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Total Synthesis of 4-Acetyloxymethyl-1,6,9-trimethyl-1,9-diazaanthracene-2,5,8,10-tetraone, A Nybomycin Acetate Analogue.

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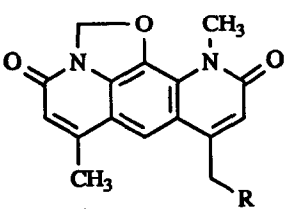
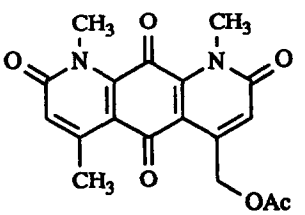
Abstract: 4-Acetyloxymethyl-1,6,9-trimethyl-1,9-diazaanthracene-2,5,8,10-tetraone **2** (a potential metabolite of nybomycin) was prepared in thirteen steps with a hetero Diels-Alder reaction as a key step.

Nybomycin (**1a**) and nybomycin acetate (**1b**), antibiotics produced by streptomyces cultures[1,2], exhibit good activity against Gram-positive bacteria. Nybomycin acetate (**1b**) also possess significant broad-spectrum activity against a range of murine leukemias and solid tumors but failed to enter human trials because of it's insolubility and also, in part, because it only showed a moderate level of antitumor activity. Nevertheless, the compound represents a novel "lead" compound. This led us to design nybomycin acetate congeners, based on potential metabolite structures, as antineoplastic agents. The congener **2** was designed as an analogue of a potential oxidative metabolite of nybomycin acetate. We now wish to report the first total synthesis of **2**.

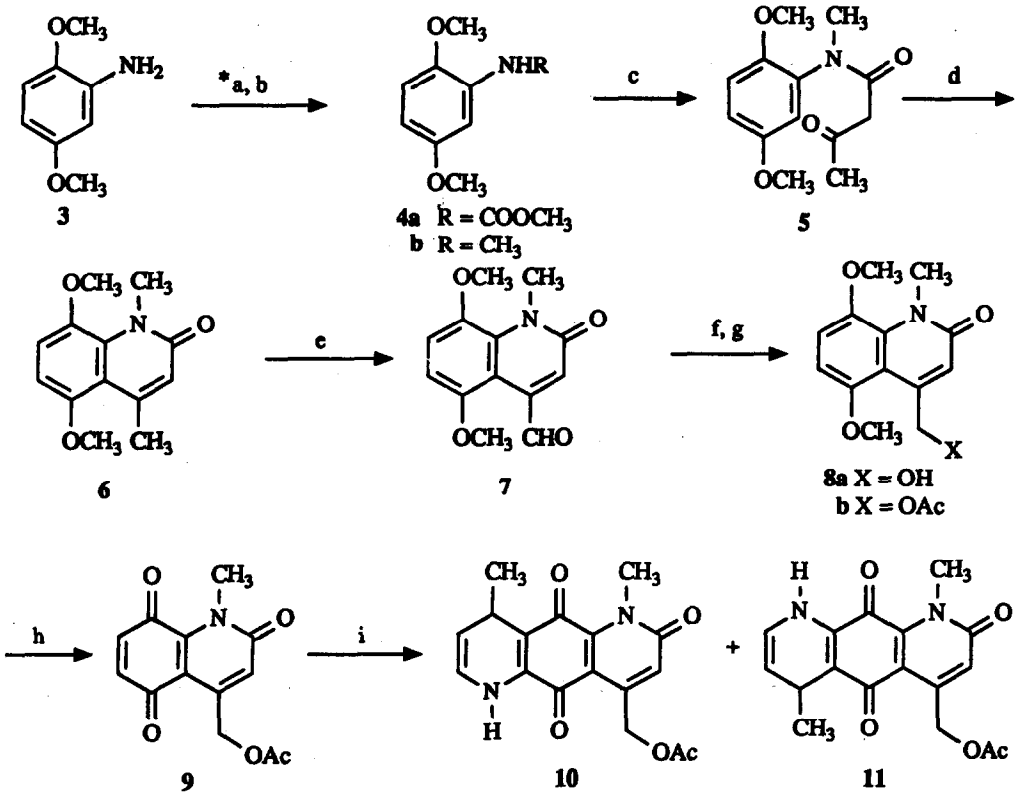


1a. R = H
b. R = OAc



2

The synthesis of **2** features a hetero Diels-Alder reaction of a 1-azadiene with the dienophile **9** and the subsequent conversion of the dihydropyridine **11** to the α-pyridone **16**. 2,5-Dimethoxyaniline (**3**) was treated with methyl chloroformate and 15 % aqueous sodium hydroxide-ether to give the carbamate **4a** (mp 60-60.5 °C, 90 %). Reduction of **4a** (lithium aluminum hydride) afforded the *N*-methylaniline **4b** (90 %) (**Scheme 1**). Treatment of **4b** with diketene in benzene heated at reflux provided the acetoacetamide **5** (mp 68.5-69 °C, 84 %) that underwent

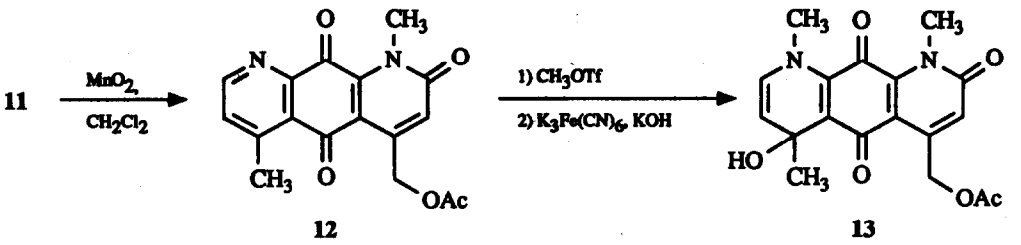


*a. $ClCOOCH_3$, NaOH, ether; b. $LiAlH_4$, ether, rt; c. diketene, benzene, reflux; d. polyphosphoric acid, 100 °C; e. SeO_2, dioxane, reflux,24h f. $NaBH_4$, EtOH, rt; g. pyridine, acetic anhydride, rt; h. ceric ammonium nitrate, acetonitrile-H_2O; i. 1-dimethylamino-1-aza-1,3-pentadiene, CH_2Cl_2, rt.

Scheme 1

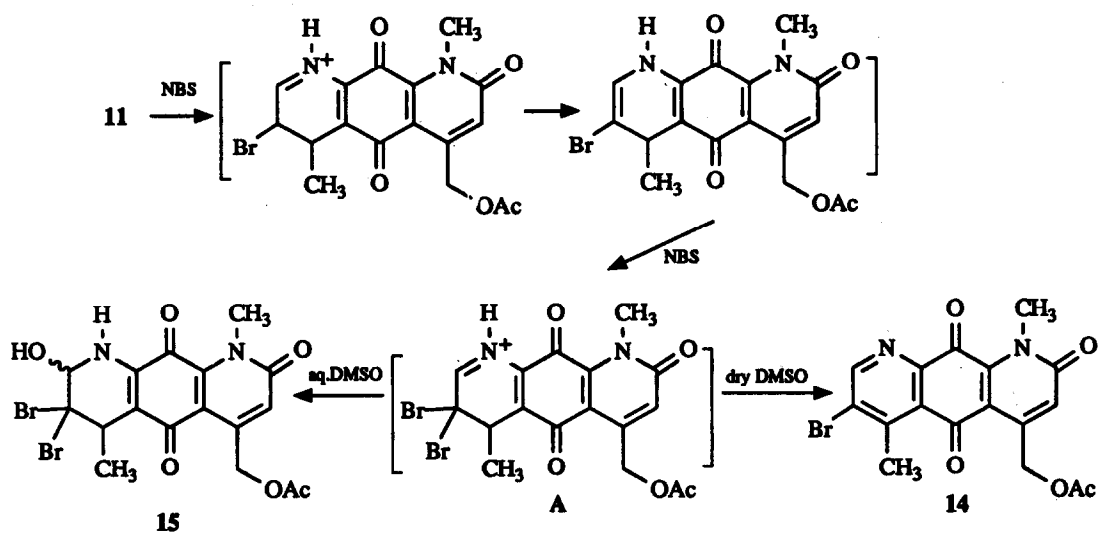
acid-catalyzed cyclization (polyphosphoric acid) to give the 2-quinolone **6** (mp 122.5-123.5 °C, 82 %).[2] The oxidation of **6** with selenium dioxide in anhydrous dioxane (reflux) provided the aldehyde **7** (mp 191-192 °C, 82 %)[3] whereas oxidation in aqueous dioxane resulted in the formation of both aldehyde **7** and alcohol **8a**. Aldehyde **7** was reduced (sodium borohydride-ethanol[4]) and the resulting alcohol, **8a**, was treated with acetic anhydride-pyridine in the presence of dimethylaminopyridine to give **8b** (mp 112-113 °C, 87 %). Oxidative demethylation of **8b** with ceric ammonium nitrate (CAN) provided the dienophile **9** (mp 113-114 °C, 88 %).[5] The dienophile **9** was treated with 1-dimethylamino-1-aza-1,3-pentadiene in dichloromethane at room temperature (argon) to give the dihydropyridine **11** (mp 158-158.5 °C, 76 %) along with a minor amount of the less polar regioisomer **10** (mp 182-183 °C, 11 %).[6] The regioselectivity of the cycloaddition was attributed to the relative electron deficiencies of the carbonyl groups of dienophile.[7]

Aromatization of **11** with manganese dioxide in dichloromethane gave **12** (mp 199-200 °C, 88 %) but the attempted conversion of **12** to the α-pyridone by treatment of its methotriflate salt with potassium hydroxide and potassium ferricyanide[8] gave the tertiary allylic alcohol **13** instead of the expected α-pyridone (Scheme 2). The



Scheme 2

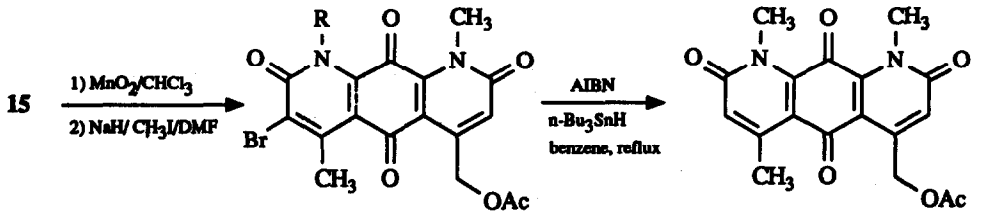
tertiary alcohol was formed by simple hydroxide attack on the pyridinium salt because the same product could be obtained without potassium ferricyanide. Therefore, the direct conversion of **11** to α-pyridone **16a** was attempted. Treatment of **11** with *N*-bromosuccinimide in anhydrous DMSO (24 °C) afforded the bromopyridine **14** (mp 209-211 °C, 68 %).[9] The same reaction in aqueous DMSO provided the dibromohydrin **15** (mp 112-113 °C, 72 %) as a diastereoisomeric mixture.[10] The formation of both **14** and **15** can be postulated to proceed from the common dibrominated intermediate, A, as shown in Scheme 3. Oxidation of the carbinolamine **15** (activated



Scheme 3

manganese dioxide in chloroform) with concomitant elimination of hydrogen bromide[11] provided the α-pyridone **16a** (mp > 250 °C, 70 %). Methylation of **16a** (sodium hydride-methyl iodide in anhydrous DMF) gave the *N*-methylpyridone **16b** (mp 253-254 °C, 58 %) that was debrominated under free radical conditions[12] (tri-*n*-butyltinhydride and azobisisobutyronitrile in benzene at reflux) to give the target compound **2** (55 %) (Scheme 4).[13] Thus, the synthesis of **2** was realized in 13 steps, 4.3 % overall yield, from 2,5-dimethoxyaniline.

The synthetic sequence employed for **2** can be extended to a series of other nybomycin congeners. Further work on the synthesis of these analogues as well as the evaluation of **2** as an antineoplastic agent is in progress.



Scheme 4

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6. Structure assignment for the regioisomers (**10** and **11**) was based on ^{1}H-NMR. The C3 vinyl proton in **10** appears at δ 6.78 whereas in the case of **11** it appears at δ 6.97. The observed shielding of H-3 in **10** can be attributed to cross conjugation.
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12. Coblens, K. E.; Muralidharan, V. B.; Ganem, B. *J. Org. Chem.* **1982**, *47*, 5041.
13. All new compounds gave satisfactory analytical data. Compound **2** had: mp 193-193.5 °C; ^{1}H-NMR δ ($CDCl_3$) 6.90 (s, 1 H), 6.63 (s, 1 H), 5.48 (s, 2 H), 3.75 (s, 3 H), 3.73 (s, 3 H), 2.55 (s, 3 H), 2.20 (s, 3 H); IR (KBr) 2970, 2927, 1740, 1677, 1648, 1590 cm^{-1}. *Anal.* calcd for $C_{18}H_{16}N_2O_6$: C, 60.67; H, 4.53; N, 7.86. Found: C, 60.75; H, 4.53; N, 7.85.

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