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Synthetic study of kedarcidin chromophore: atropselective construction of the ansamacrolide

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Abstract

The ansamacrolide moiety of kedarcidin has been constructed with complete atropselectivity via intramolecular Sonogashira coupling.

Keywords: diynes; macrolides; ansa compounds; cyclization.

Kedarcidin is a new antitumor antibiotic consisting of a carrier apoprotein and an extremely cytotoxic nine-membered enediyne chromophore (**1**).[1,2] The structural complexity of **1**, as well as the unique mode of action, makes it a challenging and fascinating target of total synthesis. To date, some progress has been made towards the development of a viable synthesis plan for **1**.[3,4] However, neither advanced synthesis of the ansamacrolide moiety nor control of the atropselectivity has been reported. We describe herein an atropselective synthesis of the ansamacrolide moiety of **1**, which represents one of the largest obstacles to total synthesis of **1** (Fig. 1).

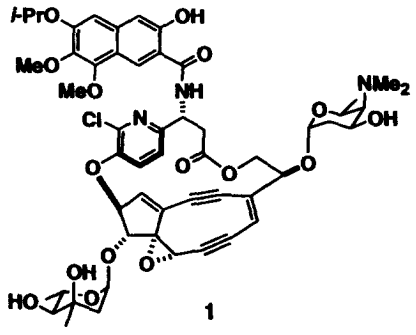

Figure 1.

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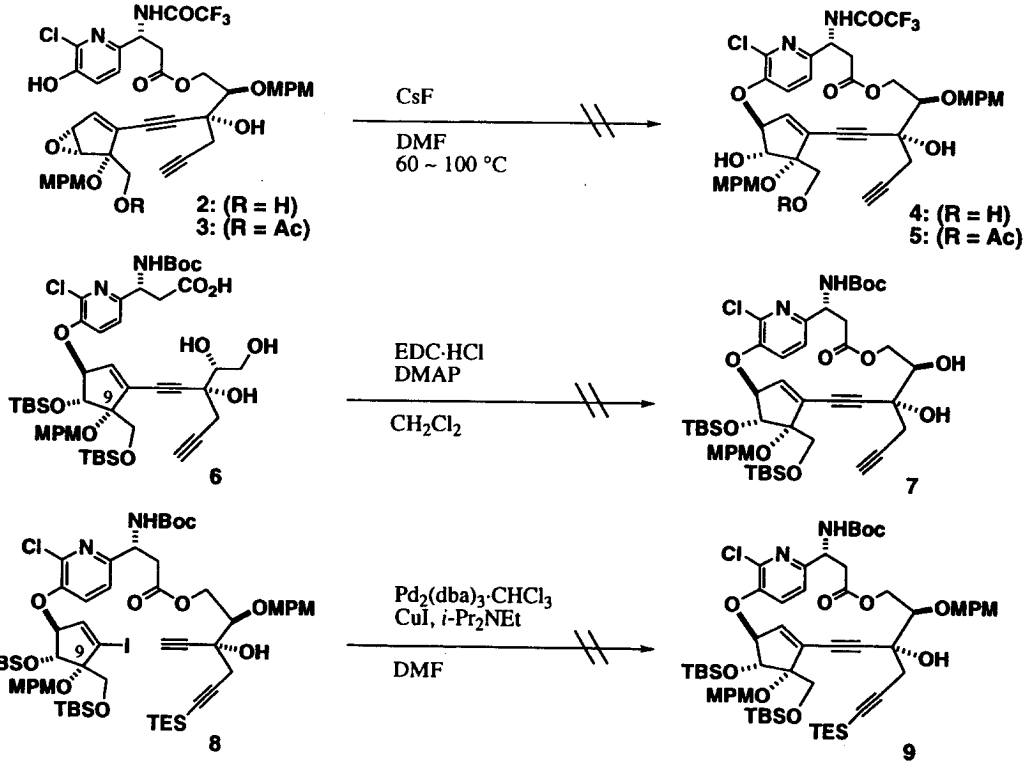
We initially attempted three possible approaches to construct the ansamacrolide structure of **1** (Scheme 1), a CsF-mediated aryl ether formation of **2** and **3**,[4] a macrolactonization of **6**,[5] and a palladium(0)-catalyzed Sonogashira coupling of **8**.[6] However, these attempts were unsuccessful and no clear products could be obtained, except in the last case where 39% of **8** was recovered. The lack of ether formation in **2** and **3** could be primarily attributed to the unfavorable trajectory of the hydroxy group on the pyridine ring to the epoxide. The failure of the lactonization of **6** and C–C bond formation of **8** to occur may be attributable to a transannular steric repulsion between the pyridine ring and the protected hydroxymethyl group at C9.[7] Based on these analyses, we attempted a palladium(0)-catalyzed C–C bond formation using precursors **20** and **21** with a rigid acetonide group, which does not project toward the β-face of the cyclopentene ring.

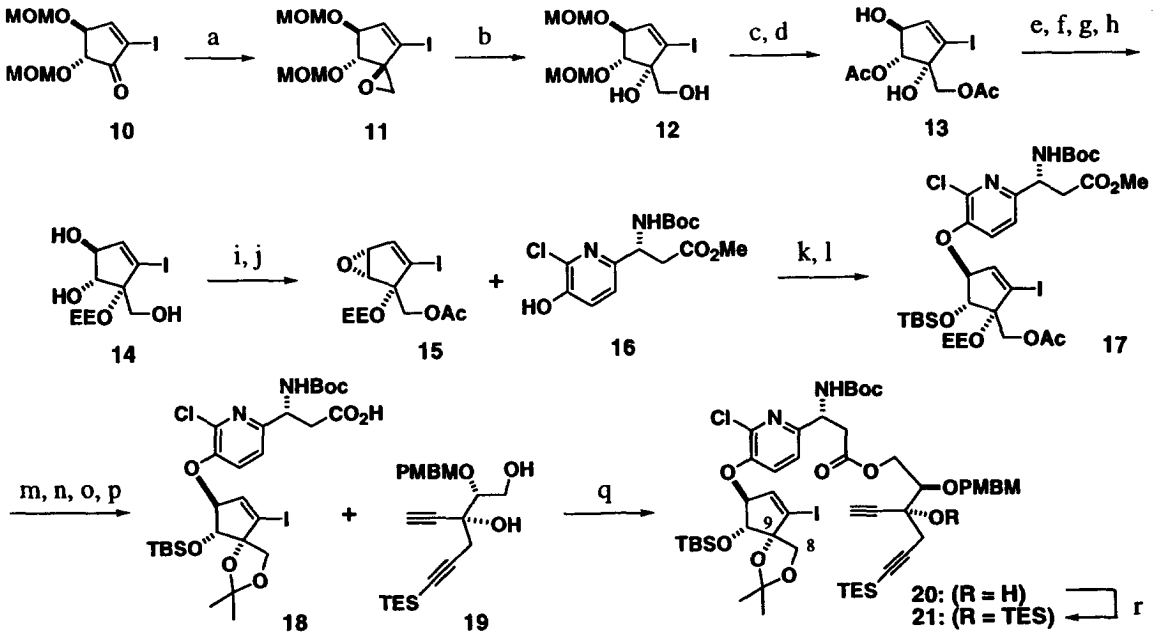


MPM: *p*-methoxybenzyl, TBS: *tert*-butyldimethylsilyl, Boc: *tert*-butoxycarbonyl, TES: triethylsilyl

Scheme 1.

Synthesis of **20** and **21** was carried out as shown in Scheme 2. Treatment of the enantiomerically pure iodoenone **10**[8] with dimethylsulfonium methylide[9] gave the β-epoxide **11**, as the major diastereomer (4.8:1), which was exposed to aqueous acid to afford the diol **12**. After protecting the diol as its diacetate, removal of both MOM groups with PPTS in 2-butanone under reflux[10] was accompanied by acetyl group migration from the tertiary alcohol to the neighboring secondary alcohol to give **13**. Further protecting group manipulation of **13** to **14**, epoxide formation under Mitsunobu conditions,[11] and acetylation of the primary alcohol gave the epoxide **15**. Coupling of **15** with the β-2-chloroazatyrosine derivative **16**[2] according to the previously reported conditions (CsF, DMF, 60°C),[4] and subsequent protection of the secondary alcohol as a TBS ether, gave aryl ether **17** in 72% yield over two steps. Successive methanolysis of the acetate and ethoxyethyl ether, followed by acetonide formation of the resultant diol, and saponification of the methyl ester, gave carboxylic acid **18**. Condensation of the acid **18** with the

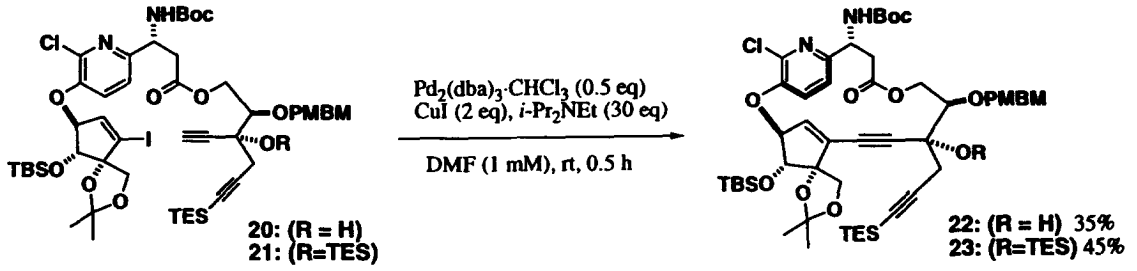
primary alcohol of the alkyne moiety **19** using EDC·HCl and DMAP gave the cyclization precursor **20**. Silylation of **20** with TESCl gave the alternative cyclization precursor **21**.



Scheme 2. Reagents and conditions: (a) Me_3SI, *n*-BuLi, THF, –85°C to rt, 60%; (b) 5% $HClO_4$ (aq), THF, 61%; (c) Ac_2O, Et_3N, DMAP, CH_2Cl_2, 91%; (d) PPTS, 2-butanone, reflux, 74%; (e) TBSCl, imidazole, DMF, 96%; (f) ethyl vinyl ether, PPTS, CH_2Cl_2, 97%; (g) TBAF, THF, –40°C, 85%; (h) K_2CO_3, MeOH, 98%; (i) DIAD, PPh_3, toluene; (j) Ac_2O, pyridine, 62% (two steps); (k) CsF, DMF, 60°C; (l) TBSCl, imidazole, DMF, 50°C, 72% (two steps); (m) K_2CO_3, MeOH, 91%; (n) PPTS, MeOH, 93%; (o) 2-methoxypropene, PPTS, DMF, 90%; (p) 0.33M KOH (aq), THF, MeOH, 96%; (q) EDC·HCl, DMAP, CH_2Cl_2, 75%; (r) TESCl, imidazole, DMF, >99%. PMBM: *p*-methoxybenzyloxymethyl

Intramolecular Sonogashira coupling of **20** was then examined (Scheme 3). Based on numerous experiments, the optimal conditions for this cyclization were determined to be as follows: $Pd_2(dba)_3 \cdot CHCl_3$ (0.5 equiv.), CuI (2 equiv.) and *i*-Pr_2NEt (30 equiv.) in degassed DMF (1 mM) at room temperature for 0.5 h, producing ansamacrolide **22** [MALDI-TOFMS, calcd for $C_{51}H_{73}ClN_2O_{12}Si_2Na$ $(M+Na)^+$: 1019.4289; found: 1019.4432] as a single atropisomer in 35% yield.[12] Use of THF or CH_3CN as a solvent, $Pd(PPh_3)_4$ as a catalyst, *N*-methylpyrrolidine as a base,[13] and catalytic use of $Pd_2(dba)_3 \cdot CHCl_3$ and CuI resulted in lower yield of **22**. Moreover, the reaction of the silylated precursor **21** under the similar coupling conditions gave the ansamacrolide **23** [MALDI-TOFMS, calcd for $C_{57}H_{87}ClN_2O_{12}Si_3Na$ $(M+Na)^+$: 1133.5153; found: 1133.5142] in a higher yield of 45% as a single atropisomer. The only detectable side-product (<10% yield) was a trace amount of homocoupled dimer of **20** or **21**.[14] The stereochemistry of the atropisomers **22** and **23** was unambiguously determined by ROESY ^1H NMR experiments (Fig. 2). The definitive characteristics were the ROESY cross peaks between H4′ and H10 in **22**, and between H4′ and H10; H4′ and H8a in **23**. Based on these results, we achieved complete substrate-based control of the atropisomerism by tuning the transannular interaction between the pyridine ring and the substitutents of the cyclopentene ring. The difference in steric bulk between the stereodemanding chlorine atom and H4′ on the pyridine ring as well as the moderate steric hindrance due to the rigid C8-methylene group play important roles in this complete stereocontrol.[15]

In conclusion, the atropselective construction of the ansamacrolide moiety of kedarcidin chromophore



Scheme 3.

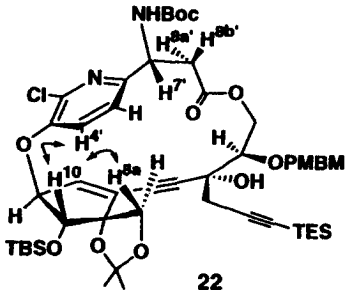


Figure 2. ROESY correlations of **22** (500 MHz, $CDCl_3$)

has been established. Further studies directed toward the total synthesis of **1** are currently being conducted in our laboratory.

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12. Compound **22**: a colorless oil; $[\alpha]_D^{28}$ 115.6 (*c* 0.158, $CHCl_3$); FT-IR (film) ν: 3435, 2955, 2929, 2874, 2857, 1733, 1717, 1653, 1614, 1559, 1515, 1448, 1369, 1299, 1251, 1170, 1113, 1081, 1030, 970, 839, 778, 739, 668, 508 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 0.21 (3H, s, TBS), 0.25 (3H, s, TBS), 0.61 (6H, q, *J*=8.0 Hz, TES), 0.97 (9H, s, TBS), 0.98 (9H, t, *J*=8.0 Hz, TES), 1.44 (9H, s, Boc), 1.45 (3H, s, acetonide), 1.47 (3H, s, acetonide), 2.53 (1H, dd, *J*=14.0, 12.0 Hz, H8′), 2.58 (1H, d, *J*=16.5 Hz, H5), 2.69 (1H, d, *J*=16.5 Hz, H5), 2.96 (1H, dd, *J*=14.0, 4.0 Hz, H8′), 3.51 (1H, s, OH), 3.81 (3H, s, PMBM), 3.97 (1H, dd, *J*=13.5, 1.5 Hz, H14), 3.97 (1H, d, *J*=8.5 Hz, H8), 4.00 (1H, dd, *J*=5.5, 1.5 Hz, H13), 4.06 (1H, d, *J*=3.5 Hz, H10), 4.08 (1H, d, *J*=8.5 Hz, H8), 4.08 (1H, dd, *J*=13.5, 5.5 Hz, H14), 4.54 (2H, s, PMBM), 4.75 (1H, d, *J*=7.0 Hz, PMBM), 4.92 (1H, d, *J*=7.0 Hz, PMBM), 5.15 (1H, m, H7′), 5.43 (1H, dd, *J*=3.5, 2.0 Hz, H11), 5.55 (1H, d, *J*=9.5 Hz, NH), 5.84 (1H, d, *J*=2.0 Hz, H12), 6.89 (2H, d, *J*=8.5 Hz, PMBM), 7.07 (1H, d, *J*=8.0 Hz, H4′), 7.10 (1H, d, *J*=8.0 Hz, H5′), 7.24 (2H, d, *J*=8.5 Hz, PMBM); ^{13}C NMR (125 MHz, $CDCl_3$): δ –4.48 (TBS), –4.33 (TBS), 4.21 (3C, TES), 7.56 (3C, TES), 18.27 (TBS), 25.86 (3C, TBS), 26.47 (acetonide), 26.70 (acetonide), 27.83 (C5), 28.34 (3C, Boc), 41.22 (C8′), 51.67 (C7′), 55.29 (PMBM), 68.13 (C14), 69.89 (PMBM), 70.27 (C8), 71.59 (C4), 79.98 (Boc), 80.20 (C2), 81.64 (C10), 83.75 (C13), 86.44 (C6), 88.60 (C9), 89.08 (C11), 95.29 (C3), 95.87 (PMBM), 101.11 (C7), 110.98 (acetonide), 113.96 (2C, PMBM), 122.99 (C5′), 128.95 (PMBM), 129.58 (2C, PMBM), 132.47 (C4′), 132.51 (C1), 139.29 (C12), 146.73 (C2′), 148.38 (C3′), 154.30 (C6′), 154.76 (Boc), 159.49 (PMBM), 169.86 (C9′); MALDI-TOFMS, calcd for $C_{51}H_{73}ClN_2O_{12}Si_2Na$ $(M+Na)^+$: 1019.4289; found: 1019.4432.

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