of potassium hydride and 86 μL, 1.0 mmol of pentan-3-one) were added through a syringe at room temperature. After 3 h of additional stirring, TLC indicated 100% conversion to products. The reaction was quenched by carefully adding a saturated aqueous solution (1 mL) of ammonium chloride. This mixture was partitioned between diethyl ether and water. The isolated organic layer was dried (Na_2SO_4) and evaporated. The resulting residue was chromatographed by preparative TLC on silica gel (two 20 × 20 cm plates), using hexane/diethyl ether (4:1, v/v) as the eluent to afford 78 mg (73% yield) of a mixture of ketones **6a** and **6b** as an oil. This mixture was separated by using reverse-phase HPLC with CH_3OH/H_2O (95:5, v/v) as the mobile phase. Pure **6a** had the following: $[\alpha]^{20}_D$ +2.8° (*c* 0.80, $CHCl_3$); ^1H NMR data are reported in Table VI; low-resolution mass spectrum (GC–MS) at 70 eV, *m/z* (relative intensity) 428 (5, M^+), 413 (5), 396 (6), 373 (7), 275 (2), 255 (8), 229 (4), 213 (12), 57 (100); UV 280 nm (ε 55); circular dichroism data are reported in Table IV. Pure **6b** had the following: $[\alpha]^{20}_D$ +5.2° (*c* 0.46, $CHCl_3$); ^1H NMR data are reported in Table VI; low-resolution mass spectrum (GC–MS) at 70 eV, see data given for **6a**; UV 282 nm (ε 72); circular dichroism data are reported in Table IV.

(24*R*)- and (24*S*)-Dimethyl-6β-methoxy-3α,5-cyclocholest-25(27)-ene[20] (7a and 7b). An oven-dried three-necked flask equipped with a magnetic stirring bar, rubber septa, and a Gooch tube was filled with powdered potassium hydride (58 mg, 1.45 mmol, 14 equiv) and two crystals of triphenylmethane (red colored indicator for excess base) and charged with an atmosphere of argon. At room temperature dry Me_2SO (6 mL) was added. The resulting red froth was vigorously stirred for 1 h before adding solid methyltriphenylphosphonium iodide (700 mg, 1.73 mmol, 17 equiv): stored in the 50-mL flask attached via the Gooch tube. The now clear yellow solution (implying excess Wittig salt) was stirred 15 min before the mixture of ketones **6a** and **6b** (44 mg, 0.106 mmol) in dry THF (1 mL) was added. This solution was stirred overnight, quenched with water, and partitioned between diethyl ether and water. The isolated organic layer was evaporated and the resultant residue chromatographed over a column (10 cm × 1 cm) of silica gel, using hexane/diethyl ether (9:1, v/v) as the eluent. An oily mixture of alkenes **7a** and **7b** was isolated in 40% yield (17.5 mg) and could not be separated by reverse-phase HPLC. For ^1H NMR data on **7a** and **7b**, see Table V. The mixture was then converted to the free hydroxy dienes without further data processing.

(24*R*)- and (24*S*)-24,26-Dimethylcholesta-5,25(27)-dien-3β-ol[20] (25-Dehydroaplysterol, 8a and 8b). A solution of **7a** and **7b** (17.5 mg) and toluenesulfonic acid (ca. 2 mg) in aqueous dioxane (2 mL) was heated at reflux for 1 h, and then partitioned between diethyl ether and water. The isolated organic layer was dried (Na_2SO_4) and evaporated. The residue (15 mg, 86% yield) was purified by HPLC to afford an inseparable mixture of **8a** and **8b**. The physical and spectral data for this mixture have been reported previously.[20] For ^1H NMR data on each diene, see Table II.

(24*R*)-24,26-Dimethyl-6β-methoxy-3α,5-cyclocholest-25-(27)-ene[20] (7a). Pure **6a** was converted to **7a** by General Procedure B. ^1H NMR data are reported in Table V.

(24*S*)-24,26-Dimethyl-6β-methoxy-3α,5-cyclocholest-25-(27)-ene[20] (7b). Pure **6b** was converted to **7b** by General Procedure B. ^1H NMR data are reported in Table V.

(24*R*)-24,26-Dimethylcholesta-5,25(27)-dien-3β-ol[20] (8a). Alkene **7a** was converted to **8a** by General Procedure C. ^1H NMR data are reported in Table II.

(24*S*)-24,26-Dimethylcholesta-5,25(27)-dien-3β-ol[20] (8b). Alkene **7b** was converted to **8b** by General Procedure C. ^1H NMR data are reported in Table II.

(24*R*)-24,26-Dimethyl-6β-methoxy-3α,5-cyclo-27-norcholestan-25-one[20] (11). A solution of 25-dehydroaplysterol (40 mg, 0.09 mmol) taken from a natural source[8] and toluenesulfonyl chloride (50 mg, 0.26 mmol) in pyridine (20 mL) was stirred overnight at room temperature. Water (5 mL) was added and the mixture stirred for 1 h. The mixture was partitioned between diethyl ether and water, the isolated organic layer evaporated, and the residue dissolved in absolute methanol (30 mL) along with some potassium acetate (50 mg, 0.51 mmol) followed by heating at reflux overnight. The mixture was partitioned between diethyl ether and water, the isolated organic layer evaporated, and the residue purified by HPLC. The residue (16 mg) was dissolved in CH_2Cl_2 (1.0 mL) and added dropwise via syringe to 1 equiv of ozone in exactly 1.0 mL of CH_2Cl_2 at −78 °C.[21] After 5 min one drop of dimethyl sulfide was added and the solution stirred for 10 min. The solvent was evaporated and the residue purified by HPLC to afford **11** as an oil. The physical and spectral data for this compound have been reported previously.[20] For 300-MHz ^1H NMR data, see Table VI. For chiroptical data, see Table IV.

Acknowledgment. Financial support by the National Institutes of Health (GM-06840, RR-00612, and GM-28352) is gratefully acknowledged. In addition we are grateful for the use of the 360-MHz FT NMR spectrometer provided by the Stanford Magnetic Resonance Laboratory (NSF Grant No. GP-23633 and NIH Grant No. RR-0711) and for the mass spectral service provided by Annemarie Wegmann. We are indebted to W. C. M. C. Kokke for assistance in HPLC separations and to Ruth Records for measuring the chiroptical data.

Registry No. 1, 87307-28-6; 2, 69101-83-3; **3a**, 87307-29-7; **3b**, 87334-97-2; **4a**, 87307-30-0; **4b**, 87334-98-3; **5a**, 87307-31-1; **5b**, 87334-99-4; **6a**, 87391-81-9; **6b**, 70284-77-4; **7a**, 87307-32-2; **7b**, 87335-00-0; **8a**, 70284-75-2; **8b**, 70354-61-9; **12a**, 71486-08-3; **12b**, 52936-69-3; **13a**, 87307-33-3; **13b**, 87335-01-1; **14a**, 70284-74-1; **14b**, 70284-78-5; **15**, 87419-54-3; methylenetriphenylphosphorane, 3487-44-3; 2-methyl-3-pentanone, 565-69-5; 3-pentanone, 96-22-0.

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Synthesis of the Civet Constituent *cis*-(6-Methyltetrahydropyran-2-yl)acetic Acid

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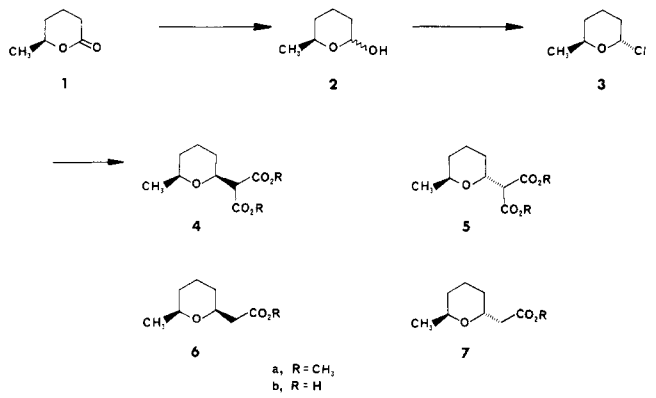
Received June 1, 1983

Synthesis of the civet constituent *cis*-(6-methyltetrahydropyran-2-yl)acetic acid (**6b**) is described. In the key step, *trans*-2-chloro-6-methyltetrahydropyran (**3**) reacted with dimethyl sodiomalonate with inversion to afford *cis*-dimethyl (6-methyltetrahydropyran-2-yl)malonate (**4a**). Hydrolysis and decarboxylation of **4a** provided **6b**.

(+)-(*S*,*S*)-*cis*-(6-Methyltetrahydropyran-2-yl)acetic acid (**6b**) was recently identified as a minor constituent of civet, the costly glandular secretion of the civet cat, which is utilized in perfumery.[1] The structure was confirmed by

0022-3263/83/1948-4479$01.50/0

Scheme I



synthesis,[1] and several alternative syntheses of racemic and optically pure **6b** were reported soon thereafter.[2,3]

We anticipated that *cis*-(6-methyltetrahydropyran-2-yl)acetic acid (**6b**) might be preparable in a straightforward manner by nucleophilic substitution of *trans*-2-chloro-6-methyltetrahydropyran (**3**) with a nucleophile such as malonate. This approach, exploiting the very reactive nature of α-halo ethers[4] has been utilized in the synthesis of *C*-nucleosides from glycosyl halides,[5,6] and on occasion in the preparation of a simple tetrahydropyrans.[7] The stereochemical course of the reaction between malonate anion and a glycosyl halide apparently depends upon whether direct S_N2 displacement with inversion or competitive S_N1 displacement on oxonium ion intermediates with loss of stereochemical control prevails.[5,8] Participating substituents present in the glycosyl halides complicate the stereochemical outcome even further. The proposed synthesis of **6b** offered the opportunity to investigate this nucleophilic substitution on a simple substrate.

Results and Discussion

The desired 2-chloro-6-methyltetrahydropryan was synthesized as depicted in Scheme I. 5-Oxohexanoic acid was prepared by hydrolysis of 1,3-cyclohexadione with aqueous sodium hydroxide. In our hands, this procedure was less tedious and afforded a better yield than a reported procedure that utilized barium hydroxide.[9,10] Reduction of 5-oxohexanoic acid with aqueous sodium borohydride provided lactone 1,[10,11] but his lactone underwent rapid polymerization to form a semicrystalline solid, behavior for which other simple six-membered ring lactones are notorious.[12] Since freshly prepared lactone 1 is a mobile liquid that remains fluid even at −20 °C, previous characterizations of lactone 1 as a solid melting at 17–19 °C[13,14] presumably refer to the polymer. As expected, lactone 1 could be regenerated in good yield from the polymer by hydrolysis.

Reduction of lactone 1 to lactol 2 with DIBAH proved unexpectedly difficult, despite close precedent.[15] Thus, treatment of freshly distilled lactone 1 with DIBAH at −78 °C, followed by warming to 0 °C, and an acidic workup afforded a complex mixture consisting of some product, starting material, and numerous unidentified byproducts. In contrast, low-temperature reduction of the freshly distilled lactone 1 with lithium aluminum hydride produced a good yield of the desired stable lactol **2**.[16-18] While overreduction of lactone 1 to 1,5-hexanediol did not occur, the polymer of lactone 1 was reduced in modest yield to a mixture of lactol **2** and 1,5-hexanediol.

When lactol **2** as a 2:1 mixture of cis and trans epimers[19] was briefly treated with hydrogen chloride gas at 0 °C, *trans*-2-chloro-6-methyltetrahydropyran (**3**) was the only detectable product. Obtention of the trans isomer is a consequence of the very facile interconversion between the epimeric chlorides under the reaction conditions and the thermodynamic stability of **3** in which the chloride occupies the axial position due to the anomeric effect.[8,20] *trans*-2-Chloro-6-methyltetrahydropyran, which could be isolated and distilled, was considerably more stable than would have been expected from previous reports on related compounds.[21] A sample stored in $CDCl_3$ for a week at 20 °C became slightly colored but exhibited an unchanged ^1H NMR spectrum.

Treatment of α-chloro ether **3** in 1,2-dimethoxyethane or toluene with dimethyl (or diethyl) sodiomalonate at 0 °C rapidly afforded *nearly exclusively* the cis malonate **4a**, contaminated with only 4% of the trans isomer **5a**. Thus the displacement reaction occurred with much greater stereoselectivity than similar displacements on many related pyranosyl chlorides. Procurement of the desired cis isomer could have been the result of either an S_N2 displacement or an S_N1 generation of a mixture of **4a** and **5a**, subsequently epimerized via base-catalyzed retro-Michael ring opening and reclosure to the more stable cis isomer **4a**. An S_N1 mechanism seemed improbable in view of the mild reaction conditions, particularly since no excess base was present at the end of the reaction and since related glycosyl malonates do not epimerize under the reaction conditions. Furthermore, the high degree of stereocontrol appeared to exceed that attributable to equilibration. Indeed, deliberate epimerization of **4a** with sodium methoxide afforded a 65:35 mixture of **4a** and **5a**. Consequently, formation of **4a** from **3** must occur via S_N2 displacement.

Hydrolysis of malonate ester **4a** to **4b** occurred with complete retention of the cis stereochemistry. Decarboxylation of **4b** afforded the desired *cis*-(6-methyltetrahydropyran-2-yl)acetic acid (**6b**), accompanied by 10% of

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the corresponding trans isomer **7b**. The spectral and chromatographic properties of **6a** and **6b** matched those of authentic samples.[1]

Experimental Section

General Procedures. Routine ^1H NMR spectra were recorded at 60 MHz on a Varian EM 360 spectrometer; higher resolution ^1H NMR spectra were recorded at 80 MHz on a Varian CFT-20 spectrometer. Unless otherwise noted, ^1H NMR spectra were obtained in $CDCl_3$ solution with an internal tetramethylsilane reference. IR spectra were recorded on a Unicam SP 1000 spectrophotometer. Low-resolution mass spectra were recorded on a Hewlett-Packard 5984A spectrometer, and high-resolution mass spectra were recorded on a Kratos MS-30 spectrometer. Gas chromatography was performed on a HP 5830A chromatograph with flame ionization detection on a 6 ft × $^1/_8$ in. 10% SE-30 column at 150 to 200 °C. Reactions were generally stirred magnetically under nitrogen. The organic phases were generally washed with saturated NaCl and then dried over anhydrous $MgSO_4$. Solutions were evaporated in vacuo on a rotary evaporator.

5-Oxohexanoic Acid.[9] 1,3-Cyclohexanedione (34.95 g, 0.300 mol) was stirred and refluxed with NaOH (24.44 g, 0.611 mol, 204 mol %) in water (200 mL) for 30 h. The solution was cooled and acidified to pH 1 with concentrated HCl. The precipitate was removed by filtration to afford a clear yellow filtrate, which was extracted four times with ethyl acetate. The precipitate was air dried and extracted with ethyl acetate. The combined ethyl acetate extracts were dried over Na_2SO_4, the solvent was evaporated, and the residue was Kugelrohr distilled (160–165 °C (2 mmHg)) to provide the product (34.2 g, 84% yield): ^1H NMR δ 1.5–2.6 (6 H, m), 2.08 (3 H, s), 11 (1 H, s); IR (neat) 2500–3600, 1700, 1400, 1235 cm^{-1}.

6-Methyltetrahydropyran-2-one (1) was prepared by reduction of 5-oxohexanoic acid with aqueous $NaBH_4$ at pH 7 at 10–20 °C.[10,11] After 2 h, the reaction was acidified to pH 1 with concentrated HCl, extracted six times with ethyl acetate, dried, and Kugelrohr distilled (115–135 °C (1 mmHg)) to afford the product (13.02 g, 78% yield): ^1H NMR δ 1.32 (3 H, d, CH_3), 1.5–2.1 (4 H, m, CH_2CH_2), 2.4 (2 H, m, $CH_2C{=}O$), 4.3 (1 H, m, CHO—O); mass spectrum, *m/e* (relative intensity) 114.0684 (calcd 114.0681, 4), 99 (3), 71 (6), 70 (33), 42 (100).

Lactone 1 formed a partially crystalline polymer after several days: ^1H NMR δ 1.18 (3 H, d), 1.6 (4 H, m), 2.22 (2 H, m), 4.85 (1 H, m). The polymer could be hydrolyzed as follows. The polymer (7.70 g, 67.5 mmol) was dissolved a solution of NaOH (3.90 g, 97.5 mmol, 144 mol %) in ethanol (30 mL) and water (6 mL). After 12 h, the solvent was evaporated, 6 M HCl was added until acidic, and the product was extracted into ethyl acetate as before and Kugelrohr distilled to afford 1 (5.92 g, 77% yield).

6-Methyltetrahydropyran-2-ol (2). Lactone 1 was reduced with $LiAlH_4$ at −25 °C:[16] ^1H NMR in accord with literature;[19] IR (neat) 3450, 2975 cm^{-1}; mass spectrum, *m/e* (relative intensity) 99 (100), 81 (66).

***trans*-2-Chloro-6-methyltetrahydropyran (3).** Lactol 2 (232 mg, 2.0 mmol) was dissolved in anhydrous ether (2.5 mL) at 0 °C, and HCl gas was bubbled in for 3 min. Most of the ether and excess HCl was evaporated (40 °C bath), and the residue was extracted twice with fresh ether (2.5 mL). The extract was dried over $CaCl_2$ for 10 min, and the ether was evaporated to afford crude 3, which was generally utilized immediately in the next step. Crude 3 could be purified by Kugelrohr distillation (70–110 °C (20 mmHg)) to afford 142 mg (53% yield) of a clear liquid: ^1H NMR δ 1.16 (3 H, d, CH_3), 1.3–2.1 (6 H, m), 4.0 (1 H, m, CH-O), 6.18 (1 H, br s, O-CH-Cl); mass spectrum, found 99.0803 (calcd 99.0810).

***cis*-Dimethyl (6-Methyltetrahydropyran-2-yl)malonate (4a).** Dimethyl malonate (264 mg, 2.00 mmol) was added dropwise to a stirring suspension of NaH (110 mg of 50% dispersion in mineral oil, previously rinsed twice with hexanes, 2.29 mmol, 115 mol %) in 1,2-dimethoxyethane (2 mL, distilled from $LiAlH_4$) at 0 °C. After 5 min, crude 3 prepared from 2 (2.0 mmol) dissolved in 1,2-dimethoxyethane (1 mL) was added at 0 °C to this nearly homogeneous solution of dimethyl sodiomalonate. After 10 min at 0 °C, water (0.5 mL) was added, the ether layer was decanted, and the aqueous layer was extracted with ether. The ether layer was dried, and the solvent was evaporated to provide crude **4a** (392 mg, 85% yield), contaminated with dimethyl malonate and other volatile impurities. Kugelrohr distillation (100–125 °C (1.5 mmHg)) provided a mixture of **4a** and the trans isomer **5a** in a 96:4 ratio (240 mg, 52% yield): ^1H NMR (80 MHz) δ 1.12 (3 H, d, CH_3), 1.1–2.0 (6 H, m), 3.42 (1 H, d, $CH(CO_2R)_2$), 3.71 (3 H, s, CH_3), 3.72 (3 H, s, CH_3), 3.2–4.0 (2 H, m, O-CH); mass spectrum, *m/e* (relative intensity) 230.1150 (M^+, calcd 230.1154, 1), 215 (1), 174 (44), 171 (76), 132 (100), 99 (58); GC (200 °C) **4a**, 2.77, **5a**, 3.33 min (96:4).

***trans*-Dimethyl (6-Methyltetrahydropyran-2-yl)malonate (5a).** Cis malonate **4a** (18 mg, 0.078 mmol) was dissolved in methanol (0.2 mL) in which Na (2 mg, 0.08 mmol, 100 mol %) had previously been dissolved. After 12 h, the solvent was evaporated, and ether followed by 1 M HCl (0.2 mL) was added. The ether layer was decanted, and the aqueous layer was extracted twice more with ether. The organic layer was dried, the solvent was evaporated, and the residue was Kugelrohr distilled to afford **4a** and **5a** in a 65 to 35 ratio (8 mg, 45% yield): ^1H NMR (80 MHz) δ 1.21 (3 H, d, CH_3); GC (200 °C) 2.77, 3.33 (65:35); mass spectrum, see **4a**.

***cis*-(6-Methyltetrahydropyran-2-yl)malonic acid (4b).** Ester **4a** (370 mg, 1.61 mmol) was dissolved in methanol (1.5 mL), and aqueous NaOH (3.75 M, 1.2 mL, 4.5 mmol, 280 mol %) was added. After 1 h at 20 °C, much of the methanol was evaporated at 40 °C in vacuo, the residue was extracted twice with ether, 6 M HCl was added to pH 2–3, and the product was extracted into three portions of ether. The ether extracts provided **4b** and the trans isomer **5b** in a 96 to 4 ratio (263 mg, 81% yield): ^1H NMR (80 MHz) δ 1.16 (3 H, d, CH_3), 1.1–2.0 (6 H, m), 3.49 (1 H, d, $CH(COO)_2$), 3.5–4.2 (2 H, m).

***cis*-(6-Methyltetrahydropyran-2-yl)acetic acid (6b).** Malonate **4b** (263 mg, 1.30 mmol) was heated to 150 °C under N_2 for 5 min. Kugelrohr distillation (120–140 °C, (2.5 mmHg)) afforded the product contaminated with 10% of the trans isomer **7b** (149 mg, 72%) as a colorless oil, which solidified (mp 45–47 °C). Recrystallization from pentane raised the melting point to 49–51 °C (lit.[1] mp 52–53 °C), ^1H NMR consistent with literature.[1] The ^1H NMR matched an authentic sample prepared by an independent route,[1] which in our hands afforded a 60:40 ratio of **6b** and **7b**. GC and ^1H NMR of the methyl esters **6a**, and **7a** prepared from **6b** and **7b** with diazomethane were also identical with authentic samples.

Acknowledgement is made to the Donors of the Petroleum Research Fund, administered by the American Chemical Society, for support of this research under Grant 12870-G1.

Registry No. 1, 823-22-3; *cis*-2, 69493-13-6; *trans*-2, 69493-14-7; 3, 87393-73-5; **4a**, 87393-74-6; **4b**, 87393-75-7; **5a**, 87393-76-8; **6a**, 69493-12-5; **6b**, 69493-11-4; **7a**, 69493-15-8; **7b**, 69493-16-9; 1,3-cyclohexanedione, 504-02-9; 5-oxohexanoic acid, 3128-06-1; dimethyl malonate, 108-59-8; dimethyl sodiomalonate, 18424-76-5.