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STEREOSELECTIVE EPOXIDATION OF HYDROXYENONES. THE SYNTHESIS OF THE SIDECHAIN OF CLEROCIDIN

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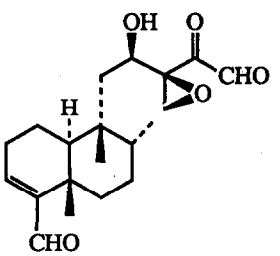
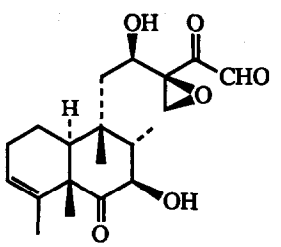
ABSTRACT: *The sidechains of clerocidin 1 and terpentecin 2 contain a unique chiral assembly [$C_5H_5O_4$]. Models for the stereospecific synthesis of this structural feature are reported.*

The fungal metabolites clerocidin **1**[1] and terpentecin **2**[2] are both associated with a highly oxygenated sidechain which incorporates a unique assembly of five carbon atoms connected to four oxygen atoms. The natural carbobicyclic clerodane diterpenoids **1** and **2** exhibit antibiotic and antitumour activities which may well be associated with their sidechain.[3] In connection with our structure–activity studies, we required a flexible route directed towards clerocidin **1** and its structural analogues. The synthesis of suitable precursors of the carbobicyclic decalin portion has been completed.[4]

We now report on [i] an examination of diastereoselection in the epoxidation of chiral hydroxyenones **5** yielding the ***syn***[5]-epoxides **6** and the ***anti***[5]-epoxides **7** and [ii] approaches towards the diastereospecific synthesis of the model compound **3**.



1 – Clerocidin



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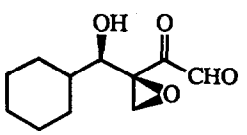
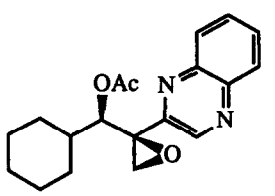


3

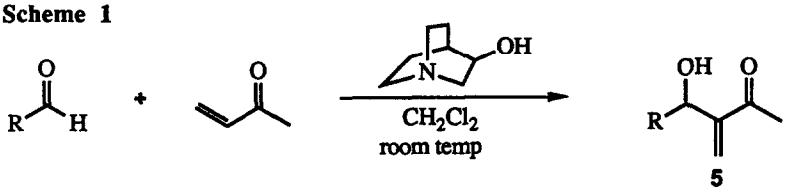


4

Hydroxyenones **5** are readily available from aldehydes and methylvinyl ketone by the Baylis–Hillman reaction[6] [Scheme 1]. As reported by Drewes, Freese, Emslie, and Roos,[7] we have also found that

3–hydroxyquinuclidine is a more efficient catalyst than quinuclidine or DABCO.[8] The key transformation [5 → *syn*–epoxides **6** + *anti*–epoxides **7**] [Table 1] may be regarded as a hybrid of Sharpless epoxidation[9] of allylic alcohols and Weitz–Scheffer epoxidation[10] of αβ–unsaturated ketones. At first sight these two reactions are incompatible: the Sharpless epoxidation of allylic alcohols is not normally achievable when the alkene bears electron-withdrawing substituents, whereas the Weitz–Scheffer reaction involves nucleophilic attack by peroxy-anions [H—O—O⁻ or R—O—O⁻] upon the alkene which is polarised by one or more electron–withdrawing substituents. We have now established that chiral hydroxyenones **5** are, in fact, smoothly epoxidised under Sharpless reaction conditions and that the transformation is remarkably diastereoselective. This extension of Sharpless methodology has interesting synthetic and mechanistic implications.

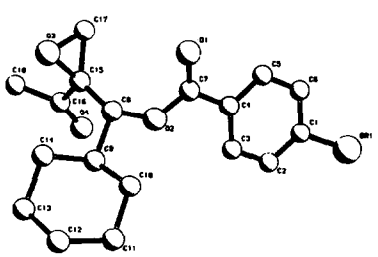
Scheme 1



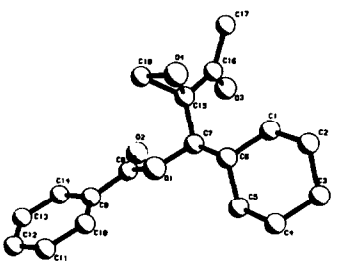
5

	R	Yield
5a	Me	72%
5b	Et	66%
5c	i-Pr	62%
5d	c-Hexyl	51%

Epoxidation of these hydroxyenones **5a** - **5d** has been examined under a variety of conditions. No oxidation was observed with *m*-chloroperbenzoic acid [entry 4]. However, epoxidation of the racemic hydroxyenones [**5a** - **5d**] proceeded normally under the base–catalysed conditions associated with the Weitz–Scheffer reaction [entries 1 - 3]. The products were mixtures of the racemic ***syn***[5]-epoxides **6** and ***anti***[5]-epoxides **7**. Under these conditions [entries 1 - 2] or by chiral phase-transfer catalysis[11] [entry 3], the formation of the ***anti***-epoxides **7** was slightly favoured. The relative configurations of the ***syn***-epoxide **6d** and the ***anti***-epoxide **7d** were established by their conversion into the crystalline derivatives whose *X*-ray crystal structures are shown below. The ***syn***-epoxide **6d** and the ***anti***-epoxide **7d** were used as reference compounds for the assignment of relative configuration to the epoxides **6a** - **6c** and **7a** - **7c** by comparison of their ^{1}H-NMR spectra.

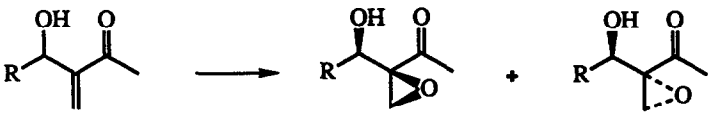


6d-*p*-bromobenzoate
[m.p. 71–73 °C]



7d-benzoate
[m.p. 79–80 °C]

Table 1



5 6 7

Entry	R	Conditions	Yields	Syn-6 / Anti-7
1	c-Hexyl	H_2O_2 / NaOH / MeOH / 0°C	76%	40 : 60
2	c-Hexyl	TBHP / NaOH / MeOH / -40°C	70%	33 : 67
3	c-Hexyl	BQBr[a] / CHP[a] / Tol / NaOH / -20°C[11]	78%	40 : 60
4	c-Hexyl	mCPBA / CH_2Cl_2 / 20°C / 3 days	–	–
5	c-Hexyl	$Ti(Oi\text{-}Pr)_4$ / TBHP / CH_2Cl_2 / -15°C	78%	100[b]
6	Me	$Ti(Oi\text{-}Pr)_4$ / TBHP / CH_2Cl_2 / -15°C	63%	100[b]
7	Et	$Ti(Oi\text{-}Pr)_4$ / TBHP / CH_2Cl_2 / -15°C	72%	100[b]
8	i-Pr	$Ti(Oi\text{-}Pr)_4$ / TBHP / CH_2Cl_2 / -15°C	70%	100[b]

a : BQBr = N-benzyl quininium bromide and CHP = cumyl hydroperoxide

b : the ***anti***-diastereoisomer **7** was not detected (^{1}H NMR) in the crude reaction product

In remarkable contrast with the low diastereoselectivity exhibited in the favoured formation of the *anti*–epoxides **7** [Table 1, entries 1–3], **the diastereospecific formation of *syn*-epoxides 6 was observed under Sharpless conditions** [Table 1, entries 5 - 8]. The presence of the allylic hydroxyl group is essential for the success of this ***syn***-epoxidation. No reaction was observed in the attempted Sharpless epoxidation of the *O*-trimethylsilyl derivative of hydroxyenone **5d**. We propose that coordination of the titanium atom to the allylic hydroxyl and to the carbonyl oxygen atom generates a six–membered chelate in which the titanium atom is also coordinated to the hydroperoxide. Internal oxygen atom transfer in this organo-titanium intermediate then leads **stereospecifically** to the ***syn***-epoxides **6**. The possibility of kinetic resolution of racemic **5** leading to the **enantiospecific** formation of ***syn***–epoxides **6** using enantiomerically pure chiral Sharpless reagents is under experimental scrutiny.

Oxidation [SeO_2, dioxan, b.p., 24 h] of the *O*-acetate of the ***syn***-epoxide **6d** gave the corresponding *O*-acetate of the model compound **3**, which was characterised as the quinoxaline derivative **4** [m.p. 107–109 °C].

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