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A NEW ROUTE TO PERHYDRO- AND TETRAHYDRO- FURO-2,3b FURANS VIA RADICAL CYCLISATION

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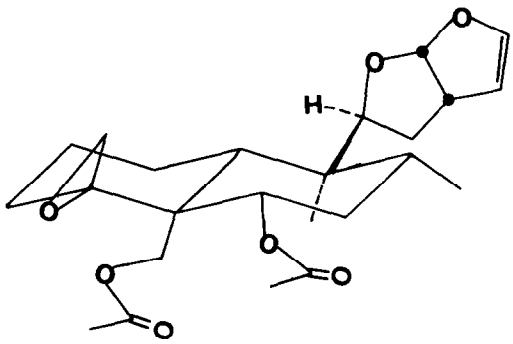
SUMMARY

Perhydrofuro-2,3b furans have been prepared in high yield by radical cyclisation of unsaturated bromo acetals. Their transformation into tetrahydro derivatives is described along with a radical annelation to 2,3- dihydrofurans by tributyltin iodoacetate.

The partially hydrogenated furo-2,3b furan ring is embodied in a large number of natural products, particularly in some insect antifeeding compounds such as clerodine 1[1].



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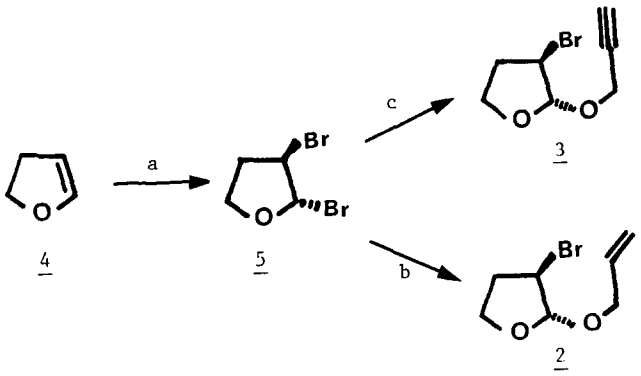
Among various approaches aimed at the synthesis of this kind of skeleton[2], we examined the possibility of using radical reactions as they usually avoid acidic or basic conditions, which is a perequisite for handling such systems.

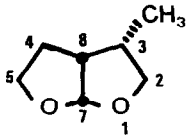
Reductive bromoacetal cyclisation by tributyltin hydride has been shown by Stork et.al[3] to proceed in high yields and stereoselectivity on various substrates. We therefore considered radical cyclisation of bromoacetals 2 and 3 for the construction of the desired subunits. These starting compounds were easily prepared according to Scheme I.



Scheme I

Reagents : a : Br_2, CH_2Cl_2, - 15°C ; b : $HO-CH_2-CH=CH_2$, DMAP, CH_2Cl_2 ;
c : $HO-CH_2-C\equiv CH$, DMAP, CH_2Cl_2.

In the presence of 1.1 equivalent of Bu_3SnH and with initiation by AIBN (PhH, 80°C, 8h), cyclisation of 2 and 3 occured smoothly, leading to 6 and 7 in almost quantitative yields.



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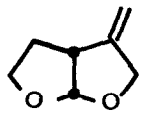

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6 and 7 were identified by their NMR and mass spectra :

6 NMR 1H (400 MHz, $CDCl_3$) (ppm) : 1.01 (3H,d,CH_3) ; 1.85 (2H,m,H-4) ; 2.38 (1H,m,H-4) ; 2.76 (1H,m,H-8) ; 3.36 (1H,m,H-2) ; 3.83 (3H,m,H-2 H-5) ; 5.68 (1H,d,H-7) (J=5Hz).

NMR 13C (50,1 MHz, $CDCl_3$) (ppm) : 11.48(CH_3) ; 24.99 (C-4) ; 35.96 (C-3) ; 46.50 (C-8) ; 69.03 (C-5) ; 76.67 (C-2) ; 109.87 (C-7).

MASS m/e : 128 $(M)^+$; 98 ; 83

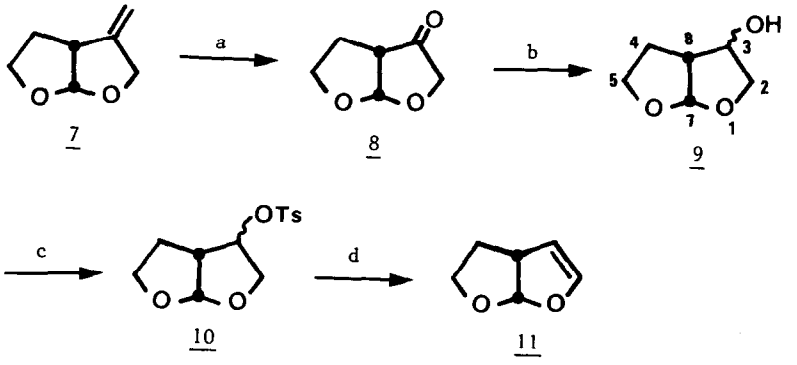
7 NMR 1H (200 MHz, $CDCl_3$) (ppm): 1.90 (1H,dd,H-4) ; 2.15 (1H,m,H-4) ; 3.26 (1H,m,H-8) ; 3.73 (1H,m,H-5) ; 3.82 (1H,m,H-5) ; 4.45 (2H,m,H-2 and H-2) ; 5.01 (2H,m,$=CH_2$) ; 5.78 (1H,d,H-7) (J=6Hz).

NMR ^{13}C (50.3 MHz, $CDCl_3$) (ppm) : 34.29 (C-4) ; 47.42 (C-8) ; 67.54 (C-5) ; 72.13 (C-2) ; 105.92 (C-9) ; 109.74 (C-7) ; 150.39 (C-3)

MASS 126 (M^+) ; 125 $(M-1)^+$; 97 ; 80 ; 79

The configuration of the methyl group in 6 was assigned on the basis of coupling constant values between protons H-8 and H-4 ; H-8 and H-4 ; H-8 and H-3 and finally H-8 and H-7. We also observed that catalytic hydrogenation of 7 (PtO_2, 1 atm) leads almost exclusively to 6. In this reaction, hydrogen is delivered from the less hindered side of the molecule, i.e. cis to the ring junction hydrogens.

Transformation into tetrahydrofuro-2,3b furan was achieved according to the following reaction sequence (Scheme II).



7 8 9 10 11

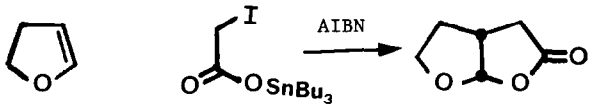
Scheme II

Reagents : a : O_3, -70°C, CH_2Cl_2, $(CH_3)_2S$; b : $LiAlH_4$, Et_2O, 0°C ; c : TsCl, pyridine, 0°C ; d : DBU, 180°C.

Reduction of the ketone 8 with lithium aluminium hydride gave only one isomer of alcohol 9 (the ^1H NMR spectra gave a single doublet for H-7 : J = 5 Hz). Elimination of the tosyl group in 10 required heating with DBU (1,5 Diazabicyclo [5.4.0.] undecene -5)[5]. NMR Spectra with exhaustive proton-proton decoupling were in agreement with structure 11.

11 NMR 1H (400 MHz, $CDCl_3$) (ppm) : 2.30 (2H,H-4) ; 3.58 (1H,m,H-8) ; 3.75 (2H,m, H-5) ; 4.81 (1H,t,H-2) (J=3 Hz) ; 6.10 (1H,d,H-7) (J=6 Hz) ; 6.46 (1H,t,H-3) (J=3 Hz).

We also prepared the perhydrofuro-2,3b furan 13 via the radical annelation reaction reported by Kraus et.al[6]. This consists in the AIBN induced radical addition to a double bond of the readily available tributyltin iodoacetate[7] 12, followed by cyclisation to the γ-lactone.



4 12 13

This reaction proceeded smoothly with the dihydro-2,3 furan 4 allowing a straightforward preparation of perhydrofuro-2,3b furan 13. This compound was identified by comparison with a sample prepared by a completely different approach[2].

After completion of this work, three other approaches[8] have appeared.

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4. Substitution of bromine occurs with retention of configuration as clearly displayed by the 1H NMR spectra of 2 and 3 where the acetal proton appears as a singulet.

5. To avoid extraction, compound 11 was flushed from the reaction mixture by an argon stream and trapped at -78°C.
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