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A Simple Synthesis of (±)-*cis*-(6-Methyltetrahydro-2-pyranyl)acetic Acid, a Constituent of Civet

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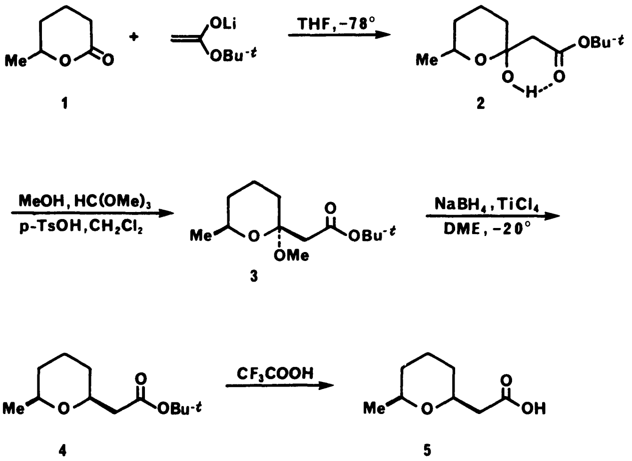
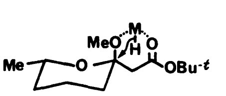
Synopsis. The title compound was synthesized stereoselectively starting with readily available 5-hexanolide in a 47% overall yield.

cis-(6-Methyltetrahydro-2-pyranyl)acetic acid (**5**) was isolated as a minor constituent of civet, which is utilized in perfumery, by Mauer et al. in 1979.1) Since then, several synthetic methods for the preparation of **5** have been reported.2) We now wish to report a more simple synthesis of **5**, which involves a stereoselective reduction of the cyclic acetal **3**.

t-Butyl (2-methoxy-6-methyltetrahydro-2-pyranyl)acetate (**3**) was prepared from the reaction of 5-hexanolide with the lithium enolate of *t*-butyl acetate3) followed by the subsequent treatment of the cyclic hemiacetal **2** with methanol and trimethyl orthoformate in dichloromethane in the presence of a catalytic amount of *p*-toluenesulfonic acid. The magnesium enolate of *t*-butyl acetate4) also could be used for the preparation of **2**. Although the yield was slightly reduced, the reaction proceeded under milder conditions. In each case **3** was obtained in stereochemically pure form. The stereochemistry of **3** was determined on the basis of the reported ^{1}H NMR examination.5)





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The sodium borohydride reduction of **3** to **4** was found to be feasible using titanium tetrachloride as a catalyst. Thus, **3** was allowed to react with 1 equivalent of sodium borohydride in the presence of 1.5 equivalent of the catalyst in 1,2-dimethoxyethane at −20 °C, and the reduced product **4** was produced stereoselectively in an 80% isolated yield. The reaction occurred immediately and cleanly, and the ester moiety was not affected under the present conditions.6) The use of excess sodium borohydride or the catalyst, prolonged reaction time, and elevated reaction temperature led to complicated mixture of products arising from the reduction of the ester moiety. 1,2-Dimethoxyethane was essential for the reaction, and the use of diethyl ether, THF, benzene, and dichloromethane was not effective. The use of lithium aluminum hydride instead of sodium borohydride was also ineffective.

The specific formation of **4** in the reduction of **3** may be explained in terms of the involvement of the intermediate **6**.7)

The ester cleavage of **4** was carried out in trifluoroacetic acid to give **5** in a 79% yield. Since the present method is operationally simple and highly selective, it offers advantages over the porevious methods for the preparation of **5**.2)

Experimental

The IR spectra were recorded on a Hitachi 285 spectrometer. The ^{1}H NMR spectra were recorded on a Hitachi R-90B spectrometer in CDCl$_3$ with tetramethylsilane as an internal standard. The high and low resolution mass spectra were determined with a JEOL JMS-D300 spectrometer. Thin-layer chromatography was performed using Merck Silica Gel 60 GF$_{254}$. All solvents were dried over appropriate agents and distilled under nitrogen prior to use. All reactions were carried out in a nitrogen atmosphere.

***t*-Butyl (2-Hydroxy-6-methyltetrahydro-2-pyranyl)acetate (2).** To a stirred solution of lithium diisopropylamide (LDA) (10 mmol), which was prepared by the treatment of diisopropylamine (1.0 g, 10 mmol) with butyllithium (10 mmol, 1.5 M[†] in hexane solution) in THF (20 ml) at −78 °C, was added *t*-butyl acetate (1.2 g, 10 mmol). After stirring for 20 min at the same temperature 5-hexanolide2c) (1.1 g, 10 mmol) was added to the reaction mixture and it was stirred for additional 4 h. The resulting mixture was quenched by adding aqueous ammonium chloride and extracted with ether three times. The combined extract was washed with brine, dried over anhydrous magnesium sulfate, and evaporated to give a crude **2** (2.2 g), which was not further purified and used in the next step. Compound **2** was alternatively prepared as follows. Diisopropylamine (4.1 g, 40 mmol) was added to an ethereal solution (30 ml) of ethylmagnesium bromide (20 mmol) at 0 °C and the mixture was stirred for 1 h at the same temperature. To the resulting turbid solution were successively added *t*-butyl acetate (1.2 g,

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[†] 1 M=1 mol dm^{-3}.

10 mmol) and 5-hexanolide (1.1 g, 10 mmol), and the mixture was stirred for additional 30 min. The resulting mixture was quenched by adding aqueous ammonium chloride and extracted with ether three times. The combined extract was dried over anhydrous magnesium sulfate, and concentrated in vacuo. The resulting crude product was not further purified and used in the next step.

***t*-Butyl (2-Methoxy-6-methyltetrahydro-2-pyranyl)acetate (3).** A solution of the crude **2** (2.2 g), trimethyl orthoformate (2 ml), methanol (1 ml), and *p*-toluenesulfonic acid (95 mg, 0.5 mmol) in dichloromethane (20 ml) was stirred at room temperature overnight. The resulting mixture was washed with aqueous sodium hydrogencarbonate and dried over anhydrous sodium sulfate. Evaporation of the solvent gave a crude oil which was distilled using Kugelrohr to afford **3** (1.8 g, 75% from **1**). Bp 110 °C (bath temperature)/0.1 Torr[††]; IR (neat) 1725 cm^{-1}; ^{1}H NMR δ=1.12 (d, J=6.2 Hz, 3H), 1.45 and 1.3—2.0 (s and m, combined 15H), 2.38 (d, J=13.4 Hz, 1H), 2.67 (d, J=13.4 Hz, 1H), 3.25 (s, 3H), 3.4—3.8 (m, 1H); MS, *m/z* (rel intensity) 244 (M$^+$, 0.2), 213 (6.2), 119 (95.8), 57 (100). Found: *m/z* 244.1666. Calcd for $C_{13}H_{24}O_4$: M, 244.1675.

***t*-Butyl *cis*-(6-Methyltetrahydro-2-pyranyl)acetate (4).** To a stirred suspension of sodium borohydride (0.19 g, 5 mmol) and **3** (1.2 g, 5 mmol) in 1,2-dimethoxyethane (20 ml) was added dropwise titanium tetrachloride (0.43 g, 7.5 mmol) at −20 °C. An exothermic reaction immediately occurred and the suspension turned to a green solution, which was poured into aqueous ammonium chloride and extracted with ether three times. The combined extract was washed with brine, dried over anhydrous sodium sulfate, and concentrated in vacuo. Distillation of the residue gave **4** (0.86 g, 80%). Bp 95 °C (bath temperature)/0.2 Torr; IR (neat) 1725 cm^{-1}; ^{1}H NMR δ=1.14 (d, J=6.2 Hz, 3H), 1.44 and 1.3—1.9 (s and m, combined 15H), 2.25 (dd, J=14.8, 6.2 Hz, 1H), 2.47 (dd, J=14.8, 6.8 Hz, 1H), 3.3—3.9 (m, 2H); MS, *m/z* (rel intensity) 214 (M$^+$, 0.1), 199 (0.8), 99 (84), 57 (100). Found: 214.1573. Calcd for $C_{12}H_{22}O_3$: M, 214.1569.

***cis*-(6-Methyltetrahydro-2-pyranyl)acetic Acid (5).** To a solution of **4** (0.21 g, 1 mmol) in dichloromethane (4 ml) was added trifluoroacetic acid (0.2 ml), and the mixture was stirred at room temperature overnight. Evaporation of the solvent gave a crude solid which was recrystallized from petroleum ether to afford **5** (0.13 g, 79%). Mp 51—52 °C (lit,[2a] 50—52 °C).

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[††] 1 Torr=133.322 Pa.