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Three-Component Assembly of Amines, Boronic Acids, and a Polyfunctionalized Furanose: A Concise Entry to Furanose-Based Carbohydrate Templates

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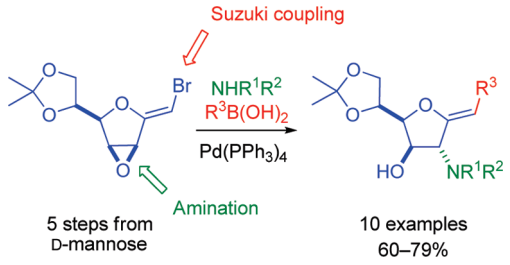
Received June 15, 2009



A highly functionalyzed furanose derivative, accessible in five steps from D-mannose, comprising a halo-alkenyl allylic-oxirane system, undergoes a palladium catalyzed one-pot, three component, assembly with boronic acids (or alkyl boranes) and amines to give, in a complete regio- and stereocontrolled manner, a sugar based derivative with two sites of molecular diversity.

The muticomponent assembly reaction has emerged as a powerful means for rapid generation of molecular complexity and diversity.[1] In particular, the orthogonal and sequential functionalization of a simple molecule bearing multiple reaction sites may serve as a powerful synthetic strategy that should provide enormous opportunity for diversity-oriented synthesis as well as target-oriented synthesis.[2] In this sense, the design of novel molecular platforms that allow a stereodetermined, three-dimensional orientation of pharmacophores remains an important goal in drug discovery.[3] In this context, the successful use of carbohydrates as scaffolds in the area of peptidomimetics[4] has triggered a considerable research effort on the use of sugar derivatives as templates in bioactive compound discovery.[5] Thus, carbohydrate templates have been generated from pyranoses, furanoses, disaccharides, and bicyclic derivatives, and most of these strategies have relied on the stepwise derivatization of *orthogonally protected* carbohydrate derivatives.[6−8]

Recently, we inititated a research project aimed at building small libraries of functionalized carbohydrates.[9] In this context, we have became interested in developing synthetic strategies in which the incorporation of some of the appendages on the carbohydrate templates could be effected by means of palladium-catalyzed reactions on *orthogonally functionalized* carbohydrate derivatives. We reported the preparation of epoxy *exo*-glycal **1** (four steps from D-mannose) and its transformation into allylic amines, e.g., **2**, via an intermediate π-allyl palladium complex (Scheme 1a).[10] We also reported the Suzuki cross-coupling reaction[11] of halo-*exo*-glycals, e.g., **3**,[12] leading to substituted *exo*-glycals, e.g., **4** (Scheme 1b).[13] We envisioned that

(1) (a) Dmling, A. *Chem. Rev.* **2006**, *106*, 17–89. (b) *Multicomponent reactions*; Zhu, J., Bienaymé, H., Eds.; Wiley: Weinheim, 2005. (c) Ramón, D. J.; Yus, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 1602–1634.

(2) (a) Schreiber, S. L. *Science* **2000**, *287*, 1964–1969. (b) Burke, M. D.; Schreiber, S. L. *Angew. Chem., Int. Ed.* **2004**, *43*, 46–58. (c) Newman, D. J.; Gragg, G. M. *J. Nat. Prod.* **2007**, *70*, 461–477. (d) Koehn, F. E.; Carter, G. T. *Nature Rev. Drug Discovery* **2005**, *4*, 206–220.

(3) Ariens, E. J.; Beld, A. J.; Rodrigues de Miranda, J. F.; Simonis, A. M. In *The Receptors: A Comprehensive Treatise*; O'Brien, R. D., Ed.; Plenum: New York, 1979; pp 33−91.

(4) (a) Hirschmann, R.; Nicolaou, K. C.; Pietranico, S.; Salvino, J.; Leahy, E. M.; Sprengeler, P. A.; Furst, G.; Smith, A. B. III; Strader, C. D.; Cascieri, M. A.; Candelore, M. R.; Donaldson, C.; Vale, W.; Maechler, L. *J. Am. Chem. Soc.* **1992**, *114*, 9217–9218. (b) Hirschmann, R.; Nicolaou, K. C.; Pietranico, S.; Leahy, E. M.; Salvino, J.; Arison, B.; Cichy, M. A.; Spoors, P. G.; Shakespeare, W. C.; Sprengeler, P. A.; Hamley, P.; Smith, A. B. III; Reisine, T.; Raynor, K.; Maechler, L.; Donaldson, C.; Vale, W.; Freidinger, R. M.; Cascieri, M. R.; Strader, C. D. *J. Am. Chem. Soc.* **1993**, *115*, 12550–12568.(c) Nicolaou, K. C.; Salvino, J. M.; Raynor, K.; Pietranico, S.; Reisine, T.; Freidinger, R. M.; Hirschmann, R. In *Peptides: Chemical Structure and Biology*; Proceedings of the 11th American Peptide Symposium; Marshall, G. R., Ed.; Escom: Leiden, 1990; pp 881−884.

(5) Recent reviews on the preparation of carbohydrate derived templates: (a) Murphy, P. V. *Eur. J. Org. Chem.* **2007**, 4177–4180. (b) Velter, I.; LaFerla, B.; Nicotra, F. *J. Carbohydr. Chem.* **2006**, *25*, 97–138. (c) Becker, B.; Condie, G. C.; Le, G. T.; Meutermans, W. *Mini-Rev. Med. Chem.* **2006**, *1*, 1164–1194. (d) Meutermans, W.; Le, G. T.; Becker, B. *Chem. Med. Chem.* **2006**, *1*, 1164–1194. (e) Murphy, P. V.; Dunne, J. L. *Curr. Org. Synth.* **2006**, *3*, 403–437. (f) Cipolla, L.; Peri, F.; LaFerla, B.; Redaelli, C.; Nicotra, F. *Curr. Org. Synth.* **2005**, *2*, 153–173. (g) Le, G. T.; Abbenante, G.; Becker, B.; Grathwohl, M.; Halliday, J.; Tometzki, G.; Zuegg, J.; Meutermans, W. *Drug Discovery Today* **2003**, *8*, 701–709. (h) Kanemitsu, T.; Kanie, O. *Trends Glycosci. Glycotechnol.* **1999**, *11*, 267–276. (i) Sofia, J. J.; Silva, D. J. *Curr. Opin. Drug Discovery Dev.* **1999**, *2*, 365–376.

(6) (a) Hünger, H.; Ohnsmann, J.; Kunz, H. *Angew. Chem., Int. Ed.* **2004**, *43*, 1104–1107. (b) Opatz, T.; Kallus, C.; Wunberg, T.; Schmidt, W.; Henke, S.; Kunz, H. *Eur. J. Org. Chem.* **2003**, 1527–1536. (c) Wunberg, T.; Kallus, C.; Opatz, T.; Henke, S.; Schmidt, W.; Kunz, H. *Angew. Chem., Int. Ed.* **1998**, *37*, 2503–2505.

(7) (a) Jain, R.; Kamau, M.; Wang, C.; Ippolito, R.; Wang, H.; Dulina, R.; Anderson, J.; Gange, D.; Sofia, M. J. B. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 2185–2189. (b) Sofia, M. J.; Hunter, R.; Chan, T. Y.; Vaughan, A.; Dulina, R.; Wang, H.; Gange, D. *J. Org. Chem.* **1998**, *63*, 2802–2803.

(8) (a) Elmouelhi, N.; Aich, U.; Paruchuri, V. D. P.; Meledeo, M. A.; Campbell, C. T.; Wang, J. J.; Srinivas, R.; Khanna, H. S.; Yarema, K. J. *J. Med. Chem.* **2009**, *52*, 2515–2530. (b) Castoldi, S.; Cravini, M.; Micheli, F.; Piga, E.; Russo, G.; Seneci, P.; Lay, L. *Eur. J. Org. Chem.* **2004**, 2853–2862.

(9) (a) Gómez, A. M.; Barrio, A.; Pedregosa, A.; Valverde, S.; López, J. C. *Tetrahedron Lett.* **2003**, *44*, 8433–8435. (b) Gómez, A. M.; Pedregosa, A.; Barrio, A.; Valverde, S.; López, J. C. *Tetrahedron Lett.* **2004**, *45*, 6307–6310. (c) Gómez, A. M.; Barrio, A.; Amurrio, I.; Jarosz, S.; Valverde, S.; López, J. C. *Tetrahedron Lett.* **2006**, *47*, 6243–6246.

(10) Gómez, A. M.; Pedregosa, A.; Valverde, S.; López, J. C. *Chem. Commun.* **2002**, 2022–2023.

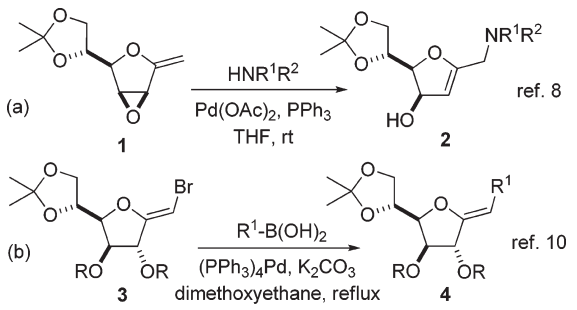
(11) (a) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457–2483. (b) Suzuki, A. In *Metal-Catalyzed Cross-Coupling Reactions*; Diederich, F., Stang, P. J., Eds.; VCH: Weinheim, 1998; pp 49−97. (c) Suzuki, A. *J. Organomet. Chem.* **1999**, *576*, 147–168.

(12) Gómez, A. M.; Danelón, G. O.; Pedregosa, A.; Valverde, S.; López, J. C. *Chem. Commun.* **2002**, 2024–2026.

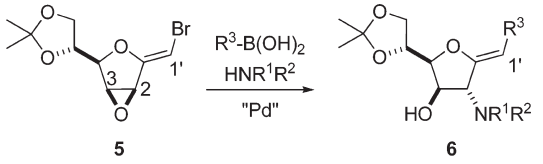
(13) Gómez, A. M.; Pedregosa, A.; Valverde, S.; López, J. C. *Tetrahedron Lett.* **2003**, *44*, 6111–6116.

DOI: 10.1021/jo9012817 Published on Web 07/14/2009

SCHEME 1. Palladium-Catalyzed Reactions on Functionalized Furanose Systems 1 and 3



SCHEME 2. Proposed Palladium-Catalyzed, Three-Component Assembly of Tetrahydrofuran Template 6 by Reaction of Polyfunctionalized Furanose Derivative 5, Boronic Acids, and Amines



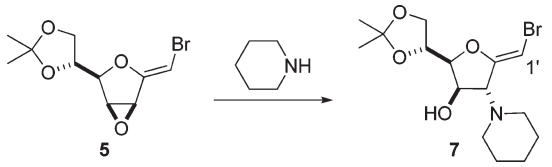
these two reactions could be combined in a one-pot operation on a conveniently functionalized *exo*-glycal, i.e., **5**, and in this paper, we report on the implementation of such an approach leading to a variety of furanoid derivatives, e.g., **6** (Scheme 2).

Compound **5** possesses two sites susceptible to activation with palladium catalysis: (i) the allylic epoxide, by allylic ionization and (ii) the vinyl bromide through oxidative addition, and it was uncertain which functionality would be more reactive.[14−16] With that in mind, the successful implementation of our proposed transformation (**5** → **6**, Scheme 2) will require a subtle handling of these functionalities.

In our hands, the Suzuki cross-coupling reaction of **5**, with different boronic acids, under several reaction conditions, led to complex reaction mixtures. On the other hand, attempted palladium-catalyzed amination of compound **5**, under experimental conditions similar to those previously applied to compound **1** (room temperature, Scheme 1a), resulted in no incorporation of the amino derivative (Table 1, entry *i*). It was found, however, that refluxing of the above-mentioned solution provided amino alcohol **7** in 80% yield (Table 1, entry *ii*).

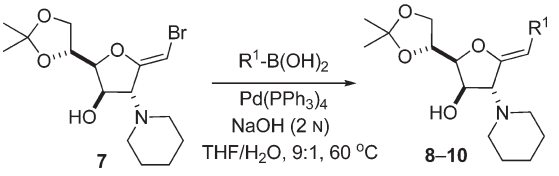
The fact that the stereochemistry at C-1′ was maintained in compound **7** suggested that no π-allyl palladium intermediate has been involved in the transformation. This was confirmed when a refluxing ethanolic solution containing piperidine and compound **5** exclusively also furnished allylic amine **7** in 88% yield (Table 1, entry *iii*). These observations seemed to indicate that the reaction was taking place by uncatalyzed nucleophilic opening of the epoxide and that the presence of bromine in the vinyl oxirane deactivates the system toward allylic ionization with palladium[14−16] (Scheme 1a vs Table 1, entries *i* and *ii*).

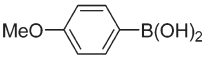
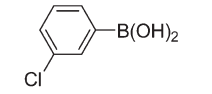
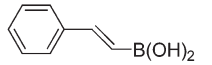
TABLE 1. Reaction of Compound 5 with Piperidine



entry	reaction conditions	*T* (°C)	yield (%)
i	$Pd(OAc)_2$, PPh_3, THF	rt	0
ii	$Pd(OAc)_2$, PPh_3, THF	reflux	80
iii	EtOH	reflux	88

TABLE 2. Synthesis of Furanoid Derivatives 8−10 by Suzuki Cross-Coupling Reaction of Alkenyl Bromide 7 with Boronic Acids



entry	R^1-B(OH)$_2$	product	yield (%)
i		**8**	73
ii		**9**	79
iii		**10**	72

We next decided to test the cross-coupling reaction of amino alcohol **7**, with different boronic acids, keeping in mind the possible deleterious interaction between the amino group and the boronic acid.[17] Our results (Table 2) showed that aromatic allylic amines[17] **8**−**10** could be obtained in good yields by treatment of vinyl bromide **7** with aryl or vinyl boronic acids in the presence of $Pd(PPh_3)_4$ and NaOH in a THF/H_2O solution at 60 °C.

After having established the viability of the two-step sequence for the transformation, we next turned our attention to the one-pot multicomponent assembly of compound **5** with amines and boronic acids. We found that experimental conditions similar to those applied for the Suzuki coupling of amine **7** with boronic acids ($Pd(PPh_3)_4$, NaOH, THF/H_2O, 60 °C, Table 2) allowed the desired one-pot, three-component reaction furnishing derivatives **8**−**13** in good yields (Table 3). In all instances where a comparison is possible (Table 3, entries *i*−*iii*), the one-pot transformation was found to be more efficient than the alternative stepwise

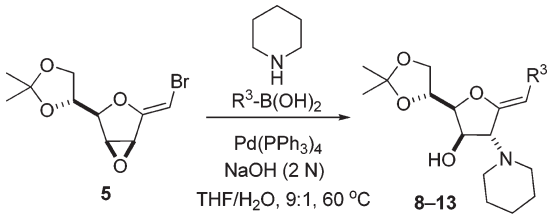
(14) For studies on allylic ionization versus oxidative addtion into vinyl C−Br bonds, see: (a) Comer, E.; Organ, M. G.; Hynes, S. J. *J. Am. Chem. Soc.* **2004**, *126*, 16087–16092. (b) Organ, M. G.; Arvanitis, E. A.; Dixon, C. E.; Cooper, J. T. *J. Am. Chem. Soc.* **2002**, *124*, 1288–1294.

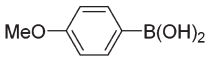
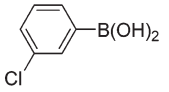
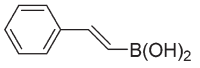
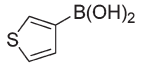
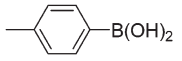
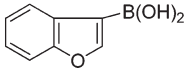
(15) For studies on 1-acetoxy-2-bromo-2-alkenes, see: (a) Nwokogu, G. C. *J. Org. Chem.* **1985**, *50*, 3900–3908. (b) Nwokogu, G. C. *Tetrahedron Lett.* **1984**, *25*, 3263–3266. (c) Trost, B. M.; Oslob, J. D. *J. Am. Chem. Soc.* **1999**, *121*, 3057–3064.

(16) For studies on α,β-epoxy vinyl triflates: Yamamoto, K.; Heathcock, C. H. *Org. Lett.* **2000**, *2*, 1709–1712.

(17) Organ, M. G.; Mayhew, D.; Cooper, J. T.; Dixon, C. E; Lavorato, D. J.; Kaldor, S. W.; Siegel, M. G. *J. Comb. Chem.* **2001**, *3*, 64–67.

TABLE 3. One-Pot Multicomponent Assembly of Furanoid Derivatives 8−13 by Reaction of Alkenyl Bromide 5 with Piperidine and Boronic Acids



entry	R^1-B(OH)$_2$	product	yield (%)
i		**8**	63
ii		**9**	79
iii		**10**	60
iv		**11**	72
v		**12**	72
vi		**13**	75

synthesis. This transformation could be applied to a variety of aryl and heteroaryl boronic acids (Table 3).

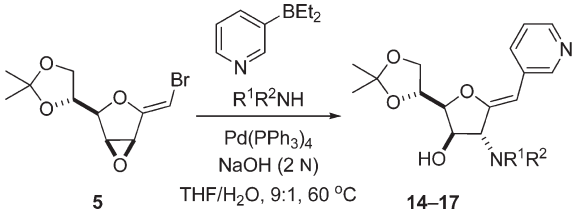
Alkyl boranes have also been used in *B*-alkyl Suzuki cross-coupling reactions.[18] So, we next sought to extend this methodology to the coupling of **5** with alkyl boranes and primary/secondary amines. In Table 4, we display our results on the three-component assembly of vinyl bromide **5** with diethyl(3-pyridyl)borane and different amines leading to furanose derivatives **14**−**17**. Good yields of 2-deoxy-2-amino exoglycals were obtained, and no appreciable difference was observed in terms of yields between primary and secondary amines.

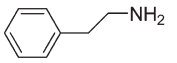
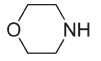
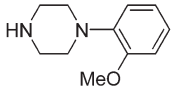
These studies have revealed the remarkable effect of bromine at position C-1′ in the reactivity of the α,β-epoxy vinyl systems **18**[19] versus **20** (Scheme 3). Thus, it appears that the presence of bromine in **20** deactivates the allylic system toward Pd-mediated ionization leading to **19**, a result in contrast with that observed for compounds of type **18** (e.g., **1**, Scheme 1a) and also with the behavior in related systems with nonterminal vinyl bromides.[14−16]

In summary, we have reported a novel method for the preparation of furanose-derived templates that relies on the palladium-catalyzed, one-pot, multicomponent assembly of a furanose-derived halogenated allyl epoxide with boronic acids (or alkyl boranes) and amines.[20] The reaction takes place with complete regio- and stereocontrol, by regioselective nucleophilic opening of the oxirane with the amine, followed by Suzuki (or *B*-alkyl Suzuki) cross-coupling reaction of the alkenyl bromide with the boronic acid (or alkyl borane). The latter takes place with retention of the configuration at the olefin.[11,18]

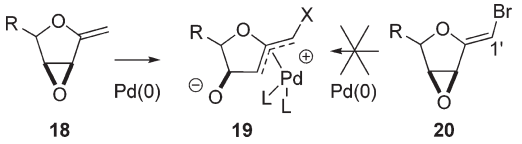
This approach could be easily extended to the generation of carbohydrate libraries with more than two appendages, since the simultaneous incorporation of the two substituents (C-1′ and C-2) is accompanied by the unveiling of a free hydroxyl group at O-3, which would still allow the incorporation of a third appendage. Further work with the polyfunctionalized furanose derivative system **5** is currently underway in our laboratory.

TABLE 4. One-Pot Multicomponent Assembly of Furanose Derivatives 15−18 by Reaction of Epoxy Alkenyl Bromide 5 with Diethyl(3-pyridyl-)borane and Amines



entry	R^1R^2NH	product	yield (%)
i		**14**	78
ii		**15**	75
iii		**16**	71
iv		**17**	74

SCHEME 3. Pd(0)-Mediated Allylic Ionization of α,β-Epoxy Vinyl Derivatives 18 and 20



Experimental Section

General Procedure A: Suzuki Cross-Coupling of Alkenyl Bromide 7 with Boronic Acids. To a mixture of alkenyl bromide **7**

(18) Chemler, S. R.; Trauner, D.; Danishefsky, S. J. *Angew. Chem., Int. Ed.* **2001**, *40*, 4544–4568.

(19) For compounds related to **18**, see: (a) Hirota, K.; Takasu, H.; Tsuji, Y.; Sajiki, H. *Chem. Commun.* **1999**, 1827–1828. (b) Dalla, V.; Pale, P. *Tetrahedron Lett.* **1996**, *37*, 2777–2780. (c) Chuche, J.; Pale, P. *Eur. J. Org. Chem.* **2000**, 1019–1025.

(20) In this sense, this protocol could be regarded as reminiscent of the Petasis reaction, since it permits the three-component coupling of boronic acids and amines with our substrate: (a) Petasis, N. A.; Zavialov, I. A. *J. Am. Chem. Soc.* **1997**, *119*, 445–446. (b) Petasis, N. A.; Akritopoulou, I. *Tetrahedron Lett.* **1993**, *34*, 583–586.

(1.0 mmol) and the corresponding arylboronic acid (1.3 mmol) in THF (5 mL) was added aqueous NaOH (2 N, 3 mmol). The resulting mixture was degassed under argon and cooled to −40 °C. The ensuing suspension was heated to 60 °C and stirred at that temperature under argon. After the starting materials were consumed (TLC: petroleum ether/EtOAc 2:8), the mixture was diluted with EtOAc and washed with brine. The organic layer was dried, concentrated, and subjected to silica gel column chromatography.

General Procedure B: One-Pot Multicomponent Asembly. To a mixture of compound **5** (1.0 mmol), the corresponding amine (3.0 mmol), and the appropriate boronic acid (1.3 mmol) in THF (5 mL) was added aqueous NaOH (2 N, 3 mmol). The solution was degassed under argon during 10 min, and then $Pd(PPh_3)_4$ (0.05 mmol) was added. The resulting suspension was heated to 60 °C and stirred at that temperature under argon. After the starting materials were consumed (TLC), the mixture was diluted with EtOAc and washed with brine. The organic layer was dried, concentrated, and subjected to silica gel column chromatography.

(2*S*,3*R*,4*R*,*Z*)-2-((*R*)-2,2-Dimethyl-1,3-dioxolan-4-yl)-5-(4-methoxybenzylidene)-4-(piperidin-1-yl)tetrahydrofuran-3-ol, 8. From 7. Following general procedure A, cross-coupling of **7** (50 mg, 0.14 mmol) with *p*-methoxyphenylboronic acid (26 mg, 0.18 mmol) afforded after flash chromatography (EtOAc/hexane 70%) compound **8** (31.4 mg, 73%) as a colorless oil: $[\alpha]^{25}_D$ +75.3 (*c* 1.5, $CHCl_3$); ^{1}H NMR δ ($CDCl_3$, 300 MHz) 7.49 (d, 2 H, J = 8.9 Hz,), 6.85 (d, 2 H, J = 8.9 Hz), 5.40 (s, 1 H), 4.49 (b s, 1 H), 4.43 (m, 2 H), 4.24 (m, 1 H), 4.13 (dd, 1 H, J = 8.6, 3.8 Hz), 3.81 (s, 3 H), 3.51 (s, 1 H), 2.58 (m, 4 H), 1.58 (m, 4 H), 1.50 (s, 3 H), 1.44 (m, 2 H), 1.40 (s, 3 H). ^{13}C NMR δ ($CDCl_3$, 75 MHz) 157.5, 152.4, 129.1, 128.9, 113.8, 109.7, 102.8, 85.0, 76.6, 73.7, 71.5, 67.6, 55.4, 51.7 (×2), 27.0, 26.3 (×2), 25.4, 24.5; API-ES positive 390.0 $(M+1)^+$. Anal. Calcd for $C_{22}H_{31}NO_5$ (389.22): C, 67.84; H, 8.02; N 3.60. Found: C, 67.63; H, 7.96, N 3.55.

From 5. The same compound was obtained following method B for the one-pot multicomponent assembly procedure using epoxide **5** (100 mg, 0.36 mmol), piperidine (107 μL, 1.1 mmol), and *p*-methoxyphenylboronic acid (71 mg, 0.47 mmol). Silica gel chromatography (EtOAc/hexane 70%) provided pure **8** (88 mg, 63%).

Acknowledgment. Generous financial support from Janssen-Cilag is gratefully acknowledged. This research was supported with funds from the Dirección General de Enseñanza Superior (Grants PPQ2003-00396 and CTQ2006-15279-C03-02). A.P. and A.B. thank Janssen-Cilag and the Ministerio de Educacion y Ciencia, respectively, for predoctoral scholarships.

Supporting Information Available: Preparation and physical data for compounds **7**−**17**. This material is available free of charge via the Internet at http://pubs.acs.org