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Natural Product Synthesis

Total Synthesis of the C-1027 Chromophore Core: Extremely Facile Enediyne Formation through SmI_2-Mediated 1,2-Elimination**

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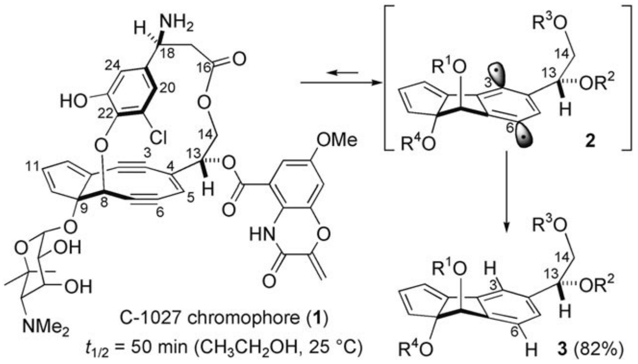
The antitumor antibiotic C-1027[1] is a complex between the reactive chromophore **1** (Scheme 1) and an apoprotein.[2] The chromophore **1** is responsible for DNA recognition and damage, and the apoprotein functions as an effective drug-delivery system. As the free chromophore, **1** is the most labile enediyne studied to date:[3,4] It is transformed into **3** in 82% yield by Masamune–Bergman rearrangement and subsequent hydrogen abstraction (ethanol, 25 °C) with a half-life of 50 min.[5] In a biological setting, the *p*-benzyne biradical **2** abstracts hydrogen atoms from DNA in a sequence-selective manner to cause oxidative double-strand cleavage.



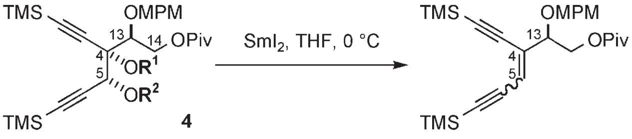
Scheme 1. Structure of the C-1027 chromophore and its Masamune–Bergman rearrangement.

The structure of **1** is highly unusual. Its complicated fused-ring system comprises a cyclopentadiene ring, a nine-membered enediyne ring, and a chlorocatechol-containing 17-membered macrolactone that displays nonbiaryl atropisomerism. We reported previously the synthesis of the framework **7** (Scheme 2) by a route that featured atropselective macrocyclization prior to the formation of the nine-membered ring.[6] Herein we describe the design and development of new and effective methodology for the construction of enediyne structures. This approach enabled the first synthesis of the exceedingly unstable core structure of the chromophore **1**.[7]

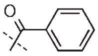
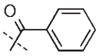
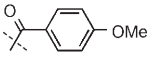
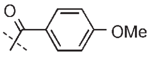
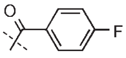
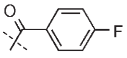
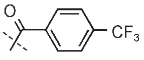
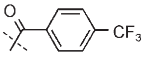
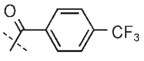
The synthesis of the nine-membered enediyne ring **14** from diyne **7** required the highly chemoselective formation of the C4,C5 alkene from the protected C4,C5,C13,C14-tetraol structure in the presence of other sensitive functionalities (Scheme 2). Moreover, to isolate the targeted compound **14** in reasonable yield before its self-degradation through rearrangement, the reductive 1,2-elimination reaction needed to be complete within 10 min below room temperature.[8] The olefination was unsuccessful when existing methodologies were used, including our own,[9] so we sought alternative reaction conditions and substrates.

Model experiments with **4** revealed that an SmI_2-mediated elimination reaction[10] had significant potential for the formation of enediynes (Table 1).[11] The acyclic enediyne **5** was generated efficiently in the presence of SmI_2 in THF from the dimesylate **4a** (Table 1, entry 1); however, the reaction was faster for the dibenzoate **4b** (Table 1, entry 2). The reactivity of dibenzoate substrates was found to be highly sensitive to the substituents on the benzene rings (Table 1, entries 2–5): The reaction was slower when an electron-donating methoxy group was present (Table 1, entry 3) and

Table 1: SmI_2-mediated 1,2-elimination reaction.



5 (E : Z 1 : 0.4–0.8)

Entry	4	R^1	R^2	*t*	Yield [%]
1	a	Ms	Ms	2 h	94
2	b			0.7 h	80
3	c[a]			7 h	87
4	d			0.5 h	98
5	e			5 min	95
6	f		Ms	1 min	93

[a] The reaction mixture was warmed from 0 °C to room temperature. Piv = pivaloyl, TMS = trimethylsilyl.

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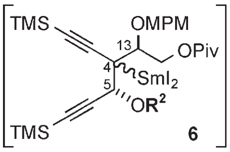
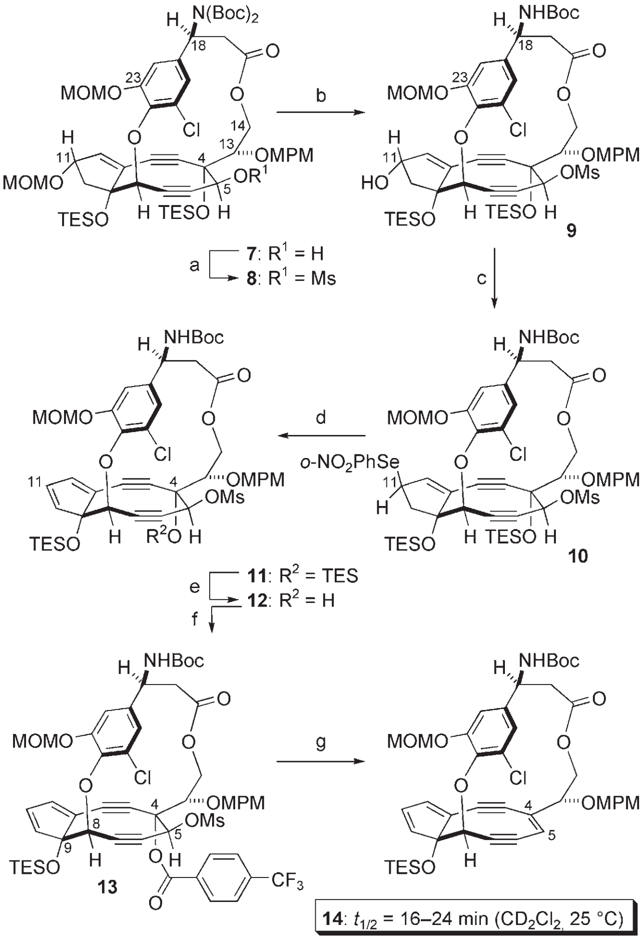
significantly faster with an electron-withdrawing trifluoromethyl substituent (Table 1, entry 5). Remarkably, the transformation of the mesylated mono-*p*-trifluoromethylbenzoate **4f** into **5** (Table 1, entry 6) took only 1 min. Thus, a facile 1,2-elimination method was discovered by means of substrate design.

A likely mechanism for the elimination reaction involves expulsion of the benzoate group from the α-oxy benzylic radical species generated upon SmI_2-promoted carbonyl reduction of the benzoate at C4, followed by reduction of the resulting C4 radical to afford the organosamarium intermediate **6**. Elimination of the ester at C5 then delivers the C4,C5 alkene **5** (Table 1). The high reactivity of the electron-deficient *p*-trifluoromethylbenzoates **4e** and **4f** reflects their potency in accepting electrons from SmI_2. Formation of the C4,C13 alkene from **6** was not observed, as the C5 benzoate and mesylate groups in the substrates are better leaving groups than the OMPM group at C13.

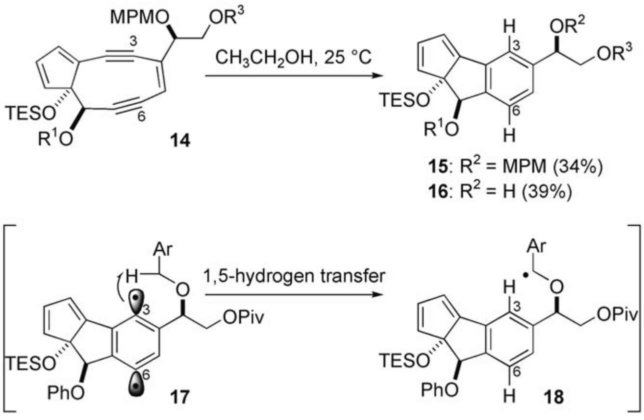


Having developed a powerful olefination of the protected tetraol **4**, we turned our attention to the construction of the cyclic enediyne structure with the macrolactone bridge (Scheme 2). The prerequisites for reaching the final olefination step were judicious protecting-group manipulations and the construction of the cyclopentadiene substructure in the presence of the unstable nine-membered diyne.[6,12] Following the conversion of the secondary alcohol **7** into its mesylate **8**, one MOM group (at the C11 hydroxy group) and one of the two Boc groups on the amino group at C18 were removed selectively to give **9** by treatment with Me_2BBr in CH_2Cl_2 at −80 °C.[13] The MOM ether at C23 remained intact under these conditions, presumably as a result of the lower Lewis basicity of the phenolic oxygen atom. The liberated allylic alcohol in **9** underwent S_N2 displacement in the presence of *o*-nitrophenyl selenocyanate and tributylphosphine to form the selenide **10**,[14] which was oxidized with hydrogen peroxide to afford the cyclopentadiene **11** through a smooth *syn* elimination. Next, the C4 hydroxy group was deprotected selectively by treatment with TBAF at −80 °C, and the resulting tertiary alcohol **12** was subjected to benzoylation with *p*-trifluoromethylbenzoyl chloride and DMAP to provide **13**. Finally, the 1,2-elimination of **13** in [D8]THF in the presence of SmI_2 was complete within 5 min at 0 °C[15] to give the C-1027 chromophore core **14** in 87 % yield (as determined by ^1H NMR spectroscopy in CD_2Cl_2). This efficient transformation demonstrates clearly the high chemoselectivity and functional-group compatibility of the elimination reaction: Potentially reactive functionalities, such as the doubly allylic OTES group at C9 and the propargylic OAr moiety at C8, remained untouched.

Surprisingly, **14**, which has the same fused-ring system as the natural product **1**, appears to be significantly more labile ($t_{1/2} \approx 20$ min; CD_2Cl_2, 25 °C) than **1** and reacts rapidly in ethanol. This unexpected physicochemical property prompted us to investigate the cycloaromatization reaction further (Scheme 3). The treatment of **14** with ethanol generated **16** (39 %), without the MPM protecting group, in addition to **15** (34 %). We believe the alcohol **16** to originate



Scheme 2. Total synthesis of the C-1027 chromophore core: a) MsCl, Et_3N, CH_2Cl_2, 0 °C, 86 %; b) Me_2BBr, CH_2Cl_2, −80 °C, 89 %; c) *o*-$NO_2PhSeCN$, nBu_3P, THF, 0 °C→RT; d) H_2O_2, THF, room temperature, 54 % (2 steps); e) TBAF, THF, −80 °C, 76 %; f) *p*-$CF_3C_6H_4COCl$, DMAP, CH_2Cl_2, 0 °C, 99 %; g) SmI_2, [D8]THF, 0 °C, 5 min, 87 %. Boc = *tert*-butoxycarbonyl, DMAP = 4-dimethylaminopyridine, MOM = methoxymethyl, MPM = *p*-methoxyphenylmethyl, Ms = methanesulfonyl, TBAF = tetrabutylammonium fluoride, TES = triethylsilyl.



Scheme 3. Possible reaction of **14** involving 1,5-hydrogen transfer.

from intramolecular 1,5-hydrogen abstraction by the phenyl radical at C3 in **17** to form the better stabilized benzylic radical **18**,[16] followed by the addition of molecular oxygen and oxidative cleavage.[4] This pathway would contribute to the shorter half-life of **14** relative to that of **1**, which has no proximal hydrogen atoms in a 1,5-relationship with C3 or C6.

In summary, an extremely facile SmI_2-mediated 1,2-elimination was developed with *p*-trifluoromethylbenzoate as an electron acceptor. This method enabled the synthesis of the unusually labile C-1027 chromophore core in the form of compound **14**. The powerful yet mild nature of this methodology should enable access not only to the chromophore **1**, related enediyne natural products, and their analogues,[17] but also to other natural and non-natural unsaturated compounds with highly complex structures.

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