SYNTHESIS OF (±)11-OXACARBACYCLIN

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(±)11-Oxacarbacyclin (1) has been synthesized from 4-oxo-cis- and
trans-1,2-cyclopentanedicarboxylic acid (3 and 4).
KEYWORDS—prostacyclin analogue; Wittig reaction;
carbacyclin analogue; arachidonic acid cascade

Prostacyclin (2a), a very important metabolite of arachidonic acid, has
been shown to be a potent inhibitor of human platelet aggregation and a relaxer
of certain vascular tissues. 1) The short half life time under physiological
conditions limits the clinical use of this compound. Therefore, our research
has focussed on the synthesis of orally active and chemically stable analogues
of prostacyclin. 2, 3) The present paper describes the synthesis of
(±)11-oxacarbacyclin (1).

The acid anhydride (5), HOOC
which was obtained from the
cis dicarboxylic acid (3) 4) by
heating with Ac2O at 140°C
or the trans dicarboxylic
acid (4) 4) by heating with meta-
phosphoric acid at 200°C, was reduced with NaBH4 in aq.THF to the hydroxy
lactone (6) in 78% yield. Subsequent Jones oxidation of 6 afforded the lactone
(7) which retains the cis ring junction.

The introduction of the ω-chain was accomplished by an indirect method as
follows. Acetalization of 7 by the usual method afforded the acetal (8) in 83%
yield as colorless needles, mp 76°C. Reduction of 8 with diisobutylaluminum
hydride (DIBAL-H) followed by the Wittig reaction with carbomethoxymethylene-
triphenylphosphorane in toluene at 100°C yielded the α,β-unsaturated ester (10)
in 76% yield from 8. On heating at 50°C in the presence of K2CO3 in MeOH,
the primary alcohol in 10 was converted into the tetrahydrofuran ring (11) via
the Michael type addition. Direct conversion of the lactol (9) to 11 was accomplished in good yield by heating with carboxethoxymethyleneetetraphenylphosphorane in xylene under reflux. Although 11 showed one spot on TLC (AcOEt: hexane 1:2) and each signal of the methyl ester and the acetal in $^1$H-NMR was observed as a singlet, at 3.70 and 3.92, respectively, the aldehyde derived from 11 was observed as two adjacent spots (Rf 0.72 and 0.62 in AcOEt:hexane 1:2) on TLC. This fact suggests that compound 11 consists of a mixture of the C$_{12}$$^a$-methyl ester and the C$_{12}$$^b$-methyl ester (PG numbering).

The ester function was converted to the aldehyde by the following route. The methyl ester moiety in 11 was reduced with LiAlH$_4$ in ether to the corresponding alcohol (12), which was converted to the tosylate (13) by the usual method. Treatment of 13 with NaI in HMPA afforded the iodide (14) in 98% yield. The dehydrohalogenation reaction of 14 to the vinyl compound (15) by treatment with t-BuOK in DMSO at room temperature and subsequent Lemieux-Johnson oxidation (NaIO$_4$-O$_2$SO$_4$) afforded a mixture (Rf 0.72 and 0.63 in AcOEt:hexane 1:2) of the C$_{12}$$^a$- and the C$_{12}$$^b$-aldehyde. On treatment with K$_2$CO$_3$ in MeOH at 50-60°C, a mixture of the C$_{12}$$^a$-epimeric aldehydes was isomerized to the sole compound having Rf 0.72 which was considered to be the thermodynamically more stable C$_{12}$$^b$-aldehyde (16).

Wittig reaction of 16 with 2-oxo-heptylidenedibutylphosphorane in ether at room temperature afforded in 58% yield the enone (17) which on reduction with NaBH$_4$ in MeOH gave a mixture of the C$_{15}$$^a$-epimeric alcohols (18). As attempts to separate them into the C$_{15}$$^a$- and the C$_{15}$$^b$-alcohol were unsuccessful, we were forced to alter the first synthetic plan to separate each alcohol in the last stage of the synthesis. By deacetalization in the usual manner followed by protection of the C$_{15}$-alcohol with dihydropyran in the presence of p-toluenesulphonic acid, 18 was converted via the compound (19) into the tetrahydropyranol ether (20) in 98% yield. In order to introduce the $\alpha$-chain, 20 was subjected to the Wittig reaction with 4-sodiocarboxybutylidenedi- triphenylphosphorane in DMSO. This Wittig reaction, followed by treatment with CH$_2$N$_2$, afforded the ester (21) in a much better yield (98%) than that of the corresponding ketone in carbacyclin (2b) synthesis. The ester (21) could be separated into the 5(E)- and 5(Z)-isomer as follows. The hydrolysis of the tetrahydropyranol ether in 21 with 3.5% HCl afforded the alcohol (22). By hydrolysis with 5% aq.NaOH and subsequent Jones oxidation, 22 was converted via the compound (23) into the enone which could be separated into the more polar fraction and the less polar fraction by careful column chromatography. The more polar fraction (25) was tentatively assigned to the 5(E)-isomer and the less polar fraction (24) to the 5(Z)-isomer, as in the assignment for carbacyclin (2b) and its 5(Z)-isomer. Reduction of 25 with NaBH$_4$ afforded a mixture of the C$_{15}$$^a$-epimeric alcohols which could be separated into the C$_{15}$$^a$-alcohol (26) and the C$_{15}$$^b$-alcohol (27) via the methyl ester. The configuration of the C$_{15}$-alcohol was tentatively assigned according to a general rule in PG chemistry in which the configuration of the C$_{15}$$^a$-OH was assigned to a more polar fraction on TLC. The hydrolysis of 26 and 27 with 5% aq.NaOH yielded 27 and 28, respectively.
11-Oxacarbacyclin(1) inhibited collagen-induced platelet aggregation, but it was appreciably less active (ca. 10^-2) than carbacyclin. Details of biological data will be published elsewhere.

![Chemical structures](image)

REFERENCES AND NOTES

5) The ratio of 5(E) to 5(Z) was 2.2.
6) The C_{15}^\alpha-alcohol (26, 250mg), the C_{15}^\beta-alcohol (27, 313mg) and the mixture (26 and 27, 212mg) were obtained from 25 (847mg).
7) Colorless oil. IR(neat): 3330, 3360, 1730, 1710, 1125, 1050, 970 cm^{-1}. ^1H-NMR(CDC)δ: 0.88(3H, t, J=6Hz, CH\_3), 3.20-3.50(1H, d, J=7,4Hz, C\_12-H), 3.60-3.85(1H, m, C\_15-H), 3.90-4.29(2H, m, C\_10-H), 5.25(1H, t, J=6Hz, C\_5-H), 5.67-5.80(2H, m, C\_13-H and C\_14-H). MS m/e: 336(M\^+), 318, 263, 237.

(Received December 9, 1983)