



1: X = NH<sub>2</sub> Mitomycin C

3: Albotomitomycin A

4: Isomitomycin A

2: X = OMe Mitomycin A

is known to produce mitomycins.<sup>6</sup> They also found an astonishing fact that **2**, **3**, and **4** form an equilibrium mixture in which mitomycin A (**2**) is the heavily favored isomer.<sup>7</sup> These exciting findings suggest that isomitomycin A (**4**) is a synthetic equivalent of mitomycin C (**1**). In this communication we report a highly efficient total synthesis of racemic isomitomycin A (**4**), which paves the way for a practical synthesis of mitomycins.

Treatment of a mixture of the readily available chalcone **5**<sup>8</sup> and the furan **6**<sup>9</sup> in CH<sub>2</sub>Cl<sub>2</sub> with 0.1 equiv of SnCl<sub>4</sub> at -78 °C gave, upon acidic workup, the adduct **7** in 98% yield<sup>10</sup> (Scheme I). The azido butenolide **7** underwent facile intramolecular azide-olefin cycloaddition<sup>11</sup> to give exclusively the tetracyclic aziridine **8** (toluene, 110 °C, 2 h, 93%). The stereochemistry of the side chain of **8** was confirmed by extensive NOE studies. Aminolysis of the strained lactone **8** with 1.6 equiv of 3-(3,4-dimethoxybenzyl-oxy)propylamine (**9**)<sup>12</sup> furnished directly the hydroxy lactam **10** (CH<sub>2</sub>Cl<sub>2</sub>, 40 °C, 1 h, 87%), whose hydroxy group was subsequently methylated to give the ether **11** (MeI, *t*-BuOK/*t*-BuOH, THF, room temperature, 79%). Manipulation of the side chain was performed in the following manner. The ketone **11** was converted to the olefin **12** in 77% yield in a three-step sequence ((1) NaBH<sub>4</sub>, MeOH, room temperature; (2) SOCl<sub>2</sub>, 2,6-lutidine, CH<sub>2</sub>Cl<sub>2</sub>, room temperature; (3) LiBr, DBU, DMSO, 80 °C). Ozonolysis of the olefin **12** (MeOH, -78 °C) and subsequent reduction with NaBH<sub>4</sub> afforded the alcohol **13**. The alcohol **13** was converted to the carbamate **14** in the conventional manner ((1) ClCO<sub>2</sub>Ph, pyridine, room temperature; (2) NH<sub>3</sub>, MeOH, room temperature, 80%). Since our model studies had revealed unusual instability of the isomitomycin A system under acidic conditions, it was necessary to deprotect the veratryl ether **14** at this stage under mild conditions to give the alcohol **15** (DDQ, H<sub>2</sub>O, CH<sub>2</sub>Cl<sub>2</sub>, room temperature, 97%).<sup>13</sup> Reduction of the lactam **15** to the amine **17** was achieved in 68% yield via oxazine **16** through a one-pot, two-stage sequence ((1) DIBAL, THF, room temperature; (2) NaBH<sub>3</sub>CN, MeOH, THF, room temperature). Hydrogenolysis of the phenolic benzyl ether **17** (H<sub>2</sub> (1 atm), 10% Pd/C, EtOH, room temperature) followed by oxidation with DDQ (H<sub>2</sub>O, DMSO, acetone, -78 °C) furnished the desired *p*-quinone **18** in 77% yield. Finally, deprotection of the propanol group was achieved in the following manner. Swern oxidation<sup>14</sup> of the alcohol **18** gave the aldehyde **19** in 90% yield. The aldehyde **19** underwent the retro-Michael reaction upon treatment with pyrrolidine (5 equiv) and acetic acid (10 equiv) in CH<sub>2</sub>Cl<sub>2</sub> at room temperature, giving isomitomycin A (**4**) in 70% yield.<sup>15</sup> The synthetic iso-

mitomycin was identical with an authentic sample in TLC behavior and spectroscopic properties.<sup>16</sup> Equilibration of synthetic **4** (Al(O-*i*-Pr)<sub>3</sub>, MeOH, room temperature, 2 days) furnished mitomycin A (**2**) in 91% yield, which was subsequently converted to mitomycin C (**1**) by ammonolysis in MeOH.<sup>17</sup>

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**Supplementary Material Available:** NMR spectra of key intermediates and synthetic isomitomycin A (5 pages). Ordering information is given on any current masthead page.

(15) Isomitomycin A could not survive under deprotection conditions of other existing amine protecting groups.

(16) We are indebted to Drs. T. Hirata and K. Shirahata, Kyowa Hakko Kogyo Co., Ltd., Tokyo, for a sample of authentic isomitomycin A.

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### Solid-Phase Peptide Synthesis Using a Cobalt(III) Spacer between the Resin and the Peptide

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One of the most important steps in the successful synthesis of peptides using solid phase peptide synthesis (SPPS) is the attachment of the first amino acid to the solid support.<sup>1</sup> This is usually accomplished by using any number of spacer groups which have been developed recently for attaching amino acid derivatives to the solid support.<sup>2,12</sup> Among the available spacer groups the benzyl ester linkage of Boc-amino acids is still the most widely used spacer.<sup>1,3</sup> The disadvantage of this spacer is that removal of a peptide from this resin requires the use of liquid HF or other strongly acidic media (e.g., HBr in trifluoroacetic acid), does not allow the removal of protected peptides, and frequently results in lower peptide yields.<sup>3</sup>

In this communication we describe novel chemistry leading to the synthesis of a new spacer for the attachment of amino acids to solid supports used in SPPS. We have extended the solution phase peptide methodology with cobalt(III) protecting groups<sup>6-10</sup> to solid phase peptide methodology. The advantage of using this new spacer is the ready removal of the synthesized peptides, including protected peptides, under very mild conditions and in high yield. This new spacer is based on bis(ethylenediamine)-cobalt(III) chemistry.<sup>4,5</sup> With use of the newly synthesized

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(7) This reaction was named as "Mitomycin Rearrangement".

(8) Fukuyama, T.; Yang, L.-H. *Tetrahedron Lett.* **1986**, *27*, 6299. This compound can now be synthesized from commercially available 2,6-dimethoxytoluene in 64% overall yield.

(9) Prepared from readily available 5-ethylthiobutenolide in 77% yield (Me<sub>3</sub>SiCl, Et<sub>3</sub>N, ZnCl<sub>2</sub>, acetonitrile, room temperature).

(10) Although we do not have a direct evidence, this unusually high stereoselectivity might be attributable to the Lewis acid-promoted Diels-Alder reaction through endo addition.

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