3070, 2950, 2250 (CN), 1780 (CO), 1440, 1375, 1210, 1020, 740, 690 cm^{-1}; MS m/e 255 (M^+), 200 ($PhSeCOCH_3^+$), 158 ($PhSeH^+$), 43 ($COCH_3^+$); calcd for $C_{10}H_9NO_2{}^{80}Se$ m/e 254.9798, found m/e 254.9856.

Ethyl 1-acetoxy-1-(phenylseleno)acetate (2h): ^1H NMR δ 1.16 (t, 3 H, J = 7 Hz, CH_2CH_3), 2.13 (s, 3 H, $COCH_3$), 4.05 (q, 2 H, J = 7 Hz, CH_2CH_3), 6.32 (s, 1 H, CH), 7.13–7.73 (m, 5 H, Ph); IR 3070, 3000, 1760 (CO), 1580, 1480, 910, 860, 690, 650, 610, 500, 470 cm^{-1}; MS m/e 302 (M^+), 200 ($PhSeCOCH_3^+$), 158 ($PhSeH^+$), 78 (PhH^+); calcd for $C_{12}H_{14}O_4{}^{80}Se$ m/e 302.0028, found m/e 302.0025. Anal. Calcd: C, 47.85; H, 4.69. Found: C, 47.64; H, 4.81.

Acknowledgment. We are grateful to the UNESCO and the Japanese Ministry of Education, Science, and Culture for making K.S.'s participation in this project possible. We also thank Dr. Andrew E. Feiring of Experimental Station, E. I. du Pont de Nemours & Co., Inc., for his valuable suggestion.

Supplementary Material Available: ^1H NMR spectra of new compounds (9 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

Synthesis of (2*RS*,4′*R*,8′*R*)-α-Tocopherol and Related Compounds via a 2-Chlorochroman

Noal Cohen* and Beatrice Schaer

Roche Research Center, Hoffmann-La Roche, Inc., Nutley, New Jersey 07110

Michelangelo Scalone

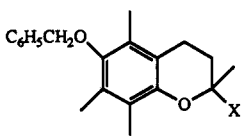
Pharma Division, Preclinical Research, F. Hoffmann-La Roche Ltd., Basle, Switzerland, CH-4002

Received May 21, 1992

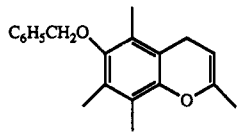
We describe a new synthetic route to 2,2-disubstituted chromans involving coupling of the novel 2-chlorochroman **4** with nucleophiles.[1] This approach has been employed in a synthesis of (2*RS*,4′*R*,8′*R*)-α-tocopherol[2] as the corresponding benzyl ether **1** and was stimulated by a desire to find additional applications for intermediates such as **2**[3] and **3**.[3] The latter compounds are readily available via the cyclocondensation of trimethyl hydroquinone with methyl vinyl ketone, a key reaction discovered several years ago in our laboratories,[4] and are thus attractive starting points for the development of new routes to the tocopherol class of antioxidants. In this context, we envisioned chloride **4** as being easily obtained from hemiketal **3** and serving as an electrophilic chroman component in various coupling processes.

Highly reactive cyclic α-halo ethers have recently found synthetic utility outside of the carbohydrate field. In particular, Bates (Bihovsky) and co-workers[5] have described reactions of 2-chlorotetrahydropyrans and related intermediates with various nucleophiles. A search of the literature revealed that 2-halochromans, on the other hand, are a relatively rare species.[6] We were particularly concerned about the properties of compounds such as **4** in which the halogen is attached to a tertiary center. Not only did we expect such substances to be unstable, we were also aware that their reactivity pattern in nucleophilic coupling processes would probably lead to substantial amounts of elimination products (chromenes). While these caveats certainly turned out to be justified, we have, nonetheless, uncovered some synthetically useful transformations of the chlorochroman **4**.

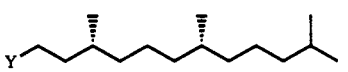
Treatment of the hemiketal **3** with HCl in ether at 0 °C[5a] gave **4** in 93% yield as a solid which could be stored indefinitely at 0 °C without deterioration but which rapidly decomposed on exposure to moisture or silica gel. Substitution reactions of **4** with various nucleophiles, not unexpectedly, gave mixtures of the desired coupling products and the elimination product chromene **10**.[7] Exposure of **4** to dimethyl sodiomalonate in THF[5a] gave diester **7** in 23% yield. This product is a precursor to chroman-2-acetic acids (e.g. **8**) of established utility in α-tocopherol synthesis.[3a,4,8] All attempts to obtain nitrile **9**, a potential precursor to antioxidant chroman-2-carboxylic acids,[3b,9] by treatment of **4** with alkali metal cyanides proved fruitless, the chromene **10** again being the major identifiable product. Even phase-transfer conditions afforded only trace quantities of the desired nitrile.



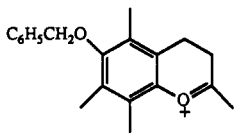
1; X= (4*R*,8*R*)-4,8,12-trimethyltridecyl
2; X= OCH_3
3; X= OH
4; X= Cl
5; X= C_2H_5
6; X= $CH_2CH{=}CH_2$
7; X= $CH(CO_2CH_3)_2$
8; X= CH_2CO_2H
9; X= CN



10



11; Y= OH
12; Y= CH_2OH
13; Y= CH_2Br
14; Y= CH_2MgBr



15

The reactions of **4** with Grignard reagents (ethylmagnesium bromide, allylmagnesium chloride, C_{16}-side

(1) This work is the subject of U.S. Patents No. 4,752,646 (June 21, 1988), 4,806,661 (Feb 21, 1989), and 4,824,971 (April 25, 1989), Hoffmann-La Roche, Inc.

(2) This form of vitamin E is also known as 2-ambo-α-tocopherol and is a 1:1 mixture of epimers. See: Kasparek, S. In *Vitamin E. A Comprehensive Treatise*; Machlin, L. J., Ed.; Marcel Dekker: New York, 1980; pp 7–65 and references cited therein.

(3) (a) Cohen, N.; Scott, J. W.; Bizzarro, F. T.; Lopresti, R. J.; Eichel, W. F.; Saucy, G. *Helv. Chim. Acta* **1978**, *61*, 837. (b) For studies related to those described herein, see: Cohen, N.; Schaer, B.; Saucy, G.; Borer, R.; Todaro, L.; Chiu, A.-M. *J. Org. Chem.* **1989**, *54*, 3282.

(4) (a) Scott, J. W.; Bizzarro, F. T.; Parrish, D. R.; Saucy, G. *Helv. Chim. Acta* **1976**, *59*, 290.

(5) (a) Bates, H. A.; Deng, P. N. *J. Org. Chem.* **1983**, *48*, 4479. (b) Bates, H. A.; Farina, J. *Ibid.* **1985**, *50*, 3843. (c) Bates, H. A.; Rosenblum, S. B. *Ibid.* **1986**, *51*, 3447. (d) Bihovsky, R.; Selick, C.; Giusti, I. *Ibid.* **1988**, *53*, 4026. (e) Bihovsky, R. *Trends in Organic Chemistry*, in press. (f) For recent related studies involving organothallium reagents, see: Markó, I. E.; Southern, J. M.; Kantam, M. L. *SYNLETT* **1991**, 235.

(6) (a) Clark-Lewis, J. W.; Dainis, I.; Ramsay, G. C. *Aust. J. Chem.* **1965**, *18*, 1035. (b) Weinges, K.; Paulus, E. *Liebigs Ann. Chem.* **1965**, *681*, 154.

(7) A pure sample of this substance was best prepared by treatment of 2-methoxychroman **2** with phosphorus pentoxide in refluxing toluene, see the Experimental Section. This chromene has been employed in an asymmetric approach to certain key α-tocopherol intermediates. These studies will be reported separately by one of us (M.S.).

(8) Cohen, N.; Banner, B. L.; Neukom, C. *Synth. Commun.* **1982**, *12*, 57.

(9) Scott, J. W.; Cort, W. M.; Harley, H.; Parrish, D. R.; Saucy, G. *J. Am. Oil Chem. Soc.* **1974**, *51*, 200.

0022-3263/92/1957-5783$03.00/0

chain reagent 14) were studied in some detail. After considerable experimentation, these couplings were developed to a synthetically useful level. It was found that the desired reaction course was favored in diethyl ether whereas THF seemed to promote elimination. Also, low temperatures gave improved yields of the coupling products 1, 5,[3b] and 6.[3b] In all cases, the main byproduct was again chromene 10 which was extremely difficult to separate from the desired materials; however, we found that treatment of the crude product with methanolic *p*-toluenesulfonic acid converted the chromene to more polar materials (2, 3) which were readily removed by chromatography allowing isolation of pure 2,2-disubstituted chromans in 40–60% yields. We also carried out several experiments in which 4 was treated with vinylmagnesium bromide and ethynylmagnesium bromide. Unfortunately, these reagents produced complex mixtures containing only small amounts of the desired products, under a variety of reaction conditions. The (4*R*,8*R*)-C_{16}-bromide 13[10] was secured from (3*R*,7*R*)-C_{15}-alcohol 11[4,11] by means of a straightforward five-step homologation sequence (via 12,[10] see the Experimental Section).

In summary, we have prepared the novel 2-chlorochroman 4 from very readily available intermediates and demonstrated its synthetic potential as a precursor to certain 2,2-disubstituted chromans including the α-tocopherol derivative 1. Our results strongly suggest the intermediacy of oxonium ion 15 in the coupling reactions described.[3b,12]

Experimental Section

General Information. All of the reactions described below were carried out under an atmosphere of argon. Column chromatography was performed using EM silica gel 60 (0.063–0.2 mm). Thin-layer chromatography was employed to monitor reactions and determine product purity and was performed using EM silica gel 60 F-254 precoated plates. Hexanes–ether mixtures were generally used as the mobile phases. Spots were detected with UV light and phosphomolybdic acid–ceric sulfate sprays followed by heating. ^{1}H NMR spectra (100 or 200 MHz) were obtained in $CDCl_3$ solution. Chemical shifts are reported relative to Me_4Si as an internal standard. Infrared spectra were obtained in $CHCl_3$ solution. GC analyses were carried out using a Hewlett-Packard 5700A instrument with a 6-ft, 5% FFAP column, 160 °C isothermal, helium carrier gas flow 2.0, flame ionization detector. Anhyd ether and THF were obtained by distillation from sodium benzophenone ketyl immediately prior to use. The "usual" workup conditions involve three extractions with the indicated solvent, washing the combined organic extracts with saturated brine, drying the solution over anhydrous magnesium sulfate, suction filtration, and concentration of the filtrate under water aspirator pressure. The residue was then dried to constant weight under high vacuum.

***rac*-2-Chloro-3,4-dihydro-2,5,7,8-tetramethyl-6-(phenylmethoxy)-2*H*-1-benzopyran (4).** To a solution of 5 g (16 mmol) of 2-hydroxychroman 3[3] in 50 mL of anhyd ether was added 5 g of 4-A molecular sieves. The mixture was stirred (Teflon paddle) with ice-bath cooling while HCl gas was bubbled in for 30 min. Stirring was continued at 0 °C for 30 min, and then the solvent was removed in vacuo. The residue was treated with 500 mL of hexanes, and the solution was separated by decantation. The hexanes solution was then treated with 10 g of anhydrous $CaCl_2$, and the mixture was stirred for 2 h. The solids were filtered with suction, and the filtrate was concentrated in vacuo to a volume of ca. 20 mL. Crystallization was induced by cooling to −10 °C and stirring, and then the remaining solvent was removed in vacuo, giving 4.9 g (92.8%) of 2-chlorochroman 4 as a colorless solid. The IR spectrum showed no OH absorption: ^{1}H NMR δ 7.46 (m, 5, Ph), 4.71 (s, 2, PhCH_2O), 2.22, 2.20, 2.13, 2.09 ppm (4 s, 12, 3ArCH_3 and CH_3CCl) (the CH_3COH resonance of the starting material occurs as a singlet at 1.65 ppm and was absent); EIMS *m*/*z* 294 (M − HCl) (M^+ not observed). The chlorochroman decomposed upon attempted column or thin-layer chromatography and was used without further purification. It was stored at 0 °C protected from moisture. We did not attempt to obtain a melting point or microanalysis of this compound because of its obvious instability.

***rac*-[3,4-Dihydro-2,5,7,8-tetramethyl-6-(phenylmethoxy)-2*H*-1-benzopyran-2-yl]propanedioic Acid Dimethyl Ester (7).** A 370 mg (9.25 mmol) sample of 60 % sodium hydride–mineral oil dispersion was washed free of oil with hexanes and treated with 20 mL of anhyd THF. The resulting slurry was stirred with ice bath cooling while 1.056 g (8 mmol) of dimethyl malonate was added dropwise. After being stirred for 10 min at 0 °C, the sodiomalonate mixture was treated dropwise, with a solution of crude chlorochroman 4 derived from 1.25 g (4 mmol) of chromanol 3, in 4 mL of dry THF. Stirring at 0 °C was continued for 1.5 h at which point the reaction mixture was poured into water and extracted three times with ether. The ether extracts were processed in the usual manner giving a yellow, oily residue which was dissolved in 5 mL of petroleum ether (bp 30–60 °C). Upon stirring, the mixture produced a white precipitate which was isolated by filtration. Recrystallization from petroleum ether gave 0.4 g (23.4 %) of diester 7 as a colorless solid: mp 80–81 °C; IR 1754, 1738 cm^{-1} (ester C=O); ^{1}H NMR δ 7.42 (m, 5, Ph), 4.71 (s, 2, PhCH_2O), 3.88 (s, 1, CH(CO_2CH_3)$_2$), 3.76 (s, 6, (CO_2CH_3)$_2$), 2.62 (t, *J* = 7 Hz, 2, ArCH_2), 2.21, 2.16, 2.04 (3 s, 9, ArCH_3), 1.57 ppm (s, 3, CH_3CO); EIMS *m*/*z* 426 (M^+). Anal. Calcd for $C_{25}H_{30}O_6$: C, 70.40; H, 7.09. Found: C, 70.29; H, 7.22.

***rac*-3,4-Dihydro-2-ethyl-6-(phenylmethoxy)-2,5,7,8-tetramethyl-2*H*-1-benzopyran (5).**[3b] A solution of 4.95 g (14.98 mmol) of 2-chlorochroman 4 in 60 mL of anhyd ether was stirred at −78 °C while 10.8 mL (30.24 mmol) of 2.8 M ethereal ethylmagnesium chloride (Aldrich) was added dropwise. The reaction mixture was stirred at −78 °C for 30 min and then warmed to −10 °C and stirred in an ice bath for 7 h before being poured into 50 mL of cold, saturated ammonium chloride solution. The mixture was worked up with ether in the usual manner giving 4.95 g of a yellow oil. This material was dissolved in 40 mL of methanol and 10 mL of ether containing 10 mg of *p*-toluenesulfonic acid monohydrate. The solution was stirred at room temperature for 21 h and then concentrated in vacuo. The residue was chromatographed on 75 g of silica gel. Elution with 40:1 hexanes–ether afforded 2.93 g (60.4%) of 5 as an oil. The spectroscopic properties were identical to those reported previously.[3b] Anal. Calcd for $C_{22}H_{28}O_2$: C, 81.44; H, 8.70. Found: C, 81.36; H, 8.70.

***rac*-3,4-Dihydro-6-(phenylmethoxy)-2-(2-propenyl)-2,5,7,8-tetramethyl-2*H*-1-benzopyran (6).**[3b] Using the procedure of the preceding experiment, 6 was obtained in 57.2% yield, starting from 4 (4.95 g; 14.98 mmol) and 2 M allylmagnesium chloride in THF (12 mL; 24 mmol), as a colorless oil. The spectroscopic properties were identical to those reported previously.[3b] Anal. Calcd for $C_{23}H_{28}O_2$: C, 82.10; H, 8.39. Found: C, 81.96; H, 8.35.

(4*R*,8*R*)-1-Bromo-4,8,12-trimethyltridecane (13). A solution of 10.44 g (45.8 mmol) of alcohol 11[4,11] (GC purity 98.6%; $[\alpha]^{25}_D$ +4.2° (*c* 2, hexanes)) in 150 mL of anhyd pyridine was stirred in an acetone–ice bath while 17.4 g (91.3 mmol) of *p*-toluenesulfonyl chloride was added in one portion. The mixture was stirred in the cooling bath for 2 h and then kept at 0 °C for 40 h before being quenched by the addition of 300 mL of ice water. The product was isolated in the usual manner with ether (the ether extracts were additionally washed with 3 N HCl) giving 16.6 g (94.9%) of (3*R*,7*R*)-3,7,11-trimethyldodecyl *p*-toluenesulfonate.

A mixture of this tosylate (43.45 mmol) and 4.25 g (86.7 mmol) of sodium cyanide, in 80 mL of ethanol and 20 mL of water, was

(10) The racemic modification (diastereomeric mixture) of this compound has been reported: (a) Karrer, P.; Favarger, M.; Merz, A.; Milhaud, G. *Helv. Chim. Acta* **1948**, *31*, 1505. (b) Sato, K.; Kurihara, Y.; Abe, S. *J. Org. Chem.* **1963**, *28*, 45.

(11) Mayer, H.; Schudel, P.; Rüegg, R.; Isler, O. *Helv. Chim. Acta* **1963**, *46*, 630.

(12) The use of benzopyrylium salts as electrophiles in coupling processes leading to chromanones and chromenes has been reported: (a) Goldsmith, D. J.; Helmes, C. T., Jr. *Synth. Commun.* **1973**, *3*, 231. (b) Iwasaki, H.; Takashi, K.; Yamamoto, Y.; Akiba, K. *Tetrahedron Lett.* **1987**, *28*, 6355. (c) Iwasaki, H.; Akiba, K. *Heterocycles* **1987**, *26*, 2857. (d) Lee, Y.-G.; Ishimaru, K.; Iwasaki, H.; Ohkata, K.; Akiba, K. *J. Org. Chem.* **1991**, *56*, 2058 and references cited therein.

stirred and refluxed for 2.5 h. Most of the ethanol was removed in vacuo, and the residue was treated with 75 mL of water and 75 mL of saturated brine and worked up in the usual manner with ether. This afforded 10.25 g (99.5%) of (4*R*,8*R*)-4,8,12-trimethyltridecanenitrile as a yellow oil. GC analysis revealed a purity of 95.2%: $[\alpha]^{25}_D$ +3.93° (*c*, 2, hexanes); IR 2249 cm^{-1} (CN); ^1H NMR δ 2.34 ppm (m, 2, CH_2CN); ^{13}C NMR (400 MHz, $CDCl_3$) 120.02 (CN), 39.36, 37.22 (2 CH_2), 36.26, 32.78 (CH), 32.27, 32.08 (CH), 28.01 (CH), 24.80, 24.20, 22.74 (CH_3), 22.58 (CH_3), 19.73 (CH_3), 18.88 (CH_3), 14.95 (CH_2CN) ppm; EIHRMS *m/z* 238.2535 ($M + H^+$) ($C_{16}H_{31}N + H^+$ requires 238.2535).

A mixture of this nitrile (43.25 mmol) and 18.4 g (0.33 mol) of potassium hydroxide in 162 mL of ethylene glycol and 13.5 mL of water was stirred in a 150 °C oil bath for 4 h and then cooled to 0–5 °C and poured into 300 mL of 6 N HCl. The mixture was worked up with ethyl acetate in the usual manner, giving 11.1 g (100%) of (4*R*,8*R*)-4,8,12-trimethyltridecanoic acid as an oil.

A solution of this acid in 50 mL of toluene was stirred at room temperature while 25 mL of Red-Al in toluene (Aldrich, 3.4 M) was added dropwise. After being stirred for 3 h at room temperature, the reaction mixture was decomposed by the cautious addition of 5 mL of ethanol. The mixture was then treated with 300 mL of 6 N HCl and worked up with ethyl acetate in the usual manner. Kugelrohr distillation (160 °C bath temperature, 1 mmHg) of the residue gave 7.0 g of (4*R*,8*R*)-4,8,12-trimethyltridecanol (**12**) as a colorless liquid having a GC purity of 94.5%. The distillation residue contained starting acid and was re-reduced with 6 mL of Red-Al as described above. This provided an additional 1.8 g (total yield 8.8 g; 84.2%) of alcohol **12** having a GC purity of 95.8%. A 1.67-g sample of this material was further purified by chromatography on 50 g of silica gel. Elution with 9:1 and 4:1 hexanes–ether gave 1.53 g of alcohol **12**: $[\alpha]^{25}_D$ +1.67° (*c* 2, hexanes); IR 3623 cm^{-1} (OH); ^1H NMR δ 3.63 ppm (t, 2, *J* = 6.5 Hz, CH_2OH); ^{13}C NMR (400 MHz, $CDCl_3$) 63.55 (CH_2OH), 39.42, 37.34 (3 CH_2), 32.94, 32.84 (CH), 32.67 (CH), 30.42, 28.04 (CH), 24.82, 24.47, 22.71 (CH_3), 22.62 (CH_3), 19.75 (2 CH_3) ppm; FABHRMS *m/z* 241.2541 (M – H) ($C_{16}H_{34}O$ – H requires 241.2531).

To a solution of 9.6 g (39.6 mmol) of **12** in 30 mL of anhyd DMF was added 10.7 g (40.84 mmol) of triphenylphosphine. The solution was stirred in an acetone–ice bath (–10 °C) while 2.1 mL (41 mmol) of bromine was added dropwise. The temperature rose to 5 °C. The reaction mixture was stirred at room temperature for 1 h and then poured into 100 mL of water and 150 mL of hexanes. After filtration, the layers were separated and the aqueous phase was extracted twice with hexanes. The hexanes layers were combined, washed with saturated sodium bicarbonate solution, dried, filtered through a plug of silica gel, and concentrated in vacuo. Kugelrohr distillation (150–160 °C bath temperature, 1 mmHg) of the residue gave bromide **13** in two fractions: 5.15 g of 95.8% GC purity and 3.55 g of 97.9% GC purity (72.2% yield). Redistillation of the larger fraction gave a colorless liquid, bp 120 °C (0.15 mm) having a GC purity of 97.9%; $[\alpha]^{25}_D$ –3.01° (*c* 2, hexanes); ^1H NMR δ 3.40 ppm (t, *J* = 7 Hz, 2, CH_2Br); ^{13}C NMR (400 MHz, $CDCl_3$) 39.40, 37.39, 32.94, 37.29, 35.48, 34.32, 32.82 (CH), 32.25 (CH), 30.56, 28.01 (CH), 24.79, 24.38, 22.68 (CH_3), 22.58 (CH_3), 19.76 (CH_3), 19.63 (CH_3) ppm; EIMS *m/z* 304, 306 (M^+, ca. equal intensities); EIHRMS *m/z* 304.1756 (M^+) ($C_{16}H_{33}Br$ requires 304.1766).

(2*RS*,4′*R*,8′*R*)-α-Tocopheryl Benzyl Ether (1). A Grignard (**14**) solution was prepared from 0.28 g (11.2 mmol) of magnesium and 3.4 g (11.2 mmol) of bromide **13** in 25 mL of anhyd ether. Grignard formation was induced with a few drops of 1,2-dibromoethane, and the mixture was stirred and refluxed for 3.5 h. To a stirred solution of 2.6 g (7.87 mmol) of 2-chlorochroman **4** in 25 mL of anhyd ether, cooled to –10 °C (ice–acetone bath), was added the Grignard solution dropwise. The resulting mixture was stirred at 0 °C for 18 h and then treated with 100 mL of saturated ammonium chloride solution. Workup with ether in the usual manner gave 4.95 g of an oil which was dissolved in 50 mL of methanol and 30 mL of ether containing 200 mg of *p*-toluenesulfonic acid monohydrate. After being stirred at room temperature for 24 h, the solution was concentrated in vacuo and the residue was chromatographed on 200 g of silica gel. Elution with 40:1 hexanes–ether gave 1.82 g (44.5%) of **1** as a viscous oil. The identity of this material was confirmed by spectral and TLC comparison with an authentic sample of (2*R*,4′*R*,8′*R*)-α-tocopheryl benzyl ether.

6-(Phenylmethoxy)-2,5,7,8-tetramethyl-4*H*-1-benzopyran (10). An authentic sample of this chromene was best prepared as follows: The 2-methoxychroman **2**, in toluene (8 mL/g) was treated with 0.2 parts by weight of phosphorus pentoxide at room temperature. The orange-red suspension was stirred in an oil bath at 110 °C for 10 min and then approximately 25% of the solvent was slowly distilled off during 1 h. After being cooled, the supernatant toluene solution was decanted onto sodium carbonate (0.13 g/mmol substrate) and the mixture was stirred vigorously for 0.5 h and filtered through Celite, and the filtrate was concentrated in vacuo. Recrystallization of the residue from acetone afforded the chromene **10**, in 73% yield, as an off-white solid: mp 73–77 °C. EIMS *m/z* 294 (M^+), 203, 188, 91; ^1H NMR (C_6D_6) δ 7.40–7.50 (m, 2 Ph), 7.10–7.25 (m, 3, Ph), 4.58 (s, 2 $PhCH_2O$), 4.46 (m, 1, CH=), 3.05 (br s, 2, CH_2CH=), 2.20 (s, 3, CH_3), 2.15 (s, 3, CH_3), 2.02 (s, 3, CH_3), 1.78 ppm (d, 3, *J* = 1.1 Hz, CH_3C=). Anal. Calcd for $C_{20}H_{22}O_2$: C, 81.60; H, 7.53. Found: C, 81.30; H, 7.80.

Acknowledgment. We are grateful to the staff of the Physical Chemistry Department, Hoffmann-La Roche, Inc., Nutley, NJ, for obtaining many of the spectral and microanalytical measurements required in this work.

Mechanism for the Reaction of Tributyltin Radicals with Aldehydes

Yury Zelechonok and Richard B. Silverman*

Department of Chemistry, Northwestern University, Evanston, Illinois 60208-3113

Received June 1, 1992

The mechanism for the tributyltin hydride-initiated reaction of ketones with alkenes can be exemplified by the cyclization of δ,ε-alkenyl ketones (**1**, Scheme I).[1] This mechanism involves tin radical addition to the carbonyl oxygen followed by carbon radical cyclization. The same mechanism could apply as well to δ,ε-alkenyl aldehydes (**1**, R = H)[2] or to the addition of tributyltin radicals to other aldehydes.[3] However, it is well-known that radical abstraction of aldehydic hydrogen atoms is a facile process.[4] Consequently, an alternative mechanism to that shown in Scheme I for the cyclization of δ,ε-alkenyl aldehydes can be envisioned (Scheme II). This mechanism has precedence in the tributyltin radical reaction of methyl selenol esters of δ,ε-alkenyl acids.[5] Previously reported examples of tributyltin radical additions to aldehydes could be rationalized by either mechanism shown in Schemes I and II. In order to differentiate these two mechanistic pathways we have examined the reaction of tributyltin deuteride with various aldehydes. The results of these experiments are described in this note.

(1) Enholm, E. J.; Burroff, J. A. *Tetrahedron Lett.* **1992**, *33*, 1835 and references cited therein.
(2) Beckwith, A. L. J.; Roberts, D. H. *J. Am. Chem. Soc.* **1986**, *108*, 5893.
(3) (a) Kuehlein, Neumann, W. P.; Mohring, H. *Angew. Chem., Int. Ed. Engl.* **1968**, *7*, 455. (b) Pereyre, M.; Quintard, J. P.; Godet, J. Y.; Valade, J. *Organomet. Chem. Synth.* **1971**, *1*, 269.
(4) (a) Minisci, F. *Top. Curr. Chem.* **1976**, *62*, 1. (b) Gottschalk, P.; Neckers, D. C. *J. Org. Chem.* **1985**, *50*, 3498. (c) Walling, C.; Huyser, E. S. *Org. React.* **1963**, *13*, 108.
(5) (a) Schwartz, C. E.; Curran, D. P. *J. Am. Chem. Soc.* **1990**, *112*, 9272. (b) Boger, D. L.; Mathvink, R. J. *J. Org. Chem.* **1992**, *57*, 1429.

0022-3263/92/1957-5785$03.00/0