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Total Synthesis of Berkeleyamide A and its 10-*epi* Isomer

Narayan S. Chakor,*[a] Sabrina Dallavalle,[a] Leonardo Scaglioni,[a] and Lucio Merlini[a]

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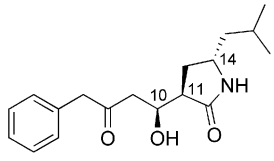
A short and efficient synthesis of the novel cytotoxic natural product berkeleyamide A, isolated from a deep-water *Penicillium rubrum*, has been accomplished. L-Leucinol was used as the only chiral starting material. A diastereoselective aldol condensation is the key step in the synthesis.

Introduction

The Berkeley Pit lake system near Butte, Montana, is part of the largest EPA superfund site in North America. The Pit is filled to a depth of about 274 meters with heavily acidic and metal-laden water. New fungal and bacterial species have been found to have adapted to the extreme and harsh conditions inside the pit. Stierle and co-workers identified more than 100 types of microbes in the lake that manage to survive in the unique, noxious ecosystem.[1] One of the first microbes to be studied was isolated from a water sample taken from a depth of 270 meters and identified as *Penicillium rubrum* Stoll. The organic extracts of this fungus contained several novel bioactive compounds, among which were berkeleyamide A–D. Berkeleyamide A (**1a**) was shown to exhibit activity against caspase 1 and MMP-3 in the low to submicromolar range (IC_{50} = 0.33 μM).[2]



Berkeleyamide A (**1a**)

Results and Discussion

As a part of a research program aimed at studying new natural compounds endowed with potential antitumor activity, we developed a stereoselective synthesis of **1a**, which may, in principle, have value in the preparation of other berkeleyamides as well as its analogues.

Stierle et al.[2] assigned the absolute configuration at C10 as (10*S*) by using Mosher's method, whereas the relative configuration at the chiral lactam ring was established by 1D NOE difference spectroscopy, H11 and H14 showing a *trans* relationship. However, uncertainty remained over the absolute configuration of the C11 and C14 stereogenic centers.

Consequently, we initially focused on the synthesis of a diastereomer arbitrarily chosen with the (*S*) configuration at C14, by assuming the natural L-configuration in the biosynthetic pathway. Thus, L-leucine was envisaged as the starting material for the construction of the lactam ring. At the beginning of this year, when this work was already at an advanced stage, two total syntheses, different from ours, appeared in the literature; the first by Brimble's[3] group and the second by Avery et al.[4] Moreover, Brimble's group confirmed the absolute stereochemistry of **1a** as (10*S*,11*R*,14*S*).

Our retrosynthetic approach was envisioned to proceed through a Grignard reaction between a magnesium benzyl halide and aldehyde **2**. The key step involved a diastereoselective aldol condensation for the assembly of a protected 3-hydroxypropanal and lactam **3** fragments. As the *syn*/*anti* outcome is controlled by the enolate geometry and as the lithium enolate of lactam **3** must have an *E* geometry, stereoselective formation of the *anti* aldol products should be favored. Moreover, the preferred formation of (10*R*,11*R*) diastereomer **1b** should be expected as a consequence of diastereofacial selection. Therefore, inversion at C10 was planned as the last step (Scheme 1).

Pyrrolidinone **7** was obtained from commercially available L-leucinol (**4**) that was converted into compound **6** by using a literature method.[5] Conversion of leucinol into its bis-toluene-*p*-sulfonate **5** followed by heating under reflux in THF with an excess amount of potassium *tert*-butoxide and diethyl malonate gave 3-ethoxycarbonylpyrrolidinone **6**. Finally, Krapcho decarbethoxylation gave tosyl-protected pyrrolidinone **7** in 85% yield (Scheme 2).

With lactam **7** in hand, attention was focused on the key aldol condensation. Conversion of 1,3-propanediol (**8**) to aldehyde **9** proceeded easily in two steps by monoprotection

[a] Dipartimento di Scienze Molecolari Agroalimentari, Università di Milano,
Via Celoria 2, 20133 Milano, Italy
Fax: +39-02-50316801
E-mail: nschakor@gmail.com

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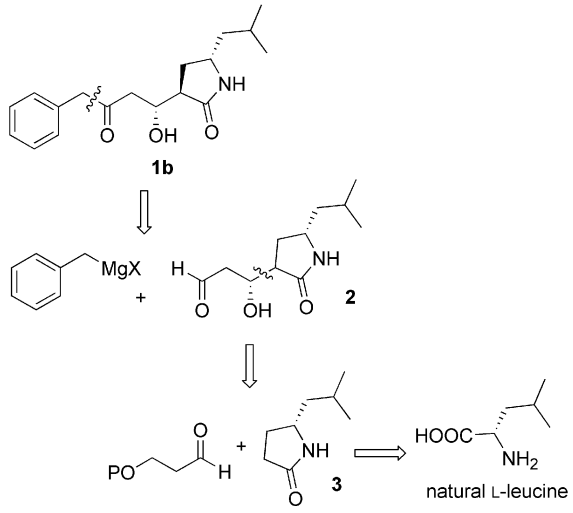
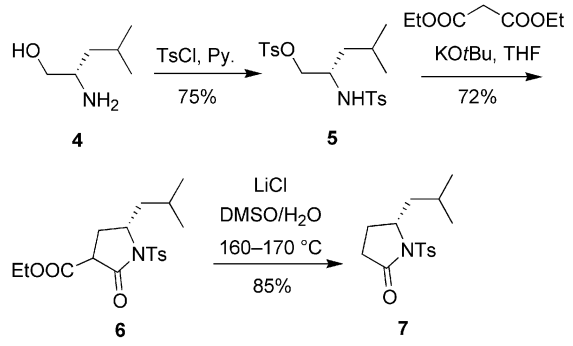


Scheme 1. Retrosynthetic approach to 10-*epi*-berkeleyamide A (**1b**).

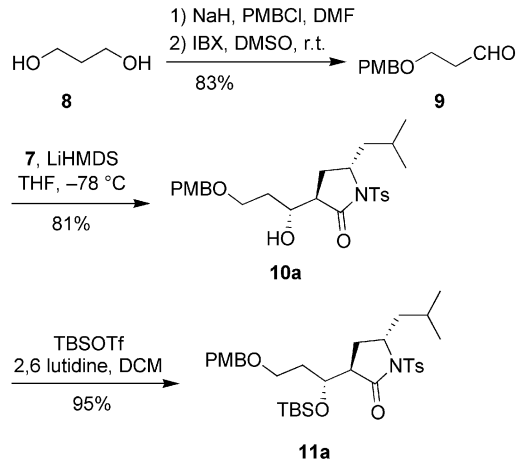


Scheme 2.

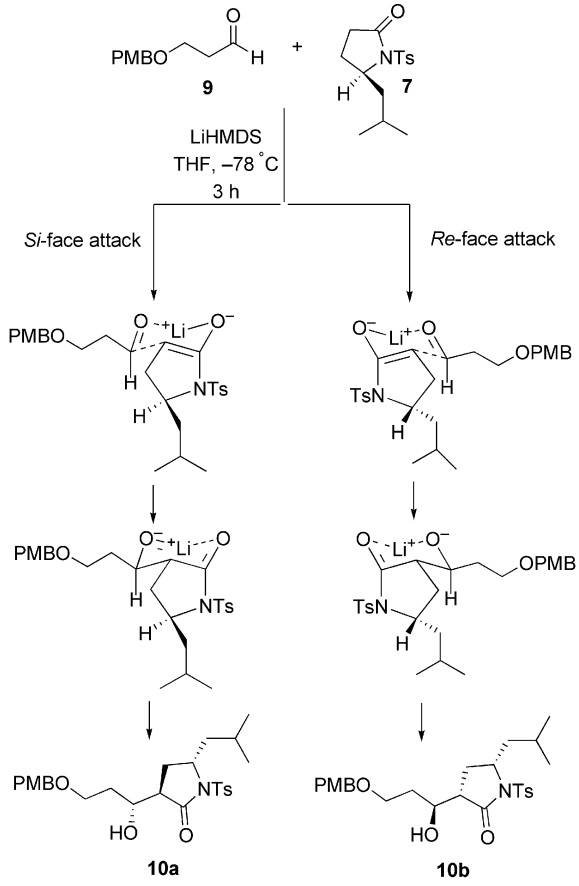
with PMBCl,[6] followed by oxidation with IBX. Addition of aldehyde **9** to the lithium enolate of lactam **7** delivered a major product with only a minor amount of another diastereomer (19:1 *dr*). As diastereomers **10** were hardly separable, the mixture was treated with TBSOTf to obtain the corresponding less-polar OTBS-protected derivatives **11a/b**, which were separated by column chromatography to give **11a** as the major product (>95%, Scheme 3). The C11–C14 relative configuration in **11a** was determined by TROESY measurements.

The 10,11 diastereoselection is controlled by the enolate geometry and can be predicted on the basis of the six-membered cyclic Zimmerman–Traxler-type transition state. Thus, as the lithium enolate of lactam **7** must have *E* geometry, stereoselective formation of the *anti* aldol products should be favored. The diastereofacial selection, and therefore the relation between the new centers and that at C14, can be explained on the basis of a preferred *Si*-face attack by the enolate, due to the presence of the bulky isobutyl group on the lactam ring. (Scheme 4).

Attention was then focused on the incorporation of the benzyl moiety. As we opted to proceed through a Grignard condensation, removal of the tosyl and PBM protecting groups from **11a** was followed by oxidation of primary alcohol **13** with IBX to give **14**. Various attempts to react

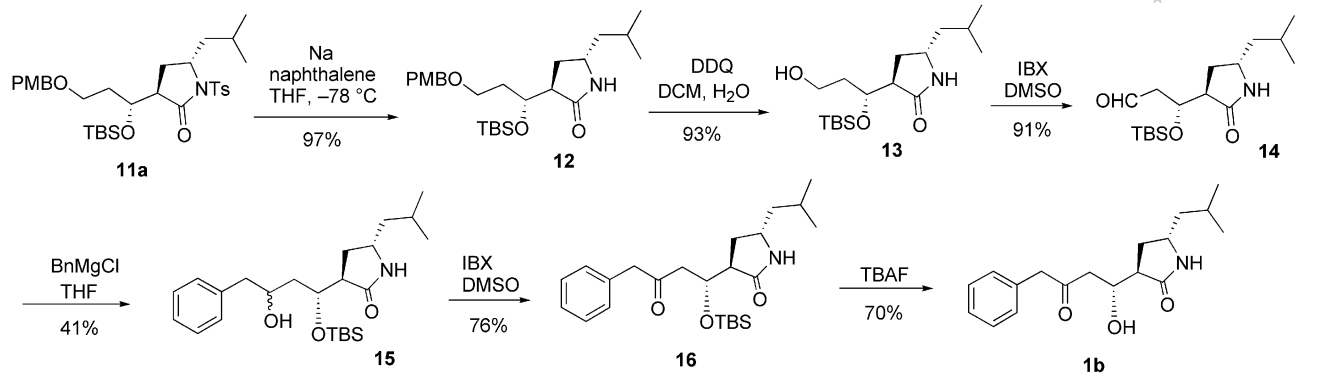


Scheme 3.



Scheme 4. Possible transition-state models for aldol addition.

14 with benzylmagnesium bromide disappointingly resulted in a complex mixture of products, whereas a 2–3-fold excess of the benzylmagnesium chloride in THF gave expected product **15**, although in low yield. Oxidation of the secondary alcohol with IBX and removal of the silyl protecting group with TBAF furnished (10*R*,11*R*,14*S*)-berkeleyamide (**1b**, Scheme 5). The structure and stereochemistry of this compound were confirmed by NMR experiments. The C11–C14 relative configuration in **1b** was determined by

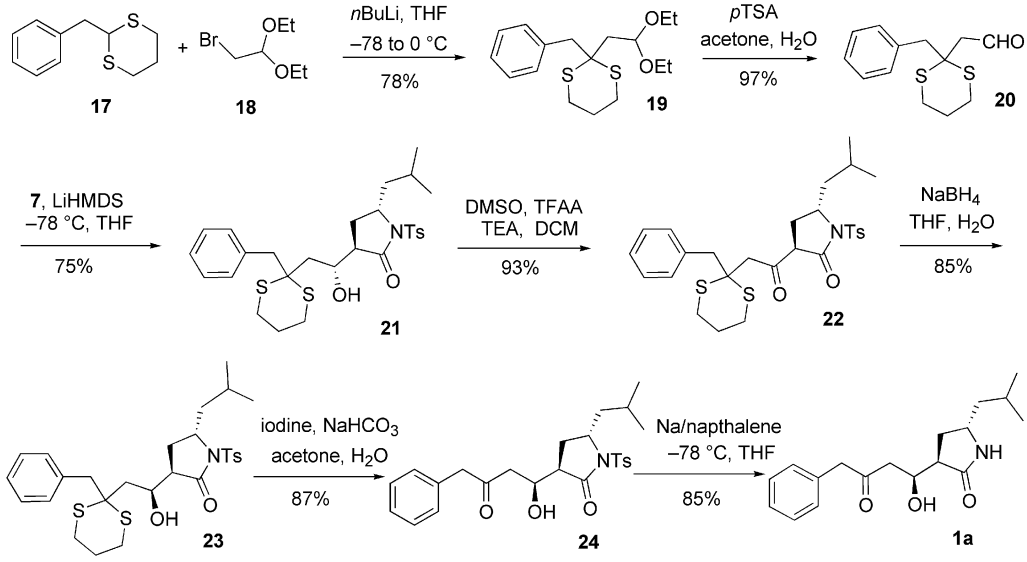


Scheme 5.

TROESY measurements. A NOE correlation between H11 and H15 and the absence of NOE between H11 and H14 clearly established the H11–H14 *anti* stereochemistry. The spectroscopic data completely matched those reported by Brimble et al.[3]

Due to the difficulties encountered during Grignard condensation, the synthetic pathway was reevaluated. We envisioned that the key aldol reaction could be postponed to a later stage, using an aldehyde-bearing fragment already containing the ketone functionality, masked by an appropriate protecting group. Accordingly, 2-benzyl-1,3-dithiane (**17**)[7] was treated with commercially available 2-bromo-1,1-diethoxyethane by using *n*BuLi in THF to give acetal **19**, which was subsequently deprotected to obtain 2-(2-benzyl-1,3-dithian-2-yl)acetaldehyde (**20**). Aldol condensation between this aldehyde and lactam **5** proceeded as expected to give as a major product alcohol **21** (19:1 *dr*, Scheme 6). The stereochemical outcome of the reaction can again be rationalized by using a six-membered Zimmermann–Traxler chair-like transition state, as described previously for compound **10a**, whereas the facial selectivity can be explained as directed by the bulky group on the lactam ring. As TROESY measurements confirmed the 11–14 *trans*-relationship, the absolute stereochemistry of **21** must be (10*R*,11*R*,14*S*).

Once aldol reaction product **21** was obtained, we had to set the *S* configuration at C10. Disappointingly, all the attempts made to invert the C10 configuration, either through Mitsunobu,[8] Cainelli,[9] or Mukaiyama[10] reactions, failed, giving very rapidly the elimination product. Thus, compound **21** was oxidized with DMSO and TFAA to the corresponding ketone. Gratifyingly, reduction with sodium borohydride gave a single diastereomer, different from **21**, whose stereochemistry at C10 predictably had to be *S*, in agreement with Felkin–Anh conformational model of the transition state. The difference in magnitude of the observed vicinal $J_{10,11}$ coupling constants (6.5 Hz in **21**, 3.2 Hz in **23**, see the Supporting Information) also supported inversion at C10. Deprotection of the keto group with iodine/$NaHCO_3$ followed by removal of the tosyl group with Na/naphthalene, afforded the natural compound (10*S*,11*R*,14*S*)-berkeleyamide A (**1a**, Scheme 6). The spectroscopic data of the obtained compound completely matched those reported for the natural product. This new



Scheme 6.

sequence was shorter and simpler than the previous one and allowed the desired compound to be obtained through a convergent rather than sequential approach, giving the flexibility to develop various analogues of the natural product.

Conclusions

In conclusion, a short and efficient synthesis of the natural compound (–)-berkeleyamide A was designed and carried out. Crucial step for our strategy was a stereoselective aldol condensation applied for the installation of the side chain on the lactam moiety. Compared to those previously reported,[3,4] our synthesis appears to be shorter, requiring only a total of 10 steps from commercially available L-leucinol (**4**) and 2-benzyl-1,3-dithiane (**17**) in 16% overall yield. The synthetic sequence requires cheap and simple reagents and L-leucinol as the only chiral reactant. Moreover, it is scalable and amenable to the preparation of analogues that may be of interest for structure–activity relationship studies, due to the biological activity of these compounds.

Experimental Section

General Information: All reagents and solvents were reagent grade or were purified by standard methods before use. Melting points were determined in open capillaries. NMR spectra were recorded at 300 or 600 MHz. Mass spectra were recorded with a Fourier transform ion cyclotron resonance (FT-ICR) mass spectrometer. Solvents were routinely distilled prior to use; anhydrous tetrahydrofuran (THF) and ether (Et_2O) were obtained by distillation from sodium–benzophenone ketyl; dry dichloromethane was obtained by distillation from phosphorus pentoxide. All reactions requiring anhydrous conditions were performed under a positive nitrogen flow, and all glassware were oven dried and/or flame dried. Isolation and purification of the compounds were performed by flash column chromatography on silica gel 60 (230–400 mesh). Analytical thin-layer chromatography (TLC) was conducted on Fluka TLC plates (silica gel 60 F_{254}, aluminum foil).

(5*S*)-5-Isobutyl-1-(toluene-4-sulfonyl)pyrrolidin-2-one (7): To a stirred solution of pyrrolidinone **6**[4] (3 g, 8.16 mmol, 0.40 mL) in DMSO (32 mL) was added LiCl (1.38 g, 32.6 mmol) and water (0.4 mL). The reaction mixture was heated at 170 °C for 10 h, then cooled to room temperature. Saturated aqueous NH_4Cl (150 mL) was added, and the mixture was then extracted with diethyl ether (3 × 150 mL). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated. The residue was purified by flash column chromatography (EtOAc/hexane, 2:8) to afford **7** (2.07 g, 85%) as a white crystalline solid; m.p. 111 °C. $[\alpha]_D^{20}$ = +64 (*c* = 0.22, $CHCl_3$). R_f = 0.6 (EtOAc/hexane, 35:65). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.89 (m, 2 H, *o*-H Ts), 7.28 (m, 2 H, *m*-H Ts), 4.38 (m, *J* = 9.4 Hz, 1 H, 5-CH), 2.50 (m, 1 H, 3-CH), 2.38 (s, 3 H, Ph-CH_3), 2.26 (m, 1 H, 3-H), 2.10 (m, 1 H, 4-H), 1.82 (m, 2 H, 4-H, 6-H), 1.65 (m, 1 H, 7-H), 1.47 (m, 1 H, 6-H), 0.97 (d, *J* = 6.6 Hz, 3 H, CH_3), 0.93 (d, *J* = 6.6 Hz, 3 H, CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 173.5, 144.9, 136.2, 129.5, 128.3, 59.2, 43.2, 30.5, 25.4, 23.9, 21.7, 21.3 ppm. $C_{15}H_{21}NO_3S$ (295.40): calcd. C 60.99, H 7.17, N 4.74; found C 61.08, H 7.10, N 4.63.

(3*R*,5*S*,1′*R*)-3-[1′-Hydroxy-3′-(4-methoxybenzyloxy)propyl]-5-isobutyl-1-(toluene-4-sulfonyl)pyrrolidin-2-one (10a) and (3*S*,5*S*,1′*S*)-3-[1-Hydroxy-3-(4-methoxybenzyloxy)propyl]-5-isobutyl-1-(toluene-4-sulfonyl)pyrrolidin-2-one (10b): To a stirred solution of pyrrolidinone **7** (2.0 g, 6.76 mmol) in THF (40 mL) was added LiHMDS (1 M in THF, 8.12 mmol, 8.15 mL) at –78 °C. The reaction mixture was stirred for 45 min, then aldehyde **9** (1.32 g, 6.76 mmol) in THF (16 mL) was added dropwise at –78 °C. The resulting reaction mixture was stirred for 3 h. Saturated aqueous NH_4Cl (150 mL) was added, and the aqueous phase was extracted with diethyl ether (3 × 120 mL). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated. The residue was purified by flash column chromatography (EtOAc/hexane, 28:72) to afford a mixture of isomers **10a** (<95%)/**10b** (<5%) as an oil (2.68 g, 81%). R_f = 0.48 (EtOAc/hexane, 40:60). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.90 (m, 2 H, *o*-H Ts), 7.29 (m, 2 H, *m*-H Ts), 7.20 (m, 2 H, Ph-H), 6.86 (m, 2 H, Ph-H), 4.32 (m, 2 H, Ph-CH_2), 4.25 (m, 1 H, 5-H), 4.09 (m, 1 H, 4′-H), 3.80 (s, 3 H, Ph-OMe), 3.42 (m, 2 H, 6′-H), 2.75 (m, 1 H, 3-H), 2.41 (s, 3 H, Ph-CH_3), 2.28 (m, 1 H, 4-CH), 1.36–1.89 (m, 7 H, 4-H, 6-H, 7-H,5′-H), 0.97 (d, *J* = 6.6 Hz, 3 H, 8-CH_3), 0.93 (d, *J* = 6.6 Hz, 3 H, 9-CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 175.8, 159.3, 145.3, 136.0, 130.4, 129.8, 129.5, 129.3, 128.6, 114.0, 113.8, 73.06, 70.3, 66.8, 57.4, 55.4, 43.1, 33.9, 27.5, 25.7, 23.8, 21.9, 21.3 ppm.

(3*R*,5*S*,1′*R*)-3-[1′-(*tert*-Butyldimethylsilanyloxy)-3′-(4-methoxybenzyloxy)propyl]-5-isobutyl-1-(toluene-4-sulfonyl)pyrrolidin-2-one (11a): To an ice-cold stirred solution of **10a** + **10b** (2.3 g, 4.69 mmol) in CH_2Cl_2 (40 mL) was added 2,6-lutidine (1.09 mL, 9.39 mmol) and TBSOTf (1.29 mL, 5.6 mmol) at 0 °C. The resulting mixture was stirred for 1 h at 0 °C, then water (30 mL) was added. The aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated under reduced pressure. The crude mixture of diastereomers was separated by flash column chromatography (EtOAc/hexane, 18: 82) to obtain **11a** as a viscous oil (2.68 g, 95%). $[\alpha]_D^{25}$ = +30.8 (*c* = 0.12, MeOH). R_f = 0.59 (EtOAc/hexane, 25:75). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.91 (m, 2 H, *o*-H Ts), 7.29 (m, 2 H, *m*-H Ts), 7.21 (m, 2 H, Ph-H), 6.86 (m, 2 H, Ph-H), 4.32 (m, 3 H, Ph-CH_2, 5-H), 4.05 (m, 2 H, 4′-H), 3.80 (s, 3 H, Ph-OCH_3), 3.41 (t, *J* = 6.3 Hz, 2 H, 6′-H), 2.82 (ddd, *J* = 3.9, 5.1, 8.9 Hz, 1 H, 3-H), 2.39 (s, 3 H, Ph-CH_3), 2.15 (m, 1 H, 4-H), 1.60–1.94 (m, 5 H), 1.42 (m, 1 H, 7-H), 1.00 (d, *J* = 6.6 Hz, 3 H, CH_3), 0.96 (d, *J* = 6.6 Hz, 3 H, CH_3), 0.76 (s, 9 H, $SiCMe_3$), 0.02 (s, 6 H, SiMe) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 172.7, 159.1, 144.8, 136.2, 130.5, 129.4, 129.3, 128.4, 113.7, 72.3, 68.6, 66.6, 57.1, 55.3, 46.1, 43.8, 32.9, 26.1, 25.7, 25.5, 23.8, 21.7, 21.4, 17.9, –6.11, –6.12 ppm. $C_{32}H_{49}NO_6SSi$ (603.89): calcd. C 63.64, H 8.18, N 2.32; found C 63.71, H 8.22, N 2.21.

(3*R*,5*S*,1′*R*)-3-[1′-(*tert*-Butyldimethylsilanyloxy)-3′-(4-methoxybenzyloxy)propyl]-5-isobutylpyrrolidin-2-one (12): To a solution of naphthalene (1.52 g, 11.92 mmol) in dry THF (32 mL) was added Na (0.274 g, 11.92 mmol), and the mixture was sonicated until a deep-green solution of sodium naphthalenide was obtained (10–15 min). The solution was further stirred for 2 h at room temperature then it was dropped into a solution of **11a** (1.2 g, 1.98 mmol) in THF (60 mL) at –78 °C until the green color persisted. The resulting reaction mixture was stirred at –78 °C for 3 h, then quenched with saturated aqueous NH_4Cl and extracted with EtOAc (3 × 50 mL). The combined organic layers were dried (Na_2SO_4) and concentrated. The crude product was purified by flash column chromatography (EtOAc/hexane, 40:60) to afford **12** (0.866 g, 97%) as a colorless oil. $[\alpha]_D^{25}$ = –4.4 (*c* = 0.09, MeOH). R_f = 0.48 (EtOAc/hexane, 1:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.24 (m, 2 H, Ph-H), 6.86 (m, 2 H, Ph-H), 5.76 (br. s, 1 H, NH), 4.40 (m, 2 H, Ph-CH_2), 4.18 (m, 1 H, 4′-*H*), 3.79 (s, 3 H, Ph-OCH_3), 3.40–3.70 (m, 3 H, 6′-H,

5-H), 2.70 (m, 1 H, 3-H), 2.30 (m, 1 H, 4-H), 1.50–1.95 (m, 4 H, 4-H, 5′-H, 7-H), 1.23–1.40 (m, 2 H, 6-H), 0.91 (d, J = 6.2 Hz, 6 H, 2 CH_3), 0.86 (s, 9 H, $SiCMe_3$), 0.05 (s, 6 H, SiMe) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 177.0, 158.7, 130.63, 129.3, 113.7, 72.5, 69.8, 67.2, 55.4, 51.3, 46.8, 46.5, 32.9, 29.5, 25.9, 25.7, 25.4, 23.0, 22.8, 22.5, 18.0, –6.1, –6.2 ppm. $C_{25}H_{43}NO_4Si$ (449.70): calcd. C 66.77, H 9.64, N 3.11; found C 66.89, H 9.72, N 3.02.

(3*R*,5*S*,1′*R*)-3-[1′-(*tert*-Butyldimethylsilanyloxy)-3′-hydroxypropyl]-5-isobutylpyrrolidin-2-one (13): To a solution of **12** (0.866 g, 1.78 mmol) in a mixture of CH_2Cl_2 (56 mL) and H_2O (2.4 mL) was added DDQ (0.525 g, 2.31 mmol) portionwise. After stirring vigorously at room temperature for 3 h, the mixture was hydrolyzed with saturated $NaHCO_3$ and extracted with Et_2O (3 × 40 mL). The combined organic layers were washed with brine, dried (Na_2SO_4), filtered, and concentrated. The residue was purified by flash chromatography (EtOAc/hexane, 75:25) to give the title compound (1.41 g, 93%) as a colorless oil. $[\alpha]_D^{25}$ = –5.0 (c = 0.10, MeOH). R_f = 0.23 (EtOAc/hexane, 75:25). ^1H NMR (300 MHz, $CDCl_3$): δ = 5.98 (br. s, 1 H, NH), 4.19 (m, 1 H, 4′-H), 3.70 (m, 3 H, 6′-H, 5-H), 2.87 (m, 1 H, 3-H), 2.28 (m, 1 H, 4-H), 1.83 (m, 2 H, 4-H), 1.61 (m, 1 H, 7-H), 1.14–1.53 (m, 2 H, 5′-H), 0.92 (d, J = 6.6 Hz, 6 H, CH_3), 0.88 (s, 9 H, $SiCMe_3$), 0.09 (s, 6 H, SiMe) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 178.0, 71.0, 59.7, 51.9, 46.7, 35.8, 29.7, 26.0, 25.7, 25.3, 22.8, 22.6, 18.0 ppm. $C_{17}H_{35}NO_3Si$ (329.55): calcd. C 61.96, H 10.70, N 4.25; found C 62.12, H 10.60, N 4.17.

(3*R*,3′*R*,5′*R*)-3-(*tert*-Butyldimethylsilanyloxy)-3-(5′-isobutyl-2′-oxopyrrolidin-3′-yl)propionaldehyde (14): To a solution of **13** (0.50 g, 1.50 mmol) in DMSO (5 mL) was added IBX (0.531 g, 1.89 mmol) under an atmosphere of N_2, and the resulting mixture was stirred for 6 h at room temperature. The reaction mixture was quenched by adding H_2O (2 mL) and then it was stirred for 10 min. The suspension was filtered through a Celite pad and washed with diethyl ether. The filtrate was extracted with diethyl ether (3 × 25 mL). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated. The crude product was purified by flash chromatography (EtOAc/hexane, 6:4) to afford aldehyde **14** (0.45 g, 91%) as a colorless oil. $[\alpha]_D^{25}$ = –6.4 (c = 0.12, $CHCl_3$). R_f = 0.46 (EtOAc/hexane, 75:25). ^1H NMR (300 MHz, $CDCl_3$): δ = 9.73 (s, 1 H, CHO), 6.61 (br. s, 1 H, NH), 4.58 (m, 1 H, 4′-*H*), 3.62 (m, 1 H,5-*H*), 2.87 (dd, J = 16.2, 5.1 Hz, 1 H, 3-H), 2.74 (m, 1 H, 5′-H), 2.56 (dd, J = 16.2, 7.4 Hz, 1 H, 5′-H), 2.22 (m, 1 H, 4-*H*), 1.77 (m, 1 H, 4-H), 1.60 (m, 1 H, 7-H), 1.38 (m, 1 H, 6-H), 1.29 (m, 1 H, 6-H), 0.89 (d, J = 6.9 Hz, 6 H CH_3), 0.84 (s, 9 H, $SiCMe_3$), 0.07 (s, 3 H, SiMe), 0.05 (s, 3 H, SiMe) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 201.1, 176.7, 67.8, 51.2, 47.5, 46.6, 46.1, 29.7, 25.7, 22.9, 22.3, 17.9 ppm. $C_{17}H_{33}NO_3Si$ (327.53): calcd. C 62.34, H 10.16, N 4.28; found C 62.18, H 10.01, N 4.20.

(3*R*,5*S*,1′*R*)-3-[1′-(*tert*-Butyldimethylsilanyloxy)-3′-hydroxy-4′-phenylbutyl]-5-isobutylpyrrolidin-2-one (15): To a stirred solution of aldehyde **14** (0.400 g, 1.22 mmol) in THF (15 mL) was added $PhCH_2MgCl$ (2.0 M in THF, 1.82 mL, 3.66 mmol) dropwise at 0 °C. The resulting reaction mixture was stirred for 3 h at 0 °C. The reaction was quenched with saturated aqueous NH_4Cl and extracted with EtOAc (3 × 30 mL). The organic layers were combined, dried (Na_2SO_4), filtered, and concentrated. The crude product was purified by flash column chromatography (EtOAc/hexane, 4:6 to 8:2) to afford **15** (0.210 g, 41%) as a yellow oil. R_f = 0.34 (EtOAc/hexane, 75:25). ^1H NMR (300 MHz, $CDCl_3$): δ = 7.13–7.40 (m, 5 H, Ph-H), 5.78 (br. s, 1 H, NH), 4.07 (m, 1 H, 8-H), 3.84 (m, 1 H, 10-H), 3.67 (m, 1 H, 14-H), 2.86 (m, 2 H, 7-H), 2.67 (dd, J = 6.6, 13.3 Hz, 11-H), 2.18 (m, 1 H, 19-H), 1.20–1.90 (m, 6 H, 9-H, 19-H, 15-H, 16-H), 0.89 (d, J = 6.6 Hz, 6 H, CH_3), 0.83 (s, 9 H, $SiCMe_3$), –0.04 (s, 3 H, SiMe), –0.06 (s, 3 H, SiMe) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 177.8, 138.8, 129.5, 128.5, 126.3, 71.8, 69.5, 51.7, 46.7, 45.9, 45.3, 40.3, 31.0, 29.8, 25.8, 25.4, 22.9, 22.5, 18.0, –4.5, –4.6 ppm. $C_{24}H_{41}NO_3Si$ (419.67): calcd. C 68.69, H 9.85, N 3.34; found C 68.79, H 9.74, N 3.21.

(3*R*,5*S*,1′*R*)-3-[1′-(*tert*-Butyldimethylsilanyloxy)-3′-oxo-4-phenylbutyl]-5-isobutylpyrrolidin-2-one (16): To a solution of **15** (0.400 g, 0.953 mmol) in DMSO (6 mL) was added IBX (0.66 g, 2.38 mmol) under an atmosphere of N_2, and the resulting mixture was stirred for 16 h at room temperature. Then the solution was quenched by adding H_2O (2.5 mL) and stirred for 10 min. The suspension was filtered through a Celite pad and washed with diethyl ether. The filtrate was extracted with Et_2O (3 × 25 mL). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated. The crude product was purified by flash chromatography (EtOAc/hexane, 25:75) to afford compound **16** (0.302 g, 76%) as a yellow oil. $[\alpha]_D^{25}$ = –31.2 (c = 0.1, $CHCl_3$). R_f = 0.69 (EtOAc/hexane, 1:1). ^1H NMR (300 MHz, $CDCl_3$): δ = 7.14–7.36 (m, 5 H, Ph-H), 5.63 (br. s, 1 H, NH), 4.39 (m, 1 H, 10-*H*), 3.73 (s, 2 H, 7-H), 3.63 (m, 1 H, 14-H), 3.24 (dd, J = 17.2, 6.90 Hz, 1 H, 9-H), 2.65 (dd, J = 17.2, 6.02 Hz, 1 H, 9-H), 2.17 (m, 1 H, 19-H), 1.80 (m, 1 H, 19-H), 1.59 (m, 1 H, 16-H), 1.18–1.43 (m, 3 H, 15-H), 0.90 (d, J = 6.6 Hz, 6 H, CH_3), 0.83 (s, 9 H, $SiCMe_3$), 0.05 (s, 3 H, SiMe), 0.03 (s, 3 H, SiMe) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 206.9, 177.1, 134.1, 129.6, 128.7, 127.1, 69.5, 51.4, 50.8, 46.6, 46.4, 45.3, 31.4, 29.8, 25.9, 25.8, 25.5, 25.4, 23.0, 22.4, 18.0 ppm. $C_{24}H_{39}NO_3Si$ (417.66): calcd. C 69.02, H 9.41, N 3.35; found C 69.11, H 9.33, N 3.24.

2-Benzyl-2-(2,2-diethoxyethyl)-1,3-dithiane (19): *n*BuLi (2.7 M in heptane, 3.64 mL, 9.89 mmol) was added dropwise to a solution of **17** (2.08 g, 9.89 mmol) in THF (45 mL) stirred at –78 °C under an argon atmosphere. After completion of the addition, the bath temperature was raised to –25 °C and kept for 3–4 h before cooling again to –78 °C. Freshly distilled **18** (1.48 mL, 9.89 mmol) was added dropwise to the above solution. The bath temperature was allowed to raise slowly to 0 °C. When TLC showed completion of the reaction, the reaction mixture was poured into ice water and extracted with diethyl ether. The ethereal phase was separated, washed with water and brine, dried (Na_2SO_4), filtered, and concentrated. The crude product was purified by flash chromatography (EtOAc/hexane, 4:96) to afford the title compound (2.52 g, 78%) as a colorless oil. R_f = 0.38 (EtOAc/hexane, 8:92). ^1H NMR (300 MHz, $CDCl_3$): δ = 7.43 (m, 2 H, Ph-H), 7.27 (m, 2 H, Ph-H), 4.87 (t, J = 4.8 Hz, 1 H, CH), 3.68 (q, J = 6.7 Hz, 2 H, CH_2), 3.60 (q, J = 6.7 Hz, 2 H, CH_2), 3.27 (s, 2 H, CH_2), 2.69–2.98 (m, 4 H, CH_2), 2.24 (d, J = 4.8 Hz, 2 H), 1.82–2.08 (m, 2 H, CH_2), 1.24 (t, J = 6.7 Hz, 6 H, CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 131.6, 131.2, 128.2, 127.7, 127.5, 126.9, 101.5, 61.7, 49.3, 46.4, 45.2, 40.2, 26.4, 24.6, 24.9, 24.4, 15.5 ppm. $C_{17}H_{26}O_2S_2$ (326.52): calcd. C 62.53, H 8.03; found C 62.62, H 8.12.

2-(2-Benzyl-1,3-dithian-2-yl)acetaldehyde (20): A solution of **19** (1.35 g, 4.13 mmol) and *p*TsOH (157 mg, 0.82 mmol) in acetone/water (10:1, 23 mL) was heated to reflux with stirring until TLC showed completion of the reaction. The solvent was removed by rotary evaporation. The residue was extracted with diethyl ether and washed with saturated aqueous $NaHCO_3$, water, and brine. The organic layer was dried (Na_2SO_4), filtered, and concentrated. The crude product was purified by flash chromatography (EtOAc/hexane, 8:92) to afford **20** (1.18 g, 97%) as a colorless oil. R_f = 0.52 (EtOAc/hexane, 2:8). ^1H NMR (300 MHz, $CDCl_3$): δ = 9.71 (br. s, 1 H, CHO), 7.30 (m, 5 H, Ph-H), 3.34 (s, 2 H, CH_2), 2.90 (m, 4 H, CH_2), 2.79 (s, 2 H, CH_2), 2.01 (m, 2 H, CH_2) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 199.8, 134.7, 131.2, 128.2, 127.6, 49.4, 46.4,

26.5, 24.5 ppm. $C_{13}H_{16}OS_2C$ (252.40): Calcd. C 61.86, H 6.39; found C 61.94, H 6.45.

(3*R*,5*S*,1′*R*)-3-[2′-(2-Benzyl-1,3-dithian-2-yl)-1′-hydroxyethyl]-5-isobutyl-1-(toluene-4-sulfonyl)pyrrolidin-2-one (21): To a stirred solution of pyrrolidinone **7** (1.33 g, 3.79 mmol) in THF (32 mL) was added LiHMDS (1 M in THF, 0.761 g, 6.0 mL, 4.55 mmol) at –78 °C, and the solution was stirred for 45 min. Aldehyde **20** (0.950 g, 3.71 mmol) in THF (16 mL) was added dropwise at –78 °C, and the reaction mixture was stirred for 3 h. After addition of saturated aqueous NH_4Cl (130 mL), the aqueous phase was extracted with diethyl ether (3 × 100 mL). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated. The residue was purified by flash column chromatography (EtOAc/hexane, 18:82) to afford **21** as an oil (1.85 g, 75%). $[\alpha]_D^{25}$ = +35.0 (*c* = 0.09, MeOH). R_f = 0.57 (EtOAc/hexane, 25:75). ^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.94 (m, 2 H, *o*-H Ts), 7.37 (m, 2 H, Ph-H), 7.34 (m, 2 H, *m*-H Ts), 7.24–7.31 (m, 3 H, Ph-H), 4.37 (dddd, *J* = 1.1, 3.1, 8.1, 11 Hz, 1 H, 14-H), 4.25 (ddd, *J* = 1.6, 6.5, 9.5 Hz, 1 H, 10-H), 3.93 (br. s, 1 H, OH), 3.41 (d, *J* = 13.8 Hz, 1 H, 7-H), 3.18 (d, *J* = 13.8 Hz, 1 H, 7-H), 2.80 (m, 4 H, SCH_2C*H*HS), 2.68 (ddd, *J* = 6.5, 8.5, 11.4 Hz, 1 H, 11-H), 2.45 (s, 3 H, Ph-CH_3), 2.24 (dd, *J* = 9.5, 15.2 Hz, 1 H, 19-H), 1.84–2.05 (m, 5 H, 19-H, CH_2CH_2S), 1.77 (dd, *J* = 1.6, 15.2 Hz, 1 H, 9-H), 1.67 (m, 1 H, 16-H), 1.48 (ddd, *J* = 4.0, 11.0, 15.2 Hz, 1 H, 15-H), 1.02 (d, *J* = 6.6 Hz, 3 H, CH_3), 0.98 (d, *J* = 6.6 Hz, 3 H, CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 174.6, 145.2, 136.0, 135.8, 131.6, 129.6, 128.5, 127.8, 127.0, 69.7, 57.2, 52.6, 46.5, 45.8, 43.4, 41.5, 27.8, 26.7, 26.5, 25.6, 24.7, 23.9, 21.8, 21.3 ppm. HRMS (ESI+): calcd. for $C_{28}H_{37}NO_4S_3Na$ 570.17769; found 570.17887.

(3*R*,5*S*)-3-[2′-(2-Benzyl-1,3-dithian-2-yl)acetyl]-5-isobutyl-1-(toluene-4-sulfonyl)pyrrolidin-2-one (22): To a solution of dimethyl sulfoxide (0.30 mL, 4.36 mmol) in CH_2C1_2 (10 mL) at –78 °C was added trifluoroacetic anhydride (0.40 mL, 2.94 mmol), and the mixture was stirred for 10 min. Alcohol **21** (400 mg, 0.731 mmol) in CH_2C1_2 (5 mL) was added, and the solution was stirred for 30 min at –78 °C. After addition of triethylamine (1.62 mL, 15.97 mmol), the mixture was warmed to room temperature over 1 h. The solution was diluted with CH_2Cl_2 (50 mL), washed with 5% HCl and water (2×), dried (Na_2SO_4), filtered, and concentrated. The crude product was purified by flash chromatography (EtOAc/hexane, 15:85) to give the title compound as a yellow oil (370 mg, 93%). $[\alpha]_D^{25}$ = +20.0 (*c* = 0.11, MeOH). R_f = 0.71 (EtOAc/hexane, 3:7). ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 7.85 (m, 2 H, *o*-H Ts), 7.44 (m, 2 H, Ph-H), 7.05–7.25 (m, 5 H, Ph-H), 4.27–4.48 (m, 2 H, 11-H, 14-H), 3.34 (s, 4 H), 2.55–3.00 (m, 4 H, CH_2), 2.39 (s, 3 H, Ph-CH_3), 2.00–2.35 (m, 2 H, CH_2), 1.50–195 (m, 5 H), 0.96 (d, *J* = 6.06 Hz, 3 H, CH_3) 0.92 (d, *J* = 6.06 Hz, 3 H, CH_3) ppm. ^{13}C NMR (75 MHz, [D$_6$]DMSO): δ = 201.0, 174.1, 145.2, 135.5, 135.9, 135.8, 131.1, 130.2, 130.1, 128.5, 128.4, 128.3, 60.2, 59.3, 50.3, 43.3, 30.4, 26.0, 25.8, 25.2, 24.9, 24.1, 23.8, 21.7 ppm. $C_{28}H_{35}NO_4S_3$ (545.78): calcd. C 61.62, H 6.46, N 2.57; found C 61.55, H 6.54, N 2.68.

(3*R*,5*S*,1′*S*)-3-[2′-(2-Benzyl-1,3-dithian-2-yl)-1′-hydroxyethyl]-5-isobutyl-1-(toluene-4-sulfonyl)pyrrolidin-2-one (23): To a solution of **22** (150 mg, 0.275 mmol) in THF/water (4:1, 15 mL) was added $NaBH_4$ (31 mg, 0.825 mmol) at 0 °C whilst stirring. After 30 min, AcOEt (30 mL) was added. The organic layer was washed with 0.1 N HCl, dried (Na_2SO_4), and concentrated. The crude residue was purified by flash chromatography (EtOAc/hexane, 2:8) to give **23** as a yellow oil (127 mg, 85%). $[\alpha]_D^{25}$ = +40.0 (*c* = 0.09, MeOH). R_f = 0.54 (EtOAc/hexane, 30:70). ^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.96 (m, 2 H, Ph-H), 7.34 (m, 2 H, Ph-H), 7.27–7.32 (m, 5 H, Ph-H), 4.58 (ddd, *J* = 1.7, 3.2, 9.7 Hz, 1 H, 10-H), 4.40 (ddd, *J* = 3.2, 8.4, 11.0 Hz, 1 H, 14-H), 3.33 (d, *J* = 14 Hz, 1 H, 7-H), 3.22 (d, *J* = 14 Hz, 1 H, 7-H), 3.01 (s, 1 H, OH), 2.95 (m, 1 H, SC*H*H), 2.80–2.90 (m, 3 H, SCH_2C*H*HS), 2.57 (ddd, *J* = 3.2, 8.4, 11.3 Hz, 1 H, 11-H), 2.45 (s, 3 H, Ph-CH_3), 2.37 (ddd, *J* = 8.4, 12.1, 8.4 Hz, 1 H, 19-H), 2.14 (dd, *J* = 9.7, 5.1 Hz, 1 H, 9-H), 2.05 (m, 2 H, CH_2CH_2S), 1.90 (ddd, *J* = 4.0, 11.0, 13.0 Hz, 1 H, 15-H), 1.83 (m, 1 H, 19-H), 1.79 (dd, *J* = 1.7, 15.1 Hz, 1 H, 9-H), 1.69 (m, 1 H, 16-H), 1.47 (m, 1 H, 15-H), 1.05 (d, *J* = 6.6 Hz, 3 H, CH_3), 0.99 (d, *J* = 6.6 Hz, 3 H, CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 173.4, 144.9, 136.1, 135.1, 131.2, 130.0, 129.5, 128.5, 128.0, 127.2, 66.5, 57.3, 52.4, 47.8, 45.9, 43.9, 41.4, 26.8, 26.4, 25.6, 24.6, 24.1, 23.9, 21.8, 21.4 ppm. $C_{28}H_{37}NO_4S_3$ (547.80): calcd. C 61.39, H 6.81, N 2.56; found C 61.48, H 6.90, N 2.48.

(3*R*,5*S*,1′*S*)-3-(1′-Hydroxy-3′-oxo-4′-phenylbutyl)-5-isobutyl-1-(toluene-4-sulfonyl)pyrrolidin-2-one (24): Iodine (183 mg, 0.721 mmol) was added to a mixture of **23** (120 mg, 0.219 mmol) and $NaHCO_3$ (123 g, 1.46 mmol) in acetone (1.20 mL) and water (0.12 mL), and the solution was stirred at 0 °C until TLC showed completion of the reaction. The excess amount of iodine was destroyed with aqueous $Na_2S_2O_3$; the mixture was diluted with diethyl ether and washed first with aqueous $Na_2S_2O_3$ until the iodine color completely vanished and then with brine. The organic layer was dried (Na_2SO_4), filtered, and concentrated. The crude product was purified by flash chromatography (EtOAc/hexane, 32:68) to afford **24** as a colorless solid (87 mg, 87%). M.p. 95 °C. $[\alpha]_D^{25}$ = +22.7 (*c* = 0.11, MeOH). R_f = 0.23 (EtOAc/hexane, 3:7). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.89 (m, 2 H, *o*-H Ts), 7.31 (m, 2 H, *m*-H Ts), 7.16 (m, 2 H, Ph-H), 4.19–4.41 (m, 2 H, 10-H, 14-H), 3.68 (s, 2 H, 7-H), 2.85 (m, 1 H, 9-H), 2.62 (m, 2 H, 9-H), 2.42 (s, 3 H, Ph-CH_3), 2.12 (m, 1 H, 19-H), 1.83 (m, 1 H, 19-H), 1.64 (br. s, 1 H), 1.42 (m, 1 H), 0.99 (d, *J* = 6.5 Hz, 3 H, CH_3), 0.94 (d, *J* = 6.5 Hz, 3 H, CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 208.3, 173.2, 145.0, 136.0, 133.4, 129.5, 129.4, 128.9, 128.3, 127.3, 66.1, 57.1, 50.6, 45.9, 43.4, 25.9, 25.5, 23.8, 21.7, 21.2 ppm. HRMS (ESI+): calcd. for $C_{25}H_{31}NO_5SNa$ 480.18151; found 480.18172.

Berkeleyamide A (1a): To a solution of naphthalene (144 mg, 1.12 mmol) in dry THF (1.7 mL) was added Na (25 mg, 1.12 mmol) in small pieces. The mixture was stirred for 2 h at room temperature, and then it was added to a solution of **24** (43 mg, 0.093 mmol) in THF (2.2 mL) at –78 °C until the green color persisted. The resulting reaction mixture was stirred at –78 °C for 30 min, then quenched with saturated aqueous NH_4Cl and extracted with EtOAc (3 × 15 mL). The combined organic layers were dried (Na_2SO_4) and concentrated. The crude product was purified by flash column chromatography (EtOAc/hexane, 9:1) to afford **1a** (24 mg, 85%) as a viscous liquid. $[\alpha]_D^{25}$ = –39.7 (*c* = 0.11, MeOH).[11] R_f = 0.33 (EtOAc/hexane, 9:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.09–7.38 (m, 5 H, Ph-H), 5.83 (br. s, 1 H, NH), 4.37 (m, 1 H, 10-H), 3.74 (s, 2 H, 7-H), 3.64 (m, 1 H, 14-H), 2.85 (dd, *J* = 3.2, 17.4 Hz, 1 H, 9-H), 2.70 (dd, *J* = 8.8, 17.4 Hz, 1 H, 9-H), 2.46 (m, 1 H, 11-H), 2.31 (m, 1 H, 19-H), 1.72 (m, 1 H, 19-H), 1.58 (m, 1 H, 16-H), 1.42 (m, 1 H, 15-H), 1.28 (m, 1 H, 15-H), 0.91 (d, *J* = 6.6 Hz, 6 H, CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 208.7, 177.7, 133.7, 129.6, 128.8, 127.2, 66.7, 51.0, 50.8, 46.5, 46.1, 45.7, 28.6, 25.3, 23.0, 22.4 ppm. HRMS (ESI+): calcd. for $C_{18}H_{25}NO_3Na$ 326.17266; found 326.17239.

(3*R*,5*S*,1′*R*)-3-(1′-Hydroxy-3′-oxo-4′-phenylbutyl)-5-isobutylpyrrolidin-2-one [10-*epi*-berkeleyamide A (1b)]: To a solution of **16** (0.250 g, 0.59 mmol) in THF (20 mL) was added TBAF (1.0 M in THF, 0.89 mL, 0.90 mmol) at 0 °C. The mixture was stirred for 1 h and then quenched with saturated aqueous NH_4Cl. The organic layer was separated, and the aqueous layer was extracted with

EtOAc (3 × 20 mL). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated. The crude product was purified by flash chromatography (EtOAc/hexane, 7:3) to afford **1b** (127 mg, 70%) as a pale-yellow solid. M.p. 50–51 °C. $[a]_D^{25}$ = –7.2 (*c* = 0.13, MeOH).[3] R_f = 0.53 (EtOAc/hexane, 8:2). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.17–7.37 (m, 5 H, Ph-H), 5.95 (s, 1 H, NH), 4.50 (s, 1 H, OH), 4.19 (m, 1 H, 10-H), 3.79 (s, 2 H, 7-H), 3.65 (m, 1 H, 14-H), 2.83 (dd, *J* = 16.1, 8.3 Hz, 1 H, 9-H), 2.64 (dd, *J* = 16.1, 3.2 Hz, 1 H, 9-H), 2.48 (q, *J* = 8.2 Hz, 1 H, 11-H), 2.02 (dt, *J* = 12.6, 8.2 Hz, 1 H, 19-H), 1.80 (ddd, *J* = 12.6, 9.2, 3.2 Hz, 1 H, 19-H), 1.58 (m, 1 H, 16-H), 1.38 (m, 1 H, 15-H), 1.26 (m, 1 H, 15-H), 0.91 (d, *J* = 6.6 Hz, 6 H, CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 208.0, 178.8, 133.9, 129.7, 128.8, 127.2, 69.9, 51.2, 51.0, 46.5, 45.8, 45.7, 44.0, 30.7, 25.3, 23.0, 22.8, 22.2 ppm. HRMS (ESI+): calcd. for $C_{18}H_{25}NO_3Na$ 326.17266; found 326.17242.

Supporting Information (see footnote on the first page of this article): Copies of the ^{1}H and ^{13}C NMR spectra for compounds **1a**, **1b**, **7**, **10**–**16**, and **19**–**24**.

Acknowledgments

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