Stereoselective Formal Total Synthesis of (–)-Swainsonine from Garner's Aldehyde

Sabbavarapu Narayana Murthy, Yadavalli Venkata Durga Nageswar*

Organic Chemistry Divison-I, Indian Institute of Chemical Technology, Hyderabad 500 607, India
Fax +91(40)27160512; E-mail: dryvdnageswar@gmail.com

Received 2 December 2010; revised 16 December 2010

Abstract: A simple and facile stereoselective formal total synthesis of (–)-swainsonine has been reported starting from Garner's L-serine derived oxazolidine aldehyde. Our synthetic strategy involves stereoselective allylation and Still olefination as key intermediary reaction steps.

Key words: swainsonine, indium, allylation, Garner's aldehyde, Still olefination, indolizidine alkaloid

Due to their significant glycosidase inhibition activity numerous azasugars have been isolated from plant sources as well as microorganisms in the development of therapeutically potent glycosidase inhibitors.[1] Over the years, several synthetic drugs have been developed with a polyhydroxylated piperidine skeleton which have a wide spectrum of biological activity. These include miglitol and miglustat, imino sugars and synthetic analogues of D-glucose that acts as drugs against diabetes mellitus type-2 and Gaucher's type-1 disease, respectively (Figure 1).[2]

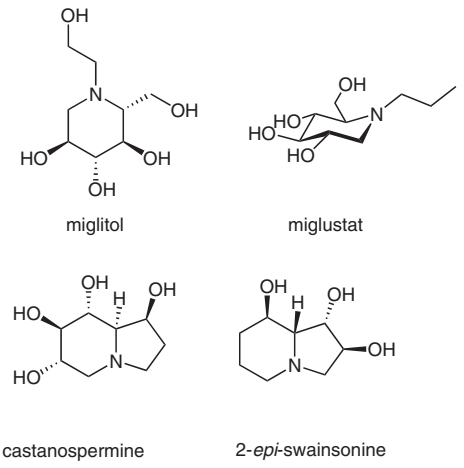


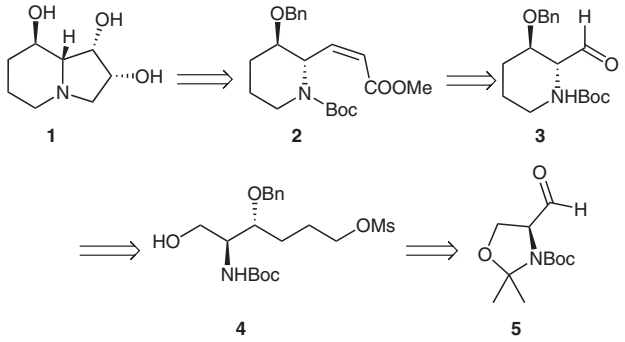
Figure 1 Some of glycosidase inhibitors with a polyhydroxylated piperidine skeleton

Naturally occurring (–)-swainsonine, and its counterpart (+)-swainsonine, with a polyhydroxylated piperidine skeleton belongs to a class of indolizidine alkaloids that has diverse biological activity.[3] The indolizidine ring system is found in many alkaloids isolated from different plant species, such as Asclepiadaceae, Convolvulaceae, Moraceae, and Orchidaceae.[4] These alkaloids are broadly classified into two classes based on the family of species from which they have been isolated. These alkaloids are widely found in nature with the 1-azabicyclo[4.3.0]nonane structural skeleton possessing a broad range of structural and stereochemical features. To date numerous total syntheses have been reported. Mooto et al.[5] reported the total synthesis of (–)-swainsonine from triple reductive amination of a keto-dialdehyde. Trost et al.[6] used tris(dibenzylideneacetone)dipalladium and Trost's chiral ligand, *N*,*N*′-(1*R*,2*R*)-cyclohexane-1,2-diylbis[2-(diphenylphosphino)benzamide], in a palladium-catalyzed desymmetrization reaction. Katsuki et al.[7] have concisely synthesized (–)-swainsonine from a *meso*-pyrrolidine derivative using a (salen)manganese-catalyzed oxidative-desymmetrization. Pearson et al. used D-isoascorbic acid[8] and inexpensive D-ribose[9] to afford (–)-swainsonine. Carretero et al.[10] developed the total synthesis of (–)-swainsonine involving kinetic resolution of a racemic alcohol followed by intramolecular Michael addition as the key step. Pyne et al.[11] utilized the Sharpless asymmetric epoxidation and the nucleophilic ring opening of a chiral vinyl epoxide with an amine. In a novel approach by Blechert et al.,[12] a ruthenium-catalyzed metathesis rearrangement reaction was used. Even though a wide range of synthetic strategies have been reported for the synthesis of (–)-swainsonine, these potent molecules and their analogues are still challenging targets for synthetic organic chemists in the development of practical, relatively short, and efficient synthetic protocols that involve simple reactions. In this regard, we report herein an alternative practical synthesis of (–)-swainsonine via an L-serine-derived oxazolidine aldehyde.

Our retrosynthetic analysis of (–)-swainsonine is shown in Scheme 1. The key steps involved are indium-mediated stereoselective allylation of **5** and the Still reaction with intermediate **3**. The intermediate **3** can be obtained from L-serine-derived oxazolidine aldehyde after a series of functional group manipulations (Scheme 1).

The synthesis of (–)-swainsonine (**1**, Scheme 2) started with the preparation of Garner's aldehyde **5** from readily available L-serine.[13] Garner's aldehyde **5** was subjected to allylation by the literature procedure[14] with allyl bromide to afford a diastereomeric mixture of the homoallylic alcohol **6** (*anti*/*syn* 3:1) that could not be separated by column chromatography. After silylation of homoallylic

SYNTHESIS 2011, No. 5, pp 0755–0758
Advanced online publication: 21.01.2011
DOI: 10.1055/s-0030-1258418; Art ID: Z30510SS

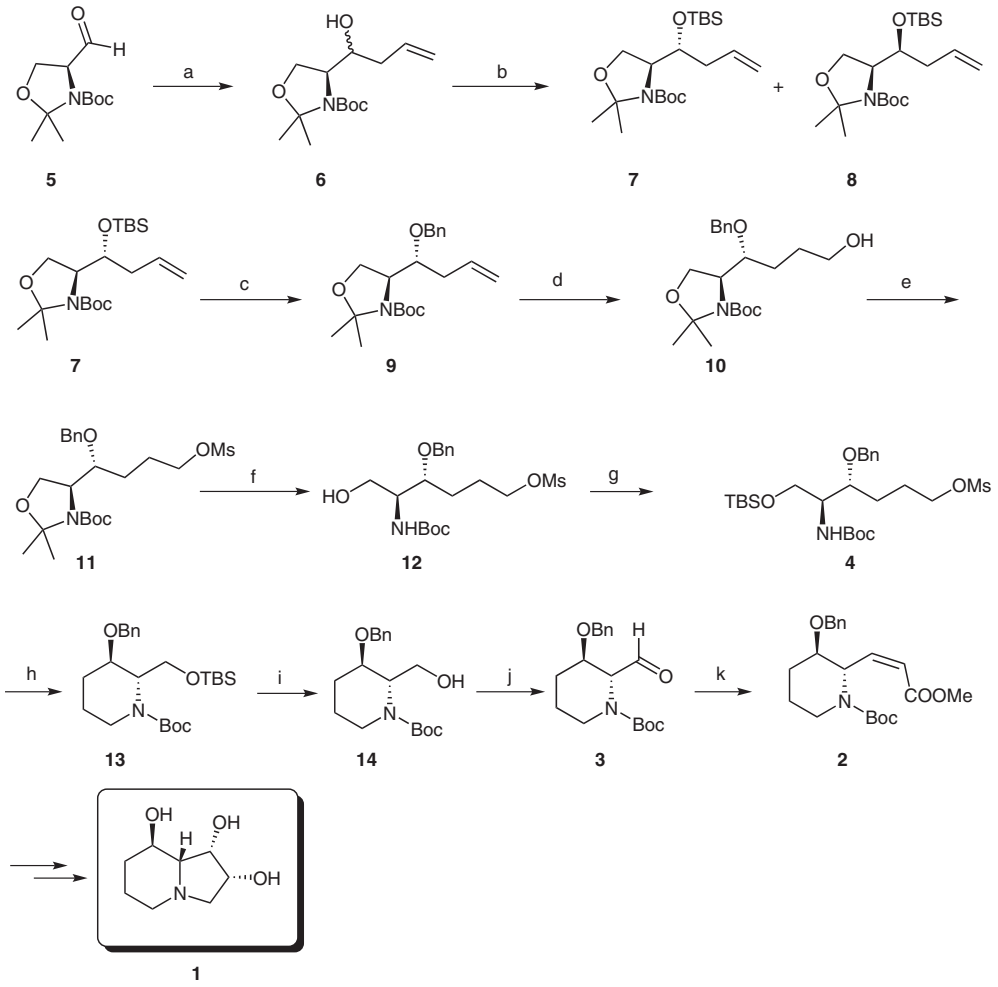


Scheme 1 Retrosynthetic analysis of (–)-swainsonine

alcohol in **6** with *tert*-butyldimethylsilyl chloride, the two diastereomers **7** and **8** can be readily separated by column chromatography. In order to assign the absolute stereochemistry at the newly generated stereocenter in the major diastereomer, the diastereomer was desilylated to yield diastereomerically pure alcohol **7′**, which on treatment with triflic anhydride in the presence of pyridine as base produced the cyclic carbamate **15** (Scheme 3).

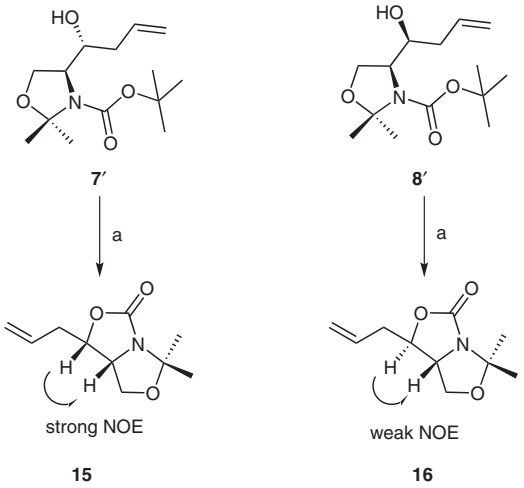
The absolute stereochemistry of the major diastereomeric homoallylic alcohol was further supported by 1D NOE ^{1}H NMR studies and compared with the literature data.[15] Strong NOE was observed between the bridgehead proton and the adjacent proton attached to the quaternary carbon in the five-membered cyclic carbamate due to the *cis*-substitution pattern.

After establishing the absolute stereochemistry of the homoallylic alcohol **7**, it was benzylated to afford **9** in 85% yield, which on hydroboration using borane–dimethyl sulfide produced the corresponding alcohol **10** in 89% yield. Then alcohol **10** was transformed into oxazolidine mesylate **11** in excellent yield (90%) on treatment with mesyl chloride in the presence of triethylamine. Then the acetonide in **11** was deprotected to obtain **12** in 88% yield using cerium(III) chloride heptahydrate and oxalic acid, and the resulting alcohol **12** was silylated using *tert*-butyldimethylsilyl chloride and imidazole and cyclized using sodium hydride. The intermediates **11**, **12**, and **4** were found to be unstable and were isolated and the crude products were subsequently transformed. The silylated alcohol **13**



Scheme 2 *Reagents and conditions*: (a) allyl bromide, indium metal, THF, sat. NH_4Cl soln (cat.), 3 h, 85%; (b) TBDMSCl, CH_2Cl_2, imidazole, 24 h, 95%; (c) (i) TBAF, THF, 1.5 h, 92%; (ii) BnBr, NaH, TBAI, THF, r.t., 24 h, 85%; (d) BH_3–DMS, THF, 0 °C, 2 h, 89%; (e) MsCl, Et_3N, CH_2Cl_2, 0 °C, 2 h, 90%; (f) $CeCl_3 \cdot 7\,H_2O$, $(CO_2H)_2$, MeCN, r.t., 2 h, 88%; (g) TBDMSCl, CH_2Cl_2, imidazole, 2 h, 84%; (h) NaH, THF, 0 °C, 24 h, 87%; (i) TBAF, THF, 3 h, 81%; (j) Dess–Martin periodinane, CH_2Cl_2, 3 h, 80%; (k) $(CF_3CH_2O)_2POCH_2CO_2Me$, 18-crown-6, KHMDS, THF, –78 °C, 82%.

on reaction with tetrabutylammonium fluoride yielded hydroxymethylpiperidine derivative **14** in 81% yield, oxidation of which by Dess–Martin periodinane[16] afforded **3** in 80% yield. This Boc-protected 2-formylpiperidine derivative **3** on reaction with bis(2,2,2-trifluoroethyl) phosphonate under Still reaction conditions[17] gave *Z*-isomer **2** as the major product. The spectral and analytical data of **2** were compared with that reported in the literature. Synthesis of **1** from **2** has already been reported.[18]



Scheme 3 *Reagents and conditions*: (a) Tf_2O, CH_2Cl_2, pyridine.

In conclusion, formal total synthesis of (–)-swainsonine has been achieved in an efficient manner from readily available L-serine.

Solvents were dried and purified by conventional methods prior to use. The progress of all the reactions were monitored by TLC using glass plates precoated with silica gel-60 F254 to a thickness of 0.5 mm (Merck). Column chromatography was performed on silica gel (60–120 mesh) using EtOAc and hexane as the eluents. Optical rotation values were recorded on a Horiba high sensitive polarimeter and IR spectra were recorded with a Perkin-Elmer FT-IR spectrophotometer. ^{1}H NMR spectra were recorded at 200, 300, 400, and 500 MHz and ^{13}C NMR spectra were recorded at 75 MHz using TMS as an internal standard in $CDCl_3$. Mass spectra were obtained on Finnigan MAT1020B or micromass VG 70e70H spectrometer operating at 70 eV using a direct inlet system. All HRMS were recorded on QSTAR XL hybrid MS/MS system equipped with an ESI source (IICT, Hyderabad). Literature procedures were followed for the preparation of **5**[14] and other intermediates[18,19] not given below.

***tert*-Butyl (*R*)-4-[(*R*)-1-Hydroxybut-3-enyl)-2,2-dimethyloxazolidine-3-carboxylate (7′)**

To a magnetically stirred soln of **7** (1.0 mmol) in anhyd THF (2 mL), a soln of TBAF (3.0 mmol) in THF was added and stirring was continued at r.t. for 1.5 h. When the reaction was complete (TLC), the mixture was partitioned between H_2O and Et_2O. The organic layer was washed with sat. aq $NaHCO_3$ soln and brine and dried (anhyd Na_2SO_4). The resultant crude oil was purified by column chromatography to yield **7′** as a colorless oil in 92% yield; R_f = 0.25 (30% EtOAc–hexane).

$[\alpha]_D^{25}$ +25. 2 (*c* 1.1, $CHCl_3$).

IR (KBr): 3401, 2978, 2936, 1690, 1514, 1374, 1249, 1170, 1053, 858, 770 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.88 (m, 1 H), 5.11 (m, 2 H), 4.02–3.76 (m, 4 H), 3.32 (br s, 1 H), 2.20–2.11 (m, 2 H), 1.56 (s, 3 H), 1.47 (m, 12 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 156.3, 138.7, 114.2, 92.9, 79.4, 70.8, 63.9, 62.5, 33.5, 28.5, 28.1, 25.1.

HRMS: *m*/*z* [M + Na]$^+$ calcd for $C_{14}H_{25}NNaO_4$: 294.1681; found: 294.1669.

***tert*-Butyl (2*S*,3*R*)-3-(Benzyloxy)-2-[(*tert*-butyldimethylsilyoxy)methyl]piperidine-1-carboxylate (13)**

To a suspension of NaH (60%, 3.9 mmol) in anhyd THF (2 mL) at 0 °C was added **4** (1.0 mmol) in THF (2 mL). The mixture was stirred at r.t. for 24 h and then the reaction was quenched by addition of H_2O and extracted with Et_2O. The combined ether layers were washed with brine, dried (anhyd Na_2SO_4), and evaporated. The resultant crude product was subjected to column chromatography (silica gel) to give **13** as a colorless oil in 87% yield; R_f = 0. 5 (5% EtOAc–hexane).

$[\alpha]_D^{25}$ +31. 5 (*c* 1.0, $CHCl_3$).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.44 (m, 5 H), 4.79(d, *J* = 12.0 Hz, 1 H), 4.61 (d, *J* = 12.0 Hz, 2 H), 3.81 (m, 4 H), 2.92 (m, 1 H), 2.01 (m, 2 H), 1.83 (m, 2 H), 1.60 (s, 9 H), 1.01 (s, 9 H), 0.18 (s, 6 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 155.4, 138.7, 128.1, 127.2, 79.3, 71.0, 69.8, 61.1, 55.2, 39.3, 28.3, 25.7, 19.3, 18.0, –5.5.

HRMS: *m*/*z* [M + Na]$^+$ calcd for $C_{24}H_{41}NNaO_4Si$: 458.2702; found: 458.2692.

***tert*-Butyl (2*S*,3*R*)-3-(Benzyloxy)-2-(hydroxymethyl)piperidine-1-carboxylate (14)**

To a soln of **13** (1.0 mmol) in anhyd THF (2 mL), a soln of TBAF (3.0 mmol) in THF was added and the stirring was continued at r.t. for 3.0 h. When the reaction was complete (TLC), the mixture was partitioned between H_2O and Et_2O. The organic layer was washed with sat. aq $NaHCO_3$ soln and brine and dried (anhyd Na_2SO_4). The resultant crude oil was purified by column chromatography to yield **14** as a colorless oil in 81% yield; R_f = 0.22 (30% EtOAc–hexane).

$[\alpha]_D^{25}$ –40.3 (*c* 0.9, $CHCl_3$).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.31 (m, 5 H), 4.63 (d, *J* = 12.0 Hz, 1 H), 4.51 (m, 2 H), 3.99 (m, 1 H), 3.72 (dd, *J* = 10.2, 8.8 Hz, 1 H), 3.65 (m, 2 H), 2.80 (m, 1 H), 2.40 (br s, 1 H), 1.86 (m, 2 H), 1.58 (m, 1 H), 1.45 (s, 9 H), 1.39 (m, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 156.2, 138.5, 128.1, 127.3, 79.7, 71.3, 69.9, 60.3, 55.3, 39.5, 28.2, 24.9, 19.4.

MS (ESI): *m*/*z* = 344 [M + Na]$^+$.

***tert*-Butyl (2*S*,3*R*,*Z*)-3-(Benzyloxy)-2-(3-methoxy-3-oxoprop-1-enyl)piperidine-1-carboxylate (2)**

To a soln of 18-crown-6 (5.0 mmol) and methyl bis(2,2,2-trifluoroethoxy)phosphonoacetate (1.12 mmol) in anhyd THF at –78 °C was added KHMDS (1.12 mmol). The mixture was stirred for 1.5 h at this temperature and a soln of aldehyde **3** (1.0 mmol) in THF (2 mL) was added slowly. The resulting mixture was stirred at –78 °C until the reaction was complete (TLC). The reaction was quenched by the addition of aq NH_4Cl soln and extracted with Et_2O. The combined ether layers were washed with brine and dried (anhyd Na_2SO_4). The crude product was purified by column chromatography to give **2** as a colorless oil in 82% yield; R_f = 0.30 (20% EtOAc–hexane).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.21 (m, 5 H), 6.38 (dd, *J* = 11.6, 8.4 Hz, 1 H), 6.16 (m, 1 H), 5.89 (dd, *J* = 11.6, 1.6 Hz, 1 H), 4.89 (d, *J* = 12 Hz, 2 H), 4.10 (m, 1 H), 3.70 (s, 3 H), 3.63 (m, 1 H), 2.92 (m, 1 H), 1.96 (m, 2 H), 1.86 (m, 2 H), 1.41 (s, 9 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 165.2, 154.9, 144.6, 139.3, 128.2, 127.5, 126.3, 120.2, 79.9, 74.1, 70.6, 51.1, 39.5, 29.9, 28.1, 25.8, 19.0.

MS (ESI): m/z = 376 $[M + 1]^+$.

Acknowledgment

We are thankful to Council of Scientific and Industrial Research (CSIR), New Delhi for providing a fellowship to S.N.M.

References

(1) (a) Watson, A. A.; Fleet, G. W. J.; Asano, N.; Molyneux, R. J.; Nash, R. J. *Phytochemistry* **2001**, *56*, 265. (b) Asano, N.; Nash, R. J.; Molyneux, R. J.; Fleet, G. W. J. *Tetrahedron: Asymmetry* **2000**, *11*, 1645. (c) Hakansson, A. E.; Ameijde, A. V.; Gugleilmini, L.; Horne, G.; Nash, R. J.; Evinson, E. L.; Kato, A.; Fleet, G. W. J. *Tetrahedron: Asymmetry* **2007**, *18*, 282.

(2) (a) Aoki, K.; Nakamura, A.; Ito, S.; Nezu, U.; Iwasaki, T.; Takahashi, M.; Kimura, M.; Terauchi, Y. *Diabetes Res. Clin. Pract.* **2007**, *78*, 30. (b) Alfasano, P.; Pampin, S.; Estrada, J.; Rey, J. C. R.; Giraldo, P.; Sancho, J.; Pocovi, M. *Blood Cells Mol. Dis.* **2005**, *35*, 268.

(3) (a) Guengerich, F. P.; DiMari, S. J.; Broquist, H. P. *J. Am. Chem. Soc.* **1973**, *95*, 2055. (b) Schneider, M. J.; Ungemach, F. S.; Broquist, H. P.; Harris, T. M. *Tetrahedron* **1983**, *39*, 29. From the fungus *Metarhizium anisopliae*: (c) Hino, M.; Nakayama, O.; Tsurumi, Y.; Adachi, K.; Shibata, T.; Terano, H.; Kohsaka, M.; Aoki, H.; Imanaka, H. *J. Antibiot.* **1985**, *35*, 926. (d) Patrick, M. S.; Adlard, M. W.; Keshavarz, T. *Biotechnol. Lett.* **1995**, *17*, 433. From the legume *Swainsona canescens*: (e) Colegate, S. M.; Dorling, P. R.; Huxtable, C. R. *Aust. J. Chem.* **1979**, *32*, 2257. From the locoweed *Astragalus lentiginosus*: (f) Molyneux, R. J.; James, L. F. *Science* **1982**, *216*, 190. From Weir vine: (g) Molyneux, R. J.; McKenzie, R. A.; O'Sullivan, B. M.; Elbein, A. D. *J. Nat. Prod.* **1995**, *58*, 878. (h) For a review of the synthesis and biological activity of swainsonine and other glycosidase inhibitors, see: Nishimura, Y. *Studies in Natural Products Chemistry*, Vol. 10; Atta-ur-Rahman, Ed.; Elsevier: Amsterdam, **1992**, 495–583.

(4) Gellert, E. *J. Nat. Prod.* **1982**, *45*, 50.

(5) Zhao, H.; Hans, S.; Cheng, X.; Mooto, D. R. *J. Org. Chem.* **2001**, *66*, 1761.

(6) Trost, B. M.; Patterson, D. E. *Chem. Eur. J.* **1999**, *5*, 3279.

(7) Punniyamurthy, T.; Irie, R.; Katsuki, T. *Chirality* **2000**, *12*, 464.

(8) Pearson, W. H.; Hembre, E. J. *J. Org. Chem.* **1996**, *61*, 7217.

(9) Pearson, W. H.; Ren, Y.; Powers, J. D. *Heterocycles* **2002**, *58*, 421.

(10) De Vicente, J.; Arrayas, R. G.; Canada, J.; Carretero, J. C. *Synlett* **2000**, 53.

(11) Lindsay, K. B.; Pyne, S. G. *J. Org. Chem.* **2002**, *67*, 7774.

(12) Buschmann, N.; Ruckert, A.; Blechert, S. *J. Org. Chem.* **2002**, *67*, 4325.

(13) Dondoni, A.; Perrone, D. *Org. Synth.* **2000**, *77*, 64.

(14) Paquette, L. A.; Mitzel, T. M.; Isaac, M. B.; Crasto, C. F.; Schomer, W. W. *J. Org. Chem.* **1997**, *62*, 4293.

(15) Lemke, A.; Buschleb, M.; Ducho, C. *Tetrahedron* **2010**, *66*, 208.

(16) Dess, D. B.; Martin, J. C. *J. Am. Chem. Soc.* **1991**, *113*, 7277.

(17) Still, W. C.; Gennari, C. *Tetrahedron Lett.* **1983**, *24*, 4405.

(18) Martin, R.; Murruzzu, C.; Pericas, M. A.; Riera, A. *J. Org. Chem.* **2005**, *70*, 2325.

(19) Flamant-Robin, C.; Wang, Q.; Chiaroni, A.; Sasaki, N. A. *Tetrahedron* **2002**, *58*, 10475.