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# SYNTHETIC STUDIES ON BORON CONTAINING ANTIBIOTICS

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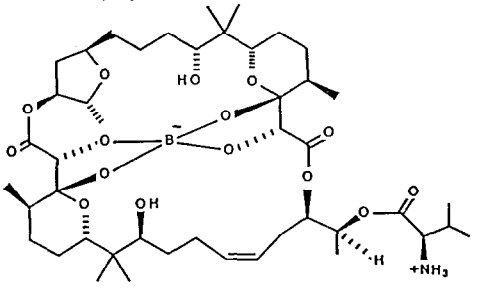
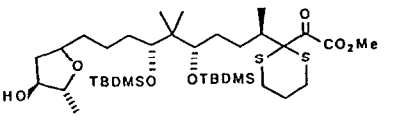
Abstract : The preparation of two fragments containing the backbone of the antibiotic boromycin is described.

In continuation of synthetic work on the boron containing antibiotic aplasmomycin, we wish to report preparation of fragments suitable for the synthesis of boromycin 1. The retrosynthetic analysis parallels that used in earlier work[4], and requires two major pieces 2 and 3.



1



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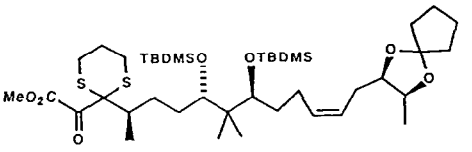


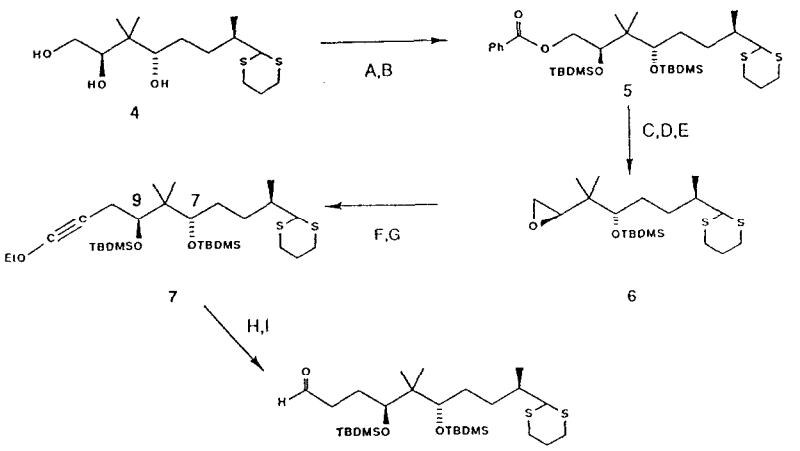
3

The starting material for fragment 2 is triol 4[3,4] which was differentially protected and converted to epoxide 6 by the following sequence: 1. reductive removal of the benzoate, 2. conversion to the mesylate, 3. epoxide formation via desilylation with fluoride ion[5]

Epoxide 6 was surprisingly unreactive towards two carbon homologation reagents ; however, smooth opening was realized with lithium ethoxyacetylide in the presence of boron trifluoride etherate[6]. The intermediate alcohol was briefly isolated and silylated with t-butyldimethylsilyl triflate[7] at low temperature. Hydrolysis of the ethoxyacetylide 7 to an ester proved to be unexpectedly difficult. Aqueous acid gave large amounts of the δ -lactone derived from cleavage of the 9-silyl ether. This problem was circumvented by thermolysis of 7 in ethanol solution in a sealed tube at 120° C[8]. Reduction of the ester with DIBAL at -78° C gave the aldehyde 8.

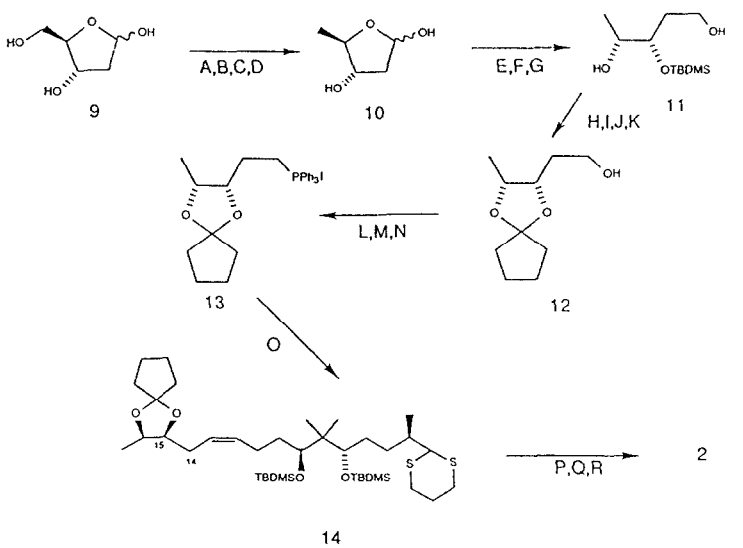
Lactol 10 was prepared from 2-deoxy-D-ribose by the four step sequence : 1. methyl furanoside formation, 2. transformation of the primary alcohol to the corresponding iodide[9], 3. catalytic hydrogenation to the terminal methyl group , and 4. acidic hydrolysis of the ketal. Oxidation of 10 with pyridinium dichromate in the presence of 4 Å molecular sieves, t-butyldimethylsilylation[10] , and lithium borohydride reduction provided diol 11([ α ]$_D$ -10° (c 1.24, methanol)). Adjustment of the protecting groups of 11 was accomplished by the four step sequence : 1. benzoylation of the primary alcohol, 2.

SCHEME 1




Reagents : A. PhCOCN, MeCN, -40° C,75%; B. t-BuMe$_2$SiOTf, 2,6-lutidine, $CH_2Cl_2$ , 0° C,85%: C. DIBAL,$CH_2Cl_2$ , -78 ° C,95%; D. Mesyl chloride, $NEt_3$, $CH_2Cl_2$ , -5° C,98%; E. (n-Bu)$_4$NF, THF, RT, 70%; F. Lithium ethoxyacetylide, $BF_3$-$Et_2O$, THF, -78° C ; G. t-BuMe$_2$SiOTf, 2,6-lutidine,$CH_2Cl_2$, -30° C, 79%; H. EtOH, 120° C, 2 hrs., 96% ; I. DIBAL, $CH_2Cl_2$, -78° C, 94%.

SCHEME 2



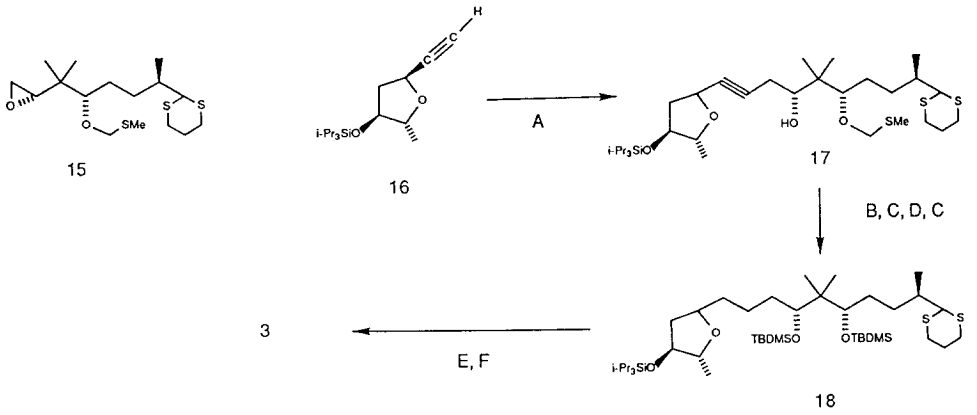

Reagents : A. MeOH, cat. $H_2SO_4$, RT,100%; B. $Ph_3P$, imidazole, $I_2$, MeCN-toluene (2:1), 70° C,81%; C. $H_2$, 10% Pd/C, $K_2CO_3$, MeOH, RT, 96%; D. 0.1 N HCl, THF, RT, 78%; E. PDC, 4 A sieves, DMF, RT, 73%; F. t-BuMe$_2$SiCl, imidazole, DMF, RT, 66%; G. $LiBH_4$, $Et_2O$, RT ,81%; H. PhCOCN, $NEt_3$, MeCN, -20° C, 88%; I. (n-Bu)$_4$NF, THF, O° C, 86%; J. 1-Methoxycyclopentene, PPTS, $CH_2Cl_2$, RT,100%; K. LiOH, DME, RT, 100%; L. MsCl, $NEt_3$, $CH_2Cl_2$, 0° C,100%; M. NaI, $CaCO_3$, MeCN, 35° C, 86%; N. $Ph_3P$, MeCN, 70° C, 97%; O. n-BuLi, 8, THF, -78° C, 95%; P. MCPBA, $CH_2Cl_2$, 0° C, 86%; Q. a. MeLi, THF, -78° C b. methyl oxalyl fluoride, 70% ; R. $P_2I_4$, $NEt_3$, $CH_2Cl_2$, RT, 100%.

fluoride desilylation, 3. cyclopentylidene ketalization and , 4. lithium hydroxide hydrolysis. Iodide displacement of the mesylate derived from 12 and treatment with triphenylphosphine gave the phosphonium salt 13.

The phosphonium salt 13 was deprotonated with n-butyllithium and treated with the aldehyde 8 in the presence of hexamethylphosphoric triamide to give exclusively cis-14 in 95%yield.

Introduction of the oxalate subunit by metallation of the dithiane was complicated by deprotonation at the allylic position (C-14) followed by expulsion of the C-15-ether functionality. This problem was solved by increasing the acidity of the dithiane by conversion to the monosulfoxide with MCPBA. The material was then metallated with methyllithium at -78° C and acylated with methyl oxalyl fluoride[11]. Deoxygenation of the sulfoxide with phosphorus (II) iodide[12] gave the completed southern subunit (100%,[ α ]$_D$ -7.4° (c 2.19, chloroform))

SCHEME 3




Reagents : A. 16 and n-BuLi, THF, -78° C; $BF_3$-$Et_2O$; 15, 75%; B. Potassium diazodicarboxylate, pyridine, HOAc, RT,78%; C. t-$BuMe_2SiOTf$, 2,6-lutidine, $CH_2Cl_2$, -30° C, 90% and 91%; D. $AgNO_3$, 2,6-lutidine ,THF-$H_2O$(4:1), RT,73%; E. n-BuLi, TMEDA, THF, -30° C; dimethyloxalate, HMPA , -78° C, 87%; F. $(n\text{-}Bu)_4NF$, THF, RT, 100%.

The starting materials for the northern piece were the epoxide 15 and the acetylene 16[4]. As shown in Scheme 3 these were coupled by formation of the lithium acetylide of 16 with n-butyllithium followed by activation with boron trifluoride etherate. The reaction proceeded smoothly at -78° C giving 17 in 78% yield. In comparison, the corresponding cuprate based coupling reaction in the aplasmomycin synthesis required two days at -30° C. The acetylene was saturated with diimide generated from potassium diazodicarboxylate[13]. The protecting groups were then adjusted to the more suitable t-butyldimethylsilyl ether. The saturated compound 18 was metallated with n-butyllithium as previously described and acylated with dimethyl oxalate to 3, thus completing the synthesis of the northern section.

Our previous experience has shown that 2 and 3 have suitable functionality for the completion of the boromycin synthesis.

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2. Present address : Central Research and Development Department, E. I. DuPont deNemours, Wilmington DE.
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