Pergamon

Tetrahedron 55 (1999) 8443–8456

TETRAHEDRON

AN EFFICIENT TRANSFORMATION OF QUINIC ACID TO SHIKIMIC ACID DERIVATIVES

Cristina Alves,[b] M. Teresa Barros,*[a] Christopher D. Maycock,*[b] and M. Rita Ventura[b]

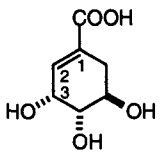
[a]Faculdade de Ciências e Tecnologia da Universidade Nova de Lisboa, Departamento de Química, 2825 Monte da Caparica.

[b]Instituto de Tecnologia Química e Biológica, Universidade Nova de Lisboa, Rua da Quinta Grande 6, Apartado 127, 2780 Oeiras, Portugal

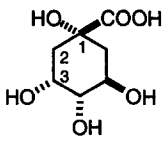
Received 27 November 1998; revised 28 April 1999; accepted 13 May 1999

Abstract: The synthesis of (-)-methyl shikimate and (-)-methyl 3-*epi*-shikimate and the 3-aminoshikimate derivative have been achieved via short and efficient routes from quinic acid.

(-)-Shikimic acid **1** is a key intermediate in the biosynthesis of aromatic aminoacids (phenylalanine, tyrosine and tryptophan), precursors to the folate coenzymes and various isoprenoid quinones.[1] As the shikimate pathway is exclusively utilised by plants, fungi and microorganisms, specific enzyme inhibitors could possess valuable herbicidal or antibiotic activities. In fact, the herbicidal compound *N*-phosphonomethylglycine (glyphosate, marketed as Roundup®)[2] is active due to its extreme affinity for the enzyme 5-enolpyruvyl-shikimate-3-phosphate synthase. As a result, great interest has been demonstrated in the synthesis of shikimate analogues with potential enzyme inhibitory activities.[3] In this paper, we describe our synthesis of (-)-methyl shikimate, (-)-methyl 3-*epi*-shikimate and the corresponding C-3 amino derivatives, from (-)-quinic acid **2**.



1



2

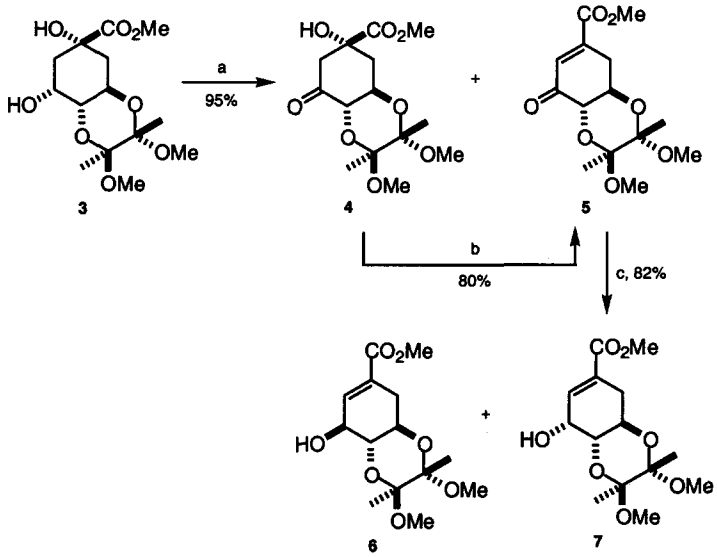
Quinic acid **2**, a hydrated form of shikimic acid, is readily available from natural sources and is commercially available at a rate 60 times cheaper than shikimic acid[4] (Aldrich). Its conversion to shikimic acid has been studied by several groups with varying degrees of success.[3-5]

Recently, several reports have described the conversion of shikimic acid into various C-3 substituted derivatives such as the 3-amino,[6] 3-fluoro[7] and 3-*epi*.[8] The published synthesis of the 3-amino compound, for example, proved to be somewhat problematic, mainly due to the hydroxyl protecting groups used. We envisioned that the selection of a suitable protecting group for the *trans* vicinal diol system of quinic acid was essential to the success of the conversion to shikimic acid derivatives. Protecting groups for these systems have become available over the last few years and have shown their utility in numerous synthetic programs.[9,10] Thus oxidation of the remaining secondary hydroxyl group, corresponding to the 3-positon of skikimic acid, would

0040-4020/99/$ - see front matter
PII: S0040-4020(99)00431-7

allow regioselective elimination of the elements of water and produce the shikimic acid nucleus.[11] Manipulation of the ketonic carbonyl should allow a common and flexible route to many of the compounds of interest, particularly the 3-amino compound. Here we demonstrate that this strategy is valid and provides an efficient route to shikimic acid derivatives.

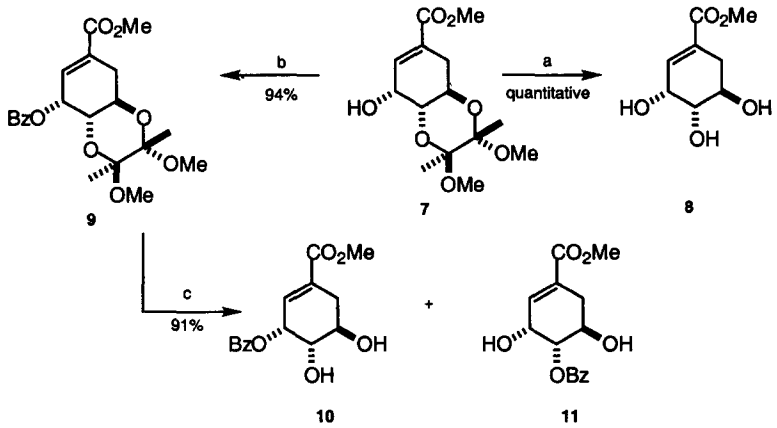
Our strategy was based upon the manipulation of the C-3 functionality of the cyclohexyl ring of quinic acid, after selective protection of the vicinal *trans* hydroxyl groups of a methyl ester derivative of quinic acid with 2,2,3,3-tetramethoxybutane. This would allow regioselective dehydration to form the shikimic acid nucleus and also create a rigid decalin-like system which should undergo stereoselective reductions at the carbonyl group.



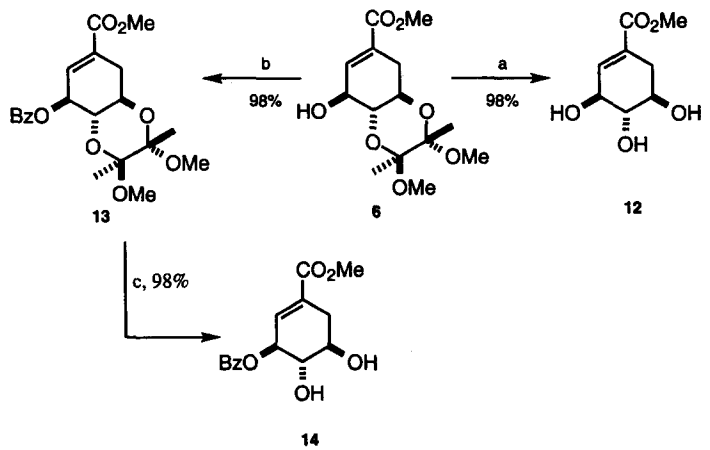
Scheme 1: a) Oxalyl chloride, DMSO, (*i*-Pr)$_2$NEt, CH_2Cl_2, -60 °C/r.t., 95%. b) Ac_2O, (*i*-Pr)$_2$NEt, CH_2Cl_2, DMAP, r.t., 80%. c) DIBAL-H, THF, -78 °C, 82% (**6**:**7** 14.6:1), 73% of **6** (isolated) or L-Selectride®, THF, -78 °C, 75% (**6**:**7** 0:1), 75% of **7** (isolated).

Compound **3** is already described in the literature[10a] and was prepared by us with slight modifications to the published method. Swern oxidation of **3** afforded the expected ketone **4** (74%)[10b] and some α,β-unsaturated ketone **5** (21%) as a result of tertiary hydroxyl elimination (Scheme 1). As enone **5** was the next desired product, we forced the elimination by activating the tertiary hydroxyl group with acetic anhydride and diisopropylethylamine (Scheme 1), and obtained it in 75% overall yield from **3**. Our next goal was the chemoselective reduction of the ketonic carbonyl group (Scheme 1). By employing DIBAL-H as the reducing agent we obtained the two diastereoisomers **6** and **7** with d.r. 14.6:1 (proton NMR data), respectively. After recrystallisation, pure alcohol **6** was isolated in 73% yield. Using L-Selectride®,[12] diastereoisomer **7** was obtained exclusively in 75% yield. In both reductions, only a slight excess of reducing agent was added in order to minimise the simultaneous reduction of the ester function. This resulted in the recovery of starting material. The high 1,2-*cis* stereoselectivity of L-Selectride® is well documented and is believed to be due to the steric bulk of the reducing agent inducing attack at the side opposite to a vicinal group in cyclohexanones. In fact

even with remote alkyl groups the reduction with L-Selectride® normally forms predominantly the axial alcohol. DIBAL-H is a non-polar reducing agent and the aluminium atom probably complexes with the carbonyl oxygen atom. Hydride attack is then controlled by the relative energies of the two product-like transition states and the more stable product predominates which is the equatorial aluminium alkoxide. Thus, with these two methods of reduction we were able to obtain selectively both of the C-3 epimers. Removal of the diol protecting group from compound **7** afforded (-)-methyl shikimate **8** efficiently in quantitative yield (Scheme 2). The physical data for **8** were in accord with those reported in the literature.[13] In a similar fashion, compound **6** yielded (-)-methyl 3-*epi*-shikimate **12** which was identified by comparison with the data previously reported[8] (Scheme 3).



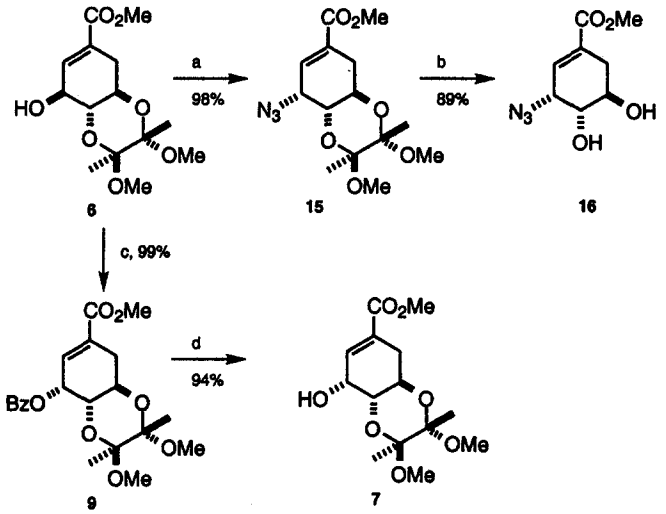
Scheme 2: a) CF_3COOH, H_2O, CH_2Cl_2, r.t., quantitative. b) BzCl, DMAP, pyr, 0 °C/r.t., 94%. c) CF_3COOH, H_2O, CH_2Cl_2, reflux, 91% (3.7:1).



Scheme 3: a) CF_3COOH, H_2O, CH_2Cl_2, r.t., 98%. b) BzCl, DMAP, pyr, 0 °C/r.t., 98%. c) CF_3COOH, H_2O, CH_2Cl_2, reflux, 98%.

Protection of the hydroxyl group of **7** with benzoyl chloride and DMAP in pyridine afforded benzoate **9**, which after cleavage of the acetal, under reflux, afforded diol **10** and the benzoate migration product **11** (3.7:1 **10**:**11**) (Scheme 2). That this was not the 4-*epi* shikimic acid derivative, which is produced by double bond migration, but a benzoate migration product, permitted by the *cis* disposition of the two vicinal hydroxyl groups, was demonstrated by subjecting the *trans* isomer **13** to the same reaction conditions. The benzoate **13** was obtained in excellent yield from **6** by simple esterification. Cleavage of the acetal of **13** produced only diol **14** (Scheme 3) and no migration or other reorganisational products were observed.

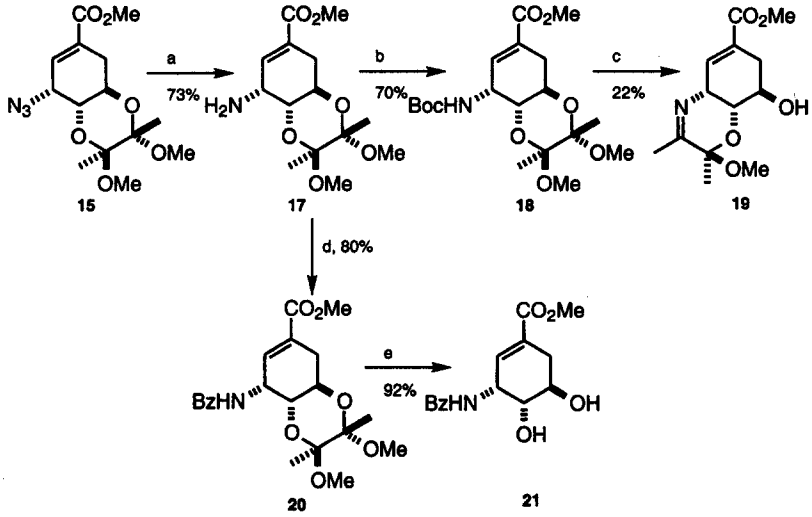
Mitsunobu reactions on the free hydroxyl group of compound **6**, inverted the configuration at C-3 (Scheme 4). Employing benzoic acid this reaction afforded benzoate **9** and after cleavage of the benzoate group, the C-3 epimer **7** was obtained (Scheme 4). By employing hydrazoic acid instead of benzoic acid in the Mitsunobu reaction, a nitrogen function was introduced at C-3 in the form of azide **15** (Scheme 4). Deprotection of the vicinal diequatorial diol using the usual method, afforded the azido diol **16**, a precursor to the 3-amino analogue of shikimic acid. The spectroscopic data for **16** are identical to those described in the literature.[6]



Scheme 4: a) DIAD, HN_3, PPh_3, THF, 0 °C, 98%. b) CF_3COOH, H_2O, CH_2Cl_2, reflux, 89%. c) DIAD, BzOH, PPh_3, THF, 0 °C, 99%. d) MeONa, MeOH, 0 °C/r.t., 94%

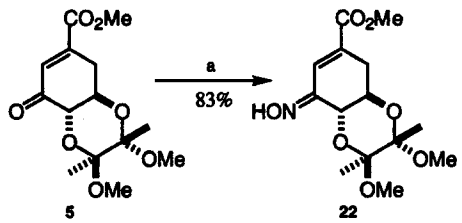
Reduction of azide **15** with triphenylphosphine/water afforded amine **17** in good yield (Scheme 5). Treatment of amine **17** with Boc_2O afforded the Boc-derivative **18** in 70% yield, along with a by-product for which we have not yet determined the structure. Cleavage of the 2,3-dimethoxybutan-2,3-dioxy acetal from **18** gave bicyclic compound **19** instead of the expected Boc-amide diol (Scheme 5). An explanation for this result is that the removal of the Boc group occurs under the drastic deprotection conditions employed. Reaction of the so-formed free amino group at the carbonyl group of the partially removed acetal protecting group then afforded the bicyclic imine. The same product was obtained when the amine **17** was treated similarly with

aqueous trifluoroacetic acid. The Boc protecting group is not compatible with the reagents normally necessary for removal of the vicinal diol protecting group.



Scheme 5: a) PPh_3, THF, H_2O, reflux, 73%. b) Boc_2O, $(i\text{-}Pr)_2NEt$, $CHCl_3$, r.t., 70%. c) CF_3COOH, H_2O, CH_2Cl_2, r.t., 22%. d) BzCl, DMAP, pyr, 0 °C/r.t., 80%. e) CF_3COOH, H_2O, CH_2Cl_2, reflux, 92%.

Benzoylamide **20** was cleanly obtained from the amine **17** using benzoyl chloride. After deprotecting **20** with trifluoroacetic acid and water, we obtained the benzoylamide diol **21**, in excellent yield (Scheme 5). No migration of the benzoyl moiety of **21** to an adjacent hydroxyl group was observed. No other carbamate protecting groups were tried but we suspect that problems due to cyclisation to the oxazolidinone may arise on deprotecting the adjacent hydroxyl groups.



Scheme 6: a) $H_2NOH.HCl$, $NaOAc.3H_2O$, MeOH, H_2O, r.t., 83%.

Finally, attempts were made to introduce the nitrogen atom at C-3 of enone **5** directly *via* the oxime **22** (Scheme 6). The oxime was obtained in good yield, but unfortunately its reduction to an amino group proved to be very difficult and we abandoned this strategy and opted for the route described above.

In conclusion, a short, efficient and versatile route has been developed for the transformation of quinic acid to (-)-methyl shikimate, (-)-methyl 3-*epi*-shikimate and 3-aminoshikimate derivatives, starting from the relatively inexpensive (-)-quinic acid. The group used for the protection of the *trans* vicinal diol system is compatible with this approach up to a point. This strategy should provide a way to other shikimic acid

derivatives and may have some advantages over the synthesis[6,7,8] employing shikimic acid as the starting material.

Experimental Section

General. Melting points were determined with a capillary apparatus and are uncorrected. ^{1}H NMR spectra were obtained at 300 MHz in $CDCl_3$ or D_2O with chemical shift values (δ) in ppm downfield from tetramethylsilane, and ^{13}C NMR spectra were obtained at 100.61 MHz in $CDCl_3$ or D_2O. DEPT was used as an aid to structure elucidation and carbon assignments. Microanalyses were performed by the ITQB analytical services using a combustion apparatus. IR (ν, cm^{-1}) were measured on a FTIR spectrophotometer. Medium pressure preparative column chromatography: silica gel Merck 60 H. Preparative TLC: silica gel Merck 60 GF_{254}. Analytical TLC: Aluminum-backed silica gel Merck 60 F_{254}. Specific rotations ($[\alpha]_D^t$) were measured on an automatic polarimeter. Reagents and solvents were purified and dried according to ref 14. All the reactions were carried out in an inert atmosphere (argon or nitrogen), unless otherwise indicated.

Methyl (1S,3S,4R,5R)-1,5-dihydroxy-3,4-[(2S,3S)-2,3-dimethoxybutan-2,3-dioxy)]cyclohexan-1-carboxylate (3). To a solution of methyl (1R,3R,4S,5R)-1,5-dihydroxy-3,4-(isopropylidenedioxy) cyclohexane-1-carboxylate (5.195 g, 0.021 mol) and 2,2,3,3-tetramethoxybutane[10a] (4.14 g, 0.023 mol) in methanol (25 mL) at r.t., was added trimethyl orthoformate (9.22 mL, 0.084 mol) and *p*-toluenesulfonic acid (0.182 g, 1.05 mmol).The mixture was refluxed for 1 h and, after cooling, solid $NaHCO_3$ was added and the solvent evaporated. The residue was dissolved in diethyl ether (10 mL) and water (10 mL) was added. The aqueous phase was extracted with ethyl acetate (3 x 10 mL) and the combined organic extracts were dried ($MgSO_4$) and concentrated to give an orange solid. Recrystallisation from AcOEt/hexane (1:3) afforded **3** (5.744 g, 85%) as white needles. $[\alpha]_D^{20}$ +116.3 (c 1.06, CH_2Cl_2). m.p. 138-140 °C, (lit.[10a] 139.8-140.2 °C). FT-IR (KBr): 3443, 3333 (O-H); 2989, 2955, 2928, 2893, 2843, 2827 (C-H); 1728 (C=O, ester). Anal. Calcd. for $C_{14}H_{24}O_8$ (320.34258): C 52.49, H 7.55. Found: C 52.56, H 7.52.

Methyl (4S,5R)-4,5-[(2S,3S)-2,3-dimethoxybutan-2,3-dioxy)]-3-oxo-cyclohex-1-en-1-carboxylate (5) and methyl (1S,4S,5R)-1-hydroxy-4,5-[(2S,3S)-2,3-dimethoxybutan-2,3-dioxy)]-3-oxo-cyclohexan-1-carboxylate (4). A three necked, round bottomed flask was equiped with a magnetic stirrer and a thermometer. The flask was charged with CH_2Cl_2 (7 mL) and oxalyl chloride (0.74 mL, 8.6 mmol), which had been distilled immediately before use. The solution was cooled to -60 °C, and DMSO (1.28 mL, 18 mmol) in CH_2Cl_2 (2 mL) was added dropwise at a rapid rate. After 5 min at the same temperature, alcohol **3** (2.4 g, 7.5 mmol) in CH_2Cl_2 (7 mL) was added dropwise while maintaining the internal temperature at -50 to -60 °C. An excess of diisopropylethylamine (6.5 mL, 37.5 mmol) was slowly added at -50 to -60 °C. The system was then brought to r.t., and stirred for further 30 min. Water was added and the aqueous layer was separated and extracted with CH_2Cl_2 (3 x 15 mL). The organic layers were combined, dried ($MgSO_4$) and concentrated. Purification by column chromatography (AcOEt/hexane 2/8 to 1/1) afforded α,β-unsaturated ketone **5** (0.907 g, 21.2%) and ketone **4** (1.75 g, 74%), both as white solids. Compound **5**: $[\alpha]_D^{20}$ +73.3 (c 1.25, $CHCl_3$). m.p. 98-99 °C. ^{1}H

NMR ($CDCl_3$): δ 6.80 (1H, d, J=3.2 Hz, H-2); 4.31 (1H, d, J=11.6 Hz, H-4); 4.09 (1H, dd, J=11.6 Hz, J=5.3 Hz, H-5); 3.84 (3H, s, CO_2CH_3); 3.30 (3H, s, OCH_3); 3.25 (3H, s, OCH_3); 3.07 (1H, dd, J=18.2 Hz, J=5.2 Hz, H-6); 2.64 (1H, ddd, J=18.2 Hz, J=11.0 Hz, J=3.2 Hz, H-6); 1.43 (3H, s, CH_3); 1.34 (3H, s, CH_3). ^{13}C NMR ($CDCl_3$): δ 194.3 (C=O, ketone); 165.7 ($C(O)OCH_3$); 144.5 (C=C, C-1); 132.6 (C=C, C-2); 100.2, 99.2 ($2xC(CH_3)OCH_3$); 75.0, 67.0 (C-4, C-5); 52.8 ($C(O)OCH_3$); 48.3, 48.0 ($2xOCH_3$); 30.4 (C-6); 17.5, 17.4 ($2xCH_3$). FT-IR (KBr): 2995, 2980, 2958, 2914 (C-H); 1737 (C=O, ester); 1703 (C=O, α,β-unsat. ketone). Anal. Calcd. for $C_{14}H_{20}O_7$ (300.3107): C 55.99, H 6.71. Found: C 55.96, H 6.72. Compound **4**:[10b] $[\alpha]_D^{20}$ +82.7 (c 1.05, $CHCl_3$). m.p. 212-214 °C. FT-IR (KBr): 3487 (O-H); 2997, 2947, 2924, 2862, 2839 (C-H); 1749 (C=O, ester); 1732 (C=O, sat. ketone).

Methyl (4S,5R)-4,5-[(2S,3S)-2,3-dimethoxybutan-2,3-dioxy)]-3-oxo-cyclohex-1-en-1-carboxylate (5). To a solution of **4** (3.46 g, 10.9 mmol) in CH_2Cl_2 (10 mL), at 0 °C, was added diisopropylethylamine (5.7 mL, 32.6 mmol), acetic anhydride (1.54 mL, 16.3 mmol) and a catalytic amount of 4-(dimethylamino)pyridine (DMAP). The reaction was stirred at r.t. overnight. Water (10 mL) was added, the aqueous layer was separated and extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were dried ($MgSO_4$) and concentrated. Purification by column chromatography (AcOEt/hexane 4/6) gave enone **5** (2.06 g, 80%) as a white solid. The characterisation data for **5** is described in the previous experiment.

Methyl (3S,4S,5R)-3-hydroxy-4,5-[(2S,3S)-2,3-dimethoxybutan-2,3-dioxy)]-cyclohex-1-en-1-carboxylate (6) and methyl (3R,4S,5R)-3-hydroxy-4,5-[(2S,3S)-2,3-dimethoxybutan-2,3-dioxy)]-cyclohex-1-en-1-carboxylate (7). To a solution of enone **5** (3.52 g, 11.7 mmol) in THF (20 mL), at -78 °C, was added dropwise DIBAL-H (1 M solution in hexane, 17.6 mL, 17.6 mmol), and the reaction was stirred for 10 min before being quenched by the addition of saturated NH_4Cl (10 mL). The mixture was allowed to warm to r.t., extracted successively with diethyl ether (2 x 10 mL) and ethyl acetate (2 x 10 mL), and the combined organic layers were dried ($MgSO_4$) and concentrated. Purification by column chromatography (AcOEt/hexane 2/8 to 7/3) furnished starting material **5** (0.075 g, 2 %), and a mixture of the two hydroxy enoates epimers **6** and **7** (2.9 g, 82%) as a white solid. The ratio between the two epimers **6** and **7** was determined by ^1H NMR spectroscopy after purification (**6/7** 14.6:1). The major epimer **6** was isolated by crystallisation using pentane/diethyl ether (2.6 g, 73 % from initial ketone **5**) and its purity was confirmed by ^1H NMR spectroscopy. Compound **6** (major diastereoisomer, white solid): $[\alpha]_D^{20}$ +134.6 (c 1.43, $CHCl_3$). m.p. 142-143 °C. ^1H NMR ($CDCl_3$): δ 6.73 (1H, dd, J=2.7 Hz, J=1.2 Hz, H-2); 4.47 (1H, m, H-3); 3.81 (1H, dd, J=10.5 Hz, J=5.9 Hz, H-5); 3.75 (3H, s, CO_2CH_3); 3.65 (1H, dd, J=10.5 Hz, J=8.4 Hz, H-4); 3.30 (3H, s, OCH_3); 3.28 (3H, s, OCH_3); 2.74 (1H, ddd, J=17.4 Hz, J=5.9 Hz, J=1.2 Hz, H-6); 2.35 (1H, dddd, J=17.4 Hz, J=10.5 Hz, J=3.9 Hz, J=2.7 Hz, H-6); 1.35 (3H, s, CH_3); 1.33 (3H, s, CH_3). ^{13}C NMR ($CDCl_3$): δ 166.4 ($C(O)OCH_3$); 138.2 (C=C, C-2); 128.7 (C=C, C-1); 99.3, 99.2 ($2xC(CH_3)OCH_3$); 74.0 (C-4 or C-5); 69.9 (C-4 or C-5); 65.3 (C-3); 52.0 ($C(O)OCH_3$); 48.0, 47.9 ($2xOCH_3$); 29.6 (C-6); 17.7 ($2xCH_3$). FT-IR (KBr): 3483, 3423 (O-H); 2976, 2960, 2895, 2835; 1718 (C=O, ester); 1651 (C=C). Anal. Calcd. for $C_{14}H_{22}O_7$ (302.3266): C 55.62, H 7.33. Found: C 55.60, H 7.52.

Methyl (3R,4S,5R)-3-hydroxy-4,5-[(2S,3S)-2,3-dimethoxybutan-2,3-dioxy)]-cyclohex-1-en-1-carboxylate (7). To a solution of **5** (0.120 g, 0.4 mmol) in THF (2 mL), at -78 °C, was added dropwise L-Selectride® (1 M

solution in THF, 0.48 mL, 0.48 mmol), and the reaction was stirred for 10 min before being quenched by the addition of saturated NH_4Cl (2 mL). The mixture was allowed to warm to r.t., extracted with ethyl acetate (3 x 4 mL), and the combined organic layers were dried ($MgSO_4$) and concentrated. Purification by preparative TLC (AcOEt/hexane 4/6) furnished exclusively alcohol **7** (0.091 g, 75 %) as a viscous oil. A minor amount of starting material was also identified by TLC comparision, but not isolated. Compound **7**: $[\alpha]_D^{20}$ +41.5 (c 1.68, $CHCl_3$). ^1H NMR ($CDCl_3$): δ 6.91 (1H, dd, J=5.0 Hz, J=2.6 Hz, H-2); 4.39 (1H, m, H-3); 4.1 (1H, m, H-4); 3.76 (3H, s, CO_2CH_3); 3.63 (1H, dd, J=10.0 Hz, J=3.0 Hz, H-5); 3.27 (3H, s, OCH_3); 3.25 (3H, s, OCH_3); 2.83 (1H, dd, J=18.0 Hz, J=6.0 Hz, H-6); 2.25 (1H, ddd, J=18.0 Hz, J=10.0 Hz, J=3.0 Hz, H-6); 1.34 (3H, s, CH_3); 1.30 (3H, s, CH_3). ^{13}C NMR ($CDCl_3$): δ 166.5 ($C(O)OCH_3$); 135.0 (C=C, C-2); 131.7 (C=C, C-1); 100.0, 99.2 ($2xC(CH_3)OCH_3$); 70.5 (C-4 or C-5); 65.0 (C-4 or C-5); 62.4 (C-3); 52.0 ($C(O)OCH_3$); 48.0, 47.9 ($2xOCH_3$); 30.0 (C-6); 17.8, 17.6 ($2xCH_3$). FT-IR (KBr): 3477 (O-H); 2993, 2951, 2922, 2835 (C-H); 1724 (C=O, ester); 1651 (C=C). MS (EI): 302 (15, M^+), 271 (17, M^+-OCH_3), 153 (41), 139 (19), 117 (25), 75 (32), 59 (14). Hrms: Found: 302.1346, $C_{17}H_{22}O_7$ requires 302.1365.

Methyl (3R,4S,5R)-3,4,5-trihydroxy-cyclohex-1-en-1-carboxylate (8) ((-)-methyl shikimate). Trifluoroacetic acid (0.160 mL, 2.08 mmol) and water (0.031 mL, 1.74 mmol) were added to a solution of **7** (0.088 g, 0.291 mmol) in CH_2Cl_2 (5 mL). The reaction was stirred at r.t. for 12 h. Removal of solvent, excess trifluoroacetic acid and 2,3-butanedione afforded an oil which was treated with diethyl ether several times. This treatment gave (-)-methyl shikimate **8** (0.055 g, quantitative) as a white solid. Crystalline product **8** was obtained from ethyl acetate. The physical data for this synthetic material were in accord with those reported in the literature.[13] $[\alpha]_D^{21}$ –135.5 (c 1.5, MeOH), (Lit.[13b] $[\alpha]_D^{21}$ -136.8 ±2 (c 1.9, MeOH)), m.p. 112-113 °C (Lit.[13a,13b] m.p. 115 °C or 117 °C). ^1H NMR (D_2O): δ 7.06 (1H, dd, J=2.1 Hz, J=1.2 Hz, H-2); 4.69 (1H, d, J=3.9 Hz, H-3); 4.28 (1H, m, H-4 or H-5); 4.02 (4H, s, H-4 or H-5 and CO_2CH_3); 2.99 (1H, dd, J=18.0 Hz, J=5.1 Hz, H-6); 2.48 (1H, dd, J=18.0 Hz, J=6.3 Hz, H-6). ^{13}C NMR (D_2O): δ 170.7 (C=O, ester); 138.8 (C=C, C-2); 131.3 (C=C, C-1); 72.8 (C-4 or C-5); 68.3 (C-4 or C-5); 67.5 (C-3); 50.9 ($C(O)OCH_3$); 32.0 (C-6). FT-IR (KBr): 3456-3223 (O-H); 2906 (C-H); 1718 (C=O); 1656 (C=C). Anal. Calcd. for $C_8H_{12}O_5$ (188.18148): C 51.06, H 6.43. Found: C 50.93, H 6.57.

Methyl (3R,4S,5R)-3-benzoyloxy-4,5-[(2S,3S)-2,3-dimethoxybutan-2,3-dioxy)]-cyclohex-1-en-1-carboxylate (9). To a solution of alcohol **7** (0.075 g, 0.248 mmol) in pyridine (1.5 mL) at 0 °C, was added benzoyl chloride (0.043 mL, 0.37 mmol) and a catalytic amount of DMAP. After stirring at r.t. overnight, the reaction was quenched with saturated aqueous $NaHCO_3$ (2 mL) and allowed to stir for 15 min. The mixture was extracted with CH_2Cl_2 (3 x 5 mL). The combined organic layers were dried ($MgSO_4$) and concentrated. Purification by preparative TLC (AcOEt/hexane 4/6) gave benzoate **9** (0.101 g, 94%) as a very viscous foam, that solidified on standing. $[\alpha]_D^{20}$ –87.25 (c 1.15, $CHCl_3$). m.p. 107-108 °C. ^1H NMR ($CDCl_3$): δ 8.06 (2H, dd, J=6.0 Hz, J=1.5 Hz, Ar ortho); 7.54 (1H, t, J=6.3 Hz, Ar para); 7.44 (2H, t, J=6.6 Hz, Ar meta); 6.97 (1H, dd, J=2.4 Hz, J=1.2 Hz, H-2); 5.76 (1H, d, J=4.8 Hz, H-3); 4.30 (1H, m, H-5 or H-5); 3.82 (1H, dd, J=10.8 Hz, J=4.2 Hz, H-4 or H-5); 3.76 (3H, s, CO_2CH_3); 3.34 (3H, s, OCH_3); 3.27 (3H, s, OCH_3); 2.92 (1H, dd, J=17.7 Hz, J=6.0 Hz, H-6); 2.36 (1H, m, H-6); 1.32 (3H, s, CH_3); 1.21 (3H, s, CH_3). ^{13}C NMR ($CDCl_3$): δ 166.3

(C=O, ester); 166.1 (C=O, ester); 133.7 (C=C, C-2); 132.9 (Ar); 132.2 (C=C, C-1); 130.4, 129.8, 128.3, 128.1 (Ar); 99.7, 99.2 (2x$\underline{C}(CH_3)OCH_3$); 69.1 (C-4 or C-5); 67.0 (C-4 or C-5); 63.0 (C-3); 52.2 (C(O)O$\underline{C}H_3$); 48.1, 48.0 (2xO$\underline{C}H_3$); 30.2 (C-6); 17.8, 17.5 (2x$\underline{C}H_3$). FT-IR (KBr): 2997, 2953 (C-H); 1726 (C=O); 1714 (C=O). Anal. Calcd. for $C_{21}H_{26}O_8$ (406.43579): C 62.06, H 6.45. Found: C 62.08, H 6.61.

Methyl (3R,4S,5R)-3-benzoyloxy-4,5-dihydroxy-cyclohex-1-en-1-carboxylate (10) and methyl (3R,4S,5R)-4-benzoyloxy-3,5-dihydroxy-cyclohex-1-en-1-carboxylate (11). Trifluoroacetic acid (0.268 mL, 3.48 mmol) and water (0.052 mL, 2.91 mmol) were added to a solution of **9** (0.198 g, 0.487 mmol) in CH_2Cl_2 (5.2 mL). The reaction was stirred and refluxed for 3 h. Removal of solvent, excess trifluoroacetic acid and 2,3-butanedione afforded an oil which was treated with diethyl ether several times. This treatment gave an unseparable mixture of diols **10** and **11** (0.130 g, 91%, ratio 3.7:1 **10:11**) as a colourless oil. Compound **10**: ^{1}H NMR ($CDCl_3$): δ 7.99 (2H, dd, J=7.2 Hz, J=1.2 Hz, Ar ortho); 7.55 (1H, t, J=7.5 Hz, Ar para); 7.40 (2H, t, J=7.8 Hz, Ar meta); 6.86 (1H, m, H-2); 5.81 (1H, d, J=4.5 Hz, H-3); 4.17-4.09 (1H, m, H-4 or H-5); 3.87 (1H, dd, J=9.3 Hz, J=4.2 Hz, H-4 or H-5); 3.75 (3H, s, $CO_2C\underline{H}_3$); 3.05 (broad s, O$\underline{H}$); 2.94 (1H, dd, J=18.3 Hz, J=5.7 Hz, H-6); 2.26 (1H, dd, J=18.3 Hz, J=8.1 Hz, H-6). ^{13}C NMR ($CDCl_3$): δ 166.3 (C=O, ester); 166.2 (C=O, ester); 133.5 (C=C, C-2); 133.1, 132.0, 129.8 (Ar); 129.4 (C=C, C-1); 128.5 (Ar); 72.0 (C-4 or C-5); 68.8 (C-4 or C-5); 67.2 (C-3); 52.2 (C(O)O$\underline{C}H_3$); 31.8 (C-6). Compound **11**: ^{1}H NMR ($CDCl_3$): more significant signals: δ 5.24 (1H, dd, J=7.5 Hz, J=3.9 Hz, H-4); 4.78 (1H, broad s, H-3 or H-5); 4.36 (1H, dd, J=12.9 Hz, J=5.4 Hz, H-3 or H-5); 3.76 (3H, s, $CO_2C\underline{H}_3$); 2.81 (1H, dd, J=18.6 Hz, J=5.1 Hz, H-6); 2.41 (1H, dd, J=18.6 Hz, J=5.4 Hz, H-6). FT-IR (film), mixture: 3468 (O-H); 2953, 2912 (C-H); 1720 (C=O, esters); 1656 (C=C).

Methyl (3S,4S,5R)-3-benzoyloxy-4,5-[(2S,3S)-2,3-dimethoxybutan-2,3-dioxy]-cyclohex-1-en-1-carboxylate (13). To a solution of alcohol **6** (0.110 g, 0.364 mmol) in pyridine (3 mL) at 0 °C, was added benzoyl chloride (0.064 mL, 0.55 mmol) and a catalytic amount of DMAP. After 2 h at r.t., the reaction was quenched with saturated aqueous $NaHCO_3$ (2 mL) and allowed to stir for 15 min, and the mixture was extracted with CH_2Cl_2 (3 x 5 mL). The combined organic layers were dried ($MgSO_4$) and concentrated. Purification by preparative TLC (AcOEt/hexane 3/7) gave benzoate **13** (0.145 g, 98%) as a white solid. $[\alpha]_D^{20}$ +205.1 (c 1.17, $CHCl_3$). m.p. 62-64 °C. ^{1}H NMR ($CDCl_3$): δ 8.05 (2H, t, J=9.0 Hz, Ar ortho); 7.57 (1H, t, J=6.0 Hz, Ar para); 7.44 (2H, t, J=9.0 Hz, Ar meta); 6.76 (1H, dd, J=3.0 Hz, J=1.4 Hz, H-2); 5.80 (1H, m, H-3); 4.04 (1H, d, J=12.0 Hz, H-4); 3.96 (1H, m, H-5); 3.75 (3H, s, $CO_2C\underline{H}_3$); 3.30 (3H, s, O$\underline{C}H_3$); 3.29 (3H, s, O$\underline{C}H_3$); 2.84 (1H, ddd, J=15.0 Hz, J=5.7 Hz, J=3.0 Hz, H-6); 2.41 (1H, m, H-6); 1.33 (3H, s, C$\underline{H}_3$); 1.29 (3H, s, C$\underline{H}_3$). ^{13}C NMR ($CDCl_3$): δ 166.1 (C=O, ester); 165.8 (C=O, ester); 134.8 (C=C, C-2); 133.2, 130.3 (Ar); 129.8 (C=C, C-1); 129.7, 128.4, (Ar); 99.4, 99.2 (2x$\underline{C}(CH_3)OCH_3$); 72.2 (C-4 or C-5); 70.5 (C-4 or C-5); 65.5 (C-3); 52.1 (C(O)O$\underline{C}H_3$); 48.0, 47.8 (2xO$\underline{C}H_3$); 29.3 (C-6); 17.6 (2x$\underline{C}H_3$). FT-IR (KBr): 2995, 2953, 2906, 2835 (C-H); 1724 (C=O, ester). MS (CI): 407 (31, M^++H), 375 (100, M^+-OCH_3), 343 (49), 317 (21), 285 (13), 253 (42). Hrms: Found: 407.1704, $C_{21}H_{27}O_8$ (M^++H) requires 407.1706.

Methyl (3S,4S,5R)-3-benzoyloxy-4,5-dihydroxy-cyclohex-1-en-1-carboxylate (14). Trifluoroacetic acid (0.304 mL, 3.3 mmol) and water (0.050 mL, 5.98 mmol) were added to a solution of **13** (0.224 g, 0.55 mmol) in

CH_2Cl_2 (5 mL). The reaction was stirred and refluxed for 3 h. Removal of solvent, excess trifluoroacetic acid and 2,3-butanedione afforded an oil which was treated with diethyl ether several times. This treatment gave diol **14** (0.157 g, 98%) as a white solid. $[\alpha]_D^{20}$ +49.6 (c 0.53, CH_2Cl_2). m.p. 76-77 °C. ^1H NMR ($CDCl_3$): δ 8.06 (2H, dd, J=6.0 Hz, J=3.0 Hz, Ar ortho); 7.59 (1H, t, J=9.0 Hz, Ar para); 7.47 (2H, t, J=9.0 Hz, Ar meta); 6.74 (1H, dd, J=3.0 Hz, J=1.3 Hz, H-2); 5.68 (1H, d, J=6.0 Hz, H-3); 3.95-3.83 (2H, m, H-4, H-5); 3.78 (3H, s, $CO_2C\underline{H}_3$); 2.98 (1H, dd, J=15.0 Hz, J=3.0 Hz, H-6); 2.34 (1H, m, H-6). ^{13}C NMR ($CDCl_3$): δ 167.0 (C=O, ester); 166.0 (C=O, ester); 134.4 (C=C, C-2); 133.6, 130.7, 129.9 (Ar); 129.2 (C=C, C-1); 128.5, (Ar); 75.3 (C-4 or C-5); 75.2 (C-4 or C-5); 69.6 (C-3); 52.2 ($C(O)O\underline{C}H_3$); 31.6 (C-6). FT-IR (KBr): 3524, 3495 (O-H); 2949, 2910 (C-H); 1710 (C=O); 1699 (C=O); 1655 (C=C). MS (EI): 292 (9, M^+), 170 (6, M^+-OBz), 105 (100), 77 (19). Hrms: Found: 292.0953, $C_{15}H_{16}O_6$ (M^+) requires 292.0947.

Methyl (3S,4S,5R)-3,4,5-trihydroxy-cyclohex-1-en-1-carboxylate (12) ((-)-3-*epi*-methylshikimate). Trifluoroacetic acid (0.364 mL, 4.73 mmol) and water (0.071 mL, 3.95 mmol) were added to a solution of **6** (0.200 g, 0.66 mmol) in CH_2Cl_2 (7 mL). The reaction was stirred at r.t. for 12 h. Removal of the solvent, excess trifluoroacetic acid and 2,3-butanedione under vacuum afforded an oil which was triturated with diethyl ether several times. This treatment gave (-)-3-*epi*-methyl shikimate **12** (0.122 g, 98%) as a white solid that crystallised from ethyl acetate. $[\alpha]_D^{20}$ –16.2 (c 1.06, dried MeOH), (Lit.[8] $[\alpha]_D$ –13.4 (c 0.5, MeOH)). m.p. 120-122 °C, (Lit.[8] 132 °C). ^1H NMR (D_2O): δ 6.89 (1H, broad s, H-2); 4.47 (1H, broad s, H-3); 4.01 (1H, m, H-4 or H-5); 3.97 (3H, s, $CO_2C\underline{H}_3$); 3.69 (1H, m, H-4 or H-5); 3.01 (1H, dd, J=16.6 Hz, J=5.8 Hz, H-6); 2.44 (1H, m, H-6). ^{13}C NMR (D_2O): δ 170.3 (C=O, ester); 140.8 (C=C, C-2); 129.8 (C=C, C-1); 78.0 (C-4 or C-5); 73.3 (C-4 or C-5); 70.4 (C-3); 54.3 ($C(O)O\underline{C}H_3$); 33.6 (C-6). FT-IR (KBr): 3533-3207 (O-H); 1701 (C=O); 1655 (C=C). Anal. Calcd. for $C_8H_{12}O_5$ (188.18148): C 51.06, H 6.43. Found: C 51.03, H 6.54.

Methyl (3R,4S,5R)-3-benzoyloxy-4,5-[(2S,3S)-2,3-dimethoxybutan-2,3-dioxy)]-cyclohex-1-en-1-carboxylate (9). To a solution of alcohol **6** (0.200 g, 1.32 mmol), triphenylphosphine (0.347 g, 1.32 mmol) and benzoic acid (0.162 g, 1.32 mmol) in THF (8 mL), at 0 °C, was added dropwise a solution of diisopropyl azodicarboxylate (DIAD, 0.261 mL, 1.32 mmol). After stirring for 1 h, the solvent was removed and the residue was redissolved in diethyl ether and water. The aqueous layer was extracted with diethyl ether (2 x 5 mL) and ethyl acetate (5 mL). The combined organic layers were dried ($MgSO_4$) and concentrated. Purification by column chromatography (AcOEt/hexane 1/9) afforded benzoate **9** (0.265 g, 99%) as a very viscous foam, that solidified afterwards. The characterisation data of **9** is described in a previous experiment.

Methyl (3R,4S,5R)-3-hydroxy-4,5-[(2S,3S)-2,3-dimethoxybutan-2,3-dioxy)]-cyclohex-1-en-1-carboxylate (7). To a solution of **9** (0.265 g, 0.65 mmol) in MeOH (5 mL), at 0 °C, was added sodium methoxide (0.530 g, 9.8 mmol) in small portions, and the reaction was stirred at r.t. for 2 h. Saturated aqueous NH_4Cl solution (5 mL) was added. After 10 min, diethyl ether was added (5 mL) and the organic layer was separated. The aqueous layer was saturated with NaCl and extracted with ethyl acetate (3 x 5 mL). The combined organic layers were dried ($MgSO_4$) and concentrated. Purification by preparative TLC (AcOEt/hexane 4.5/5.5) afforded alcohol **7** (0.185 g, 94%) as a colourless oil. The characterisation data of **7** is described in a previous experiment.

Methyl (3R,4S,5R)-3-azido-4,5-[(2S,3S)-2,3-dimethoxybutan-2,3-dioxy)]-cyclohex-1-en-1-carboxylate (15). To a solution of **6** (0.225 g, 0.84 mmol) in THF (8 mL), at 0 °C, was added triphenylphosphine (0.332 g, 1.27 mmol), hydrazoic acid (1.27 M in benzene, 1.6 mL, 1.27 mmol) and DIAD (0.250 mL, 1.27 mmol) in THF (2 mL), dropwise. The reaction mixture was stirred at r.t. for 1 h. The solvent was evaporated and the residue was purified by column chromatography (AcOEt/hexane 2.5/97.5) to afford azide **15** (0.269 g, 98%) as white crystals. $[\alpha]_D^{20}$ –69.9 (c 1.07, $CHCl_3$). m.p. 80-82 °C. ^1H NMR ($CDCl_3$): δ 6.78 (1H, dd, J=5.7 Hz, J=2.4 Hz, H-2); 4.27 (1H, d, J=4.8 Hz, H-3); 4.06 (1H, m, H-4 or H-5); 3.83-3.74 (1H, m, H-4 or H-5); 3.77 (3H, s, CO_2CH_3); 3.29 (6H, s, 2xOCH_3); 2.83 (1H, dd, J=18.0 Hz, J=6.0 Hz, H-6); 2.26 (1H, dddd, J=18.0 Hz, J=10.5 Hz, J=3.0 Hz, J=1.2 Hz, H-6); 1.36 (3H, s, CH_3); 1.32 (3H, s, CH_3). ^{13}C NMR ($CDCl_3$): δ 166.0 ($C(O)OCH_3$); 132.5 (C=C); 132.0 (C=C); 100.0, 99.2 (2x$C(CH3)OCH_3$); 70.4 (C-4 or C-5); 62.7 (C-4 or C-5); 57.2 (C-3); 52.2 ($C(O)OCH_3$); 48.1, 48.0 (2xOCH_3); 30.1 (C-6); 17.8, 17.6 (2xCH_3). FT-IR (KBr): 2999, 2957, 2933, 2924, 2839 (C-H); 2112, 2077 (N_3); 1726 (C=O); 1651 (C=C). Anal. Calcd. for $C_{14}H_{21}O_6N_3$ (327.33934): C 51.37, H 6.47, N 12.84. Found: C 51.08, H 6.41, N 12.93.

Methyl (3R,4S,5R)-3-azido-4,5-dihydroxy-cyclohex-1-en-1-carboxylate (16). To a solution of azide **15** (0.130 g, 0.397 mmol) in CH_2Cl_2 (5 mL) was added trifluoroacetic acid (0.219 mL, 2.84 mmol) and water (0.043 mL, 2.37 mmol). The reaction was refluxed at 40-60 °C for 2 h. The volatiles were removed and the residue obtained was purified by preparative TLC (AcOEt/hexane 7/3) to afford the azido diol **16** (0.075 g, 89%) as a colourless oil, with spectroscopic data identical with those in the literature.[6] $[\alpha]_D^{20}$ –272.9 (c 2.45, $CHCl_3$). ^1H NMR ($CDCl_3$): δ 6.82 (1H, ddd, J=4.5 Hz, J=2.4 Hz, J=1.2 Hz, H-2); 4.37 (1H, m, H-3); 3.96 (1H, m, H-4 or H-5); 3.78 (4H, broad s, H-4 or H-5, and CO_2CH_3); 2.94 (1H, dd, J=18.0 Hz, J=6.0 Hz, H-6); 2.81 (2H, broad s, OH); 2.25 (1H, dd, J=18.0 Hz, J=8.3 Hz, H-6). ^{13}C NMR ($CDCl_3$): δ 166.2 (C=O, ester); 132.4 (C=C); 131.8 (C=C); 72.6 (C-4 or C-5); 66.9 (C-4 or C-5); 59.1 (C-3); 52.3 ($C(O)OCH_3$); 32.0 (C-6). FT-IR (KBr): 3474-3379 (O-H); 2953, 2912, 2852 (C-H); 2119, 2110 (N_3); 1722 (C=O); 1656 (C=C). Anal. Calcd. for $C_8H_{11}O_4N_3$ (213.19429): C 45.07, H 5.20, N 19.71. Found: C 45.06, H 5.30, N 19.41.

Methyl (3R,4S,5R)-3-amino-4,5-[(2S,3S)-2,3-dimethoxybutan-2,3-dioxy)]-cyclohex-1-en-1-carboxylate (17). To a solution of azide **15** (0.488 g, 1.49 mmol) in THF (20 mL) and water (0.200 mL) was added triphenylphosphine (0.428 g, 1.64 mmol), and the reaction was refluxed at 60 °C for 4 h. The volatiles were removed and the residue obtained was purified by column chromatography (AcOEt/hexane 7/3 – 100% AcOEt) to afford the amine **17** (0.326 g, 73%) as a colourless viscous oil. $[\alpha]_D^{20}$ –6.13 (c 0.815, CH_2Cl_2). ^1H NMR ($CDCl_3$): δ 6.92 (1H, dd, J=2.4 Hz, J=1.2 Hz, H-2); 3.94 (1H, m, H-3 or H-4 or H-5); 3.75 (3H, s, CO_2CH_3); 3.65-3.60 (2H, m, H-3 and/or H-4 and/or H-5); 3.27 (3H, s, OCH_3); 3.26 (3H, s, OCH_3); 2.80 (1H, dd, J=17.1 Hz, J=6.0 Hz, H-6); 2.26 (1H, ddd, J=17.1 Hz, J=10.2 Hz, J=2.1 Hz, H-6); 1.33 (3H, s, CH_3); 1.32 (3H, s, CH_3). ^{13}C NMR ($CDCl_3$): δ 166.4 ($C(O)OCH_3$); 138.2 (C=C, C-2); 128.7 (C=C, C-1); 99.3, 99.2 (2x$C(CH_3)OCH_3$); 74.0 (C-4 or C-5); 69.9 (C-4 or C-5); 65.3 (C-3); 52.0 ($C(O)OCH_3$); 48.0, 47.9 (2xOCH_3); 29.6 (C-6); 17.7 (2xCH_3). FT-IR (film): 3587-3412 (N-H); 2993, 2953 (C-H); 1720 (C=O); 1649 (C=C). MS (EI): 301 (10, M^+), 270 (18, M^+-OCH_3), 212 (6), 170 (8), 153 (58), 138 (73), 120 (15), 94 (100), 73 (7). Hrms: Found: 301.1523, $C_{14}H_{23}O_6N$ (M^+) requires 301.1525.

Methyl (3R,4S,5R)-3-*tert*-butyloxycarbonylamino-4,5-[(2S,3S)-2,3-dimethoxybutan-2,3-dioxy)]-cyclohex-1-en-1-carboxylate (18). To a solution of **17** (0.045 g, 0.149 mmol) in $CHCl_3$ (3 mL) at r.t., was added diisopropylethylamine (0.078 mL, 0.447 mmol) and a solution of di-*tert*-butyl dicarbonate (0.098 g, 0.447 mmol) in $CHCl_3$ (2 mL). After stirring for 24 h the reaction mixture was washed with saturated aqueous $NaHCO_3$ solution (3 mL) and extracted with CH_2Cl_2 (3 x 8 mL). The organic layer was dried ($MgSO_4$) and concentrated. Purification by preparative TLC (AcOEt/hexane 2/8) afforded the protected amine **18** (0.042 g, 70%) as a white solid foam, and 0.009 g of a by-product, as a white solid, which has not yet been identified. Compound **18**: $[\alpha]_D^{20}$ -46.2 (c 0.13 CH_2Cl_2). m.p. 157-158 °C. ^1H NMR ($CDCl_3$): δ 7.02 (1H, dd, J=2.4 Hz, J=1.2 Hz, H-2); 4.89 (1H, broad s, H-3); 4.38 (1H, broad s, H-4 or H-5); 3.83 (1H, m, H-4 or H-5); 3.75 (3H, s, CO_2CH_3); 3.27 (6H, s, 2xOCH_3); 2.78 (1H, dd, J=17.0 Hz, J=5.1 Hz, H-6); 2.23 (1H, ddd, J=17.0 Hz, J=8.4 Hz, J=2.7 Hz, H-6); 1.47 (9H, s, $C(CH_3)_3$); 1.31 (3H, s, 2xCH_3). ^{13}C NMR ($CDCl_3$): δ 166.7 (C=O); 155.8 ($OC(CH_3)_3$); 135.9 (C=C, C-2); 120.3 (C=C, C-1); 99.8, 99.1 (2x$C(CH_3)OCH_3$); 68.2 (C-4 or C-5); 63.3 (C-4 or C-5); 52.0 ($C(O)OCH_3$); 48.1, 47.9 (2xOCH_3); 47.8 (C-3); 29.6 (C-6); 28.3 ($OC(CH_3)_3$); 17.7, 17.6 (2xCH_3). FT-IR (KBr): 3412, 3350 (N-H); 2987, 2949, 2920, 2897, 2835 (C-H); 1722 (C=O); 1712 (C=O). Anal. Calcd. for $C_{19}H_{31}O_8N$ (401.45989): C 56.84, H 7.78, N 3.49. Found: C 56.79, H 7.52, N 3.34.

Methyl (1R,4R,6R,7R)-2-aza-7-hydroxy-4-methoxy-3,4-dimethyl-5-oxabicyclo[4.4.0]deca-2,9-diene-9-carboxylate (19). To a solution of compound **18** (0.039 g, 0.097 mmol) in CH_2Cl_2 (2 mL) was added trifluoroacetic acid (0.053 mL, 0.7 mmol) and water (0.014 mL, 0.58 mmol). The reaction was stirred at r.t. for 16 h. The volatiles were removed and the viscous residue was purified by preparative TLC (AcOEt/EtOH 9.5/0.5) to afford compound **19** (0.006 g, 22%) as a white solid and another fraction (0. 14 g), as a viscous oil, which was a complex mixture as indicated by the ^1H NMR spectrum. Compound **19**: $[\alpha]_D^{20}$ +78.9 (c 1.0, $CHCl_3$). m.p. 122-124 °C. ^1H NMR ($CDCl_3$): δ 6.99 (1H, broad s, H-10); 4.31 (1H, broad s, H-1 or H-6 or H-7); 4.22 (1H, broad s, H-1 or H-6 or H-7); 4.00 (1H, m, H-1 or H-6 or H-7); 3.76 (3H, s, CO_2CH_3); 3.11 (3H, s, OCH_3); 2.69 (1H, broad d, J=15.6 Hz, H-8); 2.42 (1H, broad d, J=20.1 Hz, H-8); 1.50 (6H, s, 2xCH_3). ^{13}C NMR ($CDCl_3$): δ 169.5 (C=O); 165.2 (C=N); 135.8 (C=C, C-10); 127.0 (C=C, C-9); 96.3 (C-4); 68.8, 66.9, 53.2 (C-1, C-6, C-7); 51.9 ($C(O)OCH_3$); 50.3 (OCH_3); 29.4 (C-8); 22.4, 21.7 (2xCH_3). FT-IR (KBr): 3167 br (O-H); 2991, 2953, 2939, 2918 (C-H); 1712 (C=O, ester); 1670 (C=N); 1651 (C=C). Anal. Calcd. for $C_{13}H_{19}O_5N$ (269.29951): C 57.98, H 7.11, N 5.20. Found: C 58.06, H 7.24, N 5.07.

Methyl (3R,4S,5R)-3-benzoylamino-4,5-[(2S,3S)-2,3-dimethoxybutan-2,3-dioxy)]-cyclohex-1-en-1-carboxylate (20). To a solution of amine **17** (0.058 g, 0.192 mmol) in pyridine (2 mL)at 0 °C, was added benzoyl chloride (0.034 mL, 0.288 mmol) and a catalytic amount of DMAP. After 2 h at r.t., the reaction was quenched with saturated aqueous $NaHCO_3$ (3 mL) and allowed to stir for 15 min. The mixture was extracted with CH_2Cl_2 (3 x 5 mL). The combined organic layers were dried ($MgSO_4$) and concentrated. Purification by preparative TLC (AcOEt/hexane 3/7) afforded amide **20** (0.062 g, 80%) as white crystals. $[\alpha]_D^{20}$ –226.5 (c 0.245, $CHCl_3$). m.p. 175-176 °C. ^1H NMR ($CDCl_3$): δ 7.76 (2H, dd, J=9.0 Hz, J=3.0 Hz, Ar ortho); 7.52-7.42 (3H, m, Ar para and meta); 7.25 (1H, dd, J=2.7 Hz, J=1.2 Hz, H-2); 6.60 (1H, d, J=3.0 Hz, NH); 4.77 (1H, d, J=6.0 Hz, H-3); 3.99-3.92 (2H, m, H-4 and H-5); 3.75 (3H, s, CO_2CH_3); 3.32 (3H, s, OCH_3); 3.29 (3H, s,

OCH_3); 2.83 (1H, dd, J=17.1 Hz, J=4.8 Hz, H-6); 2.31 (1H, dddd, J=17.1 Hz, J=9.6 Hz, J=2.7 Hz, J=1.2 Hz, H-6); 1.35 (3H, s, CH_3); 1.31 (3H, s, CH_3). ^{13}C NMR ($CDCl_3$): δ 167.5 (C=O, ester); 166.6 (C=O, amide); 135.2 (C=C, C-2); 134.5 (C=C, C-1); 131.5, 129.9, 128.6, 127.0 (Ar); 99.8, 99.3 (2x$C(CH_3)OCH_3$); 68.3 (C-4 or C-5); 63.6 (C-4 or C-5); 52.0 ($C(O)OCH_3$); 48.3, 48.2 (2xOCH_3); 47.8 (C-3); 29.7 (C-6); 17.6 (2xCH_3). FT-IR (KBr): 3267 (N-H); 2991, 2951, 2904, 2877, 2831 (C-H); 1724 (C=O, ester); 1641 (C=O, amide). MS (EI): 405 (6, M^+), 374 (8, M^+-OCH_3), 316 (9), 257 (26), 224 (14), 198 (6), 122 (5), 105 (100), 77 (25). Hrms: Found: 405.1748, $C_{21}H_{27}O_7N$ (M^+) requires 405.1787.

Methyl (3R,4S,5R)-3-benzoylamino-4,5-dihydroxy-cyclohex-1-en-1-carboxylate (21). To a solution of compound **20** (0.100 g, 0.247 mmol) in CH_2Cl_2 (3 mL) was added trifluoroacetic acid (0.136 mL, 1.77 mmol) and water (0.014 mL, 1.48 mmol). The reaction was stirred at 40-60 °C for 2 h. The volatiles were removed and the residue obtained was purified by preparative TLC (AcOEt/EtOH 9.5/0.5) to afford the diol **21** (0.066 g, 92%) as a white solid. $[\alpha]_D^{20}$ –116.0 (c 0.15, $CHCl_3$). m.p. 72-74 °C. ^1H NMR ($CDCl_3$): δ 7.76 (2H, d, J=9.0 Hz, Ar ortho); 7.52-7.45 (1H, m, Ar para); 7.42 (2H, t, J=9.0 Hz, Ar meta); 6.83 (1H, dd, J=3.0 Hz, J=1.3 Hz, H-2); 6.50 (1H, d, J=6.0 Hz, NH); 5.12 (1H, d, J=3.0 Hz, H-3); 4.03-3.94 (2H, m, H-4 and H-5); 3.76 (3H, s, CO_2CH_3); 2.85 (1H, dd, J=18.0 Hz, J=3.0 Hz, H-6); 2.36 (1H, dd, J=18.0 Hz, J=6.0 Hz, H-6). ^{13}C NMR ($CDCl_3$): δ 168.5 (2xC=O); 134.7 (C=C, C-2); 133.5 (C=C, C-1); 132.0, 130.6, 128.6, 127.1 (Ar); 71.3 (C-4 or C-5); 67.4 (C-4 or C-5); 52.1 ($C(O)OCH_3$); 48.1 (C-3); 30.1 (C-6). FT-IR (KBr): 3381, 3369 (N-H, O-H); 1714 (C=O, ester); 1637 (C=O, amide); 1604 (C=C). Anal. Calcd. for $C_{15}H_{17}O_5N$ (291.30593): C 61.85, H 5.88, N 4.80. Found: C 61.74, H 6.08, N 4.53.

Methyl (4S,5R)-4,5-[(2S,3S)-2,3-dimethoxybutan-2,3-dioxy)]-3-hydroxyimino-cyclohex-1-en-1-carboxylate (22). Ketone **5** (0.397 g, 1.32 mmol), $HN_2OH.HCl$ (0.174 g, 1.58 mmol), $NaOAc.3H_2O$ (0.234 g, 1.7 mmol) were dissolved in $MeOH/H_2O$ (2.6 mL, 1:1). The reaction mixture was stirred at r.t. overnight and then extracted with diethyl ether (4 mL) and ethyl acetate (2 x 4 mL), the combined organic extracts were dried ($MgSO_4$) and concentrated. Purification by column chromatography (AcOEt/hexane 3/7) afforded oxime **22** (0.347 g, 83%) as white crystals. $[\alpha]_D^{20}$ –5.87 (c 0.45, $CHCl_3$). m.p. 205-206 °C. ^1H NMR ($CDCl_3$): δ 7.68 (1H, d, J=2.4 Hz, H-2); 4.43 (1H, d, J=10.8 Hz, H-4); 3.99-3.90 (1H, m, H-5); 3.81 (3H, s, CO_2CH_3); 3.32 (3H, s, OCH_3); 3.25 (3H, s, OCH_3); 2.92 (1H, dd, J=18.0 Hz, J=5.4 Hz, H-6); 2.42 (1H, ddd, J=18.0 Hz, J=10.8 Hz, J=2.4 Hz, H-6); 1.39 (3H, s, CH_3); 1.34 (3H, s, CH_3). ^{13}C NMR ($CDCl_3$): δ 166.5 ($C(O)OCH_3$); 148.6 (C-1 or C=N); 134.0 (C-1 or C=N); 122.4 (C-2); 99.8, 99.3 (2x$C(CH_3)OCH_3$); 69.0, 67.1 (C-4, C-5); 52.3 ($C(O)OCH_3$); 48.2, 47.9 (2xOCH_3); 29.5 (C-6); 17.6, 17.5 (2xCH_3). FT-IR (KBr): 3269, 3257 (O-H); 2995, 2955, 2908 (C-H); 1724 (C=O, ester). Anal. Calcd. for $C_{14}H_{21}O_7N$(315,32534): C 53.33, H 6.71, N 4.44. Found: C 53.32, H 6.67, N 4.23.

Acknowledgment: We thank Junta Nacional de Investigação Científica e Tecnológica and Fundação para a Ciência e a Tecnologia for grants conceded to C. A. and M. R. V. (Praxis XXI/BD/4527/94).

REFERENCES AND NOTES

1. Haslam E. *Shikimic acid: Metabolism and Metabolites*; John Wiley and Sons: Chichester, 1993.
2. Grossbard, E.; Atkinson, D. *The Herbicide Glyphosate*; Butterworths: Boston, 1985.
3. Reviews: Jiang, S. D., Singh, G. *Tetrahedron* **1998**, *54*, 4697. Campbell, M. M.; Sainbury, M.; Searle, P. A. *Synthesis* **1993**, 179. For a recent example: Shinada, T.; Yoshida, Y.; Ohfune, Y. *Tetrahedron Lett.* **1998**, *39*, 6027.
4. Review: Barco, A.; Benetti, S.; De Risi, C.; Marchetti, P.; Pollini, G. P.; Zanirato, V. *Tetrahedron: Asymmetry* **1997**, *8*, 3515.
5. For the most direct routes see: Snyder, B. D.; Rapoport, H. *J. Am. Chem. Soc.*, **1973**, *95*, 7821, and references therein.
6. Adams, H.; Bailey, N. A.; Brettle, R.; Cross, R.; Frederickson, M.; Haslam, E.; MacBeath, F. S.; Davies, G. M. *Tetrahedron* **1996**, *52*, 8565.
7. Brettle, R.; Cross, R.; Fredrickson, M.; Haslam, E.; MacBeath, F. S.; Davies, G. M. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 1275.
8. Brettle, R.; Cross, R.; Fredrickson, M.; Haslam, E.; MacBeath, F. S.; Davies, G. M. *Tetrahedron* **1996**, *52*, 10547.
9. Ley, S. V.; Priepke, H. W. M.; Warriner, S. L. *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 2290.
10. a) Montchamp, J.-L.; Tian, F.; Hart, M. E.; Frost, J. W. *J. Org. Chem.* **1996**, *61*, 3897. b) Tian, F.; Montchamp, J.-L.; Frost, J. W. *J. Org. Chem.* **1996**, *61*, 7373.
11. Hanessian, S.; Pan, J.; Carnell, A.; Bouchard, H.; Lesage, L. *J. Org. Chem.* **1997**, *62*, 465.
12. Krishnamurthy, S.; Brown, H. C. *J. Am. Chem. Soc.* **1976**, *98*, 3383. Brown, H. C.; Krishnamurthy, S. *J. Am. Chem. Soc.* **1972**, *94*, 7159.
13. a) Grewe, R.; Jensen, H.; Schnoor, M. *Chem. Ber.* **1956**, *89*, 898. b) Grewe, R.; Jeschke, J.-P. *Chem. Ber.* **1956**, *89*, 2080.
14. Perrin, D. D.; Armarego, W. L. F.; Perrin, D. R. *Purification of Laboratory Chemicals*, 2nd ed.; Pergamon Press: New York, 1980.