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Homologues of Dihydro-12-oxo-phytodienoic Acid and Jasmonic Acid by Mixed Kolbe Electrolysis

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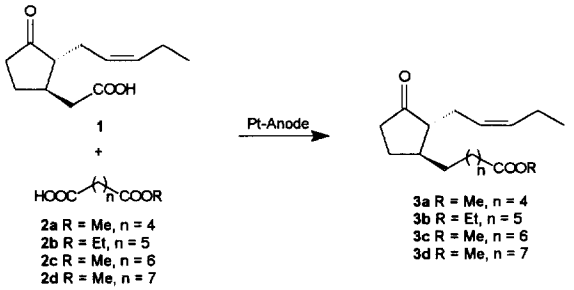
Abstract: A new short and highly flexible pathway to derivatives **3a-d** and **5** of dihydro-12-oxo-phytodienoic acid, using an electrochemical C-C bond coupling in an one-step procedure, is described. Jasmonic acid can be coupled with carboxylic acids in a mixed Kolbe electrolysis in acceptable yields. Functional groups are tolerated and, hence, the method offers a simple route to the title compounds which are otherwise difficult to prepare.

Jasmonic acid **1** and several of its biosynthetic precursors like, for example, dihydro-12-oxo-phytodienoic acid constitute a family of important plant hormones.[1] They induce the expression of specific genes that code for proteins (Jasmonate Induced Proteins, JIPs)[2] involved in the plants defence repertoire. Other, typically jasmonate induced responses are the phenomenon of senescence,[3] the emission of ethylene[4] and the biosynthesis of low-molecular toxins of alkaloid[5] or terpenoid[6] origin. Even the movement of touch-sensitive tendrils[7] are controlled by compounds from this octadecanoid signalling pathway. To understand the structure-function relationship of such compounds, on a molecular level, it is essential to have short and variable approaches to different derivatives and biosynthetic precursors of jasmonic acid **1**.

Here we describe a novel strategy for the synthesis of the methyl ester of dihydro-12-oxo-phytodienoic acid **3c** (dihydro-12-oxo-PDA), and some lower or higher homologues, based on an electrochemical coupling of jasmonic acid **1** with appropriate bifunctional carboxylic acids (half esters; 4-6 eq.) in one step (Scheme 1). It will be shown that the Kolbe electrolysis is generally applicable for the preparation of such compounds. The cross coupling reactions proceed without competing side reactions at the double bond of **1** and also without the formation of the dimer of jasmonic acid, except in example c where jasmonic acid is used in excess (cf. Table 1). Previous routes to the desired compounds were multi-step sequences including protection-deprotection steps.[8]

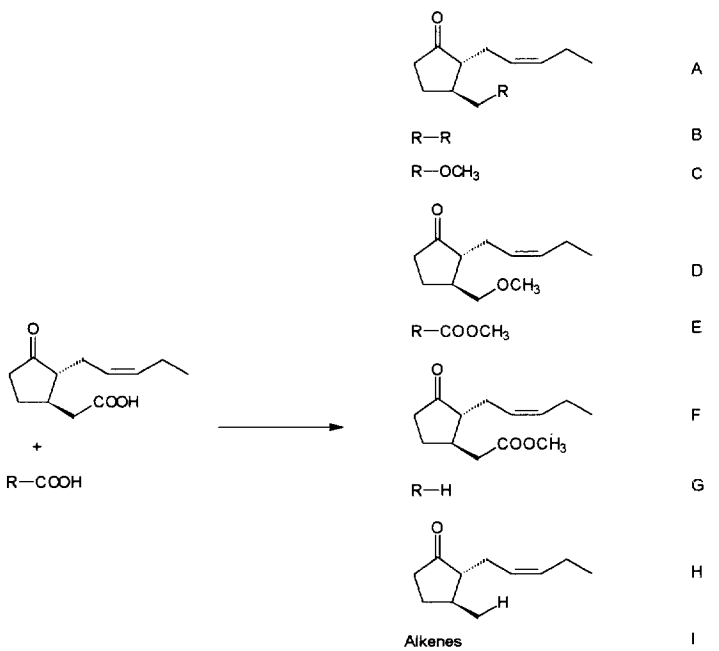


Scheme 1: Anodic cross-coupling of jasmonic acid with half esters of dicarboxylic acids

Yields and selectivities of the Kolbe synthesis[9] are strongly dependent on the structure of the acid and on reaction conditions, such as current density, temperature, pH, additives, solvent, the supporting electrolyte and electrode material. High current densities and high carboxylate concentrations favour the formation of dimers because of a high radical concentration at the electrode surface. High temperatures favour side-reactions, like for example disproportionation and additions to double bonds, over the coupling reaction.[10] A weakly acidic medium, achieved by neutralising the carboxylic acids with an alkali metal alkoxide to an extent of 2-30 %, is preferable for the Kolbe reaction. Additional anions and most electrode materials, except platinum, prevent the generation of the carboxylate layer at the anode surface that appears to be necessary for high yields of the coupling product. Methanol is the most suitable solvent for Kolbe electrolysis. Its oxidation is inhibited by the formation of the carboxylate layer.

The mixed Kolbe electrolysis first demonstrated by Wurtz[11] has become a powerful synthetic tool, for example it has been used in a number of efficient syntheses of pheromones.[9,12] An important advantage of this method is that functional groups in the carboxylic acid components are tolerated and, hence, protecting-deprotecting steps become unnecessary. As the intermediate radicals combine statistically, besides the expected cross-coupling product, two symmetrical dimers are generated. If the less costly acid is used in excess, the number of the major products is reduced to two, simplifying the isolation of the mixed dimer.

In addition to the desired unsymmetrical coupling (A) and the symmetrical coupling of the component taken in excess (B) other by-products were detected by GC-MS (Scheme 2). By optimising reaction conditions, i. e reaction temperature, the number and amount of by-products can be suppressed.



Scheme 2: Products of the mixed Kolbe electrolysis in methanol: A = desired product, B = product of the symmetrical coupling reaction, C/D = Hofer-Moest products, E/F = acidic esterification, G/H = decarboxylation, I = carbocation formation followed by E1-elimination

Coupling of jasmonic acid **1** with half esters of medium to long chain diacids **2** leads to esters **3** (Scheme 1, Table 1). We used four different half esters of long chain diacids to demonstrate that Kolbe electrolysis is a general method for the synthesis of derivatives of jasmonic acid. The yields are comparable

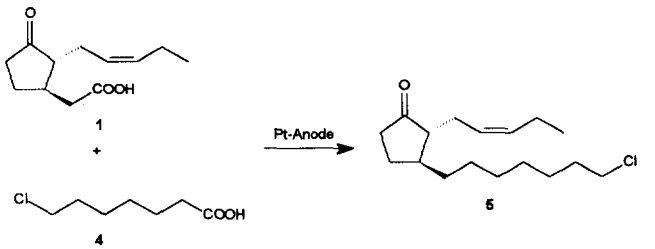
with mixed Kolbe electrolysis of other five-membered ring compounds.[13] This is remarkable, because the carboxylate group of jasmonic acid is sterically hindered.

Table 1: Results of the mixed Kolbe electrolysis of jasmonic acid **(1)** and half esters **2a-d** of diacids[18]

compound	R	n	ratio **1 : 2**	yield (%)[a] **3**
a	Me	4	1 : 5.2	18
b	Et	5	1 : 4.2	43
c	Me	6	1 : 5	28
c	Me	6	5 : 1	19[14]
d	Me	7	1 : 5.5	10[15]

[a] overall yield after work-up and purification by column chromatography

This method is not only applicable for half esters of dicarboxylic acids, but also for other functionalised carboxylic acids. 7-Chloro-enanthic acid **(4)** couples with jasmonic acid to give the desired product **5** in 24 % yield (Scheme 3).



Scheme 3: Coupling of jasmonic acid with 7-chloro-enanthic acid **(4)**

In conclusion, we have found a general method for the synthesis of early intermediates of the octadecanoid signalling pathway, in plants, by coupling commercially available jasmonic acid with half esters of dicarboxylic acids in an one-step procedure in yields up to 43 %.

The free acids of the esters **3a-d** (n = 4-7) have already been used in induction experiments in tomato, barley and Lima bean plants.[16] The series of C_{16} to C_{19} analogues of dihydro-12-oxo-PDA showed a clear and comparable up-regulation of certain JIP's in the tomato and barley test systems, but failed to give a down- regulation of other proteins as is typical for jasmonic acid. Moreover, in the Lima bean different profiles of volatiles were induced by treatment with jasmonic acid and the long-chain dihydro-12-oxo-PDA analogues, respectively. The data clearly support the existence of independent signalling pathways of the early and late intermediates of the octadecanoid signalling pathway in plants.[17]

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References and Notes

1. Sembdner, G.; Parthier, B. *Annu. Rev. Plant Physiol. Mol. Biol.* **1993**, *44*, 569-589.
2. Weidhase, R. A.; Kramell, H.; Lehmann, J.; Liebisch, H.; Lerbs, W.; Parthier, W. *Plant Sci. (Limmerick, Irel.)* **1987**, *51*, 177-186.
3. Ueda, J.; Kato, J. *Plant Physiol.* **1980**, *66*, 246-249.
4. Saniewski, M.; Czapski, J. *Experentia* **1985**, *41*, 256-257.

5. Gundlach, H.; Müller, M.J.; Kutchan, T.M.; Zenk, M.H. *Proc. Natl. Acad. Sci. USA* **1992**, *89*, 2389-2393.
6. Hopke, J.; Donath, J.; Blechert, S.; Boland, W. *FEBS Lett.* **1994**, *352*, 146-150.
7. Falkenstein, E.; Groth, B.; Mithöfer, A.; Weiler, E.W. *Planta* **1991**, *185*, 316-322.
8. Crombie, L.; Mistry, K.M. *J. Chem. Soc. Perkin Trans. I* **1991**, *8*, 1981-1991.
9. Schäfer, H. J. *Top. Curr. Chem.* **1990**, *152*, 91-151.
10. Woolford, R.G. *Can. J. Chem.* **1962**, *40*, 1846-1850; b) Woolford, R.G.; Arbic, W.; Rosser, A. *Ibid.* **1964**, *42*, 1788-1791.
11. Wurtz, A. *Ann. Chim. Phys.* **1855**, *44*, 291.
12. Jensen, U.; Schäfer, H.J. *Chem. Ber.* **1981**, *114*, 292-297; b) Knolle, J.; Schäfer, H.J. *Angew. Chem.* **1975**, *87*, 777; *Angew. Chem. Int. Ed. Engl.* **1975**, *14*, 758.
13. a) Seebach, D.; Renaud, P. *Helv. Chim. Acta* **1985**, *68*, 2342-2349; b) Ceder, O.; Nilsson, H.G.; *Acta Chem. Scand.* **1977**, *B 31*, 189-192.
14. The half ester is the more expensive compound and therefore the jasmonic acid was applied in excess.
15. The electrolysis was not optimised.
16. Wasternack, C.; Hopke, J.; Boland, W. unpublished results.
17. Blechert, S.; Brodschelm, W.; Hölder, S.; Kammerer, L.; Kutchan, T.M.; Müller, M.J.; Xia, Z. Q.; Zenk, M. *Proc. Natl. Acad. Sci. USA* **1995**, *92*, 4099-4105.
18. **General experimental procedure:** In an undivided methanol-cooled beaker type glass cell of 20 mL equipped with a Pt-foil anode (1.54 cm^2) and a steel cathode (to avoid catalytic hydrogenation of the double bond of the jasmonic acid) (distance between anode and cathode 0.7 cm) jasmonic acid and the coacid (4-6 eq) were dissolved in MeOH and neutralised to 10 % with NaOMe. The best results were achieved by using a current density of 0.5 A/cm^2 (voltage 200-300 V)[19] at a temperature of -15°C. The end of the electrolysis was shown by an increase of voltage. Purification is performed by column chromatography on silica gel with pentane / ether.
NMR-shifts: 3a: ^{1}H-NMR ($CDCl_3$, 400 MHz) δ = 5.22 (1H, dt, ^3J = 10.8 Hz, ^3J = 7.2 Hz), 5.05 (1H, dt, ^3J = 10.8 Hz, ^3J = 7.2 Hz), 3.60 (3H, s), 2.31-1.12 (20H, m), 0.88 (3H, t, ^3J = 7.5 Hz); ^{13}C-NMR ($CDCl_3$, 400 MHz) δ = 220.6, 173.7, 133.4, 125.4, 55.0, 51.4, 41.0, 38.0-20.5 (9C), 14.1; **3b**: ^{1}H-NMR ($CDCl_3$, 400 MHz) δ = 5.35 (1H, dt, ^3J = 10.8 Hz, ^3J = 7.2 Hz), 5.17 (1H, dt, ^3J = 10.8 Hz, ^3J = 7.2 Hz), 4.06 (2H, q, ^3J = 7.14), 2.31-1.12 (20H, m), 0.88 (3H, t, ^3J = 7,5 Hz); ^{13}C-NMR ($CDCl_3$, 400 MHz) δ = 220.8, 173.8, 133.4, 125.4, 60.2, 55.0, 41.1, 38.0-20.6 (10C), 14.3, 14.2; **3c** : ^{1}H-NMR ($CDCl_3$, 400 MHz) δ = 5.35 (1H, dt, ^3J = 10.8 Hz, ^3J = 7.2 Hz), 5.17(1H, dt, ^3J = 10.8 Hz, ^3J = 7.2 Hz), 3.60 (3H, s), 2.43-1.12 (24H, m), 0.89 (3H, t, ^3J = 7.4 Hz); ^{13}C-NMR ($CDCl_3$, 400 MHz) δ = 220.8, 174.3, 133.5, 125.5, 65.9, 55.0, 51.5, 41.1-20.6 (11C),14.2; **3d**: ^{1}H-NMR ($CDCl_3$, 400 MHz) δ = 5.35 (1H, dt, ^3J = 10.8 Hz, ^3J = 7.2 Hz), 5.18 (1H, dt, ^3J = 10.8 Hz, ^3J = 7.2 Hz), 3.60 (3H, s), 2.31-1.12 (26H, m), 0.89 (3H, t, ^3J = 7.5 Hz); ^{13}C-NMR ($CDCl_3$, 400 MHz) δ = 220.8, 174.3, 133.4, 125.5, 55.0, 51.4, 41.1, 38.1-20.6 (12C), 14,2; **5**: ^{1}H-NMR ($CDCl_3$, 400 MHz) δ = 5.41 (1H, dt, ^3J = 10.8 Hz, ^3J = 7.4 Hz), 5.05 (1H, dt, ^3J = 10.8 Hz, ^3J = 7.4 Hz), 3.53 (2H, t), 2.43-1.21 (22H, m), 0.93 (3H, t, ^3J = 7.4 Hz); ^{13}C-NMR ($CDCl_3$, 400 MHz) δ = 220.8, 173.7, 133.5, 125.4, 64.2, 55.0, 45.2, 41.1-20.5, 14.2.
19. Electrolysis with lower voltage should be possible by using special cells with a smaller distance between the electrodes, such as the flow-through cell with a 0.5 mm electrode gap described in the literature.[20]
20. Klotz-Berendes, B.; Schäfer, H.J.; Grehl, M.; Fröhlich, R. *Angew. Chem.* **1995**, *107*, 218-220; *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 189-191.

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