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CYCLIZATION MECHANISM OF TRANS-β-MONOCYCLOHOMOFARNESIC ACID AND RELATED COMPOUNDS

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Cyclization of trans-β-monocyclohomofarnesic acid and the related compounds was closely examined in order to elucidate the reaction mechanism. It was revealed that the cyclization of trans-β-monocyclohomofarnesic acid proceeds via formation of the cationic intermediate followed by concerted lactonization to give trans-anti-trans norambreinolide stereoselectively.

Biomimetic cyclization of polyene has been applied to polycyclic terpenoid and steroid synthesis because of its high stereoselectivity.[1] Although a lot of effective synthetic methods have been developed, there has been relatively little known about the reaction mechanism.[2,3] We have already reported the acid-catalyzed cyclization mechanism of homogeranic acid.[4] In the course of development in our study, the elucidation of the cyclization mechanism of trans-β-monocyclohomofarnesic acid (1a) resulting in stereoselective formation of trans-anti-trans norambreinolide (3) seemed to be one of the attractive problems.[5] Therefore the cyclization of (1a) and the related compounds was closely examined to elucidate the reaction mechanism in this type.

Acids (1) and (2) were easily prepared from dihydro-β and α-ionone respectively.[5] Cyclization was carried out typically by dropwise addition of Lewis acid to the dilute solution of (1) or (2). The major cyclization products were assigned to the structures (3)-(8) by MS, IR, ^{1}H-NMR, and ^{13}C-NMR spectra.[6] The structure (6) was confirmed by X-ray analysis. The ratio and yield of the products were estimated by peak area measurement of capirally G.L.C. analysis. The results are shown in Table 1.

On the basis of these results, the principal courses of the cyclization are summarized in Scheme 1. If the cyclization of (1a) proceeded via anti-addition to the ring olefin, the stereoisomers of norambreinolide possesing cis-fused AB ring would have been obtained predominantly. But (3) and its stereoisomers possesing trans-fused AB ring could be obtained as the main product in almost all the cases. Therefore in this type of cyclization the formation of a cationic intermediate (9) was presumed at the first stage. Such a kind of intermediate, the formation of which has been already suggested, is wellknown to react with the olefin in the side chain forming trans-fused AB ring.[3,7-9] The successive lactonization was concluded to occur simultaneously with the formation of AB ring without forming the second intermediates such as (10), (11), and (12).

Table 1 Relative amount ratio of cyclization product of (1) and (2) catalyzed by stannic chloride[a,b)]

Entry	Acid	Solvent	Cat. (ml)	Temp (°C)	Time (min)	Ratio of product (%)						
						(3)	(4)	(5)	(6)	(7)	(8)	others
1	(1a)	CH_2Cl_2	2.0	-78	60	82	0	10	7	0	1	0
2	(1a)	CH_2Cl_2	0.2	20	20	40	28	9	8	1	10	4
3	(1a)	CH_2Cl_2	0.2	20	60	32	46	8	4	2	7	1
4	(1a)	PhH	0.2	20	20	37	6	5	2	1	48	1
5	(1b)	CH_2Cl_2	0.5	-20	40	0	0	96	0	2	0	2
6	(1b)	CH_2Cl_2	0.2	20	20	0	0	100	0	0	0	0
7	(2)	CH_2Cl_2	2.0	-78	60	11	0	6	74	4	-	5
8	(2)	$PhCH_3$	2.0	-78	60	36	2	10	46	0	-	6
9	(2)	CH_2Cl_2	0.2	20	10	25	15	12	23	12	-	13
10	(2)	PhH	0.2	20	10	64	7	9	8	1	-	11

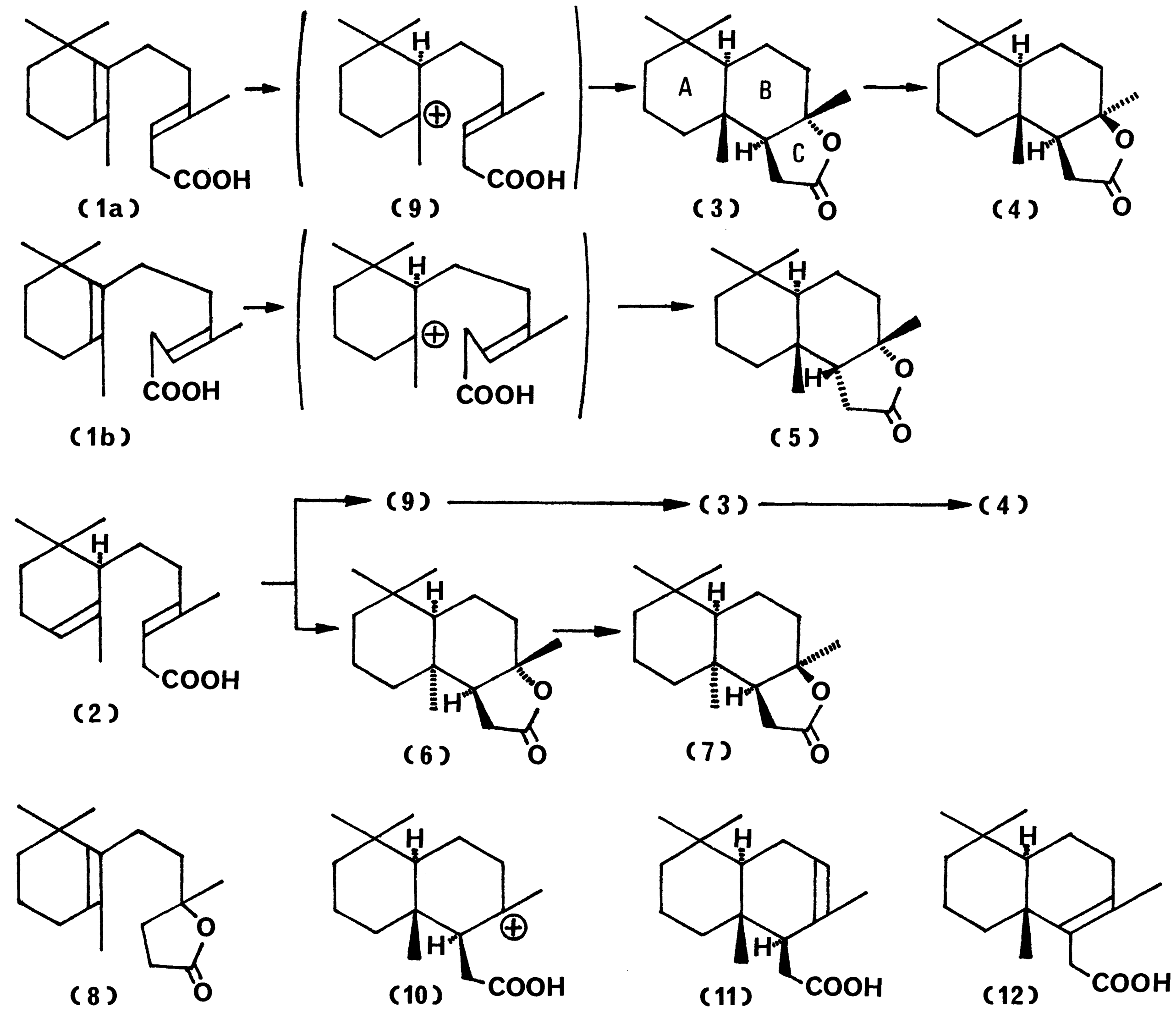
a) Cyclization was carried out by dropwise addition of stannic chloride to (1) or (2) (10-100mg) in solvent (3ml).

b) Other kinds of Lewis acid ($SnBr_4$, $TiCl_4$, BF_3:Et_2O, etc.) and protic acid (H_2SO_4, CF_3COOH, etc.) did not give the remarkable effect on the stereoselectivity of the cyclization.

The evidence for this is as follows. If the cationic intermediate (10) were formed in the course of the cyclization, the subsequent lactonization would have preferentially afforded the more stable isomer (4) rather than (3). Similarly, if the bicyclic olefinic acids (11) and (12) were once generated by the partial cyclization of (1a), they would have cyclized to afford (4) and (5) respectively.[10,11)] The lactone (5) could not be obtained as the main product in any reaction conditions. The lactone (4) was obtained in high ratio in some cases (Entry 3), but (4) has been already reported to be obtained by acid-catalyzed isomerization of (3) which is the initial cyclization product.[5)] In conclusion, the cyclization of (1a) proceeds via formation of (9) followed by concerted lactonization to afford (3) stereoselectively. The good yield (69% yield; Entry 1) and the preferential formation of trans-fused γ-lactone in this case may be ascribed to the effective termination of the cationic cyclization by carboxyl group to form γ-lactone ring. The exclusive formation of (5) from (1b) supported the mechanism described above. The better yield (88% yield Entry 6) and higher stereoselectivity in the formation of (5) compared with (3) were considered due to the higher stability of (5) than (3).[12)]

It seemed quite informative for the elucidation of the reaction mechanism to

Scheme 1 Principal courses of cyclization of (1) and (2)



compare and contrast the result of the cyclization of trans-α-monocyclohomofarnesic acid (2) with that of (1a). If (9) was really present in the course of the cyclization of (1a), (3) might be also obtained by the cyclization of (2). As was expected, (2) in benzene solution cyclized in the presence of catalytic amount of stannic chloride at room temperature to give (3) as the main product in moderate yield (55% yield; Entry 10). But the cyclization of (2) in dichloromethane at -78°C gave cis-syn-trans norambreinolide (6) predominantly (62% yield; Entry 7). Interconversion between (3) and (6) was not ovserved in any reaction conditions. In view of these results we were forced to adopt an alternative mechanism for the stereochemical course of the cyclization of (2), which must not involve the intermediate (9) because (9) had been already proved to give (3) stereoselectively under the same reaction condition. Therefore it seemed reasonable to presume that the pathway to give (6) involves an all synchronized mechanism with the preservation of the stereochemical relationships, or involves a conformationally frozen monocyclic carbonium ion followed by concerted lactonization.[7,13] Thus taking an unfavorable quasi-boat conformation in the formation of B ring, (2) might cyclize to give (6) stereoselectively. Although two pathways to give (3) or (6) competed each other depending on solvent and temperature, the effect of the reaction conditions is still obscure.

In the previous work of Lucius[11)] any appreciable difference in the cyclization product of the esters of (1) and (2) was not reported. In contrast to the report, we found that (1) and (2) cyclized to give the different compounds respectively, and particularly by establishing unambiguously the structure (6) for the cyclization product of (2), the difference in the cyclization mechanism of (1) and (2) has been clearly demonstrated. In conjunction with the previous results of the highly stereoselective cyclization of homogeranic acid, our investigation shows that the lactonization concerted with cyclization is one of the most efficient synthetic methods for trans-fused γ-lactone which is more difficult to obtain than cis-fused one.

References

1) W. S. Johnson, Angew. Chem., 88, 33 (1976).

2) G. Stork and A. W. Burgstahler, J. Am. Chem. Soc., 77, 5068 (1955).

3) W. S. Johnson, S. L. Gray, J. K. Crandall, and D. M. Bailey, J. Am. Chem. Soc., 86, 1966 (1964).

4) A. Saito, H. Matsushita, Y. Tsujino, T. Kisaki, T. Kato, and M. Noguchi, Chem. Lett., 1978, 1065.

5) A. Saito, H. Matsushita, Y. Tsujino, and H. Kaneko, Chem. Lett., 1981, 757.

6) Analytical data of these compounds are as follows;

   a) All the spectra of (3) and (4) were identical with norambreinolide and norisoambreinolide derived from natural source.

   b) The spectra of (5) and (8) have been already reported in ref 5).

   c) (6): IR($CHCl_3$) ν=1760cm^{-1}; MS m/e 250 (M^+); ^{1}H-NMR($CDCl_3$) δ=0.89(3H,s), 1.16 (6H,s), 1.39(3H,s); ^{13}C-NMR($CDCl_3$) δ=18.5, 20.9, 24.3, 26.7, 29.1, 29.3, 31.2, 32.6, 34.0, 35.2, 37.1, 37.7, 51.7, 57.1, 85.4, 176.3; m.p. 103-104 °C;

   d) (7): IR($CHCl_3$) ν=1755cm^{-1}; MS m/e 250 (M^+); ^{1}H-NMR($CDCl_3$) δ=0.91(3H,s), 1.10 (6H,s), 1.51(3H,s); ^{13}C-NMR($CDCl_3$) δ=19.0, 21.7, 26.9, 28.6, 30.9, 32.5, 33.3, 33.8, 33.9, 34.3, 35.5, 36.6, 46.6, 54.6, 85.5, 175.7; m.p. 99-100 °C;

7) E. E. Tamelen and J. P. McCormick, J. Am. Chem. Soc., 91, 1847 (1969).

8) T. Kato, M. Tanemura, S. Kanno, T. Suzuki, and Y. Kitahara, Bioorg. Chem., 1, 84 (1971).

9) S. Torii, K. Uneyama, I. Kawamura, and M. Kuyama, Chem. Lett., 1978, 455.

10) S. Torii, K. Uneyama, and H. Ichimura, J. Org. Chem., 43, 4680 (1978).

11) G. Lucius, Arch. Pharm., 291, 57 (1958).

12) L. Ruzicka, C. F. Seidel, and L. L. Engel, Helv. Chim. Acta, 14, 621 (1931).

13) E. E. Tamelen and D. R. James, J. Am. Chem. Soc., 99, 950 (1977).

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