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# SYNTHESIS OF NEW STABLE ANALOGUES OF PROSTACYCLIN: (±)-6a-OXO-6,9-METHANO-15-HYDROXYPROSTA-5,13-DIENOIC ACIDS

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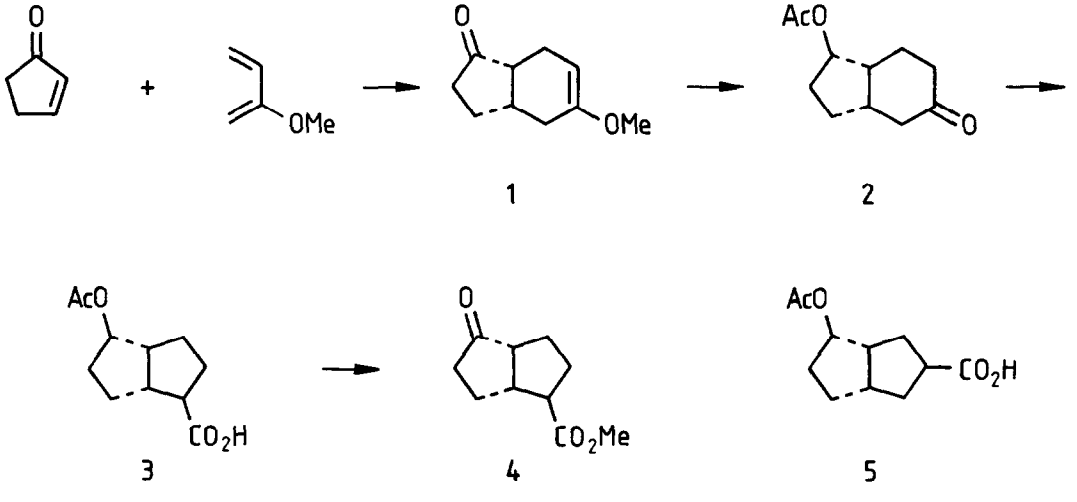
Abstract The synthesis is described of (±)-6a-oxo-6,9-methano-15-hydroxyprosta-5,13-dienoic acids as stable analogues of prostacyclin with blood platelet aggregation inhibiting activity.

Considerable effort has been devoted to the preparation of chemically stable analogues of prostacyclin.[1] We report here the synthesis of a new class of biologically active analogues in which the 6,9 ether linkage of 11-deoxyprostacyclin is replaced by a carbonyl group to give the stable enone (15).

Scheme 1

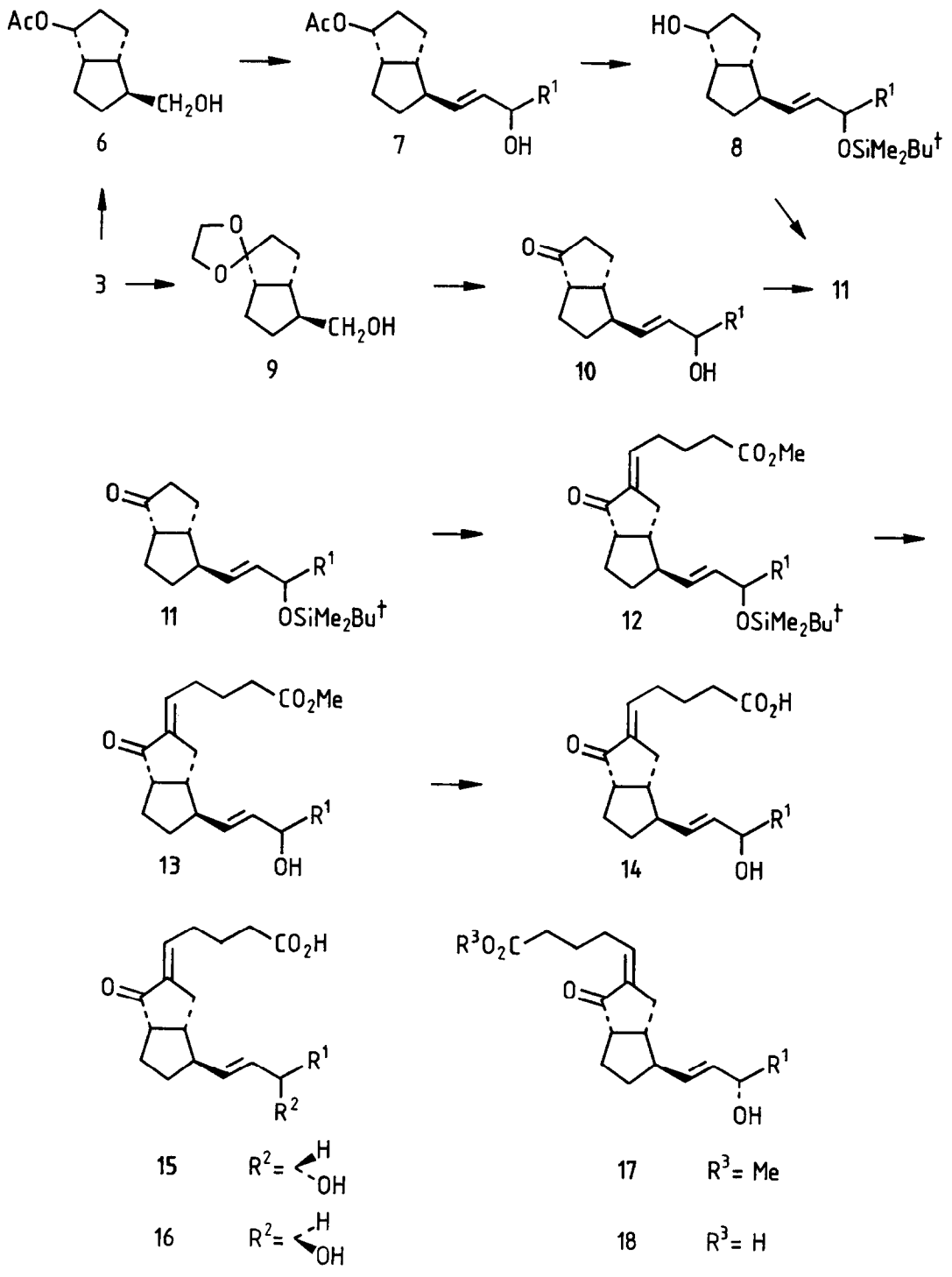


The synthesis commenced with the hydrindanone (1) prepared[2] by the addition of 2-methoxybutadiene[3] to 2-cyclopentenone in 27% yield. The observed regiospecificity of this reaction was in accord with our expectations based upon Frontier-orbital theory, and confirmed a reported conversion of (1) into cis-jasmone.[2] The latter report also concurred with our own observations that only the cis ring-fused hydrindanone is formed in contrast to the mixture of cis and trans ring-fused products encountered with the addition of other butadienes to 2-cyclopentenone.[4] Reduction (DIBAL, $Et_2O$, 0°C, 97% yield) of the carbonyl group of (1) followed by acetylation ($Ac_2O$, $C_5H_5N$, 95%) and subsequent hydrolysis (HCl, MeOH, 20°C, 5 min, 100%) of the enol ether function gave (2).

The key step in the synthesis was the oxidative ring contraction of (2) to the bicyclo[3,3,0]octanecarboxylic acid (3) employing thallic nitrate (1 eq) in acetic acid (0.5 hr, filter, reflux 0.5 hr, 45%). The direction of ring contraction is controlled by the preferred direction of enolisation of the carbonyl group, which is in turn determined by the nature of the ring junction.[5] That the acid thus obtained had the structure (3), rather than (5) was established by a full spectroscopic analysis. For this purpose (3) was converted to the methyl ester (HCl, MeOH, 72%) and then oxidised (PCC, $CH_2Cl_2$, r.t., 94%) to give (4) which was purified by preparative g.l.c. The relationship between the carbonyl and ester groups was established as follows. As expected the off-resonance decoupled $^{13}C$ nmr spectrum of (4) contained three doublets for tertiary carbons at 52.1, 45.4 and 50.3 ppm which could be assigned to C1, C5 and C6 respectively by comparison with predicted values.[6] Selective decoupling at individual proton resonance frequencies permitted identification of the chemical shifts of the attached protons as H1 2.7 (td, J = 9.5 x 2,5 Hz), H5 3.04 (tdd, J = 7.5 x 2, 9.5, 4.0 Hz) and 2.54 (q,7.5 Hz) ppm. Further confirmation of these assignments was provided by proton-proton decoupling experiments and successive exchange of H1 and H6 by deuterium when (4) was treated with sodium methoxide in deuteromethanol.

Two routes proved suitable for attachment of an ω-side chain to (3). In the first method, ($R^1$ = pentyl) reduction ($B_2H_6$, THF), of (3) gave the alcohol (6) in 67% yield, which was oxidised to the aldehyde, followed by Wittig-Horner elaboration and reduction [PCC/$CH_2Cl_2$; $(MeO)_2P(O)CHNaCOR^1$,/THF; "K-Selectride" (Aldrich), HMPTA, -70°C, 67%] to yield (7). Silylation, (95%),[7] and subsequent hydrolysis of the acetoxy group ($K_2CO_3$,MeOH,40°C, 90%) provided (8) which was oxidised to (11). In the second sequence, ($R^1$ = cyclohexyl), which has the merit that it permitted separation of the C15 epimers, the intermediate (4) was converted to the ethylene ketal, (100%), and then reduced with "L-Selectride" (100%), to give (9). The latter was then oxidised to the aldehyde (PCC,$CH_2Cl_2$, 100%) which was subjected to a Wittig-Horner reaction [$(MeO)_2P(O)CH_2COR^1$, NaH, THF,100%][8]. Reduction with "L-Selectride" (100%) gave the separable epimeric alcohols and the ketal was then hydrolysed (60% v/v AcOH/$H_2O$, 100%) to yield (10), which was silylated, (100%),[7] to provide (11).

Scheme 2


AcO
CH2OH
6
AcO
R1
OH
7
HO
R1
OSiMe2But
8
3
O
O
CH2OH
9
O
R1
OH
10
11
O
R1
OSiMe2But
11
CO2Me
O
R1
OSiMe2But
12
CO2Me
O
R1
OH
13
CO2H
O
R1
OH
14
CO2H
O
R1
R2
15
R2= H OH
16
R2= H OH
R3O2C
O
R1
OH
17
R3= Me
18
R3= H

The attachment of the α-side chain was effected by means of an aldol condensation (LBTMSA., THF, 1.2 eq., - 70°; $MeO_2C(CH_2)_3CHO$ 2.0 eq., -70°, 74%), followed by mesylation ($MeSO_2Cl$, 1.3 eq., $Et_3N$, 1.2 eq., r.t.) and elimination (D.B.U., 5 eq., benzene r.t., 60%) to give (12).[9] Successive hydrolysis of the silyl group of (12) ($AcOH:H_2O:THF$ 13:7:2, 40°, 81%) and saponification of the ester (LiOH, $MeOH/H_2O$ 3:1, 90%) yielded (14).[10] When the C15 epimers (prostaglandin numbering) of (10) were separated, elaboration as above of the more polar isomer (silica gel, EtOAc:Hexane 1:4) yielded the C15 -isomer (eg. 15 $R^1$ = cyclohexyl) whereas the less polar isomer gave (eg. 16 $R^1$ = cyclohexyl). The configurations of the epimers could be assigned on the basis of their t.l.c. polarities and comparison of pharmacological activities, by analogy to generally established behaviour-property relationships in prostaglandin chemistry.

Irradiation of (13) with a low pressure mercury lamp yielded a 1:1 mixture of the 5Z (17) and 5E (13) isomers which could be separated by preparative t.l.c. ($SiO_2$, EtOAc:Hexane 1:4).[11] The Z-isomer slowly isomerised back to the E-isomer on storage (40% over a period of 27 months at 0°). However, the corresponding Z-acid (18) isomerised back to the E-acid (14) fairly rapidly on standing presumably as a consequence of autocatalysis, since the isomerisation of the ester (17) is expedited by acid.

Preliminary pharmacological studies show that (15) is approximately 1000 times less active than prostacyclin sodium salt in inhibiting collagen induced aggregation of whole blood, but compares favourably with non-prostaglandin inhibitors of platelet aggregation.

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## REFERENCES

1. W. Bartmann and G. Beck, Angew. Chem., Int. Ed. Engl., 1982,24,751.
2. Hasegawi Perfumery Ltd., Jap. Kokai Pat 53,108,949 (1978).
3. Upjohn Co., Brit. Pat., 1,479,333 (1977).
4. F. Fringuelli, F. Pizzo, A. Taticchi, T.D.J. Halls and E. Wenkert, J.Org.Chem., 1982,47,5056.
5. A. Romeo and G. Ortar, Tetrahedron, 1972,28,5337.
6. J.K. Whitesell and R.S. Matthews, J. Org. Chem., 1977 42 3878.
7. E.J. Corey and A. Venkateswarlu, J. Am. Chem. Soc., 1972 94 6190.
8. May & Baker Ltd., Brit. Pat., 1,468,830 (1977).
9. Yields are quoted for $R^1$ = cyclohexyl. Similar yields were obtained for $R^1$ = pentyl.
10. All new compounds gave proton NMR spectra consistent with the assigned structures.
11. $^1H$ NMR. ($CDCl_3$). The resonance of the enone proton of the 5Z isomer (17) was typically upfield, δ = 5.9 - 6.1 (m, 1H) to that of the 5E isomer (13), δ = 6.5 - 6.6 (m, 1H).

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