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SYNTHESIS OF ANTITUMOR ANSAMYCINS. 1. SERIAL SIGMATROPIC CONSTRUCTION OF THE C_{11}-C_{21} ANSA SUBUNIT OF MACBECIN I

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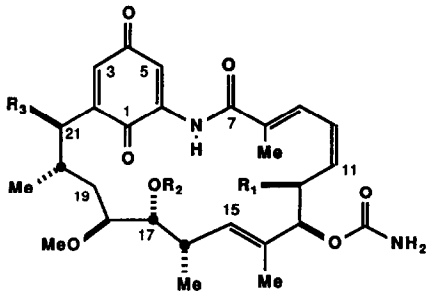
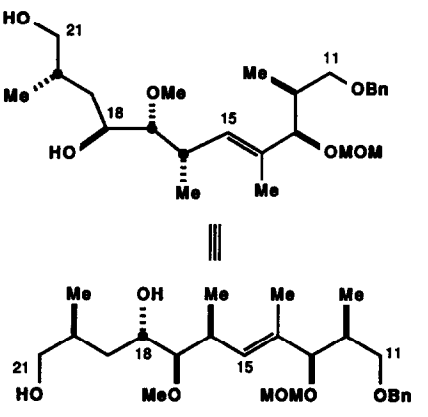
Summary: *Diol 4, comprising the C_{11}-C_{21} ansa subunit of the antitumor antibiotic macbecin I, has been prepared by a sequence incorporating sequential [2,3] Wittig rearrangements to establish the carbon skeleton and remote functionality of the macbecin ansa system.*

The benzoquinoid ansamycin macbecin I (1)[1] and the structurally related herbimycins (2, 3)[2] have attracted interest as synthetic targets[3] as a result of their broad spectrum of biological activity, which includes antiviral and pronounced *in vivo* antitumor activity with low acute toxicity. A recent communication by Baker and Castro[4] describing the total synthesis of macbecin I prompts us to report our investigation of a fundamentally different approach to 1, in which the essential structural and stereochemical elements of the macbecin ansa system are rapidly developed by sequential and highly diastereoselective [2,3] Wittig rearrangements.



	R_1	R_2	R_3
1 ; macbecin I	Me	Me	OMe
2 ; herbimycin A	OMe	Me	OMe
3 ; herbimycin B	OMe	H	H



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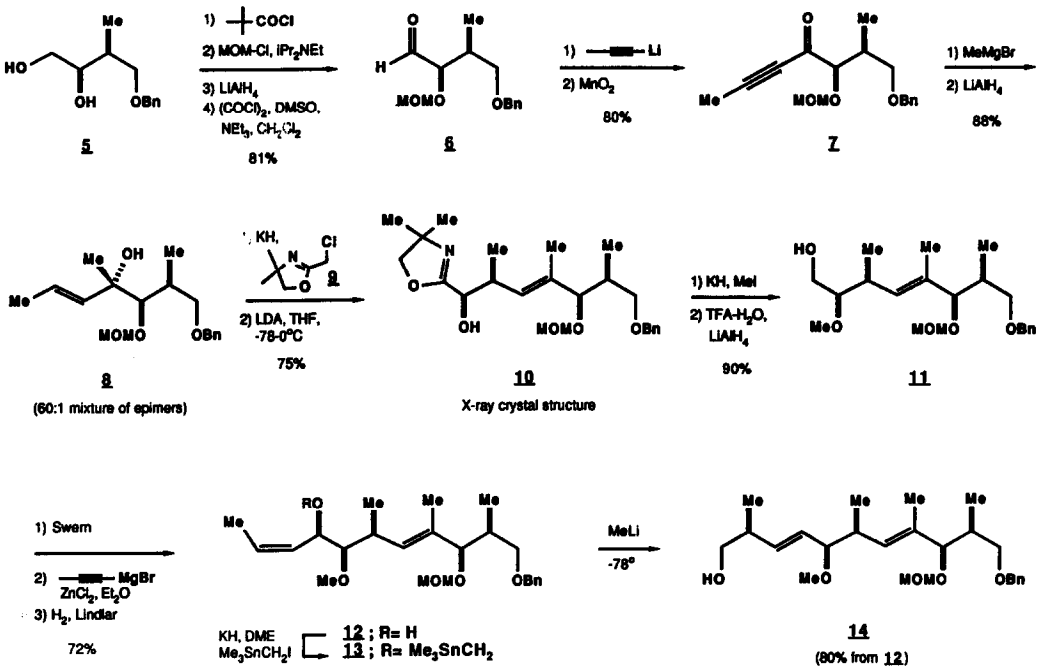
Serial application of highly stereoselective [3,3] and [2,3] sigmatropic reactions has emerged as a powerful and inherently versatile strategy for the linear construction of polyketide-derived acyclic targets.[5] The ansa system of macbecin I, containing three distinct sets of noncontiguous chirality, is well-suited for elaboration through a scheme in which sequential sigmatropic events establish the C_{16}-C_{17} and C_{20}-C_{21} bonds of the macbecin ansa framework and concurrently install remote stereochemical elements at C_{16}, C_{17} and C_{20} of the ansa system. Critical to the success of this iterative strategy is the availability of a sigmatropic protocol capable of generating the trisubstituted E olefinic linkage between C_{14} and C_{15} of the macbecin ansa bridge.

Our recent observation that the [2,3] Wittig rearrangement of tertiary α-alkoxy ethers[6] provides an efficient and highly diastereoselective route to remotely-functionalized, geometrically-defined trisubstituted olefins presented a reliable solution to this problem, and we initiated a preparation of [2,3] Wittig substrate **8** (Scheme 1). Racemic alcohol **5**[7] was transformed to aldehyde **6** by sequential protection of the primary and secondary alcohols, reductive deacylation and Swern oxidation.[8] Addition of propynyl lithium to **6** and subsequent oxidation of the epimeric adducts afforded propynyl ketone **7**. Chelation-controlled addition[9a] of methyl Grignard reagent to **7** and reduction of the resulting propargylic alcohol established tertiary alcohol **8** as a 60:1 epimeric mixture (determined by GC analysis). Alkylation of **8** with chloromethyl oxazoline **9** yielded the corresponding ether, which underwent [2,3] Wittig rearrangement to give oxazoline **10** (35:1 with an unidentified stereoisomer), as confirmed by single crystal X-ray analysis.[6a]

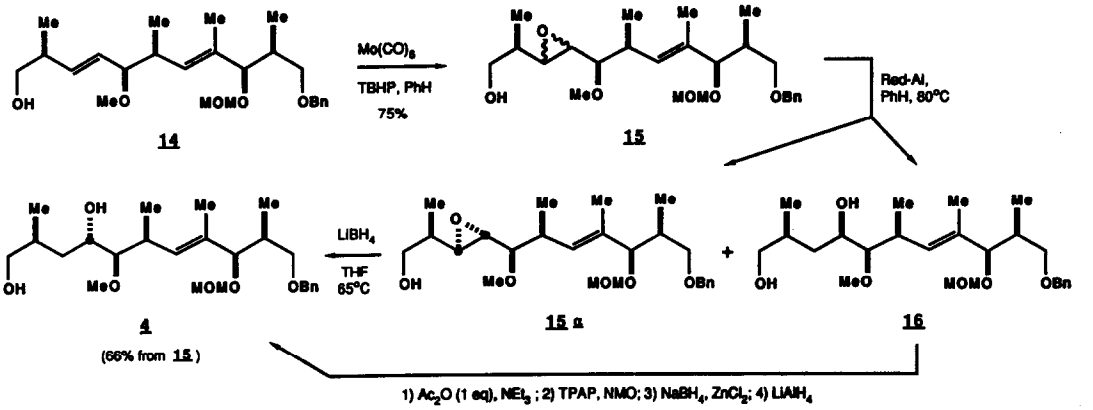
Scheme 1



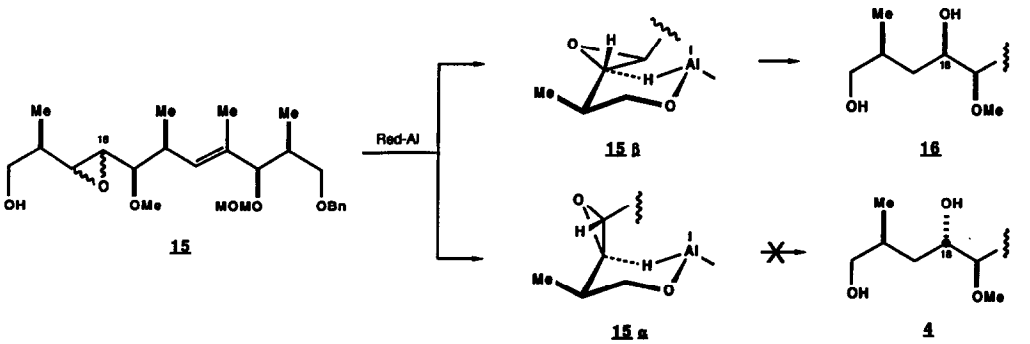
A second sequence of chelation-controlled homologation and [2,3] Wittig rearrangement establishes the final skeletal elements of the macbecin I ansa framework. O-Methylation of **10** and reductive cleavage[10] of the oxazoline group afforded alcohol **11**. Oxidation of **11** to the aldehyde was followed by addition of propynyl Grignard reagent using Mead's protocol[9b] and Lindlar reduction of the resulting acetylenic alcohol yielding **12** (>98% of the desired epimer). Alkylation of **12** afforded α-stannyl ether **13**, which upon transmetallation underwent [2,3] Wittig rearrangement[11] to give, as the only isolated product, alcohol **14**, comprising the C_{11}-C_{21} carbon framework of the macbecin ansa system.

The final stereogenic center corresponding to C_{18} of the macbecin ansa bridge was introduced by the sequence outlined in Scheme 2. Directed epoxidation[12] of **14** afforded an inseparable mixture (α:β = 1:1.6)

Scheme 2



of epoxides **15**, prompting us to turn our attention to a scheme in which these diastereomeric epoxides could be individually transformed to diol **4**. Treatment of the mixture of **15α** and **15β** with Red-Al ($NaH_2Al(OCH_2CH_2OMe)_2$) resulted in the remarkably chemoselective and regiocontrolled opening of β-epoxide **15β**, affording a mixture of alcohol **16** and unreacted **15α** which was easily separated by flash chromatography. We attribute the dramatic difference in reactivity for epoxides **15α** and **15β** to a steric compression between the C_{20} methyl substituent and the C_{18} methine which retards internal hydride delivery for the former substrate. The regiochemistry of reduction is presumably the consequence of initial coordination of the reagent to the C_{21} hydroxyl followed by directed hydride addition to the epoxide.[13] Exclusive delivery of hydride to C_{19} is observed from the reduction of epoxides **15** with the polyhydridic reagents Red-Al and $LiBH_4$; a contrasting selectivity is observed with the monohydridic reagent DIBAL-H, which affords predominately the undesired 1,3 diol products. Separation of epoxide **15α** from alcohol **16**, followed by regioselective reduction of the former with $LiBH_4$ yielded diol **4**, in which the desired C_{18} stereochemistry had been installed. The epimeric diol **16** was conveniently transformed to **4** by a four step sequence which supports our stereochemical assignment at C_{18} in this series.[8] Selective protection of the primary alcohol, followed by oxidation at C_{18}, chelation-controlled reduction[9c] and deacylation afforded diol **4**. The combined sequences of Scheme 2 furnished the desired **4** in 66% overall yield from epoxides **15**.



In summary, we have completed a stereorational, linear synthesis of racemic **4**, comprising the fully-functionalized C_{11}-C_{21} subunit of the macbecin I ansa system. Intermediate **4** has been successfully

transformed to a known precursor of macbecin I, a conversion described in the accompanying communication. Our scheme leading to 4 demonstrates an iterative sigmatropic protocol which is direct and stereoselective, and we anticipate the straightforward extension of this general approach to syntheses of the ansa system of the herbimycins and structurally-related ansamycins. Finally, we note that intermediates (e.g. 14) resulting from the iterative [2,3] Wittig sequence represent versatile precursors from which a wide range of polyketide-derived natural products can be prepared, a potential which will be examined in future reports.

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