Synthesis of Lactate Derivatives via Reductive Radical Addition to α-Oxyacrylates

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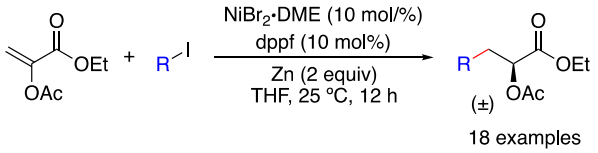
Graphical Abstract



ABSTRACT

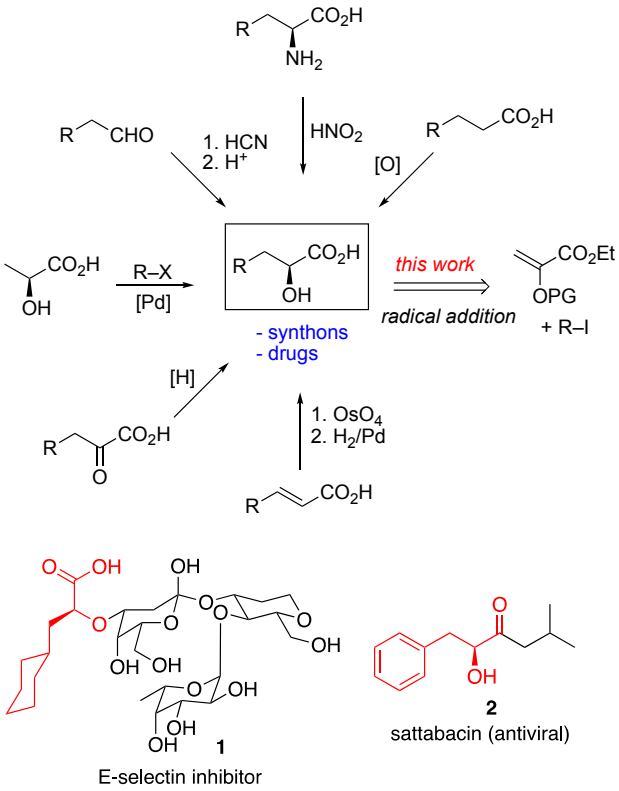
Lactate derivatives are important synthetic precursors to a variety of pharmaceutical products. Previously reported methods to prepare lactates require multiple steps or have limited scopes. Herein, we report a Ni-catalyzed reductive addition of a variety of alkyl iodides to α-oxyacrylates to afford substituted lactates. Exploring the scope of radical acceptors reveals that electron-deficient alkenes, ranging from cyclohexenone to *para*-caboxystyrene, undergo efficient coupling with alkyl iodides. This method represents an alternative strategy access lactate derivatives.

1. Introduction

Lactic acid and its derivatives are synthons to a large variety of pharmaceutical products.[1] For instance, cyclohexyl lactic acid is a building block for selective E-selectin inhibitor **1** (Scheme 1).[2] Phenyllactic acid is a precursor to the natural product sattabacin **2**, which shows

antiviral activity.[3] While lactic acid is manufactured by microbial fermentation, accessing its substituted variants requires multiple steps. With some methods, the scope of accessible lactate variants is dependent on available amino acids. Previous methods for preparing substituted lactates include α-hydroxylation of acids,[4] diazotization of amino acids,[5] nucleophilic addition of cyanide to aldehydes,[2] C–H activation of lactic acid,[6] hydrogenation of the β-ketoacids,[7] and dihydroxylation of acrylic acids followed by reduction (Scheme 1).[2]

Scheme 1. Strategies for Preparing Lactate Derivatives



The addition of radicals to alkenes represents a widely applied approach for preparing complex molecules from simple precursors.[8-11] Conventional radical initiators include peroxides, azo compounds, tin hydrides, and SmI_2.[12] However, by-products generated from these stoichiometric reagents restrict scale-up processes. Transition metal catalysts, such as Fe,[13] Ti[14] and Cu,[15] could enable sustainable catalytical radical addition to alkenes. Ni has been

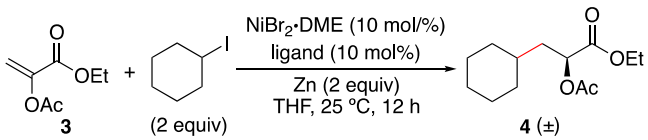
characterized to catalytically initiate radical formation from aryl[16] and alkyl halides.[17,18] Recently, reports from Shenvi,[19] Weix[20], our group[21], and others[22,23,24,25,26] reveal that radicals initiated by Ni catalysts can undergo addition to alkenes. Herein, we demonstrate that Ni-catalyzed radical addition can be applied to the preparation of lactate derivatives via reductive coupling of alkyl iodides to α-oxyacrylates. The use of reducing conditions with alkyl halides as the coupling partners avoids stoichiometric organometallic reagents in conventional cross-coupling reactions and improves functional group tolerance.[27]

2. Results and Discussion

We examined reaction conditions for the postulated reductive addition reaction using α-acetoxyacrylate ester **3** as the model substrate and iodocyclohexane as the coupling partner (Table 1). α-Acetoxyacrylate ester **3** could be readily prepared by refluxing ethyl pyruvate in acetic anhydride in the presence of catalytic acid. With a common catalyst precursor, $NiBr_2 \cdot DME$,[28] we explored various ligands in the presence of HFIP (hexafluoroisopropanol) as the proton source. While the monodentate triphenylphosphine gave trace product **4** (entry 1), bidentate ligands, including dppe (1,2-bis(diphenylphosphino)ethane), dppp (1,3-bis(diphenylphosphino)propane), dppb (1,4-bis(diphenylphosphino)propane, dpppe (1,5-bis(diphenylphosphino)pentane), and dppf (1,1'-bis(diphenylphosphino)ferrocene) led to good conversions (entries 2-6). In particular, ligands with large bite angles,[29] such as dppb and dppf, gave the highest yields. *N*-ligands are commonly used in Ni catalysis. The use of bpy (bipyridine) afforded **4** in 40% yield (entry 7). Proton sources with higher pK_as than HFIP decreased the yields (entries 8-10). The use of Mn as the reductant led to formation of **4** in 38% yield (entry 11), but other reductants, including In, Mg, and Fe, led to trace product. It is noteworthy that the

reaction does not require air-free conditions. Repeating the standard reaction in air generated **4** in 70% NMR yield and 69% isolated yield (Table S3).

Table 1. Catalyst Optimization



Entry	Ligand	Proton Source	Yield (%)[a]
1	PPh_3	HFIP	1
2	dppe	HFIP	62
3	dppp	HFIP	65
4	dppb	HFIP	78 (73)[b]
5	dpppe	HFIP	62
6	**dppf**	**HFIP**	**79 (76)[b]**
7	bpy	HFIP	40
8	dppf	*t*BuOH	42
9	dppf	*i*PrOH	31
10	dppf	H_2O	24
11	dppf[c]	HFIP	38

[a] GC yield with mesitylene as the internal standard.

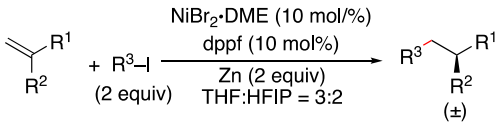
[b] Isolated yields in parenthesis.

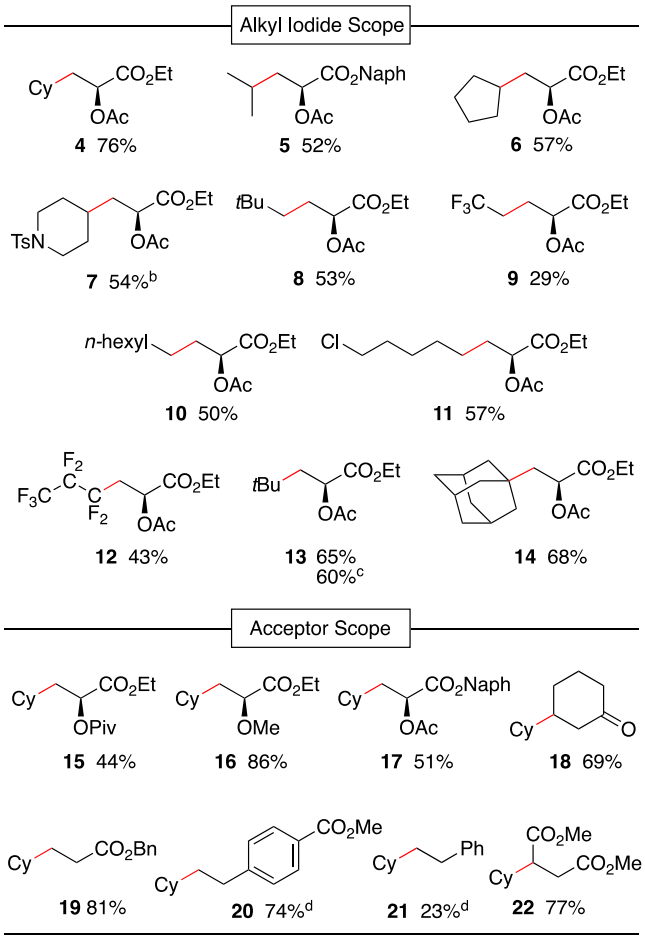
[c] Mn was used as the reductant in place of Zn.

With the optimized conditions, $NiBr_2$·DME in combination with dppf and Zn, we explored the scope of alkyl iodides (Table 2). A vareity of secondary alkyl iodides undergo addition to **3**, as well as primary and tertiary alkyl iodides, to afford lactate derivatives **4**-**14**. The success of different electrophiles suggests that the conditions are relatively insensitive to the sterics of the alkyl group. In the formation of **13**, *t*BuI could be replaced by *t*BuBr to generate **13** in comparable yields, but other alkyl bromides are inactive under these conditions. When both a chloride and an iodide are present in the substrate, the iodide reacts preferentially, leaving the chloride intact in the formation of **11**.

Subsequently, we evaluated different alkene acceptors. Replacing the acetate of **3** with the bulkier pivalate led to formation of **15** in lower yield. A methyl protected α-oxyacrylate underwent efficient addition with CyI to give **16** in 86% yield. The α-oxy group, despite providing a captodative effect,[30] is not essential for obtaining reactivity. Iodocyclohexane added to cyclohexanone and benzyl acrylate to give **18** and **19**, respectively. Methyl 4-vinylbenzoate underwent cyclohexyl addition to afford **20** in 74% yield, but parent styrene produced the addition product in 23% yield with dicyclohexylation as the major-byproduct. These results are consistent with the preference of the nucleophilic alkyl radicals to add to electron-deficient alkenes.

Table 2. Scopes of Alkyl Iodides and Alkene Acceptors[a]





[a] Isolated yields. Reaction conditions: 0.2 mmol olefin, 0.3 mL THF, 0.2 mL HFIP, 25 °C, 12 hrs.

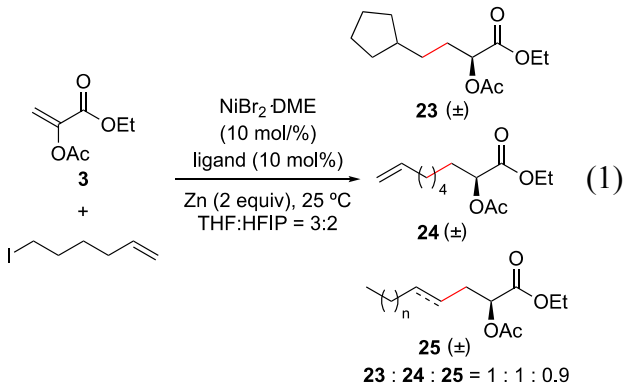
[b] 1 equiv iodide.

[c] *t*BuBr instead of *t*BuI.

[d] NMR yield with mesitylene as the internal standard.

We then carried out experiments to probe whether a radical intermediate is formed. Addition of one equivalent TEMPO to the coupling of **3** with iodocyclohexane under standard conditions completely inhibited the reactivity. The addition of 6-iodo-1-hexene to **3** led to a mxiture of **23**, **24**, and **25** in the ratio of 1:1:0.9 (eq 1). The internal alkene product **25** was characterized by ^{1}H NMR spectroscopy, but the precise position of the internal double bond was not determined. The formation of **23** may suggest a hexenyl radical intermediate that underwent cyclization at the rate

of 10^5 s^{-1},[31] but a Ni-mediated insertion pathway cannot be ruled out. Even though a radical is formed, Ni may only serve as an initiator and the reaction may proceed through a radical chain mechanism via S_H2 iodide atom transfer.[32]



(1)

3. Conclusion

In summary, we have developed a Ni-catalyzed reductive coupling of alkyl iodides with electron-deficient alkenes, including α-oxyacrylates. This reaction can be readily applied to preparing lactate derivatives. Based on previous studies of Ni-catalyzed cross-coupling reactions, it is reasonable to propose that Ni initiates radical formation from the alkyl iodide, which then adds to the electron-deficient alkenes. However, current data is insufficient to distinguish radical pathways from Ni-mediated addition.

4. Experimental Section

All reactions were carried out under dry nitrogen. Solvents (free of inhibitors) were dried and deoxygenated by passing through alumina in a solvent purification system, other than HFIP which was used as received. Chloroform-*d* was purchased from Cambridge Isotope Laboratories. Ethyl 2-acetoxyacrylate (**3**) and ethyl 2-methoxyacrylate were synthesized according to literature procedures.[33,34] ^1H and ^{13}C NMR spectra were recorded on a Bruker 400 MHz Avance spectrometer. The chemical shifts (δ) are given in parts per million and referenced to residual solvent peaks. The following abbreviations were used to describe multiplicities: s = singlet, d =

doublet, t = triplet, q = quartet, sept = septet, m = multiplet, br = broad. IR spectra were recorded on a Nicolet 6700 FT-IR spectrometer. High resolution mass spectra (HRMS) were collected on an Agilent 6224 TOF LC/MS. Reactions were monitored by thin-layer chromatography (TLC) on Merck TLC silica gel 60 F254 plates and compounds were visualized by UV light (254 nm) or KMnO4 staining. Column chromatography was performed on Merck silica gel 60 (0.015−0.040 mm).

4.1. General Procedure for the Alkylation Reaction

A 2 mL crimp-top GC vial was charged with NiBr2(DME) (6.2 mg, 0.02 mmol, 0.1 equiv), dppf (11 mg, 0.02 mmol, 0.1 equiv), and activated Zn powder[35] (26.2 mg, 0.4 mmol, 2 equiv). The vial was crimped shut and the olefin (0.2 mmol, 1 equiv) was injected through the septum as a solution in 0.3 mL THF followed by 0.2 mL HFIP. The iodide (1-2 equiv) was then added (as a solution in THF, if solid) and the vial was shaken at 1000 rpm for 12 hours at 25 °C. The reaction was diluted with EtOAc and quenched by the addition of 1 M HCl (aq). The aqueous phase was extracted with three portions of EtOAc. The combined organic phase was then passed through a plug of silica. An aliquot of the organic phase was used for GC or GC/MS analysis with mesitylene as an internal standard. Solvent was removed and the mixture was purified by chromatography on silica gel with EtOAc/hexane as the eluent to give the products as colorless oils.

4.2. Preparation of $NiBr_2$·DME

The thimble of a 250 mL Soxhlet apparatus was charged with 10 g anhydrous $NiBr_2$. The apparatus was flushed with N_2, the boiling flask was charged with 150 mL 1,2-DME, and the condensor was attached. The solvent was heated to reflux and the solid was extracted for 1 week, under N_2. Occasionally, the solid mass of $NiBr_2$ was broken up with a spatula. Excess solvent

was removed by distillation under vacuum and the resulting orange solid was dried under vacuum overnight. The $NiBr_2$·DME (8.5 g, 63%) was stored in a N_2-filled glovebox. A higher yield can be obtained by allowing the extraction to run for a longer period of time, as some $NiBr_2$ remains in the thimble after one week.

4.3. Substrate Synthesis

4.3.1. Ethyl 2-(pivaloyloxy)acrylate

A 100 mL RBF was charged with pivalyl chloride (2.2 mL, 18 mmol, 4 equiv), Et_3N (2.5 mL, 18 mmol, 4 equiv), and 20 mL of DCM under N_2. The solution was cooled to 0 °C and ethyl pyruvate (0.5 mL, 4.5 mmol, 1 equiv) was added dropwise. The reaction was stirred at 0 °C for one hour, then at room temperature overnight. The mixture was quenched with H_2O and the phases were separated. The aqueous phase was extracted with three portions of DCM. The combined organic phase was washed with 1 M $HCl_{(aq)}$, then saturated $NaHCO_{3\,(aq)}$, then brine, then dried over $MgSO_4$. Solvent was removed and the residue was purified via column chromatography on silica gel with 10:1 hexane:EtOAc as the eluent. The product was obtained as a colorless oil (760 mg, 84%). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 6.03 (d, *J* = 1.6 Hz, 1H), 5.41 (d, *J* = 1.6 Hz, 1H), 4.24 (q, *J* = 7.1 Hz, 2H), 1.32 (t, *J* = 7.1 Hz, 3H), 1.26 (s, 9H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 176.8, 161.7, 145.3, 113.5, 61.8, 39.0, 26.7, 14.2. TLC: R_f = 0.42 (10:1 hexane:EtOAc). HRMS (APCI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{10}H_{17}O_4$ 201.1121, found 201.1130.

4.3.2. Ethyl 2-(naphthalen-2-yloxy)acrylate

A 25 mL RBF was charged with naphthalen-2-yl 2-oxopropanoate (1.00 g, 4.67 mmol, 1 equiv), TsOH-H_2O (80 mg, 0.46 mmol, 0.1 equiv), and 12 mL of Ac_2O under N_2. The solution was heated to reflux for 48 hours. The reaction was cooled to room temperature and quenched

with H_2O. The reaction mixture was extracted three times with EtOAc. The combined organic phase was washed with water then brine and dried over Na_2SO_4. Solvent was removed and the residue was purified via column chromatography on silica gel with 10:1 hexane:EtOAc as the eluent. The product was obtained as a colorless oil (915 mg, 77%). ^{1}H NMR (400 MHz, Chloroform-*d*): δ 7.87 (d, J = 8.3 Hz, 1H, overlap), 7.83 (ddd, *J* = 12.9 ,8.3, 2.3 Hz, 2H, overlap), 7.62 (d, J = 2.3 Hz, 1H), 7.55 – 7.45 (m, 2H), 7.35 – 7.21 (dd, J = 8.3, 2.3 Hz 1H, overlap), 6.32 (d, *J* = 2.0 Hz, 1H), 5.68 (d, *J* = 2.0 Hz, 1H), 2.29 (s, 1H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 169.2, 160.4, 148.1, 144.4, 133.8, 131.8, 129.7, 127.9, 127.9, 126.8, 126.1, 120.8, 118.7, 115.6, 20.6. TLC: R_f = 0.24 (10:1 hexane:EtOAc). HRMS (APCI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{15}H_{13}O_4$ 257.0808, found 257.0808.

4.4. Characterization

4.4.1. Ethyl 2-acetoxy-3-cyclohexylpropanoate (**4**)

^{1}H NMR (400 MHz, Chloroform-*d*): δ 5.03 (dd, *J* = 9.5, 4.2 Hz, 1H), 4.19 (q, *J* = 7.1 Hz, 2H), 2.14 (s, 3H), 1.84 – 1.59 (m, 7H), 1.51 – 1.36 (m, 1H), 1.27 (t, *J* = 7.1 Hz, 3H), 1.24 – 1.05 (m, 3H), 0.94 (m, 2H). ^{13}C NMR (101 MHz, Chloroform-*d*): δ 171.1, 170.8, 70.8, 61.4, 38.6, 34.0, 33.8, 32.4, 26.5, 26.3, 26.1, 20.9, 14.3. TLC: R_f = 0.33 (8:1 hexane:EtOAc). HRMS (APCI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{13}H_{23}O_4$ 243.1591, found 243.1601.

4.4.2. Naphthalen-2-yl 2-acetoxy-4-methylpentanoate (**5**)

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.86 (d, J = 8.3 Hz, 1H, overlap), 7.86 – 7.80 (ddd, *J* = 12.4, 7.3, 2.3 Hz, 2H, overlap), 7.58 (d, J = 2.3 Hz, 1H), 7.54 – 7.45 (m, *J* = 12.4, 2.3 Hz, 2H), 7.26 – 7.24 (dd, J = 7.3, 2.3 Hz, 1H, overlap), 5.27 (dd, *J* = 9.5, 4.0 Hz, 1H), 2.20 (s, 3H), 2.07 – 1.79 (m, 3H), 1.05 (dd, *J* = 12.5, 6.2 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.9, 169.8, 148.0, 133.8, 131.7, 129.7, 127.9, 127.8, 126.8, 126.0, 120.9, 118.5, 71.4, 39.9, 24.9, 23.2, 21.8, 20.8.

TLC: R_f = 0.23 (8:1 hexane:EtOAc). HRMS (APCI-TOF) *m/z*: $[M+NH_4]^+$ calcd for $C_{18}H_{24}NO_4$ 318.1700, found 318.1711.

4.4.3. Ethyl 2-acetoxy-3-cyclopentylpropanoate (**6**)

^{1}H NMR (400 MHz, Chloroform-*d*) δ 4.98 (dd, *J* = 8.7, 4.4 Hz, 1H), 4.20 (q, *J* = 7.1 Hz, 2H), 2.14 (s, 3H), 2.13 – 1.84 (m, 2H), 1.85 – 1.76 (m, 2H), 1.67 – 1.60 (m, 2H), 1.60 – 1.47 (m, 2H), 1.38 – 1.14 (t, J = 7.1 Hz, 3H), 1.19 – 1.07 (m, 2H), 0.88 (m, *J* = 1.2 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.8, 170.8, 72.4, 61.4, 37.3, 36.6, 33.0, 32.4, 25.3, 25.0, 20.9, 14.3. TLC: 0.27 R_f = 0.27 (20:1 hexane:EtOAc). HRMS (APCI-TOF) *m/z*: $[M+Na]^+$ calcd for $C_{12}H_{20}NaO_4$ 251.1254, found 251.1263.

4.4.4. Ethyl 2-acetoxy-3-(1-tosylpiperidin-4-yl)propanoate (**7**)

^{1}H NMR (400 MHz, Chloroform-*d*): δ 7.63 (d, *J* = 7.8 Hz, 2H), 7.31 (d, *J* = 7.8 Hz, 2H), 4.98 (dd, *J* = 8.9, 3.7 Hz, 1H), 4.17 (q, *J* = 7.1 Hz, 2H), 3.77 (d, *J* = 11.0 Hz, 2H), 2.43 (s, 3H), 2.21 (q, *J* = 10.3 Hz, 2H), 2.08 (s, 3H), 1.87 – 1.63 (m, 4H), 1.34 (m, 3H), 1.24 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, Chloroform-*d*): δ 170.5, 170.3, 143.6, 133.2, 129.7, 127.9, 70.3, 61.6, 46.4, 46.3, 37.2, 31.9, 31.8, 30.9, 21.7, 20.8, 14.2. TLC: R_f = 0.33 (6:1 hexane:EtOAc). HRMS (APCI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{19}H_{28}NO_6S$ 398.1632, found 398.1629.

4.4.5. Ethyl 2-acetoxy-5,5-dimethylhexanoate (**8**)

^{1}H NMR (400 MHz, Chloroform-*d*): δ 4.97 – 4.89 (dd, *J* = 6.5, 5.5 Hz 1H), 4.20 (qd, *J* = 7.2, 3.1 Hz, 2H), 2.13 (s, 3H), 1.88 – 1.69 (m, 2H), 1.27 (td, *J* = 7.2, 3.1 Hz, 5H), 0.88 (s, 9H). ^{13}C NMR (101 MHz, Chloroform-*d*): δ 170.8, 170.5, 73.1, 61.4, 39.1, 30.2, 29.3, 26.7, 20.8, 14.3. TLC: R_f = 0.33 (10:1 hexane:EtOAc). HRMS (APCI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{12}H_{23}O_4$ 231.1591, found 231.1602.

4.4.6. Ethyl 2-acetoxy-5,5,5-trifluoropentanoate (**9**)

^{1}H NMR (400 MHz, Chloroform-*d*) δ 5.04 (dd, *J* = 7.4, 4.2 Hz, 1H), 4.23 (q, *J* = 7.1 Hz, 2H), 2.36 – 2.02 (m, 4H), 2.17 (s, 3H), 1.29 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 170.3, 169.3, 126.5 (q, *J* = 276 Hz), 70.7, 61.9, 30.0 (q, *J* = 30 Hz), 24.0 (q, *J* = 3.3 Hz), 20.7, 14.2. TLC: R_f = 0.36 (10:1 hexane:EtOAc). HRMS (APCI-TOF) *m/z*: $[M\text{-}H_2O]^+$ calcd for $C_9H_{11}F_3O_3$ 224.0655, found 224.0648.

4.4.7. Ethyl 2-acetoxydecanoate (**10**)

^{1}H NMR (400 MHz, Chloroform-*d*) δ 4.95 (t, *J* = 6.4 Hz, 1H), 4.20 (qd, *J* = 7.1, 1.1 Hz, 2H), 2.13 (s, 3H), 1.85 – 1.74 (m, 2H), 1.41 (s, 2H), 1.27 (t, *J* = 7.1 Hz, 13H), 0.87 (t, *J* = 6.7 Hz, 3H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 170.8, 170.6, 72.6, 61.4, 32.0, 31.2, 29.5, 29.3, 29.3, 25.2, 22.8, 20.8, 14.3, 14.2. TLC: R_f = 0.50 (10:1 hexane:EtOAc). HRMS (APCI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{14}H_{27}O_4$ 259.1904, found 259.1913.

4.4.8. Ethyl 2-acetoxy-8-chlorooctanoate (**11**)

^{1}H NMR (400 MHz, Chloroform-*d*): δ 4.96 (t, *J* = 6.4 Hz, 1H), 4.20 (q, *J* = 7.1 Hz, 2H), 3.53 (t, *J* = 6.7 Hz, 2H), 2.13 (s, 3H), 1.85 – 1.73 (m, 4H), 1.49 – 1.32 (m, 6H), 1.27 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 170.7, 170.4, 72.4, 61.4, 45.1, 32.6, 31.1, 28.5, 26.7, 25.1, 20.8, 14.3. TLC: R_f = 0.23 (10:1 hexane:EtOAc). HRMS (APCI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{12}H_{22}ClO_4$ 265.1207, found 265.1203.

4.4.9. Ethyl 2-acetoxy-4,4,5,5,6,6,6-heptafluorohexanoate (**12**)

^{1}H NMR (400 MHz, Chloroform-*d*) δ 5.46 (dd, *J* = 8.5, 3.7 Hz, 1H), 4.25 (q, *J* = 7.2 Hz, 2H), 2.85 – 2.59 (m, 2H), 2.16 (s, 3H), 1.30 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 169.8, 168.3, 116.5 (m), 113.9 (m), 65.6, 62.5, 32.4 (t, *J* = 21.7 Hz), 30.4, 20.6, 14.1. TLC: R_f = 0.63 (20:1 hexane:EtOAc). HRMS (APCI-TOF) *m/z*: $[(M+H)]^+$ calcd for $C_{10}H_{12}F_7O_4$ 329.0624, found 329.0635.

4.4.10. Ethyl 2-acetoxy-4,4-dimethylpentanoate (**13**)

^{1}H NMR (400 MHz, Chloroform-*d*) δ 5.04 (dd, *J* = 9.2, 3.0 Hz, 1H), 4.18 (q, *J* = 7.1 Hz, 2H), 2.12 (s, 3H), 1.85 – 1.66 (m, 2H), 1.27 (t, *J* = 7.1 Hz, 3H), 0.96 (s, 9H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ ^{13}C NMR (101 MHz, Chloroform-*d*) δ 171.2, 170.7, 70.9, 61.5, 44.2, 30.6, 29.7, 20.9, 14.2. TLC: R_f = 0.33 (10:1 hexane:EtOAc). HRMS (APCI-TOF) *m/z*: $[M+Na]^+$ calcd for $C_{11}H_{20}NaO_4$ 239.1254, found 239.1262.

4.4.11. Ethyl 2-acetoxy-3-(adamantan-1-yl)propanoate (**14**)

^{1}H NMR (400 MHz, Chloroform-*d*) δ 5.08 (dd, *J* = 9.4, 2.5 Hz, 1H), 4.18 (q, *J* = 7.1 Hz, 2H), 2.12 (s, 3H), 2.07 – 1.89 (m, 3H), 1.83 – 1.44 (m, 14H), 1.27 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.5, 170.7, 69.5, 61.5, 45.0, 42.5, 37.0, 32.4, 28.7, 21.0, 14.3. TLC: R_f = 0.25 (20:1 hexane:EtOAc). HRMS (APCI-TOF) *m/z*: $[M-(H_2O)+H]^+$ calcd for $C_{15}H_{23}O_3$ 251.1642, found 251.1639.

4.4.12. 3-Cyclohexyl-1-ethoxy-1-oxopropan-2-yl pivalate (**15**)

^{1}H NMR (400 MHz, Chloroform-*d*): δ 5.00 (dd, *J* = 9.8, 4.2 Hz, 1H), 4.17 (qd, *J* = 7.1, 5.3 Hz, 2H), 1.81 – 1.60 (m, 7H), 1.49 – 1.37 (m, 1H), 1.32 – 1.25 (m, 4H), 1.24 (s, 9H), 1.23 – 1.12 (m, 2H), 1.04 – 0.85 (m, 2H). ^{13}C NMR (101 MHz, Chloroform-*d*): δ 178.2, 171.1, 70.5, 61.3, 38.8, 38.4, 34.3, 33.8, 32.3, 27.2, 26.5, 26.4, 26.2, 14.3. TLC: R_f = 0.31 (20:1 hexane:EtOAc). HRMS (APCI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{16}H_{29}O_4$ 285.2060, found 285.2069.

4.4.13. Ethyl 3-cyclohexyl-2-methoxypropanoate (**16**)

^{1}H NMR (400 MHz, Chloroform-*d*): δ 4.22 (qq, *J* = 7.3, 3.7 Hz, 2H), 3.80 (dd, *J* = 9.0, 4.2 Hz, 1H), 3.37 (s, 3H), 1.77 – 1.60 (m, 5H), 1.58 – 1.40 (m, 3H), 1.29 (t, *J* = 7.1 Hz, 3H), 1.27 – 1.06 (m, 3H), 1.01 – 0.80 (m, 2H). ^{13}C NMR (101 MHz, Chloroform-*d*): δ 173.5, 78.9, 60.9, 58.2,

40.6, 33.9, 32.7, 26.6, 26.4, 26.2, 14.4. TLC: R_f = 0.18 (20:1 hexane:EtOAc). HRMS (APCI-TOF) *m/z*: $[M+Na]^+$ calcd for $C_{12}H_{22}NaO_3$ 237.1467, found 237.1461.

4.4.14. Naphthalen-2-yl 2-acetoxy-3-cyclohexylpropanoate (**17**)

^{1}H NMR (400 MHz, Chloroform-*d*): δ 7.90 – 7.74 (m, 3H), 7.57 (d, *J* = 2.1 Hz, 1H), 7.48 (ddd, *J* = 7.2, 5.0, 1.6 Hz, 2H), 7.23 (dd, *J* = 8.9, 2.1 Hz, 1H), 5.29 (dd, *J* = 9.4, 4.5 Hz, 1H), 2.20 (s, 3H), 2.04 – 1.65 (m, 7H), 1.63 – 1.57 (m, 1H), 1.39 – 1.14 (m, 3H), 1.13 – 0.95 (m, 2H). ^{13}C NMR (101 MHz, Chloroform-*d*): δ 171.0, 169.9, 148.1, 133.8, 131.7, 129.7, 127.9, 127.8, 126.8, 126.0, 120.9, 118.5, 70.9, 38.6, 34.2, 33.8, 32.5, 26.5, 26.4, 26.2, 20.9. TLC: R_f = 0.30 (10:1 hexane:EtOAc). HRMS (APCI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{21}H_{25}O_4$ 341.1747, found 341.1747.

4.4.15. [1,1'-Bi(cyclohexan)]-3-one (**18**)

^{1}H NMR (400 MHz, Chloroform-*d*): δ 2.42 – 2.29 (m, 2H), 2.29 – 2.16 (m, 1H), 2.08 (t, *J* = 12.9 Hz, 2H), 1.94 – 1.80 (m, 1H), 1.80 – 1.49 (m, 7H), 1.37 (qd, *J* = 12.6, 3.5 Hz, 1H), 1.29 – 1.04 (m, 4H), 1.01 – 0.90 (m, 2H). ^{13}C NMR (101 MHz, Chloroform-*d*): δ 212.9, 45.7, 44.8, 42.8, 41.7, 30.1, 30.0, 28.6, 26.7, 26.7, 26.7, 25.8. TLC: R_f = 0.36 (20:1 hexane:EtOAc). HRMS (APCI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{12}H_{21}O$ 181.1592, found 181.1587.

4.4.16. Benzyl 3-cyclohexylpropanoate (**19**)

^{1}H NMR (400 MHz, Chloroform-*d*): δ 7.46 – 7.28 (m, 5H), 5.11 (s, 2H), 2.44 – 2.32 (m, 2H), 1.74 – 1.59 (m, 5H), 1.58 – 1.49 (m, 2H), 1.32 – 1.06 (m, 4H), 1.00 – 0.77 (m, 2H). ^{13}C NMR (101 MHz, Chloroform-*d*): δ 174.1, 136.3, 128.7, 128.3, 128.3, 66.2, 37.3, 33.1, 32.5, 32.1, 26.7, 26.4. TLC: R_f = 0.38 (20:1 hexane:EtOAc). HRMS (APCI-TOF) *m/z*: $[M+Na]^+$ calcd for $C_{16}H_{22}NaO_2$ 269.1512, found 269. 1518.

4.4.17. Dimethyl 2-cyclohexylsuccinate (**22**)

^{1}H NMR (400 MHz, Chloroform-*d*): δ 3.69 (s, 3H), 3.65 (s, 3H), 2.79 – 2.65 (m, 2H), 2.45 (dt, *J* = 13.5, 8.9 Hz, 1H), 1.73 (br d, *J* = 13.5 Hz, 2H), 1.62 (br t, *J* = 13.5 Hz, 4H), 1.34 – 0.92 (m, 5H). ^{13}C NMR (101 MHz, Chloroform-*d*): δ 175.1, 173.1, 51.9, 51.7, 47.1, 40.1, 33.4, 30.8, 30.3, 26.4, 26.3. TLC: R_f = 0.29 (10:1 hexane:EtOAc). HRMS (APCI-TOF) *m/z*: $[M+Na]^+$ calcd for $C_{12}H_{20}NaO_4$ 251.1254, found 251.1246.

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