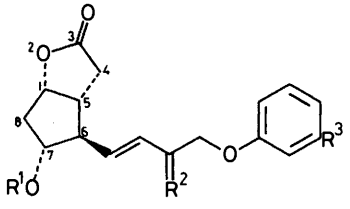
Intramolecular Acetalization of 5-Hydroxy Ketones and Enones.[1] A Novel Transformation of Important Prostaglandin Intermediates under Acidic Conditions

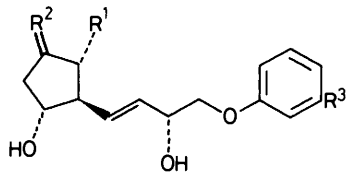
Sigfrid Schwarz,* Gisela Weber, Hans-Joachim Palme, and Manfred Wentzke
VEB Jenapharm, Division of Research, Otto-Schott-Strasse 15, DDR-6900 Jena, German Democratic Republic
Günther Reck
Central Institute of Molecular Biology of the Academy of Sciences of the GDR, DDR-1115 Berlin, German Democratic Republic
Hans Schick
Central Institute of Organic Chemistry of the Academy of Sciences of the GDR, DDR-1199 Berlin, German Democratic Republic

Intermediates in the synthesis of ω-tetranor 16-aryloxy prostaglandins, which are 5-hydroxy enones, undergo quantitative intramolecular transformation into cyclic methyl acetals in acidic methanolic solution. The reaction proceeds *via* the corresponding 5-hydroxy-3-methoxy ketones, which partly exist as hemiacetals. The structure of the compounds investigated was elucidated by ^{1}H NMR spectroscopy and by X-ray analysis of the acetal (**11**).

Racemic or enantiomerically pure enones of structures (**1**)–(**4**)[2] are important intermediates in the synthesis of clinically relevant ω-tetranor 16-aryloxy prostaglandins, *e.g.* cloprostenol (**8**), sulprostone (**9**), or enprostil (**10**).[3] Recently we have described a novel efficient approach to the synthesis of the racemic compound (**1**),[4] which is a precursor of the veterinarily used prostaglandin $F_{2\alpha}$ analogue cloprostenol (**8**). Continuing our studies, we have been investigating the reactivity of the enone (**1**) and related compounds under various conditions. In this paper we report on a novel transformation of the 5-hydroxy enone moiety of the racemic prostaglandin intermediates (**3**) and (**4**) in acidic methanolic solution.



(**1**) $R^1 = SiMe_3$, $R^2 = O$, $R^3 = Cl$
(**2**) $R^1 = SiMe_3$, $R^2 = O$, $R^3 = H$
(**3**) $R^1 = H$, $R^2 = O$, $R^3 = Cl$
(**4**) $R^1 = R^3 = H$, $R^2 = O$
(**5**) $R^1 = H$, $R^2 = \alpha$-OH, β-H, $R^3 = Cl$
(**6**) $R^1 = R^3 = H$, $R^2 = \alpha$-OH, β-H
(**7**) $R^1 = CCl_3CO$-NH-CO, $R^2 = O$, $R^3 = Cl$



(**8**) $R^1 = CH_2$–(Z)–CH=CH–CO_2H, $R^2 = \alpha$-OH, β-H, $R^3 = Cl$
(**9**) $R^1 = CH_2$–(Z)–CH=CH–CO-$NHSO_2Me$, $R^2 = O$, $R^3 = H$
(**10**) $R^1 = CH_2$–(Z)–CH=CH–CO_2Me, $R^2 = O$, $R^3 = H$

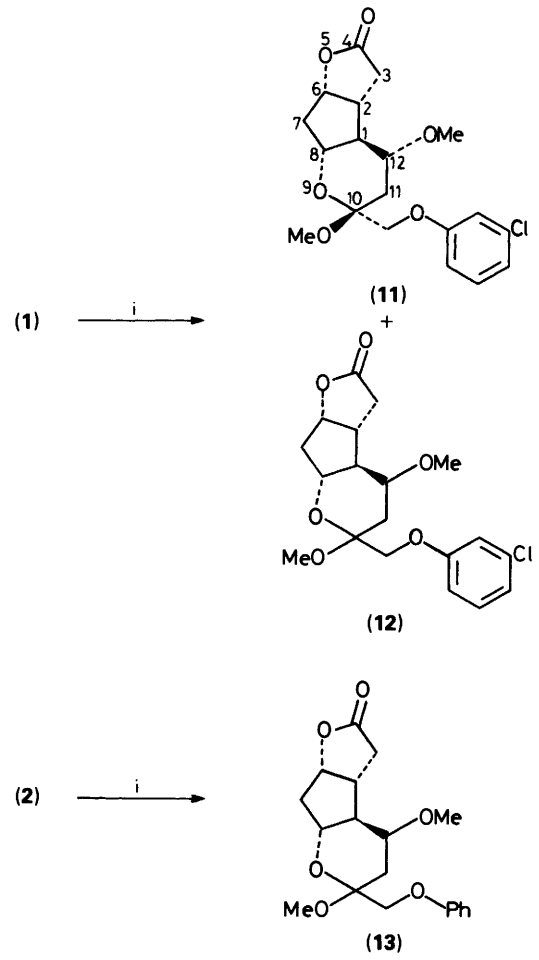
Results and Discussion

When compound (**1**) was dissolved in methanol containing sulphuric acid, silyl ether cleavage to give the enone (**3**) occurred immediately and a mixture of the diastereoisomeric acetals (**11**) and (**12**) (*ca.* 9:1) precipitated within 12 hours at room temperature in almost quantitative yield. Fractional crystallization of the crude product combined with flash chromatography[5] afforded the pure compounds (**11**) and (**12**). Treatment of the enone (**2**) with methanolic sulphuric acid gave the acetal (**13**) (Scheme 1).

Detailed studies have shown that the acetals (**11**), (**12**), and (**13**) are formed *via* the methoxy ketones (**14**) and (**16**), which proved to exist in equilibrium with the hemiacetals (**15**) and (**17**) (*vide infra*). Treatment of the acetals (**11**) and (**13**) with toluene-*p*-sulphonic acid in acetone led to compounds (**14**/**15**) and (**16**/**17**) in high yield, whereas the acetal (**12**) gave the enone (**3**) under the same conditions (Scheme 2).

Evidently, the initial addition of methanol to the enone moiety of compounds (**3**) and (**4**) leads to an increased flexibility of the aryloxy side chain and to a higher electrophilicity of the carbonyl group, thus allowing the hydroxy group in the δ-position to attack the carbonyl group with formation of a six-membered ring. In agreement with this suggestion the hydrogenated compound (**18**),[6] which by analogy with the methoxy ketones (**14**) and (**16**) is in a tautomeric equilibrium with the hemiacetal (**19**), afforded the acetal (**20**) in a rapid and quantitative reaction when exposed to methanolic sulphuric acid (Scheme 3).

Structural Assignments.—The structure of the compounds investigated was elucidated by spectroscopic means and by X-ray analysis. In the ^{1}H NMR spectrum (80 MHz) the transformation of the open-chain ketones (**3**), (**4**), and (**18**) into the corresponding cyclic acetals (**11**), (**12**), (**13**), and (**20**) gives rise to a dramatic change in shift and pattern of the signals due to the $-CH_2-O-Ar$ protons. The results are summarized in Table 1. The $-CH_2-O-Ar$ resonance in the spectra of enones (**3**) and (**4**) appears as a sharp singlet in the δ 4.7 region (entries 1 and 2), while the spectra of the acetals (**11**), (**12**), (**13**), and (**20**) show completely resolved AB patterns for these protons at considerably higher fields (entries 15–18). An analogous trend is observed for the transformation of the enones (**3**) and (**4**) into the enols (**5**) and (**6**), with the exception that the $-CH_2-O-Ar$ signal in the spectra of compounds (**5**) and (**6**) appears as a



Scheme 1. Conversion of the enones (**1**) and (**2**) into the acetals (**11**), (**12**), and (**13**). *Reagents and conditions:* i, MeOH, H^+, room temp., 12 h.

multiplet in each case (entries 3 and 4). In view of these findings the observed resonances in the spectra of the ketones (**14**), (**16**), and (**18**) suggest that these compounds exist predominantly in the hemiacetal forms (**15**), (**17**), and (**19**), respectively.

As can be seen by comparing entries 7 and 12, the presence or absence of the methoxy group in the aryloxy side chain results in a significant effect on the state of the tautomeric equilibrium between the open-chain ketones and the cyclic hemiacetals. The hemiacetal (**15**) and the methoxy ketone (**14**) are present in chloroformic solution at room temperature in a 90:10 ratio, whereas under the same conditions a 1:1 mixture of the ketone (**18**) and the hemiacetal (**19**) was found. Additionally, spectra of compounds (**14**/**15**) and (**18**/**19**), recorded in other solvents, showed that the ratio between the 5-hydroxy ketone and the hemiacetal is solvent-dependent (entries 5, 6, 7, and 10, 11, 12). In dipolar aprotic solvents the open-chain tautomer seems to be favoured (entries 6 and 11). The quantitative transformation of the equilibrated compounds (**14**/**15**), (**16**/**17**), and (**18**/**19**) into the corresponding cyclic acetals (**11**), (**12**), (**13**), and (**20**) by acidic methanol is trivial in principle.[7] However, an alternative shift of these equilibria was demonstrated, too. When trichloroacetyl isocyanate (TAI)[8] was added to chloroform solutions of compounds (**14**/**15**) and (**18**/**19**), the open-chain carbamates (**21**) and (**22**) were formed as the only detectable products (Scheme 4). The observed $-CH_2-O-Ar$ signals in the spectra of these esters proved to be similar to the corresponding resonance of compound (**7**) in position and pattern (Table 1, entries 8, 13, and 14).

The structure elucidation of the acetal (**11**) was completed by

Table 1. ^1H NMR data for the $-CH_2-O-Ar$ protons: δ_H(80 MHz) in ppm with respect to $SiMe_4$ as internal standard.

Entry	Compound	δ_H	Solvent	Intensity	Multiplicity
1	(**3**)	4.67	$CDCl_3$	2 H	s
2	(**4**)	4.67	$CDCl_3$	2 H	s
3	(**5**)	3.96	$(CD_3)_2CO$	2 H	m
4	(**6**)	3.89	$CDCl_3$	2 H	m
5	(**15**)	3.94	$(CD_3)_2CO$	1.8 H	m
	(**14**)	4.82		0.2 H	s
6	(**15**)	5.09[a]	$(CD_3)_2SO$	1 H	m
	(**14**)	4.04[a]		1 H	s
7	(**15**)	3.89	$CDCl_3$	1.8 H	m
	(**14**)	4.57		0.2 H	s
8	(**21**)	4.57	$CDCl_3$	2 H	s
9	(**17**)	3.92	$CDCl_3$	1.8 H	m
	(**16**)	4.56		0.2 H	s
10	(**19**)	3.92	$(CD_3)_2CO$	0.7 H	m
	(**18**)	4.79		1.3 H	s
11	(**19**)	3.91	$[^2H_7]$[c] DMF	0.2 H	m
	(**18**)	4.91		1.8 H	s
12	(**19**)	3.87	$CDCl_3$	1 H	m
	(**18**)	4.54		1 H	s
13	(**22**)	4.55	$CDCl_3$	2 H	s
14	(**7**)	4.67	$CDCl_3$	2 H	s
15	(**11**)	3.69–3.81	$CDCl_3$	1 H	d[b]
		4.01–4.13		1 H	d[b]
16	(**12**)	3.62–3.75	$CDCl_3$	1 H	d[b]
		3.96–4.09		1 H	d[b]
17	(**13**)	3.71–3.84	$CDCl_3$	1 H	d[b]
		4.05–4.18		1 H	d[b]
18	(**20**)	3.81–3.94	$[^2H_7]$[c] DMF	1 H	d[b]
		4.09–4.22		1 H	d[b]

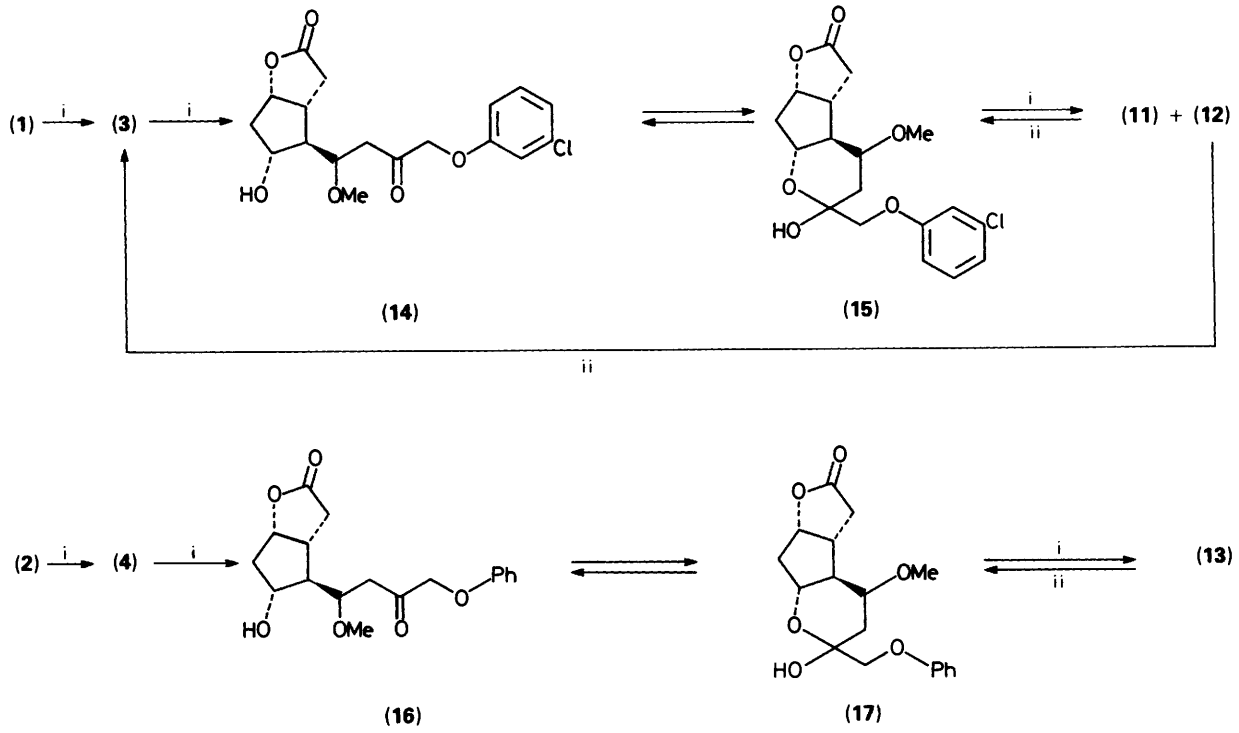
[a] With respect to hexamethyldisiloxane as external standard. [b] *J* 10 Hz. [c] Heptadeuteriodimethylformamide.

X-ray analysis. Details of the analysis are given in the Experimental section. A stereo plot of the molecule is shown in the Figure. The configurations of the chiral centres in the illustrated enantiomer are 1*S*,2*R*,5*S*,7*R*,8*R*, and 10*R* (crystallographic numbering).[9] However, the inverse configuration also exists, because the crystal structure is centrosymmetric. The central six-membered ring has a chair conformation. The asymmetry parameters[10,11] $\Delta[C_2\ C(2)] = 0.4$ and $\Delta[C_2\ C(4)] = 0.5$ indicate half-chair conformations for both five-membered rings.

Like the acetal (**11**), the acetals (**12**), (**13**), and (**20**) are single diastereoisomers. The acetal (**12**) is assumed to be the 12-epimer of compound (**11**), since there is no argument for a highly stereoselective addition of methanol to the enone moiety of compound (**3**). Though the X-ray analysis of the acetals (**20**) and (**13**) has not been accomplished yet, the substituents in their tetrahydrofuran ring are assumed to have the same configuration as in compound (**11**).

The enone (**23**), which is an intermediate in the synthesis of natural prostaglandins,[12] was subjected to acidic methanol, too. However, neither the addition of methanol to the 13-double bond nor the formation of the corresponding cyclic acetal was detected to a significant extent. This is in accordance with results of Brewster *et al.*,[13] who showed that the enone (**24**), when treated with toluene-*p*-sulphonic acid in methanolic solution, remained unaffected in the side chain. The enones (**3**) and (**4**) clearly show a better susceptibility to nucleophiles than the enone (**23**), a fact which has been observed in other cases, too.*

* For instance, compounds (**3**) and (**4**) are reduced smoothly and stereoselectively to the enols (**5**) and (**6**) at −70 °C by di-isobornyloxy aluminium isopropoxide,[14] while the enone (**23**) reacts with the same reagent at a considerably higher temperature only to give a nearly 1:1 mixture of diastereoisomeric enols (**25**).



Scheme 2. Methoxy ketones (**14**) and (**16**), and the corresponding hemiacetals (**15**) and (**17**) as intermediates in the conversion of the enones (**1**) and (**2**) into the acetals (**11**), (**12**), and (**13**). *Reagents and conditions:* i, MeOH, H^+, room temp., 12 h; ii, acetone, *p*-$MeC_6H_4SO_3H$, room temp., 12 h.

Recently Roberts *et al.*[15] reported on an urinary metabolite of prostaglandin D_2, which proved to be the spirolactone (**26**). Compound (**26**) originates from the precursor (**27**).[16] Here, the *cis*-orientation of the 11-hydroxy group and the saturated side chain seems to allow ring closure to occur between positions 11 and 15.

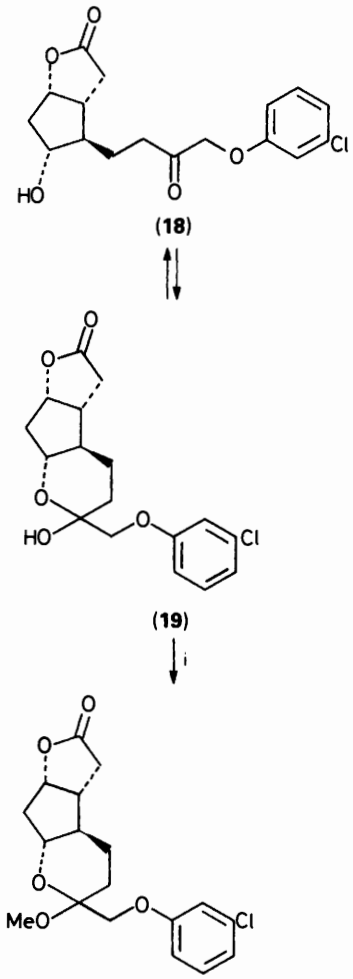
Experimental

^1H NMR spectra were recorded at 80 MHz on a Tesla BS 487c instrument. Unless stated otherwise, $CDCl_3$ was used as solvent and chemical shifts are reported as δ values in ppm downfield from tetramethylsilane as internal standard. Low-resolution electron impact (EI) and chemical ionization (CI) mass spectra were obtained on a GC/MS-Datensystem HP 5985 B spectrometer. IR spectra were run on a UR 20 spectrometer (Carl Zeiss Jena). UV spectra were taken on a UV VIS SPECORD (Carl Zeiss Jena). Flash chromatography was performed on Kieselgel 60 (Merck A. G. Darmstadt, 0.04–0.063 mm) or Silasorb 600 (Lachema n.p. Brno, ČSSR, 20 μm).

10-(3-*Chlorophenoxymethyl*)-10,12-*dimethoxy*-5,9-*dioxatricyclo*[6.4.0.0^{2,6}]*dodecan*-4-*one* (**11**) *and* (**12**).—(1*SR*,5*RS*,6*RS*,7*RS*)-6-[4-(3-Chlorophenoxy)-3-oxobut-1(*E*)-en-1-yl]-7-trimethylsiloxy-2-oxabicyclo[3.3.0]octan-3-one (**1**) (6 g, 14.7 mmol) was dissolved in methanol–conc. sulphuric acid (85:15; 40 ml). After 24 h, the precipitated crystals were filtered off, washed with cold (0 °C) methanol, and dried. Crystallization (× 2) from methanol gave the (1*SR*,2*RS*,6*SR*,8*RS*,10*RS*,12*RS*)-*acetal* (**11**) (4.5 g, 80%), m.p. 146–148 °C (Found: C, 59.6; H, 6.3; Cl, 9.2. $C_{19}H_{23}ClO_6$ requires C, 59.6; H, 6.05; Cl, 9.3%); ν_{max}(KBr) 1 770 (γ-lactone), 1 600, 1 585sh, and 1 480 cm^{-1} (Ph); λ_{max}(MeOH) 274 (ε 1 837 dm^3 mol^{-1} cm^{-1}) and 282 nm (1 761); δ_H 3.19 (3 H, s, OMe), 3.30 (3 H, s, OMe), 3.75 (1 H, d, *J* 10 Hz, C*H*H–O), 4.07 (1 H, d, *J* 10 Hz, CH*H*–O), 4.85 (1 H, m, CH–O lactone), and 6.62–7.37 (4 H, m, C_6H_4Cl); *m/z* (CI) 383 (M^+ + 1, 65%), 351 (25, M^+ − CH_3OH − 1), 317 (10, M^+ − $2CH_3OH$ − 1), 241 (40, M^+ − $CH_2OC_6H_4Cl$), 193 (100), and 141 (30, $CH_2OC_6H_4Cl$).

The mother liquors of the crystallization of the acetal (**11**), which contain the acetals (**11**) and (**12**) (1:1), were combined and concentrated by rotary evaporation. The residue (1.4 g) was subjected to flash chromatography on Silasorb, using chloroform–ethyl acetate (3:1) as eluant. The fractions containing mainly the acetal (**12**) were collected and evaporated. Repeated crystallization of the product gave the (1*SR*,2*RS*,6*SR*,8*RS*)-*acetal* (**12**) (0.2 g, 3.5%), m.p. 108–111 °C (from MeOH) (Found: C, 59.9; H, 6.15; Cl, 9.3%); ν_{max}(KBr) 1 770 (γ-lactone), 1 600, 1 585, and 1 480 cm^{-1} (Ph); λ_{max}(MeOH) 275 (ε 1 760 dm^3 mol^{-1} cm^{-1}), and 282 nm (1 558); δ_H 3.21 (3 H, s, OMe), 3.37 (3 H, s, OMe), 3.68 (1 H, d, *J* 10 Hz, C*H*H–O), 4.02 (1 H, d, *J* 10 Hz, CH*H*–O), 4.86 (1 H, m, CH–O lactone), and 6.62–7.37 (4 H, m, C_6H_4Cl); *m/z* (CI) 383 (M^+ +1, 100%), 351 (70, M^+ − CH_3OH + 1), 317 (20, M^+ − $2CH_3OH$ − 1), 241 (90, M^+ − $CH_2OC_6H_4Cl$), and 141 (10, $CH_2OC_6H_4Cl$).

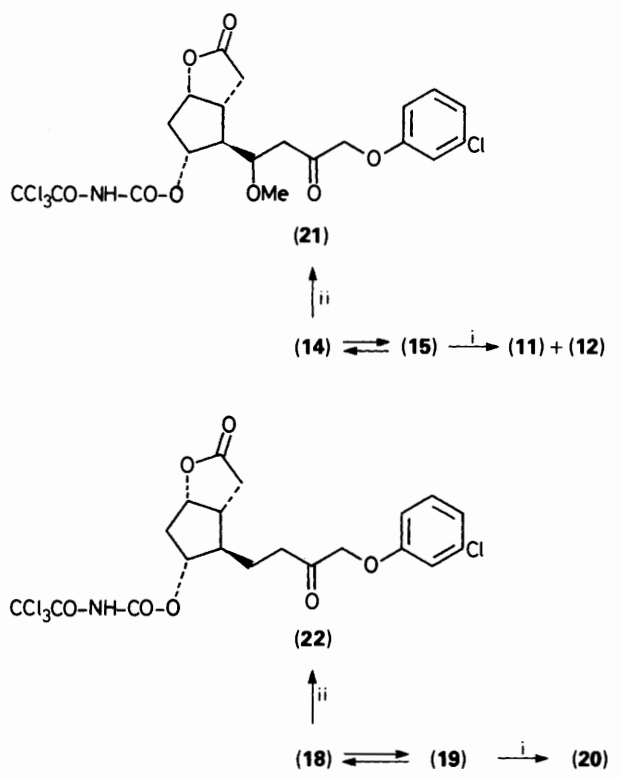
(1SR,2RS,6SR,8RS)-10,12-*Dimethoxy*-10-*phenoxymethyl*-5,9-*dioxatricyclo*[6.4.0.0^{2,6}]*dodecan*-4-*one* (**13**).—A solution of (1*SR*,5*RS*,6*RS*,7*RS*)-6-[3-oxo-4-phenoxybut-1(*E*)-en-1-yl]-7-trimethylsiloxy-2-oxabicyclo[3.3.0]octan-3-one (**2**) (0.5 g, 1.3 mmol) in methanol–conc. sulphuric acid (85:15; 20 ml) was kept for 72 h at room temperature. The solution was then heated to 40 °C and methanol (15 ml) was distilled off *in vacuo*. To the resulting mixture was added saturated aqueous sodium hydrogen carbonate (50 ml). The mixture was extracted with chloroform (3 × 10 ml). The combined chloroform extracts were washed with water (2 × 10 ml), dried (Na_2SO_4) and concentrated by rotary evaporation. The residue, a mixture of the acetal (**13**) and enone (**4**) (9:1), was subjected to flash chromatography with chloroform–ethyl acetate (1:1) as eluant



Scheme 3. Transformation of the saturated ketones (**18**) into the acetal (**20**). *Reagents and conditions:* i, MeOH, H^+, room temp., 2 h.

affording the pure *acetal* (**13**) (302 mg, 65%) as crystals, m.p. 116–120 °C (from methanol) (Found: C, 65.6; H, 7.3. $C_{19}H_{24}O_6$ requires C, 65.5; H, 6.9%); ν_{max}(KBr) 1 770 (γ-lactone), 1 605, 1 595, and 1 505 cm^{-1} (Ph); λ_{max}(MeOH) 271 (ε 1 501 dm^3 mol^{-1} cm^{-1}) and 277 nm (1 285); δ_H 3.21 (3 H, s, OMe), 3.31 (3 H, s, OMe), 3.77 (1 H, d, *J* 10 Hz, C*H*H–O), 4.12 (1 H, d, *J* 10 Hz, CH*H*–O), 4.86 (1 H, m, CH–O lactone), and 6.75–7.50 (5 H, m, Ph); *m/z* (CI) 349 (M^+ + 1, 60%), 317 (100, $M^+ - CH_3OH$ + 1), 285 (30, $M^+ - 2CH_3OH$ + 1), and 241 (40, $M^+ - CH_2OC_6H_5$).

(1RS,2RS,6SR,8RS)-10-(3-*Chlorophenoxymethyl*)-10-*methoxy*-5,9-*dioxatricyclo*[6.4.0.0^{2,6}]*dodecan*-4-*one* (**20**).—(1*SR*,5*RS*,6*RS*,7*RS*)-6-[4-(3-Chlorophenoxy)-3-oxo-butyl]-7-hydroxy-2-oxabicyclo[3.3.0]octan-3-one (**18**) (2 g, 4.9 mmol) was dissolved in methanol–conc. sulphuric acid (85:15; 10 ml). After 6 h the precipitated crystals were filtered off, washed with methanol, and dried. Crystallization from methanol gave the *acetal* (**20**) (1.46 g, 85%), m.p. 202–203 °C (Found: C, 61.1; H, 6.15; Cl, 10.0. $C_{18}H_{21}ClO_5$ requires C, 61.3; H, 6.00; Cl, 10.05%); ν_{max}(KBr) 1 765 (γ-lactone), 1 600, 1 585sh, and 1 480 cm^{-1} (Ph); λ_{max}(MeOH) 274 (ε 1 666 dm^3 mol^{-1} cm^{-1}) and 281 nm (1 462); δ_H([$^2H_7$]DMF) 3.20 (3 H, s, OMe), 3.87 (1 H, d, *J* 10 Hz, C*H*H–O), 4.15 (1 H, d, *J* 10 Hz, CH*H*–O), 4.94 (1 H, m, CH–O lactone), and 6.87–7.50 (4 H, m, C_6H_4Cl); *m/z* (CI) 353 (M^+ + 1, 100%), 319 (90, $M^+ - CH_3OH - 1$), 287 (90, M^+



Scheme 4. Transformation of the equilibrated ketones (**14**/**15**) and (**18**/**19**) by acidic methanol and by trichloroacetyl isocyanate (TAI). *Reagents and conditions:* i, MeOH, H^+, room temp., 12 h; ii, $CHCl_3$, TAI, room temp.

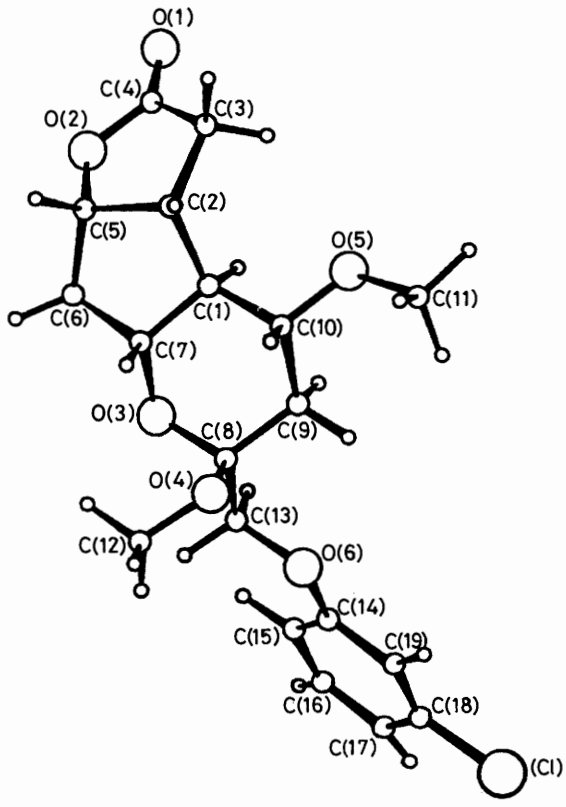
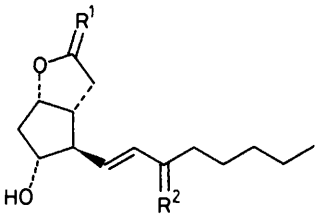


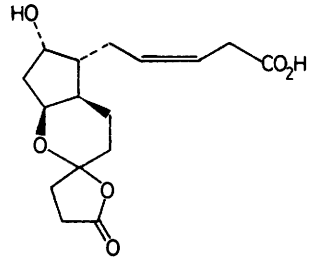
Figure. Crystal structure of the acetal (**11**).



(23) $R^1 = R^2 = O$

(24) R^1 = H, OH, R^2 = O

(25) R^1 = O, R^2 = H, OH



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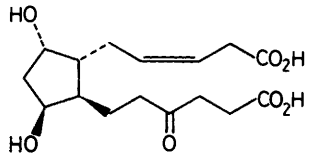

(27)

– $2CH_3OH$ – 1), 211 (40, $M^+ - CH_2OC_6H_4Cl$), and 141 (10, $CH_2OC_6H_4Cl$).

(1RS,2RS,6SR,8RS)-10-(3-*Chlorophenoxymethyl*)-10-*hydroxy*-5,9-*dioxatricyclo*[6.4.0.$0^{2,6}$]*dodecan*-4-*one* (**19**/**18**).—(1*SR*,5*RS*,6*RS*,7*RS*)-6-[4-(3-Chlorophenoxy)-3-oxobut-1(*E*)-en-1-yl]-7-hydroxy-2-oxabicyclo[3.3.0]octan-3-one (**3**) (2 g, 5.9 mmol), dissolved in acetone (20 ml), was added to a pre-hydrogenated suspension of palladium on magnesium carbonate (500 mg catalyst, containing 5% Pd). The mixture was shaken under hydrogen atmosphere until the hydrogen uptake stopped (133 ml). The hydrogen atmosphere was removed by nitrogen, the catalyst was filtered off, and the filtrate was concentrated by rotary evaporation, yielding compound (**19**/**18**) (2 g, *ca.* 100%) as an oil, which solidified after 2 weeks; $\nu_{max}(CHCl_3)$ 1 765 (γ-lactone), 1 722 (CO), 1 600, 1 585sh, and 1 485 cm^{-1} (Ph); λ_{max}(MeOH) 274 (ε 1 528 $dm^3\ mol^{-1}\ cm^{-1}$) and 281 nm (1 328); δ_H 3.87 [1 H, m, CH_2–O (**19**)], 4.54 [1 H, s, CH_2–O (**18**)], 4.86 (1 H, m, CH–O lactone), and 6.62–7.37 (4 H, m, C_6H_4Cl); *m*/*z* (CI) 339 (M^+ + 1, 5%), 321 (2, $M^+ - H_2O$ + 1), 213 (65), 197 (20, $M^+ - CH_2OC_6H_4Cl$), 185 (100), and 141 (30, $CH_2OC_6H_4Cl$); *m*/*z* (EI) 338 (M^+, 10%), 320 (3, $M^+ - H_2O$), 197 (20, $M^+ - CH_2OC_6H_4Cl$), 179 (40, 197 – H_2O), 141 (20, $CH_2OC_6H_4Cl$), and 55 (100).

(1SR,2RS,6SR,8RS,12RS)-10-(3-*Chlorophenoxymethyl*)-10-*hydroxy*-12-*methoxy*-5,9-*dioxatricyclo*[6.4.0.$0^{2,6}$]*dodecan*-4-*one* (**15**/**14**).—The acetal (**11**) (1.0 g, 2.6 mmol) was dissolved in acetone (20 ml), containing toluene-*p*-sulphonic acid (0.89 g, 5.2 mmol). The solution was kept for 3 days at room temperature. Then water (50 ml) was added and the mixture was extracted with dichloromethane (5 × 25 ml). The combined extracts were washed with saturated aqueous sodium hydrogen carbonate (2 × 25 ml) and water (2 × 25 ml), dried (Na_2SO_4), and concentrated by rotary evaporation. The crude product was purified by flash chromatography with chloroform–ethyl acetate (1:1) as eluant, affording the oily hemiacetal (**15**/**14**)

Table 2. Summary of crystal data and details of data collection.

Crystal data:	
Formula	$C_{19}H_{23}ClO_6$
Formula wt.	382.84
a/Å	8.659(3)[a]
b/Å	5.607(3)
c/Å	38.362(59)
β/°	91.99(9)
V/Å^3	1 861.5
Space group	$P2_1/n$
Z	4
D_c/g cm^{-3}	1.366
F(000)	808
T/K	296
Data collection:	
Crystal size/mm	0.32 × 0.21 × 0.15
λ(Mo-K_α)/Å	0.710 73
μ/cm^{-1}	2.33
Data sphere/°	$3.0 < 2\theta < 48$
Scan mode	ω–2θ
Scan rate (°/min)	variable, 1.2–4.0
Miller Index range	*h* 0 to 9, *k* 0 to 6
	l –43 to 43
Unique reflections measured	2 923
Unique reflections used	
$[I_o > \sigma(I)]$	2 275
Check reflections	0 $\bar{1}$ 17, 1 $\bar{1}$ 20
Intensity variations	≤ 1.8% relative
Absorption correction	None

[a] By least squares refinement on diffractometer angles for 25 automatically centred reflections.

Table 3. Fractional atomic co-ordinates for (**11**).

Atom	*x*/*a*	*y*/*b*	*z*/*c*
Cl	0.269 7(2)	0.335 9(3)	0.457 99(4)
O(1)	1.253 5(5)	–0.451 3(7)	0.719 79(10)
O(2)	1.028 6(4)	–0.293 9(7)	0.733 43(9)
O(3)	0.638 8(4)	–0.002 0(6)	0.662 16(8)
O(4)	0.602 3(4)	0.383 5(6)	0.639 96(9)
O(5)	1.067 0(4)	0.198 5(7)	0.622 61(9)
O(6)	0.491 7(4)	0.162 7(7)	0.577 79(9)
C(1)	0.918 5(5)	0.040 9(9)	0.668 65(10)
C(2)	1.029 6(6)	0.068 3(9)	0.700 72(10)
C(3)	1.185 1(6)	–0.055 8(10)	0.697 99(10)
C(4)	1.166 2(6)	–0.285 4(10)	0.717 46(10)
C(5)	0.947 7(6)	–0.069 1(9)	0.729 59(10)
C(6)	0.779 5(6)	–0.110 1(10)	0.716 56(10)
C(7)	0.765 1(5)	0.058 5(9)	0.685 45(10)
C(8)	0.634 2(6)	0.145 3(10)	0.631 57(10)
C(9)	0.786 7(6)	0.151 4(10)	0.613 66(10)
C(10)	0.922 9(5)	0.216 1(10)	0.638 75(10)
C(11)	1.092 2(7)	0.383 6(10)	0.598 56(10)
C(12)	0.469 9(6)	0.426 1(10)	0.660 14(10)
C(13)	0.507 2(6)	0.027 0(10)	0.609 12(10)
C(14)	0.392 9(6)	0.078 4(10)	0.551 59(10)
C(15)	0.307 9(7)	–0.128 8(10)	0.553 70(16)
C(16)	0.210 2(7)	–0.190 8(10)	0.525 66(16)
C(17)	0.196 7(7)	–0.050 7((10)	0.496 19(10)
C(18)	0.283 9(6)	0.155 1(10)	0.494 81(10)
C(19)	0.383 1(6)	0.222 5(10)	0.522 19(10)

Table 4. Bond lengths and angles of (**11**).

Cl–C(18)	1.740(4)	O(6)–C(13)	1.425(5)	C(8)–C(9)	1.510(5)
O(1)–C(4)	1.200(5)	O(6)–C(13)	1.380(5)	C(8)–C(13)	1.525(5)
O(2)–C(4)	1.360(5)	C(1)–C(2)	1.543(5)	C(9)–C(10)	1.540(5)
O(2)–C(5)	1.447(5)	C(1)–C(7)	1.499(5)	C(14)–C(15)	1.379(6)
O(3)–C(7)	1.429(4)	C(1)–C(10)	1.512(5)	C(14)–C(19)	1.388(6)
O(3)–C(8)	1.435(4)	C(2)–C(3)	1.522(6)	C(15)–C(16)	1.390(6)
O(4)–C(8)	1.404(5)	C(2)–C(5)	1.542(5)	C(16)–C(17)	1.378(7)
O(4)–C(12)	1.425(5)	C(3)–C(4)	1.500(6)	C(17)–C(18)	1.381(7)
O(5)–C(10)	1.416(4)	C(5)–C(6)	1.541(5)	C(18)–C(19)	1.386(6)
O(5)–C(11)	1.410(5)	C(6)–C(7)	1.524(5)		

C(4)–O(2)–C(5)	110.6(3)	O(3)–C(8)–O(4)	111.1(3)
C(7)–O(3)–C(8)	111.9(3)	O(3)–C(8)–C(9)	112.7(3)
C(8)–O(4)–C(12)	116.9(3)	O(3)–C(8)–C(13)	102.2(3)
C(10)–O(5)–C(11)	113.2(3)	O(4)–C(8)–C(9)	105.4(3)
C(13)–O(6)–C(14)	118.0(3)	O(4)–C(8)–C(13)	113.6(3)
C(2)–C(1)–C(7)	100.8(3)	C(9)–C(8)–C(13)	112.2(3)
C(2)–C(1)–C(10)	120.6(3)	C(8)–C(9)–C(10)	112.6(3)
C(7)–C(1)–C(10)	109.3(3)	O(5)–C(10)–C(1)	109.4(3)
C(1)–C(2)–C(3)	115.4(3)	O(5)–C(10)–C(9)	112.2(3)
C(1)–C(2)–C(5)	103.5(3)	C(1)–C(10)–C(9)	106.4(3)
C(3)–C(2)–C(5)	104.5(3)	O(6)–C(13)–C(8)	106.8(3)
C(2)–C(3)–C(4)	104.2(3)	O(6)–C(14)–C(15)	124.3(4)
O(1)–C(4)–O(2)	119.9(4)	O(6)–C(14)–C(19)	114.3(4)
O(1)–C(4)–C(3)	128.5(4)	C(15)–C(14)–C(19)	121.4(4)
O(2)–C(4)–C(3)	111.5(4)	C(14)–C(15)–C(16)	118.5(4)
O(2)–C(5)–C(2)	106.0(3)	C(15)–C(16)–C(17)	121.7(5)
O(2)–C(5)–C(6)	110.6(3)	C(16)–C(17)–C(18)	118.4(4)
C(2)–C(5)–C(6)	107.1(3)	Cl–C(18)–C(17)	119.6(3)
C(5)–C(6)–C(7)	102.2(3)	Cl–C(18)–C(19)	118.7(4)
O(3)–C(7)–C(1)	112.7(3)	C(17)–C(18)–C(19)	121.6(4)
O(3)–C(7)–C(6)	112.5(3)	C(14)–C(19)–C(18)	118.4(4)
C(1)–C(7)–C(6)	104.2(3)		

(434 mg, 45%); ν_{max}($CHCl_3$) 3 440–3 200 (OH), 1 765 (γ-lactone), 1 720 (CO), 1 600, 1 585sh, and 1 485 cm^{-1} (Ph); λ_{max}(MeOH) 275 (ε 1 606 dm^3 mol^{-1} cm^{-1}) and 282 nm (1 445); δ_H 3.31 (3 H, s, OMe), 3.89 [1.8 H, m, CH_2–O (**15**)], 4.57 [0.2 H, s, CH_2–O (**14**)], 4.85 (1 H, m, CH–O lactone), and 6.62–7.37 (4 H, m, C_6H_4Cl); *m/z* (CI) 369 (M^+ + 1, 10%), 351 (45, $M^+ - H_2O + 1$), 317 (35, $M^+ - H_2O - CH_3OH - 1$), 141 (50, $CH_2C_6H_4Cl$), and 128 (100); *m/z* (EI) 368 (M^+, 15%), 351 (5, $M^+ - H_2O + 1$), 336 (5, $M^+ - CH_3OH$), 227 (20, $M^+ - CH_2OC_6H_4Cl$), 209 (15, 227 – H_2O), 195 (40, 227 – CH_3OH), 177 (55, 195 – H_2O), 141 (50, $CH_2OC_6H_4Cl$), and 111 (100).

(1SR,2RS,6SR,8RS)-10-*Hydroxy*-12-*methoxy*-10-*phenoxymethyl*-5,9-*dioxatricyclo*[6.4.0.$0^{2,6}$]*dodecan*-4-*one* (**17**/**16**).—The acetal (**13**) (1.0 g, 2.9 mmol) was dissolved in acetone (20 ml), containing toluene-*p*-sulphonic acid (0.99 g, 5.8 mmol). The solution was kept for 3 days at room temperature. Work-up and purification of the crude product by methods analogous to those for compound (**15**/**14**) gave the oily hemiacetal (**17**/**16**) (489 mg, 51%); ν_{max}(KBr) 3 650–3 160 (OH), 1 760br (CO), 1 605, 1 590sh, and 1 505 cm^{-1} (Ph); λ_{max}(MeOH) 271 (ε 1 355 dm^3 mol^{-1} cm^{-1}) and 277 nm (1 160); δ_H 3.32 (3 H, s, OMe), 3.92 [1.8 H, m, CH_2–O (**17**)], 4.56 [0.2 H, s, CH_2–O (**16**)], 4.86 (1 H, m, CH–O lactone), 6.75–7.50 (5 H, m, Ph); *m/z* (CI) 335 (M^+ + 1, 30%), 317 (20, $M^+ - H_2O + 1$), 285 (25, $M^+ - H_2O - CH_3OH + 1$), and 243 (100).

X-Ray Structure Determination of Compound (**11**).—All X-ray measurements were made on an Enraf–Nonius CAD-4 diffractometer with monochromated Mo-K_α radiation. The experimental details for the intensity data collection are given in Table 2. All structural calculations were performed with a PDP 11/34 minicomputer using the Enraf–Nonius SDP program package with local modifications. The scattering factors for both non-hydrogen and hydrogen atoms were taken from ref. 11. The structure was solved by direct methods and refined by full-matrix least squares procedures to $R = \Sigma[(F_o) - (F_c)]/\Sigma(F_o) = 0.063$ using unit weights. Hydrogen atoms were located by a difference electron-density map, but their parameters were not refined. The final atomic co-ordinates are given in Table 3. Bond lengths and angles are listed in Table 4. Listings of thermal parameters and hydrogen atom parameters have been deposited at the Cambridge Crystallographic Data Centre.*

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* See Instructions for Authors, *J. Chem. Soc., Perkin Trans. 1*, 1990, Issue 1.

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