Facile Nucleophilic Cleavage of Selenide with Dimedone. Synthesis of Novel 6-Demethylmitomycins

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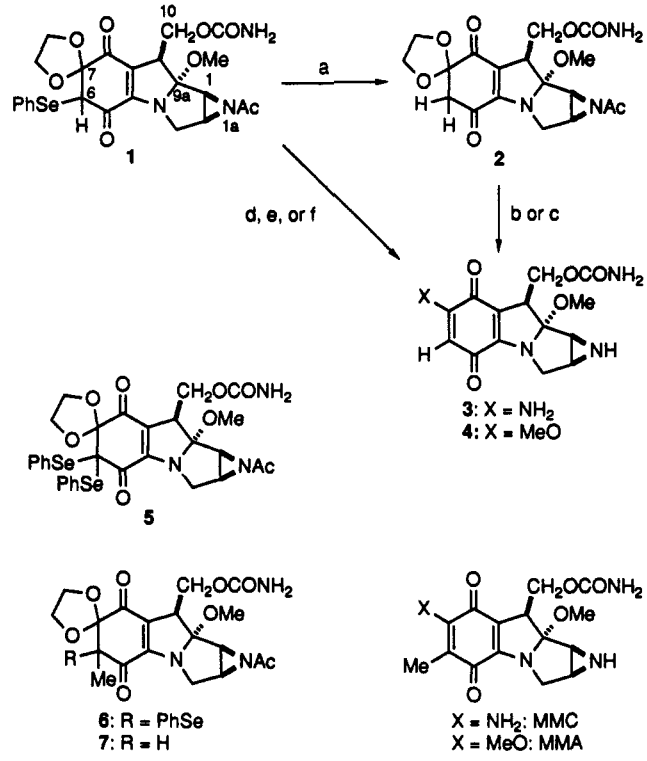
Mitomycin C (MMC) has been extensively used in cancer chemotherapy against a variety of solid tumors, but its use is limited by side effects, such as severe bone marrow suppression or gastrointestinal damage. Consequently, a number of derivatives targeting more effective activity or less toxicity have been synthesized in our laboratory[1] or by other groups[2] to overcome these disadvantages. In the course of our studies of mitomycin chemistry, we have been able to obtain 6-demethyl-7,7-(ethylenedioxy)-6-(phenylseleno)mitosane (1).[3] By the deselenenylation of 1 to yield 2 and the subsequent conversion of 2 to the mitomycin (MM) skeletons, it has been possible to prepare 6-demethylmitomycins[4] not previously accessible. Further, we found that dimedone is also an effective agent for the deselenenylation of 1. Herein, we report our results on nucleophilic deselenenylation with dimedone and the synthesis of novel 6-demethylmitomycins (Scheme I).

In a previous paper,[3] we described the synthesis of 6-demethyl-7,7-(ethylenedioxy)-6-(phenylseleno)mitosane (1) and its conversion to C-6-methyl-labeled mitomycins. We also reported therein the free-radical deselenenylation of 7,7-(ethylenedioxy)-6-(phenylseleno)-mitosane (6) using the *n*-Bu_3SnH–Et_3B system at room temperature.[5] Therefore, we first tried to remove the phenylseleno group of 1 using this method. The deselenenylation of 1 was smoothly accomplished by treatment with *n*-Bu_3SnH in the presence of a catalytic amount of Et_3B at room temperature, which afforded 6-demethyl-7,7-(ethylenedioxy)mitosane (2)[6] in 98% yield. This ethylidene acetal was further treated with ammonia or K_2CO_3 in methanol at room temperature for the amination or transalkoxylation at the C-7 position with simultaneous

Scheme I [a]



[a] Key: (a) *n*-Bu_3SnH, Et_3B, THF; (b) NH_3, MeOH; (c) K_2CO_3, MeOH; (d) dimedone, NEt_3, MeCN; (e) NH_3, MeOH-MeCN; (f) dimedone, K_2CO_3, MeOH.

1a-*N*-deacetylation[7] to afford 6-demethyl MMC (3) and 6-demethyl MMA (4) in 79% and 48% yields, respectively. While this free-radical deselenenylation gives superior yields, tin selenide byproducts often require careful separation from the desired products, and protection from the atmosphere is necessary.

It was observed that the phenylseleno group of 1 was labile and afforded small amounts of disproportionation products 2 and 5 in aqueous acetonitrile.[8] These findings suggested that the phenylseleno group at the C-6 position might be easily removable by nucleophilic attack on selenium.[9] Although reductive or radically initiated methods[10] are frequently used in the removal of the phenylseleno group, nucleophilic deselenenylations[9] are less well known for the conversion of the phenylseleno group to hydrogen. Under these circumstances, we tried to remove the phenylseleno group using dimedone as a soft carbon nucleophile. 7,7-(Ethylenedioxy)-6-(phenylse-

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(4) Several C-6-substituted mitosene analogues, related compounds of mitomycins, were synthesized and examined for antitumor activity: Casner, M. L.; Remers, W. A.; Bradner, W. T. *J. Med. Chem.* **1985**, *28*, 921.

(5) Nozaki, K.; Oshima, K.; Utimoto, K. *J. Am. Chem. Soc.* **1987**, *109*, 2547.

(6) Mp: 122–125 °C. ^1H NMR: (270 MHz, pyridine-d_5) δ 2.08 (s, 3 H), 3.11 (s, 3 H), 3.25 (d, J = 16.2 Hz, 1 H), 3.46 (dd, J = 1.9, 4.4 Hz, 1 H), 3.51 (dd, J = 1.9, 12.9 Hz, 1 H), 3.56 (d, J = 16.2 Hz, 1 H), 3.79 (d, J = 4.4 Hz, 1 H), 3.92–4.05 (m, 2 H), 4.08–4.18 (m, 2 H), 4.28–4.37 (m, 1 H), 4.31 (d, J = 12.9 Hz, 1 H), 4.60 (t, J = 11.0 Hz, 1 H), 5.72 (dd, J = 4.6, 10.8 Hz, 1 H), 7.4–7.9 (br s, 2 H). FAB-MS: m/z 408 (M^+ + 1). Anal. Calcd for $C_{18}H_{21}N_3O_8 \cdot 0.6H_2O$: C, 51.70; H, 5.35; N, 10.05. Found: C, 51.57; H, 5.07; N, 9.75.

(7) Kanda, Y.; Kasai, M. *J. Org. Chem.* **1990**, *55*, 2515.

(8) After 2 days at room temperature, compounds 2 (9.8%) and 5 (1.2%) were obtained along with the recovered 1 (73%).

(9) The deselenenylation of α-selenocarbonyl compounds upon treatment with several soft nucleophiles have been reported to date. PhSH–NEt_3: Takahashi, T.; Nagashima, H.; Tsuji, J. *Tetrahedron Lett.* **1978**, *19*, 799. NaSPh–18-crown-6: Shimizu, M.; Takeda, R.; Kuwajima, I. *Bull. Chem. Soc. Jpn.* **1981**, *54*, 3510. LiSePh: Reich, H. J.; Renga, J. M.; Reich, I. L. *J. Am. Chem. Soc.* **1975**, *97*, 5434. Zima, G.; Barnum, C.; Liotta, D. *J. Org. Chem.* **1980**, *45*, 2736. In addition, the base-induced intermolecular rearrangement of the phenylseleno group of α-(phenylseleno) ketones is known: Liotta, D.; Saindane, M.; Brothers, D. *J. Org. Chem.* **1982**, *47*, 1598. Liotta, D.; Saindane, M.; Monahan, R.; Brothers, D.; Fivush, A. *Synth. Commun.* **1986**, *16*, 1461.

(10) For recent reviews, see: Paulmier, C. *Selenium Reagents and Intermediates in Organic Synthesis*; Pergamon: Oxford, 1986. *Organoselenium Chemistry*; Liotta, D., Ed.; Wiley: New York, 1987. Back, T. G. In *The Chemistry of Organic Selenium and Tellurium Compounds*; Patai, S., Ed.; Wiley: Chichester, 1987; Vol. 2.

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leno)mitosane 6 was used as a model compound and treated with dimedone in the presence of triethylamine in acetonitrile at room temperature for 4 h to afford the resultant 7,7-(ethylenedioxy)mitosane (7)[7] in 94% yield along with 5,5-dimethyl-2-(phenylseleno)-1,3-cyclohexanedione in 41% yield based on 6.[11]

On the basis of these results, we applied the above method to the synthesis of the 6-demethyl MMs 3 and 4. Deselenenylation of 1 was accomplished by the reaction with dimedone in the presence of triethylamine in acetonitrile at room temperature. Subsequent C-7-amination and 1a-*N*-deacetylation were also simultaneously accomplished by adding a methanol solution of ammonia (6.8 M) to the reaction mixture which afforded 3 in 74% yield. In the case of the synthesis of 4, one-pot conversion from 1 was possible. Thus, treatment of 1 with dimedone and K_2CO_3 in methanol at room temperature afforded 4 in 70% yield based on 1. For the demonstration of the synthetic utility of this method, we next tried to convert 6 directly into MMC or MMA. Treatment of 6 with dimedone and ammonia in methanol at room temperature afforded MMC in 81% yield. Similarly, MMA was obtained by the treatment of 6 with dimedone and K_2CO_3 in methanol at room temperature in 65% yield.[12]

In conclusion, these results demonstrate the practical usefulness of the nucleophilic deselenenylation with dimedone at the C-6 position of MM intermediates. Moreover, from the view point of easy handling of the reaction, these methods are also useful in the syntheses of C-6-methyl radiolabeled MMs[13] that are usually carried out on a micromolar scale.

Experimental Section

General. Unless otherwise noted, materials were obtained from commercial suppliers except mitomycins and used without further purification. Melting points were measured on a Yanagimoto micro melting point apparatus and are uncorrected.

Deselenenylation of 7,7-(Ethylenedioxy)-6-(phenylseleno)mitosane (6). To a solution of 6 (50.7 mg, 0.0880 mmol) in MeCN (3.0 mL) was added NEt_3 (100 μL) and dimedone (41.9 mg, 0.299 mmol) and the resulting mixture stirred at room temperature for 4 h. The reaction mixture was diluted with $CHCl_3$, washed with brine, and dried over Na_2SO_4. After the solvent was removed with a rotary evaporator, the residue was purified by column chromatography (silica gel, $CHCl_3$-MeOH (9:1)), followed by trituration with $CHCl_3$–*n*-hexane to afford 7[7] (34.8 mg, 0.0824 mmol, 94%) as a yellow powder, mp 88–90 °C.

6-Demethylmitomycin C (3). To a solution of 1 (56.2 mg, 0.100 mmol) in MeCN (1.0 mL) was added NEt_3 (50 μL) and dimedone (29 mg, 0.21 mmol) and the resulting mixture stirred at room temperature for 4 h. After the starting material was consumed, NH_3 in MeOH (6.8 M, 1.0 mL) was added to the reaction mixture, and the reaction mixture was allowed to stand at room temperature for 18 h. The precipitated purple crystals were filtered, and the filtrate was concentrated with a rotary evaporator. The residue was dissolved in a small amount of CH_2Cl_2, and the precipitated crystals were collected. The combined crystals were dried under vacuum to afford 3 (23.7 mg, 0.0741 mmol, 74%), mp 240–250 °C dec. ^1H NMR: (270 MHz, pyridine-d_5) δ 2.08 (br s, 1 H), 2.73 (br s, 1 H), 3.13 (br s, 1 H), 3.20 (s, 3 H), 3.59 (br d, J = *ca.* 13 Hz, 1 H), 4.04 (dd, J = 4.5, 11.4 Hz, 1 H), 4.58 (d, J = 12.9 Hz, 1 H), 5.08 (br t, J = *ca.* 11 Hz, 1 H), 5.43 (dd, J = 4.5, 10.4 Hz, 1 H), 5.75 (s, 1 H), 7.0–9.0 (br s, 4 H). ^{13}C NMR: (100 MHz, DMSO-d_6) δ 31.4 (C-2), 35.2 (C-1), 42.8 (C-9), 49.2 (9a-OMe), 49.4 (C-3), 60.7 (C-10), 95.5 (C-6), 105.7 (C-9a), 109.9 (C-8a), 153.2 (C-7), 155.6 (C-4a), 156.5 (10-OCONH$_2$), 174.7 (C-8), 177.3 (C-5). FAB-MS: m/z 321 (M^+ + 1), 343 (M^+ + Na). EI-HRMS: calcd for $C_{14}H_{16}N_4O_5$ m/z 320.1121, found 320.1110. UV: (MeOH) 214 (log ε 4.26), 356 (log ε 4.27), 540 (log ε 2.29) nm [MMC: 217 (log ε 4.36), 359 (log ε 4.38), 560 (log ε 2.36) nm]. Anal. Calcd for $C_{14}H_{16}N_4O_5$·0.2H_2O: C, 51.91; H, 5.10; N, 17.30. Found: C, 52.05; H, 5.24; N, 16.97.

6-Demethylmitomycin A (4). To a solution of 1 (503 mg, 0.895 mmol) in MeOH (30 mL) was added K_2CO_3 (185 mg, 1.34 mmol) and dimedone (156 mg, 1.11 mmol) and the resulting mixture stirred at room temperature for 24 h. The reaction mixture was diluted with $CHCl_3$, washed successively with saturated $NaHCO_3$ aqueous solution and brine, and dried over Na_2SO_4. After the solvent was removed with a rotary evaporator, the residue was purified by column chromatography (silica gel, $CHCl_3$–MeOH (30:1–10:1)), followed by trituration with $CHCl_3$–*n*-hexane to afford 4 (209 mg, 0.624 mmol, 70%) as a red powder, mp 108–110 °C. ^1H NMR: (270 MHz, pyridine-d_5) δ 2.17 (br s, 1 H), 2.77 (br s, 1 H), 3.17 (br s, 1 H), 3.23 (s, 3 H), 3.55 (br d, J = *ca.* 13 Hz, 1 H), 3.58 (s, 3 H), 4.03 (dd, J = 4.3, 11.2 Hz, 1 H), 4.29 (d, J = 12.6 Hz, 1 H), 5.10 (br t, J = 11 Hz, 1 H), 5.42 (dd, J = 4.3, 10.4 Hz, 1 H), 5.69 (s, 1 H), 7.4–7.9 (br s, 2 H). ^{13}C NMR: (67.5 MHz, pyridine-d_5) δ 32.8 (C-2), 36.9 (C-1), 44.7 (C-9), 49.7 (9a-OMe), 50.5 (C-3), 56.5 (7-OMe), 62.3 (C-10), 104.3 (C-6), 107.1 (C-9a), 114.9 (C-8a), 152.9 (C-4a), 158.0 (10-OCONH$_2$), 162.0 (C-7), 176.0 (C-8), 182.0 (C-5). FAB-MS: m/z 336 (M^+ + 1). EI-HRMS: calcd for $C_{15}H_{17}N_3O_6$ m/z 335.1117, found 335.1159. UV: (MeOH) 214 (log ε 4.20), 313 (log ε 4.15), 510 (log ε 3.23) nm [MMA: 216 (log ε 4.24), 321 (log ε 4.04), 521 (log ε 3.13) nm]. Anal. Calcd for $C_{15}H_{17}N_3O_6$·0.2$CHCl_3$: C, 50.82; H, 4.83; N, 11.70. Found: C, 50.69; H, 4.91; N, 11.31.

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(11) The relatively low yield of 5,5-dimethyl-2-(phenylseleno)-1,3-cyclohexanedione could account for its instability to silica gel used for the purification.

(12) In the case of the reductive cleavage of the selenide 6 with nickel boride, which is known as an efficient deselenenylating agent, MMA was obtained only in 14% yield along with 1a-acetyl MMA (16%). This is due to the instability of (1a-acetyl) MMA under reductive conditions; cf. Back, T. G.; Birss, V. I.; Edwards, M.; Krishna, M. V. *J. Org. Chem.* **1988**, *53*, 3815.

(13) Arai, H.; Kasai, M. *J. Labelled Compd. Radiopharm.* **1991**, *29*, 903.