Tetrahedron Vol. 40, No 15, pp 2893 to 2899, 1984
Printed in the U.S.A.

0040-4020/84 $3.00 + .00
Pergamon Press Ltd

SYNTHESIS OF (1,5-CIS-5,6-TRANS-6,7-TRANS)-2-OXA-3-METHOXY-6-ETHOXYCARBONYL-7-BENZOYL OXY BICYCLO /3.3.0/ OCTANE : AN USEFUL SYNTHON IN THE PROSTAGLANDINS FIELD.

Alessandro Bongini[a], Gianfranco Cainelli[a], Daria Giacomini[a], Giorgio Martelli[b], Mauro Panunzio[a], Giuseppe Spunta[b].

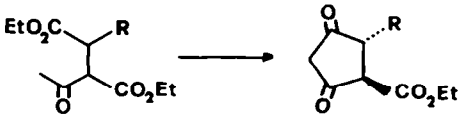
a) Istituto Chimico "G.Ciamician", Università and C.S.F.M.-C.N.R. 40126 Bologna Italy

b) Istituto dei Composti del Carbonio Contenenti Eteroatomi. C.N.R., Ozzano Emilia Italy.

Abstract: The target molecule (11), a precursor of PG, has been prepared by a novel fully stereoselective methodology "via" cyclopentandione (2), starting from ethyl acetoacetate and ethyl-2-bromo-pentenoate.

The cyclopentane moiety is contained in several important naturally occurring compounds such as steroids, rethrolones, prostanoids etc. and simple routes to this 5-ring system are therefore always in demand.[1,2]

Of special synthetic interest, in our opinion, is the base induced cyclization of γ-keto-esters which leads directly to cyclopentanones suitably functionalized for further elaboration into prostanoids, cis-jasmone[3], etc.



This synthesis appears to be of general applicability because the choice of the side chain is quite optional. This simple and direct approach has however received only scant attention until now owing to the lack of reliable chemoselective methods of discriminating between the two ring-carbonyls.[4] We wish to report here a simple and efficient solution of this problem which allows a novel entrance to prostaglandins, a group of hormones which have been and still are the object of numerous synthetic studies.[5] In this work we describe an efficient fully stereoselective synthesis of the intermediate (11) (SCHEME 1) which can be converted in few steps to the naturally occurring prostaglandins. It is worthy of mention that, since the intermediate (5) may be easily resolved,[6] our sequence allows a chiral synthesis of PG_2 starting from inexpensive and ready available starting materials.

Alkylation of ethyl acetoacetate with ethyl-2-bromo-4-pentenoate[7] in DMF and K_2CO_3[8] afforded the acyclic precursor (1) in 50 %

yield as a mixture of diastereoisomers. Treatment of (1) with 3 equivalents of LDA in THF at room temperature for 3 hours, followed by quenching at 0°C with aqueous HCl led to the expected cyclopentandione (2) in 98 % yield as a single isomer. We have assigned to it the structure depicted above on the basis of its spectroscopic properties[9] and on the known equilibration of the side chains to the trans configuration under equilibrating conditions in prostaglandin precursors bearing activating groups directly linked to the cyclopentane ring[10]. Conversion of (2) to the bis-acetals derivative (3) was effected in 70 % yield by treatment of (2) in a Dean-Stark apparatus with ethylene glycol and catalytic amounts of p-toluenesulfonic acid (PTSA) in boiling benzene. Then exposure of (3) to sulfuric acid-silica gel in methylene chloride at room temperature for 5 hours[11] led exclusively to the monoacetal (4) in quantitative yield. The remarkable difference in the rate of hydrolysis shown by the two dioxolane rings, may be ascribed to the electron withdrawing effect of the ester group which reduces the reactivity of the dioxolane ring in α-position to it. The structure of (4) has been determined by its spectroscopic properties and by the lack of UV absorption under basic conditions which excluded the presence of a carbonyl group in α-position to the ester group. After a survey of several reducing agents known to produce selectively the 9- α -alcohol (prostaglandin numbering) in similar compounds, it was gratifying for us to find that treatment of (4) with K-Selectride[12] in THF at -78 °C for 3 hours under rigorously controlled conditions, gave the desidered 9-α-hydroxy acetal (5) with total stereoselectivity in 70 % yield. The purity of this and the following compounds was checked by ^{13}C NMR and their configuration was assigned comparing the values reported in Table 1 with those of compounds having a known configuration[3,13]. Finally protracted treatment (30 h) of the alcohol (5) with sulfuric acid-silica gel in methylene chloride at room temperature furnished quantitatively the expected hydroxy ketone (6) in 94% yield (SCHEME 1). Protection of the hydroxyl group of (6) under mild conditions with 3,4-dihydro-2H-pyran in methylene chloride in the presence of pyridinium p-toluenesulfonate[14] - to give (7), followed by reduction of the C-11 carbonyl group with $NaBH_4$ in ethanol, afforded the 11- α -alcohol (8) in 93 % overall yield starting from (7). Analysis of the ^{13}C NMR spectrum showed that (8a), obtained from (8) after remotion of the pyranyl group, was a single product[15] (TABLE 1). The completion of the synthesis of target compound proved straightway. Esterification of (8) with benzoyl chloride in pyridine in the presence of dimethylaminopyridine (DMAP)[16], followed by ozonolysis of the resulting benzoate (9) in methylene chloride, reductive working up with dimethylsulfide and finally treatment of the crude aldehyde (10) with methanol in the presence of BF_3 etherate afforded (11) in 70 % yield starting from (9).

EXPERIMENTAL SECTION

Melting point are uncorrected. Infrared spectra (IR) were recorded as film on a Perkin Elmer 710 B spectrometer and the frequencies are given in reciprocal centimeters. ^1H NMR spectra and ^{13}C NMR spectra were determined in $CDCl_3$ or C_6D_6 solutions on Varian EM 390 and Varian FT 80 respectively, and the chemical shifts

are expressed as δ value in parts per million from internal standard (TMS). Mass spectra were taken on a Varian Mat 111 instrument (70 eV). U.V. spectra were recorded on a 402 UVS Perkin Elmer instrument. Thin layer chromatography (TLC) was performed on silica gel sheets (1B2F Baker) and column chromatography on Chromatospac Prep. 10 (Jobin-Ivon instrument) using silica gel (H 60 Merk).

Optical rotation were measured on a Perkin-Elmer Model 241. Tetrahydrofuran (THF) was obtained anhydrous and oxygen free by distillation over sodium benzophenone ketyl under argon. Methylene Chloride was distilled over P_2O_5. Diisopropylamine was refluxed over molecular sieves (Type 4 A, Fluka) and distilled at atmospheric pressure.

3,4-di-(ethoxycarbonyl)-hept-6-en-2-one.(1)

Ethyl acetoacetate (14.26 ml, 0.11 mol) was added to a suspension of powdered and dried (overnight, 100°C) K_2CO_3 (15,18 g, 0.11 mol) in DMF (50 ml).The suspension was stirred at room temperature for 15 min and then ethyl-2-bromo-4-pentenoate (23.25 g, 0.11 mol) was added in one portion and the mixture stirred overnight. The reaction mixture was quenched with dilute (1/1) HCl and extracted with ether. The organic layers were washed several times with dilute HCl in order to eliminate DMF. After drying over Na_2SO_4, the solvent was removed with a Rotavapor and the oil residue distilled (b.p.$_1$ 104-110°C) to give (1) (14.13 g, 50%).

Found C, 60.81; H, 7.88; $C_{13}H_{20}O_5$ (MW 256.28) requires C, 60.92; H, 7.87%.

I.R. (neat) 1735 (sb)

^{1}H NMR ($CDCl_3$) 6.1-5.1 (m 3 H); 4 (2 q 4 H); 3.85 (d J=2.5 Hz 1 H); 3.5 (m 1 H); 2.4 (m 2 H); 2.1 (s 3 H); 1.05 (2 t 6 H); m/z 256 (M^+)

4,5-trans-4-ethoxycarbonyl-5-(2-propen-1-yl)--1,3-cyclopentan-dione.(2)

n-Butyllithium (78 ml, 0.117 mol; 15% solution in hexane) was added at 0°C with stirring under argon to a solution of diisopropylamine (16.37 ml, 0.117 mol), in THF (100 ml). After 30 min., the LDA solution is withdrawn and added dropwise with a syringe to a solution of (1) (10 g, 0.039 mol) in THF (150 mL) maintained at 0°C. The reaction mixture was allowed to reach room temperature and stirred for 1 h. After cooling,the reaction mixture was diluted with 300 mL of water and extracted with ether. The ethereal solution was washed with water and the pooled aqueous extracts were acidified with dilute HCl and extracted with three 100 mL portions of ether. The combined organic extracts were dried over anhydrous Na_2SO_4 and distilled under reduced pressure. The target compound was isolated as a clear pale yellow oil (7.98 g, 97%).

Found C, 62.92; H, 6.72; $C_{11}H_{14}O_4$ (MW 210.22) requires C, 62.85; H, 6.71%

IR (neat) 3000 (b); 1740 (s); 1590 (s);

^{1}H NMR ($CDCl_3$) 9.1 (bs 1 H OH); 6.1-5.1 (m 3 H); 5.05 (m 1 H); 4.25 (q 2 H); 3.4 (d J=2.5 Hz 1 H); 3.2 (m 1 H); 2.5 (m 2 H); 1.3 (t 3 H).

4,5-trans-4-ethoxycarbonyl-5-(2-propen-1-yl)--cyclopentan-1,3-dione bis ethylene acetal (3).

A mixture of (2) (0.330 g; 0;0016 mol) benzene (20 ml) and p-toluensulfonic acid (catalytic amount) was treated with ethylene glycol (0.7 ml, 0.0125 mol) and refluxed in a Dean-Stark trap. Extraction with ether and washing with $NaHCO_3$ (5% aqueous solution) and then water gave (4) (0.334 g; 70%)with a good degree of purity.

Found C, 60.5; H, 7.45; $C_{15}H_{22}O_6$ (MW 298.33) requires C, 60.39; H, 7.43%

I.R. (neat) 1735 (s)

^{1}H NMR ($CDCl_3$) 6.1-4.8 (m 3 H); 4.1 (q 2 H); 3.95 (m 8 H); 2.85 (sm 2 H); 2.2 (bm 4 H); 1.03 (t 3 H).

m/z 298 (M^+); 253 (M^+-OEt)

4,5-trans-4-ethoxycarbonyl-5-(2-propen-1-yl)-cyclopentan-1,3-dione-3-ethylene acetal.(4)

A solution of sulfuric acid (0.2 ml of 50% aqueous solution) was added with continuous magnetic stirring to a suspension of silica gel (2.73 g;Silica Gel 60, MercK, for column chromatography, 70-230 Mesh) in methylene chloride (10 ml). After 2-3 min, the water phase disappeared due to adsorption on the silica gel surface. The acetal (3) (0.910 g; 0.003 mol) was added and the stirring is continued at room temperature for 5. h. The solid phase was separated by suction filtration on a sintered glass funnel and the solid is washed several times with methylene chloride. The combined solutions were washed with sodium hydrogen carbonate, brine and water. Evaporation of the solvent under reduced pressure gave pure (4) as a solid (m.p. 47°C) in quantitative yield.

Found C, 61.29; H, 7.12; $C_{13}H_{18}O_5$ (MW 254.28) requires C, 61.41; H, 7.14%.

I.R. (Nujol) 1740 (sb).

^{1}H NMR (C_6D_6) 6.1-4.8 (m 3 H); 4.1 (q 2 H); 3.65 (m 4 H); 3.2 (sm 2 H); 2.8-2.45 (q_{AB} J=18 Hz 2 H); 2.4 (m 2 H); 1.05 (t 3 H).

m/z 254 (M^+); 209 (M^+-OEt)

1,2-cis-2,3-trans-2-(2-propen-1-yl)-3-ethoxy - carbonyl-cyclopentan-1-ol-4-one ethylene acetal.(5)

A solution of K-Selectride (Aldrich, 0.5 M solution in THF) (10 ml, 0.005 mol) was slowly added to a stirred solution of ketone (4) (0.860 g; 0.0034 mol) in THF (30 ml) under argon at -78 °C. After 4 h the temperature was allowed to rise to 0 °C and the excess of reagent was hydrolyzed by addition of water. 3 M aqueous sodium hydroxide (1 ml; 3 M solution) was then added followed by H_2O_2 (1 ml; 36% solution) and the mixture was stirred at 0 °C for 1 h. Ethereal work-up followed by flash chromatography gave the alcohol (5) as colourless oil (0.614 g; 70%)

Found C, 61.01; H, 7.88; $C_{13}H_{20}O_5$ (MW 256.29) requires C, 60.92; H, 7.87%.

I.R. (film) 3500 (b) 1735 (s) cm^{-1}

^{1}H NMR (C_6D_6) 6.1-4.8 (m 3 H); 4.2 (bs 1 H); 4.1 (q 2 H); 3.65 (m 4 H); 3.2-2 (complex pattern 7 H); 1.05 (t 3 H).

m/z 256 (M^+); 238 (M^+-H_2O)

1,2-cis-2,3-trans-2-(2-propen-1-yl)-3-ethoxy-carbonyl-cyclopentan-1-ol-4-one (6).

Protracted treatment (30 hours) of (5) (0.230 g; 0.0009 mol)in methylene chloride with sulfuric acid-silica gel system (0.690 g. SiO_2; 3 drops of H_2SO_4 50% solution; 5 ml CH_2Cl_2) following the previous reported (see 4) procedure, led to (6) (0.180 g; 94%)

Found C, 62.13; H, 7.61; $C_{11}H_{16}O_4$ (MW 212.24) requires C, 62.25; H, 7.6%

IR (film) 3500 (b) 1725 (s)

^{1}H NMR ($CDCl_3$) 6.2-4.9 (m 3 H); 4.55 (bm 1 H); 4.25 (q 2 H); 3.3-2.2 (complex pattern 7 H); 1.2 (t 3 H).

m/z 212 (M^+); 194 (M^+-H_2O)

1,2-cis-2,3-trans-2-(2-propen-1-yl)-3-ethoxy-carbonyl-cyclopentan-1-ol-4-one-1-THP (7).

A solution of (6) (0.180 g; 0.00085 mol) and dihydropyran (0.155 ml, 0.0017 mol) in dry methylene chloride (15 ml) containing PPTS (Pyridinium p-toluene-sulfonate) (0.02 gr) was stirred for 4 h at room temperature. The solution was then diluted with ether and washed once with

brine to remove the catalyst. Evaporation of the solvent gave an essentially quantitative yield of (8) (0.240 gr).
Found C, 64.96; H, 8.15; $C_{16}H_{24}O_5$ (MW 296.36)requires C, 64.84; H, 8.16%
I.R. (film) 1755 (s) 1730 (s) 1020 (s)

1,2-cis-2,3-trans-3,4-trans-2-(2-propen-1-yl)-3-ethoxycarbonyl-cyclopentan-1,4-diol-1-THP.(8)

A solution of (7) (0.620 g; 0.0021 mol) in ethanol (10 ml) was added dropwise at 0 °C to a suspension containing ethanol (20 ml), water (5 ml), and $NaBH_4$ (0.238 gr, 0.0063 mol). After a further 1 h at 0 °C sodium chloride was added until the solution was saturated and the mixture then extracted with ether (4 X 30 ml). The combined extracts were dried ($MgSO_4$) and evaporated to give crude (8) as an oil. This material was purified by column chromatography on silica gel using hexane-ethyl acetate 7/3 as eluting solvent giving as pale yellow oil (8) (0.582 g; 93%).
Found C, 64.34; H, 8.8; $C_{16}H_{26}O_5$ (MW 298.40) requires C, 64.41; H, 8.78%.
I.R. 3500 (b) 1730 (s) 1020

1,2-cis-2,3-trans-3,4-trans-2-(2-propen-1-yl)-3-ethoxycarbonyl-cyclopentan-4-benzoyloxy-1-ol-1-THP (9).

A mixture of (8) (0.620 g; 0.002 mol), triethylamine (0.350 ml; 0.0025 mol) and DMAP (dimethylaminopyridine) (0.150 g; 0.0012 mol) were dissolved in CH_2Cl_2 (30 ml) and cooled to 0°C. Benzoyl chloride (0.300 ml; 0.0026 mol) in CH_2Cl_2 (10 ml) was added dropwise with stirring to the reaction solution over 20 min and the mixture was then stirred for an additional 1.5 hours at 0°C. The solution was partitioned between ethyl acetate and 1 N HCl, the organic phase was washed with 5% $NaHCO_3$ solution, dried over Na_2SO_4 and evaporated in vacuo to give (9) as colourless oil (0.687 g; 85%).
Found C, 68.51; H, 7.5; $C_{23}H_{30}O_6$ (MW 402.48) requires C, 68.64; H, 7.51%

1,5-cis-5,6-trans-6,7-trans-2-oxa-3-methoxy-6-ethoxycarbonyl-7-bezoyloxy-bicyclo/3.3.0/-octane (11).

A solution of (9) (0.300g; 0.00074 mol) in methylene chloride (50 ml) was cooled to -78°C. Ozone was passed through the solution at the rate of 0.5 l/min. until the solution become deep blue. While still at -78°C the system was flushed with nitrogen until colourless solution, the temperature was then allowed to rise to 0°C and dimethylsulfide (1.5 ml) was added. The resulting solution was stirred at 0°C for 1 hour, then at room temperature for an additional hour. The solvent was removed in vacuo and the residue treated with BF_3Et_2O (0.300 ml) in anhydrous methanol (20 ml) for 2 hours at 50°C. The solution was partitioned between ether and 5% $NaHCO_3$ solution. The organic phase was washed with brine, dried over Na_2SO_4 and evaporated in vacuo. Flash chromatography (hexane/ethyl acetate 7/3) of the residue gave the target compound (11) as a pale yellow oil. (0.206 g; 83%)
Found C, 64.59; H, 6.64; $C_{18}H_{22}O_6$ (MW 334.36) requires C, 64.66; H, 6.63.
IR (neat) 1740, 1730. ^1H NMR (C_6D_6) (major isomer) 8.1-7.2 (m 5 H Ar); 5.7 (m 1 H C_3H) 4.95 (m 1 H C_7H); 4.45 (m 1 H C_1H); 3.95 (q 2 H); 3.15 (s 3 H); 3.6-2.8 (m 2 H C_5H and C_6H); 2.3-1.8 (m 4 H C_8H and C_4H); 0.95 (t 3 H).
^{13}C NMR (C_6D_6) (major isomer) 172.4 (Et$\underline{C}$=O); 165.6 (Ph-$\underline{C}$=O); 132.9, 130.8, 129.9, 128.5 ($\underline{C}$ Ar); 106.4 ($\underline{C}_3$); 81.9 ($\underline{C}_7$); 79.1 ($\underline{C}_1$); 60.8 (O$\underline{C}H_2$); 56.6 (O$\underline{C}H_3$); 54.6 ($\underline{C}_6$); 45.2 ($\underline{C}_5$); 39.9 ($\underline{C}_8$); 38.1 ($\underline{C}_4$); 14.0 ($CH_2\underline{C}H_3$) m/z 334 (M^+); 212 (M^+-Ph-COOH)

SCHEME 1

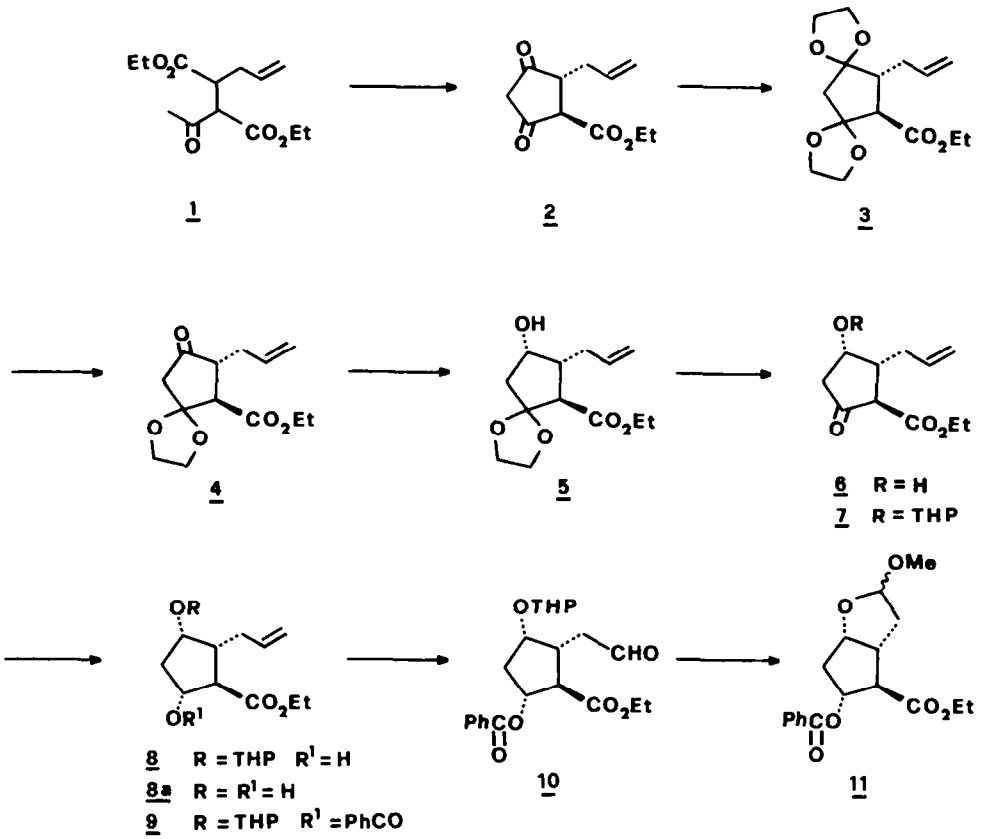

EtO2C
CO2Et
O
1
2
3
4
5
OH
OR
6 R = H
7 R = THP
OR1
8 R = THP R1 = H
8a R = R1 = H
9 R = THP R1 = PhCO
OTHP
CHO
PhCO
10
OMe
11

TABLE 1 ^{13}C NMR Chemical Shifts and Assignments for Cyclopentanoid derivatives.[a]

C(N)[b]	3	4	5	6	8a
C (8)	47.8	51.9	46.8	46.6	49.1
C (9)	113.3	211.0	71.0	68.7	74.0
C (10)	48.3	48.5	47.1	48.9	43.6
C (11)	113.3	112.1	117.5	210.5	76.7
C (12)	58.7	54.9	57.8	57.9	58.1
COOEt	170.3	170.3	171.2	170.1	175.2

[a]Chemical shifts in ppm downfield from Me_4Si. Spectra were taken in C_6D_6 at 20.00 MHz in the Fourier mode on using a VARIAN FT80 spectrometer. [b]Prostaglandins numbering.

Ackowledgement: This research was assisted financially by a grant from the National Research Council (Progetto Finalizzato Chimica Fine e Secondaria del C.N.R.).

References and notes

1) R.A.Ellison,Synthesis,397,(1973)

2) T.L.Ho,Synth.Commun.,4,265,(1974)

3) G.Cainelli,M.Panunzio,G.Martelli, G.Spunta.Submitted to Gazz.Chim.Ital.

4) P.F.Beal,J.C.Babcock,F.H.Lincoln,J.Am. Chem.Soc.,88,3131,(1966). O.G.Plantema, H.de Koning,H.O.Huisman,Recl.Trav.Chim Pays-Bas,102,268,(1983);96,129,(1977).

5) J.S.Bindra and R.Bindra,Prostaglandin Syntheses,Academic Press,NewYork,(1977); S.M.Roberts and R.F.Newton Prostaglandins and Tromboxanes,Butterworths, London,(1982); S.M.Roberts and F. Scheinmann,New Synthetic Routes to Prostaglandins and Thromboxanes, Academic Press,London,(1982)

6) Resolution of(3) has been carried out on the corresponding acid trough the formation of the (+) efedrine salt ($[\alpha]_D$ = 22° c = 1.01 Ethylacetate).

7) D.D.Phillips,J.Am.Chem.Soc.,76,5385,(1954)

8) D.A.White,Synth.Commun.,7,559,(1977)

9) The J_{8-11}= 3 Hz is in agreement with a trans configuration of the two side chains: H.B.Kagan,Stereochemistry,George Thieme Verlag;Stuttgart,(1977),Vol.1 pag.89

10) M.Miyano,M.A.Stealey,J.Org.Chem.,40, 1748, (1975); N.Finch,L.Della Vecchia, J.J.Fitt, R.Stephani,I.Vlattas,J.Org. Chem. 38,4412,(1973)

11)F.Huet,A.Lechevallier,M.Pellet,J.M.Conia, Synthesis,63,(1978)

12)H.C.Brown,S.Krishnamurthy,Tetrahedron, 35,567, (1979); E.J.Corey,R.K.Varma, J.Am.Chem.Soc., 93,7319,(1971)

13)G.Cainelli,A.Bongini,M.Panunzio,D.Giacomini, G.Martelli,G.Spunta, Unpublished results

14)N.Miyashita,A.Yoshikoshi,P.A.Grieco, J.Org.Chem. 42,3772,(1977)

15)The introduction of the pyranyl group appears to be a critical factor for the stereoselective reduction of the C_{11}-carbonyl, since the direct reduction of the unprotected 9-α-hydroxy ketone (8) led to a mixture of isomeric alcohols[10]

16)G.Hofle,WSteglich,H.Vorbruggen,Angew. Chem.Int.Ed.Engl.,17,569,(1978).