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FACILE PREPARATION OF 2,6-DIMETHYL-2,6-TETRAHYDROPYRANCARBOLACTONE, A VERSATILE INTERMEDIATE FOR THE SYNTHESES OF (±)-FRONTALIN, (±)-CINENIC ACID, AND (±)-LINALOYL OXIDE

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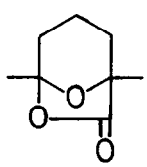
Abstract: 2,6-Dimethylcyclohexanone has been converted via its 2,6-dihydroxy derivative by base-catalyzed oxygenation to 2,6-dimethyl-2,6-tetrahydropyrancarbolactone which can be used as a key intermediate for the syntheses of the title natural products in racemic forms.

In a recent paper, we have described a novel carbon–carbon bond cleavage reaction of α-azohydroperoxide which is formed from 2-methyl-2-hydroxycyclohexanone phenylhydrazone by autoxidation.[1] In the course of study, 2,6-dimethyl-2,6-dihydroxycyclohexanone was found to be inapplicable to the reaction owing to the elimination of the hydroxyl group when treated with phenylhydrazine. Instead, the substrate underwent a base-catalyzed oxygenation rather smoothly in spite of the fact that it has no active hydrogen on the carbon α to the carbonyl group. The reaction afforded 2,6-dimethyl-2,6-tetrahydropyrancarbolactone (1) which has a basic structure of 6,8-dioxabicyclo[3.2.1]octane that is widespread in plants and animals.[2] Here we report the novel oxygenation and its application to the syntheses of (±)-frontalin (2), (±)-cinenic acid (3), and (±)-linaloyl oxide (4). The oxygenation is shown in Scheme I.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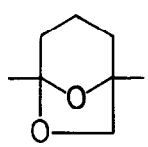
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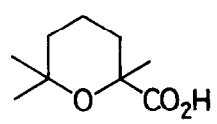

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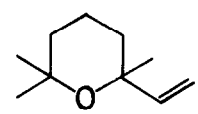
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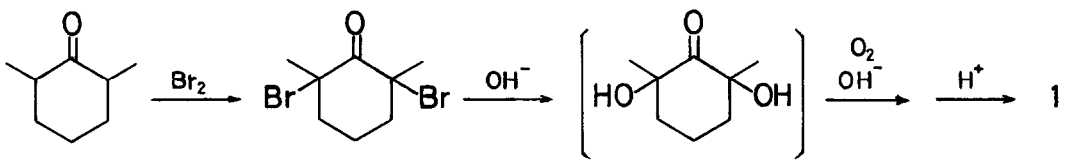
2,6-Dimethyl-2,6-dibromocyclohexanone (5)[3] was obtained from 2,6-dimethylcyclohexanone by dibromination with bromine almost quantitatively. Then, 589 mg (2.07 mmol) of 5 in a mixture of 2 ml of methanol and 5 ml of water dissloving 0.8 g of sodium hydroxide, was stirred magnetically at 50 °C under oxygen. The absorption of oxygen became very slow after 16 h when the oxygen consumption amounted to about 43 ml (1.8 mmol). The reaction mixture was neutralized and extracted with ethyl acetate, giving 63 mg of a yellow oil.[4] The neutral solution was acidified to pH 2 and extracted with ethyl acetate, giving 240 mg of a dark red oil,[5] which, after refluxing in chloroform with *p*-toluenesulfonic acid and washing with aq sodium hydrogen carbonate, gave 207 mg (64%) of crude 1.

Glass-tube distillation gave 131 mg (41%) of analytically pure 1 as a pale yellow oil.[6]

The oxygenation proceeds via 2,6-dihydroxy derivative 6 since 5 is converted to 6[7] in more than 90% yield within 40 min under the reaction conditions.

Scheme I



5 6

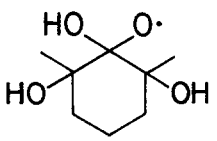


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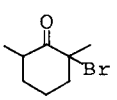
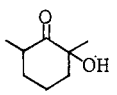
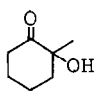
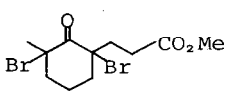
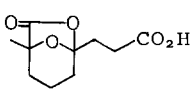
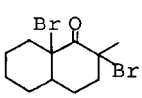
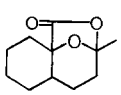
Table I. Base-Catalyzed Oxygenation of α-Bromo-α-methylcyclohexanones[a]

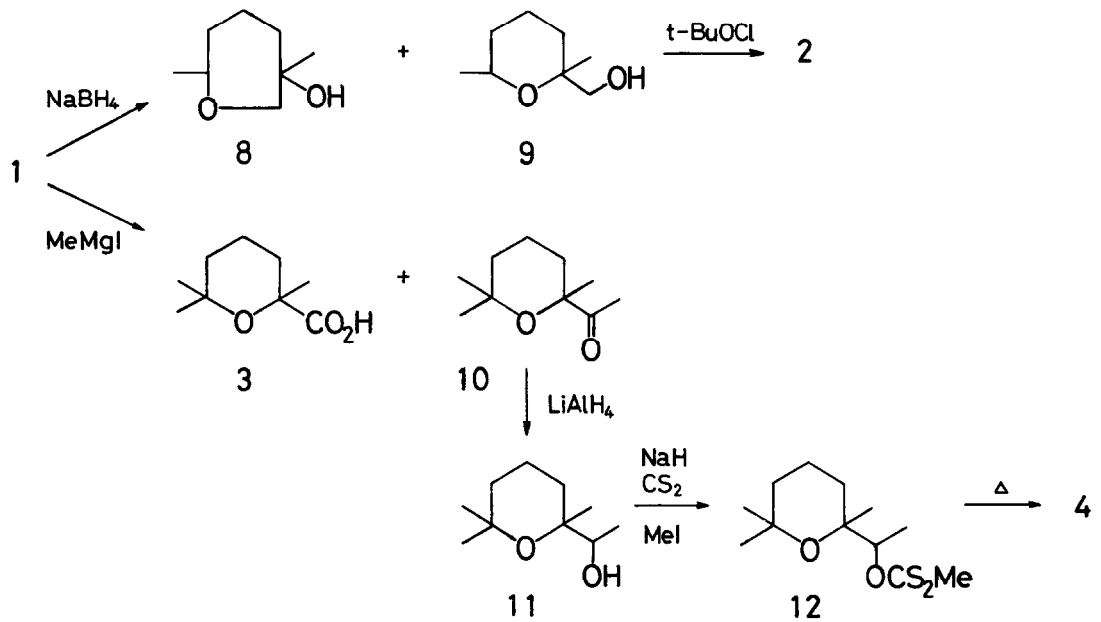
substrate	time h	O_2[b] %	product % yield[c]			
5	16	86	1	64 (41)	6	10
	19	107	1[d]	42 (26)		10
	19	58		60 (50)		20
	23	97		90 (74)[e]		
	38	78		20 (14)[f]		

[a] In 4M NaOH (MeOH–H_2O, 2:5) at 50 °C. [b] (mole of O_2 absorbed/mole of substrate) x 100. [c] The values in parentheses are distilled yields. [d] A small amount of $CH_3CO(CH_2)_3CH(CH_3)CO_2H$ was contained. [e] A 2:1 mixture of the lactone [C(1)–C(2) cleavage product] and its isomer [C(1)–C(6) cleavage product]. [f] A 2:1 mixture of the lactone [C(1)–C(2) cleavage product] and its isomer [C(1)–C(8a) cleavage product].

The oxy radical 7 generated from the corresponding oxyanion is possibly involved in the carbon–carbon bond cleavage.[8] The results for related substrates shown in Table I indicate that the carbon–carbon bond is vulnerable to oxygenation under the basic conditions. It is also apparent that the reaction time and the yield are highly dependent on the substrate structure. Interestingly the selectivity in cleavage is observed for the unsymmetrical substrates which have two choices of bond cleavage. The scope of the present reaction will be reported in due course.

Frontalin, an aggregating pheromone of the southern pine beetle, *Dendroctonus frontalis*,[9] has been synthesized in racemic and enantiomeric forms by several groups.[10] Our synthetic process is very simple as illustrated in Scheme II.

Scheme II



Reduction of 1 with $NaBH_4$ (2 equiv.) in dry ether was carried out in the presence of 30 equiv. of BF_3–etherate at 0 °C for 1 h and then at reflux temperature for 2 h to give 8 in 26% yield and 9 in 36% yield.[11] Treatment of 8 with *t*-BuOCl gave 2 in 61% yield.[12] The alcohol 9 was converted to 2 in a similar manner in 41% yield.

The reaction of 1 with 1.5 equiv. of MeMgI in ether at room temperature for 7 h gave α-cinenic acid (3),[13,14] a component of sapogenin, in 53% yield along with 10 (23%).[15] However, when 2.5 equiv. of MeMgI was used, the reaction gave the ketone 10 (59%) as a main product and the acid 3 (24%) as a minor one. Linaloyl oxide (4)[14] was obtained from 10 via 11 and 12 in 20% yield as shown in Scheme II.

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References and Notes

1. M. Utaka, Y. Fujita, and A. Takeda, *Chem. Lett.*, 1982, 1607.
2. B. P. Mundy, G. W. Dirks, R. M. Larter, A. C. Craig, K. B. Lipkowitz, and J. Carter, *J. Org. Chem.*, 46, 4005 (1980) and references cited therein.
3. The IR and NMR spectra of crude 5 indicated the presence of two isomers. The material was used in the subsequent reaction without purification.
4. The oil contained 6 as a major component.
5. The oil showed a similar ^{1}H NMR spectrum to that for 1 except for the presence of signals due to acidic hydrogen and a minor amount of impurities.
6. 1: bp ~100 °C (bath temp, 18 Torr); IR (neat) 1790 cm^{-1}; ^{1}H NMR (CCl_4) δ 1.42 (s, 3H), 1.58(s, 3H), 1.7–2.0(m, 6H); ^{13}C NMR ($CDCl_3$) 17.7(t), 20.4(q), 23.9 (q), 30.3(t), 30.7(t), 80.3(s), 109.4(s), 175.6(s); CI-MS m/e (isobutane) 157 (MH^+); (NH_3) 174(MNH_4^+), 157(MH^+). Anal. Calcd for $C_8H_{12}O_3$: C, 61.52; H, 7.74. Found: C, 61.62; H, 7.67.
7. Satisfactory IR and NMR spectra were obtained.
8. An anodic oxidation of 1-decalone in alkaline solution, resulting in the C–C bond cleavage, was supposed to proceed via α-hydroxy *t*-alkoxy radicals. See F.Barba, A.Guirado, I.Barba, and M. Lopez, *Tetrahedron Lett.*, 23, 463 (1982).
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11. 8: IR (neat) 3440 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.13(d, 3H), 1.18(s, 3H), 1.50(m, 6H), 2.30(s, 1H), 3.20(d, 1H), 3.60(m, 1H), 3.94(d, 1H); ^{13}C NMR ($CDCl_3$) 18.2(q), 19.4(t), 22.5(q), 29.9(t), 33.4(t), 66.6(d), 71.5(t), 73.9(s). 9: IR (neat) 3460 cm^{-1} ; ^{1}H NMR ($CDCl_3$) δ 1.14(d, 3H), 1.17(s, 3H), 1.50(m, 6H), 2.55(s, 1H), 3.34(s, 2H), 3.60(m, 1H); ^{13}C NMR ($CDCl_3$) 19.7(t), 22.6(q), 26.7(q), 31.9(t), 32.7(t), 62.6(t), 66.7(d), 73.6(s).
12. We thank Prof. Tadashi Sato for the donation of IR and NMR spectra of (±)-frontalin.
13. M. Nagai, O. Tanaka, and S. Shibata, *Chem. Pharm. Bull.*, 19, 2349 (1971).
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