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Synthetic Studies Relating to the C1-C9 "Eastern" Half of Rosaramicin[1]

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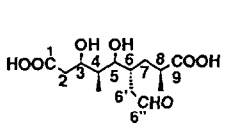
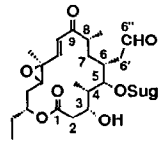
Summary: A pyranodisic homologation approach to the "eastern half" of rosaramicin is described. The synthetic plan calls for two one-carbon chain extensions, but these occur at "off-template" sites where asymmetric centers are neither destroyed nor created. However, these one-carbon displacements pose special unexpected difficulties and procedures for overcoming these are described.

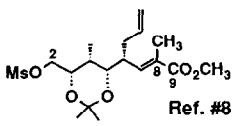
Rosaramicin, **1**,[2] is a sixteen-membered macrolide antibiotic whose structure is reminiscent of tylosin,[3] leucomycin,[4] and carbomycin.[5] An elegant synthesis of (+) rosaramicin was described very recently by Schlessinger[6] and earlier, a novel route to the (±)-3-deoxy analogue using the macrolactone approach was achieved by Still and Novack, which showed that many of the substituents could be introduced stereoselectivity upon the macrolactone.[7] Challenger and Proctor have recently reported the synthesis of compound **2**, which contains eight of the nine carbons, and four of the five chiral centers of the "eastern half", **3**, of rosaramicin.[8] The latter achievement prompts us to report our own results relating to the synthesis of **2**.



3

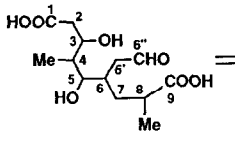


1

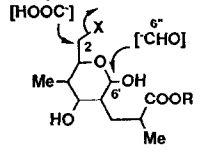


2

Scheme 1



3'



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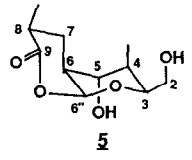

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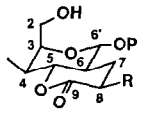
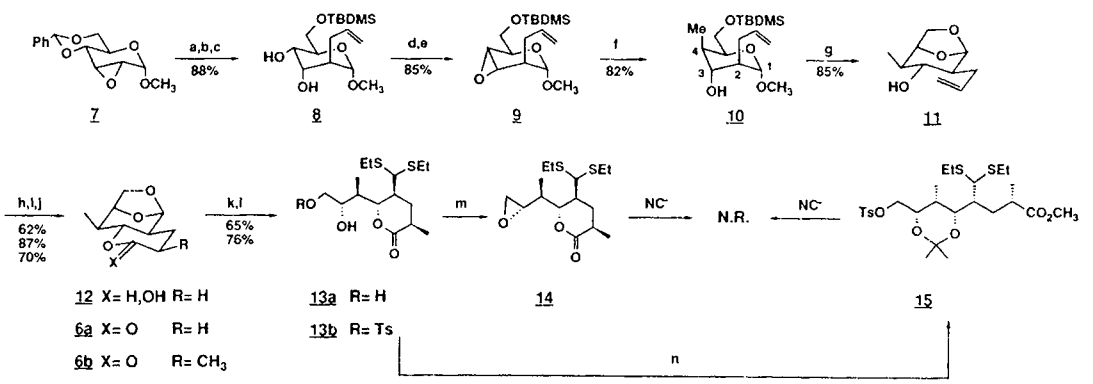


6a R=H
6b R=Me

The four contiguous chiral centers of **3** could obviously be developed by "on-template" manipulations of an appropriate hexopyranose precursor.[9] However, the remote, isolated C8 stereocenter posed a challenge for (a) stereocontrolled creation, and (b) ready verification of configuration, and it seemed that this problem could be solved by the pyranosidic homologation technique described by us recently.[10] Thus, if the array, **3**, is folded into **3'**, as shown in Scheme 1, the pyranose **4** is seen to result. Notably, the two one-carbon additions at C2 and C6' occur at "off-template" sites where no asymmetry is involved. Two options are now available for further folding of **4**, leading to the lactones **5** and **6b**, both of which are shown with the C8-CH_3 in the preferred equatorial orientations. However, on conformational grounds, **6b** is clearly the more attractive chiron[9] and accordingly, our synthetic efforts were directed toward that target.

Scheme 2

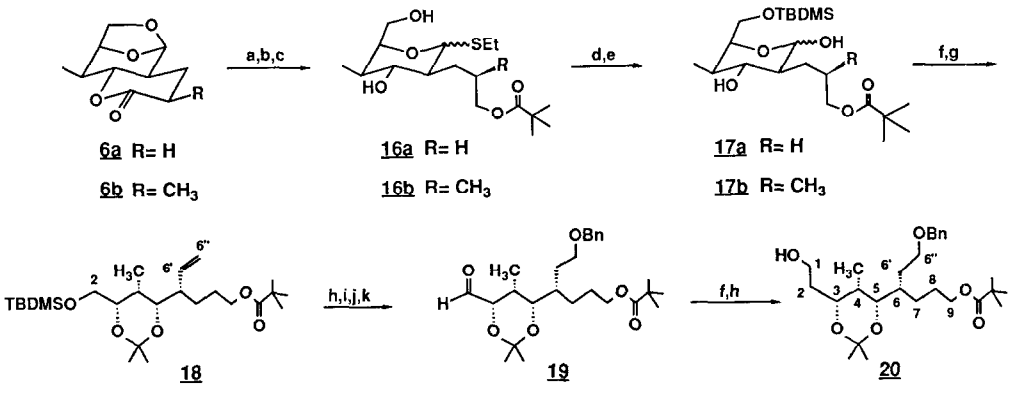


a) allyl magnesium chloride, THF. b) CSA, CH_3OH. c) t-BDMSCl (1.1 eq.). d) phosgene iminium chloride (2 eq.). e) CH_3Li see ref. 14. f) CH_3Li/CH_3MgCl, toluene, 100°C. g) H_2SO_4, THF:H_2O, 25°C. h) $PdCl_2/CuCl_2/O_2$, DMF:H_2O, 25°C. i) PDC, Ac_2O, CH_2Cl_2. j) LDA, CH_3I, THF-HMPA. k) EtSH, $BF_3 \cdot Et_2O$. l) p-TsCl, NEt_3, CH_2Cl_2. m) KCN, 18-crown-6. n) CH_3OH, PPTS, 2,2-dimethoxypropane, CH_2Cl_2, reflux, 3 h.

Allyl magnesium chloride reacted with the well known epoxide **7**,[11] and the product[12] was processed to give the diol **8**. The required configuration for the C4-CH_3 could be ensured by

use of the altro epoxide **9**[13] and this was obtained from **8** by means of our recently described procedure.[14] Epoxide **9** then reacted smoothly with dimethyl magnesium[15] to give the idopyranoside **10**, which, from the values $J_{1,2}$=1Hz and $J_{3,4}$=2 Hz, exists >90% in the $^4C_1$ conformation shown. Acid hydrolysis of **10** led to 1,6-anhydro sugar **11**, which underwent intramolecular oxy-palladation to give the lactol **12**. Lactone **6a** was then readily obtained and α-alkylation afforded the target **6b**, contaminated with approximately 10% of the axial C8 epimer.

Scheme 3



a) $LiAlH_4$, Et_20 (91% for 6a, 89% for 6b). b) pivaloyl chloride, pyridine (88% for 6a, 91% for 6b). c) EtSH, BF_3 • Et_20 (60% for 6a, 65% for 6b). d) t-BDMSCl, imidazole (92% for 6a and 6b). e) $HgCl_2$, $CaCO_3$, 4:1 CH_3CN:H_20 (90% for 16a, 91% for 16b). f) Ph_3PCH_2, THF (58% for 17a, 47% for 17b). g) 2,2-dimethoxypropane, PPTS (95%). h) 1. BH_3 • THF; 2. 3N NaOH, 30% H_2O_2, (65% for 18, 69% for 20). i) NaH, n-Bu_4NI, BnBr, DMF (72%). j) n-Bu_4NF, THF (90%). k) 1. Oxalyl chloride, DMSO, CH_2Cl_2; 2. NEt_3 (79%).

The pyranoside ring was opened by mercaptolysis, and selective sulfonation of the major product, **13a**, afforded the tosylate **13b** and thence the epoxide **14**. Surprisingly, the latter proved completely resistant to reaction with potassium or sodium cyanide under a variety of conditions. Similar resistance was observed with the linear equivalent **15**, obtained in one step

by reaction of **13b** with dimethoxy propane under acid catalysis. Application of forcing conditions to either **14** or **15** caused destruction of the molecule. Displacements of **14** or **15** also failed with other one-carbon nucleophiles, including Et_2AlCN, 2-lithiodithiane and $LiC(SEt)_3$.

The seemingly trivial procedure for installing the C1 carboxyl equivalent therefore emerged as a major obstacle, and it became clear that introduction of the one-carbon units at C2 and C6' should not rely on nucleophilic displacement reactions.

Our exploratory studies were based on the more accessible des-methyl analogue **6a** (Scheme 3). Interestingly, mercaptolysis stopped at the thioglycoside stage **16a**, instead of yielding a dithioacetal e.g., **13a**. The hemiacetal **17a** obtained therefrom was subjected to the Wittig methylenation, which led to the protected alkene **18**, having the C6" carbon in place. A similar sequence on the aldehyde **19** served to introduce the C1 carbon as a precursor for compound **20**.

Since Still and Novack[7] have shown that C8-CH_3 can be introduced after macrolactonization, compound **20** is a plausible intermediate for the "eastern" half. However, we have processed the lactone **6b** to give the key intermediate **17b**, and found that the C8-CH_3 has remained unaffected.

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