Practical Synthesis of the C-1027 Aminosugar Moiety

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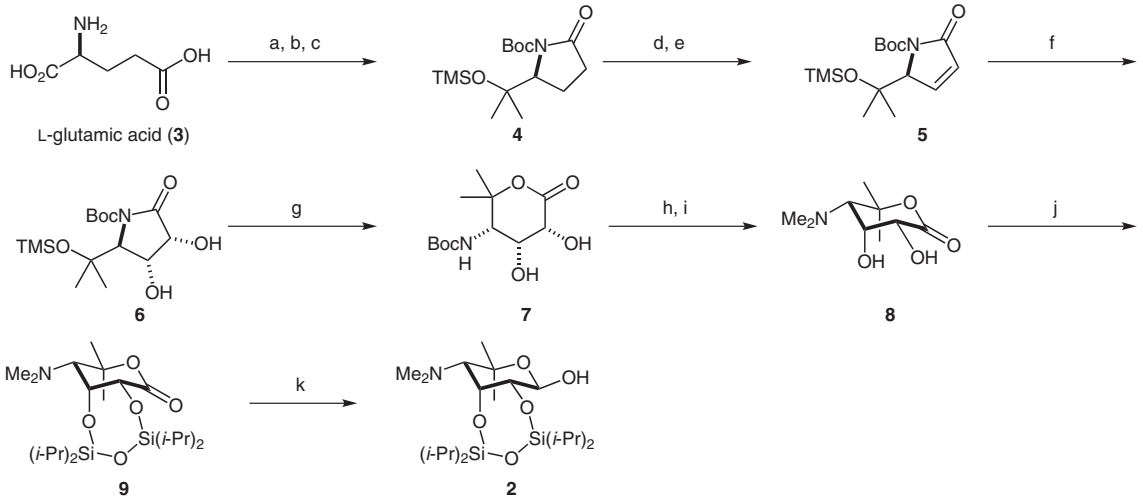
Abstract: A concise and reliable synthetic route to the aminosugar moiety of the C-1027 chromophore was developed. The aminosugar moiety was synthesized from L-glutamic acid in 11 steps and 13% overall yield.

Key words: C-1027, enediyne, carbohydrate, natural products, synthesis

The enediyne antibiotic C-1027,[1] isolated from the culture supernatant of *Streptomyces globisporus* C-1027 in 1988, possesses the most potent antitumor activity in the family of chromoprotein antibiotics.[2] C-1027 is composed of a biologically active chromophore and a stabilizing apoprotein.[3,4] Synthesis of chromophore **1**, which has the highly strained, labile nine-membered enediyne,[5] has attracted the attention of many chemists.[6,7] In 1993, we reported the synthesis of the aminosugar moiety via intramolecular carbamate rearrangement and determined its absolute configuration.[3b,8] However, a recent synthetic study of **1** indicated that glycosylation at a relatively early stage was preferable and it required an ample supply of the aminosugar moiety **2** (Figure 1). Unfortunately, our synthesis of **2** suffered from lengthy steps and a low overall yield. Thus, we developed a more concise and reliable synthetic route to **2**. For the purpose of the stereoselective glycosylation[6b] and global deprotection at the end of the synthesis, 1,1,3,3,-tetraisopropoxydisiloxanylidene (TIPDS) protection of **2** should be a suitable choice.

The aminosugar moiety **2** features a *gem*-dimethyl at C5, a *cis*-dihydroxy group at C2 and C3, and an *N*,*N*-dimethylamino group at the C4 position. Stereoselective construction of the three C2–C4 consecutive stereogenic centers was a major challenge in the synthesis (Scheme 1). The synthesis began with L-glutamic acid (**3**). According to the literature procedure, **3** was converted into γ-lactam ethyl ester.[9] Selective methylation of the ester functionality and subsequent trapping of the hydroxy group as a trimethylsilyl ether gave **4** after *tert*-butoxycarbonyl (Boc) protection of the lactam nitrogen. Introduction of the double bond and subsequent dihydroxylation of **5** using osmium tetroxide and *N*-methylmorpholine *N*-oxide provided *cis*-diol **6** as a single diastereomer.[10] Alkaline hydrolysis of the imide function selectively cleaved the γ-lactam, followed by the addition of *p*-toluenesulfonic acid, to give desired δ-lactone **7**.

For the selective hydrolysis of the lactam, Boc protection of the amide group was essential. When hydrolysis of the



Scheme 1 *Reagents and conditions*: (a) $SOCl_2$, EtOH then 150 °C, 0.02 bar, 89%; (b) MeLi, THF, –78 °C then TMSCl, Et_3N, r.t., 68%; (c) $(Boc)_2O$, Et_3N, MeCN, 90%; (d) $LiN(SiMe_3)_2$, THF, –78 °C then PhSeCl; (e) 30% aq H_2O_2, pyridine, 79% (2 steps); (f) cat. OsO_4, NMO, acetone, H_2O, 91%; (g) LiOH, THF, H_2O then TsOH, CH_2Cl_2, 82%; (h) TFA–CH_2Cl_2 (1:1); (i) $NaBH_3CN$, aq HCHO, formic acid, 79% (2 steps); (j) $TIPDSCl_2$, imidazole, DMF, 56%; (k) DIBAL-H, CH_2Cl_2, –78 °C, 90%.

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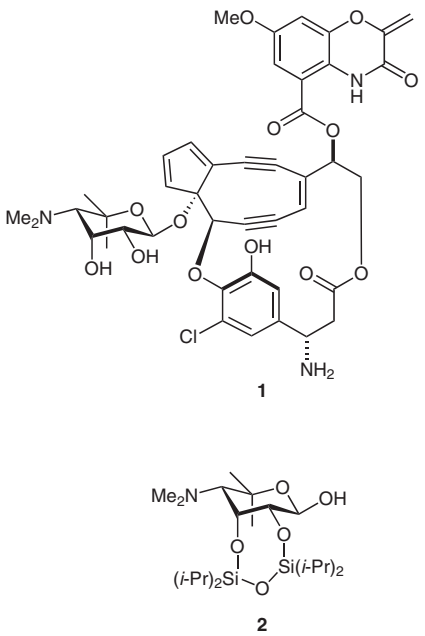
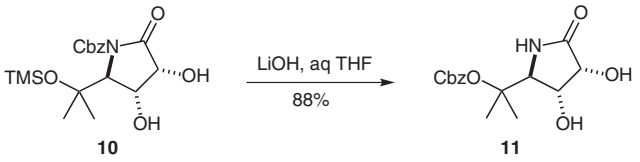


Figure 1 Structures of C-1027 chromophore **1** and aminosugar moiety **2**

corresponding imide **10** protected by a carbobenzyloxy (Cbz) group was attempted, the γ-lactam was not cleaved and instead the Cbz group migrated to the C5 hydroxy group (Scheme 2). A similar migration of the alkoxycarbonyl group to the primary alcohol often occurred even if the Boc group was used.[11] In the hydrolysis of **6**, steric hindrance between the *gem*-dimethyl and the *tert*-butoxycarbonyl group suppressed intramolecular attack of the alkoxide. Acidic removal of the Boc group followed by reductive methylation of the resulting amine gave dimethylamine **8**. Protection of the vicinal diol with TIPDSCl provided **9**.[12] Reduction with DIBAL-H afforded desired hemiacetal **2** together with a small amount (<10%) of open-chain aldehyde.[13]



Scheme 2 Migration of carbobenzyloxy group of **10**

In conclusion, we have developed a concise synthetic route to the C-1027 aminosugar moiety **2**. The present synthesis (11 steps in 13% overall yield from L-glutamic acid), superior to the previous route (18 steps, 0.49%), will facilitate the synthetic study of the C-1027 chromophore **1**. Further studies directed toward the total synthesis of **1** are currently under way in our laboratory.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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(12) **Selected Data for 9**
Colorless needles; mp 162–164 °C (EtOAc); $[\alpha]_D^{29}$ +8.6 (*c* 1.00, CH_2Cl_2). FT-IR (film): ν = 2944, 1742, 1458, 1275, 1179, 1114, 1041, 1014, 884, 801, 695 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 0.94–1.15 (28 H, m, TIDPS), 1.45 (3 H, s, H6), 1.61 (3 H, s, H6), 2.53 (6 H, s, NMe_2), 2.71 (1 H, d, *J* = 1.6 Hz, H4), 4.43 (1 H, d, *J* = 2.4 Hz, H2), 4.82 (1 H, dd, *J* = 2.4, 1.6 Hz, H3). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 12.8, 13.3, 14.0, 14.3, 16.8, 16.9, 17.2, 17.2, 17.3, 17.6, 17.6, 17.9, 25.7, 24.6 (C6), 31.4 (C6), 45.0 (NMe_2), 68.7 (C4), 71.8 (C3), 76.7 (C2), 87.4 (C5), 169.3 (C1). ESI-HRMS: *m/z* calcd for $C_{21}H_{43}NNaO_5Si_2^+$ [M + Na^+]: 468.2572; found: 468.2575.
(13) **Selected Data for 2**
Colorless oil; $[\alpha]_D^{27}$ –19.0 (*c* 1.00, $CHCl_3$). FT-IR (film): ν = 3386, 2867, 1465, 1386, 1364, 1248, 1137 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.03–1.13 (28 H, m, TIPDS), 1.30 (3 H, s, H6), 1.60 (3 H, s, H6), 2.46 (1 H, d, *J* = 2.4 Hz, H4), 2.55 (6 H, s, NMe_2), 2.76 (1 H, br s, OH), 3.49 (1 H, dd, *J* = 8.0, 3.2 Hz, H2), 4.73 (1 H, dd, *J* = 3.2, 2.4 Hz, H3), 5.01 (1 H, br d, *J* = 8.0 Hz, H1). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.0, 13.1, 13.3, 13.6, 14.4, 17.1, 17.1, 17.4, 17.4, 17.5, 17.5, 17.6, 23.7 (C6), 30.8 (C6), 44.5 (NMe_2), 69.4 (C4), 74.8 (C3), 78.1 (C2), 78.4 (C5), 90.5 (C1). ESI-HRMS: *m/z* calcd for $C_{21}H_{46}NO_5Si_2^+$ [M + H^+]: 448.2909; found: 448.2910.