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Regioselective Cyclopropanation Reactions using Iodonium Ylides: Synthesis of Prostaglandin Precursors

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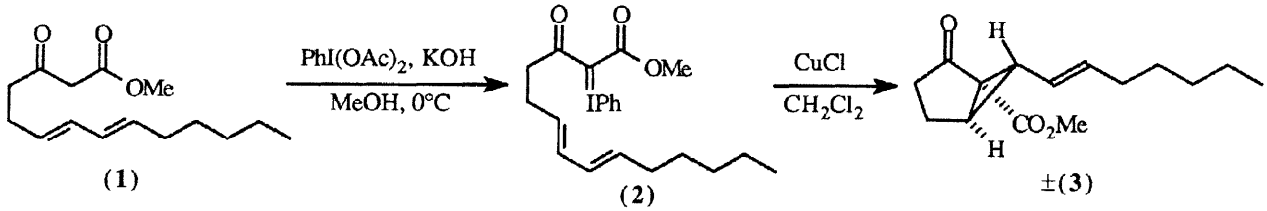
Abstract: Iodonium ylides of methyl 3-oxo-*trans,trans*-6,8-tetradecadienoate (**1**) and diprotected methyl 3,5-di(t-butyldimethyl-silyloxy)-2,6,8-tetradecatrieneoate (**5**) undergo regio- and stereoselective intramolecular cyclopropanation with Cu(I)Cl catalysis to form key bicyclo[3.1.0] intermediates for prostaglandin synthesis.

Since the elucidation of the structure of prostaglandin E_1 in 1962,[1] extensive efforts have been devoted towards the synthesis of a wide array of prostaglandin analogs.[2-6] A case in point is the cyclopropanation-homoconjugation addition method[7-13] which still plays an important role in prostaglandin synthesis because it allows direct control of side-chain stereochemistry. Moreover, the decomposition of α-diazo carbonyl compounds is the only method available for the synthesis of these bicyclic[3.1.0] cyclopropanated intermediates.[8-12] Because of our interest in organohypervalent iodine and the advantage of substitution of iodonium ylides for diazodicarbonyls (potential carcinogenicity and explosiveness of diazo compounds), [14-16] we sought to adapt this methodology to the synthesis of prostaglandins A_2, $F_{2\alpha}$, and 11-deoxyprostaglandin E_1.

Methyl 3-oxo-*trans,trans*-6,8-tetradecadienoate[10,12] (**1**) was converted to iodonium ylide **2** by treatment with iodobenzene diacetate and potassium hydroxide in methanol at 0°C in 85% yield as a white solid. The decomposition of iodonium ylide **2** with a catalytic amount of Cu(I)Cl in dry dichloromethane at room temperature afforded a racemic endo/exo mixture of methyl 6-(*trans*-1-heptenyl)-2-oxobicyclo[3.1.0]hexane-1-carboxylate (**3**) in 75% yield. The cyclopropanation reaction occurs *via* syn addition to the double bond controling the relative stereochemistry at C_6, and it clearly displays a regioselectivity for the bicyclo[3.1.0] ring system rather than the larger bicyclo[5.1.0] ring system.[17] Using known procedures, the bicyclo[3.1.0] cyclopropanated intermediate (**3**) can be converted to 11-deoxyprostaglandin E_1[10] or prostaglandin A_2.[12]



(**1**) (**2**) ±(**3**)

Methyl 5-hydroxy-3-oxo-*trans,trans*-6,8-tetradecadienoate (**4**)[11] was treated with t-butyl-dimethylsilyl chloride and imidazole in dry dimethylformamide to yield the diprotected methyl 3,5-di(t-butyldimethyl-silyloxy)-2,6,8-tetradecatrienoate (**5**) in 92% yield as a yellow oil. The protected silyl enol ether **5** was converted to iodonium ylide **6** by treatment with iodobenzene diacetate and potassium hydroxide in methanol at

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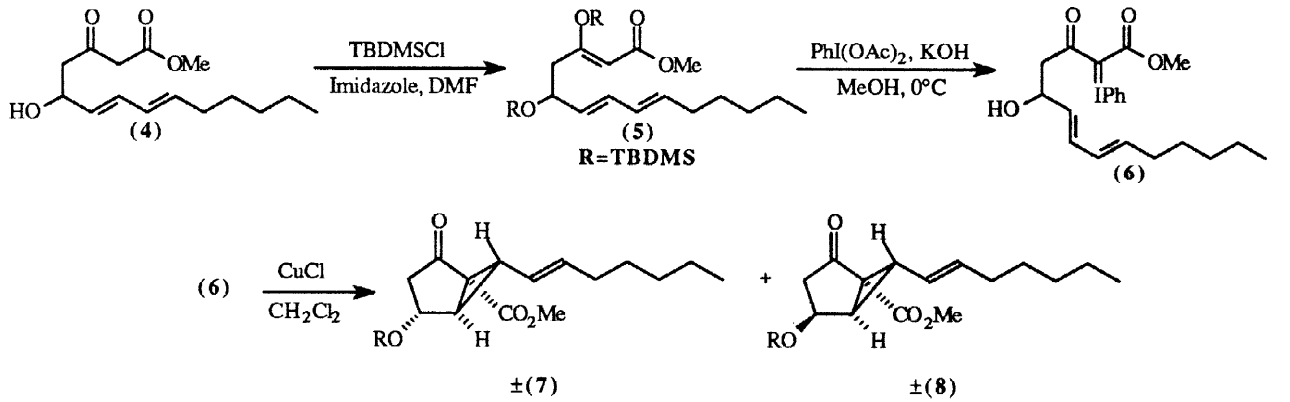
0°C in 50% yield and was obtained as a yellow oil. Decomposition of iodonium ylide **6** with a catalytic amount of Cu(I)Cl in dry dichloromethane gives the bicyclo[3.1.0] hexane products **7** and **8** in 37% and 34% yield respectively. These two racemic diastereoisomers were separated by column chromatography, and methyl 4-t-butyldimethylsilyloxy-6-(*trans*-1-heptenyl)-2-oxobicyclo-[3.1.0]hexane-1-carboxylate (7) can be converted using a minor modification of literature methods to prostaglandin $F_{2\alpha}$.[11]



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