2,3,7,8,12,13-hexaethyltripyrrane (92 mg), 3,4-diethylpyrrole (30 mg), and 2-hydroxy-1-naphthaldehyde (80 mg), zinc acetate (80 mg), and *p*-toluenesulfonic acid (100 mg) in methanol (40 mL) was stirred at 25 °C for 20 min. To the resulting dark reddish solution was added a THF solution (40 mL) of chloranil (100 mg), and the mixture was stirred for 1 h. Workup and chromatography on silica gel (Wakogel C-200) with chloroform as eluant gave the Zn^{II} complex of 4. Demetalation with HCl followed by recrystallization from chloroform–hexane afforded compound 4 (33 mg, 20%): δ ($CDCl_3$, at 298 K) −3.00 (br, 2 H, NH), 0.91, 1.84, 1.92 (each t, 3 H, 3 H, 6 H, CH_3), 2.56, 2.82, 4.00, 4.12 (each m, 2 H, 2 H, 4 H, 8 H, CH_2CH_3), 5.27 (br, 1 H, OH), 6.81–8.27 (m, 6 H, naphthyl H), 10.01, 10.22 (each s, 1 H, 2 H, meso H); λ_{max} ($CHCl_3$) 411, 509, 541, 576, 626 nm.

Alkylation of compound 4 was carried out as typically shown below for the preparation of 5-(2-(4-nitrobenzyl)-1-naphthyl)-octaethylporphyrin (1). A mixture of compound 4 (200 mg), potassium carbonate (20 mg), and 4-nitrobenzyl bromide (100 mg) in dry acetone (20 mL) was stirred under reflux for 1 h. Workup involving chromatography on silica gel (Wakogel C-200) with dichloromethane as eluant and recrystallization from dichloromethane–hexane gave compound 1 (216 mg, 90%): δ (at 313 K) −3.11, −2.78 (each s, each 1 H, NH), 0.71, 1.80, 1.93, 1.95 (each t, each 6 H, CH_3), 2.57, 3.94, 4.09 (each m, 4 H, 4 H, 8 H, CH_2CH_3), 5.11 (s, 2 H, OCH_2), 6.54, 7.31 (each d, each 2 H, phenyl H), 7.00–8.38 (m, 6 H, naphthyl H), 9.99, 10.17 (each s, 1 H, 2 H, meso H); λ_{max} ($CHCl_3$) 409, 506, 539, 574, 625 nm. Anal. Calcd for $C_{53}H_{58}N_5O_3$: C, 78.29; H, 7.19; N, 8.61. Found: C, 78.35; H, 7.03; N, 8.48. Compound 2: δ (at 313 K) −3.10, −2.77 (each s, each 1 H, NH), 0.70, 1.83, 1.94 (each t, 6 H, 6 H, 12 H, CH_3), 2.60, 3.96, 4.09 (each m, 4 H, 8 H, CH_2CH_3), 5.07 (s, 2 H, OCH_2), 6.71–6.90 (m, 5 H, phenyl H), 6.70–8.37 (m, 6 H, naphthyl H), 10.03, 10.22 (each s, 1 H, 2 H, meso H); λ_{max} ($CHCl_3$) 409, 506, 538, 574, 625 nm. Anal. Calcd for $C_{53}H_{59}N_4O$: C, 82.88; H, 7.74; N, 7.29. Found: C, 82.86; H, 7.72; N, 7.11. Compound 3: δ (at 313 K) −2.42, −2.18 (each s, each 1 H, NH), 0.42 (t, 3 H, $CH_2CH_2CH_2CH_3$), 0.72 (q, 2 H, $CH_2CH_2CH_2CH_3$), 1.00 (m, 2 H, $CH_2CH_2CH_2CH_3$), 1.15 (t, 2 H, $CH_2CH_2CH_2CH_3$), 0.85, 1.92, 2.03, 2.05 (each t, each 6 H, CH_3), 2.62, 2.80, 4.08, 4.15 (each m, 2 H, 2 H, 4 H, CH_2CH_3), 6.82–8.43 (m, 6 H, naphthyl H), 10.03, 10.22 (each s, 1 H, 2 H, meso H); λ_{max} ($CHCl_3$) 409, 505, 536, 574, 626 nm. Anal. Calcd for $C_{53}H_{58}N_5O_3$: C, 81.81; H, 8.38; N, 7.63. Found: C, 81.98; H, 8.45; N, 7.37.

(20) Aoyama, Y.; Saita, K.; Toi, H.; Ogoshi, H.; Okamoto, Y. *Tetrahedron Lett.* **1987**, *28*, 4853.

Synthesis of (−)-Shikimate and (−)-Quinate 3-Phosphates by Differentiation of the Hydroxyl Functions of (−)-Shikimic and (−)-Quinic Acids

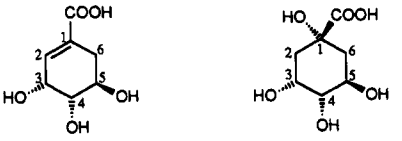
Latifa Chahoua, Michel Baltas, Liliane Gorrichon, Pierre Tisnès,* and Chantal Zedde

Laboratoire de Synthèse et Physicochimie Organique, URA CNRS 471 Université Paul Sabatier-118, route de Narbonne, 31062 Toulouse Cedex, France

Received April 20, 1992

Shikimic acid **1a** is a central intermediate in the shikimate pathway along which the aromatic amino acids and a multitude of other aromatic and alicyclic compounds are biosynthesized in bacteria, fungi, and plants.[1,2] Shikimate 3-phosphate (**10a**) is the substrate for 5-enolpyruvoylshikimate 3-phosphate synthase (EPSPS) which is the target for the broad-spectrum herbicide *N*-(phosphonomethyl)glycine (glyphosate).[3]

Chart I

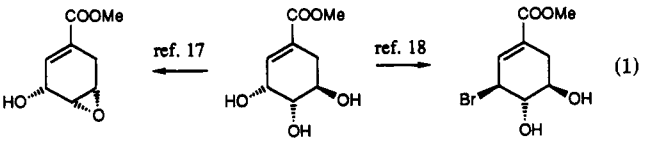


1a **1b**

The (−)-shikimate 3-phosphate has been obtained by enzymatic phosphorylation of shikimic acid using shikimate kinase and ATP.[4,5] Bartlett[6] has described a total synthesis of racemic shikimate 3-phosphate, but to our knowledge no report exists for the chemical synthesis of the natural (−)-derivative.

Quinic acid **1b** is involved only in plants, but it can constitute a source of carbon in bacteria.[7] Its presence can be related to a regulation of the shikimate pathway.[8] However, the presence of significant quantities of quinic acid (more than 5% of the weight of dried vegetal in some instances) suggests other possible metabolic activities and/or other relations with the shikimate pathway, for instance, through quinate 3-phosphate **10b**.[9]

We hereby report the first chemical synthesis of both (−)-shikimate and (−)-quinate 3-phosphates. It poses the problem of selective hydroxyl-group functionalization. A limited number of such processes of discrimination have been reported in these series. One strategy was based on acetal formation involving the cis 3,4-diol of **1a**[10-12] and of **1b**[13] or analogous carbonate[14] and borate[15] cyclic esters. Another approach[17] consisted of the reaction of methyl shikimate with triphenylphosphine–dialkyl azodicarboxylate (eq 1) leading to a *syn*-hydroxy epoxide.



(1)

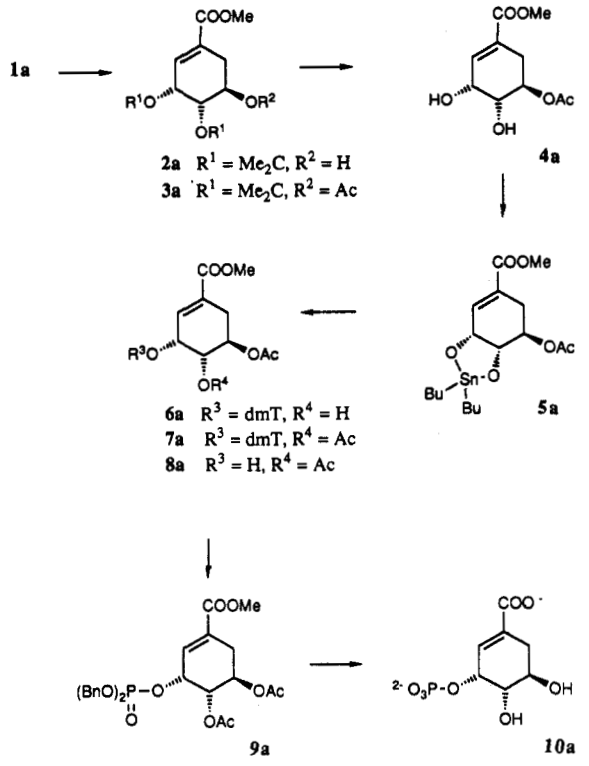
Recently, Ganem's group[18] reported a selective modification of 3- and 4-hydroxyl groups using 2-acetoxyisobutyryl bromide (eq 1) giving a bromoacetate.

A method for versatile functionalization of the 3-hydroxyl group is applied in this work to the preparation of the title compounds. This methodology using the 3,4-*O*-stannylene derivatives rests upon the dimeric structure

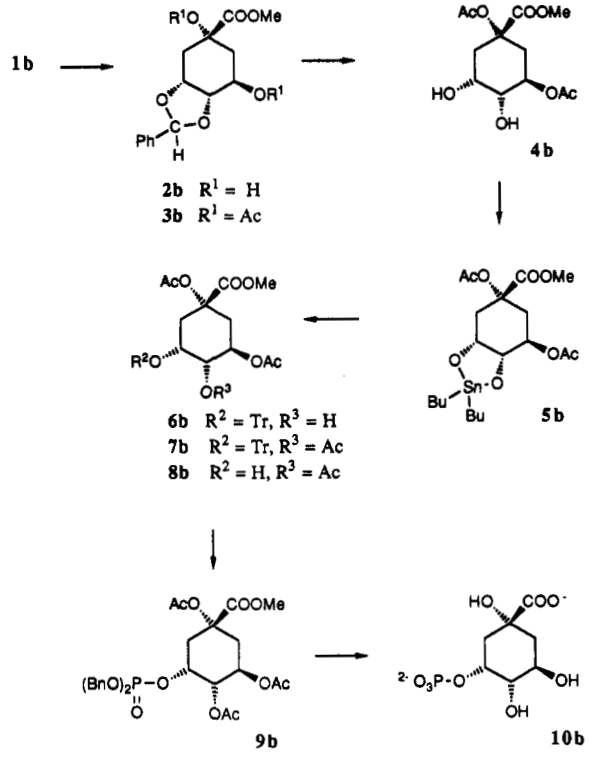
(1) Haslam, E. In *The shikimate pathway*; Butterworths: London, 1974.
(2) Weiss, U.; Edwards, J. M. In *The biosynthesis of aromatic compounds*; John Wiley and Sons: New York, 1980.
(3) Amrhein, N.; Deus, B.; Gehrke, P.; Steinrucken, H. C. *Plant Phys.* **1980**, *66*, 830–834.
(4) De Feyter, R. C.; Pittard J. *J. Bacteriol.* **1986**, *165*, 226–232.
(5) Millar, G.; Lewendon, A.; Hunter, M. G.; Coggins, J. R. *Biochem. J.* **1986**, *237*, 427–437.
(6) Bartlett, P. A.; McQuaid, L. A. *J. Am. Chem. Soc.* **1984**, *106*, 7854–7860.
(7) Charleff, R. S. *J. Gen. Microbiol.* **1974**, *81*, 337–355.
(8) Graziana, A.; Boudet, A. M. *Plant Cell Physiol.* **1980**, *21*, 793–802.
(9) Neish, A. C. In *Biochemistry of phenolic compounds*; Harbone, J. B.; Academic Press: London, New York, 1964; p 318.
(10) Lesuisse, D.; Berchtold, G. A. *J. Org. Chem.* **1985**, *50*, 888–890.
(11) Hanessian, S.; Beaulieu, P.; Dubé, D. *Tetrahedron Lett.* **1986**, *27*, 5071–5074.
(12) Nikolaides, N.; Ganem, B. *Tetrahedron Lett.* **1989**, *30*, 1461–1464.
(13) Zamir, L. O.; Luthe, C. *Can. J. Chem.* **1984**, *62*, 1169–1175.
(14) Mc Gaowan, D. A.; Berchtold, G. A. *J. Am. Chem. Soc.* **1982**, *104*, 7036–7041.
(15) Delfourne, E.; Veronique, J.; Gorrichon, L.; Munoz, A.; Lamandé, L. *Tetrahedron* **1989**, *45*, 2605–2614.
(16) Flores-Parra, A.; Paredes-Tepox, C.; Joseph-Nathan, P.; Contreras, R. *Tetrahedron* **1990**, *46*, 4137–4148.
(17) Mc Gowan, D. A.; Berchtold, G. A. *J. Org. Chem.* **1981**, *46*, 2381–2383.
(18) Wood, H. B.; Ganem, B. *J. Am. Chem. Soc.* **1990**, *112*, 8907–8909.

0022-3263/92/1957-5798$03.00/0

Scheme I



Scheme II



of *O*-stannylene acetals which allows a differentiation of the nucleophilic character of the two oxygen atoms.[19] It has proved to be fruitful in carbohydrate and nucleoside chemistry.[20]

(-)-Shikimate 3-phosphate was synthesized according to Scheme I.

Methyl shikimate obtained quantitatively from **1a**, using Amberlite resin in methanol,[21] gave exclusively **2a** by acid-catalyzed reaction with 2,2-dimethoxypropane. Compound **2a** was readily converted in two steps by acylation (**3a**) and cleavage of the acetal protection into the 3,4-diol **4a** (94% yield) which was then transformed into the key intermediate **5a** by reaction with dibutyltin oxide. The strategy consisted then in the selective reaction of this *O*-stannylene acetal with an electrophile to differentiate the 3- and 4-positions. The substitution reaction with the dimethoxytrityl group, when carried out for short reaction times ($t < 1$ h), was found to be regiospecific yielding the 3-O-protected derivative **6a**. For longer periods this group migrates partially from the 3- to the 4-position. After acetylation of the remaining 4-hydroxyl group **7a**, the dimethoxytrityl group was eliminated in the presence of aqueous acetic acid and tetrahydrofuran giving the monoalcohol **8a** without any migration of the acetate group. This monoalcohol **8a** was then phosphorylated in a two-step procedure[22] using the dibenzyl *N,N*-diisopropylphosphoramidite electrophile and then an oxidation reaction of the phosphorous atom. The resulting protected phosphate ester **9a** (45% yield from **4a**) was then debenzylated with bromotrimethylsilane before the saponification of the carboxylic ester groups to avoid possible phosphate group migration.[6,23] The (-)-shikimate 3-phosphate (**10a**) was obtained as a sodium salt in an overall yield of 32% from (-)-shikimic acid.

In the quinic series the 3,4-O-stannylene derivative **5b** was readily obtained from the known 1,5 diol **2b**.[10] After regiospecific temporary protection of the 3-position by a trityl group (compound **6b**) and acetylation of the remaining 4-hydroxy function (compound **7b**), the monoalcohol **8b** was obtained by cleavage of the trityl group by trichloroacetic acid. The phosphorylation of the 3-hydroxyl group was carried out following a sequence of reactions analogous to that involved in the shikimic series. Finally after deprotection the (-)-quinate 3-phosphate **10b** was obtained as a triethylammonium salt in 20% yield from (-)-quinic acid.

In conclusion, this methodology based on *O*-stannylene acetals offers a reasonable route to (-)-shikimate and (-)-quinate 3-phosphates in fair yields. A shorter synthetic pathway involving the reaction of a phosphorus-containing electrophile with the *O*-stannylene acetals (**5a,5b**) led to complex mixtures and does not constitute up to now a preparative improvement. Other applications of selective functionalizations in these series are in progress.

Experimental Section

Methyl (-)-Shikimate. To a suspension of 1.6 g of Amberlite IR 120 resin in 30 mL of methanol was added under stirring 1 g (5.7 mmol) of (-)-shikimic acid, and the mixture was heated at reflux for 12 h. Filtration and evaporation of the solvent left methyl shikimate (1.00 g, 95%) as a white solid, mp 114-115 °C: ^{1}H NMR (CD_3OD, 250 MHz) δ 6.79 (m, 1 H, H_2), 4.37 (m, 1 H, H_3, J = 4.2, 3.4, 1.6 Hz), 4.00 (td, 1 H, H_5, J = 7.2, 5.0 Hz), 3.74 (s, 3 H), 3.69 (dd, 1 H, H_4, J = 7.2, 4.2 Hz), 2.70 (m, 1 H, H_{6e}, J = 18.2, 5.0, 1.6 Hz), 2.20 (m, 1 H, H_{6a}, J = 18.2, 5.0, 1.6 Hz); ^{13}C NMR (CD_3OD, 50.3 MHz) δ 166.7, 139.1 (C_2), 130.2 (C_1), 72.6 (C_5), 68.4 (C_4), 67.3 (C_3), 52.4 (OCH_3), 31.5 (C_6). Anal. Calcd for $C_8H_{12}O_5$: C, 51.06; H, 6.43. Found: C, 50.57; H, 6.41.

Methyl 3,4-*O*-Isopropylidene-(-)-shikimate (2a). Methyl shikimate (0.86 g, 4.6 mmol) was added to a solution of 12 mL

(19) Grindley, T. B.; Thangarasa, R. *Can. J. Chem.* **1990**, *68*, 1007-1019.
(20) David, S.; Hanessian, S. *Tetrahedron* **1985**, *41*, 643-663.
(21) Delfourne, E.; Despeyroux, P.; Gorrichon, L.; Véronique, J. *J. Chem. Res., Synop.* **1991**, 56-57.
(22) Kuo-Long, Yu; Fraser-Reid, B. *Tetrahedron Lett.* **1988**, *29*, 979-982.
(23) Chouinard, P. M.; Bartlett, P. A. *J. Org. Chem.* **1986**, *51*, 75-78.

of 2,2-dimethoxypropane and 24 mg (cat.) of camphorsulfonic acid. After 15 min at room temperature the solution was neutralized with saturated $NaHCO_3$ and extracted with ether. The organic phase was dried and concentrated, and the crude product was purified by silica gel column chromatography (eluant ethyl acetate–petroleum ether (1:1)) to give **2a** (1g, 96%) as a white solid: mp 185 °C; ^1H NMR ($CDCl_3$, 200 MHz) δ 6.90 (m, 1 H, H_2, J = 3.7 Hz), 4.73 (m, 1 H, H_3, J = 6.2, 3.7 Hz), 4.08 (dd, 1 H, H_4, J = 7.5, 6.2 Hz), 3.88 (m, 1 H, H_5, J = 8, 7.5, 4.5 Hz), 3.75 (s, 3 H), 2.79 (m, 1 H, H_6, J = 17.5, 4.5 Hz), 2.22 (m, 1 H, $H_{6'}$, J = 17.5, 8 Hz), 1.44, 1.39 (2s, 2 × 3 H); ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ 166.7, 134.1 (C_2), 130.3 (C_1), 109.6, 77.6 (C_4), 72.2 (C_3), 68.4 (C_5), 52.1, 29.2 (C_6), 27.9, 25.7; mass spectrum (EI) m/z 229 (MH^+, 0.5), 109 (51), 59 (52), 43 (100).

Methyl 5-*O*-Acetyl-3,4-*O*-isopropylidene-(−)-shikimate (3a). To a solution of 1 g (4.4 mmol) of **2a** in 20 mL of methylene chloride was added 0.55 g (4.5 mmol) of 4-(dimethylamino)pyridine and 0.4 mL (4.4 mmol) of acetic anhydride. The solution was stirred for 2 h at rt and then diluted with water and extracted with CH_2Cl_2, and the organic phase dried. The solvent was evaporated to give 1.18 g (100%) of the product as a white solid: mp 72–74 °C; ^1H NMR ($CDCl_3$, 200 MHz) δ 6.89 (m, 1 H, H_2, J = 3.5, 1.7 Hz), 5.14 (m, 1 H, H_5, J = 4.6, 6.7, 6.4 Hz), 4.72 (m, 1 H, H_3, J = 3.5, 6.3 Hz), 4.21 (dd, 1 H, H_4, J = 6.3, 6.4 Hz), 3.75 (s, 3 H), 2.77 (m, 1 H, H_6, J = 1.7, 4.6, 17.7 Hz), 2.32 (m, 1 H, $H_{6'}$, J = 1.7, 6.7, 17.7 Hz), 2.05 (s, 3 H), 1.39, 1.37 (2s, 2 × 3 H); ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ 170.2, 166.4, 134.2 (C_2), 129.5 (C_1), 110.0, 74.0 (C_4), 71.9 (C_3), 69.9 (C_5), 52.1, 27.8, 26.4 (C_6), 26.0, 21.1. Anal. Calcd for $C_{13}H_{18}O_6$: C, 57.77; H, 6.71. Found: C, 57.32; H, 6.70.

Methyl 5-*O*-Acetyl-(−)-shikimate (4a). To a solution (33 mL) of acetic acid–water–THF (19.5:10.5:3) was added under stirring 1.6 g (5.9 mmol) of acetal **3a**. The mixture was heated to 70 °C for 6 h, the solvent was evaporated, and the crude product was purified by HPLC chromatography (eluant ethyl acetate–petroleum ether (7:3)) to give 1.29 g (94%) of **4a**: ^1H NMR ($CDCl_3$, 250 MHz) δ 6.82 (m, 1 H, H_2, J = 1.8, 3.7 Hz), 5.15 (m, 1 H, H_5, J = 7.7, 5.7, 5.2 Hz), 4.39 (m, 1 H, H_3, J = 3.7, 4.1 Hz), 3.84 (dd, 1 H, H_4, J = 7.7, 4.1 Hz), 3.73 (s, 3 H), 3.62 (s, 2 H, OH), 2.82 (m, 1 H, H_6, J = 18.5, 5.2, 1.8 Hz), 2.28 (m, 1 H, $H_{6'}$, J = 18.5, 5.7, 1.8 Hz), 2.05 (s, 3 H); ^{13}C NMR ($CDCl_3$, 62.9 MHz), δ 171.2, 166.7, 136.8 (C_2), 129.4 (C_1), 69.9 (C_5), 69.1 (C_4), 66.1 (C_3), 52.2, 28.1 (C_6), 21.2. Anal. Calcd for $C_{10}H_{14}O_6$: C, 52.17; H, 6.13. Found: C, 51.53; H, 6.04.

Methyl 5-Acetyl-3-*O*-(dimethoxytrityl)-(−)-shikimate (6a). To a solution of 1.29 g (5.6 mmol) of **4a** in 100 mL of benzene was added 1.4 g (5.6 mmol) of dibutyltin oxide. The solution was refluxed under stirring in a Dean-Stark trap (1 h). Solvent was evaporated to give crude product **5a** as a white solid which was used without further purification. To a solution of 2.58 g (5.6 mmol) of this compound in 50 mL of DMF was added 2.11 g (5.6 mmol) of dimethoxytrityl chloride. The mixture was stirred for 30 min and then diluted with water and extracted with ether (three times). The organic phase was dried and evaporated, and the crude product was purified by HPLC chromatography (eluant ethyl acetate–petroleum ether (2:8)) to give 2.03 g (68%) of **6a** as a pale yellow solid: mp 66 °C; ^1H NMR ($CDCl_3$, 250 MHz) δ 7.66–6.66 (m, 13 H), 7.02 (m, 1 H, H_2, J = 2.0, 1.5 Hz), 5.45 (m, 1 H, H_5, J = 5.2, 4.1, 6.3 Hz), 4.51 (m, 1 H, H_3), 3.28, 3.27 (2 s, 9 H), 3.07 (m, 1 H, H_4), 2.94 (m, 1 H, H_6, J = 18.5, 5.2 Hz), 2.58 (d, 1 H, OH, J = 4.0 Hz), 2.45 (m, 1 H, $H_{6'}$, J = 18.5, 4.1, 1.5 Hz), 1.48 (s, 3 H); ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ 169.4, 166.4, 159.6, 159.5, 146.2, 137.7 (C_2), 136.6, 136.4, 129.8 (C_1), 113.8, 88.3, 70.0 (C_5), 69.6 (C3), 67.0 (C_4), 54.8, 51.5, 28.4 (C6), 27.4, 20.6. Anal. Calcd for $C_{31}H_{32}O_8$: C, 69.9; H, 6.06. Found: C, 68.4; H, 6.07.

Methyl 4,5-*O*-Diacetyl-3-*O*-(dimethoxytrityl)-(−)-shikimate (7a). 4-(Dimethylamino)pyridine (0.122 g, 1 mmol) and acetic anhydride (100 μL, 1 mmol) were added to a stirred solution of **6a** (0.46 g 0.87 mmol) in CH_2Cl_2 (25 mL). The mixture was heated to 50 °C for 1 h, cooled, diluted with water, and extracted with CH_2Cl_2. The organic phase was dried over $MgSO_4$ and evaporated to give fully protected methyl shikimate **7a** (0.5 g 100%) as a pale yellow solid: mp 68–70 °C; ^1H NMR (C_6D_6, 250 MHz) δ 8.00–6.6 (m, 13 H), 6.44 (m, 1 H, H_2, J = 0.6, 1.8, 2.5, 1.0 Hz), 5.51 (ddd, 1 H, H_5, J = 5, 3.5, 6.4 Hz), 5.20 (ddd, 1 H, H_4, J = 6.4, 3.6, 0.6 Hz), 4.68 (m, 1 H, H_3, J = 3.6, 2.5, 1.8, 1 Hz), 3.28 (s, 6 H), 3.27 (s, 3 H), 2.82 (m, 1 H, H_6, J = 19, 2.5, 5, 2.5 Hz), 2.46 (m, 1 H, $H_{6'}$, J = 19, 3.5, 1.0, 1.0 Hz), 1.77 (s, 3 H), 1.48 (s, 3 H); ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ 169.4, 168.9, 166.2, 159.5, 138.7 (C_2), 136.7, 136.6, 128.5 (C_1), 113.7, 87.9, 69.5 (C_4), 67.7 (C_5), 67.5 (C_3), 54.8, 51.3, 28.2 (C_6), 20.7, 20.4; IR ($CHCl_3$) 1738, 1720, 1606, 1250 cm^{-1}. Anal. Calcd for $C_{33}H_{34}O_9$: C, 68.98; H, 5.96. Found: C, 68.06; H, 5.96.

Methyl 4,5-*O*-Diacetyl-(−)-shikimate (8a). A 0.5-g (0.87 mmol) portion of the methyl 4,5-*O*-diacetyl-3-*O*-(dimethoxytrityl)shikimate was added to a solution of acetic acid in water (80%, 10 mL). The mixture was stirred for 15 min and then the solvent evaporated. The crude product was purified by HPLC chromatography (eluant ethyl acetate–petroleum ether (7:3)) to give 0.21 g (89%) of the desired compound: ^1H NMR (C_6D_6, 250 MHz) δ 6.88 (m, H_2), 5.42 (m, 1 H, H_5, J = 7.8, 5.5, 5.0 Hz), 5.18 (dd, 1 H, H_4, J = 7.8, 4.3 Hz), 4.40 (m, 1 H, H_3), 3.32 (s, 3 H), 2.81 (m, 1 H, H_6, J = 1.6, 5, 18 Hz), 2.50 (s, 1 H, OH), 2.40 (m, 1 H, $H_{6'}$, J = 1.5, 5.5, 18 Hz), 2.10, 2.04 (2s, 2 × 3 H); ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ 170.4, 169.9, 166.3, 136.3 (C_1), 129.3 (C_2), 70.2 (C_4), 66.9 (C_3), 65.0 (C_5), 52.2, 28.1 (C_6), 21.0, 20.9; MS (DCI, NH_3) m/z 290 (M + 18, 100), 110 (21).

Methyl 4,5-*O*-Diacetyl-(−)-shikimate Dibenzyl 3-Phosphate (9a). Tetrazole (0.115 g, 1.65 mmol) was added under argon to a stirred solution of dibenzyl *N,N*-diethylphosphoramidite (0.26 g, 0.77 mmol) and of monoalcohol **8a** (0.21 g, 0.77 mmol) in dry CH_2Cl_2 (20 mL). The reaction mixture was stirred for 2 h at room temperature, and then it was cooled to −40 °C and a solution of *m*-CPBA (0.27 g, 1.54 mmol) in CH_2Cl_2 (4 mL) was rapidly added. The reaction was allowed to continue for 2 h, and then it was diluted with a saturated solution of Na_2SO_3 (25 mL) and washed with $NaHCO_3$ (25 mL) and NaCl (25 mL). The organic phase was dried ($MgSO_4$) and evaporated and the crude product purified by HPLC chromatography (eluant ethyl acetate–petroleum ether (1:1)). Product **9a** was obtained as a clear oil (0.304 g, 74%): $[\alpha]^{20}_D$ −88 (*c*, 0.52, $CHCl_3$); ^1H NMR ($CDCl_3$, 250 MHz) δ 7.34 (s, 10 H), 6.74 (m, 1 H, H_2, J = 4.0, 2.0 Hz), 5.24 (m, 3 H), 5.04 (dd, 4 H), 3.27 (s, 3 H), 2.9 (m, 1 H, H_6, J = 18.7, 5.5, 2.0 Hz), 2.36 (m, 1 H, $H_{6'}$, J = 18.7, 6.5 Hz), 2.03, 1.95 (2s, 2 × 3H); ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ 170.0, 169.8, 165.7, 132.4 (d, C_2), 131.5 (C_1), 135.7, 128.6, 128.1, 128.0, 70.2 (d, C_3), 69.7 (d, CH_2Ph), 68.8 (d, C_4), 66.2 (C_5), 52.3 (OCH_3), 29.0 (C_6), 20.9, 20.7; ^{31}P NMR ($CDCl_3$, 81 MHz) δ −1.16; IR ($CHCl_3$) 1739, 1250, 1020, 980 cm^{-1}; MS ((DCI, NH_3) m/z 550 (M + 18, 69), 553 (MH^+, 16), 290 (100), 255 (79).

Shikimate (−)-3-Phosphate (10a). A solution of 0.2 g (0.38 mmol) of tetraester **9a**, in 3 mL CH_2Cl_2 at 0 °C, was treated with a precooled solution of bromotrimethylsilane (0.2 mL, 1.5 mmol). The mixture was stirred for 1 h, the solvent was evaporated, and the crude product was dissolved in 5 mL of water. It was allowed to stand for 10 min at 0 °C and then extracted with $CHCl_3$. The aqueous phase was lyophilized to give 0.106 g (80%) of methyl 4,5-*O*-diacetyl-shikimate 3-phosphate. A solution of NaOH (1 N, 4 mL) was added to the phosphate. After being stirred for 3 h at 0 °C the mixture was acidified at pH = 8 with HCl and then lyophilized. The crude product was applied to an anion-exchange column DEAE Sephadex A-25, HCO_3^- form) and eluted with a linear gradient of triethylammonium bicarbonate (0–0.5 M, pH = 8.2). The fractions absorbing at λ = 240 nm were combined and lyophilized. Cation exchange (Dowex 50W-X8, Na^+ form) and lyophilization afforded 92 mg (99%) of (−)-shikimate 3-phosphate as the trisodium salt: $[\alpha]^{20}_D$ −56.2 (*c* 0.4, H_2O); ^1H NMR (D_2O, 250 MHz) δ 6.73 (m, 1 H, H_2), 4.85 (m, 1 H, H_3), 4.13 (m, 1 H, H_5, J = 4.7, 5.2, 7.5 Hz), 3.93 (dd, 1 H, H_4, J = 4.2, 7.5 Hz), 2.72 (m, 1 H, H_6, J = 1.6, 4.7, 18 Hz), 2.22 (m, 1 H, $H_{6'}$, J = 1.5, 5.2, 18 Hz); ^{13}C NMR (D_2O, 62.9 MHz) δ 175.1, 135.6 (C_1), 135.3 (d, C_2) 73.0 (d, C_3), 72.6 (d, C_4), 69.4 (C_5), 32.9 (C_6); ^{31}P NMR (D_2O, 81 MHz) δ 1.15.

Methyl 3,4-*O*-benzylidene-(−)-quinate (2b) was obtained in 72% yield from D-(−)-quinic acid following the procedure described by Berchtold et al.[10]

Methyl 3,4-*O*-Benzylidene-1,5-*O*-diacetyl-(−)-quinate (3b). A total of 1.4 g (12 mmol) of 4-(dimethylamino)pyridine and 1.08 mL (12 mmol) of acetic anhydride was added to a solution of 1.6 g (5.71 mmol) of ester **2b** in 40 mL of methylene chloride. The solution was stirred for 2 h at room temperature and then diluted with water and extracted with CH_2Cl_2 (two times) and the organic phase dried ($MgSO_4$). The solvent was evaporated to give 1.79

g (83%) of the products as a white solid: mp 132–133 °C; ^{1}H NMR ($CDCl_3$, 250 MHz), δ 7.50 (m, 2 H, Ar), 7.37 (m, 3 H, Ar), 5.83 (s, 1 H), 5.33 (m, 1 H, H_5, J = 11.1, 4.5, 6.7 Hz), 4.50 (m, 1 H, H_3, J = 6.5, 3.1, 5.0 Hz), 4.24 (dd, 1 H, H_4, J = 6.7, 6.5 Hz), 3.71 (s, 3 H, OCH_3), 2.87 (m, 1 H, H_2, J = 16.0, 3.1, 2.3 Hz), 2.46 (m, 1 H, $H_{2'}$, J = 16.0, 5.0 Hz), 2.43 (m, 1 H, H_6, J = 13.5, 4.5, 2.3 Hz), 2.06 (s, 3 H), 2.05 (s, 3 H), 1.88 (m, 1 H, $H_{6'}$, J = 13.5, 11.1 Hz); ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ 171.4, 170.1, 137.0, 129.6, 128.4, 126.9, 104.4, 78.1 (C_1), 76.0 (C_5), 75.0 (C_4), 71.0 (C_3), 52.8 (OCH_3), 34.5 (C_6), 30.7 (C_2), 21.1, 20.9; IR 1740 cm^{-1}; mass spectrum (EI) m/z 378 (M^+, 17), 136 (12), 105 (53), 43 (100). Anal. Calcd for $C_{19}H_{22}O_8$: C, 60.31; H, 5.86. Found: C, 60.33; H, 5.82.

Methyl 1,5-*O*-Diacetyl-(−)-quinate (4b). A 1.79-g (4.73-mmol) portion of **3b** was added to a solution of acetic acid in water (80%, 50 mL) and kept under stirring at room temperature (12 h). After evaporation of the solvent and purification by silica gel chromatography (eluant ethyl acetate), 1.27 g (92%) of compound **4b** was obtained as a white solid: mp 114–115 °C; $[\alpha]^{20}_D$ −27.5 (c 1, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 250 MHz) δ 5.22 (m, 1 H, H_5, J = 10.5, 4.5, 9.0 Hz), 4.19 (m, 1 H, H_3, J = 3.0, 3.8, 3.5 Hz), 3.68 (s, 3 H), 3.60 (dd, 1 H, H_4, J = 9.0, 3.0 Hz), 3.05 (s, 2 H), 2.57 (m, 1 H, H_2, J = 15.5, 3.5, 2.5 Hz), 2.43 (m, 1 H, H_6, J = 13.5, 4.5, 2.5 Hz), 2.14 (dd, 1 H, H_2, J = 15.5, 3.8 Hz), 2.06 (s, 3 H), 2.05 (s, 3 H), 1.82 (dd, 1 H, H_6, J = 13.5, 10.5 Hz); ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ 171.5, 171.2, 170.3, 79.4 (C_1), 72.6 (C_4), 69.9 (C_5), 68.5 (C_3), 52.7, 36.1 (C_6), 33.8 (C_2), 21.1; IR (KBr) 3480, 3400, 1750, 1740 cm^{-1}; mass spectrum (EI) m/z 291 (MH^+, 3), 273 (19), 89 (27), 61 (16), 43 (100). Anal. Calcd for $C_{12}H_{18}O_8$: C, 49.65; H, 6.25. Found: C, 49.82; H, 6.24.

Methyl 1,5-*O*-Diacetyl-3-*O*-trityl-(−)-quinate (6b). Stannylene derivative **5b** was obtained as previously described in the shikimate series. Trityl chloride (2.39 g, 8.6 mmol) was added under stirring to a solution of compound **5b** (4.27 g, 8.2 mmol) in 70 mL of DMF. The solution was heated to 45 °C for 1 h, and then aqueous dioxane (4%, 16 mL) was added and the mixture kept for 1 h at 45 °C. After dilution with water and extraction with ether, the organic phase was dried over $MgSO_4$ and the solvent was evaporated. Crude product was purified by silica gel column chromatography (eluant ethyl acetate–petroleum ether (3:7)). Compound **6b** was obtained (2.8 g, 65%) as a white solid: mp 112 °C; ^{1}H NMR ($CDCl_3$, 250 MHz) δ 7.49 (m, 5 H), 7.30 (m, 10 H), 4.94 (q, 1 H, H_5, J = 4, 3.4 Hz), 4.29 (ddd, 1 H, H_3, J = 3, 10.5, 4.5 Hz), 3.55 (s, 3 H), 2.72 (m, 1 H, H_2, J = 13.5, 4.5, 1.5 Hz), 2.57 (m, 1 H, H_4, J = 3, 4, 2.5 Hz), 2.20 (d, 1 H, OH, J = 2.5 Hz), 2.16 (m, 2 H, H_6, $H_{6'}$), 2.03 (s, 3 H), 1.99 (dd, 1 H, $H_{2'}$, J = 13.5, 10.5), 1.84 (s, 3 H); ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ 171.6, 169.7, 168.9, 144.4, 127.5, 128.8, 128.0, 88.0, 79.0 (C_1), 69.9 (C_5), 69.3 (C_3), 67.5 (C_4), 52.1, 32.9 (C_2), 32.8 (C_6), 21.1, 20.8; IR 3440, 1740 cm^{-1}. Anal. Calcd for $C_{31}H_{32}O_8$: C, 69.91; H, 6.06; O, 24.03. Found: C, 69.48; H, 6.23; O, 23.90.

Methyl 1,4,5-*O*-Triacetyl-(−)-quinate (8b). 4-(Dimethylamino)pyridine (0.147 g, 1.2 mmol) and acetic anhydride (120 μL, 1.2 mmol) were added to a stirred solution of **6b** (0.534 g, 1 mmol) in CH_2Cl_2 (30 mL). The mixture was heated to 50 °C for 1 h, cooled, diluted with water, and extracted with CH_2Cl_2. The organic phase was dried over $MgSO_4$ and evaporated to give methyl 1,4,5-*O*-triacetyl-3-*O*-trityl-(−)-quinate (**7b**) as a white solid (0.576 g, 100%), mp 154 °C, which was used without further purification for the following detritylation step. To a solution of 0.5 g (0.86 mmol) of this compound in 5 mL of CH_2Cl_2 was added 0.284 g (3.44 mmol) of trichloroacetic acid. The solution was stirred for 15 min and then diluted with water and extracted with CH_2Cl_2. The organic phase was dried ($MgSO_4$) and the solvent evaporated. After purification by HPLC chromatography (eluant ethyl acetate–petroleum ether (6:4)) the monoalcohol **8b** was obtained (0.241 g, 87%) as a white solid: mp 120 °C; ^{1}H NMR ($CDCl_3$, 250 MHz) δ 5.47 (m, 1 H, H_5, J = 9.6, 4.5, 10.7 Hz), 4.95 (dd, 1 H, H_4, J = 9.6, 3.6), 4.32 (q, 1 H, H_3, J = 3.6, 3, 3.5 Hz), 3.78 (s, 3 H), 3.35 (s, 1 H), 2.64 (m, 1 H, H_2, J = 15.4, 3, 3.5 Hz), 2.53 (m, 1 H, H_6, J = 13.7, 2, 4.5 Hz), 2.24 (dd, 1 H, $H_{2'}$, J = 15.4, 3.5 Hz), 2.11, 2.10, 2.0 (3 s, 3 × 3 H), 1.90 (dd, 1 H, $H_{6'}$, J = 13.7, 10.7 Hz); ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ 171.1, 170.2, 170.0, 169.9, 79.1 (C_1), 74.1 (C_4), 67.0 (C_3), 66.6 (C_5), 52.7, 36.7 (C_6), 33.7 (C_2), 21.7, 21.1, 20.9; IR ($CHCl_3$), 3400, 1740 cm^{-1}. Anal. Calcd for $C_4H_{20}O_9$: C, 50.6; H, 6.07; O, 43.33. Found: C, 50.24; H, 6.03; O, 42.99.

Methyl 1,4,5-Triacetyl-(−)-quinate Dibenzyl 3-Phosphate (9b). It was obtained as previously described for the shikimate derivative as a clear oil (79%): $[\alpha]^{20}_D$ −25.6 (c 0.47, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 250 MHz) δ 5.53 (m, 1 H, H_5, J = 10, 10.8, 4.5 Hz), 5.2–4.8 (m, 6 H, 2 CH_2, H_3, H_4), 3.7 (s, 3 H), 2.82 (m, 1 H, H_2, J = 15.6, 3.3 Hz), 2.54 (m, 1 H, H_6, J = 13.6, 4.5, 3 Hz), 2.32 (ddd, 1 H, $H_{2'}$, J = 15.6, 3.2, 2 Hz), 2.01, 1.94, 1.91 (3s, 3 × 3 H), 1.81 (dd, 1 H, $H_{6'}$, J = 13.6, 10.8 Hz); ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ 170.8, 170.3, 170.1, 169.7, 135.6, 128.7, 128.1, 128.0, 78.3 (C_1), 73.1 (d, C_3), 72.3 (d, C_4), 69.4 (m) 65.9 (C_5), 52.9, 37.3 (C_2), 32.6 (C_6), 20.9, 20.8, 20.7; ^{31}P NMR (C_6D_6, 81 MHz) δ -0.16; mass spectrum (EI) m/z 594 (M^+, 14), 593 (44), 350 (34), 178 (100).

(−)-Quinate 3-Phosphate Tris(triethylammonium) Salt (10b). A solution of 0.13 g (0.22 mmol) of tetraester **9b** in 2 mL of CH_2Cl_2 at 0 °C was treated with a precooled solution of bromotrimethylsilane (0.116 mL, 0.88 mmol). The mixture was stirred for 1 h, solvent was evaporated, and the crude product was dissolved in 4 mL of water and allowed to stand for 10 min at 0 °C and then extracted with $CHCl_3$. The aqueous phase was lyophilized to give 72 mg (80%) of methyl (−)-1,4,5-*O*-triacetyl-quinate 3-phosphate: $[\alpha]^{20}_D$ −12.5 (c 0.5, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 250 MHz), δ 7.37 (s, 2 H), 5.50 (m, 1 H, H_5, J = 10, 10.5 MHz), 4.89 (m, 2 H), 3.79 (s, 3 H), 2.72 (m, 1 H, H_2, J = 15 Hz), 2.50 (m, 1 H, H_6, J = 13.3 Hz), 2.37 (dd, 1 H, $H_{2'}$, J = 15, 4.2 Hz), 2.14, 2.09, 2.03 (3s, 3 × 3 H), 1.77 (dd, 1 H, $H_{6'}$, J = 13.3, 10.5 Hz); ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ 171.8, 171.4, 170.7, 170.0, 78.6 (C_1), 72.4 (C_3), 72.3 (C_4), 66.2 (C_5), 52.9, 37.4 (C_2), 31.9 (C_6), 21.0, 20.9, 20.6; ^{31}P NMR δ −0.01.

A solution of NaOH (1 N, 3.6 mL) was added to the phosphate previously obtained (0.15 g, 0.36 mmol). After being stirred for 3 h at 0 °C the mixture was acidified to pH = 8 with HCl and then lyophilized. The crude product was purified with an anion-exchange column (DEAE Sephadex A-25, HCO_3^- using a linear gradient of triethylammonium bicarbonate (0–0.5 M pH = 8.2). Fractions containing the quinic structure were combined and lyophilized to afford 88 mg of the compound **10b**: ^{1}H NMR (D_2O, 200 MHz) δ 4.55 (m, 1 H, H_3), 3.98 (m, H_5, J = 9.5, 8.7, 4.5 Hz), 3.55 (m, 1 H, H_4), 3.14 (q, 18 H, CH_2N), 2.03 (m, 3 H, H_2, H_2H_6), 1.81 (dd, 1 H, $H_{6'}$, J = 13.8, 9.5 Hz), 1.21 (t, 27 H, CH_3); ^{13}C NMR (D_2O, 62.9 MHz) δ 183.0, 78.3 (C_1), 76.6 (d, C_3), 76.5 (d, C_4), 69.4 (C_5), 42.5 (C_2), 39.3 (C_6); ^{31}P (D_2O, 81 MHz) δ 2.51.

Supplementary Material Available: ^{13}C and ^{31}P NMR spectra of compounds **9a**, **10a**, **9b**, and **10b** (8 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.