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A Short and Efficient Synthesis of Crocetin-dimethylester and Crocetindial

Daniel Frederico, Paulo Marcos Donate,* Mauricio Gomes Constantino, Erika Soares Bronze, and Mirela I. Sairre

Departamento de Química, Faculdade de Filosofia, Ciências e Letras de Ribeirão Preto, Universidade de São Paulo, 14040-901 Ribeirão Preto, SP, Brazil

pmdonate@usp.br

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Abstract: In this paper we describe an efficient six-step synthesis of crocetin-dimethylester that could be further reduced to a "four-step" synthesis through the use of in situ procedures. The simplicity of the whole process, the ready availability of starting materials, and the high overall yield render this strategy a very attractive synthesis of this very important compound, which is the key intermediate for the synthesis of several carotenoids and other polyene natural products.

The polyene chains **1**−**2** (Figure 1) are the starting materials for the syntheses of carotenoids, which are compounds widely distributed among plants, animals, and certain bacteria, that are used as natural pigments for foodstuffs.[1] It is well-known that certain carotenoids have important biochemical and biological functions, and have nutritional importance as provitamin A in man.[2] Recently, the use of carotenoids as chemoprevention agents against certain types of cancer has been reported.[3] The usage of carotenoids as food additives has been dramatically increased.

Crocin (**3**) and crocetin (**4**) esters are the coloring principles of saffron, which find uses in medicine as well as flavoring and coloring agents.[4] The crocetin-dimethylester (**1**) is a very useful compound because it can be easily converted to crocetindial (**2**) and crocin or crocetin

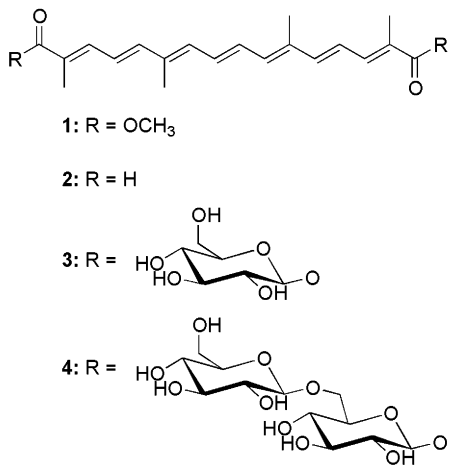

FIGURE 1. Structure of polyene chains.

derivatives,[5] and can be used as starting material for the syntheses of carotenoids and many other natural products.[1,4a,5]

The traditional synthetic approaches for compounds **1**−**4** involve the bismetal acetylide coupling/partial hydrogenation[1,6] or the Wittig and related reactions.[1,7] However, these procedures invariably produce a mixture of isomers, requiring careful, tedious, and unproductive isolation−purification processes.[1,2c] The highly efficient Julia's sulfone olefination protocol[8] has found wide use in the preparation of simple double bonds and conjugated polyenes, but the presumed instability of some intermediates has limited the general utilization of this method.[9] For this reason, the search continues for new, selective,

(1) (a) Isler, O., Ed. *Carotenoids*; Birkhäuser Verlag: Basel, Switzerland, 1971. (b) Isler, O. *Pure Appl. Chem.* **1979**, *51*, 447. (c) Widmer, E. *Pure Appl. Chem.* **1985**, *57*, 741. (d) Pfander, H., Ed. *Key to Carotenoids*, 2nd ed.; Birkhäuser Verlag: Basel, Switzerland, 1987. (e) Bernhardt, K.; Mayer, H. *Pure Appl. Chem.* **1991**, *63*, 35. (f) Paust, J. *Pure Appl. Chem.* **1991**, *63*, 45. (g) Britton, G.; Liaaen-Jensen, S.; Pfander, H., Eds. *Carotenoids*; Vol. 2, Synthesis; Birkhäuser: Neward, Switzerland, 1996.

(2) (a) Goodwin, T. W., Ed. *Chemistry and Biochemistry of Plant Pigments*; Academic Press: London, UK, 1976. (b) Bauernfeind, J. C. *Carotenoids as Colorants and Vitamin A Precursors*; Academic Press: New York, 1981. (c) Britton, G.; Goodwin, T. W., Eds. *Carotenoid: Chemistry and Biochemistry*; Pergamon Press: Oxford, UK, 1982. (d) Bendich, A.; Olson, J. A. *FASEB J.* **1989**, *3*, 1927. (e) Olson, J. A. *J. Nutr.* **1989**, *119*, 94. (f) Krinsky, N. I. *Carotenoids: Chemistry and Biology*; Plenum: New York, 1990. (g) Miki, W. *Pure Appl. Chem.* **1991**, *63*, 141. (h) Britton, G. *FASEB J.* **1995**, *9*, 1551.

(3) (a) Ames, B. N. *Science* **1983**, *221*, 1256. (b) Krinsky, N. I. *Clin. Nutr.* **1988**, *7*, 107. (c) Bendich, A. *J. Nutr.* **1989**, *119*, 112. (d) Ziegler, R. G. *J. Nutr.* **1989**, *119*, 116. (e) Ziegler, R. G. *Am. J. Clin. Nutr.* **1991**, *53*, 2515. (f) Malone, W. F. *Am. J. Clin. Nutr.* **1991**, *53*, S305. (g) Sengupta, A.; Das, S. *Eur. J. Cancer Prevent.* **1999**, *8*, 325. (h) Pérez-Gálvez, A.; Mínguez-Mosquera, M. I. *J. Agric. Food Chem.* **2001**, *49*, 4864 and references therein.

(4) (a) Pfander, H.; Wittwer, F. *Helv. Chim. Acta* **1975**, *58*, 1608. (b) Gainer, J. L.; Jones, J. R. *Experientia* **1975**, *31*, 548. (c) Gainer, J. L.; Wallis, D. A.; Jones, J. R. *Oncology* **1976**, *33*, 222. (d) Nair, S. C.; Pannikar, B.; Panikkar, K. R. *Cancer Lett.* **1991**, *57*, 109. (e) Salomi, M. J.; Nair, S. C.; Panikkar, K. R. *Nutr. Cancer* **1991**, *16*, 67. (f) Morimoto, S.; Umezaki, Y.; Shoyama, Y.; Saito, H.; Nishi, K.; Irino, N. *Planta Med.* **1994**, *60*, 438. (g) Escribano, J.; Alonso, G. L.; Coca-Prados, M.; Fernandes, J. A. *Cancer Lett.* **1996**, *100*, 23. (h) Konashima, T.; Takasaki, M.; Tokuda, H.; Morimoto, S.; Tanaka, H.; Kawata, E.; Xuan, L. J.; Saito, H.; Sugiura, M.; Molnar, J.; Shoyama, Y. *Phytother. Res.* **1998**, *12*, 400.

(5) Pfander, H.; Wittwer, F. *Helv. Chim. Acta* **1979**, *62*, 1944.

(6) (a) Inhoffen, H. H.; Isler, O.; Bey, G. V. D.; Raspé, G.; Zeller, P.; Ahrens, R. *Liebigs Ann. Chem.* **1953**, *580*, 7. (b) Mildner, P.; Weedon, B. C. L. *J. Chem. Soc.* **1953**, 3294. (c) Ahmad, R.; Weedon, B. C. L. *J. Chem. Soc.* **1953**, 3299. (d) Isler, O.; Lindlar, H.; Montavon, M.; Rüegg, R.; Zeller, P. *Helv. Chim. Acta* **1956**, *39*, 249. (e) Manchand, P. S.; Rüegg, R.; Schwieter, U.; Siddons, P. T.; Weedon, B. C. L. *J. Chem. Soc.* **1965**, 2019.

(7) (a) Buchta, E.; Andree, F. *Chem. Ber.* **1960**, *93*, 1349. (b) Pommer, H.; Kuhn, R. *Angew. Chem.* **1960**, *72*, 911. (c) Pommer, H.; Nürrenbach, A. *Pure Appl. Chem.* **1975**, *43*, 527. (d) Pommer, H. *Angew. Chem.* **1977**, *89*, 437. (e) Zumbrunn, A.; Uebelhart, P.; Eugster, C. H. *Helv. Chim. Acta* **1985**, *68*, 1519.

(8) (a) Julia, M.; Arnould, D. *Bull. Soc. Chim. Fr.* **1973**, 743. (b) Julia, M.; Arnould, D. *Bull. Soc. Chim. Fr.* **1973**, 746. (c) Olson, G. L.; Cheung, H.-C.; Morgan, K. D.; Neukom, C.; Saucy, G. *J. Org. Chem.* **1976**, *41*, 3287. (d) Fischli, A.; Mayer, H.; Simon, W.; Stoller, H.-J. *Helv. Chim. Acta* **1976**, *59*, 397. (e) Otera, J.; Misawa, H.; Onishi, T.; Suzuki, S.; Fujita, Y. *J. Org. Chem.* **1986**, *51*, 3834. (f) Hagen, J.; Klaus, K.; Manfred, H. Eur. Patent 523 534, 1992.

(9) (a) Buchta, E.; Andree, F. *Ann.* **1961**, *640*, 29. (b) Surmatis, J. D.; Ofner, A. *J. Org. Chem.* **1961**, *26*, 1171. (c) Okukado, N.; Uchikawa, O.; Nakamura, Y. *Chem. Lett.* **1988**, 1449. (d) Choi, H.; Ji, M.; Park, M.; Yun, I.-K.; Oh, S.-S.; Baik, W.; Koo, S. *J. Org. Chem.* **1999**, *64*, 8051 and references therein.

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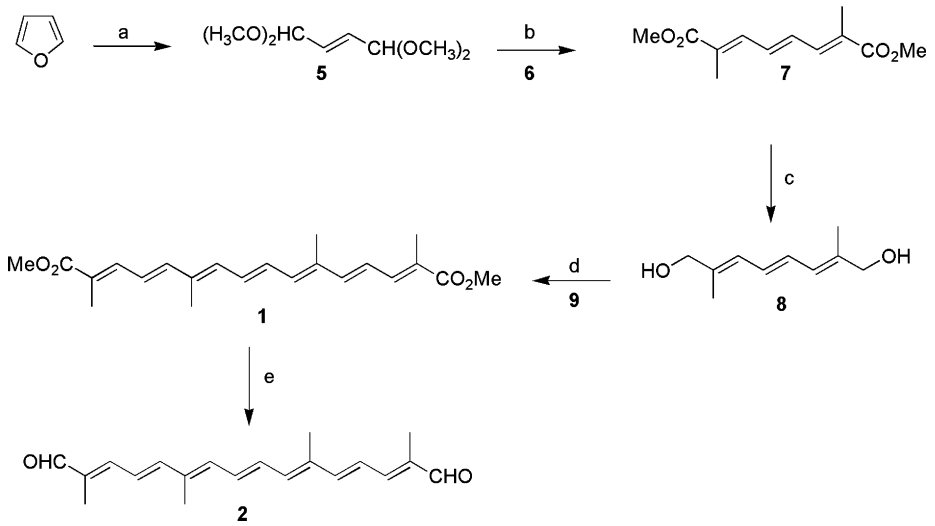
SCHEME 1. Synthesis of Crocetin-dimethylester (1) and Crocetindial (2)[a]



[a] Reagents: (a) (i) Br_2, CH_3OH, (ii) Na_2CO_3, 75%; (b) Amberlyst-15, CH_2Cl_2, H_2O (2 equiv), **6** (2 equiv), 73%; (c) $LiAlH_4$, THF, 93%; (d) MnO_2, CH_2Cl_2, **9** (2 equiv), 75%; (e) (i) DIBALH, CH_2Cl_2, (ii) H_2O, (iii) MnO_2, 55−63%.

and efficient routes for the synthesis of polyene chains, carotenoids, and related natural products.[10]

In this paper, we describe a short and efficient synthetic route to obtain crocetin-dimethylester (**1**) using in situ procedures, involving one-pot hydrolysis of ketals or oxidation of alcohols followed by Wittig reactions. Compound **1** was later converted in crocetindial (**2**) in a two-step process.

The synthesis starts by treatment of furan with a solution of bromine in methyl alcohol followed by sodium carbonate, according to the procedure described by Grée et al.,[11] to give the fumaraldehyde dimethylacetal **5** as a colorless oil with a 75% yield (Scheme 1). Compound **5** was submitted to an in situ hydrolysis-Wittig reaction sequence by treatment with Amberlyst-15 in a two-phase solvent system consisting of a mixture of methylene chloride and water,[12] and 2 equiv of 2-(triphenyl-λ^5-phosphanylidene)propionic acid methyl ester (phosphorane **6**) (prepared in two steps from methyl 2-bromopropionate in 41% overall yield[13] or alternatively in four steps from ethyl bromoacetate in 87% overall yield[14]) to give only the all-*E* isomer of compound **7**, in 73% yield from dimethyl acetal **5**, as a white solid.[15]

Reduction of **7** with lithium aluminum hydride produced diol **8**, which was purified by recrystallization from *n*-hexane to give a white solid in 93% yield.[18] Compound **8** was submitted to an in situ oxidation-Wittig reaction[16] sequence with manganese dioxide and 2 equiv of the 2-methyl-4-(triphenyl-λ^5-phosphanylidene)but-2-enoic acid methyl ester (phosphorane **9**) (prepared in four steps in 32% overall yield from the commercially available tiglic acid).[6a,7a,13,17,19] The all-*E* isomer of compound **1** was thus obtained in 75% yield from **8** as a brick-red solid after purification through silica gel column chromatography. This reaction also supplied (∼15% yield) the geometric isomer of compound **1** with the double bond in carbons 4 and/or 12 with *Z* stereochemistry. The reaction of **1** with diisobutylaluminum hydride in methylene chloride at −20 °C afforded the corresponding diol, which was submitted to oxidation with manganese dioxide without further purification to give compound **2** in 55−63% yield as a red solid.

In summary, the crocetin-dimethylester (**1**) was obtained from furan by a short and efficient six-step synthesis (or four isolation−purification operations) with an overall yield of 38%. This compound was then converted in crocetindial (**2**) in two steps (or one isolation−purification operation) in 55−63% overall yield. The careful, tedious, and yield-lowering isomer separation and product purification steps associated with the conventional syntheses of the polyene chain of carotenoids can be circumvented by the methodology reported here. This strategy can possibly be applied to the synthesis of several kinds of related natural products.

Experimental Section

(2*E*)-1,1,4,4-Tetramethoxybut-2-ene (5). Freshly distilled furan (9.40 mL, 129 mmol) and anhydrous methyl alcohol (65 mL) were placed in a 250-mL three-necked flask and cooled to −45 °C under a nitrogen atmosphere. A solution of bromine (6.80 mL; 133 mmol) in methyl alcohol (65 mL) was added dropwise at such a rate that the temperature did not exceeded −25 °C. At the end of the addition, the reaction mixture was stirred for 2 h at −10 °C. Powdered anhydrous sodium carbonate (40 g) was added portionwise over a period of about 30 min and the

(10) Zeng, F.; Negishi, E. *Org. Lett.* **2001**, *3*, 719 and references therein.
(11) Grée, R.; Tourbah, H.; Carrié, R. *Tetrahedron Lett.* **1986**, *27*, 4983.
(12) Coppola, G. M. *Synthesis* **1984**, 1021.
(13) Isler, O.; Gutmann, H.; Montavon, M. *Helv. Chim. Acta* **1957**, *40*, 1242.
(14) Jansen, F. J. H. M.; Lugtenburg, J. *Pure Appl. Chem.* **1994**, *66*, 963.
(15) Fischetti, W.; Mak, K. T.; Stakem, F. G.; Kim, J.-I.; Rheingold, A. L.; Heck, R. F. *J. Org. Chem.* **1983**, *48*, 948.
(16) Wei, W.; Taylor, R. K. *J. Org. Chem.* **2000**, *65*, 616.
(17) Ingold, K. V.; Roberts, B. P. *Free Radical Substitution Reactions*; John Wiley & Sons: New York, 1971; p 22.
(18) (a) Inhoffen, H. H.; Bey, G. V. D. *Liebigs Ann. Chem.* **1953**, *583*, 100. (b) Inhoffen, H. H.; Krause, H. J.; Bork, S. *Liebigs Ann. Chem.* **1954**, *585*, 132.
(19) Duffield, J. J.; Pettit, G. R. *J. Nat. Prod.* **2001**, *64*, 472.

reaction mixture was stirred for 18 h at room temperature. The mixture was then filtered and the solvent was removed under vacuum. The residue was purified by distillation (65−70 °C, 1 mmHg) and compound **5** (17.1 g; 97 mmol) was obtained in 75% yield.

Dimethyl (2*E*,4*E*,6*E*)-2,7-Dimethylocta-2,4,6-triene-1,8-dioate (7). A solution of compound **5** (0.636 g; 3.6 mmol) in methylene cloride (15 mL) was added to a solution of phosphorane **6** (2.54 g; 7.3 mmol) in methylene cloride (40 mL). Amberlyst-15 (0.420 g) and water (0.13 mL; 7.2 mmol) were added and the suspension was stirred for 1 h at room temperature. The solvent was removed under vacuum and the residue was purified by column chromatography through silica gel, using a mixture of *n*-hexane and ethyl acetate (8.5:1.5) as eluent. After evaporation of the solvent, compound **7** was obtained in 73% yield (0.589 g; 2.6 mmol).

***(2E,4E,6E)*-2,6-Dimethylocta-2,4,6-triene-1,8-diol (8).** A solution of compound **7** (0.180 g; 0.8 mmol) in dry THF (6 mL) was added to lithium aluminum hydride (0.075 g; 1.98 mmol) in dry THF (30 mL) at 0 °C. The mixture was stirred at this temperature for 10 min. The reaction was quenched by successive addition of water (0.12 mL), 15% aqueous sodium hydroxide (0.12 mL), and again water (0.24 mL). The solid was removed by filtration and the solvent was evaporated. The residue was recrystallized from *n*-hexane to give compound **8** in 93% yield (0.125 g; 0.74 mmol).

Dimethyl (2*E*,4*E*,6*E*,8*E*,10*E*,12*E*,14*E*)-2,6,11,15-Tetramethylhexadeca-2,4,6,8,10,12,14-heptaene-1,16-dioate (1). A mixture of compound **8** (0.040 g; 0.24 mmol), phosphorane **9** (0.195 g; 0.52 mmol), and manganese dioxide (0.310 g; 3.56 mmol) in dry methylene chloride (15 mL) was stirred at room temperature for 24 h. The reaction was monitored by TLC (8.5:1.5 *n*-hexane:ethyl acetate) until the starting material was no longer detectable. The solid was removed by filtration through a pad of magnesium sulfate, which was then washed with additional methylene chloride. The solvent was removed under vacuum and the residue was purified by column chromatography through silica gel, using a mixture of *n*-hexane and ethyl acetate (8.5:1.5) as eluent. After evaporation of the solvent, compound **1** was obtained in 75% yield (0.064 g; 0.18 mmol).

(2*E*,4*E*,6*E*,8*E*,10*E*,12*E*,14*E*)-2,6,11,15-Tetramethylhexadeca-2,4,6,8,10,12,14-heptaene-1,16-dial (2). To a solution of compound **1** (0.030 g; 0.084 mmol) in dry methylene chloride (5 mL) was added a solution (0.5 M) of diisobutylaluminum hydride in dry methylene chloride (0.50 mL; 0.252 mmol) at −20 °C. The mixture was stirred at this temperature for 30 min in the dark. Subsequently, water (0.2 mL) was added and the suspension was strongly stirred for 5 h at room temperature. Manganese dioxide (0.120 g; 1.26 mmol) was then added and the reaction mixture was stirred at room temperature for an additional 12-h period. The solid was removed by filtration through a pad of magnesium sulfate and washed several times with methylene chloride. The solvent was removed under vacuum and the residue was purified by column chromatography through silica gel, using a mixture of *n*-hexane and ethyl acetate (1:1) as eluting solvent. After evaporation of the solvent, compound **2** was obtained in 55−63% yield (0.013−0.015 g; 0.046−0.53 mmol).

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Supporting Information Available: General methods and characterization data for compounds **1**, **2**, **5**, **7**, and **8**. This material is available free of charge via the Internet at http://pubs.acs.org.

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