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Total Synthesis of (+)-7-Deoxypancratistatin from Furan

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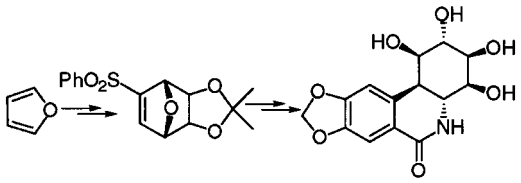
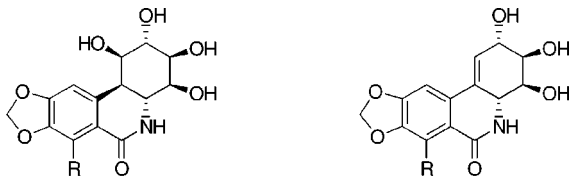
ABSTRACT



A new total synthesis of (+)-7-deoxypancratistatin 1 has been accomplished in 19 steps (8% overall yield) from two readily available compounds, furan and *trans*-1,2-bis(phenylsulfonyl)ethylene.

The use of *Amaryllidaceous* plant extracts for medicinal purposes dates back to at least the fourth century,[1] and a large number of alkaloids which possess a wide spectrum of biological activities have been isolated from these species. Among them, pancratistatin, narciclasine, lycoricidine, and 7-deoxypancratistatin constitute an emblematic group (Figure 1).[2]



1. R = H, 7-deoxypancratistatin
2. R = OH, pancratistatin
3. R = H, lycoricidine
4. R = OH, narciclasine

Figure 1.

The unique structural feature of these compounds with a phenanthridone skeleton and four or six contiguous stereogenic centers in the C-ring together with their promising biological activities (including antineoplasic,[3] growth regulatory,[4] mitogenic,[5] and antimitotic[6]) have made them attractive synthetic targets.[7]

In the case of 7-deoxypancratistatin **1**,[8] this compound has been shown in in vitro antiviral assays to exhibit a better therapeutic index than pancratistatin **2** due to decreased toxicity.[3f]

To the best of our knowledge, six total syntheses of (+)-7-deoxypancratistatin, **1**, have been reported to the date.[9] In

(1) Hartwell, J. L. *Lloydia* **1967**, *30*, 379.

(2) For a review on the *Amaryllidaceae* alkaloids, see, for instance: (a) Martin, S. F. In *The Alkaloids*; Brossi, A. R., Ed.; Academic Press: New York, 1987; Vol. 30, pp 251−376. (b) Lewis, J. R. *Nat. Prod. Rep.* **1993**, *10*, 291. (c) Lewis, J. R. *Nat. Prod. Rep.* **1995**, *12*, 339. (d) Polt, R. L. *Amarillidaceae Alkaloids with Antitumor Activity. Organic Synthesis: Theory and Application*; Hudlicky, T., Ed.; JAI Press: Greenwich, CT, 1996; Vol. 3, pp 109−148. (e) Lewis, J. R. *Nat. Prod. Rep.* **1996**, *13*, 171. (f) Lewis, J. R. *Nat. Prod. Rep.* **1998**, *15*, 107. (g) Hoshino, O. In The Amaryllidaceae Alkaloids . *The Alkaloids*, Vol. 51; Cordell, G. A., Ed.; Academic: San Diego, CA, 1998. (h) Lewis, J. R. *Nat. Prod. Rep.* **1999**, *16*, 389.

(3) See, for instance, ref 2b and the following: (a) Cerotti, G. *Nature* **1967**, *11*, 595. (b) Jiménez, A.; Santos, A.; Alonso, G.; Vázquez, D *Biochim. Biophys. Acta* **1976**, *425*, 342. (c) Pettit, G. R.; Gaddamidi, V.; Herald, D. L.; Singh, S. B.; Cragg, G. M.; Satgawa, Y. *J. Chem. Soc., Chem. Commun.* **1984**, 1693. (d) Pettit, G. R.; Gaddamidi, V.; Herald, D. L.; Singh, S. B.; Cragg, G. M.; Schmidt, J. M.; Boettner, F.; Williams, M.; Satgawa, Y. *J. Nat. Prod.* **1986**, *49*, 995. (e) Pettit, G. R.; Cragg, G. M.; Singh, S. B.; Duke, J. A.; Doubek, D. L. *J. Nat. Prod.* **1990**, *53*, 176. (f) Gabrielsen, B.; Monath, T. P.; Huggins, J. W.; Pettit, G. R.; Kirsi, J. J.; Schubert, E. M.; Dare, J.; Ussery, M. A. *J. Nat. Prod.* **1992**, *55*, 1569.

(4) Ghosal, S.; Singh, S.; Kumar, Y.; Srivastava, R. S. *Phytochemistry* **1989**, *28*, 611.

(5) Ghosal, S.; Lochan, R.; Ashutosh, K. Y.; Srivastava, R. S. *Phytochemistry* **1985**, *24*, 1825.

(6) Evidente, A.; Arigoni, O.; Liso, R.; Calabrese, G.; Randazzo, G. *Phytochemistry* **1986**, *25*, 2739.

(7) See refs 2b and 2f. See also: Rigby, J. H. *Synlett* **2000**, 1. In particular, see p 10.

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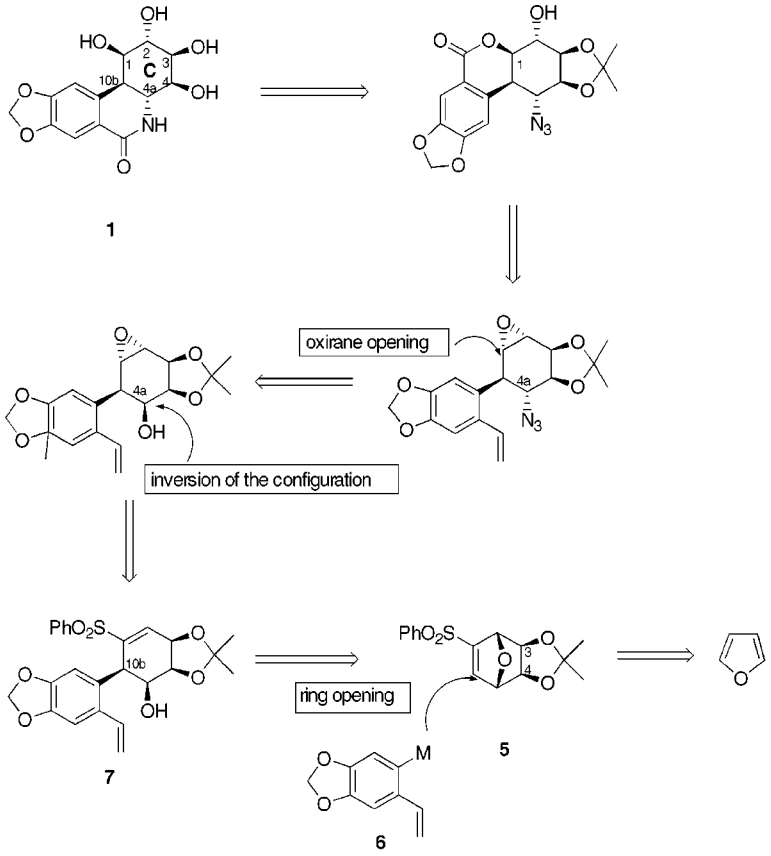
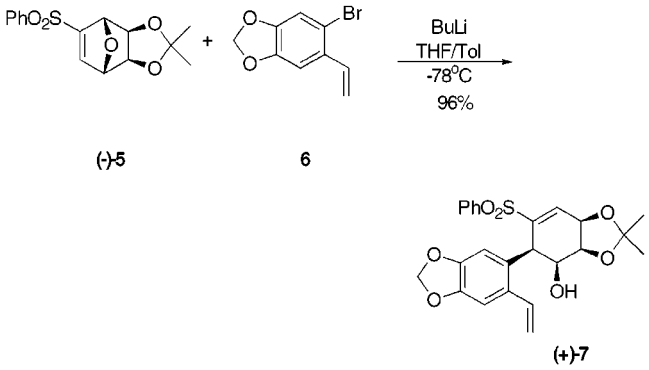
Scheme 1



this paper we wish to describe a new total synthesis of (+)-7-deoxypancratistatin, **1**, from furan, via the vinyl sulfone **5**[10] (Scheme 1). The ring opening of **5**[11] using the metalated aromatic system **6**[12] would provide the correct configuration at C_{10b}. This transformation constitutes one of the key strategic elements of our synthetic route to the target molecule. The relative configuration of the nitrogen at C_{4a} could be obtained by inversion of the configuration of the hydroxyl group obtained from the ring opening process.[13] Finally, the *trans* diol at C_1-C_2 suggested opening of epoxide. This moiety would be generated, with the correct configuration, by nucleophilic epoxidation of the cyclohexenol **7**. Desired opening of the oxirane, with concomitant lactone formation, would constitute the last key step of the route and was envisioned to arise from the oxidation of the aryl olefin. These few transformations would provide control of the configuration of the six stereocenters in the C-ring. Finally, the lactone−lactam transformation[9a] would afford the 7-deoxypancratistatin skeleton.

Treatment of (−)-**5**[10] with the functionalized aryl bromide **6** in the presence of BuLi afforded the desired cyclohexenol (+)-**7** in 96% yield (Scheme 2).

Scheme 2

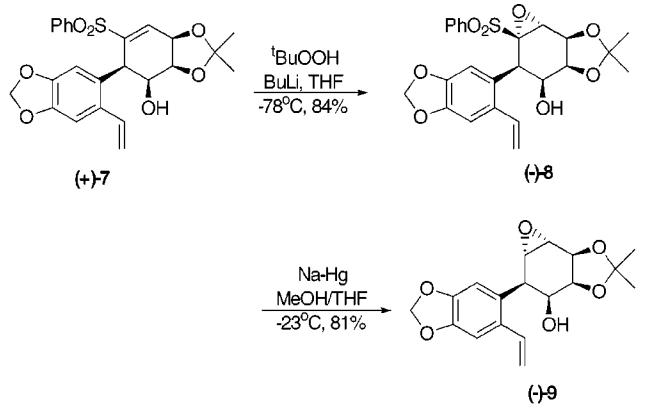


Conversion of (+)-**7** into epoxide (−)-**8**, as a single stereoisomer, was carried out by treatment with ^{t}BuOOLi (Scheme 3). Compound (−)-**8** was obtained in 84% yield

(8) This compound has been isolated by Ghosal et al. See ref 4.

(9) (a) Paulsen, H.; Stubbe, M. *Liebigs Ann. Chem.* **1983**, 535. These authors synthesized **1** in their route to lycoricidine (prior to its isolation from natural sources) from D-glucose. (b) Hudlicky, T.; Tian, X.; Königsberger, K. *Synlett* **1995**, 1125 (from bromobenzene, in 13 steps and 2.6% overall yield or 11 steps and 3% overall yield). (c) Keck, G. E.; McHardy, S. F.; Murry, J. A. *J. Am. Chem. Soc.* **1995**, *117*, 7289 (from D-gulonolactone, in 22 steps and 5% overall yield). (d) Hudlicky, T.; Tian, X.; Königsberger, K.; Maurya, R.; Rouden, J.; Fan, B. *J. Am. Chem. Soc.* **1996**, *118*, 10752 (from bromobenzene in 11 steps and 3% overall yield). (e) Keck, G. E.; Wager, T. T.; McHardy, S. F. *J. Org. Chem.* **1998**, *63*, 9164 (from piperonal in 19 steps and 20% overall yield). (f) Keck, G. E.; Murry, J. A.; McHardy, S. F. *J. Org. Chem.* **1999**, *64*, 4465 (from D-gulonolactone in 22 steps and 5% overall yield). (g) For a synthesis of *ent*-7-deoxypancratistatin, see: Akgün, H.; Hudlicky, T. *Tetrahedron Lett.* **1999**, *40*, 3081.

Scheme 3

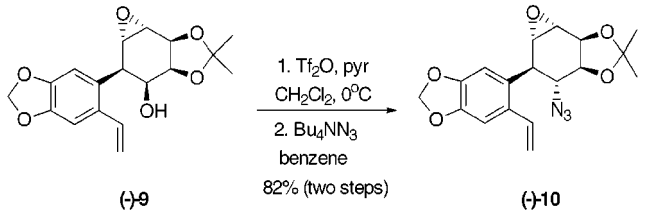


and showed the desired configuration in C_1 and C_2 (7-deoxypancratistatin numbering). This kind of epoxidation is a well-known process[14] and has also been optimized previously in a similar substrate.[15,16]

Treatment of (−)-**8** with a sodium amalgam in a MeOH/THF mixture afforded (−)-**9** in 81% yield (Scheme 3). The MeOH/THF ratio appears to be important for the success of the process. In this way, the best yield was obtained when a ratio 5:1 (MeOH:THF) was employed.

Cyclohexenol (−)-**9** was converted into the azido derivative by a two-step sequence (Scheme 4), which began by

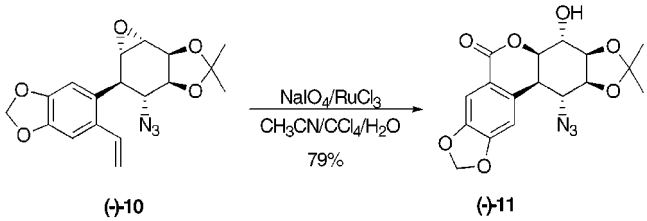
Scheme 4



activation of the hydroxyl group using Tf_2O and pyridine. Further treatment with Bu_4NN_3[17] provided (−)-**10**.

At this point, the synthetic path required the opening of the oxirane ring. The solution was conceived on the basis of the assumption that the acid group, obtained by oxidation of the aryl olefin, could carry out the intramolecular cyclization with concomitant oxirane opening. In this way, treatment of (−)-**10** with $NaIO_4$ and $RuCl_3H_2O$ in a CCl_4/CH_3CN/H_2O mixture[18] afforded lactone (−)-**11** in 79% yield (Scheme 5).

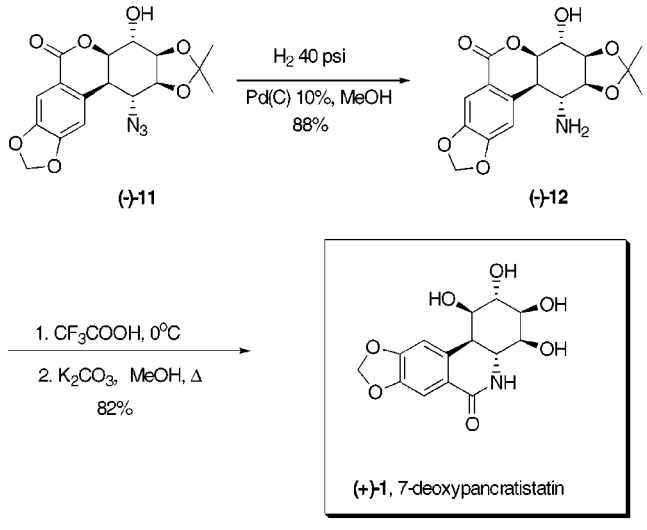
Scheme 5



The ^1H NMR spectrum showed a characteristic double doublet at 2.82 ppm (J = 12, 2.9 Hz) which confirmed the trycyclic skeleton presence, the *syn* relationship of H_{10b} and H_1 (J = 2.9 Hz), and the *trans* relationship of H_{10b} and H_{4a} (J_{trans} = 12 Hz), following 7-deoxypancratistatin numbering.

Completion of the synthesis from this point required three steps which at first glance would appear to be largely independent of one another: (1) reduction of the azido group to amino moiety, (2) removal of the acetonide group, and (3) transformation of the lactone structure to lactam one. However, it was found that a precise ordering of these steps was required. It did not prove possible to effect the lactone to lactam rearrangement unless the acetonide was removed prior to this step. Thus, following this order, treatment of (−)-**11** under hydrogenolysis conditions cleanly afforded amine (−)-**12** (Scheme 6), which was converted to the

Scheme 6



corresponding triol by removal of the acetonide with trifluoroacetic acid[19] (Scheme 6).

Finally, this compound was treated, without further purification, with K_2CO_3 in dry MeOH[9a] (Scheme 6),

(10) Optically pure (−)-**5** was obtained in 10 steps and 26% overall yield from furan and 1,2-bis(phenylsulfonyl)ethylene. Absolute configuration of (−)-**5** was determined by X-ray crystallography on a suitable intermediate. See: Arjona, O.; Iradier, F.; Plumet, J.; Martínez-Alcazar, M. P.; Hernández-Cano, F.; Fonseca, I. *Tetrahedron Lett.* **1998**, *39*, 6741.

(11) Arjona, O.; de Dios, A.; Fernández de la Pradilla, R.; Plumet, J.; Viso, A. *J. Org. Chem.* **1994**, *59*, 3906.

(12) Lithium derivative of **6** (M = Li) was prepared from aryl bromide **6** (M = Br) using BuLi. For the synthesis of **6** (M = Br) from piperonal, see: Conrad, P. C.; Kwiatkowski, P. L.; Fuchs, P. L. *J. Org. Chem.* **1987**, *52*, 586.

(13) Aceña, J. L.; Arjona, O.; Iradier, F.; Plumet, J. *Tetrahedron Lett.* **1996**, *37*, 105.

(14) Clark, C.; Hermans, P.; Meth-Cohn, O.; Moore, C.; Taljaard, H. C.; Van Vuuren, G. *J. Chem. Soc., Chem. Commun.* **1986**, 1378.

(15) Aceña, J. L.; Arjona, O.; Plumet, J. *Tetrahedron: Asymm*etry **1996**, *7*, 3535.

affording the natural product (+)-7-deoxypancratistatin, **1**, $[\alpha]^{25}_{D}$ +70.4 (*c* 0.32, DMF), and also characterized by comparison with the data reported by Keck and Hudlicky.[9]

The route described herein affords (+)-7-deoxypancratistatin in 8% overall yield over 19 steps from furan, or 30% overall yield over 9 steps from (−)-**5**. Ring opening of an enantiomerically pure 7-oxanorbornenic system and intramolecular lactonization with concomitant oxirane opening constitute the two key steps of the synthesis.

In conclusion, the chemistry described herein provides an indication of the utility of 7-oxanorbornenic systems as sustrates for construction of the highly functionalized *trans* phenanthridone ring core found in several *Amaryllidaceae* alkaloids.[20]

Acknowledgment. Dedicated to Professor Rolf Huisgen on the occasion of his 80th birthday. We thank Dr. M. Rico for detailed NMR studies. This work was supported by the DGICYT (Ministerio de Educación y Cultura, Spain, Grant 96/0641). One of us (M.L.) thanks Universidad Complutense de Madrid for a Grant. We also thank Servicio de Resonancia (U.C.M.) for NMR service.

Supporting Information Available: Full experimental details and spectral data for compounds **7**−**12**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(16) This reaction has been studied in terms of diastereoselectivity on acyclic and cyclic oxigenated vinyl sulfones. Coordination and/or conformational effects have been invoked in order to explain the diastereoselectivity of the process. See: (a) Jackson, R. F.; Standen, S. P.; Clagg, W.; McCamley, A. *Tetrahedron Lett.* **1992**, 33, 6197; (b) Bueno, A. B.; Carreño, M. C.; García Ruano, J. L. *Tetrahedron Lett.* **1993**, *34*, 5007; (c) Aceña, J. L.; Arjona, O.; Fernández de la Pradilla, R.; Plumet, J.; Viso, A. *J. Org. Chem.* **1994**, *59*, 6419.

(17) Danishefsky, S. J.; DeNino, M. P.; Chen, S. *J. Am. Chem. Soc.* **1988**, *110*, 3929.

(18) Carlsen, H. J.; Katsuki, T.; Martin, V. S.; Sharpless, K. B. *J. Org. Chem.* **1981**, *46*, 3936.

(19) Leblanc, Y.; Fitzsimmons, B. J.; Adams, J.; Pérez, F.; Rokach, J. *J. Org. Chem.* **1986**, *51*, 789.

(20) For a review on the synthetic utility of 7-oxanorbornenic derivatives, see: Arjona, O.; Cossy, J.; Plumet, J.; Vogel, P. *Tetrahedron* **1999**, *55*, 13521 and references therein.