Microwave-Assisted Synthesis of Cyclopentanones Using the Relevant Phosphorus Ylides

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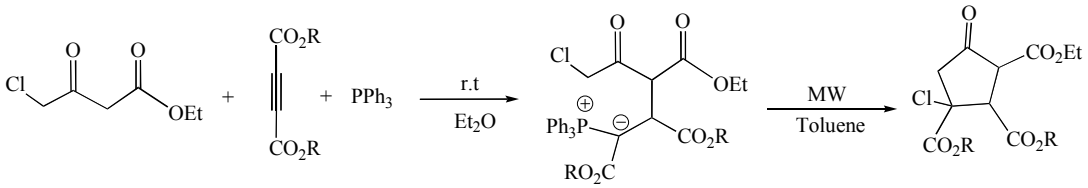
Abstract: A one-pot synthesis of cyclopentanone derivatives from phosphorus ylide under lab-type microwave assisted methodology was described. The phosphorus ylides were obtained *via* the reaction of activated acetylenic compounds, ethyl 4-chloroacetoacetate and triphenylphosphine. The structure of phosphorus ylides was assigned by ^{1}H, ^{13}C and ^{31}P-NMR. The phosphorus ylides as precursor were crystallized as two enantiomers (R,R) and (S,S) and one of the phosphorus ylide structures was confirmed by single X-ray crystallography.



Keywords: Cyclopentanone, dialkyl acetylenedicarboxylates, enantiomers, phosphorus ylide, three-component reactions, X-ray crystallography.

1. INTRODUCTION

Cyclopentanones are one of the most widely distributed carbon skeletal structures in natural and unnatural organic compounds. The entropy for cyclization leading to the five-membered ring is much suitable to other ring size [1]. Numerous methods for the synthesis of cyclopentanone derivatives have been published [2-4]. However, because of the importance of cyclopentanone derivatives and especially the high functionalized derivatives, new methods for their synthesis are still on extreme demand [4, 5]. On the other hand, the formation of several carbon-carbon bonds in a one-flask multistep reaction, sometimes called a tandem or cascade reaction, is of high value in the construction of complex organic molecules and the methodology has received much attention these days [6-10]. As part of our current studies on the development of new routes in organic compound synthesis, we report an efficient procedure for direct synthesis of ylide **4** from the reaction of ethyl 4-chloroacetoacetate **1** and electron deficient acetylenic compounds **2** in the presence of triphenylphosphine **3**. Ylide **4** was converted to cyclopentanones in toluene as the solvent under microwave and reflux conditions (Scheme **1**). Herein we investigated a one-pot reaction of ethyl 4-chloroacetoacetate **1** and electron deficient acetylenic compounds **2** in the presence of triphenylphosphine **3** at room temperature which afforded ylide **4** derivatives in good isolated yields (Scheme **1**).

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2. RESULTS AND DISCUSSION

The procedure was simple and easy to handle. Structures of compounds **4a** and **4b** are characterized by mass, IR, ^{1}H, ^{13}C and ^{31}P-NMR spectroscopy. By employing recrystalization technique and slow evaporation method, the crystal form of compound **4b** was prepared. By using single X-ray diffraction, the structure of compound **4b** was assigned as a model for phosphorus ylide compounds (Fig. **1**).

Configuration of compound **4b** confirms by single X-ray diffraction (see experimental). Herein, in X-ray diffraction of **4b** two isomers were observed with (R,R) and (S,S) configuration (Fig. **2**), whereas in solution state NMR of this compound, the spectral data showed two major and minor isomers. The rational reason for this phenomenon is attributed to the ability of resonance of carbanion with carbonyl group of ester in the solution form of **4b**. While in crystalline solid state, because of rigidity of molecules, two separate enantiomers of **4b** were appeared.

The ^{1}H NMR spectrum for major isomer of **4a** exhibited one triplet at $\delta = 1.18$ ($^{3}J = 7.4$) and two singlet at $\delta = 3.08$ and 3.65 ppm for the methyl protons along with the characteristic signals for aromatic protons at 7.47-7.74 ppm. The carbonyl group resonances in ^{13}C NMR spectra for major isomer of **4a** appear at 167.0, 169.5 (d, $^{2}J_{CP} = 5.2$ Hz), 174.3 (d, $^{3}J_{CP} = 18.8$ Hz) and 195.5 ppm.

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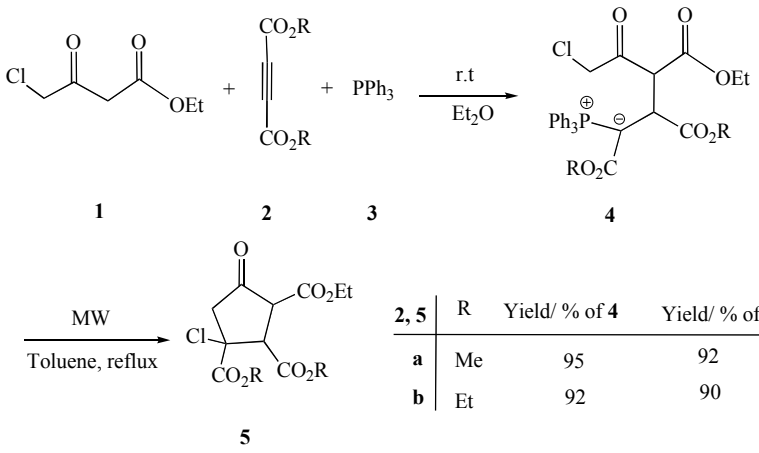


2, 5	R	Yield/ % of **4**	Yield/ % of **5**
a	Me	95	92
b	Et	92	90

Scheme 1. Synthesis of phosphorus ylide and cyclopentanone derivatives.

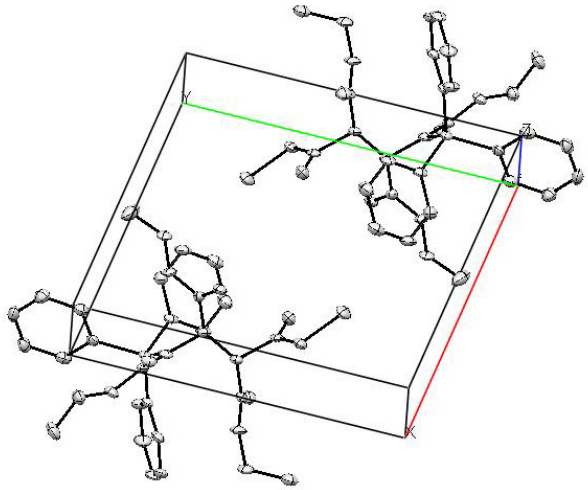


Fig. (1). X-ray structure of compound **4b** as two enantiomers R,R and S,S.

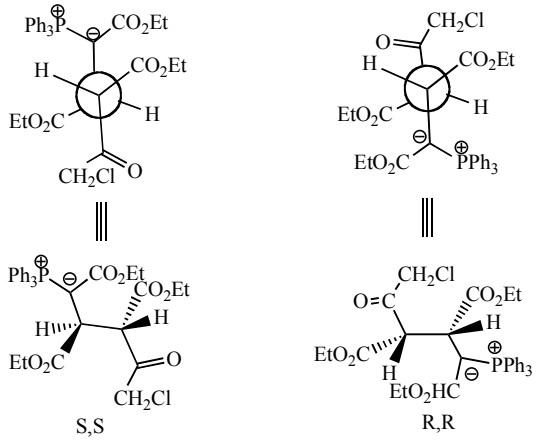


Fig. (2). Newman projection of compound **4b** that was elucidated by X-ray.

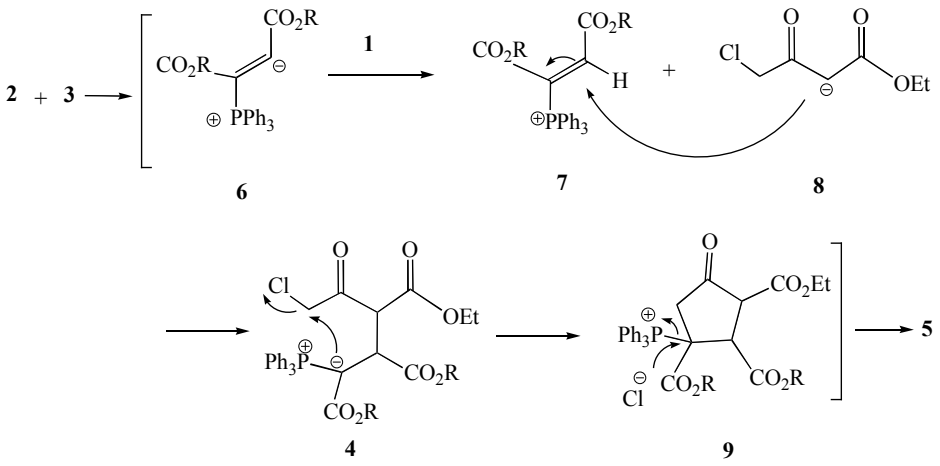
The phosphoruse ylides **4** are as stable and important compounds for the next step of cyclization reaction. For example, one of the famous reactions is using phosphoruse ylides for wittig reaction to the synthesis of alkenes, but the conditions of reaction for doing them are not easy in the bench-type heating. Therefore, for performing this type of reactions, we need a power source of heating and energy which is produced from Microwave. Herein, we used a new technology of laboratory microwave (*MICROSYNTH* from Mylestone Company) [11] as a suitable source of energy for converting phosphorus ylide **4** to cyclic building blocks.

We have described a new class of highly fuctionalized cyclopentanone **5** from a stable phosphorus ylides which contain a convenience leveaing group. The details of this formation are described by a homogeneous source of energy as a uniform heating of the mixture of reaction in the chamber of microwave machine that will be performed as well-done method of organic synthesis. Yield **4** was changed to cyclopentanone **5** in toluene under microwave and reflux conditions, in power of 800W and 110 ^{o}C for 40 minuts. Compounds **5a-b** were assigned by IR, ^{1}H-NMR, ^{13}C and ^{31}P-NMR and mass spectral data. In ^{31}P NMR, spectrum was not observed phosphorus signal. By the cyclization of ylide **4**, PPh_3 was eliminated from the ylide compound and monitored by TLC. The ^{1}H-NMR spectrum of **5a** exhibited one triplet at δ = 1.32 (^{3}J = 7.4), two singlet at δ = 3.78 and 3.80 ppm for the methoxy protons. The carbonyl group resonances in ^{13}C-NMR spectra of **5a** appear at 161.0, 169.0, 170.3 and 198.2 ppm. The mass spectra of **5a** displayed the molecular ion peaks at 306.

A tentative mechanism for this transformation is proposed in Scheme **2**. It is conceivable that the reaction involves the initial formation of zwiterionic **6** between dialkyl acetylenedicarboxylate **2** and triphenylphosphine **3**. Intermediate **6** that are formed under microwave conditions react with ethyl 4-chloroacetoacetate **1** and produced intermediate **7** and **8**. Negative charge in intermediate **8** was attacked to **7** and produced yield **4**. Cyclization of yield **4** with elimination of triphenylphosphine leads to the cyclopentanone **5**.

3. CONCLUSION

In summary, the reaction of ethyl 4-chloroacetoacetate and electron deficient compounds in the presence of triphenylphosphine which afforded ylide derivatives in excellent yields. In this research, the structure of phosphorus ylide as a model was assigned by X-ray diffraction and observed two enantiomer configurations. Ylide derivatives



Scheme 2. Possible mechanism for the formation of products **4** and **5**.

were converted to cyclopentanone derivatives in toluene under reflux and microwave conditions. The advantages of our work are as follows: (1) The reaction is performed under mild condition, (2) No catalyst is required for this reaction and (3) The simplicity of the present procedure makes it an interesting alternative to the complex multistep approaches. Finally, using the microwave conditions, they will be introduced as a facile methodology to do the reactions by important viewpoints such as short time of reactions, less by-products, selectivity of products and clean procedure for organic synthesis.

4. MATERIAL AND METHODS

All chemicals obtained from Fluka were used without further purification. Melting points were measured on a Kofler hot stage apparatus and are uncorrected. ^{1}H NMR, ^{13}C NMR and ^{31}P NMR spectra were obtained with a Bruker FT-500 spectrometer in chloroform-d1, and tetramethylsilane (TMS) was used as an internal standard. Mass spectra were recorded with a Finnigan Mat TSQ-70 spectrometer. Infrared (IR) spectra were acquired on a Nicollet Magna 550-FT spectrometer. Elemental analyses were carried out with a Perkin-Elmer model 240-C apparatus. The results of elemental analyses (C, H, N) were within ±0.4% of the calculated values.

General Procedure

To a stirred solution of ethyl 4-chloroacetoacetate **1** (2 mmol) and dialkyl acetylenedicarboxylate **2** (2 mmol) in 10 mL Et_2O, triphenylphosphine (2 mmol) slowly was added. The reaction mixture was stirred for 2 h at room temperature until the reaction was complete (reaction mixture monitored by TLC). The mixture of reaction was purified by preparative TLC on silica gel column chromatography (Merck 230-400 mesh) using n-hexane-EtOAc as eluent to afford the pure compound **4**.

[5-chloro-3-(ethoxycarbonyl)-1,2-bis(methoxycarbonyl)-4-oxopentyl] (triphenyl) phosphorane ylide (4a)

Yellow powders, yield: 1.08 g (95%). IR (KBr) (ν_{max}/cm^{-1}): 1730, 1727, 1681, 1623, 1434, 1305 and 1155 cm^{-1}. Anal. Calcd for $C_{30}H_{30}ClO_7P$ (568.99): C, 63.33, H, 5.31; Found: C, 63.24, H, 5.25%. NMR data for major isomer: ^{1}H NMR: 1.18 (3 H, t, $^{3}J_{HH}$ = 7.4 Hz, Me), 3.08 (3 H, s, MeO), 3.65 (3 H, s, MeO), 4.07-4.11 (1 H, m, CH), 4.12-4.19 (1 H, m, CH), 4.34 (2 H, q, $^{3}J_{HH}$ = 7.4 Hz, CH_2O), 4.34-4.38 (1 H, m, CH), 4.56-4.4.59 (1 H, m, CH), 7.47-7.56 (6 H, m, 6 CH), 7.59-7.74 (9 H, m, 9 CH) ppm. ^{13}C NMR: 14.3 (Me), 48.8 (CH_2), 51.3 (MeO), 52.0 (MeO), 58.5 (d, $^{2}J_{CP}$ = 2.3 Hz, CH), 61.5 (CH_2O), 65.2 (d, $^{3}J_{CP}$ = 4.9, CH), 82.5 (d, $^{1}J_{CP}$ = 127.4, CH), 128.5 (d, $^{2}J_{CP}$ = 2.4, 6 CH), 132.2 (d, $^{3}J_{CP}$ = 4.5, 6 CH), 133.0 (3 CH), 133.8 (d, $^{1}J_{CP}$ = 130.5, 3 C), 167.0 (C=O), 169.5 (d, $^{2}J_{CP}$ = 5.2, C=O), 174.3 (d, $^{3}J_{CP}$ = 18.8, C=O) 195.5 (C=O) ppm. ^{13}P NMR: 24.15 [P(C6H5)$_3$]. NMR data for minor isomer: ^{1}H NMR: 1.21 (3 H, t, $^{3}J_{HH}$ = 7.5 Hz, Me), 3.06 (3 H, s, MeO), 3.66 (3 H, s, MeO), 3.97-4.01 (1 H, m, CH), 4.02-4.06 (1 H, m, CH), 4.54 (2 H, q, $^{3}J_{HH}$ = 7.4 Hz, CH_2O), 4.34-4.38 (1 H, m, CH), 4.56-4.4.59 (1 H, m, CH), 7.47-7.56 (6 H, m, 6 CH), 7.59-7.74 (9 H, m, 9 CH) ppm. ^{13}C NMR: 13.9 (Me), 48.9 (CH_2), 51.7 (MeO), 52.1 (MeO), 56.7 (d, $^{2}J_{CP}$ = 2.3 Hz, CH), 61.3 (CH_2O), 65.5 (d, $^{3}J_{CP}$ = 5.0, CH), 82.6 (d, $^{1}J_{CP}$ = 128.1, CH), 128.3 (d, $^{2}J_{CP}$ = 3.0, 6 CH), 132.1 (d, $^{3}J_{CP}$ = 4.6, 6 CH), 133.2 (3 CH), 133.9 (d, $^{1}J_{CP}$ = 130.6, 3 C), 167.9 (C=O), 169.7 (d, $^{2}J_{CP}$ = 5.3, C=O), 175.1 (d, $^{3}J_{CP}$ = 18.5, C=O) 195.7 (C=O) ppm. ^{13}P NMR: 23.7 [P(C6H5)$_3$].

[5-chloro-3-(ethoxycarbonyl)-1,2-bis (ethoxycarbonyl) -4 -oxopentyl] (triphenyl) phosphorane ylide (4b)

Yellow powders, yield: 1.09 g (92%). IR (KBr) (ν_{max}/cm^{-1}): 1729, 1728, 1682, 1624, 1435, 1310 and 1158 cm^{-1}. EI-MS: 597 (M^{+}, 5), 561 (62), 552 (92), 335 (97), 45 (100). Anal. Calcd for $C_{32}H_{34}ClO_7P$ (597.04): C, 64.38, H, 5.74; Found: C, 64.25, H, 5.62%. NMR data for major isomer: ^{1}H NMR: 1.14 (3 H, t, $^{3}J_{HH}$ = 7.4 Hz, Me), 1.19 (3 H, t, $^{3}J_{HH}$ = 7.3 Hz, Me), 1.23 (3 H, t, $^{3}J_{HH}$ = 7.5 Hz, Me), 3.39-3.44 (1 H, m, CH), 3.70-3.73 (1 H, m, CH), 3.96 (2 H, q, $^{3}J_{HH}$ = 7.5 Hz, CH_2O), 4.03 (2 H, q, $^{3}J_{HH}$ = 7.3 Hz, CH_2O), 4.09 (2 H, q, $^{3}J_{HH}$ = 7.3 Hz, CH_2O), 4.43-4.47 (1 H, m, CH), 4.49-4.53 (1 H, m, CH), 7.28-7.46 (6 H, m, 6 CH), 7.58-7.64 (9 H, m, 9 CH) ppm. ^{13}C NMR: 13.8 (Me), 13.9 (Me), 14.0 (Me), 49.2 (CH_2), 57.4 (d, $^{2}J_{CP}$ = 3.5 Hz, CH), 60.9 (CH_2O), 61.0 (CH_2O), 61.1 (CH_2O), 66.3 (d, $^{3}J_{CP}$ = 5.3, CH), 83.4 (d, $^{1}J_{CP}$ = 129.0, CH), 128.2 (d, $^{2}J_{CP}$ = 3.0, 6 CH), 132.3 (d, $^{3}J_{CP}$

= 4.6, 6 CH), 132.9 (3 CH), 134.0 (d, $^{1}J_{CP}$ = 130.2, 3 C), 167.1 (C=O), 170.2 (d, $^{2}J_{CP}$ = 5.5, C=O), 173.8 (d, $^{3}J_{CP}$ = 19.2, C=O) 195.7 (C=O) ppm. ^{13}P NMR: 23.9 [P(C6H5)$_3$]. NMR data for minor isomer: ^{1}H NMR: 1.13 (3 H, t, $^{3}J_{HH}$ = 7.5 Hz, Me), 1.21 (3 H, t, $^{3}J_{HH}$ = 7.3 Hz, Me), 1.25 (3 H, t, $^{3}J_{HH}$ = 7.5 Hz, Me), 3.52-3.57 (1 H, m, CH), 3.74-3.78 (1 H, m, CH), 3.97 (2 H, q, $^{3}J_{HH}$ = 7.5 Hz, CH_2O), 4.05 (2 H, q, $^{3}J_{HH}$ = 7.3 Hz, CH_2O), 4.11 (2 H, q, $^{3}J_{HH}$ = 7.3 Hz, CH_2O), 4.35-4.43 (1 H, m, CH), 4.47-4.58 (1 H, m, CH), 7.47-7.50 (6 H, m, 6 CH), 7.66-7.74 (9 H, m, 9 CH) ppm. ^{13}C NMR: 14.1 (Me), 14.2 (Me), 14.3 (Me), 49.7 (CH_2), 57.5 (d, $^{2}J_{CP}$ = 3.6 Hz, CH), 61.2 (CH_2O), 61.3 (CH_2O), 61.4 (CH_2O), 66.7 (d, $^{3}J_{CP}$ = 5.5, CH), 83.5 (d, $^{1}J_{CP}$ = 129.5, CH), 128.4 (d, $^{2}J_{CP}$ = 3.4, 6 CH), 132.5 (d, $^{3}J_{CP}$ = 4.7, 6 CH), 133.1 (3 CH), 134.1 (d, $^{1}J_{CP}$ = 130.3, 3 C), 168.1 (C=O), 170.3 (d, $^{2}J_{CP}$ = 5.8, C=O), 174.6 (d, $^{3}J_{CP}$ = 20.4, C=O) 197.3 (C=O) ppm. ^{13}P NMR: 23.5 [P(C6H5)$_3$].

Crystal Data of Compound 4b

Crystallographic data (excluding structure factors) for the structure in this Letter have been deposited with the Cambridge Crystallographic Data Centre as supplementary publications CCDC 830374. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK, (fax: +44-(0)1223-336033 or e-mail: deposit@ccdc.cam.ac.uk). Summary of Data CCDC 830374; Formula: $C_{32}H_{34}ClO_7P$; Unit cell parameters: a 9.812(3) b 11.515(4) c 13.790 (4); alpha 88.437(5) beta 76.108(6) gamma 80.269(6); space group P-1.

General Procedure for Preparation of Compounds 5a-b

Ylide **4** was refluxed in toluene for 4 h under microwave conditions (In power of 800 w and T=110 ^{o}C). The solvent was removed under reduced pressure and the viscous residue was purified by preparative TLC on silica gel column chromatography (Merck 230-400 mesh) using n-hexane-EtOAc as eluent to give compound **5**.

3-ethyl 1,2-dimethyl 1-chloro-4-oxo-1,2,3- cyclopentane tricarboxylate (5a)

Yellow oil, yield: 0.56 g (92%). IR (KBr) (ν_{max}/cm^{-1}): 1727, 1725, 1720, 1480, 1379, 1326, 1208 and 1140 cm^{-1}. ^{1}H NMR: 1.32 (3 H, t, $^{3}J_{HH}$ = 7.4 Hz, Me), 3.78 (3 H, s, MeO), 3.80 (3 H, s, MeO), 3.81-3.85 (1 H, m, CH), 3.86-3.87 (1 H, m, CH), 4.23 (2 H, t, $^{3}J_{HH}$ = 7.4 Hz, CH_2O), 4.34-4.38 (1 H, m, CH), 4.56-4.59 (1 H, m, CH) ppm. ^{13}C NMR: 14.2 (Me), 37.1 (CH_2), 45.0 (CH), 46.8 (CH), 51.9 (MeO), 52.5 (MeO) 61.7 (OCH_2), 132.9 (C), 161.0 (C=O), 169.0 (C=O), 170.3 (C=O), 198.2 (C=O) ppm. Anal. Calcd for $C_{12}H_{15}ClO_7$ (306.69): C, 46.99, H, 4.93; Found: C, 46.82, H, 4.83%.

3-ethyl 1,2-diethyl 1-chloro-4-oxo-1,2,3-cyclopentane tricarboxylate (5b)

Yellow Oil, yield: 0.60 g (90%). IR (KBr) (ν_{max}/cm^{-1}): 1730, 1727, 1725, 1548 and 1472 cm^{-1}. ^{1}H NMR: 1.27 (3 H, t, $^{3}J_{HH}$ = 7.4 Hz, Me), 1.30 (3 H, t, $^{3}J_{HH}$ = 7.3 Hz, Me), 1.32 (3 H, t, $^{3}J_{HH}$ = 7.4 Hz, Me), 3.81-3.83 (2 H, m, 2 CH), 4.18-4.21 (2 H, q, $^{3}J_{HH}$ = 7.4 Hz, CH_2O), 4.22-4.24 (2 H, q, $^{3}J_{HH}$ = 7.3 Hz, CH_2O), 4.26-4.28 (2 H, q, $^{3}J_{HH}$ = 7.4 Hz, CH_2O), 4.34-4.38 (1 H, m, CH), 4.56-4.59 (1 H, m, CH) ppm. ^{13}C NMR: 14.1 (Me), 14.2 (Me), 14.3 (Me), 37.2 (CH2), 45.3 (CH), 46.6 (CH), 60.9 (CH_2O), 61.4 (CH_2O), 61.7 (CH_2O), 133.5 (C), 160.6 (C=O), 169.2 (C=O), 169.9 (C=O), 198.5 (C=O) ppm. Anal. Calcd for $C_{14}H_{19}ClO_7$ (334.75): C, 50.23, H, 5.72; Found: C, 50.10, H, 5.68%.

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