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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 C₃ and C₄ 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 has materials with potential herbicidal, anti-fungal or bacteriocidal activity. Indeed the commercially important broad spectrum, post-emergence herbicide glyphosate⁵ (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.



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 reported⁶

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 3 β -stereochemistry. We therefore targeted a set of allylic 3 β -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





(-)-Shikimic acid 1 was extracted from the ground seeds and carpels of *Illicium anisatum* (star aniseed)¹⁰ according to a known procedure¹¹ 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.



Protection of the free 5-hydroxyl functionality of acetal 5 under standard conditions afforded acetate 6 (Ac₂O, C₅H₅N; 96%), methyl ether 7 (Ag₂O, MeI, Δ ; 94%), malonate ether 8 (N₂C(CO₂Me)₂, Rh₂(OAc)₄, C₆H₆, 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 (CH₂Cl₂, Et₂O 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 CH₂Cl₂); 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 species⁷⁻⁹ 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 previously¹³ 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 ¹H 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 study¹⁶ 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%).



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.



Treatment of bromides 10-13 with azide ion in warm methanol afforded a series of 3-azides 18-25 $(v_{max} 2100 \text{ cm}^{-1})$ in high yield; bromides 11-13 each afforded a single 3 α -azide 23-25 $(J_{3,4} 4 \text{ Hz}; 80-90\%)$. Bromide 10 reacted less selectively and gave a mixture of two isomeric 3 α -azides 18 $(J_{3,4} 4 \text{ Hz}; 48\%)$ and 19 $(J_{3,4} 4 \text{ Hz}; 13\%)$ together with traces of a 3 β -azide 21 $(J_{3,4} 8.5 \text{ Hz}; 8\%)$; 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 nucleus¹⁷ 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 reduction¹⁹ (PPh₃, H₂O) 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**.



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, H₂O, 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 (PPh₃/H₂O) 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 ¹³C nmr spectra recorded in deuterium oxide. Spectral data (coupling constants) showed the solution structures of 1 and 3 in D₂O 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 ¹³C 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.



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].

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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 ¹³C 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 aniseed¹⁰ (900 g) were subjected to soxhlet extraction¹¹ 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, H₂O); [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+NH₄+; v_{max} (nujol) 3480, 3390, 3220, 1680, 1650 cm⁻¹; $\delta_{\rm H}$ (D₂O) 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-6 α), 2·12 (1H, ddt, J 18, 6·5, 1·5 Hz, H-6 β); δ_{C} (D₂O) 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.); $[\alpha]_D - 50.4^\circ$ (*c* 0.5, H₂O); (Found: C, 48.7; H, 6.7; N, 8.35. C₇H₁₁NO₄ requires C, 48.55; H, 6.4; N, 8.1%); *m/z* (+Cl) 174, MH⁺; v_{max} (nujol) 3700-3100, 1560 cm⁻¹; δ_H (D₂O) 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-6 β); δ_C (D₂O) 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 4¹² (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. C₁₅H₁₆O₅ requires C, 65.2; H, 5.85%); m/z (+CI) 277, 294, MH⁺, M+NH₄⁺; ν_{max} (film) 3700-3100, 1720, 1655, 1495 cm⁻¹; δ_{H} (CDCl₃) 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, -CO₂Me), 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 (CDCl₃) 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 (PhCH-), 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. C15H16O5 requires C, 65.2; H, 5.85%); m/z (+CI) 277, 294, MH+, M+NH₄⁺; v_{max} (film) 3700-3100, 1720, 1655, 1495 cm⁻¹; δ_{H} (CDCl₃) 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, -CO₂Me), 3.06 (1H, broad d, J 5Hz, -OH), 2.78 (1H, ddt, J 18, 5, 1 Hz, H-6 α), 2.24 (1H, ddt, J 18, 9, 1Hz, H-6 β); δ_{C} (CDCl₃) 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 (PhCH-), 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 ethanolwater as colourless needles; m.p. 70-71°C; (Found: C, 63.85; H, 5.65. C₁₇H₁₈O₆ requires C, 64.15; H, 5.7%); m/z (+CI) 319, 336, MH⁺, M+NH₄⁺; v_{max} (nujol) 1740, 1725, 1660 cm⁻¹; δ_{H} (CDCl₃) 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, -CO₂Me), 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, MeCO₂-); δ_{C} (CDCl₃) 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 (PhCH-), 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* (+Cl) 319, 336, MH⁺, M+NH₄⁺; v_{max} (nujol) 1740, 1725, 1660 cm⁻¹; δ_H (CDCl₃) 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, -CO₂Me), 2-89 (1H, ddt, *J* 18, 5, 1-5 Hz, H-6 α), 2-39 (1H, ddt, *J* 18, 7, 1-5 Hz, H-6 β), 2-09 (3H, s, MeCO₂-); δ_C (CDCl₃) 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 (PhCH-), 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. C₁₆H₁₈O₅ requires C, 66·2; H, 6·25%); m/z (+EI) 291 (MH⁺); v_{max} (film) 1720, 1660 cm⁻¹; δ_H (CDCl₃) 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, -CO₂Me), 3.65 (1H, m, H-5), 3.48 (3H, s, -OMe), 2.82 (1H, m, H-6a), 2.39 (1H, dm, H-6β). (*R*)-isomer: $R_f 0.35$, pale yellow oil; (Found: C, 66.2; H, 6.1. C₁₆H₁₈O₅ requires C, 66.2; H, 6.25%); m/z (+EI) 291 (MH⁺); v_{max} (film) 1720, 1660 cm⁻¹; $\delta_{\rm H}$ (CDCl₃) 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, -CO₂Me), 3.63 (1H, m, H-5), 3.46 (3H, s, -OMe), 2.74 (1H, m, H-6 α), 2.44 (1H, dm, H-6 β).

Methyl 3(R), 4(S)-benzylidenedioxy-5(R)-[1', 1'-bis(carbomethoxy)methyl]oxy-1cyclohexene-1-carboxylate 8. A solution of methyl 3(R), 4(S)-benzylidenedioxy-5(R)-hydroxy-1cyclohexene-1-carboxylate 5 (8.00 g, 28.99 mmol) and dimethyl diazomalonate²¹ (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+NH₄⁺; v_{max} (film) 1720, 1660 cm⁻¹; δ_H (CDCl₃) 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, -CH(CO₂Me)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, -CO₂Me), 3.79 (6H, s, -CH(CO₂Me)₂), 2.90 (1H, ddt, J 17.5, 4.5, 1.5 Hz, H-6 α), 2.50 (1H, ddt, J 17.5, 7, 1 Hz, H-6 β); δ_{C} (CDCl₃) 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 (PhCH-), 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-1carboxylate 9. A solution of methyl 3(R),4(S)-benzylidenedioxy-5(R)-hydroxy-1-cyclohexene-1carboxylate 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. C₂₁H₃₀SiO₅ requires C, 64.6; H, 7.75%); m/z (+EI) 391, MH⁺; v_{max} (film) 1720, 1660 cm⁻¹; $\delta_{\rm H}$ (CDCl₃) 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, -CO₂Me), 2.70 (1H, dm, H-6 α), 2.37 (1H, dm, H-6 β), 0.85 (9H, s, 'Bu), 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. C₁₅H₁₅O₅Br requires C, 50·7, H, 4·25, Br, 22·5%); m/z (+CI) 355, 357, 372, 374, MH+, M+NH₄+; v_{max} (film) 3700-3100, 1720, 1650, 1600, 1580, 1495 cm⁻¹; $\delta_{\rm H}$ (CDCl₃) 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, -CO₂Me), 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} (CDCl₃) 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+NH₄⁺; v_{max} (film) 1720, 1650, 1600, 1585, 1490 cm⁻¹; δ_H (CDCl₃) 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, 8.5, 3, 1.5 Hz, H-3), 3.81 (3H, s, -CO₂Me), 2.97 (1H, ddt, J 18.5, 5.5, 1.5Hz, H-6\alpha), 2.64 (1H, dddd, J 18.5, 8.5, 3, 1.5 Hz, H-6β), 1·96 (3H, s, MeCO₂-); δ_{C} (CDCl₃) 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. C₁₆H₁₇O₅Br requires C, 52.05; H, 4.65; Br, 21.65%); m/z (+EI) 289 (M-Br⁺); v_{max} (nujol) 1720, 1650 cm⁻¹; $\delta_{\rm H}$ (CDCl₃) 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, -CO₂Me), 3.66 (1H, m, H-5), 3.41 (3H, s, OMe), 2.93 (1H, dm J 18 Hz, H-6\alpha), 2.55 (1H, dm, J 18 Hz, H-6\beta); $\delta_{\rm C}$ (CDCl₃) 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-1cyclohexene-1-carboxylate 13. A solution of methyl 4(S)-benzoyloxy-3(S)-bromo-5(R)-hydroxy-1cyclohexene-1-carboxylate 10 (630 mg, 1·77 mmol) and dimethyl diazomalonate²¹ (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. C₂₀H₂₁O₉Br requires C, 49·5; H, 4·35; Br, 16·45%); *m/z* (+EI) 405 (M-Br⁺); v_{max} (nujol) 1720, 1650 cm⁻¹; $\delta_{\rm H}$ (CDCl₃) 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(CO₂Me)₂), 3·95 (1H, m, H-5), 3·72 (6H, s, -CH(CO₂Me)₂), 3·68 (3H, s, -CO₂Me), 3·02 (1H, m, H-6\alpha), 2·65 (1H, m, H-6\beta).

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, CHCl₃); (Found: C, 57.05; H, 4.9; N, 13.15.

C₁₅H₁₅N₃O₅ requires C, 56·8; H, 4·75; N, 13·25%); m/z (+CI) 318, MH⁺; v_{max} (nujol) 3600-3200, 2100, 1720, 1690, 1650 cm⁻¹; $\delta_{\rm H}$ (CDCl₃) 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, -CO₂Me), 3·13 (1H, dddd, J 18, 6·5, 2, 1 Hz, H-6\alpha), 2·75 (1H, broad d, J 4Hz, -OH), 2·46 (1H, dddd, J 18, 10, 4, 3 Hz, H-6 β); δ_{C} (CDCl₃) 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+NH₄⁺; v_{max} (film) 3700-3100, 2100, 1720, 1660, 1600, 1585, 1495 cm⁻¹; δ_{H} (CDCl₃) 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, -CO₂Me), 3·02 (1H, ddt, J 18·5, 5·5, 1·5 Hz, H-6a), 2·56 (1H, ddt, J 18·5, 7, 1.5 Hz, H-6 β), 1.60 (1H, broad s, -OH); δ_{C} (CDCl₃) 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+NH₄⁺; v_{max} (film) 3700-3140, 2100, 1710, 1670, 1600, 1585, 1495 cm⁻¹; δ_H (CDCl₃) 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, -CO₂Me), 2.89 (1H, ddt, J 19, 5.5, 2 Hz, H-6 α), 2.64 (1H, broad d, J 4 Hz, -OH), 2.45 (1H, ddt, J 19, 6.5, 2Hz, H-6 β); δ_{C} (CDCl₃) 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. C₁₇H₁₇N₃O₆ requires C, 56·8; H, 4·75; N, 11·7%); *m/z* (+Cl) 377, M+NH₄⁺; v_{max} (film) 2100, 1750, 1720, 1660, 1600, 1585, 1490 cm⁻¹; $\delta_{\rm H}$ (CDCl₃) 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, -CO₂Me), 3·02 (1H, ddt, *J* 19, 5, 2 Hz, H-6\alpha), 2·78 (1H, ddt, *J* 19, 6, 2 Hz, H-6\beta), 2·12 (3H, s, MeCO₂-); $\delta_{\rm C}$ (CDCl₃) 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+NH₄⁺; v_{max} (film) 2100, 1720, 1660, 1600, 1585, 1490 cm⁻¹; δ_H (CDCl₃) 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, -CO₂Me), 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, MeCO₂-); δ_C (CDCl₃) 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+; v_{max} (film) 2100, 1720, 1660, 1600, 1585, 1490 cm⁻¹; δ_H (CDCl₃) 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, -CO₂Me), 3.46 (3H, s, -OMe), 2.62 (2H, m, H-6\alpha and H-6\beta); δ_C (CDCl₃) 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-1cyclohexene-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. C₂₀H₂₁N₃O₉ requires C, 53·7; H, 4·75; N, 9·4%); *m/z* (+CI) 448, MH⁺; v_{max} (film) 2100, 1720, 1660, 1600, 1585, 1490 cm⁻¹; δ_H (CDCl₃) 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, $-CH(CO_2Me)_2$), 4.59 (1H, m, H-3), 4.20 (1H, m, H-5), 3.81 (6H, s, $-CH(CO_2Me)_2$), 3.68 (3H, s, $-CO_2Me$), 2.86 (1H, ddt, J 18.5, 5, 2 Hz, H-6 α), 2.65 (ddt, J 18.5, 5, 1.5 Hz, H-6 β).

Methyl 1(R),2(R),6(R)-2-hydroxy-8-phenyl-7-aza-9-oxabicyclo[4.3.0]nona-4,7-diene-4carboxylate 29. A solution of methyl 3(R)-azido-4(R)-benzoyloxy-5(R)-hydroxy-1-cyclohexene-1carboxylate 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. C₁₅H₁₅NO₄ requires C, 65·95; H, 5·55; N, 5·15%); m/z (+CI) 274, MH⁺; v_{max} (film) 3700-3000, 1715, 1655, 1640, 1600, 1580, 1495 cm⁻¹; δ_H (CDCl₃) 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, -CO₂Me), 2·85 (1H, ddd, J 17·5, 5, 1 Hz, H-3\alpha), 2·75-2·50 (broad s, -OH), 2·27 (1H, ddt, J 17·5, 10, 2·5 Hz, H-3\beta); δ_C (CDCl₃) 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-4carboxylate 31 and methyl 5(R)-acetoxy-3(R)-benzoylamino-4(R)-hydroxy-1-cyclohexene-1carboxylate 34. A solution of methyl 5(R)-acetoxy-3(R)-azido-4(R)-benzoyloxy-1-cyclohexene-1carboxylate 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%), Rf 0.66, as a colourless oil. (Found: C, 64.4; H, 5.7; N, 4.0. C₁₇H₁₇NO₅ requires C, 64.75; H, 5.45; N, 4.45%); m/z (+FAB) 316, MH⁺; v_{max} (film) 1740, 1720, 1660, 1645, 1580, 1500 cm⁻¹; δ_{H} (CDCl₃) 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, -CO₂Me), 2.85 (1H, ddt, J 17, 5, 1 Hz, H-3a), 2.32 (1H, ddt, J 17, 8.5, 2.5 Hz, H-3β), 2.14 (3H, s, MeCO₂-); δ_C (CDCl₃) 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. C₁₇H₁₉NO₆ requires C, 61.25; H, 5.75; N, 4·2%); m/z (+CI) 334, MH+; v_{max} (film) 3570, 3400, 1720, 1640, 1600, 1580, 1500 cm⁻¹; δ_{H} (CDCl₃) 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, -CO₂Me), 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, MeCO₂-); δ_{C} (CDCl₃) 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. C₁₅H₁₇NO₅ requires C, 61.85; H, 5.9; N, 4.8%); *m/z* (+CI) 292, MH⁺; v_{max} (film) 3700-2500, 1715, 1650, 1600, 1585, 1490 cm⁻¹; δ_H (CDCl₃) 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, -CO₂Me), 2.95 (1H, ddt, *J* 19, 5, 2 Hz, H-6\alpha), 2.48 (1H, ddt, *J* 19, 6, 2 Hz, H-6\beta), 3.00-1.50 (3H, broad s, -OH and -NH₂); δ_C (CDCl₃) 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. C₁₅H₁₇NO₅ requires C, 61·85; H, 5·9; N, 4·8%); m/z (+CI) 292, MH⁺; v_{max} (film) 3700-2800, 1715, 1655, 1600, 1585, 1490 cm⁻¹; δ_H (CDCl₃) 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, -CO₂Me), 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-6\alpha), 2·46 (4H, m, H-6\beta, -NH₂ 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. C₈H₁₁N₃O₄ requires C, 45·05; H, 5·2; N, 19·7%); *m/z* (+FAB) 214, 236, MH⁺, M+Na⁺; v_{max} (film) 3700-3040, 2100, 1710, 1655 cm⁻¹; δ_H (CDCl₃) 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, -CO₂Me), 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 (CDCl₃) 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⁺; v_{max} (film) 3700-3000, 2500, 1700, 1650, 1590 cm⁻¹; δ_H (CD₃OD) 6.76 (1H, m, H-2), 3.99 (1H, dt, J 6.5, 4.5 Hz, H-5), 3.72 (1H, s, -CO₂Me), 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-6\alpha), 2.23 (1H, ddt, J 18.5, 4.5, 2 Hz, H-6\beta); δ_C (CD₃OD) 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).

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