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Articles

Synthesis of Mimosamycin

Bart Kesteleyn and Norbert De Kimpe*

Department of Organic Chemistry, Faculty of Agricultural and Applied Biological Sciences, University of Gent, Coupure Links 653, B-9000 Gent, Belgium

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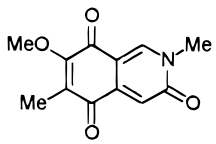
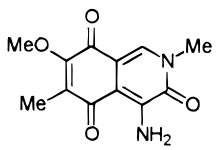
Mimosamycin (**1**) was synthesized in eight steps with an overall yield of 13% from 2-methoxy-3-methyl-1,4-benzoquinone by regioselective introduction of a chloromethyl group at C-6 and a methoxycarbonylmethyl group at C-5 and subsequent reaction of the intermediate methyl (*o*-(chloromethyl)phenyl)acetate derivative **16** with methylamine. Oxidation of the 5,7,8-trimethoxy-2,6-dimethyl-1,4-dihydroisoquinoline-3(2*H*)-one **17** thus obtained, using cerium(IV) ammonium nitrate as a selective oxidizing agent, gave mimosamycin (**1**) in good overall yield.

Introduction

Mimosamycin (**1**) (7-methoxy-2,6-dimethyl-3,5,8(2*H*)-isoquinolinetrione) was the first member of a new class of naturally occurring 3,5,8(2*H*)-isoquinolinetrione antibiotics, isolated as a satellite metabolite from the streptothricin-producing microorganism *Streptomyces lavendulae* No. 314.[1] Later, mimosamycin together with several structurally related pigments, e.g., 4-aminomimosamycin (**2**), 7-amino-7-demethoxymimosamycin (**3**), and the sulfur-containing perfragillin (**4**), have been identified in marine sponges of the genera *Reniera*,[2] *Petrosia*,[3] *Xestospongia*,[4] and in the bryozoan *Membranipora perfragilis*.[5]



1 (mimosamycin)



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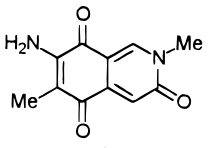

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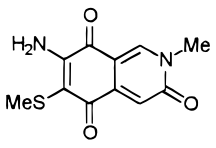

4

Mimosamycin has been found to be active against mainly mycobacteria, including the streptomycin-resistant strains of *Mycobacterium tuberculosis*.[1] Furthermore, mimosamycin proved to be active against some Gram-positive bacteria,[1] but it was completely inactive against Gram-negative bacteria and most fungi[1] except *Cladosporium cucumerinum*.[4] Mimosamycin is also structurally related to the saframycins, which represent a more complex class of "dimeric" isoquinoline quinones with antitumor activity.[2] Mimosamycin has been synthesized previously from 7-hydroxy-6-methylisoquinoline by an appropriate oxidation sequence to create the 3,5,8-

* To whom correspondence should be addressed. Phone: 32 9 264.59.51. Fax: 32 9 264.62.43.

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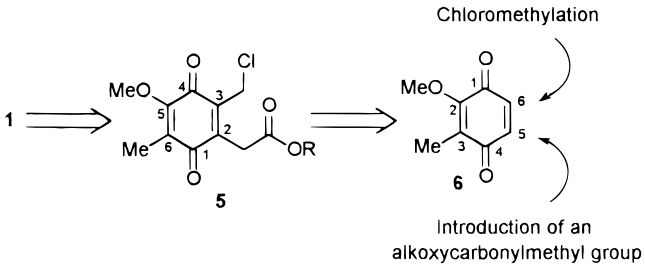
Scheme 1



(2*H*)-isoquinolinetrione ring system[6] and, starting from 2-methoxy-3-methyl-1,4-benzoquinone, by construction of the lactam moiety either by cycloaddition with 2-aza-1,3-bis(*tert*-butyldimethylsilyloxy)-1,3-butadiene[7] or via a classical approach using a low-yielding multistep sequence.[8] In view of the interesting antibiotic properties found in this class of 3,5,8(2*H*)-isoquinolinetrione antibiotics and related heterocyclic derivatives, we report herein a new and efficient route to mimosamycin.

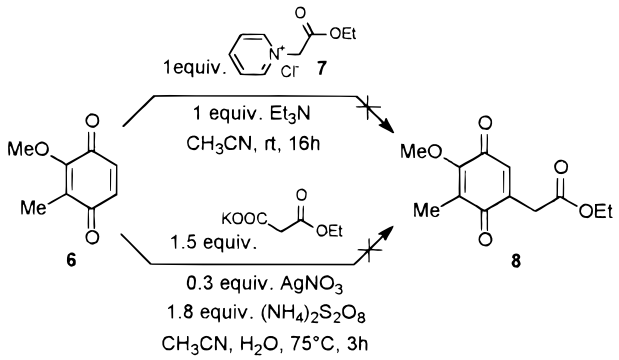
Results and Discussion

A retrosynthetic analysis of the structure of mimosamycin (**1**) (Scheme 1) shows that the lactam moiety can be constructed by reaction of methylamine with an appropriately substituted *p*-benzoquinone **5** bearing a halomethyl group at C-3 and an alkoxycarbonylmethyl group at C-2. Therefore, because 2-methoxy-3-methyl-1,4-benzoquinone (**6**) is available as a starting material from the oxidation of the dimethyl ether of 2-methylresorcinol with sodium dichromate,[9] the feasibility of the strategy depends on the regioselective introduction of both the halomethyl group and the alkoxycarbonylmethyl group.

2-Methoxy-3-methyl-1,4-benzoquinone (**6**) is known to react with nucleophiles selectively to the C-1 carbonyl by Michael addition because the carbonyl group at C-4 is in extended conjugation with the methoxy group at C-2.[9] To our surprise, however, two well-established procedures for the introduction of an alkoxycarbonylmethyl group in *p*-quinones,[10] namely, reaction of **6** with a pyridinium ylide, created in situ by reaction of the pyridinium salt **7** with triethylamine, and also the radical introduction of the same alkoxycarbonylmethyl group, using the potassium salt of ethyl malonate in the presence of silver nitrate and ammonium persulfate, afforded only complex reaction mixtures from which compound **8** could not be isolated (Scheme 2).

In a final attempt, the *p*-benzoquinone **6** was reacted with 5 equiv of ketene dimethyl acetal at 110 °C for 1 h, leading to a mixture of benzofuran **9** (15%) and 3,5,7-trimethoxynaphthoquinone **10** (31%) as a result of 1:1-addition and 1:2-addition of **6** with ketene dimethyl acetal, respectively, together with the hydroquinone **11** (6%) (Scheme 3). The same mixture of reaction products **9**, **10**, and **11** was also obtained in yields of 10%, 10%,

Scheme 2



and 16%, respectively, when a nonpurified sample of **6** was refluxed for 16 h in toluene in the presence of 5 equiv of ketene dimethyl acetal. It is known from the literature[11] that the formation of 1:2-adducts from the reaction of *p*-benzoquinones with ketene acetals is stimulated by either the presence of weak acids or the use of polar aprotic solvents, both by stabilizing the intermediate zwitterion resulting from the addition of one molecule of ketene acetal and thereby allowing the addition of the second ketene acetal. Apolar solvents, however, allow only the addition of one molecule of ketene acetal, leading selectively to benzofurans. Thus, upon reaction of a carefully purified sample of 2-methoxy-3-methyl-1,4-benzoquinone (**6**) with 5 equiv of ketene dimethyl acetal under reflux in toluene for 24 h, compound **9** was obtained as the only reaction product in 44% yield, together with 52% of unreacted starting material **6**, which could be recovered by means of flash chromatography. Upon reflux in 80% methanol, hydrolysis of the ortho ester function of **9** led to the methoxycarbonylmethyl-containing hydroquinone **12** in 93% yield, which was subsequently protected by methylation using dimethyl sulfate and potassium carbonate in refluxing acetone to give **13** in 79% yield.

For the introduction of the halomethyl group, using anhydrous conditions to avoid the hydrolysis of the methyl ester function, compound **13** was reacted with excess paraformaldehyde in the presence of a solution of 33% HBr in glacial acetic acid or dry HCl in ether; however, using these reaction conditions either no reaction products or complex reaction mixtures were obtained. The chloromethylation of **13** could be accomplished only when concentrated solutions of HBr or HCl in water were used and only after long reaction times and in the presence of a large excess of zinc(II) chloride as catalyst. However, under these reaction conditions, the hydrolysis of the methyl ester function could not be prevented. The best results were obtained when **13** was reacted with 20 equiv of paraformaldehyde in a mixture of 12 M HCl and acetic acid and 10 equiv of zinc(II) chloride as Lewis catalyst at room temperature for 3 days, leading to a mixture of chloromethylphenyl acetic acid **14** and benzopyranone derivative **15** in a ratio of 6:4 (Scheme 4). Upon reflux of this crude reaction mixture in acetone with 5 equiv of potassium carbonate, complete conversion of the chloromethylphenyl acetic acid **14** into

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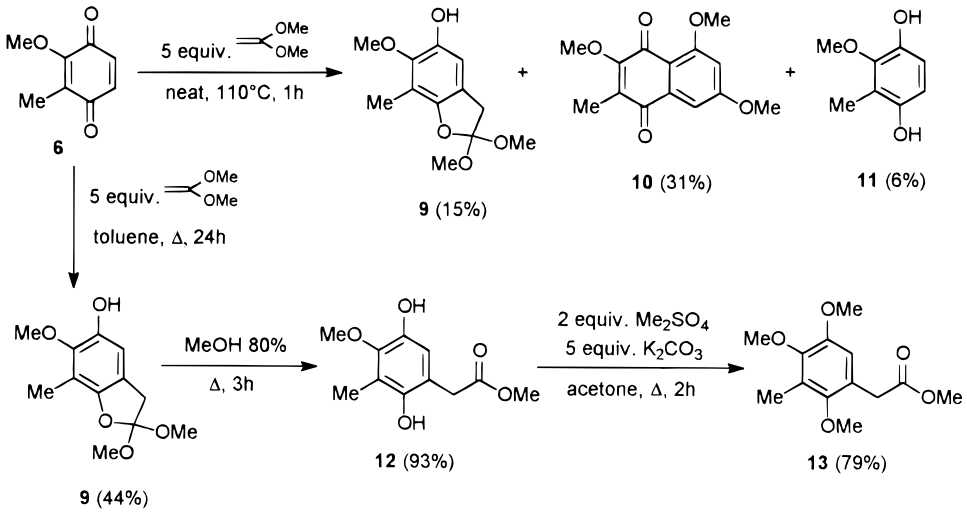
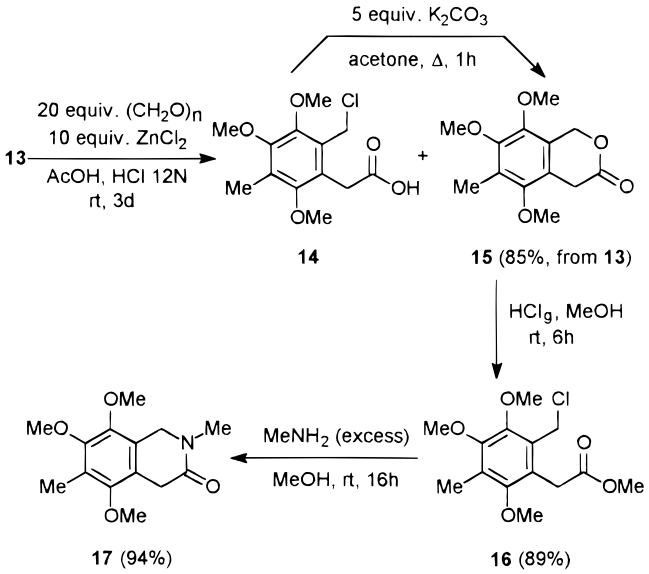
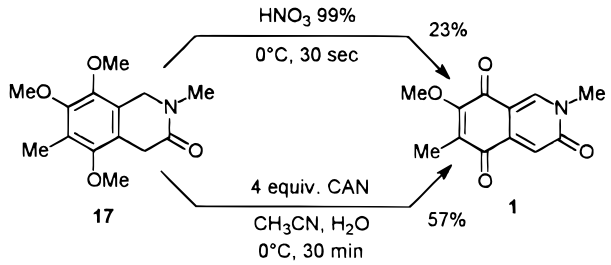
Scheme 3



Scheme 4



Scheme 5



benzopyran **15** in an overall yield of 85% for both steps was accomplished. For the conversion of lactone **15** to the desired lactam **17**, compound **15** was first treated with a dry solution of methanol saturated with hydrochloric acid at room temperature for 6 h, leading to the intermediate methyl (*o*-(chloromethyl)phenyl)acetate derivative **16** in a crude yield of 89%. Reaction of **16** with excess methylamine in methanol gave, after overnight reaction at room temperature, lactam **17** in 94% yield.

The oxidation of lactam **17** to mimosamycin using silver(II) oxide in 6 M HNO_3 and dioxane was reported previously.[8] The authors reported this oxidation to give only 18% of a mixture rich in mimosamycin from which the pure mimosamycin could not be isolated by means of flash chromatography. In our hands, these conclusions were confirmed, and we found also that the presence of side products from this reaction might result from an overoxidation process because prolonged reaction times (up to 8 h) completely diminished the presence of mimosamycin in the reaction mixture. Oxidation of 1,2,4-trimethoxybenzene derivatives have been reported in the literature to give mixtures of the ortho and para quinones,[12] and therefore we were tempted to improve the oxidation of lactam **17** by the use of other oxidizing agents such as fuming nitric acid or cerium(IV) ammonium nitrate.

Using fuming nitric acid as an oxidizing agent, the reaction of lactam **17** with 99% HNO_3 at 0 °C for 30 s led to mimosamycin in 23% after isolation by flash chromatography and recrystallization from ethyl acetate (Scheme 5). However, the best result was obtained by reaction of **17** with 4 equiv of cerium(IV) ammonium nitrate in aqueous acetonitrile at 0 °C for 30 min, which gave rise to a reaction mixture containing only a small amount of side products from which mimosamycin could be isolated in 57% yield by recrystallization from ethyl acetate. None of the side products from either oxidation procedure could ever be isolated in pure form to allow their characterization.

Experimental Section

General Methods. ^1H (270 MHz) and ^{13}C (68 MHz) NMR peak assignments were performed with the aid of the DEPT technique, 2D-COSY spectra, and HETCOR spectra.

Ketene Dimethyl Acetal. Several references are available in the literature for the synthesis of ketene dimethyl acetal.[13] None of these procedures, however, proved to be of practical use in our hands. Therefore we used a modified procedure from the synthesis of ketene diethyl acetal,[14] which allowed ketene dimethyl acetal to be synthesized in an overall yield of 53% in two steps from trimethyl orthoacetate and in a purity of ~90%, which was found to be sufficient for the cycloaddition reaction with 2-methoxy-3-methyl-1,4-benzoquinone (**6**). Ketene di-

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methyl acetal was prepared as follows. To a cooled (0 °C) solution of trimethyl orthoacetate (0.8 mol, 96 g) and pyridine (0.8 mol, 63.2 g) was added bromine (0.8 mol, 41.2 mL) dropwise over a period of 1 h. The reaction mixture was kept at room temperature for 2 h and poured into dry ether (500 mL), which caused pyridinium bromide to precipitate. Filtration and evaporation of the filtrate in vacuo afforded crude trimethyl bromoorthoacetate. Distillation (bp 68−69 °C/14 mmHg) gave pure trimethyl bromoorthoacetate (99.4 g, 62%). A vigorously stirred mixture of sodium (1 g atom, 23 g) in *p*-xylene (200 mL) was heated in an oil bath at 140−150 °C in a three-necked flask provided with a dropping funnel and two reflux condensers. When *p*-xylene started to reflux, trimethyl bromoorthoacetate (0.5 mol, 99.4 g) was added over a period of 20 min, causing a vigorous reaction. Heating was continued at the same temperature for 30 min after which the suspension was allowed to cool to room temperature, allowing a deep blue solid to precipitate. The supernatant was collected by decantation and distilled using a Vigreux column (∼80 cm) (bp 89−92 °C/760 mmHg) to give ketene dimethyl acetal (37.5 g, 85%), purity ∼90% (by NMR). The 10% of impurities was recognized as to be merely trimethyl orthoacetate.

Synthesis of 2,2,6-Trimethoxy-7-methyl-2,3-dihydrobenzo[*b*]furan-5-ol (9), 3,5,7-Trimethoxy-2-methyl-1,4-naphthoquinone (10), and 2-Methoxy-3-methylhydroquinone (11). 2-Methoxy-3-methyl-1,4-benzoquinone (**6**)[9] (3 mmol, 0.46 g) and ketene dimethyl acetal (15 mmol, 1.32 g) were mixed at room temperature and subsuquently heated at 110 °C in an open recipient for 1 h. Flash chromatography on silica gel using ethyl acetate/light petroleum ether (1:4) as an eluent gave 2,2,6-trimethoxy-7-methyl-2,3-dihydrobenzo[*b*]furan-5-ol (**9**) (110 mg, 15%) as a pale yellow oil as the first fraction. ^{1}H NMR ($CDCl_3$): δ 2.19 (3H, s, Me), 3.19 (2H, d, J = 0.7 Hz, CH_2), 3.42 (6H, s, $(MeO)_2$), 3.77 (3H, s, MeO), 5.26 (1H, s, OH), 6.64 (1H, d, J = 0.7 Hz, =CH). ^{13}C NMR ($CDCl_3$): δ 9.4 (Me), 37.5 (CH_2), 50.4 ($(MeO)_2$), 61.0 (MeO), 108.6 (=CH), 113.2 (C_{quat}), 119.5 (C_{quat}), 125.0 (C_{quat}), 143.4 (=C−O), 144.9 (=C−O), 149.1 (=C−O). IR (NaCl): ν_{max} 3429 (OH), 1465, 1285, 1052, 733 cm^{-1}. MS *m*/*z* (%): 240 (M$^+$, 64), 225 (47), 209 (55), 194 (37), 193 (100). Anal. Calcd for $C_{12}H_{16}O_5$: C 59.99, H 6.71. Found: C 59.64, H 6.55. Using the same solvent system, 2-methoxy-3-methylhydroquinone (**11**) (30 mg, 6%) eluted as a second compound from the column. Evaporation of the solvent gave a solid compound, which was recrystallized from chloroform to afford **11** as white needles, mp 110−111 °C. ^{1}H NMR ($CDCl_3$): δ 2.19 (3H, s, Me), 3.78 (3H, s, MeO), 4.48 (1H, s, OH), 5.24 (1H, s, OH), 6.48 (1H, d, J = 8.6 Hz, =CH), 6.68 (1H, d, J = 8.6 Hz, =CH). ^{13}C NMR ($CDCl_3$): δ 9.3 (Me), 60.9 (MeO), 111.0 (=CH), 112.4 (=CH), 117.8 (=C_{quat}), 142.8 (=C−O), 145.9 (=C−O), 147.7 (=C−O). IR (KBr): ν_{max} 3254 (OH), 1492, 1253, 1076, 795 cm^{-1}. MS *m*/*z* (%): 154 (M$^+$, 100), 139 (70), 111 (29). Anal. Calcd for $C_8H_{10}O_3$: C 62.33, H 6.54. Found: C 61.79, H 6.60. Elution with ethyl acetate/light petroleum ether (1:1) gave 3,5,7-trimethoxy-2-methyl-1,4-naphthoquinone (**10**) (240 mg, 31%) as a yellow powder (from methanol), mp 139−140 °C (Lit.[15] mp 141−142 °C). ^{1}H NMR ($CDCl_3$): δ 2.02 (3H, s, Me), 3.94 (3H, s, MeO), 3.96 (3H, s, MeO), 4.10 (3H, s, MeO), 6.68 (1H, d, J = 2.6 Hz, =CH-6), 7.26 (1H, d, J = 2.6 Hz, =CH-8). ^{13}C NMR ($CDCl_3$): δ 8.9 (Me), 55.9 (MeO), 56.4 (MeO), 61.1 (MeO), 103.2 (=CH-8), 103.5 (=CH-6), 113.7 (=C_{quat}), 128.2 (=C_{quat}), 136.2 (=C_{quat}), 158.9 (=C−O), 161.8 (=C−O), 164.7 (=C−O), 179.1 (C=O), 185.7 (C=O). IR (KBr): ν_{max} 1658 (C=O), 1625 (C=O), 1591 (C=C) cm^{-1}. MS *m*/*z* (%): 262 (M$^+$, 47), 247 (12), 154 (100), 139 (75). Anal. Calcd for $C_{14}H_{14}O_5$: C 64.12, H 5.38. Found: C 63.91, H 5.55.

A carefully purified sample of **6** (5.5 mmol, 0.84 g), obtained by flash chromatography with ethyl acetate/light petroleum ether (1:9) as an eluent, and ketene dimethyl acetal (27.5 mmol, 2.42 g) were heated under reflux in toluene (50 mL) for 24 h and evaporated in vacuo. Flash chromatography on silica gel using ethyl acetate/light petroleum ether (1:4) as an eluent, first gave **6** (0.44 g, 52%) as a yellow band and then 2,2,6-trimethoxy-7-methyl-2,3-dihydrobenzo[*b*]furan-5-ol (**9**) (0.58 g, 44%) as a pale yellow oil.

Methyl (2,5-Dihydroxy-4-methoxy-3-methylphenyl)-acetate (12). 2,2,6-Trimethoxy-7-methyl-2,3-dihydrobenzo[*b*]-furan-5-ol (**9**) (1 mmol, 240 mg) was heated under reflux in 80% methanol (10 mL) for 3 h. The reaction was concentrated in vacuo to 2 mL, water was added, and the suspension was extracted with dichloromethane and dried ($MgSO_4$). Flash chromatography on silica gel with ethyl acetate/light petroleum ether (1:1) as eluent gave pure **12** (210 mg, 93%) as a colorless oil. ^{1}H NMR ($CDCl_3$): δ 2.22 (3H, s, Me), 3.58 (2H, s, CH_2), 3.74 (3H, s, MeO), 3.76 (3H, s, MeO), 5.32 (1H, s, OH), 6.57 (1H, s, =CH), 7.14 (1H, s, OH). ^{13}C NMR ($CDCl_3$): δ 9.7 (Me), 37.7 (CH_2), 52.7 (MeO), 60.8 (MeO), 114.0 (=CH), 116.7 (=C_{quat}), 120.4 (=C_{quat}), 142.6 (=C−O), 145.5 (=C−O), 147.0 (=C−O), 174.6 (C=O). IR (NaCl): ν_{max} 3410 (OH), 1722 (C=O) cm^{-1}. MS *m*/*z* (%): 226 (M$^+$, 66), 194 (68), 167 (60), 166 (68). Anal. Calcd for $C_{11}H_{14}O_5$: C 58.40, H 6.24. Found: C 58.00, 6.08.

Methyl (2,4,5-Trimethoxy-3-methylphenyl)acetate (13). A mixture of methyl (2,5-dihydroxy-4-methoxy-3-methylphenyl)acetate (**12**) (1 mmol, 230 mg), dimethyl sulfate (2 mmol, 250 mg), and potassium carbonate (5 mmol, 0.63 g) in acetone (20 mL) was heated under reflux for 2 h, cooled to room temperature, filtered, and evaporated in vacuo. Flash chromatography on silica gel using ethyl acetate/light petroleum ether (1:4) as eluent gave **13** (200 mg, 79%) as an oil. ^{1}H NMR ($CDCl_3$): δ 2.22 (3H, s, Me), 3.63 (2H, s, CH_2), 3.68 (3H, s, MeO), 3.71 (3H, s, MeO), 3.78 (3H, s, MeO), 3.82 (3H, s, MeO), 6.65 (1H, s, =CH). ^{13}C NMR ($CDCl_3$): δ 9.7 (Me), 35.4 (CH_2), 51.0 (MeO), 56.0 (MeO), 60.2 (MeO), 60.8 (MeO), 111.4 (=CH), 122.2 (=C_{quat}), 125.5 (=C_{quat}), 147.3 (=C−O), 149.2 (=C−O), 150.8 (=C−O), 172.4 (C=O). IR (NaCl): ν_{max} 1736 (C=O) cm^{-1}. MS *m*/*z* (%): 254 (M$^+$, 100), 239 (28), 207 (37), 195 (76), 165 (21). Anal. Calcd for $C_{13}H_{18}O_5$: C 61.41, H 7.13. Found: C 61.82, H 7.38.

5,7,8-Trimethoxy-6-methyl-1*H*-benz[*c*]pyran-3(4*H*)-one (15). To a mixture of methyl (2,4,5-trimethoxy-3-methylphenyl)acetate (**13**) (2 mmol, 0.5 g), paraformaldehyde (40 mmol, 1.2 g), and zinc(II) chloride (20 mmol, 2.7 g) in acetic acid (5 mL) was added dropwise concentrated hydrochloric acid (15 mL), and the reaction was stirred at room temperature for 3 days in a stoppered flask. The reaction mixture was poured into water, extracted with dichloromethane, dried ($MgSO_4$), and evaporated in vacuo. The residue was dissolved in acetone (20 mL) and heated under reflux for 1 h in the presence of potassium carbonate (10 mmol, 1.38 g). The reaction mixture was allowed to cool to room temperature, filtered, and evaporated in vacuo. Flash chromatography on silica gel using ethyl acetate/light petroleum ether (1:4) as eluent gave pure **15** (0.43 g, 85%) as white needles (from ethanol), mp 92.0−92.4 °C. ^{1}H NMR ($CDCl_3$): δ 2.21 (3H, s, Me), 3.66 (2H, s, CH_2C=O), 3.69 (3H, s, MeO), 3.82 (3H, s, MeO), 3.85 (3H, s, MeO), 5.35 (CH_2O). ^{13}C NMR ($CDCl_3$): δ 9.5 (Me), 30.0 (CH_2C=O), 60.3 (MeO), 60.9 (MeO), 61.0 (MeO), 65.4 (CH_2O), 119.3 (=C_{quat}), 122.8 (=C_{quat}), 126.1 (=C_{quat}), 145.2 (=C−O), 150.6 (=C−O), 151.3 (=C−O), 170.7 (C=O). IR (NaCl): ν_{max} 1744 (C=O) cm^{-1}. MS *m*/*z* (%): 252 (M$^+$, 34), 237 (10), 193 (25), 91 (100). Anal. Calcd for $C_{13}H_{16}O_5$: C 61.90, H 6.39. Found: C 61.84, H 6.12.

Methyl (6-Chloromethyl-2,4,5-trimethoxy-3-methylphenyl)acetate (16). To a saturated solution of dry HCl in dry methanol (10 mL, distilled from sodium) was added 5,7,8-trimethoxy-6-methyl-1*H*-benz[*c*]pyran-3(4*H*)-one (**15**) (1.7 mmol, 0.42 g), and the reaction mixture was stirred for 6 h in a stoppered flask at room temperature. The reaction was quenched by the addition of water, extracted with dichloromethane, dried ($MgSO_4$), and evaporated in vacuo to give crude **16** (0.46 g, 89%) as an oil, which was used without further purification in the next step (purity > 95%). ^{1}H NMR ($CDCl_3$): δ 2.22 (3H, s, Me), 3.69 (3H, s, MeO), 3.72 (3H, s, MeO), 3.82 (2H, s, CH_2C=O), 3.83 (3H, s, MeO), 3.91 (3H, s, MeO), 4.70 (2H, s, CH_2Cl). ^{13}C NMR ($CDCl_3$): δ 9.9 (Me), 31.6 (CH_2C=O), 38.2 (CH_2Cl), 52.2 (MeO), 60.1 (MeO), 60.8 (MeO), 61.2 (MeO), 123.0 (=C_{quat}), 126.8 (=C_{quat}), 128.5 (=C_{quat}), 148.3

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(=C−O), 151.4 (=C−O), 153.7 (=C−O), 172.1 (C=O). IR (NaCl): ν_{max} 1733 (C=O) cm^{-1}. MS *m*/*z* (%): 302/4 (M^+, 100), 267 (10), 243/5 (27).

5,7,8-Trimethoxy-2,6-dimethyl-1,4-dihydroisoquinoline-3(2*H*)-one (17). To a solution of crude methyl (6-chloromethyl-2,4,5-trimethoxy-3-methylphenyl)acetate (**16**) (1.4 mmol, 0.42 g) in methanol (30 mL) was added dropwise a solution of methylamine 10% in water (10 mL), and the reaction mixture was stirred for 24 h in a stoppered flask. The solvent was concentrated in vacuo to 5 mL, water was added, and the suspension was extracted with chloroform, dried ($MgSO_4$), and evaporated in vacuo. Flash chromatography on silica gel using ethyl acetate as eluent gave pure **17** (0.35 g, 94%) as white flakes (from ether), mp 104 °C. ^{1}H NMR ($CDCl_3$): δ 2.19 (3H, s, Me), 3.12 (3H, s, N−Me), 3.57 (2H, s, CH_2C=O), 3.68 (3H, s, MeO), 3.81 (3H, s, MeO), 3.86 (3H, s, MeO), 4.48 (2H, s, CH_2N). ^{13}C NMR ($CDCl_3$): δ 9.0 (Me), 30.6 (CH_2C=O), 34.1 (N−Me), 48.1 (CH_2N), 59.9 (MeO), 59.9 (MeO), 60.1 (MeO), 120.7 (=C_{quat}), 122.0 (=C_{quat}), 124.4 (=C_{quat}), 144.6 (=C−O), 149.7 (=C−O), 150.9 (=C−O), 168.0 (C=O). IR (NaCl): ν_{max} 1650 (C=O) cm^{-1}. MS *m*/*z* (%): 265 (M^+, 100), 250 (12), 234 (66), 208 (16), 193 (44). Anal. Calcd for $C_{13}H_{19}NO_4$: C 61.64, H 7.56. Found: C 61.88, H 7.65.

Synthesis of Mimosamycin by Oxidation of 5,7,8-Trimethoxy-2,6-dimethyl-1,4-dihydroisoquinoline-3(2*H*)-one (17) with Nitric Acid. To 5,7,8-trimethoxy-2,6-dimethyl-1,4-dihydroisoquinoline-3(2*H*)-one (**17**) (0.37 mmol, 100 mg) was added at 0 °C fuming nitric acid (1 mL), and the mixture was stirred for 30 s. The reaction was quenched by the addition of a saturated solution of sodium hydrogen carbonate until all nitric acid was neutralized. The aqueous solution was extracted with ethyl acetate, dried ($MgSO_4$), and evaporated in vacuo. Flash chromatography on silica gel with acetone/chloroform (1:4) and recrystallization from ethyl acetate gave pure mimosamycin (20 mg, 23%) as yellow needles.

Synthesis of Mimosamycin by Oxidation of 5,7,8-Trimethoxy-2,6-dimethyl-1,4-dihydroisoquinoline-3(2*H*)-one (17) with Cerium(IV) Ammonium Nitrate. To a cooled (0 °C) solution of 5,7,8-trimethoxy-2,6-dimethyl-1,4-dihydroisoquinoline-3(2*H*)-one (**17**) (0.75 mmol, 200 mg) in acetonitrile (5 mL) was added dropwise a solution of cerium(IV) ammonium nitrate (3 mmol, 1.63 g) in water (10 mL), and after stirring for an additional 30 min at the same temperature, the reaction mixture was poured into water and extracted with ethyl acetate. The combined organic extracts were stirred with potassium carbonate (1 g) for 1 h, filtered, and evaporated in vacuo. Recrystallization from ethyl acetate gave mimosamycin as yellow needles, mp 228.5−229 °C (lit.[1a] mp 219−231 °C). ^{1}H NMR ($CDCl_3$): δ 2.06 (3H, s, Me), 3.67 (3H, s, N−Me), 4.17 (3H, s, MeO), 7.09 (1H, s, =CH-4), 8.27 (1H, s, =CH-1). ^{13}C NMR ($CDCl_3$): δ 9.6 (Me), 38.4 (N−Me), 61.3 (MeO), 111.3 (=C_{quat}), 116.7 (=CH-4), 133.2 (=C_{quat}), 138.9 (=C_{quat}), 142.1 (=CH-1), 159.5 (=*C*-OMe), 162.8 (N−C=O), 177.3 (C=O), 183.5 (C=O). IR (NaCl): ν_{max} 1636 (C=O), 1581 (C=O), 1549 (C=C) cm^{-1}. MS *m*/*z* (%): 233 (M^+, 100), 218 (82), 205 (72), 190 (47), 162 (32), 134 (33). The analytical and spectral data are in accordance with those of the natural mimosamycin as published in the literature.[1c]

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