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A Simple Synthesis of (+)-Isocarbacyclin *via* a Convergent Process

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A convergent and practical synthesis of (+)-isocarbacyclin has been accomplished, incorporating novel methods for linking α and ω appendages with a chiral bicyclo[3.3.0]octane nucleus.

The inherent hydrolytic lability of prostacyclin (PGI_2) (**1**), a potent vasodilator and inhibitor of platelet aggregation, has led to the development of a broad range of chemically stable analogues with similar biological properties.[1] Among these analogues, (+)-isocarbacyclin (**2**)[2] in a preclinical study is becoming recognized as one of the most promising therapeutic agents for cardiovascular and circulatory disorders. An enormous amount of synthetic effort has been expended in devising a more efficient route to (**2**);[3,4] we now report a convergent and practical synthesis of (**2**) based on novel methods for the attachment of α and ω appendages to a chiral bicyclo[3.3.0]octane nucleus.

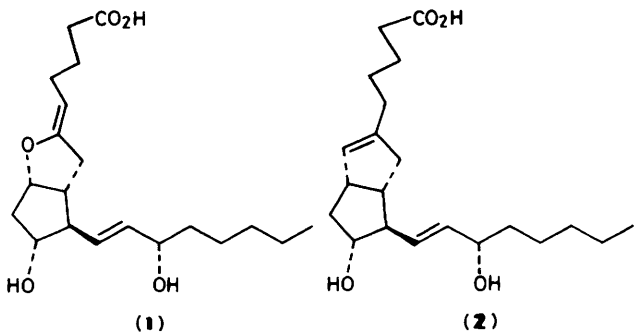
Since we had already developed a regiocontrolled construction of the optically active bicyclic β-oxo methyl ester (**12a**) *via* rhodium(II)-catalysed intramolecular C–H insertion,[4] the first crucial problem was the direct introduction of an ω appendage into a bicyclic β-oxo ester (**12**) coupled with smooth dealkoxycarbonylation. For the introduction of the ω appendage, Pinhey's α-alkenylation[5] with 'alkenyl-lead(IV) triacetate' seemed the method of choice, though the reported results were only concerned with alkenyl groups without functionality. In order to test the applicability of Pinhey's method and the subsequent dealkoxycarbonylation, the reactions of various esters of 2-oxocyclopentanecarboxylic acid (**5a—e**) with the (*E*)-alkenyl-lead reagent (**4**) were first explored. Treatment of (**5a—e**) with a mixture of lead tetra-acetate (2 equiv.) and (*E*,*E*)-dialkenylmercury (**3**)† (2.1 equiv.) in chloroform–pyridine at 20 °C for 1.5 h led to the formation of the corresponding adducts (**6a—e**)‡ with complete retention of the alkene geometry [results expressed as R, % isolated yield (% yield based on the unchanged ester): Me, 60 (78); $PhCH_2$, 61 (81); Bu^t, 36 (75); $CH_2{=}CHCH_2$, 34 (76); Cl_3CCH_2, 39 (65)]. It is clear that the efficiency of the reaction is highly dependent on the ester moiety; the methyl ester (**5a**) and the benzyl ester (**5b**) were found to be among the most effective.

† The reagent (**3**) was prepared from the corresponding iodide in 78% yield by sequential treatment with n-butyl-lithium and $HgCl_2$ in tetrahydrofuran (THF) at −78 °C followed by chromatography on silica gel deactivated with 0.5% of triethylamine.

‡ All new compounds were fully characterised by ^1H n.m.r. (400 MHz), i.r., and high resolution mass spectral analysis. Yields refer to spectroscopically and chromatographically homogeneous materials.

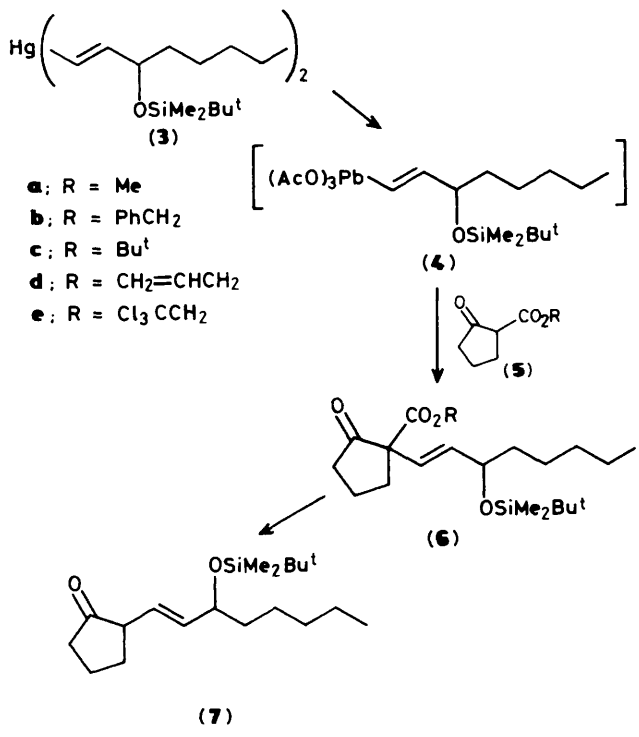
We then focused our efforts on removal of alkoxycarbonyl groups from the adducts (**6a** and **b**). Dealkoxycarbonylation§ was studied using a variety of reported methods;[6] however, the reaction proved to be formidably difficult and so a more expeditious method was sought. Eventually we discovered that exposure of (**6b**) to Raney nickel (W-2) in ethanol in the presence of triethylamine at 20 °C caused smooth debenzyloxycarbonylation to furnish the α-(*E*)-alkenylated ketone (**7**) in 83% yield, with no trace of the saturated ketone or the conjugated enone. In view of the lack of practical methods for α-alkenylation of cyclic ketones with regio- and stereo-control,[7] our new procedure *via* β-oxo benzyl esters seems of great promise.

We applied this reaction to the bicyclic β-oxo benzyl ester (**12b**), synthesised as follows. (*R*)-Methyl 2-oxocyclopentylacetate (**8**)[8] {93% enantiomeric excess, $[\alpha]_D^{20}$ +123° (*c* 1.0, MeOH)] was converted into the β-oxo methyl ester (**9**) *via* acetalization with (±)-butane-2,3-diol according to a reported method.[4] Smooth transesterification of (**9**) with benzyl alcohol and subsequent diazo transfer were followed by $Rh_2(OAc)_4$-catalysed cyclization to afford the bicyclic β-oxo ester (**12b**) in 53% yield. The key introduction of an optically pure ω appendage into (**12b**) by Pinhey's method proceeded smoothly to give the desired adduct (**13**) as pure exocyclic

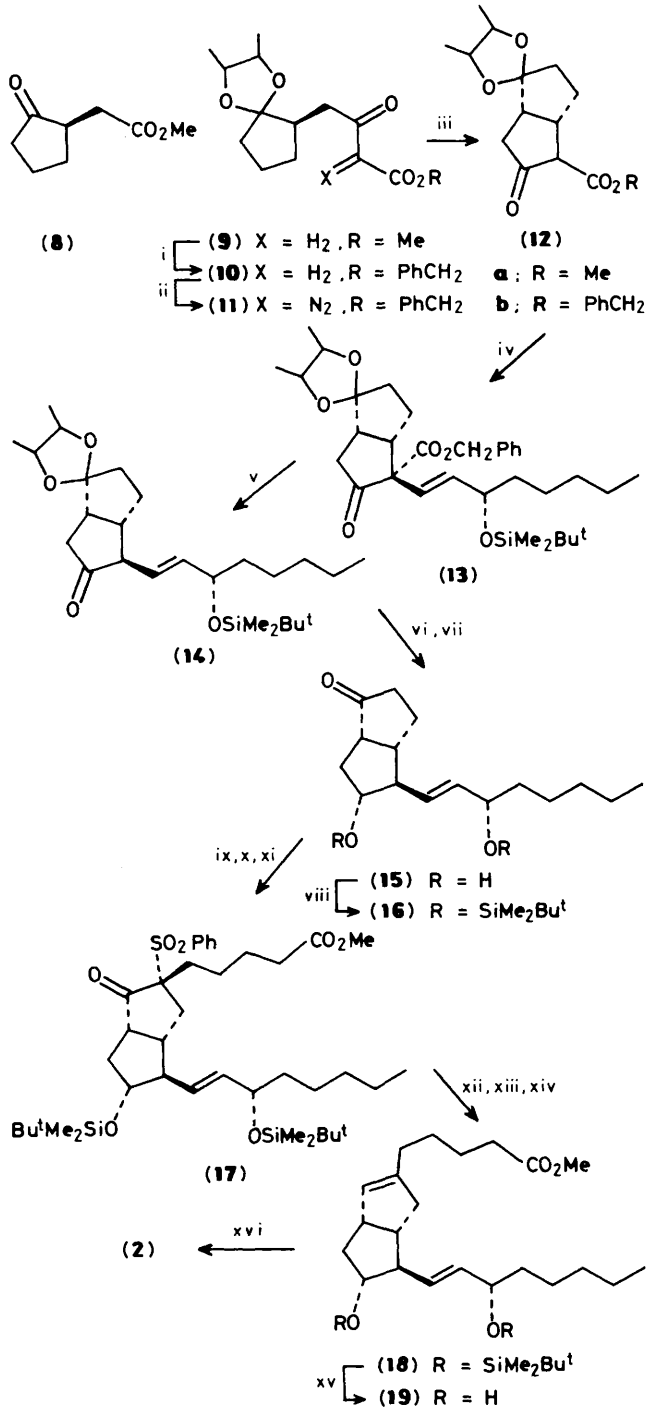


(**1**) (**2**)

§ Attempts at the dealkoxycarbonylation of (**6c** and **d**) met with failure; treatment of (**6e**) with Zn dust in Me_2SO–AcOH gave (**7**) in less satisfactory yield.



Scheme 1



Scheme 2. *Reagents and conditions:* i, $PhCH_2OH$, toluene, 130 °C, 6 h, 95%; ii, TsN_3 (Ts = *p*-toluene sulphonyl), Et_3N, MeCN, 23 °C, 2 h, 89%; iii, $Rh_2(OAc)_4$ (2 mol%), CH_2Cl_2, 15 °C, 0.5 h, 62%; iv, (*S*,*S*)-(**3**) (2.1 equiv.), $Pb(OAc)_4$ (2 equiv.), pyridine, $CHCl_3$, 23 °C, 0.5 h, then (**12b**) added, 23 °C, 1 h, 89% (based on consumed starting material, 64% conversion); v, Raney Ni(W-2) (1.7 g per mmol), Et_3N (0.2 equiv.), EtOH, 20 °C, 0.5 h, then Et_3N (1 equiv.) added, 0 °C, 10 min, 73%; vi, $NaBH_4$, MeOH, −50 °C, 0.5 h; vii, 10% HCl–MeOH–THF (1 : 1 : 10), 30 °C, 6 h, 63% from (**14**); viii, Bu^tMe_2SiCl, Pr^i_2NEt, 4-*N*,*N*-dimethylaminopyridine (DMAP), dimethylformamide, 23 °C, 6 h, 95%; ix, $LiN(SiMe_3)_2$, $(PhS)_2$, THF–$PO(NMe_2)_3$ (10 : 1), 20 °C, 1 h, 90%; x, MCPBA, CH_2Cl_2, −10 °C, 8 h, 68%; xi, Bu^tOK, $I[CH_2]_4CO_2Me$, Me_2SO, 23 °C, 8 h, 71%; xii, $NaBH_4$, MeOH, 0 °C, 0.5 h, 95%; xiii, $MeSO_2Cl$, DMAP, pyridine, 23 °C, 12 h, 96%; xiv, 10% Na–Hg, MeOH, −10 °C, 8 h, 87%; xv, Bu^n_4NF, THF, 35 °C, 8 h, 95%; xvi, 3% NaOH–MeOH (1 : 3), 40 °C, 5 h, 90%.

double bond isomer in 57% yield, along with 36% of the starting ester (**12b**). Reductive removal of the benzyloxycarbonyl group from (**13**) under the foregoing conditions followed by epimerization at the position α to the carbonyl group with triethylamine furnished the target α-alkenylated ketone (**14**) as pure exocyclic double bond isomer in 73% yield with no sign of double bond migration. Stereocontrolled reduction of (**14**) with sodium borohydride and subsequent hydrolysis provided the oxo diol (**15**),¶ $[\alpha]_D^{23}$ +158.5° (*c* 1.85 in $CHCl_3$), and the C-15 (prostaglandin numbering) epimer of *ent*-(**15**), $[\alpha]_D^{23}$ − 117.2° (*c* 0.58, $CHCl_3$), derived from the antipode of (**8**), in 63 and 3% yield, respectively.

With the efficient elaboration of (**15**) achieved, the stage was now set for the introduction of the α appendage and regiocontrolled construction of the endocyclic olefin. We envisaged that these problems could be resolved by incorporating a phenylsulphonyl group α to the carbonyl group. This idea was realized as follows. Sulphenylation of the kinetic enolate of the ketone (**16**) with diphenyl disulphide[9] and subsequent oxidation with *m*-chloroperbenzoic acid (MCPBA) were followed by alkylation with methyl 5-iodopentanoate to provide the α-alkylated β-oxo sulphone (**17**), $[\alpha]_D^{23}$ +48.6° (*c* 1.16, THF), in 44% yield, together with 1% of its C-6 epimer. Reduction of (**17**) with sodium borohydride followed by mesylation and reductive elimination with sodium amalgam[10] furnished the endocyclic olefin (**18**), $[\alpha]_D^{23}$ −16.2° (*c* 1.2, MeOH), in 79% yield. After desilylation, the homochirality of the diol (**19**), $[\alpha]_D^{23}$ +9.9° (*c* 1.04, MeOH) was confirmed by ^1H n.m.r. analysis of the corresponding bis-[(*R*)-(+)-α-methoxy-α-trifluoromethylphenylacetate].[11] Alkaline hydrolysis of (**19**) completed the total synthesis of (+)-isocarbacyclin (**2**), m.p. 78—80 °C, $[\alpha]_D^{23}$ +8.75° (*c* 0.72, MeOH).

¶ The homogeneity of (**15**) and (**19**) (single isomers) was confirmed by ^{13}C n.m.r. (100 MHz) analysis.

The convergent process devised here should provide ready access not only to (+)-isocarbacyclin but also to its novel analogues with modified α and ω appendages for biological and pharmacological investigations.

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