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Short Enantioselective Syntheses of *trans*-5-Alkylprolines from New Functionalized Amino Alcohols

Jeanne Alladoum, Sylvain Roland, Emmanuel Vrancken, Pierre Mangeney,* and Catherine Kadouri-Puchot*

Université Pierre et Marie Curie-Paris 6, Laboratoire de Chimie Organique UMR 7611, Institut de Chimie Moléculaire FR 2769, 4 place Jussieu, case courrier 47, 75005 Paris, France

cathy.kadouri-puchot@upmc.fr; pierre.mangeney@upmc.fr

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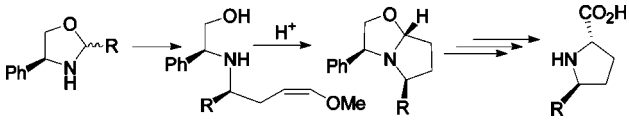

Amino alcohols, having an enol ether function, cyclized in acidic medium to give quantitatively diastereosomerically pure bicyclic compounds that were transformed in five steps in enantiopure *trans*-5-alkylproline derivatives.

Among the 20 proteinogenic amino acids, proline with its cyclic nature and its secondary amine plays a specific role in peptides and proteins secondary structure formation.[1] Due to their major role in chemistry and biology, this α-amino acid and its derivatives remain synthetic targets of great interest. The ever growing number of reactions involving these compounds as chiral organocatalysts[2,3] or scaffolds for the construction of peptidomimetics[4] is a good reason for developing new methods for their preparation.[5] In these fields, 5-alkylprolines **1** bearing a bulky substituent constitute a particularly interesting class of compounds.[6] As a matter of fact, such amino acids possessing alkyl substituents have emerged as an important tool for governing peptide conformation; thus, the stereoselective synthesis of substituted proline derivatives remains a challenging task.

In the course of our research on the enantioselective synthesis of substituted aminoacids from functionalized β-amino-alcohols,[7] we have recently developed a diastereoselective synthesis of enantiomerically enriched enol ethers **3**, by addition of the lithium derivative of the methylallylether to oxazolidines (or imines) **2** derived from phenylglycinol.[8] According as that **3** are direct precursors of **4**, we decided to study the possibility of using these compounds for the development of straightforward syntheses of enantiopure *trans*-5-alkyl-proline derivatives as shown in Scheme 1. As a matter of fact, among the several routes already described for the selective synthesis of trans 2,5-substituted pyrrolidines **5**, which can be potential precursors of 5-alkylprolines **1**, we turned our attention on their preparations reported by Higashiyama[9] and Katritzky[10] by addition of Grignard reagents to bicyclic oxazolidines **4**.[11]

As expected, the synthesis of the β-aminoalcohols **3a**−**d** from oxazolidines **2a**−**c** and imine **2d**, and their subsequent cycliza-

(1) For a review, see: (a) Yaron, A.; Naider, F. *Crit. Rev. Biochem. Mol. Biol.* **1993**, *28*, 31. For some selected examples, see: (b) Halab, L.; Gosselin, F.; Lubell, W. D. *Biopolymers* **2000**, *55*, 101–122. (c) Beausoleil, E.; Lubell, W. D. *J. Am. Chem. Soc.* **1996**, *118*, 12902–12908. (d) Che, Y.; Marshall, G. R. *Biopolymers* **2006**, *81*, 392–406. (e) Williams, K. A.; Deber, C. M. *Biochemistry* **1991**, *30*, 8919. (f) Wallén, E. A. A.; Christiaans, J. A. M.; Saarinen, T. J.; Jarho, E. M.; Forsberg, M. M.; Venäläinen, J. I.; Männistö, P. T.; Gynther, J. *Bioorg. Med. Chem.* **2003**, *11*, 3611–3619.

(2) For some selected reviews, see: (a) List, B. *Tetrahedron* **2002**, *58*, 5573–5590. (b) List, B. *Acc. Chem. Res.* **2004**, *37*, 548–557. (c) Dalko, P. I.; Moisan, L. *Angew. Chem., Int. Ed.* **2004**, *43*, 5138–5175. (d) List, B. *Chem. Commun.* **2006**, *819*, 824.

(3) For some selected recent examples of proline organocatalysis, see: (a) Rodríguez, B.; Bruckmann, A.; Bolm, C. *Chem.*−*Eur. J.* **2007**, *13*, 4710–4722. (b) Mitchell, C. E. T.; Brenner, S. E.; García-Fortanet, J.; Ley, S. V. *Org. Biomol. Chem.* **2006**, *4*, 2039–2049. (c) Puleo, G. L.; Masi, M.; Iuliano, A. *Tetrahedron: Asymmetry* **2007**, *18*, 1364–1375. (d) Chi, Y.; Gellman, S. H. *J. Am. Chem. Soc.* **2006**, *128*, 6804–6805. (e) Tang, Z.; Yang, Z.-H.; Chen, X.-H.; Cun, L.-F.; Mi, A.-Q.; Jiang, Y.-Z.; Gong, L.-Z. *J. Am. Chem. Soc.* **2005**, *127*, 9285–9289. (f) Kotrusz, P.; Alemayehu, S.; Toma, S.; Schmalz, H.-G.; Adler, A. *Eur. J. Org. Chem.* **2005**, *4904*, 4911. (g) Wang, X.-J.; Zhao, Y.; Liu, J.-T. *Org. Lett.* **2007**, *9*, 1343–1345. (h) Maya, V.; Raj, M.; Singh, V. K. *Org. Lett.* **2007**, *9*, 2593–2595. (i) Enders, D.; Gasperi, T. *Chem. Commun.* **2007**, *88*, 90. (j) Chen, J.-R.; An, X.-L.; Zhu, X.-Y.; Wang, X.-F.; Xiao, W.-J. *J. Org. Chem.* **2008**, *73*, 6006–6009.

(4) For some examples, see: (a) Aubry, C.; Oulyadi, H.; Dutheuil, G.; Leprince, J.; Vaudry, H.; Pannecoucke, X.; Quirion, J.-C. *J. Peptide Sci.* **2006**, *12*, 154–160. (b) An, S. S. A.; Lester, C. C.; Peng, J.-L.; Li, Y.-J.; Rothwarf, D. M.; Welker, E.; Thannhauser, T. W.; Zhang, L. S.; Tam, J. P.; Scheraga, H. A. *J. Am. Chem. Soc.* **1999**, *121*, 11558–11566. (c) Trabocchi, A.; Rolla, M.; Menchi, G.; Gurna, A. *Tetrahedron Lett.* **2005**, *46*, 7813–7816. (d) Tong, Y.; Fobian, Y. M.; Wu, M.; Boyd, N. D.; Moeller, K. D. *J. Org. Chem.* **2000**, *65*, 2484–2493. (e) Arasappan, A.; Chen, K. X.; Njooroge, G.; Parekh, T., N.; Girijavallabhan, V. *J. Org. Chem.* **2002**, *67*, 3923–3926. (f) Genin, M. J.; Mishra, R. K.; Jonhson, R. L. *J. Med. Chem.* **1993**, *36*, 3481–3483. (g) Duan, S.; Moeller, K. D. *Tetrahedron* **2001**, *57*, 6407–6415. (h) Belvisi, L.; Colombo, L.; Colombo, M.; Di Giacomo, M.; Manzoni, L.; Vodopivec, B.; Scolastico, C. *Tetrahedron* **2001**, *57*, 6463–6473. (i) Bittermann, H.; Gmeiner, P. *J. Org. Chem.* **2006**, *71*, 97–102.

(5) For review on the synthesis of substituted prolines, see: Karoyan, P.; Sagan, S.; Lequin, O.; Quancard, J.; Lavielle, S.; Chassaing, G. *Targets Heterocycl. Syst.* **2004**, *8*, 216–273.

(6) For the synthesis of 5-alkyl proline derivatives, see: (a) Manfré, F.; Kern, J.-M.; Biellmann, J.-F. *J. Org. Chem.* **1992**, *57*, 2060–2065. (b) Halab, L.; Bélec, L.; Lubell, W. D. *Tetrahedron* **2001**, *57*, 6349–6446. (c) Beausoleil, E.; L'Archevêque, B.; Bélec, L.; Atfani, M.; Lubell, W. D. *J. Org. Chem.* **1996**, *61*, 9447–9454. (d) Pyne, S. G.; Javidan, A.; Skelton, B. W.; White, A. H. *Tetrahedron* **1995**, *51*, 5157–5168. (e) Davis, F. A.; Zhang, H.; Seung, H. L. *Org. Lett.* **2001**, *3*, 759–762. (f) Brun, M.-P.; Martin, A.-S.; Garbay, C.; Bishoff, L. *Tetrahedron Lett.* **2003**, *44*, 7011–7013. (g) Van Esseveldt, B. C. J.; Vervoot, P. W. H.; van Delft, F. L.; Rutjes, F. P. J. T. *J. Org. Chem.* **2005**, *70*, 1791–1795. (h) Davis, F. A.; Fang, T.; Goswani, R. *Org. Lett.* **2002**, *4*, 1599–1602. (i) Shiosaki, K.; Rapoport, H. *J. Org. Chem.* **1985**, *50*, 1229–1239. (j) Hussaini, S. R.; Moloney, M. G. *Tetrahedron Lett.* **2004**, *45*, 1125–1127. (k) Gu, Y. G.; Xu, Y.; Krueger, A. C.; Madigan, D.; Sham, H. L. *Tetrahedron Lett.* **2002**, *43*, 955–957. (l) Wallén, E. A. A.; Christiaans, J. A. M.; Gynther, J.; Vepsäläinen, J. *Tetrahedron Lett.* **2003**, *44*, 2081–2082. (m) Wallèn, E. A. A.; Christiaans, J. A. M.; Saarinen, T. J.; Jarho, E. M.; Forsberg, M. M.; Venäläinen, J. I.; Männistö, P. T.; Gynther, J. *Bioorg. Med. Chem.* **2003**, *11*, 3611–3619. (n) Davis, F. A.; Yang, B.; Deng, J. *J. Org. Chem.* **2003**, *68*, 5147–5152. (o) Agami, C.; Comesse, S.; Guesné, S.; Kadouri-Puchot, C.; Martinon, L. *Synlett* **2003**, *1058*, 1060.

(7) (a) Agami, C.; Comesse, S.; Kadouri-Puchot, C. *J. Org. Chem.* **2002**, *67*, 1496–1500. (b) Agami, C.; Comesse, S.; Kadouri-Puchot, C. *J. Org. Chem.* **2002**, *67*, 2424–2428. (c) Guesné, S.; Comesse, S.; Kadouri-Puchot, C. *Lett Org. Chem.* **2006**, *3*, 318–319.

(8) Alladoum, J.; Roland, S.; Vrancken, E.; Kadouri-Puchot, C.; Mangeney, P. *Synlett* **2006**, *1855*, 1858.

(9) Higashiyama, K.; Inoue, H.; Takahashi, H. *Tetrahedron* **1994**, *50*, 1083–1092.

(10) Katritzky, A. R.; Cui, X.-L.; Yang, B.; Steel, P. J. *J. Org. Chem.* **1999**, *64*, 1979–1985.

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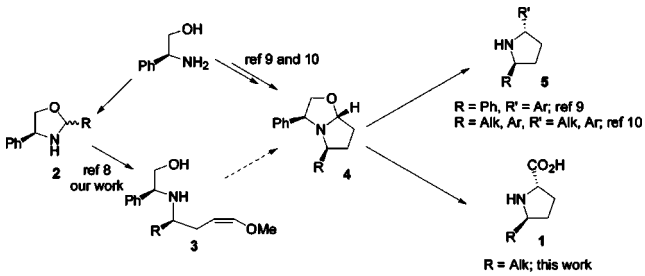
SCHEME 1



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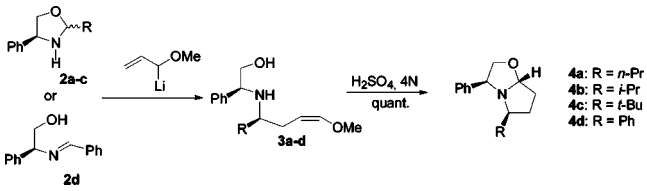

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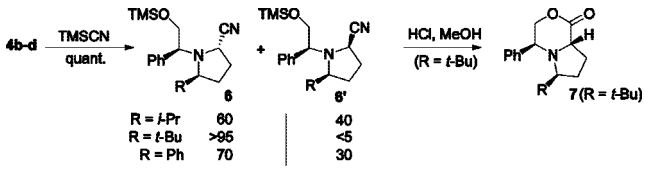


tion by H_2SO_4 4N gave spontaneously and quantitatively the bicyclic oxazolidines **4a**−**d** in a totally diastereoselective manner, as shown in Scheme 2.[12]

With the aim of synthesizing proline derivatives, we first tested the addition of trimethylsilylcyanide (Scheme 3).[13,14] Whereas these reactions occurred quantitatively to give the corresponding cyanopyrrolidines, only the *tert*-butyl derivative **4c** afforded the diastereoisomerically pure cyanopyrrolidine **6**. In contrast, the *i*-Pr and the phenyl derivatives, respectively **4b** and **4d**, were found to be less selective and gave an inseparable mixture of two diastereoisomers **6** and **6′**.

So, to propose a more general route toward 5-alkyl prolines, we investigated the reactivity of vinyl Grignard reagent. As reported above, the addition of Grignard reagents on bicyclic compounds **4** has already been described. An excellent stereocontrol was observed by Higashiyama[9] by addition of aryl magnesium reagents to **4** (R = Aryl). In contrast, the selectivity obtained by Katritzky[10] in additions of several Grignard reagents to compounds **4** (when R = allyl) was found to be dependent on the nature of this reagent. We decided therefore to reexamine this reaction on the more sterically hindered **4** (R = *i*-Pr and *t*-Bu). Additionally, the possibility of using lithium derivatives was also tested (Scheme 4).

As shown in Table 1, the selectivity was found to be insensitive to the nature of the organometallic (R′Li or R′MgX) reagents (Table 1, entries 1−7) as well as the steric hindrance

SCHEME 4

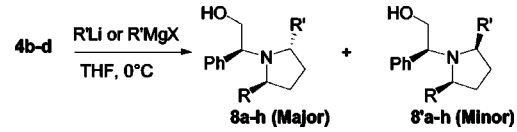


TABLE 1. Selectivity of Compounds

exp	SM	R	R′	Pdt	yield (%)	dr[a] **8/8′**
1	**4b**	*i*-Pr	MeLi	**8a**	67	>95/5
2	**4b**	*i*-Pr	MeMgBr	**8a**	75	>95/5
3	**4b**	*i*-Pr	*n*-BuLi	**8b**	72	>95/5
4	**4b**	*i*-Pr	*n*-BuMgCl	**8b**	quant	>95/5
5	**4c**	*t*-Bu	MeMgBr	**8c**	68	>95/5
6	**4c**	*t*-Bu	*n*-BuLi	**8d**	48	>90/10
7	**4c**	*t*-Bu	*n*-BuMgCl	**8d**	quant	>90/10
8	**4d**	Ph	PhMgCl	**8e**	89	>90/10
9	**4b**	*i*-Pr	C_2H_3MgBr	**8f**	quant	>95/5
10	**4c**	*t*-Bu	C_2H_3MgBr	**8g**	quant	>95/5
11	**4d**	Ph	C_2H_3MgBr	**8h**	75	90/10

[a] Diastereoisomeric ratios were determined by ^1H NMR analysis of the crude mixture.

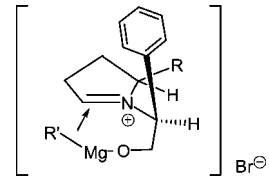


FIGURE 1. Attack of the Grignard reagent on the iminium intermediate.

of the R (*i*-Pr or *t*-Bu) substituent. In all cases, an excellent stereocontrol was observed resulting in the formation of the same diastereomer with organolithium or Grignard reagents. However, the best yields of 5-alkyl pyrrolidines **8** (R′ = alk) were achieved when Grignard reagents were used (see entries 2, 4, 5, and 7). Therefore, only the addition of vinyl Grignard reagent was attempted giving rise to the totally stereoselective formation of **8**, which was obtained in excellent yield (entries 9, 10). Additionally, addition of this reagent to compound **4d** was also studied (entry 11). In this case, a decrease in selectivity and yield was observed. The configuration of the new stereogenic center in **8** was confirmed by comparison of the NMR data of pyrrolidine **8e** and those reported in the literature[9] and, a posteriori, by comparison of NMR data of the compound **7a** (R = *i*-Pr) obtained from **8f** (see below). As reported, these additions were found to occur with a *trans*-stereoselectivity relatively to the R substituent, such stereocontrol being attributed to the nucleophilic attack of the organometallic reagent on the less hindered face of an iminium intermediate resulting of an opening of the oxazolidine ring (Figure 1).

The next step in the synthesis of the proline derivatives was the oxidation of the double bond of the 2-vinylpyrrolidines **8f**−**g**. Initial attempts were performed onto the hydrochloride of **8f**, to protect the nitrogen atom from oxidation. But, on ozonolysis (O_3, then Me_2S or NEt_3[15]), this hydrochloride gave mainly the bicyclic compound **4b** accompanied by only a small amount of the desired hemiacetal **9a** (Scheme 5). The unexpected formation of **4b** can be explained as a result of a nitrogen assisted elimination reaction occurred in the intermediate ozonide, upon treatment with triethylamine, with the loss of vinyl group and

(11) For the synthesis of 2,5-pyrrolidines by opening bicyclic oxazolidines, see also: (a) Huang, P. Q.; Arsenyadis, S.; Husson, H.-P. *Tetrahedron Lett.* **1987**, *28*, 547–550. (b) Arsenyadis, S.; Huang, P. Q.; Piveteau, D.; Husson, H.-P. *Tetrahedron* **1988**, *44*, 2457–2470. (c) Katritzky, A. R.; Cui, X.-L.; Yang, B.; Steel, P. J. *Tetrahedron Lett.* **1998**, *39*, 1697–1700.

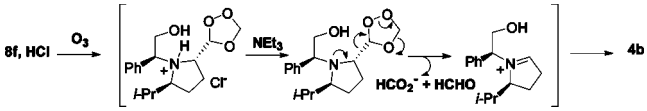
(12) The stereochemistry of compound **4d** was determined by comparing its NMR spectra and $[\alpha]_D$ with those reported in the literature: ref 10.

(13) Warmuth, R.; Munsch, T. E.; Stalker, R. A.; Li, B.; Beatty, A. *Tetrahedron* **2001**, *57*, 6383–6397.

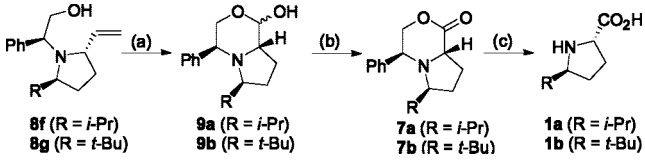
(14) Chakraborty, T. K.; Hussain, K. A.; Reddy, G. V. *Tetrahedron* **1995**, *51*, 9179–9190.

(15) Hon, Y.-S.; Lin, S.-W.; Chen, Y.-J. *Tetrahedron* **1995**, *51*, 5019–5034.

SCHEME 5



SCHEME 6[a]



[a] Reaction conditions: (a) O_3, TFA/CH_2Cl_2, −78 °C, then DMS; then NaOH 5N, (b) TPAP, NMO, CH_3CN, rt, 80% for **7a** and 92% for **7b** (two steps); (c) H_2, MeOH/H_2O/TFA, $Pd(OH)_2$, 95% for **1a**, 73% for **1b**.

the concomitant departure of formic acid and formaldehyde. Hemiacetals **9a**−**b** were obtained quantitatively when ozonolysis was performed in a mixture of TFA/methylene chloride.[16] Oxidation of **9a**−**b** with TPAP[17] afforded lactones **7a**−**b** in a diastereoisomerically pure form (Scheme 6). The stereochemistry of lactone **7a** was determined by an X-ray radiocrystallographic analysis and found to be 4*S*,6*S*,8a*S*.[18] Structural data of lactone **7b** (R = *t*-Bu) revealed it to be identical to those obtained after hydrolysis of the cyano derivative **6** (R = *t*-Bu) in Scheme 3. This correlation showed that the addition of the nitrile ion occurred also on the less hindered face of the iminium ion obtained by opening of the oxazolidine ring.

Finally, hydrogenolysis of the two lactones **7a** and **7b** with Pearlman's catalyst in the presence of one equivalent of TFA led to the enantiomerically pure 5-alkyl proline derivatives **1a**−**b**.[19] It is noteworthy that all the steps involved in the transformation of the vinyl pyrrolidines **8** into the proline derivatives **1** need no purification of the intermediates.

In conclusion, we have shown that the β-amino alcohols **3**, easily obtained by diastereoselective addition of methoxypropene-derived lithium reagent onto oxazolidines (or imines) of phenylglycinol, are valuable synthons for the stereoselective synthesis of bicyclic intermediates that are precursors of diastereoisomerically pure 5-alkylated pyrrolidines. Finally, in three steps from the 5-vinyl-pyrrolidines **8**, we have synthesized 5-alkylated proline derivatives **1** in an enantiomerically pure form.

Experimental Section

General Procedure for the Syntheses of Bicyclic Compounds (4a−d). A solution of amino alcohol **3a**−**d** (10 mmol) in ether (40 mL) was washed several times with a solution of sulfuric acid 4N (40 mL) until the entire product passed in the aqueous layer. This aqueous layer was then separated from the organic one, neutralized with a solution of NaOH 2 M, and extracted with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$, and the solvent was evaporated to give corresponding bicyclic compounds **4a**−**d** in quantitative yield.

[3*S*,5*R*,7a*R*]-3-Phenyl-5-propylhexahydropyrrolo[2,1-b]oxazole (4a). Oil. (Et_2O/Pentane: 10/90). Yield: quant. $[\alpha]_D^{20}$: +45 (*c* 1.5, $CHCl_3$). ^1H NMR ($CDCl_3$): 7.42−7.24 (m, 5H), 5.04 (dd, *J* = 5.4, 2.4 Hz, 1H), 4.39 (dd, *J* = 8.3, 7.1 Hz, 1H), 4.20 (t, *J* = 6.7 Hz, 1H), 3.65 (dd, *J* = 8.3, 6.3 Hz, 1H), 2.92−2.89 (m, 1H), 2.24−2.08 (m, 2H), 1.97−1.91 (m, 1H), 1.60−1.51 (m, 2H), 1.34−1.26 (m, 3H), 0.89 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR ($CDCl_3$): 143.1, 128.4, 126.9, 126.5, 98.9, 72.8, 68.0, 66.6, 38.4, 30.6, 30.1, 19.7, 14.4. Anal. Calcd for $C_{15}H_{21}NO$: C, 77.88; H, 9.15; N, 6.05. Found: C, 77.26; H, 8.89; N, 5.85.

[3*S*,5*S*,7a*R*]-5-Isopropyl-3-phenyl-hexahydro-pyrrolo[2,1-b]oxazole (4b). Oil. (Et_2O/Pentane: 10/90). Yield: quant. $[\alpha]_D^{20}$: + 58 (*c* 1.2, $CHCl_3$). ^1H NMR ($CDCl_3$): 7.42−7.24 (m, 5H), 5.03 (dd, *J* = 5.2, 1.9 Hz, 1H), 4.35 (dd, *J* = 8.3, 7.1 Hz, 1H), 4.22 (t, *J* = 6.4 Hz, 1H), 3.63 (dd, *J* = 8.3, 6.1 Hz, 1H), 2.83 (dd, *J* = 7.1, 5.6 Hz, 1H), 2.20−2.12 (m, 1H), 2.04−1.91 (m, 2H), 1.74−1.61 (m, 2H), 0.88 (d, *J* = 6.8 Hz, 3H), 0.86 (d, *J* = 6.6 Hz, 3H). ^{13}C NMR ($CDCl_3$): 143.4, 128.4, 126.8, 126.6, 99.2, 72.9, 72.6, 69.1, 32.0, 30.2, 25.7, 19.9, 17.6. HRMS: Calcd for $C_{15}H_{21}NO$ ($M + H^+$) *m*/*z* = 232.16959, obsd *m*/*z* = 232.16942.

[3*S*,5*S*,7a*R*]-5-*tert*-Butyl-3-phenyl-hexahydro-pyrrolo[2,1-b]oxazole (4c). Oil. (Et_2O/Pentane: 10/90). Yield: quant. $[\alpha]_D^{20}$: +44 (*c* 1.2, $CHCl_3$). ^1H NMR ($CDCl_3$): 7.42−7.24 (m, 5H), 4.96 (dd, *J* = 3.3, 1.8 Hz, 1H), 4.33−4.24 (m, 2H), 3.63 (dd, *J* = 7.8, 4.5 Hz, 1H), 2.75−2.72 (m, 1H), 2.11−1.99 (m, 3H), 1.76−1.71 (m, 1H), 0.83 (s, 9H). ^{13}C NMR ($CDCl_3$): 143.7, 128.3, 126.6, 126.5, 99.5, 77.2, 72.3, 71.3, 35.4, 31.0, 26.5, 24.4. IR ($CHCl_3$): 3448, 2951, 1603, 1360, 1037, 700 cm^{-1}. Anal. Calcd for $C_{16}H_{23}NO$: C, 78.32; H, 9.45; N, 6.52. Found: C, 78.01; H, 9.54; N, 6.44.

[3*S*,5*S*,7a*R*]-3,5-Diphenylhexahydropyrrolo[2,1-b]oxazole (4d). Solid. (Et_2O/Pentane: 10/90). Yield: quant. Mp: 47−49 °C. $[\alpha]_D^{20}$: +38 (*c* 0.6, EtOH). ^1H NMR ($CDCl_3$): 7.41−7.19 (m, 10H), 5.18 (dd, *J* = 5.6, 2.0 Hz, 1H), 4.42 (dd, *J* = 8.3, 7.1 Hz, 1H), 4.22 (t, *J* = 6.1 Hz, 1H), 4.05 (dd, *J* = 9.7, 5.7 Hz, 1H), 3.75 (dd, *J* = 8.3, 5.3 Hz, 1H), 2.60−2.27 (m, 2H), 2.06−1.98 (m, 1H), 1.87−1.77 (m, 1H). ^{13}C NMR ($CDCl_3$): 143.1, 142.8, 128.4, 128.3, 127.1, 127.0, 126.8, 126.4, 98.3, 72.0, 69.5, 66.6, 35.2, 30.4. Anal. Calcd for $C_{18}H_{19}NO$: C, 81.47; H, 7.22; N, 5.28. Found: C, 81.34; H, 7.35; N, 5.27.

General Procedure for the Synthesis of the Pyrrolidines (8f−h). To a solution of bicycle **4** (4.3 mmol) in THF (30 mL) at 0 °C was added a solution of vinyl Grignard reagent in THF (13 mmol). The reaction was then allowed to warm up and was stirred for 2 h at room temperature. When the reaction was complete, the solution was hydrolyzed carefully with NH_4Cl. The aqueous layer was extracted with Et_2O, and the organic layers were dried over $MgSO_4$ and evaporated to give the corresponding vinylated pyrrolidine.

[2*S*,2(2*S*,5*S*)]-2-(2-Isopropyl-5-vinylpyrrolidin-1-yl)2-phenylethanol (8f). Oil. Yield: quant. $[\alpha]_D^{20}$: +130 (*c* 1, $CHCl_3$). ^1H NMR ($CDCl_3$): 7.30−7.15 (m, 5H), 5.85 (ddd, *J* = 17, 10, 9.4 Hz, 1H), 5.13−5.03 (m, 2H), 4.04 (dd, *J* = 7.7, 6.5 Hz, 1H), 3.79 (dd, *J* = 10.2, 7.7, 1H), 3.71−3.62 (m, 2H), 2.88 (dt, *J* = 9.25, 3.5 Hz, 1H), 1.89−1.75 (m, 1H), 1.70−1.36 (m, 4H), 0.71 (d, *J* = 6.75 Hz, 3H), 0.61 (d, *J* = 6.75 Hz, 3H). ^{13}C NMR ($CDCl_3$): 140.7, 139.5, 129.7, 128.3, 127.5, 115.8, 67.3, 63.5, 62.8, 31.6, 31.1, 23.6, 20.3, 15.4. HRMS Calcd for $C_{17}H_{25}NO$ ($M + H^+$) *m*/*z* = 260.20089, obsd *m*/*z* = 260.20053.

[2*S*,2(2*S*,5*S*)]-2-(2-*tert*-Butyl-5-vinylpyrrolidin-1-yl)-2-phenylethanol (8g). Solid. Yield: quant. Mp: 69 °C. $[\alpha]_D^{20}$: +32 (*c* 1.7, $CHCl_3$). ^1H NMR ($CDCl_3$): 7.24−7.19 (m, 5H), 6.17 (ddd, *J* = 16.6, 10.5, 5.5 Hz, 1H), 5.20 (dt, *J* = 10.5, 1.6 Hz, 1H), 5.08 (dt, *J* = 17.2, 1.6 Hz, 1H), 4.14 (dd, *J* = 9.75, 5.5 Hz, 1H), 3.75 (t, *J* = 10 Hz, 1H), 3.68−3.62 (m, 1H), 3.50 (dd, *J* = 10.25, 5.5 Hz, 1H), 3.02 (dd, *J* = 8.9, 4.1 Hz, 1H), 1.71−1.60 (m, 1H), 1.48−1.05 (m, 3H), 0.85 (s, 9H). ^{13}C NMR ($CDCl_3$): 140.4, 138.6, 129.3, 128.2, 127.5, 116.8, 67.9, 66.9, 62.5, 62.3, 35.5, 30.6, 27.7, 25.5. IR ($CHCl_3$): 3416, 2958, 1470, 1215, 1027, 756 cm^{-1}. HRMS Calcd for $C_{18}H_{27}NO$ ($M + H^+$) *m*/*z* = 274.21654, obsd *m*/*z* = 274.21627.

(16) (a) Carretero, J. C.; Arrayàs, R. G. *J. Org. Chem.* **1998**, *63*, 2993–3005. (b) Dieter, R. K.; Watson, R. *Tetrahedron Lett.* **2002**, *43*, 7725–7728.

(17) Dauban, P.; Dubois, L.; Dau, M. E. T.; Dodd, R. H. *J. Org. Chem.* **1995**, *60*, 2035–2043.

(18) Atomic coordinates, bond lengths and angles, and thermal parameters of compound **7a** have been deposited at the Cambridge Crystallographical Data Center with the deposition number CCDC 661332.

(19) The *trans* stereochemistry of the proline derivatives was ascertained on the basis of the NMR analysis: the ^1H NMR spectra of compounds **1a**−**b** showed an apparent triplet for the α proton, a feature for the *trans* diastereoisomer (see ref 6c).

[2*S*,(2*S*,5*S*)]-2-Phenyl-2-(2-phenyl-5-vinylpyrrolidin-1-yl)ethanol (8h). Oil (Et_2O/pentane: 15/85). Yield: 75%. $[\alpha]_D^{20}$: +37 (*c* 1.4, $CHCl_3$). ^1H NMR ($CDCl_3$): 7.17−6.96 (m, 10H), 5.88 (td, *J* = 17, 9, 8 Hz), 5.16−5.04 (m, 2H), 4.03−3.88 (m, 3H), 3.52 (d, *J* = 7 Hz, 2H), 2.35−2.17 (m, 3H), 1.63−1.49 (m, 2H). ^{13}C NMR ($CDCl_3$): 47.7, 140.6, 138.7, 129.9, 128.3, 127.9, 127.4, 126.8, 126.6, 116.0, 67.0, 63.8, 63.2, 62.9, 34.1, 31.3. Anal. Calcd for $C_{20}H_{23}NO$: C, 81.87; H, 7.90; N, 4.77. Found: C, 81.48; H, 7.97; N, 4.44.

General Procedure for the Synthesis of Lactones (7a) and (7b). A solution of pyrrolidine **8f** or **8g** (0.74 mmol) in TFA (20 mL) and CH_2Cl_2 (10 mL) was ozonolyzed at −20 °C for 1 h. Then DMS (7.4 mmol) was added and the solution was stirred at room temperature overnight. The solvent and TFA were evaporated. The residue was dissolved in CH_2Cl_2 (20 mL), and washed with a solution of NaOH 2M. The organic layer was dried over $MgSO_4$ and the solvent was evaporated to give the hemiketal as an oil which was used without purification in the oxidation step. The hemiketal (0.85 mmol) was dissolved in acetonitrile (20 mL). Molecular sieves (500 mg) was introduced and then, TPAP (0.025 mmol) and N-methylmorpholine (1.7 mmol) were rapidly added to the solution. The reaction was stirred for about 2−3 h. When the reaction was complete, the solvent was evaporated and the crude product was dissolved in AcOEt and filtered through a short pad of silica gel. The solvent was evaporated to give the corresponding lactones.

[4*S*,6*S*,8a*S*]-6-Isopropyl-4-phenylhexahydropyrrolo[2,1-c][1,4]-oxazin-1-one (7a). Solid. Yield: 80%. Mp: 132 °C. $[\alpha]_D^{20}$: −76 (*c* 1.0, $CHCl_3$).^1H NMR ($CDCl_3$): 7.36−7.19 (m, 5H), 4.17−4.13 (m, 2H), 4.06 (dd, *J* = 7.75, 3.75 Hz, 1H), 3.81 (dd, *J* = 9.4, 6.1 Hz, 1H), 2.70−2.62 (m, 1H), 2.38−2.27 (m, 1H), 2.07−1.92 (m, 1H), 1.78−1.63 (m, 1H), 1.57−1.51 (m, 1H), 1.50−1.29 (m, 1H), 0.63 (d, *J* = 7 Hz, 3H), 0.53 (d, *J* = 6.75 Hz, 3H). ^{13}C NMR ($CDCl_3$): 173.3, 139.8, 128.7, 128.1, 127.6, 72.7, 71.3, 63.6, 59.8, 29.8, 25.8, 22.9, 20.2, 15.1. Anal. Calcd for $C_{16}H_{21}NO_2$: C, 74.10; H, 8.16; N, 5.40. Found: C, 73.55; H, 8.37; N, 5.35.

[4*S*,6*S*,8a*S*]-6-*tert*-Butyl-4-phenylhexahydropyrrolo[2,1-c]-[1,4]oxazin-1-one (7b). Solid. Yield: 92%. Mp: 103−104 °C. $[\alpha]_D^{20}$: −22 (*c* 1, $CHCl_3$). ^1H NMR ($CDCl_3$): 7.36−7.19 (m, 5H), 4.40 (dd, *J* = 11.75, 4.5 Hz, 1H), 4.26 (dd, *J* = 11.75, 7.75 Hz, 1H), 4.09−3.91 (m, 2H), 2.72 (dd, *J* = 8.75, 4.75 Hz, 1H), 2.25−1.85 (m, 3H), 1.71−1.61 (m, 1H), 0.66 (s, 9H).^{13}C NMR ($CDCl_3$): 172.3, 139.8, 128.6, 127.6, 127.4, 75.3, 69.8, 62.1, 61.0, 35.4, 28.8, 26.9, 25.7. IR ($CHCl_3$): 3020, 1741, 1215, 1170, 756 cm^{-1}. Anal. Calcd for $C_{17}H_{23}NO_2$: C, 74.69; H, 8.48; N, 5.12. Found: C, 74.56; H, 8.85; N, 4.77.

Lactone **7b** was also obtained from the cyano derivative **6** (R = *t*-Bu) by treatment with a solution of HCl (1 M in Et_2O, 10 equiv) in MeOH during 1 night. A saturated solution of $NaHCO_3$ was added and the mixture was extracted with dichloromethane. The organic layers were dried over $MgSO_4$, then evaporated to give the crude product. Flash chromatography afforded the lactone **7b** (yield: 80%), which was totally identical to the compound obtained previously.

General Procedure for Hydrogenolysis of Bicyclic Lactones. Compounds **7a** or **7b** (0.15 mmol) were dissolved in aqueous methanol (20:1, MeOH:H_2O, 3 mL). Trifluoroacetic acid (0.15 mmol) and Pearlman's catalyst (1 equiv by mass) were added to the mixture, which was degassed and was stirred under hydrogen for 1 night. The suspension was then filtered under a pad of Celite. After evaporation, amino acids **1a** or **1b** were purified by trituration with diethyl ether.

[2*S*,5*S*]-5-Isopropylpyrrolidine-2-carboxylic acid (1a). Yield 95%. $[\alpha]_D^{20}$: −34 (*c* 0.3, HCl 1.2M). ^1H NMR (CD_3OD): 3.86 (t, *J* = 9.1 Hz, 1H), 3.23−3.12 (m, 1H), 2.16−2.02 (m, 1H), 1.89−1.28 (m, 4H), 0.62 (d, *J* = 7.4 Hz, 3H), 0.53 (d, *J* = 7.7 Hz, 3H). ^{13}C NMR (CD_3OD): 68.3, 32.2, 30.0, 20.5, 19.5. HRMS: Calcd for $C_8H_{16}NO_2$ ($M + H^+$) *m*/*z* = 158.11756, obsd *m*/*z* = 158.11747.

[2*S*,5*S*]-5-*tert*-Butylpyrrolidine-2-carboxylic acid (1b). Yield 73%. $[\alpha]_D^{20}$: −30 (*c* 0.3, HCl 1.2M). ^1H NMR (CD_3OD): 3.96 (t, *J* = 7.7 Hz, 1H), 3.53 (dd, *J* = 10.3, 6.7 Hz, 1H), 2.41−2.30 (m, 1H), 2.13−1.81 (m, 3H), 1.03 (s, 9H). ^{13}C NMR (CD_3OD): 71.2, 63.0, 33.4, 30.1, 27.1, 26.4. HRMS: Calcd for $C_9H_{18}NO_2$ ($M + H^+$) *m*/*z* = 172.13321, obsd *m*/*z* = 172.13318.

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Supporting Information Available: General procedure to obtain compounds **3a**−**d** and **8a**−**e**, product characterization for all new compounds synthesized and X-ray data for lactone **7a**. ^1H and ^{13}C spectra of compounds **1a**−**b**, **3a**−**c**, **4a**−**c**, **6**, **7a**−**b**, **8f**−**h**. This material is available free of charge via the Internet at http://pubs.acs.org.

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