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Tetrahedron Letters 45 (2004) 6439–6442
Tetrahedron Letters

Synthesis of the fully functionalized nine-membered diyne core of the C-1027 chromophore

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Received 25 May 2004; revised 21 June 2004; accepted 29 June 2004

Abstract—We report the synthesis of the fully functionalized seco-acid of the C-1027 chromophore. The key reaction is a $LiN(TMS)_2/CeCl_3$-promoted acetylide–aldehyde condensation to construct the highly strained nine-membered diyne. Appropriate functionalization of the substrates significantly affects the yield of the cyclization. The present findings will be the basis of further studies toward the total synthesis of the C-1027 chromophore.

C-1027 is a member of the subset of chromoprotein antitumor agents that are composed of protein and small-molecule (chromophore) components.[1,2] The C-1027 chromophore **1**,[3] when separated from the binding protein, has extremely limited stability in solution and has been shown to undergo spontaneous cycloaromatization in the absence of any activator. This high reactivity, coupled with structural features such as the chlorocatechol-containing ansa-bridge with atropisomerism, the highly strained bicyclo[7.3.0]trienediyne, the appended benzoxazine,[4] and the aminosugar[5] contribute to making the synthesis of **1** a formidable challenge.[6–8]

We planned to construct the aglycon moiety of **1** through macrolactonization at C16[9] and formation of the nine-membered ring by linking C5 and C6 (Fig. 1). Cyclization of the nine-membered ring could be induced with a 1:1 mixture of $LiN(TMS)_2$ and $CeCl_3$[10] in THF, a reaction previously shown to be practical with simple substrates.[6a,11,12] However, the feasibility of this reaction, particularly given the highly complex structure of **1**, was uncertain. Here, we demonstrate the synthesis of a fully functionalized diyne core bearing the β-tyrosine moiety through efficient nine-membered ring formation of a judiciously selected intermediate.

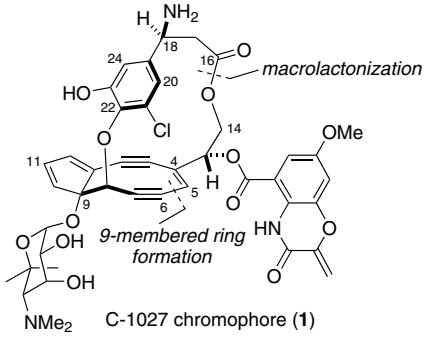

Figure 1. Structure of the C-1027 chromophore (**1**).

Construction of the bicyclo[7.3.0]diyne core began with the previously reported aryl ether **2** (Scheme 1).[9,13] The intermolecular Sonogashira coupling[14] of **2** with **3** afforded the adduct **6**. The acetylenic TMS of **6** was selectively removed in the presence of the four *O*-silyl groups using TBAF at −55 °C to generate **7** in 77% yield over two steps. Liberation of the primary alcohol from DMTr-protected **7** was realized with $ZnBr_2$ to afford **8** (64% yield) without affecting the other acid labile protective groups (MOM, TMS, TES, TBS, and Boc). Alcohol **8** was smoothly oxidized to aldehyde **9** using Dess–Martin reagent[15] in 95% yield. However, treatment of **9** with $LiN(TMS)_2$ and $CeCl_3$ produced the cyclized product **10** in only 13% yield.

Keywords: C-1027; Enediyne; Chromoprotein antibiotics; Nine-membered diyne; Cyclization.
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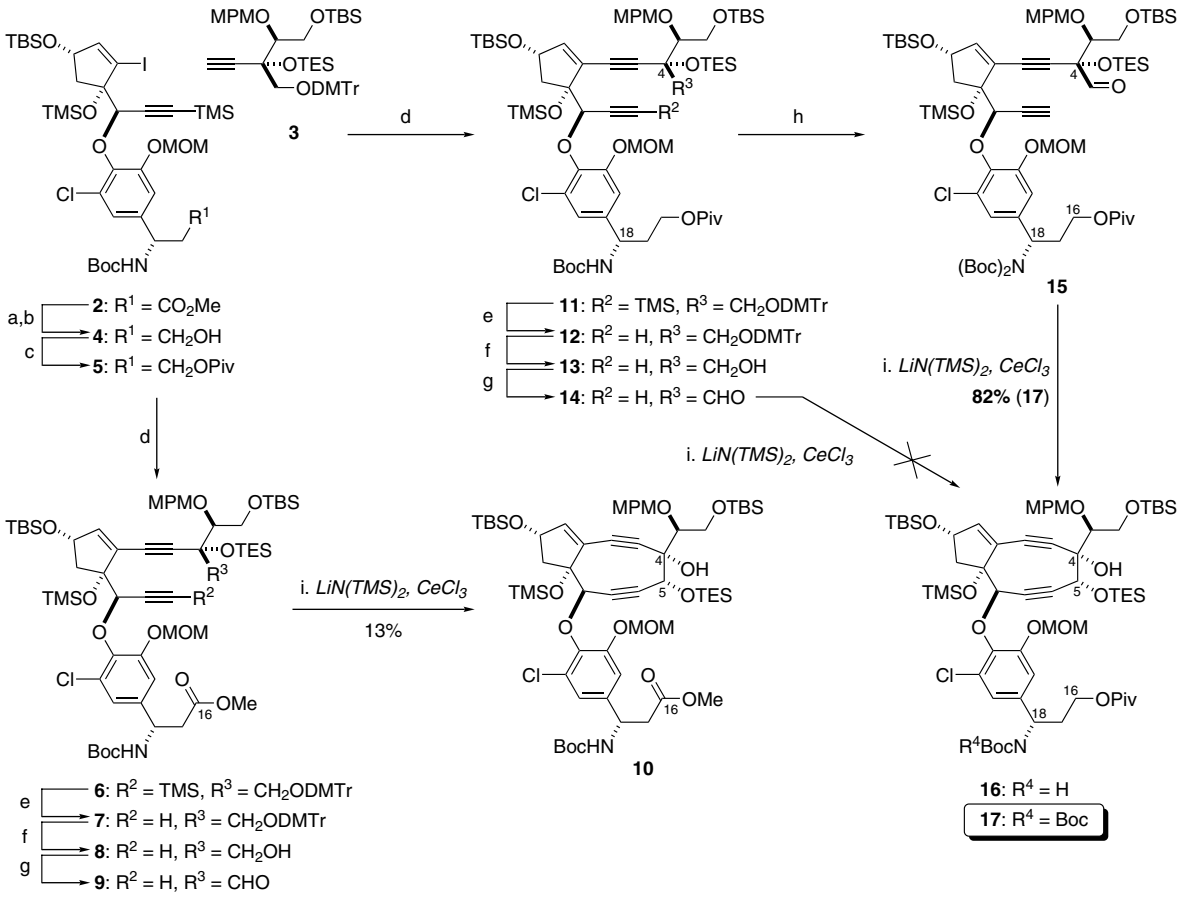
doi:10.1016/j.tetlet.2004.06.136



Scheme 1. Reagents and conditions: (a) DIBAL-H, CH_2Cl_2, −78 °C; (b) $NaBH_4$, EtOH, 0 °C, 82% (two steps); (c) PivCl, DMAP, Et_3N, rt, 100%; (d) **3** (1.3 equiv), $Pd_2(dba)_3{\cdot}CHCl_3$ (30 mol%), CuI (30 mol%), *i*-Pr_2NEt, DMF, rt; (e) TBAF, THF, −55 °C, 77% (**7**, two steps) from **2**, 52% (**12**, two steps) from **5**; (f) $ZnBr_2$, CH_2Cl_2, 0 °C, 64% (**8**), 61% (**13**); (g) Dess–Martin periodinane, CH_2Cl_2, rt, 95% (**9**), 90% (**14**); (h) $(Boc)_2O$, DMAP, CH_3CN, 40 °C, 72%; (i) $LiN(TMS)_2$ (30 equiv), $CeCl_3$ (31 equiv), THF (2 mM), −20 °C to rt, 13% (**10**), 0% (**16**), 82% (**17**).

We therefore redesigned our substrate in an effort to improve the cyclization yield. The C16-ester of **9** was replaced with its reduced form in order to eliminate acidic α-protons that could cause undesired side reactions. Stepwise reduction of ester **2** led to alcohol **4**, the pivaloyl protection of which afforded **5** in 82% yield over three steps. Sonogashira-coupling between **3** and **5**, followed by TBAF treatment, resulted in **12** (52% yield for two steps). Selective removal of the DMTr group of **12** using $ZnBr_2$ then produced primary alcohol **13**. After conversion of **13** to aldehyde **14**, $LiN(TMS)_2/CeCl_3$-promoted cyclization was attempted, but this led only to a complex mixture with no desired product **16**.

Masking the acidic C18-NH of **14** had a dramatic effect on improving the cyclization yield. Introduction of another Boc group to the C18-nitrogen of **14** using $(Boc)_2O$ and DMAP afforded bis-carbamate **15** (72% yield), and subsequent treatment of **15** with $LiN(TMS)_2$ (30 equiv) and $CeCl_3$ (31 equiv) in THF gave rise to the nine-membered diyne **17** in 82% yield as a sole isomer.[16] The difference in the cyclization yields of **9**, **14**, and **15** clearly demonstrate that removal of acidic protons is crucial for this base-promoted condensation.

The stereochemistry of the newly formed secondary alcohol of **17** was unambiguously determined by a ROESY experiment (Fig. 2). Interestingly, upon formation of the nine-membered ring, the TES group at the C4-OH of **15** was intramolecularly transposed to the C5-hydroxy group of **17**, thus indicating the spatial proximity between the C4- and C5-hydroxy groups. Diyne **17** was chemically unstable upon heating ($t_{1/2}$ = 3 h in C_6D_6 at 50 °C), which is similar to previously synthesized model compounds.[17]

As shown in Scheme 2, the new substrate design for the cyclization was successfully applied to the differentially protected compound **18**, which was prepared through a similar route to **15**. When bis-Boc protected **18** was subjected to the $LiN(TMS)_2/CeCl_3$-mediated cyclization

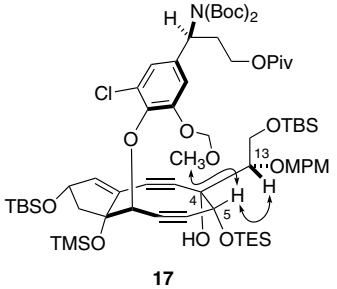
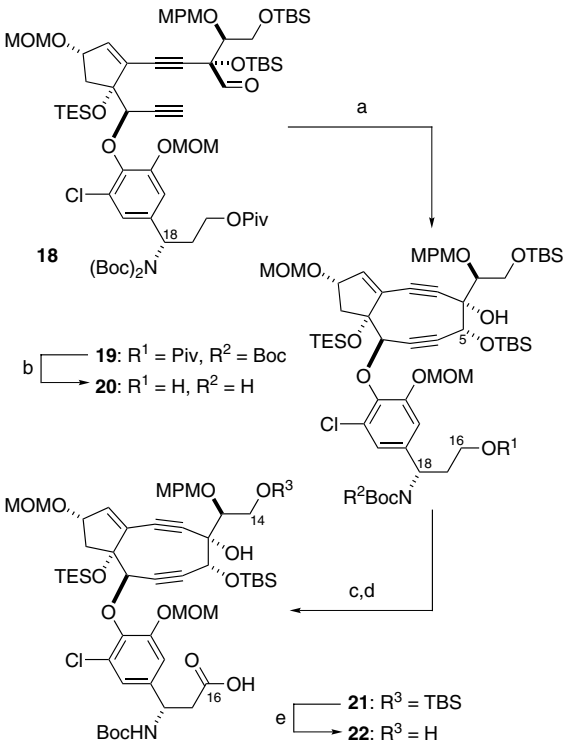


Figure 2. ROESY correlations of **17** (500 MHz, $CDCl_3$).



Scheme 2. Reagents and conditions: (a) $LiN(TMS)_2$ (26 equiv), $CeCl_3$ (28 equiv), THF (2 mM), −30 °C to rt, 78%; (b) DIBAL-H, CH_2Cl_2, −85 °C, 70%; (c) Dess–Martin periodinane, CH_2Cl_2, rt; (d) $NaClO_2$, NaH_2PO_4, 2-methyl-2-butene, *t*-BuOH/H_2O (5:1), 72% (two steps); (e) PPTS, MeOH, rt, 45%.

conditions, nine-membered diyne **19** was isolated as a single isomer in 78% yield. Subsequent DIBAL-H reduction of **19** simultaneously removed both Piv and Boc groups to generate mono-Boc alcohol **20**. The primary alcohol was then oxidized to the corresponding carboxylic acid **21** via a two-step protocol: (i) Dess–Martin periodinane treatment; and (ii) $NaClO_2$ oxidation. Finally, the primary TBS group at C14 of **21** was selectively removed using PPTS in MeOH, leading to the fully functionalized seco-acid **22** (45% yield).[18,19]

In conclusion, the highly strained nine-membered diyne **22** possessing the β-tyrosine moiety was synthesized via $LiN(TMS)_2/CeCl_3$-promoted acetylide–aldehyde condensation. The key feature in this synthesis is the exploitation of a variety of protective groups that enabled not only the timely exposure of suitable functional groups, but also the effective cyclization of highly functionalized substrates (**15** and **18**). Further studies on the total synthesis of the C-1027 chromophore based on the above findings are currently underway in this laboratory.

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16. **17**: pale yellow oil; $[\alpha]_D^{20}$ −61.7 (*c* 0.89, $CHCl_3$); FT-IR (film) *v* 2956, 1731, 1612, 1576, 1514, 1392, 1345, 1251,

1157, 1080, 1006, 913 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.06 (3H, s, TBS), 0.07 (3H, s, TBS), 0.11 (3H, s, TBS), 0.12 (3H, s, TBS), 0.20 (9H, s, TMS), 0.50 (6H, dq, J = 15.5, 8.0 Hz, TES), 0.84 (9H, t, J = 8.0 Hz, TES), 0.89 (9H, s, TBS), 0.94 (9H, s, TBS), 1.16 (9H, s, Piv), 1.40 (18H, s, Boc), 1.94 (1H, dd, J = 13.5, 4.5 Hz, H10), 2.20–2.30 (1H, m, H17), 2.57 (1H, ddd, J = 15.0, 10.5, 4.5 Hz, H17), 3.13 (1H, dd, J = 13.5, 7.0 Hz, H10), 3.38 (1H, s, C4-OH), 3.49 (3H, s, MOM), 3.68 (1H, dd, J = 8.5, 2.0 Hz, H13), 3.77 (3H, s, MPM), 3.96 (1H, dd, J = 11.0, 8.5 Hz, H14), 4.10–4.20 (2H, m, H16), 4.24 (1H, dd, J = 11.0, 2.0 Hz, H14), 4.40 (1H, s, H5), 4.42 (1H, d, J = 11.0 Hz, MPM), 4.82 (1H, ddd, J = 7.0, 4.5, 2.5 Hz, H11), 4.84 (1H, d, J = 11.0 Hz, MPM), 5.04 (1H, s, H8), 5.21 (1H, d, J = 7.0 Hz, MOM), 5.22 (1H, d, J = 7.0 Hz, MOM), 5.35 (1H, dd, J = 10.5, 5.5 Hz, H18), 6.07 (1H, d, J = 2.5 Hz, H12), 6.77 (2H, d, J = 8.5 Hz, MPM), 7.07 (1H, d, J = 2.0 Hz, H20), 7.09 (1H, d, J = 2.0 Hz, H24), 7.16 (2H, d, J = 8.5 Hz, MPM); ^{13}C NMR (50 MHz, $CDCl_3$) δ −5.4, −5.3, −4.7, 2.2, 4.4, 6.6, 18.0, 18.2, 25.8, 26.0, 27.1, 27.9, 30.8 (C17), 38.7, 47.0 (C10), 55.0 (C18), 55.2, 56.3, 61.3 (C16), 65.7 (C14), 67.3 (C11), 73.5, 74.9 (C5), 76.8 (C8), 79.7 (C4), 82.5, 83.2 (C13), 87.7 (C9), 89.3 (C7), 89.5 (C6), 90.6 (C2), 95.1, 98.5 (C3), 113.5, 114.1 (C24), 122.4 (C20), 128.5 (C21), 128.7 (C1), 129.8, 131.0, 137.2 (C19), 141.5 (C12), 141.7 (C22), 150.9 (C23), 152.9, 159.1, 178.4; MALDI-TOFMS calcd for $C_{69}H_{112}ClNO_{16}Si_4Na$ 1380.66 ($M+Na^+$), found 1380.62.

17. Cope rearrangement of the nine-membered cyclic 1,5-diyne **17** to the bis-allene is considered to be the major decomposition pathway (see Ref. 11a).
18. **22**: pale yellow oil; $[\alpha]_D^{28}$ −84.6 (c 0.98, $CHCl_3$); FT-IR (film) ν 2954, 2066, 1715, 1613, 1514, 1367, 1251, 1104, 922 cm^{-1}; ^1H NMR (500 MHz, CD_3OD) δ −0.05 (6H, s, TBS), 0.73 (6H, q, J = 8.0 Hz, TES), 0.81 (9H, s, TBS), 1.00 (9H, t, J = 8.0 Hz, TES), 1.40 (9H, s, Boc), 2.04 (1H, dd, J = 14.0, 5.0 Hz, H10), 2.50–2.70 (2H, m, H17), 3.18 (1H, dd, J = 14.0, 7.5 Hz, H10), 3.37 (3H, s, MOM), 3.51 (3H, s, MOM), 3.65 (1H, dd, J = 7.5, 3.0 Hz, H13), 3.78 (3H, s, MPM), 3.83 (1H, dd, J = 11.0, 7.5 Hz, H14), 4.01 (1H, dd, J = 11.0, 3.0 Hz, H14), 4.48 (1H, d, J = 11.0 Hz, MPM), 4.51 (1H, s, H5), 4.70 (2H, s, MOM), 4.70 (1H, br, H11), 4.76 (1H, d, J = 11.0 Hz, MPM), 4.92 (1H, br, H18), 5.19 (1H, s, H8), 5.24 (1H, d, J = 6.5 Hz, MOM), 5.29 (1H, d, J = 6.5 Hz, MOM), 6.21 (1H, d, J = 2.0 Hz, H12), 6.79 (2H, d, J = 8.5 Hz, MPM), 7.05 (1H, br s, H20), 7.10 (1H, br s, H24), 7.20 (2H, d, J = 8.5 Hz, MPM); MALDI-TOFMS calcd for $C_{52}H_{76}ClNO_{15}Si_2Na$ ($M+Na^+$) 1068.43, found 1068.23.
19. Macrolactonization of **22** under Yamaguchi conditions (Ref. 9) afforded the cyclized product albeit in low yield (5%). Optimization of the reaction is now in progress, and will be reported in due course. For Yamaguchi esterification, see: Inanaga, J.; Hirata, K.; Saeki, H.; Katsuki, T.; Yamaguchi, M. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 1989–1993.