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Synthesis of a 5-Methylene Analogue of 5-Enolpyruvylshikimic Acid

Malcolm M. Campbell*, Hélèna S. Rabiasz, Malcolm Sainsbury*, Philip A. Searle
School of Chemistry, University of Bath, Claverton Down, Bath BA2 7AY, U.K.
and
Gareth M. Davies
ICI Pharmaceuticals, Mereside, Alderley Park, Macclesfield, Cheshire SK10 4TG, U.K.

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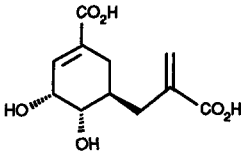
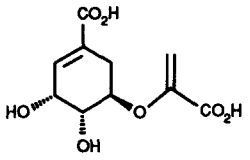
Abstract: The synthesis of (±)-3-(1-carboxy-3α,4α-dihydroxycyclohex-1-en-5β-yl)-2-methylidenepropionic acid, a methylene analogue of 5-enolpyruvylshikimic acid, from methyl 3α,4α-isopropylidene-5β-iodomethylcyclohex-1-ene-1-carboxylate is described. The starting compound is obtained from (±)-methyl homogabaculate. In addition, both enantiomers of methyl homogabacuate have been synthesised from a Diels-Alder cycloaddition of 1-^{t}butoxycarbonyl-1,2-dihydropyridine and the N-acryloyl derivative of Oppolzer's bornane 10,2-sultam.

As a continuation of our studies[1] of potential inhibitors of the enzymes which control key steps in the shikimic acid pathway[2] we now record the synthesis of the methylene analogue (1) of 5-enolpyruvyl shikimic acid (2).



1



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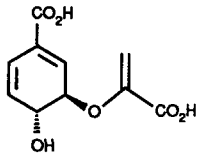


3

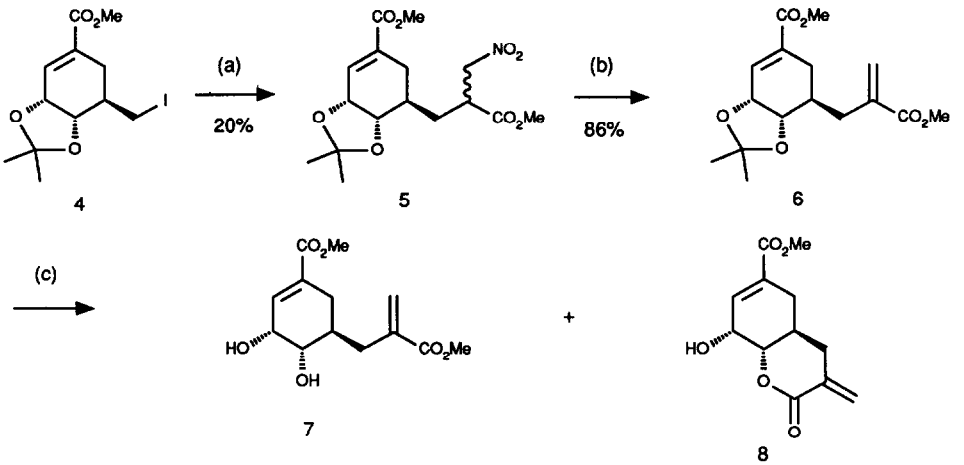
The shikimic acid pathway operates in plants and microorganisms to provide aromatic amino acids essential for growth. A series of steps lead from glucose to chorismic acid (3), after which the pathway branches in several directions leading not only to the aromatic amino acids, but to diverse other compounds. Chorismic acid is formed from 5-enolpyruvylshikimic acid 3-phosphate, a reaction mediated by the enzyme chorismate synthase. Although the mechanism of this step is still controversial,[3] we considered that the enzyme and/or later steps in the sequence may be inhibited by replacing the oxygen atom bonded to C-5 in the natural substrate by a methylene group. The required compound (1) has now been synthesised by reacting the known iodide (4)[1b] with the dianion of methyl 3-nitropropanoate[4] to afford the nitro ester (5). On treatment with DBU this product eliminates nitrous acid furnishing the acetal diester (6) in 86% yield. Removal of the acetal group from this product by reaction with 50% aq. acetic acid gave the diol diester (7)

(47%). A smaller amount of the lactone (8) (15%) was also isolated (Scheme 1). These two compounds can be separated by chromatography and the diol diester (7) hydrolysed to the target molecule, in racemic form.

The formation of the lactone (8) is potentially useful since it provides a means of differentiating between the C-3 and C-4 hydroxyl groups in this series. Phosphorylation of the 3-hydroxyl group would, for example, provide access to the methylene analogue of 5-enolpyruvylshikimic acid 3-phosphate (5ESP-3P) should a closer mimic of the enzyme substrate be required. Indeed, very similar bicyclic lactones have been utilised in the syntheses of 5-EPS-3P both by Ganem[5] and by Bartlett.[6]

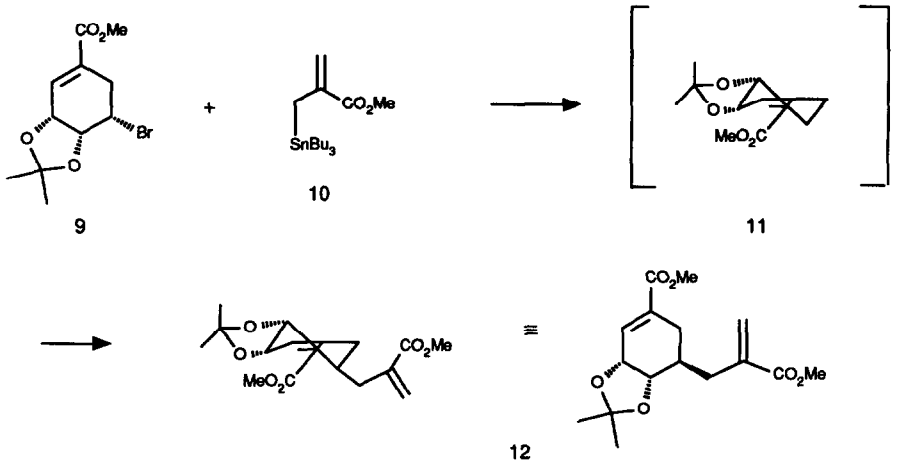
In an alternative approach to the potential enzyme inhibitor (1) a coupling reaction between the 5-bromoshikimic acid derivative (9) and the allyl stannane (10)[7] was investigated. We speculated that in such a process the intermediate shikimate radical (11) would be subject to steric approach control, thereby favouring the product (12) in which the C-5 side chain group occupies a pseudo equatorial position. The advantage of this route, apart from its brevity, is that the starting material is homochiral shikimic acid (13).

In practice the 3,4-acetonide (14) of methyl shikimate reacted with carbon tetrabromide and triphenylphosphine to afford the 5α-bromide (9) as expected, but when this was treated with the allyl stannane and AIBN (see scheme 2) a mixture of the epimeric esters (12) and (15) was formed. The yield in this reaction was 65%; however, the isomers were difficult to separate and only 8.5% of the desired compound (12) was obtained.



Scheme 1 Reagents: (a) $NO_2(CH_2)_2CO_2Me$, 2 equiv. LDA, THF, DMPU, -78 to 0°C, 13 h; (b) DBU, THF, 20°C, 4 h; (c) 50% aq. AcOH, THF, 60°C, 36 h.

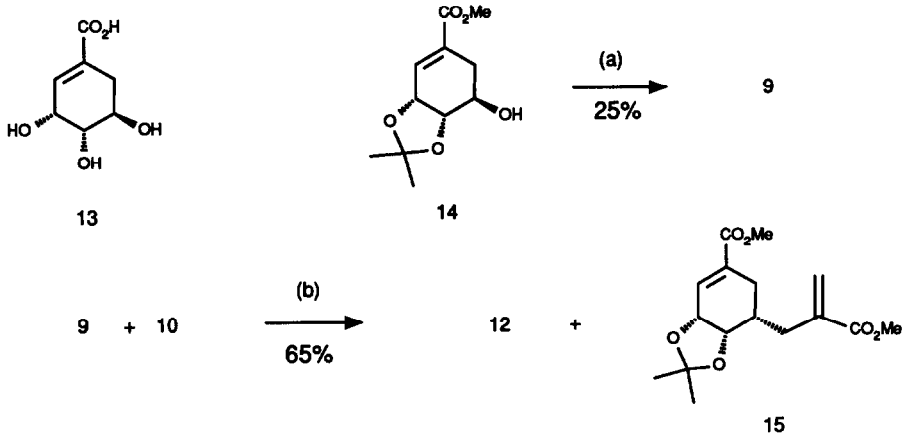
The key step in the preparation of the iodide (4) is a Diels-Alder addition between methyl acrylate and 1-^{t}butoxycarbonyl-1,2-dihydropyridine (16)[8], followed by ring opening of the adduct (17) to yield the N-^{t}butoxycarbonyl derivative of methyl homogabaculate (18)[1b]. This compound is then converted into the sulphonimide (19) and thence into the required iodide as summarised in scheme 3.



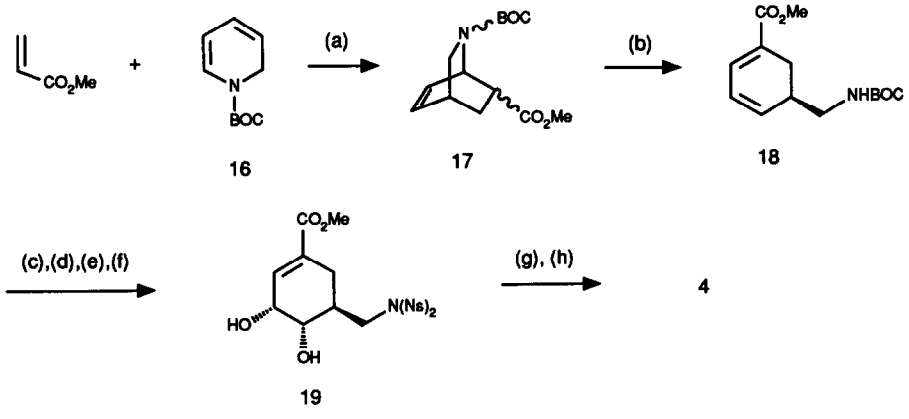
It is well established that high levels of asymmetric induction may be achieved in Diels-Alder reactions, through the use of various chiral auxiliaries[9] attached to the diene or dienophile, or of chiral Lewis acid catalysts. [10] Thus in order to introduce asymmetry into our synthesis we have used an acrylate (20) bearing Oppolzer's bornane 10,2-sultam,[11] however, asymmetric induction in Diels-Alder reactions utilising this type of dieneophile is usually dependent upon the presence of a suitable Lewis acid. We have investigated a range of such catalysts as promoters for the reaction between the chiral acrylate (20) and 1-^{t}butoxycarbonyl-1,2-dihydropyridine (16), but of these only zinc iodide was found to be effective. Even so the product yield was only 11%. We observed that when Lewis acids are added they accelerate the decomposition of the 1,2-dihydropyridine so that, although present in excess, the heterocycle was exhausted before all of the chiral acrylate had reacted.

In contrast to the Lewis acid catalysed reactions, a thermal Diels-Alder cycloaddition of acrylate (20) and the dihydropyridine (16), proceeded cleanly to afford four products: the diastereomeric *endo* (21 and 22), *exo* (23 and 24) adducts in a total yield of 85% (see Scheme 4). The ^{1}H NMR spectrum of the mixture indicated that the *endo:exo* ratio was 10:1 and that the two *endo* isomers and also the two *exo* isomers are formed in about equal amounts. Crystallisation of the mixture of adducts yielded the *endo* isomer (21) as a single diastereomer, and the other *endo* isomer (22) was obtained upon concentration of the mother liquor. Alternatively the two *endo* adducts were separated by chromatography and for each the diastereomeric excess (d.e.) was estimated to be greater than 98%. The ^{1}H NMR spectrum of either of the *endo* adducts showed the resonance of the ^{t}butoxycarbonyl protons to consists of a pair of singlets of unequal intensity, reflecting a dynamic inversion of the amino substituent. On heating the NMR samples to about 60°C the rate of inversion at the nitrogen atom exceeds that of the timescale of the NMR experiment and the signals coalesce to a single peak. The individual adducts were subjected to methanolysis and reacted with potassium carbonate and methanol to remove the auxiliary group. This afforded the corresponding enantiomers (25) and (26), these were then ring opened by treatment with lithium hexamethyldisilazide to afford the antipodal dienes (18) and

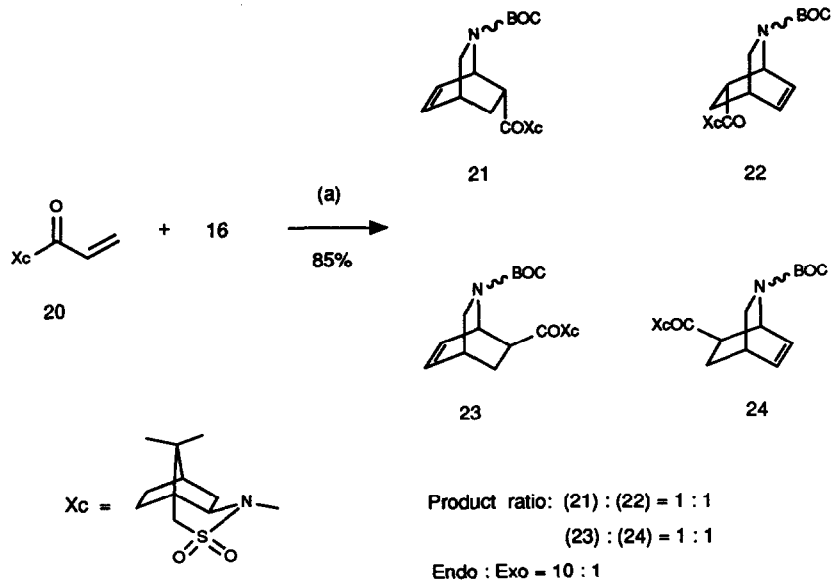
(27)[1b] (see Scheme 5). The specific rotations of (25) and (26) were compared with values for the enantiomers of the methoxycarbonyl derivatives (28) and (29) respectively previously described by Marazano[12]. Very similar rotations were noted (see Figure 1) and on this basis we are able to assign absolute stereochemistries to our compounds. Similarly, the specific rotation of the (-)-diene (27) correlates well with that displayed by the acid (30), an intermediate in the synthesis of natural (-)-gabaculine (31)[13].



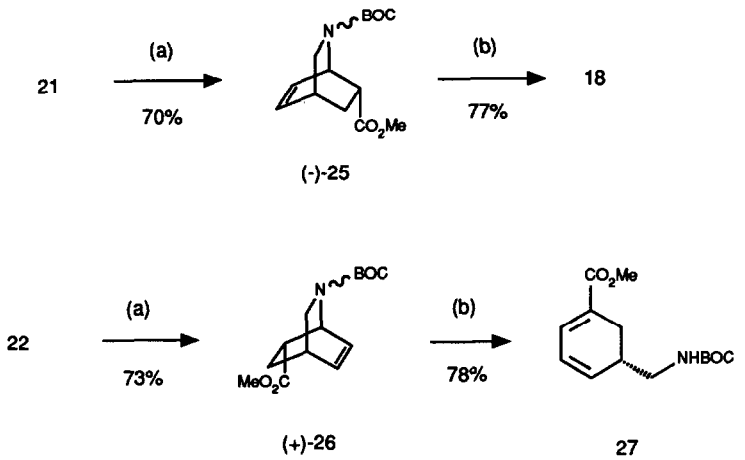
Scheme 2 Reagents: (a) CBr_4, PPh_3, THF, 40° C, 5 h; (b) PhMe, AIBN, Δ.



Scheme 3 Reagents: (a) PhMe, Δ; (b) $(TMS)_2NLi$, THF, -78°C; (c) TFA; (d) NsCl, Et_3N, THF; (e) NaH, NsCl, DMF; (f) OsO_4, NMO, Me_2CO; (g) $Me_2C(OMe)_2$, Me_2CO, p-TSA; (h) KI, 18-crown-6, PhMe, Δ



Scheme 4 Reagents: (a) PhMe, reflux, 2.5 days.



Scheme 5 Reagents: (a) K_2CO_3, MeOH, 20°C, 2.5h; (b) *n*-BuLi, $(TMS)_2NH$, THF, -78 to 20°C, 1h.

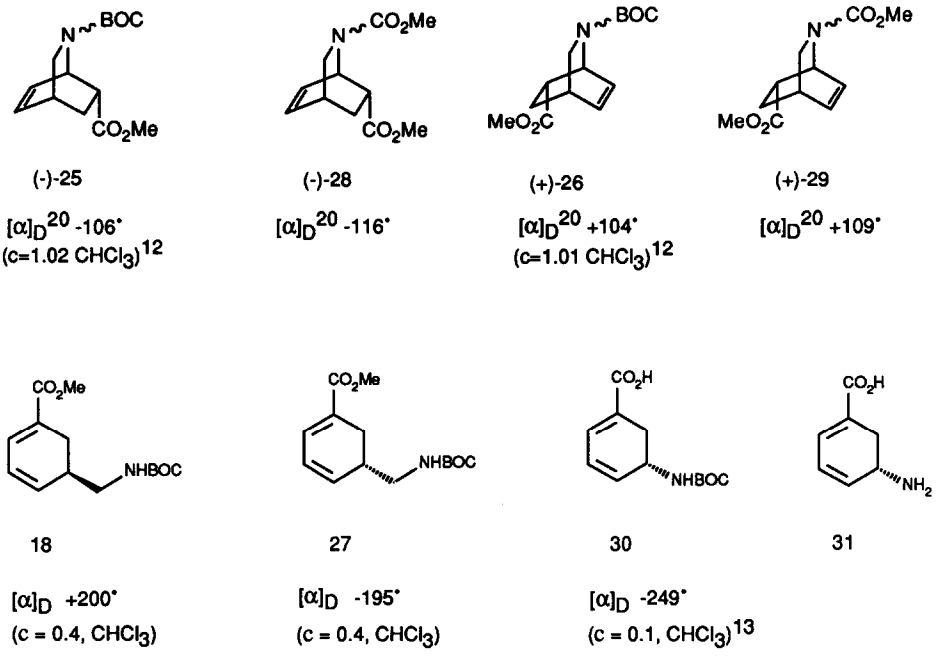


Figure 1

Experimental

All solvents were dried and distilled before use. Petrol refers to petroleum ether boiling in the range 60-80°C and light petrol refers to that boiling in the range 40-60°C. Tetrahydrofuran was pre-dried over sodium wire and then boiled over sodium benzophenone ketyl under a nitrogen atmosphere until anhydrous. This was redistilled immediately prior to use. Osmium tetroxide was used as a solution in ^{t}butanol.

Medium pressure flash column chromatography was routinely employed using Amicon Matrex or Merck 9385 silica gel. All dilute aqueous solutions used were 2 M unless otherwise stated.

Infrared spectra were recorded in the range 4000-600 cm^{-1} using a Perkin-Elmer 1310 spectrophotometer. Samples were prepared as liquid films, Nujol mulls or chloroform solutions, as indicated. ^1H NMR spectra were recorded on a JEOL GX FT 270 (270 MHz) spectrometer although, where indicated, JEOL GX FT 400 (400 MHz) or Varian EM-360 (60 MHz) instruments were used. ^{13}C NMR spectra were recorded on a JEOL GX FT 270 spectrometer at 67.8 MHz. Chemical shifts (δ) are expressed in ppm downfield from internal tetramethylsilane. Mass spectra were recorded using a VG Analytical 7070E instrument with a VG 2000 data

system. Chemical ionisation (C.I.) was employed using isobutane as the reagent gas, although where indicated, ammonia was also used.

Methyl 3α,4α-isopropylidenedioxy-5β-[2-methoxycarbonyl-1-nitroprop-3-yl]-cyclohex-1-ene-1-carboxylate (5)

A solution of diisopropylamine (0.39 cm^3, 2.75 mmol) in THF (4 cm^3) and DMPU (2 cm^3) was cooled to -35°C under a nitrogen atmosphere. A solution of ^{n}butyl lithium in hexanes (1.6 M, 2.75 mmol) was added, the reaction mixture stirred for 10 min, cooled to -78°C and stirred for a further 20 min. Methyl 3-nitropropanoate (0.13 cm^3, 1.25 mmol) was added and the solution stirred for a further 1 h. A solution of the iodide (4) (200 mg, 0.57 mmol) in THF (1 cm^3) and DMPU (0.5 cm^3) was added dropwise via a cannula. After stirring at -78°C for 5 h, the solution was allowed to warm to 0°C and stirred for a further 8 h. The reaction mixture was poured into saturated aqueous ammonium chloride solution (2 cm^3), diluted with water (10 cm^3) and extracted with ethyl acetate (3 x 30 cm^3). The combined extracts were dried ($MgSO_4$) and concentrated under reduced pressure. Column chromatography (petrol-ethyl acetate 17:3 then 7:3) yielded starting material (4) (120 mg, 60%) and the title compound as a yellow oil (40 mg, 20%): R_F 0.33 (petrol-ethyl acetate 7:3); $\nu_{max}(CHCl_3)$ 1735 (C=O), 1715 (C=O) cm^{-1}; m/z (C.I.) 358 (MH^+, 31%), 342 (M^+-CH_3, 100).

Methyl 3α,4α-isopropylidenedioxy-5β-[2-methoxycarbonylprop-1-en-3-yl]-cyclohex-1-ene-1-carboxylate (6)

(a) A solution of the nitro compound (5) (40 mg, 0.11 mmol) in THF (2 cm^3) was treated with 1,8-diazabicyclo[5.4.0]undec-7-ene (0.20 cm^3, 0.13 mmol). The solution was stirred at 20°C for 4 h, filtered and concentrated under reduced pressure. Column chromatography (petrol-ethyl acetate 4:1) yielded the title compound as a colourless oil (30 mg, 86%): R_F 0.58 (petrol-ethyl acetate 7:3); $\nu_{max}(CHCl_3)$ 1710 (C=O) cm^{-1}; $\delta_H(CDCl_3)$ 1.39 (3H, s, Me), 1.43 (3H, s, Me), 1.91 (1H, ddt, J_{gem} 17.5, $J_{6\beta,5}$ 7.0, $J_{6\beta,2}$ 1.6, $J_{6\beta,3}$ 1.6 Hz, 6β-H), 2.11 (2H, m, 5-H, 3′-H), 2.53 (1H, dd m, J_{gem} 17.5, $J_{6\alpha,5}$ 4.0 Hz, 6α-H), 2.71 (1H, dd, J_{gem} 17.0, $J_{3',5}$ 9.0 Hz, 3′-H), 3.75 (3H, s, Me), 3.76 (3H, s, Me), 3.98 (1H, dd, $J_{4,5}$ 7.0, $J_{4,3}$ 5.5 Hz, 4-H), 4.59 (1H, m, 3-H), 5.56 (1H, br s, 1′-H), 6.24 (1H, d, $J_{1',3'}$ 1.3 Hz, 1′-H), 6.88 (1H, m, 2-H); $\delta_C(CDCl_3)$ 25.8 (C-6), 26.2 (Me), 28.1 (Me), 33.8 (C-3′), 35.6 (C-5), 51.9 (OMe), 52.0 (OMe), 71.1 (C-4), 77.2 (C-3), 109.1 (CMe_2), 127.0 (C-1′), 132.5 (C-1), 134.0 (C-2), 138.2 (C-2′), 167.0 (C=O), 167.3 (C=O); [Found: m/z M^+, 410.1429 $C_{16}H_{22}O_6$ requires 410.1414).

(b) Alternative preparation of (6) from methyl shikimate:

(a) Methyl 3α,4α-isopropylidenedioxy-5β-hydroxycyclohex-1-ene-1-carboxylate (14) was obtained from methyl shikimate, through heating at reflux with 2,2-dimethoxypropane in acetone containing a catalytic amount of 4-toluenesulphonic acid. The compound was isolated as a colourless oil in 70% yield. This product (4.3g, 0.019mol) in dry THF (150cm^3) was treated with carbon tetrabromide (18.8g, 0.056mol) and heated almost to reflux. Triphenylphosphine (19.4g, 0.074mmol) was then slowly introduced and the suspension which formed was then heated to boiling for 2h. Then the reaction mixture was cooled and the solvent removed under reduced pressure to leave a dark brown oil. This was chromatographed, eluting with

petrol:ethyl acetate 9:1 - 4:1 mixtures, to afford methyl 3α,4α-isopropylidenedioxy-5α-bromocyclohex-1-ene-1-carboxylate (9) as a pale yellow oil, which slowly crystallised as needles, m.p. 103-5° C (petrol) (3.8g, 70%): $\delta_H(CDCl_3)$ 1.39 (3H, s, CCH_3) and 1.44 (3H, s, CCH_3), 2.86(1H, dddd J_{gem} 16.85, $J_{6\beta,5}$ 11.0, 2.75, 2.75, H-6β), 2.94(1H, dd J_{gem} 16.85, $J_{6\alpha,5}$ 5.55Hz, H-6α), 3.78(3H, s, CO_2Me), 4.18(1H, ddd $J_{5,6\beta}$ 11.0, $J_{5,6\alpha}$ 5.55, 2.0 Hz H-5), 4.58(1H, dm J 5.3 Hz, H-4), 4.73(1H, m, H-3), 6.77(1H, dm J 2.3Hz, H-2)[Found: C,45.5; H, 5.2; $C_{11}H_{15}O_4Br$ requires: C, 45.4; H, 5.2%]

To methyl 3α,4α-isopropylidenedioxy-5α-bromocyclohex-1-ene-1-carboxylate (930mg, 3.19mmol) in toluene (120 cm^3) was added methyl 2-methylidene-3-tributylstannylpropionate (10) (2.5g, 5.56mmol) and AIBN (*ca* 0.1g). The solution was heated to reflux for 3h under an atmosphere of nitrogen, the solvent was then removed and the residue chromatographed, eluting with petrol:ethyl acetate 9:1. The first fraction was a yellow oil (61.4mg) containing the title compound and the 5β-epimer in the ratio 5:8. Further elution afforded the same two diastereomers again as a yellow oil (497mg), but now in the ratio 10:3. A third fraction gave the pure title compound as a colourless oil (87mg) [physical data as for (a) above].

Methyl 3α,4α-hydroxy-5β-[2-methoxycarbonylprop-1-en-3-yl]cyclohex-1-ene-1-carboxylate (7)

A solution of the acetonide (6) (30 mg, 0.097 mmol) in THF (1 cm^3), glacial acetic acid (1 cm^3) and water (1 cm^3) was heated to 50-60°C under a nitrogen atmosphere for 36 h. The reaction mixture was poured into saturated aqueous sodium bicarbonate solution (3 cm^3) and extracted with dichloromethane (2 x 5 cm^3). The combined extracts were dried (Na_2SO_4) and concentrated under reduced pressure. Column chromatography (petrol-ethyl acetate 1:1 to 3:7) yielded the title compound as a colourless solid (12 mg, 47%): R_F 0.40 (petrol-ethyl acetate 1:3); $\nu_{max}(CHCl_3)$ 3520 (OH), 3400 (OH), 1710 (C=O), 1660 (C=C), 1630 (C=C) cm^{-1}; $\delta_H(CDCl_3)$ 1.93 (1H, dddd, J_{gem} 18.0, $J_{6\beta,5}$ 9.0, $J_{6\beta,2}$ 2.1, $J_{6\beta,3}$ 1.3 Hz, 6β-H), 2.15 (1H, m, 5-H), 2.29 (1H, dd, J_{gem} 13.7, $J_{3',5}$ 8.1 Hz, 3'-H), 2.54 (1H, br dd, J_{gem} 18.0, $J_{6\alpha,5}$ 5.0 Hz, 6α-H), 2.72 (1H, ddd, J_{gem} 13.7, $J_{3',5}$ 4.0, $J_{3',1'}$ 0.9 Hz, 3'-H), 2.82 (1H, br s, OH), 3.39 (1H, br s, OH), 3.50 (1H, dd, $J_{4,5}$ 10.0, $J_{4,3}$ 4.2 Hz, 4-H), 3.74 (3H, s, Me), 3.77 (3H, s, Me), 4.32 (1H, br t, $J_{3,4}$ 4.2, $J_{3,2}$ 4.2 Hz, 3-H), 5.68 (1H, d, $J_{1',3'}$ 0.9 Hz, 1'-H), 6.29 (1H, d, J 1.3 Hz, 1'-H), 6.87 (1H, ddd, $J_{2,3}$ 4.2, $J_{2,6\beta}$ 2.1, $J_{2,6\alpha}$ 1.0 Hz, 2-H); $\delta_C(CDCl_3)$ 28.5 (C-6), 33.5 (C-3'), 34.5 (C-5), 52.0 (OMe), 52.2 (OMe), 65.8 (C-4), 71.6 (C-3), 128.2 (C-1'), 132.6 (C-1), 135.9 (C-2), 137.6 (C-2'), 167.1 (C=O), 168.2 (C=O); m/z (C.I., NH_3) 288 (MNH_4^+, 82%), 253 (100). Earlier fractions contained the lactone (8) as a colourless solid (3.5 mg, 15%): R_F 0.49 (petrol-ethyl acetate 1:3); $\nu_{max}(CHCl_3)$ 3550 (OH), 3350 (OH), 1710 (C=O), 1655 (C=C), 1635 (C=C) cm^{-1}; $\delta_H(CDCl_3)$ 2.01 (1H, dddd, J_{gem} 18.0, $J_{6\beta,5}$ 9.5, $J_{6\beta,2}$ 2.5, $J_{6\beta,3}$ 1.2 Hz, 6β-H), 2.26-2.48 (2H, m, 5-H, 3'-H), 2.62 (1H, d, $J_{OH,3}$ 3.3 Hz, 3-OH), 2.79-2.92 (2H, m, 3'-H, 6α-H), 3.78 (3H, s, OMe), 4.23 (1H, dd, $J_{4,5}$ 11.0, $J_{4,3}$ 3.8 Hz, 4-H), 4.50 (1H, m, 3-H), 5.66 (1H, m, 1'-H), 6.48 (1H, m, 1'-H), 6.95 (1H, dd, $J_{2,3}$ 5.5, $J_{2,6\beta}$ 2.5 Hz, 2-H); $\delta_C(CDCl_3)$ 27.8 (C-5), 30.7 (C-6), 34.2 (C-3'), 52.2 (OMe), 63.5 (C-4), 82.3 (C-3), 129.1 (C-1'), 132.9 (C-1), 133.0 (C-2'), 134.2 (C-2), 164.8 (C=O), 166.4 (C=O); m/z (C.I., NH_3) 256 (MNH_4^+, 100%).

3α,4α-Dihydroxy-5β-[2-carboxyprop-1-en-3-yl]cyclohex-1-ene-1-carboxylic acid (1)

A solution of the diester (7) (11 mg, 0.041 mmol) in water (1 cm^3) and THF (0.5 cm^3) was treated with

aqueous sodium hydroxide solution (1.0 M, 0.09 cm^3) and stirred at 20°C under a nitrogen atmosphere for 4 h. The solution was acidified by adding Amberlite IRA-120 (+) ion exchange resin and filtered. The resin was washed with water and the combined filtrate and washings were lyophilised to yield the title compound as a cream solid (8.5 mg, 86%): R_F 0.47 (ethyl acetate - acetic acid 98:2); $\delta_H(D_2O)$ 1.93 (1H, dd m, J_{gem} 18.0, $J_{6\beta,5}$ 7.0 Hz, 6β-H), 2.14 (2H, m, 3′-H, 5-H), 2.42 (1H, dd m, J_{gem} 18.0, $J_{6\beta,5}$ 3.5 Hz, 6α-H), 2.68 (1H, dd, J_{gem} 19.0, $J_{3',5}$ 9.0 Hz, 3′-H), 3.66 (1H, dd, $J_{4,5}$ 8.2, $J_{4,3}$ 4.0 Hz, 4-H), 4.32 (1H, dd, $J_{3,4}$ 4.0, $J_{2,3}$ 4.0 Hz, 3-H), 5.74 (1H, s, 1′-H), 6.24 (1H, s, 1′-H), 6.80 (1H, m, 2-H); $\delta_C(D_2O)$ 26.9 (C-3′), 32.9 (C-6), 33.6 (C-5), 65.1 (C-4), 71.2 (C-3), 128.0 (C-1′), 131.5 (C-1), 136.5 (C-2), 137.7 (C-2′), 171.0 (C=O); m/z (-ve FAB) 241 ($M-H^-$, 5%).

Thermal Diels-Alder Reaction Using Chiral Auxiliary

A solution of the dihydropyridine (16) (5.38 g, 29.7 mmol) and the N-acryloyl sultam (20) (4.00 g, 14.9 mmol) in toluene (100 cm^3) was heated to reflux, under a nitrogen atmosphere, for 2.5 days. Toluene was evaporated under reduced pressure to leave a yellow oil. Column chromatography (petrol-ethyl acetate 4:1 then 7:3) yielded the mixed adducts (5.72 g, 85%) as a colourless solid. The ^1H NMR spectrum indicated two *endo* adducts as the major products, in 1:1 ratio, and a minor amount of the *endo* adducts present, with a *endo:exo* ratio of approximately 10:1. Repeated column chromatography and recrystallisations from petrol-ethyl acetate yielded the pure *endo* adducts:

Endo A (21) (0.96 g, 14%): m.p. 238-240°C (dec.) (from petrol-ethyl acetate); R_F 0.55 (petrol-ethyl acetate 7:3); (Found: C, 61.4; H, 7.75; N, 6.3. $C_{23}H_{34}N_2SO_5$ requires C, 61.3; H, 7.6; N, 6.2%); $\nu_{max}(CHCl_3)$ 1680 (C=O) cm^{-1}; $\delta_H(CDCl_3)$ 0.96 (3H, s, Me), 1.11 (3H, s, Me), 1.44 and 1.47 (9H, 2 x s, CMe_3), 0.90-1.60 (8H, m, 2 x 8-H, 2 x 3′-H, 2 x 5′-H, 2 x 6′-H), 2.26 (1H, m, 4′-H), 2.77 (1H, m, 4-H), 2.93 (1H, m, 3-H), 3.23 (1H, m, 3-H), 3.45 (2H, m, 2 x 10′-H), 3.60 (1H, m, 7-H), 3.84 (1H, dd, *J* 7.2, 5.2 Hz, 2′-H), 4.89 and 5.04 (1H, 2 x m, 1-H), 6.30-6.60 (2H, m, 5-H, 6-H); m/z (C.I.) 451 (MH^+, 3%), 435 (4), 395 (100), 377 (3), 351 (28).

Endo B (22) (1.04 g, 16%): m.p. 230-232°C (dec.) (from petrol-ethyl acetate); R_F 0.50 (petrol-ethyl acetate 7:3); (Found: C, 61.1; H, 7.7; N, 6.2. $C_{23}H_{34}N_2SO_5$ requires C, 61.3; H, 7.6; N, 6.2%); $\nu_{max}(CHCl_3)$ 1680 (C=O) cm^{-1}; $\delta_H(CDCl_3)$ 0.96 and 0.99 (3H, 2 x s, Me), 1.20 (3H, s, Me), 1.44 and 1.47 (9H, 2 x s, CMe_3), 1.25-2.07 (9H, m, 2 x 8-H, 2 x 3′-H, 4′-H, 2 x 5′-H, 2 x 6′-H), 2.88 (2H, m, 3-H, 4-H), 3.22 (1H, m, 3-H), 3.46 (2H, m, 2 x 10′-H), 3.66 (1H, m, 7-H), 3.83 (1H, m, 2′-H), 4.98 and 5.12 (1H, 2 x m, 1-H), 6.12-6.56 (2H, m, 5-H, 6-H); m/z (C.I.) 451 (MH^+, 7%), 395 (100).

(-)-2-(^{t}Butoxycarbonyl)-7-*endo*-(methoxycarbonyl)-2-azabicyclo[2.2.2]oct-5-ene (-)-(25)

A solution of the *endo* adduct (21) (0.96 g, 2.13 mmol) in methanol (65 cm^3) was treated with potassium carbonate (0.96 g) and stirred at 20°C for 2.5 h. The reaction mixture was poured into water (200 cm^3), saturated brine added (100 cm^3) and extracted with dichloromethane (2 x 200 cm^3). The combined extracts were dried ($MgSO_4$) and concentrated under reduced pressure. Column chromatography (petrol-ethyl acetate 4:1) yielded the title compound as a colourless solid (0.40 g, 70%): $[\alpha]_D^{20}$ -106° (*c* 1.02 in $CHCl_3$), spectral data identical to the racemic compound (25) previously described[1b].

(+)-2-(^{t}Butoxycarbonyl)-7-*endo*-(methoxycarbonyl)-2-azabicyclo[2.2.2]oct-5-ene (+)-(26)

The title compound was prepared from the *endo* adduct (22) using a similar procedure to that detailed above. The product was isolated as a colourless solid (0.45 g, 73%): $[\alpha]_D^{20}$ +104° (*c* 1.01 in $CHCl_3$), spectral data identical to the racemic compound (26) previously described[1b].

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