Pergamon

Tetrahedron Letters 39 (1998) 8495–8498

TETRAHEDRON LETTERS

Synthesis Of Optically Active 2,3-Substituted-1,2,3,4-tetrahydro-4-quinolones Using Polyleucine

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Received 22 April 1998; accepted 15 June 1998

Abstract: Polyleucine catalyzes the asymmetric epoxidation of enone (**1**) in a non-aqueous medium to provide epoxy-ketones (**2**) and (**3**) (81 and 84% yields respectively ; >98% *ee*). The epoxy-ketones (**2**) and (**3**) are subsequently cyclized to give 1,2,3,4-tetrahydro-4-quinolones (**4**) and (**5**) respectively.

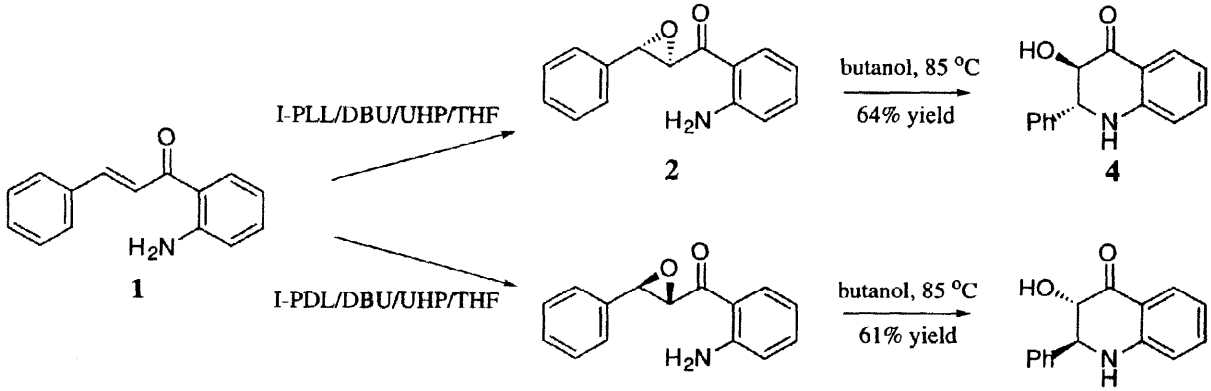
Asymmetric epoxidation reactions catalyzed by polyamino acids were discovered by Juliá and Colonna in the 1980's.[1] Their work showed that a variety of different chalcones could be oxidized to optically active epoxides in high yield and excellent enantiomeric excess[2] using a *three-phase* system comprising poly-(L)-alanine (or poly-(L)-leucine), aqueous hydrogen peroxide / NaOH and an organic solvent. We found that a *two-phase* oxidation system involving poly-(L)-leucine, urea hydrogen peroxide (UHP) in an organic solvent containing DBU was much more efficient.[3] For example chalcone (0.5 g) was oxidized using UHP (1.2 equivalent), DBU (0.3 equivalent) in THF (2.5 mL) with poly-(L)-leucine (100 mg) as catalyst to give epoxide (≥90 % *ee*) in 2.3 h. Since the molecular weight of the catalyst is *ca.* 2500,[4] the catalyst turnover is *ca.* 50 and the turnover frequency *ca.* 25 in this reaction.

Given the simplicity and ease of operation of this new oxidation system we were anxious to investigate the use of a variety of substrates in this new reaction medium[5] and to try and expand the use of polyamino acids in synthesis,[6] for example the preparation of heterocyclic compounds such as 2-aryltetrahydroquinolones, as described herein.

The initial interest in 2-aryl-1,2,3,4-tetrahydroquinolones was generated by de Diebach and Kramer in 1945.[7] To date only limited information exists in the literature concerning the potential of 2'-aminochalcones (**1**) to serve as precursors for 2-aryl-3-substituted-4-quinolones in racemic form.[8,9] We wondered whether the epoxides (**2**) and (**3**) could be made in high enantiomeric excess from the aminochalcone (**1**) using Juliá-Colonna methodology and whether subsequent cyclization of each epoxide would result in the formation of only one diastereomer of the target compound.

0040-4039/98/$ - see front matter
PII: S0040-4039(98)01249-0

Aminochalcone (**1**) was synthesized using an aldol condensation. Asymmetric epoxidation of (**1**) using immobilised poly-(L)-leucine (I-PLL) or poly-(D)-leucine (I-PDL) under the new biphasic reaction conditions gratifyingly furnished the epoxides (**2**) and (**3**) respectively in 81-84% yield and > 98% *ee*. These epoxides were cyclized in hot butanol to afford the 2,3-disubstituted-1,2,3,4-tetrahydro-4-quinolones (**4**) and (**5**) in good yield and >98% *de* (scheme 1). The orientation of the hydroxy and phenyl substituents on the heterocyclic ring could not be determined by NMR spectroscopy.[10] However, an X-ray structure determination[11] of quinolone (**4**) (m.p. 186 °C) surprisingly[9] revealed a *trans*-configuration which shows that the new ring was formed with inversion of configuration at C-2. It is also of interest to note that in the solid state the molecules related by a 2-fold screw axis are held together by strong hydrogen bonds [O1-H1=0.93, H1···O2=1.87, O1···O2=2.77Å and <O1-H1···O2=163°] and this produces a helix along the *b*-axis (figure 1).



Scheme 1

The rate and stereoselectivity observed in the oxidation of aminochalcone (**1**) into the epoxide (**2**) was somewhat unexpected given that electron-donating substituents usually slow down the Juliá-Colonna reaction. For example, 4'-methoxychalcones epoxidize relatively slowly under the biphasic conditions[12] while poly-(L)-alanine-catalyzed epoxidation of 2'-methoxychalcone under triphasic conditions gives the corresponding oxirane in only 54% yield and 50% *ee*.[13] Indeed, in a series of experiments (table 1), we found that 2'-aminochalcone (**1**) was oxidized at a rate and with a selectivity more akin to systems containing electron-withdrawing substituents (**6**,**7**). In contrast 2'-methylaminochalcone (**10**) did not epoxidize completely in 7 hours but gave an *ee* of 96%, while 4'-aminochalcone (**11**) was not epoxidized at all.[14] The "ortho-amino" effect is also observed on comparing the two chlorine-containing chalcones (**12**) and (**13**).

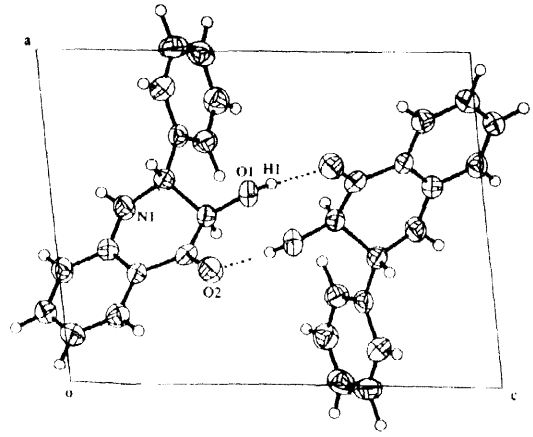


Figure 1
Crystal Structure of (**4**) showing the hydrogen bonded helix along *b*.

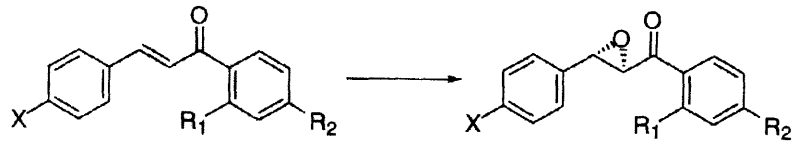


Table 1 Epoxidation of Various Chalcones under Juliá-Colonna Biphasic Conditions[a]

Compound	R^1	R^2	X	Yield (%)	Enantiomeric Excess[b] (%)	Rate (Time to completion in hours)
1	NH_2	H	H	81	>98	2.0
6	NO_2	H	H	91	91	1.0
7	Cl	H	H	90	89	0.75
8	CH_3	H	H	94	81	1.5
9	$NHCOCF_3$	H	H	59	91	3.5
10	$NHCH_3$	H	H	62	96	62 % conversion after 7 h
11	H	NH_2	H	----	----	no reaction after 4 h
12	H	H	Cl	62	62	(c)
13	NH_2	H	Cl	91	>98	2.0

(a) Typical reaction conditions were as follows: I-PLL (0.10 g), THF (0.90 mL), DBU (0.040 mL, 0.27 mmol) and urea hydrogen peroxide (0.023 g, 0.25 mmol) were placed in a 5 mL flask and stirred at room temperature for 15 minutes, at which time the chalcone (0.22 mmol) was added, then the reaction was allowed to stir at room temperature until completion. (b) Estimated by HPLC using a Chiralpak AD column (error ±2%). (c) Triphasic reaction conditions.

We speculate that the *ortho*-amino group, through hydrogen bonding (figure 2), fixes the conformation of the aryl substituent, allowing the substrate better to approach the nucleophile such that the stereochemistry-defining attack at C-3 takes place from the *si*-face. The presence of an *N*-methylamino substituent at the same position orients the molecule in the same way (hence the high stereoselectivity) but the extra alkyl substituent experiences unfavourable steric interactions (hence the very low rate of reaction).

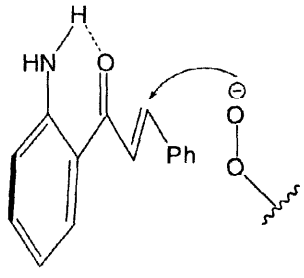


Figure 2

In summary, incorporation of an *ortho*-amino substituent into the arylketone moiety of a chalcone may be useful in enhancing the optical purity of products derived from a Juliá-Colonna oxidation. The epoxides produced in such a process readily form optically pure 2,3-trans-disubstituted tetrahydroquinolones.

Acknowledgements. We would like to thank the EPSRC, the DTI, Glaxo-Wellcome and Chiroscience LINK Fellowship programme for funding this work, and in particular, Drs G. Tughan and R. McCague for useful discussions.

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10. NMR data for (**4**): δ_H (300 MHz, $CDCl_3$) 3.69 (1H, br s, OH), 4.41-4.68 (2H, m), 6.68 (1H, d, J = 7.9 Hz), 6.81 (1H, t, J = 7.9 Hz), 7.28-7.63 (6H, m), 7.89 (1H, d, J = 7.9 Hz); δ_C (75 MHz, $CDCl_3$) 64.8, 75.5, 115.7, 118.7, 127.9, 128.0, 128.9, 129.0, 136.2, 138.4, 151.5, 194.9.
11. Crystal data for (**4**): Formula $C_{15}H_{13}NO_2$, M.W.=239.26, monoclinic, space group $P2_1$ (no.4), a=9.043(3), b=5.6770(12), c=11.5645(11)Å, β=94.986(7)°, U=591.4(2)Å^3, Z=2, D_c=1.344 Mg/m^3, μ(Mo-Kα)=0.09 mm^{-1}, F (000)=252, crystal size = 0.30x0.20x0.20 mm, T=293(2) K. The intensity data were collected on a FAST area detector diffractometer. The structure was solved by direct methods and refined on F^2 by full-matrix least-squares (non-H atoms anisotropic, H-atoms isotropic) to final R_1=0.0444 and wR_2=0.0943 for 1552 unique data and 215 parameters. Full details have been deposited with the Cambridge Crystallographic Data Centre.
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