Tetrahedron Letters, Vol. 34, No. 8, pp. 1373-1376, 1993
Printed in Great Britain

0040-4039/93 $6.00 + .00
Pergamon Press Ltd

A Stereoselective Approach To The Angucyclinone Antibiotics: A Total Synthesis Of The C-1 Epimer Of (±)-Rubiginone B1.

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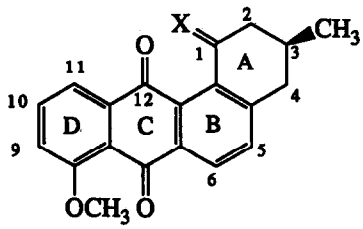
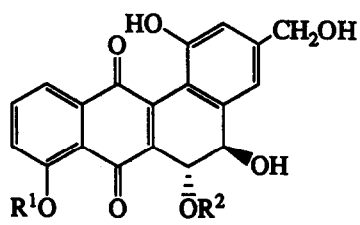
Abstract: *A stereoselective Lewis acid-promoted cycloaddition reaction of 5-hydroxy-1,4-naphthoquinone and dienol (12) gave a key intermediate (14) which was transformed into the title compound (18) in 35% overall yield.*

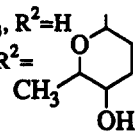
The discovery of new members of the angucyclinone group of antibiotics[1] in recent years has stimulated intense interest in this area. Among these compounds are rubiginone B1 (1) and B2 (2)[2], which have been shown to potentiate vincristine cytotoxicity, PD-116740 (3)[3] which has exhibited activity against L1210 lymphocytic leukemia and human colon adenocarcinoma cell lines, and TAN 1085 (4)[4] which has shown angiogenesis inhibitory activity.



(1) X= HO, H (*S*)
(2) X= O

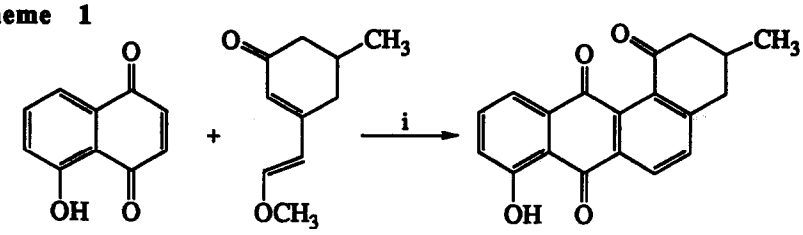


(3) R^1=CH_3, R^2=H
(4) R^1=H, R^2=



Several synthetic approaches to these compounds have been developed[5,6,7,8] and have resulted in the total synthesis of (±)-ochromycinone[7,8] (5). A very elegant Diels-Alder approach to (5) was utilised by Guingant and Barreto[8] (Scheme 1). The power of their strategy was the direct formation of the angularly fused benz[*a*]anthraquinone ring system. However, although the spontaneous aromatisation of the B-ring of the intermediary cycloadduct is beneficial in their strategy, it limits the versatility for the synthesis of a wider range of these antibiotics.

Scheme 1

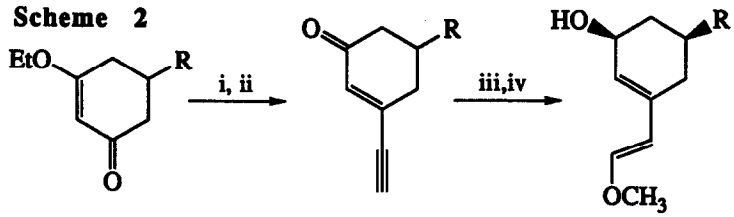


(6) (5)

i, $B(OAc)_3$, CH_2Cl_2, 20 °C.

We felt that a modification of the diene system would facilitate the isolation of the intermediate cycloadduct(s) and enable us to utilise the inherent stereochemistry and functionality obtained from the Diels-Alder process. A stereoselective reduction of the carbonyl group of diene (6) would not only allow this, but would also introduce chirality adjacent to the dienyl moiety. We now report our preliminary findings:
Two dienol systems (11) and (12) were synthesised starting from the ethyl enol ethers of cyclohexane-1,3-dione (7) and it 5-methyl analogue (8) in 88 and 81% yields respectively (Scheme 2). ^1H n.m.r. analysis of (12) confirmed the high stereoselectivity of the reduction (>95%) and assignment of the *cis* relative stereochemistry* was made by analogy to the reduction of 5-methyl-3-vinylcyclohex-2-enone[9].

Scheme 2



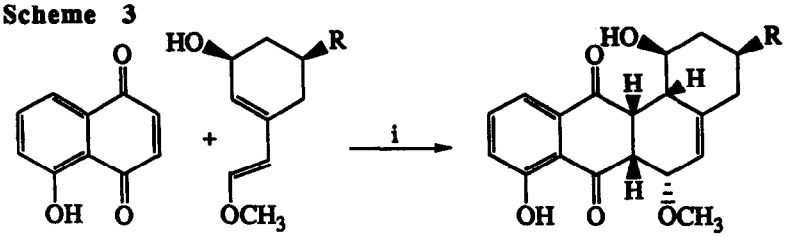
(7) R=H (9) R=H (11) R=H
(8) R=CH_3 (10) R=CH_3 (12) R=CH_3

Reagents: i, HC≡CMgBr, THF; ii, 1M HCl; iii, MeOH, N-methylmorpholine, benzene; iv, $LiAlH_4$, THF, -78°C-RT, 3 h, then NaOH and H_2O.

The tetra-*O*-acetyl diborate-promoted reaction of the dienes (11) and (12) with 5-hydroxy-1,4-naphthoquinone gave, after purification, the racemic cycloadducts (13) and (14) in yields of 91 and 73% respectively (Scheme 3). ^1H n.m.r. analysis of the crude reaction mixtures showed in each case the formation of a single stereoisomeric product[10]. The relative stereochemistries were determined from the coupling constants of the resonances of the protons at the newly formed chiral centres[11,12].

* for simplicity only one enantiomer has been depicted

Scheme 3



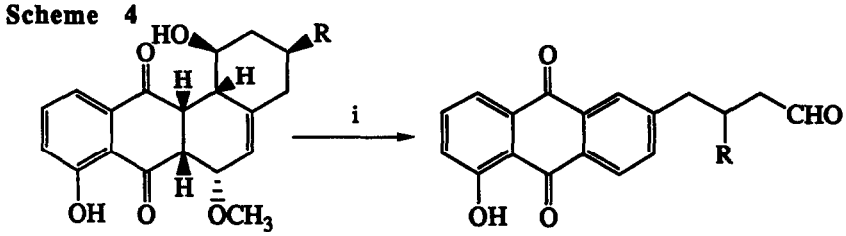
(11) R=H
(12) R=CH_3

(13) R=H
(14) R=CH_3

i, 1 equivalent $[(AcO)_2B]_2O$, CH_2Cl_2, -5 - 0°C.

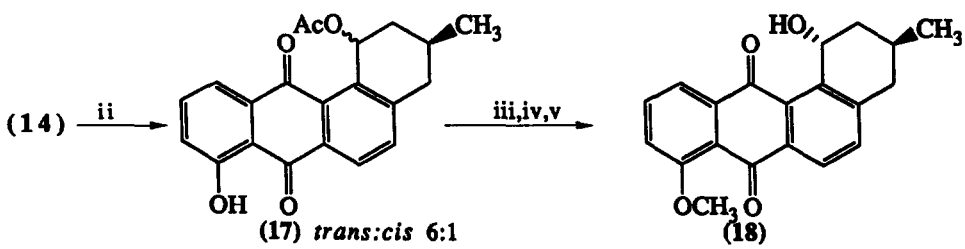
The high yields and stereoselectivity achieved in the cycloaddition reactions make (13) and (14) attractive intermediates for the syntheses of angucyclinones such as (1), (3), and (4). Our initial aim was the synthesis of analogues of rubiginone B1 (1) (Scheme 4). The normally facile process for the aromatisation of the B-ring of cycloadducts such as (13) or (14) would provide the desired aromatic nucleus. Treatment of (13) and (14) under either basic or acidic conditions resulted instead in the formation of the anthraquinones (15) and (16) in high yields through fragmentation of the C1-C12b bond. This problem was overcome by treatment of (14) with tetra-*O*-acetyl diborate in THF which gave the corresponding acetate (17) as a 6:1 mixture of the *trans* and *cis* isomers[13]. Subsequent successive methylation and deacetylation gave the C-1 epimer of (±)-rubiginone B1 (18)[11,14] in a yield of 48% from (14).

Scheme 4



(13) R=H
(14) R=CH_3

(15) R=H
(16) R=CH_3



(17) *trans:cis* 6:1

(18)

reagents: i, either acid or base; ii, $[(AcO)_2B]_2O$, THF; iii, MeI, K_2CO_3, acetone; iv, NaOMe, MeOH/THF; v, recrystallisation Et_2O/Hex.

In conclusion, a stereoselective Diels-Alder reaction has been developed for the construction of the benz[*a*]anthraquinone nucleus of the angucyclinone class of antibiotics, and the cycloadduct (**14**) has been transformed into the C-1 epimer of (±)-rubiginone B1 in an overall yield of 35% by way of commercially available 5-hydroxy-1,4-naphthoquinone. Further investigations into the syntheses of (**1**), (**3**), and (**4**) using this approach, and an asymmetric synthesis of the dienes (**11**) and (**12**), are currently underway.

References and Notes:

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10. During the preparation of this manuscript a related stereoselective Diels-Alder reaction of 5-acetoxy-2-bromonaphthoquinone and 1-*t*-butyldimethylsiloxy-3-vinylcyclohex-2-ene was reported; Kim, K.; Reibenspies, J.; Sulikowski, G. *J. Org. Chem.* **1992**, *57*, 5557-5559.
11. The structures of new compounds were assigned on the basis of 300 MHz ^{1}H NMR, 75 MHz ^{13}C NMR, infrared, and mass spectral data. All new compounds gave satisfactory elemental analyses and/or parent ion identification by high resolution mass spectrometry.
12. ^{1}H NMR of (**14**); δ(300 MHz, $CDCl_3$ + D_2O) 1.00 (3 H, d, *J* 6 Hz, CH_3), 1.11 (1 H, q, *J* 11.5, 11.5, and 11.5 Hz, H-2_{ax}), 1.71-1.82 (2 H, m, H-3,-4_{ax}), 2.08 (1 H, dd, *J* 11.5 and 2.5 Hz, H-2_{eq}), 2.15-2.23 (1 H, m, H-12b), 2.34 (1 H, dd, J 11, 2.5 Hz, H-4_{eq}), 3.00 (3 H, s, OCH_3), 3.16 (1 H, t, *J* 4.5 and 4.5 Hz, H-6a), 3.74 (1 H, t, *J* 5.5 and 5.5 Hz, H-12a), 4.03br (1 H, t, *J* 4 and 4 Hz, H-6), 4.90 (1 H, dt, *J* 4.5, 11, and 11 Hz, H-1), 5.70-5.80 (1 H, m, H-5), 7.16 (1 H, dd, *J* 8 and 1 Hz, H-9), 7.35 (1 H, dd, *J* 7.5 and 1 Hz, H-11), 7.57 (1 H, t, *J* 8 and 8 Hz, H-10).
13. On the basis of the ^{1}H NMR spectrum of (**17**) the relative stereochemistry of the major stereoisomer at C-1 and C-3 was assigned as *trans*. The epimerisation at C-1 is presumably occurring by an S_N1-like process and is the subject of further investigation.
14. ^{1}H NMR of (**18**); δ(300 MHz, $CDCl_3$) 1.12 (3 H, d, *J* 6 Hz, CH_3), 1.45 (1 H, tdd, *J* 13, 13, 4 and 2 Hz, H-2_{ax}), 2.24 (1 H, dq, *J* 13, 4.5 and 2.5 Hz, H-2_{eq}), 2.26-2.40 (1 H, m, H-3), 2.44 (1 H, dd, *J* 17 and 11.5 Hz, H-4_{ax}), 3.02br (1 H, dm, *J* 17 Hz, H-4_{eq}), 4.04 (3 H, s, OCH_3), 4.87 (1 H, dd, *J* 4 and 2 Hz, C-1 OH), 5.17 (1 H, dt, 4, 4, and 2 Hz, H-1), 7.31 (1 H, dd, *J* 8.5 and 1 Hz), and 7.82 (1 H, *J* 8, and 1 Hz) (H-9 and -11), 7.52 (1 H, d, *J* 8 Hz, H-5), 7.70 (1 H, t, *J* 8 and 8 Hz, H-10), and 8.16 (1 H, d, *J* 8 Hz, H-6).

(Received in UK 16 November 1992)