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β-Silyl Styrene As a Dienophile in the Cycloaddition with 3,5-Dibromo-2-pyrone for the Total Synthesis of (±)-Pancratistatin

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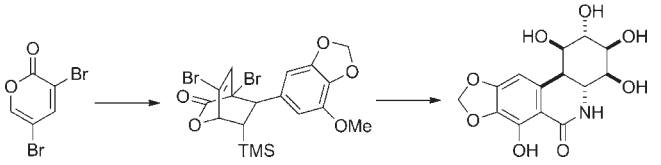
ABSTRACT



A new synthetic route to (±)-pancratistatin was devised utilizing β-silyl styrene as a dienophile in the cycloaddition with 3,5-dibromo-2-pyrone. The TMS group incorporated in the cycloadduct permitted a facile elimination process for the eventual installation of the C(1)–OH function. Subsequent transformations including Curtius rearrangement and Bischler–Napieralski reactions completed the total synthesis of (±)-pancratistatin.

First isolated by Pettit and co-workers in 1984 from the bulbs of Hawaiian *Hymenocallis littoralis* (originally *Pancratium litterale*),[1] pancratistatin **1** has attracted tremendous attention over the past decades due to the highly potent selective anticancer activities.[2] The molecular basis of anticarcinogenesis has been attributed to its disruption of peptide biosynthesis, based on the structural similarity to the close relative narciclasine **2** (Figure 1). However, further clinical development is hampered by its low bioavailability as well as poor water solubility.

1: R = OH, pancratistatin
3: R = H, *trans*-dihydronarciclasine

2: X = OH, narciclasine
4: X = H, lycoricidine

Figure 1. Selected examples of natural isocarbostyryls.

Despite the moderate molecular size, pancratistatin is a quite challenging synthetic target because of its structural complexity that includes six contiguous stereogenic centers on ring C, five substituents on the aromatic A ring, and highly strained B-ring lactam. Since the first total synthesis reported by Danishefsky and Lee in 1989,[3] a number of elegant synthetic strategies and routes have been devised and resulted in eight completed total syntheses.[4]

As a part of our ongoing study exploring the utility of 3,5-dibromo-2-pyrone in target-oriented synthesis,[5] we have reported the first total synthesis of (±)-*trans*-dihydronarciclasine **3**,[5e] by using the highly *endo*-selective

(1) Pettit, G. R.; Gaddamidi, V.; Cragg, G. M.; Herald, D. L.; Sagawa, Y. *J. Chem. Soc., Chem. Commun.* **1984**, 1693.

(2) For reviews on the synthesis, see: (a) Manpadi, M.; Kornienko, A. *Org. Prep. Proced. Int.* **2008**, *40*, 107. (b) Chapleur, Y.; Chretien, F.; Ahmed, S. I.; Khaldi, M. *Curr. Org. Synth.* **2006**, *3*, 341. (c) Jin, Z. *Nat. Prod. Rep.* **2005**, *22*, 111. (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. For reviews or leading articles on the biological activities, see: (h) Pettit, G. R.; Orr, B.; Ducki, S. *Anti-Cancer Drug Des.* **2000**, *15*, 389. (i) 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. (j) 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.

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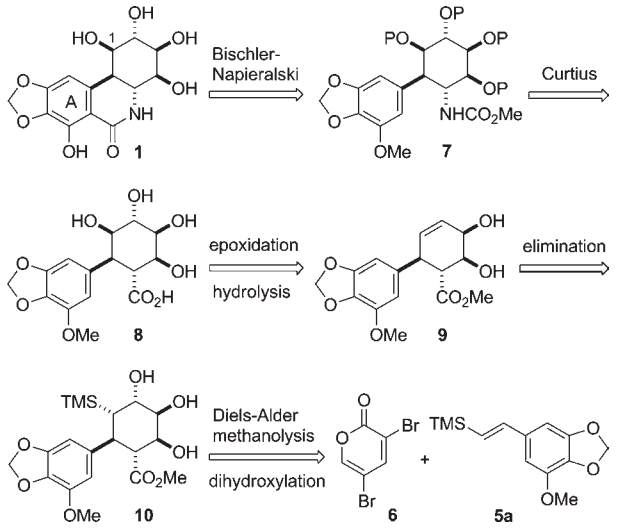
Diels–Alder cycloaddition reaction of 3,5-dibromo-2-pyrone with a styrene type dienophile as a key reaction. We have further envisioned that the same synthetic strategy could also be effective for pancratistatin, as it differs only with the C(1)–OH function. Reported herein is the successful extension of our 2-pyrone strategy for the synthesis of (±)-pancratistatin, which yet required substantial experimentations in spite of the structural similarity.

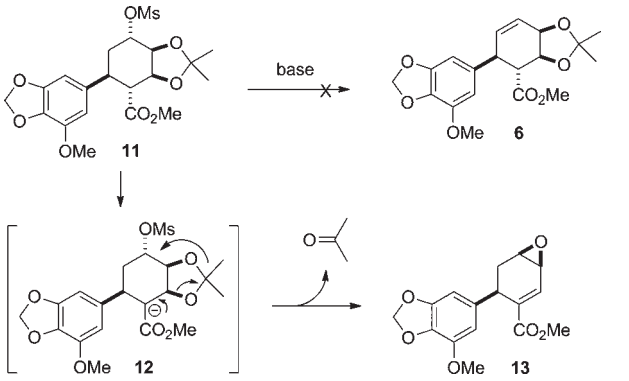
Scheme 1. Retrosynthesis of Pancratistatin



Notable features of our synthetic plan include (1) installation of the key C(1)–OH group via epoxidation and the hydrolysis reaction of cyclohexene **9** (**9** → **8**, Scheme 1) and (2) the use of (*E*)-*β*-silyl styrene **5a** as a dienophile partner in the cycloaddition with 3,5-dibromo-2-pyrone **6**. The resultant *β*-hydroxy silane **10** would be readily eliminated to afford alkene **9**.

Initially we planned to make cyclohexene **9** from mesylate **11** readily accessed from the corresponding alcohol intermediate employed in our synthesis of *trans*-dihydronarciclasine.[5e] However, all the attempts to bring about the elimination reaction into **6** were not successful (Scheme 2). Epoxide **13** was obtained instead as a major product in most cases, presumably via the process involving deprotonation, elimination, and epoxide formation.

Scheme 2. Elimination Reaction of Mesylate **11**



Consequently, a new synthetic route was elaborated, this time, to go through *β*-hydroxy silane **10**, making use of its facile elimination process (*vide supra*, Scheme 1). The required (*E*)-*β*-silyl styrene **5a** was prepared from alkyne **14** by following the route shown in Scheme 3.[6] Conversion into TMS-alkyne **15** followed by a hydroalumination reaction provided *β*-silyl styrene **5** as a mixture of *E*- and *Z*-isomers. As demonstrated in the literature,[7] the stereochemical outcome of the hydroalumination is highly solvent-dependent. In toluene, the reaction afforded exclusively *Z*-isomer **5b** in 67% yield. The reaction in pentane gave the best results, with respect to the *E*/*Z* ratio (5:1) and product yield (78% total yield). Despite the presence of the *Z*-isomer (~17%), the ensuing cycloaddition with 3,5-dibromo-2-pyrone gave 5-*endo*-6-*exo*-*trans*-bicyclolactone **16a** only, with no trace of either 5-*endo*-6-*endo*-*cis*- *or* 5-*exo*-6-*exo*-*cis*-bicyclolactone. Therefore, the stereochemistry of *β*-silyl styrene was inconsequential in this case. Apparently, the cycloaddition reaction proceeded in a stepwise rather than concerted manner.[8] The exclusive formation of 5-*endo*-6-*exo*-*trans*-bicyclolactone **16a** from the cycloaddition with pure (*Z*)-*β*-silyl styrene **5b** further corroborates its stepwise nature. In addition, (*Z*)-*β*-silyl styrene **5b** used in excess (1.3 equiv) in the cycloaddition was found to be isomerized into (*E*)-isomer **5a**. Therefore, the cycloaddition reaction with (*Z*)-isomer **5b** would go through zwitterionic intermediate **17a**, for example, as a result of a 1,6-addition type reaction. Rotation about the C–C bond gives more stable, less sterically crowded **18a**, resulting in the formation of bicyclolactone **16a**. Retro-1, 6-addition of **18a** would account for the generation of (*E*)-*β*-silyl styrene **5a** in the reaction mixture. The (*E*)-*β*-silyl styrene **5a** was later prepared more conveniently from bromide **19** via the Suzuki coupling reaction with trifluoroborate **20**.[9]

(3) Danishefsky, S.; Lee, J. Y. *J. Am. Chem. Soc.* **1989**, *111*, 4829.

(4) (a) Tian, X.; Hudlicky, T.; Konigsberger, K. *J. Am. Chem. Soc.* **1995**, *117*, 3643. (b) Trost, B. M.; Pulley, S. R. *J. Am. Chem. Soc.* **1995**, *117*, 10143. (c) Doyle, T. J.; Hendrix, M.; Van Derveer, D.; Javanmard, S; Haseltine, J. *Tetrahedron* **1997**, *53*, 11153. (d) Magnus, P.; Sebhat, I. K. *J. Am. Chem. Soc.* **1998**, *120*, 5341. (e) Rigby, J. H.; Maharoof, U. S. M.; Mateo, M. E. *J. Am. Chem. Soc.* **2000**, *122*, 6624. (f) Pettit, G. R.; Melody, N.; Herald, D. L. *J. Org. Chem.* **2001**, *66*, 2583. (g) Kim, S.; Ko, H.; Kim, E.; Kim, D. *Org. Lett.* **2002**, *4*, 1343. (h) Li, M.; Wu, A.; Zhou, P. *Tetrahedron Lett.* **2006**, *47*, 3707.

(5) (a) Chang, J. H.; Kang, H.-U.; Jung, I.-H.; Cho, C.-G. *Org. Lett.* **2010**, *12*, 2016. (b) Tam, N. T.; Jung, E.-J.; Cho, C.-G. *Org. Lett.* **2010**, *12*, 2012. (c) Tam, N. T.; Cho, C.-G. *Org. Lett.* **2008**, *10*, 601. (d) Tam, N. T.; Chang, J.; Jung, E.-J.; Cho, C.-G. *J. Org. Chem.* **2008**, *73*, 6258. (e) Shin, I.-J.; Choi, E.-S.; Cho, C.-G. *Angew. Chem., Int. Ed.* **2007**, *46*, 2303. (f) Tam, N. T.; Cho, C.-G. *Org. Lett.* **2007**, *9*, 3319. (g) Kim, H.-Y.; Cho, C.-G. *Prog. Heterocycl. Chem.* **2007**, *18*, 1. (h) Ryu, K.; Cho, Y.-S.; Cho, C.-G. *Org. Lett.* **2006**, *8*, 3343.

(6) Direct synthesis of **15** from aryl bromide **19** via the Sonogashira coupling reaction with TMS-acetylene was not successful.

(7) (a) Sheshenev, A.; Baird, M. S.; Bolesov, I. G.; Shshkov, A. S. *Tetrahedron* **2009**, *65*, 10552. (b) Eisch, J. J.; Foxton, M. W. *J. Org. Chem.* **1971**, *36*, 3520. (c) Slaugh, L. H. *Tetrahedron* **1966**, *22*, 1741.

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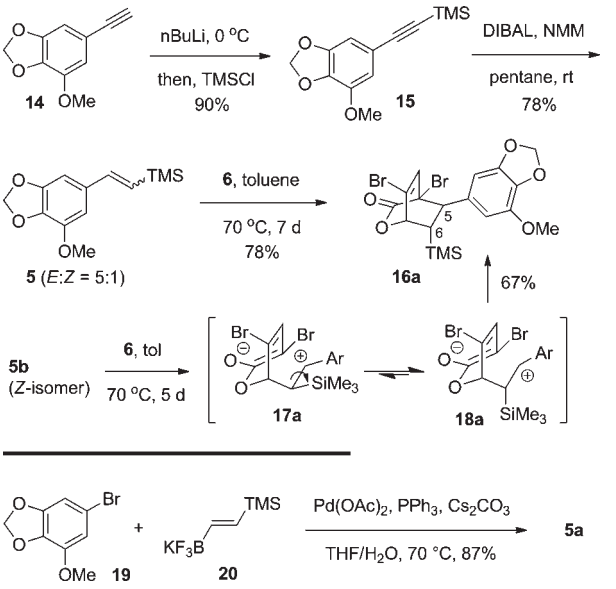
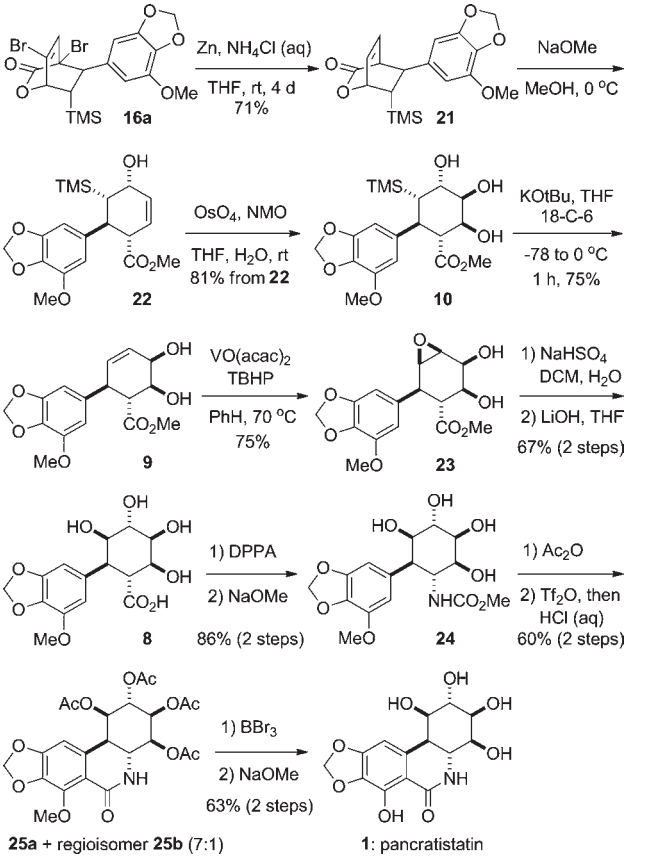
(9) Molander, G. A.; Felix, L. A. *J. Org. Chem.* **2005**, *70*, 3956.

Scheme 3. Preparation and Cycloaddition of β-Silyl Styrene **5**



Bicyclolactone **16a** was treated with excess Zn to remove the bromine atoms prior to the lactone opening with NaOMe, which gave the desired ester **22** along with a small amount of an inseparable double bond migrated α,β-unsaturated ester (Scheme 4). Maintaining the reaction temperature to not exceed 0 °C is necessary to suppress the double bond isomerization. Dihydroxylation with OsO_4 provided triol **10** in 81% yield from lactone **21** over two steps.[10] Subsequent Peterson elimination of this β-hydroxysilane afforded olefin **9** which was treated with $VO(acac)_2$/TBHP[11] to give epoxide **23**. A sodium hydrogen sulfate mediated hydrolysis of the epoxide[12] and ester hydrolysis provided acid **8** in 67% yield over two steps from **23**. The Curtius rearrangement of the resultant acid followed by treatment with NaOMe gave carbamate **24** in 86% overall yield. The remaining steps to the final pancratistatin including protection of the hydroxyl groups, formation of the lactam B ring, and global removal of the protecting groups were achieved by using the conditions developed by Magnus et al.[4d] The Bischler–Napieralski reaction on **24** under Banwell's modified conditions,[4a,13] conducted after the peracetylation, provided lactam as a mixture of **25a** and inseparable regioisomer **25b** (7:1) in a combined yield of 60% over two steps from **24**. They became readily separable later as only the desired regioisomer **25a** underwent BBr_3-mediated demethylation reaction. Finally, the acetyl groups were removed to furnish (±)-pancratistatin **1**.

Scheme 4. End Game Synthesis of (±)-Pancratistatin



In summary, a new synthetic route to (±)-pancratistatin was devised utilizing β-silyl styrene as a dienophile in the cycloaddition with 3,5-dibromo-2-pyrone. The TMS group incorporated in the cycloadduct permitted a facile elimination process for the eventual installation of the C(1)–OH function. Subsequent transformations including Curtius rearrangement and Bischler–Napieralski reactions completed the total synthesis of (±)-pancratistatin.

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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.

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