to show differences in chemical shifts through variation in delocalization at the peptide nitrogen.

The analysis of our calculated structural shift deviations with respect to hydrogen bonding and amide proton exchange kinetics of BPTI showed no clear patterns, despite the classification of various amides into, for example, those which are buried with intraresidue hydrogen bonds and those with a high degree of solvent exposure. Other factors that might effect the nitrogen shifts, such as different ω torsion angles, steric effects from different ϕ or ψ angles, or nonneighbors, or anisotropy and ring current effects were also considered. Variations in ω_{i-1} and ψ_{i-1} angles gave some correlations within subsets of amides. Figure 3 shows such a possible correlation for the residues in the β sheet region of BPTI.[11,24]

In summary, we have shown that a sufficiently accurate assignment of the ^{15}N chemical shifts in a small protein is practical. The correlation of this data to secondary structural features produces some qualitative relationships; however, further NMR studies on compounds with known structural data are necessary to separate the multiple factors contributing to chemical shift deviations arising from conformational effects.

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Supplementary Material Available: Listing of chemical shifts and assignments (1 page). Ordering information is given on any current masthead page.

(24) The apparent dependence on ψ_{i-1} may arise from changes in the electronegativity of the oxygen of the adjacent carbonyl resulting from nonbonded interaction with the $i-1$th amide nitrogen. Similar effects on ^{13}C shifts in cyclic carbonyl groups β to equatorial halogens have been observed (Metzger, P.; Casadevall, E.; Casadevall, A.; Pouet, M.-J. *Can. J. Chem.* **1980**, *58*, 1503–1511).

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Total Synthesis of (±)-Mitomycins via Isomitomycin A

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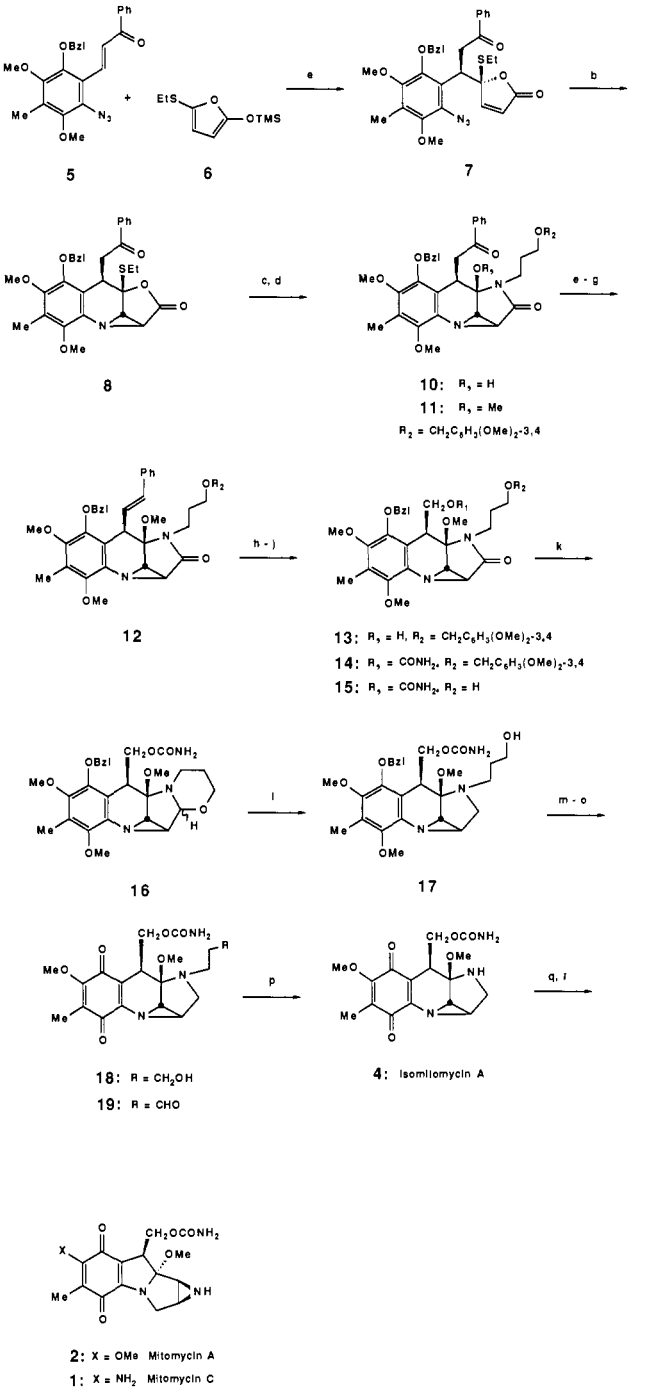
Mitomycin C **1** is one of the most effective antitumor agents currently used for chemotherapy.[1] Recent studies on the mode of action have revealed a direct evidence of DNA cross-linking by **1**.[2] Although a number of synthetic chemists have been trying to synthesize this small, yet formidable molecule,[3] only one successful total synthesis has been reported to date.[4] While construction of the reactive quinone and aziridine rings presents serious difficulties, the major synthetic problem is how to prevent the elimination of methanol from the 9a position.[5] Scientists at Kyowa Hakko have recently isolated and characterized two novel antitumor antibiotics, albomitomycin A (**3**) and isomitomycin A (**4**), from cultures of *Streptomyces caespitosus*, a strain which

Scheme I[a]



[a] (a) $SnCl_4$ (0.1 equiv), CH_2Cl_2, −78 °C; 3 N HCl, THF, CH_2Cl_2, room temperature. (b) Toluene, 110 °C, 2 h. (c) **9** (1.6 equiv), CH_2Cl_2, 40 °C, 1 h. (d) MeI (5 equiv), 1 M *t*-BuOK/*t*-BuOH (1.1 equiv), THF, room temperature. (e) $NaBH_4$, MeOH, room temperature. (f) $SOCl_2$ (2 equiv), 2,6-lutidine (10 equiv), CH_2Cl_2, room temperature. (g) LiBr (5 equiv), DBU (5 equiv), DMSO, 80 °C, 10 h. (h) O_3, MeOH, −78 °C; $NaBH_4$, MeOH, −78 °C to room temperature. (i) $ClCO_2Ph$, pyridine, room temperature; NH_3, MeOH, room temperature. (j) DDQ (1.5 equiv), H_2O–CH_2Cl_2 (1:20), room temperature. (k) DIBAL, THF, room temperature. (l) $NaBH_3CN$, MeOH, THF, room temperature. (m) H_2 (1 atm), 10% Pd/C, EtOH, room temperature. (n) DDQ (1.5 equiv), H_2O–DMSO–acetone (1:5:40), −78 °C. (o) $(COCl)_2$, DMSO, CH_2Cl_2, −78 °C; Et_3N. (p) pyrrolidine (5 equiv), AcOH (10 equiv), CH_2Cl_2, room temperature, 3 h. (q) Al(O-*i*-Pr)$_3$ (1 equiv), MeOH, room temperature, 2 days. (r) NH_3, MeOH, room temperature.

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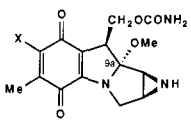
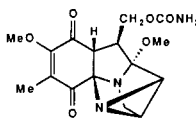
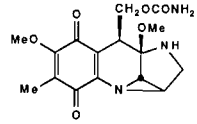


1: X = NH_2 Mitomycin C
2: X = OMe Mitomycin A



3: Albomitomycin A



4: Isomitomycin A

is known to produce mitomycins.[6] 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.[7] 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**[8] and the furan **6**[9] in CH_2Cl_2 with 0.1 equiv of $SnCl_4$ at −78 °C gave, upon acidic workup, the adduct **7** in 98% yield[10] (Scheme I). The azido butenolide **7** underwent facile intramolecular azide–olefin cycloaddition[11] 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-dimethoxybenzyloxy)propylamine (**9**)[12] furnished directly the hydroxy lactam **10** (CH_2Cl_2, 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) $NaBH_4$, MeOH, room temperature; (2) $SOCl_2$, 2,6-lutidine, CH_2Cl_2, room temperature; (3) LiBr, DBU, DMSO, 80 °C). Ozonolysis of the olefin **12** (MeOH, −78 °C) and subsequent reduction with $NaBH_4$ afforded the alcohol **13**. The alcohol **13** was converted to the carbamate **14** in the conventional manner ((1) $ClCO_2Ph$, pyridine, room temperature; (2) NH_3, 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_2O, CH_2Cl_2, room temperature, 97%).[13] 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) $NaBH_3CN$, MeOH, THF, room temperature). Hydrogenolysis of the phenolic benzyl ether **17** (H_2 (1 atm), 10% Pd/C, EtOH, room temperature) followed by oxidation with DDQ (H_2O, 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[14] 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_2Cl_2 at room temperature, giving isomitomycin A (**4**) in 70% yield.[15] The synthetic isomitomycin was identical with an authentic sample in TLC behavior and spectroscopic properties.[16] Equilibration of synthetic **4** ($Al(O\text{-}i\text{-}Pr)_3$, MeOH, room temperature, 2 days) furnished mitomycin A (**2**) in 91% yield, which was subsequently converted to mitomycin C (**1**) by ammonolysis in MeOH.[17]

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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.

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(9) Prepared from readily available 5-ethylthiobutenolide in 77% yield (Me_3SiCl, Et_3N, $ZnCl_2$, acetonitrile, room temperature).

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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.[1] 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.[2,12] Among the available spacer groups the benzyl ester linkage of Boc-amino acids is still the most widely used spacer.[1,3] 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.[3]

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[6-10] 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.[4,5] With use of the newly synthesized

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