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A Short and Efficient Synthesis of (2\text{S},3\text{S},4\text{S})-\text{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, \(\alpha,\beta\)-unsaturated lactam, dihydroxylation

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

Calyulin 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.\textsuperscript{5,6} Our earlier effort showed that the C33–C37 fragment can be synthesized starting from the commercially available Garner’s aldehyde.\textsuperscript{7} The highlight of the synthesis is the diastereoselectivity of dihydroxylation (\(>99:1\) favoring the \textit{anti}-product 3a). Comparison of our results to those by Shioiri and co-workers,\textsuperscript{8} who obtained a selectivity of 55:45 (\textit{syn/anti}) 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.\textsuperscript{7} Dihydroxylation under the Upjohn conditions (Os\textsubscript{4}, NMO)\textsuperscript{9} provided the diol 3a in a modest 50% isolated yield. It is well known that electron-deficient double bonds are slug-

Figure 1

Scheme 1 Diastereoselectivity of the dihydroxylation; (a) by Koskinen and co-workers,\textsuperscript{7} and (b) by Shioiri and co-workers.\textsuperscript{8}
gish towards osmylation. The catalytic cycle shuts down and the reaction stops totally because of the rising pH 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-butylidimethylsilyl 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, FeCl₃ adsorbed on silica or biphasic 1 M HCl/CH₂Cl₂) 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 started from (Scheme 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-workers¹²a and Ikota¹²b 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 five¹²a and six¹²b 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 in acetonitrile. The methyl ether 12 was then subjected to deprotection and reductive amination, which provided the N,N-dimethylaniline 13 in 38% yield (over two steps). The ¹H 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.
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 (Bu₂ClSn)₂O in benzene at reflux provided 15 in 73% yield, while the milder (Bu₃Sn)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 TBSCI 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(dibutylchlorostannylene)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. Et₃N, benzene and toluene were distilled from metallic Na.
THF was distilled from Na/benzophenone, CH₂Cl₂ from CaH₂, and DMF from molecular sieves (4Å/100mL). Other solvents and reagents were used as obtained from the supplier. Analytical TLC was performed on Merck silica gel 60 (230–400 mesh). Column chromatography was performed using Merck silica gel 60 (230–400 mesh) and p.a. grade solvents. ¹H and ¹³C NMR spectra were recorded in CDCl₃ with a Bruker Avance 400 (¹H: 399.98 MHz; ¹³C: 100.59 MHz) spectrometer. The chemical shifts are reported in ppm relative to residual CHCl₃ (δ = 7.26 ppm for ¹H and 77.0 ppm for ¹³C). 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-Methoxy-carbonyl][vinyl]-2,2-dimethoxyoxazolidine-3-carboxylate (2)
18-Crown-6-ether (2.8 mg, 10 mmol) was added to the mixture, which was allowed to react for 3.5 h at r.t. before it was quenched with sat. NH₄Cl (10 mL) and the solution was partitioned between EtOAc (30 mL) and H₂O (30 mL). The aqueous layer was extracted with EtOAc (3 mL). The combined organic layers were dried (Na₂SO₄) and evaporated. Purification by column chromatography (EtOAc–hexanes, 30%) afforded the TBS ether 6. Yield: 1.555 g (100%); colorless oil; [α]D20 +29.2 (c 1.11, CH₂Cl₂).

### Preparation of FeCl₃ Adsorbed on Silica
Ferrichloride hexahydrate (1.21 g, 4.5 mmol) was dissolved in ace-tone (16 mL). To this yellow solution was added FeCl₃–SiO₂ (prepared as described above; 10 mg). The solution was stirred for 5 min before the solvents were evaporated in vacuo. Further drying was performed under high vacuum. The FeCl₃–SiO₂ was collected as a yellow powder.

### (S)-tert-Butyl 4-[1(S,2S)-2-(Methoxy-carbonyl)-1,2-dihydroxy-ethyl]-2,2-dimethoxyoxazolidine-3-carboxylate (3a)
Z-enoate 2 (3.18 g, 11.2 mmol, 100 mol%) was dissolved in anhydrous toluene (5 mL) was added slowly to the solution. The reaction was complete in 45 min and sat. NaHCO₃ was poured into the flask. Phases were separated and the aqueous layer was extracted with CH₂Cl₂ (3 x 20 mL). The combined organic layers were dried (Na₂SO₄) and evaporated. Purification by column chromatography (MTBE–hexanes, 15%) afforded the TBS ether 6. Yield: 1.555 g (100%); colorless oil; [α]D20 +29.2 (c 1.11, CH₂Cl₂).

### (S)-tert-Butyl 4-[1(S,2S)-2-(Methoxy-carbonyl)-1,2-bis(benzoxyl)-2,2-dimethoxyoxazolidine-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 NaHCl (10 mL) and the solution was partitioned between EtOAc (10 mL) and H₂O (10 mL). The aqueous layer was extracted...
with EtOAc (2 × 10 mL) and the combined organic phases were dried (Na2SO4) and concentrated. The crude product was purified by column chromatography (EtOAc–hexanes, 20%) to afford benzyl ether 9.

Yield: 310 mg (66%); colorless oil; [α]D190 = −24.3 (c 0.96, CHCl3).

1H NMR (CDCl3, 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 = 12.0 Hz, 1 H), 7.30–7.34 (m, 10 H).

13C NMR (CDCl3, 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.


tert-Butyl (2S,3S,4S)-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. NaHCO3. Solvents were evaporated in vacuo and the crude product was partitioned between Et2O (5 mL) and sat. NaHCO3 (5 mL). The aqueous layer was extracted with Et2O (4 × 5 mL), and the combined organic layers were dried with Na2SO4 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.

[a]D190 = −28.8 (c 0.95, CHCl3).

1H NMR (CDCl3, 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).

13C NMR (CDCl3, 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 C23H32NO5Na: 482.2155; found: 482.2139.

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

Mp 173.5–174.5 °C (EtOAc–hexanes); [α]D190 = −30.9 (c 0.66, CHCl3).

1H NMR (CDCl3, 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 = 7.7, 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).

13C NMR (CDCl3, 100 MHz): δ = 41.8, 51.5, 58.6, 61.5, 69.5, 72.5, 72.6, 77.2, 79.7, 127.5, 127.52, 127.55, 127.82, 127.84, 128.24, 128.25, 138.0, 138.3, 170.8.


(5)-Methyl 2-(tert-Butyloxy)carbamino)-3-methoxypropanoate (18)

tert-Butyloxy carbonyl L-serine methyl ester (3.30 g, 15.0 mmol, 100 mol%) was dissolved in MeCN (130 mL) and Ag2O (17.8 g, 76.8 mmol, 510 mol%) was added successively. The flask was protected from light and the reaction mixture was allowed to react at r.t. for 24 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; [α]D190 = 49.4 (c 1.28, CH2Cl2).

1H NMR (CDCl3, 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. dd, J = 3.3, 8.4 Hz, 1 H), 5.38 (d, J = 8.1 Hz, 1 H).

13C NMR (CDCl3, 100 MHz): δ = 28.2, 52.4, 53.9, 59.2, 79.9, 155.4, 171.1.
HRMS: m/z [M+ + Na] calcd for C10H15NO5Na: 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). At –78 °C and the Still–Gennari phosphonate (1.86 mL, 8.8 mmol, 100 mol%) was added, followed by citric acid monohydrate (182 mg, 0.87 mmol, 75 mol%) and OsO4 (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. Na2SO3 (3 mL). After 15 min, the mixture was concentrated in vacuo and the crude residue was partitioned between EtOAc (15 mL) and H2O (15 mL). The phases were separated and the aqueous layer was extracted with EtOAc (2 × 15 mL). The combined organic phases were dried (Na2SO4) and concentrated in vacuo to afford diol 14.

Yield: 299 mg (99%); colorless highly viscous oil; [α]20D = 2.3 (c 1.10, CH3Cl).

1H NMR (CDCl3, 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), 4.65 (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).

13C NMR (CDCl3, 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 C17H20NO8Na: 284.1110; found: 284.1104.

(3aS,4S,6aS)-tert-Butyl 4-(Methoxymethyl)-2,2-dimethyl-6-oxo-3aH-1,3-dioxol[4,5-c]pyrrole-5-(4H)-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 NaHCO3 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 NaHCO3 (5 mL). The aqueous layer was extracted with EtOAc (2 × 5 mL) and the combined organic layers were dried (Na2SO4) 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; [α]20D = +27.8 (c 1.14, CH3Cl).

1H NMR (CDCl3, 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).

13C NMR (CDCl3, 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.


(2S,3S,4S)-1-(tert-Butyloxyphenyl)-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 Ac2O (30 μL, 0.33 mmol, 600 mol%). After 80 min the reaction reached completion and the solution was partitioned between Et2O (10 mL) and 1 M HCl solution (20 mL). The aqueous layer was extracted with Et2O (3 × 10 mL) and the combined organic layers were washed with sat. CuSO4 (10 mL), dried (MgSO4) 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; [α]20D = +13.8 (c 1.11, CH3Cl).

1H NMR (CDCl3, 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,
$J = 3.0, 10.2 \text{ Hz}, 1 \text{ H}), 4.18 \ (dd, J = 2.5, 2.8 \text{ Hz}, 1 \text{ H}), 5.44 \ (d, J = 5.5 \text{ Hz}, 1 \text{ H}), 5.78 \ (d, J = 5.7 \text{ Hz}, 1 \text{ H}).$

$\text{\textsuperscript{13}C NMR (CDCl}_3, 100 MHz): \delta = 20.3, 20.7, 28.0, 59.5, 61.3, 69.7, 69.8, 70.3, 84.1, 149.6, 167.9, 169.3, 170.0.$

HRMS: $m/z [M^+ + \text{Na}]$ calcd for C$_{15}$H$_{23}$NO$_8$Na: 368.1321; found: 368.1327.

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References


