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DIASTEREOSELECTIVE [2,3] WITTIG REARRANGEMENT OF CARBOHYDRATE-DERIVED TERTIARY ALLYLIC ETHERS. 2. SYNTHESIS OF AN ADVANCED RAPAMYCIN INTERMEDIATE FROM D-GLUCOSE.

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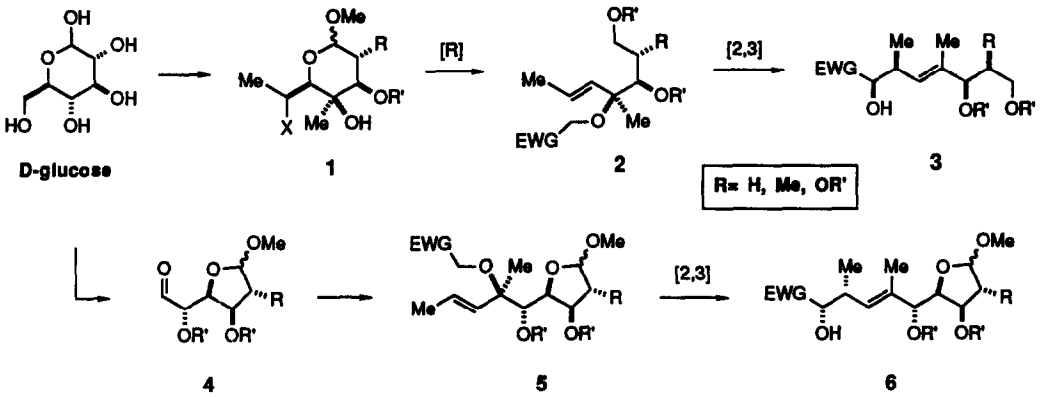
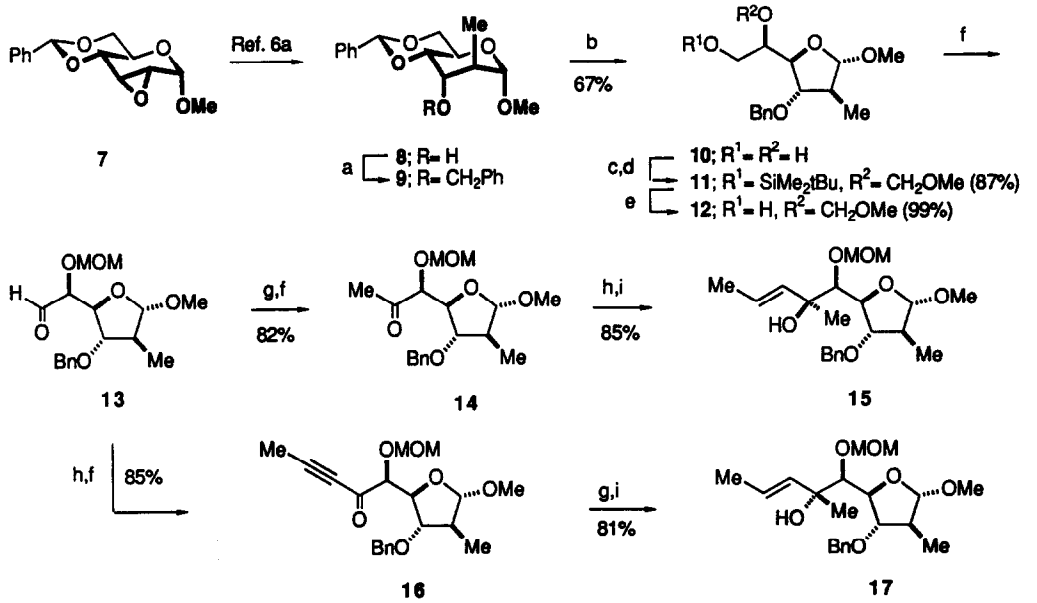
Summary: *The advanced rapamycin intermediate 26 has been prepared by an iterative sigmatropic sequence incorporating the diastereoselective [2,3] Wittig rearrangement of a D-glucofuranose-derived tertiary allylic ether.*

Recent studies in our laboratories have focused on the development of a comprehensive strategy for the construction of polyketide-derived natural products, based on the serial application of diastereoselective sigmatropic reactions.[1] Particularly useful as a vehicle for the synthesis of highly-oxygenated acyclic targets is the [2,3] Wittig rearrangement[2] of α-alkoxy, tertiary allylic ethers, a reaction which delivers geometrically defined trisubstituted olefins incorporating the structural and stereochemical elements of polypropionate systems.[3] In the preceding communication we described a scheme in which a tertiary allylic ether **2** (R= OMe, R'= Bn), the product of reductive dehalogenation of 6-halopyranose **1**, serves as the stereochemical platform for initiation of a sigmatropic construction of the benzoquinoid ansamycins.[4] As part of our synthetic program directed at rapamycin,[5] we have investigated an alternative utilization of carbohydrate templates for the assembly of sigmatropic substrates, via the chelation-mediated homologation of suitably functionalized furanose aldehydes **4**. We now report the [2,3] Wittig rearrangement of allylic ethers **5**, providing a stereocontrolled entry to products of general structure **6**, and the application of this scheme to the preparation of an advanced rapamycin intermediate.



To examine the basic feasibility of our plan, tertiary allylic alcohols **15** and **17** were prepared from the D-glucose-derived C_2-methylpyranose **8**[6] as shown in Scheme 1. O-Benzylation of **8** and acid-catalyzed isomerization to the furanose gave diol **10**, accompanied by 20-30% of the pyranose and anhydropyranose derivatives which, when resubjected to the reaction conditions, afforded additional **10**.[7] Following differentiation of the primary and secondary hydroxyl groups, Swern oxidation of alcohol **12** afforded the corresponding aldehyde, from which methyl ketone **14** was obtained by a standard addition-oxidation sequence. Chelation-

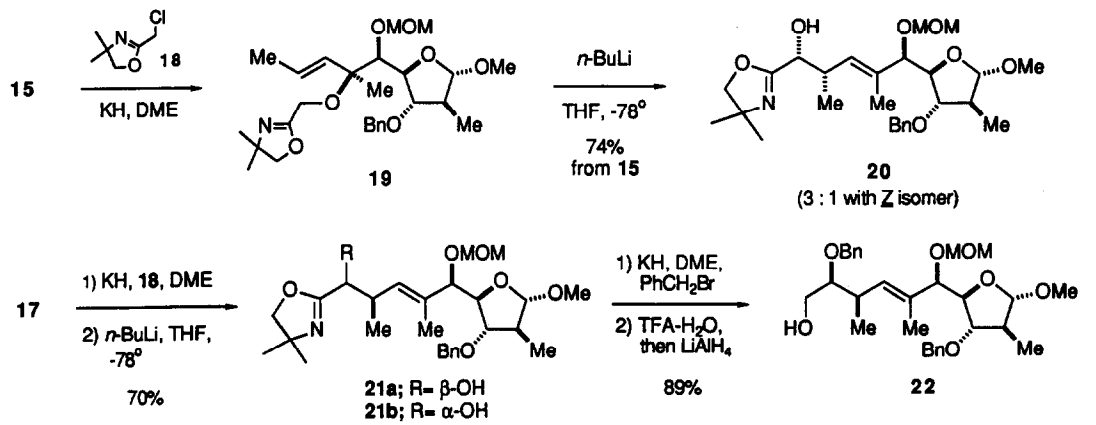
Scheme 1



Reagents: (a) KH, $PhCH_2Br$, DME; (b) MeOH, HCl; (c) *t*-$BuMe_2SiCl$, imidazole, THF; (d) $MeOCH_2Cl$, *i*-Pr_2NEt; (e) *n*-Bu_4NF, THF; (f) $(COCl)_2$, DMSO, NEt_3, CH_2Cl_2; (g) MeMgBr, THF, -78°; (h) MeCCMgBr, THF, -78°; (i) $LiAlH_4$, THF, 45°.

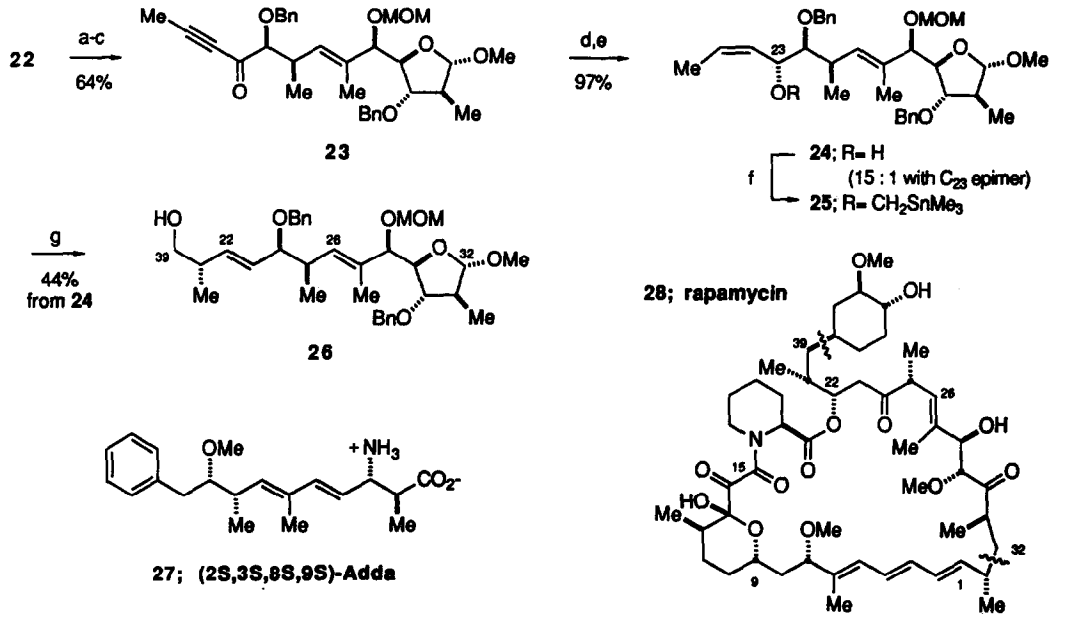
controlled addition[8] of propynyl Grignard to **14** and reduction to the E allylic alcohol afforded an 8:1 mixture of **15** and the epimeric **17**.[9] Selective preparation of alcohol **17** was accomplished by a similar scheme, involving addition of propynyl Grignard to **13** and oxidation of the epimeric adducts to give ketone **16**. A final chelation-controlled addition of methyl Grignard reagent, followed by reduction of the resulting propargyl alcohol, gave alcohol **17** as a single diastereomer.

Scheme 2



O-Alkylation of *syn* alcohol **15** with chloromethyloxazoline **18**[10] and treatment of the resulting ether **19** with *n*-BuLi resulted in rapid [2,3] rearrangement, yielding a 3:1 mixture of **20** and its Z isomer.[9,11] The formation of a Z olefinic byproduct from **19** is consistent with earlier observations regarding the [2,3] rearrangement of *syn* substrates,[3a,b] and further suggests that the presence of β and γ oxygen substituents has a negligible effect on the stereochemical outcome of the chelation-mediated sigmatropic event. In contrast, O-alkylation of *anti* alcohol **17** and [2,3] Wittig rearrangement of the resulting ether afforded a preparatively inseparable 4.5 : 1 mixture of **21a** and the epimeric **21b**.[9] Following benzylation and reductive cleavage[12] of the oxazoline group, alcohol **22** was easily separated from the minor epimer by flash chromatography.

Scheme 3



Reagents: (a) $(COCl)_2$, DMSO, NEt_3, CH_2Cl_2; (b) MeCCMgBr, THF, -78°; (c) MnO_2, CH_2Cl_2; (d) $ZnCl_2$, $NaBH_4$, Et_2O, 0°; (e) H_2, Lindlar, MeOH; (f) KH, Me_3SnCH_2I, DME; (g) MeLi, THF, -78°.

[2,3] Wittig products **20** and **21** represent versatile polyketide intermediates which are well-suited for further sigmatropic homologation.[1] Oxazoline **20** comprises the basic carbon framework of (2S,3S,8S,9S)-Adda, **27**, a β-amino acid constituent of the hepatotoxic peptides nodularin and motuparin,[13] while **21** corresponds to the fully-functionalized C_{23}-C_{32} fragment of rapamycin, **28**, a powerful immunomodulating agent that has been the focus of recent synthetic attention.[14] As a further demonstration of the utility of carbohydrate-based [2,3] Wittig products, alcohol **22** has been transformed to **26**, representing the 13-carbon "effector" subunit[5c] of rapamycin, by means of a [2,3] sigmatropic homologation which introduces the C_{38} stereogenic center of **28**. Ketone **23** was prepared from **22** by a sequence consisting of Swern oxidation, addition of propynyl Grignard reagent and oxidation of the epimeric adducts, whereupon chelation-controlled hydride addition and Lindlar reduction afforded Z alkenol **24**.[15] Alkylation of **24** afforded α-stannyl ether **25**, which upon transmetallation underwent smooth [2,3] Wittig rearrangement[16] to give diene **26**, accompanied by ca. 13% of recovered alcohol **24**.[17]

The [2,3] sigmatropic homologation of glucofuranose-derived allylic ethers presents an efficient,

stereorational entry to advanced polyketide synthons that complements our previously reported scheme for the utilization of carbohydrates as a source of non-racemic sigmatropic substrates.[4] Extension of the approach described herein to the sigmatropic development of other furanose and pyranose templates and applications to the synthesis of biologically significant natural products of polyketide origin will be the subject of future reports.

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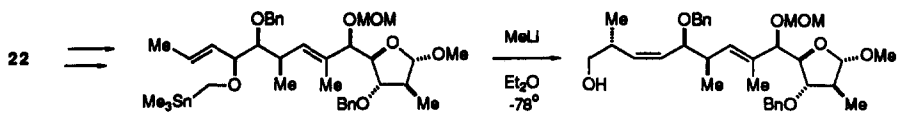
15. Attempts to prepare **26** by rearrangement of E-*syn* ether **i** yielded the Z product **ii**, contrasting the behavior of similarly functionalized tertiary ethers[3b] and substrates which lack α-alkoxy substituents.[16] The Z selectivity observed for **i** appears to be general for secondary E-*syn* ethers (J. Eshelman, unpublished results) and represents a novel, sigmatropic entry to Z-disubstituted acyclic olefins.



i ii

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