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A Novel and Concise Synthesis of (±) 2-*epi*-Validamine[1]

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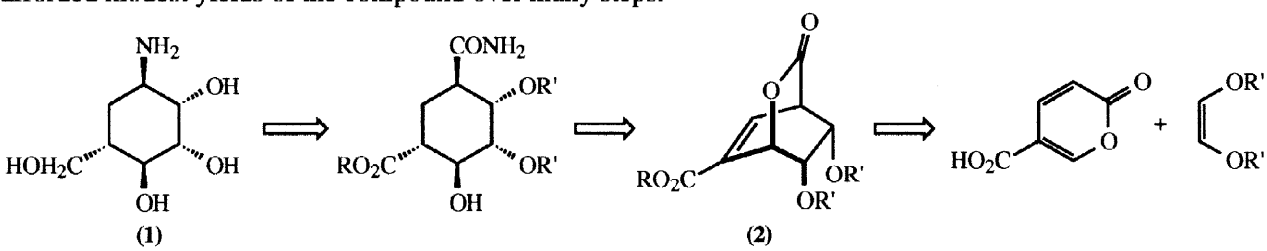
Abstract: (±) 2-*epi*-Validamine has been synthesised in five steps by the chemical manipulation of the bicyclic lactone cycloadduct of ethyl coumalate and vinylene carbonate.

Naturally occurring and synthetic carbocyclic analogues of saccharides, commonly referred to as carbasugars, show many interesting biological activities that arise from their ability to inhibit carbohydrate handling enzymes such as glycosidases.[2] Hence, carbasugars have been the focus of much synthetic endeavors. To date, they have been synthesised by chemical manipulation of starting materials obtained from bacterial oxidation of benzenes,[3] 7-oxanorbornenic acid,[4] other carbohydrates[5] and quinic acid.[6]

In this paper, we describe a novel approach to the synthesis of carbasugars using cycloaddition of pyrones as a key initial step. It complements the existing routes by allowing a more efficient synthetic access to a number of carbasugars which are difficult to prepare by other methods. To showcase this approach, we describe the total synthesis of commercially important 2-*epi*-validamine (**1**). This compound was first isolated from the fermentation broth of *Streptomyces hygroscopicus* (subsp. *limoneus*).[7] As a constituent of validamycin antibiotics, 2-*epi*-validamine is currently used commercially against sheath blight of rice plants and in the prevention of damping off of cucumber seedlings.[8] Previous syntheses of 2-*epi*-validamine have afforded modest yields of the compound over many steps.[4,6]



(1) (2)

Scheme 1

Our methodology is based on Diels-Alder cycloadditions of appropriately substituted 2-pyrones with their electronically matched dienophiles to obtain, efficiently and stereoselectively, bicyclic lactones such as (**2**).[9]

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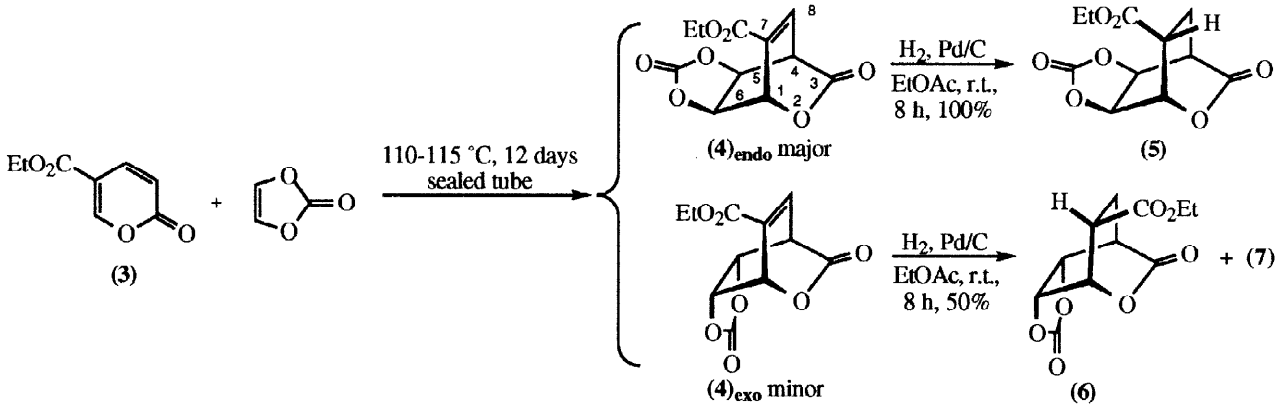
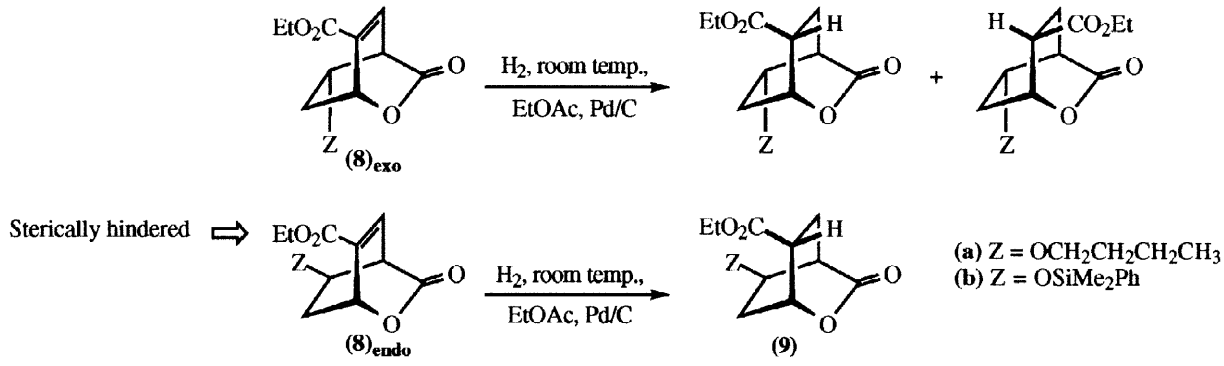
After ring opening, these afford densely substituted six membered rings which are excellent starting points for the synthesis of natural products.[9,10] The utility of this approach to the synthesis of key intermediates in the total synthesis of avermectin and milbemycin has already been shown.[11] However, the methodology is a particularly useful one for the synthesis of carbasugars as the retrosynthetic analysis of 2-*epi*-validamine (**1**) demonstrates (Scheme 1).

The first step in this synthesis is the cycloaddition of an alkyl coumalate and a suitable *cis* 1,2-bishydroxyalkene. Remarkably, we found that ethyl coumalate undergoes a very efficient cycloaddition to vinylene carbonate, even though this dienophile is relatively weak and has previously found little use in Diels-Alder cycloadditions.[12] Cycloaddition is highly stereoselective with an *endo*/*exo* ratio of 6 as observed by crude NMR spectroscopic analysis (Scheme 2).



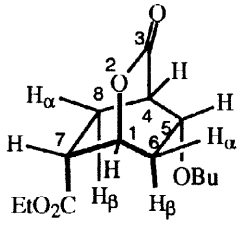
Scheme 2

The next step is the hydrogenation of the C7-C8 alkene of the bicyclic lactone. The stereochemistry of the hydrogenation of bicyclic lactones has not been previously established.[13] We therefore, carried out a preliminary investigation to gauge the effect of *endo*/*exo* substitution at the 5-position of bicyclic lactones on the diastereofacial selectivity of hydrogenation. We found that in general, 5-substituted *endo* cycloadducts, e.g. **(8a-b)$_{endo}$**, afford a single product whereas the *exo* cycloadducts **(8a-b)$_{exo}$** give an inseparable mixture of two epimers (Scheme 3). Stereochemistry of this hydrogenation can be easily explained because in the *endo* cycloadducts, the 5-substituent significantly blocks contact with catalyst and prevents delivery of hydrogen from that face.The relative configuration of **(9a-b)** was established from analysis of NMR spectroscopic data and is based on the empirical rules previously set by Harano *et al.* ($J_{1\text{-}6exo} > J_{1\text{-}6endo}$ and $J_{4\text{-}5exo} > J_{4\text{-}5endo}$).[9,14]



Scheme 3

Based on the observation of high field NMR spectra of a number of saturated cycloadducts, we can now extend these empirical rules to allow an easy determination of the relative configuration of these bicyclic systems at C-7. In general, in saturated bicyclic lactones H-8_α can be distinguished from H-8_β by comparison of the size of coupling to H-4 ($J_{4\text{-}8\alpha} > J_{4\text{-}8\beta}$).[15] H-$8_\alpha$ Can be distinguished from H-8_β as it shows W coupling (ca 1.5 Hz) to H-5_α. The configuration at C-7 can be determined by reference to size of the coupling of H-7 to H-8_α. If H-7 is in the α position (C-7 substituent is at the β position) then it has a large coupling to H-8_α (>10 Hz). If H-7 is in the β position (C-7 substituent is at the α position) then it has a smaller coupling to H-8_α (<9 Hz). Furthermore, if H-7 is in the α position, (C-7 substituent is at the β position) then its signal appears as a dddd (16 lines) due to coupling to H-1, and H-8_β and H-8_α as well as a W coupling (ca 2 Hz) to H-6_α. Assignment of the NMR coupling constants for one saturated bicyclic lactone is shown (Scheme 4).



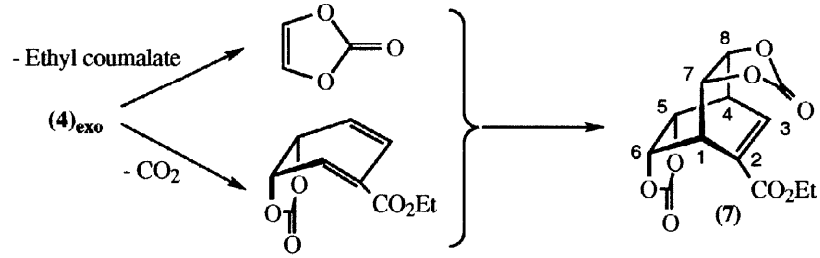
$J_{1,6\beta} = 1.4$ Hz
$J_{1,6\alpha} = 4.3$ Hz
$J_{1,7} = 3.6$ Hz
$J_{4,8\alpha} = 3.8$ Hz
$J_{4,8\beta} = 2.0$ Hz
$J_{4,5} = 3.3$ Hz

$J_{6\alpha,6\beta} = 15.2$ Hz
$J_{8\alpha,8\beta} = 13.8$ Hz
$J_{5,6\alpha} = 9.5$ Hz
$J_{5,6\beta} = 3.0$ Hz
$J_{7,8\alpha} = 12.4$ Hz
$J_{7,8\beta} = 6.8$ Hz

$J_{7,6\alpha} = 2.2$ Hz
$J_{5,8\alpha} = 1.6$ Hz

Scheme 4

Hydrogenation of $(4)_{endo}$ at room temperature proceeds smoothly to afford a quantitative yield of the required product. However, the outcome of the hydrogenation of the *exo* cycloadduct $(4)_{exo}$ was quite unexpected. Hydrogenation of $(4)_{exo}$ afforded two compounds which were separable by chromatography. The major product was identified as hydrogenated bicyclic lactone (**6**) and was obtained in 50% yield. The minor product, obtained in 30% yield, was not the expected epimer of (**6**). Following NMR spectroscopic studies, structure (**7**) was proposed which was later confirmed by X-ray crystallography (Figure 1).[16] The mechanism for formation of (**7**) is unclear although it presumably involves recombination of the dihydrobenzene obtained by loss of CO_2, and vinylene carbonate obtained from cycloreversion of $(4)_{exo}$ (Scheme 5). However, since formation of (**7**) requires the presence of both hydrogen and palladium on charcoal, it is likely that the mechanism is considerably more complicated.



Scheme 5

Our next task was to selectively manipulate the lactone functions in (**5**).[17] We investigated the ring opening reaction of this compound with a range of reagents. Selective hydrolysis of the lactone was achieved under acidic conditions. The rate of the reaction and thus the yield of the isolated product (**10a**), critically depends on the acidity of the medium. For instance, in a 1:1 solution of acetic acid and water, after 80 hours at room temperature, only 25% hydrolysis of the bridgehead lactone was observed. In contrast, in a 1:1 solution of trifluoroacetic acid and water, reaction was complete after 12 hours (Scheme 6).

We also investigated the ammonolysis of the bicyclic lactone (**5a**). Treatment of (**5a**) with a solution of ammonia in methanol affords the eliminated product (**11**) in 74% yield at room temperature, and methyl ester (**10b**) in 78% yield at -78 °C (Scheme 6). On the other hand, amide (**10c**) is obtained from treatment of this compound with ammonia in 1,4-dioxane at room temperature.

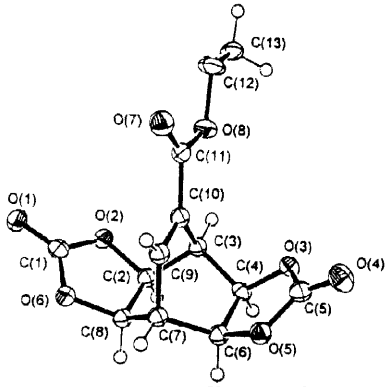


Figure 1

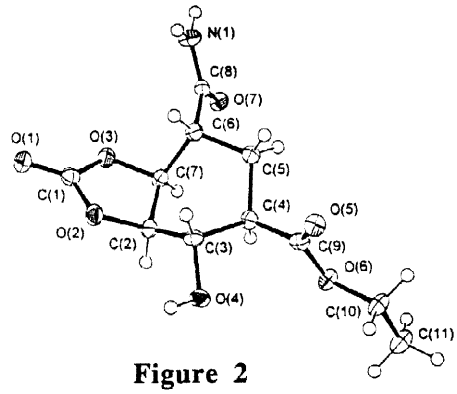
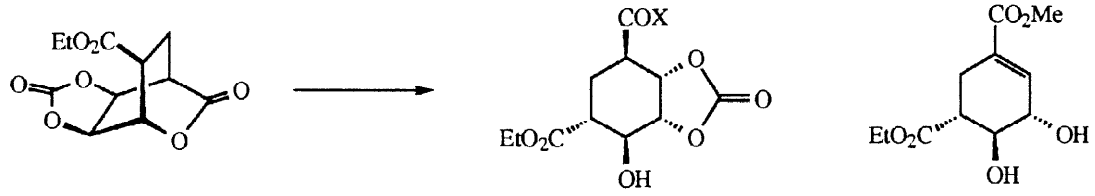


Figure 2

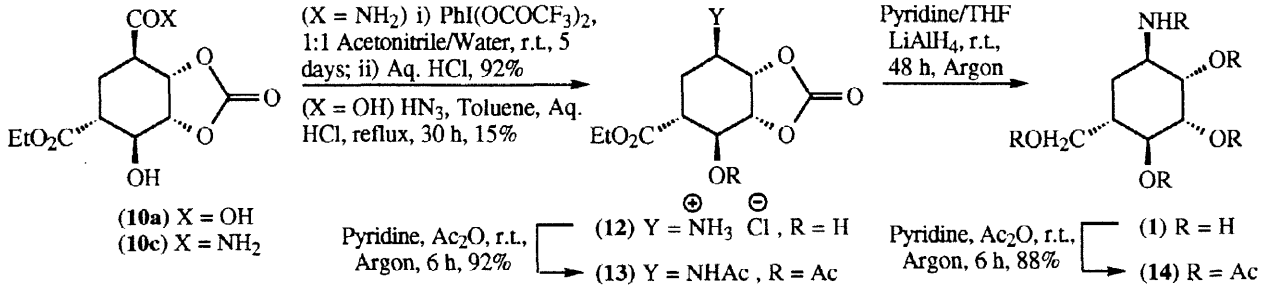
Compounds (**10a-c**) were obtained with the relative configuration at the carboxyl substituents unchanged as confirmed by X-ray crystallography.[18] This was an important observation since epimerisation of the ethyl ester to its thermodynamically more favoured α configuration in (**5a**) is facile[9] and could have occurred during hydrolysis/ammonolysis of (**5a**). X-ray crystal structure of amide (**10c**) confirms that the six-membered ring adopts a boat conformation with all substituents in pseudoequatorial position (Figure 2).



(**5a**) (**10a**) X = OH; (**10b**) X = OMe; (**10c**) X = NH_2 (**11**)

Scheme 6

Conversion of the carboxylic acid function to an amine was achieved either by treatment of acid (**10a**) with hydrazoic acid followed by thermal degradation (Schmidt rearrangement), or by Hofmann degradation of amide (**10c**) under oxidative conditions,[19] to give amine (**12**) which was isolated as its hydrochloride salt. The latter route proved to be more efficient. As expected, the reactions proceeded with complete retention of relative configurations in both cases. Compound (**12**) is insoluble in tetrahydrofuran and dimethoxyethane. Therefore we prepared the N,O-bisacetyl derivative (**13**) which is soluble in tetrahydrofuran. Full reduction of



Scheme 7

this compound with an excess of reducing agent is accompanied by the removal of acetyl group from nitrogen[20] and the carbonate function to afford 2-*epi*-validamine (**1**). The same overall yield was obtained by direct reduction of (**12**) in a mixture of tetrahydrofuran and pyridine in which this compound is completely soluble. Finally, 2-*epi*-validamine (**1**) was converted to its pentaacetate (**14**) for the purpose of characterisation.[4-6]

In summary, we have utilised a novel methodology to develope a concise (5 steps) and very efficient (60% overall yield) synthesis of 2-*epi*-validamine. The extension of this methodology to the synthesis of a number of other carbasugars is currently under investigation and will be reported in due course.

ACKNOWLEDGEMENT

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EXPERIMENTAL

NMR spectra were obtained on Bruker AMX360 and AMX400 spectrometers operating respectively at 360 and 400 MHz for ^1H, and 90.6 and 101 MHz for ^{13}C. Assignments of NMR spectra are confirmed by COSY and NOSEY techniques where necessary. Mass spectra were obtained on a Jeol AX505W mass spectrometer using electron impact (EI), chemical ionisation (CI) or fast atom bombardment (FAB) techniques.

Ethyl 2-oxo-2H-pyran-5-carboxylate (3): 4-Dimethylaminopyridine (0.24 g, 2.00 mmol) was added to a stirred suspension of coumalic acid (1.40 g, 10.00 mmol) in dichloromethane (50 mL) maintained at room temperature. After 15 minutes, ethanol (3 mL) and N,N'-dicyclohexylcarbodiimide (2.06 g, 10.00 mmol) were added. After 18 hours solvent was removed by evaporation under vacuum, residue was dissolved in ethyl acetate (100 mL) and filtered through a bed of celite. Removal of solvent under vaccum and purification by chromatography on silica gel (petroleum ether/ethyl acetate 1:1 v/v) yielded a white solid (1.44 g, 86%), mp 43 °C; ^1H NMR ($CDCl_3$) δ 1.37 (3 H, t, J = 7.1 Hz, CH_3), 4.36 (2 H, q, J = 7.1 Hz, OCH_2), 6.33 (1 H, dd, $J_{3,6}$ = 1.0 Hz, $J_{3,4}$ = 9.7 Hz, H-3), 7.79 (1 H, dd, $J_{4,6}$ = 2.5 Hz, $J_{3,4}$ = 9.7 Hz, H-4), 8.30 (1 H, dd, $J_{3,6}$ = 1.0 Hz, $J_{4,6}$ = 2.5 Hz, H-6); ^{13}C NMR ($CDCl_3$) δ 14.2 (CH_3), 61.6 (OCH2), 112.15 (C-5), 115.2 (C-3), 141.7 (C-4), 158.0 (C-6), 159.9 (C-2), 162.9 ($\underline{C}O_2Et$); IR (Nujol) 2923.3, 1748.0, 1701.3, 1556.5, 1019.6 cm^{-1}; MS m/z 186 ($M+NH_4^+$), 169 (MH^+), 157, 140, 112, 95; HRMS calculated for $C_8H_8O_4$ 168.0423; found 168.0427.

Ethyl 5_{endo},6_{endo}-(dihydroxycarbonate)-3-oxo-2-oxabicyclo[2.2.2]oct-7-ene-7-carboxylate (4_{endo}): A solution of ethyl 2-oxo-2H-pyran-5-carboxylate (**3**) (0.25 g, 1.50 mmol) in vinylene carbonate (2 mL) containing few crystals of butylatedhydroxytoluene (BHT) was heated in a sealed tube at 110 °C for 12 days. Purification by chromatography on silica gel (petroleum ether/diethyl ether 1:1 v/v) afforded a white solid (0.31 g, 81%); mp 97 °C; ^1H NMR ($CDCl_3$) δ 1.35 (3 H, t, J = 7.1 Hz, CH_3), 4.27 (3 H, m, H-4 and OCH_2), 5.12 (1 H, ddd, $J_{5,8}$ = 0.7 Hz, $J_{4,5}$ = 3.7 Hz, $J_{5,6}$ = 7.7 Hz, H-5), 5.22 (1 H, dd, $J_{1,6}$ = 4.2 Hz, $J_{5,6}$ = 7.7 Hz, H-6), 5.99 (1 H, dd, $J_{1,8}$ = 2.3 Hz, $J_{1,6}$ = 4.2 Hz, H-1), 7.38 (1 H, ddd, $J_{5,8}$ = 0.7 Hz, $J_{1,8}$ = 2.3

Hz, $J_{4,8}$ = 7.0 Hz, H-8); ^{13}C NMR ($CDCl_3$) δ 14.1 (CH_3), 45.7 (C-1), 62.3 (OCH_2), 70.6 (C-4), 71.8 (C-6), 72.4 (C-5), 134.6 (C-7), 137.1 (C-8), 152.6 (CO_3), 160.95 (C-3), 165.6 ($\underline{C}O_2Et$); IR ($CDCl_3$) 2925.1, 1786.6, 1711.2, 1309.7, 1045.1 cm^{-1}; MS m/z (CI/ammonia) 255 (MH^+), 168, 140, 112, 94, 85; HRMS calculated for $C_{11}H_{10}O_7$ 254.0426; found 254.0431.

Ethyl 5_{exo},6_{exo}-(dihydroxycarbonate)-3-oxo-2-oxabicyclo[2.2.2]oct-7-ene-7-carboxylate (4_{exo}): This compound was isolated as side product in above reaction as white solid (0.052 g, 14%), mp 111 °C; ^1H NMR ($CDCl_3$) δ 1.34 (3 H, t, J = 7.1 Hz, CH_3), 4.28 (1 H, dd, $J_{4,5}$ = 3.6, Hz $J_{4,8}$ = 6.6 Hz, H-4), 4.83 (2 H, m, H-5 and H-6), 5.90 (1 H, t, $J_{1,6}$ = $J_{1,8}$ = 2.6 Hz, H-1), 7.27 (1 H, dd, $J_{1,8}$ = 2.6 Hz, $J_{4,8}$ = 6.6 Hz, H-8); ^{13}C NMR ($CDCl_3$) δ 14.2 (CH_3), 46.2 (C-4), 62.5 (OCH_2), 70.5 (C-1), 73.1 (C-6), 73.6 (C-5), 136.6 (C-7), 136.7 (C-8), 152.7 (CO_3), 160.85 (C-3), 164.8 ($\underline{C}O_2Et$); IR ($CDCl_3$) 2926.8, 1785.3, 1710.5, 1445.0, 1055.1 cm^{-1}; MS m/z (CI/ammonia) 272 ($M+NH_4^+$), 255 (MH^+), 288, 189, 166, 86; HRMS calculated for $C_{11}H_{10}O_7$ 254.0426; found 254.0402.

Ethyl 5_{endo},6_{endo}-(dihydroxycarbonate)-3-oxo-2-oxabicyclo[2.2.2]octane-7_{endo}-carboxylate (5): A stirred mixture of **(4_{endo})** (0.202 g, 0.80 mmol) and 10% palladium on charcoal (0.10 g) in ethyl acetate (30 mL) was subjected to hydrogen gas at room temperature and pressure. After required amount of hydrogen had been consumed, catalyst was removed by filteration through a bed of celite. Removal of solvent afforded a white solid (0.205 g, 100%): mp 117 °C; ^1H NMR ($CDCl_3$) δ 1.31 (3 H, t, J = 7.2 Hz, CH_3), 2.09 (1 H, ddd, $J_{4,8a}$ = 4.0 Hz, $J_{7,8a}$ = 11.8 Hz, $J_{8a,8b}$ = 15.3 Hz, H-8_a), 2.88 (1 H, ddd, $J_{4,8b}$ = 2.0 Hz, $J_{7,8b}$ = 7.1 Hz, $J_{8a,8b}$ = 15.3 Hz, H-8_b), 3.19 (1 H, ddd, $J_{1,7}$ = 3.6, Hz $J_{7,8a}$ = 11.8 Hz, $J_{7,8b}$ = 7.1 Hz, H-7), 3.21 (1 H, ddd, $J_{4,8b}$ = 2.0 Hz, $J_{4,5}$ = 3.2 Hz, $J_{4,8a}$ = 4.0 Hz, H-4), 4.21 (2 H, m, OCH_2), 4.99 (2 H, m, H-5 and H-6), 5.31 (1 H, t, $J_{1,6}$ = $J_{1,7}$ = 3.6 Hz, H-1); ^{13}C NMR ($CDCl_3$) δ 14.0 (CH_3), 16.3 (C-8), 38.5 (C-7), 38.8 (C-4), 62.5 (OCH_2), 70.5 (C-6), 71.2 (C-5), 74.2 (C-1), 152.6 (CO_3), 168.2 (C-3), 169.45 ($\underline{C}O_2Et$); IR ($CDCl_3$) 2817.3, 1818.9, 1777.7, 1735.4, 1173.3 cm^{-1}; MS m/z (CI/ammonia) 274 ($M+NH_4^+$), 257 (MH^+), 230, 114, 78; HRMS calculated for $C_{11}H_{13}O_7$ (MH^+) 257.0661; found 257.0715.

Ethyl 5_{exo},6_{exo}-(dihydroxycarbonate)-3-oxo-2-oxabicyclo[2.2.2]octane-7_{exo}-carboxylate (6) and **Ethyl 5_{endo}:6_{endo},7_{endo}:8_{endo}-bis(dihydroxycarbonate)bicyclo[2.2.2]oct-2-ene-3-carboxylate (7):** A stirred mixture of **(4_{exo})** (0.256 g, 0.80 mmol) and 10% palladium on charcoal (0.10 g) in ethyl acetate (25 mL) was subjected to hydrogen gas at room temperature and pressure. After required amount of hydrogen had been consumed, catalyst was removed by filteration through a bed of celite. Removal of solvent under vacuum followed by chromatography (silica gel, petroleum ether/ethyl acetate (1:3) v/v) afforded a 1:1 inseparable mixture of two compounds as a gum (0.20 g). Compound **(6)** (0.128 g, 50%) was soluble in chloroform and was obtained as a clear gum. ^1H NMR ($CDCl_3$) δ 1.30 (3 H, t, J = 7.3 Hz, CH_3), 1.99 (1 H, ddd, $J_{4,8a}$ = 1.9, Hz $J_{7,8a}$ = 10.7 Hz, $J_{8a,8b}$ = 14.8 Hz, H-8a), 2.69 (1 H, dt, $J_{7,8b}$ = 3.8 Hz, $J_{4,8b}$ = 4.0 Hz, $J_{8a,8b}$ = 14.8 Hz, H-8b), 2.88 (1 H, ddd, $J_{1,7}$ = 1.8 Hz, $J_{7,8b}$ = 3.8 Hz, $J_{7,8a}$ = 10.7 Hz, H-7), 3.28 (1 H, m, $J_{4,5}$ = 1.6 Hz, $J_{4,8a}$ = 1.9, Hz $J_{4,8b}$ = 4.0 Hz, H-4), 4.26 (2 H, m, OCH_2), 4.96 (1 H, dd, $J_{4,5}$ = 1.6 Hz, $J_{5,6}$ = 8.6 Hz, H-5), 5.08 (1 H, dd, $J_{1,6}$ = 1.8 Hz, $J_{5,6}$ = 8.6 Hz, H-6), 5.23 (1 H, t, $J_{1,6}$ = $J_{1,7}$ = 1.8 Hz, H-1); ^{13}C NMR ($CDCl_3$) δ 14.0 (CH_3), 19.85 (C-8), 38.2 (C-7), 39.4 (C-4), 62.55 (OCH_2), 73.4 (C-6), 74.8 (C-5), 76.2 (C-1), 152.8 (CO_3), 168.5 (C-3), 169.5 ($\underline{C}O_2Et$); IR ($CDCl_3$) 2985.9, 1810.9,

1733.9, 1225.7, 1089.3 cm^{-1}; MS m/z (FAB/thioglycerol) 257 (MH^+), 229, 211, 171, 139, 95; HRMS calculated for $C_{11}H_{13}O_7$ (MH^+) 257.0661; found 257.0715. Compound **(7)** (0.061 g, 30%) was insoluble in chloroform and was obtained as a white solid: ^1H NMR (DMSO-d_6) δ 1.25 (3 H, t, J = 7.3 Hz, CH_3), 3.95 (1 H, dt, $J_{3,4}$ = 1.0 Hz, $J_{4,5}$ = 3.0 Hz, H-4), 4.11 (1 H, dt, $J_{1,5}$ = 3.1 Hz, $J_{1,2}$ = 6.3 Hz, H-1), 4.21 (2 H, q, J = 7.3 Hz, OCH_2), 5.00-5.07 (4 H, m, H-5, H-6, H-7 and H-8), 7.28 (1 H, dd, $J_{3,4}$ = 1.0 Hz, $J_{1,2}$ = 6.3 Hz, H-2); ^{13}C NMR (DMSO-d_6) δ 13.9 (CH_3), 43.1 (C-1), 44.0 (C-4), 66.2 (OCH_2), 72.8 (C-6/C-5), 73.0 (C-7/C-8), 131.6 (C-3), 143.5 (C-2), 153.5 (CO_3), 162.7 (CO_2Et); IR ($CDCl_3$) 2854.1, 1792.8, 1723.7, 1458.7, 1376.9, 1260.1 cm^{-1}; MS m/z (EI) 296 (M^+), 251, 212, 167, 105; HRMS calculated for $C_{13}H_{12}O_8$ (M^+) 296.0543; found 296.0532.

Cycloadducts (8a) and (8b): These were prepared according to general procedure for cycloadditions described above and were characterised as follows: **($8a_{endo}$)** oil, ^1H NMR ($CDCl_3$) δ 0.83 (3 H, t, J = 7.0 Hz, ether CH_3), 1.26 (2 H, m, CH_2), 1.27 (3 H, t, J = 7.0 Hz, ester CH_3), 1.43 (2 H, m, CH_2), 1.54 (1 H, dm, $J_{6endo,6exo}$ = 14.0 Hz, H-6_{endo}), 2.57 (1 H, ddd, $J_{6endo,6exo}$ = 14.0 Hz, $J_{6exo,5}$ = 7.7 Hz, $J_{1,6}$ = 3.8 Hz, H-6_{exo}), 3.39 (2 H, m, ether OCH_2), 4.01 (1 H, m, H-5), 4.06 (1 H, dd, $J_{4,8}$ = 6.1 Hz, $J_{4,5}$ = 3.3 Hz, H-4), 4.21 (2 H, q, J = 7.0 Hz, OCH_2), 5.63 (1 H, m, H-1), 7.18 (1 H, dd, $J_{4,8}$ = 6.1 Hz, $J_{5,8}$ = 1.2 Hz, H-8); ^{13}C NMR ($CDCl_3$) δ 13.8 (ether CH_3), 14.2 (ester CH_3), 19.1 (ether CH_2), 31.5 (ether CH_2), 34.75 (C-6), 47.4 (C-4), 61.2 (ester OCH_2), 69.15 (ether OCH_2), 71.4 (C-5), 73.3 (C-1), 136.0 (C-7), 138.05 (C-8), 162.1 (C-3), 170.8 (ester CO_2Et); **($8a_{exo}$)** oil; ^1H NMR ($CDCl_3$) δ 0.90 (3 H, t, J = 7.0 Hz, ether CH_3), 1.32 (3 H, t, J = 7.0 Hz, ester CH_3), 1.35 (2 H, m, CH_2), 1.53 (2 H, m, CH_2), 2.06-2.17 (2 H, m, H-6_{endo} and H-6_{exo}), 3.39 and 3.62 (2 H, m, ether OCH_2), 3.82 (1 H, m, H-5), 3.99 (1 H, dd, $J_{4,8}$ = 6.7 Hz, $J_{4,5}$ = 3.0 Hz, H-4), 4.25 (2 H, m, OCH_2), 5.65 (1 H, m, H-1), 7.23 (1 H, dd, $J_{4,8}$ = 6.7 Hz, $J_{5,8}$ = 2.2 Hz, H-8); ^{13}C NMR ($CDCl_3$) δ 13.8 (ether CH_3), 14.2 (ester CH_3), 19.2 (ether CH_2), 31.7 (ether CH_2), 33.7 (C-6), 47.4 (C-4), 61.4 (ester OCH_2), 69.2 (ether OCH_2), 73.1 (C-5/C-1), 73.4 (C-1/C-5), 137.7 (C-8), 138.5 (C-7), 162.0 (C-3), 169.8 (ester CO_2Et); **($8b_{endo}$)** oil; ^1H NMR ($CDCl_3$) δ 0.39 (6 H, s, 2 x CH_3Si), 1.34 (3 H, t, J = 7.0 Hz, ester CH_3), 1.55 (1 H, dm, $J_{6endo,6exo}$ = 14.0 Hz, H-6_{endo}), 2.52 (1 H, ddd, $J_{6endo,6exo}$ = 14.0 Hz, $J_{6exo,5}$ = 7.5 Hz, $J_{1,6}$ = 3.8 Hz, H-6_{exo}), 3.78 (1 H, dd, $J_{4,8}$ = 6.3 Hz, $J_{4,5}$ = 3.4 Hz, H-4), 4.28 (2 H, m, OCH_2), 4.34 (1H, m, H-5), 5.64 (1 H, m, H-1), 7.18 (1 H, dd, $J_{4,8}$ = 6.3 Hz, $J_{5,8}$ = 1.8 Hz, H-8), 7.37-7.53 (3 H, m, aromatic H), 7.58-7.62 (2 H, m, aromatic H); ^{13}C NMR ($CDCl_3$) δ -1.6 and -1.45, (CH_3Si), 14.3 (ester CH_3), 37.4 (C-6), 50.9 (C-4), 61.4 (OCH_2), 64.7 (C-5), 73.5 (C-1), 128.3 (aromatic C), 130.4 (aromatic C), 133.5 (aromatic C), 136.0 (C-7), 136.65 (aromatic C), 138.7 (C-8), 162.4 (C-3), 171.0 ($\underline{C}O_2Et$); **($8b_{exo}$)** oil; ^1H NMR ($CDCl_3$) δ 0.39 (3 H, s, CH_3Si), 0.42 (3 H, s, CH_3Si), 1.28 (3 H, t, J = 7.0 Hz, ester CH_3), 2.02 (2 H, m, H-6_{endo} and H-6_{exo}), 3.61 (1 H, dd, $J_{4,8}$ = 6.7 Hz, $J_{4,5}$ = 3.3 Hz, H-4), 4.09 (1 H, m, H-5), 4.21 (2 H, m, OCH_2), 5.59 (1 H, m, H-1), 7.14 (1 H, dd, $J_{4,8}$ = 6.7 Hz, $J_{5,8}$ = 2.3 Hz, H-8), 7.38-7.57 (5 H, m, aromatic H); ^{13}C NMR ($CDCl_3$) -1.45 and -1.4, (CH_3Si), 14.2 (ester CH_3), 35.9 (C-6), 51.1 (C-4), 61.45 (OCH_2), 66.4 (C-5), 73.5 (C-1), 128.2 (aromatic C), 130.2 (aromatic C), 133.45 (aromatic C), 136.7 (C-7), 137.1 (aromatic C), 138.1 (C-8), 162.1 (C-3), 170.9 ($\underline{C}O_2Et$).

Hydrogenated cycloadducts ($9a_{endo}$) and ($9b_{endo}$): These were prepared according to general procedure for hydrogenation described above and were characterised as follows: **(9a)** oil, ^1H NMR ($CDCl_3$) δ

0.89 (3 H, t, J = 7.0 Hz, ether CH_3), 1.35 (2 H, m, CH_2), 1.26 (3 H, t, J = 7.0 Hz, ester CH_3), 1.45 (2 H, m, CH_2), 1.75 (1 H, ddd, $J_{6\beta,6\alpha}$ = 15.0 Hz, $J_{5,6\beta}$ =3.0 Hz, $J_{1,6\beta}$ = 1.4 Hz, H-6β), 1.92 (1 H, dddd, $J_{8\beta,8\alpha}$ = 14.0 Hz, $J_{7,8\alpha}$ = 12.0 Hz, $J_{4,8\alpha}$ = 3.8 Hz, $J_{1,8\alpha}$ (W coupling) = 1.6 Hz, H-8$_\alpha$), 2.32 (1 H, dddd, $J_{6\beta,6\alpha}$ = 15.0 Hz, $J_{6\alpha,5}$ = 9.5 Hz, $J_{1,6\alpha}$ = 4.3 Hz, $J_{7,6\alpha}$ (W coupling) = 2.2 Hz, H-6$_\alpha$), 2.66 (1 H, ddd, $J_{8\beta,8\alpha}$ = 14.0 Hz, $J_{7,8\beta}$ = 7.0 Hz, $J_{4,8\beta}$ = 2.0 Hz, H-8β), 2.94 (1 H, ddd, $J_{4,8\alpha}$ = 3.8 Hz, $J_{4,5}$ = 3.3 Hz, $J_{4,8\beta}$ = 2.0 Hz, H-4), 3.03 (1 H, dddd, $J_{7,8\alpha}$ = 12.0 Hz, $J_{7,6\beta}$ = 6.9 Hz, $J_{1,7}$ = 3.6 Hz, $J_{7,6\alpha}$ (W coupling) = 2.2 Hz, H-7), 3.33 (2 H, m, ether OCH_2), 3.82 (1 H, dddd, $J_{5,6\alpha}$ = 9.5 Hz, $J_{6\beta,5}$ = 3.0 Hz, $J_{1,5}$ = 3.3 Hz, $J_{5,8\alpha}$ (W coupling) = 1.6 Hz, H-5), 4.17 (2 H, q, J = 7.0 Hz, ester OCH_2), 4.87 (1 H, ddd, $J_{1,6\alpha}$ = 4.0 Hz, $J_{1,6\beta}$ = 1.4 Hz, $J_{1,7}$ = 3.6 Hz, H-1); ^{13}C NMR ($CDCl_3$) δ 13.9 (ether CH_3), 14.2 (ester CH_3), 17.8 (C-8), 19.4 (ether CH_2), 31.0 (ether CH_2), 31.85 (C-6), 39.9 (C-4/C-7), 41.6 (C-4/C-7), 61.4 (ester OCH_2), 68.6 (ether OCH_2), 71.0 (C-5), 75.1 (C-1), 172.1 (C-3), 174.5 ($\underline{C}O_2Et$); **(9b)** oil; ^{1}H NMR ($CDCl_3$) δ 0.38 (6 H, s, 2 x CH_3Si), 1.27 (3 H, t, J = 7.0 Hz, ester CH_3), 1.73 (1 H, dm, $J_{6\beta,6\alpha}$ = 14.0 Hz, H-6β), 1.92 (1 H, dddd, $J_{8\beta,8\alpha}$ = 14.0 Hz, $J_{7,8\alpha}$ = 12.0 Hz, $J_{4,8\alpha}$ = 3.7 Hz, $J_{1,8\alpha}$ (W coupling) = 1.4 Hz, H-8$_\alpha$), 2.26 (1 H, dddd, $J_{6\beta,6\alpha}$ = 15.0 Hz, $J_{6\alpha,5}$ = 9.2 Hz, $J_{1,6\alpha}$ = 4.2 Hz, $J_{7,6\alpha}$ (W coupling) = 2.1 Hz, H-6$_\alpha$), 2.68 (1 H, ddd, $J_{4,8\alpha}$ = 3.8 Hz, $J_{4,5}$ = 3.3 Hz, $J_{4,8\beta}$ = 2.0 Hz, H-4), 3.04 (1 H, m, H-4), 4.20 (3 H, m, OCH_2 and, H-5), 4.85 (1 H, m, H-1), 7.33-7.57 (5 H, m, aromatic H); ^{13}C NMR ($CDCl_3$) δ -1.4 (CH_3Si), 14.3 (ester CH_3), 17.7 (C-8), 33.6 (C-6), 41.7 (C-4/C-7), 43.3 (C-7/C-4), 61.4 (OCH_2), 64.6 (C-5), 75.2 (C-1), 128.2 (aromatic C), 130.1 (aromatic C), 133.4 (aromatic C), 137.1 (aromatic C), 170.9 (C-3), 174.6 ($\underline{C}O_2Et$).

Ethyl 1α-(hydroxy)-2β,3β-(dihydroxycarbonate)-cyclohexane-6β-carboxylate-4α-carboxylic acid (10a): Compound **(5)** (0.05 g, 0.20 mmol) was stirred in trifluoroacetic acid (2 mL) and water (2 mL) at room temperature. After 14 h solvents were removed under vacuum to give a yellow gummy solid (0.054 g, 100%): ^{1}H NMR (CD_3CO_2D) δ 1.24 (3 H, t, J = 7.2 Hz, CH_3), 2.14 (1 H, m, $J_{4,5\alpha}$ = 5.5 Hz, $J_{5\alpha,6}$ = 9.6 Hz, $J_{5\beta,5\alpha}$ = 20.0 Hz, H-5α), 2.18 (1 H, dt, $J_{4,5\beta}$ = 10.6 Hz, $J_{5\beta,6}$ = 5.5 Hz, $J_{5\beta,5\alpha}$ = 20.0 Hz, H-5β), 2.67 (1 H, m, $J_{5\beta,6}$ = 5.5 Hz, $J_{5\alpha,6}$ = 9.7 Hz, $J_{1,6}$ = 5.0 Hz, H-6), 3.30 (1 H, dt, $J_{3,4}$ = $J_{4,5\alpha}$ = 5.4 Hz, $J_{4,5\beta}$ = 10.5 Hz, H-4), 4.12 (1 H, dd, $J_{1,2}$ = 7.2, Hz, $J_{1,6}$ = 5.1 Hz, H-1), 4.20 (2 H, m, OCH_2), 4.83 (1 H, t, $J_{1,2}$ = $J_{2,3}$ = 7.2 Hz, H-2), 5.23 (1 H, dd, $J_{3,4}$ = 5.3 Hz, $J_{2,3}$ = 7.2 Hz, H-3); ^{13}C NMR (CD_3CO_2D) δ 14.1 (CH_3), 24.7 (C-5), 41.05 (C-4), 43.7 (C-6), 62.6 (OCH_2), 71.5 (C-1), 77.3 (C-3), 81.2 (C-2), 155.9 (CO_3), 174.3 ($\underline{C}O_2Et$), 174.9 ($\underline{C}O_2H$); IR 3503.8, 2988.1, 1878.1, 1786.5, 1605.4, 1078.1 cm^{-1}; MS m/z (CI/ammonia) 275 (MH^+), 258, 212; HRMS calculated for $C_{11}H_{14}O_8$ 274.1209, found 274.1210.

Ethyl methyl 1α-(hydroxy)-2β,3β-(dihydroxycarbonate)-cyclohexane-4α,6β-dicarboxylate (10b): Ammonia (3.50 mL, 2.0 M solution in methanol) was added to **(4_{endo})** (0.05 g, 0.20 mmol) at -78 °C and the resulting solution was stirred under dry argon for 40 minutes. Removal of solvent and chromatography on silica gel (petroleum ether/ethyl acetate gradient 2:1 to 1:2 v/v) afforded a pale yellow gum (0.045 g, 78%): ^{1}H NMR ($CDCl_3$) δ 1.30 (3 H, t, J = 7.3 Hz, CH_3), 2.05 (1 H,ddd, $J_{4,5\alpha}$ = 4.1 Hz, $J_{5\alpha,6}$ = 11.6 Hz, $J_{5\beta,5\alpha}$ = 18.6 Hz, H-5α), 2.46 (1 H, dt, $J_{1,6}$ = $J_{5\beta,6}$ = 4.1 Hz, $J_{5\alpha,6}$ = 11.6 Hz, H-6), 2.47 (1 H, dt, $J_{5\beta,6}$ = 4.1 Hz, $J_{4,5\beta}$ = 11.6 Hz, $J_{5\beta,5\alpha}$ = 18.6 Hz, H-5β), 3.28 (1 H, dd, $J_{3,4}$ = $J_{4,5\alpha}$ = 4.1 Hz, $J_{4,5\beta}$ = 11.6 Hz, H-4), 3.80 (3 H, s, CO_2CH_3), 4.07 (1 H, dd, $J_{1,6}$ = 4.1 Hz, $J_{1,2}$ = 7.1 Hz, H-1), 4.23 (2 H, q, J = 7.3 Hz, OCH_2), 4.71 (1 H, t, $J_{1,2}$ = $J_{2,3}$ = 7.1 Hz, H-2), 5.09 (1 H, dd, $J_{3,4}$ = 3.9 Hz, $J_{2,3}$ = 7.0 Hz, H-3); ^{13}C

NMR ($CDCl_3$) δ 14.1 (CH_3), 24.1 (C-5), 40.7 (C-4), 42.75 (C-6), 52.9 ($CO_2\underline{C}H_3$), 61.7 (OCH_2), 71.7 (C-1), 75.9 (C-3), 80.25 (C-2), 153.6 (CO_3), 171.1 ($\underline{C}O_2Et$), 172.2 ($\underline{C}O_2Me$); IR ($CDCl_3$) 3503.7, 2958.2, 1810.3, 1733.6, 1038.4 cm^{-1}; Ms m/z (CI/isobutane) 288 (M^+), 258, 171, 112, 91; HRMS calculated for $C_{12}H_{16}O_8$ 288.0191, found 288.0192.

Ethyl 1α-(hydroxy)-2β,3β-(dihydroxycarbonate)-cyclohexane-6β-carboxylate-4α-carboxylamide (10c): Ammonia (2.50 mL, 0.5 M solution in 1,4 dioxane) was added to **(4_{endo})** (0.05 g, 0.20 mmol) and the resulting solution was stirred under dry argon at room temperature. After 6 hours solvent was removed under vacuum to give pale yellow gum. Purification by chromatography on silica gel (petroleum ether/ethyl acetate gradient 1:3-1:10 v/v) afforded a white solid which was crystallised from dichloromethane/acetone/ethyl acetate (3:2:1) (0.05 g, 91%): ^1H NMR [$(CD_3)_2CO$] δ 1.32 (3 H, t, J = 7.2 Hz, CH_3), 1.99 (1 H, m, $J_{4,5\alpha}$ = 5.3 Hz, $J_{5\alpha,6}$ = 14.8 Hz, $J_{5\beta,5\alpha}$ = 18.0 Hz, H-5α), 2.09 (1 H, ddd, $J_{5\beta,6}$ = 9.8 Hz, $J_{4,5\beta}$ = 10.2 Hz, $J_{5\beta,5\alpha}$ = 18.0 Hz, H-5β), 2.61 (1 H, ddd, $J_{1,6}$ = 5.5, Hz, $J_{5\beta,6}$ = 9.8 Hz, $J_{5\alpha,6}$ = 14.8 Hz, H-6), 3.19 (1 H, q, $J_{3,4}$ = $J_{4,5\alpha}$ = 5.3, Hz, $J_{4,5\beta}$ = 10.2 Hz, H-4), 4.01 (1 H, dd, $J_{1,6}$ = 5.5 Hz, $J_{1,2}$ = 7.3 Hz, H-1), 4.22 (2 H, q, J = 7.2 Hz, OCH_2), 4.71 (1 H, t, $J_{1,2}$ = $J_{2,3}$ = 7.3 Hz, H-2), 5.26 (1 H, dd, $J_{3,4}$ = 5.4 Hz, $J_{2,3}$ = 7.3 Hz, H-3), 6.38 and 7.41 (2 H, bs, $CONH_2$); ^{13}C NMR [$(CD_3)_2CO$] δ 14.4 (CH_3), 26.4 (C-5), 41.75 (C-4), 44.0 (C-6), 61.25 (OCH_2), 72.0 (C-1), 77.65 (C-3), 82.0 (C-2), 154.7 (CO_3), 173.4 ($\underline{C}O_2Et$), 173.8 ($CONH_2$); IR (Nujol) 3498.3, 2991.2, 1878.2, 1756.0, 1658.9, 1453.2, 1105.8 cm^{-1}; MS m/z (CI/isobutane) 274 (MH^+), 268, 248, 230, 184, 140, 90; HRMS calculated for $C_{11}H_{15}NO_5$ (MH^+) 274.0927, found 274.0919.

Ethyl methyl 1α-2β-(dihydroxy)cyclohex-3-ene-4,6β-dicarboxylate (11): Ammonia (3.50 mL, 2.0 M solution in methanol) was added to **(4_{endo})** (0.05 g, 0.20 mmol) and the resulting solution was stirred under dry argon at room temperature. After 2 hours solvent was removed under vacuum and the residue was purified by chromatography on silica gel (petroleum ether/ethyl acetate 1:5 v/v) to give a clear gum (0.04 g, 74%); ^1H NMR ($CDCl_3$) δ 1.30 (3 H, t, J = 7.2 Hz, CH_3), 2.43 (1 H, m, $J_{5\alpha,6}$ = 11.2 Hz, $J_{5\beta,5\alpha}$ = 17.8 Hz, H-5α), 2.71 (1 H, dd, $J_{5\beta,6}$ = $J_{1,6}$ = 5.7 Hz, $J_{5\alpha,6}$ = 11.2 Hz, H-6), 2.81 (1 H, m, $J_{5\beta,3}$ = 0.9 Hz, $J_{5\beta,6}$ = 5.7 Hz, $J_{5\beta,5\alpha}$ = 17.8 Hz, H-5β), 3.89 (1 H, dd, $J_{1,2}$ = 8.1 Hz, $J_{1,6}$ = 5.7 Hz, H-1), 4.22 (2 H, q, J = 7.2 Hz, OCH_2), 4.35 (1 H, ddd, $J_{2,3}$ = 5.6 Hz, $J_{1,2}$ = 8.1 Hz, H-2), 6.79 (1 H, dd, $J_{3,5\beta}$ = 0.9 Hz, $J_{2,3}$ = 5.6 Hz, H-3), 3.70 (3 H, s, $CO_2C\underline{H}_3$); ^{13}C NMR ($CDCl_3$) δ 14.1 (CH_3), 27.6 (C-5), 44.5 (C-6), 52.1 ($CO_2\underline{Me}$), 61.3 (OCH_2), 72.0 (C-2), 73.0 (C-1), 129.0 (C-4), 138.3 (C-3), 166.3 ($\underline{C}O_2Et$), 173.6 ($\underline{C}O_2Me$); IR ($CDCl_3$) 3424.1, 2954.4, 1720.6, 1658.3, 1256.8 cm^{-1}; MS m/z FAB (thioglycerol) 245 (MH^+), 217, 171, 153, 109, 91; HRMS calculated for $C_{11}H_{16}O_6$ 244.0945; found 244.0933.

1α-(Hydroxy)-2β,3β-(dihydroxycarbonate)-6β-ethylcarboxylate-cyclohexyl-4α-amine hydrogenchloride (12): *Route A:* A paste of sodium azide (6.50 g, 0.10 mol) in minimum warm water was added to toluene (40 mL) and the resulting suspension was cooled to 0 °C. 98% Sulphuric acid (50 mL) was added via dropping funnel over a period of 20 minutes while maintaining the mixture at 0 °C. After 45 minutes organic layer containing hydrazoic acid was separated, dried over sodium sulphate and stored in an air tight bottle. Acid **(10a)** (0.05 g, 0.18 mmol) was dissolved in a mixture of toluene (2 mL) and hydrochloric acid (1M, 3 mL) at room temperature. A solution of hydrazoic acid in toluene (3 mL, as prepared above) was

added and the resulting solution was refluxed for 30 h. Removal of solvents under vacuum afforded a pale yellow gum. NMR spectrum of a crude sample showed it contained 15% of the title compound with the rest being staring material. *Route B:* Amide **(10c)** (0.064 g, 0.24 mmol) was added to a solution of [I,I(bistrifluoroacetoxy)iodo]benzene (0.11 g, 0.24 mmol) in acetonitrile (3 mL) and water (3 mL). This solution was stirred at room temperature in dark for 5 days. Reaction was diluted with water (5 mL) and hydrochloric acid (1M, 10 mL) and was extracted with petroleum ether in ethyl acetate (1:9 v/v, 3 x 25 mL). Combined organic layers were dried over sodium sulfate and solvent was removed under vacuum to recover starting material (0.005 g, 8%). Aqueous layer was evaporated to give the title compound as a foam (0.063 g, 92%), ^{1}H NMR [$(CD_3)_2CO/D_2O$ (1:1)] δ 1.65 (3 H, t, J = 7.2 Hz, CH_3), 2.20 (1 H, m, $J_{4,5\alpha}$ = 5.6 Hz, $J_{5\alpha,6}$ = 14.2 Hz, $J_{5\beta,5\alpha}$ = 19.7 Hz, H-5$_\alpha$), 2.61 (1 H, dt, $J_{5\beta,6}$ = 5.4 Hz, $J_{4,5\beta}$ = 14.1 Hz, $J_{5\beta,5\alpha}$ = 19.8 Hz, H-5$_\beta$), 2.90 (1 H, ddd, $J_{5\beta,6}$ = 5.3 Hz, $J_{1,6}$ = 8.6 Hz, $J_{5\alpha,6}$ = 14.0 Hz, H-6), 3.91 (1 H, ddd, $J_{4,5\alpha}$ = 5.6 Hz, $J_{3,4}$ = 8.7 Hz, $J_{4,5\beta}$ = 14.0 Hz, H-4), 4.11 (2 H, m, OCH_2), 4.32 (1 H, dd, $J_{1,2}$ = 7.7 Hz, $J_{1,6}$ = 8.7 Hz, H-1), 4.93 (1 H, dd, $J_{1,2}$ = 7.8 Hz, $J_{2,3}$ = 8.4 Hz, H-2), 5.15 (1 H, dd, $J_{2,3}$ = 8.4 Hz, $J_{3,4}$ = 8.7 Hz, H-3); ^{13}C NMR [$(CD_3)_2CO/D_2O$ (1:1)] δ 13.9 (CH_3), 23.9 (C-5), 42.1 (C-6), 47.7 (C-4), 62.1 (OCH_2), 67.8 (C-1), 76.2 (C-3), 79.4 (C-2), 154.55 (CO_3), 173.3 ($\underline{C}O_2Et$); IR 3498.4, 2965.1, 1767.2, 1654.9, 1456.7, 1089.7 cm^{-1}; MS m/z (CI/ammonia) 246 (MH^+), 203, 185, 155; HRMS calculated for $C_{10}H_{15}NO_6$ (MH^+) 246.2110; found 246.2089.

Ethyl 1α-(acetoxy)-2β,3β-(dihydroxycarbonate)-4α-aectamido-6β-carboxylate-1-cyclohexanol (13): Pyridine (2 mL) was added to a stirred solution of **(12)** (0.05 g, 0.18 mmol) in acetic anhydride (2 mL) maintained at 0 °C and under an atmosphere of dry argon. The resulting solution was brought to room temperature and was stirred for 6 hours. Evaporation of volatile materials under vacuum and purification by chromatography on silica gel (ethyl acetate) gave a clear oil (0.055 g, 92%), ^{1}H NMR ($CDCl_3$) δ 1.26 (3 H, t, J = 7.2 Hz, CH_3), 2.03-2.11 (8 H, m, H-5β, H-5α, NAc and OAc), 2.88 (1 H, dd, $J_{1,6}$ = $J_{5\beta,6}$ = 6.3 Hz, $J_{5\alpha,6}$ = 15.5 Hz, H-6), 4.15 (2 H, q, J = 7.2 Hz, OCH_2), 4.33 (1 H, ddt, $J_{3,4}$ = $J_{4,5\beta}$ = 7.0 Hz, $J_{4,NH}$ = 7.2 Hz, $J_{4,5\alpha}$ = 12.7 Hz, H-4), 4.87 (1 H, t, $J_{1,2}$ = $J_{2,3}$ = 7.1 Hz, H-2), 4.97 (1 H, t, $J_{2,3}$ = $J_{3,4}$ = 6.7 Hz, H-3), 5.49 (1 H, dd, $J_{1,6}$ = 6.3 Hz, $J_{1,2}$ = 7.1 Hz, H-1), 6.86 (1 H, d, $J_{4,NH}$ = 7.2 Hz, NH) ; ^{13}C NMR ($CDCl_3$) δ 14.0 (CH_3), 20.7 (NAc or OAc), 23.2 (OAc or NAc), 26.4 (C-5), 40.5 (C-6), 46.0 (C-4), 61.7 (OCH_2), 70.2 (C-1), 77.6 (C-2), 77.6 (C-3), 153.5 (CO_3), 169.4 (CO_2Et), 170.8 (N$\underline{C}$OMe or O$\underline{C}$OMe), 170.9 (O$\underline{C}$OMe or N$\underline{C}$OMe); IR ($CDCl_3$) 3386.6, 1820.8, 1735.7, 1654.3, 1375.4 cm^{-1}; MS m/z (CI/ammonia) 330 (MH^+), 264, 221, 176; HRMS calculated for $C_{14}H_{19}NO_8$ 330.1678 (MH^+); found 330.1677.

1α,2β,3β-(Triacetoxy)-4α-acetamido-6β-(acetoxymethyl)-1,2,3-cyclohexanetriol (14): *From (13)* Lithium aluminium hydride (1.0 mL, 1M solution in THF) was added to a solution of **(13)** (0.05 g, 0.15 mmol) in dry THF (3 mL) maintained under an atmosphere of dry argon at room temperature. The grey suspension was stirred for 48 hours, then cooled to 0 °C before addition of few drops of distilled water. Volatile materials were removed under vacuum. The crude product was dissolved in acetic anhydride (4 mL), cooled to 0 °C and pyridine (4 mL) was added under an atmosphere of dry argon. This solution was stirred at room temperature for 6 h. Evaporation of volatile materials under vacuum and purification by chromatography

on silica gel (ethyl acetate) afforded a yellow gum which was crystallised from ethyl acetate/chloroform (7:1) as colourless prisms (0.057 g, 98%). *From (12)* Lithium aluminium hydride (2.5 mL, 1M solution in THF) was added to a solution of **(12)** (0.05 g, 0.15 mmol) in dry THF (7 mL) and pyridine (2 mL) maintained under an atmosphere of dry argon at room temperature. The solution was stirred for 48 hours, then cooled to 0 °C before addition of few drops of distilled water. Volatile materials were removed under vacuum. The crude product was dissolved in acetic anhydride (5 mL), cooled to 0 °C and pyridine (5 mL) was added under an atmosphere of dry argon. This solution was stirred at room temperature for 6 h. Evaporation of volatile materials under vacuum and purification by chromatography on silica gel (ethyl acetate) afforded a yellow gum which was crystallised from ethyl acetate/chloroform (7:1) as colourless prisms (0.051 g, 88%), mp 125-126 °C (Lit.[6] 123-125 °C), (Found, C, 52.73; H, 6.52; N 3.54. $C_{17}H_{25}NO_9$ requires C, 52.71; H, 6.46; N 3.62), ^{1}H NMR ($CDCl_3$) δ 1.85 (1 H, dt, $J_{4,5\beta}$ = 4.6 Hz, $J_{5\beta,6}$ = 9.5 Hz, $J_{5\beta,5\alpha}$ = 15.0 Hz, H-5β), 1.97 (2 H, m, H-5α and H-6), 2.01 (3 H, s, CH_3CO), 2.02 (3 H, s, CH_3CO), 2.05 (3 H, s, CH_3CO), 2.07 (3 H, s, CH_3CO) and 2.11 (3 H, s, CH_3CO), 4.06-4.14 (2 H, dm, OCH_2), 4.28 (1 H, m, $J_{4,5\beta}$ = 4.6 Hz, $J_{3,4}$ = 5.7 Hz, $J_{4,NH}$ = 6.7 Hz, $J_{4,5\alpha}$ = 7.4 Hz, H-4), 5.14 (1 H, dd, $J_{1,6}$ = 7.8 Hz, $J_{1,2}$ = 8.4 Hz, H-1), 5.17 (1 H, dd, $J_{2,3}$ = 5.3 Hz $J_{1,2}$ = 8.3 Hz, H-2), 5.27 (1 H, dd, $J_{2,3}$ = 5.3 Hz, $J_{3,4}$ = 5.7 Hz, H-3), 6.09 (1H, d, $J_{4,NH}$ = 6.7 Hz, NH); ^{13}C NMR ($CDCl_3$) δ 20.65-20.85 (4 x OAc), 23.2 (NAc), 27.7 (C-5), 36.2 (C-6), 46.3 (C-4), 63.8 (OCH_2), 69.4 (C-2), 70.1 (C-3), 70.5 (C-1), 169.7-170.05 (4 x CH_3CO), 170.75 (NAc); IR ($CDCl_3$) 3355.2, 2935.1, 1747.4, 1664.9, 1240.4 cm^{-1}; M/S m/z EI 388 (MH^+), 387 (M^+), 355, 296, 222, 207; HRMS calculated for $C_{17}H_{25}NO_9$ 387.1529, found 387.1501.

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