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AN EIGHT STEPS SYNTHESIS OF AN ORALLY ACTIVE ANTIHYPERTENSIVE CARBA-PROSTACYCLIN ANALOG

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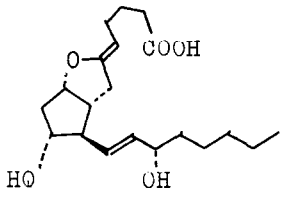
Abstract: A short synthesis of carbacyclin analog 1 (code no. EMD 46 335) starting from cyclopentadiene is described, with on overall yield of better than 5 %.

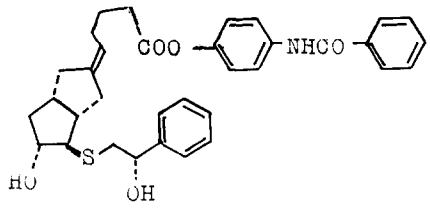
There is a need for a prostacyclin analog that is stable both chemically and metabolically. Chemical stability can be achieved by replacing to oxygen atom of the enolether function by a carbon atom (→ carbacyclin[1]). Metabolical stability can - for instance - be enhanced by adding a substituent to the C_{15} or C_{16} carbon atom.
To proceed on this line: since PGI_3[2] is more active than PGI_2, replacement of the C_{16-20}-n-pentyl chain by a phenyl group should furthermore result in an enhancement of activity. Replacement of the C_{13-14}-vinyl moiety by a S-CH_2-link was thought to provide compounds more convenient to synthesize.

We also were interested in designing a prodrug to the active part that does not only give rise to an enhanced shelf stability but also was to facilitate purification (i.e. 5 E,Z-separation) on the last step of its synthesis. On the other hand, it had to be labil enough to readily be activated in vivo and in vitro.

These considerations led to the preparation of the carbacyclin-analog benzamidophenylester 1 which indeed displayed all the desired features mentioned above.

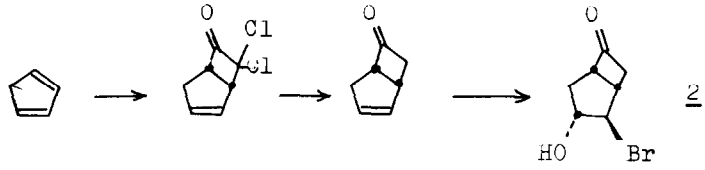


Prostacyclin, PGI_2



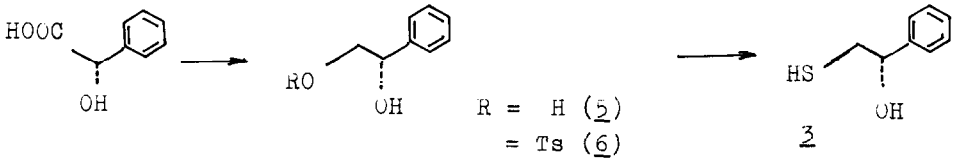
1 (EMD 46335)

Its synthesis started from the known bromohydrin 2[3] readily available in three steps from cyclopentadiene as described by E.J. Corey[4] and S. Roberts[3], and the



2

"lower side chain" thiol 3 which was obtained from L-(+)-mandelic acid (4): $LiAlH_4$ reduction according to lit.[5], gave S-(+)-phenylethane-1,2-diol 5[7]

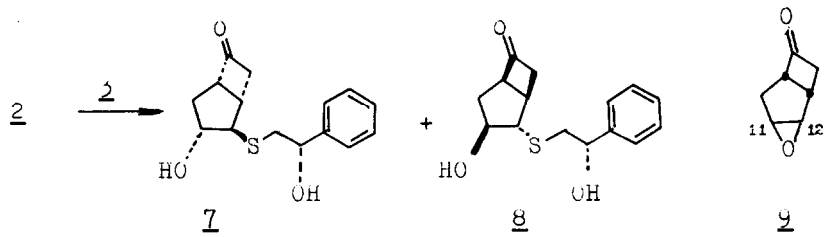


R = H (5)
= Ts (6)

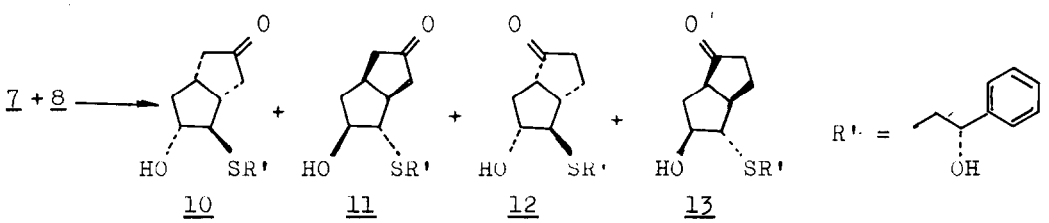
3

($[\alpha]_D^{20}$ 52.2° (c = 0.77, benzene), 33.2° (c = 0.1, CH_3OH) which was tosylated at the primary OH-group in pyridine at 0 °C overnight (6[7]: $[\alpha]_D^{20}$ 53.6°. (c = 0.1, $CHCl_3$), m.p. 76 °C), and then subjected to thiolation (H_2S, CH_3OH, 1. $NaOCH_3$, 2. $HNiPr_2$, r.t.; 3[7]: m.p. ~ -5 °C, $[\alpha]_D^{20}$ 33.2° (c = 0.1, CH_3OH); NMR: δ 7.32 (phenyl), 4.82 (t, benzyl), 1.42 (t, SH) ppm; no traces of the enantiomer were seen after addition of chiral shift reagents).

The addition of one equivalent of 3 and 1.1 eq. of 2 molar aqueous sodium hydroxide to bromohydrin 2 in methanol at room temperature and standing overnight gave, after work up and crystallization, a 1:1 mixture[7] of isomer 7 and 8 (m.p. 82 °C; $[\alpha]_D^{20}$ 36.9° (c = 0.1, $CHCl_3$); nmr: δ 7.4 (phenyl), 4.88 (2d, benzyl), 3.7 (2d, H_{11}) ppm; ir:ν = 3450,2980, 1780 cm^{-1}; ms: m/e$^-$: 218,201,172,107; t.l.c.: CH_2Cl_2-3 % CH_3OH, R_F 0.1, detection: vanillin-phosphoric acid (VPA)), in about 70 % yield.



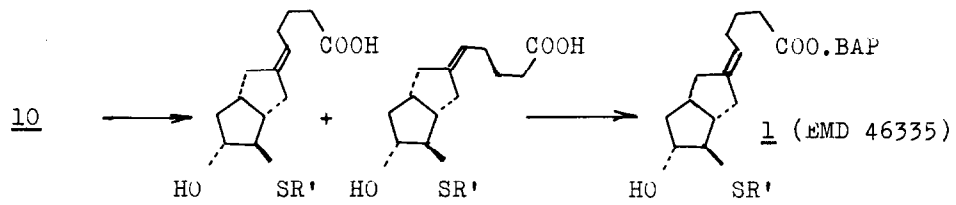
Clearly, the reactive intermediate is epoxide 9[2] which, however, can not be spotted on t.l.c. since it is immediately attacked by the thiol, once generated. Surprisingly, thiol addition occurs almost regiospecifically at carbon 12 (prostaglandin numbering) with only minute amounts of products arising from attack at C_{11} (less than 5 %; compare lit.[3]). Since isomers 7 and 8 could only be separated with difficulties, by column chromatography or fractional crystallization, the mixture of it was subjected to ring expansion by diazomethane - freshly prepared from N-nitrosomethyl urea as an ether-tetrahydrofuran (THF) solution without distillation (the hazards of this reagent can be deminished considerably by first dissolving N-nitrosomethyl urea in THF and letting flow down this solution at the inside of an erlenmeyer to a gently stirred (magnetically) and cooled mixture of ether and aqueous potassium hydroxide, using new and clean glassware). Addition of methanol (and/or water) to the ketone solution enhanced the reaction rate and after one hour conversion was 80 - 90 %. Excess CH_2N_2 was then destroyed by careful addition of acetic acid, and volatile materials were stripped off, to give rise to a yellowish oil which consisted of a mixture of each ~ 25 % of 10 and 11, each ~ 10 % of 7, 8, 12, and 13, and higher homologs.



Separation of the could easily be accomplished by column chromatography on silica gel (MERCK LOBAR^R column, size C) eluting with a 7:3 mixture of methy tert. butyl ether (MTB) and cyclohexane to give pure 10 in 23 % yield. (10[7]: oil; $[\alpha]_D^{20}$ 19.7° (c = 0.1, $CHCl_3$); nmr: δ 7.32 (phenyl), 4.80 (2d, benzyl), 4.13 (2d, H_{11}) ppm; ir: ν = 3300, 2950, 2920, 2860, 1722 cm^1; ms: m/e: 186, 168, 138, 122, 107; t.l.c. MTB, R_F 0.3; VAP; 11: oil $[\alpha]_D^{20}$ 55.6° (c = 0,1, $CHCl_3$); nmr: δ 7.3 (phenyl), 4.88 (2d, benzyl), 4.14 (2d, H_{11}), 2.98 (2d, SCH_2) ppm; ir: ν 3300, 1722 cm^{-1}; t.l.c.: MTB, R_F 0.25, VPA)

On TLC, isomers 10 and 11 can clearly be distinguished from all the other compounds by spraying with VPA, heating the plate, so the spots become visible, and then spilling water over it: only 10 and 11 then change their color from dark blue to light yellow.

Wittig olefination[1] of 10, utilizing the ylide prepared from phosphonium salt 16 and potassium tert. butoxide in THF at room temperature, gave rise to a 6:4 mixture of E, Z-isomers 14 and 15, which were not separated but immediately esterified with p-benzamidophenol (prepared from benzoic anhydride and p-aminophenol according to lit.[6]) in dichloromethane-dimethylformamide at room temperature, taking advantage of the dicyclohexylcarbo-



$Ph_3\overset{+}{P}-(CH_2)_4COOH,Br^-$ (16) BAP = p-Benzamidophenyl

diimide-dimethylaminopyridine procedure, and crystallized from an ether/acetone mixture to give pure 1 in 33 % yield from 10. (1[7]: m.p. 128 °C; $[\alpha]_D^{20}$ 35.6° (c = 0.1, $CHCl_3$); nmr: δ 7.9 - 7.0 (phenyl), 5.34 (t, vinyl), 4.80 (2d, benzyl) ppm; ir: ν 3350, 2940, 1745, 1655, 1190, 700 cm^{-1}; ms: only benzamidophenol fragments; t.l.c.: MTB-cyclohexane-1 % acetic acid; R_F 0.4, VPA).

EMD 46 335 (1) proved to be highly active in lowering the blood pressure of renal hypertensive dogs, given per os. Detailed pharmacological results will be reported in due course.

We thank Dr. Schulze and Dr. Harting of E. MERCK Pharmacol. Res. Labs. for performing the medical tests.

References and Notes

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7. Elemental analysis gave satisfactory results.

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