LETTERS

Synthetic Study of Kedarcidin Chromophore: Advanced Models and Their Chemical Behavior

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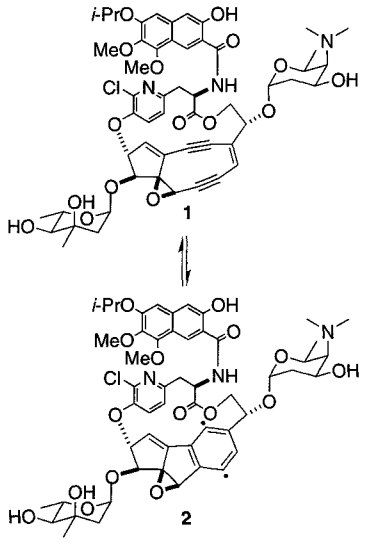
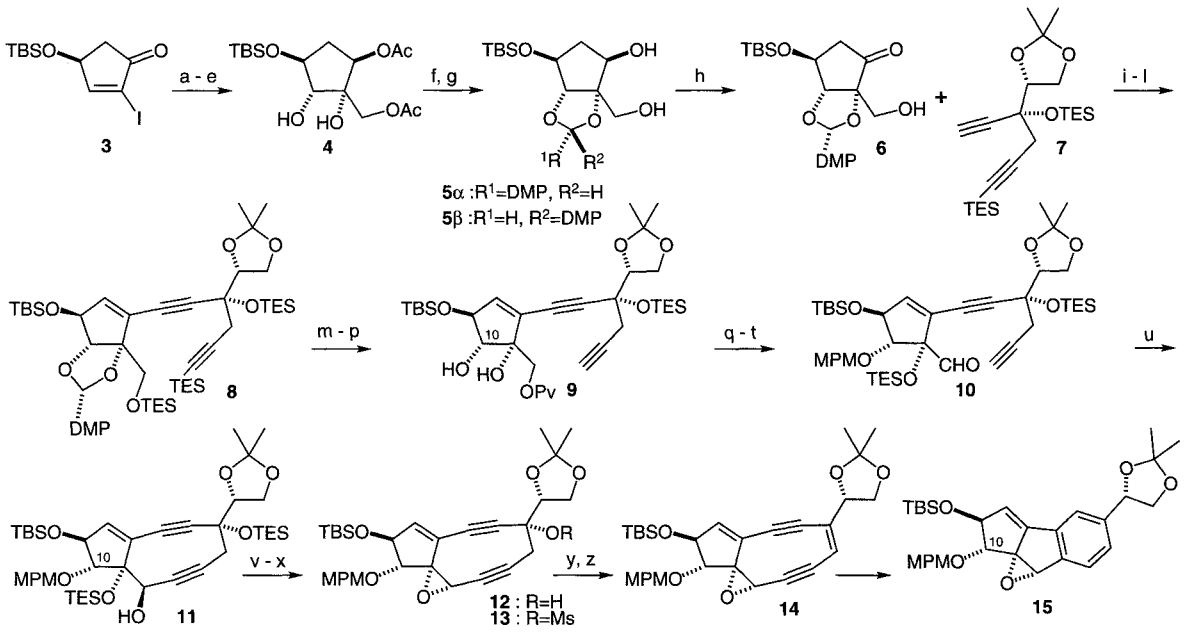
Abstract: The stereocontrolled synthesis of the appropriately functionalized *ent*-8,9-epoxybicyclo-[7.3.0]dodecadienediyne core **14** of kedarcidin chromophore **1** was achieved.

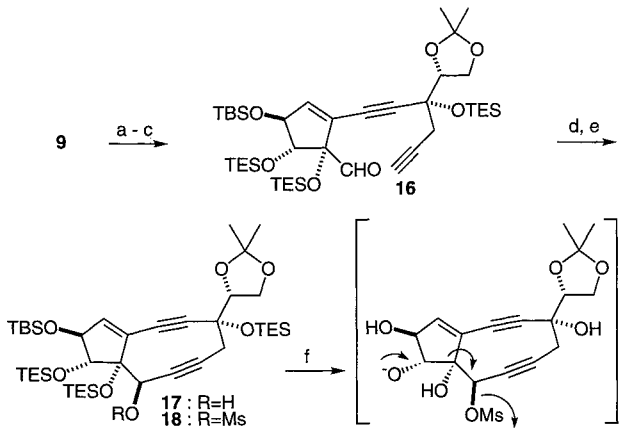
We recently succeeded in synthesizing and characterizing the less functionalized nine-membered cyclic enediynes[1,2] and suggested that the chromophore of the potent antitumor antibiotic chromoprotein kedarcidin[3], the nine-membered cyclic enediyne **1**, should be equilibrated with its *p*-benzyne biradical form **2** and be stabilized kinetically under conditions in which the biradical intermediate **2** does not easily abstract hydrogen atoms.[2,4] The synthesis of more advanced model compounds and **1** is challenging and may help to elucidate the details of this intriguing characteristic.[5] We report here an enantioselective route to the highly oxygenated *ent*-8,9-epoxybicyclo[7.3.0]dodecadienediyne core moiety **14** of kedarcidin chromophore and that the C10 oxygen functionality greatly affects the chemical stability of the related molecules such as nine-membered diyne **11** and epoxide **15**.

The highly oxygenated cyclopentene moiety was synthesized from the readily available, optically pure iodoenone **3**.[6] Hydroxymethylation of **3** via consecutive stereoselective Luche reduction, Heck reaction, and DIBAL reduction, followed by acetylation and *cis*-dihydroxylation with OsO_4, gave the highly functionalized cyclopentane derivative **4** stereoselectively (Scheme 1). Acetalization of the diol with 3,4-dimethoxybenzaldehyde (DMP-CHO) in the presence of 10-camphorsulfonic acid (CSA) gave two diastereomeric acetals (2:1) with respect to the benzylic position, which were easily separated after being converted to the diols **5**α and **5**β. Regioselective oxidation of the major diastereomer **5**α to hydroxy ketone **6** was accomplished by treating the dibutylstannylene acetal with NBS.[7]





Scheme 1. Reagents and conditions: a) $NaBH_4$, $CeCl_3 \cdot 7H_2O$, MeOH, -78°C, 94% (cis:trans=15:1). b) CO, Et_3N, MeOH, $PdCl_2(PPh_3)_2$, 60°C, 97%. c) DIBAL, CH_2Cl_2, -78°C. d) Ac_2O, pyridine, 96% (2 steps). e) OsO_4, NMO, acetone, H_2O, 87%. f) 3,4-dimethoxybenzaldehyde, TsOH, benzene reflux, 30 min. g) K_2CO_3, MeOH, 65% (2 steps). h) Bu_2SnO, toluene reflux, then NBS, $CHCl_3$, 83%. i) BuLi, $CeCl_3$, THF, -78°C, 84%. j) TESCl, pyridine, >99%. k) MsCl, DMAP, Et_3N, CH_2Cl_2, 99%. l) DBU, xylene reflux, 30 min, 81%. m) DDQ, CH_2Cl_2, H_2O, 97%. n) $AgNO_3$, 2,6-lutidine, THF:EtOH:H_2O (1:1:1), 94%. o) K_2CO_3, MeOH, 75%. p) PvCl, pyridine, CH_2Cl_2, 99%. q) MPMOC(=NH)CCl_3, CSA, CH_2Cl_2. r) TESCl, imidazole, DMF, 60°C. s) DIBAL, CH_2Cl_2, -78°C, 39% (3 steps). t) Dess-Martin Periodinane, CH_2Cl_2, 96%. u) LiHMDS, $CeCl_3$, THF, -20°C → r.t., 65%. v) MsCl, Et_3N, DMAP, CH_2Cl_2, 67%. w) Bu_4NF, THF, 0°C, 1h, 69%. x) TBSOTf, 2,6-lutidine, THF, -78°C, 76%. y) MsCl, Et_3N, CH_2Cl_2. z) DBU (10 mol. eq), CD_2Cl_2, CH_2Cl_2:1,4-C_6H_8 (1:1), r.t., 2.5 h, 32% (3 steps).



Scheme 2. Reagents and conditions: a) TESCl, imidazole, DMF, 60°C, 99%. b) DIBAL, CH_2Cl_2, -78°C, 77%. c) Dess-Martin Periodinane, CH_2Cl_2, 96%. d) LiHMDS, $CeCl_3$, THF, -30°C → r.t., 73%. e) MsCl, Et_3N, DMAP, CH_2Cl_2, >99%. f) Bu_4NF, THF, 0°C.

Addition of the organocerium reagent prepared from optically pure diyne **7**[1] to **6** gave a 1.8:1 diastereomeric mixture of tertiary alcohols in a yield of 84%.[8] After protecting the primary alcohol as a triethylsilyl (TES) ether, the mixture was transformed to the single enediyne **8** via dehydration. Since the 3,4-dimethoxybenzylidene acetal group was destroyed by oxidation of the primary alcohol derived from **8**,[9] **8** was converted to mono-pivalate **9** as shown in Scheme 1. If both of the diols of **9** were protected as TES ethers, the lithium hexamethyldisilazide (LiHMDS)/$CeCl_3$-mediated cyclization of **16** proceeded smoothly to give unstable nine-membered diyne **17**[10] in a good yield (Scheme 2).[1,5,11] However, the treatment of mesylate **18** with Bu_4NF to hydrolyze the silyl ethers and then form an epoxide did not give the desired epoxide, presumably via a Grob-type fragmentation reaction.[12] Therefore, the (C10) secondary hydroxyl and tertiary hydroxyl groups of **9** were protected as MPM and TES ethers, respectively. The primary hydroxyl group was then deprotected and oxidized to aldehyde **10**.

Cyclization of **10** with LiHMDS/$CeCl_3$ at -20 °C to room temperature occurred both smoothly and stereoselectively (Scheme 1).[1,5,11] The cyclized nine-membered diyne **11** was immediately converted to epoxydiyne **12**[10] through mesylation and subsequent treatment with Bu_4NF, because **11** was more labile to undergo Cope rearrangement even at room temperature than the previously reported **19** by a factor of about 3.[1,11,13] Compound **12** was thus immediately mesylated to **13** and its elimination by DBU at room temperature in CD_2Cl_2 was monitored by ^1H NMR. The smooth formation of epoxyenediyne **14**[10] and its considerably long life time was confirmed by NMR, as exemplified in the related system **20**.[2] The spontaneous cycloaromatization reaction of **14** in a mixture of CH_2Cl_2 and 1,4-cyclohexadiene (1:1) at room temperature was completed in 2.5 h and yielded **15**.[10] The half-life of **14** was about 0.5 h, which is almost identical to that of **20**.[2] The cycloaromatization product **15** was stable enough to be purified by silica gel column chromatography, in contrast with **21** derived from **20**.[2] The increased apparent stability of **15** appears to be due to kinetic stabilization: The transition state energy of epoxide-opening might be increased by the inductive effect of the additional oxygen functionality at C10.

Since the antipodes of **3** and **7** are readily available,[6a,11] the enantiomer of **14** should also be synthesized by the present route. Thus we established the first stereocontrolled route to the highly oxygenated core structure of kedarcidin chromophore **1** and found that the C10 hydroxyl group affects the chemical behavior of the nine-membered diynes and related compounds. Further synthetic studies directed toward **1** are underway.

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References and Notes

(1) Iida, K.; Hirama, M. *J. Am. Chem. Soc.* **1994**, *116*, 10310-10311.

(2) Iida, K.; Hirama, M. *J. Am. Chem. Soc.* **1995**, *117*, 8875-8876.

(3) Leet, J. E.; Schroeder, D. R.; Hofstead, S. J.; Golik, J.; Colson, K. L.; Huang, S.; Klohr, S. E.; Doyle, T. W.; Matson, J. A. *J. Am. Chem. Soc.* **1992**, *114*, 7946-7948; Leet, J. E.; Schroeder, D. R.; Langley, D. R.; Colson, K. L.; Huang, S.; Klohr, S. E.; Lee, M. S.; Golik, J.; Hofstead, S. J.; Doyle, T. W.; Matson, J. A. *J. Am. Chem. Soc.* **1993**, *115*, 8432-8443.

(4) Yoshida, K.; Minami, Y.; Otani, T.; Tada, Y.; Hirama, M. *Tetrahedron Lett.* **1994**, *35*, 5253-5256.

(5) For reviews of related synthetic studies, see: Lhermitte, H.; Grierson, D.S. *Contemp. Org. Synth.* **1996**, *3*, 93-124; Hirama, M. "Synthesis and Chemistry of Neocarzinostatin Analogs," In *Recent Progress in the Chemical Synthesis of Antibiotics and Related Microbial Products, Vol 2*; Lukacs, G. Ed.; Springer-Verlag: Berlin, **1993**; pp. 293-329.

(6) (a) Hirama, M.; Gomibuchi, T.; Fujiwara, K.; Sugiura, Y.; Uesugi, M. *J. Am. Chem. Soc.* **1991**, *113*, 9851-9853; Johnson, C. R.; Adams, J. P.; Braun, M. P.; Senanayake, C. B. W.; Wovkulich, P. M.; Uskokovic, M. R. *Tetrahedron Lett.* **1992**, *33*, 917-918. (b) For synthetic studies of the related highly functionalized cyclopentenones, see: Toyama, K.; Iguchi, S.; Oishi, T.; Hirama, M. *Synlett* **1995**, 1243, and references cited therein.

(7) Kong, X.; Grindley, T. B. *J. Carbohydr. Chem.* **1993**, *12*, 557-571 and references cited therein.

(8) When the primary alcohol of **6** was protected as a TES ether, the addition reaction did not proceed at all. This suggests that chelation is a critical driving force. Lithium reagents without $CeCl_3$ caused a β-elimination to yield an enone.

(9) Oxidation conditions: Swern oxd., SO_3 • py/DMSO/Et_3N, Pr_4N • RuO_4, Dess-Martin Oxd., PDC, *etc.*

(10) **12**: ^1H NMR (600MHz, CD_2Cl_2) δ 0.12(3H, s, SiC**H**$_3$), 0.15(3H, s, SiC**H**$_3$), 0.91(9H, s, SiC(C**H**$_3$)$_3$), 1.31(3H, s, H^{16}), 1.42(3H, s, H^{16}), 2.33(1H, dd, *J*=17.3, 0.9Hz, H^5), 2.76(1H, dd, *J*=17.3, 0.9Hz, H^5), 2.93(1H, brs, C^4-O**H**), 3.25(1H, brs, H^8), 3.77(3H, s, -OC**H**$_3$), 3.91-3.94(1H, m, H^{14}), 4.01(1H, d, *J*=4.4Hz, H^{10}), 4.04-4.08(2H, m, H^{13}, H^{14}), 4.46(1H, d, *J*=11.1Hz, C**H**$_2$C$_6$H$_4$OCH$_3$), 4.63(1H, d, *J*=11.1Hz, C**H**$_2$C$_6$H$_4$OCH$_3$), 5.02(1H, dd, *J*=4.4, 2.1Hz, H^{11}), 6.21(1H, d, *J*=2.1Hz, H^{12}), 6.85(2H, d, *J*=8.7Hz, MPM), 7.21(2H, d, *J*=8.7Hz, MPM); ^{13}C NMR (150MHz, CD_2Cl_2) δ -4.31(q, SiCH$_3$), 3.96(q, SiCH$_3$), 18.56(s, SiC(CH$_3$)$_3$), 25.40(q, C^{16}), 26.23(q, SiC(CH$_3$)$_3$), 26.78(q, C^{16}), 33.60(t, C^5), 48.69(d, C^8), 55.98(q, OCH$_3$), 66.88(t, C^{14}), 73.19(s, C^9), 73.40(t, CH$_2$C$_6$H$_4$OCH$_3$), 78.21(s, C^4), 79.69(d, C^{13}), 80.18(d, C^{11}), 82.81(d, C^{10}), 86.57(s, C^6 or C^7), 87.80(s, C^6 or C^7), 89.75(s, C^2), 98.84(s, C^3), 111.08(s, C^{15}), 114.50(d, C$^{3'}$), 122.94(s, C^1), 129.05(s, C$^{1'}$), 130.50(d, C$^{2'}$), 144.20(d, C^{12}), 160.30(s, C$^{4'}$).

14: ^1H NMR (200MHz, CD_2Cl_2) δ 0.17(3H, s, SiC**H**$_3$), 0.20(3H, s, SiC**H**$_3$), 0.95(9H, s, SiC(C**H**$_3$)$_3$), 1.37(3H, s, H^{16}), 1.46(3H, s, H^{16}), 3.63(1H, d, *J*=1.8Hz, H^8), 3.79(1H, dd, *J*=8.4, 6.5Hz, H^{14}), 3.79(3H, s, OC**H**$_3$), 4.10(1H, d, *J*=4.6Hz, H^{10}), 4.17(1H, dd, *J*=8.4, 6.5Hz, H^{14}), 4.52(1H, d, *J*=11.1Hz, C**H**$_2$C$_6$H$_4$OCH$_3$), 4.65(1H, td, *J*=6.5, 1.1Hz, H^{13}), 4.73(1H, d, *J*=11.1Hz, C**H**$_2$C$_6$H$_4$OCH$_3$), 4.95(1H, dd, *J*=4.6, 2.1Hz, H^{11}), 6.06(1H, brdd, *J*=1.8, 1.1Hz, H^5), 6.37(1H, d, *J*=2.1Hz, H^{12}), 6.88(2H, d, *J*=8.8Hz, MPM), 7.24(2H, d, *J*=8.8Hz, MPM).

15: ^1H NMR (600MHz, CD_2Cl_2) δ 0.15(3H, s, SiC**H**$_3$), 0.16(3H, s,

SiC**H**$_3$), 0.91(9H, s, SiC(C**H**$_3$)$_3$), 1.43(3H, s, H^{16}), 1.50(3H, s, H^{16}), 3.60(1H, t, *J*=8.1Hz, H^{14}), 3.78(3H, s, OC**H**$_3$), 4.26(1H, dd, *J*=8.1, 6.3Hz, H^{13}), 4.38(1H, d, *J*=4.3Hz, H^{10}), 4.45(1H, s, H^8), 4.47(1H, d, *J*=11.0Hz, C**H**$_2$C$_6$H$_4$OCH$_3$), 4.53(1H, d, *J*=11.0Hz, C**H**$_2$C$_6$H$_4$OCH$_3$), 5.05(1H, dd, *J*=8.1, 6.3Hz, H^{14}), 5.32(1H, dd, *J*=4.3, 1.7Hz, H^{11}), 6.11(1H, d, *J*=1.7Hz, H^{12}), 6.87(2H, d, *J*=8.7Hz, MPM), 7.25(1H, dd, *J*=7.8, 1.4Hz, H^5), 7.29(2H, d, *J*=8.7Hz, MPM), 7.49(1H, d, *J*=7.8Hz, H^6), 7.56(1H, brs, H^3); FT-IR (film) ν 4544, 2928, 2858, 1734, 1615, 1518, 1464, 1375, 1251, 1069, 909, 837, 781, 503, 489 cm^{-1}.

17: ^{1}H NMR (600MHz, $CDCl_3$) δ 0.11(3H, s, SiC**H**$_3$), 0.12(3H, s, SiC**H**$_3$), 0.65(6H, q, *J*=8.0Hz, SiC**H**$_2$CH$_3$), 0.66(6H, q, *J*=8.0Hz, SiC**H**$_2$CH$_3$), 0.72(6H, q, *J*=8.0Hz, SiC**H**$_2$CH$_3$), 0.91(9H, s, SiC(C**H**$_3$)$_3$), 0.95(6H, t, *J*=8.0Hz, SiCH$_2$C**H**$_3$), 0.96(6H, t, *J*=8.0Hz, SiCH$_2$C**H**$_3$), 0.97(6H, t, *J*=8.0Hz, SiCH$_2$C**H**$_3$), 1.36(3H, s, H^{16}), 1.41(3H, s, H^{16}), 2.18(1H, d, *J*=8.7Hz, C^8-O**H**), 2.55(1H, d, *J*=16.8Hz, H^5), 2.59(1H, dd, *J*=16.8, 0.7Hz, H^5), 3.89(1H, brd, *J*=8.7Hz, H^8), 3.96(1H, dd, *J*=8.2, 7.6Hz, H^{14}), 4.05(1H, dd, *J*=8.2, 6.4Hz, H^{14}), 4.16(1H, dd, *J*=7.6, 6.4Hz, H^{13}), 4.20(1H, d, *J*=5.7Hz, H^{10}), 4.71(1H, dd, *J*=5.7, 1.8Hz, H^{11}), 6.02(1H, d, *J*=1.8Hz, H^{12}); ^{13}C NMR (150MHz, $CDCl_3$) δ -4.40(q, Si**C**H$_3$), -4.30(q, Si**C**H$_3$), 5.16(t, Si**C**H$_2$CH$_3$), 5.69(t, Si**C**H$_2$CH$_3$), 6.50(t, Si**C**H$_2$CH$_3$), 6.88(q, SiCH$_2$**C**H$_3$x2), 7.06(q, SiCH$_2$**C**H$_3$), 18.10(s, Si**C**(CH$_3$)$_3$), 25.62(q, C^{16}), 25.94(q, SiC(**C**H$_3$)$_3$), 26.51(q, C^{16}), 35.21(t, C^5), 65.19(d, C^8), 67.19(t, C^{14}), 78.54(s, C^4), 78.67(d, C^{10}), 79.77(d, C^{11}), 83.38(d, C^{13}), 88.83(s, C^9), 89.63(s, C^6), 90.73(s, C^2), 93.76(s, C^7), 97.86(s, C^3), 110.61(s, C^{15}), 126.35(s, C^1), 141.48(d, C^{12}).

(11) Sato, I.; Akahori, Y.; Iida, K.; Hirama, M. *Tetrahedron Lett.* **1996**, *37*, 5135-5138.

(12) For related fragmentation, see: Grob, C. A. *Angew. Chem. Int. Ed. Engl.* **1969**, *8*, 535-546; Grob, C. A.; Schiess, P. W. *Angew. Chem. Int. Ed. Engl.* **1967**, *6*, 1-15.

(13) Half life of **11** at 22°C in $CHCl_3$ was 20 h, while that of **19** at 50°C in Toluene-d_8 was 6 h.