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IODOCYCLISATION OF UNSATURATED LACTOLS AND ACETALS . A NEW ROUTE TO FURO-2,3b-FURANS AND PYRANS .

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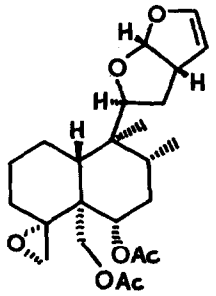
Summary : Cyclisation by iodine or other electrophilic reagents of unsaturated lactols or acetals has been studied and proved to be an efficient route to substituted furo-2,3b-furans or pyrans .

Fused ring cyclic ketals are frequently encountered in natural products . Furo-2,3b-furans or pyrans, for example, are present in many natural insect antifeeding compounds and are thought to be responsible to some extent for the biological activity of clerodin [1] 1, azadirachtin [2] [3] 2, and the aflatoxins [4] 3 . They can be also considered as masked polyaldehydes .



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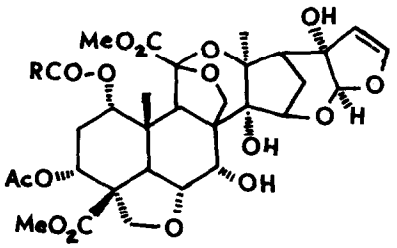

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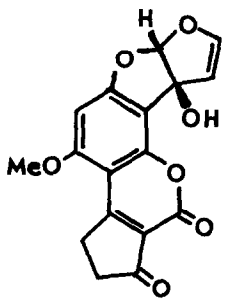

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We have previously reported that the cyclisation of unsaturated lactols proceeds smoothly giving the corresponding saturated furo-2,3b-furans in high yield [5] (Fig. 1) .

As a mixture of the two possible isomers was obtained in this reaction, we have investigated various ways to improve its selectivity and to generalize it towards systems with different ring sizes or functional groups such as an angular hydroxy group .

Efforts to improve the selectivity were made using iodine and other related electro-

philic reagents such as ICl, or N-iodosuccinimide (NIS) under a variety of conditions . The results are summarised in Table I . NIS in proprionitrile (- 80°C) was found to be very mild and efficient giving quantitative yields of 5 . Addition of solid $NaHCO_3$ did not improve the yield or the selectivity of this reaction over a 75/25 ratio .

The major isomer 5t displays the same stereochemistry as clerodin as assigned by high field NMR studies [5] .

Table I

	Solvent	θ°C	Time	Ratio 5t/5c	Yield 5t + 5c
NIS	CH_3CH_2CN	- 80°	3 days	75/25	95 %
	THF	- 45°	12 h	60/40	80 %
	THF	- 20°	12 h	50/50	80 %
	CCl_4	- 20°	12 h	≃ 50/50	incomplete
ICl	CH_3CH_2CN	- 90°	24 h	60/40	75 %
I_2	CH_3CN	- 15°	3 h	75/25	60 %

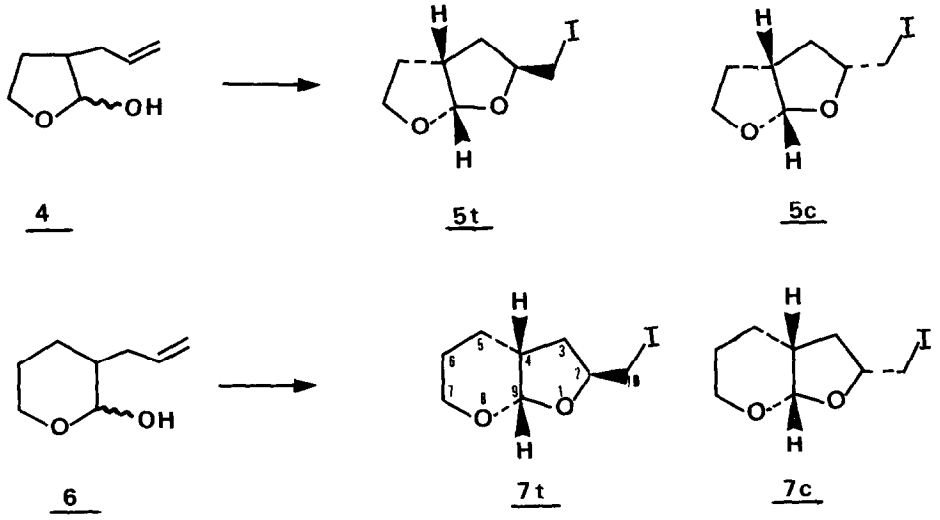

Figure 1

The related furo-2,3b-pyran 7 were prepared according to the following sequence (Fig. 1) : alkylation of δ-valerolactone (LDA, - 70°C, allyl bromide) ; reduction into lactol 6

(DIBAH, - 78°C, THF) and cyclisation (NIS, CH_3CH_2CN, - 60°C, 2 days) gives 7 as a 50/50 mixture of isomers (yield : 45 %) . ^1H NMR (250 MHz)($CDCl_3$)(two isomers) : 5.15 (d), 5.07 (d), (H_9) ; 4.40 (m), 3.90 (m), 3.5 - 3.3 (m), (H_2) (H_6) (H_4) ; 3.12 (m), 2.35 - 1.35 (m) .

We then studied the preparation of compounds such as 8 bearing an angular hydroxy group such as azadirachtin 2 or aflatoxin 3 . The starting acetal 12 was easily prepared as depicted on Fig. 2 . Compound 12 was obtained as a single isomer, whose stereochemistry was assigned as indicated on Fig. 2 ; ^1H NMR (250 MHz) ($CDCl_3$) : 5.94 (m, 1H) (H_7) ; 5.14 (m, 2H) (H_8) ; 4.62 (s) (H_2) ; 4.00 (m, 1H), 3.84 (m, 1H) (H_5) ; 3.78 (m, 1H), 3.48 (m, 1H) (H_9) ; 2.34 (d, 2H) (H_6) ; 1.94 (m, 2H) (H_4) ; 1.56 (m, 2H) (H_{10}) ; 1.38 (m, 2H) (H_{11}) ; 0.92 (t, 3H) (H_{12}) .

Acetal 12 could be easily cyclised with iodine in moderate yield (45 %) . After column chromatography (SiO_2, AcOEt-C_6H_{12}, 50/50), a mixture of two isomers (≃ 85/15) was obtained . There, ^1H and ^{13}C spectra were very similar and consistent with structure 8 (7) .

Assignment of side chain stereochemistry was difficult . The coupling constant between H_2 and the two H_3 $H_{3'}$ protons : $J_{H_2H_3}$ = 9 Hz, $J_{H_2H_{3'}}$ = 6 Hz could not be used in the absence of reliable assignment of H_3 and $H_{3'}$. Nuclear Overhauser effects (NOE) were also deceptive . However comparison of ^{13}C spectra of both isomers with the ^{13}C spectra of the isomeric mixture 5t + 5c, pointed out similar shift patterns between the major and the minor isomers for similar carbons . Thus the stereochemistry of major isomer 8t was tentatively assigned as depicted on Fig. 2 .

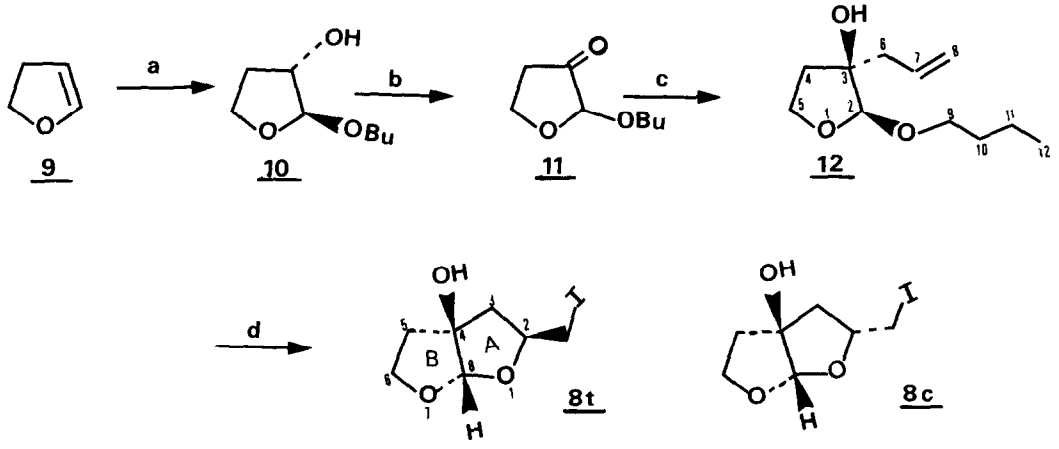

Figure 2 : a = mcpba, BuOH, 0°C, 6 hrs ; b = DMSO, H_3PO_4, DCC (6) ;
c = CH_2=CH-CH_2MgBr, Et_2O ; d = I_2 (1.1 eq.), CH_3CN, RT, 6 hrs .

It is to be pointed out that epimerisation at C-2 must occur during the cyclisation in order to obtain the more stable cis ring junction .

From this result, it is obvious that the iodocyclisation is quite general and can be compared with the iodocyclisation of unsaturated benzylic ethers leading to tetrahydrofuran systems recently reported by BARTLETT and HOLMES [9] .

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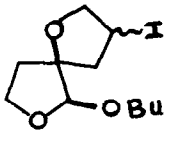
(7) ^{1}H NMR (400 MHz) ($CDCl_3$) : major isomer - 1.93 (dd, 1H) (H_3) ($J_{H_3H_3'}$ = 13 Hz) ($J_{H_3H_2}$ = 9 Hz) ; 2.13 (m, 2H) (H_5) ; 2.40 (dd, 1H) ($H_{3'}$) ($J_{H_{3'},H_3}$ = 13 Hz) ($J_{H_{3'},H_2}$ = 6 Hz) ; 3.2 (m, 2H) (H_9) ; 3.98 (m, 2H) (H_6) ; 4.13 (m, 1H) (H_2) ; 5.35 (s, 1H) (H_8) .
minor isomer - 1.81 (dd, 1H) ($H_{3\alpha}$) (J = 13 Hz and 9 Hz) ; 2.13 (m, 2H) (H_5) ; 2.30 (dd, 1H) ($H_{3\beta}$) (J = 13 Hz and 6 Hz) ; 3.2 (H_9) ; 3.98 (H_6) ; 4.13 (m, 1H) (H_2) ; 5.30 (s, 1H) (H_8) . ^{13}C NMR (100.5 MHz)($CDCl_3$) : major isomer - 113.35 (C_8) ; 88.69 (C_4) ; 79.35 (C_2) ; 68.34 (C_6) ; 46.30 (C_3) ; 40.33 (C_5) ; 9.10 (C_9) .
minor isomer - 113.92 ; 89.09 ; 64.50 ; 45.30 ; 40.65 ; 8.61 .
Mass spectrum (E.I.) - m/e : 270 ; 143 ; 142 ; 141 ; 129 ; 128 ; 114 ; 113 ; 97 .

(8) Another product could be isolated from the reaction mixture, for which the following structure is proposed on the basis of mass (C.I.) and ^{1}H high field NMR spectra . Its



formation corresponds to the less favourable endo trigonal cyclisation on the -OH group .

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