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New and Efficient Enantiospecific Synthesis of (-)-Methyl 5-*epi*-Shikimate and Methyl 5-*epi*-Quinate from (-)-Quinic Acid.

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Abstract: (-)-Methyl 5-*epi*-shikimate and methyl 5-*epi*-quinate were synthesized efficiently from readily available and inexpensive (-)-quinic acid **1** as a common starting material on a new, short and simple sequence of reactions. © 1997 Elsevier Science Ltd.

Shikimic acid, quinic acid, and related compounds are known to be biologically important.[1] In addition their structures have been used as starting material for several natural product syntheses.[2] From the synthetic point of view, the possibility of preparing different epimers of shikimic and quinic acids or derivatives would be an interesting aim.

At the moment, we are involved in the preparation from (-)-quinic acid of various A-ring[3] stereoisomers for a range of vitamin D analogs. To do this, we need large amounts of (-)-methyl shikimate as well as (-)-methyl 5-*epi*-shikimate.

A number of reports have appeared on the synthesis of several ketals of (+)-methyl 5-*epi*-shikimate from (-)-quinic acid,[2a-e] and (+)-methyl 5-*epi*-shikimate by asymmetric Diels-Alder reaction.[4] On the other hand, there are two reports describing the synthesis of (-)-5-*epi*-shikimic acid derivatives from D-ribose. Tadano *et al.*[2f] prepared (-)-methyl tri-*O*-benzyl 5-*epi*-shikimate in 10 steps with 7% overall yield. Singh *et al.*[5] obtained (-)-5-*epi*-shikimic acid and (-)-methyl 5-*epi*-shikimate in more than 12 steps and with less than 16% of overall yield.

Here we report a short and simple sequence of reactions for the preparation, in monochiral form, of (-)-methyl 5-*epi*-shikimate and methyl 5-*epi*-quinate on a large scale using readily available and inexpensive (-)-quinic acid **1** as a common starting material.

We originally attempted to prepare the (-)-methyl 5-*epi*-shikimate through inversion of the chirality at the C-5 center of the methyl shikimate 3,4-ketal derivative (such as **3**, Scheme 1), which is obtained from quinic acid. However, this inversion was found to be difficult under diverse Mitsunobu conditions,[6] tending to the recovery of starting material or to degradation products. An alternative approach was inversion by nucleophilic displacement of secondary mesilates with CsF.[7] In these conditions at low temperatures no reaction was produced, and at 90-100°C aromatization products were formed. Thus, the desired inversion of this secondary hydroxyl group was not possible. In other processes, we used cesium carboxylates in DMF,[8] or in the presence of 18-crown-6 ether,[9] or (chloromethylene)dimethylammonium chloride[10] with potassium benzoate, among others. No (-)-methyl 5-*epi*-shikimate was obtained.

Since direct inversion at C-5 center of **3** was impossible, it was thought that a good alternative would be oxidation of C-5 hydroxyl group and on which a selective reduction could then be performed. The synthesis of **4** (Scheme 1) has been reported by Grierson *et al.*[2a] In our hands it was not possible to reproduce their results. Firstly, acetylation of the secondary hydroxyl group in **I** (Figure 1) with Ac_2O/Py did not proceed. Only when AcCl/Py in methylene dichloride was used did the reaction take place. The next step was dehydration of **II**: in their reaction conditions we recovered the starting material. However, if we used an excess of $POCl_3$, the reaction evolved with compound **II** disappearing, but with a ≈1:1 mixture of products **III** and **IV**,[11] being obtained and proving impossible to separate.

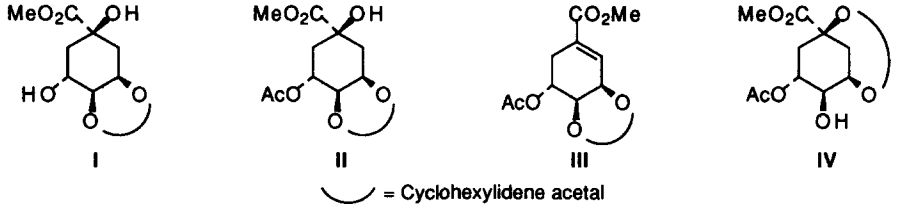
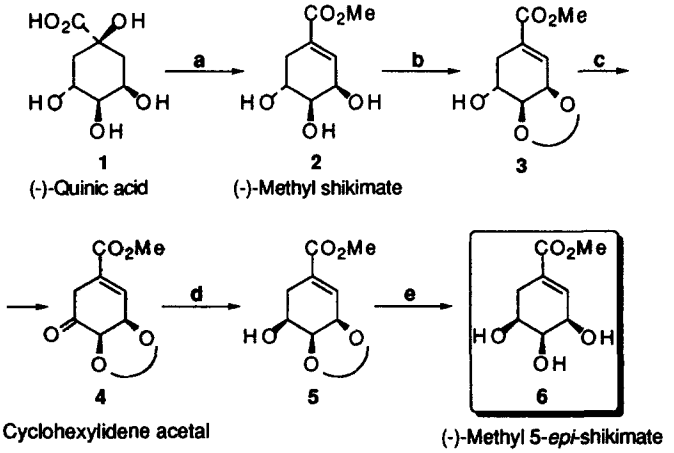


Chart 1

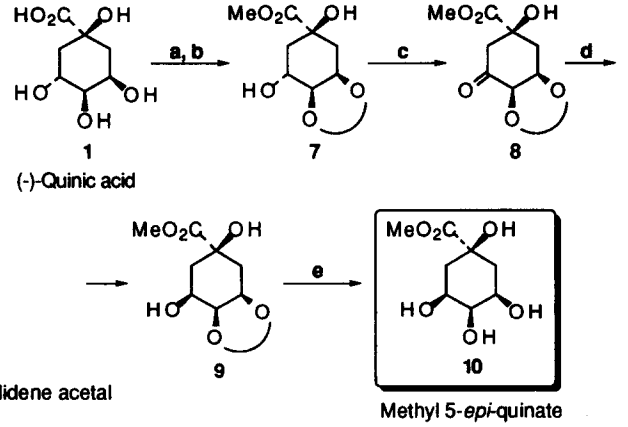
Because of the absence of any good method to synthesize (-)-methyl 5-*epi*-shikimate efficiently on a large scale we developed a new approach. Thus, (-)-methyl shikimate was prepared by esterification of commercially available shikimic acid or from quinic acid by known procedure[12] (Scheme 1). Acetalisation of **2** with cyclohexanone in the presence of *p*-toluenesulfonic acid then proceeded with 74% yield, affording the acetal **3**. Dess-Martin oxidation of the free secondary alcohol in **3** provided the ketone **4** quantitatively. Hydride reduction of the keto group with $NaBH_4$ in MeOH afforded exclusively the α-alcohol **5**, which came from the attack at the less hindered β-face. The ketal was deprotected with CF_3CO_2H-H_2O to the desired (-)-methyl 5-*epi*-shikimate **6** in 5 steps and 60% overall yield from the commercially available shikimic acid.



Reagents: **a.** Reference 12; **b.** Cyclohexanone, *p*-TsOH, toluene, reflux, 5 h (74%); **c.** Dess-Martin, CH_2Cl_2, rt, 2 h; **d.** $NaBH_4$, MeOH, -25 °C, 30 min (88% from **3**); **e.** CF_3CO_2H, H_2O, rt, 30 min (92%).

Scheme 1

On the other hand, the first enantiospecific synthesis of methyl 5-*epi*-quinate **10** is illustrated in Scheme 2. Our approach to **10** began with acetalisation of quinic acid **1** with cyclohexanone in the presence of *p*-TsOH, furnishing a lactone which was opened up with sodium in methanol to give methyl ester **7** in 78% yield. Dess-Martin oxidation of the secondary alcohol in compound **7** afforded the ketone **8**. Treatment of **8** with sodium borohydride in methanol formed diol **9** which through deprotection with trifluoroacetic acid-H_2O and recrystallisation with EtOAc/MeOH provided methyl 5-*epi*-quinate **10** in an overall yield of 60% from quinic acid.



Reagents: **a.** Cyclohexanone, *p*-TsOH, toluene, reflux, 7 h (98%); **b.** NaOMe, MeOH, rt, 5 h (80%); **c.** Dess-Martin, CH_2Cl_2, rt, 2 h (92%); **d.** $NaBH_4$, MeOH, -30 °C, 30 min (90%); **e.** CF_3CO_2H, H_2O, rt, 30 min (93%).

Scheme 2

The above mentioned structures were determined by means of their spectroscopical data. The structural assignment of the compounds described in this paper is based on the analysis of their ^1H- and ^{13}C-NMR spectra. Additional DEPT experiments and the correct assignment were confirmed by ^1H-^{13}C heteronuclear correlation experiments.[13]

In conclusion, the procedure described provides an easy entry to (-)-methyl 5-*epi*-shikimate and methyl 5-*epi*-quinate, and constitutes an improvement on other reported methods. The simplicity of this approach and the biological importance of these compounds is noteworthy.

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13. Select data for compounds **6** and **10**: *(-)-Methyl 5-epi-shikimate 6*. M.p. (recrystallized from EtOAc): 112-113 °C; $[\alpha]_D^{22}$= -34.5° (c 0.48, EtOH); IR (KBr): ν 3333, 1713, and 1649 cm^{-1}; ^{1}H-NMR (MeOH-d_4, 400 MHz): δ 2.61 (dddd, 1H, H_{6sax}, $^{2}J_{HH}$ 17.2, $^{3}J_{HH}$ 9.6, $^{3}J_{HH}$ 6.0, $^{4}J_{HH}$ 2.9 Hz), 2.74 (dd, 1H, H_{6seq}, $^{2}J_{HH}$ 17.2, $^{3}J_{HH}$ 6.0 Hz), 3.93 (s, 3H, Me), 4.02 (ddd, 1H, H_5, $^{3}J_{HH}$ 9.6, $^{3}J_{HH}$ 6.0, $^{3}J_{HH}$ 1.8 Hz), 4.14 (br s, 1H, H_4), 4.51 (br s, 1H, H_3), and 6.86 (br s, 1H, H_2); ^{13}C-NMR (MeOH-d_4, 100.6 MHz): δ 29.98 (C_6), 52.67 (MeO), 69.71 (C_5), 70.01 (C_3), 72.62 (C_4), 130.12 (C_1), 140.59 (C_2), and 168.76 (C=O); Anal. Calcd. (%) for $C_8H_{12}O_5$: C, 51.06; H, 6.43. Found: C, 50.7; H, 6.1; MS (70 eV): *m/z* 188 (M^+, 2%), 170 (10), 156 (78), 129 (80), 97 (100), 69 (75), and 41 (60); HRMS (*m/z*) calcd. for $C_8H_{12}O_5$: 188.0685. Found: 188.0686.
(-)-Methyl 5-epi-quinate 10. M.p. (recrystallized from EtOAc/MeOH): 148-149 °C; IR (KBr): ν 3493, 3270, and 1709 cm^{-1}; ^{1}H-NMR (MeOH-d_4, 300 MHz): δ 2.05 (dd, 2H, H_2+H_6, $^{2}J_{HH}$ 24.2, $^{3}J_{HH}$ 12.1 Hz), 2.29 (dd, 2H, H_2+H_6, $^{2}J_{HH}$ 12.1, $^{3}J_{HH}$ 3.3 Hz), 3.86 (m, 2H, H_3+H_5), 3.93 (s, 3H, MeO), and 4.03 (br s, 1H, H_4); ^{13}C-NMR (MeOH-d_4, 75.5 MHz): δ 38.37 (C_2+C_6), 53.07 (MeO), 69.00 (C_3+C_5), 73.23 (C_1), 74.40 (C_4), and 176.18 (C=O); Anal. Calcd. (%) for $C_8H_{14}O_6$: C, 46.60; H, 6.84. Found: C, 46.4; H, 6.6; MS (70 eV): *m/z* 207 (MH^+, 3%), 170 (13), 147 (47), 132 (100), 129 (77), 111 (83), 103 (84) and 43 (85); HRMS (*m/z*) calcd. for $C_8H_{15}O_6$ (MH^+): 207.0869. Found: 207.0881.

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