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LEWIS ACID MEDIATED CYCLIZATION OF *ORTHO*-ALLYL SUBSTITUTED HOMOCHIRAL ANTHRAQUINONE DIOXOLANES

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Abstract: Tin(IV) chloride N,N-dimethylformamide and titanium(IV) chloride mediated cyclizations of *ortho*-allyl-substituted homochiral hydroxyanthraquinone acetals results in high diastereoselection in the generation of two stereocentres.

Asymmetric synthesis of substituted cyclohexanes by Lewis acid-mediated intramolecular addition of an alkene to an acetal derived from a homochiral diol is still a relatively under-utilised process.[1] While investigating the potential of such reactions for syntheses of novel anthracyclines we showed that modest diastereoselectivity could be achieved in the development of chirality at both the masked carbonyl carbon of the acetal and a prochiral carbon of the alkene.[2] Thus, tin(IV) chloride-N,N-dimethylformamide induced cyclization of (1) resulted in a significant predominance of (6) over its three diastereomers (4), (5), and (7). This result prompted us to investigate further the synthetic potential of such reactions, and results are presented in the Table.

Table: Cyclizations of Methallyl Dioxolanes

Dioxolane	Reagent	Products (%)[A]									
1	$SnCl_4$/dmf/-78°	**4**	5	**5**	12	**6**	40	**7**	13	**16**	7
1	$TiCl_4$/-78°	**4**	18	**5**	6	**6**	10	**7**	6	**16**	4
2	$SnCl_4$/-78°	**8**	13	**9**	4	**10**	65	**11**	4	**17**	7
2	$TiCl_4$/-78°	**8**	20	**9**	0	**10**	50	**11**	0	**17**	15
1	$BF_3.OEt_2$/-78°	**12**	10	**14**	6					**16**	33
2	$BF_3.OEt_2$/-78°	**13**	12	**15**	10					**17**	13

[A] All products were separated by p.l.c. and their stereochemistry assigned from high field n.m.r. studies.

The results establish that use of an excess of titanium(IV) chloride induces a similar cyclization of (1), but with a reversal of the stereoselectivity in the cleavage of the acetal C-O bond so that the diastereomer (4) rather than (6) becomes predominant. This difference indicates that use of the more acidic titanium reagent favours chelation-controlled[3] opening of the dioxolane ring[4] which is directed by the adjacent methoxy group. Moreover, we have optimised a synthesis of the 4-demethoxy analogue (2),[2] and have established that its cyclization using either tin(IV) chloride-N,N-dimethylformamide or titanium(IV) chloride favours formation of the *cis*-diastereomer (10).

Cyclization via an S_N2 - like process in which the dioxolane ring is maintained in an ion pair intermediate is the suggested pathway when either tin(IV) chloride or titanium(IV) chloride is used at -78°. Thereafter, the direction of attack of chloride at C 9 would appear to be governed largely by the orientation of this ion pair. The lowered stereoselectivity at both C 7 and C 9 when there is an adjacent methoxy group on the anthraquinone may be due to multidentate co-ordination of the Lewis acid involving the quinone carbonyl, the methoxy oxygen, and the acetal oxygens. Boron trifluoride etherate induced cyclizations of either (1) or (2) proceed without useful stereoselection, but each gives a pair of novel stereoisomeric dioxepins (12 and 14) and (13 and 15) in addition to naphthacenediones (16 or 17). In these cases cyclization probably involves a free oxocarbenium ion.

The high diastereoselection achieved in the opening of the dioxolane ring of (2) and the excellent 1,3-asymmetric induction achieved in the generation of two stereocenters in the formation of (10) indicates that such cyclizations hold considerable promise for asymmetric synthesis of novel anthracyclines of potential chemotherapeutic value. The ability to modulate the stereoselectivity by utilizing chelation or non-chelation control further broadens this potential.

References

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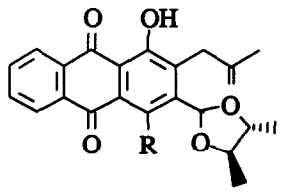
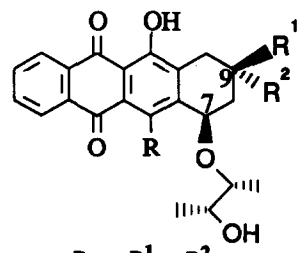
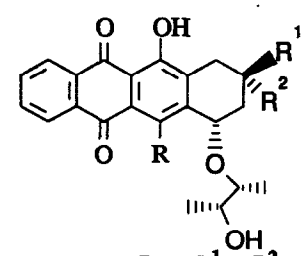
4. For chelation control of acetal opening see Corcoran, R.C., *Tetrahedron Lett.*, 1990, **31**, 2101.



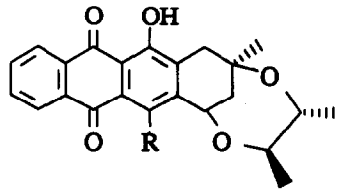
(1) R = OMe
(2) R = H



	R	R^1	R^2
(4)	OMe	Me	Cl
(5)	OMe	Cl	Me
(8)	H	Me	Cl
(9)	H	Cl	Me



	R	R^1	R^2
(6)	OMe	Me	Cl
(7)	OMe	Cl	Me
(10)	H	Me	Cl
(11)	H	Cl	Me



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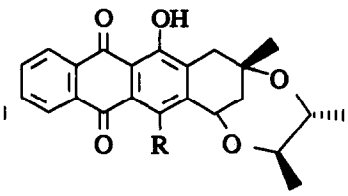

(14) R = OMe
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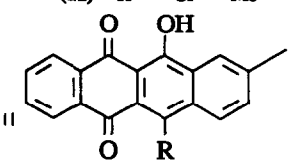

(16) R = OMe
(17) R = H

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