Tetrahedron Letters, Vol.32, No.34, pp 4267-4270, 1991
Printed in Great Britain

0040-4039/91 $3.00 + .00
Pergamon Press plc

The Enantioselective Fluoroacetamide Acetal Claisen Rearrangements of *N*-Fluoroacetyl-*trans*-(2*R*,5*R*)-2,5-Dimethylpyrrolidine[1)]

Takashi Yamazaki, John T. Welch,* Janet S. Plummer, and Rayomand H. Gimi

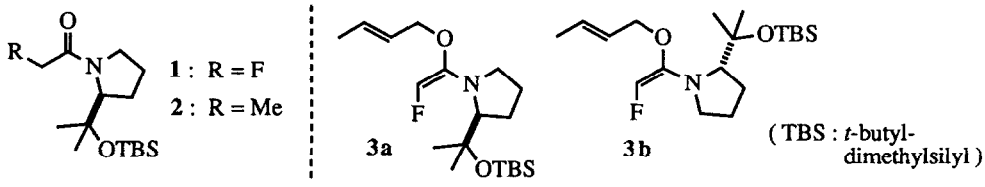
Department of Chemistry, State University of New York at Albany, Albany, New York 12222

Key words: Enantioselective amide acetal Claisen rearrangement; *N*-Fluoroacetyl-*trans*-(2*R*,5*R*)-2,5-Dimethylpyrrolidine; Acetyl-*trans*-(2*R*,5*R*)-2,5-Dimethylpyrrolidine; Determination of stereochemistry; Methyl trifluoromethanesulfonate

Abstract: Optically active monofluorinated amides were prepared via the amide acetal Claisen rearrangement and the establishment of the absolute stereochemistry of the rearranged products proved that the chiral auxiliary directed the approach of the crotyl fragment to the *Si* face of the (*E*)-*N*,*O*-ketene acetal. The general utility of this type of rearrangement is also discussed.

The asymmetric synthesis of fluorinated materials is important not only for the preparation of biologically active substances[2)] or for the construction of novel ferroelectric devices[3)] but also as a test of synthetic strategy. However, optically active fluorinated compounds where at least one of the asymmetric carbons bears a fluorine or a fluoroalkyl group are extremely difficult to prepare.[4)] We report below one effective solution to this problem, the enantioselective amide acetal Claisen rearrangement via *N*-fluoroacetyl-*trans*-(2*R*,5*R*)-2,5-dimethylpyrrolidine, **4**.

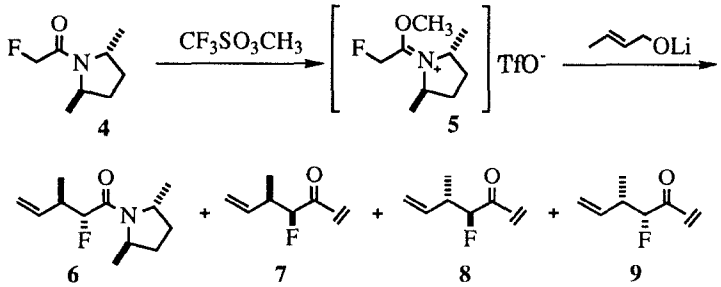
The power of the Claisen rearrangement,[5)] which has been successfully applied to fluorinated substrates,[6,7)] suggested that judicious choice of a chiral auxiliary would allow synthesis of optically active fluorinated materials from fluoroacetate precursors. Earlier studies suggested the amide acetal Claisen rearrangement might be particularly well suited to this strategy.[8)] However, amide acetal Claisen rearrangement of **1**, based on the successful studies with the *N*-propionylprolinol derivative **2**, yielded only a stereorandom mixture of products. It was postulated that the auxiliary failed in the reaction of **1** because there was little control of the *N*,*O*-ketene acetal double bond geometry and only poor selectivity for one of two conformationally isomeric intermediates such as **3a** or **3b**. *N*,*O*-Ketene acetal geometry could be influenced by careful selection of reaction conditions, while the latter problem could be addressed by employing a chiral auxiliary with C_2 symmetry.[9)]



The products of the amide acetal Claisen rearrangement of *N*,*O*-ketene acetals prepared *in situ* from *N*-fluoroacetyl-*trans*-(2*R*,5*R*)-2,5-dimethylpyrrolidine, **4**, were formed as a diastereomeric mixture (Table), as determined by ^{19}F NMR, in an overall isolated yield of 61% (75% conversion yield).[10)] If a chairlike transition

state was presumed for the rearrangement, then **7** and **9** would be formed from (*E*)-*N*,*O*-ketene acetal and in a like manner would **6** and **8** be formed from the corresponding (*Z*)-*N*,*O*-ketene acetal. The product stereochemical assignments were made by synthesis of the correlation compounds in the following manner. The racemic *u*- and *l*-2-fluoro-3-methylpent-4-enoic acids (9.0:1 mixture of *u* to *l* prepared by our previously reported method[6]) were condensed with *trans*-(2*S*,5*S*)-2,5-dimethylpyrrolidine via their acid chlorides to unambiguously establish the relative configuration of **7** and **9** as *u* and of **6** and **8** as *l*.[11] The absolute stereochemistry of

Table ^{19}F NMR Chemical Shifts for the Rearranged Products **6** to **9**

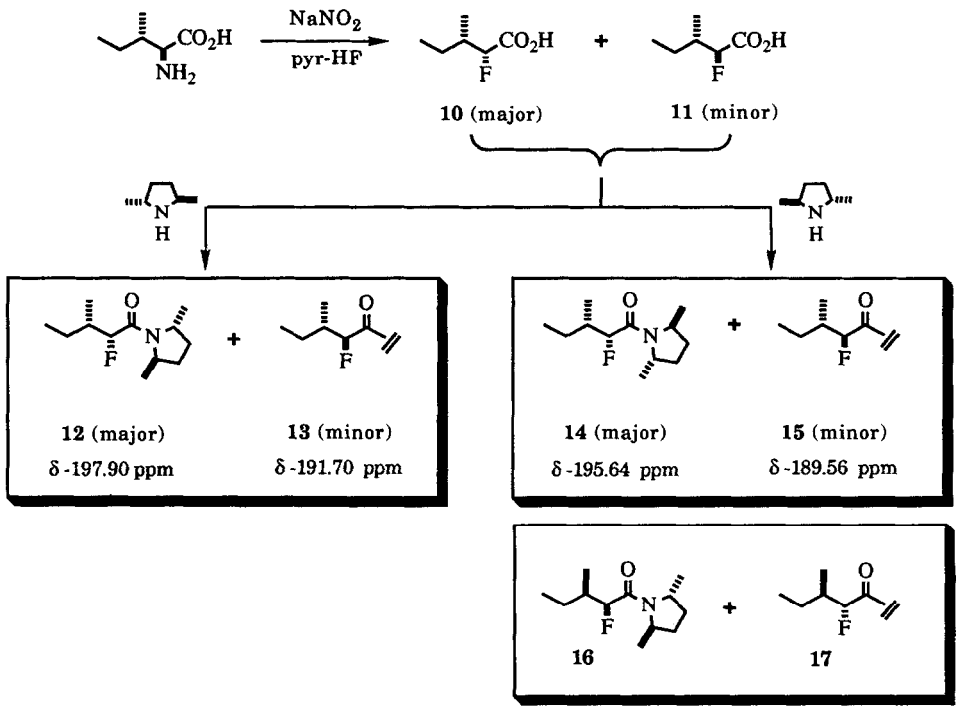


Compound	**6**	**7**	**8**	**9**
ratio	1.1	13.4	3.0	1.0
^{19}F NMR (δ ppm in $CDCl_3$)*	-188.62 (-189.51)	-191.98 (-195.76)	-190.80 (-191.80)	-192.94 (-197.96)

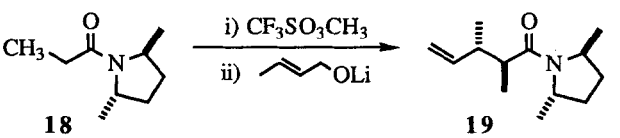
* In the parentheses were shown ^{19}F NMR chemical shifts of each compounds after hydrogenation

products, on the other hand, was determined by preparation of **10** and **11** (12.5:1 mixture) by the deamino-fluorination of (2*S*,3*S*)-isoleucine.[12] This mixture was converted via the formation of active anhydride[13] into **12** and **13**, by condensation with *trans*-(2*R*,5*R*)-2,5-dimethylpyrrolidine, and into **14** and **15**, by condensation with enantiomeric *trans*-(2*S*,5*S*)-2,5-dimethylpyrrolidine. Since **14** and **15** are enantiomers of **16** and **17**, respectively, their spectra are identical and ^{19}F NMR shifts can be used for correlation with **7** and **6**. Catalytic reduction of **6**-**9** over palladium on carbon formed **17**, **16**, **13**, and **12**, respectively. Comparison of NMR data (Table and Scheme) clearly illustrated that the absolute stereochemistry of the products is as shown in each scheme and was also consistent with the chairlike transition state predicted by molecular mechanics.[14] It was anticipated that the chiral auxiliary would act by restricting the motion of the crotyl fragment, allowing *ul* approach only from the *Si* face of the *N*,*O*-ketene acetal. The *ul* trajectory which would be required for bonding at *Re* face of the *N*,*O*-ketene acetal would be effectively encumbered by the chiral auxiliary. The effectiveness of *trans*-2,5-dimethylpyrrolidine in controlling the diastereoselectivity of amide acetal Claisen rearrangement seems to be quite general. The rearrangement of the *N*,*O*-ketene acetal formed on the reaction of *N*-propionyl-*trans*-(2*S*,5*S*)-2,5-dimethylpyrrolidine, **18**, with (*E*)-crotyl alcohol under the conditions described is extraordinarily

Scheme Preparation of Correlation Materials



selective[15] forming in a ratio of >10:1,[16] as determined by ^{1}H and ^{13}C NMR, a product in 50% isolated yield and 60% conversion (Scheme). As our previous report established the consistent preference for the formation of the (*Z*)-*N*,*O*-ketene acetal in the reactions of propionamides, consideration of the diastereofacial influence of *trans*-2,5-dimethylpyrrolidine established above leads to the assignment of the stereochemistry of the major



product of this rearrangement to be *N*-(2*S*,3*S*)-2,3-dimethylpent-4-enoyl-*trans*-(2'*S*,5'*S*)-2',5'-dimethylpyrrolidine **19**. Further studies to confirm this assignment and to explore the scope and limitations of this process are underway.

REFERENCES

1. Financial support of this work by the National Science Foundation Grant number CHE-8901986, and DARPA Contract DAAL 0398KO198 is gratefully acknowledged.
2. a) Welch, J. T.; Eswarakrishnan, S. In *Fluorine in BioOrganic Chemistry*; Wiley: New York, **1990**. b) *Fluorine-containing Molecules---Structure, Reactivity, Synthesis, and Applications*, Liebman, J. F.; Greenberg, A.; Dolbier, Jr., W. R., Eds.; VCH: New York, **1988**. c) Welch, J. T. *Tetrahedron* **1987**, *43*, 3123.

3. a) Walba, D. M.; Razavi, H. A.; Clark, N. A.; Parmar, D. S. *J. Am. Chem. Soc.* **1988**, *110*, 8686. b) Kitazume, T.; Ohnogi, T.; Ito, K. *ibid.* **1990**, *112*, 6608.
4. For previous literature dealing with this problem, see the following representative examples. a) Differding, E.; Lang, R. W. *Tetrahedron Lett.* **1989**, *29*, 6087 (asymmetric fluorinating reagents). b) Kitazume, T.; Okamura, N.; Ikeya, T.; Yamazaki, T. *J. Fluorine Chem.* **1988**, *39*, 107. c) Seebach, D.; Renaud, P.; Schweizer, W. B.; Züger, M. F.; Brienne, M.-J. *Helv. Chim. Acta* **1984**, *67*, 1843. d) Lin, J.-T.; Yamazaki, T.; Kitazume, T. *J. Org. Chem.* **1987**, *52*, 3211 (enzymatic transformation). e) Welch, J. T.; Seper, K. *ibid.* **1988**, *53*, 2991 (optically active imines). f) Bravo, P.; Piovosi, E.; Resnati, G.; Fronza, G. *ibid.* **1989**, *54*, 5171. g) Yamazaki, T.; Ishikawa, N.; Iwatsubo, H.; Kitazume, T. *J. Chem. Soc., Chem. Commun.* **1987**, 1340 (optically active sulfoxides). h) Acs, M.; von dem Bussche, Ch.; Seebach, D. *Chimia* **1990**, *44*, 90 (optical resolution).
5. For general reviews on the Claisen rearrangement see, a) Ziegler, F. E. *Chem. Rev.* **1988**, *88*, 1423. b) Blechert, S. *Synthesis* **1989**, 71. c) Hill, R. K. In *Asymmetric Synthesis*, Morrison, D. J., Ed.; Academic: New York, **1984**; vol 3, 503.
6. a) Welch, J. T.; Samartino, J. S. *J. Org. Chem.* **1985**, *50*, 3663. b) Welch, J. T.; Eswarakrishnan, S. *ibid.* **1985**, *50*, 5909.
7. a) Metcalf, B. W.; Jarvi, E. T.; Burkhart, J. P. *Tetrahedron Lett.* **1985**, *26*, 2861. b) Yokozawa, T.; Nakai, T.; Ishikawa, N. *ibid.* **1984**, *25*, 3991. c) Camps, F.; Messeguer, A.; Sanchez, F.-J. *Tetrahedron* **1988**, *44*, 5161. d) Yuan, W.; Berman, R. J.; Gelb, M. H. *J. Am. Chem. Soc.* **1987**, *109*, 8071. e) Kolb, M.; Gerhart, F.; Francoi, J. P. *Synthesis* **1988**, 469. f) Yamazaki, T.; Ishikawa, N. *Bull. Chim. Soc. Fr.* **1986**, 937.
8. a) Welch, J. T.; Eswarakrishnan, S. *J. Am. Chem. Soc.* **1987**, *109*, 6716. b) Kurth, M. J.; Brown, E. G. *Synthesis* **1988**, 362.
9. Whitesell, J. K. *Chem. Rev.* **1989**, *89*, 1581.
10. Experimental procedure was as follows. Methyl trifluoromethanesulfonate (0.14 mL, 1.24 mmol) was treated with amide **4** (162 mg, 1.02 mmol) for 0.5 h at room temperature, and the formed salt was washed with *n*-pentane three times and the volatiles were removed under high vacuum (<5 min at room temperature). This salt was then dissolved in freshly distilled methylene chloride (5 mL) and was added into the solution of lithium crotyloxide, prepared from methyllithium (1.5 M, 2.7 mL, 4.1 mmol) and (*E*)-crotyl alcohol (0.26 mL, 3.05 mmol). After stirring 24 h at ambient temperature and evaporating the volatiles, the usual workup and purification procedure by chromatography on silica gel yielded the desired rearranged product as a diastereomeric mixture (133 mg, 0.624 mmol, 61% yield, 81% conversion). R_f 0.82 and 0.75 (AcOEt/*n*-hexane = 2/1), bp 90 - 95 °C/0.05 mmHg (bath temperature), $[\alpha]_D^{22}$ +25.42° (*c* 0.85, CH_2Cl_2).
11. For the nomenclature, see. Seebach, D.; Prelog, V. *Angew. Chem. Int. Ed. Engl.* **1982**, *21*, 654.
12. Olah, G. K.; Prakash, G. K. S.; Chao, Y.-L. *Helv. Chim. Acta* **1981**, *64*, 2528.
13. Vaughan, Jr., J. R.; Osato, R. L. *J. Am. Chem. Soc.* **1952**, *74*, 676.
14. Molecular mechanics calculations using C. Still's Macromodel Program clearly indicated that the pyrrolidine ring was significantly deformed.
15. For **19**, bp 75 - 80 °C/0.05 mmHg (bath temperature), $[\alpha]_D^{22}$ -30.15° (*c* 1.21, CH_2Cl_2).
16. Products that would be derived from the (*E*)-*N*,*O*-ketene acetal were not observed.

(Received in USA 28 March 1991)