Tetrahedron Letters, Vol.31, No.42, pp 5997-6000, 1990
Printed in Great Britain

0040-4039/90 $3.00 + .00
Pergamon Press plc

(1*E*,3*E*)-4-Acetoxy-1-phenyldimethylsilyl-1,3-butadiene as a Surrogate for (1*E*,3*E*)-1,4-Diacetoxy-1,3-butadiene: A Highly Efficient Synthesis of (±)-Shikimic Acid

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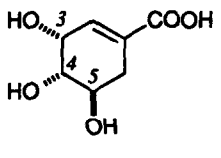
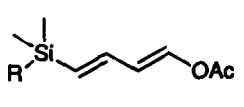
Summary: The 5-step synthesis of (±)-shikimic acid has been achieved in 55% overall yield from (1*E*,3*E*)-4-acetoxy-1-phenyldimethylsilyl-1,3-butadiene, starting with its Diels-Alder reaction with 2-(trimethylsilyl)ethyl acrylate and featuring the use of Fleming's one-pot procedure for the conversion of the phenyldimethylsilyl group to the hydroxyl as the salient, pivotal step in the synthesis.

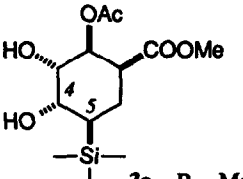
Shikimic acid (**1**) is a pivotal intermediate in the biosynthesis of a number of biologically important natural products including aromatic amino acids, lignins, and essential cofactors such as folic acid and isoprenoid quinones.[1] The synthesis of this biologically active natural product in both racemic and optically active forms continues to attract the keen interest of chemists as they try to showcase their new methodologies.[2] We have previously reported the 9-step synthesis of (±)-shikimic acid (**1**) starting from (1*E*,3*E*)-4-acetoxy-1-trimethylsilyl-1,3-butadiene (**2a**).[3] While this synthesis is efficient (23% overall yield from **2a**) and is regio- and stereochemically controlled throughout the synthesis, conversion of the 5-trimethylsilyl group in the key intermediate **3a** to the desired hydroxyl group required elimination to form the 4,5-double bond and subsequent reintroduction of the C-4 and 5 hydroxyls. In view of a recent development in the use of the phenyldimethylsilyl group as a latent hydroxyl,[4] it was deemed highly attractive to employ phenyldimethylsilylated diene **2b** in the synthesis of shikimic acid. In the following, we describe the use of (1*E*,3*E*)-4-acetoxy-1-phenyldimethylsilyl-1,3-butadiene (**2b**) as a surrogate for (1*E*,3*E*)-1,4-diacetoxy-1,3-butadiene as applied to an extremely efficient synthesis of (±)-shikimic acid (**1**).



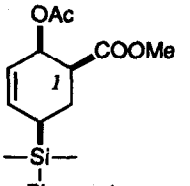
1



2a R = Me
2b R = Ph



3a R = Me
3b R = Ph



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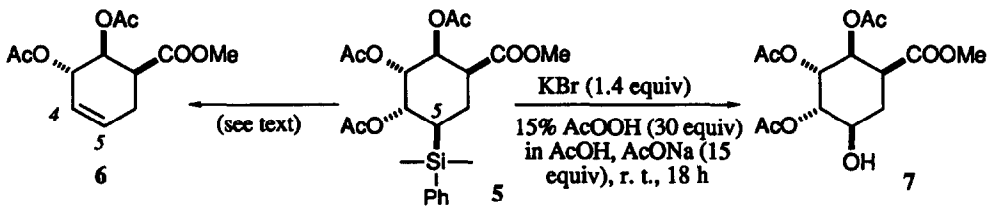
Scheme I

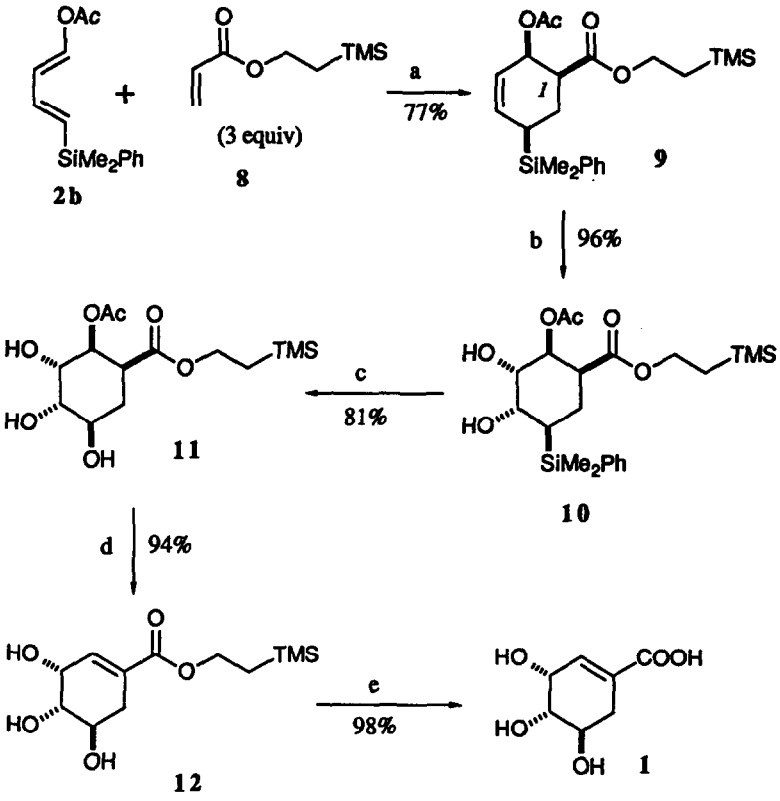


The requisite phenyldimethylsilylated diene **2b** was readily obtained utilizing the convenient one-pot procedure developed for the synthesis of **2a**.[3] Thus, deprotonation of allyl(phenyl)dimethylsilane with *sec*-BuLi/TMEDA, followed by quenching with DMF at -78 °C and treatment of the resulting aminol salt with acetic anhydride, provided the desired diene **2b**[5] in 74% overall yield. The 1E,3Z-isomer of the diene was also isolated in 14% yield. Separation of these two isomers can be readily achieved by gravity silica gel column chromatography. However, this separation is unnecessary since the 1*E*,3Z-isomer is not very reactive in the present Diels-Alder reaction. As in the case of diene **2a**, the reaction of diene **2b** with excess methyl acrylate in refluxing xylene (40 h) produced a 10:1 mixture of **4** and its C-1 epimer in 83% yield. The pure cycloadduct **4** was first converted into diol [OsO_4 (cat.), NMO;[6] 89%], and then into triacetate **5** (Ac_2O, pyridine; 92%).

In an effort to introduce the hydroxyl at C-5 in **5** with retention of configuration, the use of Fleming's two-step procedure (i. HBF_4, ii. MCPBA)[4,7] was explored. However, the initial treatment of **5** with HBF_4•OEt_2 in CH_2Cl_2 resulted in the quantitative formation of olefin **6**. The problem of this facile elimination of the AcO-$SiMe_2Ph$ unit in **5** was circumvented by the use of the buffered, one-pot oxidation procedure recently developed by Fleming[8] (see **5** → **7** in Scheme I). The desired alcohol **7** was obtained in 94% yield with virtually no contamination by olefin **6**.

In a number of syntheses of (±)-shikimic acid, the step that deals with the hydrolysis of the acetate and methyl ester groups of methyl triacetylshikimate has been problematic; such a hydrolysis is often accompanied by the formation of an aromatized product, *m*-hydroxybenzoic acid. Therefore, it seemed advantageous to carry out the shikimate ester hydrolysis upon the 3,4,5-triol utilizing mildly basic conditions. To this end, the synthesis of (±)-shikimic acid was initiated starting with the Diels-Alder reaction between diene **2b** and 2-(trimethylsilyl)ethyl acrylate (**8**)[9] (Scheme II). The all-cis cycloadduct **9**[10] was isolated in 77% yield together with a small amount of its C-1 epimer (7%). Upon subjection of diol **10**,[11] obtained from pure **9**, to Fleming's one-pot protocol,[8] triol **11**[12] was produced stereochemically pure in excellent yield. Introduction of the C-1 olefin was achieved smoothly with DBU.[3] Treatment of triol-ester **12** with (n-Bu)$_4$NF/THF followed by purification through a cation exchange column (Amberlite CG-50 type 1 resin with distilled water) and lyophilization produced pure shikimic

Scheme II[a]



[a]Conditions and reagents: (a) hydroquinone monomethyl ether (catalytic), xylenes, reflux, 40h; (b) OsO_4 (catalytic), *N*-methylmorpholine-*N*-oxide (NMO) (1.21 equiv), THF/H_2O (1:1), room temperature, 8 h; (c) KBr (1.33 equiv), 15% AcOOH (30 equiv) in AcOH, AcONa (15 equiv), room temperature, 18 h; (d) DBU (1.35 equiv), THF, room temperature, 4 h; (e) (n-Bu)$_4$NF (2.71 equiv), THF, room temperature, 12 h.

acid (**1**) in 98% yield. This represents one of the most efficient syntheses of (±)-shikimic acid ever reported – 5 steps from (1*E*,3*E*)-4-acetoxy-1-phenyldiemthylsilyl-1,3-butadiene (**2b**) in 55% overall yield.

The synthesis described above illustrates the use of diene **2b** as an equivalent of (1*E*,3*E*)-1,4-diacetoxy-1,3-butadiene where one of the acetoxyls is kept as a latent functional group. In view of the reactive nature of **2b** as a Diels-Alder diene as well as its ready accessibility, this diene should serve as a convenient surrogate for diacetoxybutadiene.

Acknowledgment. We thank the National Institutes of Health for a grant (CA-25185) that supported this work.

References and Footnotes

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5. For **2b**: $bp_{1.0}$ 126-127 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.354 (s, 6H, $SiMe_2$), 2.15 (s, 3H, OAc), 5.97 (dd, 1H, *J* = 18.3, 0.7 Hz, 1-H), 6.07 (ddd, 1H, *J* = 12.3, 10.6, 0.7 Hz, 3-H), 6.49 (ddd, 1H, *J* = 18.3, 10.6, 0.5 Hz, 2-H), 7.34 - 7.36 (m, 3H, Ar-H), 7.47 (dd, 1H, *J* = 12.3, 0.5 Hz, 4-H), and 7.50 - 7.53 ppm (m, 2H, Ar-H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ -2.57 (q), 20.44 (q), 118.1 (d), 127.8 (d), 129.0 (d), 131.8 (d), 133.8 (d), 138.4 (s), 139.5 (d), 140.4 (d), and 167.4 ppm (s).
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9. For **8**: $bp_{1.8}$ 52-54 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.022 (s, 9H, $SiMe_3$), 1.01-1.06 (m, 2H, Me_3SiCH_2), 4.23-4.28 (m, 2H, OCH_2), 5.80 (dd, 1H, *J* = 10.3, 1.6 Hz, 3-H-trans to the ester), 6.11 (dd, 1H, *J* = 17.3, 10.3 Hz, 2-H), and 6.388 ppm (dd, 1H, *J* = 17.3, 1.6 Hz, 3-H-cis to the ester); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ -1.45 (q), 17.37 (t), 62.70 (t), 128.9 (d), 130.1 (t), and 166.3 ppm (s).
10. For **9**: ^{1}H NMR (300 MHz, C_6D_6) δ -0.088 (s, 9H, $SiMe_3$), 0.177 (s, 3H) and 0.185 (s, 3H) [$SiMe_2Ph$], 0.81-0.97 (m, 2H, Me_3SiCH_2), 1.48-1.58 (m, 1H, 6_{eq}-H), 1.70 (s, 3H, OAc), 1.91-2.05 (m, 1H, 5-H), 2.07 (ddd, 1H, *J* = 13.7, 13.7, 12.1 Hz, 6_{ax}-H), 2.44 (ddd, 1H, *J* = 12.1, 4.1, 4.0 Hz, 1-H), 4.12-4.30 (m, 2H, OCH_2), 5.58 (dd, 1H, *J* = 9.7, 2.2 Hz, 4-H), 5.84 (ddd, 1H, *J* = 5.6, 4.1, 0.9 Hz, 2-H), 6.00 (ddd, 1H, *J* = 9.7, 5.6, 2.9 Hz, 3-H), 7.16-7.20 (m, 3H, Ar-H), and 7.37-7.42 ppm (m, 2H, Ar-H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ -5.48 (q), -4.84 (q), -1.48 (q), 17.49 (t), 19.91 (q), 20.84 (t), 26.28 (d), 44.11(d), 62.69 (t), 66.45 (d), 122.7 (d), 127.8 (d), 129.3 (d), 134.0 (d), 134.5 (d), 136.8 (s), 170.0 (s), and 172.4 ppm (s).
11. For **10**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.221 (s, 9H, $SiMe_3$), 0.379 (s, 3H) and 0.393 (s, 3H) [$SiMe_2Ph$], 0.89-0.95 (m, 2H, Me_3SiCH_2), 1.34 (ddd, 1H, *J* = 13.4, 11.4, 3.5 Hz, 5-H), 1.65 (ddd, 1H, *J* = 13.6, 13.4, 13.4 Hz, 6_{ax}-H), 1.80 (ddd, 1H, *J* = 13.6, 3.7, 3.5 Hz, 6_{eq}-H), 1.92 (d, 1H, *J* = 8.0 Hz, 4-OH), 1.97 (s, 3H, OAc), 2.81 (ddd, 1H, *J* = 13.4, 3.7, 3.3 Hz, 1-H), 2.85 (d, 1H, *J* = 2.9 Hz, 3-OH), 3.64 (ddd, 1H, *J* = 11.4, 8.0, 2.9 Hz, 4-H), 3.81 (ddd, 1H, *J* = 3.2, 3.2, 2.9 Hz, 3-H), 4.07-4.14 (m, 2H, OCH_2), 5.39 (dd, 1H, *J* = 3.3, 3.2 Hz, 2-H), 7.34-7.37 (m, 3H, Ar-H), and 7.55-7.59 ppm (m, 2H, Ar-H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ -3.84 (q), -3.51 (q), -1.48 (q), 17.49 (t), 20.76 (q), 22.81 (t), 25.01 (d), 41.20 (d), 62.90 (t), 69.60 (d), 70.19 (d), 72.86 (d), 128.0 (d), 129.2 (d), 134.1 (d), 138.1 (s), 169.6 (s), and 172.7 ppm (s).
12. For **11**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.386 (s, 9H, $SiMe_3$), 0.88 - 0.94 (m, 2H, Me_3SiCH_2), 1.83 (ddd, 1H, *J* = 13.4, 12.5, 12.5 Hz, 6_{ax}-H), 2.05 (s, 3H, OAc), 2.17 (br ddd, 1H, *J* = 13.4, 4.4, 3.2 Hz, 6_{eq}-H), 3.03 (br ddd, 1H, *J* = 12.5, 3.2, 3.1 Hz, 1-H), 3.58 (br dd, 1H, *J* = ca. 9.0, 3.0 Hz, 4-H), 3.79-3.90 (br m, 1H, 5-H), 3.9 - 4.2 (br peak, 3H, OH), 4.08 (br dd, 1H, *J* = 3.0, 3.0 Hz, 3-H), 4.14-4.18 (m, 2H, OCH_2), and 5.37 ppm (br dd, 1H, *J* = 3.1, 3.0 Hz, 2-H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ -1.49 (q), 17.56 (t), 20.85 (q), 29.33 (t), 40.06 (d), 63.40 (t), 69.15 (d), 69.99 (d), 72.46 (d), 73.73 (d), 170.0 (s), and 172.1 ppm (s).

(Received in USA 9 July 1990)