ORGANIC LETTERS

2010
Vol. 12, No. 13
3014−3017

Diastereoselective Intramolecular Additions of Allyl- and Propargylsilanes to Iminium Ions: Synthesis of Cyclic and Bicyclic Quaternary Amino Acids

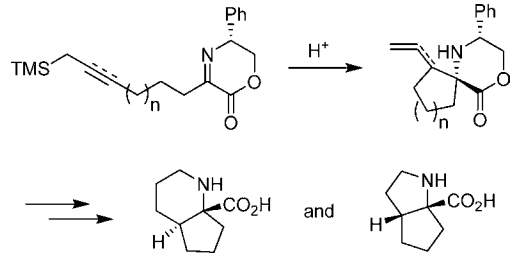
Santos Fustero,*,†,‡ Natalia Mateu,†,‡ Antonio Simón-Fuentes,† and José Luis Aceña*,‡

Departamento de Química Orgánica, Universidad de Valencia, E-46100 Burjassot, Spain, and Laboratorio de Moléculas Orgánicas, Centro de Investigación Príncipe Felipe, E-46012 Valencia, Spain

santos.fustero@uv.es; jlacenya@cipf.es

Received May 4, 2010

ABSTRACT



Chiral imino lactones derived from (*R*)-phenylglycinol containing an allyl- or propargyltrimethylsilyl group in the side chain readily cyclized in the presence of acidic reagents to afford spirocyclic compounds with high diastereoselectivity. Removal of the chiral auxiliary produced 2-substituted 1-aminocycloalkanecarboxylic acids, whereas further cyclizations by means of metathesis or hydroamination reactions led to bicyclic derivatives of pipecolic acid and proline.

Intramolecular addition reactions to *N*-alkyl- and *N*-acyliminium ions usually play a pivotal role for constructing nitrogen-containing cyclic compounds.[1] For instance, when allyl- or propargylsilyl functionalities are selected as the internal nucleophiles, this strategy constitutes a convenient access to cyclic homoallyl- or homoallenylamines, respectively.[2] In the context of our current work employing chiral imino lactones derived from (*R*)-phenylglycinol,[3] we envisioned that cyclization of the derived iminium ions **1** having an allyl- or propargyltrimethylsilane at the end of the chain would lead to spirocyclic compounds **2** bearing a vinyl or allenyl group, respectively, installed on the newly created ring (Scheme 1). It would be anticipated that the preexisting chiral center would induce a high degree of stereocontrol in the

† Universidad de Valencia.
‡ Centro de Investigación Príncipe Felipe.

(1) (a) Royer, J.; Bonin, M.; Micouin, L. *Chem. Rev.* **2004**, *104*, 2311–2352. (b) Maryanoff, B. E.; Zhang, H.-C.; Cohen, J. H.; Turchi, I. J.; Maryanoff, C. A. *Chem. Rev.* **2004**, *104*, 1431–1628.

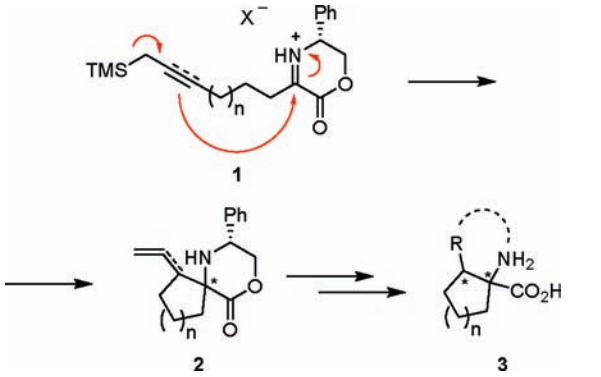
(2) For examples, see: (a) Hiemstra, H.; Sno, M. H. A. M.; Vijn, R. J.; Speckamp, W. N. *J. Org. Chem.* **1985**, *50*, 4014–4020. (b) Chalard, P.; Remuson, R.; Gelas-Mialhe, Y.; Gramain, J.-C. *Tetrahedron: Asymmetry* **1998**, *9*, 4361–4368. (c) Luker, T.; Koot, W.-J.; Hiemstra, H.; Speckamp, W. N. *J. Org. Chem.* **1998**, *63*, 220–221. (d) Sun, P.; Sun, C.; Weinreb, S. M. *J. Org. Chem.* **2002**, *67*, 4337–4345. (e) Amorde, S. M.; Judd, A. S.; Martin, S. F. *Org. Lett.* **2005**, *7*, 2031–2033. (f) Amorde, S. M.; Jewett, I. T.; Martin, S. F. *Tetrahedron* **2009**, *65*, 3222–3231.

(3) (a) Fustero, S.; Albert, L.; Aceña, J. L.; Sanz-Cervera, J. F.; Asensio, A. *Org. Lett.* **2008**, *10*, 605–608. (b) Fustero, S.; Mateu, N.; Albert, L.; Aceña, J. L. *J. Org. Chem.* **2009**, *74*, 4429–4432.

(4) For intermolecular diastereoselective alkyl additions to the iminic carbon in related molecules, see: (a) Harwood, L. M.; Vines, K. J.; Drew, M. G. B. *Synlett* **1996**, 1051–1053. (b) Miyabe, H.; Yamaoka, Y.; Takemoto, Y. *J. Org. Chem.* **2005**, *70*, 3324–3327. (c) Pigza, J. A.; Molinski, T. F. *Org. Lett.* **2010**, *12*, 1256–1259.

10.1021/ol1010246
Published on Web 06/01/2010

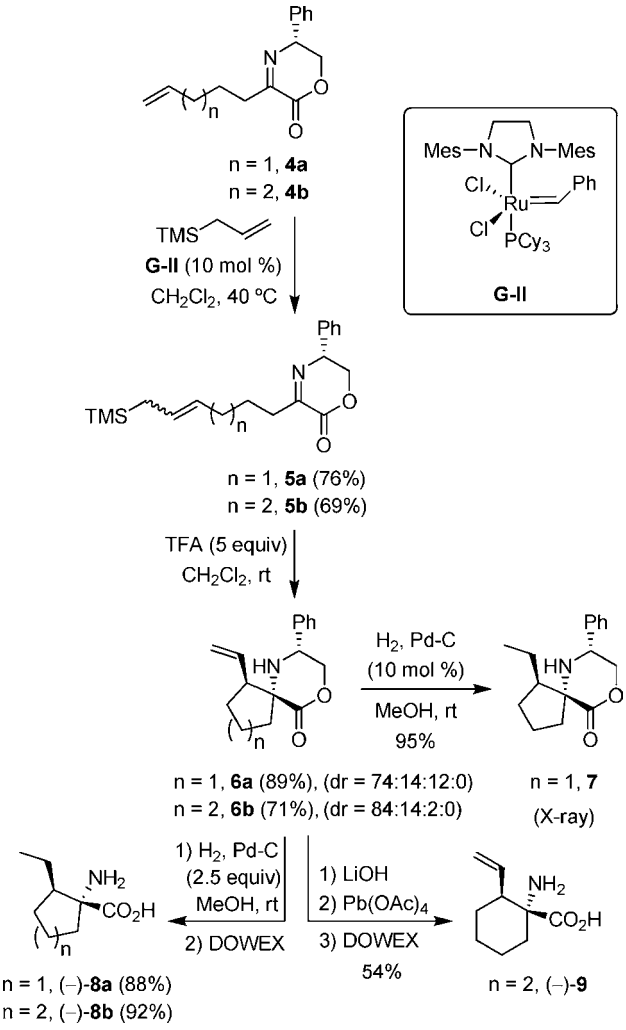
Scheme 1. Synthetic Strategy



formation of the quaternary center.[4] These spirocycles **2** would be precursors of a variety of 1-aminocycloalkanecarboxylic acids **3** (1-ACACs), an important class of conformationally constrained mimics of proteinogenic amino acids,[5,6] which can also be used for the preparation of oligomers showing defined secondary structures.[7] In addition, compounds **2** would be appropriate intermediates for the synthesis of more complex bicyclic amino acids.

Starting from our previously reported imino lactone **4a** and its higher homologue **4b**,[8] elongation using a cross-metathesis reaction with allyltrimethylsilane in the presence of second-generation Grubbs catalyst (**G-II**) afforded allylsilanes **5a**,**b** as an inconsequential mixture of *trans* and *cis* isomers (ca. 90:10 ratio)[9] (Scheme 2). Next, cyclization was carried out using an excess of TFA in CH_2Cl_2 to yield spirocycles **6a**,**b** in good yields as the major products of a mixture of four possible diastereoisomers (dr = 74:14:12:0 and 84:14:2:0, respectively).[10] After chromatographic purification, the major products **6a** and **6b** were isolated in 66% and 60% yields, respectively. Subsequent hydrogenation of **6a** afforded saturated derivative **7**, which served to establish

Scheme 2. Cyclization of Allylsilanes **5a**,**b**



the configuration of both newly formed stereogenic centers by X-ray diffraction analysis of a single crystal (Figure 1). Conversely, extensive hydrogenation of both **6a** and **6b** also

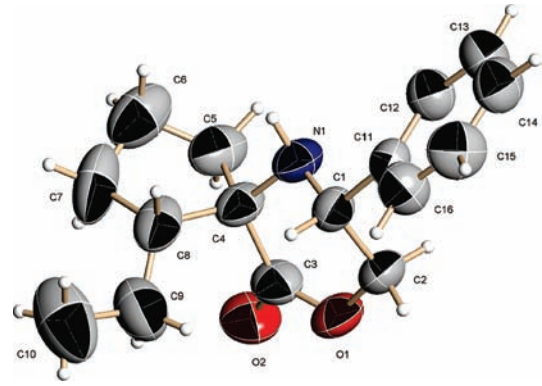


Figure 1. X-ray diffraction analysis of compound **7**.

(5) For reviews, see: (a) Cativiela, C.; Díaz-de-Villegas, M. D. *Tetrahedron: Asymmetry* **2000**, *11*, 645–732. (b) Park, K.-H.; Kurth, M. J. *Tetrahedron* **2002**, *58*, 8629–8659. (c) Maity, P.; König, B. *Biopolymers (Pept. Sci.)* **2008**, *90*, 8–27. (d) Cativiela, C.; Ordóñez, M. *Tetrahedron: Asymmetry* **2009**, *20*, 1–63.

(6) For our previous asymmetric syntheses of 2,2-difluoro-1-ACACs, see: (a) Fustero, S.; Sánchez-Roselló, M.; Rodrigo, V.; del Pozo, C.; Sanz-Cervera, J. F.; Simón, A. *Org. Lett.* **2006**, *8*, 4129–4132. (b) Fustero, S.; Sánchez-Roselló, M.; Rodrigo, V.; Sanz-Cervera, J. F.; Piera, J.; Simón-Fuentes, A.; del Pozo, C. *Chem.—Eur. J.* **2008**, *14*, 7019–7029. (c) Fustero, S.; Rodrigo, V.; Sánchez-Roselló, M.; Mojarrad, F.; Vicedo, A.; Moscardó, T.; del Pozo, C. *J. Fluorine Chem.* **2008**, *129*, 943–950.

(7) Nagano, M.; Tanaka, M.; Doi, M.; Demizu, Y.; Kurihara, M.; Suemune, H. *Org. Lett.* **2009**, *11*, 1135–1137, and references cited therein.

(8) Imino lactones **4a**,**b** were prepared by condensation of the corresponding α-keto esters with (*R*)-phenylglycinol; see ref 3a. .

(9) The pure *cis* isomer of **5a** was also obtained by a different synthetic route based on the partial hydrogenation of a triple bond, and its subsequent cyclization to **6a** afforded the same stereochemical result as the *trans*/*cis* mixture.

(10) The diastereomeric ratio was measured by HPLC. Only three out of four diastereoisomers were detected both by HPLC and NMR.

(11) Wede, J.; Volk, F.-J.; Frahm, A. W. *Tetrahedron: Asymmetry* **2000**, *11*, 3231–3252.

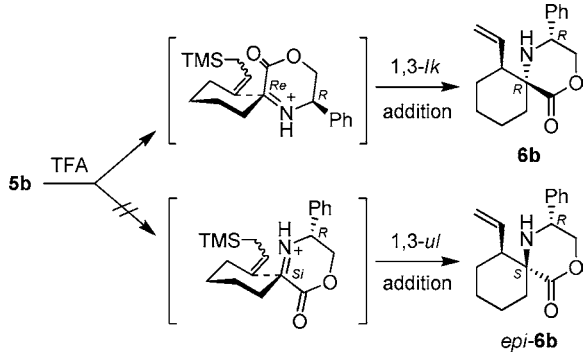
(12) Schinzer, D.; Dettmer, G.; Ruppelt, M.; Sólyom, S.; Steffen, J. *J. Org. Chem.* **1988**, *53*, 3823–3828.

(13) (a) Borzilleri, R. M.; Weinreb, S. M. *Synthesis* **1995**, 347–360. (b) Ofial, A. R.; Mayr, H. *J. Org. Chem.* **1996**, *61*, 5823–5830.

removed the chiral auxiliary to produce amino acids **8a**[11] and **8b**, respectively. Other deprotection procedures were also evaluated in order to preserve the vinyl group. For instance, lactone opening in **6b** with LiOH followed by oxidative cleavage of the phenylglycinol moiety with $Pb(OAc)_4$ produced unsaturated six-membered amino acid **9**.

The stereoselectivity observed in the cyclization step may be rationalized by considering the corresponding transition states. In the case of **5b**, a chairlike transition state having the allylsilane quasi-equatorial is preferred[2d] (Scheme 3). Therefore, the allylsilane approaches the

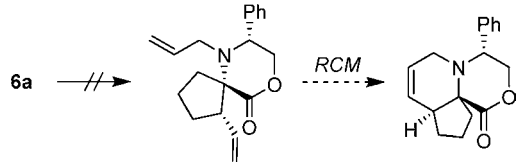
Scheme 3. Transition States in the Cyclization of **5b** to **6b**



iminium carbon mainly through the *Re* face opposite the bulky phenyl group in a quasi-axial fashion,[4] thus leading to **6b** as the major diastereoisomer. The dr was somewhat lower in the cyclization of **5a** due to the less significant steric constraints associated with a five-membered transition state.

Then, we focused our attention on the cyclization of a propargylsilane-substituted iminium ion. The appropriate substrate was prepared by reaction of the already known Grignard reagent **10**[12] with diethyl oxalate to give α-keto ester **11** in moderate yield (based on the starting bromide precursor), which was further converted into imino lactone **12** by condensation with (*R*)-phenylglycinol (Scheme 4).

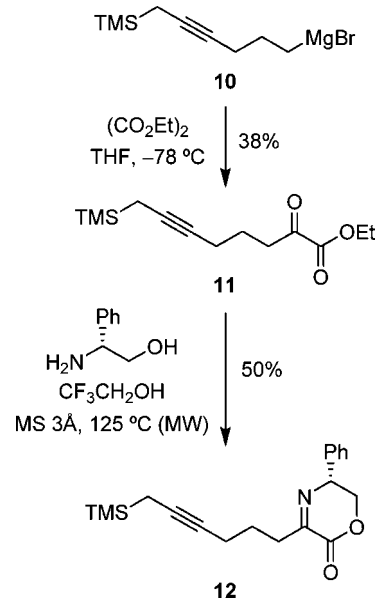
(14) *N*-Allylation of **6a** was also tested but resulted in a complex mixture of products under several reaction conditions.



(15) *Cis*-fused 2-azabicyclo[4.3.0]nonane-1-carboxylic acids were previously prepared and used as scaffolds for *β*-turn mimics, see: (a) Verbist, B. M. P.; De Borggraeve, W. M.; Toppet, S.; Compernolle, F.; Hoornaert, G. J. *Eur. J. Org. Chem.* **2005**, 2941–2950. For a recent synthesis of different bicyclic pipecolic acids, see: (b) Radchenko, D. S.; Kopylova, N.; Grygorenko, O. O.; Komarov, I. V. *J. Org. Chem.* **2009**, *74*, 5541–5544.

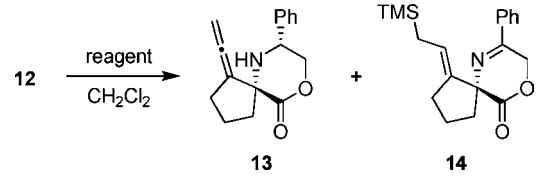
(16) (a) Widenhoefer, R. A.; Han, X. *Eur. J. Org. Chem.* **2006**, 4555–4563. (b) Müller, T. E.; Hultzsch, K. C.; Yus, M.; Foubelo, F.; Tada, M. *Chem. Rev.* **2008**, *108*, 3795–3892.

Scheme 4. Synthesis of Propargylsilane **12**



Treatment of **12** with TFA led to the expected allene **13** in >95:5 diastereoselectivity, together with isomerized imine **14** (43:57 ratio), the latter product arising from an ene reaction with inverse electron demand[13] (Table 1,

Table 1. Cyclization of Propargylsilane **12**

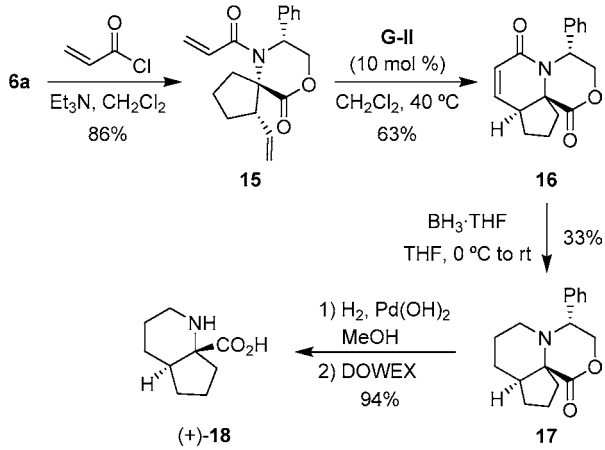


entry	reagent	temp (°C)	yield of **13** (%)	yield of **14** (%)
1	TFA	25	27	35
2	BF_3·OEt_2	0 to 25	24	56
3	$TiCl_4$	−78	57	13
4	HCO_2H (neat)	25	57	5

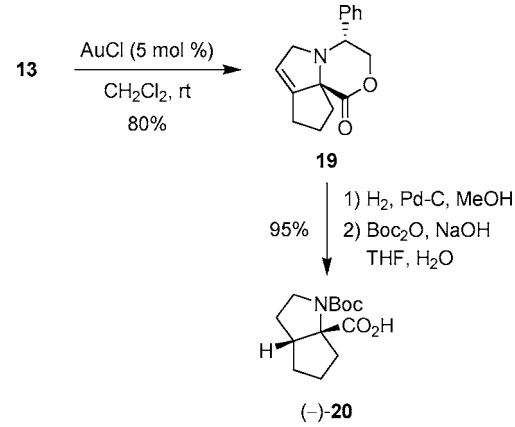
entry 1). Although both products were easily separated by column chromatography, we tested other Lewis or Brønsted acids in order to minimize the amount of **14**, and the best conditions found involved the use of neat formic acid to produce **13** as the major product of a 92:8 mixture (entry 4).

Next, we undertook the preparation of bicyclic amino acid derivatives by expedient transformations of the vinyl or allenyl functionalities in the corresponding cyclization products. Thus, acrylamide **15** was easily prepared from spirocyclic amine **6a** and cyclized afterward by means of a ring-closing metathesis to yield tricyclic lactone **16** (Scheme 5). Since the presence of the lactam carbonyl impeded the efficient removal of the phenylglycinol moiety,[14] **16** was

Scheme 5. Synthesis of Bicyclic Pipecolic Acid **18**



Scheme 6. Synthesis of *N*-Boc-bicycloproline **20**



treated first with BH_3·THF to afford saturated derivative **17**, which was further hydrogenated to afford *trans*-fused bicyclic pipecolic acid **18**.[15]

Alternatively, allenylamine **13** was subjected to a gold(I)-catalyzed intramolecular hydroamination reaction[16,17] which proceeded uneventfully to produce tricyclic compound **19**[18] (Scheme 6). Finally, hydrogenation of **19** and *N*-Boc protection of the resulting amino acid afforded bicycloproline derivative **20**.[19]

In conclusion, an efficient access to cyclic and bicyclic amino acids has been achieved using as key synthetic step the intramolecular addition of allyl- or propargylsilanes to an iminium ion. The target compounds represent an attractive group of conformationally constrained amino acids that could be incorporated into peptidomimetic structures with potential biological activities.[20] Further applications of this methodology are currently being studied in our laboratories.

Acknowledgment. We thank the Ministerio de Educación y Ciencia (CTQ2007-61462) and Generalitat Valenciana (GVPRE/2008/013) for their financial support. N.M. thanks the Universidad de Valencia for a predoctoral fellowship, and J.L.A. thanks the MEC for a Ramón y Cajal research contract.

Supporting Information Available: Experimental procedures and NMR spectra for all new compounds, as well as crystallographical data for compound **7**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL1010246

(17) For a recent article combining both iminium ion additions and gold-catalyzed hydroaminations, see: Breman, A. C.; Dijkink, J.; van Maarseveen, J. H.; Kinderman, S. S.; Hiemstra, H. *J. Org. Chem.* **2009**, *74*, 6327–6330.

(18) In contrast, a similar hydroamination protocol was unsuccessful using vinylic derivative **6a**.

(19) For a previous synthesis of (+)-**20**, see: (a) Ranatunga, S.; Del Valle, J. R. *Tetrahedron Lett.* **2009**, *50*, 2464–2466. For the synthesis of other bicycloproline derivatives, see: (b) Turner, P. G.; Donohoe, T. J.; Cousins, R. P. C. *Chem. Commun.* **2004**, 1422–1423. (c) Yip, Y.; Victor, F.; Lamar, J.; Johnson, R.; Wang, Q. M.; Barket, D.; Glass, J.; Jin, L.; Liu, L.; Venable, D.; Wakulchik, M.; Xie, C.; Heinz, B.; Villarreal, E.; Colacino, J.; Yumibe, N.; Tebbe, M.; Munroe, J.; Chen, S.-H. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 251–256. (d) Casabona, D.; Jiménez, A. I.; Cativiela, C. *Tetrahedron* **2007**, *63*, 5056–5061.

(20) For examples, see: (a) Palmer, J. T.; Bryant, C.; Wang, D.-X.; Davis, D. E.; Setti, E. L.; Rydzewski, R. M.; Venkatraman, S.; Tian, Z.-Q.; Burrill, L. C.; Mendonca, R. V.; Springman, E.; McCarter, J.; Chung, T.; Cheung, H.; Janc, J. W.; McGrath, M.; Somoza, J. R.; Enriquez, P.; Yu, Z. W.; Strickley, R. M.; Liu, L.; Venuti, M. C.; Percival, M. D.; Falgueyret, J.-P.; Prasit, P.; Oballa, R.; Riendeau, D.; Young, R. N.; Wesolowski, G.; Rodan, S. B.; Johnson, C.; Kimmel, D. B.; Rodan, G. *J. Med. Chem.* **2005**, *48*, 7520–7534. (b) Sheppeck, J. E.; Gilmore, J. L.; Yang, A.; Chen, X.-T.; Xue, C.-B.; Roderick, J.; Liu, R.-Q.; Covington, M. B.; Decicco, C. P.; Duan, J. J.-W. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 1413–1417. (c) Maltais, F.; Jung, Y. C.; Chen, M.; Tanoury, J.; Perni, R. B.; Mani, N.; Laitinen, L.; Huang, H.; Liao, S.; Gao, H.; Tsao, H.; Block, E.; Ma, C.; Shawgo, R. S.; Town, C.; Brummel, C. L.; Howe, D.; Pazhanisamy, S.; Raybuck, S.; Namchuk, M.; Bennani, Y. L. *J. Med. Chem.* **2009**, *52*, 7993–8001. See also ref 19c.