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α-Nitrocycloalkanones as a New Source for the One-Pot Synthesis of Functionalized 1,4-Diketones, γ-Oxoaldehydes, γ-Ketoesters, and Methyl ω-Oxoalkanoates

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Abstract: Methyl ω-oxoalkanoates were obtained *via* ring cleavage of α-nitrocycloakanones by refluxing these compounds in a methanolic solution of KOH, then treating the obtained mixture, at 0 °C, with an aqueous solution of $KMnO_4/MgSO_4$. 1,4-Diketones, γ-oxoaldehydes, and γ-ketoesters were also prepared by conjugated addition of α-nitrocycloakanones to the appropriate conjugated enones, in MeOH/Ph_3P, then by, *in situ*, ring cleavage-Nef reaction following the above conditions.

Ring cleavage often represents a particularly effective route to α,ω-difunctionalized framworks. In this context 2-nitrocycloalkanones[1] are of great importance because a peculiar reactivity of these compounds is the cleavage of the C(1)-C(2) bond by action of external nucleophiles. This reverse Claisen type condensation affords consistent array of functionalized molecules,[2,3] while intramolecular nucleophilic attack to the 2-nitrocarbonyl residue has been extensively used by Hesse and his coworkers in their elegant "Zip Reaction" to effect cycloenlargement.[4] Since 2-nitrocycloalkanones are readily available from the corresponding ketones or olefins by several nitrating processes,[5] these substrates are profitable precursors in many synthetic procedures.

In continuation with our studies devoted to the ring cleavage of 2-nitrocycloalkanones we have now found that these compounds can be conveniently used as central source (Scheme 1) for the one-pot preparation of *(i)* ω-functionalized aldehydes **3**, well known powerful building blocks,[6,7] expecially for the synthesis of natural products,[8] *(ii)* functionalized 1,4-diketones **6** and γ-oxoaldehydes **7**, both valuable class of compounds because of their importance for the synthesis of cyclopentenones and heterocyclic systems such as furans, pyrroles, thiophenes, and pyridazines,[9] and *(iii)* γ-oxo esters **8**, which are highly usefull intermediates for the preparation of lactones, lactam antibiotics, isoquinolines and lactonic sex pheromones.[10]

In the past, numerous methods have been reported for the synthesis of the compounds **3**,[8] **6**,**7**,[9c-f] and **8**,[10,11] however, most of these suffer from drawbacks such as the use of harsh conditions, employment

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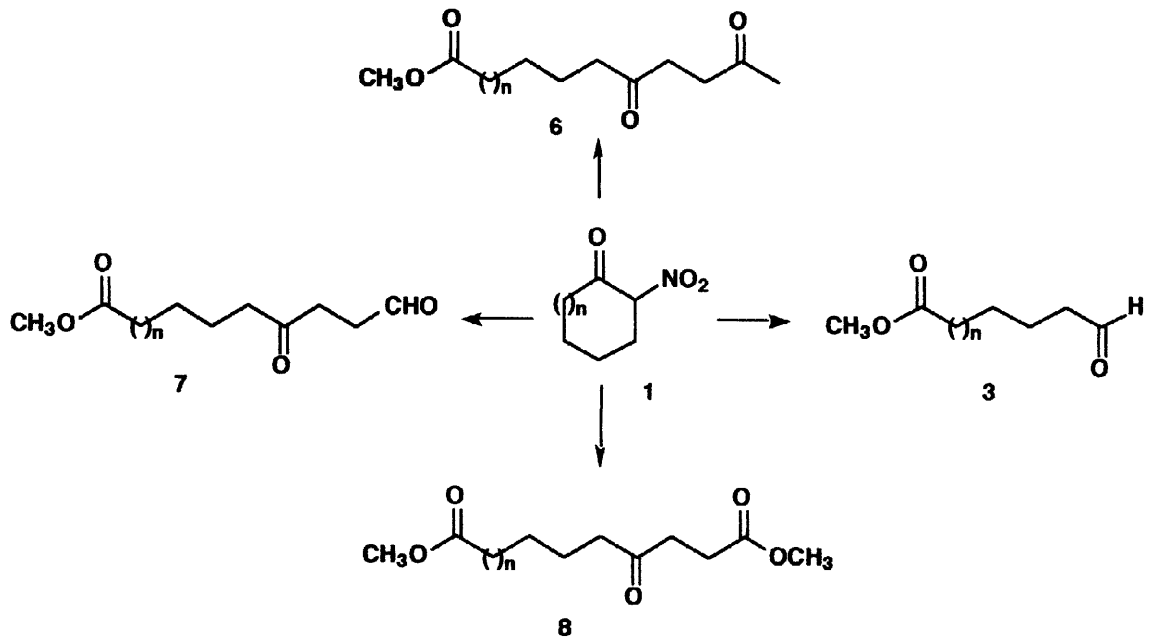
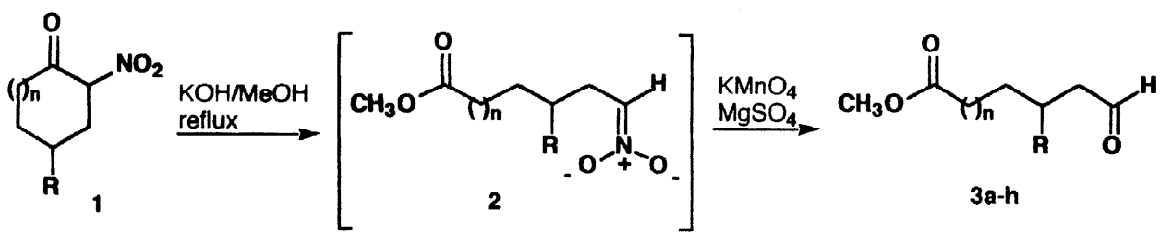


Scheme 1

of expensive chemical and/or tedious procedures. Furthermore, no method is general for the synthesis of all these classes of molecules, so that, other sources for their preparation are welcomed.



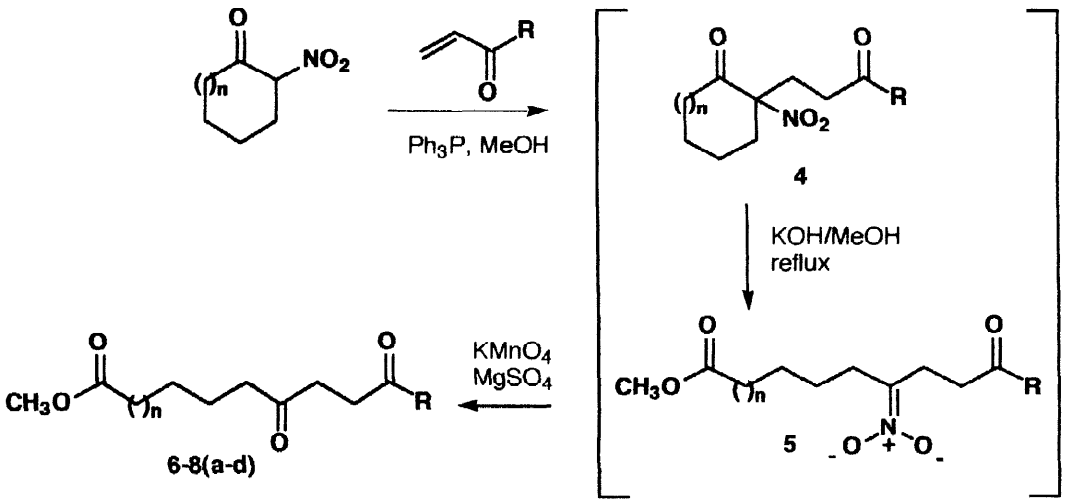
	n	R	Yield (%) of 3
a	0	H	60
b	1	H	77
c	1	Me	66
d	1	*t*-Bu	60
e	2	H	75
f	6	H	63
g	7	H	61
h	10	H	84

Scheme 2

Following our previous experience on the ring cleavage of compounds **1** we tested different procedures with the aim to find the right conditions to perform more steps in the same flask, in order to provide, one-pot, the title compounds.

Our method, to afford the methyl ω-oxoalkenoates **3** (Scheme 2), consists of the ring cleavage of **1** with methanol, as nucleophile, under basic conditions (KOH) and, *in situ*, Nef conversion of the obtained nitronate **2** with an aqueous solution of $KMnO_4/MgSO_4$. The compounds **3** are so obtained in satisfactory to good yields (60-84%).

The syntheses of functionalized γ-oxo derivatives **6-8** are achieved by conjugate addition of the cyclic nitro ketones with the appropriate enone (acrolein, methyl vinyl ketone or methyl acrylate, Scheme 3) in methanol and in the presence of a catalytic amount of triphenylphosphine (2-12 h, see experimental) then, after addition of methanolic-KOH and refluxing for 8 h the ring cleavage of the intermediates **4** take place, and the formed nitronates **5** can be directly treated with $KMnO_4/MgSO_4$ and the 1,4-dicarbonyl derivatives **6-8** are so synthesized, one-pot, in moderate to high yields (50-92%).



6	n	R	Yield (%)
a	1	CH_3	87
b	2	CH_3	75
c	7	CH_3	93
d	10	CH_3	80

7	n	R	Yield (%)
a	1	H	92
b	2	H	75
c	7	H	73
d	10	H	70

8	n	R	Yield (%)
a	1	OCH_3	70
b	2	OCH_3	67
c	7	OCH_3	50
d	10	OCH_3	50

Scheme 3

It is important to point out that both the methodologies are independent of the size of the ring and afford the compounds **3**, **6-8** one-pot and with simple and economical chemicals.

In conclusion, since α-nitrocycloalkanones are commercially available from different sources,[5] their use as the immediate precursors for the title compounds represents a general and efficient entry to these molecules. Moreover, this procedure appears as a further evidence of the high versatility of cyclic nitro ketones, and extends their application in organic synthesis.

Experimental

General: All ^{1}H-NMR spectra were recorded in $CDCl_3$ at 300 MHz. Chemical shifts are expressed in ppm downfield from TMS as internal standard. *J* values are given in Hertz. Mass spectra were determined on a Hewlett-Packard GC/MS 5970 by means of the EI technique (70 eV). The reactions were monitored by TLC or GC performed on a Carlo Erba Fractovap 4160 using a capillary column of Duran Glass, stationary phase OV1. The α-nitrocycoalkanones are commercially available or prepared by standard provedure.[5] All the products were purified by flash chromatography on Merck silica gel (0.040-0.063 mm).[12]

General Procedure for the Synthesis of Methyl ω-Oxoalkanoates (3): A solution of compound **1** (10 mmol) in an alcoholic solution (200 ml) of KOH (15 mmol) was refluxed for 8 h. Then, after cooling at 0 °C, an aqueous solution (150 ml) of potassium permanganate (12 mmol) and magnesium sulphate (15 mmol) was slowly added. Upon complete addition the reaction mixture was stirred for 12 h at room temperature, and then filtered through a short Florisil pad. After extraction with Et_2O, the organic phase was dried, evaporated and the crude product was purified by flash chromatography.

Methyl 5-Oxopentanoate (3a): IR (film) 2730, 1750, 1730 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.87-2.04 (m, 2H, *J* = 7.2 Hz), 2.37 (t, 2H, *J* = 7.2 Hz), 2.55 (dt, 2H, *J* = 7.2 and 1.3 Hz), 3.67 (s, 3H), 9.76 (m, 1H); MS *m/z* 102, 99, 87, 74 (100%), 71, 59, 55. Anal. Calcd for $C_6H_{10}O_3$: C, 55.37; H, 7.44. Found: C, 55.45; H, 7.38.

Methyl 6-Oxohexanoate (3b): IR (film) 2730, 1740, 1720 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.55-1.75 (m, 4H), 2.25-2.38 (m, 2H), 2.39-2.52 (m, 2H), 3.68 (s, 3H), 9.77 (m, 1H); MS *m/z* 116, 113, 101, 95, 87 (100%), 74, 67, 59, 55. Anal. Calcd for $C_7H_{12}O_3$: C, 58.32; H, 8.39. Found: C, 58.45; H, 8.38.

Methyl 4-Methyl-6-Oxohexanoate (3c): IR (film) 2730, 1740, 1720 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.95 (d, 3H, *J* = 4.9 Hz), 1.40-1.85 (m, 3H), 2.25-2.50 (m, 4H), 3.68 (s, 3H), 9.78 (s, 1H); MS *m/z* 127, 115, 101, 87 (100%), 74, 69, 59, 55. Anal. Calcd for $C_8H_{14}O_3$: C, 60.74; H, 8.92. Found: C, 60.85; H, 9.02.

Methyl 4-*t*-Butyl-6-Oxohexanoate (3d): IR (film) 2730, 1750, 1730 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.9 (s, 9H), 1.2-2.7 (m, 7H), 3.68 (s, 3H), 9.8 (m, 1H); MS *m/z* 169, 157, 153, 135, 115, 112, 83, 74, 57 (100%). Anal. Calcd for $C_{11}H_{20}O_3$: C, 65.97; H, 10.06. Found: C, 66.06; H, 10.13.

Methyl 7-Oxoheptanoate (3e): IR (film) 2730, 1750, 1730 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.2-1.74 (m, 6H), 2.30 (t, 2H, *J* = 7.3 Hz), 2.6 (t, 2H, *J* = 7.0 Hz), 3.65 (s, 3H), 9.77 (m, 1H), ; MS *m/z* 158

(M^+), 127, 99, 83, 74, 69, 59, 55 (100%). Anal. Calcd for $C_8H_{14}O_3$: C, 60.74; H, 8.62. Found: C, 60.68; H, 8.70.

Methyl 11-Oxoundecanoate (3f): IR (film) 2730, 1750, 1720 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.2-1.8 (m, 14H), 2.25-2.5 (m, 4H), 3.67 (s, 3H), 9.77 (m, 1H); MS *m/z* 215 (M^+ + 1), 186, 183, 171, 157, 139, 121, 111, 98, 74 (100%), 69, 55. Anal. Calcd for $C_{12}H_{22}O_3$: C, 67.26; H, 10.35. Found: C, 67.33; H, 10.27.

Methyl 12-Oxododecanoate (3g): IR (film) 2730, 1720, 1710 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.2-1.4 (m, 12H), 1.5-1.75 (m, 4H), 2.30 (t, 2H, J = 7.2 Hz), 2.55 (t, 2H, J = 7.2 Hz), 3.67 (s, 3H), 9.77 (m, 1H); MS *m/z* 156, 143, 115, 101, 97, 87, 83, 74 (100%), 55. Anal. Calcd for $C_{13}H_{24}O_3$: C, 68.38; H, 10.59. Found: C, 68.30; H, 10.65.

Methyl 15-Oxopentadecanoate (3h): IR (film) 2725, 1730, 1710 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.2-1.4 (m, 18H), 1.54-1.70 (m, 4H), 2.30 (t, 2H, J = 7.2 Hz), 2.53 (t, 2H, J = 7.2 Hz), 3.67 (s, 3H), 9.77 (m, 1H); MS *m/z* 252, 242, 227, 199, 195, 177, 143, 121, 111, 98, 74 (100%), 69, 55. Anal. Calcd for $C_{16}H_{30}O_3$: C, 71.07; H, 11.18. Found: C, 71.13; H, 11.25.

General Procedure for the Synthesis of 1,4-Dicarbonyl Derivatives (6-8): To a solution of compound **1** (10 mmol) in methanol (20 ml) was added the appropriate conjugated enone (methyl vinyl ketone (MVK) or acrolein or methyl acrylate, 11 mmol) and a catalytic amount (10%) of Ph_3P. After stirring at room temperature for 2-12 h (2 h for MVK and acrolein, 12 h for methyl acrylate) an alcoholic solution (150 ml) of KOH (15 mmol) was added and the solution refluxed for 8 h. After cooling at 0 °C, an aqueous solution (150 ml) of potassium permanganate (12 mmol) and magnesium sulphate (15 mmol) was slowly added, and after the complete addition the reaction mixture was stirred for 12 h at room temperature, and then filtered through a short Florisil pad. After extraction with Et_2O, the organic phase was dried, evaporated and the crude products **6-8** were purified by flash chromatography.

Methyl 6,9-Dioxodecanoate (6a): IR (film) 1730, 1708 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.65-156 (m, 4H), 2.18 (s, 3H), 2.28-2.37 (m, 2H), 2.45-2.52 (m, 2H), 2.65-2.74 (d, 4H, J = 2.4 Hz), 3.66 (s, 3H); MS *m/z* 214 (M^+), 196, 183, 171, 154, 137, 111, 99 (100%), 83, 71, 55. Anal. Calcd for $C_{11}H_{18}O_4$: C, 61.66; H, 8.47. Found: C, 61.77; H, 8.38.

Methyl 7,10-Dioxoundecanoate (6b): IR (film) 1730, 1708 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.22-1.37 (m, 2H), 1.5-1.68 (m, 4H), 2.28 (s, 3H), 2.27-2.35 (t, 2H, J = 7.4 Hz), 2.4-2.5 (t, 2H, J = 7.4 Hz), 2.62-2.72 (dd, 4H, J = 2.6 and 2.7 Hz), 3.65 (s, 3H); MS *m/z* 228 (M^+), 1210, 197, 185, 179, 157, 151, 114, 99 (100%), 71, 69, 55. Anal. Calcd for $C_{12}H_{20}O_4$: C, 63.14 H, 8.83. Found: C, 63.13; H, 8.95.

Methyl 12,15-Dioxohexadecanoate (6c): IR (film) 1730, 1700 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.21-1.71 (m, 16H), 2.19 (s, 3H), 2.25-2.35 (t, 2H, J = 7.5 Hz), 2.4-2.5 ((t, 2H, J = 7.5 Hz), 2.7 (m, 4H), 3.68 (s, 3H); MS *m/z* 298 (M^+), 280, 267, 227, 195, 167, 149, 114 (100%), 99, 71, 55. Anal. Calcd for $C_{17}H_{30}O_4$: C, 68.42; H, 10.13. Found: C, 68.34; H, 10.15.

Methyl 15,18-Dioxononadecanoate (6d): IR (film) 1733, 1715 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.15-1.4 (m, 22H), 1.5-1.7 (m, 3H), 2.11-2.2 (t, 2H, J = 7.5 Hz), 2.28-2.34 (t, 2H, J = 7.5 Hz), 2.7 (m, 4H), 3.68 (s, 3H) ; MS *m/z* 340 (M^+), 309, 269, 237, 209, 191, 153, 135, 114,(100%), 99, 71, 55. Anal. Calcd for $C_{20}H_{36}O_4$: C, 70.54; H, 10.66. Found: C, 70.64; H, 10.73.

Methyl 6,9-Dioxononanoate (7a): IR (film) 2727, 1730, 1708 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.6-1.7 (m, 4H), 2.3-2.4 (t, 2H, J = 7.5 Hz), 2.48-2.56 (t, 2H, J = 7.5 Hz), 2.70-2.78 (m, 4H), 3.67 (s, 3H), 9.8 (s, 1H); MS *m/z* 182, 169, 151, 143, 123, 111, 100, 85 (100%), 83, 73, 55. Anal. Calcd for $C_{10}H_{16}O_4$: C, 59.98; H, 8.05. Found: C, 60.06; H, 7.97.

Methyl 7,10-Dioxodecanoate (7b): IR (film) 2727, 1735, 1710 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.22-1.67 (m, 6H), 2.30 (t, 2H, J = 7.5 Hz), 2.46 (t, 2H, J = 7.3 Hz), 2.67-2.77 (m, 4H), 3.68 (s, 3H), 9.8 (s, 1H); MS *m/z* 213 (M^+ - 1), 181, 167, 153, 135, 130 (100%), 115, 98, 87, 69, 59, 55. Anal. Calcd for $C_{11}H_{18}O_4$: C, 61.63; H, 8.47. Found: C, 61.56; H, 8.55.

Methyl 12,15-Dioxopentadecanoate (7c): IR (film) 2730, 1730, 1710 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.2-1.37 (m, 12H), 1.52-1.68 (m, 4H), 2.27-2.35 (t, 2H, J = 7.3 Hz), 2.41-2.51 (t, 2H, J = 7.4 Hz), 2.72-2.78 (m, 4H), 3.7 (s, 3H), 9.9 (s, 1H); MS *m/z* 284 (M^+), 253, 227, 185, 167, 149, 135, 101, 100 (100%), 85. Anal. Calcd for $C_{16}H_{28}O_4$: C, 67.57; H, 9.92. Found: C, 67.60; H, 9.97.

Methyl 15,18-Dioxooctadecanoate (7d): IR (film) 2750, 1735, 1720 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.2-1.35 (m, 18H), 1.52-1.7 (m, 4H), 2.31 (t, 2H, J = 7.4 Hz), 2.45 (t, 2H, J = 7.5 Hz), 2.71-2.79 (m, 4H), 3.68 (s, 3H), 9.8 (s, 1H); MS *m/z* 294, 143, 127, 114 (100%), 95, 71, 55. Anal. Calcd for $C_{19}H_{34}O_4$: C, 69.90; H, 10.50. Found: C, 69.99; H, 10.43.

Dimethyl 4-Oxononanedioate (8a): IR (film) 1732, 1710 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.59-1.67 (m, 4H), 2.29-2.37 (m, 2H), 2.45-2.55 (m, 2H), 2.57-2.64 (m, 2H), 2.68-2.70 (m, 2H), 3.67 (s, 3H), 3.68 (s, 3H); MS *m/z* 230 (M^+), 198, 167, 130, 115 (100%), 111, 98, 73, 55, 41, 31. Anal. Calcd for $C_{11}H_{18}O_5$: C, 57.38; H, 7.88. Found: C, 57.46; H, 7.96.

Dimethyl 4-Oxodecanedioate (8b): IR (film) 1732, 1720 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.59-1.67 (m, 6H), 2.28-2.35 (m, 2H), 2.45-2.50 (m, 2H), 2.56-2.62 (m, 2H), 2.68-2.75 (m, 2H), 3.67 (s, 3H), 3.69 (s, 3H); MS *m/z* 244 (M^+), 213, 181, 157, 153, 130, 115, 98, 83, 55 (100%), 41, 31. Anal. Calcd for $C_{12}H_{20}O_5$: C, 59.00; H, 8.25. Found: C, 59.09; H, 8.17.

Dimethyl 4-Oxopentadecanedioate (8c): IR (film) 1740, 1725 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.2-1.38 (m, 12H), 1.51-1.67 (m, 4H), 2.26-2.35 (m, 2H), 2.38-2.49 (m, 2H), 2.51-2.61 (m, 2H), 2.68-2.78 (m, 2H), 3.65 (s, 3H), 3.69 (s, 3H); MS *m/z* 284, 283, 251, 227, 130 (100%), 115, 98, 69, 55, 39. Anal. Calcd for $C_{17}H_{30}O_5$: C, 64.94; H, 9.62. Found: C, 65.02; H, 9.53.

Dimethyl 4-Oxooctadecanedioate (8d): IR (film) 1735, 1720 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.15-1.29 (m, 18H), 1.55-1.65 (m, 4H), 2.30 (t, 2H, J = 7.5 Hz), 2.44 (t, 2H, J = 7.4 Hz), 2.52-2.55 (m, 2H), 2.69-2.78 (m, 2H), 3.67 (s, 3H), 3.69 (s, 3H); MS *m/z* 324, 293, 269, 130 (100%), 115, 98, 69, 55, 39. Anal. Calcd for $C_{20}H_{36}O_5$: C, 67.38; H, 10.18. Found: C, 67.47; H, 10.24.

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