



Nitroalkenes as Precursors to the Aromatic Spiroketal Skeleton of γ -Rubromycin. A Nef-type Reaction Mediated by Pearlman's Catalyst

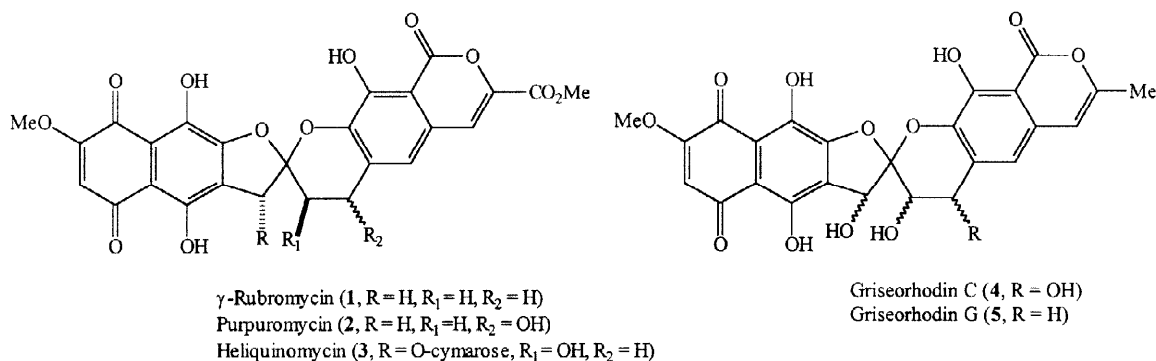
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Abstract: The first synthesis of the benzannelated spiroketal core of γ -rubromycin using Henry condensations and a novel Nef-type reaction induced by Pearlman's catalyst is described. © 1998 Elsevier Science Ltd. All rights reserved.

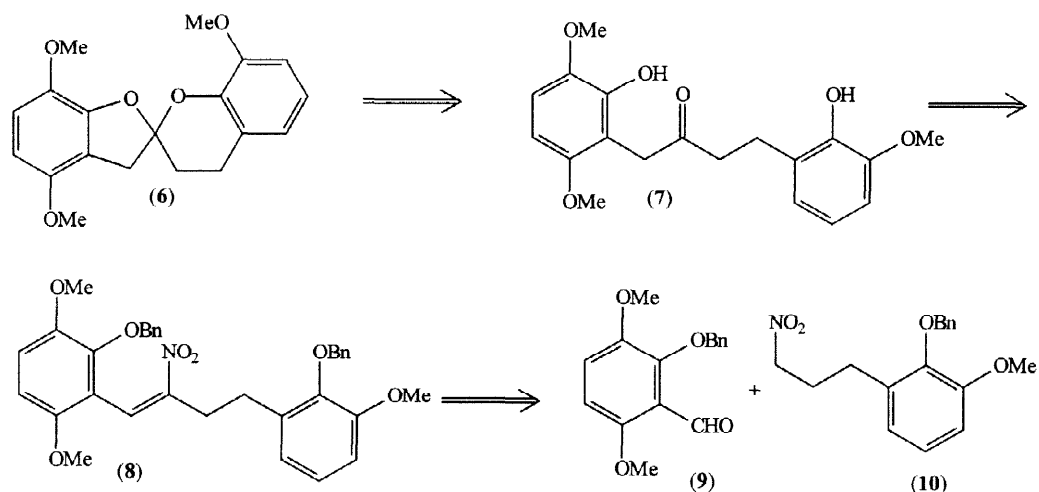
γ -Rubromycin (**1**),¹ purpurumycin (**2**),² heliquinomycin³ (**3**), and griseorhodin C (**4**) and G (**5**)⁴ are antibiotic pigments that display a variety of biological activities.⁵ This unique class of compounds possesses benzannelated furan and pyran rings sharing one common carbon atom, thereby forming a spiroketal system. The synthesis of these compounds has yet to be achieved.



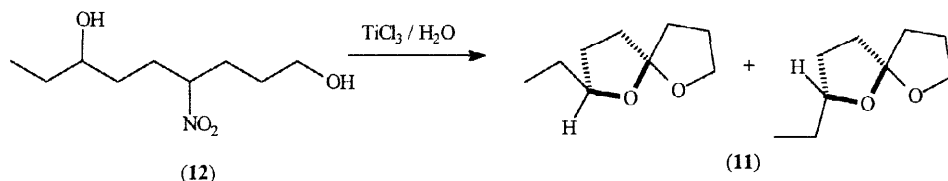
As part of our programme aimed at the synthesis of biologically active quinones, we wished to investigate the assembly of the model benzannelated spiroketal (**6**). Surprisingly, this type of simple tetracyclic system has never been synthesised. The obvious disconnection for the spiroketal is to the corresponding dihydroxyketone (**7**), in which the hydroxy groups are phenolic. We envisaged the preparation of (**7**) by C-C bond formation between two suitable moieties using the carbonyl group, or an equivalent, as the focal point for uniting the functionalised precursors. A particularly attractive carbonyl equivalent was the nitro group, which is readily converted into the desired carbonyl by the Nef reaction.⁶ A compound such as (**8**) should thus be a suitable precursor for (**7**).

Retrosynthesis of (**8**) suggests two feasible precursors: a substituted benzaldehyde (**9**) and the nitroalkane (**10**). Examination of the literature showed that related compounds have been synthesised and condensed to afford appropriately coupled units.⁷ We believed that the desired precursors (**9**) and (**10**) could easily be assembled from commercially available substrates.

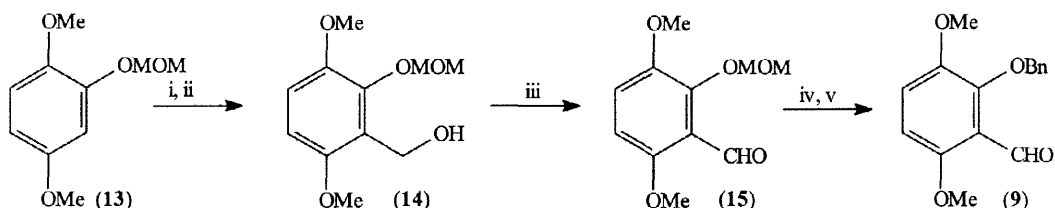
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To our surprise, the use of Nef methodology for the formation of *aromatic* spiroketals⁸ has not been reported in the literature. However, related formation of simple spiroketal systems such as (11) *via* the nitro intermediate (12) have been documented.⁹



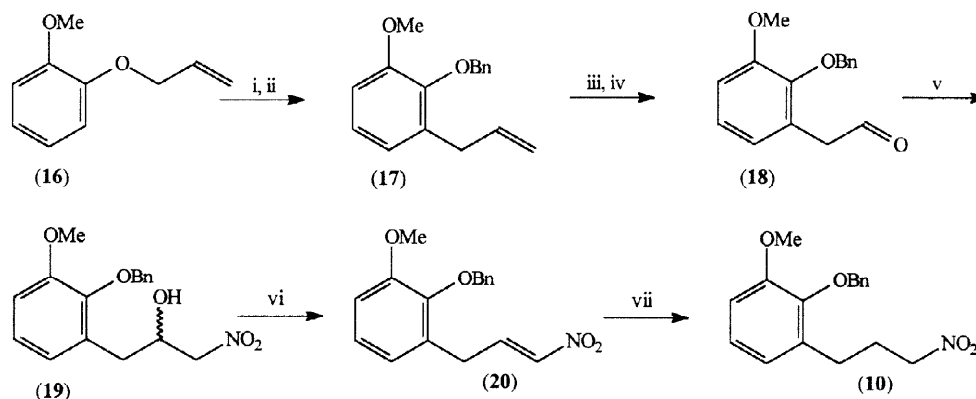
Baeyer-Villiger oxidation of 2,5-dimethoxybenzaldehyde with the magnesium salt of monoperoxyphthalic acid (MMPP), followed by protection of the resultant phenol as the methoxymethyl ether (MOM), afforded (13).¹⁰ As shown in **Scheme 1**, treatment of (13) with *n*-butyllithium followed by quenching with paraformaldehyde gave benzyl alcohol (14). Oxidation of (14) with pyridinium chlorochromate yielded aldehyde (15). Removal of the methoxymethyl protecting group was effected by treatment with *p*-toluenesulfonic acid, after which the resultant phenol was protected as the benzyl ether to give the first precursor (9). We found it necessary to use the methoxymethyl ether as a directing group for the introduction of the formyl group, because when the benzyl analogue of (13) was treated with *n*-butyllithium and paraformaldehyde, the only characterisable product resulted from condensation of aldehyde with the methylene unit of the benzyl group.



Scheme 1 Reagents and conditions: i, *n*-BuLi, THF, TMEDA, -78°C ; ii, $(\text{CH}_2\text{O})_n$, 87% over 2 steps; iii, PCC, celite, CH_2Cl_2 , 86%; iv, *p*-TsOH, dioxan/ H_2O , 55°C , 96%; v, BnBr, K_2CO_3 , DMF, 70°C , 93%.

To prepare the second precursor (10), treatment of guaiacol with allyl bromide in the presence of potassium carbonate gave the corresponding ether (16) in a yield of 99% (**Scheme 2**). Heating (16) at 180°C for 24h effected Claisen rearrangement to afford the phenol, which was immediately treated with benzyl bromide and base to yield (17). Ozonolysis of (17) afforded (18), which underwent Henry condensation

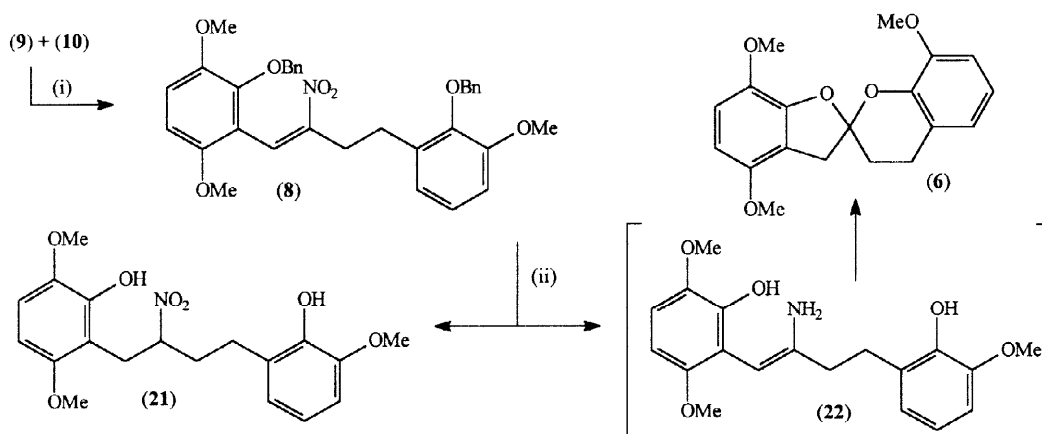
(nitromethane, cetyltrimethylammonium bromide (CTABr) and sodium hydroxide¹¹) to produce alcohol (**19**) quantitatively. Dehydration to yield (**20**) was effected by treatment of (**19**) with methanesulfonyl chloride in the presence of diisopropylethylamine.¹² Finally, reduction of (**20**) with sodium borohydride¹³ afforded the second precursor (**10**).



Scheme 2 Reagents and conditions: i, 180°C, 91%; ii, BnBr, K₂CO₃, Me₂CO, 86%; iii, O₃, MeOH, -40°C; iv, Zn, AcOH, 84%; v, MeNO₂, CTABr, 0.025M NaOH, 100%; vi, MsCl, ^tPr₂NEt, CH₂Cl₂, 96%; vii, NaBH₄, MeOH/THF, 70%.

As outlined in the retrosynthesis, a second Henry condensation of (**9**) with (**10**) was now required. This was achieved by treatment with ammonium acetate in acetic acid in a microwave oven,¹⁴ and afforded the desired nitroolefin (**8**) in a yield of 58% (**Scheme 3**). Exposure of (**8**) to Pearlman's catalyst [Pd(OH)₂ on carbon] in 96% ethanol together with one drop of concentrated hydrochloric acid and cyclohexene¹⁵ under an atmosphere of hydrogen afforded the spiroketal (**6**) directly in 62% yield, together with a 17% yield of the nitro compound (**21**). We surmise that the spiroketal is produced *via* the intermediate enamine (**22**), which was hydrolysed under the reaction conditions. ¹H NMR spectroscopy showed that (**6**) exists in two conformations in solution, as heating (**6**) in toluene-*d*₈ up to 363K resulted in coalescence of most of the duplicated signals.¹⁰

This represents the first synthesis of the bis-benzannelated 1,6-dioxaspiro[4.5]decane system. To our knowledge, this is also the first example of Pearlman's catalyst effecting a Nef-type reaction on a conjugated nitro compound.¹⁶ However, this example does not yield the free carbonyl (**7**) but leads directly to the spiroketal (**6**) since free phenolic groups are also liberated in the presence of Pearlman's catalyst.



Scheme 3 Reagents and conditions: i, NH₄OAc, AcOH, 58%; ii, Pd(OH)₂/C, H₂, EtOH, c. HCl, cyclohexene, 62% (**6**), 17% (**21**).

Work is now in progress towards increasing the proportion of (6) relative to (21) as outlined in Scheme 3. The use of Pearlman's catalyst in performing this Nef-type reaction on related nitroalkenes is also being investigated. The synthesis of γ -rubromycin (1), purpuromycin (2), heliquinomycin (3) and griseorhodin A (4) and G (5) will then be attempted utilising the developed methodology.

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