Efficient syntheses of (−)-shikimate and (−)-quinate 3-phosphate via \textit{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 (−)-quinate 3-phosphate can be synthesized by selective protection of their \textit{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.

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The first chemical syntheses of (−)-shikimate 3-phosphate and (−)-quinate 3-phosphate were reported in 1992.\textsuperscript{1} Both of these syntheses required protection of the \textit{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.\textsuperscript{2} Furthermore, the TMB reagent has been used to convert (−)-quinic acid into (−)-shikimic acid.\textsuperscript{3} These results prompted us to propose that the TMB could be used in the syntheses of both (−)-shikimate 3-phosphate and (−)-quinate 3-phosphate.

Our synthesis of (−)-shikimate-3-phosphate is described in Scheme 1. The \textit{trans} vicinal diol of \textsuperscript{1}\textsubscript{1a,4} was protected with TMB using the known procedure.\textsuperscript{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\textsuperscript{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 phosphorylated\textsuperscript{6} to afford \textsuperscript{4}\textsuperscript{7} in 72% yield. The one-step debenzylation and deprotection steps were accomplished simultaneously.

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

Scheme 1.

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

Scheme 2.

Some of our effort has focused on the syntheses of intermediates 4 and 10\textsuperscript{9} from 7 and 9, respectively, using phosphorous oxychloride in pyridine\textsuperscript{10} (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.\textsuperscript{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 (−)-quinate 3-phosphate were obtained using the TMB reagent for the protection of trans vicinal diols in methyl-(−)-shikimate or methyl-(−)-quinate, 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.
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References


4. Shikimic acid, used for the preparation of 3, was purchased from Sigma.

5. The $^1$H and $^{13}$C NMR data are consistent with the reported values in Ref. 3b.


7. Compound 4: pale yellow syrup. $^1$H NMR (CDCl$_3$, 400 MHz) $\delta$ 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). $^{13}$C NMR (CDCl$_3$, 100 MHz) $\delta$ 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 ($\times$2), 69.2 ($\times$2), 62.4, 52.2, 48.1, 47.9, 30.3, 17.8, 17.7. LRMS (m/z) 562.9 (M$^+$, 95%), 531.1 (M$^+$−OMe, 100%).

8. Compound 7: white solid. Mp 103–105°C. $^1$H NMR (CDCl$_3$, 400 MHz) $\delta$ 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). $^{13}$C NMR (CDCl$_3$, 100 MHz) $\delta$ 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, 17.9, 17.6. LRMS (m/z) 580.9 (M$^+$, 75%), 549.1 (M$^+$−OMe, 100%).

9. Compound 10: pale yellow syrup. $^1$H NMR (CDCl$_3$, 400 MHz) $\delta$ 6.80 (dd, $J$=5.0, 2.3 Hz, 1H), 5.53 (t, $J$=5.0 Hz, 1H), 4.07 (dd, $J$=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 (ddd, $J$=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). $^{13}$C NMR (CDCl$_3$, 100 MHz) $\delta$ 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.