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Total Synthesis of (+)-Strictifolione

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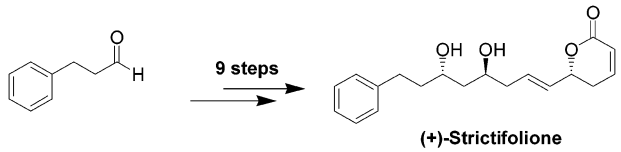
ABSTRACT



The synthesis of (+)-strictifolione was achieved from 3-phenylproprionaldehyde by using enantioselective allyltitanations to control the stereogenic centers at C6, C4′, and C6′ and a cross-methathesis to control the configuration of the double bond at C1′−C2′.

Recently, a number of 5,6-dihydro-α-pyrone derivatives having an alkyl side chain at the C6 position, with 1,3- or 1,5-diol units, have been isolated from plants. The biological activities of these compounds have not been completely studied, but it seems that the activity depends on the substituents on the alkyl side chain. Some of these compounds have been found to exhibit antifungal activity such as passifloricin A,[1] to inhibit the cell cycle progression in the M-phase and to be an immunosuppressive agent such as (−)-pironetin,[2] to exhibit cytotoxic activity such as callystatin A[3] and leptomycin B,[4] or to be an anticancer agent such as fostriecin[5] (Figure 1). In the course of our program to synthesize 6-substituted 5,6-dihydro-α-pyrones, we became interested in the synthesis of (+)-strictifolione.

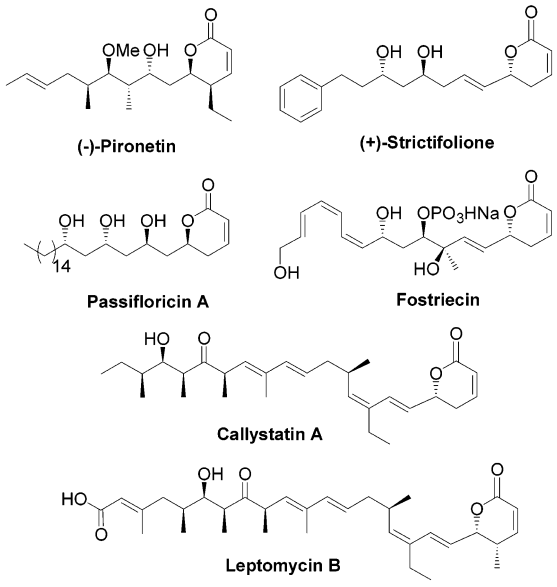


Figure 1.

(+)-Strictifolione was isolated from *Cryptocaria strictifolia* and has shown to display antifungal activity.[6] Its structure was elucidated from the ^{1}H NMR spectra of an acetonide

(1) Echeverri, F.; Arango, V.; Quiñones, W.; Torres, F.; Escobar, G.; Rosero, Y.; Archbold, R. *Phytochemistry* **2001**, *56*, 88.

(2) (a) Kobayashi, S.; Tsuchiya, K.; Harada, T.; Nishide, M.; Kurokawa, T.; Nakagawa, T.; Shimada, N.; Kobayashi, K. *J. Antibiot.* **1994**, *47*, 697. (b) Kobayashi, S.; Tsuchiya, K.; Kurokawa, T.; Nakagawa, T.; Shimada, N.; Iitaka, Y. *J. Antibiot.* **1994**, *47*, 703. (c) Tsuchiya, K.; Kobayashi, S.; Harada, T.; Nishikiori, T.; Nakagawa, T.; Tatsuta, K. *J. Antibiot.* **1997**, *50*, 259.

(3) (a) Kobayashi, M.; Higuchi, K.; Murakami, N.; Tajima, H.; Aoki, S.; *Tetrahedron Lett.* **1997**, *38*, 2859. (b) Murakami, N.; Wang, W.; Aoki, S.; Kobayashi, M. *Tetrahedron Lett.* **1997**, *38*, 5533.

(4) (a) Hamamoto, T.; Seto, H.; Beppu, T. *J. Antibiot.* **1983**, *36*, 646. (b) Yoshida, M.; Nishikawa, M.; Nishi, K.; Abe, K.; Horinouchi, S.; Beppu, T.; Shimada, N.; Kobayashi, K. *Exp. Cell. Res.* **1990**, *187*, 150.

(5) (a) Hokanson, G. C.; French, J. C. *J. Org. Chem.* **1985**, *50*, 462. (b) Scheithauer, W.; Von Hoff, D. D.; Clark, G. M.; Shillis, J. L.; Elslager, E. F. *Eur. J. Cancer Clin. Oncol.* **1986**, *22*, 921. (c) Fry, D. W.; Boritzki, T. J.; Jackson, R. C. *Cancer Chemother. Pharmacol.* **1984**, *13*, 171. (d) Leopold, W. R.; Shillis, J. L.; Mertus, A. E.; Nelson, J. M.; Roberts, B. J.; Jackson, R. C. *Cancer Res.* **1984**, *44*, 1928.

(6) Juliawaty, L. D.; Kitajima, M.; Takayama, H.; Achmad, S. A.; Aimi, N. *Phytochemistry* **2000**, *54*, 989−993.

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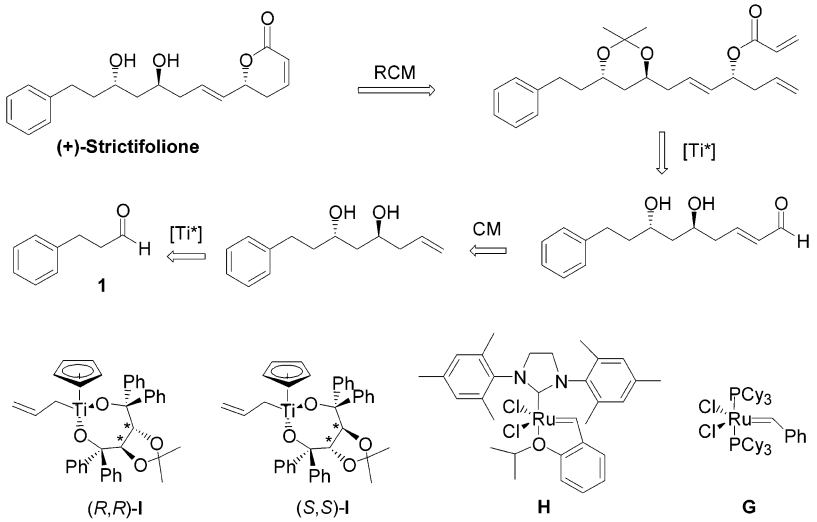
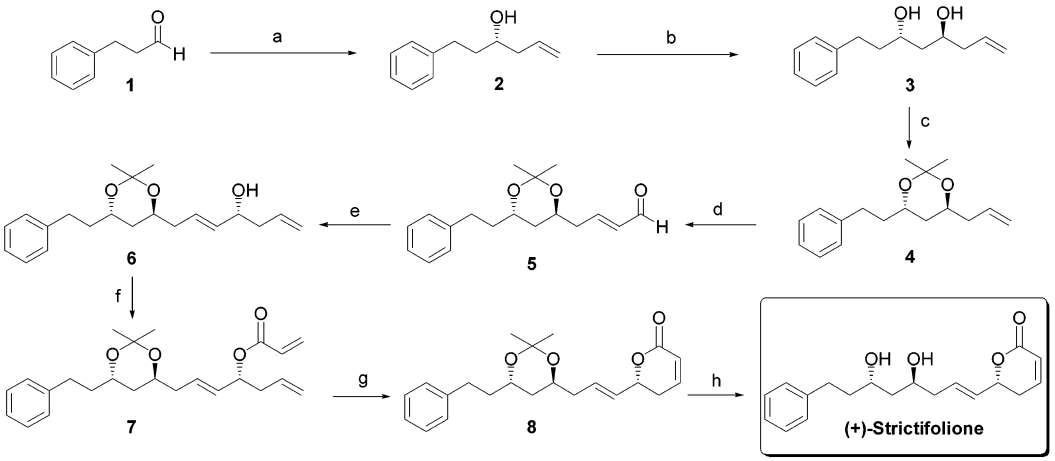
Scheme 1. Retrosynthetic Analysis of (+)-Strictifolione and Structure of the Titanium Complexes and Ruthenium Catalysts



Scheme 2. Total Synthesis of (+)-Strictifolione[a]



[a] Conditions: (a) (*S*,*S*)-**I**, ether, −78 °C, 4 h, 83%. (b) (1) OsO_4, NMO, acetone/H_2O, $NaIO_4$, 25 °C; (2) (*R*,*R*)-**I**, ether, −78 °C, 4 h, 76% for the two steps. (c) DMP/acetone, CSA, 25 °C, 95%. (d) acrolein, catalyst **H** (5 mol%), CH_2Cl_2, 25 °C, 70%. (e) (*S*,*S*)-**I**, ether, −78 °C, 4 h, 84%. (f) acryloyl chloride, $^iPr_2NEt$, CH_2Cl_2, −78 °C, 92%. (g) Catalyst **G** (5 mol%), refluxing CH_2Cl_2, 82%. (h) 1 N HCl, MeOH, 40 °C, 87%.

derivative. The (*S*)-absolute configuration of the stereogenic centers at C4′ and C6′ was established by the Mosher method. The (*R*)-absolute configuration at C6 was assumed on the basis of the Cotton effect in the CD spectrum and confirmed by the synthesis of the two isomers at C6 with the (*R*)- and (*S*)-configurations. The first total synthesis of (+)-strictifolione was achieved from (*S*)-malic acid in 18 steps.[7]

Due to a recent report on a catalytic asymmetric approach to (+)-strictifolione,[8] we would like to disclose our short total synthesis of (+)-strictifolione from the commercially available 3-phenylpropionaldehyde by using three enantioselective allyltitanations to control the stereogenic centers, a cross-metathesis reaction to introduce the (*E*)- double bond at C1′−C2′,[9] and a ring-closing metathesis reaction to build up the lactone ring. The retrosynthetic scheme is summarized in Scheme 1.

When 3-phenylpropionaldehyde **1** was treated with the allyltitanium complex (*S*,*S*)-**I** according to the reported procedure,[10] homoallylic alcohol **2** was obtained in 83% yield with an enantiomeric excess greater than 95%.[11] After the oxidative cleavage of the olefin (OsO_4/NMO, $NaIO_4$), the obtained aldehyde was treated directly with the allyltitanium

(7) Juliawaty, L. D.; Watanabe, Y.; Kitajima, M.; Achmad, S. A.; Takayama, H.; Aimi, N. *Tetrahedron Lett.* **2002**, *43*, 8657.
(8) Tosaki, S.; Nemoto, T.; Ohshima, T.; Shibasaki, M. *Org. Lett.* **2003**, *5*, 495.
(9) Cossy, J.; BouzBouz, S.; Hoveyda, A. H. *J. Organomet. Chem.* **2001**, *624*, 327.
(10) Hafner, A.; Duthaler, R. O.; Marti, R.; Rihs, J.; Rothe-Streit, P.; Schwarzenbach, F. *J. Am. Chem. Soc.* **1992**, *114*, 2321.
(11) BouzBouz, S.; Cossy, J. *Tetrahedron Lett.* **2000**, *41*, 3363.

complex (*R*,*R*)- **I** at −78 °C (Scheme 1) and transformed to 1,3-diol **3** with an overall yield of 76% for the two steps[12] (Scheme 2). The *anti* relative stereochemistry of the 1,3-diol **3** was established by its conversion to the corresponding acetonide **4** (CSA, acetone, dimethoxypropane, 25 °C, 20 min, 95% yield, dr > 95/5). The *anti* relative configuration of the hydroxy groups was confirmed by the analysis of the ^{13}C NMR spectra (δ = 24.79 and 24.77 ppm for the methyl groups and 100.18 ppm for the quaternary center).[13]

As we have shown recently that (*E*)-hexa-1,5-dien-3-ols can be obtained very easily from homoallylic alcohols by using a cross-metathesis reaction followed by an enantioselective allyltitanation, we used this methodology to control the (*E*)-double bond at C1′−C2′ and the C6 stereogenic center of (+)-strictifolione. The treatment of a mixture of **4** and acrolein (3 equiv) with Hoveyda's catalyst **H** (5 mol%) (Scheme 1), in refluxing methylene chloride, afforded the unsaturated aldehyde **5** in 70% yield with an *E*/*Z* ratio superior to 30/1. Aldehyde **5** was transformed to the desired homoallylic alcohol **6** in 84% yield by using the allyltitanium complex (*S*,*S*)-**I** (Scheme 1). The (*R*)-absolute configuration of the newly formed stereogenic center was assigned by using Trost's madelic ester method.[14]

The construction of the lactone was achieved in two steps from the allylic alcohol **6**, which was converted into the unsaturated ester **7** in 92% yield by treatment with acryloyl chloride (^{i}Pr$_2$NEt, CH_2Cl_2, −78 °C) followed by a ring-closing metathesis reaction induced by Grubbs' catalyst **G**[15] (Scheme 1) that led to lactone **8** in 82% yield. This lactone was subjected to deprotection (MeOH, 1 N HCl, 40 °C) producing (+)-strictifolione in 87% yield, the spectroscopic data of which were identical (IR, MS, and ^{1}H and ^{13}C NMR) to those of the natural one. The synthesis of (+)-strictifolione was accomplished in nine steps with an overall yield of 23% (Scheme 2).

Supporting Information Available: Spectroscopic data for compounds **5** and **7** and the spectrum of (+)-strictifolione. This material is available free of charge via the Internet at http://pubs.acs.org.

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(12) BouzBouz, S.; Cossy, J. *Org. Lett.* **2000**, *2*, 501.

(13) Rychnovsky, S. D.; Rogers, B. N.; Richardson, R. I. *Acc. Chem. Res.* **1998**, *31*, 9.

(14) Trost, B. M.; Belletire, J. L.; Godleski, S.; McDougal, P. G.; Balkovec, J. M.; Baldwin, J. J.; Christy, M. E.; Ponticello, G. S.; Varga, S. L.; Springer, J. P. *J. Org. Chem.* **1986**, *51*, 2370.

(15) Grubbs, R. H.; Chang, S. *Tetrahedron* **1998**, *54*, 4413.