An Enantioconvergent Approach to Prostanoids

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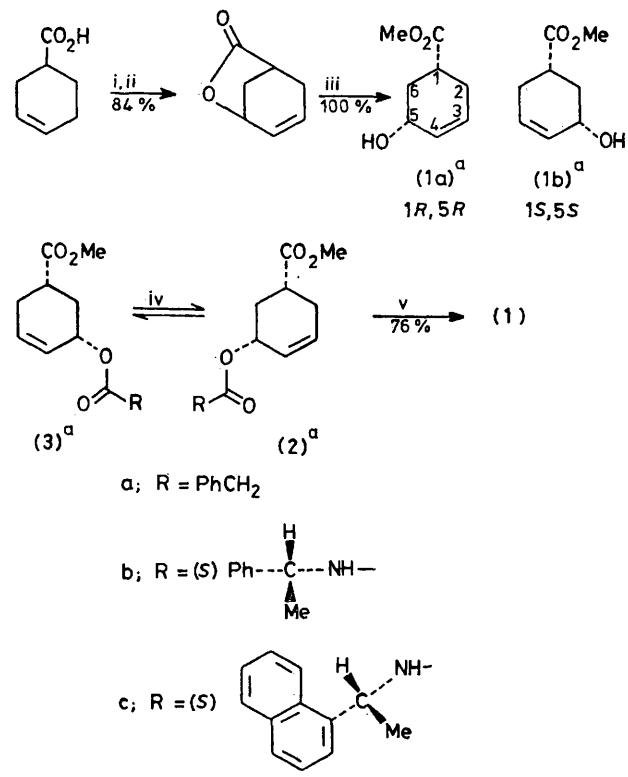
Summary A chiral synthesis of a prostaglandin analogue by a novel method which does not rely on classical resolution provides access to prostaglandin derivatives.

THE importance of the prostanoids and related compounds makes the availability of such compounds in optically pure form critical in exploring their biological applications. Few syntheses achieve this without resorting to a classical resolution in which the undesired enantiomer is discarded.[1] We report a method for synthesising this class of compounds which provides a single enantiomeric series with no intrinsic loss of material.

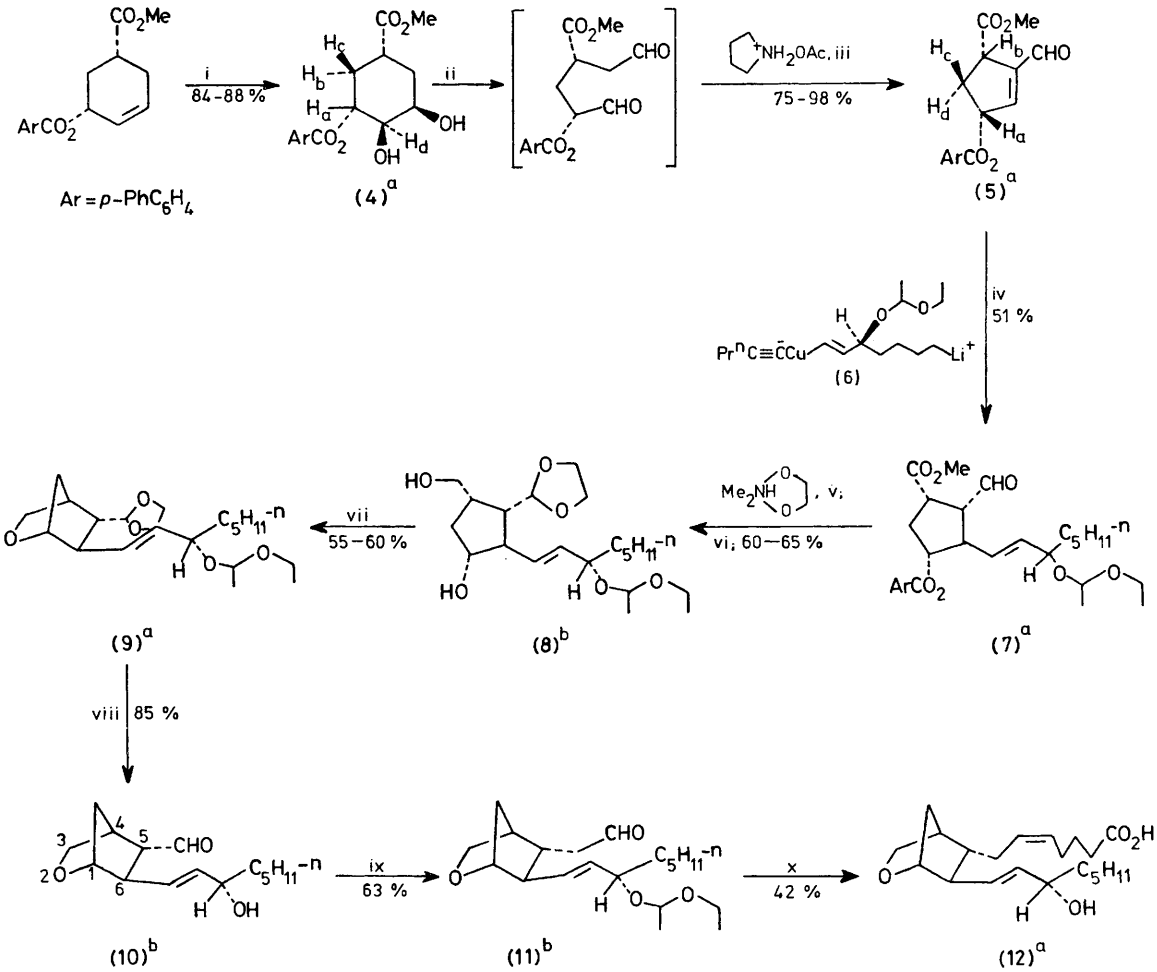
The key intermediate (**1**) was obtained as shown in Scheme 1 starting from the Diels–Alder adduct of butadiene and acrylic acid.[2] The symmetry properties of (**1**) are such that a 1,3-hydroxy-shift interconverts the two enantiomers. This interconversion can be brought about by mercury(II) trifluoroacetate-catalysed allylic rearrangement of the urethane (**2**) and (**3**).[3a] Treatment of the optically active (**2a**) under these conditions led to racemization, verifying that equilibrium had been reached. The use of (*S*)-1-phenylethylamine and (*S*)-1-α-naphthylethylamine led to ratios of (**2**) : (**3**) of *ca.* 1 : 1 and *ca.* 2 : 1, respectively.[3b] Separation of the diastereoisomers and resubjecting (**3**) to the equilibration conditions allows the racemate to converge into a single enantiomeric series, in an 'enantioconvergent' process. Correlation of the optically active (**1a**) prepared from an optically active Diels–Alder adduct of known configuration[4] establishes the absolute configuration as depicted. The *p*-phenylbenzoate of (**1a**), $[\alpha]_D$ +88·5°, $[\alpha]_{436}$ +218° (*c* 4·45, $CHCl_3$), > 91% optically pure, was hydroxylated to give (**4**) (see Scheme 2), whose stereochemistry was assigned from the 270 MHz n.m.r. spectrum of compounds in the racemic series ($J_{ab} = J_{ad} = 7{\cdot}0$, $J_{ac} = 2{\cdot}5$ Hz). Oxidation to the dialdehyde and ring closure to (**5**), m.p. 130—133 °C, proceeded without epimerization as determined by 270 MHz n.m.r. spectroscopy (δ_a 6·0, δ_b 3·8, δ_c 2·9, and δ_d 2·3; $J_{ac} = 8{\cdot}0$, $J_{ad} = 5$,



SCHEME 1. *Reagents:* i, I_2, KI, $NaHCO_3$, H_2O, room temp.; ii, 1,5-diazabicyclo[4.3.0]non-5-ene, C_6H_6, room temp.; iii, MeOH, NaOMe; iv, 0·25 equiv. $(CF_3CO_2)_2Hg$, THF, reflux; v, Cl_3SiH, Et_3N, C_6H_6 reflux (ref. 3b).

THF = tetrahydrofuran

[a] Structural assignment supported by spectral data and either high resolution mass spectroscopy and/or combustion analysis. In some instances, full characterization was obtained for compounds in the racemic series rather than the optically active series.



SCHEME 2. *Reagents:* i, 1 mol % OsO_4, $NaClO_3$, H_2O, room temp.; ii, $NaIO_4$, THF, H_2O, room temp.; iii, C_6H_6, 50 °C; iv, hexamethylphosphoric triamide, Et_2O, THF, −78 °C (15 min), −40 °C (1 h), −20 °C (3 h); v, HOAc, MeCN, room temp.; vi, $LiAlH_4$, 0 °C → room temp.; vii, *p*-$MeC_6H_4SO_2Cl$, pyridine, 0 °C, then NaH, dimethylformamide, room temp.; viii, MeCO-CO_2H, THF, BF_3–Et_2O, room temp.; ix, $EtOCH{=}CH_2$, $POCl_3$, Et_3N, then $Ph_3P^+CH_2OMeCl^-$, Bu^tLi, 0 °C → room temp., then $Hg(OAc)_2$, THF, H_2O, then KI, H_2O; x, $Ph_3P^+CH^-[CH_2]_3CO_2^-Na^+$, Me_2SO, then HOAc, THF, H_2O, 25 °C.

THF = tetrahydrofuran.

[a] See note a, Scheme 1. [b] Structural assignment supported by spectral data; compound normally used in the next step without purification.

J_{bc} = 9, and J_{bd} = 6 Hz).[5] After two recrystallizations from dichloromethane–hexane the rotation increased from $[\alpha]_D$ +178, $[\alpha]_{436}$ +430 (*c* 1·20, $CHCl_3$) to $[\alpha]_D$ +193·3, $[\alpha]_{436}$ +848 (*c* 1·19, $CHCl_3$) with no further change upon additional recrystallization. That the latter compound was optically pure was confirmed by comparison of the synthetic prostanoid prepared from it with an authentic sample.[6] Many prostanoids can be prepared from this compound. We synthesized the prostanoid (**12**) because of the great interest in endo-peroxide analogues [endo-peroxides related to (**12**) being pivotal biosynthetic intermediates] and the fact that previously this compound was only available from PGE's.

Conjugate addition of the optically pure vinyl cuprate (**6**) to (**5**) to introduce the lower side chain [C(13)—C(20)] proceeded surprisingly well to give (**7**) ($[\alpha]_D$ −75·4°, $[\alpha]_{546}$ −91·7°, *c* 1·0, $CHCl_3$) considering that such additions to conjugated aldehydes are virtually unknown[8] and the presence of an allylic acyloxy group has frequently led to elimination of that group.[9] The stereohomogeneity of the aldehyde and the stereochemical assignment were confirmed by the presence of a single aldehydic proton at δ 9·76, the failure to undergo equilibration with 1,5-diazabicyclo-[5.4.0]undec-5-ene (which has been shown to equilibrate these aldehydes), the expectation that the cuprate would approach from the least-hindered direction, and the subsequent transformations. The stereocontrol in this step is noteworthy. Protection of the aldehyde and reduction of the diester to the diol gave (**8**) which in turn was cyclized to the oxabicyclo[2.2.1]heptane (**9**), $[\alpha]_D$ −32°, $[\alpha]_{578}$ −33° (*c* 1·3, $CHCl_3$).

To confirm the stereohomogeneity, both protecting groups were removed by acetal exchange with pyruvic acid in the presence of boron trifluoride–diethyl ether to give (**10**), $[\alpha]_D$ −13°, $[\alpha]_{436}$ −23° (*c* 2·3, $CHCl_3$). This aldehyde showed a single aldehydic absorption at δ 9·79. In the

racemic series, when a mixture of aldehydes stereoisomeric at C(5) was obtained, two absorptions for the aldehydic proton were observed at δ 9·65 and 9·79 which upon equilibration with 1,5-diazabicyclo[4.3.0]non-5-ene (CH_2Cl_2, room temp.) gave a single aldehyde with only the δ 9·79 absorption. Comparison with equilibrations in bicyclo[2.2.1]-heptanes confirmed that the *trans* configuration at C(5) and C(6) is the more stable.[10] Since equilibration of the isomers of the aldehyde (**7**) in the racemic series led to a single epimer at the carbon atom bearing the aldehyde group which ultimately generates only (**10**), the stereochemistry of (**7**) is also a result of thermodynamic control.

Homologation of the aldehyde with the methoxymethyl-enephosphorane took place more satisfactorily with t-butyl-lithium than with n-butyl-lithium to generate the reagent from the salt. The intermediate enol ether was hydrolysed without disturbing the acetal at C(15) with mercury(II) acetate in aqueous tetrahydrofuran (THF); work-up with aqueous potassium iodide[11] yielded (**11**) (*CH*O δ 9·8; $[\alpha]_D$ −5°, $[\alpha]_{546}$ −6·5°, *c* 1·6, $CHCl_3$). Standard Wittig chain extension and hydrolysis[12] gave the desired product (**12**), $[\alpha]_D$ −8·5°, $[\alpha]_{436}$ −14·0° (*c* 1·5, EtOAc) (authentic sample[13] $[\alpha]_D$ −8·4°, $[\alpha]_{436}$ −14·0°, *c* 1·0, EtOAc). Comparison of its chromatographic and spectroscopic properties with those of an authentic sample confirmed the identity and the optical purity of (**12**).

This approach to chiral prostanoids and its analogues benefits from the ability to obtain optically pure products *via* chemically versatile intermediates. For example, a carboxy inversion would allow conversion of the intermediates into the PGF and PGE series.[14] Carba-analogues of prostacyclins could be obtained from (**8**), and C(8) and C(9) substituted analogues as well as alternative endo-peroxide analogues can be obtained from (**7**).

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