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Access to Constrained Fluoropseudopeptides via Ring-Closing Metathesis of Fluoroalkenes

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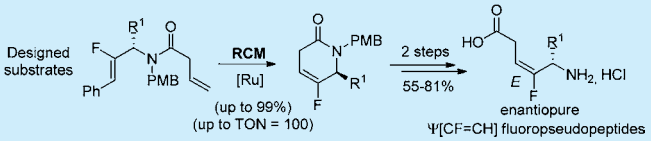
Supporting Information

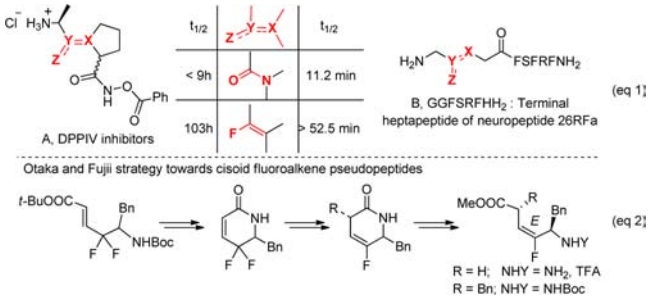
ABSTRACT: Bis-alkene substrates, containing one fluoroalkene and linked by an amide moiety, have been designed and synthesized to be subjected to ring-closing metathesis reactions. The substitution of fluoroalkene by a phenyl group enhanced the reactivity, and the resulting fluorinated lactams were obtained in high yields except when a hindered alkyl group was present in the molecule. The cycles were then subjected to ring opening in order to develop a new route to constrained fluoropseudopeptides bearing a fluoroalkene as a peptide bond mimic.



Peptides are ubiquitous molecules for the living world.[1] They have countless biological roles and generate a lot of interest for academic and industrial researchers.[2] Nevertheless, their use as therapeutic agents is still limited by a few factors, for example, low cellular uptake and fast metabolization in vivo. To overcome these drawbacks, peptidomimetics have been developed.[3] Among them, pseudopeptides (replacement of scissile peptide bond by isoelectronic and isosteric moiety) have emerged as an interesting solution to increase the half-life of compounds. Numerous peptide bond mimics have been reported. Among them, we are particularly interested in the fluoroalkene moiety, which is an effective peptide bond mimic[4] already known for its tendency to stabilize peptide from enzymatic degradation.[5]

Indeed, in a study concerning dipeptidyl peptidase inhibitors, Welch showed a half-time multiplied by 11 for a fluoroalkene chemical with respect to the amide bond (compound A, Scheme 1, eq 1).[5a] In the same way, we showed that the replacement of the first dipeptide of the terminal heptapeptide of neuropeptide 26RFa by a fluoropseudodipeptide containing a fluoroalkene as peptide bond mimic increased by a factor 5 the half-life of the molecule in human serum (compound B, Scheme 1, eq 1).[5b] Another feature of the fluoroalkene is the possible design of transoid or cisoid conformers in order to undertake structural studies as proposed by Otaka and Fujii concerning a pepdide transporter PEPT1.[6] In their elegant paper, they reported the sole stereoselective synthesis of cisoid pseudopeptide bearing a fluoroalkene as peptide bond mimic. Their strategy was based on (i) cyclization, (ii) defluorination, and (iii) ring-opening reactions to afford exclusively the cisoid conformer (Scheme 1, eq 2). An elegant alternative to the formation of fluoroalkene pseudopeptides as exclusive cisoid conformer would be the use of ring-closing metathesis (RCM) reaction as a crucial step as in the synthesis sequence depicted in the following retrosynthesis Scheme 2. The RCM reaction to design peptidomimetics bearing an alkene as peptide bond

Scheme 1. Comparison of Fluoroalkene Resistance (eq 1) and the Single Way Described To Reach the Cisoid Conformer for Fluoropseudopeptide (eq 2)



Scheme 2. Retrosynthesis of Fluoroalkene Pseudopeptides

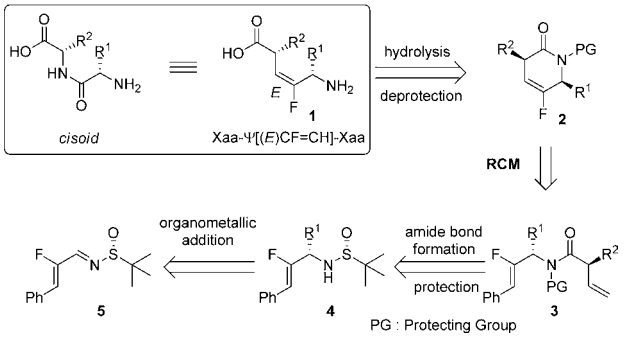


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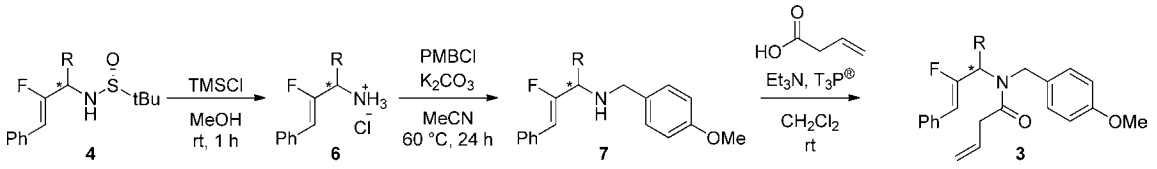
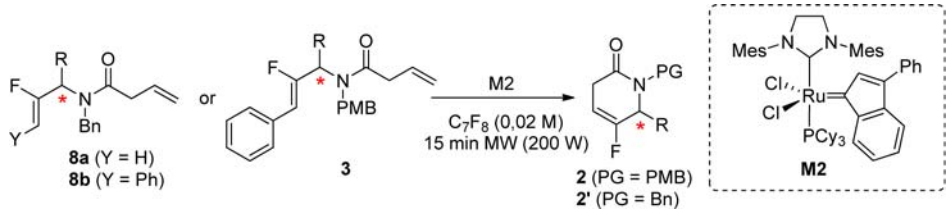
Table 1. Access to Bis-alkenes 3 from Chiral Substrates 4



entry	R	compd	yield (%) 6[a]	7[a]	3[a]
1	H[b]	**a**			
2	(*S*)-Me	**b**	quant	64	82
3	(*R*)-Me	**c**	quant	51	74
6	(*S*)-Ph	**d**	quant	70	97
7	(*R*)-Ph	**e**	quant	69	93
4	(*S*)-*i*Pr	**f**	quant	66	54
5	(*R*)-*i*Pr	**g**	quant	58	37
8	*rac*-Bn	**h**	quant	98	78

[a]Yield based on isolated product after flash chromatography. [b]Compound **a** was synthesized according to previous report.[11,12]

Table 2. Ring-Closing Metathesis



entry	substrate	R	catalyst loading (mol %)	temp (°C)	side products[a] (%)	yield[b,c] (%)
1	**8a**	H	4	120	7	88
2	**8a**	H	2	120	1	46
3	**8b**	H	1	80	0	100
4	**8b**	H	2	70	0	100
5	**3a**	H	2	70	0	100 (99)
6	**3b**	(*S*)-Me	2	70	0	100 (95)
7	**3c**	(*R*)-Me	2	70	0	100 (91)
8	**3d**	(*S*)-Ph	2	70	0	95 (94)
9	**3d**	(*S*)-Ph	2	70	0	100 (98)
10	**3d**	(*S*)-Ph	2	60	10	69
11	**3d**+**3e**	*rac*-Ph	2	70	0	100 (93)
12	**3f**	(*S*)-*i*Pr	2	80	major	0
13	**3f**	(*S*)-*i*Pr	4	100	major	0
14	**3f**	(*S*)-*i*Pr	4	120	major	0
15	**3h**	*rac*-Bn	2	80	0	20
16	**3h**	*rac*-Bn	4	120	0	100 (84)

[a]Side products (%) refer to numerous undesired and uncharacterized compounds produced during the RCM process. [b]Yields were determined by ^{1}H NMR spectroscopy using 2,4-dinitrofluorobenzene as internal standard. [c]Yield based on isolated product after flash chromatography are shown in parentheses.

mimic (Ψ[CH=CH]) in replacement of a peptidic bond has already been described[7] as, for example, in the pioneering and elegant work reported by Guibé et al.[7a] and more recently by Lamaty et al. to generate cyclic pseudopeptides by cyclization−cleavage using RCM.[7e]

However, among the thousands of reports dealing with the metathesis reaction, fewer than 10 publications have reported a RCM process involving reluctant fluoroalkenes, and none of them deals with peptide chemistry.[8] Recently, based on previous reports by Grubbs[9] and then by Dorta,[10] indicating the beneficial effect of a substitution pattern on alkene partner, we applied with success this "modification of substrates" strategy to the fluoroalkenes, allowing us to reach an unprecedented TON as well as success under milder experimental conditions (60−80 °C) than usual.[11] Herein, we report the synthesis of constrained pseudopeptides bearing a fluoroalkene as peptide bond mimic via a crucial RCM reaction step.

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tert-Butanesulfinylimine **5**, prepared via a four-step synthesis sequence already reported,[11,12] was subjected to organometallic addition to afford chiral sulfinamides **4**. We used (*R*)-*tert*-butanesulfinamide auxiliary in order to obtain the major diastereomer with a newly created stereogenic center in (*S*) configuration, as found in native peptides, through addition of Grignard reagents.[13] Each diastereoisomer was isolated and engaged in the next steps (Table 1). Deprotection of the *tert*-butanesulfinamide was quantitative, whatever the substrate was. Then we introduced a *p*-methoxybenzyl (PMB) group on the amine moiety with moderate to excellent yields. Finally, we created the amide bond with 3-butenoic acid, using T3P as coupling reagent, in very good yields excepted for the more sterically hindered **4f**/**4g**, bearing an isopropyl group as the side chain. It has to be noted that other protecting groups of amine (FMOC, BOC, and even the chiral Ellman's auxiliary) were assessed without any success (see the Supporting Information).[12]

The bis-alkenes **3** were subjected to the RCM reaction in order to synthesize the six-membered ring precursors of constrained pseudopeptides. It has to be noted that several ruthenium precatalysts have been tested and the **M2** catalyst proved to be the most efficient with our fluorinated substrates.[11] Main results for RCM reaction are given in Table 2. The beneficial role of the phenyl substituent on the fluoroalkene moiety is shown by comparing the first entries of Table 2. Indeed, whereas 4 mol % of **M2** catalyst at 120 °C was necessary for substrate **8a** to provide a good yield in cycle **2′** with small amounts of side products (Table 2, entries 1 and 2), the use of phenyl-substituted bis-olefin **8b** allowed us to decrease the catalyst loading as well as the reaction temperature. As a matter of fact, quantitative yield in the desired cycle **2′** was achieved with only 1 mol % of catalyst at 80 °C (Table 2, entry 3) or with 2 mol % of catalyst at 70 °C (Table 2, entry 4). The replacement of the benzyl group on nitrogen by a PMB group had no impact, and cycle **2a** was obtained in quantitative yield (Table 2, entry 5). Pleasingly, the substrates **3b** and **3c**, bearing a methyl group as R group on the side chain, were converted quantitatively, furnishing excellent (95% and 91%) isolated yields in cycles **2b** and **2c**, respectively (Table 2, entries 6 and 7). The RCM reaction did not seem to be influenced by the steric hindrance of the methyl group, so the results may be theoretically equivalent with a phenyl group. The experimentation confirmed this hypothesis; cycle **2d** was synthesized in excellent yield with 2 mol % of catalyst at 70 °C. The reaction was carried out on a 0.1 mmol (Table 2, entry 8) or 0.5 mmol scale (Table 2, entry 9) of substrate **3d** without loss of efficiency, furnishing 94% and 98% yields of **2d**, respectively. The reaction performed on a racemic mixture of **3d** and **3e** gave also an excellent yield of cyclic compound. The reaction carried out with more hindered substrates **3f** bearing an isopropyl group as side chain proved to be inefficient whatever the catalyst loading or the temperature of the reaction (Table 2, entries 12−14). Whereas a Thorpe−Ingold effect could have been expected in this case, only side products were observed in NMR experiments without any trace of the desired cycle **2f**. Other catalysts were tested, including bis-NHC catalyst, which was highly stable at high temperature, but, unfortunately, without success. Finally, the benzyl group, with a steric hindrance intermediate between the methyl/phenyl and isopropyl group, required higher temperature and catalyst loading, compared to methyl and phenyl substituents, to provide full conversion of **3h** and very good (84%) yield of cycle **2h** (Table 2, entries 15 and 16).

These results seem to indicate that the efficiency of the RCM reaction with our specific substrates **3** are conditioned by the steric hindrance of the side chain bearing an alkyl or an aryl substituent. Worthy of note is that we have to take into account that substrates **3** contain an amide moiety, which should make the substrate primarily under a transoid form, whereas for an effective cyclization, the cisoid one is required.[14] This was confirmed by NOESY and ROESY NMR experiments, pointing out that when the main form was the most stable transoid form in the media the more difficult was the RCM reaction (Table 3).

Table 3. Influence of Transoid/Cisoid Amide Configuration on the RCM Reaction

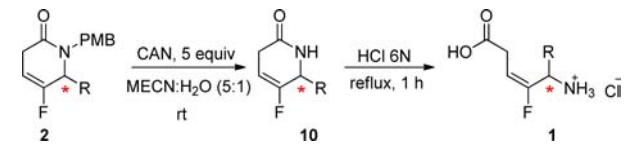
entry	substrate	R	Y	T/C ratio[a]	temp (°C)	yield[b,c] (%)
1	**3a**	H	PMB	50/50	70	100 (99)
2	**3b**	Me	PMB	73/27	70	100 (95)
3	**3d**	Ph	PMB	74/26	70	100 (98)
4	**3h**	Bn	PMB	78/22	120	100 (84)
5	**3f**	*i*-Pr	PMB	87/13	80 to 120	0
6	**9e**	Ph	H	100/0	80 to 120	0
7	**9g**	*i*-Pr	H	100/0	80 to 120	0

[a]T/C: transoid/cisoid ratio was determined by NMR experiments. [b]Yields were determined by ^{1}H NMR spectroscopy using 2,4-dinitrofluorobenzene as internal standard. [c]Yields based on isolated product after flash chromatography are shown in parentheses.

These observations are in accordance with the fact that the RCM reaction requires the *cis* configuration for which both alkenes are ready to cyclize. Additional experiments and molecular modeling will be reported in due course to support this hypothesis.

Finally, with the cyclic precursors in hand, we envisioned obtaining the fluoropseudopeptides by a two-step sequence synthesis (Table 4). First, we carried out the PMB deprotection of the nitrogen by treatment with CAN reagent in a mixture of acetonitrile and water. The obtained yields are moderate to good in secondary lactam **10**. A final ring-opening step under acidic conditions[7e] allowed us to quantitatively recover the desired compounds **1** in hydrochoride salt form. These last

Table 4. Access to Fluoropseudopeptides



			yield[a] (%)	
entry	substrate	R	**10**	**1**
1	**2a**	H	81	quantitative
2	**2d**	Ph	76	quantitative
3	*rac*-**2d**	Ph	55	quantitative

[a]Yield based on isolated product after flash chromatography.

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steps were carried out on substrates **2a** and **2d**, the latter being the most sensitive molecule to racemization due to the benzylic position, in order to prove the feasibility of the strategy. We obtained Gly-[Ψ(*E*)CF=CH]Gly and Gly-[Ψ(*E*)CF=CH]-PhGly as enantiopure fluoropseudopeptides.

It has to be noted that every single step of the synthesis was performed on pure enantiomer as well as on racemic mixture for all asymmetric substrate in order to control the possible epimerization of the stereogenic center. Control analyses were monitored by NMR and chiral HPLC experiments, and no trace of racemization was observed during the synthesis[12] for any carried out step.

To conclude, we synthesized activated fluorinated bis-alkenes, including asymmetric substrates. We successfully carried out the RCM reaction with reluctant fluoroalkenes bearing an amide linker, except for the substrate including a sterically hindered isopropyl group as the side chain. Taking into account the few reports on metathesis reaction with fluoroalkenes, these results are highly relevant. Finally, some of the synthesized lactams have been deprotected and opened to furnish a novel path toward constrained cisoid fluoropseudopeptides bearing a fluoroalkene moiety as peptide bond mimic.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b01631.

Experimental procedures, characterization data, and NMR spectra of new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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