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THE SYNTHESIS OF EPOXYPIPEROLIDES AND PIPEROLIDES.

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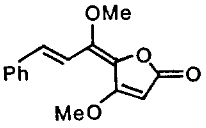
A general synthesis of alkynyl orthoesters leads to intermediates that couple with 2-trimethylsilyloxy-4-methoxyfuran to give compounds from which epoxypiperolide and isomers are available as well as all piperolide isomers.

Piperolide **1**[1], epoxypiperolide **2**[1a,2] and (-)-<u>threo</u>-7,8-dihydroxypiperolide, **3**[3] are members of a series of naturally occurring, physiologically active butenolides related to the fadyenolides, **5** and **6**.[4] 5,6-<u>E</u>-Piperolide, **4**, is also found in the natural mixture, but may well be a photoproduct.[5] We have previously shown that **1**, **4**, **5** and **6** are available from methyl tetronate <u>via</u> **7**,[4,6] or **8**[7].



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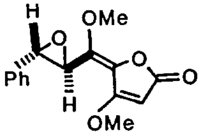

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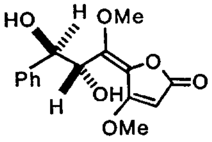

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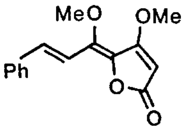

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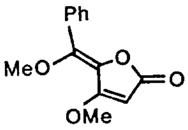

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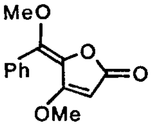

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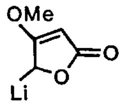

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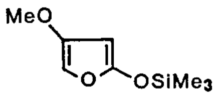

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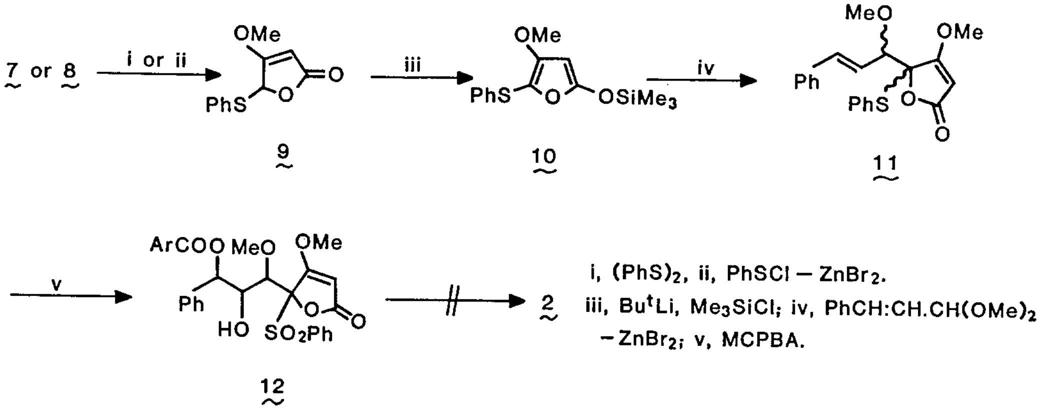
However, epoxypiperolide, **2**, which is not available from piperolide by direct oxidation[8], and its hydrate **3** have proved elusive due to their extensive and labile functionality. Our first attempt[9] to synthesise **2** involved the reactions shown in Scheme 1.

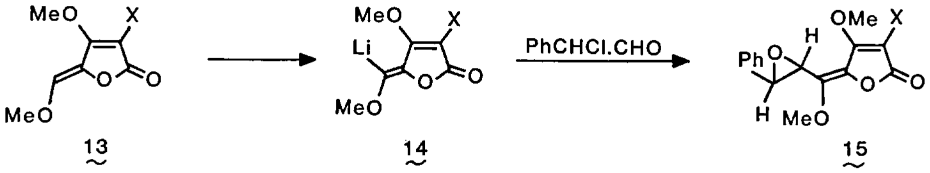


i, $(PhS)_2$, ii, $PhSCl - ZnBr_2$.
iii, Bu^tLi, Me_3SiCl; iv, $PhCH:CH.CH(OMe)_2 - ZnBr_2$; v, MCPBA.

Scheme 1

Compound 9 is available in *ca* 90% yield from either 7 or 8 and is readily converted to 10, which after distillation is taken to 11 in 70% yield from 9. Compound 12 is obtained from 11 as one isomer (stereochemistry not established) in quantitative yield. However, all of many attempts to eliminate phenyl sulphinic acid from 12 to give 2 or an ester of 3 were unsuccessful, and this approach had to be abandoned.

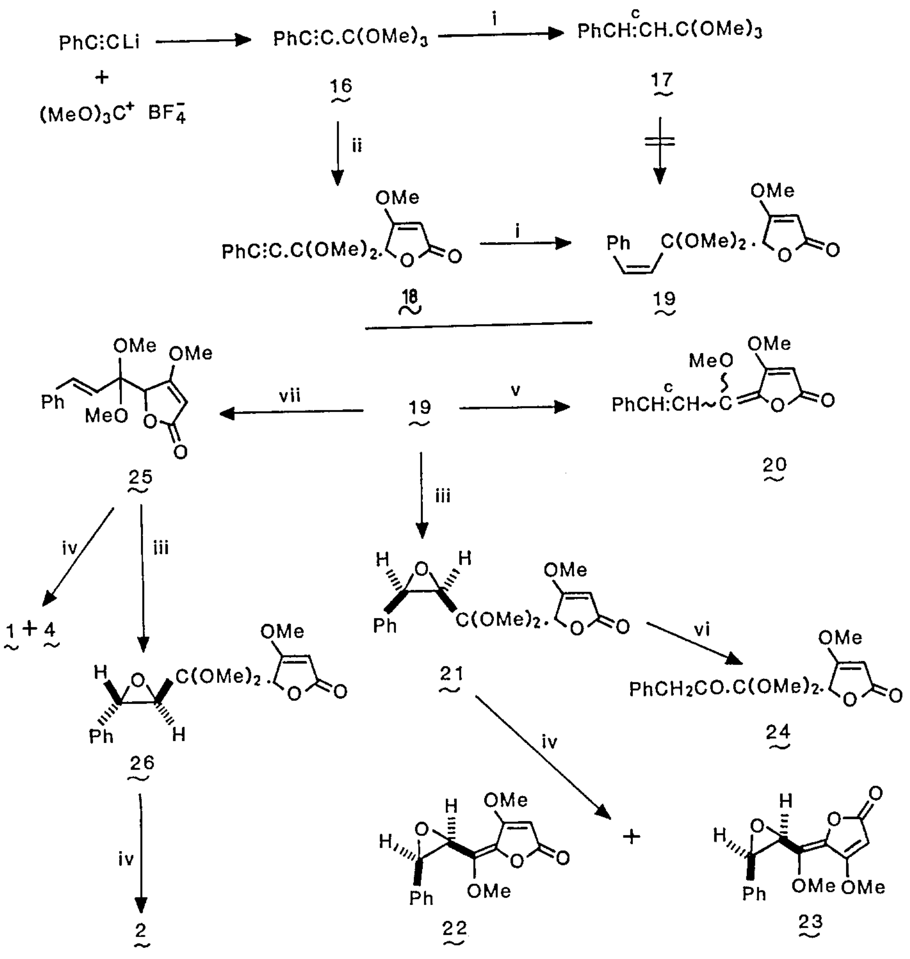
We next looked at the reactions shown in Scheme 2.



Scheme 2

Compound 13 (X = H) is available in 93% yield from methyl tetronate and methyl formate[9], but on metallation gives only 13 (X = Li) rather than 14 (X = H). Dimetallation to give 14 (X = Li) followed by reaction with aldehydes gave complex mixtures. We did not wish to introduce a C-3 protecting group (X = $SiMe_3$,SnR_3), not only because it involved more steps, but because, more seriously, the removal of the protecting group in the presence of the labile epoxide function was likely to be problematical.

We had previously shown that cinnamaldehyde type acetals ($ArCH:CH.CH(OMe)_2$) readily condense in a 1,2-fashion with 8,[7,9] and that 8 also condenses with orthoesters $RC(OMe)_3$[7] (R = H, CH_3, Ph). A combination of these two reactions would yield intermediates of promise for the synthesis of 2. However, unsaturated orthoesters are difficult of obtention. After some experimentation we found that condensation of phenylethynyl lithium with trimethoxycarbonium fluoroborate[10] (Scheme 3) using a rigorously anhydrous work-up, gave 16 in 90% yield. Lindlar reduction to 17 is quantitative, but condensation of 17 with 8 unfortunately goes in a 1,4-fashion entirely. However, 16 itself condenses with 8 to give 18 (77%) which is readily reduced to pure, recrystallised 19, a key compound, in 80% yield.



i, Lindlar cat., H$_2$; ii, 8, BF$_3$.OEt$_2$; iii, MCPBA/CH$_2$Cl$_2$; iv, LiOMe, toluene; v, Bu^{t}Li, -95°C; vi, ZnBr$_2$; vii, MeOH/H$^+$.

Scheme 3

With *t*-butyl lithium 19 gives a 97% yield of piperolides, mainly (80%) 20 the previously unknown isomers with the 7,8-*Z*-double bond. Surprisingly, at -95°C there was almost as much of the very hindered 7,8-*Z*, 5,6-*E*-isomer as the 7,8-*Z*, 5,6-*Z*-piperolide. At rather higher temperature the latter dominates and is readily separated. A full account of these interesting eliminations will be given elsewhere. This constitutes the first synthesis of these unnatural piperolides and completes the piperolide series.

Epoxidation of 19 gives 21 as a diastereoisomeric mixture (1.3:1) in 83% yield. The major isomer (stereochemistry under investigation) crystallises out and was carried forward, though use of the mixture may be as good. In this case reaction of both ^{t}BuLi and LiN(SiMe$_3$)$_2$ gave complex mixtures but fresh lithium methoxide in refluxing toluene gave an isolated yield of 39% of epoxypiperolides 22 and 23 (2:1), readily separated by preparative h.p.l.c. The yield on this step is not as high as we would have liked, but 21 is well provided with a plethora of labile functionality ready for rearrangements. For example, reaction of 21 with zinc bromide gives the ketone 24 in 93% yield. This sequence provides the first synthesis of any epoxypiperolides.

It remained to enter the natural 7,8-*E*-series. Photochemical and iodine induced rearrangement of 19 to the 7,8-*E*-isomer, 25, failed. However, allowing 19 to stand in anhydrous methanol in the presence of an acid resin catalyst gave 25 quantitatively, presumably by capture of an intermediate stabilised allylic cation produced from the acetal. Reaction of 25 with lithium methoxide gives a readily separable mixture of the natural piperolides, 1 and 4 (2.8:1) in 83% yield.

Epoxidation as before of the very labile acetal 25 gave 26 as a diastereoisomeric mixture (3:2) which was not separated but reacted with lithium methoxide to give 35% of a mixture of epoxypiperolides. Natural epoxypiperolide was not available for direct comparison, as it is not stable and our sample had decomposed on standing. However, among the epoxypiperolides, the natural isomer has a unique ^{1}H n.m.r. with a methoxy group below δ4.0 and the major fraction of our mixture, isolated by preparative h.p.l.c. had an identical ^{1}H n.m.r. spectrum, thus verifying the first synthesis of racemic expoxypiperolide.

Scheme 3 therefore represents a versatile process in which all piperolide isomers and three characterised epoxypiperolides are produced from the *same* intermediate.

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