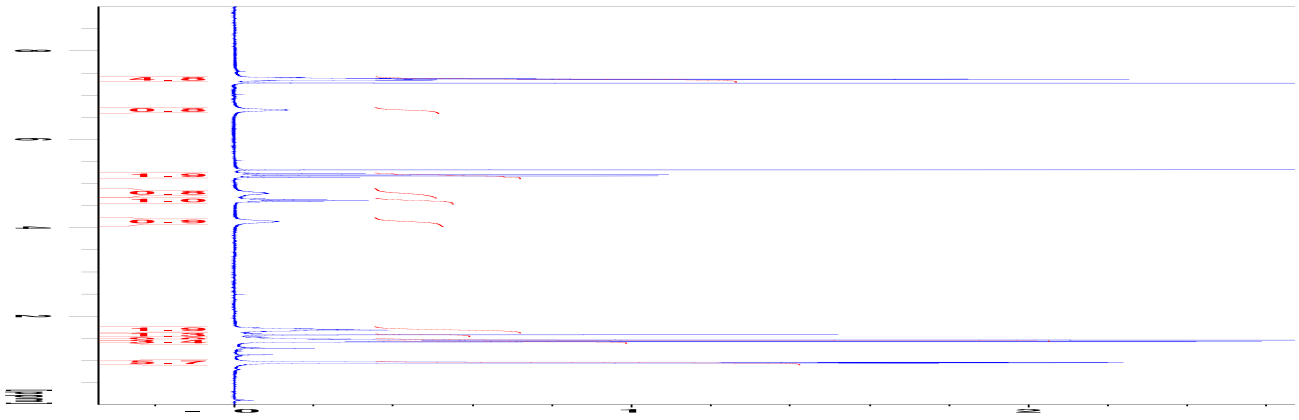

1.5M
1.0M
0.5
[counts]
0
5
10
15

Benzyl (*tert*-butoxycarbonyl)-*L*-leucyl-*D*-alaninate (LD-15la)

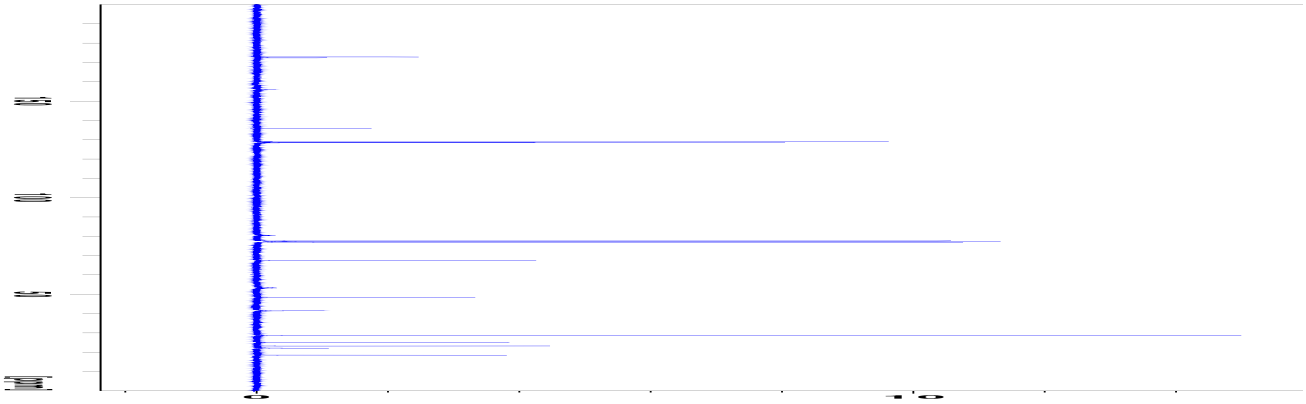


White solid, 99 % yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38-7.35 (m, 5H), 6.66 (br, 1H), 5.18 (dd, *J* = 22.2, 12.3 Hz, 2H), 4.78 (br, 1H), 4.61 (quint, *J* = 7.1 Hz, 1H), 4.13 (br, 1H), 1.69 (m, 2H), 1.45 (s, 9H), 1.44 (m, 1H), 1.42 (d, *J* = 7.1 Hz, 3H), 0.95 (d, *J* = 4.2 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.8, 172.3, 156.0, 135.6, 128.8, 128.6, 128.3, 80.4, 67.3, 53.2, 48.3, 41.4, 28.5, 25.0, 23.2, 22.1, 18.5; HRMS (ESI) m/z calcd for $C_{21}H_{32}N_2O_5$ 392.2311; found 415.2186 $(M+Na)^+$

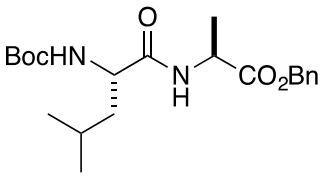
^{1}H NMR spectrum:



^{13}C NMR spectrum:

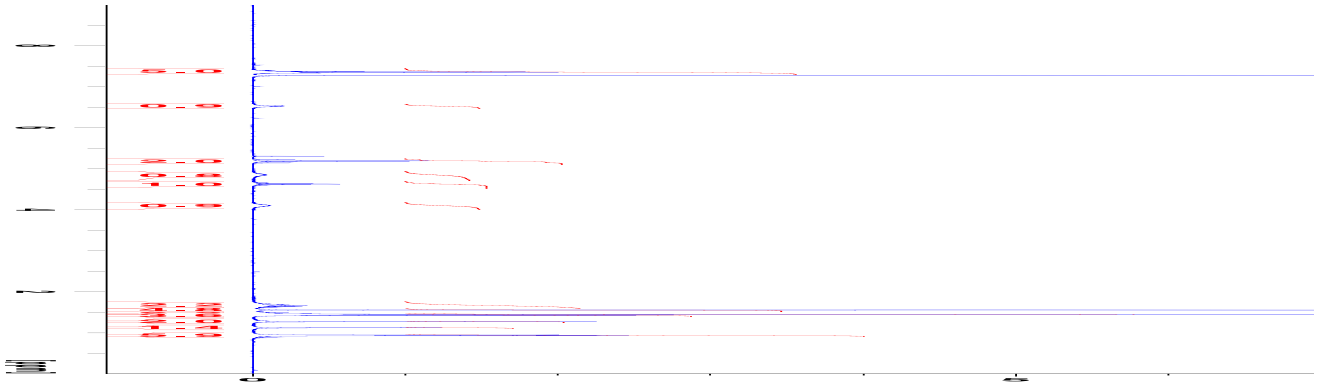


Benzyl (*tert*-butoxycarbonyl)-*L*-leucyl-*L*-alaninate (LL-15la)

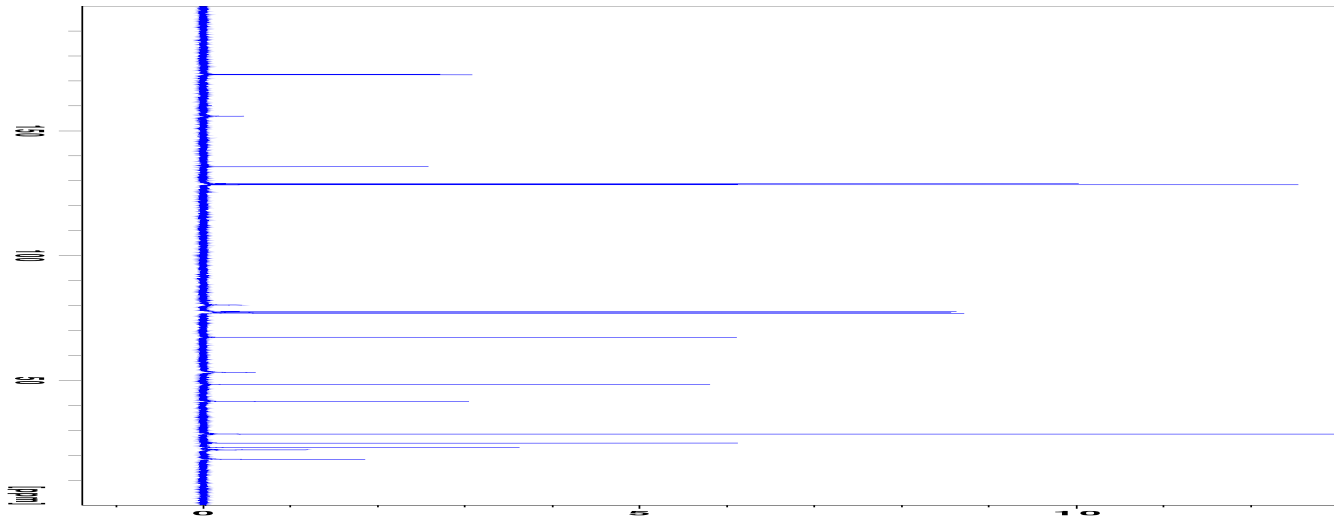


White solid, 91 % yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38-7.35 (m, 5H), 6.52 (br, 1H), 5.18 (dd, *J* = 22.2, 12.3 Hz, 2H), 4.84 (br, 1H), 4.63 (quint, *J* = 7.1 Hz, 1H), 4.10 (br, 1H), 1.70-1.62 (m, 2H), 1.58 (s, 1H), 1.45 (s, 9H), 1.44 (m, 1H), 1.43 (d, *J* = 7.1 Hz, 3H), 0.94 (d, *J* = 4.2 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.7, 172.4, 155.9, 135.6, 128.8, 128.6, 128.3, 80.2, 67.3, 53.2, 48.3, 41.6, 28.5, 24.9, 23.1, 22.1, 18.4; HRMS (ESI) m/z calcd for $C_{21}H_{32}N_2O_5$ 392.2311; found 399.2485 $(M+Li)^+$

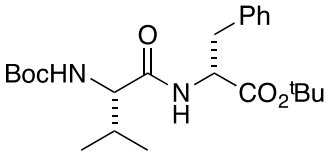
^{1}H NMR spectrum:



^{13}C NMR spectrum:

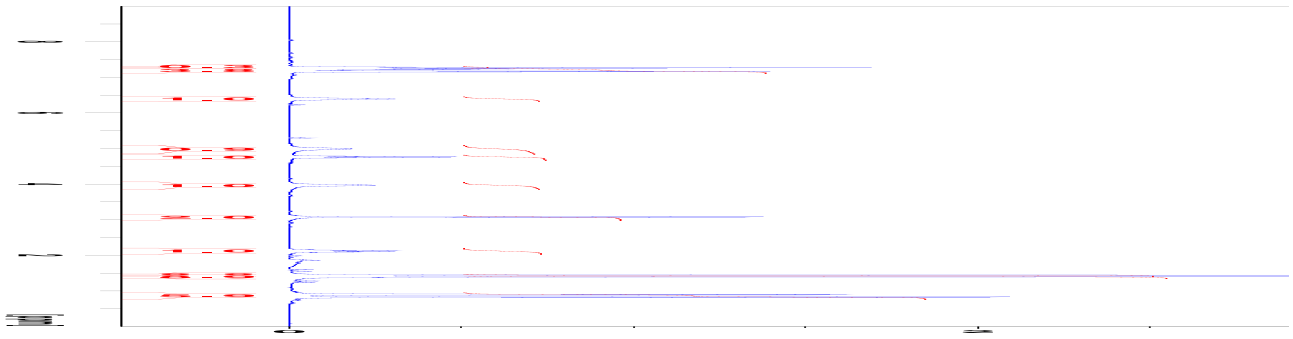

0
5
10

***tert*-Butyl (*tert*-butoxycarbonyl)-*L*-valyl-*D*-phenylalaninate (LD-15vf)**

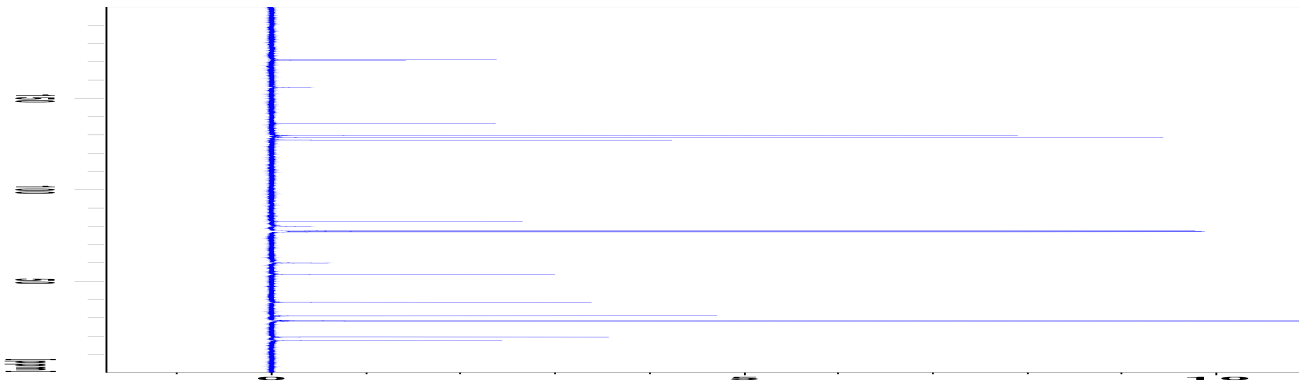


White solid, 90 % yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29-7.16 (m, 5H), 6.39 (br, 1H), 4.99 (br, 1H), 4.76 (dd, *J* = 13.9, 6.4 Hz, 1H), 3.97 (br 1H), 3.08 (d, *J* = 6.2 Hz, 2H), 2.1 (m, 1H), 1.44 (s, 9H), 1.40 (s, 9H), 0.90 (d, *J* = 6.7 Hz, 3H), 0.82 (d, *J* = 6.7 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.2, 170.6, 155.9, 136.3, 129.6, 128.6, 127.2, 82.5, 80.0, 59.9, 53.7, 38.5, 31.0, 28.5, 28.1, 19.4, 17.4; HRMS (ESI) m/z calcd for $C_{23}H_{36}N_2O_5$ 420.2624; found 443.2552 $(M+Na)^+$

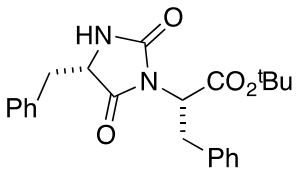
^{1}H NMR spectrum:



^{13}C NMR spectrum:

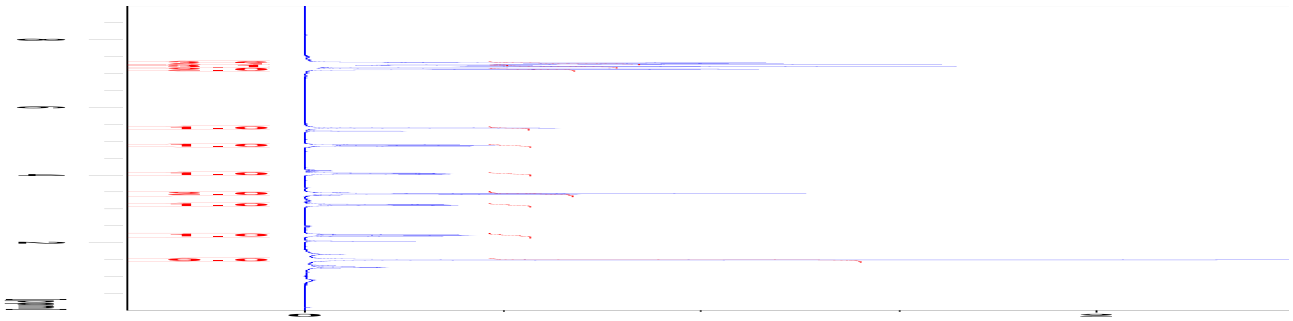


***tert*-Butyl (*S*)-2-((*S*)-4-benzyl-2,5-dioxoimidazolidin-1-yl)-3-phenylpropanoate (LL-16ff)**

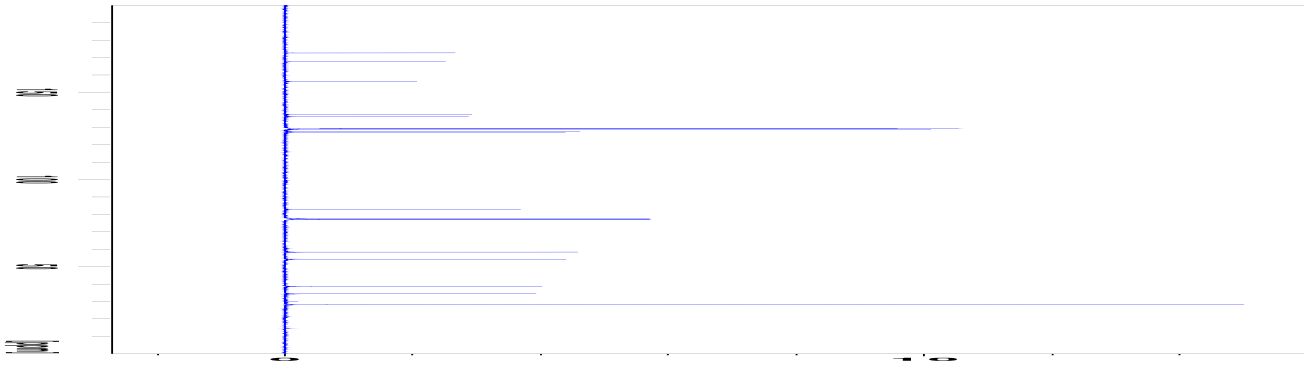


Pale yellow solid, 72 % yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33-7.11 (m, 10H), 5.39 (br, 1H), 4.88 (dd, *J* = 10.1, 6.9 Hz, 1H), 4.04 (dd, *J* = 10.7, 3.3 Hz, 1H), 3.46-3.43 (m, 2H), 3.12 (dd, *J* = 13.9, 3.5 Hz, 1H), 2.22 (dd, *J* = 13.8, 10.9 Hz, 1H), 1.49 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.6, 167.6, 156.2, 137.2, 136.1, 129.3, 129.2, 129.1, 128.7, 127.5, 127.0, 82.9, 58.3, 54.1, 38.6, 34.4, 28.1; HRMS (ESI) m/z calcd for $C_{23}H_{36}N_2O_4$ 394.1893; found 417.1807 $(M+Na)^+$

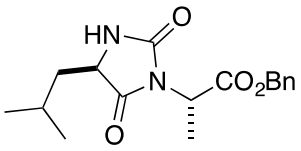
^{1}H NMR spectrum:



^{13}C NMR spectrum:

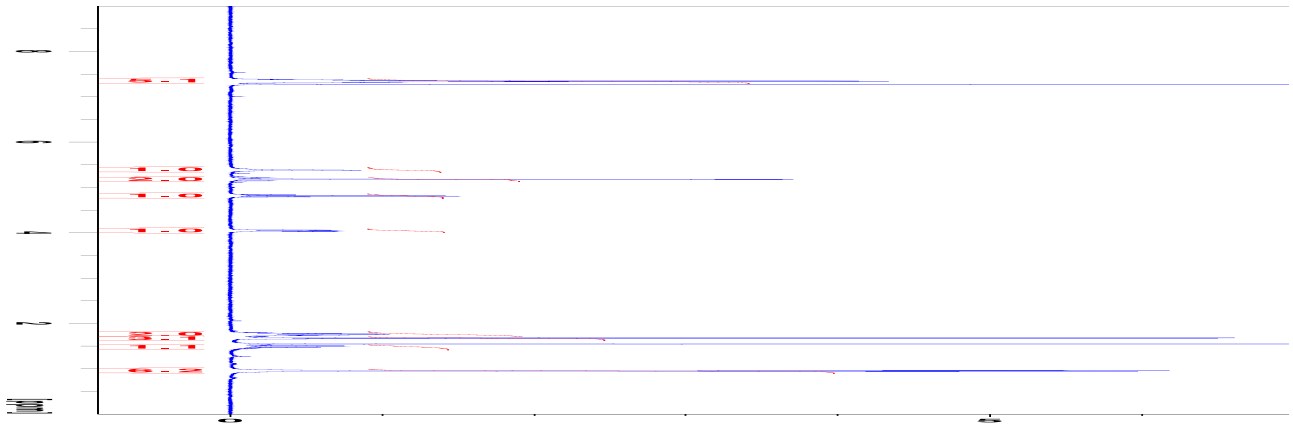


Benzyl (*S*)-2-((*R*)-4-isobutyl-2,5-dioxoimidazolidin-1-yl)propanoate (DL-16la)

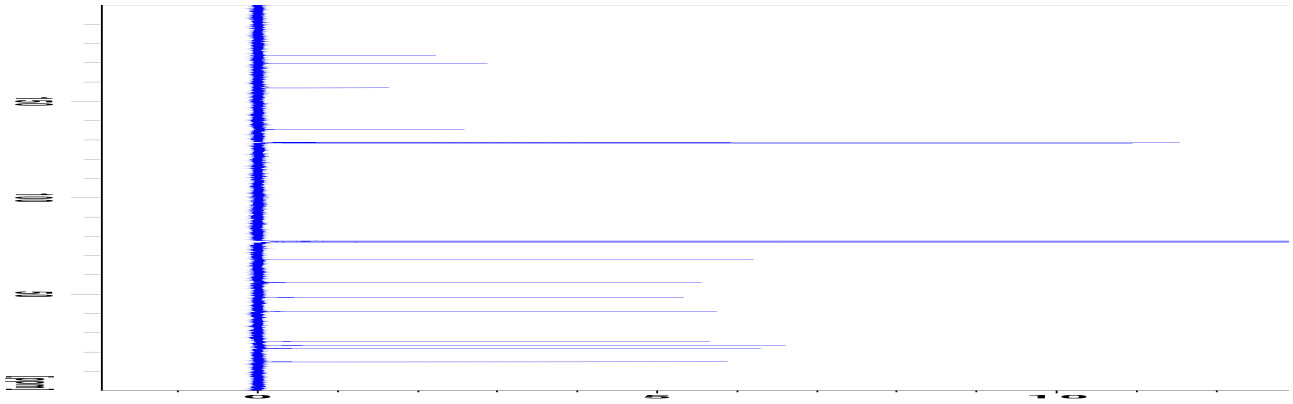


White solid, 44 % yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40-7.30 (m, 5H), 5.38 (br 1H), 5.22-5.14 (m, 2H), 4.82 (q, *J* = 7.4, 1H), 4.05 (m, 1H), 1.80 (m, 2H), 1.67 (d, *J* = 7.4, 3H), 1.50-1.46 (m, 1H), 0.95 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.9, 169.5, 156.9, 135.5, 128.8, 128.6, 128.3, 67.7, 56.0, 48.3, 41.0, 25.2, 23.2, 21.8, 14.8; HRMS (ESI) m/z calcd for $C_{17}H_{22}N_2O_4$ 318.1580; found 319.1646 $(M+H)^+$

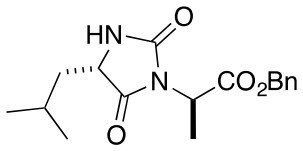
^{1}H NMR spectrum:



^{13}C NMR spectrum:

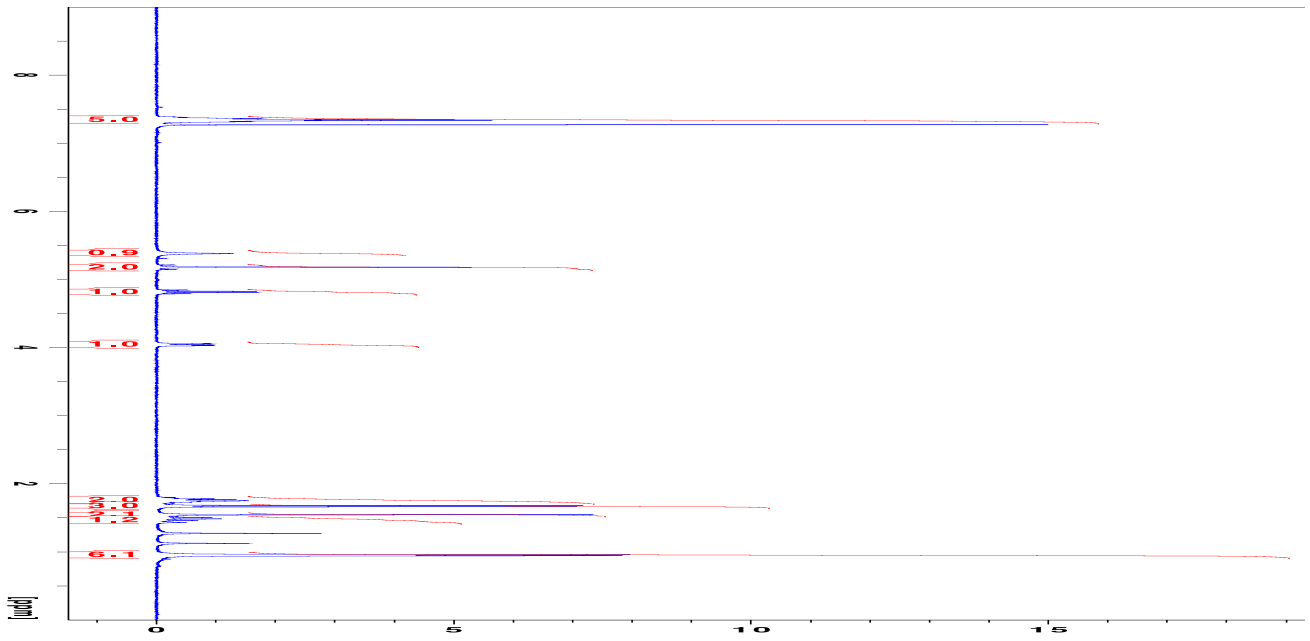


Benzyl (*R*)-2-((*S*)-4-isobutyl-2,5-dioxoimidazolidin-1-yl)propanoate (LD-16la)

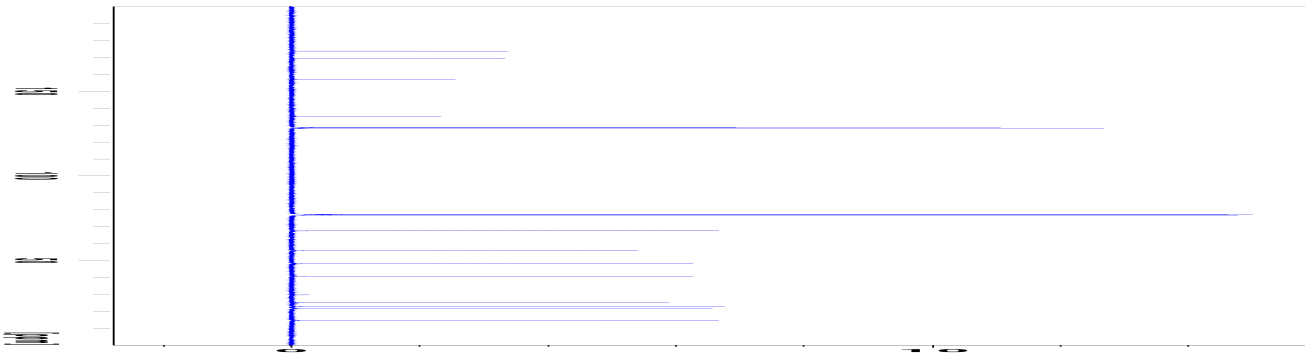


White solid, 39 % yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40-7.30 (m, 5H), 5.38 (br 1H), 5.22-5.14 (m, 2H), 4.82 (q, *J* = 7.4, 1H), 4.05 (m, 1H), 1.80 (m, 2H), 1.67 (d, *J* = 7.4, 3H), 1.54-1.46 (m, 1H), 0.95 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.7, 169.3, 156.7, 135.3, 128.5, 128.4, 128.1, 67.5, 55.8, 48.1, 40.8, 25.0, 23.0, 21.6, 14.6; HRMS (ESI) m/z calcd for $C_{17}H_{22}N_2O_4$ 318.1580; found 341.1491 $(M+Na)^+$

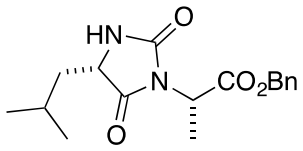
^{1}H NMR spectrum:



^{13}C NMR spectrum:

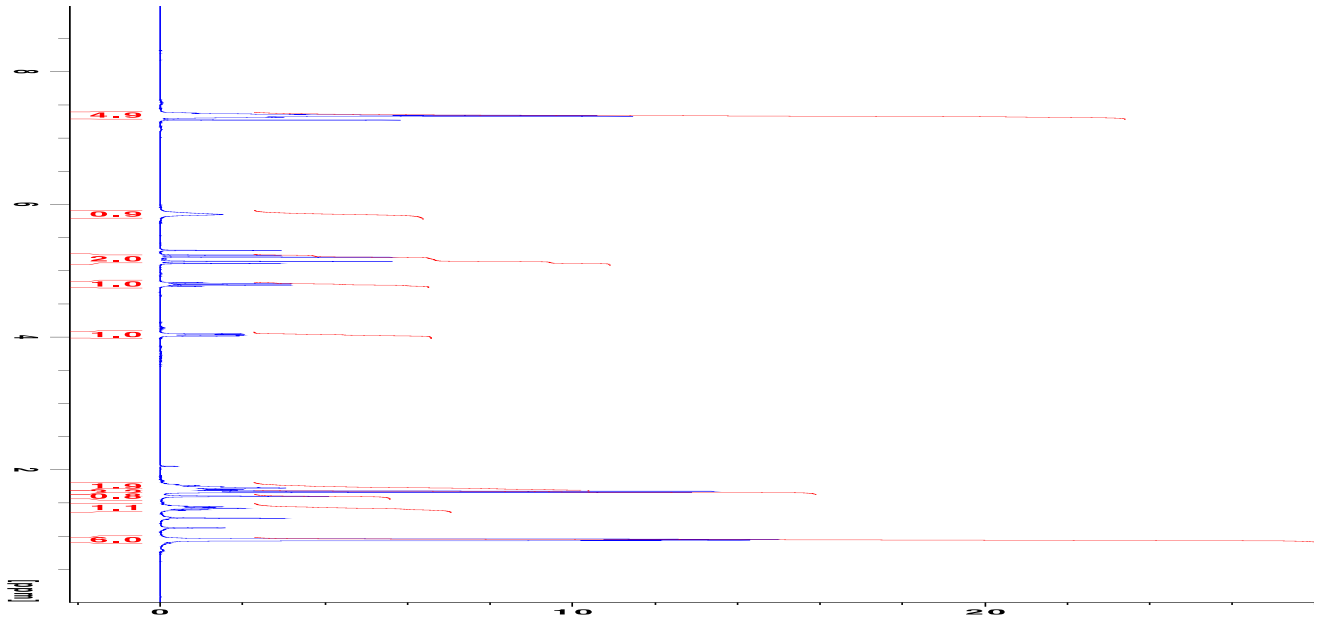


Benzyl (*S*)-2-((*S*)-4-isobutyl-2,5-dioxoimidazolidin-1-yl)propanoate (LL-16la)

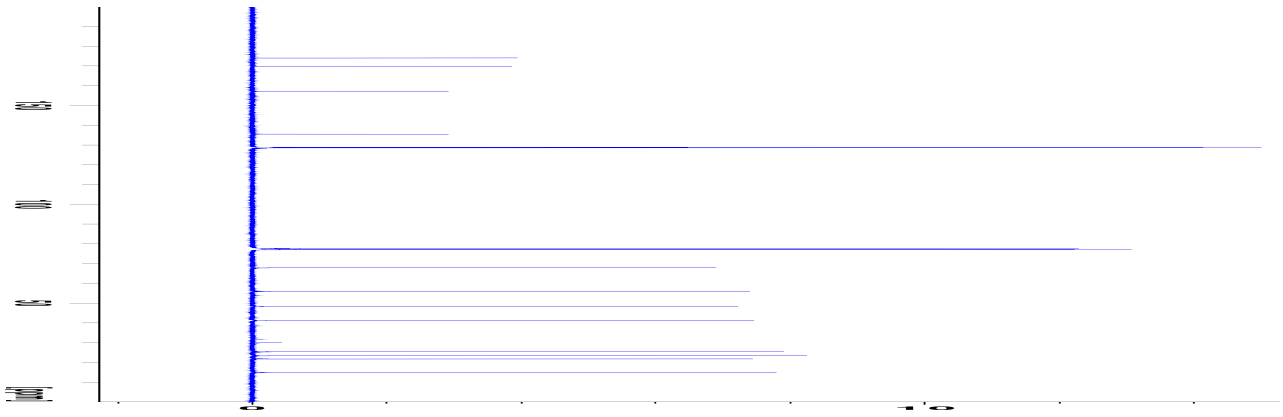


White solid, 39 % yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40-7.30 (m, 5H), 5.85 (br, 1H), 5.17 (dd, *J* = 38.1, 12.3 Hz, 2H), 4.79 (q, *J* = 7.3 Hz, 1H), 4.06-4.01 (m, 1H), 1.81-1.69 (m, 2H), 1.67 (d, *J* = 7.4 Hz, 3H), 1.50-1.36 (m, 1H), 0.95 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.0, 169.5, 157.0, 135.5, 128.8, 128.6, 128.5, 67.8, 55.9, 48.3, 41.1, 25.3, 23.3, 21.7, 14.9; HRMS (ESI) m/z calcd for $C_{17}H_{22}N_2O_4$ 318.1580; found 319.1642 $(M+H)^+$

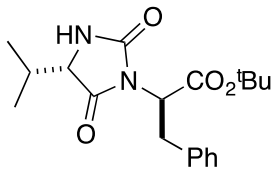
^{1}H NMR spectrum:



^{13}C NMR spectrum:

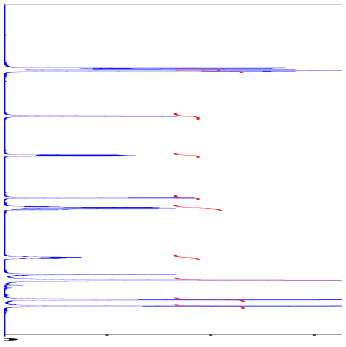

0
10

***tert*-Butyl (*R*)-2-((*S*)-4-isopropyl-2,5-dioxoimidazolidin-1-yl)-3-phenylpropanoate (LD-16vf)**

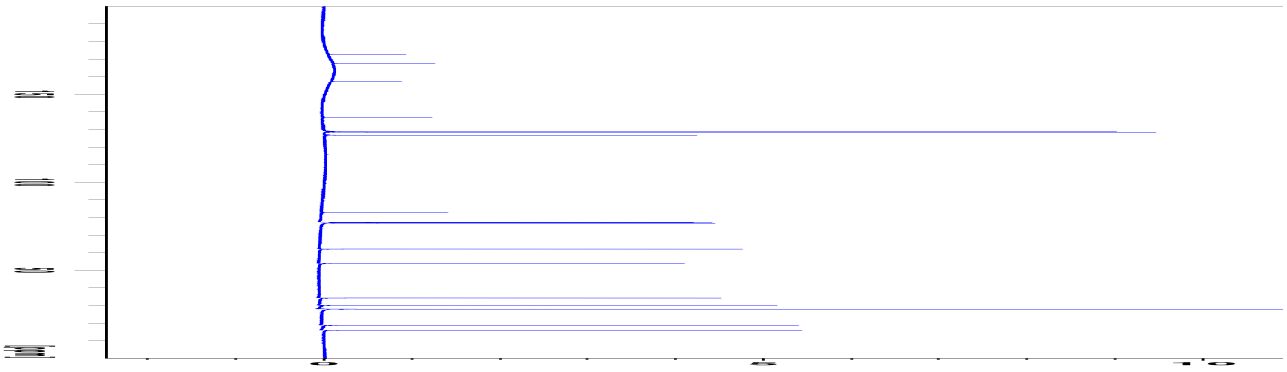


Solid, 57 % yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29-7.16 (m, 5H), 5.96 (br, 1H), 4.89 (dd, *J* = 11.3, 5.5 Hz, 1H), 3.72 (dd, *J* = 3.8, 1.3 Hz, 1H), 3.5-3.39 (m, 2H), 2.16-2.02 (m, 1H), 1.47 (s, 9H), 0.95 (d, *J* = 7.0 Hz, 3H), 0.78 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.6, 167.6, 157.1, 137.0, 128.9, 128.4, 126.7, 82.7, 62.0, 53.8, 34.2, 30.0, 27.9, 18.7, 16.0; HRMS (ESI) m/z calcd for $C_{19}H_{26}N_2O_4$ 346.1893; found 369.1814 $(M+Na)^+$

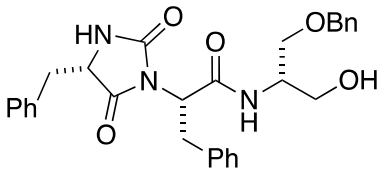
^{1}H NMR spectrum:



^{13}C NMR spectrum:

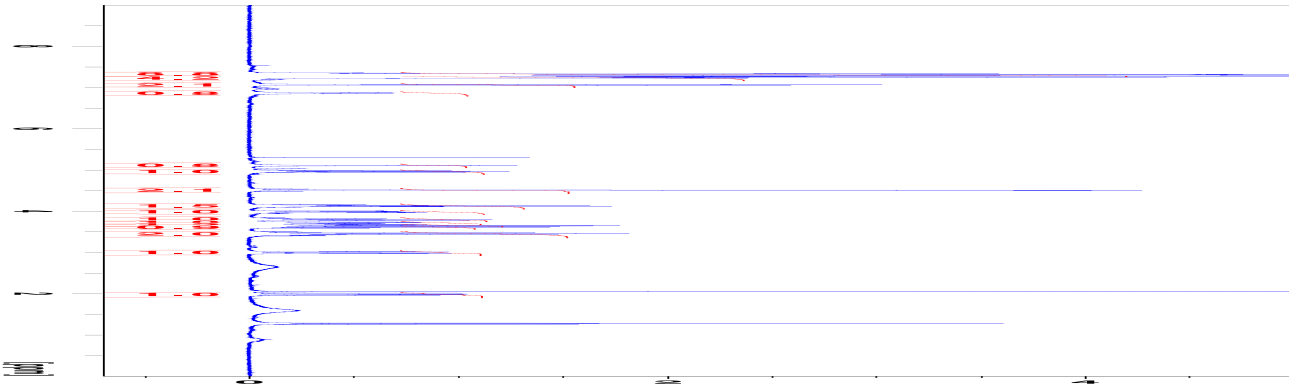


(*S*)-2-((*S*)-4-benzyl-2,5-dioxoimidazolidin-1-yl)-*N*-((*S*)-1-(benzyloxy)-3-hydroxypropan-2-yl)-3-phenylpropanamide (LLD-17ffs')

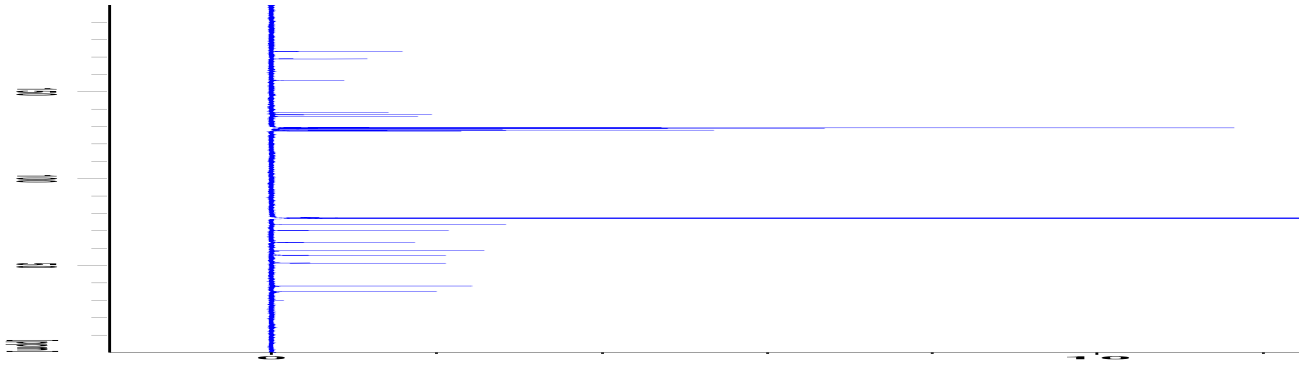


Solid, 68 % yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37-7.18 (m, 13 H), 7.10-7.01 (m, 2H), 6.86 (d, *J* = 7.6 Hz, 1H), 5.11 (s, 1H), 4.97 (dd, *J* = 10.7, 6.5 Hz, 1H), 4.51 (s, 2H), 4.18-4.07 (m, 2H), 4.03-3.93 (m, 1H), 3.85-3.69 (m, 2H), 3.69-3.58 (m, 2H), 3.52-3.37 (m, 2H), 3.00 (dd, *J* = 13.8, 3.6 Hz, 1H), 1.99 (dd, *J* = 13.9, 10.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.1, 168.8, 156.6, 137.8, 136.7, 135.9, 129.4, 129.2, 129.2, 128.9, 128.7, 128.1, 127.9, 127.6, 127.3, 73.6, 70.0, 63.2, 58.4, 55.9, 51.4, 38.2, 34.9; HRMS (ESI) m/z calcd for $C_{29}H_{31}N_3O_5$ 501.2264; found 500.2174 $(M-H)^-$

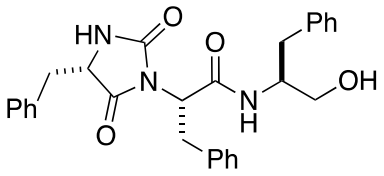
^{1}H NMR spectrum:



^{13}C NMR spectrum:

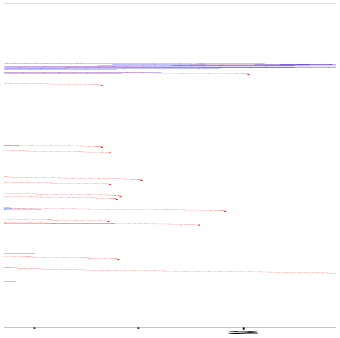


(*S*)-2-((*S*)-4-Benzyl-2,5-dioxoimidazolidin-1-yl)-*N*-((*S*)-1-hydroxy-3-phenylpropan-2-yl)-3-phenylpropanamide (LLL-17fff)

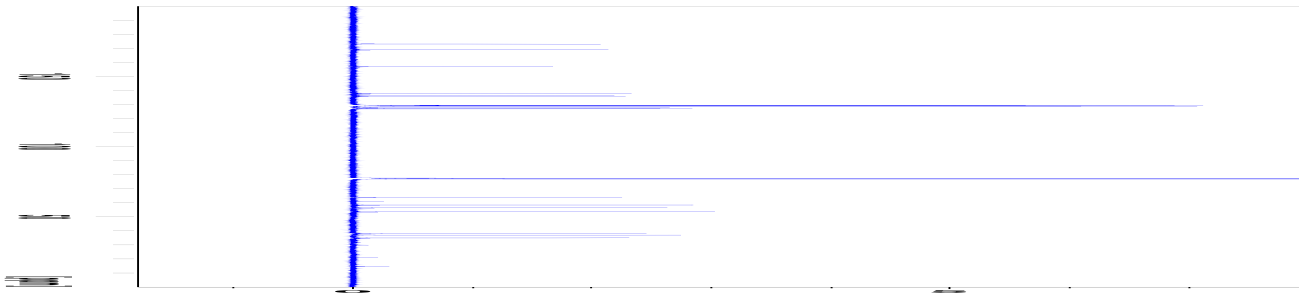


Solid, 83 % yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37-7.15 (m, 14H), 7.08 (m, 2H), 6.79 (d, *J* = 7.2 Hz, 1H), 5.05 (s, 1H), 4.90 (dd, *J* = 10.5, 6.8 Hz, 1H), 4.22-4.10 (m, 1H), 4.05-3.98 (m, 1H), 3.71 (dd, *J* = 11.3, 3.6 Hz, 1H), 3.61 (dd, *J* = 11.2, 5.2 Hz, 1H), 3.35-3.23 (m, 2H), 2.99 (dd, *J* = 13.8, 3.6 Hz, 1H), 2.92-2.86 (m, 2H), 1.95 (dd, *J* = 13.8, 10.7 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.1, 169.0, 156.8, 137.9, 136.5, 135.8, 129.5, 129.4, 129.2, 129.1, 128.9, 128.8, 127.6, 127.4, 126.8, 63.9, 58.4, 56.4, 53.8, 38.1, 37.0, 34.9; HRMS (ESI) m/z calcd for $C_{28}H_{29}N_3O_4$ 471.2158; found 470.2062 $(M-H)^-$

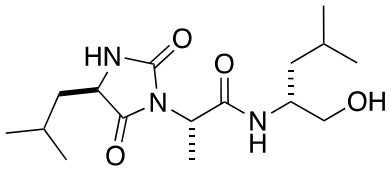
^{1}H NMR spectrum:



^{13}C NMR spectrum:

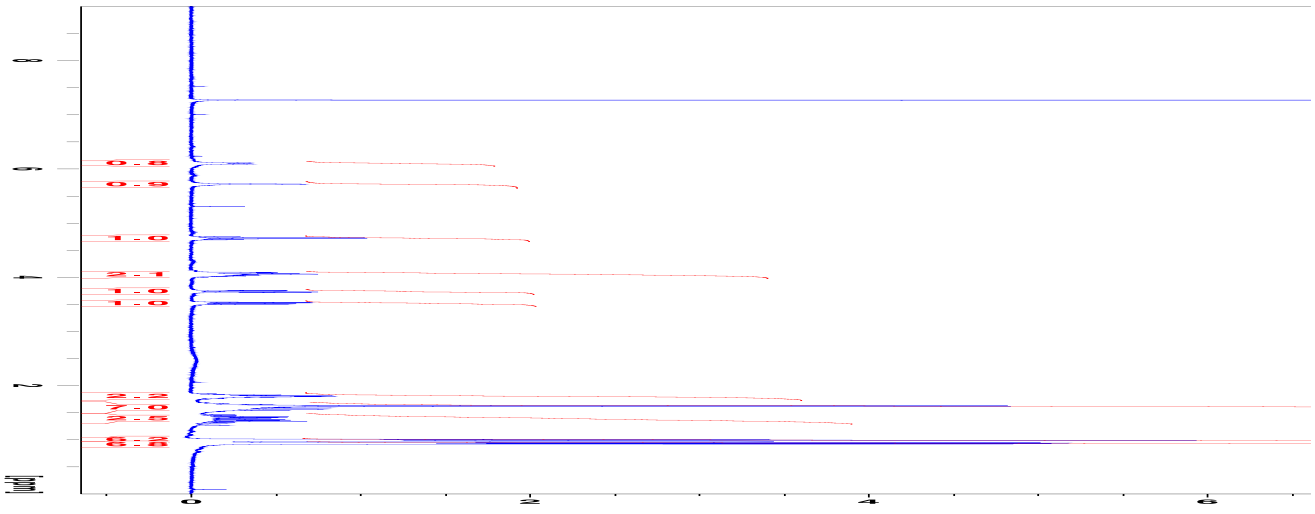


(*S*)-*N*-((*R*)-1-Hydroxy-4-methylpentan-2-yl)-2-((*R*)-4-isobutyl-2,5-dioxoimidazolidin-1-yl)propanamide (DLD-17lal)

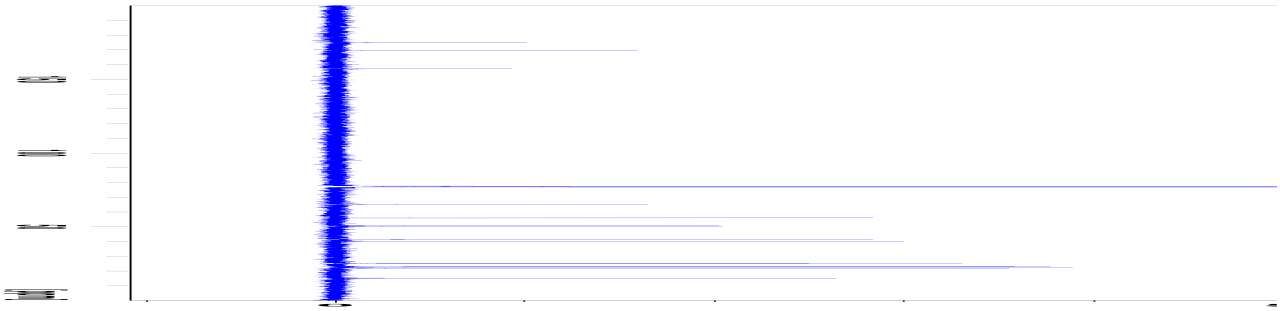


White solid, 88 % yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.10 (br, 1H), 5.72 (br, 1H), 4.72 (q, *J* = 7.3 Hz, 1H), 4.11-3.98 (m, 2H), 3.74 (dd, *J* = 11.2, 3.5 Hz, 1H), 3.52 (dd, *J* = 11.3, 5.5 Hz, 1H), 1.88-1.73 (m, 2H), 1.70-1.49 (m, 6H), 1.49-1.30 (m, 2H), 0.99 (t, *J* = 6.6 Hz, 6H), 0.94 (dd, *J* = 6.6, 2.9 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.8, 169.7, 157.4, 65.2, 56.0, 50.6, 50.1, 41.1, 40.2, 25.2, 25.1, 23.3, 23.2, 22.4, 21.8, 15.1; HRMS (ESI) m/z calcd for $C_{16}H_{29}N_3O_4$ 327.2158; found 328.2253 $(M+H)^+$

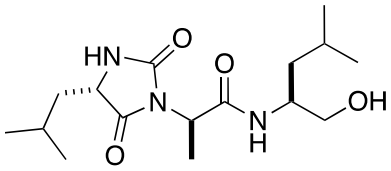
^{1}H NMR spectrum:



^{13}C NMR spectrum:

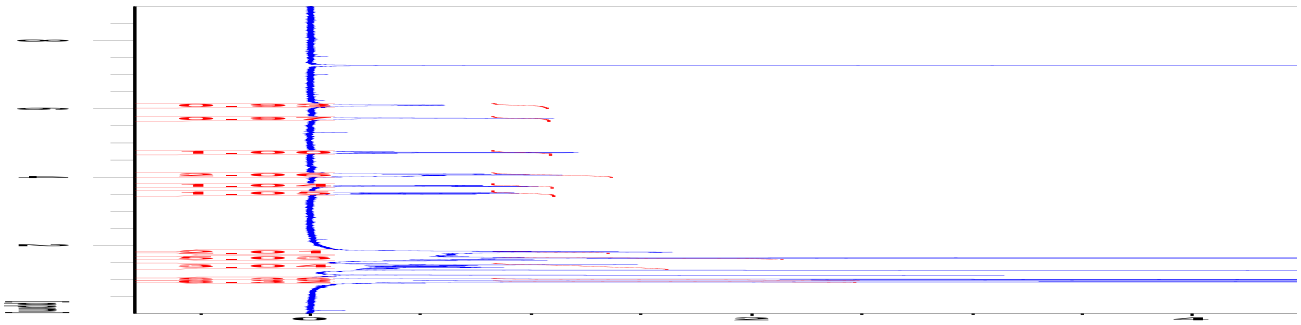


***R*)-*N*-((*S*)-1-Hydroxy-4-methylpentan-2-yl)-2-((*S*)-4-isobutyl-2,5-dioxoimidazolidin-1-yl)propanamide (LDL-17lal)**

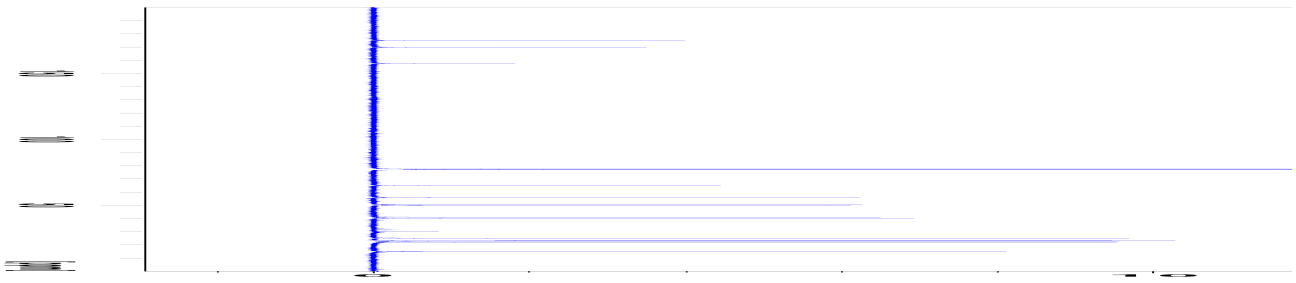


White solid, 63 % yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.10 (br, 1H), 5.72 (br, 1H), 4.72 (q, *J* = 7.3 Hz, 1H), 4.11-3.98 (m, 2H), 3.74 (dd, *J* = 11.3, 3.3 Hz, 1H), 3.52 (dd, *J* = 11.3, 5.5 Hz, 1H), 1.88-1.76 (m, 2H), 1.66-1.58 (m, 5H), 1.49-1.30 (m, 3H), 0.99 (t, *J* = 6.6 Hz, 6H), 0.94 (dd, *J* = 6.6, 2.9 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.0, 169.7, 157.6, 65.0, 55.9, 50.5, 50.0, 41.1, 40.2, 25.2, 25.1, 23.3, 23.2, 22.4, 21.8, 15.0; HRMS (ESI) m/z calcd for $C_{16}H_{29}N_3O_4$ 327.2158; found 328.2228 $(M+H)^+$

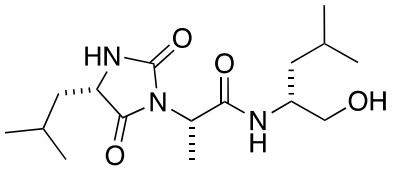
^{1}H NMR spectrum:



^{13}C NMR spectrum:

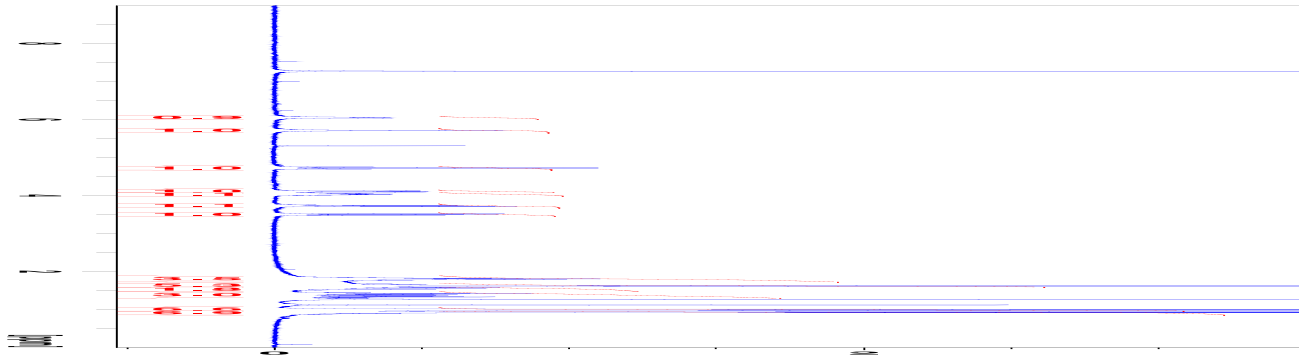


(*S*)-*N*-((*R*)-1-Hydroxy-4-methylpentan-2-yl)-2-((*S*)-4-isobutyl-2,5-dioxoimidazolidin-1-yl)propanamide (LLD-17lal)

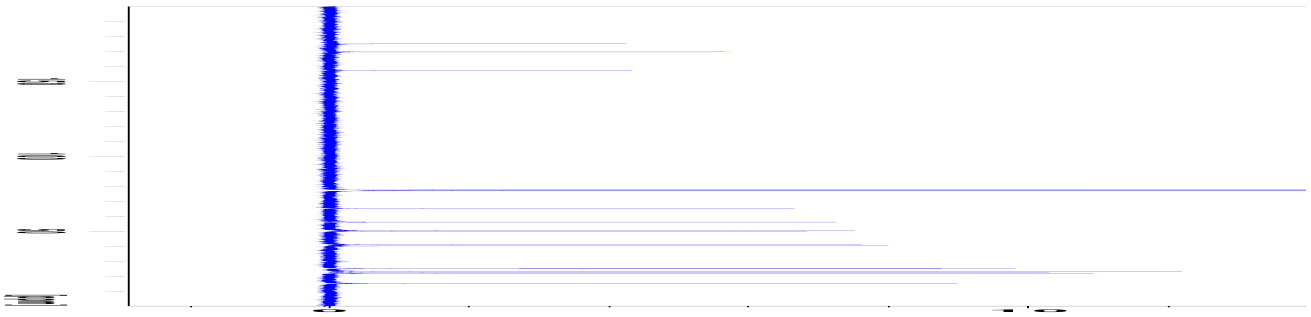


White solid, 58 % yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.05 (br, 1H), 5.71 (br, 1H), 4.73 (q, *J* = 7.3 Hz, 1H), 4.11 (m, 1H), 4.08-3.99 (m, 1H), 3.73 (dd, *J* = 11.2, 3.5 Hz, 1H), 3.52 (dd, *J* = 11.3, 5.5 Hz, 1H), 1.86-1.76 (m, 2H), 1.65-1.53 (m, 5H), 1.47-1.29 (m, 3H), 0.99 (t, *J* = 6.6 Hz, 6H), 0.94 (dd, *J* = 6.6, 3.4 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.1, 169.7, 157.5, 65.1, 56.1, 50.5, 49.9, 41.0, 40.1, 25.1, 25.0, 23.2, 23.1, 22.4, 21.8, 15.2; HRMS (ESI) m/z calcd for $C_{16}H_{29}N_3O_4$ 327.2158; found 328.2276 $(M+H)^+$

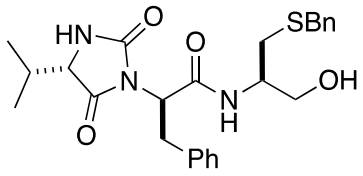
^{1}H NMR spectrum:



^{13}C NMR spectrum:

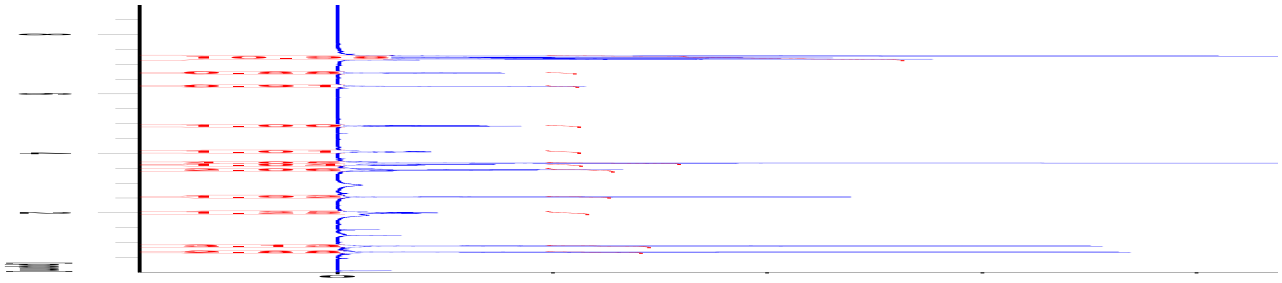


(*R*)-*N*-((*R*)-1-(Benzylthio)-3-hydroxypropan-2-yl)-2-((*S*)-4-isopropyl-2,5-dioxoimidazolidin-1-yl)-3-phenylpropanamide (LDL-17vfc')

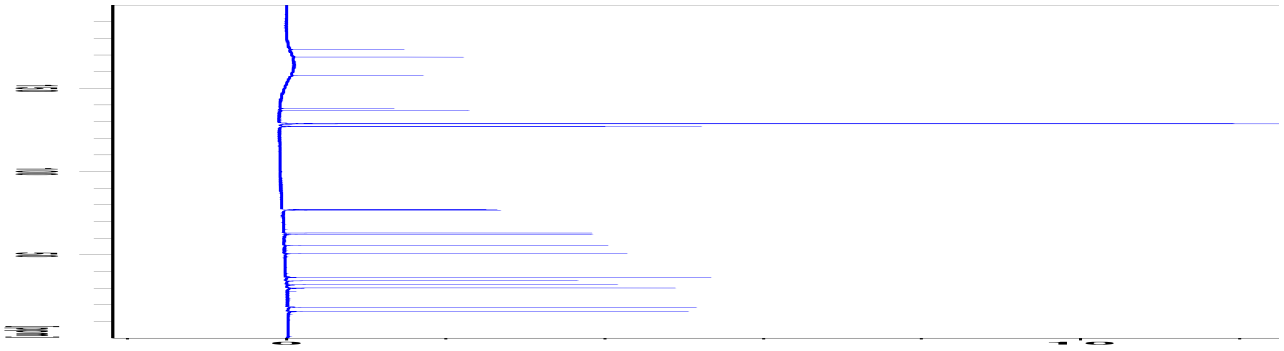


White solid, 85 % yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31-7.13 (m, 10H), 6.70 (d, *J* = 7.9 Hz, 1H), 6.25 (s, 1H), 4.92 (dd, *J* = 10.5, 6.5 Hz, 1H), 4.05 (m, 1H), 3.71-3.64 (m, 4H), 3.64-3.58 (m, 1H), 3.50-3.39 (m, 2H), 2.93 (br, 1H), 2.54 (d, *J* = 6.8 Hz, 2H), 2.05-1.95 (m, 1H), 0.89 (d, *J* = 7.0 Hz, 3H), 0.68 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.2, 168.7, 157.5, 137.8, 136.4, 128.9, 128.9, 128.6, 127.2, 127.0, 63.1, 62.1, 55.5, 50.6, 36.3, 34.4, 32.1, 30.1, 18.6, 16.0; HRMS (ESI) m/z calcd for $C_{25}H_{31}N_3O_4S$ 469.2035; found 470.2146 $(M+H)^+$

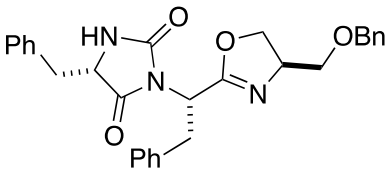
^{1}H NMR spectrum:



^{13}C NMR spectrum:

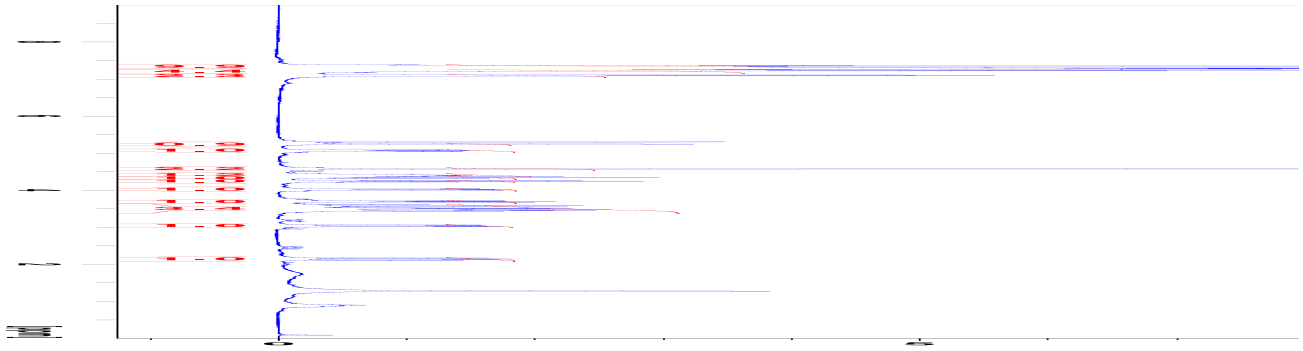


(*S*)-5-Benzyl-3-((*S*)-1-((*R*)-4-((benzyloxy)methyl)-4,5-dihydrooxazol-2-yl)-2-phenylethyl)imidazolidine-2,4-dione (LLD-1ffs')

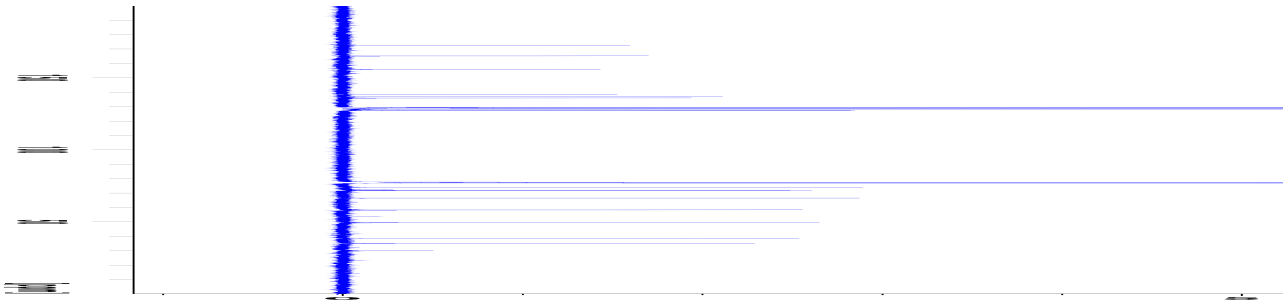


White solid, 45 % yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41-7.15 (m, 13H), 7.10 (m, 2H), 5.24 (br, 1H), 5.07 (dd, *J* = 11.6, 4.6 Hz, 1H), 4.58 (s, 2H), 4.46-4.37 (m, 1H), 4.34 (m, 1H), 4.24 (m, 1H), 4.02 (dd, *J* = 10.5, 3.0 Hz, 1H), 3.70 (dd, *J* = 9.5, 4.1 Hz, 1H), 3.61-3.43 (m, 3H), 3.03 (dd, *J* = 13.9, 3.5 Hz, 1H), 2.14 (dd, *J* = 13.8, 10.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.5, 165.2, 155.8, 138.3, 136.9, 136.0, 129.4, 129.2, 128.7, 128.6, 127.9, 127.9, 127.6, 127.1, 73.7, 72.0, 71.5, 66.5, 58.2, 49.2, 38.4, 34.9; HRMS (ESI) m/z calcd for $C_{29}H_{29}N_3O_4$ 483.2158; found 484.2246 $(M+H)^+$

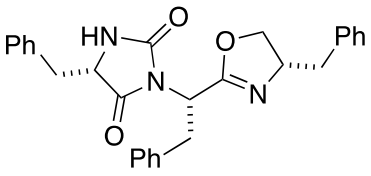
^{1}H NMR spectrum:



^{13}C NMR spectrum:

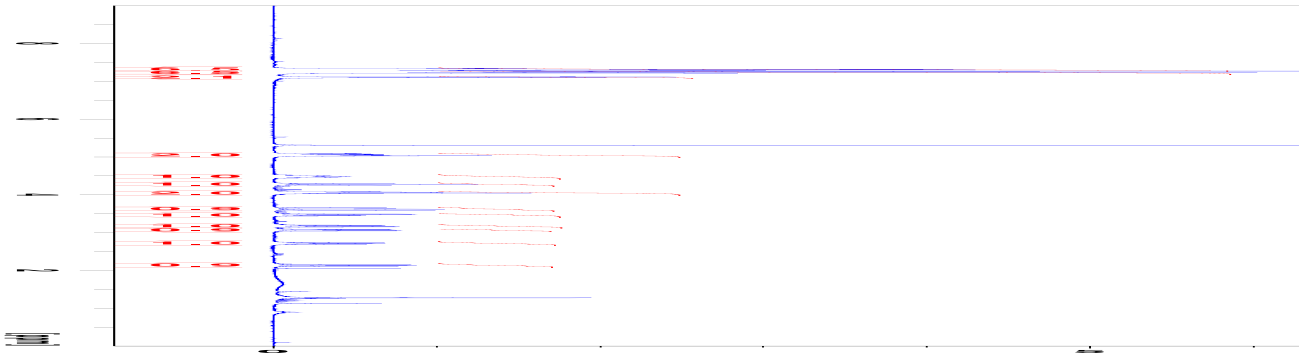


(*S*)-5-Benzyl-3-((*S*)-1-((*S*)-4-benzyl-4,5-dihydrooxazol-2-yl)-2-phenylethyl)imidazolidine-2,4-dione (LLL-1fff)

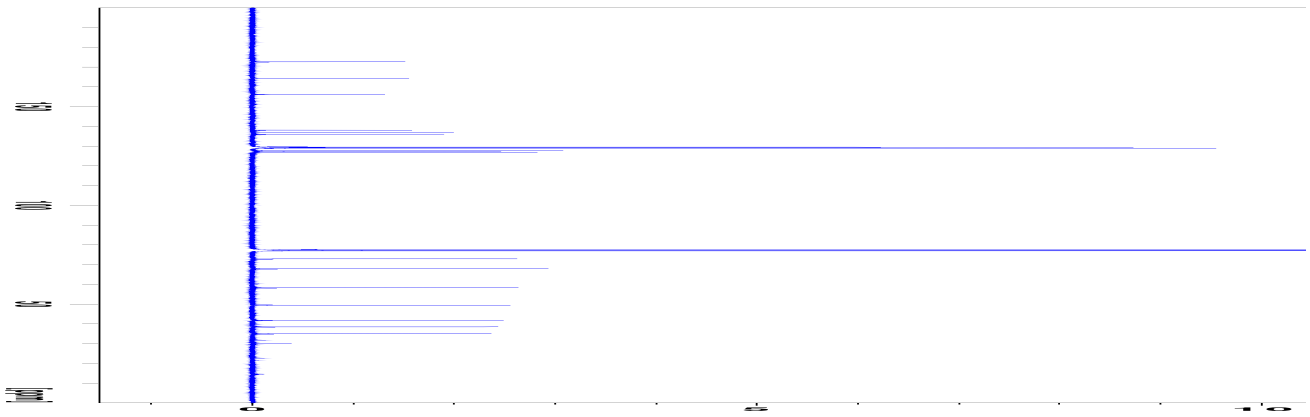


Solid, 39 % yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35-7.20 (m, 13H), 7.11 (m, 2H), 5.07 (m, 1H), 5.03 (br, 1H), 4.48 (m, 1H), 4.28 (t, *J* = 8.9 Hz, 1H), 4.1-4.01 (m, 2H), 3.62 (dd, *J* = 14.1, 11.8 Hz, 1H), 3.47 (dd, *J* = 14.2, 5.2 Hz, 1H), 3.17 (dd, *J* = 13.8, 5.3 Hz, 1H), 3.06 (dd, *J* = 13.8, 3.6 Hz, 1H), 2.71 (dd, *J* = 13.8, 8.6 Hz, 1H), 2.13 (dd, *J* = 13.9, 10.7 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.6, 164.1, 155.9, 138.1, 136.9, 136.0, 129.5, 129.4, 129.2, 128.8, 127.6, 127.2, 126.7, 72.8, 67.9, 58.2, 49.4, 41.8, 38.4, 34.9; HRMS (ESI) m/z calcd for $C_{28}H_{27}N_3O_3$ 453.2052; found 454.2153 $(M+H)^+$

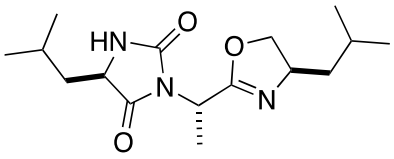
^{1}H NMR spectrum:



^{13}C NMR spectrum:

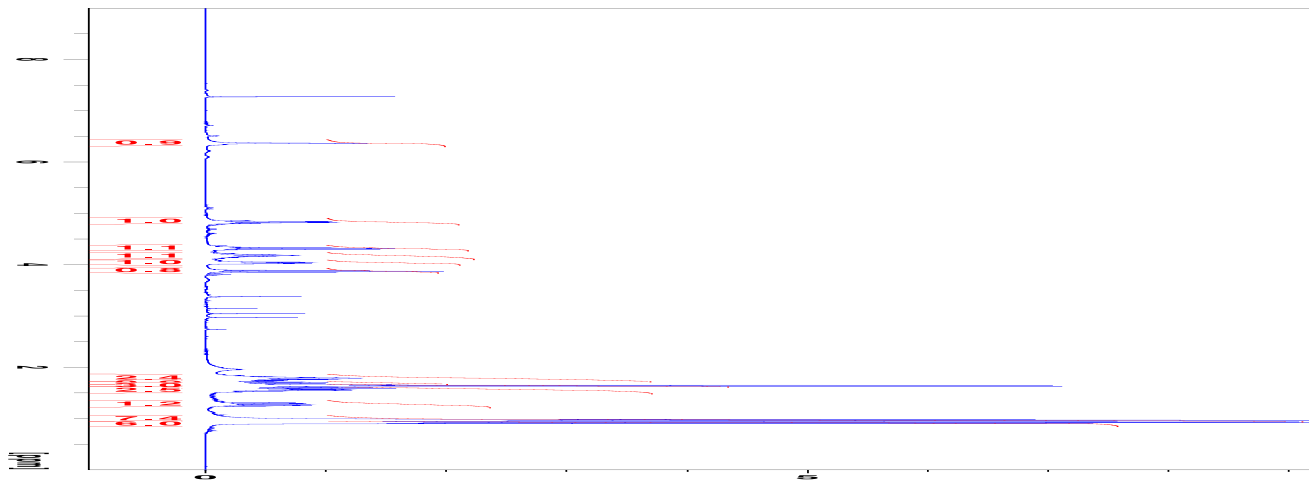


(*R*)-5-Isobutyl-3-((*S*)-1-((*R*)-4-isobutyl-4,5-dihydrooxazol-2-yl)ethyl)imidazolidine-2,4-dione (DLD-1lal)

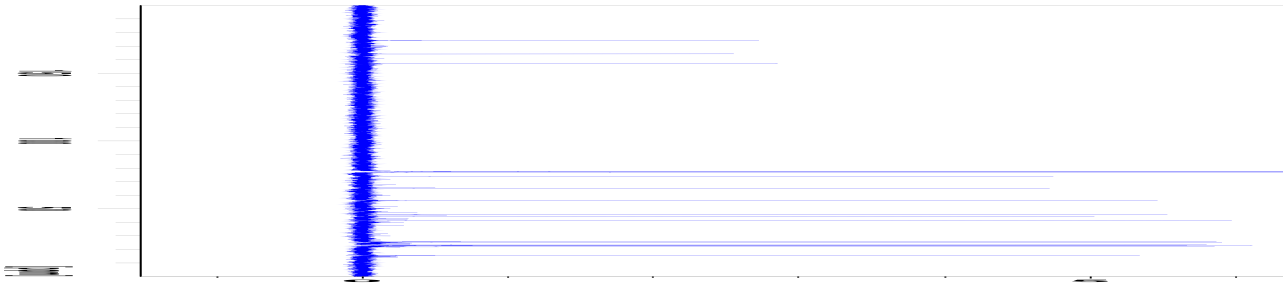


Oil, 41 % yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.36 (br, 1H), 4.82 (m, 1H), 4.31 (m, 1H), 4.18 (m, 1H), 4.04 (m, 1H), 3.87 (t, *J* = 7.6 Hz, 1H), 1.87-1.67 (m, 3H), 1.64 (d, *J* = 7.2 Hz, 3H), 1.62-1.50 (m, 2H), 1.28 (m, 1H), 0.97 (m, 6H), 0.92 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.9, 164.1, 157.0, 73.9, 65.2, 55.8, 45.4, 44.2, 41.0, 25.6, 25.3, 23.3, 23.2, 22.7, 21.8, 15.5; HRMS (ESI) m/z calcd for $C_{16}H_{27}N_3O_3$ 309.2052; found 310.2142 $(M+H)^+$

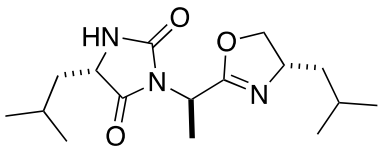
^{1}H NMR spectrum:



^{13}C NMR spectrum:

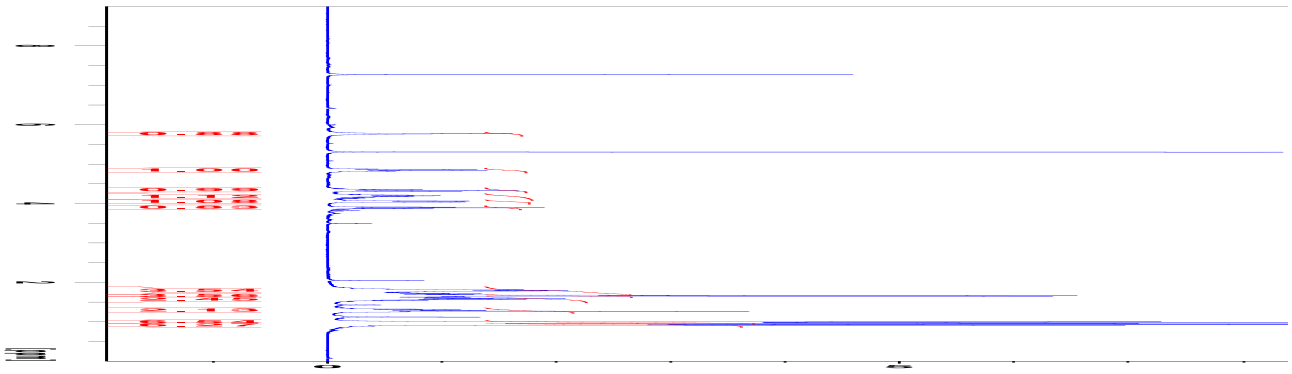


(*S*)-5-Isobutyl-3-((*R*)-1-((*S*)-4-isobutyl-4,5-dihydrooxazol-2-yl)ethyl)imidazolidine-2,4-dione (LDL-1Ial)

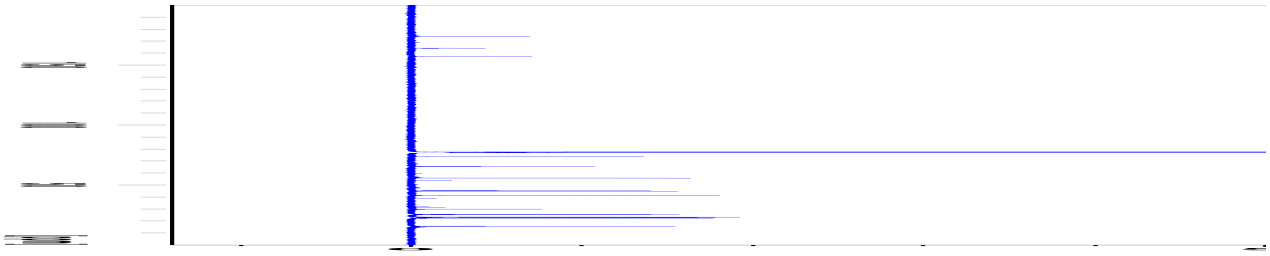


Oil, 40 % yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.77 (s, 1H), 4.85 (q, *J* = 7.1 Hz, 1H) 4.33 (m, 1H), 4.25-4.09 (m, 1H), 4.05 (m, 1H), 3.89 (t, *J* = 7.6 Hz, 1H), 1.85-1.75 (m, 2H), 1.66 (d, *J* = 7.2 Hz, 3H), 1.62-1.53 (m, 2H), 1.35-1.24 (m, 2H), 0.98 (t, *J* = 6.8 Hz, 6H), 0.93 (t, *J* = 6.4 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.8, 164.1, 156.8, 74.0, 65.2, 55.8, 45.5, 44.3, 41.1, 29.9, 25.6, 25.4, 23.3, 22.7, 21.9, 15.6; HRMS (ESI) m/z calcd for $C_{16}H_{27}N_3O_3$ 309.2052; found 310.2140 $(M+H)^+$

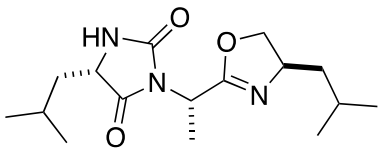
^{1}H NMR spectrum:



^{13}C NMR spectrum:

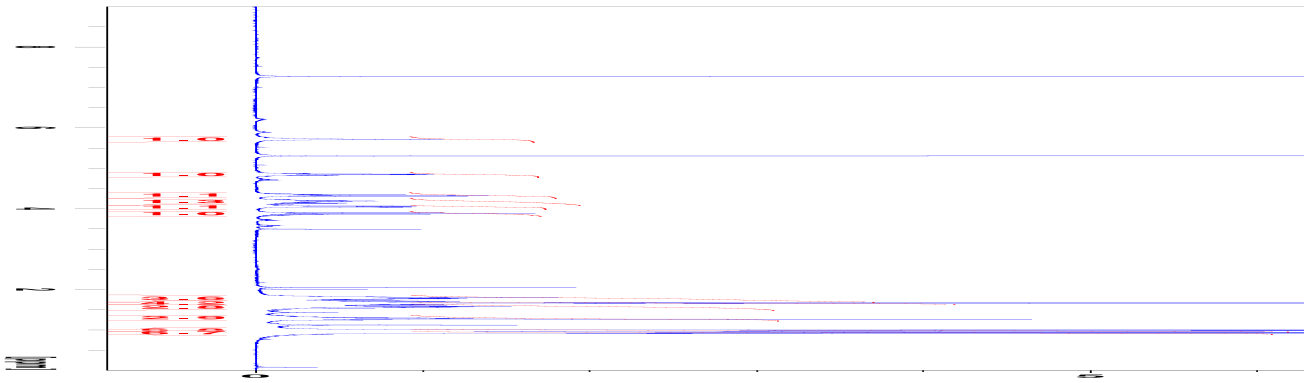


(*S*)-5-Isobutyl-3-((*S*)-1-((*R*)-4-isobutyl-4,5-dihydrooxazol-2-yl)ethyl)imidazolidine-2,4-dione (LLD-1lal)



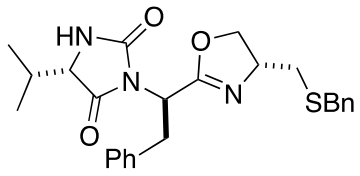
Oil, 39 % yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.71 (br, 1H), 4.84 (m, 1H), 4.38-4.30 (m, 1H), 4.24-4.15 (m, 1H), 4.05 (m, 1H), 3.88 (m, 1H), 1.86-1.76 (m, 2H), 1.67 (d, *J* = 7.2 Hz, 3H), 1.61-1.52 (m, 2H), 1.36-1.22 (m, 2H), 0.98 (m, 6H), 0.93 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.9, 164.1, 156.8, 74.0, 65.2, 55.8, 45.5, 44.3, 41.1, 25.6, 25.3, 23.3, 23.1, 22.8, 21.8, 15.6; HRMS (ESI) m/z calcd for $C_{16}H_{27}N_3O_3$ 309.2052; found 310.2120 $(M+H)^+$

^{1}H NMR spectrum:



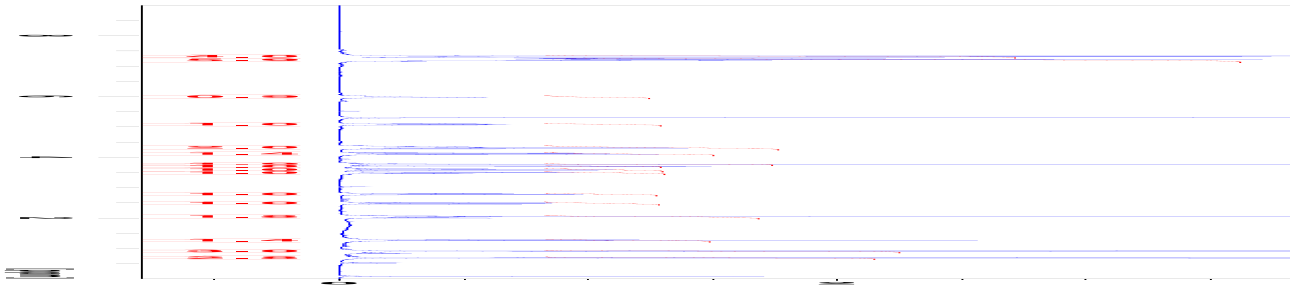
^{13}C NMR spectrum:

(*S*)-3-((*R*)-1-((*R*)-4-((Benzylthio)methyl)-4,5-dihydrooxazol-2-yl)-2-phenylethyl)-5-isopropylimidazolidine-2,4-dione (LDL-1vfc')

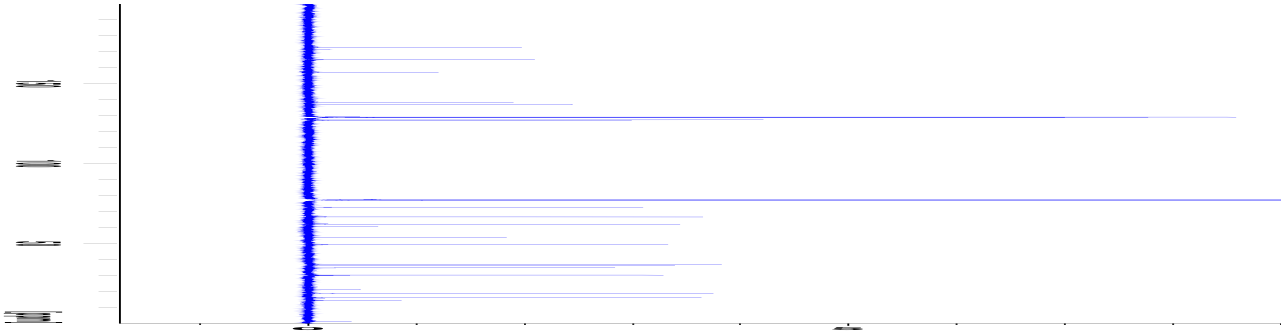


Yellow solid, 49 % yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33-7.13 (m, 10H), 5.97 (br, 1H), 5.09 (m, 1H), 4.39-4.26 (m, 2H), 4.16-4.08 (m, 1H), 3.77 (s, 2H), 3.71 (m, 1H), 3.60 (dd, *J* = 14.5, 11.7 Hz, 1H), 3.49 (dd, *J* = 14.5, 5.1 Hz, 1H), 2.79 (dd, *J* = 13.4, 4.4 Hz, 1H), 2.48 (dd, *J* = 13.4, 7.9 Hz, 1H), 2.10-2.00 (m, 1H), 0.91 (d, *J* = 7.0 Hz, 3H), 0.69 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.8, 165.0, 157.3, 138.5, 136.8, 129.1, 129.0, 128.8, 128.7, 127.3, 127.0, 66.6, 62.1, 53.6, 49.2, 36.9, 36.2, 34.7, 30.3, 18.9, 16.1; HRMS (ESI) m/z calcd for $C_{25}H_{29}N_3O_3S$ 451.1930; found 452.2041 $(M+H)^+$

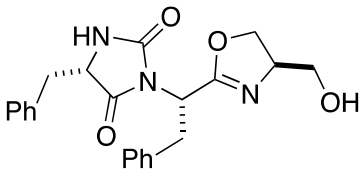
^{1}H NMR spectrum:



^{13}C NMR spectrum:

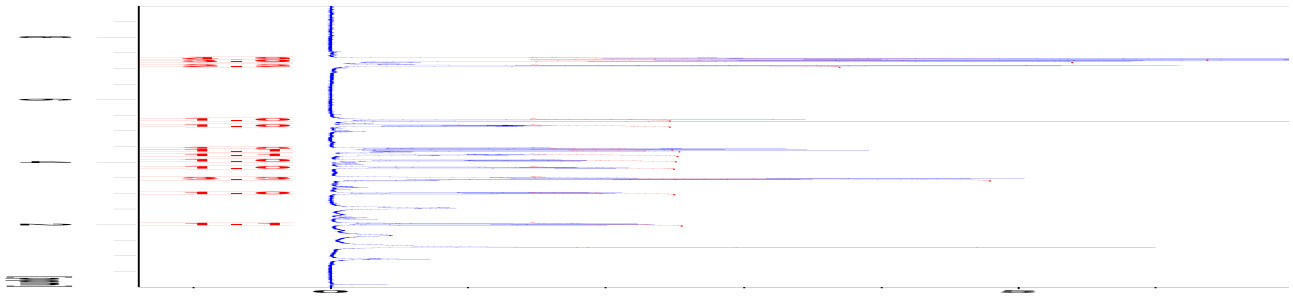


(*S*)-5-Benzyl-3-((*S*)-1-((*R*)-4-(hydroxymethyl)-4,5-dihydrooxazol-2-yl)-2-phenylethyl)imidazolidine-2,4-dione (LLD-1ffs)

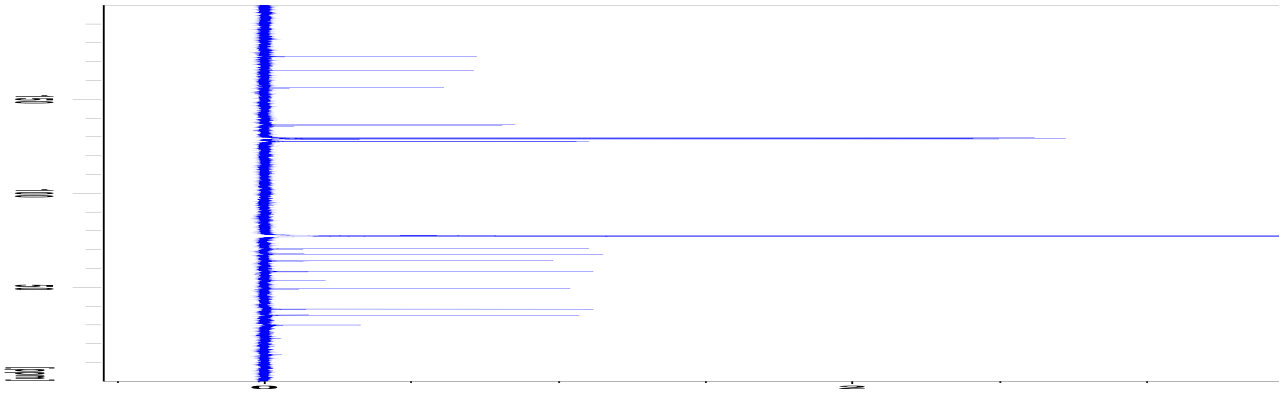


Solid, 89 % yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36-7.22 (m, 8H), 7.09 (m, 2H), 5.36 (s, 1H), 5.16 (m, 1H), 4.44 (m, 1H), 4.40 (m, 1H), 4.27-4.20 (m, 1H), 4.05 (m, 1H), 3.82 (m, 1H), 3.55-3.41 (m, 3H), 3.00 (dd, *J* = 13.8, 3.7 Hz, 1H), 2.54 (m, 1H), 2.01 (dd, *J* = 13.8, 10.9 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.5, 165.4, 156.1, 136.7, 136.0, 129.5, 129.2, 129.1, 128.8, 127.6, 127.3, 70.7, 67.6, 64.1, 58.4, 49.3, 38.4, 35.1; HRMS (ESI) m/z calcd for $C_{22}H_{23}N_3O_4$ 393.1689; found 394.1787 $(M+H)^+$

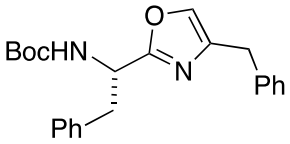
^{1}H NMR spectrum:



^{13}C NMR spectrum:

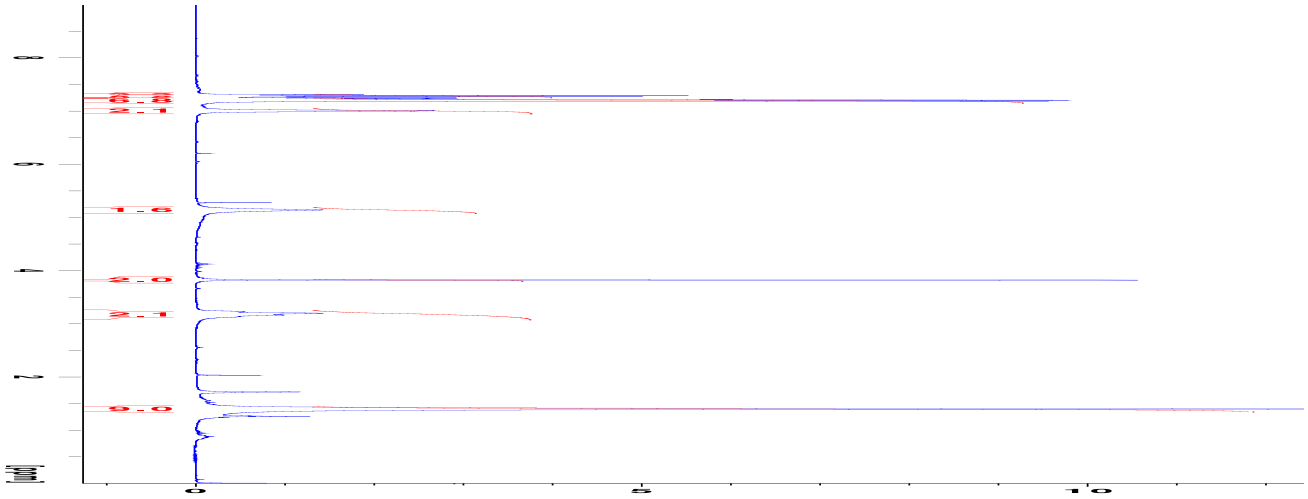


***tert*-Butyl (*S*)-(1-(4-benzyloxazol-2-yl)-2-phenylethyl)carbamate (L-20ff)**

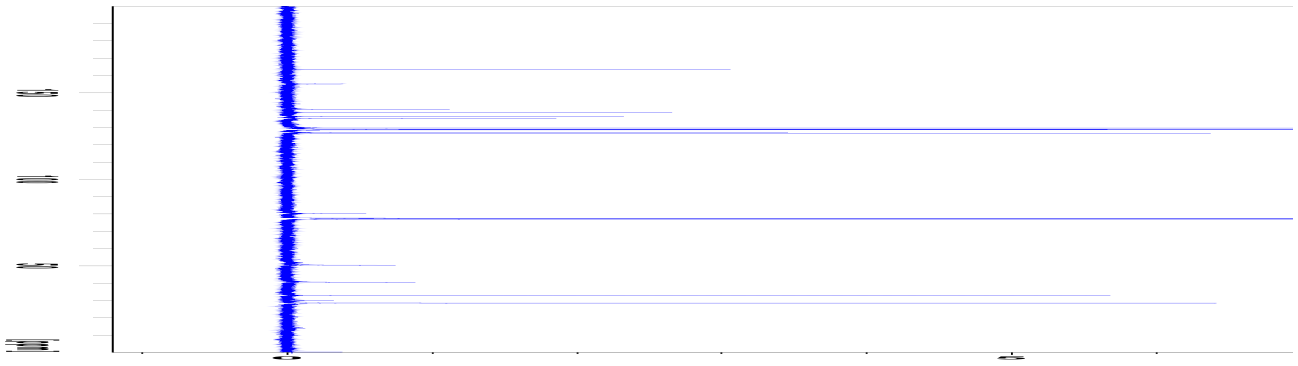


Solid, 40 % yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32-7.17 (m, 10H), 7.01 (m, 2H), 5.14 (br, 1H), 3.82 (s, 2H), 3.25-3.11 (m, 2H), 1.40 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.6, 155.1, 140.5, 138.5, 136.3, 135.1, 129.6, 128.9, 128.7, 128.6, 127.0, 126.7, 80.1, 50.4, 40.5, 32.9, 28.5; HRMS (ESI) m/z calcd for $C_{23}H_{26}N_2O_3$ 378.1943; found 379.1984 $(M+H)^+$

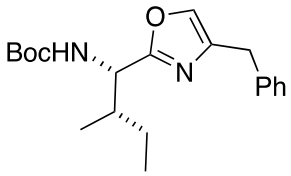
^{1}H NMR spectrum:



^{13}C NMR spectrum:

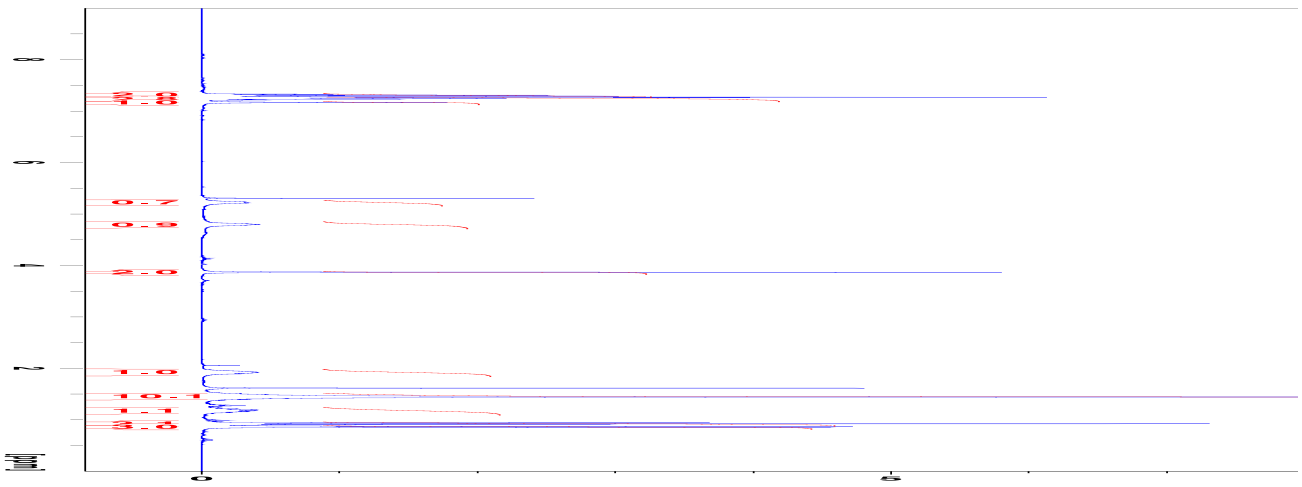


***tert*-Butyl ((1*S*,2*S*)-1-(4-benzyloxazol-2-yl)-2-methylbutyl)carbamate (L-20if)**

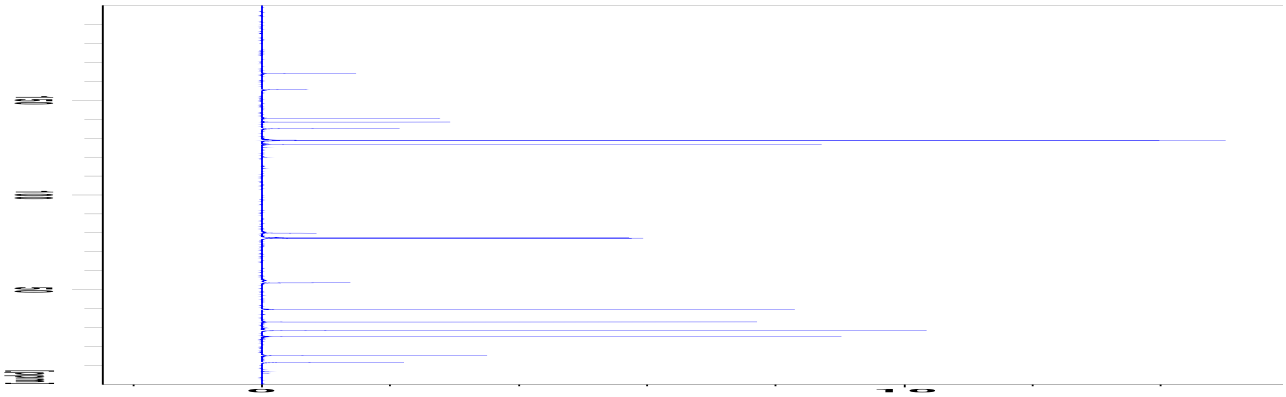


Solid, 37 % yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33-7.21 (m, 5H), 7.17 (s, 1H), 5.22 (m, 1H), 4.80 (m, 1H), 3.87 (s, 2H), 1.90 (m, 1H), 1.52-1.38 (m, 1H), 1.44 (s, 9H), 1.18 (m, 1H), 0.92 (t, *J* = 7.4 Hz, 3H), 0.86 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.0, 155.5, 140.5, 138.4, 134.9, 128.9, 128.6, 126.6, 79.9, 56.6, 39.7, 33.0, 28.5, 25.3, 15.3, 11.6; HRMS (ESI) m/z calcd for $C_{20}H_{28}N_2O_3$ 344.2100; found 345.1980 $(M+H)^+$

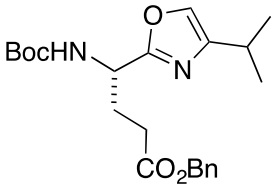
^{1}H NMR spectrum:



^{13}C NMR spectrum:

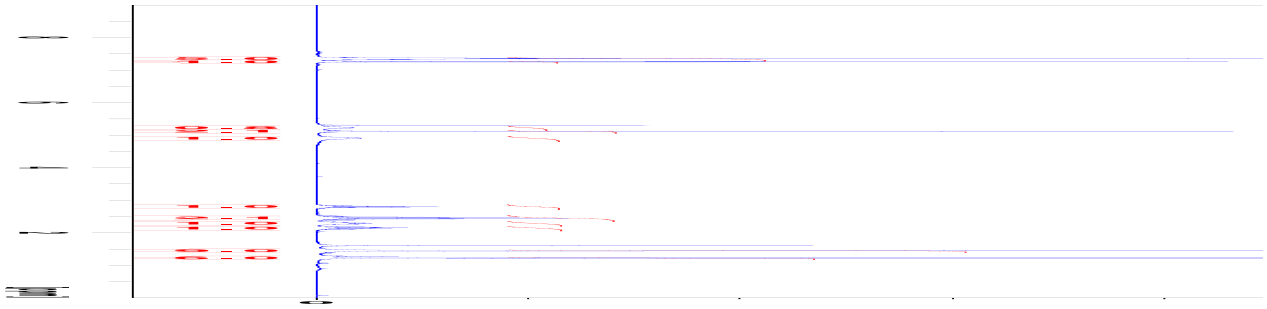


Benzyl (*S*)-4-((*tert*-butoxycarbonyl)amino)-4-(4-isopropyloxazol-2-yl)butanoate (L-20e'v)

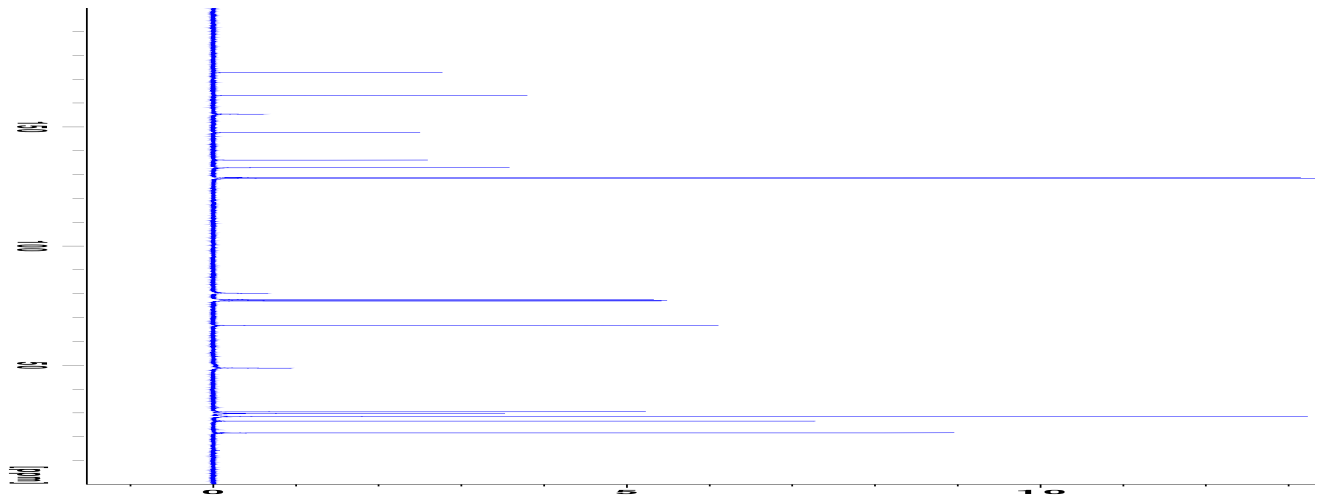


Oil, 57 % yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40-7.30 (m, 5H), 7.25 (d, *J* = 1.2 Hz, 1H), 5.23 (br, 1H), 5.12 (s, 2H), 4.91 (br, 1H), 2.80 (m, 1H), 2.54-2.37 (m, 2H), 2.35-2.22 (m 1H), 2.20-2.07 (m, 1H), 1.45 (s, 9H), 1.22 (d, *J* = 6.9 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.7, 163.0, 155.3, 147.5, 136.0, 132.8, 128.7, 128.4, 80.1, 66.6, 48.7, 30.4, 29.6, 28.5, 26.5, 21.6, 21.5; HRMS (ESI) m/z calcd for $C_{22}H_{30}N_2O_5$ 402.2155; found 403.2164 $(M+H)^+$

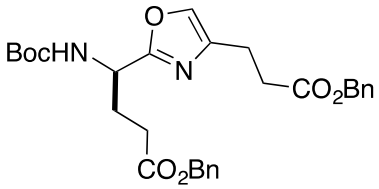
^{1}H NMR spectrum:



^{13}C NMR spectrum:

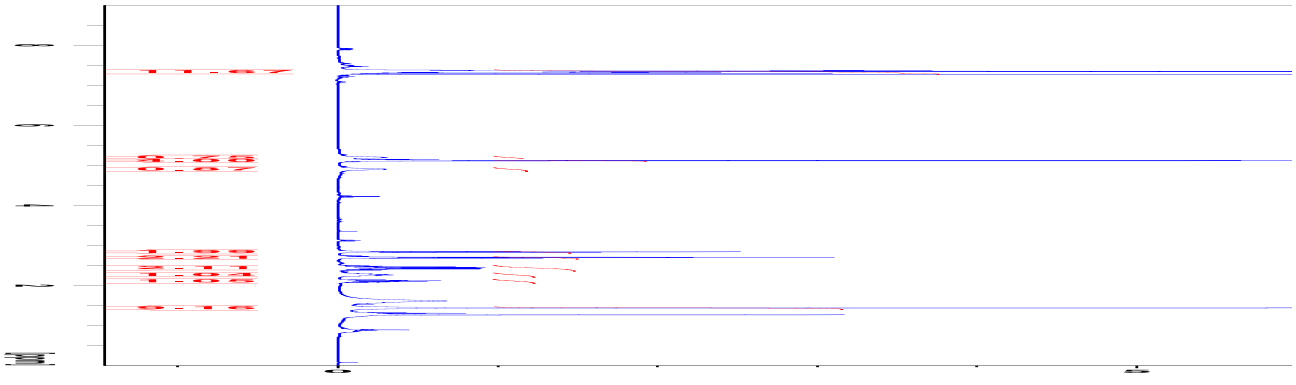

0
5
10

Benzyl (*R*)-4-(4-(3-(benzyloxy)-3-oxopropyl)oxazol-2-yl)-4-((*tert*-butoxycarbonyl)amino)butanoate (D-20e'e')

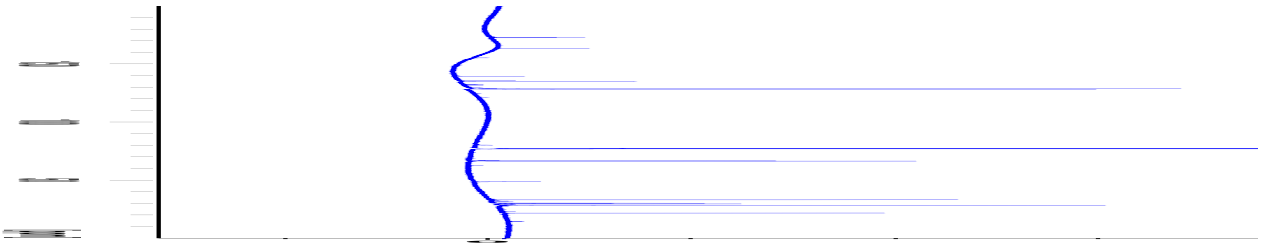


Oil, 39 % yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39-7.28 (m, 11H), 5.20 (br, 1H), 5.12 (m, 4H), 4.91 (br, 1H), 2.84 (m, 2H), 2.70 (m, 2H), 2.51-2.37 (m, 2H), 2.32-2.22 (m, 1H), 2.17-2.05 (m, 1H), 1.44 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.5, 172.4, 163.2, 155.2, 139.2, 135.9, 135.8, 134.6, 128.6, 128.3, 128.2, 128.2, 80.2, 66.5, 66.4, 48.5, 32.9, 30.2, 29.7, 29.4, 28.3, 21.6; HRMS (ESI) m/z calcd for $C_{29}H_{34}N_2O_7$ 522.2366; found 523.2589 $(M+H)^+$

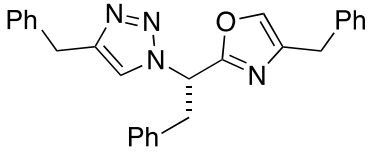
^{1}H NMR spectrum:



^{13}C NMR spectrum:

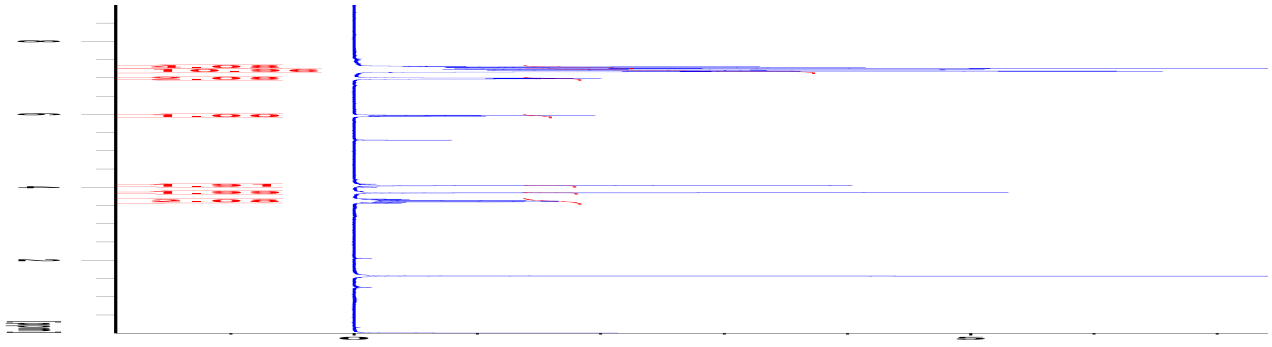


(*S*)-4-Benzyl-2-(1-(4-benzyl-1*H*-1,2,3-triazol-1-yl)-2-phenylethyl)oxazole (L-2fff)

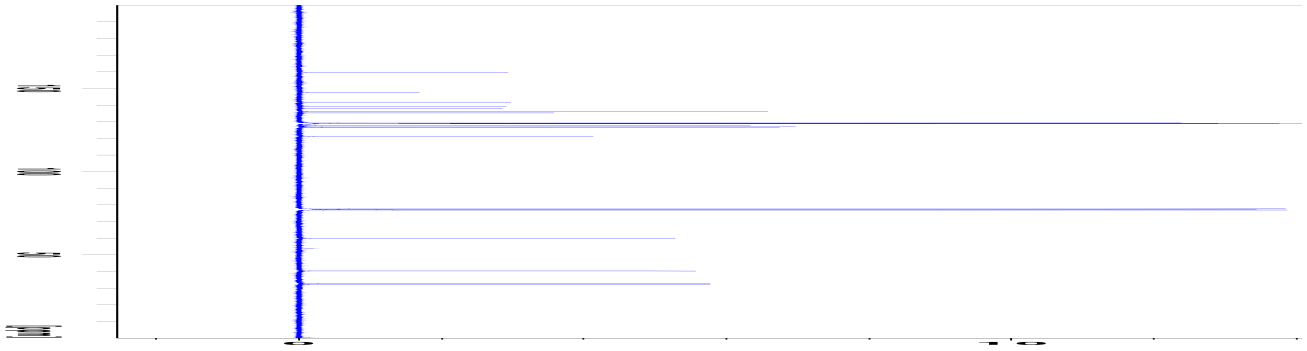


Solid, 40 % yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33-7.15 (m, 15H), 6.99 (m, 2H), 5.96 (t, *J* = 7.8 Hz, 1H), 4.04 (s, 2H), 3.85 (s, 2H), 3.62 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.6, 147.7, 141.3, 139.1, 138.1, 136.2, 135.2, 129.2, 128.9, 128.8, 128.8, 128.8, 128.7, 127.5, 126.8, 126.6, 121.2, 59.8, 40.3, 32.9, 32.4; HRMS (ESI) m/z calcd for $C_{27}H_{24}N_4O$ 420.1950; found 421.1885 $(M+H)^+$

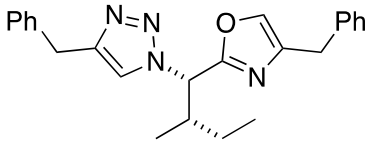
^{1}H NMR spectrum:



^{13}C NMR spectrum:

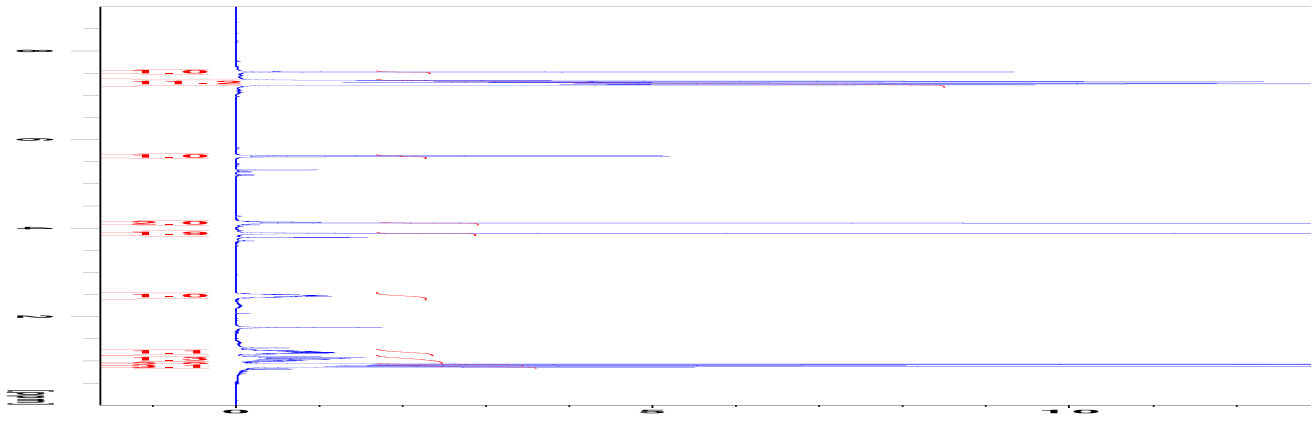


4-Benzyl-2-((1*S*,2*S*)-1-(4-benzyl-1*H*-1,2,3-triazol-1-yl)-2-methylbutyl)oxazole (L-2fif)

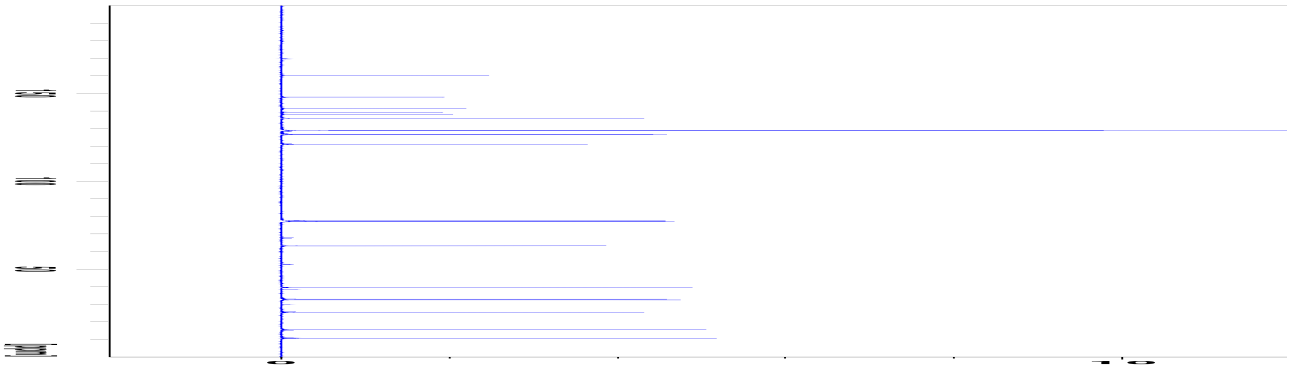


Solid, 37 % yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 (s, 1H), 7.35-7.22 (m, 11H), 5.62 (d, *J* = 10.2 Hz, 1H), 4.11 (s, 2H), 3.88 (s, 2H), 2.53-2.41 (m, 1H), 1.26-1.14 (m, 1H), 1.12-0.97 (m, 1H), 0.92 (d, *J* = 6.7 Hz, 3H), 0.88 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.1, 147.9, 141.3, 139.1, 138.0, 135.8, 128.9, 128.8, 128.7, 126.8, 126.6, 120.8, 63.2, 39.6, 32.9, 32.4, 25.3, 15.6, 10.5; HRMS (ESI) m/z calcd for $C_{24}H_{26}N_4O$ 386.2107; found 387.2030 $(M+H)^+$

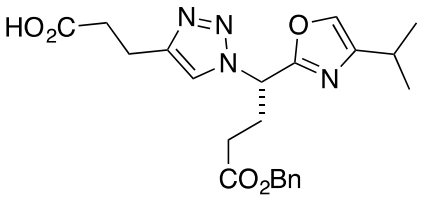
^{1}H NMR spectrum:



^{13}C NMR spectrum:

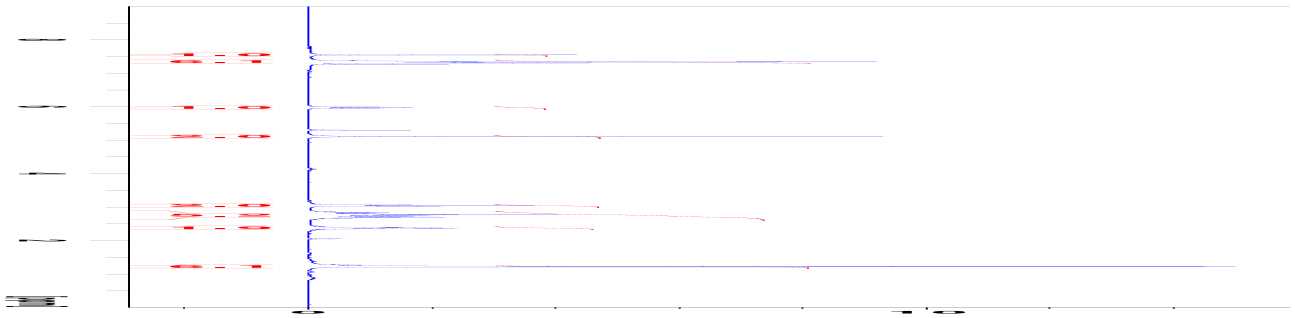


(*S*)-3-(1-(4-(Benzyloxy)-1-(4-isopropyloxazol-2-yl)-4-oxobutyl)-1*H*-1,2,3-triazol-4-yl)propanoic acid (L-2ee'v)

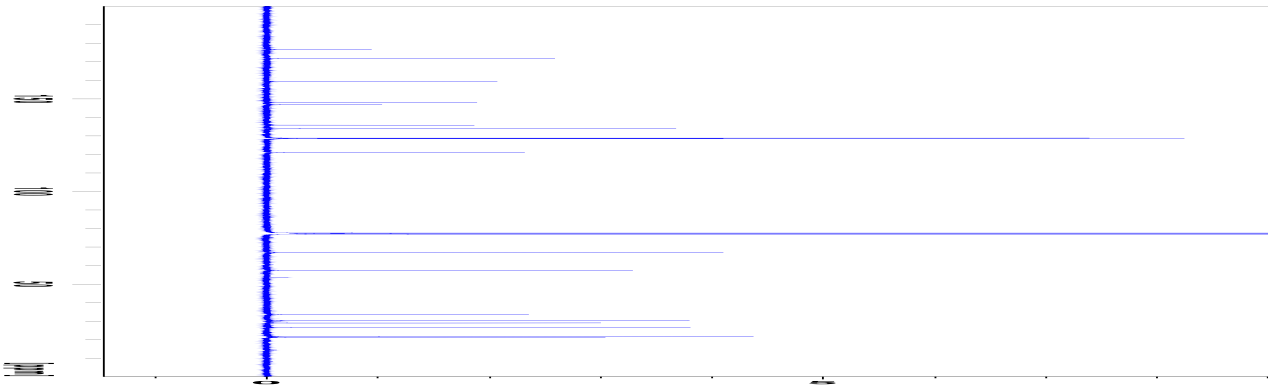


White solid, 64 % yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55 (s, 1H), 7.39-7.29 (m, 6H), 5.967 (t, *J* = 7.8 Hz, 1H), 5.11 (s, 2H), 3.04 (t, *J* = 7.2 Hz, 2H), 2.87-2.66 (m, 5H), 2.37 (m, 2H), 1.22 (d, *J* = 6.8 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.6, 171.9, 159.2, 148.2, 146.9, 135.8, 134.1, 128.8, 128.6, 128.5, 121.0, 66.9, 57.4, 33.5, 30.2, 29.0, 26.5, 21.5, 21.5, 21.0; HRMS (ESI) m/z calcd for $C_{22}H_{26}N_4O_5$ 426.1903; found 449.1795 $(M+Na)^+$

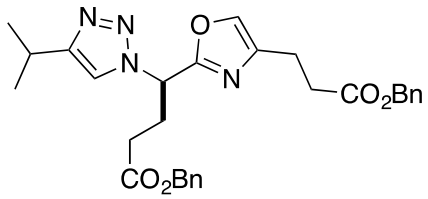
^{1}H NMR spectrum:



^{13}C NMR spectrum:

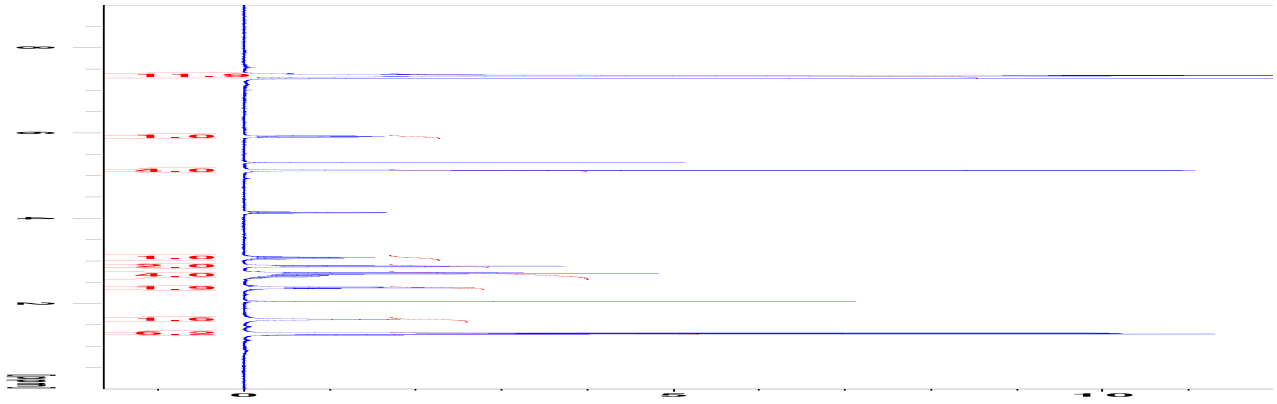


Benzyl (*R*)-4-(4-(3-(benzyloxy)-3-oxopropyl)oxazol-2-yl)-4-(4-isopropyl-1*H*-1,2,3-triazol-1-yl)butanoate (L-2ve'e')

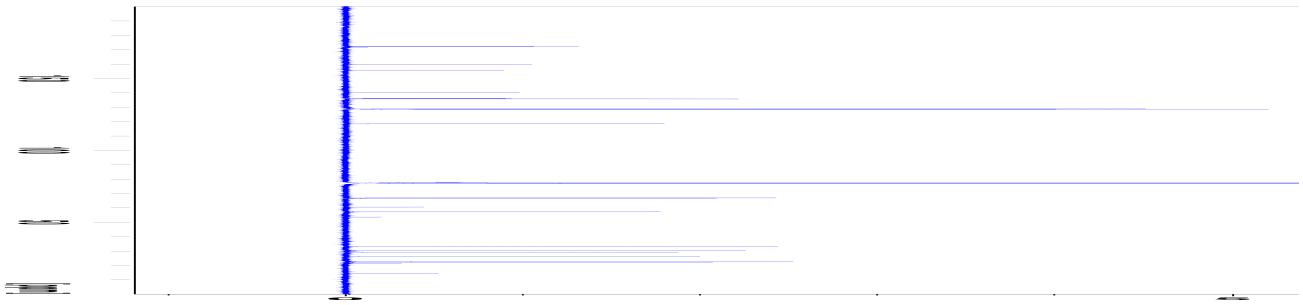


White solid, 61 % yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40-7.30 (m, 12H), 5.91 (dd, *J* = 8.8, 6.8 Hz, 1H), 5.13 (s, 2H), 5.12 (s, 2H), 3.07 (m, 1H), 2.88 (t, *J* = 7.3 Hz, 2H), 2.71 (t, *J* = 7.6 Hz, 2H**),** 2.68-2.58 (m, 2H), 2.40-2.33 (m, 2H), 1.31 (d, *J* = 2.9 Hz, 3H), 1.29 (d, *J* = 2.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.5, 171.9, 159.6, 155.3, 140.1, 136.1, 135.8, 135.7, 128.8, 128.8, 128.6, 128.5, 128.4, 118.4, 66.9, 66.6, 57.2, 33.0, 30.2, 29.1, 26.1, 22.6, 22.6, 21.8; HRMS (ESI) m/z calcd for $C_{29}H_{32}N_4O_5$ 516.2373; found 517.2419 $(M+H)^+$

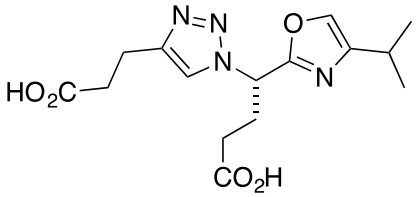
^{1}H NMR spectrum:



^{13}C NMR spectrum:

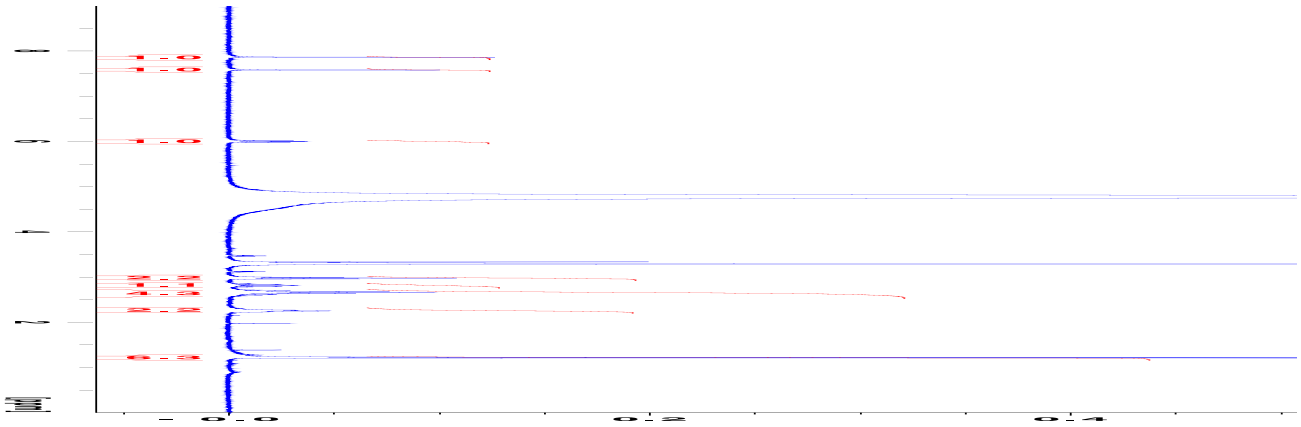


(*S*)-4-(4-(2-Carboxyethyl)-1*H*-1,2,3-triazol-1-yl)-4-(4-isopropyloxazol-2-yl)butanoic acid (L-2eev)

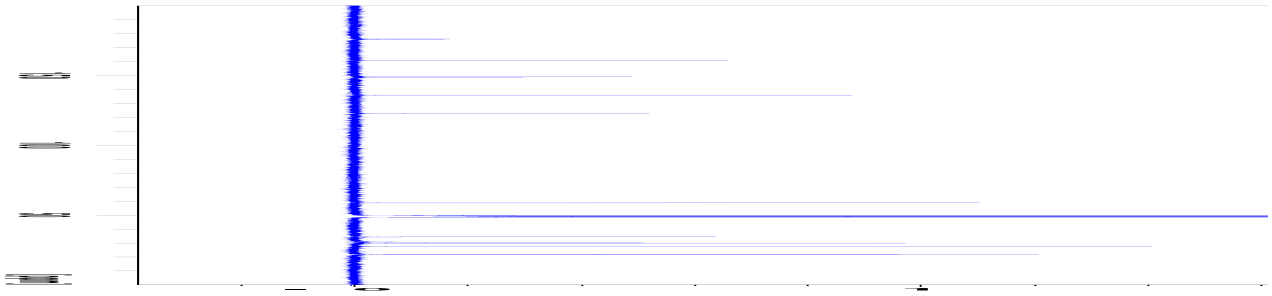


Colorless oil, 100 % yield. ^{1}H NMR (400 MHz, MeOD) δ 7.86 (s, 1H), 7.58 (s, 1H), 6.00 (dd, *J* = 8.9, 6.7 Hz, 1H), 2.98 (t, *J* = 7.4 Hz, 2H), 2.81 (m, 1H), 2.73-2.56 (m, 4H), 2.26 (m, 2H), 1.22 (d, *J* = 6.92 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.2, 175.6, 161.0, 149.1, 148.4, 135.8, 122.8, 58.7, 34.3, 30.6, 29.5, 27.5, 21.9, 21.8, 21.7; HRMS (ESI) m/z calcd for $C_{15}H_{20}N_4O_5$ 336.1434; found 359.1319 $(M+Na)^+$

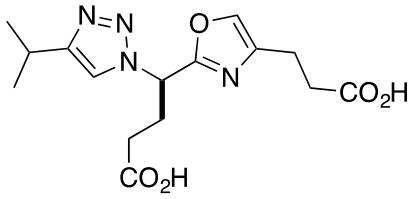
^{1}H NMR spectrum:



^{13}C NMR spectrum:

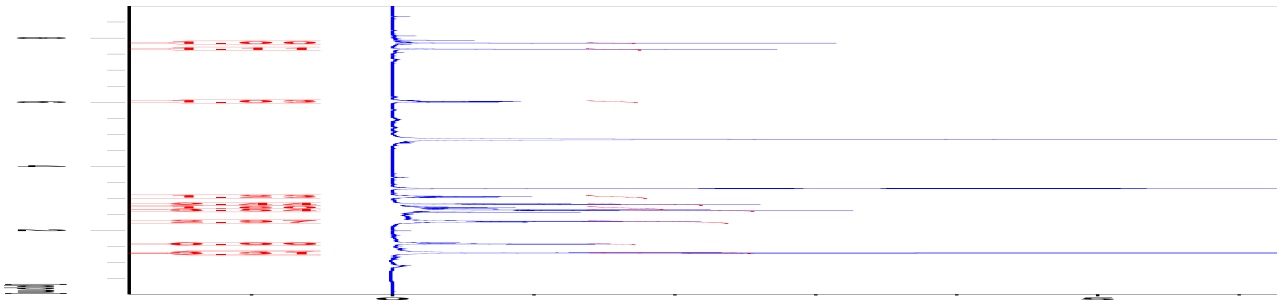


(*R*)-4-(4-(2-Carboxyethyl)oxazol-2-yl)-4-(4-isopropyl-1*H*-1,2,3-triazol-1-yl)butanoic acid (D-2vee)

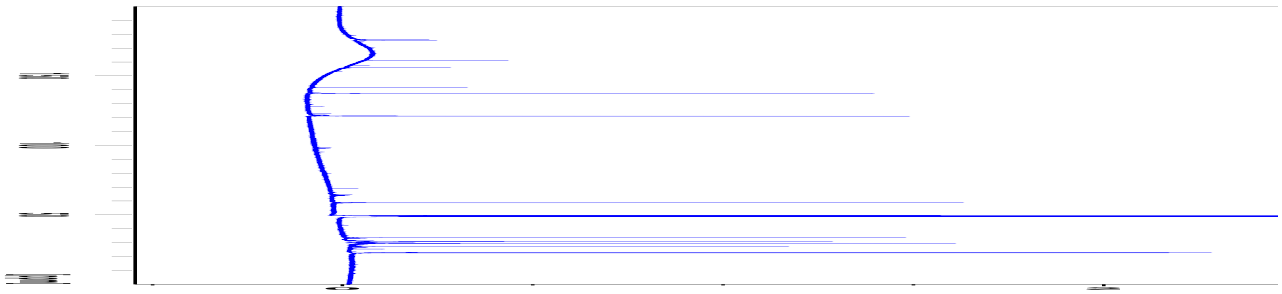


Colorless oil, 100 % yield. ^{1}H NMR (400 MHz, MeOD) δ 7.84 (s, 1H), 7.65 (s, 1H), 6.01 (dd, *J* = 9.0, 6.6 Hz, 1H), 3.04 (m, 1H), 2.81 (t, *J* = 7.4 Hz, 2H), 2.75-2.65 (m, 2H), 2.65-2.59 (m, 3H), 2.32-2.22 (m, 3H), 1.29 (m, 3H), 1.28 (m, 3H); ^{13}C NMR (100 MHz, MeOD) δ 176.3, 175.6, 161.2, 156.0, 141.6, 137.4, 121.0, 58.6, 33.6, 30.7, 29.5, 27.0, 22.8, 22.7, 22.5; HRMS (ESI) m/z calcd for $C_{15}H_{20}N_4O_5$ 336.1434; found 337.1532 $(M+H)^+$

^{1}H NMR spectrum:



^{13}C NMR spectrum:



E. References

1. D. Xin, E. Ko, L. M. Perez, T. R. Ioerger and K. Burgess, *Org. Biomol. Chem.*, 2013, **11**, 7789-7801.
2. D. Xin, L. M. Perez, T. R. Ioerger and K. Burgess, *Angew. Chem. Int. Ed.* , 2014, **53**, 3594-3598.
3. E. Ko, A. Raghuraman, L. M. Perez, T. R. Ioerger and K. Burgess, *J. Am. Chem. Soc.*, 2013, **135**, 167-173.
4. D. Xin, A. Holzenburg and K. Burgess, *Chem. Sci.*, 2014, **5**, 4914-4921.
5. J. Taechalertpaisarn, B. Zhao, X. Liang and K. Burgess, *J. Am. Chem. Soc.*, 2018, **140**, 3242-3249.
6. J.-I. Yamaguchi, M. Harada, T. Kondo, T. Noda and T. Suyama, *Chem. Lett.*, 2003, **32**, 372-373.
7. D. Zhang, X. Xing and G. D. Cuny, *J. Org. Chem.*, 2006, **71**, 1750-1753.
8. T. Fukuyama and H. Tokuyama, *Aldrichimica Acta*, 2004, **37**, 87-96.
9. T. Morwick, M. Hrapchak, M. DeTuri and S. Campbell, *Org. Lett.*, 2002, **4**, 2665-2668.
10. P. B. Alper, S.-C. Hung and C.-H. Wong, *Tetrahedron Lett.*, 1996, **37**, 6029-6032.
11. H. C. Kolb, M. G. Finn and K. B. Sharpless, *Angew. Chem. Int. Ed.*, 2001, **40**, 2004-2021.