SYNTHETIC STUDIES OF THE NARGENICINS. 2. SYNTHESIS OF THE "NORTHERN HALF" OF NARGENICIN A_1[1]

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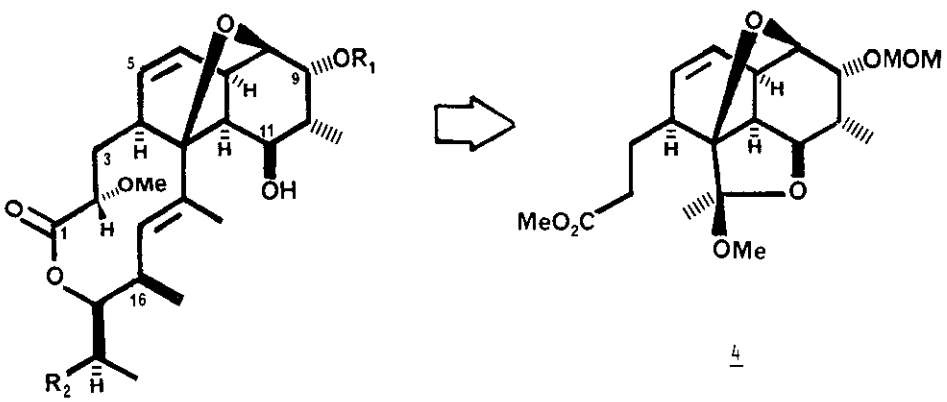
Abstract - The synthesis of intermediate 4, corresponding to the C_1-C_{14} fragment of the nargenicin macrolides, is described.

The nargenicins (1-3) constitute a new class of macrolide antibiotics recently isolated from fermentations of soil-dwelling microorganisms by workers at Pfizer[2] and Upjohn[3]. Current interest in these compounds stems from their pronounced activity against drug-resistant microbial strains[4], their novel biogenesis[5] and the formidable synthetic challenge presented by the unique connectivity and complex stereochemistry of these structurally fascinating decanolides. Recently we described an approach to the 11-oxatricyclo[4.4.$1^{1,6}$.$0^{2,7}$]undecene nucleus of the nargenicins.[1a] Herein we report the synthesis of tricyclic intermediate 4, representing the fully-functionalized "northern half" of nargenicin A_1 and its congeners.



4

1; R_1=  , R_2= OH, Nargenicin A_1

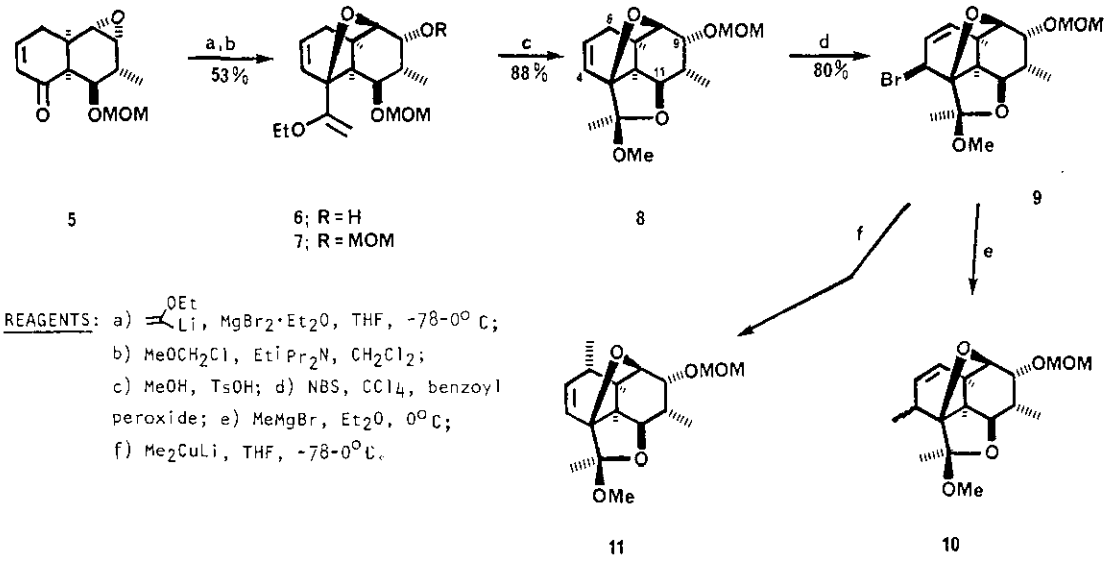
2; R_1= , R_2= H, 18-deoxy Nargenicin A_1

3; R_1= H, R_2= OH, Nodusmicin

Treatment of the previously reported enone 5[1] with ethoxyvinyl lithium at -78°C in the presence of $MgBr_2$-Et_2O resulted in the formation of an initial adduct, which upon warming to room temperature underwent intramolecular epoxide opening to give tricyclic 6[6]

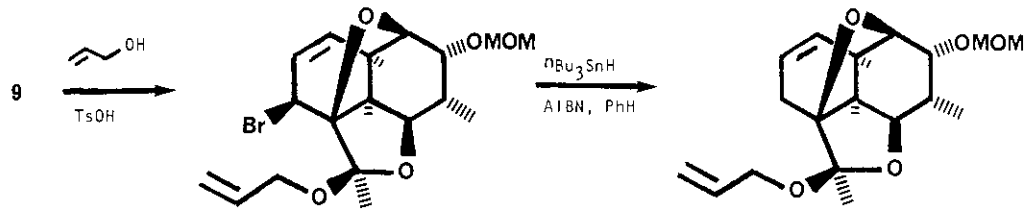
(Scheme I). Protection of the hydroxyl group followed by treatment with methanol and p-toluenesulfonic acid gave the tetracyclic ketal 8; selective cleavage of the C_{11} methoxymethyl ether in the latter transformation presumably involves participation of the enol ether (or the mixed ketal derived therefrom). Interestingly, ketal 8 is present as a single stereoisomer, as evidenced by ^1H and ^{13}C NMR. We have assigned the β-configuration to the methoxy substituent based on NOE studies of a subsequent intermediate (vide infra).

Scheme I



We next investigated strategies for introduction of a three-carbon subunit corresponding to the C_1-C_3 segment of the nargenicin macrolide system. Treatment of ketal 8 with N-bromosuccinamide resulted in allylic bromination with concurrent olefin migration[7] to give 9. Assignment of the β-configuration to bromide 9 is based on NOE experiments which show enhancement of the allylic C_4-H resonance upon irradiation of the C_8-H methine signal. Additionally, enhancement of the signal attributed to the C_{21} methyl group supports our assignment of the ketal stereochemistry. Attempts to introduce a C_4 substituent by coupling 9 with organometallic reagents were frustrated by a lack of regio- and stereochemical control. Thus, addition of lithium dimethyl cuprate to 9 resulted in S_n2' addition to give 11, while treatment with methyl Grignard reagent afforded a mixture of the epimeric adducts 10.

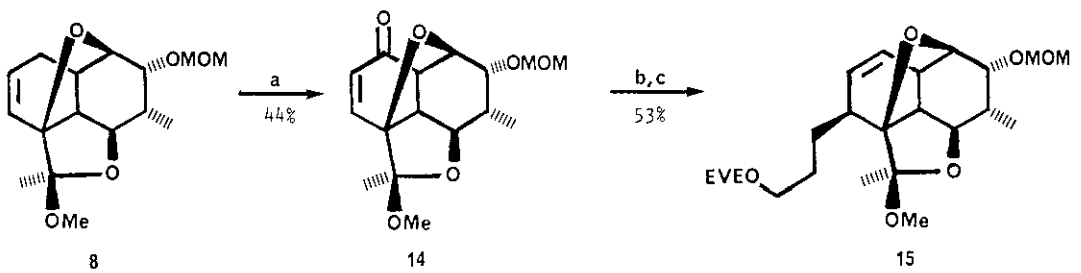
Scheme II



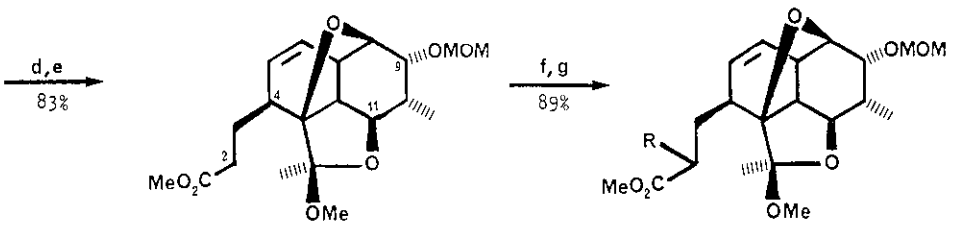
12 13

A recent report describing the synthesis of oxygen heterocycles via endo cyclization of sterically constrained 6-heptenyl radicals[8] led us to investigate this approach to introduction of the C_1-C_3 segment (Scheme II). Treatment of bromide 9 with allyl alcohol gave the mixed ketal 12; as in the case of ketal 8, a single stereoisomeric product was obtained. Unfortunately, all attempts to induce cyclization of this material via the allylic radical resulted in formation of olefin 13 corresponding to reductive dehalogenation of 12. Consequently, we turned our attention to alternative strategies for introduction of the three-carbon sidechain (Scheme III).

Scheme III



8 14 15



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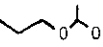
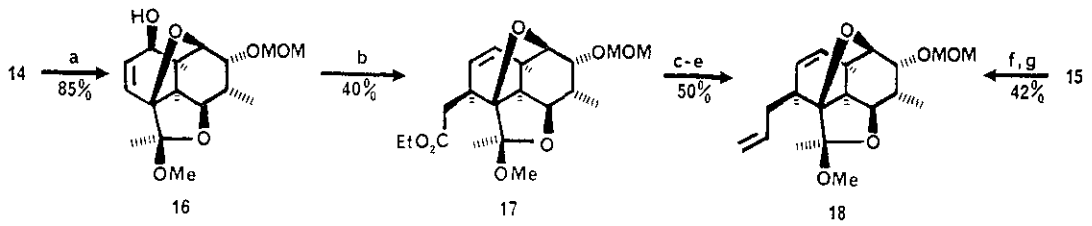
19, R = β-OMe
20; R = α-OMe

REAGENTS: a) CrO_3·3,5-dimethylpyrrazole, CH_2Cl_2, -20°C; b) LiCu(CN)  THF, -78°C, then $(NMe_2)_2POCl$; c) Li, NH_3, THF, tBuOH; d) Jones, -20°C, acetone-H_2O; e) CH_2N_2, Et_2O; f) LDA, MoOPH, THF, -78-0°C, g) KH, MeI.

Treatment of olefin 8 with excess chromium trioxide-3,5-dimethylpyrrazole complex[9] gave enone 14, with no evidence of allylic transposition. Introduction of the requisite three-carbon fragment[10] was then accomplished by cuprate addition to 14 followed by enolate trapping. Reduction[11] of the enol phosphoimidate afforded a single olefinic product, 15. The desired intermediate 4 was obtained by deprotection-oxidation and esterification with diazomethane.

An inspection of models suggests that cuprate addition to enone 14 will occur from the desired β-orientation, since the opposing face is effectively blocked by the ketal methyl substituent. Additionally, we reasoned that the oxa-bridge and/or the methoxy group might function as coordinating ligands, directing β-attack. That we had indeed established the correct stereochemistry of the C_1-C_3 fragment was confirmed by an alternative sequence for introduction of this substituent (Scheme IV). Reduction of enone 14 gave a single alcohol 16[12] which upon treatment with triethyl orthoacetate in refluxing xylene afforded Claisen product 17. Conversion of 17 to the aldehyde and Wittig methylenation furnished olefin 18, which was identical in all respects to a sample prepared from 15 by deprotection, mesylation and elimination.

Scheme IV



REAGENTS: a) $LiEt_3BH$, THF, -78°C; b) $(OEt)_3CCH_3$, TsOH, xylene, 140°C; c) $LiAlH_4$, Et_2O, 0°C; d) Collins, CH_2Cl_2; e) Ph_3PCH_2, THF, 0°-RT; f) HCl, THF-H_2O; g) MsCl, pyridine, then ^tBuOK, DMSO.

Finally, the C_2-methoxy substituent present in the nargenicins can be introduced in a nonstereoselective manner by enolate oxidation[13] of 4 and alkylation of the resulting α-hydroxy ester. Obtained was a 1:1 mixture of epimeric esters 19 and 20. A more efficient protocol for control of C_2 stereochemistry may prove to be via oxidation of a C_2-deoxy macrolide intermediate late in our synthetic plan. Efforts directed at conversion of the "northern half" intermediate 4 to the naturally occurring nargenicins are in progress and will be reported in due course.

ACKNOWLEDGEMENT

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6. All new compounds were characterized by IR, 500 MHz PMR, 90 MHz CMR and combustion analysis.
7. The regiochemistry of bromination was unambiguously determined by proton decoupling studies. In addition, the splitting patterns of the C_5 and C_6 olefinic protons are identical to those observed for authentic samples of the seco esters derived from nargenicin A_1 and nodusmicin.
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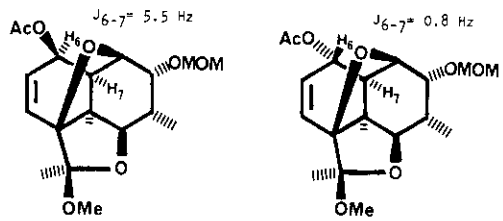
12. Our assignment of the β-configuration to alcohol 16 is based on the observed coupling constant (5.4 Hz) between H_6 and H_7. By contrast, the epimeric α-alcohol should exhibit minimal H_6-H_7 coupling since the relevant dihedral angle approaches 90° in models. Solvolysis of bromide 9 (AgOAc, benzene) affords a mixture of acetates i and ii; as expected, only a small (<1 Hz) H_6-H_7 coupling is observed for ii.



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