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THE 4-PENTEN-4-OLIDE GROUP: A NOVEL, MULTIDIRECTIONAL PARTICIPANT IN CATIONIC OLEFIN CYCLIZATION[1,2]

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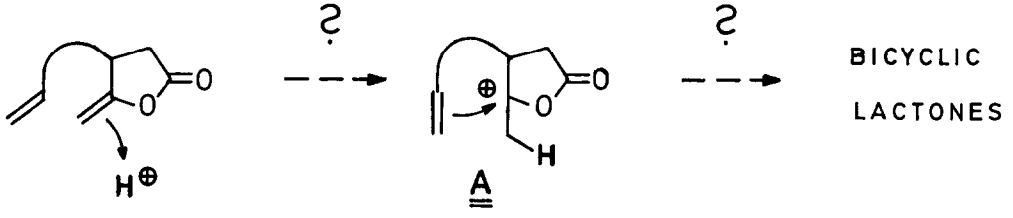
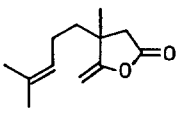
Summary: *The alkenyl-substituted 4-penten-4-olide* **1** *on treatment with various acids is selectively converted to 5-, 6-, or 7-membered carbocyclic lactones or keto acids.*

The synthesis of terpenes in vivo presents a fascinating variety of cationic cyclizations, evident already at the monoterpene level from the ten or more cyclization modes of geranyl/neryl diphospate.[3] In vitro biomimetic cyclizations have paralleled this efficiency in several cases, initiating these polycyclizations at the site of a trisubstituted double bond or epoxide, acetal (enol ether) or allylic alcohol, and terminating them with alkyl, aryl, fluorine or silylmethyl-substituted double bonds or alkinyl groups.[4] A novel group to be tested in this respect is the enol ester moiety, as present in 4-penten-4-olides.[2] Simple derivatives of the latter have been found to undergo acid-catalyzed rearrangement of hydrogen or methyl to produce endocyclic pentenolide isomers.[1b,2c] The presumed acyloxy carbocation intermediates **A** should be disposed towards internal interception by CC double bonds to produce cyclic lactones.



In this letter we report on the results of acid-induced cyclizations of an alkenylpentenolide **1** (readily prepared in >50% yield from nerol/geraniol on a 10-g scale[2b]), exhibiting an unexpected diversity of in vitro cyclization modes (see Scheme 1 and Table 1). Tin tetrachloride gave clean conversion of **1** to a mixture of bicyclic lactones **2** and **3**, from which **2** was identified after separation by Lobar column chromatography. Similarly, boron trifluoride treatment or heating of **1** in $CDCl_3$ to 140° gave ca. 1:1 mixtures of **2/3** which changed exclusively to **3** on longer reaction periods (entries 1-3 in Table 1). Acid catalysis was responsible in the latter case also (DCl from solvent decomposition), as confirmed by a control experiment in quinoline (entry 4). The cyclization/isomerization sequence **1** → **2** → **3** was more effectively achieved with Nafion-H,[5] tetrafluoroboric acid, or 50% aqueous sulfuric acid (entries 5-7). The isopropylidene lactone **3** was also obtained from the γ-ketoacid **4**[2c] with Nafion-H (entry 8), suggesting that the above results

Scheme 1. Cyclization Products from 3-Methyl-3-(4-methyl-3-pentenyl)-4-penten-4-olide (**1**)[8]



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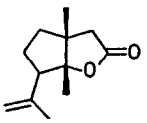

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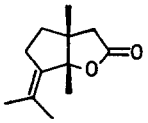

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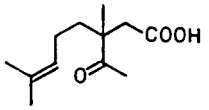

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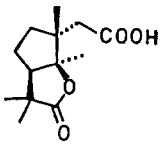

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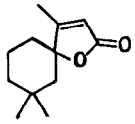
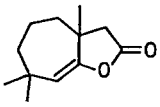
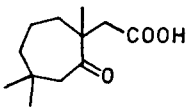


6 91%



7 66% (from **8**)



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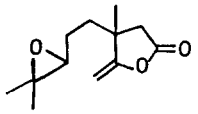
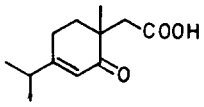


9 99%



10 52%

Table 1. Conditions and Yields of the Cyclization of **1**.

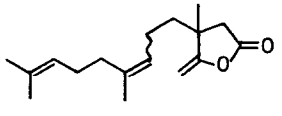
Entry	Reagent (Equivv.)	Solvent	Temp.[°C]	Time	Product	Yield [%][a] (Conversion)	Purity (Ratio)	Analysis Method
1	$SnCl_4$ (.15)	CH_2Cl_2	0	6 h	**2**	27	88	GC,[13]
2	$BF_3 \cdot OEt_2$ (.22)	CH_2Cl_2	-18	6 d	**2/3**	97	(59:41)	GC
3	"DCl"	$CDCl_3$	140	3.5 h	**2/3**	(100)	(50:50)	^{1}H NMR
				24 h	**3**	(100)	>95	^{1}H NMR
4	-	Quinoline	170	18.5 h	-	(0)	-	^{1}H NMR
5	Nafion-H (.06)	CH_2Cl_2	40	6 h	**3**	95	96	GC
6	$HBF_4 \cdot OEt_2$ (.7)	CH_2Cl_2	20	22 h	**3**	98	98	GC
7	50 H_2SO_4 (22)	CCl_4	20	17 h	**3**	88	80	GC
8	1. 5 N KOH (→**4**)							
	2. Nafion-H (.05)	CCl_4	60	1 h	**3**	67	>95	^{1}H NMR
9	100% H_2SO_4 (19)	CCl_4	20	7 min	**5**	58	>95	^{1}H NMR
	HCOOH (5.4)							
10	100% H_2SO_4 (70)	CCl_4	20	15 min	**6**	91	99	GC
11	95% H_2SO_4 (14)	CCl_4	20	1 min	**8**[b]	38	>95	^{1}H NMR
12	MCPB (1.1)	CH_2Cl_2	-10 to -5	50 min	**9**	99	(55:45)[c]	^{13}C NMR
13	1. MCPB (see 12)							
	2. $HBF_4 \cdot OEt_2$ (.38)	CH_2Cl_2	20	42 h	**10**	52	>95	^{13}C NMR

a) Isolated yield of product with purity or composition indicated.
b) About equal amount of **2/3** formed also.
c) Diastereomer ratio.

are due to the following sequence: (a) acid-assisted nucleophilic ring-opening of the lactone portion of **1**, followed by (b) acid-catalyzed Kriewitz-Prins cyclization,[6] (c) proton loss from the resulting bicyclic isopropyl cation to yield about equal amounts of **2** and **3**, and (d) isomerization of **2** to the more stable isopropylidene compound **3**. In line with this, a Koch-Haaf reaction[7] performed on **1** gave the bicyclic lactone acid **5** in 58% yield (entry 9).[8,9] An attempt to reduce the activity of the interfering nucleophiles was successful, when 95% sulfuric acid was employed: After 1 h at 20° 48% of a new cyclization product, the spirolactone **6**, were obtained. Use of pure (100%) sulfuric acid increased the yield of **6** to 91%, while less active (95%) sulfuric acid even permitted to isolate the cycloheptanone acid **8** (entries 10 and 11). The formation of **8** results from trapping of the presumed initial ring closure intermediate, i.e. protonated **7**, which otherwise by 1,2-ring contraction and proton loss would form the spirolactone **6**. The enol lactone **7**, a known compound,[10] was prepared by dehydration of **8**;[10] both **7** and **8** on sulfuric acid treatment were converted to **6** (12 and 90% yield, respectively).

These results suggest that the trisubstituted C=C group of **1** is protonated more easily than the enol ester double bond.[12,13] This is in accord with results of the bromination and iodination of **1**, which occur at the trisubstituted double bond exclusively,[1] and also from 3-chloroperbenzoic acid oxidation of **1**, leading to the epoxide **9** in 99% yield (entry 12). The epoxyalkyl enol lactone **9** on acid treatment did not follow the cyclization mode **1** → **6** or the one known of the epoxy polyene series.[3,11] Instead, the cyclohexenone acid **10** was obtained (entry 13), resulting from epoxide → ketone rearrangement, followed by aldol condensation with the enol lactone moiety.

The products obtained from **1** show that an enol ester group does participate in carbocationic cyclizations, albeit in unexpected ways. Cation stabilzation by the acyloxy (enol ester) unit apparently is inferior to that of a methyl group, as judged by the **1** → **6** conversion.[13] It seemed feasible to extend some of these new cyclization modes to other substrates such as **11**, the isoprenologue of **1** (prepared from farnesol[2b]). Indeed, **11** with boron trifluoride gave bicyclic lactones **12** corresponding to **2** (71%), and on treatment of **11** with 95% sulfuric acid the decalin spirolactone **13** was obtained (38%) which parallels the formation of **6** from **1**.



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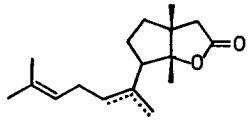

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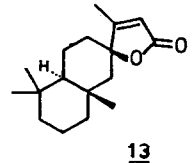

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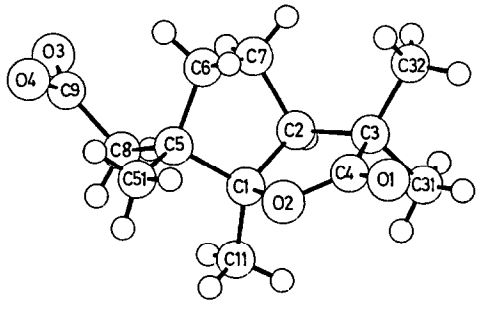
Acknowledgements: *This work was supported by Deutsche Forschungsgemeinschaft and Fonds der Chemischen Industrie. We are grateful to BASF AG and Bayer AG for gift samples, and to Dr. E. Guntrum (Hoechst AG) for discussions.*

References and Notes

1. (a) Taken from the Ph.D. Thesis of W.K., Würzburg 1986; (b) Presented in part at the Chemiedozententagung, Dortmund, March 14-18, 1983; Abstr. A24, p 38, Verlag Chemie, Weinheim 1983.
2. For previous papers on 4-penten-4-olides and references see (a) V. Jäger, H.J. Günther, Tetrahedron Lett. 1977, 2543; (b) H.J. Günther, E. Guntrum, V. Jäger, Liebigs Ann. Chem. 1984, 15; (c) E. Guntrum, W. Kuhn, W. Spönlein, V. Jäger, submitted.
3. Cf., f.e., L. Ruzicka in "Perspectives in Organic Chemistry" (A. Todd, ed), p 265ff, Interscience, 1956; O.W. Thiele, "Lipide, Isoprenoide mit Steroiden", p 197ff, G. Thieme, Stuttgart 1979; T.K. Devon, A.I. Scott, "Handbook of Naturally Occurring Compounds", Vol II, Terpenes, Academic Press, London 1982.
4. Reviews: W.S. Johnson, Angew. Chem. 1976, 88, 33; Angew. Chem. Int. Ed. Engl. 1976, 15, 9; P.A. Bartlett in "Asymmetric Synthesis", Vol 3 (J.D. Morrison, ed), p 342f, Academic Press, Orlando, 1984.
5. For a review on Nafion-H see G.A. Olah, Synthesis, in press.
6. J. Thiem in Houben-Weyl-Müller, Vol 6/1a, pt 2 (H. Kropf, ed), p 793f, G. Thieme, Stuttgart 1980.
7. H. Koch, W. Haaf, Liebigs Ann. Chem. 1958, 618, 251; review: J. Falbe, "Carbon Monoxide in Organic Synthesis", p 120f, Springer, Berlin 1970. Modified conditions were used: 3 mmol of **1**/8 mmol of formic acid in 7 ml of CH_2Cl_2 were treated with 100% sulfuric acid (56 mmol)/formic acid (8 mmol) mixed just prior to addition; quenching of the reaction after 7 min by pouring the mixture on ice.
8. Structures and configurations of compounds **2-10** are supported by elemental analyses, IR, ^1H, and ^{13}C NMR data. Some characteristic data are: **3**: bp 120°/2 Torr; 1765 and 1670 cm^{-1} (film, C=O and C=C). The structure of **3** was proven further by ozonolysis and reduction/diol cyclization.[1a] - **5**: mp 109-110° (from pentane/ether); 1775 and 1710 cm^{-1} (CCl_4, C=O of lactone and COOH, resp.). - **6**: mp 59-59.5°; 1745 and 1640 cm^{-1} (film; C=O and C=C). - **10**: mp 89-90°; 1713, 1680 and 1633 cm^{-1} (in CCl_4; C=O of COOH and enone, C=C).
9. The structure and configuration of **5** were determined by X-ray analysis. Crystals of **5** are orthorhombic, space group $P2_12_12_1$ (Z=4), a=797.1 (4), b=1067.6 (8), c=1459.7 (8) pm, V=1241·10^6 pm^3. 1425 independent reflections were collected on a Syntex $P2_1$, automatic four-circle diffractometer (Mo-K_α, $2° \leq 2\theta \leq 52°$); solution of the structure by MULTAN. Full matrix least-square refinement for all non-hydrogen atoms including anisotropic thermal parameters resulted in $R=R_w=0.058$ ($1/w=\sigma^2$; all reflections included). Standard deviation of CC bond lengths 0.004 Å. Computer drawing (crystallographic numbering):



10. S.C. Welch, R.L. Walters, J. Org. Chem. 1974, 39, 2665.
11. See, f.e., E.E. van Tamelen, J.P. Cormick, J. Am. Chem. Soc. 1969, 91, 1847.
12. Hydrolysis of acyclic enol acetates is initiated by C-protonation in strong acid, and by O-protonation in less acidic medium: S.Y. Attia, J.P. Berry, K.M. Koshy, Y.-K. Leung, E.P. Lyznicki, Jr., V.J. Nowlan , K. Oyama, T.T. Tidwell, J. Am. Chem. Soc. 1977, 99, 3401; V.J. Nowlan, T.T. Tidwell, Acc. Chem. Res. 1977, 10, 252.
13. Linalyl acetic acid, the precursor of **1**, on acid treatment undergoes a closely related cyclization/rearrangement to produce the (saturated) spirolactone analogue to **6**: V. Jäger, W. Kuhn, J. Buddrus, following Letter. This suggests very similar stabilization of a tertiary acyloxy carbocation (from **1**, cf. **A**) and a secondary cation intermediate.

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