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A Short and Facile [2 + 2] Photocycloaddition Protocol Toward Construction of a Levuglandin Skeleton

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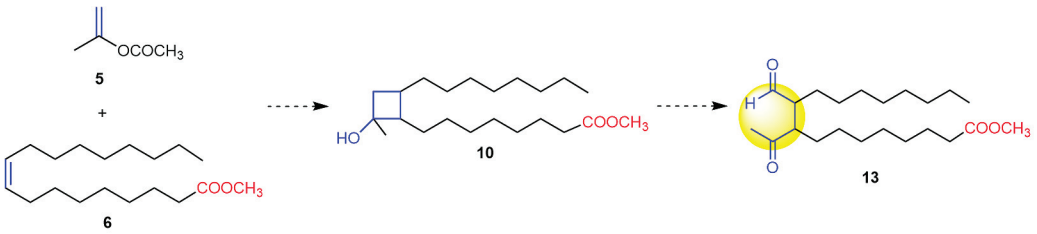

Abstract

The γ-ketoaldehyde functionality of levuglandins (LGs) has a great propensity for various diseases such as Alzheimer's, atherosclerosis, and renal diseases. The synthesis of LGs constitutes a challenge for synthetic organic chemists due to their complex structures and low abundance in nature which has prompted us to develop its quick synthesis. This study aimed to explore a novel route for the construction of a levuglandin skeleton. We envisaged that the photocycloaddition of an appropriate alkene with equivalent propyne would give the cyclobutene adduct. The oxidative cleavage of the photocycloadduct can lead to the formation of the keto-aldehyde functionality. In this study, the readily available isopropenyl acetate (**5**) and methyl oleate (**6**) were used as starting materials to synthesize the target compound **13**. The key step involves photocycloaddition of compounds **5** and **6**, a regio-controlled elimination of the hydroxy group of compound **10**, forming a cyclobutene derivative, as well as an oxidative cleavage of the cyclobutene derivative gives the framework of levuglandin. The intriguing chemistry of elimination resulting in the inseparable mixture of regioisomeric cyclobutenes has also been discussed. The route was simple and economical and helped for the creation of γ-ketoaldehyde functionality which is vital for the activity of levuglandins and can be extended for the construction of prostanoid skeleton through aldol condensation of the γ-ketoaldehydes.

Keywords
- levuglandins
- photocycloaddition
- γ-ketoaldehydes

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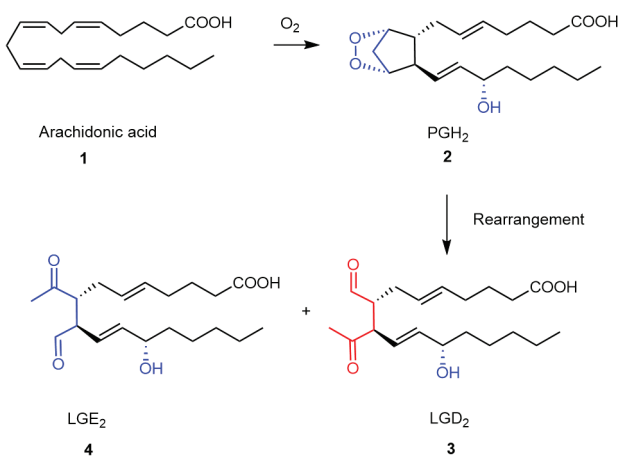


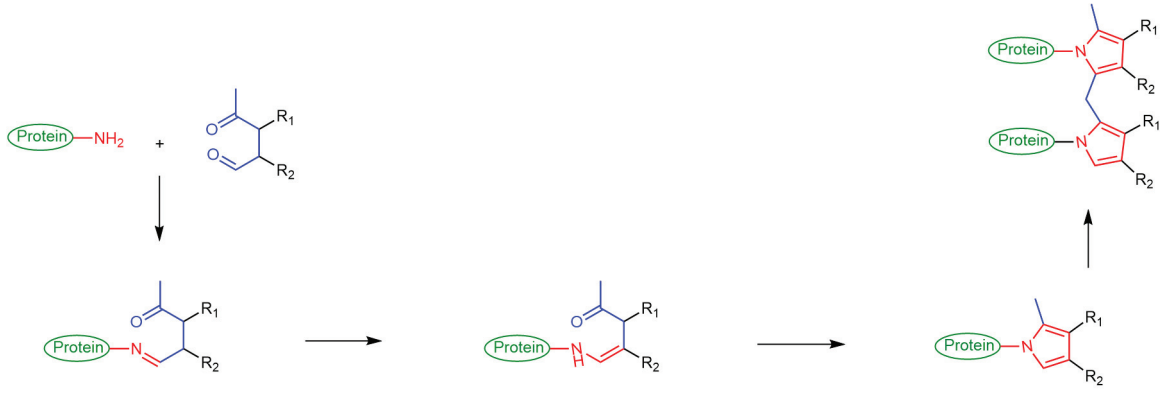
Scheme 1 Rearrangement of PGH_2: generation of LGD_2 and LGE_2.

Introduction

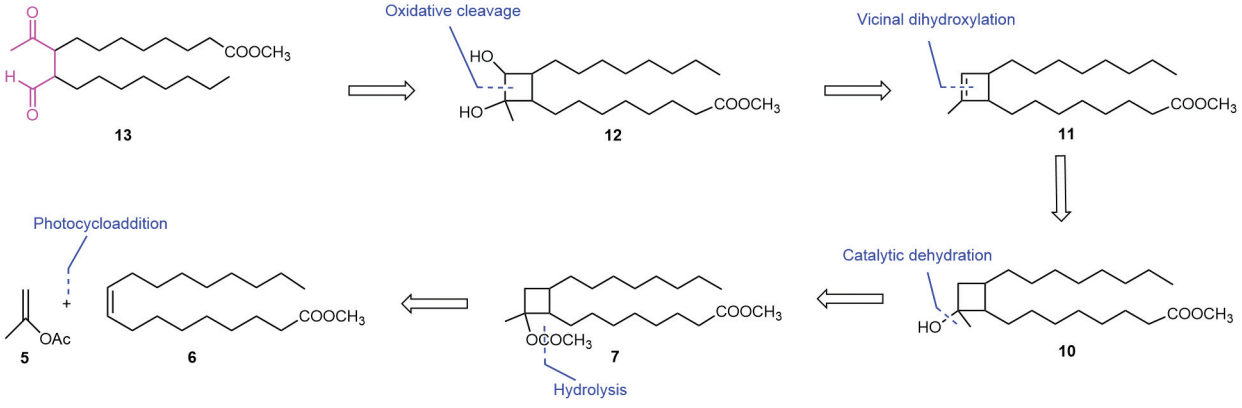
Lipids are an essential component of the cell membranes[1] and their oxidative products are often employed in various biological systems that contribute to the functioning of many physiological processes.[2–4] Levuglandins (LGs) D_2 and E_2 having prostanoid side chains which are pharmacologically active are the result of the lipid peroxidation process.[5] The investigation of the chemistry of prostaglandin endoperoxide PGH_2 (**2**), which is formed by cyclooxygenase metabolite from arachidonic acid **1**, led to the discovery of LGs.[6] Salomon et al reported that the rearrangement of PGH_2 (**2**) leads to the formation of the two levulinaldehydes LGD_2 (**3**) and LGE_2 (**4**) (►**Scheme 1**).[7–9]

The γ-ketoaldehyde functionality of LGs has a great propensity for rapid covalent adduction with protein–protein crosslink and protein polymerization occurring in conjunction with the bindings which are reported to be linked with various diseases such as Alzheimer's, atherosclerosis, and renal diseases (►**Scheme 2**).[10] The mean levels of LG-protein adducts are raised in the plasma of individuals having atherosclerosis and renal disease as compared with healthy individuals and provide a quantitative assessment of oxidative stress.[11–13] The synthesis of LGs constitutes a challenge for synthetic organic chemists due to their complex structures and low abundance in nature. There are only a few approaches for the synthesis of LGs and their analogs in the literature, even though these compounds work as biomarkers and have a wide range of bioactivities.[14–17] Thus, a practical alternative source to facilitate the requisite carbon skeleton is required.

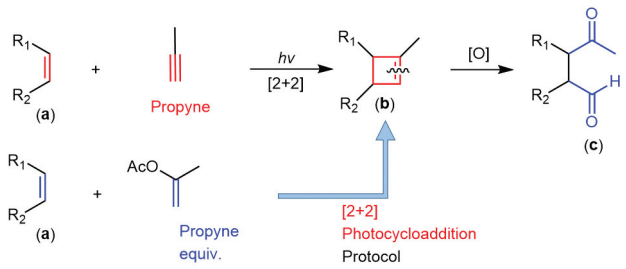
In this study, a retrosynthetic approach was conducted to suggest a rational synthetic route to construct the key structural unit of LGs (compound **13**) using sequential steps of [2 + 2] photocycloaddition, elimination, and oxidative cleavage from cheap and readily available starting materials, viz. isopropenyl acetate **5** and methyl oleate **6** (►**Scheme 3**).



Scheme 2 Covalent adduction of protein with γ-ketoaldehyde.



Scheme 3 Retrosynthetic plan for levuglandin framework **13**.



Scheme 4 Strategy toward the γ-ketoaldehydes.

We envisaged that the photocycloaddition of an appropriate alkene (**a**) with propyne/propyne equivalent would give the cyclobutene adduct (**b**). The oxidative cleavage of the photocycloadduct (**b**) can lead to the formation of the ketoaldehyde functionality (**c**) (►**Scheme 4**). The difficulty of handling propyne prompted us to consider isopropenyl acetate **5** as its equivalent.

Material and Methods

General Information

All the chemicals were purchased from Sigma Aldrich, SD Fine-Chem, and Spectrochem Ltd. (St. Louis, Missouri, United States). Solvents were distilled before use and stored on oven-dried molecular sieves. Infrared spectra were recorded on a Perkin-Elmer PC-16 FTIR spectrophotometer. Ultraviolet (UV) spectra were recorded on a Perkin-Elmer Lambda-19 spectrometer. Nuclear magnetic resonance (NMR) spectra (^{1}H NMR and ^{13}C NMR) were recorded on a Bruker 400/500 MHz NMR spectrometer (125/100 MHz for ^{3}C NMR respectively) using chloroform-*d* as a solvent and tetramethylsilane as an internal standard. Mass spectra were recorded on the Thermo-Fisher DSQ II GCMS instrument. Column chromatography was performed using Acme's silica gel (60–120 mesh size, CAS No.112926–00–8) and the elution was done using light petroleum and ethyl acetate. The percent yields are reported based on the isolated material after column chromatography. Thin layer chromatography was performed using Acme's silica gel for TLC and spots were visualized under UV light or in iodine vapor.

Synthesis of Photocycloadducts

Methyl oleate (**6**) (1.00 g, 3.4 mmol) and isopropenyl acetate (**5**) (0.34 g, 3.4 mmol) were dissolved in acetone (600 mL). The solution was placed in an immersion well-type photoreactor and irradiated for 6 hours at 10 to 15°C, with a 250 W low-pressure mercury vapor lamp. After the completion of the reaction, the solvent was removed under reduced pressure to give a crude product, which was chromatographed over a column of silica gel. Elution of the column using light petroleum/ethyl acetate (90:7) afforded the adduct **7** (0.23 g, 18% yield) as a colorless liquid. Further elution of the column with light petroleum/ethyl acetate (90:10) furnished adduct **8** (0.24 g, 17% yield) as a colorless liquid. Compound **7**, chemically named "methyl 8-(2-acetoxy-2-methyl-4-octylcyclobutyl)octanoate": IR (KBr, cm^{-1}) 2875, 2838, 1735, 1723, 1240. ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.66 (s, 3H, CH_3), 2.38 (s, 3H, CH_3), 2.32–2.10 (m, 2H, 2CH), 2.05 (m, 2H, CH_2), 1.62 (s, 3H, CH_3), 1.56–0.90 (m, 28H, 14CH_2), 0.87 (t, J = 6.75 Hz, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ 177.55, 177.41, 81.68, 51.39, 50.01, 39.84, 38.30, 34.01, 33.98, 33.91, 31.85, 31.82, 29.73, 29.58, 29.50, 29.38, 29.25, 29.07, 29.01, 28.98, 27.60, 24.32, 22.78, 13.52. MS (EI): *m/z* (%) calcd. for $C_{24}H_{44}O_4$ [M]$^+$ 396.32; found 396.21.

Synthesis of Hydroxy Acid 9

To a stirred solution of cycloadduct (**7**) (4.00 g, 12 mmol) in methanol (50 mL) was added aqueous potassium hydroxide (10%, 3.5 mL) over 15 minutes at 27°C. The mixture was stirred for another 2.5 hours, neutralized with aqueous HCl solution (1:4), and extracted with ethyl acetate (25 mL × 3). The combined organic extracts were washed with water and brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The crude was column-chromatographed using a mixture of light petroleum/ethyl acetate (90:10) to give the target product. Compound **9**, chemically named "8-(2-hydroxy-2-methyl-4-octylcyclobutyl)octanoic acid": IR (KBr, cm^{-1}) 2561–3255, 1750, 1712, 1163. ^{1}H NMR (400 MHz, $CDCl_3$): δ 11.85 (s, 1H, COOH), 2.59 (s, 3H, CH_3), 2.43 (m, 2H, 2CH), 2.34 (m, 2H, CH_2), 2.17 (s, 1H, OH superimposed with CH_2), 1.97–1.27 (m, 28H, 14CH_2), 0.86 (t, J = 6.00 Hz, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ 179.50, 81.77, 50.08, 45.93, 38.86, 38.33, 35.59, 32.71, 32.44, 31.86, 31.17, 30.56, 29.55, 29.23, 29.01, 28.46, 27.59, 27.08, 24.11, 23.04, 14.15. MS (EI): *m/z* (%) calcd. for $C_{21}H_{40}O_3$ [M]$^+$ 340.54; found 340.80.

Synthesis of Hydroxy Ester 10

Hydroxy acid (**9**) (3.00 g, 8 mmol) was dissolved in dry methanol (20 mL), then concentrated sulfuric acid (0.01 mL) was added at 27°C. The resulting mixture was stirred for 1 hour, neutralized with a saturated solution of sodium bicarbonate, and extracted with ethyl acetate (25 mL × 3). The combined organic layers were washed with water and brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure to give a crude product, which was purified by column chromatography (light petroleum/ethyl acetate) to afford compound **10**. Compound **10**, chemically named "methyl 8-(2-hydroxy-2-methyl-4-octylcyclobutyl)octanoate": IR (KBr, cm^{-1}) 3380, 2891, 1742, 1150. ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.66 (s, 3H, CH_3), 2.30 (t, J = 10 Hz, 2H, CH_2), 2.19 (m, 2H, CH_2), 1.88 (s, 1H, OH), 1.73 (m, 2H, 2CH), 1.61 (s, 3H, CH_3), 1.50–1.10 (s, 26H, 13CH_2), 0.95 (t, J = 7.00 Hz, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ 174.19, 71.94, 54.98, 52.49, 51.34, 48.65, 37.45, 32.62, 31.32, 30.01, 29.91, 29.35, 29.16, 28.87, 28.67, 28.08, 27.87, 27.50, 25.47, 24.21, 21.23, 13.92. MS (EI): *m/z* (%) calcd. for $C_{22}H_{42}O_3$ [M]$^+$ 354.31; found 354.0.

Synthesis of Inseparable Regio Isomers 11 and 14

Hydroxy ester (**10**) (2.50 g, 7 mmol) was dissolved in dry toluene (20 mL), then, a solution of sulfuric acid in toluene (1%, 5 mL) was added at 0°C. The mixture was allowed to warm up to room temperature and poured into a saturated

solution of sodium bicarbonate to neutralize the acid. The mixture was extracted in ethyl acetate (25 mL × 3), washed with water and brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure to give a crude product. Column chromatography of the crude product gave an inseparable mixture of **11** and **14** as a colorless liquid. IR, ^{1}H NMR, and ^{13}C NMR spectra of the mixed compounds (**11** and **14**) are included in the Supporting Information (►**Figs. S17–S20** [online only]).

Synthesis of Diol 12

Compounds **11** and **14** obtained above (1.70 g, 5 mmol) were dissolved in a solution of tetrahydrofuran (THF) and water (v:v =1:1, 10 mL), then, potassium permanganate (1.00 g, 6 mmol) was added over 1 hour. The mixture was stirred for another 3.5 hours, filtered on a celite pad, and concentrated under reduced pressure. The resulting mixture was extracted with ethyl acetate (25 mL × 3). The combined extracts were washed with water and brine, dried over anhydrous sodium sulfate, and concentrated to give a crude product, which was purified by column chromatography to afford the target product. Compound **12**, chemically named "methyl 8-(2,3-dihydroxy-2-methyl-4-octylcyclobutyl) octanoate": IR (KBr, cm^{-1}) 3284, 2918, 2851, 1739. ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.18 (dd, J_1 = 7.2 Hz, J_2 = 3.20 Hz, 1H, CH), 3.68 (s, 2H, CH_3), 2.45 (m, 2H, 2CH), 2.29 (t, 2H, J = 7.6 Hz, CH_2), 2.19 (s, 2H, exchangeable OH), 1.82 (m, 2H, CH_2), 1.64 (m, 3H, CH_3 merged with the signal of methylene groups), 1.61–1.20 (m, 24H, 12CH_2), 0.89 (t, J = 7.2 Hz, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ 174.33, 75.53, 74.33, 51.52, 37.86, 37.79, 34.05, 34.02, 33.77, 33.72, 31.85, 31.80, 30.98, 29.47, 29.32, 29.11, 29.01, 28.90, 24.78, 22.67, 22.65, 14.12. MS (EI): *m/z* (%) calcd. for $C_{22}H_{42}O_4$ [M]$^+$ 370.31; found 370.22.

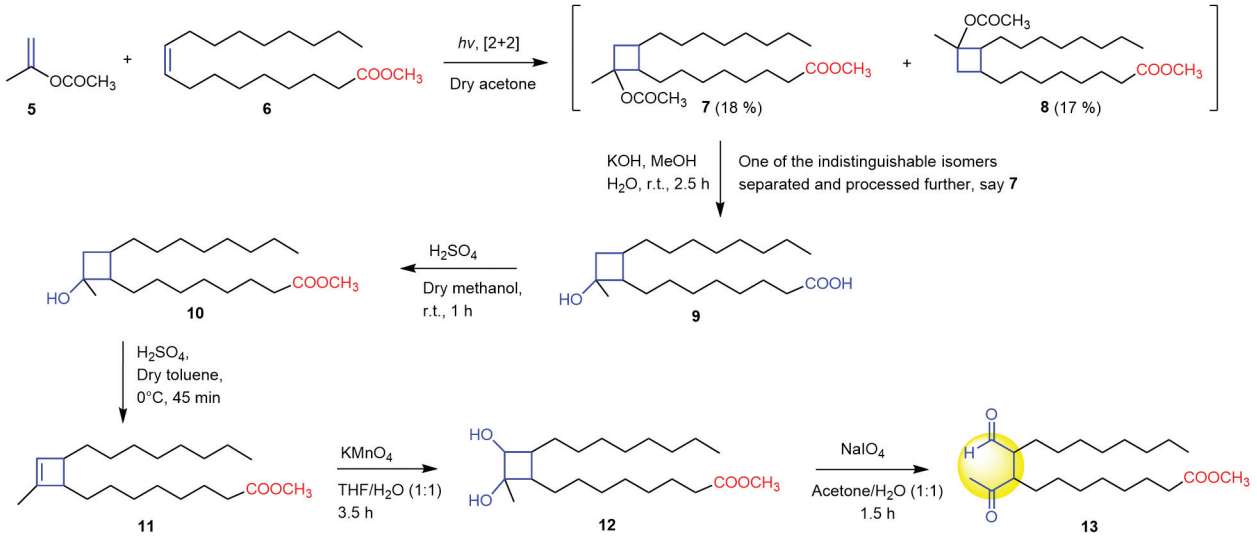
Synthesis of γ-Ketoaldehyde 13

Solution A: diol (**12**) (0.80 g, 4 mmol) was dissolved in a solution of acetone and water (v:v = 1:3, 15 mL), and solution B: sodium periodate (0.43 g, 2 mmol) was dissolved in a solution of acetone and water (v:v = 1:1, 10 mL) were prepared prior the experiment. Solution B was added to solution A for 15 minutes. The reaction mixture was stirred for 1.5 hours and quenched with ethyl glycol (1.00 g, 16 mmol). The resulting mixture was extracted with ethyl acetate (25 mL × 3), washed with water and brine, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure to give a crude product, which was chromatographed using light petroleum/ethyl acetate (90:10) to afford the final product. Compound **13**, chemically named "methyl 9-acetyl-10-formyloctadecanoate": IR (KBr, cm^{-1}) 2964, 2935, 1750, 1710. ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.37 (s, 1H, CHO), 3.68 (s, 3H, CH_3), 2.45 (m, 2H, 2CH), 2.34 (m, 2H, CH_2), 2.19 (s, 3H, CH_3), 1.71–0.96 (m, 26H, 13CH_2), 0.89 (t, J = 6.8 Hz, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ 198.93, 196.23, 174.33, 51.52, 37.87, 35.75, 34.06, 33.92, 33.76, 33.70, 31.80, 30.70, 29.72, 29.43, 29.23, 29.01, 28.90, 24.83, 24.70, 23.65, 19.24, 15.12. MS (EI): *m/z* (%) calcd. for $C_{22}H_{40}O_4$ [M]$^+$ 368.29; found 368.11.

Results and Discussion

Approaching the building of the LG framework **13**, first a $\pi^{2s} + \pi^{2s}$ photocycloaddition of **5** and **6** was performed in acetone using a low-pressure mercury vapor lamp in a quartz immersion well type of photoreactor and irradiated under a UV light (~254 nm) while maintaining the reaction temperature between 10 and 15°C for 3.5 hours. After thin-layer chromatography-monitoring the completion of the reaction, the mixture was concentrated under reduced pressure to give a thick yellow liquid which was chromatographed over a column of silica gel. The isomers **7** (R_f = 0.75) and **8** (R_f = 0.60) were obtained in almost equal amounts after chromatography (►**Scheme 5**).

The structures of the isomers **7** and **8** could be easily deduced from their spectral features. However, it is difficult to distinguish between **7** and **8**. Thus, one of the isolated



Scheme 5 Synthesis of γ-ketoaldehydes **13**.

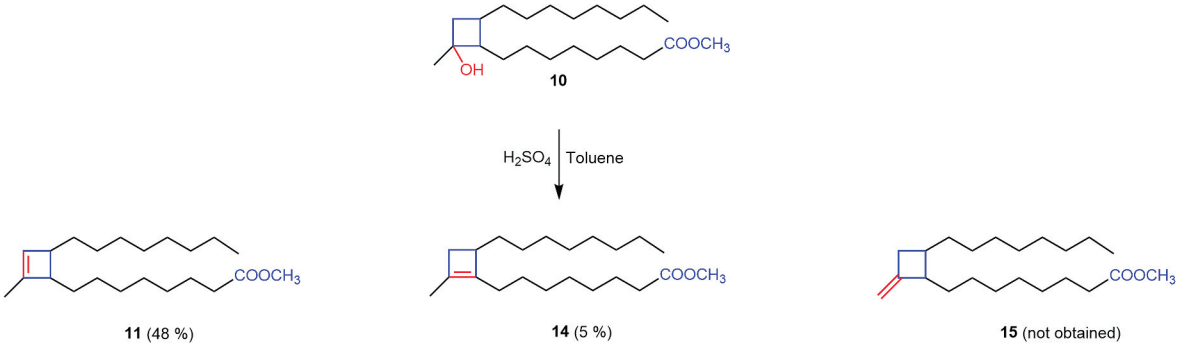
isomers that exhibited a band at 1,240 cm^{-1} for the C–O–C stretching of acetate along with bands at 1,723 and 1,735 cm^{-1} for CO absorptions was considered as **7** to participate in the next steps. The ^{1}H NMR spectrum of **7** exhibited a triplet at δ 0.87, singlets at 3.66, 2.38, and 2.05 for the protons of four methyl groups along with a multiplet between δ 1.56 and 0.90 for the methylene protons. It displayed multiplets between δ 1.62 and 0.97, 2.18 and 2.01 for the methylene protons along with a multiplet at δ 2.12 to 2.10 for the methine protons. The ^{13}C NMR spectrum of **7** gave resonances at δ 51.36, 27.60, 24.32, and 13.52 for four carbons along with signals for methylene carbons between δ 38.30 and 28.98. It also showed a signal at δ 81.68 for the carbon attached to the acetate group and two carbonyls at δ 177.45 and 177.41. The spectra of other separated isomer (**8**) are included in Supporting Information (►**Figs. S5–S8**). The IR spectrum showed bands at 1,166 cm^{-1} for C–O–C stretching of the acetate group as well as at 1,750 and 1,730 cm^{-1} for CO groups. The ^{1}H NMR spectrum of compound **8** gave a triplet at δ 0.87, singlets at δ 3.59, 2.31, and 1,61 for the protons of four methyl groups along with multiplets at δ 1.98–1.86 and 2.28–2.20 for the methine protons. Its ^{13}C NMR spectrum displayed signals at δ 51.37, 22.27, 20.64, and 14.23 for four methyl carbons, and 15 lines between δ 38.30 and 28.98 for the methylene carbons. It also displayed a signal at δ 80.09 for the carbon attached to the acetate group and two signals at δ174.28, 174.24 for the carbonyl groups.

The acetate group of the cyclobutane ring in cycloadduct **7** serves as a handle for its elaboration to **13**. Hydroxy acid **9** was obtained from base hydrolysis of **7** as a colorless liquid. The structure of acid **9** was confirmed by its spectral analysis. The FTIR of **9** showed a broad band at 3,450 to 2,450 cm^{-1} confirming the presence of acid functionality. The ^{1}H NMR of **9** exhibited a broad signal at δ 11.85 for the proton of the acid group. The ^{13}C NMR spectrum of **9** showed signals at δ 179.50 and 81.77 for the carbon attached to a hydroxy group and a carbonyl group, respectively. To protect the sensitive acid functionality, the hydroxy acid **9** was then converted into its corresponding methyl ester **10** using catalytic amounts of concentrated sulfuric acid in dry methanol at room temperature. The structure of the ester **10** was elucidated using spectral analysis. Its IR spectrum showed an absorption band at 3,380 cm^{-1} for the –OH group. The ^{1}H NMR spectrum of **10** exhibited a sharp singlet at δ 3.66 indicating the presence of the methyl ester along with a signal at δ 1.88 for the proton of –OH group. It also displayed a signal at δ 71.94 for the carbon connected to –OH and a signal at δ 169.29 for the carbonyl carbon of the acetate group in its ^{13}C NMR. The elimination of the hydroxy group in **10** can in principle result in the formation of three different products **11**, **14**, and **15** (►**Scheme 6**). The catalytic dehydration of **10** was attempted initially using *p*-toluenesulfonic acid in toluene; however, the reaction did not proceed. Then we performed the reaction using sulfuric acid in dry toluene which smoothly furnished the mixture of **11** and **14** in the ratio of 92.5:7.5 after column chromatography purification. It should be noted that the exocyclic cyclobutane ester **15** was not obtained here. The ^{1}H NMR spectrum of the mixture exhibited singlets at δ 3.67 and 3.43 for ester methyl protons of **11** and **14**, respectively. The relative ratio of **11** and **14** in the mixture was determined from the characteristic singlets of ester methyl groups at δ 3.43 and 3.67 in the ^{1}H NMR spectrum (►**Fig. 1**).

The ^{13}C NMR showed a total of four olefinic carbons between δ 133.01 and 130.14 along with signals for two carbonyls at δ 174.74 and 174.38. This confirmed the presence of **11** and **14** in the mixture. Interestingly the ester **11** was obtained as a major product even though the cyclobutene ester **14** is more likely to form.

The stage was now ready for the cleavage of the double bond in the cyclobutene ring of **11**. In the literature, numerous methods for the oxidation of olefins using various reagents have been reported.[18–25] We chose potassium permanganate in THF-water for the vicinal dihydroxylation of **11** as reported by Simandi and colleagues.[26,27] Thus the mixture of cyclobutenes **11** and **14** was treated with potassium permanganate in THF-water at room temperature. After continuous stirring for 3.5 hours, the reaction was filtered on a celite pad, and the solvent was removed under reduced pressure followed by column chromatography of the residue to furnish the diol **12** (48%) as a colorless liquid. It was interesting to note that the diol **16** was not obtained at all (►**Scheme 7**).

It was interesting to note that the more sterically hindered double bond in **14** did not participate in the hydroxylation



Scheme 6 Dehydration of hydroxy ester **10**.

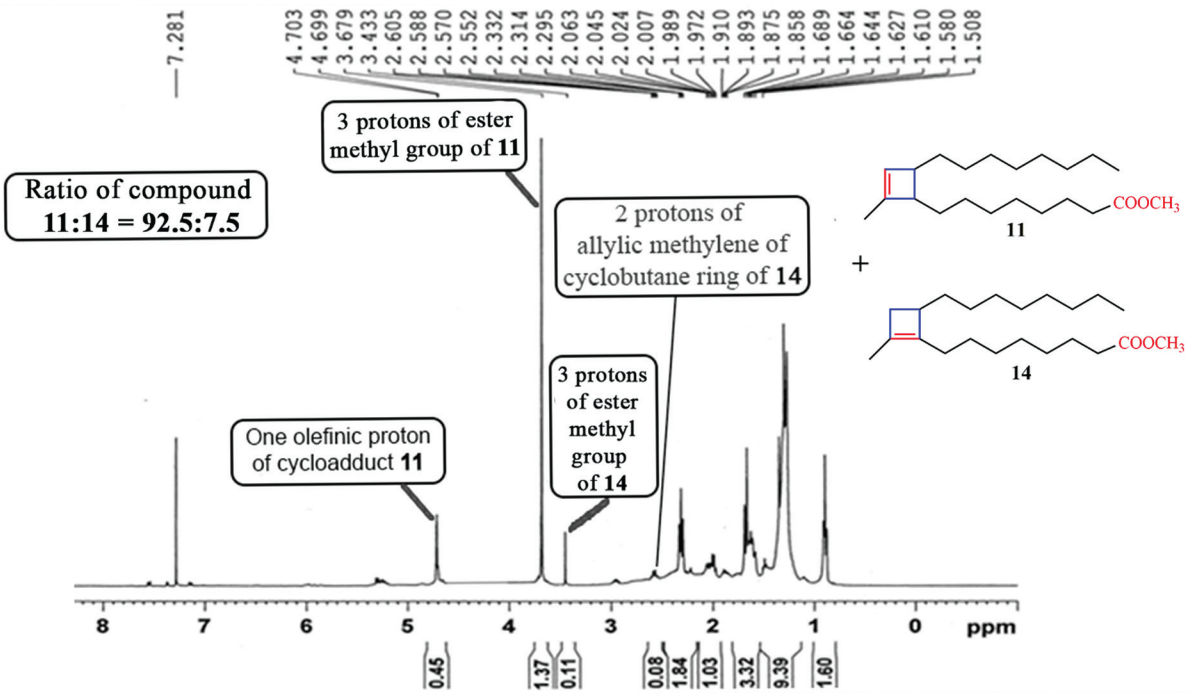
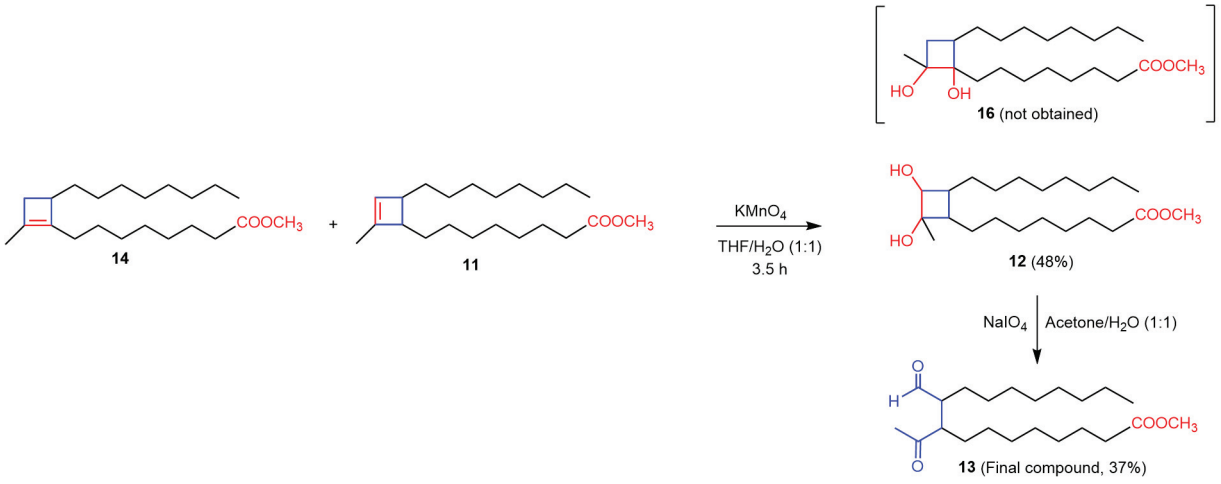


Fig. 1 ^{1}H NMR spectra of the mixture of compounds **11** and **14**.



Scheme 7 Synthesis of γ-ketoaldehyde **13**.

reaction. The structure of the diol **12** was fully discernible from its spectral characteristics. Its IR spectrum showed a broad absorption band centered at 3,284 cm^{-1} confirming the presence of –OH groups as well as a strong band at 1,739 cm^{-1} for carbonyl of ester. Its ^{1}H NMR spectrum showed a singlet at δ 2.19 for two protons of hydroxy groups along with a multiplet centered at δ 2.45 and a doublet at δ 4.18 for the methine protons. The ^{13}C NMR spectrum exhibited the signals at δ 75.53 and 74.33 for the carbons of secondary and tertiary –OH groups as well as a signal at δ 174.33 for the carbonyl carbon of ester. The precursor diol **12** was subjected to oxidative cleavage using sodium metaperiodate in acetone-water (1:1) for 1.5 hours at 10°C. The reaction mixture was quenched by the addition of ethylene glycol and then extracted with ethyl acetate. The removal of the solvent under reduced pressure gave a thick yellow liquid which was chromatographed over a column of silica gel to furnish the γ-ketoaldehyde **13** as a colorless liquid (►**Scheme 7**). The structure of **13** was confirmed by its spectral analysis. Its IR spectrum showed bands at 1,730 and 1,710 cm^{-1} for the presence of carbonyl groups. Its ^{1}H NMR spectrum exhibited a sharp singlet at δ 9.37 for the aldehydic proton. Its ^{13}C NMR spectrum also showed three signals at δ 198.93, 196.29, and 174.33 for the three carbonyl carbons.

The methodology presented above would also provide a short and economical route via the [2 + 2] photocycloaddition approach with appropriate alkene and propyne equivalents for the synthesis of LGs, isolevuglandins, and many compounds of prostanoid class.

Conclusion

This short communication demonstrates a synthetic route toward the construction of LG moiety. The key feature of the present study is the creation of γ-ketoaldehyde functionality which is vital for the activity of LGs. The carbon chain in methyl oleate can be suitably modified based on the desired functionalities on the two long side chains in LGs. Moreover, the present approach can also be extended for the construction of a prostanoid skeleton through aldol condensation of the γ-ketoaldehydes.

Supporting Information

^{1}H NMR, ^{13}C NMR, mass, and IR spectra of compounds **7** (or **8**), **9**, **10**, **11**, and **14** (mixed), **12**, and **13** are available in the Supporting Information (Figs. **S1**–**S28** [online only]) 002E

Conflict of Interest

None declared.

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