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CATIONIC CYCLIZATION OF GERANONITRILE AND RELATED COMPOUNDS VIA THEIR BROMOHYDRINS: APPLICATION TO THE SYNTHESIS OF (±)-SNYDEROLS1)

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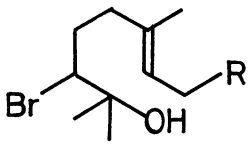
Cationic cyclization of bromohydrins of geranonitrile and homogeranonitrile in the presence of boron trifluoride complexes proceeded smoothly, giving mixtures of bromo cyclic olefins in satisfactory yields. This cyclization method was applied to the synthesis of (±)-snyderols.

An increasing number of sesquiterpenes with a 1,1-dimethyl-2-bromocyclohexane moiety have been isolated and characterized as natural products of marine origin.2) Biomimetic cationic cyclization initiated by a bromine cation or its equivalents have been employed for the synthesis of representative members of these sesquiterpenes.3) However, the applicability is obstructed by low-yield formation (5-20 %) of the bromo cyclic compounds. We have searched for an efficient cyclization reaction leading to the preparation of the natural products. We report herein the novel reactivity of bromohydrins of geranonitrile and its related compounds in the presence of Lewis acids and describe its application to the synthesis of (±)-snyderols.

The result of reactions of (3E)-7-bromo-8-hydroxy-4,8-dimethyl-3-nonenenitrile (**1**, R = CN) (bromohydrin of geranonitrile), its higher homologues, and related compounds with boron trifluoride complexes is summarized in Table 1. The data in Table 1 indicates that cyclization reactions of bromohydrins of geranonitrile (**1**, R = CN) and homogeranonitrile (**1**, R = CH_2CN) proceeded smoothly in broad outlines, giving mixtures of three isomeric tri-,4) di-,4) and tetra-substituted bromo cyclic olefins (**2** ∿ **4**, R = CN and CH_2CN) in high yields (94 and 78%) under suitable conditions. In contrast with this, the reaction of bromohydrin of bishomogeranonitrile (**1**, R = CH_2CH_2CN) produced mainly both a bromotetrahydrofuran derivative (**5**, R = CH_2CH_2CN) and its transformation product,5) hydroxy ketone (**6**, R = CH_2CH_2CN), forming the corresponding olefins (**2** ∿ **4**, R = CH_2CH_2CN) only in low yield (23-24%). Evidently the yield of the desired cyclic olefins decreased in passing from the geranonitrile (**1**, R = CN) (∿80%) to its higher homologues (**1**, R = CH_2CN) (∿60%) and (**1**, R = CH_2CH_2CN) (∿30%), indicating that the reactivity of the double bond towards the Lewis acids increased in that sequence. In fact, substitution of the cyano group of bromohydrin of homogeranonitrile (**1**, R = CH_2CN) by poorly electron-withdrawing groups (R = CH_2OAc, CH_2OMe, and CH_2I) (runs 17-22) led to formation of the corresponding cyclic olefins (**2** ∿ **4**) in low yields (15-34%). The result would be explained by the difference between the hydroxyl group and double bond in the

Table 1. Reactions of geranonitrile bromohydrin (1, R = CN), its higher homologues, and related compounds with boron trifluoride complexes a)



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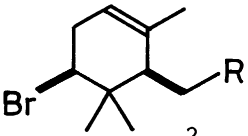

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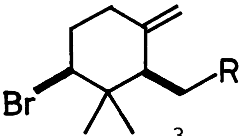

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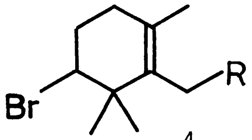

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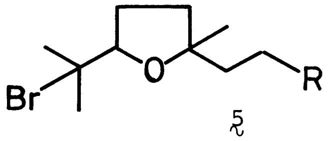

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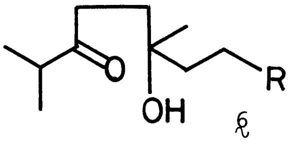

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Run	Bromohydrin 1, R	Lewis acid	Solvent	Time (h)	Product			
					Bromocyclohexane		Ether	Alcohol
					(%) b)	2: 3: 4	5 (%) b)	6 (%) b)
1	CN c)	$BF_3 \cdot OEt_2$	CH_2Cl_2	2	80	45:10:45 d)		
2			C_6H_6	5	73	44:12:44 d)		
3		$BF_3 \cdot 2MeOH$	CH_2Cl_2	7	70	50:14:36 d)		
4			C_6H_6	12	80	50: 0:50 d)		
5		$BF_3 \cdot 2AcOH$	CH_2Cl_2	1.5	94	46:15:39 d)		
6			C_6H_6	15	81	40:20:40 d)		
7	CH_2CN e)	$BF_3 \cdot OEt_2$	CH_2Cl_2	41	71	38:24:38 f)	20	
8			C_6H_6	18	39	37:27:36 f)	27	
9			CH_3CN	16	54	15:17:68 f)	23	
10		$BF_3 \cdot 2MeOH$	CH_2Cl_2	17	63	13:16:71 f)	10	
11			C_6H_6	1	46	37:28:35 f)	17	
12		$BF_3 \cdot 2AcOH$	CH_2Cl_2	0.5 g)	78	43:24:33 f)	13	
13			C_6H_6	0.5	50	35:22:43 f)	17	
14			CH_3CN	2.5	64	20: 5:75 f)	17	
15	$(CH_2)_2CN$ h)	$BF_3 \cdot 2MeOH$	CH_2Cl_2	2.5	34		12	33
16		$BF_3 \cdot 2AcOH$		0.7	23		62	13
17	CH_2OAc i)	$BF_3 \cdot 2MeOH$	CH_2Cl_2	16	34		40	20
18		$BF_3 \cdot 2AcOH$		2 g)	32		24	35
19	CH_2OMe i)	$BF_3 \cdot 2MeOH$	CH_2Cl_2	16	15		48	26
20		$BF_3 \cdot 2AcOH$		2 g)	26		22	35
21	CH_2I	$BF_3 \cdot 2MeOH$	CH_2Cl_2	16	23		36	29
22		$BF_3 \cdot 2AcOH$		2 g)	23		14	55

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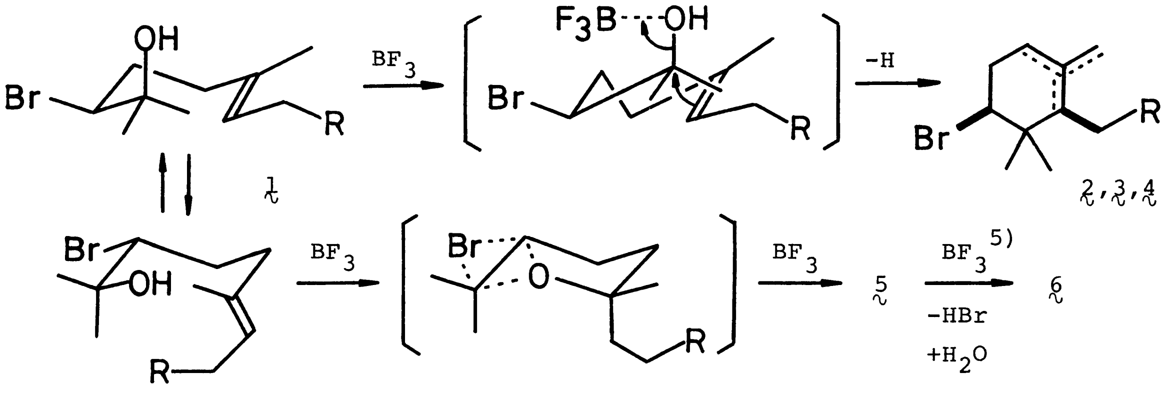
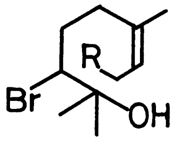
a) All the reactions were carried out at 20 °C in the indicated solutions containing 0.2-0.5 M concentrations of 1 and 5 mol equivalents of the Lewis acid, unless otherwise stated, and ceased when the spot of 1 diappeared on TLC. b) Isolated yields. c) Ref. 3b. d) Estimated by the ^1H NMR spectra; cf., ref. 3b. e) Prepared by bromohydroxylation (NBS in aq acetone) of homogeranonitrile f) Estimated by HPLC (μ-Porasil, hexane:ethyl acetate = 20:1, RI). g) Performed at 0 °C. h) Prepared from bishomogeraniol in a usual manner [R. M. Coates, D. A. Ley, and P. L. Cavender, J. Org. Chem., 43, 4915 (1978)]. i) Mixtures of the E- and Z-isomers.

Scheme 1. Plausible pathway for cyclization of the bromohydrins.



relative reactivity towards the Lewis acids, as shown in Scheme 1. This rationalization is based on the fact that the whole reaction proceeds in a concerted manner: (i) treatment of (4Z)-8-bromo-9-hydroxy-5,9-dimethyl-4-decenenitrile6) (bromohydrin of homoneronitrile) (7, R = CH_2CN) under the same conditions as run 12 (Table 1) produced a 57:20:23 mixture of tri-, di-, and tetra-substituted bromo cyclic olefins in 74% yield, from which each olefin was separated by HPLC over μ-Porasil (hexane:ethyl acetate = 20:1). While the last olefin was identified as 4 (R = CH_2CN), the former two were assigned formulas 8 and 9 (R = CH_2CN) isomeric geometrically from those 2 and 3 (R = CH_2CN), respectively, and (ii) prolonged treatment (14 h) of 4 (R = CN) or a 4:1 mixture of 2 and 3 (R = CN) under the same conditions as run 3 (Table 1) led to recovery of the respective starting olefins. Here it is emphasized that the relevant cyclization does not always require the presence of the bromine atom,7) which appears to control the conformation of transition state of the cyclization; namely, (3E)-8-hydroxy-4,8-dimethyl-3-nonenenitrile8) (10), when treated under the same conditions as runs 3 (i) and 5 (ii) (Table 1), underwent rather rapid cyclization [i, 1.25 h, and ii, 1 h] to give a mixture of 2,6,6-trimethyl-2-cyclohexenylacetonitrile (11) and its Δ^1-isomer (12) in good yields (i, 74%, 11:12 = 1:1, and ii, 95%, 11:12 = 1:2].



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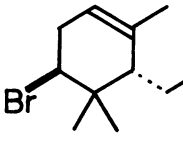

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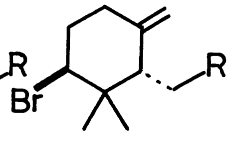

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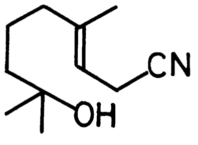

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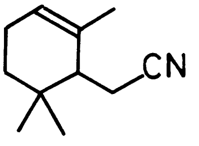

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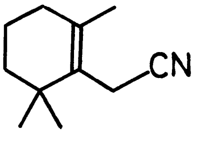

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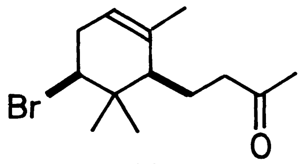
We have applied this cyclization method to the synthesis of (±)-α- and (±)-β-snyderols.9) Homogeranonitrile was converted, <u>via</u> its bromohydrin, into a mixture of cyclic bromo nitriles10) (2 ∿ 4, R = CH_2CN) in 78% yield (run 12), which without further purification was treated with methyllithium to yield a mixture of the corresponding methyl ketones10) (13 ∿ 15). The mixture, when submitted to the Grignard reaction with vinylmagnesium bromide, gave rise to a mixture of allyl alcohols in 82% yield (from the nitriles), from which two alcohols were isolated by HPLC under the aforementioned conditions in 27 and 15% overall yields. These alcohols (16) and (17) were identified as (±)-α- and (±)-β-snyderols, respectively, by comparison of the spectral data of natural and synthetic samples.11,12)



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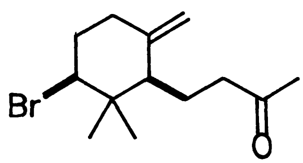

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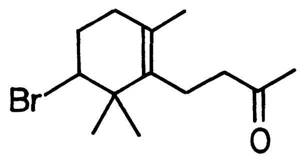

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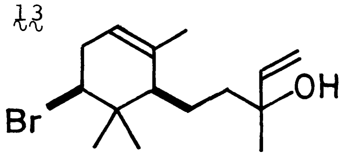

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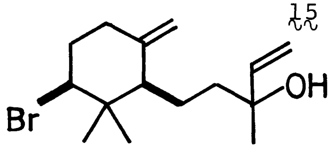

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4) The *cis*-configuration of the bromine atom and cyanomethylene group in 2 and 3 was assigned on the mechanistic ground as well as by analogy of the related cyclizations.[3]

5) Compound 5 (R = CH_2CH_2CN), when treated with the acid $BF_3\cdot 2MeOH$ in dichloromethane at 0 °C for 2 h, was transformed into 6 (R = CH_2CH_2CN) in 27% yield with recovery of the starting compound(5) (54%).

6) Prepared from nerol in a usual manner; *cf*., E. J. Corey and I. Kajiwara, Tetrahedron Lett., 1972, 487.

7) *Cf*., T. Kametani, K. Suzuki, H. Kurobe, and H. Nemoto, J. Chem. Soc., Chem. Commun., 1979, 1128.

8) Prepared by reduction (Bu_3SnH in C_6H_6, reflux, 3 h) of 1 (R = CN).

9) B. M. Howard and W. Fenical, Tetrahedron Lett., 1976, 41.

10) Each component of the mixtures of the bromo cyclic olefins and the methyl ketones was isolated by HPLC over μ-Porasil (hexane:ethyl acetate = 20:1).

11) Homoneronitrile was converted, *via* 7 (R = CH_2CN), 8 and 9 (R = CH_2CN), and the respective methyl ketones, into two allyl alcohols isomeric from 16 and 17 in relative configuration of the cyclohexane substituents. However, these alcohols exhibited IR and NMR spectra different from those of natural snyderols.

12) We are grateful to Dr. Tadahiro Kato and Dr. Bruce M. Howard for generously supplying spectral data and samples of snyderols, respectively.

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