

Recent Developments in the Synthesis of Fatty Acid Derivatives

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Synthesis of New Oleochemicals: Products of Friedel-Crafts Reactions of Unsaturated Fatty Compounds

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Introduction

Unsaturated fatty compounds are of interest as renewable raw materials (1). These compounds can be functionalized at the C,C-double bond by electrophilic addition reactions to give new oleochemicals with potentially new and interesting properties. The alkylaluminum chloride-induced Friedel-Crafts acylation of unsaturated fatty compounds (Fig. 1), such as oleic acid [**1a**], 10-undecenoic acid [**2a**], petroselinic acid [**3a**], and erucic acid [**4a**], and the respective esters and alcohols yield the corresponding β,γ -unsaturated ketones (2,3).

In this paper, we give some examples of ethylaluminum dichloride (EtAlCl_2)-induced acylations with different acylating agents such as saturated acyl chlorides, dicarboxylic acid dichlorides, cyclic anhydrides, unsaturated acyl chlorides, and aromatic and heteroaromatic acyl chlorides.

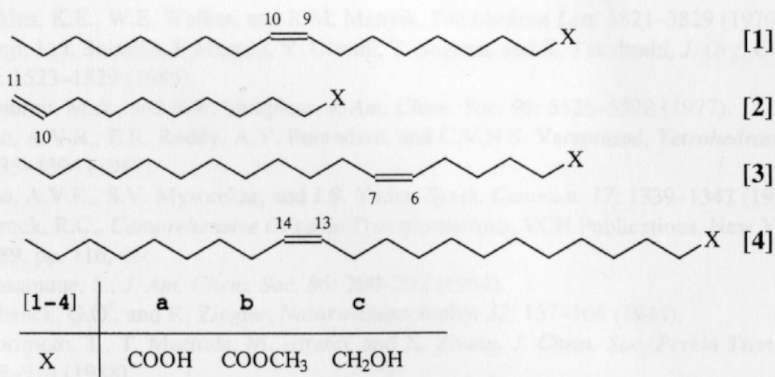


Fig. 1. Unsaturated fatty compounds: oleic acid [**1a**], 10-undecenoic acid [**2a**], petroselinic acid [**3a**], erucic acid [**4a**], and the respective esters [**1b**]-[**4b**] and alcohols [**1c**]-[**4c**].

Results

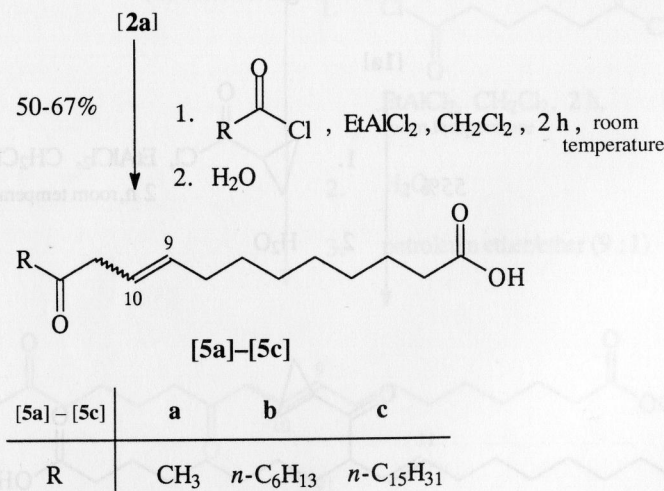
Acylation with Saturated Acyl Chlorides

The reaction of 10-undecenoic acid [**2a**], for example, with an acyl chloride such as acetyl chloride, heptanoyl chloride, hexadecanoyl chloride, and EtAlCl_2 in a ratio of 1:1:2 in dichloromethane gave the corresponding β,γ -unsaturated keto carboxylic acid [**5a**]–[**5c**] (Scheme 1) after a reaction time of 2 h at room temperature with high regioselectivity. The products were obtained as a mixture of (*E*)/(*Z*)-stereoisomers ($[(E):(Z)] = 3:1$) in isolated yields of 50–67%. Catalytic hydrogenation of the unsaturated ketocarboxylic acids [**5a**]–[**5c**] gave the saturated products in quantitative yields (2).

The Lewis acid-induced acylation of unsaturated fatty compounds combined with the following reactions allows the synthesis of natural products derived from fats. Acylation of 10-undecenoic acid [**2a**] with heptanoyl chloride gave 12-oxo-9-octadecenoic acid; reduction with NaBH_4 afforded the racemate of ricinelaic acid [**6**], a natural product (Fig. 2).

The acylation of oleic acid [**1a**] with cyclopropanecarboxylic acid chloride gave in the presence of EtAlCl_2 the corresponding branched β,γ -unsaturated keto-carboxylic acid [**7**] (Scheme 2). Product [**7**] was obtained as a mixture of 9- and 10-regioisomers in a ratio of 1:1 as pure (*E*)-adduct.

The corresponding reaction of 10-undecenoic acid [**2a**] afforded the cyclopropyl allyl ketone [**8**] (Fig. 3). The solid product was obtained as a mixture of (*E*)/(*Z*)-stereoisomers in a ratio of 2.3:1 and in an isolated yield of 71%.



10-undecenoic acid:acyl chloride: $\text{EtAlCl}_2 = 1:1:2$

SCHEME 1. Ethylaluminum dichloride-induced Friedel-Crafts acylation of 10-undecenoic acid [**2a**] with acyl chlorides.

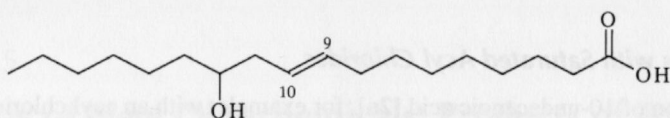
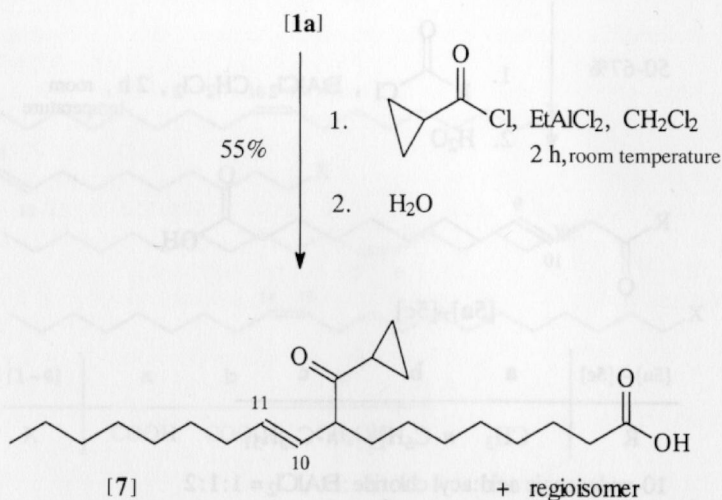


Fig. 2. Racemate of ricinelaidic acid [6] obtained by acylation of 10-undecenoic acid [2a] with heptanoyl chloride followed by reduction of the carbonyl group.

Diacylation products should be obtained by acylation reactions with dicarboxylic acid dichlorides. We carried out the reaction of methyl 10-undecenoate [2b] with adipic acid dichloride and EtAlCl_2 in a ratio of 2:1:4 (Scheme 3). After a reaction time of 2 h at room temperature, the product was crystallized from petroleum ether/ether (9:1) and identified as the methyl diketocarboxylate [9]. The acylation took place at only one acyl chloride functionality of the dicarboxylic acid dichloride. The second acyl chloride functionality reacted with one equivalent of EtAlCl_2 in a Grignard analogous reaction to give the ethyl ketone.

Acylation with Unsaturated Acyl Chlorides

The double unsaturated ketocarboxylic acid [10] was obtained by acylation of oleic acid [1a] with crotonic acid chloride (Scheme 4). Product [10], an allyl vinyl ketone, was formed as a mixture of the 9- and 10-regioisomers (3).



SCHEME 2. Ethylaluminum dichloride-induced acylation of oleic acid [1a] with cyclopropanecarboxylic acid chloride.

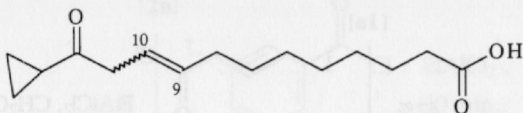
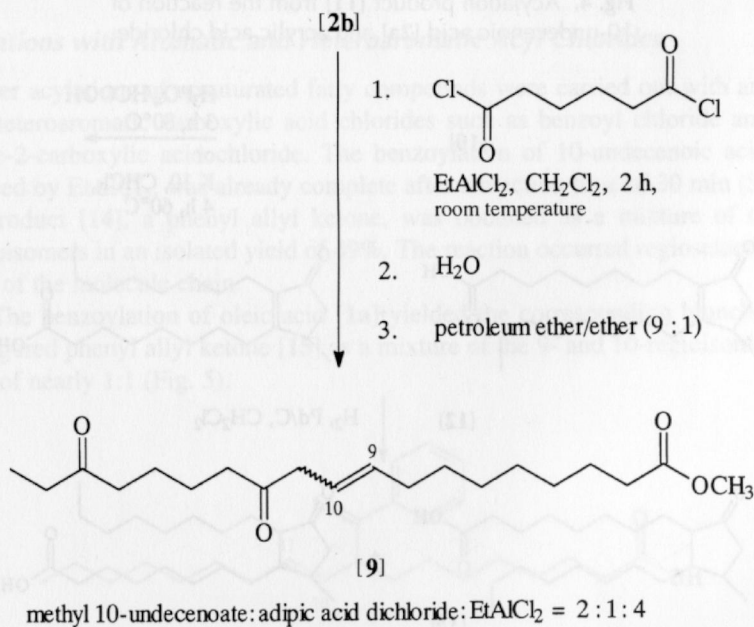


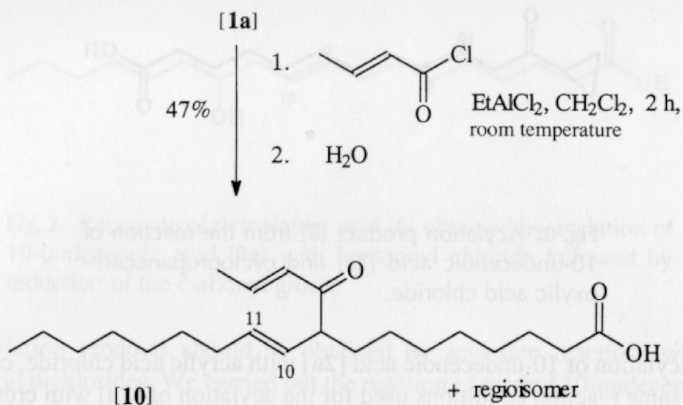
Fig. 3. Acylation product [8] from the reaction of 10-undecenoic acid [2a] and cyclopropanecarboxylic acid chloride.

The acylation of 10-undecenoic acid [2a] with acrylic acid chloride, carried out under the same reaction conditions used for the acylation of [1a] with crotonic acid chloride, gave the corresponding allyl vinyl ketone [11] as a mixture of the (*E*)- and (*Z*)-stereoisomers ($[(E):(Z)] = 3:1$, Fig. 4). Because of their allyl vinyl keto functionality, [10] and [11] should be suitable substrates for the Nazarov reaction.

The Nazarov cyclization of acylation product [10] was carried out in two different ways. The first method we applied was the typical procedure used for Nazarov reactions (Scheme 5). The regioisomeric mixture of [10] was heated for 3 h in a mixture of phosphoric acid and formic acid, yielding the expected cyclopentenone



SCHEME 3. Ethylaluminum dichloride-induced acylation of methyl 10-undecenoate [2b] with adipic acid dichloride.



SCHEME 4. Ethylaluminum dichloride-induced acylation of oleic acid [1a] with crotonic acid chloride.

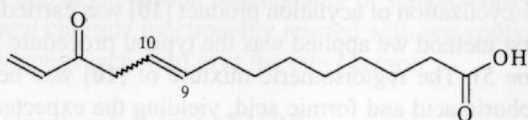
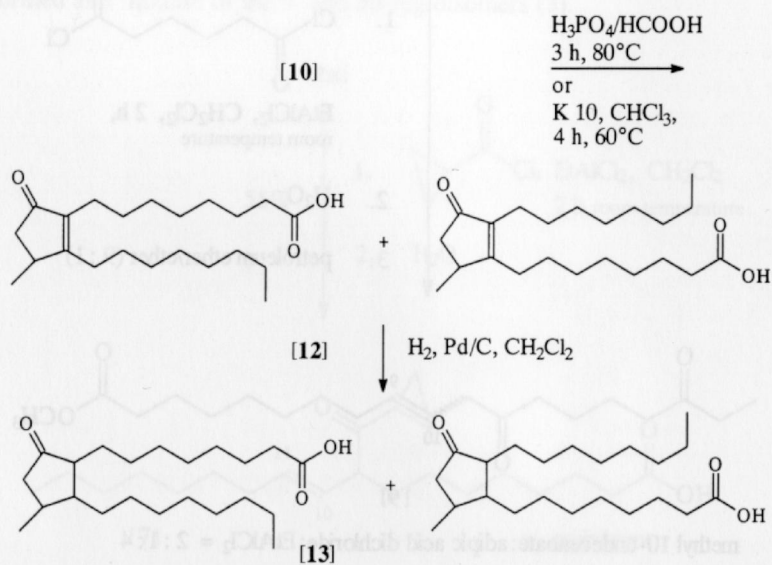
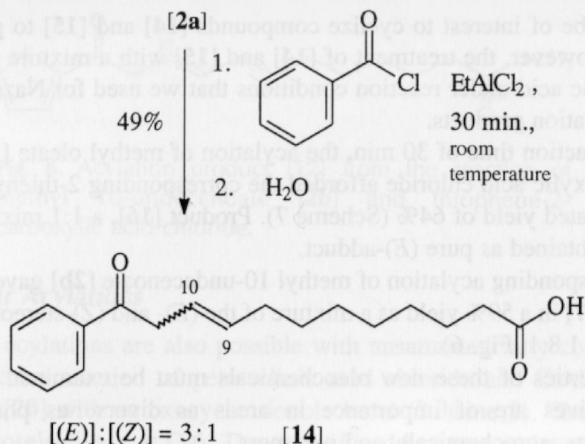


Fig. 4. Acylation product [11] from the reaction of 10-undecenoic acid [2a] and acrylic acid chloride.



SCHEME 5. Nazarov cyclization of acylation product [10] obtained from the reaction of oleic acid [1a] and crotonic acid chloride.



SCHEME 6. Ethylaluminum dichloride–induced acylation of 10-undecenoic acid [2a] with benzoyl chloride.

derivatives [12]. By the second method, the allyl vinyl ketone was heated for 4 h in chloroform in the presence of montmorillonite K10. Both methods gave the cyclopentenone [12] as a regioisomeric mixture. Catalytic hydrogenation afforded the corresponding cyclopentanone derivatives [13].

Acylation with Aromatic and Heteroaromatic Acyl Chlorides

Further acylations of unsaturated fatty compounds were carried out with aromatic and heteroaromatic carboxylic acid chlorides such as benzoyl chloride and thiophene-2-carboxylic acid chloride. The benzylation of 10-undecenoic acid [2a], induced by EtAlCl₂, was already complete after a reaction time of 30 min (Scheme 6). Product [14], a phenyl allyl ketone, was obtained as a mixture of (*E*)/(*Z*)-stereoisomers in an isolated yield of 49%. The reaction occurred regioselectively at C-11 of the molecule chain.

The benzylation of oleic acid [1a] yielded the corresponding branched (*E*)-configured phenyl allyl ketone [15] as a mixture of the 9- and 10-regioisomers in a ratio of nearly 1:1 (Fig. 5).

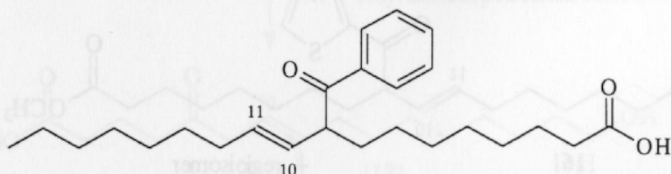


Fig. 5. Acylation product [15] from the reaction of oleic acid [1a] and benzoyl chloride.

It should be of interest to cyclize compounds [14] and [15] to give indanone derivatives. However, the treatment of [14] and [15] with a mixture of phosphoric acid and formic acid under reaction conditions that we used for Nazarov reactions gave no cyclization products.

After a reaction time of 30 min, the acylation of methyl oleate [1b] with thiophene-2-carboxylic acid chloride afforded the corresponding 2-thienyl allyl ketone [16] in an isolated yield of 64% (Scheme 7). Product [16], a 1:1 mixture of regioisomers, was obtained as pure (*E*)-adduct.

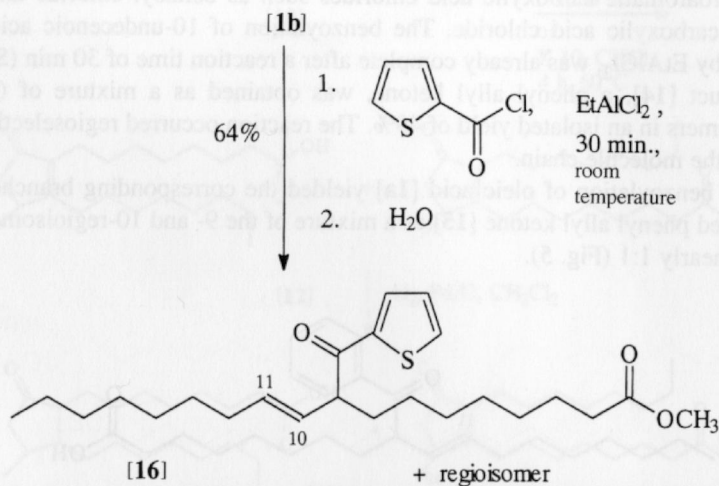
The corresponding acylation of methyl 10-undecenoate [2b] gave the 2-thienyl allyl ketone [17] in a 59% yield as a mixture of the (*E*)- and (*Z*)-stereoisomers ([(*E*)-17]:[(*Z*)-17] = 1.8:1, Fig. 6).

The properties of these new oleochemicals must be examined because thiophene derivatives are of importance in areas as diverse as pharmaceuticals, veterinary drugs, agrochemicals, and polymers.

Acylation with Cyclic Anhydrides

Cyclic anhydrides are known to be useful acylating agents (2). On reaction of 10-undecenol [2c] with glutaric anhydride, the ω -hydroxy carboxylic acid [18] with an additional β,γ -unsaturated keto functionality could be synthesized (Scheme 8). After recrystallization, the product was obtained as pure (*E*)-isomer.

The EtAlCl_2 -induced acylation of oleic acid [1a] with succinic anhydride afforded the corresponding β,γ -unsaturated keto dicarboxylic acid [19] as a 1:1 mixture of regioisomers with an (*E*)-configured double bond (Fig. 7).



SCHEME 7. Ethylaluminum dichloride-induced acylation of methyl oleate [1b] with thiophene-2-carboxylic acid chloride.

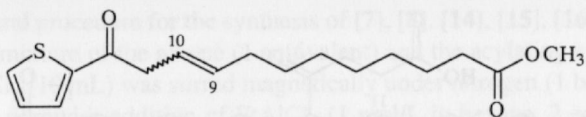


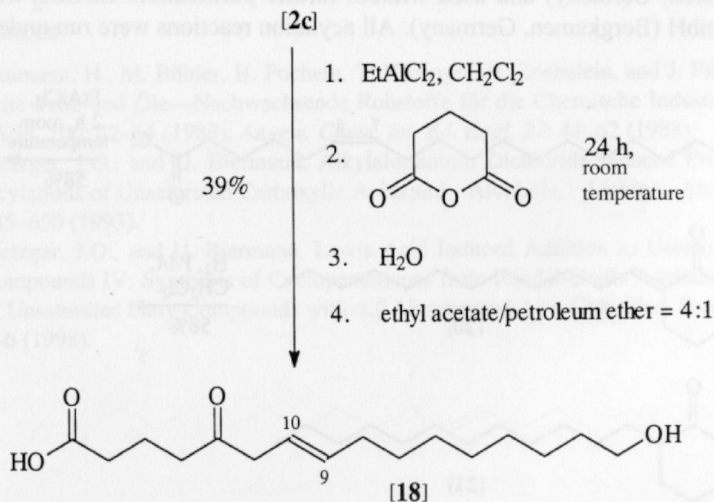
Fig. 6. Acylation product [17] from the reaction of methyl 10-undecenoate [2b] and thiophene-2-carboxylic acid chloride.

Intramolecular Acylations

Intramolecular acylations are also possible with unsaturated fatty compounds (2). The intramolecular reaction of petroselinic acid chloride and EtAlCl_2 gave the cyclic product [20] with an exocyclic double bond (Scheme 9). The ring closure took place regioselectively at C-6. The pure (*E*)-adduct was isolated in a yield of 58%. The unsaturated ketone [20] could be easily hydrogenated to give 2-dodecylcyclohexanone [21].

Conclusion

The alkylaluminum halide-induced Friedel-Crafts acylation is a very general and synthetically useful reaction that allows the functionalization of unsaturated fatty compounds. Acylations were carried out with different acylating agents such as acyl chlorides, dicarboxylic acid dichlorides, cyclic anhydrides, unsaturated acyl chlorides, and aromatic and heteroaromatic carboxylic acid chlorides, yielding a large



SCHEME 8. Ethylaluminum dichloride-induced acylation of 10-undecenol [2c] with glutaric anhydride.

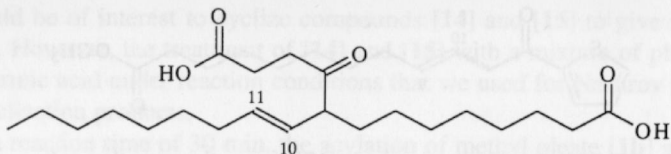


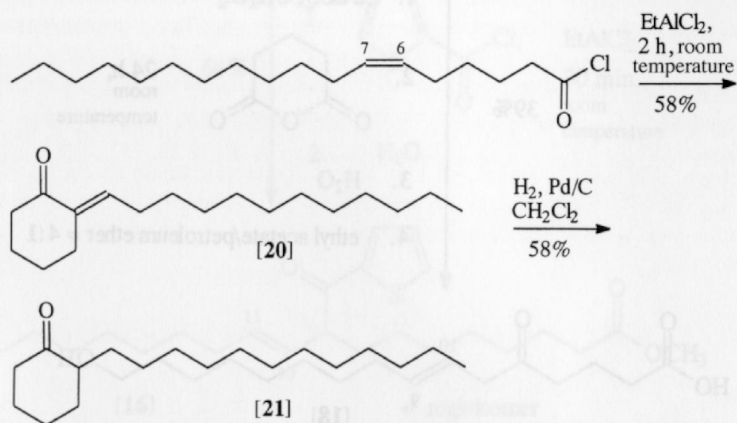
Fig. 7. Acylation product [19] from the reaction of oleic acid [1a] and succinic anhydride.

variety of new and highly functionalized oleochemicals containing an allylketo functionality.

Experimental

Experimental instructions are given for the synthesis of products [7], [8], [9], [14], [15], [16], and [17]. The synthesis of all other products reported in this paper is described in the literature (2,3).

Oleic acid (new sunflower, 82% oleic acid, 3.5 % palmitic acid, 0.6% stearic acid, 12% $C_{18:2}$), and methyl oleate (new sunflower, 82.8% methyl oleate, 3.6% methyl stearate, 3.5% methyl palmitate, 8.4% $C_{18:2}$) were obtained from Henkel KGaA (Düsseldorf, Germany). The amounts of the starting olefins used in the reactions were calculated on the basis of 100% purity. 10-Undecenoic acid was obtained from Atochem (Paris La Defense, France). Cyclopropanecarboxylic acid chloride, benzoyl chloride, and thiophene-2-carboxylic acid chloride were obtained from Aldrich (Deisenhofen, Germany) and used without further purification. $EtAlCl_2$ was from Witco GmbH (Bergkamen, Germany). All acylation reactions were run under N_2 .



SCHEME 9. Intramolecular $EtAlCl_2$ -induced acylation of petroselinic acid chloride.

The general procedure for the synthesis of [7], [8], [14], [15], [16], and [17] was as follows: a mixture of the alkene (1 equivalent) and the acylating agent (1 equivalent) in CH_2Cl_2 (10 mL) was stirred magnetically under nitrogen (1 bar) for 5 min at -15°C . After dropwise addition of EtAlCl_2 (1 mol/L in hexane, 2 equivalents), the sample was stirred for an additional 45 min at room temperature. The reaction was quenched by the addition of Et_2O (100 mL) and H_2O (40 mL); 10% HCl was added until the precipitated aluminum salts had dissolved. The organic layer was separated and washed with H_2O (3×30 mL). The organic layer was dried (Na_2SO_4) and the solvent evaporated. In the case of the synthesis of [9], methyl 10-undecenoate [2b], adipic acid dichloride, and EtAlCl_2 were used in a ratio of 2:1:4. The reaction procedure was carried out as described above. For characterization products, [7], [8], [14], and [15] were purified by column chromatography [28 cm \times 2 cm, silica gel 60 (Merck), 70–230 mesh] with the eluent petroleum ether/EtOAc (9:1, 100 mL and 7:3, 250 mL). Fractions containing the acylation product were collected, the solvent was evaporated, and the residue dried at $20^\circ\text{C}/0.01$ mbar. The acylation products [9], [16], and [17] were purified by "Kugelrohr" distillation (5×10^{-3} bar, 250°C for [9], 170°C for [16] and 200°C for [17]). All products were characterized unambiguously by their ^1H - and ^{13}C -NMR data and by mass spectrometry.

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References

1. Baumann, H., M. Bühler, H. Fochem, T. Hirsinger, H. Zobelein, and J. Falbe, *Natürliche Fette und Öle—Nachwachsende Rohstoffe für die Chemische Industrie*, *Angew. Chem.* 100: 42–64 (1988); *Angew. Chem. Int. Ed. Engl.* 27: 41–62 (1988).
2. Metzger, J.O., and U. Biermann, Alkylaluminium Dichloride Induced Friedel-Crafts Acylations of Unsaturated Carboxylic Acids and Alcohols, *Liebigs Ann. Chem.*, 645–650 (1993).
3. Metzger, J.O., and U. Biermann, Lewis Acid Induced Addition to Unsaturated Fatty Compounds IV: Synthesis of Cyclopentenones from Friedel-Crafts Acylation Products of Unsaturated Fatty Compounds with α,β -Unsaturated Acyl Chlorides, *Fett/Lipid* 100: 2–6 (1998).