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

Tzenge-Lien Shih [a,*] and Shih-Hsiung Wu [a,b,*]

[a] *Institute of Biological Chemistry, Academia Sinica, NanKang 115, Taipei, Taiwan*

[b] *Institute of Biochemical Sciences, National Taiwan University, Taiwan*

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**Abstract**

(−)-Shikimate 3-phosphate and (−)-quinate 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. 

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

The first chemical syntheses of (−)-shikimate 3-phosphate and (−)-quinate 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 (−)-quinate 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 phosphorylated[6] to afford **4**[7] in 72% yield. The one-step debenzylation and deprotection steps were accomplished simultaneously

* Corresponding authors.

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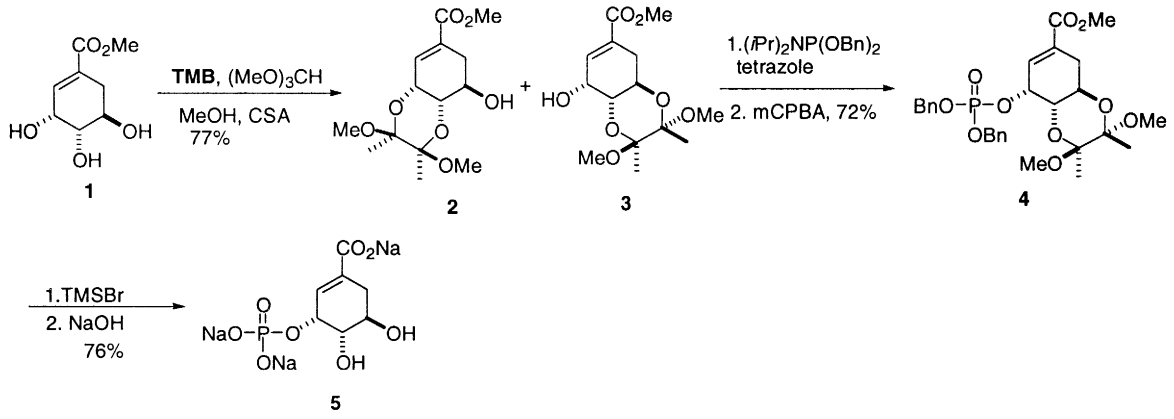
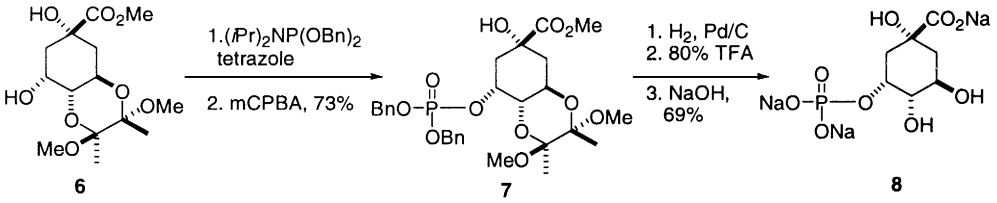
using bromotrimethylsilane in methylene chloride. Saponification and purification provides **5** in 76% yield.[1a] Its $^1$H NMR data is consistent with the reported value.[1a]




Scheme 1.

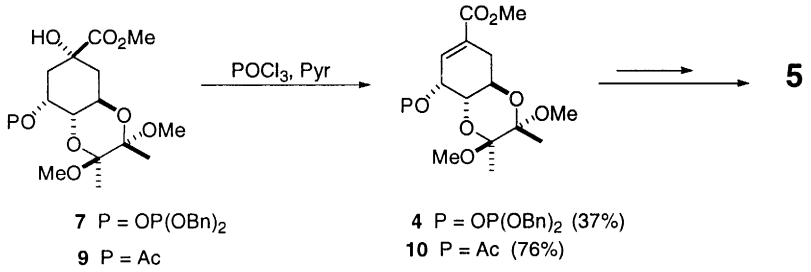
The synthesis of (−)-quinate 3-phosphate is outlined in Scheme 2. The C-3 position of compound **6**[2] was phosphorylated using the same procedure as described above, providing **7**[8] in 73% yield. Compound **7** was hydrogenated over Pd/C (in MeOH, rt, overnight)[6] followed by acid hydrolysis (80% 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 $^1$H 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 pyridine[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.[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.




Scheme 3.

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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.
6. Yu, K.-L.; Fraser-Reid, B. *Tetrahedron Lett.* **1988**, *29*, 979.
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 (×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%).
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, 17.8, 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 (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). $^{13}C$ 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.
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