SYNTHESIS OF 2-SUBSTITUTED 4(*R*)-HYDROXY-2-CYCLOPENTEN-1-ONE, A PROSTAGLANDIN INTERMEDIATE WITH METHYL OLEATE FROM PALM OIL

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ABSTRACT

Methyl oleate, 1 was obtained from palm methyl esters through removal of saturated esters in a urea complex formation followed by silver nitrate impregnated silica gel column chromatography. The oleate was then reacted with 2,3-O-isopropylidene-D-glyceraldehyde 2, to form an aldol compound which, after lactonization, formation of tosylate and cyclic cyanohydrin, and oxidation of the double bond afforded 2-(6-carbomethoxyhexyl)-4(R)-hydroxy-2-cyclopenten-1-one 11, a prostaglandin intermediate.

Keywords: prostaglandin intermediate, methyl oleate.

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INTRODUCTION

Prostaglandins (PGs) are bioactive lipid acids with a C_{20} skeleton derived from polyunsaturated fatty acids (Bergstrom *et al*., 1968). PGs play important roles in the human body by controlling a wide variety of physiological responses including the stimulation of smooth muscle, dilation of the small arteries and bronchus, reduction of blood pressure and inhibition of gastric secretion (Robert, 1977; Noyori and Suzuki, 1984). In addition, PGE_2 and PGF_2 are drugs for inducing labour as well as for the interruption of pregnancy (Bygdeman and Eliasson, 1963; Bygdeman, 1964; Bygdeman *et al*., 1967) while PGE_1, a powerful vasodilator, is used clinically to treat male erectile dysfunction and peripheral vascular diseases such as Büerger's and Raynaud's diseases.

There are several methods for producing PGs, the most important being those of Corey *et al*. (1969) and Just *et al*. (1969). The Corey route uses cyclopentadiene as the starting material while the Just route starts off with norbornadiene to produce a Corey lactone, the PG intermediate. Since the successful construction of the intermediate, extensive research on PG synthesis has been undertaken. Most of the works are based on the synthesis of 2-substituted 4-hydroxy-2-cyclopentenone which, by the conjugate addition of a nucleophile, produces a PG. Sih *et al.* (1972) used ethyl 9-oxodecanoate and ethyl oxalate to synthesize an optically active 4R-hydroxy-diketone which, after benzoylation and reduction followed by dibenzoylation, produced a chiral 2-substituted 4-hydroxyenone in 60% yield.

Interest in the key intermediate - 4-hydroxyenone – caused Stork and Takahashi (1977) to use a chiral glyceraldehyde and methyl oleate as the starting materials for synthesizing the PG precursor. Assessing the techniques available, our synthesis of the PG intermediate from palm methyl esters was based on the method by Stork and Takahashi (1977). This was because palm methyl esters contain a high content (36%-41%) of methyl oleate (Siew *et al*., 1993).

EXPERIMENTAL

Materials

Refined palm oil was obtained from the Malaysian Palm Oil Board (MPOB). Analytical grade solvents - diethyl ether, methanol, acetone, dichloromethane, ethyl acetate, hexane, petroleum ether, pyridine and tetrahydrofuran (THF) - were acquired from Fluka, Switzerland. The general chemicals - urea, magnesium sulphate ($MgSO_4$),

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anhydrous sodium sulphate (Na_2SO_4), sodium chloride (NaCl), potassium hydroxide (KOH), sodium hydroxide, sulphuric acid (H_2SO_4), hydrochloric acid (HCl), sodium bicarbonate ($NaHCO_3$), ammonium chloride (NH_4Cl), potassium permanganate ($KMnO_4$) and silver nitrate ($AgNO_3$) - were obtained from Merck, Germany. The sources and suppliers of the other materials and chemicals are listed in brackets after the chemical names.

General Procedure

The melting point was determined in a Gallenkamp capillary melting point apparatus and used uncorrected. The optical rotation was recorded on a Model D Polarimeter (Bellingham & Stanley Ltd, United Kingdom) after dissolving the product in chloroform.

Thin Layer Chromatography (TLC)

TLC was performed on pre-coated aluminium sheet silica gel G60 (0.2 mm, Merck, Germany) with a solvent system of diethyl ether in petroleum ether. The plate was developed by dipping in a solution of *p*-anisaldehyde (1 ml, Sigma Chemical Co.) and H_2SO_4 (2 ml) in methanol (100 ml) and heated to 110°C for 1 min. Meanwhile, $AgNO_3$ impregnated silica gel thin layer chromatography ($AgNO_3$-TLC) was done by spraying the pre-coated silica gel plate with a solution of $AgNO_3$ (2 g, 0.02 mol) in methanol (10 ml). After elution with the solvent system of diethyl ether in petroleum ether, the $AgNO_3$-TLC plate was developed by dipping in a solution of *p*-anisaldehyde (1 ml) and H_2SO_4 (2 ml) in methanol (100 ml) and heated to 110°C for 1 min.

Column Chromatography

Column chromatography was performed using silica gel G60 (25 g, 70-230 mesh, Merck Ltd) with diethyl ether in petroleum ether as the eluant. The eluate was evaporated under N_2 and monitored by TLC. Meanwhile, the $AgNO_3$ impregnated silica gel ($AgNO_3$-SiO_2) column chromatography was performed by mixing $AgNO_3$ powder (4 g) with silica gel (20 g) and celite (10 g, Sigma Chemical Co.) in hexane (50 ml). After placing the sample at the top of the slurry, the column was eluted with diethyl ether in petroleum ether. The solvent extract was evaporated under N_2 and monitored by $AgNO_3$-TLC.

Gas Chromatography (GC)

GC analysis was performed on a Philips PU4600 gas chromatograph using capillary columns (DB1, 30 m x 0.32 mm, i.d. x 1 μm; J & W Scientific Co.) and a flame ionization detector (FID). Hydrogen was used as the carrier gas at 60 kpa head column pressure. The detector and injector temperatures were 300°C and 280°C, respectively, and the column temperature was programmed from 90°C to 300°C at 4°C min^{-1}. In case of the hydroxylated products, the samples were converted to trimethylsilyl ether (OTMS) by treating with N,O-bis(trimethylsilyl) trifluoroacetamide (BSTFA, Supelco Inc.) and heating to 90°C for 30 min before the GC analysis. The equivalent chain length (ECL) was determined by injecting the sample and a series of methyl esters of aliphatic C_{12}-C_{22} fatty acids simultaneously into the GC column and a graph of the logarithm of retention time versus carbon number plotted. The chromatograms and results were recorded using a Spectra Physics SP4600 integrator.

Spectroscopic Analysis

Infrared (IR) spectra were analysed on a Perkin-Elmer 1600 series FTIR grating spectrophotometer. Proton (^1H) NMR spectra were recorded on a JEOL JNM-FX90Q FT-NMR spectrometer operating at 90 MHz. Samples were dissolved in d_3-$CDCl_3$ and the chemical shifts (δ_H) reported in ppm downfield from tetramethylsilane (TMS). The coupling constants (*J*) were quoted in Hz. EI mass spectroscopic analysis was provided by the EPSR National Mass Spectrometry Centre, Department of Chemistry, University of Swansea.

Isolation of Methyl Oleate, *1* from Refined Palm Oil

Refined palm oil (100 g) was dissolved in 0.5 M methanolic KOH (250 ml) and the mixture refluxed for 2 hr. After refluxing, the reaction mixture was acidified with 1 M aqueous H_2SO_4 until pH 4.0 and water (500 ml) added. The mixture was transferred to a separating funnel and extracted with three portions of diethyl ether (250 ml). The combined ethereal extract was washed with a saturated aqueous $NaHCO_3$, dried over anhydrous $MgSO_4$ and evaporated to afford a mixture of crude methyl esters of the refined palm oil (91.0% yield).

Urea (100 g, 1.7 mol) was dissolved in boiling methanol (1 litre) and the crude palm methyl esters (91 g) added in portions. After cooling, the crystals formed were separated by suction in a Büchner funnel. From the filtrate, the palm methyl ester fraction was extracted with three portions of petroleum ether (500 ml) after the addition of water (1 litre). The petroleum ether extract was evaporated under vacuum to yield the unsaturated palm methyl esters (29.8% yield). The presence of the unsaturated esters was identified by $AgNO_3$-TLC by comparing their R_f values with authentic standards. The unsaturated fraction (29.8 g) was then subjected to

$AgNO_3$-SiO_2 column chromatography using 4% diethyl ether in petroleum ether to afford methyl oleate, *1* (24.9% yield).

Preparation of Aldol Product, *3*. Reaction of Methyl Oleate, *1* with D-Glyceraldehye, *2*

The aldol product *3* was prepared according to the method previously reported (Stork and Takahashi, 1977) with a slight modification. Briefly, a solution of methyl oleate, *1* (10 g, 33.7 mmol) in dry tetrahydrofuran, THF (10 ml) was added to a solution of lithium diisopropylamide, LDA (3.6 g, 33.7 mmol, Sigma Chemical Co.) in dry THF (15 ml) at -78°C. The reaction was carried out under N_2 and after stirring for 30 min a solution of hexamethylphosphoramide, HMPA (2 ml, 10% v/v, Sigma Chemical Co.) in dry THF (2 ml) and 2,3-*O*-isopropylidene-D-glyceraldehyde, *2* (4.4 g, 33.7 mmol) in dry THF (5 ml) was added dropwise. Glyceraldehyde *2* was obtained in 92% yield from 1,2:5,6-di-*O*-isopropylidene-D-mannitol according Daumas *et al*. (1989). The reaction mixture was stirred at -78°C for 2 hr, at 0°C for 1 hr and at room temperature for 8 hr after which it was quenched with saturated aqueous NH_4Cl and poured into diethyl ether (100 ml). After separation, the organic layer was washed with saturated NaCl (300 ml) and water (300 ml), dried over anhydrous Na_2SO_4 and concentrated *in vacuo* to give a crude product (9.9 g). Column chromatography on silica gel with 40% diethyl ether in petroleum ether furnished the desired product *3* (4.6 g, 11.0 mmol, 32.6%).

Preparation of γ-Lactone *5* and Tosylate *6*

The hydroxyl group of *3* (11.0 mmol) was protected using chloromethyl methyl ether (11.2 mmol, Sigma Chemical Co.) according to Stork and Takahashi (1977) afforded *4* in 41.2% yield. The protected aldol *4* (1 g, 2.1 mmol) was dissolved in THF (15 ml) and treated with 10% H_2SO_4 (10 ml, 10.2 mmol). The reaction mixture was kept at room temperature for 48 hr and then neutralized with 1 M NaOH. The mixture was extracted with petroleum ether (60 ml), dried over anhydrous Na_2SO_4 and concentrated *in vacuo* to furnish a crude extract containing a γ-lactone. Column chromatography on silica gel with 30% ethyl acetate in petroleum ether afforded γ-lactone *5* (0.7 mmol, 33.3% yield).

The γ-lactone *5* (3 g, 7.5 mmol) was treated with tosyl chloride (2.2 g, 11.4 mmol, Sigma Chem. Co.) in pyridine (10 ml) at 0°C for 12 hr and then at room temperature for 2 hr. The mixture was extracted with diethyl ether (150 ml). The solvent extract was washed with saturated NaCl, dried over anhydrous Na_2SO_4 and concentrated *in vacuo* to yield a tosylate, *6* (1.8 g, 3.3 mmol, 44.0 %), {IR (neat) cm^{-1} 2930, 2925, 2854, 1778, 1436, 1346, 1040}.

Synthesis of Cyclic Cyanohydrin and its Ester

The tosylate *6* (3.3 mmol) was added to a solution of diisobutylaluminium hydride (0.6 g, 4.2 mmol, Sigma Chem. Co.) in toluene (20 ml) at -40°C and the mixture stirred for 1 hr. After stirring, the resulting mixture was diluted with dichloromethane (40 ml), washed with saturated NaCl, dried over anhydrous Na_2SO_4 and evaporated *in vacuo*. The residue was treated with hydrogen cyanide in ethanol (10 ml) and concentrated ammonia (NH_3) (2 ml). After the addition of water (50 ml), the reaction mixture was extracted with diethyl ether (150 ml) and washed with saturated NaCl, dried and concentrated under vacuum.

The crude extract was chromatographed on a silica gel column with 15% ethyl acetate in petroleum ether to afford cyanohydrin *7* (1.8 mmol, 54.6%) (IR cm^{-1}: 3454, 2253). The cyanohydrin (1.8 mmol) was added to a solution of ethyl vinyl ether (4.2 mmol, Sigma Chem. Co.) in diisopropylethylamine (2 g, 15.5 mmol) and concentrated HCl (20 ml). The mixture was stirred at 0°C for 9 hr and the excess HCl neutralized with 1 M NaOH before workup. The mixture was extracted with diethyl ether (75 ml) and the organic layer washed with saturated NaCl, dried and evaporated under vacuum to give a crude product which, after silica gel column fractionation with 20% ethyl acetate in petroleum ether, afforded an ethoxyethyl compound *8* (0.8 g, 1.1 mmol, 61.1% yield). Compound *8* was dissolved in benzene (100 ml) and sodium hexamethyldisilazane (0.2 g, 1.1 mmol, Sigma Chem. Co.) added, and the mixture refluxed for 6 hr.

After cooling, the mixture was poured into saturated NH_4Cl (250 ml). The organic layer was washed with saturated NaCl (450 ml), dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. Column chromatography on silica gel with 20% ethyl acetate in petroleum ether gave a cyanohydrin product *9* (0.6 g, 1.0 mmol, 90.9% yield) (IR cm^{-1}: 2866, 2255). The cyclic cyanohydrin *9* (1.0 mmol) was dissolved in a mixture of methanol and THF (1:2, 30 ml) and to the reaction mixture was added a solution of $NaIO_4$ (10 g, 50 mmol, Sigma Chem. Co.) and $KMnO_4$ (5 g, 30 mmol, Merck Ltd) in 0.1N HCl (50 ml) with stirring for 1 hr. The mixture was extracted with diethyl ether (150 ml) and the ethereal layer treated with diazomethane. After drying under magnesium sulphate, the solvent was evaporated under a stream of N_2 to afford a cyanohydrin ester *10* (0.9 mmol, 90.0% yield).

Conversion of *10* to *2-(6*-carbomethoxyhexyl)-4*(R)*-hydroxy-2-cyclopenten-1-one, *11*

The cyanohydrin ester *10* (0.9 mmol) was dissolved in diethyl ether: THF (2:1, 30 ml) and 2%

NaOH added (15 ml). The reaction mixture was stirred at 0°C for 1 hr and 0.1N HCl (15 ml) added. The crude product was extracted with diethyl ether (150 ml), washed with a saturated NaCl (200 ml) and distilled water (200 ml). After drying over $MgSO_4$, the solvent extract was concentrated using a rotary evaporator to yield a crude product which, after silica gel column fractionation with 30% diethyl ether in petroleum ether *2*-(6-carbomethoxyhexyl)-4(*R*)-hydroxy-2-cyclopenten-1-one, *11* (0.8 mmol, 88.9% yield), {m.p. 62-63°C, $[\alpha]_D^{25}$ = +18.5° (*c* 0.9 CH_3OH); IR ($CHCl_3$) cm^{-1} 3448, 1748, 1720, 1658; ^1H NMR (ppm) δ_H 1.2-1.45 (m, 12H, CH_2), 2.35 (bd, 1H, *J*=3.5 Hz), 2.82 (bd, 1H, *J*=15 Hz), 3.60 (s, 3H, OCH_3), 5.01 (m, 1H), 7.20 (m, 1H, *J*=4.5 Hz); MS(EI) of the TMS derivative; m/z 73, 74, 228, 239, 280, 281, 294, 312}.

RESULTS AND DISCUSSION

Isolation of Methyl Oleate, *1*

The first step in the synthesis of PG precursor *11* is the isolation of methyl oleate, *1* from refined palm oil. The oil was refluxed with methanolic KOH to afford palm methyl esters in 91% yield. The methyl esters were fractionated by urea inclusion as described by Murawski and Egge (1975). The unsaturated material remained in solution. Addition of water and extraction with petroleum ether followed by evaporation *in vacuo* afforded the unsaturated fraction in 32.7% yield. The unsaturated fraction was subjected to the $AgNO_3$-SiO_2 column chromatography (Nichols, 1952). The silver ion formed co-ordination complexes with olefins and provided a basis for separating mono- and polyunsaturated fatty acid methyl esters. This technique is widely used for isolating fatty acid methyl esters from different sources. By employing the $AgNO_3$ silica gel column chromatography and eluting the unsaturated fraction with 4% diethyl ether in petroleum ether, the methyl oleate, *1* (24.9% yield, 98% purity by GC) was isolated. The presence of methyl oleate was detected by comparing its GC retention time with the authentic standard (Rt=22.51 min). In addition, its IR, ^1H NMR and MS spectroscopic data were in agreement with the literature values.

Synthesis of the Prostaglandin Intermediate

Since the 4-hydroxycyclopentenone derivative *11* is chiral, this study used 2,3-*O*-isopropylidene-D-glyceraldehyde, *2* as the second starting material to prepare the lactone ring via lactonization of the protected γ-hydroxy ester. The appropriate technique to transform methyl oleate to a protected γ-hydroxy ester was through an aldol condensation of the ester with an aldehyde according to the method of Stork *et al*. (1975).

***Aldol condensation of methyl oleate,* 1 *with lithium diisopropylamide (LDA) and D(+)-glyceraldehyde,* 2.** Treatment of methyl oleate, *1* with LDA in THF at –78°C in the presence of HMPA afforded lithium enolate. The enolate was then reacted with isopropylidene-D(+)-glyceraldehyde, *2* to form the aldol product which after column chromatography with 40% diethyl ether in petroleum ether afforded *3* in 32.6% yield (*Figure 1*). The use of hexamethylphosphoramide was very important in order to produce *cis*-enolate as the main product (Ireland and Willard, 1975). The IR spectrum of *3* showed absorption bands at 1735 (C=O stretch), 1715 and 3488 cm^{-1} (O-H stretch) due to carbonyl functions and the hydroxyl group. A doublet was observed at 1735 and 1715 cm^{-1} were in compliant with reported literature values.

Lactonization of the aldol product 5. The following step in the PG precursor synthesis was the preparation of γ-lactone from the aldol product *3*. The lactone is the precursor for the cyclopentane skeleton. The cyclization of *3* to the γ-lactone was achieved by reacting the hydroxy group γ with the carbonyl group. This process was used by Mann *et al*. (1987) in their transformation of (S)-5-hydroxymethylfuran-2(5H)-one from an aldol product to γ-lactone. Transforming the aldol product *3* to γ-lactone by Mann's procedure is also possible provided that the β-hydroxy group of *3* is protected prior to the lactonization. The protection of the hydroxy group was carried out by treating compound *3* with chloromethyl methyl ether in diisopropylethylamine to give the protected product *4* in 41.2% yield. Chloromethyl methyl ether was used by Kluge *et al*. (1972) as it was stable in pH 4-12. The IR spectral analysis of *4* showed no absorption band at 3488 cm^{-1} which indicated an absence of the OH group while the carbonyl group was observed at 1737 cm^{-1}.

After protecting the β-hydroxy group, the lactonization of *4* to γ-lactone *5* (33.3% yield) was done by treating with aqueous sulphuric acid in tetrahydrofuran. The IR analysis of *5* showed an absorption band at 1778 cm^{-1} (C=O stretch) (Lit: 1780 cm^{-1}) (Silverstein *et al*., 1981), the characteristic band for the γ-lactone ring.

***Conversion of γ-lactone* 5 *to tosylate* 6 *and the cyclopentane ring* 9.** The next step in the preparation of PG was conversion of the γ-lactone to its tosylate followed by cyclization to the cyclopentane derivative. The hydroxylactone *5* was converted to its tosylate ester *6* (44.0% yield) in the usual way. Further treatment of tosylate *6* with diisobutylaluminium hydride in toluene followed by

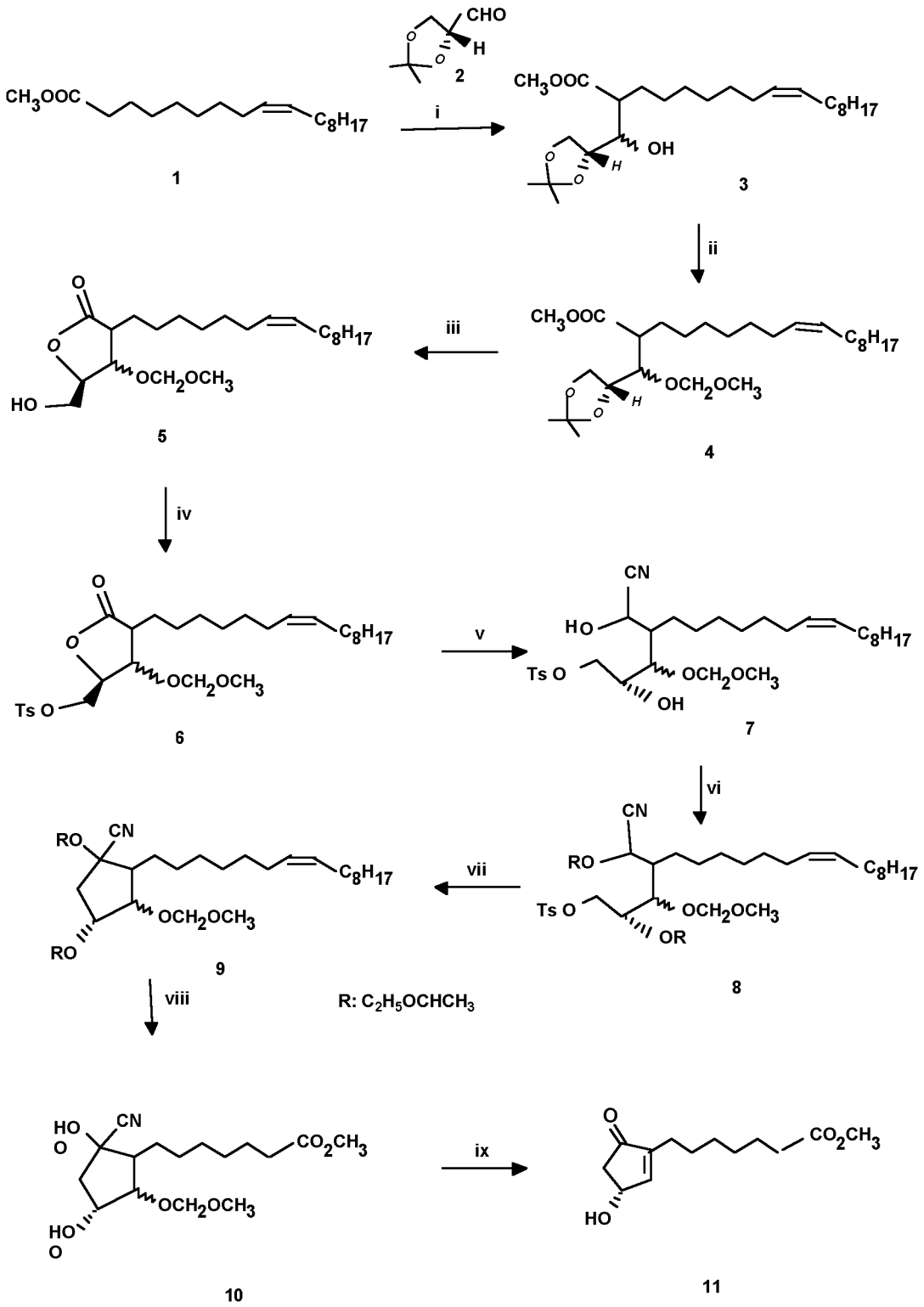

Figure 1. (i) LDA, HMPA, THF,-78°C, 2 hr (ii) $ClCH_2OCH_3$, $(^iC_3H_7)_2C_2H_5N$; 0°C, 1 hr (iii) H_2SO_4, H_2O, THF, rt, 48 hr (iv) TsCl, pyr, 0°C, 12 hr, rt, 2 hr (v) $(^iBu)_2AlH$, HCN, NH_3 (vi) $C_2H_5OCH=CH_2$, HCl (vii) $[(CH_3)_3Si]_2NNa$ (viii) $NaIO_4$/ $KMnO_4$, HCl, CH_2N_2 (xi) NaOH, THF, 0°C, 1 hr; HCl.

the addition of hydrogen cyanide afforded the hydroxyaldehyde cyanohydrin 7 in 54.6% yield. The disappearance of the IR absorption band at 1778 cm^{-1} indicated that the lactone ring had been opened and that the bands at 3454 and 2253 cm^{-1} were due to the presence of hydroxy and nitrile (C—N) groups respectively. Protection of the two hydroxy groups of compound 7 with ethyl vinyl ether was carried out according to Meyers *et al*. (1979) to afford *8* in 61.1% yield. The protected cyanohydrin *8* was then refluxed with sodium hexamethyldisilazane in benzene to give a cyclic cyanohydrin *9* (90.9% yield), a cyclopentane derivative. The use of sodium hexamethyldisilazane for the cyclization of cyanohydrin has been reported by Stork *et al*. (1975). The IR absorption band at 2866 cm^{-1} arises from a cyclopentane ring [lit: 2868 cm^{-1}, C-H stretching (Wiberg and Nist, 1961].

Preparation of 2-(6-carbomethoxyhexyl)-4(R)-hydroxy-2-cyclopenten-1-one* 11*, a prostaglandin intermediate. The final step in the synthesis of the PG precursor was transformation of the cyclic cyanohydrin *9* to a hydroxycyclopentenone derivative *11*, a PG intermediate. Firstly, oxidation of the double bond and removal of the ethoxyethyl groups of the cyanohydrin *9* with $KMnO_4$ and $NaIO_4$ in dilute HCl and methanol followed by methylation with diazomethane afforded *10* in 90.0% yield. Secondly, removal of the methoxymethyl groups by treating the cyanohydrin ester *10* with dilute HCl in THF followed by elimination of the cyano group with aqueous NaOH afforded hydroxycyclopentenone *11* in 88.9% yield. The spectroscopic data (IR, MS and ^1H NMR), specific rotation $[\alpha]_D^{25} = +18.5^o$ (*c* 1.0 CH_3OH) (Lit: 17.6°) and melting point 62°C-63°C (Lit: 60-61°) were in agreement with previously reported data (Sih *et al*., 1975) and it was concluded that compound *11* was 2-(6-carbomethoxyhexyl)-4(R)-hydroxy-2-cyclopenten-1-one, a PG intermediate.

CONCLUSION

This study showed that methyl oleate can be isolated as a single compound from palm methyl esters through urea fractionation followed by $AgNO_3$-SiO_2 column chromatographic processes. Methyl oleate was isolated from refined palm oil after it was converted to methyl esters in 24.9% yield. Although this technique is commonly used to isolate the individual esters from various oils and fats in classical literature (Murawski and Egge, 1975; Ackman and Sipos, 1965), its application to palm oil, especially palm methyl esters, has not been attempted. Methyl oleate can serve as a starting material for the synthesis of a PG intermediate.

Methyl oleate can be converted to a PG intermediate 2-(6-carbomethoxyhexyl)-4(*R*)-hydroxy-2-cyclopenten-1-one, *11* - through a multi-step chemical synthesis. Methyl oleate, *1* and 2,3-*O*-isopropylidene-D-glyceraldehyde *2* were reacted to give an aldol *3* (32.6% yield). Protection of the secondary alcohol and removal of the isopropylidene group were followed by cyclization to γ-lactone *5* (33.3%). Transformation to tosylate *6* (44.0% yield) and reduction of the lactone formed the cyanohydrin *7* (54.6%). The protection of *7* gave ethoxyethyl ether *8* (61.1% yield) which on refluxing in benzene with sodium hexamethyldisilazane, gave the cyclopentane derivative *9* (90.9%). Oxidation of the double bond, removal of the ethoxyethyl group and esterification then gave cyanohydrin ester *10* (90.0%) which after elimination of the methoxymethanol and HCN yielded enone *11* (88.9% yield), the PG intermediate.

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