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A Strategy for the Asymmetric Aminohomologation of α,*β*-Dihydroxy Aldehydes: Application to the Synthesis of the Southwest Tripeptide Segment of Echinocandin B

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The synthesis of the (2*S*,3*S*,4*S*)-3,4-dihydroxyhomotyrosine amino acid segment, present in echinocandin B, in its activated form ready for peptide coupling is described. The key steps of the approach are the enantioselective AD reaction of 4-methoxycinnamic acid methyl ester, a completely diastereoselective [2 + 2] hydroxyketene−imine cycloaddition, and the TEMPO-assisted cycloexpansion of the resulting 3-hydroxy *β*-lactam to the corresponding α-amino acid *N*-carboxy anhydride (NCA). The smooth opening of the latter upon treatment with L-Thr(OSi^{t}BuPh$_2$)OMe and further acylation with the *N*-Cbz protected L-4-*tert*-butyldiphenylsilyloxy proline rendered the southwest portion of echinocandin B.

The echinocandins, Figure 1, are cyclic hexapeptides, isolated from *Aspergillus ruglosus*, that are characterized by their high antifungal and antiyeast activities.[1,2] The related lypopeptide L-688,786 (**1**) exhibits potent activity in animal models of *Pneumocystis carinii* pneumonia (PCP), in addition to the activity against several species of *Candida*.[2] Both PCP and *Candida* infections are problematic in immunocomprised patients, particularly those infected with HIV.[1] The structures of echinocandin B and **1** contain the unusual amino acid (2*S*,3*S*,4*S*)-3,4-dihydroxyhomotyrosine **2** linked, on one side, to a threonine derivative and, on the other side, to a 4-hydroxyproline moiety.[3] While the synthesis of the amino acid (2*S*,3*R*)-3-hydroxyhomotyrosine present in echinocandins C and D as well as the synthesis of these cyclic hexapeptides have been described,[3,4] to our knowledge there appears to be no reports concerning the synthesis of echinocandin B. On the other hand, structure−activity studies have revealed the amino acid **2** to be a crucial element for echinocandin B to exhibit biological properties.[5] Furthermore, echinocandin B can also be converted into echinocandin C.[6] Consequently, a concise approach to the amino acid dihydroxyhomotyrosine **2** becomes a key point for the synthesis of echinocandins and synthetic analogues thereof.[5,7]

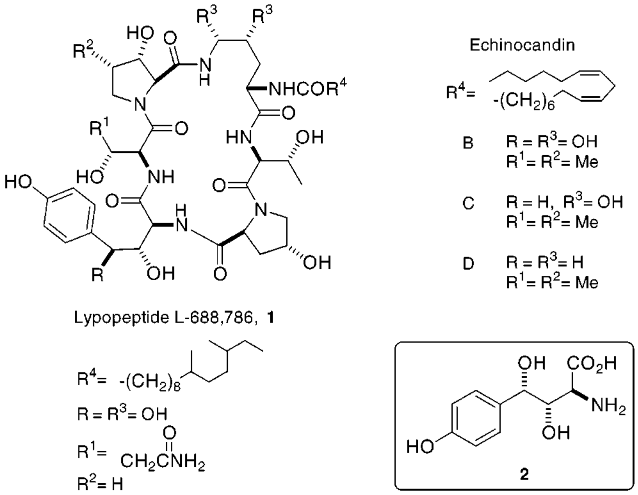

Figure 1.

One of the most direct approaches to α-amino acids involves the aminohomologation of aldehydes or, in other terms, the asymmetric carboxylation of imines.[8] The most commonly applied carboxylating and/or formylating agents are cyanide ion (the Strecker synthesis),[9] isocyanides (the Ugi reaction),[10] and heteroatom-stabilized carbanions.[11,12] In most of these cases, the acyl anion is typically employed in a masked form, and thus, masked α-amino aldehydes, carboxylic acids, or esters are formed, which subsequently have to be unmasked. On the other hand,

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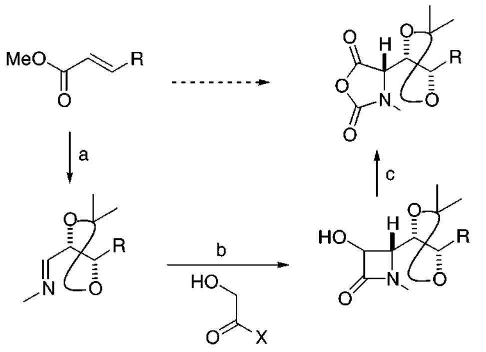

Figure 2. General strategy for aminohomologation of carboxylic acids with concomitant amino group protection and carboxyl group activation: (a) Sharpless AD-imine formation; (b) ester enolate−imine condensation or ketene−imine [2 + 2] cycloaddition; (c) TEMPO-assisted one-pot oxidation and Baeyer−Villiger rearrangement.

control of the newly created stereogenic center can be achieved either by a stereogenic center positioned α to the imine nitrogen or by chiral auxiliaries in the carbanion, albeit the degree of asymmetric induction is, in some instances, disappointing.

Our strategy, Figure 2, to β,γ-dihydroxy-α-amino acids uses glycolic acid that derivatizes imines in such a way that a four-membered ring is formed, an α-hydroxy β-lactam.[13] Then the oxidation of the carbinol and subsequent Baeyer−Villiger rearrangement of the resulting intermediate α-keto β-lactam provides, in a one-pot procedure, an α-amino acid *N*-carboxy anhydride (NCA).[14] Thus, in contrast to the existing methods for the asymmetric carboxylation of imines, our strategy leads to simultaneously amino-protected and carboxy-activated forms of α-amino acids ready for subsequent peptide couplings.[15] The success and generality of the strategy is predicated, on one hand, on the highly predictable stereoselectivity of the ketene−imine cycloaddition reaction[13,16] and, on the other hand, on the enantioselective Sharpless AD reaction[17] as the means by which a number of enantiomerically enriched α,β-dihydroxy aldehyde-derived imines are readily and economically available. For example, the dihydroxylated derivative **4a**, Scheme 1, was formed from **3a** according to the Sharpless procedure in 85% isolated yield and $\geq$99% ee.[18] Acetal protection in **4a** led to **5a**, which upon DIBAL reduction produced the aldehyde **6a** in 82% yield over the two steps. Subsequent imine formation and further reaction with acetoxyacetyl chloride and triethylamine gave **7a**, which was then converted into the α-hydroxy β-lactam **11** in 84% yield. Of interest, from the careful examination of ^{1}H and ^{13}C NMR spectra of the crude reaction products no peaks assignable to compound **8a** were observed. On the contrary, when the imine derived from **6a** was treated with benzyloxyketene, generated from benzyloxyacetyl chloride and triethylamine, a 75:25 mixture of β-lactams **9a** and **10a** was obtained.[19] This different behavior of both ketenes toward other closely related imines could be corroborated later. Thus, while the reaction of benzyloxyketene, generated as above, with the imines derived from **6b** and **6c** gave β-lactams **9b**/**10b** and **9c**/**10c** in 75:25 and 80:20 diastereomeric ratios, respectively, the reaction of acetoxyketene with the same imines afforded β-lactams **7b** and **7c** with no traces of the corresponding isomers **8**, as judged by ^{1}H and ^{13}C NMR of the corre-

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(18) The enantiomeric excess of products **4** was determined by HPLC, using a Chiralpak AS chiral column and an 2-propanol/hexane 10:90 mixture as the eluant. The racemic samples of diols **4** were prepared and their chromatograms showed the peaks for each enantiomer with a clear baseline resolution. The chromatogram corresponding to the nonracemic sample showed the peak for one enantiomer and no peak for the other was detected. On this basis, an enantiomeric exccess of $>$99% was established. For the preparation of **4** from **3** using dihydroquinidine *p*-chlorobenzoate (DHQD-pClBz) as the chiral auxiliary, see: Fleming, P. R.; Sharpless, K. B. *J. Org. Chem.* **1991**, *56*, 2869.

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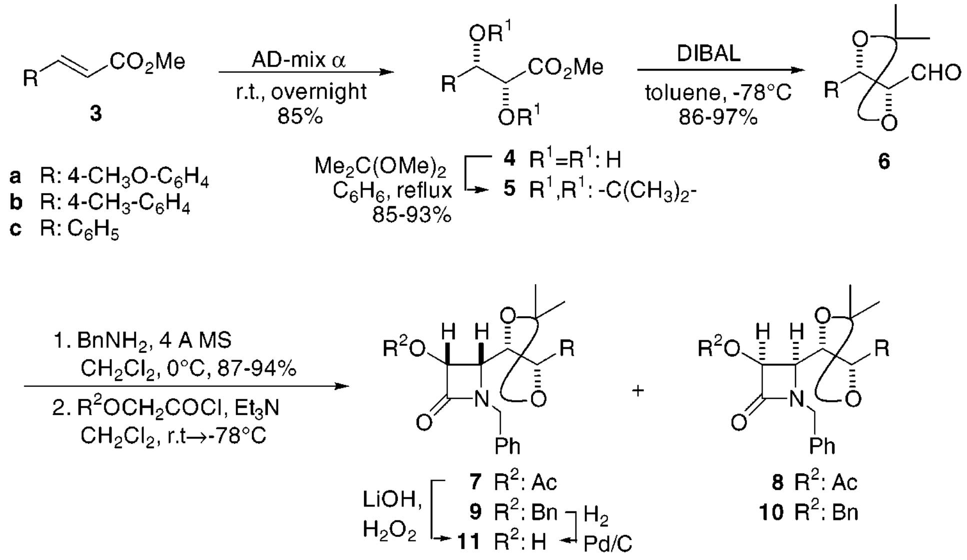
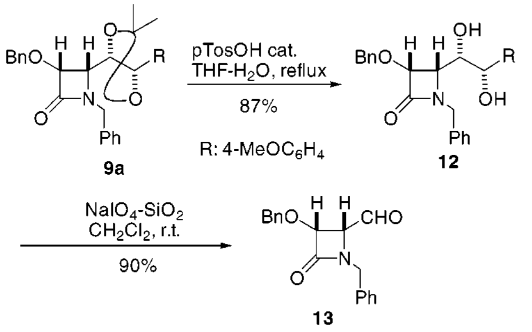
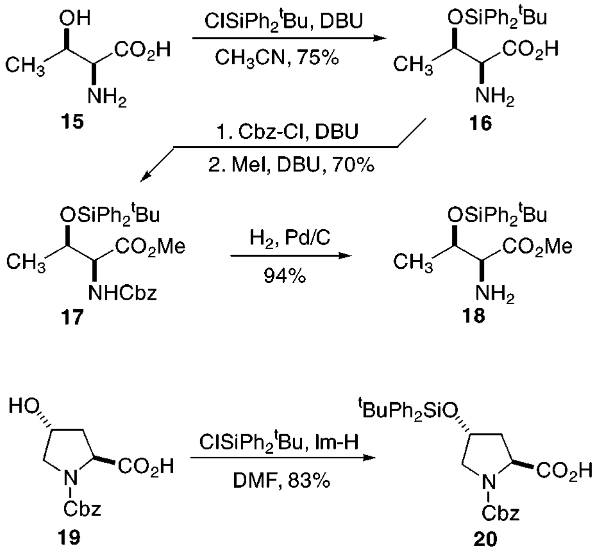
Scheme 1



Scheme 2

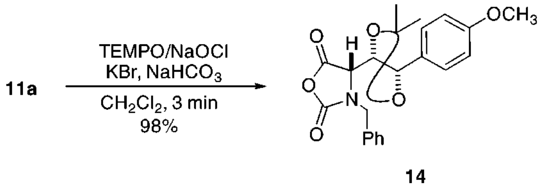


Scheme 3



sponding crude reaction products. The uniform stereochemical course of these reactions was established by conversion of **7a** and **9a** into the same α-hydroxy β-lactam **11a**. On the other hand, the relative cis configuration of each β-lactam product was determined on the basis of the ^{1}H NMR coupling constants corresponding to both hydrogens at C_3 and C_4 positions ($J_{3,4} \approx 5$ Hz), whereas the absolute configuration of the major isomers was determined by chemical correlation with **13**, Scheme 2. Thus, removal of the acetonide protective group in **9a** was followed by oxidative cleavage of the resulting glycol **12** to give the known 4-formyl azetidin-2-one **13** (Scheme 2).[20a]

Once we had established the best conditions for high diastereoselective β-lactam formation, the synthesis of the homotyrosine framework of echinocandin B was undertaken. To this end, the 3-hydroxy β-lactam **11a** obtained from **7a** as above, was converted into the NCA **14**, eq 1, by using a solution of commercial bleach and a catalytic amount of 2,2,6,6-tetramethylpiperidinyl-1-oxyl (TEMPO). The transformation occurred almost instantaneously (3−5 min) to produce **14** in nearly quantitative yield. Thus, the access to this NCA, which traditionally would require the previous synthesis of the corresponding α-amino acid,[15] can now be obtained from a non α-amino acid precursor in a very concise and practical fashion. From this approach two additional key elements are especially noteworthy. First, the creation of the α-amino stereogenic center of the dihydroxyhomotyrosine segment with essentially complete diastereoselectivity and, second, the generation of the amino acid as an active species thus overcoming the need of additional protection and activation steps for peptide couplings.[21] Accordingly, the coupling of **14** with L-threonine should provide the dipeptide segment found in the west part of echinocandin B. To this end, the L-threonine derivative **18** was prepared as shown in Scheme 3. Namely, L-threonine was first transformed into the *O-tert*-butyldiphenylsilyl de-



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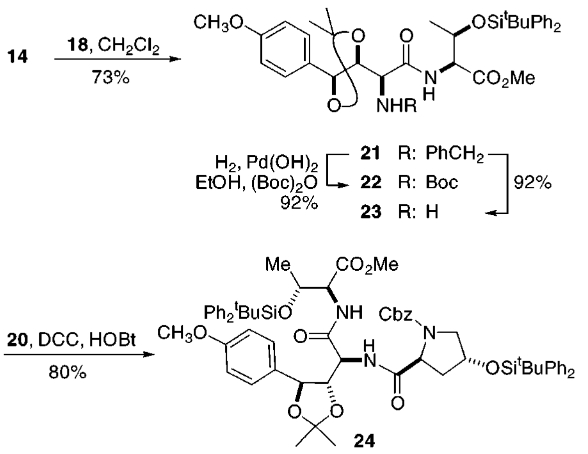
Scheme 4



rivative **16**[22] according to the procedure of Orsini et al.[23] Subsequent amino protection and “in situ” esterification with methyl iodide and DBU[24] in benzene as solvent gave **17** in 70% yield over the two steps. Final hydrogenolysis of **17** afforded pure **18** in high yield. Likewise, the L-proline derivative **20** was also prepared by standard silylation of the commercially available **19**. As Scheme 4 illustrates, the coupling of **14** with a slight excess of **18** in methylene chloride at room-temperature overnight provided, after purification by column chromatography, the dipeptide product **21** in 73% yield. The one-pot[25] *N*-debenzylation of **21** and subsequent Boc-protection gave **22** in 92% yield as the alternatively protected adduct. With **21** in hand, the southwest portion of this cyclic hexapeptide appeared to be more readily built-up. Thus, the coupling of **23**, obtained from standard hydrogenolysis of **21**, with **20** under usual DCC−HOBt conditions[26] furnished the tripeptide **24** in 80% yield, after column chromatography.

In summary, the use of the Sharpless AD in combination with our β-lactam-derived NCA method[27] represents, from a conceptual standpoint, a new aminohomologation strategy of α,β-unsaturated carboxylic acid esters that, in its turn, enables direct peptide couplings.

Experimental Section

Melting points were determined with capillary apparatus and are uncorrected. Proton nuclear magnetic resonance (300 MHz) spectra and ^{13}C spectra (75 MHz) were recorded at 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 (77.7 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 mm 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 Chiralpak AS) with flow rates using 1 mL/min and 0.5 mL/min respectively, using a DAD system. 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. MeOH was dried over magnessium metal and iodine. HRMS analyses[29] were obtained by the LSIMS ionization system using a 3-nitrobenzyl alcohol matrix and poly(ethylene glycol) as the internal standard.

General Procedure for Ketalization of 4. To a solution of the corresponding diol **4** (20 mmol) in benzene (200 mL) was added 2,2-dimethoxypropane (4.88 mL, 40 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 160 mL of liquid was collected. Additional 2,2-dimetoxypropane (1.22 mL, 10 mmol) and benzene (100 mL) were added, and the mixture was kept at reflux for 30 min again, and a further 80 mL of distillate was collected. To the resulting residue were added Et_2O (160 mL) and a saturated aqueous solution of $NaHCO_3$ (40 mL). The organic phase was separated and washed with a saturated solution of $NaHCO_3$ (80 mL) and brine (60 mL). 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).

Methyl (2*R*,3*S*)-2,3-dihydroxy-2,3-di-*O*-isopropylidene-3-(4-methoxyphenyl)propionate 5a: yield 4.52 g (85%); oil; $[\alpha]^{25}_{D} = -20.9$ ($c = 1.0$, CH_2Cl_2); IR (film) 1755 cm^{-1} (CO); ^{1}H NMR ($CDCl_3$, δ) 7.25 (d, 2H, $J = 7.1$ Hz), 6.80 (d, 2H, $J = 8.84$ Hz), 5.00 (d, 1H, $J = 2.57$ Hz), 4.24 (d, 1H, $J = 3.02$ Hz), 3.67, 3.65, 1.51 and 1.46 (s, 3H); ^{13}C NMR ($CDCl_3$, δ) 171.2, 160.3, 131.9, 129.8, 128.4, 114.5, 114.4, 111.8, 81.7, 81.0, 55.7, 52.8, 27.4, 26.2; MS (FAB) 266.1140 ($C_{14}H_{18}O_5$ requires 266.1154).

Methyl (2*R*,3*S*)-2,3-dihydroxy-2,3-di-*O*-isopropylidene-3-(4-methylphenyl)propionate 5b: yield 4.50 g (90%); oil; $[\alpha]^{25}_{D} = -33.8$ ($c = 1.0$, CH_2Cl_2); IR (film) 1756 cm^{-1} (CO); ^{1}H NMR ($CDCl_3$, δ) 7.29 (d, 2H, $J = 8.05$ Hz), 7.15 (d, 2H, $J = 7.98$ Hz), 5.10 (d, 1H, $J = 7.82$ Hz), 4.31 (d, 1H, $J = 7.78$ Hz), 3.74, 2.32, 1.58, and 1.53 (s, 3H); ^{13}C NMR ($CDCl_3$, δ) 171.2, 138.8, 134.9, 129.7, 126.9, 111.9, 81.7, 81.2, 52.8, 27.4, 26.3, 21.6.

Methyl (2*R*,3*S*)-2,3-dihydroxy-2,3-di-*O*-isopropylidene-3-phenylpropionate 5c: yield 4.39 g (93%); oil; $[\alpha]^{25}_{D} = -28.5$ ($c = 1.0$, CH_2Cl_2); IR (film) 1755 cm^{-1} (CO); ^{1}H NMR ($CDCl_3$, δ) 7.42−7.32 (m, 5H), 5.13 (d, 1H, $J = 7.69$ Hz), 4.33 (d, 1H, $J = 7.65$ Hz), 3.74, 1.58, and 1.53 (s, 3H); ^{13}C NMR ($CDCl_3$, δ) 171.1, 138.1, 128.9, 128.9, 126.9, 111.9, 81.6, 81.1, 52.7, 27.3, 26.2.

General Procedure for the Synthesis of β-Lactams. To a solution of the corresponding methyl ester **5** (13.5 mmol) in toluene (50 mL) cooled to −78 °C was added dropwise a 1 M solution of diisobutylaluminum hydride 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 (3 × 60 mL). The combined organic phase was washed with brine (60 mL) and dried over $MgSO_4$ and the solvent evaporated under reduced pressure to give the respective aldehyde **6** as an oil, which was used as such in the next step. A mixture of thus prepared aldehyde **6**, 4A MS,

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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 α-(acetoxy)acetyl chloride (1.6 mL, 15 mmol) or benzyloxyacetyl chloride (2.38 mL, 15 mmol) in dry methylene chloride (20 mL). The resulting mixture was stirred overnight at room temperature and then was washed with water (20 mL), 0.1 N HCl (20 mL), and a saturated aqueous solution of $NaHCO_3$ (20 mL). 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 7a: yield 5.11 g (89%); mp 101−103 °C; $[\alpha]^{25}_{D} = +12.3$ ($c = 1.0$, CH_2Cl_2); IR (KBr) 1763 cm^{-1} (CO), 1751 cm^{-1} (CO); ^{1}H NMR ($CDCl_3$, δ) 7.38 (m, 5H), 7.12 (d, 2H, $J = 8.61$ Hz), 6.85 (d, 2H, $J = 8.74$ Hz), 5.81 (d, 1H, $J = 4.93$ Hz), 4.95 (d, 1H, $J = 14.83$ Hz), 4.55 (d, 1H, $J = 7.91$ Hz), 4.22 (d, 1H, $J = 14.97$ Hz), 4.20 (t, 1H, $J = 7.71$ Hz), 3.81 (q, 1H, $J = 4.95$ Hz, $J' = 7.73$ Hz), 3.77, (s, 3H), 1.53 (s, 3H), 1.45 and 1.39 (s, 3H); ^{13}C NMR ($CDCl_3$, δ) 169.7, 165.3, 160.5, 135.7, 129.3, 129.1, 128.5, 114.7, 110.3, 82.0, 81.9, 73.9, 58.5, 55.9, 46.2, 27.8, 27.7, 20.2; EIMS *m/z* 426 (M$^+$). Anal. Calcd for $C_{24}H_{27}NO_6$ (425.48): C, 67.82; H, 6.40; N, 3.29. Found: C, 67.45; H, 6.52; N, 3.40.

Data for 7b: yield 4.86 g (88%); mp 93−95 °C; $[\alpha]^{25}_{D} = +16.1$ ($c = 1.0$, CH_2Cl_2); IR (KBr) 1780 cm^{-1} (CO), 1750 cm^{-1} (CO); ^{1}H NMR ($CDCl_3$, δ) 7.35−7.03 (m, 9H), 5.78 (d, 1H, $J = 4.94$ Hz), 4.90 (d, 1H, $J = 14.8$ Hz), 4.50 (d, 1H, $J = 7.9$ Hz), 4.22 (d, 1H, $J = 14.9$ Hz), 4.19 (m, 1H), 3.78 (q, 1H, $J = 4.8$ Hz), 2.27, 1.51, 1.37 and 1.35 (s, 3H); ^{13}C NMR ($CDCl_3$, δ) 169.4, 165.1, 138.8, 135.7, 134.1, 129.8, 129.4, 129.2, 129.0, 128.3, 128.0, 127.8, 110.2, 81.9, 73.8, 58.3, 58.1, 46.0, 27.6, 21.4, 19.8. Anal. Calcd for $C_{29}H_{27}NO_5$ (409.48): C, 70.40; H, 6.65; N, 3.42. Found: C, 70.47; H, 6.61; N, 3.50.

Data for 7c: yield 4.48 g (84%); mp 77−80 °C; $[\alpha]^{25}_{D} = +18.6$ ($c = 1.0$, CH_2Cl_2); IR (KBr) 1763 cm^{-1} (CO), 1751 cm^{-1} (CO); ^{1}H NMR ($CDCl_3$, δ) 7.44−7.21 (m, 10H), 5.85 (d, 1H, $J = 4.94$ Hz), 4.94 (d, 1H, $J = 14.6$ Hz), 4.60 (d, 1H, $J = 7.87$ Hz), 4.27 (d, 1H, $J = 14.65$ Hz), 4.24 (t, 1H, $J = 7.86$ Hz), 3.85 (dd, 1H, $J = 7.73$ Hz), 1.58, 1.44 and 1.40 (s, 3H); ^{13}C NMR ($CDCl_3$, δ) 169.1, 164.8, 137.1, 135.1, 128.9, 128.8, 128.0, 127.6, 110.1, 81.8, 73.6, 58.1, 45.8, 27.3, 19.7. Anal. Calcd for $C_{23}H_{25}NO_5$ (395.45): C, 69.86; H, 6.37; N, 3.54. Found: C, 69.70; H, 6.30; N, 3.50.

3-Hydroxyazetidin-2-one 11a. To a solution of 3-acetoxy *β*-lactam **7a** (4.25 g, 10 mmol) in a mixture of THF (50 mL) and water (34 mL) at 0 °C were added LiOH (0.48 g, 20 mmol) and a 30% solution of H_2O_2 (6.1 mL, 60 mmol). The resulting solution was stirred at the same temperature for 1 h, and then a solution of Na_2SO_3 (1.5 M, 33.3 mL, 50 mmol) was added. Most of the THF was removed from the mixture under vacuum. The resulting residue was dissolved in methylene chloride (50 mL), the solution was washed with a saturated solution of $NaHCO_3$ (2 × 100 mL) and dried over $MgSO_4$, and the solvent was finally removed under reduced pressure. The crude product thus obtained was purified by crystallization from diethyl ether: yield 3.22 g (84%); mp 227−229 °C; $[\alpha]^{25}_{D} = -15.1$ ($c = 1.0$, CH_2Cl_2); IR (KBr) 1725 cm^{-1} (CO); ^{1}H NMR ($CDCl_3$, δ) 7.6−7.24 (m, 5H), 6.87−6.82 (d, 2H, $J = 8.93$ Hz), 6.76−6.72 (d, 2H, $J = 8.89$ Hz), 5.02 (d, 1H, $J = 15.36$ Hz), 4.81 (q, 1H, $J = 11.53$ Hz, $J' = 4.94$ Hz), 4.65 (d, 1H, $J = 9.15$ Hz), 4.19 (d, 1H, $J = 15.38$ Hz), 3.91 (dd, 1H, $J = 9.11$ Hz, $J' = 2.15$ Hz), 3.74 (s, 3H), 3.64 (q, 1H, $J = 4.94$ Hz, $J' = 2.20$ Hz), 3.04 (d, 1H, $J = 4.94$ Hz, $J' = 11.57$ Hz), 1.54 and 1.45 (s, 3H). ^{13}C NMR ($CDCl_3$, δ) 170.1, 160.6, 135.5, 129.7−128.2, 114.8, 110.7, 81.5, 80.5, 78.0, 56.8, 55.9, 46.3, 28.1, 27.9. Anal. Calcd for $C_{22}H_{25}NO_5$ (383.44): C, 68.91; H, 6.57; N, 3.65. Found: C, 68.59; H, 6.13; N, 3.86.

Oxidation of Diol 12. Silica gel precoated with $NaIO_4$ (prepared by adding 10 g of silica gel to a vigorously stirred solution of 2.57 g of $NaIO_4$ in 5 mL of water)[28] (2.0 g) was suspended on 5 mL of methylene chloride. To this slurry, was added a solution of diol **12** (0.433 g, 1 mmol) in methylene chloride (5 mL), and the resulting mixture was stirred at room temperature for 1 h. Then the solution was filtered and the solvent evaporated to give essentialy pure compound **13** as a white solid: yield 0.266 g (90%); mp 114−116 °C; $[\alpha]^{25}_{D} = +87.66$ (lit.[20a] mp 114−116 °C; $[\alpha]^{25}_{D} = +86.7$).

Preparation of α-Amino Acid *N*-Carboxyanhydride 14. To a magnetically stirred solution of 3-hydroxyazetidine-2-one **11a** (0.57 g, 1.5 mmol) in 25 mL of methylene chloride were added 2,2,6,6-tetramethylpiperidin-1-oxyl (TEMPO) (0.003 g, 0.015 mmol) and a solution of potassium bromide (0.018 g, 0.15 mmol) in water (0.25 mL) at room temperature. The solution was cooled to −5 to 0 °C (ice−salt bath), and aqueous sodium hypochlorite (Aldrich, 23,930−5) (15 mL) buffered at pH 7 (0.9 g of sodium hydrogen carbonate for 45 mL of a concentrate buffer solution phosphate, Aldrich 22,358-1) was added. The resulting reaction mixture was stirred at 0 °C for 3 min. The organic layer was separated and washed with 30 mL of 10% HCl containing 0.75 g of KI, a 10% solution of $Na_2S_2O_3$ (15 mL), and water (15 mL). The resulting solution was dried over $MgSO_4$, and the solvent was evaporated under reduced pressure to afford the corresponding NCA: yield 0.6 g (98%); oil; ^{1}H NMR ($CDCl_3$, δ) 7.39−7.22 (m, 5H), 7.13 (d, 2H, $J = 8.61$ Hz), 6.85 (d, 2H, $J = 8.75$ Hz), 5.02 (d, 1H, $J = 15.37$ Hz), 4.94 (m, 1H0, 4.15 (m, 2H), 4.08 (d, 1H, $J = 15.38$ Hz), 3.78 (s, 3H), 1.54 and 1.44 (s, 3H); ^{13}C NMR ($CDCl_3$, δ) 166.1, 160.8, 136.2, 135.5, 134.4, 129.9−128.4, 114.9, 111.2, 81.9, 79.9, 59.4, 56.0, 47.3, 27.9, 27.5; EIMS (*m/z*) 255, 177 (BP).

Dipeptide Product 21. To a solution of the NCA **14** (0.397 g, 1 mmol) in CH_2Cl_2 (5 mL) was added (*S*)-Thr(OSi^tBuPh_2)-OMe **18** (0.56 g, 1.5 mmol) and the resulting mixture stirred at room temperature for 24 h. Then diethyl ether (10 mL) was added, the organic layer was washed with 0.1 N HCl (2 × 5 mL) and with a saturated aqueous solution of $NaHCO_3$ (2 × 5 mL) and dried over $MgSO_4$, and the solvent was evaporated under reduced pressure to afford compound **21**, which was purified by column chromatography (eluent hexane/ethyl acetate 3:1): yield 0.53 g (73%); oil; $[\alpha]^{25}_{D} = -6.7$ ($c = 1.0$, CH_2Cl_2); IR (film) 1743 cm^{-1} (CO), 1677 cm^{-1} (CO); ^{1}H NMR ($CDCl_3$, δ) 8.20 (d, 1H, $J = 9.75$ Hz), 7.69−7.33 (m, 15H), 7.25 (d, 2H, $J = 8.74$ Hz), 6.81 (d, 2H, $J = 8.75$ Hz), 5.04 (d, 1H, $J = 8.01$ Hz), 4.48 (1H), 4.40 (d, 1H, J = oo Hz), 4.15 (m, 2H), 3.87 (d, 1H, $J = 13.01$ Hz), 3.75 (s, 3H), 3.63 (s, 3H), 3.41 (d, 1H, $J = 5.35$ Hz), 1.60 and 1.53 (s, 3H), 1.06 (s, 9H), 0.66 (d, 3H, $J = 6.40$ Hz); ^{13}C NMR ($CDCl_3$, δ) 172.0, 171.6, 160.2, 140.0, 136.4, 134.4, 133.5, 130.5−127.8, 109.8, 84.2, 80.3, 70.6, 64.1, 57.9, 55.8, 52.9, 52.7, 27.9, 27.4, 20.7, 19.8; MS (FAB) 725.3601 ($C_{42}H_{53}N_2O_7Si$ requires 725.3622).

Dipeptide Product 22. To a solution of **21** (0.52 g, 0.72 mmol) and $(Boc)_2O$ (0.33 g, 1.5 mmol) in EtOAc (5 mL) was added 10% $Pd(OH)_2$ on charcoal (0.052 g), and the mixture was kept under hydrogen (1 atm) at room temperature for 16 h. Then, the suspension was filtered through a pad of Celite and evaporated to yield **22**, which was purified by column chromatography (eluent hexane/ethyl acetate 3:1 to 1:1): yield 0.50 g (92%); oil; $[\alpha]^{25}_{D} = -7.9$ ($c = 1.0$, CH_2Cl_2); IR (film) 3505 cm^{-1} (NH), 1748 cm^{-1} (CO), 1720 cm^{-1} (CO), 1683 cm^{-1} (CO); ^{1}H NMR ($CDCl_3$, δ) 7.66−7.35 (m, 12H), 6.90 (d, 2H, $J = 8.68$ Hz), 5.38 (d, 1H, $J = 8.86$ Hz), 4.67 (d, 1H, $J = 8.79$ Hz), 4.45 (m, 3H), 4.40 (d, 1H, $J = 8.79$ Hz), 3.80, 3.61, 1.56 and 1.55 (s, 3H), 1.49 and 1.02 (s, 9H), 0.99 (d, 3H, $J = 6.23$ Hz); ^{13}C NMR ($CDCl_3$, δ) 171.2, 170.5, 160.5, 136.4−128.3, 114.8, 110.0, 82.6, 79.9, 70.8, 58.6, 55.9, 53.1, 52.9, 30.4, 28.9, 27.8, 27.6, 27.5, 21.4, 19.9; MS (FAB) 867.2643 ($C_{40}H_{54}N_2O_9CsSi$ requires 867.2653).

Tripeptide Product 24. A mixture of the dipeptide **21** (0.725 g, 1 mmol), MeOH (5 mL), and 10% Pd on charcoal (0.072 g) was kept under hydrogen (1 atm) at room temperature overnight. Then, the solution was filtered through a pad of Celite and the solvent evaporated under reduced pressure to afford compound **23** (0.58 g, 92%). A solution of thus obtained crude **23**, the amino acid **20** (0.87 g, 1.8 mmol), DCC (0.37 g, 1.8 mmol), and HOBt (0.2 g, 1.5 mmol) in THF (5 mL) was stirred at 0 °C for 1 h and at room temperature for an additional 1 h. The solution was filtered and the solvent removed under vacuum. The resulting residue was dissolved in EtOAc (40 mL) and washed with a saturated aqueous solution of $NaHCO_3$ (20 mL), 1 N citric acid (20 mL), saturated $NaHCO_3$ (20 mL), and water. The organic phase was dried over $MgSO_4$ and the solvent evaporated under reduced pressure to give the title compound, which was purified by column chromatography (eluent hexane:ethyl acetate 1:1): yield 0.89 g (80%); oil; $[\alpha]^{25}_{D} = -8.9$ ($c = 1.0$, CH_2Cl_2); IR (film) 1751, 1655−1700 (broad) cm^{-1} (CO); ^1H NMR ($CDCl_3$, δ) 7.63−7.22 (m, 25H), 7.20 (d, 2H, $J = 8.11$ Hz), 7.05 (d, 1H, $J = 8.89$ Hz), 6.75 (d, 2H, $J = 8.17$ Hz), 5.15 (d, 1H, $J = 12.21$ Hz), 5.05 (d, 1H, $J = 12.26$ Hz), 4.73 (d, 1H, $J = 7.76$ Hz), 4.59, 4.45 and 4.28 (m, 2H), 4.07 (m, 1H), 3.62 and 3.58 (s, 3H), 3.51, 3.08, 2.14 and 1.91 (m, 1H), 1.53 (s, 6H), 0.99 and 0.97 (s, 9H), 0.97 (s, 3H); ^{13}C NMR ($CDCl_3$, δ) 172.5, 171.1, 169.9, 160.3, 157.1, 136.7, 136.4, 136.2, 136.1, 134.2, 133.9, 133.7, 133.3, 130.7, 130.6, 130.5, 130.5, 129.5, 129.4, 129.4, 129.3, 129.1, 18.9, 128.7, 128.6, 128.4, 128.4, 128.3, 128.2, 128.0, 114.6, 109.8, 81.9, 79.7, 72.2, 70.6, 68.2, 60.5, 58.7, 55.7, 52.9, 52.8, 51.6, 38.6, 27.8, 27.5, 27.4, 27.3, 21.3, 19.7, 19.6; MS (FAB) 1142.5041 ($C_{64}H_{77}N_3O_{11}NaSi$ requires 1142.4994).

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Supporting Information Available: Experimental procedures and characterization data for compounds **4a**−**c**, **9a**−**c**, **11a**, **12**, **16**−**18**, and **20**, including copies of some representative ^1H and ^{13}C NMR spectra, HPLC chromatograms, and HRMS spectra.[29] This material is available free of charge via the Internet at http://pubs.acs.org.

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