Pergamon

Tetrahedron Letters 39 (1998) 5429–5432

TETRAHEDRON LETTERS

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

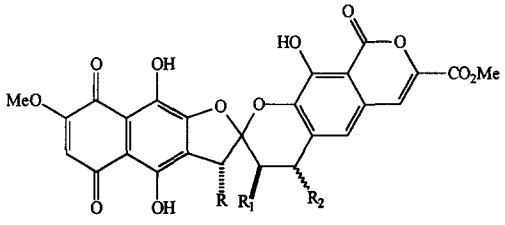
Tanya Capecchi, Charles B. de Koning* and Joseph P. Michael

Centre for Molecular Design, Department of Chemistry, University of the Witwatersrand, PO Wits 2050, South Africa

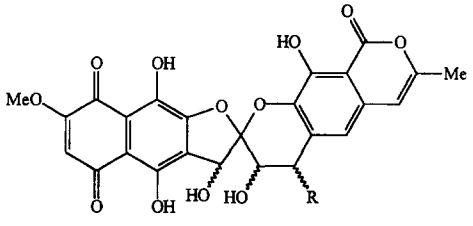
Received 22 April 1998; accepted 19 May 1998

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.

γ-Rubromycin (**1**),[1] purpuromycin (**2**),[2] heliquinomycin[3] (**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.



γ-Rubromycin (**1**, R = H, R_1 = H, R_2 = H)
Purpuromycin (**2**, R = H, R_1 = H, R_2 = OH)
Heliquinomycin (**3**, R = O-cymarose, R_1 = OH, R_2 = H)



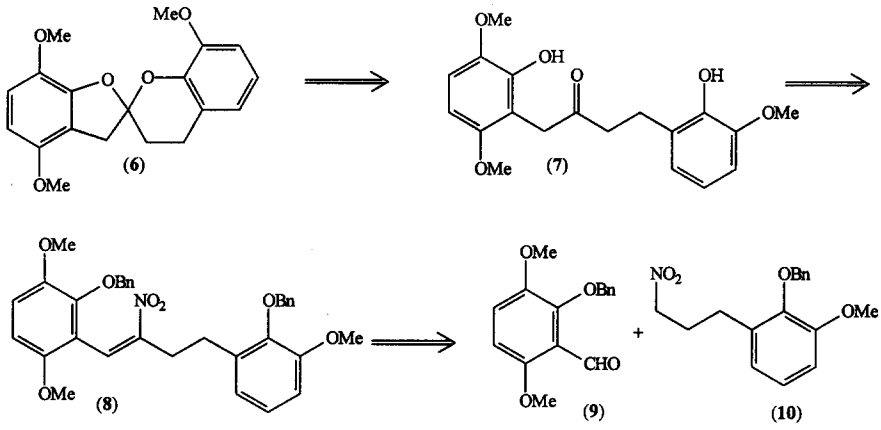
Griseorhodin C (**4**, R = OH)
Griseorhodin G (**5**, R = H)

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**).

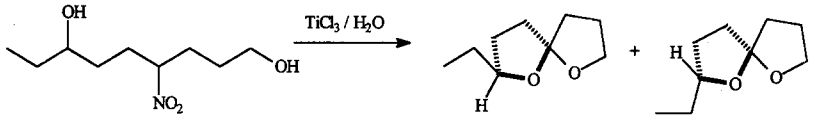
Retrosynthesis of (**8**) suggests two feasible precursors: a substituted benzaldehyde (**9**) and the nitroalkane (**10**). Examination of the literature showed that related compounds have been synthesised and condensed to afford appropriately coupled units.[7] We believed that the desired precursors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

email: dekoning@aurum.chem.wits.ac.za

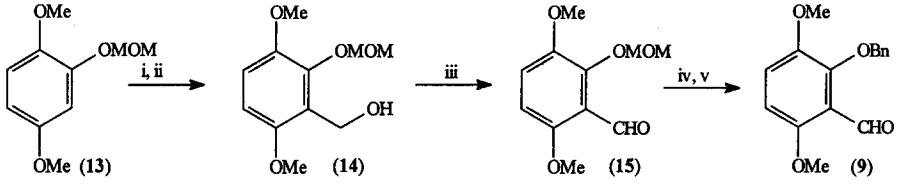
0040-4039/98/$19.00
PII: S0040-4039(98)01046-6



To our surprise, the use of Nef methodology for the formation of *aromatic* spiroketals[8] 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]



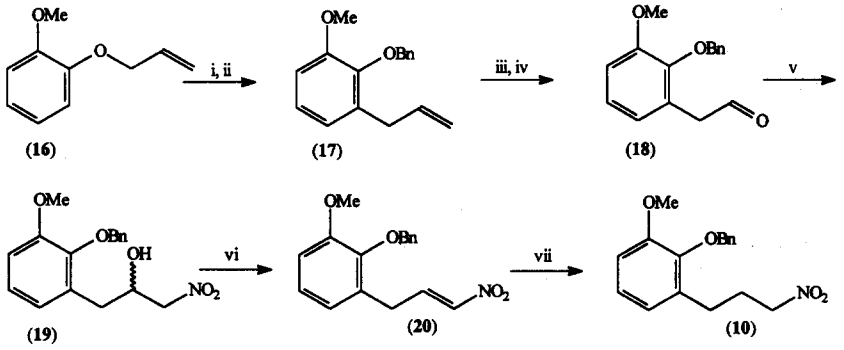
Baeyer-Villiger oxidation of 2,5-dimethoxybenzaldehyde with the magnesium salt of monoperoxyphthalic acid (MMPP), followed by protection of the resultant phenol as the methoxymethyl ether (MOM), afforded (**13**).[10] As shown in **Scheme 1**, treatment of (**13**) with *n*-butyllithium followed by quenching 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, $(CH_2O)_n$, 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

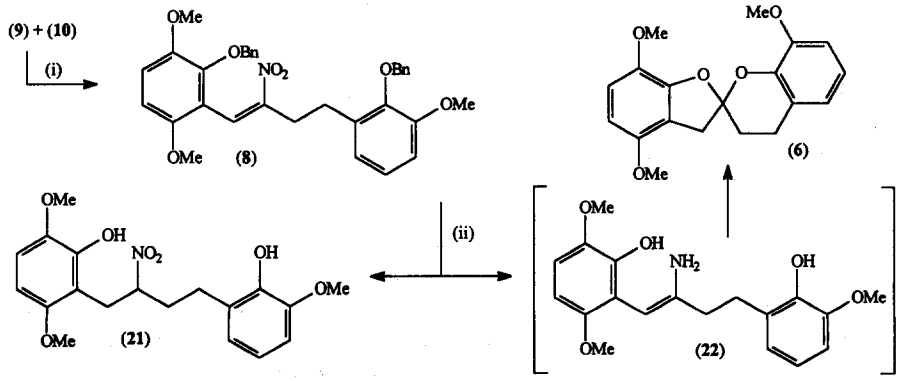
(nitromethane, cetyltrimethylammonium bromide (CTABr) and sodium hydroxide[11]) to produce alcohol (**19**) quantitatively. Dehydration to yield (**20**) was effected by treatment of (**19**) with methanesulfonyl chloride in the presence of diisopropylethylamine.[12] Finally, reduction of (**20**) with sodium borohydride[13] afforded the second precursor (**10**).



Scheme 2 *Reagents and conditions:* i, 180°C, 91%; ii, BnBr, K_2CO_3, Me_2CO, 86%; iii, O_3, MeOH, -40°C; iv, Zn, AcOH, 84%; v, $MeNO_2$, CTABr, 0.025M NaOH, 100%; vi, MsCl, $^iPr_2NEt$, CH_2Cl_2, 96%; vii, $NaBH_4$, 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 cyclohexene[15] 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, NH_4OAc, AcOH, 58%; ii, $Pd(OH)_2/C$, H_2, 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.

Acknowledgements: This work was supported by the Foundation for Research Development (FRD) and the University of the Witwatersrand.

References and Notes:

1. Brockmann, H.; Zeeck, A. *Chem. Ber.* 1970, **103**, 1709-1726.
2. (a) Coronelli, C.; Pagani, H.; Bardone, M.R.; Lancini, G.C. *J. Antibiot.* 1974, **27**, 161-168. (b) Bardone, M.R.; Martinelli, E.; Zerilli, L.F.; Coronelli, C. *Tetrahedron* 1974, **30**, 2747-2754.
3. (a) Chino, M.; Nishikawa, K.; Umekita, M.; Hayashi, C.; Yamazaki, T.; Tsuchida, T.; Sawa, R.; Hamada, M.; Takeuchi, T. *J. Antibiot.* 1996, **49**, 752-757; (b) Chino, M.; Nishikawa, K.; Tsuchida, T.; Sawa, R.; Nakamura, H.; Nakamura, K.T.; Muraoka, Y.; Ikeda, D.; Naganawa, H.; Sawa, T.; Takeuchi, T. *J. Antibiot.* 1997, **50**, 143-146.
4. (a) Eckardt, K.; Tresselt, D.; Ihn, W. *J. Antibiot.* 1978, **31**, 970-973; (b) Stroshane, R.M.; Chan, J.A.; Rubalcaba, E.A.; Garretson, A.L.; Aszalos, A.A.; Roller, P.P. *J. Antibiot.* 1979, **32**, 197-204.
5. (a) The rubromycins exhibit activity against the reverse transcriptase of human immunodeficiency virus-1. Goldman, M.E.; Salituro, G.S.; Bowen, J.A.; Williamson, J.M.; Zink, L.; Schleif, W.A.; Emini, E.A. *Mol. Pharmacol.* 1990, **38**, 20-25 (b) Purpuromycin is a potential topical agent for vaginal infections. Trani, A.; Dallanoce, C.; Panzone, G.; Gianbattista, R.; Ripamonti, F.; Goldstein, B.P.; Ciabatti, R. *J. Med. Chem.* 1997, **40**, 967-971. (c) Heliquinomycin is an inhibitor of DNA helicase. See reference 3.
6. Pinnick, H.W. The Nef Reaction, *in* "Organic Reactions", Ed: Paquette, L.A.; Vol. 38, Chapter 3, pp. 655-792, John Wiley & Sons Inc., New York, 1990.
7. Kodukulla, R.P.K.; Trivedi, G.K.; Vora, J.D.; Mathur, H.H. *Synth. Commun.* 1994, **24**, 819-832.
8. Aromatic spiroketals have been synthesised by other methods. For example, the griseusins: (a) Kometani, T.; Takeuchi, Y.; Yoshii, E. *J. Org. Chem.* 1983, **48**, 2311-2314; (b) Brimble, M. A.; Nairn, M. R. *J. Chem. Soc., Perkin Trans. 1* 1992, 579-583.
9. (a) Rosini, G.; Ballini, R.; Petrini, M.; Marotta, E. *Angew. Chem. Int. Ed. Engl.* 1986, **25**, 941-942; (b) Rosini, G.; Ballini, R.; Marotta, E., *Tetrahedron* 1989, **45**, 5935-5942; (c) Ballini, R.; Petrini, M.; Rosini, G. *Tetrahedron* 1990, **46**, 7531-7538; (d) Ballini, R.; Petrini, M. *J. Chem. Soc., Perkin Trans. 1* 1992, 3159-3160.
10. All new compounds were characterised spectroscopically and by elemental analysis or high resolution mass spectrometry. Selected data: Spiro[4,7-dimethoxybenzofuran-2(3*H*),2'-(8'-methoxychroman)] (**6**) (Found M^+, 328.1303 $C_{19}H_{20}O_5$ requires 328.1311.); ^{1}**H** (200 MHz) (Toluene-d_8) (where possible, values for the minor conformer have been given in square brackets) δ 6.84-6.14 (m, 3H, H-5', H-6' and H-7'); 6.45 (d, *J* 8.9 Hz, 1H, H-6); 6.10 (d, *J* 8.9 Hz, 1H, H-5); 4.05 [3.83] (s, 2H, H-3); 3.45 [3.51] (s, 3H, OC$\underline{H}_3$); 3.40 [3.43] (s, 3H, OC$\underline{H}_3$); 3.34 [3.32] (s, 3H, OC$\underline{H}_3$); 3.11-3.07 (m, 1H, H-3'); 2.95-2.88 (m, 2H, H-4'); 2.61-2.08 (m, 1H, H-3'); ^{13}**C** (50.32 MHz) (Toluene-d_8) δ 160.17 [160.09] (C-7a); 153.22 [153.35] (C-8'a); 147.79 [146.96] (C-7); 146.38 [146.07] (C-4); 144.51 [144.41] (C-8'); 142.66 [142.09] (C-3a); 137.52 [137.15] (C-4'a); 122.77 (Ar-C); 119.67 [119.54] (Ar-C); 112.55 [112.77] (C-2); 110.63 [109.94] (Ar-C); 109.38 [109.11] (Ar-C); 100.98 [100.14] (Ar-C); 56.37 [56.27] (O$\underline{C}H_3$); 55.55 [55.55] (O$\underline{C}H_3$); 55.37 [55.55] (O$\underline{C}H_3$); 34.16 [28.76] (C-4'); 26.94 [28.65] (C-3'); 22.69 [26.40] (C-3).
11. Ballini, R.; Bosica, G. *J. Org. Chem.* 1997, **62**, 425-427.
12. Knight, J.; Parsons, P.J. *J. Chem. Soc., Perkin Trans. 1* 1989, 979-984.
13. Varma, R.S.; Kabalka, G.W. *Synth. Commun.* 1985, **15**, 151-155.
14. Varma, R.S.; Dahiya, R.; Kumar, S. *Tetrahedron Lett.* 1997, **38**, 5131-5134.
15. Prugh, J.D.; Rooney, C.S.; Deana, A.A.; Ramjit, H.G. *Tetrahedron Lett.* 1985, **26**, 2947-2950.
16. Other methods have been reported for the conversion of nitroolefins into carbonyl or related compounds mediated by metals and metal reagents. For example (a) Pd/C: Varma, R.S.; Varma, M.; Kabalka, G.W. *Synth. Commun.* 1986, **16**, 91-96; (b) Raney Ni: Monti, D.; Gramatica, P.; Speranza, G.; Manitto, P. *Tetrahedron Lett.* 1983, **24**, 417-418; (c) $CrCl_2$: Varma, R.S.; Varma, M.; Kabalka, G.W. *Tetrahedron Lett.* 1985, **25**, 3777-3778.