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Synthetic studies of pseurotin A: preparation of an advanced lactam aldehyde intermediate

Judith M. Mitchell and Nathaniel S. Finney*†

Department of Chemistry and Biochemistry, University of California, San Diego, La Jolla, CA, 92093-0358, USA. E-mail: finney@oci.unizh.ch

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An efficient synthesis of the lactam core of pseurotin A has been accomplished. Key features of this synthesis include a tandem oxidation–cyclization to form the lactam from an acetylenic amide precursor. Although coupling of a lactam aldehyde with an appropriate side chain was not effective, it is anticipated that incorporating a partial side chain at an earlier stage should permit completion of the total synthesis of pseurotin A.

Introduction

Chitin-poly-β-(1,4)-GlcNAc is an essential component of the cell wall of virtually all infectious fungi.[1] As this polymer is absent in humans, the enzyme responsible for chitin biosynthesis (chitin synthase, CS) is an appealing therapeutic target. Despite this, little progress has been made in the development of chitin synthase inhibitors. The most extensively studied naturally occurring inhibitors are the polyoxins and nikkomycins,[2] which share as a common structural feature a ribosyl amino acid core. While these are among the most potent known inhibitors of CS, they have proven ineffective *in vivo*. A handful of other natural products are also known to be competitive inhibitors of CS. Among the most potent is pseurotin A (Fig. 1), which is notably distinct in structure from the polyoxins and nikkomycins, and we undertook the synthesis of pseurotin A as part of our broader program in chitin synthase inhibition.[3]

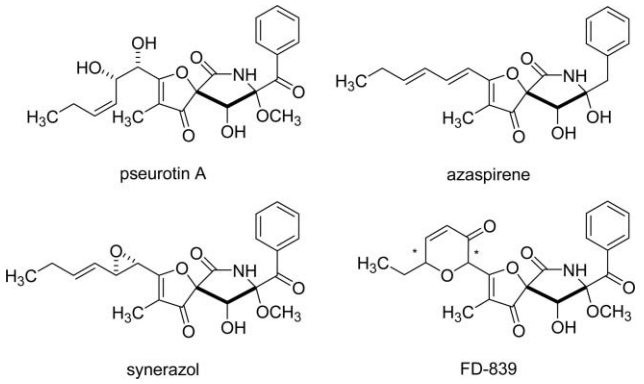

Fig. 1 Pseurotin A and related natural products. (Asterisks denote stereocenters of unknown configuration.)

Pseurotin A was first isolated from cultures of *Pseudeurotium ovalis ssp.* in 1976 and its structure was elucidated by Tamm *et al.* in 1981.[4] Pseurotin A, 8-*O*-desmethylpseurotin A and three structurally related molecules, azaspirene, and synerazol and FD-839, have subsequently been isolated from cultures of *Aspergillus fumigatus ssp.* It was discovered in 1993 that pseurotin A is a competitive inhibitor of chitin synthase,[5] as well as an apomorphine antagonist,[6] and in 1996 it was found to induce the proliferation of nerve cells.[7] Azaspirene has since been shown to inhibit angiogenesis,[8] while synerazol and FD-839 exhibit antifungal antibiotic activity;[9,10] FD-839 is also reported to inhibit growth in leukemia cell cultures. In addition to this remarkable range of biological activities, these molecules possess as a common structural feature a unique and highly functionalized heterospirocyclic framework containing an *N*-acyl hemiaminal and three contiguous stereogenic centers, one of them quaternary. Pseurotin A and related natural products are thus both challenging and important synthetic targets.

Tamm *et al.* have previously reported efforts directed to the synthesis of pseurotin A,[11] and recently Tadano *et al.* and Hayashi *et al.* published the first total syntheses of pseurotin A.[12–14] We report here our synthetic studies on pseurotin A (developed concurrently with Tadano's and Hayashi's work)[15] which culminate in the synthesis of a highly functionalized lactam precursor to pseurotin A.

Results and discussion

Retrosynthesis and synthetic overview

Retrosynthetic analysis (Scheme 1) was based on the precedent for the formation of 2*H*-furan-3-ones from acyclic precursors (*e.g.*, **B**→**A**).[11c] Unraveling of the left-hand ring required a β-diketone (**B**) as a precursor, which was anticipated to arise from the corresponding β-hydroxyketone, in turn derived from an aldol-type coupling of an aldehyde-bearing lactam (**C**) and an ethyl ketone (**D**). This disconnection is distinct from those previously reported,[11–13] all of which relied on an ethyl-ketone bearing-lactam or lactone being coupled with an aldehyde (Scheme 2). In principle this disconnection allows for a more convergent synthesis of pseurotin A, although in practice it proved to be a liability (*vide infra*). Lactam **C** was anticipated to arise from an unprecedented intramolecular cyclization of a primary amide onto an α-dicarbonyl (**E**) generated *in situ via* oxidation of an alkyne (**F**). The required alkyne-containing amide (**F**) could potentially be prepared *via* the desymmetrization of an equivalent of tetraol **G** (rather than drawing from the chiral pool), which was expected to derive from a simple alkene precursor, **H**.

Synthesis of the lactam core

Synthesis commenced with conversion of commercially available 1-chloro-2-chloromethyl-2-propene to the corresponding bisbenzoate (**H**→**1**, Scheme 3). Dihydroxylation under standard conditions afforded diol **2**, which was subsequently protected as the 4-phenylcyclohexylidene acetal (**3**), obtained as an inseparable and essentially indistinguishable pair of achiral diastereomers. (This acetal was chosen for its UV activity, in order to facilitate HPLC analysis and chromatographic isolation.) Benzoate cleavage produced diol **4**, again as an indistinguishable mixture of diastereomers.

Direct silylation of **4** provided the corresponding TBS ether in modest yield (42%; 83% based on recovered starting material).

† *Present address*: Organisch-chemisches Institut, Universität Zürich, Winterthurerstrasse 190, 8057 Zürich.

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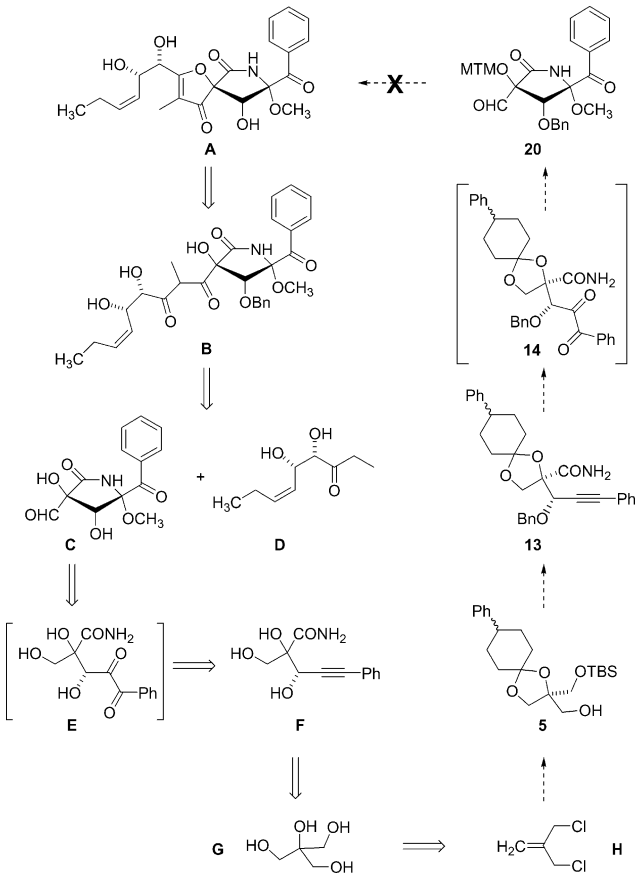
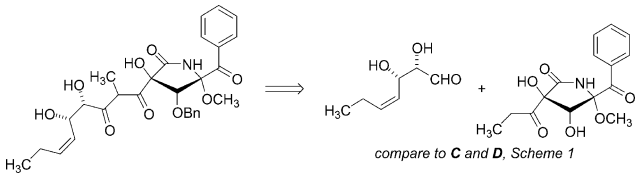
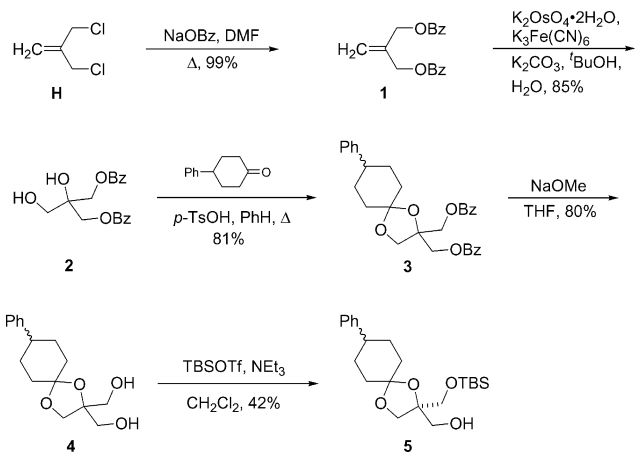


Scheme 1 Restrosynthesis and synthesis of Pseurotin A.



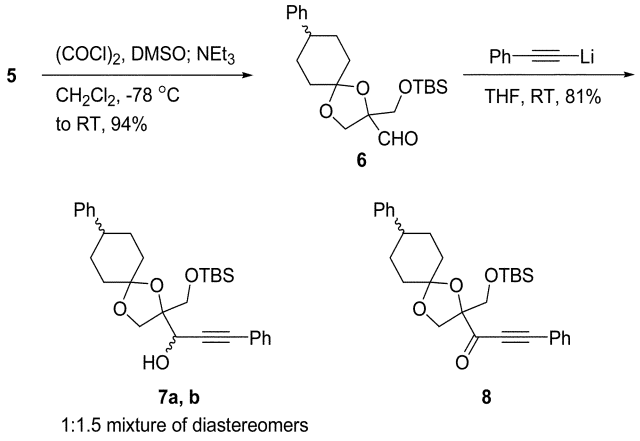
Scheme 2 The conceptual disconnection from other syntheses.



Scheme 3 Synthesis of the fully differentiated tetraol **5**.

Oversilylation was surprisingly facile, and it proved simplest, operationally, to run the reaction to partial conversion and separate the desired monosilylated product from remaining starting material. Differentiation of the diol could also be effected in 73% overall yield by sequential monoacylation (Ac_2O, pyridine, quant.), silylation (TBSOTf, NEt_3, CH_2Cl_2, 99%) and deacylation ($CH_3O^-Na^+$, CH_3OH, 73%). Preliminary studies on the enantioselective desymmetrization of **4** by enzymatic acylation have identified conditions for the selective preparation of either enantiomer of the monoacyl derivative of **4**.[16] In principle this allows for the enantioselective preparation of **5**, although this has not been further developed. With convenient differentiation of diol **4** established, installation of the phenylacetylene fragment was undertaken.

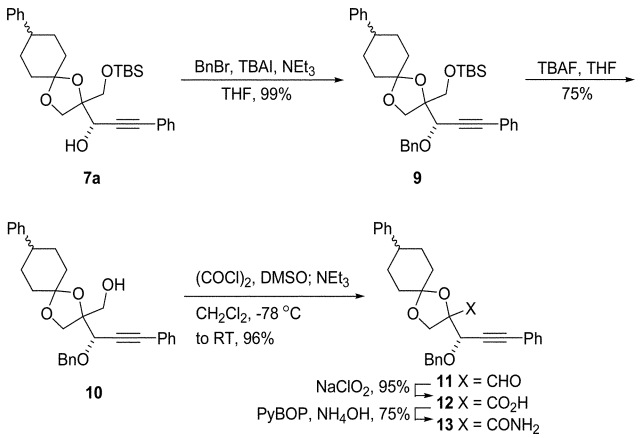
Swern oxidation of alcohol **5** (Scheme 4) provided aldehyde **6** and set the stage for diastereoselective phenylacetylide addition. All attempts led to the formation of **7** as a separable mixture of diastereomers at the new stereocenter, slightly favoring the undesired diastereomer.[17] The diastereoselectivity varied from 1 : 1.5 to 1 : 2, depending on the solvent (THF *vs.* Et_2O, *e.g.*), counterion (Li^+ *vs.* Na^+, *e.g.*) and presence of additive (TMEDA, $EtAlCl_2$, DMPU, *etc.*). Aldehyde **6** failed to react under Carreira's conditions for asymmetric acetylide addition.[18]



Scheme 4 Synthesis of propargylic alcohol **7**.

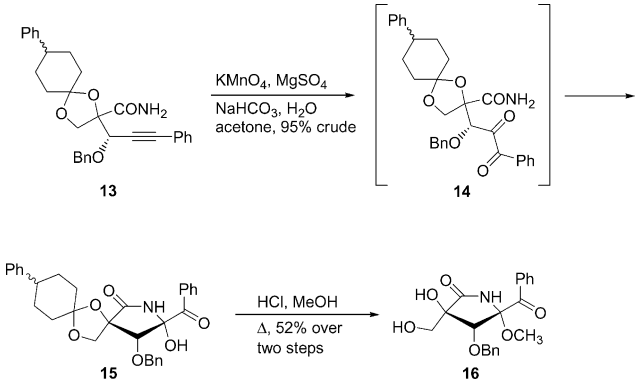
Enantioselective reduction of the corresponding propargylic ketone (**8**) was also explored. Among the numerous potentially selective reductions studied were those employing $(ipc)_2BH$ and chiral oxazaborolidine reagents.[19,20] The selectivity with these and other chiral reducing agents was not significantly better than that of the acetylide addition, although the oxidation–reduction sequence did allow efficient recycling of the undesired diastereomer **7b**. In the end, the diastereomers were separated chromatographically, allowing access to **7a** in diastereomerically pure form. (Prior to determination of the relative configuration, **7a** and **7b** were each carried forward separately; only details for the transformations of **7a** are presented here.)

With the phenylacetylene fragment in place it was necessary to address the conversion of the required amide precursor to the oxidative cyclization. Alcohol **7a** was first protected as the benzyl ether, and the silyl ether was then removed by treatment with fluoride (Scheme 5). Oxidation of alcohol **10** followed by treatment with PyBOP and ammonium hydroxide then provided amide **13** in good yield.[21,22]



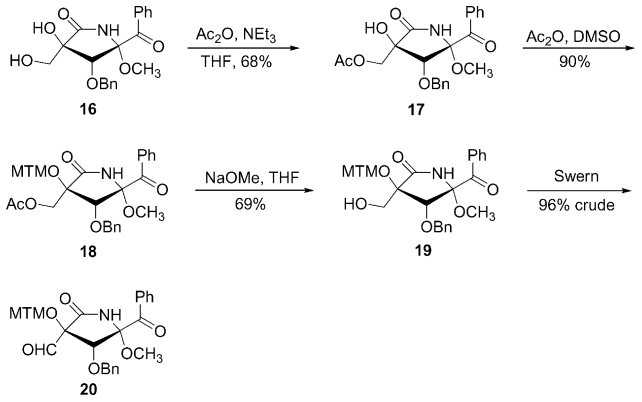
Scheme 5 Synthesis of alkyne **5**.

This set the stage for the tandem oxidation–cyclization to form the lactam core of pseurotin A. Oxidation of **13** with potassium permanganate under neutral conditions afforded the desired five-membered lactam **15** in excellent raw yield (Scheme 6).[23] The intermediate α-dicarbonyl (**14**) was not observed, nor was the alternative six-membered lactam. While lactam **15** proved extremely difficult to purify, treatment of crude **15** with acidic methanol introduced the necessary methyl ether with concomitant acetal cleavage to yield diol **16**. This transformation proceeded in variable yield, although no byproducts could be isolated. We believe that this is due to the degradation of the α-diketone intermediate regenerated under acidic conditions, consistent with the instability of **15** to silica gel chromatography. Notably, **16** was formed as a single diastereomer possessing the natural configuration at the acetal stereocenter,[24] and this represents one of only three times that the lactam core of pseurotin A has been prepared in fully functionalized form.[12,13]



Scheme 6 Formation and cyclization of the key α-diketone intermediate.

Conversion of diol **16** to the corresponding aldehyde was the final obstacle before coupling with the appropriate ketone could be attempted. Oxidation in the presence of the unprotected tertiary hydroxyl proved problematic, and a series of protecting group manipulations were required. Monoacetate **17** was prepared in good yield by treatment of **16** with Ac_2O and NEt_3 (Scheme 7). Incubation of **17** with excess Ac_2O and DMSO then produced methylthiomethyl (MTM) ether **18**. Subsequent acetate cleavage afforded the desired alcohol **19**, which was oxidized to the corresponding aldehyde **20**.



Scheme 7 Synthesis of aldehyde **4**.

At this stage, X-ray crystallographic analysis of *epi*-**18**, prepared from **7b** *via* the same synthetic route as that described for **18** from **7a**, provided the long-awaited determination that **18**, and thus acetylide adduct **7a**, possessed the correct relative configuration at the secondary stereogenic center (Fig. 2).

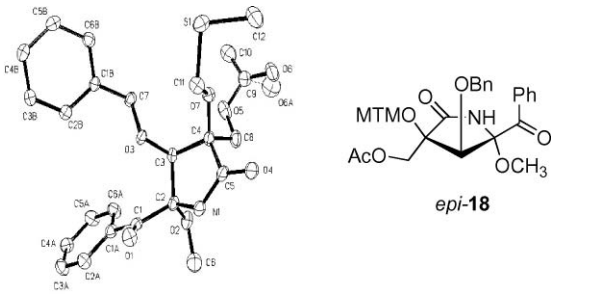
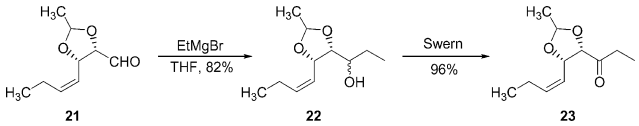


Fig. 2 X-Ray crystal structure of *epi*-**18** (H atoms omitted for clarity).

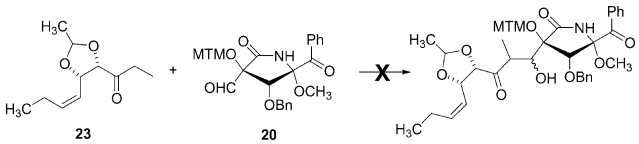
The requisite coupling partner, ethyl ketone **23** was readily prepared from the known aldehyde **21**, which can be prepared in five steps from D-glucose.[11e] Grignard reaction of ethylmagnesium bromide and **21** produced alcohol **22**, followed by Swern oxidation to afford **23** in good yield (Scheme 8).



Scheme 8 Preparation of the 'left half' ethyl ketone.

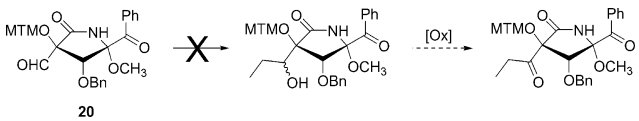
Elaboration of aldehyde lactam

With both components in hand, the crucial aldol condensation of aldehyde **20** and ketone **23** was undertaken (Scheme 9). However, the fragments failed to couple as anticipated. While the instability of the aldehyde component was initially considered as the source of the problem, it was soon determined that ketone **23** could not be induced to couple with any substrate: treatment of ketone **23** with base under a variety of conditions led to decomposition, even in the presence of simple electrophiles such as benzaldehyde.



Scheme 9 Coupling—or lack thereof—between ketone **23** and aldehyde **20**.

In light of this result, it was decided to modify the lactam core so that coupling to aldehyde **21** (Scheme 8) could be attempted. Successful aldol condensations between aldehyde **21** and various sterically-hindered ethyl ketones were reported in the early synthetic studies of pseurotin A,[11d,e] providing ample precedent for the desired reaction. (This approach has since been used in both reported total syntheses.)[12,13] Thus, the only modification our original synthetic route required was the addition of an ethyl fragment to aldehyde **20** with subsequent oxidation to the corresponding ketone (Scheme 10). However, treatment with ethyllithium or ethylmagnesium bromide led only to recovered starting material, even at elevated temperatures. A variety of other nucleophiles were screened (lithium acetylide, *e.g.*), but in no case was addition to **20** observed. While there is no clear explanation for the intransigence of this aldehyde, it was clear



Scheme 10 Inadequacy of aldehyde **20** as an electrophile.

that an alternate strategy involving earlier extension of the side chain would be required for the preparation of pseurotin A.

Conclusion

We have described here our first-generation synthetic approach to the chitin synthase inhibitor, pseurotin A. This target is important not only in that it is a competitive inhibitor of this important fungal enzyme, but also in that it is structurally distinct from the polyoxins and nikkomycins, which have proven ineffective in treating human fungal infections. Notable elements of our approach include the enzymatic desymmetrization of a meso intermediate to set the quaternary stereocenter, and the oxidation of an acyclic amide–alkyne to generate an α-diketone which undergoes diastereoselective *in situ* cyclization to form the lactam core of pseurotin A. Advanced aldehyde intermediates based on this lactam failed to couple with even the simplest carbanions, delineating the need for a new synthetic strategy. The details of an alternate route, in which the side chain is incorporated earlier in the synthesis, will be described in a subsequent manuscript.

Experimental

General

All reactions were carried out in oven or flame dried glassware under an atmosphere of nitrogen in dry solvent, except where noted. THF and CH_2Cl_2 were dried by passage through an activated column of alumina, and pyridine and acetonitrile were distilled from CaH_2. All other reagents were used as obtained, unless otherwise stated. Thin layer chromatography was performed on silica gel 60 (F_{254}, 250 nm, EM Science) plates and visualized with UV light or stained with $KMnO_4$, dinitrophenylhydrazine (DNP), or phosphomolybdic acid (PMA). Flash column chromatography was performed using silica gel (Selecto Scientific, 32–63 nm) or reverse phase (EM Science, silica gel 60, RP-18) as indicated. ^{1}H-NMR data are reported in ppm relative to the solvent ($CHCl_3$ at 7.26 ppm); coupling constants have been rounded to the nearest 0.5 Hz. Proton decoupled ^{13}C-NMR spectra are reported in ppm relative to solvent as internal standard ($CDCl_3$ at 77.0 ppm).

1,3-Dibenzoyl-(2-methylidene)-1,3-propanediol (1). Sodium benzoate (15.7 g, 109 mmol, 2.5 equiv.) was added to methallyl dichloride (5.00 mL, 43.2 mmol, 1 equiv.) in DMF (80 mL), and the solution was heated to 80 °C under N_2. After 12 hours the reaction was cooled to room temperature, then quenched slowly with saturated aqueous NH_4Cl (200 mL). The reaction was further diluted with H_2O (200 mL), then extracted with Et_2O (3 × 250 mL). The combined ethereal extracts were washed with H_2O (2 × 200 mL). The organic phase was dried over Na_2SO_4 and concentrated under reduced pressure to yield **1** (12.8 g, 43.2 mmol, ≥99%) as a brown oil. **1**: ^{1}H NMR (400 MHz, $CDCl_3$), δ: 8.05 (d, $J = 7.5$ Hz, 4H), 7.56 (t, $J = 7.5$ Hz, 2H), 7.43 (t, $J = 7.5$ Hz, 4H), 5.46 (s, 2H), 4.97 (s, 4H). FTIR (neat), cm^{-1}: 3067(w), 2952(w), 1723(s), 1602(m), 1452(m), 1274(s), 1110(s). TLC (20% EtOAc–hexanes), *R*f: 0.46 (UV, anisaldehyde).

1,3-Dibenzoyl-(2-hydroxymethyl)-1,2,3-propanetriol (2). To a solution of **1** (12.8 g, 43.2 mmol, 1 equiv.) in 1 : 1 H_2O–^{t}BuOH (800 mL) were added $K_3Fe(CN)_6$ (43.2 g, 131 mmol, 3.0 equiv.), K_2CO_3 (18.0 g, 130.2 mmol, 3.0 equiv.), and $K_2OsO_4{\cdot}2H_2O$ (0.83 g, 2.3 mmol, <0.1 equiv.). The biphasic reaction was degassed three times by evacuating and backfilling with N_2, then stirred at room temperature under N_2. After 18 hours $Na_2S_2O_4$ (150 g) was added and the reaction was stirred for another hour. The reaction was diluted with saturated aqueous NH_4Cl (500 mL), then extracted with EtOAc (3 × 500 mL). The organic phase was dried over Na_2SO_4 and concentrated under reduced pressure to yield **2** (12.1 g, 36.9 mmol, 85%) as a yellow oil. **2**: ^{1}H NMR (400 MHz, $CDCl_3$), δ: 8.00 (d, $J = 7.5$ Hz, 4H), 7.52 (t, $J = 7.5$ Hz, 2H), 7.37 (t, $J = 7.5$ Hz, 4H), 4.50 (s, 4H), 3.76 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$), δ: 166.5, 133.1, 129.5, 129.1, 128.2, 73.5, 65.2, 63.5. FTIR (neat), cm^{-1}: 3455(m), 3067(w), 2960(w), 1731(s), 1607(w), 1458(m), 1277(s), 1112(s). HRMS (MALDI-FTMS), *m/z*: Calcd for $C_{18}H_{18}O_6$ (M + Na$^+$): 353.0996. Found: 353.0987. TLC (5% CH_3OH–CH_2Cl_2), *R*f: 0.21 (UV, $KMnO_4$).

1,3-Dibenzoyl-(2-hydroxymethyl)-1,2,3-propanetriol, 4-phenylcyclohexylidene acetal (3). Phenylcyclohexanone (7.9 g, 45 mmol 1.1 equiv.) and *p*-toluenesulfonic acid (1.6 g, 8.4 mmol, 0.2 equiv) were added to a solution of **2** (14 g, 41 mmol, 1 equiv.) in benzene (500 mL) in a flask equipped with a Dean Stark apparatus and heated to reflux. After 12 hours the reaction was cooled to room temperature and diluted with EtOAc (500 mL), then washed with H_2O (1 × 500 mL), saturated aqueous $NaHCO_3$ (1 × 500 mL), and saturated aqueous NaCl (1 × 500 mL). The organic phase was dried over Na_2SO_4 and concentrated under reduced pressure to afford a brown oil. Purification of the residue by flash column chromatography (1% CH_3OH–CH_2Cl_2) yielded **3** (16 g, 33 mmol, 81%) as a brown oil. **3**: ^{1}H NMR (400 MHz, $CDCl_3$), δ: 8.09 (d, $J = 7.0$ Hz, 4H), 7.58 (t, $J = 7.0$ Hz, 2H), 7.46 (t, $J = 7.0$ Hz, 4H), 7.33–7.19 (m, 5H), 4.62–4.52 (m, 4H), 4.21–4.17 (m, 2H), 2.57 (m, 1H), 2.02–1.74 (m, 8H). ^{13}C NMR (100 MHz, $CDCl_3$), δ: 165.7, 146.0, 145.9, 133.0, 129.5, 129.4, 129.36, 129.31, 128.3, 128.2, 128.13, 128.10, 126.7, 126.6, 125.89, 125.86, 111.0, 110.7, 80.2, 79.8, 68.2, 67.9, 65.3, 65.2, 43.2, 42.9, 36.3, 36.0, 31.5, 31.1. FTIR (neat), cm^{-1}: 3067(w), 3034(w), 2944(m), 2861(w), 1724(s), 1607(m), 1451(m), 1268(s), 1107(s), 711(s). HRMS (MALDI-FTMS), *m/z*: Calcd for $C_{30}H_{30}O_6$ (M + Na$^+$): 509.1934. Found: 509.1915. TLC (20% EtOAc–hexanes), *R*f: 0.40 (UV, DNP).

(2-Hydroxymethyl)-1,2,3-propanetriol, 4-phenylcyclohexylidene acetal (4). Sodium methoxide (7.50 g, 139 mmol, 4.4 equiv.) was added to a solution of **3** (5.3 g, 31.5 mmol, 1 equiv.) in THF (500 mL) under N_2. After 12 hours the reaction was quenched with saturated aqueous NaCl (100 mL) and extracted with EtOAc (3 × 400 mL), then dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash column chromatography (1% CH_3OH–CH_2Cl_2) to afford **4** (7.0 g, 25.3 mmol, 80%) as a white solid. **4**: ^{1}H NMR (400 MHz, $CDCl_3$), δ: 7.19–7.33 (m, 5H), 3.98 (s, 2H), 3.74 (d, $J = 12.0$ Hz, 1H), 3.70 (d, $J = 12.0$ Hz, 1H), 3.30 (br s, 1H), 2.54–2.60 (m, 1H), 1.71–1.91 (m, 8H). ^{13}C NMR (100 MHz, $CDCl_3$), δ: 145.8, 128.1, 126.5, 125.9, 109.8, 82.8, 67.8, 64.0, 43.0, 36.4, 31.1. FTIR (neat), cm^{-1}: 3418(s), 2936(s), 2874(m), 1500(w), 1450(w), 1118(s), 1083(m), 1043(s). HRMS (MALDI-FTMS), *m/z*: Calcd for $C_{16}H_{22}O_4$ (M + Na$^+$): 301.1410. Found: 301.1401. TLC (5% CH_3OH–CH_2Cl_2), *R*f: 0.34 (UV, DNP).

1-*O*-*tert*-Butyldimethylsilyl-(2-hydroxymethyl)-1,2,3-propanetriol, 4-phenylcyclohexylidene acetal (5). TBSCl (0.71 g, 4.71 mmol, 1.15 equiv.) was added to a solution of diol **4** (1.23 g, 4.42 mmol, 1 equiv.) and imidazole (0.36 g, 5.29 mmol, 1.30 equiv.) in THF (100 mL) at 0 °C. The reaction was allowed to warm to room temperature over 12 hours while stirring under N_2. The reaction was then diluted with EtOAc (150 mL) and washed with saturated aqueous NaCl (2 × 200 mL). The organic phase was dried over Na_2SO_4 and concentrated under reduced pressure to afford a brown oil. Purification by flash column chromatography (10% CH_3OH–CH_2Cl_2) yielded **5** (0.72 g, 1.85 mmol, 41%) as a yellow oil, as well as unreacted diol **4** (0.52 g, 1.87 mmol, 42%). **5**: ^{1}H NMR (400 MHz, $CDCl_3$), δ: 7.33–7.19 (m, 5H), 4.06 (d, $J = 9.0$ Hz, 1H), 3.94 (d, $J = 9.0$ Hz, 1H), 3.74–3.62 (m, 4H), 2.58–2.53 (m, 1H), 2.33 (br s, 1H), 1.97–1.70 (m, 8H). ^{13}C NMR (100 MHz, $CDCl_3$), δ: 146.1, 128.1, 126.6, 125.9, 109.8, 82.3, 67.9, 65.3, 64.7, 43.1, 36.6, 36.0, 31.6, 31.5, 25.9, 18.2, −5.39, −5.42. FTIR (neat), cm^{-1}: 3480(m), 2951(s), 2858(s), 1607(w), 1475(m),

1252(m), 1093(s), 839(s). HRMS (MALDI-FTMS), *m/z*: Calcd for $C_{22}H_{36}O_4Si$ (M + Na^+): 415.2275. Found: 415.2255. TLC (5% CH_3OH–CH_2Cl_2), *R*f: 0.46 (UV, DNP).

1-*O*-*tert*-Butyldimethylsilyl-(2-hydroxymethyl)-1,2-dihydroxy-propan-3-al, 4-phenylcyclohexylidene acetal (6). To a −78 °C solution of oxalyl chloride (0.32 mL, 3.68 mmol, 2.03 equiv.) in CH_2Cl_2 (12 mL) was added DMSO (0.33 mL, 4.65 mmol, 2.57 equiv.) under N_2. After ten minutes alcohol **5** (0.70 g, 1.81 mmol, 1 equiv.) was added in CH_2Cl_2 (8 mL) and the mixture stirred for 45 minutes. NEt_3 (0.80 mL, 5.74 mmol) was then added, and the reaction was warmed to room temperature. After two hours the reaction was diluted with CH_2Cl_2 (50 mL) and washed with saturated aqueous NH_4Cl (1 × 50 mL) and saturated aqueous NaCl (1 × 50 mL). The organic phase was dried over Na_2SO_4 and concentrated under reduced pressure to afford aldehyde **6** (0.65 g, 1.57 mmol, 87%) as a yellow oil. **6**: ^{1}H NMR (400 MHz, $CDCl_3$), δ: 9.78 (d, J = 4.0 Hz, 1H), 7.35–7.20 (m, 5H), 4.29–4.26 (m, 1H), 4.06–3.99 (m, 1H), 3.91–3.83 (m, 1H), 2.61–2.60 (m, 1H), 1.73–2.07 (m, 8H), 0.95–0.94 (m, 9H), 0.15–0.13 (m, 6H). ^{13}C NMR (100 MHz, $CDCl_3$), δ: 201.9, 146.1, 146.0, 128.18, 128.16, 126.64, 126.60, 125.93, 111.45, 111.22, 87.12, 86.7, 66.9, 66.8, 64.2, 63.9, 43.3, 43.0, 36.04, 36.03, 35.9, 35.5, 31.34, 31.30, 31.2, 25.84, 25.80, 18.34, 18.31, −5.34, −5.36, −5.40, −5.42. FTIR (neat), cm^{-1}: 3034(w), 2944(s), 2861(s), 2713(w), 1736(s), 1607(w), 1254(s), 1094(s), 839(s). HRMS (MALDI-FTMS), *m/z:* Calcd for $C_{22}H_{34}O_4Si$ (M + Na^+): 413.2118. Found: 413.2119. TLC (20% EtOAc–hexanes), *R*f: 0.63 (UV, DNP).

1-*O*-*tert*-Butyldimethylsilyl-(2-hydroxymethyl)-1,2,3-trihydroxy-5-phenylpent-4-yne, 4-phenylcyclohexylidene acetal (7). Lithium phenylacetylide (1.80 mL, 1.80 mmol, 1.00 M in THF, 1.08 equiv.) was added to a solution of aldehyde **7** (0.65 g, 1.66 mmol, 1 equiv.) in THF (15 mL) under N_2. After three hours the reaction was diluted with EtOAc (50 mL) and washed with saturated aqueous NaCl (2 × 50 mL). The organic phase was dried over Na_2SO_4 and concentrated under reduced pressure to afford a viscous brown oil. Purification by flash column chromatography (2% EtOAc–hexanes) yielded the two propargylic alcohol diastereomers of alcohol **7** (**7a**, 0.18 g, 0.37 mmol, 30%; **7b**, 0.49 g, 1.00 mmol, 60%). **7a**: ^{1}H NMR (400 MHz, $CDCl_3$), δ: 7.20–7.34 (m, 10H), 4.70 (d, J = 9.0 Hz, 1H), 4.23 (d, J = 9.0 Hz, 1H), 4.14 (d, J = 9.0 Hz, 1H), 4.10 (d, J = 9.5 Hz, 1H), 3.66 (d, J = 9.5 Hz, 1H), 3.19 (d, J = 9.0 Hz, 1H), 2.50–2.59 (m, 1H), 1.70–2.12 (m, 8H), 0.92 (s, 9H), 0.13 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$), δ: 146.2, 146.1, 131.6, 131.5, 128.3, 128.2, 128.10, 128.07, 126.7, 126.6, 125.9, 122.5, 110.6, 110.3, 87.6, 87.5, 85.9, 85.8, 83.7, 82.9, 69.0, 68.7, 66.2, 65.8, 65.3, 64.9, 43.3, 43.1, 36.7, 35.9, 35.5, 31.6, 31.3, 31.2, 25.9, 18.3, −5.4. FTIR (neat), cm^{-1}: 3447(m), 3034(m), 2953(s), 2930(s), 2858(s), 1747(w), 1615(w), 1491(m), 1254(s), 1096(s), 838(s). HRMS (MALDI-FTMS), *m/z*: Calcd for $C_{30}H_{40}O_4Si$ (M + Na^+): 515.2588. Found: 515.2586. TLC (5% CH_3OH–CH_2Cl_2), *R*f: 0.52 (UV, DNP).

1-*tert*-Butyldimethylsilyloxy-2-benzyl-(2-hydroxymethyl)-1,2,3-trihydroxy-5-phenylpent-4-yne, 4-phenylcyclohexylidene acetal (9). Benzyl bromide (0.45 mL, 3.76 mmol) was added to a solution of tetrabutylammonium iodide (0.35 g, 0.95 mmol, 1.11 equiv.), sodium hydride (0.33 g, 8.25 mmol, 60% dispersion in oil, 2.43 equiv.), and alcohol **7a** (1.67 g, 3.39 mmol, 1 equiv.) in THF (50 mL) under N_2. After five hours the reaction was diluted with EtOAc (100 mL) and washed with saturated aqueous NaCl (3 × 150 mL). The organic phase was dried over Na_2SO_4 and concentrated under reduced pressure to afford benzyl ether **9** (1.96 g, 3.36 mmol, 99%) as a yellow oil. **9**: ^{1}H NMR (400 MHz, $CDCl_3$), δ: 7.46–7.19 (m, 15H), 4.93 (d, J = 12.0 Hz, 1H), 4.65 (d, J = 12.0 Hz, 1H), 4.57 (s, 1H), 4.17–4.09 (m, 2H), 3.94 (d, J = 10.0 Hz, 1H), 3.73 (d, J = 10.0 Hz, 1H), 2.59–2.50 (m, 1H), 2.22–1.65 (m, 8H), 0.90 (s, 9H), 0.11–0.07 (m, 6H). ^{13}C NMR (100 MHz, $CDCl_3$), δ: 146.6, 146.5, 137.7, 137.5, 131.64, 131.58, 128.32, 128.29, 128.16, 128.13, 128.0, 127.9, 127.5, 126.8, 126.7, 125.8, 122.6, 110.6, 110.3, 87.5, 87.3, 85.8, 85.7, 85.3, 84.6, 71.5, 71.3, 70.7, 70.4, 67.9, 67.4, 63.2, 63.1, 43.5, 43.3, 36.6, 36.3, 35.9, 31.8, 31.71, 31.67, 31.4, 26.0, 22.8, 18.4, 14.3, −5.25, −5.28. FTIR (neat), cm^{-1}: 3062(w), 3029(m), 2950(s), 2929(s), 2857(s), 1615(w), 1492(m), 1374(w), 1254(m), 1090(s), 837(s). HRMS (MALDI-FTMS), *m/z*: Calcd for $C_{37}H_{46}O_4Si$ (M + Na^+): 605.3057. Found: 605.3046. TLC (10% EtOAc–hexanes), *R*f: 0.52 (UV, DNP).

3-*O*-Benzyl-(2-hydroxymethyl)-1,2,3-trihydroxy-5-phenylpent-4-yne, 4-phenyl-cyclohexylidene acetal (10). Tetrabutylammonium fluoride (5.1 mL, 5.1 mmol, 1.0 M in THF, 1.5 equiv.) was added to a solution of silyl ether **9** (2.0 g, 3.4 mmol, 1 equiv.) in THF (100 mL). After 12 hours the reaction was diluted with EtOAc (100 mL) and washed with saturated aqueous NaCl (3 × 150 mL). The organic phase was dried over Na_2SO_4 and concentrated under reduced pressure. Purification by flash column chromatography (10% EtOAc–hexanes) afforded alcohol **10** (1.1 g, 2.5 mmol, 75%). **10**: ^{1}H NMR (400 MHz, $CDCl_3$), δ: 7.22–7.54 (m, 15H), 4.97 (d, J = 11.5 Hz, 1H), 4.65 (d, J = 11.5 Hz, 1H), 4.56 (s, 1H), 4.24 (d, J = 9.5 Hz, 1H), 4.13 (d, J = 9.5 Hz, 1H), 3.98–3.92 (m, 2H), 2.57–2.60 (m, 1H), 2.20–1.72 (m, 9H). ^{13}C NMR (100 MHz, $CDCl_3$), δ: 146.20, 146.18, 137.11, 137.08, 131.7, 131.6, 128.51, 128.48, 128.3, 128.1, 127.9, 127.8, 126.7, 126.6, 125.9, 122.2, 122.1, 110.8, 110.5, 87.9, 87.7, 84.9, 84.8, 84.0, 83.4, 71.9, 71.7, 71.4, 71.3, 68.0, 67.8, 63.7, 63.6, 43.3, 43.1, 36.6, 36.3, 36.1, 31.60, 31.57, 31.3. FTIR (neat), cm^{-1}: 3497(m), 3029(m), 2933(s), 2863(s), 2242(w), 1599(w), 1491(s), 1453(m), 1093(s), 1070(s), 936(m). HRMS (EI), *m/z*: Calcd for $C_{31}H_{32}O_4$ (M^+): 468.2301. Found: 468.2311. TLC (20% EtOAc–hexanes), *R*f:0.38 (UV, DNP).

3-*O*-Benzyl-(2-hydroxymethyl)-2,3-dihydroxy-5-phenylpent-4-ynal, 4-phenyl-cyclohexylidene acetal (11). To a −78 °C solution of oxalyl chloride (0.42 mL, 4.83 mmol, 2.00 equiv.) in CH_2Cl_2 (20 mL) was added DMSO (0.43 mL, 6.06 mmol, 2.51 equiv.) under N_2. After ten minutes alcohol **10** (1.13 g, 2.41 mmol, 1 equiv.) was added in CH_2Cl_2 (10 mL) and the mixture stirred for one hour. NEt_3 (1.0 mL, 7.17 mmol, 2.98 equiv.) was then added, and the reaction was warmed to room temperature. After two hours the reaction was diluted with CH_2Cl_2 (100 mL) and washed with saturated aqueous NaCl (3 × 100 mL). The organic phase was dried over Na_2SO_4 and concentrated under reduced pressure to afford aldehyde **11** (1.04 g, 2.23 mmol, 93%). **11**: ^{1}H NMR (400 MHz, $CDCl_3$), δ: 9.87 (d, J = 7.5 Hz, 1H), 7.49–7.18 (m, 15H), 4.94–4.89 (m, 1H), 4.66–4.59 (m, 1H), 4.34–4.28 (m, 1H), 4.13–4.07 (m, 1H), 2.61–2.55 (m, 1H), 2.28–1.65 (m, 8H). ^{13}C NMR (100 MHz, $CDCl_3$), δ: 202.0, 201.4, 146.1, 146.0, 131.8, 131.7, 128.9, 128.34, 128.29, 128.26, 128.22, 128.17, 128.0, 126.8, 126.7, 126.0, 121.8, 112.6, 112.3, 89.1, 88.4, 87.9, 83.2, 83.1, 71.3, 71.2, 70.9, 70.7, 68.1, 67.7, 43.4, 43.1, 36.3, 35.7, 35.2, 31.6, 31.4, 31.3, 31.2, 29.8, 24.2. FTIR (neat), cm^{-1}: 3076(w), 3043(w), 2931(s), 2869(m), 2226(w), 1736(s), 1491(m), 1450(m), 1089(s), 1071(s). HRMS (MALDI-FTICR), *m/z*: Calcd for $C_{31}H_{30}O_4$ (M + Na^+): 489.2036. Found: 489.2039. TLC (20% EtOAc–hexanes), *R*f: 0.50 (UV, DNP).

3-*O*-Benzyl-(2-hydroxymethyl)-2,3-dihydroxy-5-phenylpent-4-ynoic acid, 4-phenylcyclohexylidene acetal (12). To a solution of aldehyde **11** (1.04 g, 2.23 mmol, 1 equiv.) in ^{t}BuOH (50 mL) and H_2O (16 mL) were added 2-methyl-2-butene (5.00 mL, 10.0 mmol, 2.0 M in THF, 4.93 equiv.), NaH_2PO_4 (0.38 g, 2.75 mmol, 1.23 equiv.), and sodium chlorite (0.79 g, 6.99 mmol,

3.14 equiv.). After three hours, the reaction was diluted with EtOAc (150 mL) and washed with saturated aqueous NaCl (3 × 100 mL). The organic phase was dried over Na_2SO_4 and concentrated under reduced pressure to yield acid **12** (1.06 g, 2.20 mmol, 99%) as a foamy white solid. **12**: ^{1}H NMR (400 MHz, $CDCl_3$), δ: 7.48–7.18 (m, 15H), 4.94–4.90 (m, 1H), 4.74–4.65 (m, 2H), 4.49–4.44 (m, 1H), 4.26–4.22 (m, 1H), 2.54–2.36 (m, 1H), 2.39–1.61 (m, 8H). ^{13}C NMR (100 MHz, $CDCl_3$), δ: 173.4, 145.8, 136.5, 136.2, 131.72, 131.68, 128.9, 128.3, 128.23, 128.20, 127.94, 127.88, 126.8, 126.6, 126.0, 121.7, 113.6, 113.2, 88.7, 86.8, 86.3, 83.0, 71.5, 71.2, 69.6, 43.3, 43.0, 35.6, 35.2, 34.9, 31.5, 31.4, 30.8, 29.8. FTIR (neat), cm^{-1}: 3431(w), 3059(w), 3034(m), 2929(s), 2864(m), 2234(w), 1728(s), 1607(m), 1491(m), 1452(m), 1087(s), 1070(s). HRMS (EI), *m/z*: Calcd for $C_{31}H_{30}O_5$ (M^+): 482.2093. Found: 482.2097. TLC (10% CH_3OH–CH_2Cl_2), *R*f: 0.50 (UV, DNP).

3-*O*-Benzyl-(2-hydroxymethyl)-2,3-dihydroxy-5-phenylpent-4-ynamide, 4-phenylcyclohexylidene acetal (13). To a solution of acid **12** (1.07 g, 2.22 mmol, 1 equiv.) in THF (50 mL) were added NEt_3 (0.70 mL, 5.02 mmol, 2.26 equiv.) and PyBOP (1.38 g, 2.60 mmol, 1.17 equiv.). After ten minutes 28% NH_3 in H_2O (1.40 mL, 11.9 mmol, 5.36 equiv.) was added and the mixture was allowed to stir for 12 hours. The reaction was then diluted with EtOAc (100 mL) and washed with saturated aqueous NaCl (3 × 100 mL). The organic phase was dried over Na_2SO_4 and concentrated under reduced pressure. Purification of the residue by flash column chromatography (1% CH_3OH–CH_2Cl_2) afforded amide **13** (0.80 g, 1.66 mmol, 75%) as a foamy white solid. **13**: ^{1}H NMR (400 MHz, $CDCl_3$), δ: 7.57–7.23 (m, 15H), 6.99 (br s, 1H), 6.94 (br s, 1H), 5.02–4.98 (m, 1H), 4.89 (s, 1H), 4.76 (d, J = 12.0 Hz, 1H), 4.54–4.48 (m, 1H), 4.29 (d, J = 9.2 Hz, 1H), 2.70–2.60 (m, 1H), 2.50–1.71 (m, 8H). ^{13}C NMR (100 MHz, $CDCl_3$), δ: 174.8, 145.7, 145.6, 136.7, 136.5, 131.44, 131.40, 128.4, 128.05, 128.02, 127.98, 127.81, 127.77, 127.51, 127.49, 126.5, 126.4, 125.8, 122.8, 121.8, 112.6, 112.3, 87.9, 87.8, 86.9, 86.3, 84.0, 83.9, 71.7, 71.5, 71.34, 71.28, 69.8, 69.6, 43.0, 42.8, 35.4, 35.3, 35.2, 35.0, 31.3, 30.6. FTIR (neat), cm^{-1}: 3478(s), 3356(m), 3029(m), 2936(s), 2865(m), 2250(m), 1693(s), 1573(m), 1492(m), 1452(m), 1088(s). HRMS (MALDI-FTICR), *m/z*: Calcd for $C_{31}H_{31}NO_4$ (M + Na^+): 504.2145. Found: 504.2126. TLC (2% CH_3OH–CH_2Cl_2), *R*f: 0.32 (UV, DNP).

2-Benzoyl-3-*O*-benzyl-2,3,4-trihydroxy-4-hydroxymethylpyrrolidin-5-one (15). Magnesium sulfate (1.50 g, 12.5 mmol, 2.41 equiv.) and sodium bicarbonate (0.28 g, 3.29 mmol, 0.64 equiv.) were added to a solution of amide **13** (2.49 g, 5.17 mmol, 1 equiv.) in acetone (190 mL) and H_2O (110 mL). Potassium permanganate (3.52 g, 22.3 mmol, 4.31 equiv.) was then added and the reaction was allowed to stir for one hour. Sodium nitrite (3.50 g, 50.7 mmol, 9.81 equiv.) and 10% H_2SO_4 (30 mL) were then added to quench the reaction. EtOAc (200 mL) was added and the reaction washed with saturated aqueous NaCl (2 × 250 mL). The organic phase was dried over Na_2SO_4 and concentrated under reduced pressure to afford lactam **15** (2.53 g, 4.93 mmol, 95% crude) which was used in the next reaction without purification.

2-Benzoyl-2-*O*-methyl-3-*O*-benzyl-2,3,4-trihydroxy-4-hydroxymethylpyrrolidin-5-one (16). Concentrated hydrochloric acid (2.5 mL) was added to a solution of crude acetal **15** (2.53 g, 4.93 mmol, 1 equiv.) in ordinary CH_3OH (80 mL) and the mixture heated to reflux. After 12 hours the reaction was cooled to room temperature and diluted with EtOAc (200 mL), then washed with saturated aqueous NaCl (3 × 200 mL). The organic phase was dried over Na_2SO_4 and concentrated under reduced pressure. Purification by flash column chromatography (5% CH_3OH–CH_2Cl_2) afforded lactam diol **16** (0.95 g, 2.56 mmol, 52%) as a white solid. **16**: ^{1}H NMR (400 MHz, CD_3OD), δ: 8.32 (d, J = 7.5 Hz, 2H), 7.61 (t, J = 7.5 Hz, 1H), 7.44–7.18 (m, 8H), 4.97 (d, J = 11.5 Hz, 1H), 4.40 (s, 1H), 4.35 (d, J = 11.5 Hz, 1H), 4.04–3.87 (m, 2H), 3.66 (d, J = 10.5 Hz, 1H), 3.18 (s, 3H). ^{13}C NMR (100 MHz, CD_3OD), δ: 196.6, 175.7, 134.9, 131.7, 129.5, 129.3, 129.2, 129.1, 129.0, 128.8, 85.6, 82.0, 75.0, 64.8, 63.6, 52.0. FTIR (neat), cm^{-1}: 3316(s), 2935(w), 1725(s), 1683(m), 1467(w), 1115(m). HRMS (MALDI-FTICR), *m/z*: Calcd for $C_{20}H_{21}NO_6$ (M + Na^+): 394.1261. Found: 394.1262. TLC (10% CH_3OH–CH_2Cl_2), *R*f: 0.35 (UV, DNP).

2-Benzoyl-2-*O*-methyl-3-*O*-benzyl-2,3,4-trihydroxy-4-acetoxymethylpyrrolidin-5-one (17). Acetic anhydride (0.34 mL, 3.6 mmol, 1.41 equiv.) was added to a solution of lactam diol **16** (0.95 g, 2.55 mmol, 1 equiv.), NEt_3 (0.43 mL, 3.08 mmol, 1.21 equiv.), and DMAP (0.12 g, 1.02 mmol, 0.40 equiv.) in THF (20 mL). After 12 hours the reaction was diluted with EtOAc (100 mL) and washed with saturated NH_4Cl (3 × 75 mL). The organic phase was dried over Na_2SO_4 and concentrated under reduced pressure. Purification by flash column chromatography (2% CH_3OH–CH_2Cl_2) yielded acetate **17** (0.71 g, 1.72 mmol, 68%). **17**: ^{1}H NMR (400 MHz, $CDCl_3$), δ: 8.25 (d, J = 7.5 Hz, 2H), 7.64 (t, J = 7.5 Hz, 1H), 7.51 (t, J = 7.5 Hz, 2H), 7.33 (br s, 1H), 7.19–7.13 (m, 3H), 6.72 (d, J = 6.8 Hz, 2H), 4.75 (d, J = 12.5 Hz, 1H), 4.50 (s, 1H), 4.48 (d, J = 10.0 Hz, 1H), 4.19 (d, J = 12.5 Hz, 1H), 3.83 (d, J = 10.0 Hz, 1H), 3.66 (br s, 1H), 3.30 (s, 3H), 2.12 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$), δ: 191.8, 173.4, 170.6, 135.6, 134.0, 133.9, 129.4, 128.7, 128.1, 127.9, 127.7, 95.6, 85.9, 78.6, 74.5, 62.9, 51.4, 21.0. FTIR (neat), cm^{-1}: 3319(m), 2927(w), 2853(w), 1732(s), 1693(m), 1451(w), 1376(w), 1234(m), 1100(m). HRMS (EI), *m/z*: Calcd for $C_{22}H_{23}NO_7$ (M^+): 413.1468. Found: 413.1442. TLC (5% CH_3OH–CH_2Cl_2), *R*f: 0.27 (UV, DNP).

2-Benzoyl-2-*O*-methyl-3-*O*-benzyl-2,3,4-trihydroxy-4-acetoxymethylpyrrolidin-5-one, methylthiomethyl ether (18). Acetic anhydride (9.20 mL, 97.5 mmol, 57.4 equiv.) and DMSO (9.20 mL, 130 mmol, 76.2 equiv.) were combined with acetate **17** (0.70 g, 1.70 mmol, 1 equiv.) and stirred under N_2. After 40 hours the reaction was diluted with CH_2Cl_2 (100 mL) and washed with saturated aqueous NaCl (2 × 100 mL) and H_2O (1 × 100 mL). The organic phase was dried over Na_2SO_4 and concentrated under reduced pressure to yield MTM ether **18** (0.70 g, 1.50 mmol, 90%). **18**: ^{1}H NMR (400 MHz, $CDCl_3$), δ: 8.29 (d, J = 8.0 Hz, 2H), 7.64 (t, J = 8.0 Hz, 1H), 7.51 (t, J = 8.0 Hz, 2H), 7.19–7.11 (m, 4H), 6.65 (d, J = 7.0 Hz, 2H), 5.10 (d, J = 13.0 Hz, 1H), 4.87 (d, J = 10.8 Hz, 1H), 4.77 (d, J = 10.8 Hz, 1H), 4.52–4.50 (m, 2H), 4.01 (d, J = 13.0 Hz, 1H), 4.67 (d, J = 10.0 Hz, 1H), 3.26 (s, 1H), 2.24 (s, 3H), 2.10 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$), δ: 191.8, 171.4, 169.8, 135.7, 133.9, 133.8, 129.3, 128.7, 128.1, 127.8, 127.5, 95.5, 86.6, 82.7, 74.6, 70.8, 58.6, 50.9, 21.0, 14.6. FTIR (neat), cm^{-1}: 2925(w), 1744(s), 1721(s), 1693(m), 1449(w), 1231(m), 1100(m), 1033(m). HRMS (EI), *m/z*: Calcd for $C_{24}H_{27}NO_7S$ (M + H^+): 474.1586. Found: 474.1568. TLC (5% CH_3OH–CH_2Cl_2), *R*f: 0.73 (UV, DNP).

Crystal structure determination of compound *epi*-18

Crystal data. $C_{24}H_{27}NO_7S$, 473.53, triclinic, a = 8.9592(7), b = 9.2569(6), c = 15.3512(11) Å, cell angle α = 79.4720(10), cell angle β = 83.1290(10), cell angle γ = 69.3510(10)°, U = 1169.19(15) Å^3, T = 218(2) K, space group $P\bar{1}$, Z = 2, μ = 0.183 mm^{-1}, 7140 reflections measured, 4097 independent reflections (R_{int} = 0.0196) which were used in all calculations. The final $wR(F^2)$ was 0.1614.‡

2-Benzoyl-2-*O*-methyl-3-*O*-benzyl-2,3,4-trihydroxy-4-hydroxymethylpyrrolidin-5-one, methylthiomethyl ether (19). Sodium methoxide (0.16 g, 2.96 mmol, 5.92 equiv.) was added to a solution of acetate **18** (0.24 g, 0.50 mmol, 1 equiv.) in THF (6 mL).

‡ CCDC reference number 283232. For crystallographic data in CIF or other electronic format see DOI: 10.1039/b512701g.

After 12 hours the reaction was diluted with EtOAc (50 mL) and washed with saturated aqueous NaCl (3 × 50 mL). The organic phase was dried over Na_2SO_4 and concentrated under reduced pressure to yield alcohol **19** (0.15 g, 0.33 mmol, 69%) as a white solid. **19**: ^{1}H NMR (400 MHz, $CDCl_3$), δ: 8.27 (d, J = 7.5 Hz, 2H), 7.63 (t, J = 7.5 Hz, 1H), 7.51 (t, J = 7.5 Hz, 2H), 7.35–7.10 (m, 4H), 6.69 (d, J = 7.0 Hz, 2H), 5.07 (d, J = 11.5 Hz, 1H), 4.88 (d, J = 11.5 Hz, 1H), 4.72 (d, J = 9.5 Hz, 1H), 4.49 (s, 1H), 4.16 (dd, J = 3.0 Hz, J = 13.0 Hz, 1H), 3.87 (dd, J = 11.0 Hz, J = 13.0 Hz, 1H), 3.75 (d, J = 9.5 Hz, 1H), 3.25 (s, 3H), 2.78 (dd, J = 3.0 Hz, J = 11.0 Hz, 1H), 2.34 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$), δ: 191.9, 172.4, 135.9, 134.0, 133.7, 129.2, 128.7, 128.0, 127.9, 127.8, 95.4, 86.4, 84.3, 74.8, 70.3, 57.8, 51.0, 14.8. FTIR (neat), cm^{-1}: 3439(m), 2956(m), 2923(m), 2853(m), 1716(s), 1693(s), 1458(w), 1097(s). HRMS (MALDI-FTICR), m/z: Calcd for $C_{22}H_{25}NO_6S$ (M + Na^+): 454.1295. Found: 454.1292. TLC (5% CH_3OH–CH_2Cl_2), Rf: 0.35 (UV, DNP).

2-Benzoyl-2-*O*-methyl-3-*O*-benzyl-2,3,4-trihydroxy-4-carbaldehydopyrrolidin-5-one, methylthiomethyl ether (20). To a −78 °C solution of oxalyl chloride (0.03 mL, 0.13 mmol, 1.10 equiv.) in CH_2Cl_2 (0.50 mL) was added DMSO (0.03 mL, 0.35 mmol, 2.70 equiv.) under N_2. After ten minutes alcohol **19** (0.06 g, 0.13 mmol, 1 equiv.) was added in CH_2Cl_2 (1 mL) and the mixture stirred for one hour. NEt_3 (0.06 mL, 0.43 mmol, 3.31 equiv.) was then added, and the reaction was warmed to room temperature. After two hours the reaction was diluted with CH_2Cl_2 (30 mL) and washed with saturated aqueous NaCl (3 × 30 mL). The organic phase was dried over Na_2SO_4 and concentrated under reduced pressure to afford aldehyde **20** (0.05 g, 0.12 mmol, 96%). **20**: ^{1}H NMR (400 MHz, $CDCl_3$), δ: 9.68 (s, 1H), 8.15 (d, J = 7.5 Hz, 2H), 7.56–6.89 (m, 9H), 5.46 (d, J = 5.5 Hz, 2H), 4.76 (s, 1H), 4.52 (d, J = 11.0 Hz, 1H), 4.35 (d, J = 11.0 Hz, 1H), 3.28 (s, 3H), 2.31 (s, 3H). MS (ESI), m/z: Calcd for $C_{22}H_{23}NO_6S$ (M + Na^+): 452. Found: 452. TLC (5% CH_3OH–CH_2Cl_2), Rf: 0.30 (UV, DNP).

(*Z*)-(3*R*,4*S*)-2,3,4-trihydroxynon-5-ene (22). Ethylmagnesium bromide (8.30 mL, 8.30 mmol, 1.0 M in THF, 1.52 equiv.) was added to a solution of aldehyde **21** (0.93 g, 5.46 mmol, 1 equiv.) in THF (20 mL) under N_2. After three hours the reaction was diluted with EtOAc (50 mL) and washed with saturated aqueous NaCl (3 × 50 mL). The organic phase was dried over Na_2SO_4 and concentrated under reduced pressure to yield alcohol **22** (0.89 g, 4.44 mmol, 82%) as a yellow oil. **22**: ^{1}H NMR (400 MHz, $CDCl_3$), δ: 5.71–5.54 (m, 2H), 5.08–5.04 (m, 1H), 4.82 (t, J = 8.5 Hz, 1H), 3.92–3.81 (m, 1H), 3.47–3.41 (m, 1H), 2.19–2.01 (m, 2H), 1.49–1.39 (m, 5H), 1.03–0.95 (m, 6H). ^{13}C NMR (100 MHz, $CDCl_3$), δ: 136.6, 124.2, 100.7, 80.7, 74.3, 71.0, 27.2, 21.2, 19.9, 14.2, 10.1. FTIR (neat), cm^{-1}: 3488(m), 2965(s), 2936(s), 2878(s), 1699(w), 1479(m), 1409(m), 1145(s), 1097(s), 905(m). TLC (5% CH_3OH–CH_2Cl_2), Rf: 0.68 (UV, DNP).

(*Z*)-(3*R*,4*S*)-3,4-dihydroxynon-5-en-2-one (23). To a −78 °C solution of oxalyl chloride (0.58 mL, 6.67 mmol, 1.50 equiv.) in CH_2Cl_2 (14 mL) was added DMSO (0.63 mL, 8.88 mmol, 2.00 equiv.) under N_2. After ten minutes alcohol **22** (0.89 g, 4.44 mmol, 1 equiv.) was added in CH_2Cl_2 (7 mL) and the mixture stirred for one hour. NEt_3 (1.90 mL, 13.63 mmol, 3.07 equiv.) was then added, and the reaction was warmed to room temperature. After two hours the reaction was diluted with CH_2Cl_2 (50 mL) and washed with saturated aqueous NH_4Cl (1 × 50 mL) and saturated aqueous NaCl (1 × 50 mL). The organic phase was dried over Na_2SO_4 and concentrated under reduced pressure to afford ketone **23** (0.85 g, 4.29 mmol, 96%) as a pale yellow oil. **23**: ^{1}H NMR (400 MHz, $CDCl_3$), δ: 5.62 (dt, J = 11.0 Hz, J = 7.5 Hz, 1H), 5.15–5.08 (m, 2H), 4.96 (t, J = 6.8 Hz, 1H), 4.36 (d, J = 8.0 Hz, 1H), 2.64–2.54 (m, 1H), 2.42–2.32 (m, 1H), 2.14–1.99 (m, 2H), 1.51 (d, J = 5.0 Hz, 3H), 0.99–0.95 (m, 6H). ^{13}C NMR (100 MHz, $CDCl_3$), δ: 209.5, 138.2, 122.1, 102.2, 83.5, 75.8, 33.4, 21.5, 19.6, 13.9, 6.8. FTIR (neat), cm^{-1}: 2971(m), 2938(m), 2879(m), 1719(s), 1460(m), 1408(m), 1146(s), 1094(m). HRMS (CI), m/z: Calcd for $C_{11}H_{19}O_3$ (M + H^+): 199.1334. Found: 199.1341. TLC (5% CH_3OH–CH_2Cl_2), Rf: 0.65 (UV, DNP).

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