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[3,3]-Sigmatropic rearrangements of fluorinated compounds

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Abstract

[3,3]-Sigmatropic rearrangements of fluorinated compounds are reviewed.

Introduction

Claisen and Cope rearrangements have proven to be highly useful reactions for the selective formation of carbon–carbon bonds. The reactions tolerate a wide variety of functional groups and substitution patterns. There have been a number of studies on the effect of substituents on the Claisen [1–3] and Cope [4] rearrangements. Donor or acceptor groups at various sites of the six-atom backbone can have a rate-accelerating or -retarding effect. In the light of current interest in the synthesis of fluorinated organic compounds, it is of interest to examine the use of [3,3]-sigmatropic rearrangements to introduce fluorine into organic compounds.

Cope rearrangement of fluorinated dienes

Polar substituents in the 3-position of a 1,5-diene have been predicted [4] and observed [5] to accelerate the Cope rearrangement. In the rate-enhanced oxy-Cope rearrangement, the donor oxygen originates on an sp^3 carbon in the 3-position which is converted to an sp^2 carbon. Thus one might predict that a donor fluorine in the 3-position would also accelerate the reaction. However, Dolbier *et al.*, who studied the Cope rearrangement of (*E*)- and (*Z*)-1-fluoro-1,5-hexadienes to 3-fluoro-1,5-hexadiene, found that the activation energy for the rearrangement of the 3-fluorodiene to a 1-fluorodiene is of the same order of magnitude as that of the 3-methyl and the unsubstituted hexadiene [6]. Thus, unlike oxygen, a single fluorine on an sp^3 carbon appears to have very little effect. However, in one case, fluorine substitution does affect the equilibrium. Rearrangements of monofluorobullvalenes result in a mixture containing 80–85% of the isomer with sp^3-bound fluorine [7] [eqn. (1)]. This result, in contrast to the oxy-Cope

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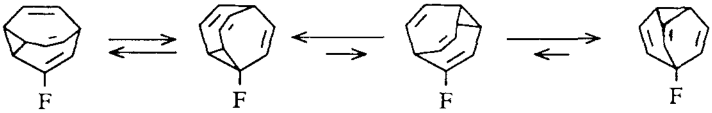
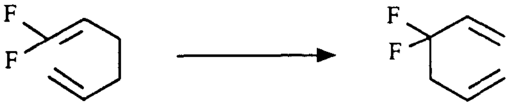
rearrangement, may be due to the special character of the bullvalene ring system.



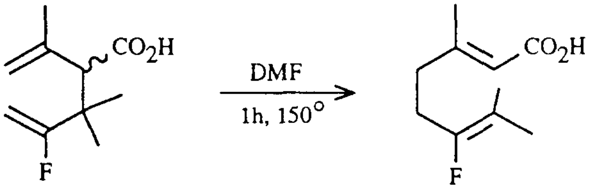
(1)

Dolbier *et al.* studied the rearrangement of 1,1-difluoro-1,5-hexadiene and found that the reaction occurred readily [8], as shown in eqn. (2). Geminal fluorines on sp^2 carbon are destabilized relative to geminal fluorines on sp^3 carbon by approximately 5 kcal mol^{-1}.



(2)

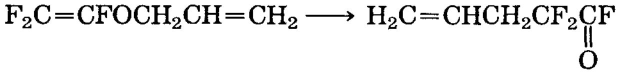
In the case where fluorine substitution is on carbon 2 (an sp^2 carbon), the product which results still has fluorine bound to sp^2 carbon. Carpenter predicted a rate-retarding effect for polar substitution at C-2 [4]. In at least one case where fluorine is on carbon 2, rearrangement occurs as shown by Camps *et al.* [9] [eqn. (3)]. During the reaction the carboxy group is brought into conjugation with the double bond lowering the activation energy compared with many Cope rearrangements [10]. In addition, both double bonds in the product are more substituted than in the starting material. The relatively mild reaction temperature is probably due to the presence of the carboxy group and not the fluorine.



(3)

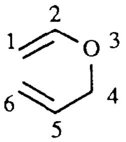
Claisen rearrangement of allyl fluorovinyl ethers

Rearrangement of allyl fluorovinyl ethers with fluorine in the terminal position gives rise to α-fluorocarbonyl compounds as shown in eqn. (4). Because of the importance of α-fluorocarbonyl compounds [11], this reaction is of special synthetic significance.



$$F_2C{=}CFOCH_2CH{=}CH_2 \longrightarrow H_2C{=}CHCH_2CF_2\underset{\underset{O}{\|}}{C}F \qquad (4)$$

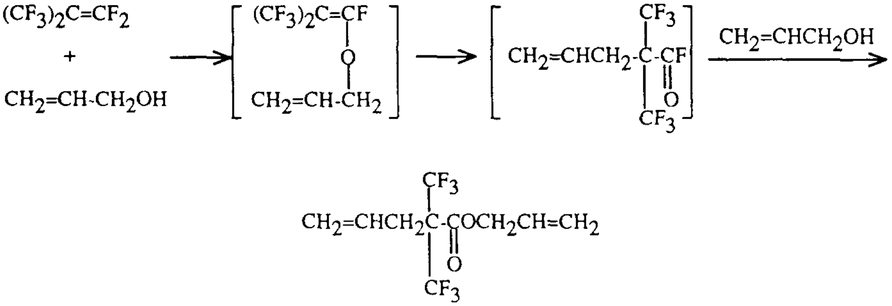
Burrows and Carpenter predicted [2] and observed [1] acceleration when an electron acceptor was placed on the 2-, 4- or 5-carbon. The Claisen rearrangement in these cases was more rapid than for the unsubstituted allyl vinyl ether. In contrast, the rate was slowed by the presence of an electron acceptor, CN, on the 1- or 6-carbon. They predicted a rate acceleration for



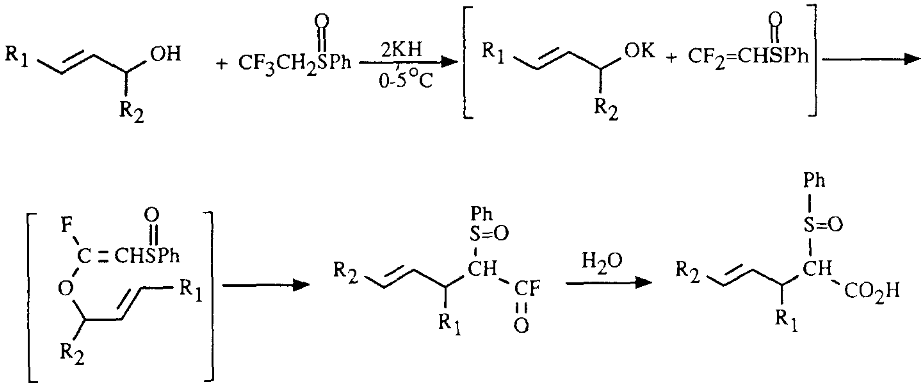
an electron donor on the 1-, 2- or 4-carbon [2]. Indeed, the Ireland and Mueller modification of the Claisen rearrangement with a donor siloxy group at carbon 2 is run under remarkably mild conditions [12].

One of the earliest observations of acceleration of the Claisen rearrangement was made by Krespan in 1967 [13]. He attempted to prepare a number of vinyl allyl ethers with fluorine substitution in the vinyl moiety. However, the reaction of allyl alcohol and octafluoroisobutene resulted in a 4-pentenyl ester. The intermediate vinyl allyl ether, with fluorine bound at C-2, underwent rearrangement below 50 °C as shown in Scheme 1. Zakharkin and Lebedev [14] observed a similar rearrangement of fluorinated alkenyl carboranes under mild conditions. Nakai and coworkers [15] took advantage of the acceleration of the Claisen rearrangement when fluorine is substituted at C-2 to produce a fluorine-free product! They generated *in situ* α-fluoro-β-phenylsulfinyl vinyl ethers from allylic alcohols and trifluoroethylphenylsulfoxide as shown in Scheme 2.

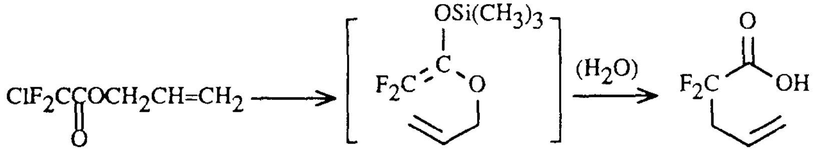
Even more dramatic accelerations of the reaction were observed by Normant *et al.* when there were more halogens bound directly to the vinyl system [16]. Normant and coworkers found that with increasing fluorine substitution, lower temperatures could be used to accomplish the rearrangement. Thus, $Cl_2C{=}CFO$allyl rearranges at −20 °C, while $ClFC{=}CFO$allyl rearranges at −35 °C and $F_2C{=}CFO$allyl rearranges at −50 °C [17]. Capitalizing on these observations, other groups have been able to prepare 2,2-difluoro-4-pentenoates at low temperature [18, 19]. In a variation, allyl chlorodifluoroacetate was found to undergo a Reformatsky–Claisen reaction four times faster than the trichloroacetate [eqn. (5)] [20]. The difluoroketene silyl acetal is the apparent intermediate.



Scheme 1.



Scheme 2.

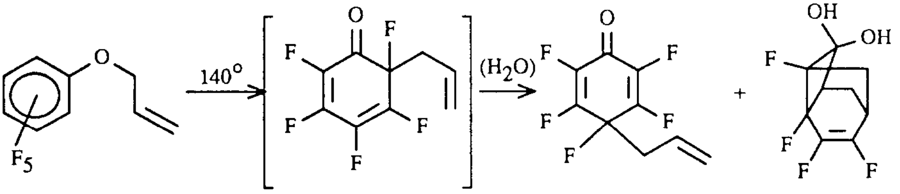


(5)

When fluorine is substituted only at C-1, the rearrangement rate is somewhat dependent on the other substituents in the molecule. Thus, while studying the ester enolate Claisen rearrangements of allyl α-fluoroacetates and α-fluoropropanoates, Welch and coworkers [21] trapped and observed the intermediate monofluoroketene silyl acetate at -85 °C in the ^{19}F NMR spectrum. However, on warming to 20 °C, the signal arising from sigmatropic rearrangement of the acetal was found. In contrast, the rearrangement of *N*,*O*-ketene acetals from fluorinated and non-fluorinated acids occurred under comparable conditions [22].

Interestingly, in one case, a 1,1-difluoro olefin with no donor atom at C-2, the Claisen rearrangement was run at 80 °C for 1 h [23]. This high temperature is surprising in the light of the observation of Dolbier *et al.* concerning geminal-fluorine substitution [8].

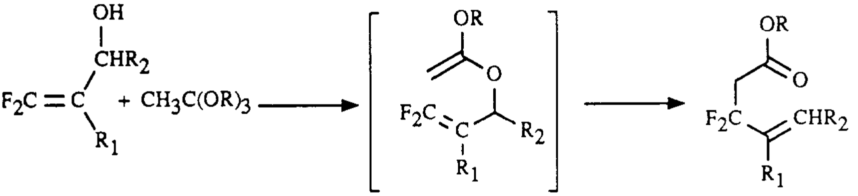
A special case of the Claisen rearrangement is found in the fluoroaromatic allyl ethers. On thermolysis, both pentafluorophenyl and heptafluoronaphthyl allyl [24–26] and propargyl [27, 28] ethers undergo rearrangement at 140 °C. The intermediate Claisen rearrangement product from pentafluorophenyl allyl ether reacts further by a Cope rearrangement, an intramolecular Diels–Alder reaction and other subsequent intramolecular rearrangements to give the observed products as shown in eqn. (6) [26]. The allenyl intermediates derived from the propargyl ethers also undergo subsequent rearrangement [27, 28].



(6)

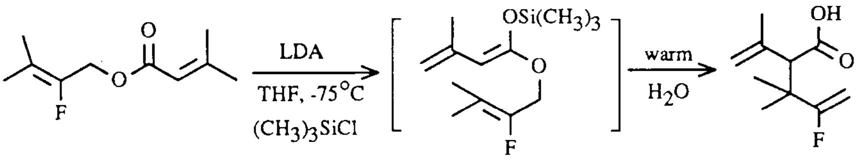
Claisen rearrangement of vinyl fluoroallyl ethers

Fluorinated allyl alcohols can be used to prepare esters that are converted to enol derivatives capable of undergoing the Claisen rearrangement. When the fluorine is in the 6-position, β-fluorocarboxylic acid derivatives are formed as shown in eqn. (7). Several examples are included in Table 1. The reaction conditions were virtually the same for both fluorinated and unfluorinated substrates [23, 29]. Interestingly, no acceleration of rearrangement of the esters derived from 3,3-difluoroallyl alcohols compared with their non-fluorinated analogs was observed. This result is surprising because Dolbier and coworkers have shown that geminal fluorines bound to sp^3 carbon have considerable thermodynamic advantage over sp^2 carbon [8, 30].



(7)

In contrast, when the fluorine is substituted in the 2-position of the allyl alcohol (C-5 of the vinyl allyl ether), dramatic acceleration of the Claisen rearrangement results [9]. Thus, when 2-fluoro-3-methyl-2-butenyl 3-methyl-2-butenoate was treated with LDA at −75 °C, followed by trimethylsilyl chloride and warming to room temperature, a facile Claisen rearrangement occurred as shown in eqn. (8) [9]. In this case, since both starting material and product contain a vinylic fluoride, thermodynamic stabilization cannot be a driving force for the conversion.



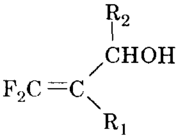
(8)

The effect of CF_3 substituents on [3,3]-sigmatropic rearrangements

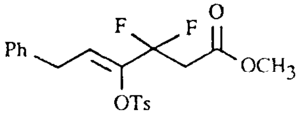
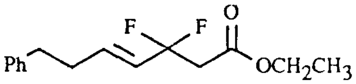
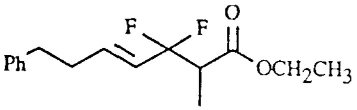
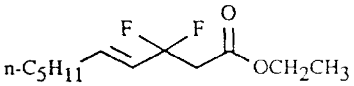
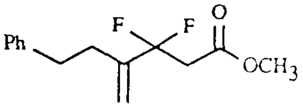
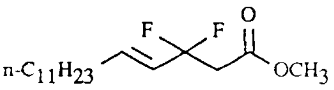
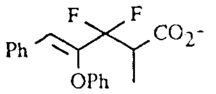
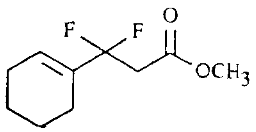
The effect of CF_3 substitution on Claisen rearrangements has been studied. Substitution of CF_3 at the C-1 position appears to have very little effect on

TABLE 1

Claisen rearrangement of enol esters derived from fluorinated alcohols:



$F_2C{=}C(R_1)CH(R_2)OH$

Alcohol		Orthoester	Product	Yield (%)	Ref.
R_1	R_2				
OTs	CH_2Ph	$CH_3C(OCH_2CH_3)_3$		84[a]	23
H	CH_2CH_2Ph	$CH_3C(OCH_2CH_3)_3$		76[b]	29
H	CH_2CH_2Ph	$CH_3CH_2C(OCH_2CH_3)_3$		69[b]	29
H	n-C_5H_{11}	$CH_3C(OCH_2CH_3)_3$		37[b]	29
CH_2CH_2Ph	H	$CH_3C(OCH_3)_3$		72	29
H	n-$C_{11}H_{23}$	$CH_3C(OCH_3)_3$		60[b]	29
OPh	CH_2Ph	–[c]		57	23
$–CH_2CH_2CH_2CH_2–$		$CH_3(OCH_3)_3$		78	29

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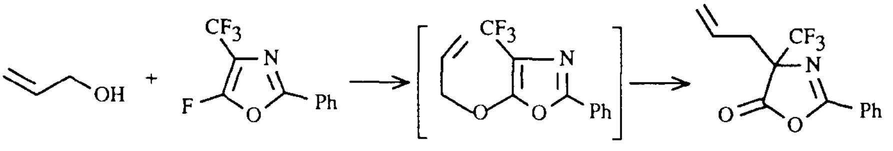
[a] Text gives ethyl ester, but equation shows methyl ester. From ^{19}F NMR spectroscopy, the product was estimated to be 94:6, *Z*:*E*.

[b] From NMR spectroscopy, products are assigned as *E*.

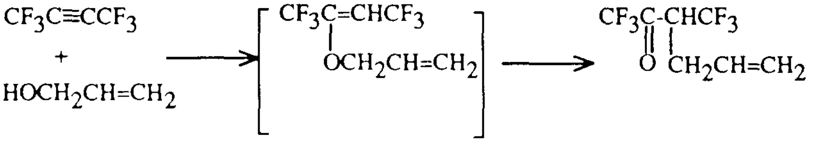
[c] Ireland enolate Claisen of propionate ester.

the rearrangement of allylic ketene silyl acetals [31]. They react under almost the same conditions observed by Ireland and Mueller during pioneering studies on this modification of the Claisen rearrangement [12]. Burger and coworkers [32–34] found that treatment of 5-fluoro-2-phenyl-4-trifluoromethyloxazoles with a variety of allylic [32, 34], propargylic [32] and benzylic-type [33] alcohols at room temperature resulted in fluoride elimination followed by spontaneous [3,3]-sigmatropic rearrangement as shown in eqn. (9).



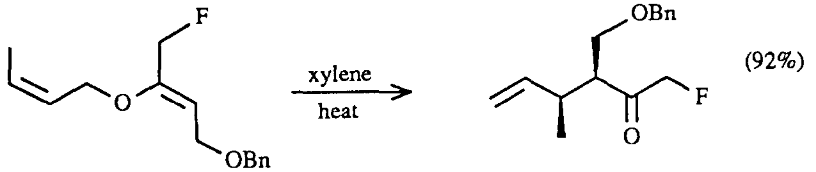
(9)

Substitution of CF_3 at C-2 caused a 70-fold increase in rate which was attributed to destabilization of the starting vinyl ether by the trifluoromethyl group [35]. This same destabilization may account for the fact that Krespan [13] was unable to isolate allyl 1,2-bis(trifluoromethyl)vinyl ether from the reaction of allyl alcohol and hexafluoro-2-butyne. Instead, the product that distilled below 90 °C was completely rearranged as shown in eqn. (10).



$$\begin{array}{l}\mathrm{CF_3C{\equiv}CCF_3}\\ \quad +\\ \mathrm{HOCH_2CH{=}CH_2}\end{array} \longrightarrow \left[\begin{array}{l}\mathrm{CF_3\underset{|}{C}{=}CHCF_3}\\ \quad\mathrm{OCH_2CH{=}CH_2}\end{array}\right] \longrightarrow \begin{array}{l}\mathrm{CF_3\underset{\|}{C}\text{-}\underset{|}{C}HCF_3}\\ \quad\mathrm{O\ CH_2CH{=}CH_2}\end{array} \qquad (10)$$

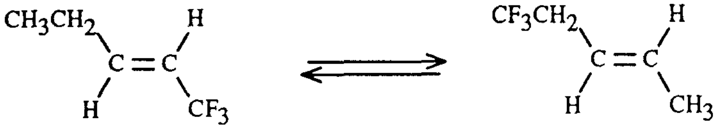
A fluoromethyl, CH_2F, group at C-2 did not cause noticeable acceleration of the reaction [36]. Thus, the temperature needed for the conversion shown in eqn. (11) is typical of most Claisen rearrangements.



(11)

When the CF_3 group is in the C-4 position, activation parameters are virtually identical to the parent compound, indicating no effect from the trifluoromethyl group [35]. Similarly, when a CF_3 group was located in the 3-position of allylic or propargylic alcohols (C-6 of the resulting vinyl allyl ether), Claisen rearrangement could be smoothly effected with ethyl orthoacetate under the usual conditions [37]. However, in one case a CF_3-substituted propargyl alcohol with a bulky aryl substituent on C-4 was reported not to undergo the Claisen rearrangement [38].

For the Cope reaction, Gajewski and coworkers [35] found that CF_3 substitution on a vinyl carbon in a 1,5-diene gave an activation free energy that was within 1 kcal mol^{-1} of that observed for the unsubstituted case. This result is in contrast with the observation of Dolbier and Medinger [39] that allylic CF_3 is more stable than vinylic CF_3 as shown in the hypothetical equilibrium [eqn. (12)] with $\Delta H = -1.8$ kcal mol^{-1}.



(12)

Conclusions

It is difficult to generalize the effect of fluorine substitution on [3,3]-sigmatropic rearrangements. In agreement with Carpenter's prediction [2], compounds with donor groups, fluorine or oxygen at C-1 and C-2 accelerate the Claisen rearrangement. In other compounds that have been studied, fluorine does not appear to exert a dramatic influence.

References

1 C. J. Burrows and B. K. Carpenter, *J. Am. Chem. Soc.*, *103* (1981) 6983.
2 C. J. Burrows and B. K. Carpenter, *J. Am. Chem. Soc.*, *103* (1981) 6984.
3 M. J. S. Dewar and E. F. Healy, *J. Am. Chem. Soc.*, *106* (1984) 7127.
4 B. K. Carpenter, *Tetrahedron*, *34* (1978) 1877.
5 D. A. Evans and A. M. Golob, *J. Am. Chem. Soc.*, *97* (1975) 4765.
6 W. R. Dolbier Jr., A. C. Alty and O. Phanstiel IV, *J. Am. Chem. Soc.*, *109* (1987) 3046.
7 J. F. M. Oth, R. Merenyi, H. Rottele and G. Schroder, *Tetrahedron Lett.*, (1968) 3941.
8 W. R. Dolbier Jr., K. S. Medinger, A. Greenberg and J. F. Liebman, *Tetrahedron*, *38* (1982) 2415.
9 F. Camps, A. Messeguer and F.-T. Sanchez, *Tetrahedron*, *44* (1988) 5161.
10 E. G. Foster, A. C. Cope and F. Daniels, *J. Am. Chem. Soc.*, *69* (1947) 1893.
11 S. Rozen and R. Filler, *Tetrahedron*, *41* (1985) 1111.
12 R. E. Ireland and R. H. Mueller, *J. Am. Chem. Soc.*, *94* (1972) 5897.
13 C. G. Krespan, *Tetrahedron*, *23* (1967) 4243.
14 L. I. Zakharkin and V. N. Lebedev, *Zh. Obsh. Khim.*, *41* (1971) 817.
15 T. Nakai, K. Tanaka, K. Ogasawara and N. Ishikawa, *Chem. Lett.*, (1981) 1289.
16 J. F. Normant, O. Reboul, R. Sauvetre and J. Villieras, *C. R. Acad. Sci. Ser. C*, *274* (1977) 1954.
17 J. F. Normant, O. Reboul, R. Sauvetre, H. Deshayes, D. Masure and J. Villieras, *Bull. Soc. Chem. Fr.*, (1974) 2072.
18 M. Kolb, F. Gerhart and J.-P. Francois, *Synthesis*, (1988) 469.
19 W. Yuan, R. T. Berman and M. H. Gelb, *J. Am. Chem. Soc.*, *109* (1987) 8071.
20 H. Greuter, R. W. Lang and A. J. Romann, *Tetrahedron Lett.*, *29* (1988) 3291.
21 J. T. Welch, J. S. Plummer and T.-S. Chou, *J. Org. Chem.*, *56* (1991) 353.
22 J. T. Welch and S. Eswarakrishnan, *J. Org. Chem.*, *50* (1985) 5909.
23 B. W. Metcalf, E. T. Jarvi and J. P. Burkhart, *Tetrahedron Lett.*, *26* (1985) 2861.
24 G. M. Brooke, *J. Chem. Soc., Perkin Trans. 1*, (1974) 233.
25 G. M. Brooke, R. S. Matthews and N. S. Robson, *J. Fluorine Chem.*, *16* (1980) 461.
26 G. M. Brooke, D. H. Hall and H. M. M. Shearer, *J. Chem. Soc., Perkin Trans. 1*, (1978) 780.
27 G. M. Brooke, *J. Chem. Soc., Perkin Trans. 1*, (1982) 107.
28 G. M. Brooke and D. I. Wallis, *J. Fluorine Chem.*, *20* (1982) 173.
29 T. Taguchi, T. Morikawa, O. Kitagawa, T. Mishima and Y. Kobayashi, *Chem. Pharm. Bull.*, *33* (1985) 5137.

30 W. R. Dolbier Jr., *Acc. Chem. Res.*, *14* (1981) 195.

31 T. Yozogawa, T. Nakai and N. Ishikawa, *Tetrahedron Lett.*, *25* (1984) 3991.

32 K. Burger, K. Geith and K. Goa, *Angew. Chem., Int. Ed. Engl.*, *27* (1988) 848.

33 K. Burger, K. Goa, K. Geith and C. Schierlinger, *Synthesis*, (1989) 840.

34 K. Burger, K. Goa and K. Geith, *J. Fluorine Chem.*, *41* (1988) 429.

35 J. J. Gajeweski, K. R. Gee and J. Jurayj, *J. Org. Chem.*, *55* (1990) 1813.

36 Y. Nakahara, M. Shimizu and H. Yoshioka, *Tetrahedron Lett.*, *29* (1988) 2325.

37 Y. Hanzawa, K. Kawagoe, A. Yamada and Y. Kobayashi, *Tetrahedron Lett.*, *26* (1985) 219.

38 B. A. Pawson, K.-K. Chan, J. DeNoble, R.-J. L. Han, V. Piermattie, A. C. Specian, S. Srisethnil, P. W. Trown, O. Bohoslawec, L. J. Machlin and E. Gabriel, *J. Med. Chem.*, *22* (1979) 1059.

39 W. R. Dolber Jr. and K. S. Medinger, *Tetrahedron*, *38* (1982) 2411.