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

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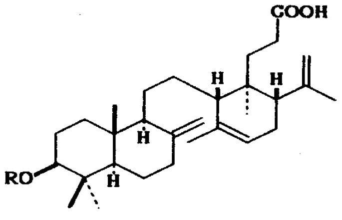
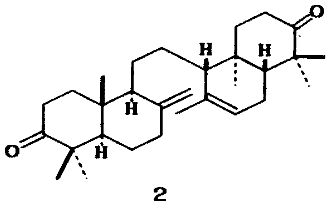
Synthesis of lansiolic acid is completed through the regioselective reduction of α,γ-onoceradienedione as a key step, and this unique regioselectivity is discussed based on the conformation analysis of 3-keto-4,4,10-trimethyldecalin system.

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), lansiosides A - C (1b - 1d),2,3) α,γ-onoceradienedione (2), and lansic 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 $NaBH_4$ 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



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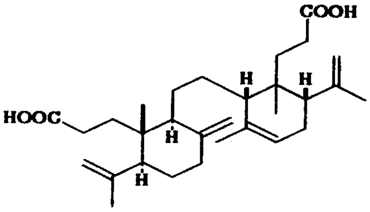

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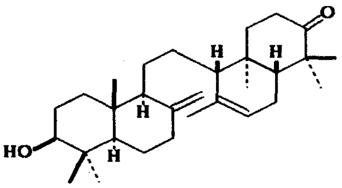
The diketone 2 was obtained in ca 0.05% yield from the dichloromethane extract of L. domesticum by ordinary and then reverse phase column chromatography. Selective reduction of 2 under a variety of conditions was examined and the results are summarized in Table I. The highest regioselectivity was achieved by using 10 equiv of $NaBH_4$ in isopropyl alcohol at -70℃ 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.



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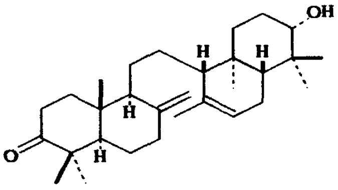

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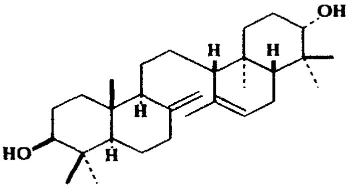

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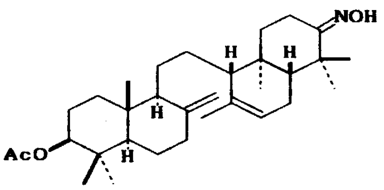
The major keto alcohol 4 was converted to oxime 7 in 73% yield by treatment with acetic anhydride/pyridine/4,4-dimethylaminopyridine and hydroxylamine. Beckmann fragmentation of 7 by p-toluenesulfonyl chloride in pyridine afforded seco-nitrile 8 (29% yield). Hydrolysis of 8 with KOH in ethanol gave a 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℃ 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℃, the CD amplitude of 5 with exocyclic double bond showed a significant decrease of $\Delta\varepsilon$ 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℃. Thermodynamic calculations based on these spectral data[8] showed that the former compound contains about 20% of the twist-boat conformer at -70℃, while 4 still maintains more than 93% of the chair conformer at the same temperature. α,γ-Onoceradienedione (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℃. 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 I. Regioselective Reduction of α,δ-Onoceradienedione

				Condition		Product yield(%)			
Entry	Reagent	Equiv.	Solvent	°C,	h	2	4	5	6
1	LiAl(O-*t*-Bu)$_3$H	4	THF	60,	8	100	0	0	0
2	LiAlH$_4$	4	THF	0,	2	18	13	10	59
3	NaBH$_4$	1	EtOH/H$_2$O	0,	3.5	41	23	9	27
4	NaBH$_4$	10	(CH$_3$)$_2$CHOH	30,	0.3	10	29	12	49
5	NaBH$_4$	10	(CH$_3$)$_2$CHOH	0,	0.5	10	32	10	48
6	NaBH$_4$	10	(CH$_3$)$_2$CHOH	-10,	0.7	37	36	11	16
7	NaBH$_4$	1	(CH$_3$)$_2$CHOH	-70,	15	83	12	5	0
8	NaBH$_4$	4	(CH$_3$)$_2$CHOH	-70,	10	74	17	5	4
9	NaBH$_4$	10	(CH$_3$)$_2$CHOH	-70,	1	13	35	3	49



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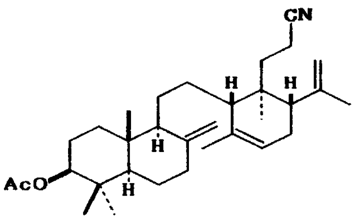

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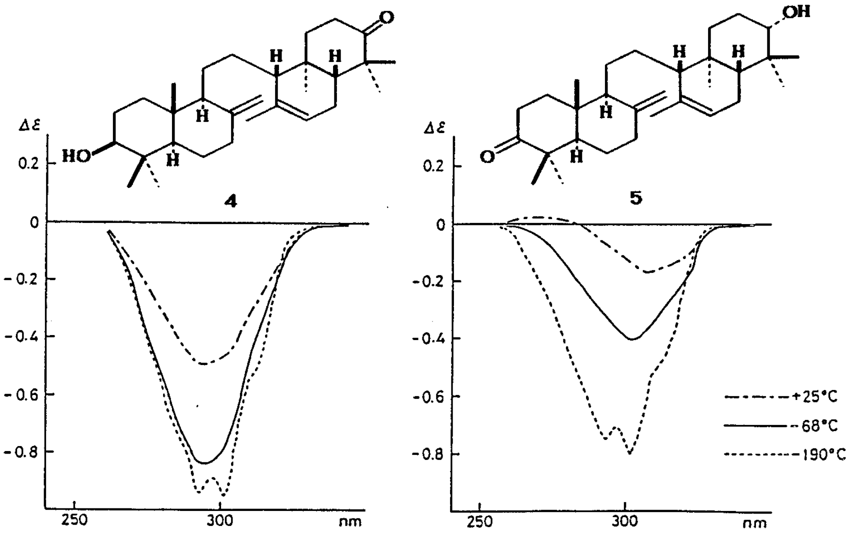
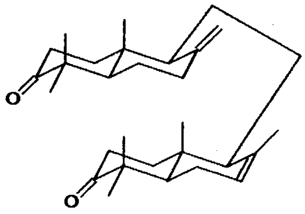


Fig. 1 CD Spectra of 4 and 5 in Ether/Isopentane/Ethanol (5:5:2)



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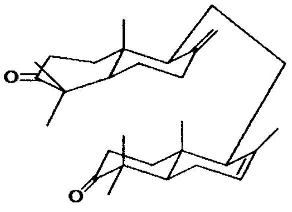

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