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SIMPLE, STEREOCONTROLLED TOTAL SYNTHESIS OF A BIOLOGICALLY ACTIVE ANALOG OF THE PROSTAGLANDIN ENDOPEROXIDES (PGH_2, PGG_2)

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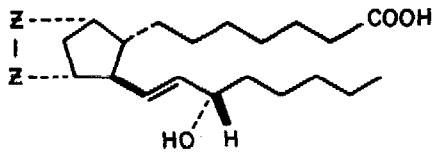
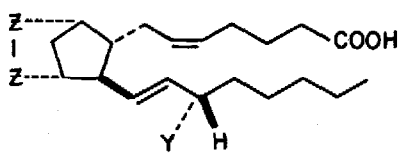
Several years ago the bicyclo[2.2.1]heptene derivative 1[1] was synthesized as an analog of the endoperoxide 2 which had been postulated[2] to be an intermediate in the synthesis of the "primary" prostaglandins (e.g., PGE_1 or $PGF_{1\alpha}$) from C_{20} fatty acid precursors. The bicycloheptene analog was found[1] to retard the biosynthesis of PGE_1, but not $PGF_{1\alpha}$, from eicosatrienoic acid. In the meantime the endoperoxides 3 and 4 (PGG_2 and PGH_2) have been isolated and confirmed as intermediates in PG biosynthesis,[3] and also shown to be potent agonists in blood platelet aggregation and smooth muscle contraction.[4,5] Further, the azo analog of PGH_2 (4), 5, has been synthesized and demonstrated to be at least as active as 3 or 4 with regard to muscle contraction, platelet aggregation and serotonin release from platelets.[6] Because of these developments it seemed of interest to study the etheno analog of PGH_2, 6, in the systems in which PGH_2 is active or potentially active. We report here a new and highly effective synthetic approach to (±)-6 and also some biological effects of this readily accessible, stable endoperoxide analog.



1, ZZ = HC=CH

2, ZZ = O-O



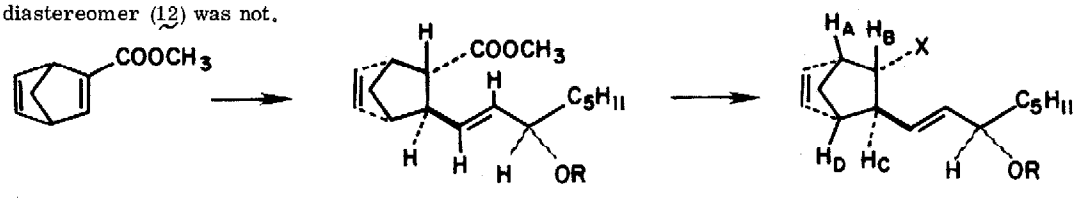
3, Y = OOH, ZZ = O-O

4, Y = OH, ZZ = O-O

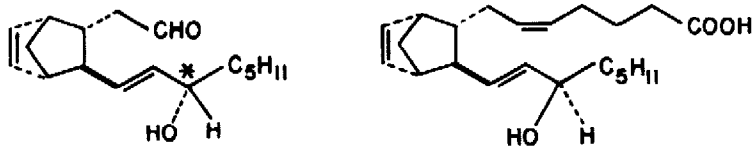
5, Y = OH, ZZ = N=N

6 Y = OH, ZZ = HC=CH

The synthesis of 6 was carried out starting with the adduct (7)[7] of cyclopentadiene and methyl propiolate and the reaction with the mixed Gilman reagent[8] derived from (±)-trans-1-lithio-1-octen-3-ol t-butyl dimethylsilyl ether and 1-pentynylcopper hexamethylphosphorus triamide complex[8] (1.2 equiv, ether solution, -78° under argon for 1 hr) which afforded in 86% yield the addition product 8.[8] The stereochemistry assigned to 8, corresponding to conjugate addition of vinyl and α-protonation, both from the exo direction, is supported by ample precedent[9] and also by pmr spectral data on 8 and the corresponding aldehyde 9 (e.g., $J_{AB} \cong J_{BC} \cong 4$ Hz; $J_{CD} = 0$ Hz).[10] Reduction of the ester 8 with 1.5 equiv of diisobutylaluminum hydride in methylene chloride at -78° for 1 hr (followed by quenching with methanol) produced a mixture of the aldehyde 9 and the corresponding primary alcohol which was stirred with pyridinium chlorochromate[11] (ca. 0.8 equiv) in methylene chloride to afford pure aldehyde 9 (diastereomeric mixture) in ca. 85% yield. Reaction of 9 with methoxymethylenetriphenylphosphorane (1.5 equiv)[12] in toluene-THF (ca. 3.4:1) at 0° for 1 hr afforded the enol ether 10 which was directly converted to a mixture of hydroxy aldehyde 11 and the diastereomer at C* by exposure to acetic acid-water-THF (3:1:1) at 55° for 17 hr (70% yield from 9). The hydroxy aldehyde 11 was readily separated from the diastereomer by chromatography on silica gel using 1:1 ether-hexane for elution (the R_f values found for 11 and the diastereomer on silica gel plates with this solvent system were 0.37 and 0.26 respectively). Reaction of 11 (i.e., the less polar diastereomer) with the ylide prepared from 4-carboxybutyl-triphenylphosphonium bromide and sodium methylsulfinylcarbanide[13] in DMSO in the usual way afforded 88% of the desired (±)-endoperoxide analog 6. Similarly, from the more polar diastereomer of 11 the 15β-epimer (12) of the PGH_2 analog 6 was obtained. The R_f values found for 6 and the 15β-epimer 12 on silica gel plates using four developments with 19:1 methylene chloride-methanol were 0.36 and 0.42 respectively, i.e., the relative polarities are reversed from those of the precursor hydroxy aldehyde 11 and its diastereomer. The assignment of stereochemistry depended on the finding (see below) that the more polar diastereomer (6) was highly biologically active as an endoperoxide mimic whereas the less polar diastereomer (12) was not.



7 8 9, X = CHO; 10, X = CH=CHOCH3



R= Si(CH3)2 tBu

11 12

The process described previously for the conversion of 15β-hydroxy prostanoids to the 15α-hydroxy (natural) epimers was utilized for the transformation of 12 to 6, thereby making the synthesis of 6 stereo-controlled in the sense that no significant amounts of unusable diastereomers are formed. As before,[14] 12 was esterified (CH_2N_2), converted to the 15-mesylate at -20°, and the resulting methyl ester mesylate was exposed to excess potassium superoxide for 20 min at 0° in 1:1:1 DMF-DMSO-DME in the presence of 18-crown-6. After isolation the desired product 6 was obtained in >90% yield.

The biological effects of 6 and 12 were studied using human platelet-rich plasma. Addition of 6 (i.e., the more polar etheno PGH_2 analog) to platelet-rich plasma induced aggregation (measurements as in refs. 4-6), and this effect was not abolished by indomethacin (IM). The concentration giving 50% aggregation was approximately 10 times the corresponding concentration of PGG_2 (Fig. 1). The less polar etheno analog (12) neither induced platelet aggregation nor inhibited aggregation induced by collagen or PGG_2 (Fig. 1). The more polar isomer, 6, induced release of ^{14}C-serotonin[4-6] at concentrations which gave aggregation of platelets, whereas the less polar isomer, 12, was inactive in this system and did not inhibit release by other agents such as collagen or PGG_2.

The PGG_2-like biological activity of 6 coupled with a short and efficient pathway of synthesis and its stability suggest a useful role for this substance in biological studies.[15]

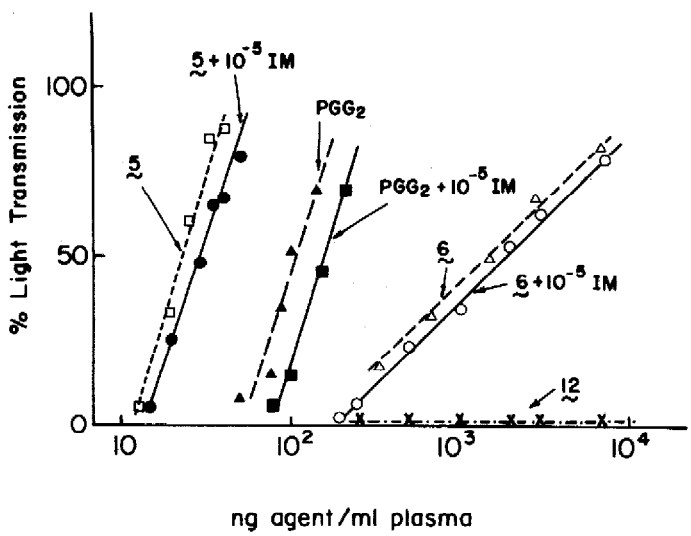


Fig. 1

References and Notes

1. P. Wlodawer, B. Samuelsson, S. M. Albonico and E. J. Corey, J. Amer. Chem. Soc., 93, 2815 (1971).
2. For a review see, B. Samuelsson, Fed. Proc., 31, 1442 (1972).
3. M. Hamberg and B. Samuelsson, Proc. Nat. Acad. Sci. USA, 70, 899 (1973).
4. M. Hamberg, J. Svensson, T. Wakabayashi, and B. Samuelsson, ibid., 71, 345 (1974).
5. M. Hamberg, J. Svensson and B. Samuelsson, ibid., 72, 2994 (1975).
6. E. J. Corey, K. C. Nicolaou, Y. Machida, C. L. Malsten and B. Samuelsson, ibid., 72, 3355 (1975).
7. Prepared in excellent yield from excess cyclopentadiene and methyl propiolate in a little benzene at reflux. Distilled product (b.p. 80–83° at 12 mm) tended to decompose on storage even at low temperature and consequently was generally used in the next step without delay. See, K. Alder, H. Wirtz and H. Koppelberg, Ann., 601, 138 (1956).
8. Satisfactory infrared, pmr and mass spectral data were obtained on all intermediates described herein using chromatographically homogeneous samples.
9. See (a) E. J. Corey, R. Hartmann and P. A. Vatakencherry, J. Amer. Chem. Soc., 84, 2611 (1962), and (b) S. W. Baldwin and J. C. Tomesch, J. Org. Chem., 39, 2382 (1974).
10. Since both the Gilman reagent and the conjugated carbonyl acceptor (7) used in the synthesis of 8 were racemic, the product was, as expected, a 1:1 mixture of diastereomers (not readily separable by chromatography) corresponding to 15α- and 15β-prostanoid configurations. In addition a very small amount (ca. 4%) of another diastereomeric by-product mixture was formed which was easily separated by chromatography (higher R_f than 8 on silica gel plates using 4:1 ether-hexane). The diastereomers of 8 were separated at a later stage in the synthesis.
11. E. J. Corey and J. W. Suggs, Tetrahedron Letters, 2647 (1975).
12. The ylide was generated by reaction of methoxymethyltriphenylphosphonium chloride (1.6 equiv in toluene) and lithium diisopropylamide (1.5 equiv in THF) at 0° for 5 min.
13. E. J. Corey, N. M. Weinshenker, T. K. Schaaf and W. Huber, J. Amer. Chem. Soc., 91, 5675 (1969).
14. E. J. Corey, K. C. Nicolaou, M. Shibasaki, Y. Machida and C. S. Shiner, Tetrahedron Letters, 3183 (1975). See also, E. J. Corey, K. C. Nicolaou and M. Shibasaki, Chem. Commun., 658 (1975).

15. This research was supported by the U. S. National Science Foundation and the Swedish Medical Research Council (Project 03X-217).