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# INTRAMOLECULAR CYCLOADDITIONS OF KETENIMINIUM SALTS. A NOVEL APPROACH TOWARD PROSTAGLANDINS

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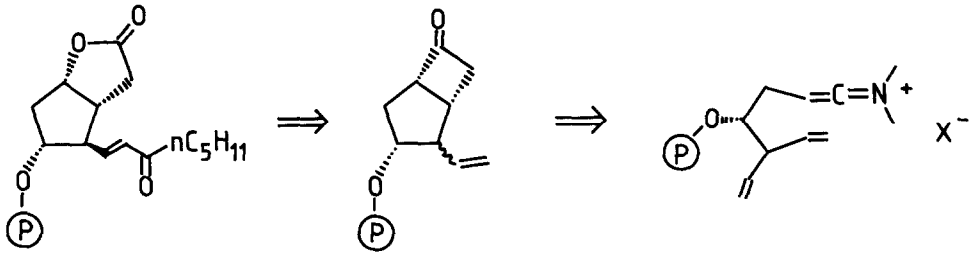
Summary: The intramolecular [2+2] cycloaddition of an α,β-unsaturated keteniminium salt is the key step of a short synthetic route toward prostaglandins.

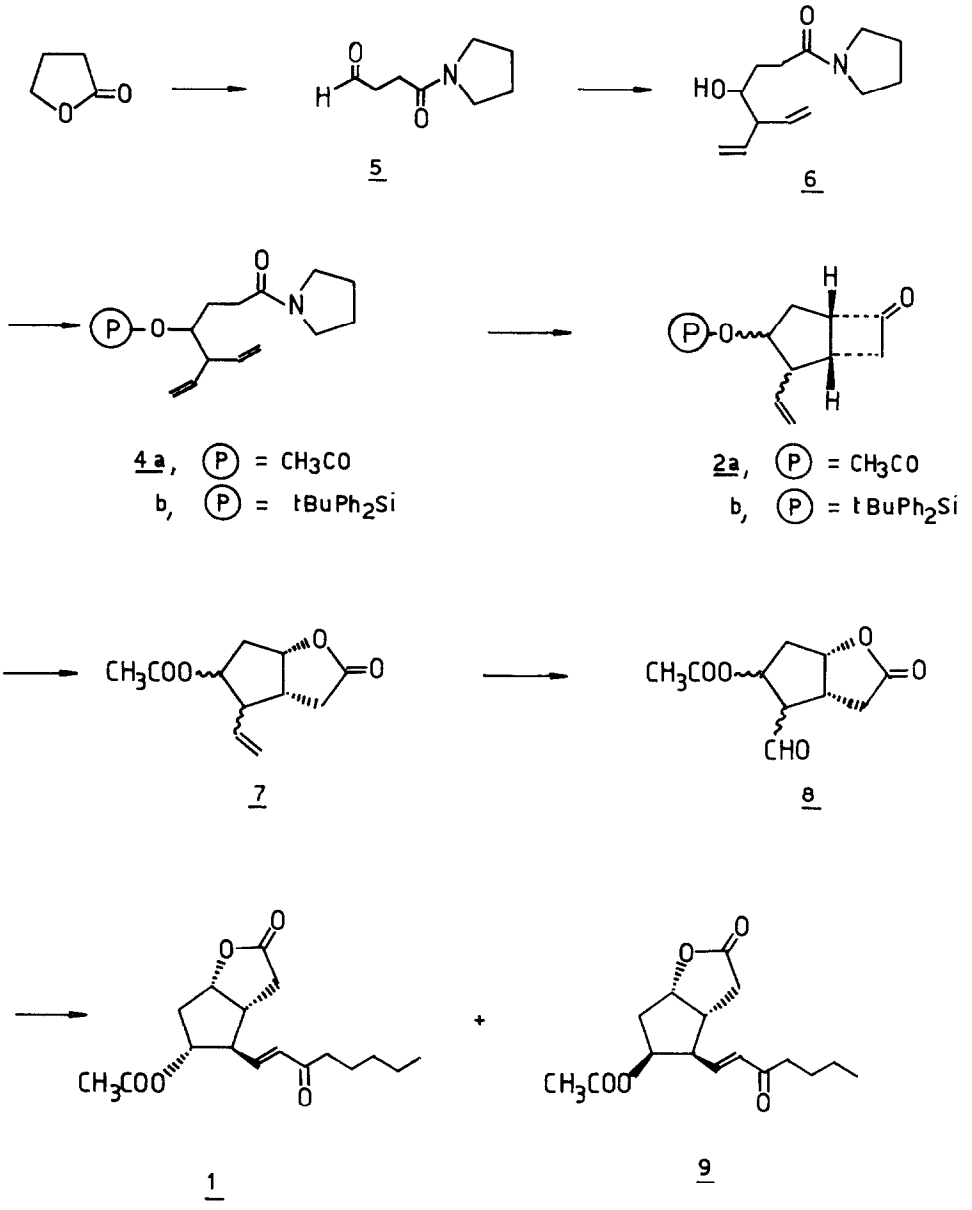
The stereospecific [2+2] cycloaddition of ketenes or keteniminium salts to olefins is a practical method of synthesis of cyclobutanones[1]. It is the key step in the vicinal alkylation of an alkene[2]. Two major developments of this methodology have been recently reported. It has been shown that cyclobutanones of high optical purity can be obtained from chiral keteniminium salts and olefins[3]. Moreover, we and others have illustrated the utility of the intramolecular cycloaddition of ketenes and keteniminium salts to olefins as a general synthetic method[4].




1 (Ⓟ = protecting group) 2 3

Scheme 1

This communication describes an application of this strategy to the synthesis of an advanced intermediate 1 toward prostaglandins (Scheme 1). It was anticipated that 1 could be readily obtained from the bicyclo[3,2,0] heptanone precursor 2 prepared by the intramolecular cycloaddition of the keteniminium salt 3.




Scheme 2

A potential precursor of 3 is amide 4a which was readily prepared by a simple sequence of operations. Treatment of γ-butyrolactone with pyrrolidine (4 equiv. reflux, 16hrs) followed by Swern oxidation (1 equiv. of oxalyl chloride, 2 equiv. of DMSO, $CH_2Cl_2$; -60°C then $Et_3N$, 15 min, -60°C then 30 min at 20°C) gave 5 in 85% yield. Slow addition (2.5 hrs) of a THF solution of 5 and pentadienyl bromide (3 equiv.) to a suspension of zinc (3.2 equiv.) in THF yielded an oily hydroxyamide 6 which was directly acylated ($CH_3COCl$ - pyridine) to give 4a (72 %).

The cycloaddition was effected by adding triflic anhydride (2 equiv. in $CH_2Cl_2$, 10 hrs) to a mixture of 4a and collidine (1.2 equiv.) in refluxing dichloromethane. Hydrolysis ($H_2O$-$CCl_4$, 90°C) of the crude iminium salts and chromatography on silica gel ($CH_2Cl_2$) gave 2a (94%) as a mixture of four diastereoisomers 2a in the ratio 4:2:2:1 (glc).

Baeyer-Villiger oxidation of bicyclo [3,2,0] heptanones 2a with m-chloroperbenzoic acid-$NaHCO_3$ gave the ring expanded product 7 resulting from highly selective ($\geq$93%) migration of the methine group[5]. The crude mixture of diastereoisomeric lactones was directly ozonized ($O_3$, $CH_3OH$ -70°C then $(CH_3)_2S$) to aldehyde 8 which was used without purification in the Wittig-Horner reaction ($(C_2H_5O)_2P(O)CH_2COC_6H_{11}$, NaH, THF, -10°C to 20°C). Chromatography on silica gel (benzene-ethyl acetate 2:1), gave two major fractions which were proven[6] to be lactones 1 (16%) and 9 (30 %). Thus the reaction sequence allows the establishement of three stereocenters with high selectivity. It is highly probable that control of the stereochemistry of the side-chain relative to the lactone is the result of equilibration at the aldehyde stage or during the Wittig-Horner reaction. Clearly the remaining problem in this strategy is the control of the stereochemistry of the oxygenated function which is quite remote from the reacting centers in the cycloaddition step.

The stereoselectivity was significantly improved by using a bulkier protecting group for the alcohol function of 6. Thus amide 4b was obtained in 70% yield by reacting 6 with t-butyldiphenylsilyl chloride in DMF in the presence of imidazole at 60°C. The cycloaddition was effected as described above for 4a. Hydrolysis ($H_2O$-$CCl_4$, 90°C), gave bicyclo[3.2.0] heptan-6-one 2b (70%) as a mixture of diastereoisomers in the ratio 20:30:6 (glc). The stereoselectivity has thus been considerably improved. Compound 2b was transformed into 2a ($Bu_4N^+F^-$, THF, 20° then $CH_3COCl$-pyridine, 47%) which was submitted to the sequence described above. This led to a mixture of two epimeric lactones 1 and 9 in the ratio 1:55. Thus, increasing the bulk of the protecting group improved the stereoselectivity in favour of the 11-epi (PG numbering) series.

These results clearly indicate the power of the intramolecular [2+2] cycloaddition reaction of keteniminium salts to efficiently generate prostaglandin intermediates. We are currently examining the use of chiral keteniminium salts to generate intermediates 1 and 9 in optically pure forms.

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