Enantioselective Synthesis of N^{α}-Fmoc Protected (2*S*,3*R*)-3-Phenylpipecolic Acid. A Constrained Phenylalanine Analogue Suitably Protected for Solid-Phase Peptide Synthesis

Ding-Guo Liu, Yang Gao, Xiangzhu Wang, James A. Kelley, and Terrence R. Burke, Jr.*

Laboratory of Medicinal Chemistry, Center for Cancer Research, National Cancer Institute, National Institutes of Health, Bldg. 376, Boyles Street, NCI-Frederick, P.O. Box B, Frederick, Maryland 21702-1201

tburke@helix.nih.gov

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Reported herein is the first enantioselective preparation of (2*S*,3*R*)-3-phenylpipecolic acid as a conformationally constrained phenylalanine analogue bearing N^{α}-protection suitable for solid-phase peptide synthesis. Stereochemistries at both the 2- and 3-positions are derived inductively from a single chiral center provided by the commercially available Evans chiral auxiliary, (4*S*)-4-benzyl-1,3-oxazolidin-2-one. By constraining ϕ and χ^1 torsion angles, this novel amino acid analogue can serve as a useful tool for the induction of defined geometry in phenylalanine-containing peptides.

Biological activities of peptides are highly dependent on backbone conformation and on the three-dimensional orientation of amino acid side chains. Accordingly, induction of "biologically active conformations" in peptides and peptide mimetics is an important area of investigation that frequently entails utilization of constrained amino acid analogues.[1−3] In the case of phenylalanine (**1**), important design considerations may include restriction of side chain χ^1 and χ^2 torsion angles as well as the ϕ torsion angle between C^{α} and N^{α} positions. A number of cyclic conformationally constrained phenylalanine derivatives have been reported.[4] These include exocyclic N^{α} analogues **2**,[5] **3**,[6] and **4**,[7] which constrain χ^1, χ^2, and both $\chi^1$and χ^2 angles, respectively, as well as endocyclic N^{α} analogue **5**,[8] which simultaneously constrains χ^1, χ^2, and ϕ torsion angles (Figure 1). Pipecolic acid substituted with a phenyl group at the 3-position (**6**, Figure 1) represents an endocyclic N^{α} phenylalanine analogue having its χ^1 and ϕ angles constrained. Recent use of a C-3-substituted pipecolic acid as an amino acid analogue in solid-phase synthesis[9] highlights the potential utility of the pipecolic acid nucleus in the design of constrained amino acid analogues. Despite its potential versatility as a conformationally constrained phenylalanine analogue, to date 3-phenylpipecolic acid has been described only as a racemic mixture of diastereomers.[10] We report herein the first enantioselective synthesis of N^{α}-Fmoc protected (2*S*,3*R*)-3-phenylpipecolic acid (**7**) as a constrained phenylalanine analogue suitably protected for use in solid-phase peptide synthesis.

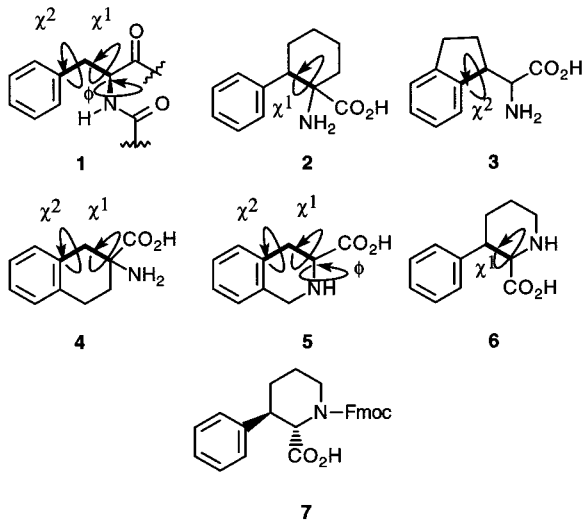

Figure 1. Structures of selected ring-utilizing conformationally constrained phenylalanine analogues.

Synthesis

Introduction of chirality at both the 2- and 3-positions was achieved through sequential stereochemical induction originating from commercially available Evans auxiliary **9**[11] (Scheme 1). The first stereocenter to be introduced was at the 3-position. Beginning with known **10**[12] allowed 1,4-addition of the allylic functionality to be achieved diastereoselectively via a copper bromide-

* To whom correspondence should be addressed. Tel: (301) 846-5906; Fax: (301) 846-6033.

(1) Babine, R. E.; Bender, S. L. *Chem. Rev.* **1997**, *97*, 1359−1472.
(2) Ripka, A. S.; Rich, D. H. *Curr. Opin. Chem. Biol.* **1998**, *2*, 441−452.
(3) Hruby, V. J.; Balse, P. M. *Curr. Med. Chem.* **2000**, *7*, 945−970.
(4) Gibson, S. E.; Guillo, N.; Tozer, M. J. *Tetrahedron* **1999**, *55*, 585−615.
(5) Cativiela, C.; Avenoza, A.; Pars, M.; Peregrina, J. M. *J. Org. Chem.* **1994**, *59*, 7774−7778.
(6) Josien, H.; Chassaing, G. *Tetrahedron: Asymmetry* **1992**, *3*, 1341−1354.
(7) Schiller, P. W.; Weltrowska, G.; Nguyen, T. M. D.; Lemieux, C.; Chung, N. N.; Marsden, B. J.; Wilkes, B. C. *J. Med. Chem.* **1991**, *34*, 3125−3132.
(8) Julian, P. L.; Karpel, W. J.; Magnani, A.; Meyer, E. W. *J. Am. Chem. Soc.* **1948**, *70*, 180−183.
(9) Souers, A. J.; Ellman, J. A. *J. Org. Chem.* **2000**, *65*, 1222−1224.
(10) Pillai, K. M. R.; Kapil, R. S.; Nand, N. *Ind. J. Chem.* **1990**, *29B*, 892−894.
(11) Evans, D. A.; Britton, T. C.; Ellman, J. A.; Dorow, R. L. *J. Am. Chem. Soc.* **1990**, *112*, 4011−4030.
(12) Rück, K.; Kunz, H. *Synthesis* **1993**, *10*, 1018−1028.

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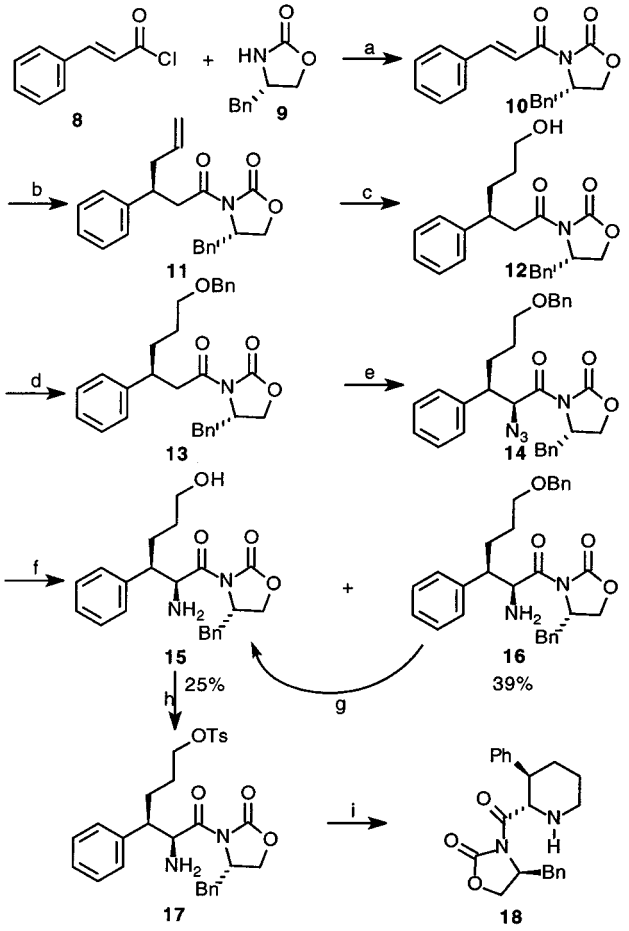
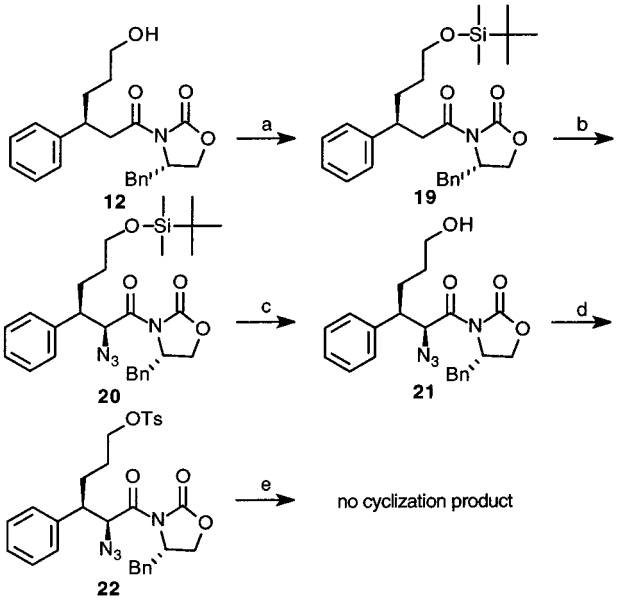
Scheme 1[a]



[a] (a) **9**, n-BuLi, **8**, THF, −78 °C, 90%; (b) allylmagnesium bromide, CuBr·Me_2S, THF, −78 °C, 98%; (c) (*i*) BH_3, THF, 0 °C; (*ii*) $NaBO_3$·H_2O, H_2O, 65%; (d) Ag_2O, BnBr, CH_2Cl_2, 100%; (e) $[(CH_3)_3Si]_2NK$, trisyl azide, −78 °C, then HOAc, KOAc, 30−35 °C, 73%; (f) 10% Pd·C, EtOH, H_2 (30 psi); (g) 10% Pd·C, EtOH, HOAc, H_2 (30 psi), 60%; (h) TsCl, pyridine, 0 °C, 48%; (i) $NaHCO_3$, CH_3CN, reflux, 16%.

dimethyl sulfide complex, providing known **11** in 98% yield.[13,14] It was envisioned that stereoselective creation of a 2-amino group could be readily accomplished by known procedures. This would then allow piperidine ring formation via nucleophilic attack onto the three carbon chain originating from the 3-position following suitable derivatization. Therefore, a multistep approach was used to introduce this latter functionality. Hydroboration of alkene **11** at 0 °C, followed by sodium perborate oxidation,[15] gave alcohol **12** in 65% yield over two steps. To minimize potential base-catalyzed lactonization during subsequent benzylation, mild conditions were employed (Ag_2O and BnBr)[16] to afford **13** in 100% yield based on a quantitative recovery of unreacted **12**. Introduction of a 2-amino functionality was initiated by asymmetric azidation at the C-α position according to the method of Evans.[17] This involved enolization of **13** with potassium

Scheme 2[a]



[a] (a) TBSCl, imidazole, DMF, 95%; (b) $[(CH_3)_3Si]_2NK$, trisyl azide, THF, −78 °C, then HOAc, KOAc, 30−35 °C, 92%; (c) HF·pyridine, THF, 0 °C, 95%; (d) TsCl, pyridine, 0 °C, 39%; (e) (*i*) Ph_3P, H_2O, THF; (*ii*) NaOAc, EtOH, reflux.

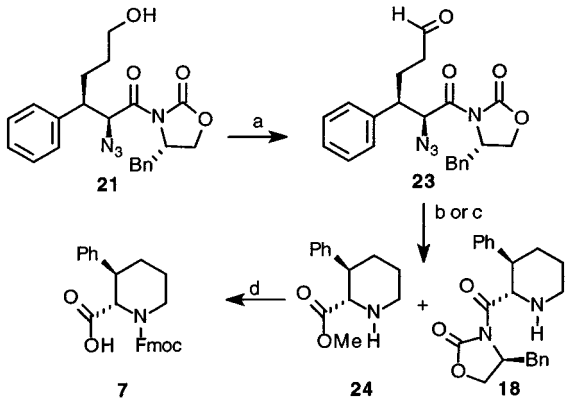
hexamethyldisilazide followed by treatment first with 2,4,6-triisopropylbenzenesulfonyl azide (trisyl azide) and then with acetic acid. Azide **14** resulted upon exposure to potassium acetate at 30−35 °C. Hydrogenation of **14** (30 psi H_2 over 10% Pd·C) gave amino alcohol **15** along with benzyl-containing **16**, which was converted to **15** by further hydrogenation in the presence of acetic acid. In an effort to effect a direct ring closure of **15** to **18**, Kilonda's cyclization protocol was employed.[18] Here, amino alcohol **15** was initially protected in situ as its methanesulfonate salt. Bromination of the primary alcohol was then attempted using Ph_3P and CBr_4. Unexpectedly, bromination failed. As an alternative, chemoselective tosylation of the hydroxyl group was achieved by treatment of **15** with TsCl/pyridine at 0 °C to afford **17** in 48% yield. The failed bromination, together with a low yield of tosylation, suggested unusual steric crowding. This was substantiated when refluxing **17** with $NaHCO_3$ in acetonitrile provided the desired piperidine derivative **18** in very low yield (16%).

The low yield of cyclized product combined with a cumbersome multistep benzylation/debenzylation procedure led us to examine alternative approaches toward **18**. As shown in Scheme 2, protection of alcohol **12** as its *tert*-butyldimethylsilyl (TBS) ether **19**, followed by asymmetric azidation, provided **20** in 92% yield. When subsequently attempted removal of the TBS group using tetrabutylammonium fluoride (TBAF) gave a complex mixture resulting from partial removal of the Evans auxiliary, a milder reagent (HF·pyridine) was employed.[19] This effected smooth removal of the TBS group to provide alcohol **21** in 95% yield. Tosylation of **21** to **22** (39% yield), followed by reduction with Ph_3P and treatment with base, disappointingly failed to give the desired **18**.

Since satisfactory ring closure by nucleophilic displacement had proven to be unsuccessful in two attempts

(13) Wu, M. J.; Wu, C. C.; Lee, P. C. *Tetrahedron Lett.* **1992**, *33*, 2547−2548.
(14) Chang, C. J.; Fang, J. M.; Liao, L. F. *J. Org. Chem.* **1993**, *58*, 1754−1761.
(15) Kabalka, G. W.; Shoup, T. M.; Goudgaon, N. M. *J. Org. Chem.* **1989**, *54*, 5930−5933.
(16) Bouzide, A.; Sauvé, G. *Tetrahedron Lett.* **1997**, *38*, 5945−5948.
(17) Evans, D. A.; Evrard, D. A.; Rychnovsky, S. D.; Früh, T.; Whittingham, W. G.; DeVries, K. M. *Tetrahedron Lett.* **1992**, *33*, 1189−1192.
(18) Kilonda, A.; Compernolle, F.; Hoornaert, G. J. *J. Org. Chem.* **1995**, *60*, 5820−5824.
(19) Nicolaou, K. C.; Webber, S. E. *Synthesis* **1986**, *3*, 453−461.

Scheme 3[a]



[a] (a) oxalyl chloride, DMSO, CH_2Cl_2, −78 °C, then NEt_3, 100%; (b) 10% Pd·C, HCO_2NH_4, MeOH, 17%; (c) 10% Pd·C, H_2 (40 psi), MeOH, 52%; (d) (*i*) 1 N NaOH, 1,4-dioxane, H_2O, 0 °C; (*ii*) CO_2(s), Fmoc-OSu, 40%.

(Schemes 1 and 2), an alternative cyclization strategy was explored that relied on imine formation (Scheme 3). Azido alcohol **21** was subjected to Swern oxidation,[20] with resulting aldehyde **23** then being ring closed by reductive amination using 10% Pd·C and ammonium formate. This provided piperidine compound **18** in 17% yield accompanied by free Evans reagent (**9**). Use of more vigorous conditions (hydrogenating aldehyde **23** at 40 psi H_2 over 10% Pd·C), gave methyl ester **24** as the main product in 52% yield (no **18** was detected). Ester **24** was readily converted by known procedures[21,22] to a mixture of Fmoc protected products, with purification by HPLC providing **7** as a white solid.

Conclusions

Reported herein is the first enantioselective preparation of (2*S*,3*R*)-3-phenylpipecolic acid bearing N^{α}-protection suitable for solid-phase peptide synthesis. Because the stereochemistries at both the 3- and 2-positions are derived inductively from a single chiral center provided by a commercially available Evans chiral auxiliary, (4*S*)-4-benzyl-1,3-oxazolidin-2-one, the optical antipode of the product reported herein ((2*R*,3*S*)-3-phenylpipecolic acid), would theoretically be readily obtainable starting from commercially available (4*R*)-4-benzyl-1,3-oxazolidin-2-one. With synthetic access to the pipecolic nucleus bearing (2*S*)-configuration at the N^{α}-center provided, a new conformationally constrained phenylalanine analogue results with the same absolute configuration as naturally occurring phenylalanine. This novel amino acid analogue provides a useful platform for the induction of defined geometry in phenylalanine-containing peptides.

Experimental Section

General Procedures. Elemental analyses were obtained from Atlantic Microlab, Inc., Norcross, GA. Solvent was removed by rotary evaporation under reduced pressure, and silica gel chromatography was performed using high performance silica gel (60 Å pore, 10 μ particle size). Anhydrous solvents were obtained commercially and used without further drying. Analytical HPLC was conducted using a Vydac C_{18} Peptide & Protein column (10 mm ID × 250 mm; solvent A = 0.1% aqueous TFA; solvent B = 0.1% TFA in acetonitrile; flow rate = 2 mL/min.). Unless otherwise indicated, ^{1}H NMR were run at 250 MHz. Positive ion FAB mass spectra (FABMS) were obtained on a VG-7070-EHF mass spectrometer using either glycerol or 3-nitrobenzyl alcohol as the matrix. For compounds so indicated, accurate mass measurement of the protonated molecule (MH^+) and other structurally diagnostic ions was carried out at a resolution of 3500 employing a limited range voltage scan under data system control. The appropriate FAB matrix ions were used for internal mass reference. The measured accurate mass, in conjunction with the structural constraints imposed by other chemical information, allowed calculation of a unique elemental composition for each compound.

(4*S*)-3-((3*S*)-3-Phenylhex-5-enoyl)-4-benzyl-1,3-oxazolidin-2-one (11). To a slurry of CuBr·SMe_2 (1.0 g, 4.88 mmol) in THF (20 mL) was added a solution of allylmagnesium bromide (8.4 mL, 8.4 mmol) at −78 °C under argon, and the resulting mixture was stirred at −78 °C (1.5 h). A solution of **10**[12] (1.0 g, 3.25 mmol) in THF (30 mL) was added to the above mixture at −78 °C, and stirring was continued (2.5 h). The reaction was quenched by addition of saturated NH_4Cl; the mixture was extracted with ethyl acetate, and this extract was evaporated to a residue, which was purified by silica gel flash chromatography (ethyl acetate:hexane, 1:8) to afford **11**[13] as a white solid (1.1 g, 98% yield), mp = 90.6−91.8 °C, $[\alpha]^{22}_D$ = +64.7 (*c* 2.22, $CHCl_3$). ^{1}H NMR ($CDCl_3$) δ: d 7.17−7.37 (10H, m), 5.73 (1H, ddt, *J* = 16.9, 10.0, 7.1 Hz), 4.99−5.10 (2H, m), 4.09 (1H, dd, *J* = 9.0, 2.7 Hz), 4.01 (1H, m), 3.23−3.48 (3H, m), 3.22 (1H, dd, *J* = 13.4, 3.4 Hz), 2.67 (1H, dd, *J* = 13.4, 10.0 Hz), 2.48 (2H, t, *J* = 7.1 Hz).

(4*S*)-3-((3*S*)-6-Hydroxy-3-phenylhexanoyl)-4-benzyl-1,3-oxazolidin-2-one (12). To a solution of **11** (1.0 g, 2.9 mmol) in THF (8 mL) was added under argon BH_3, 1.0 M in THF, (2.9 mL, 2.9 mmol) at 0 °C, and the mixture was stirred at 0 °C (1 h). To the mixture was then added H_2O (8 mL) and $NaBO_3$·H_2O (290 mg, 2.9 mmol), and the mixture was warmed to room temperature and stirred (3 h). The mixture was diluted with ethyl acetate, subjected to an extractive workup (ethyl acetate), and evaporated to a residue, which was purified by silica gel flash chromatography (ethyl acetate:hexane, from 1:4 to 3:4) to afford **12** as a white solid (687 mg, 65% yield), mp = 106−108 °C, $[\alpha]^{20}_D$ = +58.6 (*c* 1.26, $CHCl_3$). ^{1}H NMR ($CDCl_3$) δ: d 7.15−7.35 (10H, m), 4.50 (1H, m), 4.09 (1H, dd, *J* = 9.0, 2.7 Hz), 4.01 (1H, m), 3.62 (2H, t, *J* = 6.6 Hz), 3.16−3.43 (4H, m), 2.67 (1H, dd, *J* = 13.4, 10.0 Hz), 1.78 (2H, m), 1.49 (2H, m). FABMS, *m*/*z*: 368 (MH^+). Anal. Calcd for $C_{22}H_{25}NO_4$: C, 71.91; H, 6.86; N, 3.81. Found: C, 71.74; H, 6.76; N, 3.81.

(4*S*)-3-[(3*S*)-3-Phenyl-6-(phenylmethoxy)hexanoyl]-4-benzyl-1,3-oxazolidin-2-one (13). To a solution of **12** (485 mg, 1.32 mmol) in CH_2Cl_2 (3 mL) were added Ag_2O (460 mg, 1.98 mmol) and BnBr (0.24 mL, 1.98 mmol). The mixture was stirred (2 days), filtered, and evaporated to a residue, which was purified by silica gel flash chromatography (ethyl acetate: hexane, from 1:10 to 1:1) to afford **13** as a viscous oil (224 mg, 100% yield based on recovered starting **12** (306 mg)), $[\alpha]^{21}_D$ = +41.7 (*c* 0.69, $CHCl_3$). ^{1}H NMR ($CDCl_3$) δ: d 7.15−7.40 (15H, m), 4.48 (1H, m), 4.47 (2H, s), 4.07 (1H, dd, *J* = 9.0, 2.7 Hz), 3.98 (1H, m), 3.44 (2H, t, *J* = 6.6 Hz), 3.40 (1H, m), 3.17−3.32 (3H, m), 2.66 (1H, dd, *J* = 13.4, 10.0 Hz), 1.80 (2H, m), 1.55 (2H, m). FABMS, *m*/*z*: 458 (MH^+). Anal. Calcd for $C_{29}H_{31}NO_4$: C, 76.12; H, 6.83; N, 3.06. Found: C, 76.22; H, 6.96; N, 2.86.

1-[(4*S*)-2-Oxo-4-benzyl(1,3-oxazolidin-3-yl)](2*S*,3*R*)-2-azido-3-phenyl-6-(phenylmethoxy)hexan-1-one (14). To a solution of $[(CH_3)_3Si]_2NK$ (0.5 M in toluene, 2.4 mL, 1.20 mmol) in THF (4 mL) was added under argon a solution of **13** (474 mg, 1.04 mmol) in THF (3 mL) at −78 °C, and the mixture was stirred at −78 °C (40 min). To the mixture was added a cooled solution (−78 °C) of trisyl azide (386 mg, 1.25 mmol) in THF (3 mL), and the mixture was stirred at −78 °C (2 min). The reaction was quenched by addition of AcOH (0.3 mL, 5.2 mmol) and KOAc (1.02 g, 10.4 mmol), and the mixture was

(20) Mancuso, A. J.; Huang, S. L.; Swern, D. *J. Org. Chem.* **1978**, *43*, 2480−2482.
(21) Carpino, L. A.; Han, G. Y. *J. Am. Chem. Soc.* **1970**, *92*, 5748−5749.
(22) Burke, T. R., Jr.; Knight, M.; Chandrasekhar, B. *Tetrahedron Lett.* **1989**, *30*, 519−522.

stirred at 30−35 °C (1.5 h). Ethyl acetate was added, and the mixture was washed with saturated $NaHCO_3$, H_2O, and brine; then, the organic phase was dried (Na_2SO_4) and evaporated to a residue. Purification by silica gel flash chromatography (ethyl acetate:hexane, from 1:20 to 1:5) afforded **14** as a colorless oil (377 mg, 73% yield), $[\alpha]^{20}_D = +137.4$ (*c* 0.94, $CHCl_3$). ^1H NMR ($CDCl_3$) δ: d 7.13−7.36 (15H, m), 5.30 (1H, d, $J = 10.0$ Hz), 4.47 (2H, s), 4.03 (1H, m), 3.91 (1H, dd, $J = 9.0$, 1.8 Hz), 3.45 (2H, t, $J = 6.6$ Hz), 3.41 (1H, m), 3.10−3.23 (2H, m), 2.68 (1H, dd, $J = 13.4$, 9.8 Hz), 2.20 (1H, m), 1.92 (1H, m), 1.47−1.56 (2H, m). FABMS, *m*/*z*: 499 (MH^+), 471 (6.8, MH^+-N_2). Accurate mass calcd for $C_{29}H_{31}N_4O_4$ (MH^+), 499.2345; found, 499.2339. Calcd for $C_{29}H_{31}N_2O_4$ ($MH^+ - N_2$), 471.2284; found, 471.2270. The accurate mass difference between *m*/*z* 499 and *m*/*z* 471 corresponds to a neutral loss of N_2. Calcd for N_2, 28.0062; found, 28.0069.

1-[(4*S*)-2-Oxo-4-benzyl(1,3-oxazolidin-3-yl)](2*S*,3*R*)-2-amino-6-hydroxy-3-phenylhexan-1-one (15). A mixture of **14** (377 mg, 0.76 mmol) and 10% Pd·C (80 mg) in ethanol (30 mL) was hydrogenated under 30 psi H_2 (10 h). The mixture was filtered through Celite, and the filtrate was evaporated to give a residue, which was purified by silica gel flash chromatography (MeOH:$CHCl_3$, from 1:100 to 1:10) to afford product **15** as a white solid (72 mg, 25% yield) along with incompletely deprotected **16** (140 mg, 39% yield), mp = 129−130 °C, $[\alpha]^{21}_D = -130.8$ (*c* 0.65, $CHCl_3$). ^1H NMR ($CDCl_3$) δ: d 7.18−7.37 (10H, m), 5.64 (1H, s), 4.42 (1H, m), 4.09 (1H, m), 3.97 (1H, m), 3.76 (1H, dd, $J = 12.0$, 3.2 Hz), 3.52 (2H, t, $J = 6.1$ Hz), 3.00−3.19 (3H, m), 1.76 (1H, m), 1.26−1.43 (3H, m). FABMS, *m*/*z*: 383 (MH^+). Anal. Calcd for $C_{22}H_{26}N_2O_4$: C, 69.09; H, 6.85; N, 7.32. Found: C, 68.78; H, 6.88; N, 7.14.

Conversion of Intermediate 16 to 15. A mixture of **16** (140 mg, 0.30 mmol) in ethanol (10 mL) with four drops of acetic acid was hydrogenated over 10% Pd·C (50 mg) under 30 psi H_2 (5 h). The mixture was filtered through Celite, and the filtrate was evaporated to provide a residue, which was purified by silica gel flash chromatography (MeOH:$CHCl_3$, from 1:100 to 1:10) to afford **15** (68 mg, 60% yield).

6-[(4*S*)-2-Oxo-4-benzyl(1,3-oxazolidin-3-yl)](5*S*,4*R*)-5-amino-6-oxo-4-phenylhexyl 4-Methylbenzenesulfonate (17). To a solution of **15** (68 mg, 0.18 mmol) in pyridine (2 mL) was added TsCl (68 mg, 0.36 mmol) at 0 °C, and the mixture was stirred at 0 °C (overnight). Pyridine was evaporated to provide a residue, which was purified by silica gel flash chromatography (MeOH:$CHCl_3$, from 1:100 to 1:20) to afford **17** as a colorless oil (46 mg, 48% yield), $[\alpha]^{24}_D = -92.8$ (*c* 0.83, $CHCl_3$). ^1H NMR ($CDCl_3$) δ: d 7.71 (2H, d, $J = 8.4$ Hz), 7.06−7.30 (13H, m), 5.44 (1H, s), 4.37 (1H, m), 4.00 (1H, dd, $J = 3.3$, 1.8 Hz), 3.89 (1H, m), 3.83 (1H, t, $J = 6.2$ Hz), 3.82 (1H, t, $J = 6.2$ Hz), 3.71 (1H, dt, $J = 11.7$, 3.3 Hz), 3.06 (1H, dd, $J = 13.9$, 9.5 Hz), 2.98−3.03 (2H, m), 2.84 (1H, dd, $J = 8.4$, 3.3 Hz), 2.41 (3H, s), 1.71 (1H, m), 1.31−1.42 (2H, m), 1.12 (1H, m). FABMS, *m*/*z*: 537 (MH^+). Accurate mass calcd for $C_{29}H_{33}N_2O_6S$ (MH^+), 537.2059; found, 537.2035.

(4*S*)-3-[((2*S*,3*R*)-3-Phenyl(2-piperidyl))carbonyl]-4-benzyl-1,3-oxazolidin-2-one (18). A mixture of **17** (46 mg, 0.086 mmol) and $NaHCO_3$ (36 mg, 0.43 mmol) in acetonitrile (3 mL) was refluxed (2 days), and then solvent was evaporated to provide a residue, which was purified by silica gel flash chromatography (MeOH:$CHCl_3$, from 1:100 to 1:20) to afford **18** as a white solid (5 mg, 16% yield), mp = 156−159 °C, $[\alpha]^{21}_D = -7.0$ (*c* 0.63, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ: d 7.20−7.31 (8H, m), 6.91−6.93 (2H, m), 4.40 (1H, m), 4.18 (1H, dd, $J = 13.3$, 5.1 Hz), 3.91 (1H, dd, $J = 12.0$, 6.0 Hz), 3.83 (1H, dd, $J = 12.0$, 2.9 Hz), 3.78 (1H, d, $J = 10.5$ Hz), 3.37 (1H, m), 3.28 (1H, dd, $J = 13.6$, 10.5 Hz), 3.00 (1H, dd, $J = 13.3$, 6.0 Hz), 2.81 (1H, td, $J = 13.3$, 3.5 Hz), 1.87 (1H, ddd, $J = 26.2$, 11.3, 3.1 Hz), 1.75 (1H, ddd, $J = 13.3$, 3.1, 2.6 Hz), 1.64 (1H, ddd, $J = 26.2$, 13.0, 3.1 Hz), 1.42 (1H, dddd, $J = 26.2$, 12.9, 5.1, 3.5 Hz). FABMS, *m*/*z*: 365 (MH^+). Accurate mass calcd for $C_{22}H_{25}N_2O_3$ (MH^+), 365.1865; found, 365.1857.

(4*S*)-3-[(3*S*)-3-Phenyl-6-(1,1,2,2-tetramethyl-1-silapropoxy)hexanoyl]-4-benzyl-1,3-oxazolidin-2-one (19). To a solution of **12** (3.0 g, 8.16 mmol) in DMF (30 mL) were added TBSCl (1.48 g, 9.80 mmol) and imidazole (1.39 g, 20.4 mmol), and the mixture was stirred at room temperature (5 h). DMF was evaporated, and the resulting residue was dissolved in ethyl acetate (100 mL). This solution was washed with saturated $NaHCO_3$, H_2O, and brine, and then the organic phase was dried (Na_2SO_4) and evaporated to a provide a residue. Purification by silica gel flash chromatography (ethyl acetate:hexane, from 1:20 to 1:4) afforded **19** as a white solid (3.72 g, 95% yield), mp = 102.7−103.4 °C, $[\alpha]^{23}_D = +43.7$ (*c* 2.02, $CHCl_3$). ^1H NMR ($CDCl_3$) δ: d 7.17−7.34 (10H, m), 4.49 (1H, m), 4.07 (1H, dd, $J = 9.2$, 2.6 Hz), 3.98 (1H, t, $J = 8.3$ Hz), 3.57 (2H, t, $J = 6.6$ Hz), 3.43 (1H, dd, $J = 15.4$, 8.3 Hz), 3.17−3.27 (3H, m), 2.66 (1H, dd, $J = 13.6$, 9.9 Hz), 1.81 (1H, m), 1.71 (1H, m), 1.46 (1H, m), 1.38 (1H, m), 0.88 (9H, s), 0.03 (3H, s), 0.02 (3H, s). FABMS, *m*/*z*: 482 (MH^+). Anal. Calcd for $C_{28}H_{39}NO_4Si$: C, 69.82; H, 8.16; N, 2.91. Found: C, 69.73; H, 8.18; N, 2.92.

1-[(4*S*)-2-Oxo-4-benzyl(1,3-oxazolidin-3-yl)](2*S*,3*R*)-2-azido-3-phenyl-6-(1,1,2,2-tetramethyl-1-silapropoxy)hexan-1-one (20). To a solution of $[(CH_3)_3Si]_2NK$, 0.5 M in toluene (18.5 mL, 9.25 mmol), in THF (20 mL) was added a solution of **19** (3.72 g, 7.72 mmol) in THF (20 mL) at −78 °C under argon, and the mixture was stirred at −78 °C (40 min). To the mixture was added a cooled solution (−78 °C) of trisyl azide (3.58 g, 11.6 mmol) in THF (5 mL), and the mixture was stirred at −78 °C (2 min); then, the reaction was quenched by addition of AcOH (2.2 mL, 38.6 mmol) and KOAc (7.58 g, 77.2 mmol), and the mixture was stirred at 30−35 °C (1.5 h). The mixture was diluted with ethyl acetate, washed with saturated $NaHCO_3$, H_2O, and brine, dried over anhydrous Na_2SO_4, and evaporated to provide a residue, which was purified by silica gel flash chromatography (ethyl acetate:hexane, from 1:20 to 1:5) to afford **20** as a colorless oil (3.73 g, 92% yield), $[\alpha]^{20}_D = +112.0$ (*c* 1.65, $CHCl_3$). ^1H NMR ($CDCl_3$) δ: d 7.14−7.33 (10H, m), 5.28 (1H, d, $J = 10.3$ Hz), 4.03 (1H, m), 3.90 (1H, dd, $J = 8.8$, 1.5 Hz), 3.57 (2H, t, $J = 6.6$ Hz), 3.42 (1H, t, $J = 8.1$ Hz), 3.19 (1H, dd, $J = 13.2$, 2.9 Hz), 3.12 (1H, m), 2.67 (1H, dd, $J = 13.2$, 10.3 Hz), 2.18 (1H, m), 1.86 (1H, m), 1.35−1.42 (2H, m), 0.88 (9H, s), 0.03 (3H, s), 0.02 (3H, s). FABMS, *m*/*z*: 523 (MH^+). Anal. Calcd for $C_{28}H_{38}N_4O_4Si$: C, 64.34; H, 7.33; N, 10.72. Found: C, 64.53; H, 7.39; N, 10.42.

1-[(4*S*)-2-Oxo-4-benzyl(1,3-oxazolidin-3-yl)](2*S*,3*R*)-2-azido-6-hydroxy-3-phenylhexan-1-one (21). To a solution of **20** (680 mg, 1.30 mmol) in THF (15 mL) in a plastic vial was added HF·pyridine (1.35 mL) at 0 °C, and the mixture was stirred at 0 °C (30 min) and then at room temperature (3 h). The mixture was cooled to 0 °C, diluted with ethyl acetate, and neutralized by addition of saturated $NaHCO_3$ until evolution of CO_2 ceased. The mixture was subjected to an extractive workup (ethyl acetate) and evaporated to a residue, which was purified by silica gel flash chromatography (ethyl acetate:hexane, from 1:2 to 7:10) to afford **21** as a colorless oil (504 mg, 95%), $[\alpha]^{20}_D = +161.4$ (*c* 0.83, $CHCl_3$). ^1H NMR ($CDCl_3$) δ: d 7.11−7.30 (10H, m), 5.28 (1H, d, $J = 10.3$ Hz), 4.02 (1H, m), 3.89 (1H, dd, $J = 8.8$, 1.5 Hz), 3.59 (2H, t, $J = 6.6$ Hz), 3.42 (1H, t, $J = 8.8$ Hz), 3.16 (1H, dd, $J = 14.0$, 3.7 Hz), 3.11 (1H, m), 2.65 (1H, dd, $J = 14.0$, 10.3 Hz), 2.16 (1H, m), 1.87 (1H, m), 1.38−1.46 (2H, m). FABMS, *m*/*z*: 409 (MH^+). Anal. Calcd for $C_{22}H_{24}N_4O_4$: C, 64.69; H, 5.92; N, 13.72. Found: C, 64.70; H, 6.08; N, 13.45.

6-[(4*S*)-2-Oxo-4-benzyl(1,3-oxazolidin-3-yl)](5*S*,4*R*)-5-azido-6-oxo-4-phenylhexyl 4-methylbenzenesulfonate (22). To a solution of **21** (100 mg, 0.24 mmol) in pyridine (2.5 mL) was added TsCl (93 mg, 0.49 mmol) at 0 °C, and the mixture was stirred at 0 °C (overnight). Pyridine was evaporated to provide a residue, which was purified by silica gel flash chromatography (ethyl acetate:hexane, from 1:10 to 1:2) to afford **22** as a colorless oil (54 mg, 39% yield), $[\alpha]^{24}_D = +103.6$ (*c* 0.92, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ: d 7.72 (2H, d, $J = 8.4$ Hz), 7.18−7.32 (8H, m), 7.10−7.14 (4H, m), 5.25 (1H, d, $J = 9.2$ Hz), 4.09 (1H, m), 3.88−3.99 (3H, m), 3.54 (1H, *t*, *J* = 8.1 Hz), 3.16 (1H, dd, $J = 13.6$, 3.3 Hz), 3.05 (1H, ddd, $J = 11.7$, 9.2, 3.7 Hz), 2.67 (1H, dd, $J = 13.6$, 9.5 Hz), 2.42 (3H, s), 2.02 (1H, m), 1.79 (1H, m), 1.43−1.54 (2H, m). FABMS, *m*/*z*: 563 (MH^+). Anal. Calcd for $C_{29}H_{30}N_4O_6S$: C, 61.91; H, 5.37; N, 9.96. Found: C, 62.11; H, 5.51; N, 9.81.

Methyl (2*S*,3*R*)-3-Phenylpiperidine-2-carboxylate (24). To a solution of oxalyl chloride, 2 M in CH_2Cl_2 (0.61 mL, 1.22 mmol), in CH_2Cl_2 (1 mL) was added a solution of DMSO (174 μL, 2.45 mmol) in CH_2Cl_2 (1 mL) at −78 °C, and the mixture was stirred at −78 °C (20 min). To the mixture was added a solution of **21** (100 mg, 0.24 mmol) in CH_2Cl_2 (3 mL) at −78 °C, and the mixture was stirred at −78 °C (20 min); then, triethylamine (341 μL) was added and stirring continued at −78 °C (20 min). The mixture was allowed to come to ambient temperature, diluted with ethyl acetate, and washed sequentially with 1 N HCl, saturated $NaHCO_3$, and brine. Drying over anhydrous Na_2SO_4 and evaporation provided a residue, which was filtered through a short silica gel column to give crude aldehyde **23**. This was dissolved in MeOH (10 mL) and hydrogenated over 10% Pd·C (20 mg) under 40 psi H_2 (overnight). Filtration through Celite and evaporation provided a residue, which was purified by silica gel flash chromatography (MeOH:$CHCl_3$, from 1:100 to 1:20) to afford **24** as a white solid (28 mg, 52% yield), mp = 176.5 °C dec, $[\alpha]^{20}_D$ = +35.0 (*c* 0.36, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ: d 7.13−7.26 (5H, m), 3.45 (1H, d, J = 10.2 Hz), 3.36 (3H, s), 3.17 (1H, m), 2.67−2.74 (2H, m), 1.99 (1H, m), 1.68−1.79 (2H, m), 1.56 (1H, m). FABMS, *m*/*z*: 220 (MH^+). Accurate mass calcd for $C_{13}H_{18}NO_2$ (MH^+), 220.1338; found, 220.1354.

(2*S*,3*R*)-1-[(Fluoren-9-ylmethyl)oxycarbonyl]-3-phenylpiperidine-2-carboxylic Acid (7). To a solution of **24** (50 mg, 0.23 mmol) in a mixture of 1,4-dioxane (3 mL) and H_2O (2 mL) was added a 1:1 mixture of 1 N NaOH (10 mL) and 1,4-dioxane portionwise at 0 °C. Following complete hydrolysis of the methyl ester (2 h), the mixture was buffered by addition of a small quantity of dry ice; then, Fmoc-OSu (78 mg, 0.23 mmol) was added, and the mixture was stirred at ambient temperature (overnight). Following adjustment of the pH to 6.5 at 0 °C using a 2 M solution of $KHSO_4$, dioxane was removed by evaporation and the solution was diluted with H_2O. The mixture was acidified to pH 5 using a 2 M solution of $KHSO_4$, subjected to an extractive workup (ethyl acetate), and evaporated to a residue, which was purified by silica gel flash chromatography (ethyl acetate:hexane, from 1:1 to 1:50 MeOH:$CHCl_3$) to afford semipure **7** as a white solid (81 mg). Analysis by HPLC indicated approximately 25% contamination. Therefore, further purification by preparative HPLC (retention time = 21.1 min) provided 18 mg from 37 mg of semipure material, resulting in a 40% effective overall yield of title compound **7**. ^{1}H NMR (400 MHz, DMSO-d_6, 50 °C) δ: d 7.82 (2H, m), 7.57 (2H, m), 7.35 (2H, m), 7.30−7.17 (8H, m), 4.83 (1H, brs), 4.38 (2H, brs), 4.23 (1H, m), 3.80 (1H, m), 3.50 (1H, brs), 3.08 (1H, brs), 1.84−1.75 (1H, m), 1.72−1.62 (1H, m), 1.41−1.22 (2H, m). FABMS, *m*/*z*: 428 (MH^+). Accurate mass calcd for $C_{27}H_{26}NO_4$ (MH^+), 428.1862; found, 428.1847. Calcd for $C_{26}H_{24}NO_2$ ($MH^+ - HCO_2H$), 382.1807; found, 382.1784. The accurate mass difference between *m*/*z* 428 and *m*/*z* 382 corresponds to a neutral loss of HCO_2H. Calcd for HCO_2H, 46.0055; found, 46.0063.

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