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SYNTHETIC STUDIES OF THE NARGENICINS: SYNTHESIS OF THE OXA-BRIDGED OCTALIN NUCLEUS

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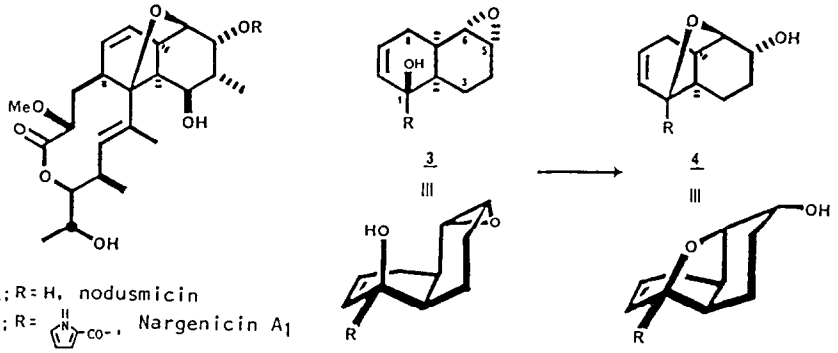
Summary: An efficient, stereocontrolled entry to the 11-oxatricyclo[4.4.1^{1,6}.0^{2,7}]undecene system of the nargenicin antibiotics is presented.

The nargenicin macrolides (1,2) are a group of structurally fascinating antibiotics recently isolated by workers at Pfizer[1] and Upjohn.[2] A characteristic feature of these compounds is the densely functionalized 11-oxatricyclo[4.4.1^{1,6}.0^{2,7}]undecene nucleus. Our interest in the nargenicins as synthetic targets has prompted the development of an efficient entry to this unique ring system. We now report the synthesis of oxa-bridged octalin 12 which incorporates the critical structural and stereochemical elements of the parent antibiotics.

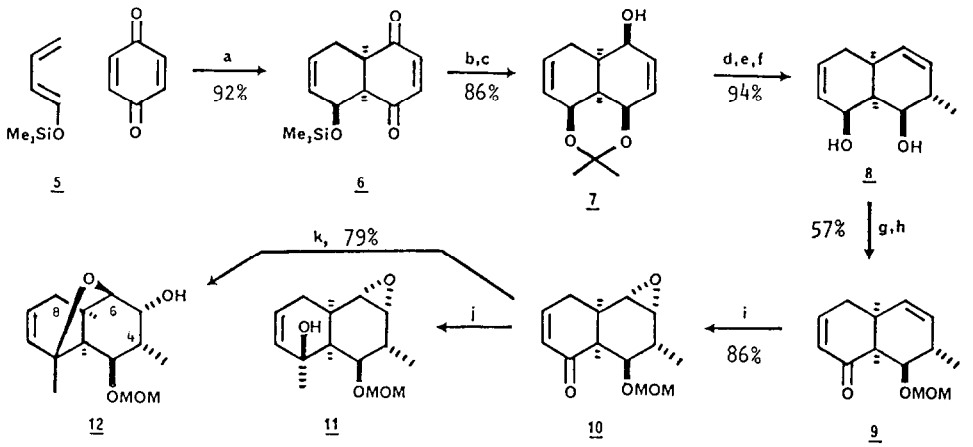


The key step in our synthetic plan is the nucleophilic opening of a C_5-C_6 epoxide (i.e., 3 → 4) to generate the ether bridge and the desired diaxial orientation of the C_5 and C_6 oxygen substituents. The oxa bridge spans two axial sites, and an examination of models suggests that tricyclic intermediate 4 is remarkably strain-free. Tertiary alcohol 3 could result from 1,2 addition of a carbon nucleophile to the corresponding enone, an event that would introduce a functionalized C_1 substituent. Thus our initial synthetic efforts have been directed at epoxide 10.

The required cis-fused decalin system is established by Diels-Alder reaction of benzoquinone with 1-trimethylsilyloxy-1,3-butadiene 5 to afford crystalline 6.[3] Differentiation of the enedione was accomplished by stereoselective reduction[4] and ketalization to give 7. Our plan next called for introduction of the C_4 methyl group with concurrent allylic reorgan-

ization, a transformation which proved unexpectedly difficult (Scheme 2). Oxidation of 7 to enone 13 and cuprate addition proceeded smoothly to give 14; however, tosylhydrazone formation and elimination[5] gave only the trans-fused olefin 15.[6] Alternatively, phosphoimidate 16 was obtained by trapping of the cuprate adduct; attempts to prepare the corresponding olefin by dissolving metal reduction[7] were frustrated by preferential cleavage of the allylic ketal. Reduction of ketone 14 afforded a mixture of epimeric C_6 alcohols, which upon mesylation and elimination yielded the undesired C_6-C_7 olefin 17.

Scheme 1

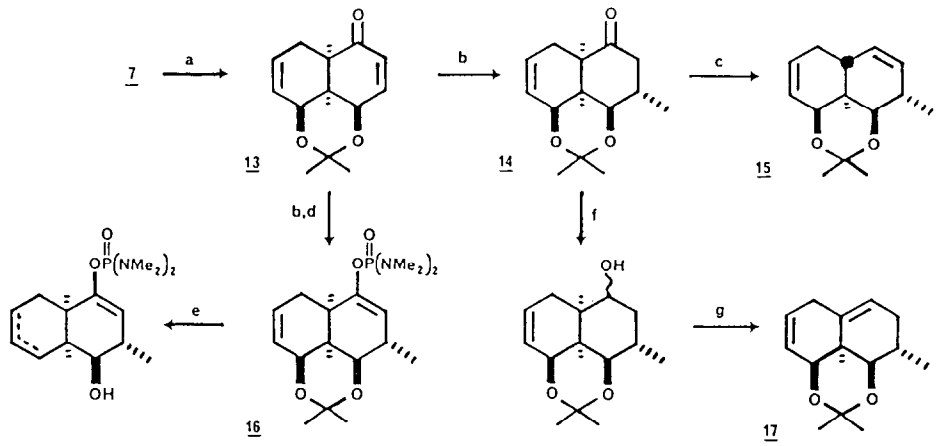


a) benzene, R.T.; b) DIBAL, 2.3 eq, 0°; c) $(CH_3)_2C(OMe)_2$, PPTS; d) nBuLi, MsCl, -78°; e) CH_3Cu-BF_3·Et_2O; f) 1 N HCl, THF; g) PDC; h) $EtN(iPr)_2$, MOMCl; i) MCPBA; j) MeLi; k) MeMgBr

We next investigated S_n2' strategies for introduction of the C_4 methyl substituent. As expected, acetylation of 7 followed by reaction with dimethyl cuprate resulted in S_n2 addition.[8] However, treatment of the corresponding mesylate with methyl copper-BF_3·Et_2O complex[9] followed by acidic workup gave the crystalline diol 8 in excellent yield.[10] Further elaboration of 8 by allylic oxidation, protection of the hydroxyl group and epoxidation afforded the desired 10.

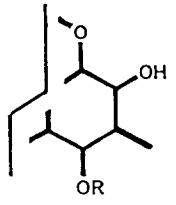
With epoxide 10 in hand we turned our attention to introduction of the C_1 substituent and formation of the ether bridge. Addition of MeLi or MeMgBr to 10 followed by low temperature quenching gives the expected alcohol 11. However, when the Grignard adduct is warmed to ambient temperature, a further reaction occurs to give a new product which contains a single, secondary hydroxyl group as evidenced by formation of the monobenzoate or oxidation to the ketone with PDC. A similar result is obtained from addition of $MgBr_2$·Et_2O to the MeLi adduct. The newly formed alcohol lacks NMR signals attributable to a C_5-C_6 epoxide, and we propose that the intermediate magnesium alkoxide participates in a Lewis acid assisted cyclization to give the oxa-bridged product 12.[3]

The structural and stereochemical assignments of 12 were confirmed by proton decoupling experiments. The C_4 proton is identified by irradiation of the multiplet of 2.30 ppm, which collapses the methyl doublet at 1.07 ppm to a singlet and the signals at 3.83 ppm and 3.54

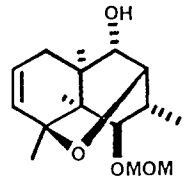


a) PDC; b) $LiCuMe_2$; c) H_2N-NHTs, then MeLi (2.5 eq); d) $ClPO(NMe_2)_2$; e) Na, NH_3, tBuOH; f) $LiAlH_4$; g) MsCl, DBU.

ppm to doublets of 5.3 and 3 Hz. Benzoylation of 12 results in a downfield shift of the 3.83 ppm triplet to 5.22 ppm, implicating this resonance as the hydroxyl methine; on irradiation at 3.83 δ, the 4.04 ppm signal becomes a singlet, placing the hydroxyl group adjacent to an oxygen-bearing carbon. Finally, irradiation at 3.54 ppm results in collapse of the doublet at 2.23 ppm. These studies establish the fragment A and preclude the alternative product of epoxide opening 18. The large (11.5 Hz) coupling constant between H_3 and H_4 is in agreement with that reported for nargenicin A_1,[1a] and confirms a diaxial relationship between these protons, placing both the MOM-protected C_3 hydroxyl and the C_4 methyl group in equatorial orientations. The values for the remaining coupling constants are in good agreement with the proposed structure. Of note is the absence of significant coupling between H_6-H_7 and H_2-H_7; models of 12 indicate that the dihedral angle approaches 90° for each of these pairs.



A



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The synthetic scheme described above rapidly establishes the novel functional and stereochemical elements of the nargenicin octalin system. This approach readily accommodates introduction of a functionalized C_1 substituent, corresponding to the macrolide sidechain, by appropriate choice of Grignard reagent in the addition to enone 10. Application of this strategy to the synthesis of the nargenicin antibiotics is in progress.

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3. All new compounds have been characterized by ^{1}H and ^{13}C NMR, IR, mass spec and TLC. Satisfactory combustion analyses have been obtained for compounds 6, 7, 8, and 12. Physical and spectral data for key intermediates: 7: amor. solid (mp. 74.5-76); IR (KBr): 3500 cm^{-1}; ^{1}H NMR (360 MHz, $CDCl_3$, δ): 5.99 (m, 1H), 5.86 (m, 1H) 5.80 (m, 1H), 5.74 (m, 1H), 4.49 (m, 1H), 4.38 (bd, 1H), 4.07 (m, 1H), 2.66 (bs, 1H), 2.50 (m, 1H), 2.11 (m, 3H), 1.44 (s, 3H), 1.34 (s, 3H); ^{13}C NMR: (90 MHz, $CDCl_3$, ppm) 134.6 (d), 133.0 (d), 130.8 (d), 129.3 (d), 103.7 (s), 70.4 (d), 67.4 (d), 65.6 (d), 36.8 (d), 36.7 (d), 31.2 (q), 27.2 (q), 25.7 (t). 8: needles (m.p. 131-132); IR (KBr): 3500 cm^{-1}; ^{1}H NMR (360 MHz, $CDCl_3$, δ): 5.83 (m, 2H), 5.65 (m, 2H), 4.54 (bs, 1H), 4.07 (t, 1H, J = 3.5 Hz), 2.50-2.41 (m, 2H), 2.27-2.12 (m, 3H), 1.93 (bs, 1H, OH), 1.09 (d, 3H, J = 7.5 Hz). 10: oil; IR (plate): 1675 cm^{-1}; ^{1}H NMR (360 MHz, $CDCl_3$, δ): 7.04 (m, 1H), 6.11 (dd, 1H, J = 8, 1.5 Hz), 4.46 (AB q, 2H), 3.62 (bs, 1H), 3.35-3.18 (m, 2H), 3.23 (s, 3H), 2.90-2.73 (m, 2H), 2.49-2.35 (m, 3H), 1.15 (d, 3H, J = 7.5 Hz). 12: oil; IR (plate): 3500, ^{1}H NMR (360 MHz, $CDCl_3$, δ): 5.80 (m, 1H), 5.63 (m, 1H), 4.70 (AB q, 2H), 4.04 (d, 1H, J = 5.3 Hz), 3.83 (t, 1H, J = 5.3 Hz), 3.54 (dd, 1H, J = 11.5, 3 Hz), 3.40 (s, 3H), 2.61-2.51 (m, 2H), 2.33-2.26 (m, 2H), 2.23 (d, 1H, 3 Hz), 1.52 (s, 3H), 1.07 (d, 3H, 6.8 Hz); ^{13}C NMR (90 MHz, $CDCl_3$, ppm): 141.3, 129.8, 97.9, 86.9, 84.1, 81.7, 74.9, 57.6, 48.2, 39.2, 37.0, 35.3, 23.5, 15.2.

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6. An authentic sample of trans-fused 15 was prepared by epimerization of 14 (NaOMe, MeOH), followed by tosylhydrazone elimination.

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10. Attempts to isolate pure samples of the ketal of diol 8 were unsuccessful and resulted in hydrolysis and/or decomposition. An examination of models suggests that the isopropylidene system will exist in a twist chair conformation, accounting for the sensitivity of the ketal to hydrolytic conditions. Diol 8 shows spectral and chromatographic properties similar to but distinct from the trans diol prepared by deketalization of 15.

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