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α-ACYLIMINIUM ION SYNTHESIS OF ELAEOKANINE B

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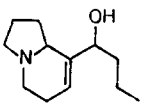
Abstract: Elaeokanine B has been synthesized utilizing the acid-catalyzed cyclisation of hydroxylactam 9 as key step in the formation of the chloride 10.

The fairly recently discovered Elaeocarpus alkaloids[1] possess a characteristic indolizidine structure which can be simply constructed via an α-acyliminium cyclisation[2]. Our interest in this type of compound arose upon consideration of the necessary olefin substrate possessing in addition to the π-nucleophile a vicinal oxygen substituent. Since it was anticipated that the latter heteroatom could interfere with the cationic type of process involved[3] we decided to investigate the synthesis of elaeokanine B (1) via this route. Other recent total syntheses employ a variety of different synthetic techniques[4]

As a model compound the protected allyl oxy derivative 2 was investigated, which could be prepared by coupling of the 1-OH protected (Z)-penten-2-diol 1,5 to succinimide[5] and subsequent $NaBH_4/H^{\oplus}$ reduction[6]. Indeed it was found that HCOOH-cyclisation (r.t., 18 hr) gave only a yield of 20% of the diformate 3 as the sole identifiable material, other acid conditions including the use of HCl-MeOH (vide infra) leading to negative results. As a most likely explanation for the failure of the ring closure may be regarded the competition of the oxygen nucleophile for the cationic intermediate thereby effectively reducing the acid strength of the medium.



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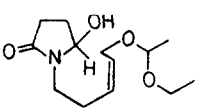

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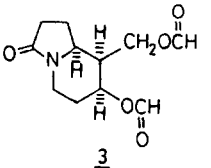

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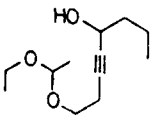

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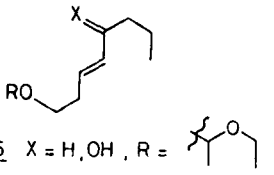
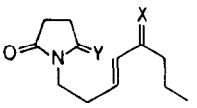


5 X = H,OH, R =

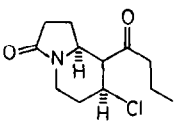
6 X = O, R = H



7 X = Y = O

8 X =  , Y = O

9 X =  , Y = H,OH



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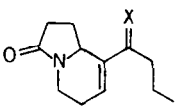

11 X = O

12 X = H,OH

A high yield of the target alkaloid, however, could be obtained in the following manner. The MVE protected butyn-3-ol-1 was condensed with butyraldehyde (BuLi, Et_2O, -70°C, 77%) to the alcohol 4. LAH reduction of 4 (1.5 eq $LiAlH_4$, THF, ΔT, 88%) afforded the E-alkene 5 which was oxidized (CrO_3/pyridine CH_2Cl_2, 80%) to the α,β unsaturated ketone and finally carefully hydrolyzed to alcohol 6 (HCl/MeOH 0° - 5°). Oxidation reduction coupling of 6 with succinimide provided 7 in 51% yield after column chromatography. In order to protect the carbonyl group in the next reduction step as well as to enhance the nucleophilic character of the olefinic bond in the ensuing cyclisation a prior acetalization to 8 proved necessary. The latter step was efficiently carried out with the aid of ethylenedioxy(bis)trimethylsilane/TMSOTf[7] (-8°- 0°C/ 3 hr). The OH-lactam 9 then was obtained quantitatively upon $NaBH_4/H^{\oplus}$ treatment of 8 and "base work-up" as an oil, ^{1}H-NMR ($CDCl_3$) of 9 δ 3.83 s (OCH_2CH_2O), 5.17 m (C<u>H</u>OH), 5.2-5.9 m (=CH). As mentioned before the next acid-catalyzed

cyclisation step of α-oxy olefines provided undesired byproducts which proved also to be the case in the HCOOH ring closure of 9. A dramatic improvement, however, occurred upon HCl/MeOH treatment of 9 (r.t., 18 hr) affording the chloride 10 quantitatively as a single stereoisomer. ^{1}H-NMR ($CDCl_3$, 250 MHz) δ 3.54 m $W_{\frac{1}{2}}$ = 25 Hz (NC<u>H</u> tert), 4.06 m $W_{\frac{1}{2}}$ = 27 Hz (C<u>H</u>Cl), 4.15 m (NC<u>H</u> sec). The observed $W_{\frac{1}{2}}$ values clearly indicate a 1,3 diaxial relation for the NC<u>H</u> and C<u>H</u>Cl protons involved, which in all probability points to a synchronous antiperiplanar mode of cyclisation[8]. One explanation for the anomalous behaviour of the $Cl^{\ominus}$ ion acting as the nucleophile of choice in the ring closure instead of the CH_3OH may be a template directing effect of the ketal group which functions both as the site of the necessary H^+ and Cl^- ions involved. This assumption has some interesting implications of which the indirect proof of the near-concertedness of three consecutive reactions viz the elimination of water from the protonated OH-lactam, the formation of the new carbon-carbon bond and the termination of the reaction by the capture of the nearby weak nucleophile Cl^- is obvious. Furthermore it can also be assumed that ring closure is faster than acetal hydrolysis[9].

The synthesis was completed by dehydrohalogenation with excess DABCN in toluene (18 hr, reflux) to give a quantitative yield of the unsaturated ketone 11, ^{1}H-NMR ($CDCl_3$) δ 6.98 m (<u>H</u>C=). The latter was reduced with $NaBH_4$ (0°C, 18 hr) quantitatively to the already known[10] lactam alcohol 12, which upon treatment with Dibal-H in Et_2O gave elaeokanine B (1).

The aforementioned results again confirmed the high synthetic potential of the α-acyliminium technique in the synthesis of alkaloids. In addition the question on the applicability of functionally substituted olefins as substrates in cationic cyclisations via the latter method has been satisfactorily answered.

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9. Verified by attempted cyclisation of the corresponding α,β unsaturated ketone which did not react under the reaction conditions.
10. Cf ref. 4b.

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