Diastereoselective Synthesis of β²-Amino Acids

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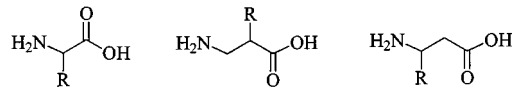
As part of an ongoing project concerning the synthesis of nonnatural amino acids, we have now developed a general strategy for the preparation of β²-amino acids (or 2-aminocarboxylic acid derivatives). Our procedure involves the synthesis of the sultam β-alaninate precursor **5** whose alkylation led with high yields and excellent diastereoselectivity to the precursor of β²-homophenylalanine, β²-homoalanine, and β²-homoleucine. Subsequent deprotection and Boc-protection yielded the expected β²-amino acids. X-ray analysis of the alkylation product established that (−)-sultam yielded (*R*)-β²-amino acids, conversely (+)-sultam yielded the enantiomer. The topicity of this alkylation is in agreement with the alkylation of Oppolzer's precursor for the synthesis of α-amino acids and opposite to that observed for gem-dialkylation.

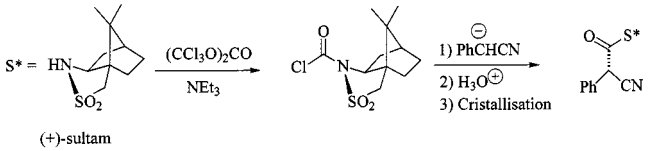
Introduction

Short oligomers made of six to seven β-amino acids have been shown to form stabilized helical structures which are more highly resistant to enzymatic metabolism than their congeners containing α-amino acids.[1] This recent demonstration has created a need for efficient syntheses of these nonproteinogenic amino acids; the different strategies explored in the past few years have been reviewed.[2] Most of the β³-substituted amino acids may be obtained enantiomerically pure after homologation of the corresponding commercially available α-amino acids or from chemical differentiation of the "naturally mixed" α- and β-amino acid aspartic acid.

β²-Amino acids have been prepared mainly by alkylation of a chiral enolate.[3][4] One procedure involves aminomethylation, with *N*-chloromethyl benzamide or 1-(aminomethyl)benzotriazole derivatives of an oxazolidinone chiral auxiliary, Evans' method.[5] According to this strategy, the side-chain of the β²-amino acids is first introduced by *N*-acylation of the oxazolidinone, thus requiring the preparation of the corresponding acyl chloride. However, both yields and diastereoisomeric excesses were good to excellent.[5] Another strategy recently reviewed[4] proceeds by the alkylation of a common precursor, i.e. lithiated hydropyrimidine. In this case, the precursor derived from β-alanine has to be resolved by preparative chromatography on a chiral column.

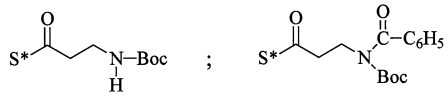
We have recently described[6] the preparation of enantiomerically pure 2-phenyl-3-amino propanoic acid (i.e. β²-homophenylglycine) by enantiomeric carboxylation of metalated phenylacetonitrile with sultam carbonyl chloride (Scheme 1). However, this strategy turns out to be restricted to the obtention of this peculiar β²-amino acid.





Scheme 1. Acylation of metalated phenylacetonitrile with sultam carbonyl chloride[6]

A long-standing interest in the synthesis of nonproteinogenic amino acids led us to propose a sultam-derived β-alanine analogue as a common precursor for the obtention of a β²-amino acid. We first prepared **1**, thinking that alkylation of its dianion would proceed smoothly; however, all our attempts have failed. Double protection of the nitrogen as in the precursor **2** was also unsuccessful as formation of the enolate of **2** led to β-elimination; in the presence of benzyl bromide *N*,*N*-Boc-benzoyl benzylamine was isolated as the major product.



1 **2**

As an extension to our previous work on the syntheses of both constrained analogues of phenylalanine[7] and C-α

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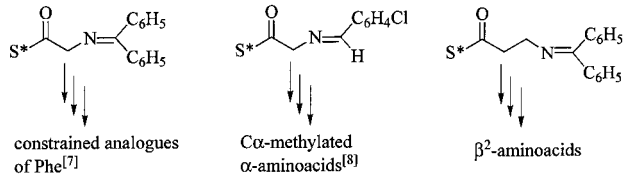
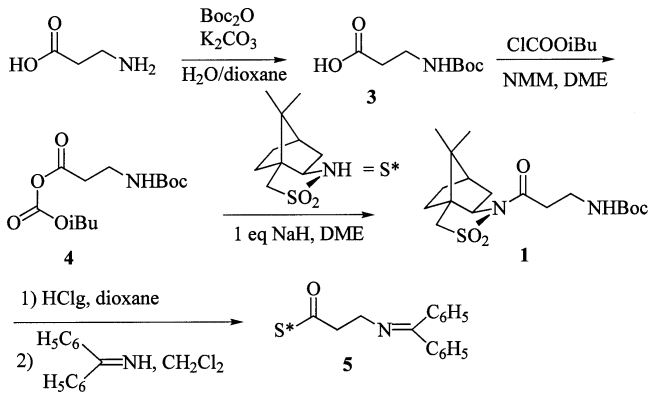
methylated α-amino acids,[8] we have prepared an homologous chiral precursor suitable for the obtention of β^2-amino acids, the chiral moiety S* standing for Oppolzer's sultam.[9]



Results

1. Preparation of the Chiral Precursor 5

The sultam-derived β-alanine imine **5** was obtained from the corresponding Boc-β-alanine and sultam, as shown in Scheme 2.

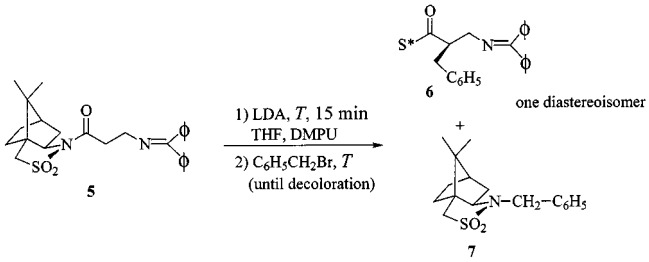


Scheme 2. Synthesis of the chiral precursor **5**: a sultam derivative of β-alanine-imine

The chiral compound **5** was prepared by coupling of the sodium anion of sultam with a mixed anhydride **(4)** of *N*-Boc-β-alanine **3**. After Boc deprotection and transimination, **5** was obtained as a crystalline solid, in 73% overall yield starting from Oppolzer's sultam. All these steps may be performed on 0.1 mol scale. Better yields and purities were obtained when anhydride **4** was added to a solution of the sodium salt of sultam after filtration of the *N*-methyl morpholinium hydrochloride salt through a pad of Celite. Boc removal with gaseous HCl led to the hydrochloride salt of the amino function which was then slowly (two days at room temperature) but quantitatively transiminated with benzophenone imine in dichloromethane, with concomitant precipitation of ammonium chloride. The chiral precursor **5** can be kept for long periods at 4°C in a stoppered flask.

2. Alkylation of the Chiral Precursor 5

Lithium enolate was generated from **5** by treatment at −78°C with one equivalent of either lithium diisopropylamide (LDA) or *n*-butyl lithium in THF/DMPU (3:2). Addition of 1.5 equivalents of benzyl bromide and subsequent stirring at −78°C (until decoloration) led, after quenching at −78°C, to the alkylated product **6** in high yield and as a unique diastereoisomer (NMR of the crude extract). HMPT or DMPU was required for the alkylation to proceed (Scheme 3).



Scheme 3. Lithiation of the sultam β-alaninate precursor **5** and reaction with benzyl bromide; ϕ = C_6H_5

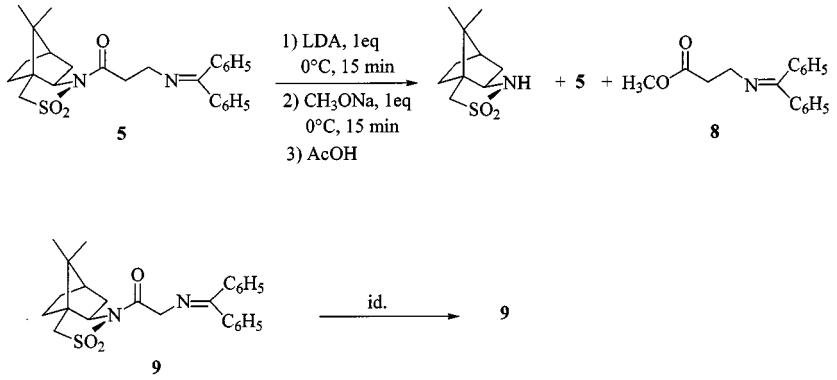
The diastereoselectivity of this alkylation was always excellent, whatever the temperature. However, a by-product was formed with an increase in the temperature (Table 1). *N*-benzyl sultam **7** must come from competitive ketene formation and subsequent benzylation of the lithiated anion of the chiral auxiliary. The corresponding β-alanine imine or alkylated β-alanine imine was not identified at the end of the extraction procedure; it is probably too unstable to aqueous treatment.

Table 1. Influence of the temperature on the alkylation of precursor **5**

Temperature *T* [°C][a]	**6** (%)	**7** (%)
−78	100	0
−45	100	0
−20	15	85
4	50	50

[a] The enolate was generated at the temperature indicated for 15 min then, after addition of the electrophile, the reaction was stirred at the temperature indicated.

The reactivity of the enolate generated from the β-alanine imine **5** was different from that of its congener **9**.[7] Precursors **5** and **9** were treated in parallel first with 1 equiv. of LDA at 4°C for 15 min to preform, quantitatively, the enolate and then the reaction mixtures were quenched with 1 equiv. of MeONa at 4°C for 15 min. Only the β-alanine-derived enolate **5** underwent elimination to yield the ketene, which then reacted with sodium methoxide, as evidenced by the formation of the methyl ester **8** (Scheme 4). Evans et al. have also reported the decomposition of lithium and sodium enolates via a ketene pathway as a function of temperature.[10] No elimination product was detected with the glycine building block **9**, in agreement with alkylation prod-

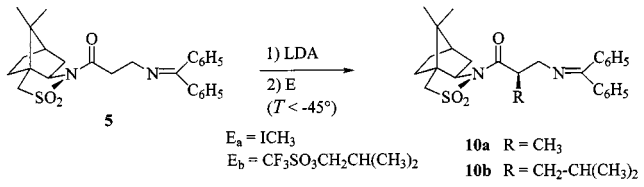


Scheme 4. Comparison of the stability of the enolates generated from β-alanine-derived precursor **5** and glycine analogue **9**

ucts obtained quantitatively, even after 4 to 5 days stirring at room temperature.[7]

In precursor **5**, the β-relation of the imine and carboxamide functions confers to its enolate a better delocalization of the electrons toward the oxygen atom than the enolate derived from the corresponding glycinate precursor **9**. This increased charge has at least two consequences, one negative and one positive, i.e. a competitive ketene formation at temperature $T > -20°C$, so the alkylation must be performed at $T \leq -45°C$, and an increase in the diastereoselectivity of the alkylation, respectively. Indeed, whatever the temperature (even with $T > -20°C$, i.e. with concomitant elimination) no trace of the other diastereoisomers was detected (*de* > 99%) in the NMR spectra of the crude extracts with the different electrophiles used in this study. It is plausible that the chelated lithiated species must be even more stabilized with the β-alaninate precursor **5** than the glycinate analogue **9**.

The conditions found for the synthesis of the β²-homophenylalanine precursor **6** (i.e. base, temperature, equiv. of electrophile) have been extended to the preparation of β²-homoalanine and β²-homoleucine. Alkylation by methyl iodide was straighforward, leading also to one diastereoisomer **10a** (Scheme 5). However, neither 1-bromo-2-methyl propane nor the iodo derivative $ICH_2CH(CH_3)_2$ was reactive enough, below −45°C, to yield the expected product **10b**; at higher temperature the alkylated sultam was recovered. However, with a better leaving group, i.e. triflate, the β²-homoleucine precursor **10b** was obtained, even at −78°C, in good yield as a unique diastereoisomer (Scheme 5).



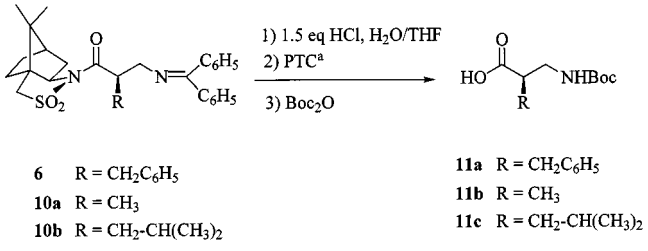
Scheme 5. Alkylation of β-alaninate precursor **5** to yield β²-homoalanine **10a** and β²-homoleucine **10b** precursors

3. Topicity of the Alkylation

The alkylation of glycinate-derived enolate, substituted with Oppolzer′s sultam, occurs on the kinetic (*Z*)-enolate with a *Si*-approach of the reactants,[11] even at room temperature and long reaction time with hindered electrophiles.[7] The (−)-sultam enantiomer yields the (*S*)-amino acid precursor. However, methylation of the monoalkylated precursorss instead of the glycinate-derived enolate leads to the opposite stereochemistry, i.e. probably corresponding to an attack on the *Re*-face of the (*E*)-enolate.[8] For this reason, the topicity of the alkylation of the β-alaninate derivative **5** has been unambigously assigned by an X-ray determination of the alkylation product **6**; the [α] or β²-homophenylalanine derivatives already described in the literature were also too small to be conclusive.[4] The (−)-sultam enantiomer yields the (*R*)-β²-homophenylalanine precursor (Figure 1), conversely (+)-sultam leads to (*S*)-β²-homophenylalanine. The course of this alkylation is identical to that observed with the glycinate precursor, the priority order being inverted with β²-amino acid.

4. Deprotection and Isolation of Boc-β²-Amino Acids

The Boc-β²-amino acids **11** were isolated after hydrolysis of the imine function (1.5 equiv. HCl, THF/H_2O), saponification under phase-transfer conditions (5 equiv. $LiOH \cdot H_2O$ and LiBr, 0.4 equiv. nBu_4NBr in MeCN) and Boc-protection. The overall yield was around 60% for these steps (Scheme 6).



Scheme 6. Deprotection steps of alkylated precursor and Boc protection of β²-homoamino acids; [a] PTC: phase-transfer conditions: 5 equiv. of $LiOH \cdot H_2O$, 0.4 equiv. of nBu_4NBr, 5 equiv. of LiBr in MeCN

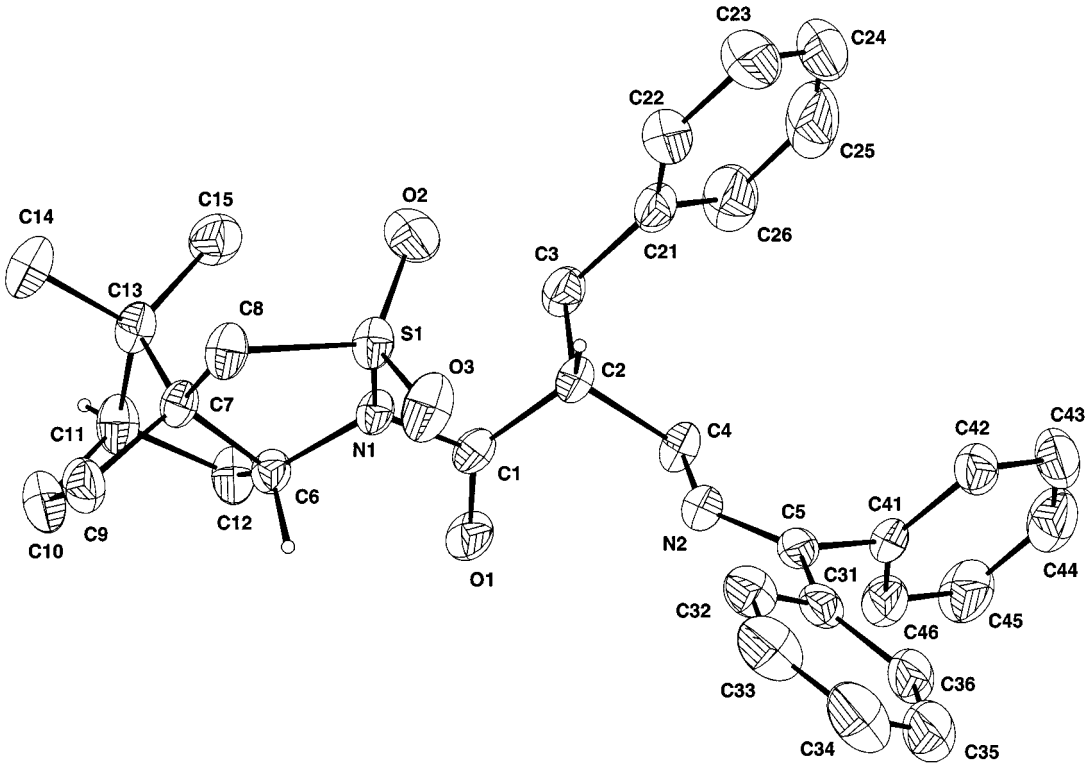
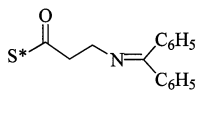
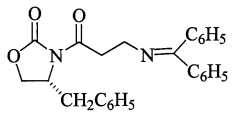


Figure 1. Cameron view[18] of (*S*)-β^2-homophenylalanine precursor

During the course of this study, we have also prepared the analogous imine precursor **12** with Evans′s benzyl oxazolidinone instead of the sultam as the chiral moiety.



5



12

Titanium enolates of precursors **5** and **12** ($TiCl_4$, NEt-*i*Pr_2) could not be quenched by methyl iodide, only decomposition products were observed whatever the temperature. The lithiated enolate of **12** was more reactive than the enolate of precursor **5**; for example, 1-iodo-2-methyl propane led to the corresponding β^2-homoleucine precursor, whereas triflate was required for the enolate derived from **5**. However, the diastereoisomeric excesses were always lower with precursor **12**; with benzyl bromide the *de* was 80%, with 1-iodo-2-methyl propane both diastereoisomers were obtained in a 1:1 ratio, even at −78°C. Thus, the sultame β-alaninate-derived Schiff base **5** proved to be the best precursor for the preparation of β^2-amino acids.

Conclusion

The sultam β-alaninate-derived Schiff base **5** constitutes a new precursor for the synthesis of β^2-homoamino acids. Both enantiomers of this precursor can be prepared on a large scale and kept over long periods. The lithiated enolate of **5** reacts smoothly with various electrophiles although the alkylation must be performed at temperatures below −20°C to avoid elimination by ketene formation, thus requiring reactive electrophiles. The key step for the synthesis of β^2-amino acids is now the preparation of the electrophiles corresponding to the β^2-amino acid side chain, as in Evans′ strategy, i.e. an iodide or triflate with precursor **5** and an acyl chloride with Evans′ oxazolidinone.[5]

Both strategies may be scaled up and appear to be complementary. They should allow the preparation of gram-scale amounts of both precursors and, finally, the preparation of functionalized β^2-oligopeptides to further investigate the reactivity of these molecules.

Experimental Section

***N*-[3-(*N*′-Benzoyl−*N*′−Boc)aminopropionyl] Sultam (2):** To a solution in dimethoxyethane (30 mL) of (−)-sultam (4.3 g, 20 mmol), previously dried by azeotropic distillation (two times) with toluene, was added NaH (0.66 g, 22 mmol) at −15°C. In parallel, in another flask, to a solution of *N*-benzoyl alanine (3.86 g, 20 mmol) in DME (40 mL) was added, at −15°C, *N*-methylmorpholine (2.45 mL, 22 mmol) and then isobutyl chloroformate (2.9 mL, 22 mmol). After 15 min stirring at −15°C, this preformed mixed anhydride was rapidly introduced, after filtration through a Celite pad, into the sodium salt of (−)-sultam. After 1 h stirring at −10°C and 1 h at room temperature, the crude mixture was quenched with AcOH (1 equiv., 1.25 mL) in CH_2Cl_2 (5 mL). The organic layer was washed (three times) with saturated NH_4Cl solution and dried with anhydrous $MgSO_4$. The solvent was evaporated in a rotary evapor-

ator and the residual yellow oil was purified by flash chromatography (cyclohexane/AcOEt, 8:2) to give *N*-(3-benzoylaminopropionyl) sultam (6.3 g, 81% yield), m.p. 115−116°C. − ^{1}H NMR (200 MHz, $CDCl_3$) δ = 7.74 (m, 2 H, H arom), 7.5−7.35 (m, 3 H, H arom), 3.89−3.73 (m, 3 H, H^2, H^{12}), 3.46 (AB system, J_{AB} = 14 Hz, 2 H, H^{10}), 3.03 (m, 2 H, H^{11}), 2.2−1.8 (m, 5 H, H^3 H^4 H^5 H^6), 1.3−1.5 (m, 2 H, $H^{5'}$ $H^{6'}$), 1.1 (s, 3 H, CH_3), 0.94 (s, 3 H, CH_3). − $C_{20}H_{26}N_2O_4S$ (390.5): calcd. C 61.54, H 6.67, N 7.18, found C 61.32, H 6.81, N 7.25. − [α] = −95 (*c* = 1, $CHCl_3$). − To a solution of *N*-(3-benzoylaminopropionyl) sultam (6.24 g, 16 mmol) in THF (50 mL) was added dimethylaminopyridine (0.390 g, 3.2 mmol) and Boc_2O (7 g, 32 mmol). After stirring for about 12 h at room temperature, the reaction mixture was refluxed for 2 h. After cooling the solution was washed twice with a saturated NH_4Cl solution. The organic layer was dried with $MgSO_4$ and concentrated in vacuo leading to a red oil, which was purified by flash chromatography (cyclohexane/AcOEt, 7:3), to give **2** as an amorphous powder (7.17 g, 91% yield). − ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.52−7.35 (m, 5 H, H arom), 4.15 (m, 2 H, H^{12}), 3.85 (m, 1 H, H^2), 3.46 (AB system, J_{AB} = 14 Hz, 2 H, H^{10}), 3.12 (m, 2 H, H^{11}), 2.21−1.85 (m, 5 H, H^3 H^4 H^5 H^6), 1.34−1.45 (m, 2 H, $H^{5'}$ $H^{6'}$), 1.18 (s, 3 H, CH_3), 1.14 (s, 9 H, Boc), 0.95 (s, 3 H, CH_3). − $C_{25}H_{34}N_2O_6S$ (490.6): calcd. C 61.22, H 6.94, N 5.71, found C 61.23, H 7.02, N 5.63. − [α] = −62 (*c* = 1, $CHCl_3$).

***N*-*tert*-Butyloxycarbonylamino-3-propionic Acid (3):** To a solution of β-alanine (8.9 g, 0.1 mol) in water (125 mL) and dioxane (250 mL) containing K_2CO_3 (27.7 g, 0.2 mol) was added Boc_2O (24 g, 0.11 mol) dropwise at 4°C. After 24 h stirring at room temperature, the dioxane was removed in vacuo, the aqueous layer washed twice with AcOEt and then acidified with 1 N HCl (pH 2−3). The aqueous layer was extracted three times with CH_2Cl_2, the combined organic layers washed with saturated NaCl solution and dried with anhydrous $MgSO_4$. The solvent was removed in vacuo, yielding **3** as a white powder which was used without further purification (18.2 g, 96% yield), m.p. 78−79°C. − ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 6.3 (broad peak, 0.4 H, NH *cis*/*trans* isomerism), 5.1 (broad peak, 0.6 H, NH *cis*/*trans* isomerism), 3.42 (m, 2 H, CH_2), 2.59 (m, 2 H, CH_2), 1.45 (s, 9 H, Boc). − $C_8H_{15}NO_4$ (189.2): calcd. C 50.79, H 7.94, N 7.41, found C 50.70; H 8.13, N 7.41.

***N*-(3-*tert*−Butyloxycarbonylaminopropionyl) Sultam (1):** To a solution in dimethoxyethane (30 mL) of (−)-sultam (4.3 g, 20 mmol), previously dried by azeotropic distillation (two times) with toluene, was added NaH (0.66 g, 22 mmol) at −15°C. In parallel, in another flask, to a solution of the acid **3** (3.78 g, 20 mmol) in DME (40 mL) was introduced, at −15°C, *N*-methylmorpholine (2.45 mL, 22 mmol) and then isobutyl chloroformate (2.9 mL, 22 mmol). After 15 min stirring at −15°C, this preformed mixed anhydride **4** was rapidly introduced, after filtration through a Celite pad, into the sodium salt of (−)-sultam. After 1 h stirring at −10°C and 1 h at room temperature, the crude mixture was quenched with AcOH (1 equiv., 1.25 mL) in CH_2Cl_2 (5 mL). The organic layer was washed three times with saturated NH_4Cl solution and dried with anhydrous $MgSO_4$. The solvent was evaporated in a rotary evaporator and the residual yellow oil was purified by flash chromatography (cyclohexane/AcOEt, 8:2) leading to **1** as a white fluffy material (6.86 g, 89% yield). − ^{1}H NMR (200 MHz, $CDCl_3$): δ = 5.2 (broad peak, 1 H, NH), 3.82 (q, 1 H, H^2), 3.45 (m, 4 H, H^{10} H^{12}), 2.89 (m, 2 H, H^{11}), 2.2−1.85 (m, 5 H, H^3 H^4 H^5 H^6), 1.4 (s, 9 H, Boc), 1.33 (m, 2 H, $H^{5'}$ $H^{6'}$), 1.12 (s, 3 H, CH_3), 0.94 (s, 3 H, CH_3). − $C_{18}H_{30}N_2O_5S$ (386.5): calcd. C 55.96, H 7.77, N 7.25, found C 55.96, H 7.95, N 7.12. − [α] = −78 (*c* = 1, $CHCl_3$).

***N*-[3-(*N'*-Diphenylmethylene)aminopropionyl] Sultam (5):** A solution at 4°C of **1** (8.98 g, 20 mmol) in dioxane (100 mL) was saturated with gaseous HCl for 1 h. After 1 h stirring at 4°C, the solvent was evaporated in vacuo, the residual yellow powder dissolved in CH_2Cl_2 (250 mL) and reacted with benzophenone imine (3.8 g, 21 mmol) for 48 h at room temperature. The reaction mixture was filtered through a Celite pad and concentrated in vacuo. The residual yellow powder was purified by flash chromatography (cyclohexane/AcOEt, 8:2, then 7:3) to yield **5** as a white solid (6.6 g, 73% yield starting from sultam), m.p. 122−123°C. − ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.51−7.1 (m, 10 H, H arom), 3.8 (m, 1 H, H^2), 3.63 (m, 2 H, H^{12}), 3.39 (AB system, J_{AB} = 14 Hz, 2 H, H^{10}), 3.1 (m, 1 H, H^{11}), 3.0 (m, 1 H, $H^{11'}$), 2.1−1.93 (m, 2 H, H^3), 1.8 (m, 3 H, H^5 H^6 H^4), 1.3 (m, 2 H, $H^{5'}$ $H^{6'}$), 1.07 (s, 3 H, CH_3), 0.89 (s, 3 H, CH_3). − $C_{26}H_{30}N_2O_3S$ (450.6): calcd. C 69.33, H 6.67, N 6.22, found C 69.19, H 6.74, N 6.10. − [α] = −65 (*c* = 1, $CHCl_3$).

General Procedure for the Alkylation of Precursor 5: The precursor **5** previously dried by azeotropic distillation (three times) with toluene was dissolved in anhydous THF and DMPU (30 and 20 mL, respectively for 10 mmol of precursor). This mixture was then cooled to −78°C under argon and 1.1 equiv. of LDA (2 M in THF) was added slowly. After 15 min stirring at −78°C, the corresponding electrophile (1.5 equiv.) was added dropwise, and the solution stirred at either −78°C or −45°C for 2 hours. Then, the reaction solution was quenched with AcOH (0.3 mL) in THF (0.7 mL), for 10 mmol of precusor **5**. After dilution with Et_2O, the organic layer was washed three times with saturated NH_4Cl solution and dried with anhydrous $MgSO_4$. The organic layer was concentrated in vacuo and the residual orange oil was purified by either recrystallization or flash chromatography.

***N*-[2-Benzyl-3-(*N'*-diphenylmethylene)aminopropionyl] Sultam (6):** Alkylation of precursor **5** (4.5 g, 10 mmol) with benzyl bromide (2.1 mL, 15 mmol) was performed according to the alkylation procedure above. Purification of the crude oil (cyclohexane/AcOEt, 9:1) gave a white solid (3.9 g, 72% yield), m.p. 153−154°C. − ^{1}H NMR (200 MHz, $CDCl_3$) δ: 7.66−7.13 (m, 15 H, H arom), 3.9−3.7 (m, 3 H, H^2 H^{12}), 3.5−3.3 (m, 3 H, H^{11} H^{10}), 3.12 (m, 1 H, H^{13}), 3.0 (m, 1 H, $H^{13'}$), 2.05−1.72 (m, 5 H, H^3 H^4 H^5 H^6), 1.4−1.2 (m, 2 H, $H^{5'}$ $H^{6'}$), 0.86 (s, 3 H, CH_3), 0.67 (s, 3 H, CH_3). − ^{1}H NMR (400 MHz, C_6D_6): δ = 7.2 (m, 15 H, H arom), 4.52 (m, 1 H, H^{11}), 4.34 (ABX system, J_{AB} = 14 Hz, J_{AX} = 7 Hz, 1 H, H^{12}), 3.78 (ABX system, J_{AB} = 14 Hz, J_{BX} = 7 Hz, 1 H, $H^{12'}$), 3.6 (m, 1 H, H^2), 3.38 (ABX system, J_{AB} = 14 Hz, J_{AX} = $J_{BX = 7}$ Hz, 2 H, H^{13}), 2.78 (AB system, J_{AB} = 14 Hz, 2 H, H^{10}), 1.96 (m, 2 H, H^3), 1.37 (m, 3 H, H^4 H^5), 1.15 (m, 1 H, H^6), 0.82 (s and m, 4 H, $H^{5'}$ and CH_3), 0.6 (m, 1 H, $H^{6'}$), 0.48 (s, 3 H, CH_3). − $C_{33}H_{36}N_2O_3S$ (540.7): calcd. C 73.33, H 6.67, N 5.18, found C 73.25, H, 6.69, N, 5.09. − $[\alpha]_D^{20}$ = −20 (*c* = 1, $CHCl_3$).

***N*-Benzyl Sultam (7):** *N*-Benzyl sultam **7** was identified in the NMR spectrum of the crude alkylation product with benzyl bromide when the alkylation was conducted at *T* = −20°C. *N*-Benzyl sultam was independently prepared by benzylation of the sodium salt of sultam. To a solution of (−)-sultam (1 g, 4.6 mmol) in THF (20 mL) was added NaH (165 mg, 5.1 mmol). After 30 min stirring at room temperature, benzyl bromide was added (0.65 mL, 5.1 mmol) and the reaction mixture was stirred for 16 h. After concentration in vacuo, the colorless oil was dissolved in AcOEt and washed three times with saturated NH_4Cl solution. The organic layer was dried with $MgSO_4$ and concentrated, leading to a white powder which was triturated with pentane (1.19 g, 85% yield), m.p. 96−98°C. − ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.4−7.3 (m, 5 H, H arom), 4.15 (d, *J* = 14 Hz, 1 H, H^{11}), 3.78 (d, *J* = 14 Hz, 1 H,

$H^{11'}$), 3.18 (AB system, J_{AB} = 14 Hz, 2 H, H^{10}), 3.11 (m, 1 H, H^2), 1.85 (m, 2 H, H^3), 1.73 (m, 1 H, H^4), 1.47 (m, 2 H, H^5, H^6), 1.35 (m, 1 H, $H^{5'}$), 1.22 (m, 1 H, $H^{6'}$), 1.08 (s, 3 H, CH_3), 0.9 (s, 3 H, CH_3). − $C_{17}H_{23}NO_2S$: calcd. C, 66.89, H 7.54, N 4.59, found C 66.94, H 7.62, N 4.56. − $[\alpha]_D^{20}$ = −25 (*c* = 1, $CHCl_3$).

Methyl 3-(*N'*-Diphenylmethylene)aminopropionate (8): To a solution of β-alanine (0.89 g, 10 mmol) in MeOH (40 mL) was added dropwise thionyl chloride (0.8 mL, 11 mmol). After 48 h stirring, methanol was evaporated in vacuo leading to a white yellow solid which was used without further purification. This chlorhydrate was reacted in CH_2Cl_2 (40 mL) with benzophenone imine (2 g, 11 mmol) for 72 h at room temperature. The reaction mixture was filtered through a Celite pad and concentrated in vacuo, the residual brownish oil was purified by flash chromatography (cyclohexane/AcOEt, 8:2) to yield a colorless oil (2.53 g, 95%). − ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.62 (m, 2 H, H arom), 7.47 (m, 3 H, H arom), 7.35 (m, 3 H, H arom), 7.2 (m, 2 H, H arom), 3.69 (s, 3 H, CH_3), 3.67 (t, *J* = 7 Hz, 2 H, H^3), 2.75 (t, *J* = 7 Hz, 2 H, H^2). − $C_{17}H_{17}NO_2$ (267.3): calcd. C 76.40, H 6.37, N 5.24, found C 76.43, H 6.50, N 5.17.

***N*-[3-(*N'*-Diphenylmethylene-2-methyl)aminopropionyl] Sultam (10a):** Alkylation of precursor **5** (2.25 g, 5 mmol) with methyl iodide (0.46 mL, 7.5 mmol) was performed according to the alkylation procedure. Recrystallization (CH_2Cl_2/pentane) led to a white solid (1.72 g, 75% yield), m.p. 171−172°C. − ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.63−7.19 (m, 10 H, H arom), 3.91 (m, 1 H, H^2), 3.75 (ABX system, J_{AB} = 14 Hz, J_{AX} = 7 Hz, 1 H, H^{12}), 3.56 (m, 1 H, H^{11}), 3.5 (AB system, J_{AB} = 14 Hz, 2 H, H^{10}), 3.35 (ABX system, J_{AB} = 14 Hz, J_{BX} = 7 Hz, 1 H, $H^{12'}$), 2.06 (m, 2 H, H^3), 2.0−1.83 (m, 3 H, H^4 H^5 H^6), 1.49−1.26 (m, 2 H, $H^{5'}$ $H^{6'}$), 1.29 (d, *J* = 8 Hz, 3 H, H^{13}), 1.18 (s, 3 H, CH_3), 0.99 (s, 3 H, CH_3). − $C_{27}H_{32}N_2O_3S$ (464.6): calcd. C 69.83, H 6.90, N 6.03, found C 69.74, H 7.05, N 5.98. − [α] = −57 (*c* 1, $CHCl_3$)

Isobutyl Triflate: To a solution of pyridine (2.4 mL, 30 mmol) and isobutyl alcohol (2.8 mL, 30 mmol) in CH_2Cl_2 (8 mL) was added triflic anhydride (5.6 mL, 33 mmol) in CH_2Cl_2 (20 mL) dropwise at 4°C. The reaction solution was stirred for 10 min at 4°C and then washed with H_2O (20 mL). The organic layer was dried with $MgSO_4$ and then concentrated in vacuo to yield the isobutyl triflate (2.4 g, 69% yield). Teb: 39°C (15 Torr). − ^{1}H NMR (400 MHz, CDCl3): δ = 4.3 (d, *J* = 7 Hz, 2 H, Hα), 2.1 (m, 1 H, Hβ), 1.03 (s, 3 H, CH_3), 0.98 (s, 3 H, CH_3). − ^{13}C NMR (200 MHz, $CDCl_3$) δ: 115.5 (CF_3), 82.9 (Cα), 28.4 (Cβ), 18.2 (CH_3).

***N*-(3-(*N'*-Diphenylmethylene)-2-isobutylaminopropionyl) Sultam (10b):** Alkylation of precursor **5** (10.35 g, 23 mmol) with isobutyl triflate (5.81 g, 28 mmol) was performed according to the alkylation procedure. Filtration through a silica pad and recrystallization (CH_2Cl_2/pentane) led to a white solid (5.9 g, 51% yield). m.p. 142−143°C. − ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.63−7.18 (m, 10 H, H arom), 3.91 (m, 1 H, H^2), 3.74 (ABX system, J_{AB} = 14 Hz, J_{AX} = 7 Hz, 1 H, H^{12}), 3.57 (m, 1 H, H^{11}), 3.47 (AB system, J_{AB} = 14 Hz, 2 H, H^{10}), 3.40 (ABX system, J_{AB} = 14 Hz, J_{BX} = 7 Hz, 1 H, $H^{12'}$), 2.08 (m, 2 H, H^3), 1.9 (m, 3 H, H^4 H^5 H^6), 1.58 (m, 3 H, H^{13} H^{14}), 1.39 (m, 2 H, $H^{5'}$ $H^{6'}$), 1.35 (s, 3 H, CH_3), 0.98 (s, 3 H, CH_3), 0.93 (2d, *J* = 6 Hz, 6 H, H^{15} H^{16}). − $C_{30}H_{38}N_2O_3S$ (506.7): calcd. C 71.15, H 7.51, N 5.53, found C 71.10, H 7.56, N 5.46. − $[\alpha]_D^{20}$ = −36 (*c* = 1, $CHCl_3$)

From the Alkylated Precursor to the Corresponding *N*-Boc-Protected Homoamino Acid. − General Procedure: To a 1 N HCl solution (1.5 equiv.) was added a precooled (at 4°C) solution of the alkylated precursor in THF (10 mL for 4 mmol). After one night stirring at room temperature, THF was evaporated by rotary evaporation. The aqueous layer was diluted with water and washed three times with Et_2O and then concentrated in vacuo. The residual chlorhydrate (characterized by NMR spectroscopy) was dissolved in CH_3CN (10 mL for 4 mmol) and then reacted with $LiOH \cdot H_2O$ (5 equiv.), LiBr (5 equiv.), and tetrabutylammonium bromide (0.4 equiv.) for 3 hours. After concentration in vacuo and dilution with water, the aqueous layer was acidified with 3 N HCl (to pH 1−2). This aqueous layer was extracted three times with CH_2Cl_2. The solid obtained after evaporation of the aqueous layer was dissolved in EtOH (20 mL) and reacted with Boc_2O (1.2 equiv.) in the presence of $NaHCO_3$ (4 equiv.). After overnight stirring at room temperature, the reaction solution was filtered through a Celite pad. Concentration by rotary evaporation led to a white solid which was dissolved in H_2O. This aqueous layer was extracted twice with CH_2Cl_2 and then acidified to pH 2 with 3 N HCl. The acidic aqueous layer was extracted three times with CH_2Cl_2. After washing three times with saturated NaCl solution, the combined organic layers were concentrated in vacuo, leading a residual solid which was recrystallized.

(*R*)-3-*tert*-Butyloxycarbonyl-β^2-homophenylalanine (11a): According to the general procedure, deprotection and Boc-protection of 4 mmol of alkylated precursor **6** led to a white solid (878 mg, 75%) after recrystallization from Et_2O, m.p. 78−80°C. − ^{1}H NMR of the chlorhydrate of sultam β^2-homophenylalanine (400 MHz, $CDCl_3$): δ = 8.21 (broad peak, 1 H, NH_3), 7.28−7.17 (m, 5 H, H arom), 4.17 (broad peak, 1 H, H^2), 3.8 (m, 2 H, H^{11} H^{10}), 3.79−3.37 (m, 2 H, H^{12} $H^{10'}$), 3.16 (m, 1 H, $H^{12'}$), 3.03 (ABX system, J_{AB} = 13 Hz, J_{AX} = 8 Hz, 1 H, H^{13}), 2.94 (m, 1 H, $H^{13'}$), 1.95 (m, 1 H, H^3), 1.87−1.72 (m, 4 H, $H^{3'}$ H^4 H^5 H^6), 1.72 (m, 1 H, $H^{5'}$), 1.28 (m, 1 H, $H^{6'}$), 0.89 (s, 3 H, CH_3), 0.65 (s, 3 H, CH_3). Boc-β^2-homophenylalanine **11a**: ^{1}H NMR (200 MHz, $CDCl_3$): δ 10−9 (very broad peak, 1 H, COOH), 7.29 (m, 2 H, H arom), 7.22 (m, 3 H, H arom), 6.7 (broad peak, 0.5 H, NH *cis*/*trans* isomerism), 5.7 (broad peak, 0.5 H, NH *cis*/*trans* isomerism), 3.45 and 3.1 (m, 1 H, H^4), 3.1 (m, 1 H, H^3), 3.06 (m, 1 H, H^2), 2.92 and 2.75 (m, 1 H, $H^{3'}$), 1.47 and 1.44 (two s, 9 H, Boc *cis*/*trans* isomerism). − ^{13}C NMR (400 MHz, $CDCl_3$) δ: 179.5 and 178.3 (C^1), 158.4 and 156.3 (C^5), 138.5, 134.4, 129 and 127 (C arom), 81.5 and 80.2 (C^6), 47.9 and 47.5 (C^2), 42.3 and 41.6 (C^4), 36.3 and 36.1 (C^3), 28.7 and 28.6 (CH_3). − $C_{15}H_{21}NO_4$ (279.3): calcd. C 64.52, H 7.53, N 5.02, found C 64.55, H 7.71, N 4.87. − [α] = 18 (*c* 1, $CHCl_3$). − Dicyclohexylamine salt of **11a**: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.25 (m, 5 H, H arom), 7.18 (broad peak, 1 H, NH), 5.57 (broad peak, 1 H, NH), 3.30 (m, 1 H, H^4), 3.16 (m, 1 H, $H^{4'}$), 3.05 (m, 1 H, H^2), 2.90 (m, 2 H, H cyclohexyl), 2.72 (m, 2 H, H^3), 1.97 (m, 4 H, H cyclohexyl), 1.79 (m, 4 H, H cyclohexyl), 1.65 (m, 2 H, H cyclohexyl), 1.43−1.34 (s and m, 13 H, Boc and H cyclohexyl), 1.19 (m, 6 H, H cyclohexyl). − $C_{27}H_{44}N_2O_4$ (460.7): calcd. C 70.43, H 9.56, N 6.09, found C 70.36, H 9.68, N 5.97.

(*R*)-3-*tert*-Butyloxycarbonyl-β^2-homoalanine (11b): According to the general procedure, deprotection and Boc protection of 9 mmol of alkylated precursor **10a** gave white crystals (1.07 g, 59%) after recrystallization from Et_2O, m.p. 79−80°C. ^{1}H NMR of the chlorhydrate of sultam β^2-homoalanine (400 MHz, $CDCl_3$): δ = 8.08 (broad peak, 3 H, NH_3), 4.18 (m, 1 H, H^2), 3.86 (AB system, J_{AB} = 14 Hz, 1 H, H^{10}), 3.54 (m, 3 H, H^{10} H^{11} H^{12}), 3.13 (m, 1 H, $H^{12'}$), 2.06 (m, 2 H, H^3), 1.93 (m, 3 H, H^4 H^5 H^6), 1.59 (m, 1 H, $H^{6'}$), 1.36 (m and d, *J* = 7 Hz, 4 H, $H^{5'}$ H^{13}), 1.14 (s, 3 H, CH_3), 0.98 (s, 3 H, CH_3). − Boc-β^2-homoalanine **11b:** ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.5 (broad peak, 0.4 H, NH *cis*/*trans* isomerism), 5.06 (broad peak, 0.6 H, NH *cis*/*trans* isomerism), 3.47−3.12 (m, 2 H, H^4), 2.72 (m, 1 H, H^2), 1.46 (d, 9 H, Boc *cis*/*trans* isomerism), 1.22 (d, 3 H, H^3). − ^{13}C NMR (400 MHz,

$CDCl_3$) δ: 181.1 and 179.9 (C^1), 158.2 and 156.5 (C^5), 81.4 and 80 (C^6), 44.5 and 43.1 (C^4), 40.6 and 40.4 (C^2), 28.7 (CH_3), 15 (C^3). − [α] = −20 (*c* = 2, MeOH), ref.[12] [α] = −18 (*c* = 2, MeOH) and ref.[13] [α] = −18 (*c* = 2.3, MeOH). − $C_9H_{17}NO_4$ (203.2): calcd. C 53.20, H 8.37, N 6.90, found C 53.08, H 8.55, N 6.96. − Dicyclohexylamine salt of **11b** $C_{21}H_{40}N_2O_4$ (384.6): calcd. C 65.62, H 10.42, N 7.29, found C 65.69, H 10.54, N 7.29.

(*R*)-3-*tert*-Butyloxycarbonyl-β²-homoleucine 11c: According to the general procedure, deprotection and Boc protection of 16.5 mmol of alkylated precursor **10b** gave a yellow oil (1.53 g, 57%). − ^{1}H NMR of the chlorhydrate of β²-homoleucine (400 MHz, $CDCl_3$): δ = 8.37 (broad peak, 3 H, NH_3), 4.49 (m, 1 H, H^2), 4.17 (AB system, J_{AB} = 14 Hz, 1 H, H^{10}), 3.74 (m, 2 H, $H^{10'}$ H^{11}), 3.56 (m, 1 H, H^{12}), 3.35 (m, 1 H, $H^{12'}$), 2.23 (m, 3 H, H^3 H^5), 2.04 (m, 2 H, H^4 H^6), 1.81 (m, 3 H, H^{13} H^{14} $H^{5'}$), 1.63 (m, 1 H, $H^{13'}$), 1.36 (m, 1 H, $H^{6'}$), 1.36 (s, 3 H, CH_3), 1.19 (s, 3 H, CH_3), 1.16 (2d, *J* = 6 Hz, 6 H, H^{15} H^{16}). − Boc-β²-homoleucine **11c:** ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.55 (broad peak, 1 H, COOH), 7.02 and 5.27 (broad peak, 1 H, NH *cis*/*trans* isomerism), 3.59 (m, 1 H, H^7), 3.55 and 3.44 (m, 1 H, $H^{7'}$), 2.90 (m, 1 H, H^2), 1.91 (m, 1 H, H^4), 1.70 (m and d, 10 H, H^3 and Boc), 1.48 (m, 1 H, $H^{3'}$), 1.15 (2d, 6 H, H^5 H^6). − ^{13}C NMR (400 MHz, $CDCl_3$) δ: 180.9 and 179.6 (C^1), 159.4 and 156.3 (C^8), 81.5 and 80 (C^9), 44.4 and 44.1 (C^2), 43.3 and 42.1 (C^7), 39.3 and 39 (C^3), 28.7 (CH_3), 26.1 (C^4), 22.8 (C^5, C^6). − $C_{12}H_{23}NO_4$ (245.3): calcd. C 58.77, H 9.39, N 5.71, found C 58.76, H 9.49, N 5.87. − [α] = −10 (*c* = 1, $CHCl_3$).

***N*-[3-(*N'*-Diphenylmethylene)aminopropionyl]oxazolidinone 12:** *N*-(3-*tert*-butoxycarbonylaminopropionyl)oxazolidinone was prepared by treating Boc-β-alanine, previously activated with isobutyl chloroformate, with the sodium salt of (*S*)-4-benzyl-2-oxazolidinone, in a similar way as described for the preparation of the precursor **5**. Starting from 4.6 g (26 mmol) of (*S*)-4-benzyl-2-oxazolidinone and 5.2 g (27.5 mmol) of *N*-Boc-β-alanine, *N*-(3-*tert*-butoxycarbonylaminopropionyl)oxazolidinone was obtained as a white powder (6.74 g, 74% yield). − ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7, period36−7, period20 (m, 5 H, H arom), 5.05 (broad peak, 1 H, NH), 4.68 (m, 1 H, H^2), 4.21 (m, 2 H, H^1), 3.51 (m, 2 H, H^5), 3.32 (ABX system, J_{AB} = 13 Hz, J_{AX} = 3 Hz, 1 H, H^3), 3.14 (m, 2 H, H^4), 2.79 (ABX system, J_{AB} = 13 Hz, J_{BX} = 10 Hz, 1 H, $H^{3'}$), 1.45 (s, 9 H, Boc). − A solution of *N*-(3-*tert*-butoxycarbonylaminopropionyl)oxazolidinone (6.74 g, 19 mmol) in dioxane (100 mL) was saturated with gaseous HCl at 0°C. After removal of the solvent under reduced pressure, the residual white powder was dissolved in CH_2Cl_2 (100 mL) and treated for 5 days with benzophenone imine (3.7 g, 20 mmol). The reaction mixture was fitered through Celite and evaporation of the solvent yielded a colorless oil which crystallized upon trituration in CH_2Cl_2/pentane (7.59 g, 97%). − m.p. 109−110°C. − ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.64−7.28 (m, 15 H, H arom), 4.71 (m, 1 H, H^2), 4.18 (m, 2 H, H^1), 3.77 (t, *J* = 7 Hz, 2 H, H^5), 3.37 (m, 2 H, H^4), 3.30 (ABX system, J_{AB} = 14 Hz, J_{AX} = 4 Hz, 1 H, H^3), 2.81 (ABX system, J_{AB} = 14 Hz, J_{BX} = 10 Hz, 1 H, $H^{3'}$). − $C_{26}H_{24}N_2O_3$ (412.5): calcd. C 75.73, H 5.82, N 6.80, found C 75.64, H 5.85, N 6.66. − [α] = +55 (*c* = 1, $CHCl_3$).

X-ray Crystal Structure of 6: Crystal data and data-collection information are summarized in Table 2. Data were corrected for Lorentz and polarization effects. No absorption correction was applied. The structure was solved by direct methods using SHELXS,[14] all other calculations used CRYSTALS.[15] Atomic scattering factors and anomalous dispersion terms were taken from ref.[16] Full-matrix least-squares refinement based on |*F*| and a Chebychev weighting scheme[17] were performed. All non hydrogen atoms were anisotropically refined. Hydrogen atoms were introduced in calculated positions and were allocated one overall refinable isotropic thermal parameter. Crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-117653. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [Fax: (internat.) + 44-1223/336-033; E-mail: deposit@ccdc.cam.ac.uk].

Table 2. Crystal data and data collection information for $C_{33}H_{36}N_2O_3S$

Molecular mass	540.7
Crystal size [mm]	0.4 × 0.4 × 0.6
a [Å]	25.419(6)
b [Å]	6.963(4)
c [Å]	17.321(5)
β [°]	100.97(2)
V [Å^3]	3010(2)
Z	4
Crystal system	monoclinic
Space group	*C*2
Linear absorption coefficient μ [cm^{-1}]	1.35
Density ρ [g·cm^{-3}]	1.19
Diffractometer	CAD4 Enraf−Nonius$_o$
Radiation	Mo-K_α (λ = 0.71069 Å)
Scan type	ω/2θ
Scan range [°]	0.8 + 0.345 tgθ
θ limits [°]	1−25
Temperature of measurement [K]	295
Octants collected	*h*: 0, 29; *k*: 0, 8; *l*: −20, 20
No. of data collected	2958
No. of unique data collected	2884 (R_{int} = 0.02)
No. of unique data used for refinement	2348 (F_o)^2 > 3σ(F_o)^2
$R = \Sigma\|\|F_o\| - \|F_c\|\|/\Sigma\|F_o\|$	0.0420
Rw[a] = $[\Sigma w(\|F_o\| - \|F_c\|)^2/\Sigma w\|F_o\|^2]^{1/2}$	0.0499
S	1.08
Extinction parameter	800
No. of variables	354
Δρ(min) [e·Å^{-3}]	−0.277
Δρ(max) [e Å^{-3}]	0.226

[a] $w = w'\{1 - [(|\|F_o\| - \|F_c\||)/6\cdot\sigma(F_o)]^2\}^2$ with $w' = 1/\Sigma r\ A_r T_r(X)$ with 3 coefficients 5.96, 0.804, and 4.45 for a Chebyshev Series, for which *X* is F_c/F_c(max)

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