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STEREOSPECIFIC TOTAL SYNTHESIS AND ABSOLUTE CONFIGURATION OF A MACROCYCLIC LACTONE ANTIBIOTIC, A26771B

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Summary: The total synthesis of a sixteen-membered macrocyclic lactone antibiotic, A26771B and its absolute configuration are described by using D-glucose as a chiral source.

A 16-membered macrocyclic lactone antibiotic A26771B (1), produced by *Penicillium turbatum*, possesses a novel structure and an interesting antibacterial activity[1]. The structure was determined by spectral evidence to bear some similarities to a whole family of medicinally important macrolide antibiotics[2], but the absolute configuration remained to be determined. The nonstereospecific synthesis of diastereomers of the methyl ester was recently reported[3]. This communication describes the first total synthesis of A26771B (1) and defines its absolute configuration.

Based on stereochemical consideration (Celmer's model)[2] of macrolide antibiotics produced by *Actinomycetes* organisms, it seems very likely that the chiro centers at C-5 and C-15 have S- and R-configurations, respectively. Therefore, we projected a stereospecific synthesis of the 5S,15R-isomer by using D-glucose derivatives as chiral sources[4].

The structure 1 can be devided to three portions which structurally correspond to compound 3 (C1-C6 portion) and Wittig reagents 6 (C7-C12 portion) and 9 (C13-C16 portion). Compounds 3 and 9 were prepared from D-glucose and 6 was from hexanediol.

The starting 5-deoxy-1,2-O-isopropylidene-D-*xylo*-hexose, which was prepared by a five-step sequence (80%) from D-glucose by modified literature procedure[5], was converted into the dithioacetal 2[6] [95%, mp 59°C, $[\alpha]_D^{16}$ +78° ($CHCl_3$)] by treatment with BF_3-Et_2O and EtSH (20°C, 1 h). Benzylation (benzyl bromide, NaH, THF, 50°C, 12 h) of 2 followed by removal of thioacetal ($CdCO_3$, $HgCl_2$, aq. acetone, 20°C, 3 h) afforded the labile aldehyde 3 as a syrup [80%, NMR[6] δ 3.44 (2H, t, J=6Hz, $\underline{CH_2}OR$), 9.70 (1H, sharp d, J=~1Hz, CHO)].

Selective tosylation (TsCl, Et_3N, CH_3CN, 0° to 20°C, 15 h) of 1,6-hexanediol gave the mono-tosylate 4 (55%), which was oxidized by pyridinium chlorochromate (CH_2Cl_2, 20°C, 1 h) followed by treatment with ethylene glycol and TsOH (CH_3CN, 20°C, 15 h) to give the acetal 5 (80%, syrup) Bromination (LiBr, acetone, 60°C, 1 h) followed by treatment with triphenylphosphine (CH_3CN, 80°C, 4 days) furnished Wittig reagent 6 (86%, needles from acetone-hexane, mp 158°C).

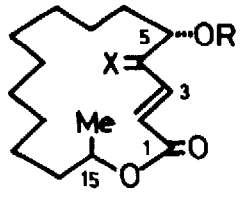
A tosylate 8 was obtained as a volatile syrup [$[\alpha]_D^{20}$ -25° (MeOH)] from methyl 4,6-dideoxy-α-D-*xylo*-hexopyranoside[4a] (7) by a four-step sequence: (1) $NaIO_4$, aq. MeOH, 20°C, 2 h; (2) $NaBH_4$, aq. MeOH, 20°C, 1 h; (3) TsCl, Et_3N, CH_2Cl_2, 20°C, 15 h; (4) Amberlyst 15 (H type) resin, MeOH, reflux, 20 h. Reaction of 8 with NaI (acetone, 60°C, 3 h) followed by treatment with triphenylphosphine (benzene, 80°C, 15 h) afforded unambiguously the optically pure Wittig

reagent 9 having R-configuration [85%, needles from EtOAc-MeOH, mp 227°C, $[\alpha]_D^{23}$ -1.8° (MeOH), lit.[7] (+)-S-isomer: mp 217-220°C, $[\alpha]_D$ +2° (MeOH)].

The stage was thus set for the formation of the 16-carbon skeletal product by the repeated Wittig reactions. The first Wittig reaction (NaH, DMSO, THF, 20°C, 1 h) of 3 with 6 gave quantitatively a homogeneous olefin 10 [syrup, $[\alpha]_D^{20}$ +33° ($CHCl_3$)], the E-stereochemistry of which was defined by the 18Hz coupling constant of the vinylic protons. Exposure of 10 to aq. CF_3COOH (5°C, 15 h) provided the labile aldehyde 11 (82%), which was used without purification to the next step. The second Wittig reaction of 11 (1 equiv) with 9 (2 equiv) was accomplished by transforming 9 into its ylide (1.4 equiv of NaH in DMSO and 1.7 equiv of n-BuLi in hexane, 20°C), followed by addition of 11 (THF, 20°C, 30 min), to furnish after silica gel column chromatography (hexane-EtOAc 5:2) the 16-carbon product 12 [66%, syrup, $[\alpha]_D^{19}$ +36° ($CHCl_3$)]. Whenever a sole base (NaH in DMSO or BuLi) was used for the generation of the ylide, the reaction gave much less yield of 12. Reduction (3 atm H_2, Pd-black, MeOH, 15 h) of 12 gave the saturated alcohol 13 [96%, mp 68°C, $[\alpha]_D^{18}$ -3.5° (MeOH)], which was selectively silylated (t-$BuMe_2SiCl$, Py, 20°C, 3 h) and then totally acetylated (Ac_2O, Py, 20°C, 15 h) to afford the masked product 14 [74%, syrup, $[\alpha]_D^{18}$ -0.7° ($CHCl_3$), NMR δ 0.04 (6H, s, Me_2Si), 0.90 (9H, s, t-BuSi), 1.20 (3H, d, J=6Hz, Me-16), 2.03, 2.07 and 2.10 (12H, s, OAc X 4), 3.63 (2H, t, J=6.5Hz, CH_2-1)]. Desilylation (CHF_2COOH, aq. CH_3CN, 50°C, 5 h) of 14 followed by catalytic oxidation of the resulting primary alcohol afforded the corresponding carboxylic acid 15, which was converted (CH_2N_2, Et_2O, 20°C, 30 min) into the methyl ester 16 [84% from 14, syrup, $[\alpha]_D^{17}$ -5.7° ($CHCl_3$), IR (CCl_4) ∿1750 cm^{-1} (OAc, COOMe), NMR δ 1.20 (3H, d, J=6Hz, Me-16), 2.03, 2.08 and 2.12 (12H in total, s, OAcX4), 3.70 (3H, s, COOMe)]. The chemical array, including the absolute stereochemistry, of C1-C5 and C15 positions completely corresponds to that of the macrolide aglycons, supporting the usefulness of D-glucose for the chiral sources[4].

Selective deacetylation (t-BuOK, aq. t-BuOH, 30°C, 2 min) of 16 accompanying the desired β-elimination gave exclusively the E-unsaturated ester 17 [syrup, NMR δ 3.76 (3H, s, COOMe), 6.15 (1H, dd, $J_{2,3}$=16Hz, $J_{2,4}$=∿2Hz, H-2), 6.96 (1H, dd, $J_{3,4}$=5Hz, H-3)], which was converted (2,2-dimethoxypropane, TsOH, acetone, 20°C, 1 h) into the acetonide 18 [76%, syrup, $[\alpha]_D^{17}$ -13° ($CHCl_3$), UV λ_{max}^{MeOH} 213 nm (ε 10,800), NMR δ 1.46 (6H, s, acetonide), 2.07 (3H, s, OAc), 3.81 (3H, s, COOMe)]. When treated with LiOH (aq. THF, 20°C, 2 days), 18 quantitatively furnished the hydroxy acid 19 [syrup, NMR δ 5.2 (2H, broad s, OH and COOH), 6.12 (1H, dd, $J_{2,3}$=16Hz, $J_{2,4}$=2Hz, H-2), 6.96 (1H, dd, $J_{3,4}$=5Hz, H-3)]. However, all attempts[8,9] to bring about lactonization met with abject failure. Therefore, after removal of the isopropylidene group, which might be responsible for the failure, a number of published lactonization methods[9] were again tested.

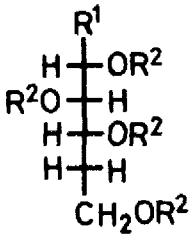
Thus, according to modified Masamune's method[9b] (diethylphosphorochloridate, Et_3N, THF, 20°C, 3 h and then thallium benzenethiolate, 20°C, 1 h), 19 was converted into the benzenethiol ester 20 [93%, syrup, NMR δ 6.45 (1H, dd, $J_{2,3}$=16Hz, $J_{2,4}$=∿1Hz, H-2), 6.90 (1H, dd, $J_{3,4}$=4.5Hz, H-3), 7.47 (5H, s, Ph)], which was deacetonated by difluoroacetic acid (aq. MeOH, 20°C, 2 h) to give the triol 21 [80%, needles from EtOAc-hexane, mp 68.5°C, $[\alpha]_D^{19}$ -17° ($CHCl_3$), IR ($CHCl_3$) 1680, 1640 cm^{-1} (CH=CH-COSPh), UV λ_{max}^{MeOH} 228 (ε 17,600), 265 nm (ε 6,600), NMR δ 1.20 (3H, d, J=6.5Hz, Me-16), 3.73 (1H, m, H-5), 4.20 (1H, m, H-4), 6.55 (1H, dd, $J_{2,3}$=16Hz, $J_{2,4}$=∿1Hz, H-2),



1: R=$COCH_2CH_2COOH$, X=O

22: R=H, X=$\overset{OH}{H}$

23: R=$COCH_2CH_2COOH$, X=$\overset{OH}{H}$

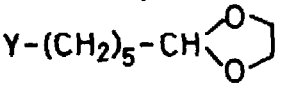


2: $R^1=CH(SEt)_2$, R^2=H

3: R^1=CHO, R^2=Bzl

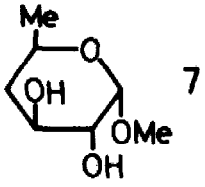
$TsO-(CH_2)_5-CH_2OH$

4

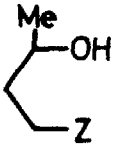


5: Y=OTs

6: $Y=P^+Ph_3Br^-$

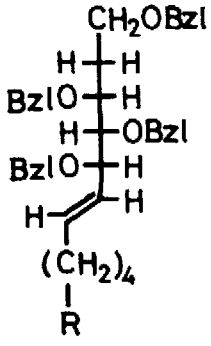


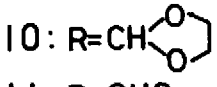
7



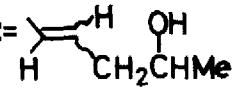
8: Z=OTs

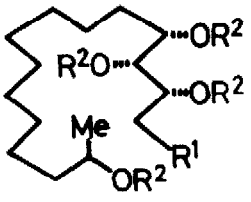
9: $Z=P^+Ph_3I^-$



10: R= 

11: R=CHO

12: R= 

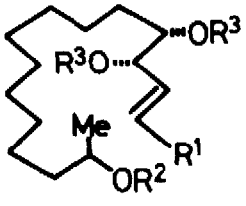


13: $R^1=CH_2OH$, R^2=H

14: $R^1=CH_2OSiMe_2{}^tBu$, R^2=Ac

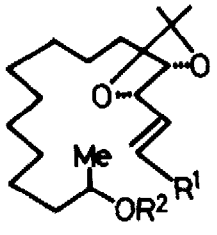
15: R^1=COOH, R^2=Ac

16: R^1=COOMe, R^2=Ac



17: R^1=COOMe, R^2=Ac, R^3=H

21: R^1=COSPh, $R^2=R^3$=H



18: R^1=COOMe, R^2=Ac

19: R^1=COOH, R^2=H

20: R^1=COSPh, R^2=H

7.01 (1H, dd, $J_{3,4}$=5Hz, H-3), 7.53 (5H, s, Ph)]. Cyclization (67 mg Na_2HPO_4, 55 mg CF_3COOAg, 23 ml benzene, Ar, 70°C, 3 days) of 21 (46 mg) afforded the 16-membered-ring lactone 22 [10%, needles, mp 87°C, NMR δ 1.27 (3H, d, J=6.5Hz, Me-16), 3.42 (1H, m, H-5), 4.12 (1H, m, H-4), 5.0 (1H, m, H-15), 6.13 (1H, dd, $J_{2,3}$=16Hz, $J_{2,4}$=1.5Hz, H-2), 6.95 (1H, dd, $J_{3,4}$=6Hz, H-3)] after silica gel column chromatography (on silica gel TLC, Rf 0.28 and 0.38 for 21 and 22, hexane-acetone 3:2). Selective succinylation (succinic anhydride, i-Pr_2EtN, CCl_4, 50°C, 2 h) of 22 gave predominantly a waxy product 23 [72%, $[\alpha]_D^{16}$ -20° (MeOH), IR ($CHCl_3$) 1720, 1650 cm^{-1} (CH=CH-COO-), NMR δ 2.71 (4H, s, succinyl CH_2CH_2), ∿4.4 (1H, m, H-4), ∿5.0 (2H, m, H-5 and 15), 6.16 (1H, dd, $J_{2,3}$=16Hz, $J_{2,4}$=∿1.5Hz, H-2), 6.91 (1H, dd, $J_{3,4}$=5Hz, H-3)] after preparative TLC (Rf 0.81 and 0.41 for 22 and 23, $CHCl_3$-EtOH 5:1, positive 2,6-dichlorophenolindophenol colour reaction for organic acid[10]). Finally, oxidation of 23 with Ac_2O and DMSO (20°C, 15 h) afforded synthetic A26771B (1) as needles (EtOAc-hexane), identical with the natural product, mp and mmp 125-126°C, $[\alpha]_D^{20}$ -14° (MeOH), in 71% yield. Synthetic and natural products exhibited identical IR, UV, NMR, CD [$[\theta]_{260}^{max}$ -2300 (MeOH)] and ORD spectra, and showed identical TLC mobilities with several different solvent systems (detected by H_2SO_4 and by bioautography using *Sarcina lutea*).

This study thus establishes the absolute stereochemistry of a macrocyclic lactone antibiotic A26771B produced by *Penicillium* to be 5S,15R-configuration, which follows Celmer's model[2] for macrolides produced by *Actinomycetes*.

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References and Notes:

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