Stereocontrolled Synthesis of a Prostanoid Synthon by Oxidative Cleavage of Substituted Norbornene Derivatives

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Summary Novel cyclopentanoid precursors (±)-2α-cyanomethyl-1α,4α-diacetoxy-3β-methoxymethylcyclopentane (**21**) and (±)-2α-cyanomethyl-1α,4α-diacetoxy-3β-trityloxymethylcyclopentane (**25**) for the prostanoids have been prepared by oxidative cleavage of substituted norbornene diethers [(**4**) and (**6**)], and their utility demonstrated by conversion into the known prostaglandin intermediates (**27**) and (**28**).

THE high and widespread biological activity of the prostanoids[1] has encouraged the development of synthetic methods[2] for the preparation of these natural hormones. We report the synthesis of a key cyclopentanoid precursor, 2α-cyanomethyl-1α,4α-diacetoxy-3β-methoxymethylcyclopentane (**21**) based on the oxidative cleavage of an unsymmetrically substituted norbornene derivative (**4**). During this investigation an intramolecular rearrangement of an acetate group[3] within a *cis*-1,3-diol system was encountered which offered a means of differentiating, at a late stage in the synthesis, between the primary alcoholic functions on the α and β faces of the cyclopentane ring; it was thus possible to use the readily accessible symmetrically protected norbornene diether (**6**) as the starting material for the second part of this investigation.

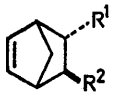
5α-Carboxymethyl-6β-dimethoxymethylbicyclo[2,2,1]-hept-2-ene (**1**) was obtained from cyclopentadiene and β-formylacrylic acid pseudo ester.[4] Reduction ($LiAlH_4$) of (**1**) gave the *endo*-alcohol (**2**) (61%) in an isomerically homogeneous form. Benzylation ($PhCH_2Br$, NaH) of the alcohol (**2**) gave the benzyl ether (**3**) b.p. 155—158°/0·05 mm (98%). Hydrolysis (40% aqueous dioxan, H_2SO_4) of (**3**), followed by reduction ($LiAlH_4$) and methylation (CH_3I, NaH) gave after distillation (**4**) b.p. 112—116°/0·05 mm [83% from (**3**)]. This diether (**4**) is suitably protected for oxidative cleavage which provides the 9,11 (prostaglandin numbering) *cis*-diol system of the prostanoids.

The norbornene benzyl methyl ether (**4**) could be oxidised on a small scale (<0·1M) using a molar amount of sodium periodate and a catalytic amount of osmium tetroxide in aqueous dioxan. However, reductive ozonolysis[5] was more convenient in the larger scale experiments. The crude dialdehyde oxidation product (**7**) was treated with an excess of methyl-lithium in ether and gave a mixture of diols (**8**), which was directly oxidised (CrO_3) to the diketone (**9**) [b.p. 175—180°/0·1 mm, M^+ 318, τ ($CDCl_3$) 7·83 (s) and 7·87 (s) $-COCH_3$]. Baeyer–Villiger oxidation of this ketone gave the diacetate (**10**) [τ ($CDCl_3$) 8·02 (s) and 8·08 (s) $-OCOCH_3$] [28% overall from (**4**)].

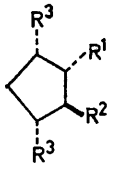
The benzyl group was removed from the diester (**10**) (5%Pd–C, EtOH) (97%) under rigorously controlled neutral conditions. The presence of acid or base catalysed the easy rearrangement of the secondary acetate (**15**) to the primary acetate (**18**) and an equilibrium mixture (40:60 by n.m.r.) was obtained. Tosylation of the primary alcohol (**15**) followed by displacement of the tosyl group (NaCN) gave the nitrile (**21**) [$M + 1$ 270·1363, ν (neat) 2250 cm^{-1}; τ ($CDCl_3$) 7·94 (s) and 8·02 (s), $OCOCH_3$] [25% overall from (**10**)]; this comparatively low conversion efficiency is largely

accounted for by the slow competitive rearrangement of the acetate group of (**15**) into (**18**) during the tosylation stage.

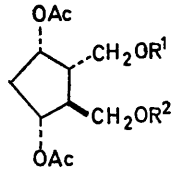
The acetate rearrangement was used to advantage in the following alternative synthesis of (**25**). 5α,6β-Bis(benzyloxymethyl)bicyclo[2,2,1]hept-2-ene (**6**) [b.p. 148—150°/0·25 mm] (99%) was prepared by the direct benzylation of the known diol (**5**).[6] The dibenzyl ether (**6**) was conveniently cleaved by reductive ozonolysis to the dialdehyde (**11**) [ν (neat) 2720 and 1725 cm^{-1}]. The crude dialdehyde (**11**) was treated immediately with an excess of methyl-lithium (from methyl bromide) in ether to yield the diol mixture (**12**), which was oxidised (CrO_3) to the diketone (**13**)



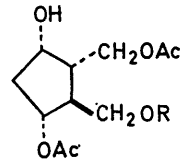
(1) R^1=CO_2Me, R^2=$CH(OMe)_2$
(2) R^1=CH_2OH, R^2=$CH(OMe)_2$
(3) R^1=CH_2OCH_2Ph, R^2=$CH(OMe)_2$
(4) R^1=CH_2OCH_2Ph, R^2=CH_2OMe
(5) R^1=R^2=CH_2OH
(6) R^1=R^2=CH_2OCH_2Ph



(7) R^1=CH_2OCH_2Ph, R^2=CH_2OMe, R^3=CHO
(8) R^1=CH_2OCH_2Ph, R^2=CH_2OMe, R^3=CH(OH)Me
(9) R^1=CH_2OCH_2Ph, R^2=CH_2OMe, R^3=Ac
(10) R^1=CH_2OCH_2Ph, R^2=CH_2OMe R^3=OAc
(11) R^1=R^2=CH_2OCH_2Ph, R^3=CHO
(12) R^1=R^2=CH_2OCH_2Ph, R^3=CH(OH)Me
(13) R^1=R^2=CH_2OCH_2Ph, R^3=Ac
(14) R^1=R^2=CH_2OCH_2Ph, R^3=OAc



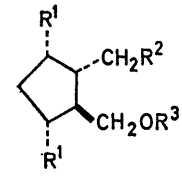
(15) R^1=H, R^2=Me
(16) R^1=R^2=H
(17) R^1=R^2=CPh_3



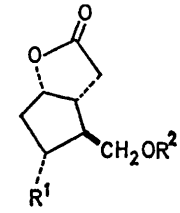
(18) R=Me
(19) R=H
(20) R=CPh_3

[τ ($CDCl_3$) 7·90 (s) (6H), $-COCH_3$]. Baeyer–Villiger oxidation of the diketone gave the diacetate (**14**) [τ ($CDCl_3$) 8·05 (s) and 8·09 (s) $^-OCOCH_3$] [19% overall from (**6**)].

The benzyl groups were removed from (**14**) (5% Pd–C, EtOH) and (**16**) isomerised by refluxing in pyridine. The equilibrium mixture thus obtained in 90% overall yield, consisting of the primary acetate (**19**) (60%) and the secondary acetate (**16**) (40%) (n.m.r.), was treated with Ph_3CCl



(21) R^1=OAc, R^2=CN, R^3=Me
(22) R^1=OH, R^2=OH, R^3=CPh_3
(23) R^1=OH R^2=p-Me·$C_6H_4SO_2O$, R^3=CPh_3
(24) R^1=OAc, R^2=p-Me·$C_6H_4SO_2O$, R^3=CPh_3
(25) R^1=OAc, R^2=CN, R^3=CPh_3



(26) R^1=OH, R^2=Me
(27) R^1=OAc, R^2=Me
(28) R^1=OH, R^2=H

to give the bistrityloxy-derivative (**17**) m.p. 172—174°, and the diacetate (**20**) m.p. 52—54° [τ ($CDCl_3$) 8·06 (s) (6H) $OCOCH_3$] [44% from (**25**)].

Deacetylation (K_2CO_3) of (**20**) gave the triol (**22**) which was tosylated on the primary alcoholic function. The oily monotosylate (**23**) was acetylated and the tosyl group displaced (NaCN), yielding the key prostanoid intermediate (**25**) [ν (neat) 2250 cm^{-1}, n.m.r. τ ($CDCl_3$) 7·95 (s) and 8·04 (s) $-OCOCH_3$].

The utility of these nitrile intermediates [(**21**) and (**25**)] as prostaglandin synthons was demonstrated by their respective conversion into the lactone acetate (**27**)[7] and the lactone diol (**28**)[8] whose transformation to natural prostaglandins have previously been described. Alkaline hydrolysis (K_2CO_3, MeOH, 25°) of the ester functions in (**21**), followed by acid (conc. HCl, 100°) hydrolysis of the nitrile group gave directly the hydroxy-lactone (**26**) (98%) [ν (neat) 1770 cm^{-1}]. Acetylation gave the acetoxy-lactone (**27**) (96%). Detritylation (80% aqueous-HAc, 25°) of the equivalent nitrile (**25**) followed by deacetylation (K_2CO_3, MeOH, 25°) and acid hydrolysis (conc. HCl, 100°) of the nitrile function afforded directly the lactone diol (**28**) [60% from (**25**)]. These products were identical by t.l.c., and n.m.r. and i.r. spectroscopy with the authentic materials.

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