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# CYCLIZATION OF E,E-HOMOFARNESIC ACID AND ITS RELATED COMPOUNDS

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Acid-catalyzed cyclization of homofarnesic acid was examined in detail. E,E- and Z,E-homofarnesic acid in dichloromethane cyclyzed by catalysis of boron trifluoride etherate at -20 °C to afford trans-anti-trans and trans-syn-cis norambreinolide in 38% and 52% yield respectively. Cyclization mechanism was discussed.

Trans-anti-trans norambreinolide 3, one of the tobacco constituents,[1] has been synthesized by several methods.[2-5] Most of them have been the oxidative degradation of natural compounds, and little attention has been paid to the cyclization of polyenic acids. Though only Lucius investigated the cyclization of homofarnesic acid, 3 could not be found in the reaction mixture.[6] The lactone, 3, seems impossible to be obtained under the drastically acidic condition employed in his cyclization, because trans-γ-lactone fused to cyclohexane ring is wellknown to isomerize easily to the cis isomer under the acidic condition.[7,8] On the other hand, we have already reported that 3 is effectively synthesized by acid-catalyzed cyclization of trans-β- and α-monocyclohomofarnesic acid, 8 and 9, under the selected conditions.[9,10] As the more advanced step, we investigated the possibility of the stereoselective cyclization of acyclic homofarnesic acid for the purpose of one-step synthesis of 3.

E,E- and Z,E-homofarnesic acid, 1 and 2, were obtained as a 8:2 mixture by bromination of E,E-farnesol followed by nitrilation and hydrolysis. Acids, 1 and 2, were purified by column chromatography as their ethyl esters. After alkaline hydrolysis, thus obtained acids (>98% purity) were submitted to the cyclization. Cyclization was carried out by dropwise addition of acid-catalyst

(1-10 equiv.) to 1 or 2 (10-100 mg) dissolved in organic solvent (3 ml). The cyclization product was analyzed by a capillary GLPC (OV-101 glass capillary column; $\phi$=0.25 mm x 50 m) and the tricyclic lactones 3-7 were identified by the coincidence in retention time with the authentic samples.[9,10] The ratio and yield of them were also measured by the capillary GLPC. Results are shown in Table 1.

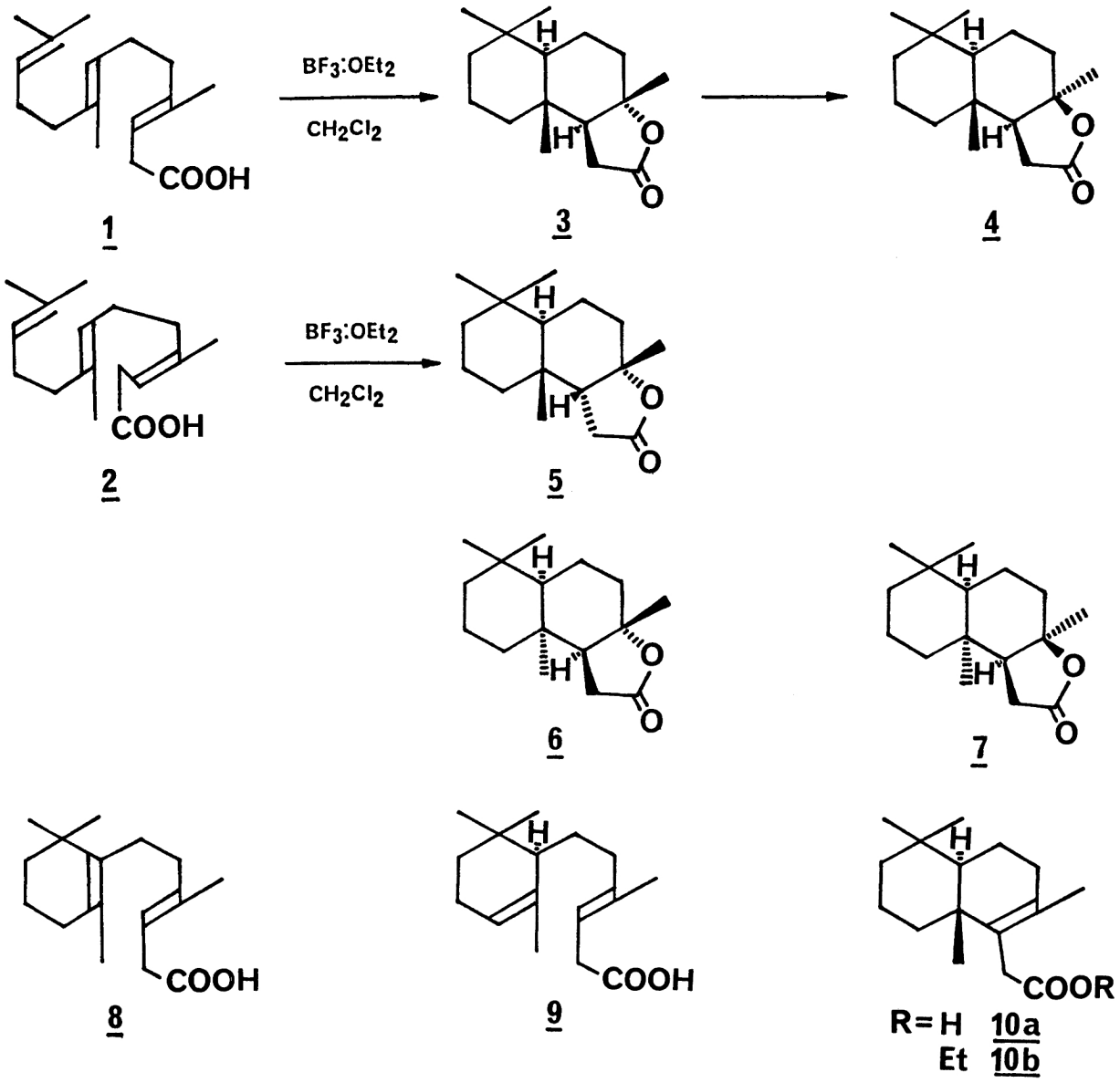
After several trials to find the cyclization condition, the cyclization of 1 was achieved with boron trifluoride etherate in dichloromethane at -20 °C for 60 min to afford 3 in 38% yield (Entry 5). The yield of 3 was reproduced in several repeated experiments. Other solvents and Lewis acids led to inferior results. In the case catalyzed by stannic chloride in acetonitrile (Entry 1), the highest ratio of 3 among the GLPC-detectable compounds was observed, but the absolute yield was rather poor because of the polymerization that always accompanies with this type of reaction. Increase of the ratio of 4 due to the isomerization of 3 was observed with a rise in temperature and a passage of time

Table 1. Relative amount ratios of acid-catalyzed cyclization products of 1 and 2[a)]

| Entry | Acid | Solvent | Cat. | Temp °C | Time min | Ratio of product (%) | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | 3 | 4 | 5 | 6 | 7 | others |
| 1 | 1 | $CH_3CN$ | $SnCl_4$ | -20 | 60 | 66(11)[b)] | 5 | 8 | 9 | 1 | 11 |
| 2 | 1 | $CH_2Cl_2$ | $SnCl_4$ | -20 | 60 | 31(14) | 19 | 0 | 1 | 0 | 49 |
| 3 | 1 | $CH_2Cl_2$ | $SnCl_4$ | 20 | 60 | 18( 7) | 28 | 2 | 0 | 4 | 48 |
| 4 | 1 | $CH_2Cl_2$ | $SnCl_4$ | 20 | 180 | 2( 1) | 38 | 10 | 0 | 1 | 49 |
| 5 | 1 | $CH_2Cl_2$ | $BF_3:OEt_2$ | -20 | 60 | 53(38) | 2 | 12 | 6 | 0 | 27 |
| 6 | 1 | $CH_3CN$ | $BF_3:OEt_2$ | -20 | 60 | 60(16) | 0 | 6 | 8 | 0 | 26 |
| 7 | 2 | $CH_3NO_2$ | $SnCl_4$ | -20 | 60 | 0 | 0 | 58(42) | 0 | 15 | 27 |
| 8 | 2 | $CH_2Cl_2$ | $BF_3:OEt_2$ | -20 | 60 | 0 | 0 | 77(52) | 0 | 17 | 6 |

a) The ratios were estimated by GLPC-detectable peak area measurement.

b) ( ): Yield. The yields were estimated by the GLPC calibration curve of the authentic samples.




(Entries 2-4).[9] Inferior yield of 3 in the cyclization of acyclic 1 compared with the cyclization of monocyclic 8 (69% yield)[9] is due to the difficulty caused by one more ring formation. Free carboxyl group served as an efficient terminator of the cyclization. Cyclization of ethyl ester of 1 was interrupted at the stage of bicyclic ring to afford 10b in 58% yield because of low nucleophilicity of ester group, and only trace of the tricyclic lactones was detected in the reaction mixture.

Cyclization of 1 is considered to proceed synchronously to afford 3. Neither of the mono nor bicyclic acid was detected in the reaction mixture. Possible intermediates, 8 and 10a, were almost recovered under the cyclization

condition shown in Entry 5. Another conceivable intermediate, 9, cyclized to afford 6 mainly under the same condition. Therefore the cyclization of 1 is concluded to proceed via a concerted mechanism to afford 3. By the same mechanism, cyclization of 2 afforded 5 in 52% yield (Entry 8).

In this work 3 was obtained by the cyclization of 1 in contrast to the previous investigation reported by Lucius.[6c] The formation of the polycyclic compounds more than tricyclic by concerted polyene cyclization has often resulted in very poor yield.[6,11] In this case, the synthetic target 3 was able to be obtained in fairly good yield by the acyclic polyene cyclization. Concerted lactonization was revealed to be one of the efficient methods to obtain trans-fused γ-lactones. The extensive application of concerted lactonization to the stereoselective synthesis of naturally occuring trans-fused γ-lactones is under investigation.

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