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(*E*)-β-Borylstyrene in the Diels–Alder Reaction with 3,5-Dibromo-2-pyrone for the Syntheses of (±)-1-*epi*-Pancratistatin and (±)- Pancratistatin

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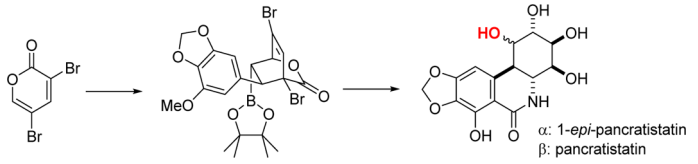
ABSTRACT



New synthetic routes to (±)-1-*epi*-pancratistatin and (±)-pancratistatin were devised using (*E*)-β-borylstyrene as a dienophile for the key Diels–Alder reaction with 3,5-dibromo-2-pyrone. The boronate in the cycloadduct was oxidized to provide the pivotal C1-hydroxyl group of the titled compounds.

Pancratistatin **1**, along with its related Amaryllidaceae natural products (Figure 1), is one of the most actively pursued synthetic targets primiarily due to its potent anticancer activities.[1] The mode of action on the anticarcinogenisis is not clear but believed to be associated with the disruption of peptide biosynthesis.[2] While the immediate clinical development is hampered by its low bioavailability as well as poor water solubility, it is still a highly attractive and promising anticancer drug candidate. Structurally, pancratistatin is built on a heavily fused tricyclic framework entailing six contiguous stereogenic centers on ring C, five substituents on the aromatic A ring, and a highly strained B-ring lactam.

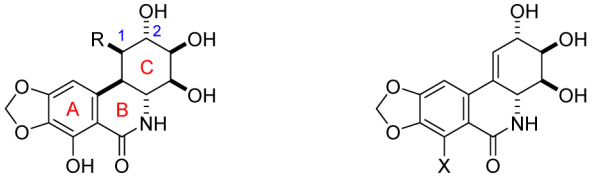


Figure 1. Selected natural isocarbostyryls.

As a part of our ongoing study exploring the synthetic utility of 3,5-dibromo-2-pyrone toward target-oriented synthesis,[3] we have reported the syntheses of pancratistatin **13**[3b] as well as its close relative *trans*-dihydronarciclasine **2**.[3g]

(1) For reviews on the synthesis, see: (a) Jin, Z. *Nat. Prod. Rep.* **2011**, *28*, 1126. (b) Manpadi, M.; Kornienko, A. *Org. Prep. Proced. Int.* **2008**, *40*, 107. (c) Chapleur, Y.; Chretien, F.; Ahmed, S. I.; Khaldi, M. *Current Org. Synth.* **2006**, *3*, 341. (d) Rinner, U.; Hudlicky, T. *Synlett* **2005**, 365. (e) Prabhakar, S.; Tavares, M. R. *Alkaloids Chem. Biol.* **2001**, *15*, 433. (f) Polt, R. *Organic Synthesis: Theory and Applications*; Hudlicky, T., Ed.; JAI: Greenwich, CT, 1997; Vol. 3, p 109. (g) Martin, S. F. In *The Alkaloid*; Bross, A. R., Ed.; Academic: New York, 1987; Vol. 40, p 251.

(2) For reviews or leading articles on the biological activities, see: (a) Griffin, C.; Karnik, A.; McNulty, J.; Pandey, S. *Mol. Cancer Ther.* **2011**, *10*, 57. (b) Pettit, G. R.; Orr, B.; Ducki, S. *Anti-Cancer Drug Des.* **2000**, *15*, 389. (c) Gabrielsen, B.; Monath, T. P.; Huggins, J. W.; Kirsi, J. J.; Hollingshead, M.; Shannon, W. M.; Pettit, G. R. In *Natural Products as Antiviral Agents*; Chu, C. K.; Cutler, H. G., Eds.; Plenum: New York, 1992, pp 121–135. (d) Pettit, G. R.; Gaddamidi, V.; Cragg, G. M.; Herald, D. L.; Singh, S. B.; Cragg, G. M.; Schmidt, J. M.; Boettner, F. E.; Williams, M.; Sagawa, Y. *J. Nat. Prod.* **1986**, *49*, 995.

(3) (a) Jung, Y.-G.; Lee, S.-C.; Cho, H.-K.; Darvatkar, N. B.; Song, J.-Y.; Cho, C.-G. *Org. Lett.* **2013**, *15*, 132. (b) Jung, Y.-G.; Kang, H.-U.; Cho, H.-K.; Cho, C.-G. *Org. Lett.* **2011**, *13*, 5890. (c) Chang, J. H.; Kang, H.-U.; Jung, I.-H.; Cho, C.-G. *Org. Lett.* **2010**, *12*, 2016. (d) Tam, N. T.; Jung, E.-J.; Cho, C.-G. *Org. Lett.* **2010**, *12*, 2012. (e) Tam, N. T.; Cho, C.-G. *Org. Lett.* **2008**, *10*, 601. (f) Tam, N. T.; Chang, J.; Jung, E.-J.; Cho, C.-G. *J. Org. Chem.* **2008**, *73*, 6258. (g) Shin, I.-J.; Choi, E.-S.; Cho, C.-G. *Angew. Chem., Int. Ed.* **2007**, *46*, 2303. (h) Tam, N. T.; Cho, C.-G. *Org. Lett.* **2007**, *9*, 3391. (i) Kim, H.-Y.; Cho, C.-G. *Progress in Heterocyclic Chem.* **2007**, *18*, 1. (j) Ryu, K.; Cho, Y.-S.; Cho, C.-G. *Org. Lett.* **2006**, *8*, 3343.

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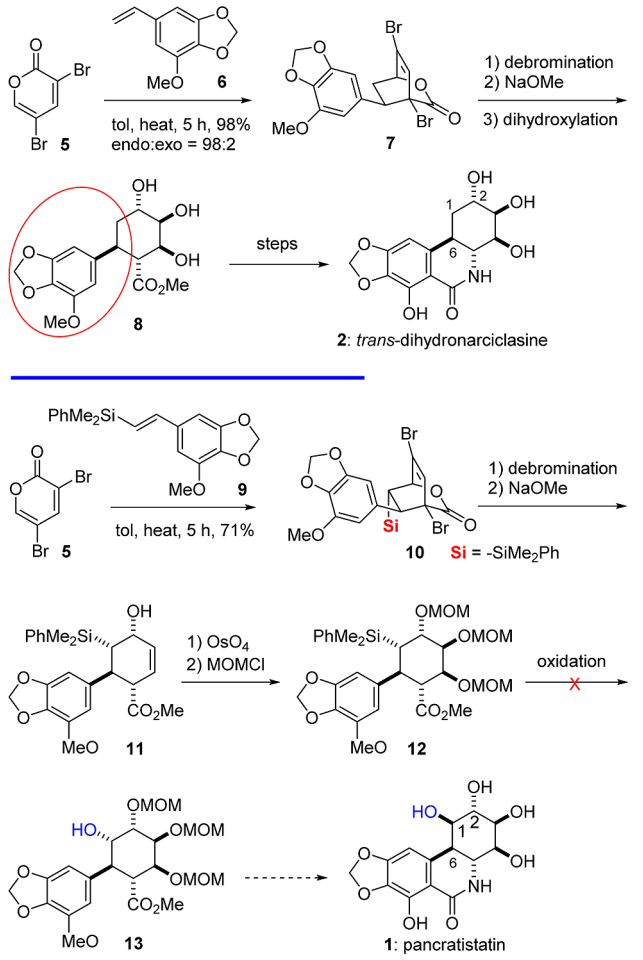
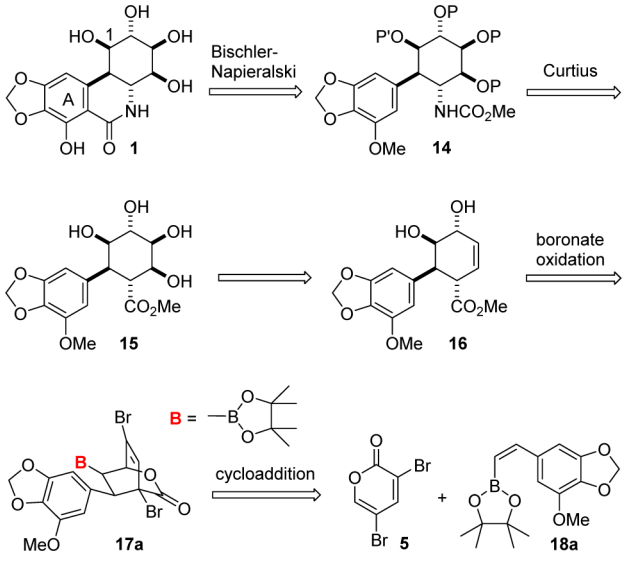
In the synthesis of *trans*-dihydronarciclasine, styrene **6** was employed as a dienophile in the inverse electron-demand Diels–Alder reaction with 3,5-dibromo-2-pyrone **5**, which afforded bicyclolactone **7** in high yield and *endo*-selectivity (Scheme 1).

Scheme 1. Previous Syntheses of *trans*-Dihydronarciclasine and Pancratistatin



Subsequent transformations including debrominations, methanolysis, and OsO_4-mediated dihydroxylation provided the key intermediate **8** equipped with all functional groups required to complete the synthesis of *trans*-dihydronarciclasine. In this synthesis, the styrene dienophile **6** takes up the left side of the molecule marked with the red circle. For further practice of our 2-pyrone strategy to the synthesis of pancratistatin,[4] we needed a synthetic equivalent of the hydroxyl group at the β-position of the styrene dienophile for the installation of the C1–OH group of pancratistatin. Toward this end, β-silyl styrene **9** was prepared and heated for the Diels–Alder reaction with 3,5-dibromo-2-pyrone **5**. The resultant *endo*-cycloadduct **10** was converted into ester **12** before the subjection into the Fleming–Tamao oxidation conditions. However, all the attempts to oxidize the silyl group into the hydroxyl group were fruitless.[5] These failures forced us to conceive another route involving elimination and epoxidation of the resultant double bond, which eventually allowed the completion of the synthesis.[3b] During the investigation, we had looked into the possible use of a more readily oxidizable boronyl ester as a synthetic equivalent of the hydroxyl group (Scheme 2).

Scheme 2. Retrosynthesis of (±)-Pancratistatin



As shown, pancratistatin **1** can be retrosynthetically translated into the pivotal intermediate ester **16**. Further analysis would call for bicyclolactone **17a**, the *endo*-cycloadduct between 3,5-dibromo-2-pyrone **5** and (*Z*)-β-borylstyrene dienophile **18a**. A literature search revealed two isolated reports on (*E*)-β-borylstyrene used as a dienophile in a Diels–Alder reaction, but none on (*Z*)-β-borylstyrene. In those two examples, a (*E*)-β-borylstyrene dienophile required either high reaction temperature (190 °C) or highly activated *o*-quinodimethanes as a diene partner.[6] Due to the lack of proper literature precendents on the β-borylstyrene dienophile, we have prepared (*Z*)-β-styrylboronate **19a**[7] for the

(4) (a) Akai, S.; Kojima, M.; Yamauchi, S.; Kohji, T.; Nakamura, Y.; Sato, K.-i. *Asian J. Org. Chem.* **2013**, *2*, 299. (b) Cagide-Fagín, F.; Nieto-García, O.; Lago-Santomé, H.; Alonso, R. *J. Org. Chem.* **2012**, *77*, 11377. (c) Dam, J. H.; Madsen, R. *Eur. J. Org. Chem.* **2009**, 4666. (d) Li, M.; Wu, A. M.; Zhou, P. J. *Tetrahedron Lett.* **2006**, *47*, 3707. (e) Kim, S.; Ko, H.; Kim, E.; Kim, D. *Org. Lett.* **2002**, *4*, 1343. (f) Rigby, J. H.; Maharoof, U. S. M.; Mateo, M. E. *J. Am. Chem. Soc.* **2000**, *122*, 6624. (g) Magnus, P.; Sebhat, I. K. *J. Am. Chem. Soc.* **1998**, *120*, 5341. (h) Doyle, T. J.; Hendrix, M.; VanDerveer, D.; Javanmard, S.; Haseltine, J. *Tetrahedron* **1997**, *53*, 11153. (i) Hudlicky, T.; Tian, X.; Königsberger, K.; Maurya, R.; Rouden, J.; Fan, B. *J. Am. Chem. Soc.* **1996**, *118*, 10752. (j) Trost, B. M.; Pulley, S. R. *J. Am. Chem. Soc.* **1995**, *117*, 10143. (k) Tian, X. R.; Hudlicky, T.; Königsberger, K. *J. Am. Chem. Soc.* **1995**, *117*, 3643. (l) Danishefsky, S.; Lee, J. Y. *J. Am. Chem. Soc.* **1989**, *111*, 4829.

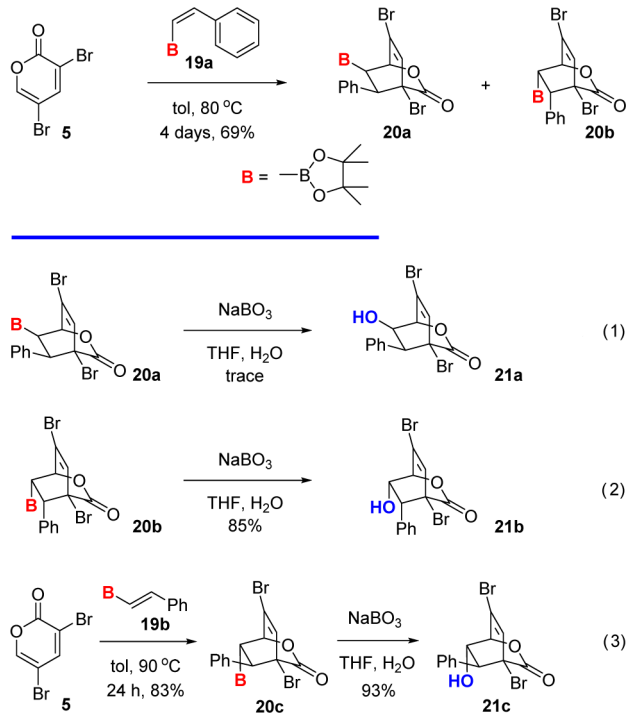
(5) (a) Mader, M. M.; Norrby, P.-O. *J. Am. Chem. Soc.* **2001**, *123*, 1970. (b) Fleming, I.; Henning, R.; Parker, D. C.; Plaut, H. E.; Sanderson, P. E. J. *J. Chem. Soc. Perkin Trans. 1* **1995**, 317.

(6) (a) Yoshida, H.; Mukae, M.; Ohshita, J. *Chem. Commun.* **2010**, *46*, 5253. (b) Batey, R. A.; Thadani, A. N.; Lough, A. J. *J. Am. Chem. Soc.* **1999**, *121*, 450.

(7) Deloux, L.; Srebnik, M. *J. Org. Chem.* **1994**, *59*, 6871.

model cycloaddition reaction with 3,5-dibromo-2-pyrone **5** (Scheme 3).

Scheme 3. Diels–Alder Reaction with β-Borylstyrene and Oxidation Reaction

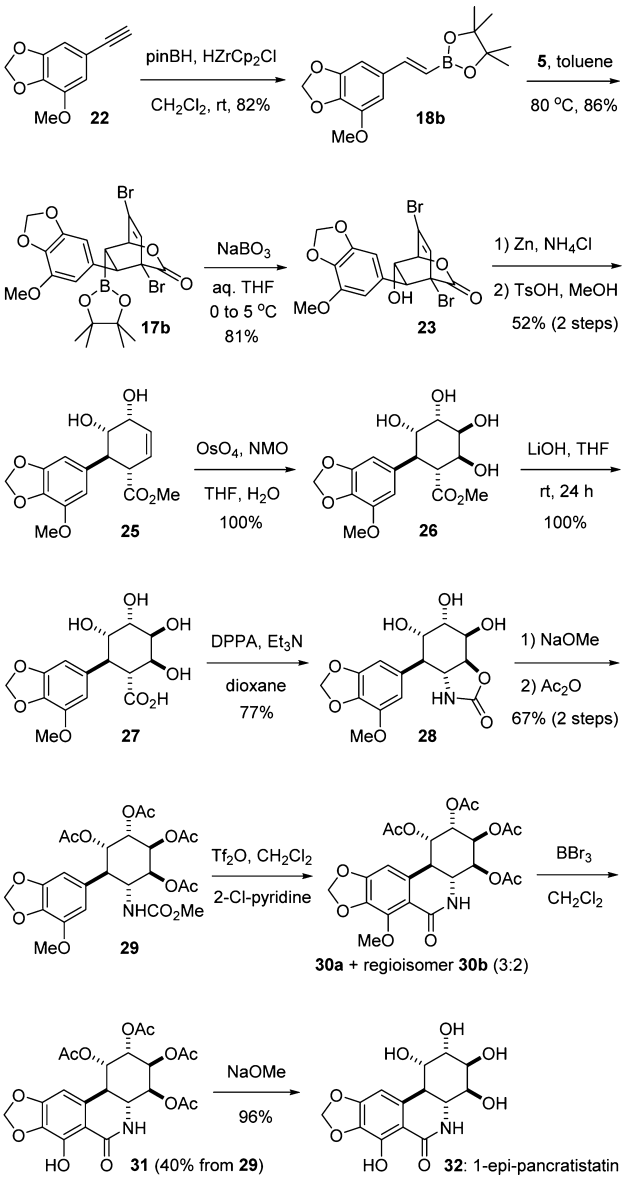


Despite our concern, (*Z*)-β-borylstyrene **19a** produced the cycloadducts **20a** and **20b** in the isolation yields of 46% and 23%, respectively, when heated in toluene at 80 °C. However, subsequent oxidation of the boronate group turned out to be problematic. While *exo*-adduct **20b** was readily oxidized to give alcohol **21b** in 85% yield (eq 2), *endo*-isomer **20a** did not afford the expected alcohol product **21a** (eq 1), when treated with sodium perborate under the standard reaction conditions.[8] Attempted oxidation under various other literature conditions gave no improvement. Rather than digging into these interesting results in further detail, we came to believe that the orientation of the boronate group would bring about such an unexpected reactivity difference. Thus, we opted to prepare (*E*)-β-borylstyrene **19b**[9] for the cycloaddition reaction with 3,5-dibromo-2-pyrone **5** (eq 3). When heated in toluene, the reaction provided mostly *endo*-adduct **20c** where the boronate group is oriented away from the olefin bridge. To our delight, oxidation with sodium perborate afforded the corresponding alcohol **21c** in 93% yield. Encouraged by the model study, we started the synthesis of (±)-pancratistatin by preparing the fully substituted (*E*)-β-borylstyrene **18b** from alkyne **22** (Scheme 4).

When heated in toluene, (*E*)-β-borylstyrene **18b** was smoothly cycloadded to the diene 3,5-dibromo-2-pyrone

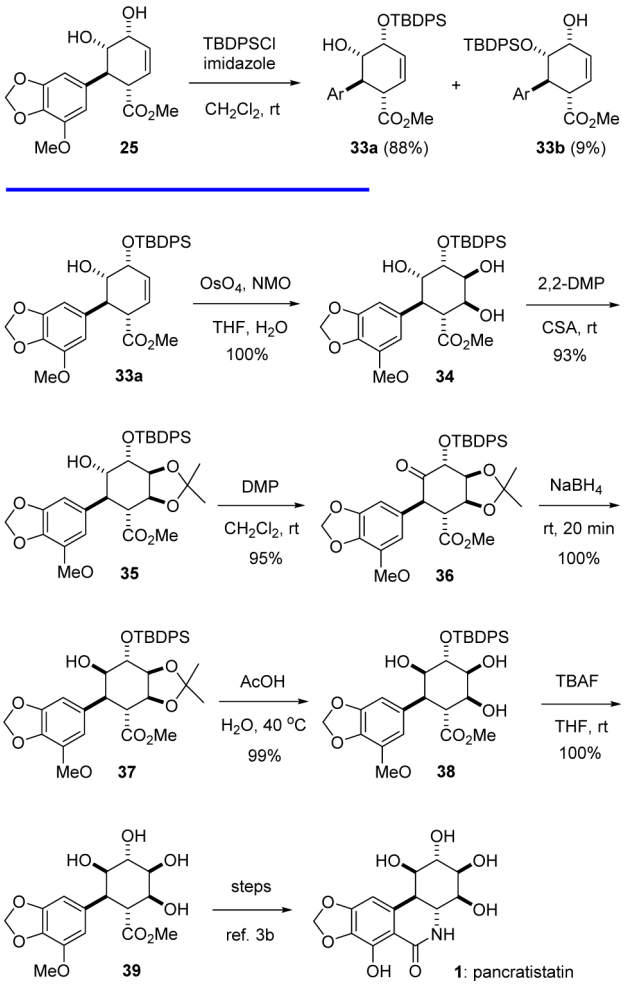
(8) Hussain, M. M.; Li, H.; Hussain, N.; Ureña, M.; Carroll, P. J.; Walsh, P. J. *J. Am. Chem. Soc.* **2009**, *131*, 6516.
(9) Pereira, S.; Srebnik, M. *Organometallics* **1995**, *14*, 3127.

Scheme 4. Synthesis of (±)-1-*epi*-Pancratistatin



5 to afford *endo*-bicyclolactone **17b** in 86% yield after 20 h. Treatment with sodium perborate provided the desired alcohol **23** in 81% yield. Debromination and methanolysis gave diol **25**. Subsequent Upjohn dihydroxylation with OsO_4/NMO provided the corresponding tetraol **26** in quantitative yield. The methyl ester was hydrolyzed into acid **27** for the ensuing Curtius rearrangement. Treatment with DPPA/DMAP afforded imidazolidinone **28** in 77% yield. Evidently, the initailly formed isocyanate intermediate underwent an addition reaction with the nearby hydroxyl group. Successive treatments with NaOMe and Ac_2O provided methyl carbamate **29** in 67% total yield over two steps. The Bischler–Napieralski lactam formation under the Banwell's modified conditions gave lactam **30a** and its regioisomer **30b** as an inseparable mixture (3:2).[10] Demethylation reaction of the mixture provided **31** free from its regioisomer in 40% overall

Scheme 5. Synthesis of (±)-Pancratistatin



yield from tetraacetate **29** (two steps). Finally, removal of ester protecting groups furnished hitherto unknown (±)-1-*epi*-pancratistatin **32**.[11]

(10) (a) In, J.; Hwang, S.; Kim, C.; Seo, J. H.; Kim, S. *Eur. J. Org. Chem.* **2013**, 965. (b) Banwell, M. G.; Bissett, B. D.; Busato, S.; Cowden, C. J.; Hockless, D. C. R.; Holman, J. W.; Read, R. W.; Wu, A. W. *J. Chem. Soc., Chem. Commun.* **1995**, 2551.

The same route can also be applied to the synthesis of pancratistatin with the configurational inversion of the C1-hydroxyl group at an appropriate stage during the synthesis. Toward this, diol **25** was chosen for selective protection of the C2-hydroxyl group. To our convenience, a simple silylation with TBDPSCl under the usual reaction conditions provided the desired C2-OTBDPS **33a** in 88% yield (Scheme 5). The dihydroxylation and subsequent protection of the resulting syn-1,2-diol gave acetonide **35**. Unfortunately, attempted Mitsunobu inversion of the C1-OH group resulted in no success, presumably due to the steric hindrance. As a quick alternative, a pathway involving oxidition/reduction was followed, instead. Thus, alcohol **35** was oxidized into ketone **36** which was then reduced with $NaBH_4$ to provide the desired alcohol **37** in 95% overall yield. In the reduction, the hydride was delivered exclusively from the face opposite to the bulky aryl group. Successive removal of the acetonide and TBDPS protecting groups afforded tetraol **39**. The rest of the synthesis en route to (±)-pancratistatin **1** is identical to our previously reported process.[3b]

In summary, new synthetic routes to (±)-1-*epi*-pancratistatin and (±)-pancratistatin were devised, utilizing (*E*)-*β*-borylstyrene as a dienophile for the inverse electron-demand Diels–Alder cycloaddition with 3,5-dibromo-2-pyrone. The boronate in the cycloadduct was readily oxidized to ultimately provide the C1-OH of (±)-1-*epi*-pancratistatin **32** and (±)-pancratistatin **1**.

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Supporting Information Available. Details of experimental procedures and characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

(11) 3,4-Acetonide of 1-*epi*-pancratistatin has been prepared during the semisynthesis of (+)-pancratistatin from (+)-narciclasine. (a) Pettit, G. R.; Melody, N.; Herald, D. L. *J. Org. Chem.* **2001**, *66*, 2583. (b) Marion, F.; Anereau, J.-P.; Fahy, J. Nitrogenated derivatives of pancratistatin. PCT Int. Appl. WO2010012714, July 29, 2009.

The authors declare no competing financial interest.