Synthesis of trimethyl (2*S*,3*R*)- and (2*R*,3*R*)-[2-$^2H_1$]-homocitrates and dimethyl (2*S*,3*R*)- and (2*R*,3*R*)-[2-$^2H_1$]-homocitrate lactones—an assay for the stereochemical outcome of the reaction catalysed both by homocitrate synthase and by the Nif-V protein†‡

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Trimethyl (3*R*)-homocitrate **17**, trimethyl (2*S*,3*R*)-[2-$^2H_1$]-homocitrate **17a** and (2*R*,3*R*)-[2-$^2H_1$]-homocitrate **17b**, as well as dimethyl (3*R*)-homocitrate lactone **18**, (2*S*,3*R*)-[2-$^2H_1$]-homocitric lactone **18a** and (2*R*,3*R*)-[2-$^2H_1$]-homocitric lactone **18b** have been synthesised. D-Quinic acid **12** was used as the source of the (3*R*)-centre in the unlabelled target compounds **17** and **18**. (−)-Shikimic acid **19** and the (−)-[2-^2H]-shikimic acid derivative **32** respectively were used in the synthesis of the labelled compounds. In the latter syntheses, Sharpless directed epoxidation of the olefin in the 5-deoxy ester diols **23** and **35** ensured a reaction from the same face as the allylic and homoallylic alcohols, and the reduction of the protected epoxides **25** and **37** ensured that the label was introduced in a stereoselective manner. The ^{1}H NMR spectra of the labelled products present an assay for the stereochemistry of the biological reactions catalysed by homocitrate synthase and by the protein from the *nifV* gene.

Introduction

Homocitric acid **3** is a key intermediate in the biosynthetic pathway to the essential amino acid L-lysine **9** in fungi and euglenids. It is synthesised in this pathway as shown in step (i) of Scheme 1 by the reaction of acetyl CoA **1** with α-ketoglutarate **2** catalysed by the enzyme homocitrate synthase (EC 4.1.3.21).[2] The pathway involves the intermediate α-aminoadipic acid **7**, required in the biosynthesis of penicillins and cephalosporins and there has been a suggestion that homocitrate synthase limits α-aminoadipic acid formation in penicillin biosynthesis.[3] Homocitric acid **3** is also required in nitrogen fixation where reaction (i) in Scheme 1 is catalysed by the protein derived from the *nifV* gene.[4] Patients with the disease propionic acidaemia have been shown to excrete homocitric acid **3**.[5]

The steps in the lysine pathway to α-aminoadipic acid **7** closely parallel those steps in the citrate cycle from the reaction of acetyl CoA **1** with oxaloacetic acid **10** to give citric acid **11**, *via* isocitrate and α-ketoglutarate to glutamic acid. It has been shown that homocitrate synthase catalyses the attack of acetyl CoA **1** on the carbonyl group of α-ketoglutarate **2** from the *re*-face,[6] unlike the more common *si*-citrate synthase (EC 4.1.3.7) which catalyses the attack of acetyl CoA **1** on the carbonyl group of oxaloacetate **10** from the *si*-face as shown in Scheme 2.[7] The stereochemistry at the acetate methyl group has been shown to be inverted during the reaction catalysed by *si*-citrate synthase as shown in Scheme 2, by using (*R*)- and (*S*)-[2-$^2H_1$,2-$^3H_1$]-acetyl CoA **1** ($H_A = {}^3H$, $H_B = {}^2H$) and **1** ($H_A = {}^2H$, $H_B = {}^3H$) respectively in the reaction.[8] However this aspect of the stereochemistry in the analogous reactions catalysed by homocitrate synthase and by the *nifV* gene protein has yet to be investigated. Unlike citric acid **11**, homocitric acid **3** has an asymmetric centre and so the two hydrogens, H_A and H_B, arising from acetate in this product are diastereotopic. Assignment of stereochemistry to the chemical shifts arising from these hydrogens in the ^{1}H NMR spectrum will therefore allow the stereochemistry of step (i) in Scheme 1 to be assessed by ^{3}H NMR spectroscopy when (*R*)- and (*S*)-[2-$^2H_1$,2-$^3H_1$]-acetylCoA are used in the enzymatic reaction. We have therefore determined to synthesise trimethyl (3*R*)-homocitrate **17**, (2*S*,3*R*)-[2-$^2H_1$]-trimethyl homocitrate **17a** and (2*R*,3*R*)-[2-$^2H_1$]-trimethyl homocitrate **17b** and the corresponding dimethyl homocitric lactones **18**, **18a** and **18b**, using reactions which are stereochemically unambiguous. Since homocitrate **3** from the enzymic reactions can readily be converted to the esters **17** and **18** without racemisation,[9] an assay for the stereochemistry of the enzymic reaction will be provided by such a synthesis.

Results and discussion

Since quinic acid **12** could serve as the source of the 3*R* centre of homocitrate by specifically removing the hydroxyl group at C-5 and oxidatively cleaving the vicinal *cis*-3,4-diol, we used the method of Shing and Tang[10] to prepare the derivative **13**, in which the *cis*-3,4-diol moiety is protected. Conversion of this protected derivative to the thiocarbonylimidazole derivative **14** in 89% yield was achieved by reaction with 1,1′-thiocarbonyldiimidazole in dichloromethane, as shown in Scheme 3. Reduction using Bu_3SnH and AIBN in toluene at reflux then afforded the protected

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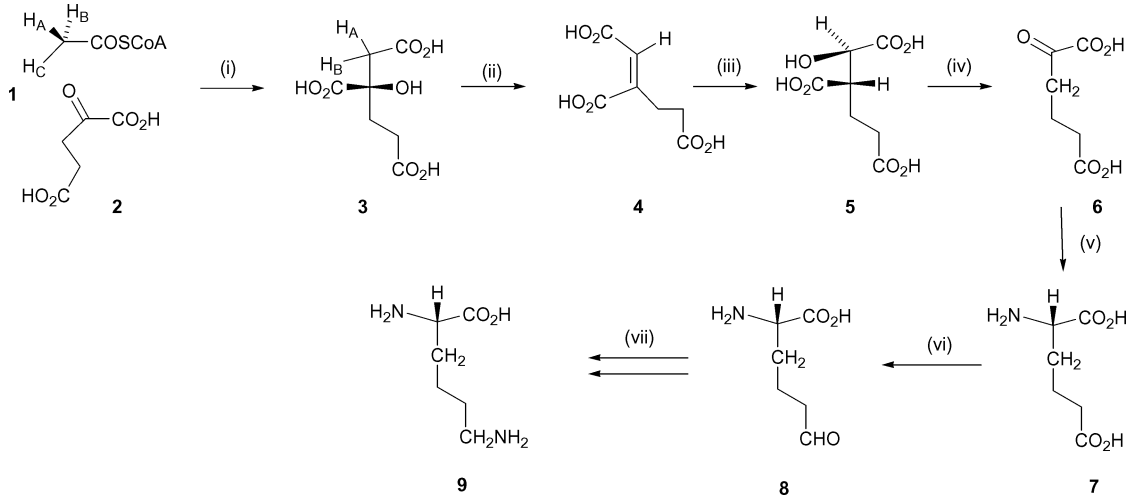
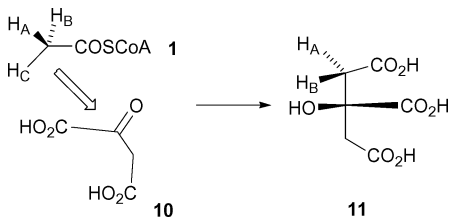
† Part of this work has been published as a preliminary communication in ref. 1.

‡ Electronic supplementary information (ESI) available: NMR spectra for all described compounds. See DOI: 10.1039/b515937g



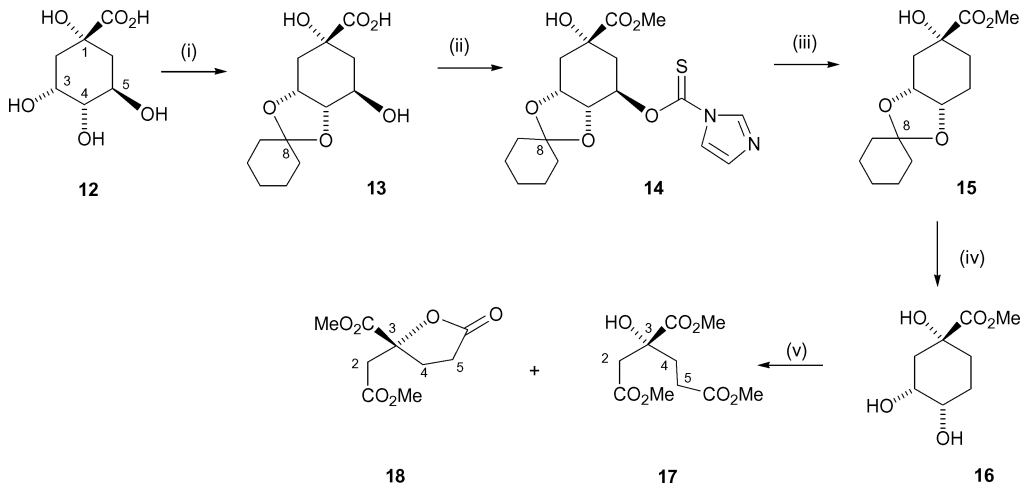
Scheme 1 *Enzymes of the fungal pathway to lysine*: (i) homocitrate synthase (EC 4.1.3.21); (ii) and (iii) homoaconitase (EC 4.2.1.36); (iv) homoisocitrate dehydrogenase (EC 1.1.1.87); (v) aminoadipate aminotransferase (EC 2.6.1.39); (vi) aminoadipate reductase (EC 1.2.1.31); (vii) other enzymes in the biosynthetic pathway to lysine in fungi and euglenids.



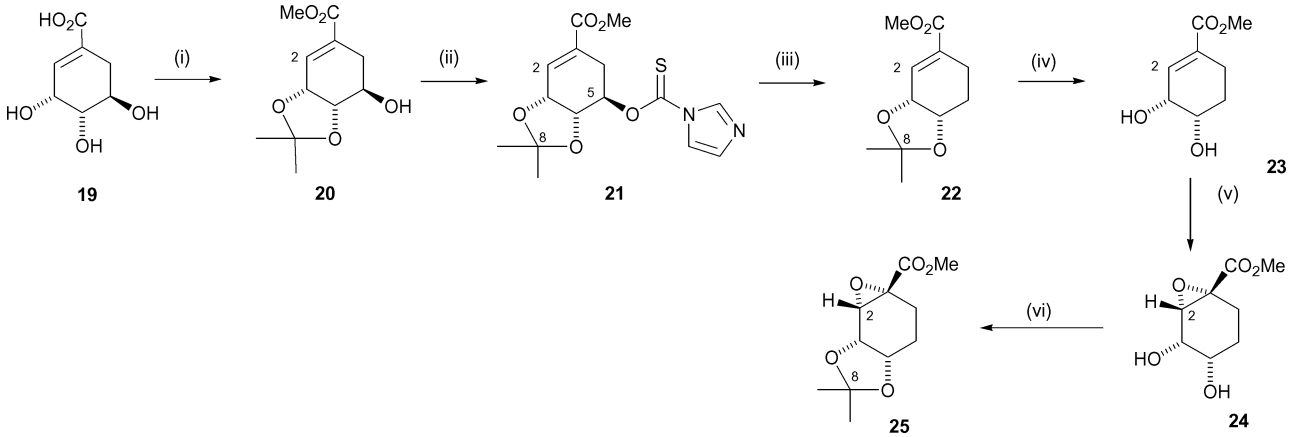
Scheme 2 Stereochemistry of the reaction catalysed by *si*-citrate synthase (EC 4.1.3.7).

5-deoxyquinate **15** in 83% yield. Deprotection using Amberlite IR-120 (H^+) gave the diol **16** in 70% yield and this was cleaved using periodate on silica gel followed by oxidation with H_2O_2 and formic acid. *In situ* methylation of the product gave a mixture which was separated by chromatography on silica gel to afford, as oils, trimethyl (3*R*)-homocitrate **17** in 36% yield and dimethyl (3*R*)-homocitric lactone **18** in 15% yield.

Having obtained the unlabelled target molecules, the next step was to synthesise the two compounds **17** and **18** in which the hydrogen atoms on the carbon derived from acetate in the enzymic reaction were diastereomerically deuteriated using methods which would allow unambiguous assignment of their stereochemistry. A possible synthetic intermediate for such a synthesis would be the 5-deoxyshikimate ester **23** in which the allylic and homoallylic hydroxyl groups would direct Sharpless epoxidation[11] of the double bond to the lower face of the molecule. Protection of the hydroxyl groups and reduction of the epoxide should deliver deuteride to the opposite face of the molecule from the epoxide oxygen. To this end, we prepared the isopropylidine derivative **20** from commercial (−)-shikimic acid **19** by the method of Chahoua *et al.*[12] and this was converted into the thiocarbonylimidazole derivative **21** by reaction with 1,1′-thiocarbonyldiimidazole in dichloromethane as shown in Scheme 4. Reduction using tri-*n*-butyltin hydride and AIBN in toluene at reflux under argon then gave the 5-deoxy derivative **22** in good yield. Deprotection



Scheme 3 *Reagents and conditions*: (i) ref. 10; (ii) 1,1′-thiocarbonyldiimidazole, CH_2Cl_2, rt, 16 h (89%); (iii) Bu_3SnH, AIBN, toluene, reflux, 3 h (83%); (iv) Amberlite IR-120 (H^+), MeOH, reflux, 3 h (70%); (v) (a) $NaIO_4$-silica gel, CH_2Cl_2, (b) H_2O_2, HCO_2H, rt, 6 h, (c) Amberlite IR-120 (H^+), MeOH, reflux, 16 h (36% **17** + 15% **18**).



Scheme 4 *Reagents and conditions*: (i) ref. 12; (ii) 1,1′-thiocarbonyldiimidazole, CH_2Cl_2, rt, 16 h (95%); (iii) Bu_3SnH, AIBN, toluene, reflux, 3 h (72%); (iv) Amberlite IR-120 (H^+), MeOH, reflux, 3 h (79%); (v) ^{t}BuOOH, CH_2Cl_2, $V(acac)_3$, 0 °C then rt, 24 h (57%); (vi) $(MeO)_2CMe_2$, (±)-10-camphorsulfonic acid, CH_2Cl_2, rt, 3 h (quant., unpurified).

was now required so that epoxidation of the double bond would be directed to the same face as the 3- and 4-hydroxyl groups. This was achieved in 79% yield using Amberlite IR-120 (H^+) in methanol, and epoxidation of the product **23** was carried out using *tert*-butylhydroperoxide and vanadyl acetylacetonate in dichloromethane, giving the diol epoxide **24** in 57% yield. W-Coupling between H-2 and H-4, observed in the ^{1}H NMR spectrum of this compound, suggested that these hydrogens were *quasi*-equatorial as shown in Fig. 1 and so implied that the expected (2*S*)-stereochemistry had been obtained. Reprotection of the secondary alcohol groups was now necessary to prevent their involvement in subsequent steps and this was carried out in quantitative yield using 2,2-dimethoxypropane and (±)-10-camphorsulfonic acid, giving the product **25**.

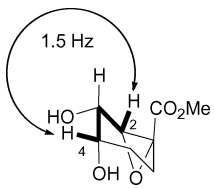
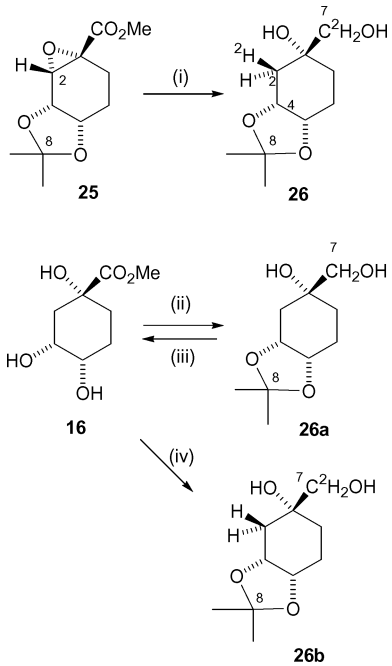


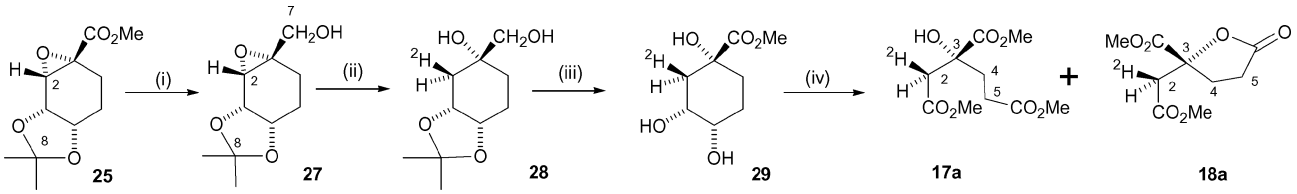
Fig. 1 W-Coupling between H-2 and H-4 in the epoxide **24**.

It was now necessary to introduce a deuterium label stereospecifically at C-2 whilst retaining the *R* stereochemistry at C-1 (corresponding to C-3 in homocitric acid). This was achieved in 83% yield by reacting the epoxide **25** with lithium aluminium deuteride to obtain product **26** as shown in Scheme 5. The unlabelled analogue **26a** of this compound was prepared independently from the quinic acid derived **16** as shown in Scheme 5 by protection followed by reduction using $LiAlH_4$. Comparison of the spectra of the shikimate-derived product **26** and the quinate-derived product **26a** confirmed the stereochemistry at the centre C-1 in the former compound. To reach our target molecule required that we oxidised the deuteriated primary alcohol group in the product **26** to an acid but all attempts to achieve this failed. In contrast, oxidation of the unlabelled compound **26a** using oxygen and a platinum catalyst, followed by methylation and deprotection, gave the desired methyl 5-deoxyquinate **16**. This suggested that an isotope effect had prevented oxidation of



Scheme 5 *Reagents and conditions*: (i) $LiAl^2H_4$, Et_2O, −78 °C, 5 h, then 0 °C, 1 h (83%); (ii) (a) $(MeO)_2CMe_2$, (±)-10-camphorsulfonic acid, CH_2Cl_2, rt, 1 h, (b) $LiAlH_4$, Et_2O, −78 °C, 5 h, then 0 °C, 1 h (89%); (iii) (a) O_2, Pt, $NaHCO_3$, H_2O–MeOH, 55 °C, 16 h (b) Amberlite IR-120 (H^+), MeOH, reflux, 16 h, (65%); (iv) (a) $(MeO)_2CMe_2$, (±)-10-camphorsulfonic acid, CH_2Cl_2, rt, 1 h, (b) $LiAl^2H_4$, Et_2O, −78 °C, 5 h, then 0 °C, 1 h (89%).

the deuteriated primary alcohol group in the compound **26** and indeed when the dideuterio-compound **26b** was prepared from methyl deoxyquinate **16** as in Scheme 5, this was also resistant to oxidation. The problem was circumvented by first selectively reducing the ester in compound **25**, as shown in Scheme 6, using sodium borohydride which did not affect the epoxide. The product **27** was then reduced with lithium aluminium deuteride to afford the desired alcohol **28** in 83% yield. This compound was oxidised using oxygen and platinum oxide and treated with methanol and Amberlite IR-120 (H^+) to give the deprotected methyl ester **29** in

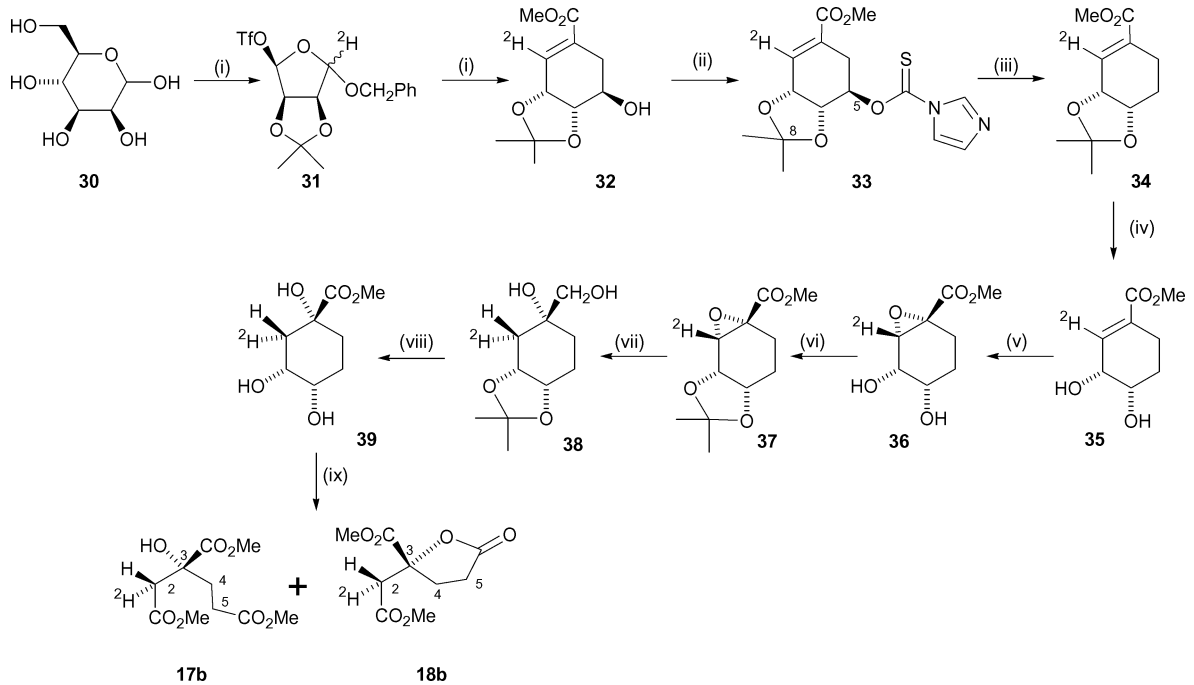


Scheme 6 *Reagents and conditions*: (i) $NaBH_4$, THF, 0 °C, rt, 14 h (92%); (ii) $LiAl^2H_4$, Et_2O, −78 °C, 5 h, then 0 °C, 1 h (83%); (iii) (a) O_2, Pt, $NaHCO_3$, H_2O–MeOH, 55 °C, 16 h, (b) Amberlite IR-120 (H^+), MeOH, reflux, 16 h (69%); (iv) (a) $NaIO_4$–silica-gel, CH_2Cl_2, rt, 10 min, (b) H_2O_2, HCO_2H, rt, 6 h, (c) Amberlite-120 (H^+), MeOH, reflux, 16 h (38% **17a** + 16% **18a**).

69% yield. Oxidative cleavage of the diol using sodium periodate and silica gel in dichloromethane followed by methylation using methanol and Amberlite IR-120 (H^+) gave a mixture from which trimethyl (2*S*,3*R*)-[2-$^2H_1$]-homocitrate **17a** and dimethyl (2*S*,3*R*)-[2-$^2H_1$]-homocitric lactone **18a** could be separated.

To obtain the diastereoisomeric (2*R*)-[2-$^2H_1$]-compounds, **17b** and **18b**, we prepared the protected [2-$^2H_1$]-shikimate **32** by adapting the method by Floss *et al.*[13] The labelled protected lyxofuranoside derivative **31** was first prepared from D-mannose **30** by modification of a method developed by Fleet *et al.*[14] for the unlabelled compound and its derivatives as shown in Scheme 7. This compound was then converted into the protected [2-$^2H_1$]-shikimate ester **32** by the method described by Fleet *et al.* for the unlabelled *tert*-butyl ester.[14b] The protected [2-$^2H_1$]-shikimate ester **32** was then converted into the thiocarbonylimidazole derivative **33** in quantitative yield by reaction with 1,1′-thiocarbonyldiimidazole in dichloromethane. This was reduced using tri-*n*-butyltin hydride and AIBN in toluene at reflux under argon to give the 5-deoxy compound **34**, and deprotection using Amberlite IR-120 (H^+) in methanol at reflux gave the deuteriated methyl 5-deoxyshikimate **35**. The epoxide **36** was then obtained in 59% yield using the method that we had previously employed to prepare the unlabelled compound **24**. Reprotection using 2,2-dimethoxypropane and (±)-10-camphorsulfonic acid in dichloromethane gave the isopropylidene derivative **37** in quantitative yield and this was reduced with lithium aluminium hydride in diethyl ether to give the alcohol **38**. Deprotection to the diol **39**, oxidative cleavage and methylation as before gave compounds **17b** and **18b** in 40% and 15% yields respectively. The coupling constants $J_{2,3}$ in the ^1H NMR spectra of the epimerically deuteriated compounds **39** (2.9 Hz) and **29** (6.8 Hz) in $C^2H_3O^2H$ are in line with the expectation from the stereochemistry assigned to C-2.

The ^1H NMR spectra of the various samples of trimethyl homocitrate **17**, **17a** and **17b** are shown in Fig. 2 and those for the samples of dimethyl homocitric lactone **18**, **18a** and **18b** in Fig. 3. These spectra clearly define the chemical shifts due to the protons which are derived from acetyl CoA **1** in the reaction catalysed by homocitrate synthase or by the nif-V protein and so an assay is now available to assess the absolute stereochemistry of these biosynthetic reactions.



Scheme 7 *Reagents and conditions*: (i) refs 13,14; (ii) 1,1′-thiocarbonyldiimidazole, CH_2Cl_2, rt, 16 h (quant.); (iii) Bu_3SnH, AIBN, toluene, reflux, 3 h (80%); (iv) Amberlite IR-120 (H^+), MeOH, reflux, 3 h (80%); (v) ^{t}BuOOH, CH_2Cl_2, $V(acac)_3$, 0 °C, then rt, 24 h (59%); (vi) $(MeO)_2CMe_2$, (±)-10-camphorsulfonic acid, CH_2Cl_2, rt, 3 h (quant., unpurified); (vii) $LiAlH_4$, Et_2O, −78 °C, 5 h, then 0 °C, 1 h (87%); (viii) (a) O_2, Pt, $NaHCO_3$, H_2O–MeOH, 55 °C, 16 h, (b) Amberlite IR-120 (H^+), MeOH, reflux, 16 h (65%); (ix) (a) $NaIO_4$–silica-gel, CH_2Cl_2, rt, 10 min, (b) H_2O_2, HCO_2H, rt, 6 h, (c) Amberlite-120 (H^+), MeOH, reflux, 16 h (40% **17b** + 15% **18b**).

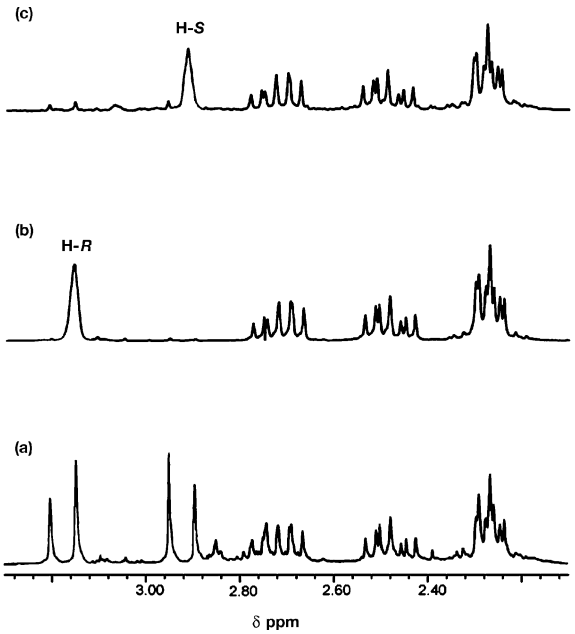


Fig. 2 Part of the 300 MHz ^{1}H NMR spectra in C^2HCl_3 of (a) trimethyl (3*R*)-homocitrate **17**; (b) trimethyl (2*S*,3*R*)-[2-^{2}H$_1$]-homocitrate **17a**; and (c) trimethyl (2*R*,3*R*)-[2-^{2}H$_1$]-homocitrate **17b**.

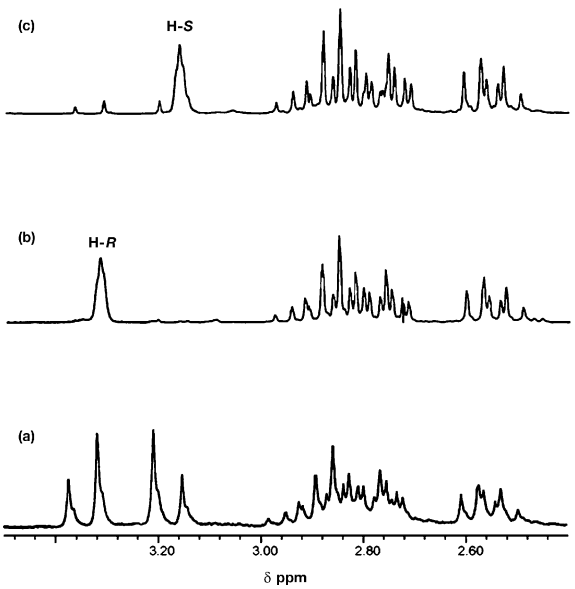


Fig. 3 Part of the 300 MHz ^{1}H NMR spectra in C^2HCl_3 of (a) dimethyl (3*R*)-homocitric lactone **18**; (b) dimethyl (2*S*,3*R*)-[2-^{2}H$_1$]-homocitric lactone **18a**; and (c) dimethyl (2*R*,3*R*)-[2-^{2}H$_1$]-homocitric lactone **18b**.

Conclusion

We have completed the total synthesis of trimethyl (3*R*)-homocitrate **17**, trimethyl (2*S*,3*R*)-[2-^{2}H$_1$]-homocitrate **17a** and (2*R*,3*R*)-[2-^{2}H$_1$]-homocitrate **17b**, and of dimethyl (3*R*)-homocitrate lactone **18**, (2*S*,3*R*)-[2-^{2}H$_1$]-homocitric lactone **18a** and (2*R*,3*R*)-[2-^{2}H$_1$]-homocitric lactone**18b**. The ^{1}H NMR spectra of the labelled products present an assay for the stereochemistry of the biological reactions catalysed by homocitrate synthase and by the protein from the *nifV* gene.

Experimental

Melting points were determined on a Kofler hot-stage apparatus and are uncorrected. Optical rotations (given in units of 10^{-1} deg cm^{-2} g^{-1}) were measured on a Perkin-Elmer PE241 polarimeter using a 1 dm path length micro cell. IR spectra were recorded on a Perkin-Elmer 1720 Fourier transform instrument. ^{1}H NMR spectra were recorded on Bruker DPX300 (300 MHz) and AMX500 (500 MHz) Fourier transform instruments. *J* values are given in Hz. ^{13}C NMR spectra (broad band ^{1}H decoupled) were recorded on Bruker DPX300 (75.5 MHz) and AMX500 (125.8 MHz) Fourier transform instruments. Distortionless enhancement polarisation transfer (DEPT) experiments were used to help assign ^{13}C NMR resonances where necessary. Either tetramethylsilane (0.00 ppm) or residual solvent peaks were used as internal references in the NMR spectra unless otherwise stated. Mass spectra were recorded on Kratos MS80F and MS25 double focusing spectrometers by Dr A. Abdul-Sada (Sussex). 3-NBA refers to 3-nitrobenzyl alcohol. Accurate mass measurements were recorded by the EPSRC National Mass Spectrometry Service, Swansea. Microanalyses were performed by Medac Ltd (Brunel). Column chromatography was performed using Fluka silica gel 60 (200–400 mesh ASTM). Petroleum ether refers to that fraction of hexanes of bp 60–80 °C.

Methyl (1*R*,3*R*,4*S*,5*R*)-3,4-*O*-cyclohexylidine-5-(1*H*-imidazole-1-carbonothioyloxy)-1,3,4-trihydroxycyclohexanecarboxylate (14)

1,1′-Thiocarbonyldiimidazole (5.52 g, 31.0 mmol) was added to a solution of methyl 3,4-*O*-cyclohexylidenequinate **13**[10] (7.4 g, 25.8 mmol) in dichloromethane (50 ml) and the resultant yellow solution was stirred at room temperature under argon for 16 h. The solvent was removed *in vacuo* to give a yellow oil which was purified by column chromatography on silica gel eluting with diethyl ether to give methyl (1*R*,3*R*,4*S*,5*R*)-3,4-*O*-cyclohexylidine-5-(1*H*-imidazole-1-carbonothioyloxy)-1,3,4-trihydroxycyclohexanecarboxylate **14** as a white solid (9.1 g, 89%), mp 146.5–147.5 °C; $[\alpha]_D^{24}$ −50.8 (*c* 1.5, $CHCl_3$); found: C, 54.5; H, 6.05; N, 7.3; $C_{18}H_{24}N_2O_6S$ requires C, 54.5; H, 6.1; N 7.1%); *m*/*z* (+ve FAB, (3-NBA)) 397 $[M + H]^+$; ν_{max} (KBr)/cm^{-1} 3133 (OH) and 1741 (ester); δ_H (500 MHz, C^2HCl_3) 1.39 (2H, m, cyclohexylidene), 1.54–1.68 (6H, m, cyclohexylidene), 1.82 (2H, m, cyclohexylidine), 2.04 (1H, dd, $J_{6A,6B}$ 13.0, $J_{6A,5}$ 11.6, H-6A), 2.34 (1H, dd, $J_{2A,2B}$ 15.7, $J_{2A,3}$ 4.2, H-2A), 2.42 (1H, m, H-2B), 2.47 (1H, m, H-6B), 3.79 (3H, s, OCH_3), 3.89 (1H, s, OH), 4.37 (1H, dd, $J_{4,5}$ 6.9, $J_{4,3}$ 5.7, H-4), 4.59 (1H, m, H-3), 6.10 (1H, ddd, $J_{5,6A}$ 11.6, $J_{5,4}$ 6.9, $J_{5,6B}$ 4.5, H-5), 7.04 (1H, s, H-imidazole), 7.65 (1H, s, H-imidazole) and 8.36 (1H, s, H-imidazole); δ_C (125.8 MHz, C^2HCl_3) 24.01, 24.27, 25.23, 34.76 and 35.33 (cyclohexylidene), 36.18 (C-2), 38.07 (C-6), 53.56 (OCH_3), 73.81 (C-4), 74.33 (C-1), 75.93 (C-3), 81.11 (C-5), 111.26 (cyclohexylidene), 118.49, 131.22 and 137.22 (3 × C-imidazole), 174.55 (ester) and 183.52 (C=S).

Methyl (1*R*,3*R*,4*S*)-3,4-*O*-cyclohexylidine-1,3,4-trihydroxycyclohexanecarboxylate (15)

A solution of methyl (1*R*,3*R*,4*S*,5*R*)-3,4-*O*-cyclohexylidine-5-(1*H*-imidazole-1-carbonothioyloxy)-1,3,4-trihydroxycyclohexanecarboxylate **14** (3.0 g, 7.58 mmol) and 2,2′-azobisisobutyronitrile

(AIBN) (124 mg, 0.76 mmol) in toluene (100 ml), under argon was heated at reflux. Tri-*n*-butyltin hydride (2.44 ml, 9.09 mmol) was added dropwise over 10 min and the solution was heated at reflux for 3 h. The mixture was cooled to room temperature and the solvent was removed *in vacuo* to give an orange oil. The crude product was purified by column chromatography on silica gel eluting with petroleum ether–ethyl acetate (9 : 1) to remove tin residues, and petroleum ether–ethyl acetate (3 : 2) to obtain methyl (1*R*,3*R*,4*S*)-3,4-*O*-cyclohexylidine-1,3,4-trihydroxycyclohexanecarboxylate **15** as a colourless oil (1.70 g, 83%); $[\alpha]_D^{25}$ −13.2 (*c* 1, $CHCl_3$); *m*/*z* (+ve FAB, (PEG matrix)) found 271.1550, $[C_{14}H_{22}O_5 + H]^+$ requires 271.1545; ν_{max} (film)/cm^{-1} 1735 (ester); δ_H (300 MHz, C^2HCl_3) 1.39–1.66 (10H, m, cyclohexylidene), 1.74–1.98 (4H, m, H-6 + H-5), 2.19 (2H, m, H-2), 3.62 (1H, s, OH), 3.79 (3H, s, OCH_3), 4.20 (1H, dd, $J_{4,5A}$ 12.1, $J_{4,5B}$ 5.3, H-4) and 4.38 (1H, dd, $J_{3,2A}$ 9.8, $J_{3,2B}$ 4.5, H-3); δ_C (75.5 MHz, C^2HCl_3) 24.10, 24.44, 24.62, 25.42 and 31.82 (cyclohexylidene), 35.37 (C-5), 35.73 (C-6), 38.45 (C-2), 53.08 (OCH_3), 72.42 (C-4), 72.99 (C-3), 73.60 (C-1), 109.62 (cyclohexylidine) and 175.84 (ester).

Methyl (1*R*,3*R*,4*S*)-1,3,4-trihydroxycyclohexanecarboxylate (16)

A mixture of methyl (1*R*,3*R*,4*S*)-3,4-*O*-cyclohexylidine-1,3,4-trihydroxycyclohexanecarboxylate **15** (12.9 g, 47.7 mmol) and Amberlite IR-120 (H^+) (6.5 g) in methanol (120 ml) was heated at reflux for 3 h and allowed to cool to room temperature. The solution was filtered and the resin was washed with methanol (2 × 50 ml). The filtrates were combined and the solvent was removed *in vacuo* to give a yellow oil which was purified by column chromatography on silica gel eluting with ethyl acetate to give methyl (1*R*,3*R*,4*S*)-1,3,4-trihydroxycyclohexanecarboxylate **16** as a colourless oil (6.40 g, 70%); $[\alpha]_D^{23}$ −9.4 (*c* 0.97, $CHCl_3$); *m*/*z* (ES+) found 191.0919, $[C_8H_{14}O_5 + H]^+$ requires 191.0919; ν_{max} (film)/cm^{-1} 3379 (OH) and 1727 (ester); δ_H (300 MHz, C^2HCl_3) 1.84 (4H, m, H-5 + H-6), 2.01 (1H, dd, $J_{2A,2B}$ 14.6, $J_{2A,3}$ 3.1, H-2A), 2.14 (1H, dd, $J_{2B,2A}$ 14.6, $J_{2B,3}$ 2.3, H-2B), 3.61 (1H, m, H-4), 3.80 (3H, s, OCH_3), 3.96 (1H, s, OH) and 4.02 (1H, m, H-3); δ_C (75.5 MHz, C^2HCl_3) 24.61 (C-5), 33.75 (C-6), 37.71 (C-2), 53.49 (OCH_3), 70.15 (C-4), 70.72 (C-3), 74.37 (C-1) and 176.47 (ester).

Trimethyl (3*R*)-homocitrate (17) and dimethyl (3*R*)-homocitric lactone (18)

A solution of sodium periodate (1.2 g in 5 ml H_2O, 5.61 mmol) was added dropwise to a vigorously stirred suspension of chromatographic grade silica gel (5.0 g) in dichloromethane (50 ml) to form a suspension. Methyl (1*R*,3*R*,4*S*)-1,3,4-trihydroxycyclohexanecarboxylate **16** (500 mg, 2.61 mmol) in dichloromethane (5 ml) was added and the reaction was monitored by TLC until disappearance of the starting material was observed (typically 10 min). The mixture was filtered and the silica gel was thoroughly washed with dichloromethane (4 × 25 ml). The solvents were removed *in vacuo* to give a colourless oil to which hydrogen peroxide (1.0 ml, 27%) and formic acid (5.0 ml) were added. The mixture was stirred for 6 h at room temperature and the solvents were removed *in vacuo* to give a yellow oil. The oil was dissolved in methanol (50 ml) and Amberlite IR-120 (H^+) resin (1 g) was added. The solution was heated at reflux for 16 h and filtered. The resin was washed with methanol (4 × 20 ml) and the solvent was removed *in vacuo* to yield a yellow oil which was purified by column chromatography on silica gel using a gradient of petroleum ether–diethyl ether to give trimethyl (3*R*)-homocitrate **17**, as a colourless oil (237 mg, 36%); $[\alpha]_D^{23}$ −10.2 (*c* 1.6, $CHCl_3$); *m*/*z* (CI) found 249.0975, $[C_{10}H_{16}O_7 + H]^+$ requires 249.0974; ν_{max} (film)/cm^{-1} 1740 (ester); δ_H (300 MHz, C^2HCl_3) 2.07 (2H, m, H-5), 2.27 (1H, ddd, $J_{4A,4B}$ 16.0, $J_{4A,5A}$ 9.4, $J_{4A,5B}$ 6.4, H-4A), 2.51 (1H, ddd, $J_{4B,4A}$ 16.0, $J_{4B,5}$ 8.7, $J_{4B,5}$ 7.4, H-4B), 2.71 (1H, d, $J_{2A,2B}$ 16.4, H-2A), 2.97 (1H, d, $J_{2B,2A}$ 16.4, H-2B), 3.67 (3H, s, OCH_3), 3.68 (3H, s, OCH_3) and 3.81 (3H, s, OCH_3); δ_C (75.5 MHz, C^2HCl_3) 28.11 (C-5), 33.85 (C-4), 43.28 (C-2), 51.81 (OCH_3), 51.98 (OCH_3), 53.17 (OCH_3), 74.29 (C-3), 171.05 (ester), 173.30 (ester) and 175.05 (ester). Dimethyl (3*R*)-homocitric lactone **18** (85 mg, 15%), was also obtained as a colourless oil; $[\alpha]_D^{24}$ −10.6 (*c* 9.0, $CHCl_3$) [lit.[15] $[\alpha]_D$ −10.6 (*c* 1.0, $CHCl_3$)]; *m*/*z* (ES+) found 234.0974, $[C_9H_{12}O_6 + NH_4]^+$ requires 234.0978; ν_{max} (film)/cm^{-1} 1789 (lactone) and 1740 (ester); δ_H (300 MHz, C^2HCl_3) 2.31 (1H, ddd, $J_{4A,4B}$ 13.2, $J_{4A,5A}$ 10.3, $J_{4A,5B}$ 9.8, H-4A), 2.42–2.71 (3H, m, H-4B + H-5), 2.91 (1H, d, $J_{2A,2B}$ 16.8, H-2A), 3.09 (1H, d, $J_{2B,2A}$ 16.8, H-2B), 3.64 (3H, s, OCH_3) and 3.74 (3H, s, OCH_3); δ_C (75.5 MHz, C^2HCl_3) 27.72 (C-4), 31.40 (C-5), 41.33 (C-2), 52.13 (OCH_3), 53.23 (OCH_3), 82.83 (C-3), 169.04 (ester), 170.99 (ester) and 175.41 (lactone).

Methyl 3,4-*O*-isopropylideneshikimate (20)

(–)-Shikimic acid **19** (10 g, 57.4 mmol) was converted into methyl 3,4-*O*-isopropylideneshikimate **20** (13.0 g, 99%) using the method of Chahoua *et al.*[12] It was obtained as a colourless oil; $[\alpha]_D^{24}$ −82.6 (*c* 11.5, $CHCl_3$); *m*/*z* (ES+) found 246.1345, $[C_{11}H_{16}O_5 + NH_4]^+$ requires 246.1341; *m*/*z* (CI) 229 $[M + H]^+$; ν_{max} (film)/cm^{-1} 3426 (OH) and 1718 (ester); δ_H (300 MHz, C^2HCl_3) 1.40 (3H, s, CH_3), 1.44 (3H, s, CH_3), 2.24 (1H, ddd, $J_{6A,6B}$ 17.3, $J_{6A,5}$ 8.2, $J_{6A,2}$ 1.5, H-6A), 2.69 (1H, m, OH), 2.78 (1H, dd, $J_{6B,6A}$ 17.3, $J_{6B,5}$ 4.4, H-6B), 3.77 (3H, s, OCH_3), 3.89 (1H, m, H-5), 4.09 (1H, dd, $J_{4,5}$ 7.4, $J_{4,3}$ 6.4, H-4), 4.75 (1H, m, H-3) and 6.92 (1H, br, H-2); δ_C (75.5 MHz, C^2HCl_3) 25.85 (CH_3), 28.09 (CH_3), 29.48 (C-6), 52.29 (OCH_3), 68.88 (C-5), 72.35 (C-4), 78.01 (C-3), 109.85 (C-9), 130.71 (C-1), 134.06 (C-2) and 166.69 (ester).

Methyl 3,4-*O*-isopropylidine-5-*O*-thiocarbonylimidazoleshikimate (21)

1,1′-Thiocarbonyldiimidazole (5.6 g, 31.5 mmol) was added to a solution of methyl 3,4-*O*-isopropylideneshikimate **20** (6.5 g, 28.6 mmol) in dichloromethane (100 ml) and the resultant yellow solution was stirred at room temperature under argon for 16 h. The solvent was removed *in vacuo* to give a yellow oil which was purified by column chromatography on silica gel eluting with diethyl ether to give methyl 3,4-*O*-isopropylidine-5-*O*-thiocarbonylimidazoleshikimate **21** as a white solid (8.9 g, 95%), mp 136–139 °C; $[\alpha]_D^{24}$ −100.7 (*c* 19.3, $CHCl_3$); *m*/*z* (ES+) found 339.1015, $[C_{15}H_{18}N_2O_5S + H]^+$ requires 339.1014; ν_{max} (KBr)/cm^{-1} 1721 (ester); δ_H (300 MHz, C^2HCl_3) 1.30 (3H, s, CH_3), 1.33 (3H, s, CH_3), 2.43 (1H, ddd, $J_{6A,6B}$ 17.6, $J_{6A,5}$ 7.1, $J_{6A,2}$ 1.5, H-6A), 2.93

(1H, dd, $J_{6B,6A}$ 17.6, $J_{6B,5}$ 4.5, H-6B), 3.68 (3H, s, OCH_3), 4.37 (1H, dd, $J_{4,5}$ 6.9, $J_{4,3}$ 6.0, H-4), 4.73 (1H, dd, $J_{3,4}$ 6.0, $J_{3,2}$ 3.6, H-3), 5.75 (1H, ddd, $J_{5,6A}$ 7.1, $J_{5,4}$ 6.9, $J_{5,6B}$ 4.5, H-5), 6.89 (1H, m, H-2), 6.90 (1H, dd, J 1.7 and 0.9, H-imidazole), 7.48 (1H, s, H-imidazole) and 8.18 (1H, s, H-imidazole); δ_C (75.5 MHz, C^2HCl_3) 25.87 (CH_3), 25.90 (C-6), 27.73 (CH_3), 52.24 (OCH_3), 71.92 (C-4), 73.53 (C-3), 79.21 (C-5), 110.45 (C-9), 117.91 (C-imidazole), 129.30 (C-1), 130.88 (C-imidazole), 134.09 (C-2), 136.75 (C-imidazole), 165.80 (ester) and 183.12 (C=S).

Methyl 3,4-*O*-isopropylidine-5-deoxyshikimate (22)

A solution of methyl 3,4-*O*-isopropylidine-5-*O*-thicarbonylimidazoleshikimate **21** (8.7 g, 25.7 mmol) and AIBN (380 mg, 2.30 mmol) in toluene (200 ml) was heated at reflux under argon. Tri-*n*-butyltin hydride (7.8 ml, 28.9 mmol) was added dropwise over 10 min and the solution was heated at reflux for 3 h. The mixture was cooled to room temperature and the solvent was removed *in vacuo* to give an orange oil. The crude product was purified by column chromatography on silica gel eluting with petroleum ether–ethyl acetate (9 : 1) to remove tin residues, and petroleum ether–ethyl acetate (3 : 2) to give methyl 3,4-*O*-isopropylidine-5-deoxyshikimate **22** as a colourless oil (3.91 g, 72%); $[\alpha]_D^{25}$ +30.6 (*c* 5, $CHCl_3$); *m/z* (ES+) found 230.1391, $[C_{11}H_{16}O_4 + NH_4]^+$ requires 230.1392; *m/z* (CI) 213 $[M + H]^+$; ν_{max} (film)/cm^{-1} 1717 (ester); δ_H (300 MHz, C^2HCl_3) 1.34 (3H, s, CH_3), 1.36 (3H, s, CH_3), 1.76 (1H, m, H-6A), 2.02 (1H, m, H-6B), 2.20–2.33 (2H, m, H-5), 3.74 (3H, s, OCH_3), 4.33 (1H, ddd, $J_{4,5A}$ 5.6, $J_{4,3}$ 5.3, $J_{4,5B}$ 2.9, H-4), 4.57 (1H, m, $J_{3,4}$ 5.3, $J_{3,2}$ 3.5, H-3) and 6.76 (1H, m, H-2); δ_C (75.5, C^2HCl_3) 19.41 (C-5), 25.25 (CH_3), 26.45 (C-6), 28.10 (CH_3), 52.12 (OCH_3), 71.83 (C-4), 72.35 (C-3), 109.17 (C-9), 132.87 (C-1), 135.30 (C-2) and 167.49 (ester).

Methyl 5-deoxyshikimate (23)

A mixture of methyl 3,4-*O*-isopropylidine-5-deoxyshikimate **22** (2.0 g, 9.43 mmol) and Amberlite IR-120 (H^+) (1.5 g) in methanol (50 ml) was heated at reflux for 16 h and allowed to cool to room temperature. The solution was filtered and the resin was washed with methanol (2 × 50 ml). The filtrates were combined and the solvent was removed *in vacuo* to give a yellow oil which was purified by column chromatography on silica gel eluting with ethyl acetate to give methyl 5-deoxyshikimate **23** as a colourless solid (1.27 g, 79%), mp 68.5–69.8 °C; $[\alpha]_D^{22}$ −86.2 (*c* 1.0, MeOH); *m/z* (EI) found 172.0735, $C_8H_{12}O_4$ requires 172.0736; *m/z* (EI) 172 $[M]^+$; ν_{max} (KBr)/cm^{-1} 1711 (ester); δ_H (300 MHz, C^2HCl_3) 1.75 (1H, m, H-6A), 1.96 (1H, m, H-6B), 2.28 (1H, m, H-5A), 2.49 (1H, m, H-5B), 3.76 (3H, s, OCH_3), 3.69 (1H, m, H-4), 4.29 (1H, m, H-3) and 6.80 (1H, m, H-2); δ_C (C^2HCl_3) 21.58 (C-5), 26.36 (C-6), 52.27 (OCH_3), 67.26 (C-4), 67.79 (C-3), 132.92 (C-1), 137.43 (C-2) and 167.53 (ester).

Methyl (1*R*,2*S*)-1,2-epoxy-5-deoxyshikimate (24)

Freshly prepared *tert*-butyl hydroperoxide in dichloromethane[16] (3.5 M in dichloromethane, 0.84 ml, 2.94 mmol) was added dropwise to a stirred solution of methyl-5-deoxyshikimate **23** (250 mg, 1.47 mmol) and vanadyl acetylacetonate (20 mg, 7.35 × 10^{-5} mol) in dichloromethane (20 ml) at 0 °C under argon. The colour of the solution changed from green to brown upon addition of the peroxide. The mixture was stirred at room temperature for 24 h, the solution was cooled to 0 °C and the excess *tert*-butyl hydroperoxide was destroyed by addition of saturated aqueous sodium sulfite (2 ml). After stirring for 30 min at room temperature the solution was filtered through a thin pad of silica gel and the solvents were removed *in vacuo* to give a yellow oil which was purified by column chromatography on silica gel eluting with ethyl acetate to give methyl (1*R*,2*S*)-1,2-epoxy-5-deoxyshikimate **24** as colourless crystals (157 mg, 57%), mp 63.5–64 °C; $[\alpha]_D^{22}$ −64.5 (*c* 0.45, MeOH); *m/z* (ES+) found 206.1029, $[C_8H_{12}O_5 + NH_4]^+$ requires 206.1028; ν_{max} (KBr)/cm^{-1} 3381 (OH) and 1734 (ester); δ_H (500 MHz, $C_6^2H_6$) 0.99 (1H, m, $J_{5A,5B}$ 14.4, $J_{5A,6A}$ 7.4, $J_{5A,6B}$ 6.6, $J_{5A,4}$ 3.0, H-5A), 1.34 (1H, dddd, $J_{5B,5A}$ 14.4, $J_{5B,4}$ 7.4, $J_{5B,6B}$ 6.8, $J_{5B,6A}$ 5.6, H-5B), 1.80 (1H, dddd, $J_{6A,6B}$ 15.8, $J_{6A,5A}$ 7.4, $J_{6A,5B}$ 5.6, $J_{6A,2}$ 0.9, H-6A), 2.11 (1H, ddd, $J_{6B,6A}$ 15.8, $J_{6B,5B}$ 6.8, $J_{6B,5A}$ 6.6, H-6B), 3.19 (3H, s, OCH_3), 3.25 (1H, br ddd, $J_{4,5B}$ 7.4, $J_{4,3}$ 4.7, $J_{4,5A}$ 3.0, H-4), 3.35 (1H, dt, $J_{2,3}$ 3.4, $J_{2,6A} = J_{2,4} = 1.5$, H-2) and 3.42 (1H, dd, $J_{3,4}$ 4.7, $J_{3,2}$ 3.4, H-3); irradiation at H-4 converted H-2 to dd, $J_{2,3}$ 3.4, $J_{2,6A}$ 1.5; δ_C (75.5 MHz, C^2HCl_3) 20.30 (C-5), 24.86 (C-6), 53.20 (OCH_3), 60.33 (C-1), 61.16 (C-2), 66.50 (C-4), 68.81 (C-3) and 169.68 (ester).

Methyl (1*R*,2*S*)-3,4-*O*-isopropylidine-1,2-epoxy-5-deoxyshikimate (25)

Methyl (1*R*,2*S*)-1,2-epoxy-5-deoxyshikimate **24** (250 mg, 1.32 mmol) was dissolved in dichloromethane (10 ml) and 2,2-dimethoxypropane (10 ml) and stirred with (±)-10-camphorsulfonic acid (25 mg) at room temperature for 3 h. The solution was washed with aqueous sodium carbonate (1 M, 10 ml) and dried ($MgSO_4$), and the solvents were removed *in vacuo* to give methyl (1*R*,2*S*)-3,4-*O*-isopropylidine-1,2-epoxy-5-deoxyshikimate **25** as a colourless oil (301 mg, quant.) which was not further purified; $[\alpha]_D^{37}$ −69.5 (*c* 3, $CHCl_3$); *m/z* (ES+) found 246.1330, $[C_{11}H_{16}O_5 + NH_4]^+$ requires 246.1341; ν_{max} (film)/cm^{-1} 1738 (ester); δ_H (300 MHz, $C^2H_3CO^2H$) 1.31 (3H, s, CH_3), 1.42 (3H, s, CH_3), 1.51 (1H, m, H-5A), 1.73 (1H, m, H-5B), 2.13 (2H, m, H-6), 3.66 (1H, d, $J_{2,3}$ 3.3, H-2), 4.02 (1H, ddd, $J_{4,5}$ 6.5, $J_{4,3}$ 7.3, $J_{4,5'}$ 10.5, H-4) and 4.45 (1H, dd, $J_{3,4}$ 7.3, $J_{3,2}$ 3.3, H-3); δ_C (75.5 MHz, C^2HCl_3) 20.27 (C-6), 24.27 (C-5), 25.51 (CH_3), 27.59 (CH_3), 53.15 (OCH_3), 56.67 (C-2), 59.01 (C-1), 71.89 (C-4), 72.45 (C-3), 109.5 (C-9) and 170.63 (ester).

(1*R*,2*R*,3*R*,4*S*)-[2-$^2H_1$]-3,4-*O*-Isopropylidine-1-hydroxy-D-1-[C^2H_2-hydroxymethyl]-cyclohexan-3,4-diol (26) from the epoxide (25)

Lithium aluminium deuteride (37 mg, 0.88 mmol) was added to a solution of methyl (1*R*,2*S*)-3,4-*O*-isopropylidine-1,2-epoxy-5-deoxyshikimate **25** (100 mg, 0.44 mmol) in diethyl ether (10 ml) at −78 °C under argon. The mixture was stirred at −78 °C for 5 h, methanol (1 ml) was added and the mixture was stirred at 0 °C for 1 h. The solvent was removed *in vacuo*. The resulting solid was dissolved in ethyl acetate and filtered. The solvent was removed *in vacuo* to give a white solid which was purified by column chromatography on silica gel eluting with ethyl acetate to yield (1*R*,2*R*,3*R*,4*S*)-[2-$^2H_1$]-3,4-*O*-isopropylidine-1-hydroxy-D-1-[C^2H_2-hydroxymethyl]-cyclohexan-3,4-diol **26** as a colourless oil (74 mg, 83%); $[\alpha]_D^{28}$ −38.6 (*c* 6.0, $CHCl_3$); ν_{max} (film)/cm^{-1} 3399

(OH); δ_H (300 MHz, $C^2H_3O^2H$) 1.29 (3H, s, CH_3), 1.47 (3H, s, CH_3), 1.55 (2H, m, H-6), 1.69 (1H, m, H-5A), 1.73 (1H, d, $J_{2,3}$ 5.5, H-2), 1.90 (1H, m, H-5B), 4.10 (1H, m, H-4) and 4.23 (1H, m, H-3); δ_C (75.5 MHz, C^2HCl_3) 24.76 (C-5), 26.02 (C-6), 28.56 (CH_3), 30.04 (CH_3), 33.64 (t, C-2), 70.98 (m, C-7), 71.25 (C-1), 73.81 (C-3), 73.92 (C-4) and 108.69 (C-8).

(1*R*,3*R*,4*S*)-3,4-*O*-Isopropylidine-1-hydroxymethyl-1-hydroxycyclohexan-3,4-diol (26a) from methyl deoxyquinate (16)

A solution of methyl 5-deoxyquinate **16** (200 mg, 1.05 mmol), 2,2-dimethoxypropane (5 ml) and (±)-10-camphorsulfonic acid (2.5 mg) in dichloromethane (5 ml) was stirred for 1 h at room temperature. The solution was washed with aqueous sodium carbonate (1 M, 10 ml) and dried ($MgSO_4$). The solvents were removed *in vacuo* to give a colourless oil. The oil was dissolved in diethyl ether (10 ml) and lithium aluminium hydride (139 mg, 3.66 mmol) was added at −78 °C under argon. The mixture was stirred at −78 °C for 5 h, methanol (1 ml) was added and the mixture was stirred at 0 °C for 1 h. The solvent was removed *in vacuo*. The resulting solid was dissolved in ethyl acetate and filtered. The solvent was removed *in vacuo* to give a white solid which was purified by column chromatography on silica gel eluting with ethyl acetate to yield (1*R*,3*R*,4*S*)-3,4-*O*-isopropylidine-1-hydroxymethyl-1-hydroxycyclohexan-3,4-diol **26a** as a colourless oil (189 mg, 89%); $[\alpha]_D^{25}$ −30.0 (*c* 5.0, $CHCl_3$); *m*/*z* (ES+) found 203.1280, $[C_{10}H_{18}O_4 + H]^+$ requires 203.1283; ν_{max} (film)/cm^{-1} 3392 (OH); δ_H (300 MHz, $C^2H_3O^2H$) 1.31 (3H, s, CH_3), 1.48 (3H, s, CH_3), 1.56 (2H, m, H-6), 1.69 (1H, m, H-5A), 1.75 (1H, m, H-2A), 1.89 (1H, m, H-2B), 1.92 (1H, m, H-5B), 3.32 (1H, d, $J_{7A,7B}$ 14.8, H-7A), 3.36 (1H, d, $J_{7B,7A}$ 14.8, H-7B), 4.14 (1H, dd, $J_{4,5}$ 11.0, $J_{4,3}$ 5.7, H-4) and 4.23 (1H, dd, $J_{3,2}$ 11.5, $J_{3,4}$ 5.6, H-3); δ_C (75.5 MHz, $C^2H_3O^2H$) 26.24 (C-5), 27.19 (CH_3), 29.69 (CH_3), 31.23 (C-6), 37.88 (C-2), 70.15 (C-7), 73.71 (C-1), 75.55 (C-3), 75.90 (C-4) and 110.36 (C-8).

Methyl 5-deoxyquinate (16) by oxidation of the alcohol (26a)

Platinum oxide (222 mg, 0.98 mmol) in water (5 ml) was reduced at room temperature in a Parr apparatus at 50 psi hydrogen for 30 min. The catalyst was sonicated for a few min and transferred to a flask containing a solution of (1*R*,3*R*,4*S*)-3,4-*O*-isopropylidine-1-hydroxymethyl-1-hydroxycyclohexan-3,4-diol **26a** (200 mg, 0.98 mmol) and $NaHCO_3$ (246 mg, 2.94 mmol) in water–acetone (20 ml, 3 : 1). Oxygen was passed through the solution using a gas dispersion tube and the reaction was stirred at 55 °C for 16 h. The platinum was recovered by centrifugation (20 min at 15 000 rpm) and the solvent was removed from the supernatant *in vacuo*. The resulting solid was suspended in methanol (25 ml), Amberlite IR-120 (H^+) (1 g) was added, and the mixture was heated under reflux for 16 h and was allowed to cool to room temperature. The solution was filtered and the resin was washed with methanol (2 × 50 ml). The filtrates were combined and the solvent was removed *in vacuo* to give a yellow oil which was purified by column chromatography on silica gel eluting with ethyl acetate, to give methyl 5-deoxyquinate **16** as a colourless oil (121 mg, 65%); $[\alpha]_D^{23}$ −9.1 (c 0.95, $CHCl_3$), with spectral data identical to the sample of methyl 5-deoxyquinate **16** prepared above.

(1*R*,3*R*,4*S*)-3,4-*O*-Isopropylidine-1-hydroxy-D-1-[C^2H_2-hydroxymethyl]-cyclohexan-3,4-diol (26b) from methyl deoxyquinate (16)

A solution of methyl 5-deoxyquinate **16** (200 mg, 1.05 mmol), 2,2-dimethoxypropane (5 ml) and (±)-10-camphorsulfonic acid (2.5 mg) in dichloromethane (5 ml) was stirred for 1 h at room temperature. The solution was washed with aqueous sodium carbonate (1 M, 10 ml) and dried ($MgSO_4$). The solvents were removed *in vacuo* to give a colourless oil. The oil was dissolved in diethyl ether (10 ml) and lithium aluminium deuteride (153 mg, 3.66 mmol) was added at −78 °C under argon. The mixture was stirred at −78 °C for 5 h, methanol (1 ml) was added and the mixture was stirred at 0 °C for 1 h. The solvent was removed *in vacuo*. The resulting solid was dissolved in ethyl acetate, filtered and the solvent was removed *in vacuo* to give a white solid which was purified by column chromatography on silica gel, eluting with ethyl acetate to yield (1*R*,3*R*,4*S*)-3,4-*O*-isopropylidine-1-hydroxy-D-1-[C^2H_2-hydroxymethyl]-cyclohexan-3,4-diol **26b** as a colourless oil (189 mg, 89%), *m*/*z* (CI) 221 ($[M + NH_4]^+$); $[\alpha]_D^{24}$ −38.6 (*c* 7.0, $CHCl_3$); ν_{max} (film)/cm^{-1} 3392 (OH); δ_H (300 MHz, C^2HCl_3) 1.28 (3H, s, CH_3), 1.49 (3H, s, CH_3), 1.61–1.83 (5H, m, H-6 + H-2 + H-5A), 2.14 (1H, d, $J_{5B,5A}$ 15.06, H-5B), 4.11 (1H, dd, $J_{4,5}$ 11.0, $J_{4,3}$ 5.7, H-4) and 4.29 (1H, m, H-3); δ_C (75.5 MHz, C^2HCl_3) 24.76 (C-5), 26.01 (CH_3), 28.58 (CH_3), 30.06 (C-6), 34.03 (C-2), 69.46 (m, C-7), 71.24 (C-1), 73.78 (C-3), 73.96 (C-4) and 108.67 (C-8).

(1*R*,2*S*,3*S*,4*S*)-3,4-*O*-Isopropylidine-1-hydroxymethyl-1,2-epoxycyclohexan-3,4-diol (27)

Sodium borohydride (108 mg, 2.89 mmol) was added to a solution of methyl (1*R*,2*S*)-3,4-*O*-isopropylidine-1,2-epoxy-5-deoxyshikimate **25** (300 mg, 1.31 mmol) in THF (10 ml) at 0 °C under argon. The mixture was allowed to warm to room temperature and stirred for 14 h. Excess reagents were destroyed by dropwise addition of methanol (2 ml) at 0 °C. The solvents were removed *in vacuo* to give an off-white solid which was purified by column chromatography, eluting with diethyl ether to give (1*R*,2*S*,3*S*,4*S*)-3,4-*O*-isopropylidine-1-hydroxymethyl-1,2-epoxycyclohexan-3,4-diol **27** as a colourless oil (240 mg, 92%); $[\alpha]_D^{24}$ −69.5 (*c* 14.0, $CHCl_3$); *m*/*z* (ES+) found 218.1391, $[C_{10}H_{16}O_4 + NH_4]^+$ requires 218.1392; *m*/*z* (+ve FAB, (3-NBA)) 201 ($[M + H]^+$); ν_{max} (film)/cm^{-1} 3445 (OH); δ_H (300 MHz, C^2HCl_3) 1.29 (3H, s, CH_3), 1.45 (3H, s, CH_3), 1.59–1.69 (3H, m, H-6 + H-5A), 1.91 (1H, m, H-5B), 2.15 (1H, br s, OH), 3.43 (1H, d, $J_{2,3}$ 3.4, H-2), 3.61 (1H, dd, $J_{7A,7B}$ 12.4, $J_{7A,OH}$ 8.3, H-7A), 3.73 (1H, dd, $J_{7B,7A}$ 12.4, $J_{7B,OH}$ 4.3, H-7B), 3.95 (1H, ddd, $J_{4,5B}$ 6.8, $J_{4,3}$ 7.3, $J_{4,5A}$ 9.9, H-4) and 4.33 (H, dd, $J_{3,2}$ 3.4, $J_{3,4}$ 7.3, H-3); δ_C (75.5 MHz, C^2HCl_3) 21.91 (C-5), 24.58 (C-6), 25.43 (CH_3), 27.66 (CH_3), 54.42 (C-2), 61.68 (C-1), 63.99 (C-7), 72.30 (C-3), 73.14 (C-4) and 108.67 (C-8).

(1*R*,2*R*,3*R*,4*S*)-[2-$^2H_1$]-3,4-*O*-Isopropylidine-1-hydroxymethyl-1-hydroxycyclohexan-3,4-diol (28)

Lithium aluminium deuteride (42 mg, 1.0 mmol) was added to a solution of (1*R*,2*S*,3*S*,4*S*)-3,4-*O*-isopropylidine-1-hydroxymethyl-1,2-epoxycyclohexan-3,4-diol **27** (100 mg, 0.50 mmol) in diethyl ether (10 ml) at −78 °C under argon. The

mixture was stirred at −78 °C for 5 h, methanol (1 ml) was added and the mixture was stirred at 0 °C for 1 h. The solvent was removed *in vacuo*. The resulting solid was dissolved in ethyl acetate and filtered. The solvent was removed *in vacuo* to give a white solid which was purified by column chromatography on silica gel, eluting with ethyl acetate to yield (1*R*,2*R*,3*R*,4*S*)-[2-^{2}H$_1$]-3,4-*O*-isopropylidine-1-hydroxymethyl-1-hydroxycyclohexan-3,4-diol **28** as a colourless oil (85 mg, 83%); $[\alpha]_D^{28}$ −77.0 (*c* 6.0, $CHCl_3$); *m*/*z* (ES+) found 204.1344, $[C_{10}H_{17}{}^2HO_4 + H]^+$ requires 204.1346; ν_{max} (film)/cm^{-1} 3399 (OH); δ_H (300 MHz, C^2HCl_3) 1.31 (3H, s, CH_3), 1.48 (3H, s, CH_3), 1.56 (2H, m, H-6), 1.69 (1H, m, H-5A), 1.75 (1H, d, $J_{2S,3}$ 5.6, H-2*S*), 1.91 (1H, dddd, $J_{5B,5A}$ 14.4, $J_{5B,4}$ 10.9, $J_{5B,6A}$ 6.8, $J_{5B,6B}$ 5.9, H-5B), 3.32 (1H, d, $J_{7A,7B}$ 14.8, H-7A), 3.37 (1H, d, $J_{7B,7A}$ 14.8, H-7B), 4.14 (1H, dd, $J_{4,5A}$ 11.0, $J_{4,3}$ 5.7, H-4) and 4.23 (1H, dd, $J_{3,4} = J_{3,2} = 5.7$, H-3); δ_C (75.5 MHz, C^2HCl_3) 25.03 (C-5), 26.21 (C-6), 28.81 (CH_3), 30.42 (CH_3), 33.85 (t, C-2), 70.78 (C-7), 71.51 (C-1), 74.08 (C-3), 74.18 (C-4) and 108.94 (C-8).

Methyl (2*R*)-[2-^{2}H$_1$]-5-deoxyquinate (29)

Platinum oxide (257 mg, 1.13 mmol) in water (5 ml) was reduced at room temperature in a Parr apparatus at 50 psi hydrogen for 30 min. The catalyst was sonicated for a few min and transferred to a flask containing a solution of (1*R*,2*R*,3*R*,4*S*)-[2-^{2}H$_1$]-3,4-*O*-isopropylidine-1-hydroxymethyl-1-hydroxycyclohexan-3,4-diol **28** (230 mg, 1.13 mmol) and $NaHCO_3$ (285 mg, 3.40 mmol) in water–acetone (20 ml, 3 : 1). Oxygen was passed through the solution using a gas dispersion tube and the reaction was stirred at 55 °C and atmospheric pressure for 16 h. The platinum was recovered by centrifugation (20 min at 15 000 rpm) and the solvent was removed from the supernatant *in vacuo*. The resulting solid was suspended in methanol (25 ml), Amberlite IR-120 (H^+) (1 g) was added, and the mixture was heated at reflux for 16 h and was allowed to cool to room temperature. The solution was filtered and the resin was washed with methanol (2 × 50 ml). The filtrates were combined and the solvent was removed *in vacuo* to give a yellow oil which was purified by column chromatography on silica gel eluting with ethyl acetate, to give methyl (2*R*)-[^{2}H$_1$]-5-deoxyquinate **29** as a colourless oil (149 mg, 69%); $[\alpha]_D^{30}$ −18.5 (*c* 11.0, $CHCl_3$); *m*/*z* (ES+) found 209.1249, $[C_8H_{13}{}^2HO_5 + NH_4]^+$ requires 209.1248; ν_{max} (film)/cm^{-1} 3379 (OH) and 1726 (ester); δ_H (300 MHz, C^2HCl_3) 1.60 (1H, m, H-6A), 1.80–1.98 (4H, m, H-6B + H-5 + H-2*S*), 3.66 (1H, m, H-4), 3.71 (3H, s, OCH_3) and 3.83 (1H, dd, $J_{3,2}$ 6.8, $J_{3,4}$ 2.9, H-3); δ_C (125.8 MHz, C^2HCl_3) 24.35 (C-5), 33.35 (C-6), 37.08 (t, C-2), 53.18 (OCH_3), 69.63 (C-4), 70.28 (C-3), 73.89 (C-1) and 176.21 (ester).

Trimethyl (2*S*,3*R*)-[2-^{2}H$_1$]-homocitrate (17a) and dimethyl (2*S*,3*R*)-[2-^{2}H$_1$]-homocitric lactone (18a)

A solution of sodium periodate (188 mg in 1.4 ml H_2O, 0.88 mmol) was added dropwise to a vigorously stirred suspension of chromatographic grade silica gel (1.4 g) in dichloromethane (10 ml) to form a suspension. Methyl (2*R*)-[^{2}H$_1$]-5-deoxyquinate **29** (140 mg, 0.73 mmol) in dichloromethane (1.5 ml) was added at room temperature and the reaction was monitored by TLC until disappearance of the starting material was noted (typically 10 min). The mixture was filtered and the silica gel was thoroughly washed with dichloromethane (4 × 10 ml). The solvents were removed *in vacuo* to give a colourless oil to which hydrogen peroxide (0.5 ml, 27%) and formic acid (1.8 ml) were added. The mixture was stirred for 6 h at room temperature and the solvents were removed *in vacuo* to give a yellow oil. The oil was dissolved in methanol (25 ml) and Amberlite IR-120 (H^+) resin (1 g) was added. The solution was heated at reflux for 16 h and filtered. The resin was washed with methanol (4 × 10 ml) and the solvent was removed *in vacuo* to yield a yellow oil which was purified by column chromatography on silica gel using a gradient of petroleum ether–diethyl ether to give trimethyl (2*S*,3*R*)-[2-^{2}H$_1$]-homocitrate **17a** (69 mg, 38%) as an oil; $[\alpha]_D^{24}$ −7.6 (*c* 13.0, $CHCl_3$); *m*/*z* (ES+) found 267.1295, $[C_{10}H_{15}{}^2HO_7 + NH_4]^+$ requires 267.1303; δ_H (300 MHz, C^2HCl_3) 2.02 (2H, m, H-5), 2.23 (1H, ddd, $J_{4A,4B}$ 16.0, $J_{4A,5A}$ 9.4, $J_{4A,5B}$ 6.4, H-4A), 2.46 (1H, ddd, $J_{4B,4A}$ 16.0, $J_{4B,5}$ 8.7, $J_{4B,5'}$ 7.4, H-4B), 2.90 (1H, s, H-2*R*), 3.63 (3H, s, OCH_3), 3.64 (3H, s, OCH_3) and 3.77 (3H, s, OCH_3); δ_C (75.5 MHz, C^2HCl_3) 28.29 (C-4), 34.00 (C-5), 43.19 (t, C-2), 51.99 (OCH_3), 52.15 (OCH_3), 53.32 (OCH_3), 74.43 (C-3) and 171.21, 173.50 and 175.24 (3 × ester) and dimethyl (2*S*,3*R*)-[2-^{2}H$_1$]-homocitric lactone **18a** (25 mg, 16%) as an oil; $[\alpha]_D^{24}$ −4.8 (*c* 6.5, $CHCl_3$); *m*/*z* (ES+) found 235.1037, $[C_9H_{11}{}^2HO_6 + NH_4]^+$ requires 235.1040; ν_{max} (film)/cm^{-1} 1789 (lactone) and 1740 (ester); δ_H (300 MHz, C^2HCl_3) 2.22 (1H, ddd, $J_{4A,4B}$ 13.2, $J_{4A,5A}$ 10.3, $J_{4A,5B}$ 9.8, H-4A), 2.38–2.65 (3H, m, H-4B + H-5), 2.98 (1H, s, H-2B), 3.58 (3H, s, OCH_3) and 3.70 (3H, s, OCH_3); δ_C (75.5 MHz, C^2HCl_3) 27.98 (C-4), 31.37 (C-5), 41.30 (t, C-2), 52.38 (OCH_3), 53.49 (OCH_3), 83.01 (C-3), 169.22 and 171.19 (2 × ester) and 175.55 (lactone).

Methyl 3,4-*O*-isopropylidene-[2-^{2}H]-shikimate (32) ultimately from D-mannose (30)

Sodium hydride was washed with anhydrous diethyl ether (60%; 3.75 g, 93.9 mmol) under nitrogen and suspended in dry DMF (100 ml). The mixture was cooled to 0 °C. A solution of methyl dimethoxyphosphoryl acetate (21.1 g, 0.10 mol) in dry DMF (50 ml) was added dropwise to the stirred mixture during 20 min. The mixture was stirred at room temperature for 1 h to give a clear solution. A solution of benzyl [1-^{2}H]-2,3-*O*-isopropylidene-5-*O*-trifluoromethylsulfonyl-α-D-lyxofuranoside **31**[13,14] (25.7 g, 62.5 mmol) in dry DMF (50 ml) was added, followed by 15-crown-5 (0.2 ml). The reaction was stirred at room temperature for 20 h, cooled to 0 °C, quenched with cold aqueous potassium dihydrogen orthophosphate (1 M; 150 ml) and extracted with chloroform (4 × 250 ml). The combined extracts were washed with cold water (50 ml) and dried ($MgSO_4$). The solvent was removed *in vacuo* to yield a yellow oil which was purified by column chromatography on silica gel, eluting with diethyl ether, to give methyl (benzyl 5,6-dideoxy-6-dimethoxyphosphoryl-2,3-*O*-isopropylidene-D-[1-^{2}H]-lyxo-heptofuranoside)uronate as a yellow oil (20.9 g, 69%). This intermediate (11.0 g, 23.2 mmol) was dissolved in methanol (150 ml) and hydrogenated over palladium–charcoal (10%; 3.5 g) at room temperature and atmospheric pressure for 30 h. The mixture was filtered through Celite® and the solvent was removed *in vacuo* to yield a syrup which was dissolved in dry tetrahydrofuran (45 ml) and added dropwise during 5 min to a stirred suspension of sodium hydride (60%; 1.20 g, 30.2 mmol, 1.3 eq., washed with 2 × 10 ml anhydrous diethyl ether under nitrogen) in dry tetrahydrofuran (60 ml). The reaction was exothermic and a white gelatinous precipitate was observed.

After 45 min the mixture was cooled to 0 °C, quenched with cold aqueous potassium dihydrogen orthophosphate (1 M, 150 ml), and extracted with chloroform (3 × 500 ml). The combined extracts were dried ($MgSO_4$) and filtered through a pad of silica gel. The solvents were removed *in vacuo*. Column chromatography on silica gel, eluting with diethyl ether–petroleum ether yielded methyl 3,4-*O*-isopropylidene-[2-^{2}H]-shikimate **32** as a white solid (3.73 g, 71%); $[\alpha]_D^{26}$ −80.3 (*c* 8.0, $CHCl_3$); *m/z* (ES+) found 247.1407, $[C_{11}H_{15}{}^2HO_5 + NH_4]^+$ requires 247.1404; ν_{max} (KBr)/cm^{-1} 3465 (OH) and 1721 (ester); δ_H (300 MHz, C^2HCl_3) 1.40 (3H, s, CH_3), 1.44 (3H, s, CH_3), 2.26 (1H, ddd, $J_{6A,6B}$ 17.3, $J_{6A,5}$ 8.2, $J_{6A,2}$ 1.5, H-6A), 2.76 (1H, dd, $J_{6B,6A}$ 17.3, $J_{6B,5}$ 4.4, H-6B), 3.42 (1H, m, OH), 3.77 (3H, s, OCH_3), 3.92 (1H, m, H-5), 4.12 (1H, dd, $J_{4,5}$ 7.4, $J_{4,3}$ 6.4, H-4) and 4.76 (1H, d, $J_{3,4}$ 6.4, H-3); δ_C (75.5 MHz, C^2HCl_3) 25.76 (CH_3), 27.98 (CH_3), 29.29 (C-6), 52.16 (OCH_3), 68.45 (C-5), 72.15 (C-4), 77.67 (C-3), 109.66 (C-9), 130.30 (C-1), 136.30 (t, C-2) and 166.63 (ester).

Methyl 3,4-*O*-isopropylidine-5-*O*-thiocarbonylimidazole-[2-^{2}H]-shikimate (33)

1,1′-Thiocarbonyldiimidazole (5.0 g, 28 mmol) was added to a solution of methyl 3,4-*O*-isopropylidene-[2-^{2}H]-shikimate **32** (4.37 g, 19 mmol) in dichloromethane (50 ml) and the resultant yellow solution was stirred under argon for 16 h. The solvent was removed *in vacuo* to give a yellow oil which was purified by column chromatography on silica gel, eluting with diethyl ether to give methyl 3,4-*O*-isopropylidine-5-*O*-thiocarbonylimidazole-[2-^{2}H]-shikimate **33** as a white solid (6.61 g, quant.), mp 138–140 °C; $[\alpha]_D^{26}$ −100.3 (*c* 4.0, $CHCl_3$); *m/z* (ES+) found 340.1074, $[C_{15}H_{17}{}^2HN_2O_5S + H]^+$ requires 340.1077; *m/z* (EI) 339 ($[M]^+$); ν_{max} (KBr)/cm^{-1} 1721 (ester); δ_H (300 MHz, C^2HCl_3) 1.35 (3H, s, CH_3), 1.38 (3H, s, CH_3), 2.46 (1H, dd, $J_{6A,6B}$ 17.6, $J_{6A,5}$ 7.1, H-6A), 2.98 (1H, dd, $J_{6B,6A}$ 17.6, $J_{6B,5}$ 4.5, H-6B), 3.72 (3H, s, OCH_3), 4.40 (1H, dd, $J_{4,5}$ 6.9, $J_{4,3}$ 6.0, H-4), 4.76 (1H, d, $J_{3,4}$ 6.0, H-3), 5.79 (1H, ddd, $J_{5,6A}$ 7.1, $J_{5,4}$ 6.9, $J_{5,6B}$ 4.5, H-5), 6.87 (1H, s, H-imidazole), 7.52 (1H, d, *J* 1.2, H-imidazole) and 8.23 (1H, s, H-imidazole); δ_C (75.5 MHz, C^2HCl_3) 26.05 (CH_3), 26.07 (C-6), 37.93 (CH_3), 52.50 (OCH_3), 72.03 (C-4), 73.74 (C-3), 87.37 (C-5), 110.73 (C-9), 118.12 (C-imidazole), 129.46 (C-1), 131.12 (C-imidazole), 134.26 (t, C-2), 136.95 (C-imidazole), 166.05 (ester) and 183.27 (C=S).

Methyl 3,4-*O*-isopropylidine-5-deoxy-[2-^{2}H]-shikimate (34)

A solution of methyl 3,4-*O*-isopropylidine-5-*O*-thiocarbonyl-imidazoleshikimate **33** (5.0 g, 14.7 mmol) and AIBN (250 mg, 1.53 mmol) in toluene (250 ml), was heated at reflux under argon. Tri-*n*-butyltin hydride (5.3 ml, 19.8 mmol) was added dropwise over 10 min and the solution was heated at reflux for a further 3 h. The mixture was cooled to room temperature and the solvent was removed *in vacuo* to give an orange oil. The crude product was purified by column chromatography on silica gel, eluting first with petroleum ether–ethyl acetate (9 : 1) to remove tin residues and then with petroleum ether–ethyl acetate (3 : 2) to give methyl 3,4-*O*-isopropylidine-5-deoxy-[2-^{2}H]-shikimate **34** as a colourless oil (2.52 g, 80%); $[\alpha]_D^{25}$ +31.2 (*c* 7.5, $CHCl_3$); *m/z* (CI) 231 ($[M + NH_4]^+$); ν_{max} (film)/cm^{-1} 1719 (ester); δ_H (300 MHz, C^2HCl_3) 1.33 (3H, s, CH_3), 1.35 (3H, s, CH_3), 1.75 (1H, m, H-6A), 2.00 (1H, m, H-6B), 2.17–2.23 (2H, m, H-5), 3.73 (3H, s, OCH_3), 4.32 (1H, ddd, $J_{4,5A}$ 5.6, $J_{4,3}$ 5.3, $J_{4,5B}$ 2.9, H-4) and 4.55 (1H, d, $J_{3,4}$ 5.3, H-3); δ_C (75.5 MHz, C^2HCl_3) 19.31 (C-5), 25.22 (CH_3), 26.43 (C-6), 28.09 (CH_3), 52.09 (OCH_3), 71.73 (C-4), 72.33 (C-3), 109.14 (C-9), 132.65 (C-1), 136.97 (t, C-2) and 167.46 (ester).

Methyl 5-deoxy-[2-^{2}H]-shikimate (35)

A mixture of methyl 3,4-*O*-isopropylidine-5-deoxyshikimate **34** (1.9 g, 8.92 mmol) and Amberlite IR-120 (H^+) (1.5 g) in methanol (50 ml) was heated at reflux for 16 h and allowed to cool to room temperature. The solution was filtered and the resin was washed with methanol (2 × 50 ml). The filtrates were combined and the solvent was removed *in vacuo* to give a yellow oil which was purified by column chromatography on silica gel, eluting with ethyl acetate to give methyl 5-deoxy-[2-^{2}H]-shikimate **35** as a colourless solid (1.23 g, 80%), mp 68.3–69.1 °C; $[\alpha]_D^{25}$ −80.4 (*c* 5.5, MeOH); *m/z* (ES+) found 191.1145, $[C_8H_{12}O_4 + NH_4]^+$ requires 191.1142; ν_{max} (KBr)/cm^{-1} 1703 (ester); δ_H (300 MHz, C^2HCl_3) 1.74 (1H, m, H-6A), 1.96 (1H, m, H-6B), 2.28 (1H, m, H-5A), 2.48 (1H, m, H-5B), 3.70 (1H, br s, OH), 3.77 (3H, s, OCH_3), 3.94 (1H, m, H-4), 4.13 (1H, br s, OH) and 4.29 (1H, m, H-3); δ_C (75.5 MHz, C^2HCl_3) 21.37 (C-5), 25.94 (C-6), 52.04 (OCH_3), 66.98 (C-4), 67.55 (C-3), 132.29 (C-1), 137.25 (t, C-2) and 167.52 (ester).

Methyl (1*R*,2*S*)-1,2-epoxy-5-deoxy-[2-^{2}H]-shikimate (36)

Freshly prepared *tert*-butyl hydroperoxide in dichloromethane[16] (1.8 M in dichloromethane, 3.2 ml, 5.76 mmol) was added dropwise to a solution of methyl-5-deoxy-[2-^{2}H]-shikimate **35** (500 mg, 2.89 mmol) and vanadyl acetylacetonate (38 mg, 0.11 mmol) in dichloromethane (50 ml) stirred at 0 °C under argon. The colour of the solution changed from green to brown upon addition of the peroxide. The mixture was stirred at room temperature for 24 h, the solution was cooled to 0 °C and the excess *tert*-butyl hydroperoxide was destroyed by addition of saturated aqueous sodium sulfite (4 ml). After stirring for 30 min at room temperature the solution was filtered through a thin pad of silica and the solvents were removed *in vacuo* to give a yellow oil which was purified by column chromatography on silica gel, eluting with ethyl acetate to give methyl (1*R*,2*S*)-1,2-epoxy-5-deoxy-[2-^{2}H]-shikimate **36** as colourless crystals (322 mg, 59%), mp 63.3–63.9 °C; $[\alpha]_D^{25}$ −63.9 (*c* 6.0, MeOH); *m/z* (ES+) found 207.1084, $[C_8H_{11}{}^2HO_5 + NH_4]^+$ requires 207.1091; ν_{max} (KBr)/cm^{-1} 3394 (OH) and 1728 (ester); δ_H (300 MHz, $C_6{}^2H_6$) 1.07 (1H, m, $J_{5A,5B}$ 14.4, $J_{5A,6A}$ 7.4, $J_{5A,6B}$ 6.6, $J_{5A,4}$ 3.0, H-5A), 1.40 (1H, dddd, $J_{5B,5A}$ 14.4, $J_{5B,4}$ 7.4, $J_{5B,6B}$ 6.8, $J_{5B,6A}$ 5.6, H-5B), 1.89 (1H, ddd, $J_{6A,6B}$ 15.8, $J_{6A,5A}$ 7.4, $J_{6A,5B}$ 5.6, H-6A), 2.21 (1H, ddd, $J_{6B,6A}$ 15.8, $J_{6B,5B}$ 6.8, $J_{6B,5A}$ 6.6, H-6B), 3.28 (3H, s, OCH_3), 3.34 (1H, dd, $J_{4,5B}$ 7.4, $J_{4,5A}$ 3.0, H-4) and 3.50, (1H, d, $J_{3,4}$ 4.7, H-3); δ_C (75.5 MHz, C^2HCl_3) 20.63 (C-5), 24.36 (C-6), 52.96 (OCH_3), 59.63 (C-1), 60.53 (t, C-2), 66.28 (C-4), 68.58 (C-3) and 169.85 (ester).

Methyl (1*R*,2*S*)-3,4-*O*-isopropylidine-1,2-epoxy-5-deoxy-[2-^{2}H]-shikimate (37)

Methyl (1*R*,2*S*)-1,2-epoxy-5-deoxy-[2-^{2}H]-shikimate **36** (250 mg, 1.32 mmol) was dissolved in dichloromethane (10 ml) and 2,2-dimethoxypropane (10 ml) and stirred at room temperature with (±)-10-camphorsulfonic acid (25 mg) for 3 h. The solution was washed with aqueous sodium carbonate (1 M, 10 ml)

and dried ($MgSO_4$). The solvents were removed *in vacuo* to yield methyl (1*R*,2*S*)-3,4-*O*-isopropylidine-1,2-epoxy-5-deoxy-[2-^{2}H]-shikimate **37** as a colourless oil (301 mg, quant.) which was used without further purification.

(1*R*,2*S*,3*R*,4*S*)-[2-$^2H_1$]-3,4-*O*-Isopropylidine-1-hydroxymethyl-1-hydroxycyclohexan-3,4-diol (38)

Lithium aluminium hydride (248 mg, 6.54 mmol) was added to a solution of methyl (1*R*,2*S*)-1,2-epoxy-3,4-isopropylidine-5-deoxy-[2-^{2}H]-shikimate **37** (500 mg, 2.18 mmol) in diethyl ether (50 ml) at −78 °C under argon. The mixture was stirred at −78 °C for 5 h, methanol (2 ml) was added and the mixture was stirred at 0 °C for 1 h. The solvent was removed *in vacuo*. The resulting solid was dissolved in ethyl acetate and filtered. The solvent was removed *in vacuo* to give a white solid which was purified by column chromatography on silica gel, eluting with ethyl acetate to yield (1*R*,2*S*,3*R*,4*S*)-[2-$^2H_1$]-3,4-*O*-isopropylidine-1-hydroxymethyl-1-hydroxycyclohexan-3,4-diol **38** as a colourless oil (385 mg, 87%); $[\alpha]_D^{26}$ −49.7 (*c* 10.3, $CHCl_3$); *m*/*z* (ES+) found 221.1610, $[C_{10}H_{17}{}^2HO_4 + NH_4]^+$ requires 221.1612; δ_H (500 MHz, $C^2H_3O^2H$) 1.30 (3H, s, CH_3), 1.48 (3H, s, CH_3), 1.56 (2H, m, H-6), 1.71 (1H, m, H-5A), 1.86 (1H, d, $J_{2,3}$ 5.5, H-2B), 1.92 (1H, m, H-5B), 3.20 (1H, d, $J_{7A,7B}$ 14.8, H-7A), 3.24 (1H, d, $J_{7B,7A}$ 14.8, H-7B), 4.02 (1H, dd, $J_{4,5}$ 11.0, $J_{4,3}$ 5.7, H-4) and 4.10 (1H, dd, $J_{3,2}$ 5.5, $J_{3,4}$ 5.3, H-3); δ_C (75.5 MHz, $C^2H_3O^2H$) 26.28 (C-5), 27.27 (C-6), 29.76 (CH_3), 31.26 (CH_3), 37.59 (t, C-2), 70.14 (C-7), 73.67 (C-1), 75.52 (C-3), 75.85 (C-4) and 110.32 (C-8).

Methyl (2*S*)-[2-$^2H_1$]-5-deoxyquinate (39)

Platinum oxide (223 mg, 0.98 mmol) in water (5 ml) was reduced at room temperature in a Parr apparatus at 50 psi hydrogen for 30 min. The catalyst was sonicated for a few min and transferred to a flask containing a solution of (1*R*,2*S*,3*R*,4*S*)-[2-$^2H_1$]-3,4-*O*-isopropylidine-1-hydroxymethyl-1-hydroxycyclohexan-3,4-diol **38** (200 mg, 0.98 mmol) and $NaHCO_3$ (248 mg, 2.95 mmol) in water–acetone (20 ml, 3 : 1). Oxygen was passed through the solution using a gas dispersion tube and the reaction was stirred at 55 °C for 16 h. The platinum was recovered by centrifugation (20 min at 15 000 rpm) and the solvent was removed from the supernatant *in vacuo*. The resulting solid was suspended in methanol (25 ml), Amberlite IR-120 (H^+) (1 g) was added and the mixture was heated at reflux for 16 h and was allowed to cool to room temperature. The solution was filtered and the resin was washed with methanol (2 × 50 ml). The filtrates were combined and the solvent was removed *in vacuo* to give a yellow oil which was purified by column chromatography on silica gel, eluting with ethyl acetate, to give methyl (2*S*)-[2-$^2H_1$]-5-deoxyquinate **39** as a colourless oil (122 mg, 65%); $[\alpha]_D^{30}$ +24.2 (*c* 9.1, $CHCl_3$); *m*/*z* (ES+) found 209.1243, $[C_8H_{13}{}^2HO_5 + NH_4]^+$ requires 209.1248; ν_{max} (film)/cm^{-1} 3400 (OH) and 1732 (ester); δ_H (300 MHz, $C^2H_3O^2H$) 1.60 (1H, m, H-6A), 1.80–1.98 (3H, m, H-6B + H-5), 2.03 (1H, s, H-2*R*), 3.66 (1H, m, H-4), 3.71 (3H, s, OCH_3) and 3.83 (1H, t, $J_{3,2} = J_{3,4} =$ 2.9, H-3); δ_C (75.5 MHz, C^2HCl_3) 24.12 (C-5), 33.35 (C-6), 37.02 (t, C-2), 52.99 (OCH_3), 69.83 (C-4), 70.41 (C-3), 74.10 (C-1) and 175.94 (ester).

Trimethyl (2*R*,3*R*)-[2-$^2H_1$]-homocitrate (17b) and dimethyl (2*R*,3*R*)-[2-$^2H_1$]-homocitrate lactone (18b)

A solution of sodium periodate (161 mg in 1.2 ml H_2O, 0.75 mmol) was added dropwise to a vigorously stirred suspension of chromatographic grade silica gel (1.2 g) in dichloromethane (10 ml) to form a flaky suspension. Methyl (2*S*)-[2-$^2H_1$]-5-deoxyquinate **39** (120 mg, 0.63 mmol) in dichloromethane (1.2 ml) was added and the reaction was monitored by TLC until the disappearance of the starting material was noted (typically 10 min). The mixture was filtered and the silica gel was thoroughly washed with dichloromethane (4 × 10 ml). The solvents were removed *in vacuo* to give a colourless oil to which hydrogen peroxide (0.4 ml, 27%) and formic acid (1.5 ml) were added. The mixture was stirred for 6 h at room temperature and the solvents were removed *in vacuo* to give a yellow oil. The oil was dissolved in methanol (25 ml) and Amberlite IR-120 (H^+) resin (1 g) was added. The solution was heated at reflux for 16 h and filtered. The resin was washed with methanol (4 × 10 ml) and the solvent was removed *in vacuo* to yield a yellow oil which was purified by column chromatography on silica gel using a gradient of petroleum ether–diethyl ether to give trimethyl (2*R*,3*R*)-[2-$^2H_1$]-homocitrate **17b** (62 mg, 40%) as an oil; $[\alpha]_D^{30}$ −13.5 (*c* 10.0, $CHCl_3$); *m*/*z* (ES+) found 267.1304, $[C_{10}H_{15}{}^2HO_7 + NH_4]^+$ requires 267.1303; *m*/*z* (CI) 267.2 ([M + NH_4]$^+$); ν_{max} (film)/cm^{-1} 3429 (OH) and 1737 (ester); δ_H (300 MHz, C^2HCl_3) 2.00 (2H, m, H-5), 2.22 (1H, ddd, $J_{4A,4B}$ 16.0, $J_{4A,5A}$ 9.4, $J_{4A,5B}$ 6.4, H-4A), 2.46 (1H, ddd, $J_{4B,5A}$ 16.0, $J_{4B,5}$ 8.7, $J_{4B,5'}$ 7.4, H-4B), 2.64 (1H, s, H-2*S*), 3.62 (3H, s, OCH_3), 3.63 (3H, s, OCH_3) and 3.75 (3H, s, OCH_3); δ_C (75.5, C^2HCl_3) 28.32 (C-4), 33.45 (C-5), 43.16 (t, C-2), 52.03 (OCH_3), 52.18 (OCH_3), 53.34 (OCH_3), 74.46 (C-3) and 171.23, 173.52 and 175.26 (3 × ester) and dimethyl (2*R*,3*R*)-[2-$^2H_1$]-homocitric lactone **18b** (21 mg, 15%) as an oil; $[\alpha]_D^{27}$ −5.2 (*c* 11.0, $CHCl_3$); *m*/*z* (ES+) found 235.1037, $[C_9H_{11}{}^2HO_6 + NH_4]^+$ requires 235.1040; ν_{max} (film)/cm^{-1} 1790 (lactone) and 1741 (ester); δ_H (300 MHz, C^2HCl_3) 2.30 (1H, ddd, $J_{4A,4B}$ 13.2, $J_{4A,5A}$ 10.3, $J_{4A,5B}$ 9.8, H-4A), 2.45–2.69 (3H, m, H-4B + H-5), 2.91 (1H, s, H-2*S*), 3.65 (3H, s, OCH_3) and 3.77 (3H, s, OCH_3); δ_C (75.5 MHz, C^2HCl_3) 27.97 (C-4), 31.31 (C-5), 41.26 (t, C-2), 52.37 (OCH_3), 53.48 (OCH_3), 83.00 (C-3), 169.23 and 171.19 (2 × ester) and 175.58 (lactone).

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