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The Synthesis of 5'-Deoxyjuglomycin A and 5'-Methoxyjuglomycin A.

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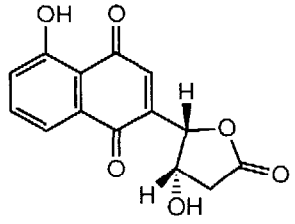
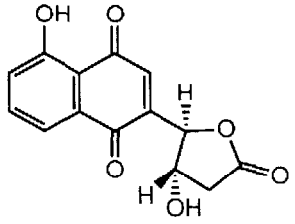
Abstract: *The syntheses of 5'-deoxyjuglomycin A (17) and 5'-methoxyjuglomycin A (18) are reported in which the key step involves ceric ammonium nitrate oxidative cleavage of the furo[3,2-b]naphtho[2,1-d]furans (7,8). The synthesis of 5'-methoxyjuglomycin A (18) represents a formal synthesis of juglomycins A and B, (1) and (2).*

Juglomycins A and B, (**1**) and (**2**), have been isolated from the culture filtrate of the fungus Streptomyces sp. 190-2[1]. These naphthoquinonoid antibiotics have been shown to possess some inhibitory action against a variety of organisms[1] but more importantly they are proposed to act as bioreductive alkylating agents[2]. To date only one synthesis of racemic juglomycins A and B has been reported by Giles *et al.*[3] in which the γ-lactone was assembled via cyclisation of a diol ester. We now wish to report the syntheses of 5'-deoxyjuglomycin A (**17**) and 5'-methoxyjuglomycin A (**18**) the latter of which represents a formal synthesis of juglomycins A and B, (**1**) and (**2**)[3].

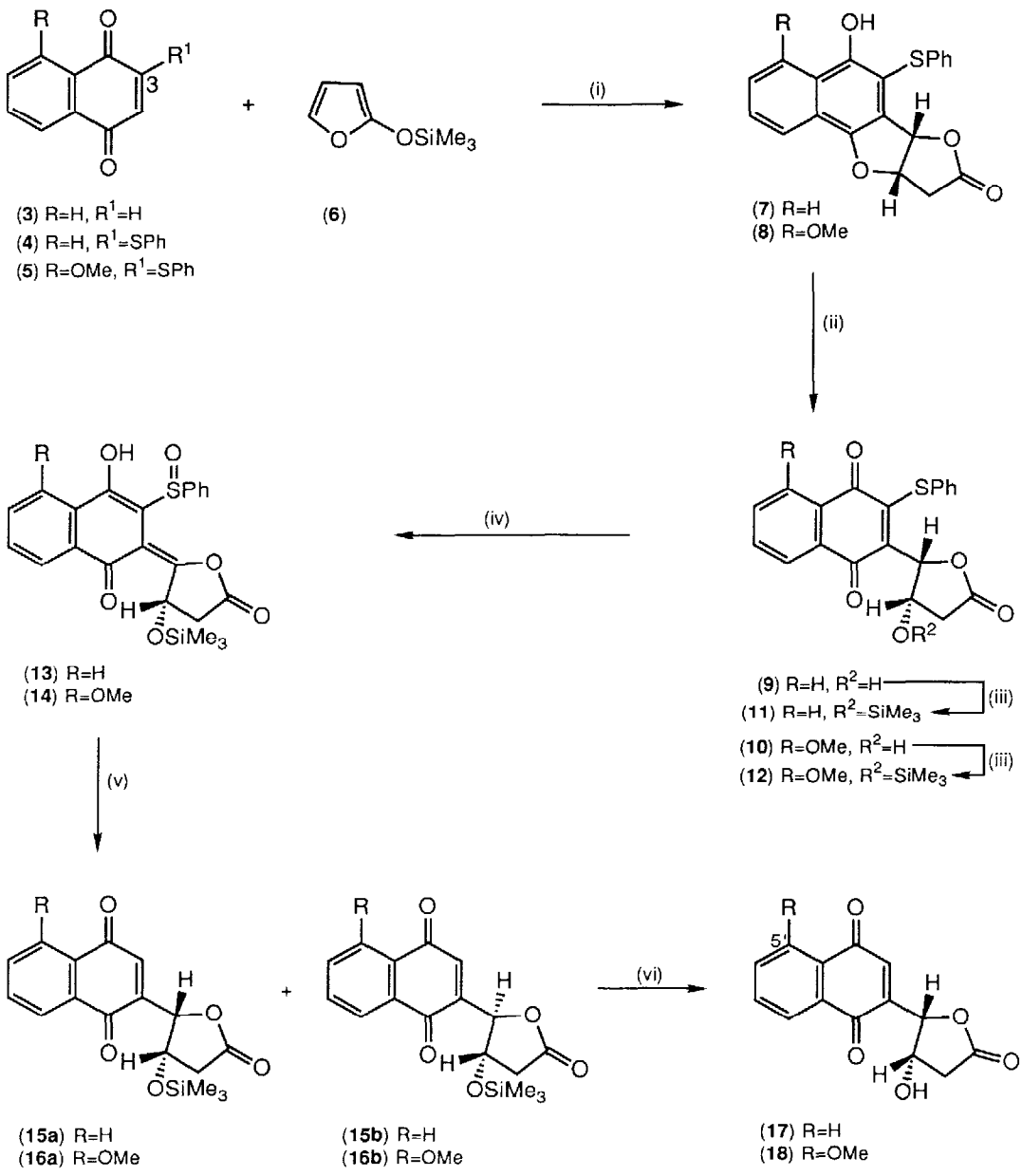


Juglomycin A (**1**)



Juglomycin B (**2**)

The key step in our approach involves a ceric ammonium nitrate oxidative cleavage of a furo[3,2-b]-naphtho[2,1-d]furan (**7**,**8**) to give the juglomycin ring system (see Scheme 1). Initial construction of the furo[3,2-b]naphtho[2,1-d]furan ring system has recently been reported[4] via the addition of 2-trimethylsilyloxy-furan (**6**) to naphthoquinones. In the present work it was found that naphthoquinone (**3**) failed to react with 2-trimethylsilyloxyfuran (**6**) to give a furo[3,2-b]naphtho[2,1-d]furan. It was therefore proposed that a



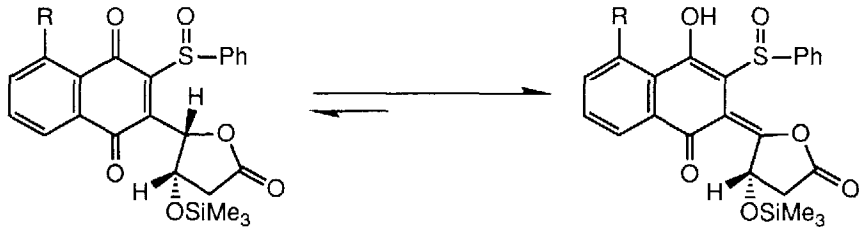
Reagents: (i) 2 equiv. (**6**), CH_3CN then MeOH [(**7**), 51%]; 8 equiv. (**6**), MeOH [(**8**), 66%]; (ii) 2 CAN, CH_3CN [(**9**), 77%; (**10**), 66%]; (iii) 1-(trimethylsilyl)imidazole, CH_2Cl_2 [(**11**), 94%; (**12**), 80%]; (iv) mCPBA, NaOAc, CH_2Cl_2 [(**13**), 68%; (**14**), 61%]; (v) $2Bu_3SnH$, cat. AIBN, toluene, heat [(**15a**, **15b**), 69%; (**16a**, **16b**), 79%]; (vi) PPTS, MeOH [(**17**), 65%; (**18**), 69%].

Scheme 1

substituent at C-3 of the quinone was required for adduct formation. Thus, a thiophenol group was introduced as this could be reductively removed after formation of the juglomycin A ring system.

Addition of 2-trimethylsilyloxyfuran (**6**) to the naphthoquinone-sulphides (**4,5**)[5,6] provided the adducts (**7,8**) in 51% and 66% yields respectively[7]. The low solubility of quinone (**5**) in acetonitrile necessitated the use of methanol as solvent in this case.

Formation of the juglomycin A ring system was then effected in good yield by oxidative cleavage of the furo[3,2-b]naphtho[2,1-d]furans (**7,8**) using ceric ammonium nitrate (CAN). Removal of the thiophenol group was then accomplished in the following manner. The alcohols (**9,10**) were protected as the silyl ethers (**11,12**). Oxidation of the sulphide using mCPBA (buffered with NaOAc) gave the sulphoxides (**13,14**) which were shown to exist as the enol tautomers by ^{1}H nmr and IR spectroscopy[8] (Scheme 2). Subsequent treatment of the sulphoxides (**13,14**) with tributyltinhydride and azobisisobutyronitrile gave a 2.2 : 1 mixture of the silyl ethers (**15a,15b**) and (**16a,16b**) respectively. Finally, deprotection of the silyl ethers (**15,16**) gave, after recrystallisation, 5'-deoxyjuglomycin A (**17**) and 5'-methoxyjuglomycin A (**18**) for which the ^{1}H nmr data and melting points were in agreement with the literature[3].



R = H or OMe

(**13**) R = H
(**14**) R = OMe

Scheme 2

Giles *et al.*[3] have successfully converted 5'-methoxyjuglomycin A (**18**) to a mixture of juglomycin A (**1**) and juglomycin B (**2**) using aluminium chloride. The existence of sulphoxides (**13,14**) as the enol tautomers supports the structure proposed by Giles *et al.*[3] for the intermediate involved in this O-demethylation step.

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7. All new compounds gave satisfactory spectroscopic and analytical data.
8. (**14**): m.p. 160-161°C; (Found: C, 59.6; H, 5.1. $C_{24}H_{24}O_7SSi$ requires C, 59.5; H, 5.0%); ν_{max} (Nujol) 3200-3450 (OH), 1793 s (C=O, γ-lactone), 1673 s (C=O), 1591 (C=C) and 1060 s cm^{-1} (S=O); δ_H (270 MHz, $CDCl_3$) 0.04 (9H, s, $SiMe_3$), 2.78-3.14 (2H, m, CH_2), 3.91 (3H, s, OMe), 4.96-5.16 (1H, br. m, 4-H) and 7.24-7.96 (8H, m, Ar-H); m/z 484 (M^+, 8%), 394 (M - $C_3H_{10}OSi$, 6), 360 (M - C_6H_4SO, 5), 324 (27) and 73 ($SiMe_3$, 100).

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