SYNTHESIS OF BIOLOGICALLY ACTIVE 6-AZAPROSTACYCLIN DERIVATIVES[1]

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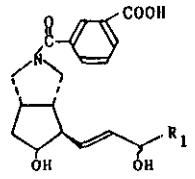
Abstract —— Biologically active 6-azaprostacyclin derivatives were synthesized by use of 1,3-dipolar cycloaddition as a key step.

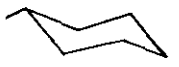
Prostacyclin (PGI_2) has a very potent activity in inhibition of blood platelet aggregation leading to the wide application for the treatment of thrombosis, stroke and heart attack. However, PGI_2 is rather unstable molecule, whose instability is arising from the presence of an enol ether functionality. Therefore, a lot of biologically active prostacyclin analogs were synthesized including the 6-azaprostacyclins[2] and the carbacyclins which have a benzoic acid group as the α-chain.[3]

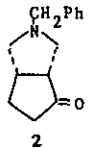
In this paper, we wish to report the synthesis of dl-6-azaprostacyclin derivatives, **1a** and **1b**, whose skeleton can be constructed by 1,3-dipolar cycloaddition developed in our labolatory.[4]



1a R_1 =

1b R_1 =





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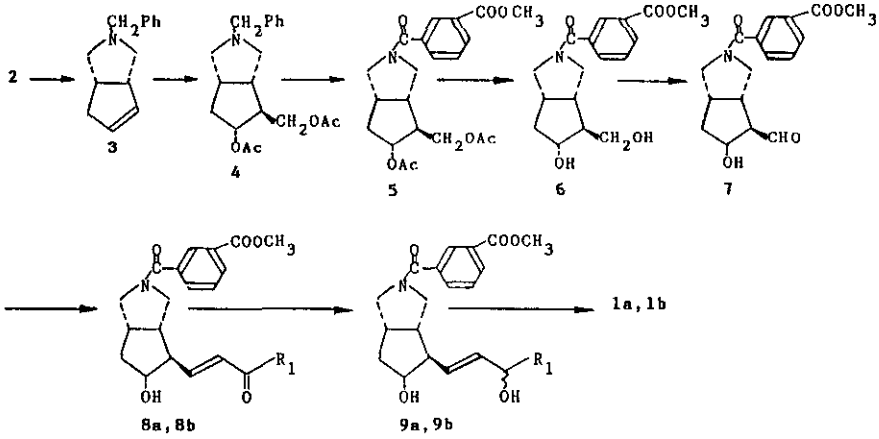
N-Benzyl-3-azabicyclo[3.3.0]octan-8-one (**2**)[4] was synthesized by 1,3-dipolar cycloaddition of an intermediary iminium ylide formed from N-benzyl-N-(methoxymethyl)trimethylsilylmethylamine to 2-cyclopenten-1-one in the presence of a catalytic amount of trifluoroacetic acid. Tosylhydrazone formation 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 reaction[7] 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 (Et_3N, 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 reagent[8] gave the corresponding aldehyde **7**, which was then converted with the sodium salt of dimethyl (2-oxoheptyl)phosphonate[9] to the enone **8a** (67% from **6**). Similarly, Wittig reaction of the aldehyde **7** with cyclohexyl (triphenylphosphoranylidene)methyl ketone[10] in THF (reflux, 4 h) afforded the enone **8b** (33% from 6). Reduction of **8a** and **8b** with zinc borohydride[9] in DME (25°C, 2 h) gave the C-15 (prostanoic 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}H-nmr ($CDCl_3$) δ: 0.88 (3H, br t, J=6.3Hz, CH_3), 1.26 (8H,br s,-$(CH_2)_4$-), 5.54~5.78 (2H,m,CH=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}H-nmr ($CDCl_3$) δ: 5.25~5.72 (2H,m,CH=CH), 7.46~8.25 (4H,m,C_6H_4); FAB mass $(M+Na)^+$ at m/z 435.

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