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Preparation of Protected *syn*-α,*β*-Dialkyl *β*-Amino Acids That Contain Polar Side Chain Functionality†

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Abstract: We report the synthesis of *syn*-α,*β*-dialkyl *β*-amino acid derivatives suitably protected for solid-phase synthesis that give rise to residues containing positively charged lysine-like side chains. These amino acids, as well as *syn*-α,*β*-dialkyl *β*-amino acids that contain diverse hydrophobic side chains, are prepared in good de and ee. The key step in this route involves Davies's protocol for the conjugate addition of a chiral lithium amide to α,*β*-unsaturated *tert*-butyl esters (Davies, S. G.; Ichihara, O.; Walters, I. A. S. *J. Chem. Soc., Perkin Trans. 1* **1994**, *9*, 1141). *syn*-α,*β*-Dialkyl *β*-amino acids are interesting building blocks because of their sheet-forming propensity and because of their presence in bioactive compounds.

syn-α,*β*-Dialkyl *β*-amino acids are relatively rare in Nature but have been identified in several important metabolites. For example, dolastatins 11 and 12 contain (2*S*,3*R*)-2-methyl-3-aminopentanoic acid within a cyclic depsipeptide.[1] The dolastatins inhibit the growth of murine lymphocytic leukemia cells.[1b,c] Majusculamide C, a related cyclic depsipeptide, is cytotoxic and exhibits fungicidal activity against several plant pathogens.[2] The importance of *syn*-α,*β*-dialkyl *β*-amino acids is not limited to their biological occurrence. *syn*-α,*β*-Dialkyl *β*-amino acids have proven useful in the development of sheet-forming *β*-peptide foldamers.[3] The relative configuration of the C_α and C_β alkyl substituents of these amino acids enforces an anti $NC_\beta-C_\alpha C(=O)$ torsion angle, which corresponds to an extended conformation of the *β*-amino acid backbone atoms.

The availability of appropriately substituted *β*-amino acid monomers[4] is one factor that dictates the pace of *β*-peptide foldamer research. Convenient synthetic routes for monomers that are predisposed to form helical structures[5] have accelerated the pace of discoveries involving *β*-peptide helices.[5k] In contrast, many questions involving *β*-peptide sheet structure remain unanswered. For example, what side chains, side-chain orientations, and side chain−side chain pairings are required for hairpin structure in parallel and in antiparallel systems? Is it possible to engineer a *β*-peptide hairpin that is structured in water? Progress in *β*-peptide sheet research has lagged behind the study of *β*-peptide helix structure because a general, scalable synthesis of *syn*-α,*β*-dialkyl *β*-amino acids with protein-like side chains has not been described.

A synthesis that fit several criteria was required. (1) For convenience, the synthesis should afford products in high diastereomeric and enantiomeric purity in every case. (2) The route must readily provide diverse hydrophobic side chains in both the α and *β* positions of the amino acid. (3) The synthetic methodology must allow the incorporation of polar side chains that confer water solubility on *β*-peptide oligomers. These features are critical for our long-range goal of studying *β*-peptide sheet secondary structure in water.

Methodologies that provide a limited set of *syn*-α,*β*-dialkyl *β*-amino acids are known.[6] For instance, L-aspartic acid has been used to generate *syn*-α,*β*-dialkyl *β*-amino acids,[3a,b,d,7] and ester enolates have been used in conjunction with *tert*-butylsulfinyl imines to afford these compounds.[8] The alkylation of β^3-amino acids, which are readily obtained from α-amino acids via Arndt−Eistert homologation,[5a] was investigated as a means by which to obtain *syn*-α,*β*-dialkyl *β*-amino acids.[9] Unfortunately, these alkylations are not very diastereoselective, and in

† Dedicated to Professor E. J. Walsh (Allegheny College) on the occasion of his 68th birthday.

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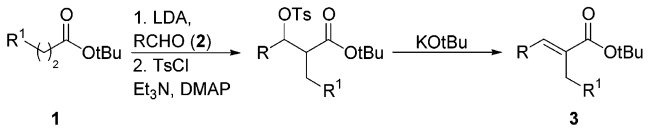
TABLE 1. Synthesis of α,β-Unsaturated β-Amino Esters



entry	ester	alde-hyde	R	R¹	prod	yield[a] (%)	dr (*E*/*Z*)[b]
1	**1a**	**2a**	CH_3	Boc(Bn)N-$(CH_2)_3$	**3a**	nc[c]	91:9
2	**1b**	**2b**	Boc(Bn)N-$(CH_2)_4$	H	**3b**	nc[c]	85:15
3	**1b**	**2c**	$(CH_3)_2CHCH_2$	H	**3c**	63[d]	95:5
4	**1b**	**2d**	$(c\text{-}C_6H_{11})CH_2$	H	**3d**	20	93:7
5	**1b**	**2e**	Bn	H	**3e**	nc[c]	nc[c]
6	**1c**	**2a**	CH_3	Ph	**3f**	82	87:13
7	**1d**	**2a**	CH_3	4-(CH_3O)Ph	**3g**	48	94:6
8	**1e**	**2a**	CH_3	TMP[e]	**3h**	54	91:9

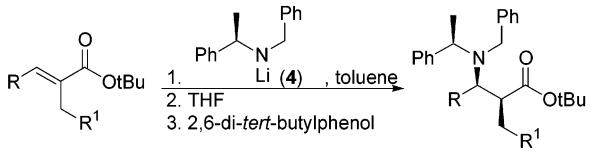
[a] Yield over three steps. [b] By ^{1}H NMR. [c] NC = not calculated because significant impurities were present. [d] ∼2% of a trace impurity remained present after column chromatography. eTMP = 3,4,5-trimethoxyphenyl.

some cases separation of the diastereomers is impossible via column chromatography. A particularly promising report by Davies and co-workers described the conjugate addition of (*R*)-*N*-benzyl-*N*-(α-methylbenzyl)lithium amide to a small set of α,β-unsaturated esters to afford *syn*-α,β-dialkyl β-amino acids in excellent de in each case.[10] However, none of these routes has yet provided access to *syn*-α,β-dialkyl β-amino acids with polar side chains.[11] Here, we report extension of the conjugate addition protocol developed by Davies et al.[10] to prepare protected *syn*-α,β-dialkyl β-amino acids that contain lysine-like side chains. A diverse set of *syn*-α,β-dialkyl β-amino acids with hydrophobic side chains is also reported.

α,β-Unsaturated ester (**3**) starting materials for the conjugate addition reactions were obtained via an aldol/elimination strategy as shown in Table 1. *tert*-Butyl esters **1** were converted to the corresponding lithium enolates using LDA, and aldehydes **2** were added. The crude aldol products were converted to the corresponding tosyl esters, which were allowed to react with potassium *tert*-butoxide to afford α,β-unsaturated esters **3** in modest overall yields.[12] Ester **3e** was obtained as a 1:1 mixture with the undesired phenyl conjugated isomer *tert*-butyl-2-methyl-4-phenylbut-3-enoate.

The results of the conjugate addition reactions are shown in Table 2. Entries 1 and 2 describe conjugate additions that lead to β-amino esters that contain side chains bearing protected amino groups. An *N*-Boc-protected nitrogen provided only recovered starting material in the conjugate addition step[10] with (*R*)-*N*-benzyl-*N*-(α-methylbenzyl)lithium amide (**4**) (data not shown), but an *N*-Boc-*N*-benzyl-protected nitrogen led to successful addition reactions with **4** (Table 2, entries 1 and 2). Amino esters **5a** and **5b** were obtained in modest yields and in good de as estimated by ^{1}H NMR after column chromatography. β-Amino esters that contain hydrophobic side chains were also reliably produced in good yields via conjugate addition with **4**. Amino esters **5g** and **5i** could not be completely purified by column chromatography. However, these materials were carried on to provide pure protected β-amino acids (vide infra). The ability to carry through materials that are not rigorously pure bodes well for the scalability of this methodology.

TABLE 2. Conjugate Addition to α,β-Unsaturated Esters



entry	ester	R	R¹	product	yield (%)	de[a]
1	**3a**	CH_3	Boc(Bn)N-$(CH_2)_3$	**5a**	12[b]	90
2	**3b**	Boc(Bn)N$(CH_2)_4$	H	**5b**	20[b]	98
3	**3c**	$(CH_3)_2CHCH_2$	H	**5c**	66	98
4	**3d**	$(c\text{-}C_6H_{11})CH_2$	H	**5d**	53	93
5	**3f**	CH_3	Ph	**5f**	nc[c]	89
6	**3g**	CH_3	4-(CH_3O)-Ph	**5g**	67	86
7	**3h**	CH_3	TMP[d]	**5h**	nc[c]	89

[a] By ^{1}H NMR. [b] Yield from ester **1**. [c] NC = not calculated because significant impurities were present. [d] TMP = 3,4,5-trimethoxyphenyl.

With β-amino esters **5** in hand, deprotection strategies to provide Fmoc protection of the β-amino group were examined. Esters **5a** and **5b** provided the greatest challenge. Our initial attempts to obtain **7a** and **7b** involved treatment with TFA to remove the *tert*-butyl ester group and concomitant removal of the *N*-Boc group, which was subsequently reintroduced. Unfortunately, column chromatography of the Boc-protected tertiary amino acids was difficult, and yields were consistently low. The hydrogenolysis of the three benzylic groups was attempted using a variety of conditions. In all cases, the side-chain benzyl group was not cleaved. Given these difficulties, an alternative strategy to obtain **7a** and **7b** was pursued.

The benzylic groups derived from (*R*)-*N*-benzyl-*N*-(α-methylbenzyl)lithium amide (**4**) were removed under transfer hydrogenation conditions (Table 3). The side-chain benzyl group was not cleaved under these conditions. The free amine was protected as the benzyloxy carbamate, and the *tert*-butyl ester was cleaved with TFA along with concomitant removal of the *N*-Boc group. Reintroduction of the *N*-Boc group afforded protected amino acids **6** which could be purified via column chromatography. Dissolving metal reduction to remove the *N*-benzyl group, followed by Fmoc-protection, afforded

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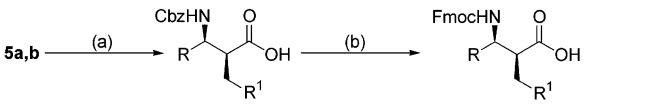
(11) Tang et al. (ref 8b) reported an *N*-sulfinyl *syn*-α,β-dialkyl-β-amino ester that contained an azido group on the α side chain. However, this material was obtained as a mixture of four diastereomers that could only be separated by HPLC, and the conversion of this material to a protected β-amino acid with an amine side chain was not demonstrated.

(12) For details on the major/minor isomer assignments, see the Supporting Information.

TABLE 3. Protecting Group Manipulation of β-Amino Acids That Contain Lysine Side Chains[a]

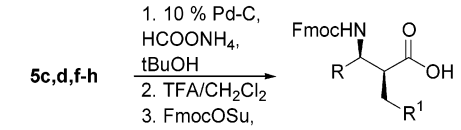


6a R = CH_3, R^1 = $(CH_2)_3N(Bn)Boc$ **7a** R = CH_3, R^1 = $(CH_2)_3NHBoc$
6b R = $(CH_2)_4N(Bn)Boc$, R^1 = H **7b** R = $(CH_2)_4NHBoc$, R^1 = H

entry	ester	*Z*-acid	yield (%)	product	yield (%)	ee[b] (%)	de[b] (%)
1	**5a**	**6a**	53	**7a**	69	91	97
2	**5b**	**6b**	56	**7b**	59	99	94

[a] Conditions: (a) (i) 10% Pd−C, $HCOONH_4$, (ii) Cbz-OSu, $NaHCO_3$, acetone/water, (iii) 80% TFA in CH_2Cl_2, (iv) Boc_2O, Et_3N; (b) (i) Na, NH_3, THF, (ii) Fmoc-OSu, $NaHCO_3$, acetone/water. [b] Determined by examining the corresponding Mosher amides by ^{19}F NMR (see the Supporting Information).

TABLE 4. Protecting Group Manipulation of β-Amino Acids That Contain Hydrophobic Side Chains



7c,d,f-h

entry	ester	R	R^1	product	yield (%)	ee[a] (%)	de[a] (%)
1	**5c**	$(CH_3)_2CHCH_2$	H	**7c**	63	96	>92
2	**5d**	$(c\text{-}C_6H_{11})CH_2$	H	**7d**	42	92	>99
3	**5f**	CH_3	Ph	**7f**	40[b]	99	>99
4	**5g**	CH_3	4-(CH_3O)Ph	**7g**	74	89	>99
5	**5h**	CH_3	TMP[c]	**7h**	14[b]	88	>96

[a] Determined by examining the corresponding Mosher amides by ^{19}F NMR (see the Supporting Information). [b] Yield from ester **3**. [c] TMP = 3,4,5-trimethoxyphenyl.

the desired Fmoc-protected β-amino acids **7a** and **7b** with Boc protection on the side chain nitrogen. The stereochemical purity of these monomers was assessed by examining the corresponding Mosher amides by ^{19}F NMR (see Supporting Information). Over 1 g of protected *syn*-α,β-dialkyl β-amino acid **7a** or **7b** could be obtained in a time frame of approximately 2 weeks.

The conversion of β-amino esters **5c**,**d**,**f**,**g**,**h** to the corresponding Fmoc-acids (**7c**,**d**,**f**,**g**,**h**) involved transfer hydrogenation to remove both benzylic groups, removal of the *tert*-butyl ester group with TFA and treatment with Fmoc-OSu (Table 4). The Fmoc-protected β-amino acids were obtained with good stereochemical purity (as determined by examining the corresponding Mosher amides by ^{19}F NMR) in all cases and in good yields (except for **7h**). The absolute configuration of these amino acids was confirmed through an X-ray crystal structure of a parallel β-peptide hairpin that contained residues **7c** and **7f**.[13] This route provides *syn*-α,β-dialkyl β-amino acids with hydrophobic side chains in about 1 week and is quite scalable. For instance, over 7 g of **7f** was obtained in one round of synthesis.

In summary, we have developed an efficient synthetic route to *syn*-α,β-dialkyl β-amino acids containing polar side chains that exploits a conjugate addition protocol developed by Davies and co-workers.[10] Access to this class of β-amino acid monomers will open the door to the investigation of β-peptide sheet secondary structure in water. The synthetic route also provides *syn*-α,β-dialkyl β-amino acids that contain diverse hydrophobic groups. Both monomer types can be generated on a multigram scale. The enantiomers of β-amino acids **7** could be readily obtained by using commerically available (*S*)-*N*-benzyl-*N*-(α-methylbenzyl)amine instead of the (*R*) isomer.

Experimental Section

A representative synthetic procedure for a β-amino acid bearing a side chain containing an amino group is provided below. Other procedures can be found in the Supporting Information.

(2*S*,3*R*,α*R*)-*tert*-Butyl-7-(benzyl-*tert*-butoxycarbonylamino)-3-(*N*-benzyl-*N*-α-methylbenzylamino)-2-methylheptanoate (5b). A flame-dried flask was charged with distilled THF (150 mL) and cooled to 0 °C. Distilled *i*-Pr_2NH (5.43 mL, 38.8 mmol) was added via syringe, followed by 2.5 M *n*-BuLi in hexane (15.9 mL, 37.3 mmol). The solution was allowed to warm to rt and was then cooled to −78 °C via a dry ice−acetone bath. *tert*-Butyl propionate (**1b**, 5.39 mL, 35.8 mmol) was added to this solution dropwise via syringe pump over ∼20 min, and the solution was stirred for 45 min. Aldehyde **2b** (10.9 g, 37.3 mmol) was added, and the solution was stirred 15 min. Saturated aq NH_4Cl was added, and the reaction mixture was allowed to warm to rt. THF was removed via rotary evaporation, and the remaining solution was diluted with water. The aqueous layer was extracted with Et_2O three times. The combined organic extracts were dried over $MgSO_4$ and concentrated. The crude aldol product was dissolved in CH_2Cl_2 (186 mL) and cooled to 0 °C. DMAP (5.01 g, 41.0 mmol) was added followed by TsCl (7.82 g, 41.0 mmol) and Et_3N (10.4 mL, 74.5 mmol). The solution was stirred overnight at rt, washed two times with 1 M HCl, dried over $MgSO_4$, and concentrated. The crude tosylates were purified by SiO_2 column chromatography eluting with hexane/Et_2O (5:1; v/v) affording two inseparable diastereomers (TLC R_f = 0.20 and 0.14), 16.99 g as a light yellow oil: EI−MS *m*/*z* (M + Na) calcd for $C_{31}H_{45}O_7NSNa$ 598.7, obsd 598.2. The tosyl esters were dissolved in Et_2O (200 mL) and cooled to −78 °C. KO-*t*-Bu (3.64 g, 32.5 mmol) was added, and the reaction mixture was stirred until the reaction appeared to be complete by TLC (∼2 h). The reaction mixture was concentrated; the residue was partitioned between Et_2O and 1 M HCl. The layers were separated, and the aqueous layer was extracted one additional time with Et_2O. The combined organic layers were dried over $MgSO_4$ and concentrated. Crude **3b** was partially purified by SiO_2 column chromatography eluting with Et_2O/hexanes (1:9; v/v). An 85:15 *E*/*Z* mixture was obtained as a clear oil (TLC R_f = 0.10), 9.51 g. Significant inseparable impurity resonances were apparent. Line broadening in the ^1H spectrum and resonance doubling observed in the ^{13}C spectrum were attributed to tertiary carbamate rotamers: ^1H NMR ($CDCl_3$, 300 MHz) δ 7.26 (m, 5H), 6.63 (tq, 1H, *J* = 7.5, 1.3 Hz) [5.75 (t, 0.18H, *J* = 7.2 Hz)], 4.41 (s, 2H), 3.18 (m, 2H), 2.11 (m, 2H), 1.76 (s, 3H) [1.83 (s, 0.65H)], 1.48 (m, 22H); ^{13}C NMR ($CDCl_3$, 75.4 MHz) δ 166.9, 166.8, 155.4, 155.1, 140.1, 138.1, 129.4, 128.9, 128.0, 127.2, 126.6, 79.2, 78.9, 50.0, 49.5, 45.8, 28.0, 27.6, 27.3, 25.4, 11.9; EI−MS *m*/*z* (M + Na) calcd for $C_{24}H_{37}O_4NNa$ 426.4, obsd 426.2. Conjugate addition of **4** to **3b** (9.51 g, 23.6 mmol) was carried out using the conditions described by Davies.[10] The crude material was purified by two rounds of SiO_2 column chromatography. The first column was eluted with a gradient of hexane to hexane/Et_2O (5:1; v/v) to remove 2,6-di-*tert*-butylphenol. The second column was eluted with 2.5% Et_2O in benzene. The product **5b** (TLC R_f = 0.18 in 1:9 Et_2O/hexane) was obtained as an oil, 4.64 g (20% yield over three steps), estimated >98% de by ^1H NMR integration: ^1H NMR ($CDCl_3$, 300 MHz) δ 7.38−7.21 (m, 15H), 4.40

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(m, 2H), 3.98 (q, 1H, $J = 6.8$), 3.91 (A of AB, 1H, $J = 15.2$), 3.77 (B of AB, 1H, $J = 15.2$), 3.12 (m, 3H), 2.73 (m, 1H), 2.38 (m, 1H), 1.50−1.38 (m, 23H), 1.26 (d, 3H, $J = 6.9$), 0.89 (d, 3H, $J = 7.0$); ^{13}C NMR ($CDCl_3$, 75.4 MHz) δ 175.5, 155.9, 155.5, 144.6, 142.4, 138.6, 128.3, 128.2, 128.00, 127.96, 127.8, 126.9, 126.7, 126.3, 79.7, 79.3, 60.8, 59.4, 50.9, 50.3, 49.8, 46.5, 43.8, 30.5, 28.3, 27.9, 25.2, 19.7, 16.8; EI−MS *m*/*z* (M + H) calcd for $C_{39}H_{55}O_4N_2$ 615.9, obsd 615.3.

(2*S*,3*R*)-(7-(Benzyl-*tert*-butoxycarbonylamino)-3-benzyloxycarbonylamino-2-methylheptanoic Acid (6b). Amino ester **5b** (4.64 g, 7.54 mmol) was dissolved in *t*-BuOH (75 mL), and ∼3 g of 10% Pd−C was added, followed by $HCOONH_4$ (2.38 g, 37.7 mmol). The reaction mixture was heated at a light reflux overnight, cooled, filtered through Celite, and concentrated. The residue was dissolved in 2:1 acetone/water (75 mL) and cooled to 0 °C. $NaHCO_3$ (6.33 g, 75.3 mmol) and Cbz-OSu (2.44 g, 9.80 mmol) were added, and the reaction mixture was stirred at rt overnight. The acetone was removed under reduced pressure, and the mixture was acidified to pH 2 with 1 M HCl, extracted three times with CH_2Cl_2, dried over $MgSO_4$, and concentrated. The crude residue was partially purified by SiO_2 column chromatography eluting with 1:1 Et_2O/hexane (TLC $R_f = 0.34$). The product was obtained as an oil, 3.37 g. This material was dissolved in 80% TFA in CH_2Cl_2 (65 mL) and stirred for 2 h. The TFA/CH_2Cl_2 solvent was evaporated using a stream of nitrogen, and the remaining residue was dissolved in benzene and evaporated two times to remove residual TFA. The residue was dissolved in THF (60 mL) and cooled to 0 °C. Et_3N (13.5 mL, 97.1 mmol) and Boc_2O (1.99 g, 9.11 mmol) were added, and the reaction mixture was stirred at rt for 2 days. The reaction mixture was concentrated, and the residue was partitioned between CH_2Cl_2 and 1 M HCl. The aqueous layer was extracted three times with CH_2Cl_2, and the combined organic layers were dried over $MgSO_4$ and concentrated. The crude residue was purified by SiO_2 column chromatography eluting with 2:1 Et_2O/hexane with 0.5% acetic acid (TLC $R_f = 0.21$). The product acid was obtained as an oil, 2.05 g (56% yield over two steps). Two sets of resonances, attributed to tertiary carbamate rotamers, were observed by NMR: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 11.09 (br s, 0.87H), 7.33−7.21 (m, 10H), 5.22 and 5.98 (m, 1H, atropisomeric), 5.10 (m, 2H), 4.37 (m, 2H), 3.82 and 3.94 (m, 1H, atropisomeric), 3.13 (m, 2H), 2.64 (m, 1H), 1.51−1.14 (m, 15H), 1.14 (d, 3H, $J = 7.2$); ^{13}C NMR ($CDCl_3$, 75.4 MHz) δ 178.7, 169.8, 156.2, 155.7, 138.3, 136.4, 128.3, 128.2, 127.9, 127.5, 127.0, 79.7, 66.6, 53.1, 50.3, 49.7, 46.1, 43.8, 31.0, 28.3, 27.6, 27.3, 23.3, 13.3; EI−MS *m*/*z* (M − H) calcd for $C_{28}H_{37}O_6N_2$ 497.6, obsd 497.2.

(2*S*,3*R*)-7-(Benzyl-*tert*-butoxycarbonylamino)-3-(9*H*-fluoren-9-ylmethoxycarbonylamino)-2-methylheptanoic Acid (7b). Ammonia (200 mL) was condensed in a three-neck round-bottom flask at −78 °C. Sodium (576 mg, 25.1 mmol) was added, and the resulting blue solution was stirred for 30 min. A solution of **6b** (2.08 g, 4.18 mmol) in THF (46 mL) was added dropwise to the reaction solution, and the reaction solution was stirred for 30 min at −78 °C. The reaction was quenched by the addition of NH_4OAc (2.1 g, 27.2 mmol), and the ammonia was allowed to evaporate. Precautions were taken to ensure that water did not enter the reaction vessel during evaporation. Once evaporation was complete, the remaining THF was removed under reduced pressure. The residue was dissolved in water and lyophilized. The resulting white crust was dissolved in 2:1 acetone/water (60 mL). The pH was checked to ensure that it was neutral. $NaHCO_3$ (5.10 g, 60.7 mmol) and FmocOSu (6.14 g, 18.2 mmol) were added, and the mixture was stirred at rt overnight. The acetone was removed under reduced pressure, and the remaining mixture was acidified to pH 2 with 1 M HCl and then extracted three times with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$ and concentrated. The crude residue was purified by SiO_2 column chromatography eluting with a gradient of 2:1 hexane/acetone to 1:2 hexane/acetone with 0.5% acetic acid. The product was recrystallized by dissolving the material in chloroform (rt), adding hexane until the solution became turbid, and refrigerating for 30 min. After filtration, the desired product was obtained as a white solid, 1.22 g (59% yield) (TLC $R_f = 0.11$ in 1:1 acetone/hexanes): mp 146−148 °C; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 12.37 (br s, 0.76H), 8.03 (d, 2H, $J = 7.3$), 7.86 (m, 2H), 7.58−7.45 (m, 4H), 7.25 (d, 1H, $J = 9.3$), 6.90 (t, 1H, $J = 5.2$), 4.56−4.35 (m, 3H), 3.79 (m, 1H), 3.05 (m, 2H), 1.57−1.26 (m, 13H), 1.16 (d, 3H, $J = 6.8$); ^{13}C NMR (DMSO-d_6, 75.4 MHz): δ 176.2, 156.2, 155.6, 144.0, 143.9, 127.6, 127.1, 125.3, 125.2, 120.1,77.3, 65.1, 52.8, 47.0, 44.4, 32.5, 29.3, 28.3, 23.1, 13.9; EI−MS *m*/*z* (M − H) calcd for $C_{28}H_{35}O_6N_2$ 495.6, obsd 495.2; $[\alpha]_D = -1.20$ (*c* 3.33 × 10^{-1}, CH_3OH). The enantiomeric purity was determined as 99% ee (> 94% de) by integration of the trifluoromethyl ^{19}F resonances in the corresponding (*R*) and (*S*) Mosher amides (see the Supporting Information).

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Supporting Information Available: General procedures, experimental procedures for **2b**, **3c**,**d**,**f**−**h**, **5a**,**c**,**d**,**g**, **6a**, and **7a**,**c**,**d**,**f**−**h**, and ^{1}H NMR and ^{13}C NMR spectra of compounds **1a**, **2b**, **3a**−**d**,**f**−**h**, **5a**−**d**,**f**−**h**, **6a**,**b**, and **7a**−**d**,**f**−**h**. This material is available free of charge via the Internet at http://pubs.acs.org.

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