Total Synthesis of Enantiopure Potassium Aeshynomate

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S Supporting Information

ABSTRACT: Potassium aeshynomate (1) is the leaf-opening factor of the nyctinastic plant *Aeshynomene indica* L. In this article a convenient and efficient strategy for the total synthesis of enantiomerically pure 1 is described, starting from the L-arabinose derived chiron *ent*-6. The realized synthetic scheme involves a postcoupling oxidation approach and securely determines the absolute configuration of the targeted natural product, which remained unknown until now.



INTRODUCTION

Many plant species and especially members of the Leguminosae family open their leaves during the day and fold them at night. This diurnal leaf movement, named nyctinasty,¹ is controlled by their internal biological clocks² and has been of great interest to researchers since Darwin's time.³ On a molecular basis, the circadian rhythmic movement of the leaves is initiated by the regulated balance of endogenous bioactive substances with opposing activities: leaf-opening and leaf-closing factors (LOFs and LCFs, respectively).⁴ Each nyctinastic plant uses unique leaf-movement factors, but these are usually conserved within the same genus.^{4–6} Continuous research has been conducted on isolation, structure elucidation^{4,7} and chemical synthesis^{8,9} of LOFs and LCFs, which are useful chemical probes in the elucidation of the molecular mechanisms governing the nyctinastic movement.^{4,5,9,10}

Potassium aeshynomate (1, Figure 1) is the leaf-opening factor of the nyctinastic plant *Aeshynomene indica* L., isolated in



Figure 1. Structures of potassium aeshynomate (1) and potassium (2R,3R)-2,3,4-trihydroxy-2-methylbutanoate (2).

small quantities by Yamamura et al.^{7g} A. *indica* (Indian jointvetch) is an invasive and noxious weed in rice paddies.¹¹ It is also occasionally responsible for toxic effects to certain animals.¹²

Several nyctinastic factors are phenolic compounds.¹³ Structure elucidation of **1** revealed an amide constituted of a phenolic moiety (caffeic acid) and a novel γ -amino acid subunit. Although the relative *anti*-stereochemistry of the γ -amino acid substituents was easily determined by NOE experiment, the absolute stereochemistry of this natural product remained undefined.^{7g} This *anti*-relation was later confirmed by Grison's group,^{8d} which reported the first stereoselective syntheses of 1 and its three stereoisomers using a Sharpless asymmetric dihydroxylation as the key-step. However, the absolute stereochemistry of all four different isomers was not assigned, and the compounds produced were not enantiopure.

A few years ago we reported the synthesis of potassium (2R,3R)-2,3,4-trihydroxy-2-methylbutanoate (2), a leaf-closing substance of the leguminous tropical plant *Leucaena leucocephala*, from D-arabinose.^{8c} The structural similarity between the amino acid residue of 1 and the hydroxy-carboxylic acid 2 has prompted us to investigate a practical synthetic scheme for the preparation of enantiopure 1, which could be used as an ecological friendly herbicide. Through this synthesis, the determination of the natural product absolute configuration was also an objective.

RESULTS AND DISCUSSION

On the basis of our previous synthesis^{8c} of (2R,3R)-2,3,4trihydroxy-2-methylbutanoate (2) and its resemblance with the targeted LOF (1) we envisioned a versatile retrosynthetic plan (Scheme 1), which uses as key-intermediate the protected amino-alcohol 5. Thus, according to path a, 1 may be derived from the coupling of caffeic acid (3) and the amino-ester 4. This approach is similar to the one previously described^{8d} but uses enantiopure 4, the oxidation product of 5. The latter could be prepared from diol 6, which, in turn, is easily accessible from D-(or L-)arabinose through erythrose acetonide (7). Alternatively (path b), the oxidation step could be performed just before the final deprotection step. The required alcohol 8 could be reached upon amide bond formation between 5 and protected caffeic acid derivative 9. The flexibility of this designed plan relies on its ability to use a common intermediate (5) to reach 1, in both paths. Moreover, since the absolute

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Scheme 1. Retrosynthetic Analysis



stereochemistry of the natural product remained undefined, its applicability on both D- and L-arabinose originated syntheses was also an additional crucial selection factor.

We have initially made the assumption that potassium aeshynomate (1) shares with 2 not only common structural features but the same absolute configuration as well. Therefore, diol 6, which is easily prepared on a multigram scale from D-arabinose (in practically 4 steps^{8c,14-16}), served as the starting material of our first attempted synthesis of 1 (Scheme 2).

Scheme 2. Synthesis of Amine 13^a



^{*a*}(a) Refs 8c, 14–16; (b) NaH, THF, rt, 30 min, then TBSCl, 24 h, 86% (combined yield); (c) phthalimide, Ph₃P, DIAD, THF, 0 °C to rt, 24 h, 99%; (d) $H_2NCH_2CH_2NH_2$, EtOH, 70 °C, 3 h, 97%. DIAD = diisopropyl azodicarboxylate, TBS = *tert*-butyldimethylsilyl.

Notably, the quaternary center is unambiguously formed with the correct stereochemistry during a stereospecific aldol reaction between the corresponding D-erythrose acetonide (7) and formaldehyde. In order to distinguish the two primary hydroxyl groups in 6 we have applied a modification of our previously published monosilylation protocol.¹⁶ Thus, we realized that by decreasing the addition rate of electrophile the more hindered desired silyl ether 11 was formed as the predominant product (ratio of ca. 1.4:1). Next, a Mitsunobu reaction with phthalimide¹⁷ was employed for the substitution of the free hydroxyl group in 11. Unmasking the amine in the resulted 12 using various hydrazinolysis protocols proved unproductive. In the best case only 20% of 13 was obtained. In

contrast, the reaction in ethanolic ethylenediamine¹⁸ gave smoothly the same amine. It is worth mentioning that for large scale runs it was more convenient to perform the Mitsunobu reaction using the mixture of regioisomers 10 and 11 since, because of steric hindrance, the latter selectively gives the corresponding phthalimide. This event prompted us to examine the same reaction with diol 6, but neither 12 nor its regioisomer were formed. In any case, the unwanted regioisomer (10) was recycled to diol 6 applying a simple TBAF mediated desilylation.

Having a few grams of amine 13 in our hands¹⁹ we then sought to investigate a suitable way to reach diol 19 (Scheme 3). Thus, protection of the amine group gave carbamate 14, which was subsequently desilylated to primary alcohol 15, almost quantitatively. The next step involved oxidation of the free hydroxyl group. It was expected that this reaction would easily produce the Cbz-protected lactam 16 rather than the corresponding carboxylic acid.²⁰ However, in most cases, this transformation failed to produce either of them in a clean way under various oxidative conditions²¹ tested (Table 1). Instead, a complicated reaction mixture was formed from which 16 was isolated in rather low yields. Unprotected lactam 17 was formed, again in low yield, when the combination of TEMPO/ NaClO₂/NaOCl was used.²² To our delight the TEMPO/ NaOCl/KBr protocol²³ was more reliable, furnishing 16 in 83%. The transformation of 16 to ester 18 was achieved using a two-step procedure, which involved the opening of lactam ring with LiOH followed by esterification with N,N-dimethylformamide di-tert-butyl acetal.²⁴ Lactam 17 was also isolated as byproduct. All attempts to purify the intermediate carboxylic acid or to form the tert-butyl ester with other methods (e.g., DCC, ^tBuOH and CuCl²⁵) were unsuccessful. Removal of the acetonide in 18 under mild conditions (PPTS) produced diol 19. At this point, comparing the optical rotation of this advanced derivative with the one reported from Grison et al.^{8d} we came to the conclusion that our original hypothesis was incorrect, and the natural product has the opposite absolute configuration.²⁶

Before repeating the synthesis using L-arabinose as starting material we were curious to further explore *path a* of the designed retrosynthetic analysis. Therefore, we proceeded with carbamate **19** (Scheme 4). Palladium catalyzed hydrogenolysis uneventfully yielded the free amine **20**, which was then coupled to caffeic acid in the presence of BOP.^{8d} Surprisingly, after several chromatographic purifications, we could not obtain pure amide **21**.²⁷ An attempt to purify starting amine **20** before coupling led to partial decomposition.

Armed with the knowledge gained with the derivatives of Darabinose and puzzled with the coupling result of amino-ester **20** we decided to examine the second synthetic approach (*path b*) starting with L-arabinose. For this reason, an identical approach to the one realized previously (Scheme 2) was adopted in order to reach enantiomerically pure amine **25** in a very good overall yield (Scheme 5).

The amide forming reactions for the L-series were first tested with amino-alcohol **26** (Scheme 6). This was easily obtained from **25** upon desilylation. Since *path b* involved a postcoupling oxidation step we were forced to use a protected caffeic acid derivative. BOP-mediated coupling of **26** with the bisilylated carboxylic acid **28**²⁹ was disappointing. A complicated reaction mixture was formed, while almost half of the starting material remained unreacted.

Scheme 3. Synthesis of Diol 19^a



^{*a*}(a) CbzCl, Na₂CO₃, CH₂Cl₂, H₂O, 0 °C, 2 h, 91%; (b) TBAF, THF, rt, 90 min, 100%; (c) see Table 1; (d) (1) LiOH, THF, H₂O, 0 °C, 30 min; (2) Me₂NCH(O^tBu)₂, PhH, 80 °C, 2 h, 35% of 17 and 52% of 18 (overall from 16); (e) PPTS, MeOH, 45 °C, 24 h, 73%. Cbz = carboxybenzyl, PPTS = pyridinium *p*-toluenesulfonate, TBAF = tetrabutyl ammonium fluoride.

Table 1. Oxidation of Alcohol 15

entry	conditions ^a	product	yield (%) ^b
1	А	-	_
2	В	-	-
3	С	17	25
4	D	16	34
5	E	16	53
6	F	16	83

^{*a*}Reaction conditions. A: TEMPO, TCCA, NaHCO₃, NaBr, acetone, H₂O, 0 °C, 2 h. B: TEMPO, BAIB, MeCN, H₂O, rt, 24 h. C: TEMPO, NaClO₂, NaOCl, NaH₂PO₄/Na₂HPO₄ buffer (pH 6.7), MeCN, 35 °C, 30 h. D: TPAP, NMO, MeCN, rt, 3 h. E: PDC, DMF, rt, 24 h. F: TEMPO, NaOCl, KBr, NaHCO₃, acetone, 0 °C, 3 h. ^{*b*}Yields refer to isolated products. BAIB = bisacetoxyiodobenzene, PDC = pyridinium dichromate, NMO = *N*-methyl morpholine *N*-oxide, TCCA = trichloroisocyanuric acid, TEMPO = (2,2,6,6-tetramethyl-piperidin-1yl)oxyl, TPAP = tetrapropylammonium peruthenate.

Scheme 4. Synthesis of Amide 21^a



^{*a*}(a) H₂, Pd/C, MeOH, rt, 24 h, 100%; (b) caffeic acid (3), BOP, Et₃N, DMF, rt, 2 h, 51% (see ref 27). BOP = (benzotriazol-1-yloxy)tris(dimethylamino)phosphonium hexafluorophosphate.

Then, we turned our attention back to amine **25**. We were pleased to discover that couplings of **25** with diacetate **31**³⁰ gave the expected amide **29** in moderate yields employing either BOP or DCC (Scheme 7). However, proceeding with the deprotection step we realized that **29** mostly decomposed when exposed to neutral desilylation conditions (TBAF/AcOH). This event could only be attributed to the sensitivity of the phenolic acetyl groups.

To overcome this obstacle, another protected caffeic acid derivative had to be selected. Having in mind^{8d} that the final deprotection step (acetonide and *tert*-butyl ester) required the use of acidic conditions we concluded that probably caffeic acid

Scheme 5. Synthesis of Amine 25^a



"(a) Refs 14, 15, 28; (b) NaH, THF, rt, 30 min, then TBSCl, 24 h, 90% (combined yield); (c) phthalimide, Ph₃P, DIAD, THF, 0 °C to rt, 24 h, 93%; (d) $H_2NCH_2CH_2NH_2$, EtOH, 70 °C, 3 h, 96%.

Scheme 6. Coupling Reaction of Amino-Alcohol 26^a



^a(a) TBAF, THF, rt, 3 h, 92% ; (b) 28, BOP, Et₃N, DMF, rt, 12 h.

Scheme 7. Coupling Reaction of Amine 25 with 31^a



^{*a*}(a) **31**, BOP, Et_3N , CH_2Cl_2 , rt, 3 h, 52%; (b) **31**, DCC, DMAP, CH_2Cl_2 , rt, 24 h, 43%; (c) TBAF, AcOH, THF, rt, 2 h. DCC = dicyclohexylcarbodiimide, DMAP = 4-dimethylaminopyridine.

С

Scheme 8. Completion of the Synthesis^a



"(a) 34, DCC, DMAP, CH_2Cl_2 rt, 24 h, 97%; (b) EDC, DMAP, CH_2Cl_2 , rt, 24 h, 99%; (c) TBAF, AcOH, THF, rt, 48 h, 92%; (d) TEMPO, NaOCl, KBr, NaHCO₃, acetone, 0 °C, 3 h, 82%; (e) (1) LiOH, 1,4-dioxane, H₂O, 10 °C, 20 min; (2) Me₂NCH(O'Bu)₂, PhH, 80 °C, 3 h, 51% of 36, 35% of 37 and 30% of 38 (overall from 35); (f) LiOH, MeOH, H₂O, 0 °C, 45 min, 100%; (g) TFA, rt, 2 h; (h) PPTS, MeOH, 45 °C, 24 h, 98%; (i) TFA, rt, 20 min, 100%; (j) MeOK, MeOH, rt, 5 min, 100%. EDC = 3-(ethyliminomethyleneamino)-*N*,*N*-dimethylpropan-1-amine hydrochloride, MOM = methoxymethyl, TFA = trifluoroacetic acid.

derivative 34^{31} (Scheme 8) would be one of the most suitable to use. Formation of the amide 32 was smoothly achieved when 34 was coupled to amine 25 in the presence of DCC or EDC, with the latter giving a reaction mixture easier to purify. Deprotection of 32 to the corresponding primary alcohol (33) and oxidation applying the earlier tested TEMPO protocol (Scheme 3) both occurred uneventfully. The resulted lactam (35) was then shortly exposed to lithium hydroxide in a mixture of 1,4-dioxane and water to give the intermediate carboxylic acid, which, without purification, was esterified upon reaction with N,N-dimethylformamide di-tert-butyl acetal. Along with the desired ester (36), tert-butyl ester 37 and lactam 38 were also obtained because of the initial rupture of caffeic acid. In contrast to the analogous lactam opening of 16 (Scheme 3), a reaction run in THF-water was found to be relatively slower and subsequently produced ester 36 in lower yield (40%), whereas aqueous methanol gave quantitatively methyl ester 39.32 The final steps required removal of the protecting groups (MOM, tert-butyl and acetonide) and transformation to the potassium salt. The first global deprotection approach involved treatment of 36 with neat TFA at room temperature. Although we were able to detect by NMR the formation of the fully unprotected amide 40, the major product remained the one having the acetonide intact

after 2 h. At this point we started to detect decomposition. Aqueous TFA was even worse, causing faster decomposition. Consequently, a stepwise deprotection approach was adopted. Thus, MOM groups and acetonide were selectively removed when a methanolic solution of **36** was heated in the presence of PPTS. Ester **41** was stable enough to be chromatographically purified. Stirring **41** in neat TFA for a few minutes led quantitatively to amide **40**, which was very carefully titrated³³ with potassium methanolate in methanol^{8d} to deliver the targeted natural product, potassium aeshynomate (1).³⁴ The ¹H and ¹³C NMR chemical shifts of our synthetic **1** were in agreement³⁵ with those reported by Grison et al.^{8d}

CONCLUSION

The work described in this article presents a convenient and efficient synthetic approach toward the LOF compound potassium aeshynomate (1). This total synthesis was accomplished using the readily available L-arabinose derived chiron (diol *ent*-6) employing a versatile chiral pool route and furnishing enantiopure 1 in 18% overall yield in a 10-step sequence.³⁶ Moreover, the absolute stereochemistry of 1 was securely determined. Because of its compactness and the ability to scale up involving multigram quantities, this work represents

an attractive scheme for the facile preparation of the targeted natural product.

EXPERIMENTAL SECTION

General Procedures. All commercially available reagent-grade chemicals were used without further purification. All solvents were purified by standard procedures before use. Dry solvents were prepared by literature methods and stored over molecular sieves. Whenever possible, reactions were monitored using commercially available precoated TLC plates (layer thickness 0.25 mm) of silica gel 60 F_{254} . Compounds were visualized by use of a UV lamp and/or using as stain p-anisaldehyde-methanolic solution upon warming. Flash column chromatography was performed in the usual way with silica gel 60 M (0.04-0.063 mm) using as eluents the solvents indicated in each case. Yields are reported for isolated compounds with >96% purity established by NMR unless otherwise indicated. Optical rotations were determined at room temperature with an automatic digital polarimeter. FT-IR spectra were obtained using KBr pellets or neat. NMR spectra were recorded with a 300 MHz spectrometer (¹H: 300 MHz, ¹³C: 75 MHz) or a 500 MHz spectrometer (¹H: 500 MHz, ¹³C: 125 MHz) in the deuterated solvent indicated. Chemical shifts are given in ppm and J values in Hz using solvent or TMS as an internal reference. Assignments of protons were confirmed on the basis of 2D NMR experiments (1H-1H COSY, HSQC and HMBC, recorded using a standard pulse program library). High resolution mass spectra (HRMS) were recorded on microTOF single-quadrupole mass spectrometer. For each known compound ¹H and/or ¹³C NMR along with their HRMS spectra were used to establish identity.

1-O-(tert-Butyldimethylsilyl)-2,3-O-isopropylidene-2-Cmethyl-D-erythritol (11). NaH 95% (390 mg, 16.4 mmol) was suspended in dry THF (100 mL), and a solution of diol $6^{8c,14-16}$ (2.74 g, 15.5 mmol) in dry THF (100 mL) was added at rt under an Ar atmosphere. The mixture was stirred vigorously for 30 min, and then a solution of TBSCl (2.35 g, 15.5 mmol) in dry THF (100 mL) was added dropwise over a period of 45 min. The resulting suspension was stirred for 24 h at rt. Then, the reaction mixture was poured in diethyl ether (200 mL). The resulting slurry was washed with a 10% aq. Na₂CO₃ solution (200 mL), the aqueous phase was extracted with EtOAc (4×200 mL), and the combined organic phases were dried over Na2SO4. The solvents were removed under reduced pressure, and the residual oil was purified by flash column chromatography (5% EtOAc in hexanes) to give silvl ether 11 (2.28 g, 51%) and silvl ether 10 (1.59 g, 35%) as a white amorphous solid and a greenish oil, respectively. ¹H and ¹³C NMR spectra of 10 and 11 were identical with those reported in the literature.¹⁶ 10: HRMS (ESI) calcd. for $C_{14}H_{30}NaO_4Si$ [M + Na]⁺ 313.1806, found 313.1808. 11: HRMS (ESI) calcd. for $C_{14}H_{30}NaO_4Si [M + Na]^+$ 313.1806, found 313.1809.

2-(((4R,5S)-5-(tert-Butyldimethylsilyloxymethyl)-2,2,5-trimethyl-1,3-dioxolan-4-yl)methyl)isoindoline-1,3-dione (12). A mixture of alcohol 11 (820 mg, 2.8 mmol), phthalimide (830 mg, 5.6 mmol) and triphenylphosphine (1.48 g, 5.6 mmol) was dissolved in dry THF (45 mL) under an argon atmosphere and then was cooled to 0 °C. DIAD (1.1 mL, 5.6 mmol) was added dropwise at 0 °C, and the mixture was left to stir at rt for 24 h. Then it was concentrated under reduced pressure. The residual yellow oil was purified by flash column chromatography (5% EtOAc in hexanes) to give imide 12 (1.17 g, 99%) as a pale yellow oil: $R_f = 0.36$ (25% EtOAc in hexanes); $[\alpha]^{25}_{D} =$ +23.1 (c 4.33, CHCl₃); FTIR (neat) 3022, 2982, 2932, 2858, 1720, 1617 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 7.82–7.80 (m, 2H, C= CH), 7.68-7.66 (m, 2H, C-CH=CH), 4.18 (d, J = 10.2 Hz, 1H, CH-O), 4.08 (dd, J = 13.9, 10.7 Hz, 1H, CHH-N), 3.86 (d, J = 14.3 Hz, 1H, CHH-N), 3.79 (d, J = 10.1 Hz, 1H, CHH-O), 3.30 (d, J = 10.1 Hz, 1H, CHH-O), 1.37 (s, 6H, CH₃-C-CH₃ and C-CH₃), 1.24 (s, 3H, CH₃-C-CH₃), 0.88 (s, 9H, C(CH₃)₃), 0.07 (s, 3H, Si-CH₃), 0.06 (s, 3H, Si-CH₃) ppm; ¹³C NMR (125 MHz, CDCl₃) δ 168.1, 133.7, 132.1, 123.1, 108.0, 81.2, 80.5, 65.1, 37.9, 28.5, 26.5, 25.7, 22.0, 18.0, -5.6, -5.8 ppm; HRMS (ESI) calcd. for C₂₂H₃₃NNaO₅Si [M + Na]⁺ 442.2020, found 442.2027.

((4*R*,5*S*)-5-(*tert*-Butyldimethylsilyloxymethyl)-2,2,5-trimethyl-1,3-dioxolan-4-yl)methanamine (13). Ethylenediamine (4.6 mL, 69 mmol) was added dropwise to a magnetically stirred solution of imide 12 (3.63 g, 8.7 mmol) in EtOH (260 mL) under an Ar atmosphere at rt. The reaction mixture was heated at 70 °C for 3 h, at which point TLC indicated complete consumption of the starting material. The solvents were removed under reduced pressure, and the residual oil was purified by flash column chromatography (15% MeOH in CH₂Cl₂) to give amine 13 (2.43 g, 97%) as a yellow oil: $R_f = 0.58$ (17% MeOH in CH₂Cl₂); $[\alpha]^{25}_{D} = -8.90$ (c 2.83, CHCl₃); FTIR (neat) 3462, 3392, 2981, 2955, 2932, 2856 cm⁻¹; ¹H NMR (500 MHz, $CDCl_3$) δ 3.81 (t, J = 6.2 Hz, 1H, CH–O), 3.66 (d, J = 9.9 Hz, 1H, CHH-O), 3.21 (d, J = 9.9 Hz, 1H, CHH-O), 3.00-2.92 (m, 2H, CH₂-N), 1.71 (br s, 2H, NH₂), 1.39 (s, 3H, CH₃-C-CH₃), 1.37 (s, 3H, CH₃-C-CH₃), 1.32 (s, 3H, C-CH₃), 0.89 (s, 9H, C(CH₃)₃), 0.06 (2 \times s, 6H, Si(CH_3)_2) ppm; ^{13}C NMR (125 MHz, CDCl_3) δ 106.9, 84.9, 81.3, 65.2, 41.2, 28.4, 26.4, 25.7, 22.3, 18.0, -5.7, -5.8 ppm; HRMS (ESI) calcd. for $C_{14}H_{32}NO_3Si [M + H]^+ 290.2146$, found 290.2149.

(4R,5S)-Benzyl ((5-(tert-butyldimethylsilyloxymethyl)-2,2,5trimethyl-1,3-dioxolan-4-yl)methyl)carbamate (14). Amine 13 (245 mg, 0.85 mmol) was dissolved in CH_2Cl_2 (4.2 mL), and a solution of Na2CO3 (377 mg, 3.55 mmol) in water (4.2 mL) was added. The reaction was cooled at 0 °C, benzyl chloroformate (0.36 mL, 2.54 mmol) was dropwise added, and the mixture was vigorously stirred for 2 h at the same temperature. Then, the organic layer was separated, the aqueous one was extracted with CH_2Cl_2 (6 × 5 mL), and the combined organic extracts were dried over Na2SO4 and evaporated in vacuo. The residual oil was purified by flash column chromatography (8% EtOAc in hexanes) to give carbamate 14 (327 mg, 91%) as a pale yellow oil: $R_f = 0.55$ (25% EtOAc in hexanes); $[\alpha]^{25}_{D} = -9.10$ (c 1.50, CHCl₃); FTIR (neat) 3358, 3021, 2984, 2954, 2930, 2854, 1730, 1509 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 7.34-7.29 (m, 5H, ArH), 5.45 (br s, 1H, NH), 5.10 (br s, 2H, ArCH₂), 3.90 (t, J = 6.6 Hz, 1H, CH–O), 3.67 (d, J = 10.0 Hz, 1H, CHH-O), 3.60– 354 (m, 1H, CHH-N), 3.45-3.40 (m, 1H, CHH-N), 3.22 (d, J = 10.0 Hz, 1H, CHH-O), 1.36 (s, 3H, CH₃-C-CH₃), 1.33 (s, 3H, CH₃-C-CH₃), 1.31 (s, 3H, C-CH₃), 0.90 (s, 9H, C(CH₃)₃), 0.08 (s, 6H, Si(CH₃)₂) ppm; ¹³C NMR (125 MHz, CDCl₃) δ 156.2, 136.5, 128.3, 127.9, 127.7, 107.3, 81.4, 80.8, 66.5, 65.1, 40.1, 28.3, 26.3, 25.7, 22.5, 18.0, -5.7, -5.8 ppm; HRMS (ESI) calcd. for C₂₂H₃₇NNaO₅Si [M + Na]⁺ 446.2333, found 446.2327.

(4R,5S)-Benzyl ((5-hydroxymethyl-2,2,5-trimethyl-1,3-dioxolan-4-yl)methyl)carbamate (15). Silyl ether 14 (327 mg, 0.77 mmol) was dissolved in THF (7.7 mL), and a 1.0 M solution of TBAF in THF (0.80 mL, 0.80 mmol) was added under an Ar atmosphere at rt. After 90 min of vigorous stirring, EtOAc (5 mL) was added, and the mixture was washed with saturated brine (4 mL). The organic layer was separated, and the aqueous one was back-extracted with EtOAc (6 \times 5 mL). The combined organic extracts were dried over Na₂SO₄ and evaporated in vacuo. The residue was purified by flash column chromatography (30% EtOAc in hexanes) to give alcohol 15 (238 mg, 100%) as a pale yellow oil: $R_f = 0.32$ (50% EtOAc in hexanes); $[\alpha]^2$ = +5.75 (c 3.23, CHCl₃); FTIR (neat) 3447, 3360, 3069, 3031, 2987, 2932, 2872, 1708, 1522 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 7.37-7.31 (m, 5H, ArH), 5.24 (br s, 1H, NH), 5.12 (s, 2H, ArCH₂), 3.97 (dd, J = 6.9, 3.7 Hz, 1H, CH-O), 3.61-3.54 (m, 1H, CHH-O), 3.47 (br s, 2H, CH₂-N), 3.42-3.37 (m, 1H, CHH-O), 1.43 (s, 3H, CH₃-C-CH₃), 1.38 (s, 3H, CH₃-C-CH₃), 1.33 (s, 3H, C-CH₃) ppm; $^{13}\mathrm{C}$ NMR (125 MHz, CDCl_3) δ 156.4, 136.4, 128.5, 128.2, 128.1, 108.0, 81.6, 81.5, 66.9, 65.1, 39.9, 28.2, 26.4, 22.0 ppm; HRMS (ESI) calcd. for C₁₆H₂₃NNaO₅ [M + Na]⁺ 332.1468, found 332.1460.

Oxidation of 15 with TEMPO/NaClO₂/NaOCl. Alcohol 15 (90 mg, 0.3 mmol) was dissolved in acetonitrile (0.5 mL). A pH 6.7 buffer phosphate solution Na₂HPO₄/NaH₂PO₄ (1 mL), NaClO₂ (50 mg, 0.6 mmol) and TEMPO (30 mg, 0.19 mmol) were sequentially added at room temperature. The reaction mixture was heated at 35 °C, and a 5% aq. NaOCl solution (3 drops) was added. The reaction mixture was further stirred for 6 h at 35 °C. Then, additional amounts of TEMPO (10 mg, 0.06 mol) and the NaOCl solution (1 drop) were added, and the mixture was stirred for 24 h at 35 °C. After that, water was added (1 mL), and the PH of mixture was adjusted initially to 8

with a 2.0 M aq. NaOH and finally to 9 with a 6% aq. Na₂SO₃ solution. The reaction mixture was cooled to rt, extracted with diethyl ether (4 \times 10 mL), and the aqueous layer was acidified (pH 5) with a 1% aq. HCl solution. The aqueous layer was extracted with EtOAc (4 \times 10 mL), and the combined organic phases were dried over Na₂SO₄ and evaporated in vacuo. Purification of the residue by flash column chromatography (2% MeOH in EtOAc) gave lactam 17 (13 mg, 25%) as a white solid. The data for 17 matches that reported for 17 in Scheme 3.

(3aR,6aR)-Benzyl 2,2,3a-trimethyl-4-oxodihydro-3aH-[1,3]dioxolo[4,5-c]pyrrole-5(4H)-carboxylate (16). Oxidation with TPAP/NMO. Alcohol 15 (90 mg, 0.3 mmol) and N-methyl morpholine N-oxide monohydrate (390 mg, 3.0 mmol) were dissolved in acetonitrile (1.2 mL). TPAP (10 mg, 0.03 mmol) was added, and the mixture was stirred for 3 h at rt. Upon completion, the reaction was quenched with an excess of 2-propanol. The solvent was evaporated in vacuo, and the residue was filtered over a pad of silica gel using CH_2Cl_2 . The filtrate concentrated under reduced pressure, and the crude product was subjected to flash column chromatography (15% EtOAc in hexanes) to give lactam 16 (30 mg, 34%) as a colorless oil. The data for 16 matches that reported for 16 in Scheme 3.

Oxidation with PDC. PDC (565 mg, 1.5 mmol) was added to a solution of alcohol 15 (90 mg, 0.3 mmol) in dry DMF (2 mL). The orange suspension was stirred for 24 h at rt and quenched by the addition of water (1 mL). The solution was extracted with diethyl ether (5 \times 5 mL). The combined organic layers were washed with water (2 mL) and saturated brine (2 mL), dried over Na₂SO₄, and the volatiles were evaporated. The residue was purified by flash column chromatography (15% EtOAc in hexanes) to give lactam 16 (47 mg, 53%) as a colorless oil. The data for 16 matches that reported for 16 in Scheme 3.

Oxidation with TEMPO/NaOCI/KBr. A solution of alcohol 15 (238 mg, 0.77 mmol) in acetone (4 mL) was added to a 5% aq. NaHCO₃ solution (2 mL) containing KBr (10 mg, 0.08 mmol), and the resulting slurry was cooled to 0 °C. TEMPO (133 mg, 0.85 mmol) was then added followed by 5% aq. NaOCl solution (2 mL). The mixture was stirred for 3 h at 0 °C, and then the reaction was quenched by addition of a 5% aq. HCl solution (0.1 mL). The mixture was extracted with CH_2Cl_2 (4 × 5 mL). The combined organic extracts were dried over Na₂SO₄ and evaporated in vacuo. The residue was purified by flash column chromatography (15% EtOAc in hexanes) to give lactam 16 (195 mg, 83%) as a colorless oil: $R_f = 0.54$ (50% ethyl acetate in hexanes); $[\alpha]_{D}^{25} = -11.6$ (c 2.08, CHCl₃); FTIR (neat) 3020, 2990, 2925, 2853, 1784, 1702, 1458 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 7.43 (d, J = 7.4 Hz, 2H, ArH), 7.37-7.31 (m, 3H, ArH), 5.28 (s, 2H, ArCH₂), 4.32 (d, J = 4.0 Hz, 1H, CH–O), 3.97 (d, J = 12.6 Hz, 1H, CHH-N), 3.74 (dd, J = 12.6, 4.1 Hz, 1H, CHH-N), 1.47 (s, 3H, C-CH₃), 1.41 (s, 3H, CH₃-C-CH₃), 1.38 (s, 3H, CH₃-C-CH₃) ppm; $^{13}\mathrm{C}$ NMR (125 MHz, CDCl_3) δ 173.0, 151.1, 134.8, 128.4, 128.3, 128.0, 111.7, 83.7, 76.1, 68.2, 47.3, 27.1, 26.3, 18.3 ppm; HRMS (ESI) calcd. for C₁₆H₁₉NNaO₅ [M + Na]⁺ 328.1155, found 328.1160.

(4R,5R)-tert-Butyl 5-((benzyloxycarbonyl)aminomethyl)-2,2,4-trimethyl-1,3-dioxolane-4-carboxylate (18). To a solution of lactam 16 (106 mg, 0.35 mmol) in THF (3.8 mL) was dropwise added over a period of 3 min a 1.0 M aq. LiOH solution (1 mL) at 0 °C. The reaction mixture was stirred vigorously for 30 min, and then the solvent was evaporated in vacuo. The aqueous phase was carefully acidified to pH 3 by addition of 10% aq. AcOH solution at 0 $^\circ\text{C}$ and extracted with diethyl ether (6×4 mL). The combined extracts were washed with saturated brine (5 mL) and dried over MgSO4. Evaporation of the solvent gave intermediate carboxylic acid, which was used without further purification in the next step. This was dissolved in dry benzene (4 mL) and N,N-dimethylformamide di-tertbutyl acetal (0.33 mL, 1.39 mmol) was dropwise added to the refluxing mixture within 20 min. The reaction mixture was refluxed for 2 h, cooled and washed with water (5 mL), a saturated aq. NaHCO3 solution $(2 \times 5 \text{ mL})$ and saturated brine (5 mL). The aqueous layers were back-extracted with CH_2Cl_2 (3 × 5 mL), and the combined organic extracts were dried over MgSO4 and evaporated in vacuo. The residue was purified by flash column chromatography initially with

10% EtOAc in hexanes to obtain ester 18 (68 mg, 52% over 2 steps) and then with 2% MeOH in EtOAc to obtain lactam 17 (21 mg, 35% over 2 steps). 18: White amorphous solid; $R_f = 0.65$ (50% EtOAc in hexanes); $[\alpha]^{25}_{D} = +9.86$ (c 1.75, CHCl₃); FTIR (neat) 3346, 3064, 2982, 2942, 2874, 1720, 1706, 1541 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 7.37–7.31 (m, 5H, ArH), 5.24 (br s, 1H, NH), 5.12 (s, 2H, $ArCH_{2}$), 3.98 (t, I = 6.4 Hz, CH-O), 3.50–3.45 (m, 1H, CHH-N), 3.40-3.34 (m, 1H, CHH-N), 1.55 (s, 3H, CH₃-C-CH₃), 1.49 (s, 12H, C(CH₃)₃ and C-CH₃), 1.38 (s, 3H, CH₃-C-CH₃) ppm; ¹³C NMR (125 MHz, CDCl₃) δ 171.8, 156.3, 136.4, 128.5, 128.2, 128.1, 110.0, 82.8, 82.54, 82.49, 66.9, 41.3, 28.0, 26.8, 26.6, 23.6 ppm; HRMS (ESI) calcd. for $C_{20}H_{29}NNaO_6 [M + Na]^+ 402.1887$, found 402.1881. 17 {(3aR,6aR)-2,2,3a-trimethyldihydro-3aH-[1,3]dioxolo[4,5-c]pyrrol-4(5H)-one}: White amorphous solid; $R_f = 0.31$ (EtOAc); $[\alpha]^{25}_{D} =$ -29.6 (c 1.21, MeOH); FTIR (KBr) 3278, 2988, 2935, 1712, 1479 cm⁻¹; ¹H NMR (500 MHz, CD₃OD) δ 4.42 (d, J = 3.3 Hz, CH–O), 3.50 (dd, J = 11.9, 4.1 Hz, CHH-N), 3.32 (d, J = 11.9, 1H, CHH-N), 1.39 (s, 3H, CH₃-C-CH₃), 1.34 (s, 6H, C-CH₃ and CH₃-C-CH₃) ¹³C NMR (125 MHz, CD₃OD) δ 179.3, 112.8, 84.7, 81.4, 45.5, ppm; 27.8, 27.1, 19.0 ppm; HRMS (ESI) calcd. for C₈H₁₃NNaO₃ [M + Na]⁺ 194.0788, found 194.0795.

(2R,3R)-tert-Butyl 4-((benzyloxycarbonyl)amino)-2,3-dihydroxy-2-methylbutanoate (19). PPTS (477 mg, 1.9 mmol) was added to a magnetically stirred solution of acetonide 18 (72 mg, 0.19 mmol) in MeOH (2 mL), and the mixture was heated under an Ar atmosphere for 24 h at 45 °C. Then, the reaction mixture was cooled to rt and neutralized with solid NaHCO₃₁ and the solvent was evaporated in vacuo. The residue was purified by flash column chromatography (50% EtOAc in hexanes) to give diol 19 (47 mg, 73%) as a pale yellow oil: $R_f = 0.26$ (50% EtOAc in hexanes); $[\alpha]_{D}^{25} =$ +13.5 (c 4.50, CH₂Cl₂); FTIR (neat) 3480, 3320, 3058, 2980, 2946, 2880, 1718, 1708, 1535 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 7.37– 7.31 (m, 5H, ArH), 5.20 (br s, 1H, NH), 5.13 (d, J = 12.2 Hz, 1H, ArCHH) and 5.09 (d, J = 12.2 Hz, 1H, ArCHH), 3.72 (br s, 1H, CH-O), 3.52-3.48 (m, 1H, CHH-N), 3.50 (br s, 1H, OH), 3.11 (m, 1H, CHH-N), 2.50 (br d, J = 6.4 Hz, 1H, OH), 1.52 (s, 9H, C(CH₃)₃), 1.43 (s, 3H, C-CH₃) ppm; ¹³C NMR (125 MHz, CDCl₃) δ 174.1, 156.7, 136.3, 128.5, 128.14, 128.10, 83.8, 75.8, 75.2, 66.8, 42.8, 27.9, 22.7 ppm; HRMS (ESI) calcd. for $C_{17}H_{25}NNaO_6$ [M + Na]⁺ 362.1574, found 362.1577.

(2*R*,3*R*)-*tert*-Butyl 4-amino-2,3-dihydroxy-2-methylbutanoate (20). Carbamate 19 (40 mg, 0.12 mmol) was used to prepare 20 according to a known hydrogenolysis procedure.^{8d} The reaction was performed for 24 h under a H₂ atmosphere (1 Atm). Amine 20 (25 mg, 100%) was used in the next step without further purification.

(2R,3R)-tert-Butyl 4-((E)-3-(3,4-dihydroxyphenyl)acrylamido)-2,3-dihydroxy-2-methylbutanoate (21). Amine 20 (25 mg, 0.12 mmol) was used to prepare amide 21 (22 mg, 51%) according to a known coupling procedure.^{8d} ¹H and ¹³C spectra of the product were identical to those reported in the literature^{8d} (see ref 27).

1-O-(tert-Butyldimethylsilyl)-2,3-O-isopropylidene-2-C-methyl-L-erythritol (22). Silyl ethers **22** and **23** were prepared from diol *ent-*6^{14,15,28} following the procedure used for **11** in 90% combined yield (ratio 1:1.5). ¹H and ¹³C NMR spectra were identical with those of **10** and **11**, respectively. **22**: $R_f = 0.68$ (50% EtOAc in hexanes); $[\alpha]^{25}_{D} = +19.0$ (*c* 2.00, CHCl₃); HRMS (ESI) calcd. for C₁₄H₃₀NaO₆ [M + Na]⁺ 313.1806, found 313.1809. **23**: $R_f = 0.70$ (50% EtOAc in hexanes); $[\alpha]^{25}_{D} = +18.9$ (*c* 1.4, CHCl₃); HRMS (ESI) calcd. for C₁₄H₃₀NaO₆ [M + Na]⁺ 313.1806, found 313.1810.

2-(((4'S,5'*R*)-5'-(*tert*-Butyldimethylsilyloxymethyl)-2',2',5'trimethyl-1',3'-dioxolan-4'-yl)methyl)isoindoline-1,3-dione (24). Imide 24 was prepared from diol alcohol 23 following the procedure used for 12 in 93% yield: IR, ¹H and ¹³C NMR spectra were identical with those of 12; $[\alpha]^{25}_{D} = -23.0$ (*c* 4.00, CHCl₃); HRMS (ESI) calcd. for C₂₂H₃₃NNaO₃Si [M + Na]⁺ 442.2020, found 442.2022.

((45,5*R*)-5-(*tert*-Butyldimethylsilyloxymethyl)-2,2,5-trimethyl-1,3-dioxolan-4-yl)methanamine (25). Amine 25 was prepared from imide 24 following the procedure used for 13 in 96% yield: IR, ¹H and ¹³C NMR spectra were identical with those of **13**; $[\alpha]^{25}_{D}$ = +9.00 (*c* 2.80, CHCl₃); HRMS (ESI) calcd. for C₁₄H₃₂NO₃Si [M + H]⁺ 290.2146, found 290.2150

(4R,5S)-5-(Aminomethyl-2,2,4-trimethyl-1,3-dioxolan-4-yl)methanol (26). Silyl ether 25 (183 mg, 0.63 mmol) was dissolved in THF (6 mL), and a 1.0 M solution of TBAF in THF (1.9 mL, 1.9 mmol) was added at rt. After 3 h of vigorous stirring, EtOAc (5 mL) was added, and the mixture was washed with saturated brine (5 mL). The organic layer was separated, and the aqueous layer was backextracted with EtOAc (6×6 mL). The combined organic extracts were dried over Na₂SO₄ and evaporated in vacuo. The residue was purified by flash column chromatography (20% MeOH in DCM) to give alcohol 26 (102 mg, 92%) as a white amorphous solid. This was used in the next step without further purification: $R_f = 0.11$ (17%) MeOH in CH₂Cl₂); $[\alpha]^{25}_{D} = +1.73$ (c 6.50, MeOH); FTIR (KBr) 3398, 3312, 3066, 2986, 2937, 2855, 1578, 1458 cm⁻¹; ¹H NMR (500 MHz, CD₃OD) δ 4.04 (dd, J = 8.2, 3.3 Hz, 1H, CH–O), 3.53 (d, J = 11.2 Hz, 1H, CHH-O), 3.30 (d, J = 11.2 Hz, 1H, CHH-O), 3.20-3.06 (m, 2H, CH₂-N), 1.41 (s, 3H, CH₃-C-CH₃), 1.38 (s, 3H, CH₃-C- CH_3), 1.32 (s, 3H, C-CH₃) ppm; ¹³C NMR (125 MHz, CD₃OD) δ 109.6, 83.0, 82.4, 65.4, 40.7, 28.8, 27.1, 22.5 ppm; HRMS (ESI) calcd. for $C_8H_{18}NO_3 [M + H]^+$ 176.1281, found 176.1280.

4-((E)-3-(((4S,5R)-5-(tert-Butyldimethylsilyloxymethyl)-2,2,5trimethyl-1,3-dioxolan-4-yl)methylamino)-3-oxoprop-1-en-1yl)-1,2-phenylene diacetate (29). Coupling with BOP. Dry Et₃N (14 μ L, 0.1 mmol) was added to a magnetically stirred solution of amine 25 (28 mg, 0.1 mmol) in dry CH_2Cl_2 (0.4 mL) at rt. To this solution acid 31^{30} (28 mg, 0.11 mmol) and BOP (64 mg, 0.15 mmol) were added, and the mixture was left to stir under an Ar atmosphere for 1 h at rt. An additional amount of dry Et₃N (14 μ L, 0.1 mmol) was added, and the mixture was further stirred for 2 h at rt. Then, it was evaporated to dryness, and the residue was purified by flash column chromatography (25% EtOAc in hexanes) to give amide 29 (27 mg, 52%) as a pale yellow oil: $R_f = 0.12$ (30% EtOAc in hexanes); $[\alpha]^{25}_{D} =$ +4.31 (c 1.08, CHCl₃); FTIR (neat) 3364, 3077, 2985, 2940, 2871, 2854, 1759, 1650, 1614, 1516 cm $^{-1};~^{1}\mathrm{H}$ NMR (300 MHz, CDCl_3) δ 7.57 (d, J = 15.5 Hz, 1H, Ar–CH=), 7.34 (dd, J = 8.3, 1.9 Hz, 1H, ArH-6), 7.30 (d, J = 1.9 Hz, 1H, ArH-2), 7.19 (d, J = 8.3 Hz, 1H, ArH-5), 6.28 (d, J = 15.5 Hz, 1H, CO-CH=), 6.18 (br t, J = 6.0 Hz, 1H, NH), 3.72–3.65 (m, 2H, CH₂–N), 3.71 (d, J = 9.9 Hz, 1H, CHH-O), 3.28 (d, J = 9.9 Hz, 1H, CHH-O), 2.29 (s, 3H, CH₃-CO), 2.28 (s, 3H, CH₃-CO), 1.39 (s, 3H, CH₃-C-CH₃), 1.35 (s, 3H, CH₃-C-CH₃), 1.32 (s, 3H, C–CH₃), 0.94 (s, 9H, C(CH₃)₃), 0.12 (s, 3H, Si-CH₃) 0.11 (s, 3H, Si-CH₃) ppm; ¹³C NMR (75 MHz, CDCl₃) δ 167.90, 167.88, 165.2, 143.0, 142.4, 139.4, 137.8, 125.9, 123.8, 122.4, 121.8, 107.5, 81.5, 80.9, 65.4, 38.9, 28.4, 26.5, 25.9, 22.6, 20.6, 20.5, 18.2, -5.55, -5.58 ppm; HRMS (ESI) calcd. for C₂₇H₄₁NNaO₈Si [M + Na]⁺ 558.2494, found 558.2499.

Coupling with DCC. To a magnetically stirred solution of amine 25 (87 mg, 0.3 mmol) in dry CH_2Cl_2 (1.5 mL), acid 31³⁰ (160 mg, 0.6 mmol), DMAP (37 mg, 0.3 mmol) and DCC (155 mg, 0.75 mmol) were added at rt. The reaction mixture was left to stir under an Ar atmosphere for 24 h at rt. Then, it was washed with saturated brine (2 mL). The aqueous layer was back-extracted with DCM (6×5 mL), and the combined organic extracts were dried over Na₂SO₄ and evaporated in vacuo. For the removal of the urea byproduct, the residue was dissolved in diethyl ether (3 mL), and the suspension was stirred vigorously for 10 min at rt. This mixture was filtered through a pad of Celite on sintered glass filter and washed with diethyl ether (3 mL). The filtrate was evaporated in vacuo, and the residue was subjected to flash column chromatography (25% EtOAc in hexanes) to give amide 29 (68 mg, 43%) as a pale yellow oil. The data for 29 matches that reported above (coupling with EDC).

(E)-3-(3,4-Bis(methoxymethoxy)phenyl)-*N*-(((4*S*,5*R*)-5-(*tert*butyldimethylsilyloxymethyl)-2,2,5-trimethyl-1,3-dioxolan-4yl)methyl)acrylamide (32). *Coupling with DCC*. To a magnetically stirred solution of amine 25 (91 mg, 0.31 mmol) in dry CH_2Cl_2 (1.6 mL), acid 34^{31} (169 mg, 0.63 mmol), DMAP (38 mg, 0.31 mmol) and DCC (162 mg, 0.79 mmol) were added at rt. The reaction mixture was left to stir under an Ar atmosphere for 24 h at rt. Then, it was washed with saturated brine (2 mL). The aqueous layer was back-extracted with DCM (6×5 mL), and the combined organic extracts were dried over Na₂SO₄ and evaporated in vacuo. For the removal of the urea byproduct, the residue was dissolved in diethyl ether (5 mL), and the suspension was stirred vigorously for 10 min at rt. This mixture was filtered through a pad of Celite on sintered glass filter and washed with diethyl ether (5 mL). The filtrate was evaporated in vacuo, and the residue was subjected to flash column chromatography (20% EtOAc in hexanes) to give amide 32 (164 mg, 97%) as a pale yellow amorphous solid: $R_f = 0.64$ (50% EtOAc in hexanes); $[\alpha]^{25}_{D} = +9.55$ (c 2.78, CHCl₃); FTIR (KBr) 3358, 3068, 2980, 2932, 2870, 2857, 1656, 1624, 1509 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 7.53 (d, J = 15.5 Hz, 1H, Ar-CH=), 7.32 (d, J = 1.6 Hz, 1H, ArH-2), 7.11 (d, J = 8.4 Hz, 1H, ArH-5), 7.05 (br d, J = 8.4 Hz, 1H, ArH-6), 6.27 (br s, 1H, NH), 6.22 $(d, J = 15.5 \text{ Hz}, 1\text{H}, \text{CO-CH} =), 5.23 (2 \times \text{s}, 4\text{H}, 2 \times \text{O-CH}_2 - \text{O}),$ 3.94 (t, J = 6.8 Hz, 1H, CH-O), 3.75-3.68 (m, 1H, CHH-N), 3.69 (d, J = 10.1 Hz, 1H, CHH-O), 3.62-3.58 (m, 1H, CHH-N), 3.50 (s, 3H, CH₃-O), 3.48 (s, 3H, CH₃-O), 3.24 (d, J = 10.0 Hz, 1H, CHH-O), 1.37 (s, 3H, CH₃-C-CH₃), 1.33 (s, 3H, CH₃-C-CH₃), 1.31 (s, 3H, C-CH₃), 0.92 (s, 9H, C(CH₃)₃), 0.10 (s, 3H, Si-CH₃), 0.09 (s, 3H, Si-CH₃) ppm; ¹³C NMR (125 MHz, CDCl₃) δ 165.7, 148.5, 147.3, 140.7, 129.1, 123.2, 118.9, 116.0, 114.8, 107.3, 95.3, 95.0, 81.4, 80.5, 65.2, 56.2, 56.1, 38.6, 28.3, 26.3, 25.8, 22.5, 18.1, -5.64, -5.65 ppm; HRMS (ESI) calcd. for $C_{27}H_{45}NNaO_8Si [M + Na]^+$ 562.2807, found 562.2801.

Coupling with EDC. To a magnetically stirred solution of amine 25 (205 mg, 0.71 mmol) in dry CH_2Cl_2 (3.5 mL) acid 34^{31} (380 mg, 1.42 mmol), DMAP (87 mg, 0.71 mmol) and EDC·HCl (339 mg, 1.77 mmol) were added at rt. The reaction mixture was left to stir under an Ar atmosphere for 24 h at rt. Then, it was washed with saturated brine (2 mL) and water (2 × 2 mL). The aqueous layer was back-extracted with CH_2Cl_2 (6 × 5 mL), and the combined organic extracts were dried over Na_2SO_4 and evaporated in vacuo. The residue was subjected to flash column chromatography (20% EtOAc in hexanes) to give amide 32 (380 mg, 99%) as a pale yellow solid. The data for 32 matches that reported above (coupling with DCC).

(E)-3-(3,4-Bis(methoxymethoxy)phenyl]-N-(((4S,5R)-5-hydroxymethyl-2,2,5-trimethyl-1,3-dioxolan-4-yl)methyl)acrylamide (33). Silyl ether 32 (380 mg, 0.70 mmol) was dissolved in THF (7 mL), and a mixture of a 1.0 M solution of TBAF in THF (3.6 mL, 3.6 mmol) and glacial AcOH (0.2 mL, 3.6 mmol) was added under an Ar atmosphere at rt. After 48 h of vigorous stirring at rt, EtOAc (5 mL) was added, and the mixture was washed with saturated brine (5 mL). The organic layer was separated, and the aqueous layer was back extracted with EtOAc (6×5 mL). The combined organic extracts were dried over Na₂SO₄ and evaporated in vacuo. The residue was purified by flash column chromatography (80% EtOAc in hexanes) to give alcohol 33 (276 mg, 92%) as a pale white amorphous solid: $R_f = 0.11$ (50% EtOAc in hexanes); $[\alpha]_{D}^{25} = -4.94$ (c 1.95, CHCl₃); FTIR (KBr) 3385, 3300, 3045, 2928, 2870, 2857, 1655, 1604, 1509 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 7.55 (d, J = 15.6 Hz, 1H, Ar-CH=), 7.32 (d, J = 1.2 Hz, 1H, ArH-2), 7.11 (d, J = 8.4 Hz, 1H, ArH-5), 7.08 (dd, J = 8.5, 1.4 Hz, 1H, ArH-6), 6.75 (br t, J = 5.8 Hz, 1H, NH), 6.35 (d, J = 15.6 Hz, 1H, CO-CH=), 5.24 (s, 4H, 2 × O-CH₂-O), 4.03 (dd, J = 7.6, 5.2 Hz, 1H, CH-O), 3.83-3.78 (m, 1H, CHH-N), 3.61 (d, J = 11.0 Hz, CHH-O), 3.61-3.56 (m, 1H, CHH-N), 3.52 (s, 3H, CH_3 -O), 3.50 (s, 3H, CH_3 -O), 3.48 (d, J = 11.2 Hz, CHH-O), 1.43 (s, 3H, CH₃-O-CH₃), 1.37 (s, 6H, CH₃-O-CH₃ and C-CH₃) ppm; ¹³C NMR (125 MHz, CDCl₃) & 166.2, 148.5, 147.1, 140.7, 129.0, 123.1, 118.8, 116.0, 115.0, 107.6, 95.2, 94.9, 81.5, 80.9, 64.7, 56.03, 56.02, 38.3, 28.1, 26.3, 22.0 ppm; HRMS (ESI) calcd. for C₂₁H₃₁NNaO₈ [M + Na]⁺ 448.1942, found 448.1949.

(3aS,6aS)-5-((E)-3-(3,4-Bis(methoxymethoxy)phenyl)-acryloyl)-2,2,3a-trimethyldihydro-3aH-[1,3]dioxolo[4,5-c]-pyrrol-4(5H)-one (35). A solution of alcohol 33 (211 mg, 0.5 mmol) in acetone (1.2 mL) was added to a 5% aq. NaHCO₃ solution (1.2 mL) containing KBr (6 mg, 0.05 mmol), and the resulting slurry was cooled to 0 °C. TEMPO (108 mg, 0.69 mmol) was then added followed by 5% aq. NaOCl solution (1.2 mL). The pH was adjusted to 8 by adding solid NaHCO₃, and the mixture was stirred for 3 h at 0

°C, and then the reaction was quenched by addition of a 5% aq. HCl solution (0.5 mL). The mixture was extracted with CH_2Cl_2 (4 × 5 mL). The combined organic extracts were dried over Na₂SO₄ and evaporated in vacuo. The residue was purified by flash column chromatography (33% EtOAc in hexanes) to give lactam 35 (171 mg, 82%) as a yellowish oil: $R_f = 0.46$ (50% EtOAc in hexanes); $[\alpha]^{25}_{D} =$ +25.9 (c 1.23, CHCl₂); FTIR (neat) 3094, 2988, 2933, 2870, 2825, 1743, 1677, 1617, 1509 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 7.77 (s, 2H, Ar–CH= and CO–CH=), 7.32 (s, 1H, ArH-2), 7.22 (d, J = 8.4 Hz, 1H, ArH-6), 7.16 (d, J = 8.4 Hz, 1H, ArH-5), 5.22 (s, 2H, O- CH_2-O), 5.21 (s, 2H, O- CH_2-O), 4.36 (d, J = 3.9 Hz, 1H, CH-O), 4.10 (d, J = 13.5 Hz, 1H, CHH-N), 3.73 (dd, J = 13.5, 4.0 Hz, 1H, CHH-N), 3.49 (s, 3H, CH₃-O), 3.46 (s, 3H, CH₃-O), 1.49 (s, 3H, C-CH₃), 1.40 (s, 3H, CH₃-C-CH₃), 1.37 (s, 3H, CH₃-C-CH₃) ppm; 13 C NMR (125 MHz, CDCl₂) δ 174.6, 166.3, 149.5, 147.0, 146.0, 128.9, 123.8, 116.8, 116.5, 116.0, 111.8, 95.4, 94.9, 84.8, 75.8, 56.1 (2C), 46.5, 27.1, 26.3, 18.4 ppm; HRMS (ESI) calcd. for $C_{21}H_{27}NNaO_8 [M + Na]^+ 444.1629$, found 444.1625.

(4S,5S)-tert-Butyl 5-(((E)-3-(3,4-bis(methoxymethoxy)phenyl)acrylamido)methyl)-2,2,4-trimethyl-1,3-dioxolane-4carboxylate (36). An aq. 1.0 M LiOH solution (1.0 mL, 1.0 mmol) was dropwise added to a solution of lactam 35 (171 mg, 0.41 mmol) in 1,4 dioxane (4.5 mL) over a period of 5 min at 10 °C. The reaction mixture was stirred vigorously for another 15 min, and then the solvent was evaporated in vacuo. The resulting aqueous slurry was carefully acidified (pH = 3) by the addition of an aq. 10% AcOH solution at 0 °C and extracted with EtOAc (6×4 mL). The combined extracts were washed with saturated brine (5 mL) and dried over MgSO₄. Evaporation of the solvent gave intermediate carboxylic acid, which was used without further purification in the next step. This was dissolved in dry benzene (3 mL) and N,N-dimethylformamide di-tertbutyl acetal (0.39 mL, 1.62 mmol) was dropwise added to the refluxing mixture within 20 min. The reaction mixture was refluxed for 3 h, cooled and washed with water (2 mL), a saturated NaHCO₃ solution $(2 \times 2 \text{ mL})$ and saturated brine (2 mL). The aqueous layers were back-extracted with EtOAc (6×5 mL), and the combined organic extracts were dried over MgSO4 and evaporated in vacuo. The residue was purified by flash column chromatography initially with 10% EtOAc in hexanes to obtain ester 37 (46 mg, 35% over 2 steps), then 35% EtOAc in hexanes to obtain ester 36 (103 mg, 51% over 2 steps) and finally with 10% methanol in EtOAc to obtain lactam 38 (21 mg, 30% over 2 steps). 36: White oil; $R_f = 0.16$ (35% EtOAc in hexanes); $[\alpha]^{25}$ = +6.88 (c 4.00, CHCl₃); FTIR (neat) 3373, 3089, 2982, 2933, 2870, 2825, 1721, 1662, 1510 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 7.56 (d, J = 15.5 Hz, 1H, Ar-CH=), 7.35 (br s, 1H, ArH-2), 7.14 (d, J = 8.4Hz, 1H, ArH-5), 7.11 (br d, J = 8.5 Hz, 1H, ArH-6), 6.28 (d, J = 15.5 Hz, 1H, CO–CH=), 6.09 (br t, J = 5.9 Hz, 1H, NH), 5.26 (s, 4H, 2 × $O-CH_2-O$, 4.03 (dd, J = 7.8, 5.4 Hz, 1H, CH-O), 3.72-3.66 (m, 1H, CHH-N), 3.53 (s, 3H, CH₃-O), 3.51 (s, 3H, CH₃-O), 3.50 (m, 1H, obscured), 1.58 (s, 3H, CH₃-C-CH₃), 1.52 (s, 3H, C-CH₃), 1.52 (s, 9H, C(CH₃)₃), 1.39 (s, 3H, CH₃-C-CH₃) ppm; ¹³C NMR (125 MHz, CDCl₃) δ 172.0, 165.9, 148.7, 147.4, 141.1, 129.2, 123.4, 118.8, 116.2, 115.1, 110.1, 95.5, 95.2, 83.0, 82.7, 82.2, 56.28, 56.27, 39.7, 28.1, 26.8, 26.6, 23.7 ppm; HRMS (ESI) calcd. for $C_{25}H_{37}NNaO_9$ [M + Na]⁺ 518.2361, found 518.2360. 37: White amorphous solid; $R_f = 0.53$ (35% EtOAc in hexanes); FTIR (KBr) 3045, 2996, 2979, 2929, 2850, 2824, 1705, 1635, 1509 cm⁻¹; ¹H NMR $(500 \text{ MHz}, \text{CDCl}_3) \delta 7.51 \text{ (d, } J = 15.9 \text{ Hz}, 1\text{H}, \text{Ar-CH=}), 7.34 \text{ (d, } J$ = 1.6 Hz, 1H, ArH-2), 7.14 (d, J = 8.4 Hz, 1H, ArH-5), 7.11 (dd, J = 8.4, 1.7 Hz, 1H, ArH-6), 6.25 (d, J = 15.9 Hz, 1H, CO-CH=), 5.26 (s, 2H, O-CH₂-O), 5.25 (s, 2H, O-CH₂-O), 3.53 (s, 3H, CH₃-O), 3.52 (s, 3H, CH₃-O), 1.53 (s, 9H, C(CH₃)₃) ppm; ¹³C NMR (125 MHz, CDCl₃) δ 166.5, 148.9, 147.3, 143.1, 129.2, 123.3, 118.8, 116.2, 115.4, 95.5, 95.2, 80.4, 56.30, 56.26, 28.2 ppm; HRMS (ESI) calcd. for $C_{17}H_{24}NaO_6 [M + Na]^+$ 347.1465, found 347.1470. 38: White amorphous solid; $R_f = 0.31$ (EtOAc); $[\alpha]^{25}_{D} = +28.9$ (c 1.10, MeOH); IR, ¹H and ¹³C NMR spectra were identical with those of 17; HRMS (ESI) calcd. for $C_8H_{13}NNaO_3$ [M + Na]⁺ 194.0788, found 194.0790.

(E)-Methyl 3-(3,4-bis(methoxymethoxy)phenyl)acrylate (39). An aq. 1.0 M LiOH solution (0.13 mL, 0.13 mmol) was dropwise added to a solution of lactam **35** (18 mg, 0.04 mmol) in MeOH (0.7 mL) over a period of 5 min at 0 °C. The reaction mixture was stirred vigorously for another 40 min, and then the solvent was evaporated in vacuo. The resulting aqueous slurry was carefully acidified (pH = 3) by the addition of an aq. 10% AcOH solution at 0 °C and extracted with DCM (6 × 4 mL). The combined extracts were washed with saturated brine (1 mL), dried over MgSO₄ and evaporated in vacuo. The residue was purified by flash column chromatography (10% EtOAc in hexanes) to give ester **39** (12 mg, 100%) as a white solid: $R_f = 0.56$ (50% EtOAc in hexanes); ¹H NMR spectrum was identical with that reported in the literature; ³² HRMS (ESI) calcd. for C₁₄H₁₈NaO₆ [M + Na]⁺ 305.0996, found 305.0994.

(2S,3S)-tert-Butyl 4-((E)-3-(3,4-dihydroxyphenyl)acrylamido)-2,3-dihydroxy-2-methylbutanoate (41). To a magnetically stirred solution of acetonide 36 (76 mg, 0.15 mmol) in MeOH (1.5 mL) PPTS (385 mg, 1.15 mmol) was added, and the reaction mixture was heated at 45 °C under an Ar atmosphere for 2 h. Then, the solvent was removed in vacuo, and the residue was purified by flash column chromatography (80% EtOAc in hexanes) to give diol 41 (55 mg, 98%) as a white amorphous solid: $R_f = 0.22$ (10% MeOH in CH_2Cl_2 ; $[\alpha]^{25}_{D} = -15.5$ (c 6.88, CHCl_3); FTIR (KBr) 3432, 3040, 2980, 2925, 2854, 1719, 1655, 1458 cm⁻¹; ¹H NMR (500 MHz, CD_3OD) δ 7.38 (d, J = 15.6 Hz, 1H, Ar-CH=), 6.99 (s, 1H, ArH-2), 6.88 (d, J = 8.0 Hz, 1H, ArH-6), 6.75 (d, J = 8.1 Hz, 1H, ArH-5), 6.38 (d, J = 15.6 Hz, 1H, CO-CH=), 3.81 (dd, J = 9.2, 2.4 Hz, 1H, CH-O), 3.56 (dd, J = 13.8, 2.4 Hz, 1H, CHH-N), 3.24 (dd, J = 13.6, 9.2 Hz, 1H, CHH-N), 1.48 (s, 9H, C(CH₃)₃), 1.38 (s, 3H, C-CH₃) ppm; $^{13}\mathrm{C}$ NMR (125 MHz, CD_3OD) δ 175.6, 169.8, 148.8, 146.8, 142.4, 128.4, 122.2, 118.6, 116.6, 115.2, 83.4, 77.7, 75.6, 42.8, 28.3, 23.1 ppm; HRMS (ESI) calcd. for C₁₈H₂₅NNaO₇ [M + Na]⁺ 390.1523, found 390.1529

(25,35)-4-((*E*)-3-(3,4-Dihydroxyphenyl)acrylamido)-2,3-dihydroxy-2-methylbutanoic acid (40). Ester 41 (34 mg, 0.09 mmol) was dissolved in pure TFA (0.7 mL), and the mixture was stirred vigorously for 20 min at rt. The volatiles were removed in vacuo, and the residue was coevaporated with toluene (4 × 2 mL) to yield carboxylic acid 40 (29 mg, 100%) as a yellow solid. This was directly used in the following reaction. HRMS (ESI) calcd. for $C_{14}H_{16}NO_7$ [M – H]⁻ 310.0932, found 310.0936.

Potassium Aeshynomate (1). Carboxylic acid **40** (29 mg, 0.09 mmol) was dissolved in dry MeOH (0.55 mL), and a 0.15 M solution of potassium methanolate in methanol (0.55 mL, 0.08 mmol) was dropwise added under an Ar atmosphere. The mixture was stirred for exactly 5 min and evaporated to dryness to give the target natural product, potassium aeshynomate (1) as a yellow-brown solid (32 mg, 100%): $[\alpha]^{25}_{D} = -3.56$ (*c* 0.24, 50% aq. MeOH); lit.^{7g} $[\alpha]^{25}_{D} = -3.39$ (*c* 0.24, 50% aq. MeOH); ¹H and ¹³C NMR spectra were identical with those reported in the literature;^{7g,8d} HRMS (ESI) calcd. for C₁₄H₁₆NO₇ $[M - K]^-$ 310.0932, found 310.0930.

ASSOCIATED CONTENT

S Supporting Information

Copies of ¹H and ¹³C spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(26) For the correct enantiomer in ref 8d (with ee 29%): $[\alpha]^{25}_{D}$ –4.0 (*c* 0.4, CH₂Cl₂). For our sample (enantiopure): $[\alpha]^{25}_{D}$ +13.5 (*c* 4.5, CH₂Cl₂).

(27) Amide **21** was always accompanied by an unidentified byproduct, which had both caffeic acid and γ -amino-ester moieties.

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(33) A slight excess of potassium methanolate caused mainly the change of the aromatic ¹H shifts due to the formation of the corresponding potassium phenolates.

(34) For our synthetic 1: $[\alpha]^{25}{}_{\rm D} = -3.56$ (*c* 0.24, 50% aq. MeOH). For synthetic 1, reported by Grison et al. (ref 8d): $[\alpha]^{25}{}_{\rm D} = -4.00$ (*c* 0.24, 50% aq. MeOH). For natural 1, reported by Yamamura et al. (ref 7g): $[\alpha]^{25}{}_{\rm D} = -3.39$ (*c* 0.24, 50% aq. MeOH).

(35) We have not faced the same solubility problems reported by Grison et al. (ref 8d) in 1:1 D_2O/CD_3OD . However, comparing with the data in ref 7g, we have also noticed the same differences regarding H_4' and C_4' chemical shifts.

(36) Considering that the undesired regioisomer 22 is easily converted to 23, the total yield is practically higher.