Supplementary Information

1. Experimental Section

4-Methoxybenzonitrile 7

Compound 7 was synthesized according to a process previously described\(^1\) but in a multimolar scale. In a 10 L round bottom flask fitted with an efficient condenser were placed \(p\)-anisaldehyde 6 (544 g, 4 mol), hydroxylamine-HCl (345 g, 5 mol) and pyridine (400 mL, 5 mol) (exothermic). The flask was left to cool to rt and formic acid (800 mL) was added with cooling. Boiling stones were added and the flask was carefully heated until an exothermic reaction began (ca. 80 °C) and heating was immediately stopped. CAUTION: the reaction is very exothermic at this point and the solvents can be projected out of the flask if the condenser is not efficient enough or the flask is too small. After 1 h the reaction was over as indicated by a drop in temperature to 40 °C. The reaction mixture was poured on crushed ice (2 kg). The precipitated solid was filtered, washed with water and recrystallized in boiling MeOH. The product 7 was filtered on Büchner and dried in vacuo to constant weight. The title compound (450 g, 85%) was obtained as colourless needles. Mp 57-59 °C (lit.\(^2\) 59 °C, MeOH); \(^1\)H NMR (250 MHz, CDCl\(_3\)) \(\delta\) 7.70 – 7.53 (m, 2H, Ar-H), 7.08 – 6.85 (m, 2H, Ar-H), 3.89 (s, 3H, OCH\(_3\)); \(^1\)C NMR (63 MHz, CDCl\(_3\)) \(\delta\) 169.94 (CN), 165.25 (Ar-C), 131.84 (Ar-C), 116.69 (Ar-C), 114.32 (Ar-C), 70.42 (CH\(_3\)).

Ethyl 4-methoxybenzimidate hydrochloride 8

A solution of compound 7 (266 g, 2 mol) in dry EtOH (600 mL), under nitrogen and protected from moisture, was cooled to 0 °C. Through a pressure equalized addition funnel, AcCl (300 mL, 4.2 mol) was added dropwise followed by dry Et\(_2\)O (1 L). The solution was kept in a closed flask at 2 °C for one month. The product was filtered, washed with Et\(_2\)O and dried in vacuo to constant weight to give the title compound (230 g, 53%) as colourless crystals. Mp 115 – 116 °C (dec.) (lit.\(^3\) 132 - 134 °C; \(^1\)H NMR (250 MHz, CDCl\(_3\)) \(\delta\) 12.18 (s, 1H, NH\(_2\)). 11.51 (s, 1H, NH\(_2\)); 8.38 (d, \(J = 9.0\) Hz, 2H, Ar-H), 7.01 (d, \(J = 9.0\) Hz, 2H, Ar-H), 4.88 (q, \(J = 7.0\) Hz, 2H, CH\(_2\)), 3.87 (s, 3H, OCH\(_3\)), 1.58 (t, \(J = 7.0\) Hz, 3H, CH\(_3\)); \(^1\)C NMR (63 MHz, CDCl\(_3\)) \(\delta\) 169.94 (CN), 165.25 (Ar-C), 131.84 (Ar-C), 116.69 (Ar-C), 114.32 (Ar-C), 70.42 (CH\(_2\)), 55.53 (OCH\(_3\)), 13.62 (CH\(_3\)); \(m/z\) (ESI) 180 [MH\(^+\)].

Methyl 2-(4-methoxyphenyl)-oxazoline-4-carboxylate 9

Compound 9 was synthesized according to a process previously described for an analogous oxazoline.\(^9\) The free base of 8 (179 g, 1 mol), generated from the salt by basification with saturated aqueous Na\(_2\)CO\(_3\) and extraction in CH\(_2\)Cl\(_2\), was dissolved in MeOH (1 L). To this solution was added serine methyl ester.HCl (155 g, 1 mol). After heating under reflux for 2 h, the suspension was cooled and diluted with acetone (1 L). The precipitated NH\(_4\)Cl was filtered and washed with acetone. The solvents were evaporated, the residue was dissolved in CH\(_2\)Cl\(_2\) (500 mL) and filtered. The solvent was removed in vacuo and the product recrystallized in aqueous MeOH to give the title compound (160 g, 68%) as a colourless powder. Mp 119 – 121 °C (lit.\(^4\) 115 - 119 °C); \(^1\)H NMR (250 MHz, CDCl\(_3\)) \(\delta\) 7.98 – 7.78 (m, 2H, Ar-H), 6.98 – 6.79 (m, 2H, Ar-H), 4.90 (dd, \(J = 10.5, 7.8\) Hz, 1H, H-\(\alpha\)), 4.63 (dd, \(J = 8.7, 7.8\) Hz, 1H, CH\(_3\)), 4.53 (dd, \(J = 10.5, 8.7\) Hz, 1H, CH\(_3\)); 3.81 (s, 3H, ArOCH\(_3\)), 3.78 (s, 3H, OCH\(_3\)); \(^1\)C NMR (63 MHz, CDCl\(_3\)) \(\delta\) 171.88 (CO), 166.14 (CN), 163.92 (CO), 130.45 (Ar-C), 119.44 (Ar-C), 113.77 (Ar-C), 69.50 (C-\(\beta\)), 68.62 (C-\(\alpha\)), 55.42 (ArOCH\(_3\)), 52.72 (OCH\(_3\)); \(m/z\) (ESI) 236 [MH\(^+\)].

Sodium 2-(4-methoxyphenyl)-oxazoline-4-carboxylate 10

The synthesis was realized by slightly modifying the protocol described by Fry for an analogous derivative.\(^5\) To a suspension of the methyl ester 9 (141 g, 600 mmol) in MeOH (500 mL), cooled to 0 °C, was added a cold solution of NaOH (26.4 g, 660 mmol) in water (220 mL). The mixture was stirred vigorously for 1 h. The suspension was diluted with acetone (500 mL) and left at 2 °C for 2 h. The product was filtered on Büchner and washed with acetone (1 L) then dried in vacuo to constant weight. The title compound (167 g, 99%) was obtained as rose crystals. Mp 220 °C; \(^1\)H NMR (250 MHz, MeOD) \(\delta\) 7.97 – 7.82 (m, 2H, Ar-H), 7.02 – 6.89 (m, 2H, Ar-H), 4.72 (dd, \(J = 10.3, 8.2\) Hz, 1H, H-\(\alpha\)), 4.62 (dd, \(J = 10.3, 7.7\) Hz, 1H, CH\(_3\O\)), 4.49 (dd, \(J = 8.2, 7.7\) Hz, 1H, CH\(_3\O\)); \(^1\)C NMR (63 MHz, MeOD) \(\delta\) 179.08 (CO), 166.66 (CN), 163.92 (Ar-C), 131.26 (Ar-C), 121.00 (Ar-C), 114.71 (Ar-C), 72.50 (C-\(\beta\)), 71.86 (C-\(\alpha\)), 55.89 (OCH\(_3\)); \(m/z\) (ESI) 220 [M\(^+\)].

2-(4-Methoxyphenyl)-oxazoline-4-carboxylic acid 11
The synthesis was realized by slightly modifying the protocol described by Fry for an analogous derivative. The sodium salt 10 (167 g, 598 mmol) was suspended in water (500 mL) and this was cooled to 0 °C. A 30% aqueous formic acid solution (100 mL, 660 mmol) cooled to 0 °C was added dropwise to precipitate acid 11. The product was filtered on Büchner and washed with cold water (500 mL), then dried by repeated suspension in CH₂CN and evaporation in vacuo to constant weight. The title compound (113 g, 85%) was obtained as rose crystals that were pure enough for the next step. Mp 142 °C (dec.); m/z (ESI) 220 [M].

(R)-tert-Butyl 4-(4-bromobenzyl)-2-(4-methoxyphenyl)-oxazoline-4-carboxylate 20
Phenyloxazoline 12 (2.77 g, 10 mmol) was dissolved in toluene (100 mL), p-Bromo benzyl bromide (3.75 g, 15 mmol) and (R)-13 (83 mg, 1 mol%) were then added. The flask was flushed with nitrogen and cooled to -20 °C. CsOHH₂O (8.4 g, 50 mmol) was added, the flask was capped and the mixture was vigorously stirred for 72 h at -20 °C. The suspension was diluted with hexanes (100 mL) and filtered on a Büchner funnel. The organic layer was flash chromatographed on 100 g of silica that was eluted first with hexanes to remove excess electrophile. The product was eluted with 2:3 (EtOAc/hexanes). The solvent was removed in vacuo to give the title compound (4.4 g, 99%) as a yellow oil. ¹H NMR (250 MHz, CDCl₃) δ 7.91 – 7.81 (m, 2H, Ar-H), 7.36 – 7.27 (m, 2H, Ar-H), 7.15 – 7.06 (m, 2H, Ar-H), 6.90 – 6.80 (m, 2H, Ar-H), 4.60 (d, J = 8.9 Hz, 1H, CH₂O), 4.20 (d, J = 8.9 Hz, 1H, CH₂O), 3.77 (s, 3H, OCH₃), 3.18 (d, J = 13.8 Hz, 1H, CH₂Ar), 3.11 (d, J = 13.8 Hz, 1H, CH₂Ar), 1.44 (s, 9H, C(CH₃)₃). ¹³C NMR (63 MHz, CDCl₃) δc 171.25 (CO), 164.47 (CN), 162.23 (Ar-C), 134.81 (Ar-C), 132.06 (Ar-C), 131.06 (Ar-C), 120.79 (Ar-C), 119.50 (Ar-C), 113.53 (Ar-C), 82.04 (C(CH₃)), 78.40 (C-α), 72.79 (CH₂O), 55.18 (OCH₃), 42.51 (CH₂Ar), 27.83 (C(CH₃)); m/z (ESI) 446/448 [MH]+.

(R)-tert-Butyl 4-(4-azidobenzyl)-3-(4-methoxybenzyl)-2-oxo-1,2,3-oxathiazolidine-4-carboxylate 23
The synthesis was realized by slightly modifying the protocol described by Fry for an analogous derivative. To compound 20 (4.2 g, 9.4 mmol) in EtOH (100 mL) were added NaN₃ (1.3 g, 20 mmol), sodium ascorbate (300 mg, 15 mol%), CuI (380 mg, 20 mol%), DMEDA (264 mg, 30 mol%) and water (43 mL). The flask was purged with nitrogen and heated under reflux for 5 h. After EtOH evaporation, the aqueous layer was extracted three times with EtOAc. The pooled fractions were washed twice with 12.5% ammonia and brine. The organic layer was dried over MgSO₄ filtered and the solvent removed to give the title compound (3.88 g, 99%) as a yellow oil. ¹H NMR (250 MHz, CDCl₃) δ 8.01 – 7.88 (m, 2H, Ar-H), 7.39 – 7.22 (m, 2H, Ar-H), 7.02 – 6.85 (m, 4H, Ar-H), 4.68 (d, J = 8.9 Hz, 1H, CH₂O), 4.31 (d, J = 8.9 Hz, 1H, CH₂O), 3.89 (s, 3H, OCH₃), 3.31 (d, J = 13.8 Hz, 1H, CH₂Ar), 3.23 (d, J = 13.8 Hz, 1H, CH₂Ar), 1.54 (s, 9H, C(CH₃)₃); ¹³C NMR (63 MHz, CDCl₃) δc 171.49 (CO), 164.48 (CN), 162.31 (Ar-C), 136.56 (Ar-C), 132.62 (Ar-C), 131.80 (Ar-C), 130.26 (Ar-C), 119.68 (Ar-C), 118.69 (Ar-C), 113.60 (Ar-C), 82.11 (C(CH₃)), 78.70 (C-α), 72.82 (CH₂O), 39.42 (CH₂N), 39.42 (CH₂N), 28.09 (C(CH₃)); m/z (ESI) 409 [MH]+.

(R)-tert-Butyl 2-(4-azidobenzyl)-3-hydroxy-2-(4-methoxybenzylamino)propanoate 22
A freshly prepared solution of NaBH₄CN (4 g, 159 mmol) in AcOH (80 mL), was cooled to 0 °C and added to the oxazoline 21 (3.7 g, 10 mmol). After stirring at rt for 16 h, the solvent was removed in vacuo. The residue was partitioned between a saturated Na₂CO₃ solution and EtOAc. The basic aqueous layer was extracted twice with EtOAc and the pooled organic layers were washed twice with water and brine. The solution was dried over MgSO₄. After filtration, the solvent was removed to give the title compound (3.3 g, 89%) as an amber oil. ¹H NMR (250 MHz, CDCl₃) δH 7.34 – 7.10 (m, 4H, Ar-H), 7.02 – 6.76 (m, 4H, Ar-H), 3.78 (s, 3H, OCH₃), 3.72 (d, J = 11.5 Hz, 1H, CH₂O), 3.66 (d, J = 11.9 Hz, 1H, CH₂N), 3.60 (d, J = 11.9 Hz, 1H, CH₂N), 3.57 (d, J = 11.5 Hz, 1H, CH₂O), 2.99 (d, J = 13.5 Hz, 1H, CH₂Ar), 2.88 (d, J = 13.5 Hz, 1H, CH₂Ar), 1.45 (s, 9H, C(CH₃)₃); ¹³C NMR (63 MHz, CDCl₃) δc 172.69 (CO), 158.85 (Ar-C), 138.56 (Ar-C), 132.49 (Ar-C), 131.79 (Ar-C), 131.71 (Ar-C), 129.27 (Ar-C), 118.68 (Ar-C), 113.95 (Ar-C), 82.05 (C(CH₃)), 66.96 (C-α), 60.62 (CH₂O), 55.19 (OCH₃), 46.80 (CH₂N), 39.42 (CH₂Ar), 28.09 (C(CH₃)); m/z (ESI) 413 [MH]+.

(4R)-tert-Butyl 4-(4-azidobenzyl)-3-(4-methoxybenzyl)-2-oxo-1,2,3-oxathiazolidine-4-carboxylate 23
In a dry round bottom flask under nitrogen and stirring were added compound 22 (3 g, 7.3 mmol), imidazole (2.0 g, 29 mmol), NEt₃ (3 mL, 22 mmol) and CH₂Cl₂ (40 mL). To this mixture previously cooled to -10 °C, SOCl₂ (0.79 mL, 11.0 mmol) was added dropwise via syringe. The solution was kept for 30 min at -10 °C and allowed to return to rt during 2 h.
washed with water (100 mL) and saturated NaHCO₃. The mixture was stirred at rt for 30 min and then diluted with CH₂Cl₂.

The mixture was diluted with water (20 mL), thereafter with 10% aqueous NaHSO₃. The solution was stirred for 16 h. The solvent was evaporated to give the title compound (269 mg, 90%) as a golden oil.

To a solution of compound 24 (2.6 g, 5.5 mmol) in CH₂CN (60 mL) and water (20 mL) was added CAN (9.0 g, 16.4 mmol). The mixture was stirred at rt for 30 min and then diluted with CH₂Cl₂ (100 mL). After decantation, the organic layer was washed with water (100 mL) and NaHCO₃ (100 mL). Evaporation in vacuo yielded a wet oil which was taken up in CH₂Cl₂ and flash chromatographed on silica with CH₂Cl₂ as an eluent. The yellow oil obtained after solvent removal was crystallized in 1:2 (Et₂O/hexanes) to give the title compound (1.6 g, 80%) as beige needles. Mp 100 – 101 °C; ¹H NMR (250 MHz, CDCl₃) δ 7.26 (d, J = 8.1 Hz, 2H, Ar-H), 6.95 (d, J = 8.1 Hz, 2H, Ar-H), 5.44 (br, 1H, NH), 4.69 (d, J = 9.2 Hz, 1H, CH₂O), 4.40 (d, J = 9.2 Hz, 1H, CH₂O), 3.25 (d, J = 13.8 Hz, 1H, CH₂Ar), 3.11 (d, J = 13.8 Hz, 1H, CH₂Ar), 1.43 (s, 9H, C(CH₃)₃); ¹³C NMR (63 MHz, CDCl₃) δ 167.05 (CO), 159.50 (Ar-C), 139.87 (Ar-C), 131.38 (Ar-C), 129.93 (Ar-C), 129.21 (Ar-C), 127.61 (Ar-C), 119.39 (Ar-C), 114.05 (Ar-C), 84.76 (C(CH₃)₃). HRMS m/z (ES+) Calcd for C₁₃H₁₇LiN₄O₃S 361.1153, found 361.1151 [MLi]⁺; (R)-25 [α]D²⁰ = +66° (c 2, CH₂Cl₂) ([α]D²⁰ = -67° (c 2, CH₂Cl₂) for (S)-25).

(4R)-tert-Butyl 4-(4-azidobenzyl)-3-(4-methoxybenzyl)-2,2-dioxo-1,2,3-oxathiazolidine-4-carboxylate 24

The crude sulfamidite 23 (3.3 g, 7.2 mmol) was dissolved in CH₂CN (200 mL) and the solution was cooled to 0 °C. RuCl₃·H₂O (15 mg, 1 mol%) was added, followed by NaOCl (1.73 g, 8.1 mmol) and water (100 mL). The green-brown solution with a white precipitate was stirred for 15 min at 0 °C. After 4 h of stirring at rt, the mixture was diluted with Et₂O (100 mL) and brine (100 mL). The aqueous layer was extracted with Et₂O (3 × 100 mL) and the pooled organic fractions were washed twice with saturated NaHCO₃ and brine. The organic layer was dried over MgSO₄. After filtration, the solvents were evaporated to yield the crude product 24 that was purified by flash chromatography on silica with 1:4 (EtOAc/hexanes). Evaporation of the solvents gave the title compound (2.6 g, 75%) as a golden oil.
1.59 (s, 9H, C(CH$_3$_3)), 1.52 (s, 9H, C(CH$_3$_3)); $^1$C NMR (63 MHz, CDCl$_3$) $\delta$ C: 167.55 (CO), 148.42 (Boc-CO), 139.60 (Ar-C), 131.91 (Ar-C), 130.14 (Ar-C), 119.32 (Ar-C), 85.79 (C(CH$_3$_3)), 84.38 (C(CH$_3$_3)), 70.03 (CH$_2$O), 68.47 (C-\(\alpha\)), 36.80 (CH$_2$Ar), 27.96 (C(CH$_3$_3)), 27.71 (C(CH$_3$_3)).

**[(S)-tert-Butyl 3-((R)-2-((R)-5-tert-Butoxy-4-(4-tert-butoxy carbonylamino)propanamido)-5-oxopentanamido)-3-methoxy-3-oxoproplthio-2-(4-azidobenzyl)-2-(tert-butoxy carbonyl amino)propanoate 39]***

Under nitrogen, dipeptide 33 (249 mg, 0.66 mmol), HBTU (250 mg, 0.66 mmol) and DiPEA (127 $\mu$L, 1.1 mmol) were suspended in dry CH$_2$Cl$_2$ (15 mL) and stirred for 1 h at rt (ie activated ester).

Meanwhile in another flask, containing a degassed suspension of sulfamidate 26 (269 mg, 0.59 mmol) and cysteine methyl ester.HCl (103 mg, 0.6 mmol) in CH$_3$CN (7 mL), was added, via syringe, a degassed solution of DBU (203 mg, 1.33 mmol) in CH$_3$CN (7 mL). The resulting solution was stirred for 1 h at rt under nitrogen and then concentrated to about one fourth of its volume.

To this last solution of 37, was added, via syringe, the previously synthesized activated ester solution. Stirring was continued for 16 h at rt to afford 38. After solvents evaporation, the solution was diluted with EtOAc (20 mL). Aqueous NaH$_2$PO$_4$ (10%, 20 mL) was added and the biphasic mixture was heated with stirring at 50 °C for 2 h. The organic layer was recovered and the aqueous layer was extracted with EtOAc (3 × 20 mL). The pooled organic fractions were washed with brine, dried over MgSO$_4$ and filtered. After solvent evaporation, the crude product 39 was chromatographed on silica with 7:3 (EtOAc/hexanes). Solvents evaporation afforded the title compound (429 mg, 84%) as a colourless foam. $^1$H NMR (250 MHz, MeOD) $\delta$ H: 7.20 – 7.08 (m, 2H, Ar-H), 7.00 – 6.90 (m, 2H, Ar-H), 4.59 (dd, $J$ = 8.5, 4.8 Hz, 1H, H-\(\alpha\)-Lan), 4.29 (dd, $J$ = 8.8, 4.4 Hz, 1H, H-\(\alpha\)-Glu), 4.08 (q, $J$ = 7.1 Hz, 1H, H-\(\alpha\)-Ala), 3.73 (s, 3H, OCH$_3$), 3.40 – 3.31 (m, 2H, SCH$_2$C, CH$_2$Ar), 5.16 – 2.97 (m, 3H, CH$_2$H$_2$S, SCH$_2$C, CH$_2$Ar), 2.89 (dd, $J$ = 13.5, 8.5 Hz, 1H, CHCH$_2$S), 2.39 – 2.25 (m, 2H, CH$_2$OCO), 2.23 – 2.07 (m, 1H, CH$_2$CH$_2$CO), 2.00 – 1.84 (m, 1H, CH$_2$CH$_2$CO), 1.59 – 1.37 (m, 36H, C(CH$_3$_3)), 1.32 (d, $J$ = 7.1 Hz, 3H, CH$_3$); $^1$C NMR (63 MHz, MeOD) $\delta$ C: 175.66 (CO), 174.51 (CO), 172.20 (CO), 171.94 (CO), 171.70 (Boc-CO), 155.71 (Boc-CO), 155.67 (Boc-CO, rotamer), 140.05 (Ar-C), 133.82 (Ar-C), 132.61 (Ar-C), 119.63 (Ar-C), 84.02 (C(CH$_3$_3)), 82.84 (C(CH$_3$_3)), 80.54 (C(CH$_3$_3)), 80.48 (C(CH$_3$_3)), 66.01 (C-\(\alpha\)), 53.66 (CH-\(\alpha\)-Glu), 52.91 (OCH$_3$), 51.65 (CH-\(\alpha\)-Ala), 40.30 (CH$_2$Ar), 38.31 (SCH$_2$C), 35.62 (CH$_2$SHS), 32.70 (CH$_2$CO), 28.82 (C(CH$_3$_3)), 28.77 (C(CH$_3$_3)), 28.31 (C(CH$_3$_3)), 28.23 (C(CH$_3$_3)), 18.36 (CH$_3$); m/z (ESI) 866 [MH$^+$]; HRMS m/z (ES+) Caled for C$_{86}$H$_{106}$N$_{10}$O$_{32}$S 886.4328, found 866.4319 [MH$^+$].

**[(S)-tert-Butyl 3-((R)-2-((R)-5-tert-Butoxy-4-(4-tert-butoxy carbonylamino)propanamido)-5-oxopentanamido)-3-hydroxy-3-oxoproplthio-2-(4-azidobenzyl)-2-(tert-butoxy carbonyl amino)propanoate 40]***

To tripeptide 39 (225 mg, 0.26 mmol) dissolved in CH$_3$CN (4 mL) was added LiOH.H$_2$O (17 mg, 0.4 mmol) in water (4 mL). After stirring for 16 h at rt under nitrogen and acidification with 10% aqueous NaHSO$_4$ (1 mL), 40 was extracted three times with Et$_2$O. The pooled organic layers were washed with brine and dried over MgSO$_4$. Filtration and solvent evaporation yielded the title compound (205 mg, 93%) as a colourless foam.
with the help of water to dryness. After lyophilisation and trituration with Et₂O (to remove the traces of diethylene glycol), the title compound 4RS was obtained as a beige solid that was dried in vacuo to constant weight (70 mg, 88%). ¹H NMR (250 MHz, D₂O) δ_H 7.19 – 7.05 (m, 2H, Ar-H), 6.99 – 6.85 (m, 2H, Ar-H), 4.52 (dd, J = 8.5, 4.5 Hz, 1H, H-α-Lan), 4.30 (dd, J = 8.9, 5.2 Hz, 1H, H-α-Glu), 4.02 (q, J = 7.1 Hz, 1H, H-α-Ala), 3.33 – 3.14 (m, 2H, SCH₂C, CH₂Ar), 3.14 – 2.96 (m, 2H, CHCH₂S, CH₂Ar), 2.92 (d, J = 14.8 Hz, 1H, SCH₂C), 2.82 (dd, J = 14.1, 8.5 Hz, 1H, CHCH₂S), 2.32 (t, J = 7.3 Hz, 2H, CH₂CO), 2.21 – 2.01 (m, 1H, CH₂CH₂CO), 2.01 – 1.78 (m, 1H, CH₂CH₂CO), 1.43 (d, J = 7.1 Hz, 3H, CH₃); ¹³C NMR (63 MHz, D₂O) δ_C 174.67 (CO), 174.49 (CO), 173.22 (CO), 171.61 (CO), 170.80 (CO), 139.77 (Ar-C), 131.55 (Ar-C), 128.81 (Ar-C), 119.45 (Ar-C), 64.48 (C-α), 52.10 (CH-α-Lan), 52.03 (CH-α-Glu), 49.03 (CH-α-Ala), 40.44 (CH₂Ar), 36.84 (SCH₂C), 33.96 (CHCH₂S), 31.30 (CH₂CO), 26.28 (CH₃CH₂CO), 16.61 (CH₃); m/z (ESI) 540 [MH]+; HRMS m/z (ES+) Calcd for C₂₁H₂₇N₇O₈S 540.1871, found 540.1869 [MH]+.
2. Chiral HPLC of 4-alkylated oxazolines 14 and 20

Enantiomeric excesses were determined by HPLC on a Chiracel OD-H column (Daicel, 150 mm x 4 mm, 5 µm) with 98:2 (n-Hex/i-PrOH) as an eluent at 1 mL/min, 37 °C; retention times for isomers S and R were 9.0 min and 15.5 min, respectively.

\[(R)-\text{tert-Butyl 4-benzyl-2-(4-methoxyphenyl)-oxazoline-4-carboxylate (R)-14}\]

\[(S)-\text{tert-Butyl 4-benzyl-2-(4-methoxyphenyl)-oxazoline-4-carboxylate (S)-14}\]
(R)-tert-Butyl 4-(4-bromobenzyl)-2-(4-methoxyphenyl)-oxazoline-4-carboxylate (R)-20

(S)-tert-Butyl 4-(4-bromobenzyl)-2-(4-methoxyphenyl)-oxazoline-4-carboxylate (S)-20
3. Preparation of Maruoka's catalyst 13

The catalyst 13 described by the Maruoka group was prepared as follow (Scheme 1).7,8 Trimethoxybenzoic acid 41 was brominated in CH₂CN with NBS (step i) followed by conversion of the carboxylic acid 42 to the methyl ester 43 with TMS-Cl in MeOH (step ii).8,9 The Ullmann biaryl coupling of 43 to form bicyclic 44 was performed in NMP with activated copper bronze by adapting a general procedure (step iii).10,11 Saponification and precipitation by acidification yielded diacid 45, in multigram quantity, which was purified by recrystallization (step iv). The diacid 45 was treated with two equivalents of quinidine forming the double salt 46 (step v). Resolution of 46 by three fractional crystallizations was done by following the literature procedure (step vi).12 In this case, after resolution, the acid (R)-45 was obtained with high enantiopurity (≥ 99%, step vii). Treatment of (R)-45 with TMS-Cl in MeOH for 72 h, at rt, gave the diester (R)-44 (step viii).9 From this product the catalyst was made by following the Maruoka’s patented method (steps ix-xiii).8 After purification by preparative HPLC, the overall yield of (R)-13 from (R)-45 was 30% (steps viii-xiii). In the same way (S)-13 was also obtained from (S)-45.

Scheme 1. Synthesis of Maruoka’s catalyst. i) NBS, CH₂CN, 2 °C, 16 h, 93%; ii) TMS-Cl, MeOH, rt, 48 h, 94%; iii) Cu, NMP, 170 °C, 2 h; iv) NaOH, aq. MeOH, reflux, 16 h, then aq. HCl, 0 °C, 77%; v) quinidine (2 eq), aq. EtOH; vi) fractional crystallizations (3 x); vii) NaOH, HCl; viii) TMS-Cl, MeOH, rt, 48 h, 96%; ix) Br₂, CH₂CN, rt, 16 h, 80%; x) 3,4,5-F₃-PhBr(OH); (3 eq.), Pd(OAc)₂; (20 mol%), tri-o-tolyl-P (80 mol%), NaOMe (3 eq.), DME, 80 °C, 16 h, 75%; xi) LiAlH₄, rt, 4 h, 85%; xii) PBr₃ (3 eq.), CH₂Cl₂, 0 °C, 2 h, 91%; Bu₃NH (1.3 eq), K₂CO₃, CH₂CN, 85 °C, 16 h, 67%. 
2-Bromo-3,4,5-trimethoxybenzoic acid 42

The procedure described in Maruoka’s patent was modified as follows by using CH<sub>2</sub>CN in place of CHCl<sub>3</sub>. Small portions of NBS (89 g, 500 mmol) was added during 10 min to an ice-cold solution of 3,4,5-trimethoxybenzoic acid 41 (106 g, 500 mmol) in CH<sub>2</sub>CN (1 L). The resulting mixture was stirred for 16 h at 2 °C. The solvent was evaporated in vacuo and the resulting solids were dissolved in boiling water (1 L) containing NaOH (22 g, 550 mmol). The solution was cooled to 10 °C and acidified with an excess of HCl (pH: 3). The precipitate was filtered, washed with water and dried in vacuo to constant weight. The title compound (135.5 g, 93%) was obtained as a beige solid. Mp 145-148 °C; <sup>1</sup>H NMR (250 MHz, CDCl<sub>3</sub>) δ<sub>H</sub> 12.29 (s, 1H, OH), 7.38 (s, 1H, Ar-H), 3.94 (s, 3H, OCH<sub>3</sub>), 3.88 (s, 3H, OCH<sub>3</sub>), 3.87 (s, 3H, OCH<sub>3</sub>); <sup>13</sup>C NMR (63 MHz, CDCl<sub>3</sub>) δ<sub>C</sub> 171.20 (CO), 152.19 (Ar-C), 151.68 (Ar-C), 147.05 (Ar-C), 125.37 (Ar-C), 111.31 (Ar-C), 110.97 (Ar-C), 61.24 (OCH<sub>3</sub>), 61.07 (OCH<sub>3</sub>), 56.29 (OCH<sub>3</sub>); m/z (ESI) 289/291 [M]+.

Methyl 2-bromo-3,4,5-trimethoxybenzoate 43

To compound 42 (135.5 g, 466 mmol) in MeOH (500 mL) was added TMS-Cl (250 mL, 1.97 mol). The solution was stirred for 48 h at rt. The solvents were evaporated and the residue was dissolved in CH<sub>2</sub>Cl<sub>2</sub>. The organic layer was washed with water, aqueous saturated NaHCO<sub>3</sub> and water. The organics were dried on MgSO<sub>4</sub>, filtered and the solvent evaporated in vacuo to give the title compound (134 g, 94%) as a golden oil. <sup>1</sup>H NMR (250 MHz, D<sub>2</sub>O) δ<sub>H</sub> 7.10 (s, 1H, Ar-H), 3.87 (s, 3H, OCH<sub>3</sub>), 3.83 (s, 6H, OCH<sub>3</sub>); <sup>13</sup>C NMR (63 MHz, CDCl<sub>3</sub>) δ<sub>C</sub> 166.37 (CO), 152.04 (Ar-C), 151.23 (Ar-C), 145.40 (Ar-C), 127.41 (Ar-C), 110.06 (Ar-C), 109.43 (Ar-C), 61.11 (OCH<sub>3</sub>), 60.97 (OCH<sub>3</sub>), 56.21 (OCH<sub>3</sub>), 52.45 (OCH<sub>3</sub>); m/z (ESI) 305/307 [M]+.

4,4',5,5',6,6'-Hexamethoxybiphenyl-2,2'-dicarboxylic acid 45

In order to conduct the reaction at lower temperature and to increase yield, the synthesis was modified by following the known literature method and a solvent, NMP, was added. Compound 43 (133 g, 436 mmol) was dissolved in NMP (150 mL) and the solution was heated to 170 °C under nitrogen. Activated copper bronze (115 g, iodine (2%) in acetone, aqueous HCl (10 M)/acetone:1/1) was added in one portion and the suspension was stirred for 2 h. The dark brown mixture was cooled to 100 °C and the copper was filtered on celite and washed with boiling toluene. After solvents evaporation in vacuo (0.1 mm Hg) at 95 °C, a dark brown oil contaminated by solids was obtained. The crude product 44 was dissolved in EtOAc and washed twice with ammonium hydroxide (6 M) and water. After evaporation, a brown oil was obtained (100 g). The crude diester 44 was saponified by heating under reflux for 16 h with a solution of NaOH (50 g) in MeOH/H<sub>2</sub>O (1/1; 400 mL). The MeOH was evaporated in vacuo. The volume of the solution was adjusted to 500 mL with H<sub>2</sub>O and hydrochloric acid was added under stirring until pH 3. The suspension was cooled to 0 °C, the precipitate 45 was filtered and washed with water. The wet solid was recrystallized twice from boiling aqueous MeOH. After filtration and drying to constant weight the title compound 45 was obtained (135.5 g, 93%) as an off-white solid. Mp 248-249 °C; <sup>1</sup>H NMR (250 MHz, DMSO) δ<sub>H</sub> 7.34 (s, 2H, Ar-H), 3.91 (s, 6H, OCH<sub>3</sub>); <sup>13</sup>C NMR (63 MHz, CDCl<sub>3</sub>) δ<sub>C</sub> 166.89 (CO), 152.04 (Ar-C), 151.23 (Ar-C), 145.98 (Ar-C), 127.41 (Ar-C), 110.06 (Ar-C), 109.43 (Ar-C), 61.11 (OCH<sub>3</sub>), 60.97 (OCH<sub>3</sub>), 56.21 (OCH<sub>3</sub>), 52.45 (OCH<sub>3</sub>); m/z (ESI) 305/307 [M]+.

(R)-4,4',5,5',6,6'-Hexamethoxybiphenyl-2,2'-dicarboxylic acid (R)-45

Resolution of compound 45 was realized through the diquinidinium salt 46 by following the known method. Ee was determined on a Chiracel OD-H column (Daicel, 150 mm × 4 mm, 5 µm); mobile phase: n-Hex/i-PrOH/TFA:90/10/0.1; 0.8 mL/min; 37 °C. Retention times for isomers R and S were 8.3 min and 11.0 min, respectively. Enantiomeric purity of (R)-45 was ≥ 99%. Enantiomer (S)-45 was also obtained with an ee ≥ 99%.

Dimethyl (R)-4,4',5,5',6,6'-hexamethoxybiphenyl-2,2'-dicarboxylate (R)-44

A mixture of (R)-45 (7.4 g, 17.5 mmol) and TMS-Cl (19 mL, 150 mmol) in MeOH (200 mL) was stirred for 72 h at rt. The solvents were evaporated and the residue was dissolved in CH<sub>2</sub>Cl<sub>2</sub>. The organic layer was washed with water, aqueous saturated NaHCO<sub>3</sub> and water. The organics were dried on MgSO<sub>4</sub>, filtered and the solvent evaporated in vacuo to give the title compound (7.8 g, 95%) as a golden oil. <sup>1</sup>H NMR (250 MHz, CDCl<sub>3</sub>) δ<sub>H</sub> 7.34 (s, 2H, Ar-H), 3.91 (s, 6H, OCH<sub>3</sub>), 3.90 (s, 6H, OCH<sub>3</sub>), 3.57 (s, 12H, OCH<sub>3</sub>); <sup>13</sup>C NMR (63 MHz, CDCl<sub>3</sub>) δ<sub>C</sub> 166.89 (CO), 152.04 (Ar-C), 151.23 (Ar-C), 145.40 (Ar-C),
126.58 (Ar-C), 124.96 (Ar-C), 108.86 (Ar-C), 60.77 (OCH₃), 60.51 (OCH₃), 55.93 (OCH₃), 51.80 (OCH₃); m/z (ESI) 451 [MH⁺].

Dimethyl (R)-3,3'-dibromo-4',4',5',5',6,6'-hexamethoxybiphenyl-2,2'-dicarboxylate (R)-47

The title compound was obtained as colourless needles as previously described.² ³ ¹ H NMR (250 MHz, CDCl₃) δ₇ 7.03 – 6.83 (m, 4H, Ar-H), 4.00 (s, 6H, OCH₃), 3.88 (s, 6H, OCH₃), 3.72 (s, 6H, OCH₃), 3.29 (s, 6H, OCH₃); ¹³C NMR (63 MHz, CDCl₃) δc 167.11 (CO), 152.31 (Ar-C), 151.01 (Ar-C), 150.54 (Ar-C) (ddd, JCF = 249.4, 9.8, 4.1 Hz, Ar-C), 147.62 (Ar-C), 139.00 (dt, JCF = 251.8, 15.2 Hz, Ar-C), 132.37 (td, JCF = 8.1, 4.8 Hz, Ar-C), 128.91 (Ar-C), 127.08 (Ar-C), 125.24 (Ar-C), 114.30 – 113.91 (m, Ar-C), 113.82 (Ar-C), 61.11 (OCH₃), 51.55 (OCH₃); m/z (ESI) 711 [MH⁺].

(R)-3,3'-bis(3,4,5-trifluorophenyl)-4',4',5',5',6,6'-hexamethoxybiphenyl-2,2'-dicarboxylate (R)-48

The title compound was obtained as an anhydrous solid as previously described.² ³ ¹ H NMR (250 MHz, CDCl₃) δ₇ 7.18 – 7.00 (m, 4H, Ar-H), 4.02 (d, J = 11.3 Hz, 2H, CH₂), 3.94 (s, 6H, OCH₃), 3.93 (d, J = 11.1 Hz, 2H, CH₂), 3.75 (s, 6H, OCH₃), 3.70 (s, 6H, OCH₃), 3.01 (b, 2H, OH); ¹³C NMR (63 MHz, CDCl₃) δc 151.40 (Ar-C), 151.06 (Ar-C), 150.56 (ddd, JCF = 249.5, 9.8, 4.2 Hz, Ar-C), 146.05 (Ar-C), 139.18 (dt, JCF = 251.5, 15.3 Hz, Ar-C), 133.49 (Ar-C), 132.20 (td, JCF = 8.3, 5.2 Hz, Ar-C), 130.48 (Ar-C), 126.51 (Ar-C), 114.95 (b, Ar-C), 61.13 (OCH₃), 60.80 (OCH₃), 60.80 (OCH₃), 59.65 (CH₂); m/z (ESI) 655 [MH⁺].

(R)-3,3'-bis(3,4,5-trifluorophenyl)-4',4',5',5',6,6'-hexamethoxybiphenyl-2,2'-dimethanol (R)-49

The title compound was obtained as a white solid as previously described³ and was used without purification for the next step; m/z (ESI) 779 (1) 781 (2) 783 (1) [MH⁺].

Chiral quaternary ammonium salt (R)-13

The title compound was obtained as a white solid as previously described.² ³ ¹ H NMR (250 MHz, CDCl₃) δ₇ 7.39 – 7.09 (m, 4H, Ar-H), 4.45 (d, J = 13.7 Hz, 2H, CH₂Ar), 4.08 (s, 6H, OCH₃), 3.94 (s, 6H, OCH₃), 3.84 (d, J = 14.1 Hz, 2H, CH₂Ar), 3.78 (s, 6H, OCH₃), 3.06 (t, J = 12.5 Hz, 2H, NCH₂), 2.80 (b, 2H, NCH₂), 1.26 – 0.96 (m, 6H, CH₂), 0.80 (t, J = 5.7 Hz, 6H, CH₃), 0.24 (b, 2H, CH₂), 151.40 (Ar-C), 151.06 (Ar-C), 150.56 (ddd, JCF = 252.1, 9.2, 3.7 Hz, Ar-C), 148.11 (Ar-C), 139.54 (dt, JCF = 253.9, 15.0 Hz, Ar-C), 130.47 (td, J = 8.0, 5.3 Hz, Ar-C), 130.05 (Ar-C), 126.80 (Ar-C), 120.29 (Ar-C), 115.75 (dd, JCF = 17.9, 2.3 Hz, Ar-C), 61.63 (OCH₃), 61.18 (OCH₃), 61.01 (OCH₃), 57.76 (CH₂Ar), 57.17 (NCH₂), 24.32 (CH₂), 19.34 (CH₃), 13.24 (CH₃); m/z (ESI) 748 [M⁺].

References:

4. MALDI-TOF mass spectrometry (negative mode) of UDP-MurNAc-tripeptide.

Theoretical mass $C_{41}H_{58}N_{7}O_{26}P_{2}S : m/z = 1158.26.$

UDP-MurNAc-(S)-Ala-$\gamma$-(R)-Glu-(R,R)-$\alpha$-benzyl-lanthionine obtained from 3RR

UDP-MurNAc-(S)-Ala-$\gamma$-(R)-Glu-(R,S)-$\alpha$-benzyl-lanthionine obtained from 3RS