Towards the Syntheses of α-Trifluoromethylated Oxygenated Heterocycles and Their Precursors

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Abstract: The possibilities of synthesizing various α-trifluoromethylated oxygenated heterocycles, starting from trifluoroacetaldehyde methyl hemiacetal, through classic cyclization reactions, have been demonstrated. In this way, six-membered cyclic compounds, δ-lactones and also macrolactones, bearing a CF_3 group in a position α to the oxygen could be easily obtained through a RCM reaction. Bicyclic compounds could be also synthesized by an intramolecular Pauson–Khand reaction.

Key words: fluorine, metathesis, cyclizations, oxygenated heterocycles, trifluoroacetaldehyde

Introduction

Oxygenated heterocycles constitute an important core in various compounds implicated in different applications. The most known molecules presenting such a structure are, of course, the carbohydrates which play an important role in the biological processes. On the other hand, since Henri Moissan's first isolation of elemental fluorine in 1886, the interest in fluorine chemistry has seen an exponential growth because of the specific properties of fluorinated molecules, which opened the various field of applications.[1] Among these fluorinated compounds, trifluoromethylated ones play an important role, in particular in the design of bioactive compounds. Indeed, the introduction of such a moiety onto organic compounds generally increases the lipophilicity of the molecules and, consequently, contributes, often, to the amelioration of the biological activity.[2] Nevertheless, despite this growing interest for the trifluoromethylated compounds, methods to synthesize such products are still scarce and new methodologies are required.

In search of synthesis of potentially new bioactive fluorinated compounds, we were interested in the synthesis of trifluoromethylated oxygenated heterocycles, and in particular the α-trifluoromethylated ones. Some six-membered α-trifluoromethylated oxygenated heterocycles have been previously described in the literature. Such derivatives have found interesting applications in liquid crystal compositions[3] and in the design of derivatives of doxorubicin in the antitumor field.[4]

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The majority of previously described synthetic methods were directed towards the synthesis of trifluoromethyl sugars. Such compounds could be obtained by nucleophilic trifluoromethylation of aldose derivatives with CF_3SiMe_3.[4,5] The trifluoromethylation of glyceraldehydes with CF_3I/Zn, followed by 5 steps of ring construction have been also employed to prepare 6-deoxy-6,6,6-trifluorohexoses.[6]

Hetero Diels–Alder strategy has been also envisaged to synthesize trifluoromethylated sugars. The fluorinated starting materials can be either the dienophile (1,1,1-trifluoro-4-alkoxybut-3-en-2-one)[7] or the heterodiene (trifluoroacetaldehyde).[8] Longer strategies have been also elaborated to obtain, via multistep syntheses, trifluoromethylated sugars. The fluorinated starting material was trifluoromethylated allylic alcohols[9] or trifluoromethylated butenolides arising from the corresponding trifluoromethylated furanols.[10] Some other methods can be also found in literature about the access to trifluoromethyltetrahydrofuran or -tetrahydropyran like structures by cyclooxymercurations of unsaturated trifluoromethylated alcohols[11] or by Prins cyclization of homoallylic hemiacetals of trifluoroacetaldehyde.[12] Finally, α-trifluoromethylated γ-butyrolactones and δ-valerolactones could be obtained either by palladium-mediated intramolecular lactonization of allylic alcohols[13] or by classical lactonization of corresponding hydroxy acids coming from a Kolbe electrolysis.[14]

We wish to present here the first attempts in the elaboration of other efficient methods to achieve, quickly and efficiently, α-trifluoromethylated oxygenated heterocycles or bicyclic molecules, starting from a commercially available fluorinated starting material not too expensive and easy to handle. In the following work, we want essentially, to demonstrate the feasibility and the potentialities of these methods and underline certain occurring problems.

Retrosynthetic Analysis

In previous work, we have described efficient methods for the synthesis of α-trifluoromethylated nitrogen heterocycles or bicycles starting from the trifluoromethylated homoallylamine.[15] Consequently, by analogy, the following retrosynthetic strategies have been envisioned (Scheme 1).

In these strategies, the key steps of cyclization are the well-known reactions, namely ring-closing metathesis (RCM)[16] and Pauson–Khand reaction (PKR).[17] The advantage of such strategies was their convergent aspect, since the common key intermediates were α-trifluoromethylated homoallylic alcohols **2** which should be obtained from the stable commercial form of trifluoroacetaldehyde, the methyl hemiacetal **1**.

Synthesis of α-Trifluoromethylated Homoallylic Alcohols

Some methods have been already described to obtain such α-trifluoromethylated homoallylic alcohols. Most of them consist in the nucleophilic addition of organometallic reagents (zinc, magnesium, lithium,[18a] boron,[18b,c] and stannyl[18d] derivatives) onto the gaseous trifluoroacetaldehyde (fluoral) which is very reactive, non-commercially available and not so easy to handle. Other techniques, starting directly from the commercial methyl hemiacetal form of fluoral, have been also developed. These methods are based on the reaction of allylorganometallic derivatives under Lewis acid activation conditions.[19] We have focused our interest on these latest methods as we wished to start from the fluoral methyl hemiacetal **1**.

By comparison with our previous work on the synthesis of α-trifluoromethylhomallylamine, via iminium species,[15a,20] we first tried to condense the allyltrimethylsilane onto an oxonium species, which could arise from a Lewis activation of **1**, to obtain the α-trifluoromethylhomoallylic alcohol **2a** (Table 1).

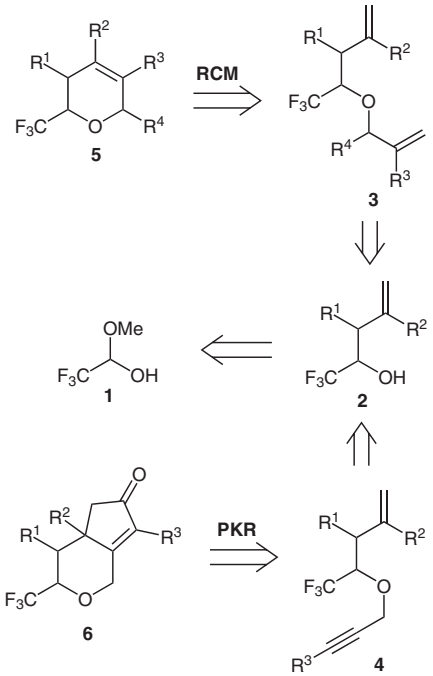
Only $ZnBr_2$ gave moderate yields (entry 3), the other Lewis acids leaving the starting material unchanged. Faced with these disappointing results, we turned our interest towards the interesting chemistry of indium species in water developed by Loh et al.[19c] (Scheme 2). Because

Biographical Sketches

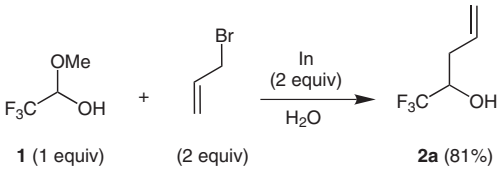
Steven Harthong was born in Lannion (France) in 1981. After studies in Rennes (France), he joined ENS-Lyon in 2002. He is finishing the Master of Science at the ENS-Lyon. During his studies he spent four months in Dr. Langlois' laboratory, working with Dr. Thierry Billard on the fluorinated oxygenated heterocycles.

Thierry Billard was born in Dole (France) in 1971. After studies at the 'Institut de Chimie et Physique Industrielles de Lyon', he received his Ph.D. from the University of Lyon in 1996 under the supervision of Dr. B. Langlois. After a post-doctoral training with Prof. L. Ghosez (Université Catholique de Louvain, Belgium), he was appointed in 1999 as a CNRS permanent researcher in the laboratory of Dr. B. Langlois. He is particularly interested in finding new methods for introduction of fluorinated moiety into molecules and their application in the synthesis of fluorinated substrates with biological interests.

Bernard R. Langlois was born near Paris (France) in 1947. After receiving his diploma from the 'Ecole Supérieure de Physique et Chimie Industrielles de Paris' in 1970, he entered the Rhône-Poulenc Co. where he worked, in different research centres (near Paris and Lyon), on organofluorine chemistry, from bench synthesis to development. In this context, he was involved in fluorinated aromatics and heterocycles, trifluoromethoxy-containing products, trifluoroacetic acid derivatives, triflic acid derivatives and radical trifluoromethylation. In the meantime, he got a Ph.D. degree from the University of Lyon in 1984 on the studies about difluorocarbene. In 1991, he moved to the University of Lyon where he is appointed as first class Research Director by the CNRS. There, his research group is developing new methodologies for the introduction of fluorine-containing moieties in organic substrates. As far as possible, these methodologies are illustrated by the synthesis of potentially bioactive compounds.



Scheme 1 Retrosynthetic analysis.



Scheme 2 Synthesis of **2a** using In-chemistry.[19c]

of the use of an excess of the expensive indium, we tried to optimize this reaction (Table 2).

Attempts to replace indium by less expensive metal failed (entries 4–8). However, we succeeded to decrease the amount of indium to only one equivalent without modifying the yield (entries 1,3). Better yield could be also obtained in a shorter time than in the previous work. The same reaction can be also realized in an organic solvent (DMF) without the presence of water in a satisfactory yield (entry 2). If we succeeded to obtain quantitative yield for the formation of **2**, the isolated yield was generally lower (around 50%) because of its very high volatility. This method has been applied to the synthesis of other α-trifluoromethylated homoallylic alcohols **2b–e** (Table 3).

The yields are better when the reaction is carried out in DMF rather than water. With our conditions, the compound **2b** could be obtained in good yield, whereas with their conditions, Loh et al. failed.[19c] Because of their volatility, **2d** and **2e** gave some problems of isolation and will not be used in the following steps. Concerning the diastereoselectivity, compounds **2b** and **2c** were obtained with

Table 1 Reaction of **1** with Allyltrimethylsilane with Lewis Acid Activation

Entry	Lewis acid	Solvent	Time (h)	Yield (%)[a]
1	$BF_3{\cdot}OEt_2$ (1.2 equiv)	CH_2Cl_2	18	0
2	$MgBr_2$ (1 equiv)	Et_2O	48	0
3	$ZnBr_2$ (1 equiv)	Et_2O	120	32
4	$Yb(OTf)_3$ (0.1 equiv)	THF–H_2O (4:1)	48	0
5	$Yb(OTf)_3$ (0.1 equiv)	DMF	6	0
6	$Yb(OTf)_3$ (0.1 equiv)	THF	6	0
7	$Yb(OTf)_3$ (0.1 equiv)	THF–H_2O (9:1)	24	0

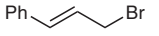
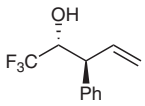
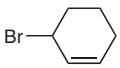
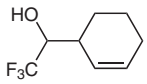
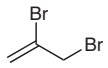
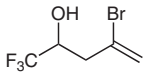
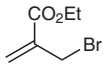
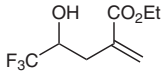
[a] Crude yields determined by ^{19}F NMR titration with internal standard ($PhOCF_3$).

Table 2 Synthesis of **2a**

Entry	Allyl bromide	Metal	Solvent	Time (h)	Yield (%)[a]
1	1 equiv	In (1 equiv)	H_2O	2	84
2	1 equiv	In (1 equiv)	DMF	5	69
3	1 equiv	In (1 equiv)	H_2O	5	96
4	1 equiv	Zn (1 equiv)	H_2O	6	0
5	1 equiv	Zn (1 equiv) + In (0.1 equiv)	H_2O	6	1
6	1 equiv	Mg (1 equiv)	THF	24	0
7	2 equiv	Mg (2 equiv)	THF	24	0
8	2 equiv	Mg (2 equiv) + US[b]	THF	24	0

[a] Crude yields determined by ^{19}F NMR titration with internal standard ($PhOCF_3$).
[b] US: Ultrasonic activation.

Table 3 Synthesis of α-Trifluoromethylated Homoallylic Alcohols **2**

Entry	Allyl bromide	Solvent	Product	Yield (%)[a]
1	 **7b**	H_2O	 **2b**	(10) (de = 80%)
2	**7b**	DMF	**2b**	90 (de = 80%)
3	 **7c**	H_2O	 **2c**	(13) (de = 60%)
4	**7c**	DMF	**2c**	80 (de = 60%)
5	 **7d**	H_2O	 **2d**	0
6	**7d**	DMF	**2d**	(25)
7	 **7e**	DMF	 **2e**	(50) 10

[a] Isolated yields. In parentheses: crude yields determined by ^{19}F NMR titration with internal standard ($PhOCF_3$).

modest to good diastereoselectivity. In the case of **2b**, the anti-conformation could be demonstrated. All these results are in accordance with literature.[21]

With these α-trifluoromethylhomoallylic alcohols in hand, we turned our attention to synthesize the precursors for cyclization by etherification or esterification of the OH group with convenient unsaturated moieties.

Synthesis of Precursors for Cyclization

Classically, the etherification of **2** was realized by deprotonation of the OH group and condensation with alkenyl halide. Because of the low nucleophilicity of the oxygen atom, due to the presence of the high electron withdrawing CF_3 moiety, the esterification with acyl chlorides required also the preliminary deprotonation of the OH group. The reaction was carried out in DMF using NaH as base, and the precursor products obtained are illustrated in Figure 1.

The low yield observed for **3aa** is essentially due to the volatility of this compound (crude yield: 80%) which led to a loss of product during evaporation of chromatographed fractions. To circumvent this drawback, an alternative way has been envisaged to obtain directly the pure

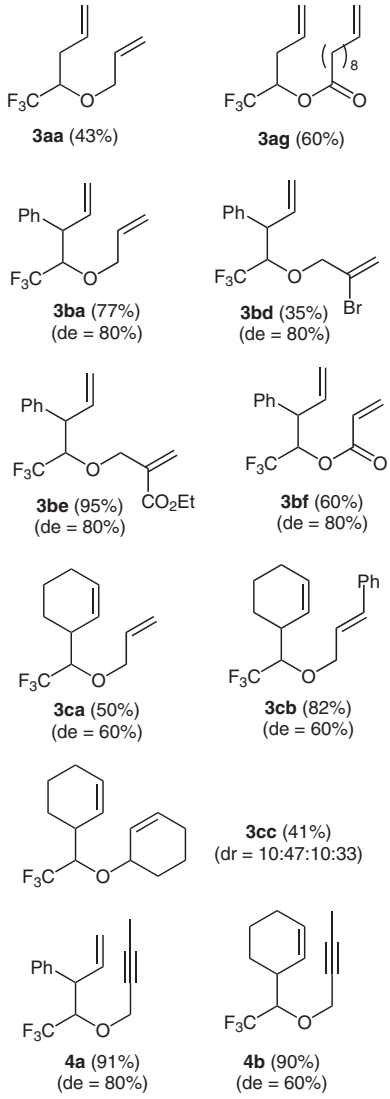


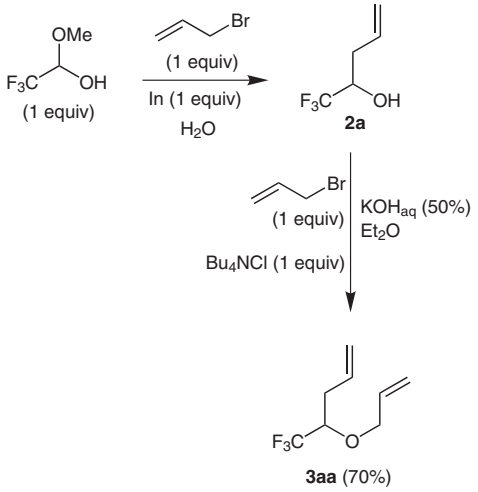
Figure 1 Precursors synthesized for cyclization.

compound without need for further purification. A one-pot two-step procedure from fluoral hemiacetal **1**, has been then elaborated. The key step is the use of a phase-transfer catalyst to allylate **2a**. At the end of the reaction, only the expected product **3aa** stays in the organic phase, the unreacted allyl bromide being hydrolyzed into allylic alcohol, consequently remains in the aqueous basic phase with the residual **2a** (Scheme 3).

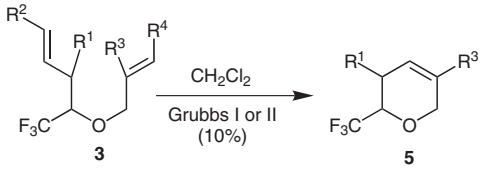
Ring-Closing Metathesis

2-(Trifluoromethyl)-3,6-dihydro-2H-pyran Derivatives

The RCM reactions of the synthesized precursors were then studied with the commercially available Grubbs I or II catalysts (Scheme 4 and Table 4).



Scheme 3 Alternative synthesis of **3aa**.



Scheme 4 RCM of **3**.

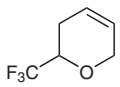
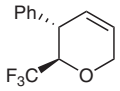
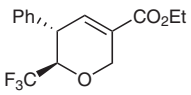
The reactions give satisfactory yields for **5aa** and **5ba** (entries 1,2) and more modest yields for **5be** (entry 4). This last result can be explained by the electronic deficiency of the conjugated double bond that involves a decreased reactivity towards metathesis. Moreover, the more active Grubbs II catalyst was required in this reaction.

No reaction was observed with the brominated diene **3bd**. Such result is in accordance with literature, which puts forward an inhibition of the reaction by the brominated double bond.[22] Attempts to realize ring-opening/ring-closing metathesis sequences with **3c** failed since only complex mixtures of fluorinated compounds were observed (entries 8–10). These results led to suppose that all the possibilities of ring closing occurred during the reaction, accompanied certainly by cross-coupling reactions.

From a practical point of view, the obtained compounds are very difficult to purify, except **5ba**. Indeed, **5aa** was too volatile to be extracted from the reacting mixture and could not be characterized other than by ^{19}F NMR spectrum (shift analogy with **5ba**) and by molecular mass determination by GC/MS. Compound **5be** was obtained as mixture with starting material **3be** that could not be separated, and again its formation has been proven by ^{19}F NMR spectrum and GC/MS.

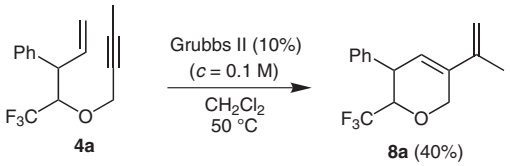
These results confirm the possibility to generate easily and rapidly α-trifluoromethylated oxygenated heterocycles. However, the major drawback of this reaction comes

Table 4 Synthesis of **5** by RCM of **3**

Entry	Diene **3**	Conditions	5	Yield (%)[a]
1	**3aa**	Grubbs I (c = 0.1 M), r.t., 24 h	 **5aa**	(70)
2	**3ba**	Grubbs I (c = 0.1 M), r.t., 24 h	 **5ba**	72 (de = 80%)
3	**3bd**	Grubbs II (c = 0.01 M), 50 °C, 24 h	–	0
4	**3be**	Grubbs II (c = 0.01 M), 50 °C, 24 h	 **5be**	(42) (de = 60%)
5	**3cb**	Grubbs I (c = 0.1 M), r.t., 24 h	–	0
6	**3cb**	Grubbs I (c = 0.1 M), 50 °C, 24 h	–	0
7	**3cb**	Grubbs I (c = 0.1 M), 110 °C (in toluene), 24 h	–	0
8	**3cb**	Grubbs II (c = 0.1 M), 50 °C, 24 h	–	complex mixture
9	**3cb**	Grubbs II (c = 0.01 M), 50 °C, 24 h	–	complex mixture
10	**3ba**	Grubbs II (c = 0.1 M), 50 °C, 24 h	–	complex mixture
11	**3cc**	Grubbs II (c = 0.01 M), 50 °C, 24 h	–	0

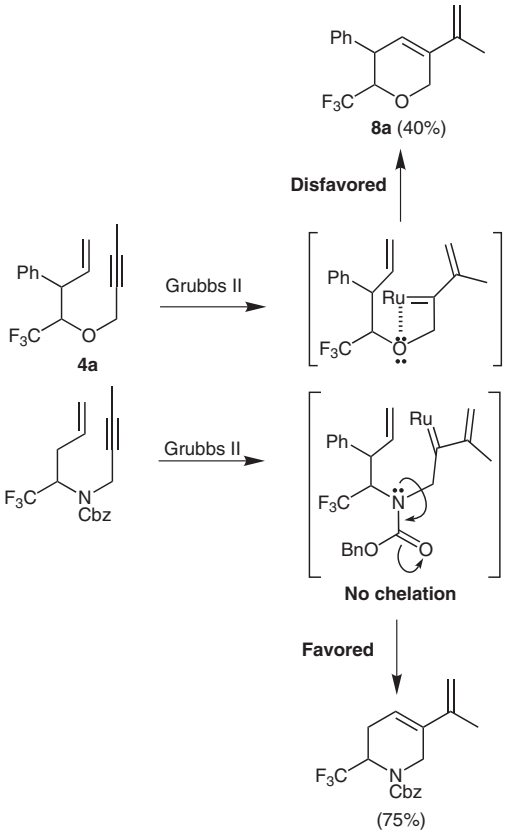
[a] Isolated yields. In parentheses: crude yields determined by ^{19}F NMR titration with internal standard ($PhOCF_3$).

from the products, which are often difficult to purify because of their volatility. To extend the potentiality of RCM to α-trifluoromethylated precursors, the enyne metathesis has been also tested, starting from **4a** to achieve the synthesis of conjugated diene (Scheme 5).



Scheme 5 RCM of the enyne **4a**.

The expected diene **8a** was obtained only in moderate yield. Such a result is not necessarily surprising compared to literature, since generally, most of enyne metathesis required the addition of ethylene to reach good yields. However, in the same conditions, good yields were obtained with the corresponding nitrogen compounds.[15a] This difference of reactivity could be rationalized by supposing a chelation between oxygen and ruthenium in the reaction intermediate arising from the attack of the Grubbs catalyst onto the triple bond. This chelation would stabilize this new carbene, disfavoring its reaction with double bond and then prohibiting the cyclization (Scheme 6). In the case of nitrogen compounds, the chelation is disfavored because of the Cbz protecting group of nitrogen, which delocalizes the free electron pair (Scheme 6). Despite its modest yield of formation, the obtained conjugated diene should constitute interesting starting material for the design of bicyclic structures, for example by Diels–Alder cycloadditions.

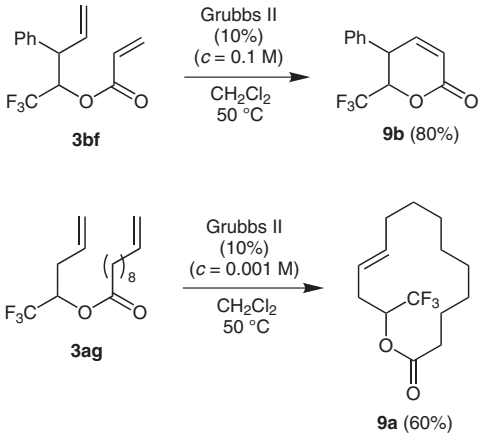


Scheme 6 Enynes metathesis: oxygen vs nitrogen compounds.

Synthesis of Lactones

The lactone core is present in many of the structures of natural products and bioactive molecules. For instance, macrolide antibiotics possess such substructures. In these last years, RCM has proved to be an efficient method to achieve such structures. Consequently, we looked into the possibility to obtain α-trifluoromethyl lactones starting from the esters **3ag** and **3bf** (Scheme 7).

The expected α-trifluoromethyl δ-lactone was obtained with good yield confirming the power of the RCM in such synthesis. More interestingly, for the first time, 14-membered α-trifluoromethyl macrolactone could be also synthesized, opening interesting perspectives in the synthesis of fluorinated analogues of macrolides. Such applications are under study in our laboratory and will be published in due course.

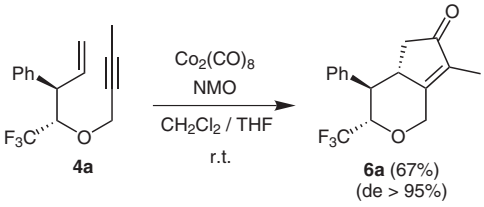


Scheme 7 Synthesis of α-trifluoromethylated lactones.

Pauson–Khand Cyclization

The Pauson–Khand reaction (PKR) is a well-known cobalt-mediated cyclization to achieve the preparation of bicyclic ketones. Because of our recent work concerning the use of such reaction into the synthesis of trifluoromethylated nitrogen bicyclic enones,[15b] we have been interested to verify if the same reaction is possible in oxygen series. Compound **4a** was used as the model substrate for this reaction (Scheme 8).

The expected α-trifluoromethylated oxygenated bicyclic enone **6a** was obtained in good yield. This cyclization is also highly diastereoselective since, starting from a pure *anti* diastereomer of **4a**, only one diastereomer has been detected by NMR. The resulting diastereomer possesses an *anti-anti-anti* configuration, which was determined by NOESY experiment (Figure 2).



Scheme 8 Pauson–Khand cyclization of **4a**.

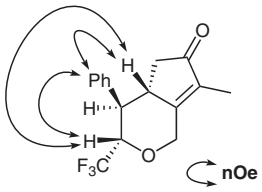


Figure 2 NOESY correlation of **6a**.

Such diastereoselectivity can be rationalized by considering the potential transition states. The NMR analysis of **4a** (*anti* diastereomer) has shown a *gauche* coupling constant between H-1 and H-2 ($^3J_{H1,H2}$ = 4.3 Hz) leading to envisage a preferential conformation pseudo-diaxial for **4a** (Figure 3). This major conformation is certainly due to the high electrostatic repulsion between the two electron-rich groups CF_3 and Ph.[23]

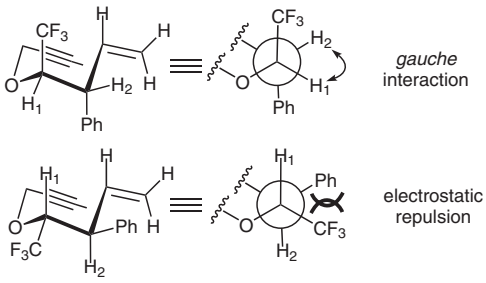


Figure 3 Preferential conformation of **4a**.

By this fact, the two potential transition states for the PKR are $\mathbf{T_1}$ and $\mathbf{T_2}$ (Figure 4). Because of a higher steric interaction between vinylic hydrogen and phenyl group in $\mathbf{T_1}$ than between the vinylic hydrogen and CF_3 in $\mathbf{T_2}$, the transition state $\mathbf{T_2}$ is favored, leading to the formation of the *anti-anti-anti* diastereomer. Such results are in accordance with similar observation previously described in literature.[24]

With this result in hand, we have envisioned the construction of a fused tricyclic structure, starting from **4b** (Scheme 9). Tricycle formations by PKR have been described,[25] but never with the fused 3 cycles.

Whatever the conditions used for this reaction, even with the use of DMSO as described in literature,[11a] the expected tricyclic compound was never obtained. With the aim to understand the reasons of this failure, the reaction has been followed, step by step. If the complexation of the triple bond by cobalt occurs quantitatively, the cyclization

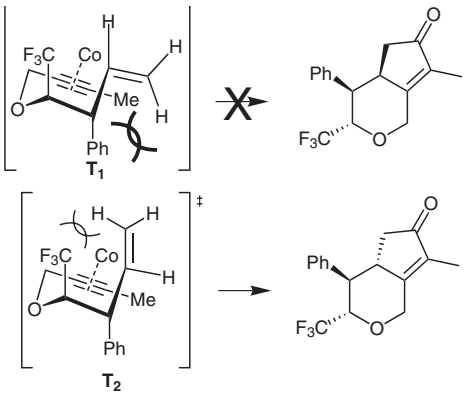
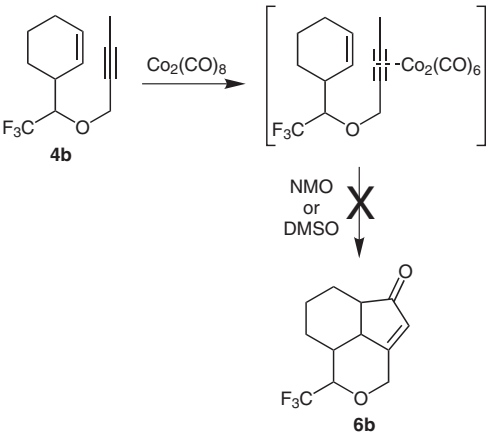


Figure 4 Transition states of PKR with **4a**.



Scheme 9 PKR with **4b**.

step fails. This led to conclude that the cyclic tension in the final product is too high and thus disfavors its formation.

Conclusion

In this work, we have shown that methyl hemiketal of fluoral constitutes an interesting fluorinated commercially available starting material, to synthesize oxygenated cyclic structure bearing a CF_3 group in α position. The ring closing metathesis allowed not only the formation of 6-membered cycles, bearing various substituents, but also the synthesis of lactones and macrolactones. With the Pauson–Khand reaction, bicyclic structure could be achieved with a high diastereoselectivity. Nevertheless, the main drawback of these reactions is essentially the difficult purification of the products due to the high volatility of certain compounds. These volatilities are linked to the presence of the CF_3 group, which is well-known to decrease the boiling point of molecules containing this entity.[1]

However, the easy synthesis of the precursors for cyclizations and the efficiency of the RCM and PKR to obtain rapidly and diastereoselectively fluorinated cyclic structures should constitute effective synthetic tools for the de-

sign of new fluorinated molecules. The synthesis of fluorinated analogues of natural products, using these methods, is under development in our laboratory. Another interest of these strategies is their potential extension to other fluoroalkyl group. Indeed, others hemiketal of fluoroalkyl aldehydes are available (with CF_3CF_2 or CF_2Cl moieties for example) and they can be used in the same manner to reach other α-fluoroalkylated oxygenated cycles. Such extension is also under study in our laboratory.

Prior to use, THF was freshly distilled over Na/benzophenone, CH_2Cl_2 was dried over molecular sieves. Anhydrous DMF was purchased from Aldrich. Other reagents were used as received. NMR spectra were recorded on Bruker Avance 300 spectrometer. ^1H, ^{13}C and ^{19}F NMR spectra were recorded in $CDCl_3$ at 300, 75 and 282 MHz, respectively. Chemical shifts are given in ppm relative to TMS (^1H, ^{13}C) or $CFCl_3$ (^{19}F) as internal references and coupling constants are given in Hz. Flash chromatography was performed on silica gel 60 M (0.04–0.063 mm). Melting points (uncorrected) were determined in capillary tubes on a Büchi apparatus.

α-Trifluoromethylated Homoallylic Alcohols 2; General Procedure

To a suspension of In powder (115 mg, 1 mmol) in H_2O or DMF (1 mL) was added allylic halide **7** (1 equiv). After stirring for 10 min, fluoral hemiacetal **1** (160 mg, 1.2 mmol) was added. The mixture was then stirred at r.t. for 5 h. A 5% aq solution of $KHSO_4$ (5 mL) was then added and the mixture was extracted with Et_2O (10 mL). The organic phase was dried ($MgSO_4$) and the solvent was evaporated in vacuo. Generally, the expected alcohol **2** was obtained pure and was engaged in the following reaction. If necessary, purification by flash chromatography could be realized.

1,1,1-Trifluoropent-4-en-2-ol (2a)

^1H NMR: δ = 5.85 (m, 1 H), 5.26 (m, 2 H), 4.02 (m, 1 H), 2.54 (m, 1 H), 2.41 (m, 1 H), 2.28 (d, *J* = 5.84 Hz, 1 H).

^{19}F NMR: δ = –79.91 (d, *J* = 6.9 Hz).

Anal. Calcd for $C_5H_7F_3O$: C, 42.86; H, 5.04. Found: C, 43.01; H, 4.82.

1,1,1-Trifluoro-3-phenylpent-4-en-2-ol (2b)

Two diastereomers, 90:10 ratio.

^1H NMR: δ = 7.36–7.41 (br, 5 H), 6.33 (ddd, 1 H, *J* = 8.5, 9.1, 17.3 Hz), 5.40 (dd, 1 H, *J* = 9.1, 1.0 Hz), 5.31 (dd, 1 H, *J* = 17.2, 1.0 Hz), 4.31 (dq, 1 H, *J* = 5.2, 6.9 Hz), 3.85 (dd, 1 H, *J* = 5.2, 8.5 Hz), 2.96 (br s, 1 H).

^{13}C NMR: δ = 140.4, 135.2, 129.3, 128.6, 127.8, 125.3 (q, *J* = 284.4 Hz), 73.6 (q, *J* = 29.5 Hz), 50.6 (q, *J* = 1.3 Hz).

^{19}F NMR: δ = –75.21 (d, 0.1 F, *J* = 6.9 Hz), –75.14 (d, 0.9 F, *J* = 6.9 Hz).

Anal. Calcd for $C_{11}H_{11}F_3O$: C, 61.11; H, 5.13. Found: C, 60.99; H, 5.04.

1-Cyclohex-2-en-1-yl-2,2,2-trifluoroethanol (2c)

Two diastereomers, 80:20 ratio.

^1H NMR: δ = 5.99 (ddd, 0.8 H, *J* = 10.2, 6.2, 3.8 Hz), 5.89 (ddd, 0.2 H, *J* = 10.1, 6.2, 3.8 Hz), 5.71 (br d, 0.8 H, *J* = 10.2 Hz), 5.52 (br d, 0.2 H, *J* = 10.1 Hz), 3.89 (ddq, 0.2 H, *J* = 5.7, 5.7, 6.9 Hz), 3.75 (ddq, 0.8 H, *J* = 7.8, 4.2, 6.9 Hz), 3.00 (d, 0.2 H, *J* = 5.7 Hz), 2.82 (d, 0.8 H, *J* = 7.8 Hz), 2.58 (m, 1 H), 2.02 (m, 2 H), 1.8 (m, 2 H), 1.59 (m, 2 H).

^{13}C NMR: δ = 133. 5, 131.5, 126.5 (q, *J* = 1.5 Hz), 123.9 (q, *J* = 1.6 Hz), 125.7 (q, *J* = 283.2 Hz), 125.6 (q, *J* = 283.4 Hz), 73.7 (q, *J* = 29.6 Hz), 73.35 (q, *J* = 29.3 Hz), 36.6 (q, *J* = 1.3 Hz), 36.2 (q, *J* = 1.3 Hz), 26.8 (q, *J* = 1.1 Hz), 22.9 (q, *J* = 1.3 Hz), 25.1, 25.0, 21.5, 21.0.

^{19}F NMR: δ = –76.02 (d, 0.2 F, *J* = 6.9 Hz), –77.01 (d, 0.8 F, *J* = 6.9 Hz).

Anal. Calcd for $C_8H_{11}F_3O$: C, 53.33; H, 6.15. Found: C, 53.57; H, 5.97.

4-Bromo-1,1,1-trifluoropent-4-en-2-ol (2d)

^1H NMR: δ = 5.75 (m, 1 H), 5.60 (m, 1 H), 4.11 (m, 1 H), 2.3 (m, 2 H).

^{19}F NMR: δ = –80.17 (d, *J* = 6.9 Hz).

Anal. Calcd for $C_5H_6BrF_3O$: C, 27.42; H, 2.76; Br, 36.49. Found: C, 27.51; H, 2.72; Br, 36.13.

Ethyl 5,5,5-Trifluoro-4-hydroxy-2-methylenepentanoate (2e)

^1H NMR: δ = 6.34 (d, 1 H, *J* = 1.1 Hz), 5.80 (m, 1 H), 4.25 (q, 2 H, *J* = 7.0 Hz), 4.12 (ddq, 1 H, *J* = 9.5, 2.8, 6.6 Hz), 3.85 (br s, 1 H), 2.77 (br dd, 1 H, *J* = 14.4, 2.8 Hz), 2.58 (br dd, 1 H, *J* = 14.4, 9.5 Hz), 1.32 (t, 3 H, *J* = 7.0 Hz).

^{13}C NMR: δ = 168.2, 135.9, 129.9, 125.38 (q, *J* = 282.1 Hz), 70.0 (q, *J* = 30.9 Hz), 61.9, 33.7 (q, *J* = 2.0 Hz), 14.4.

^{19}F NMR: δ = –80.17 (d, *J* = 6.9 Hz).

Anal. Calcd for $C_8H_{11}F_3O_3$: C, 45.29; H, 5.23. Found: C, 45.07; H, 5.51.

Ethers or Esters 3 and 4; General Procedure

To a solution of **2** (1 mmol) in DMF (2 mL) was added NaH (1.2 equiv) at 0 °C. After stirring for 10 min at 0 °C, allylic halide **7** (1 equiv) was added. The mixture was then stirred at r.t. for 5 h. Pentane (10 mL) was then added and the organic phase was washed with H_2O (10 mL). The organic phase was dried ($MgSO_4$) and the solvent was evaporated in vacuo. The crude product was purified by flash chromatography (eluent: pentane–Et_2O).

4-(Allyloxy)-5,5,5-trifluoropent-1-ene (3aa)

^1H NMR: δ = 5.78–5.98 (br, 2 H), 5.13–5.38 (br, 4 H), 4.30 (dd, 1 H, *J* = 12.4, 5.5 Hz), 4.11 (dd, 1 H, *J* = 12.4, 6.3 Hz), 3.71 (tq, 1 H, *J* = 6.4, 6.6 Hz), 2.44 (m, 2 H).

^{19}F NMR: δ = –77.18 (d, *J* = 6.6 Hz).

Anal. Calcd for $C_8H_{11}F_3O$: C, 53.33; H, 6.15. Found: C, 53.47; H, 6.39.

1-(Trifluoromethyl)but-3-en-1-ylundec-10-enoate (3ag)

^1H NMR: δ = 5.64–5.89 (br, 2 H), 5.38 (ddq, 1 H, *J* = 9.2, 4.3, 6.1 Hz), 4.92–5.22 (br, 4 H), 2.35–2.65 (br, 4 H), 2.06 (m, 2 H), 1.65 (br m, 2 H), 1.27–1.43 (br, 10 H).

^{13}C NMR: δ = 172.0, 139.1, 130.9, 123.7 (q, *J* = 280.8 Hz), 119.4, 114.2, 68.68 (q, *J* = 31.9 Hz), 33.6, 33.8, 32.6 (q, *J* = 1.6 Hz), 29.3, 29.1, 29.0, 28.9, 28.9; 24.8.

^{19}F NMR: δ = –77.37 (d, *J* = 6.1 Hz).

Anal. Calcd for $C_{16}H_{25}F_3O_2$: C, 62.73; H, 8.23. Found: C, 62.81; H, 8.17.

{1-[1-(Allyloxy)-2,2,2-trifluoroethyl]prop-2-en-1-yl}benzene (3ba)

Two diastereomers, 90:10 ratio.

^1H NMR: δ = 7.27–7.36 (br, 5 H), 6.34 (ddd, 1 H, *J* = 8.8, 9.1, 17.7 Hz), 5.76 (ddt, 1 H, *J* = 5.6, 10.9, 16.7 Hz), 5.13–5.29 (br, 4 H),

4.23 (dd, 1 H, *J* = 12.2, 5.6 Hz), 3.85–4.00 (br, 2 H), 3.73 (dd, 1 H, *J* = 8.7, 4.0 Hz).

^{13}C NMR: δ = 141.2, 135.6, 133.8, 129.1, 128.6, 127.5, 125.4 (q, *J* = 286.0 Hz), 118.6, 118.3 (C-1), 80.9 (q, *J* = 30.0 Hz), 74.8 (q, *J* = 1.1 Hz), 50.35 (q, *J* = 1.5 Hz).

^{19}F NMR: δ = –72.98 (d, 0.1 F, *J* = 5.7 Hz), –73.56 (d, 0.9 F, *J* = 6.9 Hz).

Anal. Calcd for $C_{14}H_{15}F_3O$: C, 65.62; H, 5.90. Found: C, 65.89; H, 5.99.

(1-{1-[(2-Bromoprop-2-en-1-yl)oxy]-2,2,2-trifluoroethyl}prop-2-en-1-yl)benzene (3bd)
Two diastereomers, 90:10 ratio.

^{1}H NMR: δ = 7.26–7.41 (br, 5 H), 6.37 (m, 1 H), 5.93 (m, 1 H), 5.63 (m, 1 H), 5.14–5.32 (br, 2 H), 4.32 (d, 1 H, *J* = 13.4 Hz), 4.06 (d, 1 H, *J* = 13.4 Hz), 3.99 (dq, 1 H, *J* = 4.2, 6.7 Hz), 3.79 (dd, 1 H, *J* = 8.7, 4.2 Hz).

^{13}C NMR: δ = 140.8, 135.3, 129.2, 128.52, 127.62, 127.4, 125.1 (q, *J* = 286.0 Hz), 118.9, 118.6, 81.8 (q, *J* = 28.0 Hz), 77.2 (q, *J* = 1.1 Hz), 50.2 (q, *J* = 1.6 Hz).

^{19}F NMR: δ = –72.60 (d, 0.19 F, *J* = 6.7 Hz), –73.24 (d, 0.9 F, *J* = 6.7 Hz).

Anal. Calcd for $C_{14}H_{14}BrF_3O$: C, 50.17; H, 4.21; Br, 23.84. Found: C, 50.39; H, 4.26; Br, 23.96.

Ethyl 2-({[2-Phenyl-1-(trifluoromethyl)but-3-en-1-yl]oxy}methyl)acrylate (3be)
Two diastereomers, 90:10 ratio.

^{1}H NMR: δ = 7.24–7.37 (br, 5 H), 6.34 (m, 0.9 H), 6.31 (m, 0.9 H), 6.22 (m, 0.1 H), 6.12 (m, 0.1 H), 5.91 (m, 0.9 H), 5.65 (m, 0.1 H), 5.10–5.24 (br, 2 H), 4.46 (d, 0.9 H, *J* = 13.2 Hz), 4.44 (d, 0.1 H, *J* = 13.6 Hz), 4.13–4.26 (br, 3 H), 4.03 (dq, 1 H, *J* = 4.5, 6.8 Hz), 3.67–3.79 (br, 1 H), 1.31 (t, 2.7 H, *J* = 7.2 Hz), 1.30 (t, 0.3 H, *J* = 7.2 Hz).

^{13}C NMR: δ = 165.8, 140.9, 139.6, 136.9, 136.7, 136.8, 135.6, 129.1, 129.0, 128.9, 128.5, 127.5, 127.5, 127.1, 125.3 (q, *J* = 286.2 Hz), 118.3, 117.7, 81.9 (q, *J* = 27.8 Hz), 81.8 (q, *J* = 28.0 Hz), 71.8, 61.2, 61.2, 51.5 (q, *J* = 1.3 Hz), 50.3 (q, *J* = 1.6 Hz), 14.5.

^{19}F NMR: δ = –72.89 (d, 0.1 F, *J* = 6.8 Hz), –73.49 (d, 0.9 F, *J* = 6.8 Hz).

Anal. Calcd for $C_{17}H_{19}F_3O_3$: C, 62.19; H, 5.83. Found: C, 62.06; H, 5.56.

2-Phenyl-1-(trifluoromethyl)but-3-en-1-yl Acrylate (3bf)
Two diastereomers, 90:10 ratio.

^{1}H NMR: δ = 7.22–7.41 (br, 5 H), 6.54 (dd, 1 H, *J* = 17.3, 1.2 Hz), 5.92–6.38 (br, 3 H), 5.67–5.85 (br, 1 H), 5.14–5.33 (br, 2 H), 3.84 (m, 1 H).

^{13}C NMR: δ = 164.6, 164.3, 138.8, 138.5, 135.6, 135.5, 133.4, 133.1, 129.3, 129.0, 128.7, 128.4, 127.9, 127.8, 127.4, 127.0, 123.9 (q, *J* = 282.5 Hz), 118.9, 118.8, 72.2 (q, *J* = 30.2 Hz), 71.6 (q, *J* = 30.4 Hz), 50.36 (q, *J* = 1.3 Hz), 50.18 (q, *J* = 1.3 Hz).

^{19}F NMR: δ = –73.23 (d, 0.1 F, *J* = 7.0 Hz), –73.47 (d, 0.9 F, *J* = 7.0 Hz).

Anal. Calcd for $C_{14}H_{13}F_3O_2$: C, 62.22; H, 4.85. Found: C, 62.26; H, 4.69.

3-[1-(Allyloxy)-2,2,2-trifluoroethyl]cyclohexene (3ca)
Two diastereomers, 80:20 ratio.

^{1}H NMR: δ = 6.70–6.01 (br, 3 H), 5.28 (m, 2 H), 4.32 (m, 1 H), 4.09 (m, 1 H), 3.62 (dq, 0.2 H, *J* = 5.3, 7.0 Hz), 3.47 (dq, 0.8 H, *J* = 6.6, 7.0 Hz), 2.56 (br m, 1 H), 2.02 (br m, 2 H), 1.45–1.90 (br, 4 H).

^{13}C NMR: δ = 134.3, 134.1, 130.5, 130.1, 127.2 (q, *J* = 1.3 Hz), 126.1 (q, *J* = 1.3 Hz), 126.0 (q, *J* = 286.0 Hz), 118.7, 118.5, 80.5 (q, *J* = 27.8 Hz), 79.6 (q, *J* = 27.8 Hz), 74.6 (q, *J* = 1.1 Hz), 74.4 (q, *J* = 1.1 Hz), 36.6 (q, *J* = 1.5 Hz), 26.3 (q, *J* = 1.6 Hz), 25.2, 25.2, 21.9.

^{19}F NMR: δ = –73.23 (d, 0.2 F, *J* = 7.0 Hz), –73.47 (d, 0.8 F, *J* = 7.0 Hz).

Anal. Calcd for $C_{11}H_{15}F_3O$: C, 59.99; H, 6.87. Found: C, 60.21; H, 6.65.

[(1*E*)-3-(1-Cyclohex-2-en-1-yl-2,2,2-trifluoroethoxy)prop-1-en-1-yl]benzene (3cb)
Two diastereomers, 80:20 ratio.

^{1}H NMR: δ = 7.28–7.48 (br, 5 H), 6.69 (d, 1 H, *J* = 16.2 Hz), 6.25–6.39 (br, 1 H), 5.89–5.97 (br, 1 H), 5.86 (br d, 0.8 H, *J* = 11.3 Hz), 5.61 (d, 0.2 H, *J* = 10.9 Hz), 4.47–4.59 (br, 1 H), 4.31 (dd, 1 H, *J* = 12.2, 6.8 Hz), 3.73 (dq, 0.2 H, *J* = 5.4, 6.9 Hz), 3.59 (dq, 0.8 H, *J* = 6.4, 6.9 Hz), 2.63 (m, 1 H), 2.08 (m, 2 H), 1.77–1.95 (br, 2 H), 1.52–1.70 (br, 2 H).

^{13}C NMR: δ = 136.9, 134.0, 133.9, 130.6, 130.2, 129.0, 128.4, 127.1, 127.0, 127.2 (q, *J* = 1.5 Hz), 126.1 (q, *J* = 1.3 Hz), 126.1 (q, *J* = 285.8 Hz), 126.1 (q, *J* = 285.2 Hz), 125.5, 125.2, 80.4 (q, *J* = 27.8 Hz), 79.7 (q, *J* = 27.8 Hz), 74.3 (q, *J* = 1.3 Hz), 74.0 (q, *J* = 1.3 Hz), 36.6 (q, *J* = 1.5 Hz), 26.4 (q, *J* = 1.6 Hz), 23.6 (q, *J* = 1.3 Hz), 25.3, 25.3, 21.9, 21.3.

^{19}F NMR: δ = –72.99 (d, 0.2 F, *J* = 6.9 Hz), –73.47 (d, 0.8 F, *J* = 6.9 Hz).

Anal. Calcd for $C_{17}H_{19}F_3O$: C, 68.90; H, 6.46. Found: C, 68.96; H, 6.58.

3-[1-(Cyclohex-2-en-1-yloxy)-2,2,2-trifluoroethyl]cyclohexene (3cc)
Four diastereomers, 10:47:10:33 ratio.

^{1}H NMR: δ = 5.54–5.96 (br, 4 H), 4.08 (m, 1 H), 3.48–3.78 (br, 1 H), 2.56 (m, 1 H), 1.50–2.22 (br, 12 H).

^{19}F NMR: δ = –73.53 (d, 0.1 F, *J* = 6.9 Hz), –73.62 (d, 0.47 F, *J* = 6.9 Hz), –73.71 (d, 0.1 F, *J* = 6.9 Hz), –73.90 (d, 0.33 F, *J* = 6.9 Hz).

Anal. Calcd for $C_{14}H_{19}F_3O$: C, 64.60; H, 7.36. Found: C, 64.80; H, 7.48.

{1-[1-(But-2-yn-1-yloxy)-2,2,2-trifluoroethyl]prop-2-en-1-yl}benzene (4a)
Two diastereomers, 90:10 ratio.

^{1}H NMR: δ = 7.25–7.40 (br, 5 H), 6.34 (ddd, 1 H, *J* = 17.2, 9.5, 8.7 Hz), 5.23 (br d, 1 H, *J* = 9.5 Hz), 5.15 (br d, 1 H, *J* = 17.2 Hz), 4.15–4.36 (br, 3 H), 3.74 (dd, 1 H, *J* = 4.3, 8.7 Hz), 1.76 (t, 3 H, *J* = 2.3 Hz).

^{13}C NMR: δ = 140.9, 135.8, 128.9, 128.8, 127.4, 125.4 (q, *J* = 286.0 Hz), 118.2, 84.5, 79.1 (q, *J* = 28.0 Hz), 74.0, 60.9 (q, *J* = 1.5 Hz), 50.1 (q, *J* = 1.6 Hz), 3.9.

^{19}F NMR: δ = –72.70 (d, 0.1 F, *J* = 6.9 Hz), –73.42 (d, 0.9 F, *J* = 6.9 Hz).

Anal. Calcd for $C_{15}H_{15}F_3O$: C, 67.16; H, 5.64. Found: C, 67.37; H, 5.47.

3-[1-(But-2-yn-1-yloxy)-2,2,2-trifluoroethyl]cyclohexene (4b)
Two diastereomers, 80:20 ratio.

^{1}H NMR: δ = 5.76–5.89 (br, 2 H), 4.35 (m, 2 H), 3.87 (dq, 0.2 H, *J* = 5.9, 6.9 Hz), 3.73 (dq, 0.8 H, *J* = 5.7, 6.9 Hz), 2.55 (br m, 1 H), 2.03 (m, 2 H), 1.70–1.91 (br, 5 H), 1.50–1.66 (br, 2 H).

^{13}C NMR: δ = 130.5, 130.5, 126.9 (q, *J* = 1.5 Hz), 125.96 (q, *J* = 1.5 Hz), 126.00 (q, *J* = 285.6 Hz), 125.98 (q, *J* = 285.6 Hz), 84.3, 84.2, 78.7 (q, *J* = 28.0 Hz), 78.0 (q, *J* = 8.0 Hz), 74.5, 74.4, 60.7 (q, *J* = 1.5 Hz), 60.4 (q, *J* = 1.5 Hz), 36.4 (q, *J* = 1.3 Hz), 36.3 (q, *J* = 1.3 Hz), 26.2 (q, *J* = 1.2 Hz), 23.5 (q, *J* = 1.2 Hz), 25.20, 25.18, 21.9, 21.1, 3.92, 3.89.

^{19}F NMR: δ = –72.81 (d, 0.2 F, *J* = 6.9 Hz), –73.20 (d, 0.8 F, *J* = 6.9 Hz).

Anal. Calcd for $C_{12}H_{15}F_3O$: C, 62.06; H, 6.51. Found: C, 62.17; H, 6.19.

Ring-Closing Metathesis Reaction; General Procedure

To a solution of **3** or **4** (1 equiv) in CH_2Cl_2 (see Table 4 for concentration) was added Grubbs catalyst (0.1 equiv). The reaction mixture was stirred for 24 h (see Table 4 for temperature). The mixture was then evaporated in vacuo and purified by flash chromatography (eluent: pentane–Et_2O) (Table 4).

2-(Trifluoromethyl)-3,6-dihydro-2*H*-pyran (5aa)

^{19}F NMR: δ = –79.7 (d, *J* = 6.9 Hz).

GC/MS (EI, 70 eV): *m*/*z* = 152 ($M^{+\cdot}$).

3-Phenyl-2-(trifluoromethyl)-3,6-dihydro-2*H*-pyran (5ba)

^{1}H NMR: δ = 7.23–7.40 (br, 5 H), 5.98 (ddt, 1 H, *J* = 10.3, 2.4, 2.4 Hz), 5.79 (ddt, 1 H, *J* = 10.3, 2.4, 2.4 Hz), 4.42 (m, 2 H), 4.04 (dq, 1 H, *J* = 6.8, 7.5 Hz), 3,71 (ddt, 1 H, *J* = 7.5, 2.4, 2.4, Hz, H-2).

^{13}C NMR: δ = 140.4. 129.1, 128.7, 127.8, 127.6, 125.4, 124.7 (q, *J* = 282.5 Hz), 77.6 (q, *J* = 29.3), 65.5, 41.0 (q, *J* = 1.3 Hz).

^{19}F NMR: δ = –75.43 (d, *J* = 6.8 Hz).

Anal. Calcd for $C_{12}H_{11}F_3O$: C, 63.16; H, 4.86. Found: C, 63.21; H, 4.79.

Ethyl 6-(Trifluoromethyl)-5-phenyl-5,6-dihydro-2*H*-pyran-3-carboxylate (5be)

Two diastereomers, 80:20 ratio.

^{19}F NMR: δ = –74.39 (d, 0.2 F, *J* = 6.9 Hz), –75.69 (d, 0.8 F, *J* = 6.9 Hz).

GC/MS (EI, 70 eV): *m*/*z* = 300 ($M^{+\cdot}$), 255 ($M^{+\cdot}$ – OEt).

5-Isopropenyl-3-phenyl-2-(trifluoromethyl)-3,6-dihydro-2*H*-pyran (8a)

Two diastereomers, 80:20 ratio.

^{1}H NMR: δ = 7.22–7.46 (br, 5 H), 5.68 (d, 0.2 H, *J* = 4.9 Hz), 5.57 (d, 0.8 H, *J* = 4.1 Hz) 5.35 (br s, 0.2 H), 5.25 (br s, 1 H), 5.21 (br s, 0.8 H), 4.80–5.00 (br, 1.2 H), 4.25–4.50 (br, 1.8 H), 4.05–4.18 (br, 1 H), 2.13 (t, 0.6 H, *J* = 1.3 Hz), 2.00 (t, 2.4 H, *J* = 1.5 Hz).

^{13}C NMR: δ = 146.3, 145.83; 140.6, 140.5; 129.6, 129.5; 129.19, 129.16; 128.88, 128.87; 127.8, 127.7; 125.2 (q, *J* = 284.3 Hz), 125.1 (q, *J* = 284.1 Hz); 117.4, 114.8; 79.9 (q, *J* = 27.8 Hz), 79.7 (q, *J* = 27.6 Hz); 73.5, 68.2; 47.4 (m large), 46.9 (m large); 24.8, 24.1.

^{19}F NMR: δ = –74.14 (d, 0.2 F, *J* = 6.9 Hz), –74.50 (d, 0.8 F, *J* = 6.9 Hz).

Anal. Calcd for $C_{15}H_{15}F_3O$: C, 67.16; H, 5.64. Found: C, 67.41; H, 5.83.

(11*E*)-14-(Trifluoromethyl)oxacyclotetradec-11-en-2-one (9a)

^{1}H NMR: δ = 5.55 (ddd, 1 H, *J* = 14.6, 7.5, 6.8 Hz), 5.36 (m, 1 H), 2.34–2.64 (br, 4 H), 2.04 (m, 2 H), 1.64 (br m, 2 H), 1.27–1.43 (br, 10 H).

^{13}C NMR: δ = 172.8, 136.0, 124.1 (q, *J* = 281.6 Hz), 123.7, 69.3 (q, *J* = 31.5 Hz), 34.3, 31.6 (q, *J* = 2.2 Hz), 31.6, 26.6, 25.9, 25.9, 24.4, 24.1.

^{19}F NMR: δ = –77.37 (d, *J* = 6.1 Hz).

Anal. Calcd for $C_{14}H_{21}F_3O_2$: C, 60.42; H, 7.61. Found: C, 60.69; H, 7.38.

6-(Trifluoromethyl)-5-phenyl-5,6-dihydro-2*H*-pyran-2-one (9b)

^{1}H NMR: δ = 7.35–7.52 (br, 3 H), 7.23–7.34 (br, 2 H), 6.83 (ddd, 1 H, *J* = 10.0, 4.1 Hz), 6.21 (dd, 1 H, *J* = 10.0, 2.1 Hz), 4.89 (dq, 1 H, *J* = 6.1, 6.8 Hz), 3.99 (ddd, 1 H, *J* = 6.1, 4.1, 2.1 Hz).

^{13}C NMR: δ = 160.3, 146.8, 136.9, 129.9, 129.3, 128.4, 123.3 (q, *J* = 282.7 Hz), 120.1, 79.9 (q, *J* = 31.5 Hz), 39.4 (q, *J* = 1.5 Hz).

^{19}F NMR: δ = –76.56 (d, *J* = 6.8 Hz).

Anal. Calcd for $C_{12}H_9F_3O_2$: C, 59.51; H, 3.75. Found: C, 59.60; H, 3.78.

Pauson–Khand Reaction; 3-(Trifluoromethyl)-7-methyl-4-phenyl-3,4,4a,5-tetrahydrocyclopenta[*c*]pyran-6(1*H*)-one (6a); Typical Procedure

To a solution of **4a** (268 mg, 1 mmol) in CH_2Cl_2 (6 mL) was added $Co_2(CO)_8$ (342 mg, 1 mmol). The mixture was stirred at r.t. for 3 h. Then THF (12 mL) and CH_2Cl_2 (6 mL) were added, followed by NMO (1.17 g, 10 mmol). The mixture was stirred at r.t. for 3 h. It was then filtered on a pad of Celite (eluent: Et_2O). After evaporation of the solvent in vacuo, purification by flash chromatography (eluent: pentane–Et_2O, 4:1) afforded a white solid; mp 124 °C.

^{1}H NMR: δ = 7.21–7.41 (br, 5 H), 4.99 (d, 1 H, *J* = 14.0 Hz), 4.46 (d, 1 H, *J* = 14.0 Hz), 4.25 (dq, 1 H, *J* = 10.2, 5.9 Hz), 3.16 (br m, 1 H), 2.75 (dd, 1 H, *J* = 10.2, 11.7 Hz), 2.33 (dd, 1 H, *J* = 19.0, 6.4 Hz), 2.02 (dd, 1 H, *J* = 19.0, 2.5 Hz), 1.78 (br s, 3 H).

^{13}C NMR: δ = 207.0, 163.5, 137.9, 136.0, 129.4, 128.3, 128.1, 123.9 (q, *J* = 282.1 Hz), 79.1 (q, *J* = 29.1 Hz), 65.5, 51.1 (q, *J* = 1.1 Hz), 43.8, 39.4.

^{19}F NMR: δ = –74.11 (d, *J* = 5.9 Hz).

Anal. Calcd for $C_{16}H_{15}F_3O_2$: C, 64.86; H, 5.10. Found: C, 64.72; H, 5.34.

References

(1) (a) Schofield, H. *J. Fluorine Chem.* **1999**, *100*, 7. (b) Groß, U.; Rüdiger, S. In *Organofluorine Compounds, Houben-Weyl: Methods of Organic Chemistry*, Vol. E10a; Baasner, B.; Hagemann, H.; Tatlow, J. C., Eds.; Georg Thieme: Stuttgart, **1999**, 18–26. (c) Smart, B. E. *J. Fluorine Chem.* **2001**, *109*, 3. (d) Hiyama, T. In *Organofluorine Compounds: Chemistry and Properties*; Springer-Verlag: Berlin, **2000**. (e) Dunitz, J. D. *ChemBioChem* **2004**, *5*, 614. (f) Dolbier, W. R. Jr. *J. Fluorine Chem.* **2005**, *126*, 157.

(2) Biffinger, J. C.; Kim, H. W.; DiMagno, S. G. *ChemBioChem* **2004**, *5*, 622.

(3) Ito, K.; Namekawa, M.; Ishizuka, T.; Nayuki, S. Japanese Patent JP 2000226382, **2000**; *Chem. Abstr.* **2000**, 133, 170332.

(4) Nakai, K.; Tagaki, Y.; Ogawa, S.; Tsuchiya, T. *Carbohydr. Res.* **1999**, *320*, 8.

(5) (a) Takagi, Y.; Nakai, K.; Tsuchiya, T.; Takeuchi, T. *J. Med. Chem.* **1996**, *39*, 1582. (b) Bansal, R. C.; Dean, B.; Hakomori, S.-I.; Toyokuni, T. *J. Chem. Soc., Chem. Commun.* **1991**, 796. (c) Nakai, K.; Takagi, Y.; Tsuchiya, T. *Carbohydr. Res.* **1999**, *316*, 47.

(6) Hanzawa, Y.; Uda, J.; Kobayashi, Y.; Ishido, Y.; Taguchi, T.; Shiro, M. *Chem. Pharm. Bull.* **1991**, *39*, 2459.
(7) (a) Hayman, C. M.; Larsen, D. S.; Brooker, S. *Aust. J. Chem.* **1998**, *51*, 545. (b) Hayman, C. M.; Hanton, L. R.; Larsen, D. S.; Guthrie, J. M. *Aust. J. Chem.* **1999**, *52*, 921.
(8) Leveque, L.; Le Blanc, M.; Pastor, R. *Tetrahedron Lett.* **1997**, *38*, 6001.
(9) Yamazaki, T.; Mizutani, K.; Kitazume, T. *J. Org. Chem.* **1995**, *60*, 6046.
(10) (a) Yamazaki, T.; Mizutani, K.; Kitazume, T. *Tetrahedron: Asymmetry* **1993**, *4*, 1059. (b) Yamazaki, T.; Mizutani, K.; Kitazume, T. *J. Org. Chem.* **1993**, *58*, 4346.
(11) (a) Arnone, A.; Bravo, P.; Frigerio, M.; Resnati, G.; Viani, F. *J. Chem. Res., Synop.* **1989**, 278. (b) Arnone, A.; Bravo, P.; Frigerio, M.; Resnati, G.; Viani, F. *J. Chem. Res., Miniprint* **1989**, 2201.
(12) Rychnovsky, S. D.; Hu, Y.; Ellsworth, B. *Tetrahedron Lett.* **1998**, *39*, 7271.
(13) Hanzawa, Y.; Ishizawa, S.; Ito, H.; Kobayashi, Y.; Taguchi, T. *J. Chem. Soc., Chem. Commun.* **1990**, 394.
(14) Seebach, D.; Renaud, P. *Helv. Chim. Acta* **1985**, *68*, 2342.
(15) (a) Gille, S.; Ferry, A.; Billard, T.; Langlois, B. R. *J. Org. Chem.* **2003**, *68*, 8932. (b) Ferry, A.; Billard, T.; Langlois, B. R. *Synlett* **2005**, 1027.
(16) For reviews on RCM, see: (a) Fürstner, A. *Angew. Chem. Int. Ed.* **2000**, *39*, 3012. (b) *Alkene Metathesis in Organic Synthesis*; Fürstner, A., Ed.; Springer: Berlin, **1998**.
(17) For recent reviews of the PKR, see: (a) Frühauf, H.-W. *Chem. Rev.* **1997**, *97*, 523. (b) Geis, O.; Schmalz, H.-G. *Angew. Chem. Int. Ed.* **1998**, *37*, 911. (c) Brummond, K. M.; Kent, J. L. *Tetrahedron* **2000**, *56*, 3263. (d) Fletcher, A. J.; Christie, S. D. R. *J. Chem. Soc., Perkin Trans. 1* **2000**, 1657.
(18) (a) Ishikawa, N.; Koh, M. G.; Kitazume, T.; Choi, S. K. *J. Fluorine Chem.* **1984**, *24*, 419. (b) Kumar, D. J. S.; Madhavan, S.; Ramachandran, P. V.; Brown, H. C. *Tetrahedron: Asymmetry* **2000**, *11*, 4629. (c) Ramachandran, P. V.; Padiya, K. J.; Rauniyar, V.; Reddy, M. V. R.; Brown, H. C. *Tetrahedron Lett.* **2004**, *45*, 1015. (d) Asao, N.; Liu, P. i.; Maruoka, K. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2507.
(19) (a) Kubota, T.; Iijima, M.; Tanaka, T. *Tetrahedron Lett.* **1992**, *33*, 1351. (b) Ishihara, T.; Hayashi, H.; Yamanaka, H. *Tetrahedron Lett.* **1993**, *34*, 5777. (c) Loh, T.-P.; Li, X.-R. *Tetrahedron* **1999**, *55*, 5611.
(20) (a) Blond, G.; Billard, T.; Langlois, B. R. *J. Org. Chem.* **2001**, *66*, 4826. (b) Billard, T.; Langlois, B. R. *J. Org. Chem.* **2002**, *67*, 997.
(21) Li, C.-J.; Chan, T.-H. *Tetrahedron* **1999**, *55*, 11149.
(22) (a) Katayma, H.; Nagao, M.; Ozawa, F. *Organometallics* **2003**, *22*, 586. (b) Chao, W.; Weinreb, S. M. *Org. Lett.* **2003**, *5*, 2505.
(23) Such electrostatic repulsion with a CF_3 group leading to a preferential conformation has been observed: Billard, T.; Langlois, B. R. *Tetrahedron* **1999**, *55*, 8065.
(24) Mukai, C.; Kim, J. S.; Hanaoka, M. *J. Org. Chem.* **1999**, *64*, 6822.
(25) (a) Jiang, B.; Xu, M. *Angew. Chem. Int. Ed.* **2004**, *43*, 2543. (b) Ishizaki, M.; Iwahara, K.; Niimi, Y.; Satoh, H.; Hoshino, O. *Tetrahedron* **2001**, *57*, 2729.