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CATIONIC CYCLIZATION OF LINALYL- AND GERANYL/NERYLACETIC ACID. A FACILE ENTRY TO THE BREXANE SYSTEM [1,2]

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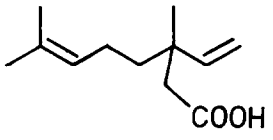
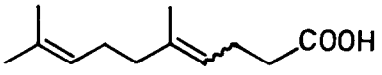
Summary: *Linalyl- and geranyl/nerylacetic acid on acid-catalysis form bicyclic lactones which with PPA afford tetrahydroindanones* ***6****,* ***7****, and the 2-brexanone* ***12****, respectively.*

Linalyl- and geranyl/nerylacetic acid **1** and **2** are interesting candidates for cationic cyclizations, due to their terpenoid yet unnatural ($C_{10}+C_2$) skeleton. Since substrates of this kind have received less attention, novel cyclization/rearrangement sequences may result from their study, such as was found, e.g., with terpenoid pentenolides.[2b,c] Furthermore, polyphosphoric acid (PPA) dehydration of alkenoic acids (or γ-lactones) in a combination of C=C migration and cyclization steps has recently been used to effect iterative cyclopentane annulation.[2a] In line with this, both **1** and **2** [3,4] were expected to ultimately form bicyclic enones on cyclodehydration. This Letter details that more complex pathways are actually met.[1]



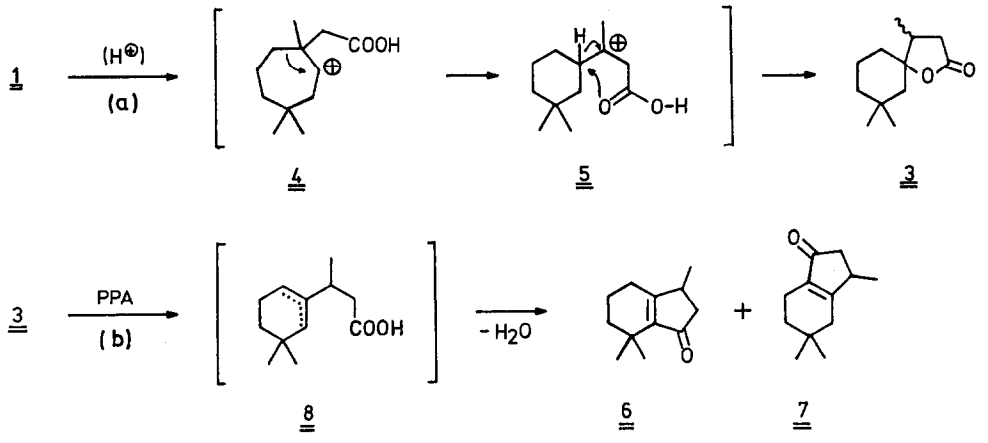
1



2

Treatment of **1** with 95% sulfuric acid or tetrafluoroboric acid in ether gave a ca. 1:1 mixture of spirolactone diastereomers **3**,[5] which can be rationalized as follows: initial protonation of the trisubstituted double bond of **1**, closure to the secondary cycloheptyl cation **4**, ring contraction to give **5**, followed by a 1,2-hydrogen shift and the final lactone closure (Scheme 1). The transformation **1** → **3** parallels the one observed with the pentenolide derived from **1**.[2c] The lactones **3** were submitted to cyclodehydration by heating with PPA[6] which led to two major products: the tetrahydroindanones **6** and **7**. Although a fair over-all yield resulted, the selectivity in the acylation of the intermediate cyclohexenylbutyric acids **8** was rather low. The bicyclic enones **6** and **7** also constituted the main products of direct PPA cyclodehydration of **1** (ca. 70% by GC, with > 10 minor products).[6b]

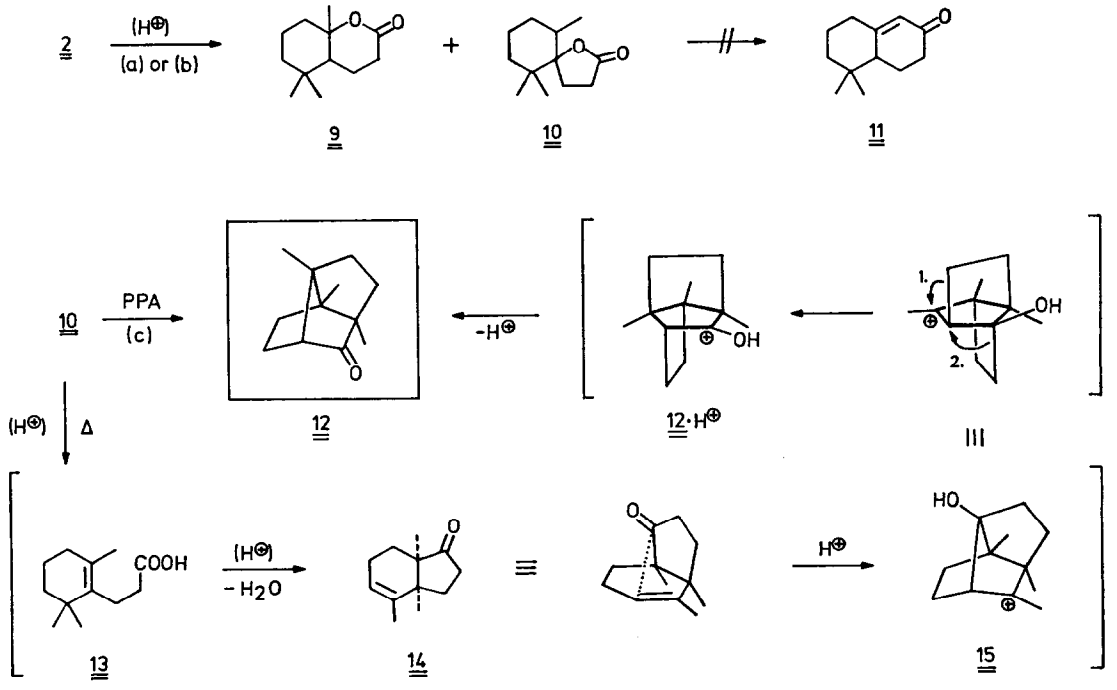
Scheme 1. Cyclization/Cyclodehydration of Linalylacetic Acid **1**



(a) $HBF_4 \cdot OEt_2$, CH_2Cl_2, 20°, 5 min; 97% of **3** (GC purity 88%).

(b) PPA, 80°, 30 min (cf ref 2a); 71% of **6/7** (GC 93%), ratio 65 : 35 (^{13}C NMR).

Scheme 2. Cyclization/Cyclodehydration of Geranyl/Nerylacetic Acid **2**



(a) $HBF_4 \cdot OEt_2$, CH_2Cl_2, 20° for 17 h; 82% after distillation, GC analysis: **9** 69%, minor products 19, 6, and 4%.[5]

(b) 5.5 g of **2**, $HBF_4 \cdot OEt_2$ (0.15 equiv), $CHCl_3$, reflux for 3 d; 86% of pale-yellow, liquid **10**, trans:cis 86 : 14 (^{13}C NMR).

(c) PPA, 80°, 20 min; for details see footnote 5.

The cyclization/cyclodehydration of geranyl/nerylacetic acid **2** was anticipated to take a similar course and produce the octalinone **11**, via the known lactones **9** and **10**,[7] respectively (see Scheme 2). The bicyclic δ-lactone **9** was obtained as the major product (69% from GC) with tetrafluoroboric acid at 20°, together with a second product (GC: 19%) presumed to be the monocyclic γ-lactone. Acid-catalysis at ca. 60° led exclusively to the bicyclic γ-lactones **10** (86% yield),[5] believed to represent the thermodynamically more stable system.

The cyclodehydration of **10** with PPA (ca. 82% of P_2O_5)[2a] at 80° occurred smoothly. After flash chromatography and several reprecipitations from ether at -80° the pure (99% by GC), rather volatile product **12** was isolated. The elemental analysis of **12** confirmed the loss of water with respect to **10**. However, HC=C absorptions as expected from **11** were absent in the NMR spectra! IR (1745 cm^{-1}), proton coupling, and ^{13}C NMR data suggested that a tricyclic compound incorporating a cyclopentanone ring and three methyl groups bound to quaternary carbon atoms had formed.[5] The problem was solved by two-dimensional INADEQUATE ^{13}C NMR spectroscopy.[8,9] Thus, all CC connectivities could be determined, which established the structure of **12** as being 1,6,7-trimethyl-2-brexanone (1,6,7-trimethyltricyclo[4.3.0.$0^{3,7}$]nonan-2one).[8]

The intriguing transformation **10**→**12** involves a number of skeletal rearrangements, interpreted as depicted in Scheme 2. The CC double bond of the first intermediate, cyclogeranylacetic acid **13**, does not migrate prior to acylation as expected, but is trapped by the acylium ion directly, with concomitant methyl migration and proton loss. O-Protonation of the resulting tetrahydroindanone **14** induces closure to the (brexyl) cation **15** which is part of two 2-norbornyl systems.[10] The protonated brexanone **12**·H^+ then arises from alternate 1,2-shifts of the two ethano bridges, for example, by passing a secondary norbornyl cation on a two-step walk as shown in Scheme 2, or, more likely, by a three-step walk with tertiary cation intermediates. Both the final cation **12**·H^+ and the product ketone **12** should represent the most stable species of each series.[11]

The novel, facile entry to the brexane system[12] and the alternating Wagner-Meerwein rearrangements (as conceived by Nickon[10]) suggest to design and study similar systems, e.g. more symmetrically substituted ones, that might contribute to the problem of nonclassical carbocations.

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References and Notes

1. (a) Part of the Ph.D. Thesis of W.K., Würzburg 1986; (b) Presented in part at the GdCh meeting, Heidelberg, Sep 16-19, 1985, Abstract D1.3, p 90, VCH, Weinheim 1985.
2. For previous papers on acid-catalyzed cyclizations/rearrangements see (a) M. Dorsch, V. Jäger, W. Spönlein, Angew. Chem. **1984**, *23*, 815; Angew. Chem. Int. Ed. Engl. **1984**, *23*, 798; (b) E. Guntrum, W. Kuhn, W. Spönlein, V. Jäger, Synthesis, in press; (c) V. Jäger, W. Kuhn, U. Schubert, preceding Letter.
3. **1** and **2** are readily available from geraniol and linalool, respectively, by Claisen-Johnson rearrangement with orthoacetate catalyzed by propionic acid, and subsequent hydrolysis. **1**: 67% (ref 4), **2**: 54% of **2** using o-nitrophenol, cf: V. Rautenstrauch, Swiss Pat 609 029 (23.12.1975), Firmenich S.A.; C.A. **1979**, *90*, 186 472. We thank Dr Rautenstrauch for additional information on unpublished work (7.11.1979 and 3.6.1983).

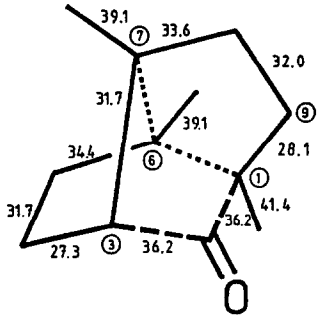
4. H.J. Günther, E. Guntrum, V. Jäger, Liebigs Ann. Chem. **1984**, 15. Note a typing error: 1N HCl is used in the work-up of 4-pentenoates to destroy excess orthoester, not "konz. Salzsäure" (p 19).

5. All compounds mentioned were fully characterized by elemental analyses, physical and spectral data, some of which follow. **3**: bp 95°/0.1 Torr (Kugelrohr); ν(C=O) 1772 cm^{-1} (film); cis/trans ratio 55 : 45 from ^{13}C NMR. - **6/7**: ν(C=O) 1695, ν(C=C) 1645 cm^{-1} (film); δ= 207.2, 136.6, 176.4 and 207.1, 128.1, 175.5 for ^{13}C signals of O=C-C=C. - **9**: ν(C=O) 1735 cm^{-1} (film). - **10**: ν(C=O) 1765 cm^{-1} (film); pure trans-**10** (3 crystallizations from pentane): 40%, mp 46 - 48° (Mondon and Erdmann, ref 7: mp 49 - 50°). - **12**: From **10** (3.9 g) with PPA (20 g, Fluka, ca 82% P_2O_5); isolation by steam distillation and flash chromatography gave fractions of mp 158 - 161° and 132 - 138° (1.52 and 0.29 g; 51%), pure by NMR. Freezing from ether: colourless crystals of mp 163 - 171°, GC purity 99% (1.07 g; 30%); after repeated freezing: mp 175 - 177°. ^1H NMR: δ(ppm, from TMS; $CDCl_3$, 400 MHz) 0.81, 0.92, 0.96 (1-, 6-, 7-CH_3); 1.34, 1.76 [2m, 4-H_n(endo), 5-, 8-, 9-H]; 1.94 [dddd; $J_{x,n}$ 12.8, $J_{x,5x}$ 11.5, $J_{x,5n}$ 5.5, $J_{x,3}$ 4.7 Hz; 4-H_x(exo)], 2.18 (d; $J_{3,4x}$ 4.7 Hz; 3-H). ^{13}C NMR: δ(as above; 100.6 MHz) 9.2, 11.2, 13.6 (1-, 6-, 7-CH_3); 25.0, 27.1, 28.8, 31.6 (C-4, C-5, C-8, C-9); 53.9, 55.8, 61.9 (C-6, C-7, C-1); 61.4 (C-3), 221.5 (C-2). IR (CCl_4): 2990, 2940, 2890, 1745, 1370 cm^{-1}.

6. (a) See literature cited in ref 2a; (b) W. Spönlein, Diploma Thesis, Würzburg 1981.

7. The cyclization **2** → **9/10** has been studied repeatedly. (a) With sulfuric acid/formic acid: G. Stork, W. Burgstahler, J Am. Chem. Soc. **1955**, *77*, 5068; A. Mondon, F. Erdmann, Angew. Chem. **1958**, *70*, 399; cf G. Ohloff, G. Schade, ibid., **1958**, *70*, 24. (b) In phosphoric acid: A. Mondon, G. Teege, Chem. Ber. **1958**, *91*, 1020.

8. CC connectivities: 2D INADEQUATE ^{13}C NMR at 100.6 MHz; 2.5 ml of $CDCl_3$ and 10 mg of $Cr(acac)_3$ added. Exact ^{13}C-^{13}C couplings were determined from one-dimensional INADEQUATE ^{13}C NMR for all but those between quaternary carbons (C-1/C-6, C-6/C-7) and those of the carbonyl-C, according to: A. Bax, R. Freeman, S.P. Kempsell, J. Am. Chem. Soc. **1980**, *102*, 4849. Couplings of C-2 were established from selective ν(C-2) irradiation as reported by: D.M. Doddrell, W. Brooks, J. Field, J. Magn. Reson. **1983**, *55*, 481. For details see ref 9b.



CC connectivities as recognized from 2D INADEQUATE ^{13}C NMR at 100.6 MHz

——— exact ^{13}C-^{13}C couplings from 1D INADEQUATE at 25 MHz

– – – CC couplings from selective C=O irradiation

····· precise values for CC couplings could not be obtained

9. Reviews: (a) R. Benn, H. Günther, Angew. Chem. **1983**, *95*, 381; Angew. Chem. Int. Ed. Engl. **1983**, *22*, 350; (b) J. Buddrus, H. Bauer, Angew. Chem., in press.

10. The unique features of the brexane system and of the rearrangements of brexyl anions, as well as several routes to brexanes/brendanes, have been pointed out by: A. Nickon, H. Kwasnik, T. Swartz, R.O. Williams, J.B. DiGiorgio, J. Am. Chem. Soc. **1965**, *87*, 1613, 1615; A. Nickon, H.R. Kwasnik, C.T. Mathew, T.D. Swartz, R.O. Williams, J.B. DiGiorgio, J. Org. Chem. **1978**, *43*, 3904; A. Nickon, R. Weglein, C.T. Mathew, Can. J. Chem. **1981**, *59*, 302; see also references given.

11. With the parent C_9H_{14} hydrocarbons both brendane and noradamantane are less strained than brexane: E.M. Engler, J.D. Andose, P.v.R. Schleyer, J. Am. Chem. Soc. **1973**, *95*, 8005. Methyl substitution may reverse the relative stability of brexane/brendane lactone analogues: P.v.R. Schleyer, personal communication.

12. For a related entry to the brexane system - from tetrahydroindenes - see S.N. Anfilogova, V.B. Nigmatova, T.I. Pekhk, N.A. Belikova, D.A. Koptev, Zh. Org. Khim. **1984**, *20*, 1873; for other routes see ref 10.

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