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A NEW SYNTHESIS OF 10,11-DIHYDRODIBENZ(b,f)OXEPIN-10-ONES: KEY INTERMEDIATES TO CULARINE ALKALOIDS

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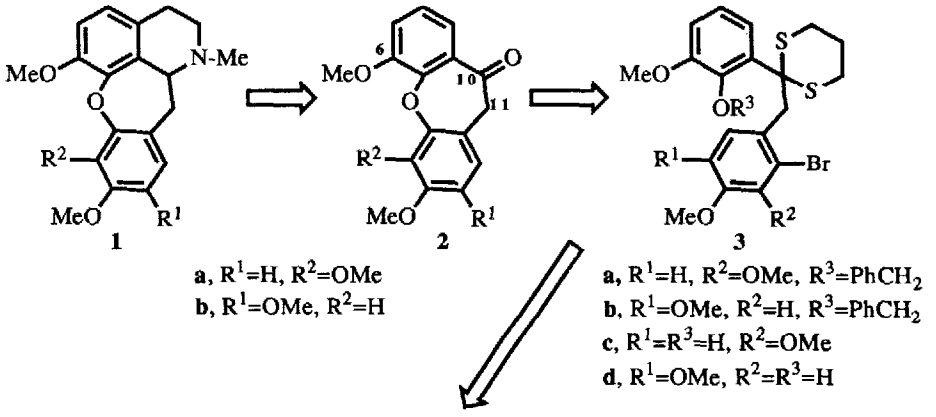
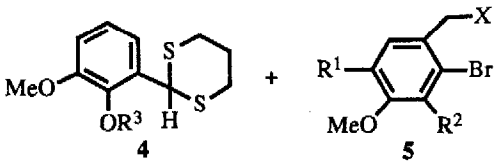
Abstract: A new synthesis of the title compounds is described, providing a route to key intermediates for the preparation of cularine alkaloids.

The cularines are a large group of isoquinoline alkaloids with a dihydrodibenzoxepine system in their skeletons.[1] The first synthesis of cularine[2] (**1b**) assembled the nitrogenated ring on the dibenzoxepinone **2b** (Manske's ketone), which was prepared by intramolecular acylation of the corresponding *o*-phenoxyphenylacetic acid. Since the yield of the latter reaction is poor when there is an oxygenated substituent *meta* to the cyclization point (C6 in **2**)[3,4] we have developed a more efficient approach based on the formation of the C10-C11 bond by alkylation of the lithium derivative of the dithiane **4** with the benzylic halides **5**, followed by an intramolecular Ullmann reaction in **3**.



a, R^1=H, R^2=OMe
b, R^1=OMe, R^2=H

a, R^1=H, R^2=OMe, R^3=$PhCH_2$
b, R^1=OMe, R^2=H, R^3=$PhCH_2$
c, R^1=R^3=H, R^2=OMe
d, R^1=OMe, R^2=R^3=H



a, R^3=$PhCH_2$
b, R^3=$MeOCH_2$

a, R^1=H, R^2=OMe, X=Cl
b, R^1=OMe, R^2=H, X=Br

Compound **4a**[5] was deprotonated with n-BuLi in THF at -78ºC, and after 1 h. a solution of chloride **5a**[6] in THF was added. The reaction mixture was allowed to rise slowly to room temperature, giving **3a** in 69% yield; use of bromide **5b**[7] afforded **3b** in

58% yield. Refluxing **3a** with EtOH/conc. HCl for 1h. removed the benzyl and dithiane groups to give the phenolic ketone in 92% yield, but Ullmann reaction of the latter (K_2CO_3, CuO, pyridine, reflux, 1h.) brought about cyclization via the carbonyl group to afford 6,7-dimethoxy-2-(2'-hydroxy-3'-methoxyphenyl)benzofurane[8] in 85% yield.[9]

Though we were able to selectively remove the benzyl group of **3a** while preserving the dithioacetal,[10] it is more convenient to be able to use a group that is more easily removed. To this end, the 2-lithio derivative (n-BuLi, THF, -78ºC, 2 h.) of the 1,3-dithiane **4b**[5] was alkylated with the benzylic halides **5**; after work-up, the crude mixture was hydrolysed under Argon atmosphere with HCl(5%)/THF (1:5 v/v, r.t., 20h.); and chromatography of the resulting product (neutral alumina grade II) gave **3c** and **3d** in 64% and 57% yields respectively.[9] The bromophenol **3c** was refluxed for 1h. with anhydrous K_2CO_3 (5 eq.) and CuO (3 eq.) in dry pyridine under Argon atmosphere to yield a mixture which showed two main products by t.l.c. that were highly fluorescent when excited at 360 nm.[11] However, hydrolysis of this crude mixture with acetonitrile/conc. HCl (2:1 v/v, reflux, 2h.) in the presence of glyoxylic acid (to trap 1,3-propanedithiol) followed by column chromatography (silicagel) afforded **2a** (60% overall yield; mp. 98-99ºC).[9,12] Compound **2b** was obtained similarly from **3d**, in 48% overall yield.[9]

The above new, straightforward route to Manske's ketone (**2b**) and its isomer **2a** opens the way to the isocularine alkaloids.[1] It also seems likely to be applicable to the synthesis of oxepinones **2** with non-methoxyl substituents, so leading to many other naturally occurring cularines; this is currently being investigated in our laboratories.

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REFERENCES AND NOTES

1.- L. Castedo, "The Chemistry and Pharmacology of Cularine Alkaloids", in *"The Chemistry and Biology of Isoquinoline Alkaloids"*, ed. Philipson et al., Springer-Verlag, 1985.
L. Castedo and R. Suau, "The Cularine Alkaloids", in *"The Alkaloids"*, vol. 29, ed. A. Brossi, Academic Press, 1986.
2.- T. Kametani and K. Fukumoto, J. Chem. Soc., 4289 (1963)
3.- M. Kulka and R.H.F. Manske, J. Am. Chem. Soc. **75**, 1322 (1953)
4.- I. Noguchi and D.B. MacLean, Can. J. Chem. **53**, 125 (1975)
5.- The corresponding protected o-vanillin in chloroform, was treated at rt for 24h.with 1.05 eq of 1,3-propanedithiol in the presence of $BF_3 \cdot Et_2O$ (0.2 eq.) and Na_2SO_4.
6.- I. Baxter, L.T. Hallan and G.A. Swan, J. Chem. Soc., 3645 (1965)
7.- G. Dai-Ho and P. S. Mariano, J. Org. Chem. **53**, 5113 (1988)
8.- A related finding was reported recently by J. Grimshaw and N. Thompson, J.Chem.Soc.Chem.Commun., 240 (1987)
9.- All new compounds were fully characterized spectroscopically and gave satisfactory elemental analyses.
10.- K. Fuji, K. Ichikawa, M. Node and E. Fujita, J. Org. Chem. **44**, 1661 (1979)
11.- In one experiment the fast-moving compound was isolated and its NMR (^1H and ^{13}C) showed no signal for the methylene group in the aliphatic region but an additional one in the aromatic region. This suggests a dibenzoxepine structure as the result of a ß-elimination of one sulphur atom. The other fluorescent compound might have a similar structure with a different oxidation level at the sulphur atoms.
12.- **2a**: ^{1}HNMR (250 MHz, $CDCl_3$), 3.83 (s, 3H, OMe), 3.96 (s, 3H, OMe), 4.01 (s, 3H, OMe), 4.02 (s, 2H, $-CH_2-$), 6.75 (d, 1H, J:8.5Hz), 6.94 (d, 1H, J:8.5Hz), 7.0-7.2 (m, 2H), and 7.62 (dd, 1H, J:7.5Hz and 2.1Hz). ^{13}CNMR (62.83 Mz, $CDCl_3$), 47.65, 56.32, 56.59, 61.59, 109.97, 117.28, 120.30, 121.49, 123.14, 123.51, 127.72,141.35, 150.25, 151.12, 151.58, 153.01 and 190.60 ppm.

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