ORGANIC LETTERS

2004
Vol. 6, No. 21
3833−3836

Synthesis of the Bicyclo[7.3.0]dodecatrienediyne Core of the C-1027 Chromophore

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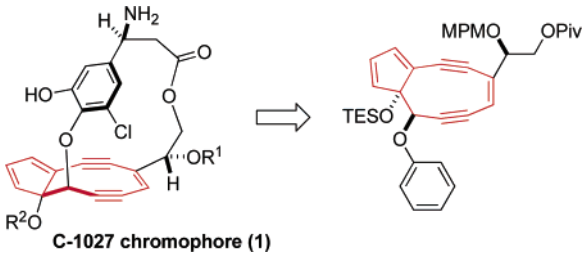
Received July 30, 2004

ABSTRACT



C-1027 chromophore (1)

C-1027, an extremely potent antitumor agent, is composed of chromophore 1 and an apoprotein. Here we report a general and efficient route to the exceedingly reactive bicyclo[7.3.0]dodecatrienediyne core of 1, utilizing selenoxide elimination and epoxide deoxygenation to build the cyclopentadiene and enediyne structures, respectively.

The chromoprotein C-1027[1] is composed of an 11-kDa apoprotein[2] and a highly reactive chromophore (**1**, Figure 1)[3] and displays potent antitumor activity. C-1027 chromophore **1** is bound noncovalently in a cleft of the apoprotein and is dissociable.[4,5] When not bound to the apoprotein, **1** quickly aromatizes via Masamune−Bergman rearrangement[6] at room temperature without any external activators (**1** → **3**).[7] *p*-Benzyne biradical **2**, generated from **1**, exerts its potent biological activity by abstracting hydrogens from the sugar portions of double-stranded DNA, which ultimately leads to oxidative cleavage.[8]

The highly reactive bicyclo[7.3.0]dodecatrienediyne structure of **1** is central to this potent biological activity. The chromophore components of other related agents such as maduropeptin,[9] kedarcidin,[10] and neocarzinostatin[11] share a

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10.1021/ol048494i CCC: $27.50
Published on Web 09/16/2004

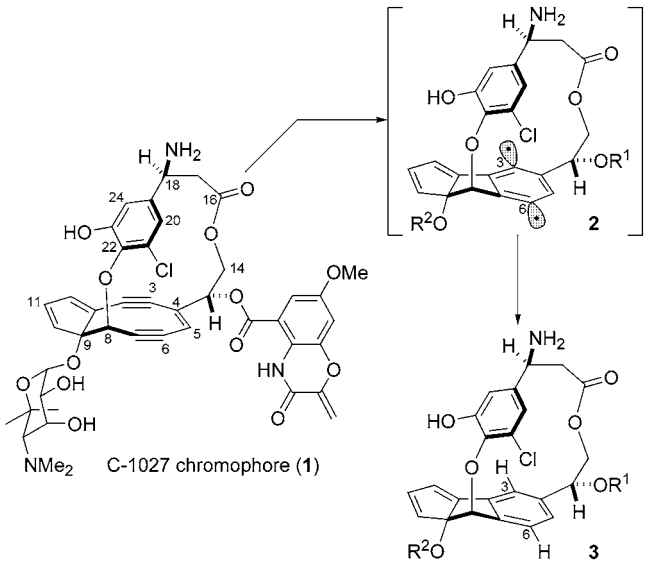
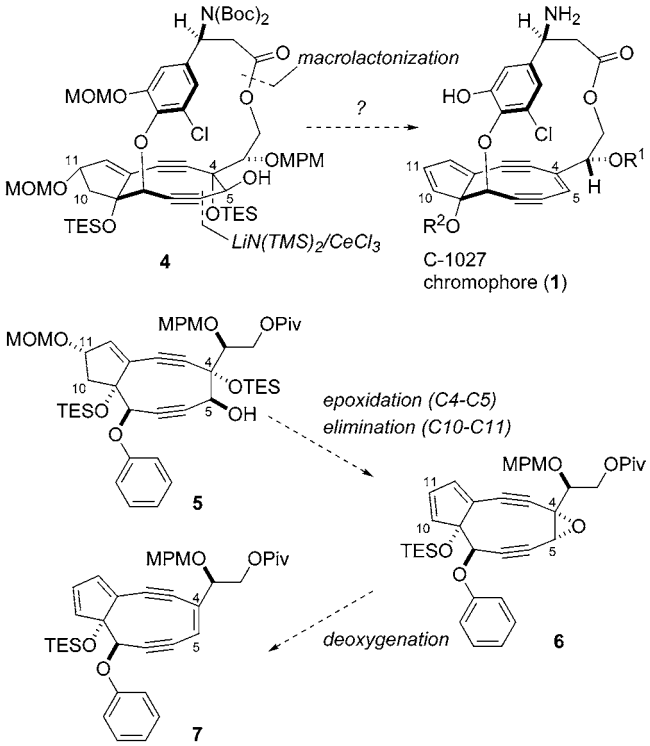


Figure 1. Structure of the C-1027 chromophore and its Masamune−Bergman rearrangement.

common bicyclo[7.3.0]dodecadiyne core but differ in the degree of oxidation and unsaturation. Chromophore **1** has the most unsaturated structure among these enediyne natural products: only two sp^3 carbons are present within the dodecacycle while the other 10 carbons are conjugated. Here, we report a general and efficient route to the trienediyne structure, which is to date the only synthetic construct that bears the fused ring system of the cyclopentadiene and enediyne structures.[12−16]

In prior work, we efficiently constructed the C-1027 chromophore framework **4** through atropselective macrolactonization and subsequent $LiN(TMS)_2/CeCl_3$-promoted nine-membered ring cyclization (Scheme 1).[17] The most formidable problem for the total synthesis of **1** from diyne **4** is apparently the formation of the reactive bicyclo[7.3.0]-dodecatrienediyne. We therefore undertook, as a model study, the synthesis of trienediyne **7** from diyne **5**, which possesses the same structure as **4** except for the β-tyrosine moiety.

Scheme 1. Synthetic Plan of the Bicyclo[7.3.0]dodecatrienediyne Structure



Because of the general instability of the strained nine-membered diynes,[18] a synthetic scheme en route to **5** should constitute a series of mild reaction conditions. Moreover, introduction of the C4−C5 olefin should be at the last stage in order to avoid the consumption of synthetic intermediates via Bergman rearrangement. Hence, the cyclopentadiene structure was planned to be constructed prior to the enediyne through dehydration of the C11 alcohol (**5** → **6**). The C4−C5 olefin was then to be directly installed

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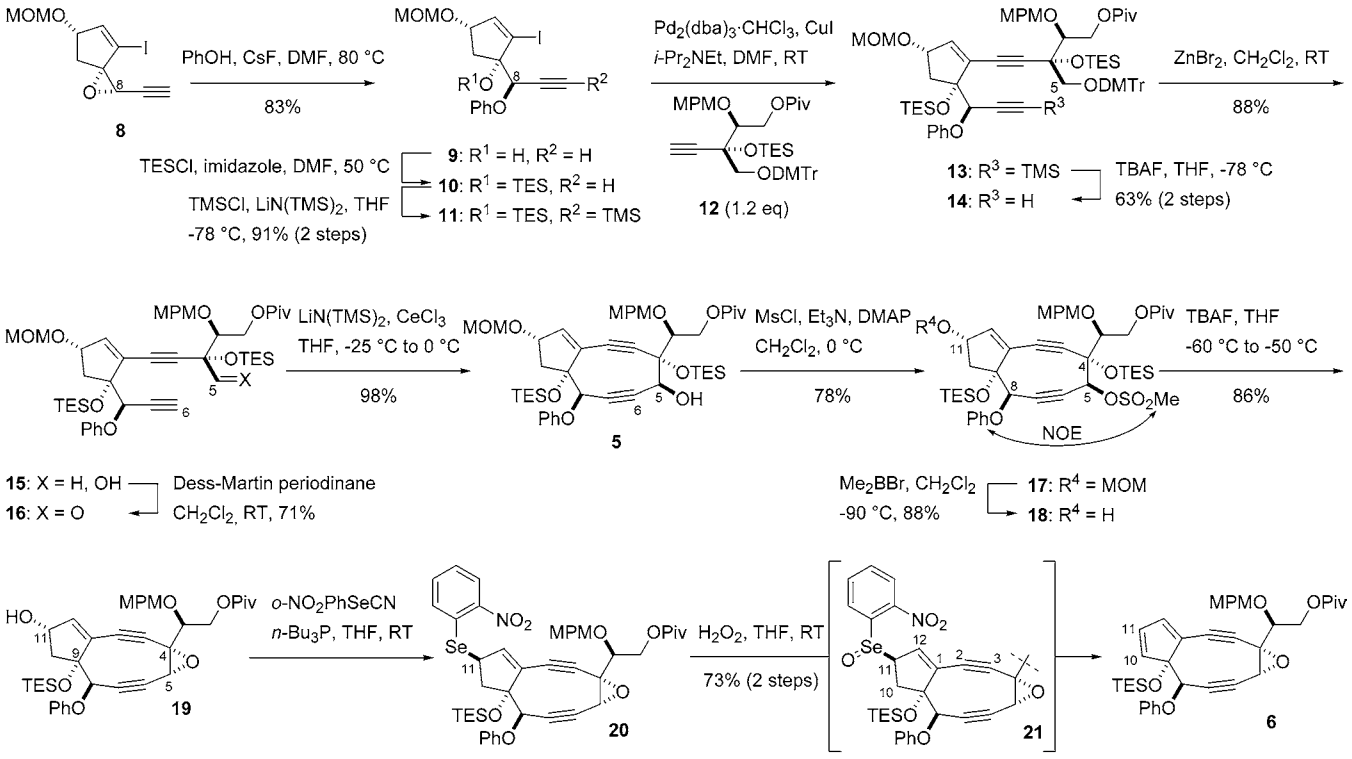
Scheme 2



via deoxygenation of epoxide **6**,[19] which in turn would be formed from the protected C4,C5-*trans*-diol **5**. Although epoxide deoxygenation has been demonstrated with various substrates in the context of natural product synthesis, the feasibility of this reaction, particularly given the highly unsaturated and strained structure of **6**, was uncertain.

Synthesis of diyne **5** started with the previously published intermediate **8**[17] (Scheme 2). First, CsF-promoted addition[12e,20] of phenol to epoxide **8** produced the aryl ether **9** in 83% yield. The tertiary alcohol of **9** was converted into TES ether **10**, and then a TMS group was introduced to the terminal acetylene to afford **11** in 91% yield over two steps. Sonogashira coupling[21] of **11** and acetylene moiety **12**[12f] in the presence of catalytic $Pd_2(dba)_3$ and CuI led to adduct **13**. The acetylenic TMS of **13** was selectively removed in the presence of the *O*-TES groups using TBAF at −78 °C to generate **14** in 63% yield over two steps. Removal of the DMTr group from **14** using $ZnBr_2$, followed by Dess−Martin oxidation (88% yield),[22] afforded aldehyde **16** in 71% yield. Next, cyclization of **16** was promoted by a 1:1 mixture of $LiN(TMS)_2$ and $CeCl_3$ in THF,[18] giving rise to the strained nine-membered diyne **5** as the sole isomer in 98% yield. After derivatization of **5** to its mesylate **17** (78% yield), the desired *trans* relationship of the C4- and C5-hydroxy groups was unambiguously determined by the NOE experiment.

After successful synthesis of the nine-membered diyne, we turned our attention to epoxide formation at C4−C5 and olefination at C10−C11. Selective deprotection of the MOM group in the presence of other potentially reactive protective groups (MPM and TES) was achieved using Me_2BBr[23] in CH_2Cl_2 at −90 °C, which resulted in alcohol **18** in 88% yield. TBAF treatment of bis-TES ether **18** under carefully controlled temperature conditions (−60 to −50 °C) led to chemoselective deprotection of the C4-OTES and concomitant epoxide formation to afford **19** in 86% yield.[13a]

Dehydration of allylic alcohol **19** turned out to be no easy task. Introduction of the leaving group to **19** did not induce *anti* elimination but typically resulted in decomposition. We therefore decided to utilize an arylselenoxide derivative, which could produce the olefin through *syn* elimination in neutral conditions. Treatment of α-alcohol **19** with 2-nitrophenyl selenocyanate and tributylphosphine in THF[24] produced *β*-selenide **20** through S_N2 displacement. The resultant **20** was oxidized with hydrogen peroxide at room temperature to afford the desired cyclopentadiene **6** in 73% yield over two steps. Fortunately, the *syn* elimination[25] was predominant over the [2,3]-sigmatropic rearrangement

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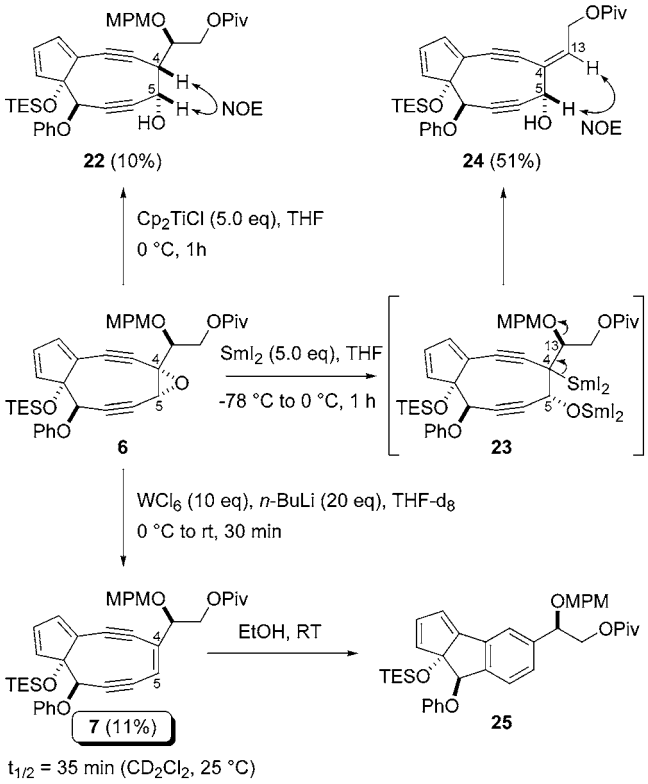
of C11-selenoxide **21** to C1,[26] presumably as a result of the pseudoequatorial orientation of the selenoxide and/or the unfavorable energy loss through deconjugation of the eneyne (C12−C1/C2−C3).

The last reaction of this model study was deoxygenation from epoxide **6** (Scheme 3). To isolate the target product **7**,

Scheme 3. Synthesis of Bicyclo[7.3.0]dodecatrienediyne through Deoxygenation



deoxygenation of **6** should be faster than the Masamune−Bergman reaction of the resultant enediyne. For this purpose, three powerful but mild metal reductants (Cp_2TiCl,[27] SmI_2,[28] and WCl_4/*n*-BuLi[29,30]), which are known to reduce epoxides to olefins, were applied to **6**. However, treatment of epoxide **6** with Cp_2TiCl only produced propargyl alcohol **22** (10% yield), which arose from C4-O cleavage and subsequent reduction at C4.[31] SmI_2-mediated reduction of **6** proceeded smoothly, but the undesired exo-olefin **24** was isolated in 51% yield. In this reaction, elimination of the C13-OMPM in organosamarium intermediate **23** preceded elimination of the samarium alkoxide at C5 that would lead to the desired product **7**.[32]

The conditions reported by Sharpless (WCl_6/*n*-BuLi) were found to generate the targeted bicyclo[7.3.0]dodecatrienediyne **7**. Upon exposure of **6** to low-valent tungsten in deuterated THF, epoxide deoxygenation took place at room temperature, and the exceedingly labile enediyne **7** was isolated in 10% yield (^{1}H NMR determination) after rapid purification with HPLC (silica gel, 5% EtOAc/hexane). In ethanol, **7** was quickly transformed to aromatized compound **25**. The half-life of **7** in deuterated dichloromethane was 35 min at 25 °C, which is even shorter than that of the natural product **1**[7] and the previously synthesized nine-membered enediyne compound.[12,33]

In summary, this study has resulted in the first synthesis of the highly reactive bicyclo[7.3.0]dodecatrienediyne core of the C-1027 chromophore **1**. By virtue of its neutral nature and high chemoselectivity, the synthetic route described here would be applicable for the total synthesis of **1** from its framework **4**. In addition to the effective service for the C-1027 chromophore synthesis, the present deoxygenation strategy represents a potentially general solution to the problem of the enediyne syntheses. Application of the present methodology to **1** and other molecules is currently underway in our laboratory.

Acknowledgment. This work was supported by CREST, Japan Science and Technology Agency (JST). A fellowship to T.S. from the Japan Society for the Promotion of Science (JSPS) is gratefully acknowledged.

Supporting Information Available: Experimental procedures and spectroscopic data for selected compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(32) For a related reaction, see: Gansäuer, A.; Rinker, B. *Tetrahedron* **2002**, *58*, 7017−7026.

(33) The reason for the unusually facile consumption of **7** awaits clarification. Intramolecular abstraction of the benzylic hydrogen of the MPM group by the C3-phenyl radical might be involved in the facile decomposition of **7**.