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Synthetic Study of the Kedarcidin Chromophore: Efficient Construction of the Aryl Alkyl Ether Linkage

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Abstract: Coupling of the azatyrosine fragment with the cyclopentadiene monoepoxide derivative corresponding to the core moiety of the kedarcidin chromophore has been effectively achieved using CsF.
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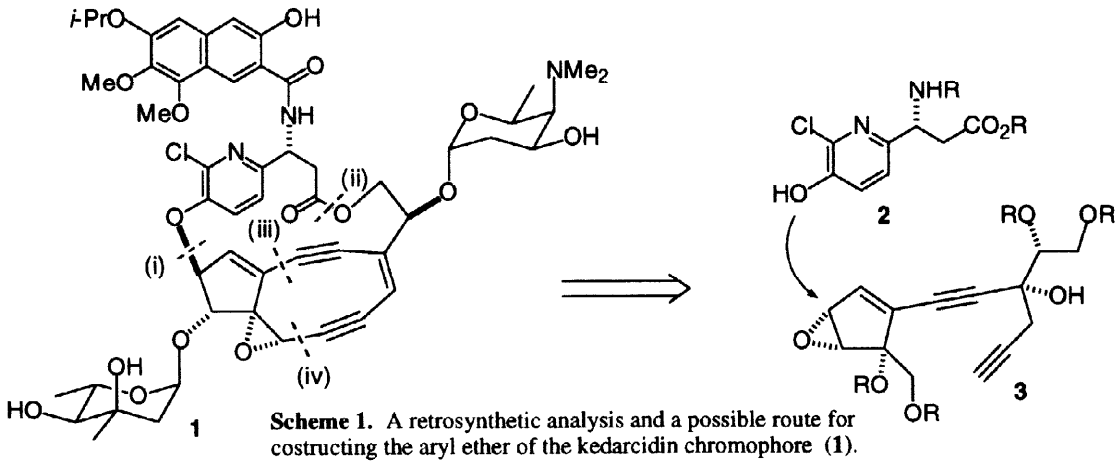
Kedarcidin is a new chromoprotein antitumor antibiotic consisting of a carrier apoprotein and an extremely cytotoxic nine-membered enediyne chromophore (**1**)[1,2]. The development of a synthetic route to the highly reactive and functionalized chromophore (**1**) represents one of the most challenging current problems in synthetic chemistry. Scheme 1 outlines a possible retrosynthetic analysis of **1** which relies on (i) an ether bond formation, (ii) an ester formation, (iii) a palladium-catalyzed C-C bond formation[3], and (iv) an acetylide-aldehyde condensation[4] to form the target ansa macrolide containing the nine-membered ring and β-azatyrosine components[2,5]. As part of a program directed toward the total synthesis of **1**, we describe herein a solution for problem (i), that is, CsF-mediated coupling of the azatyrosine fragment (**2**) with epoxide (**3**).



Scheme 1. A retrosynthetic analysis and a possible route for costructing the aryl ether of the kedarcidin chromophore (**1**).

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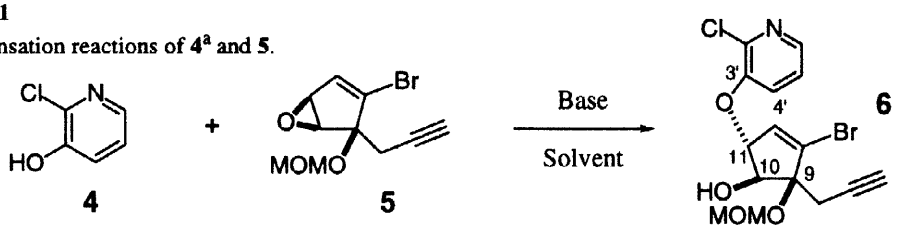
We hypothesized that the allylic epoxide (**3**) could undergo a regio- and stereoselective attack of the hydroxypyridine (**2**) to form the aryl allylic ether system required in **1**. First, we examined a model reaction using commercially available 2-chloro-3-hydroxypyridine (**4**) and an epoxide (**5**) as summarized in Table 1[6]. Reaction of potassium phenoxide of **4** with **5** in THF-HMPA (3 eq) did not proceed even under reflux (entry 1)[6c]. A two-phase reaction gave an adduct (**6**)[1] only in a low yield (entry 2). In the presence of ammonium salts, the potassium phenoxide reacted to afford **6** in moderate yields (entries 3-5). Addition of a crown ether gave a similar result (entry 6). Addition of a Lewis acid such as BF_3 improved the yield of **6** (entry 7). Extremely clean and exclusive formation of **6** was ultimately realized when CsF was used in DMF at 60 °C (entry 8)[7]. The structure of adduct (**6**) was unambiguously elucidated by ^1H and ^{13}C NMR, IR, and HRMS spectroscopy. Coupling (J=0.5 Hz) between H11 and H4' as well as three-bond heteronuclear coupling between H11 and C3' based on a COLOC experiment established the aryl ether linkage.[2] The 10,11-*trans* relationship of the oxygen functionality was established by NOEs between H11 and C9-methoxymethyl group and between H11 and C10-OH.

Table 1

Condensation reactions of **4**[a] and **5**.



Entry	Base and Additives[b]	Solvent	Temp (°C)	Time (h)	Yield (%)[c]
1	KH	THF, HMPA	65	37	0[d]
2	NaOH, Et_3NBnCl	CH_2Cl_2, H_2O (1:1)	25	120	7
3	KH, Bu_4NI	THF	65	48	29
4	KH, Et_3NBnCl	THF	65	16	59
5	KH, Bu_4NCl	DMF	60	10	58
6	KH, 18-Crown-6	THF	60	26	48
7	KH, Et_3NBnCl BF_3-OEt_2 (0.3 eq)	DMF, HMPA	60	44	70
8	CsF	DMF	60	61	99

[a] Excess **4** (2-3 eq) was used.

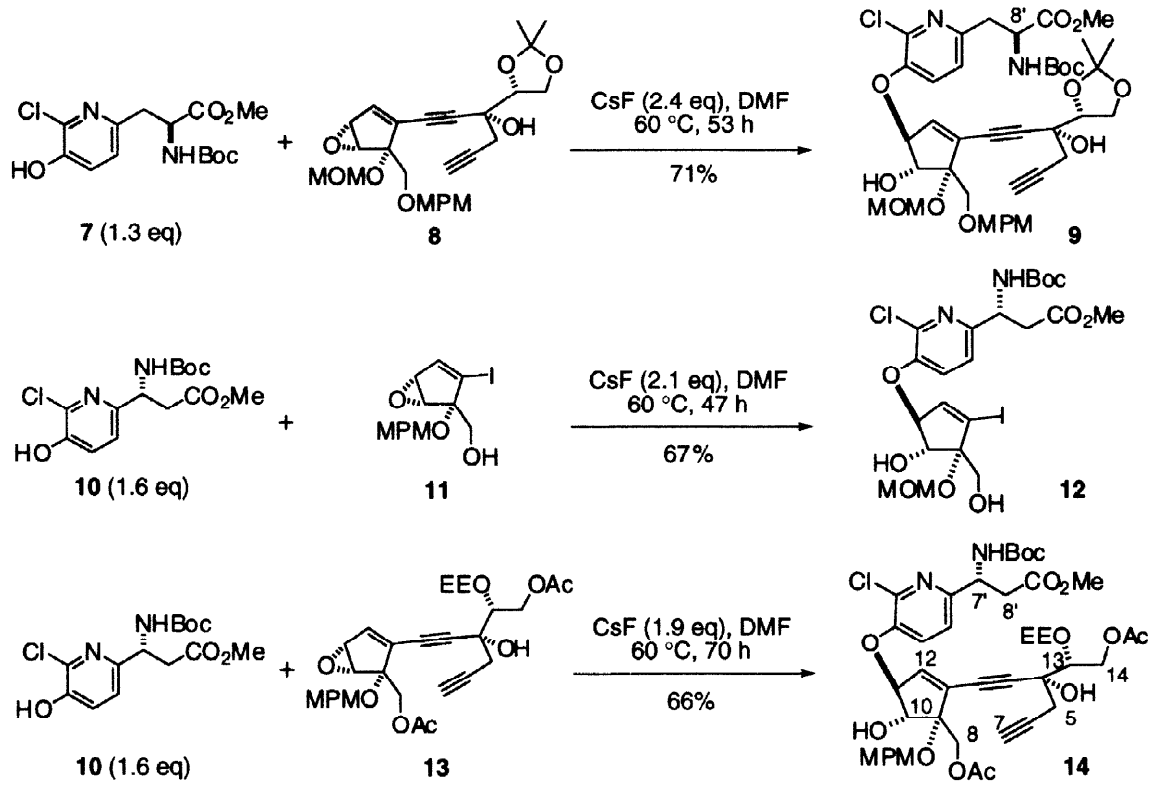
[b] Excess base and additives (2-3 eq each) were added unless otherwise indicated.

[c] The epoxide (**5**) was consumed unless otherwise indicated.

[d] **5** was recovered.

[1] Selected physical data of **6**: colorless crystals; mp 127-128 °C (ether); $[\alpha]_D^{28}$ -8.6° (c 1.34, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 2.11 (1H, t, J=2.5 Hz), 2.71 (1H, ddd, J=17.5, 2.5, 0.6 Hz), 2.80 (1H, dd, J=17.5, 2.5 Hz), 3.46 (3H, s), 3.76 (1H, d, J=10.0 Hz), 4.50 (1H, ddd, J=10.0, 4.5, 0.6 Hz), 4.68 (1H, d, J=7.0 Hz), 4.73 (1H, d, J=7.0 Hz), 5.04 (1H, ddd, J=4.5, 2.0, 0.5 Hz), 6.52 (1H, d, J=2.0 Hz), 7.63 (1H, ddd, J=8,0, 1.5, 0.5 Hz), 7.21 (1H, dd, J=8.0, 4.5 Hz), 8.04 (1H, dd, J=4.5, 1.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) d 27.34 (t), 56.24 (q), 71.99 (d), 78.11 (d), 78.14 (s), 87.58 (d), 88.23 (s), 92.56 (t), 123.18 (d), 123.66 (d), 127.19 (s), 136.26 (d), 141.76 (s), 141.76 (d), 150.43 (s); FT-IR (KBr) ν 3412, 3246, 2974, 2960, 2936, 2920, 2830, 1615, 1568, 1466, 1450, 1419, 1346, 1323, 1288, 1241, 1209, 1135, 1118, 1089, 1031, 996, 944, 903, 891, 864, 820, 789 cm^{-1}; HRMS (EI, 70 eV) calcd for $C_{15}H_{16}NO_4BrCl$ 387.9951 (M^+); found 387.9943 (M^+).

[2] The carbon numbering follows that for the kedarcidin chromophore (**1**)[1].



Scheme 2

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[3] Selected physical data of **9**: colorless oil; $[\alpha]_D^{27}$ +51.3° (c 0.50, $CHCl_3$); ^1H NMR (600 MHz, $CDCl_3$) δ 1.36 (3H, s), 1.42 (9H, s), 1.45 (3H, s), 2.11 (1H, t, *J*=2.6 Hz), 2.69 (1H, dd, *J*=16.1, 2.6 Hz), 2.73 (1H, dd, *J*=16.1, 2.6 Hz), 2.85 (1H, s), 3.19 (1H, dd, *J*=14.1, 4.8 Hz), 3.23 (1H, dd, *J*=14.1, 4.8 Hz), 3.39 (1H, d, *J*=8.6 Hz), 3.41 (3H, s), 3.70 (1H, d, *J*=9.7 Hz), 3.72 (1H, d, *J*=9.7 Hz), 3.75 (3H, s), 3.80 (3H, s), 4.04 (1H, dd, *J*=8.8, 5.8 Hz), 4.11 (1H, dd, *J*=8.8, 6.7 Hz), 4.21 (1H, dd, *J*=6.7, 5.8 Hz), 4.37 (1H, dd, *J*=8.6, 4.8 Hz), 4.52 (1H, d, *J*=11.7 Hz), 4.56 (1H, d, *J*=11.7 Hz), 4.62 (1H, dt, *J*=7.8, 4.8 Hz), 4.74 (1H, d, *J*=7.0 Hz), 4.83 (1H, d, *J*=7.0 Hz), 5.13 (1H, dd, *J*=4.8, 1.9 Hz), 5.45 (1H, brd, *J*=7.8 Hz), 6.41 (1H, d, *J*=1.9 Hz), 6.87 (2H, d, *J*=8.7 Hz), 7.01 (1H, d *J*=8.1 Hz), 7.26 (2H, d, *J*=8.7 Hz), 7.56 (1H, d, *J*=8.1 Hz); ^{13}C NMR (150 MHz, $CDCl_3$) δ 24.90 (q), 26.29 (q), 28.26 (t), 29,95 (t), 38.39 (t), 52.38 (q), 53.18 (d), 55.24 (q), 56.00 (q), 65.81 (t), 70.40 (t), 71.05 (s), 72.39 (s), 73.33 (t), 78.02 (d), 78.51 (d), 78.99 (s), 79,31 (d), 79,83 (s), 87.28 (s), 87.94 (d), 92.49 (t), 94.79 (s), 110.39 (s), 113.73 (d), 123.11 (d), 123.90 (d), 129.32 (d), 129.81 (s), 140.23 (d), 140.48 (s), 148.95 (s), 149.36 (s), 155.27 (s), 159.26 (s), 172.13 (s); FT-IR (neat) ν 3430, 3310, 2934, 1744, 1713, 1613, 1564, 1516, 1456, 1371, 1251, 1218, 1166, 1091, 1071, 1031, 990, 855, 758 cm^{-1}.

[4] ^1H NMR data of TBS ether of **14** (a 1:1 diastereomeric mixture): δ 0.02 (3/2H, s, $SiCH_3$), 0.05 (3/2H, s, $SiCH_3$), 0.14 (3/2H, s, $SiCH_3$), 0.14 (3/2H, s, $SiCH_3$), 0.86 (9/2H, s, $Si(CH_3)_3$), 0.90 (9/2H, s, $Si(CH_3)_3$), 1.16-1.35 (6H, m, $OCH(CH_3)OCH_2CH_3$), 1.45 (9H, brs, Boc), 2.05 (3/2H, s, Ac), 2.06 (3/2H, s, Ac), 2.07 (3/2H, s, Ac), 2.10 (1H, overlapped, H7), 2.11 (3/2H, s, Ac), 2.66 (1/2H, dd, J=17.2, 2.4 Hz, H5), 2.69-2.76 (1H, brs, H5), 2.78 (1/2H, dd, J=17.2, 2.4 Hz, H5), 2.85 (1H, d, J=16.6, 7.0 Hz, H8'), 3.06 (1H, d, J=16.6, 5.4 Hz, H8'), 3.46-3.58 (2H, m, $OCH(CH_3)OCH_2CH_3$), 3.64 (3H, S, OCH_3), 3.80 (3H, s, OCH_3), 3.90-4.50 (5H, m, H8, H10, H13, H14), 4.46 (1/2H, d, J=6.4 Hz, $CH_3C_6H_4$), 4.48 (1/2H, d, J=8.4 Hz, $CH_2C_6H_4$), 4.54 (1/2H, d, J=6.4 Hz, $CH_2C_6H_4$), 4.55 (1/2H, d, J=8.4 Hz, $CH_2C_6H_4$), 4.76 (1/2H, q, J=4.8 Hz, $OCH(CH_3)C_2H_5$), 4.95 (1/2H, q, J=5.4 Hz, $OCH(CH_3)C_2H_5$), 5.12 (1H, ddd, J=9.2, 7.0, 5.4 Hz, H7'), 5.25 (1H, dd, J=4.8, 1.4 Hz, H11), 5.72 (1H, brd, J=9.2 Hz, NH), 6.40 (1/2H, d, J=1.4 Hz, H12), 6.42 (1/2H, d, J=1.4 Hz, H12), 6.86 (2H, d, J=8.4 Hz, $CH_2C_6H_4OCH_3$), 7.20 (1H, d, J=8.6 Hz, H5'), 7.28 (1H, d, J=8.6 Hz, H4'), 7.28 (2H, d, J=8.4 Hz, $CH_2C_6H_4OCH_3$).

The present CsF-mediated condensation reaction was applied to more functionalized systems (Scheme 2).

α-2-Chloroazatyrosine derivative (**7**)[2] was coupled with an epoxide (**8**) using CsF in DMF at 60 ℃ to give **9**[3] in 71% yield without epimerization at C8'. When t-butyl ester corresponding to the methyl ester (**7**) was treated with **8** using KH and Et_3NBnCl in DMF at 60 ℃, the reaction resulted in the formation of a complex mixture. β-2-Chloroazatyrosine derivative (**10**)[2] was also coupled with epoxides (**11**) and (**13**) using CsF to afford **12** and **14**[4] in a 67% and 66% yield, respectively. Elimination of the protected amino group was prevented completely under these reaction conditions. Thus, the CsF-mediated condensation reaction can be applied to base-sensitive systems.

In summary, an efficient method for the regio- and stereoselective construction of the allylic aryl ether linkage of the kedarcidin chromophore (**1**) was developed. This CsF-mediated coupling reaction may facilitate the total synthesis of **1** and its analogs. Further studies directed toward the total synthesis of **1** are currently being conducted in our laboratory.

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References

[1] Leet JE, Schroeder DR, Langley DR, Colson KL, Huang S, Klohr S. E, Lee MS, Golik J, Hofstead SJ, Doyle TW, Matson JA. J. Am. Chem. Soc. 1993; 115: 8432-8433.

[2] Kawata S, Ashizawa S, Hirama M. J. Am. Chem. Soc. 1997; 119:12012-12013.

[3] Reddy RS, Iguchi S, Kobayashi S, Hirama M. Tetrahedron Lett. 1996; 37: 9335-9336.

[4] Iida K, Hirama M. J. Am. Chem. Soc. 1994; 116: 10310-10311.

[5] For synthetic studies, see: (a) Iida K, Hirama M. J. Am. Chem. Soc. 1995; 117: 8875-8876.; Kawata S, Yoshimura F, Irie J, Ehara H, Hirama M. Synlett, 1997; 250-252. (b) Myers AG, Horiguchi Y. Tetrahedron Lett. 1997; 38: 4363-4366. (c) Hornyák M, Pelyvás IF. Sztaricskai FJ. Tetrahedron Lett. 1993; 34: 4087-4090.; Vuljanic T, Kihlberg J, Somfai P. Tetrahedron Lett. 1994; 37: 6937-6940.; Toshima K, Yoshida T, Mukaiyama S, Tatsuta K. Carbohydrate Research 1991; 222: 173-188.

[6] For condensation of phenols and epoxides, see: (a) David M, Sauleau J, Sauleau A. Can. J. Chem. 1985; 63: 2449-2454. (b) Riego J, Costa A, Saa JM. Chem. Lett. 1986; 27: 1565-1566. (c) Schultz AG, Lucci RD, Fu WY, Berger MH, Erhardt J, Hagmann WK. J. Am. Chem. Soc. 1978; 100: 2150-2162. (d) Jung ME, Starkey LS. Tetrahedron Lett. 1995; 36: 7363-7366. (e) Akita H, Umezawa I, Takano M, Ohyama C, Matsukura H, Oishi T. Chem. Pharm. Bull. 1993; 41: 55-63. (f) Klunder JM, Ko YS, Sharpless KB. J. Org. Chem. 1986; 51: 3710-3712.

[7] (a) Nambu Y, Endo T. Tetrahedron Lett. 1990; 31: 1723-1726. (b) For related CsF mediated alkylations, see: Kitaori K, Furukawa Y, Yoshimoto H, Otera J. Tetrahedeon Lett. 1998; 39: 3173-3176, and references cited therein.