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7-Substituted Prostaglandin Analogues A New Synthetic Approach

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Starting from methyl 7-oxo-7-(1-cyclopentene)-heptanoate, a simple synthesis of the methyl esters of 7-oxo- and 7-hydroxy-9,11-dideoxy-PGF_1 as a model for 7-substituted prostaglandin analogues is described.

(Keywords: 7-Oxo-prostaglandins; 7-Hydroxy-prostaglandins; Nucleophilic 1,4-addition; Nef reaction; Wittig-Horner reaction)

7-Substituierte Prostaglandin-Analoge — ein neuer Syntheseweg

Ausgehend von Methyl-7-oxo-7-(1-cyclopenten)-heptanoat wird eine einfache Synthese der Methylester von 7-Oxo- und 7-Hydroxy-9,11-dideoxy-PGF_1 als Modellverbindungen für 7-substituierte Prostaglandinanaloge beschrieben.

Introduction

Methods for syntheses of new prostaglandin analogues are still of interest. In our previous paper[1] we described a simple method for the preparation of 2-substituted *cis*-2-cyclopentene-1,4-diol derivatives **1** from easily available *cis*-2-cyclopentene-1,4-diol diacetate. These compounds may be useful starting materials for the synthesis of various prostanoids. Electron-withdrawing groups at the 2 position enable the introduction of the prostaglanding "lower" chain or its precursor in a *Michael*-type nucleophilic 1,4-addition. This reaction is analogous to the well-known approach using cyclopentenone derivatives[2] but the group activating the double bond is outside the ring (Scheme 1).

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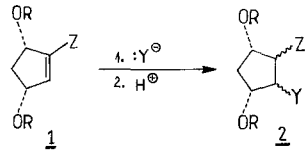
Scheme 1



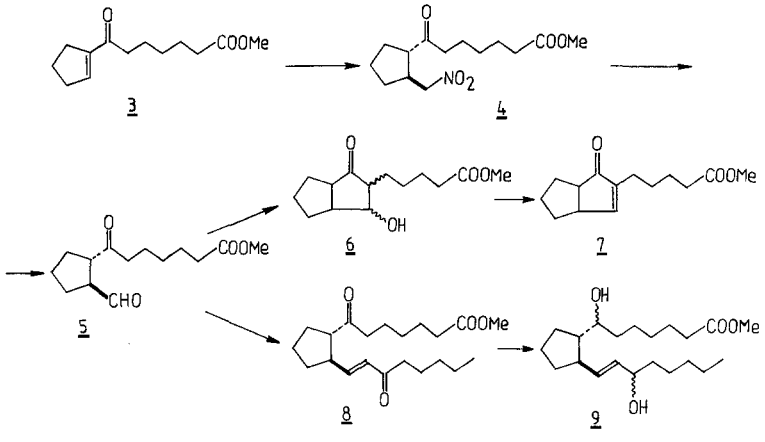
The application of the previously described[1] compound **1** [$R = SiMe_2Bu^t$, $Z = —CO—(CH_2)_5—CO_2Me$] as the substrate having already the appropriate "upper" chain seemed to be particularly interesting. Nevertheless, before starting this synthesis we decided to examine the "lower" chain introduction procedure using a simple model without OH groups in the cyclopentane ring.

Results and Discussion

Starting material for our synthesis—methyl 7-oxo(1-cyclopentene)-heptanoate (**3**)—was prepared in the reaction of pimelic acid monochloride monomethyl ester with cyclopentene in the presence of $AlCl_3$ in CH_2Cl_2, followed by β-chlorketone distillation with Na_2CO_3. This procedure was similar to that described by *Newton* et al.[3] but the yield of the product was significantly improved (from 54 to 75%) using a large excess of $AlCl_3$ (2.2 mol of $AlCl_3$ per 1 mol of the acid chloride).

The first model PG analogue—7-hydroxy-9,11-dideoxy-PGF_1 methyl ester (**9**)—was prepared according to Scheme 2.

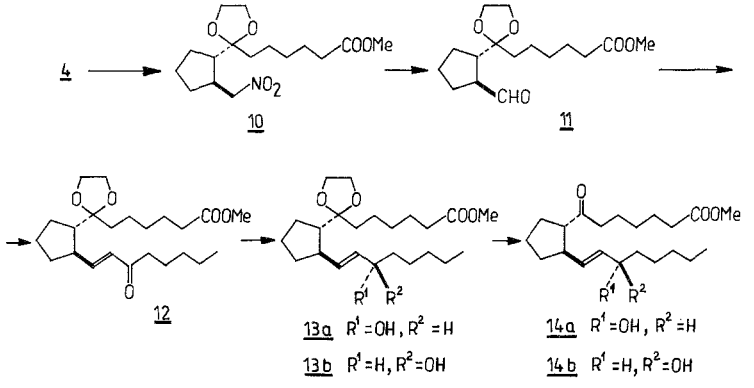
Scheme 2



Enone **3** was reacted with CH_3NO_2 in the presence of tetramethylguanidine to give nitroketone **4** in 78% yield (the *trans* isomer was formed predominantly). The nitromethyl group of **4** was transformed into the aldehyde group employing the modified *Nef* reaction described by *McMurry* and *Melton*[4]. Nitro-compound **4** was first transformed into its sodium salt, then the salt solution was poured into an aqueous solution of $TiCl_3$ and buffered with ammonium acetate. The reaction was complete after 1.5 h at room temperature and afforded practically pure aldehyde **5** in a yield above 90%. It is worth to mention that in case the reaction time was longer or the solution was not buffered ($pH < 5$), compounds **6** and **7**, and aldol condensation products of ketoaldehyde **5** were detected in the reaction mixture. Compound **7**, interesting as a synthon for 11-deoxy-10,11-propano-*PGE* analogues, can be obtained in a practically quantitative yield by treating ketoaldehyde with a catalytic amount of NaO*Me* in *Me*OH. *Wittig-Horner* reaction of unpurified aldehyde **5** with lithium dimethyl-2-oxoheptylphosphonate in *DME*[5] provided enone **8** in 60% yield. This enone was then reduced with $NaBH_4$ in *Me*OH to a mixture of approximately equal amounts of four diastereoisomers of **9**, which were partially separated by column chromatography to give two mixtures of two diastereoisomers. Attempts to separate those mixtures into individual isomers failed.

The second model compound—7-oxo-9,11-dideoxy-PGF_1 methyl ester (**14**)—was obtained in a similar manner (Scheme 3).

Scheme 3

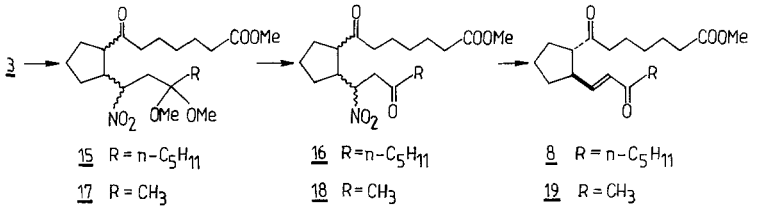


The ketone group of nitroketone **4** was protected with ethylene glycol[6] and the resulting product **10** was subjected to the modified *Nef* reaction followed by the *Wittig-Horner* reaction. The carbonyl group reduction of the resulting enone **12** (51% yield from **4**) led nearly quantitatively to the

mixture of two epimeric alcohols **13 a** and **13 b** (3 : 2), which could be easily separated by column chromatography. The carbonyl group deprotection in both epimers gave 7-oxo-9,11-dideoxy-PGF_1 (**14 a**) and 15-epi-7-oxo-9,11-dideoxy-PGF_1 (**14 b**), respectively. The configuration of the carbon atom 15 is uncertain and probably may be reverse. It was proposed on the basis of the *Rf* values of compounds **14 a** and **14 b**[7].

The preparation of enone **8** can be simplified by employing the method described by *Bakuzis* et al.[8] (Scheme 4).

Scheme 4



Thus, compound **3** was reacted with 3,3-dimethoxy-1-nitrooctane in the presence of tetramethylguanidine to give adduct **15** which after deprotection of the ketone group was treated with diisopropylamine in *Me*OH to give the product identical with the one described above (**8**, 52% total yield). In a similar manner compound **19** was prepared in 77% yield, using 3,3-dimethoxy-1-nitrobutane as a "lower" chain precursor. Compound **19** is interesting as a synthon for the synthesis of 15-methyl *PG*.

The described methods allow to prepare several 7-substituted *PG* analogues in a simple way. These compounds can be considered as 11-deoxy-PGE_1 or 11-deoxy-PGF_1 analogues having carbonyl or hydroxyl functions transferred to the 7 position; they may be of biological interest.

Efforts to utilize the methods described for *PG* "lower" chain introduction in 7-substituted PGF_1 analogues starting from compounds with the general formula **1** are in progress.

Experimental

IR spectra were measured on SPECORD-5 and ^{1}H NMR spectra on Jeol MH-100 spectrometers. All compounds gave satisfactory elemental analysis for C, H, and N.

The structures of the products described in the present paper were also confirmed by their ^{13}C NMR spectra. Detailed discussion concerning these spectra is presented separately[9].

Methyl 7-oxo-7-(1-cyclopentene)-heptanoate (**3**)

To the stirred solution of 23.5 g (0.176 mol) of $AlCl_3$ in 100 cm^3 of CH_2Cl_2, 15.4 g (0.08 mol) of pimelic acid monochloride monomethyl ester was added keeping the temperature below 10 °C. A solution of 8 cm^3 (6.2 g, 0.092 mol) of freshly distilled cyclopentene in 20 cm^3 of CH_2Cl_2 was then added dropwise at 0–5 °C. After the addition was completed, the solution was stirred at 0–5 °C for 10 min, and then poured into a mixture of 250 g of ice with 30 cm^3 of concentrated hydrochloric acid. The organic layer was separated, washed with 10% aqueous HCl, dried with $MgSO_4$ and evaporated under reduced pressure. The residue was placed into a *Claisen* flask containing 10 g of anhydrous Na_2CO_3 and distilled under reduced pressure. Redistillation of a crude product gave 13.4 g (75%) of pure enone **3** (b. p. 124–125 °C/0.2 mm Hg).

trans-1-(1-Oxo-6-methoxycarbonylhexyl)-2-nitromethylcyclopentane (**4**)

A solution of 8.96 g (0.04 mol) of **3** and 0.46 g (0.004 mol) of tetramethylguanidine in 30 cm^3 of nitromethane was stirred for 24 h at room temperature and then for the same time period at 55 °C. The reaction mixture was diluted with 5% hydrochloric acid and extracted three times with $CHCl_3$. The combined extracts were washed with saturated aqueous sodium bicarbonate and with water, dried over $MgSO_4$, and concentrated in vacuo. The crude product was purified by column chromatography (silica gel, hexane-ether 10 : 1 to 1 : 1) to give 8.2 g (72%) of pure **4** as a colourless oil.

IR (film): 1 735, 1 705, 1 550 cm^{-1}.

^{1}H NMR ($CDCl_3$): 1.14–2.07 (m, 12 H), 2.24 (t, J = 7.3 Hz, 2 H), 2.41 (t, J = 7.1 Hz, 2 H), 2.69 (m, 1 H), 2.94 (m, 1 H), 3.59 (s, 3 H), 4.15–4.47 (m, 2 H).

trans-2-(1-Oxo-6-methoxycarbonylhexyl)-cyclopentanecarboxaldehyde (**5**)

To the sodium methoxide solution prepared from 0.13 g (5.5 mmol) of sodium and 10 cm^3 of anhydrous *Me*OH, 1.43 g (5 mmol) of **4** was added and the mixture was heated to 40 °C during 0.5 h. The resulting nitronate salt solution was added in one portion to the vigorously stirred solution prepared from 8.5 g of ammonium acetate, 20 cm^3 of water, and 30 cm^3 of 15% aqueous $TiCl_3$ solution under an atmosphere of argon. The reaction was carried out at room temperature for 1.5 h. The reaction mixture was then extracted three times with ether, the combined extracts washed with three portions of saturated aqueous $NaHCO_3$ and one portion of saturated brine, and dried with $MgSO_4$. Evaporating off the solvent gave 1.2 g (95%) of practically pure aldehyde **5** as a pale-yellow oil.

IR (film): 2 700, 1 735, 1 725, 1 710 cm^{-1}.

^{1}H NMR (CCl_4): 1.10–1.93 (m, 12 H), 2.19 (t, J = 7.2 Hz, 2 H), 2.41 (t, J = 6.9 Hz, 2 H), 2.93–3.24 (m, 2 H), 3.51 (s, 3 H), 9.53 (m, 1 H).

3-(4-Methoxycarbonylbutyl)-bicyclo-[3.3.0]-oct-3-en-2-one (**7**)

To a solution of 0.25 g (1 mmol) of **5** in 3 cm^3 of anhydrous *Me*OH, 0.5 cm^3 of 0.1 *M* NaO*Me* solution in *Me*OH was added and the mixture was allowed to stand overnight at room temperature. After acidification with dilute hydrochloric acid, extraction with ether, drying with $MgSO_4$, and evaporating in vacuo, 0.22 g (93%) of a practically pure enone **7** was obtained as a colourless oil.

IR (film): 1 740, 1 700, 1 625 cm^{-1}.

^{1}H NMR (CCl_4): 1.09–1.83 (m, 10 H), 2.11 (t, J = 6.1 Hz, 2 H), 2.25 (t, J = 6.9 Hz, 2 H), 2.59 (m, 1 H), 3.18 (m, 1 H), 3.60 (s, 3 H), 7.06 (dd, J = 2.6 and 1.3 Hz, 1 H).

7,15-Dioxo-9,11-dideoxy-PGF$_1$ methyl ester (**8**)

Method A

To a stirred solution of 1.0 g (4.55 mmol) of dimethyl 2-oxoheptylphosphonate in 40 cm^3 of anhydrous *DME*, 2.9 cm^3 (4.76 mmol) of *n*-butyllithium solution (1.65 *M* in hexane) was added at —40 °C. This mixture was allowed to reach room temperature and then, after cooling to —20 °C, the solution of 1.1 g (4.33 mmol) of the crude aldehyde **5** in 3 cm^3 of *DME* was added in one portion. After stirring at 10 °C for 45 min, 3 cm^3 of *Me*OH was added and the resulting mixture was concentrated in vacuo to a volume of ca. 10 cm^3. The residue was diluted with ether, washed three times with water and once with brine, dried with $MgSO_4$, and concentrated in vacuo. The crude product was purified by column chromatography on silica gel (hexane—ether 20 : 1 to 1 : 1) to give 0.90 g (60%) of a pure enone **8** as a colourless oil.

Method B

2.19 g (10 mmol) of 3,3-dimethoxy-1-nitrooctane[8] was mixed with 0.12 g (1 mmol) of tetramethylguanidine and after 15 min 1.12 g (5 mmol) of enone **3** was added. The mixture was kept for 12 h at room temperature and, after addition of 0.2 g of *TMG*, for 6 h at 50 °C. The reaction mixture was then neutralized with a few drops of acetic acid and passed through a short column with silica gel using hexane—ethyl acetate (10 : 1 to 2 : 1) as an eluent, to remove the excess of 3,3-dimethoxy-1-nitrooctane. The resulting product was dissolved in 5 cm^3 of *Ac*OH : H_2O : *THF* mixture (3 : 1 : 1) and the solution was maintained at 60 °C for 4 h. The reaction mixture was then neutralized with aqueous $NaHCO_3$ and extracted with ether. The combined extracts were washed with saturated brine, dried over $MgSO_4$ and concentrated in vacuo. The residue was dissolved in 5 cm^3 of *Me*OH, 2 cm^3 of diisopropylamine was added, and the mixture was kept for 12 h at room temperature. After completion of the HNO_2 elimination (TLC monitoring) the reaction mixture was acidified with 5% hydrochloric acid and extracted with ether. The combined extracts were washed with saturated aqueous $NaHCO_3$ and brine, dried with $MgSO_4$, and evaporated in vacuo. The crude product was purified by column chromatography (silica gel, hexane—ether 10 : 1 to 2 : 1) to give 0.93 g (54% yield from **3**) of pure enone **8** identical with the compound prepared by the method A.

IR (film): 1 735, 1 705, 1 675, 1 625 cm^{-1}.

^{1}H NMR (CCl_4): 0.88 (t, J = 5.9 Hz, 3 H), 1.15–2.01 (m, 18 H), 2.22 (t, J = 6.9 Hz, 2 H), 2.38 (t, J = 6.8 Hz, 2 H), 2.43 (t, J = 6.9 Hz, 2 H), 2.58–2.93 (m, 2 H), 3.56 (s, 3 H), 5.99 (d, J = 15.8 Hz, 1 H), 6.65 (dd, J = 15.8 and 7.6 Hz).

7-Hydroxy-9,11-dideoxy-PGF$_1$ methyl ester (**9**) *(mixture of isomers)*

91 mg (2.4 mmol) of $NaBH_4$ was dissolved in 10 cm^3 of anhydrous *Me*OH at —10 °C and 0.35 g (1.0 mmol) of enone **8** in 2 cm^3 of *Me*OH was added in one portion. The solution was stirred at —10 °C for 0.5 h, acidified with diluted hydrochloric acid and extracted with ether. The combined extracts were washed with saturated aqueous $NaHCO_3$ and with brine, dried with $MgSO_4$, and concentrated in vacuo to give 0.34 g (98%) of a mixture of four diastereoisomers of compound **9**. This mixture was chromatographed on silica gel (CH_2Cl_2—*Et*O*Ac* 4 : 1) to give 151 mg of a less polar fraction (**9**-I) and 142 mg of a more polar one (**9**-II), each of them containing two diastereoisomers of **9**.

IR (film): 3 400, 1 735 cm^{-1}.

trans-1-(1-Ethylenedioxy-6-methoxycarbonylhexyl)-2-nitromethylcyclopentane (**10**)

A mixture of 3.0 g (10.5 mmol) of nitroketone **4**, 4 cm^3 of anhydrous ethylene glycol, 7 cm^3 of methyl orthoformate, 18 cm^3 of benzene, and a few crystals of *p*-toluenesulfonic acid was stirred at 60 °C during 6 h while new portions of *p-Ts*OH were added every hour. Low-boiling components of the mixture were then distilled off at reduced pressure and the residue was diluted with ether, washed twice with saturated aqueous $NaHCO_3$ and once with brine, dried with $MgSO_4$, and concentrated in vacuo. The crude product was purified by passing through a short column with silica gel using hexane—ether (5 : 1) as an eluent. The yield of pure acetal **10** was 3.35 g (88%).

IR (film): 1735, 1550 cm^{-1}.

^1H NMR ($CDCl_3$): 1.17–2.05 (m, 15 H), 2.28 (t, J = 7.5 Hz, 2 H), 2.61 (m, 1 H), 3.36 (s, 3 H), 3.97 (s, 4 H), 4.09–4.72 (m, 2 H).

trans-2-(1-Ethylenedioxy-6-methoxycarbonylhexyl)-cyclopentanecarboxaldehyde (**11**)

The reaction was carried out in the same manner as described for unprotected nitroketone **4**. From 1.0 g (3.0 mmol) of **10** 0.86 g (95%) of a pure aldehyde **11** was obtained.

IR (film): 2700, 1735, 1725 cm^{-1}.

^1H NMR ($CDCl_3$): 1.20–1.86 (m, 14 H), 2.29 (t, J = 7.2 Hz, 2 H), 2.64 (m, 2 H), 3.63 (s, 3 H), 3.92 (broad s, 4 H), 9.50 (d, J = 3.2 Hz, 1 H).

7-Ethylenedioxy-15-oxo-9,11-dideoxy-PGF$_1$ methyl ester (**12**)

The reaction was carried out in the same manner as described for the aldehyde **5**. The only change was the longer time of the last step of the reaction—3 h instead of 45 min—due to the lower reactivity of the aldehyde **11**. From 1.49 g (5.0 mmol) of **11** 1.20 g (61%) of **12** were obtained.

IR (film): 1740, 1675, 1625 cm^{-1}.

^1H NMR ($CDCl_3$): 0.88 (t, J = 6.0 Hz, 3 H), 1.14–1.81 (m, 20 H), 2.29 (t, J = 7.2 Hz, 2 H), 2.52 (t, J = 7.2 Hz, 2 H), 2.16–2.70 (m, 2 H), 3.64 (s, 3 H), 3.93 (broad s, 4 H), 6.00 (d, J = 16.1 Hz, 1 H), 6.82 (dd, J = 16.1 and 8.3 Hz, 1 H).

7-Ethylenedioxy-9,11-dideoxy-PGF$_1$ methyl ester (**13a**) *and 15-Epi-7-ethylenedioxy-9,11-dideoxy-PGF$_1$ methyl ester* (**13b**)

To a stirred solution of 0.75 g (1.9 mmol) of enone **12** in 30 cm^3 of anhydrous *Me*OH cooled to 0 °C, 100 mg (2.6 mmol) of powdered $NaBH_4$ were added in a few portions. The reaction mixture was stirred at 0 °C for 24 h, then acidified with dilute hydrochloric acid and extracted four times with ether. The combined extracts were washed with saturated aqueous $NaHCO_3$ and with brine, dried with $MgSO_4$, and concentrated in vacuo to give 0.74 g (98%) of a mixture of two diastereoisomers of the alcohol **13**. This mixture was chromatographed on silica gel (CH_2Cl_2—*EtOAc* 4 : 1) to give 237 mg of the less polar isomer (**13b**), 110 mg of the unseparated mixture, and 351 mg of the more polar isomer (**13a**).

Less polar isomer (**13b**):

IR (film): 3450, 1735 cm^{-1}.

^1H NMR ($CDCl_3$): 0.87 (t, J = 5.7 Hz, 3 H), 1.18–2.62 (m, 27 H), 3.64 (s, 3 H), 3.93 (broad s, 4 H), 4.0 (m, 1 H), 5.39 (dd, J = 15.2 and 6.1 Hz, 1 H), 5.61 (dd, J = 15.2 and 7.3 Hz, 1 H).

More polar isomer (**13a**):

IR (film): 3450, 1735 cm^{-1}.

^{1}H NMR ($CDCl_3$): 0.88 (t, J = 5.7 Hz, 3 H), 1.18–2.56 (m, 27 H), 3.64 (s, 3 H), 3.91 (broad s, 4 H), 4.0 (m, 1 H), 5.40 (dd, J = 15.3 and 6.1 Hz, 1 H), 5.62 (dd, J = 15.3 and 7.1 Hz, 1 H).

7-Oxo-9,11-dideoxy-PGF$_1$ methyl ester (**14 a**)

A solution of 351 mg (0.896 mmol) of acetal **13 a** in 3 cm^3 of *Ac*OH : H_2O : *THF* (3 : 1 : 1) was maintained at 40 °C for 4 h. The reaction mixture was then neutralized with aqueous $NaHCO_3$ and extracted several times with ether. The combined extracts were washed with saturated brine, dried with $MgSO_4$ and concentrated in vacuo to give 300 mg (96%) of a pure compound **14 a**.

IR (film): 3 470, 1 740, 1 710 cm^{-1}.

^{1}H NMR ($CDCl_3$): 0.87 (t, J = 5.7 Hz, 3 H), 1.18–2.01 (m, 20 H), 2.29 (t, J = 7.2 Hz, 2 H), 2.43 (t, J = 6.8 Hz, 2 H), 2.50–2.75 (m, 3 H), 3.65 (s, 3 H), 4.02 (m, 1 H), 5.32–5.73 (m, 2 H).

15-Epi-7-oxo-9,11-dideoxy-PGF$_1$ methyl ester (**14 b**)

237 mg of acetal **13 b** was hydrolyzed as described above to give 202 mg (96%) of compound **14 b**.

IR (film): 3 470, 1 740, 1 710 cm^{-1}.

^{1}H NMR ($CDCl_3$): 0.88 (t, J = 5.7 Hz, 3 H), 1.18–2.01 (m, 20 H), 2.29 (t, J = 7.3 Hz, 2 H), 2.41 (t, J = 6.8 Hz, 2 H), 2.40–2.75 (m, 3 H), 3.65 (s, 3 H), 4.01 (m, 1 H), 5.32–5.71 (m, 2 H).

7,15-Dioxo-9,11-dideoxy-17,18,19,20-tetranor-PGF$_1$ methyl ester (**19**)

Compound **19** was prepared as described for **8** (method B). Starting from 1.12 g (5 mmol) of enone **3** and 1.63 g (10 mmol) of 3,3-dimethoxy-1-nitrobutane[10], 1.13 g (77%) of the pure product **19** was obtained (quantities of the other reagents and reaction conditions were identical as described for **8**).

IR (film): 1 735, 1 710, 1 675, 1 625 cm^{-1}.

^{1}H NMR ($CDCl_3$): 1.21–1.92 (m, 12 H), 2.21 (s, 3 H), 2.29 (t, J = 6.5 Hz, 2 H), 2.46 (t, J = 6.5 Hz, 2 H), 2.62–3.05 (m, 2 H), 3.62 (s, 3 H), 6.05 (d, J = 16.4 Hz, 1 H), 6.75 (dd, J = 16.4 and 7.7 Hz, 1 H).

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