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A SIMPLE AND CONVENIENT ROUTE TO 11-DESOXYPROSTAGLANDINS

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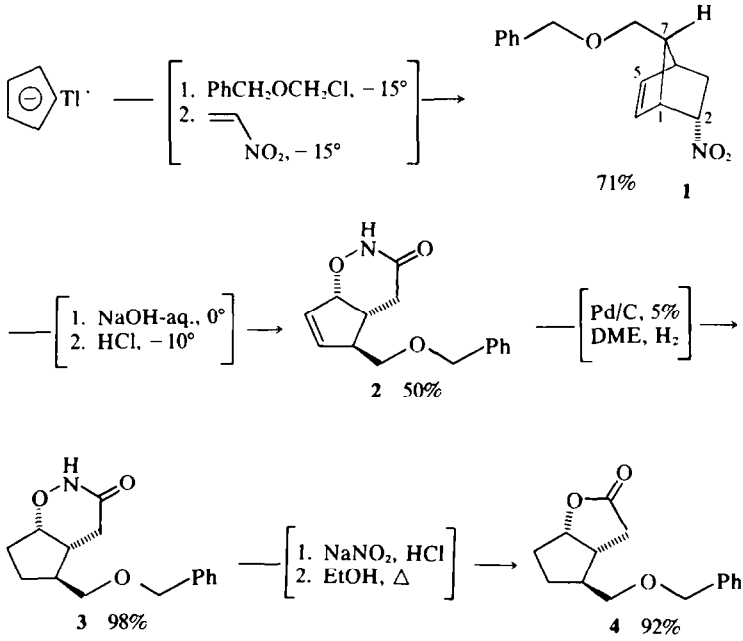
Abstract—A high yield, four-step route to the key prostaglandin intermediate **4** is described which should make 11-desoxyprostaglandins and their analogs more readily accessible. Procedure provided for the highly versatile 5-benzyloxymethylcyclopentadiene-nitroethylene adduct (**1**) would enable the preparation of PGA_2, the Corey prostaglandin intermediate and *syn*-7-benzyloxymethylnorbornenone that is related to all the primary prostaglandins.

11-DESOXYPROSTAGLANDINS have attracted attention not only because of their interesting biological properties such as antagonists of the prostaglandins in the E and F series,[1] but also due to their practical microbiological transformation to the natural hormones.[2] Nearly all the routes to 11-desoxyprostaglandins involve intermediates relating specifically to the 11-desoxy analogs and therefore suffer from lack of versatility.[3,4]

The present work describes a novel and stereospecific route to 11-desoxyprostaglandins by the further elaboration of the versatile key intermediate, *syn*-7-benzyloxymethyl-2-*endo*-nitro-bicyclo(2.2.1)hept-5-ene (**1**):



Since **4** has been transformed to 11-desoxyprostaglandins by standard methods,[4] the four-step sequence provides a direct and convenient entry to 11-desoxyprostaglandins. Additionally, the facile **1**→**4** change further illustrates the versatility of the readily accessible **1** as a key compound to diverse types of prostagandins.[5,6]

†Contribution No. 3.

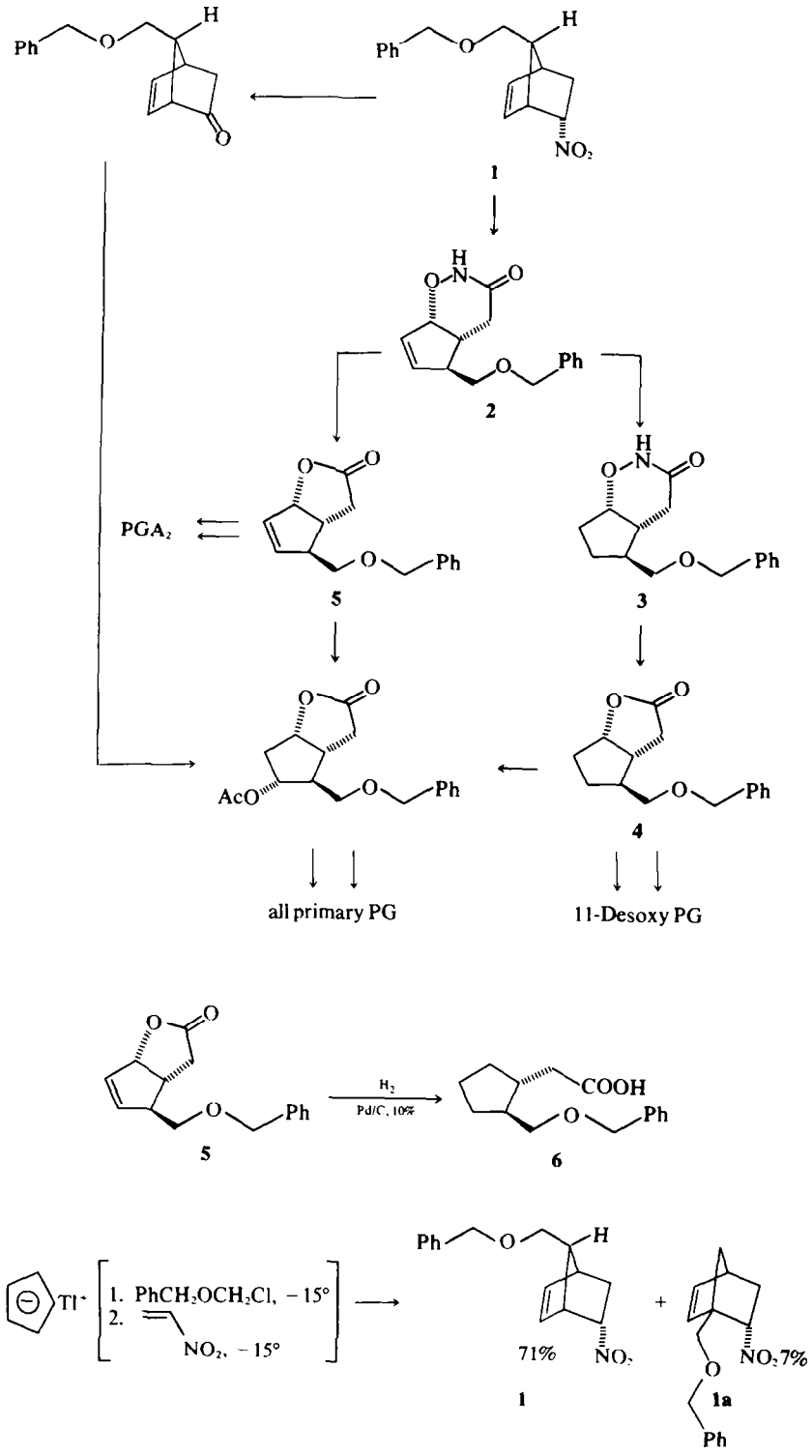
11-Desoxyprostaglandins cannot be made by the usual hydrogenation of the dehydro-precursor **5**, related to PGA_2[7] since **5** undergoes ready hydrogenolysis to **6**.

The hydrogenation of **2**→**3** in nearly 100% yields constitutes one of the focal points of the present work.

Sublimed thallium cyclopentadienide was prepared in consistent yields of 60–65% by a modified procedure of Meister.[8] 5-Benzyloxymethylcyclopentadiene, prepared by alkylation of the thallium compound with benzyloxymethylchloride,[9] was reacted *in situ*, with freshly prepared nitroethylene.[5,12] The reaction mixture on chromatography gave 71% yield of **1** and 7% yield of isomer **1a**.[10] Higher reaction temperatures, as expected, yielded a greater proportion of **1a** arising from the isomerization of 5-benzyloxymethylcyclopentadiene.

The **1**→**2** change was accomplished in one operation by quenching the salt of **1** produced *in situ*; optimum conditions were found after many trials.

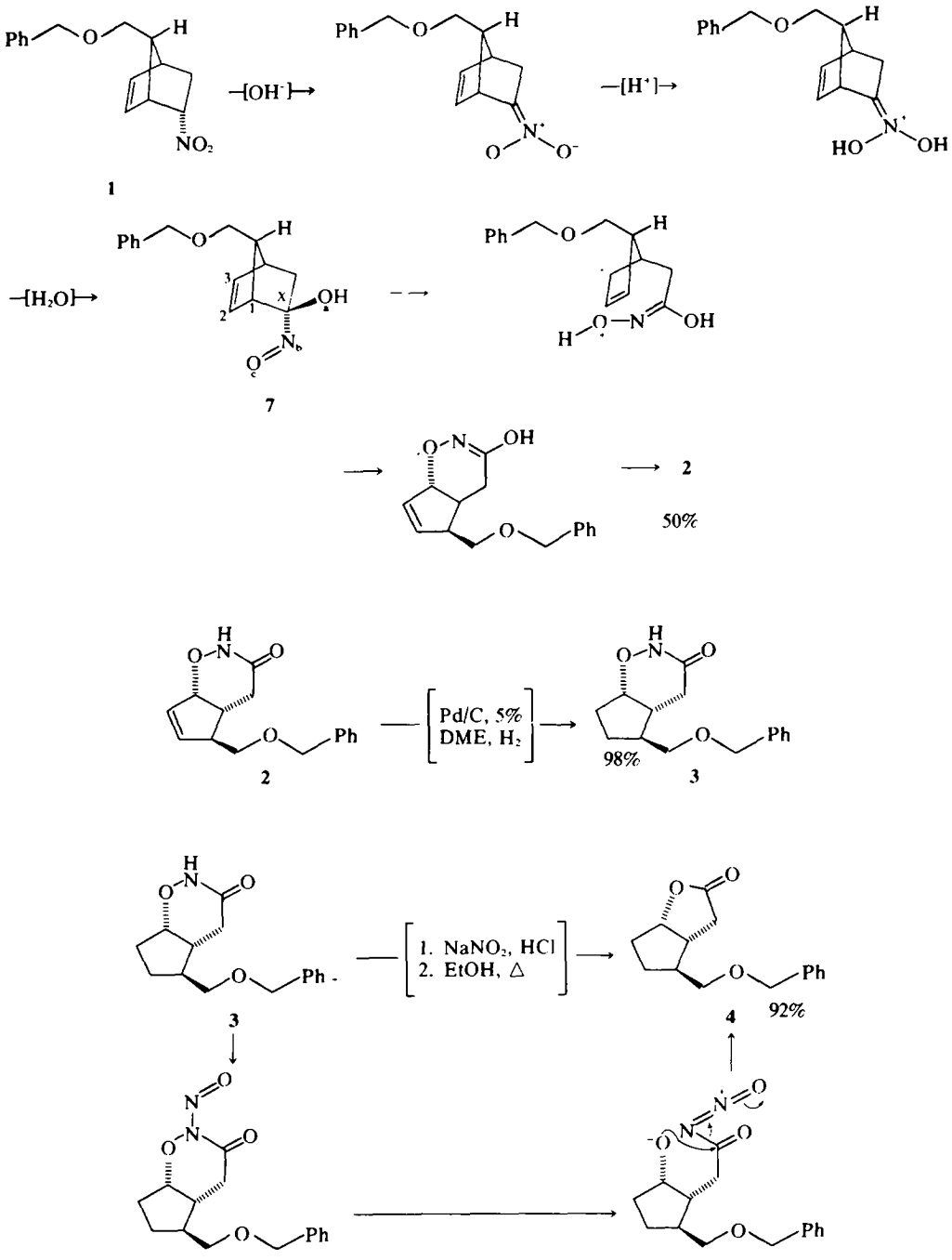
The rupture of the fragile 1-x bond in the Nef intermediate **7**[11] could lead to six products resulting from recombinations represented as **1a**, **1b**, **1c**, **3a**, **3b** and **3c**. Studies with other systems have shown that the preferred



course of the reaction is controlled by many variables, such as the nature of the substrate, the reaction temperature, the mode of quenching and the nature of the quencher. Thus, 2-*endo*-nitronorbornene and 7-*syn*-methoxymethyl-2-*endo*-nitronorbornene gave a mixture of products (resulting from recombinations represented as **3a** and **3c**), whilst **1** gave exclusively **2** (resulting from a (3,3) shift with formation of **3c** bond). The absence of products arising from formation of bonds, **1a**, **1b**, **1c** and **3b** reflect the difficulties associated with the attainment of the relevant transition states.

The cyclic hydroxamic ester **2** could be quantitatively hydrogenated to **3**.

The final step of the sequence, namely the **3**→**4** change, could be accomplished in 92% yields by a thermal N_2O extrusion from the N-nitroso derivative of **3**[5].



EXPERIMENTAL

M.ps and b.ps are uncorrected. NMR spectra were recorded on an A-60 instrument with internal TMS standard. Analytical and preparative TLC were done using silica gel with $CaSO_4$ binder. Column chromatography was carried out with silica gel and the columns were prepared in petroleum ether. Reactions were monitored, wherever possible, by TLC.

7-syn-Benzyloxymethyl-2-endo-nitro-bicyclo[2.2.1]*heptene* (1)

1. *Thallous cyclopentadienide.*[8] To a mechanically stirred and ice-cooled soln of thallous sulphate (10 g, 0·02 mole) in KOHaq (4 g in 80 ml water) was added, in drops, over 0·25 hr, freshly cracked cyclopentadiene (10 ml, 0·1296 mole). The mixture was stirred for 1 hr, filtered, washed with cold MeOH, dried (KOH) and sublimed at 80°/0·005 mm to give 6·7 g (65%) of thallium cyclopentadienide, m.p. 270°. It was found after many repetitions that 10 g batches of thallous sulphate give optimum yields.

2. *Nitroethylene.*[9-12] 2-Nitroethanol[13] (13·5 g, 0·15 mole) and resublimed phthalic anhydride (28 g, 0·225 mole) were mixed in a distillation unit equipped with a short fractionating column and an ice-cooled receiver. The apparatus was evacuated to 80 mm and the temp. maintained at 140–150° until the mixture was homogeneous. The bath temp. was increased and held at 175–180° until distillation ceased. The distillate was dried over $CaCl_2$ to give 8·8 g (80%) of pale yellow nitroethylene which is suitable for further reactions. Nitroethylene which is highly lachrymatory polymerises on standing and should be used without delay.

3. *5-Benzyloxymethylcyclopentadiene.* Under N_2, benzyloxymethylchloride (15·6 g, 0·1 mole) in dry ether (30 ml) was added dropwise to a well stirred and ice-salt cooled (~−15°) suspension of freshly sublimed thalliumcyclopentadienide in dry ether (22 g, 0·081 mole, 50 ml ether). The mixture was stirred for a further period of 6 hr while the temp. was maintained throughout the experiment at −15°. The alkylated cyclopentadiene soln was

filtered quickly into a pre-cooled (−15°) flask washed with ice-cold dry ether and was directly used for cycloaddition with nitroethylene.

4. 7 - syn - *Benzyloxymethyl* - 2 - endo - *nitrobicyclo*[2.2.1]*heptene* (**1**). Nitroethylene (6 g, 0·082 mole) in dry ether (20 ml) was added dropwise to the above alkylated cyclopentadiene at −15° and the mixture stirred overnight. Evaporation of ether under reduced pressure left a residue (20 g) which was chromatographed on silica gel. Elution with benzene: EtOAc (90:10) gave **1a**; yield, 1·5 g (7%), b.p. 120°/0·07 mm; IR: ν_{max} (neat) (cm^{-1}): 1538, 1366 (nitro); NMR: (δ) (CCl_4): 7·25 (aromatic), 6·32 (q), 5,7 (d) (olefinic protons), 5·1 (q, H–C–NO_2), 4·6 (–O–CH_2–Ph), 3·9 (q, J = 10 Hz, –O–CH_2–CH), 2·9 (br, bridgehead proton).

Further elution with benzene: EtOAc (85:15) gave the desired **1**; yield, 15 g (71%), b.p. 122°/0·07 mm; IR: ν_{max}(neat) (cm^{-1}): 1538, 1366 (nitro); NMR: (δ) (CCl_4): 7·28 (aromatic), 6·23, 5·8 (q, q, olefinic protons), 4·9 (m, H–C–NO_2), 4·4 (–O–CH_2–Ph), 3·3 (d, J = 7 Hz, –O–CH_2–CH), 3·42 and 2·9 (bridgehead protons). (Found: C, 69·86; H, 6·90. Calc for $C_{15}H_{17}NO_3$ (Mol. wt. 259): C, 69·48; H, 6·61%).

Abnormal Nef reaction of 7 - syn - *benzyloxymethyl* - 2 - endo - *nitrobicyclo*[2.2.1]*heptene*

Isolation of cyclic hydroxamic ester **2**. Ice cold NaOHaq (15 ml, 20%, 0·075 mole) was added dropwise to an ice-cooled and stirred soln of **1** in MeOH (1 g, 0·0038 mole, 5 ml). The stirring was continued at 0° for a further period of 4 hr. This Na-salt soln was then added dropwise over a period of 0·5 hr to ice-salt cooled (~−10°) conc. HCl (14 ml, 0·14 mole) and the stirring was continued for a further period of 0·5 hr. The mixture was extracted with $CHCl_3$ (4 × 50 ml) and the organic extract was washed with water and evaporated under reduced pressure. The residue (0·9 g) on quick chromatography over silica gel and elution with EtOAc: benzene (40:60) gave pure (TLC) **2** which crystallized on standing; yield, 0·5 g (50%). Recrystallization from benzene-petroleum ether gave colourless prisms, m.p. 80°, IR: ν_{max}(KBr) (cm^{-1}): 1664 (hydroxamic ester), NMR: (δ)($CDCl_3$): 8·8 (br, NH), 7·35 (aromatic), 6·14, 5·75 (broad doublets, olefinic protons), 5·12 (br, –O–C–H), 4·51 (–O–CH_2–Ph), 3·41 (d, J = 5 Hz, –O–CH_2–CH). (Found: C, 69·10; H, 6·80. Calc. for $C_{15}H_{17}NO_3$ (Mol. wt. 259): C, 69·48; H, 6·61%).

Catalytic hydrogenation of **2**

Preparation of **3**. Under stirring, a slow stream of H_2 was passed at room temp. for 1 hr through a soln of **2** (0·426 g, 0·0016 mole) in dimethoxyethane (10 ml) containing Pd–C (5%, 0·5 g). The mixture was filtered and solvents evaporated under reduced pressure to yield pure (TLC) **3**; yield 0·420 g (98%); b.p. 185–90°/0·1 mm; IR: ν_{max}(neat) (cm^{-1}): 1667 (hydroxamic ester); NMR: δ($CDCl_3$): 7·32 (aromatic), 4·5 (–O–CH_2–Ph and –O–CH), 3·4 (broad doublet, J = 5 Hz, –O–CH_2–CH).

N_2O *extrusion from* **3**

Preparation of the intermediate **4**. An ice-cold and freshly prepared soln of HNO_2 made by mixing $NaNO_2$aq (0·400 g, 0·0058 mole, 1 ml) with conc. HCl (0·6 ml, 0·006 mole, in 1 ml water) was added dropwise to an ice-cooled and stirred soln of **3** (0·180 g, 0·00069 mole) in ether (10 ml). The soln was stirred for 0·5 hr at 0° and the yellow ether layer was separated, washed with cold water, dried ($MgSO_4$) and evaporated. The residue was taken-up in abs. EtOH (10 ml) and held at reflux for 12 hr. Solvents were evaporated *in vacuo* and the residue fractionated by preparative TLC using benzene–EtOAc (8:2) as developer to give 0·156 g (92%) of pure **4**, b.p. 165–170°/1 mm; IR: ν_{max}(neat) (cm^{-1}): 1770 (lactone); NMR: δ($CDCl_3$): 7·3 (aromatic), 4·92 (br, –O–CH), 4·5 (–O–CH_2–Ph), 3·4 (broad doublet, J = 5 Hz, –O–CH_2–CH). (Found: C, 73·45; H, 7·34. Calc. for $C_{15}H_{18}O_3$ (Mol. wt. 246): C, 73·18; H, 7·32%).

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