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Efficient syntheses of (–)-shikimate and (–)-quininate 3-phosphate via *trans* vicinal diol protection with 2,2,3,3-tetramethoxybutane (TMB) of shikimic and quinic acids

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Abstract

(–)-Shikimate 3-phosphate and (–)-quininate 3-phosphate can be synthesized by selective protection of their *trans* diol functionality using 2,2,3,3-tetramethoxybutane (TMB) using D-(–)-shikimic acid and D-(–)-quinic acid as starting materials. This versatile reagent facilitates the synthesis of these important biological targets in fewer steps than previously reported. By the proper choice of protecting group for C-3 hydroxyl in D-(–)-quinic acid, it can be converted to a key intermediate in the synthesis of (–)-shikimate 3-phosphate. © 2000 Elsevier Science Ltd. All rights reserved.

Keywords: shikimic acid; quinic acid; shikimate 3-phosphate; quininate 3-phosphate; 2,2,3,3-tetramethoxybutane.

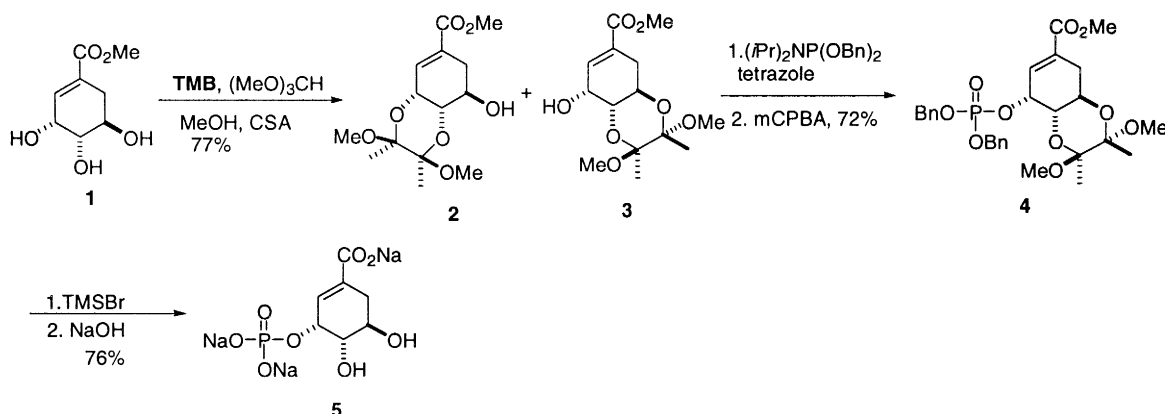
The first chemical syntheses of (–)-shikimate 3-phosphate and (–)-quininate 3-phosphate were reported in 1992.¹ Both of these syntheses required protection of the *cis* vicinal diols at C-3 and C-4 positions, respectively. This contributed to a long synthetic route.

2,2,3,3-Tetramethoxybutane (TMB) has been used in the protection of vicinal diequatorial diols in a series of carbocycles and carbohydrates.² Furthermore, the TMB reagent has been used to convert (–)-quinic acid into (–)-shikimic acid.³ These results prompted us to propose that the TMB could be used in the syntheses of both (–)-shikimate 3-phosphate and (–)-quininate 3-phosphate.

Our synthesis of (–)-shikimate-3-phosphate is described in Scheme 1. The *trans* vicinal diol of **1**^{1a,4} was protected with TMB using the known procedure.² However, we observed that the refluxing time affected the ratio of **2** and **3** in the product mixture. When the reaction time was 3 h, compounds **2** and **3**⁵ were isolated in 75–85% yield in a ratio of 1.5:1. When the reaction was allowed to reflux for 18 h, the mixture of compounds **2** and **3** was isolated in a ratio of 1:1.25. Prolonged reaction time (up to two days) provided **3** as the only isolated product in 77% yield. The C-3 position of **3** was phosphorylated⁶ to afford **4**⁷ in 72% yield. The one-step debenzoylation and deprotection steps were accomplished simultaneously

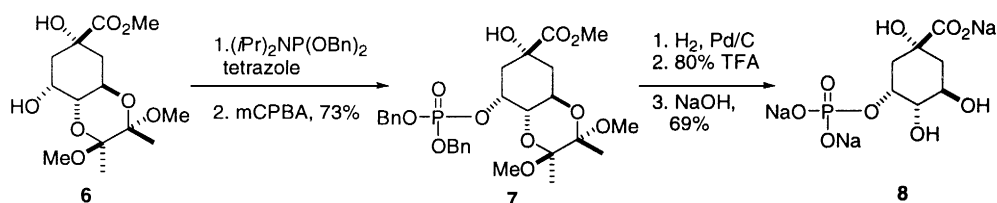
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using bromotrimethylsilane in methylene chloride. Saponification and purification provides **5** in 76% yield.^{1a} Its ¹H NMR data is consistent with the reported value.^{1a}



Scheme 1.

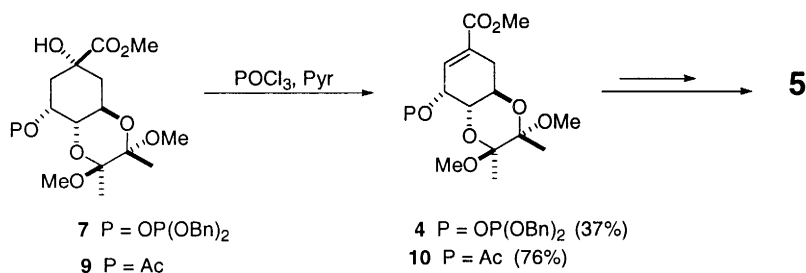
The synthesis of (-)-quinic acid 3-phosphate is outlined in Scheme 2. The C-3 position of compound **6**² was phosphorylated using the same procedure as described above, providing **7**⁸ in 73% yield. Compound **7** was hydrogenated over Pd/C (in MeOH, rt, overnight)⁶ followed by acid hydrolysis (80% TFA, rt, 4 h).^{2,3} The resulting syrup was subjected to a basic workup (1N NaOH) to obtain **8** in 69% (three steps) after purification. Its ¹H NMR data is also consistent with the reported value.^{1a}



Scheme 2.

Some of our effort has focused on the syntheses of intermediates **4** and **10**⁹ from **7** and **9**, respectively, using phosphorous oxychloride in pyridine¹⁰ (Scheme 3). Compounds **4** and **10** therefore served as precursors in the synthesis of (-)-shikimate 3-phosphate starting from (-)-quinic acid. In the examples of dehydration of **7** and **9**, we observed that the elimination takes place exclusively opposite to the TMB protected diol, yielding **4** and **10** in 37 and 76% yields, respectively. The regioselectivity of double bond formation is consistent with that observed in the synthesis of D-(-)-shikimic acid from D-(-)-quinic acid.^{3a} However, the isolated yield (37%) for **4** might be due to competing aromatization during the reaction since the phosphorous group may function as a leaving group. Indeed, a non-polar highly UV-active spot was observed by TLC which is not readily isolated by column chromatography. Furthermore, when the C-3 hydroxyl is protected with an acetyl group, the possibility of aromatization was eliminated, and a higher yield was obtained. The acetyl group of **10** can be further removed to prepare **3**.

With this method, (-)-shikimate 3-phosphate and (-)-quinic acid 3-phosphate were obtained using the TMB reagent for the protection of *trans* vicinal diols in methyl-(-)-shikimate or methyl-(-)-quinic acid, respectively. This route is more direct than previous routes to these important compounds. The regioselectivity of double bond formation in the dehydration of **7** and **9** can also be controlled by this *trans* diol protection.



Scheme 3.

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- Shikimic acid, used for the preparation of **3**, was purchased from Sigma.
- The ¹H and ¹³C NMR data are consistent with the reported values in Ref. 3b.
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- Compound **4**: pale yellow syrup. ¹H NMR (CDCl₃, 400 MHz) δ 7.25–7.39 (m, 10H), 6.76 (dd, *J*=5.5, 2.6 Hz, 1H), 5.13–5.23 (m, 2H), 5.08–5.12 (m, 1H), 5.00–5.06 (m, 2H), 4.10 (dt, *J*=16.8, 5.9 Hz, 1H), 3.74 (s, 3H), 3.69 (ddd, *J*=10.9, 4.0, 1.7 Hz, 1H), 3.23 (s, 3H), 3.22 (s, 3H), 2.83 (dd, *J*=18.0, 6.2 Hz, 1H), 2.25 (ddd, *J*=18.0, 10.3, 2.8 Hz, 1H), 1.27 (s, 3H), 1.23 (s, 3H). ¹³C NMR (CDCl₃, 100 MHz) δ 166.1, 136.2, 133.3, 132.0, 128.4, 128.3, 128.2, 127.9, 127.7, 99.9, 99.1, 70.9, 70.8, 69.4 (×2), 69.2 (×2), 62.4, 52.2, 48.1, 47.9, 30.3, 17.8, 17.7. LRMS (*m/z*) 562.9 (M⁺, 95%), 531.1 (M⁺–OMe, 100%).
- Compound **7**: white solid. Mp 103–105°C. ¹H NMR (CDCl₃, 400 MHz) δ 7.25–7.40 (m, 10H), 5.17 (t, *J*=6.4 Hz, 2H), 5.08 (dd, *J*=7.6, 4.3 Hz, 2H), 4.92 (dd, *J*=7.7, 2.9 Hz, 1H), 4.36 (ddd, *J*=14.8, 10.3, 4.6 Hz, 1H), 3.75 (s, 3H), 3.62 (dt, *J*=10.3, 2.6 Hz, 1H), 3.31 (brs, 1H), 3.23 (s, 3H), 3.19 (s, 3H), 2.21 (dt, *J*=15.5, 2.8 Hz, 1H), 1.98–2.12 (m, 2H), 1.93 (t, *J*=13.0 Hz, 1H), 1.25 (s, 3H), 1.23 (s, 3H). ¹³C NMR (CDCl₃, 100 MHz) δ 175.0, 136.3, 136.0, 128.5, 128.4, 128.3, 128.1, 127.8, 127.7, 100.2, 99.5, 74.7, 74.6, 74.5, 71.6, 69.3, 69.2, 62.2, 48.0, 47.9, 38.8, 37.9, 17.8, 17.6. LRMS (*m/z*) 580.9 (M⁺, 75%), 549.1 (M⁺–OMe, 100%).
- Compound **10**: pale yellow syrup. ¹H NMR (CDCl₃, 400 MHz) δ 6.80 (dd, *J*=5.0, 2.3 Hz, 1H), 5.53 (t, *J*=5.0 Hz, 1H), 4.07 (dtd, *J*=16.7, 10.5, 6.0 Hz, 1H), 3.74 (s, 3H), 3.69 (dd, *J*=10.9, 4.4 Hz, 1H), 3.25 (s, 3H), 3.23 (s, 3H), 2.83 (dd, *J*=17.9 Hz, 6.0 Hz, 1H), 2.26 (dddd, *J*=17.9, 10.4, 2.8, 0.9 Hz, 1H), 2.07 (s, 3H), 1.28 (s, 3H), 1.25 (s, 3H), 1.23 (brs, 1H). ¹³C NMR (CDCl₃, 100 MHz) δ 170.4, 166.3, 133.3, 132.2, 99.7, 99.1, 68.8, 66.1, 62.9, 52.2, 48.0, 47.9, 30.0, 20.9, 17.8, 17.6.
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