Synthetic Approaches toward Mitomycins: Synthesis of the Decarbamoyloxymitomycin Derivative

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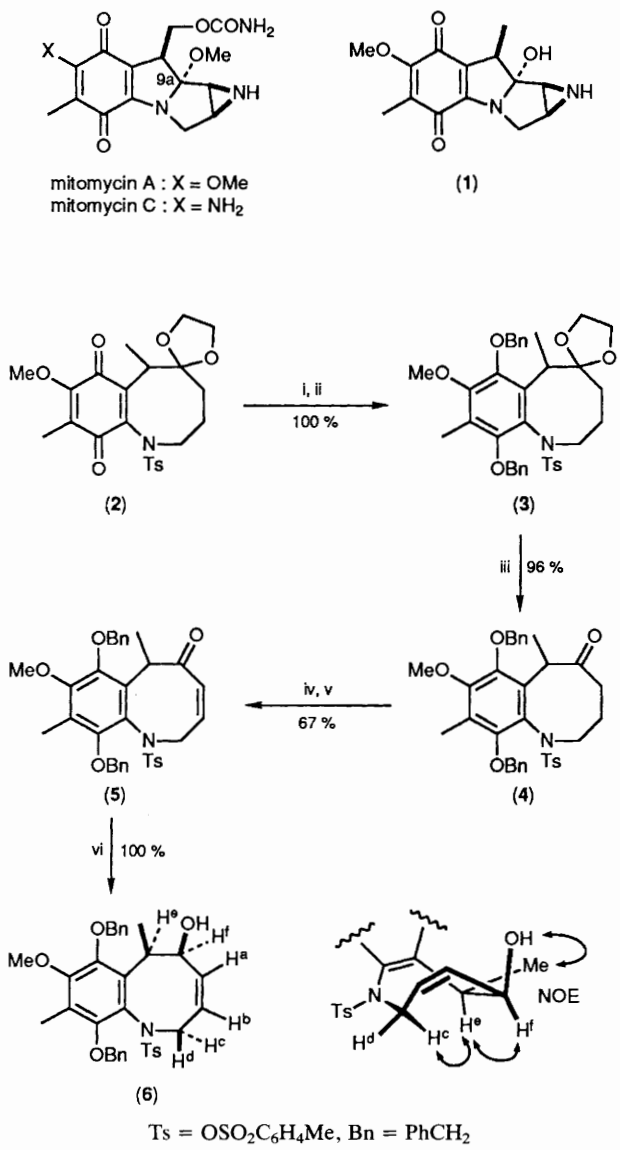
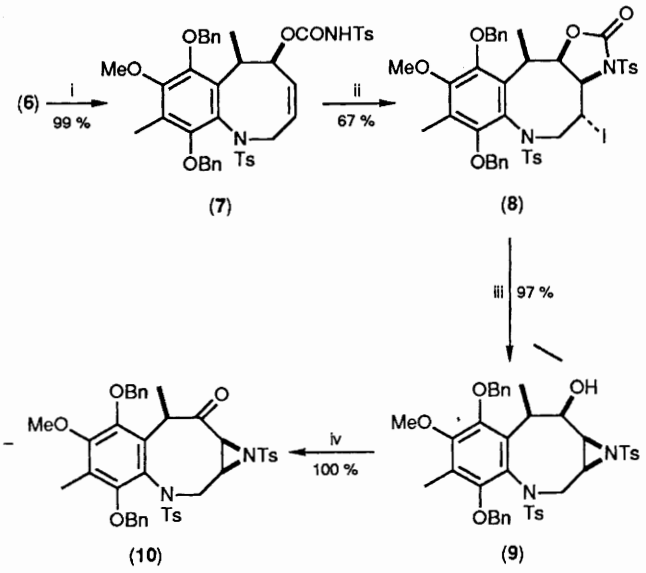
The benzazocine derivative obtained by the criss-cross annulation reaction has been successfully converted to the decarbamoyloxymitomycin derivative in a highly regio- and stereo-controlled manner.

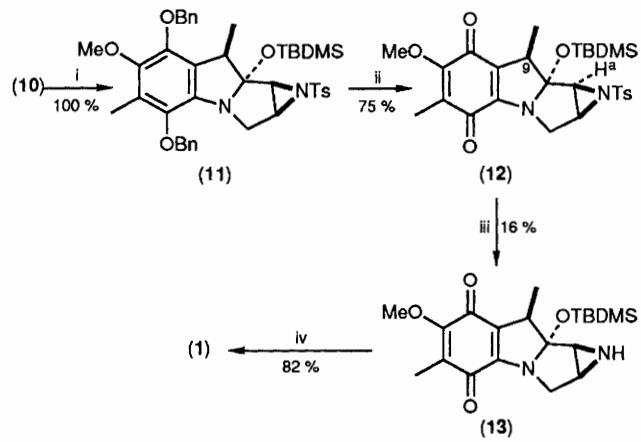
Mitomycins[1] are an important class of antitumour antibiotics among which mitomycin C[2] has been used in the treatment of various neoplastic diseases.[3] Although numerous synthetic studies[4] toward mitomycins have been carried out since its structural elucidation,[5] only Kishi[6] and Fukuyama[7] have achieved total synthesis of mitomycins. Herein we report the synthesis of the decarbamoyloxymitomycin derivative (**1**) starting with the benzazocine derivative (**2**), which has been efficiently synthesized in these laboratories with the criss-cross annulation reaction as a key step.[8]



Scheme 1. *Reagents and conditions*: i, $Na_2S_2O_4$ (5 equiv.), H_2O, $Bu^n_4NHSO_4$ (cat.), CH_2Cl_2, room temp.; ii, BnBr (10 equiv.), K_2CO_3 (5 equiv.), 18-crown-6 (cat.), tetrahydrofuran (THF), reflux, 19 h; iii, conc. HCl, THF, 0 °C, 4.5 h; iv, PhSeCl (1.5 equiv.), 10% HCl (cat.), AcOEt, room temp., 18 h; v, $NaIO_4$ (2 equiv.), H_2O, THF, room temp., 16 h; vi, DIBAL (2 equiv.), THF, −70 °C, 30 min.



Scheme 2. *Reagents and conditions*: i, Ts–N=C=O (1.2 equiv.), THF, room temp., 5 min; ii, I_2 (2.2 equiv.), K_2CO_3 (5 equiv.), THF, room temp., 4.5 h; iii, K_2CO_3 (5 equiv.), MeOH–CH_2Cl_2 (1 : 2), 35—40 °C, 3 h; iv, PCC (33 equiv.), MS4A, CH_2Cl_2, room temp., 4 h.



Scheme 3. *Reagents and conditions*: i, TBDMSOTf (2 equiv.), NEt_3 (5 equiv.), CH_2Cl_2, −78 °C → room temp.; ii, 10% Pd–C, H_2, NEt_3 (5.8 equiv.), AcOEt, 10 min; then O_2, 10 min; iii, Na-naphthalene (3 equiv.), THF, −98 °C; then O_2; iv, TBAF (15 equiv.), AcOH (20 equiv.), THF, room temp., 90 h.

The benzazocine derivative (**2**) was reduced by $Na_2S_2O_4$ and then protected as a benzyl ether to give (**3**) (100% yield). Cleavage of a ketal group by treatment with conc. HCl afforded the ketone (**4**) (96%). Next, in order to introduce an aziridine group to the eight-membered ring, (**4**) was converted to the allylic alochol (**6**). Namely, exposure of (**4**) to phenylselenenyl chloride under the acidic conditions followed by oxidation with $NaIO_4$ provided the enone (**5**), which was reduced by di-isobutylaluminium hydride (DIBAL) to give the allylic alcohol (**6**) in a highly regio- and stereo-controlled manner (67%). The stereochemistry of (**6**) was unequivocally determined from the ^1H NMR spectrum. The coupling constant between He and Hf was 4.4 Hz and J_{af} was 2.0 Hz. Furthermore, nuclear Overhauser enhancements (NOEs) were observed as shown in Scheme 1.

Many attempts to introduce an aziridine group using intermolecular reactions such as epoxidation followed by treatment with NaN_3 were unfruitful. Therefore, we undertook the aziridine formation by an intramolecular reaction. The allylic alcohol (**6**) was converted to the allylic carbamate (**7**), which was followed by exposure to I_2 to give the cyclic carbamate (**8**) (66%).[9] Treatment of (**8**) with K_2CO_3 in MeOH–CH_2Cl_2 provided the aziridine (**9**) in 97% yield. Oxidation of (**9**) with pyridinium chlorochromate (PCC) gave (**10**) in 100% yield, whose IR spectrum had an absorption at 1700 cm^{-1}, indicating the presence of a transannular effect (see Scheme 2).

With the benzazocine derivative (**10**) having an aziridine group in hand, the construction of the mitomycin skeleton with oxygen functionality at C-9a was the next task. First (**10**) was treated with methyl trifluoromethanesulphonate in CH_2Cl_2, but many products were formed. However, exposure of (**10**) to trimethylsilyl trifluoromethanesulphonate and triethylamine in CH_2Cl_2 effected the transannular cyclization;

unfortunately, the cyclized product was decomposed during the isolation process. Finally, we have found that (**10**) undergoes transannular cyclization [t-butyldimethylsilyl trifluoromethanesulphonate (TBDMSOTf) and triethylamine in CH_2Cl_2] to give (**11**) (100%) in a highly stereoselective manner.† Hydrogenolysis of (**11**) (1 atm H_2, NEt_3, 10% Pd–C/AcOEt) followed by treatment with oxygen afforded the benzoquinone (**12**) (75%). The stereochemistry of (**12**) was unequivocally determined from the ^1H NMR spectrum (COSY and NOE). Namely, irradiation of the methyl group at C-9 showed an enhancement of H^a. Cleavage of the toluenesulphonyl group was achieved by treatment with Na-naphthalene to give (**13**) (16%).[10] Finally, the decarbamoyloxymitomycin derivative (**1**) was obtained in 82% yield on treatment with tetrabutylammonium fluoride (TBAF) in THF containing acetic acid.[11]

In conclusion, we have achieved the synthesis of the decarbamoyloxymitomycin derivative (**1**) *via* the benzazocine derivative (**2**) as a key intermediate, demonstrating that (**2**) is a reasonable synthetic intermediate for the synthesis of mitomycins and their analogues. This synthesis is the first example of the introduction of an aziridine group onto a benzazocine derivative and the novel t-butyldimethylsilyl trifluoromethanesulphonate mediated transannular cyclization. Application of this strategy to the total synthesis of mitomycins is in progress.

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† The presence of benzyl ethers was crucial for the transannular cyclization. Use of a t-butyldimethylsilyl ether instead of a benzyl ether (C=O stretching frequency, 1730 cm^{-1}) afforded none of the cyclized product.

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