A *β*-Lactam-Based Stereoselective Access to *β*,*γ*-Dihydroxy α-Amino Acid-Derived Peptides with Either α,*β*-Like or Unlike Configurations

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A concise access to α,*β*-dihydroxy α-amino acid-derived *N*-carboxy anhydrides (NCAs) with either *like* or *unlike* relative configuration is described. The key steps of the synthetic route are the preparation of the nonracemic 4-alkenyl *β*-lactams, through either Horner-type olefination of a common 4-formyl *β*-lactam or the Corey−Winter alkene synthesis applied to 4-dihydroxyalkyl *β*-lactams, followed by the Sharpless AD reaction, and a subsequent ring expansion of the corresponding 4-substituted 3-hydroxy *β*-lactams promoted by TEMPO. The opening of thus-prepared NCAs upon treatment with different O- and N-nucleophiles, including α-amino esters which lead to peptides, has also been studied under various reaction conditions.

Amino acid fragments bearing monohydroxy-, dihydroxy-, trihydroxy-, and polyhydroxyalkyl substituents are encountered in lysobactin,[1] echinocandins,[2] polyoxins,[3] and other nucleoside antibiotics,[4] respectively. Therefore, the synthesis of hydroxylated α-amino acid units is of considerable relevance, and obviously, it becomes increasingly delicate as the number of hydroxy groups attached at the side chain of the amino acid residue goes up. In fact, while direct methods to access to *β*-hydroxy α-amino acids are available,[5] general and short asymmetric routes to *β*,*γ*-dihydroxy α-amino acids are scarce. In this context, the dihydroxylation of *β*,*γ*-unsaturated α-amino acids would be the most concise and general route to these dihydroxylated amino acids. However, the method cannot be applied with general success, because *β*,*γ*-unsaturated α-amino acids are very prone to both racemization and isomerization to α,*β*-dehydro α-amino acids.[6] As a logical consequence, the search for surrogates of these sensitive unsaturated α-amino acids has identified several olefinic serine and cysteine derivatives.[7] In all these instances, after the dihydroxylation process, a convenient functional group manipulation is needed to render the target α-amino acid that would still need further activation for the final peptide coupling.

Recently, we have documented a *β*-lactam-based approach to *β*,*γ*-dihydroxy α-amino acid-derived peptides, Scheme 1-path A.[8] According to this approach, from the ring expansion of 3-hydroxy *β*-lactams, α-amino acid *N*-carboxy anhydrides (NCA)[9] are obtained that can

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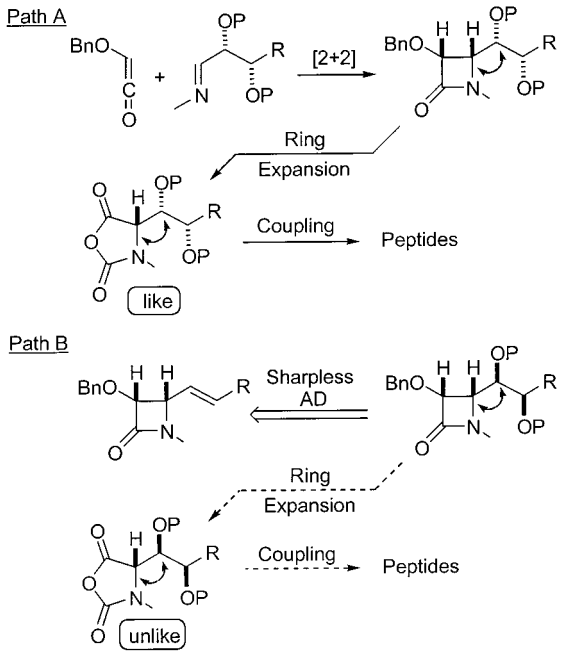
Scheme 1



directly be submitted to a peptide coupling reaction. Thus, the traditionally required carboxy group activation of the intermediate α-amino acid is avoided. The method is still slightly restricted because the exclusively accessible adducts have an α,*β-like* configuration, which often does not correspond with that of the biologically active compounds. This is so because the sense of asymmetric induction typically imparted by chiral α-oxyimines during the [2 + 2] cycloaddition reaction[10] produces the adducts with an α,*β-like* stereochemical relationship. With the aim of expanding the usefulness of our *β*-lactam approach, we herein report on a general route for access to NCAs showing an α,*β-unlike* configuration and to peptides derived therefrom. The strategy that we have devised, Scheme 1, path B, combines the stereoselective preparation of *cis*-4-vinyl-*β*-lactams and the subsequent Sharpless asymmetric dihydroxylation reaction as the key steps of the entire process.

Scheme 2

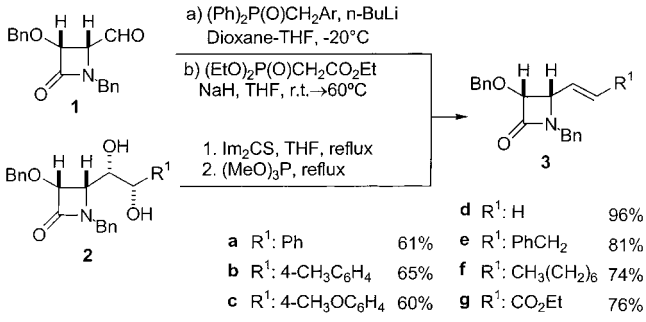


Table 1. Wittig−Horner-type Olefination of 4-Formyl *β*-Lactam 1

entry	product	R^1	*E*/*Z* ratio[a]	yield[b] (%)
1	**3a**	Ph	≥98:2	61
2	**3b**	4-CH_3Ph	≥98:2	65
3	**3c**	4-CH_3OPh	≥98:2	60
4	**3g**	CO_2Et	≥98:2	76

[a] Molar ratio determined by both ^{1}H and ^{13}C NMR spectroscopy. [b] Yields refer to pure *E* isomer, after column chromatography.

Results and Discussion

According to the plan, our first effort focused on the preparation of the corresponding enantiomerically pure 4-alkenyl *β*-lactams. To achieve this goal, we have adopted two complementary protocols, Scheme 2. The first one proved very practical for the preparation of both 4-arylvinyl-*β*-lactams and 4-alkoxycarbonylvinyl-*β*-lactams (vide infra) from a common 4-formyl *β*-lactam intermediate[11] through a Horner-type reaction.[12] Thus, *E* alkenes **3a**−**c**, bearing an aromatic R^1 group, were produced as the exclusive reaction product in good yields, Table 1, by treatment of **1** with the corresponding arylmethylphosphine oxide, which is easily accessible from the corresponding aldehydes,[13] and *n*-BuLi in mixtures of dioxane−THF. Likewise, **3g** was prepared in 76% isolated yield by reaction of **1** with the anion of the commercially available triethyl phosphonoacetate. Alternatively, a second protocol was developed for the preparation of alkenes **3d**−**f**, which bear aliphatic R^1 groups. In these instances, the Wittig−Horner-type approach using nonstabilized phosphorus ylides led to disappointing results, and instead, Scheme 2, the synthesis of **3d**−**f**, was realized through a Corey−Winter alkene synthesis[14] on *β*-lactam diols **2**. Thus, the treatment of these *vic*-diols **2** with thiocarbonyldiimidazole, followed by pyrolitic dehydration of the crude thiocarbonates in methyl phosphite as solvent,[15] furnished the desired *E* adducts **3d**−**f** in yields of 95%, 81%, and 74%, respectively. The required intemediate *β*-lactams **2**,

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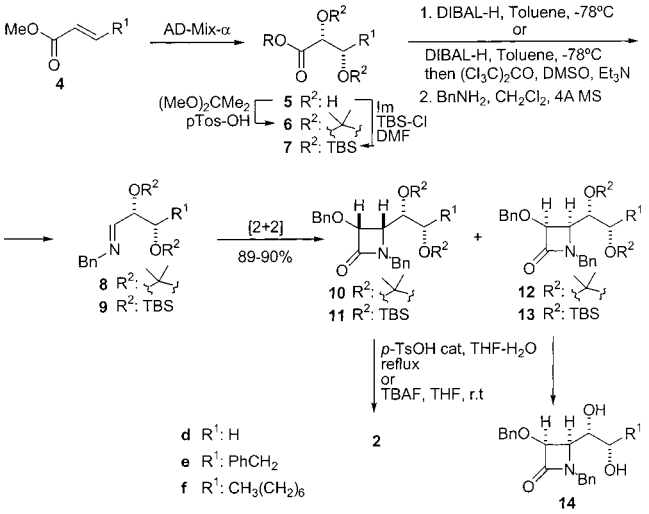
Scheme 3



Scheme 3, were obtained from a [2 + 2] ketene−imine cycloaddition reaction followed by a deprotection step. The starting imines **8** and **9** required for the first step of the synthesis were prepared from commercially available unsaturated esters **4** by a perfectly enantioselective Sharpless asymmetric dihydroxylation,[16] protection of the diol moiety in **5**, and further controlled reduction of **6** and **7** to the respective aldehyde. Condensation of the aldehydes derived from **6** with benzylamine was followed by the cycloaddition reaction of the thus prepared imines **8** with benzyloxyketene, generated from benzyloxyacetyl chloride and triethylamine, to give the corresponding *cis*-*β*-lactams **10d/12d**, **10e/12e**, and **10f/12f** in diastereomeric ratios of >98:2 (R^1 = H), 90:10 ($R^1 = CH_3(CH_2)_6$), and 60:40 ($R^1 = PhCH_2$), respectively. When imines **9e** and **9f** were used instead, a mixture of *β*-lactams **11e/13e** and **11f/13f** was obtained with slightly improved diastereoselectivities (93:7 for $R^1 = CH_3(CH_2)_6$; 84:16 for $R^1 = PhCH_2$). Separation of the major isomer out of each diastereomeric mixture was best accomplished, after cleavage of either the ketal or the silyl ether protective groups, by preparative HPLC.

Once 4-alkenyl *β*-lactams **3** were obtained, they were subjected to the osmium-catalyzed dihydroxylation reaction. During this key step, the relative configuration between the carbons at the *β*-lactam C-4 position and at the side chain is established, which will also determine the relative configuration of the final amino acid. In a preliminary study, the dihydroxylation of adducts **3c** and **3d** was performed by using DABCO as the achiral tertiary amine catalyst. Under these conditions, a mixture of the corresponding diastereomers **15c** (*unlike)* and **2c** (*like)* was produced in a 43:56 and 38:62 isomeric ratio, respectively, thus demonstrating a very poor substrate-directed stereocontrol under the conditions used.[16,17] Consequently, we then performed the reaction with the assistance of an external chiral catalyst. Thus, the dihydroxylation of **3c**, carried out in the presence of either $(DHQ)_2PHAL$ (α) or $(DHQD)_2PHAL$ (*β*) catalysts, afforded a mixture of **15c** and **2c** in ratios of 12:88 (α) and ≥99:1 (*β*), while **3d**, under the same conditions, led to **15d** and **2d** in ratios of 50:50 (α) and 85:15 (*β*), respectively (Scheme 4). Thereafter, the dihydroxylation reaction in the presence of the chiral catalysts α and *β* was extended to other substrates **3**, and from the results listed in Table 2 some generalizations are worth mentioning. Chiral ligand α uniformly favored formation of product **2**, while ligand *β* favored **15**. Ligand *β* exerted from perfect (R^1 = aromatic; entries 2, 3, 5, and 8) to high (R^1 = aliphatic; entries 10 and 12) asymmetric induction, while somewhat lower induction is imparted by ligand α. The later cases would correspond to a mismatched combination of the chiral substrate and the catalyst. On the other hand, as entries 2/3, 10/11, and 12/13 illustrate, the degree of the reaction stereoselectivity is also influenced by the reaction temperature, and the best results were produced at 0 °C. In all the cases where a mixture of both **15** and **2** was produced, each isomer could be separated efficiently by flash column chromatography. The configurational assignment for the adducts was achieved primarily by

Scheme 4

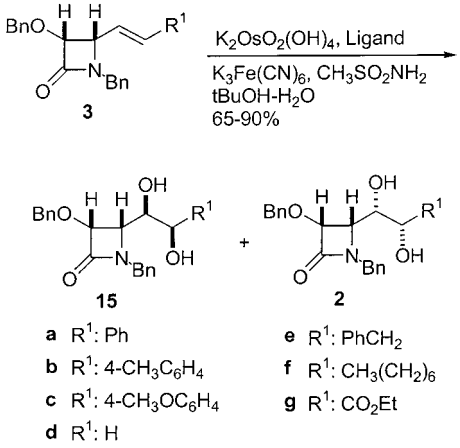


Table 2. Sharpless AD Reaction of 4-Alkenyl *β*-Lactams 3[a]

entry	compd **3**	R^1	ligand[b] (mol %)	T	**15**:**2** ratio[c]	yield[d] (%) **15**	**2**
1	**a**	Ph	α(5)	0	15:85	5	74
2			*β*(1)	20	98:2	89	
3				0	≥99:1	90[e]	
4	**b**	4-CH_3Ph	α(5)	0	10:90	7	70
5			*β*(1)	20	≥99:1	80	
6	**c**	4-CH_3OPh	α(5)	0	12:88	7	82
7			α(1)	20	*f*		
8			*β*(1)	20	≥99:1	87	
9	**d**	H	*β*(1)		62: 38	ND	
10	**e**	CH_2Ph	*β*(1)	20	73:27	72	14
11				0	81:17	ND	
12	**f**	$(CH_2)_6CH_3$	*β*(1)	20	88:12	80	8
13				0	93:7	ND	
14			α(5)	0	25:75	ND	
15	**g**	CO_2Et	α(1)	20	50:50	ND	
16			*β*(1)	20	80:20	ND	
17			*β*(1)	0	85:15	ND	

[a] Reactions typically conducted at 1 mmol scale. [b] α = $(DHQ)_2PHAL$; *β* = $(DHQD)_2PHAL$. Numbers in parentheses refer to the mol percentage of both the chiral ligand and the osmium salt, related to the substrate. [c] Determined by ^{13}C NMR by integrating the signals of CO, CHOH, and CHOH in each diastereomer. Entries 1−8 corroborated by HPLC. [d] Yields of isolated pure compounds, after column chromatography. ND means that the mixture of diastereomers was not separated, and therefore, the isolated yields were not determined. [e] Yield determined on the basis of consumed **3**. [f] Very low reaction conversion was observed.

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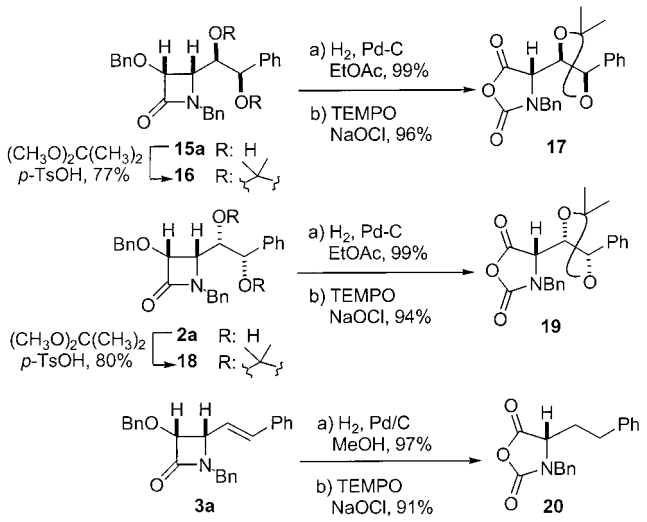
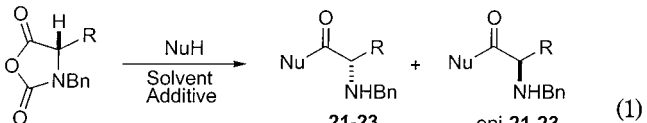
Scheme 5



comparisons with samples directly obtained through the [2 + 2] cycloaddition reaction of benzyloxyketene to the corresponding α,β-dihydroxyimine, vide supra. Finally, an X-ray structure analysis of adduct **15a** corroborated the *unlike* configuration of the isolated product.[18]

With these β-lactam products in hand, the synthesis of the corresponding NCAs was straightforward, as we have previously described for related compounds. For example, Scheme 5, the diol moiety in **15a** was first protected under standard conditions, and the resulting product **16** was subjected to hydrogenolysis,[19] followed by oxidation of the resulting α-hydroxy β-lactam with a solution of commercial bleach and a catalytic amount of TEMPO. Under these conditions, the expected NCA **17**, ready for peptide coupling, was obtained in 95% yield over the last two steps. Likewise, the β-lactam product **2a** was transformed into the corresponding NCA **19** in excellent yield. Finally, NCA **20** was also prepared in a straightforward manner from compound **3a**.

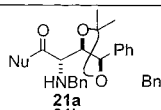
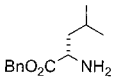
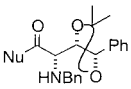
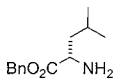
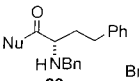
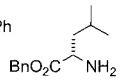
The last question we addressed was the opening of thus prepared NCAs with different nucleophiles,[20] including α-amino acid esters, to afford coupling products **21**−**23**, eq 1. NCAs **17**, **19**, and **20** were selected as appropriate



(1)

substrates for that purpose, to evaluate the influence that the relative configuration (**17** and **19**) and the stereoelectronic nature of the substituent on the NCA ring (**17** or **19** related to **20**) may have in terms of the chemical yield and the epimerization degree. The results obtained from this comparative study are summarized in Table 3, which merits some comments. While dihydroxylated NCAs **17** and **19** reacted with N-nucleophiles in methylene chloride without the formation of even traces of isomerization product *epi*-**21** or *epi*-**22**, alkyl-substituted NCA **20** (Table 3, entries 8−13) led to varying amounts of isomerization. The degree of isomerization in this particular case does not appear to be solvent sensitive (Table 3, entries 8−10), although it increases in the presence of KCN as an additive (Table 3, entry 12). A comparison between entries 2/3, 4/5, and 6/7, however, indicates the importance that the nature of the solvent can have in some instances, an aspect that we had already observed.[8a] Remarkably, even NCA **20** can be opened without any isomerization occurring when methanol is used as the solvent (Table 3, entries 15 and 16).

Table 3. Opening of NCAs with Nucleophiles under Different Reaction Conditions[a]

Entry	NCA	Product	NuH	Solvent	Additive	Yield[b]	d.r.[c]
1	**17**			CH_2Cl_2	--	82	≥98:2[d]
2		**21a**	$BnNH_2$	CH_2Cl_2	--	88	≥99:1
3		**21b**		DMF	--	87[e]	72:28
4	**19**			CH_2Cl_2	--	89	≥98:2[d]
5				DMF	--	85[e]	62:38[d]
6		**22a**	$BnNH_2$	CH_2Cl_2	--	83	≥99:1
7		**22b**		DMF	--	81[e]	83:17
8	**20**			CH_2Cl_2	--	83[e]	82:18[d]
9				Et_2O	--	82[e]	80:20
10		**23a**		DMF	--	81[e]	80:20[d]
11				DMF	NaN_3	84[e]	84:16
12				DMF	KCN	84[e]	62:38
13		**23b**	$BnNH_2$	CH_2Cl_2	--	81[e]	65:35
14		**23c**	BnOH	CH_2Cl_2	--	83[e]	86:14
15		**23d**	CH_3OH	MeOH	--	87	≥99:1
16				MeOH	NaN_3	84	≥99:1

[a] Molar ratio of NCA/NuH/additive 1:2:1. [b] Yield of pure compound after separation by flash column chromatography. [c] Diastereomeric ratio of each diastereomeric pair **21**−**23**:*epi*-**21**−**23** determined by HPLC analysis, unless otherwise stated. [d] Determined by ^{13}C NMR spectroscopy. [e] Yield of the combined mixture of epimers after column chromatography.

We can conclude that a general strategy in scope has been developed for access to α,β-dihydroxy α-amino acid-derived *N*-carboxy anhydrides (NCAs) with either *like* or *unlike* relative configuration and thus to the peptides derived therefrom. The method involves the sequential application of the [2 + 2] ketene−imine cycloaddition reaction, the Sharpless AD reaction, and the oxidative ring expansion of 3-hydroxy β-lactams. Due to the soft reaction conditions needed for these three key transformations, a broad range of substituents and functional groups can be tolerated. Several factors have been identified that influence the degree of isomerization during the opening of NCAs with N- and O-nucleophiles.

Experimental Section

Melting points were determined with a capillary apparatus and are uncorrected. Proton nuclear magnetic resonance (300MHz) spectra and ^{13}C spectra (75 MHz) were recorded at

(18) The X-ray crystal structure analysis has been performed by one of us (A.L.) at the Organisch-chemisches Institut der Universität Zürich. Crystallographic data (excluding structure factors) for compound **15a** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-154028. Copies of the data can be obtained free of charge on application to the CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK. E-mail: deposit@ccdc.cam.ac.uk.

(19) Hydrogenation of **16** and **18** was performed in ethyl acetate as solvent. The use of methanol as solvent led to simultaneous deprotection of the ketal.

(20) For a recent paper dealing with this issue, see: Sim, T. B.; Rapoport, H. *J. Org. Chem.* **1999**, *64*, 2532.

room temperature for $CDCl_3$ solutions, unless otherwise stated. All chemical shifts are reported as δ values (ppm) relative to residual $CHCl_3$ δ_H (7.26 ppm) and $CDCl_3$ δ_C (77.0 ppm) as internal standards, respectively. Mass spectra were obtained on a mass spectrometer (70 eV) using GC−MS coupling (column: fused silica gel, 15 m, 0.25 mm, 0.25 mn phase SPB-5). Optical rotations were measured at 25 ± 0.2 °C in methylene chloride unless otherwise stated. HPLC analyses were performed on analitycal columns (25 cm, phase Lichrosorb-Si60) and (25 cm, phase Chiralcel OD) with flow rates using 1 mL/min and 0.5 mL/min respectively, using a DAD. Flash chromatography was executed with Merck Kiesegel 60 (230−400 mesh) using mixtures of ethyl acetate and hexane as eluants. Et_2O and THF were distilled over sodium. Methylene chloride was shaken with concentrated sulfuric acid, dried over potassium carbonate and distilled. DMF was purified by distillation on barium oxide. CH_3CN was dried by refluxing over calcium hydride and distilled. DMSO was distilled from potassium hydroxide. MeOH was dried over magnesium metal and iodine.

General Procedure for the Preparation of 4-Vinyl β-Lactams 3. Method A. To a suspension of the corresponding arylmethyl diphenylphosphine oxide (1.5 mmol) in THF (3 mL) cooled to 0 °C was added dropwise a solution of ^{n}BuLi (1.6M in hexane, 0.93 mL, 1.5 mmol). After being stirred for 10 min at the same temperature, the mixture was cooled to −20 °C, and a solution of the aldehyde **1**[11] (0.245 g, 1 mmol) in a mixture of dry THF (1 mL) and dioxane (1 mL) was added dropwise. The reaction mixture was stirred at −20 °C for 16 h. Then H_2O (50 mL) was added at once, and the resulting mixture was extracted with ethyl acetate. The combined organic phase was dried over $MgSO_4$ and the solvent evaporated under reduced pressure to give **3**, which was purified by flash column chromatography.

Method B. In a 250 mL round flask was introduced NaH (60% in mineral oil, 0.84 g, 22 mmol), and the solution was washed successively with portions of dry hexane (3 × 40 mL). To the oil-free solid NaH was added THF (40 mL) and the suspension cooled to 0 °C. To this mixture was added dropwise triethyl phosphonoacetate (4.04 mL, 20 mmol) dissolved in THF (20 mL). The reaction mixture was stirred at room temperature for 1 h. Then, a solution of β-lactam **1** (5.9 g, 20 mmol) in THF (25 mL) was added dropwise while the temperature was kept below 25 °C. The resulting reaction mixture was stirred in a bath at 60 °C for 1 h, and then it was cooled to room temperature and diluted with ethyl acetate (100 mL). The solution was washed with H_2O, a saturated solution of NaCl, and a saturated solution of $NaHCO_3$. The organic phase was dried over $MgSO_4$, the solvent evaporated under reduced pressure, and the product purified by flash column chromatography.

Method C. A mixture of the corresponding diol **2** (1 mmol), vide infra, 1,1′-thiocarbonyldiimidazole (0.24 g, 1.2 mmol), and toluene (5 mL) was heated at 100 °C until disappearance of the starting **2** as monitored by TLC (typically 16 h). The reaction mixture was then cooled to room temperature, diluted with CH_2Cl_2, and washed with 0.1 N HCl and a saturated solution of $NaHCO_3$. After drying over $MgSO_4$, the solvent was evaporated under reduced pressure to give the corresponding crude thiocarbonate. Analytical samples of these thiocarbonates could be obtained by flash column chromatography purification (see the Supporting Information for analytical data of these intermediates). The thus-obtained crude thiocarbonate was dissolved in $(MeO)_3P$ (4 mL), and the resulting solution was kept at reflux until the intermediate thiocarbonate was consumed (typically 16 h). Then, the mixture was cooled to 40 °C, and the solvent was removed under vaccum to give the corresponding alkene **3**, which was purified by flash column chromatography.

Compound 3a: yield 0.199 g (54%); mp 75−78 °C; $[\alpha]^{20}_D$ = +88.68 (c = 1, CH_2Cl_2); IR (KBr) 1757.8 (CO), 1646.9 cm^{-1} (C=C); ^{1}H NMR ($CDCl_3$, δ) 7.34−7.17 (m, 15H), 6.50 (d, 1H, J = 15.93 Hz), 6.15 (dd, 1H, J = 15.94 Hz, J' = 9.00 Hz), 4.76 (d, 1H, J = 4.39 Hz), 4.67 (d, 1H, J = 14.67 Hz), 4.63 (d, 1H, J = 11.58 Hz), 4.56 (d, 1H, J = 11.64 Hz), 4.12 (dd, 1H, J = 8.97 Hz, J' = 4.39 Hz), 4.01 (d, 1H, J = 14.67 Hz); ^{13}C NMR ($CDCl_3$, δ) 166.4, 136.6, 136.3, 135.9, 135.3, 128.6, 128.5, 128.3, 128.2, 127.9, 127.7, 126.6, 123.2, 83.4, 83.3, 72.7, 60.3, 44.0. Anal. Calcd for $C_{25}H_{23}NO_2$ (369.46): C, 81.27; H, 6.27; N, 3.79. Found: C, 81.35; H, 6.19; N, 3.74.

General Procedure for the Preparation of β-Lactams 10 from Esters 6. To a solution of the corresponding methyl ester **6** (13.5 mmol) in toluene (50 mL) cooled to −78 °C was added dropwise a 1 M solution of diisobutylaluminum hydride (DIBALH) in hexane (20 mL, 20 mmol), ensuring that the temperature was below −70 °C during addition. The solution was stirred at the same temperature for 2 h, MeOH (6 mL) was added, and the resulting solution was poured into a cold (0 °C) solution of 1 N HCl (60 mL). The resulting solution was stirred for 1 h at 0 °C and then extracted with EtOAc. The combined organic phase was washed with brine and dried over $MgSO_4$ and the solvent evaporated under reduced pressure to give the respective aldehyde as an oil, which was used as such in the next step. A mixture of thus-prepared aldehyde, 4A MS, and benzylamine (13.5 mL, 13 mmol) in methylene chloride (50 mL) was stirred at 0 °C under a nitrogen atmosphere for 1 h. The solution was filtered, the solvent evaporated, and the residue analyzed by ^{1}H NMR to ensure complete consumption of the aldehyde. The crude imine thus obtained was dissolved in dry methylene chloride (40 mL) and cooled to −78 °C under a nitrogen atmosphere, and to the resulting solution were successively added triethylamine (3.22 mL, 23 mmol) and dropwise a solution of benzyloxyacetyl chloride (2.38 mL, 15 mmol) in dry methylene chloride (20 mL). The resulting mixture was stirred overnight at room temperature and then washed with water, 0.1 N HCl, and a saturated aqueous solution of $NaHCO_3$. The organic layer was dried over $MgSO_4$ and filtered, and the solvent was evaporated under reduced pressure to give the crude β-lactam product, which was further purified by column chromatography.

Data for 10e: yield 5.00 g (81%); mp 89−93 °C; $[\alpha]^{20}_D$ = +16.3 (c = 1, CH_2Cl_2); IR (KBr) 1757.8 cm^{-1} (CO); ^{1}H NMR ($CDCl_3$, δ) 7.34−7.02 (m, 15H), 4.96 (d, 1H, J = 11.54 Hz), 4.85 (d, 1H, J = 14.83 Hz), 4.67 (d, 1H, J = 11.53 Hz), 4.61 (d, 1H, J = 4.98 Hz), 4.17 (d, 1H, J = 14.83 Hz), 4.16 (m, 1H), 3.99 (m, 1H), 3.53 (dd, 1H, J = 4.99 Hz, J' = 8.57 Hz), 2.97 (dd, 1H, J = 3.11 Hz, J' = 14.42 Hz), 2.76 (dd, 1H, J = 8.30 Hz, J' = 14.45 Hz), 1.35, 1.20 (s, 3H); ^{13}C NMR ($CDCl_3$, δ) 168.2, 138.7, 137.3, 136.3, 130.1, 130.0, 129.9, 129.7, 129.5, 129.2, 128.9, 128.8, 128.5, 128.3, 126.9, 110.7, 81.7, 81.0, 80.9, 73.6, 59.5, 45.8, 45.6, 40.1, 28.5. Anal. Calcd for $C_{29}H_{31}NO_4$ (457.57): C, 76.12; H, 6.83; N, 3.06. Found: C, 76.25; H, 6.95; N, 3.02.

Data for 10f: yield 5.34 g (85%); mp 73−75 °C; $[\alpha]^{20}_D$ = +6.4 (c = 1, CH_2Cl_2); IR (KBr) 1752.8 cm^{-1} (CO); ^{1}H NMR ($CDCl_3$, δ) 7.33−7.24 (m, 10H), 4.96 (d, 1H, J = 11.40 Hz), 4.87 (d, 1H, J = 14.65 Hz), 4.65 (d, 1H, J = 11.50 Hz), 4.61 (d, 1H, J = 5.09 Hz), 4.20 (d, 1H, J = 14.64 Hz), 4.10 (dd, 1H, J = 5.88 Hz, J' = 8.95 Hz), 3.74 (m, 1H), 3.56 (dd, 1H, J = 5.11 Hz, J' = 8.95 Hz), 1.39, 1.25 (s, 3H), 1.65−1.10 (m, 12H), 0.88 (t, 3H, J = 6.5 Hz); ^{13}C NMR ($CDCl_3$, δ) 168.2, 137.4, 136.4, 129.2, 129.2, 129.0, 128.9, 128.7, 128.2, 110.0, 82.0, 81.2, 80.7, 73.5, 59.4, 45.6, 34.1, 32.4, 30.1, 29.8, 28.6, 28.4, 26.5, 23.2, 14.7. Anal. Calcd for $C_{29}H_{39}NO_4$ (465.63): C, 74.80; H, 8.44; N, 3.01. Found: C, 74.86; H, 8.55; N, 3.03.

General Procedure for the Preparation of β-Lactams 11 from Esters 7. The same procedure as for the preparation of **10** was employed with an exception made for the reduction of esters **7** to the corresponding aldehydes. The reduction step of **7** with DIBALH led to the corresponding overreduction products, the alcohols, which were then reoxidized to the aldehydes before continuing with imine and β-lactam formation, as follows: To a suspension of triphosgene (1.35 g, 9.9 mmol) in CH_2Cl_2 (5 mL) at −78 °C and under a nitrogen atmosphere was added dropwise dimethyl sulfoxide (0.63 mL, 8.4 mmol) and the mixture stirred for 15 min. Then a solution of the corresponding overreduction alcohol crude material in CH_2Cl_2 (6 mL) was added and the resulting mixture stirred for 15 min at the same temperature. To this solution was added dropwise a solution of triethylamine (1.35 mL, 9.9 mmol)

in CH_2Cl_2 (6 mL) while the temperature was kept below −70 °C. The resulting mixture was stirred at −78 °C for 5 min, and after removal of the cold bath, stirring was continued for an additional 2 h at room temperature. The reaction mixture was washed with 1 M HCl and a saturated solution of NaCl. The resulting solution was dried over $MgSO_4$ and the solvent evaporated under reduced pressure to give an oily product that was used as indicated in method A without further purification.

Data for 11e: yield 7.32 g (84%); oil; $[\alpha]^{20}_D = -3.65$ ($c = 1$, CH_2Cl_2); IR (KBr) 1759.0 cm^{-1} (CO); ^1H NMR ($CDCl_3$, δ) 7.40−6.94 (m, 15H), 5.12 (d, 1H, $J = 15.63$ Hz), 4.97 (d, 1H, $J = 11.56$ Hz), 4.76 (d, 1H, $J = 11.50$ Hz), 4.64 (d, 1H, $J = 5.12$ Hz), 4.22 (dd, 1H, $J = 2.00$ Hz, $J' = 4.86$ Hz), 4.14 (dd, 1H, $J = 2.02$ Hz, $J' = 5.08$ Hz), 3.99 (d, 1H, $J = 15.80$ Hz), 3.76 (m, 1H), 3.07 (d, 1H, $J = 11.97$ Hz), 2.05 (dd, 1H, $J = 12.75$ Hz, $J' = 11.06$ Hz), 0.99 and 0.69 (s, 9H), 0.11, 0.07, −0.24, and −0.71 (s, 3H). ^{13}C NMR ($CDCl_3$, δ) 169.1, 139.7, 137.4, 136.8, 130.2, 129.2, 128.9, 128.8, 128.7, 128.5, 128.4, 128.0, 126.6, 81.3, 76.6, 73.4, 73.3, 70.1, 54.7, 45.8, 38.3, 26.5, 26.2, 18.6, 18.3, −3.9, −4.3, −4.5, −5.3.

Data for 11f: yield 8.38 g (95% crude); oilo $[\alpha]^{20}_D = +2.5$ ($c = 1$, CH_2Cl_2); IR (KBr) 1758.8 cm^{-1} (CO); ^1H NMR ($CDCl_3$, δ) 7.32−7.10 (m, 10H), 4.97 (d, 1H, $J = 15.75$ Hz), 4.89 (d, 1H, $J = 11.39$ Hz), 4.68 (d, 1H, $J = 11.39$ Hz), 4.52 (d, 1H, $J = 5.08$ Hz), 4.06 (dd, 1H, $J = 2.22$ Hz, $J' = 4.60$ Hz), 3.88 (d, 1H, $J = 15.75$ Hz), 3.87 (m, 1H), 3.48 (m, 1H), 1.09 (m, 12H), 0.83 and 0.75 (s, 9H), −0.01, −0.06, −0.07, and −0.09 (s, 3H); ^{13}C NMR ($CDCl_3$, δ) 169.4, 137.6, 137.1, 129.2, 129.0, 128.9, 128.8, 128.7, 128.4, 128.0, 81.3, 74.9, 73.4, 70.2, 55.1, 45.8, 32.4, 31.5, 30.2, 29.8, 27.0, 26.6, 26.4, 23.3, 18.6, 14.8, −3.8, −3.9, −4.4.

Deprotection of 10 to 2. To a solution of the corresponding β-lactam **10** (5 mmol) in a mixture of THF (20 mL) and water (10 mL) was added *p*-toluenesulfonic acid monohydrate (0.32 g, 1.65 mmol), and the resulting mixture was stirred at reflux for 16 h. The mixture was then cooled to room temperature, and a saturated solution of sodium bicarbonate was added until all the acid was neutralized (pH neutral). The aqueous phase was extracted with ethyl acetate, the combined organic phase was dried over $MgSO_4$, and the solvent was removed under reduced pressure to give **2**, which exhibited the same characterization data as the products obtained from dihydroxylation of **3**, vide infra.

Deprotection of 11 to 2. To a solution of **11** (5 mmol) in THF (20 mL) was added a 1.1 M solution of tetrabutylammonium fluoride in THF (13.63 mL, 15 mmol), and the resulting solution was stirred at room temperature for 2 h. The reaction mixture was then filtered through a short pad of silica gel, and the pad was thoroughly eluted with dicloromethane. The resulting solution was dried over $MgSO_4$ and the solvent removed under reduced pressure to give **2**, which exhibited the same characterization data as the products obtained from dihydroxylation of **3**, vide infra.

General Procedure for the Dihydroxylation of 4-Alkenyl β-Lactams 3. To a mixture of AD-mix-α (1.4 g, 1 mol %) or AD-mix-β (1.4 g, 1 mol %) and methanesulfonylamine (0.095 g, 1 mmol) in *tert*-butyl alcohol (5 mL) and H_2O (5 mL) was added at 0 °C the corresponding β-lactam **3** (1 mmol). The resulting mixture was stirred at the temperature specified in Table 2 for 16 h. Then it was cooled at 0 °C, and Na_2SO_3 (1.5 g) was added. After bein stirred for 60 min, the reaction mixture was extracted with CH_2Cl_2 the combined organic phase dried over $MgSO_4$, and the solvent evaporated under reduced pressure. From this reaction crude product, the isomeric diols were separated by column chromatography.

Data for 15a: yield 0.34 g (85%); mp 76−79 °C; $[\alpha]^{20}_D = +122.4$ ($c = 1$, CH_2Cl_2); IR (KBr) 1734.7 cm^{-1} (CO); ^1H NMR ($CDCl_3$, δ) 7.39−7.04 (m, 15H), 4.98 (d, 1H, $J = 11.54$ Hz), 4.75 (d, 1H, $J = 11.53$ Hz), 4.68 (d, 1H, $J = 4.94$ Hz), 4.61 (d, 1H, $J = 6.00$ Hz), 4.55 (d, 1H, $J = 15.23$ Hz), 4.18 (d, 1H, $J = 15.20$ Hz), 3.87 (t, 1H, $J = 5.14$ Hz), 3.45 (t, 1H, $J = 4.62$ Hz); ^{13}C NMR ($CDCl_3$, δ) 167.8, 140.8, 136.7, 135.7, 129.4, 129.2, 129.0, 128.9, 128.8, 128.5, 128.4, 126.9, 82.0, 74.9, 74.8, 73.9, 57.6, 45.3. Anal. Calcd. for $C_{25}H_{25}NO_4$ (403.48): C, 74.42; H, 6.24; N, 3.47. Found: C, 74.55; H, 6.38; N, 3.40.

Data for 2a: yield 0.355 g (88%); mp 132−134 °C; $[\alpha]^{20}_D = +24.8$ ($c = 1$, CH_2Cl_2); IR (KBr) 1745.3 cm^{-1} (CO); ^1H NMR ($CDCl_3$, δ) 7.37−7.15 (m, 15H), 4.98 (d, 1H, $J = 11.50$ Hz), 4.85 (d, 1H, $J = 15.37$ Hz), 4.68 (d, 1H, $J = 11.58$ Hz), 4.65 (d, 1H, $J = 4.81$ Hz), 4.62 (d, 1H, $J = 5.18$ Hz), 4.27 (d, 1H, $J = 15.34$ Hz), 3.91 (t, 1H, $J = 4.94$ Hz), 3.65 (t, 1H, $J = 4.85$ Hz); ^{13}C NMR ($CDCl_3$, δ) 168.7, 137.2, 136.2, 129.5, 129.4, 129.3, 129.0, 128.9, 128.8, 128.5, 128.4, 127.4, 81.6, 75.5, 74.1, 73.9, 57.8, 45.9. Anal. Calcd. for $C_{25}H_{25}NO_4$ (403.48): C, 74.42; H, 6.24; N, 3.47. Found: C, 74.50; H, 6.35; N, 3.49.

Ketalization of 15a and 2a. To a solution of diol **15a** or **2a** (4.5 mmol) in benzene (34 mL) were added 2,2-dimethoxypropane (0.68 mL, 9 mmol) and *p*-toluenesulfonic acid monohydrate (0.043 g, 0.2 mmol). The mixture was stirred at reflux for 30 min, and then it was distilled until 24 mL of liquid was collected. Additional 2,2-dimethoxypropane (0.15 mL, 1.2 mmol) and benzene (15 mL) were added, the mixture was kept at reflux for 30 min again, and a further 10 mL of distillate was collected. To the resulting residue were added Et_2O and a saturated aqueous solution of $NaHCO_3$. The organic phase was separated and washed with a saturated solution of $NaHCO_3$ and brine. The organic solution was dried over $MgSO_4$ and the solvent removed under reduced pressure. The crude product was purified by column chromatography (eluent hexane/ethyl acetate 3:1).

Data for 16: yield 1.53 g (77%); oil; $[\alpha]^{20}_D = -5.0$ ($c = 1$, CH_2Cl_2); IR (KBr) 1756 cm^{-1} (CO); ^1H NMR ($CDCl_3$, δ) 7.43−7.26 (m, 13H), 7.16−7.11 (m, 2H), 4.88 (d, 1H, $J = 8.1$ Hz), 4.76 (d, 1H, $J = 5.1$ Hz), 4.74 (d, 1H, $J = 11.7$ Hz), 4.68 (d, 1H, $J = 15.2$ Hz), 4.63 (d, 1H, $J = 11.7$ Hz), 4.46 (dd, 1H, $J = 6.6$ Hz, $J' = 8.1$ Hz), 3.78 (dd, 1H, $J = 5.1$ Hz, $J' = 6.6$ Hz), 3.44 (d, 1H, $J = 15.2$ Hz), 1.48 (s, 6H); ^{13}C NMR ($CDCl_3$, δ) 168.6, 137.7, 137.3, 135.6, 129.6, 129.5, 129.3, 129.0, 128.6, 128.5, 109.9, 82.7, 81.4, 80.2, 73.8, 59.1, 45.3, 27.8, 27.7.

Data for 18: yield 1.61 g (80%); mp 98−101 °C; $[\alpha]^{20}_D = -4.19$ ($c = 1$, CH_2Cl_2); IR (KBr) 1743.3 cm^{-1} (CO); ^1H NMR ($CDCl_3$, δ) 7.34−6.99 (m, 15H), 4.89 (d, 1H, $J = 14.83$ Hz), 4.68 (d, 1H, $J = 7.14$ Hz), 4.54 (d, 1H, $J = 12.05$ Hz), 4.52 (d, 1H, $J = 4.90$ Hz), 4.35 (d, 1H, $J = 12.04$ Hz), 4.30 (t, 1H, $J = 7.10$ Hz), 4.08 (d, 1H, $J = 14.87$ Hz), 3.67 (dd, 1H, $J = 4.94$ Hz, $J' = 6.81$ Hz), 1.48, 1.40 (s, 3H); ^{13}C NMR ($CDCl_3$, δ) 168.1, 138.1, 137.3, 136.1, 129.3, 129.1, 128.9, 128.8, 128.7, 128.4, 128.3, 127.7, 110.5, 82.2, 82.1, 81.3, 73.1, 57.8, 45.6, 28.2, 28.0. Anal. Calcd. for $C_{28}H_{29}NO_4$ (443.54): C, 75.82; H, 6.59; N, 3.16. Found: C, 75.66; H, 6.50; N, 3.07.

Preparation of NCAs 17, 19, and 20. To a solution of the corresponding 3-benzyloxy β-lactam **16**, **18**, or **3a** (1 mmol) in methanol (15 mL) for **3a**, or ethyl acetate (15 mL) for **16** and **18**, was added 10% palladium on charcoal (0.05 g), and the mixture was kept under hydrogen (1 atm). The reaction mixture was stirred at room temperature until the dissappearance of the starting material as monitored by TLC (ca.16 h). The suspension was then filtered through a pad of Celite and evaporated to yield the debenzylated product, which was purified by column chromatography (see the Supporting Information for data). To a magnetizally stirred solution of the hydrogenated product in 15 mL of methylene chloride were added 2,2,6,6-tetramethylpiperidin-1-oxyl (TEMPO) (0.003 g, 0.01 mmol) and a solution of potassium bromide (0.012 g, 0.1 mmol) in water (0.25 mL) at room temperature. The solution was cooled to −5−0 °C (ice−salt bath), and aqueous sodium hypochlorite (Aldrich, 23,930−5) (10 mL) buffered at pH 7 (0.6 g of sodium hydrogen carbonate for 30 mL of a concentrate buffer solution phosphate, Aldrich 22,358−1) was added. The resulting reaction mixture was stirred at 0 °C for 1−3 min. The organic layer was separated and washed with 15 mL of 10% HCl containing 0.75 g of KI, a 10% solution of $Na_2S_2O_3$, and water. The resulting solution was dried over $MgSO_4$, and the solvent was evaporated under reduced pressure to afford the corresponding NCA, which was recristalized only for analytical purposes.

Data for 17: yield 0.352 g (96%); mp 110−112 °C; $[\alpha]^{20}_D = +16.5$ ($c = 1$, CH_2Cl_2); IR (KBr) 1848, 1780 cm^{-1} (CO); ^1H NMR ($CDCl_3$, δ) 7.38−7.15 (m, 8H), 7.02−6.98 (m, 2H), 5.25 (d, 1H, $J = 8.7$ Hz), 4.84 (d, 1H, $J = 15.0$ Hz), 4.20 (d, 1H, $J = 15.0$

Hz), 4.08 (d, 1H, *J* 8.7 Hz), 3.98 (s, 1H), 1.49, 1.45 (s, 3H); ^{13}C NMR ($CDCl_3$, δ) 166.1, 152.3, 135.9, 134.0, 129.8, 129.7, 129.3, 129.1, 127.1, 111.5, 79.5, 78.3, 58.7, 46.5, 27.7, 27.1. Anal. Calcd for $C_{21}H_{21}NO_5$ (367.40): C, 68.65; H, 5.76; N, 3.81. Found: C, 68.39; H, 5.73; N, 3.74.

Data for 19: yield 0.345 g (94%); oil; $[\alpha]^{20}_D = +27.2$ ($c = 1$, CH_2Cl_2); IR (KBr) 1850.0, 1776.7 cm^{-1} (CO); ^{1}H NMR ($CDCl_3$, δ) 7.48−7.23 (m, 10H), 5.08 (m, 1H), 5.04 (d, 1H, $J = 15.4$ Hz), 4.26 (m, 2H), 4.15 (d, 1H, $J = 15.4$ Hz), 1.61, 1.52 (s, 3H); ^{13}C NMR ($CDCl_3$, δ) 165.4, 152.0, 136.1, 133.7, 129.2, 128.9, 128.7, 128.6, 128.0, 126.9, 110.7, 81.3, 79.3, 58.6, 46.6, 27.1, 26.8.

Data for 20: yield 0.268 g (91%); mp 84−86 °C; $[\alpha]^{20}_D = +41.6$ ($c = 1$, CH_2Cl_2); IR (KBr) 1846, 1775 cm^{-1} (CO); ^{1}H NMR ($CDCl_3$, δ) 7.40−7.19 (m, 8H), 7.09−7.05 (m, 2H), 4.80 (d, 1H, $J = 15.2$ Hz), 4.16 (d, 1H, $J = 15.2$ Hz), 4.10 (t, 1H, $J = 3.4$ Hz), 4.10 (dd, 1H, $J = 15.2$ Hz), 4.10 (dd, 1H, $J = 3.4$ Hz, $J' = 6.5$ Hz), 2.67−2.60 (m, 2H), 2.24−2.05 (m, 2H); ^{13}C NMR ($CDCl_3$, δ) 169.1, 152.6, 139.8, 134.6, 129.7, 129.2, 128.9, 128.8, 127.1, 58.8, 46.4, 30.7, 30.1. Anal. Calcd for $C_{18}H_{17}NO_3$ (295.39): C, 73.19; H, 5.80; N, 4.76. Found: C, 73.18; H, 5.79; N, 4.84.

Opening of NCA 20 with Methanol. NCA **20** (0.148 g, 0.5 mmol) was dissolved in methanol (5 mL) and the solution stirred at room temperature for 16 h. The solvent was then removed under vacuum, and the crude material was purified by HPLC, using as eluant a mixture of ethyl acetate and hexane: yield 0.123 g (87%); oil; $[\alpha]^{20}_D = -3.5$ ($c = 1$, CH_2Cl_2); IR (KBr) 3435 (NH), 1727 cm^{-1} (CO); ^{1}H NMR ($CDCl_3$, δ) 7.37−7.06 (m, 10H), 3.77 (d, 1H, $J = 14.9$ Hz), 3.65 (s, 3H), 3.57 (d, 1H, $J = 14.9$ Hz), 3.25 (t, 1H, $J = 6.7$ Hz), 2.74−2.64 (m, 2H), 1.98−1.83 (m, 2H); ^{13}C NMR ($CDCl_3$, δ) 176.4, 141.9, 140.4, 129.1, 129.0, 128.9, 127.7, 126.5, 60.6, 52.7, 52.3, 35.7, 32.6.

Coupling of NCAs with L-LeuOBn. To a solution of the corresponding NCA (1 mmol) in the corresponding solvent (10 mL) was added L-leucine benzyl ester (2 mmol), and the resulting mixture was stirred at room temperature for 24 h. Then diethyl ether was added, the organic layer was washed with 0.1 N HCl and a saturated solution of $NaHCO_3$ and dried over $MgSO_4$, and the solvent was evaporated under reduced pressure to afford the corresponding dipeptide, which was purified by column chromatography.

Data for 21a: yield 0.447 g (82%); mp 120−122 °C; $[\alpha]^{20}_D = -1.5$ ($c = 1$, CH_2Cl_2); IR (KBr) 3330, 3301 (NH), 1736, 1655 cm^{-1} (CO); ^{1}H NMR ($CDCl_3$, δ) 7.75 (d, 1H, $J = 8.5$ Hz), 7.47−7.43 (m, 3H), 7.38−7.18 (m, 12H), 5.16 (d, 1H, $J = 8.1$ Hz), 5.15 (s, 2H), 4.65 (m, 1H), 3.98 (dd, 1H, $J = 2.7$ Hz, $J' = 8.1$ Hz), 3.79 (d, 1H, $J = 12.6$ Hz), 3.56 (d, 1H, $J = 12.6$ Hz), 3.34 (d, 1H, $J = 2.7$ Hz), 1.68−1.55 (m, 3H), 1.48, 1.41, 0.91, 0.88 (s, 3H); ^{13}C NMR ($CDCl_3$, δ) 173.3, 170.9, 139.7, 128.0, 136.0, 129.2, 129.0, 128.0, 127.7, 109.9, 84.18, 79.7, 67.7, 62.5, 53.6, 51.2, 42.1, 27.7, 27.6, 25.3, 23.4, 22.6. Anal. Calcd for $C_{33}H_{40}N_2O_5$ (544.77): C, 72.76; H, 7.40; N, 5.16. Found: C, 73.01; H, 7.13; N, 5.14.

Data for 22a: yield 0.485 g (89%); oil; $[\alpha]^{20}_D = -40.4$ ($c = 1$, CH_2Cl_2); IR (KBr) 3346 (NH), 1741, 1678 cm^{-1} (CO); ^{1}H NMR ($CDCl_3$, δ) 7.58 (d, 1H, $J = 8.0$ Hz), 7.34−7.21 (m, 15H), 5.21 (s, 2H), 4.99 (d, 1H, $J = 8.0$ Hz), 4.55−4.46 (m, 1H), 4.05 (dd, 1H, $J = 5.1$ Hz, $J' = 8.0$ Hz), 3.92 (d, 1H, $J = 13.1$ Hz), 3.68 (d, 1H, $J = 13.1$ Hz), 3.28 (d, 1H, $J = 5.1$ Hz), 1.52, 1.45 (s, 3H), 1.49−1.37 (m, 2H), 0.89−0.83 (m, 1H), 0.82 (d, 3H, $J = 6.0$ Hz), 0.75 (d, 3H, J 6.0 Hz); ^{13}C NMR ($CDCl_3$, δ) 173.2, 171.5, 139.9, 138.1, 129.2, 129.1, 129.0, 129.0, 128.9, 128.0, 110.1, 84.0, 80.5, 67.6, 63.3, 52.9, 51.0, 41.9, 27.8, 27.7, 25.3, 23.4, 22.5.

Data for 23a: yield 0.397 g (84%); mp 88−90 °C; $[\alpha]^{20}_D = -18.2$ ($c = 1$, CH_2Cl_2); IR (KBr) 3301 (NH), 1742, 1660 cm^{-1} (CO); ^{1}H NMR ($CDCl_3$, δ) 7.63 (d, 1H, $J = 9.1$ Hz), 7.38−7.11 (m, 15H), 5.17 (s, 2H), 4.74 (m, 1H), 3.78 (d, 1H, $J = 12.6$ Hz), 3.55 (d, 1H, $J = 12.6$ Hz), 3.20 (dd, 1H, $J = 5.2$ Hz, $J' = 7.5$ Hz), 2.69 (t, 2H, $J = 7.9$ Hz), 2.08−1.77 (m, 2H), 1.75−1.55 (m, 3H), 0.96−0.89 (m, 6H); ^{13}C NMR ($CDCl_3$, δ) 174.5, 173.5, 141.7, 140.0, 136.0, 129.2, 129.0, 128.9, 128.0, 126.8, 67.7, 63.0, 53.3, 50.9, 42.1, 36.2, 33.1, 25.6, 23.6, 22.4. Anal. Calcd for $C_{30}H_{36}N_2O_3$ (472.73): C, 76.22; H, 7.67; N, 5.94. Found: C, 75.99; H, 7.37; N, 5.85.

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Supporting Information Available: Characterization data for compounds **2b**−**f**, **3b**−**g**, **15b**−**f**, experimental procedures and characterization data for compounds **5a**−**f**, **6a**,**b**,**e**,**f**, **7a**,**e**,**f**, **21b**, **22b**, **23c**, and other intermediates, including copies of some representative ^{1}H and ^{13}C NMR spectra, and HPLC chromatograms. This material is available free of charge via the Internet at http://pubs.acs.org.

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