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Synthesis of *dl*-α-Tocopherol and *dl*-α-Tocotrienol[1)]

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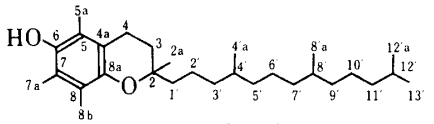
α-Tocopherol (**1**) and α-tocotrienol (**2**) were synthesized in racemic form by a method in which their side chains were constructed by the coupling reaction of a key intermediate, 6-methoxymethoxy-2,5,7,8-tetramethyl-2-(5-mercaptothiazolinyl-4-methyl-3-penten-1-yl)chroman (**7**), with geranyl bromide.

Desulfurization of the reaction product and then hydrolysis afforded α-tocotrienol, which, upon reduction, gave the desired α-tocopherol in good yield. This method, using a mercaptothiazolinyl derivative, is more convenient than previous approaches which use the Wittig or Grignard reaction for the synthesis of the side chain.

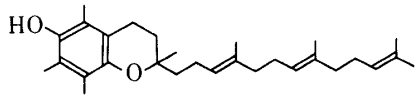
Keywords——vitamin E; α-tocopherol; α-tocotrienol; synthesis; mercaptothiazolinyl derivative

It has been known for many years that tocopherols (vitamin E), especially α-tocopherol, act as important antioxidants and radical scavengers in various metabolic processes and arrest the oxidative deterioration of cellular membranes.[2)] In connection with studies on the action of α-tocopherol, we have recently confirmed that α-tocopherol scavenges alkyl radicals more effectively than other tocopherols do.[3)] Our interest in the biological action of α-tocopherol prompted us to attempt to synthesize α-tocopherol in which the prenyl moiety is isotopically labeled. This report describes a synthetic method that we designed to afford the desired labeled α-tocopherol.

Although several methods for the synthesis of α-tocopherol (**1**) and α-tocotrienol (**2**) have been established, these reported approaches were based on the use of the Wittig or Grignard reaction to synthesize the prenyl moiety.[4)] These methods require a long process for the synthesis of the prenyl moiety, and are troublesome for synthesis of the Wittig or Grignard reagents. Akkerman *et al.*[5)] attempted to synthesize α-tocopherol by the direct alkylation of 2-(sulphinylmethyl)chroman. However, they did not obtain the alkylated chroman, rather, a compound in which the chroman ring is open. We now wish to report the synthesis of *dl*-α-tocopherol and *dl*-α-tocotrienol *via* 6-methoxymethoxy-2,5,7,8-tetramethyl-2-(5-mercaptothiazolinyl-4-methyl-3-penten-1-yl)chroman (**7**) by a direct alkylation.



1 α-tocopherol



2 α-tocotrienol

Chart 1

The starting material, 6-hydroxy-2,5,7,8-tetramethyl-2-(4-methyl-3-penten-1-yl)chroman (**3**), was readily obtained by a known method.[6)] After acetylation, **3** was oxidized with selenium dioxide in a mixture of benzene and acetic acid (1 : 2, v/v) to give aldehyde **4** in 62.4% yield. It is well known that the oxidation of methyl groups attached to olefinic carbon

atoms with selenium dioxide affords *trans*-aldehydes.[7] The isomer distribution can usually be confirmed on the basis of the chemical shifts of protons in *cis*- and *trans*-aldehydes in ^{1}H-nuclear magnetic resonance (NMR). It has been shown that a *trans*-aldehyde proton is more shielded (9.38 ppm) than a *cis*-aldehyde proton (10.11 ppm) in $CDCl_3$.[8] The chemical shift of the aldehyde proton of **4** is 9.38 ppm in $CDCl_3$. Thus, **4** should be *trans*. Compound **4** was reduced to the alcohol **5** with sodium borohydride in 82.3% yield and then converted to its brominated derivative with phosphorus tribromide in dry chloroform at 0 °C. Because this brominated compound is very unstable, it was treated without purification with 2-mercaptothiazoline and sodium hydride in dry tetrahydrofuran (THF) to obtain 6-acetoxy-2,5,7,8-tetramethyl-2-(5-mercaptothiazolinyl-4-methyl-3-penten-1-yl)chroman (**6**) in 75.3% yield from the alcohol **5**. ^{1}H-NMR double resonance experiments with **6** show that the allylic coupling constant between a vinylic proton at C-3′ and protons of a methyl group bonding to an olefinic carbon (C-4′) is 0.9 Hz. Very commonly, J_{cis} is larger (in absolute magnitude) by

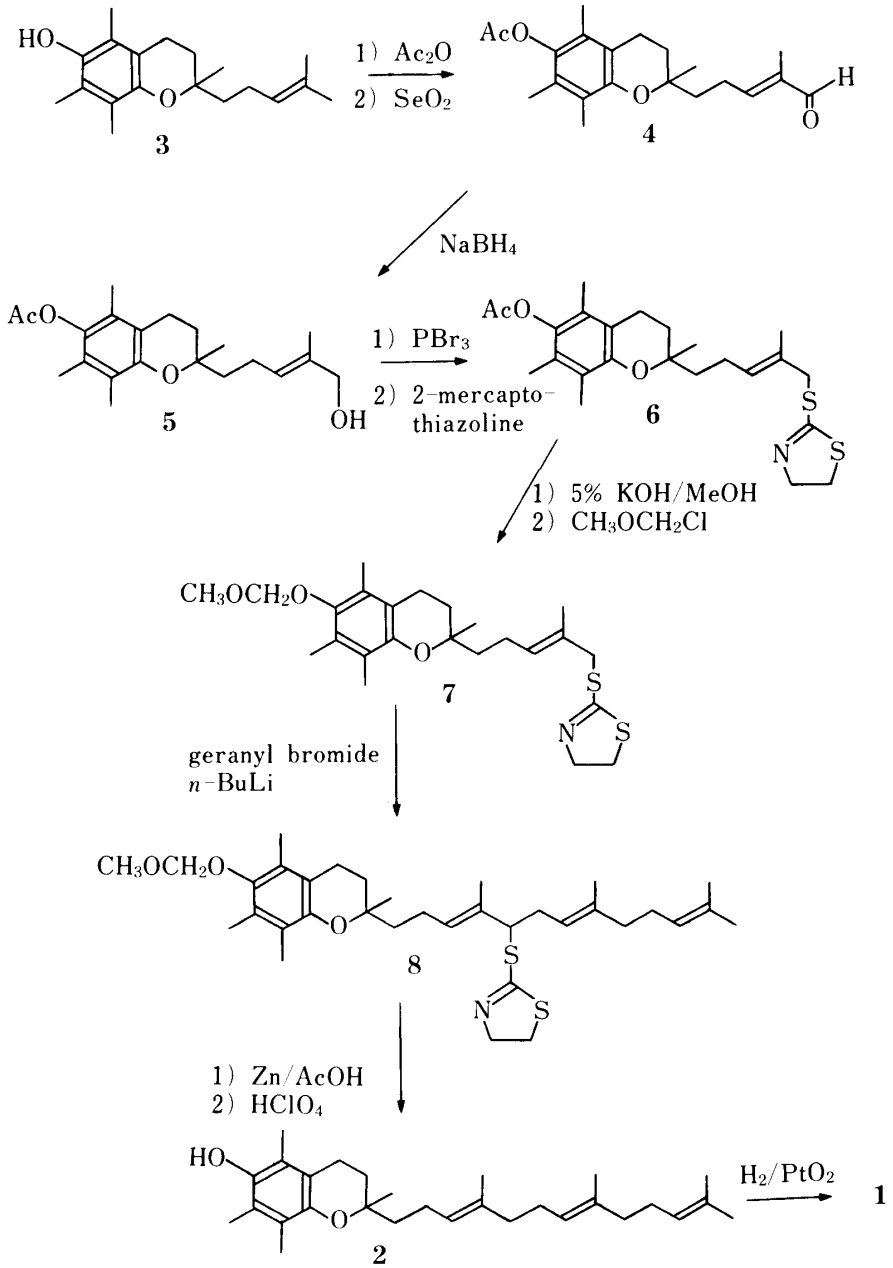


Chart 2

approximately 0.3—0.6 Hz than J_{trans} for allylic coupling constants in some acyclic systems.[9] Our data suggest that **6** is *trans* and retains the geometry of the corresponding aldehyde under these reaction conditions.

After saponification of **6** with 5% potassium hydroxide in methanol, treatment of the product with chloromethoxymethane in the presence of sodium hydride in dry THF at room temperature (to protect the chromanol moiety) afforded the methoxymethoxy derivative (**7**) in 75.0% yield. Compound **7** was then reacted with geranyl bromide and *n*-butyl lithium in a mixture of dry THF and hexamethylphosphoramide in a dry ice–acetone bath to afford 5′-mercaptothiazolinyl-α-tocotrienol methoxymethyl ether (**8**) in 78.8% yield. ^{1}H-NMR data show that the protons of the 8′a- and 12′a-*trans*-methyl groups are shielded at 1.60 ppm (s, 6H) and those of the 4′a-methyl group at 1.66 ppm (s, 3H). These results show that the geometry of the prenyl chain is all-*trans*, in accordance with the previous data.[9] Compound **8** was desulfurized with zinc powder and acetic acid to give all-*trans*-α-tocotrienol methoxymethyl ether in 63.8% yield. This compound was treated with perchloric acid in THF at 0 °C for 2 min to afford the all-*trans*-α-tocotrienol (**2**), which was identical in terms of spectral data with an authentic sample.[10] *dl*-α-Tocotrienol was reduced in ethyl acetate under 50 atmospheres of hydrogen in the presence of platinum oxide at room temperature for 3 h to give *dl*-α-tocopherol (**1**) in 91.3% yield, which was identical [infrared (IR), ultraviolet (UV), thin layer chromatography (TLC), gas chromatography (GC), mass (MS), ^{1}H-NMR and ^{13}C-NMR[11] spectra] with an authentic sample.

Our new method for the synthesis of *dl*-α-tocopherol and *dl*-α-tocotrienol should provide the compounds with isotopically labeled prenyl moieties in good yields by the use of the appropriate thiazolinyl derivatives as precursors. Such products should be usefull for studies on the biological action of α-tocopherol.

Experimental

^{1}H- and ^{13}C-NMR spectra were recorded on a Varian XL-200 spectrometer employing $CDCl_3$ as a solvent and tetramethylsilane as an internal standard. MS, UV and IR spectra were taken with spectrometers as follows: Shimadzu-LKB 9000, Cary 118C and Jasco IRA-2, respectively. Gas chromatograms were obtained on a Shimadzu GC-5A with a flame ionization detector. Silica gel C-200 (Wako, Osaka, Japan) was used for column chromatography and Silica gel PF_{254} (Merck, Darmstadt, BRD) for TLC. All other chemicals were obtained from well-known laboratory suppliers.

6-Acetoxy-2,5,7,8-tetramethyl-2-(4-methyl-5-oxo-3-penten-1-yl)chroman (4)——Selenium dioxide (5.5 g, 50 mmol) was dissolved in water (4 ml), and then mixed with acetic acid (100 ml). The mixture was added to a benzene solution of **3** (8 g, 24 mmol) with stirring. The stirring was continued for 15 h, and then the precipitate was filtered off. The filtrate was poured into cold brine (1.0 l) and the benzene layer was separated. The benzene solution was washed with water and dried over sodium sulfate. After evaporation, the residue was purified by silica gel column chromatography, using benzene as an eluent. Crystallization from pet. ether gave 5.2 g (62.7%) of light yellow crystals **4**, mp 52—53 °C. MS *m/e*: 344.4 (M^+). IR (neat): 1751, 1685 cm^{-1}. UV λ_{max}^{hexane} (ε): 277 (2900), 283 (3400), 286 (3400) nm. ^{1}H-NMR ($CDCl_3$) δ: 1.29 (s, 3H, $-CH_3$), 1.75 (s, 3H, $=C-CH_3$), 1.82 (t, 2H, $J=6.5$ Hz, $-CH_2-$), 1.98, 2.02, 2.09 (each s, 3H, $=C-CH_3$), 2.32 (s, 3H, $-COCH_3$), 2.63 (t, 2H, $J=6.5$ Hz, $=C-CH_2-$), 6.52 (t, 1H, $J=7.0$ Hz, $=C-H$), 9.38 (s, 1H, –CHO) ppm. ^{13}C-NMR ($CDCl_3$) δ: 195.0 (d, –CHO) ppm. *Anal.* Calcd for $C_{21}H_{28}O_4$: C, 73.23; H, 8.19. Found: C, 73.39; H, 8.00.

6-Acetoxy-2,5,7,8-tetramethyl-2-(5-hydroxy-4-methyl-3-penten-1-yl)chroman (5)——To a solution of 8.7 g (30 mmol) of the aldehyde **4** in 100 ml of methanol was added, with stirring at 0 °C, 1 g (30 mmol) of sodium borohydride. The stirring was continued for 4 h. This reaction mixture was poured into 300 ml of ice water and extracted with ether. The ether extract was washed with brine, 10% acetic acid and water, in turn. The ether was evaporated to obtain 8.3 g of residue. The residue was chromatographed on a silica gel column and eluted with a mixture of benzene and ethyl acetate to obtain 7.2 g (82.3%) of pure **5**, mp 54.4 °C. MS *m/e*: 346.4 (M^+). IR (neat): 3390, 1750 cm^{-1}. UV λ_{max}^{hexane} (ε): 277 (2900), 284 (3400), 286 (3400) nm. ^{1}H-NMR ($CDCl_3$) δ: 1.28 (s, 3H, $-CH_3$), 1.65 (s, 3H, $=C-CH_3$), 1.79 (t, 2H, $J=6.5$ Hz, $-CH_2-$), 1.98, 2.03, 2.11 (each s, 3H, $=C-CH_3$), 2.32 (s, 3H, $-COCH_3$), 2.60 (t, 2H, $J=6.5$ Hz, $=C-CH_2-$), 3.95 (s, 2H, $-O-CH_2-$), 5.14 (t, 1H, $J=7.0$ Hz, $=C-H$) ppm. ^{13}C-NMR ($CDCl_3$) δ: 68.7 (t, $-O-CH_2-$) ppm. *Anal.* Calcd for $C_{21}H_{30}O_4$: C, 72.80; H, 8.73. Found: C, 72.81; H, 8.63.

6-Acetoxy-2,5,7,8-tetramethyl-2-(5-mercaptothiazolinyl-4-methyl-3-penten-1-yl)chroman (6)——To a solution of

7.2 g (20 mmol) of the alcohol **5** in 100 ml of dry chloroform was added, with stirring at 0 °C, a solution of PBr_3 (5.6 g) in 50 ml of dry chloroform. The stirring was continued at 0 °C for 20 min. This mixture was then poured into ice water and extracted with chloroform. The chloroform extract was washed with water, saturated sodium bicarbonate solution and water, in turn. After being dried over sodium sulfate, the chloroform solution was evaporated at 40 °C to obtain 7.0 g of crude product. Without purification, the residue was dissolved in 50 ml of a mixture of dry THF and dimethyl sulfoxide (5 : 1). Sodium hydride (0.8 g) was added to a dry THF solution of 2.1 g (20 mmol) of 2-mercaptothiazoline with stirring. The stirring was continued for 30 min at room temperature, then the above solution of the brominated compound was added.

After one hour, the reaction mixture was poured into ice water and extracted with ether. The ether extract was washed with water, dried over sodium sulfate, and then evaporated. The residue was applied to a silica gel column and eluted with a mixture of benzene and ethyl acetate (10 : 1) to yield 7.0 g of pure **6** (75.3% from **5**). IR (neat): 1751 cm^{-1}. UV $\lambda_{max}^{methanol}$ (ε): 274 (2500), 283 (2400) nm. ^{1}H-NMR ($CDCl_3$) δ: 1.21 (s, 3H, $-CH_3$), 1.69 (s, 3H, $=C-CH_3$), 1.74 (t, 2H, $J=6.5$ Hz, $-CH_2-$), 1.95, 2.00, 2.08 (each s, 3H, $=C-CH_3$), 2.56 (t, 2H, $J=6.5$ Hz, $=C-CH_2-$), 3.25 (t, 2H, $J=8.0$ Hz, $N-CH_2-$), 3.74 (s, 2H, $S-CH_2-$), 4.12 (t, 2H, $J=8.0$ Hz, $S-CH_2-$) ppm. ^{13}C-NMR ($CDCl_3$) δ: 34.5 (t, $S-CH_2-$), 41.9 (t, $S-CH_2-$), 64.3 (t, $N-CH_2-$), 165.7 (s, $N=C(-S-)_2$) ppm. *Anal.* Calcd for $C_{24}H_{33}NO_3S_2$: C, 64.40; H, 7.43; N, 3.13. Found: C, 64.34; H, 7.40; N, 3.00.

6-Methoxymethoxy-2,5,7,8-tetramethyl-2-(5-mercaptothiazolinyl-4-methyl-3-penten-1-yl)chroman (7)——To a solution of 7.0 g (1.6 mmol) of **6** in 20 ml of methanol was added dropwise, with stirring, 10 ml of 5% potassium hydroxide in methanol. The stirring was continued at room temperature for 30 min. Then the mixture was evaporated at 30 °C. The residue was extracted with ether. The ether layer was washed with water, dried over sodium sulfate, and evaporated. The residue was dissolved in a mixture of dry THF and dimethylsulfoxide (50 : 1). Then 0.32 g of sodium hydride was added and the mixture was stirred for 30 min at room temperature. To this solution was added 1.1 g of chloromethoxymethane in 5 ml of THF, with stirring at room temperature for 20 min. The reaction mixture was poured into ice water and extracted with ether. The ether extract was washed with saturated sodium chloride solution and dried over sodium sulfate. After evaporation of ether, the residue was chromatographed on a silica gel column. Elution with benzene and ethyl acetate yielded 4.5 g (75.2%) of **7**. IR (neat): 1570 cm^{-1}. UV $\lambda_{max}^{methanol}$ (ε): 278 (2500), 285 (2400) nm. ^{1}H-NMR ($CDCl_3$) δ: 1.23 (s, 3H, $-CH_3$), 1.69 (s, 3H, $=C-CH_3$), 1.78 (t, 2H, $J=6.5$ Hz, $-CH_2-$), 2.08, 2.14, 2.18 (each s, 3H, $=C-CH_3$), 2.58 (t, 2H, $J=6.5$ Hz, $=C-CH_2-$), 3.35 (t, 2H, $J=8.0$ Hz, $N-CH_2-$), 3.60 (s, 3H, $O-CH_3$), 3.76 (s, 2H, $S-CH_2-$), 4.18 (t, 2H, $J=8.0$ Hz, $S-CH_2-$), 4.85 (s, 2H, $O-CH_2-O$), 5.46 (t, 1H, $J=7.0$ Hz, $=C-H$) ppm. ^{13}C-NMR ($CDCl_3$) δ: 57.4 (q, $O-CH_3$), 99.6 (t, $O-CH_2-O$) ppm. *Anal.* Calcd for $C_{24}H_{35}NO_3S_2$: C, 64.11; H, 7.85; N, 3.11. Found: C, 64.30; H, 7.54; N, 2.93.

5′-Mercaptothiazolinyl-α-tocotrienol Methoxymethyl Ether (8)——To a solution of 0.134 g (0.3 mmol) of **7** in 25 ml of a mixture of THF and hexamethylphosphoramide (24 : 1) being stirred under nitrogen gas in a dry ice–acetone bath was added with a syringe 2 ml of 1.6 mol *n*-butyl lithium in hexane. After one hour, 0.084 g (0.4 mmol) of geranyl bromide in 5 ml of THF was added dropwise with stirring. The stirring was continued for an additional 2 h at −78 °C. The reaction mixture was warmed to 0 °C very slowly, poured into ice water, and extracted with ethyl acetate. The organic layer was washed with water, dried over sodium sulfate, and evaporated. The residue was chromatographed on a silica gel column using benzene as an eluent to yield 0.137 g (79.0%) of a pale yellow oil **8**. IR (neat): 1570 cm^{-1}. UV $\lambda_{max}^{methanol}$ (ε): 278 (2600), 286 (2400) nm. ^{1}H-NMR ($CDCl_3$) δ: 1.24 (s, 3H, $-CH_3$), 1.60 (s, 6H, $=C-CH_3$), 1.66 (s, 3H, $=C-CH_3$), 1.69 (s, 3H, $=C-CH_3$), 2.60 (t, 2H, $J=6.5$ Hz, $=C-CH_2-$), 3.32 (t, 2H, $J=8.0$ Hz, $N-CH_2-$), 3.62 (s, 3H, $O-CH_3$), 4.20 (t, 2H, $J=8.0$ Hz, $S-CH_2-$), 4.21 (t, 1H, $J=8.2$ Hz, $S-CH-$), 4.85 (s, 2H, $O-CH_2-O$), 5.09 (br t, 2H, $=C-H$), 5.49 (t, 1H, $J=7.0$ Hz, $=C-H$) ppm. ^{13}C-NMR ($CDCl_3$) δ: 13.3, 13.4, 16.4, 17.7 (each q, $=C-CH_3$), 55.7 (d, $S-CH-$), 120.8, 124.2, 128.7 (each d, $=C-H$), 131.1, 133.0, 137.1 (each s, $=C-H$) ppm. *Anal.* Calcd for $C_{34}H_{48}NO_3S_2$: C, 69.70; H, 8.44; N, 2.39; S, 10.94. Found: C, 69.63; H, 8.77; N, 2.47; S, 11.08.

α-Tocotrienol Methoxymethyl Ether (9)——To a solution of 0.13 g of **8** in THF was added several drops of acetic acid and 0.2 g of zinc powder. The mixture was stirred for 30 min at room temperature, then poured into ice water and extracted with ether. The extract was washed with saturated sodium chloride solution, saturated sodium bicarbonate solution and water, in turn. The ether solution was evaporated and the residue thus obtained was purified by silica gel column chromatography using hexane as an eluent. The fractions containing the ether **9** were combined and evaporated to dryness. The residue was further purified by preparative TLC on a plate coated with silica gel containing 15% silver nitrate to afford 64.4 mg (63.8%) of a colorless oil **9**. IR (neat): 1055 cm^{-1}. UV $\lambda_{max}^{methanol}$ (ε): 276 (2600), 289 (3200) nm. ^{1}H-NMR ($CDCl_3$) δ: 1.14 (s, 3H, $-CH_3$), 1.60 (s, 9H, $=C-CH_3$), 1.68 (s, 3H, $=C-CH_3$), 2.08, 2.15, 2.19 (each s, 3H, $=C-CH_3$), 2.59 (t, 2H, $J=6.5$ Hz, $=C-CH_2-$), 3.62 (s, 3H, $O-CH_3$), 4.87 (s, 2H, $O-CH_2-O$), 5.12 (br t, 3H, $=C-H$) ppm. *Anal.* Calcd for $C_{31}H_{48}O_3$: C, 79.49; H, 10.25; Found: C, 79.16; H, 10.49.

***dl*-α-Tocotrienol (2)**——To a stirred solution of 10 ml of 60% perchloric acid in 10 ml of THF under nitrogen was added dropwise at 0 °C a solution of 0.13 g of **9** in THF. The stirring was continued for 2 min. Then the mixture was poured into ice water and extracted with ether. The ether solution was washed with saturated sodium chloride solution, saturated sodium bicarbonate solution and water, in turn. After evaporation of the ether solution, the residue was purified by silica gel column chromatography using benzene as an eluent to yield 0.10 g (89.4%) of **2**. IR, UV and ^{1}H-NMR spectra were identical with those of an authentic sample of α-tocotrienol.

***dl*-α-Tocopherol (1)**——A mixture of a solution of 0.10 g of α-tocotrienol in ethyl acetate and 120 mg of platinum oxide was shaken under 50 atm of hydrogen at room temperature. After the calculated amount of hydrogen had been absorbed, the catalyst was filtered off. The filtrate was concentrated. The residue was purified by silica gel column chromatography using benzene as an eluent to yield 98 mg (96.6%) of **1**. Its IR, UV, ^{1}H-NMR and ^{13}C-NMR spectra were identical with those of an authentic sample.

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