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Published in:
SYNTHESIS: STUTTGART

DOI:

Published: 01/01/2010

Please cite the original version:
A Short and Efficient Synthesis of (2S,3S,4S)-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\(^1\) and, a few years later, calyculins B, C, and D by the same group,\(^2\) 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 \(\text{ent}\)-calyculin A was published by Evans and co-workers in 1992,\(^3\) 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 \(\text{anti}\)-product 3a). Comparison of our results to those by Shioiri and co-workers,\(^8\) who obtained a selectivity of 55:45 (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 \(\text{Z}\)-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-
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-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, 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 had been cleaved. We then chose to use benzyl ether 9 with tert-butyldimethylsilyl trifluoromethanesulfonate (TBSOTf) and 2,6-lutidine 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 1H NMR spectra of 13 was in accordance with data reported in the literature.

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 and Ikota have shown that oxidation of an α,β-unsaturated 2-substituted pyrrolidinone provides the diol as a single diastereoisomer. Both groups started from (S)-pyrrolidin-1-ol and prepared differently protected diols (ent-14 derivatives) in five and six 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 (Mel/NaH, MeOTf or CH3N2) failed. Sodium hydride was
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 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 conditions, a substituted Z-enoate undergoes cyclization into lactam with high yields. 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.

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 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. 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(dibutylchlorostannane)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, CHCl₃ from CaH₂, and DMF from molecular sieves (4Å) in a nitrogen atmosphere. Other solvents and reagents were used as obtained from the supplier. Analytical TLC was performed on Merck silica gel F₂₅₄ (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 by HPLC analysis. Melting points were determined in open capillaries using a Stuart SMP3 melting point apparatus. Optical rotations were obtained with a Perkin–Elmer 343 polarimeter. High-resolution mass spectrometric data were measured with a MicroMass LCT Premier spectrometer.

(R)-tert-Butyl 4-((Z)-2-Methoxybenzylidene)[vinyl]-2,2-dimethoxazolidine-3-carboxylate (2)

18-Crown-6-ether (24.2 g, 92 mmol, 210 mol%) and K₂CO₃ (31.7 g, 228 mmol, 520 mol%) were added to the mixture, which was dissolved in anhydrous toluene (5 mL) and the solution was cooled to –13 °C before the cooling bath was changed to an ice bath. After 18 h, the reaction was quenched with H₂PO₄ (0.5 M, 160 mL), the phases were separated, and the azeotropic layer was extracted with EtOAc (4 × 100 mL). The combined organic layers were dried with Na₂SO₄ and concentrated in vacuo. The crude product was purified by column chromatography [methyl tert-butylic ether (MTBE)–hexanes, 15%] to afford the Z-enolate 2.

Yield: 11.1 g (88%); white crystals; mp 54.5–56.0 °C; [α]D²₀ +30.5 (c 1.00, CHCl₃).

¹H NMR (CDCl₃, 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).

¹³C NMR (CDCl₃, 100 MHz): δ = 23.7, 26.6, 28.3, 51.3, 55.5, 68.7, 79.9, 94.4, 119.0, 152.1, 158.1, 166.2. Anal. Calcd for C₁₄H₁₅NO₅: C, 58.93; H, 8.12; N, 4.91. Found: C, 58.98; H, 8.34; N, 4.89.

(S)-tert-Butyl 4-((1S,2S)-2-(Methoxybenzyl)-1,2-dihydroxyethyl)-2,2-dimethoxazolidine-3-carboxylate (3a)

Z-enolate 2 (3.18 g, 11.2 mmol, 100 mol%) was dissolved in anhydrous THF (50 mL) and TBSOTf (1.56 mL, 6.8 mmol, 240 mol%) was added. The mixture was stirred for 30 min at 0 °C before the solution was concentrated in vacuo. Further drying was performed under high vacuum. The yield of 3a was 1.555 g (100%); colorless oil; [α]D²₀ –16.1 (c 1.09, CHCl₃).

¹H NMR (CDCl₃, 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), 1.47 (dd, J = 8.8, 10.4 Hz, 1 H), 4.31 (dd, J = 6.5, 10.4 Hz, 1 H), 4.86 (d, J = 8.8 Hz, 1 H).

¹³C NMR (CDCl₃, 100 MHz): δ = 5.4, –5.1, –4.2, 18.0, 18.2, 24.8, 25.7, 26.0, 27.1, 28.3, 51.8, 58.7, 63.5, 74.1, 76.4, 80.0, 93.3, 152.9, 172.0. HRMS: m/z [M+H] calcd for C₁₄H₁₅NO₅Si₂Na: 370.5278; found: 370.5278.

Preparation of FeCl₃ Adsorbed on Silica

Ferrichloride hexahydrate (1.21 g, 4.5 mmol) was dissolved in acetone (16 mL). To this yellow solution was added silica (Merc 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 FeCl₃–SiO₂ was collected as a yellow powder.

(S)-tert-Butyl (3S,4S,5S)-4,5-Bis[(tert-butyldimethylsilyloxy)-6-oxo-tetrahydro-2H-pyran-3-yl]carbamate (7)

TBS ether (650 mg, 2.8 mmol, 100 mol%) was dissolved in CHCl₃ (5 mL). To this solution was added FeCl₃–SiO₂ (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 the TBS ether 7.

Yield: 0.35 mg (21%); colorless oil; [α]D²₀ +16.1 (c 1.09, CHCl₃).

¹H NMR (CDCl₃, 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), 1.47 (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).

¹³C NMR (CDCl₃, 100 MHz): δ = 5.4, –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+Na] calcd for C₂₆H₅₃NO₇Si₂Na²⁺: 570.3278; found: 570.3278.

(S)-tert-Butyl (3S,4S,5S)-4,5-Bis[(tert-butyldimethylsilyloxy)-6-oxo-tetrahydro-2H-pyran-3-yl]carbamate (7)

TBS ether (650 mg, 2.8 mmol, 100 mol%) was dissolved in CHCl₃ (5 mL). To this solution was added FeCl₃–SiO₂ (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 the TBS ether 7.

Yield: 0.35 mg (21%); colorless oil; [α]D²₀ +16.1 (c 1.09, CHCl₃).

¹H NMR (CDCl₃, 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), 1.47 (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).

¹³C NMR (CDCl₃, 100 MHz): δ = 5.4, –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+Na] calcd for C₂₆H₅₃NO₇Si₂Na²⁺: 570.3278; found: 570.3278.
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]D 20 +44.3 (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, 76.6, 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 C32H34NO7Na: 496.2311; found: 496.2329.

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 tert-butyl (2S,3S,4S)-3,4-bis(benzyloxy)-1-hydroxybutan-2-ylcarbamate (10) (29 mg, 0.061 mmol, 100 mol%) in H2O–MeCN (2:5, 1.4 mL) and Ag2O (17.8 g, 76.8 mmol, 100 mol%) was added. The mixture was stirred for 65 min then NaOAc (63.2 mg, 0.77 mmol) was added and the mixture was stirred for a further 35 min. NaBH4CN (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. NaHCO3 (5 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 Na2SO4 and concentrated in vacuo. The crude product was purified by column chromatography (EtOAc–hexanes, 30%) to afford the methyl ether 12.

Yield: 197 mg (79%); [α]D 20 −13.7 (c 1.0, CHCl3).

1H NMR (CDCl3, 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 (dd, J = 3.5 Hz, 1 H), 4.45 (dd, 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).

13C NMR (CDCl3, 100 MHz, 60 °C): δ = 28.2, 52.4, 53.9, 59.2, 79.9, 155.4, 171.1.

HRMS: m/z [M+Na]+ calcd for C29H33NO7Na: 496.2311; found: 496.2329.

(2S,3S,4S)-Methyl 2,3-Bis(benzyloxy)-4-dimethylaminol-5-methylenepentanoate (13)

Methyl ether 12 (29 mg, 0.061 mmol, 100 mol%) was dissolved in anhydrous CH2Cl2 (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 H2O–MeCN (2:5, 1.4 mL) and CH2O 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. NaBH4CN (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. NaHCO3 (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 Na2SO4 and evaporated to dryness. Purification by column chromatography (EtOAc–hexanes, 30%) provided the desired amine 13.

Yield: 9.4 mg (38%); pale-yellow oil; [α]D 20 +30.9 (c 0.66, CHCl3).

1H NMR (CDCl3, 400 MHz): δ = 2.24 (s, 6 H), 3.11 (dd, 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).

13C NMR (CDCl3, 100 MHz): δ = 41.8, 51.5, 58.6, 61.5, 69.5, 72.5, 72.6, 77.2, 77.9, 127.5, 127.52, 127.55, 127.82, 127.84, 128.24, 128.25, 138.0, 138.3, 170.8.


(5)-Methyl 2-tert-Butoxy carbamoylino)-3-methoxy-propanoate (18)

tert-Butoxy 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%) and Mel (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 (MBTE–hexanes, 1:2) gave pure methyl ether 18.

Yield: 2.88 g (82%); pale-yellow oil; [α]D 20 +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 td, 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.
\[(S,\text{t})\text{-tert-Butyl 1-Methoxy-3-oxopropan-2-ylcarbamate (17)}\]

Methyl ether \(18\) (2.05 g, 8.8 mmol, 100 mol%) was dissolved in anhydrous toluene (25 mL) and the solution was cooled to \(-78^\circ\mathrm{C}\). 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 \(-78^\circ\mathrm{C}\) before it was quenched with MeOH (3 mL). HCl (1 M, 30 mL) was added and the mixture was allowed to warm to room temperature gradually and, after 12 h, the reaction was quenched by adding sat. Na\(_2\)SO\(_4\) (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 \(\times\) 20 mL). The combined organic phases were dried (\(\text{Na}_2\)SO\(_4\)) and concentrated in vacuo. The crude aldehyde 17 was used as such in the following reaction.

\[(R,Z)-\text{Methyl 4-} (\text{t}-\text{Butoxy carbonyl amino})\text{-5-methoxypent-2-enoate (16)}\]

18-Crown-6 ether (4.65 g, 17.6 mmol, 200 mol%) and \(K_2\text{CO}_3\) (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 \(-78^\circ\mathrm{C}\) 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 \(H_3\text{PO}_4\) (40 mL). The phases were separated and the aqueous layer was extracted with EtOAc (3 \(\times\) 30 mL). The combined organic layers were dried with \(\text{Na}_2\)SO\(_4\) and concentrated in vacuo to afford diol 16.

Yield: 1.41 g (62%); pale-yellow oil; \(\text{E}z\) ratio 1:12 (NMR analysis); \([\alpha]_D^{20} +31.6 (c 1.14, \text{CH}_2\text{Cl}_2)\).

\[^1\text{H}\ NMR\ (\text{CDCl}_3, 400 MHz): \delta = 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).

\[^1\text{C}\ NMR\ (\text{CDCl}_3, 100 MHz): \delta = 25.6, 27.0, 27.9, 59.4, 60.2, 70.8, 75.4, 77.9, 83.5, 111.8, 149.7, 171.2.\]

HRMS: \(m/z [M^+ + Na]^{\text{c}}\) calcd for \(C_{14}H_{23}NO_6Na\): 324.1423; found: 324.1427.

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

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 \(\text{NaHCO}_3\) 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 \(\text{NaHCO}_3\) (5 mL). The aqueous layer was extracted with EtOAc (2 \(\times\) 5 mL) and the combined organic layers were dried (\(\text{Na}_2\)SO\(_4\)) 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; \([\alpha]_D^{20} +27.8 (c 1.14, \text{CH}_2\text{Cl}_2)\).

\[^1\text{H}\ NMR\ (\text{CDCl}_3, 400 MHz): \delta = 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\ (dd, \(J = 5.4, 5.4\) Hz, 1 H), 4.61\ (d, \(J = 5.4, 5.4\) Hz, 1 H).

\[^1\text{C}\ NMR\ (\text{CDCl}_3, 100 MHz): \delta = 25.6, 27.0, 27.9, 59.4, 60.2, 70.8, 75.4, 77.9, 83.5, 111.8, 149.7, 171.2.\]

HRMS: \(m/z [M^+ + Na]^{\text{c}}\) calcd for \(C_{14}H_{23}NO_6Na\): 324.1423; found: 324.1427.

\[(2S,3S,4S)-1-(\text{t}-\text{Butoxycarbonyl})\text{-2-(methoxymethyl)-5-oxopyrrolidine-3,4-diyl Diacateate (20b)}\]

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 \(\text{Ac}_2\text{O}\) (30 \(\mu\)L, 0.33 mmol, 600 mol%). After 80 min the reaction reached completion and the solution was partitioned between \(\text{Et}_2\text{O}\) (10 mL) and 1 M HCl solution (20 mL). The aqueous layer was extracted with \(\text{Et}_2\text{O}\) (3 \(\times\) 10 mL) and the combined organic layers were washed with sat. \(\text{CuSO}_4\) (10 mL), dried (\(\text{MgSO}_4\)) and concentrated in vacuo. The crude product was purified by column chromatography (MTBE–hexanes, 1:2) to afford diacateate 20b.

Yield: 17.3 mg (90%); colorless highly viscous oil; \([\alpha]_D^{20} +13.8 (c 1.11, \text{CH}_2\text{Cl}_2)\).

\[^1\text{H}\ NMR\ (\text{CDCl}_3, 400 MHz): \delta = 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,
\[ J = 3.0, \ 10.2 \ Hz, \ 1 \ H), \ 4.18 \ (dd, \ J = 2.5, \ 2.8 \ Hz, \ 1 \ H), \ 5.44 \ (d, \ J = 5.5 \ Hz, \ 1 \ H), \ 5.78 \ (d, \ J = 5.7 \ Hz, \ 1 \ H). \]

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

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

Acknowledgment

We thank Aapo Tammisto for his assistance in the synthesis. Financial support from the Helsinki University of Technology and the Finnish Cultural Foundation (Artturi and Aina Helenius Fund) are gratefully acknowledged.

References


