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SYNTHESIS OF STERYL ESTERS OF PHENOLIC ACIDS BY A HETEROGENEOUS WITTIG REACTION

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ABSTRACT.—Natural steryl esters of phenolic acids and their analogues [**3–17**] have been synthesized by a heterogeneous Wittig reaction from (carbocholesteryloxymethyl)-triphenylphosphonium bromide and unprotected phenolic aldehydes using K_2CO_3 as a base under sonochemical conditions. The synthetic compounds were characterized by their ^{1}H-nmr, mass, and uv spectra.

The discovery that ferulic acid occurs relatively widely in plants in different conjugated forms has opened up a new field in the study and explanation of its physiological role. Thus, steryl ferulates have been found as lipoid conjugates in rice bran oil (1), maize, wheat, and rye (2). The alcohol components of these esters are usually campestanol, campesterol, cholesterol, sitosterol, or stigmastanol (3). Steryl esters of other phenolic acids have rarely been found in nature, although cinnamates have been found in *Hoya* (4), *Euphorbia* (5), and species of other genera.

Several physiological roles have been proposed for these esters. They have been regarded as novel growth-promoting vitamins, antioxidants, photoprotectors, and effective agents in the treatment of arteriosclerosis (2). Such proposed physiological functions evoked our interest in the simple and convenient synthesis of these compounds. There has been only one previous report on the synthesis of phytostanol ferulates, using protected feruloyl chloride (6).

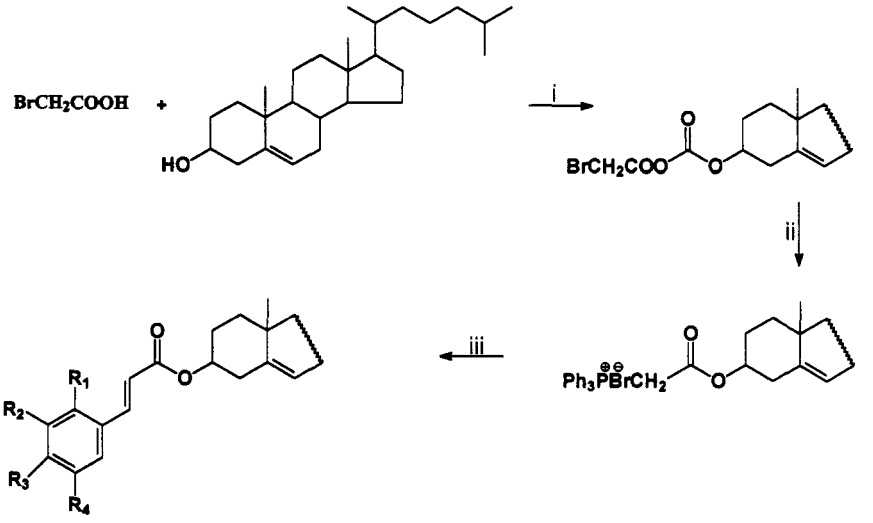
A new synthesis of some natural esters of hydroxycinnamic acids was developed recently in our laboratory, using the Wittig reaction in solid-liquid heterogeneous medium under sonochemical conditions (7). We thought it would be useful to develop this method for the preparation of other natural esters. This paper describes our work on the sonochemical reaction between different phenolic aldehydes and (carbocholesteryloxymethyl)-triphenylphosphonium bromide in heterogeneous solid-liquid medium with K_2CO_3 as a base (Scheme 1). The results obtained are shown in Table 1. In most cases, the yields were 60–90%, with a reaction time of 16–24 h. The content of the *Z*-isomer in the products obtained was less than 5%, as estimated by ^{1}H-nmr spectroscopy.

By studying the reaction on model compounds [carboethoxymethyl-triphenylphosphonium bromide and isovanillin] we have found that the rise of the water content in the reaction mixture caused a large increase in the rate of the reaction. In the liquid/liquid two-phase system, the accelerated sonochemical reaction was completed after 2 h, and yielded the *E* isomer only, with only traces of hydrolysis products.

In 1984, Chenault and Dupin reported a phase-transfer catalyzed Wittig-Horner preparation of hydroxycinnamic acids in the presence of the strong base NaOH (8). Compared to this method, that reported in this paper has an advantage in proceeding without protection of the hydroxyl groups of the aromatic aldehydes.

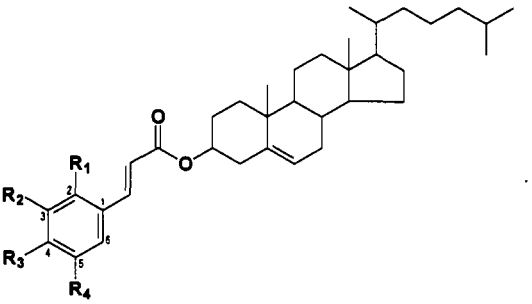
EXPERIMENTAL

GENERAL EXPERIMENTAL PROCEDURES.—^{1}H-Nmr spectra were recorded on Bruker 250 MHz and Tesla 60 MHz instruments for solutions in $CDCl_3$ or Me_2CO-d_6 with TMS as internal standard. The mass spectra were recorded with a JEOL D-300 apparatus (eims, 70 eV). The uv spectra of



SCHEME 1. i, THF, DCC, 4-DMAP; ii, C_6H_6, Ph_3P; iii, aromatic aldehyde, $CHCl_3$-1,4-dioxane (1:1), K_2CO_3, sonication.

TABLE 1. *Synthesis of Cholesteryl Esters of Substituted Cinnamic Acids* Under Sonochemical Conditions.



Compound	R_1	R_2	R_3	R_4	Reaction time (h)	Yield (%)
3	H	H	H	H	16	70
4	OH	H	H	H	27	75
5	H	OH	H	H	42	62
6	H	H	OH	H	42	61
7	H	OCH_3	H	H	23	90
8	H	H	OCH_3	H	27	77
9	OH	H	OH	H	13	62
10	H	OH	OH	H	42	68
11	H	OCH_3	OH	H	30	55
12	H	OH	OCH_3	H	27	64
13	OH	OCH_3	H	H	10	84
14	H	OCH_3	OCH_3	H	25	83
15	H	-O-CH_2-O-		H	35	71
16	H	OCH_3	OCH_3	OCH_3	30	75
17	H	OCH_3	OH	OCH_3	25	51

EtOH solutions were measured with a Specord uv-vis spectrophotometer.

SYNTHESIS OF CHOLESTERYL BROMOACETATE [**1**].—Cholesterol (1160 mg, 3 mmol), bromoacetic acid (542 mg, 3.9 mmol), DCC (803 mg, 3.9 mmol), and 4-DMAP (49 mg, 0.4 mmol) were dissolved in 40 ml of dry THF. The reaction mixture was stirred at room temperature for 1.5 h. The residue of dicyclohexylurea was filtered and washed with $CHCl_3$, and the combined solutions evaporated under vacuum. The resulting crystals were purified by cc on silica, in 74% yield (1102 mg): ^{1}H nmr ($CDCl_3$, 60 MHz) δ 5.43 (1H, m, H-6), 4.63 (1H, m, H-3α), 3.82 (2H, s, BrCH_2COO), 1.00 (3H, s, Me-19), 0.90 (3H, br s, Me-21), 0.80 (6H, br s, Me-26, Me-27), 0.66 (3H, s, Me-18); eims (70 eV) *m/z* $[M]^+$ 508/506 (0.5), 368 (100), 353 (16), 255 (12), 247 (14), 147 (28), 81 (28).

PREPARATION OF (CARBOCHOLESTERYLOXYMETHYL)-TRIPHENYL PHOSPHONIUM BROMIDE [**2**].—Compound **1** (1120 mg, 2.2 mmol) and triphenylphosphine (760 mg, 2.9 mmol) were dissolved in 13 ml of dry C_6H_6. After 22 h at room temperature the residue of the phosphonic salt was filtered and washed with *n*-hexane. Yield 95% (1691 mg); ^{1}H nmr ($CDCl_3$, 60 MHz) δ 7.45–8.25 (15H, m, aromatic), 5.46 (2H, d, *J*=16 Hz, P-CH_2COO), 5.32 (1H, m, H-6), 4.50 (1H, m, H-3α), 1.00 (3H, s, Me-19), 0.90 (6H, br s, Me-26, Me-27), 0.80 (3H, br s, Me-21), 0.66 (3H, s, Me-18).

GENERAL PROCEDURE FOR SYNTHESIS OF STERYL ESTERS.—A solution of 0.14 mmol of **2** (≙10 mg) in 0.5 ml $CHCl_3$ and a solution of 0.2 mmol of aromatic aldehyde in 0.5 ml 1,4-dioxane was mixed and added to 0.11 mmol of K_2CO_3. The reaction mixture was sonicated in a Lechpan Type UM 0.5 ultrasound bath at 25°. The reaction was monitored by tlc (Alufolien Kieselgel 60 F_{254}, Merck, *n*-hexane/Me_2CO). The reaction mixture was washed successively with 5% HCl and H_2O. The organic phase was dried over Na_2SO_4, evaporated to dryness, and subjected to cc (silica, *n*-hexane/Me_2CO) or recrystallization from MeOH. All products were characterized by their uv-, ^{1}H-nmr, and mass spectra.

Cholesteryl cinnamate [**3**].—Uv (EtOH) λ max 276 nm; ^{1}H nmr ($CDCl_3$, 60 MHz) δ 7.70 (1H, d, *J*=17 Hz, H-3′), 7.20–7.60 (5H, m, aromatic), 6.47 (1H, d, *J*=17 Hz, H-2′), 5.47 (1H, m, H-6), 4.80 (1H, m, H-3α), 1.00 (3H, s, Me-19), 0.90 (3H, br s, Me-21), 0.80 (6H, br s, Me-26, Me-27), 0.66 (3H, s, Me-18); eims (70 eV) *m/z* $[M]^+$ 516 (0.8), 386 (1.3), 368 (100), 353 (21), 255 (29), 247 (40), 213 (21), 148 (27), 147 (79), 131 (79), 81 (75).

Cholesteryl 2-hydroxycinnamate [**4**].—Uv (EtOH) λ max 232, 278, 332 nm; ^{1}H nmr (Me_2CO-d_6, 250 MHz) δ 7.98 (1H, d, *J*=16 Hz, H-3′), 7.60 (1H, d, *J*=7.5 Hz, H-6″), 7.35 (1H, s, ArOH), 7.25 (1H, t, *J*=8.2 Hz, H-4″), 6.97 (1H, d, *J*=8.2 Hz, H-3″), 6.89 (1H, t, *J*=7.5 Hz, H-5″), 6.60 (1H, d, *J*=16 Hz, H-2′), 5.42 (1H, m, H-6), 4.66 (1H, m, H-3α), 1.09 (3H, s, Me-19), 0.96 (3H, d, *J*=6 Hz, Me-21), 0.87 (6H, d, *J*=7 Hz, Me-26, Me-27), 0.74 (3H, s, Me-18); eims (70 eV) *m/z* $[M]^+$ 532 (0.8), 386 (4), 368 (100), 353 (19), 255 (19), 247 (20), 213 (13), 164 (13), 147 (40), 81 (38).

Cholesteryl 3-hydroxycinnamate [**5**].—Uv (EtOH) λ max 239, 283, 320; ^{1}H nmr ($CDCl_3$, 250 MHz) δ 7.81 (1H, d, *J*=16 Hz, H-3′), 6.85–7.26 (4H, m, aromatic), 6.40 (1H, d, *J*=16 Hz, H-2′), 5.38 (1H, m, H-6), 4.75 (1H, m, H-3α), 1.09 (3H, s, Me-19), 0.96 (3H, br s, Me-21), 0.88 (6H, d, *J*=7 Hz, Me-26, Me-27), 0.70 (3H, s, Me-18); eims (70 eV) *m/z* $[M]^+$ 532 (1.3), 386 (1.3), 368 (100), 353 (12), 255 (12), 247 (15), 213 (8), 164 (6), 147 (35), 81 (31).

Cholesteryl 4-hydroxycinnamate [**6**].—Uv (EtOH) λ max 230, 318 nm; ^{1}H nmr ($CDCl_3$, 250 MHz) δ 7.61 (1H, d, *J*=15.9 Hz, H-3′), 7.40 (2H, d, *J*=8 Hz, H-3″, H-5″), 6.83 (2H, d, *J*=8 Hz, H-2″, H-6″), 6.28 (1H, d, *J*=15.9 Hz, H-2′), 5.38 (1H, m, H-6), 4.71 (1H, m, H-3α), 1.09 (3H, s, Me-19), 0.96 (3H, br s, Me-21), 0.88 (6H, br s, Me-26, Me-27), 0.70 (3H, s, Me-18); eims (70 eV) *m/z* $[M]^+$ 532 (0.6), 386 (1.7), 368 (100), 353 (12), 255 (12), 247 (17), 213 (8), 164 (6), 147 (35), 81 (31).

Cholesteryl 3-methoxycinnamate [**7**].—Uv (EtOH) λ max 282, 320 nm; ^{1}H nmr ($CDCl_3$, 60 MHz) δ 7.58 (1H, d, *J*=16 Hz, H-3′), 6.80–7.13 (4H, m, aromatic), 6.33 (1H, d, *J*=16 Hz, H-2′), 5.37 (1H, m, H-6), 4.67 (1H, m, H-3α), 3.83 (3H, s, OCH_3), 1.09 (3H, s, Me-19), 0.96 (3H, br s, Me-21), 0.88 (6H, d, *J*=7 Hz, Me-26, Me-27), 0.70 (1H, s, Me-18); eims (70 eV) *m/z* $[M]^+$ 546 (0.6), 368 (100), 353 (13), 255 (13), 247 (15), 213 (8), 178 (8), 161 (25), 147 (23), 81 (21).

Cholesteryl 4-methoxycinnamate [**8**].—Uv (EtOH) λ max 235, 318 nm; ^{1}H nmr ($CDCl_3$, 60 MHz) δ 7.70 (1H, d, *J*=16 Hz, H-3′), 7.47 (2H, d, *J*=9 Hz, H-3″, H-5″), 6.93 (2H, d, *J*=9 Hz, H-2″, H-6″), 6.30 (1H, d, *J*=16 Hz, H-2′), 5.47 (1H, m, H-6), 4.80 (1H, m, H-3α), 3.90 (3H, s, OCH_3), 1.09 (3H, s, Me-19), 0.96 (3H, br s, Me-21), 0.88 (6H, d, *J*=7 Hz, Me-26, Me-27), 0.70 (3H, s, Me-18); eims (70 eV) *m/z* $[M]^+$ 546 (1), 368 (100), 353 (17), 255 (13), 247 (17), 213 (8), 178 (21), 161 (46), 147 (29), 81 (29).

Cholesteryl 2,4-dihydroxycinnamate [**9**].—Uv (EtOH) λ max 238, 290, 324 nm; ^{1}H nmr (Me_2CO-d_6, 250 MHz) δ 7.71 (1H, d, *J*=16 Hz, H-3′), 7.43 (1H, d, *J*=8.3 Hz, H-3″), 6.48 (1H, d, *J*=2.2 Hz, H-6″), 6.43 (1H, d, *J*=16 Hz, H-2′), 6.42 (1H, dd, J_1=8.30 Hz, J_2=2.2 Hz, H-5″), 5.40

(1H, m, H-6), 4.65 (1H, m, H-3α), 1.09 (3H, s, Me-19), 0.96 (3H, d, J=6.4 Hz, Me-21), 0.87 (6H, d, J=6.5 Hz, Me-26, Me-27), 0.73 (3H, s, Me-18); eims (70 eV) *m/z* $[M]^+$ 548 (missing), 386 (100), 368 (67), 353 (50), 301 (63), 255 (46), 247 (29), 213 (46), 163 (50), 147 (54), 81 (67).

Cholesteryl 3,4-dihydroxycinnamate [**10**].—Uv (EtOH) λ max 247, 303, 334 nm; ^{1}H nmr (Me_2CO-d_6, 250 MHz) δ 7.32 (1H, d, J=16 Hz, H-3′), 7.15 (1H, d, J=2 Hz, H-2″), 7.02 (1H, dd, J_1=8.2 Hz, J_2=2 Hz, H-6″), 6.85 (1H, d, J=8.30 Hz, H-5″), 6.24 (1H, d, J=16 Hz, H-2′), 5.40 (1H, m, H-6), 4.61 (1H, m, H-3α), 1.09 (3H, s, Me-19), 0.96 (3H, br s, Me-21), 0.88 (6H, d, J=7 Hz, Me-26, Me-27), 0.70 (3H, s, Me-18); eims (70 eV) *m/z* $[M]^-$ 548 (1.8), 386 (25), 368 (100), 353 (21), 301 (13), 255 (21), 247 (21), 213 (17), 180 (13), 163 (17), 147 (33), 81 (46).

Cholesteryl 4-hydroxy-3-methoxycinnamate [**11**].—Uv (EtOH) λ max 236, 295, 328 nm; ^{1}H nmr ($CDCl_3$, 60 MHz) δ 7.72 (1H, d, J=16 Hz, H-3′), 7.00–7.33 (3H, m, aromatic), 6.38 (1H, d, J=16 Hz, H-2′), 6.07 (1H, br s, ArOH), 5.47 (1H, m, H-6), 4.83 (1H, m, H-3α), 3.97 (3H, s, OCH_3), 1.09 (3H, s, Me-19), 0.96 (3H, br s, Me-21), 0.88 (6H, br s, Me-26, Me-27), 0.70 (3H, s, Me-18); eims (70 eV) *m/z* $[M]^+$ 562 (0.8), 386 (1), 368 (100), 353 (13), 255 (18), 247 (17), 194 (38), 177 (25), 147 (27), 81 (29), 69 (16), 57 (21).

Cholesteryl 3-hydroxy-4-methoxycinnamate [**12**].—Uv (EtOH) λ max 246, 300, 328 nm; ^{1}H nmr ($CDCl_3$, 250 MHz) δ 7.57 (1H, d, J=16 Hz, H-3′), 7.13 (1H, d, J=2 Hz, H-1″), 0.69 (3H, s, Me-18), 7.03 (1H, dd, J_1=8 Hz, J_2=2 Hz, H-5″), 6.84 (1H, d, J=8 Hz, H-6″), 6.27 (1H, d, J=16 Hz, H-2′), 5.40 (1H, m, H-6), 5.62 (1H, s, ArOH), 4.73 (1H, m, H-3α), 3.92 (3H, s, OCH_3), 1.05 (3H, s, Me-19), 0.92 (3H, d, J=6.5 Hz, Me-21), 0.86 (6H, d, J=6.5 Hz, Me-26, Me-27); eims (70 eV) *m/z* $[M]^-$ 562 (0.8), 368 (100), 353 (13), 255 (13), 247 (21), 213 (8), 194 (21), 177 (29), 147 (29).

Cholesteryl 2-hydroxy-3-methoxycinnamate [**13**].—Uv (EtOH) λ max 253 sh, 288 nm; ^{1}H nmr ($CDCl_3$, 60 MHz) δ 7.97 (1H, d, J=16 Hz, H-3′), 6.70–7.12 (3H, m, aromatic), 6.32 (1H, d, J=16 Hz, H-2′), 6.17 (1H, s, ArOH), 5.33 (1H, m, H-6), 4.67 (1H, m, H-3α), 3.83 (3H, s, OCH_3), 1.09 (3H, s, Me-19), 0.96 (3H, br s, Me-21), 0.88 (6H, br s, Me-26, Me-27), 0.70 (3H, s, Me-18); eims (70 eV) *m/z* $[M]^-$ 562 (0.2), 368 (100), 353 (13), 255 (10), 247 (15), 213 (8), 194 (6), 177 (21), 147 (25), 81 (25).

Cholesteryl 3,4-dimethoxycinnamate [**14**].—Uv (EtOH) λ max 232, 294, 325 nm; ^{1}H nmr ($CDCl_3$, 60 MHz) δ 7.70 (1H, d, J=16 Hz, H-3′), 7.00–7.33 (3H, m, aromatic), 6.33 (1H, d, J=16 Hz, H-2′), 5.47 (1H, m, H-6), 4.83 (1H, m, H-3α), 3.93 (6H, s, 2×OCH_3), 1.09 (3H, s, Me-19), 0.96 (3H, br s, Me-21), 0.88 (6H, br s, Me-26, Me-27), 0.70 (3H, s, Me-18); eims (70 eV) *m/z* $[M]^+$ 576 (1), 368 (50), 353 (8), 255 (6), 243 (12), 208 (100), 191 (12), 147 (21), 81 (17).

Cholesteryl 3,4-(methylenedioxy)cinnamate [**15**].—Uv (EtOH) λ max 235, 298, 321 nm; ^{1}H nmr ($CDCl_3$, 60 MHz) δ 7.67 (1H, d, J=16 Hz, H-3′), 6.80–7.23 (3H, m, aromatic), 6.33 (1H, d, J=16 Hz, H-2′), 6.10 (2H, s, OCH_2O), 5.53 (1H, m, H-6), 4.80 (1H, m, H-3α), 1.09 (3H, s, Me-19), 0.96 (3H, br s, Me-21), 0.88 (6H, br s, Me-26, Me-27), 0.70 (3H, s, Me-18); eims (70 eV) *m/z* $[M]^+$ 560 (0.8), 368 (100), 353 (8), 255 (13), 247 (15), 191 (23), 175 (19), 147 (29), 81 (21).

Cholesteryl 3,4,5-trimethoxycinnamate [**16**].—Uv (EtOH) λ max 306 nm; ^{1}H nmr ($CDCl_3$, 60 MHz) δ 7.63 (1H, d, J=16 Hz, H-3′), 6.83 (2H, s, aromatic), 6.40 (1H, d, J=16 Hz, H-2′), 5.53 (1H, m, H-6), 4.83 (1H, m, H-3α), 3.93 (9H, s, 3×OCH_3), 1.09 (3H, s, Me-19), 0.96 (3H, br s, Me-21), 0.88 (6H, br s, Me-26, Me-27), 0.70 (3H, s, Me-18); eims (70 eV) *m/z* $[M]^+$ 606 (2), 368 (36), 353 (8), 255 (8), 243 (12), 238 (100), 223 (24), 147 (20), 81 (24).

Cholesteryl 4-hydroxy-3,5-dimethoxycinnamate [**17**].—Uv λ max 246, 332 nm; ^{1}H nmr ($CDCl_3$, 60 MHz) δ 7.63 (1H, d, J=16 Hz, H-3′), 6.83 (2H, s, aromatic), 6.33 (1H, d, J=16 Hz, H-2′), 5.47 (1H, m, H-6), 4.80 (1H, m, H-3α), 3.97 (6H, s, 2×OCH_3), 1.09 (3H, s, Me-19), 0.96 (3H, br s, Me-21), 0.88 (6H, br s, Me-26, Me-27), 0.70 (3H, s, Me-18); eims (70 eV) *m/z* $[M]^+$ 592 (1.2), 386 (1.2), 368 (30), 353 (3), 255 (3), 247 (3), 224 (100), 207 (2), 147 (14), 81 (15).

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