Diastereoselective Cyclization of γ-δ Epoxyketones with (–)-Phenylglycinol: Synthesis of Both Enantiomers of *cis*-5-Alkyl-2-hydroxymethyl Pyrrolidines

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Abstract: A novel condensation of (–)-phenylglycinol with γ,δ-epoxyketones is reported for the preparation of both enantiomers of *cis*-5-alkyl-2-hydroxymethyl pyrrolidines. The required epoxy-derivatives were easily prepared by epoxidation of the corresponding γ,δ-unsaturated ketones. Condensation with (–)-phenylglycinol is regiospecific and stereoselective, giving only two of the four possible diastereomers. The stereochemistry of the cyclization products is dictated by the configuration of C-2 in the N-unsubstituted oxazolidine formed as intermediate.

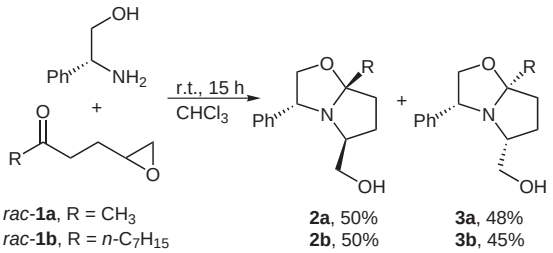
Key words: 1,2-aminoalcohols, asymmetric Synthesis, cyclizations, oxazolidines, pyrrolidines

Both mono-[1] and bicyclic[2] oxazolidines derived from enantiopure 1,2-amino alcohols have been widely used in asymmetric synthesis. In general, the transformation of the heterocycle, followed by elimination of the chiral appendage has been used in the diastereoselective synthesis of enantiopure aza-heterocycles of different sizes.

2,5-Disubstituted pyrrolidine derivatives are especially attractive because of their presence in many natural products[3] and their use as chiral auxiliaries.[4] They have also used as starting materials in the synthesis of a great variety of compounds.[5] As a consequence, the synthesis of enantiopure 2,5-disubstituted pyrrolidines has been studied in depth.[6] Some of these approaches start from chiral pool substances[7] but other methodologies, such as cyclizations,[8] palladium-catalyzed additions,[9] or trapping acyliminium ions by nucleophiles[5d] have been successfully employed.

Recently, we have prepared enantiopure 2-substituted pyrrolidines and piperidines from bicyclic oxazolidines obtained by condensation of γ or δ-chloroketones with (*R*)-phenylglycinol.[10] A logical extension of this work was the study of the condensation of epoxyketones with the same amino alcohol directed to the synthesis of 2-hydroxymethyl-5-alkyl pyrrolidines. This letter reports the first results of this reaction with epoxyketones **1a**,**b**, prepared by epoxidation of the corresponding unsaturated ketones with potassium coroate and acetone.[11]

Interestingly, the condensation of racemic **1a**,**b** with (*R*)-phenylglycinol, at room temperature for 15 hours in chloroform as solvent, was stereoselective.[12] The reactions are totally regioselective, and occurred with the carbonyl group and the most substituted carbon of the epoxide, leading to an almost equimolar mixture (48:50 for **2a**:**3a**, and 45:50 for **2b**:**3b**) of two of the four possible diastereomeric bicyclic oxazolidines[13] **2a**,**b** and **3a**,**b** in 71% and 68% yields, respectively (Scheme 1). Neither the formation of other diastereomers nor the presence of regioisomeric piperidine derivatives was detected by ^{1}H NMR in the reaction mixture.



Scheme 1

In both cases the diastereomers were separated by flash chromatography (silica gel, hexane–EtOAc 4:1) and their stereochemistry was tentatively established on the basis of NOESY experiments and corroborated by chemical correlation. To this end, **2a** was subjected to reductive ring opening by reaction with LAH in diethyl ether at 0 °C yielding **4a** in 90% yield as a single diastereomer.[14] Attempts at debenzylation of **4a** under usual reaction conditions [H_2, $Pd(OH)_2$/C, EtOH] failed, but it was easily transformed into N-Boc derivative **5a** by hydrogenolysis with Pearlman's catalyst in ethyl acetate and 1.5 equivalents of di-*tert*-butyl dicarbonate. Hydrolysis of urethane **5a** with HCl in ethyl acetate, followed by neutralization with a solution of sodium carbonate gives the known[15] (2*S*,5*S*)-2-hydroxymethyl-5-methylpyrrolidine (**6a**, Scheme 2). The same treatment on **3a** led to *ent*-**6a**, and their enantiomeric relationship was established on the basis of the identity of the physical and spectral data and the opposite signs of their specific rotations.

The stereochemistry of **3b** was also determined by chemical correlation by bromination[16] with CBr_4 and Ph_3P in methylene chloride to **4b**, followed by reaction[17] with lithium dimethyl cuprate to furnish ethyl derivative **5b** in 56% yield over the two steps. Reductive ring opening of **5b** as described for **2a** yielded compound **6b** which exhibits specific rotation and physical and spectral data identical with those previously described[18] (Scheme 3). In

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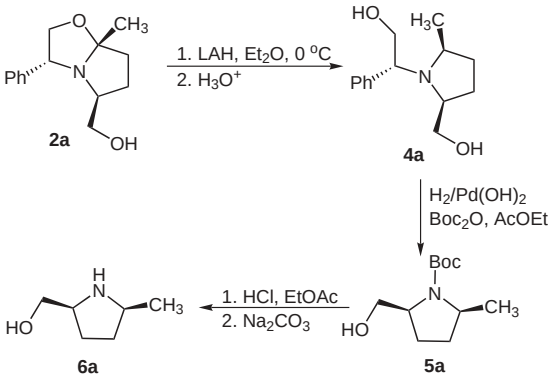
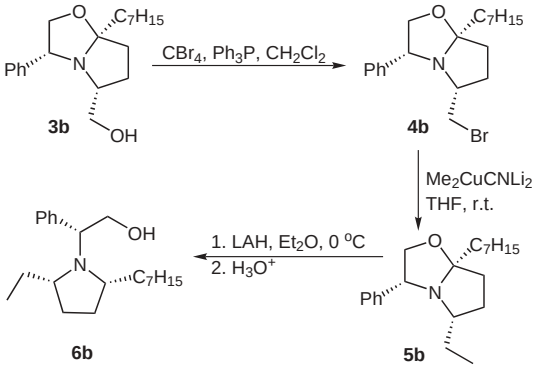


Scheme 2

addition, **2b** and **3b** were transformed into the N-Boc derivatives of (2*R*,5*R*)-5-heptyl-2-hydroxymethyl pyrrolidine and its enantiomer as described for compound **2a** in 52% and 60% total yields, respectively.[19]

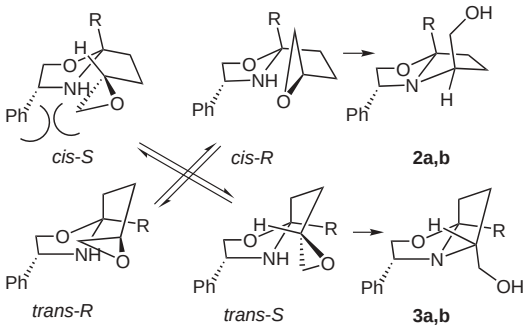


Scheme 3

The stereochemical outcome of the reaction is noteworthy because, as recently noted for a similar cyclization,[20] the configuration at C-2 in the intermediate oxazolidine determines the absolute configuration of the stereocenter created in the opening of the epoxide moiety.

The stereocontrol can be rationalized by taking into account that the reaction of (–)-phenylglycinol with racemic epoxyketones initially yields a mixture of pairs of *cis* and *trans* isomers in equilibrium through the corresponding tautomeric hydroxyimines (Scheme 4).[21] The preferential formation of **2a**,**b** from the equilibrium mixture *cis*-*R*/*trans*-*R* is a consequence of the nucleophilic displacement occurring faster in the former because the approach of the nitrogen atom to the inner carbon of the epoxide is less hindered. In the same way, the formation of **3a**,**b** from the equilibrium mixture *cis*-*S*/*trans*-*S* takes place in the latter because it is less hindered than the first one.

In summary, the described protocol allows the easy preparation of enantiopure 5-substituted-2-hydroxymethyl pyrrolidines from readily available starting products.



Scheme 4

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(11) Curci, R.; Fiorentino, M.; Troisi, L.; Edwards, J. O.; Pater, R. H. *J. Org. Chem.* **1980**, *45*, 4758.
(12) **Experimental Procedure:** To a solution of epoxyketone (3.0 mmol) in $CHCl_3$ (3 mL), cooled to 0 °C was added (–)-phenylglycinol (0.41 g, 3.0 mmol) in $CHCl_3$ (3 mL) and $MgSO_4$ (0.2 g). The mixture was stirred at that temperature

for 2 h and then warmed to r.t. and stirred for additional 13 h. The mixture was filtered, the solvent concentrated and the residue was purified by flash chromatography (silca gel, EtOAc–hexane 1:4, v/v).

(13) Spectroscopic data for compounds: **2a**: $[\alpha]_D^{25}$ +27.2 (*c* 0.7, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 1.50 (s, 3 H), 1.60–1.73 (m, 1 H), 1.81–1.89 (m, 1 H), 1.96–2.09 (m, 2 H), 2.60 (br s, 1 H), 2.78 (dd, *J* = 5.0, 10.4 Hz, 1 H), 2.97–3.08 (m, 2 H), 3.98 (dd, *J* = 7.9, 9.9 Hz, 1 H), 4.13 (dd, *J* = 6.1, 7.9 Hz, 1 H), 4.62 (dd, *J* = 6.1, 9.9 Hz, 1 H), 7.25–7.5 (m, 5 H). ^{13}C NMR (75 MHz, CD_3Cl): δ = 25.9, 27.3, 37.9, 59.7, 64.2, 64.3, 67.0, 106.5, 128.1, 128.5 (2 C), 128.9 (2 C), 135.4. Compound **2b**: $[\alpha]_D^{25}$ +7.3 (*c* 0.6, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 0.88 (t, *J* = 6.5 Hz, 3 H), 1.20–1.57 (m, 10 H), 1.58–1.73 (m, 2 H), 1.74–1.91 (m, 2 H), 1.92–2.15 (m, 2 H), 2.45 (br s, 1 H), 2.72 (dd, *J* = 4.7, 10.4 Hz, 1 H), 2.98 (dd, *J* = 3.7, 10.4 Hz, 1 H), 3.05–3.15 (m, 1 H), 4.0 (dd, *J* = 7.9, 10.0 Hz, 1 H), 4.11 (dd, *J* = 6.1, 7.8 Hz, 1 H), 4.60 (dd, *J* = 6.1, 10.0 Hz, 1 H), 7.25–7.52 (m, 5 H). ^{13}C NMR (75 MHz, CD_3Cl): δ = 14.1, 22.6, 25.2, 27.3, 29,3, 30.0, 31.8, 35.6, 39.2, 59.4, 63.8, 64.5, 66.6, 108.7, 128.2, 128.5 (2 C), 128.9 (2 C), 135.2. Compound **3a**: $[\alpha]_D^{25}$ –97.8 (*c* 0.7, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 1.48 (s, 3 H), 1.75–1.86 (m, 1 H), 1.92–2.11 (m, 3 H), 2.21–2.27 (m, 1 H), 3.10–3.15 (m, 1 H), 3.26–3.35 (m, 2 H), 3.83 (t, *J* = 8.6 Hz, 1 H), 4.05 (t, *J* = 7.6 Hz, 1 H), 4.34 (dd, *J* = 6.1, 8.6 Hz, 1 H), 7.23–7.40 (m, 5 H). ^{13}C NMR (75 MHz, CD_3Cl): δ = 26.8, 27.2, 37.8, 63.2, 69.9, 70.8, 73.5, 105.8, 126.5 (2 C), 127.4, 128.7 (2 C), 141.6. Compound **3b**: $[\alpha]_D^{25}$ –70.6 (*c* 0.5, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$) δ = 0.90 (t, *J* = 6.5 Hz, 3 H), 1.29–1.61 (m, 11 H), 1.69–1.78 (m, 1 H), 1.81–1.93 (m, 1 H), 1.95–2.12 (m, 3 H), 2.27 (br s, 1 H), 3.13 (tq, *J* = 5.7 Hz, 1 H), 3.25–3.38 (m, 2 H), 3.76 (t, *J* = 8.7 Hz, 1 H), 4.08 (dd, *J* = 7.2, 8.4 Hz, 1 H), 4.33 (dd, *J* = 7.2, 8.7 Hz, 1 H), 7.24–7.40 (m, 5 H). ^{13}C NMR (75 MHz, CD_3Cl): δ = 14.1, 22.6, 25.0, 26.9, 29.2, 29.9, 31.8, 35.0, 39.2, 63.3, 69.7, 71.0, 73.2, 108.2, 126.5 (2 C), 127.4, 128.7 (2 C), 141.7.

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(19) Data for N-Boc Pyrrolidines: **5a**: $[\alpha]_D^{25}$ –9.9 (*c* 1.2, $CHCl_3$). **ent-5a**: $[\alpha]_D^{25}$ +9.95 (*c* 1.3, $CHCl_3$). **N-Boc derivatives of (2*R*,5*R*)-5-heptyl-2-hydroxymethyl pyrrolidine**: $[\alpha]_D^{25}$ +4.1 (*c* 0.8, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 0.88 (t, *J* = 6.2 Hz, 3 H), 1.25 (m, 10 H), 1.44 (s, 9 H), 1.51–1.65 (m, 3 H), 1.82–1.97 (m, 3 H), 3.51 (t, *J* = 8.6 Hz, 1 H), 3.67 (t, *J* = 8.4 Hz, 1 H), 3.72–3.89 (m, 1 H), 3.90–4.01 (m, 1 H), 5.12 (br s, 1 H). ^{13}C NMR (75 MHz, CD_3Cl): δ = 14.1, 22.6, 26.5, 26.8, 28.4 (3 C), 28.9, 29.2, 29.5, 31.8, 35.4, 59.2, 61.1, 68.8, 80.2, 157.4. **N-Boc derivatives of (2*S*,5*S*)-5-heptyl-2-hydroxymethyl pyrrolidine**: $[\alpha]_D^{25}$ –4.0 (*c* 0.9, $CHCl_3$).

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