SYNTHESIS OF 7-(4'-FLUORO-3,3',5-TRIMETHYL[1,1'-BIPHENYL]-2-YL)-3-HYDROXY-5-OXO-5-^{13}C-HEPTANOIC ACID AND TRANS-6-[2-(4'-FLUORO-3,3',5-TRIMETHYL[1,1'-BIPHENYL]-2-YL)ETHYL]-3,4,5,6-TETRAHYDRO-6-^{13}C-4-HYDROXY-2H-PYRAN-2-ONE.

Gerald E. Stokker
Merck Sharp & Dohme Research Laboratories, West Point,
Pennsylvania 19486 U.S.A.

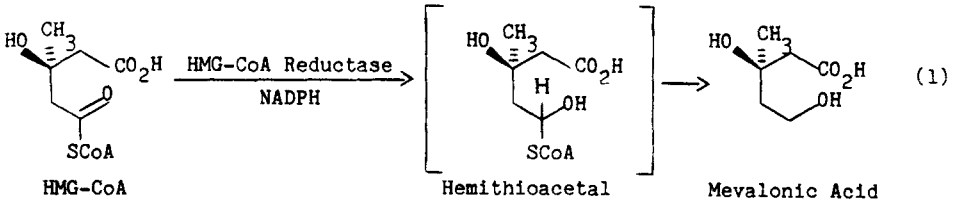
SUMMARY

The title compounds are potent HMG-CoA reductase inhibitors. A ^{13}C-label was introduced into these compounds to permit probing of their interaction with HMG-CoA reductase by ^{13}C NMR techniques in the presence and absence of added NADPH.

Key Words: HMG-CoA Reductase, 6-[^{13}C] Pyran-2-one, 5-[^{13}C] Heptanoic Acid, Cholesterol Biosynthesis.

INTRODUCTION

The highly functionalized fungal metabolites compactin (ML-236B)[1] and mevinolin (MK-803)[2] are potent inhibitors of cholesterol biosynthesis at the level of the major rate-limiting enzyme 3-hydroxy-3-methylglutaryl-coenzyme A reductase (HMG-CoA reductase), which catalyzes the conversion of HMG-CoA to mevalonic acid (eq. 1)[3]. Mevinolinic acid (1), the dihydroxy acid form of mevinolin, is one of the most potent HMG-CoA reductase inhibitors (Ki=0.6nM) reported to date.[2] Subsequent to the first reports disclosing the structure[4] and biological activity[1] of compactin, a series of studies directed toward the development of structurally simplified HMG-CoA reduc-



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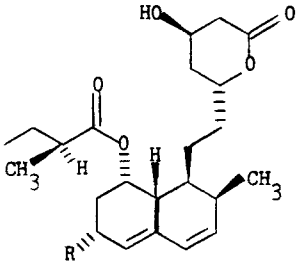
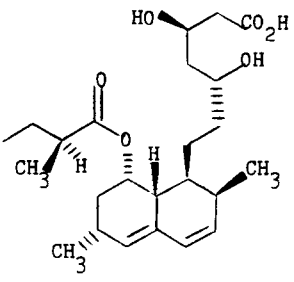
0362-4803/87/070839-11$05.50

Received September 4, 1986
Revised December 1, 1986

tase inhibitors was initiated in these laboratories. One of the most potent inhibitors to emerge from this study was the dihydroxy acid form of biphenyl lactone 2 (~2.8 times the intrinsic inhibitory activity of 1).[5]



Compactin, R=H
Mevinolin, R=CH_3



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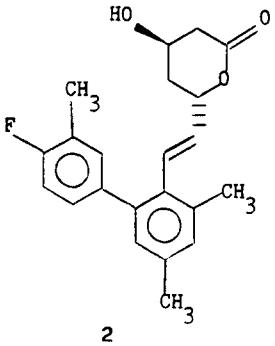

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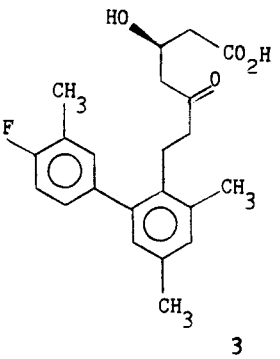
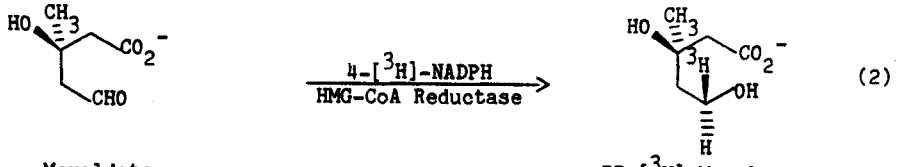


3

The corresponding dihydro-ring-opened 5-keto compound (3) also was prepared because it more closely resembles the substrate HMG-CoA. The ring-opened dihydroxy acid derived from the lactone, on the other hand, more closely resembles the half reduced substrate than does ketone 3. The observed decrease in formation of mevalonate when 3 was incubated with the isolated enzyme[6] may be due to its intrinsic inhibitory activity per se, or it may reflect initial binding to, and subsequent reduction by, the enzyme in the presence of NADPH to afford the dihydroxy acid similar to 1. The possibility of achieving an artifical second half-reduction has been demonstrated by the Cornforth group, wherein 5R-[^{3}H]-mevalonate was prepared from mevaldate using 4-[^{3}H]-NADPH in the presence of HMG-CoA reductase[7] (eq. 2).



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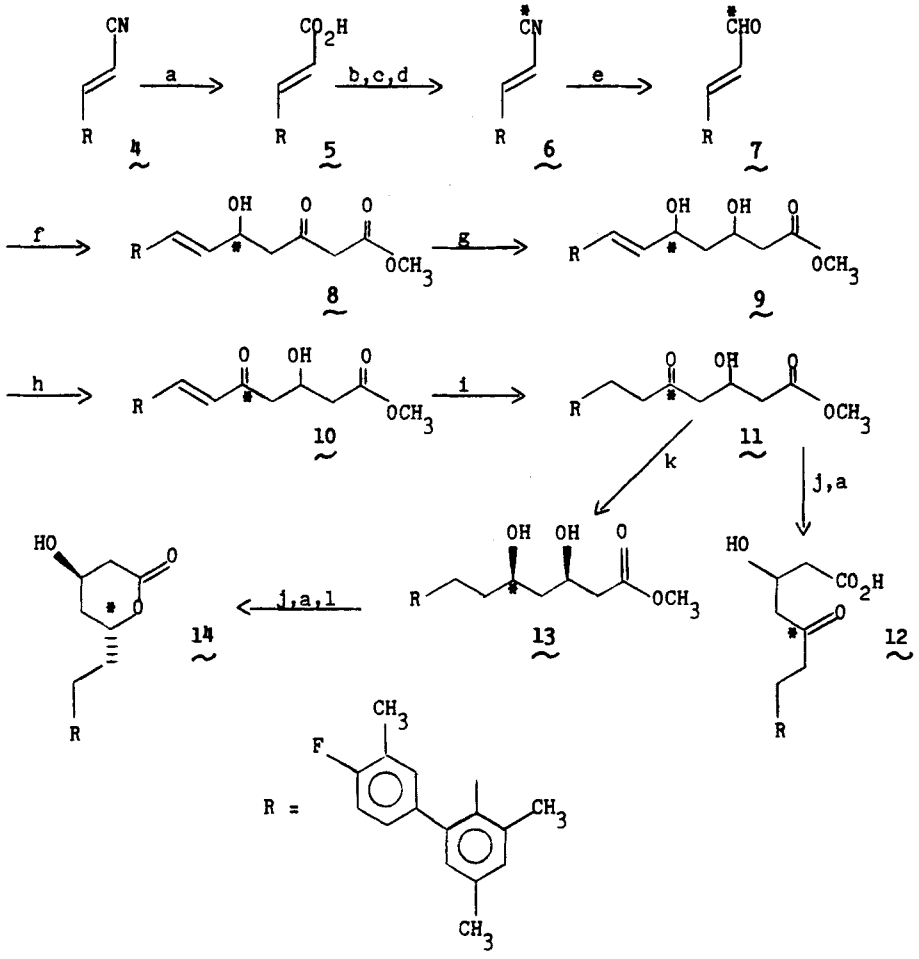
Mevaldate 5R-[^{3}H]-Mevalonate

In an attempt to facilitate determination of the mechanism of the observed intrinsic inhibitory activity of 3, [6-^{13}C]-2 and [5-^{13}C]-3 were prepared. Detailed ^{13}C-NMR studies of labelled 3 in the presence of HMG-CoA reductase, with and without added NADPH, should allow these two possibilities to be assessed experimentally.[8]

Results And Discussions

The title compounds (12 and 14) in this study were prepared as shown in Scheme I. The bromination of propenoic acid 5 in $CHCl_3$ at temperatures ranging from 0°C down to -78°C consistently yielded mixtures of threo and erythro dibromoacids (~3:1 respectively), which may be chromatographically separated. When the bromination was done in refluxing CCl_4, none of the threo isomer was detected. Only the threo product yielded the (E)-β-bromostyrene on treatment with base at elevated temperature.[9] The (E) and (Z)-β-bromostyrenes may be separated with difficulty by chromatography.[10] However, the question of separation of the erythro and threo dibromo acids and/or separation of the subsequently formed (E) and (Z)-β-bromostyrenes became a moot point because the (E) isomer reacts stereospecifically with cyanide ion catalyzed by Pd(0) at a rate about 100 times faster than that of the (Z) isomer. Thus the (E)-nitrile (6) was obtained preferentially and was easily separated chromatographically from any bromo compound, whether (E) or (Z).[11,12] Diisobutylaluminum hydride (Dibal) reduction of the nitrile provided aldehyde 7, which was condensed with the dianion of methyl acetoacetate and the product subsequently reduced with borohydride to afford diol ester 9. Selective oxidation of the hydroxyl group at C-5 was accomplished with activated manganese dioxide to yield hydroxyketoester 10, which was then conjugatively reduced to hydroxyketoester 11[13]. The hydroxyketoacid (12) was formed by basic hydrolysis of 11 followed by acidification. Lactone 14 was synthesized by a triethylborane-mediated stereoselective reduction[14] of 11 followed by basic hydrolysis, acidification and a diimide lactonization.



[a] H_3O^+ [b] Br_2 [c] $NaHCO_3$, Δ [d] $K^{*}CN$, $Pd(Ph_3P)_4$ [e] Dibal [f] $CH_2COCHCO_2CH_3$
[g] $NaBH_4$ [h] MnO_2 [i] Bu_3SnH, $Pd(Ph_3P)_4$ [j] NaOH [k] $NaBH_4$, Et_3B
[l] $EtN{=}C{=}N(CH_2)_3N(CH_3)_2$-HCl.

Experimental Section

Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ on a Varian XL300 spectrometer. Chemical shifts are reported in parts per million relative to Me_4Si as the internal standard. Elemental analyses for carbon and hydrogen, were determined using a Perkin-Elmer Model 240 elemental analyzer. Analytical thin layer chromatography (TLC) was conducted on Whatman MK6F precoated silica gel plates. Infrared (IR) spectra were run on a Perkin-Elmer 297 spectrometer. Potassium [^{13}C] cyanide was obtained from MSD Isotopes (99.3% ^{13}C).

3-(4'-Fluoro-3,3',5-trimethyl [1,1'-biphenyl]-2-yl)-2-propenoic acid (5). A solution of biphenyl-2-propenenitrile 4[15] (9.8g, 40 mmol), HOAc (100 ml) and 6N HCl (50 ml) was stirred at reflux for 20h. The reaction mixture was diluted with hot H_2O (50 ml) and then cooled slowly to 0°C. The crude acid (9g, mp 150-156°C) was recrystallized from 1:3 (v/v) toluene/hexane to afford biphenyl-2-propenoic acid 5 (8.3g, 73%), mp 162-163°C; ^1H NMR δ 2.292 (3'-CH_3, d, J=2Hz, 3H), 2.353 (CH_3 s, 3H), 2.440 (CH_3 s, 3H), 5.812 (C=CHCO_2, d, J = 16.3Hz, 1H), 6.972-7.093 (aromatic, m, 5H), 7.735 (CH=C-CO_2, d, J = 16.3Hz, 1H).

(E)-3-(4'-Fluoro-3,3',5-trimethyl[1,1'-biphenyl]-2-yl)-2-propeno-^{13}C-nitrile (6). A solution of Br_2 (570 µl, 11.1 mmol) in $CHCl_3$ (10 ml) was added dropwise (ca 1/2h) to a vigorously stirred solution of propenoic acid 5 (3.0g, 10.5 mmol) in $CHCl_3$(50 ml) at -25°C. After the addition was complete the orange solution was stirred at -25°C for an additional 1/2h before evaporation of the solvent at reduced pressure.[9] The pale orange residual gum was dissolved in DMF (30 ml) and rapidly heated to 120°C. Solid $NaHCO_3$ (3.0g, 33 mmol) was added portionwise and heating and stirring were continued for 1/2h. The pale tan mixture was cooled to ambient temperature and diluted with H_2O (300 ml). The aqueous mixture was extracted with Et_2O (2x125 ml). The organic layers were combined and backwashed with H_2O (3x100 ml), dried ($MgSO_4$), filtered and evaporated. Yield of crude β-bromostyrene was 2.4g and exhibited one major spot on TLC for the desired (E) isomer, ^1H NMR shows a(E)/(Z) of 7/1[10].

The crude β-bromostyrene was dissolved in toluene (10 ml, dried over 3Å molecular sieves) and treated with [^{13}C] KCN (1.0 g, 15.4 mmol, 99.3% ^{13}C), $Pd(Ph_3P)_4$ (100 mg), and 18-Crown-6 (200 mg). The mixture was stirred under an atmosphere of Ar at room temperature for 1/4h and finally at 75-80°C for 2h. The tan reaction mixture was cooled and diluted with H_2O (300 ml). The aqueous mixture was extracted with Et_2O (2 x 100 ml). The organic layers were combined and backwashed with H_2O (2x100 ml), dried ($MgSO_4$), filtered and evaporated to provide the crude product as a light yellow oil (2.08 g). This oil was shown by TLC [R_f of nitrile = 0.40 vs. 0.85 for bromides ($CHCl_3$/hexane (1:1)] to be a mixture of desired nitrile and unreacted bromides (neither addition of more palladium catalyst nor longer reaction times caused a total conversion to the nitrile). Chromatography of this oil on silica gel with 1:1 $CHCl_3$/hexane afforded 670 mg of recovered bromides ((E)/(Z) of 3/1) and pure (E) nitrile 6 (810 mg, 29%)[10],

mp 83-86°C; ^{1}H NMR δ 2.321 (3'CH_3, d, J = 0.98Hz, 3H), 2.357 (CH_3, s, 3H), 2.418 (CH_3, s, 3H). 5.222 (C=CHCN, dd, J = 3.17, 17.09Hz, 1H) 6.967-7.072 (aromatic, m, 5H), 7.380 (HC=C-CN, dd, J = 9.03, 17.09Hz, 1H) ^{13}C NMR ppm 118.2 (CN).

(E)-3-(4'-Fluoro-3,3',5-trimethyl[1,1'-biphenyl]-2-yl)-2-propen^{13}C-al (7). A solution of Dibal (1.5M in toluene, 2.25 ml, 3.4 mmol) was added over a 5 minute period to a stirred solution of the nitrile (6) (760 mg, 3 mmol) in dry Et_2O (20 ml) under a N_2 atmosphere at -10°C. The cooling-bath was removed and the clear (now faint yellow) solution was stirred at ambient temperature for 4h. The reaction mixture was recooled to ~0°C and then quenched with ice-cold 5% H_2SO_4 (100 ml). The ice bath was removed and the mixture was again stirred vigorously at ambient temperature for 1/2h. The mixture was extracted with Et_2O (125 ml) and the organic layer was washed with 5% H_2SO_4 (100 ml), H_2O (100 ml), dried ($MgSO_4$), filtered and evaporated. Chromatography of the residue on silica gel with $CHCl_3$ (R_f=0.6) provided the propenal (7) (520 mg, 64%), mp 79-81°C; ^{1}H NMR δ 2.304 (3'CH_3, d, J = 1.0Hz, 3H), 2.375 (CH_3, s, 3H), 2.468 (CH_3, s, 3H), 6.201 (C=CHCHO, ddd, J = 2, 7.7, 16.4Hz, 1H), 7.00-7.10 (aromatic, m, 5H), 7.458 (-CH=C-CHO, dd, J = 10.1, 16.4Hz, 1H), 9.469 (-CHO), dd, J = 7.7, 171.5Hz, 1H); ^{13}C NMR ppm 194.2 (CHO).

Methyl (E)-7-(4'-Fluoro-3,3',5-trimethyl[1,1'-biphenyl]-2-yl)-5-hydroxy-3-oxo-5-^{13}C-6-heptenoate (8). Methyl acetoacetate (430 µl, 2.6 mmol) was added dropwise to a stirred suspension of NaH (140 mg, 2.7 mmol of a 50% oil suspension which was prewashed with dry petroleum ether (2x20 ml)) in dry THF (10 ml) at -15°C under a N_2 atmosphere. The resulting solution was stirred 15 minutes at -15°C and treated with a 1.4M solution (1.2 ml, 2.7 mmol) of n-butyllithium in hexane added over 1 minute. The resulting yellow solution was stirred 15 minutes at -15°C and treated with a solution of aldehyde 7 (630 mg, 2.35 mmol) in dry THF (4ml). After the mixture was stirred for 15 minutes at -15°C, the resulting orange solution was quenched by slow addition of 1N HCl (10 ml). The reaction mixture was distributed between H_2O (100 ml), and Et_2O (150 ml). The organic layer was separated and washed with H_2O (3x100 ml), dried ($MgSO_4$), filtered, and evaporated to provide 8 as a thick golden oil (860 mg, 95%); nearly homogenous on TLC [R_f=0.22 vs. 0.72 for 7 ($CHCl_3$/MeOH (99:1)]; ^{1}H NMR δ 2.299 (3'-CH_3, d, J = 1.7Hz, 3H), 2.331 (CH_3, s, 3H), 2.343 (CH_3, s, 3H), 2.568 (-CH-CH_2CO, m, 2H), 3.451 ($COCH_2CO$, s, 2H), 3.749 (OCH_3, s, 3H), 4.57 (CH, dm,

147Hz, 1H), 5.36 (C=CHC*, ddd, 4, 6, 15Hz, 1H), 6.48 (CH=C-C*, dd, 6, 15Hz, 1H), 6.93-7.1 (aromatic, m, 5H); ^{13}C NMR ppm 68.7 (*CHOH).

Methyl (E)-7-(4'-Fluoro-3,3',5-trimethyl[1,1'-biphenyl]-2-yl)-3,5-dihydroxy-5-^{13}C-6-heptenoate (9). Sodium borohydride (15 mg, 0.57 mmol) was added with stirring to a cooled solution (5°C) of ketoester 8 (300 mg, 0.78 mmol) in MeOH (6 ml). The reaction mixture was stirred at 0°C for 15 minutes, diluted with H_2O (125 ml), cautiously acidified with 6N HCl (1 ml) and extracted with Et_2O (125 ml). The Et_2O layer was washed with H_2O (3x100 ml), dried ($MgSO_4$), and filtered. The filtrate was evaporated in vacuo to provide diol 9 as a thick golden gum (270 mg, 89%); nearly homogenous on TLC [R_f=0.09 vs. 0.22 for 8, ($CHCl_3$/MeOH (99:1)]. The ^1H NMR spectrum showed the absence of the singlet at δ 3.451 for the methylene between the ketone and ester moieties, a clear indication of complete ketone reduction.

Methyl (E)-7-(4'-Fluoro-3,3',5-trimethyl[1,1'-biphenyl]-2-yl)-3-hydroxy-5-oxo-5-^{13}C-6-heptenoate (10). The diol ester (9) (270 mg, 0.7 mmol) was dissolved in $CHCl_3$ (30 ml), treated with activated MnO_2 (2g) and the mixture was stirred at ambient temperature overnight. TLC indicated absence of starting diol [R_f=0.17 vs. 0.09 for diol ($CHCl_3$/MeOH (99:1)] and the mixture was filtered. The $MnO_2$was washed with fresh $CHCl_3$ (3x10 ml) and filtered. The combined filtrates were evaporated and the residual oil was chromatographed on silica gel with 200:1 $CHCl_3$/MeOH affording 10 (190 mg, 70%) as a yellow oil; ^1H NMR δ 2.30 (3'-CH_3, d, J = 1.95Hz, 3H), 2.36 (CH_3, s, 3H), 2.435 (CH_3, s, 3H), 2.510 (-CH_2CO_2-, d, J = 5.86Hz, 2H), 2.681 (-CO$\underline{CH_2}$CHO-, dd, J = 5.6Hz, 2H), 3.712 (OCH_3, s, 3H), 4.465 (-C(OH)$\underline{H}$-, m, 1H), 6.120 (C=CH-*CO-, dd, J = 3.42, 16.6Hz, 1H), 6.97-7.1 (aromatic, m, 5H), 7.540 (Ar-CH=C, dd, J = 6.84, 16.6Hz, 1H); ^{13}C NMR ppm 199.3 (*CO).

Methyl 7-(4'-Fluoro-3,3',5-trimethyl [1,1'-biphenyl]-2-yl)-3-hydroxy-5-oxo-5-^{13}C-heptanoate (11). Tributyltin hydride (530 µl, 2 mmol) was added dropwise over 1h to a stirred solution of the enone ester (10) (350 mg, 0.91 mmol) and $Pd(Ph_3P)_4$ (60 mg, 0.036 mmol) in dry THF (6ml) under a N_2 atmosphere at ambient temperature. After stirring for 16h the reaction mixture was distributed between H_2O (100 ml) and Et_2O (150 ml). The organic layer was separated and washed with H_2O (2x100 ml), dried ($MgSO_4$), filtered and evaporated. The brown residual oil was chromatographed on silica gel with 100:1 $CHCl_3$/acetone affording 11 (350 mg, 99%) as a pale yellow oil;

^{1}H NMR δ 2.318 (CH_3, s, 3H), 2.327 (3'-CH_3, d, J = 0.8Hz, 3H), 2.344 (CH_3 s, 3H), 2.3-2.5 ($CH_2\overset{*}{C}OCH_2CCH_2$, m, 6H), 2.78–2.86 ($ArCH_2$-, m, 2H), 3.724 ($OCH_3$, s, 3H), 4.39 (HCOH, m, 1H), 6.85 (aromatic, br s, 1H), 6.95-7.1 (aromatic, m, 4H); ^{13}C NMR ppm 209.4 ($\overset{*}{C}O$).

7-(4'-Fluoro-3,3',5-trimethyl[1,1'-biphenyl]-2-yl)-3-hydroxy-5-oxo-5-^{13}C-heptanoic acid (12). A MeOH solution (3 ml) containing the ketoester (11) (110 mg, 0.28 mmol) and 1N NaOH (375 µl) was stirred at ambient temperature for 1h. The residue, after evaporation, was distributed between H_2O (100 ml) and Et_2O (50 ml). The aqueous layer was acidified with 3N HCl to pH2. The mixture was then extracted with Et_2O (2x75 ml). The combined Et_2O layers were washed with H_2O (50 ml), brine (50 ml), dried ($MgSO_4$), filtered and evaporated. The light amber residue was crystallized from 1:2 (v/v) nBuCl/hexane to provide acid 12 as tiny colorless crystals (52 mg, 50%), mp 106-107°C; ^{1}H NMR δ 2.293 (CH_3, s, 3H), 2.296 (3'-CH_3, d, J = 2Hz, 3H), 2.319 (CH_3, s, 3H), 2.35 -2.60 ($CH_2\overset{*}{C}OCH_2CCH_2$, m, 6H), 2.76-2.84 ($ArCH_2$, m, 2H), 4.38 (HCOH, m, 1H), 6.83 (aromatic, br s, 1H), 6.99 - 7.07 (aromatic, m, 4H); ^{13}C NMR ppm 209.7 ($\overset{*}{C}O$). Anal. ($C_{21}{}^{13}CH_{25}FO_4$) Calc'd: C, 71.03, H, 6.75, found: C, 71.06, H, 6.83.

Methyl 7-(4'-Fluoro-3,3',5-trimethyl[1,1'-biphenyl]-2-yl)-3,5,dihydroxy-5-^{13}C-heptanoate (13). The 3-hydroxy-5-ketoester (11, 160 mg, 0.41 mmol) was dissolved in dry THF (2 ml) under N_2 and then treated with triethylborane (1 M in THF, 0.064 ml, 0.64 mmol). After aging for ca. 10 minutes, the reaction mixture was cooled to -98°C (MeOH liq. N_2 bath). Sodium borohydride (19 mg, 0.49 mmol) was added portion wise followed by a slow addition of MeOH (0.50 ml). After stirring for an additional 1/2h, the reaction mixture was allowed to warm to -60°C and then was quenched by the careful addition of 30% H_2O_2 (0.9 ml) in H_2O (2 ml). The mixture was stirred vigorously at ambient temperature for 1/2h and then distributed between 1N HCl (50 ml) and EtOAc (3x50 ml). The combined organic layers were washed with H_2O (2x20 ml), dried ($MgSO_4$), filtered and evaporated to provide 13 (165 mg, ~100%) as a nearly colorless gum [single spot on TLC with an R_f of 0.19 vs. 0.33 for 11 ($CHCl_3$/MeOH (99:1)]; ^{1}H NMR δ 1.2-1.6 ($CH_2\overset{*}{C}CH_2$, m, 4H), 2.292 (CH_3, s, 3H), 2.297 (3'-CH_3, d, J = 2Hz, 3H) 2.362 (CH_3, s, 3H), 2.39-2.42 ($ArCH_2$, m, 2H), 2.45-2.72 (CH_2CO_2, m, 2H), 2.983 (5-OH, t, J = 2.2Hz, 1H), 3.673 (3-OH, d, J = 2Hz, 1H), 3.69 ($\overset{*}{C}H$, dm, J = ~150Hz, 1H), 3.71 (OCH_3, s, 3H), 4.14 (3-CH, m, 1H), 6.825 (aromatic, br s, 1H),

6.97-7.1 (aromatic, m, 4H); ^{13}C NMR ppm 71.9 (CHOH).

trans-6-[2-(4'-Fluoro-3,3',5-trimethyl[1,1'-biphenyl]-2-yl)ethyl]-3,4,5,6-tetrahydro-6-^{13}C-4-hydroxy-2H-pyran-2-one (14). A MeOH solution (4 ml) containing crude 13 (160 mg, 0.41 mmol) and 1N NaOH (0.6 ml, 0.6 mmol) was stirred at ambient temperature for 1/2h. The residue, after evaporation, was dissolved in H_2O (15 ml) and the slightly cloudy solution was extracted once with Et_2O (25 ml). The aqueous layer was acidified with 3N HCl to pH2. The mixture was then extracted with Et_2O (2x60 ml). The combined organic extracts were washed with brine, dried ($MgSO_4$), filtered and evaporated. The residue was dissolved in $CHCl_3$ (10 ml) followed by the addition of 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (100 mg, 0.5 mmol) at room temperature. After stirring vigorously for 15 minutes, the reaction mixture was distributed between Et_2O (100 ml) and H_2O (50 ml). The Et_2O layer was washed with H_2O (50 ml), dried ($MgSO_4$), filtered and evaporated. The sticky solid was crystallized from 1:4 (v/v) nBuCl/hexane to provide 14[16] as colorless tiny needles (54 mg, 37%), mp 110-111°C, homogenous on TLC [R_f=0.38 ($CHCl_3$/MeOH (19:1)] and HPLC [time of elution was 4.46 minutes with a flow rate of 4 ml/minute using 2-propanol hexane (19:1) on a Whatman Partisil PXS 10/25 PAC column]; ^{1}H NMR δ 1.4-1.8 ($CH_2\overset{*}{C}CH_2$, m, 4H), 2.294 (CH_3, s, 3H), 2.306 (3'-CH_3, d, J = 1.7Hz, 3H), 2.363 (CH_3, s, 3H), 2.551 (H_eCCO_2, ddd, J = 1.5, 3.8, 17.6Hz, 1H), 2.686 (H_aCCO_2, dd, J = 4.9, 17.6Hz, 1H), 2.43-2.72 ($ArCH_2$, m, 2H), 4.58 (CH, dm, J = ~145Hz, 1H), 4.293 (HCO, m, 1H), 6.828 (aromatic, br s, 1H), 6.98-7.08 (aromatic, m, 4H); ^{13}C NMR ppm 75.3 ($\overset{*}{H}COC$). Anal. ($C_{21}{}^{13}CH_{25}FO_3$) calc'd:C, 74.20, H, 7.05, found: C, 73.97, H, 7.22.

Acknowledgement

The author extends his thanks to Dr. T. Verhoven for the preparation of nitrile 4, to J.P. Moreau for analytical support, to Dr. B.M. Trost for suggesting the reaction sequence from 5 to 6 to Dr. S.M. Pitzenberger for ^{13}C NMR and to Mrs. C.A. Gerson for manuscript preparation.

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8. The results of these studies will be published elsewhere.
9. The erythro and threo dibromoacids may be separated chromatographically with some difficulty; TLC of dibromoacids [R_f of **A** = 0.35 and R_f of **B** = 0.24 ($CHCl_3$/MeOH/HOAC/H_2O (950:50:1:1)]; mass sepc. m/z at 442 for both of the acids and their corresponding fragmentation patterns are nearly identical. If a trans-periplanar relationship of the -CO_2H and β-Br moieties is necessary for fragmentation to yield the 2-bromostyrene, then dibromoacid **A** must be the threo isomer for it gives rise to the (E)-bromostyrene.
10. The (E) and (Z) β-bromostyrenes may be separated by chromatography with difficulty; TLC of (E) and (Z) β-bromostyrenes [R_f of (E) = 0.39 and R_f of (Z) = 0.32 (hexane)]; diagnostic peaks in the ^1H NMR are for the β-proton: δ 6.00 (d, J=13.67 Hz) for the (E) isomer and 6.376 (d, J = 7.32Hz) for the (Z) isomer. The

(E) isomer gives the (E) nitrile with complete retention of geometry about the double bond. Anal. ($C_{17}H_{16}BrF$) calc'd: C, 63.76, H, 5.04, found for (E) isomer: C, 63.59, H, 5.17.

11. Neither TLC or ^1H NMR indicated the presence of the (Z) nitrile; TLC of the nitriles [R_f of (E) = 0.40 and R_f of (Z) = 0.49 ($CHCl_3$ hexane (1:1)]; the diagnostic peak in the ^1H NMR for the (Z) isomer is for the β-proton: δ 5.556 (dd, J = 1 and 3.2Hz); IR (neat) 2220 (s, CN), cm^{-1}.
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16. The characterization of the trans isomer was based on the chemical shift and coupling constants of the C-6, C-4, and C-3 protons in the NMR as described in reference 5 and references cited therein.