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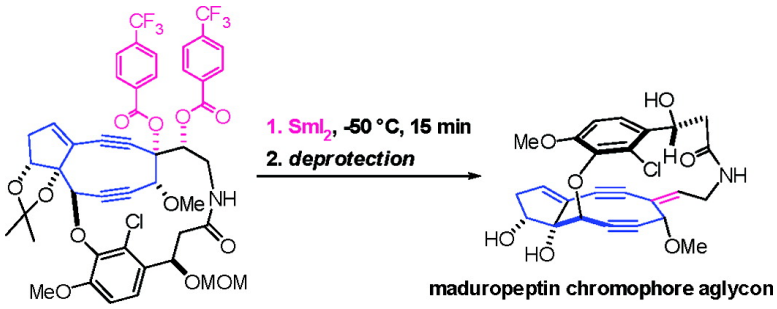

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Total Synthesis of the Maduropeptin Chromophore Aglycon

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Maduropeptin, isolated from the broth filtrate of *Actinomadura madurae*, consists of a 1:1 complex of an acidic, water-soluble carrier protein and a chromophore (Figure 1).[1] Schroeder et al. reported the structure of the maduropeptin chromophore **2** and proposed that the nine-membered ring diyne **2** was the methanol adduct of a structurally unknown labile chromophore. Isolated **2** exhibits potent antitumor and antibacterial activities by means of a mechanism distinct from that of similar enediyne natural products.[2] The highly strained system **3**, which is generated via S_N2' reaction of the C14-amide nitrogen of **2**, cycloaromatizes spontaneously to the *p*-benzyne biradical, which can efficiently cleave double-stranded DNA by hydrogen abstraction. Therefore, **2** represents a stable prodrug form of the reactive nine-membered enediyne structure.

The complex, highly unsaturated molecular architecture of **2**, which includes the bicyclo[7.3.0]enediyne and the 15-membered ansa-macrolactam with atropisomerism, clearly presents a daunting challenge for chemical synthesis.[3,4] In particular, controlling the stereoselectivity of both the C4,13-*Z*-olefin and the non-biaryl atropselectivity within the macrocycle necessitated the development and application of new strategies. Here, we report the first total synthesis of the aglycon **1** of the maduropeptin chromophore, thus demonstrating solutions to these unique synthetic problems.[5]

We hypothesized that the synthesis of **1** could be attained from the convergent assembly of three fragments (**4**,[3b] **5**, and **6**) by applying the C8-epoxide opening reaction to construct the C2′-aryl ether and Sonogashira coupling to link C1 and C2 (Figure 1). These couplings would be followed by nine-membered ring formation at C6 and subsequent macrolactamization at C9′. The C4,13-*Z*-olefin was to be constructed in the last stage of the synthesis through the facile SmI_2-mediated 1,2-elimination reaction recently developed in our laboratory for the synthesis of the C-1027 chromophore core, a structurally related enediyne natural product.[6]

Synthesis of aglycon **2** started with the stepwise condensation of the three fragments (Scheme 1). The enantioselective introduction of the C7′-hydroxy group was attained on a 30 g scale by hetero-ene reaction between 2-methoxypropene and **7** using Jacobsen's catalyst **8**.[7] The obtained **9** was subjected to ozonolysis and acid treatment to afford *β*-alkoxy ester **10** as an enantiomerically pure compound (76% for three steps, 98% ee).[3b,4d] $LiAlH_4$ reduction of ester **10** to primary alcohol **11**, followed by TBS removal using TBAF, generated triol **6**. Then, CsF-promoted coupling[3a,b,8] between epoxide **4** and the sterically hindered phenol **6** resulted in formation of the aryl ether of **12**, the C9′-primary alcohol of which was selectively protected as its TBDPS ether to produce triol **13**. After derivatization of C9,10-diol **13** to acetonide **14**, the remaining C7′-secondary alcohol and the C6-terminal acetylene were masked with MOM and TMS, respectively, leading to **16**. The C1-hydroxy group of **17** was in turn liberated with DDQ from *p*-methoxybenzyloxym-

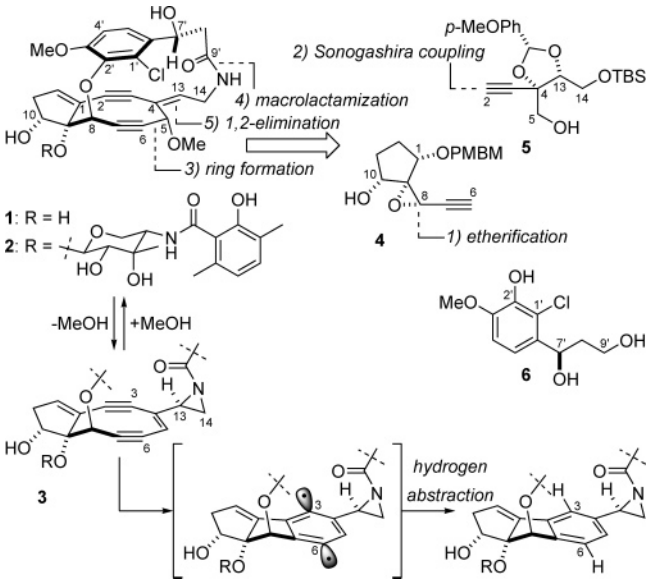

Figure 1. Structure of the maduropeptin chromophore and its retrosynthesis.

ethyl (PMBM) ether **16** and oxidized to ketone **18** using Dess−Martin reagent.[9] Lithium enolate formation and subsequent treatment with $PhNTf_2$ converted ketone **18** into enol triflate **19**, which was coupled with acetylene moiety **5** under Sonogashira conditions to deliver **20**.[10]

The stage was now set for construction of the two most characteristic rings, the nine-membered diyne and the 15-membered ansa-macrolactam. Prior to formation of the diyne ring, the C6-TMS group of **20** was removed using K_2CO_3 in methanol, then alcohol **21** was transformed to aldehyde **22** by Dess−Martin oxidation. After screening various reaction conditions, it was found that a mixture of $LiN(SiMe_2Ph)_2$[11] (9 equiv) and $CeCl_3$ (10 equiv) in THF smoothly promoted the acetylide−aldehyde condensation to furnish diyne **23** with the C5-α-hydroxy group in a completely stereoselective fashion.[12,13] The desired C5 stereochemistry presumably originated from the α-oriented conformation of the aldehyde fixed by the Ce^{3+} five-membered chelate; after derivatization of the obtained **23** to methyl ether **24** (82% yield for two steps), the structure of this intermediate was determined by the NOE data (Figure 2).

For the next lactamization, a series of standard functional group manipulations were performed. Selective removal of the TBS group from bis-silylated **24** using the controlled TBAF treatment and subsequent Mitsunobu-type displacement of C14-OH with N_3 provided azide **26**.[14] Next, C9′-protected primary alcohol **26** was converted to C9′-active ester **29** through four steps, including the TBAF-promoted deprotection of the TBDPS group, the stepwise oxidation from primary alcohol **27** to carboxylic acid **28**, and pentafluorophenyl (PFP) ester formation. Slow addition of the isolated azido-PFP ester **29** to excess triphenylphosphine in THF−

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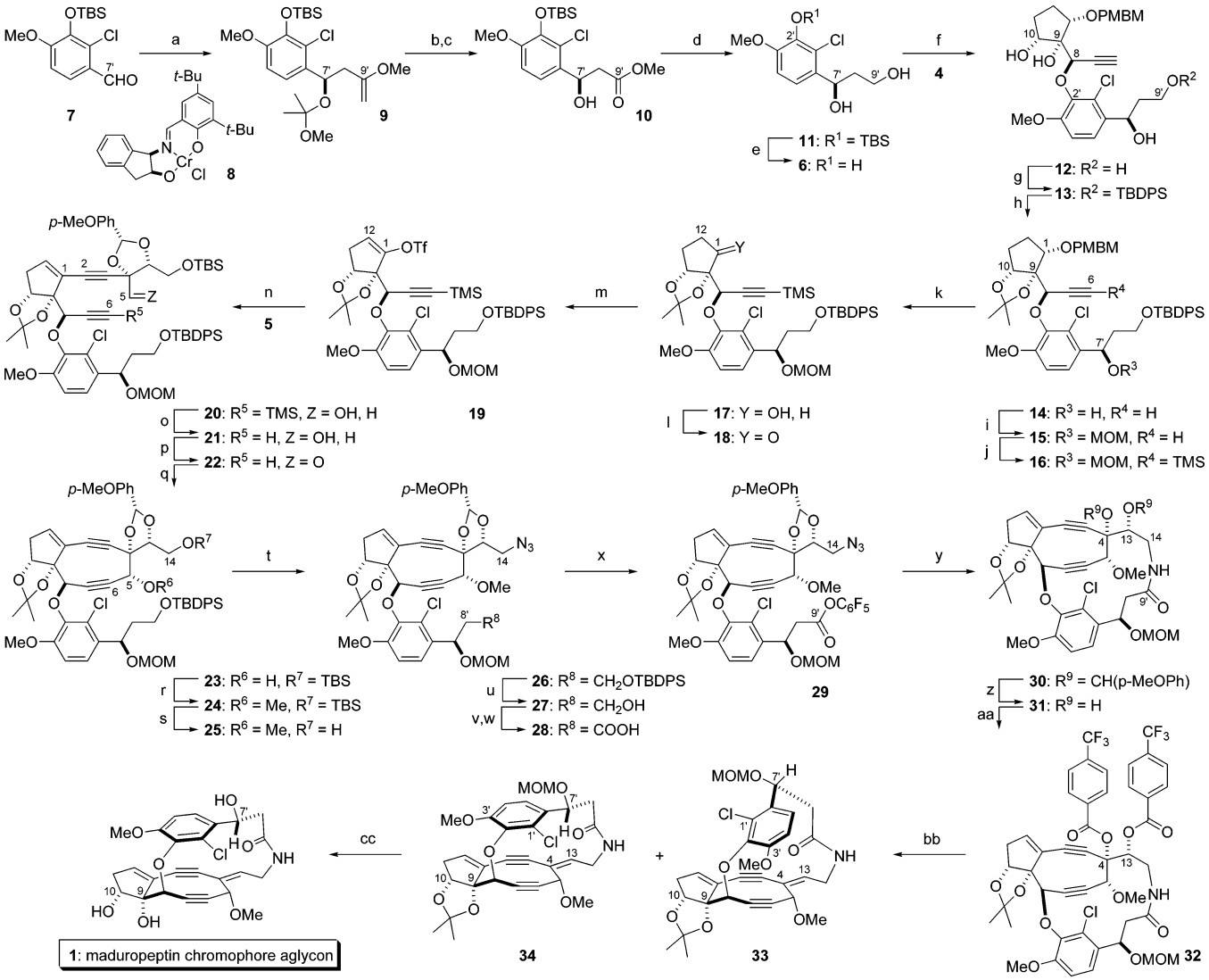
Scheme 1. Total Synthesis of the Maduropeptin Chromophore Aglycon[a]



[a] Reagents and conditions: (a) 2-methoxypropene, **8** (5 mol %), acetone, BaO, 4 °C; (b) O_3, CH_2Cl_2, −78 °C; then Me_2S; (c) PPTS, MeOH, 76% (3 steps, 98% ee); (d) $LiAlH_4$, Et_2O, reflux, 91%; (e) TBAF, THF, rt, 86%; (f) **4** (1.0 equiv), CsF, DMF, 80 °C, 74%; (g) TBDPSCl, Et_3N, DMAP, CH_2Cl_2, rt, 88%; (h) *p*-TsOH, 2,2-dimethoxypropane, MeOH, 91%; (i) MOMCl, *i*-Pr_2NEt, CH_2Cl_2, 84%; (j) $LiN(TMS)_2$, TMSCl, THF, −78 °C to rt, 82%; (k) DDQ, CH_2Cl_2/pH 7 buffer (10/1), 99%; (l) Dess−Martin periodinane, $NaHCO_3$, CH_2Cl_2, 100%; (m) $LiN(TMS)_2$, $PhNTf_2$, THF, −78 °C to rt, 87%; (n) **5** (1.0 equiv), $Pd(PPh_3)_4$ (5 mol %), CuI, *i*-Pr_2NEt, DMF; (o) K_2CO_3, MeOH, 83% (2 steps); (p) Dess−Martin periodinane, $NaHCO_3$, CH_2Cl_2, 100%; (q) $LiN(SiMe_2Ph)_2$ (9 equiv), $CeCl_3$ (10 equiv), THF (22 mM), −35 to −25 °C; (r) MeI, NaH, THF, 0 °C, 82% (2 steps); (s) TBAF, THF, 0 °C, 55%; (t) PPh_3, DEAD, $(PhO)_2P(O)N_3$, THF, rt; (u) TBAF, THF, 0 °C, 58% (2 steps); (v) Dess−Martin periodinane, CH_2Cl_2, rt; (w) $NaClO_2$, NaH_2PO_4, *t*-BuOH/2-methyl-2-butene/H_2O (6/3/2), 0 °C; (x) C_6F_5OH, EDC, DMAP, CH_2Cl_2, rt, 50% (3 steps); (y) PPh_3, Et_3N, THF/H_2O (30/1, 4 mM), 45 °C, 66%; (z) PPTS, *p*-TsOH, MeOH; (aa) *p*-(trifluoromethyl)benzoyl chloride, DMAP, CH_2Cl_2, 0 °C; (bb) SmI_2, THF, −50 °C, 15 min, 38% (**33**:**34** = 1:4.1 in DMSO-d_6, 3 steps); (cc) 8 N HCl/CF_3CH_2OH (1/2), 0 °C, 7%.

H_2O (30:1) at 45 °C resulted in formation of the 15-membered macrolactam through the intermediacy of the corresponding C14-primary amine (66% yield),[3a,15] thus realizing the synthesis of framework **30** of the chromophore. In order for the present route to be synthetically practical, it was particularly important that the cyclization reactions of both **22** and **29** could be performed under non-high-dilution conditions (22 and 4 mM, respectively) on a gram scale without decreasing the yield.

The last phase of the synthesis was the introduction of C4,13-*Z*-olefin through the SmI_2-promoted facile 1,2-elimination of *p*-(trifluoromethyl)benzoates.[6] To prepare for the key reaction, the *p*-methoxy benzylidene group of **30** was removed in the presence of the MOM group using a 1:1 molar mixture of PPTS/*p*-TsOH in methanol to afford 1,2-diol **31**, which was treated with *p*-(trifluoromethyl)benzoyl chloride and DMAP to yield **32**. Treatment of bisbenzoate **32** with SmI_2 at −50 °C for 15 min delivered the desired C4,13-*Z*-olefin as a mixture of atropisomers (**33**:**34** = 2:1, 38% for three steps); the corresponding *E*-olefin was not observed in this reaction. As shown in Figure 2, the observed NOEs unambiguously established the structures of **33** and **34**. Remarkably, potentially reactive functionalities such as the propargylic aryl and methyl ethers were unchanged, indicating the broad applicability of the present 1,2-elimination strategy. The stereoselective formation of the C4,13-*Z*-olefin can be explained by the conformational stability of the C4-organosamarium intermediate, generated by reduction of the C4-benzoate (Scheme 2). The conformation **35B**, in which both the benzoate and the macrocyclic ring are oriented upward, suffers from the resulting large steric interaction and/or increased ring strain; consequently, **35B**, which leads to the *E*-olefin, is strongly disfavored in comparison to **35A** that produces **33** and **34**. Thus, the 15-membered macrocycle appeared to kinetically control the sole formation of the *Z*-olefin.[16]

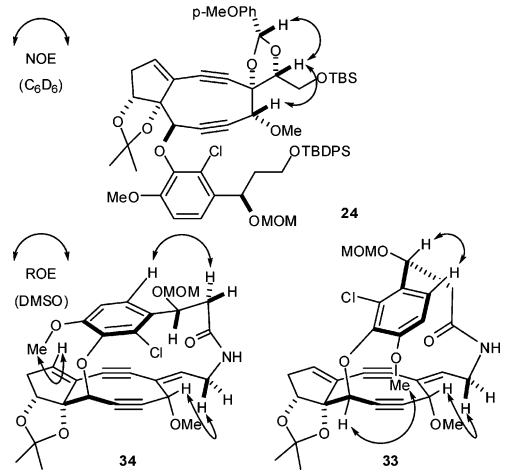
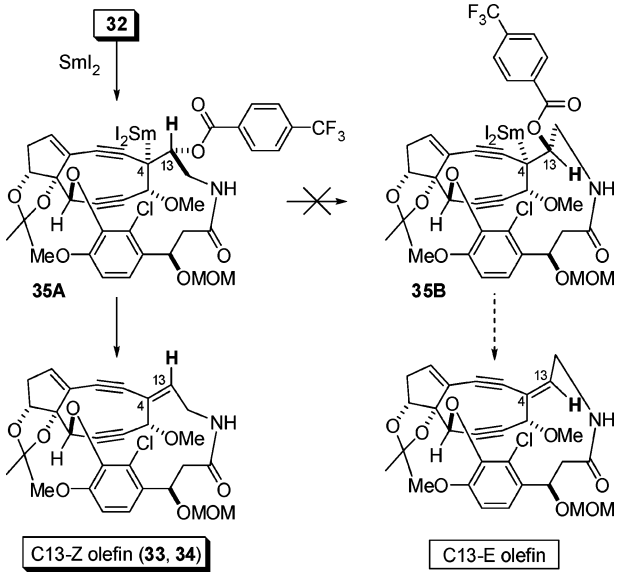


Figure 2. NOE and ROE data of the synthetic intermediates (**24**, **33**, and **34**).

Scheme 2. Mechanistic Rationale for Formation of **33** and **34** from **32**



It is noteworthy that the ratio of atropisomers **33** and **34** highly depends on polarity of the solvent,[17] and that the chromatographically separated isomers equilibrated at room temperature to provide the same mixture of isomers after several hours.[18] Most intriguing is the fact that the acid-promoted global deprotection of the mixture of **33** and **34** gave rise to aglycon **1** as the sole atropisomer that corresponds to the natural chromophore **2**. The above results indicate that the rotational barrier of the 2,6-substituted benzene was unexpectedly low in comparison to the closely related C-1027 chromophore,[6,19] and that the energy difference of the deprotected atropisomers was larger than that of their protected counterparts.

In summary, the total synthesis of the aglycon of the maduropeptin chromophore was accomplished for the first time. The key features of this synthesis are (1) the efficient convergent union of the three fragments (**4**, **5**, and **6**), (2) the cerium amide promoted nine-membered diyne ring formation, (3) the one-pot macrolactam formation from the azide-PFP ester, and (4) the SmI_2-mediated reductive 1,2-elimination for the stereoselective construction of the C4,13-*Z*-olefin. Further studies on the total synthesis of chromophore **2** and its various synthetic analogues from **1** are currently underway in our laboratory.

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Note Added after ASAP Publication. After this paper was published ASAP October 23, 2007, the structures of several compounds were modified in Figure 1 and Scheme 1. The corrected version was published ASAP October 25, 2007.

Supporting Information Available: General methods and spectroscopic and analytical data for selected compounds (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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