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C(2)-STEREOCONTROL OF δ-LACTONES VIA ACID-CATALYZED CYCLIZATION OF KETENE DITHIOACETAL HAVING AN INTERNAL HYDROXYL GROUP

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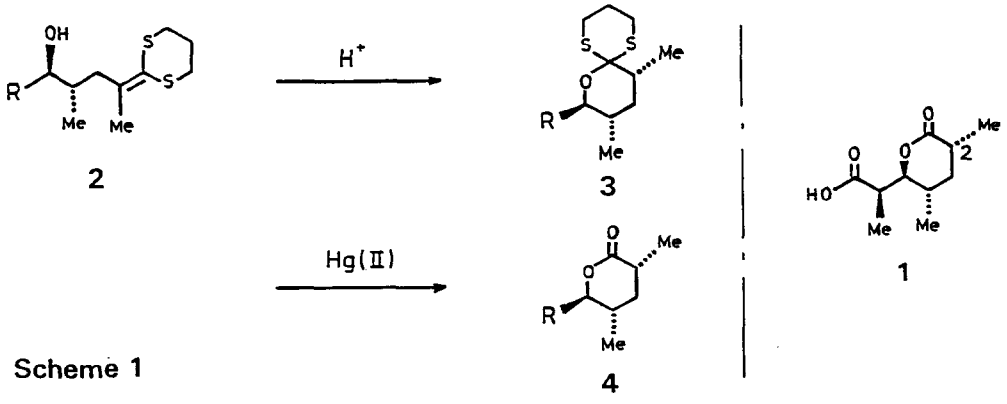
Summary: Stereocontrol of C(2)-position of δ-lactones, related to Prelog-Djerassi lactone, is effected via acid-catalyzed cyclization of ketene dithioacetal having an internal OH group (thermodynamic control), which is also applicable to remote asymmetric induction.

Prelog-Djerassi lactone (1) and its derivatives are versatile intermediates in macrolide synthesis, and a number of synthetic methods have been devised leading to this carbon framework.[1] However, control of the C(2)-methyl group has been essentially left unsolved,[2] except the cases where 2,4-meso-dimethylglutarate derivatives are concerned.[3]

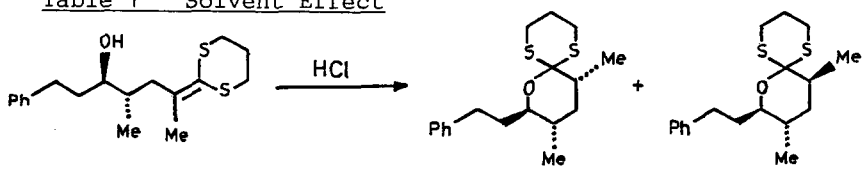
In the course of our synthetic study directed towords mycinamicin-type macrolides[4], we confronted "the C(2) problem" stated above, for which we exploited a novel and effective solution through an extensive model study. Disclosed herein is the key aspects of the new lactone stereocontrol, which depends on the acid-catalyzed hetero-cyclization of ketene dithioacetal having an internal OH group 2 to give bicyclic dithio-orthoester 3, whose ready hydrolysis gives rise to lactone 4 with stereoregulation at C(2) (Scheme 1).



Scheme 1

Cyclization of a model compound 2a was attempted under a variety of acidic conditions to obtain dithio-orthoester 3a,[5] whose α/β ratio was determined by HPLC analysis. Of the factors affecting the selectivity, the most notable

Table 1 Solvent Effect[a)]



2a 3a α β

Entry	Solvent	Conditions	Yield (%)	Ratio (α/β)[b)]
1	Toluene	0°C, 0.4h	60	2 / 1
2	CCl_4	0°C, 0.6h	67	2 / 1
3	$CHCl_3$	0°C, 0.3h	81	10 / 1
4	CH_2Cl_2	0°C, 0.3h	98	14 / 1
5	CH_3CN	0°C, 0.3h	96	11 / 1
6	Et_2O	rt, 19h	98	1 / 1
7	THF	rt, 18h	98	1 / 1
8	DMF	rt, 24h	74	2 / 1

a) Acid solution was prepared by bubbling anhydrous HCl just before use, whose concentration was determined by titration. Reactions were performed at the 0.1 - 0.4 M concentration range.
b) HPLC: ZORBAX SIL (Du Pont), hexane/CH_2Cl_2=96/4.

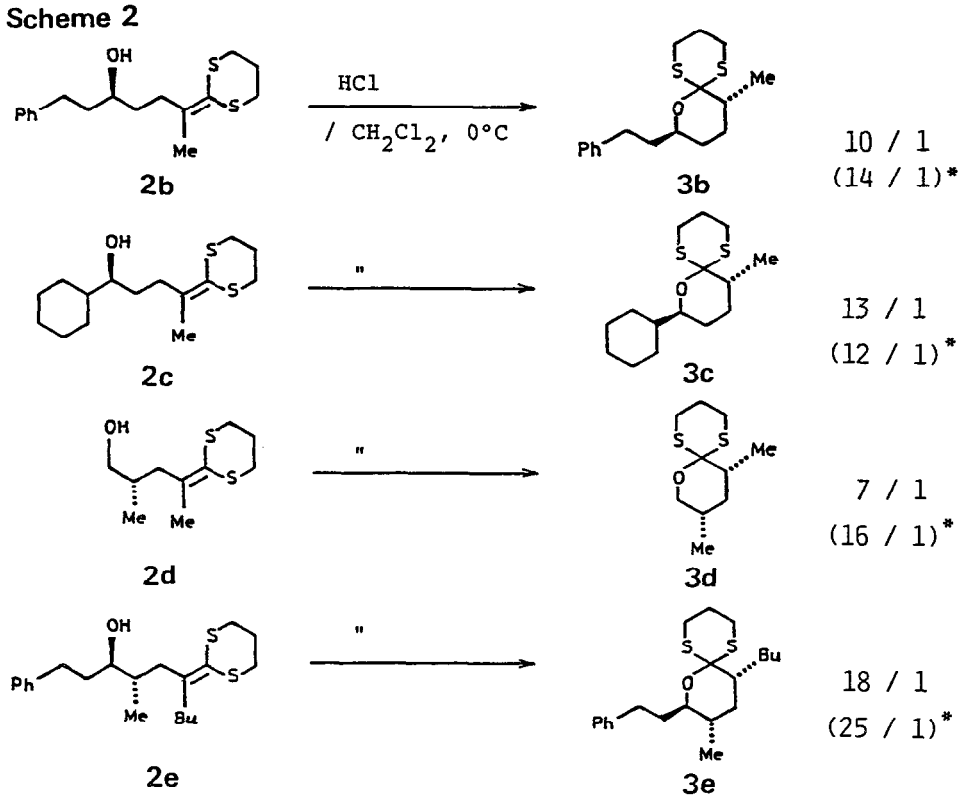
was the solvent dependency as shown in Table 1. Use of non-polar solvents gave modest yields of cyclized product 3a without any remarkable α/β ratio (entry 1, 2). Rate of cyclization was much slower in the solvent of higher polarity, where also poor selectivity resulted (entry 6, 7, 8). Modestly polar halogenated hydrocarbon or acetonitrile was found to be the solvent of choice to attain good α-selectivity, wherein the ratio reached synthetically useful level in CH_2Cl_2: 14 / 1 (entry 4).

Choice of the acid is another key factor for attaining good selectivity. Although not detailed here, use of anhydrous HCl gave the best result in light of both the yield and the selectivity. Concerned with the use of acetic acid derivatives, the lower the acidity was, the poorer the selectivity became (CF_3COOH: 7/1, CCl_3COOH: 5/1, $Cl_2CHCOOH$: 4/1, $ClCH_2COOH$: 3/1). Use of CH_3COOH resulted in the recovery of the starting material.

Profiles of the cyclization of other substrates are depicted in Scheme 2. It is noteworthy that equally good selectivities were obtained even in the cases lacking the C(4) methyl substituent as in 2b and 2c, which should have synthetical usefulness as a new method of remote stereocontrol in 1,4-relationship. 1,3-Asymmetric induction is also possible by this method (2d → 3d), although in slightly decreased selectivity. Bulky substituent at C(2) enhances the selectivity as is seen in 2e → 3e.

Hydrolysis of dithio-orthoesters 3 proceeded quite smoothly ($HgCl_2$,

Scheme 2



*Expected ratio based on MM 2 calculation.[8)]

pH 7, room temperature) to give the corresponding lactones 4 in high yields without any loss of the diastereomeric purity at C(2).

The present stereocontrol is thermodynamic in nature rather than kinetic, as evidenced by following observations: (1) In the early stage of the cyclization, the α/β ratio is low, while it comes up to the constant maximum value at the later stage (as exemplified in the time dependence of the ratio of 3b: Table 2). (2) Improvement of the ratio was observed when 1/1 mixture of 3b was subjected to HCl in CH_2Cl_2, while this equilibration is quite slow in Et_2O (essentially no change in the ratio). Thus, the stereoselectivity is a result of the repeated cyclization and ring opening (2 ⇄ 3), and the influence of the aforementioned parameters (solvents, acidity) may be interpreted in terms of the net activity of the acid for achieving the equilibrium. Existence of a rapid equilibrium could be recognizable by close analogy to the reversibility

Table 2. Time Dependence[a)]

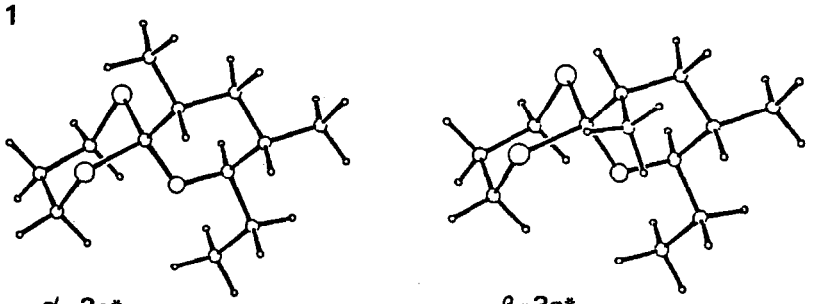
Time	Ratio 3b (α/β)	Yield (%)
10 sec	2.2 / 1	62
20 sec	3.8 / 1	81
1 min	8.1 / 1	79
2 min	10 / 1	85
16 min	10 / 1	98

a) Cyclization of 2b: HCl / CH_2Cl_2, 0°C. The reaction was stopped at the times indicated.

in the hydration of the ketene dithioacetals under acidic conditions reported by Okuyama et al.[6]

Calculation on the thermodynamic stability of the bicyclic compounds 3 is also supportive for this rationale. In Scheme 2, the expected values of the α/β ratio of 3 are shown on the basis of the MM2 calculation, which are in good accordance with the experimental data.[8] Drawings of each of the lowest-energy conformation of the α and β isomers of 3a are shown in Figure 1, whose ratio was calculated to be 14 / 1 (Cf. Table 1).

Figure 1



*Side chain ($Ph(CH_2)_2$) is replaced by C_2H_5.

Application of the present process to macrolide synthesis is now in progress.

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