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STUDIES DIRECTED TOWARD THE TOTAL SYNTHESIS OF THE RUBRADIRIN ANTIBIOTICS. 5. A CONVENIENT PREPARATION OF FUNCTIONALIZED ISOPRENE UNITS FOR THE DIELS-ALDER REACTION

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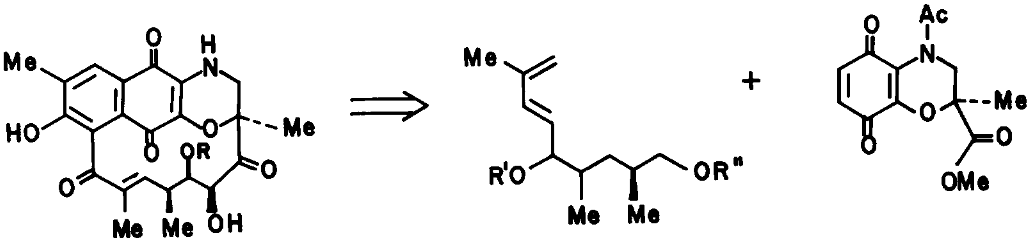
Summary: A simple procedure has been developed for the synthesis of functionalized isoprene units for use in the assembly of the rubradirin antibiotics.

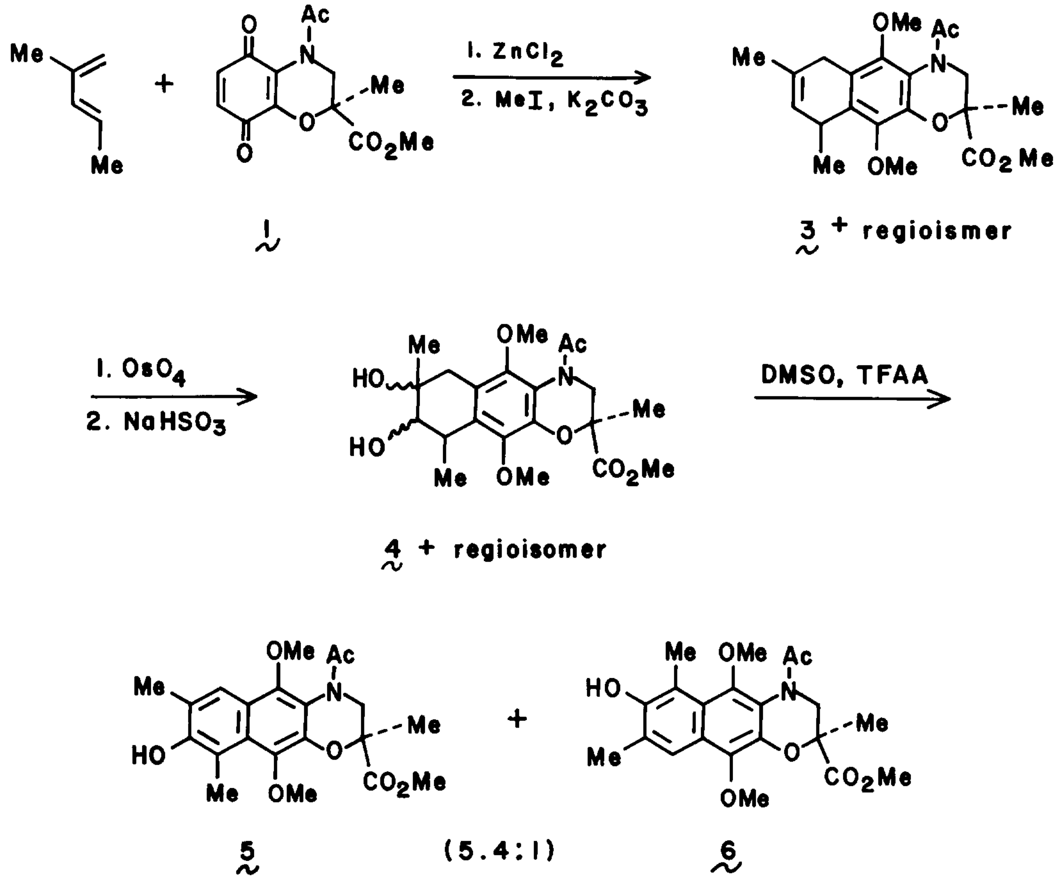
In continuation of our rubradirin efforts, we were rather intrigued with the possibility of designing a diene component which might allow us to introduce a major portion of the ansa chain during the Diels-Alder cycloaddition step.[1] This notion, displayed below in its retrosynthetic format, required that (a) we be able to process the primary cycloadduct in some way such that the A-ring is made aromatic with the simultaneous introduction of the C-10 hydroxyl group, and that (b) we develop a simple and efficient way of preparing 4-methyl-2,4-pentadienols related to 2.

Scheme 1.

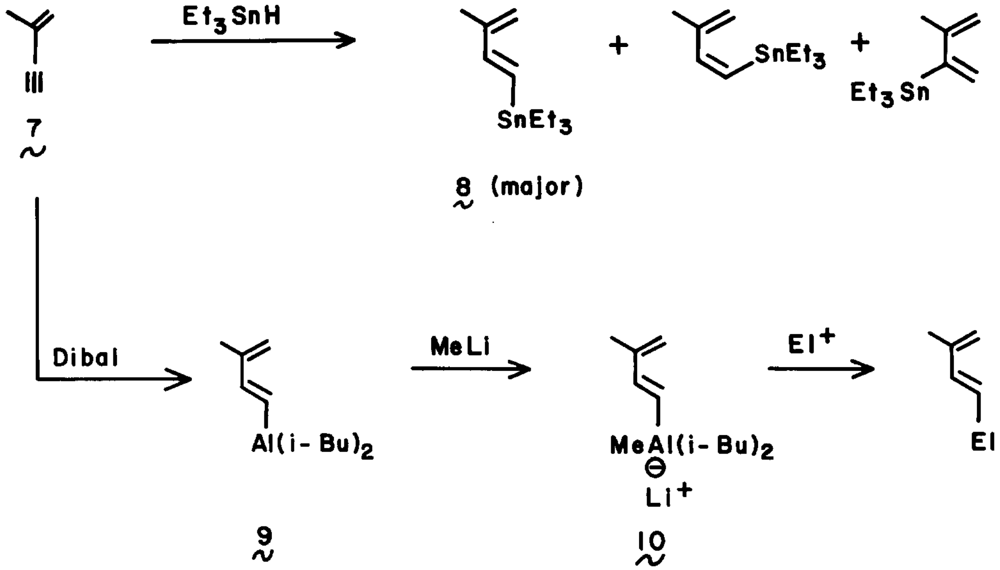


2 1

With regard to the first point, we discovered that the Diels-Alder product mixture prepared from the zinc chloride catalyzed reaction of quinone 1 with trans-2-methyl-1,3-pentadiene could be converted easily to the methylated hydroquinone derivatives 3 by the action of methyl iodide and potassium carbonate. The trisubstituted double bond of 3 was then osmylated and the diols 4 formed on bisulfite workup (64% yield overall after column chromatography) oxidized with TFAA/DMSO to yield a 5.4:1 mixture of 5 and 6. Assignments of regiochemistry to these tricyclics were made through the derived 10-methoxyquinones[2] by comparison of the chemical shift of the A-ring proton with that observed for related products whose structures had been securely established by X-ray analysis.[3] The spectral data for the major product is as follows: ^{1}H NMR ($CDCl_3$, 300 MHz), 7.69 (s, 1 H), 5.36 (br s, 1 H), 5.32 (d, 1 H, *J* = 13 Hz), 3.86 (s, 3 H), 3.69 (s, 3 H), 3.66 (s, 3 H), 2.89 (d, 1 H, *J* = 13 Hz), 2.75 (s, 3 H), 2.39 (s, 3 H), 2.10 (s, 3 H), 1.72 (s, 3 H); mass spectrum (70 eV) m/e = 403 (M^+), 346.



To successfully execute the strategy presented in Scheme 1, we now needed to address the second and major point of this paper, the discovery of an efficient process for preparing 4-methyl-2,4-pentadienols. After some consideration, we realized that hydrometallation of the readily available compound, 2-methyl-1-buten-3-yne,[4] should provide a suitable metalloisoprene which on reaction with various electrophiles might give rise to the requisite diene products. While the hydrostannylation of 7 has been reported,[5] the acquisition of the correct regio- and stereoisomer in pure form proved rather troublesome. Fortunately, the hydroalumination of 7 proceeded exceptionally well, and the desired dienylalane 9 or dienylalanate 10 could be trapped efficiently with electrophiles of both the RX and RCHO type.[6] Paraformaldehyde, hexanal, 3-cyclohexene-1-carboxaldehyde,



benzaldehyde and MEM chloride all reacted to provide the corresponding isoprenoid dienes in modest to good yield. Cyclohexanone, on the other hand, failed to trap the dienylalanate **10**, a result which is presumably due to proton transfer in lieu of addition.

We believe that the chemistry presented herein does offer one of the simplest schemes available for the construction of functionalized isoprene units, products which should serve as useful Diels-Alder dienes.[7]

Table. Preparation of Functionalized Isoprene Units

Electrophile	Aluminum Reagent	Mole Ratio **9** or **10**/substrate	Yield (%)
paraformaldehyde	**10**	1.7	42
hexanal	**10**	1.7	63
3-cyclohexene-1-carboxaldehyde	**10**	2	76
benzaldehyde	**10**	2	66
cyclohexanone	**10**	2	complex mixture
MEM chloride	**9**	2	72
MEM chloride	**10**	2	30

An exemplary procedure follows: To a solution of 0.2 mmol of 2-methyl-1-buten-3-yne in 1 ml of hexanes cooled to 0°C was added dropwise 0.2 mmol of diisobutylaluminum hydride (20% solution in hexane). The reaction mixture was stirred at room temperature for 30 min, heated at 50°C for 2 h, and then cooled to -30°C. Ethyl ether (4 ml) and 0.2 mmol of MeLi (1.3 M in ether) were added and after 30 min, 0.1 mmol of benzaldehyde was added dropwise. After 1 h at -25°∿

-30°C, the reaction mixture was kept at room temperature for 14 h. The mixture was then quenched with ice and 6 *N* NaOH at 0°C.[8] The mixture was filtered, and extracted with ether. The ethereal extracts were washed with saturated sodium chloride, dried ($MgSO_4$) and concentrated. The residue was chromatographed on silica gel using ethyl acetate-hexanes as eluent to yield 113 mg of the alcohol (66%): IR (thin film) 3350, 1610 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) 7.67-7.03 (m, 5 H), 6.42 (d, 1 H, *J* = 16 Hz), 5.82 (dd, 1 H, *J* = 16, 6.5 Hz), 5.24 (d, 2 H, *J* = 6.5 Hz), 5.00 (s, 2 H), 2.10 (br s, 1 H), 1.83 (s, 3 H); mass spectrum (70 eV) m/e = 174 (M^+).

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References and Notes

1. For part 4 in this series, see: A. P. Kozikowski, K. Sugiyama and E. Huie, *Tetrahedron Lett.*, **22**, 3381 (1981).
2. These were prepared by *O*-methylation of the mixture of **5** and **6** with Me_2SO_4/K_2CO_3 in diethyl ketone followed by oxidation with bromine in acetic acid.
3. A. P. Kozikowski, K. Sugiyama, and J. P. Springer, *J. Org. Chem.*, **46**, 2426, (1981).
4. This product, purchased from the Aldrich Company, was distilled prior to use.
5. E. N. Mal'tseva, V. S. Zavgorodnii, and A. A. Petrov, *Zh. Obshch. Khim.*, **39**, 152 (1969).
6. The vinylalanate prepared from 1-ethynylcyclohexene by hydroalumination and butyllithium treatment has been reacted with cyanogen to give the *trans*-dienenitrile in 64% yield. G. Zweifel, J. T. Snow and C. C. Whitney, *J. Am. Chem. Soc.*, **90**, 7139 (1968).
7. All new products gave satisfactory IR, ^1H NMR and mass spectral analysis.
8. For the reactions in which paraformaldehyde, hexanal and 3-cyclohexene-1-carboxaldehyde served as electrophiles ice and concentrated HCl were used in the workup procedure.

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