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Determination of Absolute Structure of Macroviracins by Chemical Synthesis

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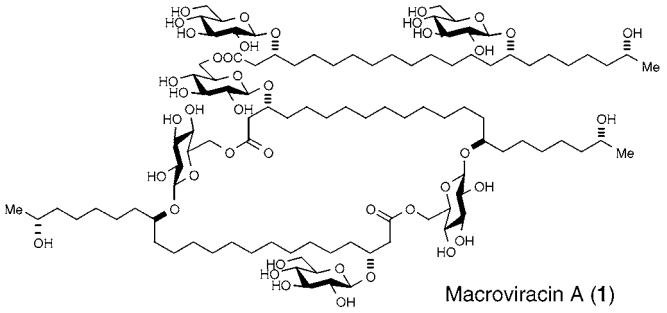
ABSTRACT



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 *Streptmyces* 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 cycloviracins[2] 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 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 B_1, establishing the absolute configuration.[4]

As methanolysis of **1** has been known to give the corresponding methyl ester in degradation studies, the benzoyl[5] 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.

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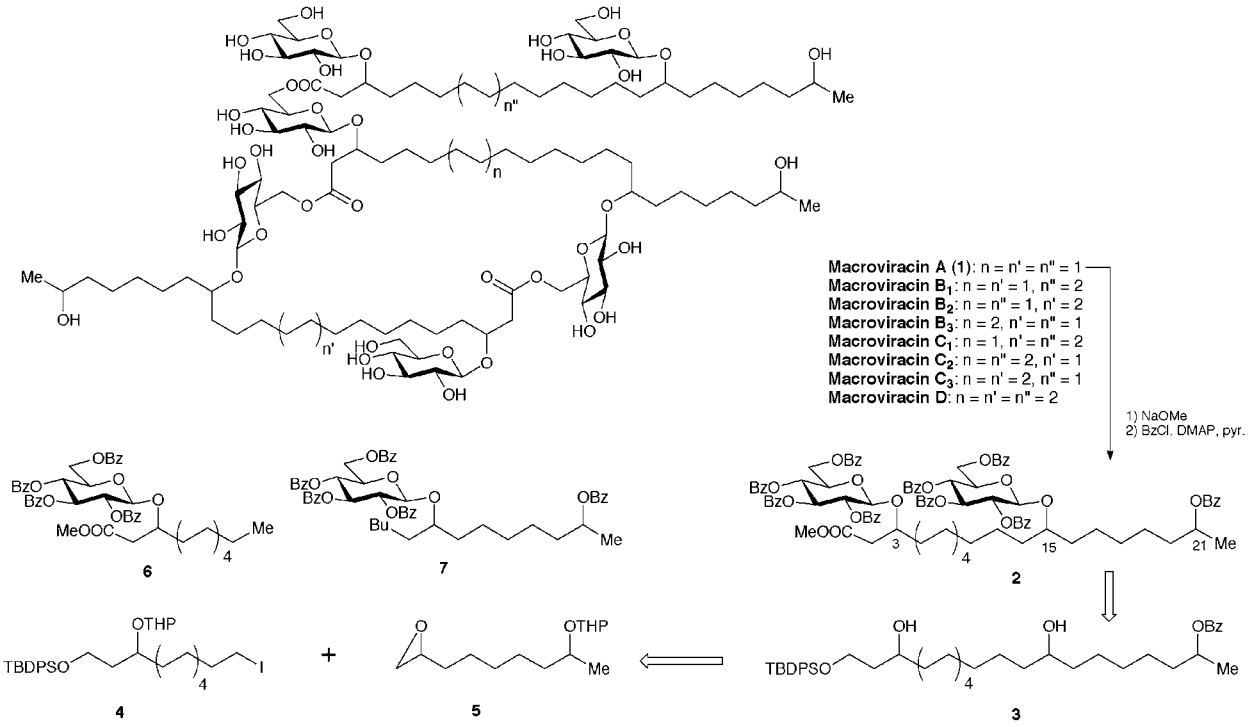
Scheme 1. Structures of Macroviracins and Retrosynthetic Analysis



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 reduction[6] of **10** and monosilylation provided a 1,3-diol derivative **11**. This underwent hydrogenation to afford alcohol **12**. Glycosidation[7] 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 CH_2Cl_2 to give the corresponding β-glucoside **14**. After de-silylation 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 monochlate[11] 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), δ_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 ^{1}H NMR spectra of the model compounds (**6a** and **6b**) were compared with that of **2**. The methyl ester **2** exhibited δ_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-Reduction[6] of the epoxide followed by an oxirane formation provided terminal epoxide **5a**. Nucleophilic addition of Bu_2CuLi 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, $[\alpha]_D$ + 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** {$[\alpha]_D$ −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** {$[\alpha]_D$ +11.4° (*c* 0.73)}. In their ^{1}H 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 $CHCl_3$ and $CDCl_3$, respectively, at 23 ± 2°.

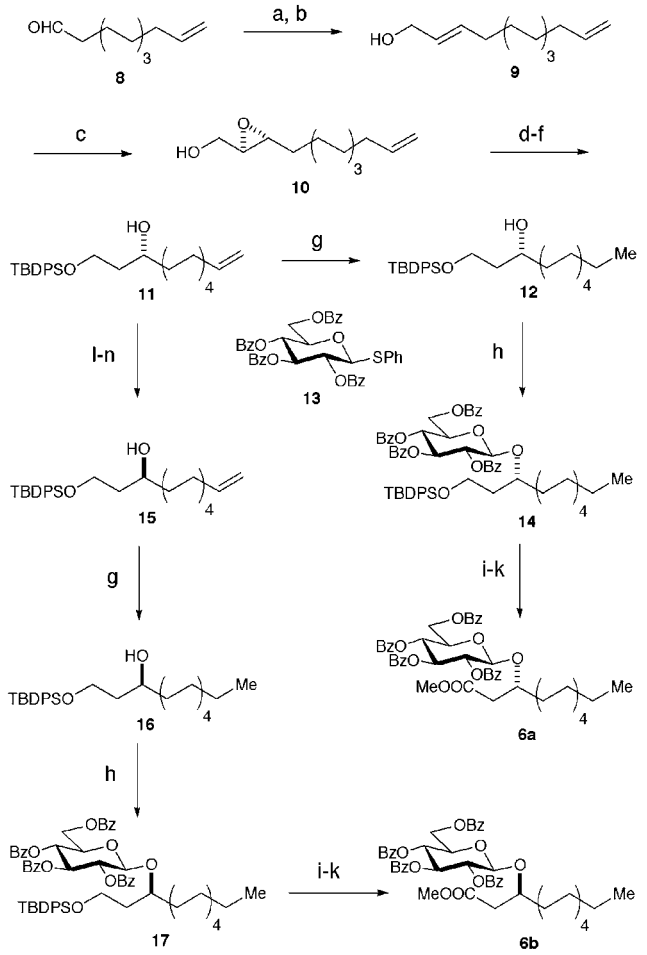
(9) Mitsunobu reaction[10] of this compound failed.

(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.

Scheme 2[a]

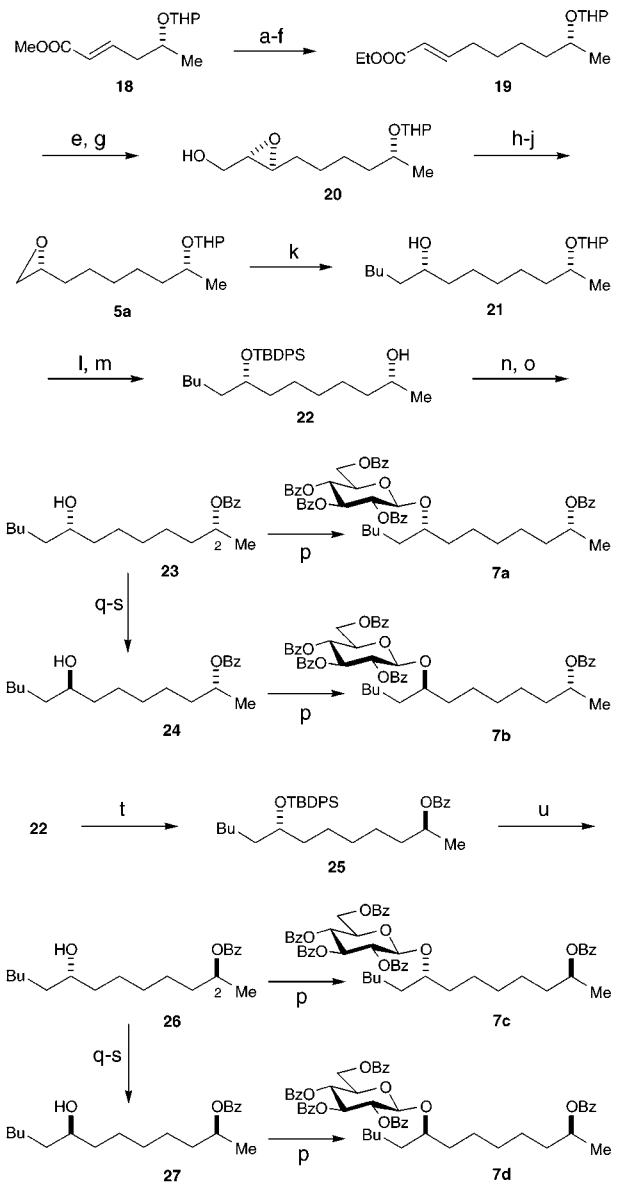


[a] Reagents and conditions: (a) $(EtO)_2P(O)CH_2CO_2Et$, NaH, THF, 0 °C; (b) DIBAL, CH_2Cl_2, −78 °C, 98% (2 steps); (c) (−)-DET, $Ti(Oi\text{-}Pr)_4$, *t*-BuO_2H, MS4A, CH_2Cl_2, −23 °C, 82%; (d) Red-Al, THF, 0 °C to rt; (e) $NaIO_4$, CH_2Cl_2−acetone−H_2O, 76% (2 steps); (f) TBDPSCl, imidazole, DMF, 0 °C, 99%; (g) H_2, 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) K_2CO_3, MeOH, rt, 79% (3 steps).

were observed at 5.09 ppm, quite similar to that of **2** {δ_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 3*R*, 15*S*, and 21*R* if **2** possesses a D-glucose residue. To confirm the estimation, 3*R*,15*S*,21*R*-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 °C to rt) in ether−hexane[13] followed by treatment with CuI provided an organocopper reagent, which reacted with

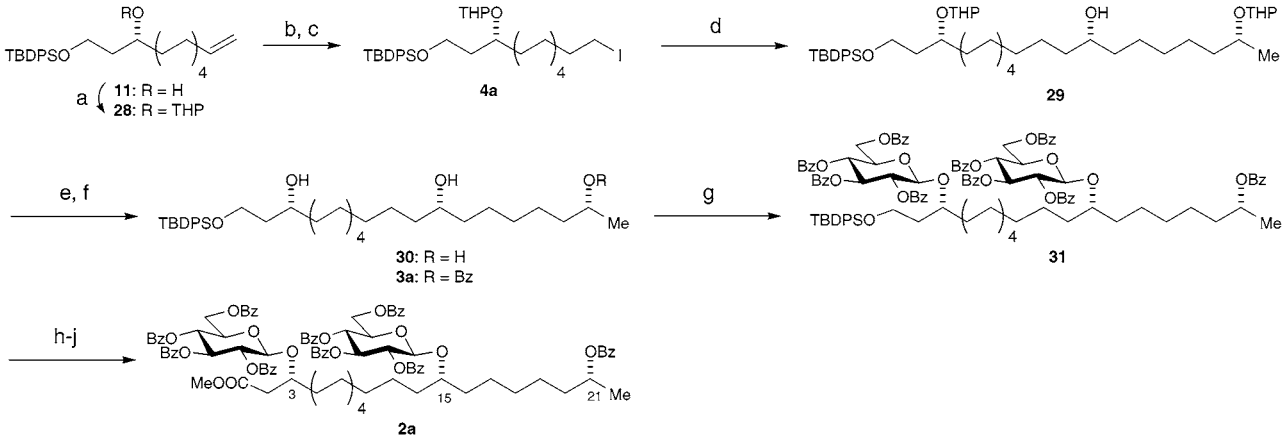
Scheme 3[a]

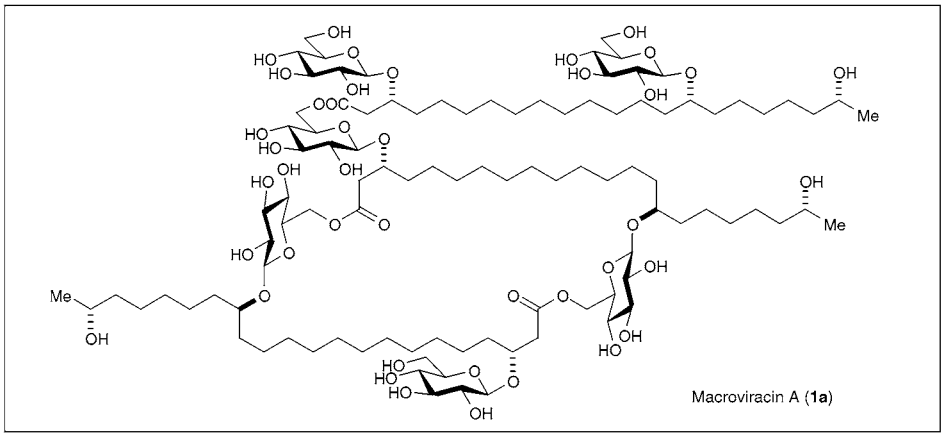


[a] Reagents and conditions: (a) $NaBH_4$, $NiCl_2{\cdot}6H_2O$, MeOH, 0 °C; (b) LAH, THF, 0 °C, 83% (2 steps); (c) *p*-TsCl, pyridine, 0 °C; (d) NaCN, DMSO, rt, 86% (2 steps); (e) DIBAL, CH_2Cl_2, −78 °C; (f) $(EtO)_2P(O)CH_2CO_2Et$, NaH, THF, 0 °C, 99%; (g) (+)-DET, $Ti(Oi\text{-}Pr)_4$, *t*-BuO_2H, MS4A, CH_2Cl_2, −23 °C, 89%; (h) DIBAL, CH_2Cl_2, 0 °C, 80%; (i) *p*-TsCl, Bu_2SnO, Et_3N, CH_2Cl_2, rt, 82%; (j) K_2CO_3, MeOH, rt, 97%; (k) *n*-BuLi, CuI, Et_2O, −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, CH_2Cl_2, −15 °C, 70% for **7a**, 74% for **7b**, 61% for **7c**, 73% for **7d**; (q) McCl, 2,6-lutidine, CH_2Cl_2, 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, Ph_3P, THF, 0 °C; (u) TBAF, THF, 0 °C to rt, 79% (2 steps).

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

Scheme 4[a]





[a] Reagents and conditions: (a) DHP, PPTS, CH_2Cl_2, rt, 99%; (b) BH_3·MeS, THF, 0 °C and then 3N NaOH, H_2O_2, 0 °C rt, 87%; (c) I_2, Ph_3P, imidazole, benzene, 10 °C, 92%; (d) *t*-BuLi, CuI, **5a**, hexane−Et_2O, −78 °C; (e) PPTS, EtOH, 50 °C, 85%; (f) BzCl, pyridine−CH_2Cl_2, −30 °C, 30%; (g) **13**, NIS, TfOH, MS4A, CH_2Cl_2, −15 °C, 49%; (h) TBAF, THF, 0 °C, 82%; (i) Jones reagent, acetone, 0 °C; (j) CH_2N_2, 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**. Benzoylation[14] of **30** with 1.05 equiv of BzCl in CH_2Cl_2-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** {$[\alpha]_D^{24}$ +9.2° (*c* 0.60, $CHCl_3$)} in good yield. The ^{1}H, ^{13}C NMR, and $[\alpha]_D$ data were identical with those of **2** {$[\alpha]_D^{24}$ +9.1° (*c* 0.22, $CHCl_3$)}, showing macroviracin A to have the structure **1a** as depicted in Scheme 4.

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

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

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