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Prostanoids: LXXXVIII.* Chlorocyclopentenone Building Blocks in the Synthesis of Marine Prostanoids

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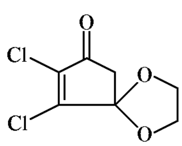
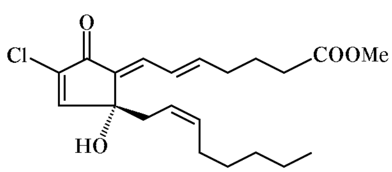
Abstract—Starting from 2,3-dichloro-4,4-ethylenedioxy-2-cyclopentenone, a practical procedure has been developed for the synthesis of a series of 4-substituted 2-chloro-4-hydroxycyclopentenones.

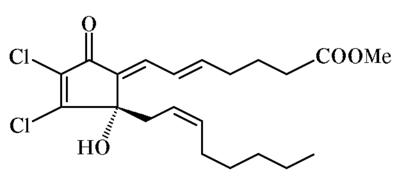
In the preceding paper [2] we have described an efficient procedure for the transformation of previously reported dichlorocyclopentenone **I** [3] into a chlorovulone II analog, 11-chloro-substituted chlorovulone II (**II**), and substantiated its pharmacological potential.



I



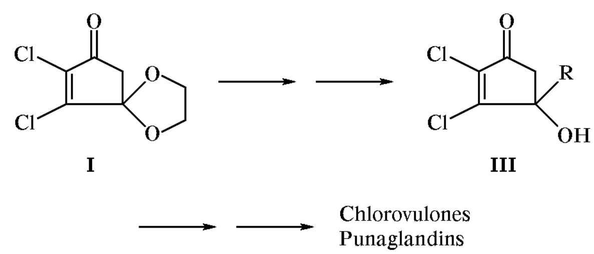
Chlorovulone II



III

The present communication deals with possible applications of compound **I** in the synthesis of cyclopentenone building blocks for natural chlorine-containing prostanoids, chlorovulones and punaglandins, which exhibit a strong antiviral and anticarcinogenic activity [4–7]. Most syntheses of chlorovulones and punaglandins are based on the use of 4-substituted 2-chloro-4-hydroxy-2-cyclopentenones **III** as starting compounds (Scheme 1). Compounds **III** were synthesized by selective reductive monodechlorination of 2,3-dichloro-4-hydroxy-2-cyclopentenones **IV** which were prepared by condensation of the corresponding Grignard and Reformatsky compounds with cyclopentenone **I**, followed by acid hydrolysis of ethylene acetals **V** thus formed (Scheme 2).

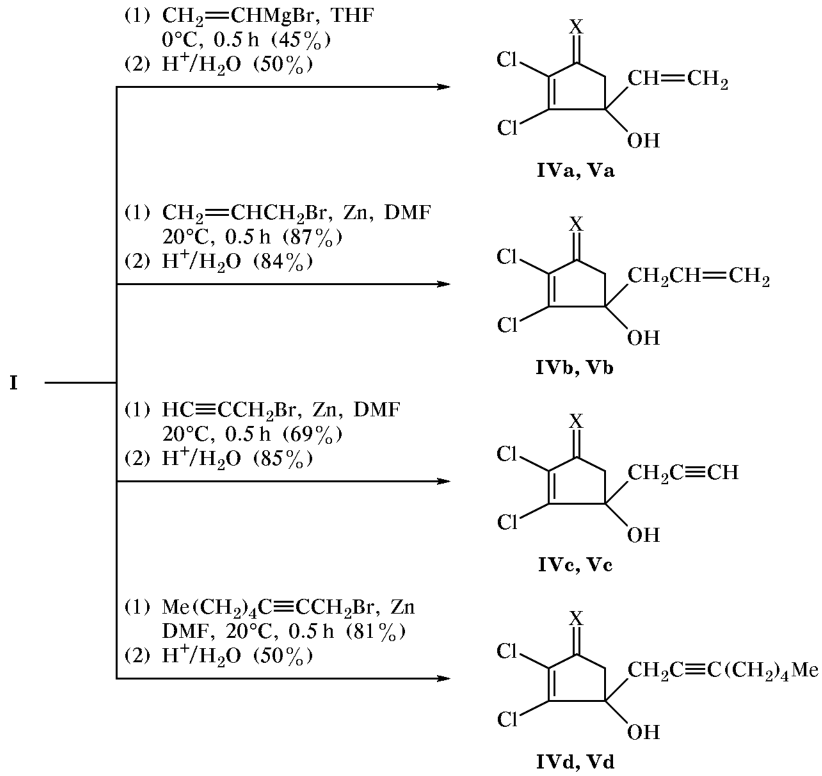
Scheme 1.



Special comments should be given to the transformation of **I** into compounds **IVa**–**IVd**. Some apprehensions were concerned with the condensation of **I** with 2-octynyl bromide (which is a disubstituted acetylene derivative) under the Reformatsky reaction conditions [8, 9] and subsequent hydrolysis of acetal **Vd**. Our experiments showed that the use of such a reactive electrophile as compound **I** ensures preparation of acetal **Vd** (as precursor of **IVd**) in a good yield. The hydrolysis of **Vd** was also successful. Here, it should be noted that we previously failed to effect acid hydrolysis of analogous acetal **VI** [9] to the corresponding ketone even under fairly severe conditions [2]. This was explained by the presence in molecule **VI** of a side-chain double (*Z*)-C=C bond which creates steric hindrances to hydrolysis. Acetal **Vd** has a linear side-chain acetylenic moiety, so that steric hindrances are lacking, and the hydrolysis occurs

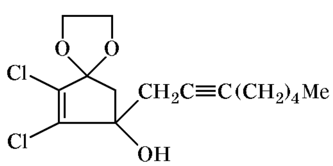
* For communication LXXXVII, see [1].

Scheme 2.

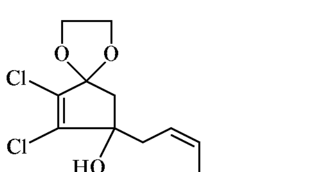


IVa–IVd, X = O; **Va–Vd**, X = OCH_2CH_2O; H^+/H_2O stands for Me_2CO–10% hydrochloric acid, 56°C, 1 h.

relatively smoothly. Presumably, the above stated also applies to the hydrolysis of compounds **Va**–**Vc**, where the side-chain double and triple bonds occupy terminal position.



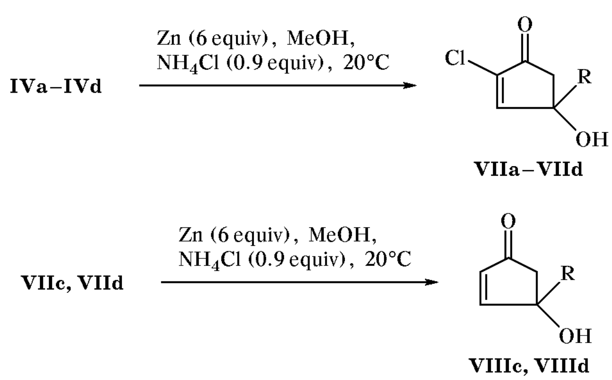
Vd



VI

Compounds **IVa**–**IVd** were smoothly dechlorinated with the system Zn–NH_4Cl–MeOH under controlled conditions. The reactions were fast and selective. Dechlorination of vinyl and allyl derivatives **IVa** and **IVb** occurred exclusively at the C^3 atom to give compounds **VIIa** and **VIIb**, respectively (Scheme 3). Monodechlorinated products **VIIc** and **VIId** obtained from acetylenic enones **IVc** and **IVd** were subjected to exhaustive dechlorination to obtain chlorine-free enones **VIIIc** and **VIIId**. Prolonged reduction of enone **IVc** with increased amount of the reducing agent (12 equiv of Zn) at elevated temperature (under reflux) led to conjugated dienone **VIIIe** (Scheme 4).

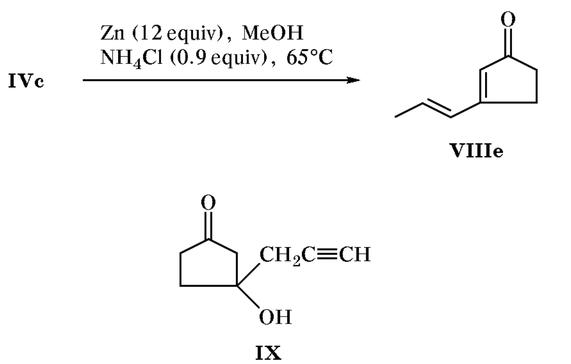
Scheme 3.



R = CH_2=CH (**a**), CH_2=$CHCH_2$ (**b**), CH≡CCH_2 (**c**), $Me(CH_2)_4C$≡CCH_2 (**d**).

Presumably, the reaction involves intermediate formation of β-hydroxycyclopentenone **IX** via saturation of the endocyclic double bond. Compound **IX** undergoes acetylene–allene rearrangement with simultaneous elimination of water and subsequent reduction of the terminal double bond in the allene fragment.

Scheme 4.



Thus we have developed a practical and efficient procedure for the transformation of readily accessible compound **I** into key chlorocyclopentenone building blocks **VIIa**–**VIId**.

EXPERIMENTAL

The IR spectra were recorded on UR-20 and Specord M-80 spectrometers from samples prepared as thin films or dispersed in mineral oil. The ^{1}H and ^{13}C NMR spectra were obtained on a Bruker AM-300 instrument at 300 and 75.47 MHz, respectively, using tetramethylsilane as internal reference and $CDCl_3$ and $(CD_3)_2CO$ as solvents.

4-Alken(yn)yl-2,3-dichloro-4-hydroxy-2-cyclopentenones IVa–IVd. Acetal **Va**–**Vd**, 2 mmol, was dissolved in a mixture of 20 ml of acetone and 4 ml of 15% hydrochloric acid. The mixture was heated for 1 h under reflux and cooled to 20°C, 4 ml of a saturated aqueous solution of sodium chloride was added, and the product was extracted into ethyl acetate (3 × 20 ml). The combined extracts were washed with an aqueous solution of sodium chloride until neutral reaction, dried over $MgSO_4$, filtered, and evaporated. The residue was purified by column chromatography on silica gel using ethyl–acetate–petroleum ether (3 : 7) as eluent.

2,3-Dichloro-4-hydroxy-4-vinyl-2-cyclopentenone (IVa). Yield 50%, oily substance. IR spectrum, ν, cm^{-1}: 1610, 1730, 3450. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 2.80–2.98 m (2H, CH_2), 3.30 br.s (1H, OH), 5.35–5.55 m (2H, =CH_2), 5.80–6.00 m (1H, CH=). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 49.16 (C^5), 77.43 (C^4), 116.98 (CH_2=), 133.34 (C^2), 137.25 (CH=), 164.78 (C^3), 193.95 (C=O).

4-Allyl-2,3-dichloro-4-hydroxy-2-cyclopentenone (IVb). Yield 84%, oily substance. IR spectrum, ν, cm^{-1}: 850, 1615, 1680, 1740, 3100, 3450. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 2.46 d.d (1H, CH_2, J = 13.6, 7.1 Hz), 2.52 d.d (1H, CH_2, J = 13.6, 7.1 Hz), 2.58 d (1H, 5-H, J = 18.5, 7.1 Hz), 2.80 d (1H, CH_2, J = 18.5, 7.1 Hz), 4.30 br.s (1H, OH), 5.05–5.17 m (2H, CH_2=), 5.60–5.75 m (1H, CH=). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 42.09 (CH_2), 46.80 (C^5), 77.04 (C^4), 120.97 (CH_2=), 130.22 (CH=), 132.73 (C^2), 165.83 (C^3), 194.43 (C=O).

2,3-Dichloro-4-hydroxy-4-(2-propynyl)-2-cyclopentenone (IVc). Yield 85%, oily substance. IR spectrum, ν, cm^{-1}: 850, 1615, 1680, 1740, 3100, 3450. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 2.50–2.90 m (5H, 2CH_2, CH), 3.16 br.s (1H, OH). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 29.13 (CH_2), 47.22 (C^5), 72.8 (CH≡), 93.97 (C≡), 77.04 (C^4), 163.55 (C^2), 134.08 (C^3), 193.65 (C=O).

2,3-Dichloro-4-hydroxy-4-(2-octynyl)-2-cyclopentenone (IVd). Yield 50%, oily substance. IR spectrum, ν, cm^{-1}: 1614, 1740, 3480. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 0.90 t (3H, CH_3), 1.20–1.55 m (6H, 3CH_2), 2.15 m (2H, CH_2), 2.55–2.90 m (5H, 2CH_2, OH), 7.39 s (1H, CH). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 13.89 (CH_3), 18.42 ($C^{4'}$), 22.08 ($C^{7'}$), 28.17 ($C^{1'}$), 29.86 ($C^{5'}$), 30.87 ($C^{6'}$), 47.79 (C^5), 72.52 ($C^{2'}$), 77.40 (C^4), 85.46 ($C^{3'}$), 133.84 (C^2), 163.42 (C^3), 193.26 (C=O).

6,7-Dichloro-8-hydroxy-8-vinyl-1,4-dioxaspiro[4.4]non-6-ene (Va). A 0.5 N solution of vinylmagnesium bromide in THF, 8 ml, was added dropwise under argon to a solution of 0.42 g (2.0 mmol) of ketone **I** in 10 ml of anhydrous THF, stirred at –20°C. The mixture was allowed to warm up to 0°C and was stirred for 0.5 h at that temperature. A saturated solution of ammonium chloride, 10 ml, was added, and the product was extracted into chloroform (3 × 30 ml). The combined extracts were dried over $MgSO_4$ and evaporated, and the residue was purified by column chromatography on silica gel using ethyl acetate–petroleum ether (1 : 1) as eluent. Yield 45%, oily substance. IR spectrum, ν, cm^{-1}: 1610, 3450. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 2.35 d.d (1H, 9-H, J = 6.1 Hz), 2.49 d.d (1H, 9-H, J = 6.1 Hz), 3.28 br.s (1H, OH), 3.80–4.20 m (4H, 2CH_2), 5.15–5.45 m (2H, CH=), 5.70–5.90 m (1H, CH=). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 50.09 (C^9), 65.80 (CH_2O), 66.04 (CH_2O), 79.03 (C^8), 112.07 (C^5), 115.18 (CH_2=), 132.28 (C^6), 132.28 (C^7), 138.67 (CH=).

8-Alken(yn)yl-6,7-dichloro-8-hydroxy-1,4-dioxaspiro[4.4]non-6-enes Vb–Vd. Zinc dust, 15.0 mmol, was added under vigorous stirring to a solution of 5 mmol of ketone **I** and 7 mmol of allyl bromide, 2-propynyl bromide, or 6-octynyl bromide in 15 ml of DMF. The reaction was fairly vigorous and was accompanied by heat evolution. After 30 min, the mixture was acidified with a saturated aqueous solution of ammonium chloride, and the product was extracted into diethyl ether (3 × 30 ml). The combined extracts were dried over $MgSO_4$ and evaporated, and the residue was purified by chromatography on silica gel using ethyl acetate–petroleum ether (1 : 1) as eluent.

8-Allyl-6,7-dichloro-8-hydroxy-1,4-dioxaspiro-[4.4]non-6-ene (Vb). Yield 87%, oily substance. IR spectrum, ν, cm^{-1}: 1615, 3100, 3450. ^1H NMR spectrum ($CDCl_3$), δ, ppm: 2.17 d (1H, 0.5CH_2, J = 14.2 Hz), 2.32 d.d (1H, CH_2, J = 13.7, 7.3 Hz), 2.46 d (1H, 9-H, J = 14.2, 7.3 Hz), 2.48 d (1H, CH_2, J = 13.7 Hz), 3.32 br.s (1H, OH), 3.85–4.20 m (4H, 2CH_2O), 5.05–5.17 5 m (2H, CH_2=), 5.60–5.75 m (1H, CH=). ^{13}C ($CDCl_3$), δ_C, ppm: 42.36 (CH_2), 47.82 (C^9), 65.92 (C^2, C^3), 78.69 (C^8), 112.22 (C^5), 119.62 (CH_2=), 131.82 (CH=), 132.18 (C^7), 139.58 (C^6).

6,7-Dichloro-8-hydroxy-8-(2-propynyl)-1,4-dioxaspiro[4.4]non-6-ene (Vc). Yield 69%, oily substance. IR spectrum, ν, cm^{-1}: 1650, 2150, 3320, 3450. ^1H NMR spectrum ($CDCl_3$), δ, ppm: 2.08 t (1H, ≡CH, J = 2.7 Hz), 2.33 d (1H, 9-H, J = 14.3 Hz), 2.55 d.d (1H, CH_2, J = 15.7, 2.7 Hz), 2.70 d.d (1H, CH_2, J = 15.7, 2.7 Hz), 2.72 d (1H, 9-H, J = 14.3 Hz), 3.25 s (1H, OH), 4.00 m (2H, CH_2O), 4.20 m (2H, CH_2O). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 29.03 (CH_2), 48.36 (C^9), 78.36 (C^8), 78.57 (C≡), 112.21 (C^5), 133.30 (C^6), 138.30 (C^7).

6,7-Dichloro-8-hydroxy-8-(2-octynyl)-1,4-dioxaspiro[4.4]non-6-ene (Vd). Yield 81%, oily substance. IR spectrum, ν, cm^{-1}: 1610, 3450. ^1H NMR spectrum ($CDCl_3$), δ, ppm: 0.86 m (3H, CH_3), 2.13 m (2H_2), 2.4–3.0 m (5H, 2CH_2, OH), 3.80–4.20 m (4H, 2CH_2). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 13.83 (CH_3), 18.51 ($C^{7'}$), 22.06 ($C^{4'}$), 28.28 ($C^{6'}$), 29.40 ($C^{5'}$), 30.81 ($C^{1'}$), 73.76 ($C^{2'}$), 84.05 ($C^{3'}$), 48.30 (C^9), 78.47 (C^8), 112.203 (C^5), 132.83 (C^6), 138.47 (C^7).

4-Alken(yn)yl-2-chloro-4-hydroxy-2-cyclopentenones VIIa–VIId (*general procedure*)**.** Zinc dust, 1 g (15.3 mmol), and ammonium chloride, 0.1 g (1.87 mmol), were added to a solution of 2.5 mmol of dichlorocyclopentenone **IVa**–**IVd** in 7 ml of methanol. The mixture was stirred at 20°C, and the progress of the reaction was monitored by TLC. When the initial compound disappeared (~15 min), the mixture was filtered, 5 ml of a saturated aqueous solution of ammonium chloride was added to the filtrate, and the product was extracted into ethyl acetate (3 × 20 ml). The combined extracts were dried over $MgSO_4$, filtered, and evaporated, and the residue was purified by chromatography on silica gel using ethyl acetate–petroleum ether (1 : 4) as eluent.

2-Chloro-4-hydroxy-4-vinyl-2-cyclopentenone (VIIa). Yield 53%, oily substance. IR spectrum, ν, cm^{-1}: 1420, 1720, 3500. ^1H NMR spectrum ($CDCl_3$), δ, ppm: 2.70–2.78 m (2H, CH_2), 3.29 br.s (1H, OH), 5.20–5.41 m (2H, =CH_2), 5.90–6,09 m (1H, CH=), 7.31 br.s (1H, CH). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 48.76 (C^5), 75.80 (C^4), 115.23 (CH_2=), 125.86 (C^2), 139.57 (CH=), 157.57 (C^3), 198.53 (C=O).

4-Allyl-2-chloro-4-hydroxy-2-cyclopentenone (VIIb). Yield 80%, oily substance. IR spectrum, ν, cm^{-1}: 850, 1615, 1680, 1740, 3100, 3250. ^1H NMR spectrum ($CDCl_3$), δ, ppm: 2.39 d.d (1H, 0.5CH_2, J = 15.1, 7.0 Hz), 2.44 d.d (1H, 0.5CH_2, J 15.1, 7.0 Hz), 2.57 d (1H, 5-H, J = 18.7 Hz), 2.70 d (1H, 5-H, J = 18.7 Hz), 3.70–3.90 br.s (1H, OH), 4.90–5.10 m (2H, CH_2=), 5.50–5.70 m (1H, CH=), 7.3 s (1H, OH). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 44.46 (CH_2), 47.21 (C^5), 75.23 (C^4), 120.33 (CH_2=), 131.37 (CH=), 135.59 (C^2), 158.88 (C^3), 198.64 (C=O).

2-Chloro-4-hydroxy-4-(2-propynyl)-2-cyclopentenone (VIIc). Yield 60%, oily substance. IR spectrum, ν, cm^{-1}: 850, 1615, 1680, 1740, 3100, 3450. ^1H NMR spectrum ($CDCl_3$), δ, ppm: 2.50–2.90 m (5H, 2CH_2, CH), 3.16 br.s (1H, OH), 7.42 s (1H, CH). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 31.23 (CH_2), 47.53 (C^5), 72.63 (≡CH), 74.94 (C≡), 78.29 (C^4), 137.18 (C^2), 156.73 (C^3), 197.41 (C=O).

2-Chloro-4-hydroxy-4-(2-octynyl)-2-cyclopentenone (VIId). Yield 76%, oily substance. IR spectrum, ν, cm^{-1}: 1614, 1740, 3480. ^1H NMR spectrum ($CDCl_3$), δ, ppm: 0.90 t (3H, CH_3), 1.20–1.55 m (6H, 3CH_2), 2.15 m (2H, CH_2), 2.55–2.90 m (5H, 2CH_2, OH), 7.39 s (1H, CH). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 13.99 (CH_3), 18.63 ($C^{4'}$), 22.19 ($C^{7'}$), 28.44 ($C^{6'}$), 31.08 ($C^{5'}$), 31.80 ($C^{1'}$), 47.53 (C^5), 73.59 ($C^{2'}$), 75.24 (C^4), 85.51 ($C^{3'}$), 136.84 (C^2), 157.23 (C^3), 197.61 (C=O).

Compounds **VIIIc** and **VIIId** were synthesized by subsequent reduction of compounds **VIIc** and **VIId**, following the procedure described above for the reduction of **IVa**–**IVd**.

4-Hydroxy-4-(2-propynyl)-2-cycopentenone (VIIIc). Yield 57%, oily substance. IR spectrum, ν, cm^{-1}: 850, 1615, 1680, 1740, 3100, 3450. ^1H NMR spectrum ($CDCl_3$), δ, ppm: 2.50–2.70 m (5H, $2CH_2$, CH), 2.90 br.s (1H, OH), 6.20 d (1H, CH, *J* = 5.7 Hz), 7.50 d (1H, CH, *J* = 5.7 Hz). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 30.90 (CH_2), 48.24 (C^5), 72.11 (≡CH), 77.64 (C≡), 78.65 (C^4), 134.34 (C^2), 163.72 (C^3), 205.94 (C=O).

4-Hydroxy-4-(2-octynyl)-2-cyclopentenone (VIIId). Yield 74%, oily substance. IR spectrum, ν, cm^{-1}: 1614, 1740, 3480. ^1H NMR spectrum ($CDCl_3$), δ, ppm: 0.90 t (3H, CH_3), 1.20–1.70 m (8H, $4CH_2$), 2.10–2.25 m (2H, CH_2), 2.50–2.70 m (5H, $2CH_2$, OH), 6.18 d (1H, CH, *J* = 5.6 Hz), 7.48 d (1H, CH, *J* = 5.6 Hz). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 13.94 (CH_3), 18.59 ($C^{7'}$), 22.13 ($C^{4'}$), 28.45 ($C^{6'}$), 31.05 ($C^{5'}$), 31.59 ($C^{1'}$), 48.32 (C^5), 73.99 ($C^{2'}$), 76.56 (C^4), 84.95 ($C^{3'}$), 134.13 (C^2), 164.06 (C^3), 205.91 (C=O).

3-[(*E*)-1-Propenyl]-2-cyclopentenone (VIIIe) was synthesized in a similar way using 30 mmol (12 equiv) of zinc dust; the mixture was heated for 2 h under reflux. Yield 35%. Oily substance. IR spectrum, ν, cm^{-1}: 1576, 1644, 1676, 1688, 1712, 1744, 3032. ^1H NMR spectrum ($CDCl_3$), δ, ppm: 1.85 d.d (3H, CH_3, *J* = 6.7, 1.3 Hz), 2.30–2.50 m (2H, 4-H), 2.60–2.70 m (2H, 5-H), 5.87 s (1H, 2-H), 6.48 d (1H, 1′-H, *J* = 16.1 Hz), 6.28 d.q (1H, 2′-H, *J* = 6.7, 1.3 Hz). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 18.62 (CH_3), 26.88 (C^4), 34.52 (C^5), 127.75 (C^2), 128.49 (CH=), 136.02 (CH=), 172.86 (C^3), 209.76 (C=O).

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