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TOTAL SYNTHESIS OF 1-THIO-α-TOCOPHEROL: A SULFUR-CONTAINING ANALOGUE OF VITAMIN E[1].

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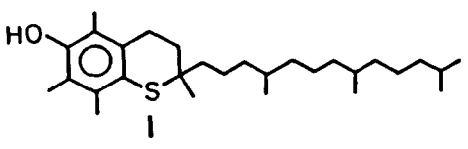
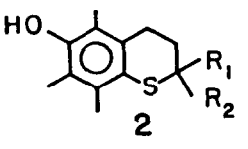
Summary: The title compound, has been synthesized in ten steps in an overall yield of 2%.

Recent work from this laboratory on the antioxidant activity *in vitro*[3] and vitamin E bioactivity *in vivo*[4] of α-tocopherol and related model compounds stimulated our interest in 1-thio-α-tocopherol, **1**. We found[5] that two purported syntheses of **1**[6,7] did not give a single compound but instead gave essentially identical mixtures containing five isomers of **1** which could be separated only by capillary GC. For three of these compounds, which together constituted 78% of the mixture, we showed by GC/MS that the heterocyclic ring had not even been formed.[5] We therefore developed a synthesis of some simple models **2a-c** of the



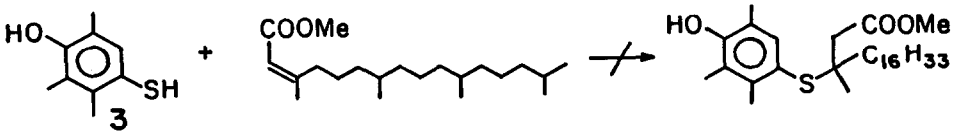
1



2

a $R_1 = R_2 = H$
b $R_1 = H, R_2 = CH_3$
c $R_1 = R_2 = CH_3$

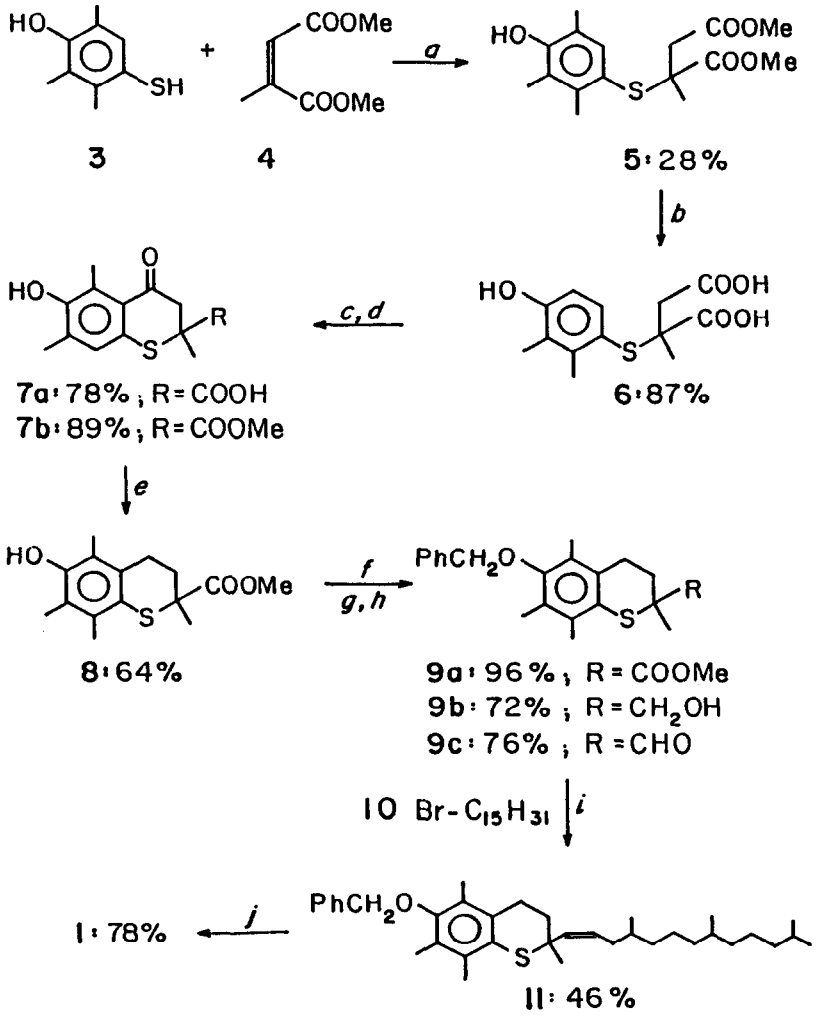
desired compound.[5] Unfortunately, this particular synthetic procedure failed in the case of **1** because the necessary initial condensation of 2,3,5-trimethyl-4-hydroxybenzenethiol, **3**, with methyl phytanoate could not be made to occur. We have therefore developed a new and unequivocal synthesis of **1**.



3

Following our earlier synthetic methodology,[5] the first step in the synthesis of **1** involved a Michael type addition[8] of **3**[9] with dimethyl citraconate, **4**, in methanol to form **5**.[10,11] The thiochromanone, **7a**, was obtained by hydrolysis of the diester to give the free dicarboxylic acid, **6**, followed by a cyclization[12] in concentrated sulfuric acid.[11] The carboxylic acid was then methylated (**7b**) and the oxo group removed by reduction using the Martin-Clemmensen method[11,13,14] thus yielding the thiochroman, **8**,

without hydrolysis of the ester group. Because **8** is sensitive both to light and oxygen the next step involved benzylation of the hydroxyl group to form **9a**. (Blocking of the OH group is, of course, also necessary for the penultimate Wittig coupling to form **11**.) The one step reduction of **9a** to the aldehyde **9c** was fraught with problems (e.g., DIBAL reduction yielded only 12% of **9c** and 72% of the alcohol, **9b**). For this reason, the ester **9a** was reduced to **9b** and the latter was oxidized to **9c** using Jones' method.[15] The following step involved a Wittig condensation[16] of the aldehyde **9c** with the phosphonium salt of the bromide, **10**,[17] to form **11**. Finally, the benzyl group was removed and the double bond was reduced using hydrogen on a palladium catalyst to form **1** in an overall yield of 2% based on starting **3**.[14,18]



a-MeOH at reflux (3 weeks) with $HC(OMe)_3$ and conc. H_2SO_4 as catalysts. b-1N NaOH, 1h at 60°C. c-conc. H_2SO_4, 1h at 25°C. d-MeOH with PTSA as catalyst, 16h at reflux. e-Toluene/HCl/H_2O and Zn/Hg amalgam, 6h at reflux. f-$PhCH_2Cl$/DMF/K_2CO_3, 16h at 25°C. g-DIBAL in n-pentane, 30 min at -70°C. h-CrO_3/acetone at 0°C. i-PPh_3/bromide **10**, 6h at 195°C, then BuLi + **9c** in DME, 3h at reflux. j-H_2/Pd-C in EtOAc, 16h at 25°C and 1 atm.pressure.

This unambiguous synthesis of 1-thio-α-tocopherol has allowed us to confirm our earlier[5] tentative identification of this compound as one of the minor products (10% yield)[19] in the five component mixture of isomers that is obtained by following the procedures outlined in refs. 6 and 7. A more efficient synthesis of 1 is currently being sought in order to obtain more readily sufficient material for in vitro[3] and in vivo[4] studies of this sulfur containing analogue of vitamin E.

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References and Notes

(1) Issued as NRCC No. 25477.

(2) Canada-France Postdoctoral Exchange Fellow.

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(7) Valashek, I.E.; Shakhova, M.K.; Samokhvalov, G.I. Zh. Org. Khim. **1982**, 18, 2494.

(8) This reaction must be carried out under acidic conditions. Under basic conditions (OH^-, K_2CO_3 , pyridine or Et_3N) the S-S coupled dimer of **3** is rapidly formed.

(9) For the synthesis of **3** see ref. 5.

(10) The isomer of **5** formed by condensation of **3** with the less-substituted end of double bond of **4** was formed in a yield of 10% (detection by GC/MS).

(11) For additional details see ref. 5.

(12) No dihydrobenzothiophene type of product could be detected.

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(14) This reaction and the subsequent purification were carried out with the exclusion of light.

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18) Selected analytical data: Yields in the scheme are given for pure analytical samples. (For NMR the samples were dissolved in $CDCl_3$/TMS) **5**: ^1H NMR (200 MHz), δ(ppm) 7.13 (1H,s), 4.80 (1H, s, OH), 3.66 (3H, s), 3.64 (3H, s), 3.1 (1H, d, AB system, J = 17 Hz), 2.63 (1H, d, J = 17Hz) 2.31 (3H, s), 2.21 (3H, s), 2.18 (3H, s), 1.26 (3H, s); MS (electron impact, 70 ev), m/e (rel. int.) 326 (M^+, 64), 235 (16), 168 (64), 167 (90), 59 (100). **6**: mp = 171-172°C. **7a**: mp = 150°C. **7b**: ^1H NMR (80 MHz), δ(ppm) 3.57 (3H, s), 2.42 (2H, s); MS, m/e (rel. int.) 294 (M^+, 68), 235 (77), 207 (33), 194 (100). **8**: ^1H NMR (80 MHz), δ(ppm) 3.0-2.65 (2H,m), 2.38-2.10 (2H,m), 2.24 (3H, s), 2.17 (6H, s); MS, m/e(rel. int.) 280 (M^+, 57), 221 (100). **9a**: ^1H NMR (80 MHz), δ(ppm) 7.71-7.15 (5H, m), 4.69 (2H, s), 2.25 (9H, s); MS, m/e (rel. int.) 370 (M^+, 7), 279 (100), 219 (44). **9b**: ^1H NMR (80 MHz), δ(ppm) 3.53 (2H, s), 2.0 (1H, s broad, OH); MS, m/e (rel. int.) 324 (M^+-H_2O, 6), 221 (100); MS of trimethyl silylated derivative 414 (M^+,5), 323 (86), 233 (18), 189 (100). **9c**: ^1H NMR (80 MHz), δ(ppm) 9.25 (1H, s, CHO); MS, m/e (rel. int.) 340 (M^+, 13), 249 (100), 221 (96), 193 (38). **11**: ^1H NMR (80 MHz), δ (ppm) 5.92-5.51 (2H,m) 1.75-0.7 (32H, m complex); MS, m/e (rel. int.) 444 (M^+-PhCH_2, 79), 221 (54), 193 (100), 181 (92). **1**: R in EtOAc/n-hexane (5/95) 0.42 (α-tocopherol 0.36); ^1H NMR (500 MHz), δ (ppm) 4.38 (1H, s, OH), 2.73 (2H, t, C^4H_2), 2.13 (3H, s), 2.12 (3H, s), 2.10 (3H, s), 1.84 (2H, t, C^3H_2), 1.32-1.05 and 0.87-0.75 (36H, phytyl tail and C^2CH_3); MS, comparison of GC/MS for **1** with the compound (number **14** of ref. 5) tentatively assigned the same structure in the mixture of 5 isomers (see ref. 5), m/e (rel. int. for **1**; rel. int. for **14** of ref. 5) 447 (34; 34), 446 (M^+, 100; 100), 222 (11; 10), 221 (55; 60); 193 (24; 24), 181 (26; 25), 178 (5; 11) retention times for **1** and **14** were essentially identical.

(19) This is compound number **14** in ref. 5.

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