

Ring Opening of Spiroepoxides Dithianedioide with Bis-nucleophiles

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Abstract

This research was aimed to apply the spiroepoxide dithianedioide for the synthesis of amino acid via ring opening of the spiroepoxide by bis-nucleophiles. First attempt was made to synthesize the bis-nucleophiles, amino alcohol, which was eventually used to the ring opening reaction of the spiroepoxide to produce the morpholine ring compound. The reaction was carried out in racemic and asymmetric method with moderate yield and high 99%. The last step produced amino acid that was still remained unsuccessful. However, it cannot be concluded yet whether the spiroepoxide dithianedioide is the right intermediate for the synthesis of amino acid.

Keywords: Amino alcohol; Morpholine ring; Spiroepoxide dithianedioide; Amino acid.

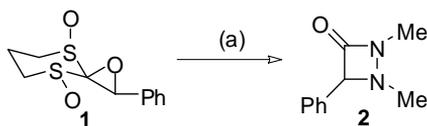
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1. Introduction

Spiroepoxide dithianedioides [1] has been successfully synthesised in only one diastereomeric form [2]. These novel structures can potentially be used in the synthesis of some important biologically active compounds, such as aza β -lactams and diaminopimelic acids. This spiroepoxide **1** has been successfully applied to the synthesis of racemic [3] and asymmetric [4] aza β -Lactams.



Scheme 1. Reagents and conditions: (a) MeNHNHMe·2HCl, NEt₃, THF, r.t., 24 h, 40 %.

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The ring opening of epoxide **1a** with bis-nucleophiles can also be applied to the synthesis of diaminopimelic acid and this work has been submitted for publication [5].

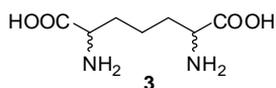
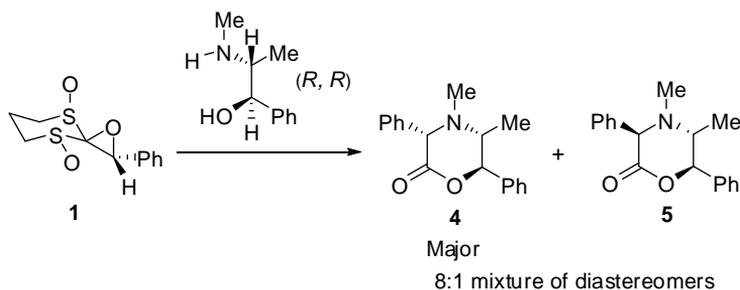


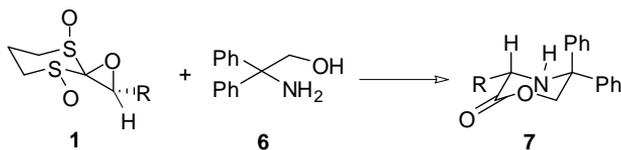
Fig. 1. DAP structure.

Using a bis-nucleophilic moiety with different reactivity has been described in the ring opening of epoxide **1**. In this case the more reactive nucleophilic substituent should ring open the epoxide, and then the other less reactive nucleophile should react in an intramolecular fashion. One of the examples involved the addition of (*R,R*) pseudoephedrine to **1a** [6], leading to two diastereomeric products, **4** and **5** which were obtained in a diastereomeric ratio of 8:1.



Scheme 2. Ring opening of epoxide by ephedrine.

This research was aimed to apply this method to the ring opening of epoxide **1** with the amino alcohol, 2-amino-2,2-diphenylethanol **6** [7]. The nitrogen nucleophile would be expected to open **1** before the hydroxy group reacts with the activated carbonyl group, resulting in formation of the morpholine derivative **7** (Scheme 3).



Scheme 3. Ring opening of epoxide by an amino alcohol.

2. Material and Method

2.1. Synthesis of 2-Amino-2,2-diphenyl ethanol **6** [7]

α,α -Diphenyl glycine (4.09 mmol, 930 mg) was added to a stirred suspension of LiAlH_4 (16.36 mmol, 620 mg) in dry THF (45 mL). The reaction mixture was heated to reflux at

80°C for 6 h. After cooling down, KOH (56 mg in 0.5 mL H₂O) was added and 5 min later H₂O (1.0 mL) was added. The reaction mixture was heated to reflux for 2 h and filtered through celite. The solvent was evaporated under vacuum. The crude product was recrystallized from DCM/hexane to yield **6** as a white crystalline product (636 mg, 73 %), *R_f* (10 % EtOH/CHCl₃) 0.25, m.p 118-123°C (DCM/hexane) (Found: C, 78.5; H, 6.8; N, 6.2; C₁₄H₁₅NO requires C, 78.8; H, 7.0; N, 6.5 [7] C, 78.7, H, 7.0)]; ν_{\max} (KBr)/cm⁻¹ 3343 (N-H), 3052 (O-H), 2830 (C-H), 1589 (C-OH), 1493 (-NH₂), 1289 (C-N), 1052 (CH₂-OH); δ_{H} (270 MHz; CDCl₃) 2.15 (3H, s, NH₂ and -OH), 4.10 (2H, m, -CH₂), 7.28-7.38 (10H, m, Ph); δ_{C} (68 MHz; CDCl₃) 62.4 (s), 70.3 (t), 126.8 (2d), 126.9 (4d), 128.4 (4d), 146.0 (2s); *m/z* (CI) 214 (M⁺ + 1); (79), 197 (99), 182 (100), 136 (27).

2.2. General procedure for the synthesis of the diphenylmorpholine compounds

Amino alcohol **6** (0.82 mmol, 175 mg) in DCM (2 mL) was added to a solution of epoxide **1** (0.68 mmol) in DCM (2 mL) was added. The reaction mixture was stirred at reflux for 24-28 h, finally the solvent was removed under reduced pressure.

2.2.1. Synthesis of (3RS)-5, 5-triphenylmorpholin-2-one **9a** using epoxide **1** (0.68 mmol, 175 mg).

The reaction mixture was evaporated off under reduced pressure. Flash column chromatography (100 % CHCl₃) yielded a white solid. Recrystallization from DCM/hexane gave **9a** as a white crystalline solid (88 mg, 39 %), *R_f* (100 % CHCl₃) 0.4, m.p. 135-136°C (DCM/hexane) (Found: C, 80.2; H, 6.0; N, 4.4 C₂₂H₁₉N O₂ requires C, 80.2; H, 5.8 N, 4.3); ν_{\max} (KBr)/cm⁻¹ 3291 (NH), 1722 (C=O); δ_{H} (270 MHz; CDCl₃) 2.59 (1H, dd, ³*J* 5.6, ⁴*J* 2.9, NH), 4.44 (1H, d, ³*J* 5.6, 3-H), 4.74 (1H, d, ²*J* 11.5, 6-H_{ax}), 5.03 (1H, dd, ²*J* 11.5, ⁴*J* 2.9, 6-H_{eq}), 7.28-7.55 (15H, m, Ph); δ_{C} (68 MHz; CDCl₃) 60.3 (s), 61.7 (d), 75.4 (t), 126.8 (d), 127.5 (d), 127.9 (d), 128.1 (d), 128.5 (d), 128.6 (d), 128.7 (d), 129.4 (d), 168.4 (s); *m/z* (EI) 329 (M⁺; 55), 285 (43), 180 (100).

2.2.2. Synthesis of (3S)-5, 5-triphenylmorpholin-2-one **9a** using epoxide (+)-**1** (0.27 mmol, 69 mg)

The reaction mixture was stirred and refluxed for 24 h. Flash column chromatography (100 % CHCl₃) yielded a white solid. Recrystallisation from DCM/hexane gave **9a** as a white crystalline solid (29 mg, 32 %), 96 % ee by HPLC, with identical ¹H-NMR and ¹³C-NMR to racemic material; $[\alpha]_{\text{D}}^{23} -21.1$ (c. 0.18 in CHCl₃).

2.2.3. Synthesis of (3RS)-phenethyl-5, 5-diphenylmorpholin-2-one **9b** using epoxide **1b** (0.09 mmol, 26 mg)

The reaction mixture was stirred and refluxed for 24 h. Flash column chromatography (100% CHCl₃) yielded a white solid. Recrystallization from DCM/hexane gave **9b** as a

white crystalline solid (21.3 mg, 66 %), R_f (100 % CHCl_3) 0.4, m.p. 147-148°C (DCM/hexane) (Found: C, 80.3; H, 6.5; N, 3.9 $\text{C}_{24}\text{H}_{23}\text{NO}_2$ requires C, 80.6; H, 6.5 N, 3.9); ν_{max} (KBr)/ cm^{-1} 3303 (NH), 1728(C=O), 1164 (C-O); δ_{H} (400 MHz; CDCl_3) 1.73 (1H, s, N-H) 2.08-2.18 (1H, m, 7-H), 2.27-2.36 (1H, m, 7-H), 2.82-2.95 (2H, m, 8-H), 3.38 (1H, dd, J 7.3, 4.0, 3-H), 4.62 (1H, d, J 11.9, 6-H), 4.82 (1H, d, J 11.9, 6-H), 7.18-7.37 (15H, m, Ph); δ_{C} (100 MHz; CDCl_3) 32.0 (t), 33.7 (t), 53.9 (d), 61.3 (s), 70.4 (t), 126.0 (d), 126.6 (d), 127.2 (d), 127.9 (d), 128.1 (d), 128.6 (d), 128.9 (d), 141.0 (s), 141.7 (s), 143.7 (s), 170.8 (s); m/z (EI) 357 (M^+ ; 30), 266 (28), 208 (90), 180 (100), 165 (68), 91 (58).

2.2.4. *Synthesis of (3S)-Phenethyl-5, 5-diphenylmorpholin-2-one 9b using epoxide (+)-1b (10.56 mmol, 3.0 g)*

The reaction mixture was stirred at reflux for 24 h and then the solvent was removed under reduced pressure. Flash column chromatography (100 % CHCl_3) yielded the morpholine compound **9b**. Recrystallization from DCM/hexane gave **9b** as a white crystalline solid (1.57 g, 42 %), 99 % ee by HPLC, showing identical ^1H -NMR and ^{13}C -NMR to racemic material; $[\alpha]_{\text{D}}^{23}$ -163.6 (c. 1.0 in CHCl_3).

2.3. *General procedure for the synthesis of the phenylmorpholine compounds*

Method A:

(*R*)-(-)-2-Phenylglycinol (0.47 mmol, 64.5 mg) in DCM (2 mL) was added to a solution of epoxide (+)-**1** (0.39 mmol) in DCM (2 mL). The reaction mixture was stirred at reflux for 24 h and finally the solvent was removed under reduced pressure.

Method B:

(*S*)-(+)-2-Phenylglycinol (1.13 mmol, 155 mg) in DCM (15 mL) was added to a solution of epoxide (+)-**1** (0.94 mmol). The reaction mixture was stirred and refluxed for 21 h. The solvent was then removed under reduced pressure.

2.3.1. *Synthesis of (3S), (5R)-Diphenylmorpholin-2-one 20a*

Method A, using epoxide (+)-**1** (2.02 mmol, 523 mg): Flash column chromatography (100 % CHCl_3) yielded **20a** as a colourless oil (55 mg, 11 %), R_f (100 % CHCl_3) 0.25, ν_{max} (KBr)/ cm^{-1} 3314 (NH), 1734 (C=O) 1185 (C-O) 1290 (C-N); δ_{H} (400 MHz; CDCl_3) 2.23 (1H, s, NH), 4.40 (1H, dd, J 8.3, 4.3, 6- H_{eq}) 4.43 (1H, dd, J 8.3, 8.1, 6- H_{ax}), 4.46 (1H, dd, J 8.1, 4.3, 5-H), 4.93 (1H, s, 3-H), 7.28-7.40 (10H, m, Ph); δ_{C} (100 MHz; CDCl_3) 57.8 (d), 64.2 (d), 75.0 (t), 127.2 (2d), 128.5 (2d), 128.6 (2d), 128.8 (2d), 129.0 (2d), 137.8 (s), 138.2 (s), 169.3 (s); m/z (EI) 253 (M^+ ; 1), 209 (72), 194 (88), 104 (100); $[\alpha]_{\text{D}}^{23}$ -69.7 (c. 4.7 in CHCl_3)

2.3.2. *Synthesis of (3S)-Phenethyl-(5R)-phenylmorpholin-2-one 20a*

Method A, using epoxide (+)-**1b** (0.45 mmol, 128 mg): The reaction mixture was stirred and refluxed for 21 h. Flash column chromatography (100 % CHCl₃) yielded a white solid that was recrystallized from DCM/hexane to obtain **20a** as a white crystalline solid (30.4 mg, 24 %), *R_f*(100 % CHCl₃) 0.19, m.p. 80°C (DCM/hexane); *v*_{max} (KBr)/cm⁻¹ 3342 (N-H), 1739 (C=O) 1122 (C-O) 1301 (C-N); *δ*_H (400 MHz; CDCl₃) 1.87 (1H, s, NH), 2.16-2.25 (1H, m, 7-H), 2.28-2.37 (1H, m, 7-H), 2.79-2.92 (2H, m, 8-H), 3.80-3.86 (1H, m, 3-H), 4.22 (1H, dd, *J* 10.3, 2.2, 6-H_{eq}) 4.26 (1H, dd, *J* 10.3, 9.0, 6-H_{ax}), 4.38 (1H, dd, *J* 9.0, 2.2, 5-H), 7.28-7.40 (10H, m, Ph); *δ*_C (100 MHz; CDCl₃) 31.8 (t), 34.8 (t), 57.4 (d), 58.3 (d), 74.8 (t), 126.2 (d), 127.1 (d), 128.5 (2d), 128.6 (2d), 128.7 (2d), 128.9 (2d), 138.0 (s), 140.6 (s), 169.8 (s); (M⁺, Found 281.1422. C₁₈H₁₉O₂N requires 281.1416) *m/z* (EI) 281 (M⁺; 17), 237 (19), 132 (51), 104 (100); [*α*]_D²³ -91.2 (c. 0.86 in CHCl₃)

2.3.3. *Synthesis of 3(S)-Phenethyl-5(S)-phenyl-morpholin-2-one 21b*

Method B, using epoxide (+)-**1b** (0.94 mmol, 268 mg): Flash column chromatography (100% CHCl₃) yielded **21b** as a white solid recrystallized from DCM/hexane, (76 mg, 29 %), *R_f*(100 % CHCl₃) 0.25, m.p. 118-121°C (DCM/hexane); *v*_{max} (KBr)/cm⁻¹ 3342 (NH), 1739 (C=O) 1122 (C-O) 1301 (C-N); *δ*_H (400 MHz; CDCl₃) 1.79 (1H, s, NH), 2.06 (1H, ddt, *J* 14.1, 8.8, 5.9, 7-H), 2.36 (1H, ddt, *J* 14.1, 7.3, 4.8, 7-H), 2.79-2.92 (2H, m, 8-H), 3.73 (1H, m, 3-H), 4.26 (1H, dd, *J* 10.7, 10.3, 6-H_{ax}) 4.38 (1H, dd, *J* 10.3, 4.4, 5-H), 4.45 (1H, dd, 10.7, 4.4, 6-H_{eq}), 7.28-7.40 (10H, m, Ph); *δ*_C (100 MHz; CDCl₃) 32.1 (t), 33.4 (t), 53.4 (d), 54.1 (d), 77.5 (t), 126.2 (d), 126.8(d), 128.3 (2d), 128.5 (2d), 128.6 (2d), 128.9 (2d), 138.5 (s), 140.8 (s), 171.5 (s); (M⁺, Found 281.1412. C₁₈H₁₉NO₂ requires 281.1416) *m/z* (EI) 281 (M⁺; 17), 237 (19), 132 (51), 104 (100); [*α*]_D²³ -32.5 (c. 1.0 in CHCl₃).

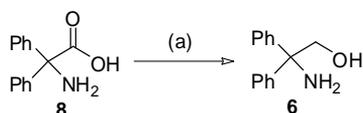
2.3.4. *Synthesis of (4S)-Methyl-(3S)-phenethyl-5-phenylmorpholin-2-one 25*

The morpholin **21b** (0.11 mmol, 31 mg) was dissolved in methanol (10 mL). Palladium hydroxide (33 mg) and trifluoroacetic acid (55 μL) was added to the stirred solution. The resultant mixture was stirred under hydrogen at room temperature for 18 h. Filtration of the solvent through celite and evaporation under reduced pressure yielded a residue. Flash column chromatography (5 % MeOH/CHCl₃) of the residue gave **25** as a yellow oil (21 mg, 65 %), *R_f*(5 % MeOH/CHCl₃) 0.35; *v*_{max} (KBr)/cm⁻¹ 3431 (NH), 1733 (C=O) 1173 (C-O) 1454 (C-N); *δ*_H (400 MHz; CDCl₃) 1.82-1.97 (2H, m, 7-CH₂), 2.58-2.70 (2H, m, 8-CH₂), 3.23 (1H, t, *J* 5.4, 3-H), 3.38 (3H, s, N-CH₃), 3.50 (1H, dd, *J* 10.8, 8.3, 6-H_{ax}) 3.59 (1H, dd, *J* 10.8, 4.4, 6-H_{eq}), 3.64 (1H, dd, 8.3, 4.4, 5-H), 7.09-7.27 (10H, m, Ph); *δ*_C (100 MHz; CDCl₃) 31.8 (t), 34.8 (t), 51.7 (q), 58.9 (d), 63.5 (d), 66.1 (t), 126.1 (d), 127.3 (d), 127.8 (2d), 128.4 (2d), 128.5 (2d), 128.6 (2d), 140.5 (s), 141.3 (s), 175.3 (s); *m/z* (EI) 295 (M⁺; 1), 282 (100), 254 (20), 222 (7), 132 (24), 117 (21), 104 (33), 91 (85);

3. Results and Discussions

3.1. Synthesis of the amino alcohol **6**

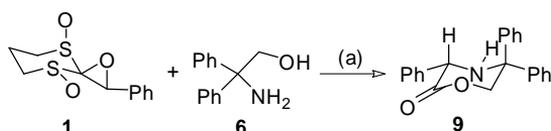
Synthesis of the amino alcohol that would be required for the ring opening of epoxide **1** was carried out following the Newman procedure, [7] and involved the reaction of 2-amino-2,2-diphenyl-carboxylic acid **8** in THF with the reducing agent LiAlH_4 to yield amino alcohol **6** in good yield (Scheme 4).



Scheme 4. Reagents and conditions: (a) LiAlH_4 , THF, reflux, 73 %.

In parallel with these studies, we needed to establish which nucleophile was to be employed in the ring opening of the spiro-epoxide to allow ready access to the amino acid moiety. It was decided to investigate amino alcohols in which the amino group was α to an aryl group so that deprotection could be effected.

A solvent study was realised for the reaction of amino alcohol **6** with epoxide **1** (Scheme 5). The reactions were carried out with six different aprotic solvents. The best yield was obtained when CH_2Cl_2 was used as the solvent. When DMF was used, no expected product was formed, only decomposition products were observed by TLC (Table 1).



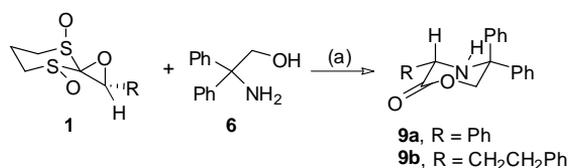
Scheme 5. Reagents and conditions: (a) solvents, r.t, 3 days.

Table 6. Effect of solvent.

Entry	Solvent	Yield (%) ^a
1	DCM	42
2	Toluene	29
3	THF	18
4	Acetonitrile	17
5	Dioxane	2
6	DMF	-

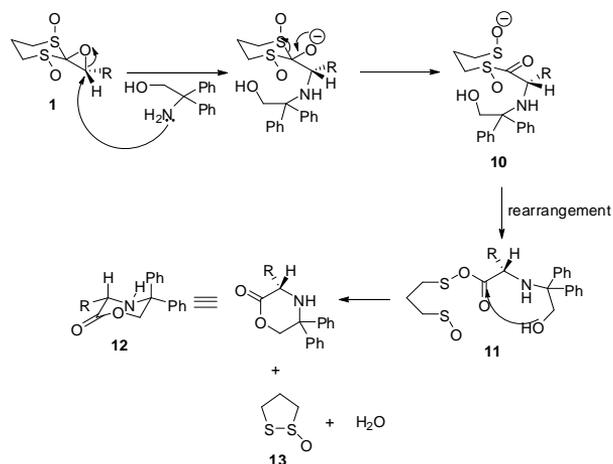
a : yield calculated by $^1\text{H-NMR}$ analysis of crude material using dibenzylether as an internal standard.

Due to the slow rate of reaction, the mixture was heated in an attempt to shorten the reaction time from 3 days to 24 hours, using DCM as solvent. The reaction conditions were applied to both the racemic and enantiopure epoxides **1**. The reaction gave the product in moderate yield and excellent ees (Scheme 6).



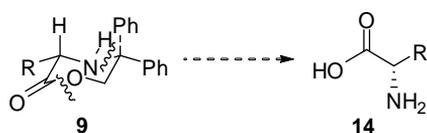
Scheme 6. Reagents and conditions: (a) CH_2Cl_2 , reflux, 24 h (**9a**, 32 %, 96 % ee; **9b**, 66 %, 99 % ee).

It is assumed that no epimerisation of the α -keto intermediate occurred during the reaction, but for **1** with 96 % ee, a small amount of epimerisation may have occurred in intermediate **11**.



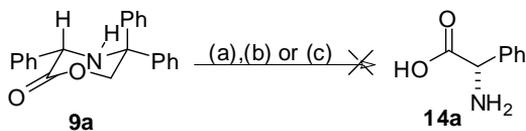
Scheme 7. Proposed mechanism of epimerisation.

The next reaction involved cleavage of the C-N bond, and hydrolysis of the ester group to release the amino acid **14** (Scheme 8).

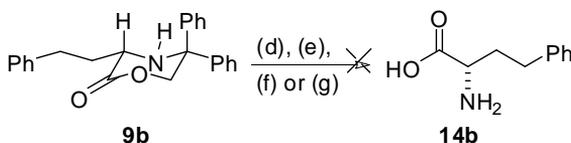


Scheme 8. Target molecule **14**.

In order to carry out this, morpholine **9** was subjected to various conditions (a-g), but none gave the amino acid **14**. Instead, the reactions generated the protonated product (a, d and g) [8], starting material (f) [9, 10, 11, 12], decomposition of starting material (b) [13] or some unidentifiable compounds (c and e) [14].

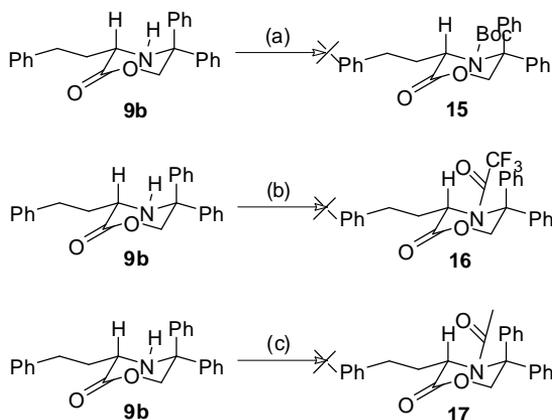


Scheme 9. Reagents and Conditions: (a) TFA, Et₃SiH, CH₂Cl₂, 5°C, r.t to reflux; (b) Me₃SiBr, CH₂Cl₂, r.t.; (c) PdCl₂ (0.7 eq.), H₂ (50 psi), THF, 24 h.



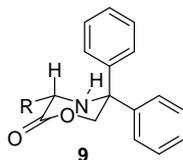
Scheme 10. Reagents and conditions: (d) TFA, r.t.; (e) PdCl₂ (0.7 eq.), H₂ (50 psi), THF, 24 h; (f) 10 mol % Pd/C, NH₄COOH, MeOH, r.t; (g) TFA, Et₃SiH, r.t.

It was assumed, from the above results, that the C-N bond was too strong to be cleaved. To make this bond weaker, attempts were made to introduce electron-withdrawing groups on the nitrogen of the morpholine compound **9**. Reactions were done to protect the nitrogen with either a Boc-group or TFA-group [15] or acetate-group [16] but none of them could be formed and only the starting material was recovered in each case.

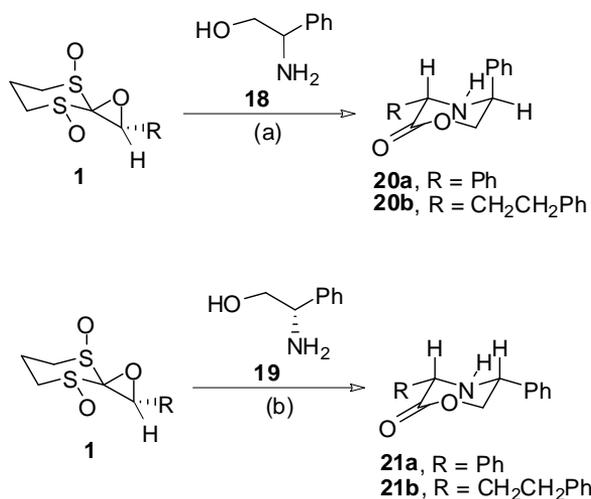


Scheme 11. Reagents and conditions: (a) Boc₂O, DMAP, THF; (b) TFAA, DMAP, py, THF; (c) Zn, HCl, toluene, MeCOCl.

Considering the results obtained, we could conclude that the morpholine compound **9** was too hindered and it was impossible to cleave the C-N bond or to perform reactions on nitrogen.



We envisaged on the opening of the epoxide with an amino alcohol containing only one phenyl group in order to reduce the steric hindrance. This would hopefully result in easier C-N bond cleavage of the morpholine moiety. Epoxide **1** ring was opened using commercially available (*R*)-(-)-2-amino-glycinol **18** and (*S*)-(+)-2-amino-glycinol **19** in DCM at room temperature to give low yields of **20** and **21** as single diastereomers (Scheme 12).

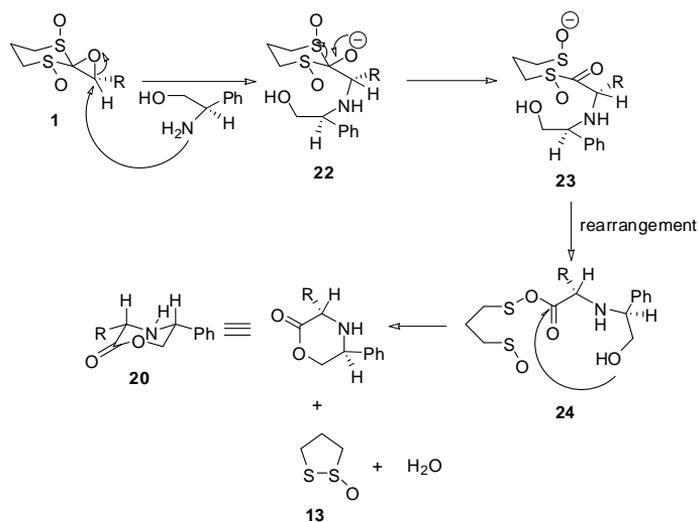


Scheme 12. Reagents and conditions: (a) CH_2Cl_2 , r.t., 24 h (**20a**, 11 %; **20b**, 27 %); (b) CH_2Cl_2 , r.t., 24 h, (**21a**, 0 %; **21b**, 29 %).

In this study, problems arose in the reaction between epoxide **1** and (*S*)-(+)-2-amino-glycinol **19**. TLC monitoring showed weak spots of the product, but it was hard to tell from $^1\text{H-NMR}$ if only a single diastereomer was formed because there appeared to be many impurities in the reaction mixture, making structural assignment very difficult.

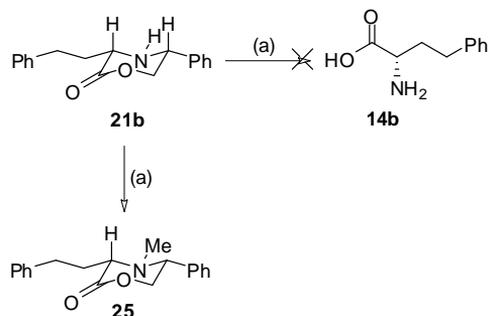
There was concern about the enantioselectivities of products **20** and **21** as it was assumed that if a single diastereomer formed it could be assumed that only one enantiomer was obtained because there is no epimerisation of the (*R*)-(-)-2-amino-glycinol

18 or (*S*)-(+)-2-amino-glycinol **19** was possible. Epimerisation would only occur in the α -keto intermediate **24** before the second nucleophilic attack (Scheme 13).



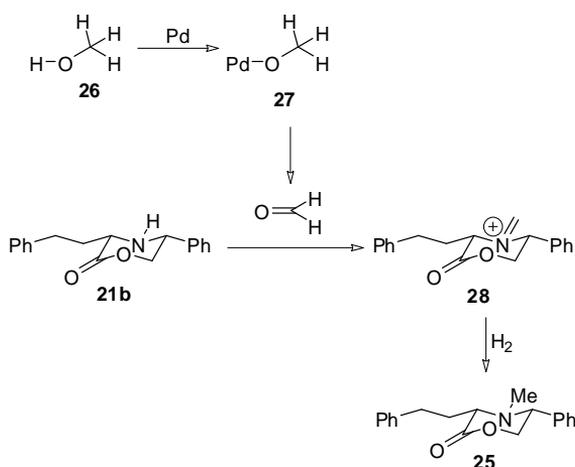
Scheme 13. Proposed mechanism.

Harwood [17] used hydrogenation to cleave the C-N bond in similar morpholine rings and this condition was applied to our substrate.



Scheme 14. Reagents and conditions: (a) H_2 , $\text{Pd}(\text{OH})_2/\text{C}$, MeOH, r.t., 18 h, 65 %.

However, the hydrogenation reaction of morpholine compound **21b** did not give a good result. The only product that formed was the nitrogen-methylated product **25**. This was assumed to be due to the reaction of palladium with methanol **26**, formed formaldehyde *insitu*, which reacted with **21b** to form iminium salt **28**. Hydrogenation only gave **25** in 33 % yield. The outcome was surprising as very similar system (Scheme 14) had been reduced uneventfully by Harwood. Although the reduction could have been conducted in a different solvent to avoid this allylation, neither time nor material was available.

Scheme 15. Proposed mechanism of formation of methylated-product **25**.

4. Conclusion

The ring opening of epoxide **1** has demonstrated that these epoxides can be used to synthesize enantiomerically and diastereomerically pure morpholine compounds **19**, **20** and **21**. Due to the steric hindrance of **19**, it is difficult to conclude at this stage whether spiroepoxide is an appropriate intermediate for the synthesis of the amino acids and furthermore, diaminopimelic acid.

Acknowledgment

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