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Indium-Catalyzed Synthesis of Keto Esters from Cyclic 1,3-Diketones and Alcohols and Application to the Synthesis of Seratrodast

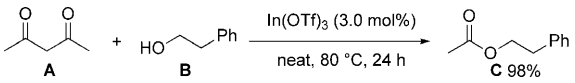
Yoichiro Kuninobu,* Atsushi Kawata, Taihei Noborio, Syun-ichi Yamamoto, Takashi Matsuki, Kazumi Takata, and Kazuhiko Takai*[a]

Abstract: Esterification reactions from cyclic 1,3-diketones and alcohols are carried out in the presence of several Lewis acids. In particular, indium(III) triflate, $In(OTf)_3$, iron(III) triflate, $Fe(OTf)_3$, copper(II) triflate, $Cu(OTf)_2$, and silver(I) triflate, AgOTf, show high catalytic activities. These reactions proceed through the carbon–carbon bond cleavage by a retro-aldol reaction and were found to be highly regioselective even in the presence of other functional groups. This type of reaction can also be applied to the preparation of the keto esters during the synthesis of seratrodast, which is an antiasthmatic and eicosanoid antagonist.

Keywords: alcohols · esterification · indium · ketones · keto esters

Introduction

Esters are one of the most fundamental and important categories in organic chemistry. Many bioactive molecules and functional materials contain ester groups. Therefore, many strategies for the synthesis of esters have been developed.[1] For example, condensation of alcohols and carboxylic acids,[2,3] or acid anhydrides,[4] or acyl halides,[5] transesterification,[6] ester-interchange reactions,[7] mercury-catalyzed reactions of carboxylic acids with alkynes,[8] metal-catalyzed oxidative procedures starting from aldehydes,[9] and enzyme-catalyzed methods[10] are well known. As an alternative synthetic method, we recently reported the indium-catalyzed synthesis of esters from 1,3-diketones and alcohols through the nucleophilic attack of an alcohol to a carbonyl group of a 1,3-diketone, and the carbon–carbon bond cleavage by a retro-aldol reaction [Eq. (1)].[11–13] An investigation of the catalysts for this synthesis revealed that iron(III) triflate, $Fe(OTf)_3$, copper(II) triflate, $Cu(OTf)_2$, and silver(I) triflate, AgOTf, also have high catalytic activities. In this paper, we first investigate the scope and limitations of the substrates using $In(OTf)_3$. Then, we describe an application of the proposed method to the synthesis of the drug, seratrodast.



(1)

Results and Discussion

Investigation of Several Catalysts

In the synthesis of esters from 1,3-dicarbonyl compounds and alcohols, $In(OTf)_3$ has a high catalytic activity.[11] Investigation of various Lewis acids showed that several metal salts have catalytic activities (Table 1). In particular, $Fe(OTf)_3$ (entry 3), which was derived from $FeCl_3$ and 3 equivalents of AgOTf, AgOTf (entry 6), and $Cu(OTf)_2$ (entry 8) showed high catalytic activities. Interestingly, the esterification occurred at the carbonyl group of the cyclopentanone framework selectively. Considering the catalytic activities, we decided on indium triflate, $In(OTf)_3$, as the key catalyst.

Indium-Catalyzed Esterification of 2-Phenylethanol with Several Cyclic 1,3-Diketones

First, we investigated the scope and limitations of various 1,3-dicarbonyl compounds using an indium catalyst. In the reaction between 2-acetylcyclopentanone (**1a**) and 2-phenylethanol (**2a**), the yield of 2-phenylethyl 6-oxoheptanoate (**3a**) was improved by adding a catalytic amount of 2,6-di-*tert*-butylpyridine (Table 2, entry 1).[14] In this reaction, the

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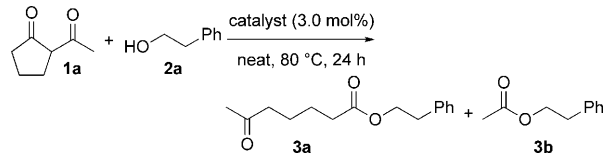
Table 1. Catalytic activities of several catalysts.[a]

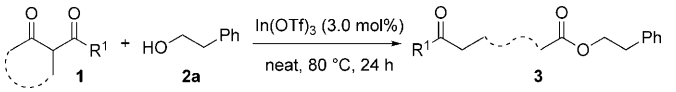


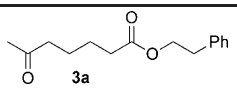
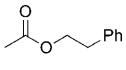
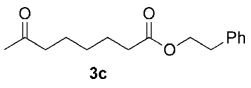
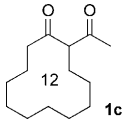
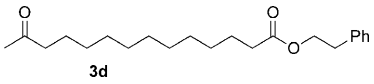
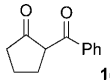
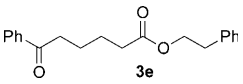
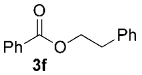
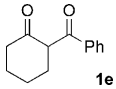
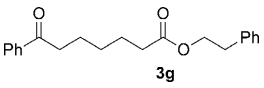
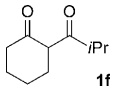
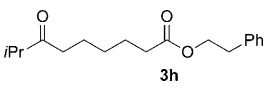
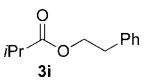
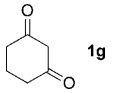
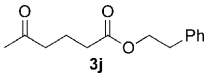
Entry	Catalyst	Yield [%][b] 3a	3b	Entry	Catalyst	Yield [%][b] 3a	3b
1	$Sc(OTf)_3$	77	2	7	$Ni(OTf)_2$[d]	88	4
2	$Fe(OTf)_2$	51	3	8	$Cu(OTf)_2$	94	6
3	$Fe(OTf)_3$[c]	96	4	9	$Zn(OTf)_2$	20	1
4	$FeCl_3$	67	3	10	$In(OTf)_3$	96	4
5	$FeCl_3{\cdot}6H_2O$	54	3	11	$Bi(OTf)_3$	43	1
6	AgOTf	93	3	12	Me_3SiOTf	47	2

[a] **2a** (1.2 equiv). [b] GC yield. [c] $FeCl_3$ (3.0 mol%), AgOTf (9.0 mol%). [d] $NiCl_2$ (3.0 mol%), AgOTf (6.0 mol%).

alcohol attacked the carbonyl group of the cyclopentanone moiety with high selectivity, and 2-phenylethyl acetate (**3b**) was not formed. The reaction of 2-acetylcyclohexanone (**1b**) with 2-phenylethanol (**2a**) in the presence of a catalytic amount of indium(III) triflate under solvent-free conditions at 80 °C for 24 h afforded 2-phenylethyl 7-oxooctanoate (**3c**) and 2-phenylethyl acetate (**3b**) in 85% and 11% yields, respectively (Table 2, entry 2). In contrast, esterification occurred at the acetyl moiety using 2-acetylcyclododecanone (**1c**) as a substrate (Table 2, entry 3). When 2-benzoylcyclopentanone (**1d**) was employed as the substrate, the five-membered ring opened, and only ε-keto ester **3e** was obtained in 92% yield (Table 2, entry 4). 2-Benzoylcyclohexanone (**1e**) and 2-isobutyrylcyclohexanone (**1f**) also produced the corresponding ζ-keto esters **3g** and **3h** in 72% and 78% yields, respectively (Table 2, entries 5 and 6). A cyclic 1,3-diketone, cyclohexane-1,3-dione (**1g**), also underwent the reaction in the presence of $In(OTf)_3$, and yielded δ-keto ester **3j** through a ring opening reaction in 95% yield without any side products (Table 2, entry 7). In contrast to 1,3-diketones, β-keto esters and 1,3-diesters did not undergo the esterification reaction.

Table 2. Indium-catalyzed reaction of cyclic 1,3-dicarbonyl compound **1** with 2-phenylethanol (**2a**).[a]



Entry	1,3-Dicarbonyl compound	Product	Yield [%][b]
1[c]	 1a	 3a	>99
		 3b	0
2	 1b	 3c	85
		3b	11
3	 1c	 3d	7
		3b	80
4	 1d	 3e	92
		 3f	0
5[d]	 1e	 3g	72
		3f	19
6	 1f	 3h	78
		3h	
		 3i	15
7	 1g	 3j	95

[a] **2a** (1.2 equiv). [b] Yield of isolated product. [c] 2,6-Di-*tert*-butylpyridine (5.0 mol%) was used as an additive. [d] **2a** (1.5 equiv), $In(OTf)_3$ (5.0 mol%).

Indium-Catalyzed Esterification of Several Alcohols with 2-Acetylcyclopentanone

Next, the scope of several alcohols was investigated using $In(OTf)_3$ (Table 3). A secondary alcohol **2b** yielded acetate **3k** in 45% yield. By adding 2,6-di-*tert*-butylpyridine as an additive, the reaction proceeded more cleanly, and improved the yield of **3k** to 60% (Table 3, entry 1). In the following investigations, it was found that the addition of a catalytic amount of 2,6-di-*tert*-butylpyridine was effective to obtain the keto esters **3** in good to excellent yields. Allyl alcohol (**2c**) afforded the corresponding allyl ester **3l** in 78% yield (Table 3, entry 2). Alcohols with carbon–carbon double and triple bonds provided the corresponding ε-keto esters, **3m**–**3o** in 84%–91% yields without isomerization of the olefin and acetylene moieties (Table 3, entries 3–5). The corresponding ε-keto esters, **3p**–**3s** were afforded from alcohols that bear bromo, ether, ester, and nitrile groups in good to excellent yields without affecting the functional groups (Table 3, entries 6–9). All reactions occurred only at the carbonyl group of the cyclopentanone framework, and single

Abstract in Japanese:
ルイス酸触媒存在下、環状 1,3-ジケトンとアルコールを反応させることにより、エステル化反応が進行した。インジウム(III)、鉄(III)、銅(II)、および銀(I)の各トリフラートが特に高い触媒活性を示した。この反応は、逆アルドール反応による炭素－炭素結合の切断を経由して進行する。本変換反応は、抗ぜんそく拮抗薬であるセラトロダストの合成にも適用できる。

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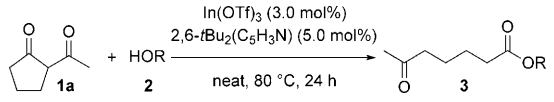
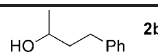
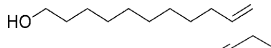
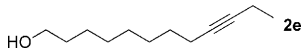
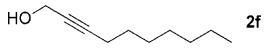
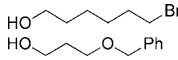
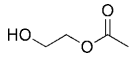
Table 3. Indium-catalyzed reaction of 2-acetylcyclopentanone (**1a**) with several alcohol **2**.[a]



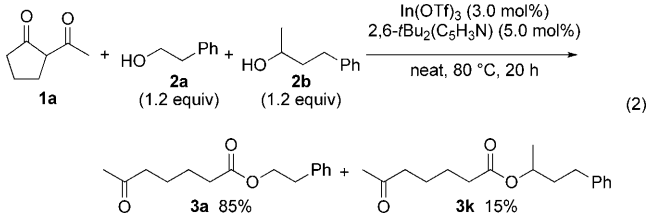
1a 2 3

Entry	Alcohol		Yield [%][b]
1		**3k**	60
2[c]		**3l**	78
3		**3m**	84
4		**3n**	88
5		**3o**	91
6		**3p**	97
7		**3q**	93
8		**3r**	64
9[c]		**3s**	84

[a] **2** (1.2 equiv). [b] Yield of isolated product. [c] **2** (1.5 equiv).

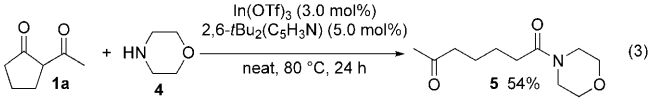
products were formed selectively. However, neither a tertiary alcohol, 1-adamanthanol, nor phenol gave the corresponding esters.

Compounds that have both primary and secondary alcohols, such as sugars, are well known. Treatment of 1,3-diketone **1a** with a 1:1 mixture of primary and secondary alcohols **2a** and **2b** in the presence of $In(OTf)_3$ as a catalyst, selectively produced ester **3a** in 85% yield [Eq. (2)].

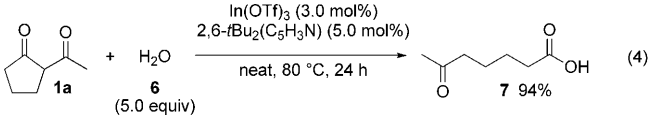


(2)

The reaction could be applied to the synthesis of keto amide and keto carboxylic acid [Eqs. (3) and (4)]. The treatment of 2-acetylcyclopentanone (**1a**) with morpholine (**4**) or water (**6**) gave the corresponding ε-keto amide **5** and ε-keto carboxylic acid **7** in 54% and 94% yields, respectively [Eqs. (3) and (4)]. In these reactions, neither *N*-acetylmorpholine nor acetic acid was formed.



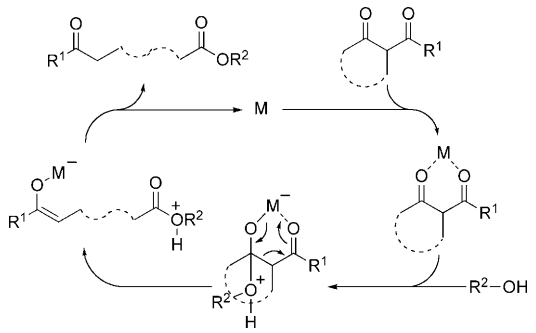
(3)



(4)

Proposed Mechanism

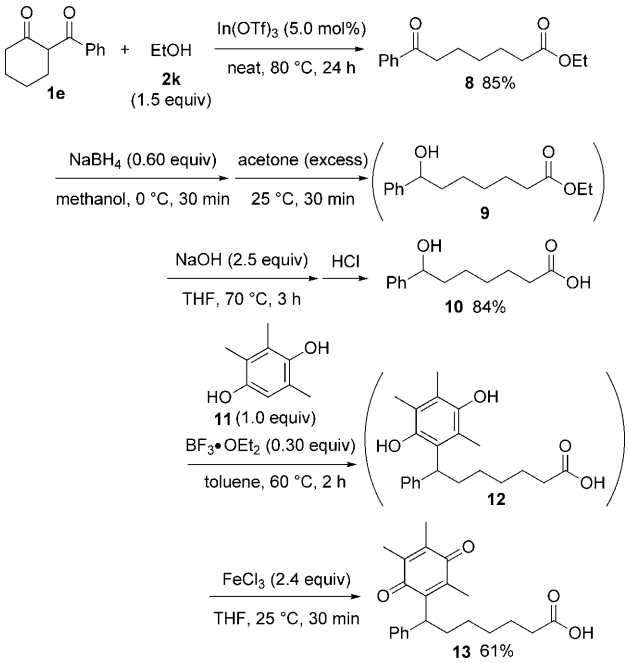
The proposed reaction mechanism is as follows (Scheme 1): (1) coordination of the cyclic 1,3-dicarbonyl compound to a metal center (Lewis acid); (2) nucleophilic attack of an alcohol on the carbonyl group of the cyclic 1,3-dicarbonyl compound; (3) carbon–carbon bond cleavage through a retro aldol-type reaction (ring-opening reaction); (4) the formed enolate is quenched by a proton to give the keto ester and regenerate the metal catalyst. In this reaction, step (3) is important because it leads to the formation of esters, and characterizes the reactivity of the reaction.



Scheme 1. Proposed mechanism for the formation of keto esters.

Synthesis of Seratrodast

Indium-catalyzed synthesis of esters can be applied to the synthesis of seratrodast, which is an antiasthmatic and eicosanoid antagonist (Scheme 2).[15] Treatment of cyclic 1,3-diketone **1e** with ethanol (**2k**) in the presence of indium triflate, $In(OTf)_3$, provided ζ-keto ester **8** in 85% yield.[16] The following procedures have already been reported.[15a] Carboxylic acid **10** was yielded in 84% yield by the reduction of



Scheme 2. Synthesis of seratrodast (**13**).

ζ-keto ester **8** with sodium borohydride and hydrolysis of the formed alcohol **9**. After the condensation of alcohol **10** with 2,3,5-trimethylbenzene-1,4-diol (**11**) in the presence of a boron trifluoride–diethyl ether complex followed by oxidation of **12**, seratrodast (**13**) was obtained in 61% yield.

Conclusions

We have succeeded in the Lewis acid-catalyzed synthesis of esters by regioselective reactions between 1,3-dicarbonyl compounds and alcohols. In particular, indium triflate, iron triflate, copper triflate, and silver triflate were effective to promote the reaction efficiently. The reaction proceeded well in the presence of several functional groups, such as olefins, acetylenes, halides, ethers, esters, and nitriles. The reaction could also be applied to the synthesis of a drug, seratrodast. We hope that this reaction will become a powerful tool in synthetic organic chemistry.

Experimental Section

General

All reactions were carried out under an argon atmosphere. 1,3-Diketones, alcohols, an amine, and $In(OTf)_3$ were purchased from Wako Pure Chemical Industries, Tokyo Kasei Kogyo Co. and Aldrich Co., and used as received.

^1H (400 MHz) and ^{13}C (100 MHz) NMR spectra were recorded using a JEOL JNM-LA400 spectrometer. Proton chemical shifts are reported relative to Me_4Si ($CDCl_3$) at $\delta = 0.00$ ppm or residual solvent peak ($CDCl_3$ at $\delta = 7.26$ ppm). Carbon chemical shifts are reported relative to $CDCl_3$ at $\delta = 77.00$ ppm. IR spectra were recorded on a Nicolet Protégé 460. HR-MS spectra were measured using a Waters LCT (ESI-TOF MS) mass spectrometer.

Structures of esters **3b**, **3f**, and **3i**, and carboxylic acid **7** were determined by comparison with the ^1H and ^{13}C NMR spectra taken from the Aldrich database. The structures of **3a**,[11] **3j**,[11] **8**,[17] **10**,[15a] and **13**[15a] were determined by comparison with the data already reported.

Synthesis

Keto ester 3a. A mixture of 2-acetylcyclopentanone (**1a**, 31.5 mg, 0.250 mmol), 2-phenylethanol (**2a**, 36.6 mg, 0.300 mmol), $In(OTf)_3$ (4.2 mg, 0.0075 mmol), and 2,6-di-*tert*-butylpyridine (2.4 mg, 0.013 mmol) was stirred at 80 °C for 24 h. The product was isolated by column chromatography on silica gel to give **3a** (62.1 mg, 0.250 mmol, >99%).

2-Phenylethyl 7-oxooctanoate (3c). IR (nujol): $\tilde{\nu} = 1740$, 1165, 910, 737 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 1.22$–1.32 (m, 2H), 1.52–1.63 (m, 4H), 2.13 (s, 3H), 2.28 (t, $J = 7.5$ Hz, 2H), 2.40 (t, $J = 7.4$ Hz, 2H), 2.93 (t, $J = 7.0$ Hz, 2H), 4.29 (t, $J = 7.0$ Hz, 2H), 7.20–7.25 (m, 3H), 7.28–7.32 ppm (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 23.2$, 24.5, 28.4, 29.7, 33.9, 35.0, 64.6, 76.7, 126.4, 128.3, 128.7, 137.7, 173.3, 208.7 ppm; HRMS (ESI): *m/z* (%) calcd for $C_{16}H_{22}O_3Na$: 285.1467 $[M+Na]^+$; found: 285.1470.

2-Phenylethyl 13-oxotetradecanoate (3d). IR (nujol): $\tilde{\nu} = 1744$, 1720, 1165 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 1.22$–1.32 (m, 10H), 1.51–1.62 (m, 4H), 2.13 (s, 3H), 2.28 (t, $J = 7.5$ Hz, 2H), 2.41 (t, $J = 7.4$ Hz, 2H), 2.94 (t, $J = 7.0$ Hz, 2H), 4.29 (t, $J = 7.0$ Hz, 2H), 7.20–7.24 (m, 3H), 7.28–7.32 ppm (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 23.9$, 24.9, 29.1, 29.20, 29.23, 29.38, 29.40, 29.42, 29.5, 29.8, 34.3, 35.2, 43.8, 64.7, 126.5, 128.5, 129.0, 137.9, 173.8, 209.3 ppm; HRMS (ESI): *m/z* (%) calcd for $C_{22}H_{34}O_3Na$: 369.2406 $[M+Na]^+$; found: 369.2407.

2-Phenylethyl 6-oxo-6-phenylhexanoate (3e). IR (nujol): $\tilde{\nu} = 1744$, 1693, 1169, 972, 907, 737 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 1.66$–1.79 (m, 4H), 2.35 (t, $J = 7.0$ Hz, 2H), 2.92–2.98 (m, 4H), 4.29 (t, $J = 7.0$ Hz, 2H), 7.20–7.22 (m, 3H), 7.27–7.30 (m, 2H), 7.46 (t, $J = 7.6$ Hz, 2H) , 7.56 (t, $J = 7.6$ Hz, 1H), 7.94 ppm (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta =$ 23.4, 24.4, 33.9, 37.9, 64.6, 126.4, 127.8, 128.3, 128.4, 128.7, 132.8, 136.8, 173.1, 199.5 ppm; HRMS (ESI): *m/z* (%) calcd for $C_{20}H_{22}O_3Na$: 333.1467 $[M+Na]^+$; found: 333.1476.

2-Phenylethyl 7-oxo-7-phenylheptanoate (3g). IR (nujol): $\tilde{\nu} = 1728$, 1092, 976, 899, 775, 755, 687 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): $\delta = 1.34$–1.42 (m, 2H), 1.61–1.69 (m, 2H), 2.31 (t, $J = 7.5$ Hz, 2H), 2.90–2.98 (m, 4H), 4.29 (t, $J = 7.0$ Hz, 2H), 7.20–7.24 (m, 3H), 7.26–7.31 (m, 2H) 7.46 (t, $J =$ 7.3 Hz, 2H) , 7.56 (t, $J = 7.3$ Hz, 1H), 7.95 ppm (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz): $\delta = 23.8$, 24.7, 28.7, 34.0, 35.0, 38.2, 64.6, 126.4, 127.9, 128.4, 128.5, 128.8, 132.8, 136.9, 137.7, 173.5, 200.0 ppm; HRMS (ESI): *m/z* (%) calcd for $C_{20}H_{22}O_3Na$: 347.1623 $[M+Na]^+$; found: 347.1633.

2-Phenylethyl 8-methyl-7-oxononanoate (3h). IR (nujol): $\tilde{\nu} = 1740$, 1717, 1169, 999, 748 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 1.08$ (d, $J = 6.9$ Hz, 6H), 1.23–1.30 (m, 2H), 1.51–1.63 (m, 4H), 2.28 (t, $J = 7.5$ Hz, 2H), 2.42 (t, $J = 7.3$ Hz, 2H), 2.54–2.61 (m, 1H), 2.93 (t, $J = 7.0$ Hz, 2H), 4.28 (t, $J =$ 7.0 Hz, 2H), 7.21–7.24 (m, 3H), 7.28–7.32 ppm (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz): $\delta = 18.2$, 23.3, 24.7, 28.7, 34.1, 35.1, 40.0, 40.8, 64.7, 126.5, 128.5, 128.9, 137.8, 173.6, 214.7 ppm; HRMS (ESI): *m/z* (%) calcd for $C_{20}H_{22}O_3Na$: 313.1780 $[M+Na]^+$; found: 313.1789.

1-Methyl-3-phenylpropyl 6-oxoheptanoate (3k). IR (nujol): $\tilde{\nu} = 1736$, 1175, 1130, 1082, 1051, 962, 746, 698 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 1.24$ (d, $J = 6.3$ Hz, 3H), 1.55–1.70 (m, 4H), 1.74–1.86 (m, 1H), 1.86–1.99 (m, 1H), 2.13 (s, 3H), 2.29 (t, $J = 6.9$ Hz, 2H), 2.45 (t, $J = 6.9$ Hz, 2H), 2.54–2.72 (m, 2H), 4.94 (tq, $J = 6.3$ and 6.6 Hz, 1H), 7.11–7.22 (m, 3H), 7.28 ppm (t, $J = 7.2$ Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 20.0$, 23.2, 24.5, 29.9, 31.8, 34.3, 37.6, 43.2, 70.4, 125.9, 128.3, 128.4, 141.5, 173.0, 208.5 ppm; HRMS (ESI): *m/z* (%) calcd for $C_{16}H_{22}O_3Na$: 299.1623 $[M+Na]^+$; found: 299.1629.

Allyl 6-oxoheptanoate (3l). IR (nujol): $\tilde{\nu} = 1744$, 1724, 1144, 984, 930 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 1.51$–1.75 (m, 4H), 2.13 (s, 3H), 2.34 (t, $J = 6.9$ Hz, 2H), 2.45 (t, $J = 6.6$ Hz, 2H), 4.56 (d, $J = 5.7$ Hz, 2H), 5.26 (dd, $J = 10.5$ and 17.4 Hz, 2H), 5.81–6.01 ppm (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 23.2$, 24.3, 29.9, 34.0, 43.2, 65.0, 118.2, 132.2, 173.0, 208.5 ppm; HRMS (ESI): *m/z* (%) calcd for $C_{10}H_{16}O_3Na$: 207.0997 $[M+Na]^+$; found: 207.0990.

10-Undecenyl 6-oxoheptanoate (3m). IR (nujol): $\tilde{\nu} = 2361$, 2341, 1740, 1722, 1171, 1146, 1084, 964, 908, 735 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 1.16$–1.42 (m, 14H), 1.50–1.66 (m, 4H), 2.02 (q, $J = 6.9$ Hz, 2H), 2.12 (s, 3H), 2.30, (t, $J = 6.9$ Hz, 2H), 2.44 (t, $J = 6.6$ Hz, 2H), 4.04 (t, $J =$ 6.6 Hz, 2H), 4.94 (dd, $J = 10.2$ and 17.1 Hz, 2H), 5.71–5.88 ppm (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 23.2$, 24.4, 25.9, 28.6, 28.9, 29.0, 29.2, 29.3, 29.4, 29.8, 33.8, 34.0, 43.2, 64.5, 114.1, 139.2, 173.5, 208.5 ppm; HRMS (ESI): *m/z* (%) calcd for $C_{18}H_{32}O_3Na$: 319.2249 $[M+Na]^+$; found: 319.2236.

9-Dodecynyl 6-oxoheptanoate (3n). IR (nujol): $\tilde{\nu} = 2359$, 2341, 1738, 1720, 1238, 1173, 1146, 1082 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 1.09$ (t, $J = 6.6$ Hz, 3H), 1.21–1.39 (m, 8H), 1.39–1.52 (m, 2H), 1.52–1.69 (m, 6H), 2.05–2.21 (m, 7H), 2.24–2.35 (m, 2H), 2.39–2.50 (m, 2H), 4.03 ppm (t, $J = 5.9$ Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 12.4$, 14.3, 18.6, 23.1, 24.4, 25.8, 28.6, 28.7, 28.95, 29.02, 29.1, 29.8, 34.0, 43.2, 64.5, 79.4, 81.6, 173.4, 208.5 ppm; HRMS (ESI): *m/z* (%) calcd for $C_{19}H_{32}O_3Na$: 331.2249 $[M+Na]^+$; found: 331.2247.

2-Decynyl 6-oxoheptanoate (3o). IR (nujol): $\tilde{\nu} = 1746$, 1722, 1148, 1082, 966 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 0.86$ (t, $J = 6.8$ Hz, 3H), 1.19–1.40 (m, 8H), 1.49 (quint, $J = 6.6$ Hz, 2H), 1.55–1.68 (m, 4H), 2.12 (s, 3H), 2.15–2.25 (m, 2H), 2.34 (t, $J = 6.9$ Hz, 2H), 2.43 (t, $J = 6.9$ Hz, 2H), 4.64 ppm (t, $J = 2.1$ Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 14.0$, 18.7, 22.6, 23.1, 24.2, 28.4, 28.7, 28.8, 29.8, 31.7, 33.8, 43.2, 52.7, 73.9, 87.7, 172.7, 208.4 ppm; HRMS (ESI): *m/z* (%) calcd for $C_{17}H_{28}O_3Na$: 303.1936 $[M+Na]^+$; found: 303.1935.

6-Bromohexyl 6-oxoheptanoate (3p). IR (nujol): $\tilde{\nu} = 2361$, 2341, 1740, 1169, 1080, 972, 644, 563 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 1.27$–1.39

(m, 2H), 1.39–1.50 (m, 2H), 1.50–1.66 (m, 6H), 1.84 (quint, $J=7.2$ Hz, 2H), 2.10 (s, 3H), 2.28 (t, $J=6.9$ Hz, 2H), 2.42 (t, $J=6.6$ Hz, 2H), 3.38 (t, $J=6.9$ Hz, 2H), 4.03 ppm (t, $J=6.9$ Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=23.1$, 24.3, 25.1, 27.7, 28.4, 29.8, 32.5, 33.6, 34.0, 43.2, 64.1, 173.3, 208.4 ppm; HRMS (ESI): *m/z* (%) calcd for $C_{16}H_{22}O_3Na$: 329.0728 $[M+Na]^+$; found: 329.0720.

3-Benzyloxypropyl 6-oxoheptanoate (3q). IR (nujol): $\tilde{\nu}=1742$, 1724, 698 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=1.53$–1.65 (m, 4H), 1.93 (quint, $J=6.3$ Hz, 2H), 2.12 (s, 3H), 2.28 (t, $J=6.9$ Hz, 2H), 2.43 (t, $J=6.6$ Hz, 2H), 3.54 (t, $J=6.3$ Hz, 2H), 4.18 (t, $J=6.6$ Hz, 2H), 4.50 (s, 2H), 7.24–7.39 ppm (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=23.1$, 24.3, 29.0, 29.8, 34.0, 43.2, 61.6, 66.6, 72.9, 126.7, 127.6, 128.3, 138.3, 173.3, 208.4 ppm; HRMS (ESI): *m/z* (%) calcd for $C_{17}H_{24}O_4Na$: 315.1572 $([M+Na])^+$; found: 315.1580.

2-Acetoxyethyl 6-oxoheptanoate (3r). IR (nujol): $\tilde{\nu}=2359$, 2341, 1747, 1717, 1232, 1146, 1067, 962, 723, 667 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=1.53$–1.67 (m, 4H), 2.06 (s, 3H), 2.12 (s, 3H), 2.29–2.37 (m, 2H), 2.39–2.48 (m, 2H), 4.25 ppm (s, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=20.8$, 23.0, 24.2, 29.8, 33.8, 43.2, 62.0, 62.1, 170.7, 173.1, 208.4 ppm; HRMS (ESI): *m/z* (%) calcd for $C_{11}H_{18}O_5Na$: 253.1052 $[M+Na]^+$; found: 253.1047.

2-Cyanoethyl 6-oxoheptanoate (3s). IR (nujol): $\tilde{\nu}=1746$, 1703, 1497, 1236, 1205, 1146, 1088, 1055, 1032, 845, 748, 698 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=1.49$–1.69 (m, 4H), 2.07 (s, 3H), 2.31 (t, $J=6.9$ Hz, 2H), 2.40 (t, $J=6.6$ Hz, 2H), 2.66 (t, $J=6.3$ Hz, 2H), 4.21 ppm (t, $J=6.3$ Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=17.8$, 22.8, 24.0, 30.0, 33.4, 42.9, 58.4, 116.7, 172.5, 208.2 ppm; HRMS (ESI): *m/z* (%) calcd for $C_{10}H_{15}NO_3Na$: 220.0950 $[M+Na]^+$; found: 220.0947.

1-(4-Morpholinyl)heptane-1,6-dione (5). IR (nujol): $\tilde{\nu}=3503$, 2341, 1713, 1636, 1234, 1115, 1034, 964, 845 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=$ 1.50–1.67 (m, 4H), 2.09 (s, 3H), 2.27 (t, $J=6.9$ Hz, 2H), 2.42 (t, $J=$ 6.6 Hz, 2H), 3.34–3.48 (m, 2H), 3.49–3.59 (m, 2H), 3.59–3.70 ppm (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=23.3$, 24.5, 29.8, 32.7, 41.8, 43.3, 45.8, 66.5, 66.8, 171.2, 208.6 ppm; HRMS (ESI): *m/z* (%) calcd for $C_{11}H_{19}NO_3Na$: 236.1263 $[M+Na]^+$; found: 236.1273.

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