TOTAL SYNTHESIS AND PROPERTIES OF PROSTAGLANDINS. 36.* CONDENSATION OF (+)2-OXABICYCLO[3.3.0]-6-OCTEN-3-ONE WITH FURYLACROLEIN AND FURYLPROPIONIC ALDEHYDE

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A study was made of the condensation of bicyclic γ-lactone I with furylacrolein and furylpropionic aldehyde. Significant differences were observed in the reactivity of the aldols obtained, and in the stereochemical trend of their dehydration reaction.

We reported in a previous communication the reaction between lactone I and cinnamic aldehyde [2]. By performing the dehydration of both syn- and anti-aldols using column chromatography (with silica gel) trans–trans- and cis–trans-dienes were isolated in pure form, with the latter predominating.

In the current work we compare the processes involved in the aldol condensation of the Li-enolate of bicyclic lactone I with the two aldehydes, whose only difference lies in the fact that one of them has a double bond (see reaction scheme). Conditions for the reaction of the lactone Li-enolate with furylacrolein and furylpropionic aldehyde were virtually the same as for those with cinnamic aldehyde [2]. Yields of the resultant aldols III + IV and VI + VII were 75% and 62%, respectively, and the anti-isomer predominated in both cases (Table 1).

In the mass spectra of these compounds we observed molecular peaks and dense side-chain fragment ions corresponding to m/z of 162 $[OCOC{=}CH{-}CH{=}CH{-}C_4H_3O]^+$, 124 $[C_7H_8O_2]^{+\cdot}$, and 123 $[(HO)CHCH{=}CH{-}C_4H_3O]^+$ in compounds III and IV, and m/z of 164 $[OCOC{=}CH{-}(CH_2)_2{-}C_4H_3O]^+$, 95 $[(CH_2)_2{-}C_4H_3O]^+$, and 81 $[CH_2{-}C_4H_3O]^+$ in compounds VI and VII (Table 2) (see scheme at top of following page). The major difference in the PMR spectra of the syn- and anti-aldols was the chemical shift value of the 1′-H proton. In the case of the syn-isomer a weak-field shift averaging 0.24 ppm was observed for this signal, which was in line with data reported in previous works [2-4] (see Table 3).

The dehydration of the aldols was carried out in a similar way to the method described in [2], using an excess of methanesulfonic chloride and dimethylaminopyridine (DMAP) in methylene chloride. A small excess of the reagents (1.5 equivs. of CH_3SO_2Cl and 2.5 equivs. of DMAP) was employed in the dehydration of unsaturated aldols III and IV, the β-elimination of intermediate mesylates being almost complete after one hour of stirring at room temperature. In both cases one product resulted, namely cis–trans-diene V, in the form of a yellow, crystalline substance, a fact that was indicated by TLC, HPLC, and PMR data (see Tables 1 and 3). The presence of a diene system cis–trans configuration was suggested by a multiplet at 7.20 ppm in the PMR spectrum of this compound. This proved to be in line with previous data [2, 5, 6]. The IR spectrum exhibited a carbonyl absorption band at 1740 cm^{-1}, which is typical of five-membered lactones with an exocyclic double bond, and bands at 1650 and 1625 cm^{-1} corresponding to conjugated C=C double bonds. Its mass spectrum was marked by an intense molecular peak and fragment ions of m/z 183 $[M - COOH]^+$ and 162 $[OCOC{=}CHCH{=}CH{-}C_4H_3O]^+$.

*For Communication 35, see [1].

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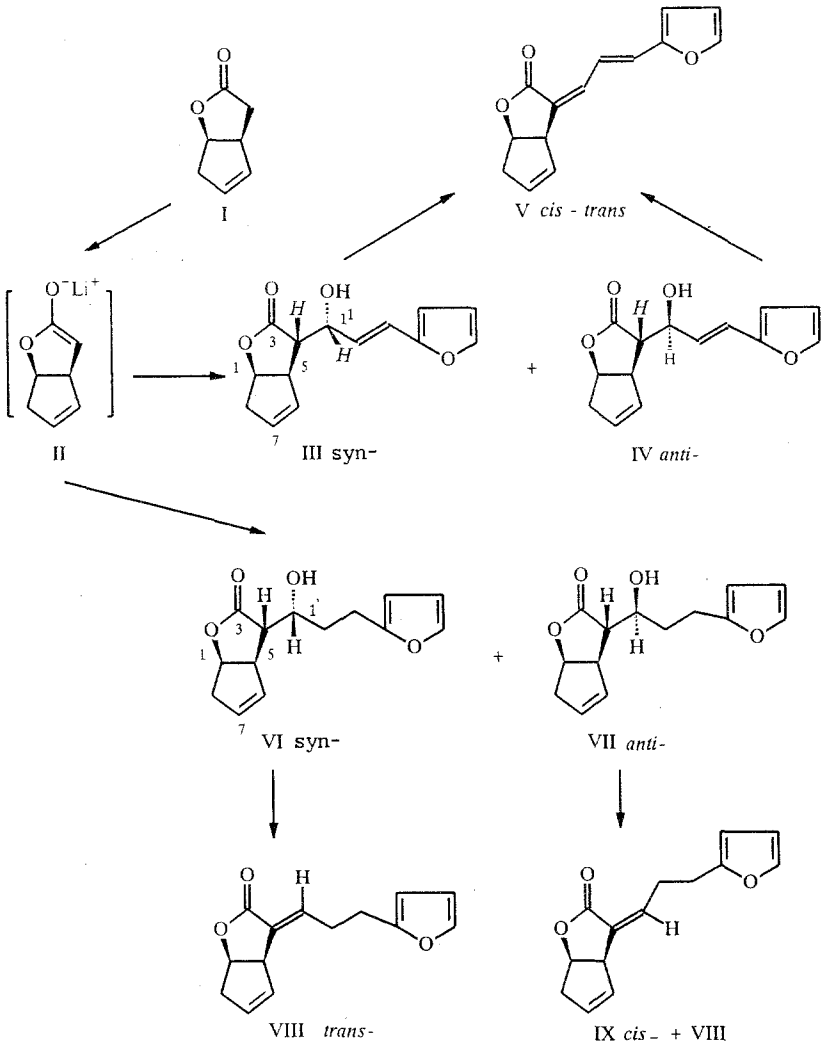
TABLE 1. Yields and Spectral Data for Synthesized Compounds III-IX

Compound	R_f system*	K system*	UV spectrum λ_{max}, nm (ε)	IP spectrum, ν, cm^{-1}	Yield, %
III	0,38 (A)	1,94 (A)	262 (21250), 270 (15625)	3625, 1760	29
IV	0,24 (A)	3,70 (A)	262 (21247), 270 (15704)	3625, 1760, 1740	45,7
V	0,43 (A)	2,20 (B)	350 (36842)	1765, 1740, 1650, 1625, 1485, 1345, 1290	62 (from III) 67 (from IV)
VI	0,36 (A)	2,00 (A)	—	3625, 1765, 1520, 1360	23
VII	0,26 (A)	2,50 (A)	—	3625, 1765, 1520, 1360	39
VIII	0,34 (B)	1,80 (B)	218 (16170)	1755, 1685, 1520, 1350	72 (from VI) 63 (from VII)
IX	0,46 (B)	1,30 (B)	220 (15384)	1755, 1675, 1520, 1380	23 (from VII)

*Hexane–ethyl acetate solvent systems, 2:1 (system A) and 3:1 (system B).



A large excess of reagents (5 equivs. of CH_3SO_2Cl, 10 equivs. of DMAP) and prolonged stirring at room temperature were essential for the dehydration of saturated aldols VI and VII. The syn-aldol then immediately yielded (along with the mesylate) just trans-enone VIII and the reaction was complete in 4 h. Under these conditions anti-aldol VII afforded both enones

TABLE 2. Mass Spectra of Synthesized Compounds

Compound	m/z (I_{rel}, %)
III	246 (86) $[M]^{+\cdot}$, 180 (37) $[OCOCHCH(OH)CH{=}CH{-}C_4H_3O]^+$, 162 (86) $[OCOC{=}CH{-}CH{=}CH{-}C_4H_3O]^+$, 124 (100) $[C_7H_8O_2]^{+\cdot}$, 123 (> 100) $[(HO)CHCH{=}CH{-}C_4H_3O]^+$
IV	246 (86), 180 (27), 162 (77), 124 (100), 123 (> 100)
V	228 (100) $[M]^{+\cdot}$, 183 (13) $[M{-}COOH]^+$, 162 (17) $[OCOC{=}CH{-}CH{=}CH{-}C_4H_3O]^+$, 155 (17), 141 (13), 128 (30), 115 (23), 91 (13), 81 (13)
VI	248 (11) $[M]^{+\cdot}$, 230 (2) $[M{-}H_2O]^{+\cdot}$, 164 (31) $[OCOC{=}CH{-}(CH_2)_2{-}C_4H_3O]^+$, 124 (43) $[C_7H_8O_2]^{+\cdot}$, 107 (20) $[C{-}(CH_2)_2{-}C_4H_3O]^+$, 95 (100) $[(CH_2)_2{-}C_4H_3O]^+$, 81 (94) $[CH_2{-}C_4H_3O]^+$
VII	248 (63), 230 (4), 164 (100), 124 (18), 107 (62), 95 (18), 81 (91)
VIII	230 (9) $[M]^{+\cdot}$, 185 (1) $[M{-}COOH]^+$, 164 (1,5) $[OCOC{=}CH(CH_2)_2{-}C_4H_3O]^+$, 149 (3) $[M{-}CH_2{-}C_4H_3O]^+$, 81 (100) $[CH_2{-}C_4H_3O]^+$
IX	230 (10), 185 (1), 164 (1), 149 (1,7), 81 (100)

VIII and IX at once, and the reaction was completed only after 16-20 h. The ratio of trans- and cis-enones was 2:1 in this mixture.

As in the case of compound V above, the mass spectra of these enones revealed molecular peaks and fragment ions with m/z of 185 $[M - COOH]^+$, 164 $[OCOC{=}CHCH_2CH_2{-}C_4H_3O]^+$ and, most distinctively, 81 $[CH_2{-}C_4H_3O]^+$. In the IR spectra the absorption band for the lactone carbonyl with the exocyclic double bond was seen at 1755 cm^{-1}, and the double bond absorption band appeared at 1675 cm^{-1} (IX) and 1685 cm^{-1} (VIII). The PMR spectra exhibited a 1′-H proton signal at 6.60 ppm for trans-enone VIII and one at 6.22 ppm for cis-enone IX, which was in line with the available data [2, 5, 6].

To summarize, a slow process was observed in the case of saturated aldols VI and VII, probably involving the cis-elimination of the anti-aldol VII mesylate and the formation of both trans- and cis-enols (predominantly the former), as well as the trans-elimination of the syn-aldol VI mesylate, which proceeded more readily, yielding just the trans-enone.

However, the presence of a double bond in aldols III and IV (as previously in the reaction products with cinnamic aldehyde [2]), which increases the lability of the α-proton, evidently facilitates the β-elimination of intermediate mesylates (including those resulting from the formation of a conjugated system). In this case, regardless of the stereoisomerism of the starting aldol, the only product is cis–trans-diene V, which is probably more thermodynamically stable.

EXPERIMENTAL

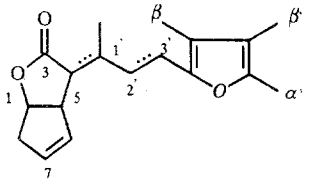
PMR spectra were recorded in $CDCl_3$ using Bruker WM-360 and Bruker WH-90 spectrometers, internal standard TMS. Mass spectra were taken on an MS 50 KRATOS mass spectrometer with ionizing electron energy of 70 eV. IR spectra were registered in $CHCl_3$ solution using a Perkin-Elmer 580 B. UV spectra were taken in ethyl alcohol on a Specord UV-Vis instrument.

A Laboratorni pristroje (Prague) liquid chromatograph with differential refractometer was used for the chromatographic investigations. Normal-phase HPLC was employed in which the column (3.0 × 150 mm) was packed with Separon™ SGX sorbent of 5 micrometer particle size. Capacity coefficients for the compounds were calculated from the equation $k = (t_R - t_o)/t_o$, where t_R is the retention time of the sorbate and t_o the retention time of the hexane. The solvent system used is shown in Table 1.

All reactions were carried out in an argon atmosphere, and monitored by means of TLC using Silufol UV-254 plates. Spot detection was performed in UV light by spraying the plates with a 10% solution of phosphomolybdic acid in ethanol then heating to 120°C. Column chromatography using Silasorb 600 (Lachema) was employed for purification purposes.

4-(1-Hydroxy-3-furyl-2-propenyl)-2-oxabicyclo[3.3.0]-6-octen-3-one (III, IV, $C_{14}H_{14}O_4$). A 10 ml sample (16 mmoles) of a 1.6 M hexane solution of BuLi was added dropwise at −5°-(−10)°C to 3 ml (17.6 mmoles) of isopropylcyclohexylamine in 5 ml of tetrahydrofuran. After 15-20 min the mixture was cooled to −70°C and 1 g (8 mmoles) of lactone I in 6 ml of tetrahydrofuran was added to it over a period of 20 min. Thirty minutes later 2 ml of glacial acetic acid, 5 ml of saturated NaCl solution, and 10 ml of water were added to the mixture, which was then extracted with ethyl acetate. After the

TABLE 3. PMR Spectra of Synthesized Compounds



Compound	Isomer shifts, δ, ppm
III	7,39 (1H, s, α'-H); 6,59 (1H, d, 3'-H); 6,38; 6,28 (2H, m, β-H, β'-H); 6,18 (1H, d d, 2'-H); 5,72 (1H, m, 7-H); 5,55 (1H, m, 6-H); 5,16 (1H, t, 1-H); 4,85 (1H, br.s, 1'-H); 3,50 (1H, m, 5-H); 2,78 (1H, m, 4-H); 2,62 (2H, m, 8-H)
IV	7,37 (1H, s, α'-H); 6,52 (1H, d, 3'-H); 6,39; 6,28 (2H, m, β-H, β'-H); 6,23 (1H, d d, 2'-H); 5,73 (1H, m, 7-H); 5,58 (1H, m, 6-H); 5,10 (1H, t, 1-H); 4,62 (1H, t, 1'-H); 3,49 (1H, m, 5-H); 3,20 (1H, m, OH); 2,75 (1H, m, 4-H); 2,65 (2H, m, 8-H)
V	7,47 (1H, s, α'-H); 7,20 (1H, m, 1'-H); 6,86; 6,70 (2H, m, β-H, β'-H); 6,48 (2H, m, 2'-H, 3'-H); 5,80 (1H, m, 7-H); 5,70 (1H, m, 6-H); 5,16 (1H, q, 1-H); 4,25 (1H, m, 5-H); 2,78 (2H, m, 8-H)
VI	7,22 (1H, s, α'-H); 6,22; 5,98 (2H, m, β-H, β'-H); 5,68 (1H, m, 7-H); 5,48 (1H, m, 6-H); 5,07 (1H, t, 1-H); 4,06 (1H, m, 1'-H); 3,46 (1H, m, 5-H); 2,83...2,51 (3H, m, 8-H, 3'-H); 2,40 (1H, m, 4-H); 1,83 (2H, m, 2'-H)
VII	7,22 (1H, s, α'-H); 6,22; 5,98 (2H, m, β-H, β'-H); 5,70 (1H, m, 7-H); 5,52 (1H, m, 6-H); 5,08 (1H, t, 1-H); 3,82 (1H, m, 1'-H); 3,28 (1H, m, 5-H); 2,85...2,51 (3H, m, 8-H, 3'-H); 2,44 (1H, m, 4-H); 1,95 (2H, m, 2'-H)
VIII	7,25 (1H, d, α'-H); 6,60 (1H, t.d, 1'-H); 6,20 (1H, m, β-H); 5,95 (1H, m, β'-H); 5,64 (1H, m 7-H); 5,40 (1H, m, 6-H); 5,00 (1H, t, 1-H); 3,90 (1H, m, 5-H); 2,80...2,52 (6H, m 8-H, 2'-H, 3'-H)
IX	7,24 (1H, d, α'-H); 6,28 (1H, m, β-H); 6,22 (1H, m, 1'-H); 6,02 (1H, m, β'-H); 5,70 (1H, m, 7-H); 5,50 (1H, m, 6-H); 5,00 (1H, m, 1-H); 3,88 (1H, m, 5-H); 3,00 (2H, m, 8-H); 2,85...2,60 (4H, m, 2'-H; 3'-H)

organic solution had been dried with Na_2SO_4 and evaporated, the residue was chromatographed using Silasorb, eluting with a 3:1 hexane–ethyl acetate solvent mixture. The two basic fractions thus obtained were each chromatographed once more, eluting with a 2:1 hexane–ethyl acetate solvent system. Yields 0.58 g (29%) of syn-isomer III, mp 76-79°C and 0.90 g (45.7%) of anti-aldol IV.

4-(3-Furyl-2-propenylidene)-2-oxabicyclo[3.3.0]-6-octen-3-one (V, $C_{14}H_{12}O_3$). A sample of 0.06 ml (0.73 mmoles) of methanesulfonic chloride and 0.18 g (1.47 mmoles) of dimethylaminopyridine were added with stirring and cooling (−10°C) to 0.12 g (0.49 mmoles) of syn-isomer III in 10 ml of methylene chloride. After stirring for 1 h at room temperature, the mixture was diluted with methylene chloride, washed with water and saturated NaCl solution, dried with Na_2SO_4, and evaporated. The residue was chromatographed using Silasorb, eluting with a 2:1 hexane–ethyl acetate solvent system. Yield 0.07 g (62.5%) of yellow crystalline compound V, mp 103-105°C.

This compound was obtained in a similar way from the anti-isomer in 67% yield.

4-(1-Hydroxy-3-furylpropyl)-2-oxabicyclo[3.3.0]-6-octen-3-one (VI, VII, $C_{14}H_{16}O_4$). A 10 ml sample (16 mmoles) of a 1.6 M hexane solution of BuLi was added dropwise at −5°-(−10)°C to 3 ml (17.6 mmoles) of isopropylcyclohexylamine in 6 ml of tetrahydrofuran. After 30 min the amide was cooled to −75°C, then 1 g (8 mmoles) of lactone I in 6 ml of tetrahydrofuran was added to it over a period of 20 min. Forty minutes later 2.28 g (18.3 mmoles) of furylpropionic aldehyde in 6 ml of tetrahydrofuran were added, again over 20 min. In a further 30 min the reaction was completed by adding 8 ml of 2 M HCl, saturated NaCl solution and water, and the mixture extracted with ethyl acetate. After the organic solution had been dried and evaporated, the resultant yellow oil was chromatographed on Silasorb 600, eluting with a 2:1 hexane–ethyl acetate solvent system. The syn- and anti-aldol fractions thus obtained were chromatographed once more, this time eluting with a 2:1 benzene–ether system. Yields 0.46 g (23%) of syn-isomer VI and 0.77 g (38.9%) of anti-isomer VII, mp 67-70°C.

4-(3-Furyl-trans-propylene)-2-oxabicyclo[3.3.0]-6-octen-3-one (VIII, $C_{14}H_{14}O_3$). A 0.15 ml sample (2 mmoles) of methanesulfonic chloride and 0.49 g (4 mmoles) of dimethylaminopyridine were added with stirring and cooling (−10°C) to 0.1 g (0.4 mmole) of syn-isomer VI in 4 ml of methylene chloride. After stirring for 4 h at room temperature, the mixture was

diluted with methylene chloride, washed with water, dried, and evaporated. The residue was chromatographed using Silasorb, eluting with a 3:1 hexane–ethyl acetate system. Yield 0.067 g (72%) of trans-enone VIII.

Trans-enone VIII (63%) of cis-enone IX (23%) were obtained in a similar way from anti-aldol VII 20 h after the start of the reaction.

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