

## AN EXPEDITIOUS TOTAL SYNTHESIS OF (+)-BLASTMYCINONE

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**Abstracts** --- Asymmetric  $\gamma$ -methylation of tetronic acid using (*S*)-2-methoxymethylpyrrolidine as a chiral auxiliary and its application to the total synthesis of (+)-blastmycinone (**1**) were described.

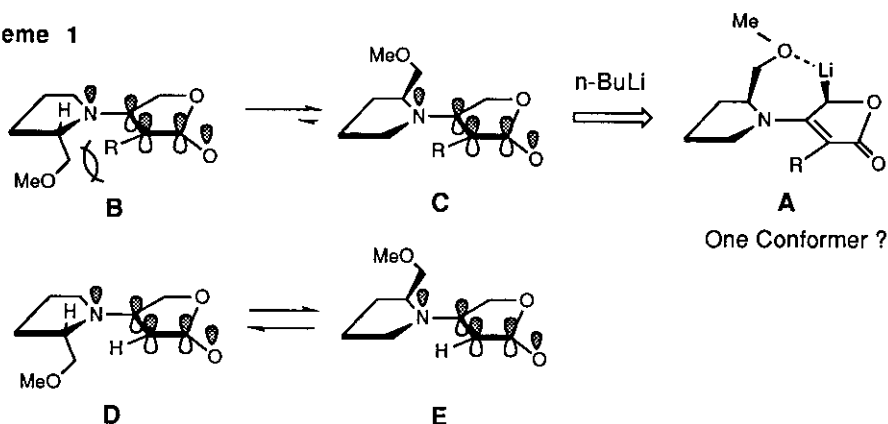
Among the natural products related to  $\gamma$ -alkylated tetronic acid, (+)-blastmycinone (**1**) derived from antimycin A<sub>3</sub> (an antibiotic effective agent against fungi and yeasts) is the representative  $\gamma$ -lactone with three contiguous asymmetric centers. Although several syntheses of it have been published,<sup>1-6</sup> most of them are categorized by the asymmetric induction which employed chiral pools such as L-lactic acid derivatives,<sup>1</sup> a sugar derivative,<sup>2</sup> L-tartaric acid,<sup>3</sup> or a chiral compound<sup>4</sup> obtained from optical resolution or others. Only two methods have been reported as the asymmetric synthesis. One of them is the [2+2]cycloaddition reaction using menthylloxymethylketene by Fráter,<sup>5</sup> but the optical purity of the product was low (70 % ee), as well as being an unnatural (-)-blastmycinone. The other is an application of the Sharpless oxidation by Sato,<sup>6</sup> which required many steps (15 steps) to reach (+)-blastmycinone.

The asymmetric  $\gamma$ -methylation of tetronic acid seems a reasonable strategy toward the synthesis of (+)-blastmycinone (**1**), because tetronic acid itself has already a  $\beta$ -hydroxy- $\gamma$ -lactone skeleton. Schlessinger reported that the asymmetric  $\gamma$ -methylation of tetronic acid using C<sub>2</sub> symmetric (+)-*trans*-2,5-dimethylpyrrolidine (Whitesell's auxiliary) afforded the product in 94 % de.<sup>7</sup> Schmidt claimed that the diastereoselectivity was enhanced to over 99 % de by using (+)-*trans*-2,5-bis(methoxymethyl)pyrrolidine (Yamaguchi's auxiliary) instead of the Whitesell's auxiliary, and the origin of this gain was due to the freeze of the conformation of the intermediate by the chelation of the lithium anion generated on the  $\gamma$ -position to the oxygen of the methoxymethyl group of pyrrolidine.<sup>8</sup> The difficulty in the preparation of the optically pure C<sub>2</sub> symmetric pyrrolidine auxiliaries in scalemic form has, however, limited their application to the total synthesis of natural products [for example (+)-blastmycinone (**1**)].

The synthesis of (+)-blastmycinone (**1**) by  $\gamma$ -methylation of tetronic acid requires  $\alpha$ -butyltetronic acid (**2**) as a starting material. We assumed that freeze of the conformer **A** in the  $\gamma$ -methylation of  $\alpha$ -substituted tetronic acid should be possible on the installation of a readily available [(*S*)-2-methoxymethylpyrrolidine (SMP)] (none-C<sub>2</sub> symmetric pyrrolidine auxiliary) at the  $\beta$ -position of the tetronic acid, because an introduced  $\alpha$ -substituent disturbs the rotation of the auxiliary due to the proposed chelation between lithium and oxygen, as well as due to the steric repulsion between the methoxymethyl group in the conformer **B** and  $\alpha$ -substituent, as shown in Scheme

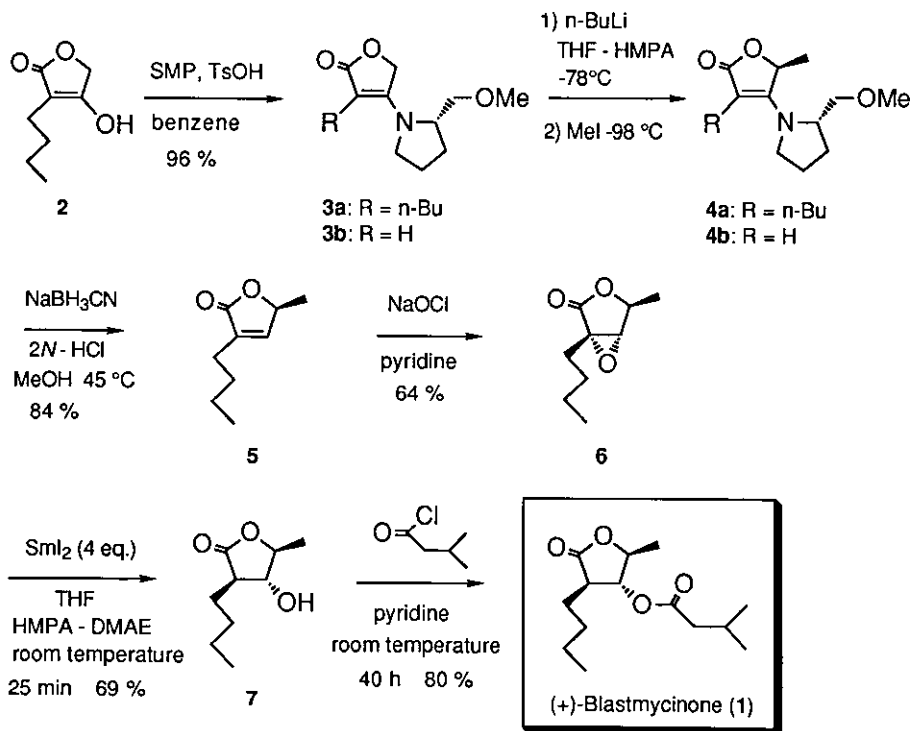
1. On the other hand, there might exist two plausible conformers **D** and **E** in the absence of a substituent on the  $\alpha$ -position, therefore, such a freeze of the conformer could not be possible.<sup>9</sup>

Scheme 1



From the above consideration, we planned the total synthesis of (+)-blastmycinone (**1**) as shown in Scheme 2. Required substrate (**3a**)<sup>10</sup> for the asymmetric  $\gamma$ -methylation was obtained in 96 % yield by the condensation of  $\alpha$ -butyltetronic acid (**2**)<sup>10,11</sup> with SMP in benzene using a Dean-Stark condenser. The treatment of *n*-butyllithium (2.5 eq.) on **3a** (R = *n*-Bu) in THF and HMPA (10 eq.) at  $-78^\circ\text{C}$  for 1 h followed by the addition of

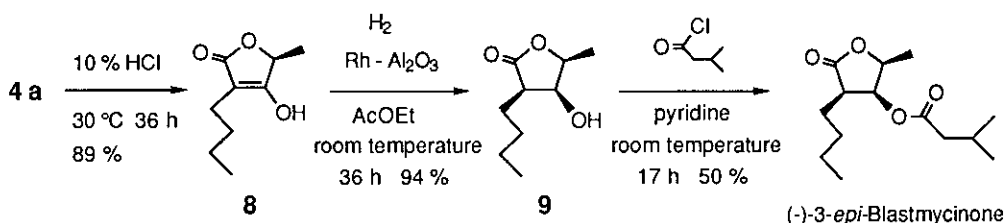
Scheme 2. An Expedient Total Synthesis of (+)-Blastmycinone



methyl iodide (10 eq.) at  $-98^{\circ}\text{C}$  afforded **4a**<sup>10</sup> (diastereomer ratio = 91 : 9) in 91 % yield. The same reaction on **3b**<sup>10</sup> (R = H) gave **4b**<sup>10</sup> (diastereomer ratio = 69 : 31) in 97 % yield.

These results indicate that the freeze of the enamine conformation **A** occurs with the asymmetric  $\gamma$ -methylation of the  $\alpha$ -substituted material. The major isomer (**4a**) was easily separated by silica gel column chromatography in 77 % yield. The *S* configuration on the  $\gamma$ -position of **4a** was determined by the transformation of **4a** to the known (-)-3-*epi*-blastmycinone as follows: hydrolysis of **4a** into tetronic acid derivative (**8**)<sup>10</sup> with 10 % hydrochloric acid, followed by hydrogenation with 5 % rhodium-alumina under hydrogen pressure (5.5 kg/cm<sup>2</sup>) gave (-)-3-*epi*-blastmycinolactol (**9**)<sup>10,12</sup> in high yield, which was converted into (-)-3-*epi*-blastmycinone  $\{[\alpha]_{\text{D}}^{23} -79^{\circ}$  (0.24, CHCl<sub>3</sub>), lit., **2a**  $[\alpha]_{\text{D}}^{18} -89^{\circ}$  (0.90, CHCl<sub>3</sub>) $\}$  by acylation with isovaleryl chloride (Scheme 3).

### Scheme 3



Because an attempted Mitsunobu reaction of lactol (**9**) with isovaleric acid for the synthesis of (+)-blastmycinone (**1**) was unsuccessful due to steric hindrance around the hydroxyl group, we tried to get (-)-blastmycinolactol (**7**) having an  $\alpha$ -hydroxyl group from methylated enamine (**4a**). Reduction of enamine (**4a**) with sodium cyanoborohydride in 2*N*-HCl and MeOH at  $45^{\circ}\text{C}$  gave olefin (**5**)<sup>10,13,14</sup> in 84 % yield, in which both the reduction of enamine and the elimination of SMP took place. Epoxidation of **5** with sodium hypochlorite<sup>4e</sup> served  $\alpha$ -epoxide (**6**)<sup>10</sup> diastereoselectively ( $\alpha:\beta = 16:1$ ). The  $\alpha$ -epoxide (**6**) was converted into (-)-blastmycinolactol (**7**)<sup>10</sup> regioselectively with samarium(II) iodide-THF-HMPA in the presence of *N,N*-dimethylaminoethanol (Inanaga's Method)<sup>15</sup> in 69 % yield. After the separation of **7**, acylation with isovaleryl chloride gave (+)-blastmycinone (**1**) in 80 % yield, whose spectroscopic data and optical rotation  $\{[\alpha]_{\text{D}}^{25} +11.2^{\circ}$  (0.85, CHCl<sub>3</sub>), lit., **2a**  $[\alpha]_{\text{D}}^{17} +10^{\circ}$  (1.2, CHCl<sub>3</sub>) $\}$ , were identical with those reported.<sup>2a</sup>

We have established a method for the shorter asymmetric total synthesis of (+)-blastmycinone (**1**) from  $\alpha$ -butyl-tetronic acid (**2**) (6 steps) with high overall yield (22 %), compared with the literatures.<sup>5,6</sup>

### ACKNOWLEDGMENT

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12. The each value of  $[\alpha]_D^{-85}$  (0.67, MeOH) was consistent after three times recrystallization. The nmr analysis using three equivalents of (*S*)-(-)-1,1'-bi-2-naphthol as a chiral shift reagent showed 8 optically pure: c.f. F. Toda, K. Mori, J. Okada, M. Node, A. Itoh, K. Oomine, and K. Fuji, *Chem. Lett.*, 1988, 131.
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