Tetrahedron Letters,Vol.30,No.35,pp 4735-4736,1989 0040-4039/89 $3.00 + .00
Printed in Great Britain Pergamon Press plc

Novel Chloroanthracyclines from Acetal-Alkene Cyclization

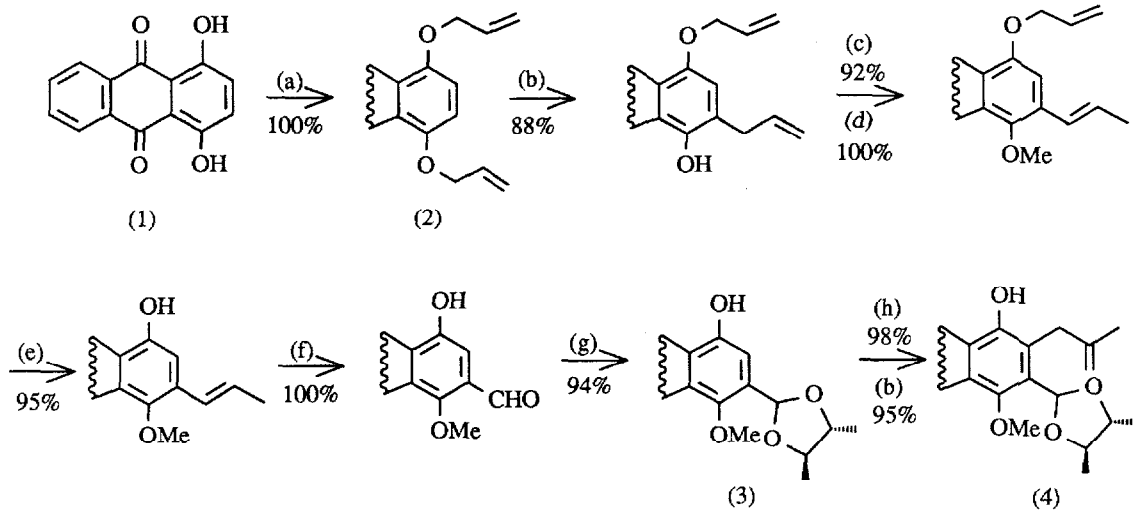
E.G. Brown, R.C. Cambie, S.E. Holroyd, M. Johnson, P.S. Rutiedge*, and P.D. Woodgate

Department of Chemistry, University of Auckland, New Zealand

Abstract: ***Quinizarin is converted in seven steps into the homochiral acetal (3) in 69% yield. Methallylation of (3) and reductive Claisen rearrangement gives (4) which is converted into four novel diastereomeric 9-chloroanthracyclines (7-10) by an unprecedented intramolecular acetal-alkene cyclization mediated by tin(IV) chloride in DMF.***

Recently we reported a synthesis of (±)-4-demethoxydaunomycinone in 29% overall yield from quinizarin (1).[1] During studies aimed at asymmetric syntheses of 4-demethoxyanthracyclinones we have found an unprecedented intramolecular acetal-alkene cyclization wherein the homochiral acetal (4) is converted into four novel diastereomeric 9-chloroanthracyclines.

The homochiral acetal (3) was prepared in 69% overall yield from quinizarin in seven steps (Scheme 1)

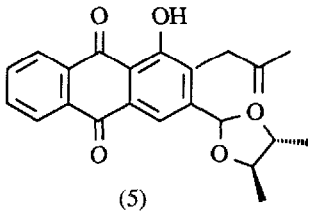


(a) CH_2=$CHCH_2Br/K_2CO_3$/DMF/55°/16h (b) $Na_2S_2O_4$/DMF/H_2O/60-70°, 90 min (c) $Me_2SO_4/K_2CO_3Me_2CO$/18 h (d) KOH/MeOH (e) HOAc/H_2SO_4/H_2O (25:1:2), reflux, 35 min (f) $OsO_4.HIO_4$ (g) (2R,3R)-2,3-butanediol/*p*-TsOH (h) $ClCH_2C(Me)$=CH_2/K_2CO_3/KI/DMF/70°, 9h

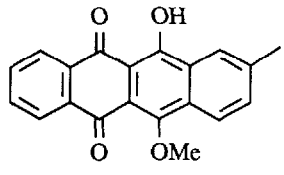
Scheme 1

via a sequence involving a controlled reductive mono-Claisen rearrangement[2] of the bis-allyl ether (2). Methallylation of the phenol (3) with 3-chloro-2-methylpropene[3] gave an isopropenyl ether which on optimised reductive Claisen rearrangement with $Na_2S_2O_4$ (1 equiv.) afforded the key intermediate (4). Use of an excess of the reducing agent (1.5 equiv.) gave the demethoxy product (5) (43%) (cf. ref. 4) and compound (4) (48%).

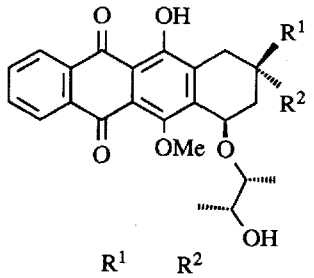
Treatment of the acetal (4) in CH_2Cl_2 with a mixture of $SnCl_4$ (10.5 equiv.) and DMF (10 equiv.) at -78° yielded the four 9-chloroanthracyclines (7-10) (70%) in a ratio of 1:2.5:8.4:2.7 in addition to the aromatic product (6) (7%). The chlorotetracycles were separated by h.p.l.c. [Lichrosorb, $CHCl_3$/THF (99:1)], characterised by h.r.m.s., ^1H- and ^{13}C n.m.r. spectra, and assigned structures from an examination of coupling constants and n.o.e. effects in the 400 MHz ^1H n.m.r. spectra. Cyclization of the acetal (4) in CH_2Cl_2 in the absence of DMF gave a much lower yield (35%) of the chloroanthracyclines and a higher yield of (6) (48%) at 0°, while no reaction took place at -23°. The rate enhancement by DMF and the cyclization to give chlorine-containing products are both unprecedented in related cyclizations reported to date.[5]



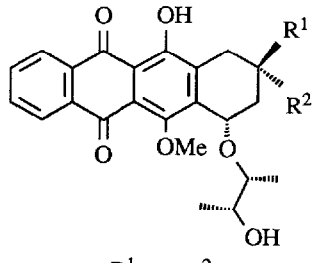
(5)



(6)



	R^1	R^2
(7)	Me	Cl
(8)	Cl	Me



	R^1	R^2
(9)	Me	Cl
(10)	Cl	Me

REFERENCES

1. Cambie, R.C.; Larsen, D.S.; Rickard, C.E.F.; Rutledge, P.S.; and Woodgate, P.D. *Aust. J. Chem.*, **1986**, *39*, 487.
2. Boddy, I.K.; Boniface, P.J.; Cambie, R.C.; Craw, P.A.; Larsen, D.S.; McDonald, H; Rutledge, P.S.; and Woodgate, P.D. *Tetrahedron Lett.*, **1982**, *23*, 4407.
3. Whereas allylation reactions are greatly facilitated by the use of DMF, this solvent interferes with methylation using Me_2SO_4.
4. Hauser, F.M.; and Hewawasam, P. *J. Org. Chem.*, **1988**, *53*, 4515.
5. Mukaiyama, T.; and Murakami, M. *Synthesis*, **1987**, 1043.

(Received in UK 23 June 1989)