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The Total Synthesis of Moenomycin A

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Abstract

Moenomycin A is the only known natural antibiotic that inhibits bacterial cell wall synthesis by binding to the transglycosylases that catalyze formation of the carbohydrate chains of peptidoglycan. We report here the total synthesis of moenomycin A using the sulfoxide glycosylation method. A newly discovered byproduct of sulfoxide reactions was isolated that resulted in substantial loss of the glycosyl acceptor. A general method to suppress this byproduct was introduced, which enabled the glycosylations to proceed efficiently. The inverse addition protocol for sulfoxide glycosylations also proved essential in constructing some of the glycosidic linkages. The synthetic route is flexible and will allow for derivatives to be constructed to further analyze moenomycin A's mechanism of action.

Moenomycin A (**1**) is a potent antibiotic that inhibits bacterial cell wall synthesis by binding to the transglycosylases that catalyze formation of the carbohydrate chains of peptidoglycan.¹ Moenomycin is the only natural product inhibitor known to directly bind to these enzymes. Its distinctive mechanism of action is matched by its unusual structure. Moenomycin A consists of a highly functionalized pentasaccharide attached via a unique phosphoglycerate linkage to a polyprenyl chain. Many approaches to the synthesis of moenomycin fragments and derivatives have been reported over the past 30 years, primarily by Welzel and coworkers, but the total synthesis of moenomycin A has not been accomplished.² We report here the first total synthesis of moenomycin A.

The moenomycin pentasaccharide presents a number of synthetic challenges. Electron-withdrawing groups on several of the monosaccharides make them poor glycosyl donors and/or acceptors. Many of the glycosidic bonds must also be formed to sterically hindered alcohols. For example, the B ring galacturonamide is a deactivated donor due to the electron-withdrawing C6 position³ and the C4 hydroxyls of the C and E rings of moenomycin are sterically hindered and particularly unreactive in glycosylation reactions.⁴ The stability of the diverse functional groups is also a concern. The F ring contains both an amide and a carbamate, which are potentially reactive under glycosylation conditions, and the A ring is sensitive to both oxidation⁵ and hydrogenation⁶ procedures.

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Our synthetic approach involved constructing the BCEF tetrasaccharide from the BC and EF disaccharide fragments, followed by attachment of the D ring. The synthesis of the protected BCEF tetrasaccharide **10** is shown in Scheme 1. Because preliminary investigations into the synthesis of the BC disaccharide revealed that the A ring would not survive the glycosylation conditions, the C6 position of the B ring **2** was protected as an ester to allow for late stage attachment of the A ring. The C2 amine of the C ring acceptor **3** was protected with a tetrachlorophthaloyl (TCP) group⁷ as reports have demonstrated that this bulky protecting group enables regioselective glycosylation at C4 in the presence of an unprotected C3 hydroxyl.⁸ In addition, the TCP protecting group allows for neighboring group participation at C2, providing β -stereochemical control during formation of the subsequent CE glycosidic linkage. The glycosylation of **2** with **3** afforded BC disaccharide **6** regioselectively and stereoselectively in 75% yield using the standard sulfoxide glycosylation protocol, which involves adding triflic anhydride to the glycosyl sulfoxide prior to adding the acceptor⁹. Disaccharide **6** was then oxidized to sulfoxide **7**.

Unlike the BC linkage, none of the other glycosidic bonds were formed using the standard glycosylation conditions. In the case of the EF β -1,2 linkage, we observed that benzenesulfinic ester formation on the C2 hydroxyl of F ring **5** led to significant loss of the glycosyl acceptor.¹⁰ PhSOTf is generated during sulfoxide glycosylations and is known to activate glycosyl sulfoxides.¹¹ Benzenesulfinic ester formation was presumed to be a downstream byproduct resulting from the reaction of PhSOTf with glycosyl sulfoxides. Using 4-allyl-1,2-dimethoxybenzene (ADMB) to scavenge PhSOTf¹² and changing the order of reagent addition during the reaction (inverse addition)¹³ suppressed benzenesulfinic ester formation and the EF disaccharide **8** was obtained in 84% yield. The 4,6-(*p*-methoxybenzylidene) group was then regioselectively opened¹⁴ to afford **9**.

Coupling of the EF and BC disaccharide fragments also required the inverse addition protocol because the BC glycosyl donor decomposed under the standard activation conditions. Inverse addition decreases decomposition because the oxacarbenium ion is generated slowly in the presence of the acceptor alcohol, which traps the reactive intermediate before it reacts with other species.¹³ Thus, when donor **7** was added to a solution containing triflic anhydride and acceptor **9**, tetrasaccharide **10** was obtained stereoselectively in 50% yield. The free hydroxyl on the C ring was then acetylated followed by removal of the PMB ether with DDQ to give **11** (Scheme 2).

The final glycosylation involved forming a β -1,6 linkage between a D ring sulfoxide and tetrasaccharide **11**. To avoid introducing a hindered, electron-withdrawing ester group on the C2 position of the D ring donor, we chose to form this glycosidic linkage with solvent control using propionitrile, which is known to give high β -stereoselectivity in glycosylations.^{9,15} As before, benzenesulfinic ester byproducts dominated the reaction in the absence of a PhSOTf scavenger. When the reaction was carried out using the scavenger ADMB and inverse addition, pentasaccharide **12** was obtained in 76% yield with complete β -stereoselectivity.

Completion of the moenomycin pentasaccharide synthesis required protecting group removal and installation of the 2-amino-cyclopentane-1,3-dione (A ring) chromophore and F ring amide and carbamate. Selective conversion of the phenyl ester and phenyl carbonate of **12** into the desired carboxamide and carbamate, respectively, was accomplished using NH_3 in IPA/ CH_2Cl_2 . The TCP protecting groups were then removed with ethylenediamine and the liberated amines were acylated *in situ* to give **13**. Hydrogenation of the benzyl groups using $\text{Pd}(\text{OH})_2/\text{C}$ in MeOH and acetylation of the hydroxyls gave **14**. Removal of the TMSE groups with BF_3 ,¹⁶ followed by coupling of the A ring¹⁷ using HATU, and global deprotection with NaOH afforded the fully deprotected pentasaccharide **15**. The identity of **15** was confirmed by correlation with the natural pentasaccharide obtained through degradation of moenomycin A. Peracetylation of **15** followed by selective deprotection of the anomeric acetate with hydrazine gave **16**. Coupling of **16** to the moenocinyl glycerate unit and deprotection, using our published procedure¹⁸, afforded moenomycin A (**1**).

This synthesis of moenomycin A is both efficient and flexible, allowing for variants of the antibiotic to be constructed in order to probe its mechanism of action. Each glycosidic linkage was synthesized stereoselectively using the sulfoxide glycosylation reaction. Two sets of reaction conditions were employed depending on the reactivity of the donor-acceptor pairs. The sulfoxide activation conditions described here, along with those described previously¹⁹, should enable the construction of most glycosidic linkages.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Scheme 1. Construction of BC, EF and BCEF oligosaccharides^a

^a Conditions: (a) TiF_2O , DTBMP, ADMB, CH_2Cl_2 , -78 to 0°C , 75%; (b) *m*CPBA, CH_2Cl_2 , -78 to 0°C , 70%; (c) TiF_2O , DTBMP, ADMB, CH_2Cl_2 , -42°C , 84%; (d) Bu_2BOTf , $\text{BH}_3\cdot\text{THF}$, -60°C , 83%; (e) TiF_2O , DTBMP, ADMB, CH_2Cl_2 , -60°C , 50%. DTBMP = 2,6-di-*tert*-butyl-4-methylpyridine, ADMB = 4-allyl-1,2-dimethoxybenzene

Scheme 2. Completion of the synthesis^a

^a Conditions: (a) Ac₂O, Py, 93%; (b) DDQ, pH 7 buffer, 79%; (c) Phenyl 2,3,4,6-tetra-*O*-benzyl-1-thio-β-D-glucopyranoside *S*-Oxide, Tf₂O, DTBMP, ADMB, propionitrile, -78 °C, 76%; (d) NH₃ in IPA/ CH₂Cl₂; (e) ethylenediamine, EtOH, 60 °C (f) Ac₂O, EtOH, (g) Ac₂O, Py, 66% over 4 steps; (h) H₂, Pd(OH)₂/C, MeOH; (i) Ac₂O, Py, 63% over 2 steps; (j) BF₃·Et₂O, CH₂Cl₂, 97%; (k) 2-amino-cyclopentane-1,3-dione, HATU, DIPEA, CH₂Cl₂/DMF, 55%; (l) NaOH, THF, 80%; (m) Ac₂O, Py, 78%; (n) H₂NNH₂-HOAc, 53%; (o) i. 2-Chloro-1,3,2-benzodioxaphosphorin-4-one, 85%; ii. (R)-3-hydroxy-2-[(2Z,6E,13E)-3,8,8,14,18-pentamethyl-11-methylene-nonadeca-2,6,13,17-tetraen-1-yloxy]propanoate, 1-adamantanecarbonyl chloride, NMM/CCl₄/Py/CH₃CN/H₂O (1:2.5:6:1:1), 62%; iii. 0.1 N LiOH, THF/H₂O (1:1), then AcOH, 47%.¹⁸