Tetrahedron Letters, Vol. 33, No. 22, pp. 3181-3184, 1992
Printed in Great Britain

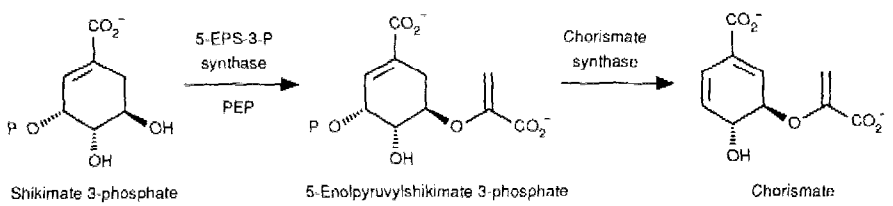
0040-4039/92 $5.00 + .00
Pergamon Press Ltd

SYNTHESIS OF METHYL (-)-HOMOGABACULINATE AND A CARBA ANALOGUE OF 5-ENOLPYRUVYLSHIKIMIC ACID

Malcolm M. Campbell*, 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.

Summary: The synthesis of (±)-3-[1 carboxy-3α,4α-dihydroxycyclohex-1-en-5β-yl]-2-methylenepropionic acid, a carba analogue of 5-enolpyruvylshikimic acid from methyl (±)-homogabaculinate is described. In addition, both enantiomers of methyl homogabaculinate have been obtained from the Diels Alder reaction of 1-*tert*-butoxy-carbonyl-1,2-dihydropyridine and the *N*-acryloyl derivative of Oppolzer's bornane 10,2-sultam.

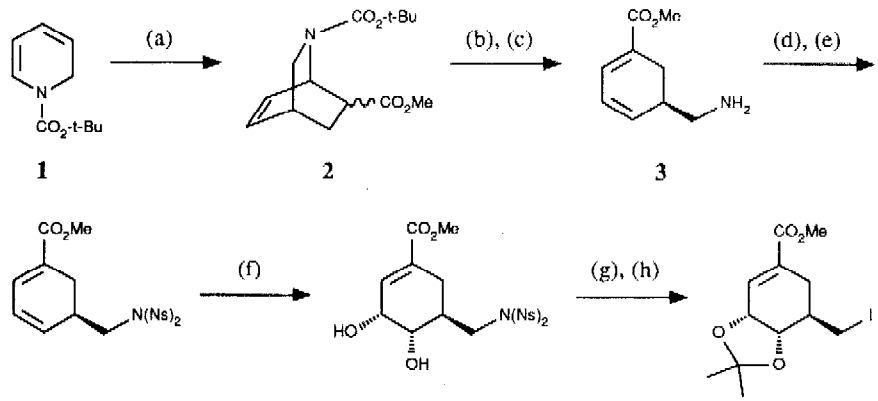
The shikimic acid pathway is of major biosynthetic importance leading from glucose to the aromatic amino acids. At a comparatively late stage in the sequence shikimic acid 3-phosphate is converted into 5-enolpyruvylshikimic acid 3-phosphate and thence into chorismic acid (**scheme 1**).[1] From chorismic acid the pathway branches, leading not only to the aromatic amino acids, but also to a diverse group of compounds including the K group of vitamins.



Scheme 1 Biosynthetic relationship of shikimic acid and chorismic acid

There is much interest in the possibility of selectively inhibiting the enzymes which regulate various steps along the pathway. We have described the syntheses of 6α-fluoroshikimic acid and a homologue of shikimic acid both[2] of which may act as structural mimics of shikimic acid itself.

We now report the synthesis of the carba analogue of 5-enolpyruvylshikimic acid from methyl homogabaculinate and illustrate how methyl homogabaculinate can be obtained in homochiral form. Previously we have described[3] the synthesis of methyl (±)-homo-gabaculinate **3** from the Diels Alder adduct **2** of methyl acrylate and 1-*tert*-butoxycarbonyl-1,2-dihydropyridine **1** and the conversion to the iodide **4** (**scheme 2**).



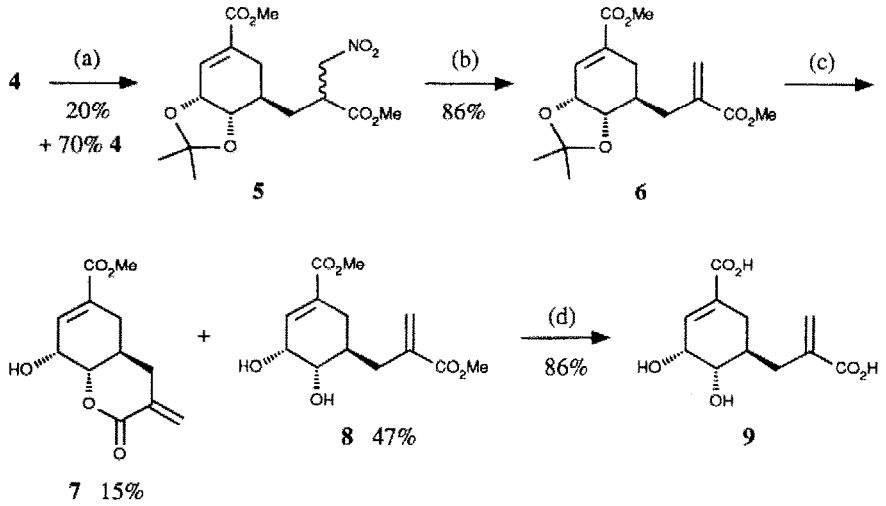
Scheme 2 Reagents: (a) CH_2CHCO_2Me, PhMe, Δ; (b) $(TMS)_2NLi$, THF, -78°C; (c) TFA; (d) NsCl, Et_3N, THF; (e) NsCl, NaH, DMF; (f) OsO_4, NMO, Me_2CO; (g) $Me_2C(OMe)_2$, Me_2CO, *p*-TSA; (h) KI, 18-crown-6, PhMe, Δ.

In the new work the iodide **4** was reacted with the dianion of methyl 3-nitropropanoate[4] to give the nitroester **5** and this, on reaction with DBU, yielded the acetal **6**. Hydrolysis of this product with aqueous acetic acid afforded both the diol **7** and the lactone **8**. The two compounds could be separated by chromatography, and the diol hydrolysed to the carba analogue of 5-enolpyruvylshikimic acid **9**. The lactone is of importance since it provides the opportunity to differentiate between the C-3 and C-4 hydroxyl groups of the parent acid. This could be used in a preparation of the corresponding 3-phosphate, should a closer mimic of the enzymic substrate be required.

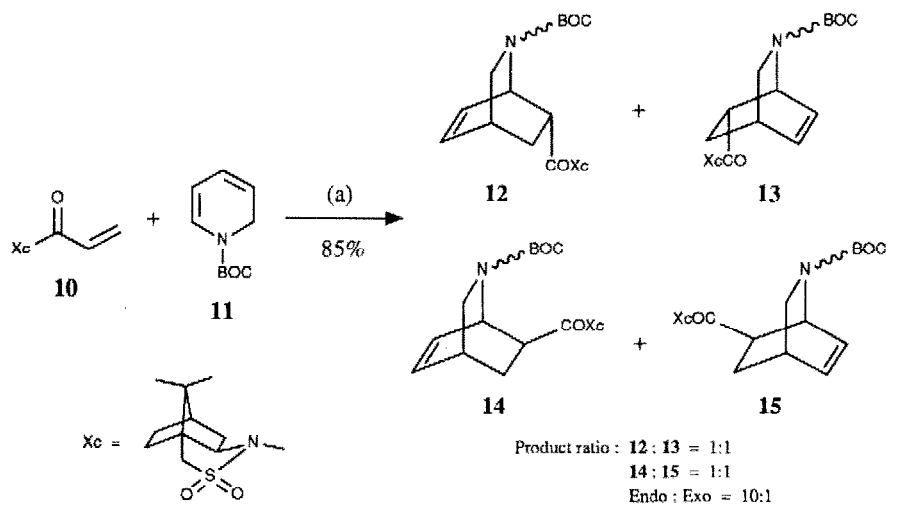
High levels of asymmetric induction in asymmetric Diels Alder reactions frequently require the use of a Lewis acid catalyst. Unfortunately however, attempts to promote an enantioselective addition between the chiral acrylate **10**[5] and 1-*tert*-butoxycarbonyl-1,2-dihydropyridine **11** with a variety of such catalysts failed. A thermal version of the reaction, in the absence of a catalyst, gave four products, the diastereomeric *endo* (**12** and **13**) and *exo* (**14** and **15**) adducts (ratio *endo*:*exo* 10:1). In each case the diastereomers were present almost equal amounts. In addition, the nitrogen substituent in each isomer had two possible orientations, *syn* or *anti* to the C-5 double bond and on heating the sample the ^1H NMR spectra of each adduct simplified as a result of increasing rates of inversion at the nitrogen atom centres. The diastereomeric *endo* compounds were separated by column chromatography and recrystallisation afforded diastereomerically pure materials (d.e. > 98% by ^1H NMR).

Removal of the chiral auxiliary from the *endo adducts* **12** and **13** afforded both of the pure enantiomers (-)-**16** and (+)-**16**. Their absolute configurations were assigned by comparison of their optical rotations with those of the known compounds (-)-**17** and (+)-**17**.[6] Ring opening of each of the enantiomers then

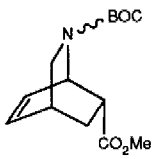
gave the antipodal dienes (+)-**18** and (-)-**18**. The laevorotation of the diene (-)-**18** correlates well with that displayed by the acid (-)-**19**, which was an intermediate in the synthesis of natural (-)-gabaculine.[7]



Scheme 3 Reagents: (a) $NO_2(CH_2)_2CO_2Me$, LDA, THF, DMPU, -78 to 20°C; (b) DBU, THF; (c) aq. AcOH, THF, 55°C; (d) NaOH, H_2O.



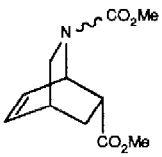
Scheme 4 Conditions: (a) PhMe, Δ.



(-)-**16**

$[\alpha]_D$ -106°

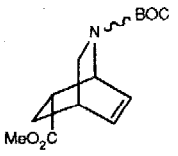
(c = 1.02, $CHCl_3$)



(-)-**17**

$[\alpha]_D$ -110°

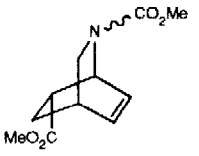
(Ref.[6])



(+)-**16**

$[\alpha]_D$ +104°

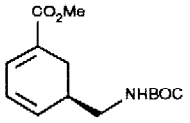
(c = 1.01, $CHCl_3$)



(+)-**17**

$[\alpha]_D$ +109°

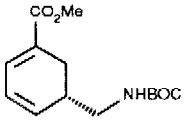
(Ref.[6])



(+)-**18**

[α] +200°

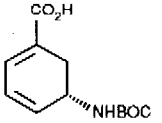
(c = 0.4, $CHCl_3$)



(-)-**18**

[α] -195°

(c = 0.4, $CHCl_3$)



(-)-**19**

[α] -249°

(c = 0.1, $CHCl_3$) ref.[7]

Acknowledgements

We are grateful to the SERC for a Quota studentship to P.A.S. and to ICI Pharmaceuticals for supplementary funding.

References

1. (a) Haslam, E.; *The Shikimate Pathway*, Butterworths, London, 1974.
   (b) Torssell, K.B.G.; *Natural Product Chemistry,* Wiley, Chichester, 1983.
   (c) Ganem, B,; *Tetrahedron,* 1978, **34**, 3353-3383.
2. Bowles, S.A.; Campbell, M.M.; Sainsbury, M. and Davies, G.M.; *Tetrahedron*, 1990, **46**, 3981-3992
3. Campbell, M.M.; Mahon, M.F.; Sainsbury, M.; Searle, P.A. and Davies, G.M.; *Tetrahedron Letters,* 1991, **32**, 951-954
4. Seebach, D.; Henning, R. and Mukhopadhyay, T.; *Chem. Ber.*, 1982, **115**, 1705-1720.
5. Oppolzer, W.; *Tetrahedron*, 1987, **43**, 1969-2004
6. (a) Mehmandoust, M.; Marazano, C.; Singh, R.; Gillet, B.; Césario, M.; Fourrey J.L. and Das, B.C.; *Tetrahedron Lett.*, 1988, **29**, 4423-4426.
   (b) Marazano, C.; Yannic, S.; Genisson, Y.; Mehmandoust M. and Das, D.C.; *Tetrahedron Lett.*, 1990, **31**, 1995-2004.
7. Bandara, B.M.R.; Birch, A.J. and Kelly, L.F.; *J. Org. Chem.*, 1984, **49**, 2496-2498.

(Received in UK 5 March 1992)