CHAPTER II

A TWO-CARBON REGIOSPECIFIC INSERTION: AN EFFICIENT SYNTHESIS OF METHYL 9,12-DIOXEOICOSANOATE, A PROSTANOID PRECURSOR
A TWO-CARBON REGIOSPECIFIC INSERTION: AN EFFICIENT SYNTHESIS OF METHYL 9,12-DIOXO-EICOSANOATE, A PROSTANOID PRECURSOR

Abstract — An expeditious synthesis of methyl 9,11-eicosa- dienoate (5) via a novel two-carbon insertion into the readily available methyl oleate (1) is reported. The diene (5) has been transformed into a prostanoid precursor, methyl 9,12-dioxoicosanoate (9), by its functionalization with singlet oxygen and further manipulation, which on base-promoted cyclisation furnished an isomeric mixture of two products 2-(6-carbomethoxy-hexyl)-3-octylcyclopent-2-enone (10) and 2-heptyl-3-(7-carbomethoxyheptyl)-cyclopent-2-enone (11).
Introduction

With the gradual unfolding of what has come to be known as arachidonic acid cascade, functionalized C_{20} fatty acids have come to acquire much chemical and biosynthetic interest. Functionalized C_{20} fatty acids are important synthetic intermediates of prostaglandins, thromboxanes and leukotrienes, referred to collectively as eicosanoids. In connection with our efforts aimed at chemical transformation of ricinoleic acid into prostaglandin E_{1}, as a first target, we were desirous of developing a general and expedient route to functionalized C_{20} fatty acids. Our work in this direction forms the subject matter of this Chapter.

Strategy

The strategy envisaged for converting methyl oleate (1) into methyl 9,12-dioxoecosanoate (2) is outlined below.

For exploring an expedient route to functionalized C_{20} fatty acids of type (2) a C_{18} + C_{2} approach appeared attractive (Fig. 1) in view of the ready accessibility of C_{18} fatty acids, such as oleic and ricinoleic acids. Methyl oleate (1) was deemed the most appropriate C_{18} model component, required for investigating the strategy.
Addition of a C₂ unit across the olefinic linkage of methyl oleate (1), leading to C₂₀ 1,3-diene (5), could be accomplished by (2+2) photocycloaddition of (1) with a suitable C₂ component followed by retroelectrocyclisation of the resulting cyclobutene derivative (4). Further elaboration of (4) to methyl 9,12-dioxoicosanoate (9) involved the generation of 1,4-diketo system at C-9 and C-12. Oxygen functions at C-9 and C-12 could be introduced by singlet oxygen oxygenation of (5) and the resulting peroxide should be easily convertible into diketone (9) by a simple redox process. The series of reactions actually carried out to effect the transformation of methyl oleate (1) into methyl 9,12-dioxoicosanoate (9) is outlined in Fig. 2.

FIG. 1: Projected C₁₈ + C₂ route
Results and Discussions

Purity of methyl oleate (1) (77%; Play and Baker, England) was stepped up to 90% by fractional distillation and further up to 96% by using "the single dose urea" technique, in 65% overall yield.

For conversion of methyl oleate (1) into the required cyclobutene derivative (4), the well explored $\pi^2 + \pi^2$ photocycloaddition reaction appeared attractive. Of the two-carbon units exploited for such reactions, our choice fell on maleic anhydride, because of its ready accessibility. Mixed (2+2) additions have been carried out on a variety of olefinic substrates. Usually the reactions are brought about by sensitisation although occasionally, when the molecule permits, direct irradiation is also effective. The main problem with these additions is the inaccessibility of the molecular absorptions and consequently many examples use dienes or double bonds in conjugation with aryl groups. Acetone-sensitised irradiation (400 W medium pressure mercury lamp) of methyl oleate (1) and maleic anhydride at 5-10° furnished a product which was isolated as the free dicarboxylic acid mixture (2) after aq. Na$_2$CO$_3$ hydrolysis [the yield of (2) from (1) was 97% corrected for recovery, 47% uncorrected].
FIG. 2: Synthesis of methyl 9,12-dioxoeicosanoate (9)
The dicarboxylic acid (2) was characterised on the basis of its spectral data. PMR $\delta$(CCl$_4$) (Fig. 6): 10.78 (b, 2H, COOH exchangeable with D$_2$O), 3.6 (s, 3H, COOCH$_3$), 3.02-2.54 (b, 2H, carboxylic acid methine protons), 2.22 (t, 2H, CH$_2$-COOCH$_3$) and IR (neat): 3020 cm$^{-1}$ (carboxylic acid O-H stretch), 1715 cm$^{-1}$ (C=O stretch). A part of the diacid (2) was converted to its triester (3), by treatment with diazomethane, and in its PMR (CDCl$_3$) the appearance of signals, of 9 proton intensity, at $\delta$3.57 (s, 3H) and $\delta$3.59 (s, 6H) was indicative of the presence of three ester groups. (3) was also characterised on the basis of its IR (neat): 1740 cm$^{-1}$ (ester C = O stretch) and Mass ($M^+$ 440) spectra.

For conversion of (2) into the cyclobutene derivative (4), the adjacent carboxyl groups had to be removed by an oxidative process. The ability to convert bis-carboxylic acids to olefins constitutes a valuable synthetic transformation, but only a few methods are known, in literature, to accomplish this reaction in acceptable yields. The lead tetraacetate method has had variable success. The decomposition of peroxy esters, transition metal catalysis and CuO, quinoline methods suffer from low yields and high reaction temperatures. Electrolytic techniques appear to circumvent some of these problems; however, it appears
limited to small scales and is rather inconvenient.

When (2), dissolved in 10% aqueous pyridine and triethylamine was electrolysed, at room temperature, between two stationary electrodes (carbon and steel) at 0-9 volts dc, for 10 hr., the cyclobutene derivative (4) was obtained only in 29% yield. Lack of a suitable electrolytic set-up precluded the study of this reaction any further.

Oxidative bis-decarboxylation of (2) with lead tetraacetate and pyridine, in a stream of dry oxygen, in refluxing benzene (30 min) furnished a product, in 45% yield, which from its 200 MHz ¹H NMR (two distinct olefinic proton singlets at $\delta 6.12$ and $\delta 6.08$) was clearly a 7:3 mixture of cis/trans (trans/cis) isomers of (4). This formation of isomeric cyclobutenes obviously results from cis, trans isomerisation of methyl oleate during photoirradiation prior to maleic anhydride addition; such cis, trans isomerisation of olefins, under the influence of light, is well-documented. Olefins can undergo cis, trans isomerisation by both direct and sensitised irradiation. Simple olefins, because of high energy absorptions (below 200 nm), are difficult to irradiate directly,
however, with more substituted olefins the UV absorptions are pushed above 200 nm. Sensitised isomerisation of an olefin is brought about by excitation transfer from a molecule, such as a ketone, in its triplet state when the energy of the ketonic excited-state is in excess of the energy of the spectroscopic states of the olefin. The relaxed triplet state of the olefin, where the termini of the double bond are twisted to an angle approaching 90°, can then decay to either isomer. The structure of (4) was fully borne out on the basis of its spectral features. 200 MHz $^1$H NMR $\delta$(CDCl$_3$) (Fig. 10): 6.12 and 6.08 (two s, 2H, olefinic H), 3.61 (s, 3H, COOCH$_3$), 2.34-2.16 (m, 4H, CH$_2$COOCH$_3$ and allylic protons at ring junction); IR (neat) 3120 cm$^{-1}$ and 1555 cm$^{-1}$ (cyclobutene ring)$^5,14$; Mass ($M^+$ 322) and microanalysis.

In order to achieve the strategic a two-carbon insertion, it was envisaged that retroelectrocyclisation of the cyclobutene derivative (4) would insert a pair of carbons between the atoms originally joined, in (1), by the double bond leading to the desired C$_{20}$ straight-chain carbon skeleton. The ring-opening of cyclobutene has shown promise of becoming a very effective synthetic process$^{15}$ and has found considerable use, into a two-carbon ring
expansion, to form seven to ten-membered rings of both alicyclic and heterocyclic type, but till now its potential in acyclic systems has not been exploited.

Cyclobutene has a strain energy of 28.5 K cal/mol\(^{16}\) sufficient to render it thermodynamically less stable than butadiene. The mixture of cyclobutene (4) is quite labile and underwent a smooth cycloreversion, on pyrolysis, to furnish a neat mixture of 1,3-dienes (5), in almost quantitative yield. This was achieved readily in gas phase\(^{17}\) e.g., on distilling (4) under reduced pressure (0.3 mm) through a heated column (~450°C) filled with glass helices. The symmetry allowed thermal cycloreversion of cyclobutenes\(^{18}\) has been studied in detail and according to Woodward-Hoffmann rules,\(^{19}\) the conrotatory opening of cyclobutenes (4) would lead to a \( \Delta,2\) mixture of four dienes, two dienes arising from each of the two cyclobutenes (Fig. 3). In practice, the product obtained showed at least four components in GC (3% silicone OV-17, 220°C) with RRT of 1, 1.35, 2.35 and 2.78 in the ratio of 2:6:21:71 respectively. This appeared to be further supported by 200 MHz NMR of the product, which showed four areas in olefinic region.
The prime requisite for the "symmetry allowed" reaction of cyclobutene is that it give butadiene by a conrotatory process. The conrotatory process appears to proceed normally with an activation energy of 33.4 K cal/mol and no minimum energy path connects reactant and product in the disrotatory case. The two conrotatory modes of opening of a cis-3,4-disubstituted cyclobutene,
having unlike substituents, lead to two different isomers (cis, trans and trans, cis) and of a trans-3,4-disubstituted cyclobutane, having like or unlike substituents, also lead to two different isomers (cis, cis and trans, trans). In fact, in the case of trans-3,4-disubstituted cyclobutane the trans, trans product formed is major and even exclusive in some cases, which is attributed to the unfavourable steric situation in the transition state leading to the cis, cis product, but there are examples, in literature, wherein cis, cis product is also formed.

The corresponding acid of the diene (5) has been isolated earlier from oil of Lagochilus occultiflorus (1.75%), but there is no report of its synthesis. The spectral features of the 1,3-diene mixture (5)[200 MHz $^1$H NMR $^2$ (CDCl$_3$)(Fig. 12): 6.44-5.14 (m, 4H, olefinic H), 3.68 (s, 3H, COOCH$_3$), 2.06 (m, 4H, allylic protons); IR (neat): 3030 cm$^{-1}$ (=C-H stretch), 980 cm$^{-1}$ (C-H out-of-plane bend); UV: $^\lambda_{	ext{max}}$ 232 nm ($\varepsilon = 1.09 \times 10^4$); Mass (M$^+$ 322)] and elemental analysis are consistent with its structure.

Having achieved a C$_{20}$ skeleton, by regiospecific C$_2$ insertion, it was desired to functionalize C-9 and C-12 positions of the diene (5), but only a few methods are
known, in literature, to bring about this transformation regiospecifically. Dihydroboration-oxidation of 1,3-dienes using disiamylborane\textsuperscript{24}, to form glycols, could have been an acceptable method but for our specific requirement of 1,4-functionalization. The reaction would lose much of its synthetic utility as it leads to a mixture of diols (1,3 and 1,4). A survey of the literature divulged that it contains many accounts of the use of singlet oxygen as a reagent in organic synthesis\textsuperscript{25} and as an important preparative tool in the synthesis of many natural products and other compounds of special interest. Therefore, for further elaboration of the 1,3-dienes (5) into the required diketone (9), oxygenation with singlet oxygen\textsuperscript{25} appeared most appropriate as it would introduce oxygen functions at the desired C-9 and C-12 positions regiospecifically via a $\pi^4s + \pi^2s$ adduct, and also because the resulting peroxide (6) should be readily amenable to conversion to the methyl 9,12-dioxoeicosanoate (9) by a simple redox process.

Singlet oxygen is the first excited electronic state of molecular oxygen ($^1\Delta g$) lying 22.5 k cal/mol above the ground state triplet. Oxygen in its $^1\Delta g$ singlet state finds similarity, in its electronic arrangement, to ethylene and participates in Diels-Alder-type cycloaddition reactions\textsuperscript{26} with 1,3-dienes to form cyclic peroxides, by addition to the
terminal carbons of the diene. For the addition of excited-
state oxygen to a diene the selection rules (Woodward-Hoff-
mann) are operative as it resembles the ground-state
addition of ethylene to a diene. Thus the transition state
for the addition involves a cis-approach of the excited
oxygen to the ends of the diene, i.e., a typical six-
membered transition state. At this point, it may be mentioned
that, though the reaction of singlet oxygen with cyclic
1,3-dienes to furnish endoperoxides is well-established,
the same reaction with acyclic 1,3-dienes has not been
studied much and often results in a mixture of products
resulting from the competing ene-reaction. S-cis and
S-trans conformational isomerism of acyclic 1,3-dienes, may
be a pertinent factor in these cases. In practice, when a
dil. soln. of the dienes (5) in MeOH: CCl₄ (1:9) containing
Rose Bengal was simultaneously irradiated (125 W medium-
pressure Hg lamp) and treated with a steady stream of dry
oxygen (46 hr, 0-5°C), a remarkably clean reaction occurred,
to furnish as the sole isolable product the desired peroxide
(6), a diastereomeric mixture, in 75% yield.

In 1983 Klans Gollink and co-workers reported that,
during photooxygenation, singlet oxygen induces cis=trans
isomerisation of the dienes involved. It is assumed that
this cis=trans isomerisation of the dienes is brought
about via exciplexes, formed by interactions of $^1O_2$ with S-trans forms of the dienes, which decompose back mainly into oxygen and isomerised dienes. Only exciplexes from cis, trans dienes undergo isomerisation, on decomposition, to form trans,trans and cis,trans isomers whereas exciplexes from trans,trans dienes decompose back into oxygen and trans,trans isomers. Thus keeping in view the inherent isomeric dienes (5) and the subsequent isomerisation that they might have undergone, during photooxyge­nation, the formation of diastereomeric endoperoxide (6) is quite rational.

The generation of singlet oxygen by the dye-sensitised photochemical excitation of triplet oxygen was referred to non-photochemical methods, known in literature, because of convenience, yield and ease of product isolation. For maximum efficiency, in sensitised photooxyge­nation, a light source should strongly emit wavelengths, for electronic excitation, corresponding to $\lambda_{max}$ of the sensitiser. Since the sensitiser employed, Rose Bengal, has a $\lambda_{max}$ of 555 nm, so a filter soln ($1\% K_2CrO_4$ in water) was circulated, within the inner jacket of the quartz immersion well, to exclude light of undesired wavelengths, i.e., transparent only above 450 nm.
The addition of singlet oxygen to conjugated dienes is sensitive to steric effects and nature of substituents of the diene; electron-donating groups increase the reactivity of 1,3-dienes and conversely electron-withdrawing groups decrease their reactivity. Thus, the long irradiation time required by the dienes (5) is reasonable, keeping in view the conformational flexibility of two long chains, a steric factor.

Many of the endoperoxides are thermally unstable and decompose violently upon heating or attempted isolation. Contrary to our apprehension, the endoperoxide (6) was fairly stable, at room temperature (30°C), and was isolated and purified by SiO₂-gel chromatography. The structure of (6) is in accord with its spectral data. In its 200 MHz "H-NMR (Fig. 14) signals at δ 5.82 (s, 2H, olefinic H) and δ 4.58-4.26 (bt, 2H, CH=CH-CH-O-O) indicate the presence of 1,4-epidioxy group, which is further supported by its 13C NMR (proton noise decoupled) δ (CDCl₃) (Fig. 16): 128.04 and 127.92 (two s, HC = CH) 78.43 (tert. c, masked by CDCl₃ signals) and IR (neat): 1740 cm⁻¹ (ester C=O stretch).

1,4-Epoxides are valuable intermediates in syntheses because they can be transformed into a variety of functionalized derivatives under various conditions of reduction and oxidation and on thermal treatment.
Epidioxy group is known to get reduced selectively, to cis-1,4-enediol, with thiourea, but when (6) was treated with thiourea (1.1 eq., THF, room temp.) no reduction could be achieved.

It is known in literature that 1,4-epidioxides rearrange to 4-hydroxyenone systems, when exposed to basic alumina, by undergoing a $\beta$-elimination reaction. Acyclic 4-hydroxyenone systems are highly labile and can in turn be rearranged to 1,4-diketones. Keeping this information in view, a direct transformation of (6) into (9) was envisioned (Fig. 4). However, when peroxide (6) was exposed to basic alumina (Grade I, room temp., 37°C), the product obtained was not the diketone (9) (no ketonic C=O stretch absorption in the IR) but turned out to be a disubstituted furan (14). The latter was recognized by its PMR $^3$C$_{(\text{CCl}_4)}$: 5.72 (s, 2H, furyl protons) and 2.52 (t, 4H, $J = 6$ Hz, aryl-CH$_2$). This formation of (14) can be rationalized as follows: It is reasonable to assume that 4-hydroxyenone derivative (12), formed by $\beta$-elimination of (6), must have undergone cyclisation followed by dehydration resulting in the formation of (14). That acyclic 4-hydroxyenone systems can undergo cyclisation-dehydration to form furans is not without precedence as it leads to more stable aromatic systems. The literature contains
accounts of synthesis of a number of 2,5-disubstituted C₁₈ furanoid acids, with an alkyl carboxyl and an alkyl group in ring positions, which constitute a novel group of compounds, but C₂₀ furanoid acids of the type are not known.

Finally, the peroxide (6) was reduced with hydrogen and Raney Ni to furnish, in over 66% yield, the saturated alcohol (7), which must be diastereomeric. In the IR spectrum of (7) the absorption at 3350 cm⁻¹ (O-H stretch)
was indicative of the presence of hydroxyl functions, which was further supported by its P	extsuperscript{MR} 6 (CDCl	extsubscript{3}); 3.55 (b, 2H, HC-OH), 2.65-2.12 (m, 4H, CH	extsubscript{2}COOCH	extsubscript{3} and O-H exchangeable with D	extsubscript{2}O); mass spectrum (M-2H	extsubscript{2}O 322) and microanalysis. The diol (7) was further characterised as its diacetate derivative (8), prepared by treatment of (7) with acetic anhydride and pyridine. The structure of (8) was fully borne out by its spectral data. IR (neat): 1740 cm	extsuperscript{-1} (C=O stretch), 1240 cm	extsuperscript{-1} (C=C(=O)-O stretch band for acetates); P	extsuperscript{MR} 6 (CCl	extsubscript{4}) (Fig. 21): 4.74 (m, 2H, acetate methine protons), 1.96 (s, 6H, OOCOCH	extsubscript{3}); Mass: (M-2CH	extsubscript{3}COOH 322). The diol (7) was oxidised with pyridinium chlorochromate\textsuperscript{38} to furnish the target molecule, methyl 9,12-dioxoicosanoate (9), in 94\% yield.

Having failed in our earlier attempt to effect the direct transformation of the endoperoxide (6) into 1,4-dione (9), a modified approach was contemplated (Fig. 5).

Rearrangement of endoperoxide (6) can be effected by treatment with triethylamine\textsuperscript{32c} and the resulting \(\gamma\)-hydroxy-\(\alpha,\beta\)-olefinic ketone (12) should be readily amenable to conversion\textsuperscript{39} to 1,4-diketone (9). Indeed, when (6) was treated with Et\textsubscript{3}N, a mixture of (9) and (12) was obtained. The crude product, on passage through a columns of active alumina underwent complete conversion of (12) into (9),
to afford the dione (9) in 24% yield. In another experiment, when Et₃N was replaced by 1,5-diazabicyclo[5.4.0]undecene-5 followed by exposure of the crude product to active alumina,

\[
\begin{align*}
&\text{Reagents: 1. DBU, CHCl₃; 2. Neutral alumina (grade I)} \\
&\text{FIG. 5}
\end{align*}
\]

the yield of diketone was enhanced to 70%. This rearrangement clearly proceeds through (12), for which there is previous precedent\textsuperscript{32c}; active alumina is an effective catalyst\textsuperscript{39} for the prototropic isomerisation of γ-hydroxy-α,β-olefinic ketones to 1,4-diones. The compound thus synthesised was identical (m.p., IR, PMR and Mass) with methyl 9,12-dioxaicosanoate, which has been prepared earlier\textsuperscript{40} by thiazolium
The diketone (9) was cyclised with 6% aqueous sodium hydroxide in methanol and the crude cyclised product was esterified with CH₂N₂ to give, after purification over SiO₂-gel, pure cyclised product in a yield of 72%. The cyclised product, which showed a single peak on TLC-FID (20% ethyl acetate/pet ether) (Fig. 27b) and GC (10% Ov₄, 220°) (Fig. 27c), was easily resolved by HPLC (Lichrosorb, RP-18 Column; acetonitrile) (Fig. 27a) indicating the material to consist of (1:1) mixture, as expected, of two compounds which should be (10) and (11). The structure of the cyclised product (10) and (11) was evident from their spectral data. IR (neat): 1738 cm⁻¹ (COOCH₃), 1705 cm⁻¹ and 1640 cm⁻¹ (cyclopentenone); UV: λmax EtOH 239 nm (ε = 9,506); PMR (CDCl₃): 3.62 (s, 3H, COOCH₃), 2.65-2.02 (m, 10H, six allylic and four protons α-to carbonyls). The cyclopentenones (10) and (11) have been prepared earlier by Samuelsson and co-workers by cyclisation-decarboxylation of methyl 9,12-dioxo-10-carbomethoxyeicosenoate.
EXPERIMENTAL

General remarks

All m.ps and b.ps are uncorrected. Petroleum ether refers to the fraction of b.p. 60-80°C. Solvent ether was dried over sodium wire. Methanol was dried over magnesium methoxide. Tetrahydrofuran was distilled from sodium-benzophenone ketyl immediately prior to use. Acetone was refluxed over KMnO₄ and then distilled from anhydrous potassium carbonate. All solvent extracts were finally washed with brine and dried over anhyd. Na₂SO₄.

The following instruments were used, unless otherwise stated, for spectral/analytical data: Perkin-Elmer Infrared spectrophotometer, model 297(IR); Perkin-Elmer spectrophotometer 402(UV); Perkin-Elmer R-32 (90 MHz) spectrometer (PMR); Varian Mat. mass spectrometer, model CH-7 (mass, 70 ev, direct inlet system); C,H,N Analyzer, Hewlett-Packard, model 185B. Gas chromatography analyses were carried out on Hewlett-Packard 7642A chromatograph (stainless steel columns, 180 cm x 0.3 cm; support 60-80 mesh chromosorb U; phase 3% silicone OV-17; carrier gas N₂) equipped with flame ionization detector.
All PMR spectra were recorded with 15-20% solution in CDCl₃ with TMS as internal reference, signals are recorded in ppm (§). While citing PMR data, the following abbreviations have been used: s(singlet), d(doublet), t(triplet), q(quartet), m(multiplet) and b(broad). IR data are reported in wavenumbers (cm⁻¹). ¹³C-NMR data are reported in parts per million (§) with chloroform-d₄ as the internal standard. While summarising mass spectral data, besides the molecular ion, nine most abundant ions m/e are reported with their relative intensities.

Silica gel for column chromatography was of 100-200 mesh (Centro Laboratories, Bombay) and was used as such (Grade II). Column chromatography in all cases was performed under medium pressure. TLC was carried out on silica gel G (Centro Laboratories) and the plates (0.25 mm) were used as such without activation.

Photoirradiation was carried out with a 400 watts medium pressure mercury lamp (Applied Photophysics Ltd.) suspended in a double-walled, water-cooled, clear-fused quartz well, without filter. Throughout the reaction a minute, steady flow of dry and oxygen-free N₂ was passed through the solution.
Photooxygination was performed with a 125 watts medium pressure mercury lamp (Applied Photophysical Ltd.), suspended in a double-walled, clear-fused quartz well. An ice-cold aqueous solution of 1% $\text{K}_2\text{CrO}_4$ was circulated through the jacket of the immersion well serving both as a filter and as a coolant. A continuous and steady stream of dry oxygen was passed through the solution. The reaction was monitored by TLC.

**Methyl Octadec-cis-9-enoate (1)**

To a solution of oleic acid (May & Baker, England; 435 g, 1.54 mol) in excess of dry methanol (700 ml) was added p-toluenesulphonic acid (1.5 g) and the solution was refluxed for 8 hr. Methanol was distilled off and the residue was diluted with ether (500 ml). The ethereal layer was washed with water (2 x 50 ml), 10% aqueous $\text{NaHCO}_3$ (3 x 50 ml) again with water (3 x 50 ml) and brine (75 ml) and dried. The solvent was removed to give crude methyl oleate (452 g; 77.8% pure by glc, 5% $\text{P(DEGS)}$, 6', 170°C). The crude material was subjected to fractionation, when the pure methyl oleate (1) (90% pure by glc) distilled at 134-135°C/0.2 mm (lit. 2b b.p. 168-170°/2 mm).

Further purification of 1. To a solution of methyl oleate (250 g, 90% pure) in 750 ml of dry methanol was added urea
(750 g) and the mixture was refluxed (2.5 hr) till the urea dissolved completely and a homogeneous solution was obtained. The solution was allowed to stand for 4-5 hr. at room temperature (36°C), after which it was filtered by suction. The solid urea complex was decomposed by stirring it with hot water (350 ml) when methyl oleate formed a separate layer. It was separated, washed with water and brine and dried over anhyd. Na₂SO₄ to give methyl oleate (1) (162 g; 64.8% yield; 96% pure by glc). Methanol was distilled off from the filtrate to give some more of urea complex, which was decomposed by hot water to give impure methyl oleate (84 g; 33.3%; 76% pure by glc).

PMR²C (CDCl₃): 5.28 (t, 2H, J = 5 Hz, -CH=CH-) 3.59 (s, 3H, J = 7 Hz, COOCH₃), 2.21 (t, 2H, J = 7 Hz, CH₂-COOCH₃), 1.99 (bm, 4H, allylic H), 1.7-1.08 (bm, 22H, CH₂'s), 0.88 (t, 3H, -CH₃).

IR²d (neat) νmax: 3008, 1745, 725 cm⁻¹.

3,1,2-Dicarboxy-(cis/trans)-3-(7-carbomethoxy-heptyl)-4-octylcyclobutane (2)

A solution of (1) (8.8 g, 30 mmole) and maleic anhydride (2.94 g, 30 mmole) in dry acetone (300 ml) was placed in an immersion well photochemical reactor, then deoxygenated with a stream of nitrogen for 20 minutes. The reaction mixture was then irradiated for 10 hr. with a 400 W medium-pressure mercury lamp, while bubbling nitrogen
continuously. Removal of solvent under vacuo furnished the crude photoadduct which was hydrolysed by aqueous Na$_2$CO$_3$ solution (5%, 100 ml), at room temperature for 16 hr. It was extracted with ether (3 x 50 ml). The ether layer was washed with water (3 x 20 ml), dried and solvent removed to recover 4.64 g of the starting oleate (1). The aqueous Na$_2$CO$_3$ portion was acidified (pH~3) with conc. HCl, saturated with solid NaCl and extracted with ether (4 x 50 ml). The combined ether extracts were washed with water (2 x 35 ml), brine (1 x 35 ml) and dried. Ether was flashed off to get a mixture of dicarboxylic acid (2), 5.73 g, as a gum (the yield of 2 from 1 was 97.11% corrected for recovery, 47% uncorrected).

PMR $\delta$ (CCl$_4$) (Fig. 6): 10.78 (b, 2H, -COOH exchangeable with D$_2$O), 3.6 (s, 3H, COOCH$_3$), 3.02-2.54 (b, 2H, carboxyl methine protons), 2.22 (t, 2H, J = 7Hz, -CH$_2$-COOCH$_3$), 1.7-1.03 (bm, 3OH, CH$_2$'s and methine-protons at ring junctions), 0.88 (t, 3H, -CH$_3$); IR (CHCl$_3$) (Fig. 7): COOH 3020, 1715; COOCH$_3$ 1735 cm$^{-1}$; 2940, 2860, 1450 cm$^{-1}$.

A part of 2 was converted to its tri-ester 3 by treatment with diazomethane and further purified by column chromatography on silica gel, which was characterised as such.

PMR $\delta$ (CCl$_4$) (Fig. 8): 3.59 and 3.57 (2S, 9H, COOCH$_3$), 2.9-2.43 (b, 2H, carbomethoxy methine protons), 2.22 (t, 2H, J = 7Hz,
CH₂-COOCH₃), 1.75-1.0 (bm, 30H, CH₂'s and CH's), 0.87 (t, 3H, -CH₃); IR(neat) (Fig. 91; COOCH₃ 1740 cm⁻¹; 2940, 2860, 1450 cm⁻¹; Mass: m/e 440(M⁺ 2%), 409(15%), 348(8%), 243(5%), 211(5), 145(100%), 113(34%), 81(50%), 68(13%), 55(80%).

(cis/trans)-3-(7-Carbomethoxyheptyl)-4-octylcyclobut-1-ene (4)

The diacid 2 (6.67 g, 15.46 mmole) was taken in dry benzene (200 ml) and pyridine (2.44 g, 30.88 mmole) was added to it. The reaction mixture was refluxed in a stream of oxygen and lead tetraacetate (13.69 g, 30.90 mmole) was added at once. Refluxing was continued for another 30 minutes and it was then brought to room temperature. Ethylene glycol (1.5 ml) was then added and reaction mixture was stirred for another 15 minutes to destroy excess lead tetraacetate. The material was then filtered through celite and washed with benzene (4 x 25 ml). The combined filtrates were washed successively with dil. HNO₃ (15%, 3 x 35 ml), water (1 x 30 ml), 5% aqueous NaHCO₃ (1 x 30 ml) and again with water (2 x 25 ml) and brine (1 x 40 ml) and dried over anhydrous sodium sulphate. The solvent was removed under reduced pressure to give a crude product (4.78 g) which was purified by column chromatography on silica gel (50 g) to
furnish an isomeric mixture of cyclobutenes 4 (2.23 g, 44.87% yield) as a liquid.

PMR (200 MHz) $\delta$(CDCl$_3$) (Fig. 10): 6.12 and 6.08 (2s, 2H, olefinic H), 3.61 (s, 3H, COOLH$_3$), 2.34-2.16 (m, 4H, allylic methine protons at ring junction and CH$_2$-COOCH$_3$), 1.68-1.12 (bm, 26H, CH$_2$'s), 0.82 (t, 3H, -CH$_3$); IR (neat) (Fig. 11): Cyclobutene ring 3120, 1555 cm$^{-1}$; COOLH$_3$ 1742 cm$^{-1}$; 3025, 2940, 2860, 1430, 1160 cm$^{-1}$.

Mass: m/e 322 (M$^+$ 24%), 291(16%), 179(6%), 150(6%), 136(14%), 123(18%), 109(32%), 96(63%), 67(100%), 41(45%).

(Found C, 78.13; H, 12.29; C$_{21}$H$_{38}$O$_2$ requires C, 78.26; H, 11.80%)

Methyl 9,11-Eicosadienoate (5)

The cyclobutene 4 (2.50 g, 7.76 mmole) was taken in a 5 ml round bottomed flask fitted to an electrically heated column (1.5 cm x 12 cm), filled with glass helices, which in turn was connected to a cold trap. The flask was heated to 210-220$^\circ$C (bath temperature) under vacuum (0.3 mm) while the temperature of the column was maintained at 425-450$^\circ$C, whereby an isomeric mixture of dienes 5 (2.47 g, 98.94% yield) distilled over as a colourless liquid.

PMR (200 MHz) $\delta$(CDCl$_3$) (Fig. 12): 6.44-5.14 (m, 4H, olefinic H), 3.68 (s, 3H, -COOLH$_3$), 2.32(t, 2H, J = 7Hz, CH$_2$-COOCH$_3$), 2.06 (m, 4H, allylic protons ), 1.78-1.16 (bm, 22H, CH$_2$'s),
Methyl 9,12-Peroxy-eicos-10-enoate (6)

A solution of diene 5 (1.70 g, 5.27 mmole) and Rose Bengal (0.5 g, 0.49 mmole) in 500 ml of dry methanol: CCl₄ (1:9) was simultaneously irradiated with 125 W medium pressure mercury lamp (RCA) and treated with a continuous stream of dry oxygen for 46 hr. at 0-5°C, while circulating on ice-cold solution of 1% aqueous potassium chromate both as a filter and as a coolant. After the reaction was complete (tlc), solvent was removed under reduced pressure, at room temperature (28°C), and the residue was chromatographed on silica gel (20 g) to give the adduct 6 (1.38 g, 74.19% yield) as a liquid.

PMR (200 MHz) 6 (CDCl₃) (Fig. 14): 5.82 (s, 2H, \(\text{CH} = \text{CH}\)), 4.58-4.26 (bt, 2H, \(\text{=CH-CH-O-0}\)), 3.61 (s, 3H, COOCH₃), 2.24 (t, 2H, \(J = 7\text{Hz}, \text{CH}_2\text{-COOCH}_3\)), 1.74-1.1 (bm, 26H, \(\text{CH}_2\)'s), 0.81 (t, 3H, \(\text{-CH}_3\));

UV: \(\lambda_{\text{max}}\) EtOH 232 nm (\(ε = 1.09 \times 10^4\)).

(Found C, 78.09; H, 11.29; \(\text{C}_{21}\text{H}_{32}\text{O}_2\) requires C, 78.26; H, 11.80%).
Rearrangement of 1,4-epidioxide 6 over basic Al₂O₃-I

To a solution of peroxide 6 (80 mg, 0.22 mmole) in 10 ml of dry methylene chloride was added basic alumina (2.5 g, grade-I). The suspension was stirred, under anhydrous conditions, at room temperature (37°C), for 16 hr. Al₂O₃ was filtered off and washed thoroughly with CH₂Cl₂ (50 ml) and ether (50 ml). The filtrate and the washings were combined and solvent was removed to get the crude 2,5-disubstituted furan 14 (0.070 g, 92.10%) as a yellow liquid.

PMR 6(CCl₄) (Fig. 17): 5.72 (s, 2H, furyl protons), 3.6 (s, 3H, COOCH₃), 2.52 (t, 4H, CH₂COOCH₃), 2.22 (t, 2H, -CH₂COOCH₃), 1.9-0.9 (bm, 21H, CH₂'s and -CH₃);

IR (neat): (Fig. 18): COOCH₃ 1742 cm⁻¹; 3010, 2935, 2860, 1560, 1430, 1170, 780, 720 cm⁻¹.

Methyl 9,12-Dihydroxyeicosanoate (7)

Peroxide 6 (0.94 g, 2.26 mmole) in methanol (20 ml) was stirred over Raney Ni (0.60 g) under hydrogen atmosphere for 16 hr. Methanol was decanted off and the catalyst was washed with methanol (3 x 15 ml). The combined solvent was
removed under reduced pressure to give the crude diol 7 (0.94 g) as a white solid, m.p. 70-75°C. It was purified by column chromatography on silica gel (17 g) to afford pure diol (0.625 g, 65.78% yield), which was recrystallized from acetonitrile, m.p. 87-89°C.

PMR δ(CDCl₃) (Fig. 19): 3.6 (s, 3H, -COOCH₃), 3.55 (b, 2H, CH-OH), 2.65-2.12 (m, 4H, -CH₂-COOCH₃ and O-H exchangeable with D₂O), 1.9-1.07 (b, 30H, CH₂'s), 0.85 (t, 3H, -CH₃);
IR (KBr) (Fig. 20): OH 3350 cm⁻¹; COOCH₃ 1740 cm⁻¹; 2940, 2860, 1470, 1340, 1020, 710 cm⁻¹;
Mass: m/e 340 (M⁺-H₂O, 2%), 327(2%), 322(2%), 195(45%), 187(73%), 183(88%), 155(92%), 83(63%), 55(100%), 41(59%).
(Found C, 70.18; H, 12.03; C₂₁H₄₂O₄ requires C, 70.39; H, 11.73%).

Diol 7 (0.025 g, 0.69 mmole), Ac₂O (0.5 ml) and dry pyridine (0.5 ml) were mixed together and kept at room temp. (35°C) in a stoppered r.b. flask for 15 hr. The reaction mixture was diluted with ether (25 ml) and washed successively with 25% HCl (3 x 10 ml), 10% aqueous NaHCO₃ (10 ml), water (2 x 10 ml) and brine (10 ml) and dried. Solvent was removed to give the crude product (0.035 g), which was purified by column chromatography on silica gel (4 g) to get pure di-acetate 8 (0.028 g, 90.32% yield) as a liquid.

PMR δ(CCl₄) (Fig. 21): 4.74 (m, 2H, -CH-0Ac), 3.58 (s, 3H, -COOCH₃), 2.21 (t, 2H, -CH₂-COOCH₃), 1.96 (s, 6H, -OCOCH₃),
1.78-1.0 (br, 30H, CH₂, s), 0.88 (t, 3H, -CH₃);
IR (neat) (Fig. 22): COOCH₃ and OCOCH₃ 1740 cm⁻¹; OCOCH₃ 1240 cm⁻¹; 2840, 2960, 1370, 1010, 710 cm⁻¹;
Mass: m/e 411 (M⁺-OCH₃ 1%), 382 (3%), 322 (M⁺-2CH₃CHOH 51%), 227 (27%), 183 (27%), 155 (14%), 81 (25%), 69 (25%), 55 (35%), 43 (100%).

Methyl 9,12-Dioxoeicosanoate (9)

(a) To a suspension of pyridinium chlorochromate (0.36 g, 1.67 mmole) in dry CH₂Cl₂ (15 ml) was added the diol 7 (0.20 g, 0.56 mmole) at room temperature (35°C). After stirring for 3 hr, the reaction mixture was diluted with ether (30 ml). The solvent was decanted and the residue was washed with ether (3 x 10 ml). The combined solvent was passed through a short silica gel column. Removal of solvent gave the crude dione (0.203 g) which was further purified by chromatography on silica gel (8 g) to give pure 9 (0.193 g, 97.96% yield) as a white solid, m.p. 61°C (lit. 40, m.p. 61°C).

PMR⁴⁰ δ(CDCl₃) (Fig. 23): 3.65 (s, 3H, COOCH₃), 2.66 (s, 4H, -CO-(CH₂)₂-CO-), 2.6-2.13 (m, 6H, -CH₂-COOCH₃ and -CO-CH₂), 2.0-1.15 (brm, 22H, CH₂'s), 0.88 (t, 3H, -CH₃);
IR⁴₀ (KBr) (Fig. 24): C=O 1700, 1705 cm⁻¹; COOCH₃ 1740 cm⁻¹; 2940, 2860, 1470, 1410, 1370, 1260, 720 cm⁻¹;
Mass: m/e 354 (M⁺ 8%), 323 (7%), 256 (14%), 140 (21%), 114 (29%), 97 (30%), 85 (100%), 69 (52%), 55 (72%), 28 (63%).
(b) To the peroxy 6 (0.1 g, 0.28 mmole) in CHC1₃ (5 ml) was added 1,5-diazabicyclo[5.4.0]undec-5-ene (0.5 g, 0.32 mmole) and stirred for 4 hr. at room temperature (35°C). CHC1₃ was removed under vacuo and the residue was charged on to a small column of alumina (6g, grade I). Elution with ethyl acetate and removal of solvent furnished the dione 9 (0.07 g, 70% yield) which was identical with diketone 9 prepared by method (a), m.p. 60°C, m.p. 59-60°C and nmr.

2-(6-Carbomethoxyhexyl)-3-octylcyclopent-2-ene(10) and 2-Heptyl-3-(7-carbomethoxy-heptyl)-cyclopent-2-ene(11)

1,4-Diketone 9 (0.1 g, 0.28 mmole) was refluxed with 5% aqueous NaOH (5 ml, 7.5 mmole) in methanol (10 ml), in a 25 ml r.b. flask, for 4 hr. Methanol was distilled off under reduced pressure and the aqueous portion was acidified with 10% aq. HCl till it became acidic (pH ~ 3). It was extracted with ether (3 x 20 ml). The ethereal layer was washed with water (3 x 15 ml), brine (15 ml) and dried. Ether was flashed off and the crude was esterified with CH₂N₂ to give crude material (0.092 g), which, after purification over SiO₂-gel (8 g), gave cyclopentenones 10 and 11 (0.069 g, 73.40% yield) as a liquid in 1:1 ratio (HPLC, Lichrosorb RP-18 column; acetonitrile) (Fig. 27a).

PMR 6 (CDCl₃ (Fig. 25): 3.62 (s, 3H, COOCH₃), 2.65-2.02 (m, 10H, active CH₂'s), 1.8-1.02 (bm, 20H, CH₂'s), 0.87 (t, 3H, -CH₃); IR 41 (neat) (Fig. 26): COOCH₃ 1738 cm⁻¹; 1705, 1640, 2940, 2860, 1435, 1360, 1170 cm⁻¹; UV 41: λ max EtOH 239 nm (ε = 9.5 x 10³).
Fig. 6: PMR spectrum of cis-1,2-dicarboxy-(cis/trans)-3-(7-carbomethoxyheptyl)-4-octylcyclobutane (2)
Fig. 7: PMR spectrum of cis-1,2-dicarboxy-(cis/trans)-3-(7-carboxymethoxycetyl)-4-octylcyclobutane (2)
Fig. 8: PMR spectrum of cis-1,2-dicarboxyhexyl-(cis/trans)-3-
(7-carboxyhexyl)-4-octycyclobutane (3)
Fig. 9. IR spectrum of cis-1,2-dicarbomethoxy(1,2-cis/trans-
1,2-carbomethoxyethyl)-4-acylcylobutane(II)
Fig. 10: 200 MHz PMR spectrum of (cis/trans)-3-(7-carbamethoxyhexyl)-4-octylcyclobut-1-ene (4)
Fig. 11: IR spectrum of (cis/trans)-3-(7-carboxmethoxyheptyl)-4-octylcyclobut-1-ene (4)
Fig. 12: 200 MHz PMR spectrum of methyl 9,11-eicosadienoate (5)
Fig. 13: IR spectrum of methyl 9,11-eicosadienoate (5)
Fig. 15: IR spectrum of 9,17-peroxyeicos-10-enoate (6)
Fig. 16: $^{13}$C-NMR of 9,12-Receivedcos-10-enoate (6)
Fig. 17: PMR spectrum of methyl 8-(5-octyl-2-furyl)-octanoate (14).
Fig. 18: IR spectrum of methyl 8-(4-octyl-2-furyl)octanoate (14)
Fig. 19: PMR spectrum of methyl 9,12-dihydroxyeicosanoate (2)
Fig. 20: IR spectrum of methyl 1,12-dihydroxydocosanoate (7)
Fig. 21: NMR spectrum of methyl 9,12-diacetoxyicosanoate (g)

[Diagram showing NMR spectrum with peaks labeled]
Fig. 12: IR spectrum of methyl 9,12-diacetoxyeicosanoate (8)
Fig. 23: PMR spectrum of methyl 9,12-dioxoicosanoate (9)
Fig. 24: IR spectrum of methyl 9,12-dioxoicosanoate (g)
Fig. 25: NMR spectrum of mixture of 2-(6-carboxethoxy-hexyl)-3-octylcyclopent-2-enone (10) and 2-hentyl-3-(7-carboxethoxyhentyl)-cyclopent-2-enone (11)
Fig. 26: IR spectrum of mixture of 2-(6-carboxethoxy-hexyl)-3-octylcyclopent-2-enone (10) and 2-heptyl-3-(7-carboxethoxyheptyl)-cyclopent-2-enone (11)
HPLC SEPARATION OF CYCLOPENTENONES

SOLVENT: ACETONITRILE
ULTROPAC COLUMN LICHROSORB RP-18 10 μm 4×250mm

1.2 m 10% OV4 Column at 220°C
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