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Research Article

ATTEMPTED SYNTHESIS OF BIS-SPIROEPOXIDE DITHIANEDIOXIDE

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ABSTRACT

The bis-spiroepoxide dithiane dioxide has been attempted to be synthesised as its role as an intermediate in the synthesis of diaminopimelic acid (DAP). The first method was carried out by reacting the 3-dithiane-2-diethylphosphonate **4** with an aqueous solution of the commercially available glutaraldehide resulting the bis-ketene dithiane dioxide **5**. The second alternative method was involving the ozonolysis of cyclopentene **7** in the synthesis of bis-ketene dithiane dioxide **5** in four step reactions which gave moderate to good yield. Unfortunately, epoxidation process for the bis-ketene dithiane dioxide **5** was still unsuccess yet.

Key words: synthesis, diaminopimelic acid, bis-spiroepoxide dithiane dioxide

INTRODUCTION

Spiroepoxide dithianedioxides (Ritmaleni and Aggarwal, 2008) has been successfully synthesised in only one diastereomeric form (Aggarwal *et al.*, 2003). 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 has been succesfully applied to the synthesis of racemic (Ritmaleni and Aggarwal, 2005) and asymmetric (Ritmaleni and Aggarwal, 2009) of aza β-Lactam.

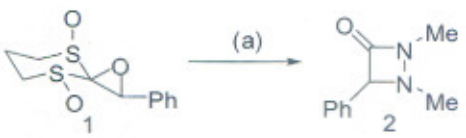

Figure 1. (a) MeNHNHMe·2HCl, NEt_3, THF, r.t., 24 h, 40 %.

This research was aimed to synthesis the bis spiroepoxide dithiane dioxide and to applied it as intermediate in the synthesis of diaminopimelic acid. Wade *et al.*, isolated α-aminopimelic acid as a component of green plants in milligram quantities. They characterised the compound successfully except for its optical rotation and configuration. (Wade *et al.*, 1957) Work *et al.*, (1955) also observed that the symmetrical diaminopimelic acids exist in two racemic modifications, (*L, L*)-form and the other as *meso*-(*D, L*)-form. One member of this class is 2,6-diaminopimelic acid (DAP) (Figure 1), which is of particular contemporary interest due to its presence in bacterial products, and because of its role as a precursor in the biosynthesis of lysine. (Williams and Yuanm 1992)

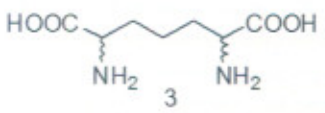

Figure 2 . DAP structure.

Diaminopimelic acid (DAP) is an important, naturally occurring amino acid biosynthesised in bacteria and higher plants. *L, L-* and *meso*-DAP serve as the penultimate biosynthetic precursors of the essential amino acid L-lysine. (Coc, 1996) *meso*-DAP functions as a cross-linking constituent of virtually all Gram-negative and some Gram-positive bacterial peptidoglycans and also serves to anchor various membrane-associated macromolecules, such as lipoprotein to the cell wall. Recognition of the pivotal roles DAP plays in microbial metabolism and cell wall structure has resulted in an increased level of interest in possible means to selectively disrupt the DAP biosynthetic pathway. DAP also acts

as bacterial toxin, a sleep-inducing factor and antitumor agent (Gao *et al.*, 1998).

METHODOLOGY

Synthesis of 5,5-Dimethoxypentanal 8

A 1000 mL three necked round-bottomed flask was fitted with a glass frit to admit ozone, a calcium hydride drying tube, a glass stopper and a magnetic stirrer bar and was charged with cyclopentene (150 mmol, 10.22 g; 13.20 mL), anhydrous DCM (500 mL) and anhydrous methanol (100 mL). The flask was cooled to –78°C, and ozone was bubbled through the solution with stirring until a blue colour remained. Nitrogen was passed through the solution until the blue colour was discharged and then the cold bath was removed. The drying tube and ozone inlet were replaced with a glass stopper and a rubber septum, and *p*-toluene sulfonic acid monohydrate (10 % w/w) (11.56 mmol, 2.2 g) was added. The solution was allowed to warm to room temperature as it stirred under nitrogen for 90 minutes. Anhydrous sodium hydrogen carbonate (46.2 mmol, 3.88 g) was then added to the flask and the mixture was stirred for 15 minutes after which time dimethyl sulfide (300 mmol, 24 mL) was added. After stirring for 13 hours the heterogeneous mixture was washed with water (100 mL). The aqueous layer was extracted with DCM (2 x 250 mL) and the combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. Flash column chromatography (2:1 petrol/ether) on silica gave aldehyde **8** as a colourless oil (8.44 g; 39 %); R_f 0.21 (2:1 petrol/ether); υ_{max} (thin film)/cm^{-1} 1723 (C=O), 1453, 1387, 1127, 1050; δ_H (400 MHz, $CDCl_3$) 1.60-1.75 (4H, m, 3-CH_2 and4-CH_2) 2.49 (2H, dt, *J* 6.4; 1.0, 2-CH_2) 3.32 (6H, s, 2 x OCH_3) 4.37 (1H, t, *J* 5.3, 5-H) 9.77 (1H, t, *J* 1.0, *CHO*) [lit. (Schreiber et al., 1982) (270 MHz; $CDCl_3$) 9.77 (1H, t, *J* 1.3, *CHO*)].

Synthesis of (±)-2-(5,5-dimethoxy-pentylidene)-[1*RS*,3*RS*]-1,3-dioxo-1,3-dithiane 9

To a stirred solution of aldehyde **8** (9.85 mmol, 1.44 g) in anhydrous THF (10 mL) under nitrogen at room temperature, were added racemic phosphonate **4** (6.57 mmol, 1.89 g) and lithium hydroxide monohydrate (6.50 mmol, 273 mg). The stirring reaction mixture was heated at 70°C for 4 hours before being allowed to cool to room temperature, then the solvent was removed *in vacuo* to give a white solid residue. Flash column chromatography (5 % EtOH/DCM) afforded **9** as a colorless oil (1.65 g; 90 %); R_f (10% EtOH/DCM) 0.46; δ_H (400 MHz, $CDCl_3$) 1.54-1.68 (4H, m, 2x CH_2) 2.33-2.41 (1H, m) 2.45-2.56 (1H, m) 2.59-2.71 (2H, m) 2.75-2.82 (1H, m) 3.01-3.14 (1H, m) 3.19-3.27 (1H, m) 3.33 (6H, s, 2 x OCH_3) 3.61-3.67 (1H, m) 4.36 (1H, t, *J* 5.1, O*CH*O) 6.67 (1H, t, *J* 7.7, C=*CH*) [Lit. (Aggarwal *et al.*, 2002) (400 MHz, $CDCl_3$) 6.68 (1H, t, *J* 7.7, C=*CH*)]; δ_C (100 MHz; $CDCl_3$) 14.9 (t), 24.0 (t), 28.7 (t), 32.0 (t), 49.0 (t), 53.1(q), 53.2 (q), 55.6 (t), 104.3 (d), 140.4 (d), 145.0 (s).

Synthesis of (±)-5-([1*RS*,3*RS*]-1,3-dioxo-1,3-dithian-2-ylidene)-pentanal 6

Bisacetonitrilepalladium (II) chloride (1 mol %) (4.24 x 10^{-5} mmol, 10.3 mg) was added to a stirring solution of racemic acetal **9** (4.21 mmol, 1.18 g) in distilled acetone (150 mL) under nitrogen. The stirring orange solution was heated under reflux for two hours before the reaction mixture was allowed to cool to room temperature and concentrated *in vacuo* to give an orange oil. Flash column chromatography (7% EtOH /DCM) gave the aldehyde **6** as orange oil (875 mg, 89%); R_f (10% EtOH/DCM) 0.22; δ_H (400 MHz; $CDCl_3$) 1.84-1.92 (2H, m, 9-CH_2) 2.35-2.43 (1H, dm, *J* 16.1, 5-H_{eq}) 2.47-2.58 (1H, m, 4-H_{ax}) 2.61-2.69 (2H, m, 8-CH_2) 2.74 (1H, ddd, *J* 16.7, 16.7, 2.8, 6-H_{ax}) 2.81 (2H, dd, *J* 13.2, 11,7, 10-CH_2) 3.01-3.13 (1H, m, 5-H_{ax}) 3.23 (1H, dt, *J* 13.8, 2.6, 4-H_{eq}) 3.61-3.67 (1H, dm, *J* 16.5, 6-H_{eq}) 6.64 (1H, t, *J* 8.4, 7-H) 9.79 (1H, s, *CHO*) [Lit. (Aggarwal et al., 2002) (400 MHz, $CDCl_3$) 9.79 (1H, s, *CHO*)]; δ_C (100 MHz; $CDCl_3$) 14.9 (t), 21.1 (t), 28.1 (t), 42.7 (t), 49.0 (t), 55.4 (t), 139.2 (d), 145.9 (s), 201.1 (d).

Synthesis of 1',5'-pentylidene-bis-[1*RS*, 3*RS*]-1,3-dioxo-2-ylidene 5

Method A, to a suspension of the phophonate **4** (1.39 mmol, 400 mg) in 1,4-dioxane (8.63 mL),was added Mg $(OH)_2$ (1.5 mmol, 90.45 mg) and glutaraldehyde (25% solution in water), (0.695 mmol, 277 µL) under nitrogen.

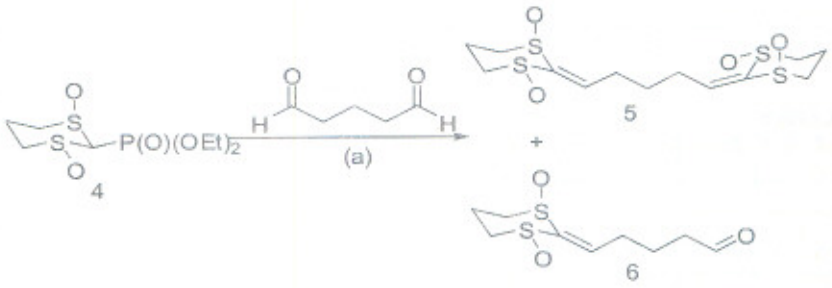

Figure 3. Reagents and Conditions: (a) $Mg(OH)_2$, dioxane, reflux, 4 h (5, 29 %; 6, 11 %).

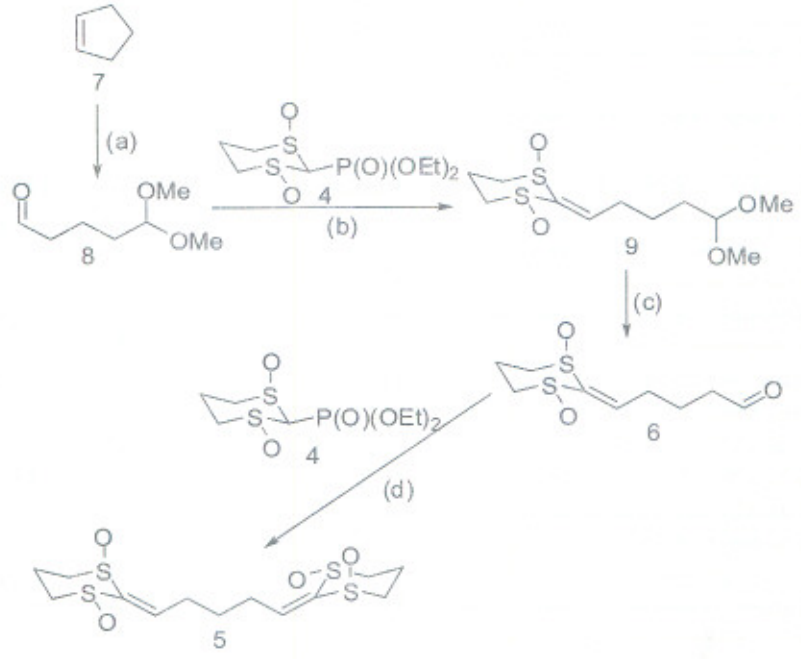

Figure 4. *Reagents and Conditions:* (a) O_3, MeOH, -78°C, *p*-TsOH, DMS, 39%; (b) $LiOH{\cdot}H_2O$, THF, 70°C, 90%; (c) $Cl_2Pd(CN)_2$ (1.0 mol%), acetone, H_2O, 70°C, 89%; (d)) $LiOH{\cdot}H_2O$, THF, 70°C, 56%.

The reaction was heated to reflux for 4 hours and allowed to cool to roomtemperature. The solvent was then removed under reduced pressure and the residue was extracted with chloroform (5 x 20 mL). The combined organic extracts were dried over $MgSO_4$, filtered and the solvent removed under reduced pressure. Flash column chromatography (10% EtOH/ $CHCl_3$) yielded **5** as a white foam (151 mg, 29%); R_f (10% EtOH/$CHCl_3$) 0.09; δ_H (270 MHz; $CDCl_3$) 1.55-1.86 (4H, m, 2 x CH_2), 2.34-2.44 (2H, dm, *J* 15.4, 2 X 5-H_{eq}), 2.49-2.57 (2H, dt, *J* 14.5, 7.3, CH_2), 2.58-2.90 (4H, m, 2 x 4-H_{ax}, 2 x 6-H_{ax}), 3.00-3.12 (2H, m, 2 x 5- H_{ax}), 3.18-3-27 (2H, dm, *J* 13.5, 2 x 4-H_{eq}), 3.60-3.67 (2H, ddm, *J* 11.6, 5.2, 2 x 6- H_{eq}), 6.64 (2H, dd, *J* 7.5, 7.2, 2 x CH) [lit. (Ritmaleni and Aggarwal, 2011) (250 MHz; $CDCl_3$) 6.62 (2H, dd, *J* 8.6, 7.0, 2 x CH)].

Method B, to a stirred solution of aldehyde **6** (1.15 mmol, 270 mg;) in anhydrous THF (2 mL) under nitrogen at room temperature was added racemic phosphonate (1.72 mmol, 496 mg) and lithium hydroxide monohydrate (1.72 mmol, 72 mg). The stirring reaction mixture was heated at 70°C for 4

hours and then cooled down to room temperature. Water (15 mL) was added to the reaction mixture and extracted with $CHCl_3$ (5 x 30 mL). The combined organic extract was dried over $MgSO_4$, filtered and the solvent removed under reduced pressure to give a white solid. Flash column chromatography (20% EtOH/ $CHCl_3$) afforded **5** as white foam (240 mg; 56%); R_f (10% EtOH/ $CHCl_3$) 0.10; with identical 1H-NMR to the compound on method A as before.

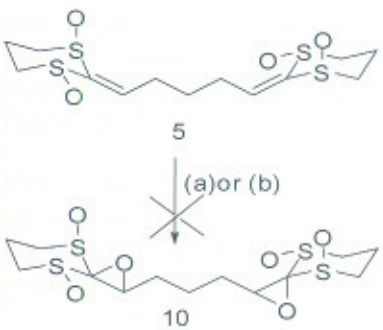

Figure 5. Reagents and Conditions: (a) H_2O_2, NaOH, -10°C, 20 min.; (b) t-BuOOH, n-BuLi, THF, -78°C to r.t,

RESULT AND DISCUSSION

To synthesise diaminopimelic acid, the epoxide **10** was required which could be obtained from bis-ketene-dithiocatal-dioxide **5**: the precursor to bis-epoxide-dithioacetal-dioxide **10** (Figure 3). The first attempt to synthesise **15** involved the reaction of an aqueous solution of the commercially available glutaraldehyde, with a solution of 1,3-dithiane-2-diethylphosphonate **4** with magnesium hydroxide as base, in dioxane. A yield of 29% was the best result that was achieved. This was due to an incomplete reaction, as 11% of **6** was isolated as a by-product (Figure 3).

The yields obtained were very low, therefore an alternative procedure was tried. Starting from cyclopentene **7**, ozonolysis was carried out, in the presence of methanol, to give the aldehyde **8** in 39 % yield. HWE reaction of **8** and **4** gave the ketene-dithioacetal-dioxide-dimethylacetal **9** in 90% yield. Hydrolysis of **9** using a palladium catalyst generated ketene-dithioacetal-dioxide-aldehyde **6** (Newman *et al.*, 1954) in an 89% yield. A second HWE reaction was then performed with **4** to give **5**, in reasonable yield (Scheme Figure 3).

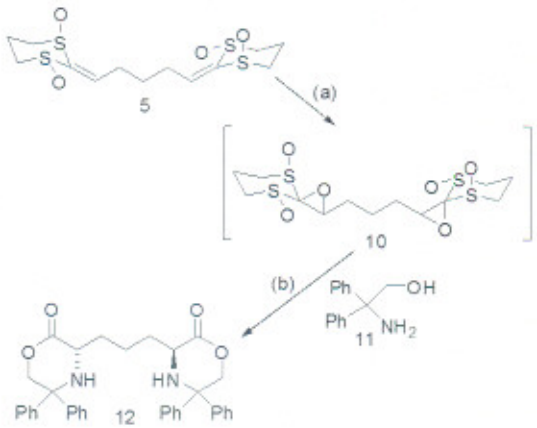

Figure 6. Reagents and Conditions: (a) H_2O_2, NaOH, -10°C, 20 min.; (b) CH_2Cl_2, r.t.

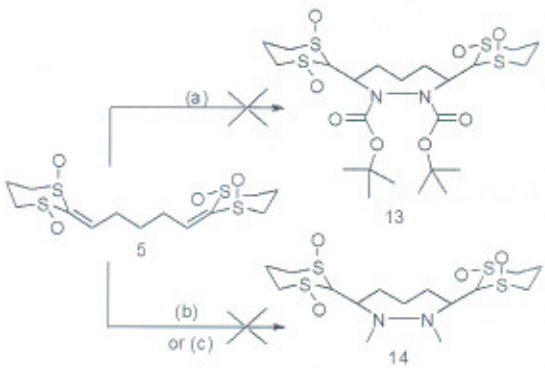

Figure 7. Reagents and Conditions: (a) Boc-NHNH-Boc, *n*-BuLi, 0°C to –78°C, NH_4Cl, 20 min.; (b) MeNHNHMe·2HCl, *n*-BuLi, THF, 0°C to –78°C, NH_4Cl, 20 min.; (c) MeNHNHMe·2HCl, Hünig's base, CH_2Cl_2

The above results show that both are reliable routes towards the synthesis of bis-ketene **5**. The first method gave a 17.7% overall yield in a 3-step reaction sequence while the second method gave a 17.5% overall yield in 4 steps.

Attempts were made at using basic hydrogen peroxide as an oxidant for the epoxidation reaction of **5**. Unfortunately, no product was observed. Monitoring by TLC showed only decomposition products. In addition, *tert*-butyl-hydrogen peroxide and *n*-BuLi in THF at –78°C were used as an

alternative oxidation system to prepare **10** from **5**. However, no reaction occurred and only starting material remained at the end of the reaction (Figure 5).

It is difficult to understand why **5** was unreactive to the epoxidation whereas the related substrate gave good yields of the corresponding epoxide. Using basic hydrogen peroxide, the bis-ketene-dithioacetal **5** was consumed and direct reaction with the amino alcohol **11** was attempted but the desired product could not be isolated (Figure 6).

Another route to the diaminopimelic acids was proposed by addition of a hydrazine derivative to **5**. The addition to **5** has been attempted using several different methods. Addition of Boc-hydrazine or hydrazine dihydrochloride salt to **5**, using *n*-BuLi as a base at -78°C, gave only the decomposition products. Attempts to synthesise **14**, involved the use of dimethyl hydrazine dihydrochloride salt with Hünig's base at room temperature in CH_2Cl_2 but no reaction occurred even when the reaction was heated up (Figure 6).

CONCLUSION

The synthesis of bis-spiroepoxide dithianedioxides has been attempted, unfortunately no one of the routes that have been tried gave the desired product.

ACKNOWLEDGEMENT

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