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COMMUNICATIONS TO THE EDITOR

The Total Synthesis and Absolute Structure of Antifungal Antibiotics (−)-PF1163A and B

Sir:

Antifungal antibiotics (−)-PF1163A and B (**1** and **2**) were isolated from the fermentation broth of *Penicillium* sp. by the Meiji Seika Kaisha group[1]. The structure of PF1163B (**2**) has been deduced by the chemical and X-ray crystallographic analyses[2]. However, the absolute structure of PF1163A (**1**) including the relative configuration remained undetermined.

Herein, we report the total synthesis of (−)-PF1163A and B (**1** and **2**) to disclose their absolute structures unambiguously.

From the retrosynthetic perspective, (−)-PF1163B (**2**) is expected to be constructed reasonably from the unique amino acid **3** and the hydroxy acid **4** (R=H) (Chart 1). The latter may be prepared from optically active citronellol.

Although we have synthesized both antipodes of **2** to determine the absolute configurations, only the synthesis of the natural product **2** is conveniently described from Boc-L-tyrosine (**5**) and (*R*)-citronellol (**8**) as follows.

Reaction of **5** with *O*-silylated hydroxyethyl bromide gave the ester **6**, the phenol of which was simultaneously protected. *N*-Methylation of **6** followed by saponification produced the carboxylic acid **7** (Scheme 1 and Table 1).

Ozonolysis of the double bond of **8** followed by Wittig olefination of the resulting aldehyde afforded the unsaturated ester **9**. This was converted by reduction and oxidation into the aldehyde **10**, which was submitted to the one-carbon elongation reaction to give the other aldehyde **11**. Asymmetric synthesis of **13** from **11** was examined under several conditions[3] with a variety of metals and allyl halides (Scheme 2). The best result was realized by the protocol reported by Hafner's group using a chiral (*S,S*)-allyltitanium reagent **12**, which was prepared from (*S,S*)-tartrate[3]. The desired (9*S*)-alcohol **13** was produced in 72% yield with 6 : 1 selectivity for the (6*R*,9*S*)-diastereomer. As direct ozonolysis of **13** gave the corresponding aldehyde in low yield, the hydroxy group was protected to give **14** by diethylisopropyl silyl group. This protecting group has been developed in our laboratories[4] to be removed under reduction conditions using hydrogen and $Pd(OH)_2$ in MeOH. Ozonolysis of **14** afforded the aldehyde **15**, which was submitted to the Wittig reaction followed by reduction with de-*O*-silylation[4] to afford the hydroxy ester **16**.

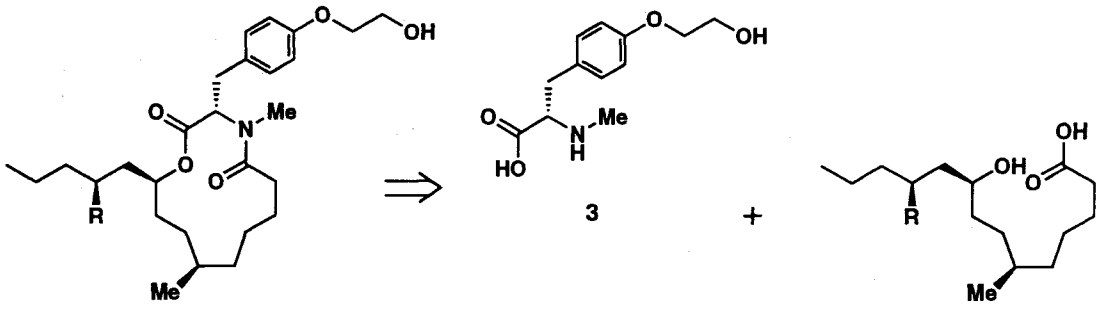
With both segments **7** and **16** in hand, we turned to the esterification and cyclization.

Conversion of **7** with β-naphthoyl chloride to the mixed anhydride[5] was followed by reaction with **16** to give the ester **17** in high yield. After removal of all protecting groups, the resulting amino acid was cyclized by bis(2-oxo-3-oxazolidinyl)phosphinic chloride (Bop-Cl)[6] to (−)-PF1163B (**2**), which was identical with the natural antibiotic in all respects. The ^{1}H-NMR spectrum exhibited similarly broad signals and was superimposable on that of the natural product[1,2].

Next, (−)-PF1163A (**1**) was synthesized following similar synthetic strategies (Scheme 3).

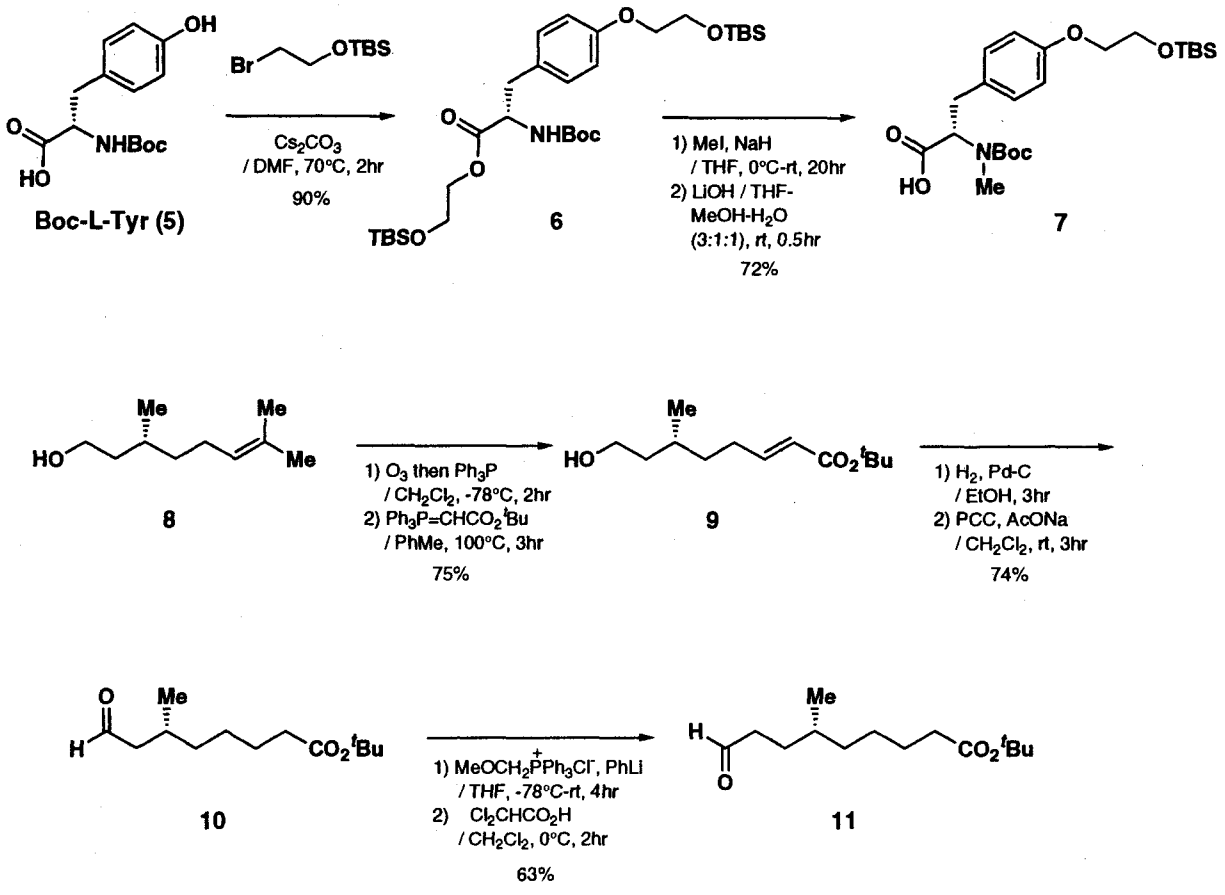
However, in **1**, even relative configurations remained

Chart 1



(-)-PF1163A (1) : R = OH
(-)-PF1163B (2) : R = H

Scheme 1



undetermined. We anticipated that all configurations except at C-11 of the hydroxy acid moiety would be the same as those of **2** and, consequently, synthesized first the C-11 diastereomers (**20** and **20′**) of the hydroxy acid from the key aldehyde **15** to determine the absolute configuration.

Enantioselective allyltitanation of **15** with the (*R,R*)-Ti-complex **18**[3] gave preferentially the (11*S*)-alcohol **19**, while reaction with (*S,S*)-Ti-complex **12** gave the diastereomeric (11*R*)-alcohol **19′** as mentioned before. Silylation of **19** to give the *O*-TBS derivative followed by treatment with H_2 and $Pd(OH)_2$ in MeOH afforded the saturated hydroxy ester **20** with selective removal of the *O*-diethylisopropylsilyl group[4]. The diastereomer **20′** was obtained from **19′** in the same way. Treatment of **20** with isopropenyl methyl ether gave no acetonated derivative, while **20′** gave the acetonide **21**, indicating that **20** and **20′** have the *anti*- and *syn*-diols, respectively. Finally, **20** proved to be suitable for the synthesis of (−)-1163A (**1**), because the methyl ester **22**, which was derived from **20** by methanolysis, was identical with the naturally derived sample[2]. These results showed that the hydroxy acid moiety of **1** has the (6*R*,9*S*,11*S*)-configuration.

Esterification of **7** with **20** was accomplished under the conditions described using β-naphthoyl chloride[5] to give the ester **23**, from which all protecting groups were removed by 95% TFA. The resulting amino acid having two hydroxy groups was submitted to cyclization[6] with preferential formation of the amido bond to give exclusively (−)-PF1163A (**1**) without formation of any lactones. The ^{1}H-NMR spectrum of **1** was completely superimposable on that of the natural product, although all the signals were very broad as reported in the previous paper[1,2].

Finally, the product **1** was identical with the natural antibiotic in all respects, completing the total synthesis and configurational analysis.

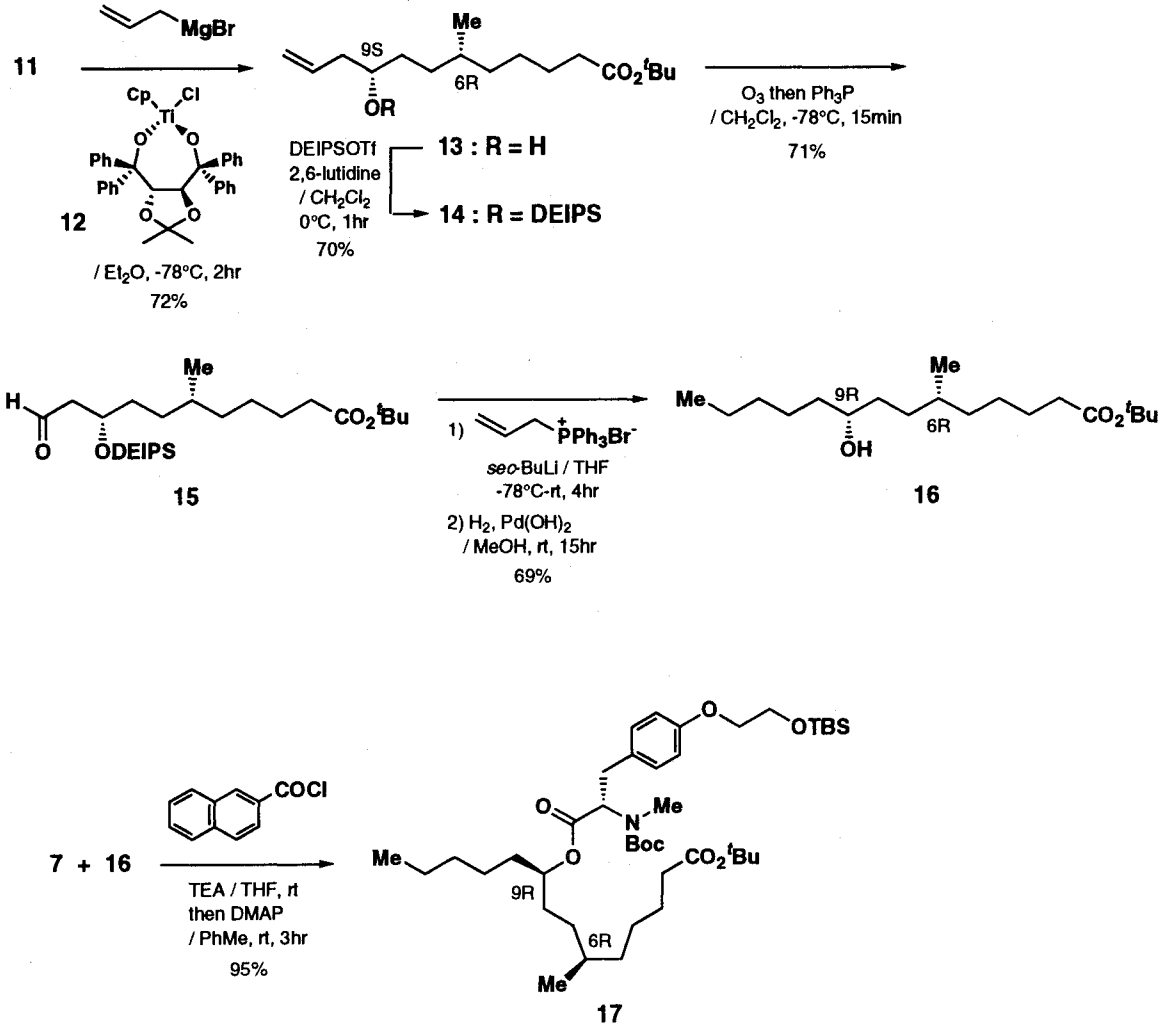
Table 1-1. Physico-chemical properties of products.

No.	$[\alpha]_D$	^{1}H-NMR (300, 400, 500 or 600MHz; $CDCl_3$; δ ppm; *J* Hz)
1	-91 (*c* 0.73, MeOH)	0.82 & 0.89 (3H, t, J=7.0 Hz), 0.85 (3H, d, J=7.0 Hz), 0.90 - 2.08 (19H, m), 2.16 - 2.30 (1H, m), 2.60 - 2.87 (1H, m), 2.94 - 3.03 (3H, s), 3.15 - 3.52 (2H, m), 3.95 (2H, m), 4.05 (2H, m), 4.80 - 4.93 (1H, m), 5.75 - 5.83 (1H, m), 6.78 - 6.87 (2H, m), 7.05 - 7.20 (2H, m)
2	-115 (*c* 0.24, MeOH)	0.83 & 0.91 (3H, t, J=7.0 Hz), 0.85 (3H, d, J=7.0 Hz), 1.10 - 1.70 (19H, m), 2.09 (1H, t, J=6.0 Hz), 2.14 - 2.48 (2H, m), 2.61 - 2.85 (2H, m), 2.88 - 3.06 (3H, m), 3.22 - 3.65 92H, m), 3.95 (2H, m), 4.05 (2H, m), 5.06 (1H,m), 5.83 (1H,m), 6.80 - 6.90 92H, m), 7.06 - 7.23 (2H, m)
6	+6.7 (*c* 1.2, MeOH)	0.08 (6H, s), 0.10 (6H, s), 0.90 (9H, s), 0.91 (9H, s), 1.42 (9H, s), 3.02 (1H, dd, *J*=14.0, 6.0 Hz), 3.04 (1H, dd, *J*=14.0, 6.0 Hz), 3.80 (2H, t, *J*=5.0 Hz), 3.91 - 4.03 (4H, m), 4.16 (2H, t, *J*=5.0 Hz), 4.56 (1H, dt, *J*=8.0, 6.0 Hz), 4.95 (1H, d, *J*=8.0 Hz), 6.82 (2H, d, *J*=8.0 Hz), 7.04 (2H, d, *J*=8.0 Hz)
7	-25 (*c* 1.1, MeOH)	0.10 (6H, s), 0.91 (9H, s), 1.35 & 1.41 (9H, s), 2.67 & 2.75 (3H, s), 2.92 - 3.13 (1H, m), 3.19 - 3.28 (1H, m), 3.96 (2H, m), 4.00 (2H, m), 4.55 & 4.68 (1H, m), 6.83 (2H, d, *J*=8.0 Hz), 7.08 & 7.11 (2H, d, *J*=8.0 Hz)
9	+6.1 (*c* 1.3, $CHCl_3$)	0.92 (3H, d, *J*=7.0 Hz), 1.22 - 1.73 (5H, m), 1.48 (9H, s), 2.19 (2H, m), 3.69 (2H, m), 5.74 (1H, dt, *J*=15.5, 1.5 Hz), 6.86 (1H, dt, *J*=15.5, 7.0 Hz)
10	+3.9 (*c* 1.2, $CHCl_3$)	0.96 (3H, d, *J*=7.0 Hz), 1.18 - 1.63 (6H, m), 1.44 (9H, s), 2.06 (1H, m), 2.21 (2H, t, *J*=7.5 Hz), 2.23 (1H, ddd, *J*=16.0, 8.0, 2.0 Hz), 2.39 (1H, ddd, *J*=16.0, 6.0, 2.0 Hz), 9.76 (1H, t, *J*=2.0 Hz)
11	+0.8 (*c* 1.0, $CHCl_3$)	0.88 (3H, d, *J*=7.0 Hz), 1.05 - 1.75 (9H, m), 1.44 (9H, s), 2.21 (2H, t, *J*=7.5 Hz), 2.39 - 2.46 (2H, m), 9.77 (1H, t, *J*=2.0 Hz)
13	-3.3 (*c* 1.2, MeOH)	0.86 (3H, d, *J*=7.0Hz), 1.07 - 1.64 (11H, m), 1.44 (9H, s), 2.15 (1H, ddd, *J*=15.0, 8.0, 7.0 Hz), 2.21 (2H, t, *J*=8.0 Hz), 2.27 - 2.35 (1H, m), 3.62 (1H, ddt, *J*=8.0, 6.0, 4.0 Hz), 5.14 (1H, dd, *J*=11.0, 0.5 Hz), 5.15 (1H, dd, *J*=14.0, 0.5 Hz), 5.83 (1H, dddd, *J*=14.0, 11.0, 7.0, 6.0 Hz)
14	-7.3 (*c* 1.1, MeOH)	0.59 (2H, ap.t, *J*=7.5 Hz), 0.65 (2H, ap.t, *J*=7.5 Hz), 0.84 (3H, d, *J*=7.0 Hz), 0.93 - 1.04 (13H, m), 1.04 - 1.66 (11H, m),1.44 (9H, s), 2.20 (2H, t, *J*=7.5 Hz), 3.70 (1H, tt, *J*=6.0, 6.0 Hz), 5.02 (1H, dd, *J*=10.0, 0 Hz), 5.03 (1H, dd, *J*=17.5, 0 Hz), 5.82 (1H, ddt, *J*=17.5, 10.0, 7.0 Hz)
15	+10 (*c* 0.96, MeOH)	0.56 - 0.70 (4H, m), 0.85 (3H, d, 7.0 Hz), 0.89 - 1.03 (13H, m), 1.03 - 1.65 (11H, m), 1.44 (9H, s), 2.21 (2H, t, *J*=8.0 Hz), 2.53 (2H, dd, *J*=6.0, 3.0 Hz), 4.14 - 4.26 (1H, m), 9.83 (1H, t, *J*=3.0 Hz)
16	+1.4 (*c* 0.59, MeOH)	0.86 (3H, d, *J*=7.0 Hz), 0.90 (3H, t, *J*=7.0 Hz), 1.08 - 1.61 (20H, m), 1.44 (9H, s), 2.21 (2H, t, *J*=8.0 Hz), 3.56 (1H, m)
17	-15 (*c* 1.1, MeOH)	0.09 (6H, s), 0.80 - 0.92 (6H, m), 0.91 (9H, s), 1.01 - 1.62 (19H, m), 1.33 & 1.38 (9H, br, s), 1.44 (9H, s), 2.20 (2H, t, *J*=7.5 Hz), 2.71 & 2.77 (3H, s), 2.91 (1H, m), 3.22 (1H, m), 3.95 (2H, m), 3.99 (2H, m), 4.71 & 4.92 (1H, m), 4.87 (1H, m), 6.82 (2H, m), 7.08 (2H, m)
19	+20 (*c* 1.6, MeOH)	0.59 - 0.69 (4H, m), 0.85 (3H, d, *J*=7.0Hz), 0.95 - 1.02 (12H, m), 1.12 - 1.68 (13H, m), 1.44 (9H, s), 2.20 (2H, t, *J*=7.5 Hz), 2.14 - 2.29 (2H, m), 3.53 (1H, s), 3.92 -4.04 (2H, m), 5.09 (1H, d, *J*=11.0 Hz), 5.10 (1H, d, *J*=18.0 Hz), 5.83 (1H, ddt, *J*=18.0, 11.0, 7.0 Hz)
20	+18 (*c* 1.2, MeOH)	0.1 & 0.07 (6H, s), 0.85 (3H, d, *J*=7.0Hz), 0.89 (9H, s), 0.93 (3H, t, *J*=7.0 Hz), 1.00 - 1.64 (17H, m), 1.44 (9H, s), 2.20 (2H, t, *J*=7.5 Hz), 3.40 - 3.60 (1H, br), 3.86 - 3.93 (1H, m), 3.99 (1H, m)
21	-	0.86 (3H, d, *J*=7.0 Hz), 1.41 (3H, s), 1.45 (3H, s), 1.46 (9H, s), 1.00 - 1.75 (13H, m), 2.21 (2H, t, *J*=7.5 Hz), 2.10 - 2.38 (2H, m), 3.76 (1H, ddt, *J*=11.5, 6.5, 3.0 Hz), 3.87 (1H, ddt, *J*=11.5, 6.5, 3.0 Hz) , 5.06 (1H, ddt, *J*=10.0, 2.0, 1.0 Hz), 5.82 (1H, ddt, *J*=17.0, 10.0, 7.5 Hz)

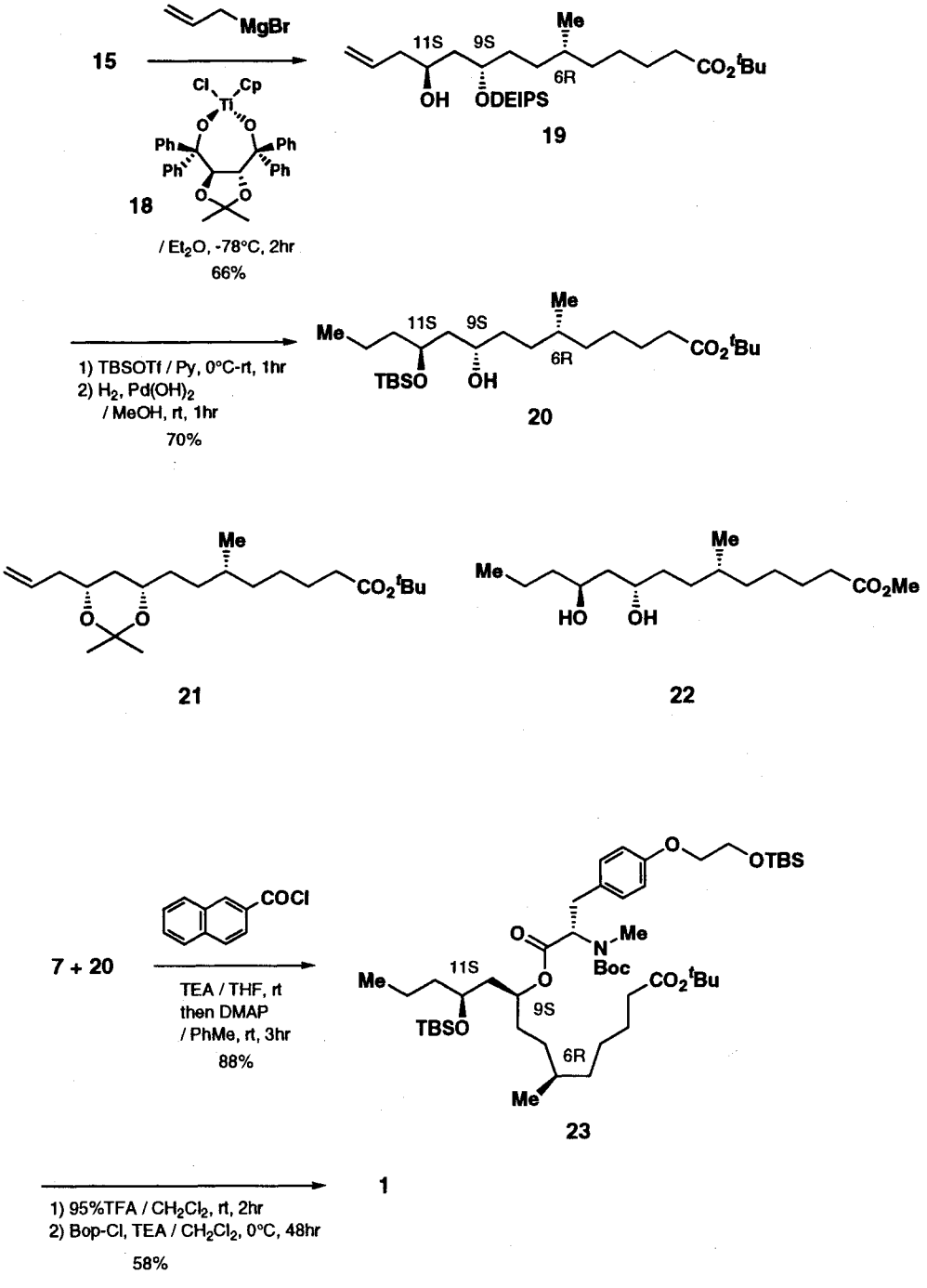
Table 1-2. Physico-chemical properties of products.

No.	$[\alpha]_D$	^{1}H-NMR (300, 400, 500 or 600MHz; $CDCl_3$; δ ppm; *J* Hz)
22	+16 (*c* 0.61, MeOH)	0.87 (3H, d, *J*=7.0 Hz), 0.94 (3H, t, *J*=7.0 Hz), 1.05 - 1.67 (15H, m), 1.61 (2H, dd, *J*=5.5,5.5 Hz), 2.00 - 2.50 (2H, br), 2.31 (2H, t, *J*=7.5 Hz), 3.67 (3H, s), 3.91 (1H, m), 3.96 (1H, m)
23	-5.2 (*c* 0.85, MeOH)	0.01 & 0.03 (6H, s), 0.10 (6H, s), 0.80 - 0.92 (6H, m), 0.88 (9H, s), 0.91 (9H, s), 1.31 & 1.36 (9H, s), 1.44 (9H, s), 1.00 - 1.70 (17H, m), 2.20 (2H, t, *J*=8.0 Hz), 2.70 & 2.76 (3H, s), 2.84 & 3.21 (2H, m), 3.66 (1H, m), 3.95 (2H, m), 3.99 (2H, m), 4.71 & 4.96 (1H, m), 4.93 (1H, m), 6.81 & 6.82 (2H, d, *J*=8.5 Hz), 7.07 & 7.11 (2H, d, *J*=8.5 Hz)

Scheme 2



Scheme 3



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References

1) NOSE, H.; A. SEKI, T. YAGUCHI, A. HOSOYA, T. SASAKI, S. HOSHIKO & T. SHOMURA: PF1163A and B, new antifungal antibiotics produced by *Penicillium* sp. I. Taxonomy of producing strain, fermentation, isolation and biological activities. J. Antibiotics in press.
2) SASAKI, T.; H. NOSE, A. HOSOYA, S. YOSHA, M. KAWAGUCHI, T. WATANABE, T. USUI, Y. OHTSUKA, T. SHOMURA, S. TAKANO & K. TATSUTA: PF1163A and B, new antifungal antibiotics produced by *Penicillium* sp. II. Physico-chemical properties and structure elucidation. J. Antibiotics in press.
3) HAFNER, A.; R. O. RUDOLF, R. MARTI, G. RIHS, P. ROTHE-STREIT & F. SCHWARZENBACH: Enantioselective allyltitanation of aldehyde with cyclopentadienyldialkoxyallyltitanium complexes. J. Am. Chem. Soc. 114: 2321~2336, 1992
4) TOSHIMA, K.; K. YANAGAWA, S. MUKAIYAMA & K. TATSUTA: The selective distinction of diethylisopropylsilyl ether in hydrogenolysis. Tetrahedron Lett. 31: 6697~6698, 1990
5) TATSUTA, K.; M. ITOH, R. HIRAMA, N. ARAKI & M. KITAGAWA: The first total synthesis of calbistrin A, a microbial product possessing multiple bioactivities. Tetrahedron Lett. 38: 583~586, 1997
6) NAKATA, M.; N. AKIYAMA, J. KAMATA, K. KOJIMA, H. MASUDA & K. TATSUTA: The total synthesis of rifamycin W. Tetrahedron 46: 4629~4652, 1990