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The first 'alkane-like' functionalization of *n*-alkyl acetates: a new method for one-pot selective syntheses of bifunctional aliphatic compounds with an acetate group

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ABSTRACT

Selective one-pot functionalization of linear alkyl acetates $C_nH_{2n+1}OCOMe$ ($n = 6, 8$), with CO and various nucleophilic substrates (*iso*-propanol, morpholine, piperidine, and anisole) in the presence of the superelectrophilic system $CBr_4{\cdot}2AlBr_3$ is performed for the first time.

Selective one-pot C–H functionalization of monofunctional aliphatic compounds is an important goal opening the way to novel bifunctional fine chemicals with desired properties that can be used for the synthesis of biologically active compounds and materials for industrial use. However, finding reagents for such reactions presents a considerable challenge, as most functional groups have low tolerance to highly reactive systems that are capable of cleaving non-activated sp^3 C–H bonds.

In this Letter we report a new approach to the one-pot synthesis of novel bifunctional compounds from alkyl acetates, $C_nH_{2n+1}OCOMe$ ($n = 6, 8$). It is important to mention that the functional group present in the starting material remains intact during the process, which occurs with good selectivity under extremely mild conditions. Novel alkane-like methodology provides access to new, very promising, and synthetically challenging functionalized alkyl acetates with various functional groups.

Our strategy was based on the use of a new potent superelectrophilic system $CBr_4{\cdot}2AlBr_3$ which can generate carbocations (R^+) effectively from saturated hydrocarbons (RH) under very mild conditions.[1,2] Generation of carbocations in the presence of superelectrophiles under a CO atmosphere results in the formation of acylium cations (RCO^+).[3] The latter, in turn, can be converted into carbonyl-containing derivatives of saturated hydrocarbons upon treatment of the intermediates with various nucleophiles (YH). Reactions of alkanes and cycloalkanes with CO initiated by polyhalomethane-based superelectrophiles[2] have made one-pot syntheses of diverse carbonyl-containing products from readily available raw materials possible. Some of the types of carbonyl-containing compounds prepared by us from saturated hydrocarbons, CO and YH in the presence of $CBr_4{\cdot}2AlBr_3$ in a one-pot procedure, are shown below (Scheme 1).[2]

Evidently, the selective involvement of a functional group at a sp^3 C–H bond in aliphatic compounds bearing an acetate group represents a more complicated problem compared to the functionalization of alkanes. Indeed, the generation of a carbocation in these 'functionalized alkanes' by a superelectrophile should be hampered by both the deactivating effect of the electron-withdrawing group and its ability to bond with the superelectrophile, resulting in diminished reactivity.[4] In the case of alkyl acetates, the possibility of cleavage of the ester bond by potent superelectrophiles as well as isomerisation and cracking of the carbocation, $[C_nH_{2n}]^+OCOMe$, cannot be ruled out. Acid-catalyzed ester cleavage has been extensively studied, and evidence has emerged suggesting that protosolvation (or electrophilic solvation) can play a role in this chemistry. Thus, methyl acetate is found to be completely protonated at the acyl-oxygen in superacidic $FSO_3H/SbF_5/SO_2$ solution at low temperature. However, even at −78 °C, protonated methyl acetate undergoes acyl-oxygen cleavage to the acetyl cation and protonated methanol. This suggests further protolytic activation of protonated methyl acetate via the carboxonium dication.[4]

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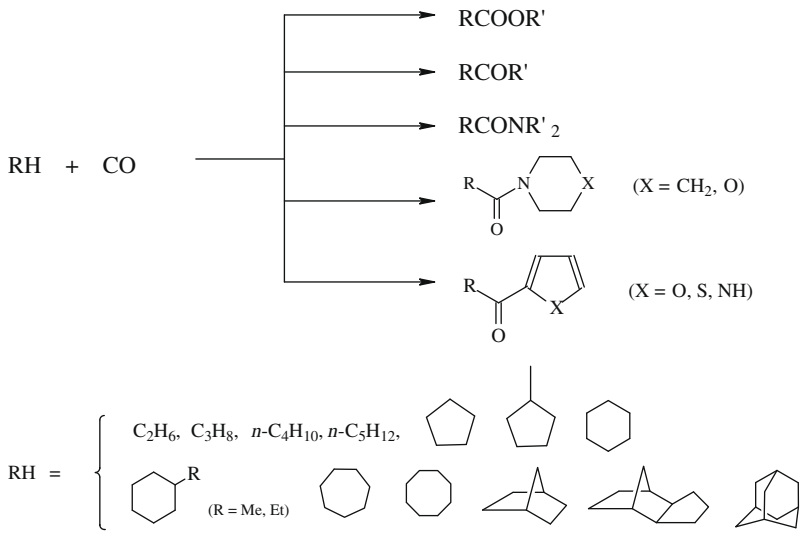
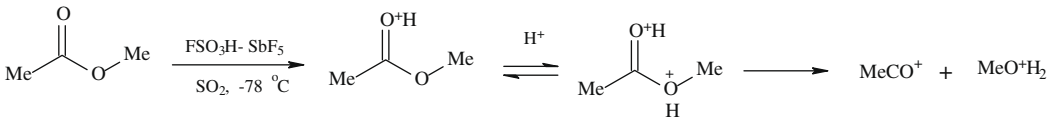


Scheme 1. Examples of one-pot alkane functionalization.



Examples of one-pot, selective C–H bond functionalizations of monofunctional linear aliphatic compounds are very rare.[5] Reactions of aliphatic alcohols, ketones, and aldehydes with ozone in magic acid in SO_2ClF solution have been reported.[5a] Primary alcohols containing tertiary or secondary C–H bonds at the γ-position or more remote from the oxonium center have been shown to undergo insertion reactions with protonated ozone to give oxidation products in good yield. In contrast, secondary C–H bonds at the γ-position of aldehydes and ketones remain unreactive toward ozone in SO_2ClF at −40 °C. Such reactions with protonated ozone occur only with higher ketone and aldehyde homologues.[5a]

Attempts to perform selective carbonylation of methyl-*n*-alkyl ketones with CO in the presence of a proton superacid have been unsuccessful.[5b] Over a wide temperature range and in the presence of a large excess of $HF–SbF_5$, the reactions either do not occur at all, or have led to mixtures consisting predominantly of degradative carbonylation products with smaller numbers of C-atoms in the alkyl group at the carbonyl than in the initial ketones, while the desired products were formed in small amounts or not at all.[5b] Under these conditions, only branched methyl alkyl ketones ($n = 7–9$) having a tertiary C-atom at the end of their chains have been selectively carbonylated with CO. However, conversions of the ketones amounted to 16–66% only, although the reactions were carried out in the presence of a 10-fold excess of $HF–SbF_5$.[5b] Attempts to functionalize esters have not been reported previously.

We found that at −20 °C or 0 °C under atmospheric CO pressure, and in the presence of a 50–100% molar excess of the superelectrophilic complex $CBr_4·2AlBr_3$, effective carbonylation of *n*-alkyl acetates, $C_nH_{2n+1}OCOMe$ ($n = 6, 8$) occurs. In situ treatment of the carbonylation product with HNu nucleophilic agents (*iso*-propanol, morpholine, piperidine, and anisole) led to the corresponding bifunctional alkanes. Both carbonylations and subsequent reactions with nucleophiles were carried out at the same temperature and under a strictly maintained CO atmosphere (Scheme 2).

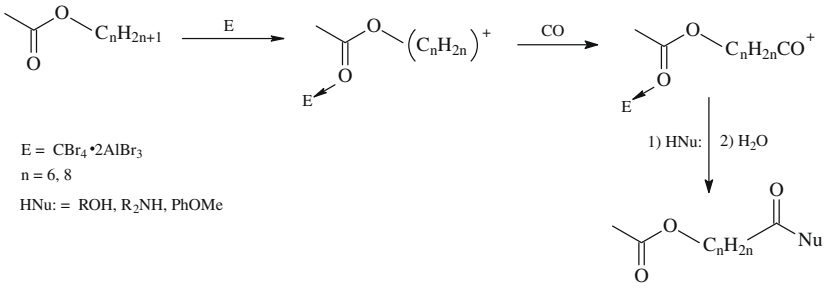
The carbonyl group is clearly a much stronger nucleophile than an sp^3 C–H bond. However, while interactions of the superelectrophile with the acetate group are reversible, the C–H bond cleavage followed by acylium cation formation under CO is virtually irreversible. As a result, the less nucleophilic center (C–H) can still react with the superelectrophile even in the presence of the much stronger CO donor.

These reactions proceeded with high regioselectivity, in each case affording predominantly a single bifunctional product with selectivities of 86–98% and, as a rule, in 72–85% yields. Conversions of the initial *n*-alkyl acetates amounted to 80–98%. No products of degradative functionalization containing a different number of carbon atoms in the alkyl group than in the initial alkyl acetates were observed.

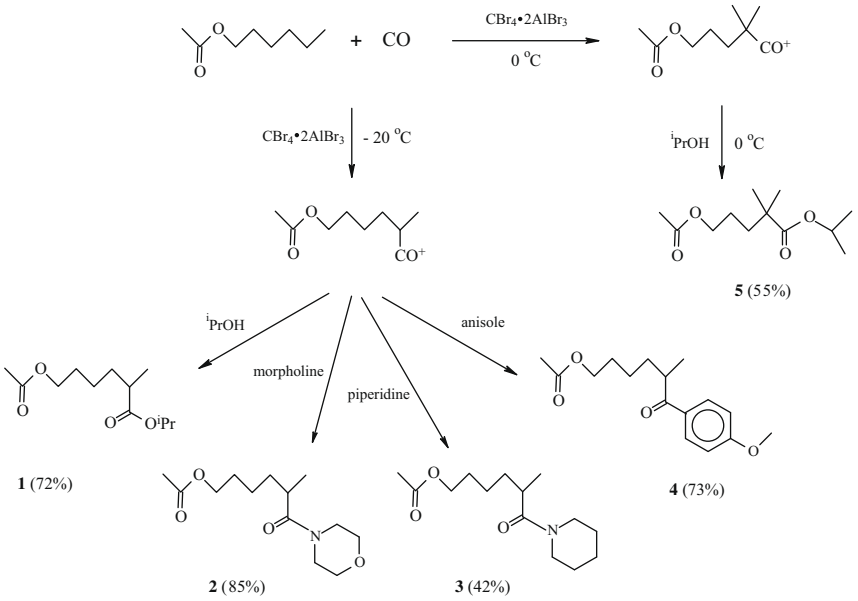
The direction of functionalization of *n*-hexyl acetate (Scheme 3) depended on the temperature during carbonylation. At −20 °C, functionalization with CO and nucleophiles (*iso*-propanol, morpholine, piperidine, and anisole) resulted in the formation of products **1**, **2**, **3,** and **4** with a non-isomerized alkyl chain, in which the functional group was located at the tertiary C-atom most distant from the initial carbonyl group. The selectivities were 85% or higher. The minor isomer formed had the *neo*-structure **5**. In contrast, when both the carbonylation of *n*-hexyl acetate and treatment of the resultant carbonylation product with *i*-PrOH were carried out at 0 °C, *neo*-diester **5** was formed with a selectivity of 88%, while its isomer **1** was produced as a minor component only.

The dependence of the outcome of the reaction on temperature probably shows that the addition of a CO molecule to the secondary $MeCO(CH_2)_4CH^+Me$ cation proceeds more rapidly than its isomerization into the tertiary cation and the subsequent addition of CO to the sterically hindered cation. The selectivities and yields of the products also depended on the nature of the nucleophile. Indeed, reaction with morpholine proceeded selectively and led to the corresponding product in high yield, while in the case of a stronger nucleophile such as piperidine, both the selectivity and yield were markedly lower.

Functionalization of *n*-octyl acetate (Scheme 4) with CO and nucleophiles (*iso*-propanol, morpholine, and anisole) afforded al-



Scheme 2. One-pot functionalization of *n*-alkyl acetates.



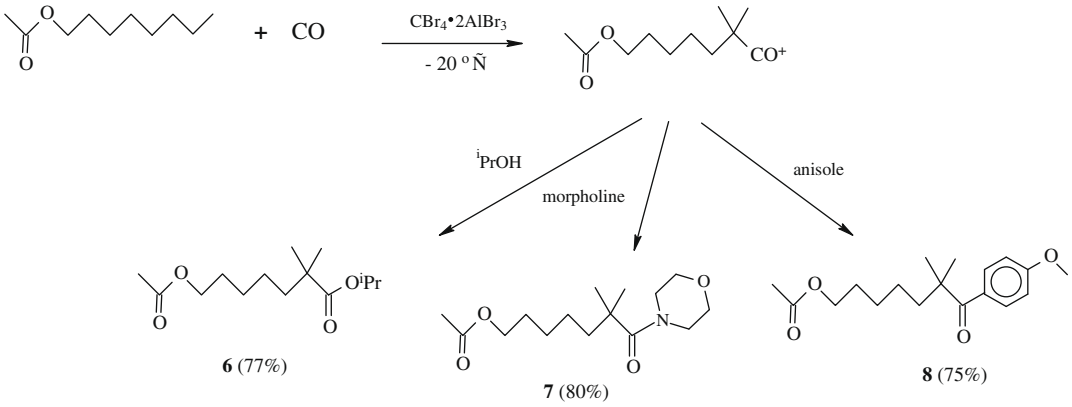
Scheme 3. One-pot functionalization of *n*-hexyl acetate.

most exclusively the bifunctional products **6**–**8** of *neo*-structure. The amounts of these *neo*-products were 95% or higher in the corresponding isomeric mixtures.

The easier formation of the *neo*-products from *n*-octyl acetate with a longer alkyl chain shows that the isomerization of a long-chained cation generated from an alkyl acetate most likely proceeds more rapidly than with shorter homologues. The elaboration of syntheses of bifunctional aliphatic compounds having *neo*-structures is of special interest because they display valuable properties, such as enhanced thermal and chemical stabilities, and low freezing points.[6]

One-pot reactions of both *n*-hexyl and *n*-octyl acetates with CO and anisole gave aromatic ketoacetates **4** or **8** in high yields and selectivities with *tert*- or *neo*-alkyl groups, respectively.

Interestingly, the carbonylation and subsequent functionalization of *n*-hexyl acetate (even at 0 °C) and its longer-chain



Scheme 4. Selective one-pot functionalization of *n*-octyl acetate.

homologue *n*-octyl acetate occur with good regioselectivity, while under the action of superacids, the corresponding C_6 and C_8 *n*-alkanes produced a mixture of isomers as well as products of their degradative carbonylation, resulting in compounds with smaller or larger numbers of C-atoms in the alkyl group at the carbonyl than in the initial alkanes.[7] The degradative carbonylation of C_6 alkanes and their higher homologues C_7–C_{10} does not occur in reactions initiated by polyhalomethane-based superelectrophiles.[8] In this case, even at −40 °C, carbonylation of C_6–C_{10} alkanes affords exclusively, carbonyl-containing products with *neo*-alkyl substituents, that is, with a quaternary carbon atom at the carbonyl group. These products were always represented by two dominating isomers, AlkC(Me)$_2$COOR and AlkC(Me)(Et)COOR.[8]

As demonstrated in the present work, the aforementioned isomers are produced in comparable amounts under conditions similar to those for *n*-octyl acetate alkoxycarbonylation. Therefore, it does not appear to be possible to obtain individual carbonyl-containing products starting from C_6–C_{10} alkanes.

The results of this work show that in the presence of the acetoxy group, a single carbocation is generated selectively in each case. Therefore, the corresponding acylium cation accumulates in the reaction medium, allowing for regioselective functionalization of the *n*-alkyl acetates. We believe that the site for hydride abstraction from the alkyl acetate molecule is dictated by two factors: (i) its remoteness from the already existing functional group, and (ii) the stability of the carbocation to be generated. For *n*-octyl acetate, the two requirements lead to a compromise resulting in the formation of the most stable tertiary cation separated from the functional group by five methylenes. In the case of *n*-hexyl acetate, at a lower temperature (−20 °C) the most distal yet less stable secondary cation is formed, whereas at a higher temperature that favors isomerizaton of the cations (0 °C), it is the more stable tertiary cation that is produced, even though this cationic center is in proximity to the functional group. The difference in the selectivities of the carbonylation of *n*-octane and *n*-octyl acetate stems from the fact that the former gives two cations that are rather similar in stability, whereas the latter is transformed into an intermediate bearing the cationic center in the position that is most remote from the ester group, $Me_2C^+(C_5H_{11})$.

In contrast to α-, β-, γ-, or δ-hydroxy acids and some of their derivatives,[9] whose syntheses, properties, applications in chemical transformations, and practical use are well known, their long-chained homologues and, in particular, compounds with branched and *neo*-alkyl chains, are unavailable. Aromatic long-chain branched and *neo*-ketoacetates have not been described earlier either.

In summary, an 'alkane-like' strategy has been used successfully for the direct and simple one-pot functionalization of monofunctional aliphatic compounds, namely *n*-hexyl and *n*-octyl acetates. This approach has provided access to new, difficult to access bifunctional aliphatic compounds with an acetate group, which are of interest for the synthesis of biologically active compounds and materials for industrial use. We believe that the field of 'alkane-like' reactions of monofunctional aliphatic compounds may be expanded beyond the scope of alkyl acetates.

All the obtained products are novel and their structures were confirmed by ^{1}H and ^{13}C NMR spectroscopy and mass-spectral analysis. Typical experiments and selected spectral characteristics are given.[10]

Acknowledgments

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10. *General procedure for compounds* **1**–**4** and **6**–**8**: At −20 °C, under atmospheric CO pressure, *n*-alkyl acetate (1.6–1.9 mmol) was added to a stirred solution of $CBr_4{\cdot}2AlBr_3$, freshly prepared from $AlBr_3$ (6.50 mmol) and CBr_4 (3.24 mmol) in anhydrous CH_2Br_2 (2.5 mL) at room temperature. After stirring for 2.5 h at −20 °C under a CO atmosphere the nucleophile (*iso*-PrOH, morpholine, piperidine, or anisole) was added to the in situ prepared carbonylation intermediate strictly under CO. The mixture was stirred additionally for 10–15 min at −20 °C and then left to warm to 0 °C over 20–30 min. Next, water (10 mL) and $CHCl_3$ (30 mL) were carefully added with stirring. The organic layer was separated and the remaining aqueous layer was extracted with $CHCl_3$ (2 × 20 mL). The combined organic extracts were dried over Na_2SO_4. The structures of the products were established by ^{1}H, ^{13}C NMR[11,12] and from GC–MS spectra;[13] conversions and isomeric ratios were determined by GC. The yields of the obtained compounds were determined by ^{1}H NMR[11,12] with 1,3,5-tribromobenzene as an internal standard.
Conditions and selected spectral data. All runs were carried out with 3.24 mmol of $CBr_4{\cdot}2AlBr_3$.
Compound (**1**): 1.6 mmol of AcO-*n*-hexyl, 2.5 mL of *iso*-PrOH; yield 72% (86% as an isomeric mixture); ^{1}H NMR (400 MHz; $CDCl_3$): δ 1.19 (3H, d, $^3J_{HH}$ 9.1 Hz) (see Ref. 11); 1.28 (6H, d, $^3J_{HH}$ 8.2 Hz); 1.35–1.75 (6H, m); 2.09 (3H, s); 2.50 (1H, m); 4.10 (2H, t, $^3J_{HH}$ 8.8 Hz); 5.06 (1H, sept, $^3J_{HH}$ 8.2 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 16.95; 21.62; 21.68; 24.19; 28.35; 33.20; 39.45; 64.18; 67.14; 171.05; 176.01. MS, *m*/*z*, (I_{rel}, %): 230, M^+ (0.5) (see Ref. 10); 171, M−OCOMe$^+$ (14); 170, M−AcOH$^+$ (5); 129, PrOCOCH(Me)CH_2^+ (96); 128 (65); 116, PrOC(OH)CHMe$^+$ (64); 87 (27); 83 (44); 74 (79); 43 (100).
Compound (**2**): 1.6 mmol of AcO-*n*-hexyl, 6.5 mmol of morpholine; yield 85% (90% as an isomeric mixture); ^{1}H NMR (400 MHz; $CDCl_3$): δ 1.17 (3H, d, $^3J_{HH}$ 9.1 Hz); 1.30–1.80 (6H, m); 2.10 (3H, s); 2.69 (1H, m); 3.72 (8H, m); 4.10 (2H, t, $^3J_{HH}$ 8.8 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 17.31; 20.66; 23.54; 28.39; 33.27; 34.75; 41.79; 45.74; 63.96; 66.52; 66.72; 170.77; 174.62.. MS, *m*/*z*, (I_{rel}, %): 257, M^+ (3); 242, (2); 214, M−Ac$^+$ (17); 198, M−OAc$^+$ (26); 156, morpholylCOCH(Me)CH_2^+ (52); 143, morpholylC(OH)CHMe$^+$ (100); 129 (27); 128 (28); 114, morpholylCO$^+$ (22); 100 (21); 88 (72).
Compound (**3**): 1.6 mmol of AcO-*n*-hexyl, 6.5 mmol of piperidine; yield 42% (85% as an isomeric mixture); ^{1}H NMR (400 MHz; $CDCl_3$): δ 1.16 (3H, d, $^3J_{HH}$ 9.1 Hz); 1.30–1.40 (6H, br m); 1.60–1.75 (6H, m); 2.10 (3H, s); 2.73 (1H, m); 3.55 (4H, m); 4.10 (2H, t, $^3J_{HH}$ 8.8 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 17.53; 20.75; 23.67; 24.44; 25.51; 28.48; 33.44; 34.91; 42.62; 46.32; 64.13; 170.78; 174.45. MS, *m*/*z*, (I_{rel}, %): 255, M^+ (3); 240, (2); 212, M−Ac$^+$ (7); 196, M−OAc$^+$ (27); 154, piperidylCOCH(Me)CH_2^+ (66); 141, piperidylCOCH(Me)$^+$ (100).
Compound (**4**): 1.6 mmol of AcO-*n*-hexyl, 1.6 mmol of anisole; yield 73% (90% as an isomeric mixture); ^{1}H NMR (400 MHz; $CDCl_3$): δ 1.25 (3H, d, $^3J_{HH}$ 8.8 Hz); 1.3–1.9 (6H, m); 2.08 (3H, s); 3.48 (1H, m); 3.93 (3H, s); 4.09 (2H, t, $^3J_{HH}$ 8.8 Hz); 7.00 (2H, d, $^3J_{HH}$ 11.9 Hz); 8.00 (2H., d, $^3J_{HH}$ 11.9 Hz), (see Ref. 13). ^{13}C NMR (100 MHz, $CDCl_3$): δ 17.38; 20.69; 23.57; 28.46; 33.07; 39.74; 55.16; 64.05; 113.53; 132.70; 161.82; 170.90; 202.36. MS, *m*/*z*, (I_{rel}, %): 164, $MeOC_6H_4COCHMe^+$ (18); 135, $MeOC_6H_4CO^+$ (100).
Procedure for compound (**5**): At 0 °C, under atmospheric CO pressure, *n*-hexyl acetate (0.31 g, 2.17 mmol) was added to $CBr_4{\cdot}2AlBr_3$ (2.91 g, 3.34 mmol) in CH_2Br_2 (2.5 mL), and the mixture was stirred over 1.5 h. Next, frozen *iso*-PrOH (2.5 mL), at −20 °C, was added to the reaction mixture. After standard treatment, a mixture of isomers **5** and **1** was obtained in a 10:1 ratio and a total yield of 60%, the conversion of *n*-hexyl acetate was close to 100%. The yield of **5** and ratio of isomers were determined by ^{1}H NMR with 1,3,5-tribromobenzene as an internal standard and by GC, respectively.
^{1}H NMR (400 MHz; $CDCl_3$): δ 1.17 (6H, s) (see Ref. 12); 1.24 (6H, d, $^3J_{HH}$ 8.2 Hz); 1.35–1.75 (4H, m); 2.09 (3H, s); 4.10 (2H, t, $^3J_{HH}$ 8.8 Hz); 5.06 (1H, sept, $^3J_{HH}$ 8.2 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 20.80; 21.56; 24.16; 24.88; 33.16; 36.48; 64.54; 67.23; 170.95; 176.86. MS, *m*/*z*, (I_{rel}, %): 230, M^+ (0.5); 171, M−OAc$^+$ (6); 170, M−AcOH$^+$ (19); 129, PrOCOCMe$_2^+$ (80); 128 (34); 83 (100); 55 (75); 43 (88).
Compound (**6**): 1.9 mmol of AcO-*n*-octyl, 2.0 mL of *iso*-PrOH; yield 77% (96% as an isomeric mixture); ^{1}H NMR (400 MHz; $CDCl_3$): δ 1.21 (6H, s) (see Ref. 12); 1.27 (6H, d, $^3J_{HH}$ 8.2 Hz); 1.50–1.75 (8H, m); 2.10 (3H, s); 4.10 (2H, t, $^3J_{HH}$ 8.8 Hz); 5.03 (1H, sept, $^3J_{HH}$ 8.2 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 20.71; 21.48; 24.26; 24.84; 26.12; 28.18; 41.70; 64.16; 66.84; 170.71; 176.95. MS, *m*/*z*, (I_{rel}, %): 259, M$^+$+H

(5); 130, $PrOCOCMe_2^+$ (8); 111, $(CH_2)_5CMe_2^+$ (40); 88, $PrOCOH^+$ (61); 69 (100); 67 (23); 55 (28).

Compound (**7**): 1.9 mmol of AcO-*n*-octyl, 5.7 mmol of morpholine; yield 80% (97% as an isomeric mixture); ^{1}H NMR (400 MHz; $CDCl_3$): δ 1.30 (6H, s); 1.30–1.75 (8H, m); 2.10 (3H, s); 3.70 (8H, m); 4.10 (2H, t, $^3J_{HH}$ 8.8 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 20.67; 24.43; 26.23; 26.60; 28.20; 38.45; 40.51; 42.13; 45.37; 64.06; 66.61; 170.77; 175.27. MS, *m*/*z*, (I_{rel}, %): 285, M^+ (5); 242, $M-Ac^+$ (10); 226, $M-OAc^+$; 171, $AcO(CH_2)_5CMe_2^+$ (9); 170, $morpholylCOC(Me)_2CH_2^+$ (16); 157, $morpholylC(OH)CMe_2^+$ (47); 129, $PrOCOCMe_2^+$ (44); 114, $morpholylCO^+$ (16); 88 (30); 69 (100).

Compound (**8**): 1.9 mmol of AcO-*n*-octyl, 1.9 mmol of anisole; yield 75% (98% as an isomeric mixture); ^{1}H NMR (400 MHz; $CDCl_3$): δ 1.37 (6H, s); 1.30–1.85 (8H, m); 2.07 (3H, s); 3.90 (3H, s); 4.03 (2H, t, $^3J_{HH}$ 8.8 Hz); 6.93 (2H, d, $^3J_{HH}$ 11.9 Hz); 7.86 (2H, d, $^3J_{HH}$ 11.9 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 20.57; 24.12; 26.15; 26.21; 27.98; 40.96; 47.07; 55.00; 64.03; 112.92; 130.20; 161.60; 170.64; 205.48. MS, *m*/*z*, (I_{rel}, %): 250 (2); 178, $PhOC_6H_4C(OH)CMe_2^+$ (7); 135, $PhOC_6H_4CO^+$ (100); 121 (2); 107, $PhOC_6H_4^+$ (12); 92 (3); 77 (20).

11. The presence of doublets (3H, d, $^3J_{HH}$ 9.1 Hz) at δ 1.16–1.19 ppm and related multiplets (1H) at 2.50–2.73 ppm in the ^{1}H NMR spectra proves that compounds **1**–**3** contain non-branched alkyl chains CH_2–C**H**–(COX)C**H**$_3$. Similarly, the structure of aromatic compound **4** was confirmed by the presence of a doublet (3H) at 1.25 ppm and a deshielded multiplet (1H) at 3.48 ppm.
12. The presence of singlets (6H) at δ 1.17–1.37 ppm establishes the *neo*-structure for compounds **5**–**8**.
13. Molecular ions are often absent in the MS of similar compounds, see: Pettersen, J. E. *Mass Spectrom. Ion Phys.* **1983**, *48*, 129.