Tetrahedron Letters No. 36, pp 3421 - 3424.
©Pergamon Press Ltd. 1979. Printed in Great Britain.

0040-4039/79/0901-3421$02.00/0

TETRAHYDROACTINIDIOLIDE DERIVATIVES - AN INTERESTING STEREOSPECIFIC ACID CATALYZED LACTONIZATION

Francis ROUESSAC,
Laboratoire de Synthèse Organique - Faculté des Sciences, route de Laval -
72017 Le Mans Cédex

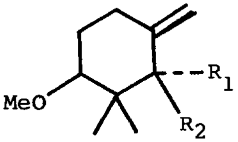
and

Henri ZAMARLIK,
Laboratoire de Chimie Organique et Biologique - Faculté des Sciences,
Avenue Monge - 37200 Tours.

On the basis of chemical and spectral evidence, the structure of the most stable lactone obtained by ring-closure of a γ-unsaturated acid is explained by the nature of the transition state.

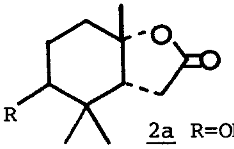
We recently proposed (1) a synthetic route to the unsaturated acid 1a, chemically separated from its epimer 1b with which it is co-obtained. We wish now to present observations which have arisen from one of our studies with these intermediates in synthesis.

Of the four γ-lactones (2a-d), regarding stereochemistry, that might be formed by acidic cyclization, we have found that both acids 1a or 1b, or any mixture of them, gave practically pure 2b in a nearly quantitative yield, if 98 % H_2SO_4 was used (r.t. 2h). The results with some other acids are shown in table I.



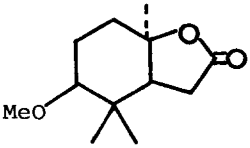
1a $R_1=CH_2CO_2H$, $R_2=H$

1b $R_1=H$, $R_2=CH_2CO_2H$

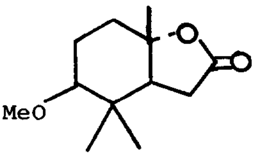


2a R=OMe

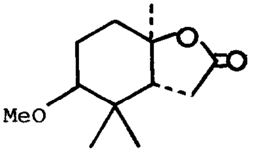
3 R=H



2b



2c



2d

Table I - Acid - Catalyzed Cyclizations of a mixture 1a/1b (65:35)

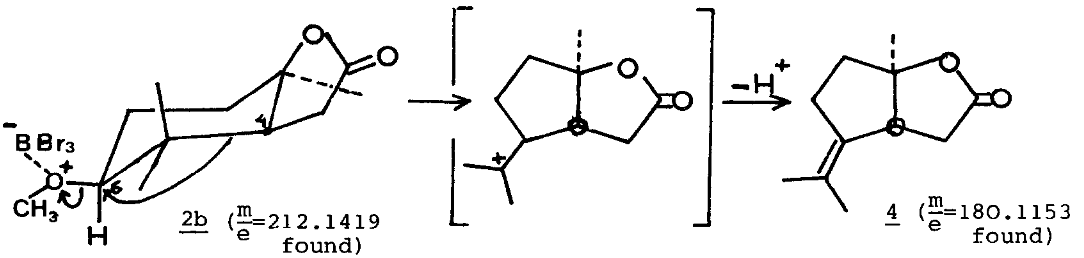
Entry	Acid	No of equiv.	t (°C)	Time(h)	Product ratio	
					2b	2a
1	$SnCl_4/C_6H_6$	0.5	20	2 (or 16)	60	40
2	HCO_2H	20	100	2	60	40
3	90 % H_2SO_4	20	18	1	80	20
4	98 % H_2SO_4	20	18	1	96	4

The exclusive formation of the cis-fused lactones 2a and 2b, expected from a thermodynamically point of view, reminds the numerous syntheses of cis-tetrahydroactinidiolide 3 (2).

The most stable lactone is 2b, since it remained practically unchanged under the conditions of entry 4 although we could yet detect the formation of about 1.5 % of cis-lactone 2a (3). Otherwise 2a gave 2b in these conditions.

Structures of 2a and 2b were assigned on chemical and spectral observations.

For instance lactone 2b is quite stable when refluxing with thionyl chloride or CH_3OH/BF_3 complex (no acid chloride or ester formation), but underwent with BBr_3 (1 equi. r.t) a facile ring contraction leading to lactone 4. This well known transformation of the A-ring of naturally occurring triterpenes (4) with retention at C-4, indicates an equatorial methoxyl group (5).

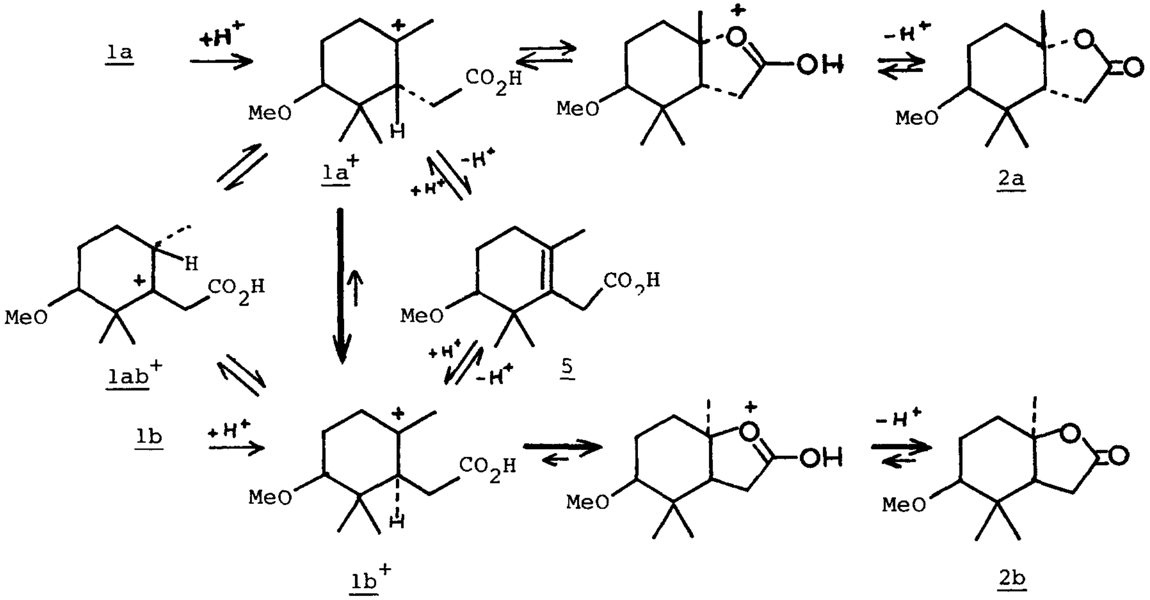


2b ($\frac{m}{e}$=212.1419 found)

4 ($\frac{m}{e}$=180.1153 found)

But the best certitude came from the comparison of the 250 MHz ^1H nmr spectra (CAMECA spectrometer) of 2b and 2a. Thus for 2b, the axial proton on C-6 exhibits a very characteristic dd (J:9.7 and 3.2 Hz) for δ = 3.04 ppm ($CDCl_3$/TMS) (6) instead of dd ($J \sim 2/2$ Hz) at δ = 2.95 ppm for 2a (7).

Obtention of 2b from 1a or 2a are surprising at the first glance. Yet these results may be rationalized by common carbenium ions. Either 5 is really formed from $1a^+$, even to a weak concentration, allowing a progressive formation of $1b^+$ by a protonation opposite to methoxyl group, or $1a^+$ gives rise to a formal reversible 1,2-hybride shift resulting with an inversion ($1a^+ \rightleftharpoons 1ab^+ \rightleftharpoons 1b^+$) (see figure). In both cases the molecule get a better spatial arrangement that decreases 1,2 and 1,3 interactions between the methoxyl group and the chain. The concentration of lactone 2a, formed under kinetic control, depends both on the nature of the acidic medium and of the reaction time (8).



Work is in progress to apply this lactonization which gives rise from a mixture of acids to a single stereoisomer in which we recognize the cis-3,5 relationship of many triterpenes.

The authors wish to express their gratitude to M S. Poignant (Nantes) for recording the high resolution proton spectra, to Prof. E.J. Brown for discussions about projects of marine products, to Prof. P.F. Casals for facilities and to the Referees for their suggestions.

References and notes

- All compounds are racemate, ony one enantiomer is represented.
- New compounds gave satisfactory elemental analyses or high resolution mass measurement.

(1) F. Rouessac and H. Zamarlik, preceding paper.

(2) - a) T. Sakan, S. Isoe and S.B. Hyeon, Tetrahedron Letters, 1623 (1967).

b) T. Kato, S. Kumazawa and Y. Kitahara, Synthesis, 573 (1972).

c) S. Torii, K. Unsyama and M. Kuyama, Tetrahedron Letters, 1512 (1976).

d) F. Rouessac and B. Goyau, Bull. Soc. Chim., 590 (1978).

(3) - by v p c analysis (SE 30 - 190°).

(4) - a) J.F. Biellmann and G. Ourisson, Bull. Soc. Chim., 348 (1960).

b) E.E. Van Tamelen and E.J. Hessler, Chem. Comm., 411 (1966).

(5) - This ring contraction was also observed when 2b was refluxed with acetyl chloride. The leaving group and the migrating bond of 2b are best suited for elimination.

(6) - Various examples in naturally occurring terpenes - See also ref. 4b.

(7) - ^1H nmr ($CDCl_3$/TMS) δ ppm : 2b - 0.98 ; 1.01 ; 1.52 ; 3.36 (4 CH_3, s) - 2a - 1.02 ; 1.04 ; 1.54 ; 3.28 (4 CH_3, s).

2b : F = 57° (pentane).
2a : F = 81° (pentane).

(8) - After 0.5 h, pure 1a was transformed (H_2SO_4, r.t.) into a mixture 2b : 2a (ratio 88 : 12).

It must be also pointed out that trans-fused lactones 2c/2d are probably present, but in too low concentrations to be analyzed (y. $<$ 1 %).

(Received in France 13 June 1979)