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Serendipitous Synthesis of *cis*- and *trans*-4-Decene-1,10-dioic Acids

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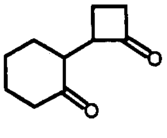
Development of useful chemistry of γ-ketocyclobutanones, such as **1**, whose preparation we have recently described,[1,2] would in general require selective reaction at one of the two carbonyl groups. A promising candidate for such selectivity appeared to be Baeyer–Villiger oxidation with basic hydrogen peroxide, which Trost has found to convert cyclobutanones almost quantitatively to butyrolactones under conditions which do "not normally affect acyclic or larger ring ketones".[3] If the anticipated conversion of **1** to lactone **2** were realized, it was envisioned that the latter might, for example, via conversion to **3** and **4**, provide a convenient pathway to compound **5**, an intermediate in Danishefsky's synthesis of *d,l*-widdrol.[4]



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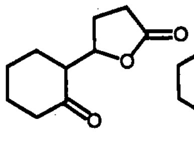

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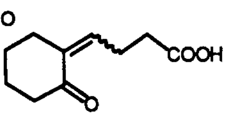

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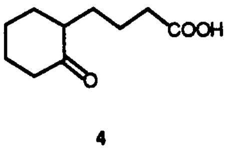

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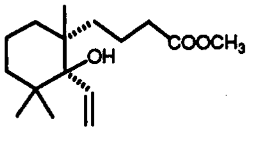

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Accordingly, the approximately 3:2 diastereomeric mixture of γ-ketocyclobutanones **1**[2] was treated with 1 equiv of hydrogen peroxide and a slight excess of sodium hydroxide for 2 h at 0 °C. A single major crystalline product was formed in 67% yield, but, to our surprise, it was neither lactone **2** nor β-elimination product **3**. After considerable consternation, it was concluded that the product was a mixture of *cis*- and *trans*-4-decene-1,10-dioic acids (**6** and **7**) on the basis of spectroscopic data. The IR spectrum clearly showed the presence of carboxylic acid functionality, and the ^{1}H NMR spectrum indicated the presence of two vinyl protons and was consistent only with the double bond being in the 4 position. The ^{13}C NMR spectrum established that the product was a mixture of isomers. Confirmation of the position of the double bond was achieved by oxidative cleavage with potassium permanganate[5] to afford a mixture of adipic acid and succinic acid, from which the latter was separated and identified by conversion to succinic anhydride.[6]

Since the mixture of **6** and **7** initially resisted separation by fractional crystallization or by chromatography, it was esterified with diazomethane, and the resulting mixture of **8** and **9** was separated by preparative TLC on AgNO$_3$-impregnated silica plates.[7] Since cis alkenes usually bind more strongly than their trans isomers, the ester with the higher R_f value was tentatively assigned structure **9**. Final confirmation of the stereochemical assignments to **8** and **9** was made from the signals for the vinyl protons in the ^{1}H NMR spectra of the two purified esters in which coupling to the allylic protons had been removed. As expected, the isomer with the higher R_f value showed an AB quartet with $J = 16$ Hz, consistent with its being the trans alkene, whereas the other isomer displayed an AB quartet with $J = 11$ Hz, consistent with a cis alkene.

6, R = H
8, R = CH$_3$

7, R = H
9, R = CH$_3$

Eventually, diacids **6** and **7** themselves were inefficiently separated by repeated column chromatography on AgNO$_3$-impregnated silica[8] and gave the spectroscopic data anticipated on the basis of those for the corresponding esters **8** and **9**. *trans*-Dioic acid **7** had mp 136–137.5 °C and *cis*-dioic acid **6** had mp 49.5–51 °C. The *cis*-diacid **6**, mp 52–53 °C,[9] has previously been isolated from the urine of individuals afflicted with Jamaican vomit disease[10] and was characterized as dimethyl ester **8**.[9] The unexpected reaction of γ-ketocyclobutanone **1** with basic hydrogen peroxide thus constitutes a simple synthesis of this natural product.

Although the formation of **6** and **7** could conceivably result from an unexpectedly facile hydroxide ion-induced fragmentation of Baeyer–Villager product **2**, as depicted in **10**, it seems more plausible that these diacids are formed via addition of hydrogen peroxide to **1** to form endoperoxide **11**, a type of process which occurs readily with many 1,4-diones.[11] Fragmentation of endoperoxide **12** to form isomeric diacids **13** has been observed upon treatment of **12** with FeSO$_4$,[12] and analogous fragmentation of **11** to **6** and **7** would presumably be accelerated by the ring strain present in **11**. As in the case of **12** → **13**, the formation

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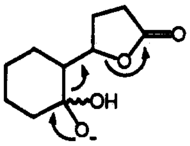
of both geometric isomers 6 and 7 presumably reflects the fact that 1 is a mixture of diastereomers and that the fragmentation reaction, whatever its detailed mechanism (possibly electrocyclic rearrangement of an alkoxide ion of 11), is sufficiently concerted to preclude rotation about the incipient double bond.



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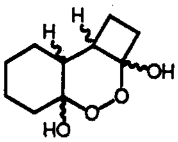

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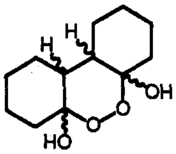

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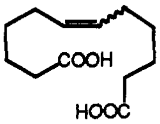

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Experimental Section

Infrared (IR) spectra are referenced to the 1601 cm^{-1} band of polystyrene. ^{1}H and ^{13}C NMR chemical shifts are reported in parts per million (δ) downfield from tetramethylsilane (TMS). Melting points are uncorrected. Analytical thin-layer chromatography (TLC) was performed on pre-coated Silica Gel 60 F_{254} plates from EM Reagents and visualization was accomplished with ceric sulfate–ammonium molybdate–sulfuric acid spray. Flash chromatography was performed in the manner of Still[13] with EM Reagents silica gel 60 (230–400 mesh). Silver-impregnated silica gel preparative TLC plates were prepared according to the procedure of Wolff et al.[14] Glass plates (8 in. × 8 in.) were coated to a thickness of 1 mm with a slurry of Merck silica gel G (84 g) and aqueous silver nitrate ($AgNO_3$) solution (170 mL, 20%), protected from light, and allowed to air-dry for 24 h prior to oven-drying (60 °C) for 24 h. Visualization was achieved by treating the plate edges with ceric sulfate–ammonium molybdate–sulfuric acid spray. The term "under N_2" refers to maintenance of a positive pressure of Airco nitrogen over the reaction mixture. Toluene was dried by distillation from calcium hydride. All other solvents were used as received.

***cis*- and *trans*-4-Decene-1,10-dioic Acids (6 and 7).** To a stirred solution of 0.19 g (1.2 mmol) of 2-(1-oxocyclobut-2-yl)cyclohexanone (1)[2] in 7.5 mL of methanol at 0 °C was added 0.12 mL (1.2 mmol) of 30% H_2O_2 and 0.12 mL (1.6 mmol) of 9.55 M NaOH. Stirring was continued for 2 h at 0 °C. The reaction mixture was poured into ca. 20 mL of water, acidified with 20 mL of 10% HCl, and extracted with ether (5 × 25 mL). The combined organic layers were dried over $MgSO_4$, filtered, and evaporated to give 0.154 g (67%) of a mixture of 6 and 7 as a white solid. Recrystallization from hexane/ether afforded 0.14 g (63%) of 6 plus 7: mp 99.5–116 °C; MS m/e 182 ($M^+ - H_2O$), 154 ($M^+ - H_2O$, CO). Repeated column chromatography on $AgNO_3$ impregnated silica[8] with 48:48:4 hexane/ether/acetic acid as eluant afforded small amounts each of separated 6 and 7.

Pure 6 was obtained by recrystallization from hexane/ether: mp 49.5–51 °C (lit.[9] mp 52–53 °C); IR (TCE) 3450–2400, 3035, 2955, 2880, 1710, 1435, 1415, 1290, 1255 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.35–1.48 (2H, m), 1.57–1.73 (2H, m), 2.04–2.14 (2H, m), 2.31–2.43 (6H, m), 5.29–5.48 (2H, m), 10.21–10.70 (br s); ^{13}C NMR ($CDCl_3$) δ 22.4, 24.2, 27.5, 28.9, 33.9, 34.1, 127.6, 131.0, 179.6, 180.2. HRMS (FAB) calcd for $C_{10}H_{17}O_4$ (MH^+) 201.1127, found 201.1132.

Pure 7 was obtained by recrystallization from hexane/ether: mp 136–137.5 °C; IR (TCE) 3470–2450, 2950, 2875, 1710, 1430, 1410, 1290, 1255 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.34–1.47 (2 H, m), 1.54–1.67 (2H, m), 1.97–2.07 (2H, m), 2.27–2.47 (6H, m), 5.36–5.53 (2H, m), 7.74–8.47 (br s); ^{13}C NMR ($CDCl_3$), 24.0, 26.7, 28.6, 32.0, 33.9, 34.0, 128.2, 131.3, 179.6, 180.2. HRMS (FAB) calcd for $C_{10}H_{17}O_4$ (MH^+) 201.1127, found 201.1132.

Succinic Anhydride and Adipic Acid from 6 and 7. The following procedure was adapted from that of Hill and McEwen.[5] To a solution of 0.372 g (2.35 mmol) of $KMnO_4$ in 4.5 mL of water at 36 °C was added a solution of 0.097 g (0.48 mmol) of the mixture of diacids 6 and 7 in 2.5 mL of 0.71 M potassium hydroxide. Upon addition, the temperature rose to 47 °C and the resulting mixture was maintained at 29–40 °C for 2.5 h. The mixture was then acidified with 1.5 mL of 2.8 M sulfuric acid and heated at 70 °C for 1 h in order to coagulate MnO_2. The reaction mixture was filtered while hot, and the collected MnO_2 was washed with ca. 40 mL of boiling water. The washes were filtered, and the combined aqueous layers were extracted with ether (6 × 25 mL). The organic extracts were dried over $NaSO_4$, filtered, and concentrated in vacuo to give 0.085 g (67%) of a mixture of succinic and adipic acids as a white solid: ^{1}H NMR (acetone-d_6) δ 1.42–1.95 (m, adipic acid), 2.12–2.53 (m, adipic acid), 2.60 (s, succinic acid), 7.66–8.40 (br s, both acids). These NMR data are consistent with the literature values reported for succinic and adipic acids.[15]

Conversion of the succinic acid to succinic anhydride was effected by a procedure adapted from that of McCabe et al.[6] To a mixture of 1.5 g of activated 3-Å molecular sieves and 15 mL of toluene was added 0.075 g of the mixture of acids prepared above. The reaction mixture was heated at reflux under N_2 and a Dean-Stark trap for 18 h. The solution was decanted from the molecular sieves and concentrated in vacuo to give a white solid which was taken up in ca. 5 mL of $CHCl_3$ at which point some of the material dissolved. The solution was filtered, and the filtrate was concentrated in vacuo to give 0.004 g of succinic anhydride, as white needles, which was spectroscopically (IR, ^{1}H NMR) identical to that reported in the literature;[15,16] mp 116–118 °C (lit.[17] mp 118–120 °C); IR ($CHCl_3$) 2960, 2920, 2860, 1870, 1790, 1045, 910 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.01 (s).

***cis*-4-Decene-1,10-dioic Acid Dimethyl Ester (8) and *trans*-4-Decene-1,10-dioic Acid Dimethyl Ester (9).** In a 50-mL Erlenmeyer flask, protected from light by foil wrapping, were placed 0.364 g (2.8 mmol) of N-methyl-N-nitro-N-nitrosoguanidine and 15 mL of ether. The mixture was cooled in an ice bath, and 1.7 mL (8.5 mmol) of 5 N NaOH was added dropwise at the rate of approximately 1 drop/5 s. The solution was stirred at 0 °C for 1.75 h. After this time the yellow organic layer containing diazomethane was drawn off by using a fire-polished pipet and was added to a cold solution of 0.143 g (0.715 mmol) of the mixture of 6 and 7 in 13 mL of ether. The resulting mixture was stirred at 0 °C for 2 h and then was quenched with 6 mL of 2% acetic acid. The separated organic layer was washed with water (2 × 20 mL), dried over Na_2SO_4, filtered, and evaporated to give 0.25 g of yellow oil. Flash chromatography (gradient, hexane to 60% ether in hexane) afforded 0.083 g (51%) of a mixture of 8 and 9 as a clear, colorless liquid. Preparative TLC on $AgNO_3$-impregnated silica plates[14] with 1:1 hexane:ether as eluant afforded 0.028 g (17%) of 8 and 0.015 g (9%) of 9. An additional 0.013 g of a mixture of the diesters was also collected.

For 8: $R_f = 0.50$ (1:1 hexane/ether); IR (film) 3010, 2950, 2860, 1740, 1445, 1360, 1260, 1200, 1170, 1095 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.32–1.45 (2H, m), 1.58–1.70 (2H, m), 2.05–2.12 (2H, m), 2.28–2.40 (6H, m), 3.63 (6H, s), 5.29–5.47 (2H, m), with irradiation at 2–3 ppm 5.42 (AB q, $J = 10.9$ Hz, $\Delta\nu = 17.2$ Hz, 2H) (lit.[9] ^{1}H NMR ($CDCl_3$) δ 1.3–1.9 (4H, m), 1.9–2.5 (8H, m), 3.69 (6H, s), 5.40 (m)); ^{13}C NMR ($CDCl_3$) δ 22.8, 24.5, 26.8, 29.0, 33.9, 34.1, 51.5, 51.5, 127.8, 130.8, 173.6, 174.1. Anal. Calcd for $C_{12}H_{20}O_4$: C, 63.13; H, 8.83. Found: C, 63.30; H, 8.88.

For 9: $R_f = 0.59$ (1:1 hexane/ether); IR (film) 3000, 2940, 2860, 1740, 1445, 1360, 1260, 1200, 1165, 1095, 975 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.31–1.44 (2H, m), 1.56–1.70 (2H, m), 1.96–2.05 (2H,

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m), 2.24–2.42 (6H, m), 3.67 (6H, s), 5.35–5.53 (2H, m), with irradiation at 2–3 ppm, 5.45 (AB q, J = 15.7 Hz, $\Delta\nu$ = 8.1 Hz, 2H); ^{13}C NMR (CDCl$_3$) δ 24.3, 27.8, 28.8, 32.0, 33.9, 34.0, 51.4, 51.4, 128.4, 131.1, 173.6, 174.1. Anal. Calcd for $C_{12}H_{20}O_4$: C, 63.13; H, 8.83. Found: C, 62.99; H, 8.88.

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