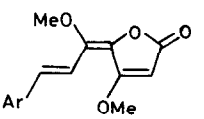
Tetrahedron Letters No. 18, pp 1627 - 1630. 0040-4039/79/0429-1627$02.00/(

THE SYNTHESIS OF PIPEROLIDE AND RELATED COMPOUNDS

Andrew Pelter*[1], Miqdad T Ayoub[1], Jutta Schultz[2],
Rudolf Hänsel[2] and Dieter Reinhardt[3].

An efficient synthesis of methyl tetronate, of use as a synthon for butenolide production, is outlined. Its use in the synthesis of piperolide and related compounds is described.

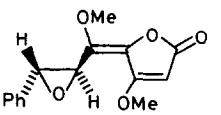
Piperolide, methylenedioxypiperolide[4] and epoxypiperolide[5] are unusual naturally occurring methyl tetronates derived from a higher plant, Piper sanctum. They have been assigned respectively structures (1a), (1b) and (2), these having been confirmed by X-ray crystallographic analysis [6]



(1)

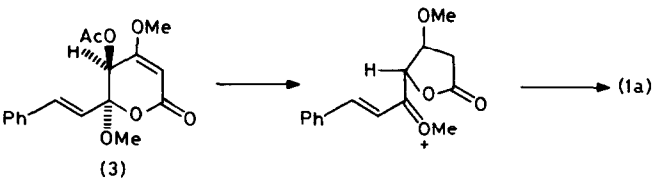
(a) Ar = Phenyl

(b) Ar = 3,4-Methylenedioxyphenyl



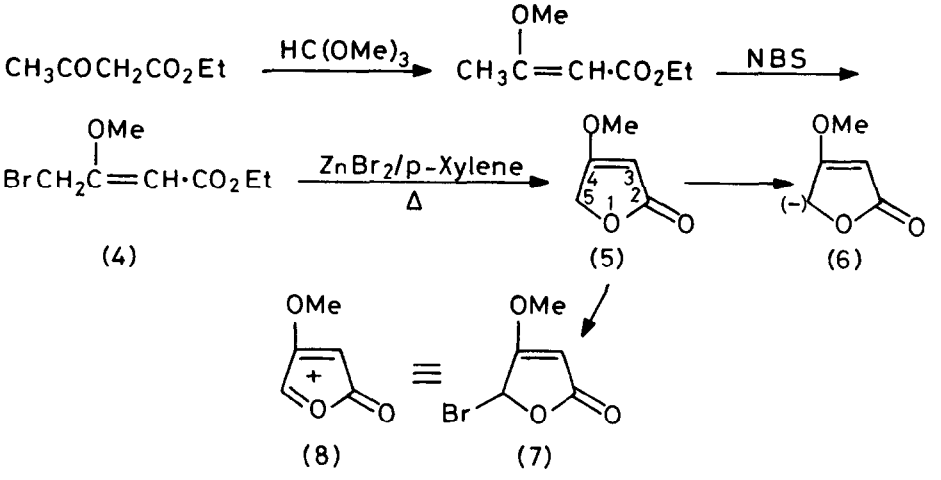
(2)

Kawain and various derivatives co-occur with the piperolides in P.sanctum. Compound (3)[7] is particularly noteworthy inasmuch as its rearrangement (Scheme 1) could lead biosynthetically to piperolides and a route to butenolides based on analogous reactions has been explored [8]



SCHEME 1

We now report a method, based on the synthon (5), for producing a variety of methyl alkylidenetetronates related to piperolide. To our surprise, no efficient synthesis of (5) has been reported,[9] but after extensive experimentation the process shown in Scheme 2 was evolved.



SCHEME 2

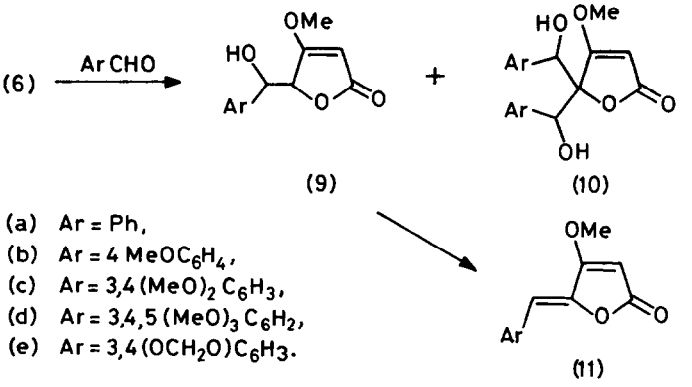
The production of (4)* is a known process that gives an overall yield of ca 95%[10], whilst the ring closure gives pure, crystalline methyl tetronate (5) in ca 75% yield. Hence (5) can be regarded as a cheap and readily available synthon for the production of a variety of butenolides, either via the anion (6) or the bromo-compound (7), which is the operational equivalent of the cation (8)

Reaction of (5) with $LiNPr^i_2$ at -78°C in THF/HMPT followed by addition of D_2O gave methyl 5-deuteriotetronate in 77% yield. Hence anion (6) was formed and reacted at C-5 in the fashion required. Reaction of (5) with one equivalent of NBS gave (7), though in this paper approaches to piperolide via (7) are omitted.

Reaction of (6) with benzaldehyde gave mixtures of (9a) and (10a) (Scheme 3), but the production of (10a) could be avoided by using a 1 1 mixture of the aldehyde and water for quenching the anion Both threo- and erythro-isomers of (9a) were formed, but the threo-isomer (69%) m p 147-8°C was easy to isolate pure and was used for subsequent reaction Dehydration of (9a) with conc H_2SO_4 at 0° yielded methyl 5,6-Z-5-benzylidenetetronate (11a) (85%) the stereochemistry of which was confirmed by X-ray analysis. Analogues 11(b - e) were synthesised by the action of aqueous potassium acetate on the corresponding mesylate [9] The stereospecific production of (11a) suggests an E1 mechanism in which the intermediate cation disposes itself so that minimum steric interactions occur.

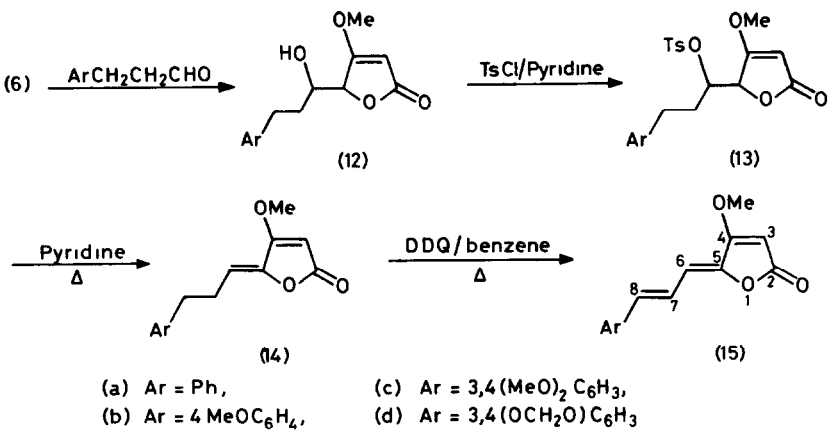
---

* We thank Firma Klinge for samples of (4)



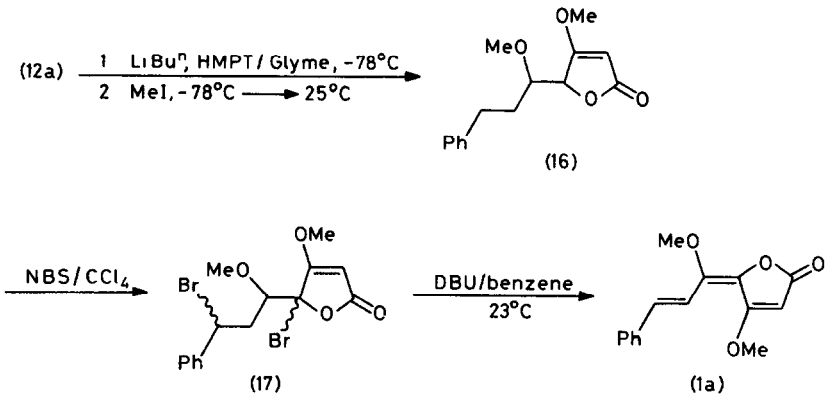
SCHEME 3

Reactions of (6) with cinnamaldehyde, cinnamonitrile and ethyl cinnamate were all complicated by preferential 1,4-addition of the anion Complex results were also obtained using 3-thiophenyl- and 3-ethoxydihydrocinnamaldehydes as saturated equivalents for the unsaturated aldehyde Attention was therefore turned to the sequence shown in Scheme 4.



SCHEME 4

The reaction of (6) with dihydrocinnaldehyde (Scheme 4) gave (12a) as a mixture of threo- (49% m.p. 180-1°C) and erythro- (40% m p. 84-5°) isomers The threo- isomer was converted to (13a) (75%) which readily eliminated TsOH to give (14a) (70%). Dehydrogenation with DDQ gave (15a) m p 128-30° (77%) as the sole product, showing that elimination here also was under steric control. The structure of (15a) was confirmed by X-ray analysis.



SCHEME 5

The oxidation of (12a) to the corresponding ketone was complicated by various rearrangement reactions and hence (12a) was methylated to (16), a reaction that had to be carried out at low temperature to avoid a ready elimination of methanol to yield (14) [8] Photocatalysed reaction of (16) with two equivalents of NBS in the presence of benzoyl peroxide presumably gave (17) However, some elimination to give (14) was apparent by h.p.l.c analysis It was expected that both eliminations of HBr from (17) would be sterically controlled and indeed addition of DBU in benzene to the crude bromination product gave a readily separable mixture of 5,6-Z-7,8-E-piperolide (1a) and (15). Only isomer (1a) was produced synthetically, though our h p l c systems were able to resolve an old sample of natural piperolide into a mixture of 5,6-Z-7,8-E and 5,6-E-7,8-E-piperolides. (4 1) Our synthetic sample was identical in all respects (m p., m.m p , i r., u v , p m r , c m.r) with authentic piperolide (Scheme 5)

Approaches to piperolide using (5) as the cation (7) will be described separately

One of us (M T Ayoub) thanks the Iraqui Government for a scholarship and the University of Mosul for leave of absence during the period 1975 - 1978

REFERENCES

1 Department of Chemistry, University College of Swansea, Swansea, U K
2. Institüt für Pharmakognosie und Phytochemie der Freien Universität, Berlin, D-1000 Berlin 33, Königin - Luise Str 2 - 4
3 Institüt für Kristallographie der Freien Universität, Berlin.
4 R Hänsel and A. Pelter, Phytochemistry, 1971, 10, 1627
5 A. Pelter and R Hänsel, Z.Naturforsch , 1972, 27b, 1186
6 R. Reinhardt and R Hänsel, Z Naturforsch , 1977, 32c, 290
7 R Hänsel, A Pelter, J Schultz and C. Hille, Chem Ber , 1976, 109, 1617
8 R. Hänsel, J. Schutz, A Pelter, M.T Ayoub and R Reinhardt, Z Naturforsch , 1978, 33b, 1020
9 M.T Ayoub, Ph D Thesis, University College of Swansea, 1978.
10. Br. Patent, 1967, 1137466
11 Ger Pat.App No 2845037 5

(Received in UK 16 February 1979)