Tetrahedron Letters,Vol.25,No.50,pp 5797-5800,1984 0040-4039/84 $3.00 + .00
Printed in Great Britain

UNUSUAL STEREOSELECTIVITY IN THE SYNTHESIS OF 4-OXA-δ-VALEROTHIOLACTONES: STRUCTURE PROOF OF β-HYDROXYTHIOAMIDE

Yoshinao Tamaru, Masuhiro Okada, Osamu Kitao, and Zen-ichi Yoshida*

Department of Synthetic Chemistry, Kyoto University, Yoshida, Kyoto 606, Japan

Summary: Stereoselectivity in the formation of 4-oxa-δ-valerothiolactone 2 from β-hydroxythioamide 1 is discussed. The structure of 1 is deduced from the structure of 2.

The ^{1}H and ^{13}C nuclear magnetic resonances have been used most commonly for the structure assignment of acyclic β-hydroxycarbonyl compounds, utilizing the following correlations. (i) When the α-substituent is sterically small (e.g., Me, Et, Ph), the erythro isomer shows the smaller vicinal coupling constant ($J_{C_\alpha HC_\beta H}$) in the ^{1}H NMR spectra[1] and the higher field resonances of C_α-methyne and C_β-carbinol carbons in the ^{13}C NMR spectra[2] compared with those of the corresponding threo isomer. (ii) When the α-substituent is sterically large (e.g., i-Pr,[3] t-Bu)[2,4] the inverse correlation holds.

Both in ^{1}H and ^{13}C NMR spectra the correlation (i) holds well for the β-hydroxythioamide 1 with any combination of substituent R^1 = Me, Et, and Ph and R^2 = Me, Et, Ph, and i-Pr.[5] However, when R^1 is isopropyl, the pairs of diastereomers 1 show irregular and very close vicinal coupling constants (cf. Table II) and also irregular chemical shifts of resonances of C_α methyne and C_β-carbinol carbons in their ^{13}C NMR spectra (e.g., figures are given in the order of C_α and C_β in ppm: 59.2, 65.6 (threo 1f); 59.4, 69.7 (erythro 1f); 58.9, 69.8 (threo 1h); 58.7, 73.1 (erythro 1h).[5]

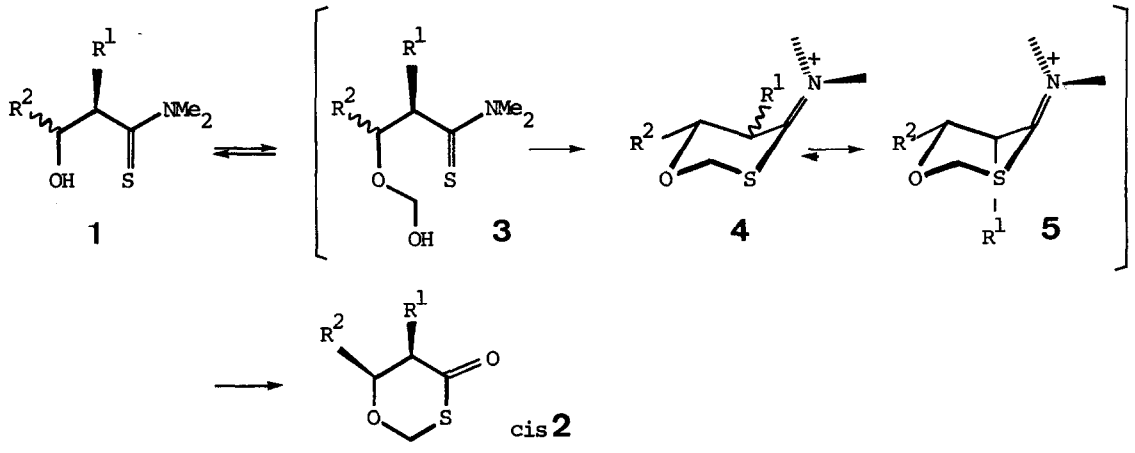
In this communication, we describe a cyclization reaction of 1 to 4-oxa-δ-valerothiolactone 2 and the structure determination of 1 based on the structure of 2.

Each of the eight pairs of diastereomers 1 (1 mmol)[6] was treated with formalin (37%, 5-10 mmol) and p-toluenesulfonic acid (1.3-1.5 mmol) in 3 mL of 1,2-dimethoxyethane under reflux for 1-7 h. The reaction was mostly completed within 2 h. The isolated yields of 2 are summarized in Table I. The products were thoroughly investigated by means of ^{1}H, ^{13}C NMR and VPC, and no isomerization of 2 was observed under the reaction conditions. In every case, except for

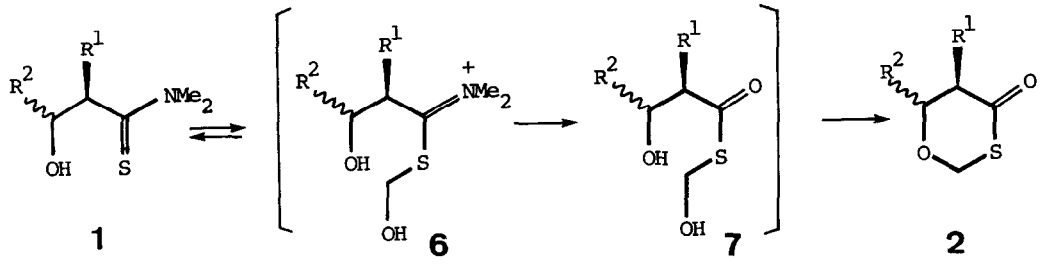
threo 1b, 2 was obtained as a single isomer.

A general trend emerges from Table I, which may be classified into three groups. (i) On the cyclization of 1 (R^1 = $PhCH_2$ and i-Pr), cis 2 and trans 2 are formed specifically from erythro 1 and threo 1, respectively (entries 7-16). The yield of 2 is moderate (44-63% isolated). When R^1 is phenyl, each of the diastereomers of 1 shows quite different reaction features. (ii) The cyclization of erythro 1 provides cis 2 in almost quantitative yield (entries 1, 3, and 5), while (iii) threo 1 is converted to 2 in low yield, the rest of the product mainly consisting of α,β-unsaturated thioamide formed by the dehydration of 1. Especially rewarding here is that the cyclization of threo 1 has caused a complete inversion of the C_α stereochemistry and exclusively provided the thermodynamically less stable cis 2a.[7]

Scheme I. Hydroxymethylation of Hydroxyl Group



Scheme II. Hydroxymethylation of Thioamide Group



This anomaly together with the behaviors summarized as groups i and ii may be rationalized according to mechanisms shown in Schemes I and II. The cyclization may proceed in two ways:

Table I. Synthesis of 4-Oxa-δ-valerothiolactone 2 from β-Hydroxythioamide 1

entry	β-hydroxythioamide 1		stereochemistry	product 2 (isolated yield)	
	R^1	R^2	of 1	cis	trans
1	Ph	Me	erythro 1a	95	0
2	Ph	Me	threo 1a	18	0[a]
3	Ph	Et	erythro 1b	95	0
4	Ph	Et	threo 1b	4	16[b]
5	Ph	i-Pr	erythro 1c	80	0
6	Ph	i-Pr	threo 1c	0	39[c]
7	$PhCH_2$	Me	erythro 1d	60	0
8	$PhCH_2$	Me	threo 1d	0	60
9	$PhCH_2$	i-Pr	erythro 1e	58	0
10	$PhCH_2$	i-Pr	threo 1e	0	55
11	i-Pr	Me	erythro 1f	47	0
12	i-Pr	Me	threo 1f	0	50
13	i-Pr	Et	erythro 1g	55	0
14	i-Pr	Et	threo 1g	0	44
15	i-Pr	$PhCH_2CH_2$	erythro 1h	63	0
16	i-Pr	$PhCH_2CH_2$	threo 1h	0	53

a) In addition to 2, N,N-dimethylcrotonothioamide was isolated in 50% yield.
b) In addition to 2, N,N-dimethyl-2-pentenothioamide was isolated in 47% yield.
c) In addition to 2, N,N-dimethyl-4-methyl-2-pentenothioamide was isolated in 7% yield.

Table II. Vicinal Coupling Constant[a] of β-Hydroxythioamide 1 and 4-Oxa-δ-valerothiolactone 2

R^1	R^2	1		2	
		erythro	threo	cis	trans
Ph	Me	2.0	8.0	3.0	10.0
Ph	Et	2.5	9.0	3.0	10.0
Ph	i-Pr	b	9.5	2.9	10.3
$PhCH_2$	Me	1.2	b	4.0	8.0
$PhCH_2$	i-Pr	1	7.5	1	7.2
i-Pr	Me	4.0	3.2	4.2	6.0
i-Pr	Et	2.5	3.5	3.6	5.5
i-Pr	$PhCH_2CH_2$	3.5	3.0	3.6	5.9

a) in Hz, measured in $CDCl_3$.
b) could not be assigned.

Hydroxymethylation of the hydroxyl group of 1 followed by cyclization and hydrolysis (Scheme I) and hydroxymethylation of thioamide group of 1, followed by hydrolysis and cyclization (Scheme II). It was shown that, by treatment with formalin and p-toluenesulfonic acid in refluxing DME, dihydrocinnamothioamide was hydrolyzed ca. 10 times faster than phenylacetothioamide, providing the corresponding amides as the main products. And hence, of the two competing processes, 1 (R^1 = i-Pr, $PhCH_2$) might favorably follow the course of Scheme II and 1 (R^1 = Ph) the course of Scheme I. The moderate yields (entries 7-16) may be due to hydrolysis of 6 to amides.[8]

The erythro isomer 1 (R^1 = Ph) might undergo the cyclization according to Scheme I (4 = 5) and provides cis 2 in high yield, but in the case of the threo isomer 1 (R^1 = Ph), owing to a severe A(1,3) strain[9] in 4 between N-Me and an equatorial phenyl group, the course of the reaction may be subtly balanced by the steric bulk of the R^2 substituents. When R^2 is methyl, the reaction may proceed via 4 and its complete epimerization to 5, and provides cis 2a after hydrolysis of 5. When R^2 is isopropyl, the steric congestion in 4 is such that the reaction may proceed according to Scheme II. The cyclization of 1 (R^2 = Et) is an intermediate case of these two and may provide a mixture of cis and trans 2.

The utility of the current cyclization process for the structure determination of 1 becomes apparent by an examination of the vicinal coupling constant of 2 shown in Table II, which indicates that the correlation of $J_{cis} < J_{trans}$ holds irrespectively of the steric bulk of the substituents R^1 and R^2.[10]

REFERENCES AND NOTES

1) A. Gaudemer, In "Stereochemistry", H. B. Kagan, Ed.; Georg Thieme Verlag: Stuttgart, 1977; Vol. 1.
2) C. H. Heathcock, M. C. Pirrung, and J. E. Sohn, J. Org. Chem., 44, 4294 (1979).
3) J. Canceill, J. J. Basselier, and J. Jacques, Bull. Soc. Chim. Fr., 1024 (1967).
4) K. K. Heng, J. Simpson, R. A. J. Smith, and W. T. Robinson, J. Org. Chem., 46, 2932 (1981).
5) Detailed ^1H and ^{13}C NMR study will be reported in a full account.
6) (a) preceeding communication. (b) Y. Tamaru, T. Harada, S. Nishi, M. Mizutani, T. Hioki, and Z. Yoshida, J. Am. Chem. Soc., 102, 7806 (1980).
7) Isomerization of cis 2a (0.13 equiv of DBU in refluxing THF) gave a mixture of cis 2a and trans 2a in a ratio of 1:4-5.
8) For the erythro 1 (R^1 = i-Pr, $PhCH_2$), the process 6 → 4 is also likely.
9) Y. Tamaru, M. Mizutani, Y. Furukawa, S. Kawamura, Z. Yoshida, K. Yanagi, and M. Minobe, J. Am. Chem. Soc., 106, 1079 (1984).
10) The substituents of cis 2 showed the higher field resonances compared with those of trans 2 in ^{13}C NMR spectra.

(Received in Japan 29 August 1984)