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A SHORT AND STEREOSELECTIVE SYNTHESIS OF THE (±) PRELOG-DJERASSI LACTONIC ACID

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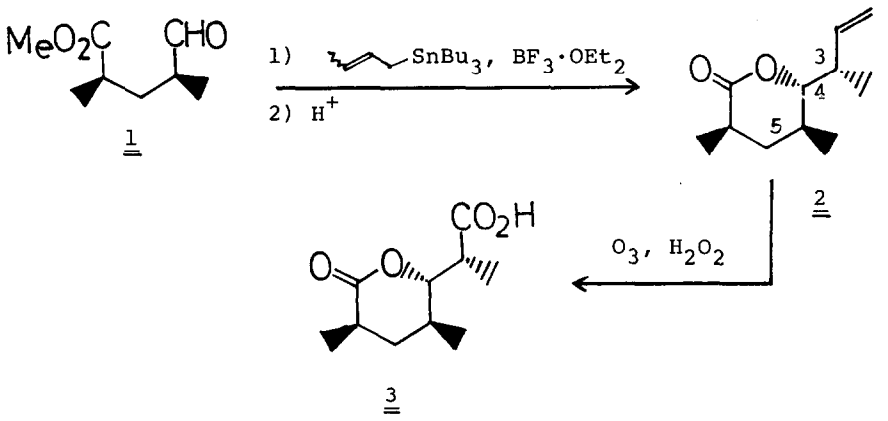
Reaction of meso-4-carbomethoxy-2-methylpentanal (1) with crotyltri-n-butyltin at -78°C in the presence of 1 eq $BF_3 \cdot OEt_2$, followed by the lactonization with $BF_3 \cdot OEt_2$, gave 6-(1-methylallyl)-3,4,5,6-tetrahydro-3,5-dimethyl-2-pyranone (2a) with the correct stereochemistry (erythro, anti-Cram) in 92% yield, which was converted to the title compound (3) in 85% yield upon the ozonolytic cleavage of the double bond.

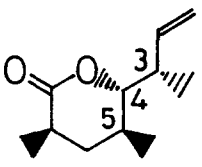
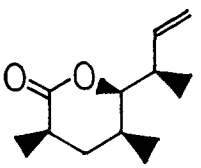
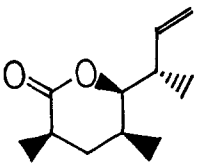
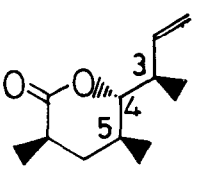
The Prelog-Djerassi lactonic acid holds a conspicuous position, especially, as a stereochemical touchstone, in the chemistry of the macrolide antibiotics. The stereoselective synthesis has been realized via the aldol condensation,[1] the ring opening reaction of cyclic compounds,[2] the oxy-mercuration,[3] or the chiral carbohydrate-based synthesis.[4] We wish to report a short and efficient, stereoselective synthesis of this important key imtermediate. Our method is based on the recent observation that the reaction of crotyltrialkyltins with aldehydes gives an erythro β-hydroxy-α-methylhomoallyl alcohol regardless of the geometry of the crotyl unit,[5] which predicts the correct stereochemical relation between C_3 and C_4 (eq 1). The important problem is whether the stereochemistry between C_4 and C_5 produced by this method is opposite to the usual Cram's rule or not. The result was quite surprising since the condensation proceeded through the anti-Cram's rule (Table 1).

As is apparent, the reaction of crotyltin *in the presence of* 1 *equivalent* $BF_3 \cdot OEt_2$ produces the desired lactone (2a) with at least 94 % stereoselectivity. The stereoselectivity decreases with the increase of $BF_3 \cdot OEt_2$. The high



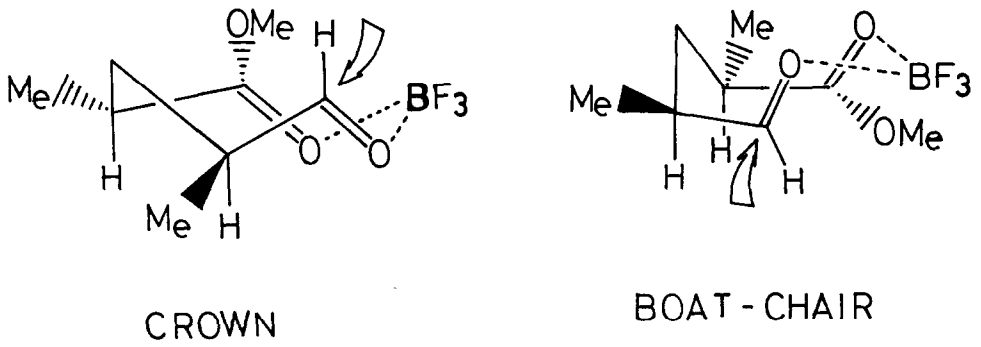
(1)

Table 1. Reaction of 1 with crotyltri-n-butyltin.[a]

$BF_3 \cdot OEt_2$ (eq)	 2a erythro,anti-Cram	 2b erythro,Cram	 2c threo,Cram	 2d threo,anti-Cram	Total yield (%)[b]
1[c]	94-97	3-4	1	1	92[d]
2[c]	83-91	5-9	1-3	2-5	90
3	41	10	17	32	90

[a] All reactions were performed in a similar manner as described in the text. The isomer ratio (%) was determined by the Glpc analysis (CW 6000) of the reaction mixture. The retention times of 2b and c were estimated from those of the reaction of crotylzirconium compounds, which normally gave the Cram product predominantly.[6] [b] Isolated yield of 2. [c] The ratio obtained from several experiments is indicated. [d] Yield of 2a.

stereoselectivity can be explained by the 8-membered cyclic intermediate (Scheme 1). The crown form leads to the anti-Cram products, since the inspection through the CPK model clearly indicates that a nucleophile is forced to attack from the direction indicated by an arrow owing to the steric repulsion.



Scheme 1. Eight-membered cyclic intermediate

On the other hand, the boat-chair form gives the Cram products. Since it is well known that the crown form of cyclooctane is more stable than the boat-chair form,[7] the reaction must proceed through the crown type. Excess $BF_3 \cdot OEt_2$ permits the coordination at each carbonyl group to prevent the formation of the 8-membered cyclic intermediate. The present development provides an efficient and one of the most convenient method for the synthesis of the (±) Prelog-Djerassi lactonic acid. Moreover, stereocontrol via the BF_3 mediated chelation holds a promise for the stereoselection of acyclic systems, since the hitherto known chelation controlled reaction proceeds in the basic media.[8]

Experimental procedure. In a 50-mL flask, kept under N_2, were placed dry CH_2Cl_2 (2 mL) and 1 (1 mmol, 158 µl), and the mixture was cooled to -78°C. Crotyltributyltin[9] (1 mmol, 0.4 mL) and $BF_3 \cdot OEt_2$ (1 mmol, 0.13 mL) were added, and stirring was continued for 30 min at this temperature. The mixture was allowed to warm to 0°C, and the reaction was quenched with water. $BF_3 \cdot OEt_2$ (2 mmol, 0.26 mL) was added and stirring was continued for 2 hr. Extraction with ether, drying, evaporation of the solvents, and filtration through silica gel gave 2a in 92 % yield.[10] Ozone was introduced into an ethyl acetate solution (5 mL) of 2a (30 mg, 0.17 mmol) at ca. -75°C. After the color of the solution changed to blue, the mixture was allowed to warm to room temperature. Treatment with H_2O_2 (30%, 0.5 mL)-H_2O (0.5 mL), subsequent heating at 60°C for 10 hr, followed by the addition of 2N NaOH (0.7 mL) produced 3 in 85% yield. Recrystallization from hexane-ether gave a pure sample, mp 116.5-117.5°C (lit[3] 116-7°C).

References and Notes

1) S. Masamune, M. Hirama, S. Mori, S. Asrof Ali, D. S. Garvey, J. Am. Chem. Soc., 103, 1568 (1981) and references cited therein.
2) J. D. White, Y. Fukuyama, J. Am. Chem. Soc., 101, 226 (1979): G. Stork, V. Nair, ibid., 101, 1315 (1979): P. A. Grieco, Y. Ohfune, Y. Yokoyama, W. Owens, ibid., 101, 4749 (1979). For nonstereoselective synthesis, see L. D. Bergelson, S. G. Batrakov, Izv. Akad. Nauk. SSSR, Ser. Khim., 1259 (1963): A. Nakamoto, S. Tanimoto, J. Inanaga, T. Katsuki, S. Ouchida, K. Inoue, M. Aiga, N. Okukado, M. Yamaguchi, Chem. Lett., 1019 (1979).
3) P. A. Bartlett, J. L. Adams, J. Am. Chem. Soc., 102, 337 (1980).
4) R. E. Ireland, J. P. Daub, J. Org. Chem., 46, 479 (1981).
5) Y. Yamamoto, H. Yatagai, Y. Naruta, K. Maruyama, J. Am. Chem. Soc., 102, 7107 (1980).
6) Crotylzirconium derivatives, prepared from the reaction of crotylmagnesium chloride or crotyllithium with bis(cyclopentadienyl)zirconium dichloride, undergo a rapid reaction with aldehydes to afford the threo product predominantly. The ratio of Cram/anti-Cram product is ca. 75/25 - 60/40: Y. Yamamoto, K. Maruyama, Tetrahedron Lett., 2895 (1981).
7) N. L. Allinger, J. Am. Chem. Soc., 81, 5727 (1959). In a similar system, Prof. Masamune proposes a model consisted of a combination of two 6-membered transition state; S. Masamune, Aldri. Chim. Acta, 11, 28 (1978). Explanation of the effect of $BF_3 \cdot OEt_2$ in our system through such a model seems to be difficult.
8) A. I. Meyers, P. J. Reider, J. Am. Chem. Soc., 101, 2501 (1979): W. C. Still, J. H. McDonald, III. Tetrahedron Lett., 1031 (1980): K. Narasaka, H. C. Pai, Chem. Lett., 1415 (1980), and references cited therein.
9) Prepared by the reported procedure (ref 5). The stereochemistry of the crotyl unit is not determined, and may be a mixture of the E and Z form.
10) Although GLC analysis of the reaction mixture indicated the presence of small amounts of isomers (2b-d), an appreciable amount of these isomers was not isolated. ^{1}H NMR of 2a (CCl_4) δ 1.01 (d, J=7 Hz, 3H), 1.04 (d, J=7 Hz, 3H), 1.22 (d, J=7 Hz, 3H), 1.3-2.2 (m, 3H), 2.2-2.7 (m, 2H), 3.91 (d-d, J=2.3 and 10 Hz, 1H), 5.11 (d-d, J=1.5 and 10 Hz, 1H), 5.14 (d-d, J=1.5 and 18 Hz, 1H), 6.07 (d-d-d, J=8, 10, and 18 Hz, 1H). 2d was isolated from the reaction of crotyl-9-BBN; ^{1}H NMR (CCl_4) δ 0.96 (d, J=6.6 Hz, 3H), 1.22 (d, J=7 Hz, 3H), 1.2-2.1 (m, 3H), 2.2-2.6 (m, 2H), 3.80 (d-d, J=2 and 10 Hz, 1H), 5.08 (d-d, J=2 and 9Hz, 1H), 5.12 (d-d, J=2 and 18 Hz, 1H), 5.82 (d-d-d, J=9, 9, and 18 Hz, 1H).

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