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Diastereoselective Reduction of 2,3-Dioxo-4-carboxy-5-substituted Pyrrolidines Using $NaBH_4$/AcOH and Heterogenous Hydrogenation Reactions

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ABSTRACT. Diastereoselective reduction of 2,3-dioxo-4-carboxy-5-(substituted)pyrrolidine **1** by $NaBH_4$/AcOH and heterogenous hydrogenation were reported. Stereochemical assignment and diastereomeric ratios of the products were determined using ^{1}H NMR and single crystal X-ray analyses. The steric factors of the C-5 substituents of the pyrrolidinone was shown to have an interesting influence on both the yield and diastereoselectivity of the reduced product.

Key words: 2,3-Dioxo-pyrrolidine, Diastereoselective, Enol reduction

INTRODUCTION

2,3-Dioxo-4-carboxy-5-substituted pyrrolidines are of great medicinal interest as they are substructures in a variety of bioactive compounds.[1] These include natural compounds such as (−)-codonopsinine, radicamine, rigidiusculamide, plakoridine and salinosporamide which display interesting biological activities.[2–4] Consequently, many types of natural or unnatural dioxopyrrolidinone and its modification have been successfully reported. Several experimental protocol have been successfully demonstrated on the preparation and exploration of 2,3-dioxo-4-carboxy-5-substituted-pyrrolidines. Some examples include decarboxylation reaction, bipiridines synthesis, oxidative cleavage for β-lactone synthesis and conversion of the 2,3-dioxopyrrolidine to enamine using amino-dehydroxylating agent of potassium cyanate.[5,6] Deprotonation of the hydroxyl group to give the enol ether and acetyl compound were also succesfully reported.[7] Interestingly, this class of 2,3-dioxopyrrolidines type of compounds has known existed predominantly in enolic tautomer which gave positive ferric chloride test.[8]

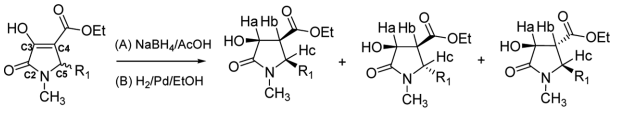
In conjunction towards the total synthesis of polyhydroxy alkaloids, we have successfully synthesized library of 2,3-dioxo-5-substituted pyrrolidines type of compounds.[9] From ^{1}H NMR analysis, the preference of the enolic tautomer structure of the 2,3-dioxo-4-carboxy-5-substituted pyrrolidines, were observed for all synthesized compounds either in deuterated $CDCl_3$ or DMSO. Remarkably, several attempts towards reduction of the 2,3-dioxo-4-carboxy-5-substituted pyrrolidines using $NaBH_4$/MeOH only led to negative results, even in the present of complexating agent of $CaCl_2$.[10] It concurred that inability of the hydride to reduce the ene of the enol tautomer led to these negative results. To our knowledge, only one successful example on direct ene-reduction of the enolic 2,3-dioxo-4-carboxy-5-substituted pyrrolidines tautomer are documented in literature. Upon treating enol 2,3-dioxo-4-carboxy-5-substituted pyrrolidines **1** with Zn dust in acidic conditions, Dehaen et al. successfully furnished the corresponding alcohols.[11]

For further understanding of this enolic reduction, we have further explored and reported herein, a different systems of heterogenous hydrogenation and borohydride reduction, as simpler and more general approach for reduction enolic 2,3-dioxo-4-carboxy-5-substituted-pyrrolidines.

EXPERIMENTAL

Experimental Protocols

IR spectra were recorded on Varian Excalibur 3100 in the spectral range of 4000 to 400 cm^{-1}. ^{1}H NMR spectra were recorded using Varian NMR Spectrometer instrument operating at 300 MHz.



1 **all *cis* X** ***cis trans* Y** **all *trans* Z**

***Scheme* 1**. Reduction of **1**.

Synthesis

$NaBH_4$/AcOH, Method A: To a stirred solution of **1** (1 mmol) in CH_2Cl_2 (50 mL) was added acetic acid (1 mmol) then $NaBH_4$ (1.1 mmol) at 0 °C. The resulting mixture was stirred for a further 1 h, then at room temperature for an additional 8 h and the solvent was then removed *in vacuo.* The residue was partitioned between EtOAc, washed with saturated $NaHCO_3$ solution. The organic phase was dried with $MgSO_4$ and concentrated *in vacuo.* The crude product was purified by column chromatography to give the hydroxy ester product.

H_2/Pd, Method B: To a stirred solution of **1** (1 mmol) in ethanol (37 ml) and Pd-C (10% wt) (1 mmol) was added. The reaction was stirred vigorously under hydrogen atmosphere for 3 h and then filtered through Celite. After removal of the solvent, the crude product was purified by column chromatography to give the hydroxy ester product.

Ethyl-4-hydroxy-1-methyl-5-oxopyrrolidine-3-carboxylate, (*all cis* Xa) and (*all trans* Za)

IR (KBr): 1729, 1693 cm^{-1}; *all cis* (Xa): ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.24–1.28 (t, *J*=7.0 Hz, 3H, CH_3), 2.88 (s, 3H, NCH_3), 3.34–3.39 (p, *J*=3.6 Hz, 1H, CH_2), 3.38–3.46 (dd, *J*=7.5 Hz, 1H, C*H*CO_2Et), 3.67–3.71 (dd, *J*=4 Hz, 1H, CH_2), 4.16–4.23 (q, *J*=7.2 Hz, 2H, OCH_2), 4.50–4.52 (d, *J*=7.5 Hz, 1H, C*H*OH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.1, 29.9, 42.8, 48.5, 61.3, 70.1, 170.2, 172.5. *all trans* (**Za**): ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.24–1.29 (t, *J*=7.2 Hz, 3H, CH_3), 2.85 (s, 3H, NCH_3), 3.10–3.18 (q, *J*=8.4 Hz, 1H, C*H*CO_2Et), 3.42–3.48 (t, *J*=9.3 Hz, 1H, CH_2), 3.48–3.55 (t, *J*=9.6 Hz, 1H, CH_2), 4.16–4.23 (q, *J*=7.2 Hz, 2H, OCH_2), 4.53–4.56 (d, *J*=8.7 Hz, 1H, C*H*OH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.1, 29.9, 45.1, 47.7, 61.5, 72.1, 171.6, 173.0.

Ethyl-4-hydroxy-1,2-dimethyl-5-oxopyrrolidine-3-carboxylate, (*all cis* Xb) and (*all trans* Zb)

IR (KBr): 1721, 1677 cm^{-1}; *all cis* Xb ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.20–1.25 (t, *J*=7.2 Hz, 3H, CH_3), 1.26–1.28 (d, *J*=6.6 Hz, 3H, CH_3), 2.79 (s, 3H, NCH_3), 3.33–3.37 (t, *J*=6.7 Hz, 1H, C*H*CO_2Et), 3.66–3.75 (p, *J*=6.6 Hz, 1H, CH_3C*H*NCH_3), 3.80–3.81 (d, *J*=3.0 Hz, 1H, O*H*), 4.12–4.20 (q, *J*=7.2 Hz, 2H, OCH_2), 4.42–4.43 (d, *J*=3.9 Hz, 1H, C*H*OH; ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.1, 15.0, 27.1, 49.1, 52.8, 60.9, 70.6, 169.4, 172.8. *all trans* Zb: IR (KBr): 1738, 1684 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.25–1.30 (t, *J*=7.0 Hz, 3H, CH_3), 1.34–1.36 (d, *J*=6.3 Hz, 3H, CH_3), 2.63–2.68 (t, *J*=8.4 Hz, 1H, C*H*CO_2Et), 2.79 (s, 3H, N*C*H_3), 3.55–3.64 (p, *J*=6.8 Hz, 1H, CH_3C*H*NCH_3), 4.17–4.24 (q, *J*=7.1 Hz, 2H, O*C*H_2), 4.54–4.58 (dd, *J*=8.5 Hz, 1H, C*H*OH), 4.81–4.82 (d, *J*=3.3 Hz, 1H, O*H*); ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.1, 19.1, 27.3, 54.3, 54.3, 61.5, 72.1, 171.5, 173.0.

Ethyl-4-hydroxy-1-methyl-5-oxo-2-propylpyrrolidine-3-carboxylate, (*all cis* Xc) (*all trans* Zc) and (*cis trans* Yc)

IR (KBr): 1738, 1703 cm^{-1}; *all cis* Xc ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.91–0.96 (t, *J*=7.2 Hz, 3H, CH_3), 1.21–1.26 (t, *J*=7.0 Hz, 3H, CH_3), 1.28–1.38 (m, 1H, CH_2), 1.39–1.53 (m, 2H, CH_2), 1.77–1.86 (m, 1H, CH_2), 2.71 (br s, 1H, OH), 2.82 (s, 3H, NCH_3), 3.44–3.48 (t, *J*=7.0 Hz, 1H, C*H*CO_2Et), 3.52–3.59 (p, *J*=5.0 Hz, 1H, C*H*$(CH_2)_2CH_3$), 4.11–4.23 (m, 2H, OCH_2), 4.42–4.44 (d, *J*=7.8 Hz, 1H, C*H*OH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.0, 14.1, 18.8, 27.5, 31.1, 48.6, 57.1, 60.8, 70.8, 169.3, 173.2 *all trans* Zc: IR (KBr): 1718, 1687 cm^{-1}, ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.90–0.95 (t, *J*=7.2 Hz, 3H, CH_3), 1.22–1.36 (m, 2H, CH_2), 1.25–1.29 (t, *J*=7.0 Hz, 3H, CH_3), 1.45–1.57 (m, 1H, CH_2), 1.73–1.84 (m, 1H, CH_2), 2.73–2.78 (t, *J*=7.6 Hz, 1H, C*H*CO_2Et), 2.80 (s, 3H, NCH_3), 3.61–3.67 (dt, *J*=7.5 Hz, 1H, C*H*$(CH_2)_2CH_3$), 4.14–4.25 (m, 2H, OCH_2), 4.49–4.52 (d, *J*=7.8 Hz, 1H, C*H*OH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 13.9, 14.1, 16.9, 27.8, 34.5, 51.6, 58.6, 61.5, 72.8, 172.2, 173.0. *cis trans* Yc: ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.90–0.95 (t, *J*=7.2 Hz, 3H, CH_3), 1.22–1.36 (m, 2H, CH_2), 1.25–1.29 (t, *J*=7.0 Hz, 3H, CH_3), 1.45–1.57 (m, 1H, CH_2), 1.73–1.84 (m, 1H, CH_2), 2.83 (s, 3H, NCH_3), 3.06-3.10 (dd, *J*=8.55 Hz, 1H, C*H*CO_2Et), 3.76–3.81(dq, *J*=3.9 Hz, 1H, C*H*$(CH_2)_2CH_3$), 4.14–4.25 (m, 2H, OCH_2), 4.53–4.56 (d, *J*=8.4 Hz, 1H, C*H*OH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 13.9, 14.1, 17.9, 28.2, 34.3, 48.4, 59.9, 61.2, 69.6, 170.3,172.6.

Ethyl-2-heptyl-4-hydroxy-1-methyl-5-oxopyrrolidine-3-carboxylate, (*all cis* Xd) (*all trans* Zd) and (*cis trans* Yd)

IR (KBr): 1738, 1706 cm^{-1}; *all cis* Xd ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.84–0.88 (t, *J*=6.7 Hz, 3H, CH_3), 1.21–1.26 (t, *J*=7.2 Hz, 3H, CH_3), 1.21–1.35 (m, 9H, CH_2), 1.39–1.50 (m, 2H, CH_2), 1.78–1.87 (m, 1H, CH_2), 2.82 (s, 3H, N*C*H_3), 3.44–3.48 (t, *J*=6.6 Hz, 1H, C*H*CO_2Et), 3.50–3.57 (p, *J*=5.1 Hz, 1H, C*H*$(CH_2)_6CH_3$), 4.13–4.21 (dq, *J*=7.2 Hz, 2H, OCH_2), 4.42–4.44 (d, *J*=7.5 Hz, 1H, C*H*OH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.0, 14.1, 22.5, 25.4, 27.5, 29.0, 29.5, 31.6, 48.6, 57.3, 60.8, 70.8, 169.3, 173.2. *all trans* Zd: ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.82–0.87 (t, *J*=6.7 Hz, 3H, CH_3), 1.22–1.29 (m, 10H, CH_2), 1.24–1.29 (t, *J*=7.2 Hz, 3H, CH_3), 1.48–1.57 (m, 1H, CH_2), 1.76–1.85 (m, 1H, CH_2), 2.73–2.78 (t, *J*=7.8 Hz, 1H, C*H*CO_2Et), 2.79 (s, 3H, NCH_3), 3.60–3.66 (dt, *J*=7.6 Hz, 1H, C*H*$(CH_2)_6CH_3$),

4.14–4.26 (m, 2H, OCH_2), 4.49–4.52 (d, *J*=7.8 Hz, 1H, CHOH); ^{13}C NMR (75 MHz, $CDCl_3$): 14.0, 14.1, 22.5, 23.5, 27.8, 29.0, 29.4, 31.6, 32.2, 51.6, 58.7, 61.5, 72.8, 172.3, 173.0. *cis trans* Yd: ^1H NMR (300 MHz, $CDCl_3$): δ 0.82–0.87 (t, *J*=6.7 Hz, 3H, CH_3), 1.22–1.29 (m, 10H, CH_2), 1.24–1.29 (t, *J*=7.2 Hz, 3H, CH_3), 1.48–1.57 (m, 1H, CH_2), 1.76–1.85 (m, 1H, CH_2), 2.83 (s, 3H, NCH_3), 3.06–3.10 (dd, *J*=8.7 Hz, 1H, C*H*CO_2Et), 3.74–3.81 (s, *J*=3.9 Hz, 1H, C*H*$(CH_2)_6CH_3$), 4.14–4.26 (m, 2H, OCH_2), 4.53–4.56 (d, *J*=8.4 Hz, 1H, C*H*OH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.0, 14.1, 22.5, 24.5, 28.7, 29.0, 29.4, 31.6, 32.1, 48.4, 60.1, 61.2, 69.6, 170.3, 172.6.

Ethyl-4-hydroxy-1-methyl-5-oxo-2-phenylpyrrolidine-3-carboxylate, (*all cis* Xe) (*all trans* Ze) and (*cis trans* Ye)

IR (KBr): 1732, 1676 cm^{-1}; *all cis* Xe ^1H NMR (300 MHz, $CDCl_3$): δ 0.82–0.87 (t, *J*=7.0 Hz, 3H, CH_3), 2.75 (s, 3H, N*C*H_3), 3.61–3.65 (t, *J*=7.3 Hz, 1H, C*H*CO_2Et), 3.62–3.73 (m, 1H, OCH_2), 3.75–3.86 (m, 1H, OCH_2), 4.55–4.57 (d, *J*=7.5 Hz, 1H, C*H*OH), 4.73–4.76 (d, *J*=7.2 Hz, 1H, ArC*H*NCH_3), 7.24–7.26 (m, 2H, ArC*H*), 7.27–7.36 (m, 3H, ArC*H*); ^{13}C NMR (75 MHz, $CDCl_3$): 13.5, 28.9, 49.1, 61.0, 63.1,70.4, 127.8, 128.6, 128.7, 134.9, 169.4, 173.3. *all trans* Ze: IR (KBr): 1732, 1689 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.18–1.23 (t, *J*=7.0 Hz, 3H, CH_3), 2.64 (s, 3H, NCH_3), 3.02–3.07 (t, *J*=8.2 Hz, 1H, C*H*CO_2Et), 3.62 (s br, 1H, OH), 4.13–4.21 (2H, dq, *J*=7.2 Hz, OCH_2), 4.60–4.63 (d, *J*=7.8 Hz, 1H, ArC*H*NCH_3), 4.66–4.68 (d, *J*=8.1 Hz, 1H, C*H*OH), 7.25–7.28 (dd, *J*=7.6 Hz, 2H, ArC*H*), 7.35–7.39 (m, 3H, ArC*H*); ^{13}C NMR (75 MHz, $CDCl_3$): 14.1, 28.4, 55.9, 61.5, 63.2, 72.4, 127.3, 128.6, 128.9, 137.7, 171.2, 173.3. *cis trans* Ye: ^1H NMR (300 MHz, $CDCl_3$): δ 1.23–1.28 (t, *J*=7.2 Hz, 3H, CH_3), 2.73 (s, 3H, NCH_3), 3.19–3.23 (dt, *J*=6.6 Hz, 1H, C*H*CO_2Et), 4.12–4.22 (m, 2H, OCH_2), 4.69–4.72 (d, *J*=7.8 Hz, 1H, C*H*OH), 4.96–4.98 (d, *J*=5.7 Hz, 1H, ArC*H*NCH_3), 7.25–7.28 (d, *J*=7.2 Hz, 1H, ArC*H*), 7.32–7.41 (m, 4H, ArC*H*); ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.1, 28.5, 52.9, 61.3, 64.1, 69.7, 126.7, 129.1, 129.2,138.1, 169.2, 173.2.

Ethyl-4-hydroxy-1-methyl-2-(4-methylphenyl)-5-oxo-2-pyrrolidine-3-carboxylate, (*all cis* Xf) (*all trans* Zf) and (*cis trans* Yf)

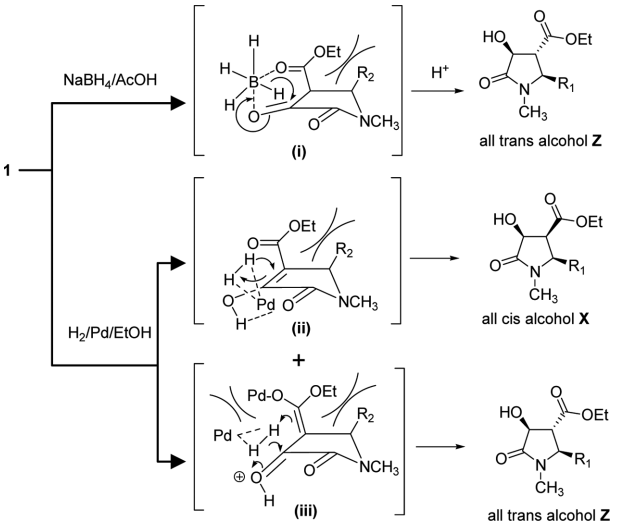
IR (KBr): 1739, 1673 cm^{-1}; *all cis* Xf ^1H NMR (300 MHz, $CDCl_3$): δ 0.86–0.90 (t, *J*=7.2 Hz, 3H, CH_3), 2.32 (s, 3H, CH_3), 2.74 (s, 3H, NCH_3), 3.58–3.62 (t, *J*=7.3 Hz, 1H, C*H*CO_2Et), 3.68–3.74 (m, 1H, OCH_2), 3.81–3.86 (m, 1H, OCH_2), 4.53–4.55 (d, *J*=7.2 Hz, 1H, C*H*OH), 4.70–4.73 (d, *J*=7.5 Hz, 1H, ArC*H*NCH_3), 7.14 (s, 4H, ArC*H*); ^{13}C NMR (75 MHz, $CDCl_3$): δ 13.5, 21.0, 28.8, 49.1, 61.0, 62.9, 70.4, 127.7, 129.2,131.8,138.6, 169.5, 173.2. *all trans* Zf: IR (KBr): 1739, 1689 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.18–1.23 (t, *J*=7.2 Hz, 3H, CH_3), 2.35 (s, 3H, CH_3), 2.62 (s, 3H, NCH_3), 3.0–3.06 (*J*=8.2 Hz, 1H, C*H*CO_2Et), 3.10 (br s, 1H, O*H*), 4.12–4.20 (dq, *J*=7.08 Hz, 2H, OCH_2), 4.56–4.58 (d, *J*=7.8 Hz, 1H, ArC*H*NCH_3), 4.63–4.66 (d, *J*=8.7 Hz, 1H, C*H*OH), 7.13–7.16 (d, *J*=8.4 Hz, 2H, ArC*H*), 7.18–7.20 (d, *J*=8.1 Hz, 2H, ArC*H*); ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.1, 21.1, 28.3, 56.0, 61.5, 63.0, 72.4, 127.3, 129.8, 134.6,138.7, 171.3, 173.1. *cis trans* Yf: ^1H NMR (300 MHz, $CDCl_3$): δ 1.23–1.28 (t, *J*=7.0 Hz, 3H, CH_3), 2.34 (s, 3H, CH_3), 2.72 (s, 3H, NCH_3), 3.17–3.22 (dt, *J*=6.6 Hz, 1H, C*H*CO_2Et), 4.12–4.20 (dq, *J*=7.0 Hz, 2H, OCH_2), 4.69–4.71 (d, *J*=7.8 Hz, 1H, C*H*OH), 4.92–4.94 (d, *J*=5.1 Hz, 1H, ArC*H*NCH_3), 7.07–7.09 (d, *J*=7.8 Hz, 2H, ArC*H*), 7.13–7.16 (d, *J*=8.4 Hz, 2H, ArC*H*); ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.1, 21.1, 28.4, 52.9, 61.3, 63.9, 69.8, 126.6, 129.8, 135.1, 138.4,169.3, 173.1.

Ethyl-4-hydroxy-2-(4-methoxyphenyl)-1-methyl-5-oxopyrrolidine-3-carboxylate, (*all cis* Xg) (*all trans* Zg) and (*cis trans* Yg)

IR (KBr): 1733, 1677 cm^{-1}; *all cis* Xg ^1H NMR (300 MHz, $CDCl_3$): δ 0.84–0.89 (t, *J* =7.0 Hz, 3H, CH_3), 2.68 (s, 3H, NCH_3), 3.55–3.60 (t, *J*=7.3 Hz, 1H, C*H*CO_2Et), 3.65–3.83 (m, 2H, OCH_2), 3.742 (s, 3H, OCH_3), 4.27 (s br, 1H, O*H*), 4.52–4.54 (d, *J*=7.2 Hz, 1H, C*H*OH), 4.69–4.67 (d, *J*=7.5 Hz, 1H, ArC*H*NCH_3), 6.80–6.83 (d, *J*=8.7 Hz, 2H, ArC*H*), 7.14–7.17 (*J*=8.7 Hz, 2H, ArC*H*); ^{13}C NMR (75 MHz, $CDCl_3$): δ 13.6, 28.7, 49.2, 55.2, 60.9, 62.6, 70.3, 113.8, 126.8, 129.1, 159.8, 169.5, 173.4. *all trans* Zg: IR (KBr): 1735, 1687; ^1H NMR (300 MHz, $CDCl_3$): δ 1.16–1.21 (t, *J*=7.0 Hz, 3H, CH_3), 2.59 (s, 3H, NCH_3), 2.99–3.05 (t, *J*=8.1 Hz, 1H, C*H*CO_2Et), 3.78 (s, 3H, OCH_3), 4.10–4.19 (m, 2H, OCH_2), 4.53–4.55 (d, *J*=8.1 Hz, 1H, ArC*H*NCH_3), 4.63–4.66 (d, *J*=8.4 Hz, 1H, C*H*OH), 5.19 (br s, 1H, O*H*), 6.87–6.89 (d, *J*=8.1 Hz, 2H, ArC*H*), 7.16–7.19 (d, *J*=7.8 Hz, 2H, ArC*H*); ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.1, 28.3, 55.2, 56.0, 61.4, 62.8, 72.4, 114.4, 128.6, 129.5, 159.9, 171.4, 173.4. *cis trans* Yg: ^1H NMR (300 MHz, $CDCl_3$): δ 1.21–1.25 (t, *J*=6.7 Hz, 3H, CH_3), 2.67 (s, 3H, NCH_3), 3.14–3.18 (t, *J*=6.7 Hz, 1H, C*H*CO_2Et), 3.78 (s, 3H, OCH_3), 4.10–4.19 (m, 2H, OCH_2), 4.69–4.71 (d, *J*=7.8 Hz, 1H, C*H*OH), 4.93–4.95 (d, *J*=5.7 Hz, 1H, ArC*H*NCH_3), 5.19 (br s, 1H, O*H*), 6.87–6.89 (d, *J*=8.1 Hz, 2H, ArC*H*), 7.10–7.13 (d, *J*=8.4 Hz, 2H, ArC*H*); ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.1, 28.3, 53.1, 55.2, 61.2, 63.6, 69.8, 114.5, 128.1, 129.9, 159.7,169.2, 173.3.

RESULTS AND DISCUSSION

As shown in *Table* 1, the reduction of the 2,3-dioxo-4-carboxy-pyrrolidines **1** using $NaBH_4$/AcOH gave moderate to good yields (57–89%). Nevertheless it gave superior diastereoselectivity, leading majority of the product to the *all trans* alcohol **Z**. During the reaction, it was anticipated that conversion of the enol tautomers to more stable keto form occurred in the aqueous acidic solution,[12] unlike in previous neutral borohydride reduction. In term of diastereoselection, the steric effect imposed by bulky C-5 substituent were markedly effecting in this reduction system to give the more thermodynamic *trans* products **Z**. For compound **1a**, which free of C-5 substituent, less diastereoselectivity were observed (*d.e*=24:0:76, entry 1). The key diastereoselectivity in this borohydride acid mediated reduction was alleged to occur from coordination of the $NaBH_4$ with both carbonyl functionalities.[9(b)] Then, the incoming hydride of $NaBH_4$ was delivered from the less hindered side of (i), forcing the carbonyl ester away from the C-5 substituent to be in stable *trans*-position state. Consequently, the oxyborohydride group attaching to the new C-2 chiral center will adopt the similar thermodynamic advantages concertedly, as depicted in *Scheme* 2.



***Scheme* 2.** Proposed mechanistic reduction of **1**.

Conversely, reduction of the enolic tautomers **1** *via syn*-hydrogenation in neutral conditions gave excellent yields of the *cis* hydroxy ester product (71–99%) (*Table* 1). Excellent diastereoselectivity can be seen with compound **1a**, which produced the *all cis* **Xa** as the sole hydroxyl ester product (*d.e*=100:0:0) (*Table* 1, entry 1). However, diastereoselection becoming less significant as the substituents at C-5 sterically increased (entries 2–7), which gave rise to mixture of all the diastereomers. Nevertheless, this *syn*-hydrogenation reaction showed that the ratio of *all cis* **X** always succeed than the other diastereomers. Oppositely, the mechanism of the *syn*-hydrogenation to enolate (iii) happened from the less hindered face leading to the *trans* reduced product **Z** (*Scheme* 2). The unlikely *trans* diastereomers was also reported by Bessen et al during hydrogenation of exocyclic pyrolidine β-enamino esters.[13] Bulkier substituent of aromatics also contributed to lower yields, which attributed by blocking off the complexation Pd/ene site (entries 5–7). It was reported that during the hydrogenation process, the C=C double bond and the OH group are involved in the reactant-Pd interaction.[13]

Noted that, the enolic hydroxyl ester **1** has three prochiral centers which are located at C-3, C-4 and C-5 positions and could produce eight possible diastereoisomers. Regardless the absolute configuration, only three main diastereomers of *all cis* **X**, *all trans* **Z** and *cis trans* **Y** were consider to present in the racemic mixture. Confirmation of all the diastereoisomers were assigned by ^{1}H NMR and 2D NMR exper-

***Table* 1.** Stereoselective reduction of **1** using $NaBH_4$/AcOH (Method A) and H_2/Pd (Method B)

Entry	Compound	R_1	Yield[a] (%)	Method A dr[b]					Yield[a] (%)	Method B dr[b]				
				X	:	Y	:	Z		X	:	Y	:	Z
1	1a	H	64[c]	24	:	-	:	76	99	100	:	-	:	-
2	1b	methyl	71	2	:	-	:	98	82	75	:	-	:	25
3	1c	propyl	79	8	:	-	:	92	99[d]	62	:	7.5	:	30.5
4	1d	heptyl	89[d]	7	:	19	:	74	94[d]	54	:	10	:	56
5	1e	Ph	79	2	:	-	:	98	71[d]	34	:	43	:	23
6	1f	4-CH_3Ph	57	2	:	-	:	98	88[d]	40	:	20	:	48
7	1g	4-CH_3OPh	74	2	:	-	:	98	78[d]	51	:	20	:	29

[a]Yield was based on the mixture of diastereomeric compound obtained after purification by column chromatography.
[b]Diastereomeric ratio was based on the isolated yield after column chromatrography.
[c]Diastereomeric ratio was determined by ^{1}H NMR spectroscopic analysis of crude reaction mixtures.
[d]Diasteromeric ratio was determined by ^{1}H NMR spectroscopic analysis and isolated yield.

***Table* 2.** ^{1}H NMR assignment for Ha and Hb for all *trans/cis* product 1a–g

Compound	Shift value (ppm)				Coupling constant (Hz)			
	all trans		*all cis*		*all trans*		*all cis*	
	Ha	Hb	Ha	Hb	Ha	Hb	Ha	Hb
1a	4.53–4.56	3.10–3.18	4.50–4.52	3.38–3.46	8.7	8.4	7.5	7.5
1b	4.54–4.58	2.63–2.68	4.42–4.43	3.33–3.37	8.5	8.4	3.9	6.7
1c	4.49–4.52	2.73–2.78	4.42–4.44	3.44–3.48	7.8	7.6	7.8	7.0
1d	4.49–4.52	2.73–2.78	4.42–4.44	3.44–3.48	7.8	7.8	7.5	6.6
1e	4.66–4.68	3.02–3.07	4.55–4.57	3.61–3.65	8.1	8.2	7.5	7.3
1f	4.63–4.66	3.00–3.06	4.53–4.55	3.58–3.62	8.7	8.2	7.2	7.3
1g	4.63–4.66	2.99–3.05	4.52–4.54	3.55–3.60	8.4	8.1	7.2	7.3

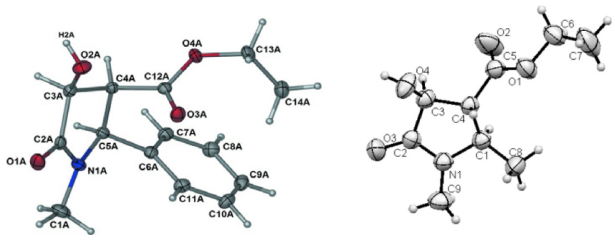


***Figure* 1.** Single X-ray structure for *all cis* **1e** and *all trans* **1b**.

iments. Generally, all proton of Ha and Hb of *trans* reduced products display higher shift values as compared to *cis* reduced product (*Scheme* 1, *Table* 2) which is in agreement with previous report.[11] This was due to deshielding effect imposed by the ethoxyester onto the Ha protons of the *all trans* product. Hence, this also contributes to higher coupling constant values. Resulted consistency of Ha coupling constant values of the all *trans* product indicate that Ha are indeed in close proximity to the ester functionality.

Furthermore, the structure of some of the *trans/cis* reduced product was confirmed by X-ray investigation as shown in *Figure* 1.[14]

CONCLUSION

In summary, we have described a general and simple method for the diastereoselective reduction of the enolic 2,3-dioxo-4-carboxyl-5-substituted pyrrolidines in mild conditions. Excellent yields with high diastereoselectivity were observed in both strategies. Currently the synthesized hydroxyl pyrrolidine are further functionalized in our laboratory towards the synthesis of other interesting biologically active compounds.

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