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REGIOSELECTIVE REDUCTION OF α,γ -ONOCERADIENEDIONE: SYNTHESIS OF LANSIOLIC ACID

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Synthesis of lansiolic acid is completed through the regioselective reduction of α,γ -onoceradienedione as a key step, and this unique regioselectivity is discussed based on the conformation analysis of 3-keto-4,4,10-trimethyldecalin system.

KEYWORDS — *Lansium domesticum*; α,γ -onoceradienedione; lansiolic acid; regioselective reduction; conformation analysis; 3-keto-4,4,10-trimethyldecalin; CD spectrum

The fruit skin of *Lansium domesticum* contains a large quantities of novel unsymmetrical onoceranoid triterpenes such as lansiolic acid (1a), lansioides A - C (1b - 1d),^{2,3)} α,γ -onoceradienedione (2), and lansiic acid (3).⁴⁾ Since some of these have important physiological activities,³⁾ we have designed a general procedure for synthesizing them. In our previous communication⁵⁾ we reported the total synthesis of 2 and 3 using a mercury(II) triflate/*N,N*-dimethyl aniline complex.⁶⁾ From the biogenetic standpoint, diketone 2 seems to be a key intermediate in the synthesis of 1 and 3, so that the two carbonyl functions of 2 were distinguished by the enzyme system of this plant. We wish to describe here the chemical differentiation of these carbonyl functions by NaBH₄ reduction, and the synthesis of lansiolic acid (1a). The regioselectivity of the carbonyl reduction of 2 is also discussed on the basis of the conformational analysis of 3-keto-4,4,10-trimethyldecalin systems by CD spectroscopy.

- 1a R = H
 1b R = *N*-acetyl- β -D-glucosamine
 1c R = β -D-glucose
 1d R = β -D-xylose

The diketone 2 was obtained in ca 0.05% yield from the dichloromethane extract of *L. domesticum* by ordinary and then reverse phase column chromatography. Selective reduction of 2 under a variety of conditions was examined and the results are summarized in Table I. The highest regioselectivity was achieved by using 10 equiv of NaBH_4 in isopropyl alcohol at -70°C for 1 h. This afforded the desired keto alcohol 4 in 35% yield along with a 3% yield of the undesired isomer 5, 49% of the diol 6, and 13% of the starting material (entry 9). The isomeric keto alcohols 4 and 5 were nicely separated by HPLC (Develosil 30-3 column, 5:1 mixture of hexane and ethyl acetate). The relative orientation of the double bonds of 4 and 5 at $\Delta^{8,26}$ and $\Delta^{14,15}$ was established by their CD spectra and LIS-NMR.

The major keto alcohol 4 was converted to oxime 7 in 73% yield by treatment with acetic anhydride/pyridine/4,4-dimethylaminopyridine and hydroxylamine. Beckmann fragmentation of 7 by *p*-toluenesulfonyl chloride in pyridine afforded seco-nitrile 8 (29% yield). Hydrolysis of 8 with KOH in ethanol gave a hydroxy carboxylic acid, which was identical with lansiolic acid (1a) in all respects.

The conformational mobility of the cyclohexane part of the 3-keto-4,4,10-trimethyldecalin system has been discussed by Tsuda et al in terms of "4,4-dimethyl group effect". They reported that the negative Cotton effect on CD spectra indicates the chair conformation and a positive Cotton effect indicates the twist-boat conformer.⁷⁾ When the CD spectra of the reduction products 4 and 5 were determined at -190°C in ether/isopentane/ethanol (5:5:2) (Figure 1), a large negative Cotton effect was observed in both compounds. This would be due to more stable chair conformers resulting from freezing the conformational equilibrium. At -70°C , the CD amplitude of 5 with exocyclic double bond showed a significant decrease of $\Delta\epsilon$ value depending on the increased contribution of a twist-boat conformer. But the CD spectrum of 4 with endocyclic double bond was very close to that at -190°C . Thermodynamic calculations based on these spectral data⁸⁾ showed that the former compound contains about 20% of the twist-boat conformer at -70°C , while 4 still maintains more than 93% of the chair conformer at the same temperature. α,γ -Onoceradiene-dione (2) can be considered to take a conformation essentially analogous to that of 4 (C/D) and 5 (A/B) in both of the decalone ring moieties, respectively. Thus 2 should exist in a 4:1 equilibrium mixture of conformers 9 and 10 at -70°C . If the unstable twist-boat conformer is more reactive than the chair conformer, the preferential reduction at the A-ring ketone could be reasonably considered to proceed via the conformer 10.

Table 1. Regioselective Reduction of α, δ -Onoceradienedione

Entry	Reagent	Equiv.	Solvent	Condition °C, h	Product yield(%)			
					2	4	5	6
1	$\text{LiAl}(\text{O}-t\text{-Bu})_3\text{H}$	4	THF	60, 8	100	0	0	0
2	LiAlH_4	4	THF	0, 2	18	13	10	59
3	NaBH_4	1	$\text{EtOH}/\text{H}_2\text{O}$	0, 3.5	41	23	9	27
4	NaBH_4	10	$(\text{CH}_3)_2\text{CHOH}$	30, 0.3	10	29	12	49
5	NaBH_4	10	$(\text{CH}_3)_2\text{CHOH}$	0, 0.5	10	32	10	48
6	NaBH_4	10	$(\text{CH}_3)_2\text{CHOH}$	-10, 0.7	37	36	11	16
7	NaBH_4	1	$(\text{CH}_3)_2\text{CHOH}$	-70, 15	83	12	5	0
8	NaBH_4	4	$(\text{CH}_3)_2\text{CHOH}$	-70, 10	74	17	5	4
9	NaBH_4	10	$(\text{CH}_3)_2\text{CHOH}$	-70, 1	13	35	3	49

Fig. 1 CD Spectra of 4 and 5 in Ether/Isopentane/Ethanol (5:5:2)

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REFERENCES

- 1) Present address: Faculty of Pharmaceutical Science, Tokushima Bunri University, Yamashirocho, Tokushima 770, Japan.
- 2) M. Nishizawa, H. Nishide, Y. Hayashi, and S. Kosela, *Tetrahedron Lett.*, **23**, 1349 (1982).
- 3) M. Nishizawa, H. Nishide, S. Kosela, and Y. Hayashi, *J. Org. Chem.*, **48**, 4462 (1983).
- 4) A. K. Kiang, E. L. Tan, F. Y. Lim, K. Habaguchi, M. Watanabe, Y. Nakadaira, K. Nakanishi, L. Fachan, and G. Ourisson, *Tetrahedron Lett.*, 3571 (1967); K. Habaguchi, M. Watanabe, Y. Nakadaira, K. Nakanishi, A. K. Kiang, and F. Y. Lim, *ibid.*, 3731 (1968).
- 5) M. Nishizawa, H. Nishide, and Y. Hayashi, *Tetrahedron Lett.*, **25**, 5071 (1983).
- 6) M. Nishizawa, H. Takenaka, H. Nishide, and Y. Hayashi, *Tetrahedron Lett.*, **24**, 2581 (1983).
- 7) Y. Tsuda, H. Yamashita, and T. Sano, *Chem. Pharm. Bull.*, **32**, 4820 (1984), and references are cited therein.
- 8) A. Moscowitz, K. Wellman, and C. A. Djerassi, *J. Am. Chem. Soc.*, **85**, 3515 (1963).

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