

SYNTHESIS OF BIOLOGICALLY ACTIVE 6-AZAPROSTACYCLIN DERIVATIVES¹

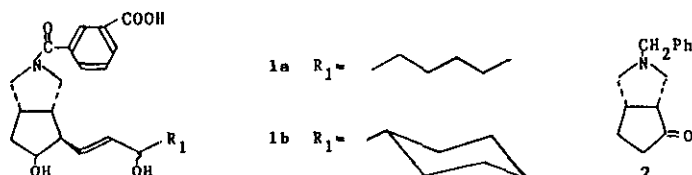
Keisuke Miyajima, Masumi Takemoto, and Kazuo Achiwa*

School of Pharmaceutical Sciences, University of Shizuoka, Oshika 2-2-1,
Shizuoka 422, Japan

Abstract — Biologically active 6-azaprostacyclin derivatives were synthesized by use of 1,3-dipolar cycloaddition as a key step.

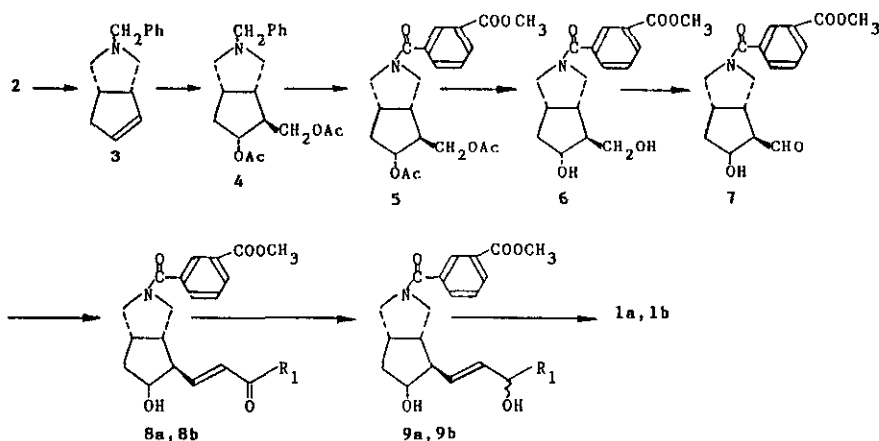
Prostacyclin (PGI₂) has a very potent activity in inhibition of blood platelet aggregation leading to the wide application for the treatment of thrombosis, stroke and heart attack. However, PGI₂ is rather unstable molecule, whose instability is arising from the presence of an enol ether functionality. Therefore, a lot of biologically active prostacyclin analogs were synthesized including the 6-azaprostacyclins² and the carbacyclins which have a benzoic acid group as the α -chain.³

In this paper, we wish to report the synthesis of dl-6-azaprostacyclin derivatives, 1a and 1b, whose skeleton can be constructed by 1,3-dipolar cycloaddition developed in our laboratory.⁴



N-Benzyl-3-azabicyclo[3.3.0]octan-8-one (2)⁴ was synthesized by 1,3-dipolar cycloaddition of an intermediary iminium ylide formed from N-benzyl-N-(methoxymethyl)trimethylsilylmethylamine to 2-cyclopenten-1-one in the presence of a catalytic amount of trifluoroacetic acid. Tosylhydrazone formation from 2 and toluene-*p*-sulfonylhydrazide in ethanol containing a catalytic amount of trifluoroacetic acid (reflux, 2 h) and following decomposition catalyzed by disodium ethylene glycolate in diethylene glycol (HMPA, reflux, 6 h)^{5,6} afforded 3 (57% from 2). Prins reaction⁷ of 3 (70°C, 3 d) gave the diacetate 4 (57%). N-Debenzylation of 4 catalyzed by palladium on carbon in ethanol (50°C, 18 h) followed by acylation with isophthalic acid monomethyl ester chloride in THF (Et₃N, DMAP, 25°C, 12 h) afforded 5 (80% from 4).

Methanolysis of 5 with hydrochloric acid in methanol (25°C, 1 h) gave the alcohol 6 (80%). Selective oxidation of 6 with the Pfitzer-Moffatt reagent⁸ gave the corresponding aldehyde 7, which was then converted with the sodium salt of dimethyl (2-oxoheptyl)phosphonate⁹ to the enone 8a (67% from 6). Similarly, Wittig reaction of the aldehyde 7 with cyclohexyl (triphenylphosphoranylidene)methyl ketone¹⁰ in THF (reflux, 4 h) afforded the enone 8b (33% from 6). Reduction of 8a and 8b with zinc borohydride⁹ in DME (25°C, 2 h) gave the C-15 (prostanoid numbering) epimeric mixture 9a (85%) and 9b (83%), respectively. Hydrolysis of 9a and 9b without separation with aqueous base (25°C, 2 h) afforded 1a (80%) and 1b (73%), respectively. These compounds (1a and 1b) showed weak inhibitory activity in blood platelet aggregation.



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- 11) Ir (neat): 3382 (OH), 1724 (C=O), 1621 cm^{-1} (N-C=O); $^1\text{H-nmr}$ (CDCl_3) δ : 0.88 (3H, br t, $J=6.3\text{Hz}$, CH_3), 1.26 (8H, br s, $-(\text{CH}_2)_4-$), 5.54~5.78 (2H, m, $\text{CH}=\text{CH}$), 7.36~8.21 (4H, m, C_6H_4); FAB mass (M^+) at m/z 401.
- 12) Ir (neat): 3400 (OH), 1719 (C=O), 1621 cm^{-1} (N-C=O); $^1\text{H-nmr}$ (CDCl_3) δ : 5.25~5.72 (2H, m, $\text{CH}=\text{CH}$), 7.46~8.25 (4H, m, C_6H_4); FAB mass ($\text{M}+\text{Na}^+$) at m/z 435.

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