ORGANIC LETTERS

2003
Vol. 5, No. 14
2523−2526

Diastereoselective Synthesis of Fluorinated, Seven-Membered β-Amino Acid Derivatives via Ring-Closing Metathesis

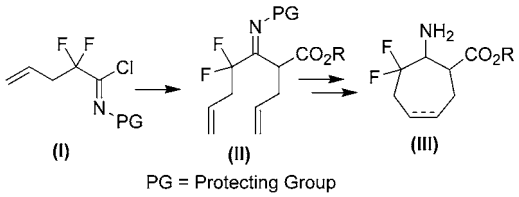
Santos Fustero,* Ana Bartolomé, Juan F. Sanz-Cervera, María Sánchez-Roselló, Juan García Soler, Carmen Ramírez de Arellano,† and Antonio Simón Fuentes

Departamento de Química Orgánica, Universidad de Valencia, E-46100 Burjassot, Spain

santos.fustero@uv.es

Received May 14, 2003

ABSTRACT



Cis and trans seven-membered γ,γ-difluorinated β-amino acid derivatives (III) have been prepared with a sequence that starts with imidoyl halides (I), which are condensed with suitable ester enolates to give intermediates (II). These, in turn, can be cyclized by means of a ring-closing olefin metathesis reaction and the product stereoselectively reduced to yield compounds (III) in good overall yields.

β-Amino acids are an important class of organic molecules that appear in Nature either free or as part of peptides or depsipeptides.[1] They are present in the structures of natural peptides displaying antibiotic, antifungal, and citotoxic properties, among others.[1] Dolastatin,[2] jasplakinolide,[3] and taxol[4] are notable examples of natural products that not only include β-amino acid units in their structure but also display extremely interesting biological activities. In contrast to their nonfluorinated derivatives, very little is known about the chemistry and biological activity of fluorine-containing β-amino acids.[5] Furthermore, the replacement of hydrogen atoms by fluorine atoms has been found to sometimes provide dramatic changes in the physical and biological properties of organic compounds.[6]

Another interesting aspect of β-amino acid chemistry is the ability of these compounds to form β-peptides. These biopolymers require fewer monomers than α-peptides to adopt a variety of stable secondary structures.[7] Cyclic β-amino acids are also extremely useful intermediates in the synthesis of natural products, β-peptides, and peptidomimetics.[8] The introduction of a ring into the structure of the

† To whom correspondence regarding X-ray analysis should be directed.

(1) (a) *Enantioselective Synthesis of β-Amino Acids*; Juaristi, E., Ed.; Wiley-VCH: New York, 1997. (b) Liu. M.; Sibi, M. P. *Tetrahedron* **2002**, *58*, 7991−8035.

(2) Pettit, G. R.; Kamano, Y.; Kizu, H.; Dufresne, C.; Herald, C. L.; Bontems, R.; Schdmidt, J. M.; Boettner, F. E.; Nieman, R. A. *Heterocycles* **1989**, *28*, 553−558.

(3) Grieco, P. A.; Hon, Y. S.; Pérez-Medrano, A. *J. Am. Chem. Soc.* **1988**, *110*, 1630−1631.

(4) Ojima, I.; Lin, S.; Wang, T. *Curr. Med. Chem.* **1999**, *6*, 927−954.

(5) (a) *Fluorine-containing Amino Acids: Synthesis and Properties*; Kukhar, V. P., Soloshonok, V. A., Eds.; Wiley: Chichester, UK, 1994. For recent papers, see: (b) Fustero, S.; Pina, B.; Salavert, E.; Navarro, A.; Ramírez de Arellano, M. C.; Simón, A. *J. Org. Chem.* **2002**, *67*, 4667−4679 and literature therein. (c) Soloshonok, V. A.; Ohkura, H.; Sorochinsky, A.; Voloshin, N.; Markovsky, A.; Belik, M.; Yamazaki, T. *Tetrahedron Lett.* **2002**, *43*, 5445−5448 and literature therein.

(6) (a) Banks, R. E.; Tatlow, J. C.; Smart, B. E. *Organofluorine Chemistry: Principles and Commercial Applications*; Plenum Press: New York, 1994. (b) *Houben-Weyl Methods of Organic Chemistry*, Workbench Edition: Georg Thieme Verlag: Stuttgart, 2000; Vols. E10a−c.

(7) Cheng, R. P.; Gellman, S. H.; DeGrado, W. F. *Chem. Rev.* **2001**, *101*, 3219−3232.

(8) Fülöp, F. *Chem. Rev.* **2001**, *101*, 2181−2204.

10.1021/ol034827k CCC: $25.00
Published on Web 06/17/2003

β-amino acid confers more rigidity to the structure of the peptides and, in many cases, an improved stability and biological activity.[9] An interesting example of a natural, cyclic β-amino acid that appears as a free molecule is cispentacin, a compound that displays potent antifungal activity, in particular against *Candida albicans*.[10]

Although the literature includes some examples of the synthesis of cyclic β-amino acids, those with seven-membered rings are particularly scarce.[8] In fact, to the best of our knowledge, no fluorinated, seven-membered β-amino acids have been described thus far.

The ring-closing olefin metathesis reaction (RCM) has been one of the most successful methods for the preparation of medium- or large-sized rings from acyclic diene precursors.[11] Two of the most widely used ruthenium catalysts for this reaction appear in Figure 1.[12]

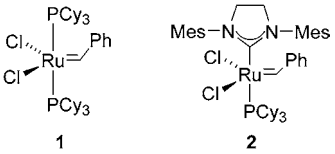
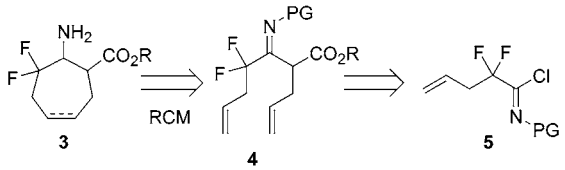


Figure 1. First- (**1**) and second-generation (**2**) Grubbs' catalysts.

Despite its versatility, however, the RCM has been used infrequently for the preparation of fluorinated nitrogen compounds.[13] Indeed, the literature contains only two examples in which nonfluorinated, six-membered β-amino acids are prepared by means of this reaction.[14]

In this letter, we describe the first diastereoselective synthesis of the *cis*- and *trans*-2-amino-3,3-difluorocyclohept-5-ene carboxylic acid derivatives **3**. The retrosynthetic analysis for the strategy we followed is shown in Scheme 1. In this approach, the key step is a ring-closing metathesis reaction that gives compounds **3**. The fluorinated imidoyl chlorides **5** were prepared with the methodology first

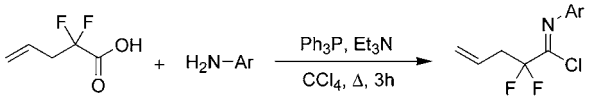
Scheme 1



PG = Protecting Group

described by Appel et al.[15] and later improved by Uneyama et al.[16] In this way, the protected imidoyl chlorides **5a**–**c** were successfully prepared as shown in Scheme 2.

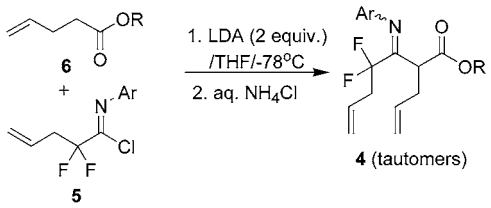
Scheme 2



5a Ar=*p*-MeOC$_6$H$_4$ (80%)
5b Ar=*o*-MeOC$_6$H$_4$ (82%)
5c Ar=*p*-FC$_6$H$_4$ (50%)

The ethyl and benzyl esters of 4-pentenoic acid (**6a**, R = Et; **6b**, R = Bn) were then treated with 2 equiv of LDA[5b] in THF at −78 °C to generate their enolates, which were then treated with 1 equiv of the imidoyl chlorides **5** to yield the fluorinated β-imino esters **4** (Table 1). In general, the yields

Table 1. Results for the Reaction between the Esters **6** and the Imidoyl Chlorides **5**



entry	3	5	Ar	R	product	yield (%)[a]
1	**6a**	**5a**	*p*-MeOC$_6$H$_4$	Et	**4a**	85
2	**6a**	**5b**	*o*-MeOC$_6$H$_4$	Et	**4b**	80
3	**6a**	**5c**	*p*-FC$_6$H$_4$	Et	**4c**	82
4	**6b**	**5a**	*p*-MeOC$_6$H$_4$	Bn	**4d**	76

[a] Yields for purified products.

for the condensation reaction between the esters **6** and the imidoyl chlorides **5** were good (Table 1). The ^{1}H and ^{19}F NMR spectra showed that, while in two cases the imino tautomer was the only product present (entries 1 and 2), in the other two cases a mixture of the imino and enamino forms was present (entries 3 and 4), with the former being more abundant.

(9) See, for example: Appella, D. H.; Christianson, L. A.; Klein, D. A.; Richards, M. R.; Powell, D. R.; Gellman, S. M. *J. Am. Chem. Soc.* **1999**, *121*, 7574−7581.

(10) Kawabata, K.; Inamoto, Y.; Sakane, K.; Iwamoto, T.; Hashimoto, S. *J. Antibiotics* **1990**, *43*, 513−518.

(11) (a) Grubbs, R. H.; Chang, S. *Tetrahedron* **1998**, *54*, 4413−4450. (b) Schuster, M.; Blechert, S. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2036−2056. (c) Armstrong, S. K. *J. Chem. Soc., Perkin Trans. 1* **1998**, 371−388. (d) Grubbs, R. H.; Miller, S. J.; Fu, G. C. *Acc. Chem. Res.* **1995**, *28*, 446−452. (e) Roy, R. *Chem. Commun.* **2000**, 519−529. (f) Percy, J. M.; Pintat, S. *Chem. Commun.* **2000**, 607−608. (g) Kariuki, B. M.; Owton, W. M.; Percy, J. M.; Pintat, S.; Smith, C. A.; Spencer, N. S.; Thomas, A. C.; Watson, M. *Chem. Commun.* **2002**, 228−229.

(12) (a) Schwab, P.; France, M. B.; Ziller, J. W.; Grubbs, R. H. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 2039−2041. (b) Scholl, M.; Ding, S.; Lee, C. W.; Grubbs, R. H. *Org. Lett.* **1999**, *1*, 953−956. (c) Jafarpour, L.; Hillier, A. C.; Nolan, S. P. *Organometallics* **2002**, *21*, 442−444.

(13) (a) Osipov, S. N.; Artyushin, O. I.; Kolomiets, A. F.; Bruneau, C.; Picquet, M.; Dixneuf, P. H. *Eur. J. Org. Chem.* **2001**, 3891−3897. (b) Fustero, S.; Navarro, A.; Pina, B.; García Soler, J.; Bartolomé, A.; Asensio, A.; Simón, A.; Bravo, P.; Fronza, G.; Volonterio, A.; Zanda, M. *Org. Lett.* **2001**, *3*, 2621−2624.

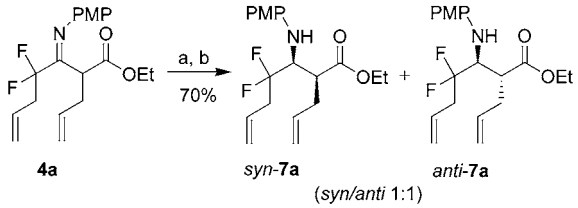
(14) (a) Abell, A. D.; Gardiner, J. *Org. Lett.* **2002**, *4*, 3663−3666. (b) Perlmutter, P.; Rose, M.; Vounatsos, F. *Eur. J. Org. Chem.* **2003**, 756−760.

(15) Appel, R.; Warning, K.; Ziehn, K. D. *Chem. Ber.* **1973**, *106*, 2093−2097.

(16) Tamura, K.; Mizukami, H.; Maeda, K.; Watanabe, H.; Uneyama, K. *J. Org. Chem.* **1993**, *58*, 32−36.

A priori, two different approaches were possible for the next step: either first reducing the C=N bond and then attempting an RCM reaction or performing the RCM reaction first and then reducing the imine. Both reaction sequences were explored. Compound **4a** was first reduced with $NaCNBH_3$ in THF/TFA[17] at 0 °C with 70% yield, albeit with no stereoselectivity, as both possible syn and anti diastereoisomers were formed in 1:1 ratio (*syn*-**7a** and *anti*-**7a**, Scheme 3). Attempts to increase the diastereoselectivity

Scheme 3[a]

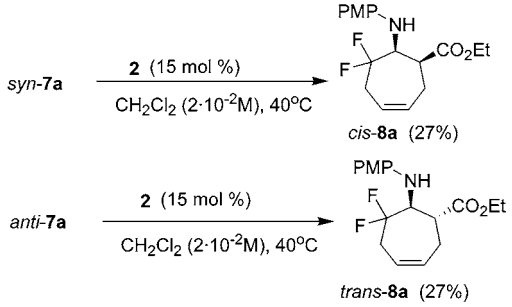


[a] Conditions: (a) $NaCNBH_3$ (3 equiv)/THF/TFA/0 °C. (b) Aqueous saturated NH_4Cl solution.

through the use of different reducing agents and conditions (e.g., $NaBH_4/ZnI_2/CH_2Cl_2$)[5b] were not fruitful.

S*yn*- and *anti*-**7a** were separated by means of column chromatography and independently treated with the commercially available ruthenium alkylidene catalyst (IHMes)-$(PCy_3)Cl_2Ru$=CHPh[12b] (**2**) in refluxing CH_2Cl_2 to check the validity of this approach. The yields for the resulting cyclized compounds *cis*- and *trans*-**8a**, however, were disappointingly low (Scheme 4).[18]

Scheme 4



The relative configuration of the ester and amino groups in compounds **8** was determined by means of X-ray diffraction techniques. A single crystal of compound **8a** was prepared, and subsequent X-ray diffraction analysis showed

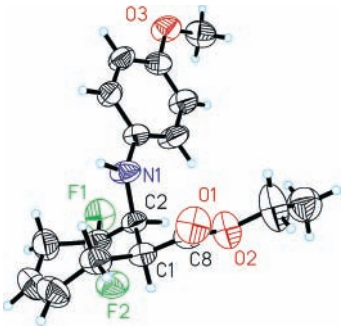
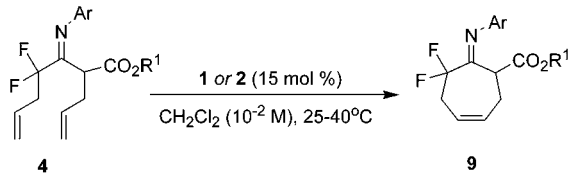


Figure 2. Ellipsoid plot of compound *cis*-**8a** (50% probability level).

that the substituents on C-1 and C-2 were in a cis relative configuration (Figure 2).[19]

Since this strategy of performing the RCM after the reduction produced poor results, the obvious alternative consisted of inverting the order of the reactions, that is, having the RCM reaction *precede* the C=N bond reduction. In principle, this alternative strategy might have the advantage of a reduced basicity of the imino group, as compared to that of the amino group, and hence a better compatibility with the catalyst. The first attempts to carry out the RCM reaction with Grubb's first-generation catalyst[12a] $(PCy_3)_2Cl_2$-Ru=CHPh (**1**) on compound **4a** yielded the desired product **9a** in 65% yield. These moderate yields prompted new attempts with the second-generation catalyst (IHMes)-$(PCy_3)Cl_2Ru$=CHPh[12b] (**2**), which had a shorter reaction time (6 h) and produced higher yields (75%). The remaining compounds **4** were treated in a similar fashion to yield the cyclized compounds **9**. The results are shown in Table 2.

Table 2. Results for the RCM Reaction of Compounds **4**



entry	Ar	R^1	catalyst	reaction temp (°C)	reaction time (h)	product	yield (%)[a]
1	*p*-$MeOC_6H_4$	Et	**1**	25	36	**9a**	65
2	*p*-$MeOC_6H_4$	Et	**1**	40	24	**9a**	60
3	*p*-$MeOC_6H_4$	Et	**2**	40	6	**9a**	75
4	*o*-$MeOC_6H_4$	Et	**2**	40	6	**9b**	90
5	*p*-FC_6H_4	Et	**2**	40	6	**9c**	60
6	*p*-$MeOC_6H_4$	Bn	**2**	40	6	**9d**	65

[a] Yields for purified products.

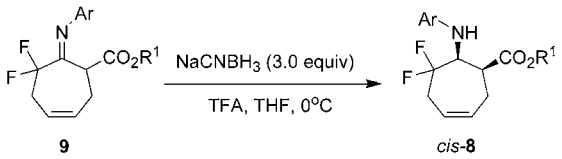
These results not only indicate that the RCM is an excellent method for preparing seven-membered rings in

(17) (a) Bartoli, G.; Cimarelli, C.; Marcantoni, E.; Palmieri, M.; Petrini, G. *J. Org. Chem.* **1994**, *59*, 5328−5335. (b) Cimarelli, C.; Palmieri, G. *J. Org. Chem.* **1996**, *61*, 5557−5563.

(18) The low yields in this reaction could be due to the fact that the free amine can chelate the ruthenium atom in the catalyst, thus decreasing its activity. See: (a) Sandford, M. S.; Love, J. A.; Grubbs, R. H. *J. Am. Chem. Soc.* **2001**, *123*, 6543−6554. (b) Wright, D. L.; Schulte, J. P., II; Page, M. A. *Org. Lett.* **2000**, *2*, 1847−1850.

(19) See Supporting Information for X-ray diffraction data of *cis*-**8a**.

Table 3. Results for the Reduction of the β-Imino Esters **9**



9 *cis*-**8**

entry	starting material	Ar	R^1	product	yield (%)[a]
1	**9a**	*p*-$MeOC_6H_4$	Et	*cis*-**8a**	90
2	**9b**	*o*-$MeOC_6H_4$	Et	*cis*-**8b**	88
3	**9c**	*p*-FC_6H_4	Et	*cis*-**8c**	80
4	**9d**	*p*-$MeOC_6H_4$	Bn	*cis*-**8d**	72

[a] Yields for purified products.

these kinds of substrates but also that catalyst **2** provides superior results. The NMR data for the products **9** showed that they consisted of a mixture of imino/enamino tautomers, with the first being predominant.

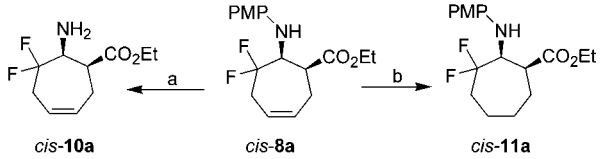
In the next step, the imine was reduced with $NaCNBH_3$ in THF at 0 °C in the presence of TFA (Table 3). This afforded the protected amino esters in yields of 72−90% with reaction times of 1−3 h. In all cases, only the cis diastereoisomer was obtained in a completely diastereoselective fashion. The physical and spectroscopic data for compound *cis*-**8a** prepared in this way were the same as those obtained for the same compound prepared from *syn*-**7a** via the alternative route (see above).

These results bolstered the conclusion that the RCM followed by reduction is more effective for the preparation of the cyclic fluorinated β-amino acids **8** than the opposite sequence, as the products are obtained both in higher yields and with complete diastereoselectivity. One possible reason for this may be the added rigidity that the cycle and the imine group impart on the structures of compounds **9**.

To probe the feasibility of the deprotection of these compounds, the *p*-$MeOC_6H_4$ (PMP) protecting group[20] of

(20) Jacob, P.; Callery, P. S.; Shulgin, A. T.; Castagnoli, N. *J. Org. Chem.* **1976**, *41*, 3627−3629.

Scheme 5[a]



cis-**10a** *cis*-**8a** *cis*-**11a**

[a] Reagents and conditions: (a) $Ce(NH_4)_2(NO_3)_6/CH_3CN-H_2O$, 0 °C, 2 h, 95% yield. (b) H_2 (1 atm), Pd/C (10%), MeOH, 2 h, 99% yield.

cis-**8a** was removed with ceric ammonium nitrate in aqueous acetonitrile, followed by treatment with aqueous $NaHCO_3$ and aqueous Na_2SO_3 sequentially to yield compound *cis*-**10a** in 95% yield (Scheme 5).

Finally, the double bond in compound *cis*-**8a** was easily reduced by means of catalytic hydrogenation with Pd/C 10% as a catalyst in MeOH, yielding compound *cis*-**11a** in quantitative yield after 2 h (Scheme 5).

In summary, the methodology presented here allows for the diastereoselective synthesis of the seven-membered, γ,γ-difluorinated β-amino acid derivatives **8**, **10**, and **11** in an effective manner. To the best of our knowledge, this is the first synthesis available for these interesting substances. Extension of this methodology to the enantioselective preparation of this and other cyclic, fluorinated β-amino acid derivatives is in progress.

Acknowledgment. We thank the Ministerio de Ciencia y Tecnología of Spain for financial support (PPQ2000-0824). A.B., J.G.S., and M.S.-R. thank the Generalitat Valenciana and the Ministerio de Educación y Cultura of Spain for predoctoral fellowships.

Supporting Information Available: Spectroscopic data, experimental details for compounds **3**−**5**, **7**−**9**, **10a**, and **11a**, and crystal data for compound *cis*-**8a** in CIF format. This material is available free of charge via the Internet at http://pubs.acs.org.

OL034827K