Natural Products

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Total Synthesis of a Protected Aglycon of the Kedarcidin Chromophore**

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The proposed structure for the chromophore of the chromoprotein enediyne antitumor antibiotic kedarcidin[1,2] has undergone several revisions because of its high reactivity and complex architecture. The structure of the kedarcidin chromophore was first proposed by scientists at Bristol-Myers Squibb in 1992.[3] Subsequently, the α-azatyrosyl fragment of the ansa-bridge was revised to the corresponding β-amino acid derivative, and the absolute structure of the whole molecule was updated as **1** in 1997.[4] In 2007, Myers and coworkers completed the formidable total synthesis of **1**, upon which, the ^{1}H NMR data led to an additional revision of the C10 stereochemistry as shown in structure **2** (Figure 1).[5]

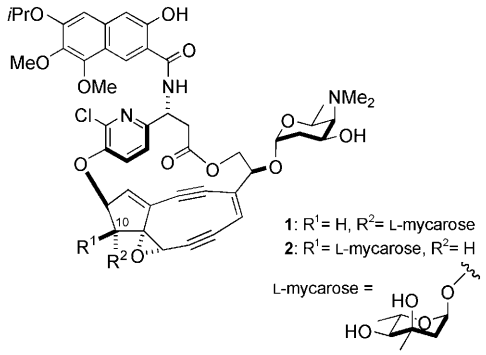
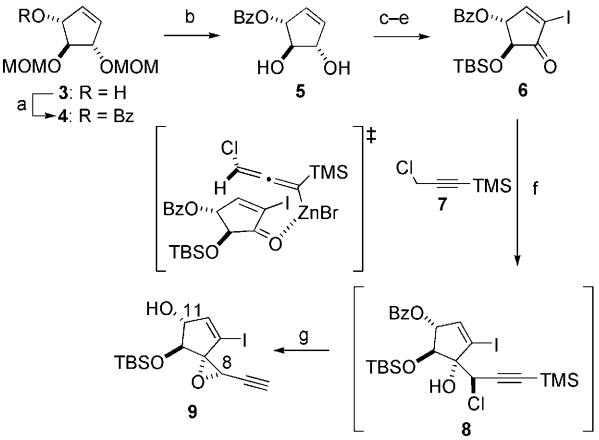


Figure 1. Structure of the kedarcidin chromophore.

In previous reports, the construction of the C8–C9 epoxide of the kedarcidin chromophore in the presence of the ansa-bridge proved to be difficult at the later stages of the synthesis.[6] Recently, however, we have developed a facile and chemoselective SmI_2-mediated reductive elimination of 1,2-diol derivatives,[7,8] which was applicable to the construction of the epoxybicyclo[7.3.0]dodecadienediyne core of **1**, enabling the formation of the epoxide moiety during the early stages of the synthesis.[9] The application of our strategy towards the synthesis of the aglycon fragment **24** of **2**, which includes the highly functionalized macrolactone and an epimeric alcohol at C10, needed to be investigated. Herein, we describe the successful application of our novel convergent strategy towards the synthesis of the protected aglycon **24**; the synthesis features alkynyl epoxide **9** as a key fragment, a nine-membered ring cyclization between C5 and C6, and a SmI_2-mediated reductive olefination in the presence of both the C8–C9 epoxide and the highly functionalized ansa-macrolide. The resulting product exhibited an NMR spectrum that was consistent with that of the natural chromophore.

The key cyclopentene alkynyl epoxide **9** was prepared from the previously reported optically pure **3** (Scheme 1).[10] After the transformation of **3** into iodoenone **6**,[11] the stereoselective synthesis was carried out by using an allenyl zinc methodology[12] to efficiently afford **9**. According to the protocol reported by Chemla et al. and Caddick and coworkers, 3-chloro-1-trimethylsilylpropyne (**7**) was reacted with zinc bromide and subsequent treatment with lithium diisopropylaminde at low temperatures to form the allenyl



Scheme 1. Synthesis of alkynyl epoxide **9**: a) BzCl (1.5 equiv), pyridine (3.0 equiv), CH_2Cl_2, RT, 16 h; b) CH_3CN/6 M HCl (5:1), RT, 70 h, 57% (2 steps); c) MnO_2 (6.0 equiv), CH_2Cl_2, RT, 15 h; d) TBSOTf (1.5 equiv), 2,6-lutidine (3.0 equiv), CH_2Cl_2, −70 °C, 1 h, 35% (2 steps); e) I_2 (2.2 equiv), pyridine (3.3 equiv), THF, RT, 3 h, 100%; f) **7** (2.0 equiv), $ZnBr_2$ (4.0 equiv), $LiN(iPr)_2$ (4.0 equiv), THF, −78 °C → −18 °C, 16 h; g) K_2CO_3 (3.0 equiv), MeOH, RT, 1 h, 51% (from **6**). Bz = benzoyl, MOM = methoxymethyl, TBS = *tert*-butyldimethylsilyl, Tf = Trifluoromethanesulfonyl.

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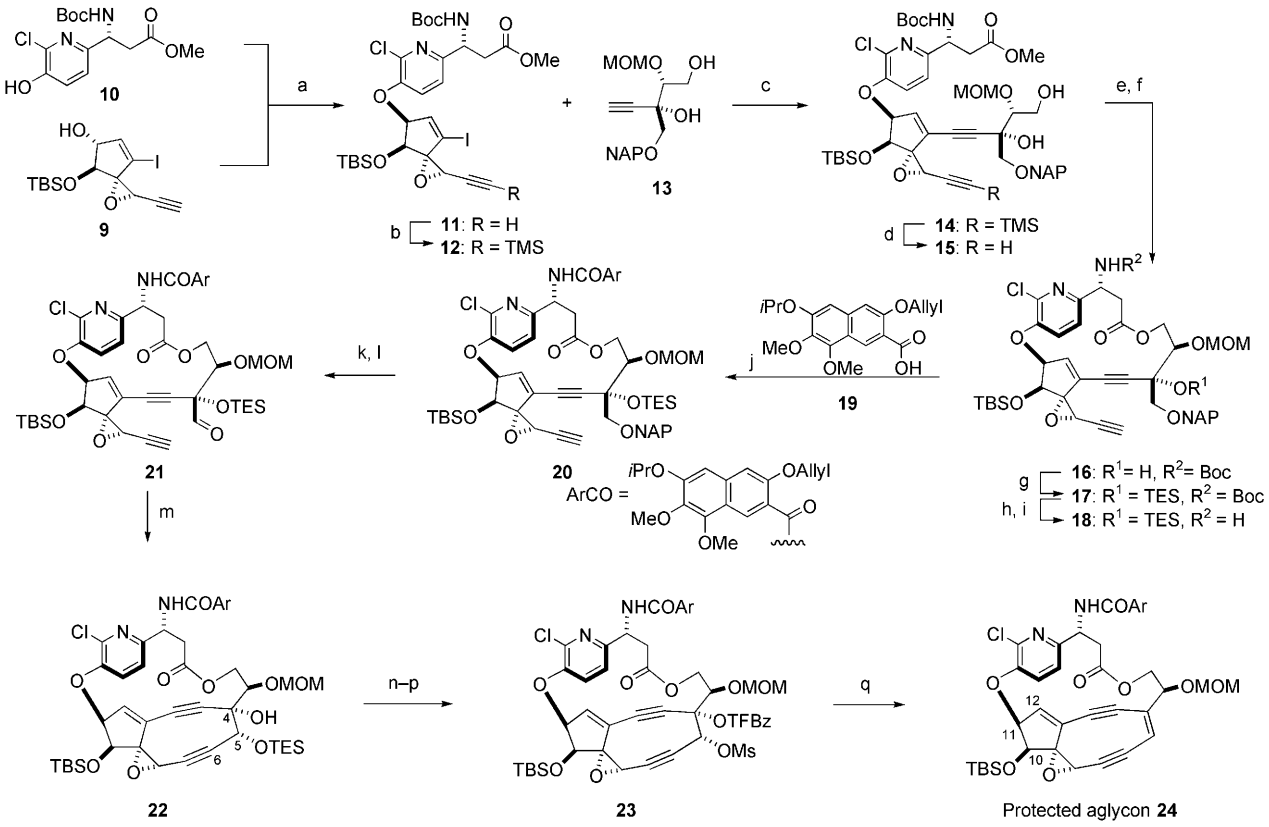
zinc reagent. Ketone **6** was then added to this reagent, and subsequent methanolysis of the benzoate using K_2CO_3 in MeOH, provided **9** almost exclusively in 51% overall yield via the chlorohydrin intermediate **8**. The stereochemistry of the newly formed alkynyl epoxide **9** was confirmed on the basis of NOE correlations between the protons on C8 and C11. This remarkable stereochemical outcome can be attributed to a transition state that minimizes the steric interactions between the substituents on the cyclopentenone ring (C11 benzoate and C10 OTBS groups) and the chlorine atom of the allenyl zinc.[12b]

The assembly of the four fragments is illustrated in Scheme 2. The aryl ether bond between **9** and the β-2-chloroazatyrosine derivative **10**[4,10] was formed by using a Mitsunobu reaction to afford **11** with stereochemical inversion.[13] Upon protection of the alkyne terminus of **11** with a TMS group (82% yield), alkenyl iodide **12** and alkyne **13**[14] were coupled by using a Sonogashira coupling[15] to afford **14**. The selective removal of the TMS group using TBAF at low temperature afforded **15** in 71% yield (two steps). Alkaline hydrolysis of the methyl ester of **15** and subsequent macrolactonization of the corresponding carboxylic acid and the primary alcohol was effectively achieved by using the protocol reported by Shiina et al.[16] to give **16** as a single atropisomer in 62% yield (two steps). The stereochemistry of **16** was determined by NOESY correlations between the protons at C8 and C4′ (Figure 2a). The remaining tertiary alcohol of **16** was protected by using a TES group and the Boc group of **17** was removed by using TBSOTf and 2,6-lutidine[17] without affecting the reactive epoxide to yield free amine **18**. Compound **18** was then immediately condensed with naphthoic acid **19**[10] to give amide **20** in 71% overall yield.

The next step in our synthetic methodology was the cyclization, in the presence of the highly functionalized ansamacrolide bridge, to form a nine-membered diyne ring. We have previously encountered severe difficulties in forming the nine-membered ring by bond formation between C7 and C8



Scheme 2. Total synthesis of protected aglycon of kedarcidin chromophore: a) **10** (1.0 equiv), DEAD (1.3 equiv), Ph_3P (1.3 equiv), benzene, 0°C, 1 h, 67%; b) TMSCl (20.0 equiv), $LiN(TMS)_2$ (22.5 equiv), THF, −60°C, 20 min, 82%; c) **13** (1.5 equiv), CuI (0.4 equiv), $Pd(PPh_3)_4$ (0.1 equiv), iPr_2NEt (3.0 equiv), DMF, RT, 1 h; d) TBAF (1.2 equiv), THF, −70°C, 30 min, 71% (2 steps); e) 0.3 M aq. KOH (2.7 equiv), THF/MeOH (2:1), RT, 5 h; f) *m*-nitrobenzoic anhydride (2.5 equiv), DMAP (5.0 equiv), CH_2Cl_2, reflux, 20 h, 62% (2 steps); g) TESCl (3.0 equiv), imidazole (6.0 equiv), DMF, RT, 1 d; h) TBSOTf (6.0 equiv), 2,6-lutidine (8.0 equiv), CH_2Cl_2, −50°C, 30 min to 0°C, 1 h; i) SiO_2, CH_2Cl_2, RT, 20 h; j) **19** (1.0 equiv), EDC·HCl (5.0 equiv), HOAt (5.2 equiv), CH_2Cl_2, RT, 23 h, 71% overall yield (from **16**); k) DDQ (10.0 equiv), CH_2Cl_2/H_2O (5:1), RT, 1.5 h; l) Dess–Martin periodinane (3.0 equiv), $NaHCO_3$ (9.0 equiv), CH_2Cl_2, RT, 1 h, 95% (2 steps); m) $CeCl_3$ (26.5 equiv), $LiN(TMS)_2$ (25.1 equiv), THF, −30°C, 20 min, 61%; n) TBAF (2.0 equiv), THF, −78°C; o) Ms_2O (3.0 equiv), pyridine (6.0 equiv), CH_2Cl_2, 0°C, 20 min; p) TFBzCl (10.0 equiv), DMAP (20.0 equiv), CH_2Cl_2, 0°C, 6 min, 35% (3 steps); q) SmI_2 (1.5 equiv), THF, −20°C, 8 min, 57%. Boc = *tert*-butoxycarbonyl, DEAD = diethyl azodicarboxylate, TMS = trimethylsilyl, NAP = 2-naphtylmethyl, TBAF = tetra-*n*-butylammonium fluoride, TES = triethylsilyl, DMAP = *N*,*N*-4-dimethylaminopyridine, EDC = 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide, HOAt = 1-hydroxy-7-azabenzotriazole, DDQ = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone, TFBz = 4-trifluoromethylbenzoyl.

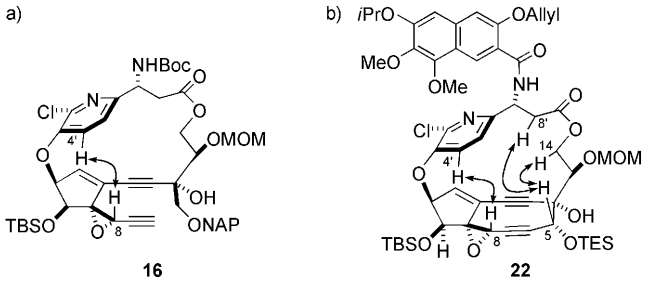
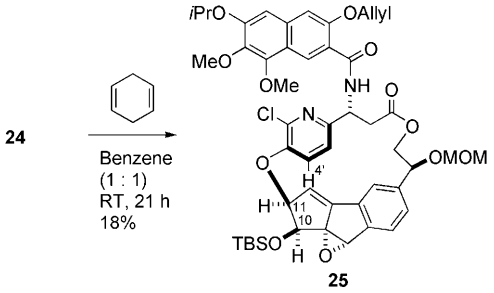


Figure 2. a) NOESY correlation (400 MHz ^{1}HNMR instrument) for **16**), and b) ROESY (600 MHz ^{1}HNMR instrument) for **22** (b).



Scheme 3. Spontaneous Masamune–Bergmann cycloaromatization of **24**.

and therefore attempted another route.[6] The cyclization precursor **21** was effectively obtained in 95% yield (two steps) by the selective removal of the NAP protecting group of the primary alcohol at C5 using excess DDQ under mild conditions[18] and subsequent Dess–Martin oxidation.[19] The cyclization **21** was carried out by using the $CeCl_3$/LHMDS-mediated protocol[20] at −30 °C to generate unstable **22** in 61% yield; during the cyclization in the TES group migrated to the newly formed secondary alcohol at C5. This acetylide/aldehyde condensation to form a bond between C5 and C6 proved to be an efficient and practical scheme.[21] The configuration of the *cis*-C4,C5-diol **22**, including the single atropisomerism, was unambiguously determined by using ROESY experiments (Figure 2b). Notably, cyclized compounds that possess free hydroxy groups on the nine-membered cyclic core, such as **22**, require careful treatment because of their instability at ambient temperatures.

Lastly, the most uncertain step involved the final reductive 1,2-elimination of the C4,C5-diol of **22** to complete the highly functionalized ansa-bridged nine-membered epoxyenediyne structure. Upon removal of the TES group of the **22** using TBAF at −78 °C, the resulting highly labile diol was immediately mesylated, and then quickly treated with 4-trifluoromethylbenzoyl chloride and DMAP at 0 °C to provide **23** in a moderate yield. Subsequently, **23** was subjected to a SmI_2-mediated 1,2-elimination at −20 °C for eight minutes to yield the protected aglycon fragment **24** of the kedarcidin chromophore as a single atropisomer in 57% yield. Again, the elimination reaction was remarkable in terms of high chemoselectivity and compatibility with the functional groups present.[7,9] The resulting unstable aglycon **24** underwent spontaneous cycloaromatization without chemical activation,[3a] in 1,4-cyclohexadiene and benzene (1:1), to give aromatized **25** via an equilibrated *p*-benzyne biradical intermediate (Scheme 3).[22]

The ^{1}H NMR spectra of synthetic **24** were compared to those of the natural chromophore. The observed coupling constants for the protons on C10 and C11 ($J = 5.6$ Hz), and on C11 and C12 ($J = 2.8$ Hz) of **24** in $CDCl_3$ were similar to those of the authentic kedarcidin chromophore (generously provided by Dr. John E. Leet).[3] Moreover, the chemical shifts of the protons on C10, C11, and C12 of **24** were comparable to those of the authentic compound (see the Supporting Information) while the synthetic compound **24** is a protected aglycon. For **25**, the absence of an NOE between the protons on C10 and C4′, and the presence of a strong NOE between the protons on C10 and C11, as well as their coupling constant ($J = 6.0$ Hz), were consistent with the data reported for the reduction-induced aromatized compound derived from the natural chromophore.[3b] The results of our spectroscopic studies strongly support the recently revised stereochemical structure as proposed by Myers and co-workers.[5]

In summary, we have developed an enantioselective synthetic route for the protected aglycon of kedarcidin chromophore with the revised stereochemistry at C10.[23] The key features of our methodology are: 1) the efficient convergent assembly of four fragments (Scheme 2), 2) a novel strategy involving alkynyl epoxide **9** as a key fragment, 3) a cerium amide promoted nine-membered diyne ring cyclization between C5 and C6, and 4) a SmI_2-mediated reductive 1,2-elimination for the chemoselective olefination in the presence of the C8–C9 epoxide and the highly functionalized ansa-macrolide. Additional studies on the total synthesis of chromophore **2** are currently underway in our laboratory.

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