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SYNTHETIC STUDIES OF POLYENE MACROLIDES, SYNTHESIS OF A C29-37 FRAGMENT FOR AMPHOTERICIN B AND NYSTATIN

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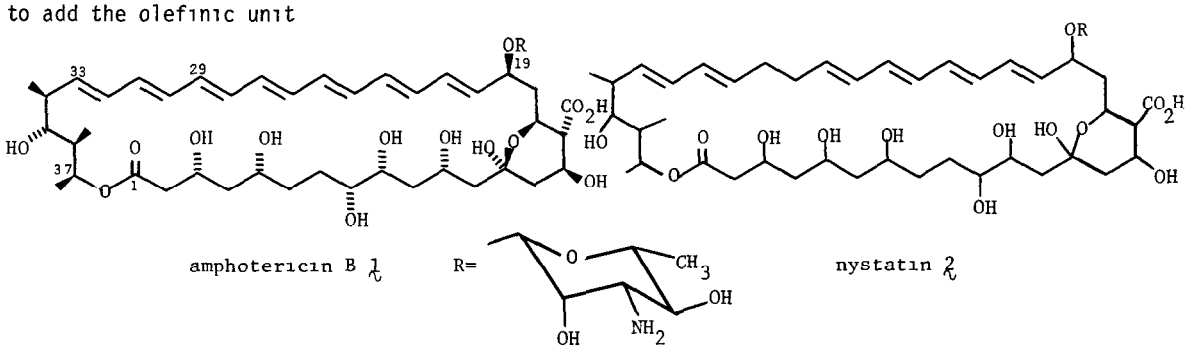
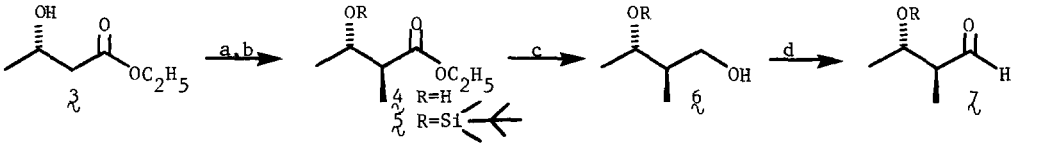
Summary An enantioselective synthesis of a C29-37 fragment common to both amphotericin B 1 and nystatin 2 is described from ethyl 3(S)-hydroxybutanoate

The polyene macrolide antibiotic group of microbial derived natural products, have a rich chemical[1] and medicinal[2] history The absolute structure of amphotericin B 1 has been established by X-ray analysis [3] The structures of other members, such as nystatin 2, have been proposed based on numerous chemical studies together with MS and NMR spectral analysis.[4] At the present time there is a noticeable lack of synthetic studies of the polyene macrolides.[5]

We wish to report an enantiospecific synthesis of a C29-C37 fragment common to both amphotericin B 1 and nystatin 2, as the first part of our efforts to develop a convergent total synthesis. Our synthetic scheme utilizes, 1 an efficient microbial reduction of a β-ketoester to generate the required chirality at C37, 2. a stereoselective alkylation of a β-hydroxyester, 3. a stereoselective aldol condensation, and 4 a Wittig-Horner reaction to add the olefinic unit

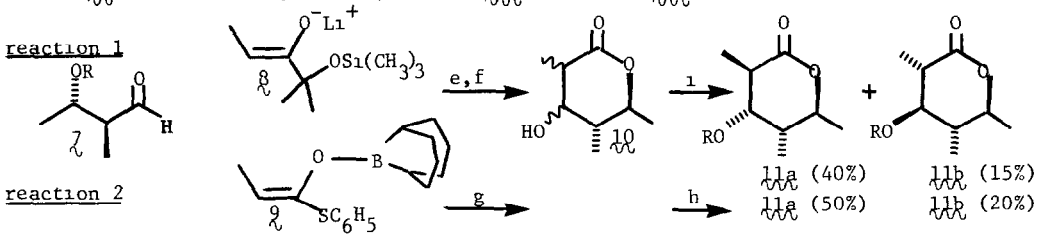


Microbial reduction of ethylacetoacetate with actively fermenting Bakers' yeast provided ethyl 3(S)-hydroxybutanoate 3 as a readily available chiral starting material [6] Alkylation of the dianion of 3 with methyliodide gave (2S,3S)-4 in 70% yield with greater than 95% stereoselectivity [7] The aldehyde 7 was prepared in 60% yield by the following steps, protection of the hydroxy group as a tert-butyldimethylsilyl ether, reduction of the ester 5 with lithium borohydride, and oxidation of the alcohol 6 with pyridinium chlorochromate.



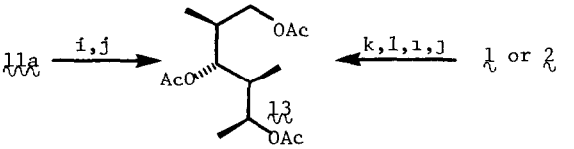
a) (1) lithium diisopropylamide (LDA) (2.2 equiv.), tetrahydrofuran (THF), -50°C, 1h. (2) add iodomethane (2.0 equiv.) and hexamethylphosphoramide (5 0 equiv.), -50°C, 1h, 70% b)t-butyldimethylsilylchloride (TBDMSCl) (1 1 equiv.), imidazole (3.0 equiv.) dimethylaminopyridine (DMAP) (0 1 equiv.), dimethylformamide (DMF), 60°C, 16h. c) $LiBH_4$ (2 equiv), THF, reflux, 16h d) pyridinium chlorochromate (PCC) (1.5 equiv), CH_2Cl_2, 25°C, 2h, 60% overall from 4.

The aldol condensation[8] of chiral aldehyde 7 was studied with two different nucleophiles· 1 the lithium enolate of 2-methyl-2-trimethylsilyloxy-3-pentanone 8 (reaction 1),[9] and 2 the E-vinyloxyborane of S-phenyl propanethioate 9 (reaction 2).[10] The adducts from reaction 1 were directly treated with periodic acid to provide a mixture of isomeric lactones 10 Silylation provided derivatives which could be readily separated by gas and liquid chromatography[11] Two major products 11a (40%) and 11b (15%) were obtained[12] The structures were initially assigned on the basis of their 470MHz ^1H NMR spectra[13] The adducts from reaction 2 were directly treated with aqueous methanolic hydrogen peroxide to provide the lactones 10 Similar silylation provided 11a (50%) and 11b (20%).[12]



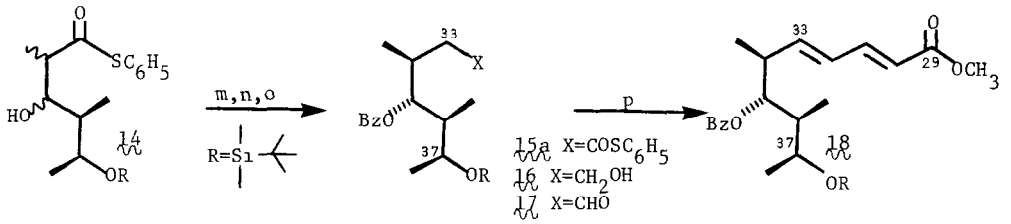
e) 8 generated by LDA (1.0 equiv.), THF, -78°, add 7, stir 10 min at -78°C, quench with 1N HCl (3 0 equiv H^+). f) HIO_6 (5 equiv), aqueous methanol (1 1), stir at 25°C, 16h g) 9 prepared as in ref 10, ether, 0°C, add 7, stir 30 min at 25°C, quench with methanolic H_2O_2 (10 equiv), stir 1h at 50°C h) TBDMSCl (1 2 equiv), imidazole (3.0 equiv), DMAP (0.1 equiv), DMF, 60°C, 24h

The chiral lactone 11a represents a potential precursor for the C33-37 fragment of both 1 and 2 In order to confirm the absolute structure of 11a, it was converted to the triacetate 13 and compared to the corresponding triacetate derived from degradation of both 1 and 2[14] All three triacetates showed identical ^1H and ^{13}C NMR spectra[15] and specific rotations as follows, synthetic 13, $[\alpha]_D^{23}$ = + 4 2° ± 0.2, 13 from 1, + 4 4° ± 0 2 (lit ref 14, + 4 6° ± 0 5 (c = 0 51, ether), 13 from 2, + 4 3° ± 0 2 (all c = 1 0, ether)



i) $LiAlH_4$ (4 equiv), THF, 25°C, 1h. j) acetic anhydride (10 equiv), pyridine (20 equiv), 25°C, 16h k) O_3, methanol, -78°C, 15 min l) H_2, PtO_2, methanol, 25°C, 2h.

We next investigated the application of the Wittig-Horner reaction to add an olefinic unit representing C29-32 to a chiral aldehyde representing C33-37 of 1 and 2. The thiol ester adduct 14 obtained by treatment of the initial adduct from reaction 2 with cold pH 7 buffered aqueous methanolic hydrogen peroxide served as an efficient precursor to the desired aldehyde 17 as follows. Protection of the hydroxy group of 14 as a benzoate ester allowed simple purification of the major desired isomer 15a by column chromatography.[16] Selective reduction of the thiol ester group with lithium borohydride gave the alcohol 16 which was oxidized with pyridinium chlorochromate to provide the aldehyde 17 in 40% overall yield from 7. Condensation of the sodium anion of methyl 4-(diisopropylphosphinyl)2-butenoate with 17 gave the desired (E,E)-dieneester 18 in 65% yield[17] which represents a C29-37 synthetic fragment of 1 and 2.



m) benzoyl chloride (1 2 equiv), pyridine (1 2 equiv), DMAP (0 1 equiv), 25°C, 24h n) $LiBH_4$ (2 equiv), THF, 0°C, 2h. o) PCC (1 5 equiv), dichloromethane, 25°C, 1h, 40% overall from 7. p) $(iC_3H_7O)_3$ $POCH_2CH=CHCOOCH_3$ (1 2 equiv), NaH (1 2 equiv), toluene, 25°C, 30 min

Further work toward the total synthesis of polyene macrolides is in progress

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11 G C conditions used were 6 ft stainless steel 1/8 in o d column containing 10% SE -30 on 80-100 mesh Chromasorb W, 150° for 2 min, then a 16° increase per min to 230° Retention times were 6 65 min for 11a and 6 96 min for 11b Liquid chromatography was performed with a Merck "Lobar" B column with a flow rate of 10 mL/min with a gradient of 10-30% ether in hexane The undesired isomer 11b eluted first

12 The percent yield indicated is the average overall isolated yield from aldehyde 7

13 11a· $[\alpha]_D^{23}$ = -0 8° (c=1 0, $CHCl_3$) ^{1}H NMR (470MHz, $CDCl_3$), 0 06 (s, 3H), 0 07 (s, 3H), 0 89 (s, 9H), 1 0 (d, J=6 77 Hz, 3H), 1 27 (d, J=7 63 Hz, 3H), 1 35 (d, J=6 45 Hz, 3H), 1 77-1 87 (m, 1H), 2,64 (qd, J=6 0, 2 3 Hz, 1H), 3.64 (t, J=2 3 Hz, 1H), 4 45 (dq, J= 10 0, 6 0 Hz, 1H), ^{13}C NMR (50 3 MHz, $CDCl_3$) -4 8 (q), -4 5 (q), 13 9 (q), 16 5 (q), 18 0 (s), 19.9 (q), 25 7 (q), 36 2 (d), 44 2 (d), 74 3 (d), 77 3 (d), 174 2 (s), Anal. Calcd for $C_{14}H_{28}O_3Si$· C, 61.72, H, 10 36, Si, 10 31

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15 13· ^{1}H NMR (470 MHz, $CDCl_3$) δ 0 92 (d, J=5 1 Hz, 3H), 0 93 (d, J=5 0 Hz, 3H), 1.15 (d, J=6 5 Hz, 3H), 2 03 (s, 3H), 2 06 (s, 3H), 2 09 (s, 3H), 2 08-2 16 (m, 2H), 3 84 (dd, J=11 0, 6 2 Hz, 1H), 3.94 (dd, J=11 0, 7 8 Hz, 1H), 4 90-4 95 (m, 2H), ^{13}C NMR (50.3 MHz, $CDCl_3$) 10 23 (q), 10 6 (q), 14 4 (q) 20 8 (q), 20 9 (q), 21 4 (q), 33 9 (d), 38 3 (d), 66 2 (t), 70 5 (d), 73 5 (d), 170 2 (s), 170 6 (s), 171 0 (s), Anal Calcd for $C_{14}H_{24}O_6$ C, 58 32, H, 8 39. Found C, 58 15, H, 8 64

16 15a: $[\alpha]_D^{23}$ = +23 3°(c=0 63, $CHCl_3$), ^{1}H NMR (470 MHz, $CDCl_3$) δ -0.002 (s, 3H), 0 008 (s, 3H), 0 87 (s, 9H), 0 99 (d, J=7 05 Hz, 3H), 1 11 (d, J=6.23 Hz, 3H), 1 35 (d, J=7 04 Hz, 3H), 2 0-2 15 (m, 1H), 3 19 (qd, J=7.04, 3 9 Hz, 1H), 3 97 (qd, J=6 3, 3 7 Hz, 1H), 5 52 (dd, J=5 62, 3 65 Hz, 1H), 7 37 (m, 5H), 7 44 (t, J=7 6 Hz, 2H), 7.56 (t, J=7 6 Hz, 1H), 8 04 (d, J=7 6 Hz, 2H) ^{13}C NMR (50 3 MHz, $CDCl_3$) -4 8 (q), -4 5 (q), 10 0 (q), 11.0 (q), 18 0 (q), 18 1 (s), 25 9 (q), 42.1 (d), 49 8 (d), 67 7 (d), 75 4 (d), 127 5 (s), 128 4 (d), 129 1 (d), 129 3 (d), 129 7 (d), 129 8 (s), 133 0 (d), 134 6 (d), 165 6 (s), 198 6 (s).

17 18· $[\alpha]_D^{23}$ = +42 8° (c=2 62, $CHCl_3$), ^{1}H NMR (470 MHz, $CDCl_3$) δ -0 028 (s, 3H), -0 020 (s, 3H), 0 847 (s, 9H), 0 94 (d, J=7 0 Hz, 3H), 1 07 (d, J=6 3 Hz, 3H), 1 14 (d, J=6 8 Hz, 3H), 2 00-2 15 (m, 1H), 2.70-2 80 (m, 1H), 3 71 (s, 3H), 3.92 (m, 1H), 5 11 (dd, J=8 9, 4 1 Hz, 1H), 5 75 (d, J=15 4 Hz, 1H), 6 08 (dd, J=15 3, 7 2 Hz, 1H), 6 19 (dd, J=15 3, 10 7 Hz, 1H), 7 19 (dd, J=15 4, 10 7 Hz, 1H), 7 45 (dd, J=7 5, 7 4 Hz, 2H), 7 57 (t, J=7 5Hz, 1H), 8 02 (d, J=7 4 Hz, 2H), ^{13}C NMR (50 3 MHz, $CDCl_3$) -4 8 (q), -4 5 (q), 9 7 (q), 13 4 (q), 18 0 (q), 18 0 (s), 25 8 (q), 38 8 (d), 41 9 (d), 51.5 (d), 67 6 (d), 77 5 (q), 119 9 (d), 128 3 (d), 128 4 (d), 129 5 (d), 130 0 (s), 133 0 (d), 144 8 (d), 145 6 (d), 165 9 (s), 167 4 (d)

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