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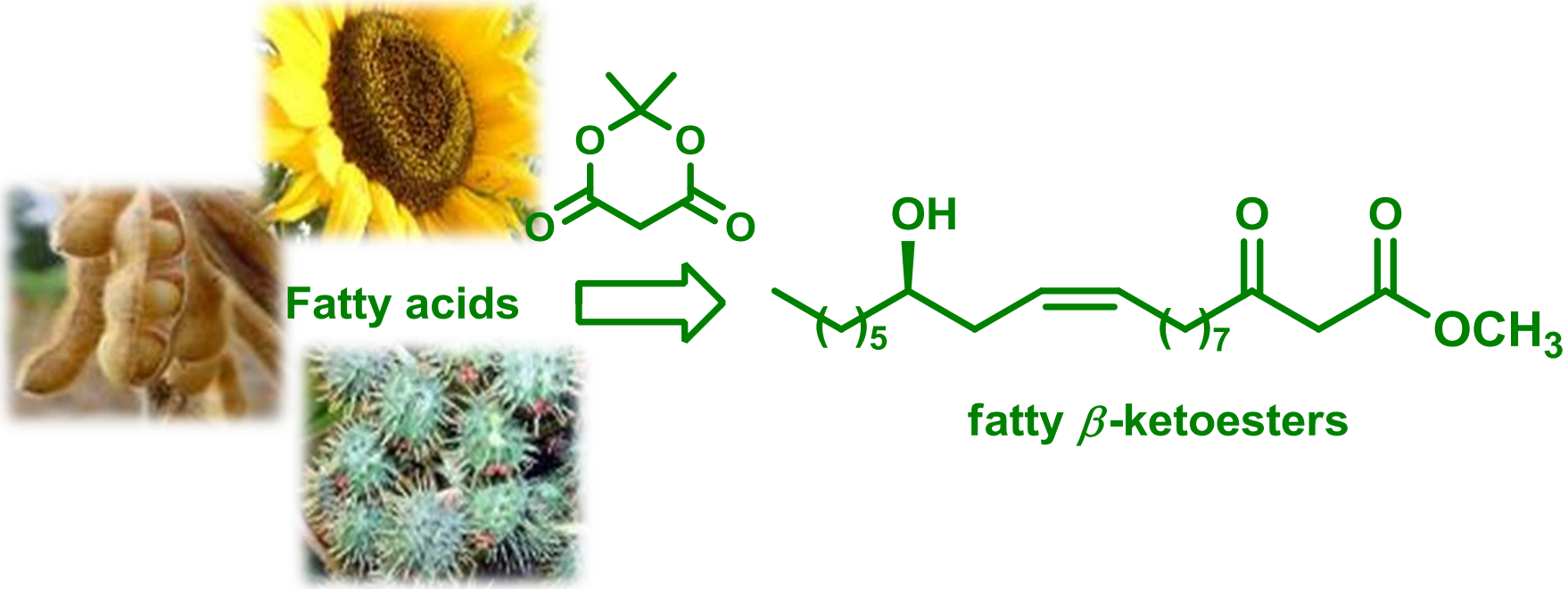

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ARTICLE TYPE

Synthesis of β-ketoesters from renewable resources and Meldrum's acid

Rafael C. Brinkerhoff[a], Hernan F. Tarazona[a], Patrick M. de Oliveira[a], Darlene C. Flores[a], Caroline Da R. Montes D'Oca[b], Dennis Russowsky[b], and Marcelo G. Montes D'Oca[a]*

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β-ketoesters are valuable building blocks for the synthesis of compounds with different biological activities. In this study, a series of fatty β-ketoesters were obtained from fatty acids and Meldrum's acid using *N,N*-dicyclohexylcarbodiimide and dimethylaminopyridine. In addition, we demonstrate for the first time the synthesis of new fatty β-ketoesters from oleic (*cis*-C18:1), elaidic (*trans*-C18:1), ricinoleic (*cis*-C18:1, 12-OH), linoleic (*cis*,*cis*-C18:2), and linolenic (*cis*,*cis*,*cis*-C18:3) acids in good yields.

β-ketoesters are extremely important and versatile organic compounds with a wide range of applications, including alpha-halogenation and alpha-azidation,[1] synthesis of thiazoles and thiophenes,[2] and use in multicomponent reactions.[1–6] Using β-ketoesters as the building blocks in multicomponent reactions yields several different structures based on the dihydropyridinone, tetrahydropyridine, or dihydropyridine skeleton, creating an extensive library of compounds with various biological activities.[4–7]

According to the literature, the transesterification process for the synthesis of β-ketoesters in solvent-free conditions without the use of catalysis results in high yields when using excess alcohol at a high temperature.[3] Primary, secondary, and tertiary alcohols have been tested in the presence of molecular sieves, resulting in good β-ketoester yields.[8] The catalysts in the transesterification reaction vary and include new silica-based hybrid materials,[9] triethylamine,[10] boric acid,[11] and triphenylphosphine.[12]

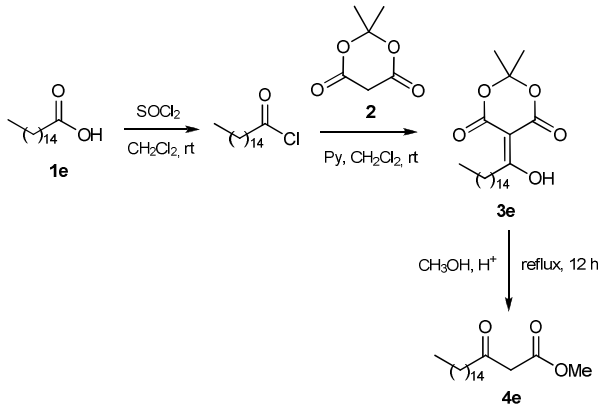
Claisen condensation is a classic method of β-ketoester synthesis. The condensation of the acid chlorides and esters catalysed by titanium tetrachloride and *N*-methylimidazole produces various β-ketoesters in good yields.[13] Crossed Claisen condensation reactions of ketene silyl acetals and methyl esters catalysed by sodium hydroxide have also resulted in good yields of various β-ketoesters.[14,15]

An important route for the synthesis of β-ketoesters is acylation of Meldrum's acid followed by a reaction with an alcohol. Oikawa *et al*.[16] showed that the acylation of various acyl chlorides with Meldrum's acid yielded the corresponding acyl Meldrum's acids, which readily underwent alcoholysis with methanol, ethanol, *tert*-butyl alcohol, benzyl alcohol, and trichloroethanol to produce various β-ketoesters.

C-acylation of Meldrum's acid by *N*-protected amino acids, using isopropenyl chloroformate (IPCF) or dicyclohexylcarbodiimide (DCC) and dimethylaminopyridine (DMAP) as the condensing agent, has been performed, and δ-amino-β-ketoesters have been obtained in high yields.[17]

In a continuation of our studies developing new fatty acid compounds,[18–20] we investigated the synthesis of β-ketoesters through acylation reactions of Meldrum's acid with different families of saturated and unsaturated carboxylic acids. In addition, we report for the first time the synthesis of new fatty β-ketoesters from oleic (*cis*-C18:1), elaidic (*trans*-C18:1), ricinoleic (*cis*-C18:1, 12-OH), linoleic (*cis*,*cis*-C18:2), and linolenic (*cis*,*cis*,*cis*-C18:3) acids.

Initially, experiments using palmitic acid (**1e**) as a model with thionyl chloride and pyridine in the presence of Meldrum's acid (**2**) were undertaken according to the literature (Scheme 1).[16] However, after a long reaction time, the fatty β-ketoester **4e** was obtained in a poor yield (43% from **1e**).



Scheme 1 Synthesis of fatty β-ketoester **4e** from Meldrum's acid (**2**) via a fatty acid chloride.

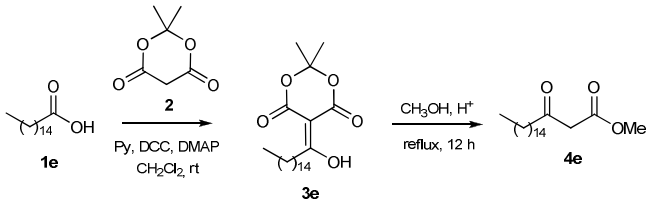
Therefore, afterward, we examined the use of DMAP and DCC as a coupling agent to synthesise the fatty β-ketoesters from Meldrum's acid and the fatty acids.

Experiments were carried out using palmitic acid (**1e**) as the model, along with Meldrum's acid (**2**), DCC, DMAP, and pyridine at room temperature under a nitrogen atmosphere. The

enol derivative **3e** was isolated and used without previous purification. Then, *β*-ketoester **4e** was obtained from a reaction of the respective enol **3e** and methanol in an acid catalyst at reflux for 12 h. The purified product **4e** was obtained in a 65% yield from **1e** (Scheme 2).

During the purification of *β*-ketoester **4e** by chromatography, a significant amount of methyl palmitate was obtained from what could only have been an acid-catalysed esterification reaction of unreacted palmitic acid (**1e**) from the acylation step with methanol.

To investigate the acylation reaction with various fatty acids (C6:0, C8:0, C10:0, C12:0, C18:0, *cis*-C18:1, *trans*-C18:1, C18:2, C18:3), we used the same protocol to obtain a wide range of fatty *β*-ketoesters, namely, **4a-d** and **4f-j**. However, the protocol resulted in the *β*-ketoester derivatives **4a-j** with saturated and unsaturated alkyl chains in moderate yields (Method A, Table 1).

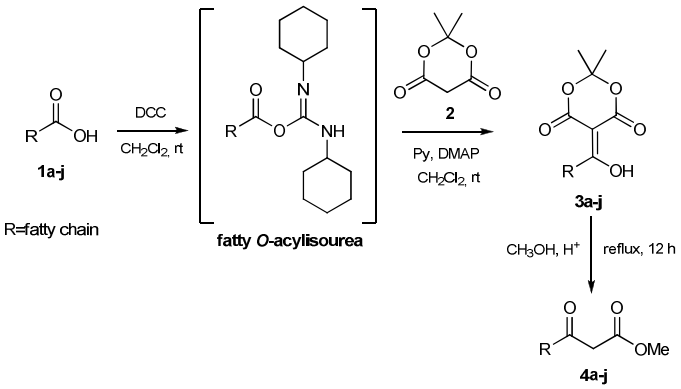


Scheme 2 Synthesis of fatty *β*-ketoester **4e** from Meldrum's acid (**2**) and fatty acid **1e** using DMAP and DCC as the coupling agents (Method A).

Next we examined a modified methodology that includes a two-step process. First, the effect of adding palmitic acid (**1e**) over DCC in the absence of Meldrum's acid (**2**) was studied. It has been proposed that the condensation reaction between DCC and carboxylic acids initially forms the *O*-acylisourea intermediate.[21] Indeed, in our experiments, after adding fatty acid over DCC, fatty *O*-acylisourea promptly formed. Next, adding 2.0 equiv of Meldrum's acid (**2**) in dichloromethane and pyridine under the same experimental conditions resulted in the formation of the enol derivative **3e** (Scheme 3). Subsequently, *β*-ketoester **4e** was obtained from the reaction of enol **3e** and methanol in an acid catalyst at reflux. Therefore, the modified protocol resulted in an increased yield (74%–84%) of the *β*-ketoester derivatives **4a-j** (Method B[22], Table 1).

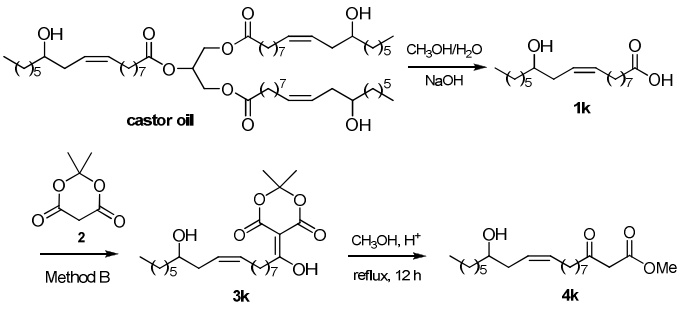
In this context, the moderated yield of fatty *β*-ketoesters **4a-j** obtained using the one-pot method (Method A) must be attributed to the consumption of DCC (the coupling agent) from the nucleophilic attack of Meldrum's acid (**2**).

In Method B, the addition of the fatty acid over DCC in the absence of Meldrum's acid, leading to the consumption of the complete fatty acid and the nucleophilic attack of Meldrum's acid (**2**) on the preformed fatty *O*-acylisourea, appears to have been crucial for the increased yield (Scheme 3).



Scheme 3 Synthesis of fatty *β*-ketoesters **4a-j** from Meldrum's acid (**2**) and the fatty acids **1a-j** (Method B).

Finally, the *β*-ketoester **4k** derivative from ricinoleic acid was synthesised (Scheme 4). Ricinoleic acid or 12-hydroxy-9-*cis*-octadecenoic acid is the major constituent (80%–90%) of castor oil (*Ricinus comunnis*)[23] and is an uncommon fatty acid that contains a double bond and a hydroxyl group in the chain. Compound **4k** was synthesised by Method B at room temperature under a nitrogen atmosphere using Meldrum's acid (**2**) and ricinoleic acid (*cis*-C18:1,12-OH, **1k**), which was obtained from the castor oil or via castor oil biodiesel hydrolysis. The purified product **4k**[28] was obtained in a 75% yield from **1k**.

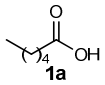
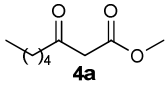
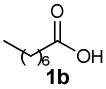
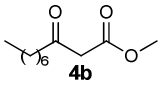
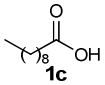
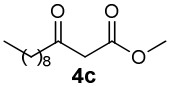
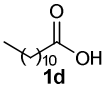
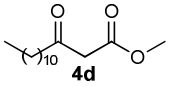
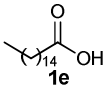
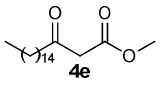
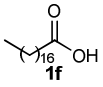
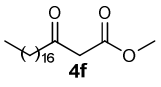
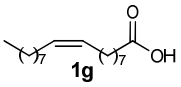
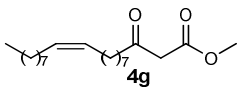
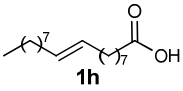
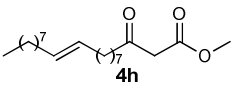
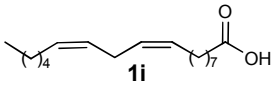
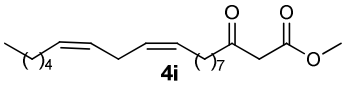
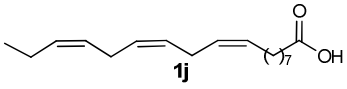
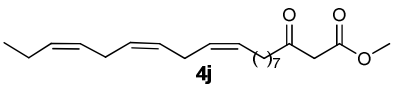


Scheme 4 Synthesis of a fatty *β*-ketoester from Meldrum's acid (**2**) and ricinoleic acid (**1k**, Method B).

Conclusions

In conclusion, we used a simple method to develop fatty *β*-ketoesters using Meldrum's acid and a wide range of fatty chains of saturated, unsaturated, and hydroxylated acids. We are currently in the process of synthesizing a series of new fatty acid dihydropyrimidinones with different structural arrangements using Biginelli's multicomponent protocol[29] in the presence of the new fatty *β*-ketoesters from renewable resources.

Table 1. Synthesis of β-ketoesters **4a-j** from fatty acids **1a-j**

Entry	Fatty acid	Fatty β-ketoester	Yield (%)	
			Method A	Method B
1	 **1a**	 **4a**	51	78
2	 **1b**	 **4b**	52	78
3	 **1c**	 **4c**	50	76
4	 **1d**	 **4d**	59	74
5	 **1e**	 **4e**	65	80
6	 **1f**	 **4f**	69	84
7	 **1g**	 **4g**	70	81 [24]
8	 **1h**	 **4h**	69	78 [25]
9	 **1i**	 **4i**	70	79 [26]
10	 **1j**	 **4j**	69	80 [27]

Acknowledgements

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Notes and References

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20 Rodrigues, M. O., Cantos, J. B., D'Oca, C. R. M., Soares, K. L., Coelho, T. S., Piovesan, L. A., Russowsky, D., Silva, P. A., D'Oca, M. G. M. *Bioorg. Med. Chem.* 2013, **21**, 6910.
21 Wiener, H., Gilon, C. *J. Mol. Catal.* 1986, **37**, 45.
22 *General procedure for synthesis of β-ketoesters **4a-k** (Method B):* fatty acid **1a-k** (1 mmol), DCC (1.1 mmol), and DMAP (0.3 mmol) were dissolved in dichloromethane (15 mL) and stirred for 30 min. Then, Meldrum's acid (2 mmol) and pyridine (3.6 mmol) were dissolved in dichloromethane (10 mL) and added dropwise. The mixture was stirred for 24 h at room temperature. The solid dicyclohexylurea formed was removed by filtration, and the filtrated organic layer was washed with an acid solution (10% HCl, 3 × 25 mL) and dried over Mg_2SO_4. The solvent was removed by reduced pressure and the respective enol **3a-k** was obtained. The crude product was dissolved in methanol (25 mL), and 5 drops H_2SO_4 were added to the mixture, which was refluxed for 12 h. The solvent was removed by reduced pressure, the residue was dissolved in dichloromethane (25 mL), and the organic layer was washed with distilled H_2O (3 × 25 mL) and dried over Mg_2SO_4. The solvent was removed by reduced pressure and the residue obtained was purified by flash column chromatography on silica gel, eluent, and either hexane/diethyl ether (97:3) to afford *β*-ketoesters **4a-j** or hexane/ethyl acetate (8:2) to obtain *β*-ketoester **4k**.
23 Lakshminarayana, G., Paulose, M. M., Kumari, N. B. *J. Am. Oil Chem. Soc.* 1984, **61**, 1871.
24 For **4g**: 81%, colorless oil. FT-IR (NaCl, film, ν = cm^{-1}) 3008.9, 2926.0, 2854.6, 1747.5, 1716.6, 1460.1, 1217.1, 758.1. ^1H NMR ($CDCl_3$): δ (ppm) 0.86 (t, 3H, J = 6.0 Hz, CH_3), 1.26 (m, 20H, CH_2), 1.57 (t, 2H, J = 6.0 Hz, CH_2 β-carbonyl), 1.99 (m, 4H, CH_2 allylic), 2.51 (t, 2H, J = 6.0 Hz, CH_2 α carbonyl), 3.43 (s, 2H, CH_2 bis-α carbonyl), 3.71 (s, 3H, OCH_3), 5.32 (m, 2H, 2CH vinylic). ^{13}C NMR ($CDCl_3$) δ (ppm) 14.0, 22.6, 23.4, 24.2, 27.1, 27.2, 28.9, 29.0, 29.2, 29.3, 29.5, 29.6, 29.7, 31.8, 43.0, 48.9, 52.3, 129.6, 129.9, 167.6, 202.8.
25 For **4h**: 78%, colorless oil. FT-IR (NaCl, film, ν = cm^{-1}) 3020.5, 2927.9, 2854.6, 11745.5, 1716.6, 1460.1, 1215.1, 758.0. ^1H NMR ($CDCl_3$): δ (ppm) 0.88 (t, 3H, J = 6.0 Hz, CH_3), 1.26 (m, 20H, CH_2), 1.59 (m, 2H, CH_2 β carbonyl), 1.96 (m, 4H, CH_2 allylic), 2.53 (t, 2H, J = 6.0 Hz, CH_2 α carbonyl), 3.45 (s, 2H, CH_2 bis-α carbonyl), 3.74 (s, 3H, OCH_3), 5.38 (m, 2H, CH vinylic). ^{13}C NMR ($CDCl_3$) δ (ppm) 14.1, 22.6, 23.4, 28.9, 29.0, 29.2 (2C), 29.3, 29.5, 29.6, 29.7, 31.9, 32.5, 32.6, 43.1, 49.0, 52.3, 130.2, 130.5, 167.7, 202.9.
26 For **4i**: 80%, colorless oil. FT-IR (NaCl, film, ν = cm^{-1}), 3014.0, 2927.1, 2856.3, 1747.2, 1716.1, 1462.7, 1438.1, 1215.0 ^1H NMR ($CDCl_3$): δ (ppm) 0.89 (t, 3H, J = 6.0 Hz, CH_3), 1.30 (m, 14H, CH_2), 1.59 (m, 2H, CH_2 β-carbonyl), 2.05 (q, J = 6.0 Hz, 4H, CH_2 allylic), 2.53 (t, 2H, J = 6.0 Hz, CH_2 α-carbonyl), 2.77 (t, 2H, J = 6.0 Hz, CH_2 bis-allylic), 3.45 (s, 2H, CH_2 bis -α carbonyl), 3.74 (s, 3H, OCH3), 5.34 (m, 4H, CH vinylic). ^{13}C NMR ($CDCl_3$) δ (ppm) 14.0, 22.5, 23.3, 25.5, 27.1 (2C), 28.9, 29.0, 29.2, 29.3, 29.5, 31.4, 43.0, 48.9, 52.3, 127.8, 128.0, 129.9, 130.1, 167.6, 202.8.
27 For **4j**: 80%, colorless oil. FT-IR (NaCl, film, ν = cm^{-1}), 3455.0, 2931.0, 2857.0, 1746.0, 1709.0, 1435.0, 1312.0, 1258.0, 1161.0, 1075.0, 971.0. ^1H NMR ($CDCl_3$): δ (ppm) 0.90 (t, 3H, J = 7.5 Hz, CH_3), 1.22 (m, 8H, CH_2), 1.51 (m, 2H, CH_2 β-carbonyl), 1.98 (m, 4H, CH_2 allylic), 2.46 (t, 2H, J = 7.5 Hz, CH_2 α-carbonyl), 2.73 (t, 4H, J = 6.0 Hz, CH_2 bis-allylic), 3.38 (s, 2H, CH_2 bis-α carbonyl), 3.66 (s, 3H, OCH_3), 5.28 (m, 6H, CH vinylic). ^{13}C NMR ($CDCl_3$) δ (ppm) 14.2, 20.4, 23.3, 25.4, 25.5, 27.1, 28.9, 29.0, 29.2, 29.5, 42.9, 48.9, 52.2, 127.0, 127.6, 128.1, 128.2, 130.1, 131.8, 167.7, 202.8.
28 For **4k**: 75%, colorless oil. FT-IR (NaCl, film, ν = cm^{-1}), 3489.2, 3018.6, 2929.8, 2856.5, 1737.8, 1714.7, 1438.9, 1215.1. ^1H NMR ($CDCl_3$): δ (ppm) 0.81 (t, 3H, J = 6.0 Hz, CH_3), 1.22 (m, 16H, CH_2), 1.40 (m, 2H, CH_2-*α*-OH), 1.52 (m, 2H, CH_2 *β*-carbonyl), 1.97 (q, 2H, J = 6.0 Hz, CH_2 allylic), 2.14 (t, 2H, J = 6.0 Hz, CH_2 allylic-*α*-OH), 2.46 (t, 2H, J = 6.0 Hz, CH_2 *α*-carbonyl), 3.38 (s, 2H, CH_2 bis-*α*-carbonyl), 3.54 (q, 1H, J = 6.0 Hz, CH carbinolic), 3.67 (s, 3H, OCH_3), 5.33 (m, 1H, CH vinylic), 5.48 (m, 1H, CH vinylic). ^{13}C NMR ($CDCl_3$) δ (ppm) 13.0, 21.6, 22.3, 24.7, 26.3, 27.9, 28.0, 28.1, 28.3, 28.5, 30.8, 34.3, 35.8, 42.0, 48.0, 51.3, 70.4, 124.2, 132.3, 166.7, 201.8.
29 Russowsky, D., Lopes, F. A., da Silva, V. S. S., Canto, K. F. S., D'Oca, M. G. M., Godoi, M. N. *J. Braz. Chem. Soc.* 2004, **15**, 165.