

Synthesis of Selected Phenylalanine Esters C1 to C4 and their Catalytic Activity on the Preparation of a Wieland Miescher Intermediate Using Acidic Media

P Caumul *

Department of Chemistry

Faculty of Science

University of Mauritius,

Réduit

E-mail: p.caumul@uom.ac.mu

H Dhallapah

Department of Chemistry

Faculty of Science

University of Mauritius,

Réduit

E-mail: hansa_11@live.com

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Abstract

The Wieland Miescher intermediate is used in the synthesis of a range of antitumour, antiviral, antimicrobial and antineurodegenerative drugs. Our work outlines the synthesis of a range of surfactant esters derived from the amino acid phenylalanine and which have been used as asymmetric catalysts to synthesize the key intermediate leading to the Wieland Miescher ketone. These reactions were carried out in water under acidic media. Satisfactory yields of up to 75% were obtained in generating the intermediate, and 92% of the subsequent Wieland Miescher Ketone was obtained with an enantiomeric purity of 72-73% e.e selective to the *S*-isomer.

Keywords: *Wieland-Miescher, Phenylalanine esters, CTAB, CMC, Methyl vinyl ketone, 2-Methylcyclohexane-1,3-dione.*

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1. INTRODUCTION

The reaction leading to the Wieland-Miescher intermediate is a very important C-C bond forming reaction which has been used in the synthesis of many key antitumour, antiviral, antineurodegenerative and antimicrobial drugs. For instance, the recent total synthesis of the anticancer drug taxol started from (*S*)-(+)-antipode (Figure 1), a precursor to the Wieland Miescher ketone (Danishefsky *et al.* 1996).

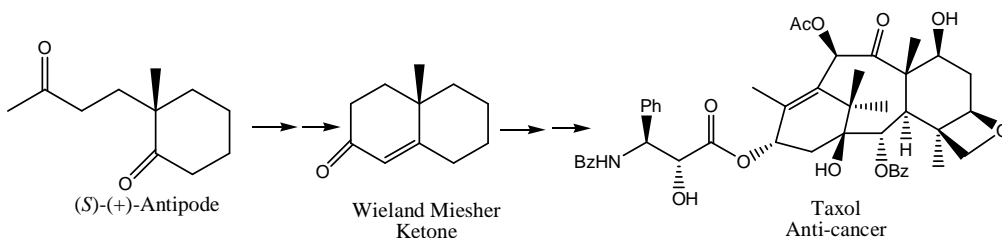
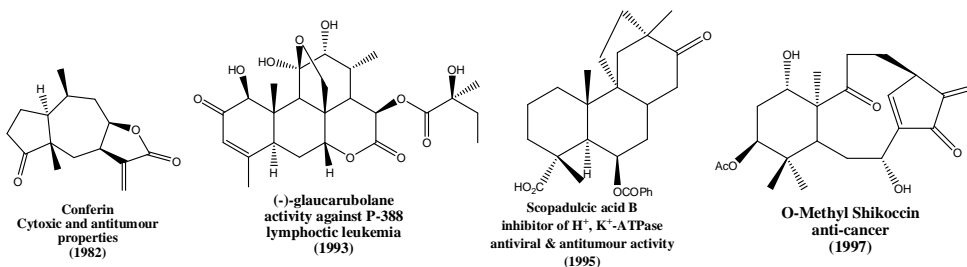


Figure 1 Synthesis of Taxol via the Wieland Miescher Ketone

Important natural products synthesized from the Miescher ketone include the compounds illustrated in Figure 2 (Waters *et al.* 2005; Paquette *et al.* 1997; Stork *et al.* 1996; An *et al.* 1996; Ziegler *et al.* 1995; Grieco *et al.* 1993; Heathcock *et al.* 1982).



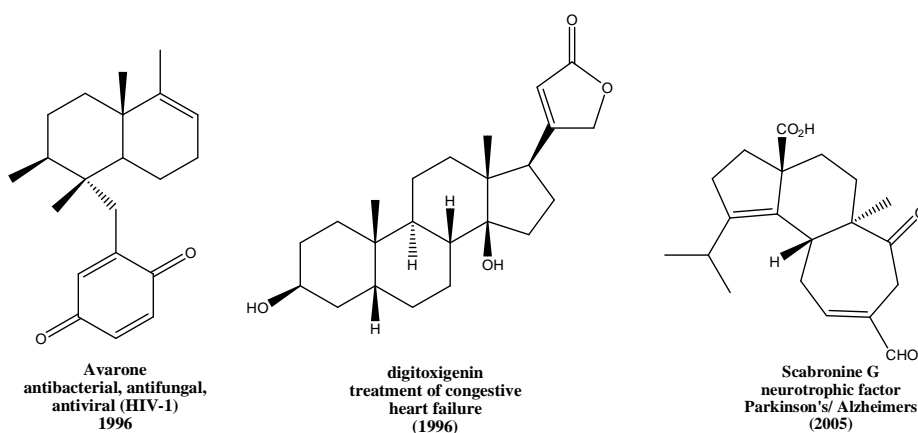


Figure 2 Examples of natural products synthesized from the Wieland Miescher ketone

Other examples include the natural sesquiterpenes- Albicanol (**a**), Pallescensin A (**b**), and Avarol (**c**). Pallescensin A (a furano sesquiterpenoid marine natural product, which has been previously isolated from the sponge *Disidea pallescens*) is involved in the chemical defence mechanism of the opisthobranch mollusks (Figure 3) which are secreted through their skin glands. Together with albicanol, Pallescensin A has also been found to possess anti-inflammatory and cytotoxic properties (Bradshaw *et al.* 2012).

Avarol which is a marine sesquiterpenoid hydroquinone, isolated from the marine sponge *Dysidea avara*, has been observed to have very interesting pharmacological properties which include anti-inflammatory and antipsoriatic effects and is thus used against skin diseases (Bradshaw *et al.* 2012).

The total synthesis of the chiral indolic diterpene derivative (-)-paspaline (**d**) (the simplest member of a rapidly growing class of complex diterpene indole alkaloid) has also been achieved from the Wieland Miescher ketone in the synthetic process (Figure 3). This family of compounds has been discovered to possess interesting biological properties such as platelet aggregation inhibition and anti-inflammatory activity (Guillena *et al.* 2007).

The Wieland Miescher ketone has been involved in the synthesis of meroterpenes, which inhibits the activity of cholesterol acyltransferase, which has the role of hydrolysing cholesterol esters in the endoplasmic reticulum. The synthesis of different steroids such as the hormone adrenosterone (**f**), as well as the oxytetracyclic core of the potent antibiotic platensimycin, which was reported by Kaliappen and Ravikumar in 2007 (Kaliappen *et al.*, 2007; Guillena *et al.*, 2007) have also been achieved from the Wieland-Miescher ketone. This confirms its importance in natural product chemistry.

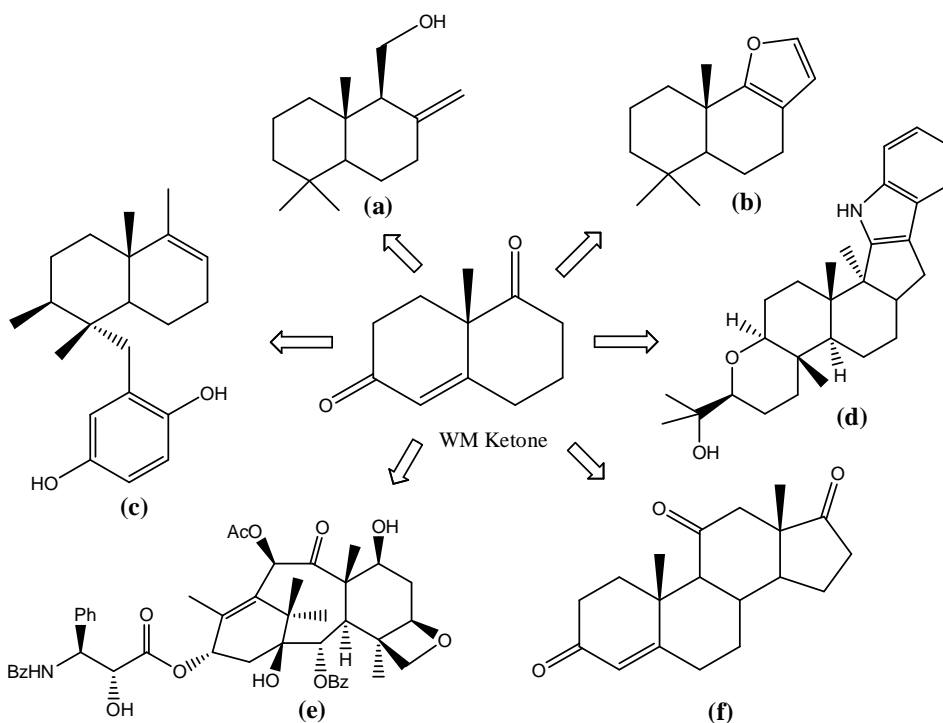


Figure 3 Synthesised natural product materials from WM Ketone

Peter Wieland and Karl Miescher reported the first racemic synthesis of the ketone building block in 1950 (Wieland *et al.* 1950). The enantiopure form was developed in 1971 by Hajos-Parrish (a) and then subsequently by Eder, Sauer and Wiechert (b) who successfully reported the asymmetric conversion of the starting diene to the cyclic ketone using proline catalyst (Eder *et al.* 1971; Hajos *et al.* 1974) (Figure 4).

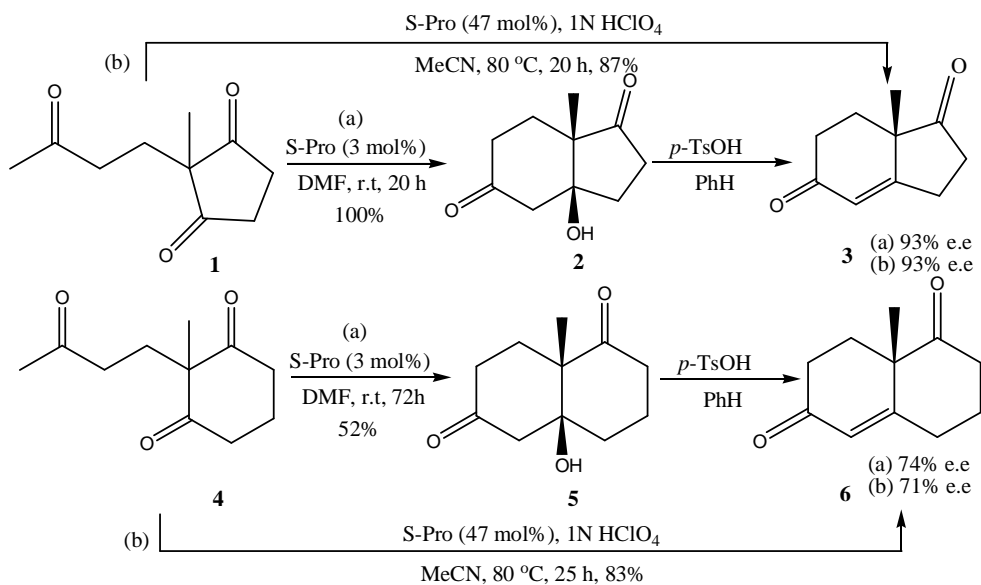


Figure 4 First Organocatalysis by (a) Hajos and Parrish (b) Eder-Sauer-Wiechert (Bradshaw *et al.* 2012).

The synthesis of the Wieland-Miescher ketone involves two steps. The first step of the reaction is found to involve a Michael addition between methyl vinyl ketone, **7** and a cyclic dione, such as 2-methyl-1,3-cyclohexanedione, **8** (Figure 5).

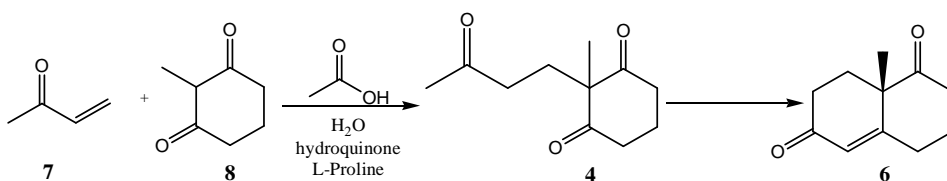


Figure 5 Synthesis of the Wieland Miescher ketone

The resonance-stabilized enolate of **8** attacks methyl vinyl ketone, **7** via 1,4-addition. Subsequent protonation and tautomerization gives prochiral **4**. The S-enantiomer of the Wieland-Miescher ketone **3** or **6** is produced via a Robinson annulation of **1** or **4** under asymmetric catalysis.

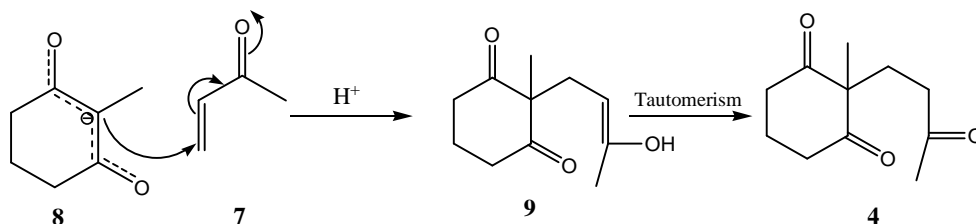


Figure 6 Mechanistic pathway for the Wieland-Miescher reaction

Eder, Sauer, and Wiechert used harsher experimental conditions to achieve the ring closure of the triketone **1** or **4**. The reaction was carried out in acetonitrile containing 1 N perchloric acid and heated at 80 °C for 20 hours. This led to yields of 83-87% with enantiomeric excess of between 71-93%. Though it has been demonstrated that *L*-proline was the catalysts of choice for this transformation, other reports have shown than *L*-phenylalanine has also shown promising results (Eder *et al.* 1971).

Nagamine *et al.* (2007) reported that Wieland–Miescher ketone analogues can be synthesized by using stoichiometric amounts of either α - or β -amino acids under different reaction conditions. From a set of 15 different α -amino acids, *L*-phenylalanine emerged as the best to promote the cyclization of the triketone **10** in DMSO at 90 °C in the presence of $HClO_4$, affording the bicyclic compound **12** in yields of up to 87% and e.e values between 86-91% (Nagamine *et al.* 2007) (Figure 7).

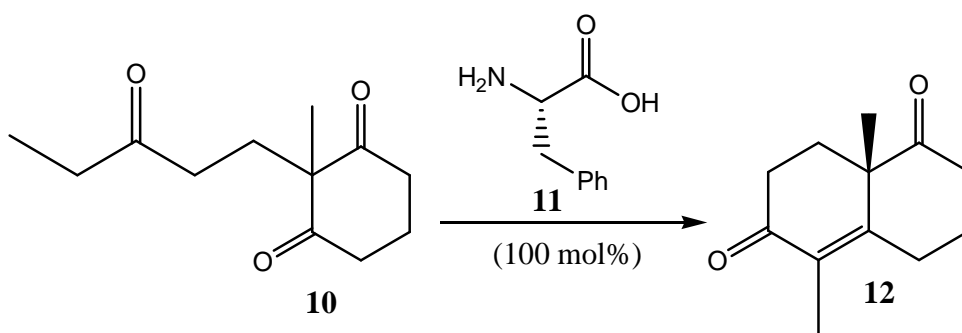


Figure 7 Cyclisation Reaction by Nagamine *et al.* (2007)

Since previous literature has shown promising results when using *L*-phenylalanine as catalyst (Nagamine *et al.* 2007; Guillena *et al.* 2007), limited work have been reported on the use of amphiphilic compounds as catalysts for Wieland Miescher reactions. Furthermore, very few reports have used protic media to synthesise the Wieland Miescher intermediates. We therefore decided to synthesise small chain ester derivatives of phenylalanine that possess an amphiphilic nature and test its catalytic efficiency on the synthesis of the intermediate **4**, en route to the preparation of the Wieland Miescher ketone via acidic media. Reports by Hailes *et al.*, have shown that amphiphilic systems make useful catalysts due to their aggregation in a micellar manner, which would enable organic reactions to be carried out in aqueous media due to their ability to solubilise substrates as well as concentrate and preorientate them in the micellar core, enhancing reaction rates, yields and selectivity (Diego-Castro *et al.* 1998; Caumul *et al.* 2005). Since previous reports have demonstrated that phenylalanine derivatives have been used to successfully enhance Diels-Alder reactions in aqueous media (Diego-Castro *et al.* 1998), esters of phenylalanine were therefore selected as catalysts for this investigation. Also the presence of the aromatic moiety in these compounds can help induce π - π interactions between the aromatic rings of the catalyst and substrate **8** which would help enhance reaction yield.

2. MATERIALS AND METHODS

The chemicals and reagents were of analytical grade (AR grade) and were purchased from Sigma-Aldrich Co. Ltd and Acros-Fisher Scientific, UK. THF was freshly distilled and dried using molecular sieves (4Å) prior to use. All air and moisture sensitive reactions were carried out under an inert nitrogen atmosphere.

Column chromatography was carried out using silica gel (60-120 mesh). TLC was performed on plates pre-coated with silica and visualization of the chromatogram was achieved by exposure to an iodine atmosphere.

^1H NMR and ^{13}C NMR spectra were recorded in 5 mm outer diameter NMR tubes in D_2O or CDCl_3 as solvents at room temperature using FT Bruker 250 MHz spectrometer. The chemical shift (δ) of each peak was assigned relative to tetramethylsilane (TMS). The observed multiplicities were assigned symbols as follows: (s) for singlet, (d) for doublet, (t) for triplet, (m) for multiplet and (br) for broad.

Melting point analysis was carried out using an Electrothermal Stuart scientific SMP 1 melting point apparatus.

Optical rotations were determined using a Billingham-Stanley Model D optical activity polarimeter. The substance to be analysed was dissolved in an appropriate solvent at a known concentration (g/ml) and placed in an analysis tube of a known length (1 dm = 10cm). The rotation observed was denoted with the Greek letter, α . The specific rotation values $[\alpha]_D$ were measured in degrees and were determined using the equation below:

$$[\alpha]_D = 100\alpha / lc$$

where l is the path length of the sample in decimetres and c is the concentration of the substance to be analysed in grams per 100 ml of solution (Carey, 2000).

Hydrochloride salts of L-Phenylalanine esters

L-Phenylalanine (1.00 g, 6 mmol) was stirred with the corresponding alcohol (15 ml) at 0°C . Thionyl chloride (1ml, 13.8 mmol) was added dropwise to the reaction mixture which was stirred at room temperature for 48 hours. Excess alcohol was evaporated in *vacuo* and the residue washed with diethyl ether to yield the compound as a white solid.

L-Phenylalanine methyl ester hydrochloride. (Yield 93%). Mpt: $159\text{-}160^\circ\text{C}$. ^1H NMR (D_2O), δ (ppm): 3.06 (dd, H, J 15.0 Hz, J 6.7 Hz, CHCHPh), 3.14 (dd, H, J 15.0 Hz, J 6.7 Hz, CHCHPh), 3.66 (s, 3H, OCH_3), 4.20 (t, H, J 7.5 Hz, CH), 7.11-7.26 (m, 5H, Ph). ^{13}C (D_2O) δ (ppm): 35.8 (CH_2Ph), 53.5 (OCH_3), 54.6 (CH),

128.3, 129.2, 134.0 (C₆H₄), 170.3 (C=O). [α]_D: -4.0° (c = 1 in water at 25 °C); [Lit [α]_D: -5.0° (c = 1 in water at 25 °C), Karim *et al.* (1986)].

L-Phenylalanine ethyl ester hydrochloride. (Yield: 90%). Mpt: 155-156 °C. ¹H NMR (D₂O), δ (ppm) : 1.13 (t, 3H, *J* 7.3 Hz, CH₂CH₃), 3.18 (m, 2H, CH₂Ph), 4.14 (m, 2H, CH₂CH₃), 4.27 (t, H, *J* 6.5 Hz, CH), 7.11-7.26 (m, 5H, Ph). ¹³C(D₂O) δ (ppm): 16.1 (CH₃), 38.5 (CH₂Ph), 57.0(OCH₂), 66.5 (CH), 131.0, 132.1, 132.3, 136.6 (C₆H₄), 172.4 (C=O). [α]_D: -8.0° (c = 2 in water at 25 °C); [Lit [α]_D: -7.8° (c = 2 in water at 25 °C), O'Donnell *et al.* (1982)].

L-Phenylalanine propyl ester hydrochloride. (Yield: 93%). Mpt: 157-158 °C. ¹H NMR (D₂O), δ (ppm): 0.73 (t, 3H, *J* 7.7 Hz, CH₃), 1.52 (m, 2H, CH₂CH₂O), 3.09-3.15 (m, 2H, CH₂Ph), 4.03 (t, 2H, *J* 7.7 Hz, CH₂CH₂O), 4.20 (t, H, *J* 6.0 Hz, CH), 7.12-7.28 (m, 5H, Ph). ¹³C (D₂O) δ (ppm): 9.6 (CH₃), 21.3 (CH₂CH₂O), 35.8 (CH₂Ph), 54.4 (OCH₂), 69.3 (CH), 128.8, 129.5, 134.0 (C₆H₄), 170.3 (C=O). [α]_D: -20.5° (c = 1.5 in water at 25 °C).

L-Phenylalanine butyl ester hydrochloride. (Yield: 94%). Mpt: 136-137 °C. ¹H NMR (CDCl₃), δ (ppm): 0.89 (t, 3H, *J* 7.0 Hz, CH₃), 1.25 (m, 2H, CH₂CH₂CH₂O), 1.5 (m, 2H, CH₂CH₂CH₂O), 3.34 (dd, H, *J* 14.0 Hz, *J* 6.5 Hz, CHCHPh), 3.43 (dd, H, *J* 14.0 Hz, *J* 6.5 Hz, CHCHPh), 4.06 (t, *J* 6.3 Hz, 2H, CH₂CH₂O), 4.34 (t, H, *J* 7.5 Hz, CH), 7.22-7.31 (m, 5H, Ph), 8.75 (br s, 3H, NH₃⁺). ¹³C (D₂O) δ (ppm) : 13.3 (CH₃), 18.8 (CH₂CH₂CH₂O), 30.8 (CH₂CH₂CH₂O), 36.0 (CH₂Ph), 54.4 (CH), 66.6 (OCH₂), 127.4, 128.5, 134.7 (C₆H₄), 169.4 (C=O). [α]_D: -22.5° (c = 1.5 in water at 25 °C).

Typical Procedure:

2-Methyl-2-(3-oxobutyl)-cyclohexan-1,3-dione

2-Methylcyclohexane-1,3-dione (0.20 g, 1.55 mmol), hydroquinone (0.005 g, 0.04 mmol) and acetic acid (10 ml, 174 mmol) were stirred together in the presence of distilled water (25 ml) and a catalyst (25 mg). Methyl vinyl ketone (0.14 ml, 1.66 mmol) was added dropwise over 5 minutes and the resulting mixture was heated under reflux for 6 hours.

The reaction was left to cool to room temperature and the mixture was extracted using DCM (3 x 25 ml). The combined organic extracts were dried over sodium sulphate, and filtered. The organic layer was purified by filtration through a pad of silica (hexane : ethyl acetate, 5 : 1) and concentrated in *vacuo* to yield a yellow oil (0.228 g, 75 %). ¹H NMR (CDCl₃), δ (ppm): 1.20 (3H, br), 1.84-1.93 (5H, m), 2.07-2.14 (2H, m), 2.29-2.40 (6H, m). ¹³C NMR (CDCl₃), δ (ppm): 17.9, 24.2, 28.9, 39.5, 41.9, 50.5, 207.7, 208.8, 210.7.

Wieland Miescher Ketone (3,4,8,8α-Tetrahydro-8α-methylnaphthalene-1,6 (2H, 7H)-dione).

2-Methyl-2-(3-oxobutyl)-cyclohexan-1,3-dione (0.20 g, 1.02 mmol) and *L*-phenylalanine (0.025 g, 0.15 mmol) were stirred together in the presence of acetic acid (10 ml, 174 mmol) and distilled water (25 ml). The resulting mixture was heated under reflux for 5 hours.

The reaction was left to cool to room temperature and the mixture was extracted using DCM (3 x 25 ml). The combined organic extracts were dried over sodium sulphate, and filtered. The organic layer was purified by filtration through a pad of silica (hexane : ethyl acetate, 5 : 1) and concentrated in *vacuo* to yield an orange oil (0.167 g, 92 %). ¹H NMR (CDCl₃), δ (ppm): 1.36 (3H, br), 1.44-1.55 (4H, m), 1.64-1.68 (4H, m); 1.76-1.84 (2H, m). ¹³C NMR (CDCl₃), δ (ppm): 21.7, 28.3, 28.7, 30.6, 30.9, 59.4, 113.0, 138.2, 170.1, 205.9. [Enantiomeric purity, 72-73% e.e to the *S*-isomer; [α]_D: +70° (c = 1 in toluene at 25 °C); [Lit [α]_D: +97° (c = 1 in toluene at 25 °C; 96-97% e.e to the *S*-isomer), Bradshaw *et al.* (2011)].

3. RESULTS AND DISCUSSIONS

With a view of carrying out the synthetic route towards the Wieland Miescher product via an environmentally friendly medium which has several advantages over conventional solvents in terms of cost and cleaner methods, we proposed to use water as the solvent which would enable the used catalyst to adopt a micellar like aggregation. It was envisaged that increasing the chain length of our

catalysts can be explained by the fact that the extended chains would be involved in holding the substrates in a position which would help give yield enhancement. Also a chain length increase would increase the amphiphilic nature of our catalyst as well as help in the formation of micellar aggregation where the substrates can be solubilised and orientated by electrostatic, hydrogen bonding and hydrophobic interactions.

The esters of phenylalanine were synthesized according to a modified procedure (Vijay *et al.*, 2008; Joondan *et al.*, 2014) where *L*-phenylalanine was reacted with thionyl chloride in dry alcohol at room temperature for 18 hours to yield the ester hydrochloride as a white powder. The yields generated using the respective alcohols are shown in Figure 8.

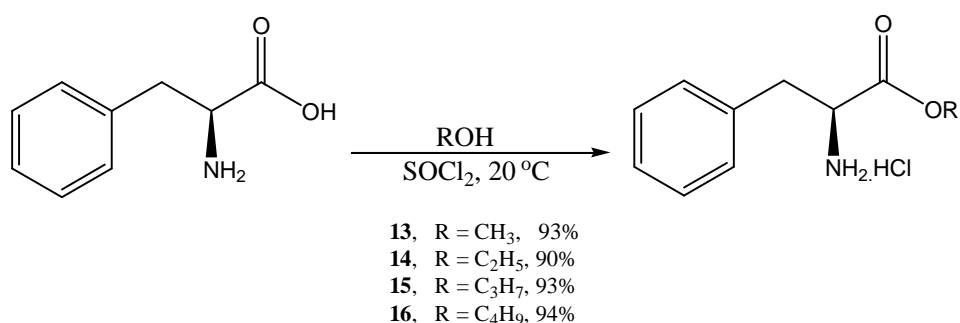


Figure 8 Synthetic route of making *L*-phenylalanine esters.

The synthesized *L*-phenylalanine esters (**13-16**) were subsequently used as catalysts for the synthesis of the triketone **4** which was to be used to make the Wieland-Miescher ketone **6** (Figure 9).

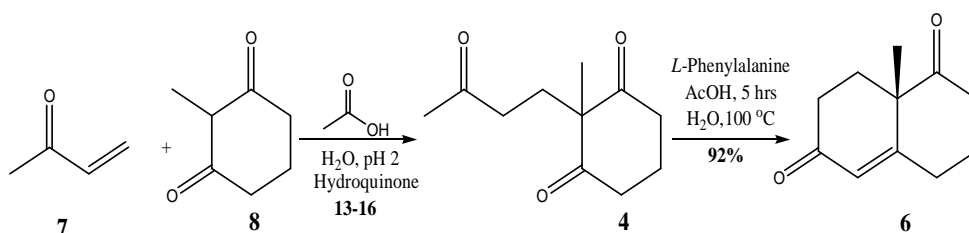


Figure 9 Synthetic pathway for making the Wieland-Miescher Ketone (**6**).

The formation of the triketone was performed in different solvents to investigate how varying the solvent polarity can affect the yield of triketone production. ^1H NMR analysis of compound **4** showed the presence of a broad singlet at peak δ 1.20 ppm, denoting the presence of protons coming from the (COCH_3) group. ^{13}C NMR analysis indicated the presence of three carbonyl peaks at δ 207.7, δ 208.7 and δ 210.7 ppm, confirming the formation of **4**.

Unsurprisingly, the use of organic solvents produced better yields compared to when using aqueous media, with THF being the more favourable solvent for this reaction. However with an aim of reducing the use of volatile organic solvents to drive organic reactions, we decided to use aqueous micellar media to carry out the synthesis of the Wieland-Miescher ketone, using our synthesized phenylalanine ester derivatives (**13-16**) as catalysts as well as two commercially available surfactants, CTAB and SDS since the use of surfactants and surfactant intermediates allow us to successfully perform organic reactions in water which is non-toxic, cheap and readily available.

Catalyst	Solvent	Time (Hr)	Temperature (°C)	% Yield
No catalyst	H2O	6	100	18
No catalyst	Hexane	6	100	27
No catalyst	THF	6	100	38
CTAB	H2O	6	100	68
SDS	H2O	6	100	40
13	H2O	6	100	67
14	H2O	6	100	69
15	H2O	6	100	73
16	H2O	6	100	75

Table 1 Synthesis of triketone, **4** using 2-methyl cyclohexane, 1,3-dione and methyl vinyl ketone.

Our results showed that extending the carbon chains of the *L*-Phenylalanine esters increased the percentage yield of the triketone produced.

The possible interaction between the synthesized phenylalanine esters and the reacting substrates is shown in Figure 10. We postulate that the presence of π - π stacking between the aromatic ring of the phenylalanine derivatives **13-16** and cyclohexan-1,3-one as well as hydrogen bonding between the carbonyl oxygen from the methyl vinyl ketone substrate and the catalytic esters, together with their increased hydrophobic interactions as we extend the ester chain length, had helped in holding and orientating the reacting substrates in position as well as keeping them in close proximity in order to favour product formation.

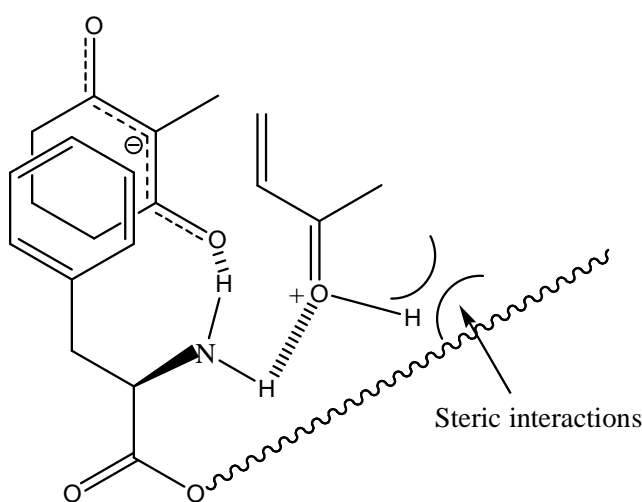


Figure 10 Postulated model showing the interactions between the phenylalanine catalysts and 2-methyl cyclohexane, 1,3-dione and methyl vinyl ketone substrate

Both commercially selected surfactants CTAB and SDS were used to investigate the use of micellar aggregation on reaction yields. The reactions were carried out at concentrations well above the CMC region where the formation of ellipsoidal or elongated structures have been reported (Tascioglu *et al.* 1996). CTAB and SDS both produced yield enhancement due to their amphiphilic nature as a result of their long chains. CTAB which contains a cationic head group showed better yield enhancement compared to SDS which contains an anionic head group, confirming that the charge on the head group can affect the reaction, with

favourable yields with cationic head groups. CTAB gave results as high as 68%. We believe that a surfactant-substrate interaction shown in Figure 11 is occurring.

The presence of the excess amount of acetic acid in the first reaction step (Figure 9) provides a protic media which will help stabilize the micellar aggregation, an observation that Diego-Castro and Hailes made for the use of surfactants in aqueous Diels-Alder reactions using acidic medium (Diego-Castro *et al.* 1998). The presence of the protic media was confirmed by the pH of the reaction, carried out at pH 2. At the same time, the conversion of the cyclic dione to enolate will allow the substrates to sit in close proximity with the catalyst as indicated in Figure 11, due to the attraction between opposite charges between the surfactant-substrates as well as the hydrophobic interaction which will align the reacting substrates near to each other as possible and would therefore favour reaction and enhance reaction yield.

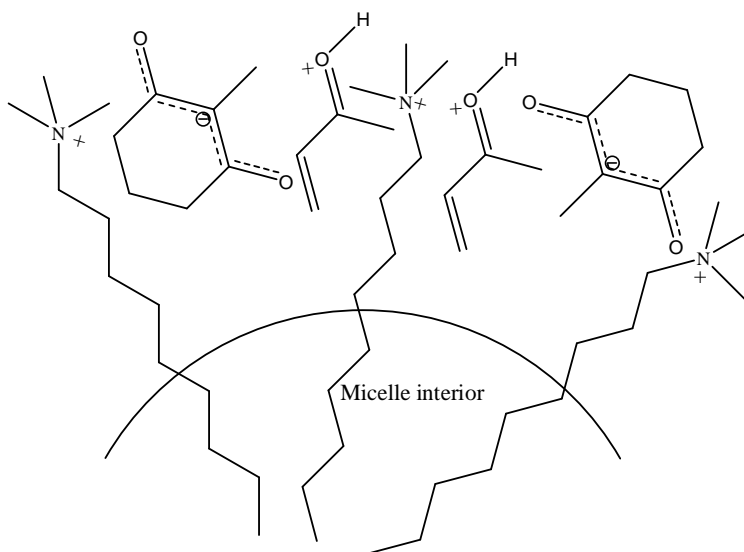


Figure 11 Postulated model showing the micellar arrangements and interactions of the reacting substrates and CTAB.

The final step involved the formation of the Wieland-Miescher ketone, **6** from the synthesized triketone, **4** using a Robinson annulation where a cyclisation of the triketone, **4** had occurred to give the resulting ketone **6**, in 92% yield (Figure 9). The enantiomeric purity was also investigated. From optical rotation analysis, it was found that the ketone **6** was obtained between 72-73% e.e selective to the *S*-isomer when compared to the literature optical rotation value (Bradshaw et al., 2011). ¹H NMR analysis showed the presence of a methyl group at δ 1.36 ppm. The formation of the olefinic bond was confirmed by the peaks at δ 113 and δ 138 ppm in the ¹³C NMR together with the presence of the two carbonyl carbons at peaks δ 170 ppm and 205 ppm, confirming the production of ketone, **6**.

In summary, we have generated promising amphiphilic compounds derived from *L*-phenylalanine, as useful catalysts to synthesise the Wieland-Miescher intermediate, giving good yields as high as 75% in aqueous protic media. Furthermore, we believe that the amphiphiles are aggregating in a micellar-like manner in water, causing solubilisation and orientation as a result of various polarity and charge effects. This was confirmed by our results using commercial CTAB and SDS which were able to successfully enhance reaction yield. As a result a very important C-C bond forming reaction used in the drug synthesis process can be carried out in aqueous media as we strive in using green-chemistry as we look for a cleaner and viable alternative in making drug analogues.

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