Site-selective incorporation of alpha- and beta-amino acid derivatives : towards new gramicidin S-based bactericides

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5 New Synthesis of α-Substituted β-amino Acids

5.1 Introduction

β-Amino acids are homologues of α-amino acids (**1**) and can be classified according to their substitution pattern (Figure 1): β^2-amino acids (**2**) have an additional methylene group next to the amine and β^3-amino acids (**3**) have an extra methylene next to the carboxyl. β^2- and β^3-amino acids are mono-substituted, but additional functionalities may be present, such as in di-, tri- or tetra-substituted β-amino acids.[1] As β-amino acids are not part of the human

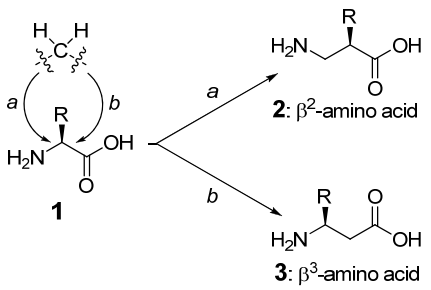
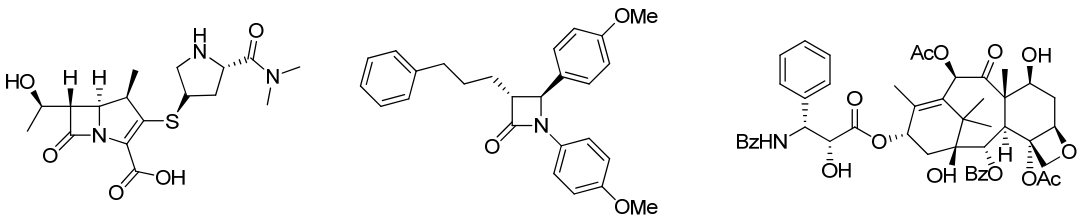


Figure 1 A methylene may be inserted next to the amine (pathway *a*), or next to the carboxylic acid (pathway *b*), resulting in β^2- and β^3-amino acids respectively.



4, Meropenem **5**, Levogyric 2-azetidinone **6**, Paclitaxel (Taxol)

Figure 2 Examples of biologically active natural products containing β-amino acid derivatives in their structure. For paclitaxel the benzoyl-phenylisoserinyl residue is indicated.

proteome, they are less extensively studied than their α-counterparts. Still, β-amino acids are produced by a wide range of mammals, microorganisms, marine organisms and plants,[2] and possess biological activity in their monomeric form or as β-lactam (for example in the medicinally relevant antibiotic meropenem **4** or the cholesterol intestinal absorption inhibitor levogyric 2-azetidinone **5**).[3] Besides that, they are also part of natural products[4,5] with various interesting properties. The most famous example, is probably the anti-cancer drug paclitaxel (**6**, Taxol®), which contains benzoyl-phenylisoserine as part of its complex structure.[6,7] *Taxus brevifolia*, the natural source of this clinically applied anti-cancer medicine, does not produce sufficient amounts to meet the demand for this terpenoid. For this reason, the production of paclitaxel relies on chemical synthesis. As such it is interesting to pursue chemical methods towards the preparation of β-amino acids.

Halfway the last decade of the twentieth century, interest from organic chemist in β-amino acids and oligomers thereof (β-peptides) grew. It was found that β-peptides built up from β^3-amino acids have a high propensity to form helical structures,[8-10] which were unique to this kind of oligomers.[11-13] Combining β^3-amino acids with other types of amino acids resulted in different structural elements, like helices,[14] sheets[15] and hairpins.[16-18] Initially, mainly β^3-amino acids were applied, as these building blocks are more readily accessible than α-substituted counterparts. To obtain β^3-amino acids with proteinogenic side chains, syntheses have been developed starting from the chiral natural amino acid pool. Advantageous is the homologation through an Arndt-Eistert-reaction, because the starting compounds, suitably protected α-amino acid, are commercially available.[9] Another method is homologation *via* a Kolbe reaction.[19] A β-amino iodide or mesylate, easily prepared from the corresponding α-

amino acid, is substituted by a cyanide, and subsequently hydrolysed to yield the homologated β-amino acid. Besides, other enantioselective, high yielding methods to obtain β^3-amino acids are available.[20-23]

β^2-amino acids, on the other hand, are less readily accessible. The possible syntheses of this type of amino acids have been extensively reviewed by Seebach and co-workers.[24] In their review it becomes apparent that there are limited approaches towards these building blocks, the most promising being the Mannich reaction and modifications thereof, (Figure 3a)

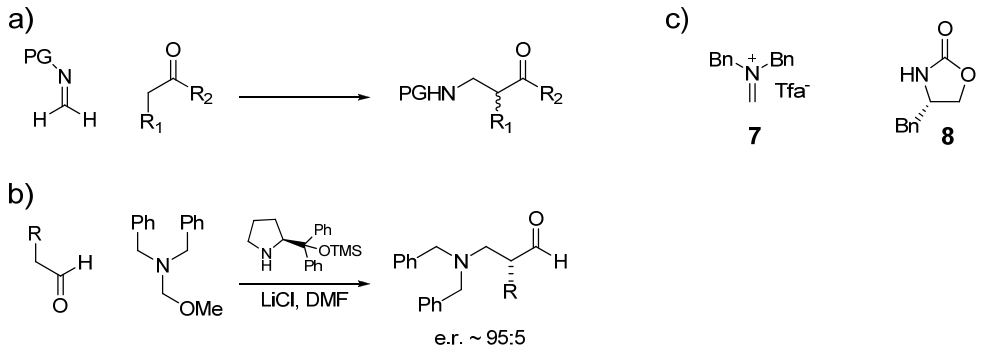


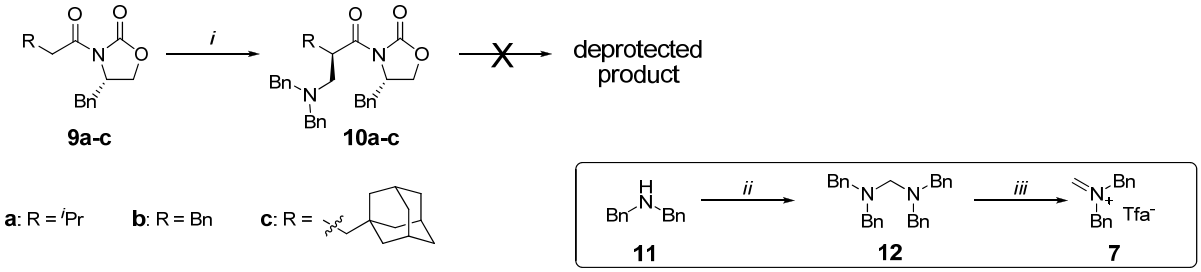
Figure 3a) General reaction equation for the Mannich reaction; *b*) Prolinol ether catalysed enantioselecive Mannich reaction;[25] *c*) Reagents applied in this Chapter.

between a carboxylic acid derivative and an imine. A stereoselective Mannich reaction may be promoted by a chiral catalyst.[25-29] As an example of this Chi and Gellman used a proline- or prolinol ether-catalysed Mannich reaction (Figure 3b),[25] and achieved enantiomeric excesses of up to 92%. The disadvantages in this case are the incomplete stereoselectivity and the difficulties associated with the separation of the epimers. Chirality may also be introduced through a chiral imine (PG has a chiral functionality),[30] or carboxylic acid equivalent (R_2 has a chiral functionality).[31] It was decided to explore a modified Mannich reaction with highly reactive dibenzyl methyleniminium trifluoroacetate **7** as aminomethylating agent and the Evans' oxazolidinone **8** as chiral inducer (Figure 3c). Application of the Evans' chiral auxiliary is a well established and reliable method to introduce chirality. Besides the enantiomerically pure product may be obtained by chromatographic separation of the intermediate diastereomers. This Chapter describes that the occasionally troublesome removal of this chiral auxiliary was effected in high yields by using lithium thiolates. Application of this

method led to the preparation of β²-amino acids that are sterically hindered, namely *iso*-propyl derivative **2a**, adamantane amino acid **2c**.

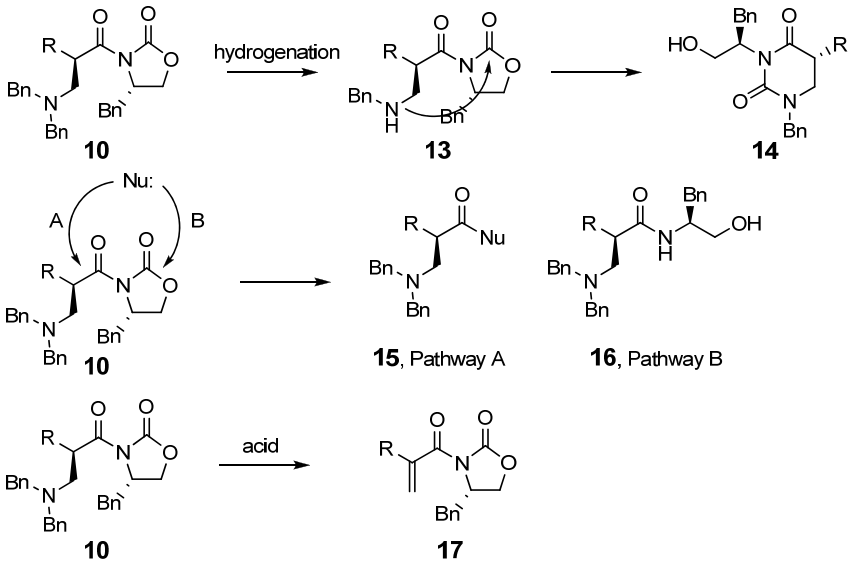
5.2 RESULTS AND DISCUSSION

The acylated oxazolidinones **9a**-**c**,[32] synthesised by reaction of the lithium salt of **8** with the corresponding acyl chloride, were used starting materials in the synthesis of the β²-amino acids (Scheme 1). Dibenzyliminium ion **7**[33] was selected as an easily accessible



Scheme 1 **Reagents and conditions** *i*) $TiCl_4$, Et_3N, CH_2Cl_2, 0 °C, then **7**, -70 °C; *ii*) formalin; *iii*) $(CF_3CO)_2O$, DCM, 0 °C.

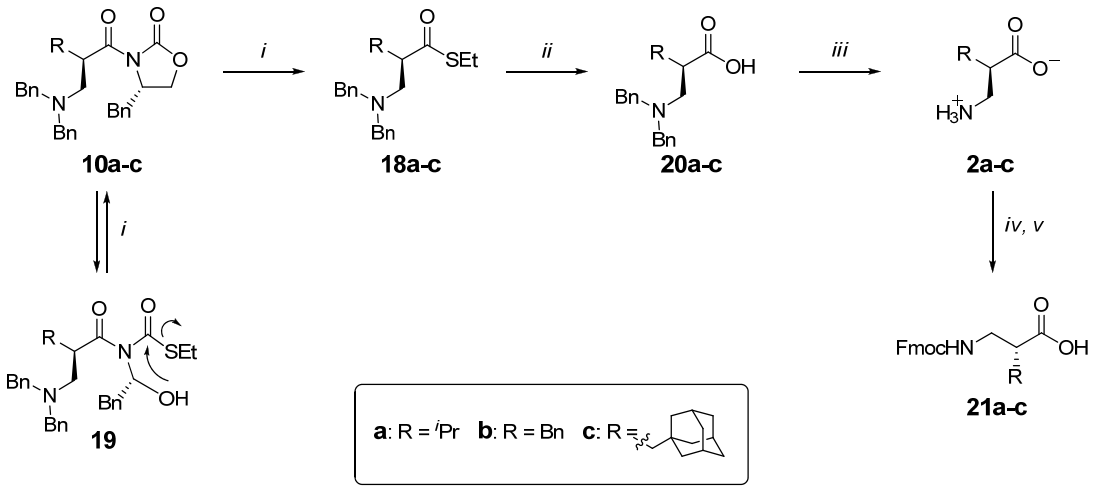
aminomethylating agent. It can be obtained from methylene bis(dibenzylamine) **12**, a shelf stable compound, which in turn can be synthesised from dibenzylamine **11** and formalin in high yields. It was found that the aminomethylation worked well with freshly prepared **8** and the titanium enolate of **9a**-**c**. The oxazolidinone protected dibenzyl-β²-homoamino acids **10a**-**c** were obtained in good yields and stereochemical purity, with the minor diastereomer separable by silica column chromatography. The next step would be either the removal of the benzyl groups on the amine, or the removal of the Evans' chiral auxiliary. Unfortunately, both proved to be very difficult (Scheme 2). The monobenzyl derivative **13**, intermediate in the hydrogenation of **10**, delivered the chiral dihydrothymine derivative **14**, after attack of the partially deprotected amine on the endocyclic carbonyl. Therefore, it became obvious that removal of the chiral auxiliary had to be accomplished first. The removal was hampered, however, by the low reactivity of **10** towards nucleophiles commonly employed for the cleavage of the acyl group, namely lithium peroxide, magnesium-, or lithium alcoholates,



Scheme 2

even after prolonged exposure to excess reagents. Commonly the attack of the nucleophile on the carbonyl of the oxazolidinone was observed, leading to non-productive amide **16**, instead of the desired product **15**. In addition, acid catalysed elimination of the dibenzylamine group, resulting in the α,β-unsaturated **17** was observed. The difficulties in the removal of the Evans' auxiliary can be explained by the severe steric hindrance around the exocyclic carbonyl, especially in the case of **10a** and **10c.**

After long experimentation it was discovered that application of lithium ethylthiolate to the cleavage of the chiral auxiliary led to fast thioester **18a**-**c** formation, in isolated yields equal or close to quatitative (Scheme 3). The beneficial effect of the thiol can be explained by the higher nucleophilicity of the thiolate anion, compared to alcoholates and the fact that when the thiolate attacks at the carbonyl of the oxazolidinone, the resulting thiocarbamate **19** reacts back to **10**. With the thioesters **18a**-**c** in hand the synthesis was continued by removal of the thio-group. Simple saponification with LiOH did not yield the product and harsher conditions were avoided rule out epimerisation of the α-centre. Treatment with thiophilic reagents, NBS, NIS and molecular iodine, did result in cleavage of the thioester, but one or two benzyls were concomitantly cleaved, in unreproducible ratios and cyclisation to the β-lactam was observed. Thiophilic salts, like $AgNO_3$ and $Hg(Tfa)_2$ were tested and both worked indeed, though the prior also led to significant amounts of an unidentified side-product.



Scheme 3 **Reagents and conditions** *i*) BuLi, EtSH, THF, 0 °C, then **10a**-**c**; *ii*) $Hg(CF_3COO)_2$, H_2O/THF; *iii*) H_2, Pd/C, MeOH/H_2O/AcOH; *iv*) FmocOSu, $NaHCO_3$, dioxane/H_2O.

Fortunately the mercury induced thioester cleavage led cleanly to the dibenzyl protected amino acid **20a**-**c**. The mercury salts could be removed by precipitation with brine and subsequent filtration. Pure **20a**-**c** were hydrogenated with palladium on charcoal and hydrogen gas in a mixture of methanol, water and acetic acid. It was noted that distillation of methanol over $NaBH_4$ was a must, as reduction in undistilled methanol led to reductive amination with formaldehyde traces in the solvent. The bare amino acids **2a**-**c** were used without any further purification. The Fmoc-group was installed under Schotten-Baumann conditions to yield the suitably protected β^2-homo-amino acids **20a**-**c** in reasonably good yield.

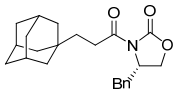
5.3 Conclusions

This chapter presents a new, successful synthesis of α-substituted β-amino acids. The key steps in the synthesis were the aminomethylation of titanium enolates **9a**-**c** with iminium ion **8** and the removal of the chiral auxiliary using lithium ethylthiolate. The sequence of reactions was applied to the synthesis of severely sterically hindered, of aromatic and of heteroatomic amino acids. It is interesting to find out if this route may be easily extrapolated to other amino acid with various side chain functionalities.

5.4 EXPERIMETAL SECTION

General

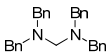
Solvents and chemicals were used as received from their supplier. Solvents were stored over 4 Å molecular sieves. Solvents for column chromatography and extractions were of technical grade and distilled prior to use. THF was distilled over $LiAlH_4$, CH_2Cl_2 over CaH_2 and MeOH over $NaBH_4$ prior to use. All reactions were performed at room temperature (15-28 °C) under inert atmosphere. Flash chromatography was performed on Screening Devices silica gel 60 (0.04-0.063 mm). TLC analysis was conducted on DC-alufolien (Merck, Kieselgel 60, F254) with detection by UV-absorption at 254 nm or by spraying with a solution of ninhydrin (3 g/L) in EtOH/AcOH (20:1 *v/v*), or $KMnO_4$ solution (20 g in 1% aq K_2CO_3), followed by charring at ± 150 °C. ^1H and ^{13}C NMR spectra were recorded with a Bruker AV-400liq spectrometer (400/100 MHz). Chemical shifts δ are given in ppm relative to TMS (0 ppm), or CD_2HOD (3.31 ppm) as internal standard. High resolution mass spectra were recorded by direct injection (2 µL of a 2µM solution in water/acetonitrile; 50:50 *v/v* and 0.1% formic acid) on a mass spectrometer (Termo Finnigan LTQ Orbitrap) equipped with an electro spray ion source in positive mode (source voltage 3.5 kV, sheath gas flow 10, capillary temperature 250˚C) with resolution R = 60000 at *m/z* 400 (mass range *m/z* = 150-2000) and dioctylphthalate (*m/z* = 391.28428) as a "lock mass". The high resolution mass spectrometer was calibrated prior to measurements with a calibration mixture (Thermo Finnigan). Optical rotations were measured on a Propol automatic polarimeter (sodium D line, λ = 589 nm) at rt. IR-spectra were recorded on a Perkin Elmer Paragon 1000.



(S)-4-benzyl-3-(3-adamantylpropanoyl)oxazolidin-2-one (**9c**)

Evans' oxazolidinone (11.2 mmol, 1.98 g) was dissolved in anhydrous THF (50 mL), cooled to 0°C and *n*BuLi (1.6 M in hexanes, 12.3 mmol, 7.7 mL) was added. The resulting suspension was stirred for 15 min before 3-adamantylpropanoyl chloride was added. When TLC indicated completion, the reaction was quenched with NH_4Cl-soln and warmed to rt. The mixture was separated, washed with H_2O and brine. The combined aqueous fractions were extracted once more with EtOAc and the organics were combined, dried over $MgSO_4$, filetered and evaporated. The crude was purified by column chromatography (0 → 6% EtOAc in PE) and crystallisation (toluene/PE) to yield the pure acylated Evans' template (2.98 g, 8.11 mmol) in 72%)

^1H NMR (400 MHz, $CDCl_3$) δ 7.34-7.24 (m, 5H), 7.20 (d, *J* = 6.9 Hz, 2H), 4.66 (ddt, *J* = 10.5, 6.9, 3.3 Hz, 1H), 4.20-4.13 (m, 2H), 3.29 (dd, *J* = 13.4, 3.2 Hz, 1H), 2.97-2.81 (m, 2H), 2.76 (dd, *J* = 13.3, 9.7 Hz, 1H), 1.96 (brs, 3H), 1.67 (dd, *J* = 29.4, 11.9 Hz, 6H), 1.54-1.40 (m, 8H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.16, 135.30, 129.32, 128.82, 127.19, 66.00, 55.10, 42.01, 38.33, 37.82, 36.97, 29.37, 28.54; IR neat (cm^{-1}): 2901.0, 2846.7, 2362.3, 1781.4, 1698.3, 1452.0, 1386.7, 1352.2, 1212.4, 1100.0; $[\alpha]_D$ = +39.0° (c = 1.0, $CHCl_3$); HRMS: calculated for $[C_{23}H_{30}NO_3]^+$: *m/z* 368.22202; found: *m/z* 368.2203.



N,N,N',N'-*tetrabenzylmethanediamine* (**12**)

Formaldehyde (37% in water; 550 mmol, 44.5 mL) was added dropwise to neat dibenzylamine (6, 1 mol, 191 mL). After addition de mixture was heated to 100 °C for 4 h. When the mixture had cooled down 250 mL of PE was added and the solids were filtered off and washed with PE to yield the product in 64-75% yield.

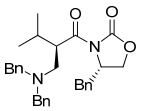
1H NMR (400 MHz, $CDCl_3$) δ 7.31-7.11 (m, 5H), 3.09 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.71, 128.94, 128.37, 128.12, 126.72, 72.21.

N,N-*dibenzyliminium trifluoroacetate* (**7**)

Aminal **12** was dissolved in CH_2Cl_2 (1 M) and cooled to 0 °C. Then trifluoroacetic anhydride (1 eq) was added, cooling was removed stirring was continued for 30 min. The solution was used without any further workup in the aminomethylation reaction.

General procedure for aminomethylation

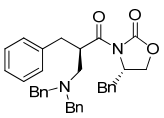
Acylated oxazolidinone **9** was dissolved in CH_2Cl_2 (0.1 M) and cooled in an ice/water bath. Titanium(IV) chloride (1 eq, 1M soln in CH_2Cl_2) was added slowly, upon which the solution turned bright yellow. The mixture was tirred for 5 min after, which Et_3N (1 eq) was added dropwise, turning the solution dark red. After stirring for 15 min the reaction mixture was cooled to -80 °C and subsequently a solution of **7** in CH_2Cl_2 (0.85 eq) was added. The reaction was left stirring overnight at -80 °C. Then the reaction was quenched at -80 °C by addition of saturated NH_4Cl-soln. After warming to rt the pH was adjusted to 2 and extracted with EtOAc. The organic layer was washed with $NaHCO_3$-soln and brine, dried over $MgSO_4$, filtered and evaporated. Purification was done by silica gel chromatography.



*(*S*)-4-benzyl-3-((*R*)-2-((dibenzylamino)methyl)-3-methylbutyl)oxazolidin-2-one* (**10a**)

Starting from 4.62 g (17.7 mmol) **9a**, 15.1 mmol (7.0 g) of the title compound was obtained as a colourless glass. Column chromatography: 10% Et_2O/PE.

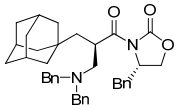
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41-7.16 (m, 15H), 4.67 (sept., *J* = 3.6 Hz, 1H), 4.30 (brs, 1H), 4.15 (m, 2H), 3.82 (d, *J* = 13.7 Hz, 2H), 3.47 (dd, *J* = 13.2, 2.9 Hz, 1H), 3.42 (d, *J* = 13.7 Hz, 2H), 3.09 (dd, *J* = 10.8 Hz, *J* = 12.0 Hz, 1H), 2.72 (dd, *J* = 13.1, 10.2 Hz, 1H), 2.59 (dd, *J* = 12.5, 3.8 Hz, 1H), 1.84 (dq, *J* = 13.4, 6.7 Hz, 1H), 0.92 (d, *J* = 6.8 Hz, 3H), 0.88 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.46, 153.35, 138.86, 135.72, 129.38, 129.04, 128.93, 128.00, 127.22, 126.84, 65.69, 58.26, 55.65, 54.20, 46.41, 38.27, 30.26, 20.29, 19.96; IR neat (cm^{-1}): 2961.1, 1772.5, 1697.5, 1382.9, 1348.5, 1209.4, 1099.9, 743.9, 699.7; $[\alpha]_D$ = +14.4° (c = 1.0, $CHCl_3$); LC/MS: Rt = 7.91 min (10 → 90% MeCN, 15 min); ESI-MS: *m/z* 471.27 $[M + H]^+$; HRMS: calculated for $[C_{30}H_{35}N_2O_3]^+$: *m/z* 471.26422; found: *m/z* 471.26382.



*(*S*)-4-benzyl-3-((*R*)-2-benzyl-3-(dibenzylamino)propanoyl)oxazolidin-2-one* (**10b**)

Starting from 1.55 g **9b** (5 mmol), 2.37 g (4.57 mmol, 91%) of **10b** was obtained after column chromatography with 5% EtOAc in PE.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30-7.12 (m, 20H), 4.67 (ddt, *J* = 10.2, 6.7, 3.1 Hz, 1H), 4.32 (t, *J* = 8.4 Hz, 1H); 3.92 (d, *J* = 7.9 Hz, 1H), 3.64 (q, *J* = 13.6 Hz, 5H); 3.26 (dd, *J* = 13.1, 1.9 Hz, 1H), 2.98 (ddd, *J* = 18.8, 12.7, 7.0 Hz, 2H), 2.68 (dd, *J* = 22.9, 12.6 Hz, 2H), 2.60 (dd, *J* = 12.5, 6.0 Hz, 1H); ^{13}C (100 MHz, $CDCl_3$) δ 174.89, 152.88, 138.96, 138.87, 135.41, 129.32, 128.93, 128.83, 128.21, 128.06, 127.17, 126.84, 126.24, 65.66, 58.31, 55.56, 55.42, 43.11, 38.01, 37.25; IR neat (cm^{-1}): 1774.4, 1697.2, 1494.7, 1452.3, 1382.9, 1348.1, 1209.3, 1195.8, 1101.3; $[\alpha]_D$ = +34.0° (c = 1.0, $CHCl_3$); LC/MS: Rt = 7.49 min (10 → 90% MeCN, 15 min run); ESI-MS: *m/z* 519.2 $[M + H]^+$; HRMS: calculated for $[C_{34}H_{35}N_2O_3]^+$: *m/z* 519.26422; found: *m/z* 519.26292.



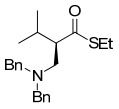
*(*S*)-4-benzyl-3-((*R*)-2-adamantyl-3-(dibenzylamino)propanoyl)oxazolidin-2-one* (**10c**)

Starting from 1.57 g (4.3 mmol) **9c**, 2.7 mmol (1.55 g, 63%) of the aminomethylated compound was obtained after purification by column chromatography (0 → 6% EtOAc/PE).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32-7.14 (m, 15H), 4.61 (tt, *J* = 10.0, 4.0 Hz, 1H), 4.40 (dd, *J* = 14.6, 7.1 Hz, 1H), 4.10-4.08 (m, 2H), 3.69 (d, *J* = 13.8 Hz, 2H), 3.56 (d, *J* = 13.8 Hz, 2H), 3.36 (dd, *J* = 13.2, 3.1 Hz, 1H), 2.70 (dd, *J* = 12.1, 6.7 Hz, 1H), 2.64 (dd, *J* = 13.2, 10.3 Hz, 1H), 2.48-2.42 (m, 1H), 1.89 (brs, 3H), 1.62 (dt, *J* = 17.9, 10.9 Hz, 7H), 1.51 (d, *J* = 11.8 Hz, 3H), 1.43-1.39 (m, 1H), 1.34 (d, *J* = 11.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.77, 153.13, 138.99, 135.57, 129.29, 128.94, 128.85, 128.12, 128.03, 127.17, 126.78, 125.21, 65.87, 58.26, 55.74, 44.46, 42.54, 38.23, 36.85, 35.65, 32.48, 28.50; IR neat (cm^{-1}): 2900.0, 2846.9, 1698.2, 1451.9, 1382.3, 1349.1, 1199.5, 1101.4, 741.2, 699.3; $[\alpha]_D$ = +30.6° (c = 1.0, $CHCl_3$); HRMS: calculated for $[C_{38}H_{45}N_2O_3]^+$: *m/z* 577.34247; found: *m/z* 577.34217.

General Procedure for Thiolytic Removal of the Evans' Template

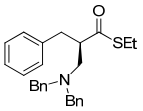
Butyl lithium (1.1 eq, 1.6 M in hexanes) was added dropwise to a stirred solution of ethanethiol in THF (3 eq, 0.3 M) at 0 °C and stirred for 15 mins. Then a solution of **10** in THF (1 M) was added slowly to the thiolate solution. When TLC indicated completion the reaction was quenched with saturated NH_4Cl and warmed to rt. The product was extracted with Et_2O and washed with $NaHCO_3$-soln. The ethereal layer was dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude product was purified by silica gel column chromatography.



*(*R*)*-S-*ethyl 2-((dibenzylamino)methyl)-3-methylbutanethioate* (**18a**)

Starting from 15.1 mmol **10a**, 13.9 mmol (92%) of thioester **18a** was obtained as an oil after column chromatography (5% MTBE in PE).

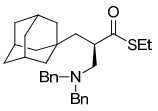
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33-7.20 (m, 10H), 3.66 (d, *J* = 13.6 Hz, 2H), 3.40 (d, *J* = 13.6 Hz, 2H), 2.95-2.86 (m, 3H), 2.64-2.58 (m, 1H), 2.53 (dd, *J* = 4.2 Hz, *J* = 12.6, 1H), 1.80 (sext, *J* = 6.8 Hz, 1H), 1.29 (t, *J* = 7.4 Hz, 3H), 0.86 (d, *J* = 6.8 Hz, 3H), 0.82 (d, *J* = 6.8 Hz, 3H); ^{13}C (100 MHz, $CDCl_3$) δ 201.92, 139.08, 128.99, 128.01, 126.85, 59.34, 58.50, 54.63, 29.84, 23.30, 20.65, 20.25, 14.83; IR neat (cm^{-1}): 2960.5, 1681.8, 1452.3, 918.1, 734.8, 696.3; $[\alpha]_D$ = +12.2° (c = 1.0, $CHCl_3$); LC/MS: Rt = 5.40 min (10 → 90% MeCN, 15 min run); ESI-MS: *m/z* 356.13 [M + H]$^+$; HRMS: calculated for $[C_{22}H_{30}NOS]^+$: *m/z* 356.30426; found: *m/z* 356.20419.



*(*R*)*-S-*ethyl 2-benzyl-3-(dibenzylamino)propanethioate* (**18b**)

Compound **18b** was obtained in 84% (2.78 mmol) from **10b** (1.70 g, 3.30 mmol) after column chromatography (50 Tol/PE) as a colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31-7.13 (m, 13H), 7.03 (d, *J* = 6.8 Hz, 2H), 3.58 (d, *J* = 13.6 Hz, 2H), 3.49 (d, *J* = 13.6 Hz, 2H), 3.10-3.02 (m, 1H), 2.87 (dd, *J* = 12.9, 8.3 Hz, 1H), 2.80 (q, *J* = 7.4 Hz, 2H), 2.77-2.72 (m, 2H), 2.51 (dd, *J* = 12.9, 5.9 Hz, 1H), 1.17 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 201.70, 138.93, 138.89, 128.94, 128.87, 128.23, 128.10, 126.93, 126.17, 58.67, 56.25, 54.93, 36.95, 23.24, 14.66; IR neat (cm^{-1}): 1679.9, 1494.7, 1452.3, 1265.2, 1028.0, 939.3; $[\alpha]_D$ = +21.8° (c = 1.0, $CHCl_3$); LC/MS: Rt = 7.92 (10 → 90% MeCN, 15 min run); ESI-MS: 404.07 [M + H]$^+$; HRMS: calculated for $[C_{26}H_{30}NOS]^+$: *m/z* 404.20426; found: *m/z* 404.20364.



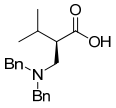
*(*R*)*-S-*ethyl 2-adamantyl-3-(dibenzylamino)propanethioate* (**18c**)

Starting from 2.11 mmol **10c** the title compound was obtained in 68% yield (1.44 mmol) after column chromatography (30 → 40% Tol/PE).

^{1}H NMR (400 MHz, $CDCl_3$) δ7.32 (d, *J* = 7.0 Hz, 4H), 7.27 (t, *J* = 7.4 Hz, 4H), 7.19 (t, *J* = 7.2 Hz, 2H), 3.54 (q, *J* = 13.6 Hz, 4H), 2.94-2.81 (m, 3H), 2.74 (dd, *J* = 12.7, 8.2 Hz, 1H), 2.34 (dt, *J* = 12.7, 6.3 Hz, 1H), 1.87 (brs, 3H), 1.59 (dd, *J* = 31.8, 12.0 Hz, 6H), 1.49-1.40 (m, 1H), 1.37 (s, 6H), 1.24 (t, *J* = 7.4 Hz, 4H), 1.09 (dd, *J* = 14.4, 2.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 203.19, 139.22, 129.19, 128.25, 127.09, 58.99, 58.89, 48.07, 44.97, 42.58, 37.08, 32.82, 28.74, 23.44, 14.90; IR neat (cm^{-1}): 2898.5, 2845.9, 2360.3, 2342.3, 1686.0, 1494.7, 1450.1, 1125.6, 947.9, 744.1; $[\alpha]_D$ = -1.2° (c = 1.0; $CHCl_3$); HRMS: calculated for $[C_{30}H_{40}NOS]^+$: *m/z* 462.28251; found: *m/z* 462.28201.

General Procedure for Thioester Hydrolysis.

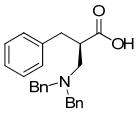
Thioester **18** was dissolved in THF/H_2O (0.2 M, 5:1 *v/v*) and $Hg(Tfa)_2$ (1.5 eq) was added, upon which the solution turned yellow, which subsided after some minutes. When TLC analysis indicated completion, brine was added and the suspension was filtered of double Whatman filter. The layers were separated and the organics were evaporated. The residue was redissolved in EtOAc washed with brine (5 ×), water, dried over $MgSO_4$, filtered and evaporated. Column chromatography was applied when necessary to yield the product as an amorphous white solid.



*(*R*)-2-((dibenzylamino)methyl)-3-methylbutanoic acid* (**20a**)

Compound **20a** (13.5 mmol) was obtained in quatitative yield from **18a** (4.79 g, 13.5 mmol).

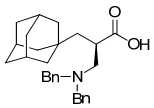
^{1}H NMR (400 MHz, $CDCl_3$) δ 11.71 (brs, 1H), 7.47-7.28 (m, 10H), 4.17 (d, *J* = 13.2 Hz, 2H), 4.03 (d, *J* = 13.2 Hz, 2H), 3.25 (t, *J* = 12.2 Hz, 1H), 2.87 (dd, *J* = 3.0 Hz, *J* = 13.0 Hz, 1H), 2.76-2.73 (m, 1H), 2.14 (sext, *J* = 6.8 Hz, 1H), 0.83 (d, *J* = 6.8 Hz, 3H), 0.79 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.93, 131.45, 130.47, 129.07, 128.95, 57.36, 50.82, 46.05, 28.72, 19.70, 18.68; IR neat (cm^{-1}): 2963.8, 1717.9, 1457.9, 1197.7, 752.0, 700.2; $[\alpha]_D$ = -38.8° (c = 1.0, $CHCl_3$); LC/MS: Rt = 5.89 min (10 → 90% MeCN, 15 min run); ESI-MS: *m/z* 312.13 [M + H]$^+$; HRMS: calculated for $[C_{20}H_{26}NO_2]^+$: *m/z* 312.19581; found: *m/z* 312.19595.



*(*R*)-2-benzyl-3-(dibenzylamino)propanoic acid* (**20b**)

Starting from 3.5 g of **18b** (8.67 g), **20b** was obtained in quatitative yield after column chromatography (50% EtOAc/PE).

^{1}H NMR (400 MHz, $CDCl_3$) δ 12.73 (brs, 1H), 7.29-7.21 (m, 13H), 7.08 (d, *J* = 6.5 Hz, 2H), 4.09 (d, *J* = 13.2 Hz, 2H), 3.86 (d, *J* = 13.3 Hz, 2H), 3.22 (dd, *J* = 13.9, 4.6 Hz, 1H), 3.10 (q, *J* = 12.7 Hz, 1H), 3.03-2.99 (m, 1H), 2.76 (dd, *J* = 12.5, 3.0 Hz, 1H), 2.53 (dd, *J* = 13.9, 8.8 Hz, 1H); ^{13}C N NMR (100 MHz, $CDCl_3$) δ 175.61, 137.82, 130.72, 130.30, 129.00, 128.85, 128.49, 126.54, 56.90, 52.04, 41.86, 35.74; IR neat (cm^{-1}): 1666.4, 1454.2, 1178.4, 1132.1, 906.5, 727.1, 696.3 ; $[\alpha]_D$ -85.2° (c = 1.0, $CDCl_3$); LC/MS: Rt = 5.63 min (10 → 90% MeCN, 15 min run); ESI-MS: *m/z* 360.0 $[M + H]^+$; HRMS: calculated for $[C_{24}H_{26}NO_2]^+$: *m/z* 360.19581; found: *m/z* 360.19598.



*(*R*)-2-adamantyl-3-(dibenzylamino)propanoic acid* (**20c**)

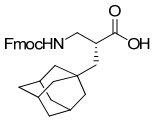
The title compound was obtained in 95% yield (0.74 mmol) starting from **18b** (0.78 mmol), after silica gel chromatotography (10 → 20% EtOAc/PE + 1% AcOH).

^{1}H NMR (400 MHz, $CDCl_3$) δ 12.39 (brs, 1H), 7.35-7.25 (m, 10H), 3.92 (d, *J* = 13.2 Hz, 2H), 3.49 (d, *J* = 13.3 Hz, 2H), 2.80 (t, *J* = 13.9 Hz, 1H), 2.56-2.48 (m, 2H), 1.91 (s, 3H), 1.87 (d, *J* = 4.5 Hz, 1H), 1.62 (dd, *J* = 36.1, 12.0 Hz, 6H), 1.45-1.37 (m, 6H), 0.77 (dd, *J* = 3.4, 14.7 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.06, 135.97, 129.34, 128.57, 127.82, 58.11, 57.37, 42.64, 42.12, 36.81, 35.59, 32.31, 28.39; IR neat (cm^{-1}): 2900.8, 2846.8, 1702.1, 1494.1, 1451.1, 1241.0, 907.1, 732.9, 646.7; $[\alpha]_D$ = -38.8° (c = 1.0, $CHCl_3$); HRMS: calculated for $[C_{28}H_{36}NO_2]^+$ *m/z* 418.27406; found: *m/z* 418.27388.

General procedure for benzyl removal and Fmoc-protection

The free acid was dissolved in MeOH/H_2O/AcOH (80:10:10 *v/v/v*), purged with argon and a catalytic amount of 10% palladium on charcoal was added. A hydrogen atmosphere was applied (1 bar) and the suspension was stirred for 16 h, after which the mixture was filtered over Whatman pads and concentrated. The product was used without any further purification.

The residue was redissolved in dioxane and FmocOSu (1.1 eq) and sat. $NaHCO_3$-soln were added and stirred for 8 h. The product was extracted with EtOAc and the organics were washed with H_2O and brine, dried over $MgSO_4$, filtered and evaporated. The crude was purified by column chromatography.



*(*R*)-3-(((9H-fluoren-9-yl)methoxy)carbonylamino)-2-adamantylpropanoic acid* (**21c**)

Starting from 0.31 g (0.74 mmol) **20c**, 0.39 mmol (52%, two steps) of the protected amino acid was obtained after purification by column chromatography (0 → 3% MeOH in DCM).

^{1}H NMR (400 MHz, $CHCl_3$, rotamers) δ 9.95 (s, 1H), 7.72 (t, *J* = 7.7 Hz, 2H), 7.56 (d, *J* = 7.4 Hz, 2H), 7.36 (dd, *J* = 15.3, 7.8 Hz, 2H), 7.28-7.21 (m, 2H), 6.73 (brs, 1H), 5.44 (t, *J* = 5.8 Hz, 1H), 4.42 (d, *J* = 6.1 Hz, 1H), 4.33 (p, *J* = 10.6 Hz, 1H), 4.23 (t, *J* = 6.2 Hz, 1H), 4.17 (t, *J* = 7.0 Hz, 1H), 3.38 (dd, *J* = 12.2, 6.6 Hz, 1H), 3.31-3.16 (m, 1H), 2.75 (brs, 1H), 1.92 (brs, 3H), 1.60 (dt, *J* = 18.8, 9.1 Hz, 8H), 1.48 (d, *J* = 10.7 Hz, 6H), 1.10-1.00 (m, 1H); ^{13}C NMR (100 MHz, $CHCl_3$) δ 181.16, 156.51, 143.77, 141.15, 127.69, 127.55, 126.93, 125.00, 119.92, 119.85, 66.82, 47.03, 44.27, 43.66, 42.02, 40.11, 36.76, 32.52, 28.41; IR neat (cm^{-1}): 2901.8, 2847.4, 1702.4, 1524.0, 1450.2, 1250.8, 757.7, 740.9; $[\alpha]_D$ = -5.8° (c = 1.0, $CHCl_3$); HRMS: Calculated for $[C_{29}H_{34}NO_4]^+$: *m/z* 460.24824; found: *m/z*/ 460.24810.

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