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

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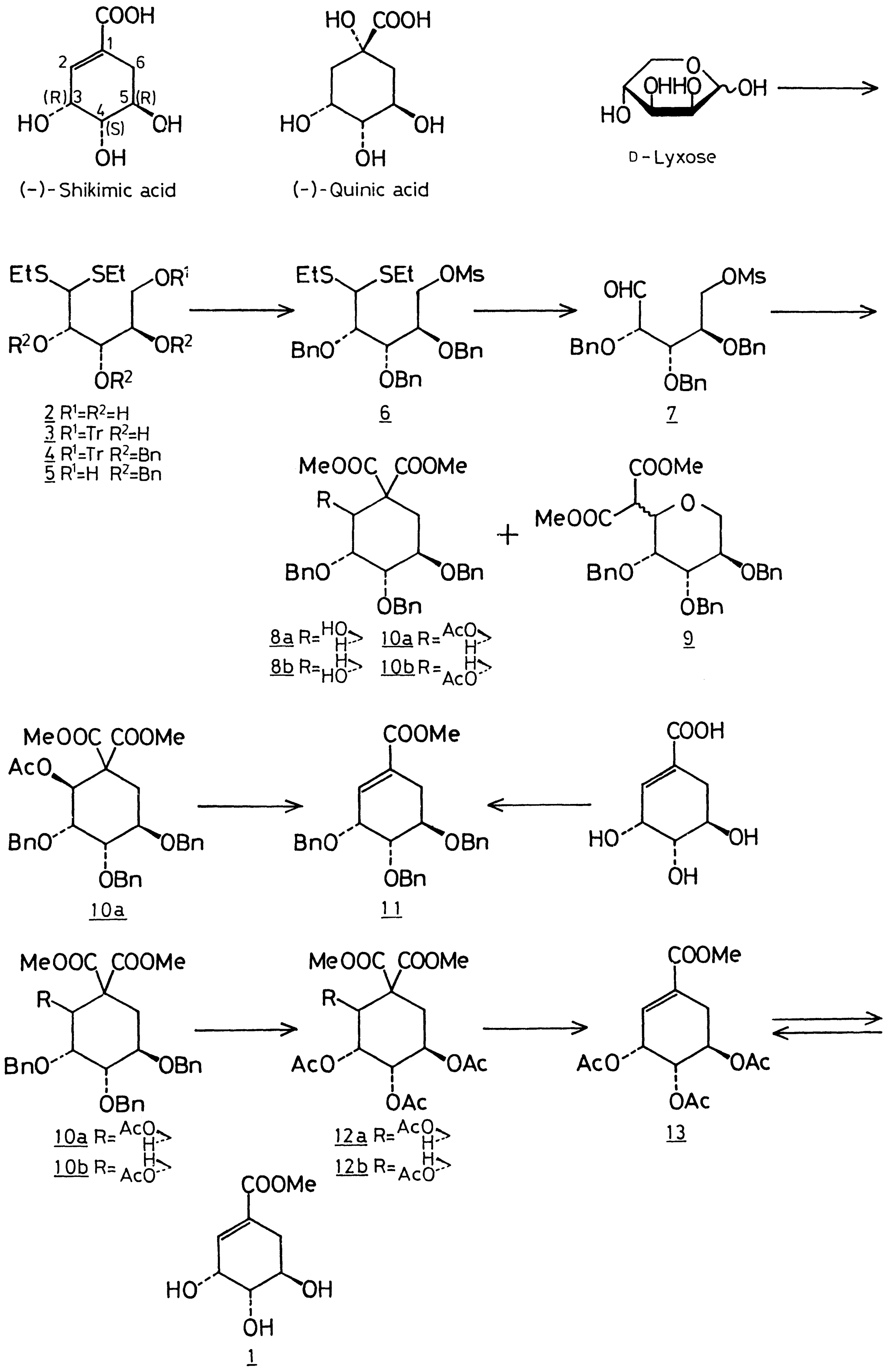
Natural methyl (-)-shikimate has been synthesized from D-lyxose, employing a double carbon-carbon bond formation of 2,3,4-tri-O-benzyl-5-O-mesyl-D-lyxose with a dianion of dimethyl malonate as a key reaction.

(-)-Shikimic acid, (3*R*,4*S*,5*R*)-3,4,5-trihydroxy-1-cyclohexene-1-carboxylic acid, is widely found in nature which plays an important role in biosynthetic pathway of essential aromatic amino acids from carbohydrates.[1,2] So far, several synthetic approaches toward shikimic acid and the related natural product, quinic acid, including their total syntheses, have been appeared in the literatures.[3-5] Although the most approaches featured by Diels-Alder cycloaddition for the construction of the cyclohexene skeleton, the syntheses also commenced from carbohydrate derivatives as chiral sources. Bestmann and Heid described an enantiospecific synthesis of shikimic acid and quinic acid starting from D-arabinose,[6] Kitagawa and coworkers synthesized shikimic acid from D-mannose,[7] and very recently Fleet and coworkers reported an enantiospecific synthesis of shikimic acid from D-mannose in a different route.[8] On the course of synthetic approaches toward optically active carbocycles from carbohydrates,[9] we herein report a synthesis of methyl (-)-shikimate (1) from D-lyxose. Our synthesis involves a double carbon-carbon bond formation of 2,3,4-tri-O-benzyl-5-O-mesyl-D-lyxose (7) with a dianion of dimethyl malonate which has been developed in our laboratory recently.[9] And our synthesis seems to have an advantage over the other chiral synthesis of 1 by reason that an introduction of carboxyl side chain can be achieved simultaneously in a cyclohexene ring formation step.

According to the literature,[10] D-lyxose was converted into the diethyl dithioacetal derivative (2). Selective O-tritylation of 2 with trityl chloride afforded the 5-O-trityl ether (3)[11] in 81% yield. Benzylation of 3 with benzyl bromide in the presence of sodium hydride and successive de-O-tritylation of the thus formed tri-O-benzyl ether (4) with *p*-toluenesulfonic acid gave 2,3,4-tri-O-benzyl-D-lyxose diethyl dithioacetal (5)[11] in 79% yield. Mesylation of 5 with mesyl chloride and successive dethioacetalization of the 5-O-mesyl derivative (6) with mercury (II) chloride and calcium carbonate gave the compound 7[12] which was subjected to the next reaction directly. Treatment of 7 with a dianion of dimethyl malonate generated by sodium hydride in THF at room temperature for 40 min, and purification of the products on silica gel column afforded a mixture of


(−)-Shikimic acid
(−)-Quinic acid
D-Lyxose
2 R¹=R²=H
3 R¹=Tr R²=H
4 R¹=Tr R²=Bn
5 R¹=H R²=Bn
6
7
8a
8b
10a
10b
9
10a
11
10a
10b
12a
12b
13
1

(*2S*,*3R*,*4S*,*5R*)- (8a), (*2R*,*3R*,*4S*,*5R*)- (8b) dimethyl 2-hydroxy-3,4,5-tribenzyloxycyclohexene-1,1-dicarboxylate, and (*3R*,*4S*,*5R*)-2-[(bismethoxycarbonyl)methyl]-3,4,5-tribenzyloxytetrahydropyran (9)13) (R_f 0.50 to 0.68 on TLC, AcOEt:hexane=1:2). The mixture was acetylated in a usual manner, and purification of the products on silica gel column afforded (*2S*,*3R*,*4S*,*5R*)- (10a),11) (*2R*,*3R*,*4S*,*5R*)- (10b),11) dimethyl 2-acetoxy-3,4,5-tribenzyloxycyclohexane-1,1-dicarboxylate, and compound 911) in 17, 15,and 8% overall yields from 5, respectively On their ^{1}H NMR spectra, 10a and 10b revealed the acetoxy methyl singlets at δ 1.95 and 1.93, respectively. The configurations on C-2 in 10a and 10b were tentatively assigned to be (*2S*) (2-axial acetoxyl, therefore 2-axial hydroxyl for 8a) and (*2R*) (2-equatorial acetoxyl, therefore 2-equatorial hydroxyl for 8b). Both of 10a and 10b could be converted into 1 as described below. Thermal decarbomethoxylation of 10a accompanying β-elimination of the acetoxyl group (in aqueous dimethyl sulfoxide in the presence of NaCl at 125 to 155 °C) proceeded to give (*3R*,*4S*,*5R*)-methyl 3,4,5-tribenzyloxy-1-cyclohexene-1-carboxylate (11)11) in 28% yield (43% of 10a was recovered). To ascertain the structure of 11, natural (-)-shikimic acid was converted into 11 in two-step reaction, 1) methyl esterification with diazomethane, 2) perbenzylation of methyl (-)-shikimate with benzyl bromide. ^{1}H NMR spectra of 11 from D-lyxose and that from natural product were superimposable, and optical rotation values of them coincided [11: from D-lyxose; $[\alpha]_D^{26}$ -114° (*c* 0.15, CHCl$_3$), 11 from (-)-shikimic acid; $[\alpha]_D^{26}$ -113° (*c* 0.20, CHCl$_3$)]. Besides, 10a and 10b were de-O-benzylated by Hanessian's procedure14) (cyclohexene, 20% Pd(OH)$_2$/C, in MeOH, reflux, 2 d), and acetylation of the products afforded (12a)11) and (12b)11) in 54 and 71% yields, respectively. Thermal decarbomethoxylation of 12a and 12b accompanying β-elimination of the 2-acetoxyl groups (in aq. dimethyl sulfoxide in the presence of NaCl at 125 °C) afforded (*3R*,*4S*,*5R*)-methyl 3,4,5-triacetoxy-1-cyclohexene-1-carboxylate (13)11) in 17 and 13% yields, respectively (47% of 12a and 18% of 12b were recovered). The structure of 13 was identified to be methyl (-)-shikimate triacetate which was prepared from methyl (-)-shikimate by acetylation (Ac$_2$O in pyridine). The optical rotation value of 13, $[\alpha]_D^{26}$ -173° (*c* 0.47, CHCl$_3$), coincided with that of the triacetate derived from methyl (-)-shikimate, $[\alpha]_D^{26}$ -179° (*c* 0.55, CHCl$_3$). Finally, de-O-acetylation of 13 with sodium methoxide afforded methyl (-)-shikimate 1 in 42% yield [1 from D-lyxose: mp 104-105 °C; $[\alpha]_D^{25}$ -132° (*c* 0.75, EtOH), 1 from (-)-shikimic acid: mp 104-105 °C; mixed mp 104-105 °C; $[\alpha]_D^{20}$ -133° (*c* 0.75, EtOH), lit.15) $[\alpha]_D^{20}$ -130° (*c* 1.88, EtOH)].

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11) All the new compounds gave satisfactory, spectral data (^1H NMR, IR, and low resolution mass spectra), and high resolution mass spectra for the molecular ions (within ± 0.3 millimass units) were also given for them. Physical and spectral data for the selected compounds are as follows, 3: syrup; $[\alpha]_D^{18}+6.0^\circ$ (*c* 1.17, $CHCl_3$). 5: syrup; $[\alpha]_D^{17}-25.2^\circ$ (*c* 1.23, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.22 (6H, t, J=8 Hz, $2xSCH_2C\underline{H}_3$), 2.64, 2.70 (4H, each q, J=8 Hz, $2xSC\underline{H}_2CH_3$), 3.79 (2H, d, J=4 Hz, H-5,5'), 4.50-4.77 (6H, m, $3xOC\underline{H}_2C_6H_5$), 5.02 (1H, d, J=11 Hz, H-1), 7.30, 7.32, 7.35 (15H, $3xOCH_2C_6\underline{H}_5$). 7: syrup; ^1H NMR ($CDCl_3$) δ 2.86 (3H, s, OSO_2CH_3), 7.31 (15H, s, $3xOCH_2C_6\underline{H}_5$), 9.66 (1H, s, CHO). 9: syrup; $[\alpha]_D^{24.5}-4.3^\circ$ (*c* 1.70, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 3.20-4.06 (6H, m, H-2,3,4,5,6,6'), 3.58, 3.67 (6H, each s, $2xCOOCH_3$), 4.27-4.80 (7H, m, $3xOC\underline{H}_2C_6H_5$, $C\underline{H}(COOCH_3)_2$), 6.83-7.50 (15H, m, $3xOCH_2C_6\underline{H}_5$). 10a: syrup; $[\alpha]_D^{24.5}-17.5^\circ$ (*c* 0.71, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.95 (3H, s, $OCOCH_3$), 3.43, 3.63 (6H, each s, $2xCOOCH_3$), 6.10 (1H, d, J=3 Hz, H-2), 6.96-7.47 (15H, m, $3xOCH_2C_6\underline{H}_5$). 10b: syrup; $[\alpha]_D^{24.5}-22.8^\circ$ (*c* 0.64, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.93 (3H, s, $OCOCH_3$), 3.47, 3.64 (6H, each s, $2xCOOCH_3$), 5.93 (1H, d, J=4.5 Hz, H-2), 6.97-7.43 (15H, m, $3xOCH_2C_6\underline{H}_5$). 11: syrup; ^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), 6.87-7.07 (1H, m, H-2). 12a: syrup; $[\alpha]_D^{23.5}+2.1^\circ$ (*c* 0.48, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.99, 2.00, 2.01, 2.07 (12H, each s, $4xOCOCH_3$), 3.70, 3.78 (6H, each s, $2xCOOCH_3$), 5.10-5.30 (2H, m, H-4,5), 5.55 (1H, t, J=3 Hz, H-2), 5.95 (1H, d, J=3 Hz, H-2). 12b: syrup; $[\alpha]_D^{26}-14.9^\circ$ (*c* 0.59, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 2.00, 2.03, 2.05, 2.09 (12H, each s, $4xOCOCH_3$), 3.73, 3.80 (6H, each s, $2xCOOCH_3$), 5.10-5.53 (3H, m, H-3,4,5), 5.82 (1H, d, J=6 Hz, H-2). 13: syrup; ^1H NMR ($CDCl_3$) δ 2.00, 2.03 (9H, each s, $3xOCOCH_3$), 3.73 (3H, s, $COOCH_3$), 5.06-5.80 (3H, m, H-3,4,5), 6.56-6.77 (1H, m, H-2).

12) Compounds 6 and 7 were somewhat unstable on silica gel.

13) The configuration on C-2 in 9 was undetermined.

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