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TOTAL SYNTHESIS OF THE MACROLIDE ANTIBIOTIC (±)-A26771B

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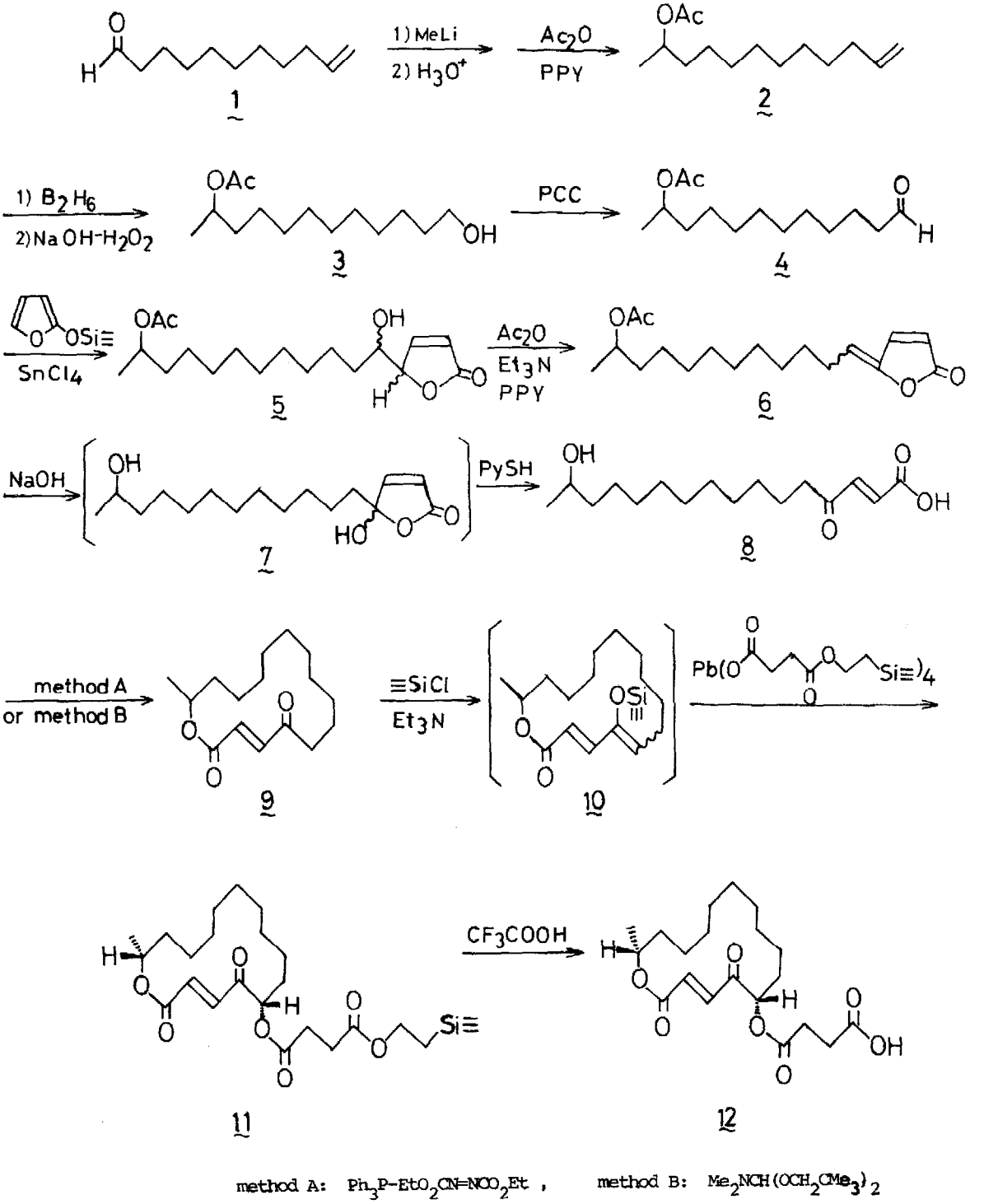
Summary: The total synthesis of the title compound is reported.

A 16-membered macrocyclic lactone antibiotic A26771B was isolated from penicillium turbatum in 1977 and the structure was assigned as 12.[1] The absolute configuration was recently established by the total synthesis from D-glucose.[2] In this paper we will describe a novel total synthesis of (±)-A26771B.

Treatment of 10-undecenal (1) with methyl lithium followed by acetylation with acetic anhydride in the presence of a catalytic amount of 4-pyrrolidinopyridine (PPY) gave 2 in 98% yield (bp 94°C/1.5 mmHg). Hydroboration of 2 under the usual conditions provided the primary alcohol (3) (84%, 135°C/1 mmHg), which was then oxidized with pyridinium chlorochromate (PCC) into 11-acetoxy-dodecanal (4, 83% oil, isolated by column chromatography). Reaction of the aldehyde (4) with trimethylsiloxyfuran[3,4] in the presence of tin (IV) chloride in dichloromethan (-78°C - r.t.) gave an oily butenolide derivative 5, in 94% yield. Dehydration of 5 with acetic anhydride, triethylamine, and PPY in dichloromethane at room temperature gave a stereoisomeric mixture (ca 1:1) of γ-alkylidene butenolide (6, 95%). Hydrolysis of 6 with sodium hydroxide in water-methanol at room temperature gave 7, which was easily isomerized to the crystalline hydroxy acid 8 (mp 100°C, 74% from 6) by the treatment with a catalytic amount of 2-pyridinethiol in benzene at room temperature.[4] To our knowledge, Ph_3P-diethyl azodicarboxylate method[5] is the best way for the lactonization of γ-keto-α,β-enoic acids.[7] Among the several experiments examined, 16-membered lactone [9, oil, MS: m/e 266 (M^+)] was obtained in the best yield (37%) along with dimer [17%; mp 86-7°C,MS: m/e 532 (M^+)] when 8 dissolved in dry THF was added to precooled (-30°C) dry THF solution of Ph_3P-diethyl azodicarboxylate. Alternatively, the lactonization was accomplished by the use of dimethyl formamide dineopentyl acetal.[6]



method A: Ph_3P-$EtO_2CN{=}NCO_2Et$, method B: $Me_2NCH(OCH_2CMe_3)_2$

To the refluxing solution of 8 (0.5 mmol) in dichloromethane (190 ml), dimethyl formamide dineopentyl acetal (0.5 mmol) dissolved in 10 ml of dry dichloromethane was added. After refluxing for additional 7 h, the solvent and volatile products were removed under reduced pressure. Separation of the residue by tlc gave 9 in 39% yield. These results are summarized in Table 1.

Table 1 Lactonization of the hydroxy acid (8).

Concentration (mmol/ml)	Temp (°C)	Time (h)	Solvent	Method	Yield(%) Monomer(9)	Yield(%) Dimer
1/400	-20	2.5	toluene	A	18	-
1/600	-30-0	15	toluene	A	14	4
1/600	-20	2	THF	A	37	17
1/400	reflux	2.5	toluene	B	20	8
1/400	reflux	25	Et_2O	B	7	-
1/400	reflux	5.5	THF	B	20	4
1/400	reflux	3	DME	B	32	6
1/400	reflux	7	CH_2Cl_2	B	39	9
1/400	reflux	1	$ClCH_2CH_2Cl$	B	39	7.5

Method A: Ph_3P-$EtO_2CN{=}NCO_2Et$, Method B: $Me_2NCH(OCH_2CMe_3)2$

The lactone (9) was easily converted with chlorotrimethylsilane and triethyl amine (in dry dichloromethane, at r.t.) into its silyl enol ether 10. After the removal of ammonium salts, the crude 10 was treated with lead(IV) tetrakis-(β-trimethylsilylethyl succinate), which was prepared from lead(IV) acetate and β-trimethylsilylethyl hydrogen succinate, to give A26771B β-trimethylsilylethyl ester 11 (40%). Debrocking of the trimethylsilylethyl group with trifluoro-acetic acid afforded A26771B in a quantitative yield. This synthetic A26771B exhibited identical spectra data and tlc mobilities with those of reported. In the case of our synthetic A26771B as well as its β-trimethylsilylethyl ester, no signals other than a couple of doublets are observed in the olefinic region in H^1NMR, though in the case of synthetic A26771B methyl ester, Hase and Nylung reported that two diastereomers can be discernible in H^1NMR.[7] Well agreement of the chemical shifts in H^1NMR of our synthetic A26771B with those of reported suggests the formation of (±)-A26771B. Synthetic (±)-A26771B and isolated intermediates indicated satisfactory spectra[8] and elemental analyses.

References and Notes

1) K. H. Michel, P. V. Demarco, and R. Nagarajan, J. Antibiot., 30, 571 (1977).
2) K. Tatsuta, A. Nakagawa, S. Maniwa, and M. Kinoshita, Tetrahedron Lett., 21, 1479 (1980).
3) M. Asaoka, N. Sigimura, and H. Takei, Bull Chem. Soc. Jpn., 52, 1953 (1979).
4) M. Asaoka, N. Yanagida, N. Sugimura, and H. Takei, Bull. Chem. Soc. Jpn., 53, 1061 (1980).
5) T. Kurihara, Y. Nakajima, and O. Mitsunobu, Tetrahedron Lett., 1976, 2455.
6) H. Vorbrüggen and K. Krolikiewicz, Angew. Chem. Int. Ed. Engl., 16, 876 (1977).
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8) Spectral data of some intermediates and A26771B:
5: IR(KBr): 1750 cm^{-1}(C=O), 1603 cm^{-1}(C=C). NMR($CDCl_3$): δ=1.15-1.7 (21H, m), 2.0 (3H, s), 3.2-3.5 (1H, broad), 3.65-3.9 (1H, m), 4.7-5.1 (2H, m), 6.1 (1H, d), 7.5 (1H, d).
6: IR(KBr): 1720, 1750 cm^{-1}(C=O). NMR($CDCl_3$): δ=1.1-1.6 (19H, m), 2.0 (3H, s), 2.15-2.5 (2H, m), 4.8 (1H, t), 5.25 and 5.7 (1H, t), 6.0-6.2 (1H, m), 7.25 and 7.55 (1H, t).
7: IR(KBr): 1730 cm^{-1}(C=O). NMR($CDCl_3$): δ=1.05-1.55 (23H, m), 3.6-4.0 (1H, m), 4.6-5.0 (2H, broad), 6.05 (1H, d), 7.15 (1H, d).
8: mp 100°C, IR(KBr): 1670, 1710 cm^{-1} (C=O), 1625 cm^{-1}(C=C). NMR($CDCl_3$): δ=1.15 (3H, d), 1.2-1.9 (18H, m), 2.65 (2H, t), 3.5-3.9 (1H, m), 6.0-6.3 (1H, broad), 6.65 (1H, d), 7.0 (1H, d).
9: IR(KBr): 1685, 1720 cm^{-1}(C=O), 1610 cm^{-1}(C=C). NMR($CDCl_3$): δ=1.1-1.9 (21H, m), 2.55 (2H, t), 4.9-5.2 (1H, m), 6.65 (1H, d, J=16Hz), 7.11 (1H, d, J=16Hz). MS: m/e 266 (M^+).
11: NMR($CDCl_3$): δ=0.05 (9H, s), 1.00 (2H, t), 1.12-2.0 (21H, m), 2.71 (4H, m), 4.21 (2H, t), 5.00-5.26 (1H, m), 5.28 (1H, t), 6.76 (1H, d, J=16Hz), 7.23 (1H, d, J=16Hz).
12: mp 131-132°C. IR(KBr): 1706, 1763 cm^{-1}(C=O). NMR($CDCl_3$) δ=1.1-2.0 (21H, m), 2.72 (4H, s), 5.00-5.28 (1H, m), 5.34 (1H, t), 6.78 (1H, d, J=16Hz), 7.22 (1H, d, J=16Hz), 9.5 (1H, broad). MS: m/e 382 (M^+).

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