53547-97-0; 7, 77635-33-7; 8, 82209-16-3; 8 acetate, 82209-18-5; 9, 82228-57-7; 10, 457-23-8; 11, 1004-36-0; 12, 82209-15-2; 13, 4780-14-7; 14, 82209-17-4; nitromethane, 75-52-5; 2-methoxy-5-methylbenzoquinone, 614-13-1.

Stereospecific Synthesis of Racemic (*cis*-6-Methyltetrahydropyran-2-yl)acetic Acid, a Constituent of the Glandular Secretion from the Civet Cat

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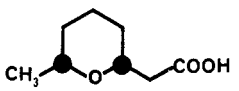
The glandular secretion of the civet cat (*Viverra civetta*) is known as civet and is one of the few animal-derived perfume materials. A recent examination of the constituents of civet[1] resulted in the isolation of a minor component (2 mg from 1 kg) whose constitution was determined by spectral[1] and synthetic means[2] to be **1**. We now report a new, simple, stereospecific synthesis of this natural product.



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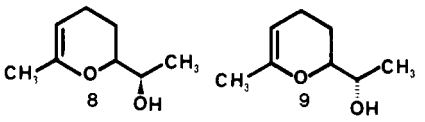
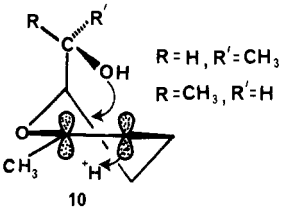
Our approach was based on the observations that (a) the 6,8-dioxabicyclo[3.2.1]octane system is reductively cleaved to form a pyran[3] and that (b) *cis*-2,6-disubstituted pyrans are thermodynamically more stable than the trans isomers.[2b] Also, as a consequence of our interest in insect pheromones having the 6,8-dioxabicyclo[3.2.1]octane skeleton,[4] we had experience with these systems as well as a supply of starting material. The overall synthetic route is outlined in Scheme I.

Dimerization of methyl vinyl ketone gave the well-characterized product **3**.[5] Sodium borohydride reduction of **3** resulted in a 50:50 mixture of the threo and erythro isomers **8** and **9**, respectively. Although the direction of



hydride delivery *does* determine the threo–erythro relationships of the alcohols and is in turn reflected in the exo–endo ratios of **4** (via **10**), these effects are not essential



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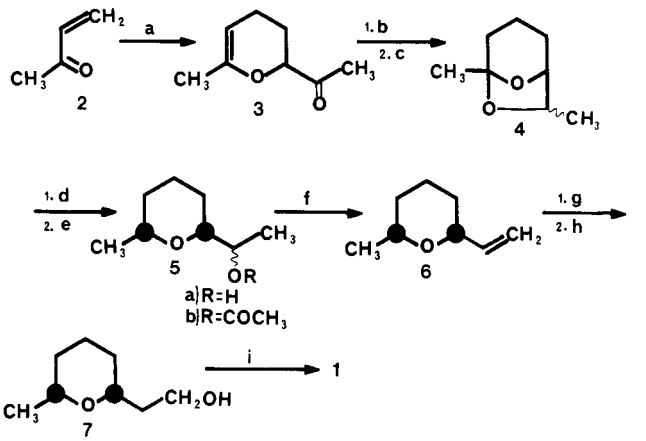
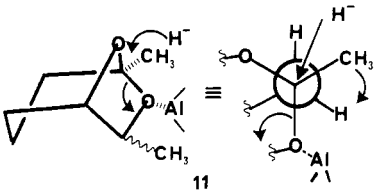
Scheme I. Synthesis of a Component of Civet[a]



[a] (a) 185 °C, 2 h; (b) $NaBH_4$/*i*-PrOH; (c) $TsOH/C_6H_6$; (d) AlH_3; (e) AcCl/Pyd; (f) 450 °C, N_2; (g) B_2H_6; (h) H_2O_2/OH^-; (i) CrO_3/H_2SO_4 or PDC.

to the success of our approach. Reduction of **4** with H_2–Pd/C gave a mixture of reduction products **5**; however, the differential reactivity of the two isomers of **4** toward reduction[3] resulted in difficulty in achieving high yields. This was easily circumvented by use of AlH_3. The formation of cis stereochemistry by this procedure is readily rationalized by considering an intermediate aluminum complex and S_N2 hydride displacement **11**.[6]



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With the required cis stereochemistry established, the only requirement in order to complete the synthesis was to effect hydroxyl group transposition from **5a** to **7**. This was achieved by pyrolysis of the acetate ester, followed by hydroboration of the resulting alkene, to give **7**. Other elimination reactions (the tosylate in Me_2SO, the hydrazone in sodium glycolate, and xanthate pyrolysis) were attempted; however, none were as effective. Oxidation of **7** with Jones reagent or PDC gave **1**.

The product, a crystalline material (mp 48–51 °C), exhibited spectral characteristics consistent with the assigned structure and in agreement with the literature data. No trace of the trans isomer, reported[1] to be a liquid, could be found.

Experimental Section

The preparations of **3** and **4** have been previously reported.

Preparation of 1-(*cis*-6-Methyltetrahydropyran-2-yl)-ethanol (5a). To a gray solution of $AlCl_3$ (107.8 g, 0.808 mol) in 250 mL of anhydrous Et_2O was added dropwise LAH (7.7 g, 0.202 mol) in 100 mL of anhydrous Et_2O in an ice bath under N_2. Swirling with ether was repeated several times until all the hydride was added and the gray slurry was stirred for 1 h.

A solution of ketal **4** (57.4 g, 0.404 mol) in 100 mL of anhydrous Et_2O was added at a rate sufficient for gentle refluxing. The mixture was refluxed for 3 h. Excess hydride was destroyed by the dropwise addition of ca. 10 mL of water, followed by 2 N

(1) Maurer, B.; Grieder, A.; Thommen, W. *Helv. Chim. Acta* **1979**, *62*, 44, 1096.
(2) (a) See ref 1. (b) Seebach, D.; Pohmakotr, M. *Helv. Chim. Acta* **1979**, *62*, 843.
(3) Lipkowitz, K. B.; Mundy, B. P.; Matsko, T. H. *J. Org. Chem.* **1976**, *41*, 371.
(4) Mundy, B. P.; Lipkowitz, K. B.; Dirks, G. W. *Heterocycles* **1977**, *6*, 51.
(5) Mundy, B. P.; Lipkowitz, K. B.; Dirks, G. W. *Synth. Commun.* **1975**, *5*, 7.
(6) (a) Colonge, J.; Buendia, J.; Guignard, H. *Bull. Soc. Chem. Fr.* **1969**, 956. (b) In their discussions on the relationships of erythro alcohol → ketal and threo alcohol → ketal, no direct comments could be made on the resulting stereochemistry after carbon–oxygen bond cleavage, since the compounds utilized in the study were not substituted at C-5.

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H_2SO_4 which was carefully added until vigorous reaction stopped. The Et_2O layer was separated, and the aqueous layer was extracted with Et_2O three times. The combined ether solution was washed with water and saturated NaCl solution and dried over anhydrous $MgSO_4$. Distillation at 85–90 °C (12 mmHg) gave 49.4 g (85% yield) of **5a**, a colorless liquid. The product was identical with an authentic sample prepared by another method.[3]

(*cis*-6-Methyltetrahydropyran-2-yl)ethyl Acetate (5b). Acetyl chloride (10.9 g, 0.139 mol) was added slowly to **5a** (20 g 0.139 mole) and dry pyridine (11.0 g, 0.139 mol) in an ice bath. The mixture was allowed to stand overnight, and then 100 mL of ice–water was poured into the flask. The organic layer was separated, and the aqueous layer was extracted three times with Et_2O. The combined Et_2O solution was washed with water and saturated NaCl solution and dried over anhydrous $MgSO_4$. Distillation at 103–106 °C (12 mmHg) gave 23.01 g (89%) of a colorless liquid, **5b**: IR (NaCl disk 2930 (s), 2850 (s), 1730 (s), 1440 (s), 1370 (s), 1240 (s), 1057 (s) cm^{-1}.

The ^1H NMR spectrum (*in parts per million relative to* Me_4Si) of each of the isomers is given below.

Isomer 1: 4.75–4.83 (m, 1 H), 3.39–3.47 (m, 1 H), 3.29–3.35 (m, 1 H), 2.05 (s, 3 H), 1.27–1.87 (m, 6 H), 1.22–1.25 (d, J = 6.60 Hz, 3 H), 1.15–1.18 (d, J = 6.60 Hz, 3 H).

Isomer 2: 4.86–4.96 (m, 1 H), 3.29–3.47 (m, 2 H), 2.07 (s, 3 H), 1.25–1.89 (m, 6 H), 1.21–1.23 (d, J = 6.60 Hz, 3 H), 1.16–1.18 (d, J = 5.9 Hz, 3 H).

For both isomers: mass spectrum, m/e 126 [M^+ – 60 (HOAc)]. Anal. Calcd for $C_{10}H_{18}O_3$: C, 64.49; H, 9.74. Found (isomer 1): C, 64.40; H, 9.93. Found (isomer 2): C, 64.53; H, 9.86.

***cis*-2-(Vinylmethyl)tetrahydropyran (6).** The pyrolysis of the ester was carried out in the vapor phase at 450 °C. The acetate **5b** (15.2 g) in a 25-mL syringe was added at the speed of 10 mL/h to the top of a vertically mounted quartz tube (0.7 cm i.d. × 30 cm) packed with broken quartz and heated with a nichrome wire. The products were swept from the reaction column by a slow stream of N_2 and collected in a cold trap. The temperature was monitored by inserting a thermocouple between the wall of the column and nichrome wire. After pyrolysis, the products were neutralized with $NaHCO_3$. The organic layer was separated, and the aqueous layer was extracted with Et_2O. The combined Et_2O solution was washed with water and saturated NaCl solution and dried over anhydrous $MgSO_4$. After distillation at 45–47 °C (12 mmHg), 8.20 g (80%) of colorless liquid was collected: ^1H NMR ($CDCl_3$ with Me_4Si) 5.81–5.94 (m, 1 H), 5.19–5.28 (dt, 1 H, J = 17.2 Hz), 5.06–5.11 (dt, 1 H, J = 10.6 Hz), 3.79–3.86 (m, 1 H), 3.46–3.54 (m, 1 H), 1.21–1.85 (m, 6 H), 1.19–1.21 ppm (d, 3 H, J = 5.9 Hz); IR (NaCl disk) 2850 (s), 2925 (s), 1650 (w), 1680 (w), 1450 (m), 1380 (m), 1317 (m), 1240 (w), 1215 (w), 1164 (w), 1153 (w), 1090 (s), 1080 (s), 1048 (s), 1026 (m), 993 (m), 923 (w), 982 (w), 810 (w), 754 cm^{-1} (w); mass spectrum, m/e 126 (M^+). Anal. Calcd for $C_8H_{14}O$: C, 76.14; H, 11.18. Found: C, 76.14; H, 11.32.

2-(*cis*-6-Methyltetrahydropyran-2-yl)ethanol (7). A solution of olefin **6** (2.50 g, 19.8 mmol) in 10 mL of dry THF was placed in a 50-mL three-necked flask equipped with a thermometer, a reflux condenser connected with a bubbler, and a dispersion tube connected with Tygon tubing to a 50-mL, three-necked flask serving as the diborane generator and equipped with a N_2 inlet and an Hg pressure equalizer. In the generator was placed 3 mL of boron trifluoride etherate in 3 mL of diglyme. Diborane was generated by the dropwise addition of 9 mL of 1 M solution of $NaBH_4$ in diglyme by using a syringe to the stirred BF_3 solution. The diborane was passed into the olefin solution (maintained at 20 °C) by applying a slight flow of dry N_2 through the generator. After addition of the $NaBH_4$ addition, the generator was heated 0.5 h at 70 °C and then disconnected from the hydroboration flask after cooling to room temperature. The excess hydride was decomposed by the addition of 1.5 mL of water. To the organoborane solution were added 3 mL of 3 N NaOH and 3 mL of 30% H_2O_2 dropwise at 30–50 °C. The reaction mixture was stirred for an additional hour, and then 30 mL of Et_2O was added. The organic phase was separated, and the aqueous phase was saturated with NaCl and then extracted twice with 15-mL portions of Et_2O. The combined extracts were washed twice with 15-mL portions of saturated NaCl solution and dried over anhydrous $MgSO_4$. After the evaporation of solvent, 2.3 g (80%) of a colorless liquid was collected at 112–115 °C (12 mmHg): ^1H NMR ($CDCl_3$ with Me_4Si) 3.77–3.79 (m, 2 H), 3.44–3.60 (m, 2 H), 3.17 (br, s, 1 H), 1.20–1.84 (m, 8 H), 1.15–1.17 ppm (d, 3 H, J = 5.9 Hz); IR (NaCl) 3400 (s), 2900 (s), 1450 (m), 1375 (m), 1325 (m), 1210 (m), 1155 (m), 1087 (s), 1050 (s), 1020 cm^{-1} (m); mass spectrum, m/e 144 (M^+). Anal. Calcd for $C_8H_{16}O_2$: C, 66.63; H, 11.18. Found: C, 66.38; H, 11.02.

(*cis*-6-Methyltetrahydropyran-2-yl)acetic Acid (1). (1) Pyridinium dichromate (4.73 g, 12.5 mmol) was added to **7** (0.513 g, 3.56 mmol) in 9.5 mL of dry DMF. The solution was stirred for 9 h at room temperature. Water (80 mL) was poured into the DMF solution, and the solution was extracted with Et_2O three times. The combined extracts were washed with water and saturated NaCl solution and dried over anhydrous $MgSO_4$. After the evaporation of solvent, the DMF and **1** were separated by column chromatography with anhydrous Et_2O as an eluent on silia gel. The acid was collected first and crystallized by evaporation of the solvent, giving acid **1**: 0.375 g (67%); mp 48–51 °C (uncor).

(2) To a solution of **7** (0.50 g, 3.47 mmol) in 10 mL of acetone was added the chromic acid oxidizing reagent (Jones reagent) at 20 °C until the characteristic orange color of the reagent persisted for 20 min. The mixture solution was stirred for 1 h, and the green salts were filtered and rinsed with acetone several times. Isopropyl alcohol was added to the acetone solution until the excess chromic acid was destroyed. The solution was neutralized with $NaHCO_3$ and the suspension was filtered. After evaporation of acetone, 10 mL of saturated NaCl solution was added, and the mixture was extracted with Et_2O three times. The combined extracts were washed with water and saturated NaCl solution and dried over anhydrous $MgSO_4$. After evaporation of ether solution **1** was collected: 0.424 g (77%); ^1H NMR ($CDCl_3$ with Me_4Si) 3.73–3.80 (m, 1 H), 3.51–3.59 (m, 1 H), 2.52–2.56 (q, 2 H), 1.24–1.87 (m, 6 H), 1.19–1.21 ppm (d, 3 H, J = 5.9 Hz); ^{13}C NMR ($CDCl_3$ with Me_4Si) 22.02 (6 C), 23.20 (3 C), 30.86 (2 C), 32.86 (4 C), 41.31 (7 C), 74.13 (5 C), 74.80 (1 C), 173.91 ppm (8 C); IR (NaCl disk) 2400–3780 (br, s), 1720 (s), 1740 (s), 1440 (m), 1380 (m), 1300 (m), 1210 (m), 1185 (m), 1076 cm^{-1} (s); mass spectrum, m/e 158 (M^+). Anal. Calcd for $C_8H_{14}O_3$: C, 60.74; H, 8.92. Found: C, 60.54; H, 9.05.

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Registry No. (±)-**1**, 82335-13-5; **4**, 1123-32-6; (±)-**5a** (isomer 1), 82335-14-6; (±)-**5a** (isomer 2), 82335-15-7; (±)-**5b** (isomer 1), 82280-94-2; (±)-**5b** (isomer 2), 82335-16-8; (±)-**6**, 82293-67-2; (±)-**7**, 82280-95-3.

New Hydronium Ion–Crown Ether Complexes[1]

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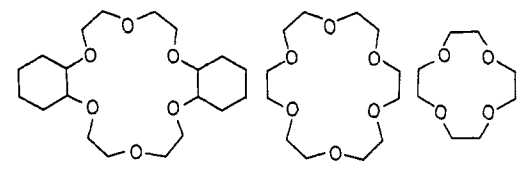
In 1972, Izatt et al.[2] reported the precipitation of 1:1 complexes of *cis-syn-cis*-dicyclohexano-18-crown-6, **1**, and



1 **2** **3**

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