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SYNTHESIS OF (±)-HOMOGABACULINE AND (±)-HOMOSHIKIMIC ACID

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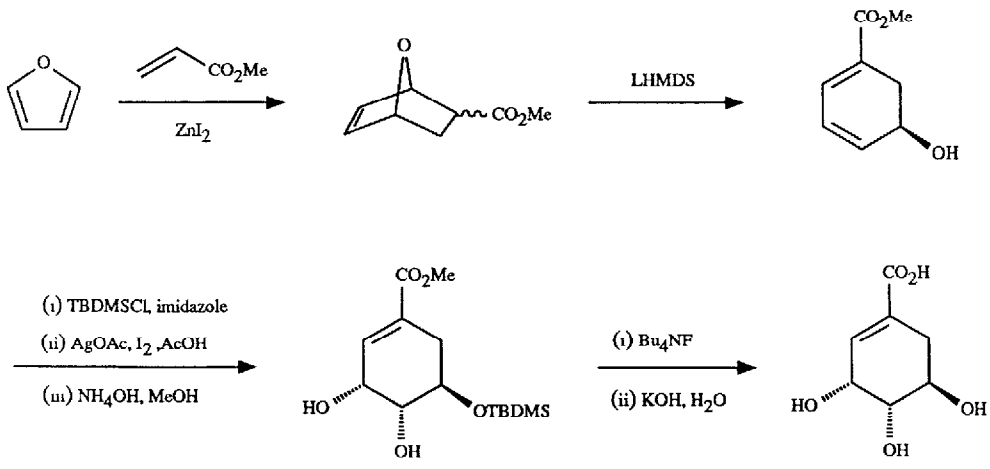
Summary: Syntheses of homogabaculine and homoshikimic acid are described utilising the base mediated ring opening of the cycloadducts of methyl acrylate and *N*-carbamoyl-1,2-dihydropyridines.

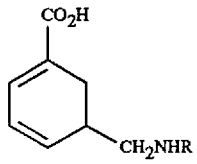
We have developed a brief and stereocontrolled synthesis of shikimic acid (1) involving a Diels Alder reaction between furan and methyl acrylate, followed by ring opening of the adducts with lithium hexamethyldisilazide (LHMDS) (scheme 1)[1] (for chiral routes based upon this strategy and intermediates see references 2a and 2b).



(1)

Scheme 1 Synthesis of shikimic acid

We now describe a further cycloaddition sequence leading to the homologue (2, R=H) of gabaculine (3) and the homologue (4) of shikimic acid (1) as potential enzyme substrates.



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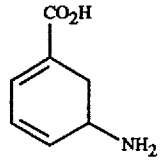

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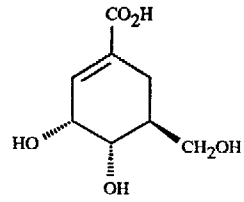
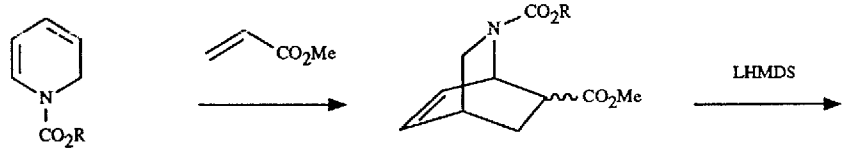
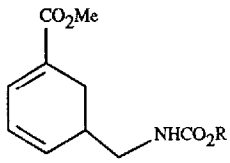


(4)

It is known[3] that the 1,2-dihydropyridine (5, R=Me) reacts with methyl acrylate to form the mixed *exo* and *endo* adducts (6, R=Me), in the ratio 7:5. The ^{t}butyl adducts (6, R=^{t}Bu) are similarly produced from the 1,2-dihydropyridine (5, R=^{t}Bu)[4], but now in the ratio 1:1. When treated with LHMDS at -78°C in THF the adducts (6, R=Me) afford the methyl 5,6-dihydrobenzoate (7), which can be hydrolysed with 2M sodium hydroxide in refluxing THF/H_2O to give homogabaculine (2, R=H) in 37% yield together with its carbamoyl derivative (2, R=CO_2Me), in 56% yield. Extended reaction periods tend to diminish the yield of products, while hydrolysis of the ester at 20°C gives only the carbamoyl compound (2, R=CO_2Me), in 65% yield.



(5) (6)



(7) (2)

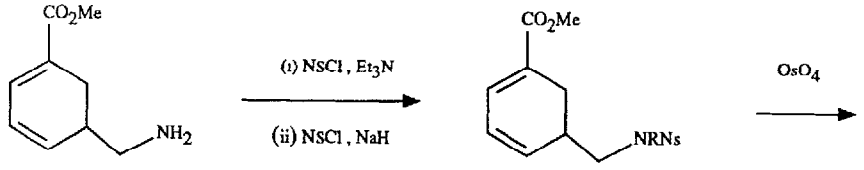
Methyl homogabaculine is formed directly from the adduct (6, R=^{t}Bu) by treatment with trifluoroacetic acid in 90% yield, and this compound when reacted with 4-nitrobenzenesulphonyl chloride (NsCl) in the presence of triethylamine affords the sulphonamide (8). Further treatment of this product with sodium hydride and 4-nitrobenzenesulphonyl chloride forms the disulphonimide (9)[5]. Overall yield for the two steps is 42%.

Osmylation[6] of the disulphonimide gives a mixture of the three diols (10), (11), and (12) in 16, 8,and 10% yields respectively, whereas a Prévost hydroxyacetoxylation reaction[1] affords two hydroxyacetates as an inseparable mixture, which on hydrolysis with aqueous ammonium hydroxide/methanol produces the diol

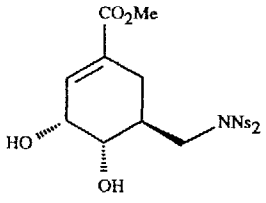
(10)[7] in 35% overall yield. This compound may then be protected, prior to treatment with potassium iodide in DMF at 130°C. This reaction leads to a mixture of the iodide (13), the diene (14), and the formate ester (15) in 23%, 9%, and 33% yields respectively, whereas treatment of the acetonide with potassium iodide in refluxing toluene containing 18-crown-6 gives only the iodide in 63% yield.

Hydrolysis of the formate ester to homoshikimic acid is accomplished in two steps: first, treatment with Amberlyst-15 acid ion exchange resin in methanol, followed by glacial acetic acid in aqueous THF at 60°C affords the triol (16) in 63% yield. This is reacted with 2M NaOH to give homoshikimic acid (4) in quantitative yield.

Alternatively the triol (16) can be prepared by treatment of the iodide (13) with sodium acetate in DMF at 110°C to give the acetate (17) (63%), hydrolysis to the alcohol (18) (aqueous ammonia, methanol, 81%) and removal of the acetonide group (acetic acid, aqueous THF, 55°C, 70%).



(8) R = H
(9) R = Ns



(10)

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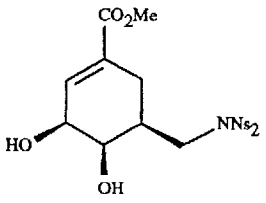

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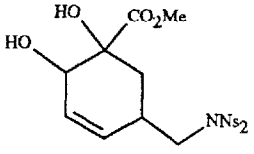

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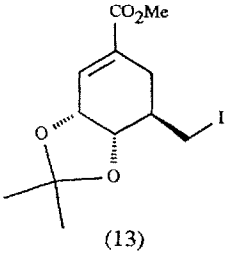

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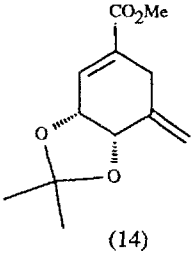

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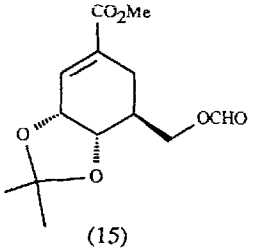

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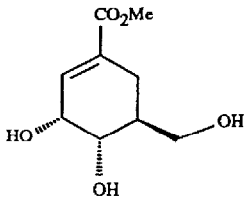
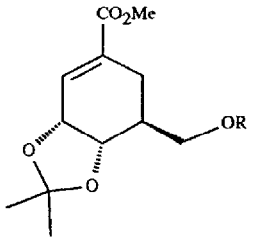


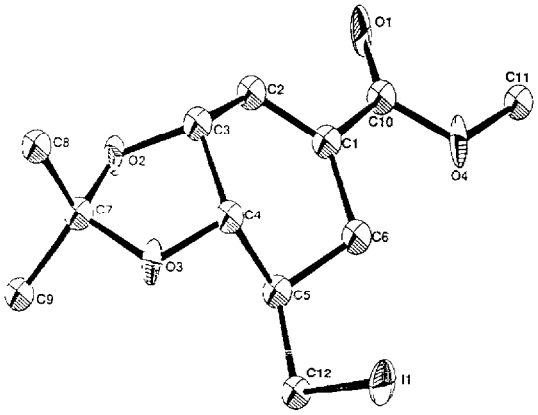
(16)



(17) R = Ac

(18) R = H

All the numbered compounds described are fully characterised. A single X-ray crystallographic determination of the iodide (13) has been carried out. Full data have been deposited at the Cambridge data bank. Relevant details are as follows:
the compound crystallised (from light petroleum ether) in space group P1 with a=5.660(2), b=8.252(4), c=15.014(3)A°, α=97.32(3), β=95.59(2), γ=94.34(3)°, U=689A^{03}, and D_c=1.687gcm^3 for Z=2 at room temperature. The structure was solved by direct methods using 1704 unique reflections with I ≥ 3σI, and refined by full matrix least squares to final residuals of R=R_w=7.87% for unit weights.



ORTEP diagram of (13).

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7. Note that the stereochemical outcome of this Prévost reaction is not that expected from a 3,4-α-epiiodonium intermediate generated through steric approach control. A possible alternative mechanism which accounts for the observed stereochemistry of the product has been discussed previously: see reference 1.

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