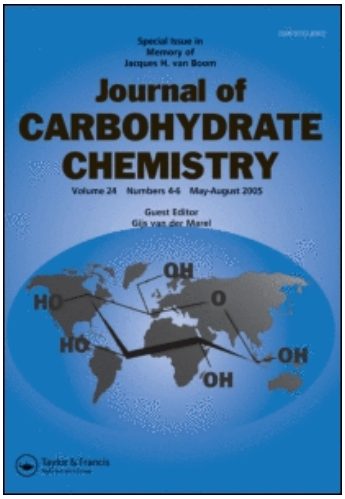

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SYNTHESIS OF METHYL (-)-SHIKIMATE FROM D-LYXOSE

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ABSTRACT

Methyl (-)-shikimate (1), the methyl ester of naturally occurring (-)-shikimic acid, has been synthesized from D-lyxose. The key reaction in the synthesis was a one-step construction of the cyclohexane ring by simultaneous C-C bond formation of both terminal carbons of a D-lyxose derived synthon (7) with the methylene carbon of dimethyl malonate. The cyclization products (9) and (9') were transformed to some derivatives of shikimic acid.

INTRODUCTION

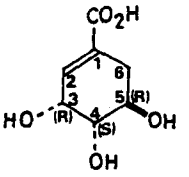
(-)-Shikimic acid, (3R,4S,5R)-3,4,5-trihydroxy-1-cyclohexene-1-carboxylic acid, is widely found in nature, and plays an important role in biosynthetic pathway from carbohydrates to essential aromatic amino acids.[1,2] In addition to extensive efforts on the elucidation of the biochemical role of shikimic acid, studies directed to the synthesis of this polyhydroxylated

cyclohexene-1-carboxylate have been carried out in several laboratories over the past thirty years. The first total synthesis of shikimic acid was achieved in 1959 by Smissman and collaborators.[3] Soon after, several syntheses of the natural product and related compounds, such as quinic acid and others, were published.[4-6] Although the early synthesis of shikimic acid in racemic form featured a Diels-Alder cycloaddition as a key step in the construction of the cyclohexene carboxylate skeleton, syntheses employing some aldoses as optically active starting materials were also reported. Bestmann and Heid described syntheses of optically pure shikimic acid and quinic acid from D-arabinose.[7] Kitagawa and collaborators reported a synthesis of shikimic acid from D-mannose.[8] Recently, Fleet and collaborators achieved another synthesis of shikimic acid from D-mannose by employing intramolecular olefination as s key step.[9]

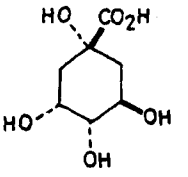
From our synthetic efforts on optically active carbocyclic compounds from aldoses,[10] we have developed a synthesis of methyl shikimate (1) from D-lyxose.[11] The present synthesis involves a one-step C-C bond formation of 2,3,4-tri-O-benzyl-5-O-mesyl-aldehyde-D-lyxose (7) with the methylene site of dimethyl malonate according to a method recently developed in our laboratory.[10a] The advantage of the present approach over other reported carbohydrate-mediated syntheses of shikimic acid, is the introduction of the carboxyl side chain simultaneously with the cyclohexene ring formation step.

RESULTS AND DISCUSSION

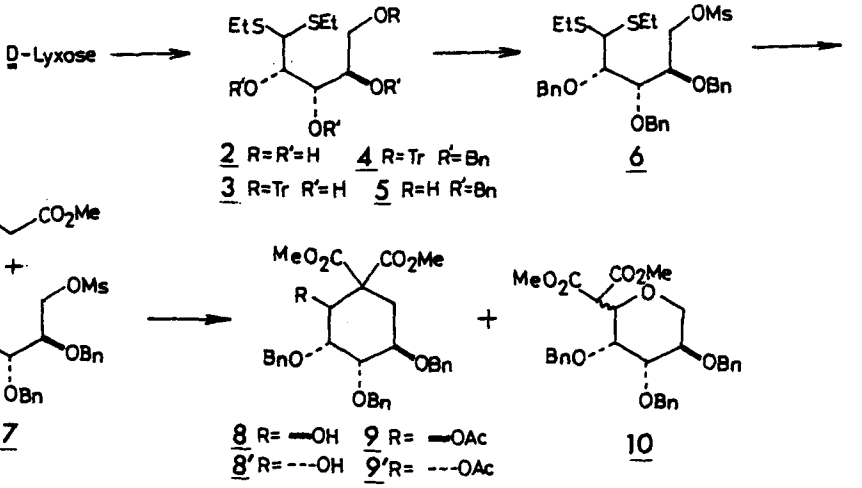
D-Lyxose was first converted to the diethyl dithioacetal 2 according to the reported procedure.[12] Preferential protection of the primary hydroxyl group in 2 as a trityl ether with trityl chloride provided the 5-O-trityl derivative 3 in 81% yield. The



(-)-Shikimic acid



(-)-Quinic acid



secondary hydroxyl groups in 3 were then benzylated with benzyl bromide in the presence of sodium hydride providing the 2,3,4-tri-O-benzyl derivative 4. This compound was hydrolyzed with p-toluenesulfonic acid, for removal of the O-trityl group, furnishing compound 5 in 79% yield. Mesylation of 5 with mesyl chloride in pyridine [5 to 6], dethioacetalization of 6 with mercury(II) chloride in aqueous acetonitrile [6 to 7], and successive treatment of 7 with dimethyl malonate in the presence of sodium hydride in THF at ambient temperature followed by acetylation gave three products 9, 9' and 10, which were separated by repeated silica gel chromatography, in 17%, 15% and 8% yield from 5, respectively.[13] The structures of the desired cyclohexane derivatives 9 and 9' were elucidated from their ^{1}H NMR spectra. In the ^{1}H spectrum of 9, a doublet appeared at δ 6.10 with J= 3 Hz. The signal was attributable to a proton on a carbon bearing an acetoxyl group (H-2). In comparison, that of the compound 9' appeared at δ 5.93 with J=4.5 Hz. From these data, we could not assign the configurations of H-2 of 9 and 9' unambiguously. However, we tentatively assign them as depicted based on the fact that the acetoxyl methyl signal of 9 (axial acetoxyl group) appeared at δ 1.95 and that of 9' (equatorial acetoxyl group) appeared at δ 1.93. Generally, an axial acetoxyl group signal tends to possess a large δ value than that of an equatorial one.[14] As observed in our previous work,[10a] formation of a C-glycoside (10) also occurred in the cyclization reaction. Although 10 is a single component, the configuration of the newly introduced carbon could not be established from the ^{1}H NMR spectrum. Thermal demethoxycarbonylation of 9 by refluxing in aqueous DMSO containing NaCl from 125 to 155 °C gave cyclohexene-1-carboxylate 11 in 28% yield (43% of 9 was recovered). The reaction was accompanied by β-elimination of the acetoxyl group. The compound 11 was identical with that derived from natural (-)-shikimic acid by 1) esterification with diazomethane and 2) O-benzylation with benzyl bromide, in all

respects ($[\alpha]_D$, IR and ^{1}H NMR). In order to complete the synthesis of 1, the benzyl groups in 9 and 9' were removed by Hanessian's conditions.[15] The O-debenzylated products were acetylated to provide the tetraacetates 12 and 12' in 54% and 71% yield, respectively. Demethoxycarbonylation of 12 and 12' accompanied by β-elimination of the β-acetoxyl groups, as described in conversion of 9 to 11, gave the triacetyl derivative of 1, compound 13, in 17% from 12 (recovery of 12, 47%) and in 13% from 12' (recovery of 12', 15%). The structure of 13 was confirmed by comparison of the ^{1}H NMR spectrum with that of the natural shikimic acid derived compound.[16] Prolonged heating or higher reaction temperature decreased the yield of 13. Finally, O-deacetylation of 13 with sodium methoxide in methanol gave methyl (-)-shikimate (1) in 42% yield after recrystallization. The melting point of the synthetic 1 was identical with that derived from natural (-)-shikimic acid. The $[\alpha]_D$ value of 1 also coincided with that derived from natural shikimic acid as reported.[17]

EXPERIMENTAL

General Procedures. Reactions were carried out at ambient temperature unless otherwise stated. Solutions were concentrated under diminished pressure below 40 °C (bath temperature). Melting points were determined with a Mitamura Riken micro apparatus and are uncorrected. Specific rotations were measured in a 1-dm tube with a Jasco DIP-4 polarimeter. Column chromatography was performed with Kieselgel 60 (Merck). TLC was carried out on glass plates coated with Kieselgel 60 GF_{254} (Merck), compounds being detected with UV light and by spraying with sulfuric acid followed by heating. IR spectra were recorded with a Hitachi Model-225 spectrometer (KBr) and with a Jasco Model A-202 spectrometer ($CHCl_3$). ^{1}H NMR spectra were recorded

with a Varian EM-390 spectrometer, and chemical shifts for a $CDCl_3$ solution are recorded in δ values from internal tetramethylsilane. High resolution mass spectra were taken on a Hitachi M-80 mass spectrometer.

N,N-Dimethylformamide (DMF) was dried over CaH_2 and then distilled. Pyridine was distilled over NaOH. Tetrahydrofuran (THF) was distilled over $LiAlH_4$ and then over sodium-benzoquinone.

5-O-Trityl-D-lyxose Diethyl Dithioacetal (3). To a solution of D-lyxose diethyl dithioacetal (2),[12] (2.50 g, 9.8 mmol) in pyridine (30 mL) were added trityl chloride (4.08 g, 14.6 mmol) and 4-dimethylaminopyridine (0.24 g, 2.0 mmol). The mixture was stirred at 70 °C for 14 h and concentrated. The residue was partitioned between dichloromethane (200 mL) and water (200 mL), and the aqueous layer was extracted with dichloromethane (200 mL x 3). The organic layers were dried over Na_2SO_4 and concentrated. The residue was chromatographed on silica gel (100 g, toluene containing 1% triethylamine, then ethyl acetate: toluene=1:15 containing 1% triethylamine). Fractions corresponding to R_f 0.24 (ethyl acetate:toluene=1:5) were concentrated to afford 3 (3.94 g, 81%) as a pale yellow syrup. 3: $[\alpha]_D^{18}$+6.0° (c 1.17, $CHCl_3$); IR $\nu_{max}^{CHCl_3}$ 3540, 3020, 1490, 1450, 1220 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.28 (6H, t, J=8 Hz, 2 x $SCH_2\underline{CH_3}$), 2.50-2.90 (7H, m, 2 x $S\underline{CH_2}CH_3$, 3 x OH), 3.23-4.21 (6H, m, H-1,2,3,4,5,5'), 7.10-7.52 (15H, m, $C(C_6H_5)_3$). High resolution mass spectrum, calcd for $C_{28}H_{34}O_4S_2$: m/z M, 498.1896, found: M, 498.1896.

2,3,4-Tri-O-benzyl-D-lyxose Diethyl Dithioacetal (5). To a suspension of sodium hydride (60% emulsion in mineral oil, 1.42 g, 35.4 mmol, washed with hexane and dried) in DMF (5 mL) was added a DMF (40 mL) solution of 3 (4.90 g, 9.8 mmol), and the mixture was stirred for 20 min. Benzyl bromide (4.2 mL, 35.4 mmol) was added and the mixture was stirred for 17 h in dark. After addition of EtOH (20 mL) and stirred for 30 min, the solution was concentrated. The residue was partitioned between dichloromethane (800 mL) and water (500 mL), and the organic layer was

washed with saturated aqueous NaCl (500 mL). The organic layer was dried over Na_2SO_4 and concentrated to afford crude 4 (R_f 0.59, ethyl acetate:hexane=1:5), which was used for the next step without purification. To a solution of the crude 4 in a mixture of methanol (40 mL) and ethyl acetate (40 mL) was added p-toluenesulfonic acid monohydrate (3.74 g, 19.7 mmol). The mixture was stirred for 1.5 h, neutralized by addition of saturated aqueous $NaHCO_3$ and concentrated. The residue was partitioned between ethyl acetate (800 mL) and water (500 mL) and the organic layer was washed with saturated aqueous NaCl (500 mL). The organic layer was dried over Na_2SO_4 and concentrated. The residue was chromatographed on silica gel (300 g, toluene and then ethyl acetate:toluene=1:20), and fractions corresponding to R_f 0.36 (ethyl acetate:toluene= 1:10) were concentrated to afford 5 (4.08 g, 79%) as a colorless syrup. 5: $[\alpha]_D^{17}$-25.2° (c 1.23, $CHCl_3$); IR $\nu_{max}^{CHCl_3}$ 3600, 3010, 1205 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.22 (6H, t, J=8 Hz, 2 x $SCH_2\underline{CH_3}$), 2.00-2.17 (1H, m, OH), 2.64, 2.70 (2H x 2, each q, J=8 Hz, 2 x $S\underline{CH_2}CH_3$), 3.79 (2H, d, J=4 Hz, H-5,5'), 4.01-4.32 (3H, m, H-2,3,4), 4.50-4.77 (6H, m, 3 x $O\underline{CH_2}C_6H_5$), 5.02 (1H, d, J=11 Hz, H-1), 7.30, 7.32, 7.35 (15H, each s, 3 x $OCH_2C_6\underline{H_5}$). High resolution mass spectrum, calcd for $C_{30}H_{38}O_4S_2$: m/z M, 526.2208, found: M, 526.2189.

Dimethyl (2S,3R,4S,5R)- (9), (2R,3R,4S,5R)-2-Acetoxy-3,4,5-tris(benzyloxy)cyclohexane-1,1-dicarboxylate and (2S or 2R,3R,4S, 5R)-3,4,5-Tris(benzyloxy)-2-[(bismethoxycarbonyl)methyl]tetrahydropyran (10). To a stirred solution of 5 (1.33 g, 2.52 mmol) in pyridine (30 mL) was added mesyl chloride (0.29 mL, 3.79 mmol) at 0 °C. The mixture was stirred for 90 min and concentrated. The residue was partitioned between dichloromethane (100 mL) and water (100 mL), and the aqueous layer was extracted with dichloromethane (100 mL x 2). The organic layers were dried over Na_2SO_4 and concentrated to give crude 6 (R_f 0.38, ethyl acetate:toluene= 1:5) as a colorless syrup, which was used for the next step without purification.

To a solution of the crude 6 in a mixture of acetonitrile (80 mL) and water (20 mL) were added mercury(II) chloride (2.74 g, 10.1 mmol) and calcium carbonate (1.14 g, 11.4 mmol). The mixture was stirred for 90 min, and the resulting insoluble solids were removed by filtration through a Celite-pad. The filtrate was diluted with dichloromethane (100 mL) and washed with 1 M aqueous KI solution (100 mL x 3). The organic layer was dried over Na_2SO_4 and concentrated to afford crude 7 (R_f 0.28, ethyl acetate:hexane=1:3), which was subjected to the the next step without purification.

To a stirred suspension of sodium hydride (60%, 202 mg, 5.05 mmol, washed with hexane) in THF (20 mL) was added dimethyl malonate (0.58 mL, 5.05 mmol), and the mixture was stirred for 40 min. To the resulting clear solution was added a THF (10 mL) solution of the crude 7 at 0 °C. The mixture was stirred at ambient temperature for 40 min, and water (10 mL) was added. The solution was diluted with saturated aqueous NaCl (150 mL), and extracted with ethyl acetate (150 mL x 3). The organic layers were dried over Na_2SO_4 and concentrated. The residue was chromatographed on silica gel (90 g, ethyl acetate: hexane=1:10 to 1:5), and fractions corresponding to R_f 0.50 to 0.68 were combined and concentrated to afford a mixture of 8, 8' and 10, which, because of a difficult separation, was used directly in the next step. The mixture was acetylated with acetic anhydride (10 mL) in pyridine (10 mL) for 1 h at 60 °C, the reaction mixture was concentrated and the residue partitioned between dichloromethane (100 mL) and water (100 mL). The aqueous layer was extracted with dichloromethane (100 mL x 3), and the organic layers were dried over Na_2SO_4 and concentrated to afford a crude mixture of 9, 9' and 10. The mixture was separated by repeated chromatography on silica gel (50 g, ethyl acetate:toluene=1:5, then three times chromatography with ethyl acetate:toluene=1:20). Finally, 254 mg of 9 (17% from 5), 213 mg of 9' (15%), and 116 mg of 10 (8%) were obtained. Compound 9 was obtained as a colorless

syrup: TLC R_f 0.54 (ethyl acetate:hexane=1:5); $[\alpha]_D^{25}$-17.5° (c 0.71, $CHCl_3$); IR $\nu_{max}^{CHCl_3}$ 3025, 2950, 2870, 1745, 1495, 1450, 1430, 1370, 1250, 1200, 1105 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.95 (3H, s, $OCOCH_3$), 2.16-2.81 (2H, m, H-6,6'), 3.43, 3.63 (3H x 2, each s, 2 x $COOCH_3$), 3.66-4.00 (2H, m, H-4,5), 4.16 (1H, t, J=3 Hz, H-3), 4.30-4.97 (6H, m, 3 x $OCH_2C_6H_5$), 6.10 (1H, d, J=3 Hz, H-2), 6.96-7.47 (15H, m, 3 x $OCH_2C_6H_5$). High resolution mass spectrum, calcd for $C_{33}H_{36}O_9$: m/z M, 576.2357, found: M, 576.2347. Compound 9' was obtained as a colorless syrup: TLC R_f 0.49; $[\alpha]_D^{25}$-22.8° (c 0.64, $CHCl_3$); IR $\nu_{max}^{CHCl_3}$ 2940, 2870, 1745, 1455, 1375, 1230, 1180, 1100 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.93 (3H, s, $OCOCH_3$), 2.73-3.00 (2H, m, H-6,6'), 3.47, 3.64 (3H x 2, each s, 2 x $COOCH_3$), 3.77-4.30 (3H, m, H-3,4,5), 4.33-4.83 (6H, m, 3 x $OCH_2C_6H_5$), 5.93 (1H, d, J=4.5 Hz, H-2), 6.97-7.43 (15H, m, 3 x $OCH_2C_6H_5$). High resolution mass spectrum, calcd for $C_{33}H_{36}O_9$: m/z M, 576.2356, found: M, 576.2352. Compound 10 was obtained as a colorless syrup: TLC R_f 0.45; $[\alpha]_D^{25}$-4.3° (c 1.69, $CHCl_3$); IR $\nu_{max}^{CHCl_3}$ 3030, 2950, 2850, 1750, 1735, 1600, 1495, 1450, 1255, 1200, 1090 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.20-4.06 (6H, m, H-2,3,4,5, 6,6'), 3.58, 3.67 (3H x 2, each s, 3 x $COOCH_3$), 4.27-4.80 (7H, m, 3 x $OCH_2C_6H_5$, $CH(COOCH_3)_2$), 6.83-7.50 (15H, m, 3 x $OCH_2C_6H_5$). High resolution mass spectrum, calcd for $C_{31}H_{35}O_8$: m/z M, 535.2330, found: M, 535.2358.

Methyl (3R,4S,5R)-3,4,5-Tris(benzyloxy)cyclohexene-1-carboxylate (11). A solution of 9 (99.5 mg, 0.17 mmol) in DMSO (3 mL) containing 7 drops of water and NaCl (30 mg) was heated at 125 °C for 30 min, at 135 °C for 30 min, at 145 °C for 90 min, finally at 155 °C for 30 min, with stirring. After cooling to ambient temperature, the solution was diluted with ethyl acetate (40 mL) and washed with water (40 mL x 3). The organic layer was dried over Na_2SO_4 and concentrated. The residue was fractionated by PTLC (ethyl acetate:toluene=1:7) to give 11 (22 mg, 28%) and unreacted 9 (43 mg, 43%). Compound 11 was obtained as a colorless syrup: TLC R_f 0.40 (ethyl acetate:toluene=1:10); $[\alpha]_D^{26}$-114° (c 0.15, $CHCl_3$), $[\alpha]_D^{26}$-113° (c 0.20, $CHCl_3$) for

the (-)-11 prepared from natural (-)-shikimic acid by 1) CH_2N_2 esterification and 2) benzylation with benzyl bromide in the presence of sodium hydride in DMF; IR $\nu_{max}^{CHCl_3}$ 3070, 3030, 2950, 2870, 1715, 1650, 1600, 1580, 1495, 1450, 1430, 1355, 1250, 1200 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.47-2.77 (2H, m, H-6,6'), 3.78 (3H, s, $COOCH_3$), 3.80-4.50 (3H, m, H-3,4,5), 4.50-4.83 (6H, m, 3 x $OCH_2C_6H_5$), 6.87-7.07 (1H, m, H-2), 7.10-7.49 (15H, m, 3 x $OCH_2C_6H_5$). The ^1H NMR spectrum of 11 was superimposable on that of the compound prepared from (-)-shikimic acid. High resolution mass spectrum, calcd for $C_{29}H_{30}O_5$: m/z M, 458.2091, found: M, 458.2091.

Dimethyl (2S,3R,4S,5R)-2,3,4,5-Tetraacetoxycyclohexane-1,1-dicarboxylate (12). To a solution of 9 (48 mg, 0.08 mmol) in methanol (6 mL) were added cyclohexene (3 mL) and 20% $Pd(OH)_2$ on charcoal (12 mg). The mixture was refluxed for 54 h. The catalyst was removed by filtration through a Celite-pad, and the filtrate was concentrated. The residue was acetylated with acetic anhydride (1 mL) in pyridine (1 mL) for 15 h and concentrated. The residue was partitioned between ethyl acetate (15 mL) and water (10 mL), and the aqueous layer was extracted with ethyl acetate (15 mL x 2). The organic layers were dried over Na_2SO_4 and concentrated. The residue was purified on PTLC (ethyl acetate: toluene=1:3) to afford 12 (19 mg, 54%) as a colorless syrup. 12: $[\alpha]_D^{24}$+2.1° (c 0.48, $CHCl_3$); IR $\nu_{max}^{CHCl_3}$ 2950, 1750, 1430, 1370, 1215, 1035 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.99, 2.00, 2.01, 2.07 (3H x 4, each s, 4 x $OCOCH_3$), 2.33-2.66 (2H, m, H-6,6'), 3.70, 3.78 (3H x 2, each s, 2 x $COOCH_3$), 5.10-5.30 (2H, m, H-4,5), 5.55 (1H, t, J=3 Hz, H-3), 5.95 (1H, d, J=3 Hz, H-2). High resolution mass spectrum, calcd for $C_{18}H_{25}O_{12}$: m/z M+H, 433.1344, found: M+H, 433.1348.

Dimethyl (2R,3R,4S,5R)-2,3,4,5-Tetraacetoxycyclohexane-1,1-dicarboxylate (12'). Compound 9' (139 mg) was O-debenzylated and then acetylated as described in the prepaartion of 12 from 9. After PTLC purification (ethyl acetate:toluene=1:1), 12' (74 mg, 71%) was obtained as a colorless syrup: TLC R_f 0.40

(ethyl acetate:toluene=1:3); $[\alpha]_D^{26}$-14.9° (c 0.59, $CHCl_3$); IR $\nu_{max}^{CHCl_3}$ 2960, 2930, 2850, 1745, 1430, 1370, 1225, 1100 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.00, 2.03, 2.05, 2.09 (3H x 4, each s, 4 x $OCOCH_3$), 2.43-3.00 (2H, m, H-6,6'), 3.73, 3.80 (3H x 2, each s, 2 x $COOCH_3$), 5.10-5.53 (3H, m, H-3,4,5), 5.82 (1H, d, J=6 Hz, H-2). High resolution mass spectrum, calcd for $C_{18}H_{25}O_{12}$: m/z M+H, 433.1344, found: M+H, 433.1336.

Methyl (3R,4S,5R)-3,4,5-Triacetoxy-1-cyclohexene-1-carboxylate, Methyl (-)-Shikimate Triacetate (13). From 12: To a solution of 12 (29 mg, 0.07 mmol) in DMSO (1 mL) containing 2 drops of water was added NaCl (12 mg). The mixture was stirred at 125 °C for 90 min and cooled to ambient temperature. The solution was diluted with ethyl acetate (20 mL) and washed with water (20 mL x 3). The organic layer was dried over Na_2SO_4 and concentrated. The residue was fractionated by PTLC (ethyl acetate:toluene=1:2) to afford 13 (3.6 mg, 17%) and unreacted 12 (14 mg, 47%). Compound 13 was obtained as a colorless syrup: TLC R_f 0.52 (ethyl acetate:toluene=1:2); $[\alpha]_D^{26}$ -173° (c 0.47, $CHCl_3$), $[\alpha]_D^{26}$-179° (c 0.55, $CHCl_3$) for triacetate of methyl shikimate prepared from natural (-)-shikimic acid; IR $\nu_{max}^{CHCl_3}$ 2950, 2925, 2850, 1750, 1720, 1660, 1435, 1370, 1240, 1220, 1140, 1105 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.00, 2.03 (3H, 6H, each s, 3 x $OCOCH_3$), 2.17-2.87 (2H, m, H-6, 6'), 3.73 (3H, s, $COOCH_3$), 5.06-5.30, 5.55-5.80 (2H, 1H, each m, H-3,4,5), 6.56-6.77 (1H, m, H-2). The ^1H NMR spectrum of 13 was superimposable on that of the triacetate of (-)-shikimic acid. High resolution mass spectrum, calcd for $C_{14}H_{18}O_8$: m/z M, 314.1000, found: M, 314.0991.

From 12': Compound 12' (74 mg) was converted to 13 (7 mg, 13%) (13 mg, 18% of 12' was recovered) as described above after heating at 125 °C for 75 min.

Methyl (3R,4S,5R)-3,4,5-Trihydroxy-1-cyclohexene-1-carboxylate, Methyl (-)-Shikimate (1). To a solution of 13 (76 mg, 0.24 mmol) in methanol (1 mL) was added sodium methoxide (1 M in methanol, 0.88 mL), and the mixture was stirred for 1 h at 0 °C. The mixture was neutralized by addition of acetic acid and

concentrated. To the residue were added chloroform and ethyl acetate (each 2 mL), and the resulting insoluble material was removed. The filtrate was concentrated to afford crude crystalline 1, which was recrystallized from ethyl acetate giving 1 (19 mg, 42%). 1: Mp 104-105 °C, mp 104-105 °C for methyl (-)-shikimate prepared from natural (-)-shikimic acid; $[\alpha]_D^{25}$-132° (c 0.75, EtOH), $[\alpha]_D^{25}$-133° (c 0.75, EtOH) for methyl shikimate prepared from natural (-)-shikimic acid, lit.[16] $[\alpha]_D^{20}$-130° (c 1.88, EtOH).

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