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STEREOCONTROLLED APPROACHES TO 9(0)-METHANOPROSTACYCLIN[1)]

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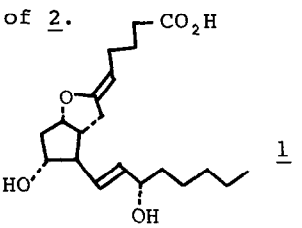
Summary: A stable PGI_2 analog (methanoprostacyclin 2) was synthesized starting from 5-norbornene-2,3-dicarboxylic anhydride.

Since the discovery of prostacyclin (PGI_2, 1), much attention has been paid to its possible medicinal potential as well as its important physiological roles. In addition, its remarkable instability has urged a number of chemists to synthesize more stable analogs with similar biological activity. Thus, in recent time, not a few synthetic modified analogs have been reported[2)].

We also intended to synthesize 9(0)-methanoprostacyclin 2 replacing the ether linkage of the cyclic enol ether of 1 by a methylene moiety. The recent communications[3)] on the synthesis of 2 have prompted us to report our different approaches to the same target 2. As an extension of our works[1)] on PG-synthesis utilizing the norbornene adduct obtained via the Diels Alder reaction, we started, this time, with 5-norbornen-2,3-dicarboxylic anhydride as a control element for the synthesis of 2.



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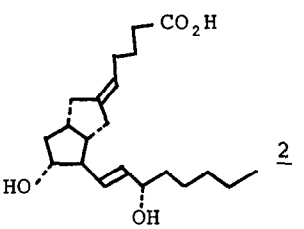


2

Lactone 3, prepared from the above carboxylic anhydride (hot H_2SO_4/H_2O), was reduced with diborane in THF (0°, 2hr), mesylated (MsCl-pyridine), and treated with NaCN in DMSO gave 4 in 76% overall yield. ir; 2250, 1780. Reduction of 4 with lithium borohydride in diglyme yielded the diol, which was treated with 1.1 eq. of benzoyl chloride and pyridine (-20°), and oxidation with Jones reagent

(H_2CrO_4) of the resulting monobenzoate gave the ketone 5 in 51% yield from 4 (mp. 119-121.5°C, ir; 2250, 1740, 1720). Baeyer-Villiger oxidation of 5 with 40% CH_3CO_3H (25°, 24hr) afforded a major lactone 6 (mp. 133.5-135°C) along with a minor regioisomer 7 in a ratio of ca 4:1. Methanolysis of 6 (H_2SO_4 in MeOH), followed by successive treatment with dihydropyran and p-toluenesulfonic acid in CH_2Cl_2 and debenzoylation (K_2CO_3 in MeOH) gave the alcohol 8.

Oxidation of 8 with pyridinium chlorochromate (PCC) in CH_2Cl_2 provided the cis aldehyde 9, which epimerized spontaneously to the trans aldehyde 10. This aldehyde 10 was immediately condensed with the sodium salt of dimethyl 2-oxo-heptyl phosphonate in THF to afford the enone 11 accompanied by the dienone 12 [11: nmr; 6.76(1H,q), 6.21(1H,m), 12: nmr; 7.17(1H,d), 6.35(1H,m), 5.97(1H,d)].

Some hardships encountered in the above course of reactions (low regioselectivity in the Baeyer-Villiger oxidation on 7 and dehydration occurred in the epimerization of 9) could be avoided by employing the trans benzoate 16 in stead of the cis one 5.

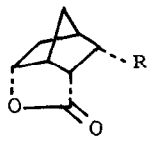
Acetalization of 5 (ethylene glycol and p-toluenesulfonic acid) and debenzoylation (K_2CO_3 in MeOH) gave the alcohol 13. Collins oxidation of 13 with (CrO_3-2 pyridine) provided the endo-aldehyde 14, (nmr δ; 9.55) which was converted to the exo-aldehyde 15 (nmr δ; 9.55) by treatment with piperidine and acetic acid in benzene at reflux 2.5hr. Reduction of 15 with $NaBH_4$, benzoylation (PhCOCl/pyridine) and deacetalization in aqueous acetic acid yielded the objective 16 (35% from 5, mp. 112-113°C, ir; 2250, 1750, 1720).

Baeyer-Villiger oxidation of 16 under milder condition (30% H_2O_2 in acetic acid) gave regioselectively the lactone 17 (mp. 91-93°C).

According to the same procedures in the cis alcohol 8, the lactone 17 was transformed to the trans alcohol 18. Oxidation of 18 with PCC, followed by condensation with the sodium salt of dimethyl 2-oxo-heptyl phosphonate gave the same enone 11 as obtained from 8.

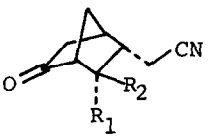
As a more effective route, the exo-aldehyde 15 could be directly converted to the enone 19 [ir; 1700, 1670, 1620, nmr; 6.6(1H,d,d), 6.0(1H,d)].

The enone 19 was reduced with $NaBH_4$ and hydrolyzed with aqueous acetic acid

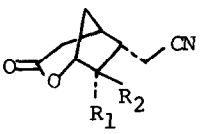


3: CO_2H

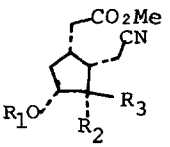
4: CH_2CN



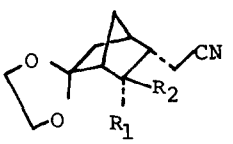
	R_1	R_2
5:	CH_2OCOPh	H
16:	H	CH_2OCOPh
20:	H	$CH=CHCHC_5H_{11}$ (OH)



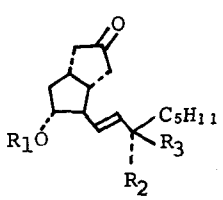
	R_1	R_2
6:	CH_2OCOPh	H
17:	H	CH_2OCOPh
21:	H	$CH=CHCHC_5H_{11}$ (OH)



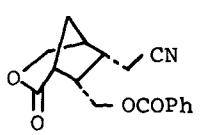
	R_1	R_2	R_3
8:	THP	CH_2OH	H
9:	THP	CHO	H
10:	THP	H	CHO
11:	THP	H	$CH=CHCOC_5H_{11}$
18:	THP	H	CH_2OH
22:	H	H	$CH=CHCH(OH)C_5H_{11}$
23:	THP	H	$CH=CHCHC_5H_{11}$ (OTHP)



	R_1	R_2
13:	CH_2OH	H
14:	CHO	H
15:	H	CHO
19:	H	$CH=CHCOC_5H_{11}$



	R_1	R_2	R_3
25:	H	OH	H
26:	H	H	OH
27:	THP	OTHP	H



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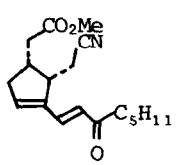

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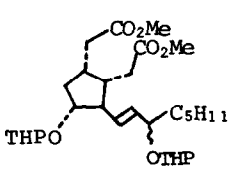

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to the alcohol 20, which was oxidized with 30% H_2O_2 and NaOAc in AcOH to give the regiospecific lactone 21 (65% from 19). Methanolysis of 21 with anhydrous potassium carbonate in MeOH gave the diol 22, which was treated with dihydropyran and p-toluenesulfonic acid in CH_2Cl_2 to the bis-THP ether 23. This ether 23 was coincided with the bis-THP ether derived from the enone 11 by successive reduction and tetrahydropyranylation. Hydrolysis of the nitrile 23 with potassium hydroxide in aqueous ethanol and esterification with diazomethane gave the diester 24 (67% yield from 23).

Dieckmann condensation of 24 (potassium t-butoxide in THF) provided a mixture of β-keto ester, which was subjected to demethoxycarbonylation with lithium iodide in pyridine and deprotection with aqueous acetic acid to give the key diol 25 and its epimer 26 in almost equal amount after separation by column chromatography on silica gel [41% yield from 24. Rf 0.12(25), 0.20(26), silica gel, AcOEt]. The diol 25 was converted to its bis-THP ether 27, which was reacted with the standard Wittig reagent [$Ph_3P=CH(CH_2)_3COONa$, in DMSO].

Deprotection of the resultant carboxylic acid with aqueous acetic acid (45°C, 2hr) led to the objective 2 and its C_5 Z isomer 28 (in a ratio; 2:28, 1:0.3) after separation of prep. TLC [Rf 0.13(2), 0.17(28), silica gel, $CHCl_3$:MeOH (10:1)].

References and Notes

1) Synthetic Studies on Cyclopentane Derivatives. Part X. Preceding paper: H. Shimomura, J. Katsube and M. Matsui, Agric. Biol, Chem., 42, 131 (1978).

2) For a recent review see: K. C. Nicolaou, G. P. Gasic and W. E. Barnette, Angew. Chem. Int. Ed. Engl. 17., 293 (1978).

3) a) K. Kojima and K. Sakai, Tetrahedron Letters., 3734 (1978).
b) K. C. Nicolaou, W. J. Sipio, R. L. Magolda, S. Seitz, and W. E. Barnette, J. Chem. Soc. Chem. Commun., 1978. 1067.
c) M. Shibasaki, J. Ueda, and S. Ikegami, Tetrahedron Letters., 433 (1979).

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