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A GENERAL SYNTHESIS OF 2,6-DIARYL-3,7-DIOXABICYCLO[3.3.0]OCTANE LIGNANS APPLICABLE TO THE SYNTHESIS OF UNSYMMETRICAL LIGNANS

Andrew Pelter, Robert. S. Ward, Peter Collins and Revuru Venkateswarlu.
Department of Chemistry, University College of Swansea, Singleton Park, Swansea SA2 8PP.

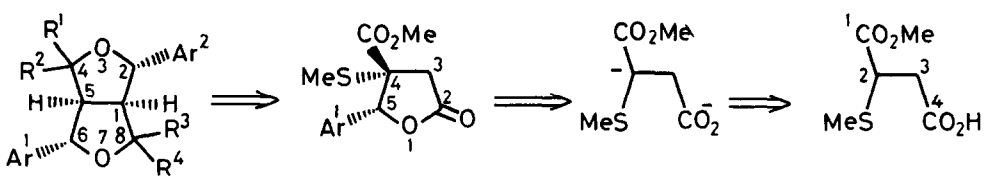
and I. Trevor Kay,
I.C.I., Plant Protection Division, Jealotts Hill, Bracknell RG12 6EY.

Utilising a new four carbon synthon suitable for regiospecific and stepwise anion production, unsymmetrically substituted 2,6-diaryl-3,7-dioxabicyclo-[3.3.0]octane lignans have been synthesised for the first time.

Lignans exhibit a wide range of physiological activity[1-6] and their synthesis is therefore a matter of intense interest.[7] The 2,6-diaryl-3,7-dioxabicyclo[3.3.0]octane lignans constitute one of the largest groups of lignans amongst which types 1, 2, and 3 are of particular interest.[1,8,9]

We have previously reported several syntheses of symmetrically substituted (Ar^1=Ar^2) compounds 1, 2 and 3.[10] These compounds have also been made by use of 2,5-bis-(trimethylsilyloxy)furan[11] and, very recently, the dianions of N,N,N,N-tetraalkyl-succinamides,[12a] as four carbon synthons. The latter method whilst short and elegant suffers from the apparent lack of ability of the dianion to condense in a <u>stepwise</u> fashion with aldehydes in the fashion that it does with alkyl halides.[12b] Thus unsymmetrical substitution has not been achieved. Furthermore the condensation gives mixtures of diastereoisomers from only one of which are the required bislactones produced, and then as minor products.[12a]

We had earlier addressed ourselves to the question of the <u>general</u> synthesis of 1, 2 and 3,[13] which we have previously interconverted[10] and arrived at the retroanalysis shown in Scheme 1.

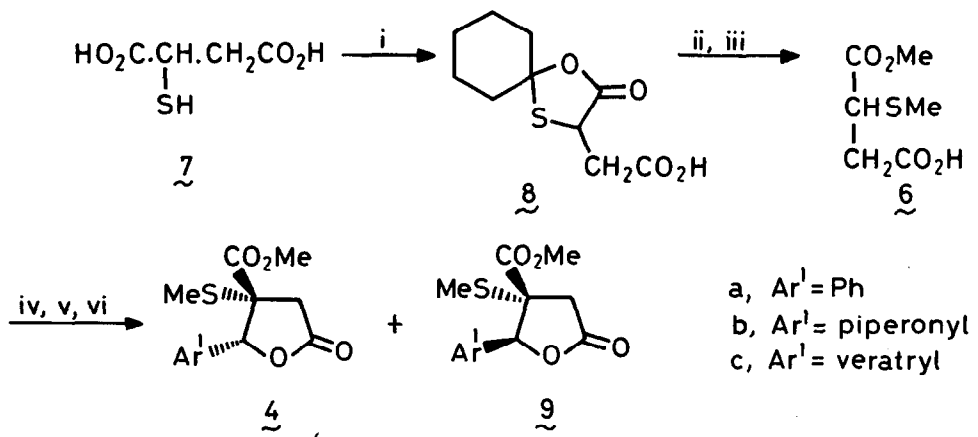


1 $R^1=R^2=R^3=R^4=H$ 4 5 6
2 $R^1=R^3=OH$; $R^2=R^4=H$
3 $R^1,R^2=R^3,R^4=O$

Scheme 1

We required a four carbon synthon in which anion formation would be stepwise and could be directed first to one and then the other of the two central carbon atoms. Dianion 5 derived from 6, should react with aldehydes at C-2 to give eventually lactone 4 (or a mixture of diastereoisomers). In compound 4 the methylthio group serves two purposes: (i) it blocks a position α to a carbomethoxy group, thus ensuring exclusive carbanion formation at C-3, (ii) it should have a favourable effect on directing attack by an aldehyde on the derived carbanion so that the incoming group is cis to the carbomethoxy group. This latter is an important point as previous syntheses of lignans using 'tandem' addition to butenolide could not be used for the synthesis of 1, 2 and 3 due to the trans disposition of the substituents introduced.[13]

The monoester 6, b.p. 150-5°/0.3°C/ mm is selectively and readily produced in 70% overall yield from commercially available mercaptosuccinic acid 7 by a process involving the thiazolidone 8 (Scheme 2). Treatment of 6 with two equivalents of LDA and an aromatic aldehyde followed by trifluoroacetic acid gave mixtures of 4a,b,c and 9a,b,c in isolated yields of 50%, 50% and 70% respectively. The ratios of 4 to 9 were ca. 2:1 and the two isomers were readily separated by trituration with ether.

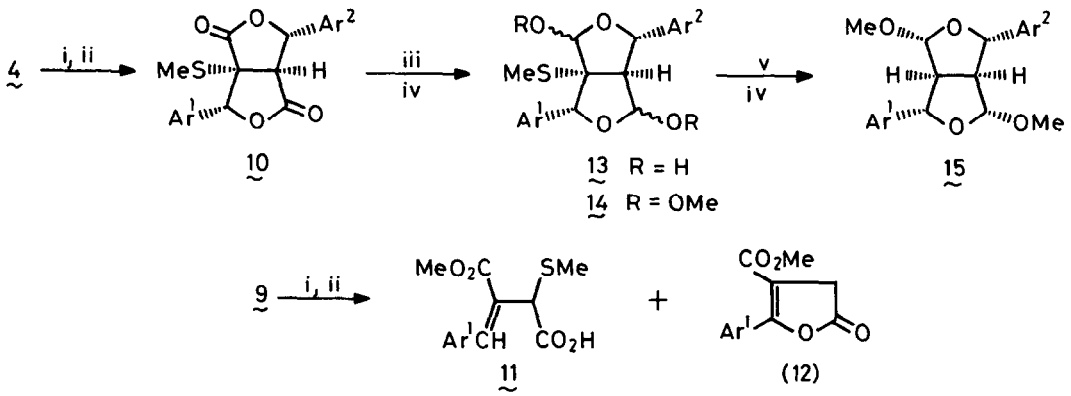


i, cyclohexanone, TosOH; ii, NaOMe; iii, MeI; iv, 2 eq. LDA; v, Ar^1CHO; vi, TFA

Scheme 2

On treatment with LDA and an aromatic aldehyde compounds 4 and 9 behaved quite differently. Thus 4c reacted with piperonal to give the desired dilactone 10c m.p. 154°C in 49% yield and 4b with veratraldehyde gave 10b m.p. 197-199°C in 58% yield (Scheme 3). However 9b gave only the rearrangement and fragmentation product 11b and the elimination product 12b when subjected to the same conditions.

The synthesis was completed by reduction of 10b with diisobutylaluminium hydride[10] to give 13b (88%) m.p. 197-199°C which was converted to 14b, (92%) m.p. 127-128°C. The methylthio group was removed with Raney-Nickel to give methyl 4,8-dimethoxy piperitol, 15b* (49%) m.p. 130-131°C. When 4c was carried through the same series of reactions using piperonal it gave the highly symmetrical lignan 15c which was identical with 15b, thus proving the overall sequence of reactions. We have previously converted compounds of type 15 to 2 and thence to 3 and 1[10]. Hence this work constitutes the first synthesis of lignans 1, 2, 3 and 13 that is generally applicable for the symmetrical and unsymmetrical lignans alike.



a, Ar^1 = Ph; Ar^2 = p-MeC_6H_4
b, Ar^1 = piperonyl; Ar^2 = veratryl
c, Ar^1 = veratryl; Ar^1 = piperonyl

i, LDA, -78°C; ii, Ar^2CHO; iii, Bu^i_2AlH; iv, MeOH/HCl; v, Ra-Ni

Scheme 3.

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* The argument relating to the assignment of stereochemistry in these compounds will be presented in the full paper. Briefly this refers to ^{13}C n.m.r. comparisons with symmetrical lignans of known structure.[10]

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