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Total Synthesis and Structure Revision of the (−)-Maduropeptin Chromophore

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Maduropeptin, a novel member among the family of chromoprotein antitumor antibiotics, was isolated from the broth filtrate of *Actinomadura madurae* by scientists at Bristol-Myers Squibb in 1991.[1,2] The isolated chromophore **1** was composed of a unique nine-membered diyne core and a glycoside side chain (Figure 1). Although **1** is the methanol adduct of a structurally undefined labile chromophore, it showed a DNA cleavage site selectivity similar to that of holoprotein.[1a] Presumably, the activation mechanism of **1** is initiated by the formation of the highly strained nine-membered enediyne ring via intramolecular S_N2' substitution of methanol by the macrolactam nitrogen. To realize its biological activity, the equilibrated *p*-benzyne biradical abstracts hydrogen atoms from double-strand DNAs,[3] whereas the glycoside side chain is essential for sequence-selective binding on the DNA.[1] The highly functionalized and complex architecture of chromophore **1** clearly presents a daunting challenge to its chemical synthesis.[4−6] In this communication, we describe the total synthesis and the structural revision of the (−)-maduropeptin chromophore.

The first phase in the total synthesis of the chromophore involves the enantioselective synthesis of the protected aglycon **2** (Figure 1).[4c] Next, *β*-selective glycosylation of the tertiary alcohol derived from **2** could be carried out following the Schmidt protocol. Trichloroacetimidate donor **3** could be prepared from lactone **4**, which has been previously reported by Nicolaou and co-workers.[5d]

Careful transformation of **2**, which was prepared from **5**,[4c,7] into the desired glycosyl acceptor **7** is outlined in Scheme 1. Removal of the acetonide group, followed by selective protection of the secondary hydroxyl group as the benzoate, gave **6** in 93% yield (2 steps). Benzoyl protection of the C10 hydroxyl group was necessary to prevent the deterioration of the nine-membered diyne core during the subsequent removal of the methoxymethyl (MOM) group. It should be noted that **6** was obtained as a mixture of atropisomers: although the isomers are chromatographically separable, the separated isomers reverted to an equilibrium mixture of the isomers within several hours at rt.[4c,8] The ratio of the isomers was strongly influenced by the polarity of the solvent. In $CDCl_3$, the ratio between the natural and unnatural atropisomers was found to be 4.5:1 using ^{1}H NMR analysis. The MOM group of **6** was removed by treatment with 4 M H_2SO_4/MeOH at rt. Protection of the resulting benzylic hydroxyl group as the benzoate provided glycosyl acceptor **7** in 30% yield (2 steps and after 2 cycles of the reaction). Although the macrolactam of **7** still exhibited atropisomerism, the natural form was dominant in CD_3OD, as confirmed using NOE experiments.

Glycosyl donor **3** was then prepared from known lactone **4**, which was enantioselectively prepared from L-serine according to Nicolaou's procedure.[5d] Lactone **4** was readily converted to trichloroacetoimidate **3** as a single anomer ($J_{H1''-H2''}$ = 6.6 Hz) via DIBAL reduction followed by treatment with CCl_3CN and DBU.

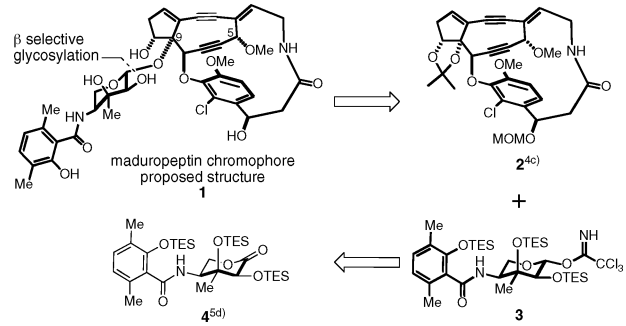
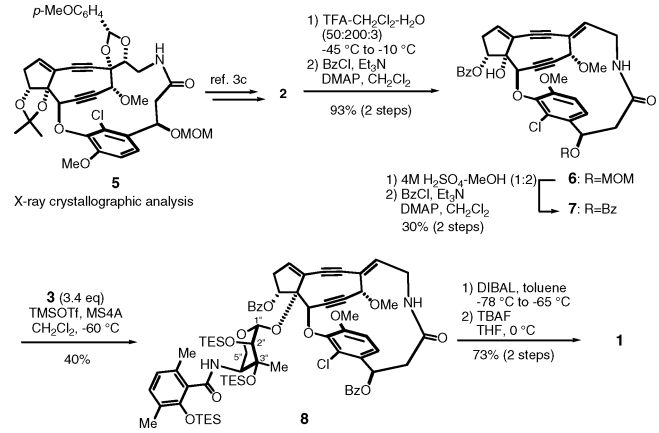


Figure 1. Structure of maduropeptin chromophore and its retrosynthesis.

Scheme 1. Synthesis of **1**



Glycosylation of the C9 tertiary hydroxyl group of **7** in CH_2Cl_2 using TMSOTf as a Lewis acid proceeded smoothly, to afford axial glycoside **8** in 40% yield,[9] without the formation of the anomeric isomer or the migration of the benzoyl group. Based on the relatively small ^{1}H NMR coupling constants between H1″ and H2″ ($J_{H1''-H2''}$ = 1.3 or 2.2 Hz in $CDCl_3$ for two atropisomers, respectively), and the corresponding ROESY experiments, the pyranose ring of **8** was determined to adopt a flipped chair conformation in relation to that of **3**. NOE correlations between the protons of the C3″ methyl group with H2″, H4″, and axial H5″ suggest that C3″ methyl exists in the axial position. This conformational change can be attributed to the steric repulsion between the C10 benzoate and the C2″ OTES groups. Finally, after removal of both benzoyl groups of **8** by DIBAL reduction, all the TES ethers were cleaved by treatment with Bu_4NF to complete the

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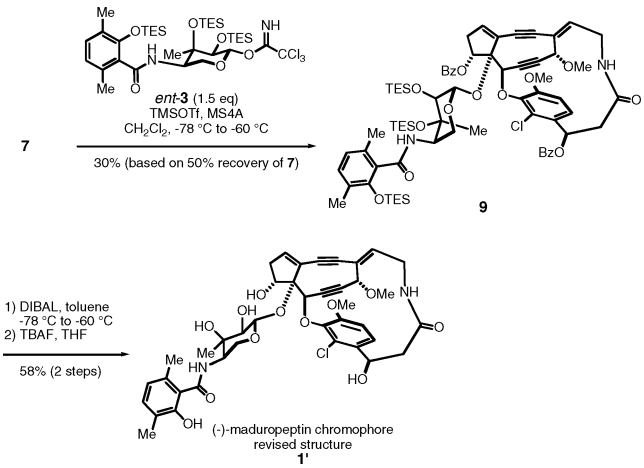
Scheme 2. Total Synthesis of the (−)-Maduropeptin Chromophore



total synthesis of **1**. In CH_2Cl_2, **1** exhibited atropisomerism that resulted in an equilibrium mixture of isomers at rt (detected by TLC analysis). Fortunately, in polar solvents such as CD_3OD or DMSO-d_6, **1** existed exclusively as the natural-type atropisomer.

Upon closer inspection, however, the ^{1}H and ^{13}C NMR spectra of synthetic **1** were found to differ from those of the natural product. In the case of ^{1}H NMR, the differences ($|\Delta\delta| > 0.1$ ppm) were observed for the signals corresponding to the C9 glycoside (H10, H1″, and H5″, see Supporting Information). Significant downfield shifts ($\Delta\delta = +1.33$ and $+2.42$ ppm) were observed for the two exchangeable protons of synthetic **1** (C10−OH and C2″−OH, respectively) that can be attributed to intramolecular hydrogen bonding. Consequently, the proposed structure of the natural chromophore of maduropeptin was revised as structure **1′**, which possesses the antipodal madurosamine moiety.

The synthesis of chromophore **1′** is shown in Scheme 2. Stereoselective glycosylation using enantiomeric sugar moiety *ent*-**3**, which was derived from D-serine, was conducted under Lewis acidic conditions (30% yield based on 50% recovery of **7**). Deprotection of the benzoyl group of **9** with DIBAL, followed by the removal of all TES groups by Bu_4NF in THF, afforded the desired chromophore **1′**. Although atropisomeric equilibration was also observed for synthetic **1′**, the natural type isomer was predominant in DMSO-d_6. ^{1}H and ^{13}C NMR spectra, as well as HRMS and NOE correlations, were in good agreement with those of the natural product.

In summary, the first total synthesis and structure revision of (−)-maduropeptin chromophore were successfully accomplished. Our studies involved the synthesis and characterization of **1** and its diastereomer **1′** possessing the antipodal madurosamine. The spectroscopic data of **1′** were in good agreement with those of the natural product. The absolute structure of the chromophore, however, remains yet to be determined.[10,11]

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Supporting Information Available: Detailed experimental procedures and spectroscopic data (^{1}H and ^{13}C NMR, FT-IR, and MS spectra) for all new compounds, and X-ray crystallographic analysis data of **5**. This material is available free of charge via the Internet at http://pubs.acs.org.

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