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A Convenient Synthesis of Substituted Pyrazolidines and Azaproline Derivatives through Highly Regio- and Diastereoselective Reduction of 2-Pyrazolines

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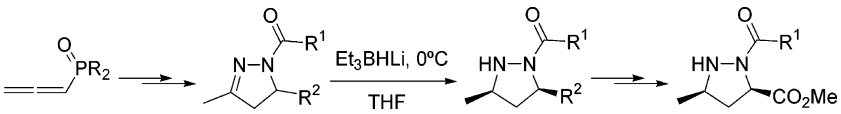

The synthesis of substituted *N*-acetyl- and *N*-aroyl-2-pyrazolines via intramolecular Michael addition of α,β-unsaturated hydrazones generated through olefination of phosphinyl and phosphonyl hydrazones with carbonyl compounds is reported. The regioselective reduction of the C−N double bond in these 2-pyrazolines using Superhydride (Et_3BHLi) gives pirazolidine derivatives with excellent levels of cis-diastereoselectivity. These 2-pyrazolines can also be obtained in one-pot reaction from allenes, hydrazides, and aldehydes; and pyrazolidines, after reduction, from allenes, hydrazides, and aldehydes. This synthetic route was developed to provide a new approach to substituted azaproline derivatives in a diastereoselective fashion.

Introduction

The development of new, rapid, and clean synthetic routes toward focused libraries of nitrogen-containing heterocycles is of great importance to both medicinal and synthetic chemists.[1] Consequently, the design and development of procedures for the generation of new heterocycles by means of multistep reactions is a matter of growing interest.[2] Pyrazole, pyrazoline **I**, and pyrazolidine **II** ring systems (Chart 1) are important heterocycles that are attracting increasing interest of many researchers,[3] not only in medicinal chemistry because of their antimicrobial,[4a] antibacterial,[4b] antipyretic,[4c] antidepressant,[4d,e] and anti-inflammatory[4f,g] activity, but also in material chemistry for their role in nanocrystal investigation[5a,b] or as brightening agents[5c] and in the construction of organic electroluminescence devices.[5d,e] Among these nitrogen-containing heterocyclic compounds with interesting applications, azaproline (azPro) **III** (Chart 1), aza-analogue of the cyclic amino acid proline, is of especial interest, and azaproline derivatives are important substrates in biologically important peptide sequences relevant to metallopeptidase activity[6] and in organocatalysis.[7] Recently, the impact of azaproline and its derivatives in stabilizing *cis*-amide bonds in selective bioactive peptides has been described.[8] For this reason, the development of new strategies for the

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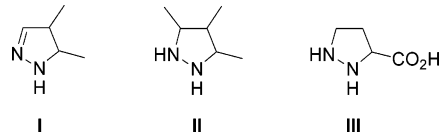
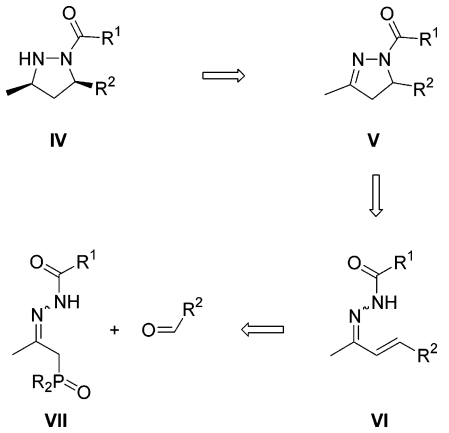
CHART 1. 2-Pyrazoline and Pyrazolidine Derivatives I−III



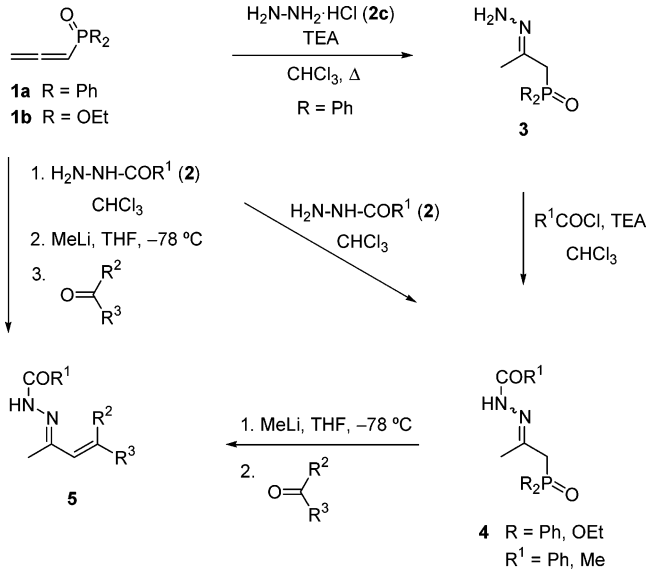
preparation of azaproline derivatives could open new alternatives for the preparation of azapeptides[9] and for organocatalysis.[7]

In this context, we are interested in the preparation of three-,[10] five-,[11] and six-membered[12] nitrogen-containing heterocycles, as well as the synthesis of new amino phosphorus derivatives[13] and their synthetic use for the construction of not only carbon−carbon double bond (C═C)[14] but also carbon−nitrogen double bond (C═N)[15] of functionalized acyclic compounds and heterocycles.[16] As part of our ongoing research programs in the area of nitrogen-containing heterocyclic compounds, we here describe an example of the regio- and diastereoselective reduction of 2-pyrazolines **V** to pyrazolidine derivatives **IV** including azPro derivatives **IV** ($R^2 = CO_2R$, Chart 2) as well as the highly regioselective preparation of new 1,3,5-trisubstituted 2-pyrazolines **V** via intramolecular Michael addition of α,β-unsaturated hydrazones **VI**, generated through olefination of phosphinyl and phosphonyl hydrazones **VII** with carbonyl compounds. The simplest method for preparation of unsaturated hydrazones involves the condensation of unsaturated carbonyl compounds with hydrazines (1,2-addition). However, in the case of ketones a mixture of products is mostly obtained because of the competitive Michael addition of the hydrazine to unsaturated ketones (1,4-addition).[17]

CHART 2. Retrosynthetic Pathway for the Preparation of Pyrazolidine Derivatives IV



SCHEME 1. Synthetic Approach to α,β-Unsaturated Hydrazones 5



Results and Discussion

As outlined in Scheme 1, the required functionalized phosphinyl and phosphonyl hydrazones **4** were easily prepared by

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TABLE 1. Preparation of α-Phosphorylated Hydrazones 3 and 4

entry	product	R	R^1	yield (%)[a] ([b])	*syn/anti* ratio[c]
1	**3a**	Ph		71	48/52
2	**4a**	Ph	Me	81 (80)	81/19 (77/23)[d]
3	**4b**	Ph	Ph	95 (85)	0/100 (0/100)[d]
4	**4c**	OEt	Ph	73	100/0

[a] Yield of isolated purified compounds **3** and **4** from phosphorylated allenes **1**. [b] Yield in parenthesis refers to yield of isolated purified compounds **4** from primary hydrazones **3**. [c] *Syn/anti* ratio was calculated by ^{31}P NMR on the crude reaction mixture. [d] *Syn/anti* ratio for **4a**,**b** prepared from primary hydrazone **3a**.

the reaction of allenic phosphine oxide **1a** (R = Ph) or phosphonate **1b** (R = OEt) with acethydrazide **2a** (R^1 = Me) or benzhydrazide **2b** (R^1 = Ph), in a way similar to that previously reported for simple hydrazines[18] or carbazates.[19] Thus, addition of acethydrazide **2a** or benzhydrazide **2b** to allene **1a** in refluxing chloroform led to the formation of *β*-hydrazono phosphine oxide **4a** and **4b**, respectively, in excellent yields (Scheme 1, Table 1, entries 2 and 3). These compounds were characterized by their spectroscopic data, which indicated that they were isolated as a mixture of *syn*- and *anti*-hydrazones in the case of compound **4a**, or as the *anti*-hydrazone, as determined by NOE experiments, in the case of compound **4b**. The process could be extended to allenes derived from phosphonate. In this case, allene **1b** (R = OEt) reacted with benzhydrazide **2b** (R^1 = Ph) in the absence of solvent, giving *β*-functionalized phosphonate **4c** (Scheme 1, Table 1, entry 4).

A different approach can also be used for the preparation of these phosphorylated hydrazones **4**, which were synthesized in two steps from allenes **1**. Addition of hydrazine monohydrochloride **2c**, in the presence of triethylamine, to allene **1a** in refuxing chloroform gave primary hydrazone **3a** (R = Ph) as a mixture of *syn*- and *anti*-isomers in good yield (Scheme 1, Table 1, entry 1). Functionalization of this primary hydrazone **3a** could be envisaged by treatment with acyl chlorides in the presence of a base. In this way, phosphorylated hydrazones **4a** and **4b** could be obtained in good yields after treatment of the primary phosphorylated hydrazone **3a** with acetyl or benzoyl chloride, respectively, in the presence of a base such as Et_3N (Scheme 1, Table 1, entries 2 and 3). The spectroscopic data of hydrazone **4b** indicated that, by using this methodology, this compound was again isolated as the *anti*-hydrazone **4b**. However, a mixture of *syn*- and *anti*-hydrazone **3a** was used as starting material for the preparation of **4b**, thus suggesting the presence of an equilibrium between the hydrazone−enehydrazine tautomeric forms.

α-Phosphorylated hydrazones **4a**−**c** could be suitable to efficiently achieve the homologation of hydrazones into their vinylogous compounds. Thus, treatment of hydrazones **4** with a base such as methyllithium (MeLi) at −78 °C, followed by addition of the corresponding carbonyl compound (Table 2), led to the formation of 1-azadienes **5** with high *E*-stereoselectivity of the carbon−carbon double bond formed and in excellent yields (Scheme 1). The structure of **5a**−**g** was inferred from spectroscopic as well as elemental analytical data. Thus, the

TABLE 2. Olefination Reaction of a Series of α-Phosphorylated Hydrazones 4

entry	product	R^1	R^2	R^3	yield (%)[a]
1	**5a**	Ph	H	Ph	95 (88)[b]
2	**5b**	Ph	H	*p*-Me-C_6H_4	94 [86][c]
3	**5c**	Ph	H	2-furyl	91
4	**5d**	Ph	H	^{i}Bu	93
5	**5e**	Ph	H	CO_2Et	81
6	**5f**	Ph	Ph	Ph	82
7	**5g**	Me	H	*p*-MeO-C_6H_4	85 (80)[b]

[a] Yield of isolated purified compounds **5** from hydrazones derived from phosphine oxides **4a**,**b** (R = Ph). [b] Yield in parenthesis refers to yield of isolated purified compounds **5** in a one-pot reaction from allene **1a**. [c] Yield in brackets refers to yield of isolated purified compounds **5** from hydrazones derived from phosphonate **4c** (R = OEt).

^1H NMR spectra of compounds **5** (R^2 = H) showed a vicinal $^3J_{HH}$ coupling constant in the range of 15.5 and 16.5 Hz between the vinylic protons of **5**, which is consistent with the *E*-configuration of the carbon−carbon double bond.[14d,e] The geometry of C−N double bond in compounds **5** was unambiguously determined by NOE experiments. Thus, an NOE (2.5%) was observed between the NH group of the hydrazone **5g** and the methyl group linked to the hydrazono moiety, suggesting an *anti*-configuration for the carbon−nitrogen double bond. The scope of the olefination reaction was not limited to aromatic (Table 2, entries 1, 2, and 7) and aliphatic aldehydes (Table 2, entry 4), since heteroaromatic aldehydes (Table 2, entry 3), ethyl glyoxalate (Table 2, entry 5), and ketones (Table 2, entry 6) could also be used. A Wadsworth−Emmons reaction of hydrazone **4c** derived from phosphonate was also achieved in almost the same yield as that obtained when hydrazone **4b** derived from phosphine oxide was used as starting material. It is noteworthy that the synthesis of α,*β*-unsaturated hydrazones **5** did not require the isolation and purification of phosphorylated hydrazones **4**. Similar overall yields were obtained in a one-pot reaction from allenes **1a** derived from phosphine oxide, when hydrazones **4**, obtained either by addition of acylhydrazides **2a**,**b** or by addition of hydrazine **2c** and subsequent reaction with acyl chlorides, after evaporation of the solvent, were directly treated with MeLi and subsequent addition of the carbonyl compound (Scheme 1).

Next, we studied the intramolecular Michael addition of conjugate hydrazones **5** for the preparation of 2-pyrazoline derivatives **6**. Formation of *N*-benzoyl-2-pyrazolines **6** (R^1 = Ph) took place by thermal treatment of α,*β*-unsaturated hydrazones **5** (R^1 = Ph) in refluxing toluene (method A, Table 3, entries 1, 2, and 6). It is importat to point out that the presence of a base (sodium methoxide, NaOMe) favored the intramolecular cyclization to give the 2-pyrazolines **6** with a considerable reduction in the reaction time (Table 3, entry 3). However, *N*-acetyl-α,*β*-unsaturated hydrazones **5** (R^1 = Me) did not react under thermal heating, and a base such as sodium methoxide and higher temperatures (refluxing DMF) were necessary (method B, Table 3, entry 8). The cyclizations of these α,*β*-unsaturated hydrazones **5** may take place through an intramolecular Michael addition of the hydrazone nitrogen to the carbon−carbon double bond. Unfortunately, α,*β*-unsaturated hydrazone **5e** (R^1 = Ph, R^2 = H, R^3 = CO_2Et), with a carboxylate group at the terminal carbon of the azadiene system, did not cyclize when using thermal conditions (method A), nor when a base and higher temperatures (method B) were used, and instead only either the starting material or decomposition products were obtained. However, similar overall yields were

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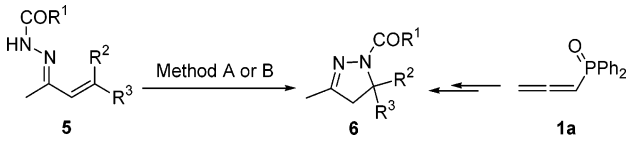
TABLE 3. Preparation of Substituted 2-Pyrazolines 6



5 6 1a

entry	product	method[a]	R^1	R^2	R^3	cyclization time (days)	yield (%)[b]
1	**6a**[20]	A	Ph	H	Ph	9	68
2	**6b**	A	Ph	H	*p*-Me-C_6H_4	9	81
3	**6c**	B	Ph	H	2-furyl	5	60
4	**6c**	C	Ph	H	2-furyl	5	64
5	**6c**[21]	D	Ph	H	2-furyl	5	61
6	**6d**	A	Ph	H	^{i}Bu	10	38
7	**6e**	B	Ph	Ph	Ph	6	70
8	**6f**	B	Me	H	*p*-MeO-C_6H_4	4	62

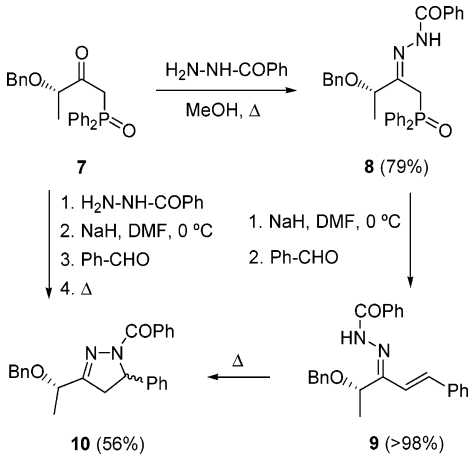
[a] Method A: Toluene, reflux. Method B: MeONa, DMF, reflux. Method C: One-pot reaction from hydrazone **4b** using NaH in refluxing DMF. Method D: Same conditions as method C in a one-pot reaction from allene **1a**. [b] Yield of isolated purified compounds **6** from α,β-unsaturated hydrazones **5**.

obtained for the preparation of the 2-pyrazoline **6c** in a one-pot reaction from hydrazone **4b** (method C, Table 3, entry 4), or from allene **1a** (method D, Table 3, entry 5) when hydrazone **4b** was first obtained (vide supra), which was then treated with 2.2 equiv of sodium hydride (NaH) in DMF followed by the addition of 2-furaldehyde and thermal treatment.

Since the pioneering work on the synthesis of 2-pyrazolines by Fischer and Knövenagel in the late nineteenth century,[22] a large number of methods of preparation of 2-pyrazolines have been developed,[3] mainly involving carbonyl derivatives and hydrazines. However, using this approach a mixture of regioisomers is usually formed. Series of specially substituted representatives have rarely been prepared using other synthetic approaches such as the 1,3-dipolar cycloaddition of diazoalkanes or nitrile imines with alkynes or alkenes.[23] As far as we know, the strategy reported here describes, for the first time, the selective preparation of 2-pyrazolines by means of a one-pot reaction from allenes, hydrazides, and carbonyl compounds without obtaining mixtures of regioisomers.

We also explored the effect of the presence of an optically active group at C-3 of the α,β-unsaturated hydrazone **VI** (vide supra, Chart 2) in the intramolecular Michael addition. The preparation of 1-azadienes **9** derived from lactate (Scheme 2) was performed in several steps. Initially, we synthesized optically pure β-ketophosphine oxide **7** by addition of (2*S*)-ethyl lactate benzyl ester to lithium salts derived from methylphosphine oxide by means of a modified procedure of the Shapiro method.[24] Condensation reaction of β-ketophosphine oxide **7** with benzhydrazide in refluxing methanol led to the formation of *syn*-hydrazone **8** in good yield (Scheme 2). The *syn*-configuration of the C−N double bond in the hydrazone **8** was confirmed by NOE experiments. When the hydrazonic proton was irradiated, there was no NOE effect with the methyl group or the benzoxy group, and a NOE effect (3.1%) was observed between the hydrazonic proton and the methylene group of hydrazone **8**. α,β-Unsaturated hydrazone **9** was

SCHEME 2. Preparation of Optically Active 2-Pyrazoline 10



prepared in almost quantitative yields by treatment of starting chiral hydrazone **8** with 2.5 equiv of NaH at 0 °C, followed by addition of benzaldehyde (Scheme 2). The ^{1}H NMR spectra of compound **9** showed a vicinal $^3J_{HH}$ coupling constant of 16.9 Hz between the vinylic protons, establishing the *E*-stereochemistry of the carbon−carbon double bond, while the *anti*-configuration of the C−N double bond was confirmed by NOE experiments, since an NOE (2.2%) was observed between the hydrazonic proton and the methyl group of hydrazone **9**. Thermal treatment of the α,β-unsaturated hydrazone **9** led to the formation of 2-pyrazoline **10** in moderate yield, as a 1:1 mixture of nonseparable diastereoisomers (Scheme 2). These results suggest that the chiral group of the α,β-unsaturated hydrazone **9** is too distant from the reaction center with a negligible influence on it. 2-Pyrazoline **10** could be also directly prepared in a one-pot reaction from β-ketophosphonate **7** when hydrazone **8** was initially synthesized by condensation reaction with hydrazide **2b** and then this compound **8** was treated with 2.2 equiv of sodium hydride (NaH) in DMF followed by the addition of benzaldehyde and thermal treatment.

Taking into account the importance of the pyrazolidine ring system in medicinal and synthetic organic chemistry, we then explored the regioselective carbon−nitrogen double bond reduction of the *N*-acyl-2-pyrazolines **V** to access the corresponding pyrazolidines **IV** (vide supra, Chart 2). To this end, several attempts using different reducing systems such as $NaBH_4$/MeOH or $NaBH_4$/TFA for the reduction of the C−N double bond in 2-pyrazolines **6** were unsuccessful. The best results in the C−N double bond reduction of **6** were achieved by using Superhydride (Et_3BHLi) in THF at 0 °C, which furnished the pyrazolidines **12** in good yields, exclusively as a sole diastereoisomer *cis*-**12**, which could be isolated by chromatographic separation (Scheme 3, Table 4).

The structures of **12a**−**e** were characterized from their spectroscopic as well as elemental analytical data. Thus, the ^{1}H NMR spectra of compounds **12c** showed an absorption at δ_H 1.26 ppm as a well-resolved doublet with coupling constant $^3J_{HH} = 6.1$ Hz for the methyl group bonded to the pyrazolidine ring. Two different protons corresponding to the methylene proton of the ring system appear at δ_H 1.94 ppm ($^2J_{HH} = 12.7$ Hz, $^3J_{HH} = 7.9$ and 10.1 Hz) for H-4_{trans} (relative stereochemistry with H-3 and H-5) and δ_H 2.66 ppm ($^2J_{HH} = 12.7$ Hz, $^3J_{HH} =$ 6.3 and 8.5 Hz) for H-4_{cis} (relative stereochemistry with H-3 and H-5). The stereochemistry of **12** was assigned on the basis of conventional ^{1}H and ^{13}C NMR data as well as NOE

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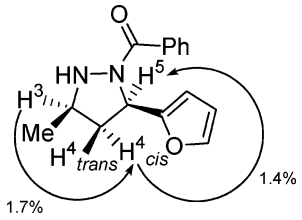

FIGURE 1. NOE observed for pyrazolidine **12c**.

SCHEME 3. Stereoselective Preparation of Pyrazolidine Derivatives 12

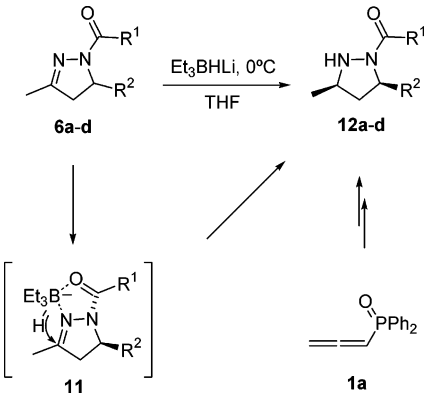

TABLE 4. Pyrazolidines 12 Prepared through Regioselective Reduction of 2-Pyrazolines 6

entry	product	R^1	R^2	yield (%)[a]
1	**12a**[26]	Ph	Ph	80
2	**12b**	Ph	*p*-Me-C_6H_4	83
3	**12c**	Ph	2-furyl	73 (67)[b]
4	**12d**	Ph	^{i}Bu	67
5	**12e**	Me	*p*-MeO-C_6H_4	60

[a] Yield of isolated purified pyrazolidines **12** from pyrazolines **6**. [b] Yield of isolated purified pyrazolidines **12** in a one-pot reaction from allene **1a**.

experiments. The 3,5-*cis*-relationship of H-3 and H-5 in the ring of pyrazolidine **12c** was evident since an NOE was observed between H-3 and H-4_{cis} (1.7%) (*cis*-relative stereochemistry) and between H-4_{cis} and H-5 (1.4%) (Figure 1). Conversely, a very small NOE was observed between H-3 and H-4_{trans} (0.28%). Likewise, an NOE was observed between H-4_{trans} and the methyl group at C-3 (1.2%), while this proton (H-4_{trans}) did not show an NOE with the hydrogen at C-5 (*trans*-relationship between these protons). These results suggest a *cis* relative stereochemistry between H-3 and H-5. The coupling constants are also consistent with those reported for other pyrazolidine derivatives.[25] A pentagonal intermediate **11** where the Superhydride may coordinate with the oxygen atom of the *N*-acyl moiety and the nitrogen atom (N-2) of the pyrazoline could explain the selective attack of the hydride by the underside of the carbon−nitrogen double bond. Thus, the formation of the *cis*-pyrazolidine **12** can be fully understood considering that the hydride attacks from the opposite side of the R^2 substituent, taking into account that the *N*-acyl group at N-1 and R^2 should adopt a *trans*-configuration because of a steric hindrance.

The scope of the selective reduction was not limited to aromatic aldehydes (Table 4, entries 1, 2, and 5) since heteroaromatic aldehydes (Table 4, entry 3) and aliphatic aldehydes (Table 4, entry 4) could also be used. It is noteworthy that similar overall yields were obtained for the preparation of the pyrazolidine **12c** (Table 4, entry 3) in a one-pot reaction from allene **1a** when 2-pyrazoline **6c** was first obtained (vide supra) and subsequent reduction with Superhydride (Et_3BHLi) in THF at 0 °C. As far as we know, the strategy reported here is the first description of the synthesis of pyrazolidines containing *cis*-substituents at the 3-position (methyl group) and 5-position (aryl or heteroaryl groups) from 2-pyrazolines by means of a one-pot reaction from allenes, hydrazides, and carbonyl compounds and subsequent reduction.

The incorporation of azPro, the nitrogen analogue of the amino acid proline where the α-carbon is replaced with a nitrogen atom, into biologically active peptides has, in some cases, led to peptidomimetics with enhanced activity or metabolic stability.[27] Peptides containing azPro were shown to stabilize the *cis*-amide conformer[8] for the acyl-azPro bond and prefer type VI *β*-turns both in crystals[28] and in organic solvents.[29] A series of azPro dipeptides with various *N*-substituents were also prepared as potent inhibitors of two proline-specific serine proteases: dipeptidyl peptidase IV and prolyl oligopeptidase,[30] while several FKBP12 ligands containing azPro derivatives were synthesized, and their neuroprotective effects were evaluated in vitro and in vivo.[31] The synthetic potential of this methodology (vide supra) can be applied to the preparation of azPro derivatives **IV** ($R^2 = CO_2R$) (vide supra, Chart 2) if pyrazolidine **12e** ($R = CO_2Et$) by **12** ($R^2 = CO_2Et$) was available. However, as reported before, the 2-pyrazoline **6** ($R^2 = H$, $R^3 = CO_2R$) containing a carboxylate group at C-5 is not accessible through intramolecular Michael addition of the starting α,*β*-unsaturated hydrazone **5e** (vide supra). Nevertheless, a straightforward alternative synthetic route to azaproline derivatives can be designed by using 2-pyrazoline **6c** with a furyl ring at C-5, keeping in mind that the furan ring is a synthetic equivalent of the carboxylate group.[32−34]

Finally, the oxidation process of the furyl ring in **12c** was explored for the preparation of azPro derivatives. However, to

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(32) The synthetic equivalence of a furan ring system and a carboxylate group has been reported since the furan can be oxidized by ozonolysis[33] or through the use of ruthenium reagents[34] and converted into a carboxylate group.

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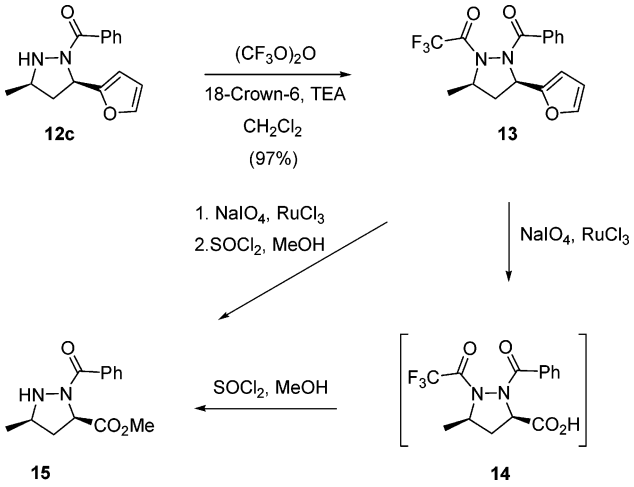
SCHEME 4. Synthesis of Azaproline Derivative 15



avoid either secondary products or the reversal to the starting 2-pyrazolines in the oxidation process, it was previously necessary to protect the N-2 of the pyrazolidine ring. Thus, N−H protection of pyrazolidine **12c** as *N*-trifluoroacetyl-protected derivatives[35] was performed by treatment with trifluoroacetic anhydride leading to *N*,*N*′-diacylated pyrazolidine **13** in excellent yields. azPro derivative **15** could be obtained in 33% yield from pyrazolidine **13** when this compound was treated with the oxidizing agent ($NaIO_4/RuCl_3$) and subsequent esterification by using thionyl chloride in methanol. In this process, the formation of the amino acid azPro **14** with a concomitant deprotection of the *N*-trifluoroacetyl group at N-2 (Scheme 4) could explain the formation of compound **15**. Azaprolines without an alkyl group at the 3-position have been prepared.[36] However, as far as we know, this strategy affords the synthesis of 5-methyl azaproline derivatives for the first time and with the *cis*-configuration between the methyl group (5-position) and the carboxylate ester moiety (3-position).

Conclusion

In conclusion, an efficient procedure for the synthesis of 2-pyrazolines **6** from unsaturated hydrazones was reported. The selective reduction of the carbon−nitrogen double bond of these heterocycles afforded only 3,5-*cis*-disubstituted pyrazolidines **12** in a stereoselective fashion. 2-Pyrazolines **6** can also be prepared in a one-pot reaction from very simple reagents such as allenes **1**, hydrazides **2**, and carbonyl compounds, and similarly pyrazolidines **12** were obtained from allenes **1**, hydrazides **2**, and carbonyl compounds followed by reduction with Superhydride. This strategy has been applied for the preparation of a new 3,5-cis- disubstituted azPro derivative **15**. 2-Pyrazolines, pyrazolidines, and azaproline derivatives are important synthons in organic synthesis for the preparation of biologically active compounds of interest to medicinal chemistry.[3−5,8,9]

(35) This protecting group can be easily removed by a weak basic treatment.

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Experimental Section

General Methods. Reagent and solvent purification, workup procedures, and analyses were performed in general as described in the Supporting Information.

General Procedure for the Preparation of *anti*- and *syn*-[2-(Diphenylphosphinoyl)-1-methylethylidene] Hydrazine (3a). To a stirred solution of phosphorylated allene **1a** (2.40 g, 10 mmol) in dry chloroform (60 mL) were added hydrazine monohydrochloride (0.82 g, 12 mmol) and triethylamine (2.11 mL, 15 mmol) under a nitrogen atmosphere. Then, the mixture was stirred and refluxed for 48 h. The crude reaction mixture was washed with water (3 × 15 mL), and the aqueous phase was extracted with CH_2Cl_2 (2 × 10 mL). The organic phase was dried over $MgSO_4$, the solvent was evaporated under vacuum, and the crude product was precipitated with diethyl ether and recrystallized from a mixture of hexanes/CH_2Cl_2 to afford **3a** (1.93 g, 71%) as a white solid: mp 164−166 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.75−7.21 (m, 10H), 5.89 (bs, 2H), 4.87 (bs, 2H), 3.38 (d, 2H, $^2J_{PH}$ = 14.5, anti), 3.27 (d, 2H, $^2J_{PH}$ =14.0 Hz, syn), 1.78 and 1.46 (s, 3H, anti and syn); ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.4 (syn), 143.2 (anti), 133.2, 132.3, 132.3, 131.9, 131.8, 131.7, 131.0, 130.9, 130.8, 130.7, 130.6, 128.9, 128.7, 128.6, 128.6, 128.5, 128.4, 128.3, 40.9 (d, $^1J_{PC}$ = 67.3 Hz, anti), 33.8 (d, $^1J_{PC}$ = 65.1 Hz, syn), 25.2 (syn), 15.3 (anti); ^{31}P NMR (120 MHz, $CDCl_3$) δ 30.9 (anti), 29.5 (syn); IR (KBr) 3381, 3342, 3058, 2942, 1630, 1437, 1186, 1124; MS (EI) *m*/*z* 272 (M^+, 13). Anal. Calcd for $C_{15}H_{17}N_2OP$: C, 66.17; H, 6.29; N, 10.29. Found C, 65.94; H, 6.32; N, 10.25.

General Procedure for the Preparation of Functionalized Hydrazones Derived from Phosphine Oxides and Phosphonate (4). Method A: To a stirred solution of phosphorylated allene **1a** or **1b** (10 mmol) in dry chloroform (50 mL) was added the corresponding hydrazide (12 mmol) under a nitrogen atmosphere. Then, the mixture was stirred and heated at reflux for 16−24 h. The solvent was evaporated under vacuum, and the crude product was precipitated with diethyl ether and recrystallized from a mixture of hexanes/CH_2Cl_2 (for β-hydrazones **4a**,**b** derived from phosphine oxides); while β-hydrazone **4c** derived from phosphonate was purified by flash chromatography (silica gel). Method B: A mixture of allene derived from phosphonate **1b** (1.76 g,10 mmol) and the corresponding hydrazide (12 mmol) under a nitrogen atmosphere was stirred and heated at 65 °C, without solvent for 16−24 h. The crude product was purified by flash chromatography (silica gel). Method C: To a 0 °C stirred solution of hydrazone **3a** (0.27 g, 1 mmol) in dry chloroform (8 mL) triethylamine (0.28 mL, 2 mmol) was added under a nitrogen atmosphere. After 30 min at 0 °C, a solution of the corresponding acyl chloride (1.2 mmol) in dry chloroform (2 mL) was added dropwise, and the mixture was stirred at room temperature for 6 h. The crude reaction mixture was washed with water (3 × 3 mL), and the aqueous phase was extracted with CH_2Cl_2 (2 × 3 mL). The organic phase was dried over $MgSO_4$, the solvent was evaporated under vacuum, and the crude product was precipitated with diethyl ether and recrystallized from a mixture of hexanes/CH_2Cl_2.

***anti*-Benzoic Acid [2-Diphenylphosphinoyl-1-methylethylidene] Hydrazide (4b).** The title compound (3.57 g, 95%) obtained as a white solid from allene **1a** (2.40 g, 10 mmol) and benzhydrazide (1.67 g, 12 mmol) as described in the general procedure (method A). The title compound (0.32 g, 85%) was also obtained from hydrazone **3a** (0.27 g, 1 mmol) and benzoyl chloride (140 μL, 1.2 mmol) as described in the general procedure (method C). The crude product was purified by precipitation with diethyl ether and recrystallization from a mixture of hexanes/CH_2Cl_2: mp 238−239 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 12.15 (bs, 1H), 8.11−7.37 (m, 15H), 3.43 (d, $^2J_{PH}$ = 14.8 Hz, 2H), 1.68 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.2, 151.0, 133.2, 133.0, 132.1, 131.6, 131.0, 130.8, 129.5, 129.2, 129.0, 128.5, 127.9, 36.9 (d, $^1J_{PC}$ = 66.4 Hz), 26.3; ^{31}P NMR (120 MHz, $CDCl_3$) δ 33.0; IR (KBr) 3198, 2939, 1686, 1537, 1284, 1165; MS (CI) *m*/*z* 377 (M^+ + 1, 100). Anal.

Calcd for $C_{22}H_{21}N_2O_2P$: C, 70.20; H, 5.62; N, 7.44. Found C, 70.42; H, 5.60; N, 7.46.

General Procedure for the Preparation of α,β-Unsaturated Hydrazones (5). Method A: To a −78 °C stirred solution of α-phosphorylated hydrazone **4** (5 mmol) in THF (80 mL) was added a solution of MeLi (6.6 mL, 10.5 mmol) under a nitrogen atmosphere. The mixture was stirred at the same temperature for 1 h, and the corresponding carbonyl compound (5.5 mmol) in THF (5 mL) was then added dropwise. The reaction mixture was stirred for 16 h and allowed to stand from −78 °C to room temperature. The solvent was evaporated under vacuum, and the crude mixture was diluted with CH_2Cl_2 (30 mL) and washed with water (2 × 10 mL), and the aqueous phase was extracted with CH_2Cl_2. The organic phase was dried over $MgSO_4$ and evaporated under vacuum. The crude product was purified by flash chromatography (silica gel, AcOEt/hexanes, 1:9). Method B (one-pot reaction from allene **1a**): To a stirred solution of phosphorylated allene **1a** (1.2 g, 5 mmol) in dry chloroform (25 mL) was added the corresponding hydrazide (6 mmol) under a nitrogen atmosphere. Then, the mixture was stirred and heated at reflux for 16 to 24 h, and the solvent was evaporated under vacuum. To a −78 °C stirred solution of the crude α-phosphorylated hydrazone **4** in THF (80 mL) was added a solution of MeLi (6.6 mL, 10.5 mmol) under a nitrogen atmosphere. The mixture was stirred at the same temperature for 1 h, and the corresponding carbonyl compound (5.5 mmol) in THF (5 mL) was then added dropwise. The reaction mixture was stirred for 16 h and allowed to stand from −78 °C to room temperature. The solvent was evaporated under vacuum, and the crude mixture was diluted with CH_2Cl_2 (30 mL) and washed with water (2 × 10 mL), and the aqueous phase was extracted with CH_2Cl_2. The organic phase was dried over $MgSO_4$ and evaporated under vacuum. The crude product was purified by flash chromatography (silica gel, AcOEt/hexanes, 1:9).

Furan-2-ylbuten-3-one-*N*-benzoylhydrazone (5c). The title compound (1.16 g, 91%) was obtained from α-phosphorylated hydrazone **4b** (1.88 g, 5 mmol) and 2-furaldehyde (0.46 mL, 5.5 mmol) as described in the general procedure. Mp 132−133 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.88 (bs, 1H), 7.81−7.37 (m, 7H), 6.71 (d, $^3J_{HH}$ = 16.6 Hz, 1H), 6.52−6.32 (m, 2H), 2.06 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.8, 152.2, 144.1, 143.1, 133.3, 131.7, 128.5, 127.1, 121.8, 112.3, 111.8, 110.4, 10.9; IR (KBr) 3310, 3118, 1646, 1513, 1480; MS (EI) *m*/*z* 254 (M^+, 7). Anal. Calcd for $C_{15}H_{14}N_2O_2$: C, 70.85; H, 5.55; N, 11.02. Found C, 70.66; H, 5.57; N, 11.06.

Intramolecular Cyclization Reaction of α,β-Unsaturated Hydrazones (5). Synthesis of Substituted 2-Pyrazolines (6). Method A: A stirred solution of α,β-unsaturated hydrazone **5** (1 mmol) in dry toluene (5 mL) was refluxed under a nitrogen atmosphere for 9 to 10 days. The solvent was evaporated under vacuum, and the crude product was purified by flash chromatography (silica gel, AcOEt/hexanes, 1:9) to give pyrazolines **6**. Method B: To a 0 °C stirred suspension of sodium methoxide (0.065 g, 1.2 mmol) in DMF (5 mL) was added dropwise and under a nitrogen atmosphere a solution of α,β-unsaturated hydrazone **5** (1 mmol) in DMF (3 mL). The reaction mixture was allowed to stand from 0 °C to room temperature and refluxed for 4−6 days. Then, the crude mixture was extracted with Et_2O (10 mL) and washed with a saturated solution of ammonium chloride (3 × 4 mL). The organic phase was dried over $MgSO_4$ and evaporated under vacuum. The crude pyrazolines **6** were purified by flash chromatography (silica gel, AcOEt/hexanes, 1:9). Method C (one-pot reaction from hydrazone **4b**): To a 0 °C stirred suspension of sodium hydride (0.053 g, 2.2 mmol) in DMF (4 mL) was added dropwise and under a nitrogen atmosphere a solution of α-phosphorylated hydrazone **4b** (1 mmol) in DMF (2 mL). The mixture was stirred at the same temperature for 1 h, and the corresponding aldehyde (1.1 mmol) in DMF (1 mL) was then added dropwise. The reaction mixture was allowed to stand from 0 °C to room temperature for 16 h and refluxed for 5 days. Then, the crude mixture was extracted with Et_2O (10 mL) and washed with a saturated solution of ammonium chloride (3 × 4 mL). The organic phase was dried over $MgSO_4$ and evaporated under vacuum. The crude pyrazolines **6** were purified by flash chromatography (silica gel, AcOEt/hexanes, 1:9). Method D (one-pot reaction from allene **1a**): To a stirred solution of phosphorylated allene **1a** (1 mmol) in dry chloroform (5 mL) was added the corresponding hydrazide (1.2 mmol) under a nitrogen atmosphere. Then, the mixture was stirred and heated at reflux for 16 h. The solvent was evaporated under vacuum, and a solution of crude product **4b** in DMF (2 mL) was added dropwise and under a nitrogen atmosphere to a 0 °C stirred suspension of sodium hydride (0.053 g, 2.2 mmol) in DMF (4 mL). The mixture was stirred at the same temperature for 1 h, and the corresponding aldehyde (1.1 mmol) in DMF (1 mL) was then added dropwise. The reaction mixture was allowed to stand from 0 °C to room temperature for 16 h and refluxed for 5 days. Then, the crude mixture was extracted with Et_2O (10 mL) and washed with a saturated solution of ammonium chloride (3 × 4 mL). The organic phase was dried over $MgSO_4$ and evaporated under vacuum. The crude pyrazolines **6** were purified by flash chromatography (silica gel, AcOEt/hexanes, 1:9).

1-Benzoyl-3-methyl-5-furan-2-yl-4,5-dihydro-1*H*-pyrazole (6c). The title compound (0.15 g, 60%) was obtained from α,β-unsaturated hydrazone **5c** (0.25 g, 1 mmol) as described in the general procedure (method B). The title compound (0.16 g, 64%) was also obtained from α-phosphorylated hydrazone **4b** (0.38 g, 1 mmol) and 2-furaldehyde (91 μL, 1.1 mmol) as described in the general procedure (method C). The title compound (0.15 g, 61%) was also obtained from allene **1a** (0.24 g, 1 mmol), hydrazide (0.17 g, 1.2 mmol), and 2-furaldehyde (91 μL, 1.1 mmol) as described in the general procedure (method D). Mp 76−77 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.73 (d, $^3J_{HH}$ = 6.6 Hz, 2H), 7.32−7.18 (m, 4H), 6.22−6.17 (m, 2H), 5.61 (dd, $^3J_{HH}$ = 5.4 Hz, $^3J_{HH}$ = 11.4 Hz, 1H), 3.10 (dd, $^2J_{HH}$ = 18.0 Hz, $^3J_{HH}$ = 11.4 Hz, 1H), 2.89 (dd, $^2J_{HH}$ = 18.0 Hz, $^3J_{HH}$ = 5.4 Hz, 1H), 1.93 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.4, 156.3, 152.1, 141.9, 134.4, 130.8, 129.8, 127.6, 110.5, 107.6, 54.1, 41.4, 16.1; IR (KBr) 2926, 1739, 1633, 1454, 1215; MS (EI) *m*/*z* 254 (M^+, 3). Anal. Calcd for $C_{15}H_{14}N_2O_2$: C, 70.85; H, 5.55; N, 11.02. Found C, 71.04; H, 5.52; N, 10.99.

General Procedure for the Reduction of Pyrazolines (6). Synthesis of Pyrazolidines (12). Method A: To a 0 °C stirred solution of pyrazolines **6** (0.5 mmol) in THF (15 mL) was added dropwise a 1 M solution in THF of lithium triethylborohydride (1.25 mL, 1.25 mmol) in THF (2.5 mL) under a nitrogen atmosphere. The reaction mixture was stirred at 0 °C for 1 h and quenched with a 2 M solution of NaOH (5 mL). The solvent was evaporated under vacuum and diluted with CH_2Cl_2 (15 mL), and the organic phase was washed with 2 M NaOH (3 × 5 mL). The organic phase was dried over $MgSO_4$ and evaporated under vacuum. The crude pyrazolidines **12** were purified by flash chromatography (silica gel, AcOEt/hexanes, 10:90). Method B (one-pot reaction from allene **1a**): To a stirred solution of phosphorylated allene **1a** (0.12 g, 0.5 mmol) in dry chloroform (2.5 mL) was added the corresponding hydrazide (0.6 mmol) under a nitrogen atmosphere. Then, the mixture was stirred and heated at reflux for 16 h, and the solvent was evaporated under vacuum. A solution of crude product **4b** in DMF (2 mL) was added dropwise and under a nitrogen atmosphere to a 0 °C stirred suspension of sodium hydride (0.027 g, 1.1 mmol) in DMF (2 mL). The mixture was stirred at the same temperature for 1 h, and the corresponding aldehyde (0.5 mmol) in DMF (1 mL) was then added dropwise. To a 0 °C stirred solution of crude pyrazolines **6** in THF (15 mL) was added dropwise a 1 M solution in THF of lithium triethylborohydride (1.25 mL, 1.25 mmol) in THF (2.5 mL) under a nitrogen atmosphere. The reaction mixture was stirred at 0 °C for 1 h and quenched with a 2 M solution of NaOH (5 mL). The solvent was evaporated under vacuum and diluted with CH_2Cl_2 (15 mL), and the organic phase was washed with 2 M NaOH (3 × 5 mL). The organic phase was dried over

$MgSO_4$ and evaporated under vacuum. The crude pyrazolidines **12** were purified by flash chromatography (silica gel, AcOEt/hexanes, 10:90).

***cis*-1-Benzoyl-5-furan-2-yl-3-methylpyrazolidine (12c).** The title compound (93 mg, 73%) was obtained from pyrazoline **6c** (127 mg, 0.5 mmol) as described in the general procedure (method A). The title compound (85 mg, 67%) was also obtained from allene **1a** (0.12 g, 0.5 mmol), hydrazide (85 mg, 0.6 mmol), and 2-furaldehyde (45 μL, 0.6 mmol) as described in the general procedure (method B). Mp 123−124 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.72−7.32 (m, 6H), 6.32−6.31 (m, 2H), 5.66 (bs, 1H), 4.01 (bs, 1H), 3.18 (bs, 1H), 2.66 (ddd, $^2J_{HH}$ = 12.7 Hz, $^3J_{HH}$ = 6.3 Hz, $^3J_{HH}$ = 8.5 Hz, 1H), 1.94 (ddd, $^2J_{HH}$ = 12.7 Hz, $^3J_{HH}$ = 7.9 Hz, $^3J_{HH}$ = 10.1 Hz, 1H), 1.26 (d, $^3J_{HH}$ = 6.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.0, 153.9, 141.98, 135.0, 130.3, 129.0, 127.4, 110.4, 107.1, 56.5, 55.3, 40.9, 16.7; IR (KBr) 3211, 2965, 1619, 1507, 1387; MS (EI) *m*/*z* 256 (M^+, 51). Anal. Calcd for $C_{15}H_{16}N_2O_2$: C, 70.29; H, 6.29; N, 10.93. Found C, 70.52; H, 6.31; N, 10.97.

General Procedure and Spectral Data of *cis*-1-Benzoyl-2-trifluoroacetyl-5-furan-2-yl-3-methylpyrazolidine (13). To a stirred solution of pyrazolidine **12c** (128 mg, 0.5 mmol) in CH_2Cl_2 (2 mL) were added dropwise and under a nitrogen atmosphere Et_3N (84 μL, 0.6 mmol), trifluoroacetic anhydride (83 μL, 0.6 mmol), and 18-crown-6 (159 mg, 0.6 mmol). The reaction mixture was stirred at room temperature for 2 h. Then, the reaction mixture was washed with H_2O (2 × 1 mL) and extracted with CH_2Cl_2 (2 × 1 mL). The organic phase was dried over $MgSO_4$ and evaporated under vacuum. The crude pyrazolidine were purified by flash chromatography (silica gel, AcOEt/hexanes, 10:90) to afford compound **13** (171 mg, 97%). Mp 79−81 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.89−7.45 (m, 6H), 6.41 (d, $^3J_{HH}$ = 7.1 Hz, 2H), 5.15 (d, $^3J_{HH}$ = 8.2 Hz, 1H), 4.43 (bs, 1H), 2.56−2.49 (m, 1H), 2.26−2.20 (m, 1H), 1.45 (d, $^3J_{HH}$ = 6.4 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.8, 154.7 (q, $^2J_{CF}$ = 38.2 Hz), 150.6, 142.6, 133.0, 132.8, 131.5, 131.1, 128.8, 128.6, 128.5, 127.2, 115.7 (q, $^1J_{CF}$ = 288.1 Hz), 110.3, 107.7, 58.8, 54.4, 36.5, 18.0; IR (KBr) 3409, 3151, 2979, 1719, 1460, 1202; MS (EI) *m*/*z* 352 (M^+, 2). Anal. Calcd for $C_{17}H_{15}F_3N_2O_3$: C, 57.96; H, 4.29; N, 7.95. Found C, 58.07; H, 4.30; N, 7.91.

General Procedure and Spectral Data of Methyl 2-Benzoyl-5-methylpyrazolidine-3-carboxylate (15). To a 0 °C stirred solution of pyrazolidine **13** (88 mg, 0.25 mmol) in a mixture of acetonitrile (0.5 mL) and CCl_4 (0.5 mL) were added dropwise $NaIO_4$ (0.81 g, 3.75 mmol) and $RuCl_3 \cdot H_2O$ (1 mg) under a nitrogen atmosphere. After 2 h at room temperature, the crude mixture was washed with H_2O (2 × 2 mL) and extracted with CH_2Cl_2 (2 × 2 mL). The organic phase was dried over $MgSO_4$ and evaporated under vacuum. The crude compound was dissolved in MeOH (1 mL), and thionyl chloride (37 μL, 0.5 mmol) was added. The reaction mixture was refluxed for 20 min, and the solvent was evaporated under vacuum. The crude product was purified by flash chromatography (silica gel, AcOEt/hexanes, 50:50) to obtain (21 mg, 33%) **15**. Mp 87−88 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.81−7.35 (m, 5H), 4.95 (t, $^3J_{HH}$ = 8.2 Hz, 1H), 4.10 (bs, 1H), 3.78 (s, 3H), 3.23 (bs, 1H), 2.70 (ddd, $^2J_{HH}$ = 12.6 Hz, $^3J_{HH}$ = 6.1 Hz, $^3J_{HH}$ = 8.9 Hz, 1H), 1.65 (ddd, $^2J_{HH}$ = 12.6 Hz, $^3J_{HH}$ = 8.2 Hz, $^3J_{HH}$ = 10.1 Hz, 1H), 1.23 (d, $^3J_{HH}$ = 6.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.6, 168.7, 134.2, 130.5, 129.0, 127.5, 59.6, 56.3, 52.3, 40.3, 16.4; IR (KBr) 3217, 2932, 1752, 1454, 1208; MS (EI) *m*/*z* 248 (M^+, 100). Anal. Calcd for $C_{13}H_{16}N_2O_3$: C, 62.89; H, 6.50; N, 11.28. Found C, 62.75; H, 6.52; N, 11.25.

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Supporting Information Available: Full characterization data, procedures for the synthesis of all new compounds, and ^{1}H and ^{13}C spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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