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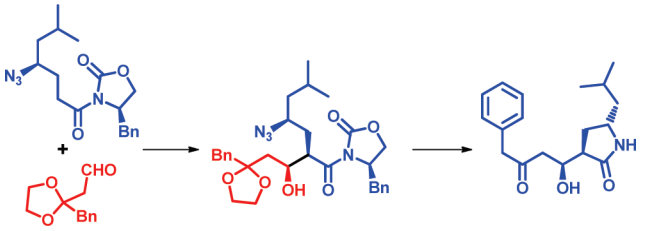
Asymmetric Total Synthesis of the Caspase-1 Inhibitor (−)-Berkeleyamide A

Swapnil J. Kulkarni,[†] Yakambram Pedduri,[†] Amar G. Chittiboyina,*[,†] and Mitchell A. Avery*[,†,‡,§]

[†]*Department of Medicinal Chemistry, School of Pharmacy,* [‡]*National Center for Natural Product Research, School of Pharmacy, and* [§]*Department of Chemistry, The University of Mississippi, University, Mississippi 38677*

mavery@olemiss.edu

Received January 21, 2010



The asymmetric total synthesis of (−)-berkeleyamide A (**1**), a naturally occurring caspase-1 inhibitor, has been achieved by employing Evans' *syn*-aldol reaction of *N*-acyl-(4*R*)-benzyl oxazolidin-2-one **3** as the key step.

Interleukin-1β converting enzyme (ICE), also known as caspase-1, is responsible for cleavage and activation of interleukin-1β (IL-1β) to its active form (17K), which in turn is involved in the pathogenesis of several inflammatory disorders.[1] Caspase-1 has been implicated in diseases such as rheumatoid arthritis, multiple sclerosis, stroke, liver failure, and neurodegenerative disorders such as Huntington's disease.[2,3] Subsequent research over the years suggests that ICE plays a pivotal role in regulation of proinflammatory cytokines, and its inhibition is a potential therapeutic target for the treatment of immune-mediated inflammatory diseases.[4]

Recently, several interesting secondary metabolites have been isolated from rare microbes evolved in extreme ecosystems, such as Berkeley Pit Lake, in search of potential anticancer and antimicrobial agents.[5] One such secondary metabolite, Berkeleyamide A **1**, was isolated from the fungi *Pencillium rubrum*, which inhibited caspase-1 and the signal transducing enzyme matrix metalloproteinase-3 (MMP-3) in low micromolar range. The structure of berkeleyamide A was elucidated using detailed NMR studies, and its stereochemistry at C10 was assigned as 10*S* with remaining uncertainty over the configuration of the C11 and C14 stereogenic centers.[6] The intriguing biological properties and ambiguity of the absolute stereochemistry at C11 and C14 prompted us to initiate the total synthesis of berkeleyamide A. During the course of our work, Brimble and co-workers[7] confirmed the absolute stereochemistry of **1** as 10*S*,11*R*,14*S* by total synthesis using [3 + 2]-dipolar cycloaddition as a key step. However, the crucial cycloaddition reaction suffers from moderate diastereoselectivity (2.1:1:1) and lower yield (~35%) of the required diastereomer.

Herein we report our modular asymmetric synthetic approach for the synthesis of berkeleyamide A (**1**) using Evans' aldol reaction as a key step for C−C bond formation between chiral imide **3** and aldehyde **4** with the introduction of the required chirality at C10 and C11 (Scheme 1). As depicted in the retrosynthetic analysis, crucial *N*-acyl-(4*R*)-benzyl oxazolidin-2-one **3** was envisioned from L-leucine by assuming the natural L-configuration in the biosynthetic pathway, whereas the other aldol coupling partner, aldehyde **4**, was envisioned from β-keto ester **5**. Thus, our disconnection approach offers a flexible strategy to synthesize all possible diastereomers of **1** by simply incorporating either L- or D-amino acid and adopting Evans' (*or*) non-Evans' *syn*/*anti*-aldol synthetic approach.[8−10]

As shown in Scheme 2, aldehyde **4** was synthesized from commercially available Meldrum's acid **6**, which was converted to β-keto ester **5** by typical acylation followed by decarboxylative methanolysis.[11] The ketone functionality in **5** was then protected as the 1,3-dioxalane[12] and the corresponding ester converted to the required aldehyde **4** by a standard two-step protocol, complete reduction to the alcohol followed by DMP oxidation in multigram quantities with overall good yield.

Next, commercially available *N*-Boc-L-leucine was converted to *N*-Boc-L-leucinal (**7**) following the literature method.[13] The resulting aldehyde was subjected to HWE olefination using triethyl phosphonoacetate[14] followed by hydrogenation to give aminoester **8** in 85% yield (Scheme 3).

Subsequent ester hydrolysis of **8** furnished γ-*N*-Boc-amino acid **9** in good yield. Large-scale synthesis of **9** was achieved, obviating the need for chromatographic purification. Our initial attempts toward the asymmetric aldol

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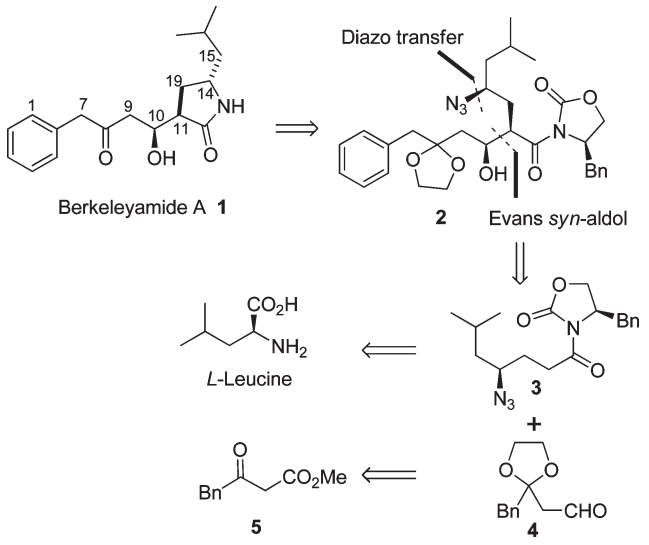
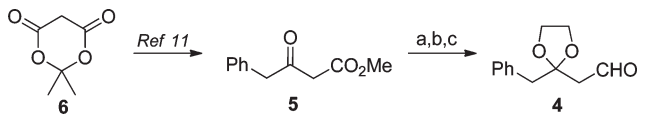
DOI: 10.1021/jo1001033 Published on Web 03/31/2010

SCHEME 1. Retrosynthetic Analysis of Berkeleyamide A



SCHEME 2. Synthesis of Aldehyde Fragment 4[a]

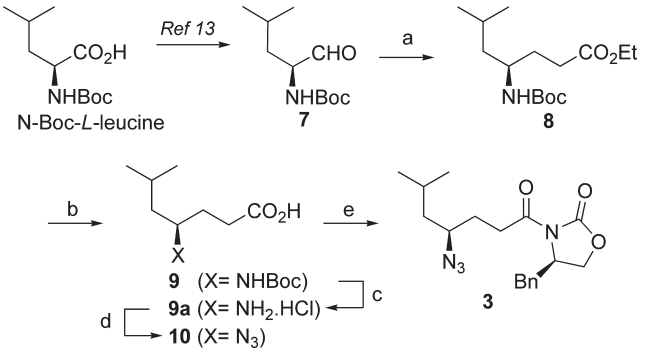


[a]Reagents and conditions: (a) 1,2-bis(trimethylsilyloxy)ethane, TMSOTf, CH_2Cl_2, rt, 8 h, 95%; (b) 2.3 M $LiAlH_4$ in THF, THF, 0 °C to rt, 2 h, 78%; (c) Dess−Martin periodinane, CH_2Cl_2, rt, 1 h, 92%.

reaction using a chiral imide derived from acid **9** gave the required aldol product, albeit with poor diastereoselectivity and low yield. The enolizable *N*-Boc-carbamate[15] functionality in **9** was then converted into the azide in two-steps Boc-deprotection followed by azido transfer reaction using shelf-stable imidazol-1-sulfonyl azide[16] to furnish γ-azido acid **10** in 77% yield. Re-evaluation of the asymmetric aldol reaction using the chiral imide of **10** was then pursued. Accordingly, acid **10** was coupled with (4*R*)-benzyl-2-oxazolidinone chiral auxiliary using a standard procedure[17] to obtain the correct stereochemistry in the aldol reaction based on literature precedents.[18]

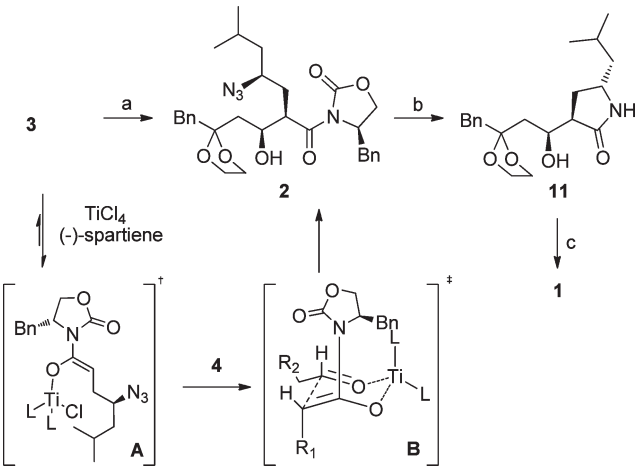
With the required fragments **3** and **4** in hand, our anticipated plan to use an asymmetric Evans' aldol reaction to couple these segments and to set the C10 and C11 stereochemistry as required proceeded smoothly. Although initial efforts involving a soft enolization method using $TiCl_4$ as a Lewis acid in the presence of a conventional base, triethyl amine or DIPEA (Hünig's base), provided the required aldol product, the best conversion was achieved with Crimmin's modification[19] using (−)-sparteine as base. As shown in Scheme 4, chiral imide **3** was treated with $TiCl_4$/(−)-sparteine to generate *Z*-enolate **A**, which was treated with

SCHEME 3. Synthesis of γ-Azido-oxazolidinone Fragment 3[a]



[a]Reagents and Conditions: (a) (i) triethyl phosphonoacetate, 1 M NaHMDS in THF, THF, 0 °C, **7**, −20 to 0 °C, 0.5 h; (ii) 5% Pd/C, H_2, 20 psi, EtOAc, 1.5 h, 85%; (b) $LiOH \cdot H_2O$, THF/MeOH/H_2O (5:1:1), rt, 2 h, 79%; (c) 4.0 M HCl in 1,4-dioxane, 0 °C to rt, 12 h; (d) imidazol-1-sulfonyl azide HCl, K_2CO_3, $CuSO_4 \cdot 5H_2O$, MeOH, rt, 14 h, 77%; (e) pivaloyl chloride, TEA, LiCl, (4*R*)-benzyl-2-oxazolidinone, THF, −20 °C to rt, 6 h, 75%.

SCHEME 4. Synthesis of Berkeleyamide A via Evans' *syn*-Aldol Reaction[a]



[a]Reactions and conditions: (a) $TiCl_4$, (−)-sparteine, **4**, CH_2Cl_2, 0 °C, 3 h, 74%; (b) 5% Pd/C, ammonium formate, MeOH, 1 h, 85%; (c) $Pd(CH_3CN)_2Cl_2$, acetone, H_2O, rt, 4 h, 77%.

aldehyde **4** to afford the aldol product **2** as a single diastereomer exclusively in 74% yield. The stereochemical outcome of the aldol reaction can be rationalized using a Zimmerman−Traxler six-membered chairlike transition state (Scheme 4). As anticipated, the facial selectivity of the aldehyde was directed by the chiral auxiliary of the enolate resulting in *re* face attack to deliver Evans' *syn*-aldol product. The absolute configuration of the resulting alcohol at the C10 position was further confirmed by Mosher ester analysis to be 10*S* as in the natural product **1** (Supporting Information). Furthermore, the *syn* selectivity of the aldol product was confirmed by ^1H NMR analysis of Mosher ester derivatives ($J_{10\text{-}11}$ = 2.95 Hz). The conversion of the aldol adduct **2** to natural product **1** required azide reduction, lactamization, and ketal deprotection. Gratifyingly, after a few attempts, transfer hydrogenation using 5% Pd/C directly provided the lactam **11** in one pot from **2** in 85% yield

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and recovered chiral auxiliary without loss of its optical purity. Final ketal deprotection[20] of **11** was then successfully achieved with $Pd(CH_3CN)_2Cl_2$ in moist acetone to yield berkeleyamide A (**1**) in 77% yield. The spectral and other data of **1** are in full agreement with the reported data of the natural product.[21] The 2D NOESY correlations of **1** are also consistent as reported.

In summary, a concise synthesis of the caspase-1 inhibitor (−)-berkeleyamide A has been achieved in nine steps starting from *N*-Boc-L-leucinal with 18% overall yield. Our synthetic endeavor of (−)-berkeleyamide A is very efficient, scalable, and highly diastereoselective with the flexibility to develop various analogues of the natural product. Using this modular approach, synthesis of the remaining diastereomers and structure−activity relationships of (−)-**1** against caspase-1 are in progress and will be disclosed in due course.

Experimental Section

Ethyl (2*E*,4*S*)-4-[(*tert*-butoxycarbonyl)amino]-6-methylhept-2-enoate (7a): To a solution of triethyl phosphonoacetate (16.4 g, 73.0 mmol) in THF (200 mL) was added solution of 1.0 M NaHMDS (65.7 mL, 65.7 mmol) slowly at 0 °C. The resulting orange solution cooled to −20 °C, and a solution of freshly prepared *N*-Boc-L-leucinal (15.72 g, 73.0 mmol) in THF (50 mL) was added dropwise at the same temperature. After addition, the mixture was warmed to 0 °C and stirred under argon for an additional 30 min and then quenched with saturated aqueous ammonium chloride solution at 0 °C. The organic layer was separated, concentrated, and the residue was dissolved in EtOAc (200 mL), washed with water and brine, dried over $MgSO_4$, and filtered. The filtrate was partially concentrated and subjected to reduction without further purification as a pale yellow oil: $[\alpha]^{20}_D = -23$ (*c* 1.50, MeOH); ν_{max} ($CHCl_3$)/cm^{-1} 3354, 2959, 1701, 1691, 1657, 1519, 1367, 1282, 1167, 1045; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.81 (dd, J = 15.4, 4.9 Hz, 1H), 5.90 (d, J = 15.6 Hz, 1H), 4.50 (d, J = 7.9 Hz, 1H), 4.32 (br s, 1H), 4.17 (q, J = 7.0 Hz, 2H), 1.67 (dt, J = 13.1, 6.5 Hz, 1H), 1.42 (s, 9H), 1.36 (m, 2H), 1.26 (t, J = 7.0 Hz, 3H), 0.91 (d, J = 6.6 Hz, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 166.4, 155.0, 148.9, 120.4, 77.3, 60.4, 49.8, 43.8, 28.4, 24.7, 22.7, 14.2; HRMS (ESI^+) calcd for $C_{15}H_{27}NO_4Na$ 308.1838, found 308.1827.

Ethyl (4*R*)-4-[(*tert*-butoxycarbonyl)amino]-6-methylheptanoate (8): To the solution of **7a** in EtOAc (100 mL) was added 5% Pd/C catalyst (1.0 g), and the reaction mixture was stirred under H_2 atmosphere for 1.5 h at 20 psi in a Parr shaker. The catalyst was removed by filtration through a pad of Celite, and the organic solvent was evaporated under reduced pressure. Then the crude obtained was purified by column chromatography using Et_2O/hexanes (1:5) to afford **8** (18.0 g, 85%) as colorless thick liquid: $[\alpha]^{20}_D = -6.20$ (*c* 1, MeOH); ν_{max} ($CHCl_3$)/cm^{-1} 3357, 2957, 1712, 1689, 1519, 1450, 1390, 1366, 1248, 1168, 1044, 1028; ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.25 (d, J = 9.0 Hz, 1H), 4.10 (q, J = 6.8 Hz, 2H), 3.71−3.56 (m, 1H), 2.33 (t, J = 7.6 Hz, 2H), 1.80 (m, 1H), 1.58 (m, 2H), 1.40 (s, 9H), 1.28 (m, 2H), 1.23 (t, J = 6.8 Hz, 3H), 0.88 (d, J = 6.5 Hz, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 173.7, 155.6, 78.9, 60.4, 48.5, 45.2, 31.0, 28.4, 24.9, 23.0, 22.3, 14.2; HRMS (ESI^+) calcd for $C_{15}H_{29}NO_4Na$ 310.1994, found 310.2002.

(4*R*)-4-[(*tert*-Butoxycarbonyl)amino]-6-methylheptanoic acid (9): To a solution of **8** (16.0 g, 55.7 mmol) in THF/MeOH (400 mL, 5:1) was added an aqueous solution of 2 M LiOH (84 mL, 168 mmol) at 0 °C. The reaction mixture was allowed to warm to room temperature and stirred for an additional 2 h. The mixture was concentrated to remove organic solvents and diluted with Et_2O (100 mL). The layers were separated, and the aqueous layer was carefully acidified with 1 N HCl at 0 °C and extracted with methylene chloride (3 × 50 mL), and the combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated to afford **9** as a white solid (11.46 g, 79%): mp 110−111 °C; $[\alpha]^{20}_D = -6.60$ (*c* 1.06, MeOH); ν_{max} (neat)/cm^{-1} 3331, 2948, 1709, 1657, 1534, 1454, 1394, 1365, 1276, 1253, 1167, 1116, 1026, 901, 872, 847; ^{1}H NMR (500 MHz, MeOD) δ 3.61 (br s, 1H), 2.33 (t, J = 7.5 Hz, 2H), 1.79 (ddd, J = 12.2, 8.1, 3.9 Hz, 1H), 1.72−1.63 (m, 1H), 1.63−1.51 (m, 1H), 1.46 (s, 9H), 1.42−1.33 (m, 1H), 1.28−1.18 (m, 1H), 0.99−0.87 (m, 6H); ^{13}C NMR (126 MHz, MeOD) δ 175.9, 156.9, 78.3, 44.3, 30.9, 30.2, 27.4, 24.7, 22.2, 21.1; HRMS (ESI^+) calcd for $C_{13}H_{26}NO_4$ 260.1862, found 260.1856.

(4*R*)-4-Amino-6-methylheptanoic Acid Hydrochloride (9a): To a solution of **9** (10.24 g, 39.5 mmol) in anhydrous 1,4-dioxane (20 mL) was added 4 M HCl in dioxane (50 mL, 200 mmol) at 0 °C. The reaction mixture was allowed to warm to room temperature and stirred for 12 h under argon to yield thick slurry. The mixture was concentrated, and resulting solid was dispersed in anhydrous ether and filtered under inert atmosphere to furnish **9a** as a white solid: mp 147−148 °C; $[\alpha]^{20}_D = -4.41$ (*c* 0.64, MeOH); ν_{max} (neat)/cm^{-1} 2873, 1724, 1702, 1602, 1503, 1438, 1298, 1234, 1121, 896; ^{1}H NMR (400 MHz, D_2O) δ 3.35−3.26 (m, 1H), 2.46 (t, J = 7.5 Hz, 2H), 1.95−1.78 (m, 2H), 1.68−1.56 (m, 1H), 1.49−1.36 (m, 2H), 0.84 (dd, J = 6.5, 3.0 Hz, 6H); ^{13}C NMR (126 MHz, D_2O) δ 177.2, 49.5, 41.0, 29.6, 27.5, 23.8, 21.7, 21.2; HRMS (ESI^+) calcd for $C_8H_{18}NO_2$ 160.1338, found 160.1342.

(4*R*)-4-Azido-6-methylheptanoic acid (10): The reagent imidazole-1-sulfonyl azide hydrochloride (3.86 g, 18.40 mmol) was added to the suspension of **9a** (3.0 g, 15.33 mmol), potassium carbonate (7.84 g, 56.7 mmol), and copper(II) sulfate pentahydrate (0.380 g, 0.153 mmol) in 80 mL of MeOH. After being stirred for 14 h, the resulting gray colored mixture was concentrated, diluted with water, and adjusted the pH to 2 with concd HCl at 0 °C. The resulting aqueous layer was extracted with ethyl acetate (3 × 30 mL), and the combined organic layer was washed with water and brine, dried over magnesium sulfate, and concentrated. The residue was purified by column chromatography (hexanes/EtOAc, 9:1) to afford **10** (2.2 g, 77%) as a colorless liquid: $[\alpha]^{20}_D = +10.77$ (*c* 1.17, MeOH); ν_{max} (neat)/cm^{-1} 2959, 2873, 2097, 1707, 1416, 1369, 1267, 1245, 1172, 922; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.38 (ddd, J = 13.6, 8.9, 4.6 Hz, 1H), 2.51 (m, 2H), 1.98 (m, 1H), 1.75 (m, 2H), 1.52 (ddd, J = 14.4, 8.7, 5.9 Hz, 1H), 1.32 (m, 1H), 0.94 (d, J = 6.6 Hz, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 178.7, 60.0, 43.3, 30.5, 29.5, 25.0, 22.9, 22.1; HRMS (ESI^+) calcd for $C_8H_{15}N_3O_2$ 186.1243, found 186.1247.

(4*R*)-3-[(4*R*)-4-Azido-6-methylheptanoyl]-4-benzyl-1,3-oxazolidin-2-one (3). To a stirred solution of **10** (1.0 g, 5.4 mmol) in THF (40 mL) was added TEA (1.52 mL, 10.8 mmol) followed pivaloyl chloride (0.66 mL, 5.4 mmol) at −20 °C. After being stirred for 2 h, LiCl (275 mg, 6.48 mmol) and (4*R*)-benzyloxazolidin-2-one (860 mg, 4.86 mmol) were added; the mixture was allowed to warm to 0 °C and then to room temperature slowly and was stirred for an additional 4 h. The mixture was concentrated, and residue was partitioned between 5% aqueous $KHSO_4$ (20 mL) and ethyl acetate (50 mL). The organic layer was washed with 1 M sodium bicarbonate (2 × 10 mL) and brine (10 mL) and then dried over magnesium sulfate and concentrated. The residue was purified by column chromatography (EtOAc/hexanes, 3:17) to yield **3** (1.4 g, 75%) as a viscous liquid: $[\alpha]^{20}_D = -73.48$ (*c* 1.14, MeOH); ν_{max} (neat)/cm^{-1} 2958, 2097, 1777, 1698, 1454, 1386, 1351, 1210, 1106,

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(21) Our optical rotation value $[\alpha]^{20}_D$ is greater than the data for $[\alpha]^{20}_D$ reported in refs 6 and 7.

1050, 745, 701; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 (t, J = 7.2 Hz, 2H), 7.29−7.23 (m, 1H), 7.19 (d, J = 6.9 Hz, 2H), 4.67 (ddd, J = 10.7, 7.0, 3.2 Hz, 1H), 4.23−4.14 (m, 2H), 3.47−3.38 (m, 1H), 3.28 (dd, J = 13.4, 3.3 Hz, 1H), 3.14−2.98 (m, 2H), 2.77 (dd, J = 13.4, 9.5 Hz, 1H), 1.95 (dtd, J = 11.4, 7.5, 4.2 Hz, 1H), 1.79 (ddt, J = 20.2, 8.1, 6.1 Hz, 2H), 1.54 (ddd, J = 14.5, 8.8, 5.9 Hz, 1H), 1.34 (ddd, J = 13.7, 8.3, 5.2 Hz, 1H), 0.94 (dd, J = 6.6, 1.4 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.5, 153.4, 135.3, 129.4, 128.9, 127.3, 66.3, 60.1, 55.1, 43.4, 37.8, 32.2, 29.1, 25.1, 22.9, 22.1; HRMS (ESI$^+$) calcd for $C_{18}H_{25}N_4O_3$ 345.1927, found 345.1937.

(4*R*)-3-{(2*R*,4*S*)-4-Azido-2-[(1*S*)-2-(2-benzyl-1,3-dioxolan-2-yl)-1-hydroxyethyl]-6-methylheptanoyl}-4-benzyl-1,3-oxazolidin-2-one (2): To a stirred solution of **3** (280 mg, 0.81 mmol) in dichloromethane (4 mL) was added freshly distilled $TiCl_4$ (94 μL, 0.85 mmol) slowly at 0 °C. After 15 min, to this yellow suspension was added the (−)-sparteine (374 μL, 1.6 mmol) dropwise to give a dark red solution, which was stirred for 1 h at the same temperature. Then a solution of **4** (184 mg, 0.89 mmol) in dichloromethane (2 mL) was added dropwise at 0 °C. After 2 h, the mixture was quenched with half-saturated aqueous solution of NH_4Cl. The organic layer was separated, and aqueous layer was further extracted with dichloromethane. The combined organic layer was washed with water and brine, dried over magnesium sulfate, and concentrated. The residue was purified using column chromatography (hexanes/EtOAc, 3:1) to give the aldol product **2** (330 mg, 74%) as a colorless viscous liquid: $[\alpha]^{20}_D$ = −50.3 (*c* 1.2, MeOH); ν_{max} (neat)/cm^{-1} 3506, 2958, 2103, 1779, 1693, 1386, 1350, 1210, 1196, 1110, 702; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34 (t, J = 7.3 Hz, 2H), 7.30 − 7.20 (m, 8H), 4.64 (ddd, J = 10.2, 6.6, 3.0 Hz, 1H), 4.28 (ddd, J = 10.4, 5.3, 2.9 Hz, 1H), 4.23−4.17 (m, 1H), 4.15−4.05 (m, 2H), 3.93 (dq, J = 12.1, 6.9 Hz, 2H), 3.75 (ddd, J = 9.2, 4.8, 2.4 Hz, 1H), 3.71−3.63 (m, 2H), 3.41 (dd, J = 11.2, 6.1 Hz, 1H), 3.35 (dd, J = 13.3, 3.2 Hz, 1H), 2.95 (q, J = 13.9 Hz, 2H), 2.69 (dd, J = 13.2, 10.1 Hz, 1H), 2.21 (ddd, J = 14.2, 10.6, 3.7 Hz, 1H), 1.85 (dd, J = 11.0, 6.8 Hz, 2H), 1.82−1.73 (m, 1H), 1.70 (ddd, J = 14.1, 8.7, 2.8 Hz, 1H), 1.55 (ddd, J = 14.4, 8.4, 6.4 Hz, 1H), 1.36 (ddd, J = 13.7, 7.7, 5.7 Hz, 1H), 0.93 (d, J = 6.6 Hz, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 173.9, 153.2, 135.9, 135.5, 130.7, 129.4, 129.0, 128.1, 127.3, 126.6, 111.4, 68.9, 65.9, 65.3, 64.9, 59.3, 55.7, 44.8, 43.8, 43.5, 40.6, 37.7, 32.1, 25.1, 22.7, 22.3; HRMS (ESI$^+$) calcd for $C_{30}H_{39}N_4O_6$ 551.2870, found 551.2875.

(3*R*,5*S*)-3-[(1*S*)-2-(2-Benzyl-1,3-dioxolan-2-yl)-1-hydroxyethyl]-5-isobutylpyrrolidin-2-one (11): To a solution of **2** (160 mg, 0.291 mmol) in MeOH (15 mL) were added ammonium formate (366 mg, 5.81 mmol) and 5% Pd/C (60 mg) and stirred for 1 h at room temperature. The mixture was concentrated and residue dissolved in ethyl acetate, washed with water and brine, dried over magnesium sulfate, and concentrated. The residue was purified by column chromatography (isopropanol/hexanes, 1:9) to afford **11** (86 mg, 85%) as a colorless viscous liquid: $[\alpha]^{20}_D$ = −11.4 (*c* 0.35, MeOH); ν_{max} ($CHCl_3$)/cm^{-1} 3224, 2925, 2954, 1687, 1454, 1269, 1128, 1030, 820, 735; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.30−7.20 (m, 5H), 6.04 (s, 1H), 4.44 (d, J = 9.7 Hz, 1H), 4.00−3.91 (m, 2H), 3.77−3.63 (m, 3H), 2.96 (dd, J = 30.2, 13.9 Hz, 2H), 2.36 (dd, J = 15.2, 6.5 Hz, 2H), 1.82 (dt, J = 14.6, 12.2 Hz, 2H), 1.71−1.64 (m, 1H), 1.64−1.55 (m, 1H), 1.43−1.35 (m, 1H), 1.32−1.23 (m, 1H), 0.91 (d, J = 6.6 Hz, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 177.7, 136.1, 130.6, 128.1, 126.6, 111.5, 66.5, 65.3, 65.0, 51.0, 46.5, 46.4, 43.9, 41.7, 27.7, 25.3, 22.9, 22.4; HRMS (ESI$^+$) calcd for $C_{20}H_{30}NO_4$ 348.2175, found 348.2176.

(−)-Berkeleyamide A (1): To a solution of **11** (23 mg, 0.066 mmol) in acetone (0.5 mL) and water (24 μL, 1.3 mmol) was added bis(acetonitrile)dichloropalladium(II) (3.43 mg, 0.013 mmol). The mixture was stirred for 4 h and concentrated. The residue was purified by column chromatography (isopropanol/hexanes, 1:9) to afford **1** (15 mg, 77%) as a colorless viscous liquid: $[\alpha]^{20}_D$ = −34.2 (*c* 0.48, MeOH), $[\alpha]^{20}_D$ = −31.1 (*c* 0.11, MeOH); ν_{max} ($CHCl_3$)/cm^{-1} 3257, 2955, 2927, 1704, 1686, 1454, 1367, 1271, 1077, 1030, 734; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 (t, J = 7.2, 3H), 7.30−7.24 (m, 1H), 7.24−7.17 (d, 2H), 6.11 (s, 1H), 4.37 (ddd, J = 8.8, 5.3, 3.4, 1H), 3.74 (s, 2H), 3.65 (td, J = 11.9, 7.7, 1H), 3.12 (s, 1H), 2.85 (dd, J = 17.3, 3.2, 1H), 2.71 (dd, J = 17.3, 8.9, 1H), 2.52−2.42 (m, 1H), 2.31 (dt, J = 13.0, 7.6, 1H), 1.72 (ddd, J = 13.2, 9.3, 4.2, 1H), 1.60 (td, J = 13.4, 6.6, 1H), 1.44−1.34 (m, 1H), 1.28 (dt, J = 13.7, 7.0, 1H), 0.91 (d, J = 6.6, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 208.5, 177.2, 133.6, 129.5, 128.7, 127.1, 66.9, 50.8, 50.7, 46.4, 46.1, 45.5, 28.8, 25.3, 22.8, 22.3; HRMS (ESI$^+$) calcd for $C_{18}H_{26}NO_3$ 304.1913, found 304.1902.

Acknowledgment. This investigation was conducted in a facility constructed with support from research facilities improvement program Grant No. C06 Rr-14503-01 from the National Center for Research Resources, National Institutes of Health. Partial support to S.J.K. from Grant No. 5P20RR021929 from the National Center for Research Resources is also acknowledged.

Supporting Information Available: Full experimental procedures and data for all remaining new compounds; ^{1}H and ^{13}C NMR spectra for compounds **1**−**4** and **8**−**11**. This material is available free of charge via the Internet at http://pubs.acs.org.