A SIMPLE SYNTHESIS OF BICYCLO[2.2.1]HEPTANE SYSTEM, A KEY POTENTIAL INTERMEDIATE FOR STABLE PROSTAGLANDIN H_2 ANALOGUE

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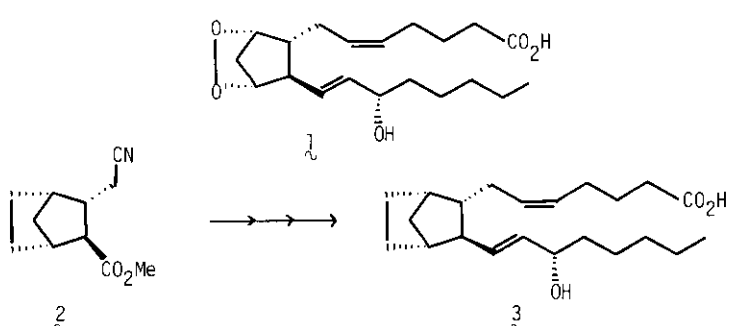
Abstract —— A simple and efficient synthesis of 6-cyanomethyl-1-methoxycarbonylbicyclo[2.2.1]heptane system leading to stable prostaglandin H_2 analogue is described.

Prostaglandin H_2 (PGH_2), an unstable metabolite of arachidonic acid in homogenates of sheep vesiculas glands,[1,2] has structure 1. The high biological potency of the new prostaglandins was exemplified by their stimulating activity on the rabbit aorta, PGH_2 was 100 to 450 times more potent than prostaglandin E_2.[3]

Here we wish to report a simple and efficient synthesis of 6-cyanomethyl-1-methoxycarbonylbicyclo[2.2.1]heptane system (2) leading to stable PGH_2 analogue (3) which may facilitate the studies of their mode of action and may also be of clinical important, although several reports about these subjects had already appeared.[4,5,6]

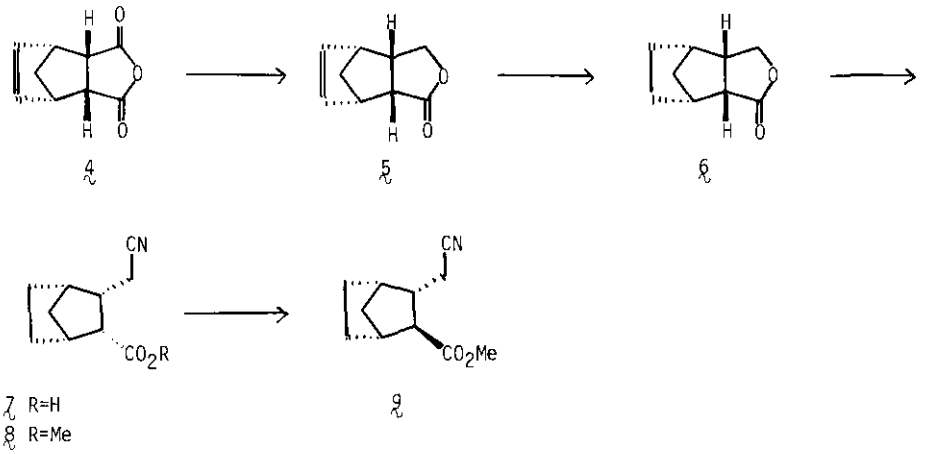
Chart 1



1 2 3

Sodium borohydride reduction of the known Diels-Alder adduct (4)[7] in dry dimethylformamide followed by acid treatment at room temperature afforded the desired γ-butyrolactone (5) in 86.9 % yield. Catalytic hydrogenation of 5 on 5 % Pd-C in methanol afforded the dihydro-γ-butyrolactone (6), m.p. 108 ∿ 111°, in quantitative yield. Introduction of cyano group by treatment of γ-butyrolactone (6) with potassium cyanide afforded the desired carboxylic acid (7). Without further purification, the crude carboxylic acid (7) was treated with an excess of diazomethane to give the corresponding α-methyl ester (8) exclusively in 77 % overall yield from the γ-butyrolactone (6). None of the β-methyl ester (9) was observed.[8] Epimerization of the α-isomer (8) to the β-isomer (9) using methanolic potassium carbonate at room temperature proceeded smoothly in 82 ∿ 94 % yield.

Chart 2



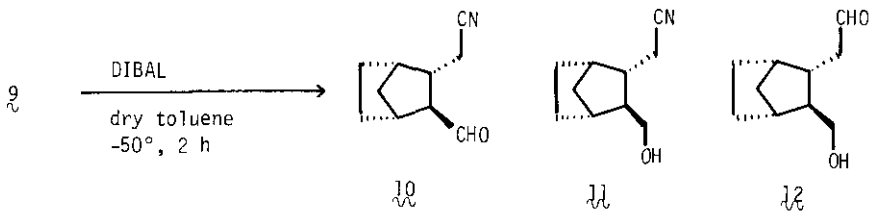
4 5 6

7 R=H
8 R=Me

9

Since the desired bicyclo[2.2.1]heptane derivative (9) was thus obtained, the reduction of cyano and methoxycarbonyl groups by diisobutyl aluminum hydride was examined under several conditions and the results are summerized in Table I.

Table I



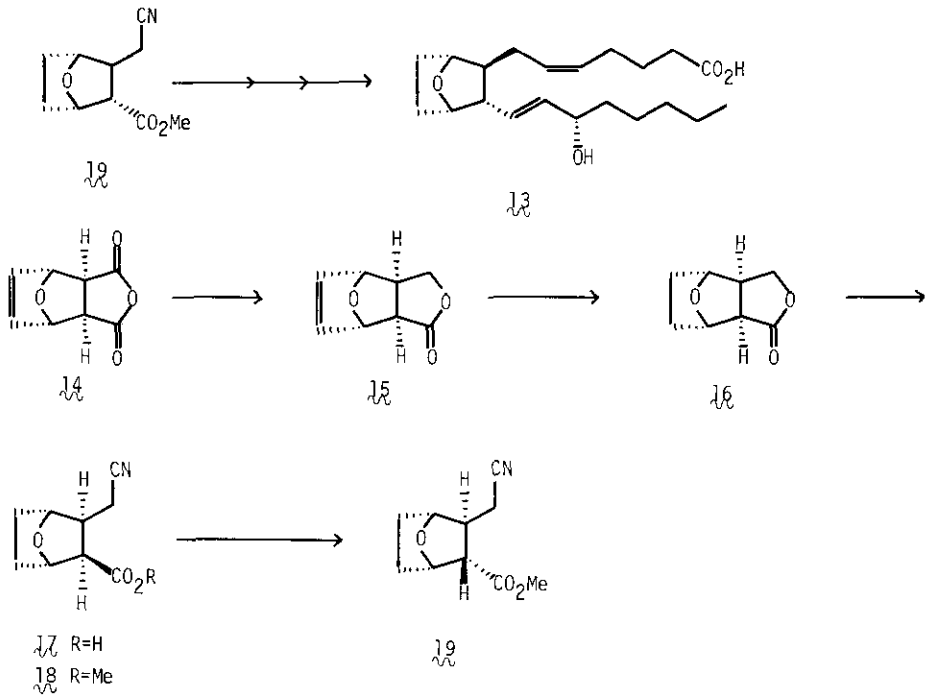
10 11 12

Reaction conditions	Products (Yield %)		
DIBAL/methyl ester (mole ratio)	10	11	12
4	33.2	24.3	0
6	0	50.1	12.5
8	0	38.8	24.5
10	0	38.5	26.8

From the point of biological activity, it is also interesting to synthesize PGH_2 analogue such as 13 which has opposite configuration at the position of C_8 to the natural PG series.

Thus, the γ-butyrolactone (15),[9] prepared from the exo-adduct (14) under the same conditions as described above, was hydrogenated over 5 % Pd-C to give the dihydro-γ-butyrolactone (16), m.p. 115 ~ 117°, in 95.3 % yield. Introduction of cyano group followed by treatment of the carboxylic acid (17) with diazomethane also afforded only the corresponding β-methyl ester (18) in 62.7 % overall yield from the γ-butyrolactone (16). Epimerization of the β-isomer gave α-isomer (19) in 97.1 % yield.

Chart 3



The synthetic method described herein would provide not only versatile methods for the synthesis of the key intermediates leading to stable PGH_2 analogues, but also the synthetic method which involves another heteroatom such as nitrogen and sulfur at the position of bridgehead.

REFERENCES AND NOTES

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10. *All structural assignments were supported by proton magnetic resonance*, infrared and mass spectral data obtained using chromatographically purified and homogeneous sample. Elemental analyses were obtained for crystalline compounds.

11. All reported yields refer to isolated products.

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