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SPECIAL FEATURE: ARTICLE

Glycosylation of an allenic erythronolide

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Abstract

A concise route to a glycosylated allenic erythronolide was achieved. Key findings include the preparation of a desosamine sulfoxide donor and the use of the donor to glycosylate bulky acceptors. Additionally, the new reagent was used to prepare allene-containing macrocycles and to realize a four-step synthesis of macrolide **6** from bis[allene] **5**. The longest linear sequence required to prepare **6** from commercial reagents was 15 steps.

Introduction

The 14-membered macrolides have been especially important in the treatment of diseases due to the wide use of erythromycin antibiotics (Fig. 1) [1, 2]. These range from the parent natural product erythromycin A (**1**) to its clinically relevant semisynthetic derivatives, e.g. clarithromycin, azithromycin, telithromycin, roxithromycin, and solithromycin (not shown). The total chemical synthesis of erythromycins and their close aglycon analogs (**1**–**4**) has underscored many advances in the field [3–17]. Most of these syntheses relied on strategies that used six-membered ring matrices and/or methods of acyclic stereocontrol to fashion fragments with the required functionality and stereochemical relationships. Of particular interest to the theory of strategic analysis, the Danishefsky synthesis of **4** stands as the only route that controlled all of the stereochemical relationships of the macrolide from a single stereoprogenitor site [18]. Although Woodward and Martin achieved the only total synthesis of glycosylated erythronolides **1** and **2** and Kang and Andrade reported variants of telithromycin [19–25], only Myers—in a coup de main—has described the preparation of numerous glycosylated erythronolides [26].

We have described efforts to gain rapid access to this macrolide structure space by way of highly functionalized macrocyclic bis[allenes] [27–29]. This novel strategy converged on **5**. The longest linear sequence to this key intermediate from commercial reagents is 11 steps. The high degree of unsaturation and conformational constraints imparted by two allenic moieties facilitated the macrocylization of stereochemical variants of the precursor— a serious challenge identified early on for this class of seco acids [3, 26]. The allenic functionality also enabled direct access (3–5 steps) to many functionalized 14-membered macrolides. These consisted entirely of aglycon structures, whereas the erythromycins (**1** and **2**) house specially functionalized glycosyl units. Consistent with structural studies of the erythromycins bound to the bacterial ribosome, all erythromycins that exhibit antibiotic activity are glycosylated with desosamine (e.g., **2**) or an elaborated variant of this glycan [30, 31]. Here, we describe the synthesis of **6**, a glycosylated allenic macrolide.

Results and discussion

We aimed to realize short routes to glycosylated macrocyclic scaffolds. We used thioglycoside donors **12** (see inset) and **9**, Scheme 1. Thiopyrimidinyl donor forms of

Dedication: This manuscript is dedicated with respect and admiration to Professor S J Danishefsky in recognition of his creative force, caring mentorship, and tremendous contributions to chemistry.

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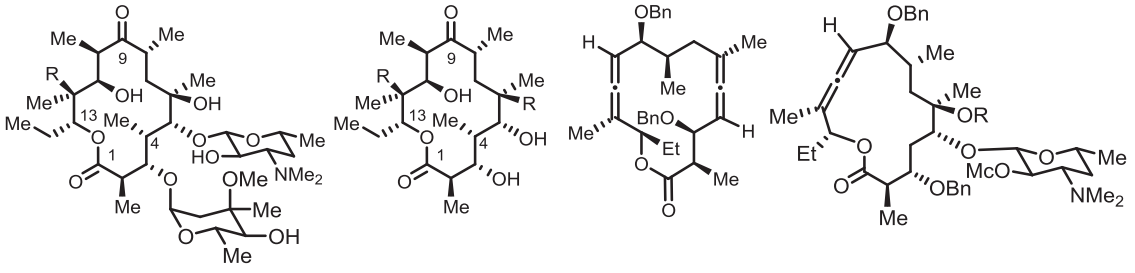
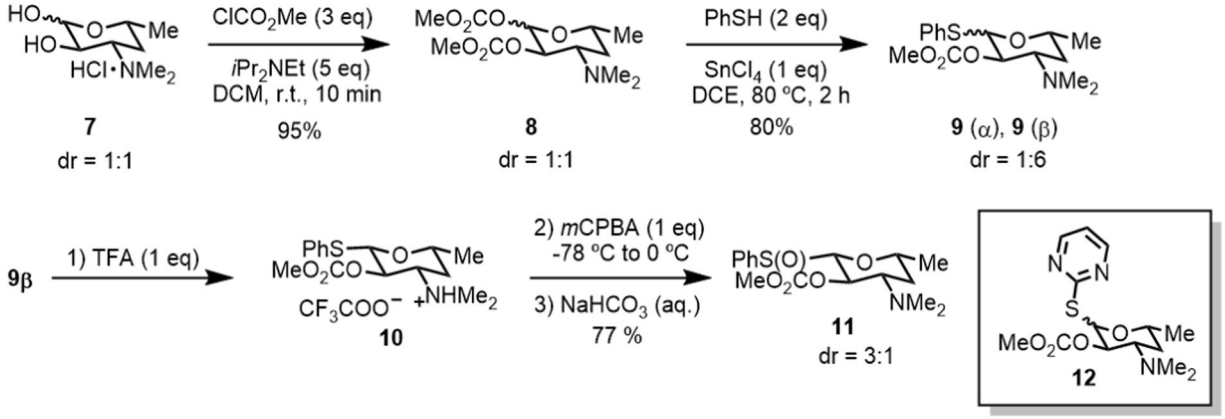


Fig. 1 Erythromycins **1, 2**, erythronolides **3, 4**, macrocyclic bis[allene] **5**, and glycosylated allenic erythronolide **6**

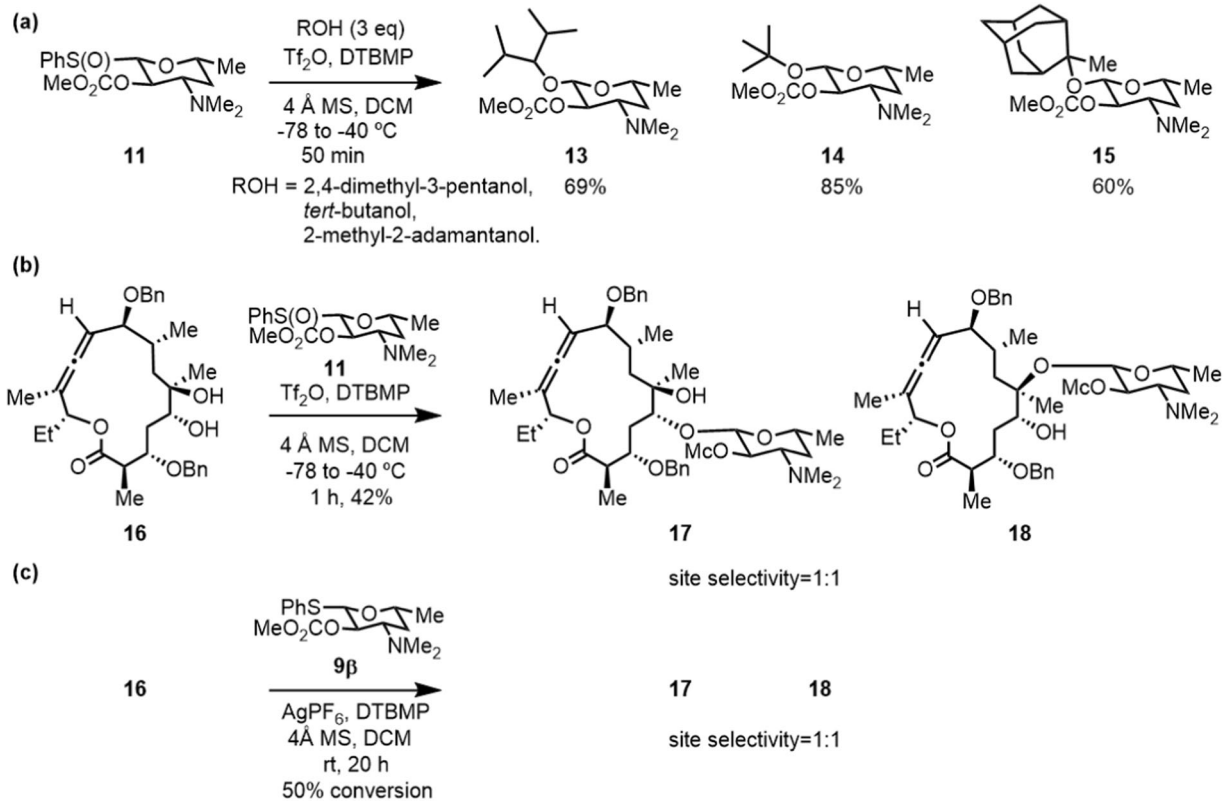


Scheme 1 Synthesis of thiophenyl glycosyl donor **9** and sulfoxide glycosyl donor **11** (DCM = dichloromethane, DCE = dichloroethane, TFA = trifluoroacetic acid, mCPBA = *meta*-chloroperbenzoic acid)

desosamine **12** have been the only donors used for erythronolide acceptors and follow the precedent set by Woodward and Toshima [3, 32]. Thiophenyl donor **9** offered other opportunities, including the option to explore the use of the corresponding sulfoxide [33]. We prepared **12** according to the known procedures and prepared **9** as outlined here beginning with desosamine. Conversion of desosamine hydrochloride to the carbonate (**7→8**) followed by installation of the thiophenyl group gave **9β** as the major isomer. This material was isolated and taken on in an effort to avoid anticipated practical difficulties associated with manipulating isomeric mixtures of glycosides and sulfoxides. The direct treatment of thioglycoside **9β** with *meta*-chloroperbenzoic acid gave the undesired *N*-oxide (not shown). However, the conversion of the amine to its trifluoroacetic acid salt prior to the addition of oxidant avoided this outcome and shunted the reaction to the desired sulfoxides (**9β→10→11**). Although the major isomer of **11** is crystalline and stable to long-term storage, this mixture of diastereomers was taken on and used together.

The incompatibility of allenes with typical glycosylation reaction conditions represents a major concern, as strong Lewis acidic salts used to activate glycosyl donors tend to react with allenes. With one exception, the reactions involving allenes and potential glycosides aimed to engage and, thereby transform, the allenic group [34]. Our interest was to effect glycosylation in the presence of a highly substituted allene and to retain that functionality for late-stage transformation. The sulfoxide donor represented an opportunity to achieve macrolide glycosylation in the presence of the allenic functionality by way of low-temperature generation of an oxocarbenium ion, which would be both expedient to us and would have thought-provoking implications. We first assessed sulfoxide **11** as a suitable desosamine donor in three simple reactions (Scheme 2a). Sterically encumbered secondary and tertiary alcohols, 2,4-dimethyl-3-pentanol, *t*-butanol, and 2-methyl-2-adamantanol, rapidly reacted in the presence of **11** under the agency of triflic anhydride to give the corresponding glycosides as single isomers and in yields ranging from 60 to 85%. Rather than optimizing the outcomes we moved from these proxy acceptors to macrolides.

Scheme 2 also summarizes our initial macrocycle glycosylation findings. Allenic diol **16** was combined with triflic anhydride and then sulfoxide donor **11** at a low temperature. The reaction mixture rapidly gave glycosylated products **17** and **18** (site selectivity = 1:1) as single

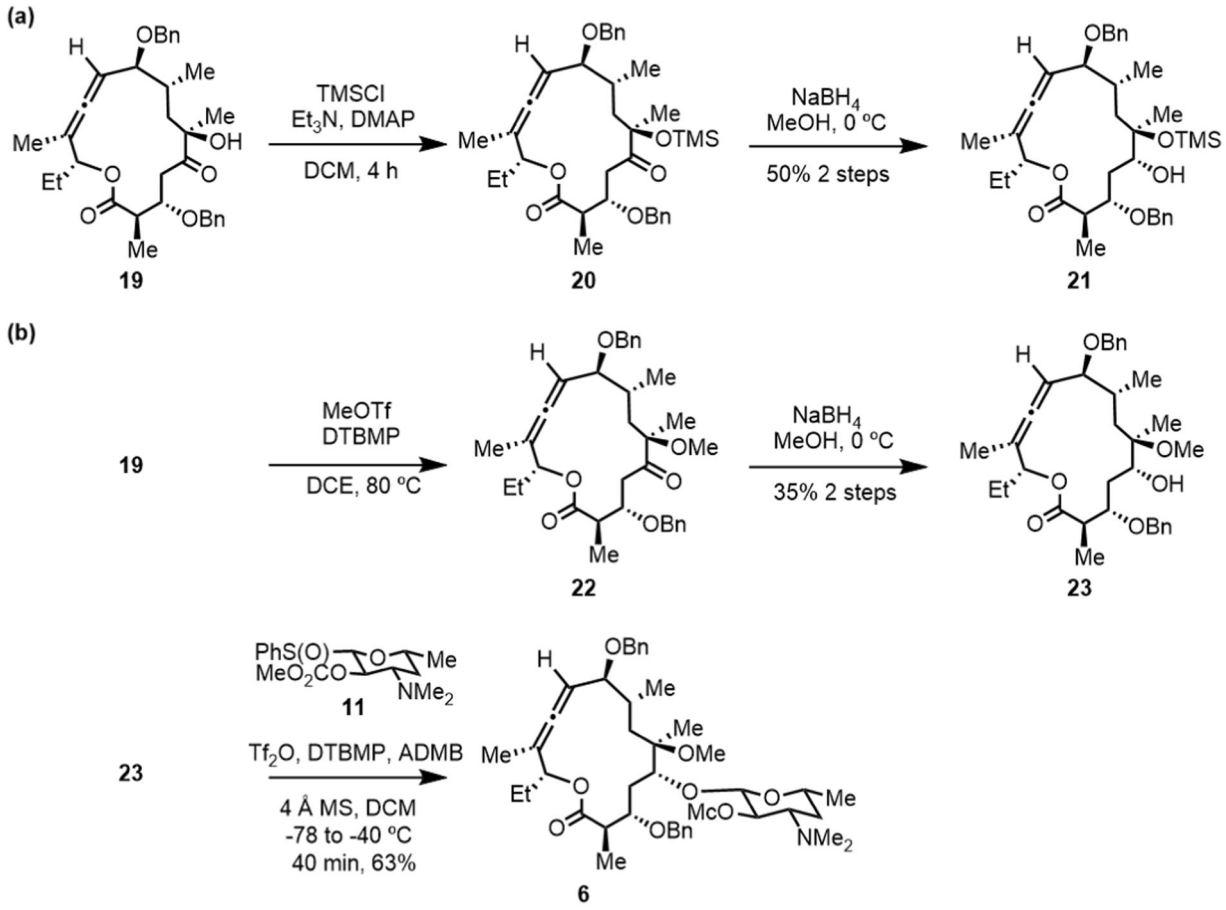


Scheme 2 Glycosylation of sulfoxide donor **11** with sterically encumbered secondary and tertiary alcohols (**a**), glycosylation of allenic macrocyclide diol **16** with sulfoxide donor **11** (**b**), and thiophenol donor **9β** (**c**) (Tf_2O = trifluoromethanesulfonic anhydride, DMAP = 4-dimethylaminopyridine, DTBMP = 2,6-di-*tert*-butyl-4-methylpyridine)

stereoisomers (Scheme 2b). In contrast, donor **9β** in the presence of silver hexafluorophosphate effected slow glycosylation, gave low yields of products with similar selectivity (site selectivity = 1:1), and was accompanied by substantial decomposition of **16** (Scheme 2c). Toshima conditions (pyrimidinyl phenylthio glycoside **12** and AgOTf) [32] gave extensive decomposition of **16** and no evidence of desired product formation (not shown). The combination of **16** with silver triflate in the absence of glycosyl donor gave rise to a similar decomposition profile. As expected, silver salts appear to undermine the desired glycosylation and engage in allenic reaction pathways. Nevertheless, we were encouraged by some of the findings and focused on the use of sulfoxide donor **11**.

Scheme 3 shows the final stage of the investigation. Our earlier report described the preparation of **5**, its conversion to **19** by allene osmylation, and its subsequent reduction to **16** (not shown) [29]. The facile *O*-trimethylsilylation of **19** via the agency of silyl chloride and catalytic 4-dimethylaminopyridine followed by sodium borohydride reduction gave the desired product as a single isomer (**19→20→21**; Scheme 3a). The structure of **21** was confirmed by the removal of the silyl group (toluene sulfonic acid in MeOH), and this product was shown to be identical with **16**. The corresponding *O*-methyl ether **23** was difficult to install. Conventional mild methylating conditions, including those with methyl iodide, dimethyl sulfate, and Meerwein's salt [35], failed to alkylate **19**. Excess methyl triflate and 2,6-di-*tert*-butyl-4-methylpyridine in hot dichloroethane was required and gave multiple minor products along with the desired methyl ether **22**. Glycosyl acceptor **23** was prepared as a single isomer by the reduction of **22** and was obtained in a moderate overall yield from **19**. The silyl ether (**21**) resisted glycosylation. The methyl ether **23** reacted and gave **6** in modest yield (30%). The primary concern in the glycosylation was the stability of the allene to the cationic donor. The secondary concern was the stability of the allene to the phenylsulfenyl triflate generated under the reaction conditions [36]. Gratifyingly, the use of 4-allyl-1,2-dimethoxybenzene significantly improved the reaction outcome and furnished glycosylated macrolide **6** in 63% yield as a single isomer (Scheme 3b).

Our findings complement exciting recent developments in synthetic macrolide antibiotics and expand on our previously described methods to gain direct access to diverse structural motifs [19–29]. We have reduced to practice many new chemical transformations based on allene epoxidation, osmylation, and other chemistries



Scheme 3 Synthetic route to the final target, glycosylated allenic macrolide **6** (ADMB = 4-allyl-1,2-dimethoxybenzene)

[37]. These unexplored structures and reactivity profiles motivated the strategy embodied in macrocyclic bis [allene] **5** [27–29]. The approach has enabled high-tempo seco acid synthesis, facile macrocyclization, selective or simultaneous manipulation of the allenyl groups in a macrolide context, and glycosylation of the macrolide scaffold.

In summary, among the most important advances of this study is the preparation of novel desosamine donors **9** and **11** and the use of these donors to glycosylate bulky and macrolide acceptors. The sulfoxide reagent **11** represents a distinct alternative to Woodward–Toshima glycosylation of the erythromycins and other macrolides. Pleasingly, the reactive species derived from glycosyl donor **11** was generated in the presence of a highly substituted allene without complication. The resultant route to glycosylated allenic erythronolide **6** is short. The sequence required four steps beginning from **5** and corresponds to fifteen steps from commercial reagents (longest linear sequence). Needless to say, compound **6** represents an opportunity to diversify—post glycosylation—into the high-value antibiotic structure space of erythromycin.

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Compliance with ethical standards

Conflict of interest The authors declare no conflict of interest.

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