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THE SHERADSKY REARRANGEMENT OF α,α'-DISUBSTITUTED CYCLOPENTANONE ARYLOXIMES : A SYNTHESIS OF THE SESQUITERPENES (±)-APLYSIN AND (±)-FILIFORMIN

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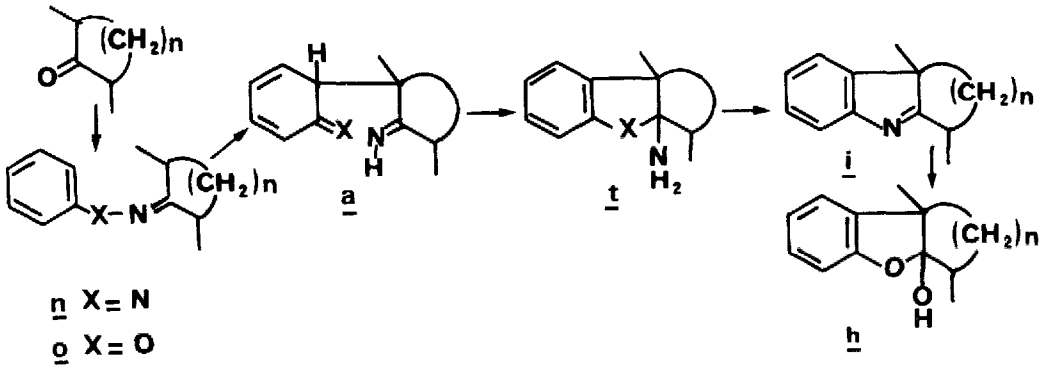
Abstract : Lactols 6a,b, obtained by the Sheradsky rearrangement of aryloximes o, were alkylated in to 9a, in which three contiguous chiral centers were controlled. Cyclization of 9a gave the marine sesquiterpenes (±)-aplysin 11 and (±)-filiformin 13.

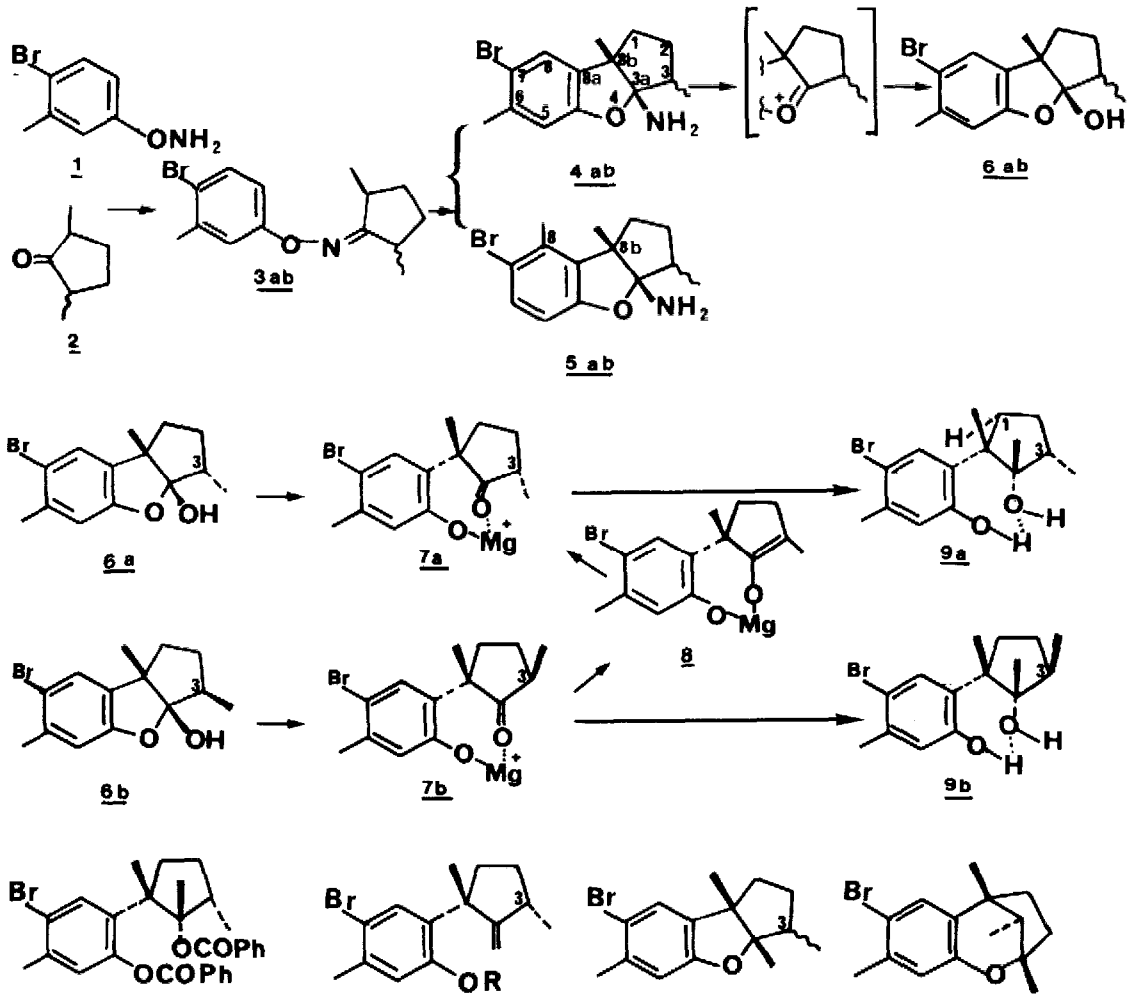
The Sheradsky rearrangement of aryloximes o[1] (Scheme), a modification of the Fischer indole[2] rearrangement of phenylhydrazones n, has apparently never been studied when starting from an α,α'-disubstituted cycloalkanone. In both cases, enolisation, followed by rearrangement and cyclisation to a similar intermediate a, should give an NH_2-substituted tricyclic compound t.



Scheme

With cyclohexanone (n=3), the Fischer indole reaction finally yields an indolenine i, upon elimination of ammonia from t (X=NH). We have recently demonstrated the easy nitrous deamination of indolenines i to hemiketals h[3], and we planned to extend the scheme to cyclopentanones (n=2), with the synthesis of benzofuranic sesquiterpenes in view. However, the Fischer "indolisation" of α-substituted cyclopentanones failed to give indolenines i[4]. Therefore, we turned to the Sheradsky rearrangement of aryloximes o (n=2), which could possibly lead to hemiketals h.

5-Aminoxy-2-bromotoluene 1 was prepared by a rather lengthy known procedure[5] and further reacted with 2,5-dimethylcyclopentanone 2 to yield oximes 3a,b, along with notable quantities of 3-bromo-m-cresol[6]. 3a and 3b could be separated and characterised ; however, owing to their instability, the crude reaction mixture was used in the following reaction.



R=-COPh : 12a
R=-H : isolaurinterol

C-3-αMe : 11a : aplysin
C-3-βMe : 11b : epiaplysin

13 : filiformin

The acid catalysed rearrangement (TsOH, MeOH, reflux) furnished three groups of products : aminals 4a,b (24%), their regioisomers 5a,b (23%) and 3-bromo-m-cresol (25%). The cyclisation was completely devoid of regioselectivity and the a/b ratio in 4 and 5 was the same as in 3 (NMR). The mixture of the four aminals (4-5a,b) was heated in 60% aqueous acetic acid. Only 4a,b were converted into hemiketals 6a,b. In 5a,b, the formation of the intermediate oxonium was prevented as there would be a strong steric interaction of the two methyl groups at C-8 and C-8b. This allowed a very clean isolation of the non-basic hemiketals 6a,b from the reaction mixture.

Alkylation of the diastereoisomeric mixture 6a,b with MeMgBr required a large excess of reagent, and prolonged reaction times. However, this reaction was highly rewarding as it fortuitously allowed a stereochemical control of the three adjacent asymmetric centres of the cyclopentane ring : in most runs, the pure (racemic) 9a[7] was the only product (60%) of the reaction (in some runs, 10% of its diastereomer at C-3 9b was obtained). This result (at least) implies epimerisation of the secondary methyl group at C-3 in 6b, through the magnesium pheno-enolate 8, which could be formed in the second step of the reaction from the quasi-rigid Mg^{++}-chelating keto-phenolates 7a and 7b. In the case of 7b, the carbonyl group is severely hindered, thus making enolisation (→ 8) faster than alkylation (→9b).

The role of metal cations in the stereoselectivity of reactions of lactols with organometallic or hydride reagents has been recently emphasised[8]. To the best of our knowledge, this had never been combined with an epimerisation of a vicinal chiral center.

The dibenzoate 10a, when heated at 350°C under reduced pressure (0.1 mmHg), led in poor yield to a mixture of (±)-aplysin 11a and benzoate 12a ((±)-isolaurinterol benzoate)[9] but not to 3-epiaplysin 11b. These results, which formally achieve a stereocontrolled synthesis of (±)-aplysin, unambiguously prove the α-configuration at C-3 in the starting pheno-alcohol 9a.

Heating alcohol 9a in acetic acid containing traces of TsOH gave (±)-aplysin 11a (21%) and a mixture (32%) of (±)-filiformin 13 and (±)3-epiaplysin 11b (3/1, NMR). Repetitive chromatography enabled us to obtain an analytical sample of pure 13 and 11b. All IR, MS, ^1H and ^{13}C NMR data for 11a, 11b and 13 were identical with those described in the literature[10].

These results compare favourably with previous syntheses of aplysin[11a-e] and of filiformin[11d].

Work is in progress in our laboratories on the synthesis of debromo-analogues, using the more expeditive synthesis of aryloximes o recently developed by Alemagna and coworkers[12].

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4. These results will be discussed elsewhere.
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7. The I.R. spectrum of 9a showed internal H bonding, and its ^1H NMR spectrum exhibited a low field signal at 2.9 ppm (ddd) ; COSY experiments showed it to be C-1-αH, whose position in the plane of the aromatic ring is in favour of the stereochemistry depicted.
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   All other compounds were fully characterised (UV, IR, MS, ^1H and ^{13}C NMR).
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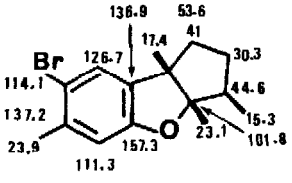
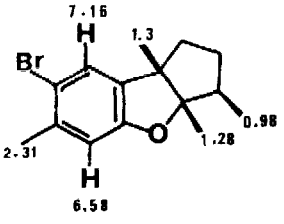
    Filiformin 13 : Kaslauskas R., Murphy R.J., Ronald J.Q. and Robert J.W., **Aust.J.Chem.**, 1976, 29, 2533.
    3-Epiaplysin 11b : our ^1H and ^{13}C NMR data are as follows ($CDCl_3$) :





    In his total synthesis of aplysin[11a], Yamada obtained a by-product that he refered to an isomer of either aplysin or of filiformin. According to the published data we think it is 3-epiaplysin.

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