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Enantiospecific Synthesis of (-)-5-*epi*-Shikimic Acid and a New Route to (-)-Shikimic Acid

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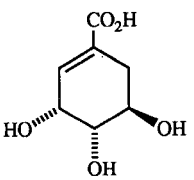
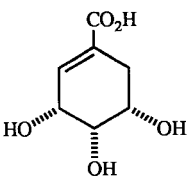
Abstract: (-)-Shikimic acid (**1**) and (-)-5-*epi*-shikimic acid (**2**) have each been prepared enantiospecifically and with high diastereoselectivity from D-ribose.

(-)-Shikimic acid (**1**) is a key biosynthetic intermediate which gives its name to the pathway by which the aromatic aminoacids and a wide range of secondary metabolites are formed in living systems.[1] The biochemical significance of **1** has led to much interest in its chemical synthesis,[1,2] and, following an early synthesis of the (-)-enantiomer **1** from D-arabinose,[3] a number of other reports have appeared on the conversion of sugars to (-)-**1**.[4] Here we report new direct routes both to (-)-**1** and to the previously unreported (-)-5-*epi*-shikimic acid (**2**)[5] from D-ribose, involving intramolecular nitrone cycloaddition (INC) reactions[6] to establish the carbocyclic ring.[7]

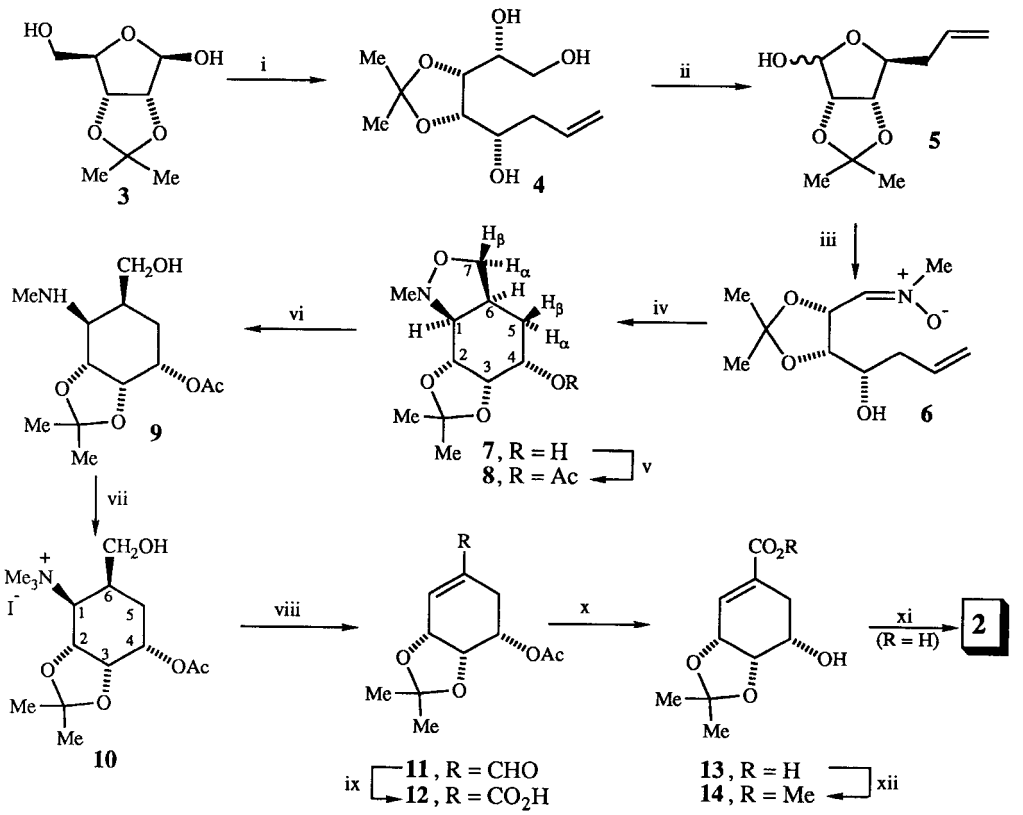


1



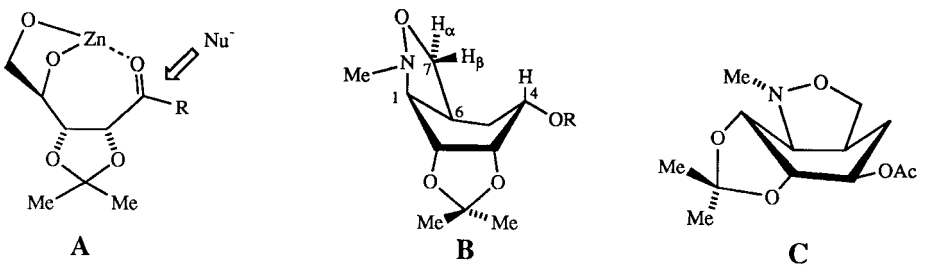
2

We have previously shown that reaction of 2,3-*O*-isopropylidene-D-ribose (**3**) with diallylzinc gives the D-*allo*-triol **4** (Scheme 1) with high diastereoselectivity,[8] a result which can be rationalized by reaction either via a Felkin-Anh transition state, or via the cyclic chelate **A** (R = H, Nu = allyl).[9] Periodate cleavage of **4** gave **5**[8] in quantitative yield, and on treatment with MeNHOH.HCl in pyridine, nitrone **6** was isolated in 98% yield after chromatography. Thermolysis of **6** (toluene, reflux, 18 h) gave the cycloadduct **7**[10] (67%) with only very minor traces of an isomer. The stereochemistry of **7** follows from ^{1}H-nmr studies on **7** and its *O*-acetyl derivative **8**.[10] Strong n.O.e. effects were observed for **8** between H-1 and H-6 and between H-6 and H-7α, implying a *cis*-ring junction; n.O.e. effects between H-7β and H-4, together with coupling constant data[10] (e.g. for **7**, $J_{1,6}$ 9.0 Hz, $J_{4,5\alpha}$ 9.5 Hz) indicate a conformation for **7** and **8** as indicated in **B**.[11]
Hydrogenation of **8** over Pearlman's catalyst gave the aminoalcohol **9** in quantitative yield, and this could be converted (87%) to the quaternary salt **10**[10] by treatment with MeI-K_2CO_3 in THF. When **10** was oxidized

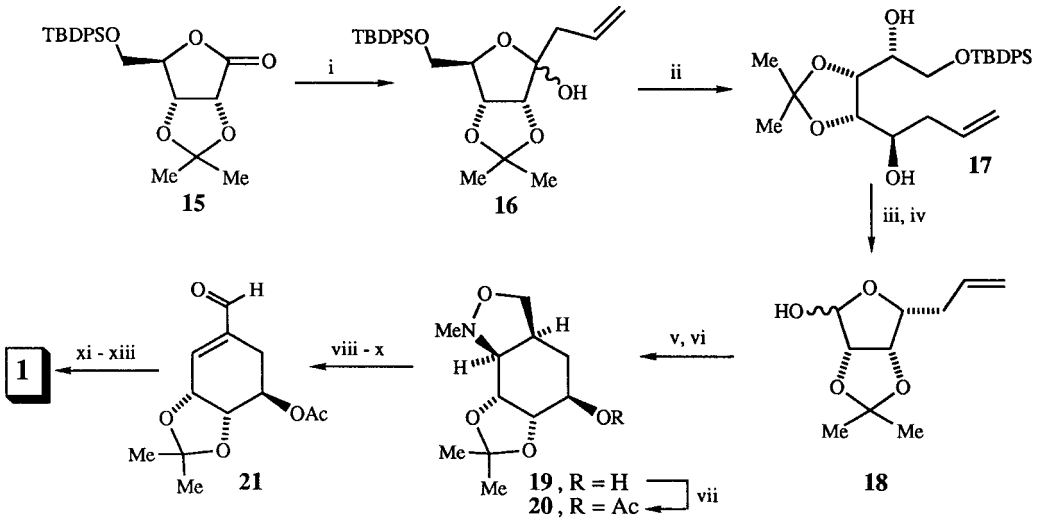


Scheme 1. i, diallylzinc, Et_2O, 0 °C; ii, $NaIO_4$, H_2O, r.t., 2 h; iii, MeNHOH.HCl, C_5H_5N, r.t., 17 h; iv, PhMe, reflux, 17h; v, Ac_2O, DMAP, C_5H_5N; vi, $Pd(OH)_2/C$, H_2, MeOH; vii, MeI, K_2CO_3, THF, r.t., 30 h; viii, DMSO, $(COCl)_2$, CH_2Cl_2, -78 °C, 50 min, then Et_3N, -78 °C to r.t.; ix, $NaClO_2$, H_2O_2, NaH_2PO_4, MeCN, r.t., 1 h; x, K_2CO_3, MeOH-H_2O, r.t.; xi, TFA-H_2O, r.t., 10 h; xii, CH_2N_2, Et_2O.

under Swern conditions, β-elimination occurred spontaneously to give the enal **11** in 79% yield, which could be readily oxidized to acid **12** (67%) using $NaClO_2$ and H_2O_2 under buffered conditions.[12] Deacetylation to give **13**, followed by acidic hydrolysis, gave (-)-5-*epi*-shikimic acid (**2**) (80% overall), m.p. 155-156.5 °C, $[\alpha]_D$ -57.6° (*c* 0.8, MeOH). Treatment of **13** with ethereal diazomethane gave the methyl ester **14** as an oil, $[\alpha]_D$ +26.8° (*c* 0.67, $CHCl_3$) [Lit., -23.9° (*c* 1.17, CH_2Cl_2),[5a] -33.0° (*c* 0.67, $CHCl_3$)[5b] for the enantiomer].



Attempts to carry out an inversion of stereochemistry at C-4 of alcohol **7**, in order to prepare shikimic acid (**1**), were unsuccessful under a variety of conditions. Other workers have reported that racemic methyl ester **14** can be converted into its C-5 epimer, but the procedure was indirect and low yielding.[5c] We thus investigated a modified route as shown in Scheme 2, in which the alternative stereochemistry appropriate for shikimic acid (**1**) was incorporated at an early stage.



Scheme 2. i, allyl MgCl, THF, -78 °C, 3 h; ii, DIBAL, PhMe, -78 °C, 3 h; iii, TBAF, THF; iv, $NaIO_4$, H_2O, r.t., 2 h; v, MeNHOH.HCl, C_5H_5N, r.t., 20 h; vi, PhMe, reflux, 18 h; vii, Ac_2O, DMAP, C_5H_5N; viii, $Pd(OH)_2/C$, H_2 (2 atm.), MeOH; ix, MeI, K_2CO_3, THF, r.t., 30 h; x, DMSO, $(COCl)_2$, CH_2Cl_2, -78 °C, 55 min, then Et_3N, -78 °C to r.t.; xi, $NaClO_2$, H_2O_2, NaH_2PO_4, MeCN, r.t., 1 h; xii, K_2CO_3, MeOH-H_2O, r.t.; xiii, TFA-H_2O, r.t.

The D-ribonolactone derivative **15**, accessible either from **3** by sequential silylation and oxidation, or from D-ribonolactone,[13] was treated with allylmagnesium chloride at low temperatures to give the lactol **16** (80%) as an anomeric mixture. Reduction of **16** with DIBAL gave a single diol **17** (88%) which was different from that obtained by selective silylation of **4**. The stereoselectivity can again be rationalized either by the Felkin-Anh model, or via a chelated transition state similar to **A** (R = allyl, Nu = H). Desilylation of **17**, followed by periodate cleavage, gave the hemiacetals **18** in high yield. Treatment with MeNHOH.HCl in pyridine, followed by heating of the crude nitrone in toluene, led to a single isoxazolidine **19** (95%), which was acetylated to give **20**. The stereochemistry of **20** followed from ^{1}H-nmr data,[14] which supported a conformation as indicated in **C**. Further manipulation as in the previous Scheme led to the aldehyde **21**[14] (57% overall). Oxidation with $NaClO_2$-H_2O_2, deacetylation, and acid hydrolysis then gave (72% overall) (-)-shikimic acid (**1**), $[\alpha]_D$-175.4° (*c* 0.59, H_2O) [Lit.[3] -179.7° (*c* 4, H_2O)].

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10. Selected data: **7**: $[\alpha]_D$-74° (*c* 4.2, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 1.27 (1H, ddd, J_{gem} 13.6, $J_{5\beta,6}$ 4.25, $J_{5\beta,4}$ 2.65, H-5β), 1.32 and 1.46 (each 3H,s), 2.01 (1H, ddd, *J* 13.6, $J_{5\alpha,4}$ 9.5, $J_{5\alpha,6}$ 7.2, H-5α), 2.40 (1H, br s, OH), 2.64 (3H, s, NMe) 2.89 (1H, dd, $J_{1,6}$ 9.0, $J_{1,2}$ 3.2, H-1), 2.96 (1H, m, H-6), 3.48 (1H, dd, J_{gem} 8.4, $J_{7\alpha,6}$ 6.3 H-7α), 4.06 (1H, br d, *J*~9.4, H-4), 4.14 (1H, t, *J* 8.3, H-7β), 4.20 (2H, m, H-2, H-3); **8**: m.p. 104 °C, $[\alpha]_D$ -144.6° (*c* 1.3, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 1.36 and 1.52 (each 3H, s), 1.38 (1H, m, H-5β), 2.09 (3H, s, OAc), 2.12 (1H, ddd, J_{gem} 13.2, $J_{5\alpha,4}$ 11.4, $J_{5\alpha,6}$ 7.05, H-5α), 2.70 (3H, s, NMe), 2.80 (1H, dd, $J_{1,6}$ 8.9, $J_{1,2}$ 2.5, H-1), 2.99 (1H, m, H-6), 3.65 (1H, dd, *J* 8.5, 6.5, H-7α), 4.16 (1H, t, *J* 8.4, H-7β), 4.28 (1H, dd, $J_{2,3}$ 7.7, $J_{2,1}$ 2.6, H-2), 4.43 (1H, ddd, $J_{3,2}$ 7.7, $J_{3,4}$ 6.6, $J_{3,5\beta}$ 1.1, 3-H), 5.3 (1H, ddd, $J_{4,3}$ 6.6, $J_{4,5\alpha}$ 11.5, $J_{4,5\beta}$ 3.3, 4-H). **10**: m.p. 102-107 °C, $[\alpha]_D$ + 3.8° (*c* 1.04, H_2O); δ_H (400 MHz, $CDCl_3$) 1.37 and 1.63(each 3H, s), 1.96 (1H, dt, *J* 13.8 and 4.2, H-5β), 2.10 (3H, s), 2.29 (1H, ddd, J_{gem} 13.8, $J_{5\alpha,4}$ 10.6, $J_{5\alpha,6}$ 4.6, H-5α), 2.97 (1H, m, H-6), 3.59 (9H, s), 3.83 (1H, ddd, H-7a), 3.89 (1H, dt, H-7b), 4.07 (1H, dd, $J_{1,2}$ 9.8, $J_{1,6}$ 3.9, H-1), 4.13 (1H, t, OH), 4.57 (1H, t, *J* 4.9, H-3), 4.97 (1H, dd, J 9.8, 5.6, H-2), 5.22 (1H, dt, *J* 10.6, 4.9, H-4).

11. The structure of **8** was confirmed by X-ray crystallography: K.J. McCullough, unpublished data.

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14. Selected data: **20** : $[\alpha]_D$ -113.8° (*c* 1.66, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 1.35 and 1.48 (each 3H, s), 1.48(1H, q, J~12, H-5β), 1.95(1H, ddd, J_{gem} 12.6, $J_{5\alpha,6}$ 6.0, $J_{5\alpha,4}$ 3.6, H-5α), 2.08 and 2.74 (each 3H, s), 2.87 (2H, m, H-1, H-6), 3.56 (1H, dd, J 8.2, 3.1, H-7a), 4.14-4.23(3H, m, H-2, H-3, H-7b), 4.83(1H, ddd, $J_{4,5\beta}$ 12.6, $J_{4,3}$ 7.5, $J_{4,5\alpha}$ 3.6, H-4). **21** : $[\alpha]_D$ -84.1° (*c* 1.38, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 1.39, 1.40 and 2.04 (each 3H, s), 2.31 (1H, dd, *J* 17.7, 6.0, H-6a), 2.65 (1H, ddt, J 17.7, 4.5, 1.4(x2), H-6b), 4.30 (1H, t, *J* 6.0, H-4), 4.82 (1H, m, H-3), 5.20(1H, td, J 6.0, 6.0, 4.6, H-5), 6.69 (1H, m, H-2), 9.54 (1H, s, CHO).