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Poly-L-leucine Catalysed Epoxidation Reactions : A Short, Stereoselective Route to Chiral α,β-Epoxyalcohols

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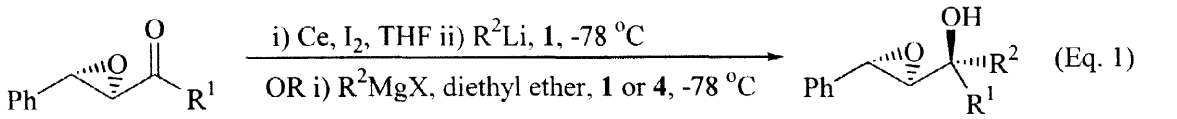
Abstract : Grignard alkylation of epoxyketones (**1**), (**4**) from Poly-L-leucine catalysed asymmetric epoxidation of α,β-unsaturated ketones provides a short, stereocontrolled route to optically pure α,β-epoxy tertiary alcohols (**2**), (**3**). These epoxyalcohols undergo Payne rearrangement in mild Lewis acid conditions to give the isomeric α,β-epoxy secondary alcohols (**5**), (**6**). Alternatively, the epoxide may be opened up in a highly regio- and stereospecific manner to give polysubstituted 1-chloro-2,3-diols (**7**), (**8**).

The synthetic value of optically pure α,β-epoxyalcohols has been widely demonstrated.[1] Although the Katsuki-Sharpless asymmetric epoxidation of allylic alcohols is the most obvious method for their preparation, it is not usually successful for the epoxidation of tertiary allylic alcohols.[2] The epoxidation of α,β-unsaturated ketones by poly-L-leucine[3] allows the possibility of a diastereoselective alkylation of the ketone functionality to give the desired epoxy tertiary alcohol in two steps. It was anticipated that the epoxide ring would play a significant rôle in the diastereoselectivity of the alkylation step due to its electronic and steric properties. The epoxyalcohols may then be manipulated in one of two ways. First, the stereospecific Payne rearrangement would provide the isomeric α,β-epoxy secondary alcohol whilst maintaining the stereochemical integrity of the molecule. Secondly, the epoxide could be opened up in a stereocontrolled manner to introduce further functionality in the molecule.

Two types of reagent were considered for the alkylation step; namely Grignard reagents and organocerium reagents[4]. Epoxychalcone (**1**) was alkylated with the butyl and methyl equivalents of both types of reagent to investigate the influence of the epoxide on the diastereoselectivity (Eq. 1, table 1).



(Eq. 1)

1 R^1 = Ph

4 R^1 = Me

2a R^1 = Ph, R^2 = Me **2b** R^1 = Me, R^2 = Ph

3a R^1 = Ph, R^2 = Bu **3b** R^1 = Bu, R^2 = Ph

2b R^1 = Me, R^2 = Ph **2a** R^1 = Ph, R^2 = Me

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Table 1. Diastereoselectivity in the Alkylation Step.

Reagent	R'	Time (h)	Yield (%)	Selectivity a:b
1: MeLi-CeI_3[3]	Ph	2	91	4 : 1
2: *n*-BuLi-CeI_3	Ph	2	80	9 : 1
3: MeMgI	Ph	1.5	89	>99 : 1
4: BuMgBr	Ph	4	60	>99 : 1
5: Ph MgBr	Me	1.5	70	6 : 1

The organocerium reagents (entries 1 and 2) afforded the desired alcohols in high yields but the observed diastereoselectivities were disappointing. It was found with these reagents that if the reaction was left for too long, decomposition or further reaction of the first-formed products occurred. The Grignard reagents gave superlative diastereoselectivities (entries 3 and 4) and in the case of MeMgI the yield was also excellent (the low yield for BuMgBr was due to the competing side-reaction of β-hydrogen abstraction from the Grignard reagent to give the corresponding secondary alcohol). In order to obtain diastereomer **2b** as the major product, 1,2-epoxy-1-phenylbut-2-one (**4**) was reacted with PhMgBr; the diastereoselectivity of this reaction was modest (entry 5). The excellent diastereoselectivity of the Grignard reaction in cases 3 and 4 suggests that the addition is chelation controlled. Coordination of the magnesium to both the ketone oxygen and the epoxide oxygen in a pseudo-chair transition state leaves one face of the ketone open to attack from another molecule of Grignard reagent. This proposed transition state is consistent with the relative stereochemistry proved by the crystal structure of **3a** (figure 1). The poorer diastereoselectivity of the Grignard addition to **4** may be attributed to the smaller cone angle submitted by the methyl substituent compared with the phenyl which may allow attack to occur on the other side of the ketone.

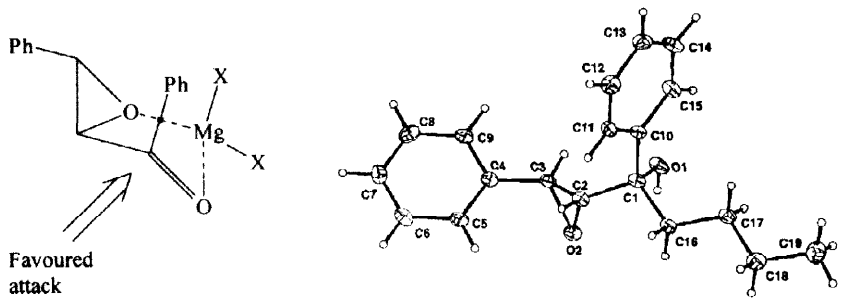
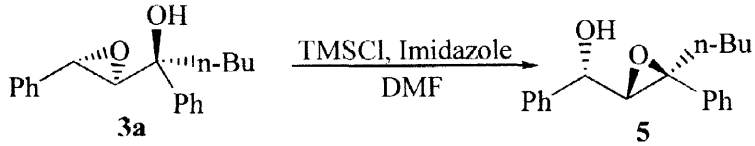


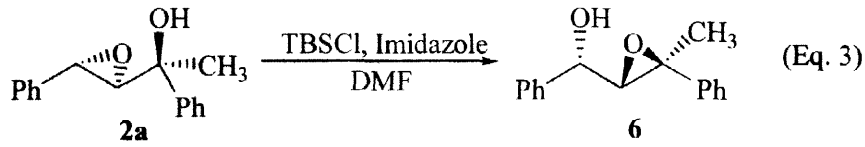
Figure 1 - Proposed transition state and crystal structure of 3a

Payne Rearrangement. Although a Payne rearrangement sets up an equilibrium between two isomeric epoxyalcohols, it was anticipated that in the case under consideration, the yield of the desired product would be high since the equilibrium was expected to lie on the side of the more substituted epoxide. No rearrangement of **3a** occurred under standard basic conditions; however, it was found that the Payne rearrangement of this compound could be induced under mild Lewis acid conditions. Thus epoxy alcohol **3a** was treated with trimethylsilyl chloride (TMSCl) and imidazole in DMF to give the isomeric α,β-epoxy secondary alcohol **5** in 80 % yield (Eq. 2). Interestingly, the product was formed as the free alcohol and not the TMS ether.



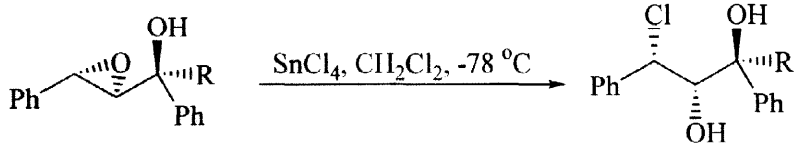
(Eq. 2)

Treatment of the less sterically encumbered tertiary alcohol (**2a**) with TMSCl and imidazole gave the silyl ether. However, Payne rearrangement of **2a** was achieved using the bulkier silicon reagent *tert*-butyldimethylsilyl chloride (TBSCl) to furnish **6** in 69 % yield.



2a **6** (Eq. 3)

Epoxide opening. There are many examples of metal halide mediated epoxide ring openings[5] and chloride migration from $TiCl_4$ has also been reported.[6] Epoxyalcohol **3a** was treated with $TiCl_4$ at -78 °C to give the ring opened product (**8**) in 35 % yield, accompanied by decomposition products. When the milder Lewis acid $SnCl_4$ was employed, the yield of halodiol (**8**) increased to 80 % (Eq. 4). It is interesting to note that no rearrangement products were obtained.[7] The ring opening had proceeded in a regio- and stereospecific



2a R = Me
3a R = *n*-Bu

7 R = Me
8 R = *n*-Bu

(Eq. 4)

manner to give one diastereoisomer. Similar ring opening of compound **2a** gave halodiol (7) in 86 % yield. X-ray analysis confirmed the regiochemistry and absolute stereochemistry of 1-chloro-2,3-dihydroxy-1,3-diphenylbutane (7) as 1*S*, 2*S*, 3*S*, indicating that the epoxide had been opened up with retention of configuration at C1. This would suggest that the $SnCl_4$ coordinates to the epoxide oxygen and then donates a chloride ligand to the electron deficient benzylic carbon in an intramolecular fashion. The relative stereochemistry of the alcohol groups is also consistent with the proposed mode of attack of the Grignard reagent (MeMgI) on the epoxyketone (**1**).

Conclusions. Excellent diastereoselectivities may be obtained in the alkylation of epoxyketones with Grignard reagents provided the R^1 substituent is larger than methyl. The resulting α,β-epoxy tertiary alcohols are prone to Payne rearrangement to give α,β-epoxy secondary alcohols. Alternatively the epoxide ring may be opened up to give highly substituted chlorodiols.

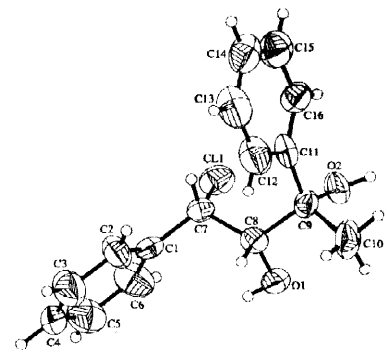


Figure 2 - Crystal structure of 7

Grignard alkylation : (1*S*, 2*R*, 3*S*)-1,3-diphenyl-1,2-epoxy-3-hydroxybutane (2a). Diethyl ether (10 mL) and THF (10 mL) were added to a nitrogen filled flask containing (1*S*,2*R*)-epoxychalcone (500 mg, 2.2 mmol, >96% e.e.) and the vessel was cooled to -78 °C. Methylmagnesium iodide (1.47 mL of a 3.0 M solution in diethyl ether (ex. Aldrich), 4.4 mmol) was added. After 2 hours, the reaction was quenched with saturated ammonium chloride solution and extracted with diethyl ether (3 x 50 mL). The combined organic layers were washed with water (50 mL), brine (50 mL), dried over magnesium sulfate and evaporated to dryness. Silica gel chromatography with petroleum ether (40/60)-diethyl ether (6:1) as the eluent furnished the diastereomerically pure **2a** in >96% e.e. (468 mg, 1.95 mmol, 89%); m.p. 100-102 °C; R_f (petroleum ether (40/60)-diethyl ether (3:1)) 0.34; (Found: C, 79.7; H, 6.75. $C_{16}H_{16}O_2$ requires: C, 80.0; H, 6.7.); $[\alpha]_D^{22}$ -45.8 (*c* 0.48 in $CHCl_3$); ν_{max}(NaCl)/cm^{-1} 3485 (O-H), 1632, 1497, 1446; δ_H (400 MHz; $CDCl_3$; Me_4Si) 1.7 (3 H, s, C(4)CH_3), 2.85 (1 H, s C(3)OH), 3.23 (1 H, d, *J* 2.2, C(2)CH), 4.03 (1 H, d, *J* 2.2, C(1)CH), 7.3 (10 H, m, C(1,3)Ph); δC (400 MHz; $CDCl_3$; Me_4Si) 27.7 (CH_3, C4), 55.9 (CH, C2), 68.6 (CH, C1), 71.4 (C, C3), 128.6-125.2 (CH, Ph), 136.8 (C, Ph), 143.6 (C, Ph); EI: *m/z* 121 (M-PhCHOCH, 34 %), 120 (121-H, 86 %), 105 (120-CH_3, 91 %), 91 (120-CHO, 100 %), 77 (105-CO, 62%).

Payne rearrangement : (1*S*, 2*S*, 3*S*)-1,3-diphenyl-2,3-epoxy-2-hydroxybutane (6). Anhydrous DMF (10 mL) was added to epoxyalcohol **2a** (100 mg, 0.42 mmol), imidazole (57 mg, 0.84 mmol) and TBSCl (316 mg, 2.1 mmol) under nitrogen. The reaction was quenched with water after 26 hours and extracted with diethyl ether (3 x 50 mL). The combined organic layers were washed with water (50 mL), brine (50 mL) and dried over magnesium sulfate. Silica gel chromatography with petroleum ether (40/60)-diethyl ether (6:1) as the eluent gave the rearranged epoxy alcohol **6** (69 %); R_f (petroleum ether (40/60)-diethyl ether (3:1)) 0.16; $C_{16}H_{20}NO_2$ $[M + NH_4]^+$ requires M^+ 258.14940, found M^+ 258.14924, error -0.6 ppm; δ_H (400 MHz; $CDCl_3$; Me_4Si) 1.60 (3 H, s, C(4)CH_3), 2.71 (1 H, d, *J* 6.6, OH), 4.44 (1 H, dd, *J* 6.6, 3.28, C(2)CH), 4.77 (1 H, d, *J* 3.28, C(1)CH), 7.3 (10 H, m, C(1,3)Ph); δ_C (400 MHz; $CDCl_3$; Me_4Si) 29 (CH_3, C4), 63 (CH, C2), 81 (CH, C1); EI: *m/z* 120 (M-PhC(O)CH_3, 100 %), 105 (120-CH_3, 20 %), 91 (120-CHO, 35 %), 77 (105-CO, 14 %).

Epoxide opening : (1*S*, 2*S*, 3*S*)-1-Chloro-2,3-dihydroxy-1,3-diphenylbutane (7). $SnCl_4$ (0.25 mL of a 1 M solution in dichloromethane, 0.25 mmol) was added to a stirred solution of **2a** (50 mg, 0.21 mmol) in anhydrous dichloromethane (5 mL) at -78 °C. After 1.5 hours the reaction was quenched with saturated ammonium chloride solution and extracted with dichloromethane (3 x 50 mL). The combined organic layers were washed with water (50 mL), brine (50 mL) and dried over magnesium sulfate. Silica gel chromatography using petroleum ether (40/60)-diethyl ether (4:1) as the eluent afforded the chlorodiol **7** (42.6 mg, 0.16 mmol, 86%), m.p. 70-71 °C; R_f (petroleum ether (40/60)-diethyl ether (3:2)) 0.37; (Found C; 69.4, H; 6.2, Cl; 12.6, $C_{16}H_{17}O_2Cl$ requires C; 69.4, H; 6.2, Cl; 12.8); $C_{16}H_{21}NO_2{}^{35}Cl$ $[M + NH_4]^+$ requires 294.12608, found 294.12586, error -0.8 ppm; $[\alpha]_D^{22}$ = +46.3 (*c*, 0.54 in $CHCl_3$); ν_{max}(NaCl)/cm^{-1} 3520 (br, s, O-H), 3085, 3060, 2978, 2930 (C-H stretch), 1446, 1494, 1599; δ_H (400 MHz; d_6-DMSO; Me_4Si) 1.53 (3 H, s, C(4)CH_3), 3.80 (1 H, dd, *J* 8.25, 2.75, C(2)CH), 5.14 (1 H, d, *J* 2.76, C(1)CH), 5.18 (1 H, s, C(3)OH), 5.26 (1 H, d, *J* 8.24, C(2)OH); δ_C (400 MHz; $CDCl_3$; Me_4Si) 28.3 (CH_3, C4), 64.4 (C, C3), 78.8 (CHCl, C1), 124.7-128.7 (CH, aromatic), 140.0-144.4 (C, aromatic).

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REFERENCES

1. Katsuki, T. and Martin,V. S. *Organic Reactions*, John Wiley & sons Inc., New York, **1996**, *48*.
2. Wu B.; Zhang, L. and Zhon, W. *Yougi Huaxue*, **1983**, *6*, 440-442.
3. Bentley, P. A.; Bergeron, S.; Cappi, M. W.; Hibbs, D. E.; Hursthouse, M. B.; Nugent, T. C.; Pulido, R.; Roberts, S. M.; and Wu, L. E. *J. Chem. Soc., Chem. Commun.*, **1997**, 739.
4. Imamoto, T.; Kusumoto, T.; Tawarayama, Y.; Sugiura, Y.; Mita, T.; Hatanaka, Y. and Yokoyama, M. *J. Org. Chem*, **1984**, *49*, 3904-3912.
5. Bonini, C. and Righi, G. *Synthesis*, **1994**, 225-238
6. Miura, K.; Takasumi, M.; Hondo, T.; Saito, H. and Hosomi, A. *Tetrahedron Lett.*, **1997**, *38*, 4587.
7. Marson, C. M.; Walker, A. J.; Pickering, J. A.; Hobson, D.; Wrigglesworth, R.; and Edge, S. J.; *J. Org. Chem.*, **1993**, *58*, 5944-5951.