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Intramolecular Cycloadditions of Keteniminium Salts. A Practical Asymmetric Synthesis of Prostaglandins.

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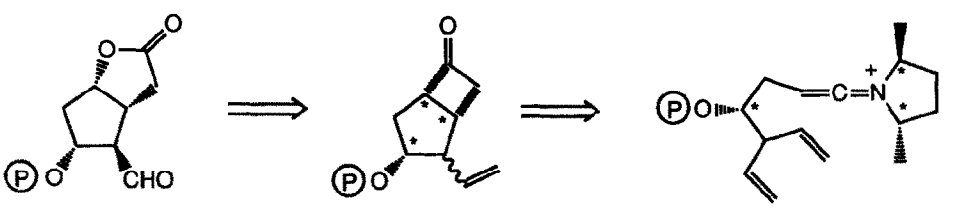
Abstract : The intramolecular [2 + 2] cycloaddition of keteniminium salt **5** derived from (2S, 5S)-dimethylpyrrolidine is the key step of a short synthetic route toward prostaglandins.

The intramolecular [2 + 2] cycloaddition of a ketene or a keteniminium salt to an olefinic double bond offers an easy access to various polycyclic systems.[1] It has been successfully used as a key step in a short synthesis of an advanced intermediate toward prostaglandins.[2]

The present communication describes an asymmetric version of this synthetic route in which a keteniminium salt derived from (2S, 5S)-dimethylpyrrolidine[3] is used as the cycloaddition reagent. The general strategy is outlined in Scheme 1.

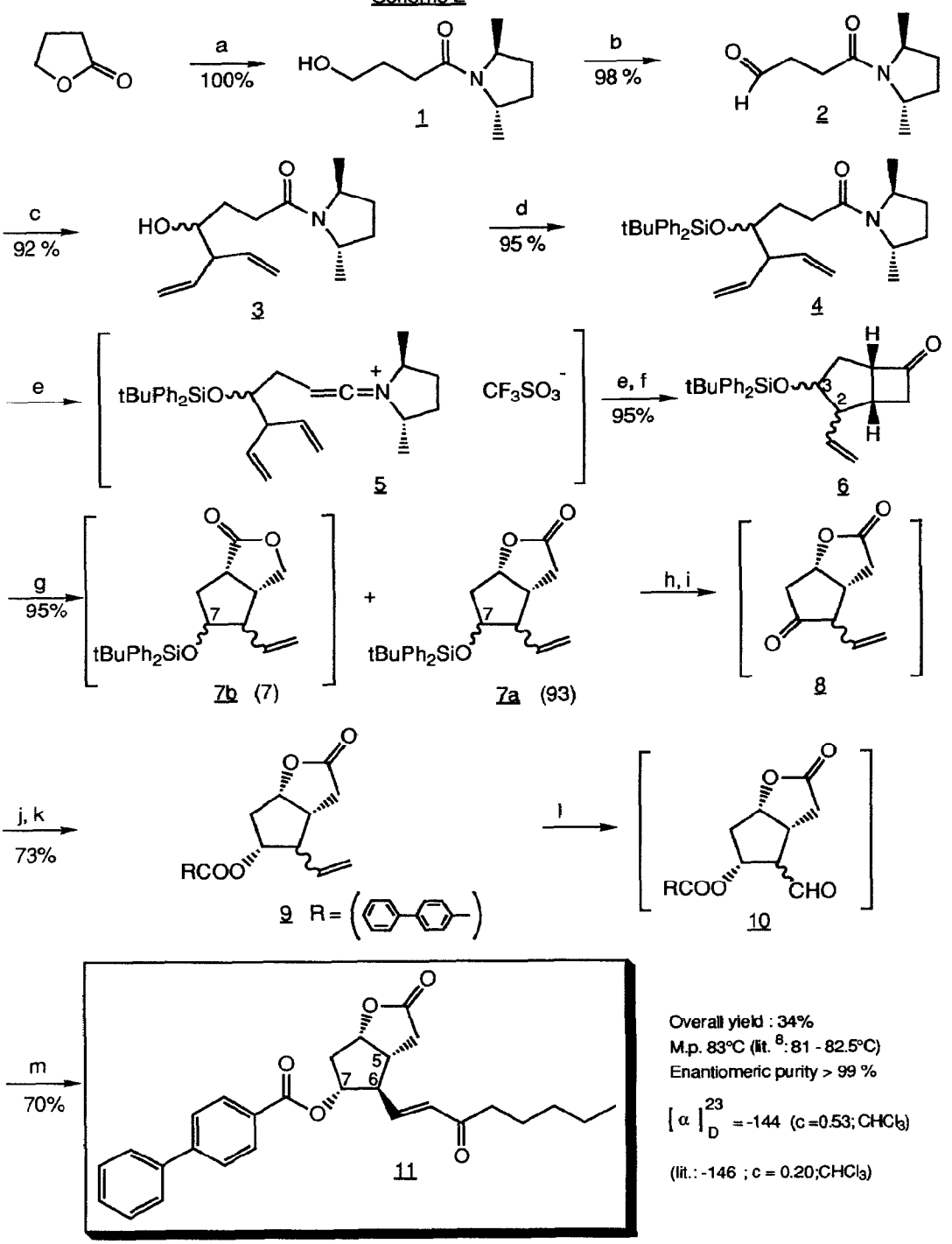


P = Protecting group

Scheme 1

The synthesis began with γ-butyrolactone (Scheme 2) which was quantitatively converted into the γ-hydroxyacid **1** by treatment (a : 2 equiv. Et_3N, reflux, 12 hrs) with 2 equiv. of (2S, 5S)-dimethylpyrrolidine. Swern oxidation (b : $(COCl)_2$, DMSO, Et_3N in CH_2Cl_2, - 60° C to - 20° C) followed by chromatography

Scheme 2


a
100%
HO
1
b
98 %
2
c
92 %
3
d
95 %
tBuPh2SiO
4
e
CF3SO3-
5
e, f
95%
6
g
95%
7b (7)
7a (93)
h, i
8
j, k
73%
RCOO
9 R=
l
CHO
10
m
70%
11
Overall yield : 34%
M.p. 83°C (lit. [8]: 81 - 82.5°C)
Enantiomeric purity > 99 %
[α]D23 = -144 (c =0.53; CHCl3)
(lit.: -146 ; c = 0.20;CHCl3)

yielded the pure γ–oxoamide **2**. The slow addition (step c) of a THF solution of **2** and pentadienyl bromide into a suspension of zinc powder in refluxing THF containing a catalytic amount of iodine led to the desired coupling product **3**. However yields were not readily reproducible as a result of a competing homocoupling of the organozinc reagent. Higher and reproducible yields (86 - 94 %) were obtained with ultrasonic activation in the absence of iodine. The coupling reaction took place with a low facial selectivity (± 25 % determined on the diastereoisomeric cyclobutanones resulting from the cycloaddition step). In principle higher selectivity could have been obtained by running the coupling reaction in the presence of a chiral catalyst, as shown recently for the reaction of diethylzinc with aldehydes.[5] However this implies that the coupling reaction be performed at ≤ 0° C, but at this temperature, the regioselectivity of coupling with pentadienylzinc bromide was low.

Protection of the hydroxyl group (d : t-$BuPh_2SiCl$, imidazole, DMF, 60° C) yielded **4**. Treatment with triflic anhydride and 2,6-di-t-butyl-4-methylpyridine (e : 1,2 dichloroethane, ultrasound, r.t.) generated the keteniminium salt **5** which cycloadded to give, after hydrolysis (f : H_2O - CCl_4, reflux), a high yield of four diastereoisomeric bicyclo-[3.2.0]-heptan-6-ones **6**, which differ by the relative configurations at C-2 and C-3 (^1H NMR at 500 MHz).

Baeyer-Villiger oxidation(g : m-CPBA, $NaHCO_3$, CH_2Cl_2, r.t.) was highly regioselective (93 : 7) in favour of the desired lactone 7a. The minor isomer 7b was readily removed by flash chromatography.

The cup shape of the bicyclic lactone 7a was expected to facilitate the establishment of the desired endo-configuration at C-7. The protecting group (k : n-$Bu_4N^+F^-$, THF) was readily removed but oxidation of 7a was surprisingly difficult. Most classical oxidation reactions did not proceed to completion and were accompanied by partial migration of the double bond, but the Dess-Martin reagent[6] (step i : CH_2Cl_2, r.t.) gave a high yield of the unrearranged ketones **8**. Reduction of **8** with $NaBH_4$ (step j, methanol, 0° C) took place exclusively from the exo-side of the bicyclic system to yield the endo-alcohol, which was directly acylated (k : p-phenylbenzoyl chloride[7,8], pyridine, r.t.).

Ozonolysis (l : O_3- 1.5 equiv. of CH_3OH - CH_2Cl_2, - 78° C then addition of 9 equiv. of Me_2S) of the double bond of **9** yielded a mixture of epimeric aldehydes **10** which were directly converted (m : dimethyl-2-oxo-heptylphosphonate + NaH, DME, 0° ⟶ 20° C) into enantiomerically pure **11**, an advanced intermediate in the synthesis of prostaglandins.[8] As expected[9], the Wittig-Horner condensation was accompanied by an epimerisation leading to the more stable trans-configuration at C_5-C_6.

Compound **11** was identical in every respect to an authentical sample prepared from enantiomerically pure Corey's lactone.

This synthetic route offers major advantages in terms of conciseness, simplicity of the reactions and high yields (overall conversion : 35 %). It would be still shorter if the coupling reaction c were effected with high diastereoselectivity. Experiments toward this goal are in progress.

Acknowledgements

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References

1. Review : Snider, B.B. *Chem. Rev.* **1988**, *88*, 793.
2. Ghosez, L.; Marko, I.; Hesbain-Frisque, A.M. *Tetrahedron Lett.* **1986**, *27*, 5211.
3. Chen, Lian-yong; Ghosez, L. *Tetrahedron Lett.* **1990**, *31*, 4467.
4. Short, R.P.; Kennedy, R.M.; Masamune, S. *J. Org. Chem.* **1989**, *54*, 1755.
5. Review : Noyori, R.; Kitamuna, M. *Angew. Chem. Ed. Int. Engl.* **1991**, *30*, 49.
6. Dess, D.B.; Martin, J.C. *J. Org. Chem.* **1983**, *48*, 4156.
7. Takano, S.; Kubodera, N.; Ogasawara, K. *J. Org. Chem.* **1977**, *42*, 786.
8. Corey, E.J.; Albonico, S.M., Koelliker, U.; Schaaf, T.K.; Varma, R.K. *J. Am. Chem. Soc.* **1971**, *93*, 1491.
9. Corey, E.J.; Wollenberg, R.H. *J. Org. Chem.* **1975**, *40*, 2265.