Available online at www.sciencedirect.com
SCIENCE DIRECT®
Tetrahedron Letters 47 (2006) 4441–4443
Tetrahedron Letters

Stereoselective approach to pentenocins using RCM: synthesis of 6-*epi*-pentenocin B☆

G. Venkata Ramana and B. Venkateswara Rao*

Organic Division III, Indian Institute of Chemical Technology, Hyderabad 500 007, India

Received 30 January 2006; revised 13 March 2006; accepted 12 April 2006
Available online 12 May 2006

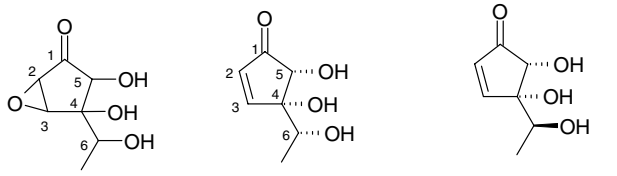
Abstract—The stereoselective synthesis of 6-*epi*-pentenocin B **3** is described using a stereoselective Grignard reaction and ring-closing metathesis (RCM) as the key steps.

Oxygenated cyclopentenones are important bioactive compounds in nature.[1] Pentenocin A **1** and B **2** were isolated[2] by Omura and co-workers in 1999 from the culture broth of *Trichoderma hamatum* FO-6903 as an active agent against recombinant human interleukin-1β converting enzyme (ICE). ICE is also known as caspase-1, a unique cystein protease that cleaves the inactive precursor of IL-1β into biologically active IL-1β, a key mediator in the pathogenesis of acute and chronic inflammation.[3] The absolute stereochemistry of pentenocin B was determined by Ohira[4] and Sugahara[3] independently, by synthesizing all the possible diastereomers, and was confirmed to be 4*S*,5*R*,6*R* as shown in **2** (Fig. 1).

In continuation of our efforts on the synthesis of biologically active oxygenated cyclopentenones by RCM,[5] a new approach was developed for the synthesis of the pentenocin skeleton. Herein, we report the synthesis of 6-*epi*-pentenocin B **3**[3,4] using a stereoselective Grignard reaction and RCM as the key steps. 2,3-*O*-Isopropylidene-D-ribose **4** was transformed into the hydroxymethyl compound **5** using a method based on a reported procedure,[6] $[\alpha]_D^{24}$ −23.086 (*c* 2.35, $CHCl_3$), lit.:[6a,b] $[\alpha]_D^{25}$ −26.5 (*c* 2.19, $CHCl_3$). The primary hydroxyl group in **5** was selectively acetylated with AcCl, DIPEA in DCM at −78 °C to give compound **6** $[\alpha]_D^{24}$ −21.98 (*c* 2.3, $CHCl_3$).

The anomeric hydroxyl functionality of **6** was protected with TBDPS–Cl to afford silyl ether **7**. Treatment of **7** with NaOMe (4 equiv) in anhydrous MeOH for a period of 12 h at room temperature yielded **8** $[\alpha]_D^{24}$ −17.83 (*c* 3.2, $CHCl_3$) as the sole diastereoisomer along with hydroxymethyl compound **5** (Scheme 1).

The structure of **8** was confirmed from its NOE spectral analysis (Fig. 2). Oxidation of alcohol **8** using Swern conditions gave aldehyde **9**, which was allowed to react with methylmagnesium iodide at −78 °C to give the expected alcohol **10** $[\alpha]_D^{24}$ −25.25 (*c* 2.0, $CHCl_3$) as the major diastereoisomer (9:1 ratio based on ^1H NMR). Based on chelation control (Fig. 3), we assumed that the major diastereoisomer was alcohol **10**.[7] The alcohol functionality in **10** was protected as the MOM ether **11** using MOM–Cl, DIPEA and TBAI (cat.), and then the TBDPS group was cleaved with TBAF to give lactol **12**. Wittig olefination of **12** yielded diene **13**. Treatment of diene **13** with Grubbs' first generation olefin metathesis catalyst in DCM furnished cyclopentenol **14**. TEMPO oxidation of the alcohol **14** gave the required protected *epi*-pentenocin B[8] **15** $[\alpha]_D^{24}$ −29.4 (*c* 1.2, $CHCl_3$). The NMR data was in good agreement with the reported



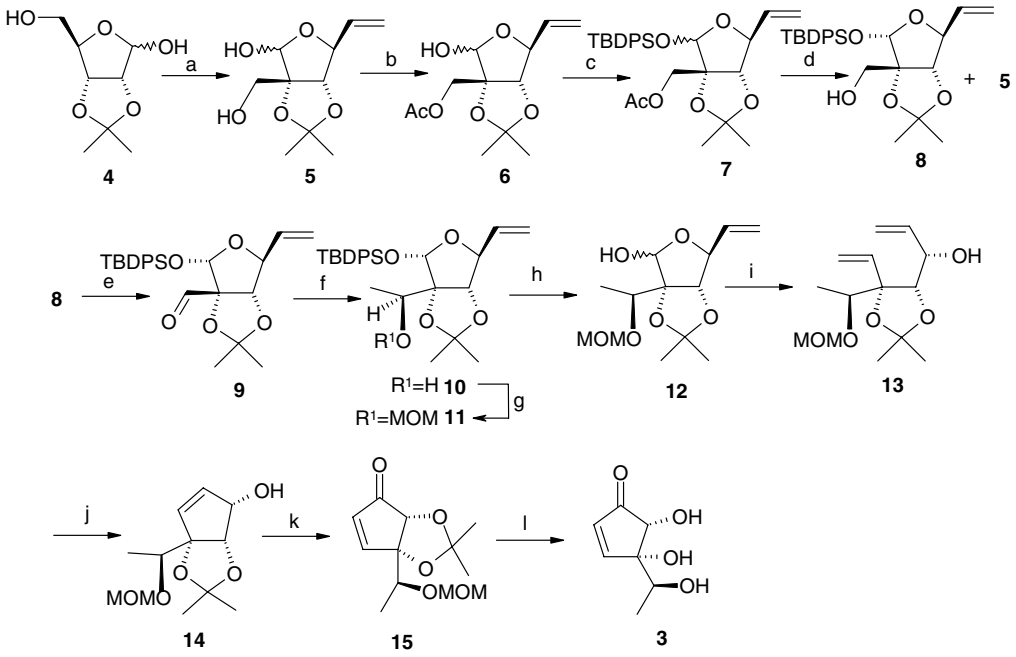
1 2 3

Figure 1.

☆ IICT Communication Number: 060115.

* Corresponding author. Tel.: +91 40 27160123x2614; fax: +91 40 27160512; e-mail: venky@iict.res.in

0040-4039/$ - see front matter © 2006 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2006.04.054



Scheme 1. *Reagents and conditions*: (a) (1) CH_2=CHMgBr, THF, −78 °C to rt, 3 h, 75%; (2) $NaIO_4$, CH_2Cl_2–H_2O (1:1), 0 °C to rt, 2 h, 80%; (3) K_2CO_3, 37% CH_2O, MeOH, 80 °C, 36 h, 85%; (b) Ac_2O, DIPEA, CH_2Cl_2, −78 °C, 1 h, 56%; (c) TBDPS–Cl, imidazole, CH_2Cl_2, 0 °C to rt, 6 h, 73%; (d) NaOMe (4 equiv), MeOH, 0 °C to rt, 12 h, (40% for **8**, 38% for **5**); (e) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −78 °C, 3 h; (f) MeMgI, ether, −78 °C, 3 h, (60% for two steps); (g) MOM–Cl, DIPEA, TBAI (0.1 equiv), CH_2Cl_2, 0 °C to rt, 48 h, 81%; (h) TBAF, THF, 0 °C to rt, 4 h, 88%; (i) $CH_3PPh_3^+I^-$, ^{t}BuOK, 18-crown-6, THF, 0 °C to rt, 24 h, 34%; (j) Grubbs' first-generation olefin metathesis catalyst (0.1 equiv), CH_2Cl_2, rt, 24 h, 79%; (k) Tempo free radical (cat.), KBr, NaOCl, $NaHCO_3$, EtOAc–toluene–water (1:1:0.2), 0 °C, 1 h, 65%; (l) 90% TFA, 0 °C, 2 h, 30%.

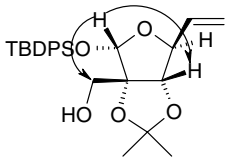


Figure 2.

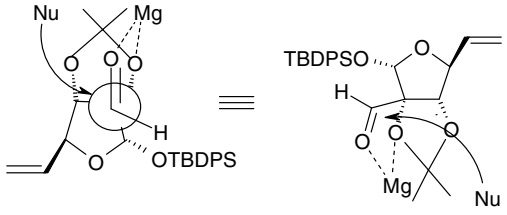


Figure 3. Transition state leading to the major diastereoisomer of **10**.

data for (+/−)-**15**.[3] Removal of the MOM and acetonide protecting groups in **15** with 90% TFA[3] completed a stereoselective synthesis of 6-*epi*-pentenocin B **3**, whose spectral[9] and physical data were in agreement with the reported values, $[\alpha]_D^{23}$ +84.15 (*c* 0.16, MeOH) lit.:[4] $[\alpha]_D$ −89 (*c* 0.42, MeOH for its *C*-6 enantiomer).

In summary, a new approach for the construction of the pentenocin skeleton has been utilized for the synthesis of 6-*epi*-pentenocin B **3**.

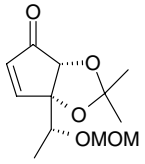
Acknowledgements

G.V.R. thanks the CSIR, New Delhi, for a research fellowship (SRF). We also thank IFCPAR for their financial support, Dr. J. S. Yadav and Dr. A. C. Kunwar for their support and encouragement.

References and notes

1. (a) Bickley, J. F.; Roberts, S. M.; Santoro, M. G.; Snape, T. J. *Tetrahedron* **2004**, *60*, 2569–2576; (b) Tilo, L.; Jurgen, S.; Andrea, P.; Norbert, A.; Ludger, W. *Phytochem.* **2004**, *65*, 1061–1071; (c) Masami, I.; Shinji, T.; Jun'ichi, K. *Tetrahedron Lett.* **1993**, *34*, 3749–3750.
2. Matsumoto, T.; Ishiyama, A.; Yamaguchi, Y.; Masuma, R.; Ui, H.; Shiomi, K.; Yamada, H.; Omura, S. *J. Antibiot.* **1999**, *52*, 754–757.
3. Sugahara, T.; Fukuda, H.; Iwabuchi, Y. *J. Org. Chem.* **2004**, *69*, 1744–1747.
4. Ohira, S.; Fujiwara, H.; Maeda, K.; Habara, M.; Sakaedani, N.; Akiyama, M.; Kuboki, A. *Tetrahedron Lett.* **2004**, *45*, 1639–1641.
5. Ramana, G. V.; Rao, B. V. *Tetrahedron Lett.* **2003**, *44*, 5103–5105.
6. (a) Jeong, A. L.; Hyung, R. M.; Hea, O. K.; Kyung, R. K.; Kang, M. L.; Bum, T. K.; Ki, J. H.; Moon, W. C.; Kenneth, A. J.; Jeong, L. S. *J. Org. Chem.* **2005**, *70*, 5006–5013; (b) Hyung, R. M.; Hea, O. K.; Kang, M. L.; Moon, W. C.; Joong, H. K.; Jeong, L. S. *Org. Lett.* **2002**, *4*, 3501–3503; (c) Ho, P.-T. *Can. J. Chem.* **1979**, *57*, 381–383; (d) Ho, P.-T. *Tetrahedron Lett.* **1978**, *19*, 1623–1626; (e) Shing, T. K. M.; Elsey, D. A.; Gillhouley, J. G. *J. Chem. Soc., Chem. Commun.* **1989**, 1280–1282.

7. Attempts to separate and confirm the stereochemistry at the newly created hydroxyl centre by preparing Mosher derivatives proved unsuccessful.
8. Compound (−)-**16**, which is a protected form of (+)-pentenocin B **2**, is also reported[3] whose rotation and ^{1}H and ^{13}C NMR data were different from **15**.



(-)-**16**

9. Spectral data for **3**: ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.15 (d, 3H, $J = 6.8$ Hz), 3.67 (quint, 1H, $J = 6.0$ Hz), 3.91 (d, 1H, $J = 6.8$ Hz), 4.82 (s, 1H), 4.84 (d, 1H, $J = 5.3$ Hz), 5.45 (d, 1H, $J = 6.8$ Hz), 6.22 (d, 1H, $J = 6.0$ Hz), 7.60 (d, 1H, $J = 6.0$ Hz). ^{13}C NMR (75 MHz, DMSO-d_6): δ 207.6, 162.2, 133.0, 79.1, 72.7, 68.8, 17.6. ESI MS: 159 ($M^{+}+1$).