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APPROACHES TO AVERMECTIN ASSEMBLY: ELABORATION OF AN α-L-OLEANDROSYL-α-L-OLEANDROSIDE DERIVATIVE

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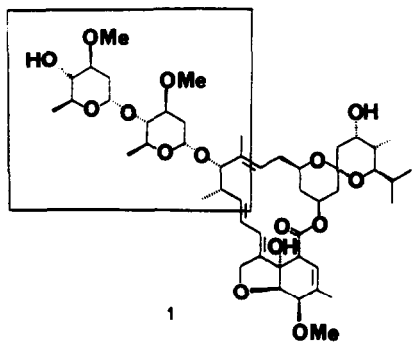
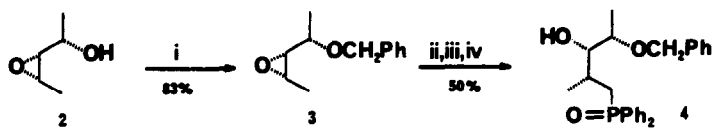
Summary: A stereospecific synthesis of the disaccharide moiety of avermectin A_{2b} has been accomplished in 11 steps from commercially available 3-pentyn-2-ol and L-rhamnal.

The avermectins and the structurally related milbemycins have been the subject of considerable synthetic studies due to their potent ectoparasiticidal and anthelmintic activities and their complex molecular structure.[1] Recently, we described a concise spirodihydropyrone strategy for the elaboration of the spiroketal portion of avermectin A_{2b} (1).[2] Herein, we report a convenient approach to the required sugar fragment 10, which is a potential precursor for the disaccharide system.



1

We considered that the target disaccharide phosphine oxide 10 should be available via the iterative construction of both glycosidic bonds starting from the alcohol 4. Thus, racemic 3-pentyn-2-ol was converted into the known epoxide 2[3] via semi-hydrogenation over Lindlar's catalyst (88%) and stereoselective (98:2) 3-chloroperoxybenzoic acid oxidation (60%). Subsequent benzylation and reaction with lithiomethyldiphenylphosphine oxide regiospecifically gave the racemic alcohol 4. This substance was easily resolved on a multigram scale using (S)-α-methylbenzyl isocyanate by recrystallization and unequivocally assigned on the basis of an X-ray crystallographic study.[4] Saponification gave optically pure alcohol 4.

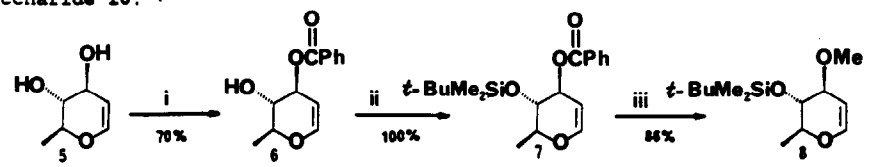


2 3 4

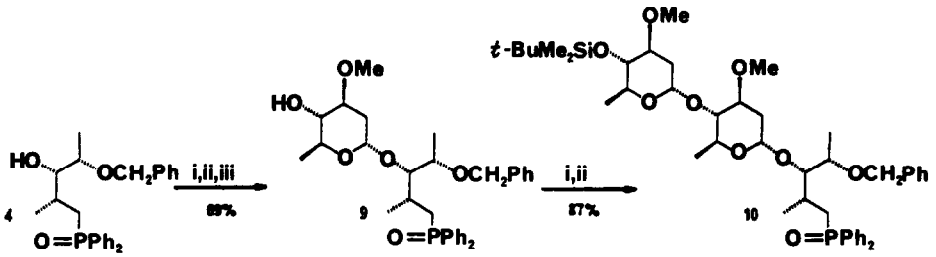
Reagents: (i) NaH, $PhCH_2Br$, DMF, 25°C; (ii) $Ph_2P(O)CH_2Li$, DME, 25°C; (iii) (S)-PhCH(Me)NCO, PhMe, 80°C; separate diastereomers; (iv) NaOEt, EtOH, reflux.

L-Rhamnal was transformed into 8 via sequential regioselective O-4-benzoylation[5] and direct conversion of the benzoate 7 to the methyl ether via reaction with methyllithium followed by methyl trifluoromethanesulfonate. Glycal 8 and alcohol 4 were easily transformed

into the corresponding α-glycoside only, using the elegant Sinaÿ phenylselenyl chloride mediated glycosidation.[6] Repetition of the glycosidation and radical deselenylation gave the target disaccharide 10.[7,8]



Reagents: (i) PhCOCl, pyridine, 0°C; (ii) $^{t}BuMe_2SiCl$, imidazole, DMF; (iii) MeLi (2.2eq), THF, -78°C; MeOTf (1.5eq); Et_3N (3eq).



Reagents: (i) 11, PhSeCl (1.5eq), 2,4,6-collidine (1.5eq), CH_3CN, 0-25°C; (ii) Ph_3SnH (2eq), PhMe, reflux; (iii) $^{n}Bu_4NF$ (2eq), THF.

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