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DIASTEREOSELECTIVE [2,3] WITTIG REARRANGEMENT OF CARBOHYDRATE-DERIVED TERTIARY ALLYLIC ETHERS. 1. SYNTHESIS OF THE C11-C18 SUBUNIT OF HERBIMYCIN A FROM D-GLUCOSE.

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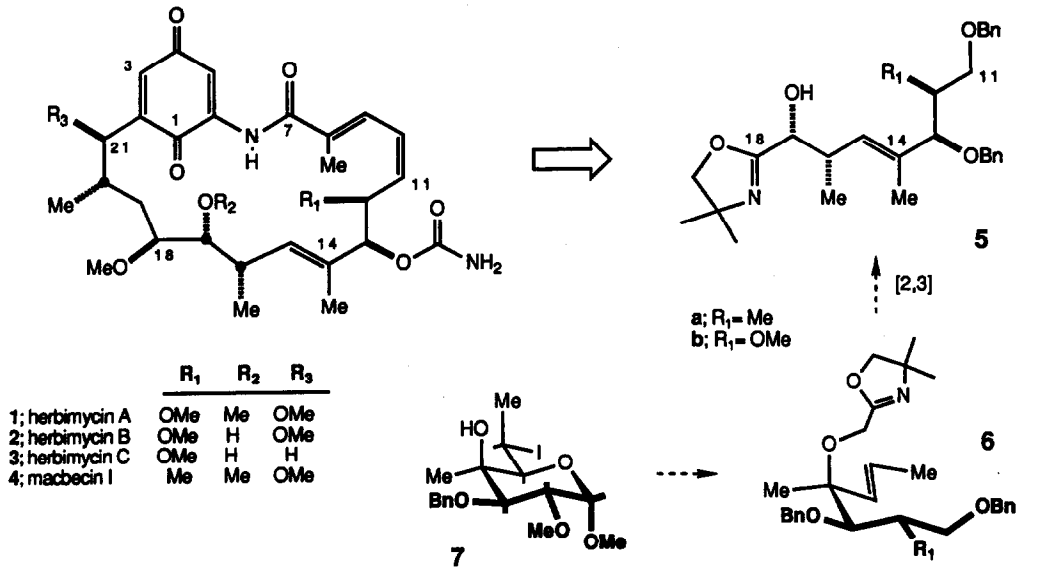
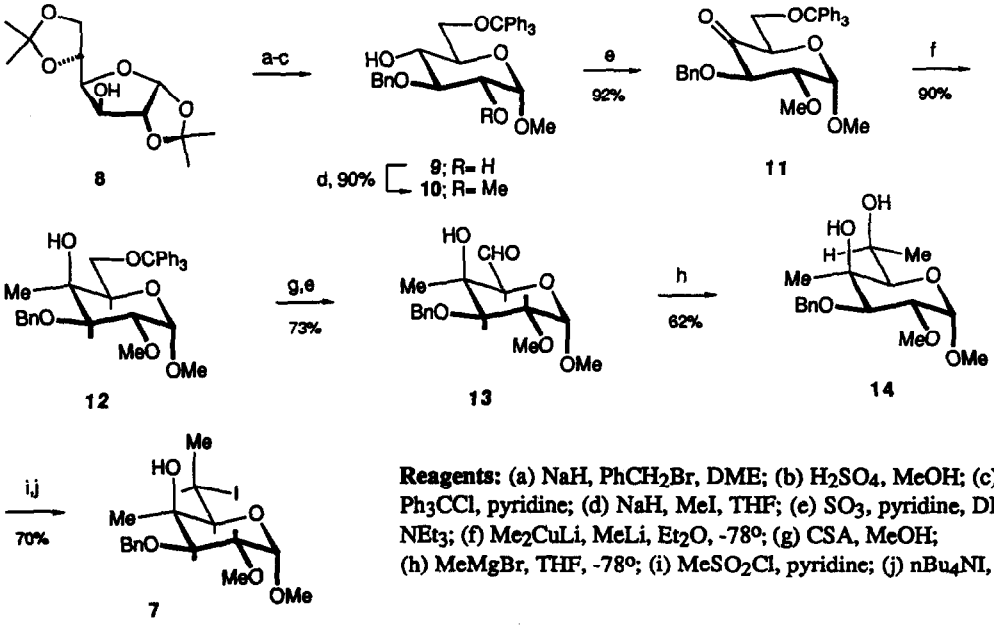
Summary: *Reductive fragmentation of the D-glucose derived iodopyranose 7 and diastereoselective [2,3] Wittig rearrangement of the resulting tertiary allylic ether affords trisubstituted olefin 19, comprising the C_{11}-C_{18} segment of the benzoquinoid ansamycin herbimycin A.*

The benzoquinoid ansamycins comprise a small family of macrocyclic lactams which have attracted attention as the result of their ability to inhibit the phosphorylating activity of protein tyrosine kinases. Notable in this regard are the herbimycins (**1-3**)[1] which exhibit pronounced antitumor and antiviral activity, in addition to activity against protozoal, fungal and helminthic infestations and pre-emergence herbicidal and anti-angiogenic properties.[2] The herbimycins bear a close structural relationship to macbecin I (**4**),[3] an antitumor ansamycin which has been the focus of recent synthetic efforts,[4] including a total synthesis of (+)-**4** by Baker[4a,b] and our synthesis of *racemic* **4** based on the serial application of diastereoselective [2,3] sigmatropic rearrangements.[5] Recently, Tatsuta and coworkers reported the first total synthesis of herbimycin A, wherein the C_{10}-C_{15} fragment of **1** was elaborated from D-mannose.[6] We now report a conceptually different approach to the herbimycin ansa system, in which the [2,3] Wittig rearrangement of a glucose-derived tertiary allylic ether **6b** establishes the key structural and stereochemical elements of an advanced herbimycin intermediate.



A pivotal step in our construction of the macbecin I ansa system was elaboration of trisubstituted olefin **5a** by means of the stereoselective [2,3] Wittig rearrangement of tertiary allylic ether **6a**.[5a] We reasoned that olefin **5b**, corresponding to the C_{11}-C_{18} subunit of herbimycin, would result from an analogous rearrangement of tertiary ether **6b**; the presence of an additional heteroatom substituent at C_{12} of the herbimycin ansa system further suggested that chiral, non-racemic **6b** could be accessed from an appropriately functionalized carbohydrate precursor. For our construction of the herbimycin system we envisioned utilization of the D-glucose template for a rapid development of [2,3] Wittig substrate **6b** based on reductive dehalogenation[7] of 6-iodopyranose **7**.

Scheme 1



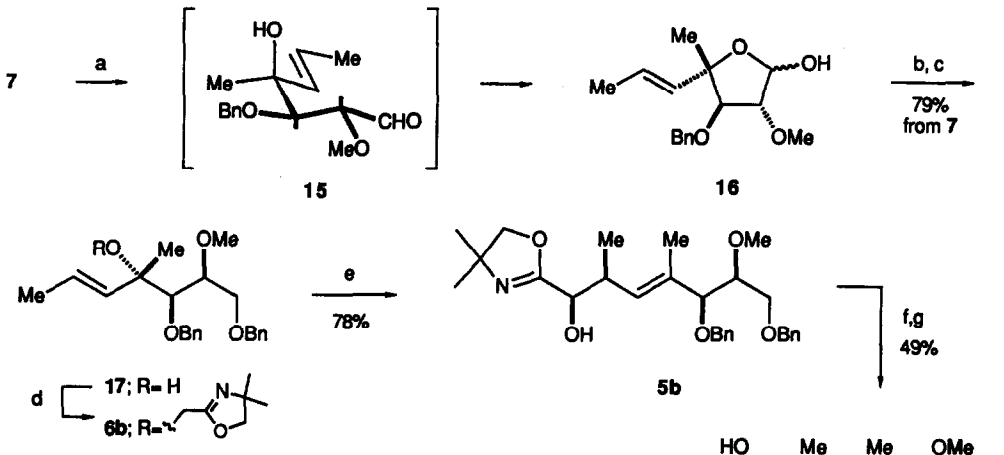
Reagents: (a) NaH, $PhCH_2Br$, DME; (b) H_2SO_4, MeOH; (c) Ph_3CCl, pyridine; (d) NaH, MeI, THF; (e) SO_3, pyridine, DMSO, NEt_3; (f) Me_2CuLi, MeLi, Et_2O, -78°; (g) CSA, MeOH; (h) MeMgBr, THF, -78°; (i) $MeSO_2Cl$, pyridine; (j) nBu_4NI, PhH.

Our preparation of iodopyranose **7** initiated with glucopyranose **9**, prepared in three steps from commercially available 1,2:5,6-di-O-isopropylidene-α-D-glucofuranose **8** (Scheme 1).[8] Regioselective O-methylation of **9** and oxidation of the resulting C_4 alcohol **10** with SO_3-pyridine complex afforded ketone **11**.[9] Treatment of **11** with MeLi-Me_2CuLi complex in Et_2O was accompanied by the expected equatorial addition,[10] yielding the desired axial tertiary alcohol **12**.[11] The stereochemistry of cuprate addition to **11** exhibited a notable solvent dependence; a similar reaction carried out in 1:1 THF : Et_2O gave the epimeric C_4 alcohol as the major product (3 : 1 with **12**). Deprotection of **12** and oxidation of the resulting diol furnished the sensitive aldehyde **13**; subsequent treatment with methyl Grignard reagent afforded diol **14**, the stereochemistry of which was assigned based on NOE studies of the derived isopropylidene.[11] Finally, diol **14** was transformed to iodoalcohol **7** by mesylation and treatment of the resulting sulfonate with tetrabutylammonium iodide in benzene. Iodide **7** was obtained as a single diastereomer; we have assigned the C_6 configuration as shown based on a presumed S_N2 displacement of mesylate and the geometry of the olefinic product of reductive dehalogenation.

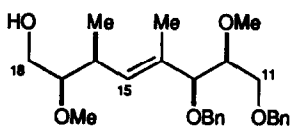
With a suitably functionalized 6-halopyranose in hand, we next examined generation of the requisite tertiary allylic ether **6b** by reductive dehalogenation of **7**.[7] Of considerable interest was the stereochemical outcome of the reductive elimination; despite the widespread use of this technique for the preparation of δ,ε unsaturated aldehydes from pyranose precursors, few examples of the reduction of secondary halides have been

reported.[12] The expectation that dehalogenation of **7** would furnish the E olefinic product was based on our assumption that reduction would proceed through a reactive conformation in which antiperiplanar orientation of the carbon-iodine and pyranose C-O bonds minimizes non-bonded interactions of the C_6 methyl substituent and C_4 of the pyranose system. Iodide **7** was rapidly consumed upon treatment with Zn dust in ethanol; interestingly, the anticipated product of reduction, aldehyde **15**, was not isolated but instead underwent cyclization to yield lactol **16** as a 3:1 mixture of anomers. Finally, reduction of **16** and mono-benzylation of the resulting diol afforded tertiary allylic alcohol **17**. At this juncture, the E olefin geometry could be assigned to **17** based on an olefinic ^{1}H NMR coupling constant of 15.5 Hz; no evidence of Z olefin isomer formation was detected.

Scheme 2



Reagents: (a) Zn, EtOH; (b) $LiBH_4$, THF; (c) $PhCH_2Br$, NaH, DME; (d) KH, 2-chloromethyl-4,5-dihydro-4,4-dimethyl-oxazole (**18**), DME; (e) LDA, THF, -78 -> 0°; (f) KH, MeI, DME; (g) TFA (1 eq), H_2O (1 eq), THF, then $LiAlH_4$.



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Previous studies in our laboratories have demonstrated that diastereoselectivity observed for the [2,3] rearrangement of anions of tertiary allylic ethers derives from a complexation of the reaction counterion by a substrate α-alkoxy substituent.[13] The effect of β- and γ-alkoxy groups on the stereochemical course of the sigmatropic event remains unexplored and the stereochemical issues surrounding the [2,3] Wittig rearrangement of tertiary substrate **6b** were thus of considerable interest. In the event, alkylation of the potassium alkoxide of **17** with chloromethyl oxazoline **18**, followed by treatment of the resulting ether **6b** with lithium diisopropylamide and subsequent [2,3] sigmatropic rearrangement afforded a single product, oxazoline **5b**.[14] O-Methylation of **5b** followed by reductive cleavage of the oxazoline system afforded **19**, corresponding to the fully-functionalized C_{11}-C_{18} subunit of the herbimycin ansa system.

The preparation of [2,3] Wittig substrate **6b** via Vasella fragmentation of a readily available D-glucose derivative represents a preparatively useful strategy for the translation of carbohydrate structural and stereochemical elements into advanced intermediates for the construction of polyketide-derived natural products. We note that the C_{12} methyl analogue of **19** has been previously converted to macbecin I **4**,[5] and anticipate that the synthesis of naturally-occuring herbimycins from **19** will follow a similar course. These studies and efforts to extend the basic strategy reported herein to other pyranose- and furanose-derived halo sugars are in progress and will be the subject of future reports.

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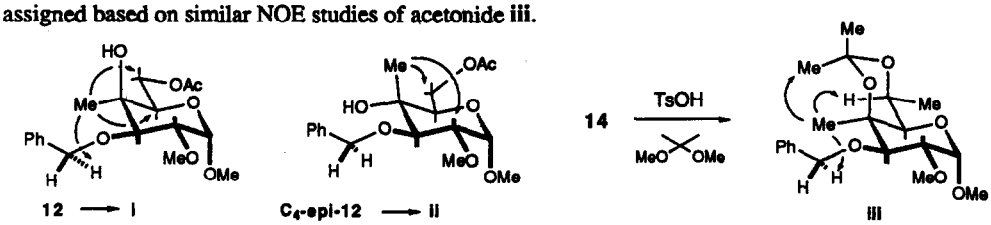
11. a) Stereochemical assignments for **12** and its C_4 epimer are based on comparative NOE studies of the derived acetates **i** and **ii**, which exhibit the indicated enhancements. The C_6 configuration of **14** was assigned based on similar NOE studies of acetonide **iii**.



12. Cf. Furstner, A., Weidmann, H. *J. Org. Chem.* **1989**, *54*, 2307.
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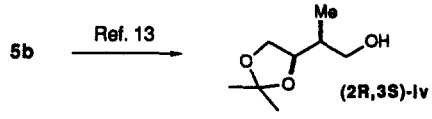
14. Stereochemistry at C_{16}-C_{17} was confirmed by degradation of **5b** to **(2R,3S)-iv** using a previously described[13] scheme:



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