Acknowledgment. Dr. A. Solladié-Cavallo is gratefully acknowledged for helpful discussions.

Registry No. 1, 74725-03-4; 2, 74725-04-5; 3, 5628-12-6; 4, 10029-01-3; 5, 74725-05-6; methyl 2,5-dimethylbenzoate, 13730-55-7; 2,5-dimethylanisole, 1706-11-2; 2,5-bis(bromomethyl)anisole, 46045-95-8; methyl 2,5-bis(bromomethyl)benzoate, 74725-06-7; *p*-phenylenediacetic acid trimethylammonium salt (1:2), 74725-07-8.

Two Stereoisomeric Macrocyclic Resorcinol–Acetaldehyde Condensation Products[1,2]

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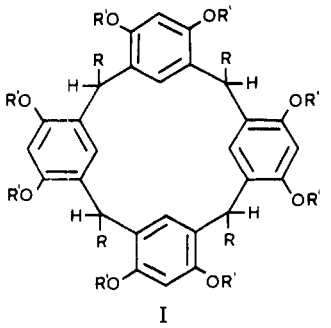
The formation of crystalline, high-melting products by the acid-catalyzed condensation of resorcinol with acetaldehyde[3-7] or higher aliphatic aldehydes[5,6] or by the reaction of resorcinol with acetylene in the presence of mercuric salts[4,8] is well-known. At first, these products were thought to be of low molecular weight and were assigned various acetal,[3c] diphenylalkane,[5,8] or vinylresorcinol[4] structures. Niederl and Vogel obtained a *single* product from the reaction of resorcinol with acetaldehyde in aqueous sulfuric acid and assigned it the macrocyclic structure I (R = CH_3; R′ = H).[6] The mass spectrum of an octamethyl ether, prepared by Erdtman et al., was in agreement with this structure (I, R = R′ = CH_3).[7]



I

We have found that under similar conditions resorcinol reacts with several aromatic aldehydes such as benzaldehyde and *p*-bromobenzaldehyde to give *two* stereoisomeric macrocycles of the same general structure (I, R = aryl, R′ = H).[9] We have therefore reinvestigated the resorcinol–acetaldehyde reaction.

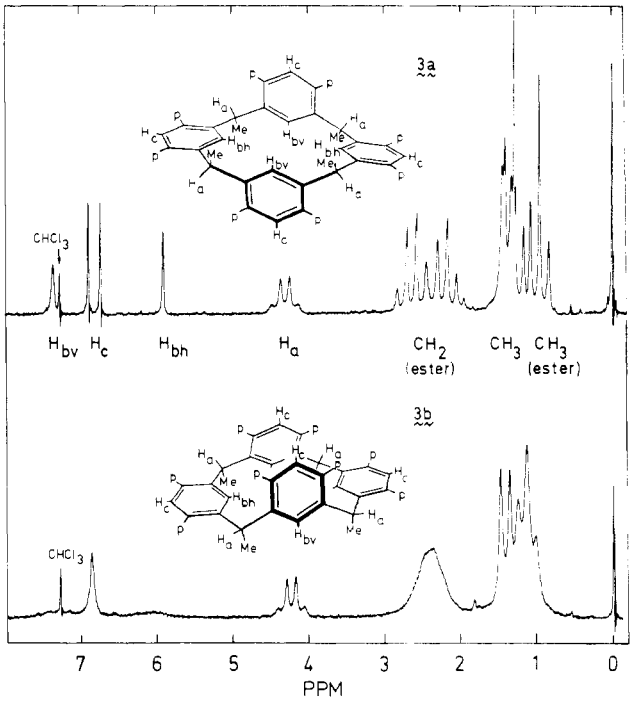
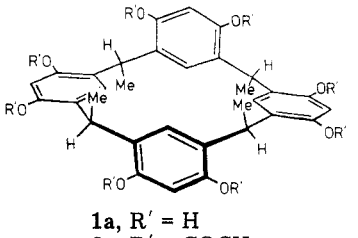


Figure 1. 60-MHz NMR spectra of the octapropionates **3a** and **3b** in $CDCl_3$ solutions at 28 °C (Me_4Si as internal standard). The $OCOCH_2CH_3$ groups are indicated by p.

The reaction of resorcinol (2.0 M) with acetaldehyde (2.0 M) in aqueous hydrochloric acid at 75 °C for 1 h gave a phenolic precipitate which was acetylated. Fractional crystallization of the acetylation product gave the two isomeric octaacetates **2a** (13%) and **2b** (47%). Similarly, propionylation gave the two octapropionates **3a** and **3b**. However, when the reaction was carried out in a mixture of ethanol and concentrated hydrochloric acid (4:1 v/v), no precipitate was obtained. On the addition of water to the solution a small amount of a phenolic product precipitated, which on acylation gave only the acetate **2b** (12%). When a mixture of ethanol, water and concentrated hydrochloric acid (2:2:1 v/v) was used, only phenol **1b** precipitated, yielding 57% of the octaacetate **2b** upon acylation. In this case no phenol **1a** was detected in the solution. Finally, direct acylation, without prior purification,[10] of the crude phenolic product, prepared according to the description of Niederl and Vogel[6] (reaction in dilute sulfuric acid for several days) gave both the octapropionate **3a** (18%) and the octapropionate **3b** (45%).



1a, R′ = H
2a, R′ = $COCH_3$
3a, R′ = COC_2H_5

(1) (a) Cyclooligomeric phenol–aldehyde condensation products. Part 3. For part II see ref 9b. (b) Taken from: Högberg, A. G. S. Ph.D. Dissertation, Royal Institute of Technology, Stockholm, Sweden, 1977.

(2) Systematic names: **1a**: *r*-2,*c*-8,*t*-14,*t*-20-tetramethylpentacyclo[19.3.1.1^{3,7}.1^{9,13}.1^{15,19}]octacosa-1(25),3,5,7(28),9,11,13(27), 15, 17, 19(26), 21,23-dodecaen-4,6,10,12,16,18,22,24-octol. **1b**: *r*-2,*c*-8,*c*-14,*c*-20-tetramethylpentacyclo[19.3.1.1^{3,7}.1^{9,13}.1^{15,19}]octacosa-1(25),3,5,7(28),9,11,13-(27),15,17,19(26),21,23-dodecaen-4,6,10,12,16,18,22,24-octol.

(3) (a) Michael, A.; Comey, A. M. *Am. Chem. J.* **1883**, *5*, 349. (b) Möhlau, R.; Koch, P. *Ber. Dtsch. Chem. Ges.* **1894**, *27*, 2887. (c) Causse, H. *Ann. Chim. (Paris)* **1894**, [7] *1*, 90.

(4) Flood, S. A.; Nieuwland, J. A. *J. Am. Chem. Soc.* **1928**, *50*, 2566.

(5) Harden, W. C.; Reid, E. E. *J. Am. Chem. Soc.* **1932**, *54*, 4325.

(6) Niederl, J. B.; Vogel, H. J. *J. Am. Chem. Soc.* **1940**, *62*, 2512. For similar results see ref 16.

(7) Erdtman, H.; Haglid, F.; Ryhage, R. *Acta Chem. Scand.* **1964**, *18*, 1249.

(8) Wenzke, H. H.; Nieuwland, J. A. *J. Am. Chem. Soc.* **1924**, *46*, 177.

(9) (a) Erdtman, H.; Högberg, S.; Abrahamsson, S.; Nilsson, B. *Tetrahedron Lett.* **1968**, 1679. (b) Högberg, A. G. S. *J. Am. Chem. Soc.* **1980**, *102*, 6046.

(10) Niederl and Vogel recrystallized the crude phenolic product from ethanol before acylation.[6] Thus, unless the material present in the mother liquors was recovered, most or all of the phenol **1a** might easily have been lost due to the much higher relative solubility of this isomer.

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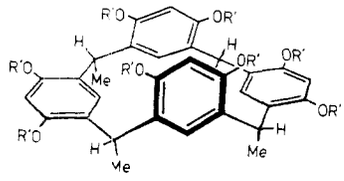
Each pair of octaesters displayed almost identical infrared and mass spectra (including the molecular peaks m/z 880 and 992, respectively), but their melting points, R_f values (TLC), and ^1H NMR spectra were different. As expected,[11] the mass spectra showed the consecutive eliminations of ketene fragments. The pure phenols **1a** and **1b** were obtained by the alkaline hydrolyses of the corresponding octapropionates.

The ^1H NMR spectra of the propionates **3a** and **3b**, in $CDCl_3$ at 28 °C, are shown in Figure 1. Isomer **3a** exhibited a well-resolved spectrum which did not change on heating the solution (in hexachlorobutadiene) to 180 °C. The signals of the aromatic protons H_b and H_c and the aliphatic protons of the ester chains were each split into a pair, indicating that the resorcinol units of the molecule occur pairwise in two different environments. On the other hand, the signals of the four ethylidene groups appeared as a single AX_3 set, indicating that the H_a (and methyl) protons are in identical positions. In the spectra of isomer **3b** as well, the signals of the H_a protons appeared as a single AX_3 set at all temperatures except at very low ones. However, the signals of the H_b and H_c protons showed a marked temperature dependence. At low temperatures the spectrum of isomer **3b** was very similar to that of isomer **3a** while at 28 °C (see Figure 1) the collapse of the H_b signals and the coalescence of the H_c signals indicated that the protons of the resorcinol moieties are exchanging between two types of environments. In the spectra of both isomers the well-resolved AX_3 set of signals of the ethylidene groups collapsed into broad humps at low temperatures (−32 °C), indicating the presence of a rotational barrier for the methyl groups.



1b, R′ = H
2b, R′ = $COCH_3$
3b, R′ = COC_2H_5

The symmetry properties and the temperature dependences of the NMR spectra of the two isomers are very similar to those of the corresponding resorcinol–benzaldehyde macrocycles.[9b] Thus by analogy, the cyclophane **1a** is assigned a cis,trans,trans configuration and a chairlike conformation with the four methyl groups in axial positions and the cyclophane **1b** an all-cis configuration and a boatlike conformation with the four methyl groups also in axial positions.

The activation energies ($\Delta G^{\ddagger}$) for pseudorotation of the flexible octaesters **2b** and **3b** were found to be $\Delta G^{\ddagger}_{306K}$ = 60.3 kJ mol^{-1} (14.4 kcal mol^{-1}) and $\Delta G^{\ddagger}_{323K}$ = 63.7 kJ mol^{-1} (15.2 kcal mol^{-1}), respectively, as determined by the coalescence point approximation.[12] Comparison of the $\Delta G^{\ddagger}$ value of the octapropionate **3b** with that of the analogous cyclophane **4** (I, R = C_6H_5; R′ = $COCH_2CH_3$), $\Delta G^{\ddagger}_{341K}$ = 73.9 kJ mol^{-1} (17.7 kcal mol^{-1}), from the resorcinol–benzaldehyde condensation indicates an increase in the energy of activation for pseudorotation of ca. 10 kJ mol^{-1} when the four methyl groups are replaced by phenyl groups.

Apparently isomer **1a** does not precipitate from the more solubilizing ethanolic reaction mixtures. Since the condensation reactions are reversible,[9b] precipitation of the less soluble isomer **1b** serves as a thermodynamic sink, driving the reaction toward the formation of one macrocyclic end product.

(11) Thomas, C. B. *J. Chem. Soc. B* **1970**, 430.
(12) Sandström, J. *Endeavour* **1974**, *33*, 111.

Experimental Section[13]

Condensation of Resorcinol and Acetaldehyde in Water. Method A. To a solution of resorcinol (11.01 g, 0.10 mol) and acetaldehyde (4.41 g, 0.10 mol) in 40 mL of water was carefully added 10 mL of concentrated hydrochloric acid. A precipitate was rapidly formed. The reaction mixture was stirred at 75 °C for 1 h, cooled in an ice bath, and filtered. The phenolic precipitate was washed and air-dried; yield 12.3 g.

Acylation of the Phenolic Products. Preparation of the Octaacetates 2a and 2b. The above product (6.15 g) was dissolved in a hot mixture of acetic anhydride (30 mL) and a few milliliters of pyridine. The excess of the solvent was removed by distillation, and the residue was triturated with methanol (ca. 10 mL). The resulting crystals were collected by filtration and air-dried. The product (8.05 g, 74% yield based on resorcinol as the starting material) was a mixture of the octaacetates **2a** and **2b** (ratio of **2a** to **2b** of 2:8 by NMR; integration of the $COCH_3$ signals). It was recrystallized twice from acetonitrile (60 mL), yielding the less soluble octaacetate **2a**: 1.4 g (13%); mp 322–324 °C dec; IR (KBr) 1745 (ester C=O) cm^{-1}; NMR ($CDCl_3$)[15a] δ 7.33 (s, 2, H_{bv}), 6.89 (s, 2, H_c), 6.74 (s, 2 H_c), 5.88 (s, 2, H_{bh}), 4.28 (q, 4, J = 7 Hz, CH), 2.33 (s, 12, $COCH_3$), 1.92 (s, 12, $COCH_3$), 1.40 (d, 12, J = 7 Hz, $CHCH_3$); mass spectrum, m/z (relative intensity) 880 (5, molecular ion), 838 (49), 796 (100), 754 (75), 712 (45), 670 (21), 628 (9), 586 (4). Anal. Calcd for $C_{48}H_{48}O_{16}$: C, 65.47; H, 5.49. Found: C, 65.47; H, 5.43.

The octaacetate **2b** (5.1 g, 47%) was crystallized from the combined mother liquors: mp 306–308 °C dec; IR (KBr) 1745 (ester C=O) cm^{-1}; NMR ($CDCl_3$, T = −33 °C) δ 7.23 (br s, 2, H_{bv}), 6.76 (s, 2, H_c), 6.61 (s, 2, H_c), 5.77 (s, 2, H_{bh}), 4.11 (br m, 4, CH), 2.28 (s, 12, $COCH_3$), 1.93 (s, 12, $COCH_3$), and 1.40 (br s, 12, $CHCH_3$); (T = 32 °C) H_b collapsed, δ 6.88 (s, 4, H_c), 4.23 (q, 4, J = 7 Hz, CH), 2.10 (br s, 24, $COCH_3$), 1.40 (d, 12, J = 7 Hz, $CHCH_3$); (T = 170 °C)[15b] δ 7.30 (s, 4, H_c), 7.07 (s, 4, H_b), 4.53 (q, 4, CH), 2.12 (br s, 24, $COCH_3$), 1.46 (d, 12, J = 7 Hz, $CHCH_3$); mass spectrum, m/z (relative intensity) 880 (2, molecular ion), 838 (31), 796 (100), 754 (71), 712 (50), 670 (27), 628 (14), 586 (6). Anal. Calcd for $C_{48}H_{48}O_{16}$: C, 65.47; H, 5.49. Found: C, 65.51; H, 5.49.

Acylation of the Phenolic Products. Preparation of the Octapropionates 3a and 3b. The octapropionates **3a** and **3b**, obtained by acylation of the phenolic product with propionic anhydride and pyridine, were separated by repeated recrystallization from ethanol. The less soluble octapropionate **3a** was obtained as crystals: mp 270–271 °C; IR (KBr) 1745 (ester C=O) cm^{-1}; NMR ($CDCl_3$)[15a] δ 7.35 (s, 2, H_{bv}), 6.90 (s, 2, H_c), 6.73 (s, 2, H_c), 5.89 (s, 2, H_{bh}), 4.29 (q, 4, CH), 2.63 (q, 8, J = 7 Hz, $COCH_2$), 2.23 (q, 8, J = 7 Hz, $COCH_2$), 1.37 (d, 12, J = 7 Hz, $CHCH_3$), 1.28 (t, 12, J = 7 Hz, CH_2CH_3), 0.95 (t, 12, J = 7 Hz, CH_2CH_3); mass spectrum, m/z (relative intensity) 992 (9, molecular ion), 936 (62), 880 (100), 824 (41), 768 (18), 712 (10), 656 (6), 600 (3), 544 (1). Anal. Calcd for $C_{56}H_{64}O_{16}$: C, 67.73; H, 6.50. Found: C, 67.92; H, 6.46.

From the combined mother liquors the octapropionate **3b** was obtained: mp 255–256 °C; IR (KBr) 1745 (ester C=O) cm^{-1}; NMR

(13) The dynamic NMR spectra were obtained by using a JEOL JNM-MH-100 spectrometer with a variable-temperature controller. The probe temperatures, T, were measured by using precalibrated chemical shift thermometers.[14] By treatment of the exchange of the H_b protons as a simple uncoupled two-site system, the $\Delta G^{\ddagger}$ values were obtained by the coalescence point approximation with the equation $\Delta G^{\ddagger}$ = $0.004573T_c[9.97 + (\log T_c)/\Delta\nu]$. The 60-MHz spectra were recorded on a Varian EM-360 spectrometer. The mass spectra were obtained on a LKB 9000 instrument with a direct inlet system. A high-boiling perfluorokerosene was used to calibrate the mass spectra. Microanalyses were performed by Alab, Uppsala, Sweden, and are reported as the mean values of double determinations. The melting points are uncorrected.
(14) Van Geet, A. L. *Anal. Chem.* **1968**, *40*, 2227.
(15) (a) Temperature-independent spectrum up to 180 °C[15b] except for broadening of the $CHCH_3$ signals at low temperatures. (b) In hexachlorobutadiene.
(16) (a) Zinke, A.; Ott, R.; Garrana, F. H. *Monatsh. Chem.* **1958**, *89*, 135. (b) Hyatt, J. *J. Org. Chem.* **1978**, *43*, 1808.

($CDCl_3$, T = −33 °C) δ 7.33 (br s, 2, H_{bv}), 6.87 (s, 2 H_c), 6.66 (s, 2, H_c), 5.88 (s, 2, H_{bh}), 4.25 (br s, 4, CH), 2.66 (q, 8, J = 7 Hz, $COCH_2$), 2.31 (q, 8, J = 7 Hz, $COCH_2$), 1.48 (br s, 12, $CHCH_3$), 1.29 (t, 12, J = 7 Hz, CH_2CH_3), 1.06 (t, 12, J = 7 Hz, CH_2CH_3); (T = 32 °C) δ 7.30 (vbr s, 2 H_{bv}), 6.86 (br s, 4, H_c), 5.95 (vbr s, 2, H_{bh}), 4.22 (q, 4, J = 7 Hz, CH), 2.42 (vbr s, 16, $COCH_2$), 1.35 (d, 12, J = 7 Hz, $CHCH_3$), 1.12 (br t, 24, CH_2CH_3); (T = 150 °C)[15b] δ 7.16 (s, 4, H_c), 6.98 (s, 4, H_b), 4.42 (q, 4, J = 7 Hz, CH), 2.44 (q, 16, J = 7 Hz, $COCH_2$), 1.40 (d, 12, J = 7 Hz, $CHCH_3$), 1.08 (t, 24, J = 7 Hz, CH_2CH_3); mass spectrum, m/z (relative intensity) 992 (6, molecular ion), 936 (47), 880 (100), 824 (49), 768 (24), 712 (14), 656 (9), 600 (4), 544 (1). Anal. Calcd for $C_{56}H_{64}O_{16}$: C, 67.73; H, 6.50. Found: C, 67.76; H, 6.45.

Condensation of Resorcinol and Acetaldehyde in Solutions Containing Ethanol. (1) The experiment was performed as in method A, but a solvent mixture (50 mL) of ethanol, water, and concentrated hydrochloric acid (2:2:1) was used. After an induction period of 15 min the gradual crystallization of a yellow compound occurred. The crystals 8.2 g) were collected by filtration. The filtrate was poured into water to give a second precipitate. Acetylation of the combined precipitates gave *only* octaacetate **2b** in 57% yield. No octaacetate **2a** could be detected (TLC, NMR).

(2) The experiment was performed as in method A, but a solvent mixture of ethanol (40 mL) and concentrated hydrochloric acid (10 mL) was used. No precipitation was observed. After 1 h the reaction mixture was cooled, neutralized with concentrated aqueous ammonia, and poured into water. A phenolic product (4.7 g) precipitated. On acetylation it gave only octaacetate **2b** (yield 12%).

Condensation of Resorcinol and Acetaldehyde in Water. Method B. When the procedure given by Niederl and Vogel[6] was followed (dilute sulfuric acid, three days reaction time), 48.9 g (79.1%) of phenolic products was obtained. This material (20.4 g) was warmed in a mixture of 60 mL of propionic anhydride and 10 mL of pyridine at 110 °C for 1 h. Cooling in the refrigerator overnight resulted in the crystallization of 9.55 g (25.7%) of the octapropionate **3a** (after washing with methanol). Evaporation of the combined mother liquor and washings and treatment of the semicrystalline residue with 50 mL of methanol gave 22.24 g (59.8%) of the octapropionate **3b**. After recrystallization (**3a** from a mixture of 50 mL of acetonitrile and 100 mL of ethanol and **3b** from 100 mL of ethanol), the two octapropionates, 8.48 g (22.8%) and 21.10 g (56.7%), respectively, exhibited melting points and spectral data identical with those of the analytically pure samples.

Phenol 1a.[2] To a slurry of 2.0 g (2 mmol) of octabutyrate **3a** in a mixture of 5 mL of acetonitrile and 15 mL of ethanol at 60 °C under nitrogen was rapidly added a solution of 2 g of potassium hydroxide in 25 mL of ethanol. After 30 min the mixture was acidified with 2 mL of acetic acid. The homogeneous solution was concentrated on a rotary evaporator, 50 mL of water was added, and the mixture was allowed to stand in the refrigerator overnight. The phenol **1a** (1.04 g, 95%) was then collected by filtration, washed thoroughly with water, and dried at 70 °C under vacuum (1 Pa): mp >350 dec; IR (KBr) 3700–2500 (OH) cm^{-1}; NMR (0.5 M NaOD in D_2O, with sodium 3-(trimethylsilyl)-propanesulfonate as an internal reference) δ 7.00 (s, 2, H_{bv}), 6.33 (s, 2, H_{bh}), 6.01 (s, 2, H_c), 5.92 (s, 2, H_c), 4.27 (br q, 4, J = 7 Hz, CH), 1.20 (br d, 12, J = 7 Hz, CH_3). Anal. Calcd for $C_{32}H_{32}O_8$: C, 70.57; H, 5.92. Found: C, 70.36; H, 5.88.

Phenol 1b.[2] A solution of 2.0 g (2 mmol) of octabutyrate **3b** in 25 mL of ethanol was hydrolyzed in the same way as described above. However, when the warm slurry of the potassium salt of the phenol **1b** was acidified with acetic acid, a homogenous solution first formed from which the phenol **1b** rapidly crystallized and could be collected by filtration: yield 1.05 g (96%) after drying at 70 °C (1 Pa); mp >350 °C dec; IR (KBr) 3700–2500 (OH) cm^{-1}; NMR (0.5 M NaOD in D_2O, with sodium 3-(trimethylsilyl)-propanesulfonate as an internal reference) δ 7.02 (br s, 4, H_b), 5.88 (s, 4, H_c), 4.38 (br q, 4, J = 7 Hz, CH), 1.42 (br d, 12, J = 7 Hz, CH_3). Anal. Calcd for $C_{32}H_{32}O_8$: C, 70.57; H, 5.92. Found: C, 70.40; H, 5.87.

Acknowledgment. The author thanks Professor Holger Erdtman for many discussions in connection with this work. The dynamic NMR measurements were performed by Ms. Gurli Hammarberg.

Registry No. 1a, 74645-05-9; **1b**, 74708-10-4; **2a**, 74629-75-7; **2b**, 74708-70-6; **3a**, 74629-76-8; **3b**, 74708-11-5; resorcinol, 108-46-3; acetaldehyde, 75-07-0.

A Rapid and Efficient Route to 4- and 5-Amino-3-oxocyclopentene Derivatives

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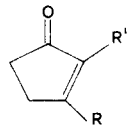
The conversion of open-chain 1,4-diketones to cyclopentenones of type 1 via intramolecular aldol reaction is a common final step in a number of synthetic schemes.[1]

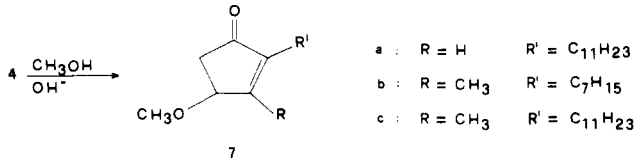


1

Only occasionally have ene dicarbonyl compounds (**3**) been employed as intermediates in the synthesis of cyclopentenone derivatives **5** (and **6**), due to their difficult preparation in the necessary cis configuration and, most of all, their easy cis–trans isomerization that prevented any efficient cyclization to **5**.[2,3]

In fact, compounds **3** were achievable only by hydrolysis of 2,5-dihydro-2,5-dimethoxyfuran derivatives (**2**), which afforded a mixture of cis–trans stereoisomers (Scheme I). The double-bond isomerization, leading to the undesired trans byproduct, was further favored in the course of the subsequent aldol condensation, usually carried out under acid-catalysis conditions. Of course, this procedure allowed only 5-hydroxy derivatives of the type either **5** or **6** to be prepared.[2,3]

Recently, instead, we have shown that trans ene dicarbonyl compounds **4**, easily obtained by reaction of pyridinium chlorochromate (PCC) with 2,5-dialkylfurans (>90%), could be converted in high yield into 5-methoxy-3-oxocyclopentene derivatives **7**.[4]



7

This result demonstrated the potential synthetic value of **4** as intermediates in the preparation of variously functionalized cyclopentenones.

In this paper we report that trans ene dicarbonyl compounds can be easily changed into 4-amino- and 5-amino-3-oxocyclopentene derivatives; in fact, by reaction

(1) R. A. Ellison, *Synthesis*, 397 (1973).
(2) T. Shono, Y. Matsumura, H. Hamaguchi and K. Nakamura, *Chem. Lett.*, 1249 (1976).
(3) M. B. Floyd, *J. Org. Chem.*, **43**, 1641 (1978).
(4) G. Piancatelli, A. Scettri, and M. D'Auria, *Tetrahedron*, **36**, 661 (1980).

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