Pergamon

Tetrahedron Letters, Vol. 36, No. 47, pp. 8599-8602, 1995
Elsevier Science Ltd
Printed in Great Britain
0040-4039/95 $9.50+0.00

0040-4039(95)01823-9

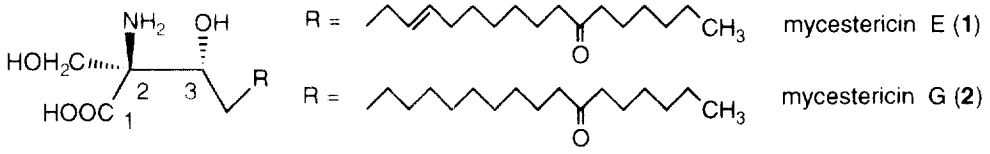
DETERMINATION OF THE ABSOLUTE CONFIGURATIONS AND TOTAL SYNTHESIS OF NEW IMMUNOSUPPRESSANTS, MYCESTERICINS E AND G

Tetsuro Fujita,* Norimitsu Hamamichi,[a] Tohru Matsuzaki,[b] Yuki Kitao,[b] Masatoshi Kiuchi[b] Manabu Node[a] and Ryoji Hirose[c]

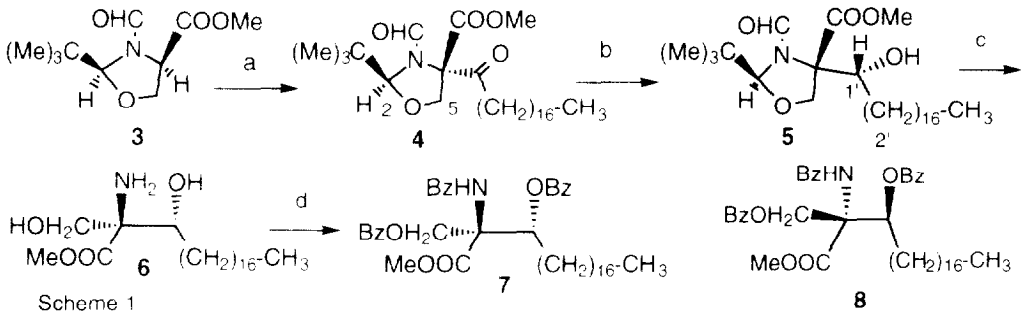
Faculty of Pharmaceutical Sciences, Setsunan University, 45-1 Nagaotoge, Hirakata, Osaka 573-01, Japan
a Kyoto Pharmaceutical University, 5 Nakauchi-cho, Misasagi, Yamashina-ku, Kyoto 607, Japan
b Faculty of Pharmaceutical Sciences, Kyoto University, Sakyo-ku, Kyoto 606-01, Japan
c Research Laboratory, Taito Company, Ltd., 1-26 Higashi Shiriike-Shinmachi, Nagata-ku, Kobe 653, Japan

Abstract: The absolute configurations of two new immunosuppressants, mycestericins E (**1**) and G (**2**), were established and both compounds were synthesized starting from 1,8-octanediol and a fully protected methyl (2*S*,4*R*)-oxazolidine-4-carboxylate **3**. Compounds **5** and **22**, with a (1'*R*)-hydroxyl group, were prepared from the β-keto esters **4** and **21**, respectively, by stereoselective reduction with metal borohydrides.

Recently, we reported the isolation of mycestericin E (**1**) as a new immunosuppressant from the culture broth of the fungus *Mycelia sterilia* ATCC 20349, which produces the immunosuppressant ISP-I, and elucidated the planar structure from spectroscopic and chemical evidence.[1] The dihydro derivative, mycestericin G (**2**), has also been isolated from the same broth. Compounds **1** and **2** showed immunosuppressive activities with IC_{50} values of 13 nM and 370 nM, respectively, against mouse allogeneic mixed lymphocyte reaction (MLR).[2] Here we report determination of the absolute configurations of mycestericins E (**1**) and G (**2**), and the first total synthesis of **1** and **2**, starting from 1,8-octanediol and methyl (2*S*, 4*R*)-2-*tert*-butyl-3-formyloxazolidine-4-carboxylate (**3**)[3a].



Determination of the absolute configurations of **1** and **2** was performed by comparison of their CD spectra with those of synthetic compounds **7** and **8**. The synthesis of **7** is outlined in Scheme 1. Stereoselective acylation[3b] of the oxazolidine **3** with stearoyl chloride afforded the β-keto ester **4**, syrup; IR ($CHCl_3$): 1750 (CO), 1725 (CO), 1680 (CO) cm^{-1}, after purification by silica gel flash column chromatography.[4] The relation between the ketone and the methyl ester was confirmed to be *s-cis* based on NOE experiments (Figure 1). Therefore, the stereoselective reduction of the β-keto ester **4** with metal borohydrides should give predominantly the (1'*R*)-hydroxy compound **5**[5] by hydride attack from the less hindered side because of the bulky formyl group at the *re*-face of the ketone. The results are summarized in the table. Treatment of (1'*R*)-**5** with 6 N HCl afforded the ester **6**, solid; mp 60-61 °C, which was benzoylated to give **7**.[6] The CD spectra of **7**, **9**[7] and **10**[7] exhibited similar negative Cotton effects at 241 nm, while **8** exhibited a positive Cotton



Scheme 1

Reagents: a) $CH_3(CH_2)_{16}COCl$ (1.2 eq.), LDA (1.2 eq.), THF, -100°C, 46 %; b) $NaBH_4$ (1.2 eq.), MeOH, 70 % (1'*R*-**5**); c) 6 N HCl, MeOH, 80 C, 1 h, 61 %; d) Bz_2O, Et_3N, 40°C, 2 h, 77 %

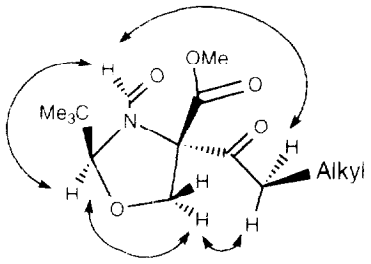


Figure 1. ⟷ NOE

Table. Reduction of **4**.

Reagents / Solvent	Temp(C)	Time(h)	**5**(1'*R*)/(1'*S*)[a]
$NaBH_4$ / MeOH	0	0.5	85 / 15
$LiBH_4$ / Et_2O	0	2	80 / 20
$Zn(BH_4)_2$ / Et_2O	0	2	85 / 15

a. Ratio of 1'*R*/1'*S* determined by HPLC.

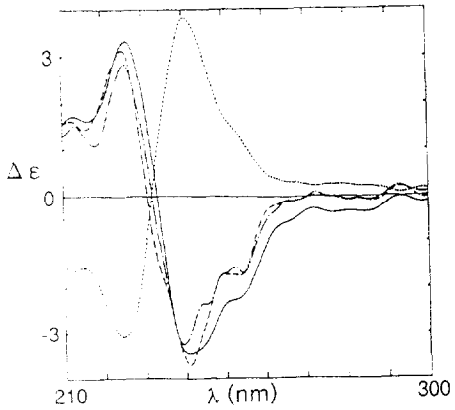


Figure 2. CD spectra of **7**, **8**, **9** and **10** (in MeOH).

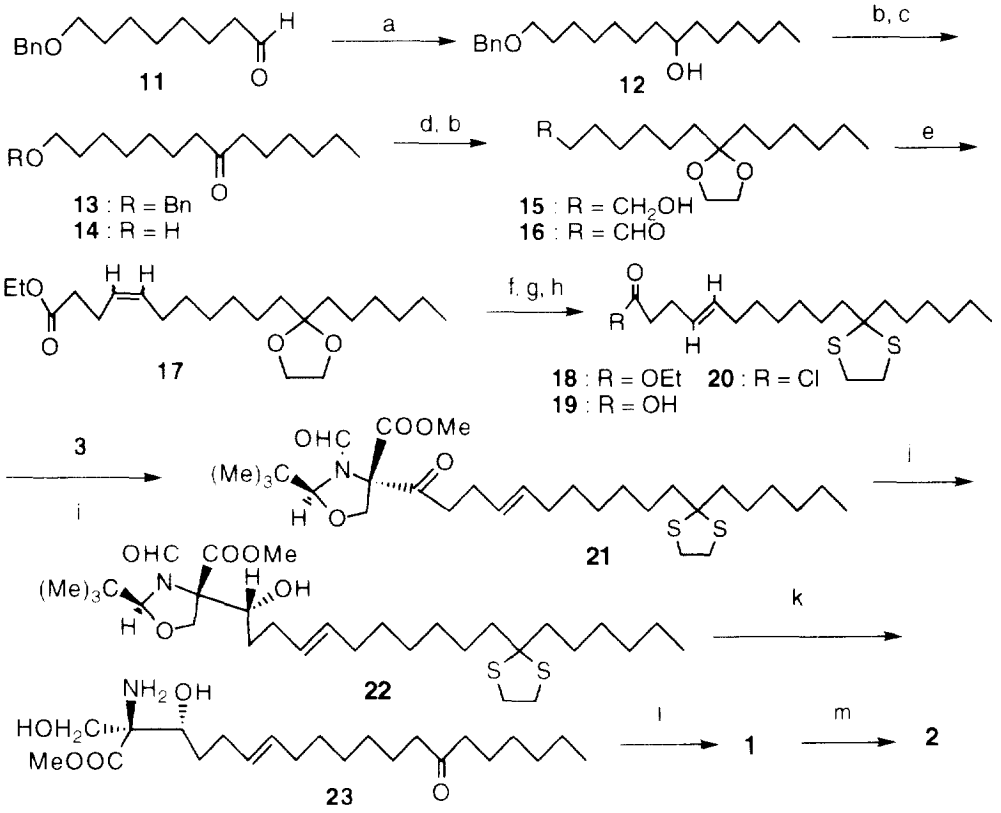
7 — — — **9**: ————

8 ····· **10**: — · — ·

effect at 241 nm (Figure 2).[8] On this basis, the configurations of **1** and **2** were assigned as 2*S*, 3*R*.

Syntheses of **1** and **2** are summarized in Scheme 2. 8-(Benzyloxy)octanal (**11**) was prepared in two steps (benzylation/NaH, THF, 60 C and Swern oxidation) from 1,8-octanediol in 41 % overall yield by an improved method based on that of Grayshan *et al.*[9] Reaction of **11** with *n*-hexylmagnesium bromide provided the hydroxy derivative **12**, which was converted to the ketone **13**, syrup; IR ($CHCl_3$): 1705 (CO) cm^{-1}. Deprotection of the benzyl group of **13** with $FeCl_3$[10] gave the alcohol **14**, mp 52-53°C,[11] and the carbonyl group was protected with ethylene glycol to give the 1,3-dioxolane **15**, syrup.[12] Alternatively, **15** was prepared from **13** in 83 % yield by dioxolanation, followed by debenzylation with H_2/10 % Pd-C. Wittig reaction of **16**, which was prepared from **15** by Swern oxidation, with (3-ethoxycarbonylpropyl)triphenylphosphonium bromide[13] provided **17**, syrup; IR ($CHCl_3$): 2910, 1725 (CO), 950 (C=CH, *E*), 675 (C=CH, *Z*) cm^{-1}, as an 89 : 11 mixture of *E* and *Z* isomers.[14] The isomerization of **17** was performed under sun light at room temperature. After purification on an $AgNO_3$-silica gel column,[15] the major product was thioketalized to give **18**, syrup.[16] The configuration of the olefin of **18** was assigned as *E*-form based on the

^{1}H-NMR and ^{13}C-NMR spectra. The acid chloride **20** was prepared from **18** by hydrolysis, followed by heating of **19** and $SOCl_2$. Stereoselective acylation of **3** with **20** afforded the β-keto ester **21**, syrup ; IR ($CHCl_3$): 1750 (CO), 1720 (CO), 1680 (CO), 970 (C=CH, *E*) cm^{-1}, after purification by silica gel flash column chromatography.[17] Reduction of **21** with $NaBH_4$ provided **22**,[18] the thioketal group of which was removed with NCS/$AgNO_3$[19] to give the ketone. Without purification, the ketone was treated with acid to give the methyl ester **23** after purification by silica gel preparative tlc.[20] Hydrolysis of **23** afforded mycestericin E (**1**), white powder; mp 183-185°C; $[\alpha]_D^{24}$ -8.5° (c 0.06, MeOH).[21] Mycestericin G[22] (**2**) also was obtained from **1** by hydrogenation. These products gave identical spectroscopic data with those of authentic mycestericins E and G.



Scheme 2

Reagents: a) $BrMgC_6H_{13}$ (1.2 eq.),THF, 0 C, 83%; b) $(COCl)_2$ (1.5eq.), DMSO (1.8 eq.), CH_2Cl_2, r.t, 89 %; c) $FeCl_3$ (3 eq.), CH_2Cl_2, r.t. 90 %; d) $HOCH_2CH_2OH$ (7.3 eq.), *p*-TsOH, 92%; e) EtO_2C-$(CH_2)_3P^+(Ph)_3Br^-$ (1.8 eq.), $KN(SiMe_3)_2$(1.5 eq.), THF, 0°C, 80 %; f) i) h ν , PhSSPh, hexane; ii) $HSCH_2CH_2SH$ (2.7 eq.), $BF_3.Et_2O$, CH_2Cl_2, r.t, 68 % from **17**; g) 1 N NaOH, MeOH; h) $SOCl_2$ (6 eq.), benzene, rf ; i) $LiN(SiMe_3)_2$ (1.5 eq.), THF, -100°C, 70 %; j) $NaBH_4$ (1.2 eq.), MeOH, 0°C, 97 % (*R*/*S* mixture); k) i) NCS, $AgNO_3$; ii) 10 % MeOH in CF_3COOH, 60°C, 38 % from **22**; l) 2 N NaOH, MeOH, r.t, 68 %; m) H_2 / 10 % Pd-C, MeOH.

References and Notes

1. Sasaki, S.; Hashimoto, R.; Kiuchi, M.; Inoue, K.; Ikumoto, T.; Hirose, R. Chiba.; K. Hoshino, Y.; Okumoto.T.; Fujita, T. *J. Antibiotics*, **1994**, 47, 420.
2. Fujita, T.; Inoue, K.; Yamamoto, S.; Ikumoto, T.; Sasaki, S.; Toyama, R.; Chiba, K.; Hoshino, Y.; Okumoto, T. *J. Antibiotics*, **1994**, 47, 208.
3. (a) Seebach, D.; Aebi, D. J. *Tetrahedron Lett.* **1984**, 25, 2545; (b) Singh, N. P.; Giannis, A.; Henk, E.; Kolter, T.; Sandhoff, K.; Schmidt, R. R. *J. Carbohydrate Chemistry*, **1990**, 9, 543.
4. **4**: $[\alpha]_D^{24}$ +3.0° (c=1.2, $CHCl_3$); ^{1}H-NMR ($CDCl_3$)δ 0.88 (3 H, t, J = 7 Hz), 0.94, 0.98 (9 H, 2s), 1.25 (28 H, m), 1.60 (2 H, m), 2.49 (1 H, m), 2.68 (1 H, dt, J = 18 Hz, J = 8 Hz), 3.85, 3.88 (3 H, 2s), 4.08, 4.16 (1 H, 2d, J = 10 Hz, J = 9 Hz), 4.61, 4.71 (1 H, 2d, J = 10 Hz, J = 9 Hz), 5.08, 5.48 (1H, 2s), 8.25, 8.32 (1 H, 2s, CHO). All new compounds gave satisfactory high-resolution CIMS and FABMS data.
5. The absolute configuration of the (1′*R*)-hydroxyl group was confirmed by the modified Mosher's method.[23] $\Delta\delta = \delta_S - \delta_R$ in ppm (270 MHz): COOMe (- 0.148), 5α-H (+ 0.010), 5β-H(- 0.039), 2′-H_2 (+ 0.076, + 0.059).
6. (2*S*,3*R*)-**7**: syrup, ^{1}H-NMR ($CDCl_3$)δ 0.88 (3 H, t, J = 7 Hz), 1.25 (30 H, m), 1.75 (1 H, m), 1.91 (1 H, m), 3.86 (3 H, s), 5.01 (1 H, d, J = 12 Hz), 5.39 (1 H, d, J = 12 Hz), 5.84 (1 H, dd, J = 11 Hz, J = 2 Hz), 7.19-7.99 (16 H, m). The CD spectrum of the (2*S*,3*S*)-isomer of **7** exhibited a positive Cotton effect at 238 nm.
7. Tribenzoyl derivatives **9** and **10** were prepared from **1** and **2**, respectively, by esterification with CH_2N_2, followed by benzoylation with benzoic anhydride and Et_3N.
8. (2*R*, 3*S*)-**8** was prepared from methyl (2*S*, 4*S*)-2-*tert*-butyl-3-formyl-oxazolidine-4-carboxylate[3] and stearoyl chloride, and the diastereoisomers, (3*S*)- and (3*R*)-hydroxy derivatives, were purified by HPLC after reduction of the β-keto ester with $NaBH_4$. The CD spectrum of the (2*R*, 3*R*)-isomer of **8** showed a negative Cotton effect at 238 nm, which was not identical with that of tribenzoyl derivatives (**9** and **10**).
9. Grayshan, R.; Keal, C. A.; Sackville, M. A. *J. Chem. Research*, **1986**, 282; **11**: syrup; ^{1}H-NMR ($CDCl_3$)δ 1.33 (6 H, m), 1.61 (4 H, m), 2.40 (2 H, td, J = 7 Hz, J = 2 Hz), 3.46 (2 H, t, J = 6 Hz), 4.50 (2 H, s), 7.26-7.35 (5 H, m, PhH), 9.76 (1 H, d, J = 2 Hz, CHO).
10. Park, M. H.; Takeda, R.; Nakanishi, K. *Tetrahedron Lett.* **1987**, 28, 3823.
11. Just, G.; Payette, D. R.. *Tetrahedron Lett.* **1980**, 21, 3219; **14**: ^{1}H-NMR ($CDCl_3$)δ 0.88 (3 H, t, J = 7 Hz), 1.26-1.32 (12 H, m), 1.53-1.60 (6 H, m), 2.38 (4 H, t, J = 7 Hz), 3.64 (2 H, t, J = 7 Hz).
12. **15**: ^{1}H-NMR ($CDCl_3$)δ 0.88 (3 H, t, J = 7 Hz), 1.28-1.32(2 H, t, J = 6 Hz), 1.56-1.59 (6 H, m), 3.64 (2 H, t, J = 6 Hz), 3.93 (4 H, s).
13. Thomas, E. J.; Whitehead, J. N. F. *J. Chem. Soc. Perkin Trans I*, **1989**, 499.
14. **17**: ^{1}H-NMR ($CDCl_3$)δ 0.88 (3 H, t, J = 7 Hz), 1.23-1.28 (19 H, m), 1.55-1.59 (4 H, m), 2.00-2.04 (2 H,dt), 2.34-2.35 (4 H, m), 3.92 (4 H, s), 4.12 (2 H, q, J = 7 Hz), 5.34 (1 H, m, C=H), 5.42 (1 H, dt, J = 10 Hz, J = 5 Hz, C=CH); ^{13}C-NMR for the olefins (*E*, *Z*) of **17**. ^{13}C-NMR ($CDCl_3$)δ 127.3 (C=, *Z*), 127.9 (C=, *E*), 131.4 (C=, *Z*), 131.7 (C=, *E*).
15. 5 % $AgNO_3$-silica gel was prepared by the method of Stowell; Stowell, J. C. *J. Org. Chem.* **1970**, 35, 244.
16. **18**: ^{1}H-NMR ($CDCl_3$)δ 0.88 (3 H, t, J = 7 Hz), 1.23-1.47 (16 H, m), 1.87-1.98 (6 H, m), 2.29-2.35 (4 H, m), 3.26 (4 H, s), 4.13 (2 H, q, J = 7 Hz), 5.39 (1 H, dt, J = 15 Hz, J = 5 Hz, C=CH, *E*), 5.47 (1 H, dt, J = 15 Hz, J = 5 Hz, C=CH, *E*); ^{13}C-NMR ($CDCl_3$)δ 14.0, 14.2, 22.5, 26.8, 27.8, 28.9, 29.4, 29.6, 31.6, 32.4, 34.3, 39.3, 43.4, 60.1, 71.6, 77.2, 127.9 (C=, *E*), 131.6 (C=, *E*), 173.1.
17. **21**: ^{1}H-NMR ($CDCl_3$)δ 0.88 (3 H, t, J = 7 Hz), 0.94, 0.98 (9 H, 2s), 1.26-1.30 (16 H, m), 1.87-1.97 (6 H, m), 2.29-2.34 (2 H, m), 2.52-2.74 (2 H, m), 3.26 (4 H, s), 3.85, 3.88 (3 H, 2s), 4.09, 4.17 (1 H, 2d), 4.60, 4.69 (1 H, 2d), 5.08, 5.48 (1 H, 2s), 5.25-5.44 (2 H, m), 8.24, 8.32 (1 H, 2s).
18. (*R*)-and (*S*)-Hydroxy **22** were unstable during silica gel column chromatography or preparative tlc. Especially, the (*S*)-compound was readily decomposed, and could not be purified.
19. Corey, E. J.; Erickson, B. W. *J. Org. Chem.* **1971**, 36, 3553.
20. **23**: syrup; $[\alpha]_D^{24}$ +14.3° (c 1.46, $CHCl_3$); ^{1}H-NMR (CD_3OD)δ 0.89 (3 H, t, J = 7 Hz), 1.23-1.36 (12 H, m), 1.41-1.56 (6 H, m), 1.93-2.02 (3 H, m), 2.13-2.25 (1 H, m), 2.43 (4 H, t, J = 7 Hz), 3.47 (1 H, d, J = 11 Hz), 3.83 (1 H, d, J = 11 Hz), 3.74 (3 H, s, COOMe), 5.40 (1 H, dt, J = 15 Hz, J = 6 Hz, C=H), 5.46 (1 H, dt, J = 15 Hz, J = 6 Hz, C=CH).
21. Natural product, mycestericin E: white powder; mp 184-186 °C; $[\alpha]_D^{24}$ -8.6° (c 0.06, MeOH).
22. Natural product, mycestericin G: white powder; mp 187-189 °C; ^{1}H-NMR (CD_3OD)δ 0.90 (3 H, t, J = 7 Hz), 1.30 (20 H, m), 1.36 (1 H, m), 1.54 (4 H, quint, J = 7 Hz), 1.62 (1 H, m), 2.44 (4 H, t, J = 7 Hz), 3.81 (1 H, d, J = 11 Hz), 3.83 (1H, m), 3.93 (1 H, d, J = 11 Hz).
23. Kusumi, T.; Fujita, Y.; Ohtani, I.; Kakisawa, H. *Tetrahedron Lett.* **1991**, 32, 2923, and references cited therein.

(*Received in Japan* 14 *August* 1995; *revised* 18 *September* 1995; *accepted* 22 *September* 1995)