Benzyl *N*-[(Benzyloxy)methyl]carbamate: An Improved Aminomethylation Electrophile for the Synthesis of (Benzyloxy)carbonyl (Cbz)-Protected Chiral β^2-Amino Acids

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α-Aminomethylation of (*R*)-DIOZ-alkylated (DIOZ = 4-isopropyl-5,5-diphenyloxazolidin-2-one) substrates is a key step in the asymmetric synthesis of β^2-amino acids, but it is unfortunately often accompanied by formation of transcarbamation by-products. Aminomethylation was tested using a range of electrophiles, and the amount of by-product formation was assessed in each case. Benzyl *N*-[(benzyloxy)methyl]carbamate electrophile **3d** is unable to form this by-product due to its inherent benzyl substitution. Use of electrophile **3d** showed an improved impurity profile in aminomethylation, thus leading to easier intermediate purification.

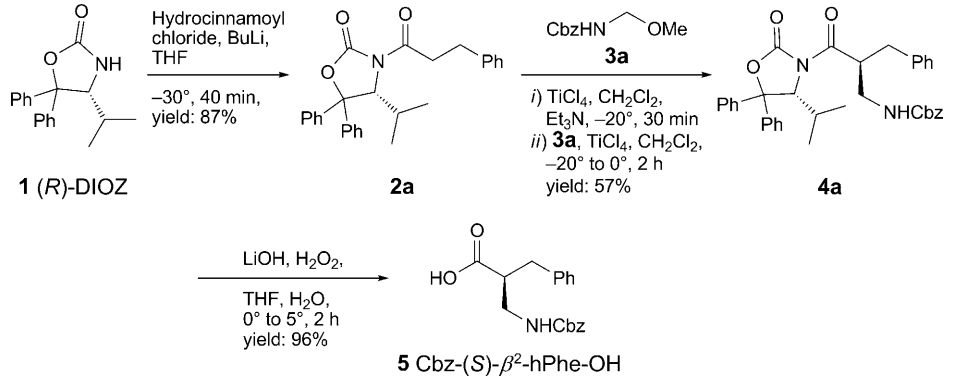
Introduction. – β-Peptides are well-known to form highly stable secondary structures such as helices, turns, and sheets [1–8], which can be designed so as to mimic the activity-related structural features of natural peptides or proteins [9–14]. Peptides constructed from β-amino acids exhibit increased stability towards degrading and metabolizing enzymes in living organisms [15][16], compared to their natural counterparts, the α-peptides. For example, β-peptide-based antibiotics are being explored as ways of evading antibiotic resistance [17].

Work on the synthesis of β-amino acids, in which an additional CH_2 group is inserted either between the C=O group and the C(α)-atom (β^3), or between the C(α)- and N-atom (β^2) was pioneered by *Seebach et al.* [18], and *Gellman* and co-workers [19]. Given the diversity of functional groups attached to the C(β)-atom and the difficulties in maintaining chirality, the chemical synthesis of β-amino acids is especially challenging. Since many β^3-amino acids are already commercially available, we turned our attention to the synthesis of β^2-amino acids as highly interesting building blocks for the synthesis of drug candidates.

Results and Discussion. – Several diastereoselective methods to give β^2-amino acids are described in the literature [20][21]. One strategy for the synthesis of such building blocks is the highly diastereoselective aminoalkylation of *N*-acyloxazolidinone-derived titanium enolates with suitable electrophiles [22–24]. An example is the asymmetric synthesis of Cbz-(*S*)-β^2-hPhe-OH (**5**), outlined in *Scheme 1*, using chiral auxiliary, (*R*)-4-isopropyl-5,5-diphenyloxazolidin-2-one ((*R*)-DIOZ; **1**) [25][26]. The synthesis was performed according to a method developed by *Seebach* and co-workers [27–31] and

carried out on large scale (100 g of **5**) in our laboratories. Attachment and removal of the auxiliary occurred smoothly (steps 1 and 3; *Scheme 1*). The key aminomethylation step delivers a (benzyloxy)carbonyl (Cbz)-protected amine side chain. Recently, *Hartman et al.* described the synthesis and use of the corresponding 9*H*-fluoren-9-yl *N*-(acetoxymethyl)carbamate (Fmoc variant) as an electrophile under *Lewis* acid catalysis ($ZnCl_2$ or BF_3) with achiral C-atom nucleophiles [32]. When we performed the Ti-catalyzed aminomethylation (or *Mannich*) step (step 2; *Scheme 1*), utilizing benzyl *N*-(methoxymethyl)carbamate (**3a**) as the electrophile, the reaction was accompanied by formation of the by-product **6a** (*Fig.*). The impurity forms, in up to 15% yield (HPLC), *via* nucleophilic substitution of the product's benzyloxy group of Cbz, by the MeO leaving group formed, when the reactive electrophile ($Cbz^+NH{=}CH_2$) is created *in situ*.

Scheme 1. *Synthesis of Cbz-(*S*)-β²-hPhe-OH* (**5**), *Starting from (*R*)-DIOZ* (**1**) *and Using Methyl Electrophile* **3a** *for the Aminomethylation Step*



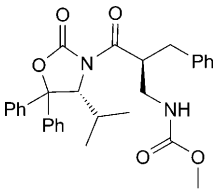
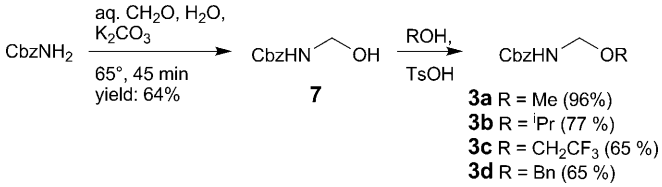


Figure. *Structure of the main by-product* **6a** *isolated after aminomethylation with methyl electrophile* **3a**

Formation of this by-product led to difficulties in purifying this material on large scale. The material was purified by column chromatography on kilograms of silica, which was made more complicated by the presence of the close-running by-product **6a**. However, observation of this by-product is not unknown, and a recent publication of *Seebach* and co-workers, in collaboration with our group, outlines the use of benzyl *N*-(isopropoxymethyl)carbamate (**3b**; *Scheme 2*) in aminomethylation reactions [33]. If electrophile **3b** is used, the increased steric bulk of the ^{i}PrO leaving group leads to reduced by-product formation, higher yields, and easier purification.

Scheme 2. *Synthesis of Electrophiles* **3a**–**3d** *for Aminomethylation*



We set out to prepare a series of benzyl *N*-(alkoxymethyl)carbamates **3a**–**3d** (*Scheme 2*) with the aim of comparing by-product formation in aminomethylation reactions. Benzyl *N*-(methoxymethyl)carbamate (**3a**) [34] and benzyl *N*-(isopropoxymethyl)carbamate (**3b**) [35] were included in our screen for completeness. As our third generation electrophiles, we chose benzyl *N*-[(2,2,2-trifluoroethoxy)methyl]carbamate (**3c**; because we envisaged that the 2,2,2-trifluoroethoxy leaving group would be less likely to act as a nucleophile) and benzyl *N*-[(benzyloxy)methyl]carbamate (**3d**; containing a BnO leaving group). When using **3d**, any nucleophilic attack would give a product still containing the required Cbz protecting group.

The synthesis of electrophiles **3a**–**3d** is outlined in *Scheme 2*. The key intermediate, benzyl *N*-(hydroxymethyl)carbamate (**7**), was prepared by mono-condensation with HCHO in 64% yield [35]. This intermediate was condensed with MeOH, ^{i}PrOH, 2,2,2-trifluoroethanol, or BnOH to give benzyl *N*-(alkoxymethyl)carbamates **3a**–**3d**, respectively, in high-to-moderate yields. Benzyl *N*-[(2,2,2-trifluoroethoxy)methyl]carbamate (**3c**) required column chromatography to remove some by-products, but removal of BnOH from benzyl *N*-[(benzyloxy)methyl]carbamate (**3d**) was easily achieved by steam distillation.

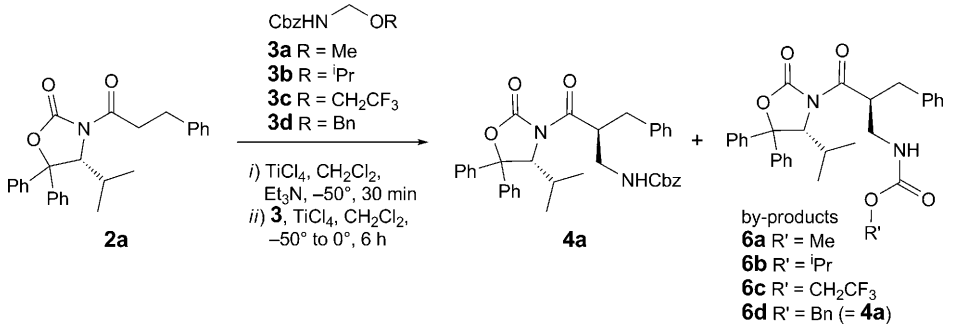
Taking the aminomethylation of (*R*)-4-isopropyl-5,5-diphenyl-3-(3-phenyl-propanoyl)oxazolidin-2-one (**2a**) as our standard reaction, aminomethylation was performed with the four electrophiles **3a**–**3d**. The results of these experiments are collected in the *Table*. The yield of each impurity, the diastereomeric ratio (dr) of products, and the percentages of the desired product and remaining starting material were calculated for each reaction, using either UPLC/MS or standard HPLC calibration curves.

We observed that, as expected, the yield of the by-products **6a**–**6d** decreased with reducing nucleophilicity of the leaving group (*i.e.*, in the order MeO > ^{i}PrO > CF_3CH_2O). Also, as predicted, the yield of the product was highest, when benzyl *N*-[(benzyloxy)methyl]carbamate (**3d**) was used, as material was not lost in forming an impurity. The diastereoselectivity remained similar for all four electrophiles (*ca.* 90:10), being only slightly higher when **3d** was applied. Overall, the yield of desired diastereoisomer increased with reducing nucleophilicity of the leaving group.

We then applied **3d** in the larger-scale synthesis (8–9 g; *Scheme 3*) of three key intermediates **4a**–**4c** with different side chains. Compounds **4a**–**4c** would give Cbz-(*S*)-β^2-hPhe-OH (**5**; *Scheme 1*) [33], Cbz-(*S*)-β^2-hLeu-OH, and Cbz-(*S*)-β^2-hLys-OH, respectively, on removal of the auxiliary, the latter requiring further side-chain manipulation to introduce the lysine side chain.

All of the aminomethylation reactions (step 2, *Scheme 3*) proceeded to give good yields and required less, or simplified, purification due to the fact that no by-product was formed. Products **4a** and **4c** were crystalline and, therefore, were purified by simple

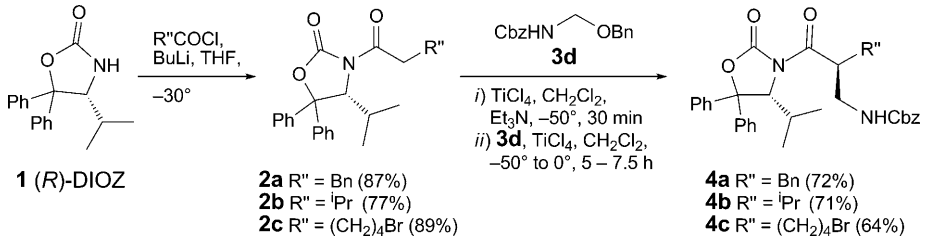
Table. *Aminomethylation Using Electrophiles* **3a**–**3d**



Entry	Electrophile R	Key impurity R′	% Impurity[a])	dr[a])	% Yield of desired diastereo-isomer[b])	% of remaining starting material[c])
1	Me	Me	8.3	88.1 : 11.9	65.0	11.3
2	^{i}Pr	^{i}Pr	6.5	88.4 : 11.6	68.9	8.6
3	CH_2CF_3	CH_2CF_3	3.9	89.0 : 11.0	64.1	15.7
4	Bn	Bn (= **4a**)	0	90.3 : 9.7	73.1	9.1

[a]) Determined by UPLC/MS. [b]) Maximum yield of desired diastereoisomer as determined by HPLC using standard calibration curves. [c]) Maximum yield of recoverable starting material as determined by HPLC using standard calibration curves.

Scheme 3. *Larger-Scale Synthesis of Key Intermediates* **4a**–**4c** *Using Benzyl Electrophile* **3d**



crystallization, whereas the product **4b** was an oil which required purification *via* column chromatography.

Conclusions. – In summary, we have demonstrated how a third-generation electrophile, benzyl *N*-[(benzyloxy)methyl]carbamate (**3d**), can be used in amino-methylation reactions for β^2-amino acid synthesis, resulting in an improved purity profile and thus easier isolation of pure products.

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Experimental Part

General. All chemicals were purchased from *Fluka* or *Sigma-Aldrich* unless otherwise mentioned. Intermediates **7** and **3b** were prepared according to an *Organic Synthesis* procedure [35], electrophile **3a** was prepared according to a literature procedure [34], and Cbz-protected β^2-amino acid **5** according to an *Organic Synthesis* procedure [33]. TLC: *Merck* silica-gel plates *60 F-254*, Art. Nr. 5729, detection with UV (254 nm). Reversed-phase (RP) HPLC: *Agilent-1100* apparatus, with a *Zorbax Eclipse XDB-C18*, 4.6 × 50 mm, 1.8-μ column, MeCN and H_2O as eluent (both containing 0.1% TFA); column temp., 35°; flow rate, 1.0 ml/min; measurement at 216 nm, the standard gradient, 5–100% MeCN over 6 min, 100% MeCN for 1.5 min, followed by 100–5% MeCN over 0.5 min. For separation of diastereoisomers formed on aminomethylation, an alternative HPLC method was utilised in order to achieve a better separation. The second standard gradient used was 40–75% MeCN over 12.5 min, then 75–100% MeCN over 0.5 min, followed by 100% MeCN over 1.5 min, with a flow rate of 2 ml/min. M.p.: *Büchi B-545* apparatus. NMR: 400-MHz *Varian*, *AS 400 Oxford* spectrometer, ^{1}H and ^{13}C shifts were referenced to (D_6)DMSO at 2.49 ppm for ^{1}H- and 39.52 ppm for ^{13}C-NMR. MS: *VG Platform* (*Fisons Instruments*), *Spectraflow 783* detector, *HP 1100* series HPLC.

Benzyl N-*[(2,2,2-Trifluoroethoxy)methyl]carbamate* (**3c**). To a soln. of *benzyl* N-*(hydroxymethyl)-carbamate* (**7**; 10.0 g, 55.2 mmol) dissolved in 2,2,2-trifluoroethanol (22.1 g, 221 mmol, 4 equiv.) and CH_2Cl_2 (100 ml) was added $TsOH \cdot H_2O$ (105 mg, 0.6 mmol, 1 mol-%), and the clear soln. was stirred at 25° for 3 h. Then, $NaHCO_3$ (232 mg, 2.8 mmol, 5 mol%) was added, and the suspension was stirred at r.t. for 1.5 h. The volatiles were removed *in vacuo* at < 40°, and the crude product was purified by column chromatography (CC) on 50 g of silica gel (SiO_2) eluting with hexane/AcOEt 8:2 to give **3c** (9.07 g, 64.5%). Colorless clear oil. HPLC (*Macherey-Nagel CC 70/4 Nucleosil 100-3 C18 HD*, 5–100% MeCN (6 min), 100% MeCN (4 min), flow rate 1 ml/min): t_R 7.40 min (not stable on column); purity 85% (215 nm). ^{1}H-NMR (400 MHz, (D_6)DMSO): 4.01 (*q*, *J* = 9.4, CF_3CH_2); 4.61 (*d*, *J* = 7.0, CH_2N); 5.06 (*s*, CH_2O); 7.38–7.28 (*m*, 5 arom. H); 8.09 (*t*, *J* = 5.9, NH, minor rotamer); 8.36 (*t*, *J* = 6.6, NH, major rotamer). ^{13}C-NMR (101 MHz, DEPT, (D_6)DMSO): 65.0 (*q*, *J* = 33.2, CF_3CH_2); 66.5 (CH_2); 73.4 (CH_2); 125.1 (*q*, *J* = 279, CF_3); 128.5 (arom. C); 128.6 (arom. C); 129.0 (arom. C); 137.3 (arom. C); 157.0 (C=O). ES-MS (pos.): 281 ($[M + NH_4]^+$). ES-MS (neg.): 262 ($[M - H]^-$).

Benzyl N-*[(Benzyloxy)methyl]carbamate* (**3d**). To a soln. of **7** (126.8 g, 700 mmol) in BnOH (360 ml, 5 equiv.) was added $TsOH \cdot H_2O$ (2.66 g, 14 mmol, 2 mol-%), and the clear soln. was stirred at 25° for 3 h. HPLC Analysis after 30 min showed < 1% of starting material present in the mixture. Na_2CO_3 (7.42 g, 70.0 mmol, 0.1 equiv.) was added, and the suspension was stirred at r.t. overnight. The mixture was heated (jacket temp. 130°), and for several hours hot steam was introduced, while the H_2O/BnOH azeotrope was removed by distillation. In the beginning, the distillate was muddy, then became clear, and a total of 16 l was distilled off. The mixture was cooled to 20°, and the liquid product started to crystallize (BnOH effectively inhibits the crystallization). The crude product was filtered, washed with H_2O, dissolved in 500 ml of *t*-BuOMe, and washed with H_2O (400 ml). The org. phase was dried (Na_2SO_4) and concentrated *in vacuo* including high vacuum to give **3d** (126 g, 64.6%). Colorless solid. HPLC (*Macherey-Nagel CC 70/4 Nucleosil 100-3 C18 HD*, 5–100% MeCN (6 min), 100% MeCN (4 min), flow rate 1 ml/min): t_R 7.58 min (not stable on column); purity 98% (215 nm). M.p. 36.4–36.5°. ^{1}H-NMR (400 MHz, (D_6)DMSO): 4.45 (*s*, CH_2O); 4.55 (*d*, *J* = 6.7, CH_2N); 5.06 (*s*, CH_2O); 7.38–7.24 (*m*, 10 arom. H); 8.27 (*t*, *J* = 6.7, NH). ^{13}C-NMR (101 MHz, DEPT, (D_6)DMSO): 66.3 (CH_2); 69.4 (CH_2); 72.0 (CH_2); 128.0 (arom. C); 128.2 (arom. C); 128.5 (arom. C); 128.6 (arom. C); 128.9 (arom. C); 129.1 (arom. C); 137.5 (arom. C); 139.0 (arom. C); 157.0 (C=O). ES-MS (pos.): 289 ($[M + NH_4]^+$). ES-MS (neg.): 270 ($[M - H]^-$).

*(*R*)-4-(1-Methylethyl)-5,5-diphenyl-3-(3-phenylpropanoyl)oxazolidin-2-one* (**2a**). (*R*)-4-Isopropyl-5,5-diphenyloxazolidin-2-one (DIOZ; 50 g, 177.7 mmol) was dissolved in THF (700 ml) under Ar, and the soln. was cooled to −30° in a dry ice/acetone bath under Ar. BuLi (1.6M in hexanes; 120 ml, 191.9 mmol) was transferred *via* cannula to the dropping funnel using N_2 pressure and was added dropwise to the suspension, keeping the temp. between −30 and −40°, to give a cream cloudy soln. The mixture was stirred at −30° for 10 min to give a clearer soln. Hydrocinnamoyl chloride (= 3-phenylpropanoyl chloride; 36.4 g/32 ml, 211.5 mmol) was dissolved in THF (100 ml) and added dropwise

to the mixture, again keeping the temp. below $-30°$ to give a clear colorless soln. The mixture was allowed to warm to 0° over 40 min at which time HPLC showed no remaining starting material. The mixture was cooled to $-10°$ and carefully diluted with sat. NH_4Cl soln. (200 ml). The mixture was stirred at this temp. for 10 min, and then further 500 ml sat. NH_4Cl soln. were added. The soln. was allowed to warm to r.t. and poured into AcOEt (600 ml), and the org. phase was separated. The org. phase was washed with 1M HCl (500 ml), $NaHCO_3$ soln. (500 ml), and brine (500 ml). The combined aq. phases were washed once more with *t*-BuOMe (500 ml). The combined org. phases were dried over (Na_2SO_4) and concentrated *in vacuo* including the high vacuum to give a brown solid (82.0 g, 112%). The crude product was purified by CC (SiO_2; CH_2Cl_2/hexane 7:3) to give **2a** (63.7 g, 86.7%). White solid. HPLC (*Macherey-Nagel CC 70/4 Nucleosil 100-3 C18 HD*, 40–75% MeCN (12.5 min), 75–100% MeCN (0.5 min), 100% MeCN (1.5 min), flow rate 2 ml/min): t_R 9.61 min; purity >99% (215 nm). M.p. 98–100°. $[\alpha]_D = +17.5$ ($c = 1.0$, $CHCl_3$). ^{1}H-NMR (400 MHz, (D_6)DMSO): 0.57 (*d*, *J* = 6.64, 3 H, *Me*$_2$CH); 0.81 (*d*, *J* = 7.00, 3 H, *Me*$_2$CH); 2.01 (*dsept.*, *J* = 6.64, 2.36, Me$_2$C*H*); 2.73 (*t*, *J* = 7.40, PhCH_2); 2.92–2.98 (*m*, 1 H, PhCH$_2$CH_2); 3.09–3.15 (*m*, 1 H, Ph); 5.56 (*d*, *J* = 2.32, Me$_2$CHC*H*); 7.04 (*d*, *J* = 6.64, 2 arom. H); 7.12–7.20 (*m*, 3 arom. H); 7.28 (*q*, *J* = 7.40, 2 arom. H); 7.36 (*t*, *J* = 7.80, 4 arom. H); 7.54 (*d*, *J* = 7.44, 2 arom. H); 7.63 (*d*, *J* = 7.40, 2 arom. H). ^{13}C-NMR (101 MHz, DEPT, (D_6)DMSO): 16.1 (*Me*$_2$CH); 21.9 (*Me*$_2$CH); 30.2 (Me$_2$*C*H); 30.5 (CH_2); 36.9 (CH_2); 65.1 (Me$_2$CH*C*H); 89.3 (Ph_2C); 125.6 (arom. C); 126.0 (arom. C); 126.7 (arom. C); 128.4 (arom. C); 128.8 (arom. C); 128.9 (arom. C); 129.0 (arom. C); 129.1 (arom. C); 129.5 (arom. C); 138.8 (arom. C(*ipso*)); 140.9 (arom. C(*ipso*)); 143.8 (arom. C(*ipso*)); 153.3 (C=O); 172.0 (C=O). Anal. calc. for $C_{27}H_{27}NO_3$: C 78.42, H 6.58, N 3.39; found: C 78.38, H 6.60, N 3.46. ES-MS (pos.): 414 ($[M+H]^+$).

General Procedure: Alkylation to Test Electrophiles. Compound **2a** (2.3 g, 5.56 mmol) was dissolved in CH_2Cl_2 (25 ml) under N_2 to give a clear colorless soln. The mixture was cooled to $-50°$ in a dry ice/acetone bath. $TiCl_4$ (6.1 ml, 1M in CH_2Cl_2, 6.11 mmol) was added dropwise to give an orange colored soln. Et_3N (0.62 g/0.75 ml, 6.11 mmol) was added dropwise (taking care for any exothermic reaction) to give a dark red soln. (a persistent red color developed after one drop of Et_3N). The soln. was then stirred at $-50°$ for further 30 min. The electrophile (6.11 mmol) was dissolved in CH_2Cl_2 (12 ml) in a separate flask and added slowly to the original flask maintaining the internal temp. below $-40°$. $TiCl_4$ (6.1 ml, 1M in CH_2Cl_2, 6.11 mmol) was added dropwise, and the mixture was transferred to an ice/brine bath at 0°. The soln. was stirred for 6 h between 0 and 5°, warming slowly for the first 3 h. Towards the end of the reaction, the soln. began to decolorize to give a yellow soln. The reaction was monitored using TLC (30% AcOEt/hexanes, UV) and HPLC, until there was minimal remaining starting material. The reaction was quenched with sat. aq. NH_4Cl soln. (25 ml) and H_2O (50 ml). The pale yellow suspension was extracted with AcOEt (2 × 150 ml; the aq. phase was yellow and org. phase colorless) and the combined org. phases washed with sat. aq. $NaHCO_3$ (100 ml) and brine (100 ml). The org. phase was dried (Na_2SO_4) and concentrated *in vacuo* to give a pale yellow oil, which foamed on rotorvap and was stored in the fridge to prevent decomposition. The exact composition of the crude product was calculated using standard calibration curves to determine the amounts of the starting material and required product.

*Benzyl {[(*S*)-2-Benzyl-3-[(*R*)-4-(1-methylethyl)-2-oxo-5,5-diphenyloxazolidin-3-yl]-3-oxopropyl}-carbamate* (**4a**). *Scale-Up Using Benzyl* N-*[(Benzyloxy)methyl]carbamate.* Compound **2a** (9.0 g, 21.8 mmol) was dissolved in CH_2Cl_2 (99 ml) under N_2 to give a clear colorless soln. The mixture was cooled to $-50°$ in an dry ice/acetone bath. $TiCl_4$ (24 ml, 1M in CH_2Cl_2, 24.0 mmol) was added dropwise to give an orange colored soln. Et_3N (2.43 g/3.34 ml, 24.0 mmol) was added dropwise (taking care for any exothermic reaction) to give a dark red soln. (a persistent red color developed after five drops of Et_3N). The soln. was then stirred at $-50°$ for a further 30 min. Benzyl *N*-[(benzyloxy)methyl]carbamate (6.51 g, 24.0 mmol) was dissolved in CH_2Cl_2 (47 ml) in a separate flask, and added slowly to the original flask, maintaining the internal temp. below $-40°$. $TiCl_4$ (24 ml, 1M in CH_2Cl_2, 24.0 mmol) was added dropwise, and the mixture was transferred to an ice/brine bath at 0°. The soln. was stirred for 6 h between 0 and 5°; warming slowly for the first 3 h. Towards the end of the reaction, the soln. began to decolorize to give a yellow soln. The reaction was monitored using TLC (30% AcOEt/hexanes, UV) and HPLC, until there was minimal remaining starting material. The reaction was quenched with sat. aq. NH_4Cl soln. (125 ml) and H_2O (250 ml). The pale yellow suspension was extracted with AcOEt (2 × 500 ml), and the combined org. phases washed with sat. aq. $NaHCO_3$ (500 ml) and brine (500 ml). The org. phase was

dried (Na_2SO_4) and concentrated *in vacuo* to give a pale yellow oil (16.6 g, 132%) containing 1.1 equiv. of BnOH (2.59 g; therefore maximum weight 12.6 + 2.59 = 15.2 g). The oil was left to stand in the fridge to induce crystallization. The crystalline product formed was triturated with 10% Et_2O in hexane (40 ml) and washed with further 20 ml to give a pale yellow crystalline solid (12.3 g, 97.6%). The product was triturated again with 20% Et_2O in hexane (40 ml) and washed with further 10 ml to give a paler yellow crystalline solid (10.1 g, 80.2%). The product was triturated a third time with 20% Et_2O in hexane (40 ml) and washed with further 10 ml to give an even paler yellow crystalline solid (9.03 g, 71.7%). HPLC (*Macherey-Nagel CC 70/4 Nucleosil 100-3 C18 HD*, 40–75% MeCN (12.5 min), 75–100% MeCN (0.5 min), 100% MeCN (1.5 min), flow rate 2 ml/min): t_R (E^+) 2.50 min, t_R(starting material) 9.61 min, t_R(BnOH) at solvent front, t_R(product) 10.13 min, t_R(diastereoisomer) 10.75 min. Remaining starting material 2.3%, dr 96.8:3.2. M.p. 130–131°. $[\alpha]_D = +97.2$ ($c = 0.98$, $CHCl_3$). ^{1}H-NMR (400 MHz, (D_6)DMSO): 0.58 (*d*, *J* = 7.04, 3 H, *Me*$_2$CH); 0.83 (*d*, *J* = 7.00, 3 H, *Me*$_2$CH); 2.01 (*sept.*, *J* = 6.64, Me$_2$C*H*); 2.37–2.42 (*m*, 1 H, PhC*H*$_2$); 2.55–2.60 (*m*, 1 H, PhC*H*$_2$); 3.18–3.22 (*m*, C*H*$_2$NH); 4.10 (*t*, *J* = 6.28, PhCH$_2$C*H*); 4.95 (*q*, *J* = 6.24, 1 H, PhC*H*$_2$O); 5.54 (*d*, *J* = 1.96, Me$_2$CHC*H*); 6.63 (*d*, *J* = 7.00, 2 arom. H); 6.98–7.06 (*m*, 3 arom. H); 7.25–7.39 (*m*, 11 arom. H); 7.55 (*d*, *J* = 7.40, 2 arom. H); 7.60 (*d*, *J* = 7.44, 2 arom. H). ^{13}C-NMR (101 MHz, DEPT, (D_6)DMSO): 15.4 (*Me*$_2$CH); 21.2 (*Me*$_2$CH); 29.5 (Me$_2$*C*H); 34.4 (CH_2); 41.3 (CH_2); 44.0 (PhCH*C*H); 64.7 (Me$_2$CH*C*H); 65.0 (CH_2); 88.3 (Ph$_2$*C*); 124.4 (arom. C); 124.9 (arom. C); 125.7 (arom. C); 127.3 (arom. C); 127.3 (arom. C); 127.4 (arom. C); 127.7 (arom. C); 127.9 (arom. C); 128.0 (arom. C); 128.0 (arom. C); 128.1 (arom. C); 128.5 (arom. C); 136.7 (arom. C(*ipso*)); 137.3 (arom. C(*ipso*)); 137.7 (arom. C(*ipso*)); 142.7 (arom. C(*ipso*)); 151.9 (C=O); 155.6 (C=O); 171.0 (C=O). ES-MS (pos.): 577 ($[M+H]^+$). Anal. calc. for $C_{36}H_{36}N_2O_5$: C 74.98, H 6.29, N 4.86; found: C 75.02, H 6.21, N 4.88.

*Methyl {(*S*)-2-Benzyl-3-[(*R*)-4-(1-methylethyl)-2-oxo-5,5-diphenyloxazolidin-3-yl]-3-oxopropyl}-carbamate* (by-product; **6a**). Compound **6a** was obtained from a large-scale reaction of the methyl electrophile. The analytical data of this product are included for reference. HPLC (*Macherey-Nagel CC 70/4 Nucleosil 100-3 C18 HD*, 40–75% MeCN (12.5 min), 75–100% MeCN (0.5 min), 100% MeCN (1.5 min), flow rate 2 ml/min): t_R 7.22 min. M.p. 128–134°. $[\alpha]_D = +94.0$ ($c = 1$, $CHCl_3$). ^{1}H-NMR (400 MHz, (D_6)DMSO): 0.75 (*d*, *J* = 7.04, 3 H, *Me*$_2$CH); 0.87 (*d*, *J* = 7.04, 3 H, *Me*$_2$CH); 1.97 (*dsept.*, *J* = 6.64, 3.52, Me$_2$C*H*); 2.51 (*dd*, *J* = 13.68, 6.64, 1 H, PhC*H*$_2$); 2.72 (*dd*, *J* = 13.64, 6.64, 1 H, PhC*H*$_2$); 3.38–3.51 (*m*, C*H*$_2$NH); 3.62 (*s*, MeO); 4.19 (*dt*, *J* = 7.44, 2.36, PhCH$_2$C*H*); 4.83 (*d*, *J* = 3.52, Me$_2$CHC*H*); 6.91 (*d*, *J* = 2.36, 2 arom. H); 7.08–7.09 (*m*, 3 arom. H); 7.24–7.39 (*m*, 10 arom. H). ^{13}C-NMR (101 MHz, DEPT, (D_6)DMSO): 15.3 (*Me*$_2$CH); 21.1 (*Me*$_2$CH); 29.5 (Me$_2$*C*H); 34.4 (CH_2); 41.4 (CH_2); 44.1 (PhCH$_2$*C*H); 51.1 (MeO); 64.7 (Me$_2$CH*C*H); 88.3 (Ph$_2$*C*); 124.4 (arom. C); 124.9 (arom. C); 125.6 (arom. C); 127.4 (arom. C); 127.6 (arom. C); 127.8 (arom. C); 127.9 (arom. C); 128.0 (arom. C); 128.0 (arom. C); 128.4 (arom. C); 137.3 (arom. C(*ipso*)); 137.7 (arom. C(*ipso*)); 142.6 (arom. C(*ipso*)); 151.9 (C=O); 155.2 (C=O); 171.9 (C=O). ES-MS (pos.): 501 ($[M+H]^+$). Anal. calc. for $C_{30}H_{32}N_2O_5$: C 71.98, H 6.44, N 5.60; found: C 72.17, H 6.32, N 5.63.

*(*R*)-3-(3-Methylbutanoyl)-4-(1-methylethyl)-5,5-diphenyloxazolidin-2-one* (**2b**). DIOZ (100 g, 355.4 mmol) was dissolved in THF (1000 ml) under Ar and cooled to −30° in a dry ice/acetone bath under Ar. BuLi (1.6M in hexanes, 233 ml, 373.2 mmol) was transferred *via* cannula to the dropping funnel using N_2 pressure and was added dropwise to the suspension, keeping the temp. between −30 and −40°, to give a yellow soln. Isovaleryl chloride (47.1 g, 48.0 ml, 391.0 mmol) was added dropwise to the mixture, again keeping the temp. under −30°. The mixture was allowed to warm to r.t. and left to stir overnight after which time HPLC showed no more starting material. The reaction was carefully quenched with 10% NH_4Cl soln. (500 ml), the mixture was diluted with *t*-BuOMe (1000 ml), and the org. phase was separated. The org. phase was washed with 10% HCl soln. (500 ml), 10% NaOH soln. (500 ml), and brine (500 ml). The org. phase was dried (Na_2SO_4) and concentrated *in vacuo* to give a white crystalline solid. The crude product was dissolved in hot ^{i}PrOH and then cooled to r.t. to give a white suspension, which was filtered to give **2b** (100 g, 77.0%). White solid. HPLC (*Macherey-Nagel CC 70/4 Nucleosil 100-3 C18 HD*, 40–75% MeCN (12.5 min), 75–100% MeCN (0.5 min), 100% MeCN (1.5 min); flow rate 2 ml/min): t_R 8.63 min; purity >99% (215 nm). M.p. 118.8–118.9°. $[\alpha]_D = +180.5$ ($c = 1.0$, CH_2Cl_2). ^{1}H-NMR (400 MHz, (D_6)DMSO): 0.60 (*d*, *J* = 6.64, 3 H, *Me*$_2$CH); 0.66 (*d*, *J* = 6.64, 3 H, *Me*$_2$CH); 0.70 (*d*, *J* = 6.64, 3 H, *Me*$_2$CH); 0.87 (*d*, *J* = 6.64, 3 H, *Me*$_2$CH); 1.81 (*sept.*, *J* = 6.64, Me$_2$C*H*); 2.03 (*dsept.*,

$J = 6.64$, 1.96, Me_2CH); 2.52–2.66 (*m*, Me_2CHCH_2); 5.57 (*d*, $J = 2.72$, Me_2CHCH); 7.29–7.38 (*m*, 8 arom. H); 7.55 (*d*, $J = 8.60$, 2 arom. H); 7.64 (*d*, $J = 8.20$, 2 arom. H). ^{13}C-NMR (101 MHz, DEPT, (D_6)DMSO): 16.3 ($CHMe_2$); 21.9 (Me_2CH); 22.5 (2 Me_2CH); 25.7 (Me_2CH); 30.1 (Me_2CH); 43.5 (CH_2); 65.2 (Me_2CHCH); 89.3 (Ph_2C); 125.5 (arom. C); 125.9 (arom. C); 128.4 (arom. C); 128.9 (arom. C); 129.1 (arom. C); 129.4 (arom. C); 138.8 (arom. C(*ipso*)); 143.8 (arom. C(*ipso*)); 153.4 (C=O); 172.0 (C=O). ES-MS (pos.): 366 ($[M+H]^+$). Anal. calc. for $C_{23}H_{27}NO_3$: C 75.59, H 7.45, N 3.83; found: C 75.72, H 7.63, N 3.83.

*Benzyl {(*S*)-3-Methyl-2-[(*R*)-4-(1-methylethyl)-2-oxo-5,5-diphenyloxazolidine-3-carbonyl]butyl}-carbamate* (**4b**). Compound **2b** (10.0 g, 27.4 mmol) was dissolved in CH_2Cl_2 (120 ml) under N_2 to give a clear colorless soln. The mixture was cooled to $-50°$ in an dry ice/acetone bath. $TiCl_4$ (28.7 ml, 1M in CH_2Cl_2, 28.7 mmol) was added dropwise to give a yellow colored soln. Et_3N (2.77 g/3.82 ml, 27.4 mmol) was added dropwise (taking care for any exothermic reaction) to give a dark red soln. (a persistent red color developed after five drops of Et_3N). The soln. was then stirred at $-50°$ for further 30 min. Benzyl *N*-[(benzyloxy)methyl]carbamate (8.17 g, 30.1 mmol) was dissolved in CH_2Cl_2 (60 ml) in a separate flask and added slowly to the original flask maintaining the internal temp. below $-40°$. $TiCl_4$ (28.7 ml, 1M in CH_2Cl_2, 28.7 mmol) was added dropwise, and the mixture was transferred to an ice/brine bath at 0°. The soln. was stirred for 5 h between 0 and 5°, warming slowly for the first 3 h. Towards the end of the reaction, the soln. began to decolorize to give a yellow soln. The reaction was monitored using TLC (30% AcOEt/hexanes, UV) and HPLC, until there was minimal remaining starting material. The reaction was quenched with 10% aq. NH_4Cl soln. (600 ml). The org. phases were separated and the aq. phase was extracted with AcOEt (2 × 250 ml), and the combined org. phases were washed with sat. aq. $NaHCO_3$ (250 ml) and brine (250 ml). The org. phase was dried (Na_2SO_4) and concentrated *in vacuo* to give a pale yellow oil (16.0 g, 111%) containing 1.1 equiv. BnOH (3.25 g; therefore maximum weight 14.5 + 3.25 = 17.75 g). The oil was left to stand in fridge to induce crystallization. The product could not be triturated directly as it was too gummy. The crude material was purified by CC on SiO_2 (100 g) eluting with 10% AcOEt/hexanes (80 × 200 ml) to give **4b** (10.3 g, 71.2%). Clear colorless oil. HPLC (*Macherey-Nagel CC 70/4 Nucleosil 100–3 C18 HD*, 40–75% MeCN (12.5 min), 75–100% MeCN (0.5 min), 100% MeCN (1.5 min), flow rate 2 ml/min): t_R(E^+) 2.50 min, t_R(starting material) 8.63 min, t_R(BnOH) at solvent front, t_R(product) 8.90 min, t_R(diastereoisomer) 9.61 min. No starting material, d.r. = 96.8 : 3.2. $[\alpha]_D = +91.9$ ($c = 1.0$, CH_2Cl_2). ^{1}H-NMR (400 MHz, (D_6)DMSO): 0.31 (*d*, $J = 6.64$, 3 H, Me_2CH); 0.48 (*d*, $J = 6.64$, 3 H, Me_2CH); 0.58 (*d*, $J = 6.64$, 3 H, Me_2CH); 0.86 (*d*, $J = 7.04$, 3 H, Me_2CH); 1.42 (*sept.*, $J = 6.64$, Me_2CH); 1.99 (*sept.*, $J = 7.04$, Me_2CH); 3.16–3.29 (*m*, CH_2NH); 3.78 (*t*, $J = 9.96$, Me_2CHCH); 4.95 (*q*, $J = 10.96$, OCH_2Ph); 5.58 (*s*, Me_2CHCH); 7.24–7.38 (*m*, 11 arom. H); 7.56 (*d*, $J = 8.20$, 2 arom. H); 7.66 (*d*, $J = 8.56$, 2 arom. H). ^{13}C-NMR (101 MHz, DEPT, (D_6)DMSO): 16.1 ($CHMe_2$); 19.4 (Me_2CH); 20.1 (Me_2CH); 21.8 (Me_2CH); 29.2 (Me_2CH); 30.0 (Me_2CH); 40.8 (CH_2NH); 48.7 ($NHCH_2CH$); 65.8 ($PhCH_2$); 65.8 (Me_2CHCH); 89.1 (Ph_2C); 125.6 (arom. C); 125.9 (arom. C); 127.1 (arom. C); 127.3 (arom. C); 128.3 (arom. C); 128.7 (arom. C); 128.9 (arom. C); 129.1 (arom. C); 129.3 (arom. C); 138.7 (arom. C(*ipso*)); 143.2 (arom. C(*ipso*)); 144.0 (arom. C(*ipso*)); 153.3 (C=O); 156.7 (C=O); 174.1 (C=O). ES-MS (pos.): 529 ($[M+H]^+$).

*(*R*)-3-(6-Bromohexanoyl)-4-(1-methylethyl)-5,5-diphenyloxazolidin-2-one* (**2c**). DIOZ (25 g, 88.9 mmol) was dissolved in THF (400 ml) under Ar and cooled to $-30°$ in a dry ice/acetone bath under Ar. BuLi (1.6M in hexanes; 60.0 ml, 96.0 mmol) was transferred *via* cannula to the dropping funnel using N_2 pressure and was added dropwise to the suspension, keeping the temp. between -30 and $-40°$, to give a cream cloudy soln. The soln. became too cold ($-50°$) and so was allowed to warm to $-30°$. The mixture was then stirred at this temp. for 10 min to give a clearer soln. 6-Bromohexanoyl chloride (22.8 g/16.3 ml, 106.6 mmol) was dissolved in THF (45 ml) and added dropwise to the mixture, again keeping the temp. below $-30°$ to give a clear colorless soln. The mixture was allowed to warm to r.t. over 2 h, and HPLC after 3 h showed no remaining starting material. The mixture was cooled to 0° in an ice bath and carefully diluted with sat. NH_4Cl soln. (200 ml). The mixture was stirred at r.t. for 10 min and poured into *t*-BuOMe (500 ml), and the org. phase was separated. The org. phase was washed with 1M HCl (500 ml), $NaHCO_3$ soln. (500 ml), and brine (500 ml). The combined aq. phases were washed once more with *t*-BuOMe (500 ml). The combined org. phases were dried (Na_2SO_4) and concentrated *in vacuo* including the high vacuum to give a pale yellow oil (43.1 g, 106%). The oil was left to stand in the fridge over the

weekend during which time crystals had formed and were triturated with hexane (200 ml), crushed, and filtered to give **2c** (36.2 g, 88.9%). White solid. HPLC (*Macherey-Nagel CC 70/4 Nucleosil 100-3 C18 HD*, 20–100% MeCN (6 min), 100% MeCN (1.5 min), 100–20% MeCN (0.5 min)): t_R(starting material) 5.47 min, t_R(acid chloride) 4.38 min, t_R(product) 7.19 min; purity 96% (215 nm). M.p. 75.7–76.3°. $[\alpha]_D = +161$ ($c = 1.0$, $CHCl_3$). ^{1}H-NMR (400 MHz, (D_6)DMSO): 0.76 (*d*, $J = 6.64$, 3 H, Me_2CH); 0.87 (*d*, $J =$ 7.00, 3 H, Me_2CH); 1.33–1.41 (*m*, CH_2); 1.51–1.62 (*m*, CH_2); 1.76–1.83 (*m*, CH_2); 1.92–1.99 (*m*, Me_2CH); 2.75–2.81 (*m*, 1 H, CH_2CO); 2.84–2.92 (*m*, 1 H, CH_2CO); 3.34 (*t*, $J = 6.64$, CH_2Br); 5.36 (*d*, $J = 3.12$, Me_2CHCH); 7.25–7.48 (*m*, 10 arom. H). ^{13}C-NMR (101 MHz, DEPT, (D_6)DMSO): 16.2 (Me_2CH); 22.0 (Me_2CH); 24.0 (CH_2); 27.4 (CH_2); 30.2 (Me_2CH); 32.5 (CH_2); 34.9 (CH_2); 35.4 (CH_2); 65.1 (Me_2CHCH); 89.3 (Ph_2C); 125.6 (arom. C); 126.0 (arom. C); 126.4 (arom. C); 129.0 (arom. C); 129.1 (arom. C); 129.5 (arom. C); 138.8 (arom. C(*ipso*)); 143.8 (arom. C(*ipso*)); 153.3 (C=O); 172.7 (C=O). ES-MS (pos.): 458/460 ($[M+H]^+$), 480/482 ($[M+Na]^+$). Anal. calc. for $C_{24}H_{28}BrNO_3$: C 62.89, H 6.16, N 3.06, Br 17.43; found: C 63.07, H 6.25, N 3.10, Br 16.94.

*Benzyl {(*S*)-6-Bromo-2-[(*R*)-4-(1-methylethyl)-2-oxo-5,5-diphenyloxazolidine-3-carbonyl]hexyl}-carbamate* (**4c**). Compound **2c** (10.0 g, 21.8 mmol) was dissolved in CH_2Cl_2 (99 ml) under N_2 to give a clear colorless soln. The mixture was cooled to −50° in a dry ice/acetone bath. $TiCl_4$ (24 ml, 1M in CH_2Cl_2, 24.0 mmol) was added dropwise to give an orange colored soln. Et_3N (2.43 g/3.34 ml, 24.0 mmol) was added dropwise (taking care for any exothermic reaction) to give a dark red soln. (a persistent red color developed after five drops of Et_3N). The soln. was then stirred at −50° for further 30 min. Benzyl *N*-[(benzyloxy)methyl]carbamate (6.51 g, 24.0 mmol) was dissolved in CH_2Cl_2 (47 ml) in a separate flask and added slowly to the original flask maintaining the internal temp. below −40°. $TiCl_4$ (24 ml, 1M in CH_2Cl_2, 24.0 mmol) was added dropwise, and the mixture was transferred to an ice/brine bath at 0°. The soln. was stirred for 7.5 h between 0 and 5°, warming slowly for the first 3 h. Towards the end of the reaction, the soln. began to decolorize to give a yellow soln. The reaction was monitored using TLC (30% AcOEt/hexanes, UV) and HPLC, until there was minimal remaining starting material. The reaction was quenched with sat. aq. NH_4Cl soln. (125 ml) and H_2O (250 ml). The pale yellow suspension was extracted with AcOEt (2×500 ml), and the combined org. phases washed with sat. aq. $NaHCO_3$ (500 ml) and brine (500 ml). The org. phase was dried (Na_2SO_4) and concentrated *in vacuo* to give a pale yellow oil (16.4 g, 121%) containing 1.1 equiv. BnOH (2.59 g; therefore, maximum weight 13.6 + 2.59 = 16.2 g). The oil was left to stand in the fridge to induce crystallization. The product could not be triturated directly as it was too gummy. The crude material was purified by CC on SiO_2 (500 g) eluting with 20% AcOEt/hexanes (80×50 ml, *Frs. 20–24* (starting material) and *Frs. 46–80* (product)) to give the product as a clear colorless oil which crystallized on standing (12.3 g, 75.9%). The diastereoisomers were not separated, and the product still contained some BnOH. The product was triturated with 10% Et_2O in hexane (20 ml) and washed with further 10 ml to give a white crystalline solid (9.79, 72.0%). The product was triturated again with 20% Et_2O in hexane (30 ml) and washed with further 10 ml to give **4c** (8.69 g, 63.9%). White crystalline solid. HPLC (*Macherey-Nagel CC 70/4 Nucleosil 100-3 C18 HD*, 40–75% MeCN (12.5 min), 75–100% MeCN (0.5 min), 100% MeCN (1.5 min), flow rate 2 ml/min): $t_R(E^+)$ 2.48 min, t_R(starting material) 9.91 min, t_R(BnOH) at solvent front, t_R(product) 10.31 min, t_R(diastereoisomer) 10.79 min. Remaining starting material 0.8%, dr 97.0 : 3.0. M.p. 97.7–98.3°. $[\alpha]_D = +98.3$ ($c = 1.0$, $CHCl_3$). ^{1}H-NMR (400 MHz, (D_6)DMSO): 0.59 (*d*, $J = 6.64$, 3 H, Me_2CH); 0.85 (*d*, $J = 6.64$, 3 H, Me_2CH); 1.08–1.37 (*m*, 2 CH_2); 2.00 (*dsept.*, $J = 6.64$, 3.72, Me_2CH); 3.09–3.24 (*m*, 2 CH_2); 3.79–3.85 (*m*, $PhCH_2CH$); 4.96 (*q*, $J = 11.32$, OCH_2Ph); 5.56 (*d*, $J = 2.32$, Me_2CHCH); 7.24–7.39 (*m*, 11 arom. H); 7.56 (*d*, $J = 7.44$, 2 arom. H); 7.65 (*d*, $J = 7.80$, 2 arom. H). ^{13}C-NMR (101 MHz, DEPT, (D_6)DMSO): 16.1 (Me_2CH); 21.8 (Me_2CH); 24.6 (CH_2); 29.1 (CH_2); 30.0 (Me_2CH); 32.7 (CH_2); 34.8 (CH_2); 42.7 ($PhCH_2CH$, $NHCH_2$); 65.7 (Me_2CHCH); 65.8 ($PhCH_2O$); 89.3 (Ph_2C); 125.5 (arom. C); 125.9 (arom. C); 128.3 (arom. C); 128.4 (arom. C); 128.5 (arom. C); 129.0 (arom. C); 129.1 (arom. C); 129.4 (arom. C); 130.0 (arom. C); 137.8 (arom. C(*ipso*)); 138.6 (arom. C(*ipso*)); 143.9 (arom. C(*ipso*)); 153.2 (arom. C(*ipso*)); 158.8 (C=O); 174.2 (C=O). ES-MS (pos.): 621/623 ($[M+H]^+$). Anal. calc. for $C_{33}H_{37}BrN_2O_5$: C 63.77, H 6.00, N 4.51, Br 12.86; found: C 64.03, H 6.05, N 4.53, Br 12.48.

*Cbz-(*S*)-β²-hPhe-OH* (**5**). Cleavage of the auxiliary to give Cbz-(*S*)-β²-hPhe-OH (**5**) was performed according to the procedure described in [33]. The conversion was carried out with a $LiOH/H_2O_2$ mixture, otherwise racemization occurred.

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