Exploratory Studies en Route to 5-Alkyl-Hyacinthacines: Synthesis of 5-*epi*-(–)-Hyacinthacine A_3 and (–)-Hyacinthacine A_3

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Received 22 December 2009

Abstract: Synthesis of 5-*epi*-(–)-hyacinthacine A_3 and (–)-hyacinthacine A_3 has been achieved from the D-xylose-derived polyhydroxylated cyclic nitrone. Our synthetic strategy is potentially general and flexible for the synthesis of both epimers of 5-alkyl-hyacinthacines.

Key words: nitrone, α-amino nitrile, iminosugars, polyhydroxylated pyrrolizidine, hyacinthacine

Naturally occurring iminosugars (polyhydroxylated alkaloids) are sugar mimics in which a nitrogen replaces the ring oxygen of the corresponding monosaccharide.[1] Many of these molecules exhibit diverse glycosidase inhibitory activities, which have made them attractive candidate agents for the treatment of diseases such as cancer,[2] viral infection,[3] metabolic disorder,[4] or as immunosuppressive agents.[5] Noteworthy members of this important class of natural products are hyacinthacines, which are polyhydroxylated pyrrolizidine alkaloids.[6]

So far 19 hyacinthacines belonging to three groups (hyacinthacine A_1–A_7, B_1–B_7, C_1–C_5) plus several hyacinthacine derivatives bearing a long side chain at C5 have been isolated (Figure 1).[6] They are generally characterized as (7a*R*)-hydro-1,2-dihydroxy-3-hydroxymethyl pyrrolizidines with an alkyl group at C5 in most cases.

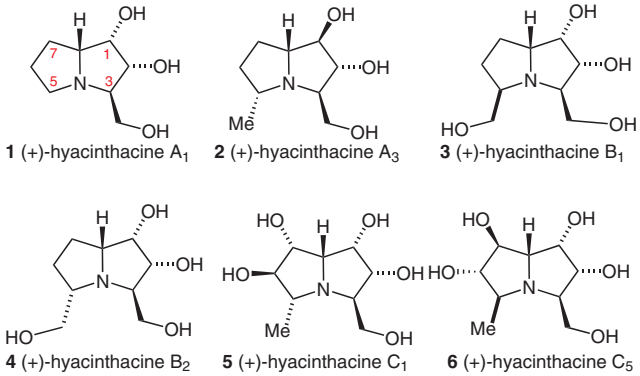


Figure 1 Selected members of hyacinthacines

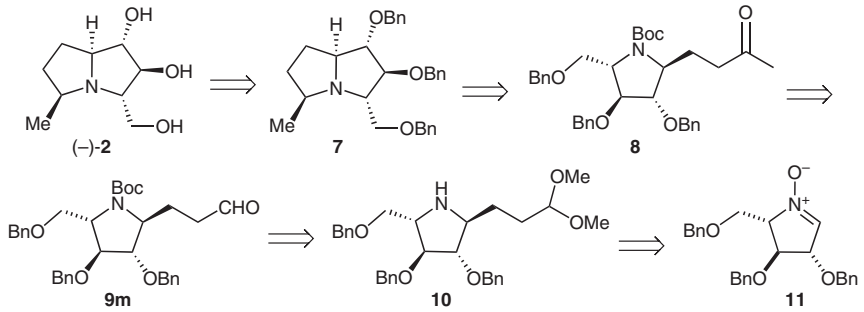
Due to their promising bioactivities and intriguing architectures, the syntheses of hyacinthacines have been extensively investigated and well documented.[7] While many of the existing synthetic methods are elegant and creative, room for improvement still exists due to the length of the current routes, and/or lack of selectivity, and/or flexibility. Taking into account the resemblance between iminosugars and monosaccharides, a flexible and stereoselective synthetic approach that took advantage of intrinsic stereochemistry of momosaccharides would be highly desirable. In the context of our ongoing interest in the synthesis and biological evaluation of the L-iminosugars,[8] noncompetitive inhibitors of glycosidase as shown by recent research, we hoped to develop a general and flexible approach for the rapid generation of the enantiomers of 5-alkyl-hyacinthacines. Our strategy was based on sugar-derived polyhydroxylated cyclic nitrones, and is illustrated here by a total synthesis of (–)-hyacinthacine A_3, the enantiomer of the naturally occurring (+)-hyacinthacines A_3 which had been synthesized by Izquierdo[7b] and Marco,[7o] respectively.

Our retrosynthetic concept for the synthesis of (–)-hyacinthacine A_3 is outlined in Scheme 1. We envisioned that amine **7**, which would furnish (–)-hyacinthacine A_3 by global debenzylation, would be synthesized from ketone **8** by intramolecular reductive amination cyclization. Ketone **8**, in turn, could be prepared from the aldehyde **9m** via a two-step sequence, that is, methyl Grignard addition and subsequent oxidation of the resulting alcohol. Amino acetal **10**, precursor of the aldehyde **9m**, was proposed to derive from the known xylose-derived cyclic nitrone **11**.[9] The proposed synthetic plan, if realized, could be quite general and flexible since a variety of analogues of (–)-hyacinthacine A_3 might be accessible by diversifying the Grignard reagents used in the addition to aldehyde **9m** as well as the starting carbohydrate-derived nitrones.

Nitrones are a versatile class of intermediate in organic synthesis, especially in 1,3-dipolar reactions.[10] The tactic of diastereoselective addition of organometallic reagents to nitrones was first reported by Coates[11] and further explored by many others, such as that of Goti,[12] Petrini,[13] Merino,[14] Trombini.[15]

In our earlier work, we developed an improved practical synthesis of the polyhydroxylated cyclic nitrone **11**.[16] According to this procedure, multigram quantities of the cyclic nitrone **11** could be obtained from D-xylose in an easy

SYNLETT 2010, No. 6, pp 0982–0986
Advanced online publication: 23.02.2010
DOI: 10.1055/s-0029-1219540; Art ID: W20209ST

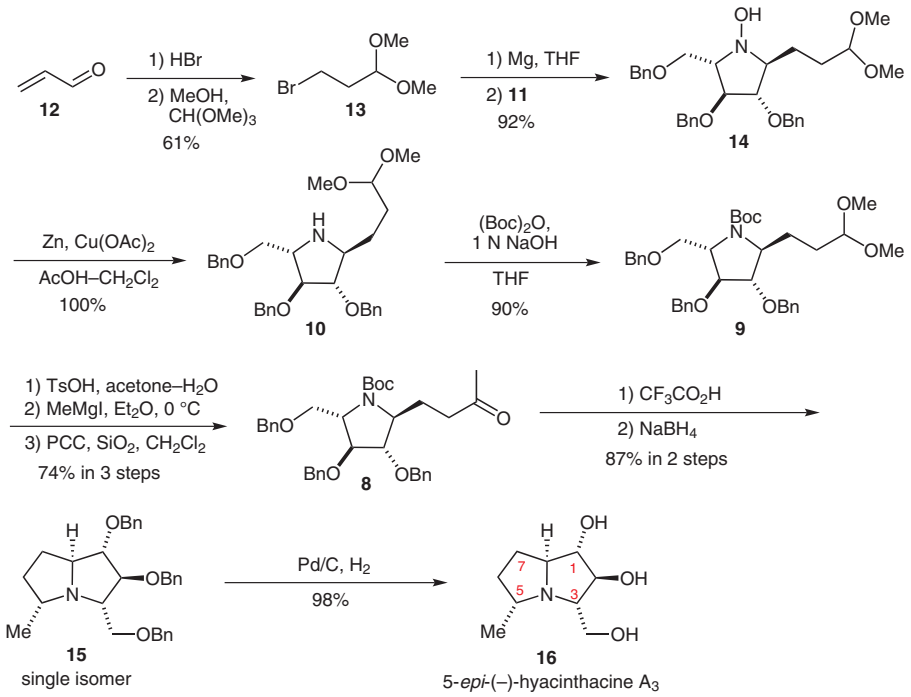


Scheme 1 First-generation retrosynthetic analysis of (–)-hyacinthacine A_3

manner. Thus, treatment of nitrone **11** with (3,3-dimethoxypropyl)magnesium bromide,[17] prepared from acrolein, afforded the hydroxylamine **14** as a single isomer in high yield (92–95%) after recrystallization at low temperature (Scheme 2). The gratifyingly high *trans* selectivity can be explained by a Felkin–Anh transition-state model[18] and is in accordance with previous results.[19] Subsequent reduction of the resulting hydroxylamine **14** with Zn, $Cu(OAc)_2$, and AcOH[20] gave amino acetal **10** in quantitative yield, and the crude product was pure enough for NMR analysis. Protection of amino acetal **10** with $(Boc)_2O$ furnished *N*-Boc-acetal **9** readily. *N*-Boc-acetal **9** was then converted into ketone **8** through a three-step, one-pot sequence, that is, acidic deprotection of the acetal, Grignard addition to the resulting aldehyde, and subsequent oxidation of the epimeric alcohols. Deprotection of ketone **8** with trifluoroacetic acid and $NaBH_4$ reduction of the resulting iminium salt afforded amine **15** in high diastereoselectivity. Palladium-catalyzed hydrogenolysis of **15** furnished the polyhydoxylated pyrrolizidine **16**. However, the NOESY spectrum indicated compound **16** was 5-*epi*-(–)-hyacinthacine A_3 {$[\alpha]_D^{20}$ –39.2 (*c* 0.51, D_2O)}, that is, the product possessed opposite stereochemistry at C5 to the desired configuration of the (–)-hyacinthacine A_3.

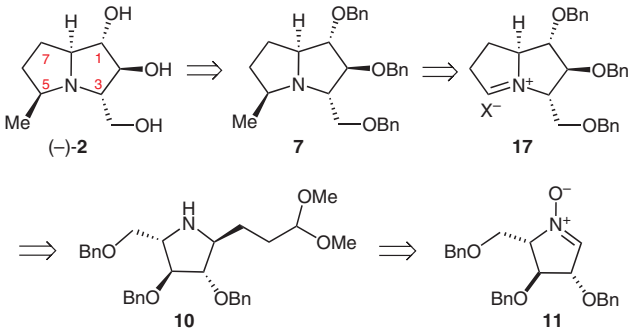
Although the stereo-outcome of the key reductive amination cyclization was neither desirable nor encouraging, we deduced that if an alternative nucleophile, such as a methyl anion instead of hydride, was used in the addition to the iminium intermediate, the correct stereochemistry for (–)-hyacinthacine A_3 might be achieved.

To test our idea and to get (–)-hyacinthacine A_3 in high selectivity, we reformulated our synthetic plan. As depicted in Scheme 3, our revised strategy remained similar to that of our first-generation retrosynthetic analysis. The major alteration to the previous synthetic plan lay in the method for forming the fully protected amine **7**. Based on the experience of synthesizing 5-*epi*-(–)-hyacinthacine A_3 (**16**), we envisaged that the C5 methyl substituent could be introduced by diastereoselective addition of methyl magnesium iodide to the polyhydroxylated bicyclic iminium salt



Scheme 2 Synthesis of 5-*epi*-(–)-hyacinthacine A_3 (**16**)

17, which could be a true iminium species or its equivalent such as the α-amino nitrile.[21] The iminium salt **17**, in turn, could be generated from the previously prepared amino acetal **10**.



Scheme 3 Second-generation retrosynthetic analysis of (–)-hyacinthacine A_3

To execute this synthesis via the revised strategy, attempts were made to prepare iminium salt **17**[22] from amino acetal **10**, but all failed. This forced us to turn our attention to the iminium salt equivalents such as α-amino nitriles, which, as a class of versatile intermediates, have been widely used in a number of synthetic applications, especially as stable iminium salt precursors.[21] Recently, the addition of an organometallic reagent to a bicyclic α-amino nitrile obtained by reductive cyanation, that is, the Bruylants reaction,[23] has been elegantly employed in the nonchiral pool synthesis of (+)-hyacinthacine B_1 by Delair.[7n]

Thus, amino acetal **10** was treated with 1 M HCl and potassium cyanide under biphasic conditions (H_2O–CH_2Cl_2 = 1:1) according to the literature[24] in an attempt to prepare the α-amino nitrile **19**, but unfortunately only trace amount of products were detected after reaction for 10 days. Much to our delight, the reaction proceeded smoothly under homogeneous conditions, that is, when only H_2O was used as the reaction solvent, producing the desired products in high yield (94%) with the expected diastereoselectivity (dr = 44:1; Scheme 4). Single-crystal X-ray analysis of the major product **19**[25] (Figure 2) and a NOESY spectrum of the minor product **18** provided rigorous proof for the proposed structures of the two products. It is worth noting that this synthetic method of α-amino nitrile **19** holds the following obvious merits in that: (a) capable of multigram-scale synthesis, (b) no column chromatography purification was involved during the synthetic sequence starting from D-xylose to the final product **19**.

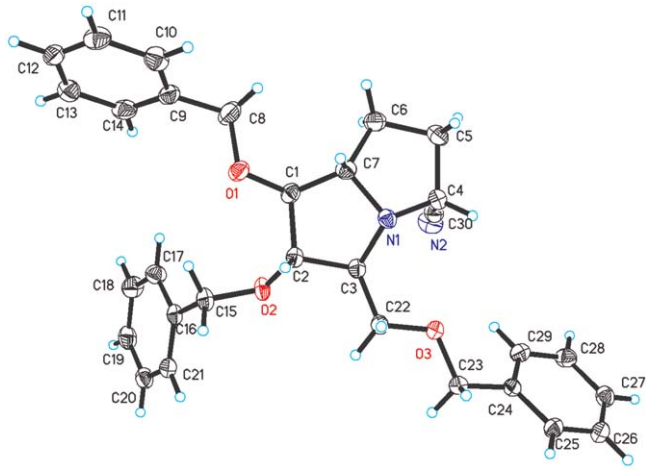


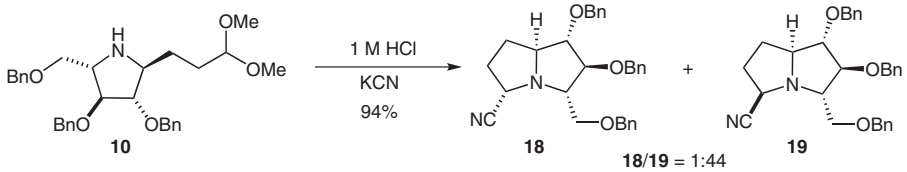
Figure 2 The X-ray crystal structure of compound **19**

Bruylants reaction between α-amino nitrile **19** and methyl magnesium iodide was then investigated (Table 1). The Bruylants reaction of the α-amino nitrile **19** gave no products in the absence of Lewis acid at room temperature, but afforded the desired product **7** at elevated temperature in

Table 1 Bruylants Reaction of α-Amino Nitrile **19** and Methyl Magnesium Iodide

Additive	Solvent	Temp	dr	Yield (%)[c]
–	THF	0 °C to r.t.	–	n.r.
–	THF	reflux	8:1[b]	50
–	toluene	90 °C	–	42
$AgBF_4$	CH_2Cl_2–THF	r.t.	8.6:1[a]	82
AgOTf	CH_2Cl_2–THF	r.t.	8:1[a]	73
$AgNO_3$	CH_2Cl_2–THF	r.t.	7:1[b]	20
CuI	CH_2Cl_2–THF	r.t.	–	n.r.
ZnI_2	CH_2Cl_2–THF	r.t.	7.8:1[b]	40
$BF_3{\cdot}OEt_2$	CH_2Cl_2–THF	r.t.	–	n.r.
TMSOTf	CH_2Cl_2–THF	r.t.	3:1[b]	45

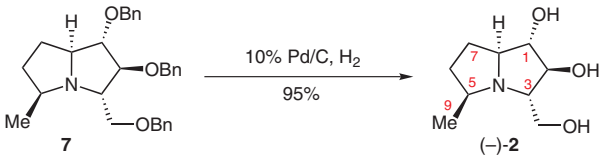
[a] Determined by ^1H NMR.
[b] Determined by isolation of the two epimers.
[c] Isolated yield.



Scheme 4 Synthesis of polyhyroxylated α-amino nitrile **19**

moderate yields. Various Lewis acids were then screened to effect the reaction. All the Ag salts screened generally catalyzed the reaction, but $AgBF_4$ gave the best result.[26] Other inexpensive Lewis acids were also investigated, ZnI_2 and TMSOTf[27] system gave less encouraging results, while CuI and $BF_3{\cdot}OEt_2$[28] system furnished no product.

After catalytic hydrogenolysis of **7**, (–)-**2** was readily obtained in 95% yield (Scheme 5). The 600 MHz NOESY spectrum (D_2O) supported the assigned stereochemistry based on the strong NOE effects observed between the C(9)–H and C(3)–H as well as between the C(9)–H and C(1)–H. The 400 MHz ^1H and ^{13}C NMR of compound (–)-**2** in D_2O were identical to those reported for the natural (+)-hyacinthacine while the optical rotation of (–)-**2** {$[\alpha]_D^{20}$ –16 (*c* 0.50, D_2O)}was opposite to that of the natural product {$[\alpha]_D^{20}$ 19.2 (*c* 0.43, D_2O)}. Therefore, compound (–)-**2** was undisputably determined as the desired product, (–)-hyacinthacine A_3.



Scheme 5 Completion of the synthesis of (–)-hyacinthacine A_3

In summary, the synthesis of (–)-hyacinthacine A_3 has been achieved in five steps with an overall yield of 69% from nitrone **11**. The approach featured stepwise Grignard addition to two sugar-derived activated imine intermediates: nitrone **11** and α-amino nitrile **19**. 5-*epi*-(–)-Hyacinthacine A_3 has also been synthesized starting from the same nitrone **11** via an alternative route with intramolecular reductive amination cyclization as the key step. We have shown that, starting from the same nitrone via the two complementary routes, both (–)-hyacinthacine A_3 and its epimer could be made. This synthetic strategy is potentially general and flexible, suitable for the diversity-oriented synthesis of 5-alkyl-hyacinthacines and their analogues, which is crucial for in-depth structure–activity study on this special class of alkaloids.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

Acknowledgment

This work is supported by The National Natural Science Foundation of China (No. 20672117), The National Basic Research Program of China (No. 2009CB526511), The Ministry of Science and Technology and the Ministry of Health of the P. R. of China (No. 2009ZX09501-006), and The Chinese Academy of Sciences.

References and Notes

(1) (a) Compain, P.; Martin, O. *Iminosugars: From Synthesis to Therapeutic Applications*; J. Wiley and Sons: Chichester, **2007**. (b) Stütz, A. E. *Iminosugars as Glycosidase Inhibitors: Nojirimycin and Beyond*; Wiley-VCH: Weinheim, **1999**. (c) Asano, N.; Nash, R. J.; Molyneux, R. J.; Fleet, G. W. J. *Tetrahedron: Asymmetry* **2000**, *11*, 1645. (d) Watson, A. A.; Fleet, G. W. J.; Asano, N.; Molyneux, R. J.; Nash, R. J. *Phytochemistry* **2001**, *56*, 265. (e) Lillelund, V. H.; Jensen, H. H.; Liang, X.; Bols, M. *Chem. Rev.* **2002**, *102*, 515. (f) Whalen, L. J.; Wong, C.-H. *Aldrichimica Acta* **2006**, *39*, 63.

(2) (a) Wrodnigg, T. M.; Steiner, A. J.; Ueberbacher, B. J. *Anti-Cancer Agents Med. Chem.* **2008**, *8*, 77. (b) Gerber-Lemaire, S.; Juillerat-Jeanneret, L. *Mini-Rev. Med. Chem.* **2006**, *6*, 1043.

(3) (a) Greimel, P.; Spreitz, J.; Stütz, A. E.; Wrodnigg, T. M. *Curr. Top. Med. Chem.* **2003**, *3*, 513. (b) Robina, I.; Moreno-Vargas, A. J.; Carmona, A. T.; Vogel, P. *Curr. Drug Metab.* **2004**, *5*, 329.

(4) (a) Butters, T. D.; Dwek, R. A.; Platt, F. M. *Chem. Rev.* **2000**, *100*, 4683. (b) Fan, J.-Q. *Trends Pharmacol. Sci.* **2003**, *24*, 355.

(5) Ye, X. S.; Sun, F.; Liu, M.; Li, Q.; Wang, Y.; Zhang, G.; Zhang, L. H.; Zhang, X. L. *J. Med. Chem.* **2005**, *48*, 3688.

(6) (a) Kato, A.; Adachi, I.; Miyauchi, M.; Ikeda, K.; Komae, T.; Kizu, H.; Kameda, Y.; Watson, A. A.; Nash, R. J.; Wormald, M. R.; Fleet, G. W. J.; Asano, N. *Carbohydr. Res.* **1999**, *316*, 95. (b) Asano, N.; Kuroi, H.; Ikeda, K.; Kizu, H.; Kameda, Y.; Kato, A.; Adachi, I.; Watson, A. A.; Nash, R. J.; Fleet, G. W. J. *Tetrahedron: Asymmetry* **2000**, *11*, 1. (c) Yamashita, T.; Yasuda, K.; Kizu, H.; Kameda, Y.; Watson, A. A.; Nash, R. J.; Fleet, G. W. J.; Asano, N. *J. Nat. Prod.* **2002**, *65*, 1875. (d) Asano, N.; Ikeda, K.; Kasahara, M.; Arai, Y.; Kizu, H. *J. Nat. Prod.* **2004**, *67*, 846. (e) Kato, A.; Kato, N.; Adachi, I.; Hollinshead, J.; Fleet, G. W. J.; Kuriyama, C.; Ikeda, K.; Asano, N.; Nash, R. J. *J. Nat. Prod.* **2007**, *70*, 993.

(7) (a) Rambaud, L.; Compain, P.; Martin, O. R. *Tetrahedron: Asymmetry* **2001**, *12*, 1807. (b) Izquierdo, I.; Plaza, M. T.; Franco, F. *Tetrahedron: Asymmetry* **2002**, *13*, 1581. (c) Cardona, F.; Faggi, E.; Liguori, F.; Cacciarini, M.; Goti, A. *Tetrahedron Lett.* **2003**, *44*, 2315. (d) Chabaud, L.; Landais, Y.; Renaud, P. *Org. Lett.* **2005**, *7*, 2587. (e) Desvergnes, S.; Py, S.; Vallee, Y. *J. Org. Chem.* **2005**, *70*, 1459. (f) Dewi-Wülfing, P.; Blechert, S. *Eur. J. Org. Chem.* **2006**, 1852. (g) Calveras, J.; Casas, J.; Parella, T.; Joglar, J.; Clapes, P. *Adv. Synth. Catal.* **2007**, *349*, 1661. (h) Zhou, L.; Chen, J.; Cao, X. P. *Synthesis* **2007**, 1359. (i) Donohoe, T. J.; Thomas, R. E.; Cheeseman, M. D.; Rigby, C. L.; Bhalay, G.; Linney, I. D. *Org. Lett.* **2008**, *10*, 3615. (j) Sengoku, T.; Satoh, Y.; Oshima, M.; Takahashi, M.; Yoda, H. *Tetrahedron* **2008**, *64*, 8052. (k) Kaliappan, K. P.; Das, P. *Synlett* **2008**, 841. (l) Chandrasekhar, S.; Parida, B. B.; Rambabu, C. *J. Org. Chem.* **2008**, *73*, 7826. (m) Affolter, O.; Baro, A.; Frey, W.; Laschat, S. *Tetrahedron* **2009**, *65*, 6626. (n) Reddy, P. V.; Koos, P.; Veyron, A.; Greene, A. E.; Delair, P. *Synlett* **2009**, 1141. (o) Ribes, C.; Falomir, E.; Carda, M.; Marco, J. A. *Tetrahedron* **2009**, *65*, 6965.

(8) (a) Asano, N.; Ikeda, K.; Yu, L.; Kato, A.; Takebayashi, K.; Adachi, I.; Kato, I.; Ouchi, H.; Takahata, H.; Fleet, G. *Tetrahedron: Asymmetry* **2005**, *16*, 223. (b) Yu, C.-Y.; Asano, N.; Ikeda, K.; Wang, M.-X.; Butters, T. D.; Wormald, M. R.; Dwek, R. A.; Winters, A. L.; Nash, R. J.; Fleet, G. W. J. *Chem. Commun.* **2004**, 1936. (c) Yu, C. Y.; Huang, M. H. *Org. Lett.* **2006**, *8*, 3021. (d) Davis, B. B.; Nash, R. J.; Watson, A. A.; Griffiths, R. C.; Jones, M. G.; Smith, C.; Fleet, G. W. J. *Tetrahedron Lett.* **1996**, *37*, 8565.

(9) For recent work on polyhydroxylated cyclic nitrones, see: (a) Holzapfel, C. W.; Crous, R. *Heterocycles* **1998**, *48*, 1337. (b) Duff, F. J.; Vivien, V.; Wightman, R. H. *Chem. Commun.* **2000**, 2127. (c) Tamura, O.; Toyao, A.; Ishibashi, H. *Synlett* **2002**, 1344. (d) Carmona, A. T.; Wightman, R. H.; Robina, I.; Vogel, P. *Helv. Chim. Acta* **2003**, *86*, 3066. (e) Cicchi, S.; Marradi, M.; Vogel, P.; Goti, A. *J. Org. Chem.* **2006**, *71*, 1614. (f) Desvergnes, S. P.; Vallee, Y.; Py, S. *Org. Lett.* **2008**, *10*, 2967. (g) Kaliappan, K. P.; Das, P.; Chavan, S. T.; Sabharwal, S. G. *J. Org. Chem.* **2009**, *74*, 6266. (h) Racine, E.; Bello, C.; Gerber-Lemaire, S.; Vogel, P.; Py, S. *J. Org. Chem.* **2009**, *74*, 1766. (i) Tamayo, J. A.; Franco, F.; Lo Re, D.; Sanchez-Cantalejo, F. *J. Org. Chem.* **2009**, *74*, 5679. (j) Tsou, E.-L.; Yeh, Y.-T.; Liang, P.-H.; Cheng, W.-C. *Tetrahedron* **2009**, *65*, 93. (k) Cardona, F.; Parmeggiani, C.; Faggi, E.; Bonaccini, C.; Gratteri, P.; Sim, L.; Gloster, T. M.; Roberts, S.; Davies, G. J.; Rose, D. R.; Goti, A. *Chem. Eur. J.* **2009**, *15*, 1627. (l) Brandi, A.; Cardona, F.; Cicchi, S.; Cordero, F. M.; Goti, A. *Chem. Eur. J.* **2009**, *15*, 7808.

(10) For recent reviews of cycloaddition of nitrones, see: (a) Gothelf, K. V.; Jørgensen, K. A. *Chem. Rev.* **1998**, *98*, 863. (b) Brandi, A.; Cicchi, S.; Cordero, F. M.; Goti, A. *Chem. Rev.* **2003**, *103*, 1213.

(11) (a) Chang, Z.-Y.; Coates, R. M. *J. Org. Chem.* **1990**, *55*, 3464. (b) Chang, Z.-Y.; Coates, R. M. *J. Org. Chem.* **1990**, *55*, 3475.

(12) Cardona, F.; Moreno, G.; Guarna, F.; Vogel, P.; Schuetz, C.; Merino, P.; Goti, A. *J. Org. Chem.* **2005**, *70*, 6552.

(13) (a) Ballini, R.; Marcantoni, E.; Petrini, M. *J. Org. Chem.* **1992**, *57*, 1316. (b) Giovannini, R.; Marcantoni, E.; Petrini, M. *J. Org. Chem.* **1995**, *60*, 5706.

(14) (a) Merino, P.; Franco, S.; Merchan, F. L.; Tejero, T. *Synlett* **2000**, 442. (b) Merino, P. In *Science of Synthesis*, Vol. 27; Padwa, A., Ed.; Thieme: Stuttgart, **2004**, 511–580. (c) Merino, P. *C. R. Chim.* **2005**, *8*, 775.

(15) (a) Lombardo, M.; Trombini, C. *Synthesis* **2000**, 759. (b) Lombardo, M.; Fabbroni, S.; Trombini, C. *J. Org. Chem.* **2001**, *66*, 1264.

(16) Wang, W.-B.; Huang, M.-H.; Li, Y.-X.; Rui, P.-X.; Hu, X.-G.; Zhang, W.; Su, J.-K.; Zhang, Z.-L.; Zhu, J.-S.; Xu, W.-H.; Xie, X.-Q.; Jia, Y.-M.; Yu, C.-Y. *Synlett* **2010**, 488.

(17) Lee, T. V.; Porter, J. R. *Org. Synth., Coll. Vol. IX* **1998**, 643.

(18) Merino, P.; Revuelta, J.; Tejero, T.; Cicchi, S.; Goti, A. *Eur. J. Org. Chem.* **2004**, 776.

(19) Merino, P.; Delso, I.; Tejero, T.; Cardona, F.; Marradi, M.; Faggi, E.; Parmeggiani, C.; Goti, A. *Eur. J. Org. Chem.* **2008**, 2929; and references cited therein.

(20) Dhavale, D. D.; Gentilucci, L.; Piazza, M. G.; Trombini, C. *Liebigs Ann. Chem.* **1992**, 1289.

(21) (a) Enders, D.; Shilvock, J. P. *Chem. Soc. Rev.* **2000**, *29*, 359. (b) Husson, H.-P.; Royer, J. *Chem. Soc. Rev.* **1999**, *28*, 383.

(22) Cook, A. G. *Enamines: Synthesis, Structure, and Reactions*; Marcel Dekker: New York, **1988**, 275–346.

(23) Bruylants, P. *Bull. Soc. Chim. Belg.* **1924**, *33*, 467.

(24) (a) Royer, J.; Husson, H.-P. *Tetrahedron Lett.* **1986**, *26*, 1515. (b) Polniaszek, R. P.; Belmont, S. E. *J. Org. Chem.* **1991**, *56*, 4868.

(25) The crystal structure of **19** has been deposited at the Cambridge Crystallographic Data Centre and allocated the deposition number: CCDC 756239.

(26) (a) Guerrier, L.; Royer, J.; Grierson, D. S.; Husson, H.-P. *J. Am. Chem. Soc.* **1983**, *105*, 7754. (b) Agami, C.; Couty, F.; Evano, G. *Org. Lett.* **2000**, *2*, 2085.

(27) Yue, C.; Royer, J.; Husson, H.-P. *J. Org. Chem.* **1992**, *57*, 4211.

(28) Sun, P.; Sun, C.; Weinreb, S. M. *Org. Lett.* **2001**, *3*, 3507.