A Practical Synthesis of the C1–C9 Fragment of Dictyostatin

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Received 5 March 2008
Dedicated with respect and admiration to Professor Reinhard W. Hoffmann, on the occasion of his 75th birthday

Abstract: A stereoselective synthesis of the C1–C9 fragment of (–)-dictyostatin has been achieved by use of a titanium(IV) chloride mediated chelation-controlled Mukaiyama aldol reaction and two modified Horner–Wadsworth–Emmons olefinations (Roush–Masamune and Still–Gennari).

Key words: antitumor agents, stereoselective synthesis, aldol reactions, titanium, olefination

The sponge-derived macrolide (–)-dictyostatin (1, Scheme 1) has been reported to exhibit paclitaxel-like effects on cellular microtubules and to inhibit human cancer cell proliferation at low nanomolar concentrations, with effects on cellular microtubules and to inhibit human cancer (–)-dictyostatin has been reported to exhibit paclitaxel-like effects on cellular microtubules and to inhibit human cancer cell proliferation at low nanomolar concentrations, with activity somewhat superior to the already very active discodermolide (ED50 0.38 nM, P338 leukemia cells). Moreover, (–)-dictyostatin (1) is also extremely active against paclitaxel-resistant cancer cell lines. The structure of (–)-dictyostatin (1) with full stereochemical assignment was established by Paterson and co-workers fairly recently (2004),2 and four total syntheses were completed in the period 2004–2007.3 A growing number of research groups have recently been involved in targeting this interesting natural product, and the syntheses of several analogues (e.g., normethylidictyostatins, epi-dictyostatins),4 discodermolide/dictyostatin hybrids,5 and various fragments and synthetic intermediates6 have been described. The development of a practical and flexible synthesis of (–)-dictyostatin (1) is still an important goal, particularly as the natural supply is extremely scarce. With the recent withdrawal of discodermolide from clinical development,7 the importance of dictyostatin (1) further increases. Our laboratory recently reported a highly stereoselective synthesis of the C10–C23 fragment 3 of (–)-dictyostatin (1) (Scheme 1).8 We now report on a practical synthesis of the C1–C9 fragment 2 (Scheme 1), containing two of its eleven stereocenters and the (2Z,4E)-2,4-dienoate unit.

We started our synthesis from commercially available methyl (R)-3-hydroxy-2-methylpropionate [(R)-Roche ester] (Scheme 2). Conversion of the (R)-Roche ester into its benzyl ether with benzyl trichloroacetimidate was followed by lithium aluminum hydride reduction of the ester to give alcohol 4 in 89% overall yield8 (Scheme 2). Oxidation of alcohol 4 with Dess–Martin periodinane9 afforded aldehyde 5 in quantitative yield, and, without purification, aldehyde 5 was immediately subjected to a titanium(IV) chloride mediated chelation-controlled Mukaiyama aldol reaction with 1-(tert-butyldimethylsiloxy)-1-(tert-butylsulfanyl)ethene (Scheme 2).10 The aldol product 6 was isolated in 94% yield and a 97:3 diastereomeric ratio in favor of the desired stereoisomer. Although it was reported that the two diastereomers could be separated by two consecutive purifications by flash chromatography,10a we still observed the presence of some isomer (≤3%) in the 13C NMR spectrum of 6. However, we decided to continue our synthesis as planned, confident that the minor isomer would be removable at a later stage of the sequence.

Reduction (LAH) of 6 gave diol 7 in 98% yield, and subsequent double silylation of diol 7 led to fully protected triol 8 (98%) (Scheme 2). Benzyl removal was accomplished by hydrogenolysis with Raney nickel in ethanol11
amide
tions.13 The olefination reaction afforded the Weinreb aldehyde (Scheme 2). Diisobutylaluminum hydride reduction gave (F3CCH2O)2P(O)CH2CO2Me, KHMDS, THF, 18-crown-6, –78 °C, DBU, MeCN, r.t., 90%; (i) DIBAL-H, THF, –78 °C, 91%; (j) DMP, CH2Cl2, r.t., 100%; (h) (EtO)2P(O)CH2C(O)N(Me)OMe, LiCl, reaction with diethyl (80%), and the resulting primary alcohol 9 was oxidized (DMP) to furnish aldehyde 10 in quantitative yield (Scheme 2). Aldehyde 10 was not purified and immediately subjected to a Horner–Wadsworth–Emmons reaction with diethyl (N-methoxy-N-methylcarbamoylmethyl)phosphonate12 under Roush–Masamune conditions.13 The olefination reaction afforded the Weinreb amide 11 in 90% yield as a single E-isomer (E/Z >100:1) (Scheme 2). Diisobutylaluminum hydride reduction gave aldehyde 12 (91%), which was subjected to a Still–Gennari olefination14 to afford methyl (2Z,4E)-2,4-di-enoate 13 in 90% yield as a single isomer (2Z/2E >100:1) (Scheme 2).14,15 The minor (7R)-isomer (≤3%), which originated during the Mukaiyama aldol reaction, was removed at this stage by flash chromatography. Finally, removal of the primary tert-butylidimethylsilyl group (HF-py, THF–py) furnished the desired C1–C9 fragment 2 of (–)-dictyostatin in good yield (Scheme 2).4d

Yield: 0.39 g (100%); pale yellow oil; Rf = 0.77 (hexanes–EtOAc, 6:4).

1H NMR (400 MHz, CDCl3): δ = 1.17 (d, J = 7.2 Hz, 3 H, CH3), 2.65–2.73 (m, 1 H, H–2), 3.66 (dd, J = 4.8, 9.2 Hz, 1 H, H–3), 3.72 (dd, J = 6.8, 9.2 Hz, 1 H, H–3), 4.55 (s, 2 H, CH2Ph), 7.10–7.36 (m, 5 H, Ph), 9.75 (s, 1 H, H–1).

S-tert-Butyl (3S,4R)-5-(Benzylxoy)-3-hydroxy-4-methylpentanethioate (6) A stirring solution of aldehyde 5 (392 mg, 2.2 mmol) in anhyd CH2Cl2 (5.0 mL) was treated at –80 °C with TiCl4 (0.49 mL, 2.2 mmol). After a few seconds, a solution of 1-(tert-butylidimethylsilyl)-1-(tert-butylsaathyl)ethene10 (814 mg, 3.3 mmol) in anhyd CH2Cl2 (2.5 mL) was slowly added. After stirring for 2 h at –80 °C, the mixture was quenched with 1 M KOH (18.0 mL). The organic phase was washed with brine (2 × 50 mL), dried (Na2SO4), filtered, and evaporated under reduced pressure. The crude product was purified by flash chromatography (hexanes–EtOAc, 85:15); this gave 6 (dr 97:3) as a colorless oil. Further purification by flash chromatography15 (benzene–EtOAc, 95:5) did not improve the dr.

Yield: 642 mg (94%); [α]D20 = –23.0 (c 0.75, CH2Cl2); Rf = 0.42 (hexanes–EtOAc, 85:15).

IR (CHCl3): 3470, 2962, 2926, 2860, 1681, 1455, 1364, 1253, 1101 cm–1.

1H NMR (400 MHz, CDCl3): δ = 0.96 (d, J = 7.2 Hz, 3 H, CH3), 1.50 (s, 9 H, tert-Bu), 1.89–1.97 (m, 1 H, H–4), 2.65 (dd, J = 8.0, 15.2 Hz, 1 H, H–2), 2.70 (dd, J = 4.0, 15.2 Hz, 1 H, H–2), 3.52 (dd, J = 6.4, 9.6 Hz, 1 H, H–5), 3.58 (dd, J = 4.8, 9.6 Hz, 1 H, H–5), 4.04 (ddd, J = 4.0, 8.0, 6.4 Hz, 1 H, H–3), 4.50 (s, 2 H, CH2Ph), 7.28–7.39 (m, 5 H, Ph).

Scheme 2 Reagents and conditions: (a) Ref. 8, 89%; (b) DMP, CH2Cl2, r.t., 100%; (c) (t-BuS)(TBSO)C=CH2, TiCl4, CH2Cl2, –80 °C, 94%, dr 97:3; (d) LAH, THF, r.t., 98%; (e) TBSOTf, 2,6-lu-
**Synthesis 2008, No. 14, 2158–2162 © Thieme Stuttgart · New York**

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1³C NMR (100 MHz, CDCl₃): δ = 11.8 (epimer at C-3, ≤3%), 14.5, 30.4, 38.3 (epimer at C-3, ≤3%), 38.6, 49.0, 49.9, 70.8 (epimer at C-3, ≤3%), 73.0, 74.1, 74.4, 126.7, 127.2, 128.7, 138.6, 200.7.

ESI-HRMS: m/z calc for C₁₇H₂₉NaO₅Si: 333.4400; found: 333.4425.

**(3S,4R)-5-(Benzyloxy)-4-methylpentane-1,3-diol (7)**

A solution of 6 (500 mg, 1.6 mmol) in anhyd THF (4.0 mL) was added to a cold (0 °C) suspension of LAH (122 mg, 3.2 mmol) in anhyd THF (4.0 mL). The mixture was warned to r.t. and stirred for an additional 2 h. The solution was cooled to 0 °C and then quenched with H₂O (0.7 mL), 2 M NaOH (1.4 mL), and H₂O (1.4 mL). After vigorously stirring for 1 h, the mixture was filtered (Na₂SO₄), and evaporated under reduced pressure. The crude product was purified by flash chromatography (hexanes–EtOAc, 6:4).

Yield: 352 mg (98%); colorless oil; [α]₀²⁺ = 0.50 (hexanes–EtOAc, 6:4).

IR (CHCl₃): 3113, 2955, 2928, 2858, 1472, 1255, 1094, 836, 775 cm⁻¹.

IR (CHCl₃): 2955, 2929, 2885, 2858, 1472, 1255, 1094, 836, 775 cm⁻¹.

**(2S,3S)-3,5-Bis(tert-butyldimethylsiloxy)-2-methylpentan-10 (10)**

A solution of alcohol 9 (0.4 g, 1.1 mmol) in anhyd CH₂Cl₂ (7.0 mL) was treated at 0 °C with pyridine (2.8 mmol) and DMP (0.56 g, 1.3 mmol). The reaction mixture was warmed to r.t., and stirred for 2 h. After completion of the reaction, sat. aq NaHCO₃ (8.0 mmol) was added. After the mixture had stirred for 30 min, the phases were separated, and the aqueous phase was extracted with Et₂O (3 × 20 mL). The combined organic extracts were washed with brine (2 × 25 mL), dried (Na₂SO₄), and evaporated under reduced pressure; this gave crude alcohol 10, which was used without further purification.

Yield: 397 mg (100%); pale yellow oil; Rₛ = 0.56 (hexanes–EtOAc, 9:1).

**[(2R,3S)-3,5-Bis(tert-butyldimethylsiloxy)-2-methylpentanol](9)**

Raney-Ni¹ was washed with H₂O until the washings were pH neutral, and then rinsed with absolute EtOH (5 × 100 mL). A solution of 8 (690 mg, 1.52 mmol) in absolute EtOH (102 mL) was added, and the mixture was degassed and then purged with H₂ (3×). After stirring for 72 h at r.t., the reaction mixture was filtered through a short pad of Celite, washed with EtOAc (2 × 100 mL), and evaporated under reduced pressure. The crude product was purified by flash chromatography (hexanes–EtOAc, 10:1).

Yield: 441 mg (80%); colorless oil; [α]₀²⁺ = –4.0 (c 1.11, CH₂Cl₂); Rₛ = 0.16 (hexanes–EtOAc, 10:1).

IR (CHCl₃): 3366, 2956, 2929, 2885, 2858, 1472, 1255, 1094, 836, 775 cm⁻¹.

1³C NMR (400 MHz, CDCl₃): δ = 0.07 (s, 6 H, Me₃Si), 0.12 (s, 6 H, Me₃Si), 0.91 (s, 9 H, tert-ButSi), 0.92 (s, 9 H, tert-ButSi), 1.04 (d, J = 7.2 Hz, 3 H, CH₃), 1.71–1.82 (m, 3 H, H-2, H-4), 2.61 (br s, 1 H, OH), 3.55 (dd, J = 5.6, 11.2 Hz, 1 H, H-5), 3.68 (t, J = 6.4 Hz, 2 H, H-1), 3.80 (dd, J = 4.0, 11.2 Hz, 1 H, H-5), 3.90–3.94 (m, 1 H, H-3).

1⁵C NMR (100 MHz, CDCl₃): δ = 4.7, –4.0, –3.8, 13.1 (epimer at C-3, ≤3%), 14.9, 18.6, 18.9, 26.5, 26.6, 38.2, 39.3, 40.5 (epimer at C-3, ≤3%), 60.4, 65.9, 73.4 (epimer at C-3, ≤3%), 74.8. ESI-HRMS: m/z calc for C₁₃H₂₅NaO₅Si: 385.2565; found: 385.2564.
A stirred solution of Weinreb amide 11 (400 mg, 0.9 mmol) in anhyd THF (9.4 mL) was treated at –78 °C with 1 M aq tartaric acid (1.2 mL) and EtOAc (13.8 mL). After the mixture had stirred for 1 h, the layers were separated, the aqueous phase was washed with H2O (2× 30 mL), and the combined organic extracts were washed with brine (2× 20 mL), dried (Na2SO4), and evaporated under reduced pressure. The crude product was purified by flash chromatography (hexanes–EtOAc, 2:1) to give 2.

Yield: 317 mg (91%); pale yellow oil; Rf 0.86 (20 mL). The combined organic extracts were washed with sat. aq NaHCO3 (30 mL), the mixture was extracted with EtOAc (4× 20 mL). The combined organic extracts were washed with sat. aq CuSO4 (3× 15 mL) and brine (2× 40 mL), dried (Na2SO4), and evaporated under reduced pressure. Purification by flash chromatography (hexanes–EtOAc, 2:1) gave 2.

Yield: 218 mg (86%); colorless oil; [α]20D = –10.5 (c 1.00, CH2Cl2); [α]20D = –14.0 (c 0.20, CHCl3); [lit.18a] [α]20D = –14.3 (c 0.21, CHCl3); Rf 0.20 (hexanes–EtOAc, 8:2).

IR (CHCl3): 3418, 2954, 2929, 2885, 2857, 1719, 1637, 1610, 1439, 1256, 1197, 1082, 1031, 1005, 837, 775 cm–1.

1H NMR (400 MHz, CDCl3): δ = 0.09 (s, 3 H, MeSi), 0.10 (s, 3 H, MeSi), 0.91 (s, 9 H, tBuSi), 0.92 (s, 9 H, tBuSi), 1.14 (d, J = 7.2 Hz, 3 H, CH3), 1.53–1.60 (m, 1 H, H-6), 1.64–1.73 (m, 1 H, H-6), 2.57–2.67 (m, 1 H, H-4), 3.64–3.67 (m, 2 H, H-7), 3.90–3.91 (m, 1 H, H-5), 6.13 (dd, J = 7.6, 15.6 Hz, 1 H, H-2), 6.87 (dd, J = 7.6, 15.6 Hz, 1 H, H-3), 9.53 (d, J = 7.6 Hz, 1 H, H-1).

13C NMR (100 MHz, CDCl3): δ = 11.3 Hz, 1 H, H-3), 7.37 (dd, J = 11.2, 15.2 Hz, 1 H, H-7), 5.61 (d, J = 11.2 Hz, 1 H, H-2), 6.02 (dd, J = 8.0, 15.6 Hz, 1 H, H-5), 6.56 (t, J = 11.2 Hz, 1 H, H-3), 7.38 (dd, J = 11.2, 15.6 Hz, 1 H, H-4).

13C NMR (100 MHz, CDCl3): δ = –3.9, –3.7, 15.4, 18.7, 26.5, 36.3, 43.3, 51.8, 60.7, 74.4, 116.4, 127.6, 146.0, 147.7, 167.6.


Acknowledgment

We thank the Ministero dell’Università e della Ricerca for financial support (PRIN prot. 2006030449) and for a postdoctoral fellowship (‘Assegno di ricerca’ to L. Pignataro) and a PhD fellowship (Borsa di dottorato ‘Progetto giovani’ to C. Zanato). C. Gennai gratefully acknowledges Merck Research Laboratories for the Merck’s Academy Development Program Award. Z. Hao (Lanzhou University, PRC) thanks the China Scholarship Council for a PhD mobility grant.

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