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The Shikimate Pathway. Part 8.[1] Synthesis of (-)-3(*R*)-Amino-4(*R*),5(*R*)-Dihydroxy-1-Cyclohexene-1-Carboxylic Acid: The 3(*R*)-Amino Analogue of (-)-Shikimic Acid

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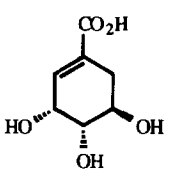
Abstract: The first successful method for the introduction of nitrogenous functionality at C-3 of the shikimate nucleus has been developed and has allowed the synthesis of (-)-3(*R*)-amino-4(*R*),5(*R*)-dihydroxy-1-cyclohexene-1-carboxylic acid [the 3(*R*)-amino analogue of (-)-shikimic acid] in seven steps from the parent acid. Copyright © 1996 Elsevier Science Ltd

The shikimate pathway is a biosynthetic pathway utilized by plants, fungi and micro-organisms for the synthesis of several essential aromatic metabolites including the three commonly occurring aromatic L-α-amino acids (Phe, Tyr, Trp) as well as the folate coenzymes and various isoprenoid quinones.[3,4] Through the course of evolution the enzymes that catalyse the transformations from acyclic C_3 and C_4 precursors to aromatics have become foreign to all higher species including mammals and the enzymology of the shikimate pathway has thus become the subject of intense research with compounds that inhibit the action of the enzymes of the shikimate pathway having been highlighted as materials with potential herbicidal, anti-fungal or bacteriocidal activity. Indeed the commercially important broad spectrum, post-emergence herbicide glyphosate[5] (marketed as Roundup®) is active against the enzyme 5-enolpyruvyl-shikimate-3-phosphate synthase (5-EPS-3-P synthase, E.C. 2.5.1.19) and inhibits the transfer of an enolpyruvyl moiety to the 5-position of the shikimate nucleus.



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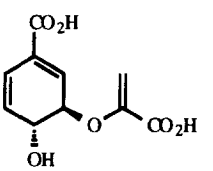

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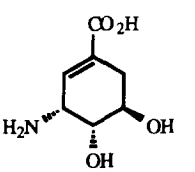
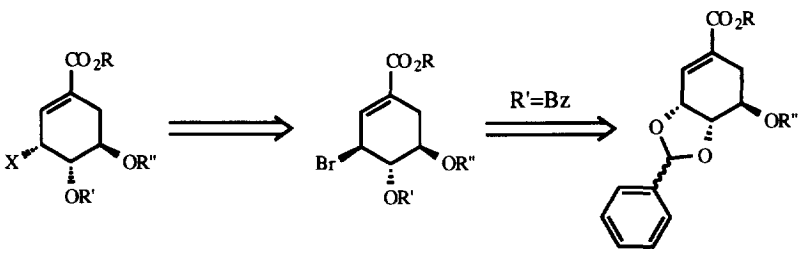


3

As part of our long standing interest in the enzymology of the shikimate pathway we have instigated a programme of research to develop routes to analogues of pathway intermediates, transition state analogues and related compounds as potential pharmaceuticals directly from (-)-shikimic acid **1** and (-)-chorismic acid **2**. In the main stem of the pathway, reactions at the C-3 hydroxyl group of (-)-shikimic acid **1**, and its precursors, play a vital role in the ultimate derivation of the aromatic skeleton *viz.* oxidation-reduction, phosphorylation and finally elimination. Our interest has focused heavily on compounds found along the early stages of the pathway; in particular we have targeted compounds that mimic (-)-shikimic acid **1**. We have recently reported[6]

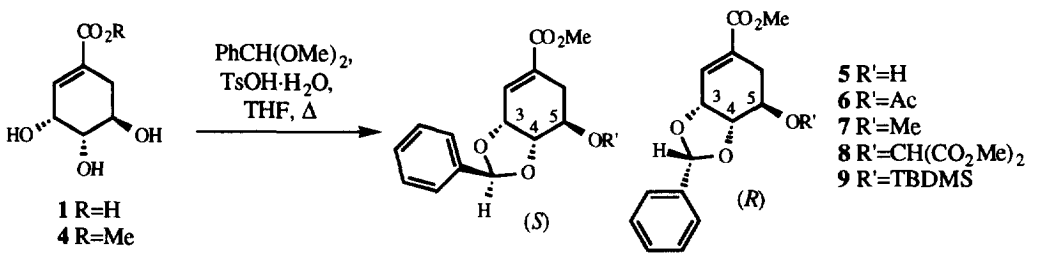
on our successful attempts to prepare γ-amino acid **3** directly from (-)-shikimic acid **1**; in this paper we wish to report more fully on our studies concerned with the introduction of nitrogen at C-3 of the shikimate ring.

In its simplest sense, the introduction of nitrogen at C-3 of the shikimate nucleus (*Scheme*; nitrogen functionality labelled as X) with retention of the natural α-stereochemistry using (-)-shikimic acid **1** as a direct precursor appeared to involve a double displacement mechanism and we envisaged this to be synthetically possible *via* the intermediacy of a series of activated intermediates with the unnatural inverted 3β-stereochemistry. We therefore targeted a set of allylic 3β-bromides as important synthetic intermediates since we felt these compounds to be directly accessible from acid **1** using the known radical chemistry of benzylidene protected diols.[7-9]



Scheme

(-)-Shikimic acid **1** was extracted from the ground seeds and carpels of *Illicium anisatum* (star aniseed)[10] according to a known procedure[11] which was modified to allow the reproducible isolation of large quantities of material (50 g) with an enhanced level of purity; treatment of acid **1** with acidified methanol under reflux (4 hours) afforded the known methyl ester **4** quantitatively.[12] Selective protection of the 3,4-*cis*-diol functionality of **4** proved to be possible using a wide range of benzaldehyde equivalents under a variety of conditions. Acid catalysed acetalation using benzaldehyde dimethyl acetal proved to be most effective on a large scale (20 g) both in terms of yield and purity of product, typically acetal **5** could be isolated after column chromatography on silica in yields of greater than 70% as a mixture of (*R*)- and (*S*)-isomers.

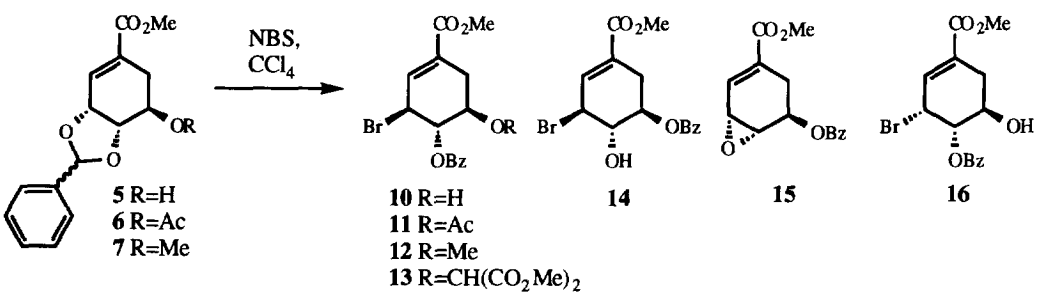


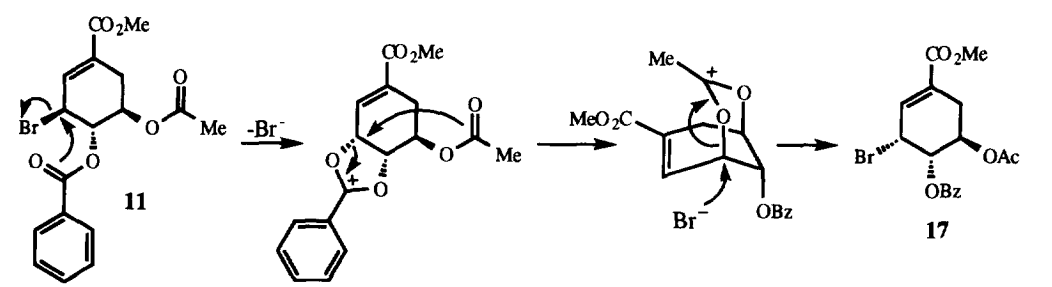
1 R=H
4 R=Me

Protection of the free 5-hydroxyl functionality of acetal **5** under standard conditions afforded acetate **6** (Ac_2O, C_5H_5N; 96%), methyl ether **7** (Ag_2O, MeI, Δ; 94%), malonate ether **8** ($N_2C(CO_2Me)_2$, $Rh_2(OAc)_4$, C_6H_6, Δ; 75%) and silyl ether **9** (TBDMSCl, imidazole, DMF; 73%). Acetals **5-9** could be separated into their component (*R*)- and (*S*)-isomers by careful column chromatography on silica and were unequivocally identified using nOe data. Irradiation of the benzylidene hydrogen atom of the more chromatographically mobile isomers of **5-9** resulted in an enhancement in the signals attributed to H-5 of the shikimate ring and not into H-3 and H-4 suggesting that these isomers had (*S*)-stereochemistry; contrastingly in identical experiments involving the

chromatographically less mobile isomers of **5-9** enhancements were noted in the signals for both H-3 and H-4 (and not for H-5) suggesting that these isomers had (*R*)-stereochemistry. In all subsequent experiments acetals **5-7** were used without prior separation as (*R*:*S*) mixtures.

An extensive study of the bromination of benzylidene acetals **5-7** showed that the synthesis of the required 3β-allylic bromides **10-12** was possible under a variety of conditions, however in many cases the desired product proved to be contaminated with one or more shikimate derived by-products and several aromatic species; yields of isolated products were often low and subject to extreme levels of irreproducibility. Molecular bromine in inert polar solvent (CH_2Cl_2, Et_2O or EtOAc) at 20°C worked both rapidly (1-3 hours) and well (60-80%) for the small scale synthesis (1 g) of bromides **10-12** (particularly so in CH_2Cl_2); the synthesis of bromide **10** from alcohol **5** was complicated by the formation of both the isomeric bromide **14** and epoxide **15** presumably *via* a benzoyl migration and ring closure sequence. Upon scale up (5 g) the rapid release of hydrogen bromide into the reaction media resulted in the subsequent aromatization of both substrate and product leading to much diminished yields of bromides **10-12**; addition of base (sodium bicarbonate or potassium carbonate) to remove the generated acid failed to obviate the problem.





The use of reagents that allow for the very slow release of molecular bromine afforded the solution to these problems. Thus use of *N*-bromosuccinimide (NBS) at 20°C in either benzene or carbon tetrachloride resulted in the slow (3 days) but controllable formation of bromides **10-12** (45-75%) with little or no shikimate derived by-products (**14**, **15** and **16**). Carbon tetrachloride was the preferred solvent, the large scale reaction being invariably cleaner, faster and yields higher and more reproducible when compared to similar reactions performed in benzene. Addition of small quantities of radical initiators (such as AIBN or dibenzoyl peroxide) failed to substantially increase the rate of reaction suggesting that the ionic part of the reaction involving the breakdown of an intermediate bromoacetal species[7-9] was rate limiting.

Repetition of the reaction at reflux temperature (77°C) resulted in a much faster reaction rate (3-16 hours) with similar levels of product yield and purity, however, bromide **11** suffered from a loss of stereochemical integrity at C-3 at more elevated temperatures and isomerized to an inseparable mixture of bromide **11** and its 3-epimer **17**; this isomerization process is thought to occur *via* a triple inversion mechanism involving the 5-acetate functionality. A similar mechanism was proposed previously[13] to account for the non-stereospecific substitution of a bromide similar to **11** by acetate anion in an early synthesis of methyl shikimate **4**; this epimerization is similar to the acid catalysed Fletcher epimerization[14,15] common in acetylated sugars.

That bromides **10-12** had the required 3β-stereochemistry was evident from coupling constant data in their ^{1}H nmr spectra, the *trans*-3,4-stereochemistry found in the products was apparent from their larger values for $J_{3,4}$ (7-9 Hz) when compared with those found in compounds with 3,4-*cis*-stereochemistry such as **1**, **4** and **5-9** (4-5 Hz); additionally, the stereochemical assignments of bromides **10-12** were unequivocally shown to be correct by an X-ray crystallographic study[16] of methyl ether **12** (*Figure*). In a manner analogous to that used to prepare malonate ether **8** from alcohol **5**, bromide **10** was converted to the malonate ether **13** (62%).

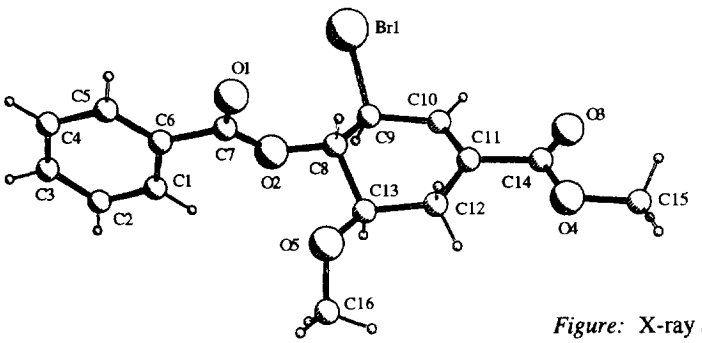
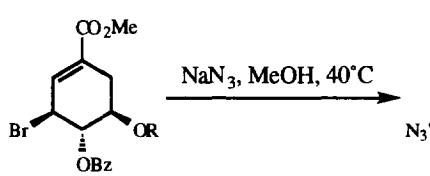
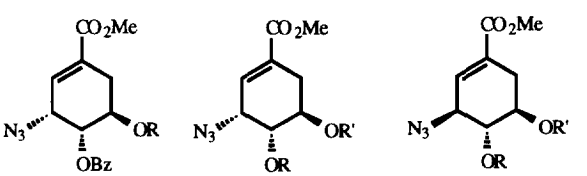


Figure: X-ray structure of **12**

We concentrated initially on the insertion of nitrogen at C-3 of the shikimate ring by the replacement of bromide ion with amines. Treatment of bromides **10-13** with several simple amines under a variety of conditions failed to afford any shikimate derived products containing nitrogen at C-3; bromide **10** underwent rapid aromatization processes, bromides **11-13** were somewhat more stable but were recovered contaminated with varying amounts of aromatic decomposition products. This lack of reactivity suggested that steric congestion in the vicinity of the 4-benzoate functionality of **10-13** precluded the necessary *cis*-approach of nucleophiles especially if they were bulky or highly angular in nature. We thus turned our attention to the use of azide anion as a nucleophile since we expected its linearity and high nucleophilicity to encourage the desired substitution processes.



10 R=H
11 R=Ac
12 R=Me
13 R=$CH(CO_2Me)_2$



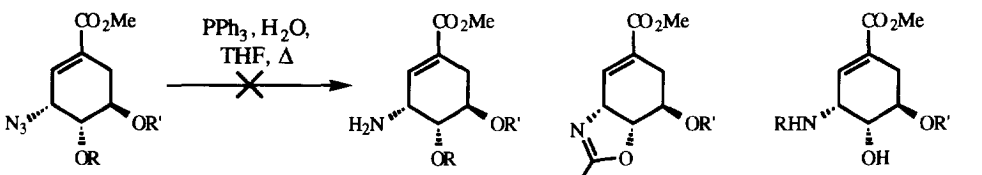
18 R=H
23 R=Ac
24 R=Me
25 R=$CH(CO_2Me)_2$

19 R=H, R'=Bz
20 R=Ac, R'=Bz

21 R=H, R'=Bz
22 R=Bz, R'=H

Treatment of bromides **10-13** with azide ion in warm methanol afforded a series of 3-azides **18-25** (ν_{max} 2100 cm^{-1}) in high yield; bromides **11-13** each afforded a single 3α-azide **23-25** ($J_{3,4}$ 4 Hz; 80-90%). Bromide **10** reacted less selectively and gave a mixture of two isomeric 3α-azides **18** ($J_{3,4}$ 4 Hz; 48%) and **19** ($J_{3,4}$ 4 Hz; 13%) together with traces of a 3β-azide **21** ($J_{3,4}$ 8·5 Hz; 8%); interestingly, the fourth possible isomeric azide **22** could not be detected in the reaction mixture by ^1H nmr. Previously reported attempts to introduce nitrogen functionality at C-3 of the shikimate nucleus[17] centred around the formation of 3-imino species by the addition of primary amines to 3-dehydro acids, these studies proved inappropriate for the synthesis of 3-amino derivatives of shikimates and quinates as substrate aromatization invariably occurred under the reaction conditions. Our studies thus provide the first successful methods for the introduction of nitrogen functionality at C-3 of the shikimate nucleus.[18]

Reduction of azido functionality was attempted using a variety of reductants. Hydrogen on a metal surface, metal hydride based reduction and sulphur based reduction systems all proved to be incompatable with the shikimate nucleus. In all cases starting material and/or aromatized decomposition products were isolated as the sole products of the reaction, however, the extremely mild conditions of Staudinger reduction[19] (PPh_3, H_2O) proved to be highly effective in the reduction of these azides. Reduction of **18**, **20** and **23** with triphenylphosphine in aqueous tetrahydrofuran proceeded smoothly at 64°C over 5 hours but failed to produce the expected free amines **26-28**, instead the reaction was found to be accompanied by rapid subsequent condensation and migration processes involving the 4-benzoate and 4-acetate functionalities to afford dihydrooxazoles **29-31** (42-67%) and benzamides **32-34** (25-35%) which could not be transformed under a variety of mild conditions into the amino acid **3**.

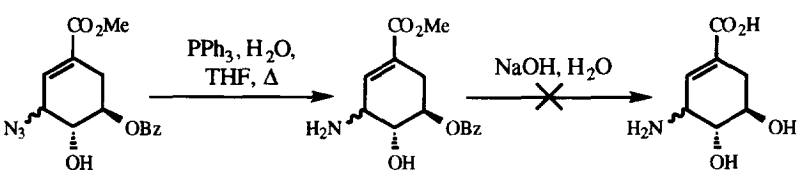


18 R=Bz, R'=H
20 R=Ac, R'=Bz
23 R=Bz, R'=Ac

26 R=Bz, R'=H
27 R=Ac, R'=Bz
28 R=Bz, R'=Ac

29 R=Ph, R'=H
30 R=Me, R'=Bz
31 R=Ph, R'=Ac

32 R=Bz, R'=H
33 R=Ac, R'=Bz
34 R=Bz, R'=Ac



19 α-N_3
21 β-N_3

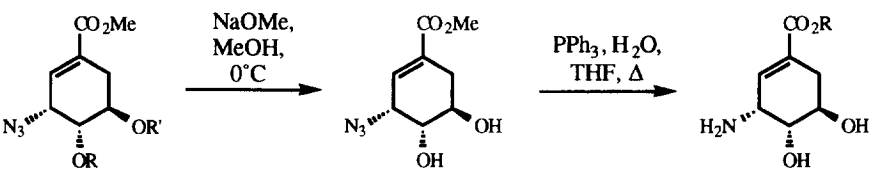
35 α-NH_2
36 β-NH_2

3 α-NH_2
37 β-NH_2

In contrast, reduction of the 5-benzoates **19** and **21** occured rapidly and smoothly under identical conditions to afford the free amines **35** and **36** in high yield (89% and 74% respectively). Subsequent saponification (NaOH, H_2O, 20°C) of **35** and **36** failed to afford the free amino acids **3** and **37**, instead compounds arising from aromatization of the shikimate ring were isolated as the sole products; saponification at 0°C proved to be similarly unsuccessful. The extreme efficacy of the aromatization process was presumed to be a consequence of the ability of the 5-benzoate moieties in **35** and **36** to function as a leaving group.

Controlled removal of the benzoyl and acetoxy functionalities of the azides **18-21** and **23** prior to reduction was seen as the key to the solution of these unforeseen problems. Thus deprotection of azides **18** and **19** was attempted with methoxide ion, reaction at 0°C affording α-azidodiol **38** (84%). Reaction temperature proved to be crucial to the success of this procedure, identical reactions performed at or near to room temperature invariably afforded mostly aromatized products. Azidodiol **38** reduced cleanly (PPh_3/H_2O) in THF at 64°C to yield the amino ester **39** (80%) which upon saponification gave 3(*R*)-amino analogue **3** of (-)-shikimic acid **1** (84%) after ion-exchange chromatography [Amberlite IR-120 (H)].

The similarity between **1** and its 3α-amino analogue **3** was apparent from their ^1H and ^{13}C nmr spectra recorded in deuterium oxide. Spectral data (coupling constants) showed the solution structures of **1** and **3** in D_2O to be similar; replacement of the 3α-hydroxyl functionality of **1** with an amino group in **3** therefore has little effect upon preferred molecular conformation. Noticeably in amino acid **3** the ^1H and ^{13}C resonances corresponding to H-3 and C-3 (the point of substitution) are shifted upfield relative to those in **1** as a result of the lower electonegativity of nitrogen when compared to oxygen, similarly H-2 and C-2 are deshielded in **3** relative to **1** although to a lesser extent.



18 R=Bz,R'=H
19 R=H, R'=Bz

38

39 R=Me
3 R=H

In summary, we have prepared a series of shikimate derivatives containing bromine at C-3 and have shown these to be highly valuable precursors for the synthesis of shikimate derivatives in which the hydroxyl functionality at C-3 of the ring has been replaced with other similar functional groups. We have developed the first successful methods for the introduction of nitrogen at C-3 of the shikimate nucleus (azide and amine) and have highlighted the utility of our methods by describing the synthesis of the 3α-amino acid **3** [the 3(*R*)-amino analogue of (-)-shikimic acid **1**].

Acknowledgements: We thank the SERC and Zeneca Pharmaceuticals for CASE studentships (to FSM, RC and MF) and The University of Sheffield for support.

EXPERIMENTAL

Melting points were determined on a Kofler hot-stage apparatus and are uncorrected. Specific rotations were measured with a Perkin-Elmer 141 polarimeter. Microanalyses were performed by The University of Sheffield Department of Chemistry Microanalytical Service and by the Microanalysis Department at Zeneca Pharmaceuticals, Alderley Park, Macclesfield, Cheshire. Mass spectra were recorded by electron impact (+EI) or by chemical ionisation (+CI) (ammonia as the ionising agent) using a Kratos MS-25 mass spectrometer or by positive fast atom bombardment (+FAB) (xenon as the ionising agent) using a Kratos MS-80 mass spectrometer as indicated. Infra-red spectra were recorded on a Perkin-Elmer 457 spectrophotometer in a nujol mull or as a neat film as indicated. All nuclear magnetic resonance spectra were recorded in the solvents

specified; ^1H and ^{13}C spectra were recorded using either a Bruker AM-250 spectrometer (operating at 250·1 MHz and 62·9 MHz respectively) or using a Bruker AM-400 spectrometer (operating at 400·1 MHz and 100·6 MHz respectively). Flash column chromatography was performed using silica gel 60 (Merck 9385). Acetone, isopropanol, ethyl acetate, methanol, petroleum ethers (b.p. 40-60°C and b.p. 60-80°C), toluene and water were distilled prior to use. Benzene was dried over sodium wire prior to use. Tetrahydrofuran was distilled from sodium-benzophenone ketyl immediately prior to use. *N*-Bromosuccinimide was recrystallized from boiling water as large colourless plates and was dried *in vacuo* over phosphorous pentoxide prior to use.

3(*R*),4(*S*),5(*R*)-Trihydroxy-1-cyclohexene-1-carboxylic acid 1.[20] The ground seeds and carpels of star aniseed[10] (900 g) were subjected to soxhlet extraction[11] with 95% ethanol (4 l) for 24 hours and the resulting dark brown extract was evaporated to dryness *in vacuo* to give a thick green oil that smelled strongly of aniseed. This oil was taken up into water (5 l) and warmed (*ca.* 80°C) whereupon a dark green oil formed on the surface which was removed by pipette and discarded. To the hot solution was added 37/40% aqueous formaldehyde (5 ml) and the solution was boiled for 5 minutes and was then allowed to cool. The precipitate that formed was removed by filtration to leave a clear amber solution which was passed down an anion exchange column of Amberlite IRA-400 (Cl) anion exchange resin (standard grade, 500 g, as the acetate). After washing with water (3 l), the product was eluted with aqueous acetic acid (25% v/v, 4 l). The resulting orange solution was evaporated to dryness *in vacuo* to yield the crude product as an orange-red solid that was taken up into the minimum volume of water and was applied to a column of 'Solka Floc' in water. Elution with water afforded a pale yellow solution that was evaporated to dryness *in vacuo* to afford the *product* **1** (50-60 g, 6-7% dry weight) as a white solid that crystallized from toluene and methanol as white prisms. m.p. 184-185°C; $[\alpha]_D$ -180·0° (*c* 4·0, H_2O); [Lit.,[11] m.p. 184°C; $[\alpha]_D$ -176·0° (*c* 2, EtOH)]; (Found: C, 48·4; H, 5·7. $C_7H_{10}O_5$ requires C, 48·3; H, 5·8%); *m/z* (+CI) 192, $M+NH_4^+$; ν_{max} (nujol) 3480, 3390, 3220, 1680, 1650 cm^{-1}; δ_H (D_2O) 6·73 (1H, dt, *J* 4, 1·5 Hz, H-2), 4·35 (1H, tt, *J* 4, 1·5 Hz, H-3), 3·93 (1H, ddd, *J* 8·5, 6·5, 5 Hz, H-5), 3·67 (1H, dd, *J* 8·5, 4 Hz, H-4), 2·64 (1H, ddt, *J* 18, 5, 1·5 Hz, H-6α), 2·12 (1H, ddt, *J* 18, 6·5, 1·5 Hz, H-6β); δ_C (D_2O) 170·1 (C=O), 137·1 (C-2), 129·8 (C-1), 71·1 (C-4), 66·5 (C-5), 65·8 (C-3), 30·4 (C-6).

3(*R*)-Amino-4(*R*),5(*R*)-dihydroxy-1-cyclohexene-1-carboxylic acid 3. A solution of methyl 3(*R*)-amino-4(*R*),5(*R*)-dihydroxy-1-cyclohexene-1-carboxylate **39** (40 mg, 0·21 mmol) in water (3 ml) was treated with sodium hydroxide (10 mg, 0·25 mmol) and the mixture was stirred overnight at room temperature. To the resulting solution was added Amberlite IR-120 (H) cationic exchange resin (*ca.* 50 mg) and the mixture was stirred for a further 5 minutes. The resin, (after removal by filtration), was resuspended in 2M ammonia solution (5 ml) and was stirred for 10 minutes. After removing the resin by filtration the solvent was removed *in vacuo* at 30°C and the resulting colourless oil was triturated with diethyl ether to afford the *product* **3** as a pale brown solid, (31 mg, 84%), that crystallised from acetone as a tan solid; m.p. 194-196°C (decomp.); $[\alpha]_D$ -50·4° (*c* 0·5, H_2O); (Found: C, 48·7; H, 6·7; N, 8·35. $C_7H_{11}NO_4$ requires C, 48·55; H, 6·4; N, 8·1%); *m/z* (+CI) 174, MH^+; ν_{max} (nujol) 3700-3100, 1560 cm^{-1}; δ_H (D_2O) 6·31 (1H, dt, *J* 4, 1·5 Hz, H-2), 4·00 (1H, dt, *J* 7·5, 5·5 Hz, H-5), 3·92 (1H, m, H-3), 3·84 (1H, m, H-4), 2·64 (1H, ddt, *J* 19, 5·5, 1·5 Hz, H-6α) 2·21 (1H, ddt, *J* 19, 5·5, 1·5 Hz, H-6β); δ_C (D_2O) 177·5 (C=O), 139·2 (C-1), 130·9 (C-2), 71·6 and 69·4 (C-4 and C-5), 51·1 (C-3), 33·5 (C-6).

Methyl 3(*R*),4(*S*)-benzylidenedioxy-5(*R*)-hydroxy-1-cyclohexene-1-carboxylate 5. A solution of methyl 3(*R*),4(*S*),5(*R*)-trihydroxy-1-cyclohexene-1-carboxylate **4**[12] (18·8 g, 0·10 mol) in tetrahydrofuran (500 ml) containing toluene-4-sulphonic acid (*ca.* 200 mg) was treated with benzaldehyde dimethyl acetal (19·0 g, 0·12 mol) and the reaction mixture was stirred and held at reflux for 3 days. After cooling the solvent was removed *in vacuo* at 30°C and the residue was taken into chloroform (200 ml), washed with saturated aqueous sodium bicarbonate solution (200 ml) and water (200 ml) and was dried over magnesium sulphate. After filtration the solution was evaporated to dryness *in vacuo* at 30°C to afford a yellow oil that was subjected to column chromatography. Elution with 3:2 v/v petroleum ether (b.p. 40-60°C)-ethyl acetate afforded the *product* **5** (20·0 g, 72%, 2:3 mixture of (*S*) and (*R*)-isomers), as a pale yellow oil. A small portion was separated into its component isomers by column chromatography. (*S*)-isomer: R_f 0·53, pale yellow oil; (Found: C, 65·4; H, 6·0. $C_{15}H_{16}O_5$ requires C, 65·2; H, 5·85%); *m/z* (+CI) 277, 294, MH^+, $M+NH_4^+$; ν_{max} (film) 3700-3100, 1720, 1655, 1495 cm^{-1}; δ_H ($CDCl_3$) 7·43 (2H, m, ArH), 7·38 (3H, m, ArH), 6·93 (1H, dt, *J* 4, 1·5 Hz, H-2), 5·96 (1H, s, PhCH-), 4·87 (1H, ddt, *J* 9, 4, 1·5 Hz, H-3), 4·34 (1H, t, *J* 9 Hz, H-4), 4·11 (1H, tt, *J* 9, 5 Hz, H-5), 3·78 (3H, s, $-CO_2Me$), 2·83 (1H, ddt, *J* 18, 5, 1·5 Hz, H-6α), 2·76 (1H, broad d, *J* 5Hz, -OH), 2·33 (1H, ddt, *J* 18, 9, 1·5 Hz, H-6β); δ_C ($CDCl_3$) 166·5 (C=O), 137·8 (Aromatic C), 133·4 (C-2), 131·1 (C-1), 129·2, 128·3 and 126·2 (Aromatic CH), 102·6 (Ph*C*H-), 77·8 (C-4), 72·4 (C-5), 67·0 (C-3), 52·1 (OMe), 28·9 (C-6). (*R*)-isomer: R_f 0·42, pale yellow oil; (Found: C, 65·4; H, 6·0. $C_{15}H_{16}O_5$ requires C, 65·2; H, 5·85%); *m/z* (+CI) 277, 294, MH^+, $M+NH_4^+$; ν_{max} (film) 3700-3100, 1720, 1655, 1495 cm^{-1}; δ_H ($CDCl_3$) 7·43 (2H, m, ArH), 7·37 (3H, m, ArH), 6·98 (1H, dt, *J* 4, 1 Hz, H-2), 5·91 (1H, s, PhCH-), 4·77 (1H, ddt, *J* 9, 4, 1Hz, H-3), 4·12 (1H, t, *J* 9 Hz, H-4), 3·86 (1H, tt, *J* 9, 5 Hz, H-5), 3·77 (3H, s, $-CO_2Me$), 3·06 (1H, broad d, *J* 5Hz, -OH), 2·78 (1H, ddt, *J* 18, 5, 1 Hz, H-6α), 2·24 (1H, ddt, *J* 18, 9, 1Hz, H-6β); δ_C ($CDCl_3$) 166·4 (C=O), 136·5 (Aromatic C), 132·9 (C-2), 131·4 (C-1), 129·6, 128·4 and 126·8 (Aromatic CH), 104·3 (Ph*C*H-), 78·6 (C-4), 73·9 (C-5), 68·9 (C-3), 52·1 (OMe), 29·5 (C-6).

Methyl 5(*R*)-acetoxy-3(*R*),4(*R*)-benzylidenedioxy-1-cyclohexene-1-carboxylate 6. A solution of methyl 3(*R*),4(*S*)-benzylidenedioxy-5(*R*)-hydroxy-1-cyclohexene-1-carboxylate **5** (15·9 g, 57·60 mmol) in dry pyridine (100 ml) was treated with acetic anhydride (9·0 g, 88·20 mmol) and the reaction mixture was stirred at room temperature overnight. The solution was then poured onto water (400 ml) and stirred for 3 hours to destroy excess acetic anhydride after which the organic material was extracted into chloroform (400 ml) and washed with 2M hydrochloric acid (2 x 400 ml), saturated aqueous sodium bicarbonate solution (2 x 200 ml) and water (200 ml) and then dried over magnesium sulphate. After filtration the solvent was removed *in vacuo* to afford the *product* **6** (17·6 g, 96%, 2:3 mixture of (*S*) and (*R*)-isomers), as a pale yellow oil. A small portion was separated into its component isomers by column chromatography eluting with 3:1 v/v petroleum ether (b.p. 40-60°C)-ethyl acetate. (*S*)-isomer: R_f 0·51, colourless solid, crystallized from ethanol-water as colourless needles; m.p. 70-71°C; (Found: C, 63·85; H, 5·65. $C_{17}H_{18}O_6$ requires C, 64·15; H, 5·7%); *m/z* (+CI) 319, 336, MH^+, $M+NH_4^+$; ν_{max} (nujol) 1740, 1725, 1660 cm^{-1}; δ_H ($CDCl_3$) 7·45 (2H, m, ArH), 7·39 (3H, m, ArH), 6·95 (1H, dt, *J* 4, 1·5 Hz, H-2), 5·94 (1H, s, PhCH-), 5·36 (1H, td, *J* 6, 5 Hz, H-5), 4·96 (1H, ddt, *J* 6, 4, 1·5 Hz, H-3), 4·44 (1H, t, *J* 6Hz, H-4), 3·81 (3H, s, $-CO_2Me$), 2·86 (1H, ddt, *J* 18, 5, 1·5 Hz, H-6α), 2·46 (1H, ddt, *J* 18, 6, 1·5 Hz, H-6β), 2·08 (3H, s, $MeCO_2$-); δ_C ($CDCl_3$) 169·9 and 166·1 (C=O) 137·5 (Aromatic C), 133·2 (C-2), 130·8 (C-1), 129·3, 128·3 and 126·3 (Aromatic CH), 102·8 (Ph*C*H-), 74·1 (C-4), 72·4 (C-5), 68·4 (C-3), 52·0 (OMe), 26·0 (C-6),

20·9 (Me). (*R*)-isomer: R_f 0·38, colourless solid, crystallized from ethanol-water as colourless needles; m.p. 78-79°C; (Found: C, 63·95; H, 5·8. $C_{17}H_{18}O_6$ requires C, 64·15; H, 5·7%); *m/z* (+CI) 319, 336, MH^+, $M+NH_4^+$; ν_{max} (nujol) 1740, 1725, 1660 cm^{-1}; δ_H ($CDCl_3$) 7·43 (2H, m, ArH), 7·38 (3H, m, ArH), 7·01 (1H, dt, *J* 4, 1·5 Hz, H-2), 5·93 (1H, s, PhCH-), 5·20 (1H, td, *J* 7, 5 Hz, H-5), 4·84 (1H, ddt, *J* 7, 4, 1·5 Hz, H-3), 4·37 (1H, t, *J* 7 Hz, H-4), 3·78 (3H, s, $-CO_2Me$), 2·89 (1H, ddt, *J* 18, 5, 1·5 Hz, H-6α), 2·39 (1H, ddt, *J* 18, 7, 1·5 Hz, H-6β), 2·09 (3H, s, $MeCO_2$-); δ_C ($CDCl_3$) 170·1 and 166·2 (C=O), 136·3 (Aromatic C), 133·1 (C-2), 130·2 (C-1), 129·7, 128·4 and 126·9 (Aromatic CH), 104·5 (Ph*C*H-), 75·1 (C-4), 73·1 (C-5), 70·2 (C-3), 52·1 (OMe), 26·7 (C-6), 21·0 (Me).

Methyl 3(*R*),4(*S*)-benzylidenedioxy-5(*R*)-methoxy-1-cyclohexene-1-carboxylate 7. A solution of methyl 3(*R*),4(*S*)-benzylidenedioxy-5(*R*)-hydroxy-1-cyclohexene-1-carboxylate **5** (7·30 g, 26·45 mmol) in methyl iodide (25 ml) was treated with freshly prepared silver oxide (6·00 g) and the mixture was stirred and held at reflux for 48 hours. After cooling the insoluble silver salts were removed by filtration and the solvent removed *in vacuo* to afford a pale yellow oil that was subjected to column chromatography. Elution with 4:1 v/v petroleum ether (b.p. 40-60°C)-ethyl acetate afforded the *product* **7** (7·21 g, 94%, 2:3 mixture of (*S*) and (*R*)-isomers), as a pale yellow oil. A small portion was separated into its component isomers by column chromatography. (*S*)-isomer: R_f 0·45, pale yellow oil; (Found: C, 66·4; H, 6·3. $C_{16}H_{18}O_5$ requires C, 66·2; H, 6·25%); *m/z* (+EI) 291 (MH^+); ν_{max} (film) 1720, 1660 cm^{-1}; δ_H ($CDCl_3$) 7·41 (5H, m, ArH), 6·98 (1H, m, H-2), 5·93 (1H, s, PhCH-), 4·85 (1H, m, H-3), 4·31 (1H, m, H-4), 3·80 (3H, s, $-CO_2Me$), 3·65 (1H, m, H-5), 3·48 (3H, s, -OMe), 2·82 (1H, m, H-6α), 2·39 (1H, dm, H-6β). (*R*)-isomer: R_f 0·35, pale yellow oil; (Found: C, 66·2; H, 6·1. $C_{16}H_{18}O_5$ requires C, 66·2; H, 6·25%); *m/z* (+EI) 291 (MH^+); ν_{max} (film) 1720, 1660 cm^{-1}; δ_H ($CDCl_3$) 7·45 (5H, m, ArH), 6·93 (1H, m, H-2), 5·92 (1H, s, PhCH-), 4·91 (1H, m, H-3), 4·31 (1H, m, H-4), 3·77 (3H, s, $-CO_2Me$), 3·63 (1H, m, H-5), 3·46 (3H, s, -OMe), 2·74 (1H, m, H-6α), 2·44 (1H, dm, H-6β).

Methyl 3(*R*),4(*S*)-benzylidenedioxy-5(*R*)-[1',1'-bis(carbomethoxy)methyl]oxy-1-cyclohexene-1-carboxylate 8. A solution of methyl 3(*R*),4(*S*)-benzylidenedioxy-5(*R*)-hydroxy-1-cyclohexene-1-carboxylate **5** (8·00 g, 28·99 mmol) and dimethyl diazomalonate[21] (4·90 g, 31·01 mmol) in dry benzene (50 ml) was treated with rhodium (II) acetate dimer (50 mg) and the mixture was stirred and held at 60°C for 4 hours. After cooling the solution was evaporated to dryness *in vacuo* and the organic material was extracted into chloroform (100 ml), washed with saturated sodium bicarbonate solution (50 ml) and water (50 ml) and dried over sodium sulphate. After filtration the solvent was removed *in vacuo* to afford a pale yellow oil that was subjected to column chromatography. Elution with 6:1 v/v petroleum ether (b.p. 40-60°C)-ethyl acetate afforded the *product* **8** (8·83 g, 75%) as a pale yellow oil. (Found: C, 58·7; H, 5·6. $C_{20}H_{22}O_9$ requires C, 59·1; H, 5·45%); *m/z* (+CI) 407, 424, MH^+, $M+NH_4^+$; ν_{max} (film) 1720, 1660 cm^{-1}; δ_H ($CDCl_3$) 7·46 (2H, m, ArH), 7·38 (3H, m, ArH), 6·93 (1H, m, H-2), 5·94 (1H, s, PhCH-), 4·92 (1H, m, H-3), 4·88 (1H, s, -C*H*(CO_2Me)$_2$), 4·53 (1H, t, *J* 6·5 Hz, H-4), 3·98 (1H, ddd, *J* 11, 7, 4 Hz, H-5), 3·81 (3H, s, $-CO_2Me$), 3·79 (6H, s, -CH(CO_2*Me*)$_2$), 2·90 (1H, ddt, *J* 17·5, 4·5, 1·5 Hz, H-6α), 2·50 (1H, ddt, *J* 17·5, 7, 1 Hz, H-6β); δ_C ($CDCl_3$) 166·8 and 166·2 (C=O), 137·7, 129·3, 128·4 and 126·3 (Aromatic), 133·5 (C-2), 130·8 (C-1), 102·7 (Ph*C*H-), 78·4 (C-3), 76·3 (C-4), 72·8 (C-5), 52·9 and 52·2 (OMe), 26·7 (C-6).

Methyl 3(*R*),4(*R*)-benzylidenedioxy-5(*R*)-*tert*-butyldimethylsilyloxy-1-cyclohexene-1-carboxylate 9. A solution of methyl 3(*R*),4(*S*)-benzylidenedioxy-5(*R*)-hydroxy-1-cyclohexene-1-carboxylate **5** (4·00 g, 14·49 mmol) in *N*,*N*-dimethylformamide (15 ml) was treated with imidazole (1·24 g, 18·24 mmol) and *tert*-butyldimethylsilyl chloride (2·40 g, 15·95 mmol) and the mixture was stirred for 2 hours. The mixture was taken up into diethyl ether (300 ml), washed with saturated sodium bicarbonate solution (2 x 80 ml) and water (4 x 50 ml) and dried over sodium sulphate. After filtration the solvent was removed *in vacuo* to afford a pale yellow oil that was subjected to column chromatography. Elution with 6:1 v/v petroleum ether (b.p. 40-60°C)-ethyl acetate afforded the *product* **9** (4·24 g, 75%, 2:3 mixture of (*S*) and (*R*)-isomers), R_f 0·67 and 0·48, as a pale yellow oil. (Found: C, 64·7; H, 7·6. $C_{21}H_{30}SiO_5$ requires C, 64·6; H, 7·75%); *m/z* (+EI) 391, MH^+; ν_{max} (film) 1720, 1660 cm^{-1}; δ_H ($CDCl_3$) 7·50-7·30 (5H, m, ArH), 6·95 (1H, m, H-2), 5·90 and 5·87 (1H, s, PhCH-), 4·95 and 4·80 (1H, m, H-3), 4·30-4·00 (2H, m, H-4 and H-5), 3·80 and 3·75 (3H, s, $-CO_2Me$), 2·70 (1H, dm, H-6α), 2·37 (1H, dm, H-6β), 0·85 (9H, s, ^tBu), 0·10 (3H, s, SiMe), 0·05 (3H, s, SiMe).

Methyl 4(*S*)-benzoyloxy-3(*S*)-bromo-5(*R*)-hydroxy-1-cyclohexene-1-carboxylate 10. A solution of methyl 3(*R*),4(*S*)-benzylidenedioxy-5(*R*)-hydroxy-1-cyclohexene-1-carboxylate **5** (5·52 g, 20·00 mmol) in carbon tetrachloride (150 ml) was treated with *N*-bromosuccinimide (3·70 g, 20·80 mmol) and the mixture was stirred and held at reflux for 24 hours. After filtration and removal of the solvent *in vacuo* the residues were subjected to column chromatography. Elution with 3:1 v/v petroleum ether (b.p. 40-60°C)-ethyl acetate afforded the *product* **10** (4·40g, 62%), R_f 0·24, as a white foam which solidified when placed in a freezer overnight. A small portion was recrystallized from isopropanol-water as colourless prisms; m.p. 92-94°C (decomp.); (Found: C, 50·3, H, 3·9, Br, 22·4. $C_{15}H_{15}O_5Br$ requires C, 50·7, H, 4·25, Br, 22·5%); *m/z* (+CI) 355, 357, 372, 374, MH^+, $M+NH_4^+$; ν_{max} (film) 3700-3100, 1720, 1650, 1600, 1580, 1495 cm^{-1}; δ_H ($CDCl_3$) 8·08 (2H, dt, *J* 7·5, 1·5 Hz, *o*-ArH), 7·61 (1H, tt, *J* 7·5, 1·5 Hz, *p*-ArH), 7·46 (2H, tt, *J* 7·5, 1·5 Hz, *m*-ArH), 6·95 (1H, ddd, *J* 5, 3·5, 2 Hz, H-2), 5·53 (1H, dd, *J* 9·5, 7·5 Hz, H-4), 4·87 (1H, ddt, *J* 7·5, 5, 1·5 Hz, H-3), 4·00 (1H, ddd, *J* 9·5, 8·5, 5·5 Hz, H-5), 3·80 (3H, s, $-CO_2Me$), 3·00 (1H, dddd, *J* 18, 5·5, 2, 1·5 Hz, H-6α), 2·54 (1H, dddd, *J* 18, 8·5, 3·5, 1·5 Hz, H-6β), 2·50 (1H, broad s, -OH); δ_C ($CDCl_3$) 166·4 and 165·7 (C=O), 136·1 and 133·5 (C-2 and Aromatic CH), 130·0 (Aromatic CH), 129·4 and 129·2 (C-1 and Aromatic C), 128·5 (Aromatic CH), 78·6 (C-4), 68·7 (C-5), 52·3 (OMe), 45·6 (C-3), 32·1 (C-6).

Methyl 5(*R*)-acetoxy-4(*S*)-benzoyloxy-3(*S*)-bromo-1-cyclohexene-1-carboxylate 11. A solution of methyl 5(*R*)-acetoxy-3(*R*),4(*R*)-benzylidenedioxy-1-cyclohexene-1-carboxylate **6** (3·98 g, 12·50 mmol) in carbon tetrachloride (150 ml) was treated with *N*-bromosuccinimide (2·30 g, 12·90 mmol) and the mixture was stirred at room temperature for 3 days. After filtration and removal of the solvent *in vacuo* the residue was subjected to column chromatography. Elution with 3:1 v/v petroleum ether (b.p. 40-60°C)-ethyl acetate afforded the *product* **11** (3·74 g, 75%), R_f 0·65, as a colourless oil. (Found: C, 51·6; H, 4·6; Br, 20·2. $C_{17}H_{17}O_6Br$ requires C, 51·4; H, 4·3; Br, 20·1%); *m/z* (+CI) 414, 416, $M+NH_4^+$; ν_{max} (film) 1720, 1650, 1600, 1585, 1490 cm^{-1}; δ_H ($CDCl_3$) 8·02 (2H, dt, *J* 7·5, 1·5 Hz, *o*-ArH), 7·61 (1H, tt, *J* 7·5, 1·5 Hz, *p*-ArH), 7·46 (2H, tt, *J* 7·5, 1·5 Hz, *m*-ArH), 7·00 (1H, ddd, *J* 3, 2·5, 1·5 Hz, H-2), 5·73 (1H, dd, *J* 8·5, 6·5 Hz, H-4), 5·27 (1H, ddd, *J* 8·5, 6·5, 5·5 Hz, H-5), 4·85 (1H, ddt, *J* 8·5, 2·5, 1·5Hz, H-3), 3·81 (3H, s, $-CO_2Me$), 2·97 (1H, ddt, *J* 18·5, 5·5, 1·5Hz, H-6α), 2·64 (1H, dddd, *J* 18·5, 8·5, 3, 1·5 Hz,

H-6β), 1·96 (3H, s, $MeCO_2$-); δ_C ($CDCl_3$) 169·9, 165·5 and 165·0 (C=O), 135·7 and 133·5 (C-2 and Aromatic CH), 129·7 (Aromatic CH), 128·9 and 128·6 (C-1 and Aromatic C), 128·5 (Aromatic CH), 73·5 (C-4), 67·8 (C-5), 52·3 (OMe), 43·6 (C-3), 28·3 (C-6), 20·7 (Me).

Methyl 4(*S*)-benzoyloxy-3(*S*)-bromo-5(*R*)-methoxy-1-cyclohexene-1-carboxylate 12. A solution of methyl 3(*R*),4(*S*)-benzylidenedioxy-5(*R*)-methoxy-1-cyclohexene-1-carboxylate **7** (7·40 g, 25·52 mmol) in carbon tetrachloride (100 ml) was treated with *N*-bromosuccinimide (4·60 g, 25·84 mmol) and the mixture was stirred at room temperature for 3 days. After filtration and removal of the solvent *in vacuo* the residue was recrystallized from ethyl acetate to afford the *product* **12** (4·24 g, 45%), as white plates. m.p. 145-147°C; (Found: C, 52·2; H, 4·7; Br, 21·4. $C_{16}H_{17}O_5Br$ requires C, 52·05; H, 4·65; Br, 21·65%); *m/z* (+EI) 289 ($M\text{-}Br^+$); ν_{max} (nujol) 1720, 1650 cm^{-1}; δ_H ($CDCl_3$) 8·05 (2H, dt, *J* 7·5, 1·5 Hz, *o*-ArH), 7·58 (1H, tt, *J* 7·5, 1·5 Hz, *p*-ArH), 7·45 (2H, tt, *J* 7·5, 1·5 Hz, *m*-ArH), 6·96 (1H, m, H-2), 5·68 (1H, dd, *J* 8·5, 7 Hz, H-4), 4·81 (1H, m, H-3), 3·75 (3H, s, $-CO_2Me$), 3·66 (1H, m, H-5), 3·41 (3H, s, OMe), 2·93 (1H, dm *J* 18 Hz, H-6α), 2·55 (1H, dm, *J* 18 Hz, H-6β); δ_C ($CDCl_3$) 165·3 and 165·2 (C=O), 135·6 (C-2), 133·3, 129·7, 129·0 and 128·4 (Aromatic), 129·5 (C-1), 76·2 (C-4), 74·9 (C-5), 57·5 (C-3), 52·2 (OMe), 44·6 (OMe), 28·4 (C-6).

Methyl 4(*S*)-benzoyloxy-5(*R*)-[1',1'-bis(carbomethoxy)methyl]oxy-3(*S*)-bromo-1-cyclohexene-1-carboxylate 13. A solution of methyl 4(*S*)-benzoyloxy-3(*S*)-bromo-5(*R*)-hydroxy-1-cyclohexene-1-carboxylate **10** (630 mg, 1·77 mmol) and dimethyl diazomalonate[21] (0·47 g, 2·97 mmol) in dry benzene (20 ml) was treated with rhodium (II) acetate dimer (10 mg) and the mixture was stirred and held at 60°C for 4 hours. After cooling the solution was evaporated to dryness *in vacuo* and the organic material was extracted into chloroform (50 ml), washed with saturated sodium bicarbonate solution (20 ml) and water (20 ml) and dried over sodium sulphate. After filtration the solvent was removed *in vacuo* to afford a pale yellow oil that was subjected to column chromatography. Elution with 6:1 v/v petroleum ether (b.p. 40-60°C)-ethyl acetate afforded the *product* **13** (534 mg, 62%) as a pale yellow oil. (Found: C, 49·2; H, 4·7; Br, 16·9. $C_{20}H_{21}O_9Br$ requires C, 49·5; H, 4·35; Br, 16·45%); *m/z* (+EI) 405 ($M\text{-}Br^+$); ν_{max} (nujol) 1720, 1650 cm^{-1}; δ_H ($CDCl_3$) 8·02 (2H, dt, *J* 7·5, 1·5 Hz, *o*-ArH), 7·52 (1H, tt, *J* 7·5, 1·5 Hz, *p*-ArH), 7·41 (2H, tt, *J* 7·5, 1·5 Hz, *m*-ArH), 6·88 (1H, m, H-2), 5·72 (1H, m, H-4), 4·86 (1H, m, H-3), 4·70 (1H, s, $-CH(CO_2Me)_2$), 3·95 (1H, m, H-5), 3·72 (6H, s, $-CH(CO_2\mathit{Me})_2$), 3·68 (3H, s, $-CO_2Me$), 3·02 (1H, m, H-6α), 2·65 (1H, m, H-6β).

Methyl 3(*R*)-azido-4(*R*)-benzoyloxy-5(*R*)-hydroxy-1-cyclohexene-1-carboxylate 18, methyl 3(*R*)-azido-5(*R*)-benzoyloxy-4(*R*)-hydroxy-1-cyclohexene-1-carboxylate 19 and methyl 3(*S*)-azido-5(*R*)-benzoyloxy-4(*R*)-hydroxy-1-cyclohexene-1-carboxylate 21. A solution of methyl 4(*R*)-benzoyloxy-3(*S*)-bromo-5(*R*)-hydroxy-1-cyclohexene-1-carboxylate **10** (1·77 g, 5·00 mmol) in methanol (50 ml) was treated with sodium azide (0·35 g, 5·40 mmol) and the solution was stirred at *ca.* 40°C overnight. After cooling the solution and removal of the solvent *in vacuo* at 30°C the organic material was extracted into chloroform (50 ml), washed with water (50 ml) and was dried over sodium sulphate. After filtration the solvent was removed *in vacuo* to afford a pale yellow oil that was subjected to column chromatography. Elution with 3:1 v/v petroleum ether (b.p. 40-60°C)-ethyl acetate afforded the *product* **21** (0·13 g, 8%), R_f 0·53, as a colourless solid that crystallized from petroleum ether (b.p. 40-60°C)-diethyl ether as colourless needles; m.p. 106-107°C; $[\alpha]_D$ -14·9° (*c* 0·5, $CHCl_3$); (Found: C, 57·05; H, 4·9; N, 13·15.

$C_{15}H_{15}N_3O_5$ requires C, 56·8; H, 4·75; N, 13·25%); *m/z* (+CI) 318, MH^+; ν_{max} (nujol) 3600-3200, 2100, 1720, 1690, 1650 cm^{-1}; δ_H ($CDCl_3$) 8·06 (2H, dt, *J* 7, 1·5 Hz, *o*-ArH), 7·61 (1H, tt, *J* 7, 1·5 Hz, *p*-ArH), 7·47 (2H, tt, *J* 7, 1·5 Hz, *m*-ArH), 6·71 (1H,td, *J* 3, 1 Hz, H-2), 5·25 (1H, td, *J* 10, 6·5 Hz, H-5), 4·29 (1H, dddd, *J* 8·5, 4, 3, 2 Hz, H-3), 4·02 (1H, ddd, *J* 10, 8·5, 4 Hz, H-4), 3·78 (3H, s, $-CO_2Me$), 3·13 (1H, dddd, *J* 18, 6·5, 2, 1 Hz, H-6α), 2·75 (1H, broad d, *J* 4Hz, -OH), 2·46 (1H, dddd, *J* 18, 10, 4, 3 Hz, H-6β); δ_C ($CDCl_3$) 166·3 and 165·6 (C=O), 134·1 and 133·4 (C-2 and Aromatic CH), 129·7 (Aromatic CH), 129·4 (Aromatic C), 128·4 (Aromatic CH), 73·4 (C-4), 71·8 (C-5), 63·2 (C-3), 52·2 (OMe), 29·6 (C-6). Further elution afforded the *product* **19** (0·21 g, 13%), R_f 0·45, as a colourless oil; (Found: C, 56·9; H, 5·1; N, 13·4. $C_{15}H_{15}N_3O_5$ requires C, 56·8; H, 4·75; N, 13·25%); *m/z* (+CI) 318, 335, MH^+, $M+NH_4^+$; ν_{max} (film) 3700-3100, 2100, 1720, 1660, 1600, 1585, 1495 cm^{-1}; δ_H ($CDCl_3$) 8·01 (2H, dt, *J* 7·5, 1·5 Hz, *o*-ArH), 7·60 (1H, tt, *J* 7·5, 1·5 Hz, *p*-ArH), 7·46 (2H, tt, *J* 7·5, 1·5 Hz, *m*-ArH), 6·92 (1H,dt, *J* 4, 1·5 Hz, H-2), 5·45 (1H, dt, *J* 7, 5·5 Hz, H-5), 4·40 (1H, tt, *J* 4, 1·5 Hz, H-3), 4·17 (m, H-4), 3·80 (3H, s, $-CO_2Me$), 3·02 (1H, ddt, *J* 18·5, 5·5, 1·5 Hz, H-6α), 2·56 (1H, ddt, *J* 18·5, 7, 1·5 Hz, H-6β), 1·60 (1H, broad s, -OH); δ_C ($CDCl_3$) 166·1 and 165·9 (C=O), 133·4 and 132·1 (C-2 and Aromatic CH), 131·3 (C-1), 129·7 (Aromatic CH), 129·5 (Aromatic C), 128·4 (Aromatic CH), 69·8 and 68·9 (C-4 and C-5), 58·9 (C-3), 52·2 (OMe), 28·1 (C-6). Further elution afforded the *product* **18** (0·75 g, 48%), R_f 0·32, as a colourless oil; (Found: C, 56·5; H, 4·5; N, 12·9. $C_{15}H_{15}N_3O_5$ requires C, 56·8; H, 4·75; N, 13·25%); *m/z* (+CI) 318, 335, MH^+, $M+NH_4^+$; ν_{max} (film) 3700-3140, 2100, 1710, 1670, 1600, 1585, 1495 cm^{-1}; δ_H ($CDCl_3$) 8·05 (2H, dt, *J* 7·5, 1·5 Hz, *o*-ArH), 7·60 (1H, tt, *J* 7·5, 1·5 Hz, *p*-ArH), 7·46 (2H, td, *J* 7·5, 1·5 Hz, *m*-ArH), 6·90 (1H, dt, *J* 4, 2 Hz, H-2), 5·32 (1H, dd, *J* 8, 4 Hz, H-4), 4·55 (1H, tt, *J* 4, 2 Hz, H-3), 4·38 (1H, m, H-5), 3·81 (3H, s, $-CO_2Me$), 2·89 (1H, ddt, *J* 19, 5·5, 2 Hz, H-6α), 2·64 (1H, broad d, *J* 4 Hz, -OH), 2·45 (1H, ddt, *J* 19, 6·5, 2Hz, H-6β); δ_C ($CDCl_3$) 166·1 and 166·1 (C=O), 133·6 and 132·2 (C-2 and Aromatic CH), 131·5 (C-1), 129·8 (Aromatic CH), 128·9 (Aromatic C), 128·5 (Aromatic CH), 73·1 (C-4), 64·8 (C-5), 56·6 (C-3), 52·2 (OMe), 30·8 (C-6).

Methyl 4(*R*)-acetoxy-3(*R*)-azido-5(*R*)-benzoyloxy-1-cyclohexene-1-carboxylate 20. A solution of methyl 3(*R*)-azido-5(*R*)-benzoyloxy-4(*R*)-hydroxy-1-cyclohexene-1-carboxylate **19** (200 mg, 0·63 mmol) in pyridine (10 ml) was treated with acetic anhydride (100 mg, 1·00 mmol) and the mixture was stirred at room temperature overnight and was then poured onto water (100 ml) and stirred for a further 3 hours to destroy excess acetic anhydride. The organic material was extracted into chloroform (50 ml) and was washed with 2M hydrochloric acid (2 x 50 ml), saturated aqueous sodium bicarbonate solution (50 ml) and water (50 ml) and was dried over sodium sulphate. After filtering the solvent was removed *in vacuo* to afford the *product* **20** (140 mg, 62%), as a pale yellow oil. (Found: C, 57·0; H, 5·1; N, 11·9. $C_{17}H_{17}N_3O_6$ requires C, 56·8; H, 4·75; N, 11·7%); *m/z* (+CI) 377, $M+NH_4^+$; ν_{max} (film) 2100, 1750, 1720, 1660, 1600, 1585, 1490 cm^{-1}; δ_H ($CDCl_3$) 7·99 (2H, tt, *J* 8·5, 1·5 Hz, *o*-ArH), 7·60 (1H, tt, *J* 8·5, 1·5 Hz, *p*-ArH), 7·45 (2H, tt, *J* 8·5, 1·5 Hz, *m*-ArH), 6·91 (1H, dt, *J* 4, 2 Hz, H-2), 5·54 (1H, ddd, *J* 8, 6, 5 Hz, H-5), 5·44 (1H, dd, *J* 8, 4 Hz, H-4), 4·43 (1H, tt, *J* 4, 2 Hz, H-3), 3·08 (3H, s, $-CO_2Me$), 3·02 (1H, ddt, *J* 19, 5, 2 Hz, H-6α), 2·78 (1H, ddt, *J* 19, 6, 2 Hz, H-6β), 2·12 (3H, s, $MeCO_2$-); δ_C ($CDCl_3$) 169·8, 165·6 and 165·1 (C=O), 133·3 and 132·0 (C-2 and Aromatic CH), 131·3 (C-1), 129·6 (Aromatic CH), 129·3 (Aromatic C), 128·4 (Aromatic CH), 69·5 (C-4),67·0 (C-5), 56·5 (C-3), 52·2 (OMe), 28·5 (C-6), 20·5 (Me).

Methyl 5(*R*)-acetoxy-3(*R*)-azido-4(*R*)-benzoyloxy-1-cyclohexene-1-carboxylate 23. A solution of methyl 5(*R*)-acetoxy-4(*S*)-benzoyloxy-3(*R*)-bromo-1-cyclohexene-1-carboxylate **11** (2·11 g, 5·30 mmol) in methanol (100 ml) was treated with sodium azide (360 mg, 5·50 mmol) and the mixture was stirred at *ca.* 40°C overnight. After cooling the solution was evaporated to dryness *in vacuo* and the residues extracted into chloroform (100 ml), washed with water (100 ml) and dried over sodium sulphate. After filtration the solvent was removed *in vacuo* to afford a yellow oil which was subjected to column chromatography. Elution with 3:1 v/v petroleum ether (b.p. 40-60°C)-ethyl acetate afforded the *product* **23** (1·68 g, 88%), R_f 0.52, as a pale yellow oil. (Found: C, 56·9; H, 5·0; N, 11·4. $C_{17}H_{17}N_3O_6$ requires C, 56·8; H, 4·75; N, 11·7%); *m/z* (+CI) 360, 377, MH^+, $M+NH_4^+$; ν_{max} (film) 2100, 1720, 1660, 1600, 1585, 1490 cm^{-1}; δ_H ($CDCl_3$) 8·03 (2H, dt, *J* 7·5, 1·5 Hz, *o*-ArH), 7·60 (1H, tt, *J* 7·5, 1·5 Hz, *p*-ArH), 7·46 (2H, tt, *J* 7·5, 1·5 Hz, *m*-ArH), 6·92 (1H, dt, *J* 4, 2 Hz, H-2), 5·49 (1H, ddd, *J* 8, 6·5, 5·5 Hz, H-5), 5·45 (1H, dd, *J* 8, 4 Hz, H-4), 4·51 (1H, tt, *J* 4, 2 Hz, H-3), 3·81 (3H, s, $-CO_2Me$), 2·94 (1H, ddt, *J* 19·5, 5·5, 2 Hz, H-6α), 2·52 (1H, ddt, *J* 19·5, 6·5, 2 Hz, H-6β), 2·03 (3H, s, $MeCO_2-$); δ_C ($CDCl_3$) 169·6, 165·6 and 165·3 (C=O), 133·5 and 132·1 (C-2 and Aromatic CH), 131·2 (C-1), 129·8 (Aromatic CH), 128·7 (Aromatic C), 128·5 (Aromatic CH), 70·0 (C-4), 66·2 (C-5), 56·5 (C-3), 52·2 (OMe), 28·4 (C-6), 20·8 (Me).

Methyl 3(*R*)-azido-4(*R*)-benzoyloxy-5(*R*)-methoxy-1-cyclohexene-1-carboxylate 24. A solution of methyl 4(*S*)-benzoyloxy-3(*R*)-bromo-5(*R*)-methoxy-1-cyclohexene-1-carboxylate **12** (1·50 g, 4·10 mmol) in methanol (10 ml) was treated with sodium azide (267 mg, 4·11 mmol) and the mixture was stirred at *ca.* 40°C overnight. After cooling the solution was evaporated to dryness *in vacuo* and the residues extracted into chloroform (100 ml), washed with water (100 ml) and dried over sodium sulphate. After filtration the solvent was removed *in vacuo* to afford a yellow oil which was subjected to column chromatography. Elution with 4:1 v/v petroleum ether (b.p. 40-60°C)-ethyl acetate afforded the *product* **24** (1·18 g, 88%), R_f 0·50, as a pale yellow oil. (Found: C, 58·0; H, 5·1; N, 12·7. $C_{16}H_{17}N_3O_5$ requires C, 58·0; H, 5·15; N, 12·7%); *m/z* (+EI) 331, M^+; ν_{max} (film) 2100, 1720, 1660, 1600, 1585, 1490 cm^{-1}; δ_H ($CDCl_3$) 8·25 (2H, dt, *J* 7·5, 1·5 Hz, *o*-ArH), 7·55 (1H, tt, *J* 7·5, 1·5 Hz, *p*-ArH), 7·46 (2H, tt, *J* 7·5, 1·5 Hz, *m*-ArH), 6·92 (1H, m, H-2), 5·58 (1H, dd, *J* 7, 4 Hz, H-4), 4·39 (1H, m, H-3), 3·93 (1H, m, H-5), 3·82 (3H, s, $-CO_2Me$), 3·46 (3H, s, -OMe), 2·62 (2H, m, H-6α and H-6β); δ_C ($CDCl_3$) 166·1 and 165·5 (C=O), 133·4 (C-2), 132·7, 131·1, 129·8 and 129·1 (Aromatic), 128·4 (C-1), 73·9 (C-4), 70·1 (C-5), 57·6 (OMe), 56·4 (C-3), 52·1 (OMe), 26·8 (C-6).

Methyl 3(*R*)-azido-4(*R*)-benzoyloxy-5(*R*)-[1',1'-bis(carbomethoxy)methyl]oxy-1-cyclohexene-1-carboxylate 25. A solution of methyl 4(*S*)-benzoyloxy-5(*R*)-[1',1'-bis(carbomethoxy)methyl]oxy-3(*S*)-bromo-1-cyclohexene-1-carboxylate **13** (730 mg, 1·51 mmol) in methanol (15 ml) was treated with sodium azide (110 mg, 1·69 mmol) and the mixture was stirred at *ca.* 40°C overnight. After cooling the solution was evaporated to dryness *in vacuo* and the residues extracted into chloroform (100 ml), washed with water (100 ml) and dried over sodium sulphate. After filtration the solvent was removed *in vacuo* to afford a yellow oil which was subjected to column chromatography. Elution with 4:1 v/v petroleum ether (b.p. 40-60°C)-ethyl acetate afforded the *product* **25** (565 mg, 84%), R_f 0·80, as a pale yellow oil. (Found: C, 54·0; H, 5·1; N, 9·7. $C_{20}H_{21}N_3O_9$ requires C, 53·7; H, 4·75; N, 9·4%); *m/z* (+CI) 448, MH^+; ν_{max} (film) 2100, 1720, 1660, 1600, 1585, 1490 cm^{-1}; δ_H ($CDCl_3$) 8·02 (2H, dt, *J* 7·5, 1·5 Hz, *o*-ArH), 7·60 (1H, tt, *J* 7·5, 1·5 Hz, *p*-ArH), 7·46 (2H, tt, *J* 7·5, 1·5 Hz, *m*-ArH), 6·91 (1H, m, H-2),

5·52 (1H, dd, *J* 7·5, 4·5 Hz, H-4), 4·79 (1H, s, -C*H*(CO_2Me)$_2$), 4·59 (1H, m, H-3), 4·20 (1H, m, H-5), 3·81 (6H, s, -CH(CO_2*Me*)$_2$), 3·68 (3H, s, -CO_2Me), 2·86 (1H, ddt, *J* 18·5, 5, 2 Hz, H-6α), 2·65 (ddt, *J* 18·5, 5, 1·5 Hz, H-6β).

Methyl 1(*R*),2(*R*),6(*R*)-2-hydroxy-8-phenyl-7-aza-9-oxabicyclo[4.3.0]nona-4,7-diene-4-carboxylate 29. A solution of methyl 3(*R*)-azido-4(*R*)-benzoyloxy-5(*R*)-hydroxy-1-cyclohexene-1-carboxylate **18** (328 mg, 1.03 mmol) in tetrahydrofuran (30 ml) containing water (0.3 ml) was treated with triphenylphosphine (300 mg, 1.15 mmol) and the mixture was stirred and held at reflux for 2 hours. After cooling the solvent was removed *in vacuo* and the residue was subjected to column chromatography. Elution with ethyl acetate afforded the *product* **29** (117 mg, 42%), R_f 0·70, as a colourless oil. (Found: C, 65·6; H, 5·6; N, 5·4. $C_{15}H_{15}NO_4$ requires C, 65·95; H, 5·55; N, 5·15%); *m/z* (+CI) 274, MH^+; ν_{max} (film) 3700-3000, 1715, 1655, 1640, 1600, 1580, 1495 cm^{-1}; δ_H ($CDCl_3$) 7.95 (2H, dt, *J* 7·5, 1·5 Hz, *o*-ArH), 7·50 (1H, tt, *J* 7·5, 1·5 Hz, *p*-ArH), 7·41 (2H, tt, *J* 7·5, 1·5 Hz, *m*-ArH), 7·23 (1H, ddd, *J* 4, 2·5, 1 Hz, H-5), 4·95 (1H, ddd, *J* 10, 4, 2·5 Hz, H-6), 4·75 (1H, dd, *J* 10, 8 Hz, H-1), 3·90 (1H, ddd, *J* 10, 8, 5 Hz, H-2), 3·77 (3H, s, -CO_2Me), 2·85 (1H, ddd, *J* 17·5, 5, 1 Hz, H-3α), 2·75-2·50 (broad s, -OH), 2·27 (1H, ddt, *J* 17·5, 10, 2·5 Hz, H-3β); δ_C ($CDCl_3$) 166·5 and 163·8 (C=O), 136·0 (Aromatic CH), 131·7 (C-2), 128·4 and 128·3 (Aromatic CH), 128·2 and 127·1 (C-1 and Aromatic C), 82·1 (C-4), 68·3 (C-5), 65·4 (C-3), 51·9 (OMe), 28·7 (C-6).

Methyl 1(*R*),2(*R*),6(*R*)-2-acetoxy-8-phenyl-7-aza-9-oxabicyclo[4.3.0]nona-4,7-diene-4-carboxylate 31 and **methyl 5(*R*)-acetoxy-3(*R*)-benzoylamino-4(*R*)-hydroxy-1-cyclohexene-1-carboxylate 34.** A solution of methyl 5(*R*)-acetoxy-3(*R*)-azido-4(*R*)-benzoyloxy-1-cyclohexene-1-carboxylate **23** (937 mg, 2·61 mmol) in tetrahydrofuran (40 ml) containing water (0·4 ml) was treated with triphenylphosphine (690 mg, 2·63 mmol) and the mixture was stirred under reflux for 4 hours. After cooling the solvent was removed *in vacuo* and the residue was subjected to column chromatography. Elution with 3:2v/v petroleum ether (b.p. 40-60°C)-ethyl acetate afforded the *product* **31** (392 mg, 48%), R_f 0·66, as a colourless oil. (Found: C, 64·4; H, 5·7; N, 4·0. $C_{17}H_{17}NO_5$ requires C, 64·75; H, 5·45; N, 4·45%); *m/z* (+FAB) 316, MH^+; ν_{max} (film) 1740, 1720, 1660, 1645, 1580, 1500 cm^{-1}; δ_H ($CDCl_3$) 7·90 (2H, dt, *J* 7·5, 1·5 Hz, *o*-ArH), 7·48 (1H, tt, *J* 7·5, 1·5 Hz, *p*-ArH), 7·40 (2H, tt, *J* 7·5, 1·5 Hz, *m*-ArH), 7·22 (1H, td, *J* 2·5, 1 Hz, H-5), 5·13 (1H, ddd, *J* 8·5, 7·5, 5 Hz, H-2), 4·95 (1H, dm, *J* 9·5 Hz, H-6), 4·83 (1H, dd, *J* 9·5, 7·5 Hz, H-1), 3·76 (3H, s, -CO_2Me), 2·85 (1H, ddt, *J* 17, 5, 1 Hz, H-3α), 2·32 (1H, ddt, *J* 17, 8·5, 2·5 Hz, H-3β), 2·14 (3H, s, $MeCO_2$-); δ_C ($CDCl_3$) 170·0, 166·2 and 163·7 (C=O), 135·9 (Aromatic CH), 131·7 (C-2), 128·3 (Aromatic CH), 127·8 and 127·0 (C-1 and Aromatic C), 78·5 (C-4), 69·8 (C-5), 65·2 (C-3), 52·0 (OMe), 25·8 (C-6), 21·0 (Me). Further elution afforded the *product* **34** (304 mg, 35%), R_f 0·05, as a colourless oil. (Found: C, 61·3; H, 5·7; N, 4·0. $C_{17}H_{19}NO_6$ requires C, 61·25; H, 5·75; N, 4·2%); *m/z* (+CI) 334, MH^+; ν_{max} (film) 3570, 3400, 1720, 1640, 1600, 1580, 1500 cm^{-1}; δ_H ($CDCl_3$) 7·74 (2H, dt, *J* 7, 1·5 Hz, *o*-ArH), 7·44 (1H, tt, *J* 7, 1·5 Hz, *p*-ArH), 7·34 (2H, tt, J 7·5, 1·5 Hz, *m*-ArH), 7·05 (1H, broad d, *J* 9 Hz, -NH), 6·75 (1H, dt, *J* 2·5, 1 Hz, H-2), 5·17 (1H, ddd, *J* 5, 4, 3·5 Hz, H-5), 5·00 (1H, m, H-3), 4·45-4·10 (1H, broad s, -OH), 4·04 (1H, td, *J* 4, 1 Hz, H-4), 3·67 (3H,s, -CO_2Me), 2·70(1H, ddt, *J* 19·5, 5, 2·5 Hz, H-6α) 2·39 (1H, dm, *J* 19·5 Hz, H-6β), 1·99 (3H, s, $MeCO_2$-); δ_C ($CDCl_3$) 170·5, 167·7 and 166·6 (C=O), 136·3 (Aromatic CH), 133·7 (C-1), 131·8 (C-2), 128·5 and 127·0 (Aromatic CH), 69·7 (C-4), 66·0 (C-5), 51·8 (OMe), 47·1 (C-3), 25·8 (C-6), 21·0 (Me).

Methyl 3(*R*)-amino-5(*R*)-benzoyloxy-4(*R*)-hydroxy-1-cyclohexene-1-carboxylate 35. A solution of methyl 3(*R*)-azido-5(*R*)-benzoyloxy-4(*R*)-hydroxy-1-cyclohexene-1-carboxylate **19** (271 mg, 0·85 mmol) in tetrahydrofuran (20 ml) containing water (0·2 ml) was treated with triphenylphosphine (240 mg, 0·92 mmol) and the mixture was stirred under reflux for 5 hours. After cooling the solvent was removed *in vacuo* and the residue was subjected to column chromatography. Elution with ethyl acetate afforded the *product* **35** (222 mg, 89%), R_f 0·09, as a colourless oil. (Found: C, 62·0; H, 6·0; N, 5·1. $C_{15}H_{17}NO_5$ requires C, 61·85; H, 5·9; N, 4·8%); *m/z* (+CI) 292, MH^+; ν_{max} (film) 3700-2500, 1715, 1650, 1600, 1585, 1490 cm^{-1}; δ_H ($CDCl_3$) 8·03 (2H, dt, *J* 7·5, 1·5 Hz, *o*-ArH), 7·56 (1H, dt, *J* 7·5, 1·5 Hz, *p*-ArH), 7·44 (2H, tt, *J* 7·5, 1·5 Hz, *m*-ArH), 6·89 (1H, dt, *J* 4, 2 Hz, H-2), 5·33 (1H, ddd, *J* 8, 6, 5 Hz, H-5), 3·95 (1H, dd, *J* 8, 4 Hz, H-4), 3·76 (1H, m, H-3), 3·76 (3H, s, $-CO_2Me$), 2·95 (1H, ddt, *J* 19, 5, 2 Hz, H-6α), 2·48 (1H, ddt, *J* 19, 6, 2 Hz, H-6β), 3·00-1·50 (3H, broad s, -OH and $-NH_2$); δ_C ($CDCl_3$) 166·7 and 166·0 (C=O), 139·3 (Aromatic CH), 133·1 (C-2), 129·7 (C-1), 129·6 and 128·3 (Aromatic CH), 127·7 (Aromatic C), 70·5 (C-4), 67·8 (C-5), 51·9 (OMe), 48·3 (C-3), 27·8 (C-6).

Methyl 3(*S*)-amino-5(*R*)-benzoyloxy-4(*R*)-hydroxy-1-cyclohexene-1-carboxylate 36. A solution of methyl 3(*S*)-azido-5(*R*)-benzoyloxy-4(*S*)-hydroxy-1-cyclohexene-1-carboxylate **21** (50 mg, 0·16 mmol) in tetrahydrofuran (10 ml) containing water (0·1 ml) was treated with triphenylphosphine (50 mg, 0·19 mmol) and the mixture was stirred under reflux for 5 hours. After cooling the solvent was removed *in vacuo* and the resulting oily residue was subjected to column chromatography. Elution with methanol afforded the *product* **36** (34 mg, 74%), R_f 0·51, as a colourless oil. (Found: C, 61·9; H, 5·9; N, 5·2. $C_{15}H_{17}NO_5$ requires C, 61·85; H, 5·9; N, 4·8%); *m/z* (+CI) 292, MH^+; ν_{max} (film) 3700-2800, 1715, 1655, 1600, 1585, 1490 cm^{-1}; δ_H ($CDCl_3$) 8·06 (2H, dt, *J* 7·5, 1·5 Hz, *o*-ArH), 7·59 (1H, tt, *J* 7·5, 1·5 Hz, *p*-ArH), 7·45 (2H, tt, *J* 7·5, 1·5 Hz, *m*-ArH), 6·75 (1H, td, *J* 2, 1 Hz, H-2), 5·23 (1H, ddd, *J* 10, 9·5, 6·5 Hz, H-5), 3·75 (3H, s, $-CO_2Me$), 3·69 (1H, dd, *J* 10, 8·5 Hz, H-4), 3·62 (1H, dm, *J* 8·5 Hz, H-3), 3·09 (1H, ddm, *J* 18, 6·5 Hz, H-6α), 2·46 (4H, m, H-6β, $-NH_2$ and -OH).

Methyl 3(*R*)-azido-4(*R*),5(*R*)-dihydroxy-1-cyclohexene-1-carboxylate 38. A solution of methyl 3(*R*)-azido-4(*R*)-benzoyloxy-5(*R*)-hydroxy-1-cyclohexene-1-carboxylate **18** (293 mg, 0·92 mmol) in methanol (30 ml) was treated with sodium methoxide (50 mg, 0·93 mmol) and the mixture was stirred at 0°C for 3 hours and was then neutralized by addition of an excess of solid carbon dioxide. After warming to room temperature the solvent was removed *in vacuo* and the organic residues were extracted into chloroform (2 x 30 ml) and were dried over sodium sulphate. After filtration and removal of the solvent *in vacuo* the residual oil was subjected to column chromatography. Elution with 3:2 v/v petroleum ether (b.p. 40-60°C)-ethyl acetate afforded the *product* **38** (166 mg, 84%), R_f 0·15, as a colourless oil. (Found: C, 44·8; H, 5·4; N, 19·5. $C_8H_{11}N_3O_4$ requires C, 45·05; H, 5·2; N, 19·7%); *m/z* (+FAB) 214, 236, MH^+, $M+Na^+$; ν_{max} (film) 3700-3040, 2100, 1710, 1655 cm^{-1}; δ_H ($CDCl_3$) 6·83 (1H, ddd, *J* 5, 2·5, 1·5 Hz, H-2), 4·37 (1H, tt, *J* 5, 1·5 Hz, H-3), 3·98 (1H, ddd, *J* 10, 8·5, 5·5 Hz, H-5), 3·79 (1H, dd, *J* 10, 5 Hz, H-4), 3·79 (3H, s, $-CO_2Me$), 3·52 (2H, broad s, -OH), 2·94 (1H, ddt, *J* 18·5, 5·5, 1·5 Hz, H-6α), 2·25 (1H, dddd, *J* 18·5, 8·5, 2·5, 1·5 Hz, H-6β); δ_C ($CDCl_3$) 166·3 (C=O), 132·3 (C-1), 131·9 (C-2), 72·6 (C-4), 66·9 (C-5), 59·2 (C-3), 52·2 (OMe), 32·1 (C-6).

Methyl 3(*R*)-amino-4(*R*),5(*R*)-dihydroxy-1-cyclohexene-1-carboxylate 39. A solution of methyl 3(*R*)-azido-4(*R*),5(*R*)-dihydroxy-1-cyclohexene-1-carboxylate **38** (173 mg, 0·81 mmol) in tetrahydrofuran

(20 ml) containing water (0·2 ml) was treated with triphenylphosphine (230 mg, 0·88 mol) and the mixture was stirred under reflux for 4 hours. After cooling the solvent was removed *in vacuo* and the residue was subjected to column chromatography. Elution with methanol afforded the *product* **39** (122 mg, 80%), R_f 0·29, as a colourless oil. (Found: C, 50·9; H, 7·2; N, 7·2. $C_8H_{13}NO_4$ requires C, 51·35; H, 7·0; N, 7·5%); *m/z* (+CI) 188, MH^+; ν_{max} (film) 3700-3000, 2500, 1700, 1650, 1590 cm^{-1}; δ_H (CD_3OD) 6·76 (1H, m, H-2), 3·99 (1H, dt, *J* 6·5, 4·5 Hz, H-5), 3·72 (1H, s, $-CO_2Me$), 3·70 (1H, dd, *J* 6·5, 1·5 Hz, H-4), 3·59 (1H, m, H-3), 2·62 (1H, ddt, *J* 18·5, 4·5, 2·5 Hz, H-6α), 2·23 (1H, ddt, *J* 18·5, 4·5, 2 Hz, H-6β); δ_C (CD_3OD) 168·9 (C=O), 140·9 (C-1), 129·3 (C-2), 71·9 (C-4), 68·4 (C-5), 52·3 (C-3), 30·7 (C-6).

REFERENCES AND NOTES

1. Part 7. Richards, T.I.; Layden, K.; Warminski, E.E.; Milburn, P.J.; Haslam, E. *J. Chem. Soc., Perkin Trans. 1*, **1987**, 2765-2773.
2. *Present address:* School of Chemistry, The University of Leeds, Leeds, U.K., LS2 9JT.
3. Haslam E. *Shikimic acid: Metabolism and Metabolites*; John Wiley and Sons: Chichester, 1993.
4. Campbell, M.M.; Sainsbury, M.; Searle, P.A. *Synthesis*, **1993**, 179-193.
5. Grossbard, E.; Atkinson, D. *The Herbicide Glyphosate*; Butterworths: Boston, 1985.
6. Brettle, R.; Cross, R.; Frederickson, M.; Haslam, E.; Davies, G.M. *Bioorg. Med. Chem. Lett.*, **1996**, *6*, 291-294.
7. Marvell, E.N.; Joncich, M.J. *J. Am. Chem. Soc.*, **1951**, *73*, 973-975.
8. Wright, J.B. *J. Am. Chem. Soc.*, **1955**, *77*, 4883-4884.
9. Hanessian, S. *Carbohydr. Res.*, **1966**, *2*, 86-88.
10. Whole star aniseed was obtained from Brome and Schimmer Ltd., Romsey Industrial Estate, Romsey, Hamphire, U.K., SO51 0HR.
11. Grewe, R.; Lorenzen, W. *Chem. Ber.*, **1953**, *86*, 928-938.
12. Grewe, R.; Jensen, H.; Schnoor, M. *Chem. Ber.*, **1956**, *89*, 898-905.
13. Grewe, R.; Kersten, S. *Chem. Ber.*, **1967**, *100*, 2546-2553.
14. Hedgley, E.J.; Fletcher Jr., H.G. *J. Am. Chem. Soc.*, **1962**, *84*, 3726-3731.
15. Hedgley, E.J.; Fletcher Jr., H.G. *J. Am. Chem. Soc.*, **1963**, *85*, 1615-1617.
16. Crystals of bromide **12** suitable for X-ray crystallographic studies were obtained by crystallization from ethyl acetate. Supplementary data for the X-ray crystallographic study of **12** including tables of bond lengths and angles have been deposited with the Director of the X-ray Crystallographic Database, Cambridge and are available upon request.
17. Baltas, M.; Despeyroux, P.; Gorrichon, L. *Bioorg. Med. Chem. Lett.*, **1993**, *3*, 1447-1452.
18. For the synthesis of the 5(*R*)-amino analogue of (-)-shikimic acid and its derivatives see: Pansegrau, P.D.; Anderson, K.S.; Widlanski, T.; Ream, J.E.; Sammons, R.D.; Sikorski, J.A.; Knowles, J.R. *Tetrahedron Lett.*, **1991**, *32*, 2589-2592.
19. Staudinger , H.; Meyer, J. *Helv. Chim. Acta*, **1919**, *2*, 635-646.
20. This extraction procedure is a modified version of that reported previously[11] allowing the isolation of large quantities of product **1** (>50 g) with very low levels of impurities.
21. Peace, B.W.; Carman, F.; Wulfman, D.S. *Synthesis*, 1971, 658-661.

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