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Macrocyclic musk compounds: Synthetic approaches to key intermediates for exaltolide, exaltone and dilactones†

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Abstract

Facile syntheses to key intermediates **7** and **31** (for exaltolide **I**), **9** (for exaltone **II**) and **17** and **23** (for dilactones **III** and **IV**), respectively, have been achieved from easily accessible aleuritic acid and 10-undecenoic acid. The compound **5** on $HgO/Br_2/CCl_4$ reaction followed by saponification and acidification gave synthon **7**, whereas **6** on oxidation with $NaNO_2$/DMSO/AcOH followed by esterification yielded **9**. Grignard coupling of **29** with **13** in the presence of Li_2CuCl_4 as the catalyst followed by hydrolysis afforded the synthon **31**. The two-carbon homologation product C_{13} diacid (**17**) from 10-undecenoic acid has been achieved by Knoevenagel condensation of **14** or **18** or by the reaction of olefin **12** with manganic acetate and acetic acid, followed by hydrogenolysis/hydrogenation. The compound **13** on oxidation with $NaNO_2$/DMSO/AcOH gave C_{11} diacid (**23**). The aldehyde **26**, obtained by α-glycol cleavage of aleuritic acid, on Knoevenagel condensation followed by hydrogenation also gave **23**.

Keywords: Synthesis, musk key intermediates, oxidation reactions: $HgO/Br_2/CCl_4$, $NaNO_2$/AcOH/DMSO, DMSO/$NaHCO_3$, two-carbon homologation, $Mn(OAc)_3$/AcOH.

1. Introduction

The odour of musk has been highly valued since time immemorial. Odorous compounds[1,2] play an important role in life processes. The odorous compounds, which were first used in religious ceremonies have been used for centuries as pharmaceutical ingredients and odorants. Ambergist musk, civet and castoreum are still some of the most precious perfumery ingredients. The exocrine odour glands of the musk deer (*Moschus moschiferus*) which are located in the skin of the abdomen in the proximity of the male genitalia are called pods. During the rutting season, male deer secretes a honey-like mass with a strong odour which is used for both territorial boundary marking and for attracting female partners over great distances. The musk deer or antelope (*Moschus moschiferus*), inhabitant of Central Asia and American musk rat (*Ondarta zibethicus rivalicius*) are the cheap sources of the odorous compounds. The musk compound is isolated[3] and characterised[4] as 3-methylcyclopentadecanone (muscone). Some of the macrocyclic musks of animal origin are muscone, civetone, dihydrocivetone, exaltone, etc. In addition, two other musks of vegetable origin, viz. exaltolide and ambrettolide from angelica root (*Angelica archangelica)* and ambrette seeds (*Abelmoschus moschatus, Hibiscus abelmoschus),* respectively, are also very well known. However, these compounds are found as intricate mixture in nature and in minute quantities.

† Dedicated to Prof. S. C. Bhattacharyya.
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There is a constant demand for these musks in bulk in perfumery industry, which has also developed artificial musks. However, the artificial musks, viz. nitroaromatic compounds and polycyclic musks are either suspected to be carcinogenic or nonbiodegradable. Hence, in recent years, the demand for artificial musks is fading whereas synthetic natural musks are gaining importance. The synthetic optically active muscone was achieved by Mamdapur *et al.*[5] from easily accessible starting materials.

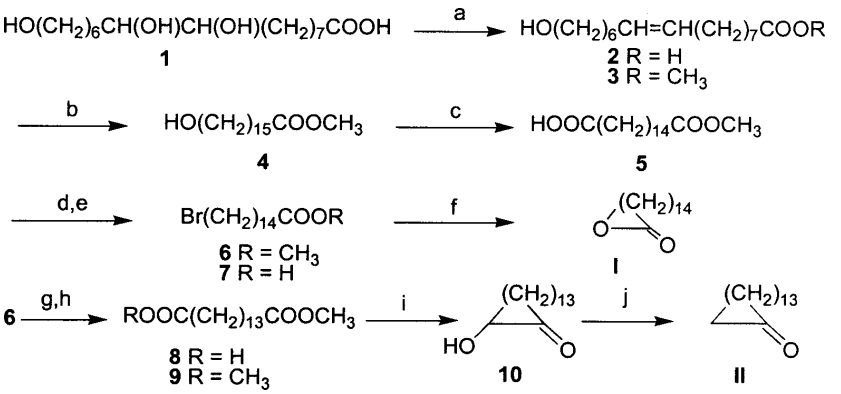
In the ever-increasing demand for musk compounds, the synthetic organic chemists play a vital role for the facile synthesis. In our endeavour, we achieved this to some extent using easily accessible chemicals as starting materials and or reagents and facile reactions for synthesising some of their key intermediates.

Cyclopentadecanolide **I** (exaltolide) and cyclopentadecanone **II** (exaltone), having musk-like odour and fixative properties, are highly valued in the perfumery industry. Several syntheses of these have been reported in the literature.[6–11]

The key intermediates in the synthesis of exaltolide and exaltone are 15-bromo or 15-hydroxypentadecanoic acid **7** or **31** and dimethyl 1,15-pentadecanedioate (**9**), respectively. In our approach, aleuritic acid (9,10,16-trihydroxyhexadecanoic acid) (**1**), a major component of shellac, was used as the starting material because of its multifunctionalities. The α-glycol function of aleuritic acid was reacted with triethyl orthoformate[12] (TEOF) in the presence of benzoic acid and the resulting intermediate pyrolysed to furnish the olefinic acid (**2**) in 90% yield. This on esterification followed by hydrogenation gave methyl 16-hydroxyhexadecanoate (**4**) in almost quantitative yield. The compound **4** on oxidation with PDC/DMF[13] gave 1,16-hexadecanedioic acid monomethyl ester (**5**) in 73% yield.

Here we have taken advantage of modified Hunsdiecker[14] method for halogenative decarboxylation with red mercuric oxide and bromine in carbon tetrachloride. This is superior to the Hunsdiecker procedure in which glassware and chemicals have to be scrupulously dry and the preparation of dry silver salt of carboxylic acid is frequently difficult as such salts are usually quite sensitive to heat. Therefore, we subjected **5** to the modified Hunsdiecker reaction to obtain methyl 15-bromopentadecanoate (**6**) in 79% yield. The absence of the signal for the acidic proton and the presence of signal at δ 3.38 (t, 2H) for CH_2Br in PMR confirmed the structure. This on saponification with one equivalent of alkali and acidification gave the required synthon 15-bromopentadecanoic acid (**7**) in 95% yield. The formal synthesis of exaltolide was achieved from key synthon (**7**) as reported in the literature.[8]

In order to achieve synthon **9** for exaltone synthesis from aleuritic acid, we have made use of recent literature[15] wherein the primary nitroalkanes and primary alkyl bromides can be directly oxidised to the corresponding acid without affecting the other functional group such as ester using sodium nitrite and acetic acid in DMSO. The reaction proceeds under mild acidic condition that renders it compatible with various sensitive functionalities and with high yields.Thus the compound **6** in the above exaltolide synthesis was thought of and was subjected to oxidation with sodium nitrite and acetic acid in DMSO to give 1,15-pentadecanedioic acid monomethyl ester (**8**) in 90% yield. The absence of signal at δ 3.38 and the presence of 4 protons between δ 2.2 and 2.4 and the presence of bands at 3500–3000, 1740 and 1710 cm^{-1} in IR confirmed the acid monomethyl



(a) TEOF, PhCOOH; MeOH, H^+; (b) H_2,10%Pd-C, EtOH; (c) PDC, DMF; (d) HgO, Br_2; (e) KOH; H^+;(f) K_2CO_3, DMSO; (g) DMSO, AcOH, $NaNO_2$; (h) MeOH, H^+; (i) Na/xylene and (j)Zn/HCl.

Scheme 1.

ester. Esterification of **8** gave the diester **9**, a synthon of exaltone, in 96% yield. The formal synthesis of exaltone **II** was achieved by using known procedure[9] of acyloin condensation followed by Clemensen reduction.

Non-natural macrocyclic ethylene tridecanedioate (ethylene brassylate) and ethylene undecanedioate have pleasant and powerful musk-like odour. Ethylene tridecanedioate is used in perfumery under the trade names Astrotone (Dupont, Rhone Pouelenc) and Musk T (Takasayo Perf. Co. Ltd). The dilactone **III** was introduced into perfumery only a few decades ago and has grown to become one of the most important musk compounds to the perfumer. It is used extensively in perfumery as fixative, intensifier of sweet floral notes and in synthetic detergents. In all the reported syntheses[6,16-18] of ethylene brassylate and ethylene undecanedioate, the final step essentially remains the same, i.e. the conversion of the diacid to dilactone using ethylene glycol, which has been patented. Expectedly, much importance is given to the development of synthetic routes for the C_{13} diacid (**17**) which is a synthon for ethylene brassylate and C_{11} diacid (**23**), which is a synthon for undecanedioate. Biotechnological methods are also gaining importance for the syntheses of these diacids.[6]

Three synthetic routes have been developed by us from 10-undecenoic acid, a pyrolysis product of ricinoleic acid, a major component of castor oil, as the starting material for the preparation of synthon C_{13} diacid (**17**) as its bifunctions are strategically well located for homologating two carbon atoms from either side.

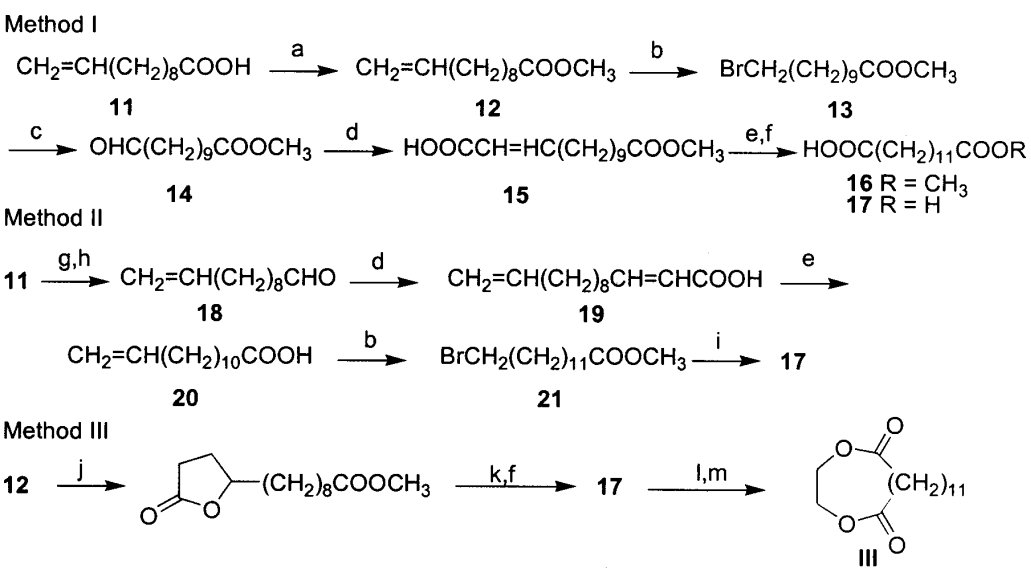
In the first approach, 10-undecenoic acid was esterified followed by bromination by anti-Markownikoff [19] addition with dry HBr to give methyl 11-bromoundecanoate (**13**) in 90% yield. The absence of terminal olefin bands in IR at 910 and 990 cm^{-1} and the absence of olefinic protons and the presence of proton signal at δ 3.4 for primary halide accounting for two protons in PMR confirmed the addition product. Here we have taken advantage of a procedure wherein primary alkyl halide is oxidised to aldehyde by the action of DMSO/$NaHCO_3$.[20] Thus, bromo compound was oxidised to give C_{11} aldehyde ester (**14**) in 75% yield. The presence of aldehyde function was confirmed by bands at 2725 and 1720 cm^{-1} in IR and a signal for one proton in PMR at δ 9.75.

Knoevenagel condensation of **14** with malonic acid in pyridine with catalytic amount of piperidine followed by hydrogenation of conjugated double bond with Mg in dry methanol,[21] saponification and acidification gave 1,13-tridecanedioic acid (**17**).

In an alternate approach to **17**, 10-undecenoic acid on reduction with LAH followed by pyridinium chlorochromate (PCC) oxidation[22] gave 10-undecenal (**18**) in 75% yield. Knoevenagel condensation of **18** with malonic acid in pyridine with catalytic amount of piperidine followed by hydrogenation of conjugated double bond with Mg in dry methanol[17] gave 12-tridecenoic acid (**20**) in 85% yield. The compound **20** was subjected to hydrobromination as above followed by oxidation[15] with $NaNO_2$/DMSO/HOAc to give the desired synthon **17**.

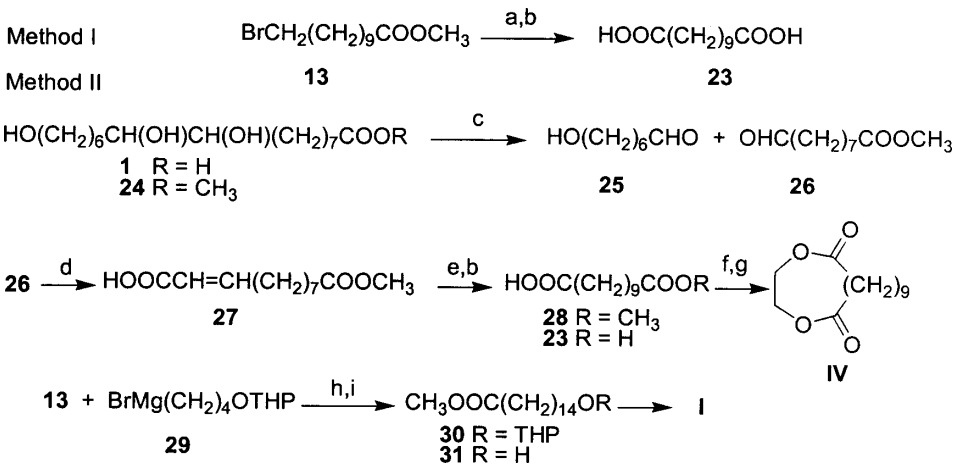
The literature report[23] on reaction of terminal olefin with manganic acetate in anhydrous acetic acid for two-carbon homologation prompted us to utilise this reaction for the synthesis of synthon **17**. Thus, compound **12** was subjected to manganic acetate prepared *in situ* [$Mn(OAc)_2$ $4H_2O/Ac_2O$/AcOH/$KMnO_4/\Delta$] to give γ-lactone (**22**) as the major compound together with some minor byproducts containing unsaturated C_{13} diacid monoesters, the structures of which could be deduced by analogy with 1-decene.[23] The analytically pure sample of γ-lactone showing the IR band at 1778 and 1735 cm^{-1} confirmed the γ-lactone and ester functions, respectively. The crude lactone (**22**) containing byproducts gave the desired product **17** after hydrogenolysis/hydrogenation followed by acidification. 1,11-undecanedioic acid (**23**), the key intermediate for the synthesis of ethylene undecanedioate **IV**, was achieved by two routes.

In the first method, oxidation of methyl 11-bromoundecanoate (**13**) obtained from the earlier synthesis (Scheme 2) was oxidised with sodium nitrite and acetic acid in DMSO[15] followed by



(a) MeOH, H^+; (b) HBr, $(PhCOO)_2$; (c) DMSO, $NaHCO_3$; (d) $CH_2(COOH)_2$, py, piperidine; (e) Mg, MeOH; (f) KOH; H^+; (g) LAH; (h) PCC; (i) DMSO, $NaNO_2$, AcOH; (j) $KMnO_4$, $Mn(OAc)_2$. $4H_2O$AcOH, Ac_2O; (k) H_2, Pd-C; (l) PTSA, $(CH_2OH)_2$, C_6H_6; (m) $MgCl_2.6H_2O$, Δ.

Scheme 2.



(a) DMSO, $NaNO_2$, AcOH ; (b) KOH; H^+; (c) $NaIO_4$; (d) $CH_2(COOH)_2$, py, piperidine; (e) Mg, MeOH; (f) PTSA, $(CH_2OH)_2$; (g) $MgCl_2.6H_2O$, Δ; (h) Li_2CuCl_4 ; (i) PTSA.

Scheme 2.

saponification and acidification to give the required synthon 1,11-undecanedioic acid (**23**) in 95% yield. In the second approach, aleuritic acid (**1**) was chosen as the starting material. Aleuritic acid was esterified to methyl ester by standard procedure followed by $NaIO_4$ cleavage of its α-glycol function. It gave a mixture of 7-hydroxyheptanal (**25**) and methyl 8-formyloctanoate (**26**). Separation of **26** by column chromatography and then using the standard procedures as above for two-carbon homologation yielded the required synthon (**23**).

The compound **13** has also been utilised in an alternative approach[10] for the synthesis of another key synthon **31** for the synthesis of exaltolide. In this approach, the Grignard coupling reaction[24] of compound **13** with compound **29** in the presence of catalytic amount of Li_2CuCl_4 in THF, followed by hydrolysis and purification, gave **31** in 54% yield. It shows the hydroxy band at 3450 cm^{-1} and ester band at 1740 cm^{-1} in IR.

The formal synthesis of **III, IV** and **I** could be achieved by the known procedure.[25,26]

2. Conclusion

The key intermediate for exaltolide, exaltone and dilactones has been achieved from commercially available aleuritic acid and 10-undecenoic acid. The required intermediates have been obtained in high yields by carrying out the facile reaction, viz. halogenative decarboxylation, two-carbon homolagations, oxidation of terminal bromides to corresponding carboxylic acids using inexpensive reagents.

3. Experimental

All b.p.s and m.p.s are uncorrected. The IR spectra were scanned with a Pye-Unicam SP3-300 spectrophotometer and only the pertinent values are expressed. The PMR spectra were recorded either with a Varian-EM-360L (60 MHz) or a Brucker AC-200 (200 MHz) spectrometer using $CDCl_3$ as the solvent. The chemical shift (δ) and the values of coupling constant (J) were expressed in ppm and Hz, respectively.

The anhydrous reactions were carried out under argon using three-necked round bottom flask equipped with a gas inlet/outlet and magnetic stirring bar. The solvents were freshly dried by standard procedures just prior to use. The reagents were either introduced with the help of a dropping funnel (for >10 mmol reactions) or a hypodermic syringe (for small-scale reactions).

3.1. *16-Hydroxy-9(E)-hexadecenoic acid (**2**)*

A mixture of aleuritic acid (**1**) (49.12 g, 161.6 mmol), triethyl orthoformate (TEOF) (84 ml) and benzoic acid (2.4 g) was heated in an oil bath gradually at 80°C to remove all alcohol formed (60 min). The temperature was raised to 179°C (inside temperature) when carbon dioxide evolution started. After 4 h, at this temperature the evolution of gases stopped practically. The excess of triethyl orthoformate was removed by distillation *in vacuo*. The residue, diluted with alcoholic alkali (18 g potassium hydroxide+180 ml ethanol+180 ml water) was refluxed for 5 h. Alcohol was distilled off and the residue was acidified with 10% sulphuric acid (600 ml) and extracted with ethyl acetate. The product was recrystallised from carbon tetrachloride. Yield: 39.26 g (90%). m.p. 66°C (lit.[12] m.p. 66–68°C). IR: 3500–3000, 1695, 1460, 980 cm^{-1}. PMR: δ 1.28 (brs, 18H), 1.5–2.6 (m, 6H), 3.1 (s, D_2O exchangeable OH, 1H), 3.68 (s, J=7 Hz, 2H), 5.3–5.6 (m, 2H), 7.8 (s, D_2O exchangeable).

3.2. *Methyl 16-hydroxy-9(E)-hexadecenoate (**3**)*

A solution of 16-hydroxy-9(*E*)-hexadecenoic acid (**2**) (30.24 g, 112 mmol) in methanol (250 ml) containing concentrated sulphuric acid (1.0 ml) was refluxed for 6 h. Then the mixture was cooled and most of the solvent was removed in vacuum. The residue was taken up in ether and the ether layer washed with sodium bicarbonate, water and brine. Removal of ether gave a viscous liquid, which was distilled under vacuum 160°C/0.5 mm. (lit.[10]160°C/0.5 mm), Yield: 31.16 g (98%). IR: 3430, 1740, 1055 and 980 cm^{-1}. PMR: δ 1.3 (brs, 18H), 1.6–2.7 (m, 6H), 2.0 (s, D_2O exchangeable OH, 1H), 3.6 (s, 3H), 3.6–3.9 (t, 2H), 5.3–5.6 (m, 2H).

3.3. *Methyl 16-hydroxyhexadecanoate (**4**)*

A solution of methyl 16-hydroxy-9(*E*)-hexadecenoate (**3**) (20 g, 70.4 mmol) in alcohol was hydrogenated with 10% Pd-carbon and hydrogen with a drop of acetic acid. The reaction was carried out in a vacuum line and the reaction mixture was stirred overnight, filtered and purified by silica gel chromatography. TLC silica gel 5% ethyl acetate in benzene (R_f 0.34). Yield: 14.1 g (70%). IR: 3450, 2940, 1740, 1470, 1060 cm^{-1}. PMR ($CDCl_3$): δ 1.28 (m, 26H), 2.25 (br, 2H), 2.4 (1H, D_2O exchangeable), 3.58 (t, 2H, J=6 Hz), 3.65 (s, 3H).

3.4. *1,16-Hexadecanedioic acid monomethyl ester (**5**)*

A mixture of methyl 16-hydroxyhexadecanoate (**4**) (12 g, 41.96 mmol), PDC (45.1 g, 120 mmol) in dry DMF (500 ml) was stirred for 24 h at room temperature. The mixture was poured in water, extracted with ethyl acetate and the organic layer washed thoroughly with water, brine and dried. Removal of solvent, followed by purification by column chromatography (silica gel, 0–20% ethyl acetate in hexane) of the residue afforded 1,16-hexadecanedioic acid monomethyl ester. Yield: 9.19 g (73%). m.p. 55°C (lit.[11] 55–55.5°C). IR: 3500–3000, 1740, 1710 cm^{-1}. PMR: δ 1.26 (m, 24H), 2.2–2.4 (t, 4H, J=5 Hz), 3.6 (s, 3H).

3.5. *Methyl 15-bromopentadecanoate (**6**)*

To a stirred mixture of 1,16-hexadecanedioic acid monomethyl ester (**5**) (9 g, 30 mmol) and red mercuric oxide (5 g, 23.2 mmol) in carbon tetrachloride (150 ml), bromine (4.8 g, 1.55 ml, 30 mmol) was added dropwise over a period of 30 min. Thereafter, the mixture was slowly heated to reflux and continued for further 2 h. It was cooled to room temperature, filtered and the solid cake washed with carbon tetrachloride. The combined organic layer was washed with water, brine and dried. Concentration of the extract and subsequent column chromatography of the residue over silica gel using ether in petroleum ether (0–20% gradient) for elution afforded methyl 15-bromopentadecanoate. Yield: 7.98 g (79.4%). m.p. 36–37°C (lit.[27] 36–38°C) IR: 2940, 1745, 1190, 1035, 650 cm^{-1}. PMR ($CDCl_3$): δ 1.28 (m, 24H), 2.25 (br, 2H), 3.38 (t, 2H, J=5 Hz), 3.6 (s, 3H).

3.6. *15-Bromopentadecanoic acid (**7**)*

The ester **6** (1.3 g, 3.88 mmol) was hydrolysed by refluxing with potassium hydroxide (217.3 mg, 3.88 mmol) in aqueous alcohol (20 ml) for 3 h. After removal of most of the solvent, aqueous HCl (2N) was added to the residue, and was extracted with ethyl acetate. The organic layer was washed with water, brine and dried over anhydrous sodium sulphate. The product was purified by column chromatography (silica gel, 0–10% ethyl acetate/hexane) to give **7**. m. p. 67°C (lit.[8] 66–67°C) Yield 1.18 g (95%). IR: 3400–3000, 1710, 1190, 1035, 650 cm^{-1}. PMR ($CDCl_3$): δ 1.28 (m, 24H), 2.25 (br, 2H), 3.38 (t, 2H, J=5 Hz), 7.3 (s, D_2O exchangeable, 1H).

3.7. *Cyclopentadecanolide (Exaltolide) (**I**)*

To a suspension of powdered potassium carbonate (1.44 g, 10.4 mmol) in DMSO (27 ml) was added dropwise 15-bromopentadecanoic acid (**7**) (802 mg, 2.5 mmol) in DMSO (12 ml) at 75°C in 4 h under vigorous stirring. After that the mixture was cooled to room temperature, cold water (20 ml) was added and the resulting mixture was extracted with hexane. The extracts were dried over anhydrous magnesium sulphate and the solvent evaporated. The crude product was purified by TLC on silica gel (hexane:ether 8:1) to afford cyclopentadecanolide. Yield: 391 mg (65%). m.p. 33°C (lit.[9] 32°C). GLC (3% OV–178, 180°C, 40 ml/min N_2) R_t 7.55 min (98.49%) IR: 1750, 1330, 1180, 730 cm^{-1}. PMR: δ 1.2–1.5 (m, 24H), 2.31 (t, J=6.6 Hz, 2H), 4.12 (t, J=5.2 Hz, 2H). Anal. Calc. for $C_{16}H_{28}O_2$ C: 76.2, H 11.1: Found C 75.96, H 10.94%.

3.8. *1,15-Pentadecanedioic acid monomethyl ester (**8**)*

A solution of methyl 15-bromopentadecanoate (**6**) (2.14 g, 6.4 mmol), sodium nitrite (1.32 g, 19.2 mmol) and acetic acid (3.68 ml, 64 mmol) in DMSO (12 ml) was stirred at 35°C for 6 h. After acidification with 10% aqueous HCl the product was extracted with ether. Concentration of the extract and subsequent column chromatography of the residue (silica gel, 0–5% methanol chloroform) afforded 1,15-pentadecanedioic acid monomethyl ester. Yield: 1.65 g (90%). m.p. 65°C (lit.[9] 66°C). IR: 3500–3000, 1740, 1710 cm^{-1}. PMR: δ 1.26 (m, 22H), 2.2–2.4 (t, 4H, J=5 Hz), 3.6 (s, 3H).

3.9. *Dimethyl 1,15-pentadecanedioate (**9**)*

1,15-Pentadecanedioic acid monomethyl ester (**8**) (1.6 g, 5.59 mmol) in methanol containing a drop of concentrated sulphuric acid was refluxed for 6 h, cooled and extracted with ether. The

ether layer was washed with sodium bicarbonate, water and brine. Removal of ether followed by column chromatography of the residue over silica gel eluting with 0–10% ethyl acetate-hexane gave dimethyl 1,15-pentadecanedioate. Yield: 1.6 g (96%). IR: 1740 cm^{-1}. PMR: δ 1.26 (m, 22H), 2.25 (t, 4H, J=5 Hz), 3.6 (s, 6H).

3.10. *2-Hydroxycyclopentadecanone (acyloin) (**10**)*

To pulverized sodium (500 mg) in xylene (6 ml) was added dimethyl 1,15-pentadecanedioate (**9**) (1.5 g, 5.0 mmol) in refluxing xylene (20 ml) under nitrogen over a period of 2 h. The stirring continued for another 30 min and the mixture was cooled to room temperature and treated in a current of nitrogen with alcohol (60 ml). The xylene layer was washed free from alkali with water and evaporated under reduced pressure to give the acyloin. Yield: 960 mg (80%). b.p. 138–141°C/0.1 mm (lit.[9] 138°C/0.1 mm). IR: 3400, 1705 cm^{-1}. PMR ($CDCl_3$): δ 1.2–1.4 (m, 24H), 2.42 (s, 2 H), 4.5 (br, 1H), 2.65 (1H, D_2O exchangeable).

3.11. *Cyclopentadecanone (Exaltone) (**II**)*

A mixture of acyloin (**10**) (900 mg, 3.75 mmol), dioxane (20 ml) and zinc (1.5 g) was heated in an oil bath at 95–100°C and dry hydrogen chloride gas was passed at the rate of 15–20 g per h for 8 h. After about 4 h, water (100 ml) was added to dissolve the crystals of zinc chloride formed. Fresh zinc wool (500 mg) was then added and dry hydrogen chloride gas was passed more slowly for another 6 h. Dioxane was removed under reduced pressure and the residue was taken in light petroleum. The petroleum layer was washed with water, the solvent evaporated and the residue purified by TLC (silica gel, benzene:ether 9:1). Yield: 589 mg (70%). m.p. 63°C (lit.[9] 63°C). IR: 2940, 1715 cm^{-1}. PMR ($CDCl_3$): δ 1.2–1.9 (m, 24H), 2.42 (s, 4H). Found C 80.1; H 12.5; $C_{15}H_{28}O$ requires C 80.3; and H 12.6%.

3.12. *Methyl 10-undecenoate (**12**)*

A solution of 10-undecenoic acid (**11**) (55.2 g, 300 mmol) in methanol (750 ml) and concentrated sulphuric acid (5 ml) was refluxed for 8 h. Most of the solvent was removed under reduced pressure, water added and the reaction mixture extracted with ether. The ether layer was washed with 5% solution of sodium bicarbonate, water, brine and dried over anhydrous sodium sulphate. Removal of the solvent, followed by vacuum distillation, b.p. 123–125°C/10 mm (lit.[28] 124°C/10 mm) yielded methyl 10-undecenoate. Yield: 55.4 g (93%). IR: 1740, 980, 914 cm^{-1}. PMR: δ 0.9–1.3 (brs, 12H), 2.0–2.3 (m, 4H), 3.6 (s, 3H), 5.6–5.7 (t, 3H).

3.13. *Methyl 11-bromoundecanoate (**13**)*

Dry HBr (g) [generated from tetralin (65 ml) and bromine (45 ml)] was passed through a cooled (10–20ºC) and stirred solution of methyl 10-undecenoate (**12**) (25.74 g, 130 mmol) and benzoyl peroxide (0.5 g, 2.4 mmol) in dry petroleum ether (60–80°C) (100 ml). After 2 h, the solvent was removed and the residue purified by column chromatography (silica gel, 0–5% ethyl acetate/hexane) to yield methyl 11-bromoundecanoate. Yield: 18.13 g (50%) b.p. 120–22°C/0.02 mm (lit.[10] 121°C/0.02 mm). IR: 1740 cm^{-1}. PMR: δ 1.3 (brs, 16H), 2.2–2.3 (m, 2H), 3.4 (t, J=5 Hz, 2H), 3.7 (s, 3H).

3.14. *Methyl 10-formyldecanoate (**14**)*

A mixture of methyl 11-bromoundecanoate (**13**) (8.93 g, 32 mmol) and sodium bicarbonate (6 g) in DMSO (60 ml) was stirred for 15 min at 165°C (inside temperature) when evolution of white

fumes was noticed. It was cooled, water (50 ml) was added and the mixture was extracted with ether. After the removal of the solvent, the residue was purified by column chromatography (silica gel 0–10% ethyl acetate/hexane) to give methyl 10-formyldecanoate. Yield: 5.35 g (78%). IR: 2725, 1720 cm^{-1}. PMR: δ 1.3 (brs, 14H), 2.0–2.6 (m, 4H), 3.6 (s, 3H), 9.75 (t, 1H).

3.15. *1,13-Tridec-2-enedioic acid monomethyl ester (**15**)*

To a cooled (0°C) and stirred solution of malonic acid (2.7 g, 26 mmol) in pyridine (50 ml) was added methyl 10-formyldecanoate (**14**) (4.58 g, 21.4 mmol) in pyridine (10 ml) and piperidine (0.05 ml). After stirring for 4 h, the reaction mixture was allowed to stand for 72 h at room temperature. It was then gently heated on a water bath (65°C) till the evolution of CO_2 ceased. It was brought to room temperature and poured into cold dilute HCl (4N). The acidic solution was extracted with ethyl acetate. The extract was washed with water, brine and dried. After concentration, the residue was purified by column chromatography (silica gel, 0–10% $CHCl_3$/MeOH) to give the 1,13-tridec-2-enedioic acid monomethyl ester. Yield: 3.84 g (70%). b.p. 145°C (lit.[29] 144–145°C). IR: 3500–3200, 1740, 1710, 1650, 980 cm^{-1}. PMR: δ 1.26 (m, 16 H), 2.25 (t, 2H, J =5 Hz), 3.6 (s, 3H), 5.7 (d, 1H) 6.7–7.2 (d, 1H).

3.16. *1,13-Tridecanedioic acid monomethyl ester (**16**)*

1,13-Tridec-2-enedioic acid monomethyl ester (**15**) (2.56 g, 10 mmol), Mg (256 mg, 10.5 mmol) and dry methanol (110 ml) was refluxed for 8 h. The reaction mixture was acidified with dil. HCl and extracted with ether. The organic layer was washed with water, brine and dried. Evaporation of the ether extract gave 1,13-tridecanedioic acid monomethyl ester. Yield: 2.32 g (90%). IR: 3500–3100, 1740, 1710 cm^{-1}. PMR: δ 1.26 (m, 18H), 2.25 (t, 4H, J=5 Hz), 3.6 (s, 3H).

3.17. *1,13-Tridecanedioic acid (**17**)*

1,13-Tridecanedioic acid monomethyl ester (**16**) (2.23 g, 8.6 mmol) was refluxed with alcoholic potash for 6 h. Then the mixture was cooled, acidified and extracted with ether. The ether layer was washed with water and brine. After removal of ether, the residue was purified by silica gel chromatography to give 1,13-tridecanedioic acid. (0–15% ethyl acetate/hexane) m.p. 113–114°C (lit.[30] 114°C). Yield: 2 g (95%). IR: 3500–3100, 1710 cm^{-1}. PMR: δ 1.26 (m, 18H), 2.25 (t, 4H, J= 5 Hz).

3.18. *10-Undecenal (**18**)*

To a solution of $LiAlH_4$ (3.75 g) in dry ether (650 ml) was added 10-undecenoic acid **(11)** (8.28 g, 45 mmol) and refluxed at 40°C for 2 h. The reaction mixture was quenched with ethyl acetate. The solution was filtered and the organic layer was washed with water, brine and dried. After removal of solvent, the residue was purified by column chromatography (silica gel 0–25% ethyl acetate in hexane) to give 10-undecen-1-ol. Yield: 7.25 g (95%). IR: 3340, 3100, 1640, 990, 910 cm^{-1}. PMR: δ 1.28 (brs, 14H), 1.8–2.1 (m, 2H), 2.48 (s, 1H, D_2O exchangeable), 3.68 (t, J=7 Hz, 2H), 4.8–6.2 (m, 3H).

10-Undecen-1-ol (6.84 g, 40.2 mmol) was added to a stirred solution of PCC (15.75 g, 75 mmol) in methylene chloride (250 ml) and the stirring was continued for 2 h at room temperature. An equal volume of dry ether was added, the solution passed through a bed of silica gel and eluted with dry ether. After removal of the solvent the residue was purified by column chromatography (silica gel, 0–15% ethyl acetate in hexane) to give 10-undecenal. Yield: 5.1 g (75%). IR: 3000, 2720, 1720 cm^{-1}. PMR: δ 1.32 (brs, 14H), 1.8–2.1 (m, 2H), 4.8–6.2 (m, 3H), 9.75 (t, 1H).

3.19. *2,12-Tridecadienoic acid (**19**)*

To a cooled (0°C) and stirred solution of malonic acid (3.35 g, 32.25 mmol) in pyridine (125 ml) was added 10-undecenal (4.91 g, 29.25 mmol) in pyridine (10 ml) and piperidine (0.1 ml). After stirring for 4 h, the reaction mixture was allowed to stand for 72 h at room temperature. Then it was gently heated on a water bath (65°C) till the evolution of CO_2 ceased. It was brought to room temperature and poured into cold dilute HCl (4N). The acidic solution was extracted with ethyl acetate. The extract was washed with water, brine and dried. After concentration, the residue was purified by column chromatography (silica gel, 0–10% $CHCl_3$/MeOH) to give a liquid **19**. Yield: 4.35 g (70%). IR: 3500–3200, 1710, 1640, 980 cm^{-1}. PMR: δ 1.3–1.6 (m, 12H), 1.8–2.3 (m, 4H), 4.7–5.6 (m, 4H), 6.6–7.1 (1H, dt, J=16 Hz).

3.20. *12-Tridecenoic acid (**20**)*

2,12-Tridecadienoic acid (**19**) (4.1 g, 19.5 mmol), Mg (0.5 g, 20.8 mmol) and dry methanol (225 ml) was refluxed for 8 h. Then the reaction mixture was acidified with dilute HCl and extracted with ether. The organic layer was washed with water and brine, and dried. After concentration, the residue was purified by column chromatography (silica gel, 0–10% $CHCl_3$/MeOH) to give 12-tridecenoic acid. Yield: 3.5 g (85%). m.p. 38ºC (lit.[31] 38–38.2ºC). IR: 3500–3200, 1710, 980 cm^{-1}. PMR: δ 1.3–1.6 (m, 16H), 1.8–2.3 (m, 4H), 4.7–5.6 (m.3H).

3.21. *13-Bromotridecanoic acid (**21**)*

Dry HBr (g) [generated from tetralin (10 ml) and bromine (5 ml)] was passed through a cooled (10–20°C) and stirred solution of 12-tridecenoic acid (**20**) (3.44 g, 16.25 mmol) and benzoyl peroxide (0.58 g, 2.4 mmol) in dry petroleum ether (60–80°C, 100 ml). After 2 h, the solvent was removed and the residue was purified by column chromatography (silica gel, 0–5% ethyl acetate/hexane) to give 13-bromotridecanoic acid. Yield: 2.35 g (49%). IR: 3500–3000, 1710, 650 cm^{-1}. PMR: δ 1.3–1.6 (m, 20H), 2.3 (t, 2H), 3.4 (t, 2H).

3.22. *1,13-Tridecanedioic acid (**17**)*

A solution of 13-bromotridecanoic acid (**21**) (1.18 g, 4 mmol), $NaNO_2$ (0.828 g, 12 mmol) and acetic acid (0.5 ml) in DMSO (10 ml) was stirred at 35°C for 6 h. After acidification with 10% aqueous solution of HCl the product was extracted with ether and purified by column chromatography (silica gel) to afford 1,13-tridecanedioic acid. Yield: 0.877 g (90%). IR: 3500–3100, 1710 cm^{-1}. PMR: δ 1.26 (m, 18H), 2.25 (t, 4H, J=5 Hz).

3.23. *Lactone ester (**22**)*

Manganous acetate tetrahydrate (24.5 g, 100 mmol) was dissolved in acetic acid (130 ml) by raising the temperature to 90ºC. Solid $KMnO_4$ (3.2 g, 20.3 mmol) was added with stirring. When the exothermic reaction subsided and the temperature dropped to 90ºC, acetic anhydride (45 ml) was added followed by the addition of anhydrous sodium acetate (50 g). Methyl 10-undecenoate (**12**) (9.9 g, 50 mmol) was added in one lot and the reaction mixture was refluxed until the brown colour of manganic acetate disappeared. Extraction and removal of the solvent yielded a lactone ester, unreacted **15** and unsaturated C_{13} mono acid esters. The analytically pure γ-lactone was obtained by preparative TLC. IR: 1770, 1735 cm^{-1}. PMR: δ 3.67 (s, 3H), 4.55 (br m, 1H).

3.24. *1,13-Tridecanedioic acid (**17**)*

The above crude lactone ester (**22**) was subjected to vacuum distillation to remove unreacted **15** and the residue left was dissolved in alkaline alcohol (10 ml), 10% Pd/C (700 mg) was added and vigorously stirred under hydrogen atmosphere. The product obtained was filtered, treated with dilute HCl and extracted with ether. The ether layer was washed with water, brine, and dried over anhydrous Na_2SO_4. The solvent was removed and the product was subsequently purified by column chromatography (silica gel) to give 1,13-tridecanedioic acid. Yield: 6.83 g (56%). IR: 3500–3100, 1710 cm^{-1}. PMR: δ 1.26 (m, 18H), 2.25 (t, 4H, J=5 Hz).

3.25. *Ethylene brassylate (**III**)*

A mixture of 1,13-tridecanedioic acid (**17**) (4 g, 16.4 mmol) and ethylene glycol (1.08 g, 17.4 mmol) in benzene (100 ml) in the presence of *p*-toluenesulphonic acid (PTSA) (1.0 g) was azeotropically distilled with continuous removal of water using Dean–Stark trap for 10 h. After the reaction, the reaction mixture was washed with hot water, brine and the solvent was removed in vacuum. To the residue obtained, $MgCl_2.6H_2O$ (0.1 g) was added and distilled by heating the reaction mixture at 200ºC in vacuum for 4 h to get ethylene brassylate. Yield: 885 mg (20%). IR: 1735 cm^{-1}. PMR: δ 0.84–1.6 (m, 22H), 2.2–2.4 (t, 4H), 4.3 (s, 4H).

3.26. *1,11-Undecanedioic acid (**23**)*

A solution of methyl 11-bromoundecanoate (**13**) (8.93 g, 32 mmol), $NaNO_2$ (6.6 g, 96 mmol) and acetic acid (18.4 ml, 320 mmol) in DMSO (60 ml) was stirred at 35ºC for 6 h. After acidification with 10% aqueous solution of HCl the product was extracted with ether and purified by column chromatography (silica gel, 0–10% ethyl acetate in hexane) to afford 1,11-undecanedioic acid monomethyl ester. Yield: 6.25 g (85%). IR: 3500–3200, 1745, 1710 cm^{-1}. PMR: δ 1.26 (m, 14H), 2.2–2.4 (t, 4H, J=5 Hz), 3.6 (s, 3H).

The monomethyl ester obtained above (5.98 g, 26 mmol) was hydrolysed by refluxing with (2 N) alcoholic KOH (15 ml) for 3 h. After the removal of most of the solvent, HCl (2N) was added to the residue and extracted with ethyl acetate. The organic layer was washed with water and brine, and dried over anhydrous sodium sulphate. The product was purified by column chromatography to give 1,11-undecanedioic acid (silica gel 0–5% methanol in chloroform). m.p. 109ºC (lit.[32]110ºC) Yield: 5.34 g (95%). IR: 3500–3200, 1710 cm^{-1}. PMR: δ 1.26 (m, 14H), 2.2–2.4 (t, 4H, J=5 Hz).

3.27. *Methyl aleuritate (**24**)*

A solution of aleuritic acid (**1**) (25 g, 83 mmol) in methanol (500 ml) containing concentrated sulphuric acid (5 ml) was refluxed for 8 h. The mixture was cooled and most of the solvent removed in vacuum, the residue taken in ether and the ether layer washed with 5% solution of sodium bicarbonate, water and brine. Removal of ether was followed by purification of the residue by column chromatography (silica gel, 0–10% ethyl acetate hexane) to give methyl aleuritate. Yield: 20.98 g (79%). m.p. 74–76°C (lit.[10] 75°C). IR: 3440, 1735, 1480 cm^{-1}. PMR: δ 1.32 (brs, 22H), 2.21 (t, J=7 Hz), 3.68 (t, J=7 Hz, 2H), 3.6 (s, 3H), 3.8–4.0 (m, 2H).

3.28. *Methyl 8-formyloctanoate (**26**)*

To a cooled (0ºC) and stirred solution of methyl aleuritate (**24**) (15.9 g, 50 mmol), in a mixture of acetonitrile/water (3:2, 750 ml) was added $NaIO_4$ (12.8 g, 60 mmol) in portions. The mixture was stirred for 30 min and filtered. The filtrate was extracted with chloroform, and the extract was washed with water, brine, dried and evaporated *in vaccuo*. The residue was purified by column chromatography (silica gel, 0–10% methanol chloroform) to give methyl 8-formyloctanoate. Yield: 8 g (86%). b.p. 87ºC /0.2 mm (lit.[10] 86–92ºC/0.2 mm). IR: 2720, 1740, 1720 cm^{-1}. PMR: δ 1.3 (s, 10H), 2.0–2.6 (m, 4H), 3.6 (s, 3H), 9.7 (t, J=1.5 Hz, 1H).

3.29. *1,11-Undec-2-enedioic acid monomethyl ester (**27**)*

To a cooled (0ºC) and stirred solution of malonic acid (4.29 g, 41.25 mmol) in pyridine (60 ml) was added methyl 8-formyloctanoate (**26**) (6.39 g, 34.4 mmol) in pyridine (10 ml) and piperidine (0.05 ml). After stirring for 4 h, the reaction mixture was allowed to stand for 72 h at room temperature. Then it was gently heated on a water bath (65ºC) till the evolution of CO_2 ceased. It was brought to room temperature and poured into cold dilute HCl (4N). The acidic solution was extracted with ethyl acetate. The extract was washed with water and brine, and dried. After concentration, the residue was purified by column chromatography (silica gel, 0–10% $CHCl_3$/MeOH) to give the 1,11-undec-2-enedioic acid monomethyl ester. Yield: 6.27 g (80%). IR: 3500–3200, 1745, 1710, 1650, 980 cm^{-1}. PMR: δ 1.26 (m, 12H), 2.25 (t, 2H, J=5 Hz), 3.6 (s, 3H) 5.7 (d, 1H) 6.7–7.2 (d, 1H).

3.30. *1,11-Undecanedioic acid monomethyl ester (**28**)*

A mixture of 1,11-undec-2-enedioic acid monomethyl ester (**27**) (6 g, 26.32 mmol), Mg (668 mg, 27.8 mmol) and dry methanol (300 ml) was refluxed for 8 h. The reaction mixture was acidified with dilute HCl and extracted with ether. The organic layer was washed with water and brine, and dried. Concentration of the ether extract gave 1,11-undecanedioic acid monomethyl ester. Yield: 5.42 g (90%). IR: 3500–3200, 1745, 1710 cm^{-1}. PMR: δ 1.26 (m, 14 H), 2.25 (t, 4H, J=5 Hz), 3.6 (s, 3H).

3.31. *1,11-Undecanedioic acid (**23**)*

1,11-Undecanedioic acid monomethyl ester (**28**) (5 g, 21.74 mmol) was refluxed with alcoholic potash for 6 h. Then the mixture was cooled, acidified and extracted with ether. The ether layer was washed with water and brine. Removal of ether and purification by silica gel chromatography (0–15% EtOAc/hexane) gave 1,11-undecanedioic acid. m.p. 109ºC (lit.[32] 110ºC), Yield: 4.41g (95%). IR: 3500–3200, 1710 cm^{-1}. PMR: δ 1.26 (m, 14H), 2.2–2.4 (t, 4H, J=5 Hz).

3.32. *Ethylene undecanedioate (**IV**)*

A mixture of undecanedioic acid (**23**) (6 g, 27.7 mmol) and ethylene glycol (1.86 g, 30 mmol) in benzene (100 ml) in the presence of *p*-toluenesulphonic acid (1 g) was azeotropically distilled with continuous removal of water using Dean–Stark trap for 10 h. After the reaction, the mixture was washed with hot water, brine and the solvent was removed in vacuum. To the residue obtained, $MgCl_2.6H_2O$ (0.1 g) was added and distilled by heating the reaction mixture at 200ºC in vacuum for 4 h to give ethylene undecanedioate (**IV**). Yield: 1.69 g (25%). IR: 1735 cm^{-1}. PMR: δ 1.26 (m, 14H), 2.2–2.4 (t, 4H), 4.3 (s, 4H).

3.33. *Methyl 15-hydroxypentadecanoate (**31**)*

A Grignard reagent was prepared from 1-tetrahydropyranyloxy-4-bromobutane (4.74 g, 20 mmol) and Mg (0.0576 g, 24 mmol) in THF (50 ml). This was cooled to –40°C, a solution of Li_2CuCl_4 in THF (6 ml of 100 mmol) was added followed by the bromoester **13** (5.58 g, 20 mmol) in THF (10 ml) after 1h. Stirring was continued for 1 h at the same temperature, the reaction mixture was gradually brought to room temperature and stirred for further 16 h. It was again cooled to 0ºC and quenched with dilute HCl (2N). The organic layer separated and the aqueous portion extracted with ether. The combined organic layer was washed with water and brine, and finally dried. After the removal of the solvent, the residue was taken in MeOH (100 ml) containing PTSA (0.2 g) and refluxed for 4 h. Most of the solvent was removed, the residue was dissolved in ether and the ether layer washed with water and brine, and dried. Removal of the solvent and column chromatography of the residue (silica gel, 0–10% EtOAc/hexane) gave methyl 15-hydroxypentadecanoate as a low-melting solid. m.p. 48–50ºC (lit.[33] 49ºC) Yield: 2.94 g (54% overall). IR: 3450, 1740, 1440 cm^{-1}. PMR: δ 1.34 (brs, 24H), 2.34 (t, J=6 Hz, 2H), 2.84 (s, D_2O exchangeable, 1H), 3.5 (s, 3H), 3.68 (t, J=7 Hz, 2H).

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