73. Studies on the Synthesis of (2*R*,4′*R*,8′*R*)-α-Tocopherol Alternative Syntheses of 2-Chroman-acetic Acid Intermediates

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Summary

As an extension of previous studies on the total synthesis of (2*R*,4′*R*,8′*R*)-α-tocopherol (**1**) [1] [2], (*S*)-(−)-2-(6-benzyloxy-2,5,7,8-tetramethylchroman)acetic acid (**6**), a pivotal intermediate, possessing the absolute configuration required for construction of **1** was prepared by optical resolution of the racemic modification **11**. The latter substance was obtained by two routes, one emanating from the hydroxy acetal **7** [1] and the other based upon the *Lewis* acid mediated cycloaddition of trimethylhydroquinone to *rac.*-3-hydroxy-3-methylpent-4-en-1-yl acetate (**16**) giving *rac.* ethyl 2-(6-hydroxy-2,5,7,8-tetramethyl-chroman)acetate (**12**).

Introduction. – In previous publications [1] [2], we have described convergent total syntheses of (2*R*,4′*R*,8′*R*)-α-tocopherol (**1**) involving the (*S*)-2-chroman-acetic acid **2** as a key, chiral intermediate. In one approach [1], the acid **2** was converted into the 2-(6-acetoxychroman)acetaldehyde (**3**) which was then treated, in a *Wittig* reaction, with a C_{14}-phosphorane yielding (2*R*,4′*R*,8′*R*)-2′,3′-didehydro-α-tocopheryl acetate. Alternatively [2], **2** was transformed into the benzyl protected *p*-toluenesulfonate **4** (*via* the ester **5** [1]) and subsequently coupled with a C_{14} *Grignard* reagent producing (2*R*,4′*R*,8′*R*)-α-tocopheryl benzyl ether directly. Because of distinct advantages in stability provided by the *O*-benzyl protected intermediates, we sought alternative, direct routes to such compounds. We wish to describe herein the preparation of (*S*)-2-(6-benzyloxychroman)acetic acid (**6**) (a useful synthon for the construction of **1**) *via* resolution of the racemic modification **11**, itself obtained by two related schemes starting from trimethylhydroquinone.

Results. – The first synthesis of **11** closely parallels that employed previously for the production of *rac.*-**2** [1]. Thus, the acetal **7**, derived from cycloaddition of methyl vinyl ketone to trimethylhydroquinone [1] was treated with benzyl chloride in DMSO containing potassium carbonate. The resultant acetal ether **8** was then hydrolysed giving the hemiacetal **9** which smoothly underwent introduction of the acetic acid moiety upon exposure to trimethyl sodiophosphonoacetate. The ester ether **10** so produced was saponified giving the desired racemic acid **11** in 75% overall yield based on trimethylhydroquinone.

An alternative approach to **11** involves cycloaddition of an intact C_6- unit to trimethylhydroquinone yielding, directly, a chroman bearing a C_2 side chain at position 2. This was accomplished by reaction of trimethylhydroquinone with the allyl alcohol **16** in the presence of *Lewis* acids[1]). This condensation was first carried out using $ZnCl_2$/HCl at 50° in which case crude hydroxy-acetate **12** was isolated in 81% yield. For preparative purposes, however, it was found most convenient to effect this cycloaddition using $AlCl_3$ in CH_2Cl_2/CH_3NO_2 [4] at −20° to room temperature[2]). The crude **12** was then immediately benzylated, giving the ether ester **13** in 77% overall yield. The allyl alcohol **16** was secured by treatment of 4-hydroxy-2-butanone[3]) with vinyl magnesium chloride affording 3-methyl-2-penten-1,3-diol [5], followed by selective acetylation.

Mild alkaline hydrolysis of **13** furnished the hydroxyether **14** which was best transformed into acid **11** by a two stage oxidation sequence. Thus exposure of **14** to chromium trioxide/pyridine complex [6] afforded aldehyde **15** in 88% yield[4]). Further oxidation of the latter intermediate with alkaline silver nitrate then produced **11** (78%), identical with the acid derived from **7**. It should be noted

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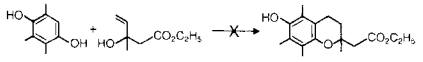
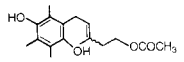
[1]) The condensation of trimethylhydroquinone (I) with hydroxy ester II [3], a process which would have led directly to a 2-chroman-acetic ester (III), was investigated but found to be unavailing. All attempts to effect this cycloaddition gave, at most, only traces of the desired chroman derivative. Similarly, the diol precursor to **16** could not be successfully condensed with trimethylhydroquinone.



I II III

[2]) It is interesting to note that whereas isophytol and trimethylhydroquinone afforded α-tocopherol at −20°, under these conditions [4], the major product from trimethylhydroquinone and **16**, at −20°, is the unstable olefinic hydroquinone mixture IV (NMR.: 5.21 (*m*, 1H, vinyl); 4.15 (*m*, 2H, CH_2O); 3.38 (br. *d*, $J=7$, 2H, $ArCH_2CH=$); 2.08 (*s*, CH_3COO, $ArCH_3$); 1.89 and 1.81 (2*s*, 3H, $CH_3C=$)). On warming to room temperature, under the reaction conditions, this mixture cyclizes to give **12**.



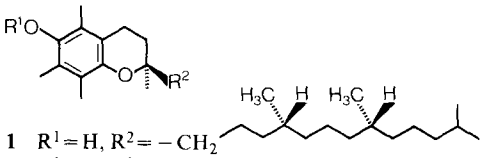
IV

[3]) This compound was generously supplied by Dr. *G. Ember*, Technical Division, *Hoffmann-La Roche Inc.*, Nutley, N.J. USA.

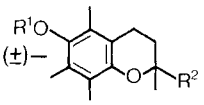
[4]) Samples of intermediates **14** and **15** were initially prepared by the route starting from acetal **7** *via* hydride reduction of **11** (→**44**) and *Rosenmund* reduction [1] of the acid chloride derived from **11** (→**15**), respectively.

that the benzyl protecting group affords sufficient stability to allow these oxidations to be effected without attack on the sensitive 6-hydroxychroman system.

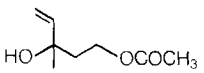
Access to the (*S*)-acid **6**, possessing the absolute configuration required for the production of natural α-tocopherol (**1**) was provided by resolution of **11** with (−)-quinine[5]). In this manner, **6** was obtained in optically pure form, in 54% yield. The (*R*)-antipode **17** was isolated by resolution of **11** with (*R*)-1-(1-napthyl)ethylamine. For comparison purposes, a sample of **6** was converted into **2** by hydrogenolysis over Pd/C. The methyl ester **5** was prepared by treatment of **6** with diazomethane.



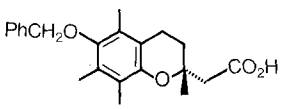
1 $R^1 = H$, $R^2 = -CH_2$ (H₃C, H, H₃C, H)
2 $R^1 = H$, $R^2 = CH_2CO_2H$
3 $R^1 = COCH_3$, $R^2 = CH_2CHO$
4 $R^1 = CH_2C_6H_5$, $R^2 = (CH_2)_2OSO_2C_6H_4$-p-$CH_3$
5 $R^1 = CH_2C_6H_5$, $R^2 = CH_2CO_2CH_3$
6 $R^1 = CH_2C_6H_5$, $R^2 = CH_2CO_2H$



7 $R^1 = H$, $R^2 = OCH_3$
8 $R^1 = CH_2C_6H_5$, $R^2 = OCH_3$
9 $R^1 = CH_2C_6H_5$, $R^2 = OH$
10 $R^1 = CH_2C_6H_5$, $R^2 = CH_2CO_2CH_3$
11 $R^1 = CH_2C_6H_5$, $R^2 = CH_2CO_2H$
12 $R^1 = H$, $R^2 = (CH_2)_2OCOCH_3$
13 $R^1 = CH_2C_6H_5$, $R^2 = (CH_2)_2OCOCH_3$
14 $R^1 = CH_2C_6H_5$, $R^2 = (CH_2)_2OH$
15 $R^1 = CH_2C_6H_5$, $R^2 = CH_2CHO$



16



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Experimental Part

General. - M.p. were determined on a *Thomas Hoover* capillary m.p. apparatus and are not corrected. Spectral measurements were performed by members of the Physical Chemistry Department of *Hoffmann-La Roche Inc.* using the following instruments: NMR., *Varian* A-60 or HA-100 spectrometer with TMS. as internal standard and, unless otherwise specified, $CDCl_3$ as solvent (chemical shifts in δ (ppm) and coupling constants in Hz); IR., *Beckmann* IR. 9 spectrometer with $CHCl_3$ as solvent unless otherwise noted (absorptions in cm^{-1}); UV., *Cary* Model 14 spectrometer with ethanol as solvent (λ_{max} in nm, ε in parentheses); MS., *Jeolco* OISG or CEC 21-110 spectrometers with a direct inlet system (70 eV). The phrase "worked-up as usual" indicates extraction or dilution with the indicated solvent, washing where appropriate, with H_2O, and/or saturated brine, drying (Na_2SO_4 or $MgSO_4$), and solvent removal in a rotary evaporator (RV.) at 30–50°. Chromatography was carried out on *E. Merck* Silica Gel 60 (0.063–0.200 mm). Thin layer chromatograms (TLC.) were run on *E. Merck* pre-coated Silica Gel 60 F-254 plates in tanks saturated with the indicated solvent mixtures. The spots were detected by: a) observation under a 254 nm source, b) spraying with a 5% solution of phosphomolybdic acid in ethanol, and c) heating. Phenolic compounds are particularly sensitive to the latter reagent and, in many cases, develop blue spots with little or no heating. Abbreviations: THF = Tetrahydrofuran, DMSO = Dimethyl sulfoxide, RT. = room temperature, RV. = rotatory evaporator, i.V. = *in vacuo* (of a water aspirator). All reactions, except hydrogenations, were carried out under an inert atmosphere of argon or nitrogen.

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[5]) In contrast to hydroxy acid *rac.*-**2** [1], **11** could not be resolved using α-methylbenzylamine.

rac.-2-*(6-Benzyloxy-2,5,7,8-tetramethylchroman)acetic acid* (**11**). a) *From* **7**. To a mixture of 293.85 g (1.245 mol) of rac.-*6-hydroxy-2-methoxy-2,5,7,8-tetramethylchroman* (**7**) [1] and 377 g (2.73 mol) of potassium carbonate in 1.2 l of DMSO was added 286 ml (314 g = 2.49 mol) of benzyl chloride. The mixture was stirred at RT. for 24 h, poured into water and worked up with ether in the usual manner to give, after final solvent removal at 65°/0.1 Torr, 519 g of crude rac.-*6-benzyloxy-2-methoxy-2,5,7,8-tetramethylchroman* (**8**) as a pale orange oil. A similarly prepared sample was evaporatively distilled (Kugelrohr) at 208-215°/0.025 Torr to give analytically pure **8** as a colorless oil which solidified to a white mass, m.p. 66-67.5°. – UV.: 227 (12,000), 257 (930), 263 (1070), 278 (1750), 285 (1900). – IR.: 3020, 2940 (OH). – NMR.: 1.55 (*s*, 3H, $H_3C-C(2)$); 2.17 (*s*, 9H, CH_3-Ar); 3.24 (*s*, 3H, OCH_3); 4.69 (*s*, 2H, $C_6H_5CH_2O$); 7.42 (*m*, 5H, C_6H_5). – MS.: (*m/e*): 326 (M^+, 20), 295 ($M^+ - OCH_3$, 17); 235 ($M^+ - C_7H_7$; 100).

$C_{21}H_{26}O_3$ (326.42) Calc. C 77.27 H 8.03% Found C 77.35 H 8.07%

To a solution of the crude acetal **8** prepared above in 1.5 l of acetone was added 1.25 l of 0.1N HCl. The turbid solution was heated at reflux as the acetone was removed by distillation over a 2 h period (head temperature to 90°). An additional 750 ml of acetone was added and the distillation process repeated over 1 h. The reaction mixture was cooled and worked up with ether in the usual manner to give 430 g of crude rac.-*6-benzyloxy-2-hydroxy-2,5,7,8-tetramethylchroman* (**9**) as a yellow-orange semisolid paste. A similarly prepared sample was triturated with petroleum ether (30-60°) and then crystallized from pentane to give analytically pure **9** as a white crystalline solid, m.p. 94.5-95.5°. – UV.: 226 (12,000), 258 (900), 265 (1000), 278 (1850), 285 (2050). – IR.: 3600, 3030, 2950 (OH). – NMR.: 1.60 (*s*, 3H, $H_3C-C(2)$); 2.12 and 2.18 (2*s*, 9H, $3CH_3-Ar$); 2.82 (*s*, 1H, OH); 4.66 (*s*, 2H, $C_6H_5CH_2O$); 7.42 (*m*, 5H, C_6H_5). – MS. (*m/e*): 312 (M^+, 15); 221 ($M^+ - C_7H_7$, 100).

$C_{20}H_{24}O_3$ (312.39) Calc. C 76.89 H 7.74% Found C 77.09 H 8.00%

To a suspension of 117 g (2.84 mol) of 56% sodium hydride in oil dispersion in 2.5 l of THF was added, dropwise over 5 h, 520 g (2.85 mol) of trimethyl phosphonoacetate (H_2 evolution). The resultant thick white suspension was stirred for 30 min and then a solution of the above crude hemiacetal **9** in 500 ml of warm THF was added over 40 min. The pale yellow-green suspension was stirred at RT. for 16 h and then at reflux for 1 h. The mixture was cooled to 3°, diluted with ice/water and worked-up with ether in the usual manner to give crude rac. *methyl 2-(6-benzyloxy-2,5,7,8-tetramethylchroman)acetate* (**10**) as 698 g of light brown oil. A similarly prepared sample was evaporatively distilled at 195-205°/0.025-0.030 Torr to give analytically pure **10** as a pale yellow oil[6]. – UV.: 203 (60,630), 227 (12,415), 289 (1900), 283 (2120). – IR.: 3020, 2940, 1735. – NMR.: 1.42 (*s*, 3H, $H_3C-C(2)$); 2.07, 2.15 and 2.19 (3*s*, 9H, $3CH_3-Ar$); 2.60 (*s*, 2H, CH_2COO); 3.75 (*s*, 3H, $COOCH_3$); 4.65 (*s*, 2H, CH_2O); 7.35 (*m*, 5H, C_6H_5). – MS. (*m/e*): 368 (M^+, 16), 277 ($M^+ - C_7H_7$, 100).

$C_{23}H_{28}O_4$ (368.45) Calc. C 74.99 H 7.66% Found C 74.96 H 7.72%

To a solution of the crude ester **10** in 2 l of ethanol was added, dropwise over 45 min, 500 ml of 10N NaOH. The dark solution was stirred at RT. for 20 h, diluted with water, washed with petroleum ether (30-60°), cooled to 3° and acidified with 12N HCl. The resultant suspension was stirred at 3° for 1 h and filtered. The solid was washed with water and dried to give 367 g (83% yield from **7**) of acid **11** as a pale yellow solid, m.p. 131-134°. A similarly prepared sample was crystallized from ethanol/water to give a white powder, m.p. 133.5-134.5°. – UV.: 228 (12,500), 258 (940), 265 (970), 281 (1980), 287 (2200). – IR.: 3500-2500 (OH), 1710 (C=O). – NMR.: 0.95 (*s*, 3H, $H_3C-C(2)$); 2.02, 2.15 and 2.19 (3*s*, 9H, $3CH_3-Ar$); 2.65 (*s*, 2H, CH_2COO); 4.67 (*s*, 2H, CH_2O); 7.37 (*m*, 5H, C_6H_5); 13.39 (*s*, 1H, COOH). – MS.: (*m/e*): 354 (M^+, 21), 263 ($M^+ - C_7H_7$, 100), 245 ($M^+ - C_7H_7 - H_2O$, 60).

$C_{22}H_{26}O_4$ (354.43) Calc. C 74.55 H 7.39% Found C 74.88 H 7.45%

b) *From* **15**. To a solution of 6.1 g (18 mmol) of aldehyde **15** (derived from **13** – see below) in 280 ml of ethanol was added a solution of 3.57 g (21 mmol) of silver nitrate in 42 ml of water. The

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[6]) One such sample slowly solidified. Crystallization from ether/petroleum ether (30-60°) then gave a white solid, m.p. 47.5-48.5°.

resulting stirred solution at RT., was then treated, dropwise, over a 0.5 h period, with a solution of 3.49 g (87 mmol) of sodium hydroxide in 100 ml of water. After stirring at RT. for 2 h, the grey mixture was filtered and the filtrate was concentrated i.V. to remove most of the ethanol. The residual solution was diluted with 200 ml of water and extracted with ether (the ether extract was discarded). The aqueous solution was acidified with 1N HCl and worked up with ether in the usual manner giving 5 g (78.4%) of acid **11** as a solid. This material was identical by spectral and TLC. comparison (benzene/ethyl acetate 1:1) with that produced in part a).

rac.-*3-Hydroxy-3-methylpent-4-en-1-yl acetate* (**16**). A 453 ml (0.62 mol) portion of 1.36M solution of CH_2=CHMgCl in THF was stirred and cooled while a solution of 30 g (0.34 mol) of 4-hydroxy-2-butanone in 150 ml of anhydrous THF was added dropwise, over a 0.5 h period. The internal temperature was maintained at $-10°$ to 0° during the addition. After stirring at RT. for 3 h, the reaction mixture was cautiously poured into 450 ml of cold, saturated, aqueous NH_4Cl- solution and the pH was adjusted to 9 by the addition of 1N H_2SO_4. The mixture was extracted first with benzene (2×500 ml and 3×250 ml), then with ether (2×250 ml) and finally (after filtration of the aqueous phase) with CH_2Cl_2 (10×300 ml). The organic extracts were dried, filtered and concentrated and the residual oil was distilled. There was obtained a total of 22.2 g (56.3%) of rac.-*3-methyl-4-pentene-1,3-diol* as a colorless liquid, in two fractions: b.p. 87–88.5°/4.5 Torr (4.8 g) and 89–90°/4.5 Torr (17.4 g) (Lit. [5] b.p. 85–86°/3 Torr). The main fraction exhibited the following spectral properties: IR.: 3500, 3600 (OH), 3100, 930, 995 (vinyl); NMR.: 1.32 (*s*, 3H, CH_3); 1.75 (*m*, 2H, CH_2); 3.62 (*m*, 4H, CH_2OH, OH); 5.17 (*m*, 2H, CH=CH_2); 5.94 (*d*×*d*, 1H, CH=CH_2). – MS.: (*m/e*): 116 (M^+, 1), 101 ($M^+ - CH_3$, 12.5), 98 ($M^+ - H_2O$, 10), 71 ($M^+ - C_2H_4OH$, 100).

A solution of 11.5 g (0.1 mol) of diol prepared in this manner, in 28 ml of pyridine was stirred with cooling to 0° while 18.5 ml of acetic anhydride was added dropwise. After stirring at RT. for 2.5 h, 30 ml of methanol was added and stirring was continued for 1 h. Ice/water was then added and the mixture was worked up with benzene in the usual manner (the organic extracts were additionally washed with saturated aqueous $NaHCO_3$-solution). The residue was distilled giving 12.7 g (81.2%) of hydroxy-ester **16** as a colorless liquid b.p. 98–105°/10 Torr. – IR.: 3420 (OH), 1725 (ester C=O), 910, 990 (vinyl). – NMR.: 1.33 (*s*, 3H, CH_3); 1.90 (*t*, *J*=6, 2H, CH_2); 2.04 (*s*, 3H, $OCOCH_3$); 2.48 (*s*, 1H, OH); 4.21 (*t*, *J*=6, 2H, CH_2OAc); 5.14 (*m*, 2H, CH=CH_2); 5.95 (*d*×*d*, 1H, CH=CH_2).

rac. *Ethyl 2-(6-Hydroxy-2,5,7,8-tetramethyl-chroman)acetate* (**12**). To 4.7 g (0.03 mol) of trimethylhydroquinone in 25 ml of anhydrous ether and 50 ml of anhydrous benzene was added 2.5 g (0.0184 mol) of $ZnCl_2$ *(Merck)* and 3.5 g (0.022 mol) of hydroxy-ester **16**, at RT. The mixture was stirred and heated at 50° while a stream of dry HCl-gas was passed in for a period of 3 h. During this period, the initial yellow-brown mixture became a dark-brown solution. After cooling, the solution was decomposed with water. The organic solution was separated and washed with water, *Claisen*'s alkali and again with water, then processed in the usual manner giving 5.2 g (81%) of crude hydroxychroman **12** as a light-brown solid, m.p. 55–63°. TLC. analysis (ether/ petroleum ether 1:1) indicated the presence of 3 minor impurities in addition to **12**. A sample of this material was recrystallized from cyclohexane and then ether/petroleum ether (60–90°) giving a colorless solid, m.p. 74.5–75.5°. – IR. (KBr): 3390 (OH), 1705 (ester C=O). – NMR.: 1.28 (*s*, 3H, H_3C–C(2)); 1.80 (*m*, 4H, 2 CH_2); 2.03 (*s*, 3H, $OCOCH_3$); 2.10 (*br. s*, 9H, 3 CH_3–Ar): 2.63 (*t*, 2H, CH_2Ar); 4.28 (*t*, 2H, CH_2OAc); 4.40 (*s*, 1H, OH). The analytical specimen m.p. 71–72° (from petroleum ether (60–90°)) was obtained from a separate experiment.

$C_{17}H_{24}O_4$ (292.41) Calc. C 69.83 H 8.27% Found C 70.10 H 8.37%

rac. *Ethyl 2-(6-Benzyloxy-2,5,7,8-tetramethyl-chroman)acetate* (**13**). A slurry of 17.3 g (0.129 mol) of anhydrous $AlCl_3$ in 200 ml of CH_2Cl_2 was stirred at 0° while 22.4 g (0.368 mol) of CH_3NO_2 was added. After stirring for 10 min at 0° (clear solution), 26.3 g (0.173 mol) of trimethylhydroquinone was added. After 5 min, the resulting dark mixture was cooled to $-20°$ and a solution of 27.3 g (0.173 mol) of hydroxy ester **16** in 750 ml of CH_2Cl_2 was added dropwise over 0.5 h. The resulting mixture was allowed to warm to RT. and stirred for an additional 2.5 h then poured onto ice/water. Work-up with CH_2Cl_2 in the usual manner (the organic extracts were additionally washed with aqueous $NaHCO_3$-solution) gave 58.6 g of crude hydroxychroman **12** as a viscous oil. TLC. analysis (hexane/ether 1:1) indicated the presence of **12** and 2 minor impurities.

Without further purification, this material was dissolved in 256 ml of DMSO and 57.5 g (0.42 mol) of anhydrous K_2CO_3 was added. The slurry was stirred while 30 g (0.237 mol) of benzyl chloride was

added over a 5 min period. Stirring was continued at RT. for 50 h at which point fresh charges of 57.5 g of K_2CO_3 and 30 g of benzyl chloride were added. After stirring for an additional 68 h, the mixture was treated with ice/water and worked up with ether in the usual manner. The residue (84.7 g) was chromatographed on 1 kg of silica gel. Elution with hexane/ether 9:1 afforded 51.2 (77.5%) of ether ester **13** as an orange oil. This material was crystallized from 40 ml of ethanol giving 32.4 g of a colorless solid, m.p. 61–62°. From the mother liquor, there was obtained an additional 6 g of **13**, m.p. 59–62°. The analytical specimen was obtained from another experiment as a colorless solid, m.p. 59–62° (from ethanol). – UV.: 280 (2075), 286 (2320). – IR.: 1735 (ester C=O). – NMR.: 1.33 (*s*, 3H, H_3C–C(2)); 1.90 (*m*, 4H, 2 CH_2); 2.06 (*s*, 3H, $OCOCH_3$); 2.24, 2.19 and 2.13 (3*s*, 9H, 3 CH_3–Ar); 2.65 (*t*, J=6, 2H, Ar–CH_2); 4.32 (*m*, 2H, CH_2OAc); 4.73 (*s*, 2H, $C_6H_5CH_2O$); 7.49 (*m*, 5H, C_6H_5). – MS. (*m/e*): 382 (M^+, 7), 291 ($M^+ - C_7H_7$, 31), 231 ($M^+ - C_7H_7 - CH_3CO_2H$, 62), 91 (C_7H_7, 100).

$C_{24}H_{30}O_4$ (382.50) Calc. C 75.36 H 7.91% Found C 75.56 H 7.85%

rac.-*2-(6-Benzyloxy-2,5,7,8-tetramethylchroman-2-yl)-ethanol* (**14**). a) *From acid* **11**. A solution of 3.54 g (10 mmol) of acid **11** in 35 ml of THF was cooled to 3° as a solution of 3.92 ml (20 mmol) of 70% sodium dihydro-bis(2-methoxyethoxy)aluminate in 16 ml of THF was added over 15 min. The solution was stirred with cooling for 1.5 h and then at RT. for another hour. The mixture was re-cooled to 3°, quenched with 10 ml of methanol, poured onto ice and worked up with ether in the usual manner to give a pale yellow oil. This material was taken up in benzene/ethyl acetate 1:1 and filtered through 25 g of silica gel. The yellow filtrate was concentrated to an oil which was triturated at −70° with ether/petroleum ether (30–60°) 1:2 and crystallized from the same solvents to give 1.44 g (42% yield) of alcohol **14** as a white solid, m.p. 65–69.5°. – UV.: 203 (23,100), 256 (420), 263 (420), 280 (850), 286 (950). – IR.: 3555, 3030, 2940 (OH). – NMR.: 1.33 (*s*, 3H, H_3C–C(2)); 2.12, 2.19 and 2.24 (3*s*, 9H, ArCH_3); 2.91 (*s*, 1H, OH); 3.91 (*t*, J=6, 2H, CH_2OH); 4.71 (*s*, 2H, CH_2O); 7.44 (*m*, 5H, C_6H_5). – MS.: (*m/e*): 340 (M^+, 27), 249 ($M^+ - C_7H_7$, 100), 231 ($M^+ - C_7H_7 - H_2O$, 68).

$C_{22}H_{28}O_3$ (340.44) Calc. C 77.61 H 8.29% Found C 77.40 H 8.32%

b) *From ester* **13**. A mixture of 25 g (0.065 mol) of ester **13**, 18.1 g (0.13 mol) of K_2CO_3, 75 ml of water and 750 ml of methanol was stirred and refluxed for 40 min. The resulting mixture was cooled, diluted with 1 l of ice/water and worked up with CH_2Cl_2 in the usual manner. There was obtained 23.8 g (100+%) of crude alcohol **14** (still containing some solvent) as an oil which crystallized on standing. This material was virtually identical by IR., NMR. spectral and TLC. comparison (benzene/ethyl acetate 1:1) with that produced as in part a above and was used without further purification.

rac.-*2-(6-Benzyloxy-2,5,7,8-tetramethylchroman)acetaldehyde* (**15**). – a) *From* **11**. A solution of 5.31 g (15 mmol) of acid **11** in 30 ml of benzene was warmed to 50° as 6.30 ml (75 mmol) of oxalyl chloride was added over 30 min. The mixture was heated a further 30 min, cooled and concentrated i.V. To the residual oil was added 60 ml of toluene, 4.5 g of anhydrous sodium acetate, 0.09 ml of quinoline S and 1.45 g of 10% Pd/C catalyst. The mixture was hydrogenated at atmospheric pressure and RT. After 2.5 h, H_2 uptake (220 ml) had ceased. The catalyst was removed by filtration and the filtrate was concentrated to a colorless oil. This material was combined with a similar sample from 1.77 g of acid **11** and the total was chromatographed on 600 g of silica gel. Elution with benzene/ethyl acetate 95:5 gave 3.34 g (49% yield) of aldehyde **15** as a waxy solid. A 2.22 g sample of this material was crystallized from ether to give two crops (total 1.64 g) of white solid, m.p. 71–74°. – UV.: 227 (12,000), 258 (1030), 264 (1040), 280 (2075), 288 (2320). – IR.: 2750 (ald. CH), 1720 (C=O). – NMR.: 1.43 (*s*, 3H, H_3C–C(2)); 2.12, 2.17 and 2.23 (3*s*, 9H, 3 CH_3–Ar); 4.70 (*s*, 2H, CH_2O); 7.40 (*m*, 5H, C_6H_5); 9.92 (*t*, J=2, 1H, CHO). – MS.: (*m/e*): 338 (M^+, 25), 247 ($M^+ - C_7H_7$, 100), 165 (87).

$C_{22}H_{26}O_3$ (338.43) Calc. C 78,08 H 7.74% Found C 77.94 H 7.81%

b) *From* **14**. The procedure of *Ratcliffe & Rodehorst* [6] was employed. To a solution of 7.1 g of anhydrous pyridine in 90 ml of purified, anhydrous CH_2Cl_2 [6] was added 3.6 g (0.036 mol) of CrO_3. The mixture was stirred at RT. for 15 min whereupon a solution of 2 g (5.88 mmol) of crude alcohol **14** (derived from **13**) in 15 ml of CH_2Cl_2 was added in one portion. After stirring at RT. for 15 min, the organic phase was decanted and the tarry residue was washed 3 times with ether. The organic phases were combined, washed with 1N NaOH and 1N HCl, then processed in the usual manner giving 1.85 g

of a yellow oily residue. This material was chromatographed on 100 g of silica gel. Elution with benzene/ethyl acetate 9:1 yielded 1.75 g (87.9%) of aldehyde **15** as a pale-yellow solid, m.p. 65–69°. This material was identical by spectral and TLC. comparison (hexane/ether 1:1) with that produced as in part a above.

(S)-(−)-2-(6-Benzyloxy-2,5,7,8-tetramethylchroman)acetic acid (**6**). To a hot solution of 35.4 g (0.10 mol) of racemic acid **11** in 350 ml of ethyl acetate was added 32.4 g (0.10 mol) of (−)-quinine. The pale yellow solution was cooled to 25°, diluted with 250 ml of ether, seeded and stored for 16 h at 3°. The solid was collected by filtration and dried to give 22.58 g of white powder, m.p. 161–162°, $[\alpha]_D^{25} = -100.0°$ ($c = 1.07$, CH_3OH). Recrystallization of this material from ethyl acetate/ether gave two crops (combined for further use) of pure salt: a) 17.54 g, m.p. 162–163°, $[\alpha]_D^{25} = -96.5°$ ($c = 1.14$, CH_3OH); b) 3.21 g (total 20.75 g = 61.2% yield), m.p. 160–160.5°, $[\alpha]_D^{25} = -98.8°$ ($c = 1.27$, CH_3OH). To a suspension of the salt in 500 ml of ether and 120 ml of water was added 61 ml of 1.0N HCl over 15 min. The mixture was stirred another 15 min until all the salt had reacted and then worked up in the usual manner to give 10.54 g of white solid. Crystallization of this material from ether/hexane gave 9.14 g (54% yield from **11**) of pure (*S*)-acid **6**, m.p. 95–97°, $[\alpha]_D^{25} = -11.0°$ ($c = 1.08$, CH_3OH). The UV., IR., NMR., and mass spectra were identical with those of racemic acid **11**. A similarly prepared sample gave the following analysis:

$C_{22}H_{26}O_4$ (354.43) Calc. C 74.55 H 7.39% Found C 74.60 H 7.56%

(R)-(+)-2-(6-Benzyloxy-2,5,7,8-tetramethylchroman)acetic acid (**17**). To a solution of 3.54 g (10 mmol) of racemic acid **11** in 35 ml of hot benzene was added 1.71 g (10 mmol) of (*R*)-1-(1-napthyl)ethylamine. The solution was cooled to 25°, diluted with 25 ml of ether, and stored for 16 h at 3°. The solid was collected by filtration, dried and crystallized from 250 ml of ethyl acetate to give 1.71 g (66% yield) of white powder, m.p. 161.5–162°, $[\alpha]_D^{25} = +9.32°$ ($c = 1.08$, CH_3OH). A 525 mg sample of this salt was acidified as described in the preceding experiment. Crystallization of the crude product from ether/petroleum ether (30–60°) gave 302 mg (56% yield from **11**) of (*R*)-acid **17** as a white solid, m.p. 95–96°, $[\alpha]_D^{25} = +11.0°$ ($c = 1.14$, C_2H_5OH). The UV., IR., NMR., and mass spectra were identical with those of racemic acid **11**.

$C_{22}H_{26}O_4$ (354.43) Calc. C 74.55 H 7.39% Found C 74.76 H 7.41%

(S)-(−)-2-Methyl (6-Benzyloxy-2,5,7,8-tetramethylchroman)acetate (**5**). To a 3° solution of *ca.* 4.1 mmol of diazomethane in 45 ml of ether was added over 15 min a solution of 708 mg (2.0 mmol) of (*S*)-**6** in 10 ml of ether. The mixture was stirred another hour with cooling, quenched with several drops of acetic acid and worked up as usual to give 741 mg of solid. Crystallization from hexane/petroleum ether (30–60°) gave 494 mg (67% yield) of ester **5** as a white powder, m.p. 51–52°, $[\alpha]_D^{25} = -2.90°$ ($c = 1.38$, C_2H_5OH). (Lit. [1] m.p. 51–52°, $[\alpha]_D^{25} = -3.44°$ ($c = 0.93$, C_2H_5OH)).

(S)-(−)-2-(6-Hydroxy-2,5,7,8-tetramethylchroman)acetic acid (**2**). A mixture of 1.77 g (5.0 mmol) of (*S*)-**6**, 35 ml of ethanol and 500 mg of 10% Pd/C catalyst was hydrogenated at atmospheric pressure and RT. After 40 min, the uptake of H_2 (173 ml) had ceased. The catalyst was removed by filtration and the filtrate concentrated to dryness. The residual solid was crystallized from ethanol/water to give 1.05 g (80% yield) of phenolic acid **2**, m.p. 149–151.5°, mixed m.p. with authentic material undepressed; $[\alpha]_D^{25} = -13.78°$ ($c = 1.05$, C_2H_5OH); (Lit. [1] m.p. 146–149°, 124–127°; $[\alpha]_D^{25} = -15.39°$ ($c = 1$, C_2H_5OH)).

REFERENCES

[1] *J. W. Scott, F. T. Bizzarro, D. R. Parrish & G. Saucy,* Helv. *59,* 290 (1976).
[2] *N. Cohen, W. F. Eichel, R. J. Lopresti, C. Neukom & G. Saucy,* J. org. Chemistry *41,* 3505 (1976).
[3] *L. Crombie & M. Manzoor-i-Khuda,* J. chem. Soc. *1957,* 2767.
[4] *P. A. Wehrli, R. I. Fryer & W. Metlesics,* J. org. Chemistry *36,* 2910 (1971).
[5] *Yu M. Portnyagin & N. W. Pak,* J. org. Chemistry U.S.S.R. *7,* 1691 (1971).
[6] *R. Ratcliffe & R. Rodehorst,* J. org. Chemistry *75,* 4000 (1970).