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Asymmetric synthesis of (−)-4-*epi*-shikimic acid

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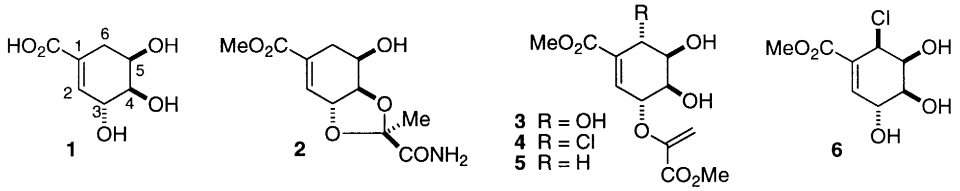
Abstract

The major cycloadduct, arising from the Diels–Alder reaction of maleic anhydride and (1*E*)-(2′,3′,4′,6′-tetra-*O*-acetyl-β-D-glucopyranosyloxy)buta-1,3-diene, is converted into methyl 3-*O*-(β-D-glucopyranosyl)-4-*epi*-shikimate and into (−)-4-*epi*-shikimic acid in overall yields of 20 and 17% (based on the diene).

Keywords: asymmetric synthesis; carbohydrates; Diels–Alder reactions; regioselection; shikimic acid and derivatives.

The 4-*epi*-shikimic acid skeleton **1** is a constituent of numerous natural products, some of which are endowed with interesting biological properties. For example, it is present in dioxolamycin **2**,[1] a cytotoxic agent produced by *Streptomyces filamentosus*, in cyathiformines B–D **3**–**5**,[2] metabolites of *Clitocybe cyathiformis*, and in pericosine A **6**,[3] an antitumour agent obtained from *Periconia byssoides*.



1 **2** **6**

The first synthesis of 4-*epi*-shikimic acid (as a racemate) *rac*-**1** was reported in 1967 by Grewe and Kersten.[4] Subsequently, the material was prepared by the groups of Rapoport[5] and Berchtold.[6] A partial synthesis of (−)-4-*epi*-shikimic acid **1** from D-quinic acid was also developed by both groups.[5,7] To date, the only asymmetric synthesis of a 4-*epi*-shikimic acid derivative is that of Posner and Wettlaufer.[8] The key reaction in their 15-step synthesis, which led to methyl 3,4,5-tri-*O*-acetyl-4-*epi*-shikimate **10**, involved an inverse-electron-demand asymmetric Diels–Alder reaction between the vinyl ether **7** and the pyranone **8** to give the cycloadduct **9** (Scheme 1). We now describe an asymmetric synthesis of 4-*epi*-shikimic acid **1** and of methyl 3-*O*-(β-D-glucopyranosyl)-4-*epi*-shikimate **11**, the first glycoside of a shikimic acid derivative.

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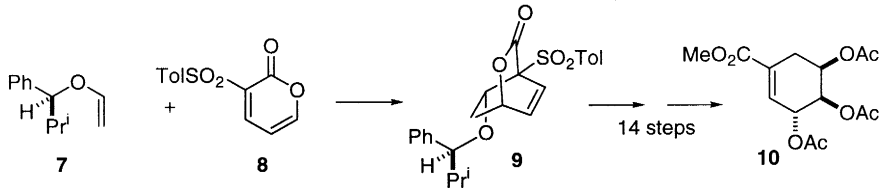
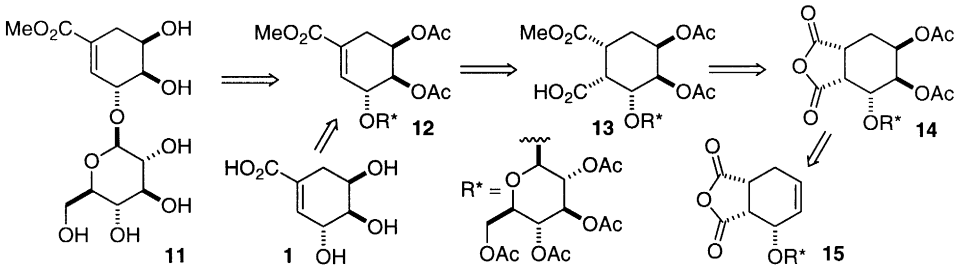


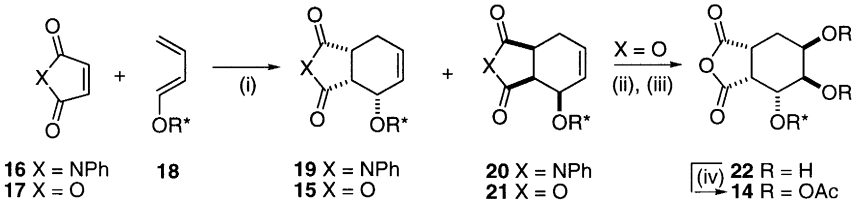
Scheme 1.

It was envisaged that the targets would be accessible from compound **12**, the retrosynthesis of which is outlined in Scheme 2. The key steps would involve: the oxidative decarboxylative elimination of the acid **13**; the regioselective methanolysis of the anhydride **14**; and the stereoselective dihydroxylation of the cyclohexene **15**.



Scheme 2.

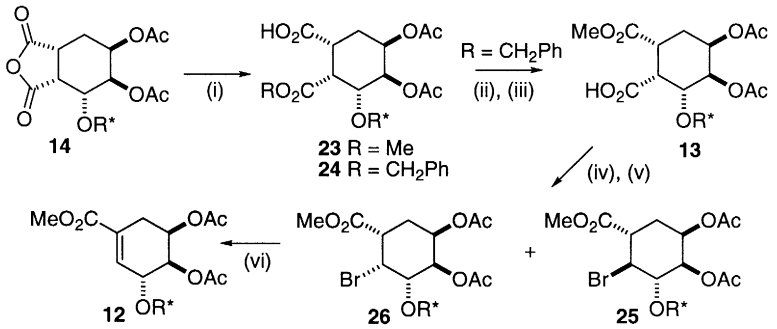
Earlier, we had shown that *N*-phenylmaleimide **16** reacted with the diene **18** (in PhH) to give a mixture of the cycloadducts **19** and **20** (ratio 86:14) (Scheme 3), from which the major cycloadduct **19** was isolated in 59% yield after crystallisation.[9] We hoped that the corresponding reaction with maleic anhydride **17** would provide the cycloadduct **15**. In the event, the reaction (in CH_2Cl_2) afforded a 75:25 mixture of the cycloadducts **15** and **21** (Scheme 3) and several crystallisations were required to provide compound **15** in a stereopure state. A solvent study revealed that the stereoselectivity of the Diels–Alder reaction could be improved to 86:14 (using Me_2SO). Moreover, subjection of the crude product to the Upjohn dihydroxylation procedure[10] followed by crystallisation gave the required diol **22**,[11] mp 208–209°C, $[\alpha]_D$ +23 (*c* 0.26, CH_2Cl_2), in 64% overall yield. Acetylation, under acidic conditions, provided the anhydride **14**,[11] mp 172–173°C, $[\alpha]_D$ +10 (*c* 0.42, CH_2Cl_2), in 84% yield.



Scheme 3. Reagents and conditions: (i) PhH, 20°C, 3 days for **16**; Me_2SO, 20°C, 18 h for **17**; (ii) OsO_4 (10 mol%), NMO (100 mol%), Me_2CO–H_2O (10:1), −10°C, 0.5 h; (iii) crystallisation (from $CHCl_3$); (iv) Ac_2O–$HClO_4$ (cat.), 2 h

As shown in Scheme 4, the anhydride **14** underwent a highly regioselective methanolysis under basic conditions to give largely compound **23**. Although this was the less-preferred outcome in the context of our projected synthesis, it was a simple matter to derive the required methyl ester **13**. Thus, subjection of the anhydride **14** to the action of benzyl alcohol provided compound **24**[11] (83% yield after crystallisation), mp 187–188°C, $[\alpha]_D$ −13 (*c* 0.5, CH_2Cl_2), which was transformed into the methyl ester **13**[11] (91% yield after crystallisation), mp 190–192°C (decomp.), $[\alpha]_D$ −31 (*c* 0.5, CH_2Cl_2), by a

methylation–hydrogenolysis sequence. The acid **13** underwent a Hunsdiecker reaction, using Barton's protocol,[12,13] to give mainly a 62:38 mixture of the bromides **25** and **26**, which was converted into the 4-*epi*-shikimate **12**[11] (53% overall yield after chromatography and crystallisation), mp 144°C, $[\alpha]_D$ −97 (*c* 0.33, CH_2Cl_2), under basic conditions.[14] It was possible to isolate the diastereomeric bromides in pure states after chromatography and crystallisation; compound **25**[11] (45% yield) showed mp 164°C, $[\alpha]_D$ −31 (*c* 0.43, CH_2Cl_2), and compound **26**[11] (31% yield) showed mp 196–197°C, $[\alpha]_D$ −75 (*c* 0.44, CH_2Cl_2).



Scheme 4. Reagents and conditions: (i) MeOH–CH_2Cl_2 (1:4), Et_3N (10 mol%), DMAP (10 mol%), 1 h (for **23**); $PhCH_2OH$ (100 mol%), Et_3N (10 mol%), DMAP (10 mol%), CH_2Cl_2, 2 h (for **24**); (ii) CH_2N_2, Et_2O–CH_2Cl_2; (iii) H_2, 10% Pd–C, CH_2Cl_2, 4 h; (iv) $(COCl)_2$ (250 mol%), DMF (cat.), CH_2Cl_2, 1 h; (v) (under Ar) 2-mercaptopyridine *N*-oxide sodium salt (125 mol%), $BrCCl_3$, 100°C, 1.5 h, addition of AlBN (cat.) in $BrCCl_3$, 100°C, 2 h; (vi) DBN (100 mol%), CH_2Cl_2, reflux, 24 h

As the first representative of a shikimic acid-based glycoside, compound **12** was subjected to an X-ray crystallographic analysis.[15] The molecular structure, shown in Fig. 1, not only validated our stereochemical and regiochemical assignments but also established the overall conformational situation. Thus, the glucose unit adopted the expected chair conformation and the shikimic acid unit the anticipated half-chair conformation. The values for ϕ [H(1′)–C(1′)–O(3)–C(3) torsional angle], ψ [C(1′)–(O3)–C(3)–H(3) torsional angle] and τ [C(1′)–O(3)–C(3) angle] were +49.7, +25.9 and 111.6(5)°, in accord with expectations based upon *exo*-anomeric and torsional effects.[16] Under transesterification conditions [dry MeOH, Amberlite® IRA-420 (OH^-), 6 days], the hexaacetate **12** was transformed into the hexaol **11**,[11,17] (95% yield after crystallisation), mp 121–123°C (decomp.), $[\alpha]_D$ −118 (*c* 0.28, MeOH).

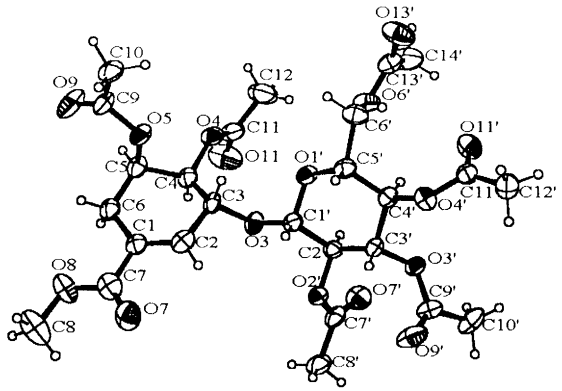


Fig. 1. Molecular structure of compound **12**

Acidic hydrolysis of compound **12** (1 M HCl, reflux, 15 h) gave a mixture of D-glucose and 4-*epi*-shikimic acid **1** which was separated by column chromatography (Dowex® 1×8–200 ion-exchange resin). The acid **1**, obtained as a syrup (ca. 80% yield), showed the reported ^1H NMR spectral properties[5]

although its specific rotation, $[\alpha]_D$ −53 (*c* 0.43, H_2O), was notably smaller than the literature values {$[\alpha]_D$ −93 (*c* 0.9, H_2O)[5] and −80.6 (*c* 1.03, H_2O)[7]}. However, the derived methyl 3,4,5-tri-*O*-acetyl-4-*epi*-shikimate **10** (prepared from **1** by the action of CH_2N_2 in MeOH–Et_2O and Ac_2O–pyridine) displayed a specific rotation, $[\alpha]_D$ −140 (*c* 0.35, MeOH), that was in excellent agreement with the literature values {$[\alpha]_D$ −137 (*c* 1.17, MeOH)[8] and −140 (*c* 0.9, MeOH)[4]}.

The aforecited results are of interest in a number of respects. Thus, the **15**→**22** transformation shows that the dihydroxylation reaction, which displays excellent stereoselectivity, can be effected in the presence of the delicate anhydride ring. The high regioselectivity associated with the alcoholysis of the anhydride ring of compound **14** is surprising. The success of the Barton–Hunsdiecker reaction and the subsequent dehydrobromination, in substrates that would be expected to be prone to aromatisation, is also noteworthy. Finally, as a consequence of the work, the first synthesis of a shikimic acid-based glycoside and the first asymmetric synthesis of 4-*epi*-shikimic acid **1** have been accomplished.

Acknowledgements

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11. This compound gave a satisfactory elemental analysis and showed spectral properties in accord with its assigned structure.
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14. A small amount (ca. 10%) of methyl 3-(2′,3′,4′,6′-tetra-*O*-acetyl-β-D-glucopyranosyloxy)benzoate,[11] mp 100–101°C, $[\alpha]_D$ −35 (*c* 0.25, CH_2Cl_2), was also produced in this reaction.
15. Crystal data for compound **12**: $C_{26}H_{34}O_{16}$, *M*=602.5, orthorhombic, space group $P2_12_12_1$, *a*=17.097(5), *b*=20.017(3), *c*=8.888(2) Å, *V*=3041.9(12) Å,^{3} *Z*=4, D_c=1.316 g cm^{-3}, μ=0.950 mm^{-1} (Cu–Kα, λ=1.54178 Å), *F*(000)=1272, *T*=293(2) K. Rigaku AFC6S diffractometer, crystal size 0.40×0.35×0.10 mm, θ_{max} 64.98°, 2764 reflections measured, 2761 unique. Structure solution by direct methods, full-matrix least-squares refinement on F^2 using SHELX97-2 with all non-hydrogen atoms anisotropic and hydrogen atoms constrained in calculated positions. The final cycle converged to *R*=0.0574 and wR^2=0.1428.
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17. For **11**: δ_H (400 MHz; CD_3OD) 2.49 and 2.58 [each 1H, ddt (*J* 4.5, 18.5 and 1.5 Hz) and ddt (*J* 4, 18.5 and 2.5 Hz), 6-H_2], 3.24 (1H, dd, *J* 8 and 9 Hz, 2′-H), 3.27–3.39 (partly obscured by solvent signals, 4′- and 5′-H), 3.40 (1H, t, *J* 9 Hz, 3′-H), 3.68 and 3.92 [each 1H, dd (*J* 6 and 12 Hz) and dd (*J* 2 and 12 Hz), 6′-H_2], 3.76 (3H, s, MeO_2C), 3.79 (1H, dd, *J* 2.5 and 7 Hz, 4-H), 4.13 (1H, dt, *J* 2.5 and 4.5 Hz, 5-H), 4.45–4.51 (1H, m, 3-H), 4.49 (1H, d, *J* 8 Hz, 1′-H) and 6.89–6.93 (1H, m, 2-H): δ_C (75 MHz; CD_3OD) 32.6 (6-CH_2), 52.8 (CH_3O), 63.1 (6′-CH_2), 69.4 (5-CH), 72.0 (4′-CH), 73.8 (4-CH), 75.3 (2′-CH), 78.4 (3′-CH), 78.6 (5′-CH), 79.6 (3-CH), 104.5 (1′-CH), 130.8 (1-C), 137.3 (2-CH) and 169.1 (ester CO).