

Reduction of Cyclic Hemiacetals. The Synthesis of Demethoxyeleutherin and Nanaomycin A

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The reduction of cyclic hemiacetals containing two stereogenic centres is highly stereoselective.

We recently reported a two step procedure for the conversion of five and six membered lactones to cyclic ethers.¹ The procedure consisted of reduction of the lactone with Bu^i_2AlH (DIBAL) followed by reduction of the lactol with boron trifluoride–diethyl ether adduct and triethylsilane. This strategy has since been used by several other researchers.² In the context of our continuing interest in the synthesis of biologically active pyranonaphthoquinone antibiotics and other ether containing natural products, the stereochemical consequences of this reduction needed to be defined.³ To answer this question we prepared a variety of hemiacetals from readily available lactones by reaction with either methyl-lithium or phenylmagnesium chloride (equation 1). The previously defined reaction conditions for the reduction had to be changed to afford good yields of ether products. The optimal conditions involved adding trifluoroacetic acid (3

equiv.) and triethylsilane (3 equiv.) to a CH_2Cl_2 solution of the hemiacetal at -78°C and allowing the reaction slowly to warm to 0°C .

Table 1 shows the results of our preliminary experiments. The 1,3-stereoselectivity (entries 1–5) was excellent. The 1,2-stereoselectivity (entries 6 and 7) was not as good, but still synthetically useful. The products from entries 6 and 7 were assigned based on the magnitude of the vicinal coupling constants. In particular, the product from entry 7 exhibited a resonance at δ 3.85 (J 13 Hz) for the benzylic methine proton.

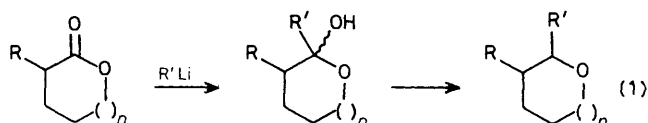




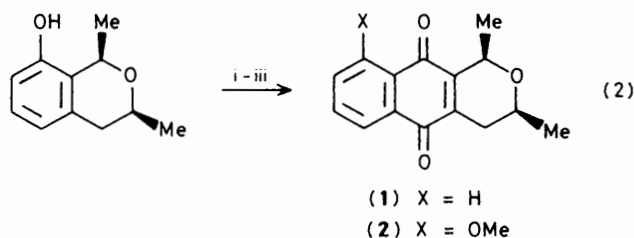
Table 1. The reduction of hemiacetals to ethers.


Entry	X	R ¹	R ²	% Yield ^a	<i>cis</i> : <i>trans</i> ratio
1	OH	Me	Me	93	100:0
2	H	Me	Pr ⁱ	70	100:0
3	H	Ph	Me	86	10:1
4	H	Ph	Pr ⁱ	75	100:0
5	H	Me	Me	88	100:0



R	n	% Yield	<i>cis</i> : <i>trans</i> ratio
Me	0	74	1:1
Me	1	75	1:100

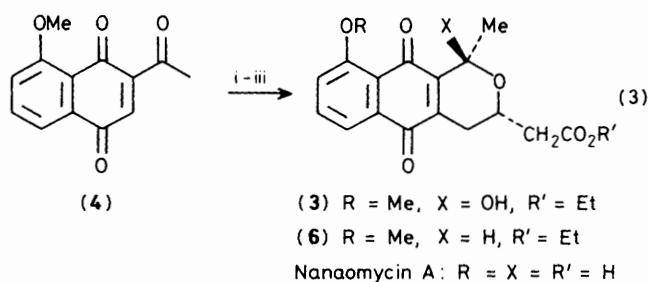
^a Yield of products purified by silica gel chromatography. All products exhibited n.m.r., i.r., mass spectroscopic/analysis consistent with the assigned structures.



Reagents: i, Fremy's salt, ii, CH₂=CHCH=CHOSiMe₃; iii, Et₃N (53%).

The product from entry 1 was converted into demethoxyeleutherin (1) as shown in equation 2. Our n.m.r. spectrum of (1) was then compared to that of eleutherin (2) to assign the *cis* stereochemistry.⁴

The antibiotic nanaomycin A became the next synthetic objective.⁵ The requisite hemiacetal (3) was synthesized in 68% yield from 2-acetyl-8-methoxy-1,4-naphthoquinone (4)⁶ and ketene acetal (5) by a tandem Diels-Alder-*retro*-Claisen (DARC) reaction followed by oxidation with ceric ammonium nitrate⁷ (equation 3). The relative stereochemistry of (3) was proven by a single crystal X-ray structure. Reduction of (3) with triethylsilane and trifluoroacetic acid afforded (6) as a single product in 95% yield. It was assigned the *cis* stereochemistry on the basis of subsequent reactions. On treatment with boron tribromide, quinone (6) was demethylated and



Reagents: i, CH₂=CHCH=C(OEt)OSiBu^tMe₂ (5); ii, F⁻; iii, Ce(NH₄)₂(NO₃)₆.

isomerized to produce the methyl ester of nanaomycin A as the main reaction product. This compound has already been converted into racemic nanaomycin A by Semmelhack and coworkers.⁸

The overall yield of nanaomycin A from quinone (4) was 55%. This represents the most efficient preparation to date. The reduction of cyclic hemiacetals, by virtue of its high stereoselectivity and operational convenience, offers a new pathway by which cyclic ethers with chiral centres can be constructed.[†]

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[†] The results are in accord with axial hydride addition (ref. 3).