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

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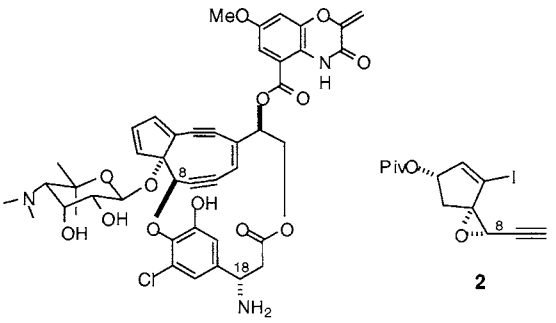
The β-tyrosine moiety of C-1027 chromophore (**1**) was enantioselectively synthesized and efficiently coupled with propargylic epoxide (**2**) using CsF.

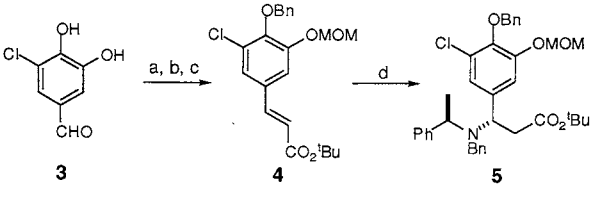
C-1027[1] is one of the most recent additions to the family of chromoprotein antibiotics which contain a carrier apoprotein and a reactive nine-membered enediyne chromophore.[2,3] In the attempt at total synthesis of the C-1027 chromophore (**1**),[4] the construction of an aryl ether linkage at C8 represents 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**).



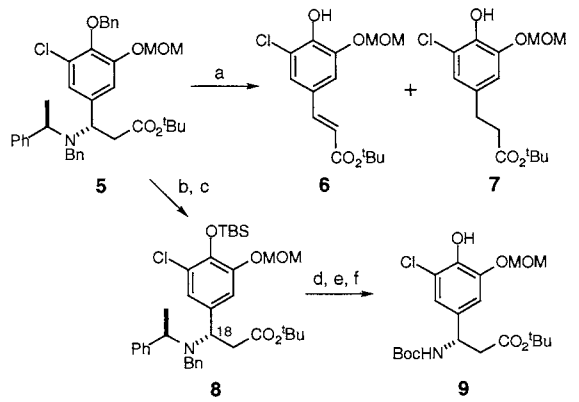
C-1027 chromophore (**1**)

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]

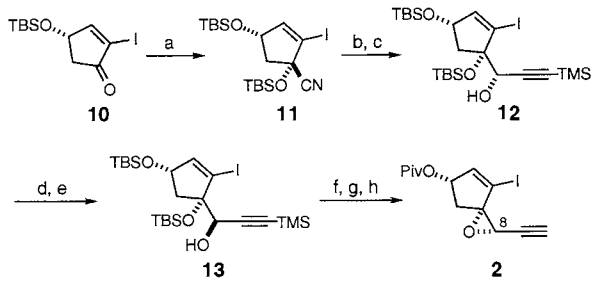


Scheme 1. Reagents and conditions: (a) BnBr, Li_2CO_3, DMF, 55 °C, 87%. (b) MOMCl, $^iPr_2NEt$, CH_2Cl_2, 92%. (c) $(^iPrO)_2P(O)CH_2$-$CO_2{}^tBu$, NaH, THF, 0 °C, 100%. (d) (*R*)-(+)-benzyl-α-methylbenzylamine, BuLi, THF, -78 °C, 83%.



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%.

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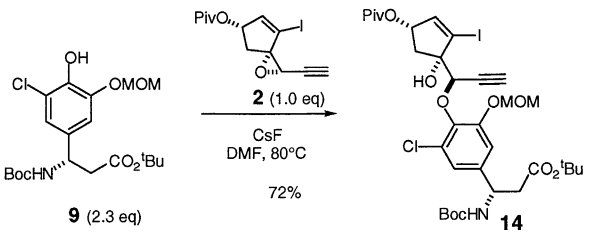
reduction of **11** followed by an acetylide addition gave a propargylic alcohol (**12**) diastereoselectively (**12**:**13**=~4:1). Stereochemical inversion of the secondary alcohol (**12**) was conducted *via* an oxidation-reduction sequence to afford **13** and **12** in the ratio of 7:1. After separation, 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

1 a) J. Hu, Y.-C. Xue, M.-Y. Xie, R. Zhang, T. Otani, Y. Minami, Y. Yamada, and T. Marunaka, *J. Antibiot.*, **41**, 1575 (1988). b) T. Otani, Y. Minami, T. Marunaka, R. Zhang, and M.-Y. Xie, *J. Antibiot.*, **41**, 1580 (1988).

2 a) K. C. Nicolaou and W.-M. Dai, *Angew. Chem., Int. Ed. Engl.*, **30**, 1387 (1991). b) M. Hirama, "Synthesis and Chemistry of Neocarzinostatin Analogs," in "Recent Progress in the Chemical Synthesis of Antibiotics and Related Microbial Products, Vol. 2," ed by G. Lukacs, Springer-Verlag, Berlin (1993), pp. 293-329.

3 a) Y. Minami, K. Yoshida, R. Azuma, M. Saeki, and T. Otani, *Tetrahedron Lett.*, **34**, 2633 (1993). b) K. Yoshida, Y. Minami, R. Azuma, M. Saeki, and T. Otani, *Tetrahedron Lett.*, **34**, 2637 (1993). c) K. Yoshida, Y. Minami, T. Otani, Y. Tada, and M. Hirama, *Tetrahedron Lett.*, **35**, 5253 (1994). d) K. Iida, S. Fukuda, T. Tanaka, M. Hirama, S. Imajo, M. Ishiguro, K. Yoshida, and T. Otani, *Tetrahedron Lett.*, **37**, 4997 (1996).

4 a) K. Iida, T. Ishii, M. Hirama, T. Otani, Y. Minami, and K. Yoshida, *Tetrahedron Lett.*, **34**, 4079 (1993). b) K. Iida and M. Hirama, *J. Am. Chem. Soc.*, **116**, 10310 (1994). c) K. Iida and M. Hirama, *J. Am. Chem. Soc.*, **117**, 8875 (1995). d) I. Sato, Y. Akahori, K. Iida, and M. Hirama, *Tetrahedron Lett.*, **37**, 5135 (1996). e) I. Sato, K. Toyama, T. Kikuchi, and M. Hirama, *Synlett*, **1998**, 1308.

5 S. Kawata and M. Hirama, *Tetrahedron Lett.*, **39**, 8707 (1998).

6 M.-L. Anhoury, P. Crooy, R. D. Neys, and J. Eliaers, *J. Chem. Soc., Perkin Trans. 1*, **1974**, 1015.

7 J. R. Pfister, *Synth. Commun.*, **18**, 1379 (1988).

8 a) S. G. Davies and O. Ichihara, *Tetrahedron: Asymmetry*, **2**, 183 (1991). b) J. F. Costello, S. G. Davies, and O. Ichihara, *Tetrahedron: Asymmetry*, **5**, 1999 (1994).

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

10 a) T. Kusumi, T. Fukushima, I. Ohtani, and H. Kakisawa, *Tetrahedron Lett.*, **32**, 2939 (1991). b) I. Ohtani, T. Kusumi, Y. Kashman, and H. Kakisawa, *J. Am. Chem. Soc.*, **113**, 4092 (1991).

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.

12 M. Hirama, T. Gomibuchi, K. Fujiwara, Y. Sugiura, and M. Uesugi, *J. Am. Chem. Soc.*, **113**, 9851 (1991).

13 K. Toyama, S. Iguchi, T. Oishi, and M. Hirama, to be submitted.

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.