



DIASTEREOSELECTIVE REDUCTION OF ENDOCYCLIC β -ENAMINO ESTER: AN APPROACH TO PREPARE DIASTEREOPURE MULTISUBSTITUTED PYRROLIDINE β -AMINO ESTERS

(Penurunan Diastereoselektif Terhadap Ester β -Enamino Endosiklik: Satu Pendekatan untuk Menyediakan Ester β -Amino Pirolidin Multi-Penukarganti Diastereotulen)

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Received: 26 November 2021; Accepted: 27 February 2022; Published: 28 April 2022

Abstract

A set of chiral multi-substituted pyrrolidine diastereomers containing β -amino ester moiety (**5a-c**) were successfully synthesized from 4-carbethoxy-3-hydroxy-2-oxo-5-phenyl-3-pyrroline (**1**). The key intermediate endocyclic β -enamino ester (**4**) was prepared by methylation of precursor **1**, followed by acid-catalyzed reduction of **4** using sodium cyanoborohydride to obtain target products (**5**) with moderate diastereoselectivity. Other exploration on the reduction of **4** includes the use of sodium triacetoxyborohydride in acetic acid and catalytic hydrogenation which are subsequently compared with the aforementioned approach in terms of selectivity. Several plausible reaction mechanisms have been proposed based on experimental data.

Keywords: pyrrolidine; β -enamino ester; diastereoselective reduction; catalytic hydrogenation; sodium cyanoborohydride.

Abstrak

Satu set diastereomer pirolidin multi-penukarganti kiral yang mengandungi bahagian ester β -amino (**5a-c**) telah berjaya disintesis daripada 4-karbetoksi-3-hidroksi-2-okso-5-fenil-3-pirolin (**1**). Perantara utama, ester β -enamino endosiklik (**4**), telah disediakan melalui metilaminasi pendahulu **1**. Kemudian, penurunan bagi **4** yang dimungkinkan oleh asid menggunakan natrium sianoborohidrid menghasilkan produk sasaran **5** dengan diastereoselektiviti yang sederhana. Tatacara lain untuk menurunkan **4** termasuk penggunaan natrium triasetoksiborohidrid dalam asid asetik dan penghidrogenan mangkin telah dibandingkan dengan kaedah terdahulu dari sudut selektiviti. Di sini, kami menghuraikan beberapa mekanisme tindakbalas yang munasabah daripada hasil eksperimen ini.

Kata kunci: pirolidin; ester β -enamino; penurunan diastereoselektif; penghidrogenan mangkin; natrium sianoborohidrid.

Introduction

β -enamino esters **A** are recognized as versatile building blocks in the synthesis of various interesting alkaloids [1] including bi- and tricyclic heterocycles such as pyrrolopyrimidines [2], pyrroloquinolines [3], indoles [4], pyrrolizidines and indolizidines [5, 6] (Figure 1). The multifunctionality of these compounds resides in the simultaneous presence of a nitrogen atom, a carbon-carbon double bond, C=C (which when reduced, gives rise to one or two chiral centre(s) and enhances the nucleophilicity of the nitrogen via the localization of its lone pair electrons) and an ester group for further chain extension or ring closure [7, 8].

Owing to their role as key intermediates for synthesizing naturally occurring compounds (Figure 2), this class of functional group has been of crucial interest to researchers especially for the chemistry of its enantio- and diastereoselective reductions.

Excellent enantioselectivity of catalytic hydrogenation over palladium hydroxide, Pd(OH)₂ enables the preparation of (+)-calvine, an alkaloid piperidine isolated from coccinellid beetles of the genus *Calvia*

[9]. Hydrogenations in the presence of 10% platinum on carbon (Pt/C) and 10% palladium on carbon (Pd/C) offers high diastereoselectivity to reduce β -enamino esters with exocyclic C=C in the asymmetrical syntheses of (+)-laburnine and (+)-tashiromine, respectively. While the ones with endocyclic double bond can be reduced using platinum dioxide-catalyzed hydrogenation with a large diastereomeric excess (d.e. = 90%) as described in the synthetic approach of constructing (-)-isoretronecanol [10, 11].

Apart from that, chemical reduction by sodium triacetoxyborohydride, NaBH(OAc)₃ in acetic acid provides greater diastereoselectivity for enamino esters with endocyclic C=C rather than their exocyclic and acyclic counterparts [10], while in the presence of magnesium iodide (MgI₂), near quantitative yield can be achieved [12]. Sodium cyanoborohydride, NaBH₃CN is a versatile reducing agent known for its ability to yield diastereopure β -amino esters as mentioned in the preparation of ($\pm$)-lythrancepine (II) and (III) [8].

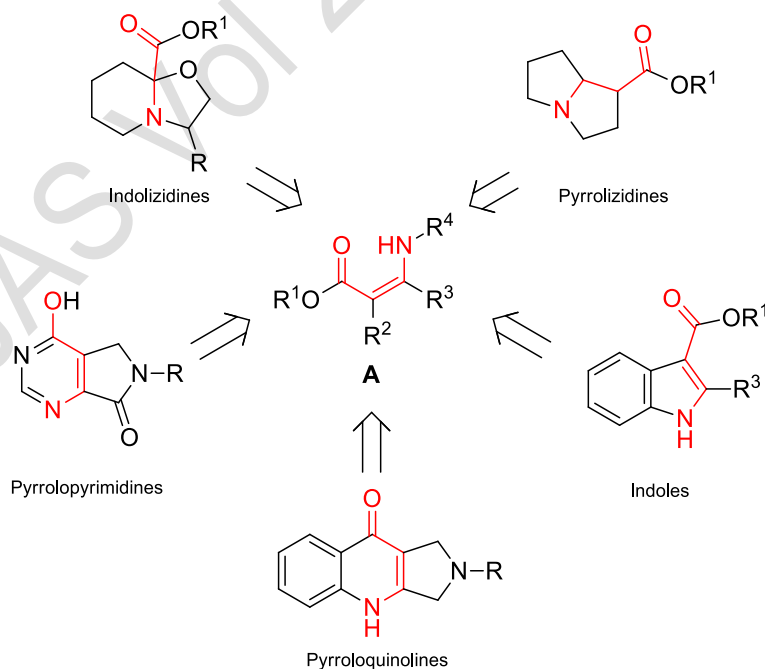


Figure 1. Bi- and tricyclic alkaloids derived from β -enamino esters

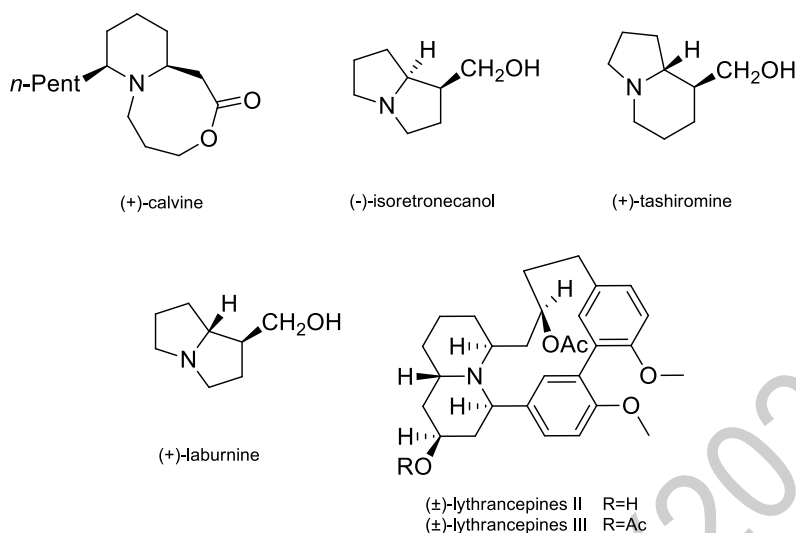


Figure 2. Naturally occurring compounds derived from selective reductions of β -enamino esters

Notably, some studies report that catalytic hydrogenations portray superior selectivity over chemical reductions when involving exocyclic and acyclic β -enamino esters [10, 13]. To our knowledge, there is yet any reported work that specifically discusses the chemistry behind the reduction of endocyclic β -enamino esters – i.e. comparison between the two approaches.

Ergo, in this short study, we describe an experiment to reduce β -enamino ester (**4**) containing endocyclic C=C. The procedures explored include hydrogenation with either 10% Pd/C or 20% Pd(OH)₂/C along with reduction using either NaBH(OAc)₃ in acetic acid or NaBH₃CN in acidic medium. Different approaches are believed to have distinct stereochemical controls and effectiveness over the reduction protocols.

Materials and Methods

All reagents and solvents were supplied by R&M Chemicals, Merck KgaA and Acros Organics. The reactions were monitored by TLC on silica gel 60 F254 plates, Merck (layer thickness 0.25 mm) and visualized with UV light (254 and 365 nm) and KMnO₄ solution as the staining reagent. For product purification using column chromatography, Merck silica gel (230-400 mesh particle size) was used. Infrared spectra were recorded on Varian 3100 Excalibur Series FT-IR

spectrometer in the range of 4000-400 cm⁻¹. ¹H-, ¹³C- and 2D NMR spectra were captured on JEOL-400 (¹H 400 MHz, ¹³C 101 MHz) NMR spectrometer.

Multicomponent reaction (MCR) to synthesize 4-carbethoxy-3-hydroxy-2-oxo-5-phenyl-3-pyrroline (**1**)

The method was adapted from literature [15]. Sodium diethyl oxalacetate (5.01 g, 24 mmol), benzaldehyde (2.4 mL, 24 mmol) and aqueous ammonia (8.0 mL, 119 mmol) were suspended in ethanol (70 mL) and refluxed. After an hour and 15 minutes, the reflux was stopped and once the mixture cooled down to room temperature, it was added to an ice bath. The mixture was acidified with concentrated HCl until it reached pH 2 while being constantly stirred. The resulting precipitate was filtered by suction and washed with distilled water. The solid was dried under vacuum overnight to give the product, 4-carbethoxy-3-hydroxy-2-oxo-5-phenyl-3-pyrroline, as a white solid (Yield: 2.67 g, 42%).

Analytical data: FT-IR (ATR) $\bar{\nu}$ (cm⁻¹) 3370 (O-H), 3311 (N-H), 2994 (C-H), 1689 (C=O); ¹H-NMR (400 MHz, CD₃OH) δ (ppm) 7.32-7.22 (m, 5H, ArH), 5.23 (s, 1H, ArCHNH), 4.10-4.01 (m, 2H, OCH₂), 1.06 (t, J = 7.1 Hz, 3H, CH₃); ¹³C-NMR (101 MHz, CD₃OH) δ (ppm) 167.4 (C=C-OH), 163.5 (O-C=O), 155.0

(NHC=O), 137.4 (ArC-CH), 128.2 (ArCH), 127.9 (ArCH), 127.1 (ArCH), 114.0 (C=C-C=O), 60.1 (OCH₂), 57.3 (ArCHNH), 13.0 (CH₃).

Leuckart reaction to synthesize 3-amino-4-carboethoxy-2-oxo-5-phenyl-3-pyrroline (2)

The method was adapted from literature [2]. To a suspension of 4-carboethoxy-3-hydroxy-2-oxo-5-phenyl-3-pyrroline (1) (2.01 g, 8 mmol) in ethanol (40 mL), ammonium formate (1.03 g, 16 mmol) was added while stirring. After heating under reflux for 24 hours with TLC monitoring, the mixture was left to cool to room temperature. The solvent was evaporated under reduced pressure and the crude product was purified using column chromatography (petroleum ether/ethyl acetate: 2/1) to yield the product, 3-amino-4-carboethoxy-2-oxo-5-phenyl-3-pyrroline, as a white solid (Yield: 1.23 g, 62%).

Analytical data: TLC (Petroleum ether/ethyl acetate : 2/1, R_f = 0.26); FT-IR (ATR) $\bar{\nu}$ (cm⁻¹) 3482 (N-H), 3385 (N-H), 3278 (N-H), 2965 (C-H), 1718 (conj. C=O), 1679 (C=O), 1625; ¹H-NMR (400 MHz, CD₃OH) δ (ppm) 7.28-7.19 (m, 5H, ArH), 5.16 (s, 1H, ArCHNH), 4.57 (s, 2H, NH₂), 4.06-3.99 (m, 2H, OCH₂), 1.07 (t, J = 7.1 Hz, 3H, CH₃); ¹³C-NMR (101 MHz, DMSO-d₆) δ (ppm) 167.3 (O-C=O), 164.8 (NHC=O), 147.4 (C=C-NH₂), 140.3 (ArC-CH), 128.6 (ArCH), 128.0 (ArCH), 127.7 (ArCH), 103.3 (C=C-C=O), 59.3 (OCH₂), 57.8 (ArCHNH), 14.7 (CH₃).

Hydrogenation of 3-amino-4-carboethoxy-2-oxo-5-phenyl-3-pyrroline (2) over 10% Pd/C

This is our in-house method [19]. To a stirred solution of 3-amino-4-carboethoxy-2-oxo-5-phenyl-3-pyrroline (2) (0.50 g, 2.03 mmol) in acetic acid (50 mL), 10% Pd/C (0.30 g, 0.26 mmol) was added slowly. The reaction mixture was stirred vigorously under hydrogen atmosphere at 1 atm with TLC monitoring. After 22 hours, the reaction was stopped and the catalyst was filtered through Celite. The solvent was removed from the filtrate under reduced pressure to give a white solid. From TLC, FT-IR and NMR characterization experiments, it was concluded that the starting material 2 was recovered.

Analytical data: TLC (Petroleum ether/ethyl acetate : 2/1, R_f = 0.26); FT-IR (ATR) $\bar{\nu}$ (cm⁻¹) 3482 (N-H), 3385 (N-H), 3278 (N-H), 2965 (C-H), 1718 (conj. C=O), 1679 (C=O), 1625; ¹H-NMR (400 MHz, DMSO-d₆) δ (ppm) 9.10 (s, 2H, NH₂), 7.27-7.12 (m, 5H, ArH), 6.46 (s, 1H, NHC=O), 5.06 (s, 1H, ArCHNH), 3.91 (qt, J = 11.0, 3.5 Hz, 2H, OCH₂), 0.98 (t, J = 7.1 Hz, 3H, CH₃); ¹³C-NMR (101 MHz, DMSO-d₆) δ (ppm) 167.3 (O-C=O), 164.8 (NHC=O), 147.4 (C=C-NH₂), 140.3 (ArC-CH), 128.6 (ArCH), 128.0 (ArCH), 127.7 (ArCH), 103.3 (C=C-C=O), 59.3 (OCH₂), 57.8 (ArCHNH), 14.7 (CH₃).

Synthesis of 4-carboethoxy-3-methylamino-2-oxo-5-phenyl-3-pyrroline (4)

The method was adapted from literature [2]. To a suspension of 4-carboethoxy-3-hydroxy-2-oxo-5-phenyl-3-pyrroline (1) (1.94 g, 8 mmol) in ethanol (40 mL), aqueous methylamine (40%) (1.4 mL, 16 mmol) was added while stirring. After heating under reflux for 24 hours with TLC monitoring, the mixture was left to cool to room temperature. After cooling in an ice bath, the resulting white crystals were filtered to give the product, 4-carboethoxy-3-methylamino-2-oxo-5-phenyl-3-pyrroline, as white crystals (Yield: 1.41 g, 69%).

Analytical data: TLC (Ethyl acetate, R_f = 0.83); FT-IR (ATR) $\bar{\nu}$ (cm⁻¹) 3351 (N-H), 2980 (C-H), 1698 (C=O), 1667 (C=O), 1633; ¹H-NMR (400 MHz, CDCl₃) δ (ppm) 7.30-7.20 (m, 5H, ArH), 6.48 (s, 1H, CH₃NH), 5.14 (s, 1H, ArCHNH), 4.04-3.93 (m, 2H, OCH₂), 3.34 (s, 3H, CH₃NH), 1.71 (s, 1H, CH₃NH), 1.03 (t, J = 7.1 Hz, 3H, CH₃); ¹³C-NMR (101 MHz, CDCl₃) δ (ppm) 167.9 (O-C=O), 166.6 (NHC=O), 147.1 (C=C-NHCH₃), 138.9 (ArC-CH), 128.4 (ArCH), 128.1 (ArCH), 127.4 (ArCH), 104.8 (C=C-C=O), 59.5 (OCH₂), 57.9 (ArCHNH), 30.2 (NHCH₃), 14.1 (CH₃).

Hydrogenation of 4-carboethoxy-3-methylamino-2-oxo-5-phenyl-3-pyrroline (4) over 10% palladium on carbon (Pd/C)

This is our in-house method [19]. To a stirred solution of 4-carboethoxy-3-methylamino-2-oxo-5-phenyl-3-pyrroline (4) (0.50 g, 1.92 mmol) in acetic acid (10 mL), 10% Pd/C (0.20 g, 0.19 mmol) was added

slowly. The reaction mixture was stirred vigorously under hydrogen atmosphere at 1 atm with TLC monitoring. After 24 hours, the reaction was stopped and the catalyst was filtered through Celite. The solvent was removed from the filtrate under reduced pressure and the residue was purified by column chromatography (gradient elution) to yield the diastereomers of 4-carboethoxy-3-methylamino-2-oxo-5-phenylpyrrolidine as yellow oils; *cis-trans* **5a** (Yield: 51.9 mg, 10.3%), *all-trans* **5b** (Yield: 22.9 mg, 4.5%) and *all-cis* **5c** (Yield: 48.3 mg, 9.6%).

Analytical data: FT-IR (ATR) $\bar{\nu}$ (cm⁻¹) 3395 (N-H), 3200 (N-H), 2981 (C-H), 1698 (C=O), 1646 (C=O); *cis-trans* **5a**: TLC (Ethyl acetate, R_f = 0.53); ¹H-NMR (400 MHz, CD₃OH) δ (ppm) 7.38-7.28 (m, 5H, ArH), 4.98 (d, J = 4.8 Hz, 1H, H-5), 4.57 (s, 1H, CH₃NH), 4.19-4.16 (dq, 2H, OCH₂), 3.60 (d, J = 8.4 Hz, 1H, H-3), 3.31 (m, 1H, H-4), 2.45 (s, 3H, CH₃NH), 1.24 (t, J = 7.6 Hz, 3H, CH₃); ¹³C-NMR (101 MHz, CD₃OH) δ (ppm) 176.0 (NHC=O), 171.1 (O-C=O), 140.4 (ArC-CH), 128.8 (ArCH), 128.1 (ArCH), 125.8 (ArCH), 61.4 (C-3), 60.8 (OCH₂), 58.0 (C-5), 53.9 (C-4), 34.0 (NHCH₃), 13.2 (CH₃). *all-trans* **5b**: TLC (Ethyl acetate, R_f = 0.13); ¹H-NMR (400 MHz, CD₃OH) δ (ppm) 7.40-7.31 (m, 5H, ArH), 4.73 (d, J = 8.2 Hz, 1H, H-5), 4.22-4.11 (m, 2H, OCH₂), 3.95 (d, J = 9.6 Hz, 1H, H-3), 3.01 (dd, J = 9.8, 8.5 Hz, H-4), 2.51 (s, 3H, CH₃NH), 1.18 (t, J = 7.3 Hz, 3H, CH₃); ¹³C-NMR (101 MHz, CD₃OH) δ (ppm) 175.6 (NHC=O), 173.4 (O-C=O), 140.0 (ArC-CH), 128.6 (ArCH), 128.3 (ArCH), 126.4 (ArCH), 62.7 (C-4), 61.4 (OCH₂), 58.2 (C-3), 55.4 (C-5), 32.2 (NHCH₃), 13.1 (CH₃). *all-cis* **5c**: TLC (Ethyl acetate, R_f = 0.31); ¹H-NMR (400 MHz, CD₃OH) δ (ppm) 7.38-7.29 (m, 5H, ArH), 5.11 (d, J = 6.4 Hz, 1H, H-5), 4.05 (d, J = 6.9 Hz, 1H, H-3), 3.86 (t, J = 6.9 Hz, 1H, H-4), 3.73-3.67 (m, 1H, OCH₂), 3.57-3.51 (m, 1H, OCH₂), 2.63 (s, 3H, CH₃NH), 0.71 (t, J = 7.1 Hz, 3H, CH₃); ¹³C-NMR (101 MHz, CD₃OH) δ (ppm) 174.6 (NHC=O), 169.4 (O-C=O), 136.6 (ArC-CH), 128.2 (ArCH), 126.3 (ArCH), 61.3 (C-3), 60.7 (OCH₂), 56.8 (C-5), 51.2 (C-4), 33.6 (NHCH₃), 12.5 (CH₃).

Hydrogenation of 4-carboethoxy-3-methylamino-2-oxo-5-phenyl-3-pyrroline (**4**) over 20% palladium hydroxide on carbon (Pd(OH)₂/C)

This method was adapted from our in-house method [19]. To a stirred solution of 4-carboethoxy-3-methylamino-2-oxo-5-phenyl-3-pyrroline (**4**) (0.50 g, 1.92 mmol) in acetic acid (10 mL), 20% Pd(OH)₂/C (0.13 g, 0.19 mmol) was added slowly. The reaction mixture was stirred vigorously under hydrogen atmosphere at 1 atm with TLC monitoring. After 24 hours, the reaction was stopped and the catalyst was filtered through Celite. The solvent was removed from the filtrate under reduced pressure and the residue was purified by column chromatography (gradient elution) to yield the diastereomers of 4-carboethoxy-3-methylamino-2-oxo-5-phenylpyrrolidine as yellow oils; *cis-trans* **5a** (Yield: 11.4 mg, 2.2%), *all-trans* **5b** (Yield: 0.7 mg, 0.1%) and *all-cis* **5c** (Yield: 10.3 mg, 2.0%).

Analytical data: FT-IR (ATR) $\bar{\nu}$ (cm⁻¹) 3358 (N-H), 3193 (N-H), 2982 (C-H), 1698 (C=O), 1646 (C=O); *cis-trans* **5a**: TLC (Ethyl acetate, R_f = 0.43); ¹H-NMR (400 MHz, CDCl₃) δ (ppm) 7.34-7.25 (m, 5H, ArH), 6.58 (s, 1H, CH₃NH), 4.98 (d, J = 3.7 Hz, 1H, H-5), 4.21-4.12 (m, 2H, OCH₂), 3.58 (d, J = 8.2 Hz, 1H, H-3), 3.27 (dd, J = 4.1 Hz, H-4), 2.46 (s, 3H, CH₃NH), 1.23 (t, J = 7.1 Hz, 3H, CH₃); ¹³C-NMR (101 MHz, CDCl₃) δ (ppm) 175.1 (NHC=O), 170.8 (O-C=O), 140.5 (ArC-CH), 129.2 (ArCH), 126.0 (ArCH), 125.7 (ArCH), 61.3 (C-3), 60.7 (OCH₂), 57.6 (C-5), 54.1 (C-4), 35.4 (NHCH₃), 14.1 (CH₃). *all-trans* **5b**: TLC (Ethyl acetate, R_f = 0.11); ¹H-NMR (400 MHz, Acetone-d₆) δ (ppm) 7.38-7.30 (m, 5H, ArH), 4.71 (d, J = 8.4 Hz, 1H, H-5), 4.15-4.12 (m, 2H, OCH₂), 3.60 (d, J = 9.6 Hz, 1H, H-3), 2.80 (m, 1H, H-4), 2.40 (s, 3H, CH₃NH), 1.16 (t, J = 7.2 Hz, 3H, CH₃); ¹³C-NMR (101 MHz, Acetone-d₆) δ (ppm) 173.8 (NHC=O), 172.0 (O-C=O), 141.2 (ArC-CH), 128.7 (ArCH), 128.2 (ArCH), 126.4 (ArCH), 64.4 (C-3), 60.8 (OCH₂), 57.8 (C-5), 57.6 (C-4), 33.9 (NHCH₃), 13.6 (CH₃). *all-cis* **5c**: TLC (Ethyl acetate, R_f = 0.26); ¹H-NMR (400 MHz, CDCl₃) δ (ppm) 7.33-7.29 (m, 3H, ArH), 7.18-7.16 (m,

2H, ArH), 6.64 (s, 1H, CH₃NH), 5.00 (d, J = 9.6 Hz, 1H, H-5), 4.10 (d, J = 9.1 Hz, 1H, H-3), 3.81-3.76 (m, 1H, H-4), 3.73-3.61 (m, 2H, OCH₂), 2.15 (s, 3H, CH₃NH), 0.93 (t, J = 7.3 Hz, 3H, CH₃); ¹³C-NMR (101 MHz, CDCl₃) δ (ppm) 175.3 (NHC=O), 169.7 (O-C=O), 137.7 (ArC-CH), 128.8 (ArCH), 127.2 (ArCH), 126.9 (ArCH), 61.2 (C-4), 59.4 (C-3), 57.6 (C-5), 52.1 (OCH₂), 31.1 (NHCH₃), 13.8 (CH₃).

Reduction of 4-carboethoxy-3-methylamino-2-oxo-5-phenyl-3-pyrrolines (4) by sodium triacetoxymethylborohydride (NaBH(OAc)₃)

The method was adapted from literature [9]. A solution of NaBH(OAc)₃ was prepared by the addition of sodium borohydride (NaBH₄) (0.73 g, 19 mmol) to glacial acetic acid (5.6 mL, 96 mmol) at 0 °C and the mixture was stirred for 30 minutes at room temperature with some evolution of hydrogen gas. Then, 4-carboethoxy-3-methylamino-2-oxo-5-phenyl-3-pyrroline (4) (1.01 g, 4 mmol) in acetonitrile (25 mL) was transferred into the previous mixture. The resulting mixture was stirred vigorously for 48 hours before being neutralized by saturated Na₂CO₃ solution. Upon extraction by dichloromethane, the organic phase was washed with brine and dried over anhydrous MgSO₄. The solvent was removed from the organic phase *in vacuo* to give a white solid. From TLC, FT-IR and NMR characterization experiments, it was concluded that the starting material 4 was recovered.

Analytical data: TLC (Ethyl acetate, R_f = 0.79); FT-IR (ATR) $\bar{\nu}$ (cm⁻¹) 3351 (N-H), 2980 (C-H), 1698 (C=O), 1667 (C=O), 1633; ¹H-NMR (400 MHz, CDCl₃) δ (ppm) 7.30-7.21 (m, 5H, ArH), 6.43 (s, 1H, CH₃NH), 5.14 (s, 1H, ArCHNH), 4.04-3.93 (m, 2H, OCH₂), 3.35 (s, 3H, CH₃NH), 1.70 (s, 1H, CH₃NH), 1.03 (t, J = 7.1 Hz, 3H, CH₃); ¹³C-NMR (101 MHz, CDCl₃) δ (ppm) 167.9 (O-C=O), 166.6 (NHC=O), 147.1 (C=C-NHCH₃), 138.9 (ArC-CH), 128.4 (ArCH), 128.1 (ArCH), 127.4 (ArCH), 104.8 (C=C-C=O), 59.5 (OCH₂), 57.9 (ArCHNH), 30.2 (NHCH₃), 14.1 (CH₃).

Reduction of 4-carboethoxy-3-methylamino-2-oxo-5-phenyl-3-pyrroline (4) by sodium cyanoborohydride (NaBH₃CN)

The method was adapted from literature [8]. Traces of bromocresol green was added to 4-carboethoxy-3-methylamino-2-oxo-5-phenyl-3-pyrroline (4) (1.00 g, 4 mmol) in methanol (20 mL) while stirring followed by NaBH₃CN (0.97 g, 15 mmol). Dilute MeOH-HCl mixture was added dropwise until the colour of the reaction mixture turned yellow. More MeOH-HCl was added to the mixture periodically to maintain the yellow colour (pH ~4) with TLC monitoring. After 24 hours, the reaction was quenched by dropwise addition of 0.1 N NaOH solution (saturated with NaCl) until the mixture turned blue. The crude product was extracted by ethyl acetate and the organic phase was washed with brine and dried over anhydrous MgSO₄. The solvent was evaporated under vacuum and the residue was purified by column chromatography (gradient elution) to give the diastereomers of 4-carboethoxy-3-methylamino-2-oxo-5-phenylpyrrolidine; *all-trans* 5b (Yield: 174.7 mg, 34.7%) and *all-cis* 5c (Yield: 97.6 mg, 19.4%).

Analytical data: FT-IR (ATR) $\bar{\nu}$ (cm⁻¹) 3391 (N-H), 3306 (N-H), 2977 (C-H), 1718 (C=O), 1698 (C=O); *all-trans* 5b: TLC (Ethyl acetate, R_f = 0.49); ¹H-NMR (400 MHz, CDCl₃) δ (ppm) 7.37-7.31 (m, 5H, ArH), 6.42 (s, 1H, CH₃NH), 4.78 (d, J = 8.2 Hz, 1H, H-5), 4.18-4.16 (m, 2H, OCH₂), 3.84 (d, J = 9.6 Hz, 1H, H-3), 3.06 (t, J = 8.9 Hz, 1H, H-4), 2.16 (s, 3H, CH₃NH), 1.20 (t, J = 7.1 Hz, 3H, CH₃); ¹³C-NMR (101 MHz, CDCl₃) δ (ppm) 173.9 (NHC=O), 171.7 (O-C=O), 139.5 (ArC-CH), 129.0 (ArCH), 128.7 (ArCH), 126.5 (ArCH), 63.6 (C-3), 61.7 (OCH₂), 57.9 (C-5), 55.9 (C-4), 31.1 (NHCH₃), 14.1 (CH₃). *all-cis* 5c: TLC (Ethyl acetate, R_f = 0.26); ¹H-NMR (400 MHz, CDCl₃) δ (ppm) 7.33-7.29 (m, 3H, ArH), 7.18-7.16 (m, 2H, ArH), 6.64 (s, 1H, CH₃NH), 5.00 (d, J = 9.6 Hz, 1H, H-5), 4.10 (d, J = 9.1 Hz, 1H, H-3), 3.81-3.76 (m, 1H, H-4), 3.73-3.61 (m, 2H, OCH₂), 2.15 (s, 3H, CH₃NH), 0.93 (t, J = 7.3 Hz, 3H, CH₃); ¹³C-NMR (101 MHz, CDCl₃) δ (ppm) 175.3 (NHC=O), 169.7 (O-C=O), 137.7 (ArC-CH), 128.8 (ArCH), 127.2 (ArCH), 126.9 (ArCH), 61.2 (C-4), 59.4 (C-3), 57.6 (C-5), 52.1 (OCH₂), 31.1 (NHCH₃), 13.8 (CH₃).

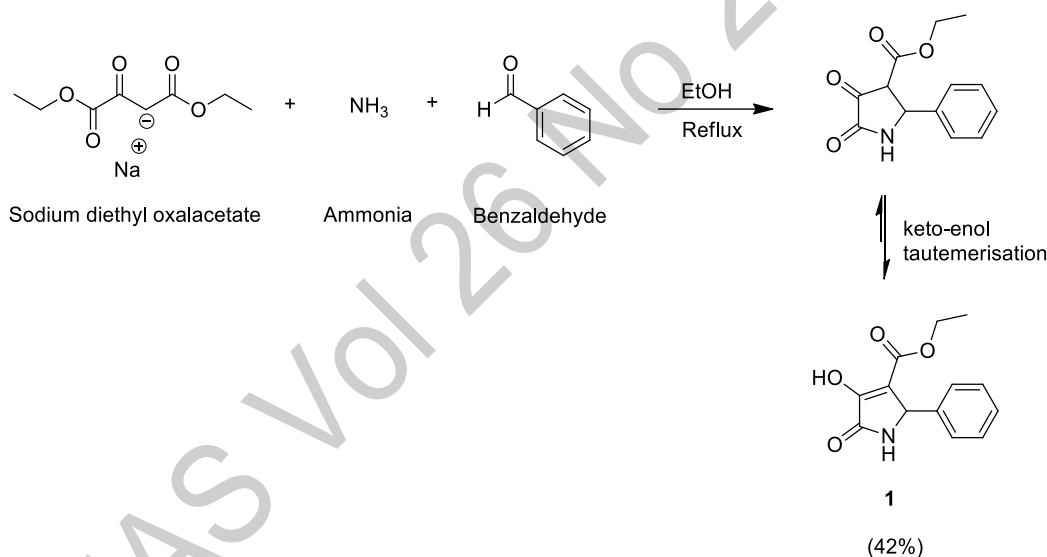
Results and Discussion

4-carbethoxy-3-hydroxy-2-oxo-5-phenyl-3-pyrroline (**1**) were prepared through one-pot multicomponent reaction (MCR) by refluxing equimolar sodium diethyl oxalacetate and benzaldehyde with excess aqueous ammonia in ethanol as developed by Metten et. al. (Scheme 1) [15]. The product was more stable in the enol rather than the keto form, consistent with previous findings [16-19]. The moderate yield was compromised for the ease of the purification process and overall facile procedure.

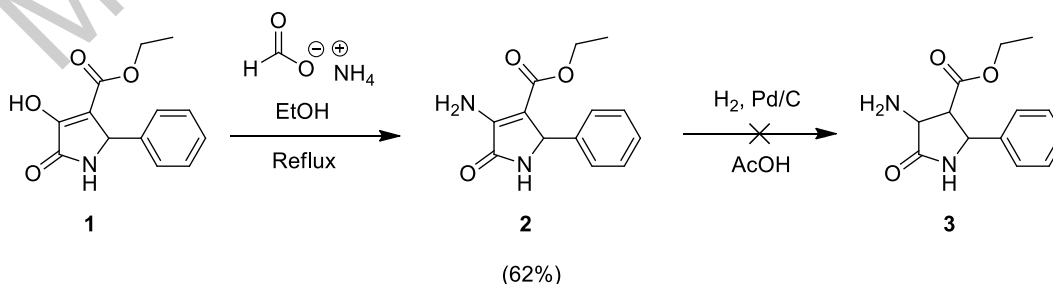
Afterwards, treatment of **1** with ammonium formate gave enamino ester **2** with a good yield via Leuckart reaction (Scheme 2) [2,3]. Hydrogenation of **2** in the presence of 10% Pd/C in methanol for 22 hours was ineffective, recovering the starting material. To our

best knowledge, there is yet to be a report on a successful reduction of primary enamino esters such as **2**. Wang and co-workers described that the enamino group has to be protected prior to the hydrogenation to gain successful conversions [20]. Other works of literature suggested that there should be at least one substituent on the enamino functionality for the procedure to work [7-13]. Perhaps, the conjugated π system and alternating intramolecular hydrogen bonding form very stable 6-membered intermediates (Figure 3) therefore preventing interaction with the metal catalyst.

However, methylation of **1** in the presence of formic acid afforded secondary β -enamino ester (**4**), which was then reacted through four different reduction systems (Scheme 3).



Scheme 1. Synthesis of 4-carbethoxy-3-hydroxy-2-oxo-5-phenyl-3-pyrroline (**1**) via one-pot MCR



Scheme 2. Amination of **1** and the attempt to catalytically hydrogenate **2** over Pd/C

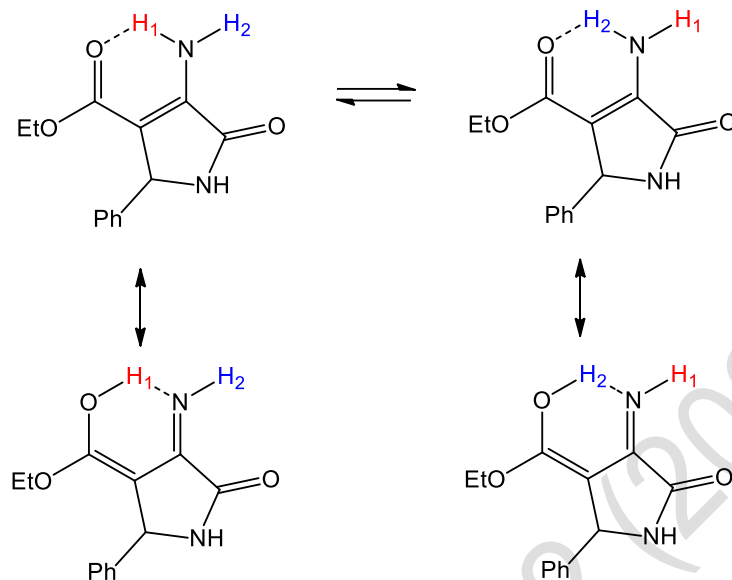
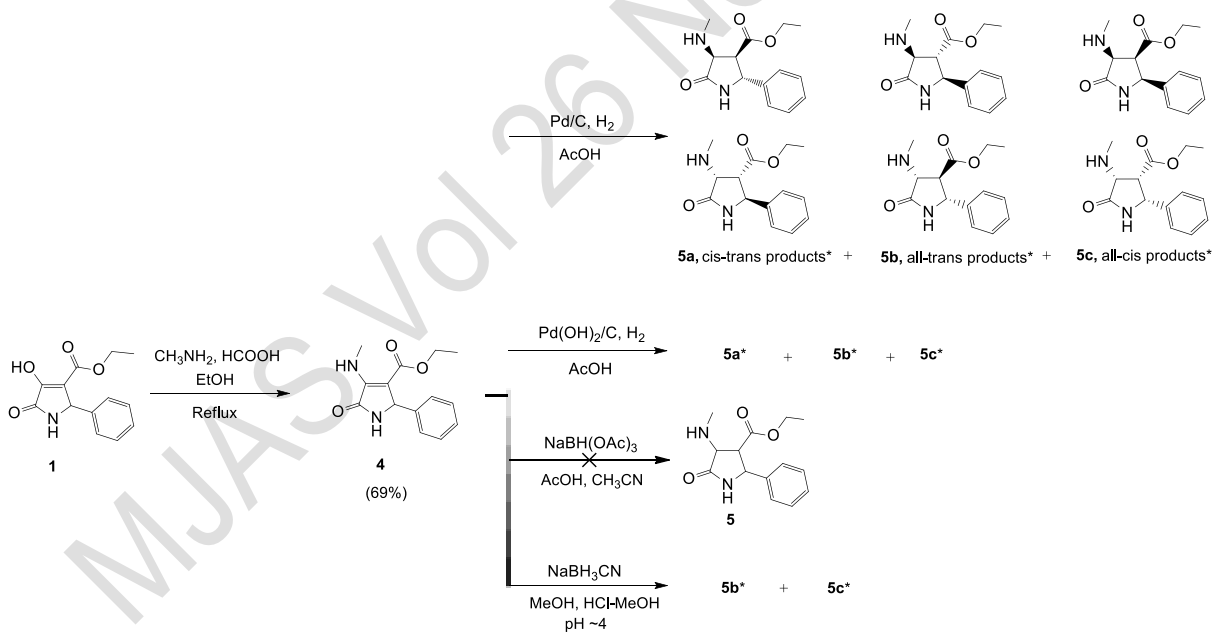


Figure 3. Intramolecular hydrogen bonding and the resonance structures of **2**.



* The absolute configuration was not determined. Thus, both possible enantiomers are displayed.

Scheme 3. Methylamination of **1** and various reduction protocols of **4**.

Pd/C hydrogenation of **4** displayed low diastereoselectivity (d.r. = 42 : 19 : 39) of three separable mixtures of β -amino ester diastereomers (**5a-c**) with low yields (4 to 10%) (Table 1). Hydrogenation of **5** in the presence of Pd(OH)₂ on charcoal was more diastereoselective (d.r. = 51 : 3 : 46) than Pd/C but afforded an even poorer yield (0.1 to 2.2%) of isomers (**5a-c**). Both catalytic processes involved the syn addition of hydrogens onto the double bond resulting in a nearly equivalent d.r. of **5a** (*cis-trans*) and **5c** (*all-cis*) products with a minor anti addition causing the formation of **5b** (*all-trans*) product, in agreement with one of our previous findings [17].

The treatment with sodium borohydride, NaBH₄ and acetic acid to form *in situ* sodium triacetoxymethylborohydride, NaBH(OAc)₃ failed to reduce compound **4**. On the other hand, reduction using sodium cyanoborohydride (NaBH₃CN) in acidic medium gained the mixture of **5b** and **5c** diastereomers, giving superior stereochemical control (d.r. = 64 : 36) than catalytic hydrogenations, with better yields. Deustch et. al. observed similar diastereomeric selectivities when reducing acyclic β -enamino ester derivatives by the same protocol [8].

Table 1. Stereoselective reduction of **4**

Reducing Agent	Isolated Product Yield (%)*			Diastereomeric ratio (d.r.)**
	5a	5b	5c	
Pd/C, H ₂	10.3	4.5	9.6	42 : 19 : 39
Pd(OH) ₂ /C, H ₂	2.2	0.1	2.0	51 : 3 : 46
NaBH(OAc) ₃	-	-	-	-
NaBH ₃ CN	-	34.7	19.4	64 : 36

*Isolated yield of each diastereomeric product obtained after purification by column chromatography.

**Diastereomeric ratio (d.r.) was determined based on the isolated yield after column chromatography.

All resulting diastereomers were studied through nuclear magnetic resonance (NMR) experiments to assign their configurations. For instance, Nuclear Overhauser Effect Spectroscopy (NOESY) correlation between the hydrogen at C-4 (3.01 ppm) and aryl proton (7.35 ppm) in **5b** (*all-trans*) product confirmed that both the hydrogen and the phenyl ring are on the same side (Figure 4) whereby in **5c** (*all-cis*) product, the correlation between the hydrogens at C-4 (3.86 ppm) and C-5 (5.11 ppm) were observed, indicating their close proximities to each other. This claim is supported by the low proton NMR (¹H-NMR) chemical shift value of the hydrogen on C-4 of **5b** compared to that of **5c** due to the anisotropic effect of being near the phenyl ring. Moreover, **5b** diastereomer showed significantly higher values of *J*_{4,5} coupling constant than **5c** (Table 2).

Alternatively, the assignment of *cis*-configuration between protons on C-4 and C-5 of **5c** isomer can be further proven by another anisotropy experienced by protons of its ester moiety indicated by their lower chemical shift values in comparison to those of **5a** (*cis-trans*) and **5b** diastereomers. On another note, the NOESY correlation between the hydrogen on C-4 (3.01 ppm) with methylamine proton (2.51 ppm) of **5b** led to the notion that the protons on C-3 and C-4 were *trans* to each other while for **5a**, its C-4 proton (3.35 ppm) correlated with the one on C-3 (3.60 ppm) thus they were assigned as *cis*.

The mechanistic pathway that we proposed for these catalytic hydrogenations is displayed in Scheme 4. Syn addition of hydrogens on either side of the C=C of the enamino ester caused both the methylamine and ester groups to be on the same side. These structural changes

gave rise to steric clashes between the ester and phenyl ring that determined which conformer was more favourable. The steric strain in **5c** (ester and phenyl groups located near to each other) contributed to a slightly lower yield compared to the thermodynamic product **5a** (the groups were on opposite sides).

Anti addition of hydrogens by metal-catalysed hydrogenation was initiated by the formation of an enolate intermediate through the protonation of one of the prochiral centres which are C-3 in **5b**, the less hindered site (Scheme 4). The following step involved the addition of another hydrogen on C-4 selectively to form a stable conformer whereby the ester group and phenyl ring were situated on different planes (lower steric strain) thus resulting in the *trans*-position between the hydrogens on C-3 and C-4 [10].

NaBH_3CN reduction began with a rate-determining step of acid protonation on C-4 of **4** from either side of the C=C of the enamino ester, thus forming respective iminium intermediates (Scheme 5) [21]. Then, an attack by cyanoborohydride from the less crowded site (away from the phenyl ring) restored the nitrogen lone pair electrons. The reagent selectively favoured the formation of **5b** over **5c** due to the greater strain between ester and phenyl groups in **5c**, consequently causing the latter to be less energetically stable.

The poor yield of $\text{Pd}(\text{OH})_2$ hydrogenation compared to Pd/C and the unsuccessful reduction by $\text{NaBH}(\text{OAc})_3$ can be explained by the bulkiness of the reagent structures causing severe steric hindrance that antagonized the reactions.

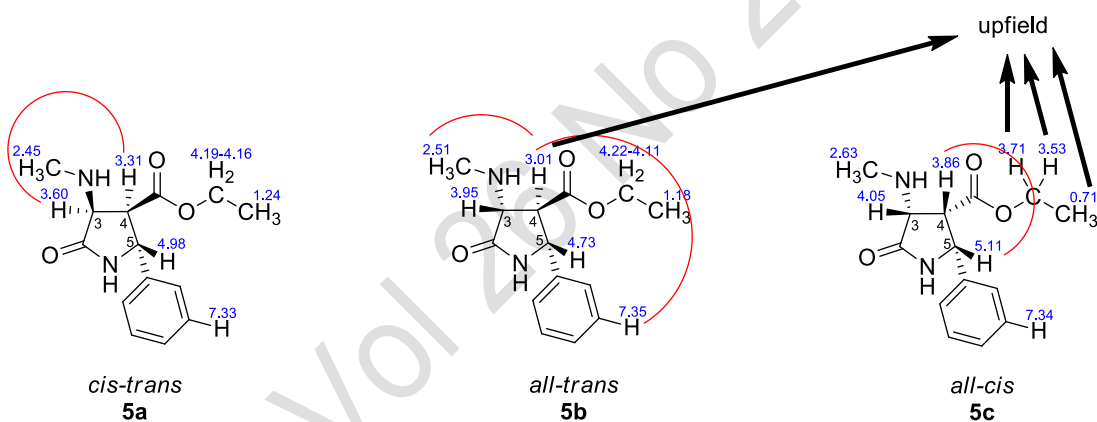
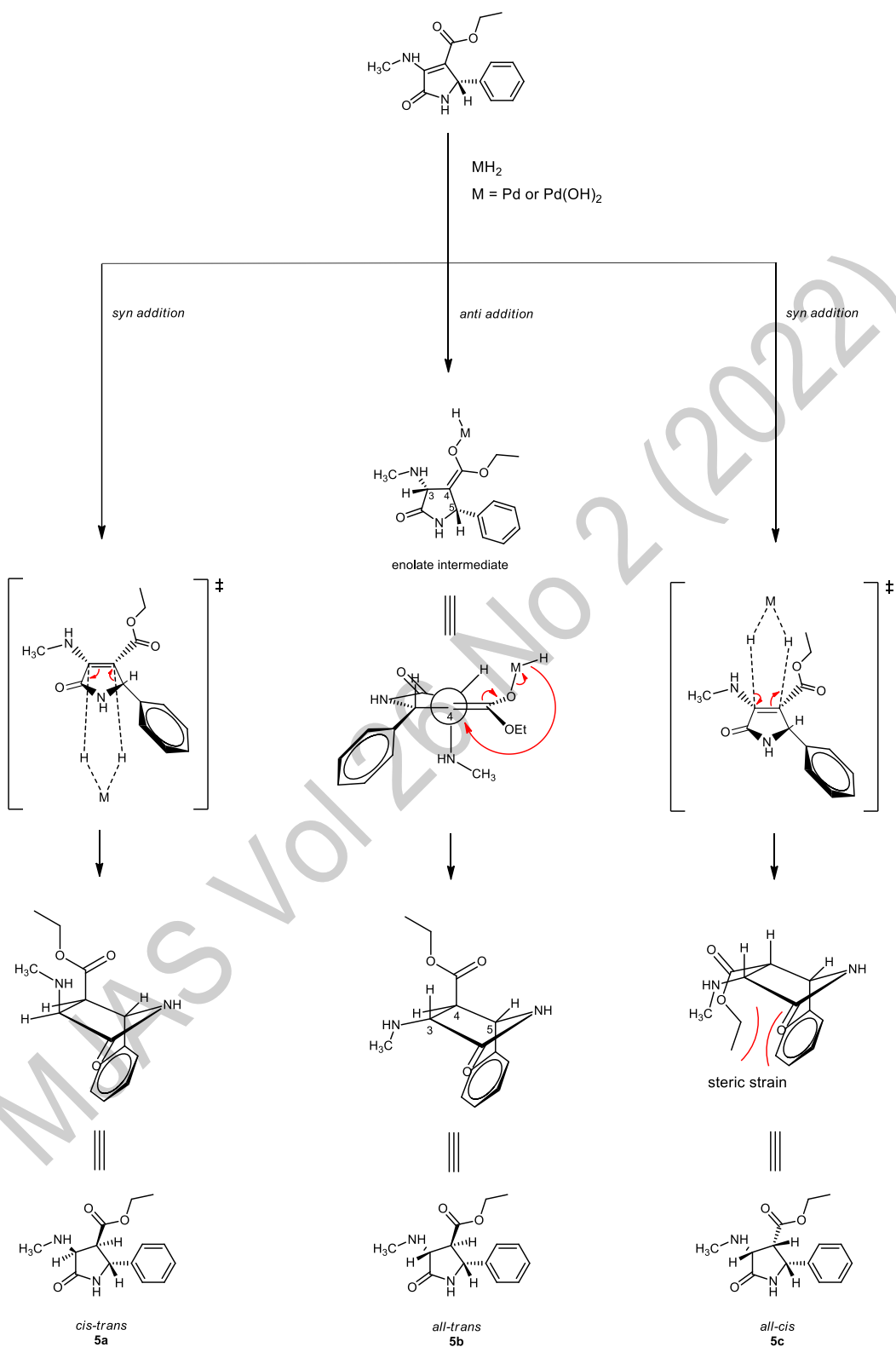


Figure 4. ^1H -NMR shift values and NOESY correlations of diastereomers **5a-c**

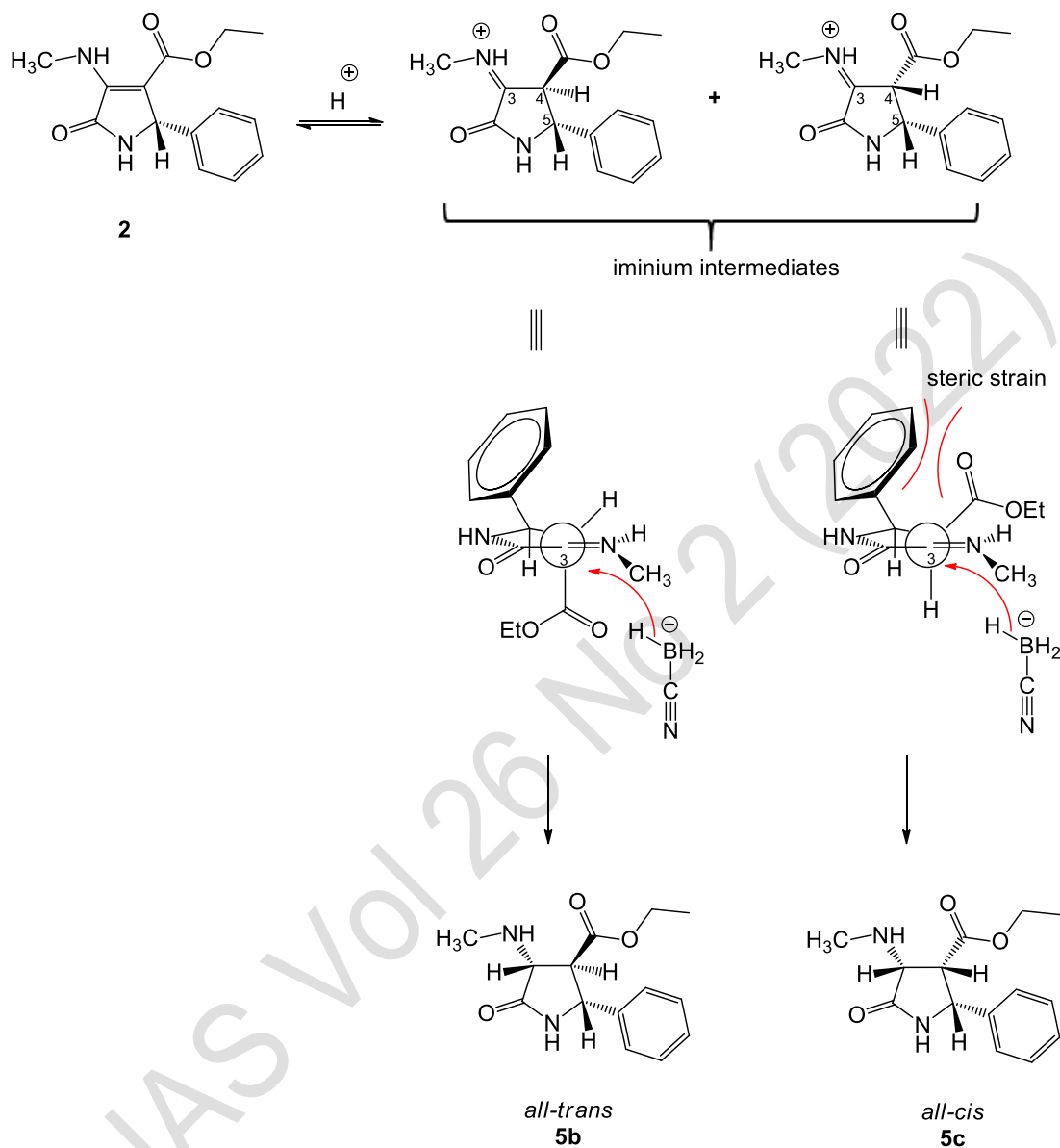
Table 2. Selected ^1H -NMR data for diastereomers **5a-c** in methanol- d_4

Compound	Shift value, δ (ppm)			Coupling constant, J (Hz)		
	H-3	H-4	H-5	H-3	H-4	H-5
5a	3.60	3.35	4.99	8.4	—*	4.8
5b	3.95	3.01	4.73	9.6	8.5	8.2
5c	4.05	3.86	5.11	6.9	6.9	6.4

*H-4 of **5a** showed a multiplet pattern



Scheme 4. Proposed mechanistic pathways for Pd and Pd(OH)₂ hydrogenation of 4



Scheme 5. Plausible reaction mechanism for reduction of **4** by NaBH_3CN .

Conclusion

Overall, the stereochemical control for this class of functional group depends strongly on the position of the ester group in regards to the phenyl ring after the protonation/reduction steps i.e. if they are on the same plane, the lower the preference for the formation of said diastereomer. This brief experiment shows that endocyclic β -enamino ester (**4**) can be reduced with

excellent diastereoselectivity by NaBH_3CN (d.r. = 64 : 36), in addition to its moderate turnover percentage (54.1%). Hydrogenations on Pd and $\text{Pd}(\text{OH})_2$ surfaces suffered from poor selectivities (d.r. = 42 : 19 : 39 and d.r. = 51 : 3 : 46, respectively) and yields (0.1 to 10.3%) with unexpected anti additions of hydrogens while $\text{NaBH}(\text{OAc})_3$ reduction recovered the starting material. Nevertheless, we have successfully employed

some of these reduction strategies to prepare chiral cyclic β -amino ester with satisfying diastereomeric purity.

Acknowledgement

We would like to thank University Teknologi MARA (UiTM) for providing the facilities to conduct the research and International Islamic University Malaysia (IIUM) along with the Malaysian Ministry of Higher Education (MoHE) for the financial support (FRGS/1/2017/STG01/UIAM/03/2 [Project ID: 11794]).

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