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A Short and Efficient Synthesis of (2*S*,3*S*,4*S*)-*tert*-Butyl 3,4-Dihydroxy-2-(methoxymethyl)-5-oxopyrrolidine-1-carboxylate

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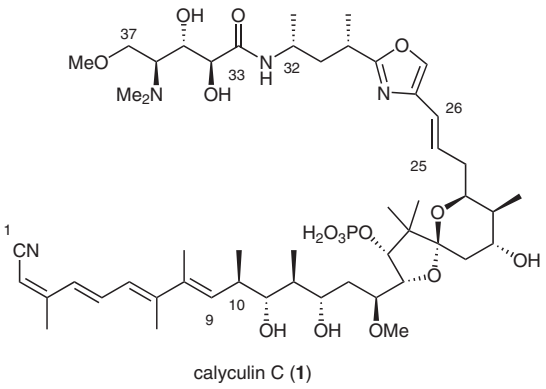
Abstract: Asymmetric synthesis of the title compound was accomplished starting from L-serine. Stannoxane-mediated lactamization provided the key intermediate in good yield.

Key words: natural products, stereoselective synthesis, olefination, α,β-unsaturated lactam, dihydroxylation

Calyculins are highly cytotoxic polyketides. Since the isolation of calyculin A in 1986 by Fusetani and co-workers[1a] and, a few years later, calyculins B, C, and D by the same group,[1b] their highly complex structures and role as protein phosphatase inhibitors (PP1 and PP2A) has attracted both synthetic chemists and biologists.[2] The first synthesis of *ent*-calyculin A was published by Evans and co-workers in 1992,[3a] and thus far a total of six syntheses of different calyculins have been published.[3–5]

Calyculin C (**1**) contains four different structural regions: C1–C9 tetraene, C10–C25 dipropionate spiroketal, C26–C32 oxazole and C33–C37 amino acid subunits (Figure 1). Both the tetraene moiety and the presence of a total of 16 stereogenic centers make it a highly challenging synthetic target. We, among others, have been interested in the synthesis of calyculin C.[5,6] Our earlier effort showed that the C33–C37 fragment can be synthesized starting from the commercially available Garner's aldehyde.[7] The highlight of the synthesis is the diastereoselectivity of dihydroxylation (>99:1 favoring the *anti*-product **3a**). Comparison of our results to those by Shioiri and co-workers,[8] who obtained a selectivity of 55:45 (*syn*/*anti*)

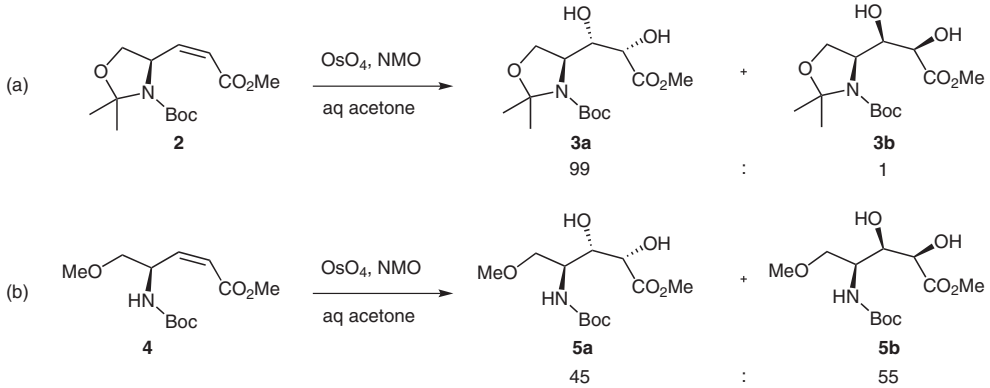


calyculin C (**1**)

Figure 1

towards the unwanted diastereoisomer **5b**, demonstrates the remarkable diastereoface-discriminating effect of the dimethyloxazoline ring unit (Scheme 1).

Modified original strategy. In our original paper we used acetate as the alcohol protecting group, which is not feasible for the eventual total synthesis. We therefore sought alternative protecting groups for the diol. In this paper we present our recent findings in the synthesis of the C33–C37 fragment of calyculin C. The synthesis commenced from *Z*-enoate **2**, which can easily be synthesized starting from commercially available L-serine in five steps.[7] Dihydroxylation under the Upjohn conditions (OsO_4, NMO)[9] provided the diol **3a** in a modest 50% isolated yield. It is well known that electron-deficient double bonds are slug-



Scheme 1 Diastereoselectivity of the dihydroxylation; (a) by Koskinen and co-workers,[7] and (b) by Shioiri and co-workers.[8]

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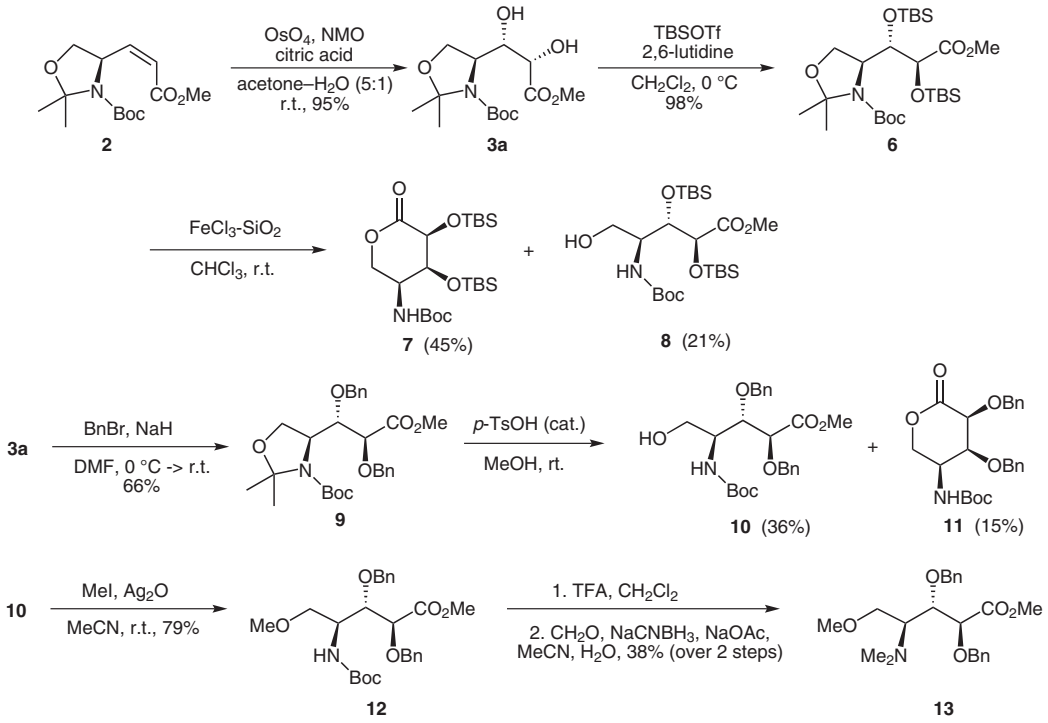


Scheme 2

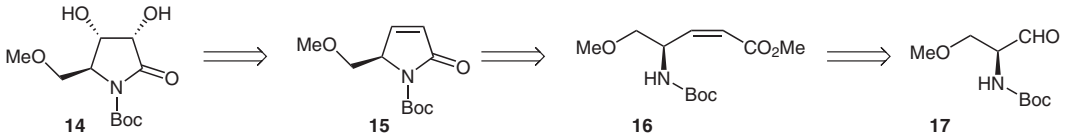
gish towards osmylation. The catalytic cycle shuts down and the reaction stops totally because of the rising pH,[10] due to the formation of basic *N*-methylmorpholine. This can be avoided through the use of acid to trap the amine, thus keeping the catalytic cycle in motion. When the dihydroxylation was performed under acidic conditions the reaction time decreased from three days down to a mere 3.5 hours, while the isolated yield almost doubled from 50 to 95% (Scheme 2).

Diol **3a** was protected as its silyl ether **6** with *tert*-butyldimethylsilyl trifluoromethanesulfonate (TBSOTf) and 2,6-lutidine. This fully protected TBS ether **6** was then subjected to *N*,*O*-acetal cleavage. Unfortunately, this step proved to be slightly more challenging than anticipated. Under a range of cleavage conditions (e.g., 80% AcOH, cat. *p*-TsOH in MeOH, $FeCl_3$ adsorbed on silica or biphasic 1 M HCl/CH_2Cl_2) the reaction produced several products with lactone **7** as the major constituent. The open chain alcohol **8** unfortunately remained as a side product, and we could also detect compounds where one of the TBS groups had been cleaved. We then chose to use benzyl ether as the protecting group and found that protection of both hydroxyls of **3a** was achieved with sodium hydride and benzyl bromide in *N*,*N*-dimethylformamide. The benzyl ether **9** was then subjected to *N*,*O*-acetal cleavage. In this case, catalytic *p*-toluenesulfonic acid in methanol proved to be the reagent of choice, albeit giving a poor yield (36%). Part of the free alcohol cyclized to lactone **11** under the acidic conditions (15%). The free alcohol **10** was immediately subjected to etherification with iodomethane and silver(I) oxide in acetonitrile. The methyl ether **12** was then subjected to deprotection and reductive amination, which provided the *N*,*N*-dimethylamine **13** in 38% yield (over two steps). The ^{1}H NMR spectra of **13** was in accordance with data reported in the literature.[11] In conclusion, we were able to synthesize a benzyl-protected C33–C37 fragment of calyculin C in an overall yield of about 7% (over six steps) starting from *Z*-enoate **2**.

However, an average yield of 64% per step in a multistep synthesis leaves lots of room for improvement. For instance, the tendency of the free alcohols (**8** or **10**) to cyclize into lactones (**7** or **11**) complicates the purification processes and diminishes the yield of the desired product. Lactone formation itself is, of course, not surprising. In order to improve our strategy, ether formation must be performed at an earlier stage to prevent lactone formation and thereby improve the yield.

Strategy based on unsaturated pyrrolidinone. Both Shioiri and co-workers[12a] and Ikota[12b] have shown that oxidation of an α,β-unsaturated 2-substituted pyrrolidinone **15** provides the diol as a single diastereoisomer. Both groups started from (*S*)-pyroglutaminol and prepared differently protected diols (*ent*-**14** derivatives) in five[12a] and six[12b] steps. These diols were enantiomeric to the natural C33–C37 fragment of calyculins. We envisioned that the pyrrolidinone **15** could be synthesized with the correct configuration starting from L-serine. The lactam ring can be formed from a suitably substituted *Z*-enoate **16**, which could, in turn, be available through *Z*-selective olefination of substituted serinal **17** (Scheme 3).

The synthesis commenced with the Boc-protected ester **18**, which was etherified with iodomethane and silver(I) oxide (Scheme 4). Other etherification attempts (MeI/NaH, MeOTf or CH_2N_2) failed. Sodium hydride was



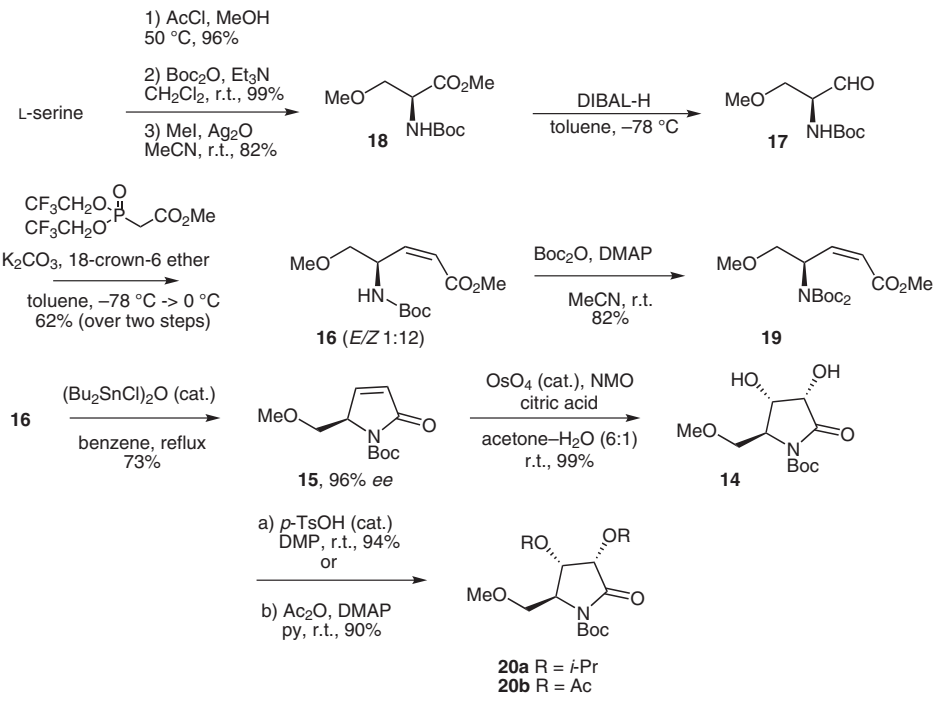
Scheme 3 Retrosynthetic analysis of **14**

found to be too strong a base and yielded only an elimination product. With methyl triflate or diazomethane the reaction did not go to completion, in these cases progress stopped after about 20% conversion. Reduction of **18** with diisobutylaluminum hydride gave aldehyde **17**, which was then subjected to Still–Gennari olefination[13] to provide the enoate **16** in good regioselectivity (*E*/*Z* ratio 1:12). Enoate **16** was then subjected to cyclization. During the synthesis of the C26–C32 fragment we noticed that, under the Ragnarsson–Grehn[14] conditions, a substituted *Z*-enoate undergoes cyclization into lactam with high yields.[15] Unfortunately, in our present case the diprotected open chain enoate **19** was obtained in an excellent yield (82%). Deprotonation of **16** with sodium hexamethyldisilazide in tetrahydrofuran at –78 °C or sodium hydride in *N*,*N*-dimethylformamide at 0 °C did not provide any cyclized product at all. We then turned our focus to Lewis acidic conditions. Thus, trimethylaluminum gave lactam **15** in 35% yield, and $(Bu_2ClSn)_2O$ in benzene at reflux provided **15** in 73% yield, while the milder $(Bu_3Sn)_2O$ did not persuade the adduct to cyclize at all.[16]

The enantiopurity of lactam **15** was determined by chiral GC analysis to be 96% ee. Our first dihydroxylation attempts were performed under the Upjohn conditions[9] but, unfortunately, this reaction provided diol **14** in very poor yields (33–45%) even after prolonged reaction times (20–40 h). Acidifying the reaction media with 75 mol% citric acid, however, had a tremendous effect.[10] Under these conditions the reaction was complete in 5.5 hours and provided the diol **14** in practically quantitative yield. In both cases – the traditional Upjohn procedure and the use of citric acid as additive – the oxidation reaction produced the alcohol **14** as a single diastereoisomer. Finally, the diol was protected as the isopropylidene acetonide **20a**. Acetate protection also worked smoothly, providing the diacetate **20b** in excellent yield, however, TBS protection with TBSOTf or TBSCl failed.

In conclusion, we have described a simple and efficient route for the synthesis of diol **14**, a key intermediate of the C33–C37 fragment of calyculin C. The seven-step route started from L-serine and gave **14** with almost complete retention of stereochemistry (96% ee). We have shown that the Still–Gennari modification of the Horner–Wadsworth–Emmons reaction is an efficient tool that can be used to produce *Z*-olefins, and that bis(dibutylchlorotin)oxide works as a suitable Lewis acid in the lactamization step. This route is amenable for scale-up, is economical and gives the desired diol **14** in an overall yield of 35% (an average of 86% per reaction step).

All reactions were carried out under an argon atmosphere in flame-dried glassware unless otherwise stated. Non-aqueous reagents were transferred under argon via syringe or cannula and dried prior to use. Et_3N, benzene and toluene were distilled from metallic Na.



Scheme 4

THF was distilled from Na/benzophenone, CH_2Cl_2 from CaH_2 and DMF from molecular sieves (4Å)/ninhydrin. Other solvents and reagents were used as obtained from the supplier. Analytical TLC was performed on Merck silica gel F_{254} (230–400 mesh). Column chromatography was performed using Merck silica gel 60 (230–400 mesh) and p.a. grade solvents. ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ with a Bruker Avance 400 (^1H: 399.98 MHz; ^{13}C: 100.59 MHz) spectrometer. The chemical shifts are reported in ppm relative to residual $CHCl_3$ (δ = 7.26 ppm for ^1H and 77.0 ppm for ^{13}C). The enantiomeric excess (*ee*) of **15** was determined with HP6890 GC apparatus. Melting points were determined in open capillaries using Stuart SMP3 melting point apparatus. Optical rotations were obtained with a Perkin–Elmer 343 polarimeter. High-resolution mass spectrometric data were measured with a Micro-Mass LCT Premier spectrometer.

(*R*)-*tert*-Butyl 4-{[(*Z*)-2-Methoxycarbonyl]vinyl}-2,2-dimethyloxazolidine-3-carboxylate (2)

18-Crown-6-ether (24.2 g, 92 mmol, 210 mol%), K_2CO_3 (31.7 g, 230 mmol, 520 mol%) and anhydrous toluene (150 mL) were mixed together and stirred at r.t. for 1.5 h before it was cooled to –13 °C (crushed ice/salt bath). The Still–Gennari phosphonate (14.1 g, 44 mmol, 100 mol%) was added and this mixture was stirred for a further 15 min before Garner's aldehyde (10.1 g, 44 mmol, 100 mol%) dissolved in anhydrous toluene (5 mL) was added slowly to the solution. The reaction mixture was stirred for 1 h at –13 °C before the cooling bath was changed to an ice bath. After 18 h, the reaction was quenched with H_3PO_4 (0.5 M, 160 mL), the phases were separated, and the aqueous layer was extracted with EtOAc (4 × 100 mL). The combined organic layers were dried with Na_2SO_4 and concentrated in vacuo. The crude product was purified by column chromatography [methyl *tert*-butyl ether (MTBE)–hexanes, 15%] to afford the *Z*-enoate **2**.

Yield: 11.1 g (88%); white crystals; mp 54.5–56.0 °C; $[\alpha]_D^{20}$ +30.5 (*c* 1.00, $CHCl_3$).

^1H NMR ($CDCl_3$, 400 MHz): δ = 1.39 (s, 9 H), 1.49 (s, 3 H), 1.53 (s, 3 H), 3.71 (s, 3 H), 3.77 (dd, *J* = 3.1, 9.2 Hz, 1 H), 4.27 (m, 1 H), 5.4 (m, 1 H), 5.84 (t, *J* = 10.4 Hz, 1 H), 6.25 (dd, *J* = 9.1, 10.9 Hz, 1 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 23.7, 26.6, 28.3, 51.3, 55.5, 68.7, 79.9, 94.4, 119.0, 151.2, 151.8, 166.2.

Anal. Calcd for $C_{14}H_{23}NO_5$: C, 58.93; H, 8.12; N, 4.91. Found: C, 58.98; H, 8.34; N, 4.89.

(*S*)-*tert*-Butyl 4-[(1*S*,2*S*)-2-(Methoxycarbonyl)-1,2-dihydroxyethyl]-2,2-dimethyloxazolidine-3-carboxylate (3a)

Z-enoate **2** (3.18 g, 11.2 mmol, 100 mol%) was dissolved in acetone–H_2O (5:1, 60 mL). To this solution were added NMO (1.89 g, 14 mmol, 125 mol%) and citric acid (1.61 g, 8.4 mmol, 75 mol%). The solution was cooled to 0 °C and OsO_4 (2.5 wt% in *t*-BuOH, 2.8 mL, 57 mg, 0.22 mmol, 2 mol%) was added to the mixture, which was allowed to react for 3.5 h at r.t. before it was quenched with solid Na_2SO_3. Acetone was evaporated in vacuo before the slurry was partitioned between EtOAc (30 mL) and H_2O (30 mL). The aqueous layer was extracted with EtOAc (3 × 30 mL) and the combined organic extracts were washed with brine (30 mL), dried (Na_2SO_4) and concentrated in vacuo. The crude product was purified by column chromatography (EtOAc–hexanes, 30%) to afford diol **3a**.

Yield: 3.40 g (95%); colorless oil; $[\alpha]_D^{20}$ –11.7 (*c* 1.00, $CHCl_3$).

^1H NMR ($CDCl_3$, 400 MHz): δ = 1.49 (m, 15 H), 3.10 (d, *J* = 8.4 Hz, 1 H), 3.71 (s, 3 H), 3.96 (dd, *J* = 5.5, 8.8 Hz, 1 H), 3.98–4.10 (m, 2 H), 4.15 (d, *J* = 9.2 Hz, 1 H), 4.33 (d, *J* = 8.8 Hz, 1 H), 4.84 (d, *J* = 10.2 Hz, 1 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 24.2, 26.2, 28.3, 52.1, 58.3, 65.3, 73.4, 73.7, 81.9, 94.4, 154.4, 171.7.

HRMS: *m*/*z* [M^+] calcd for $C_{14}H_{25}NO_7$: 319.1631; found: 319.1628.

(*S*)-*tert*-Butyl 4-[(5*S*,6*S*)-6-(Methoxycarbonyl)-2,2,3,3,8,8,9,9-octamethyl-4,7-dioxa-3,8-disiladecan-5-yl]-2,2-dimethyloxazolidine-3-carboxylate (6)

Diol **3a** (900 mg, 2.8 mmol, 100 mol%) was dissolved in anhydrous CH_2Cl_2 (30 mL) and the solution was cooled to 0 °C on an ice bath. 2,6-Lutidine (1.05 mL, 9.0 mmol, 320 mol%) was added and, 15 min later, TBSOTf (1.56 mL, 6.8 mmol, 240 mol%) was added. The reaction was complete in 45 min and sat. $NaHCO_3$ was poured into the flask. Phases were separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were dried (Na_2SO_4) and evaporated. Purification by column chromatography (MTBE–hexanes, 15%) afforded the TBS ether **6**.

Yield: 1.555 g (100%); colorless oil; $[\alpha]_D^{20}$ –29.2 (*c* 1.11, CH_2Cl_2).

^1H NMR ($CDCl_3$, 400 MHz): δ = 0.04 (s, 3 H), 0.06 (s, 3 H), 0.08 (s, 3 H), 0.13 (s, 3 H), 0.91 (s, 18 H), 1.46 (s, 12 H), 1.54 (s, 3 H), 3.74 (s, 3 H), 3.92 (dd, *J* = 7.3, 8.8 Hz, 1 H), 4.09 (m, 1 H), 4.27 (dd, *J* = 3.6, 8.8 Hz, 1 H), 4.34 (br s, 1 H), 4.42 (br s, 1 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = –5.4, –5.1, –4.2, 18.0, 18.2, 24.8, 25.7, 26.0, 27.1, 28.4, 51.8, 58.7, 63.5, 74.1, 76.4, 80.0, 93.3, 152.9, 172.0.

HRMS: *m*/*z* [M^+ + Na] calcd for $C_{26}H_{53}NO_7Si_2Na$: 570.3258; found: 570.3278.

Preparation of $FeCl_3$ Adsorbed on Silica[17]

Ferrichloride hexahydrate (1.21 g, 4.5 mmol) was dissolved in acetone (16 mL). To this yellow solution was added silica (Merck 60; 10 g) in one portion. The mixture was stirred for 5 min before the solvents were evaporated in vacuo. Further drying was performed under high vacuum. The $FeCl_3$–SiO_2 was collected as a yellow powder.

***tert*-Butyl (3*S*,4*S*,5*S*)-4,5-Bis(*tert*-butyldimethylsilyloxy)-6-oxotetrahydro-2*H*-pyran-3-ylcarbamate (7)**

TBS ether **6** (35.8 mg, 65 μmol, 100 mol%) was dissolved in $CHCl_3$ (5 mL). To this solution was added $FeCl_3$–SiO_2 (prepared as described above; 15 mg). After 17 h, the solid was filtered off and the solution was concentrated in vacuo. The crude product was purified by column chromatography (MTBE–hexanes, 15%) to afford lactone **7** as a colorless oil (14.2 mg, 45%), the open chain alcohol **8** as a colorless oil (7.0 mg, 21%) and also some unreacted TBS ether **6** (5.2 mg, 14%).

$[\alpha]_D^{20}$ –16.1 (*c* 1.09, $CHCl_3$).

^1H NMR ($CDCl_3$, 400 MHz): δ = 0.11 (s, 3 H), 0.13 (s, 3 H), 0.15 (s, 3 H), 0.20 (s, 3 H), 0.90 (s, 9 H), 0.93 (s, 9 H), 1.45 (s, 9 H), 4.12 (dd, *J* = 8.8, 10.4 Hz, 1 H),4.17–4.28 (m, 3 H), 4.31 (dd, *J* = 6.5, 10.4 Hz, 1 H), 4.86 (d, *J* = 8.8 Hz, 1 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = –5.6, –5.0, –4.6, –4.0, 18.3, 18.6, 25.9, 26.0, 28.3, 48.2, 68.1, 72.5, 72.9, 80.3, 154.9, 170.3.

HRMS: *m*/*z* [M^+ + H] calcd for $C_{22}H_{46}NO_6Si_2$: 476.2863; found: 476.2855.

(*S*)-*tert*-Butyl [(1*S*,2*S*)-2-Methoxycarbonyl]-1,2-bis(benzyloxy)-2,2-dimethyloxazolidine-3-carboxylate (9)

NaH (60% dispersion in oil, 90 mg, 2.26 mmol, 240 mol%) was washed with hexanes, mixed with DMF (4 mL), and cooled to 0 °C in an ice bath. Diol **3a** (300 mg, 0.94 mmol, 100 mol%) in DMF (4 mL) was added dropwise to the solution. The reaction mixture was stirred for 30 min and BnBr (270 μL, 2.27 mmol, 240 mol%) was added. The mixture was stirred for a further 30 min at 0 °C before it was allowed to warm to r.t. After 24 h, the reaction was quenched with sat. NH_4Cl (10 mL) and the solution was partitioned between EtOAc (10 mL) and H_2O (10 mL). The aqueous layer was extracted

with EtOAc (2 × 10 mL) and the combined organic phases were dried (Na_2SO_4) and concentrated. The crude product was purified by column chromatography (EtOAc–hexanes, 20%) to afford benzyl ether **9**.

Yield: 310 mg (66%); colorless oil; $[\alpha]_D^{20}$ –44.3 (*c* 0.96, $CHCl_3$).

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.44–1.49 (m, 15 H), 3.71 (s, 3 H), 3.82 (s, 1 H), 3.89 (dd, *J* = 7.2, 8.8 Hz, 1 H), 4.11 (d, *J* = 4.8 Hz, 1 H), 4.21 (dd, *J* = 4.0, 8.8 Hz, 1 H), 4.39–4.42 (m, 2 H), 4.61 (d, *J* = 3.2 Hz, 2 H), 4.68 (d, *J* = 12 Hz, 1 H), 7.30–7.34 (m, 10 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 23.9, 25.3, 27.6, 50.8, 57.4, 62.5, 64.6, 71.7, 77.6, 78.7, 79.1, 93.0, 126.5, 126.8, 126.9, 127.2, 127.4, 127.5, 136.4, 137.3, 151.4, 169.8.

HRMS: *m*/*z* [M$^+$ + Na] calcd for $C_{28}H_{37}NO_7Na$: 522.2468; found: 522.2451.

tert-Butyl (2*S*,3*S*,4*S*)-4-(Methoxycarbonyl)-3,4-bis(benzyloxy)-1-hydroxybutan-2-ylcarbamate (10)

PTSA (9.6 mg, 0.05 mmol, 20 mol%) was added to a solution of benzyl ether **9** (125 mg, 0.25 mmol, 100 mol%) in MeOH (2 mL). The reaction mixture was stirred at r.t. for 19 h before it was neutralized with sat. $NaHCO_3$. Solvents were evaporated in vacuo and the crude mixture was partitioned between Et_2O (5 mL) and sat. $NaHCO_3$ (5 mL). The aqueous layer was extracted with Et_2O (4 × 5 mL), and the combined organic layers were dried with Na_2SO_4 and concentrated. Purification by column chromatography (EtOAc–hexanes, 30%) afforded **10** (41.2 mg, 36%) as a yellow oil and the cyclized lactone **11** (15.7 mg, 15%) as white crystals.

$[\alpha]_D^{20}$ –28.8 (*c* 0.95, $CHCl_3$).

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.41 (s, 9 H), 2.52 (br s, 1 H), 3.76 (s, 3 H), 3.87–3.90 (m, 2 H), 4.01–4.06 (m, 1 H), 4.24 (d, *J* = 4.0 Hz, 1 H), 4.43 (d, *J* = 11.9 Hz, 1 H), 4.53 (d, *J* = 11.4 Hz, 1 H), 4.61 (d, *J* = 11.5 Hz, 1 H), 4.78 (d, *J* = 11.9 Hz, 1 H), 4.95 (s, 1 H), 5.10 (br s, 1 H), 7.26–7.35 (m, 10 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 28.3, 52.1, 62.5, 72.7, 73.5, 74.2, 78.2, 79.6, 128.0, 128.06, 128.10, 128.41, 128.45, 128.52, 136.9, 155.7, 170.9.

HRMS: *m*/*z* [M$^+$ + Na] calcd for $C_{25}H_{33}NO_7Na$: 482.2155; found: 482.2139.

tert-Butyl (3*S*,4*S*,5*S*)-4,5-Bis(benzyloxy)-6-oxotetrahydro-2*H*-pyran-3-ylcarbamate (11)

Mp 173.5–174.5 °C (EtOAc–hexanes); $[\alpha]_D^{20}$ –83.1 (*c* 1.06, $CHCl_3$).

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.42 (s, 9 H), 4.07 (d, *J* = 2.4 Hz, 1 H), 4.09 (m, 1 H), 4.14 (d, *J* = 8.5 Hz, 1 H), 4.17 (m, 1 H), 4.27 (m, 1 H), 4.66 (d, *J* = 11.7 Hz, 1 H), 4.71 (d, *J* = 12.0 Hz, 1 H), 4.86 (br s, 1 H), 5.05 (d, *J* = 11.7 Hz, 1 H), 5.14 (d, *J* = 11.9 Hz, 1 H), 7.29–7.43 (m, 10 H).

^{13}C NMR ($CDCl_3$, 100 MHz, 50 °C): δ = 28.3, 47.3, 68.2, 73.7, 74.3, 76.0, 77.2, 80.3, 128.0, 128.07, 128.09, 128.2, 128.6, 137.2, 137.7, 154.9, 169.4.

HRMS: *m*/*z* [M$^+$ + Na] calcd for $C_{24}H_{29}NO_6Na$: 450.1893; found: 450.1908.

tert-Butyl (2*S*,3*S*,4*S*)-4-(Methoxycarbonyl)-3,4-bis(benzyloxy)-1-methoxybutan-2-ylcarbamate (12)

Alcohol **10** (241 mg, 0.524 mmol, 100 mol%) was dissolved in anhydrous MeCN (7 mL). Ag_2O (558 mg, 2.41 mmol, 460 mol%) and MeI (326 μL, 5.24 mmol, 1000 mol%) were successively added to the solution. The reaction flask was protected from light and allowed to react at r.t. for 20 h. The mixture was filtered through a pad of Celite and concentrated in vacuo. The crude product was purified by column chromatography (EtOAc–hexanes, 40%) to afford the methyl ether **12**.

Yield: 197 mg (79%); $[\alpha]_D^{20}$ –13.7 (*c* 1.0, $CHCl_3$).

^{1}H NMR ($CDCl_3$, 400 MHz, 60 °C): δ = 1.41 (s, 9 H), 3.25 (s, 3 H), 3.39 (dd, *J* = 4.4, 9.5 Hz, 1 H), 3.55 (dd, *J* = 4.4, 9.5 Hz, 1 H), 3.72 (s, 3 H), 3.92 (dd, *J* = 3.5, 7.5 Hz, 1 H), 4.13 (ddt, *J* = 4.5, 7.7, 9.1 Hz, 1 H), 4.25 (d, *J* = 3.5 Hz, 1 H), 4.45 (d, *J* = 11.7 Hz, 1 H), 4.52 (d, *J* = 11.5 Hz, 1 H), 4.65 (d, *J* = 11.5 Hz, 1 H), 4.74 (d, *J* = 11.7 Hz, 1 H), 4.78 (br s, 1 H), 4.95 (s, 1 H), 7.25–7.37 (m, 10 H).

^{13}C NMR ($CDCl_3$, 100 MHz, 60 °C): δ = 28.4, 51.7, 58.7, 64.2, 71.4, 72.8, 73.6, 74.2, 79.5, 80.0, 127.6, 127.8, 127.98, 128.00, 128.3, 128.4, 137.6, 138.2, 155.4, 171.0.

HRMS: *m*/*z* [M$^+$ + Na] calcd for $C_{26}H_{35}NO_7Na$: 496.2311; found: 496.2332.

(2*S*,3*S*,4*S*)-Methyl 2,3-Bis(benzyloxy)-4-dimethylamino-5-methoxypentanoate (13)

Methyl ether **12** (29 mg, 0.061 mmol, 100 mol%) was dissolved in anhydrous CH_2Cl_2 (0.5 mL) and TFA (100 μL, 1.0 mmol, 1640 mol%) was added dropwise. The reaction mixture was allowed to react for 3 h before the solvents were evaporated in vacuo. The intermediate ammonium salt was dissolved in H_2O–MeCN (2:5, 1.4 mL) and CH_2O solution (60 μL, 0.77 mmol, 1280 mol%) was added. The mixture was stirred for 65 min then NaOAc (63.2 mg, 0.77 mmol, 1280 mol%) was added and the mixture was stirred for a further 35 min. $NaBH_3CN$ (6.6 mg, 0.11 mmol, 175 mol%) was added and the suspension was allowed to react for 24 h. The reaction was quenched with sat. $NaHCO_3$ (5 mL) and the mixture was partitioned between 0.1 M HCl (10 mL) and EtOAc (10 mL). The aqueous layer was extracted with EtOAc (3 × 10 mL) and the combined organic layers were washed with brine (10 mL), dried with Na_2SO_4 and evaporated to dryness. Purification by column chromatography (EtOAc–hexanes, 30%) provided the desired amine **13**.

Yield: 9.4 mg (38%); pale-yellow oil; $[\alpha]_D^{20}$ –30.9 (*c* 0.66, $CHCl_3$).

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 2.24 (s, 6 H), 3.11 (ddd, *J* = 2.6, 7.4, 9.8 Hz, 1 H), 3.28 (s, 3 H), 3.53 (dd, *J* = 7.6, 10.2 Hz, 1 H), 3.64 (dd, *J* = 10.2, 2.7 Hz, 1 H), 3.71 (s, 3 H), 3.90 (dd, *J* = 2.2, 9.7 Hz, 1 H), 4.31 (d, *J* = 2.2 Hz, 1 H), 4.43 (d, *J* = 11.3 Hz, 1 H), 4.53 (d, *J* = 12.3 Hz, 1 H), 4.56 (d, *J* = 11.3 Hz, 1 H), 4.87 (d, *J* = 12.3 Hz, 1 H), 7.26–7.29 (m, 10 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 41.8, 51.5, 58.6, 61.5, 69.5, 72.5, 72.6, 77.2, 79.7, 127.52, 127.55, 127.82, 127.84, 128.24, 128.25, 138.0, 138.3, 170.8.

HRMS: *m*/*z* [M$^+$ + H] calcd for $C_{23}H_{32}NO_5$: 402.2280; found: 402.2289.

(*S*)-Methyl 2-(*tert*-Butoxycarbonylamino)-3-methoxypropanoate (18)

tert-Butoxycarbonyl L-serine methyl ester (3.30 g, 15.0 mmol, 100 mol%) was dissolved in MeCN (130 mL) and Ag_2O (17.8 g, 76.8 mmol, 510 mol%) and MeI (9.50 mL, 153 mmol, 1020 mol%) were added successively. The flask was protected from light and the reaction mixture was allowed to react at r.t. for 28 h. The mixture was filtered through a pad of Celite and the solvent was evaporated. Column chromatography (MTBE–hexanes, 1:2) gave pure methyl ether **18**.

Yield: 2.88 g (82%); pale-yellow oil; $[\alpha]_D^{20}$ +9.4 (*c* 1.28, CH_2Cl_2).

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.45 (s, 9 H), 3.34 (s, 3 H), 3.59 (dd, *J* = 3.5, 9.3 Hz, 1 H), 3.79 (s, 3 H), 3.81 (dd, *J* = 2.7, 9.0 Hz, 1 H), 4.42 (app. td, *J* = 3.3, 8.4 Hz, 1 H), 5.38 (d, *J* = 8.1 Hz, 1 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 28.2, 52.4, 53.9, 59.2, 79.9, 155.4, 171.1.

HRMS: *m*/*z* [M$^+$ + Na] calcd for $C_{10}H_{19}NO_5Na$: 256.1161; found: 256.1168.

(*S*)-*tert*-Butyl 1-Methoxy-3-oxopropan-2-ylcarbamate (17)

Methyl ether **18** (2.05 g, 8.8 mmol, 100 mol%) was dissolved in anhydrous toluene (25 mL) and the solution was cooled to –78 °C. DIBAL-H (1 M in toluene, 15 mL, 15 mmol, 170 mol%) was added during 30 min and the reaction mixture was allowed to react for 6 h at –78 °C before it was quenched with MeOH (3 mL). HCl (1 M, 30 mL) was added and the mixture was allowed to warm to r.t. The phases were separated and the aqueous phase was extracted with EtOAc (2 × 20 mL). The combined organic extracts were washed with brine (20 mL), dried (Na_2SO_4) and concentrated in vacuo. The crude aldehyde **17** was used as such in the following reaction.

(*R*,*Z*)-Methyl 4-(*tert*-Butoxycarbonylamino)-5-methoxypent-2-enoate (16)

18-Crown-6 ether (4.65 g, 17.6 mmol, 200 mol%) and K_2CO_3 (6.08 g, 44.0 mmol, 500 mol%) were mixed with anhydrous toluene (30 mL). After stirring at r.t. for 1.5 h, the reaction flask was cooled to –78 °C and the Still–Gennari phosphonate (1.86 mL, 8.8 mmol, 100 mol%) was added dropwise to the vigorously stirred mixture. After 1 h, the crude aldehyde **17** (1.79 g, 8.8 mmol, 100 mol%) from the previous reaction dissolved in anhydrous toluene (20 mL) was added slowly to the mixture. After 8 h, the reaction mixture was allowed to warm to 0 °C gradually and, after 12 h, the reaction was quenched with 0.5 M H_3PO_4 (40 mL). The phases were separated and the aqueous layer was extracted with EtOAc (3 × 30 mL). The combined organic layers were dried with Na_2SO_4, concentrated under reduced pressure, and the crude product was purified by column chromatography (MTBE–hexanes, 1:2) to afford enoate **16**.

Yield: 1.41 g (62%); pale-yellow oil; *E*/*Z* ratio 1:12 (NMR analysis); $[\alpha]_D^{20}$ +31.6 (*c* 1.14, CH_2Cl_2).

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.43 (s, 9 H), 3.36 (s, 3 H), 3.52 (m, 1 H), 3.58 (dd, *J* = 3.7, 9.5 Hz, 1 H), 3.72 (s, 3 H), 5.25 (br s, 1 H), 5.32 (m, 1 H), 5.86 (dd, *J* = 1.3, 11.5 Hz, 1 H), 6.19 (dd, *J* = 8.1, 11.3 Hz, 1 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 28.3, 49.2, 51.3, 58.9, 74.2, 79.6, 120.0, 146.4, 155.5, 166.0.

HRMS: *m*/*z* [M$^+$ + Na] calcd for $C_{12}H_{21}NO_5Na$: 282.1317; found: 282.1313.

(*R*)-*tert*-Butyl 2-(Methoxymethyl)-5-oxo-2,5-dihydro-1*H*-pyrrole-1-carboxylate (15)

Enoate **16** (1.34 g, 5.2 mmol, 100 mol%) was dissolved in anhydrous benzene (50 mL) and $(Bu_2ClSn)_2O$ (143 mg, 0.26 mmol, 5 mol%) was added and allowed to dissolve. The reaction mixture was then heated at reflux for 77 h before benzene was evaporated. The crude product was purified by column chromatography (EtOAc–hexanes, 40%) to afford lactam **15**.

Yield: 860 mg (73%); pale-yellow oil; $[\alpha]_D^{20}$ +37.1 (*c* 1.40, CH_2Cl_2).

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.57 (s, 9 H), 3.31 (s, 3 H), 3.47 (dd, *J* = 7.1, 9.3 Hz, 1 H), 3.95 (dd, *J* = 3.8, 9.3 Hz, 1 H), 4.70 (m, 1 H), 6.13 (dd, *J* = 1.6, 6.0 Hz, 1 H), 7.28 (dd, *J* = 2.0, 6.0 Hz, 1 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 28.1, 59.5, 61.7, 71.7, 83.1, 127.0, 149.3, 149.5, 169.1.

HRMS: *m*/*z* [M$^+$ + Na] calcd for $C_{11}H_{17}NO_4Na$: 250.1055; found: 250.1066.

Determination of ee. Column: Supelco cyclodextrin-γ; inj. temp.: 240 °C; flow: 28 cm/s; 100–220 °C; 8 °C/min; detect. temp.: 240 °C; t_R (*S*) = 14.981 min; t_R (*R*) = 15.222 min.

(2*S*,3*S*,4*S*)-*tert*-Butyl 3,4-Dihydroxy-2-(methoxymethyl)-5-oxopyrrolidine-1-carboxylate (14)

Lactam **15** (262 mg, 1.15 mmol, 100 mol%) was dissolved in acetone–H_2O (6:1, 10 mL) and NMO (194.8 mg, 1.44 mmol, 125 mol%) was added, followed by citric acid monohydrate (182 mg, 0.87 mmol, 75 mol%) and OsO_4 (2.5 wt% in *t*-BuOH, 434 μL, 0.035 mmol, 3 mol%). After 5.5 h, the reaction reached completion and was quenched by adding sat. Na_2SO_3 (3 mL). After 15 min, the mixture was concentrated in vacuo and the crude residue was partitioned between EtOAc (15 mL) and H_2O (15 mL). The phases were separated and the aqueous layer was extracted with EtOAc (2 × 15 mL). The combined organic phases were dried (Na_2SO_4) and concentrated in vacuo to afford diol **14**.

Yield: 299 mg (99%); colorless highly viscous oil; $[\alpha]_D^{20}$ –2.3 (*c* 1.10, CH_2Cl_2).

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.53 (s, 9 H), 3.25 (br s, 1 H), 3.31 (s, 3 H), 3.59 (dd, *J* = 2.6, 10.2 Hz, 1 H), 3.76 (br s, 1 H), 3.65 (dd, *J* = 3.7, 10.2 Hz, 1 H), 4.16 (dd, *J* = 2.6, 3.3 Hz, 1 H), 4.33 (d, *J* = 5.1 Hz, 1 H), 4.60 (d, *J* = 5.1 Hz, 1 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 28.0, 59.3, 63.1, 69.1, 70.8, 71.5, 83.7, 149.6, 174.3.

HRMS: *m*/*z* [M$^+$ + Na] calcd for $C_{11}H_{19}NO_6Na$: 284.1110; found: 284.1104.

(3a*S*,4*S*,6a*S*)-*tert*-Butyl 4-(Methoxymethyl)-2,2-dimethyl-6-oxodihydro-3a*H*-[1,3]dioxolo[4,5-c]pyrrole-5-(4*H*)-carboxylate (20a)

Diol **14** (75 mg, 0.287 mmol, 100 mol%) was dissolved in 2,2-dimethoxypropane (2 mL) at r.t. and PTSA (2.5 mg, 0.013 mmol, 5 mol%) was added. The mixture was allowed to react for 18 h then a few drops of sat. aq $NaHCO_3$ were added in order to neutralize the solution. Solvents were evaporated in vacuo and the residue was partitioned between EtOAc (5 mL) and sat. aq $NaHCO_3$ (5 mL). The aqueous layer was extracted with EtOAc (2 × 5 mL) and the combined organic layers were dried (Na_2SO_4) and concentrated. The crude acetal was purified by column chromatography (EtOAc–hexanes, 50%) to afford acetal **20a**.

Yield: 81.5 mg (94%); pale-yellow, highly viscous oil; $[\alpha]_D^{20}$ +27.8 (*c* 1.14, CH_2Cl_2).

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.31 (s, 3 H), 1.39 (s, 3 H), 1.49 (s, 9 H), 3.26 (s, 3 H), 3.53 (dd, *J* = 2.0, 10.0 Hz, 1 H), 3.61 (dd, *J* = 2.6, 10.0 Hz, 1 H), 4.22 (dd, *J* = 2.1, 2.5 Hz, 1 H), 4.47 (d, *J* = 5.4 Hz, 1 H), 4.61 (d, *J* = 5.4 Hz, 1 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 25.6, 27.0, 27.9, 59.4, 60.2, 70.8, 75.4, 77.9, 83.5, 111.8, 149.7, 171.2.

HRMS: *m*/*z* [M$^+$ + Na] calcd for $C_{14}H_{23}NO_6Na$: 324.1423; found: 324.1427.

(2*S*,3*S*,4*S*)-1-(*tert*-Butoxycarbonyl)-2-(methoxymethyl)-5-oxopyrrolidine-3,4-diyl Diacetate (20b)

Diol **14** (14.5 mg, 0.056 mmol, 100 mol%) was dissolved in anhydrous pyridine (1 mL) and DMAP (1.4 mg, 0.011 mmol, 20 mol%) was added to the solution followed by Ac_2O (30 μL, 0.33 mmol, 600 mol%). After 80 min the reaction reached completion and the solution was partitioned between Et_2O (10 mL) and 1 M HCl solution (20 mL). The aqueous layer was extracted with Et_2O (3 × 10 mL) and the combined organic layers were washed with sat. $CuSO_4$ (10 mL), dried ($MgSO_4$) and concentrated in vacuo. The crude product was purified by column chromatography (MTBE–hexanes, 1:2) to afford diacetate **20b**.

Yield: 17.3 mg (90%); colorless oil; $[\alpha]_D^{20}$ +13.8 (*c* 1.11, CH_2Cl_2).

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.56 (s, 9 H), 2.10 (s, 3 H), 2.12 (s, 3 H), 3.36 (s, 3 H), 3.66 (dd, *J* = 2.3, 10.2 Hz, 1 H), 3.71 (dd,

J = 3.0, 10.2 Hz, 1 H), 4.18 (dd, J = 2.5, 2.8 Hz, 1 H), 5.44 (d, J = 5.5 Hz, 1 H), 5.78 (d, J = 5.7 Hz, 1 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 20.3, 20.7, 28.0, 59.5, 61.3, 69.7, 69.8, 70.3, 84.1, 149.6, 167.9, 169.3, 170.0.

HRMS: m/z [M^+ + Na] calcd for $C_{15}H_{23}NO_8Na$: 368.1321; found: 368.1327.

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