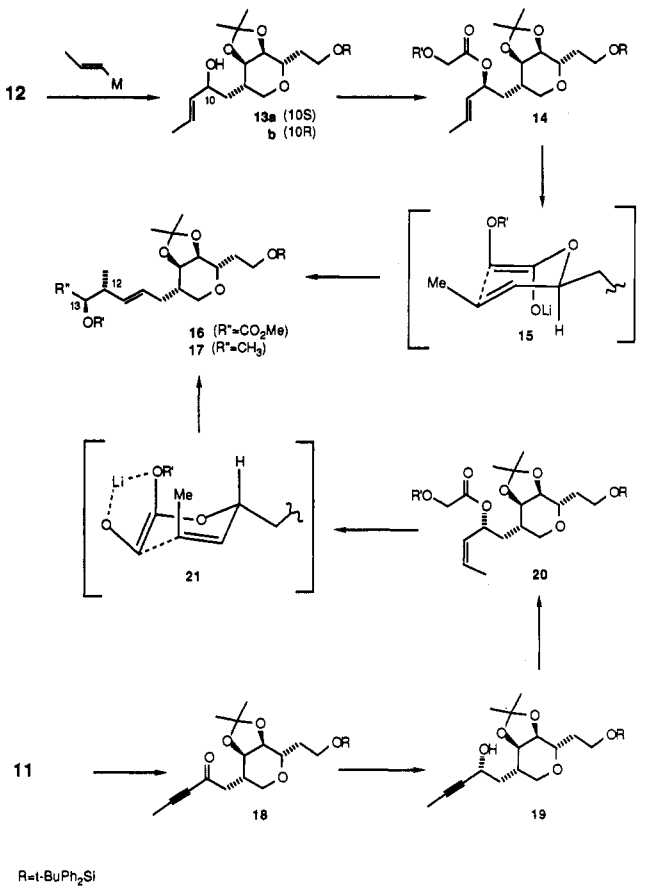
Scheme III



25 °C; 75%) then gave the natural product **1c**, $[\alpha]^{25}_D$ +7.64 (*c* 0.78, $CHCl_3$), which exhibited the expected biological activity.

In summary, we have developed a new stereospecific approach to the *C*-pyranoside nucleus found in the pseudomonic acids, along with a modification of the glycolate ester enolate Claisen rearrangement, both of which should find further application in natural product synthesis.

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Supplementary Material Available: ^1H and ^{13}C NMR data of key compounds (3 pages). Ordering information is given on any current masthead page.

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Synthetic Studies of the Rubradirins: A Strategy for the Incorporation of the Ansa Bridge

Summary: An intramolecular Wadsworth-Emmons cyclization strategy is described for the construction of a rubradirin-related model system.

Sir: Rubradirin, an ansamycin isolated in 1964 from *Streptomyces achromogenes* var. *rubradiris* by workers at the Upjohn Company,[1] is a potent inhibitor of polypeptide biosynthesis[2] and its aglycone a potent inhibitor of RNA polymerase.[3] Two biologically less active congeners, rubradirins B and C, have also been isolated from this *Streptomyces* strain.[4] In continuation of our synthetic studies of these molecules,[5] we describe herein a model study which has led to the construction of a heptasubstituted naphthalene derivative containing an aliphatic ansa bridge bereft of most of the functionality but of the same size as that found in rubradirin (Chart I).

In this effort we planned to react 2,3-dichloro-*p*-benzoquinone (**2**) with the trisubstituted diene **1** (Scheme I). After appropriate manipulation of the oxidation state of the Diels-Alder cycloadduct, a regioselective Michael addition-elimination reaction was planned using methyl *N*-methyl-β-aminopropionate as the nucleophile. We assumed that the mesomeric effect of the methoxy group would guide the entry of the amine as depicted.[5e,6] Last, reduction of the quinone, O-methylation, and conversion of the ester to a β-keto phosphonate derivative was envisioned to provide the bridged naphthalene derivative through use of an intramolecular Wadsworth-Emmons condensation reaction.[7]

The required diene **1** was prepared from 7,7-dimethoxyheptanal (**7**)[8] by reaction with isopropenylmagnesium bromide followed by acetal exchange using ethylene glycol (Scheme II). The intermediate alcohol was oxidized by the Swern procedure, and the resulting enone was treated with LDA and Me_3SiCl to provide **1**. Next, a Diels-Alder reaction of **1** with 2 equiv of 2,3-dichloro-*p*-benzoquinone[9] provided the new quinone **9**. This quinone was treated with NBS to yield an α-bromo ketone,[10] which was stirred in turn with K_2CO_3 and MeI to yield the 6-methoxynaphthoquinone **3**. Reaction of **3** with methyl *N*-methyl-β-aminopropionate[11] proceeded smoothly in

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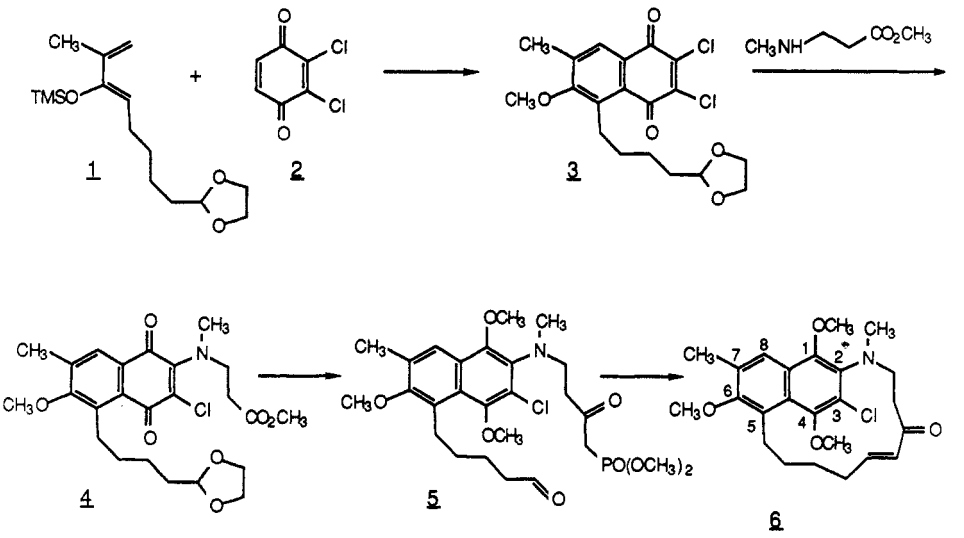
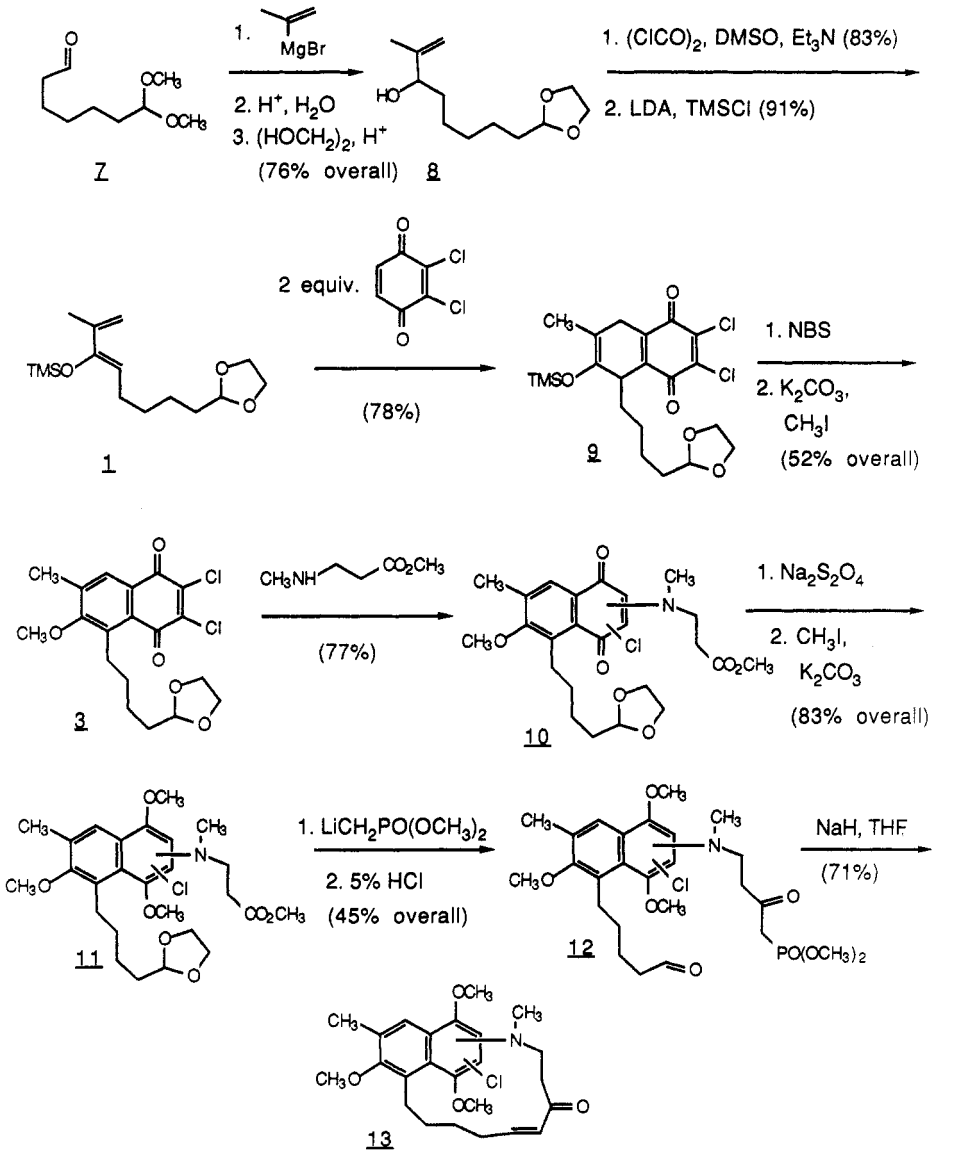
Scheme I. The Synthetic Strategy

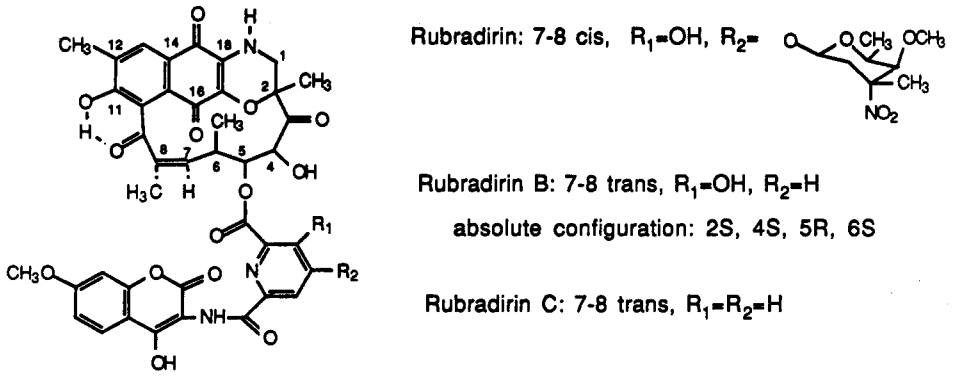


Scheme II. Synthesis of an Undesired Regioisomer

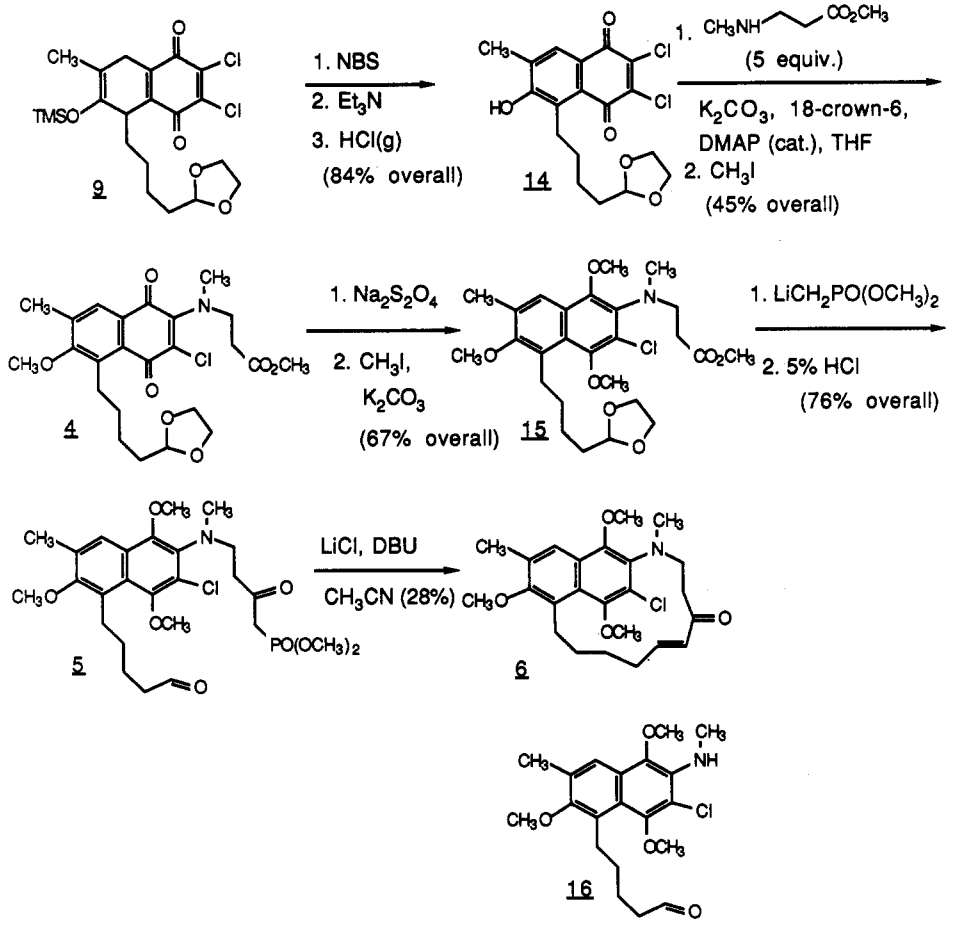


methylene chloride at room temperature to provide a single aminoquinone. Operating under the assumption that the correct regioisomer had been produced in the addition–elimination reaction, a point which we intended to check after carrying out the Wadsworth–Emmons cyclization reaction, **10** was reduced and methylated to give **11**. Ad-

Chart I



Scheme III. Synthesis of the Desired Ansamycin Model



dition of the lithium salt of dimethyl methylphosphonate[12] to **11** and acid-catalyzed cleavage of the ethylene acetal provided the cyclization precursor **12**. This intermediate was reacted with sodium hydride in THF at room temperature under high dilution conditions to furnish a crystalline solid, **13**, in 71% yield.

While the ^{1}H NMR spectrum of **13** indicated *E*-olefin stereochemistry, an X-ray analysis was deemed essential to establishing the regiochemical course of the Michael reaction. Surprisingly, this analysis showed that the undesired regioisomer had formed in the addition–elimination step. Furthermore, it was apparent from the X-ray structure that the methoxy group at the 6-position of **13** is twisted such that the CH_3–O bond is approximately perpendicular to the plane of the aromatic rings, hence inhibiting electron release by the oxygen lone pairs (steric inhibition of resonance).[13] By analogy the mesomeric effect of the methoxy group of **3** is lost, and therefore the hyperconjugative effect of the alkyl groups guide the regiochemistry of the amine addition reaction.

While several options for correcting this problem could be envisioned, the simplest solution appeared to require that one only remove the methyl group from the oxygen substituent at C-6. A phenoxide anion would be free of steric interactions, and it could moreover serve as a stronger resonance donor.

Quinone **9** was treated sequentially with NBS and triethylamine to provide **14** (Scheme III). On reaction of **14** with methyl *N*-methyl-β-aminopropionate at room

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temperature two regioisomeric products could be isolated in a 1.6:1 ratio. Upon O-methylation and spectral comparison with **10**, the major isomer was found to be of incorrect regiochemistry. After a number of additional experiments we have found that reaction of **14** with 5 molar equiv of the amine in the presence of potassium carbonate, 18-crown-6, and a catalytic amount of DMAP followed by O-methylation provides solely the desired regioisomer in 45% yield. The new quinone **4** was treated in the same way as described for **10** in Scheme II to furnish the desired cyclization precursor **5**. This phosphonate could be cyclized to **6** in at best 28% yield on employing the Wadsworth–Emmons reaction conditions described by Masamune and Roush.[14] Formation of small amounts of dimer is observed along with the β-elimination product **16**. Since in the synthesis of rubradirin itself, the center α to the carbonyl group will contain no hydrogen atoms, such a β-elimination process will be precluded, and therefore higher yields of the bridged product may be expected. The lower yield observed in the cyclization reaction of **5** compared to that found for the cyclization of **12** is expected in light of the more severe transannular interactions and bond angle distortions which must develop in the transition state for ring closure.[15]

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Supplementary Material Available: Spectral data for compounds **1**, **3**, **4**, **6**, and **8–16** and X-ray analysis of **13** (19 pages). Ordering information is given on any current masthead page.

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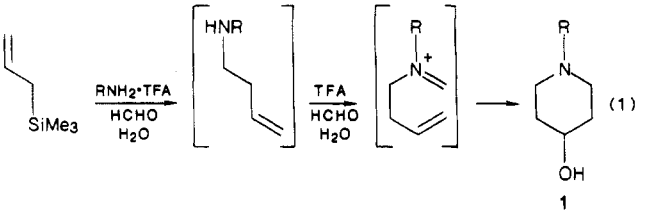
Reactions of Allylstannanes with in Situ Generated Immonium Salts in Protic Solvent: A Facile Aminomethano Destannylation Process

Summary: In situ generated immonium salts derived from primary amines and formaldehyde upon exposure to allylstannanes in protic media undergo rapid, facile aminomethano destannylation, giving rise to bishomoallylamines with no evidence of piperidine formation.

Sir: In a previous study[1] we observed that in situ generated immonium salts derived from primary amines upon exposure to allyltrimethylsilane in water undergo an aminomethano desilylation–cyclization process leading to N-substituted piperidines (cf. eq 1). Use of secondary



(1)

1

amines leads only to products of aminomethano desilylation (cf. eq 2). For example addition of 1.1 equiv of

$$C_6H_5CH_2NHMe\cdot TFA \xrightarrow[Me_3SiCH_2CH=CH_2]{HCHO,\ H_2O} \underset{50\ °C,\ 68\ h}{} C_6H_5CH_2N(Me)CH_2CH_2CH=CH_2 \quad (2)$$

2

allyltrimethylsilane to a 3.0 M solution of *N*-benzyl-*N*-methylammonium trifluoroacetate in water containing 2.3 equiv of 37% aqueous formaldehyde gives rise after 68 h at 50 °C to a 76% yield of tertiary amine **2** (eq 2). In our preliminary survey[1] on the reaction of a number of allylsilanes with immonium ions, we found, in general, that whereas yields ranged from good to excellent, *reaction times were extremely long.* In order to improve upon this process we set out to examine the reaction of allylstannanes with immonium ions. We detail below the results of this investigation.

The high reactivity and regiospecificity associated with the chemistry of allylstannanes,[2] which has been attributed to extensive interaction between the σ_{C-Sn} and π orbitals,[3] and the fact that the allylstannane double bond is more nucleophilic than an allylsilane double bond,[3] led us to investigate the reaction of in situ generated immonium ions with allylstannanes. In a preliminary experiment, a 0.27 M solution of *N*-benzylammonium trifluoroacetate in a 1:1 mixture of methanol and chloroform at ambient temperature was treated with 2.1 equiv of 37% aqueous formaldehyde and 2.0 equiv of allyltri-*n*-butylstannane. After 4 h the homogeneous reaction mixture was quenched with 5% hydrochloric acid solution and was washed with hexane–ether (4:1). Neutralization of the aqueous phase with base provided a 97% yield of *N*-benzyl-*N*,*N*-bishomoallylamine (**3**) (cf equation 3). No trace of piperidine **1** (R = benzyl) could be detected.

$$C_6H_5CH_2NH_2\cdot TFA \xrightarrow[Bu_3SnCH_2CH=CH_2]{HCHO} \underset{4\ h}{\underset{MeOH-CHCl_3}{}} C_6H_5CH_2N(CH_2CH_2CH=CH_2)_2 \quad (3)$$

3

Also examined, under identical conditions, was the reaction of *N*-methyl-*N*-benzylammonium trifluoroacetate with formaldehyde and allyltributylstannane which provided after 2 h a quantitative yield of tertiary amine **2** (eq 4).[4] It is of interest to note that whereas the reaction of

$$C_6H_5CH_2NHMe\cdot TFA \xrightarrow[Bu_3SnCH_2CH=CH_2]{HCHO} \underset{2\ h}{\underset{MeOH-CHCl_3}{}} C_6H_5CH_2N(Me)CH_2CH_2CH=CH_2 \quad (4)$$

2

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