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Synthesis of (S)-2-Boc-Amino-8-(R)-(tert-butyl)dimethylsilanyloxy) decanoic acid, a Precursor to the Unusual Amino Acid Residue of the Anticancer Agent Microsporin B

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Abstract

(S)-2-Boc-Amino-8-(R)-(tert-butyl)dimethylsilanyloxy) decanoic acid, the Boc-protected precursor of an unusual amino acid residue for the synthesis of microsporin B, was synthesized. The key steps include a Suzuki coupling followed by asymmetric homogeneous hydrogenation.

Keywords

Microsporin; Cyclic tetrapeptide; HDAC; Amino acid; Olefin metathesis; Suzuki coupling; Asymmetric homogeneous hydrogenation

We previously reported two new cyclic peptides, microsporins A and B (**1**), which were isolated from extracts of a cultured marine fungus of the genus *Microsporium cf gypseum*, obtained from a sample of the bryozoan *Buluga* sp. collected in the U.S. Virgin Islands.¹ Microsporin A and B demonstrate cytotoxic activity against human colon adenocarcinoma (HCT-116).

Histone deacetylases (HDACs) comprise a family of enzymes that catalyze the removal of acetyl groups from lysine residues of histones and mediate chromatin remodeling and gene expression.² Three families of HDACs have been identified in eukaryotes, termed Class I, II, and III. Class I (HDAC 1, 2, 3, and 8) and Class II (HDAC 4, 5, 6, 7, 9, and 10) (HDAC 11 is at the boundary between Class I and II) are Zn^{2+} -dependent enzymes that are important therapeutic targets for the treatment of cancer.³ HDAC inhibitors, potent inducers of growth arrest, differentiation, and apoptotic cell death, suppress cell proliferation in a variety of transformed cells in culture and in tumor bearing animals, have great promise as new cancer drugs⁴ and are well tolerated by cancer patients.⁵

Cyclic tetrapeptides containing the 6-oxo-7,8-epoxyoctyl side chain, such as chlamydocin⁶ and trapoxin,⁷ and cyclic tetrapeptides without the epoxy side chain, such as apicidin A,⁸ are well-known inhibitors of histones deacetylases (HDACs). We have been interested in the discovery of novel HDAC inhibitors; our results showed that microsporin A inhibits HDACs and HDAC8 strongly.^{1,9} To discover more potent HDAC inhibitors based on the structures of microsporin A and B, novel syntheses of microsporin A and B are necessary.

Recently we reported the synthesis of microsporin A on solid-phase.¹ The most efficient way to prepare microsporin B would be the direct reduction of the ketone carbonyl group of microsporin A with a chiral reducing agent; unfortunately, because of the limited availability of microsporin A, a few reagents and conditions were attempted on very small scale (<5 mg), but they failed to yield microsporin B. Therefore, a total synthesis of microsporin B seemed more reasonable. Compound **2** represents a protected version of the unusual amino acid residue in microsporin B, which needed to be accessed prior to the cyclic peptide synthesis. Here we report our synthesis of **2**. As the absolute configuration of C-28 of microsporin B has not been assigned, we decided to synthesize (*S*)-2-Boc-amino-8-(*R*)-(tert-butyltrimethylsilyloxy) decanoic acid (**2**); if the C-8 stereochemistry ultimately turns out to be incorrect, then the *S*-epimer can readily be synthesized by the same route.

As shown in Scheme 1, the initial synthetic route to **2** was designed based on a ring closing metathesis reaction, followed by lactone ring opening. Epoxide **3** was treated with allylmagnesium bromide to generate **4**, which was coupled with Boc-allylglycine to give ester **5**. Ring closing metathesis of **5** with the Grubbs second generation catalyst afforded nine-membered ring lactone **6** in a trace amount, detected by LC-MS. Different catalysts and conditions were attempted, but the yield was not improved.

An alternative synthetic route to **2** was then investigated. As shown in Scheme 2, compound **3** was converted to **4** as in the previous synthesis. Protection of **4** afforded TBS ether **7**. Suzuki coupling¹⁰ between the corresponding borane of **7**, prepared by reduction of **7** with 9-BBN, and vinyl bromide **8**, which was prepared in two steps from commercial available reagents,¹¹ with Pd(PPh₃)₄ as a catalyst, generated **9**.¹² Asymmetric homogeneous hydrogenation of **9** with DuPHOS catalyst **10**¹³ generated amino acid methyl ester **11** in a quantitative yield with 99% ee.¹⁴ Acetamide **11** was converted to the corresponding Boc carbamate (**12**) by treatment with Boc anhydride followed by hydrazinolysis.¹⁵ Hydrolysis of the methyl ester gave **2**,¹⁶ ready for peptide synthesis.

In conclusion, the six-step synthesis starting from chiral epoxide **3** generated the desired amino acid (*S*)-2-Boc-amino-8-(*R*)-(tert-butyltrimethylsilyloxy) decanoic acid (**2**) in a 39% overall yield.

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References

1. Gu W, Ceuto M, Jensen PR, Fenical W, Silverman RB. *Tetrahedron*. 2007; 63:6535.
2. Grozinger CM, Schreiber SL. *Chem Biol*. 2002; 9:3. [PubMed: 11841934]
3. Kelly WK, O'Connor OA, Marks PA. *Expert Opin Invest Drugs*. 2002; 11:1695.
4. Some recent reviews of HDAC inhibitors include: (a) Bolden JE, Peart MJ, Johnstone RW. *Nat Rev Drug Discov*. 2006; 5:769. [PubMed: 16955068] (b) Minucci S, Pelicci PG. *Nat Rev Cancer*. 2006; 6:38. [PubMed: 16397526] (c) Liu T, Kuljaca S, Tee A, Marshall GM. *Cancer Treat Rev*. 2006; 32:157. [PubMed: 16516391] (d) Suzuki T, Miyata N. *Mini-Rev Med Chem*. 2006; 6:515. [PubMed: 16719825] (e) Rodriguez M, Aquino M, Bruno I, De Martino G, Taddei M, Gomez-Paloma L. *Curr Med Chem*. 2006; 13:1119. [PubMed: 16719774] (f) Vinken M, Peggy P, Vera R, Tamara V. *Curr Drug Targets*. 2006; 7:773. [PubMed: 16787179] (g) Carey N, La Thangue NB. *Curr Opin Pharmacol*. 2006; 6:369. [PubMed: 16781195] (h) Dey P. *Curr Med Chem*. 2006; 13:2909. [PubMed: 17073637] (i) Lin HY, Chen CS, Lin SP, Weng JR, Chen CS. *Med Res Rev*. 2006; 26:397. [PubMed: 16450343]
5. Kelly WK, Marks PA. *Nat Clin Pract Oncol*. 2005:150. [PubMed: 16264908]
6. Closse A, Huguenin R. *Helv Chim Acta*. 1974; 57:533. [PubMed: 4857466]
7. Itazaki H, Nagashima K, Sugita K, Yoshida S, Kawamura Y, Yasuda Y, Matsumoto K, Ishii K, Uotani N, Nakai H. *J Antibiot*. 1990; 43:1524. [PubMed: 2276972]
8. (a) Singh SB, Zink DL, Polishook JD, Dombrowski AW, Darkin-Rattray SJ, Schmatz DM, Goetz MA. *Tetrahedron Lett*. 1996; 37:8077. (b) Darkin-Rattray SJ, Gurnett AM, Myers RW, Dulski PM, Crumley TM, Allocco JJ, Cannova C, Meinke PT, Colletti SL, Bednarek MA, Singh SB, Goetz MA, Dombrowski AW, Polishook JD, Schmatz DM. *Proc Natl Acad Sci USA*. 1996; 93:13143. [PubMed: 8917558]
9. Gu W, Nusinzon I, Smith R, Horvath CM, Silverman RB. *Bioorg Med Chem*. 2006; 14:3320. [PubMed: 16434199]
10. Burk MJ, Allen JG, Kiesman WF. *J Am Chem Soc*. 1998; 120:657.
11. Miossec B, Danion-Bougout R, Danion D. *Synthesis*. 1994:1171.

12. Data for 9 $[\alpha]_D^{20}$ -3.46 ($c = 0.7$ CHCl₃); ¹H NMR (499 MHz, CDCl₃) δ 7.05 (s, 1H), 6.68 (t, $J = 7.1$ Hz, 1H), 3.74 (s, 3H), 3.60 – 3.40 (m, 1H), 2.13 (dd, $J = 14.1, 7.0$ Hz, 2H), 2.09 (s, 3H), 1.50 – 1.13 (m, 8H), 0.86 (s, 9H), 0.83 (t, $J = 7.5$ Hz, 3H), 0.01 (s, 3H), 0.00 (s, 3H); ¹³C NMR (126 MHz, CDCl₃) δ 168.67, 165.33, 139.45, 124.98, 73.39, 52.45, 36.34, 29.90, 29.04, 28.53, 26.04, 25.24, 23.49, 18.28, 9.69, -4.28, -4.35. HR-MS [TOF, MS+Na⁺]: m/z calcd for C₁₉H₃₇NO₄SiNa 394.2390, found 394.2387.
13. Burk MJ, Feaster JE, Nugent WA, Harlow RL. J Am Chem Soc. 1993; 115:10125–10138.
14. Data of 11 $[\alpha]_D^{20}$ +24.02 ($c = 1.0$ CHCl₃); ¹H NMR (499 MHz, CDCl₃) δ 6.15 (d, $J = 7.7$ Hz, 1H), 4.58 (dd, $J = 13.1, 7.3$ Hz, 1H), 3.72 (s, 3H), 3.53 (m, 1H), 2.00 (s, 3H), 1.87 – 1.72 (m, 1H), 1.64 (m, 1H), 1.50 – 1.14 (m, 10H), 0.86 (s, 9H), 0.83 (t, $J = 7.4$ Hz, 3H), 0.01 (s, 3H), 0.01 (s, 3H); ¹³C NMR (126 MHz, CDCl₃) δ 173.46, 169.97, 73.45, 52.45, 52.28, 36.50, 32.58, 29.83, 29.56, 26.07, 25.35, 25.21, 23.30, 18.30, 9.73, -4.28, -4.32. HR-MS [TOF, MS+Na⁺]: m/z calcd for C₁₉H₃₉NO₄SiNa 396.2546, found 394.2566. %ee was measured by chiral HPLC, comparing **11** to racemic, material which was produced by hydrogenation of the enamide substrates with an achiral catalyst.
15. Data for 12 $[\alpha]_D^{20}$ +8.39 ($c = 1.0$ CHCl₃); ¹H NMR (499 MHz, CDCl₃) δ 5.00 (d, $J = 6.9$ Hz, 1H), 4.30 (d, $J = 4.6$ Hz, 1H), 3.74 (s, 3H), 3.61 – 3.46 (m, 1H), 1.79 (brs, 1H), 1.70 – 1.54 (m, 1H), 1.45 (s, 9H), 1.42 – 1.18 (m, 7H), 0.90 (s, 9H), 0.88 – 0.79 (m, 10H), 0.04 (s, 6H); ¹³C NMR (126 MHz, CDCl₃) δ 173.72, 155.56, 79.99, 73.53, 53.60, 52.38, 36.56, 32.93, 29.90, 29.61, 28.51, 28.08, 26.12, 25.47, 25.31, 18.36, 9.78, -4.23, -4.27. HR-MS [TOF, MS+Na⁺]: m/z calcd for C₂₂H₄₅NO₅SiNa 454.2597, found 454.2592.
16. Data for 12 $[\alpha]_D^{20}$ +8.21 ($c = 1.2$ MeOH); ¹H NMR (499 MHz, CD₃OD) δ 4.04 (dd, $J = 8.6, 4.6$ Hz, 1H), 3.67 – 3.49 (m, 1H), 3.34 – 3.17 (m, 1H), 1.76 (m, 1H), 1.60 (m, 1H), 1.42 (s, 9H), 1.52 – 1.13 (m, 10H), 0.88 (s, 9H), 0.85 (t, $J = 7.4$ Hz, 3H), 0.04 (s, 6H); ¹³C NMR (126 MHz, CD₃OD) δ 176.52, 158.29, 80.54, 74.87, 54.90, 37.68, 32.96, 30.95, 30.51, 28.89, 28.74, 27.01, 26.58, 26.43, 19.14, 10.10, -4.05, -4.08. HR-MS [TOF, MS+Na⁺]: m/z calcd for C₂₁H₄₃NO₅SiNa 440.2808, found 440.2787.

Scheme 1.

Initial synthetic route to (S)-2-Boc-amino-8-(R)-(tert-butyl)dimethylsilyloxy) decanoic acid (2)

Scheme 2.

Alternate synthetic route to (*S*)-2-Boc-amino-8-(*R*)-(tert-butyldimethylsilyloxy) decanoic acid (**2**)