Internal amide-triggered cycloaromatization of maduropeptin-like nine-membered enediyne

Yutaro Norizuki,[a] Kazuo Komano,[a] Itaru Sato*[b] and Masahiro Hirama*[a]

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In the Masamune–Bergman cyclization of a nine-membered non-conjugated enediyne with an internal, maduropeptin-like nucleophile, the exocyclic alkene migrated to form the nine-membered conjugated enediyne, triggered by the intramolecular addition of the amide group; final aromatized products showed up to 85% yield.

Maduropeptin was isolated from the broth filtrate of *actinomadura madurae* in 1991 by the scientists of Bristol-Myers Squibb.[1,2] Maduropeptin is a novel member of the family of chromoprotein antitumor antibiotics, consisting of a 1 : 1 complex of a nine-membered enediyne chromophore and a carrier apoprotein. The chromophore was isolated as solvent artifacts **1a–d** at the C-5 position along with an aromatized dihydroindene **2** (Fig. 1).[1b,3,4] The activity of methanol adduct **1a** was similar to that of the maduropeptin holoprotein, but 100 times smaller.[1c] It was proposed that the addition of methanol is reversible[1b,c] and that **1a** undergoes intramolecular addition of the lactam nitrogen to the exo-olefin, causing a vinylogous elimination of methanol. This results in formation of the conjugated enediyne and an aziridine functionality (**3**). The strained nine-membered enediyne equilibrates with its *p*-benzyne biradical form, which can abstract hydrogen from double stranded DNA in tumor cells.[2,4] Other than these synthetic studies toward **1a**,[5,6] only model studies on the above allylic rearrangement for acyclic[7] and ten-membered cyclic[8] compounds have been reported.

Here we describe the first internal amide-triggered cycloaromatization of a nine-membered cyclic enediyne **14**. The enantiomerically pure **14** was synthesized as shown in Scheme 1.[6] Hagihara–Sonogashira coupling between vinyl triflate **5** and terminal alkyne **6** gave **7** in 89% yield after removal of a carbon-bound trimethylsilyl group. Oxidation of the primary hydroxyl group provided aldehyde **8**. An intramolecular acetylide–aldehyde condensation reaction utilizing $CeCl_3$/lithium disilazide proceeded smoothly and **9** was isolated as a single isomer.[6,9,10] After the newly formed hydroxyl group was protected as a 2-naphthylmethyl (NAP) ether, the TBS ether was cleaved to give the primary alcohol **10**. The hydroxyl group was converted to an azide by the Bose–Mitsunobu procedure using the Shioiri reagent.[11] A

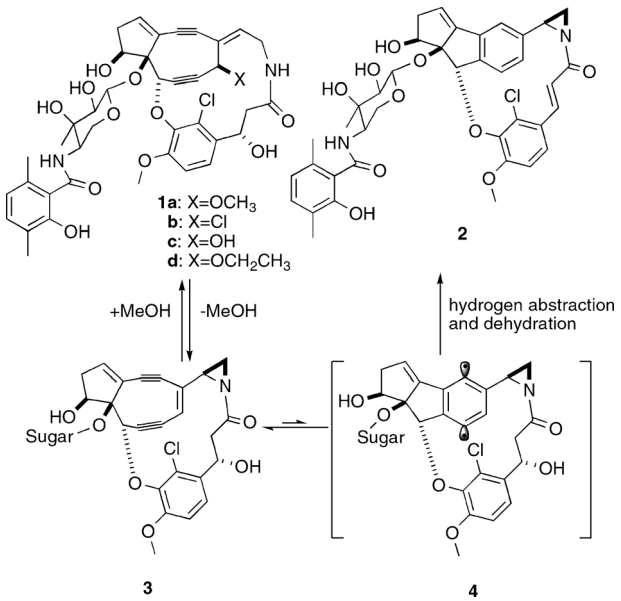
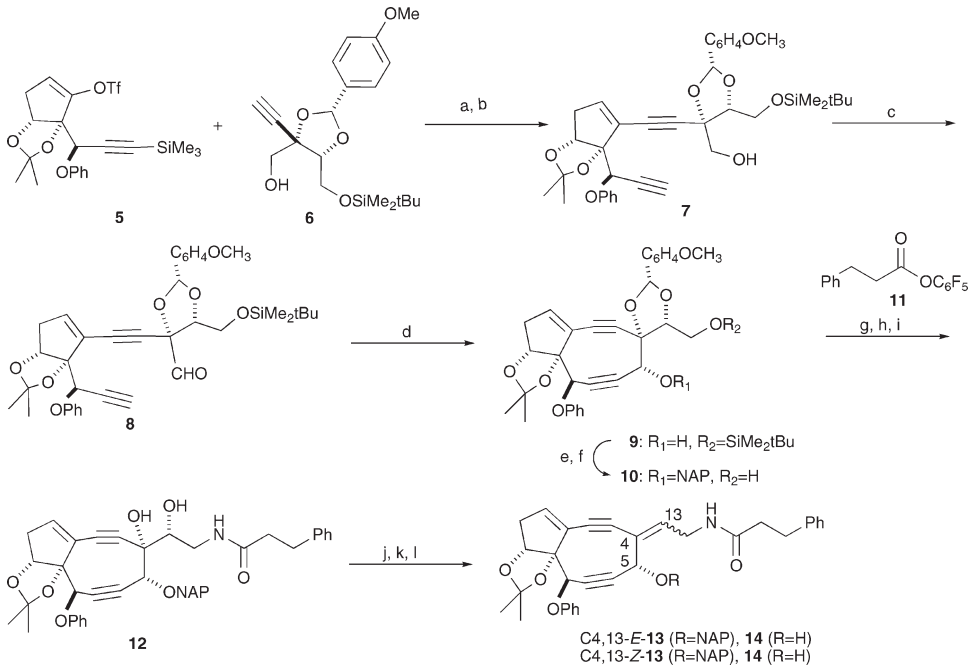


Fig. 1 Proposed structure and reaction mechanism of maduropeptin chromophore.

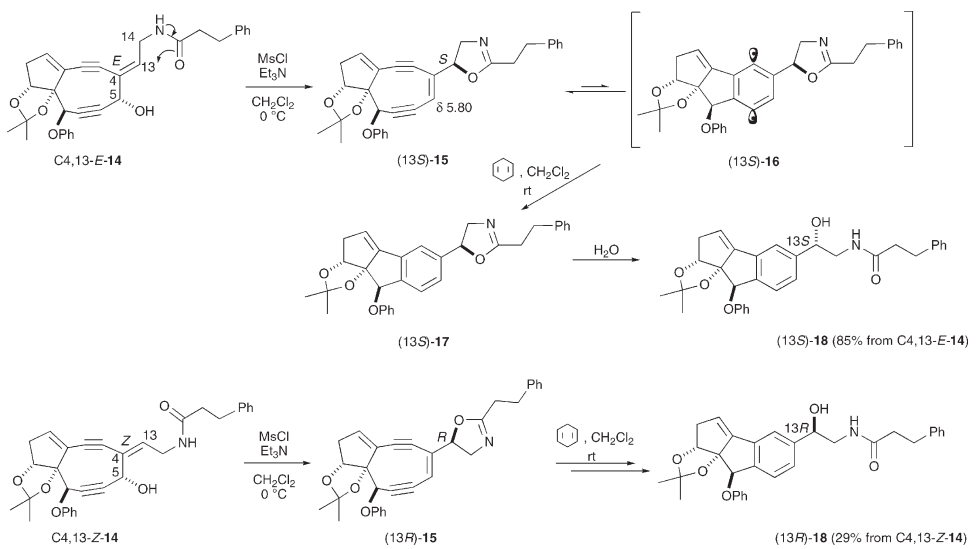
Staudinger reaction and subsequent condensation with pentafluorophenyl ester **11** gave an amide.[5b] Acid hydrolysis of the *p*-methoxybenzylidene acetal gave diol **12**. The bis-*p*-trifluoromethylbenzoate of **12** was converted into the olefin (E/Z = 6 : 1) **13** *via* SmI_2-mediated reductive elimination.[12] The geometry of the C4,13-exo double bond was unambiguously determined by comparison of NOE experiments on the isomers of **13**. Separation of the E/Z-isomers and oxidative cleavage of the NAP ether afforded the non-conjugated enediynes C4,13-*E*-**14** and C4,13-*Z*-**14**, respectively, which correspond to the maduropeptin chromophore artifact **1c**.

With the successfully synthesized non-conjugated enediynes in hand, allylic rearrangement and cycloaromatization reactions were examined. When C4,13-*E*-**14** was treated with methanesulfonyl chloride in the presence of triethylamine in CH_2Cl_2 at 0 °C, the conjugated enediyne (13*S*)-**15** was produced within 5 min (Scheme 2). The characteristic olefin proton H-5 appeared as a singlet at δ 5.80. The spectral data indicated formation of the 1,3-oxazoline *via* *O*-attack of the amide[13,14] instead of the formation of a strained *N*-acyl aziridine,[13a,15] which could be produced by *N*-attack of the amide.[16] The preferred mode of the cyclization is common in nucleophilic substitution of amides,[14] and was contrary to the degradation product (**2**) of maduropeptin chromophore. The peculiar fashion shown in **2** was

[a] *Department of Chemistry, Graduate School of Science, Tohoku University, Sendai, 980-8578, Japan. E-mail: hirama@mail.tains.tohoku.ac.jp; Fax: +81-22-795-6566*
[b] *Research and Analytical Center for Giant Molecules, Graduate School of Science, Tohoku University, Japan. E-mail: isato@mail.tains.tohoku.ac.jp*



Scheme 1 *Reagents and conditions:* (a) $Pd(PPh)_4$ (5 mol%), CuI, *i*-Pr_2NEt, 2,6-lutidine, DMF, 0 °C; (b) K_2CO_3, MeOH, 89% (2 steps); (c) Dess–Martin periodinane, $NaHCO_3$, CH_2Cl_2; (d) $CeCl_3$, $LiN(SiMe_2Ph)_2$, THF (35 mM), −40 °C; (e) 2-naphthylmethyl bromide, NaH, THF; (f) Bu_4NF, THF, 51% (4 steps); (g) $(PhO)_2P(O)N_3$, DEAD, PPh_3, THF, 94%; (h) **11**, PPh_3, Et_3N, THF, H_2O, rt to 40 °C, 76%; (i) PPTS, TsOH, MeOH, 81%; (j) *p*-$CF_3C_6H_4COCl$, DMAP, CH_2Cl_2, 0 °C, 79%; (k) SmI_2, THF, 10 min then separation, 60% for C4,13-*E*-**13**, 10% for C4,13-*Z*-**13**; (l) DDQ, CH_2Cl_2, pH 7 buffer, 80% for C4,13-*E*-**14**, 76% for C4,13-*Z*-**14**.



Scheme 2 Cycloaromatization of enediyne **14** triggered by an internal nucleophile.

possibly due to the presence of an *ansa*-macrolide. The formation of 1,3-oxazoline from **1a** reduces the ring size of the highly strained *ansa*-macrolide and would increase unfavorable transannular interaction. The diastereoface selectivity of the addition to C13 was 8 : 1. It is noteworthy that enediyne (13*S*)-**15** was isolable by rapid silica gel chromatography.[17] Treatment of the nine-membered enediyne (13*S*)-**15** with excess 1,4-cyclohexadiene in CH_2Cl_2 at room temperature afforded the cycloaromatized product (13*S*)-**18** in 85% yield from C4,13-*E*-**14**, *via* ready hydrolysis of (13*S*)-**17**. The absolute configuration of C13 was determined to be *S* by ^1H NMR analysis of its (*R*)- and (*S*)-MTPA ester derivatives.[18] Treatment of (13*S*)-**15** with methanol only gave a trace amount of **17** and **18**. Under these conditions, methanol adducts such as the one corresponding to **1a** were not detected. The reaction with excess 1,4-cyclohexadiene in methanol or ethanol also did not give any alcohol adducts and instead afforded the cycloaromatized products (13*S*)-**17** and (13*S*)-**18** in a 19–27% combined yield. When C4,13-*Z*-**14** was mesylated in the presence of triethylamine in CH_2Cl_2 at 0 °C, conjugated enediyne (13*R*)-**15** was obtained. Cycloaromatization of (13*R*)-**15** in 1,4-cyclohexadiene–CH_2Cl_2 (1 : 1) at room temperature gave only (13*R*)-**18**. Thus, it is most

likely that both *E*- and *Z*-**14** underwent a concerted allylic substitution reaction triggered by the internal amide nucleophile in a stereospecific manner, *i.e.*, *anti*-S_N2' fashion. In experimental[19] and theoretical[20] studies on S_N2' reactions without transition metals, *syn*/*anti* selectivity is often controlled by the attractive and/or repulsive interaction between a nucleophile and a leaving group. The *anti*-selective outcome in our model system is attributed to the steric repulsion between the leaving mesylate and the amide anion and/or the electrostatic repulsion between these two groups in non-polar solvents.

In conclusion, we successfully synthesized a non-conjugated nine-membered enediyne possessing an amide as an internal nucleophile, which corresponds to the maduropeptin chromophore artifacts. For the first time, we demonstrated that an intramolecular nucleophilic substitution reaction provided a nine-membered conjugated enediyne and subsequent Masamune–Bergman cyclization gave cycloaromatized products with up to 85% yield. The results would also be expedient for designing a prodrug system of labile enediynes.

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