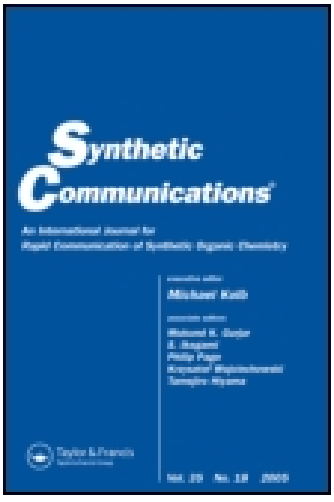

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Convenient Preparation of 2,7,8-Trimethyl-6-hydroxychroman-2-carboxylic Acid (γ-Trolox)

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Convenient Preparation of 2,7,8-Trimethyl-6-hydroxychroman-2-carboxylic Acid (γ-Trolox)

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Abstract: The title chroman is useful in synthesis and as a water-soluble analog of γ-tocopherol, a member of the vitamin E family. This new synthesis of γ-trolox proceeds via selective aromatic demethylation of Trolox, the more easily available 2,5,7,8-tetramethyl homolog compound. This route is shorter than the previous synthesis, avoids the use of cyanide and methoxybutadiene, and requires no chromatography.

Keywords: aromatic demethylation, decarbonylation, tocopherol, tocotrienol, tocol, Trolox

In 1974, a group at Hoffman-LaRoche published the syntheses and antioxidant activities of a series of carboxylic acid analogs of vitamin E (α-tocopherol, **1**).[1] Of some 30 homologous compounds, 2,5,7,8-tetramethyl-6-hydroxychroman-2-carboxylic acid **2** ("Trolox") showed the best combination of high antioxidant activity and good water solubility and was produced commercially.

Trolox (available from Sigma-Aldrich) has subsequently been proven to be a very useful starting material for the synthesis of a wide variety of chromans. Such varied uses for Trolox derivatives as anti-inflammatories,[2]

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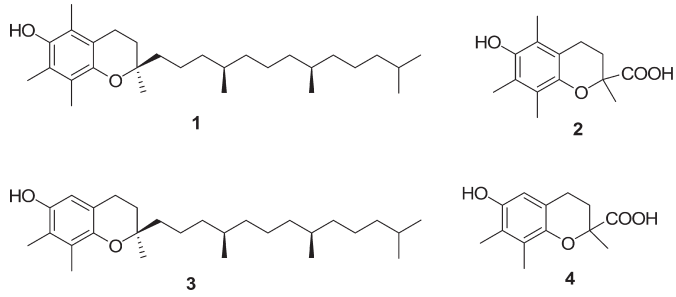
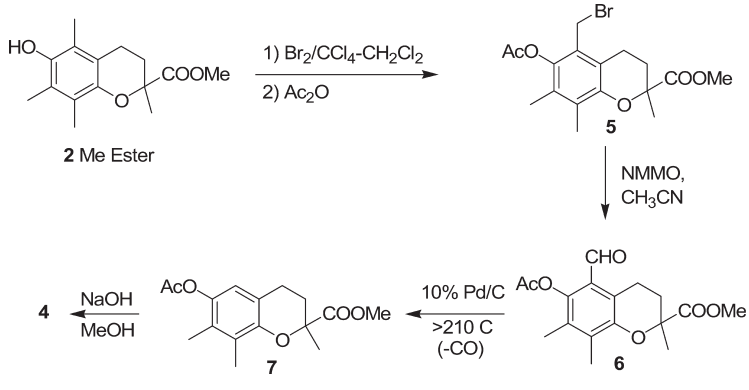
nematic liquid crystals,[3] NO-releasing drug candidates,[4] and synthons in natural product synthesis[5,6] have been published. A number of syntheses of (*S*)-**2** and its reduced analogs have also appeared.[5]



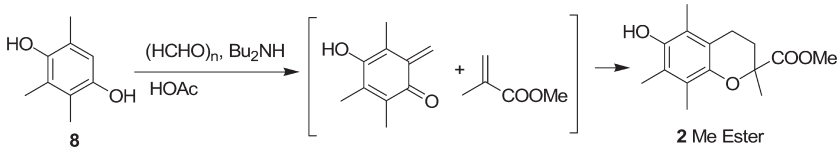
The existence of heretofore unsuspected nonantioxidant biological activities in γ-tocopherol **3**[7,8] and the related γ-tocotrienol[9,10] have prompted interest in the synthesis of these and related natural products.[11–13] As part of an effort to synthesize tocotrienols, we required as a starting material 2,7,8-trimethyl-5-hydroxychroman-2-carboxylic acid **4**, the γ-homolog of Trolox **2**.

Compound **4** had been synthesized by the Roche group[1] using a seven-step route which started with a difficult and inefficient monoprotection of 2,3-dimethylhydroquinone and required large amounts of cyanide and the expensive reagent 2-methoxybutadiene. Inspired by the chemistry of Mazzini et al.[14] who demonstrated a selective demethylation of α-tocopherol **1** to provide γ-tocopherol **3**, we decided to explore the conversion of readily available Trolox **2** into the desired γ-trolox **4**. We were gratified to find that the chemistry shown in Scheme 1 allowed preparation of **4** from the methyl ester of **2** in a five-step sequence that required no chromatography and involved only three isolated intermediates.



Scheme 1.

Although Trolox methyl ester (**2** methyl ester) is readily prepared from the commercial free acid via Fischer esterification,[3] we also provide details of a one-step synthesis of this compound. Using the hetero-Diels–Alder reaction of methacrylates with in situ–generated o-quinone methides pioneered by Shitara et al.[3] and by Buyukkidan, Bilgic, and Bilgic,[15] reaction of trimethylhydroquinone **8** with paraformaldehyde, dibutylamine, acetic acid, and excess methyl methacrylate gave an acceptible yield of **2** methyl ester. This procedure avoids the use of the high-pressure conditions used to prepare **2** methyl ester patented by Tanaka et al.[16] and is far shorter than the route of Scott et al.[1]



8 **2** Me Ester

Treatment of **2** methyl ester with bromine in a mixture of dichloromethane and carbon tetrachloride cleanly provided the 5-(bromomethyl) compound, but this material was very sensitive toward elimination of HBr to form an o-quinone methide that dimerized in situ. This problem was sidestepped by O-acetylation after completion of the bromination; bromoacetate **5** was obtained in 78% yield after recrystallization. This unusually selective bromination is well known in the case of vitamin E **1** and was studied mechanistically by Rosenau and Habicher.[17] Oxidation of bromoacetate **5** with N-methylmorpholine-N-oxide in acetonitrile afforded a 71% yield of crystalline aldehyde **6**.

Although Mazzini et al.[14] oxidized 5-formyl-α-tocopherol to the correspoding carboxylic acid and obtained γ-tocopherol by decarboxylation, it appeared to us that decarbonylation of the aldehyde would provide direct access to the γ-series. We were therefore disappointed to find that attempts to decarbonylate acetate **6** (or the corresponding phenol) using the preferred rhodium complexes[18,19] in catalytic or stoichiometric quantities under a variety of conditions gave only recovered starting material. Similarly, attempted scandium triflate–catalyzed decarbonylation[20] gave very low conversion to the desired product **7**. We were therefore gratified to observe that, upon heating at 210–220°C neat in the presence of 10% Pd/C catalyst,[21] smooth decarbonylation of **6** occurred in acceptable yield (51% of **7** after recrystallization). Ester hydrolysis of **7** under basic conditions then completed the synthesis of γ-trolox **4**.

This synthesis of **4** proceeds in fewer steps than the previously published route, involves only crystalline compounds, and requires no chromatography. The conceptual approach of degrading a readily available higher homolog to produce a desired product is seldom considered in lieu of de novo synthesis but clearly deserves attention in certain circumstances.

EXPERIMENTAL

General Methods

All reactions were carried out under nitrogen or argon atmosphere. ^{1}H NMR spectra were recorded using a Jeol Eclipse 400 instrument (400 MHz). Melting points are uncorrected. Elemental analyses were done by Atlantic Microlabs, Inc., Norcross, GA.

Trolox Methyl Ester (2 Methyl Ester)

A 1-L, three-neck flask was equipped with heating mantle, reflux condenser, and stirrer and charged with 159 ml (1.50 mol) of methyl methacrylate, 9 g (0.30 mol) of paraformaldehyde, 4.8 g (0.036 mol) of dibutylamine, and 45 ml of acetic acid. This mixture was stirred at room temperature, and 45.6 g (0.30 mol) of trimethylhydroquinone were added. This mixture was stirred under reflux for 20 h. The resulting dark mixture (solid was present) was chilled to 0–5°C and filtered (methanol wash) to give 30.7 g (39% yield) of **2** methyl ester as a light tan solid. This material was suitable for further use; a sample recrystallized from methanol [the hot solution being filtered to remove traces of insoluble poly(methyl methactylate)] gave white prisms of mp 160.5–162.5°C lit.[22] 162–164°C. NMR ($CDCl_3$): 5.65 (1H, br S, OH), 3.67 (s, 3H), 2.65–2.72 (m, 1H), 2.41–2.55 (m, 2H), 2.18 (s, 3H), 2.16 (s, 3H), 2.06 (s, 3H), 1.82–1.90 (m, 1H), 1.59 (s, 3H).

Bromoacetate 5

A 1-L, three-neck flask was charged with 15.85 g (0.060 mol) of **2** methyl ester, 240 ml of carbon tetrachloride, and 90 ml of dichloromethane. The mixture was stirred at rt in the dark, and a solution of 3.30 ml (0.064 mol) of bromine in 45 ml of carbon tetrachloride was added dropwise over 40 min. Stirring continued at rt for 2 h after completion of the bromine addition; the resulting solution was dark, but no bromine color or vapor was detectable. The mixture was purged with a stream of nitrogen for 30 min to remove most of the HBr present, then stripped to dryness on the rotovap. The resulting damp dark solid was treated with 130 ml of dichloromethane, 110 ml of glacial acetic acid, 30 ml of acetic anhydride, and 12 small drops of conc. sulfuric acid. After stirring overnight at rt, the mixture was treated with 600 ml of water and stirred for 1 h. The mixture was transferred to a separatory funnel and the layers were separated. The aqueous layer was extracted with ethyl acetate and the EtOAc layer was combined with the dichloromethane layer. The combined organic layer was washed with brine,

dried ($MgSO_4$), and stripped to dryness on the rotovap (considerable acetic acid must be removed) to give a pale orange oil that crystallized on standing.

Recrystallization from methanol afforded 18.1 g (78%) of tan solid product of mp 114–115.5°C. NMR ($CDCl_3$): 4.2–4.5 (broad, 2H, hindered rotation); 3.68 (s, 3H); 2.8–2.9 (d of q, 1H), 2.56–2.68 (m, 1H), 2.24–2.48 (d of q, 1H), 2.37 (s, 3H), 2.18 (s, 3H), 2.09 (s, 3H), 2.08 (s, 3H), 1.85–1.92 (m, 1H), 1.61 (s, 3H). Analysis: calcd. for $C_{17}H_{21}BrO_5$: C, 52.99; H, 5.49. Found: C, 53.25; H, 5.66.

Aldehyde 6

A solution of 14.6 g (0.038 mol) of bromoacetate **5** in 120 ml of dry acetonitrile was stirred at rt and treated with 13.23 g (0.114 mol, 3 eq.) of N-methylmorpholine-N-oxide. The resulting reaction mixture gave a mild exotherm and progressed from a pale yellow color through green to dark orange-brown when stirred 18 h at rt. Thin-layer chromatography (TLC) indicated completion of the reaction, and the mixture was stripped to about 40 ml on the rotovap. This concentrated solution was poured into about 600 ml of water and extracted (3 × 100 ml) with ethyl acetate. The combined ethyl acetate layers were washed with 5% HCl and with brine, dried ($MgSO_4$), and stripped to give 10.9 (89%) g of an orange syrup, which crystallized when scratched. Trituration with ether–hexane gave 8.56 g (71%) aldehyde as an off-white solid of mp 88–91°C. NMR ($CDCl_3$): 10.21 (s, 1H), 3.7 (s, 3H), 3.20–3.33 (m, 1H), 2.80–2.92 (m, 1H), 2.40–2.46 (m, 1H), 2.41 (s, 3H), 2.27 (s, 3H), 2.08 (s, 3H), 1.8–1.90 (m, 1H), 2.62 (s, 3H). Analysis: calcd. for $C_{17}H_{20}O_6$: C, 63.74; H, 6.29. Found: C, 63.63; H, 6.43.

γ-Trolox Methyl Ester Acetate 7

A mixture of 2.20 g (0.0068 mol) of aldehyde **7** and 0.40 g of 10% Pd on charcoal catalyst was placed in a 10-ml flask under a very slow stream of argon and immersed in a 210°C oil bath with stirring for a total of 8 h, at which time TLC analysis indicated complete consumption of the aldehyde and formation of a single major and two very minor products (similar results were obtained in about 4 h at 220°C, but poor results were obtained with 5% Pd/C at any loading or temperature). The cooled reaction mixture was dissolved in ethyl acetate, filtered (Celite®) to remove the catalyst, and stripped of solvent on the rotovap to give 1.78 g of gamma-trolox methyl ester acetate **7** as an orange oil, which crystallized when scratched. This crude product (89% yield) appeared to be at least 90% pure by NMR. Recrystallization from methanol afforded 1.02 g (51%) of pale yellow solid of mp 104–105°C. NMR ($CDCl_3$): 6.52 (s, 1H), 3.69 (s, 3H), 2.6–2.7 (m, 2H),

2.3–2.4 (m, 1H), 2.28 (s, 3H), 2.17 (s, 3H), 2.02 (s, 3H), 1.8–1.9 (m, 1H), 1.60 (s, 3H). Analysis: calcd. for $C_{16}H_{20}O_5$: C, 65.74; H, 6.90. Found: C, 65.65; H, 7.05.

γ-Trolox 4

A mixture of 0.80 g (0.0027 mol) of methyl ester acetate **7**, 20 ml of methanol, and 1.60 g of 50% aq. NaOH solution (0.020 mol) was sparged with nitrogen and stirred at reflux for 30 min. After cooling, the mixture was acidified with 5% HCl, extracted with chloroform, dried ($MgSO_4$), and stripped of solvent in vacuo, and the resulting solid was crystallized from ether–hexane to afford 0.49 g (89%) of **4**, mp 166–168°C (lit.[1] 167.5–168.5°C). NMR (DMSO-d_6): 6.28 (s, 1H), 2.56 (m, 2H), 2.22 (m, 1H), 2.04 (s, 3H), 1.99 (s, 3H), 1.74 (m, 1H), 1.47 (s, 3H).

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