

SYNTHESIS OF THE SOUTHERN PART OF PAMAMYCIN-607, AN AERIAL MYCELIUM-INDUCING SUBSTANCE OF STREPTOMYCES ALBONIGER

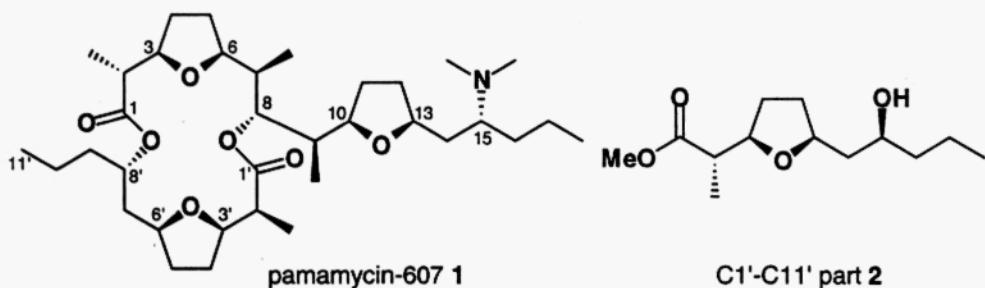
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Abstract

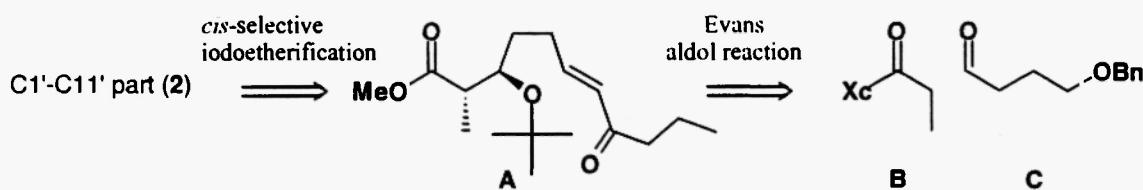
Synthesis of the southern (C1'-C11') part of pamamycin-607, an aerial mycelium-inducing substance for *Streptomyces alboniger*, was achieved via Evans aldol reaction and *cis*-selective iodoetherification as the key steps.

Introduction



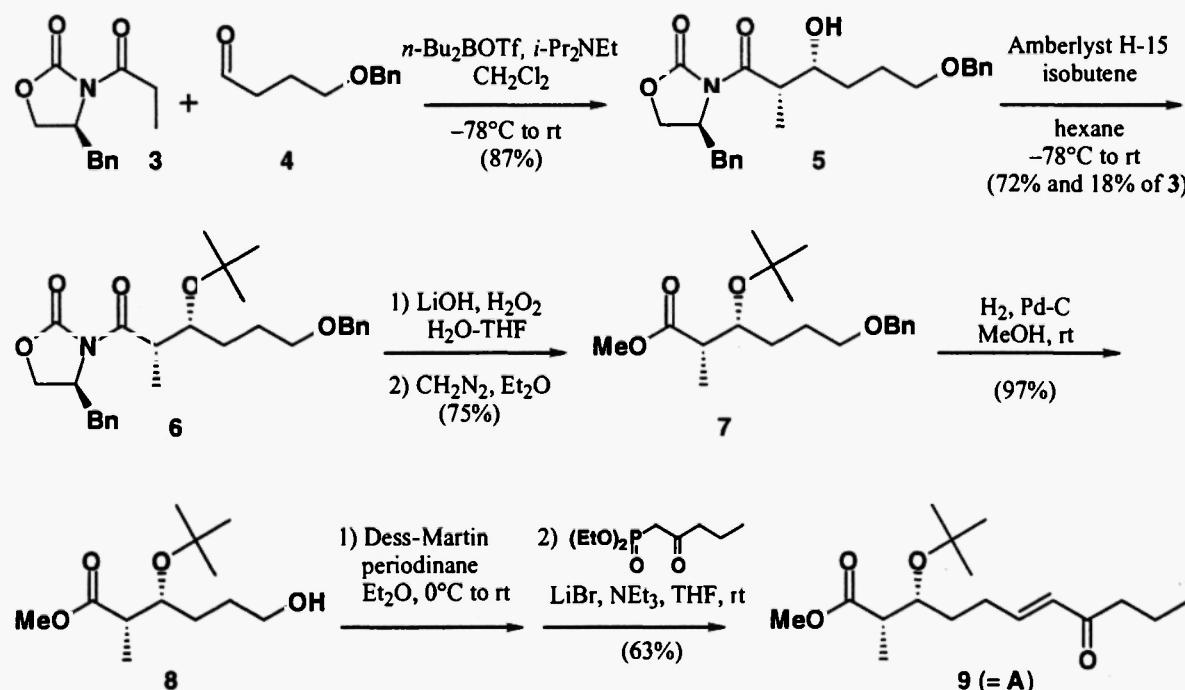
A series of antibiotic pamamycins have been isolated from various *Streptomyces* species (1). Among them, pamamycin-607 1, isolated from *Streptomyces alboniger* (2), showed aerial mycelium-inducing activity in an aerial mycelium-negative mutant of the strain and antibiotic activity against Gram positive bacteria and fungi. Many chemists have been making efforts to synthesize 1, and several synthetic studies were reported (3), due to its unique structure and biological activities. We also began the synthetic study for 1 to supply a sample for biological studies, and achieved the synthesis of the southern part 2. In this paper, we describe the enantioselective synthesis of 2.

Results and Discussion



Scheme 1. Synthetic Plan.

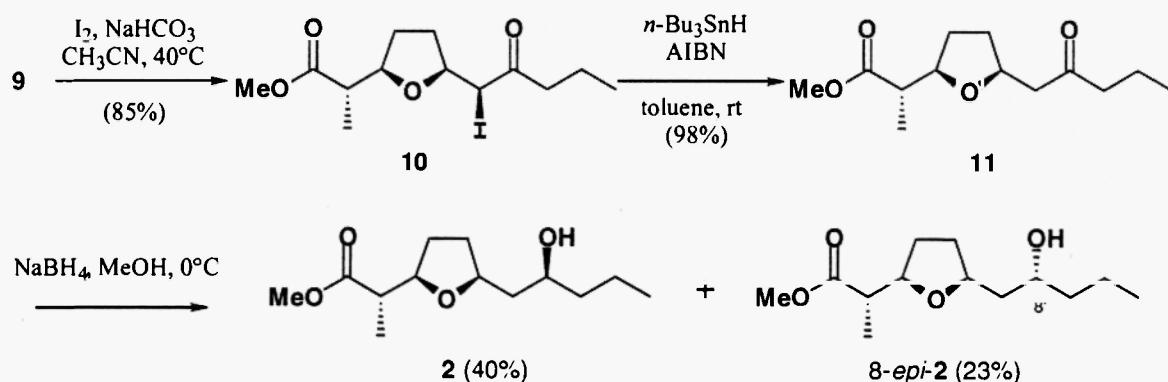
Scheme 1 shows our synthetic plan. Since we have achieved the synthesis of antibiotics bearing a similar skeleton of 1, we applied its synthetic scheme for 2 (4). The *cis*-fused tetrahydrofuran ring would be constructed by iodoetherification (5) of γ,δ -unsaturated *tert*-butoxy compound A, the *syn* aldol moiety of which could be derived from asymmetric aldol reaction of Evans chiral oxazolidinone B and aldehyde C (6).



Scheme 2. Synthesis of Enone 9.

As shown in scheme 2, Evans aldol reaction of 3 with 4 (4) yielded the *syn* alcohol 5 in 87% yield. This compound 5 was diastereomerically pure by $^1\text{H-NMR}$ analysis. After protection of the newly formed hydroxy group as *tert*-butyl ether (7), the amido bond of 6 was cleaved by treatment with LiOOH, prepared *in situ* from LiOH and H_2O_2 , and the resulting carboxy group was esterified to give 7 in 54% yield. The stereochemistry of 7 was confirmed in comparison with $^1\text{H-NMR}$ spectrum of the corresponding *anti* isomer previously reported by us (4). Removal of the benzyl protecting group of 7 gave alcohol 8. The alcohol 8 was converted to enone 9 (= A) (63%, *E* only) by Dess-Martin

oxidation (8) followed by Horner-Wadsworth-Emmons olefination. Next we tried the key iodoetherification. Reaction of **9** with iodine at the reported temperature, 5°C, did not occur. After many attempts we found that even at 40°C the reaction proceeded to afford exclusively *cis*-fused tetrahydrofuran compound **10**. Reductive removal of the iodo group of **10** with *n*-Bu₃SnH to afford **11**. Finally, reduction of the keto carbonyl group of **11** gave the desired **2** and **8-epi-2** in 40 and 23% yields, respectively (9). Total yield was 12% from **3**. **8-Epi-2** was also reported by Perlmutter *et al.* as a synthetic precursor for **1** (3e).



Scheme 3. Synthesis of **2** and its 8-Epimer.

Conclusion

In conclusion, enantioselective synthesis of the southern (C1'-C11') part of pamamycin-607 and its 8-epimer was achieved. The key steps were Evans asymmetric aldol reaction and *cis*-selective iodoetherification. Total yield was 12% in eight steps. Biological tests for **2** and the total synthetic study for **1** are under investigation.

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(9) **2**: a pale yellow oil, $[\alpha]_D^{26} = +28.5^\circ$ (*c* 0.41, CHCl_3) {lit. 3b: $[\alpha]_D^{25} = +29.5^\circ$ (*c* 1.23, CHCl_3)}. IR (film) ν_{max} cm^{-1} : 3500 (s, O-H), 1735 (s, C=O), 1260 (m), 1200 (m). $^1\text{H-NMR}$ δ (500 MHz, CDCl_3): 0.93 (3H, t, *J* = 6.8, 7.1 Hz), 1.23 (3H, d, *J* = 7.1 Hz), 1.35-1.41 (2H, m, *J* = 7.8 Hz), 1.43-1.56 (4H, m, *J* = 6.8, 7.1 Hz), 1.66-1.71 (2H, m, *J* = 7.1, 7.8 Hz), 1.93-2.07 (2H, m, *J* = 6.6 Hz), 2.58 (1H, m, *J* = 7.1 Hz), 3.66 (1H, br), 3.69 (3H, s), 3.82 (1H, q, *J* = 6.3, 6.8 Hz), 4.02-4.07 (2H, m, *J* = 7.1, 7.3 Hz). $^{13}\text{C-NMR}$ δ (125 MHz): 13.9, 14.1, 18.7, 28.5, 31.9, 39.7, 42.6, 44.8, 51.7, 71.6, 80.5, 80.9, 174.8. HRFABMS (glycerol+PEG) *m/z* (M^++H): calcd. for $\text{C}_{13}\text{H}_{25}\text{O}_4$, 245.1751; found, 245.1750.

8-*epi*-2: a pale yellow oil, $[\alpha]_D^{26} = +13.6^\circ$ (*c* 0.24, CHCl_3) {lit. 3e: $[\alpha]_D^{20} = -6.0^\circ$ (*c* 0.5, CHCl_3)}. IR (film) ν_{max} cm^{-1} : 3440 (s, O-H), 1735 (s, C=O), 1260 (m), 1200 (m). $^1\text{H-NMR}$ δ (500 MHz, CDCl_3): 0.94 (3H, t, *J* = 7.1 Hz), 1.23 (3H, d, *J* = 7.1 Hz), 1.32-1.54 (4H, m), 1.61-1.78 (4H, m, *J* = 6.8, 7.1, 7.8 Hz), 1.94-2.02 (2H, m, *J* = 6.8 Hz), 2.60 (1H, m, *J* = 7.1 Hz), 2.80 (1H, br), 3.69 (3H, s), 3.84 (1H, m, *J* = 7.3, 7.8 Hz), 4.00 (1H, q, *J* = 6.8, 7.1 Hz), 4.14 (1H, m, *J* = 6.6, 7.1 Hz). $^{13}\text{C-NMR}$ δ (125 MHz): 13.9, 14.1, 19.0, 28.8, 30.7, 39.4, 41.0, 44.7, 51.7, 68.8, 80.5, 94.7, 174.9. HRFABMS (glycerol+PEG) *m/z* (M^++H): calcd. for $\text{C}_{13}\text{H}_{25}\text{O}_4$, 245.1751; found, 245.1755.

Received on July 23, 2000