Tetrahedron Letters, Vol. 33, No. 13, pp. 1743-1746, 1992
Printed in Great Britain

0040-4039/92 $3.00 + .00
Pergamon Press Ltd

Asymmetric Michael Reactions : Enantioselective Synthesis of δ-Oxo Acids

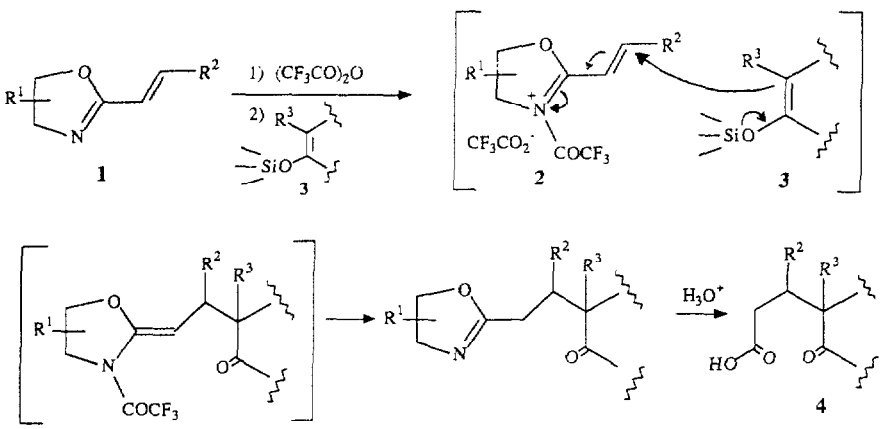
François Michelon, Annie Pouilhès, Nguyen Van Bac, Nicole Langlois*

Institut de Chimie des Substances Naturelles, C.N.R.S., F91198 Gif-sur-Yvette

Key Words : asymmetric Michael addition ; chiral α,β-unsaturated oxazolines ; silyl enol ethers ; optically active δ-oxo acids.

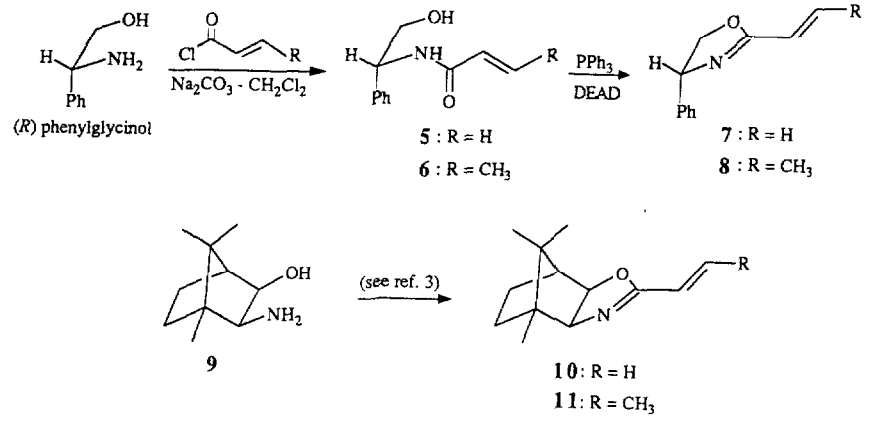
***Abstract** : β-substituted and α,β-disubstituted δ-oxo acids are synthetized with high enantiomeric excess from chiral 2-propenyl oxazolines **8** and **11**, whilst 2-vinyl oxazolines **7** and **10** are less efficient asymmetric inductors.*

It has been recently demonstrated[1] that α,β-unsaturated oxazolines **1**, after activation by N-trifluoro acetylation to **2**, act as powerful Michael acceptors, especially in the addition of silyl enol ethers **3** leading, after acidic hydrolysis, to δ-oxo acids **4** (Scheme 1).



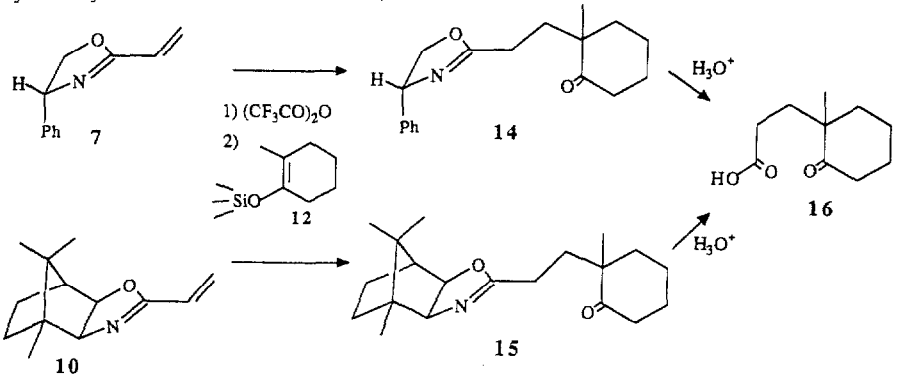
Scheme 1

These initial findings have now been extended to asymmetric conjugated additions with optically pure α,β-unsaturated oxazolines. Oxazolines **7** and **8**[2] were prepared in two steps from (*R*) phenylglycinol *via* the amides **5** and **6** respectively and subsequent cyclization under Mitsunobu conditions[3] (Scheme 2). Oxazolines **10** and **11** were prepared from the (+) camphor derived aminoalcohol **9** as described previously[4].



Scheme 2

In this study the trimethyl silyl enol ethers of 2-methyl cyclohexanone **12** and acetophenone **13**[5] were used as donors which, after Michael addition reactions, gave non-epimerizable carbonyl compounds. In a typical experiment, the enoxysilane (1.5 eq) was added at low temperature (between - 100°C and - 40°C) to a mixture of equimolecular amounts of α,β-unsaturated oxazoline, calcium carbonate and trifluoroacetic anhydride in anhydrous dichloromethane. However, the usual work-up (addition of aqueous 10% solution Na_2CO_3, extraction with CH_2Cl_2) led to the rather unstable δ-oxo-oxazolines **14** and **15**, but incomplete hydrolysis of the N-trifluoro acetyl groups under these conditions was observed. Therefore the crude products were heated in 4N hydrochloric acid (c.a. 5 h) in order to hydrolyse the N-trifluoro acetyl group and the oxazoline ring of these compounds in one pot (Scheme 3). This step gave the corresponding δ-oxo acids **16** and the starting chiral auxiliaries aminoalcohols, which were recovered (~ 85% yield) without loss of optical purity. However in the cases where the new asymmetric center is adjacent to the ketone, the *R* and *S* δ-oxo acids **16** were isolated from **7** and **10** respectively in only low enantiomeric excess[6] (Table 1).

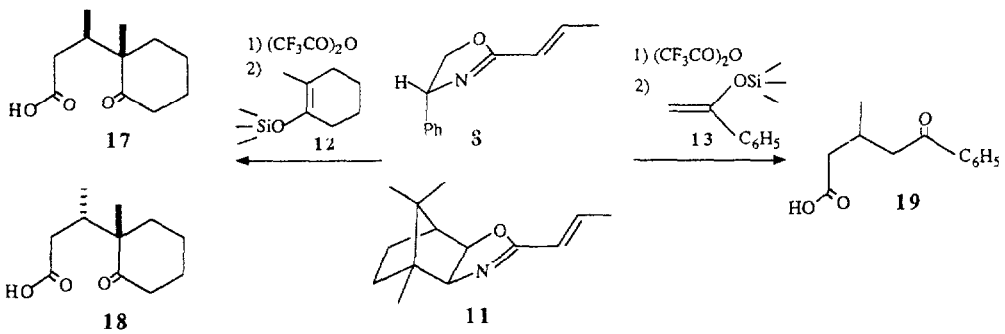


Scheme 3

Table 1 : Addition of silyl enol ether 12 to 7 and 10

α,β-Unsaturated oxazoline	t (°C)	Time (h)	Yield (%)	16 e.e. (%) (configuration)
7	- 70	1	25	14 (*R*)
10	- 70 - 100	1.5 2	30 38	19 (*S*) 18 (*S*)

For reactions of the 2-propenyl oxazolines **8** and **11** with **12**, the resultant diastereomeric δ-oxo oxazolines were separated by chromatography in modest yields. Acidic hydrolysis now led to the δ-oxo acids **17** and **18**[7], of opposite absolute configuration starting from **8** or **11** (Scheme 4). The enantiomeric excess for each compound was established by ^{1}H NMR of the corresponding methyl esters in the presence of Pr (hfbc)[8] as a chiral shift reagent (Table 2).



Scheme 4

Table 2 : Addition of silyl enol ethers 12 and 13 to 8 and 11

Oxazoline	Silyl enol	t (°C)	Time (h)	δ-Oxo acid	Yield (%)	e.e.(%)
8	**12**	- 70	6	**17**	11	70
				18	25	70
11	**12**	- 40	17	**17**	33	> 95
				18	34	> 95
8	**13**	- 70	4	**19**	70	> 95 (*R*)
11	**13**	- 40	3	**19**	65	> 95 (*S*)

The oxazoline 11 constitutes an efficient chiral auxiliary in these Michael additions. It is indeed noteworthy that both diastereomeric acids **17** and **18**, isolated from this (+) camphor derived oxazoline in nearly the same amounts, were optically pure in the limit of the analytical method.

An excellent diastereoselection was also observed in the preparation of monosubstituted δ-oxo acid **19** by addition of the enoxy silane **13** (Table 2). The indicated absolute configurations are those proposed by Enders and coll.[9] ; and hence, the two pure enantiomers of **19** are accessible by this synthetic pathway depending on the starting oxazoline.

The resistance to hydrolysis of the N-trifluoroacetyl groups has to be overcome to improve the chemical yields of additions. This point and applications of this methodology are now being studied in our laboratory.

Acknowledgement

We thank Martial Dardaine for NMR spectra and decoupling experiments.

REFERENCES

1. Langlois, N.; Dahuron, N. *Tetrahedron Lett.* **1990**, *31*, 7433-7436.
2. a) **7** : $[\alpha]_D$ = + 253° (c = 2.48, $CHCl_3$) ; IR($CHCl_3$) : 1670, 1605 cm^{-1} ; NMR [200 MHz, $CDCl_3$, J(Hz)] : 7.33 (m, 5H, aromatic H), 6.40 (dd, 1H, J *trans* = 17.5, J *cis* = 10.5, ethylenic H) ; 6.16 (dd, 1H, J *trans* = 17.5, J' = 1.7) and 5.77 (dd, 1H, J *cis* = 10.5, J' = 1.7) : ==CH_2, 5.26 (dd, 1H, J ~ 10, N-CH), 4.66 (dd, 1H, J ~ 10, J' = 8.5) and 4.13 (dd, 1H, J ~ J' = 8.5) : O-CH_2 ; SM(m/z) : 173 ($M^{+\cdot}$), 143.
   b) **8** : $[\alpha]_D$ = + 212° (c = 2.15, $CHCl_3$) ; IR : 1679, 1609 cm^{-1} ; NMR : 7.30 (m, 5H, aromatic H), 6.70 (m, 1H) and 6.12 (m, 1H, J *trans* = 16) : ethylenic H, 5.23 (dd, 1H, J ~ J' ~ 8.5, N-CH), 4.63 (dd, 1H, J ~ J' ~ 8.5) and 4.10 (dd, 1H, J ~ J' ~ 8.5) : OCH_2, 1.90 (dd, 3H, J = 7, J' = 1.5, CH_3) ; SM : 187 ($M^{+\cdot}$), 157, 156.
3. Mitsunobu, O. *Synthesis* **1981**, 1.
4. Kouklovsky, C.; Pouilhès, A.; Langlois, Y. *J. Am. Chem. Soc.* **1990**, *112*, 6672-6679.
5. Cazeau, P.; Duboudin, F.; Moulines, F.; Babot, O.; Dunogues, J. *Tetrahedron*, **1987**, *43*, 2075-2088.
6. Pfau, M.; Revial, G.; Guingant, A.; d'Angelo, J. *J. Am. Chem. Soc.* **1985**, *107*, 273-274.
7. The formulas **17** and **18** represent relative configurations (see ref. 1), the absolute configurations are not known at this stage.
8. Fraser, R. R. *Asymmetric Synthesis*, Morrison, J. D. Ed.; Academic Press N.Y.; 1983; *1*, pp. 173-196.
9. Enders, D.; Papadopoulos, K. *Tetrahedron Lett.* **1983**, *24*, 4967-4970.

(Received in France 3 December 1991)