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Bisection of an Achiral Molecule into Homochiral Halves: The First Chemical Analogue of "La Coupe du Roi"†

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Abstract: The first chemical example of "la coupe du roi", i.e., the bisection of an achiral molecule into homochiral halves, has been achieved by a reaction sequence that transforms *cis*-3,7-dimethyl-1,5-cyclooctanedione (C_{2v} symmetry) into 2-methyl-1,4-butanediol (C_1 symmetry).

The intriguing way to cut an apple known as "la coupe du roi"[2] is related to the problem of dividing an achiral object into isometric,[3] homochiral[4] halves. Referred to the chemical domain, the problem is that of bisecting an achiral molecule into isometric homochiral fragments.[2] Although a few examples of the "reverse coupe du roi", i.e. the combination of two homochiral units to give an achiral molecule, are known,[2,5-7] there are still no chemical analogues of la coupe du roi itself.[7] Here, we report an example of such a process, which develops through a sequence of reactions that chemically reproduce all the operations required to cut an apple in la coupe du roi mode (Scheme I).

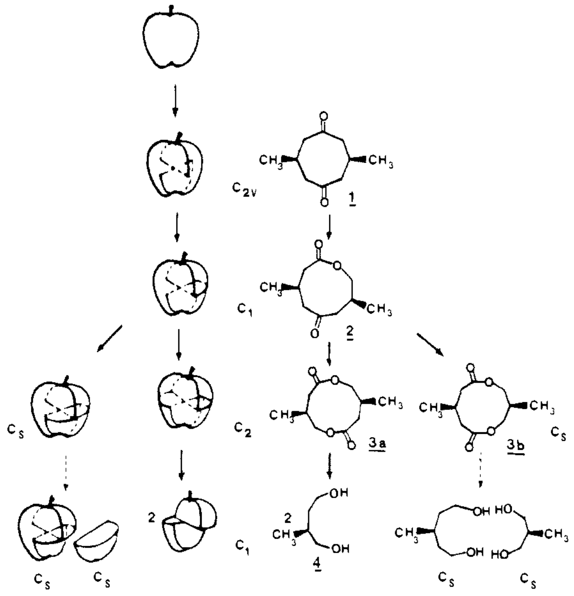
Although the model of an idealized apple possesses $C_{\infty v}$ symmetry, the chemical models reported so far have $C2_v$,[2,8] or S_4[5-7,9] symmetry. We decided to work on a cyclic C_{2v} molecule that corresponds to an apple with the two perpendicular vertical half-cuts. In order to parallel the pomaceous model, we wanted to preserve the cyclic structure throughout the sequence and to obtain an acyclic molecule only after the final bisection.

On this basis, we chose *cis*-3,7-dimethyl-1,5-cyclooctanedione (**1**) as a chemical equivalent of an apple with two perpendicular vertical half-cuts, two subsequent Baeyer–Villiger rearrangements as equivalents of the coplanar horizontal cuts, and a $LiAlH_4$ reduction as the final bisection.

Compound **1** (C_{2v} on the appropriate time scale) was prepared following the described procedure,[10] and its structure unambiguously determined by X-ray analysis[11] (Figure 1). Trifluoroperoxyacetic acid[12] promoted oxidation of **1**, carried out in the presence of an excess of anhydrous Na_2HPO_4,[13] gave, in 82% yield, racemic *cis*-4,8-dimethyloxacyclononane-2,6-dione (**2**) (deliquescent solid at room temperature), that has C_1 symmetry. A second Baeyer–Villiger reaction, performed on **2** with a large excess of the same peroxy acid, afforded pure *cis*-4,9-dimethyl-1,6-dioxacyclodecane-2,7-dione (**3a**) (mp 110 °C) in 12% yield and its constitutional isomer **3b** (3% yield), which could not be isolated free of **2**.[14] The structural assignment resided on inspection of high-field NMR spectra. For instance, **3a** (C_2 symmetry) features a doublet in the ^1H NMR methyl region (two doublets observed for C_s symmetry **3b**) and only five different signals in the ^{13}C spectrum (seven signals observed for **3b**). The final bisection was achieved by $LiAlH_4$ reduction of **3a** in refluxing diethyl ether to give C_1 symmetry 2-methyl-1,4-butanediol (**4**) in quantitative yield. This compound was identical with an authentic sample of **4**.

In order to obtain diol **4** in optically active form, lactone **2** was kinetically resolved by pig liver esterase promoted hydrolysis to afford (−)-**2**, $[\alpha]^{22}_D$ −8.7 (c 1, $CHCl_3$), which was shown to be ≥90% enantiomerically pure. Referred to the apple model, this operation corresponds to performing the first horizontal cut on a large number of apples in a random way and discarding almost all the homochiral apples of one sort. Oxidation of (−)-**2** gave dilactone (−)-**3a**: mp 106 °C; $[\alpha]^{22}_D$ −31.0 (c 0.8, $CHCl_3$). Finally, reduction of (−)-**3a** afforded (−)-(S)-**4**, $[\alpha]^{22}_D$ −13.0 (c 0.46, MeOH), which was 90% optically pure by comparison with the reported value [lit.[15] $[\alpha]^{20}_D$ −14.4 (c 0.6, MeOH)], showing that the conversion of **2** into **4** occurs without stereomutation at

Scheme I



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† Dedicated to Professor Kurt Mislow on the occasion of his 65th birthday.

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(2) Anet, F. A. L.; Miura, S. S.; Siegel, J.; Mislow, K. *J. Am. Chem. Soc.* **1983**, *105*, 1419.

(3) Mislow, K. *Bull. Soc. Chim. Belg.* **1977**, *86*, 595.

(4) The term "homochiral" is herein used in its original meaning (Lord Kelvin *Baltimore Lectures*; Clay: London, 1904; pp 618–619) and not in the new one proposed by Professor Masamune (Masamune, S.; Choy, W.; Petersen, J. S.; Sita, L. R. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 1).

(5) Schmidt, U.; Gombos, J.; Haslinger, E.; Zak, H. *Chem. Ber.* **1976**, *109*, 2628.

(6) Bartlett, P. A.; Meadows, J. D.; Ottow, E. *J. Am. Chem. Soc.* **1984**, *106*, 5304.

(7) Mislow, K. *Croat. Chem. Acta* **1985**, *58*, 353.

(8) Nouaille, A.; Horeau, A. *C. R. Acad. Sci., Ser. 2* **1985**, *300*, 335.

(9) Although an object with S_4 symmetry can be bisected into isometric homochiral halves, this group is not a subgroup of the symmetry group of an apple ($C_{\infty v}$).

(10) Gelin, S.; Gelin, R. *Bull. Soc. Chim. Fr.* **1969**, 4091. The reported configurations and melting points of **1**, mp 94 °C (lit. mp 75 °C), and of its trans isomer, mp 121 °C (lit. mp 92 °C), were incorrect.

(11) Crystal data for $C_{10}H_{16}O_2$: Mr 168.24; orthorhombic; space group $Pc2_1n$ (nonstandard setting of $Pna2_1$–No. 33); a = 5.377 (2), b = 8.326 (1), c = 20.969 (3) Å; V = 938.7 Å^3; D_{calcd} = 1.19 g cm^{-3}; Z = 4. A total of 1191 intensities were recorded ($2\theta_{max}$ 56°) on an Enraf-Nonius CAD4 automated diffractometer, of which 1094 having $I > \sigma(I)$ were corrected for Lorentz and polarization effects and used for structure solution and refinement. The structure was solved by direct methods and subsequent difference Fourier synthesis in the noncentric $Pc2_1n$ space group, which has been confirmed by successful refinement. Carbon and oxygen atoms were refined anisotropically while the hydrogen atoms were refined isotropically. The current conventional R and R_W values are 0.037 and 0.041, respectively.

(12) Fung, S.; Siddal, J. B. *J. Am. Chem. Soc.* **1980**, *102*, 6580.

0002-7863/88/1510-4363$01.50/0

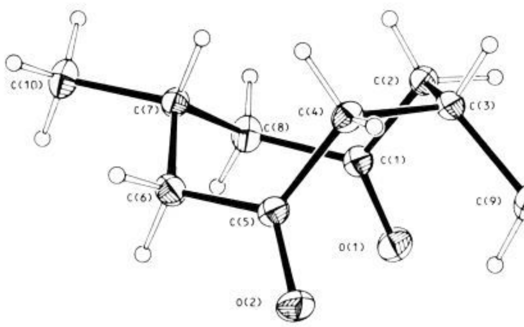

Figure 1. View of *cis*-3,7-dimethyl-1,5-cyclooctanedione. It has idealized C_s symmetry and a chair–boat conformation. Relevant bond distances (Å) are the following: C(1)–O(1), 1.214 (2); C(5)–O(2), 1.220 (2); C(1)–C(2), 1.501 (3); C(2)–C(3), 1.537 (3); C(3)–C(9), 1.523(3); C(3)–C(4), 1.540(2); C(4)–C(5), 1.510 (3); C(5)–C(6), 1.507(3); C(6)–C(7), 1.527(2); C(7)–C(10), 1.529 (3); C(7)–C(8), 1.522(2); C(1)–C(8), 1.497(3).

the stereocenters. Thus, the first bisection of an achiral object (**1**) into isometric homochiral halves (**4**) was performed. Remarkably, the symmetry of the products obtained along the reaction sequence perfectly matches, step by step, with that of an apple that is cut in la coupe du roi mode.

Experimental Section

***cis*-4,8-Dimethyloxacyclononane-2,6-dione (2).** To a stirred solution of *cis*-3,7-dimethyl-1,5-cyclooctanedione (**1**) (0.840 g, 5 mmol) in dichloromethane (20 mL) cooled at 0 °C and containing anhydrous Na_2HPO_4 (1.70 g, 12 mmol) was added trifluoroperoxyacetic acid (10 mL, 6 mmol, 0.6 M in dichloromethane) dropwise. The reaction mixture was stirred 2 h at 0 °C and 1 h at room temperature and filtered; excess anhydrous $Na_2S_2O_5$ and $NaHCO_3$ were added to the filtrate. After 15 min of stirring at room temperature, the mixture was filtered again, the filtrate concentrated under vacuum, and the residue purified by flash chromatography on silica gel with a 6:4 mixture of hexanes/diethyl ether as eluant to give **2** (0.754 g) in 82% yield. This product crystallized as long needles upon cooling in the refrigerator and melted when heated at room temperature. Anal. Calcd for $C_{10}H_{16}O_3$: C, 65.19; H, 8.75. Found: C, 65.12; H, 8.80. IR (thin film): 2955, 2880, 1745, 1700, 1460, 1355, 1290, 1265, 1220, 1100, 1040, 1020 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 4.23 (1 H, dd, J = 10.8, 6.2), 3.78 (1 H, t, J = 11.2), 1.98–2.75 (8 H, m), 1.07 (3 H, d, J = 6.4), 0.97 (3 H, d, J = 6.9). ^{13}C NMR ($CDCl_3$): δ 205.37, 164.56, 60.76, 43.27, 42.18, 34.91, 27.81, 23.99, 16.00, 10.23.

***cis*-4,9-Dimethyl-1,6-dioxacyclodecane-2,7-dione (3a) and *cis*-3,8-Dimethyl-1,5-dioxacyclodecane-6,10-dione (3b).** To a stirred solution of **2** (0.552 g, 3 mmol) in dichloromethane (30 mL) cooled at 0 °C and containing anhydrous Na_2HPO_4 (2.55 g, 18 mmol) was added trifluoroperoxyacetic acid (15 mL, 9 mmol, 0.6 M in dichloromethane) dropwise. The reaction mixture was stirred 2 h at 0 °C and 48 h at room temperature. The workup described above followed by purification by flash chromatography (7:3 and then 6:4 mixture of hexanes/diethyl ether as eluants) gave compound **3a** (0.072 g) in 12% yield; mp 110 °C. Despite several attempts, compound **3b** was obtained contaminated with unreacted **2**. The **3a** to **3b** ratio, as determined by ^{1}H NMR and by weight, was 4:1.

Analytical data for compound **3a** follow. Anal. Calcd for $C_{10}H_{16}O_4$: C, 59.98; H, 8.05. Found: C, 60.03, H, 8.00. IR ($CHCl_3$): 2955, 2880, 1745, 1460, 1355, 1290, 1260, 1220, 1100, 1040, 1015 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 4.13 (2 H, ddd, J = 11.2, 4.9, 1.5), 4.02 (2 H, t, 11.2), 2.45–2.75 (2 H, m), 2.38 (2 H, ddd, J = 13.9, 3.8, 1.5), 2.06 (2 H, dd, J = 13.6, 11.7), 0.93 (6 H, d, J = 7.2). ^{13}C NMR ($CDCl_3$): δ 172.60, 68.83, 41.22, 30.56, 16.77.

The NMR data of **3b** were obtained by substracting the resonances of **2** from the spectra of a 7:3 mixture of **3b** and **2**. ^{1}H NMR ($CDCl_3$): δ 4.28 (2 H, dd, J = 10.6, 7.1), 4.05 (2 H, dd, J = 11.6, 3.5), 2.33–2.73 (6 H, m), 1.05 (3 H, d, J = 7.7), 0.88 (3 H, d, J = 7.1). ^{13}C NMR ($CDCl_3$): δ 165.28, 61.44, 35.66, 23.59, 22.26, 15.87, 5.65.

Synthesis of 2-Methyl-1,4-butanediol (4) from 3a. To a stirred solution of **3a** (0.050 g, 0.25 mmol) in anhydrous diethyl ether (10 mL) was added $LiAlH_4$ (0.100 g, 2.63 mmol) in one portion; the mixture was refluxed overnight. The reaction mixture was then cooled to 0 °C, and wet diethyl ether (10 mL), water (0.1 mL), 10% aqueous NaOH (0.1 mL), and water (0.3 mL) were added in this order. The white precipitate was filtered, and the filtrate was concentrated under vacuum to give **4** (0.052 g) in 100% yield. This produce was identical (GC retention time, ^{1}H NMR and IR spectra) with an authentic sample of **4** prepared by $LiAlH_4$ reduction of diethyl 2-methylsuccinate carried out in analogous conditions.

Kinetic Resolution of 2 by Pig Liver Esterase Promoted Hydrolysis. To a stirred solution of **2** (0.100 g, 0.543 mmol) in a 0.3 M aqueous solution of KH_2PO_4 containing 5% (v/v) of acetone (120 mL) was added 0.5 N NaOH to adjust the pH to 7.00. Pig liver esterase (0.100 mL of a suspension in 3.2 M $(NH_4)_2SO_4$ solution) was then added and the reaction monitored by a pH meter, continuously adjusting to pH 7.00 by addition of 0.01 N NaOH solution. When 0.27 mmol of 0.01 N NaOH had been added, the mixture was frozen with a dry ice/acetone bath. Solid NaCl (20 g) was then added and the mixture was allowed to warm to room temperature and then extracted with three portions of diethyl ether. The combined organic phases were dried, concentrated under vacuum, and purified by flash chromatography (6:4 mixture of hexanes/diethyl ether as eluant) to give 0.043 g of **2**: mp 35–36 °C; $[\alpha]^{22}_{D}$ −8.7 (c 1, $CHCl_3$). This product was shown to be ≥90% enantiomerically pure by ^{1}H NMR analysis carried out on a CD_3CN solution in the presence of Eu(hfc)$_3$ in conditions preestablished on racemic **2**.

Synthesis of (−)-(*S*)-2-Methyl-1,4-butanediol. Baeyer–Villiger oxidation of (−)-**2** carried out following the procedure described for the synthesis of racemic **3a** gave compound (−)-**3a**: mp 106 °C; $[\alpha]^{22}_{D}$ −31.0 (c 0.8, $CHCl_3$); 14% yield. Reduction of (−)-**3a** with excess $LiAlH_4$ as above gave (−)-(*S*)-**4**, $[\alpha]^{22}_{D}$ −13.0 (c 0.46, MeOH), in 96% yield.

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Supplementary Material Available: Tables of thermal parameters and positional parameters with estimated standard deviations and general temperature factor expressions (3 pages). Ordering information is given on any current masthead page.

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(13) Still, W. C.; Galynker, I. *Tetrahedron* **1981**, *37*, 3981.

(14) The ^{1}H and ^{13}C NMR data of **3b** were obtained (see the Experimental Section). The estimated **3a** to **3b** ratio was 4:1; referred to the apple model, the low regioselectivity of the second Baeyer–Villiger reaction resembles the poor skill of an unexperienced cutter. It must be noted that $LiAlH_4$ reduction of **3b** (C_s symmetry) would afford two achiral fragments of different size (namely, 2-methyl-1,3-propanediol and 3-methyl-1,5-pentanediol), as would the bisection of an apple that suffered the second horizontal cut in the wrong direction.

(15) Leuenberger, H. G. W.; Boguth, W.; Barner, R.; Schmid, M.; Zell, R. *Helv. Chim. Acta* **1979**, *62*, 455.