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Asymmetric Synthesis of Fluorinated Cyclic β-Amino Acid Derivatives through Cross Metathesis

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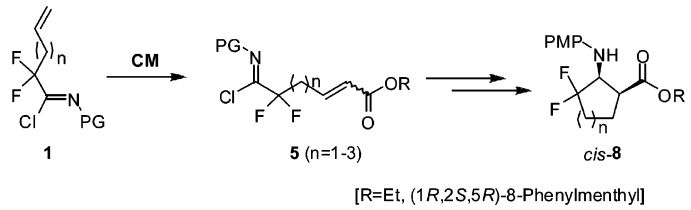
ABSTRACT



The asymmetric synthesis of several fluorinated *cis*-2-aminocycloalkane carboxylic acids (*cis*-2-ACACs) with a cross metathesis (CM) reaction as the key step has been carried out, constituting the first time a metathesis protocol has been undertaken with fluorinated imidoyl chlorides. Subsequent chemoselective hydrogenation of the olefin moiety, Dieckmann condensation, and stereoselective reduction of the iminic double bond afforded the corresponding β-amino esters with several ring sizes. The asymmetric version of the process was achieved by using (–)-8-phenylmenthol as a chiral auxiliary.

The synthesis of β-amino acid derivatives[1] has generated much attention not only due to their presence in a wide number of natural products but also because compounds bearing this structural motif have shown interesting biological properties, including antibiotic characteristics and inhibitory effects against cholesterol and fat absorption.[2] They have thus been used as important building blocks in drug research, comprising, for example, the monomeric units of β-peptides,[1] which in turn display secondary structures that are significantly more stable than their parent α-peptides. Among β-amino acid derivatives, work on 2-aminocycloalkane carboxylic acids (2-ACACs) has witnessed a surge since the pioneering research done by the Gellman and Seebach research groups.[3] Their innovation involved folding oligopeptidic chains bearing 2-ACAC moieties into helical structures to confer rigidity to the final backbone, thus giving rise to conformationally restricted peptidomimetics that have proved to be stable against metabolic degradation.[4]

Olefin metathesis is now widely considered to be one of the most powerful synthetic tools in organic chemistry for the creation of carbon−carbon double bonds.[5] The ongoing development of robust ruthenium catalysts has had a tremendous impact on the use of the cross metathesis reaction

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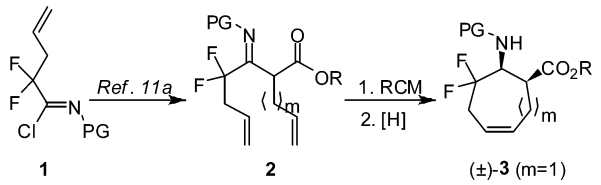
(CM);[6] in fact, as both the chemo- and stereoselectivity of this process steadily improve, it is finding increasingly ample application in the synthesis of natural products.[7] However, examples of this methodology being used for the preparation of cyclic β-amino acid derivatives are very scarce.[8] To date, only a few reports have been published on the synthesis of these derivatives, and all of these have involved a ring-closing metathesis (RCM) protocol.[9]

Moreover, despite the importance of β-amino acid derivatives, very little research has been done on their fluorinated analogues. In fact, not only have few reports related to these building blocks been published[10] but also, to the best of our knowledge, only two of these reported on the preparation of fluorinated 2-ACACs.[11] One such preparation method, developed by our research group,[11a] afforded racemic fluorinated seven-membered β-amino acid derivatives (±)-**3**. These were prepared through an RCM of the appropriate β-imino esters **2**, which had been previously synthesized by reacting imidoyl chlorides **1** with unsaturated esters (Scheme 1). This strategy, however, was of little use in the preparation

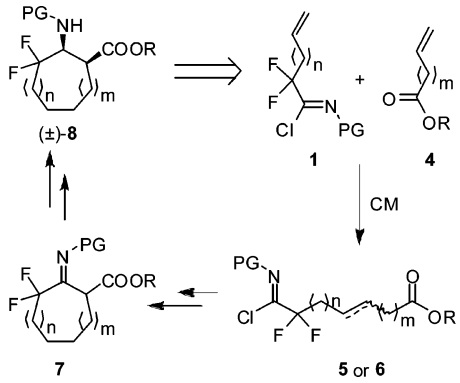
Scheme 1. Previous Preparation of Seven-Membered Cyclic Fluorinated β-Amino Acids **3** by Means of an RCM



of five- and six-membered rings as access to the corresponding RCM precursors **2** proved impossible with the aforementioned methodology.[12]

We surmised that to circumvent this problem of forming differently sized rings an alternative strategy, namely one involving a cross metathesis reaction (CM), could be used for the synthesis of these derivatives. In the present paper, we thus describe a new and efficient method for the racemic and asymmetric synthesis of fluorinated *cis*-ACACs with a CM reaction as the key step. The retrosynthetic analysis is outlined in Scheme 2.

Scheme 2. Retrosynthetic Analysis



Our strategy starts with a CM reaction of imidoyl chlorides **1** with unsaturated esters **4** to afford the coupling products **5**.[13] Subsequent chemoselective hydrogenation of the double bond on **5** and Dieckmann-type condensation lead to the cyclic β-imino esters **7**, which are then selectively reduced and deprotected to give the desired *cis*-ACACs **8**.

Given the various possible reaction pathways to products **5**, ethyl acrylates **4** ($m = 0$) and imidoyl chlorides **1** with several different side chains ($n = 1-3$) were chosen as starting materials for the CM reaction.[14] Thus, when compounds **1** and ethyl acrylate (5 equiv) were heated in toluene at 95 °C in the presence of a second-generation Grubbs catalyst [$(IMesH_2)(PCy_3)Cl_2Ru{=}CHPh$] **9** (5 mol %) for 15 h, the desired coupling products **5** were obtained in excellent yields and stereoselectivities (Table 1).

Starting fluorinated imidoyl chlorides **1** were prepared from the corresponding carboxylic acids **12** with the methodology developed by Uneyama.[15] The synthesis of imidoyl

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(10) (a) Review: Qiu, X.-L.; Meng, W.-D.; Qing, F.-L. *Tetrahedron* **2004**, *60*, 6711−6745. (b) Fustero, S.; Pina, B.; Salavert, E.; Navarro, A.; de Arellano, M. C. R.; Fuentes, A. S. *J. Org. Chem.* **2002**, *67*, 4667−4679.

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(12) When $m = 0$ (Scheme 1), competitive side reactions such as isomerization processes of the starting unsaturated esters were observed in our attempts to prepare precursors of RCM **2**. In the case of five-membered rings, applying this methodology proved impossible and led mainly to a complex mixture of products: Bartolomé, A. Ph.D. Dissertation, University of Valencia (Spain), 2002.

(13) The successful use of fluorinated imidoyl chlorides in CM reactions, *which is reported here for the first time*, shows once more the versatility of ruthenium catalysts as well as their tolerance for a wide range of functional groups.

(14) We also tested an alternative strategy using various chain lengths of imidoyl chlorides **1** combined with unsaturated esters **4** other than acrylates ($m = 1, 2$), but the reactions were considerably less efficient in terms of both yields and selectivities. The presence of the CF_2 group may be responsible for the high selectivity observed, also preventing any further isomerization of the double bond. See: Fustero, S.; Sánchez-Roselló, M.; Jiménez, D.; Sanz-Cervera, J. F.; del Pozo, C.; Aceña, J. L. *J. Org. Chem.* **2006**, *71*, 2706−2714.

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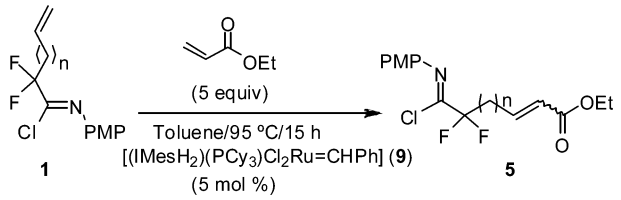
Table 1. Preparation of Disubstituted Olefins **5** by Means of a CM Reaction

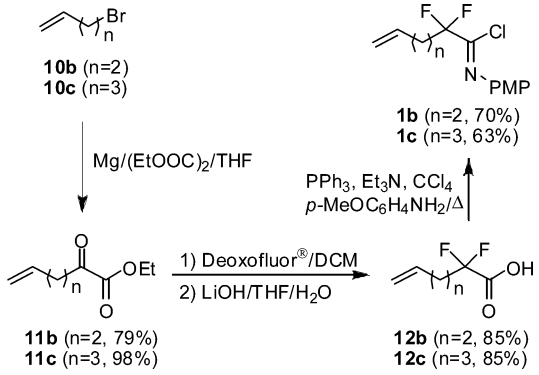


entry	1	n	5	E/Z[a] (ratio)	yield (%)
1	**1a**	1	**5a**	23:1	95
2	**1b**	2	**5b**	46:1	94
3	**1c**	3	**5c**	11:1	93

[a] The E/Z isomeric ratio was determined by means of ^{19}F NMR spectroscopy and GC-MS analysis. PMP = *p*-methoxyphenyl.

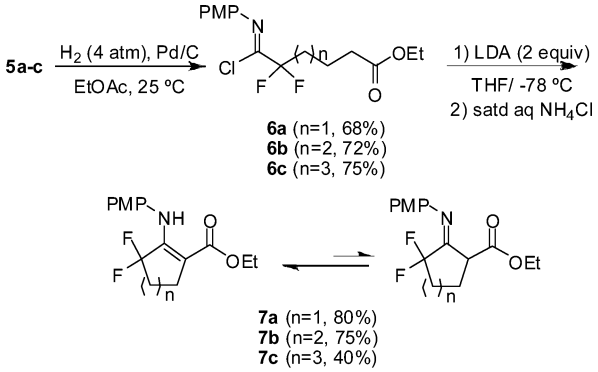
chloride **1a** from acid **12a** (n = 1)[16] was carried out as previously reported,[11a] and acids **12b** (n = 2) and **12c** (n = 3) were obtained from 4-bromo-1-butene (**10b**) and 5-bromo-1-pentene (**10c**), respectively, as shown in Scheme 2. Thus, **10b**,**c** were first transformed into their corresponding Grignard derivatives, which were then treated with diethyl oxalate to furnish α-ketoesters **11b**,**c**.[17] Reaction with Deoxofluor[18] [$(MeOCH_2CH_2)_2NSF_3$] followed by saponification of the ethyl ester with lithium hydroxide afforded acids **12b**,**c** in high yields (Scheme 3).

Scheme 3. Preparation of Starting Imidoyl Chlorides **1b**,**c**



With compounds **5** in hand, the next step in our synthetic strategy was the chemoselective hydrogenation of the olefinic moiety. Optimal reaction conditions involved treating coupling products **5** with hydrogen under pressure (4 atm) in the presence of Pd/C (10%) in ethyl acetate as solvent. These reactions generally required 24 h to proceed to completion and afforded Dieckmann precursors **6** in good yields while maintaining the ester and imidoyl chloride functionalities unaltered (Scheme 4).

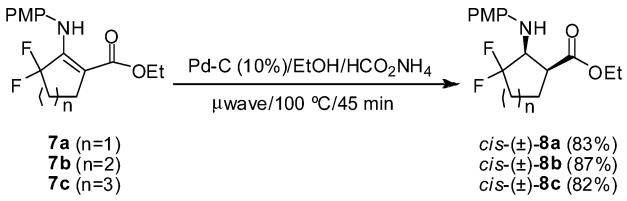
Scheme 4. Preparation of Enamino Esters **7a**−**c**



We next undertook the Dieckmann condensation of substrates **6**. The ester enolate necessary for the cyclization had to be formed with 2 equiv of LDA at −78 °C because 1 equiv is consumed by the final product. After 1 h, cyclic products **7** were obtained in moderate to good yields. Although **7a**,**b** were isolated in their enaminic form, compound **7c** proved to be a tautomeric mixture in a 3:2 ratio (Scheme 4).

The next step comprised the chemo- and stereoselective reduction of the imino-enamino moiety. After several attempts, we were delighted to find that performing a hydrogenation under microwave irradiation conditions allowed the reduction to take place with complete selectivity.[19] Thus, when **7a**−**c** were dissolved in ethanol and then heated in a microwave during 45 min at 100 °C in the presence of palladium on charcoal and with ammonium formate as a hydrogen source, the formation of the corresponding amino esters **8a**−**c** occurred efficiently, thus affording the corresponding cis diastereomers exclusively and in good yields (Scheme 5).

Scheme 5. Synthesis of β-Amino Esters **8**



The relative cis configuration between the amino and the acid groups of **8c** was determined upon comparing its NMR spectra with those of another sample of the same compound previously synthesized by our group, albeit with a different methodology.[20] In contrast, the configuration of compounds **8a**,**b** was established with the aid of NOE experiments.

Once the target molecules had been successfully prepared in a racemic manner, the next challenge was to prepare them

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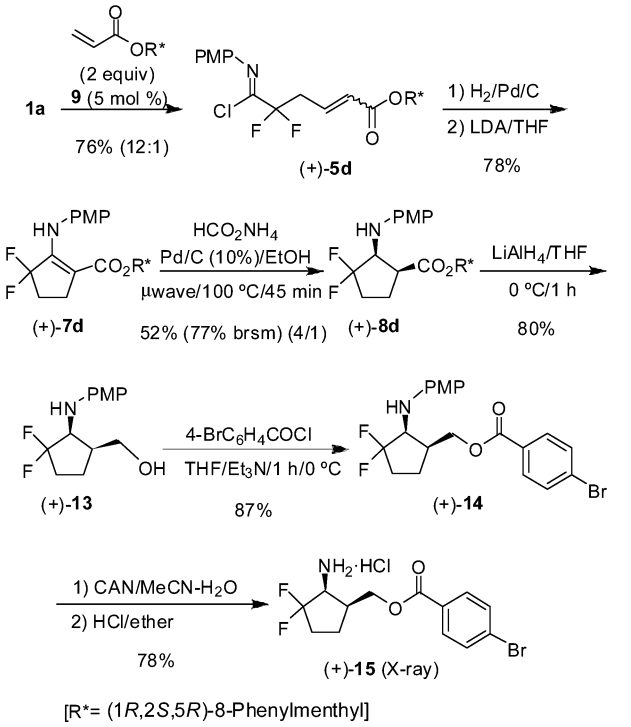
(20) See compound **11a** in ref 11a.

in enantiomerically pure form. Of the several strategies tried, the one using 8-phenylmenthol as a chiral source proved to be the most efficient. Thus, (+)-8-phenylmenthol acrylate was heated with imidoyl chloride **1a** in the presence of catalyst **9** (5 mol %). The resulting cross-coupling product (+)-**5d** was then hydrogenated and cyclized under the conditions outlined above to afford chiral enamino ester (+)-**7d** in good yield. The crucial hydrogenation step through microwave irradiation gave rise to a 4:1 mixture of diastereomers in 52% yield (77% based on recovered starting material). Longer reaction times and higher temperatures led to no significant improvement in the conversion; therefore, we chose to recycle the starting material after separation.

The major diastereomer was separated by means of flash chromatography, and its absolute configuration was determined with the aid of X-ray analysis of its hydrochloride derivative (+)-**15** (Scheme 6).[21] This amino ester was prepared through successive ester reduction with $LiAlH_4$, coupling of the newly created alcohol functionality with 4-bromo benzoyl chloride, and PMP deprotection upon treatment with CAN. Additionally, the relative cis configuration of compound **8a** was confirmed by means of its reduction with $LiAlH_4$, which afforded a compound identical in all respects to **13**. It is important to note that compound (+)-**13** constitutes a fluorinated analogue of *cis*-pentacin, which is known for its antifungal properties.[22]

In conclusion, the synthesis of several fluorinated *cis*-2-ACACs with a CM reaction as the key step has been successfully carried out. A second-generation Grubbs catalyst was found to be compatible with the presence of imidoyl chlorides, which were used here for the first time in a metathesis protocol. The described methodology provided *β*-amino esters with several ring sizes, thus improving upon previously described strategies. Initial studies concerning the asymmetric version of the process were also described; further studies are currently underway and will be reported in due course.

Scheme 6. Asymmetric Version of the Synthesis



[R*= (1*R*,2*S*,5*R*)-8-Phenylmenthyl]

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Supporting Information Available: Experimental procedures and NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(21) Full details of the X-ray structure of *cis*-(+)-**15** will be published in a full account of this work.

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