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Asymmetric Synthesis of Fluorinated Amino Macrolactones through Ring-Closing Metathesis

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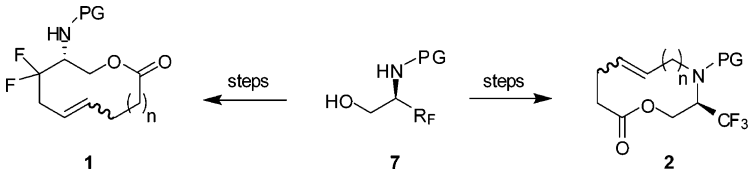

The synthesis of new chiral fluorinated amino and azamacrolactones of types **1** and **2** is described. A ring-closing metathesis (RCM) reaction constitutes the key step in this methodology, which uses fluorinated amino alcohols **7** as starting materials. The influence of the CF_2 group, which is located in the α-position relative to the carbon bearing the amino group, on the efficiency of the RCM reaction is noteworthy. This method allows for the preparation of the desired fluorinated macrolactones in excellent yields.

Introduction

Numerous macrolactones with interesting biological activities have been isolated and identified from various plants and microorganisms in recent years.[1] Among them, the discovery of erythromycin as a powerful and versatile antibiotic led to a tremendous surge in interest in both natural and semisynthetic macrolides, principally because of their antibacterial effects. However, these compounds also display other important biological activities, including antitumoral,[2] antifungal, and antibiotic[3] properties.

Of the several synthetic strategies that have been used in the synthesis of these compounds to form the lactone ring,[4] the ring-closing metathesis (RCM) of dienes has emerged as a powerful synthetic tool in the past few years,[5] mostly due to its efficacy in the preparation of numerous carbo- and heterocycles with various ring sizes, including medium-sized rings and macrocycles.[6] In the case of macrocycle preparation through RCM, the desired compounds are usually obtained as mixtures of *E* and *Z* isomers when the cycle is 11-membered or larger. The isomeric proportions are generally hard to predict, and control-

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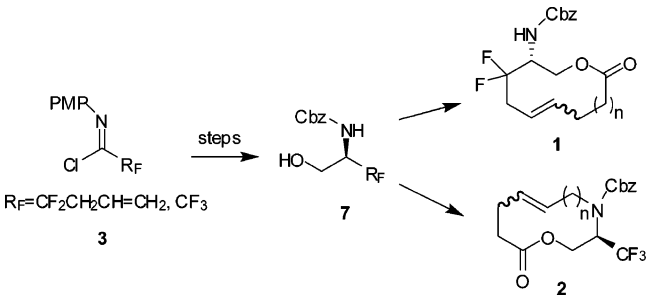
ling them is difficult due to the fact that the reaction results usually depend on the substrate and catalyst used.[7] In contrast, in the case of 10-membered lactones, the *Z* isomer is generally obtained in a stereoselective manner.

The introduction of fluorine atoms, in particular, those of trifluoromethyl and difluoroalkyl groups, into organic molecules[8] is advantageous for the biological activity of potential drugs as it generally increases bioavailability and often leads to a direct interaction with active centers in certain processes. For this reason, fluorinated compounds are increasingly being applied in fields such as medicine,[9] crop management,[10] and materials science.[11]

In sharp contrast with the number of known natural lactones, there are no examples of natural fluorinated lactones. While reports on nonfluorinated macrolide syntheses are also abundant, those for the preparation of their fluorinated counterparts are still very scarce and have mostly focused on the preparation of five- and six-membered lactones. To the best of our knowledge, only two research groups have studied the synthesis of fluorinated macrolactones to date. Very recently, Danishefsky and co-workers carried out the synthesis of fludelone, a fluorinated epothilone.[12] In this case, the introduction of a trifluoromethyl group in the macrolactone system led to enhancement of the well-known antitumoral properties of this macrolide. Previously, Haufe and co-workers had also prepared a monofluorinated derivative of lasiodiploidine, a natural 12-membered lactone.[13]

Additionally, a handful of interesting amino and azamacrolactones have been described as natural products, such as the azamacrolides that form the defensive pupal secretion of one species of *Epilachna* (the Mexican beetle).[14] In contrast with the few existing syntheses of amino or azalactones, however, none have been described for their fluorinated analogues to date,

SCHEME 1



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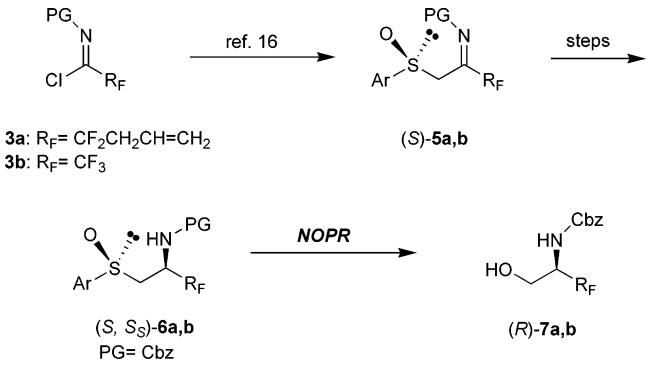

although Langlois and co-workers have described the synthesis of a related system, a 14-membered lactam that features a trifluoromethyl group.[15]

Considering the potential interest of these compounds, we have decided to undertake their synthesis. In this paper, we describe an efficient synthesis of new chiral amino macrolactones **1** and azamacrolactones **2** in enantiomerically pure form and with an RCM as the key reaction (Scheme 1). The fluorine atoms were introduced into the molecule at the building block **3** stage; this, in turn, was transformed into the fluorinated β-amino alcohols **7**, which then served as precursors of both **1** and **2** (Scheme 1). For comparison purposes, we also decided to prepare an analogue of system **1** with the CF_2 group located at a different position as well as a nonfluorinated analogue in order to determine the influence of both the presence and position of the CF_2 group on the preparation of these compounds.

Results and Discussion

Synthesis of Amino Alcohols 7. The preparation of fluorinated β-amino alcohols **7a,b** starts with the condensation of fluorinated imidoyl chlorides **3a,b**, which function as fluorinated building blocks in this synthesis, and (−)-(*S*)-methyl-1-naphthylsulfoxide **4**, used as a chiral auxiliary, to afford β-imino sulfoxides **5a,b** (Scheme 2).[16]

The diastereoselective reduction[16] of β-imino sulfoxides (*S*)-**5a,b** and the subsequent nonoxidative Pummerer reaction

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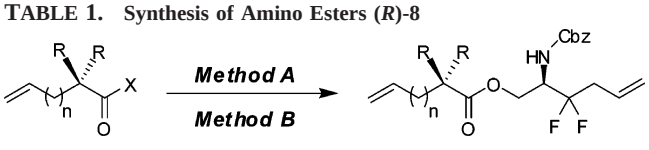
TABLE 1. Synthesis of Amino Esters (*R*)-8



entry	method	*n*	R	time (h)	yield (%)	product
1	A[a]	1	H	8	89	**8a**
2	B[b]	2	H	12	95	**8b**
3	B[b]	3	H	12	95	**8c**
4	B[b]	1	F	12	75	**8d**

[a] Method A: (X = Cl) (*R*)-**7a**, Et_3N, DMAP CH_2Cl_2, rt, 8 h. [b] Method B: (X = OH) (*R*)-**7a**, DIC, DMAP, CH_2Cl_2, 0 °C to rt, 12 h.

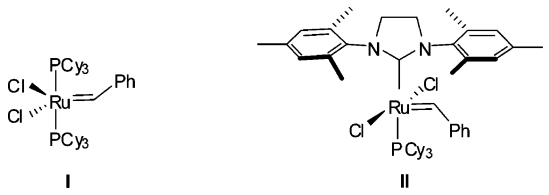


FIGURE 1. Grubbs catalysts used in RCM reactions.

(NOPR)[17] of the protected β-amino sulfoxide derivatives **6a,b** afforded the enantiomerically pure fluorinated β-amino alcohols (*R*)-**7a,b**, which were then used as starting materials for the preparation of macrolactones **1** and **2** (see Supporting Information).

Synthesis of Amino Macrolactones 1a−d. While amino ester (*R*)-**8a** was easily prepared through treatment of (*R*)-**7a** with 4-pentenoyl chloride in the presence of Et_3N and DMAP (Table 1, Method A), in the case of compounds (*R*)-**8b−d**, the corresponding acid chlorides are not commercially available. Therefore, these compounds had to be prepared through reaction of the corresponding 4-carboxylic acids with (*R*)-**7a** and diisopropylcarbodiimide as a coupling agent in dichloromethane (Table 1, Method B).

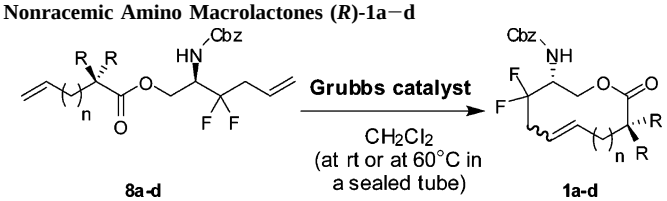
To complete the synthesis, the di- and tetrafluorinated amino macrolactones (*R*)-**1a−d** were prepared by means of a ring-closing metathesis reaction on compounds **8** with the aid of first-generation (**I**) and second-generation (**II**) Grubbs catalysts in CH_2Cl_2 (Figure 1 and Table 2).

Table 2 shows that the RCM is quite efficient in forming 10-membered rings (entries 1−5, Table 2), as can be seen from the short reaction times when catalyst **II** is used and the excellent yields of both the difluorinated (*R,Z*)-**1a** (95% yield, entry 1, Table 2) and the tetrafluorinated amino macrolactone (*R,Z*)-**1d** (96% yield at room temperature after just 10 min, entry 10, Table 2). It is worth noting that in both these cases GC−MS analysis of the reaction product showed that only one stereoisomer was formed in each case, which was determined to be the *Z* geometric isomer by means of X-ray diffraction studies (Figures 2 and 4).[7]

The structural characterization of macrolactones **1a−d**, **14** (Scheme 5), **16** (Scheme 6), and in particular the assignment of *Z,E* configuration of the carbon−carbon double bond by means of standard NMR studies was not a trivial task, as a significant number of the resonances, including those corresponding to the vinylic moiety, present very broad signals with unresolved couplings in the ^1H, ^{19}F, and ^{13}C NMR spectra recorded at room temperature. This broadening can be attributed to a conformational exchange equilibrium within the molecule, although the fact that the NMR spectra also show sharp signals under the same conditions indicates that such equilibrium affects only a localized part of the molecule. The broad resonances precluded any attempt to measure the coupling constants of the vinylic protons, which would have allowed a quick assignment of the double bond configuration. Furthermore, the broadening of the signals gave 2D correlation experiments with incomplete information that prevented a full characterization of our macrolactones.

In order to determine the structure of these compounds, a more detailed spectroscopic study had to be carried out. Thus, ^1H and ^{19}F spectra were collected over the temperature range of 260−360 K. Whereas the NMR spectra acquired at high temperatures still show broad resonances, a significant improvement was observed in the spectra at low temperatures, showing the sharpest resonances at 270 K (Figure 3). Therefore, the full characterization of compounds **1a−1d** and **16** was carried out at this temperature, including the acquisition and analysis of homonuclear COSY experiments as well as ^1H, ^{13}C HMQC,

TABLE 2. Preparation of Chiral, Nonracemic Amino Macrolactones (*R*)-1a−d



entry	*n*	precursor	R	catalyst (mol %)	temp (°C)	time (h)	yield (%)	product	*E*:*Z* ratio
1	1	**8a**	H	**II** (5)	25	4	95	**1a**	0:100
2	1	**8a**	H	**II** (5)	60	4	98	**1a**	0:100
3	1	**8a**	H	**II** (10)	60	6	76	**1a**	0:100
4	1	**8a**	H	**II** (15)	60	4	83	**1a**	0:100
5	1	**8d**	F	**II** (10)	25	10 min	96	**1d**	0:100
6	2	**8b**	H	**II** (5)	25	24	NR	**1b**	NR
7	2	**8b**	H	**II** (5)	60	8	77 (**1a**) 19 (**1b**)	**1a** **1b**	0:100 (**1a**) (**1b**)[a]
8	2	**8b**	H	**I** (5)	60	8	22	**1b**	*a*
9	3	**8c**	H	**II** (5)	25	24	4	**1c**	*a*
10	3	**8c**	H	**II** (5)	60	8	70	**1c**	*a*

[a] For both **1b** and **1c**, GC−MS showed the presence of only one geometric isomer, but these compounds appeared as a complex mixture of conformers at low temperature, and thus the double bond configuration could not be determined by means of NMR spectroscopy.

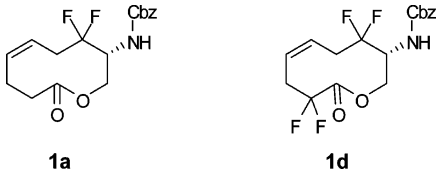


FIGURE 2. Ten-membered fluorinated lactones prepared by means of RCM.

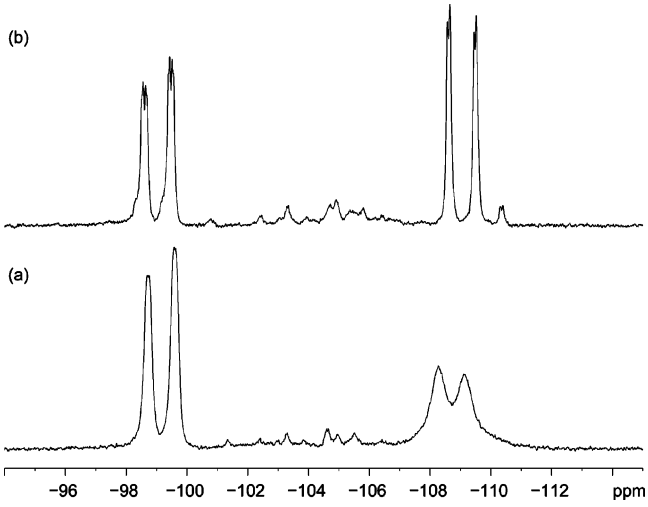


FIGURE 3. ^{19}F NMR spectra (282.37 MHz) of compound **1a** at (a) 300 K and (b) 270 K.

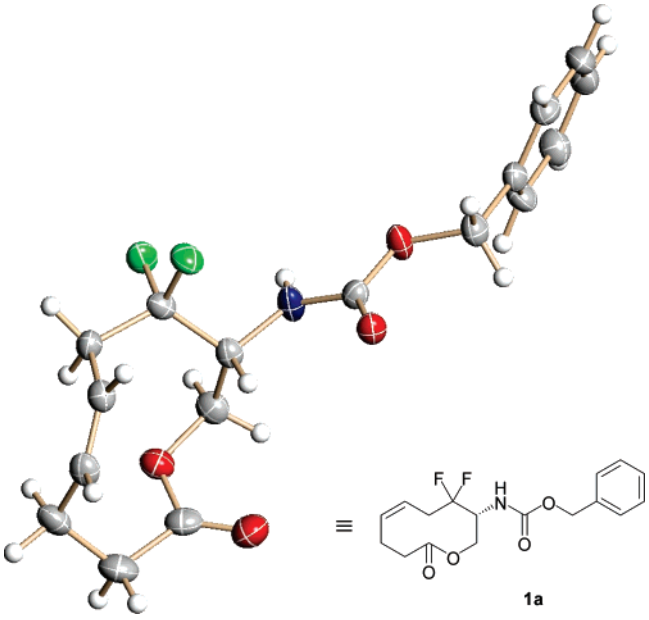
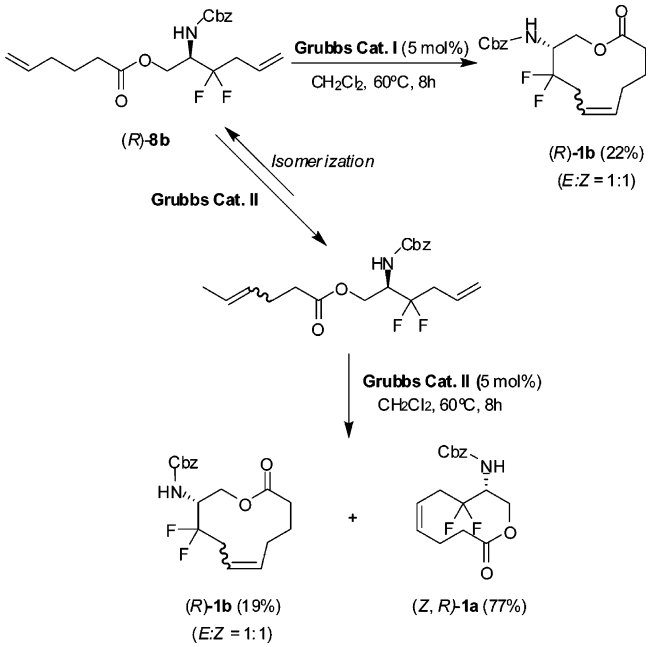


FIGURE 4. X-ray diffraction analysis of macrolactone **1a**.

and HMBC correlation spectra. Taking as a model for the assignment process the characterization of **1a** (the assignment of **1b**−**1d** and **16** follows similar arguments), the disappearance of two allylic CH_2 carbon signals in the ^{13}C/DEPT spectra from the starting material **8a** indicates that the RCM reaction has taken place. Additionally, the number of carbon signals observed agrees with the formation of a 10-membered macrolactone ring and the presence of a Cbz group. Two carbons in the ^{13}C/DEPT spectra can be ascribed to a vinylic double bond (δ 123.9 and 129.7 ppm). Also, two carbonyl resonances are found: one at

SCHEME 3



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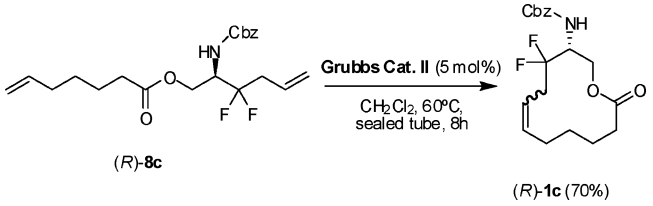


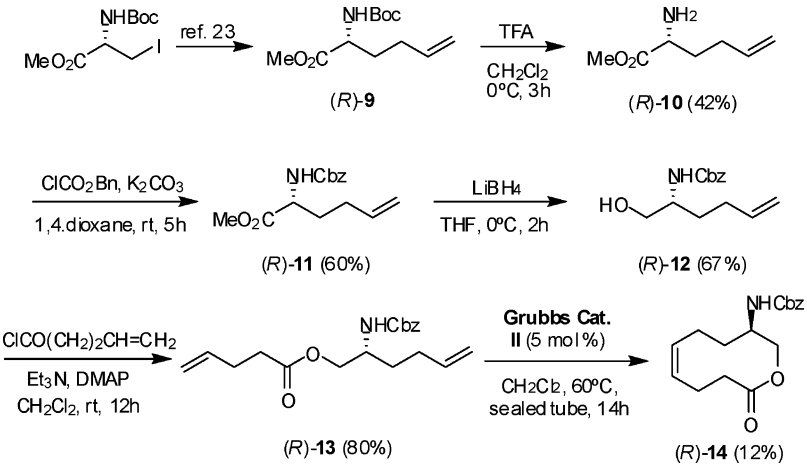
δ 156.3 ppm that is assigned to the carbonyl from the benzyl moiety and the second at δ 170.7 ppm which corresponds to the lactone carbonyl carbon. The formation of the ring was confirmed by means of ^{1}H−^{1}H COSY and ^{1}H,^{13}C heteronuclear correlations, as each ^{1}H atom in the ring gives through-bond connections with the successive ^{1}H and/or ^{13}C in the molecule. The full characterization of the molecule allowed the identification of those signals that were broadened at higher temperatures, and they were finally assigned to the atoms that form part of the macrolactone ring, which is therefore affected by the conformational exchange equilibrium. The spectra at low temperatures also allowed the measurement of several coupling constants between the ring protons. Especially relevant were the couplings between the vinylic protons, whose value was found to be 10−11 Hz and therefore in the expected range for the *Z*-configuration isomer.

X-ray diffraction analysis confirmed that the configuration of the Δ^7 double bond was *Z* in both lactones **1a** and **1d** (Figure 2). The structures for **1a** and **1d** show C(3)−C(4)−C(5)−C(6) torsion angles of 4.4(4) and 4(2)°, respectively, corresponding to a *Z* conformation for both 10-membered amino lactones (*R*,*Z*)-**1a** and (*R*,*Z*)-**1d** (Figure 4).[18]

We propose that the stereoselective formation of the *Z* configuration is probably due to the higher ring strain in the *E* isomer. Indeed, a molecular mechanics study performed with the aid of the program MacroModel[19] and MM2 force field on compounds (*R*,*Z*)- and (*R*,*E*)-**1a** showed that the *Z* isomer is more stable than the *E* isomer by 5 kcal/mol, a result which

(18) For the X-ray structure of (*R*,*Z*)-**1d**, see the Supporting Information.

SCHEME 5



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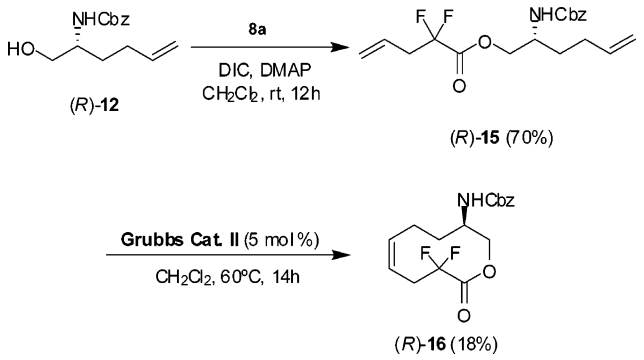

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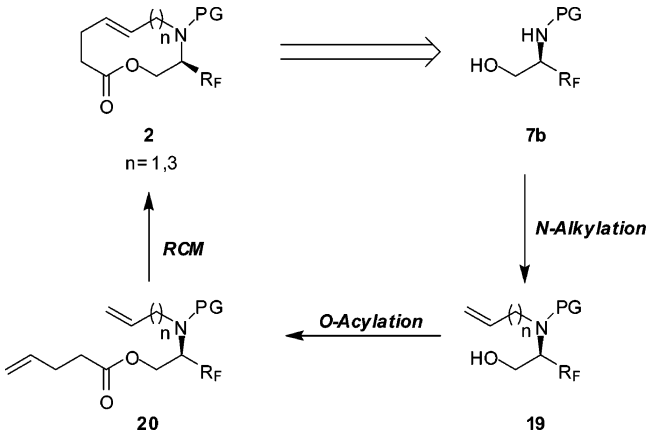

sheds light on the reason for the exclusive formation of the (*R*,*Z*)-**1a** isomer in these cases.

In contrast with the formation of 10-membered rings, 11-membered rings are noticeably more difficult to obtain with our protocol, as can be deduced from the fact that the amino lactone (*R*)-**1b** does not form at room temperature (entry 6, Table 2). Even more significantly, when catalyst **II** was used (entry 7, Table 2), the desired compound **1b** was obtained in only 19% yield. The major reaction product (77% yield) was again compound (*R*)-**1a**, which in this case may arise from an isomerization reaction previous to the RCM (Scheme 3)[20] as similar processes have already been observed by Fürstner and co-workers in the preparation of other macrolactones.[21] Moreover, both the position of the double bond at Δ^7 and the double bond configuration in the resulting product coincide with those of (*R*,*Z*)-**1a** obtained in entry 2 (Table 2) as proven by X-ray diffraction studies. This indicates that the double bond isomerization takes place exclusively in the ester double bond and not in the amine moiety. This phenomenon has been previously observed by our group.[22]

When we attempted to suppress the isomerization by using catalyst **I** instead of **II** on precursor (*R*)-**8b** (entry 8, Table 2), we found that, although the formation of the 10-membered lactone did not take place, the yield for **1b** was only 22%, with 40% of the starting material being recovered unchanged. In addition, 20% of a dimer was also isolated from the reaction. We were unable to improve this yield even after testing several different reaction conditions, such as longer times and successive additions of catalyst (Scheme 3).

The fluorinated 12-membered amino macrolactone (*R*)-**1c** was obtained in 70% yield (entry 10, Table 2) when the reaction was performed at 60 °C in a sealed tube with catalyst **II** and CH_2Cl_2 as solvent (Scheme 4).

Although GC−MS showed the formation of single geometric isomer as the major product of the RCM reaction, both **1b** and **1c** appeared as a mixture of conformers at low temperature, and thus their NMR spectra were much less resolved than for **1a**, **1d**, and **1b**. This precluded the structural assignment of the double bond configuration in **1b** and **1c**.

Finally, we attempted the synthesis of the nonfluorinated aminolactone **14** (Scheme 5) and the fluorinated analogue **16** (Scheme 6). Our intention was to compare the preparation of these compounds with that of those previously obtained, in which a CF_2 group is always present at C-7, next to the amino group.

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(20) For example, see: (a) Bourgeois, D.; Pancrazi, A.; Nolan, S. P.; Prunet, J. *J. Organomet. Chem.* **2002**, *643*−*644*, 247−252. (b) Alcaide, B.; Almendros, P.; Alonso, J. M. *Chem.*−*Eur. J.* **2003**, *9*, 5793−5799. (c) Arisawa, M.; Terada, Y.; Nakagawa, M.; Nishida, A. *Angew. Chem., Int. Ed.* **2002**, *41*, 4732−4734.

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(22) Fustero, S.; Sánchez-Roselló, M.; Jiménez, D.; Sanz-Cervera, J. F.; del Pozo, C.; Aceña, J. L. *J. Org. Chem.* **2006**, *71*, 2706−2714.

In the case of nonfluorinated lactone **14**, the key intermediate for the synthesis is the β-amino alcohol (*R*)-**12**. To prepare this compound, commercially available (*S*)-*N*-Boc-iodoalanine was first transformed into its corresponding organozinc derivative and the resulting intermediate was reacted with allyl chloride in the presence of catalytic amounts of $CuBr \cdot SMe_2$ to afford the allylated derivative (*R*)-**9**.[23] Replacement of the N-Boc group with a Cbz group, followed by reduction of (*R*)-**11** with $LiBH_4$, afforded the nonfluorinated amino alcohol (*R*)-**12** (Scheme 5).

The esterification of **12** with 4-pentenoyl chloride afforded (*R*)-**13** in 80% yield, which in turn was subjected to an RCM reaction under the same reaction conditions as those used for **1a** (entry 2, Table 2). In stark contrast with the preparation of **1a**, the nonfluorinated amino macrolactone (*R*)-**14** was obtained in only 12% yield, while 80% of the starting material was recovered unchanged. As for the fluorinated 10-membered amino lactones **1a** and **1d**, a single stereoisomer with *Z* double bond configuration was obtained (Scheme 5).

Finally, we were able to synthesize amino macrolactone (*R*)-**16** with the CF_2 group located at C-2 (Scheme 6). This is in contrast with lactone **1a**, in which this group appears at C-7. The preparation of (*R*)-**16** from (*R*)-**12** was actually quite simple: Cbz-protected nonfluorinated amino alcohol (*R*)-**12** and 2,2-difluoropentenoic acid **8a** were coupled with the acid of DIC in the presence of DMAP to afford ester (*R*)-**15**, which in turn was treated with 5 mol % of second-generation Grubbs catalyst **II** to cause the RCM reaction, thus yielding the desired amino macrolactone (*R*)-**16** as a single isomer, albeit in low yield (18%, Scheme 6).

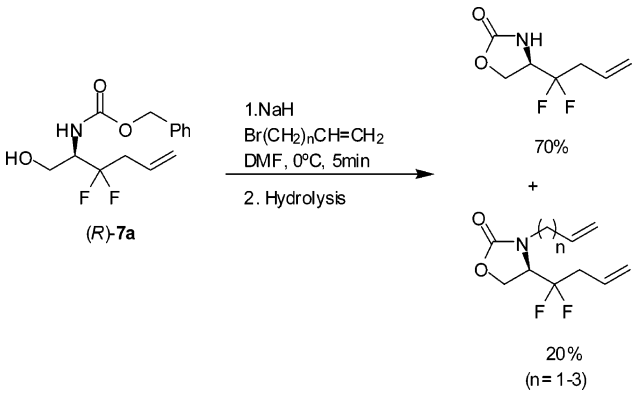
The yield for the RCM reaction that produces compounds **1a** and **1d** is noticeably higher than that for the nonfluorinated analogues **14** and **16**, a fact which clearly shows the importance of the presence of the difluoromethyl group at C-7 for the reaction to be successful. This is most likely due to the decreased Lewis basicity of the amino group caused by the presence of the contiguous CF_2 group, as it is well-known that, when free amino groups are present in a substrate, RCM reactions have been shown to have lower yields as a result of the chelation of the ruthenium catalyst.[24]

Synthesis of Chiral Nonracemic Fluorinated Azamacrolactones 2. Our second synthetic goal was the preparation of fluorinated macrolactones with a nitrogen atom as part of the ring. These are also very appealing synthetic targets, and their preparation has not yet been described in the literature. With this in mind, we decided to attempt the synthesis of azamacrolactones with a CF_3 group as ring substituent. The synthesis once again started with amino alcohol (*R*)-**7b**,[16] which was subjected to N-alkylation followed by O-acylation. This reaction sequence introduced two unsaturated chains that allowed an RCM reaction to take place later (Scheme 7).

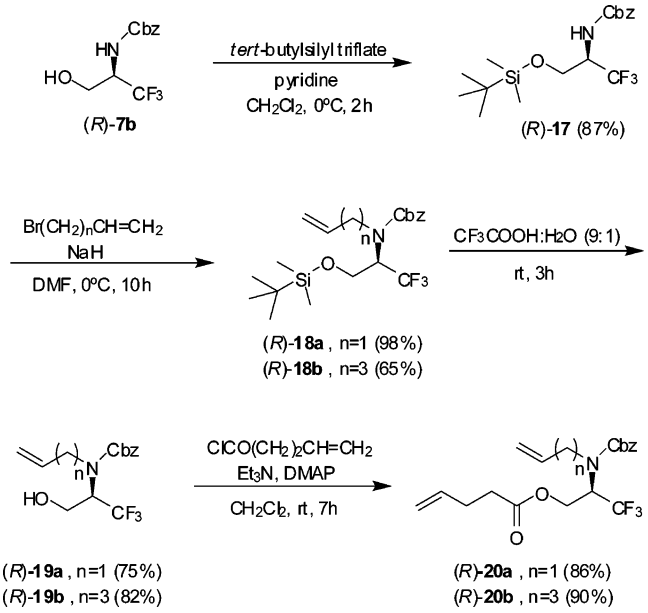
We first attempted the direct N-alkylation on the O-unprotected β-amino alcohol **7a**, but the desired N-alkylation product could not be obtained because of an intramolecular reaction between the alkoxylate oxygen and the carbamate. This afforded a mixture of the corresponding oxazolidinone and N-alkylated oxazolidinone (Scheme 8).

For this reason, it was necessary to protect the hydroxyl group in (*R*)-**7b** before the N-alkylation. Thus, after hydroxyl group protection as its *tert*-butyldimethylsilyl ether to furnish compound (*R*)-**17**, treatment with NaH in DMF followed by two alkenyl bromides with different chain lengths afforded derivatives (*R*)-**18**. These were then deprotected with a 9:1 TFA/H_2O mixture. The resulting N-alkylated (*R*)-β-amino alcohols (*R*)-**19a,b** were treated with 4-pentenoyl chloride in the presence

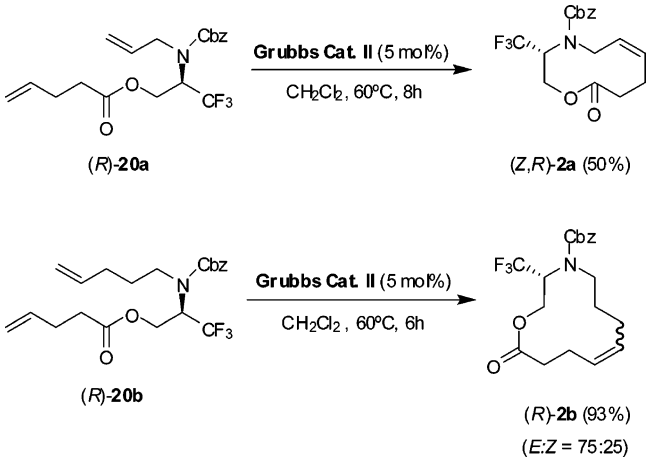
SCHEME 8



SCHEME 9



SCHEME 10



(23) Rodríguez, A.; Miller, D. D.; Jackson, R. F. W. *Org. Biomol. Chem.* **2003**, *1*, 973−977.

(24) (a) Wright, D. L.; Schulte, J. P., II; Page, M. A. *Org. Lett.* **2000**, *2*, 1847−1850. (b) Yang, Q.; Xiao, W. J.; Yu, Z. *Org. Lett.* **2005**, *7*, 871−874.

of Et_3N and DMAP to afford the dienic precursors (*R*)-**20a,b** in excellent yields (Scheme 9).

Finally, the cyclization of compounds (*R*)-**20** through an RCM reaction with second-generation Grubbs catalyst **II** in CH_2Cl_2 yielded the 10- and 12-membered azamacrolactones (*R*)-**2a,b** in moderate to good yields (Scheme 10).

Although *E:Z* mixtures are usually obtained in the preparation of macrolactones through RCM reactions,[7] the 10-membered azamacrolactone (*R*)-**2a** was obtained in 50% yield as a single isomer, as had been the case with **1a** and **1d** (Scheme 10). As with **1a**, the double bond configuration was determined by means of NMR analysis. Thus, the constant for the coupling between the vinylic protons was $J = 10.7$ Hz, a value that once again falls in the expected range for the *Z*-configuration isomer. In contrast, while the 12-membered analogue (*R*)-**2b** was obtained in excellent yield (93%, Scheme 10), it was formed as an *E:Z* isomeric mixture in a ratio of 3:1 when 5 mol % of catalyst **II** was used (GM−MS, ^{19}F NMR). The use of 15% molar equiv of catalyst **II** gave a complex reaction mixture in which compounds resulting from double bond isomerization both before and after the RCM reaction were present, in addition to the desired azamacrolactone **2b**.

Conclusions

In conclusion, we have developed a new synthetic method that can be successfully used in the preparation of nonracemic, optically active, di- and tetrafluorinated amino macrolactones **1** and trifluoromethyl azamacrolactones **2**. The efficiency of the RCM reaction in the formation of the 10-membered amino macrolactones as a single stereoisomer and in a practically quantitative manner is noteworthy since the reaction is successful under mild conditions and with short reaction times. The poor results obtained in the synthesis of nonfluorinated lactones **14** and **16** clearly highlight the importance of the presence of the CF_2 group at C-7 for the synthesis of this type of compounds through RCM.

Experimental Section

Preparation of Difluorinated Amino Macrolactones (*R*)-1 through RCM. A solution of either the second-generation Grubbs catalyst **II** [(IMes)$(PCy_3)Cl_2$Ru=CHPh] or the first-generation Grubbs catalyst **I** [$(PCy_3)_2Cl_2$Ru=CHPh] (the catalyst used and its concentration are indicated in each case) was added under N_2 atmosphere to a solution of the corresponding precursor (*R*)-**8** in dry dichloromethane (2×10^{-2} M). The reaction mixture was heated at 60 °C in a sealed tube or stirred at room temperature until TLC showed consumption of the starting material. The volatiles were then removed under reduced pressure, and the brown residue was purified by means of flash column chromatography [*n*-hexane/AcOEt (8:1)].

(+)-(3*R*)-3-[(*N*-Benzyloxycarbonyl)amino]-4,4-difluoro-3,4,5,8,9,10-hexahydro-2*H*-10-oxecinone (1a). This compound was obtained in 98% yield as a white solid when 5 mol % of the second-generation Grubbs catalyst **II** was used at 60 °C: $[\alpha]_D^{25}$ +5.92 (*c* 1.03, $CHCl_3$); ^1H NMR (600.1 MHz, toluene-d_8) δ 1.31 (m, 1H), 1.84 (m, 1H), 1.93 (m, 1H), 2.26 (m, 1H), 2.90 (m, 1H), 2.96 (m, 1H), 3.15 (t, $J = 10.7$ Hz, 1H), 4.50 (m, 2H), 4.90 (d, $J = 12.1$ Hz, 1H), 4.99 (d, $J = 12.1$ Hz, 1H), 5.09 (m, 1H), 5.20 (m, 1H), 6.98−7.11 (m, 5H); ^{13}C NMR (150 MHz, toluene-d_8) δ 23.4, 33.8, 35.0 (t, $^2J_{CF} = 24.9$ Hz), 51.7 (t, $^2J_{CF} = 22.9$ Hz), 60.8, 68.2, 123.9, 124.1 (t, $^1J_{CF} = 246.4$ Hz), 126.0, 128.8, 129.7, 132.2, 137.6, 156.3, 170.7; ^{19}F NMR (282 MHz, toluene-d_8) δ −99.5 (ddd, $^2J_{FF} = 246.8$ Hz, $J_{HF} = 36.2$ Hz, $J_{HF} = 14.0$ Hz, 1F), −109.5 (dd, $^2J_{FF} = 246.8$ Hz, $J_{HF} = 23.8$ Hz, 1F); HRMS calcd for (M^+) $C_{17}H_{19}F_2NO_4$ 339.1282, found 339.1284. The X-ray data for this compound can be found in the Supporting Information.

(+)-(10*R*)-10-[(*N*-Benzyloxycarbonyl)amino]-9,9-difluoro-1-oxa-6-cycloundecen-2-one (1b). This compound was obtained in 22% yield as a colorless oil when 5 mol % of the first-generation Grubbs catalyst **I** was used at 60 °C: $[\alpha]_D^{25}$ +4.34 (*c* 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz) δ 1.77 (m, 2H), 2.01−2.23 (m, 4H), 2.62 (m, 2H), 4.11 (m, 1H), 4.36 (m, 2H), 5.07 (s, 2H), 5.27−5.46 (m, 2H), 7.31 (5H); HRMS calcd for (M^+) $C_{18}H_{21}F_2NO_4$ 353.1439, found 353.1353. After purification, this compound showed a single peak in GC−MS, which seems to indicate that it is either the *Z* or the *E* isomer. The signals for the ^{19}F NMR and ^{13}C NMR spectra of this compound were so broad at room temperature that they provided no structural information, but at low temperature (acetone-d_6, 240 K), the NMR spectra of compound **1b** show the presence of two major conformers. However, even at 240 K, we were unable to assign the double bond configuration because of the lack of resolution of the ^1H spectrum. The listed signals correspond to the major conformer: ^1H NMR (300.13 MHz, acetone-d_6, 240 K) δ 1.45 (m, 1H), 1.65 (m, 1H), 1.90 (m, 1H), 2.00 (m, 1H), 2.21 (m, 1H), 2.33 (m, 1H), 2.41 (m, 2H), 4.75 (m, 1H), 4.96 (d, $^2J_{HH} = 12.8$ Hz, 1H), 4.99 (d, $^2J_{HH} = 12.8$ Hz, 1H), 5.33 (m, 1H), 5.44 (m, 1H), 7.00 (d, $^2J_{HH} = 9.6$ Hz, 1H), 7.20-7.35 (m, 5H); ^{13}C NMR (75.5 MHz, acetone-d_6, 240 K) δ 25.2, 32.6, 35.9, 38.8, 53.5, 62.5, 67.5, 124.8, 126.9, 129.4, 129.5, 129.8, 135.3, 138.6, 157.5, 174.3; ^{19}F NMR (282.4 MHz, acetone-d_6, 240 K δ−88.2 (dd, $^2J_{FF} = 247.5$ Hz, $^3J_{HF} = 13.3$ Hz, 1F), −106.9 (dd, $^2J_{FF} = 247.5$ Hz, $^3J_{HF} = 26.0$ Hz, 1F).

(−)-(11*R*)-11-[(*N*-Benzyloxycarbonyl)amino]-10,10-difluoro-1-oxa-7-cyclodecen-2-one (1c). This compound was obtained in 70% yield as a colorless oil when 5 mol % of the second-generation Grubbs catalyst **II** was used at 60 °C: $[\alpha]_D^{25}$ −2.43 (*c* 1.03, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz) δ 1.5 (s, 6H), 1.9 (br s, 2H), 2.29 (m, 2H), 2.59 (m, 2H), 4.23 (m, 2H), 5.08 (m, 1H), 5.36 (m, 1H), 7.28 (s, 5H); ^{19}F NMR ($CDCl_3$, 285 MHz) δ [(−104.0)−(−107.0)] (m, 2F); HRMS calcd for (M^+) $C_{19}H_{23}F_2NO_4$ 367.1595, found 367.1572. Like in **1b**, this compound showed a single peak in GC−MS after purification, which seems to indicate that it is either the *Z* or the *E* isomer. The signals for the ^{19}F NMR and ^{13}C NMR spectra of this compound were also so broad at room temperature that they provided no structural information, but at low temperature (acetone-d_6, 240 K), the NMR spectra of compound **1c** show the presence of at least four major conformers. Even at 240 K, we were unable to assign the double bond configuration because of the lack of resolution of the ^1H spectrum caused by the complexity of the conformer mixture. The listed signals correspond to the major conformer: ^1H NMR (300.13 MHz, acetone-d_6, 240 K) δ 1.37 (m, 1H), 1.50 (m, 1H), 1.64 (m, 1H), 1.70 (m, 1H), 1.85 (m, 1H), 2.07 (m, 1H), 2.30 (m, 1H), 2.38 (m, 1H), 2.47 (m, 1H), 3.03 (m, 1H), 4.05 (m, 1H), 4.19 (m, 1H), 4.35 (m, 1H), 4.97 (m, 2H), 5.27 (m, 1H), 5.55 (m, 1H), 7.22 (m, 1H), 7.20-7.40 (m, 5H); ^{13}C NMR (75.5 MHz, acetone-d_6, 240 K) δ 23.4, 25.1, 29.5, 33.6, 38.4, ($^2J_{CF} = 23.6$ Hz), 53.3 ($^2J_{CF} = 22.0$ Hz), 63.0, 67.5, 121.9 ($^3J_{CF = 6.2 Hz}$), 124.7 ($^1J_{CF} = 244.0$ Hz), 129.5, 129.8, 129.8, 135.9, 138.2, 157.2, 174,0; ^{19}F NMR (282.4 MHz, acetone-d_6, 240 K) δ−88.2 (dd, $^2J_{FF} = 247.8$ Hz, $^3J_{HF} = 12.9$ Hz, 1F), −107.1 (m, $^2J_{FF} = 247.8$ Hz, 1F).

(+)-(3*R*)-3-[(*N*-Benzyloxycarbonyl)amino]-4,4,9,9,-tetrafluoro-3,4,5,8,9,10-hexahydro-2*H*-10-oxecinone (1d). This compound was obtained in 96% yield as a white solid when 10 mol % of the second-generation Grubbs catalyst **II** was used at 25 °C: $[\alpha]_D^{25}$ +7.05 (*c* 1.05, $CHCl_3$); ^1H NMR (600 MHz, $CDCl_3$) δ 2.7 (br s, 1H), 2.72 (br s, 1H), 3.16 (m, 1H), 3.18 (m, 1H), 4.35 (t, $J = 11.3$ Hz, 1H), 4.78 (br s, 1H), 5.05 (br s, 1H), 5.18 (d, $J = 12.4$ Hz, 1H), 5.24 (d, $J = 12.4$ Hz, 1H), 5.67 (br s, 1H), 5.75 (t, $J = 11.5$ Hz, 1H), 7.37 (m, 5H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 33.5 (t, $^2J_{CF} = 23.8$ Hz), 34.8 (t, $^2J_{CF} = 24.4$ Hz), 50.5 (t, $^2J_{CF} = 20.4$ Hz), 62.0, 68.0, 115.1 (t, $^1J_{CF} = 252.9$ Hz), 122.5 (t, $^1J_{CF} = 247.0$ Hz), 128.7, 128.8, 129.0, 135.8, 155.7, 161.6; ^{19}F NMR (282 MHz,

toluene-d_8) δ −99.7 (ddd, $^2J_{FF}$ = 248.2 Hz, J_{HF} = 36.4 Hz, J_{HF} = 13.7 Hz, 1F), −100.3 (d, $^2J_{FF}$ = 259.1 Hz, 1F), −109.0 (ddd, $^2J_{FF}$ = 259.1 Hz, J_{HF} = 33.0 Hz, J_{HF} = 12.5 Hz, 1F), −109.5 (dd, $^2J_{FF}$ = 248.2 Hz, J_{HF} = 23.1 Hz, 1F); HRMS calcd for (M^+) $C_{17}H_{17}F_4NO_4$ 375.1093, found 375.1072. The X-ray data for this compound can be found in the Supporting Information.

General Procedure for the Ring-Closing Metathesis of Compounds 20a,b: Synthesis of (*R*)-2a,b. A solution of the precursor (*R*)-**20** in dry dichloromethane (2×10^{-2} M) was introduced into a sealable pressure tube under N_2 atmosphere, followed by another solution of second-generation Grubbs catalyst **II** [(IMes)(PCy_3)Cl_2Ru=CHPh] in the concentrations indicated in the individual listings below. The tube was sealed and the reaction mixture was stirred at 60 °C until TLC indicated that the reaction had been completed. The solvents were then removed under reduced pressure, and the brown residue was purified by means of flash column chromatography [*n*-hexane/AcOEt (8:1)] to give the products as colorless oils.

(*R*)-Benzyl 3-(trifluoromethyl)-2,3,9,10-tetrahydro-10-oxo-5*H*-1,4-oxazecine-4(8*H*)-carboxylate (2a). This compound was obtained in 54% yield when 5 mol % of second-generation Grubbs catalyst **II** was used at 60 °C: $[\alpha]_D^{25}$ +7.4 (*c* 1.0, CCl_3); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.92 (m, 1H), 2.33 (m, 1H), 2.70 (m, 2H), 3.91−4.25 (m, 3H), 4.55 (d, *J* = 4.5 Hz, 1H), 5.14 (d, *J* = 4.5 Hz, 2H), 5.00−5.15 (m, 1H), 5.43 (dt, *J* = 4.8, 10.7 Hz, 1H), 5.67 (dt, *J* = 3.0, 10.7 Hz, 1H), 7.29 (s, 5H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 21.3, 34.5, 41.0, 53.3 (q, $^2J_{CF}$ = 31.0 Hz), 60.8, 67.5, 123.7 (q, $^1J_{CF}$ = 282.7 Hz), 126.9, 127.3, 127.4, 127.6, 128.5, 134.7, 155.9, 170.0; ^{19}F NMR ($CDCl_3$, 282 MHz) δ −79.9 (d, J_{FH} = 8.6 Hz, 3F); HRMS calcd for (M^+) $C_{17}H_{18}F_3NO_4$ 357.1131, found 357.1187.

(+)-(3*R*)-3-Trifluoromethyl-1-oxa-4-[(*N*-benzyloxycarbonyl)-aza]-8-cyclodecen-12-one (2b). This compound was obtained in 93% yield when 5 mol % of second-generation Grubbs catalyst **II** was used at 60 °C: $[\alpha]_D^{25}$ +17.9 (*c* 1.00, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.05−2.11 (m, 3H), 2.21−2.30 (m, 2H), 2.35−2.50 (m, 3H), 3.37 (m, 1H), 3.54 (m, 1H), 4.37 (dt, *J* = 1.2, 13.4 Hz, 2H), 5.07 (m, 1H), 5.19 (s, 2H), 5.33−5.49 (m, 2H), 7.40 (s, 5H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 22.4, 25.4, 28.6, 31.2, 34.8, 53.0, 60.6, 67.1, 120.4 (q, $^1J_{CF}$ = 288.9 Hz), 128.1, 128.4, 128.7, 132.4, 136.1, 157.5, 173.1; ^{19}F NMR ($CDCl_3$, 282 MHz) δ [(−70.2)−(−71.9)], (m, 3F); HRMS calcd for (M^+) $C_{19}H_{22}F_3NO_4$ 385.1480, found 385.1500.

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Supporting Information Available: Detailed experimental procedures and spectroscopic data for compounds **8a−d**, **10−17**, **18a,b**, **19a,b**, and **20a,b**, and X-ray data for compounds **1a** and **1d**. This material is available free of charge via the Internet at http://pubs.acs.org.

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