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Organopalladium Approaches to Prostaglandins. 6.[1] Synthesis of Interphenylene Prostaglandin Endoperoxide Analogs Via Benzylpalladation of Bicyclic Alkenes.[2]

Richard C. Larock* and Srinivasan Babu
Department of Chemistry, Iowa State University, Ames, Iowa 50011

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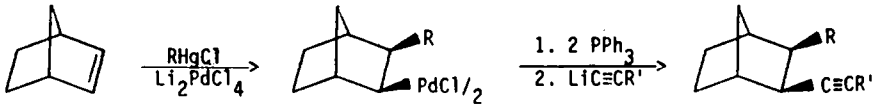
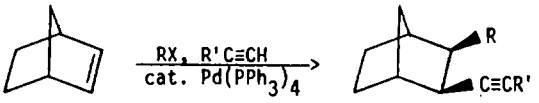
Abstract - The reactions of norbornene, norbornadiene and 7-oxanorbornene with methyl 3-(chloromethyl)phenoxyacetate (4), optically pure (S)-1-octyn-3-ol (5), and 8% $Pd(PPh_3)_4$ afford in one step satisfactory yields of the corresponding esters 6, 7 and 8 respectively, readily saponified to the first interphenylene prostaglandin endoperoxide analogs 10, 11 and 12 respectively.

There has been considerable recent interest in the synthesis of interphenylene analogs of prostaglandins A,[3,4] E,[3-12] F,[5,6,9,13-18] and I.[11,19-33] Many of these compounds have shown very interesting biological activity. We have recently prepared a number of prostaglandin endoperoxide (PGH) analogs,[34-37] primarily by organopalladium additions to bicyclic olefins and subsequent lithium acetylide displacements (eq 1). Some of these compounds have proven to be potent



(1)

inhibitors of blood platelet aggregation.[35] More recently, Chiusoli and co-workers have reported that simple aryl and vinylic halides react readily with bicyclic alkenes and acetylenes in the presence of catalytic amounts of $Pd(PPh_3)_4$ to undergo an analogous overall transformation (eq 2).[38,39] Allylic halides gave very poor results and benzylic halides apparently were not examined

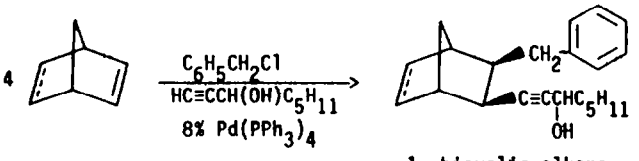


(2)

by Chiusoli. With the exception of our own thiophene-containing analogs[34,36] and several recent 7-oxabicyclo[2.2.1]heptane analogs[40-44] totally different from our compounds and prepared in a totally different manner, there have been few reports of interphenylene PGH analogs. It appeared that the Chiusoli modification of our earlier approaches using benzylic halides might afford a novel, highly efficient route to interphenylene PGH analogs. Indeed, this approach has proven successful and forms the basis of the present report.

Results and Discussion

Model studies were initially carried out at 70-80°C using benzyl chloride or bromide, 1 equiv of racemic 1-octyn-3-ol and sodium acetate in degassed anisole as the solvent, and varying amounts of $Pd(PPh_3)_4$ and several bicyclic alkenes. With norbornene, benzyl bromide gave a variety of products. However, benzyl chloride reacted smoothly affording an 81% isolated yield of cis, exo adduct 1 (plus the diastereomer obtained from addition of the two side chains to opposite ends of the carbon-carbon double bond) when 4 equiv of norbornene and 8% $Pd(PPh_3)_4$ were heated for 1 day (eq 3). With norbornadiene, 8 equivalents of the diene had to be employed to avoid diaddition,

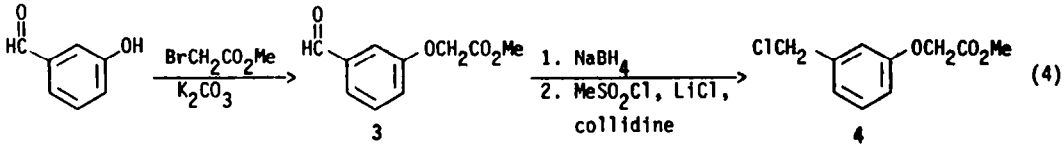


(3)

1, bicyclic alkane
2, bicyclic alkene

but a 53% yield of bicyclic alkene 2 could be isolated alongside ~5% of an unidentified, inseparable impurity. Increasing the diene to 20 equiv failed to improve the yield or the purity of the product. Using conditions similar to those of norbornene, bicyclo[2.2.2]octene and 5,6-diaza-5,6-dicarboethoxybicyclo[2.2.1]hept-2-ene gave a variety of products and were not studied further. On the other hand, 7-oxabicyclo[2.2.1]heptene successfully undergoes benzylpalladation as reported later in this paper.

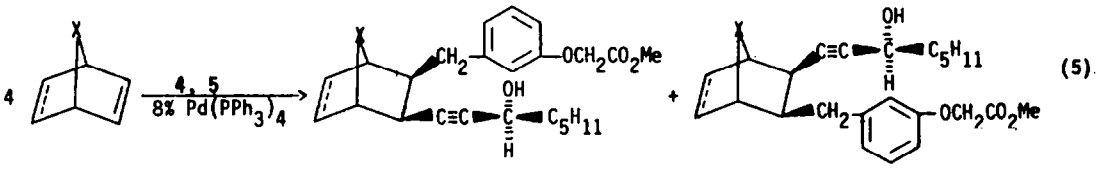
With these promising results in hand, we moved directly to the synthesis of the desired interphenylene PGH analogs. The requisite benzylic chloride 4 is readily available by the following reaction sequence (eq 4).[5] Pure (S)-1-octyn-3-ol (5) was obtained by resolution of



3 4 (4)

commercially available 1-octyn-3-ol using a modification of Fried's procedure.[45] Purity was verified by ^{1}H NMR spectral analysis using tris[3-(heptafluoropropylhydroxymethylene)-(+)-camphorato]europium(III).

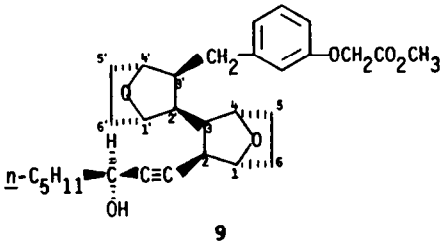
Using norbornene (4 equiv) and compounds 4 and 5 at 70°C for 1 day and following the procedure developed earlier, we have been able to obtain a 58% isolated yield of an inseparable mixture of the two anticipated diastereomers 6a and 6b (eq 5). The analogous reaction of norbornadiene (8 equiv) at 80°C for 1 day afforded compounds 7a plus 7b in 37% isolated yield,



(5)

6a (alkane, X = CH_2) 6b (alkane, X = CH_2)
7a (alkene, X = CH_2) 7b (alkene, X = CH_2)
8a (alkane, X = O) 8b (alkane, X = O)

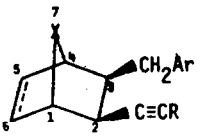
while the reaction of 7-oxanorbornene (4 equiv) at 70°C gave the expected mixture of diastereomers 8a and 8b in 34% yield, alongside 14% of a compound tentatively identified as the diaddition compound 9 (plus presumably the diastereomers expected from addition of the side chains to the bicyclic alkenes in the opposite direction). Decreasing the amount of the latter alkene to 2



9

equiv reduced the yield of the desired product to 26% and failed to eliminate the diadduct 9. Increasing the temperature to 80°C and using 4 equiv of 7-oxanorbornene increased the yield of 8a plus 8b to 45%.

The structures of esters 6, 7 and 8 were confirmed by close examination of their ^{1}H and ^{13}C NMR spectra. For discussion purposes, the following numbering system will be employed. The ^{13}C NMR spectrum for esters 6a plus 6b showed the presence of 26 different carbons, one more than anticipated for either of the esters individually, thus establishing the presence of diastereomers. In the ^{1}H NMR spectrum, the C-2 hydrogen exhibits a doublet at δ 2.62 with J = 8.7 Hz, consistent with cis, endo coupling of the hydrogens on carbons 2 and 3.[38,46-49] The two



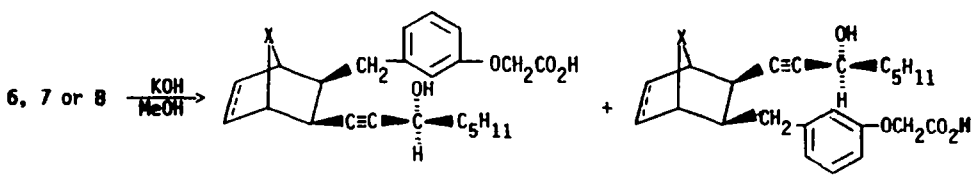
diastereomeric benzylic hydrogens appear at δ 2.42 and δ 2.86. Decoupling experiments helped to confirm the above assignments. Irradiation of the proton giving rise to a peak at δ 2.86 caused the peak at δ 2.42 to collapse to a doublet (J = 8.3 Hz) and the peak due to the proton at C-3 could now be observed at δ 1.86 as an apparent triplet with J = 6 Hz. As anticipated, irradiation of the proton giving rise to a peak at δ 2.42 caused the peak at δ 2.86 to collapse to a singlet and the peak at δ 1.86 to collapse to a very broad triplet. Similarly, irradiation of the C-3 proton giving rise to a peak at δ 1.86 caused the peak at δ 2.62 to collapse to a singlet, confirming its assignment as the proton at C-2, and converting the peaks at δ 2.42 and δ 2.86 to doublets (J = 14 Hz). Infrared spectral data and exact mass spectral data further support the structures **6a** and **6b** as drawn.

The structures of compounds **7a** and **7b** were assigned in like manner. The ^{13}C NMR spectrum indicated the presence of a broadened peak at δ 38.24 suggesting the presence of diastereomers. The ^{1}H NMR spectrum, infrared and mass spectral data were all consistent with the assigned structures.

Finally, all spectral data for compounds **8a** and **8b** were consistent with their assigned structures. The ^{13}C NMR spectrum indicated the presence of one extra carbon indicating the presence of diastereomers. The ^{1}H NMR spectrum was relatively easy to assign since the hydrogens on the bridgehead carbons C-1 and C-4 were shifted to δ 4.55 and δ 4.26 respectively, and appeared as broadened doublets (J = 4.2 Hz and J = 5.6 Hz respectively). One of the diastereotopic benzylic hydrogens (δ 2.83-2.89) was buried under the doublet due to the proton on C-2 (δ 2.86). These assignments were confirmed by decoupling studies. The peak due to the proton on C-3 appeared as a multiplet at δ 2.06-2.19. Upon irradiating the protons giving rise to the peaks at δ 2.86, this multiplet collapsed to a doublet (J = 9.9 Hz). Thus, the proton on C-3 couples with only one of the two benzylic hydrogens. Upon irradiation of the diastereomeric benzylic protons at δ 2.57 and δ 2.62, the multiplet centered at δ 2.83-2.89 due to the other benzylic proton collapses to a less complicated multiplet, thus establishing the vicinal coupling between the two benzylic hydrogens. Simultaneously, simplification of the multiplet at δ 2.06-2.19 due to the endo proton on C-3 was noted. Furthermore, irradiation of the proton giving rise to the peak at δ 2.06-2.19 effects the multiplicity of the peaks at δ 2.57 and δ 2.62. Infrared and exact mass spectral data were also consistent with the assigned structure.

The structure of the diadduct **9** derived from 7-oxanorbornene was deduced from ^{1}H and ^{13}C NMR, infrared, and exact mass spectral data. The ^{13}C NMR spectrum indicated the presence of one extra carbon, suggesting the presence of diastereomers. Unfortunately, the ^{1}H NMR spectrum could not be as readily assigned as those of the previous compounds.

Finally, the esters **6** and **7** were saponified in yields of 95% and 88% respectively by refluxing with 2N KOH in methanol for 2 h, while ester **8** gave better results (98% yield) when saponified at room temperature for 2 days (eq 6).



(6)

10a (alkane, X = CH_2)
11a (alkene, X = CH_2)
12a (alkane, X = O)

10b (alkane, X = CH_2)
11b (alkene, X = CH_2)
12b (alkane, X = O)

The biological testing of these three diastereomeric pairs of acids **10**, **11** and **12** has been carried out by E. R. Squibb and Sons, Inc. These compounds when tested on human blood platelets for arachidonic acid- and ADP-induced platelet aggregation showed surprisingly little activity.

Experimental Section

Equipment. Proton NMR spectra were recorded on either an EM-360 or a Nicolet NT-300 spectrometer. ^{13}C NMR spectra were recorded on either a JEOL-FX90Q or Nicolet NT-300 (operating at 75 MHz for carbon nuclei) spectrometer. Infrared spectra were recorded on a Beckman-42050 spectrophotometer. Mass spectral data were obtained on an MS-50 high resolution mass spectrometer.

Reagents. All chemicals were used directly as obtained commercially unless otherwise noted. Anisole was distilled over sodium under reduced pressure. Acetone was distilled over potassium carbonate and used immediately. N,N-Dimethylformamide (DMF) was distilled over calcium hydride. Methanol was distilled over magnesium methoxide. 7-Oxabicyclo[2.2.1]heptene was prepared using a literature procedure.[50] Tetrakis(triphenylphosphine)palladium(0) [$Pd(PPh_3)_4$] was prepared by the method of Coulson.[51]

Preparation of methyl 3-(chloromethyl)phenoxyacetate (4). Compound **4** was prepared in three steps starting from m-hydroxybenzaldehyde (Aldrich). To a stirred solution of m-hydroxybenzaldehyde (1.32 g, 10 mmol) and potassium carbonate (1.40 g, 10 mmol) in acetone was added methyl bromoacetate (1.52 g, 10 mmol) under nitrogen. The mixture was refluxed for 12 h, by which time the reaction mixture turned lighter and potassium bromide was observed to precipitate. After having cooled, the mixture was poured into water and extracted with ether. The extracts were then dried over sodium sulfate and concentrated on a rotary evaporator to yield the crude product. Vacuum distillation (0.2 mm Hg at 125°C) yielded the pure product **3** (1.7 g, 88% yield) as a colorless oil which turns yellow on exposure to air: ^1H NMR ($CDCl_3$) δ 3.70 (3 H, s, OCH_3), 4.60 (2 H, s, OCH_2CO_2), 7.20-7.70 (4 H, m, aryl), 9.90 (1 H, s, CHO); IR (neat) 2700 (HC=O), 1760 (MeOC=O) cm^{-1}; MS, m/z 194.05739; calcd for $C_{10}H_{10}O_4$, 194.05791.

To a flame dried, round bottom flask was added sodium borohydride (0.52 g, 13.6 mmol) and methanol (20 mL). The mixture was stirred at room temperature for a few min and then cooled to 0°C. The formyl ester **3** (2.4 g, 12.4 mmol) dissolved in methanol (20 mL), was added to the sodium borohydride solution with stirring, while backflushing with nitrogen. After 30 min, another portion of sodium borohydride (0.24 g, 6.2 mmol) was added. The reaction, as indicated by TLC, was complete within five min. The reaction mixture was then quenched at 0°C with dilute HCl and extracted with ether. The aqueous washings were extracted with ether and the combined extracts were dried over sodium sulfate. Removal of the solvent under vacuum yielded the colorless, oily hydroxy ester in almost quantitative yield (2.42 g). The virtually pure alcohol was used without further purification. ^1H NMR ($CDCl_3$) δ 2.70 (1 H, br s, OH), 3.75 (3 H, s, OCH_3), 4.6 (4 H, s, $ArCH_2$ and OCH_2CO_2), 6.7-7.6 (4 H, m, aryl); IR (thin film) 3700 (OH), 1750 (C=O) cm^{-1}; MS, m/z 196.07306; calcd for $C_{10}H_{12}O_4$, 196.07356.

To a stirred mixture of this alcohol (2.4 g, 12.3 mmol) and s-collidine (1.64 g, 13.5 mmol) under nitrogen was added lithium chloride (0.57 g, 13.5 mmol) dissolved in a minimum amount of dry DMF. On cooling to 0°C, a suspension was formed which was treated with methanesulfonyl chloride (1.54 g, 13.5 mmol). Stirring was continued for 2 h and the reaction mixture was then poured into ice. The aqueous layer was extracted with cold 1:1 ether/pentane and the combined extracts were washed with saturated copper nitrate solution until no further intensification of the blue copper solution occurred, indicating complete removal of s-collidine. The organic extracts were dried over sodium sulfate and concentrated to yield the crude halide **4**. Further purification by column chromatography using 2:1 hexanes/ethyl acetate as eluent yielded 2.15 g (82%) of pure **4**: R_f 0.51, 2:1 hexanes/ethyl acetate; ^1H NMR ($CDCl_3$) δ 3.82 (3 H, s, OCH_3), 4.62 (2 H, s, $ClCH_2$), 4.70 (2 H, s, OCH_2CO_2), 6.80-7.42 (4 H, m, aryl); IR (neat) 1760 (C=O) cm^{-1}; MS, m/z 214.03866; calcd for $C_{10}H_{11}ClO_3$, 214.03968.

Resolution of 1-octyn-3-ol. 1-Octyn-3-ol was resolved via crystallization of the ammonium salt of its half phthalate ester prepared as follows.[45] Phthalic anhydride (74 g, 0.5 mole) was added to 1-octyn-3-ol (63.1 g, 0.5 mole) (Aldrich) and was heated with stirring at 165-170°C for 21 h under nitrogen. After cooling to 60°C, benzene (100 ml) was added. After the addition of 200 ml of hexanes, the mixture was stirred at 0°C for 4 h. Filtration yielded a white solid which was washed with hexanes. The solid was dried under reduced pressure. The half phthalate ester (75 g, 0.275 mole) with a melting point of 70-71°C was obtained in 55% yield.

After dissolving the solid (75 g) in benzene (100 mL) at 60°C, hexanes (200 mL) was added to the solution. The solution was then stirred at 0°C for 3 h. After filtration, the white solid was dried under reduced pressure at 50°C for 3 h. The half phthalate ester was obtained as a white solid in 92% yield (69.2 g), mp 71-73°C.

This solid was again recrystallized from benzene (110 mL) and hexanes (180 mL) to afford the half phthalate ester in 63% yield (44 g), mp 76-77°C (lit.[45] mp 76-77°C).

The half phthalate ester was then converted to its amine salt as follows. (S)-(-)-α-Phenethyl amine (19.4 g, 0.16 mole) (Aldrich) was added dropwise via a syringe to a suspension of the half phthalate ester (44 g, 0.16 mole) in CH_2Cl_2 (36 mL) under reflux and stirred for 30 min. A small amount of amine salt as a seed was added to the solution, after cooling. The reaction mixture was then allowed to stand in a freezer overnight and the crystals formed were collected, washed with acetone, and dried under reduced pressure at room temperature. The first crop (20 g, 31% yield) was then added to CH_2Cl_2 (45 mL) and the mixture was refluxed with stirring for 30 min. After complete dissolution of the solid, the clear solution was allowed to cool to room temperature. A few seed crystals were added and the solution was kept in a freezer overnight. The crystals were filtered, washed with CH_2Cl_2 (10 mL), and dried under vacuum at room temperature (12.42 g, 62% yield; mp 133-136°C). Two further recrystallizations furnished material with a melting point of 135-136°C (lit.[45] mp 133.5-135°C).

The optical purity of the amine salt could be monitored by ^1H NMR spectral analysis. The acetylenic hydrogen doublets for the two diastereomers appear at δ 2.48 (S-S) and δ 2.52 (R-S). Only the former peak was present in the ^1H NMR spectrum of the above thrice recrystallized salt.

(S)-1-Octyn-3-ol was isolated as follows. The (S-S)-amine salt (9.58 g, mp 135-136°C) was added to 10% NaOH (55 mL) and the solution stirred at 60°C for 1 h. After cooling to room temperature, the solution was extracted three times with CH_2Cl_2 (100 mL). The combined extracts were successively washed with 1N HCl, concentrated HCl (7 mL in 20 mL of water), brine, saturated sodium bicarbonate, and brine, and dried over sodium sulfate. After removal of the solvent, the residue was distilled to give pure (S)-1-octyn-3-ol (2.69 g) as a colorless oil in 88% yield: bp 88-89°C, ~20 mm Hg; $[\alpha]_D^{20}$ $CHCl_3$ = -6.79 (literature[45] $[\alpha]_D^{20}$ = -5.5 and $[\alpha]_D^{20}$ = -6.5).

The ^1H NMR spectrum of (S)-1-octyn-3-ol (8 mg) with Eu(hfbc)$_3$ (14 mg) in 0.3 mL of $CDCl_3$ indicated a broadened singlet at δ 7.81 corresponding to the hydrogen alpha to the hydroxy group. A singlet corresponding to the R-isomer (usually about 0.3 ppm downfield relative to the S-isomer) was not observed. Hence, the alcohol obtained is ~100% optically pure.

Synthesis of compounds 1, 2, 6, 7 and 8. The procedure for the synthesis of compound 1 is representative of that used to prepare all of the above compounds. To a round bottom flask with a sidearm equipped with a reflux condenser was introduced, under nitrogen, $Pd(PPh_3)_4$ (45 mg, 0.039 mmol) and anhydrous sodium acetate (41 mg, 0.5 mmol). A solution of distilled benzyl chloride (64 mg, 0.5 mmol), racemic 1-octyn-3-ol (63 mg, 0.5 mmol), and norbornene (188 mg, 2 mmol) (Aldrich) in degassed anisole (1 ml) was added to the flask. The mixture was heated at 70°C for approximately 24 h. After cooling, dilute sulfuric acid was added and the solution was extracted with diethyl ether. After drying the ether extracts over anhydrous sodium sulfate, the solvents were removed under vacuum and the residue chromatographed on a silica gel column using hexanes/ethyl acetate mixtures as the eluent. The expected product 1 was isolated in 81% yield (126 mg): R_f 0.48, 5:1 hexanes/ethyl acetate; ^1H NMR ($CDCl_3$) δ 0.88-2.20 (19 H, m, aliphatic and OH), 2.85 (1 H, d, J = 13 Hz, HC(2)), 3.12 (2 H, m, $ArCH_2$), 4.45 (1 H, m, CHOH), 7.30 (5 H, m, aryl); ^{13}C NMR ($CDCl_3$) δ 142.35, 128.95, 128.24, 125.64 (all aryl), 86.80 and 83.75 (C≡C), 62.68 (CHOH), 46.63, 45.00, 39.80, 39.08, 38.24, 33.82, 31.54, 29.91, 28.48, 24.97, 22.63, 14.05 (all aliphatic); IR (neat) 3360 (OH) cm^{-1}; MS, m/z 310.2287; calcd for $C_{22}H_{30}O$, 310.2282.

Compound 2: 53% yield; R_f 0.48, 5:1 hexanes/ethyl acetate; ^1H NMR ($CDCl_3$) δ 1.05-2.21 (17 H, m, aliphatic and OH), 2.88 (1 H, d, J = 14 Hz, HC(2)), 3.35 (2 H, m, $ArCH_2$), 4.68 (1 H, m, CHOH), 6.38 (2 H, br s, vinylic), 7.55 (5 H, m, aryl). In addition, the following signals were seen (possibly from the accompanying impurity): δ 2.5 (m), 2.76 (m), 5.2 (br m), 5.6 (s); ^{13}C NMR ($CDCl_3$) δ 141.64, 138.53, 135.10, 128.89, 128.21, 125.72 (all aryl), 87.02 and 83.66 (C≡C), 62.82 (CHOH), 49.95, 48.50, 47.20, 45.22, 43.61, 42.61, 39.43, 38.24, 34.45, 32.50, 31.50, 24.94, 22.54, 13.61 (aliphatic) (the extraneous carbon absorptions are from the accompanying impurity); IR (neat) 3350 (OH) cm^{-1}; MS, m/z 290.2040; calcd for $C_{22}H_{26}O$ (M-18), 290.2039.

Compounds 6a and 6b: 58% yield; R_f 0.33, 3:1 hexanes/ethyl acetate; ^1H NMR ($CDCl_3$) δ 0.85-1.75 (18 H, m, aliphatic and OH), 1.86 (1 H, br t, J = 9.6 Hz, endo HC(3)), 1.97 (1 H, m, HC(4)), 2.29-2.35 (1 H, m, HC(1)), 2.42 (1 H, dd, J = 10.6 Hz, J = 10.5 Hz, diastereotopic ArCH), 2.62 (1 H, d, J = 10.7 Hz, endo HC(2)), 2.86 (1 H, br dd, J = 14.4 Hz, J = 5.1 Hz, diastereotopic ArCH), 3.85 (3 H, s, OCH_3), 4.29-4.41 (1 H, m, CHOH), 4.70 (2 H, s, OCH_2CO_2), 6.72 and 6.73 (1 H, d, J = 7.8 Hz, aryl, diastereomers), 6.79 (1 H, s, aryl), 6.85 (1 H, d, J = 7.5 Hz, aryl), 7.20 (1 H, t, J = 7.7 Hz, aryl). Irradiation of the proton giving rise to the peak at δ 2.86 causes the peak at δ 1.86 to collapse to a broad triplet (J = 6 Hz) and the peak at δ 2.42 collapses to a doublet (J = 8.3 Hz). Irradiation of the proton giving rise to the peak at δ 2.62 causes the peak at δ 1.86 to collapse to a simplified multiplet. Irradiation of the proton giving rise to the peak at δ 2.42 causes the peak at δ 2.86 to collapse to a singlet and the peak at δ 1.86 remains the same. Irradiation of the proton giving rise to the multiplet at δ 2.29-2.35 causes no change except for a sharpening of the peak at δ 1.86. Irradiation of the proton giving rise to the multiplet at δ

1.97 causes the peak at δ 2.62 to collapse to a singlet; the peaks at δ 2.86 and 2.42 are now doublets with J = 13.7 Hz and 14.5 Hz respectively, and the multiplet at δ 1.97 is a sharp singlet. ^{13}C NMR ($CDCl_3$) δ 169.49 (C=O), 157.72, 144.19, 129.15, 122.52, 115.66, 111.39 (all aryl), 86.57 and 83.79 (C≡C), 65.32 (OCH_2), 62.79 (CHOH), 52.22 (OCH_3), 46.42, 44.93, 39.85, 39.04, 38.95, 38.17, 33.77, 31.47, 29.82, 28.40, 24.97, 22.58, 14.00 (aliphatic); IR (neat) 3500 (OH), 1760 (C=O) cm^{-1}; MS, m/z 398.2457; calcd for $C_{25}H_{35}O_4$, 398.24644.

Compounds 7a and 7b: 37% yield; R_f 0.33, 3:1 hexanes/ethyl acetate; ^1H NMR ($CDCl_3$) δ 0.85-1.86 (13 H, m, aliphatic and OH), 2.43-2.48 (2 H, m, HC(4) and diastereotopic ArCH), 2.53 (1 H, d, J = 9.0 Hz, HC(2)), 2.91 (1 H, br s, HC(1)), 3.10 (1 H, dd, J = 13 Hz, J = 5.1 Hz, diastereotopic ArCH), 3.83 (3 H, s, OCH_3), 4.38 (1 H, m, CHOH), 4.66 (2 H, s, OCH_2CO_2), 6.07 (2 H, br s, vinylic), 6.73 (1 H, dd, J = 5.3 Hz, J = 2 Hz, aryl), 6.79 (1 H, s, aryl), 7.24 (1 H, d, J = 6 Hz, aryl), 7.24 (1 H, dd, J = 7.0 Hz, aryl); ^{13}C (NMR) δ 169.50 (C=O), 157.77, 145.97, 138.50, 135.65, 129.25, 122.52 (all aryl), 115.68, 111.52 (C=C), 87.19 and 83.69 (C≡C), 65.33 (OCH_2CO_2), 62.76 (CHOH), 52.21 (OCH_3), 50.24, 45.26, 43.61, 42.53, 39.40, 38.24 and 38.17 (diastereomeric), 34.35, 31.47, 24.96, 22.60, 14.00 (all aliphatic); IR (neat) 3420 (OH), 1750 (C=O) cm^{-1}; MS, m/z 396.2296; calcd for $C_{25}H_{35}O_4$, 396.2301.

Compounds 8a and 8b: 45% yield; R_f 0.55, 1:1 hexanes/ethyl acetate; ^1H NMR ($CDCl_3$) δ 0.86-1.80 (16 H, m, aliphatic and OH), 2.06-2.19 (1 H, m, endo HC(3)), 2.57 and 2.62 (1 H, dd, J = 10.8 Hz, J = 3 Hz, diastereotopic ArCH), 2.86 (1 H, d, J = 8.4 Hz, endo HC(2)), 2.83-2.89 (1 H, m, diastereotopic ArCH, buried under doublet of HC(2)), 3.81 (3 H, s, OCH_3), 4.26 (1 H, d, J = 5.6 Hz, HC(4)), 4.36-4.38 (1 H, m, CHOH), 4.55 (1 H, d, J = 4.2 Hz, HC(1)), 4.64 (2 H, s, OCH_2CO_2), 6.70 and 6.72 (1 H, d, J = 8.1 Hz, aryl, diastereomers), 6.79 (1 H, s, aryl), 7.22 (1 H, t, J = 8.0 Hz, aryl). Irradiation of the proton giving rise to the peak at δ 2.86 causes the multiplet at δ 2.06-2.19 to collapse to a doublet (J = 9.9 Hz). Irradiation of the proton giving rise to the peaks at δ 2.57 and δ 2.62 causes the multiplet at δ 2.83-2.89 to collapse to a simplified multiplet; the multiplet at δ 2.06-2.19 also collapses to a simplified multiplet. Irradiation of the proton giving rise to the peak at δ 2.06-2.19 causes changes in multiplicity at δ 2.57-2.62; ^{13}C NMR ($CDCl_3$) δ 169.47 (C=O), 157.94, 143.29, 129.51, 122.61, 115.70, 111.87 (all aryl), 84.65 and 84.34 (C≡C), 82.95 and 79.06 (C_1 and C_4), 79.00 (C_1 or C_4, diastereomeric), 65.37 (OCH_2), 62.72 (CHOH), 52.24 (OCH_3), 48.24, 40.30, 38.08, 37.69, 31.48, 29.31, 29.18, 24.94, 22.58, 14.00 (all aliphatic); IR (neat) 3420 (OH), 1760 (C=O) cm^{-1}; MS, m/z 400.22409; calcd for $C_{24}H_{32}O_5$, 400.22408.

Compound 9 and its diastereomer were also isolated from the above reaction (for numbering see structure 9): R_f 0.33, 1:1 hexanes/ethyl acetate; ^1H NMR ($CDCl_3$) δ 0.83-1.78 (20 H, m, aliphatic and OH), 2.00 (1 H, br t, J = 8.8 Hz, endo HC(3)), 2.14 (1 H, br t, J = 9.1 Hz, endo HC(2')), 2.15-2.28 (1 H, m, endo HC(3'), buried under the triplet at δ 2.14), 2.39 (1 H, br t, J = 12.5 Hz, ArCH), 2.68 (1 H, br d, J = 12.8 Hz, ArCH), 2.80 (1 H, d, J = 8.3 Hz, endo HC(2)), 3.79 (3 H, s, OCH_3), 4.18 (1 H, m, HC(1)), 4.41 (1 H, m, CHOH), 4.49-4.56 (3 H, m, HC(1', 4' and 4)), 4.63 (2 H, s, OCH_2CO_2), 6.70-6.75 (1 H, m, aryl), 6.80-6.88 (2 H, m, aryl), 7.19 (1 H, t, J = 7.6 Hz, aryl); ^{13}C NMR ($CDCl_3$) δ 169.66 (C=O), 158.04, 143.77, 129.50, 122.72, 115.63, 112.17 (all aryl), 85.68 and 83.95 (C≡C), 82.82, 80.59, 80.16, 79.32, 65.48, 62.86, 52.31, 49.72, 49.17, 48.91, 41.93, 38.27, 35.74, 31.63, 31.57, 30.82, 30.05, 29.73, 25.16, 25.07, 22.67 and 14.10 (all aliphatic); IR (neat) 3480 (OH), 1760 (C=O) cm^{-1}; MS, m/z 496.28382; calcd for $C_{30}H_{40}O_6$, 496.28250.

Synthesis of compounds 10, 11 and 12. The procedure for the hydrolysis of compound 6 to compound 10 is representative. Hydroxy ester 6 (55.7 mg, 0.14 mmol) was refluxed for 2 h in 5 mL of methanol and 1 mL of 2M KOH. After cooling, the reaction was diluted with ether, acidified with 25 ml of 2N sulfuric acid, washed with 50 ml of brine, and dried over sodium sulfate. Removal of the solvent under vacuum and purification of the residue by chromatography using 20:20:1 hexanes/ethyl acetate/glacial acetic acid yielded the pure acid 10 as a colorless oil: 95% yield; R_f 0.31, 20:20:1 hexanes/ethyl acetate/glacial acetic acid; ^1H NMR ($CDCl_3$) δ 0.86-1.93 (18 H, m, alkyl), 1.98 (1 H, m, endo HC(3)), 2.1 (1 H, s, OH), 2.34 (1 H, m, HC(1)), 2.46 (1 H, dd, J = 10.2 Hz, diastereotopic ArCH), 2.62 (1 H, d, J = 8.0 Hz, endo HC(2)), 2.88 (1 H, br d, J = 9.3 Hz, diastereotopic ArCH), 4.36 (1 H, m, CHOH), 4.66 (2 H, s, OCH_2CO_2), 4.95 (1 H, s, CO_2H), 6.73 (1 H, d, J = 7.6 Hz, aryl), 6.79 (1 H, s, aryl), 6.85 (1 H, d, J = 7.5 Hz, aryl), 7.21 (1 H, t, J = 7.8 Hz, aryl); ^{13}C NMR ($CDCl_3$) δ 157.53, 144.30, 129.28, 122.68, 115.66 and 115.59 (diastereomeric), 111.60 (all aryl), 86.93 and 83.50 (C≡C), 62.98 (CHOH), 46.42, 46.36, 45.02, 40.16, 39.13 and 39.06 (broadened, diastereomeric), 38.98, 33.90, 31.50, 29.92, 28.42, 24.98, 22.64, 14.04; IR (neat) 3600-2700 (OH, CO_2H), 1740 (C=O) cm^{-1}; MS, m/z 384.23007; calcd for $C_{24}H_{32}O_4$, 384.23000. Anal. Calcd. for $C_{24}H_{32}O_4$: C, 75.02; H, 8.39. Found: C, 75.03; H, 8.30.

Compounds 11a and 11b: 88% yield; R_f 0.30, 20:20:1 hexanes/ethyl acetate/acetic acid; ^1H NMR ($CDCl_3$) δ 0.83-1.89 (15 H, m, aliphatic and OH), 2.49-2.55 (3 H, m, diastereotopic ArCH and norbornyl HC(2) and HC(4)), 2.91 (1 H, s, HC(1)), 3.10 (1 H, br d, J = 15 Hz, ArCH), 4.38 (1 H, m, CHOH), 4.66 (2 H, s, OCH_2CO_2), 5.36 (1 H, br s, CO_2H), 6.06 (2 H, br s, vinylic), 6.75 (1 H, br d, J = 8.7 Hz, aryl), 6.79 (1 H, s, aryl), 6.85 (1 H, d, J = 7.6 Hz, aryl), 7.21 (1 H, t, J = 7.8 Hz, aryl); ^{13}C NMR ($CDCl_3$) δ 157.57, 144.05, 138.56, 135.66, 129.32, 122.62, 115.64 (all aryl), 115.56

and 111.76 (C=C), 87.53 and 83.38 (C≡C), 65.42 (OCH_2), 63.00 (CHOH), 50.30, 45.67 and 45.62 (diastereomeric), 43.70, 42.53, 42.44, 39.40, 38.13 and 38.08 (diastereomeric), 34.41, 31.47, 24.96, 22.61, 14.01 (all aliphatic); IR (neat) 3500-2700 (OH, CO_2H), 1735 (C=O) cm^{-1}; MS, m/z 382.21479, calcd for $C_{24}H_{30}O_4$, 382.21442. Anal. Calcd for $C_{24}H_{30}O_4$: C, 75.40; H, 7.90. Found: C, 75.19; H, 7.85.

Compounds 12a and 12b were prepared by the same basic procedure described above except that the reaction was run at room temperature for 2 days: 98% yield; R_f 0.31, 20:20:1 hexanes/ethyl acetate/glacial acetic acid; ^1H NMR ($CDCl_3$) δ 0.86-1.80 (16 H, m, aliphatic and OH), 2.06-2.20 (1 H, m, endo HC(3)), 2.62 (1 H, t, J = 13.8 Hz, diastereotopic ArCH), 2.84-2.90 (2 H, m, diastereotopic ArCH, buried under the doublet of HC(2)), 4.28 (1 H, d, J = 4.2 Hz, HC(4)), 4.36 (1 H, br t, J = 6.3 Hz, CHOH), 4.57 (1 H, d, J = 3.9 Hz, HC(1)), 4.66 (3 H, s, broadened at the base, OCH_2CO_2 and CO_2H), 6.76 (1 H, d, J = 7.8 Hz, aryl), 6.80 (1 H, s, aryl), 6.86 (1 H, d, J = 7.8 Hz, aryl), 7.22 (1 H, t, J = 8.1 Hz, aryl); ^{13}C NMR ($CDCl_3$) δ 157.75, 143.38, 129.63, 122.80, 115.78 and 115.72 (diastereomeric), 112.26 (all aryl), 84.69 and 84.50 (C≡C), 83.10 and 79.39 (C_1 and C_4), 65.17 (OCH_2), 62.90 (CHOH), 48.23, 40.43, 38.10, 37.72, 31.54, 29.34, 29.28, 14.00 (all aliphatic); IR (neat) 3600-2700 (HO, CO_2H), 1740 (C=O) cm^{-1}; MS, m/z 386.2093, calcd for $C_{23}H_{30}O_5$, 386.2099. Anal. Calcd for $C_{23}H_{30}O_5$: C, 71.46; H, 7.76. Found: C, 69.43; H, 7.84.

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