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The Rearrangement of some Cyclopentanone-Aryloximes : Synthesis of (±)-Aplysin, (±)-Filiformin and of their Debromo Analogues.

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Abstract : upon acid catalyzed rearrangement after Sheradsky, the aryloximes **A** gave the tricyclic aminals **C**, which suffered hydrolysis to lactols **E**. The unique alcohol **29** was then prepared through a highly stereoselective equilibration-reductive alkylation of the epimeric mixture of lactols **22a,b**. Two routes, one of which was stereospecific, allowed cyclization of **29** to (±)-aplysin **34**. The yield was 2.5 % from oximes **2a,b**. The isomeric *epi*-aplysin **35** and filiformin **36** were also obtained from **29**. The debromo analogues **37**, **38** and **39** and their trideutero derivatives **41**, **42** and **43** were synthesized along similar line and allowed unequivocal structure elucidation by NMR spectroscopy.

The marine sesquiterpene aplysin and its congeners epiaplysin, isolaurenterol and filiformin obviously originate from an unrearranged cuparane cation through methyl migrations and further abstraction of an aliphatic or phenolic proton (Chart I). Aplysin itself, which showed some antimicrobial properties[1], was isolated[2] from the sea hare *Aplysia kurodai*, whose ordinary food is a seaweed of the genus *Laurencia*, which contains related sesquiterpenes.

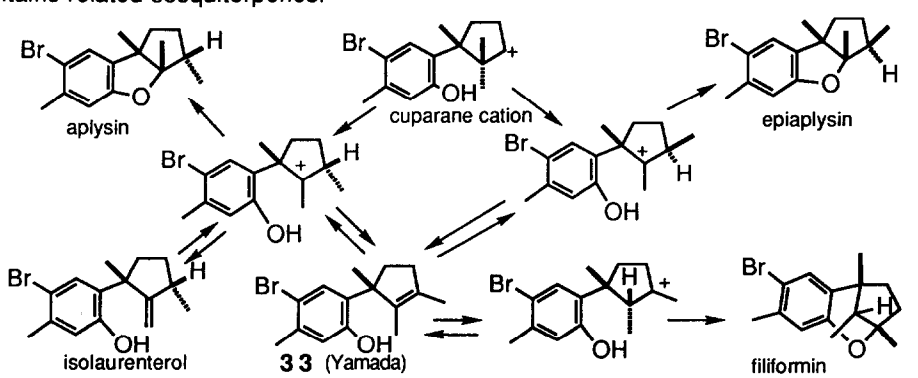
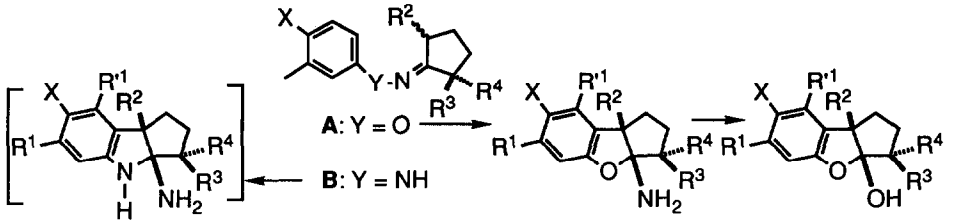


Chart 1

Apart from elaboring the cyclopentanodihydrobenzofurane ring system, the synthesis

of aplysin implies generation of two spiro carbons, and control of three consecutive stereocenters. Several non stereospecific and stereospecific solutions were given : in the early synthesis by Yamada[3], olefin **33** suffered an acid catalyzed cyclisation to aplysin and "an isomer of aplysin". Ronald[4] succeeded in the first stereoselective synthesis of aplysin by controlling the configuration of the *endo* secondary methyl group through hydrogenation of a cyclopentene intermediate. Since that time, some other syntheses of aplysin and its congeners were published[5,6].

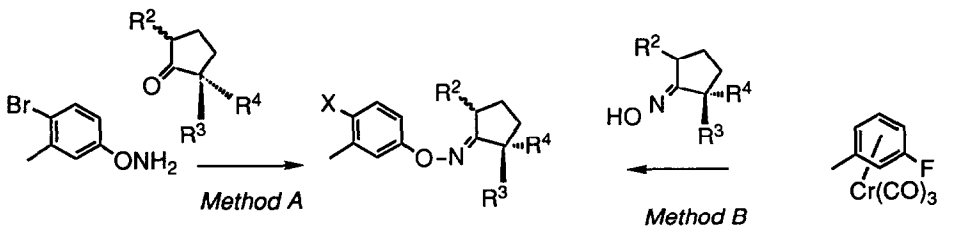


D: *gem* - diamines **C**: aminals **E**: hemiketals

Chart 2

Our first approach (Chart II) was based on our nitrous acid deamination of indolenines to dihydrobenzofuranes[7] and thus implied generation of cyclopentane-fused indolenines. However, the Fischer indolization of phenylhydrazones **B** failed to give the expected indolenines (or *gem*-diamines **D**), which spontaneously gave dimers and/or ring cleaved derivatives[8]. Therefore we rapidly turned to the oxygen counterpart of the Fischer's synthesis of indoles, namely the [3,3] rearrangement of aryloximes described by Sheradsky[9]. Extension of Sheradsky's results to the aryloximes of α,α'-disubstituted cyclopentanones **A** was supposed to yield aminals **C** and then hemiketals **E**. Following this strategy, syntheses of (±)-aplysin, (±)-epiaplysin, (±)-filiformin and of their debromo analogues are now described with experimental details[10].

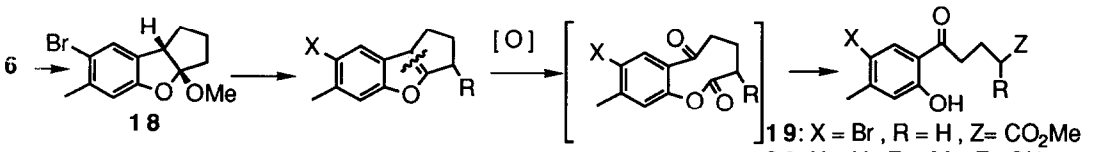
Aryloximes 1-5 (Table 1) : At the time when this work was initiated, aryloximes in the brominated series (X = Br) were obtained[11] by reacting the cyclopentanones with a suitable aminoxybenzene, whose synthesis from the corresponding phenol was itself rather long (method A). Consequently, the yields were not satisfactory.The reaction of oximes with fluorinated chromium-tricarbonyl arenes, followed by oxidative cleavage of the ligand, was shortly after disclosed by Alemagna[12], and conveniently applied to the debromo series (X= H: method B)



In all possible cases, oximes **A** were obtained as stereoisomeric mixtures[13] (**a**, **b**) that could be separated by t.l.c, but they were engaged into further reactions without any purification.

Rearrangement of the aryloximes: obtention of aminals 5-17 (Table 1) : The Sheradsky's rearrangement of aryloximes **1-5** was smoothly performed upon heating their methanolic solutions in the presence of catalytic amounts of *para*-toluenesulfonic acid. Despite numerous attempts of modifying the reaction conditions, the yields of benzofuranes remained low (40-50 %), due to a competition with the Beckman rearrangement[11] affording phenol (*ca* 25 %) as a by-product (no efforts were made to isolate the probably formed lactams). When other acids (hydrochloric, sulphuric) were tested as catalysts, phenol was the sole aromatic product to be obtained. Aminals **C** were obtained from all the reacted aryloximes, excepted **6** from **1**. The reaction was unfortunately completely devoided of regio- and stereoselectivity, and it simultaneously gave products of the aplysin series (methyl attached on C(6), even numbers) and products of the regioisomeric series (methyl attached on C(8), odd numbers). When R^3 was different from R^4, the reaction was still complicated by the formation of the stereoisomers (marks **a** and **b**), that could be separated, but whose ratio was estimated by NMR measurements.

In the case of oxime **1**, supplementary products were ketal **18** (originating from **6**), and the ketoester **19**, which obviously resulted from oxidation of an intermediate cyclopentanobenzofurane followed by methanolysis of the resulting ketolactone:



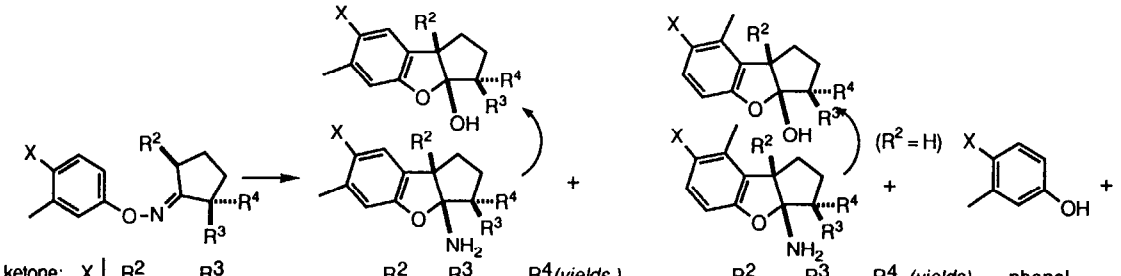
Oximes **3** similarly yielded ketonitrile **20** as a by-product. Isolation of compounds **18** and **20** was then the only result showing elimination of ammonia from aminals to occur, while the highly oxidable parent benzofuranes were not isolated.

Salient spectroscopic features common to compounds **7-17** were their UV spectra, with maxima at 210, 230 and 290 nm, and the ^{13}C chemical shift of the aminal-C(3a) at 109 ppm. On the ^1H NMR spectra, compounds with a methyl group borne by the benzylic C(8b) gave rise to a singlet at 1.35-1.45 ppm, and those with an hydrogen on C(8b) gave a double doublet (J_1= 3 Hz; J_2= 9 Hz) around 3.5 ppm, while distinction between the C(6)-Me and the C(8)-Me series was easily deducted from the substitution pattern of the arylic part of the molecule.

Lactols 21-26 (Table 1): Transformation of aminals **7-17** into lactols **21-26** was performed by heating in dilute acetic acid. However, aminals bearing methyl groups on both C(6) and C(8b) were not hydrolyzed, thus indicating that the intermediate planar oxonium (or carbonium) ion was not formed. Formation of such a cation actually tends to flatten the tricyclic system, a situation which the two neighbouring methyl groups cannot sterically manage with. This observation proved to be useful for the separation of the two regioisomeric series of compounds after successive

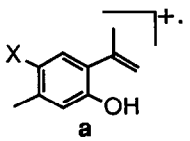
Table 1 : Aminals **C** and Lactols **E**

starting material (aminals)	X		R^2	R^3	R^4 *(yields)*		R^2	R^3	R^4 *(yields)*
7	Br					**21**	H	H	H *(70)*
8a	Br	**22a**	Me	H	Me *<- (71)*				
8b	Br	**22b**	Me	Me	H				
10	H	**23**	Me	H	H				
12a,13a	H	**25a**	H	H	Me *<- (80) ->*	**24a**	H	H	Me
12b,13b	H	**25b**	H	Me	H	**24b**	H	Me	H
14a	H	**26a**	Me	H	Me *<- (74)*				
14b	H	**26b**	Me	Me	H				



(*yields* from ketone; a=less polar:b)	X	R^2	R^3 R^4	R^2	R^3	R^4 *(yields)*	R^2	R^3	R^4 *(yields)*	phenol *(yields)*	by-products *(yields)*
1 *(99)*	Br	H	H,H	**[6]**	H	H	H *(0)*	**7**	H	H	H *(25)*	*(30)*	**18** *(14)* **19** *(9)*
2a,b *(90; 2.2:1)*	Br	Me	H,Me	**8a**	Me	H	Me *<-(21)*	**9a**	Me	H	Me *<-(20)*	*(25)*	
				8b	Me	Me	H	**9b**	Me	Me	H		
3a,b *(78 ;3:1)*	H	Me	H,H	**10**	Me	H	H	**11**	Me	H	H	*(18)*	**20** *(9)*
				12a	H	H	Me *<- (30) ->*	**13a**	H	H	Me		
				12b	H	Me	H	**13b**	H	Me	H		
4a,b *(75 ;3,1)*	H	Me	H,Me	**14a**	Me	H	Me *<-(22)*	**15a**	Me	H	Me *<-(19)*	*(25)*	
				14b	Me	Me	H	**15b**	Me	Me	H		
5 *(27)*	H	Me	Me,Me	**16**	Me	Me	Me *(10)*	**17**	Me	Me	Me *(9)*	*(31)*	

rearrangement and hydrolysis, as the neutral lactols were conveniently extracted in acidic medium while the basic unreacted aminals were not. Starting from oximes **3**, further attempts to separate the stereoisomers **10-13** were unsuccessful. Transformation of the aminals into lactols did not induce major changes in their UV spectra. The IR spectra (films) exhibited weak absorptions in the 1720 cm^{-1} area, which evidenced an equilibrium with the bicyclic ketophenols. The molecular peaks on the mass spectra had gained one mass unit and the fragmentation was dominated by the occurrence of the aromatic ion **a**, m/z 226-228 (X= Br) and m/z 148 (X= H). The ^{13}C NMR signal of the hemiketalic C(3a) was at 115-119 ppm.



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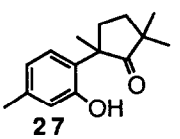

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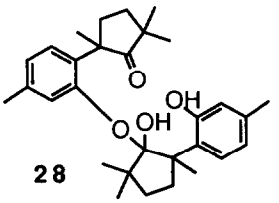

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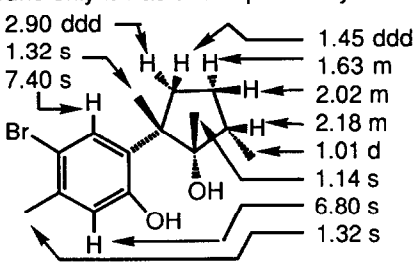
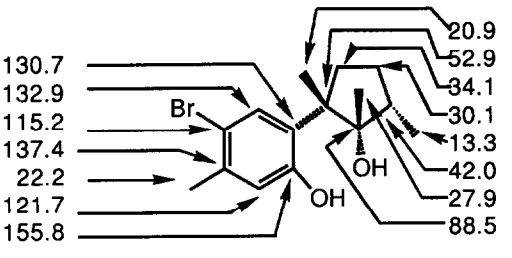
Ketone **27** and/or dimer **28** were obtain in low yield from the mixture of congested aminals **16** and **17**, in place of the lactol. This result parallels our finding concerning the Fischer cyclization of cyclopentanone phenylhydrazones[8], where the more highly substituted cyclopentanones were the pronest to yield dimeric or ring-cleaved products. With regard to the reaction described below, it is of interest to note that lactols **22a,b** and **26a,b** were respectively formed as a nearly 1:1 (unseparable) stereoisomeric mixture.

Akylation of lactols 22 and 26 : Reaction of the stereoisomeric mixture of lactols **22a,b** with an excess of methylmagnesium iodide in ether unexpectedly, but rewardingly, yielded alcohol **29** as the *sole* or as the *highly major* (racemic) *stereoisomer*. The yield of **29** was up to 55 % and in some runs only it was accompanied by a small amount (0- 15 %) of isomer **30**.



29 : ^{1}H NMR

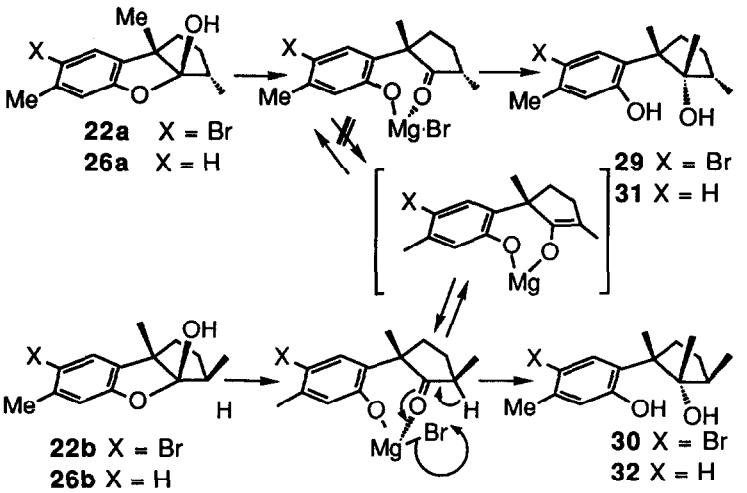


29 : ^{13}C NMR

In the debromo- series, the less acidic hemiketals **26a,b** similarly gave alcohol **31** (up to 72 %), eventually with its stereoisomer **32** (0-15 %). The ^{1}H-^{1}H homonuclear correlation NMR spectra (COSY) of **29** and **31** agreed with the depicted relative configurations. A significative feature in the spectra was the downfield shift of the (*rel*) C(1)-α-H (2.90 ppm for **29**) due to its orientation in the plane of the benzene ring. The relative configurations of **29** and of **31** were further ascertained by their transformations into natural products of known structure as described bellow.

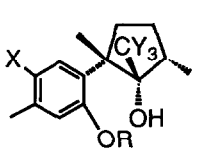
As their two stereoisomers were in a 1:1 ratio in the starting materials, in each case, the yield of the obtained major (or unique) trimethyl derivative clearly demonstrated that a stereoselective (or stereospecific) equilibration had occurred. Such an equilibration is thought to imply the magnesium

pheno-enolate salt whose geometry clearly favors both protonation and attack of the Grignard reagent from the less hindered (*rel*) β-*exo*-face. An uncontrolled proportion of α-protonation accounts for the eventual formation of **30** *vs* **29**.

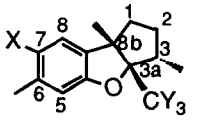


The influence of metal cations in the stereoselectivity of reactions of lactols with organometallic or hydride reagents has already been studied[14]. However, combination of this effect with an enantioselective epimerisation at a vicinal chiral center is apparently much less precedented.

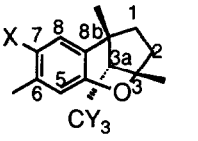
Cyclizations of alcohols 29 and 31. Syntheses of aplysin, epi-aplysin, filiformin and their debromo analogues : Upon treating alcohol **29** under Yamada's acidic cyclization conditions[3], three tricyclic compounds were actually obtained, and further separated by t.l.c. They were the following: the less polar aplysin **34** (31 %), compound **35** (7 %), whose spectroscopic features agreed with those of Yamada's "isomer of aplysin", and filiformin **36**[5] (27 %). While **34** and **36** could be undoubtly identified with the natural products, assignment of a 3-*epi*-aplysin vs 3-*epi*-filiformin structure to **35** remained uncertain.This problem was solved by performing the syntheses of the debromo-analogues **37**-**39** and of their trideuterated derivatives **41**-**43** as follows: acidic cyclization of alcohol **31** yielded compounds **37**, **38** and **39**,which were separately



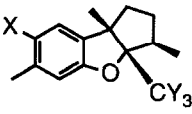
29 : X = Br, Y= H, R = H
31 : X = H, Y = H, R = H
40 : X = H, Y = D, R = H
49 : X = Br, Y =H, R = Ac



34 : X=Br, Y=H:aplysin
37 : X = Y = H
41 : X=H, Y=D



36 : X=Br, Y=H: filiformin
39 : X = Y = H
43 : X=H, Y=D



35 : X=Br, Y=H:*epi*- aplysin
38 : X = Y = H
42 : X=H, Y=D

Table 2. NMR Data of Aplysin Derivatives.

^{13}C (75 MHz) and ^{1}H (300 MHz)

n°	X	C1	C2	C3	C3a	C4a	C5	C6	C7	C8	C8a	C8b	C3-Me	C3a-Me	C6-Me	C8b-Me	Notes
34	Br	42.5	31.2	46.0	99.8	158.8	110.9	136.9	114.0	126.5	136.2	54.3	13.1	23.1	23.4	19.9	(1)
35	Br	44.7	30.2	41.0	101.9	157.2	111.3	137.2	114.1	126.7	136.9	53.6	15.3	23.1	23.9	17.4	
36	Br	42.2	37.3	85.5	46.4	152.4	117.5	136.5	114.4	128.4	130.2	44.9	20.5	7.4	23.0	22.5	(1)
37	H	42.6	31.4	46.1	98.9	158.9	109.3	137.8	120.7	122.5	-	54.0	13.1	23.1	24.1	20.0	
38	H	44.8	30.3	41.1	100.9	157.9	109.7	138.2	120.6	122.7	-	53.3	15.4	21.5	24.1	17.5	
39	H	42.3	37.3	85.1	46.6	153.1	115.7	134.4	120.9	124.8	-	44.8	20.6	7.5	23.5	21.0	

(1): in good agreement with ref. 16

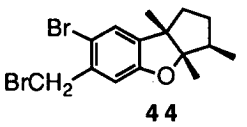
n°	X	Y	C3a-C**Y$_3$**	C5-**H**	C7-**H**	C8-**H**	C3-C**H3**	C6-C**H3**	C8b-C**H3**	Notes
34	Br	H	1.29 s	6.59 s	-	7.14 s	1.10 d	2.31 s	1.33 s	(1) (2)
35	Br	H	1.28 s	6.58 s	-	7.17 s	0.98 d	2.31 s	1.31 s	(1)
36	Br	H	0.78 d	6.59 s	-	7.19 s	1.33 s	2.29 s	1.40 s	(1) (3)
37	H	H	1.32 s	6.54 s	6.66 d	6.92 d	1.13 d	2.30 s	1.34 s	(1) (2)
38	H	H	1.29 s	6.54 s	6.69 d	6.95 d	1.00 d	2.30 s	1.33 s	(2)
39	H	H	0.79 d	6.53 s	6.69 d	7.00 d	1.35 s	2.28 s	1.42 s	
41	H	D	-	6.53 s	6.65 d	6.92 d	1.12 d	2.30 s	1.33 s	
42	H	D	-	6.53 s	6.68 d	6.95 d	1.00 d	2.30 s	1.32 s	
43	H	D	-	6.52 s	6.68 d	6.99 d	1.35 s	2.28 s	1.41 s	

(1): H-H COSY spectra

(2): in good agreement with ref. 6

(3): in good agreement with ref.17

brominated (Br_2,K_2CO_3): compound **37** thus gave aplysin **34**, confirming that **37** should be debromoaplysin. Bromination of **38** was less straightforward as, beside **35** (26 %),overbrominated products which were ascribed the structures **44** and **45** were simultaneously obtained. Similarly, compound **39** yielded filiformin **36** and the overbrominated derivative **46**.



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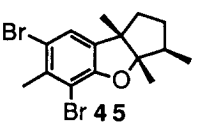

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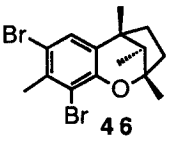

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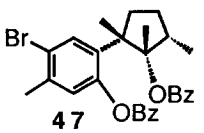
These correlations prove the validity of the above syntheses in the debromo series and allow to infer structural informations from one to the other series. In a similar fashion as for **31**, the trideuterated alcohol **40**, obtained by reacting lactol **26** with CD_3MgI, was cyclized to **41**, **42** and **43**, whose spectroscopic features left no doubt concerning the above depicted structures of **34**-**39**. The NMR spectra (Table 2) of **41** and **42** were consistent with an aplysin skeleton in both cases, as the two compounds exhibited a methyl doublet, at 1.12 and 1.00 ppm respectively , while deuteration had erased a methyl singlet (C(3a)-CD_3). Comparaison of NMR spectrum of the trideuterated compound **43** with that of the non deuterated **39**, showed that a methyl doublet has disappeared, in agreement with the filiformin structure. The configuration of the methyl group on C(3a) in **39** was deduced from the above mentioned correlation with the known filiformin, and additionally confirmed (as in filiformin itself) by its upfield shift (^1H NMR) to 0.79 ppm, due to the anisotropy of the benzene ring. This orientation is obviously favoured by the lack of interaction with the cyclopentane hydrogen atoms. Acidic treatment of alcohol **29** had generated Yamada's olefin **33**, whose further cyclization was neither regio- nor stereospecific, and thus all the benefits of the precedent stereoselective reaction had been lost. Therefore, the following indirect cyclization route was devised. Although yields were poor, this last route appeared intrinsically stereospecific : Alcohol **29** was acylated to its dibenzoate **47**, which was thermolyzed under reduced pressure at 400°C to yield isolaurinterol[15] benzoate **48**, along with aplysin **34**, but neither 3-*epi*-aplysin nor filiformin could be detected.



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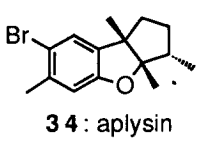

34: aplysin

This alternative synthesis of aplysin **34** from alcohol **29** confirms the *trans* relationship of the methyl groups attached to C(3) and to C(8b) in **29**.

Despite a close analogy between the two [3,3] sigmatropic processes, the Sheradsky's rearrangement of aryloximes in the cyclopentanone series appears then to be a valuable means of constructing cyclopentano[b]dihydrobenzofurane derivatives, whereas the Fischer rearrangement of the corresponding phenylhydrazones had failed to give cyclopentano[b]dihydroindoles. It was demonstrated however during this work that overcrowding the cyclopentane ring in the aryloxime series meets with the sort of difficulties more generally encountered in the phenylhydrazone series. Nevertheless, further applications of the Sheradsky's rearrangement to the synthesis of natural products are under current interest.

EXPERIMENTAL

All commercially available products were purchased from Aldrich, and were used without purification ; UV spectra were measured on a Varian 634 apparatus, IR spectra were recorded on a Beckman Acculab 4, ^1H (300 MHz) and ^{13}C (75 MHz) NMR spectra were measured using $CDCl_3$ solutions on a Bruker AC 300 : HREIMS spectra (E=-70 eV) were obtained on a JEOL JMS D-300 spectrometer: m/z (rel abundance %), Merck Kieselgel 60 Pf 254 was used for thin layer chromatography (TLC) or centrifugal chromatography (CC).

Starting materials: 2,2,5-trimethyl cyclopentanone was prepared along Dubois' procedure[18] ; tricarbonyl chromium complexes were prepared from the corresponding *m*-fluorotoluene[19]; *p*-bromo-*m*-cresol was obtained by decomposition of the diazonium salt issuing from nitrosation of *p*-bromo-*m*-toluidine[20]and 5-aminoxy-2-bromotoluene was prepared in 27 % yield from 1,3-dinitro-fluorotoluene[21] (3 steps).

Preparation of aryloxines A: *Method A* : 5-aminoxy-2-bromotoluene was condensed with ketone **K** along Rapoport's procedure. *Method B*: Oximes **0** (prepared from ketone **K** and hydroxylamine) were reacted with fluoroarene chromium complexe along Alemagna's report[12]. Aryloximes **A** could not be purified by chromatography ; yields given in table 1 refer to crude products. **1** could not be isolated ; selected data for **2a**: IR (neat) 1640, 1590, 1560 cm^{-1}; ^1H NMR 1.22 (3H, d, J= 7Hz), 1.28 (3H, d, J= 7Hz), 2.37 (3H, s); ^{13}C NMR 175.4, 159; MS 297 and 295 ($M^{+\cdot}$, 7), 186 (100). **2b**: ^1H NMR 1.22 (3H, d, J= 7Hz), 1.28 (3H, d, J= 7Hz), 2.38 (3H, s). **3a,b**: IR (neat) 1640, 1590, 1575 cm^{-1}; ^1H NMR 1.20 (3H, d, J= 7Hz), 2.28 (s) and 2.30 (s) (3H); MS 203 ($M^{+\cdot}$, 6), 108 (100). **4a,b**: ^1H NMR 1.23 (3H, d, J= 7Hz), 1.28 (3H, d, J= 7Hz), 2.28 (s) and 2.32 (s) (3H); ^{13}C NMR 175.8 and 175, 159.8 and 155.6; MS 217 ($M^{+\cdot}$, 7), 108 (100).

Scheradsky rearrangements of aryloximes A : aminals C. In a typical procedure, a solution of **A** (3 mmol) and tosylic acid (1,5 mmol) in 20 ml absolute ethanol was refluxed (2-3 hr) until disappearance of **A** (TLC). Ethanol was distilled, the residue was dissolved in CH_2Cl_2; the solution was washed with 10 % aqueous $NaHCO_3$, dried with $MgSO_4$, then evaporated. The residue was chromatographied (CC or TLC). Analytically pure **C** could be only obtained after one (sometimes several) further separation(s): eluant, CH_2Cl_2. Selected data: **7**: UV λ_{max} 206, 230, 290 nm; IR (neat) 3310, 1630, 1580 cm^{-1}; ^1H NMR 2.3 (3H, s), 3.42 (1H, dd, J= 3x9Hz); MS 269 and 267 ($M^{+\cdot}$, 100), 238 and 240 (70). **18**: UV λ_{max} 205, 220, 287; ^1H NMR 2.35 (3H, s), 3.34 (3H, s); MS 284 and 282 ($M^{+\cdot}$, 100), 146 (80). **19**: IR (neat) 1725, 1715, 1640, 1550 cm^{-1}; ^1H NMR 2.39 (3H, s), 3.7 (3H, s); MS 316 and 314 ($M^{+\cdot}$, 30), 215 and 213 (100). **8a,b:** mp 118-120°C; ^1H NMR 1.1 (d) and 1.12 (d) (3H, J= 7Hz), 1.33 (s) and 1.47 (s) (3H), 2.3 (s) and 2.37 (s) (3H); ^{13}C NMR 156.8, 110.2 and 108.8. HREIMS 290. 0638 and 295. 0662 ($M^{+\cdot}$, $C_{14}H_{18}BrNO$, 100 %); anal. calcd. for $C_{14}H_{18}BrNO$: C 56.77, H 6.12, N 4.73; found C 56.59, H 6.34, N 4.20. **9a** (less polar): mp 89-92°C; ^1H NMR 1.08 (3H, d, J= 7Hz), 1.33 (3H, s), 2.34 (3H, s); MS 297 and 295 ($M^{+\cdot}$, 80), 239

(100); anal. calcd. for $C_{14}H_{18}BrNO$: C 56.77, H 6.12, N 4.73; found C 56.34, H 6.14, N 4.56. **9b** (less polar): mp 88-89°C; ^1H NMR 1.10 (3H, d, J= 7Hz), 1.46 (3H, s), 2.37 (3H, s); (other data very similar with **9a**. Mixture of isomers **10, 11, 12 and 13**: ^1H NMR 1.12 (d, J= 7Hz), 1.14 (d, J= 7Hz), 1.32 (s), 1.4 (s), 2.24 (s), 2.29 (s), 2.34 (s); MS 203 ($M^{+\cdot}$, 100), 160 (90). **20**: IR 2210, 1640, 1600 cm^{-1}; ^1H NMR 1.4 (3H, d, J= 7Hz), 2.35 (3H, s); ^{13}C NMR 203.6, 116.9; MS 217 ($M^{+\cdot}$, 12), 135 (100). **14a,b**: ^1H NMR 1.07 (d) and 1.16 (d) (3H, J= 7Hz), 1.38 (3H, d, J= 7Hz), 2.3 (s) and 2.37 (s) (3H); MS 217 $M^{+\cdot}$, 7), 115 (100). **15a** (less polar): mp 98-100°C; ^1H NMR 1.1 (3H, d, J= 7Hz), 1.35 (3H, s), 2.32 (3H, s), analo. calcd. for $C_{14}H_{19}NO$: C 77.38, H 8.81, N 6.45; found: C 77.68, H 8.82, N 6.32. **15b** (more polar): mp 95-97°C; ^1H NMR 1.15 (3H, d, J= 7Hz), 1.5 (3H, s), 2.33 (3H, **16**: IR (film): 3500, 1575 cm^{-1}. MS: 231 ($M^{+\cdot}$, 100), 160 (100), 148 (70); ^1H NMR, 6.97 (1H, t, J = 7 Hz), 6.90 (1H,d , J= 7 Hz), 6.60 (d 1H, J= 7 Hz), 2.35 (s, 3H), 1,52 (s, 3H), 1.13 (s, 3H), 1.07 (s, 3H). ^{13}C NMR 157.1, 137.9, 134.0, 127.7, 122.6, 109.5, 53.9, 46.4, 40.4, 37.4, 23.2, 22.9, 21.5, 18.0. **17**: ^1H NMR 6.66 (1H, d, J= 7 Hz), 6.50 (s, 1H), 2.30 (s, 3H), 1.43 (s, 3H), 1.16 (s, 3H), 1.06 (s, 3H).

Obtention of lactols E and of 27 and 28. Aminal **C** (1 mmol) was heated for 3 hr at 100°C in 10 ml of 60 % aqueous acetic acid, under argon. Water (40 ml) and $NaHCO_3$ (up to pH 9) were added. The solution was extracted with CH_2Cl_2. Combined extracts were washed with 1N aqueous HCl, dried with $MgSO_4$, then evaporated. The residue was then chromatographied (TLC); eluant : CH_2Cl_2. Selected data: **21**: UV λ_{max} 205, 230, 287 nm; IR (neat) 3360, 1640, 1570; ^1H NMR 3.48 (1H, dd, J= 3x9 Hz), 6.52 (1H, d, J= 9Hz), 7.3 (1H, d, J= 9Hz); MS 270 and 268 ($M^{+\cdot}$, 100), 214 and 212 (70). **22a,b**: mp 109-111°C; ^1H NMR 1.1 (d) and 1.16 (d) (3H, J= 7Hz), 1.33 (s) and 1.39 (s) (3H, J= 7Hz), 2.29 (s) and 2.32 (s) (3H, J= 7Hz); ^{13}C NMR 156.6, 137.3, 135.1, 126.7, 120.1, 115.1, 111.1. HREIMS 298.0391 and 296.0397 ($M^{+\cdot}$, $C_{14}H_{17}BrO_2$, 70 %), 228 and 226 (100), anal. calcd. for $C_{14}H_{17}BrO_2$: C 56.58, H 5.77; found: C 56.50, H 5.73. **23a,b ,24a,b ,25 (mixture of isomers)**: ^1H NMR: 1.12 (d, J=7 Hz), 1.15 (d, J= 7Hz), 1.35 (s), 2.23 (s), 2.28 (s); ^{13}C NMR (C_{IV} + C_{II}) 158.2, 157.6, 157.2, 138.2, 138.1, 134.6, 132.0, 129.4, 129.1, 120.6, 120.4, 119.6, 52.4, 42.7, 39.5, 32.5, 32.0, 30.0, 29.7, 21.9; (C_{III} + C_I) 128.1, 128.0, 122.8, 122.0, 121.9, 121.6, 109.5, 106.9, 106.5, 51.5, 50.9, 44.3. 43.2, 21.8, 21.4, 18.3, 18.2, 13.4, 11.8; MS 204 ($M^{+\cdot}$, 80), 148 (50). **26a,b**: ^1H NMR 1.2 (3H, d, J= 7Hz), 1.38 (3H,s), 2.31 (3H, s); MS 218 ($M^{+\cdot}$, 30), 148 (100), anal. calcd. for $C_{14}H_{18}O_2$: C 77.03, H 8.31; found: C 76.89, H 8.20. **27**: IR (neat) 3500, 1730, 1580 cm^{-1}; ^1H NMR 1.07 (3H, s), 1.12 (3H, s), 1.40 (3H, s), 2.26 (3H, s); ^{13}C NMR 219.8, 155, 139.2; HREIMS 232.1416 ($M^{+\cdot}$, $C_{15}H_{20}O_2$, 10 %), 148 (100). **28**: mp 60-62°C; IR (neat) 1700 cm^{-1}; ^1H NMR 6.59 (1H, s), 6.70 (2H, d, J= 8Hz), 6.78 (1H, s), 6.93 (1H, d, J= 8Hz), 7.05 (1H, d, J= 8Hz); ^{13}C NMR 230.1, 155.0, 109.5 (hemiacetalic carbon); HREIMS 464.3005 ($M^{+\cdot}$, $C_{30}H_{40}O_4$, 5 %), 148 (100), anal. calcd. for $C_{30}H_{40}O_4$: C 77.55, H 8.68; found: 77.31, H 8.38.

Obtention of alcohols 29, 31, 40 and their stereoisomers 30 and 32. A solution of lactol **E** (1 mmol) in 3 ml of absolute ether was added at r.t. to an etheral solution of methylmagnesium iodide (trideuteromethylmagnesium iodide in the case of **40**) (6 ml, 3-3.5 eq.) The mixture was refluxed for 8 hr ; after cooling, a few drops of 1N aqueous HCl were added, and the mixture was diluted with 20 ml of a saturated NaCl aqueous solution. It was extracted with ether. Combined extracts were dried ($MgSO_4$) and evaporated. The residue was chromatographied (TLC), eluant CH_2Cl_2. Alcohols **30** and **32** were more polar than their respectives isomers **29** and **31**; compounds **29**: mp 118-120°C; UV λ_{max} 207, 230, 285; IR ($CHCl_3$ soln) 3620, 3320, 1535 cm^{-1}; HREIMS 314.0797 and 312.0744 ($M^{+\cdot}$, $C_{15}H_{21}BrO_2$, 40%) , 215 and 213 (100), unsatisfactory analysis, but monoacetate **49** (mp 117°C) gives C 57.62, H 6.49 for $C_{17}H_{23}BrO_3$ (calcd.: C 57.47, H 6.53). **30**: mp 122-124°C; ^1H NMR 0.9 (3H, d, J= 7Hz), 1.24 (3H, s), 1.43 (3H, s); ^{13}C NMR 18.8 (C3a-CH3); MS nearly identical with **29**. Compound **31**: mp 127-129°C ^1H NMR 1.32 (3H, s, C8a-CH3), 2.94 (1H, m, C1-αH); ^{13}C NMR 88.0 (C3a); MS 234 ($M^{+\cdot}$, 15), 135 (100). **32**: 107-109°C; ^1H NMR 0.9 (3H, d, J= 7Hz), 1.23 (3H, s), 1.46 (3H, s); MS nearly identical with **31**.

Cyclization of alcohols 29, 31, 40 : The alcohol (0.2 mmol) was heated (100°C) in AcOH (5 ml) containing 5 mg TsOH, during 3-4 hr (TLC monitoring), under Ar atmosphere. AcOH was then evaporated; the residue was dissolved in CH_2Cl_2 (20 ml). The solution was made neutral with $NaHCO_3$, and dried with $MgSO_4$. Separation was performed by TLC (eluant : hexane/CH_2Cl_2 1:1); in the case of alcohol **29** the separation gave **34** (aplysin, less polar, 31 %), and the 1:4 mixture (34%) of **35** (*epi*-aplysin) and **36** (filiformin) ; in the case of alcohol **31**, all three compounds were separated : **37** (less polar: debromo-aplysin: 27 %), **38** (debromo-*epi*-aplysin: 10 % and **39** (debromofiliformin: 12 %) the; trideuteriated analogue **40** gave **41**, **42** and **43** (increasing polarity), in 20 %, 8 %, 8 % yields respectively (non-optimized). For ^1H and ^{13} NMR data of compounds **34-36**, **37-39**, **41-43** see table 2; **34, (±)-aplysin**: mp 96°C (lit[3] 100°); UV, IR, MS, and NMR spectra are in good agreement with the literature's data. **(±)-*epi*-aplysin 35**: oily product; UV λ_{max} 208, 231, 293 nm; IR 2940, 1480, 1370, 1240, 1155, 1095, 880 cm^{-1}; MS: 296 and 294 ($M^{+\cdot}$, 90), 281 and 279 (100), 239 and 237 (40), 200 (50). **(±)-filiformin 36**: oily product (lit[5] cristalline product mp 61°C); all other data in good agreement with literature. **(±)-debromoaplysin 37**, colorless oil: UV, IR, MS in good agreement with literature[1]; **(±)-3a-*epi*-debromoaplysin 38**: UV λ_{max} 205, 223, 230 (sh), 280, 287 (sh); IR (neat) 1610, 1590, 1490 cm^{-1}. **(±)-debromofiliformin 39**: oil; UV λ_{max} 205, 220, 280 nm; IR (neat) 1610, 1590, 1500, 1380 cm^{-1}; MS 216 ($M^{+\cdot}$, 50), 201 (100), 159 (30).

Bromination of compounds 37, 38 and 39. To a solution of **37** (0.1 mmol ; 23 mg) in hexane (1 ml) 1 eq. of bromine was added at r.t.. After exactly 2 mn, the mixture was quenched with 3 ml of a saturated $Na_2S_2O_3$ aqueous solution, and was further extracted with hexane. Combined organic layers were dried ($MgSO_4$) and evaporated, to give 20 mg (65% after purification) of (±)-aplysin **34.** Under the same conditions **38** (0.1 mmol, 23 mg) gave **35** (8 mg, 26 %), **44** (3 mg, 8%), and

45 (4 mg,10%); **44**: MS 376 ($M^{+\cdot}$, 30), 374 ($M^{+\cdot}$, 60), 372 ($M^{+\cdot}$, 30), 361 (50), 359 (100), 357 (50); ^{1}H NMR 7.19 (1H, s), 6.77 (1H, s), 4.53 (2H, s), 1.32 (3H, s), 1.29 (3H, s), 0.98 (3H, d, J= 7Hz); **45**: MS 376 ($M^{+\cdot}$, 40), 374 ($M^{+\cdot}$, 80), 372 ($M^{+\cdot}$, 40), 361 (50), 359 (100), 357 (50); ^{1}H NMR 7.12 (1H, s), 2.50 (3H, s), 1.33 (3H, s), 1.32 (3H, s), 0.98 (3H, d, J= 7Hz). Bromination of **39** (0.1 mmol, 23 mg) gave **36** (15 mg, 48 %), **46** (2 mg, 5 %): MS 376 ($M^{+\cdot}$, 30), 374 ($M^{+\cdot}$, 60), 372 ($M^{+\cdot}$, 30), 361 (50), 359 (100), 357 (50); ^{1}H NMR 7.2 (1H, s), 2.51 (3H, s), 1.49 (3H, s), 1.35 (3H, s), 0.75 (3H, d, J= 7Hz).

Synthesis and thermolysis of 47: isolaurenterol benzoate 48 and aplysin 34: a mixture of **29** (20 mg, 0.064 mmol) and benzoyl chloride (45 mg, 0.32 mmol) in 1 ml pyridine was stirred for 2 days at r.t.; classical work-up, followed by t.l.c. separation afford pure crystalline **47** (29 mg, 82 %): mp 127°C, UV λ_{max} 225, 270 (sh), IR (KBr) 1750, 1730, 1590 cm^{-1}; MS: no $M^{+\cdot}$, 418 and 416 (M-C_7H_4O, 6), 105 (100); ^{1}H NMR 0.95 (3H, d, J= 7Hz), 1.32 (3H, s), 1.34 (3H, s); ^{13}C NMR 83.3 (C3a), 52.8 (C8b). Dibenzoate **47** (27 mg) was heated for 45 min at 400°C, under reduced pressure; the sublimated material collected and purified (t.l.c.), gave aplysin **34** (2 mg, 13 %) and isolaurenterol benzoate **48** (2 mg, 9 %): ^{1}H NMR 1.20 (3H, d, J= 7Hz), 1.42 (3H, s), 4.95 (1H, d, J= 3Hz), 5.12 (1H, d, J= 3Hz), 6.98 (1H, s), 7.91 (1H, s).

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