Enedione-Functionalized Macrocycles via Oxidative Ring Opening of Furans

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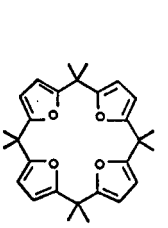
Received May 19, 1981

A series of novel polyketo macrocycles was synthesized by oxidative ring opening of the cyclic furan–acetone tetramer **1** and hexamer **2**. Reaction of **1** with bromine in acetic acid–water gave the bis(*trans*-enedione) **3**. The use of *m*-chloroperoxybenzoic acid allowed for the controlled oxidation of **1**, giving ring-opened products with the *cis*-enedione configuration. Reaction using 4.2 equiv of the peracid with **1** gave the tetra-ring-opened octaketone **5** in good yield. Analogously, the hexamer **2**, in the reaction with 6.3 equiv of peracid, gave the all-cis unsaturated dodecaketone **6**. By varying the stoichiometry of the peracid in its reaction with **1**, the tri-ring-opened and the two regioisomeric di-ring-opened *cis*-enediones **7–9**, respectively, were isolated. Acid-catalyzed isomerization of **8** and **9** gave the corresponding *trans*-enediones **3** and **10**, respectively, and the structures of these cis and trans isomers were correlated by reduction of the enedione double bonds either by using zinc in acetic acid or by catalytic hydrogenation. The X-ray structures and UV–vis spectra of **3** and **5** are discussed.

Macrocyclic chemistry has grown enormously since the pioneering studies of large-ring hydrocarbons, ketones, and lactones conducted by Ruzicka[1] during the first half of this century. Since then, macrocyclic compounds have attracted an interdisciplinary range of interests because of their diverse physical and chemical properties. Thus, a deluge of investigations have centered on the development of synthetic methodologies which enable construction of the stereochemically complex macrolide antibiotics,[2] the theoretical and physicochemical aspects of the annulenes,[3] the ion recognition and binding selectivity of the crown ethers and cryptands,[4] and the molecular complexation of small organic molecules by the cyclodextrins[5] and polycyclophanes.[6] The widespread interest in both natural and synthetic macrocyclic compounds prompted us to investigate the synthesis of some large-ring polyketones, a class of compounds in which there are only a limited number of examples.[7] We saw as an ideal source of such polyketones the known macrocycles **1**[8a,b] and **2**[8c], derived from the condensation of furan with acetone.[9] The ability



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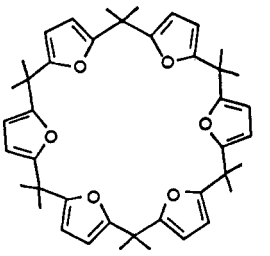
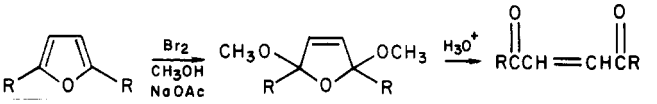


2

of furans to function as masked 1,4-dicarbonyl compounds is amply documented,[10] and in this paper we report methodology for the oxidative ring-opening of macrocycles **1** and **2** to give 20- and 30-membered carbocycles containing multiple enedione units.

Results and Discussion

The classical approach to oxidative ring opening of furans involves first the preparation of the α,α'-dimethoxydihydro derivative[10a] by treating the furan compound in buffered methanol with bromine and then hydrolysis[11] to the enedione. This route as applied to cyclic tetramer **1**



with 2–3 equiv of bromine followed by an aqueous methanolic HCl hydrolysis led to the isolation of a very small amount (<10%) of a bright yellow crystalline solid. The presence of a carbonyl stretching frequency in the IR spectrum at 1695 cm^{-1} and a molecular ion peak at m/e 464 indicated that this material must be a di-ring-opening derivative of **1**, and from the ^1H and ^{13}C magnetic resonance spectra (see Table I), it was concluded that the more symmetrical of the two possible isomers was produced. Since it is known that under acidic conditions *cis*-enediones isomerize to *trans*-enediones,[11a] the structure was formulated as the bis(*trans*-enedione) **3**. A more efficient route to this substance was attained by the slow addition of 2.5 equiv of bromine to a suspension of **1** in moist acetic acid, giving **3** in yields of 65–74% (eq 1). Single-crystal X-ray

(1) Ruzicka, L. *Chem. Ind. (London)* **1935**, *13*, 2.
(2) Masamune, S.; Bates, G. S.; Corcoran, J. W. *Angew. Chem., Int. Ed. Engl.* **1977**, *16*, 585. Back, T. G. *Tetrahedron* **1977**, *33*, 3041. Nicolauo, K. C. *Ibid.* **1977**, *33*, 683.
(3) Sondheimer, F. *Acc. Chem. Res.* **1972**, *5*, 81.
(4) Izatt, R. M.; Christensen, J. J., Eds. "Progress in Macrocyclic Chemistry"; Wiley-Interscience: New York, 1979; Vol. 1. Cram, D. J.; Cram, J. M. *Acc. Chem. Res.* **1978**, *11*, 8. Lehn, J. M. *Ibid.* **1978**, *11*, 49. Stoddart, J. F. *Chem. Soc. Rev.* **1979**, *8*, 85.
(5) Bender, M. L.; Komiyama, M. "Cyclodexrin Chemistry"; Springer-Verlag: New York, 1978. See also the section on cyclodextrins in the following authors' review on molecular inclusion phenomena: MacNicol, D. D.; McKendrick, J. J.; Wilson, D. R. *Chem. Soc. Rev.* **1978**, *7*, 65.
(6) Odashima, K; Itai, A.; Iitaka, Y.; Koga, K. *J. Am. Chem. Soc.* **1980**, *102*, 2504 and references cited therein. Jarvi, E. T.; Whitlock, H. W.; Jr. *Ibid.* **1980**, *102*, 657 and references cited therein. Tabushi, I.; Kimura, Y.; yamaura, K. *Ibid.* **1978**, *100*, 1304 and references cited therein.
(7) For some examples of macrocyclic 1,3-diketones see: Alberts, A. H.; Cram, D. J. *J. Am. Chem. Soc.* **1979**, *101*, 3545; Y.; Sugaya, T.; Nakatsuka, M.; Saegusa, T. *Ibid.* **1977**, *99*, 8366; Tabushi, I.; Kobuke, Y.; Nishiya, T. *Tetrahedron Lett.* **1979**, 3515. For the synthesis of a tetraketone derived from a furan cyclophane see: Wasserman, H. H.; Bailey, D. T. *J. Chem. Soc., Chem. Commun.* **1970**, 107. For the synthesis of some medium- and large-ring cycloalk-2-ene-1,4-diones, see: Kulkowit, S.; McKervey, M. A. *Ibid.* **1978**, 1069. For the synthesis of macrocyclic di-, tri-, and tetraketones, see: Sondheimer, F.; Gaoni, Y. *J. Am. Chem. Soc.* **1959**, *81*, 6301.
(8) (a) Ackman, R. G.; Brown, W. H.; Wright, G. F. *J. Org. Chem.* **1955**, *20*, 1147. (b) Chastrette, M.; Chastrette, F.; Sabadie, J. *Org. Synth.* **1977**, *57*, 74. (c) Kobuke, Y.; Hanji, K.; Horiguchi, K.; Asada, M.; Nakayama, Y.; Furukawa, J. *J. Am. Chem. Soc.* **1976**, *98*, 7414.
(9) For a comprehensive review on macrocyclic compounds containing heterocyclic subunits see: Newkome, G. R.; Sauer, J. D.; Roper, J. M.; Hager, D. C. *Chem. Rev.* **1977**, *77*, 513.
(10) (a) Elming, N. *Adv. Org. Chem.* **1960**, 67–115. (b) Kametani, T.; Fukumoto, K. *Heterocycles* **1978**, *10*, 469. (c) Meyers, A. I. "Heterocycles in Organic Synthesis"; Wiley-Interscience, New York, 1974; pp 222–228.
(11) (a) Hirsch, J. H.; Szur, A. J. *J. Heterocycl. Chem.* **1972**, *9*, 523. (b) MacLeod, J. K.; Bott, G.; Cabel, J. *Aust. J. Chem.* **1977**, *30*, 2516.

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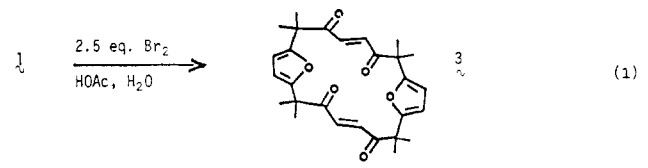
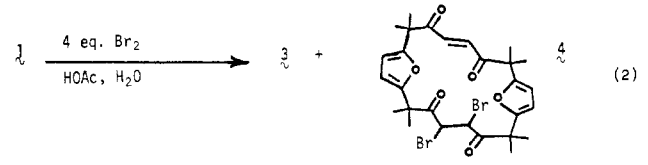


(1)

analysis[12] of **3** confirms its structural assignment (see Figure 1). Extension of this procedure by using 4 equiv of bromine with the hopes of producing a tetra-ring-opened product failed and instead gave diminished yields of **3** in addition to 40–50% of the bromine adduct **4** (eq 2).



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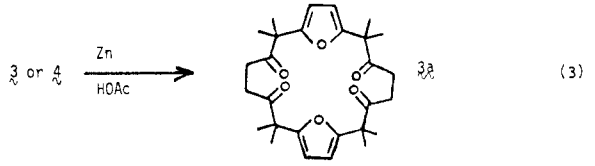
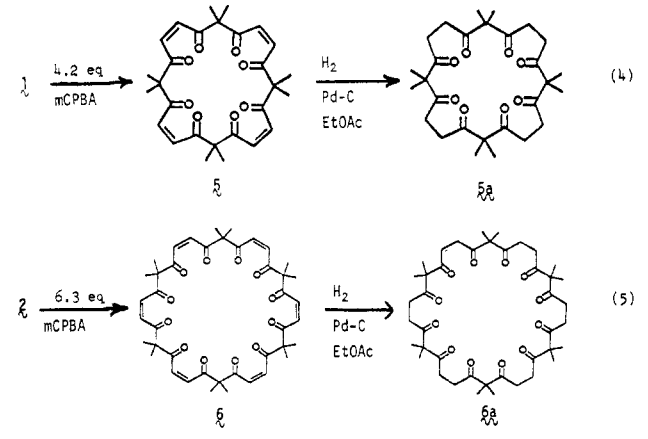


(3)

Evidently bromine addition to the enedione double bonds in **3** is competitve with further oxidation of the furan rings. Treatment of either **3** or **4** dissolved in hot acetic acid with zinc dust[13] produces in quantitative yield the reduced tetraketone **3a** (eq 3).

A simple and efficient method to effect oxidation of the furan rings in **1** uses *m*-chloroperoxybenzoic acid (MCPBA) and gives ring-opened derivatives in which the oxidation has proceeded stereospecifically producing *cis*-enediones. Furthermore, variation of the stoichiometry of the peracid, di-, tri-, and tetra-ring-opened products are available. Thus, treatment of **1** with 4.2 equiv of MCPBA with chloroform as solvent affords the tetra-ring-opened octaketone **5** in yields of up to 87% (eq 4). Likewise, the



(4)

(5)

cyclic hexamer **2** upon treatment with 6.3 equiv of MCPBA results in a 75–85% yield of dodecaketone **6**[14] (eq 5). The highly symmetrical nature of both **5** and **6** is evident from their uncomplicated ^1H and ^{13}C magnetic resonance spectra (see Table I). The cis configuration about the enedione double bonds in these compounds was suspected because of the 0.5-ppm upfield shift of the enedione vinylic protons[15] observed for **5** and **6** as compared to those in **3**. The single-crystal X-ray analysis[12] of **5** verifies the cis configuration (see Figure 2). Both **5** and **6** were reduced catalytically to give their corresponding saturated derivatives **5a** and **6a**, respectively (eq 4 and 5), which accomplishes a formal hydrolysis of the furan rings in **1** and **2**.

Table I. Selected Spectral Data for Macrocycles 3, 5, and 6

compd	^1H NMR ($CDCl_3$),[a] ppm	^{13}C NMR ($CDCl_3$), ppm	UV-vis (CH_3CN), λ_{max}, nm (log ϵ)
3	6.95 (s, 4 H), 6.10 (s, 4 H), 1.40 (s, 24 H)	194.39, 156.43, 132.47, 107.51, 48.53, 22.03	382 (3.25), 304 (3.67), 232 (4.52)
5	6.48 (s, 8 H), 1.40 (s, 24 H)	200.50, 133.91, 59.77, 21.79	shoulder at 290 (~2.9), 212 (4.4)
6	6.47 (s, 12 H), 1.40 (s, 36 H)	201.08, 135.17, 60.44, 20.93	shoulder at 295 (~3.0), 223 (4.42)

[a] The multiplicity and integration are given in parentheses.

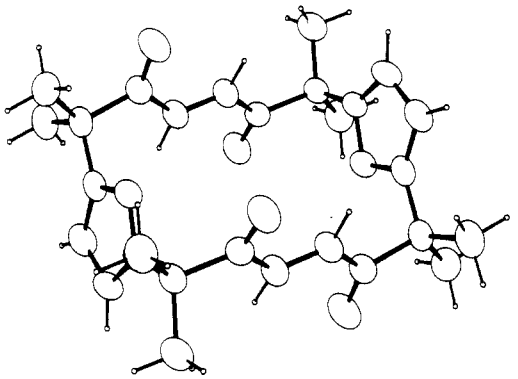


Figure 1. ORTEP representation of tetraketone **3**.[12]

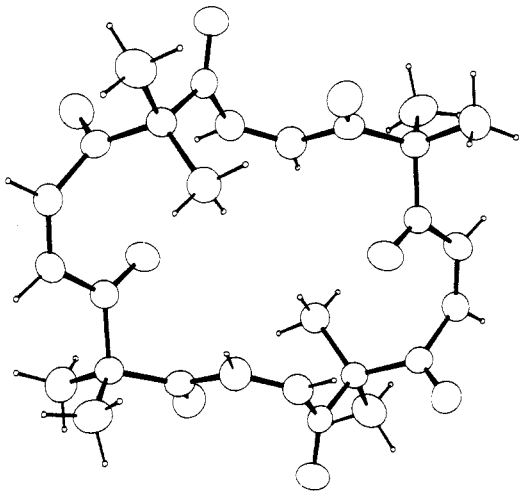
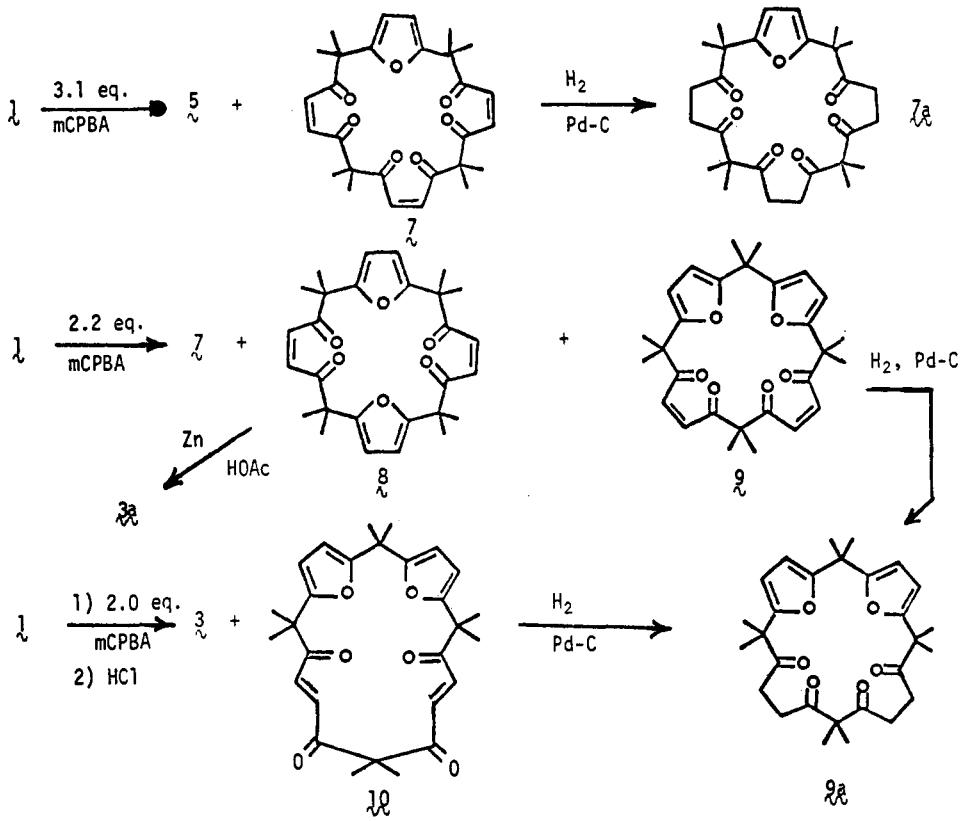


Figure 2. ORTEP representation of octaketone **5**.[12]

(12) Details of the crystal structure determination have been reported: Ward, D.; Kung, W.-J. H. *Am. Crystallogr. Assoc. Abstr.* **1980**, [2] *8* p 34.
(13) Windaus, A. *Chem. Ber.* **1903**, *36*, 3752.
(14) The structural assignment of **6** is in agreement with its spectral data (see Experimental Section). Microanalysis of **6** gave low carbon and hydrogen values, which could be explained if it is assumed that the compound contains $CHCl_3$ (from the recrystallization) to the extent of 33 mol %. Drying the sample at 78 °C under vacuum for 48 h did not alter the microanalysis significantly. The presence of $CHCl_3$ in crystalline **6** was verified by observation of the characteristic isotopic pattern for the CCl_2^+ fragment at *m/e* 83 in the mass spectrum and by the presence of the $CHCl_3$ singlet at 7.97 ppm in the ^1H NMR spectrum run in acetone-d_6 solution.
(15) The vinylic protons of the cis and trans isomers of 3-hexene-2,5-dione fall at 6.18 and 6.72 ppm, respectively: see ref. 11a.

Scheme I



An interesting conformational feature depicted in the stereostructure of **5** (see Figure 2), which must arise at least in part because of the *cis*-enedione configuration, is the significant deviation from planarity of one of the carbonyl groups with the remaining *p* orbital system in each of the enedione moieties. By contrast, the stereostructure of **3** (see Figure 1) shows an entirely coplanar arrangement of all the atoms which comprise each of the *trans*-enedione units. This difference in geometry results in markedly different UV–vis spectra in that the more extended chromophore present in the bis(*trans*-enedione) **3** absorbs at longer wavelengths than the twisted *cis*-enedione chromophore of **5** (see Table I).

The peracid-mediated oxidative ring opening of furans has received little attention,[16] and more recently some work has been reported with Cr(VI) reagents to oxidize simple 2,5-dialkylfurans to the corresponding *trans*-enediones.[17] That the oxidation of simple 2,5-dialkylfurans with MCPBA proceeds stereospecifically to give the corresponding *cis*-enedione was demonstrated by using 2,5-dimethylfuran. Thus, treatment with 1.1 equiv of MCPBA in methylene chloride at −10 °C resulted in a nearly quantitative isolated yield of spectroscopically homogeneous *cis*-3-hexene-2,5-dione (≥95% cis isomer by NMR[15]). These conditions are evidently mild enough to prevent acid-catalyzed isomerization[11a] to the trans isomer.

By varying the stoichiometry of MCPBA in the reaction with **1**, several other *cis*-enedione-functionalized macrocycles were isolated (see Scheme I). Thus, treatment of **1** with 3.1 equiv of MCPBA gave a mixture of the tri-ring-opened hexaketone **7** and a small amount of **5**, which were readily separated by medium-pressure chromatography,[18] giving pure **7** in 60% yield. Catalytic reduction of the enedione double bonds in **7** gave the saturated derivative **7a** in good yield. With 2.2 equiv of MCPBA, a three-component mixture resulted which, after separation by medium-pressure chromatography, gave the di-ring-opened regioisomers **8** and **9** in 32% and 36% yields, respectively, as well as 17% of tri-ring-opened **7**. In accordance with the *cis*-enedione configurational assignment, the vinylic enedione protons in **8** resonate at 0.95 ppm upfield[15] of those in **3**; moreover, reaction of **8** in acetic acid with zinc gives **3a**, the same reduction product as obtained from **3**. In another experiment using 2.0 equiv of MCPBA, a small amount of concentrated aqueous HCl was added to the crude reaction mixture, causing isomerization of the initially formed *cis*-enedione mixture. The two products which survived the acidic conditions are the regioisomeric di-ring-opened *trans*-enediones **3** and **10** (see Scheme I), isolated in 41% and 19% yield, respectively. That **10** differs from **9** only in the configuration about the enedione double bonds was demonstrated by catalytic reduction of each compound to give the same tetraketone **9a**. Attempts at acid-catalyzed isomerization of the *cis*-enediones **5** and **7** gave complex mixtures of products.

The oxidations of **1** and **2** employing MCPBA have thus proven to be quite efficient, mild, and selective, providing access to macrocyclic polyketones. Further manipulation of the functionality in these macrocycles is currently in progress.

Experimental Section

General Methods. All melting points were determined by using a Thomas-Hoover capillary melting point apparatus and are uncorrected. The NMR spectra were obtained in $CDCl_3$ solution by using $Si(CH_3)_4$ as an internal standard (chemical shifts

(16) Clauson-Kaas, N.; Fakstropp, J. *Acta Chem. Scand.* **1947**, *1*, 415. Lutz, R. E.; Welstead, W. J.; Bass, R. G.; Dale, J. I. *J. Org. Chem.* **1962**, *27*, 1111. Lefebvre, Y. *Tetrahedron Lett.* **1972**, 133.

(17) Birch, A. J.; Keogh, K. S.; Mamdapur, V. R. *Aust. J. Chem.* **1973**, *26*, 2671. Piancatelli, G.; Scettri, A.; D'Auria, M. *Tetrahedron* **1980**, *36*, 661.

(18) Still, W. C.; Kahn, M. Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.

being reported in parts per million downfield from the internal standard), and spectra were run on Varian T-60 (^1H) and Varian CFT-20 (^{13}C decoupled) spectrometers. Infrared (IR) spectra were obtained from samples mulled in Nujol and recorded on a Perkin-Elmer 237 grating spectrophotometer by using the polystyrene 1601-cm^{-1} peak for calibration purposes. All ultraviolet and visible spectra (UV–vis) were recorded on a Cary 219 spectrophotometer in acetonitrile solution (MCB-Omni Solv spectral grade solvent) by using matched quartz cells. Mass spectra were obtained on a Finnigan 4000 instrument, the ionization techniques being either electron impact (EI) at 70 eV or chemical ionization (CI) using ionized methane. Microanalyses were performed by Guelph Chemical Laboratories, Ltd., and by Spang Microanalytical Laboratory. The *m*-chloroperoxybenzoic acid (MCPBA) was technical grade (80–90%; the amounts used were calculated by assuming 85% peroxy acid) and was obtained from Aldrich Chemical Co. The standard work-up for reactions using MCPBA involved extraction of the crude reaction mixture with three portions of saturated aqueous $NaHCO_3$, once with saturated aqueous NaCl, and drying of the organic layer anhydrous Na_2SO_4.

Bis(*trans*-enedione) 3. A magnetically stirred, 1000-mL, single-necked, round-bottomed flask is charged with 5.00 g (11.6 mmol) of finely powdered tetramer 1,[8a,b] 650 mL of glacial acetic acid, and 20 mL of distilled water. Added dropwise to this vigorously stirred suspension is a solution of 4.64 g (29.0 mmol, 2.5 equiv) of Br_2 in 100 mL of glacial acetic acid over a period of about 3 h, during which time the suspension takes on a bright yellow color. Stirring is continued for an additional hour, and the crude product is suction filtered and washed with methanol. Crystals of crude **3** trap acetic acid, which is removed by recrystallization from $CHCl_3$. Cooling at −10 °C overnight affords 3.97 g of **3** (74%) as small cubes: mp 276–278 °C dec; ^1H NMR 1.40 (s, 24 H), 6.10 (s, 4 H), 6.95 ppm (s, 4 H); ^{13}C NMR 22.03, 48.53, 107.51, 132.47, 156.43, 194.39 ppm; IR 1698, 1540 cm^{-1}; UV–vis 382 nm (log ϵ 3.25), 304 (3.67), 232 (4.52); mass spectrum (EI), molecular ion at *m/e* 464.

Anal. Calcd for $C_{28}H_{32}O_6$: C, 72.39; H, 6.94. Found: C, 72.88; H, 6.90.

Bromine Adduct 4. The procedure is followed as for **3** above, except that 7.42 g (4.0 equiv) of Br_2 is used. The addition takes 2.5 h, and the reaction mixture is allowed to stand overnight. The crude product is suction filtered, and the ^1H NMR shows a mixture of **3**, **4**, and acetic acid. The bright yellow solid is suspended in 50 mL of ethyl acetate with gentle warming on a steam bath to dissolve the bromine adduct (**3** is quite insoluble in this solvent). The remaining solids are removed by filtration, and the filtrate is taken to dryness in vacuo. The resulting oily yellow solid is treated with ethanol and cooled at −10 °C overnight, yielding 2.90 g (40%) of the bright yellow bromine adduct **4**. Recrystallization from $CHCl_3$–EtOH (1:4) gives long, fine needles: mp 247–248 °C dec; ^1H NMR 1.43 (s, 12 H), 1.48 (s, 6 H), 1.53 (s, 6 H), 4.87 (s, 2 H), 6.13 (s, 4 H), 7.08 ppm (s, 2 H); ^{13}C NMR shows 14 signals; IR 1710, 1675, 1530 cm^{-1}; UV–vis 388 nm (log ϵ 3.03), 311 (3.47), 224 (4.32); mass spectrum (CI), an M + 1 ion showing the isotopic 1:2:1 triplet characteristic for two bromines at *m/e* 623, 625, 627.

Anal. Calcd for $C_{28}H_{32}Br_2O_6$: C, 53.86; H, 5.17. Found: C, 52.89; H, 5.11.

Reduced Tetraketone 3a. Reduction of enediones **3**, **4**, or **8** using Zn–HOAc gave in nearly quantitative yield tetraketone **3a**. A typical procedure is as follows. In a 250-mL Erlenmeyer flask is placed 75 mL of glacial acetic acid, in which 1.00 g (2.16 mmol) of bis(*trans*-enedione) **3** is dissolved with heating on a hot plate. The flask is removed from the heat, and while the mixture is still hot, 2.0 (14 equiv) of zinc dust is added in portions with efficient swirling so as to prevent bumping. The yellow solution turns colorless within seconds, and the contents of the flask are allowed to cool. The excess zinc and precipitated zinc salts are suction filtered and washed with $CHCl_3$. The colorless filtrate is poured into 2 volumes of water, the organic phase removed, and the upper aqueous phase extracted with more $CHCl_3$ (2 × 30 mL). The combined organic layers are washed with water, saturated aqueous $NaHCO_3$, and brine and dried over anhydrous Na_2SO_4. The solvent is removed in vacuo, leaving a white crystalline solid. Cold EtOH is added, and suction filtration gives 1.00 g of tetraketone **3a** (99%). Recrystallization from $CHCl_3$–EtOH (1:3) gives **3a** as small white cubes: mp 269–270 °C; ^1H NMR 1.40 (s, 24 H), 2.40 (s, 8 H), 6.03 ppm (s, 4 H); ^{13}C NMR 22.94, 30.88, 48.70, 106.38, 157.44, 209.26 ppm; IR 1706, 1600, 1550 cm^{-1}; mass spectrum (EI), molecular ion at *m/e* 468.

Anal. Calcd for $C_{28}H_{36}O_6$: C, 71.77; H, 7.74. Found: C, 72.20; H. 7.79.

Unsaturated Octaketone 5. In a magnetically stirred 250-mL Erlenmeyer flask are placed 1.00 g (2.31 mmol) of tetramer **1** and 75 mL of $CHCl_3$. The solution is brought to a boil and allowed to cool down slightly with stirring to 50–55 °C. Then added in one portion is 1.97 g (4.2 equiv) of MCPBA. The solution immediately takes on a greenish yellow color which lightens somewhat with stirring at 20 °C overnight. The usual workup is followed by concentration of the solution in vacuo to 15 mL. Addition of 40 mL of absolute EtOH and cooling for several hours at 0 °C followed by suction filtration affords 0.99 g of **5** (87%) as small white cubes: mp 208–210 °C dec; ^1H NMR 1.40 (s, 24 H), 6.48 ppm (s, 8 H); ^{13}C NMR 21.79, 59.77, 133.91, 200.50 ppm; IR 1711, 1698, 1684, 1615, 1600 cm^{-1}; UV–vis shoulder at 290 nm (log ϵ 2.9), 212 (4.4); mass spectrum (CI), *m/e* 497 (M + 1 ion).

Anal. Calcd for $C_{28}H_{32}O_8$: C, 67.73; H, 6.50. Found: C, 68.18; H, 6.47.

Unsaturated Dodecaketone 6. To a magnetically stirred 100-mL round-bottomed flask containing 0.50 g (0.77 mmol) of hexamer **2**[8c] dissolved in 35 mL of $CHCL_3$ at 20 °C is added 0.99 g (6.3 equiv) of MCPBA in one portion. After being stirred at 20 °C overnight, the mixture is worked up in the usual way, and the solvent is removed in vacuo. The pale greenish yellow solid is broken up in EtOH and allowed to stand at -10 °C for several hours. Suction filtration give 0.49 g of crude **6** (85%), which after recrystallization from $CHCl_3$–EtOH (1:4) gives 0.43 g of fluffy pale greenish yellow needles: mp 173–174 °C; ^1H NMR 1.40 (s, 36 H), 6.47 ppm (s, 12 H); ^{13}C NMR 20.93, 60.44, 135.17, 201.08 ppm; IR 1685, 1630 cm^{-1}; UV–vis shoulder at 295 nm (log ϵ 3.0), 223 (4.42); mass spectrum (CI), *m/e* 745 (M + 1 ion).

Anal.[14] Calcd for $(C_{42}H_{48}O_{12})_2 \cdot CHCl_3$: C, 63.45; H, 6.08. Found: C, 63.16; H, 6.13.

Saturated Octaketone 5a. A suspension of 0.50 g (1.0 mmol) of unsaturated octaketone **5**, 60 mg of 10% Pd on carbon, and 60 mL of EtOAc is shaken under 50 psi of H_2 for 3 h at 20 °C in a Parr apparatus. The catalyst is filtered off and washed with $CHCl_3$. The colorless filtrate is taken to dryness in vacuo, and the resulting oily solid is treated with 20 mL of EtOH and cooled at −10 °C overnight. Suction filtration affords 0.40 g of **5a** (78%). Recrystallization from $CHCl_3$–EtOH (1:4) gives long white needles: mp 187–188 °C; ^1H NMR 1.35 (s, 24 H), 2.70 ppm (s, 16 H); ^{13}C NMR 20.79, 32.72, 62.71, 207.78 ppm; IR 1702 cm^{-1}; mass spectrum (CI), *m/e* 505 (M + 1 ion).

Anal. Calcd for $C_{28}H_{40}O_8$: C, 66.65; H, 7.99. Found C, 66.21; H, 8.05.

Saturated Dodecaketone 6a. The procedure is as for **5a** above with 0.20 (0.27 mmol) of **6**, 10 mg of 10% Pd on carbon, and 25 mL of EtOAc. Crude **6a** is isolated from EtOH and recrystallized from $CHCl_3$–EtOH (1:4), giving 0.13 g of **6a** (65%) as long white needles: mp 186–187 °C; ^1H NMR 1.37 (s, 36 H), 2.65 ppm (s, 24 H); ^{13}C NMR 21.45, 32.20, 61.74, 208.12 ppm; IR 1698 cm^{-1}; mass spectrum (EI or CI), no molecular ion peak, base peak at *m/e* 126.

Anal. Calcd for $C_{42}H_{60}O_{12}$: C, 66.65; H, 7.99. Found: C, 66.40; H, 8.11.

Tri-Ring-Opened Unsaturated Hexaketone 7. To a magnetically stirred 100-mL round-bottoned flask containing 1.00 g (2.31 mmol) of tetramer **1** dissolved in 45 mL of $CHCl_3$ at 20 °C is added 1.45 g (3.1 equiv) of MCPBA in one portion. After being stirred for 4.5 h at 20 °C, the reaction mixture is worked up as usual. Removal of the solvent in vacuo leaves an oily greenish yellow solid, which is broken up in 10 mL of EtOH and cooled at −10 °C for several hours. Suction filtration gives 0.77 g of a pale greenish yellow solid whose ^1H NMR shows a mixture consisting of mostly tri-ring-opened **7** and a minor amount of tetra-ring-opened **5**. Analysis of this mixture by TLC (SiO_2; $CHCl_3$–EtOAc, 4:1) shows two spots, R_f 0.45 (**7**) and 0.35 (**5**). Flash chromatography[18] (45-mm-diameter column, 140 g of 230–400-mesh silica gel, elution with 4:1 $CHCl_3$–EtOAc, flow rate of 80 mL/min) affords 0.67 g of pure **7** (60%). Recrystallization from $CHCl_3$–EtOH (1:5) gives **7** as small pale greenish yellow prisms: mp 186–187 °C; ^1H NMR 1.38 (s, 12 H), 1.43 (s, 12 H), 6.12 (s,

2 H), AB quartet centered at 6.22 (J = 11.5 Hz, 4 H), 6.53 ppm (s, 2 H); ^{13}C NMR shows 14 signals; IR 1685, 1600, 1550 cm^{-1}; UV-vis 346 nm (log ϵ 2.85), shoulder at 280 (3.4), 221 (4.35); mass spectrum (EI), molecular ion at m/e 480.

Anal. Calcd for $C_{28}H_{32}O_7$: C, 69.98; H, 6.71. Found: C, 69.93; H, 6.85.

Reduced Hexaketone 7a. The procedure is as for **5a** above with 165 mg (0.344 mmol) of tri-ring-opened **7**, 10 mg of 10% Pd on carbon, and 20 mL of EtOAc. After evaporation of the solvent in vacuo, the colorless oil is crystallized by cooling in hexane–benzene (3:1) at −10 °C for 24 h, giving 117 mg of **7a** (70%) as very small white prisms: mp 143–144 °C; ^1H NMR 1.33 (s, 12 H), 1.38 (s, 12 H), 2.48 (s, 8 H), 2.55 (s, 4 H), 5.97 ppm (s, 2 H); IR 1700, 1540 cm^{-1}; mass spectrum, (EI), molecular ion at m/e 486.

Anal. Calcd for $C_{28}H_{38}O_7$: C, 69.11; H, 7.87. Found: C, 68.78; H, 8.02.

Di-Ring-Opened *cis*-Enediones 8 and 9. To a magnetically stirred 100-mL round-bottomed flask containing 0.70 g (1.6 mmol) of tetramer **1** dissolved in 45 mL of $CHCl_3$ at 0 °C is added 0.73 g (2.2 equiv) of MCPBA. The reaction mixture is stirred at 0 °C for 1 h and at 20 °C for an additional 2 h. After a workup in the usual manner, the solvent is removed in vacuo and the solids are broken up in 10 mL of ice-cold EtOH. Suction filtration affords 0.64 g of a mixture which, by TLC analysis (SiO_2; $CHCl_3$–EtOAc, 8:1), shows three major components, R_f 0.62, 0.52, and 0.37. Flash chromatography enables separation of this mixture (45-mm-diameter column, 150 g of 230–400-mesh silica gel, elution with 9:1 $CHCl_3$–EtOAc, flow rate of 75 mL/min), giving 0.24 g of **8** (32%; elutes first), 0.26 g of **9** (36%; elutes second), and 0.15 g of tri-ring-opened **7** (19%; elutes last). The di-ring-opened *cis*-enediones **8** and **9** can each be recrystallized from $CHCl_3$–EtOH (1:6), giving 0.19 g of **8** as tiny pale yellow prisms (mp 211–212 °C) and 0.20 g of **9** as pale greenish yellow plates, mp 165–166 °C.

Spectra for **8** include: ^1H NMR 1.45 (s, 24 H), 5.97 (s, 4 H), 6.00 ppm (s, 4 H); ^{13}C NMR 23.08, 48.19, 106.95, 134.13, 156.88, 202.26 ppm; IR 1700, 1611, 1600, 1550 cm^{-1}; UV-vis shoulder at 333 nm (log ϵ 3.0), 227 (3.53), 221 (4.41); mass spectrum (EI), molecular ion at m/e 464.

Anal. Calcd for $C_{28}H_{32}O_6$: C, 72.39; H, 6.94. Found: C, 72.29; H, 6.98.

Spectra for **9** include: ^1H NMR 1.18 (s, 6 H), 1.52 (s, 12 H), 1.58 (s, 6 H), AB q centered at 5.87 (J = 3.1 Hz, 4 H), AB q centered at 5.95 ppm (J = 12 Hz, 4 H); IR 1698, 1681, 1603, 1540 cm^{-1}; UV-vis shoulder at 332 nm (log ϵ 2.8), shoulder at 290 (3.1), 221 (4.32); mass spectrum (EI), molecular ion peak at m/e 464.

Anal. Calcd for $C_{28}H_{32}O_6$: C, 72.39; H, 6.94. Found: C, 72.50; H, 7.04.

Di-Ring-Opened *trans*-Enediones 3 and 10. To a magnetically stirred 250-mL round-bottomed flask containing 2.00 g (4.63 mmol) of tetramer **1** dissolved in 150 mL of $CHCl_3$ at 20 °C is added 1.88 g (2.0 equiv) of MCPBA. After the mixture was stirred at 20 °C for 45 min, 25 drops of concentrated HCl are added, causing a deepening of the initially pale yellow solution, and the acidified mixture is stirred for an additional 2 h. After the usual workup, the volume is reduced to 20 mL in vacuo. An equal volume of EtOH is added, causing precipitation of **3**. The suspension is cooled to 0 °C for several hours and suction filtered, giving 0.88 g of **3** (41%), identified by its ^1H NMR spectrum. The orange-yellow filtrate is then taken to dryness in vacuo, leaving an oil which, after being allowed to stand in 25 mL EtOH at −10 °C overnight, gives a second crop of crystals. Suction filtration affords 0.41 g of **10** (19%) as yellow-orange prisms: mp 159–160 °C; ^1H NMR 1.33 (s, 6 H), 1.40 (s, 12 H), 1.52 (s, 6 H), AB q centered at 6.00 (J = 3.2 Hz, 4 H), AB q centered at 6.72 ppm (J = 16 Hz, 4 H); ^{13}C NMR shows 14 signals; IR 1700, 1680, 1615, 1600, 1548 cm^{-1}; UV-vis 382 nm (log ϵ 3.03), 306 (3.38), 233 (4.47); mass spectrum (EI), molecular ion at m/e 464.

Anal. Calcd for $C_{28}H_{32}O_6$: C, 72.39; H, 6.94. Found: C, 72.22; H, 6.91.

Reduced Tetraketone 9a. The procedure is as for **5a** above and with either **9** or **10** gives **9a**. Reduction of 150 mg (0.323 mmol) of the *trans*-enedione **10** in 25 mL of EtOAc with 10 mg of 10% Pd on carbon produces 111 mg of **9a** (74%) from EtOH as white needles: mp 162–163 °C; ^1H NMR 1.27 (s, 6 H), 1.40 (s, 12 H), 1.52 (s, 6 H), 2.45 (m, 8 H), 5.88 ppm (s, 4 H); IR 1695, 1550 cm^{-1} mass spectrum (EI), molecular ion at m/e 468.

Anal. Calcd for $C_{28}H_{36}O_6$: C, 71.77; H, 7.74. Found: C, 71.32; H, 7.79.

***cis*-3-Hexene-2,5-dione.**[11a] To a magnetically stirred 100-mL round-bottomed flask containing 1.00 g (10.4 mmol) of freshly distilled 2,5-dimethylfuran in 55 mL of CH_2Cl_2 at −10 °C is added 2.33 g (1.1 equiv) MCPBA in one portion. Stirring is continued overnight, allowing the cooling bath to warm to 20 °C. The milky white suspension is worked up as usual, and removal of the solvent in vacuo leaves 1.16 g (99%) of *cis*-3-hexene-2,5-dione as a very pale yellow liquid: ^1H NMR 2.18 (s, 6 H), 6.18 ppm (s, 2H); ^{13}C NMR 29.27, 135.32, 200.11 ppm; IR (neat) 1698, 1616 cm^{-1}. This substance isomerizes to the crystalline *trans*-enedione[11a] upon being allowed to stand under N_2 at 0 °C over a period of several weeks.

Acknowledgment. A SOHIO Fellowship awarded to P.D.W. is gratefully acknowledged.

Registry No. 1, 22900-44-3; 2, 61093-57-0; 3, 78804-49-6; **3a**, 78804-50-9; 4, 78804-51-0; 5, 78804-52-1; **5a**, 78804-53-2; 6, 78804-54-3; **6a**, 78804-55-4; 7, 78804-56-5; **7a**, 78804-57-6; 8, 78804-58-7; 9, 78804-59-8; **9a**, 78804-60-1; 10, 78804-61-2; 2,5-dimethylfuran, 625-86-5; *cis*-3-hexene-2,5-dione, 17559-81-8; *trans*-3-hexene-2,5-dione, 820-69-9.

Novel Synthesis of α-Substituted Acrylic Acids[1]

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Received April 29, 1981

A facile three-step procedure has been developed for the synthesis of α-substituted acrylic acids. In the first step, a carboxylic acid having no α-substituents is condensed with 2-amino-2-methylpropanol (AMP) to form the corresponding oxazoline. The oxazoline reacts readily with paraformaldehyde to give an intermediate mixture of mono- and dimethylol derivatives which upon heating forms the α-methylene derivatives of the oxazoline. The latter, upon acid hydrolysis, yields the α-substituted acrylic acid generally in an overall yield of above 70% and the acids are usually at least 95% pure.

Introduction

α-Substituted acrylic acids are useful intermediates for the preparation of biologically active materials, lubricant additives, or polymers. Relatively few methods for the synthesis of these acids have been developed, and none of those published have practicality because of awkwardness of some reaction steps, poor yields, use of expensive, toxic or otherwise hazardous reactants or solvents, or extremes

(1) Presented in part at the Annual Meeting of the American Oil Chemists' Society, New York, NY, May 1980.

(2) Agricultural Research, Science and Education Administration.