Natural Products Synthesis

Synthesis of the C-1027 Chromophore Framework through Atropselective Macrolactonization**

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C-1027 is a chromoprotein enediyne natural product with potent in vitro and in vivo cytotoxicity against a variety of cancer cell lines.[1] It is a member of the subset of enediyne antibiotics that includes neocarzinostatin,[2] kedarcidin,[3] and maduropeptin.[4,5] Each of these agents is composed of protein and small-molecule (chromophore) components, which form a 1:1 complex. The C-1027 chromophore **1** (Figure 1) has extremely limited stability in solution and has been shown to undergo spontaneous Masamune–Bergman rearrangement without any external activator.[6] Through this rearrangement, **1** generates *p*-benzyne biradical **2**, which exerts its potent toxicity by abstracting hydrogen atoms (**2**→**3**) from the backbone of DNA to cleave the double strand.[7] This chemical instability and its complex structure distinguish **1** as a challenging target for total synthesis.[8–11]

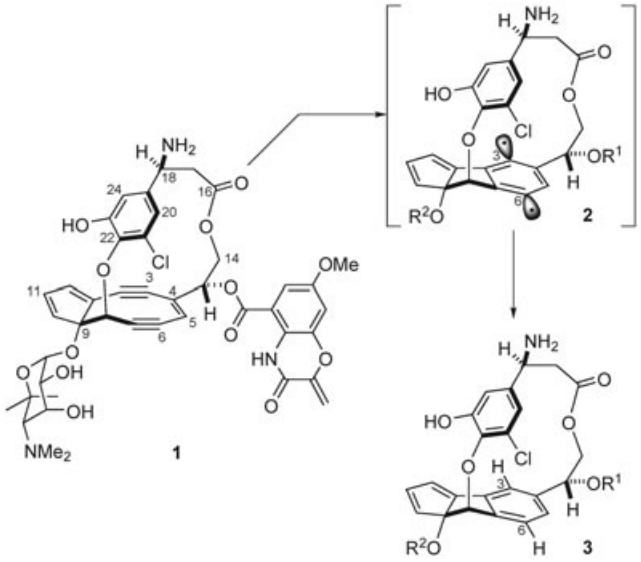

Figure 1. Structure of the C-1027 chromophore **1** and its Masamune–Bergman rearrangement to **3**.

The structure of **1** is highly unusual, characterized by a chlorocatechol-containing ansa-bridge, a strained bicyclo[7.3.0]dodecatrienediyne, an appended benzooxazine,[12] and an aminosugar.[13] The synthetic challenge presented by **1** is heightened by the presence of nonbiaryl atropisomerism arising from hindered rotation of the chlorocatechol ring in the ansa-bridge.[14,15] Herein we present the synthesis of the C-1027 chromophore framework through a newly designed atropselective macrocyclization.

Our synthetic strategy is outlined in Scheme 1. The total synthesis of **1** would be attained from its framework **4** by attaching the amino sugar[16] and the benzoxazine, followed by introducing two olefins (C4–C5 and C11–C12).[17] As the nine-membered diyne of **4** could be chemically unstable, as suggested by experiments on a model compound,[18] the macrolactone system would have to be constructed prior to the nine-membered ring.[19] We planned to form this strained nine-membered diyne **4** by $LiN(TMS)_2/CeCl_3$-promoted cyclization of **5**.[16,17,19b,20] The highly unsaturated macrocycle **5** was to be synthesized through the coupling of the three fragments **6**, **7**, and **8** in a convergent manner.

The synthesis of the five-membered ring **14** bearing the β-tyrosine moiety was improved from a previously published procedure,[21] and started with the known intermediate **9** (Scheme 2).[22] Nucleophilic addition of vinylmagnesium bromide to enone **9** occurred from the opposite side of the bulky TBS ether to afford tertiary alcohol **10** as the sole isomer.

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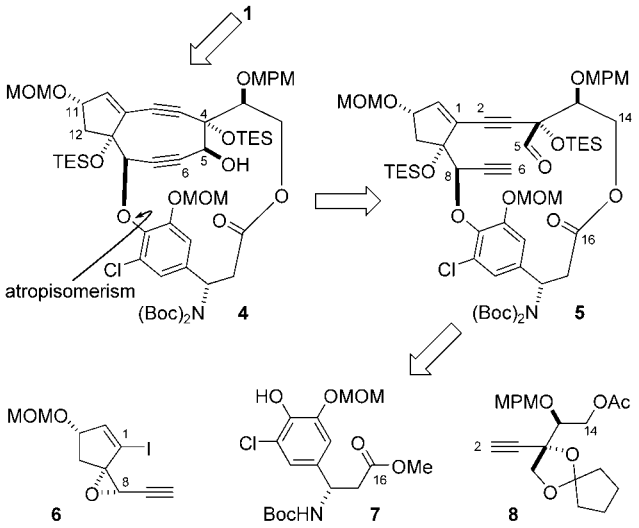
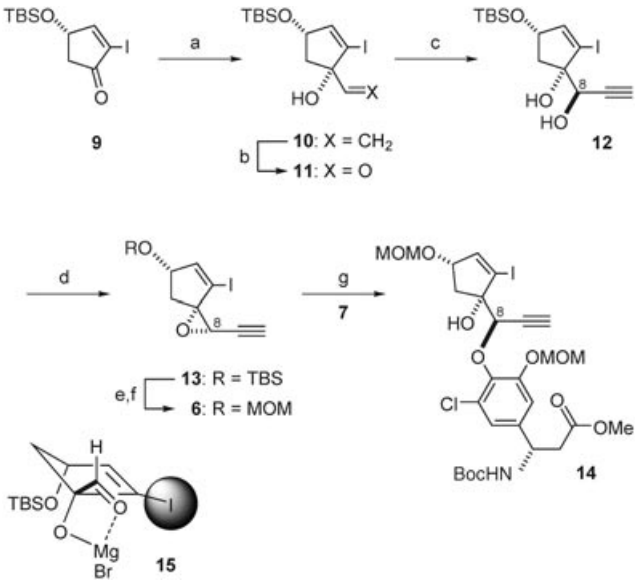


Scheme 1. Retrosynthesis of the C-1027 chromophore. MOM = methoxymethyl, MPM = *p*-methoxyphenylmethyl, TES = triethylsilyl, Boc = *tert*-butoxycarbonyl.



Scheme 2. Reagents and conditions: a) $CH_2{=}CHMgBr$, Et_2O, −70→0 °C, 83 %; b) O_3, CH_2Cl_2/MeOH/pyridine (4:4:1), −80 °C; then Me_2S, −60 °C→RT; c) HC≡CMgBr, toluene, −85 °C→RT, 62 % (over two steps); d) MsCl, CH_2Cl_2, −70 °C; then DBU, −70 °C→RT, 69 %; e) TBAF, THF, 0 °C, 95 %; f) MOMCl, iPr_2NEt, $(CH_2Cl)_2$, 40 °C, 86 %; g) **7** (1.1 equiv), CsF, DMF, 75 °C, 77 %. TBS = *tert*-butyldimethylsilyl; Ms = methanesulfonyl; DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene; TBAF = tetrabutylammonium fluoride; MOM = methoxymethyl; DMF = *N*,*N*-dimethylformamide.

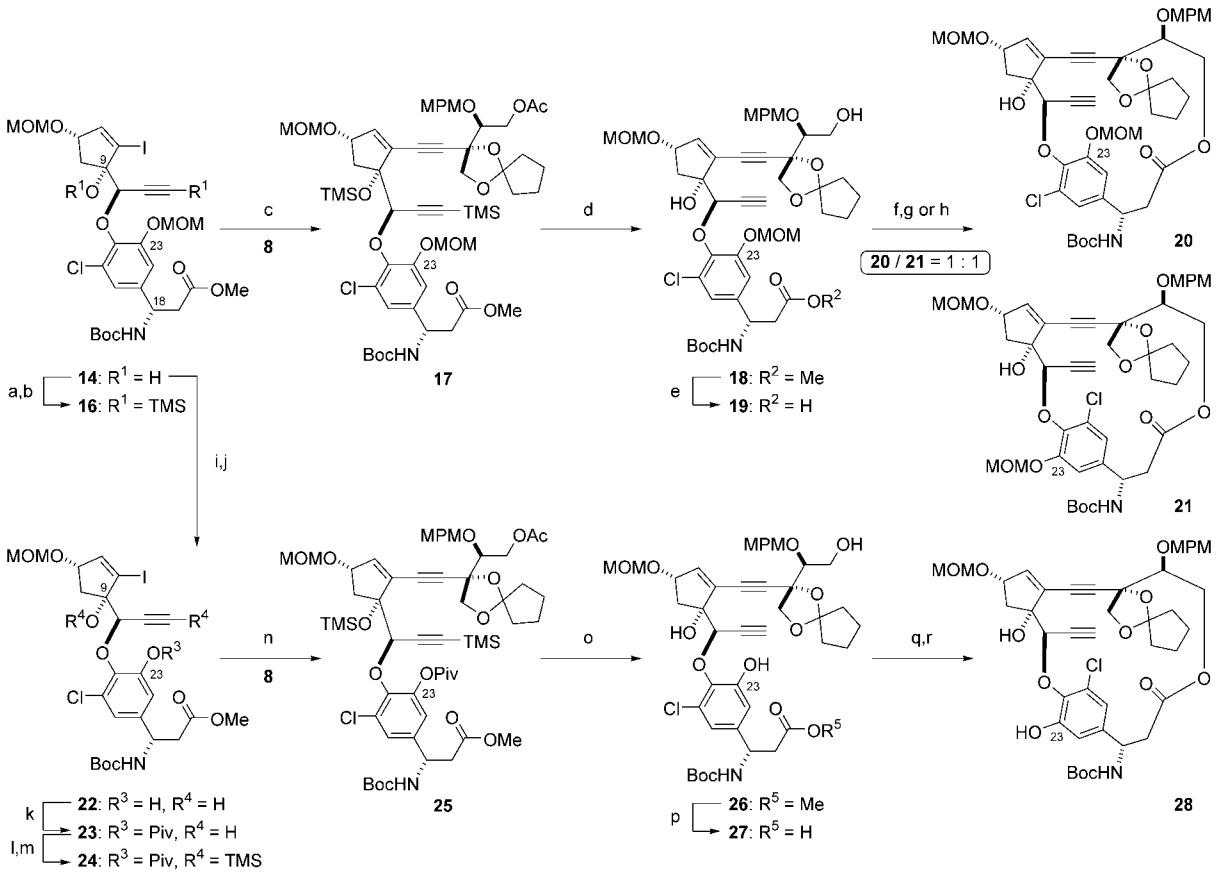
Selective ozonolysis of the terminal olefin of **10** and subsequent reductive workup generated aldehyde **11**. Treatment of **11** with ethynylmagnesium bromide in toluene exclusively produced diol **12** bearing the β-hydroxy group at C8. The stereochemical outcome of the reaction was presumably governed by magnesium chelation and the presence of the bulky iodine, forcing the nucleophile to attack from the less hindered side of the five-membered chelate **15**. The secondary alcohol of **12** was selectively mesylated with MsCl and Et_3N, and the monomesylate was converted into epoxide **13** by the addition of DBU (one-pot reaction). Next, the TBS group of **13** was replaced by a MOM group to give **6** in a two-step sequence. Finally, the β-tyrosine moiety **7**[21] was coupled to **6** by the action of CsF in DMF,[23] leading to adduct **14**.

To evaluate potential strategies for the desired atropselective macrolactonization, substrate **19** was first synthesized (Scheme 3). The tertiary alcohol of **14** was converted into the TMS ether, and the TMS group was also introduced to the terminal acetylene to afford **16**. Sonogashira coupling[24] of **16** with acetylene moiety **8**[19a] in the presence of catalytic $[Pd(PPh)_4]$ and CuI led to **17**. Treatment of **17** with K_2CO_3 in methanol resulted in simultaneous removal of the acetyl and two TMS groups to produce **18**, and subsequent saponification of the methyl ester of **18** with KOH gave rise to seco-acid **19**.

Macrolactonization of **19** was successfully realized by two methods, but with a non-atropselective outcome. Carboxylic acid **19** was treated with 2,2′-dipyridyl disulfide and PPh_3 to give the corresponding thioester, which was heated at reflux in toluene,[25] resulting in the formation of macrolactone **20** and **21** in 50 % yield (1:1).[19a] A higher yield of **20** was achieved by the powerful method recently developed by Shiina and co-workers:[26] Treatment of **19** with MNBA and DMAP at 40 °C produced macrolactones **20** and **21** (1:1.1 ratio in 65 % combined yield). Importantly, the ratio of the atropisomers was unaffected under the two different conditions, and thus the structure of the substrate was likely to be the decisive factor in the selectivity of the reaction. Furthermore, isomerization to enrich the desired atropisomer **20** was unsuccessful. Separate heating of atopisomers **20** and **21** at 160 °C in deuterated 1,2-dichlorobenzene for 12 h did not result in isomerization, which suggests that these macrocycles are highly rigid.[27,28] Consequently, selective formation of the desired atropisomer would be possible only by controlling the transition state of the macrolactonization by using an appropriately functionalized substrate.

To examine the effect of substituents of the aromatic ring on selectivity, the OMOM group at C23 of **19** was replaced with OH in the alternative substrate **27** (Scheme 3). First, bis-MOM ether **14** was successfully transformed into mono-MOM ether **22** by treatment with TFA and subsequent reattachment of Boc to the C18 amine. After conversion of phenol **22** into pivaloate ester **23**, TMS groups were introduced at 9-OH and at the C6-methyne to produce Sonogashira coupling substrate **24**. Adduct **25** was then obtained by coupling **24** with **8** in the presence of catalytic Pd^0 and CuI. Deprotection of four protecting groups (two TMS, Ac, and Piv) from **25** with K_2CO_3 in methanol and subsequent treatment with KOH resulted in seco-acid **27** with the free 23-OH group. Surprisingly, macrolactonization of **27** by using the Corey–Nicolaou thioester method generated solely the undesired atropisomer **28** in modest yield.

From NOESY data and molecular modeling (MacroModel Ver 8.0),[29] all the macrolactones (**20**, **21**, and **28**) were found to have similar conformations. The structure of **28** is shown as a representative example (Figure 2), in which it can



Scheme 3. Reagents and conditions: a) TMSCl, imidazole, DMF, room temperature, 89%; b) TMSCl, LiN(TMS)$_2$, THF, −78°C, 94%; c) **8** (1.1 equiv), [Pd(PPh$_3$)$_4$] (10 mol%), CuI (20 mol%), *i*Pr$_2$NEt, DMF, room temperature, 97%; d) K$_2$CO$_3$, MeOH, room temperature, 74%; e) KOH, THF/H$_2$O/MeOH (6:4:3), room temperature, 95%; f) 2,2′-dipyridyl disulfide, PPh$_3$, THF, room temperature, 96%; g) toluene (1 mM), 120°C, slow addition of thioester over 15 h, 25% (**20**), 25% (**21**), 28% (dimer); h) MNBA, DMAP, CH$_2$Cl$_2$ (1 mM), 40°C, slow addition of **19** over 12 h, 31% (**20**), 34% (**21**), 14% (dimer); i) TFA, CH$_2$Cl$_2$, 0°C; j) (Boc)$_2$O, NaHCO$_3$, 1,4-dioxane/H$_2$O (1:1), room temperature, 84% (over two steps); k) PivCl, DMAP, pyridine, 83%; l) TMSCl, imidazole, DMF, room temperature, 94%; m) TMSCl, LiN(TMS)$_2$, THF, −78°C, 87%; n) **8** (1.1 equiv), [Pd(PPh$_3$)$_4$] (25 mol%), CuI (40 mol%), *i*Pr$_2$NEt, DMF, room temperature, 59%; o) K$_2$CO$_3$, MeOH, room temperature, 84%; p) KOH, THF/H$_2$O (1:1), room temperature, 90%; q) 2,2′-dipyridyl disulfide, PPh$_3$, THF, room temperature, 66%; r) toluene (1 mM), 120°C, slow addition of thioester over 15 h, 31%. TMS = trimethylsilyl; MNBA = 2-methyl-6-nitrobenzoic anhydride; TFA = trifluoroacetic acid; Piv = pivaloyl.

be seen that the terminal acetylene and the chlorocatechol are perpendicular to the macrocycle plane. It is evident that the 1,5 hydroxy groups (9-OH and 23-OH) are in spatial proximity, suggesting hydrogen bonding. This hydrogen bonding could also fix the conformation of the transition state (Figure 3), which explains the sole formation of **28** from **27**. In the cyclization of **19**, the larger unfavorable steric

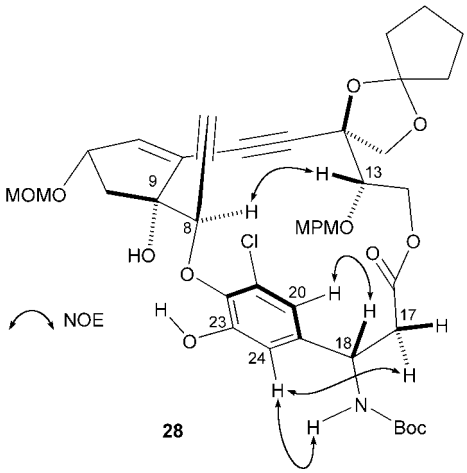


Figure 2. Three-dimensional structure of **28** based on NOESY data (C_6D_6) and molecular modeling.

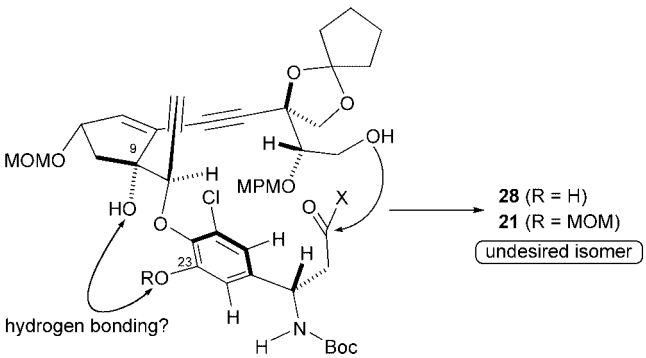


Figure 3. Potential hydrogen bonding in the transition state of the macrolactonization reaction.

interaction between the 23-OMOM group and the tertiary 9-OH group could counteract the attractive hydrogen bond, which could be the reason for the nonstereoselective outcome observed. Hence, the atropselectivity of the macrolactonization appears to be controlled by the balance between steric interaction and hydrogen bonding of the substituents at C9 and C23.

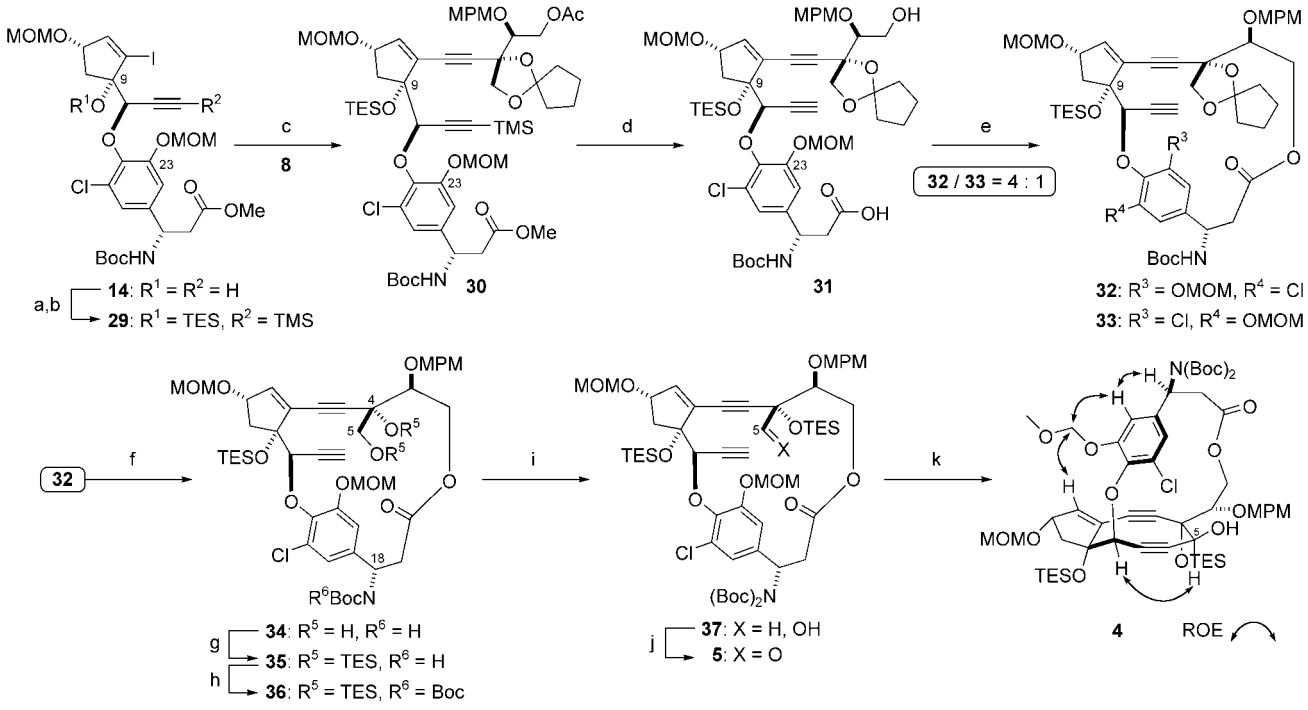
From these considerations, placement of a bulky protecting group on the tertiary 9-OH group could force an atropselective macrolactonization to the desired isomer, because both increased steric interaction with the 23-OMOM group and elimination of the hydrogen bond would impose an energetic penalty on the transition state of the unwanted atropisomer. For undertaking an experimental verification of this hypothesis, we designed a new macrolactonization substrate **31**, which bears 23-OMOM and 9-OTES groups (Scheme 4).

As shown in Scheme 4, seco-acid **31** was synthesized from **14** in a route similar to that used for **19**. The TES group was introduced at the tertiary alcohol function of **14**, and the acetylene moiety was transformed to its TMS-protected form **29**. Condensation of **8** and **29** under Sonogashira conditions led to diyne **30**, whose acetate, methyl esters, and TMS group were hydrolyzed with KOH in THF/MeOH/H_2O, without affecting the TES ether, giving **31**.

Atropselective macrolactonizaton of seco-acid **31** was effected by using the MNBA method. Upon treatment of **31** with MNBA and DMAP in refluxing CH_2Cl_2, the desired isomer **32** was formed with 4:1 atropselectivity and isolated in 61% yield.[31] Remarkably, the yield of the desired atropisomer (**32** versus **20**) was doubled by strategic protection of the 9-OH group.

With the desired ansa macrolide **32** in hand, our next focus was to construct the nine-membered diyne ring. Before doing so, the reaction conditions of protecting- and functional-group manipulations were carefully tuned. First, the cyclopentylidene ketal of **32** was selectively removed with TfOH in CF_3CH_2OH/THF[30] without affecting other acid-labile protecting groups (MOM, TES, MPM, and Boc) to afford 1,2-diol **34**. After conversion of **34** into tris-TES ether **35**, another Boc group was introduced by using $(Boc)_2O$ and DMAP to mask the acidic 18-NH proton of **35**, leading to biscarbamate **36**.[32] The primary alcohol at C5 was selectively deprotected by using HF·py to produce **37**, which was oxidized to aldehyde **5** with $(COCl)_2$ and DMSO.

Cyclization of **5** was promoted by a 1:1 mixture of $LiN(TMS)_2$ and $CeCl_3$ in THF from −50 °C to room temperature, giving rise to the strained nine-membered diyne **4** as the sole isomer in 30% yield. Thus, this $LiN(TMS)_2/CeCl_3$ reagent combination proved to be applicable to the highly complex and conformationally rigid system **5**. The stereochemical structure of **4**, including the newly formed β secondary alcohol, was unambiguously determined by ROESY experiments in [D_6]DMSO. The correct atropisomerism of **4** was again confirmed at this stage, indicating the high energy barrier to rotation of the chlorocatechol in all the synthetic intermediates. Diyne **4** slowly decomposed at room temperature, presumably through Cope rearrangement, as



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demonstrated with previously synthesized model compounds.[33]

In conclusion, we achieved the stereoselective synthesis of the C-1027 chromophore framework through atropselective macrolactonization. The key features in this synthesis were 1) strategic protection of a 1,5-diol to attain atropselective macrocyclization, and 2) $LiN(TMS)_2/CeCl_3$-promoted acetylide–aldehyde condensation to build the nine-membered diyne ring in a highly unsaturated and heavily substituted macrocycle. Further studies on the total synthesis of the C-1027 chromophore from **4** are currently underway in this laboratory.

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Keywords: alkynes · antitumor agents · atropisomerism · lactones · macrocycles

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