Synthetic Study of C-1027 Chromophore: Enantioselective Synthesis of β-Tyrosine Moiety and Effective Aryl Ether Formation

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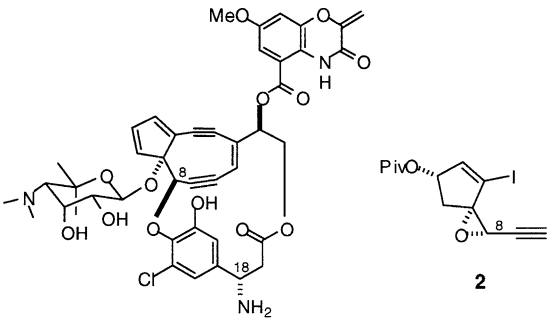
The β-tyrosine moiety of C-1027 chromophore (**1**) was enantioselectively synthesized and efficiently coupled with propargylic epoxide (**2**) using CsF.

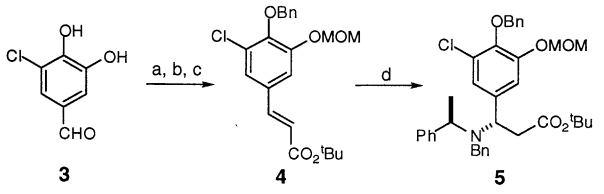
C-1027[1] is one of the most recent additions to the family of chromoprotein antibiotics which contain a carrier apoprotein and a reactive nine-membered enediyne chromophore.[2,3] In the attempt at total synthesis of the C-1027 chromophore (**1**),[4] the construction of an aryl ether linkage at C8 represents one of the major problems. Recently, we realized a CsF-mediated addition reaction of phenols to allylic epoxides with complete regio- and stereoselectivity.[5] We describe herein an enantioselective synthesis of the β-tyrosine moiety of **1** and effective coupling with the propargylic epoxide (**2**).



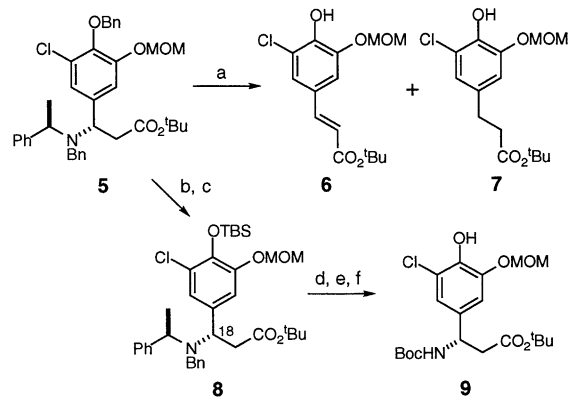
C-1027 chromophore (**1**)

Synthesis of the β-tyrosine moiety was started with a readily available 3-chloro-4,5-dihydroxybenzaldehyde (**3**) (Scheme 1).[6] After selective benzylation of the hydroxy group at the position *para* to the aldehyde,[7] the remaining hydroxy group was protected as methoxymethyl (MOM) ether and the subsequent Horner-Emmons reaction furnished a *tert*-butyl cinnamate derivative (**4**). Asymmetric conjugate addition of Davies' chiral lithium amide to **4** gave β-amino ester (**5**) in a ratio of 20:1.[8]

Hydrogenolysis of the *N*-benzyl and *N*-phenethyl groups of **5**, however, was very slow and was accompanied by elimination of the amino group to produce **6** and **7** (Scheme 2). Since removal of the *O*-benzyl group is facile, a stepwise procedure was undertaken: Selective hydrogenolysis of the *O*-benzyl ether using a Pd/C catalyst in ethyl acetate was followed by protection as a *tert*-butyldimethylsilyl (TBS) ether to give **8**. Subsequent hydrogenolysis of the *N*-benzyl and *N*-phenethyl groups using a Rh/C catalyst successfully gave the free amine[9] without the elimination, loss of chloride or cleavage of the C18-N bond. The crude product was immediately subjected to treatment with di-*tert*-butyl dicarbonate (Boc_2O) and then with tetrabutylammonium fluoride (Bu_4NF) to yield a stable β-tyrosine derivative (**9**).[11]

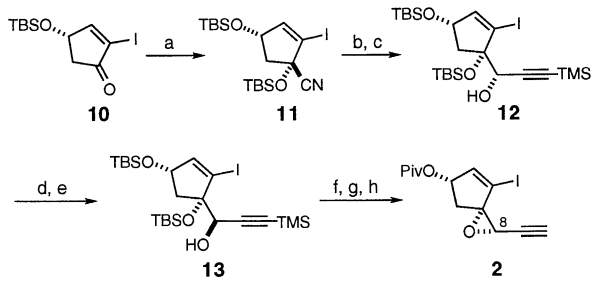


Scheme 1. Reagents and conditions: (a) BnBr, Li_2CO_3, DMF, 55 °C, 87%. (b) MOMCl, $^iPr_2NEt$, CH_2Cl_2, 92%. (c) $(^iPrO)_2P(O)CH_2$-$CO_2{}^tBu$, NaH, THF, 0 °C, 100%. (d) (*R*)-(+)-benzyl-α-methylbenzylamine, BuLi, THF, -78 °C, 83%.



Scheme 2. Reagents and conditions: (a) H_2, Pd/C, MeOH, 10 h, **6** (19%), **7** (56%). (b) H_2, Pd/C, ethyl acetate, 3 h. (c) TBSCl, Et_3N, CH_2Cl_2, 93% (2 steps). (d) H_2, Rh/C, MeOH, H_2O, AcOH. (e) Boc_2O, $NaHCO_3$, 1,4-dioxane, H_2O. (f) Bu_4NF, THF, 76% (3 steps).

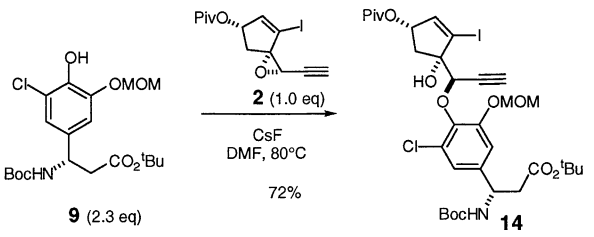
The propargylic epoxide (**2**) was synthesized from an optically active α-iodocyclopentenone derivative (**10**)[12] as shown in Scheme 3. After addition of TBSCN[13] to **10**, DIBAL



Scheme 3. Reagents and conditions: (a) TBSCN, cat. ZnI_2, toluene, 59%. (b) DIBAL, CH_2Cl_2, -78 °C. (c) TMS-C≡CLi, THF, -78 °C, 35% (2 steps). (d) Dess-Martin periodinane, CH_2Cl_2. (e) $NaBH_3CN$, ^iPrOH, H_2O, AcOH, 97% (2 steps, **13**:**12**=7:1). (f) MsCl, Et_3N, CH_2Cl_2, 0 °C. (g) Bu_4NF, THF, 84% (2 steps). (h) PivCl, pyridine, 78%.

reduction of **11** followed by an acetylide addition gave a propargylic alcohol (**12**) diastereoselectively (**12**:**13**=~4:1). Stereochemical inversion of the secondary alcohol (**12**) was conducted *via* an oxidation-reduction sequence to afford **13** and **12** in the ratio of 7:1. After separation, mesylation of **13** and treatment with Bu_4NF followed by protection with pivaloyl chloride gave the epoxide (**2**).[14]

Coupling of **9** with **2** was examined using CsF in DMF (Scheme 4).[5] At relatively high temperatures the reaction proceeded to give a desired aryl ether (**14**) in good yield:[15] The carbamate group was completely unaffected by this reaction.



Scheme 4. An efficient coupling reaction of **9** with **2**.

In conclusion, the enantioselective synthesis of the β-tyrosine moiety (**9**) of the C-1027 chromophore (**1**) was achieved and an efficient method for constructing the aryl ether linkage was established. Further studies directed toward total synthesis of **1** will be reported in due course.

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References and Notes

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9 The *S* configuration at C18 was defined using a modified Mosher method.[10]

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11 **9**: colorless needles; mp 136 °C (hexane/ethyl acetate); $[\alpha]_D^{26}$ -28 (c 1.01, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 1.38 (9H, s, ^{t}Bu), 1.41 (9H, s, Boc), 2.64 (1H, br dd, *J*=13.8, 5.7 Hz, H17), 2.68 (1H, br dd, *J*=13.8, 6.0 Hz, H17), 3.70 (3H, s, MOM), 4.92, (1H, br s, H18), 5.17 (1H, d, *J*=8.0 Hz, MOM), 5.19 (1H, d, *J*=8.0 Hz, MOM), 5.50 (1H, br s, NH), 6.20 (1H, br s, OH), 6.97 (2H, s, H20 and H24); ^{13}C NMR (125 MHz, $CDCl_3$) ppm 27.9 (^{t}Bu), 28.3 (Boc), 42.0 (C17), 51.5 (C18), 56.5 (MOM), 79.8 (Boc), 81.4 (^{t}Bu), 96.1 (MOM), 113.3 (C24), 120.0 (C21), 121.1 (C20), 134.0 (C19), 142.0 (C22), 145.3 (C23), 154.9 (Boc), 170.0 (C16); FT-IR (film) ν 3384, 2979, 1702, 1521, 1436, 1368, 1300, 1086, 1022 cm^{-1}. Found: C, 55.40; H, 6.72; Cl, 7.94; N, 3.23%. Calcd for $C_{20}H_{30}ClNO_7$: C, 55.62; H, 7.00; Cl, 8.21; N, 3.24%. The carbon numbering follows that for the C-1027 chromophore. See Ref. 3d.

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14 The configuration at C8 was determined by comparison between the NOEs of **2** and its isomeric epoxide prepared from **12**.

15 **14**: colorless amorphous; $[\alpha]_D^{29}$ -142 (c 1.10, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 1.33 (9H, s, ^{t}Bu), 1.36 (9H, s, ^{t}Bu), 1.41 (9H, s, Boc), 2.00 (1H, ddd, *J*=14.5, 5.0, 0.7 Hz, H10), 2.41 (1H, d, *J*=2.0 Hz, H6), 2.6-2.8 (2H, m, H17), 3.45 (1H, dd, *J*=14.5, 8.0 Hz, H10), 3.53 (3H, s, MOM), 4.08 (1H, s, OH), 4.97, (1H, m, H18), 5.01(1H, br s, H8), 5.22 (1H, d, *J*=6.5 Hz, MOM), 5.24 (1H, d, *J*=6.5 Hz, MOM), 5.54 (1H, ddd, *J*=8.0, 5.0, 2.0 Hz, H11), 5.56 (1H, br s, NH), 6.49 (1H, d, *J*=2.0 Hz, H12), 6.99 (1H, d, *J*=1.5 Hz, H22 or H24), 7.01 (1H, d *J*=1.5 Hz, H22 or H24); ^{13}C NMR (125 MHz, $CDCl_3$) ppm 27.1 (Piv), 27.9 (^{t}Bu), 28.3 (Boc), 38.6 (Piv), 39.4 (C10), 41.8 (C17), 50.8 (C18), 56.8 (MOM), 77.2 (C7), 77.3 (C6), 77.5 (C8), 77.9 (C11), 79.9 (Boc), 81.5 (^{t}Bu), 87.3 (C9), 95.4 (MOM), 106.5 (C1), 112.5 (C24), 121.1 (C20), 129.0 (C21), 139.3 (C19), 141.6 (C22), 143.4 (C12), 150.8 (C23), 154.9 (Boc), 169.9 (C16); FT-IR (film) ν 3292, 2976, 2933, 2286, 1720, 1481, 1367, 1283, 1160, 1014 cm^{-1}. MALDI-TOFMS Found: *m/z* 800.1797. Calcd for $C_{33}H_{45}ClINO_{10}Na$: M+Na, 800.1777.