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Asymmetric Synthesis of New β,β-Difluorinated Cyclic Quaternary α-Amino Acid Derivatives

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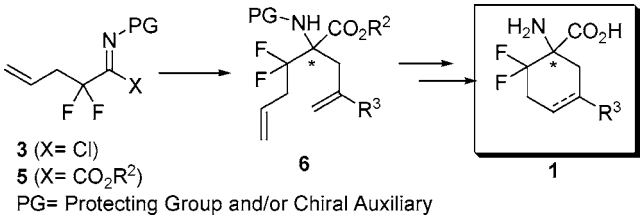
ABSTRACT



The synthesis of new β,β-difluorinated cyclic quaternary α-amino acid derivatives 1 in which a ring-closing metathesis reaction (RCM) constitutes the key step is described. The approach employs imidoyl chlorides 3 as fluorinated building blocks, and the overall process involves the stereoselective creation of a quaternary stereocenter. Complete selectivity was achieved when (*R*)-phenylglycinol methyl ether was used as chiral auxiliary, allowing for the preparation of new six-membered cyclic fluorinated α-amino acids as single enantiomers.

The use of peptides as drugs is limited by their rapid protease-catalyzed degradation, poor lipophilicity, and high conformational flexibility. The latter is a particularly important drawback as it can induce non-selective interactions with receptors different from the therapeutic target.[1] One strategy commonly used to improve the biological properties of bioactive peptides is the incorporation of α,α-disubstituted non-natural amino acids in a peptide chain.[2] The resulting peptidomimetics show a higher stability against proteases, as well as increased levels of lipophilicity and bioavailability.[3] Moreover, the level of conformational rigidity also increases, which often allows for higher selectivity toward biological receptors. When the two substituents of these α,α-disubstituted amino acids constitute a cycle, the conformational restriction is even higher, which is the reason this class of cyclic amino acids has been used in the preparation of peptide-based drugs.[4] For example, the 1-amino cyclohexanecarboxylic acid framework has been used in the design of potent cathepsin K inhibitors[5] and V_2 agonists of arginine vasopressin.[6] By the same token, the use of fluorinated analogues of natural amino acids is also a well-established

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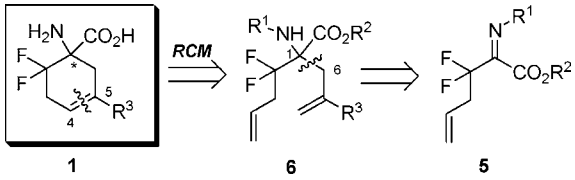
strategy, since the presence of a fluorine atom often induces significant changes in the physical properties, biological activities, and metabolic profiles of the resulting peptides.[7]

Although both acyclic and cyclic quaternary α-amino acids have been frequent synthetic targets,[2c,d] few syntheses of their fluorinated counterparts are known. Even rarer are examples of the preparation of quaternary cyclic fluorinated α-amino acids, and of the few there are, most deal with fluorinated 1-aminocyclopropane carboxylic acids.[8] To date, only a single example has been reported of the preparation of racemic heterocyclic quaternary α-amino acids with a CF_3 group by means of a ring-closing metathesis reaction (RCM).[9] Herein we describe a new synthetic strategy that provides an entry to enantiomerically pure *β*,*β*-difluorinated cyclic quaternary α-amino acids **1** and in which a RCM constitutes the key step[10] (Scheme 1, retrosynthetic analysis).

Scheme 1. Retrosynthetic Analysis

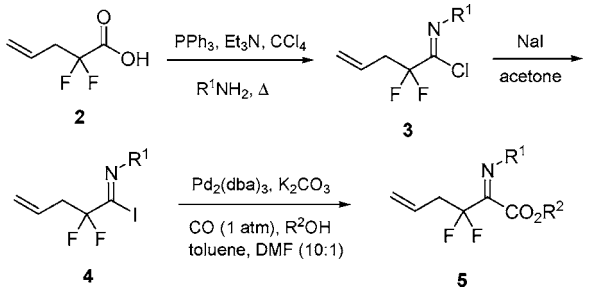


1 **6** **5**

In our approach, the *β*,*β*-difluorinated cyclic α-amino acid **1** was disconnected at the C4−C5 double bond by means of a RCM reaction. In turn, the corresponding precursor **6** was disconnected at the C1−C6 bond through an allylation reaction on imino ester **5** with a suitable organometallic species (Scheme 1). Finally, imino ester **5** is synthesized from 2,2-difluoro-4-pentenoic acid **2**.[11]

α-Imino esters **5** were prepared with the method described by Uneyama and co-workers.[12] Thus, 2,2-difluoro-4-pentenoic acid **2** was initially transformed into the corresponding imidoyl chlorides **3a**−**c**,[13] which were then converted into imydoyl iodides **4a**−**c** by reacting them with NaI in dry acetone. These reactive intermediates were treated without further purification with carbon monoxide and several alcohols in the presence of a catalytic amount of $Pd_2(dba)_3$·$CHCl_3$ complex to afford imino esters **5** in moderate yields (Table 1).[14]

Table 1. Synthesis of Imino Esters **5**



2 **3** **4** **5**

entry	**3**	R^1	R^2	**5** (yield)[a]
1	**3a**	PMP[b]	Et	**5a** (55)
2	**3a**	PMP[b]	Bn	**5b** (60)
3	**3a**	PMP[b]	TMSE[c]	**5c** (52)
4	**3b**	(*S*)-PhCH(Me)	Bn	**5d** (70)
5	**3c**	(*R*)-phegly-OMe[d]	Bn	**5e** (50)
6	**3c**	(*R*)-phegly-OMe[d]	TMSE[c]	**5f** (51)

[a] Yield of isolated product, %. [b] PMP = *p*-$MeOC_6H_4$. [c] TMSE = 2-trimethylsilylethyl. [d] (*R*)-phegly-OMe = (*R*)-$PhCH(CH_2OMe)$.

With imino esters **5** in hand, the next step was the chemoselective allylation of the imino group in the imino ester (initially in its racemic form in substrates **5a**−**c**). Several authors have previously carried out this type of transformation using organometallic (Mg, Li, Zn) derivatives.[9,15] The best preliminary results with achiral susbstrates **5a**−**c** were obtained through the use of allylzinc bromides, which caused the addition to take place exclusively at the iminic carbon in 10 min at −40 °C, thus furnishing the desired racemic α-amino esters **6a**−**d** in almost quantitative yield.[16] Compounds **6a**−**d** were then subjected to RCM through treatment with second generation Grubbs catalyst (IHMes)$(PCy_3)Cl_2Ru$=CHPh (**8**)[17] in refluxing dichloromethane to furnish cyclic α-amino esters **7a**−**d** in excellent yields (Table 2, entries 1−4).

Finally, we carried out an example of the removal of the amino acid protecting groups on compound **7c**. Thus, oxidative treatment of compound **7c** with ceric ammonium

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(14) The similarity of the retention time between dibenzalacetone (palladium ligand) and the final imino esters **5** made the purification of these compounds difficult, thus decreasing the yield of isolated products.

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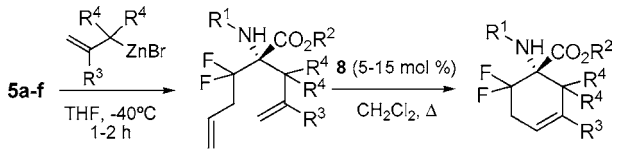
Table 2. Synthesis of Amino Esters **7a**−**g**

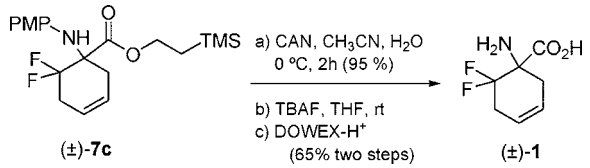


entry	**5**	R^1	R^2	R^3	**7** (yield)[c]
1	**5a**	PMP	Et	H	**7a** (88)
2	**5b**	PMP	Bn	H	**7b** (93)[d]
3	**5c**	PMP	TMSE[b]	H	**7c** (85)
4	**5b**	PMP	Bn	Me	**7d** (95)
5	**5d**	(*S*)-PhCH(Me)	Bn	H	**7e** (95) [40][e]
6	**5e**	(*R*)-phegly-OMe[a]	Bn	H	**7f** (89) [>98][e]
7	**5f**	(*R*)-phegly-OMe[a]	TMSE[b]	H	**7g** (92) [>98][e]
8	**5f**	(*R*)-phegly-OMe[a]	TMSE[b]	Me	**7h** (83) [>98][e]
9	**5f**	(*R*)-phegly-OMe[a]	TMSE[b]	H[f] (R^4 = Me)	**7i** (73) [>98][e]
10	**5f**	(*R*)-phegly-OMe[a]	TMSE[b]	COO^{t}Bu	**7j** (76) [>98][e]
11	**5f**	(*R*)-phegly-OMe[a]	TMSE[b]	Ph	**7k** (44)[g] [>98][e]

[a] (*R*)-Phegly-OMe = (*R*)-PhCH(CH_2OMe). [b] TMSE = 2-trimethylsilyl ethyl. [c] Combined yields of the two steps, %. For individual yields of each step, see Supporting Information section. [d] When the RCM was carried out with first generation Grubbs catalyst ($PCy_3)_2Cl_2Ru$=CHPh, 67% yield of **7b** was obtained instead. [e] In brackets, % of diastereomeric excess (de) obtained with chiral α-imino esters **5d**−**f**, as determined from ^{19}F NMR data. [f] R^4 = H in all entries, except in entry 9. [g] The low yield observed in this case is due to the addition step, in which **6k** was obtained in 50% yield, while 40% of the starting material was recovered unchanged. The yield for the second step, which affords **7k**, was 89%.

nitrate (CAN) allowed us to remove the PMP protecting group, thus affording the free amino functionality. The carboxyl group was easily deprotected then by means of treatment with TBAF in THF, and the final amino acid was isolated through ion exchange chromatography on Dowex-H^+ to afford pure **1** in 65% yield (Scheme 2).

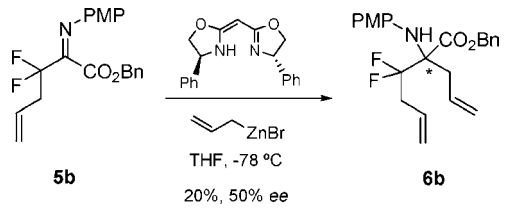
Scheme 2. Amino Acid Deprotection



Once we had successfully tested our synthetic approach on the preparation of racemic amino acid **1**, we turned our attention to the asymmetric creation of the quaternary center generated in the alkylation process. Although the enantioselective addition of organometallics to aldehydes and ketones has been studied extensively, only a few examples of the analogous addition to ketimines have been described to date.[18]

Our first attempt consisted of the addition of allylzinc bromide to imino ester **5b** at −78 °C in the presence of 1 equiv of bis-oxazoline[19] (Scheme 3), which led to the

Scheme 3. Enantioselective Allylation Attempt on **5b**



formation of the desired diene system **6b** in 50% enantiomeric excess, but in only 20% yield. When the reaction was carried out at higher temperatures, the chemical yield improved, but at the expense of selectivity (for instance, when the reaction was performed at −30 °C, 70% yield with 25% ee was obtained). Other chiral amines such as (−)-sparteine, (−)-cinchonidine, or (−)-quinine were even less successful as asymmetric organocatalysts for this addition, achieving ee's lower than those with bis-oxazoline.

Having established the limitations of this approach, we decided to evaluate the use of chiral α-imino esters derived from chiral amines in the synthesis of chiral fluorinated α-amino acids. It has been reported that the diastereoselective allylation of aldimines derived from phenylethylamine[20] or phenylglycinol[21] can be achieved with good selectivities. We thus decided to prepare chiral imino esters **5d**−**f** (Table 1, entries 4−6), which in turn were subjected to the allylation reaction. Thus, when (*S*)-1-phenylethylamine was used as the chiral amine, the formation of a 7/3 non-separable mixture of diastereoisomers was observed (Table 2, entry 5). However, much better results were obtained when imino esters **5e**,**f**, derived from (*R*)-phenylglycinol, were used as substrates in the allylation reaction. In all cases, a single diastereomer was formed (as determined from ^{1}H and ^{19}F NMR data) in these reactions, even when substituted allylzinc derivatives were used (Table 2, entries 6−11).[22]

The complete stereoselectivity observed for the allylation reaction when the methyl ether of (*R*)-phenylglycinol was used as chiral auxiliary is particularly noteworthy since the diastereoselective formation of quaternary stereocenters has always been a challenge, especially when ketimines are used as starting materials.

(18) For revisions of organometallic additions to imines see: (a) Bloch, R. *Chem. Rev.* **1998**, *98*, 1407−1438. (b) Kobayashi, S.; Ishitani, H. *Chem. Rev.* **1999**, *99*, 1069−1094. (c) Alvaro, G.; Savoia, D. *Synlett* **2002**, 651−673. (d) Ding, H.; Friestad, G. K. *Synthesis* **2005**, 2815−2829.

(19) Nakamura et al. have used chiral bis-oxazolines in the enantioselective allylation of cyclic aldimines to obtain the corresponding secondary amines with good selectivities. Nakamura, M.; Hirai, A.; Nakamura, E. *J. Am. Chem. Soc.* **1996**, *118*, 8489−8490.

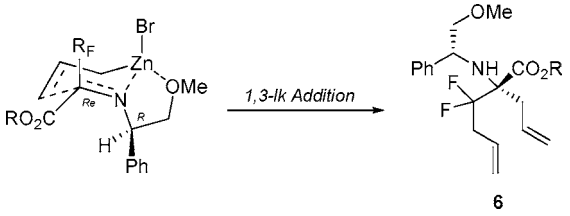
(20) (a) Hallet, D. J.; Thomas, E. J. *J. Chem. Soc., Chem. Commun.* **1995**, 657−658. (b) Alvaro, G.; Savoia, D.; Valentinetti, M. R. *Tetrahedron* **1996**, *52*, 12571−12586. (c) Alvaro, G.; Boga, C.; Savoia, D.; Umani-Ronchi, A. *J. Chem. Soc., Perkin Trans. 1* **1996**, 875−882.

(21) (a) Tam, N. T. M.; Magueur, G.; Ourivétich, M.; Crousse, B.; Bégué, J.-P.; Bonnet-Delpon, D. *J. Org. Chem.* **2005**, *70*, 699−702. (b) Magueur, G.; Crousse, B.; Bonnet-Delpon, D. *Tetrahedron Lett.* **2005**, *46*, 2219−2221. (c) Magueur, G.; Legros, J.; Meyer, F.; Ourévitch, M.; Crousse, B.; Bonnet-Delpon, D. *Eur. J. Org. Chem.* **2005**, 1258−1265.

(22) For the preparation of hindered allyl zinc derivatives (Table 2, entries 9−11), a different methodology was used: Hanessian, S.; Yang, R. Y. *Tetrahedron Lett.* **1996**, 5273−5277.

The presence of the heteroatom in the N-substituent of **5e**,**f** most likely allows a better metal chelation (as compared with the phenylethyl substituent of **5d**), thus delivering the allylic moiety from the opposite side to the phenyl group on the *re* face of the imine. This fact might explain the excellent selectivity observed in the allylation process of substrates **5e**,**f** (Scheme 4).

Scheme 4. Diastereoselectivity Control in the Formation of **6**



6

The cyclization of dienes **6f**−**k** by means of an RCM took place smoothly under the same conditions as before to afford the cyclic protected amino acids **7f**−**k** in excellent yields (Table 2, entries 6−11).

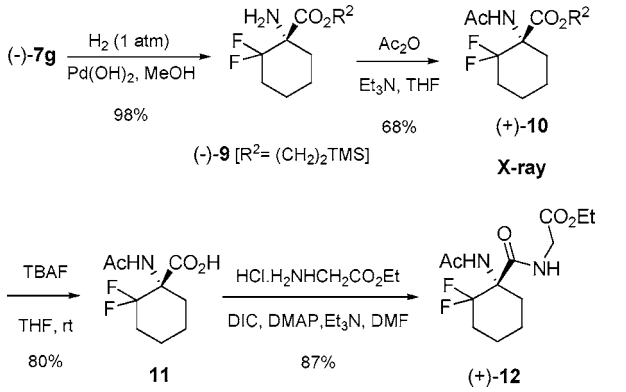
Finally, we tested the feasibility of the amino group deprotection by treating compound (−)-**7g** with $Pd(OH)_2$ in methanol with hydrogen (1 atm). The reaction proceeded smoothly, affording an almost quantitative yield of the amino ester (−)-**9** (Scheme 5). The absolute configuration of the newly created quaternary center was *S*, as confirmed by means of X-ray analysis of the *N*-acetyl derivative (+)-**10**, which was easily obtained through acetylation of compound **9** with standard techniques (Scheme 5).[23]

Treatment of (+)-**10** with TBAF yielded carboxyl-deprotected **11**, which in turn was coupled with glycine ethyl ester to afford dipeptide (+)-**12** (Scheme 5). The straightforward preparation of dipeptide (+)-**12** proves that the compound (−)-**7g** obtained by applying our synthetic methodology is ortogonally protected and that this protection can be subsequently modified as needed. Obviously, this is an important feature for the potential utility of compound (−)-**7g** in peptide formation.

In conclusion, we have described for the first time the enantioselective synthesis of β,β-difluorinated 1-aminocyclohexane-1-carboxylic acids in which an RCM reaction constitutes the key step. The use of the methyl ether of (*R*)-phenylglycinol as a chiral auxiliary on the imine nitrogen atom allowed for complete control of the diastereoselectivity in the construction of the chiral quaternary stereocenter. Finally, the deprotection of the phenylglycinol moiety afforded the final amino esters as single enantiomers. This methodology has the obvious advantage that it allows access to *ent*-**7f**−**k** by simply substituting the (*S*)-enantiomer for the (*R*)-phenylglycinol used in our study. Further studies on the reactivity of *gem*-difluorinated cyclic α-amino acid derivatives and their incorporation into peptidic sequences of biological interest are currently underway in our laboratories.

(23) For the X-ray structure of (+)-**10**, see Supporting Information.

Scheme 5. Phenyl Glycinol Deprotection in (−)-**7g** and Subsequent Dipeptide Formation



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Supporting Information Available: Experimental procedures and NMR spectra for **1**, **3**, **5**−**7**, and **9**−**12**. This material is available free of charge via the Internet at http://pubs.acs.org.

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