Determination of Absolute Structure of Macroviracins by Chemical Synthesis

Shunya Takahashi,* Moritoshi Hosoya, Hiroyuki Koshino, and Tadashi Nakata

RIKEN (The Institute of Physical and Chemical Research), Wako, Saitama 351-0198, Japan

shunyat@postman.riken.go.jp

Received February 26, 2003

ABSTRACT



The relative and absolute configurations of macroviracins have been established by the stereocontrolled synthesis of methyl ester 2a of the C_{22} carboxylic acid, a constitutive fatty acid of macroviracin A (1), and their comparison to a sample 2 derived from the natural product 1.

Macroviracins are a new class of macrocyclic compounds, which were isolated from the mycelium extracts of *Strept-myces* sp. BA-2836,¹ and classified into eight types of congeners (A–D) by the length (C_{22} or C_{24}) of the constitutive fatty acids. These natural products exhibit a powerful antiviral activity against HSV-1 and VZV, and their potency is reported to be 10 times that of acyclovir. Structurally, macroviracins are related to sugar-fatty acid lactones such as cycloviracins² and fattiviracins,³ differing remarkably in the size of the macrocyclic ring systems. Degradation studies of macroviracins suggested the corresponding constitutive acids to have the same relative stereochemistry. The absolute configuration, however, remained unsolved. Furthermore, the

10.1021/ol034338k CCC: \$25.00 © 2003 American Chemical Society Published on Web 04/05/2003

absolute configuration (D-form) of the sugar residue also has not been established. In this paper, we describe the total synthesis of methyl ester **2a** of fatty acid constituted macroviracin A (**1**) and determination of the absolute configuration of macroviracins. Very recently, Fürstner et al. disclosed the total synthesis of cycloviracin B₁, establishing the absolute configuration.⁴

As methanolysis of **1** has been known to give the corresponding methyl ester in degradation studies, the benzoyl⁵ derivative **2** prepared therefrom was regarded as an ideal synthetic target for this research. Our synthetic strategy toward **2** is illustrated in Scheme 1. Thus, removal of two sugar residues from **2** and depression of its oxidation level leads to acyclic diol **3**. This would be synthesized through a coupling reaction of a nucleophile derived from **4** and terminal epoxide **5**. As an alternate plan, we designed two types of glucosides (**6** and **7**) as the left- and right-half

⁽¹⁾ Hyodo, T.; Tsuchiya, Y.; Sekine, A.; Amano, T. Jpn. Kokai Tokkyo Koho Jpn. Pat. 11246587, Sept 14, 1999.

⁽²⁾ Tsunakawa, M.; Komiyama, N.; Tenmyo, O.; Tomita, K.; Kawano, K.; Kotake, C.; Konishi, M.; Oki, T. J. Antibiot. **1992**, 45, 1467–1471. Tsunakawa, M.; Kotake, C.; Yamasaki, T.; Moriyama, T.; Konishi, M.; Oki, T. J. Antibiot. **1992**, 45, 1472–1480.

⁽³⁾ Uyeda, M.; Yokomizo, K.; Miyamoto, Y.; Habib, E.-S. E. J. Antibiot. **1998**, *51*, 823–828. Yokomizo, K.; Miyamoto, Y.; Nagao, K.; Kumagae, E.; Habib, E.-S. E.; Suzuki, K.; Harada, S.; Uyede, M. J. Antibiot. **1998**, *51*, 1035–1039. Habib, E.-S. E.; Yokomizo, K.; Murata, K.; Uyeda, M. J. Antibiot. **2000**, *53* 1420–1423.

⁽⁴⁾ Fürstner, A.; Albert, M.; Mlynarski, J.; Matheu, M. J. Am. Chem. Soc. 2002, 124, 1168–1169. Fürstner, A.; Mlynarski, J.; Albert, M. J. Am. Chem. Soc. 2002, 124, 10274–10275.

⁽⁵⁾ For a method for determination of the absolute configuration of secondary alcohols by using benzoylated sugars, see: Trujillo, M.; Morales, E. Q.; Vázquez, J. T. J. Org. Chem. **1994**, *59*, 6637–6642.

Scheme 1. Structures of Macroviracins and Retrosynthetic Analysis



model of **2**, respectively. Prior to the synthesis of **2**, syntheses of **6** and **7** and comparison of their spectral data with those of **2** were conducted.

We began with the synthesis of the left-half models (**6a**,**b**). 10-Undecenal 8 was subjected to Wittig reaction, and subsequent DIBAL reduction afforded allyl alcohol 9 (Scheme 2). The alcohol 9 was oxidized by Sharpless epoxidation to give epoxide 10. Red-Al reduction⁶ of 10 and monosilulation provided a 1,3-diol derivative 11. This underwent hydrogenation to afford alcohol 12. Glycosidation⁷ of 12 was best realized by using 2.5 equiv of thioglycoside 13 in the presence of 6.0 equiv of N-iodosuccinimide (NIS) and a catalytic amount of triflic acid (TfOH) in CH₂Cl₂ to give the corresponding β -glucoside 14. After de-silvlation of 14, the resulting alcohol was oxidized to give methyl ester **6a** { $[\alpha]_D$ +20.7° (*c* 0.35), δ_H 2.45 (dd, *J* = 16, 6.8 Hz, H-2a), 2.89 (dd, J = 16, 5.9 Hz, H-2b), 3.59 (s, OMe)}.⁸ On the other hand, S_N2 inversion of 11^9 via the corresponding monochlate¹¹ provided the epimer **15**. Hydrogenation of **15** gave alcohol 16, which was glycosylated to give glucoside 17. This was transformed into the diastereomer **6b** $\{[\alpha]_D$ -2.0° (c 1.01), $\delta_{\rm H}$ 2.34 (dd, J = 16, 4.2 Hz, H-2a), 2.44

(dd, J = 16, 8.3 Hz, H-2b), 3.26 (s, OMe)}. The ¹H NMR spectra of the model compounds (**6a** and **6b**) were compared with that of **2**. The methyl ester **2** exhibited $\delta_{\rm H}$ 2.45 (dd, J = 16, 6.8 Hz, H-2a), 2.88 (dd, J = 16, 5.9 Hz, H-2b), and 3.59 (s, OMe), which resembled the data of **6a**. These results show that the stereochemistry of the C-3 position in **2** should be *R* if the sugar moiety is a D-form.

Synthesis of the right-half model **7** started with a transformation of ester **18**¹² into unsaturated ester **19** via a 6-step sequence including a one-carbon homologation and Wittig reaction (Scheme 3). After DIBAL reduction of **19**, the resulting allyl alcohol was oxidized to give epoxide **20**. 1,2-Reduction⁶ of the epoxide followed by an oxirane formation provided terminal epoxide **5a**. Nucleophilic addition of Bu₂-CuLi to **5a** proceeded cleanly, giving alcohol **21**. A hydroxy protection–deprotection sequence of **21** afforded 2*R*,8*S*-benzoate **23** via silyl ether **22**. Glycosidation of **23** provided β -glucoside **7a** {mp 99–100 °C, [α]_D + 2.2° (*c* 0.41)}. On the other hand, an S_N2 inversion reaction of **23**⁹ afforded 2*R*,8*R*-isomer **24**, which was glycosylated to give **7b** {[α]_D – 4.5° (*c* 0.40)}.

S_N2 inversion of **22** relied on the Mitsunobu reaction.¹⁰ The benzoate **25** thus obtained was transformed into 2*S*,8*S*-alcohol **26**, and then glucoside **7c** {mp 105–107 °C, $[\alpha]_D$ +13.6° (*c* 0.99)}. According to the method for preparation of **24** from **23**, **26** was changed to the epimer **27**, which was glycosylated to give **7d** {[α]_D +11.4° (*c* 0.73)}. In their ¹H NMR spectra, the signals corresponding to H-2 of **7b** and **7d** were observed at 5.00 ppm, while those of **7a** and **7c**

⁽⁶⁾ Finan, J. M.; Kishi, Y. Tetrahedron Lett. 1982, 23, 2719–2722.

 ⁽⁷⁾ Veeneman, G. H.; van Leeuwen, S. H.; van Boom, J. H. *Tetrahedron Lett.* 1990, *31*, 1331–1334. Konradsson, P.; Udodong, U. E.; Fraser-Reid, B. *Tetrahedron Lett.* 1990, *31*, 4313–4316.

⁽⁸⁾ Values of $[\alpha]_D$ and δ_H were measured for the solution in CHCl₃ and CDCl₃, respectively, at 23 \pm 2°.

⁽⁹⁾ Mitsunobu reaction¹⁰ of this compound failed.

⁽¹⁰⁾ Mitsunobu, O. Synthesis **1981**, 1–28.

⁽¹¹⁾ Shimizu, T.; Hiranuma, S.; Nakata, T. Tetrahedron Lett. **1996**, *37*, 6145–6148.

⁽¹²⁾ Fukui, H.; Tsuchiya, Y.; Fujita, K.; Nakagawa, T.; Koshino, H.; Nakatta, T. *Bioorg. Med. Chem. Lett.* **1997**, *7*, 2081–2086.



^{*a*} Reagents and conditions: (a) $(EtO)_2P(O)CH_2CO_2Et$, NaH, THF, 0 °C; (b) DIBAL, CH_2Cl_2 , -78 °C, 98% (2 steps); (c) (-)-DET, Ti(O*i*-Pr)₄, *t*-BuO₂H, MS4A, CH_2Cl_2 , -23 °C, 82%; (d) Red-Al, THF, 0 °C to rt; (e) NaIO₄, CH_2Cl_2 -acetone-H₂O, 76% (2 steps); (f) TBDPSCl, imidazole, DMF, 0 °C, 99%; (g) H₂, Pd/C, EtOAc, rt, 99%; (h) **13**, NIS, TfOH, MS4A, CH_2Cl_2 , -15 °C, 66% for **14**, 84% for **17**; (i) TBAF, THF, 0 °C; (j) Jones reagent, acetone, 0 °C; (k) CH_2N_2 , ether, 0 °C, 68% for **6a**, 81% for **6b**; (l) McCl, 2,6-lutidine, CH_2Cl_2 , 0 °C; (m) CsOAc, 18-crown-6, toluene, 80 °C; (n) K₂CO₃, MeOH, rt, 79% (3 steps).

were observed at 5.09 ppm, quite similar to that of 2 { $\delta_{\rm H}$ 5.08}. In respect to the C-2 (or 21 for 2) proton, clear discrimination between **7a** and **7c** was very difficult. However, there was similarity between **7a** and **2** in the splitting pattern of signals derived from the phenyl groups; see Supporting Information.

On the basis of these results, we estimated that **2** should have the stereochemistry of 3R, 15S, and 21R if **2** possesses a D-glucose residue. To confirm the estimation, 3R, 15S, 21R-methyl ester **2a** was synthesized as shown in Scheme 4. The hydroxyl group in **11** was initially protected as the corresponding THP ether to give **28**. Hydroboration of **28** followed by iodination provided iodide **4a**. Generation of alkyllithium derived from primary iodide **4a** (*t*-BuLi, -78



^{*a*} Reagents and conditions: (a) NaBH₄, NiCl₂·6H₂O, MeOH, 0 °C; (b) LAH, THF, 0 °C, 83% (2 steps); (c) *p*-TsCl, pyridine, 0 °C; (d) NaCN, DMSO, rt, 86% (2 steps); (e) DIBAL, CH₂Cl₂, -78°C; (f) (EtO)₂P(O)CH₂CO₂Et, NaH, THF, 0 °C, 99%; (g) (+)-DET, Ti(O*i*-Pr)₄, *t*-BuO₂H, MS4A, CH₂Cl₂, -23 °C, 89%; (h) DIBAL, CH₂Cl₂, 0 °C, 80%; (i) *p*-TsCl, Bu₂SnO, Et₃N, CH₂Cl₂, rt, 82%; (j) K₂CO₃, MeOH, rt, 97%; (k) *n*-BuLi, CuI, Et₂O, -60 to -40°C, 97%; (l) TBDPSCl, imidazole, DMF, rt, 90%; (m) PPTS, EtOH, 40 °C, 78%; (n) BzCl, pyridine, 0 °C, 99%; (o) TBAF, THF, 40 °C, 99%; (p) **13**, NIS, TfOH, MS4A, CH₂Cl₂, -15 °C, 70% for **7a**, 74% for **7b**, 61% for **7c**, 73% for **7d**; (q) McCl, 2,6-lutidine, CH₂Cl₂, 0 °C; (r) CsOAc, 18-crown-6, toluene, 80 °C; (s) concd HCl, MeOH, 0 °C to rt, 73% (3 steps) for **24**, 63% (3 steps) for **27**; (t) BzOH, DEAD, Ph₃P, THF, 0 °C; (u) TBAF, THF, 0 °C to rt, 79% (2 steps).

°C to rt) in ether-hexane¹³ followed by treatment with CuI provided an organocopper reagent, which reacted with

⁽¹³⁾ Bailey, W. F.; Punzalan, E. R. J. Org. Chem. 1990, 55, 5404–5406.



^{*a*} Reagents and conditions: (a) DHP, PPTS, CH₂Cl₂, rt, 99%; (b) BH₃·MeS, THF, 0 °C and then 3N NaOH, H₂O₂, 0 °C rt, 87%; (c) I₂, Ph₃P, imidazole, benzene, 10 °C, 92%; (d) *t*-BuLi, CuI, **5a**, hexane–Et₂O, -78 °C; (e) PPTS, EtOH, 50 °C, 85%; (f) BzCl, pyridine–CH₂Cl₂, -30 °C, 30%; (g) **13**, NIS, TfOH, MS4A, CH₂Cl₂, -15 °C, 49%; (h) TBAF, THF, 0 °C, 82%; (i) Jones reagent, acetone, 0 °C; (j) CH₂N₂, ether, 0 °C, 86% (2 steps).

epoxide **5a** to give a coupled product **29** in 78% yield. Upon treatment with PPTS, **29** afforded triol **30**. Benzoylation¹⁴ of **30** with 1.05 equiv of BzCl in CH₂Cl₂-pyridine at -30°C provided the desired benzoate **3a** as a major product along with several dibenzoate derivatives. Glycosidation of **3a** was performed by using 5.0 equiv of **13** in the presence of NIS (12 equiv) and TfOH (cat.) to afford β -glycoside **31** in 49% yield. Finally, removal of the silyl group of **31**, oxidation, and methylation gave the 3*R*,15*S*,21*R*-carboxylic acid methyl ester **2a** {[α]_D²⁴ +9.2° (*c* 0.60, CHCl₃)} in good yield. The ¹H, ¹³C NMR, and [α]_D data were identical with those of **2** {[α]_D²⁴ +9.1° (*c* 0.22, CHCl₃)}, showing macroviracin A to have the structure **1a** as depicted in Scheme 4. In summary, the absolute configuration of macroiviracins was unambiguously established by chemical synthesis of C_{22} -fatty acid methyl ester **2a**. Now, the total synthesis of **1a** is underway.

Acknowledgment. We are grateful to Mr. T. Hyodo (Kaken Pharm. Co.) for providing us natural macroviracins. We also express our thanks to Ms. K. Harata at RIKEN for mass spectral measurements.

Supporting Information Available: ¹H NMR spectra for compounds **6a,b**, **7a**–**d**, **2**, and **2a**; ¹³C NMR spectra for **2** and **2a**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL034338K

⁽¹⁴⁾ From the results of several model experiments, we expected that benzoylation at the C-2 position would proceed regioselectively.