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TOTAL SYNTHESIS OF ELAIOPHYLIN (AZALOMYCIN B)

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Summary: Antibiotic elaiophylin 1a has been first synthesized by a convergent route involving aldol condensation between (5*R*,6*R*,7*R*)-5-*O*-[2'-deoxy-3',4'-di-*O*-(dimethylisopropylsilyl)-α-L-fucopyranosyl]-6-ethyl-7-*O*-(diethylisopropylsilyl)-5,7-dihydroxy-3-octanone 3a and (7*S*,8*S*,15*S*,16*S*)-(3*E*,5*E*,11*E*,13*E*)-8,16-bis[(1'*R*)-1'-formylethyl]-7,15-dimethyl-1,9-dioxacyclohexadeca-3,5,11,13-tetraene-2,10-dione 4, followed by desilylation. The segments, 3a and 4, were synthesized from D-glucose and 2-deoxy-L-fucose.

The antibiotic elaiophylin 1a was first isolated in 1959 by Arcamone et al.[1] and then isolated as azalomycin B in 1960 by Arai.[2-7] Elaiophylin 1a belongs to a group of C_2-symmetrical 16-membered macrodiolides.[8] The absolute configuration of 1a has been established by X-ray crystallography under consideration of the absolute stereochemistry of its sugar moiety (2-deoxy-L-fucose).[9,10] The isolation and synthesis of the cyclic methyl acetal aglycone derivative 1b have recently been announced by Seebach et al.[11] Herein we wish to report the first total synthesis of natural elaiophylin 1a (azalomycin B), which makes use of carbohydrates as chiral source.

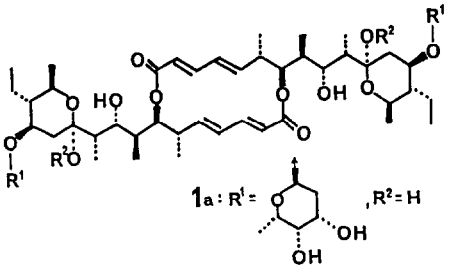
The strategic intermediate 2 would be convertible to 1a under an appropriate condition, provided that the protecting groups, R^1 and R^2 are pertinently chosen. The construction of 2 would be achieved by the aldol condensation between the ethyl ketone segment 3 and the dialdehydic 16-membered maclodiolide segment 4, both of which could be enantiospecifically synthesized from appropriate carbohydrate derivatives. The synthesis began with the construction of the segment 3, because the selection of the protecting groups, R^1 and R^2, and the removal of these groups should naturally become the crucial problems in the final stage of the conquest of 1a which seemed to be sensitive to base and acid.[4,5] The starting material 5[12] was converted into 6[13] (mp 63-64°C, $[\alpha]_D$ +16° (c 1.07, $CHCl_3$)) in one step (acetone, 0.6 equiv $BF_3 \cdot Et_2O$, 26°C, 24h) in 71% yield. Selective 5,6-de-O-isopropylidenation (75% AcOH-H_2O, 30°C, 4h) of 6, followed by sequential periodate-oxidation and sodium borohydride-reduction afforded the alcohol 7[13] ($[\alpha]_D$ +11° (c 0.90, $CHCl_3$)) in 82% yield. The alcohol 7 was converted into 8[13] ($[\alpha]_{365}$ +4° (c 1.19, $CHCl_3$)) in two steps (1. MsCl, Py; 2. $LiAlH_4$, ether, 28°C, 5h) in 77% yield. Hydrolysis of 8 (50% AcOH-H_2O, 100°C, 0.5h) followed by lithium aluminumhydride-reduction (THF, 70°C, 2h) afforded a triol, which was directly subjected to the one step epoxidation of vicinal diol (1.1 equiv Ph_3P, 1.1 equiv diethyl azodicarboxylate, 3A molecular sieves, PhH, reflux, 7h)[14] and the resulting crude epoxy alcohol 9 was silylated (DEIPSCl,[15] imidazole, CH_2Cl_2, 25°C, 1h) to give 10[13] ($[\alpha]_D$ -9° (c 1.10, $CHCl_3$)), in 41% overall yield from 8. Reaction of 10 and 2-ethyl-2-lithio-1,3-dithiane (5 equiv)(THF, -20°C, 4h) afforded the crude 11,[16] whose dithioacetal group was cleaved (1:1 $HgCl_2$-HgO, 80% aqueous acetone, 0°C, 0.5h) to give the pure ketone 12[13] (IR($CHCl_3$) ν_{max} 1710 cm^{-1}, $[\alpha]_{365}$ +20° (c 1.10, $CHCl_3$)) in 66% overall yield from 10. The glycosidation

of 2-deoxy-L-fucose moiety to C-5 hydroxyl group of 12 was accomplished by the method[17] which was previously developed in our laboratories. The glycal 13[13,18] ($[\alpha]_D$ +31° (c 1.07, acetone)) was prepared from L-fucal[19] (DMIPSCl, imidazole, DMF, 26°C, 2h) in 65% yield. Reaction (MeCN, 0°C to 20°C, 2.5h) of 12 (1 equiv) and 13 (3.5 equiv) in the presence of NBS (3.5 equiv) gave, after silica gel column chromatography, the crude major α-glycoside 14α contaminated by a considerable amount of by-products and 21% yield of the β-anomer. This sample of 14α was debrominated by using $(n\text{-Bu})_3SnH$ with AIBN as catalyst (PhH, Ar, 60°C, 0.5h) to afford 3a[13] ($[\alpha]_D$ -46° (c 1.36, $CHCl_3$)) in 30% overall yield from 12. By the procedure described in the synthesis of 3a, the ethyl ketone segment 3b[13] ($[\alpha]_D$ -41° (c 0.83, $CHCl_3$)) was also prepared from 9 and L-fucal by using only TBDMSCl as the silylating agent. In the preliminary experiments toward the deprotection of 2, treatments of 3a and 3b with tetrabutylammonium fluoride (TBAF) in THF at 20°C did not give the desired 15. Furthermore, azalomycin B was immediately decomposed by TBAF in THF even at 0°C. On the other hand, the desilylation of 3a with 3:1:3 AcOH-H_2O-THF (25°C, 7h) proceeded smoothly to afford 15[13] in moderate yield, while 3b and azalomycin B (1a) were little affected by this reagent. Thus we chose 2a as a promising key intermediate for the synthesis of 1a.

The synthesis of the second key segment 4 started from 16 which was previously prepared from D-glucose in our laboratories.[20] Deisopropylidenation (50% AcOH-H_2O, 50°C, 1h) of 16, followed by treatment of the resulting triol (90% yield, mp 134-135°C) with lead tetraacetate[21] afforded the aldehyde 17 in 95% yield. Wittig reaction (PhMe, 80°C, 0.5h) of 17 with [(2*E*)-3-methoxycarbonyl-2-propen-1-ylidene]triphenylphosphorane[22] gave 18[13] (54% yield, $[\alpha]_D$ -22° (c 1.06, $CHCl_3$), UV(EtOH)λ_{max} nm(log ε) 261(4.39)) and (2*E*,4*Z*)-isomer[23] (22% yield). Saponification (LiOH, 50% THF-H_2O, 24°C, 7h) of 18 afforded 19[13] ($[\alpha]_D$ -31° (c 1.04, $CHCl_3$), UV(EtOH)λ_{max} nm(log ε) 254(4.28)) in quantitative yield. Lactonization of 19 was best effected by using Yamaguchi method[24,8] to give the diolide 20[13] (31% yield, mp 262-263.5°C, $[\alpha]_D$ +75° (c 1.16, $CHCl_3$)). Treatment of 20 with $HgCl_2$-HgO(1:1)[4:7 CH_2Cl_2-80% aqueous acetone, 30-50°C(in a sonicator(65W, 48KHz)), 7h] afforded the dialdehyde 4[11,13] in 70% yield.

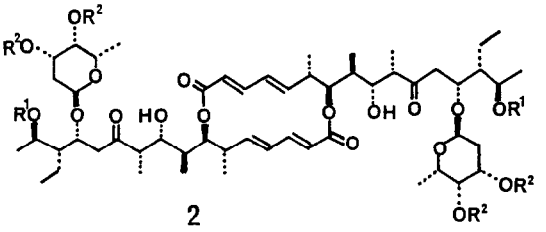
The aldol condensation between 3a and 4 was best achieved in the following manner. To a cold(-30°C) 0.13M THF solution of 4 was added an ethereal solution of *Z*-boron enolate which was prepared from 3a(4 equiv) under standard conditions[25] ($n\text{-Bu}_2BOTf$, $i\text{-Pr}_2NEt$, ether, -78°C, 0.5h). The mixture was stirred at -10°C for 2h. Quenching with pH 7 phosphate buffer solution (25°C, 3 min)[26] followed by chromatographic isolation afforded three possible diastereomeric aldol products, 2a[13] ($[\alpha]_D$ -9.3° (c 0.41, $CHCl_3$), 13%), 21[13] (24%), and 22[13] (26%) as colorless glassy solids. The desilylation of 2a (3:1:3 AcOH-1% aqueous HF·KF-THF, 30°C, 18h) gave 1a (22% yield, mp 179-182°C (AcOEt), $[\alpha]_D$ -53° (c 0.26, MeOH) identical with the authentic sample[2] of azalomycin B by 400 MHz ^1H-NMR (5:1 $CDCl_3$-CD_3OD), mp, mmp, $[\alpha]_D$, and TLC. The compounds 21 and 22 were not converted into the natural elaiophylin. The NMR examination[13] of 2a, 21 and 22 revealed that 2a and 22 were C_2-symmetric, while 21 was asymmetric. Since 2a was just assigned as the bis(1',2'-*anti*-2',3'-*syn*)-product, 22 and 21 were assumed to be the bis(1',2'-*syn*-2',3'-*syn*)- and (1',2'-*anti*-2',3'-*syn*:1",2"-*syn*-2",3"-*syn*)-product, respectively.

Although the closing stages of this total synthesis of 1a were sullied by the 2:1 preponderance of the unwanted "Cram" product 22 over the *anti*-"Cram" product 2a in the aldol reaction step, the synthesis of 1a which was senitive to acid and base was first achieved via 2a by using the appropriate O-protecting groups, such as DEIPS and DMIPS.



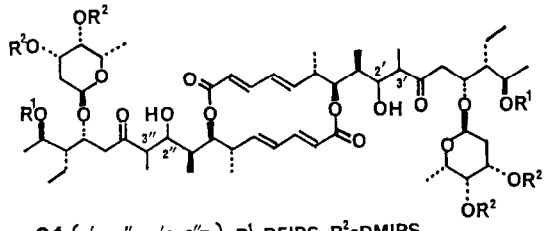
1a: R^1 = , R^2 = H

1b: R^1 = H , R^2 = Me



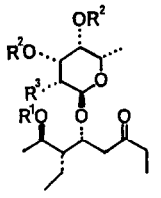
2

2a: R^1 = DEIPS, R^2 = DMIPS



21: (2′R, 2″S, 3′S, 3″R) R^1 = DEIPS, R^2 = DMIPS

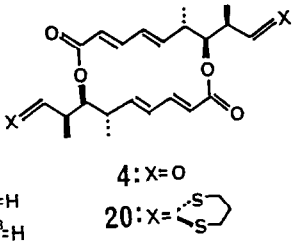
22: (2′S, 2″S, 3′R, 3″R) R^1 = DEIPS, R^2 = DMIPS



3a: R^1 = DEIPS, R^2 = DMIPS, R^3 = H

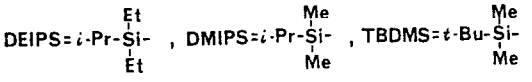
3b: R^1 = TBDMS, R^2 = TBDMS, R^3 = H

14α: R^1 = DEIPS, R^2 = DMIPS, R^3 = Br

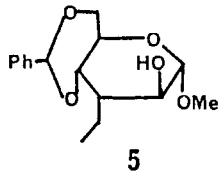


4: X = O

20: X =



DEIPS = *i*-Pr-Si(Et)(Et)- , DMIPS = *i*-Pr-Si(Me)(Me)- , TBDMS = *t*-Bu-Si(Me)(Me)-



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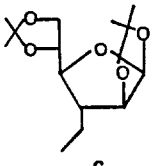

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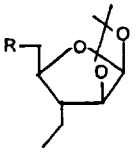
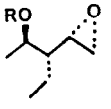


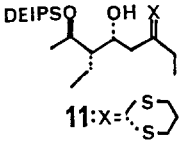
7: R = OH

8: R = H



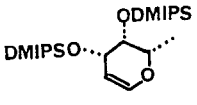
9: R = H

10: R = DEIPS

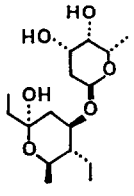


11: X =

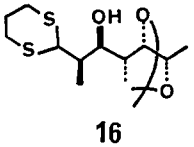
12: X = O



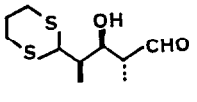
13



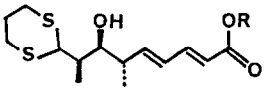
15



16



17



18: R = Me

19: R = H

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References and Notes

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13. All compounds were purified by silica gel column chromatography and were fully characterized by spectroscopic means and elemental analyses. Optical rotations were measured using a 0.2-dm or 0.5-dm tube at 20°C. Significant ^{1}H-NMR (90 MHz, 250 MHz,* 400 MHz**) spectra [δ($CDCl_3$, TMS), J(Hz)] are the following. 10: 0.67 (4H, m), 0.8-1.15 (16H, m), 1.20 (3H, d, J=6.0), 2.50 (1H, dd, J=6.0, 3.0), 2.70-2.95 (2H, m). 12: 2.20-2.90 (4H, m), 3.63 (1H, s). 13: 0.97 (14H, s), 1.28 (3H, d, J=6.0), 4.50 (1H, ddd, J=6.3, 2.0, 2.0), 6.23 (1H, dd, J=6.3, 2.0). 3a:(*) 1.13 (3H, d, J=7.0), 1.23 (3H, d, J=6.5), 1.99 (1H, ddd, H-2'$_{ax}$, J=12.8, 11.5, 3.8), 4.94 (1H, dd, H-1', J=3.8, 1.2). 3b: 2.00 (1H, ddd, J=12.9, 11.5, 3.8), 4.91 (1H, dd, J=3.8, 1.2). 15:(*) 5.06 (1H, dd, H-1', J=2.5, 2.5). 18: 3.77 (3H, s), 4.17 (1H, d, J=7.5), 5.83 (1H, d, J=15.3), 6.10-6.35 (2H, m), 7.15-7.50 (1H, m). 19: 4.18 (1H, d, J=7.5), 5.85 (1H, d, J=15.3), 6.10-6.40 (2H, m), 6.40-6.95 (2H, br), 7.15-7.55 (1H, m). 20: 1.07 (3Hx2, d, J=7.2), 1.19 (3Hx2, d, J=7.2), 1.86 (1Hx2, ddq, J=7.2, 7.2, 10.6), 2.00-2.30 (2Hx2, m), 2.44 (1Hx2, ddq, J=7.2, 1.1, 11.4), 2.75-2.95 (4Hx2, m), 4.02 (1Hx2, d, J=7.2), 5.18 (1Hx2, dd, J=10.6, 1.1), 5.60 (1Hx2, d, J=15.2), 5.62 (1Hx2, dd, J=9.5, 15.0), 6.00 (1Hx2, dd, J=15.0, 11.4), 6.98 (1Hx2, dd J=11.4, 15.2). 2a:(**) 0.55-0.70 (8H, m), 0.80-1.55 (84H, m), 1.85-1.95 (2H, m), 1.97 (2H, ddd, J=12.8, 12.0, 3.8), 2.45-2.65 (6H, m), 2.99 (2H, dd, J=8.8, 16.4), 3.36 (2H, d, J=3.2), 3.50-3.55 (2H, br), 3.70-4.05 (8H, m), 4.15- 4.25 (2H, m), 4.91 (2H, dd, J=3.6, 0.8), 5.04 (2H, dd, J=10.4, 1.2), 5.62 (2H, d, J=15.0), 5.65 (2H, dd, J=9.5, 15.0), 6.07 (2H, dd, J=15.0, 11.4), 6.97 (2H, dd, J=11.4, 15.6).
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15. Diethylisopropylchlorosilane(DEIPSCl) was prepared from diethyldichlorosilane and isopropyllithium: bp_{32} 73-74.5°C. The DEIPS protecting group was shown to be superior in all respects to the TBDMS, DIPMS, and TES groups.
16. This sample was contaminated by 2-ethyl-1,3-dithiane which could not be removed by short silica gel column chromatography.
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18. The DMIPS protecting group in 13 was quite effective in the last desilylation step of the synthesis of 1a.
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23. The unwanted (2*E*,4*Z*)-isomer could be isomerized to 18 with a catalytic amount of I_2 in PhH.
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