Available online at www.sciencedirect.com
SCIENCE DIRECT®
Tetrahedron Letters 45 (2004) 1639–1641
Tetrahedron Letters

Synthesis and structure of diastereomers of pentenocin B produced by *Trichoderma hamatum* FO-6903

Susumu Ohira,* Hiroyuki Fujiwara, Kiyomi Maeda, Masaharu Habara, Naomi Sakaedani, Megumi Akiyama and Atsuhito Kuboki

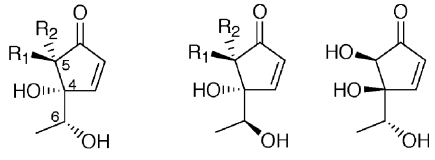
Department of Biological Chemistry, Faculty of Science, Okayama University of Science, 1-1 Ridai-cho, Okayama 700-0005, Japan

Received 21 November 2003; revised 17 December 2003; accepted 22 December 2003

Abstract—All diastereomers of pentenocin B, an inhibitor of interleukin-1β converting enzyme produced by *Trichoderma hamatum* FO-6903, were synthesized in chiral forms starting from L-threonine. Absolute configurations of natural pentenocin B were clarified to be 4*S*, 5*R*, and 6*R*.

Pentenocin B, a weak inhibitor of interleukin-1β converting enzyme, was isolated from the cultured broth of *Trichoderma hamatum* FO-6903.[1] The fundamental structure was determined by spectroscopic analysis, however, the relative and absolute stereochemistry of three asymmetric centers was not known. Here, we describe the synthesis of all possible diastereomers of pentenocin B (**1**, **2**, **3**, and **4**) starting from L-threonine. The result of the synthesis confirmed absolute configurations of natural pentenocin B to be 4*S*, 5*R*, and 6*R* as shown in **5**[2] (Fig. 1).

The key step of the synthesis is the 1,5 C–H insertion reaction of alkylidenecarbene generated from ketone to construct the chiral quaternary center.[3] Triol **1** and **2** were our first targets, because (4*S*)-*trans*-2,2,5-trimethyl-4-(methoxycarbonyl)-1,3-dioxolane (**6**) is readily prepared in a chiral form from L-threonine.[4]



1: R_1=OH, R_2=H **3**: R_1=OH, R_2=H **5**
2: R_1=H, R_2=OH **4**: R_1=H, R_2=OH

Figure 1.

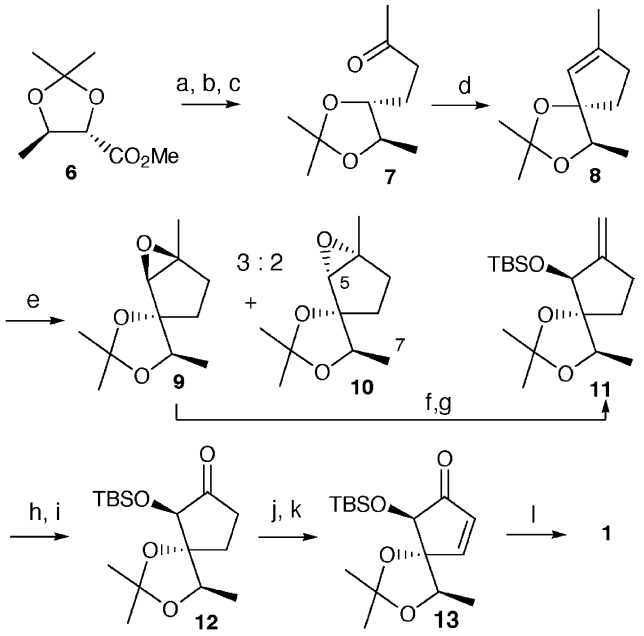
Reduction of methyl ester **6** with DIBAL followed by Wittig reaction gave an α,β-unsaturated ketone, which was hydrogenated to saturated ketone **7**. Generation of alkylidenecarbene using lithiotrimethylsilyldiazomethane[5] afforded cyclopentene **8** in moderate yield via C–H insertion reaction. Epoxidation of **8** with *m*-CPBA provided a separable 3:2 mixture of epoxides **9** and **10**. The stereochemistry of **10** was deduced based on the correlation between C-7 methyl protons and C-5 proton of **10** in its NOESY spectra[6] (Scheme 1).

Treatment of epoxide **9** with diethylaluminum 2,2,6,6-tetramethylpiperidide[7] at 0 °C cleanly furnished an allylic alcohol that was protected as TBS ether **11**. When the other basic reagents like LDA-*t*-BuOK[8] were used in this transformation, the double bond regioisomer was produced in some amount. Cleavage of the double bond of **11** followed by oxidation of TBS enol ether of **12** with palladium acetate[9] gave α,β-unsaturated ketone **13**. Deprotection with trifluoroacetic acid cleanly delivered the final compound **1** although in low yield. The ^{1}H NMR spectra of **1**[10] were quite different from those of the natural product.

Epoxide **10**, a possible intermediate for triol **2**, could not be cleaved to the allylic alcohol under various conditions. All attempts to epimerize the allylic alcohol obtained from **9** were also unsuccessful. Therefore, acetoxymethyl group substituted cyclopentene **15** (Scheme 2) was prepared from ketone **14**, which in turn was derived from **6** using a different Wittig reagent.[11] Dihydroxylation of **15** fortunately gave diol **16** as a sole product with the desired stereochemistry that was

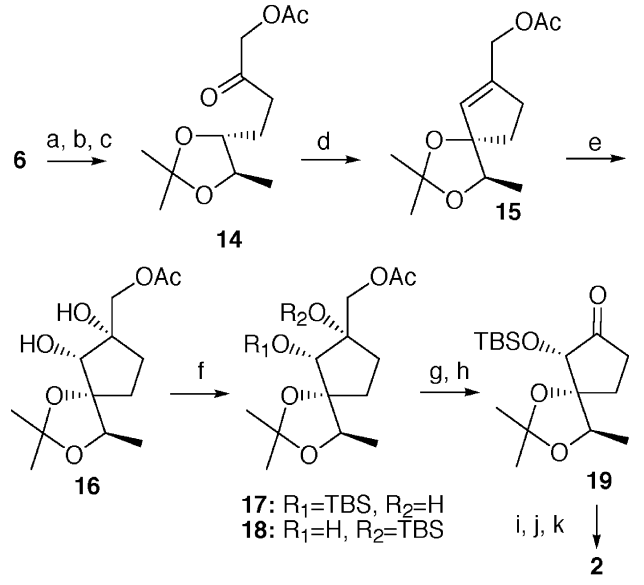
Keywords: Pentenocin; C–H insertion; Alkylidenecarbene; L-threonine.
* Corresponding author. Tel./fax: +81-86-256-9425; e-mail: sohira@dbc.ous.ac.jp

0040-4039/$ - see front matter © 2004 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2003.12.120

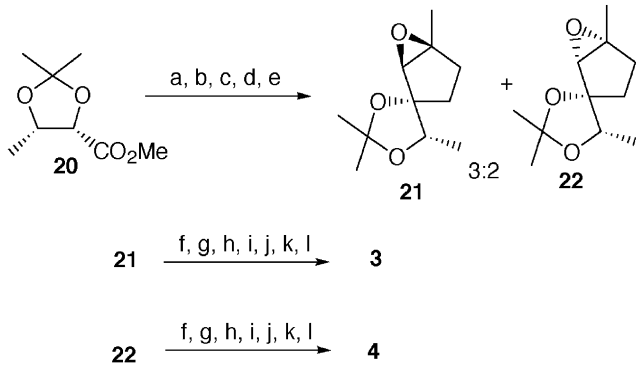


Scheme 1. Reagents and conditions: (a) DIBAL, CH_2Cl_2, −78 °C; (b) $Ph_3P{=}CHCOCH_3$, benzene, 60 °C (72% in two steps); (c) H_2, PtO_2, EtOAc (81%); (d) $TMSCHN_2$, BuLi, THF, −78∼0 °C (42%); (e) *m*-CPBA, $NaHCO_3$, CH_2Cl_2, rt (77%); (f) LiTMP, Et_2AlCl, toluene 0 °C (90%); (g) TBSOTf, Et_3N, CH_2Cl_2, rt (96%); (h) OsO_4, NMO, THF–H_2O, rt (100%); (i) $NaIO_4$, THF–H_2O, rt (96%); (j) TBSOTf, Et_3N, CH_2Cl_2, rt (98%); (k) $Pd(OAc)_2$, CH_3CN, rt (57%); (l) CF_3COOH, rt (10%).

disclosed at a later stage. Treatment of **16** with TBSOTf and triethylamine afforded an inseparable mixture of mono-silylated minor product **17** and major product **18**.



Scheme 2. Reagents and conditions: (a) DIBAL, CH_2Cl_2, −78 °C; (b) $Ph_3P{=}CHCOCH_2Ac$, benzene, 60 °C (71% in two steps); (c) H_2, Pd/C, EtOAc (92%); (d) $TMSCHN_2$, BuLi, THF, −78∼0 °C (33%); (e) OsO_4, NMO, THF–H_2O, rt (52%); (f) TBSOTf, Et_3N, CH_2Cl_2, 0 °C (81%); (g) DIBAL, CH_2Cl_2, −78 °C (58%); (h) $NaIO_4$, THF–H_2O, rt (27%); (i) TBSOTf, Et_3N, CH_2Cl_2, rt (99%); (j) $Pd(OAc)_2$, CH_3CN, rt (66%); (k) CF_3COOH, rt (55%).



Scheme 3. Reagents and conditions: (a) DIBAL, CH_2Cl_2, −78 °C; (b) $Ph_3P{=}CHCOCH_3$, benzene, 60 °C (84% in two steps); (c) H_2, Pd/C, EtOAc (86%); (d) $TMSCHN_2$, BuLi, THF, −78∼0 °C (70%); (e) *m*-CPBA, $NaHCO_3$, CH_2Cl_2, rt (76%); (f) LiTMP, Et_2AlCl, toluene, 0 °C (79%, 67%); (g) TBSOTf, Et_3N, CH_2Cl_2, rt (94%, 95%); (h) OsO_4, NMO, THF–H_2O, rt; (i) $NaIO_4$, THF–H_2O, rt (each 88% in two steps); (j) TBSOTf, Et_3N, CH_2Cl_2, rt (91%, 100%); (k) $Pd(OAc)_2$, CH_3CN, rt (49%, 93%); (l) CF_3COOH, 0 °C (27%, 54%).

Deacetylation under basic conditions induced the TBS group transfer to the primary alcohol. Reductive deacetylation with DIBAL and immediate glycol scission gave the desired product **19** from **17** and the unreacted diol from **18**. Stereochemistry of **16** was now distinct because ^1H NMR spectra of **19** were different from **12**. Conversion of ketone **19** to triol **2** was achieved in three steps in a similar manner as the synthesis of triol **1**. ^1H NMR spectra of **2**[10] were also different from those of the natural product.

Synthesis of **3** and **4** was started from (4*S*)-*cis*-2,2,5-trimethyl-4-(methoxycarbonyl)-1,3-dioxolane (**20**) that was practically available from L-threonine by Ibuka's method.[12] Ester **20** was transformed to epoxides **21** and **22** in a similar way as the synthesis of **1**. Stereochemistry of epoxide **22** (mp 52–56 °C) was confirmed by X-ray structure analysis[13] (Scheme 3).

Both epoxides could be cleaved to allylic alcohols and were converted into triols **3**[10] and **4**[10] similarly to the synthesis of **1**. Spectral properties of **4** were identical with those of the natural product, and the sign of optical rotation ($[\alpha]_D$ −58° (*c* 0.40, H_2O)) was opposite to that of the natural product ($[\alpha]_D$ +76° (*c* 1.0, H_2O)).[14] Thus, natural pentenocin B is the enantiomer of **4**. Namely, absolute configurations of natural pentenocin B are 4*S*, 5*R*, 6*R*, as shown in **5**.

Acknowledgements

We thank Professor Satoshi Omura, Kitasato Institute, for providing us with ^1H and ^{13}C NMR spectra as well as information on the optical rotation. We also thank Professor Hiroshi Nozaki, Okayama University of Science, for X-ray analysis of the epoxide **22**.

References and notes

1. (a) Matsumoto, T.; Ishiyama, A.; Yamaguchi, Y.; Masuma, R.; Ui, H.; Shiomi, K.; Yamada, H.; Omura, S. *J. Antibiot.* **1999**, *52*, 754–757; (b) Matsumoto, T.; Ishiyama, A.; Yamaguchi, Y.; Masuma, R.; Ui, H.; Shiomi, K.; Yamada, H.; Omura, S. *J. Antibiot.* **2003**, *56*, C2.
2. While this manuscript was in preparation, another group reported determination of the absolute structure of pentenocin B by synthesis of all racemic diastereomers and the natural type enantiomer. The structure they suggested was identical to ours, Sugahara, T.; Fukuda, H.; Iwabuchi, Y. *Tennen Yuki Kagobutsu Toronkai Koen Yoshishu* **2003**, *45*, 573–578.
3. (a) Ohira, S.; Ida, T.; Moritani, M.; Hasegawa, T. *J. Chem. Soc., Perkin Trans. 1* **1998**, 293–298; (b) Ohira, S.; Noda, I.; Mizobata, T.; Yamato, M. *Tetrahedron Lett.* **1995**, *36*, 3375–3376.
4. Servi, S. *J. Org. Chem.* **1985**, *50*, 5865–5867.
5. (a) Sakai, A.; Aoyama, T.; Shioiri, T. *Tetrahedron Lett.* **2000**, *41*, 6859–6863; (b) Shioiri, T.; Aoyama, T. *Synth. Org. Chem., Jpn.* **1996**, *54*, 918–928; (c) Ohira, S.; Okai, K.; Moritani, T. *J. Chem. Soc., Chem. Commun.* **1992**, 721–722.
6. ^{1}H NMR ($CDCl_3$) δ 1.27 (d, 3H, $J = 6.3$ Hz), 1.38 (s, 3H), 1.45 (s, 3H), 1.52 (s, 3H), 1.54 (m, 2H), 1.96 (m, 2H), 3.19 (s, 1H), 4.01 (q, 1H, $J = 6.3$ Hz). Correlation was observed between signals of δ 1.27 and δ 3.19.
7. Yasuda, A.; Tanaka, S.; Oshima, K.; Yamamoto, H.; Nozaki, H. *J. Am. Chem. Soc.* **1974**, *96*, 6513–6514.
8. Mordini, A.; Ben Rayana, E.; Margot, C.; Schlosser, M. *Tetrahedron* **1990**, *46*, 2401–2410.
9. Ito, Y.; Hirao, T.; Saegusa, T. *J. Org. Chem.* **1978**, *43*, 1011–1013, We used a stoichiometric amount of palladium acetate without benzoquinone to avoid the production of dihydrobenzoquinone, which caused a problem in material purification.
10. **1**: $[\alpha]_D$ −53° (*c* 0.16, MeOH); ^{1}H NMR (DMSO-d_6) δ 1.10 (d, 3H, $J = 6.5$ Hz), 3.81 (quint, 1H, $J = 6.5$ Hz), 3.90 (d, 1H, $J = 6.6$ Hz), 4.31 (t, 1H, $J = 6.5$ Hz), 5.29 (t, 1H, $J = 6.6$ Hz), 5.61 (s, 1H), 6.29 (d, 1H, $J = 6.4$ Hz), 7.26 (d, 1H, $J = 6.4$ Hz); ^{13}C NMR (DMSO-d_6) δ 19.43, 69.13, 83.62, 84.11, 133.72, 160.34, 204.35.
    2: $[\alpha]_D$ −89° (*c* 0.42, MeOH); ^{1}H NMR (DMSO-d_6) δ 1.15 (d, 3H, $J = 6.4$ Hz), 3.66 (quint, 1H, $J = 6.4$ Hz), 3.91 (d, 1H, $J = 7.2$ Hz), 4.84 (s, 1H), 4.86 (d, 1H, $J = 6.4$ Hz), 5.47 (d, 1H, $J = 7.2$ Hz), 6.22 (d, 1H, $J = 6.2$ Hz), 7.60 (d, 1H, $J = 6.2$ Hz); ^{13}C NMR (DMSO-d_6) δ 18.90, 69.99, 73.94, 80.33, 134.19, 163.48, 208.84.
    3: $[\alpha]_D$ −117° (*c* 0.12, H_2O); ^{1}H NMR (DMSO-d_6) δ 0.80 (d, 3H, $J = 6.4$ Hz), 3.79 (quint, 1H, $J = 6.4$ Hz), 4.05 (d, 1H, $J = 5.5$ Hz), 4.63 (d, 1H, $J = 6.4$ Hz), 5.38 (s, 1H), 5.90 (d, 1H, $J = 5.5$ Hz), 6.30 (d, 1H, $J = 6.3$ Hz), 7.31 (d, 1H, $J = 6.3$ Hz); ^{13}C NMR (DMSO-d_6) δ 19.60, 70.86, 82.60, 83.71, 132.80, 162.72, 205.40.
    4: $[\alpha]_D$ −58° (*c* 0.40, H_2O); ^{1}H NMR (DMSO-d_6) δ 1.13 (d, 3H, $J = 6.4$ Hz), 3.70 (qd, 1H, $J = 5.4$ Hz, 6.4 Hz), 3.92 (d, 1H, $J = 7.5$ Hz), 4.80 (d, 1H, $J = 5.4$ Hz), 4.86 (s, 1H), 5.31 (d, 1H, $J = 7.5$ Hz), 6.16 (d, 1H, $J = 6.2$ Hz), 7.49 (d, 1H, $J = 6.2$ Hz); ^{13}C NMR (DMSO-d_6) δ 19.19, 70.52, 72.02, 80.08, 133.03, 166.68, 209.51.
11. Kim, K. S.; Szarek, W. A. *Can. J. Chem.* **1981**, *59*, 878–888.
12. Ibuka, T.; Nishii, S.; Yamamoto, Y. *Chem. Express* **1988**, *3*, 53–56.
13. Suitable crystals of **22** for X-ray diffraction studies formed with space group symmetry of *P*1 (#1) and cell constants of $a = 7.465(5)$ Å, $b = 7.480(4)$ Å, $c = 9.781(5)$ Å for $Z = 2$ and calculated density of 1.246 g/cm^3. Details will be reported in due course.
14. Private communication from Professor Satoshi Omura. Higher value ($[\alpha]_D$ +101° (*c* 1.0, H_2O)) was reported for synthetic (+)-pentenocine B.[2] To check the enatiomeric purity of our samples, we examined ^{1}H NMR spectra of (*S*)-MTPA ester of the allylic alcohol from **22**. No signal for the diastereomer originating from the enantiomer of **22** was observed.