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ALLYLIC VS HOMOALLYLIC CONTROL OF STEREOSPECIFICITY IN THE EPOXIDATION OF 3(1'-HYDROXYETHYL)-5,8-DIMETHOXY-1,2-DIHYDRONAPHTHALEN-1-OL: IMPLICATIONS FOR THE SYNTHESIS OF CHIRAL ANTHRACYCLINES

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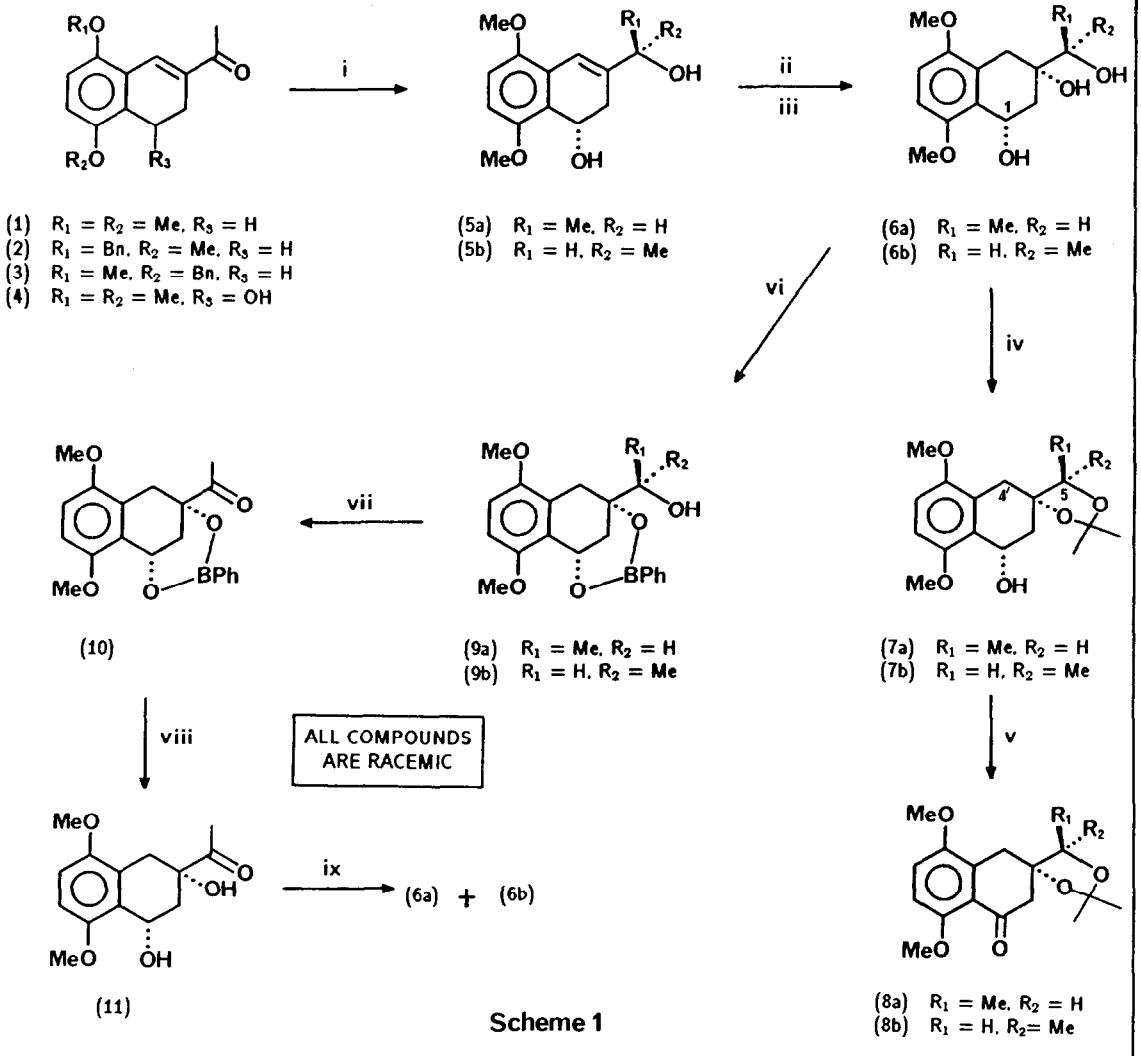
ABSTRACT: The stereochemistry of the epoxidation of the title compound with t-BuOOH catalysed by $VO(acac)_2$ is subject to exclusive homoallylic control. Secondary allylic alcohols in the side chain regain their normal controlling influence over diastereoselection only when the homoallylic group is blocked.

The epoxidation of the chiral α,β-unsaturated alcohols (1)–(3) with *t*-BuOOH and $VO(acac)_2$ [1] has provided a convenient entry to optically pure 7-deoxyanthracyclines,[2] but to date no attempts to prepare molecules bearing the final benzylic hydroxyl group by this method have been reported. Recent reports by Rodrigo[3] and Snieckus[4] have shown that the ketone (4) can be readily prepared, and can serve as an efficient intermediate in the synthesis of racemic daunomycin. Our interest in chiral anthracyclines[2,5] prompted an investigation of (4) as a possible intermediate in the synthesis of optically pure anthracycline precursors. Unlike previous intermediates, the alcohols (5) possess alcohol groups in both allylic and homoallylic positions. Although literature precedent exists for epoxidation of both allylic[1] and to a lesser extent homoallylic alcohols[1,6] under Sharpless conditions, no study of a system in which both groups co-exist has been reported. We have examined the nature of the diastereoselectivity in the epoxidation of (5), and in this communication report our findings in this area.

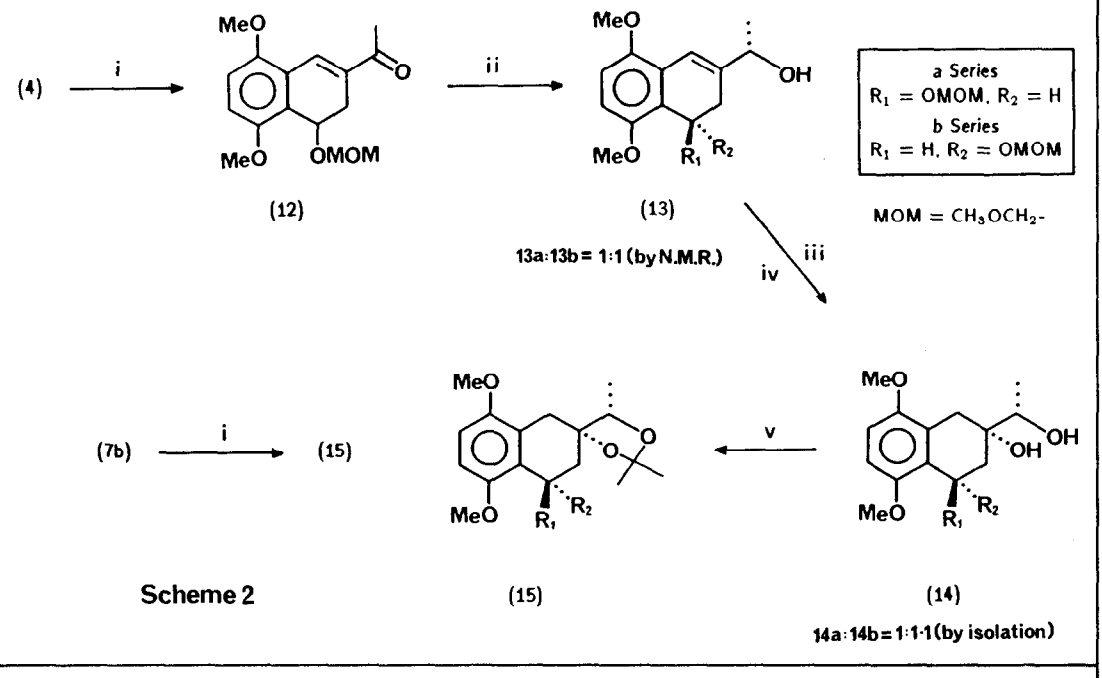
Reduction of (±)-(4) [7] with sodium borohydride in ethanol gave a mixture of the racemic diastereoisomers (5a) and (5b) in 94% yield. Direct epoxidation of this mixture with *t*-BuOOH in the presence of $VO(acac)_2$ followed by reduction with $LiAlH_4$ in ether afforded an 89% yield of the triols[8] (6a) and (6b). In separate experiments it was shown that (5a) was converted stereospecifically to (6a), and similarly (5b) to (6b). Proof of the structures of the resulting triols rested on two series of chemical transformations (Scheme 1). Thus, a mixture of (6a) and (6b) was converted into the two acetonides (7a) and (7b) which upon oxidation[9] afforded two ketones (8a) and (8b), differing only in the stereochemistry of the C-5 position.[10] Proof of this latter point was obtained from N.O.E. experiments based on the method of Ogawa[11]. Irradiation of the C-5 methyl doublet in (7b) showed an enhancement of the signals of one of the C-4′ protons, whilst a similar experiment conducted on (7a) showed no enhancement of the H4′ signals.[12]



Scheme 1

Reagents and Conditions: (i) $NaBH_4$, EtOH, 1.25 h, r.t.; (ii) *t*-BuOOH-VO(acac)$_2$, C_6H_6; (iii) $LiAlH_4$, Et_2O, 1 h reflux; (iv) 2,2-dimethoxypropane, PyOTs, CH_2Cl_2-DMF, 4 h, r.t.; (v) PCC, 3A molecular sieve, CH_2Cl_2, r.t. 1 h; (vi) $PhB(OH)_2$, TsOH, $PhCH_3$, 2 h, r.t.; (vii) PCC, 3A sieve, CH_2Cl_2, 30° 1 h; (viii)2-methylpentane-2,4-diol, HOAC, CH_2Cl_2, 24 h r.t.; (ix) $NaBH_4$, EtOH, 1 h, r.t.

The *cis* relationship between the hydroxyls at C-1 and C-3 was established by converting a mixture of (6a) and (6b) to the cyclic phenylboronates (9a) and (9b) (97%). Oxidation[9] of this latter mixture afforded a single ketone (10) (91%), which upon deprotection[13] yielded the related diol (11), with a defined *cis* relationship between the C-1 and C-3 hydroxyl groups. Reduction of (11) with sodium borohydride in ethanol regenerated (6a) and (6b) in 94% yield. The *cis* stereochemistry of the 1,3-diol moiety in both (6a) and (6b) can only arise if the face at which epoxidation occurs in (5a) or (5b) is *syn* to the homoallylic alcohol. In addition the activation of the olefinic bond can be demonstrated by the epoxidation of the α,β-



Scheme 2

Reagents and Conditions: (i) CH_3OCH_2Cl, iPr_2NEt, CH_2Cl_2, 2 h, r.t.; (ii) $NaBH_4$, EtOH, 1.5 h, r.t.; (iii) *t*-BuOOH, $VO(acac)_2$, C_6H_6; (iv) $LiAlH_4$, Et_2O, reflux, 1 h; (v) 2,2-dimethoxypropane, PyOTs.

unsaturated ketone (4). Although this reaction is slower than that of the related alcohols (5), the fact that a reaction occurs at all is significant since the ketones (1)-(3), lacking the C-1 hydroxyl group, proved totally inert to the Sharpless epoxidation conditions. Indeed, direct epoxidation of (4) followed by hydride reduction affords a convenient and rapid route to the triols (6).

These results clearly demonstrate that an extension of Terashima's application[2] of diastereoselective epoxidation to a synthesis of chiral fully oxygenated daunomycin precursors demands that the C-1 hydroxyl group in (5) be protected to prevent participation in the reaction. In complete agreement with this expectation, hydroxy ketone (4) was converted into its methoxymethyl ether (12), and the carbonyl group reduced to afford a mixture of allylic alcohols (13a) and (13b). Epoxidation (Scheme 2) and subsequent reduction of this mixture gave a separable mixture of diols (14a) and (14b). Proof of the diol structures was again provided by conversion to the acetonides (15), each of which showed an N.O.E. consistent with a common relative stereochemistry in the dioxolan ring. As a final structural proof, conversion of the alcohols (7a) and (7b) to their respective methoxymethyl ethers demonstrated that the product derived from (7b) related to (15b), confirming the *cis* disposition of the 1,3-oxygens. Derivative (15a) was therefore established as having *trans* disposition of the 1,3-oxygens.

As noted above, this report represents the first study of the vanadium catalysed hydroperoxide epoxidation of a molecule in which an allylic alcohol co-exists with a homoallylic alcohol. The results indicate that in this system, the latter exerts a directing influence which totally dominates that of the allylic alcohol. The study also provides clear guidelines for application of this methodology to the synthesis of chiral anthracyclines. Our extension and application of these results will be reported elsewhere.

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[7] All new compounds gave satisfactory combustion analyses and spectroscopic data. All products are racemic.

[8] Mixtures were separated by centrifugal preparative layer chromatography. Compound (M.p.°C) **5a** (106–8), **5b** (112–5), **6a** (115–6), **6b** (156–9), **7a** (142–4), **7b** (122–3), **8a** (130–1), **8b** (122–3), **10** (101–3), **11** (94–5), **12** (97–8), **14a** (126–8), **14b** (108.5–109.5), **15a** (144–5), **15b** (syrup).

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[10] In accordance with IUPAC rules, the numbering for the acetonides changes from the related ketones. Details are shown on figures.

[11] Ogawa, Y., Mori, H., Yamada, N. and Kon, K., *J. Antibiotics*, 1984, **37**, 44.

[12] A small apparent enhancement of a H-2′ resonance was observed upon irradiation of the C-5 methyl doublet of (7a). Instrumental limitations due to the proximity of this signal to the irradiated doublet rendered this result inconclusive. However the stereochemical disposition of the C-5 and C-3′ hydroxy groups in (7a) may be inferred from the formation of a different ketone (8a) upon oxidation to that formed from (7b).

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