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Application of a stereospecific $RhCl(PPh_3)_3$ decarbonylation reaction for the total synthesis of 7-(±)-deoxypancratistatin

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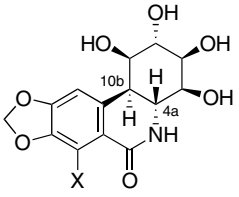
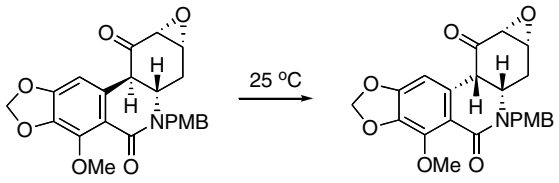
Abstract—A highly efficient total synthesis of 7-deoxypancratistatin is described. The synthesis features the ready preparation of the phenanthridone skeleton by a Stille-IMDAF cycloaddition cascade. The resulting cycloadduct is converted into a key aldehydic intermediate, which is then induced to undergo a stereospecific decarbonylation reaction using Wilkinson's catalyst to set the *trans* B–C ring junction of the target molecule.

The potent cytotoxic and antiviral properties associated with the hydroxylated phenanthridone (+)-pancratistatin (**1**),[1] coupled with its limited availability from natural resources,[2] have prompted significant efforts toward its total synthesis.[3] Pettit and co-workers reported the isolation and activity of pancratistatin in 1984,[4] but the low yield of **1** from *Hymenocallis litoralis*[5] has precluded detailed study of its anticancer activity. Although extensive synthetic work has led to a number of total syntheses of pancratistatin and its congeners,[6] the problem of supply has not been solved. In the case of the structurally related 7-deoxypancratistatin (**2**),[7] this compound has been shown by in vitro antiviral assays to exhibit a better therapeutic index than pancratistatin (**1**), due to decreased toxicity.[8] The main challenge toward designing any synthetic strategy for **1** or **2** lies in the control of the *trans*-fused B–C ring junction (C_{4a}, C_{10b}), and with the stereocontrolled installation of continuous hydroxy functionalities located around the perimeter of the C ring moiety. The *trans* B–C ring juncture is believed to be critical for the anticancer activity of these hydroxylated phenanthridones[9], but is more difficult to generate than the thermodynamically more stable *cis* ring junction.[10] For example, Rigby and co-workers had observed a decided preference for the *cis* fusion in the related pancratistatin intermediate **4**, which was readily formed by epimerization of the less stable *trans* isomer **3** at room temperature (Scheme 1).[11]



1; X = OH; Pancratistatin
2; X = H; 7-Deoxypancratistatin

A few years ago, we developed a synthetic modus operandi toward the preparation of several members of the lycorine-type Amaryllidaceae alkaloids, by exploiting an extremely facile intramolecular Diels–Alder reaction of 2-amido substituted furans (IMDAF).[12] In this letter, we wish to describe a new total synthesis of



3 (*trans*) **4** (*cis*)

Scheme 1.

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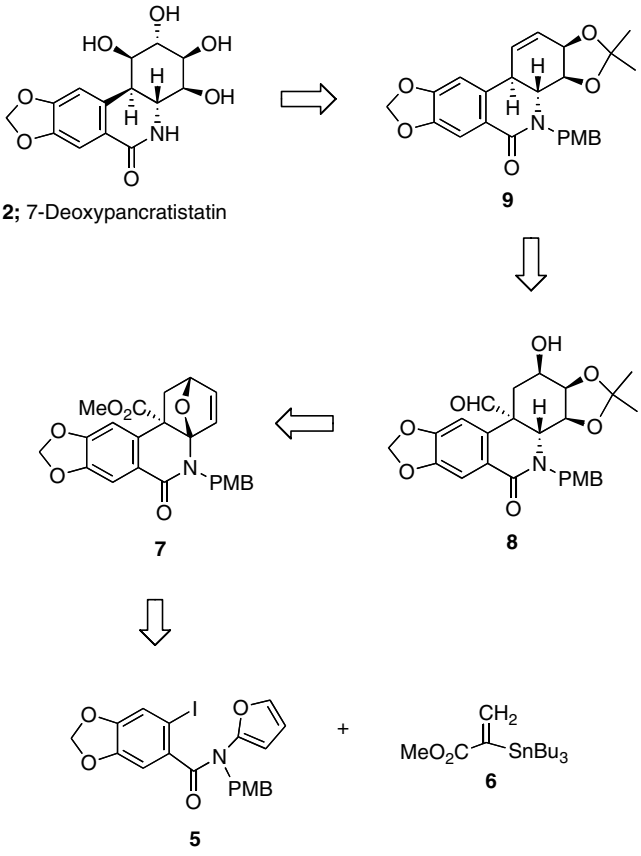
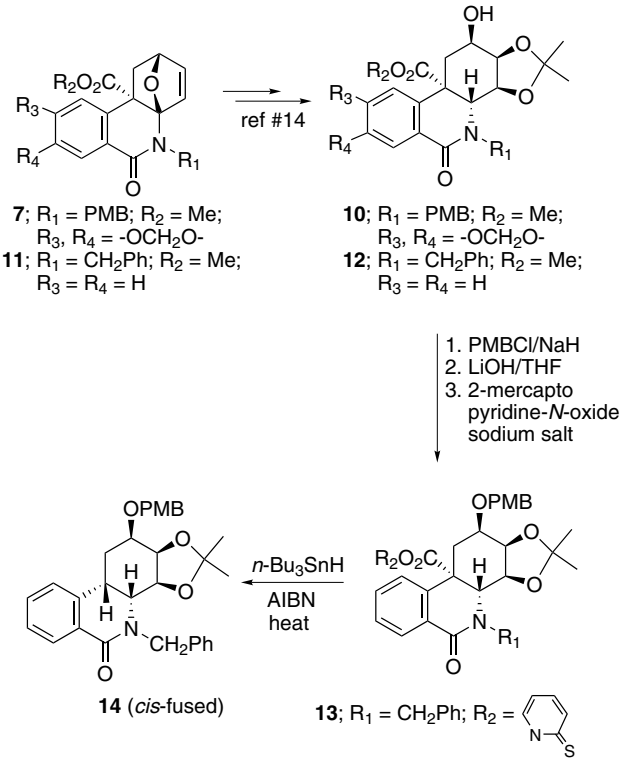


Scheme 2.

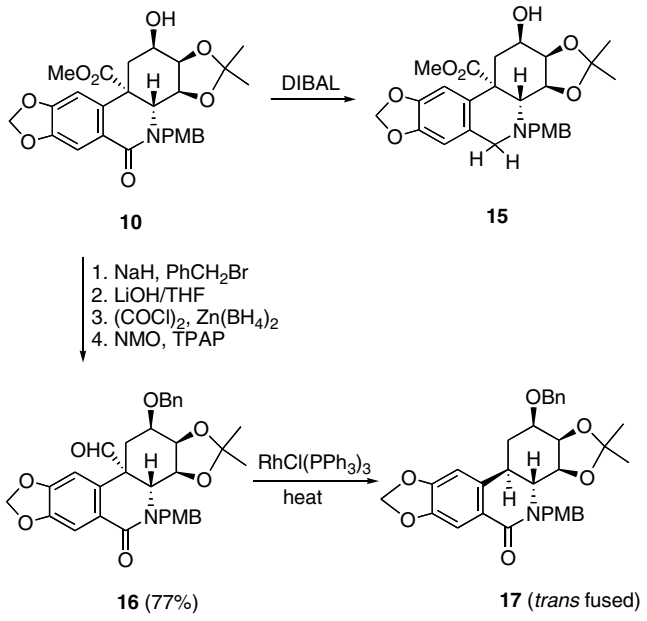


Scheme 3.

7-deoxypancratistatin (**2**) based on the above IMDAF strategy. Our plan is outlined in retrosynthetic format in Scheme 2. In this approach, the *trans* B–C ring junction is established by a $RhCl(PPh_3)_3$ promoted decarbonylation reaction of aldehyde **8**.[13] This stereospecific transformation constitutes a key strategic element of our synthetic route to the target molecule.

In a previous publication we described a highly efficient synthesis of Lycoricidine, which featured the rapid assembly of the ABC skeleton of the alkaloid via a Stille/IMDAF cycloaddition cascade.[14] The resulting cycloadduct was then used for the stereocontrolled installation of the other functionality present on the C-ring of the target molecule. Thus, cycloadduct **7** was transformed to acetonide **10** by first treating it with OsO_4/NMO, followed by reaction with 2,2-dimethoxypropane, and then subjecting the oxabicyclic skeleton to reduction using $Zn(BH_4)_2$ in the presence of TMSOTf (Scheme 3). We also used a similar sequence of reactions to convert the related *N*-benzyl lactam **11** into acetonide **12**. Our first efforts to replace the carbomethoxy group of the model lactam system **12** with a hydrogen atom to obtain the *trans*-fused ring junction involved a Barton radical decarboxylation reaction.[15] The methyl ester functionality present in **12** was converted into the corresponding thiohydroxamic ester **13**. Heating a sample of **13** with *n*-Bu_3SnH and AIBN in benzene induced a smooth radical decarboxylation. However, the only product isolated from the reaction corresponded to the *cis*-fused lactam **14**. Evidently, the initially formed benzylic radical preferred to abstract a hydrogen from *n*-Bu_3SnH to produce the thermodynamically more stable *cis*-fused product.

Under the influence of transition metal compounds, aldehydes are known to undergo ready decarbonylation to furnish carbon monoxide and the corresponding saturated hydrocarbons.[13] Rhodium complexes, such as Wilkinson's catalyst $RhCl(PPh_3)_3$ are most often employed in both stoichiometric and catalytic reactions to effect the decarbonylation.[13,16] The earlier seminal studies by Walborsky[13b] demonstrated that the decarbonylation reaction using Wilkinson's catalyst proceeds with retention of configuration, and this finding has been used by others in complex natural product synthesis.[16] With this in mind, we set out to convert the carbomethoxy group present in **10** to the corresponding aldehyde. Interestingly, the reduction of **10** with DIBAL did not produce the expected aldehyde (or alcohol), but instead gave amine **15** in high yield as the exclusive product (Scheme 4). The increased reactivity of the amido carbonyl group over the ester toward DIBAL reduction is probably related to a significant decrease in the strain energy of ring B, by changing the hybridization from sp^2 to sp^3 at the C_6 position.[17] This undesired reduction could be circumvented by converting the ester group into the corresponding acid chloride after protecting the free OH group as the benzyl ether. Selective reduction of the acid chloride with $Zn(BH_4)_2$, followed by a subsequent oxidation of the resulting alcohol using Ley's procedure[18], afforded the desired aldehyde **16**. When a solution of **16** and $RhCl(PPh_3)_3$ was heated in benzonitrile at reflux, the decarbonylation reaction pro-



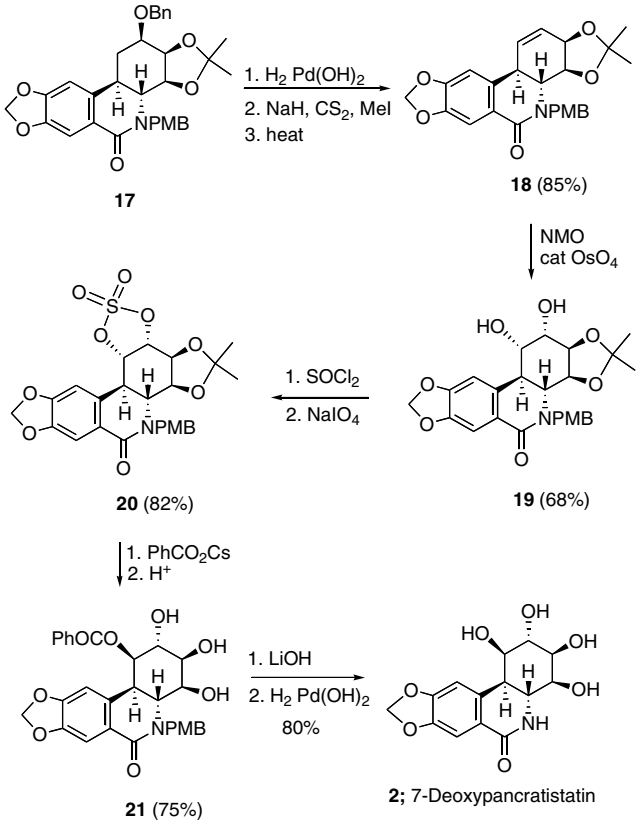
Scheme 4.

ceeded to give the desired *trans*-fused lactam **17** in 63% yield.

With the rapid construction of the *trans*-fused lactam in hand, installation of the other functional groups present on the C-ring with the correct relative stereochemistry was next investigated. What was required for the end game was to introduce a C_1-hydroxyl group and also to invert the stereochemistry at the C_2-position. To this end, a transient double bond between C_1 and C_2 was installed by carrying out a debenzylation under hydrogenolysis conditions, followed by a Chugaev elimination[19] of the xanthate ester, which proceeded in 85% overall yield (Scheme 5). Since the presence of the bulky acetonide moiety partially blocked the β-face of the π-bond of **18**, dihydroxylation occurred preferentially from the less hindered α-face to furnish two easily separable diol isomers (3:1) in almost quantitative yields. A subsequent regioselective inversion of the stereochemistry at the C_1-hydroxyl group of the major diol **19** was achieved through a three-step sequence.[3c]

Treatment of diol **19** with thionyl chloride, followed by oxidation of the resulting sulfite with $NaIO_4$ in the presence of catalytic $RuCl_3$, furnished sulfate **20** in 82% yield.[20] Reaction of sulfate **20** with cesium benzoate, followed by acid hydrolysis, resulted in the formation of triol **21** in 75% yield. The final ester hydrolysis and amide deprotection proceeded uneventfully to furnish 7-deoxypancratistatin in 80% yield.

In summary, we have described here a novel and highly efficient synthesis of (±)-7-deoxypancratistatin, which features (a) the use of a one-pot Stille/IMDAF cycloaddition cascade to construct the ring skeleton, and (b) a stereospecific decarbonylation reaction using Wilkinson's catalyst to set the *trans* B–C ring junction of the target molecule. The application of this approach



Scheme 5.

to other members of the Amaryllidaceae family of alkaloids is currently under investigation, the results of which will be disclosed in due course.

Acknowledgements

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References and notes

1. (a) Pettit, G. R.; Gaddamidi, D. L. H.; Singh, S. B.; Gragg, G. M.; Schmidt, J. M. *J. Nat. Prod.* **1986**, *46*, 995; (b) Gabrielson, 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; p 121.
2. Pettit, G. R.; Pettit, G. R., III; Groszek, R. A.; Backhaus, R. A.; Doubek, D. L.; Barr, R. J.; Meerow, A. W. *J. Nat. Prod.* **1995**, *58*, 756.
3. For some selected examples, see: (a) Danishefsky, S.; Lee, J. Y. *J. Am. Chem. Soc.* **1989**, *111*, 4829; (b) Tian, X.; Hudlicky, T.; Königsberger, K. *J. Am. Chem. Soc.* **1995**, *117*, 3643; (c) Trost, B. M.; Pulley, S. R. *J. Am. Chem. Soc.* **1995**, *117*, 10143; (d) Keck, G. E.; McHardy, S. F.; Murry, J. A. *J. Am. Chem. Soc.* **1995**, *117*, 7289; (e) Hudlicky, T.; Tian, X. R.; Königsberger, K.; Mauray, R.; Rouden, J.; Fan, B. *J. Am. Chem. Soc.* **1996**, *118*, 10752; (f) Chida, N.; Jitsuoka, M.; Yamamoto, Y.; Ohtsuka, M.; Ogawa, S. *Heterocycles* **1996**, *43*, 1385; (g) Doyle, T. J.; Hendrix, M.;

VanDerveer, D.; Javanmard, S.; Haseltine, J. *Tetrahedron* **1997**, *53*, 11153; (h) Magnus, P.; Sebhat, I. K. *Tetrahedron* **1998**, *54*, 15509; (i) Magnus, P.; Sebhat, I. K. *J. Am. Chem. Soc.* **1998**, *120*, 5341; (j) Pettit, G. R.; Melody, N.; Herald, D. L. *J. Org. Chem.* **2001**, *66*, 2583; (k) Kim, S.; Ko, H.; Kim, E.; Kim, D. *Org. Lett.* **2002**, *4*, 1343; (l) Ko, H. J.; Park, J. E.; Kim, S. *J. Org. Chem.* **2004**, *69*, 112.

4. (a) Pettit, G. R.; Gaddamidi, V.; Cragg, G. M.; Herald, D. L.; Sagawa, Y. *J. Chem. Soc., Chem. Commun.* **1984**, 1693; (b) Pettit, R. G.; Gaddamidi, V.; Cragg, G. M. *J. Nat. Prod.* **1984**, *47*, 1018.
5. Pettit, G. R.; Gaddamidi, V.; Herald, D. L.; Singh, S. B.; Cragg, G. M.; Schmidt, J. M.; Boettner, F. E.; Williams, M.; Saggawa, Y. *J. Nat. Prod.* **1986**, *49*, 995.
6. For a recent review of total syntheses in this area, see: Rinner, U.; Hudlicky, T. *Synlett* **2005**, 365.
7. Ghosal, S.; Singh, S.; Kumar, Y.; Srivastava, R. S. *Phytochemistry* **1989**, *28*, 611.
8. 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.
9. (a) Pettit, G. R.; Pettit, G. R., III; Backaus, R. A.; Boyd, M. R.; Meerow, A. W. *J. Nat. Prod.* **1993**, *56*, 1682; (b) Hudlicky, T.; Rinner, U.; Gonzalez, D.; Akgun, H.; Schilling, S.; Siengalewicz, P.; Martinot, T. A.; Pettit, G. R. *J. Org. Chem.* **2002**, *67*, 8726.
10. (a) Polt, R. In *Organic Synthesis: Theory and Applications*; Hudlicky, T., Ed.; JAI Press: Greenwich CT, 1997; vol. 3, p 109; (b) Hudlicky, T. *J. Heterocycl. Chem.* **2000**, *37*, 535; (c) Martin, S. F. The Amaryllidaceae Alkaloids. In *The Alkaloids*; Brossi, A., Ed.; Academic Press: New York, 1987; Vol. 30, Chapter 3; pp 251–376; (d) Hoshino, O. In *The Alkaloids*; Cordell, G. A., Ed.; Academic Press: New York, 1998; Vol. 51, p 323.
11. (a) Rigby, J. H.; Maharoof, U. S. M.; Mateo, M. E. *J. Am. Chem. Soc.* **2000**, *122*, 6624; for a somewhat related example, see: (b) Thompson, R. C.; Kallmerten, J. *J. Org. Chem.* **1990**, *55*, 6078.
12. (a) Wang, Q.; Padwa, A. *Org. Lett.* **2004**, *6*, 2189; (b) Padwa, A.; Ginn, J. D. *J. Org. Chem.* **2005**, *70*, 5197; (c) Padwa, A.; Bur, S. K.; Zhang, H. *J. Org. Chem.* **2005**, *70*, 6883.
13. (a) Tsuji, J.; Ohno, K. *Synthesis* **1969**, 157; (b) Walborsky, H. M.; Allen, L. E. *J. Am. Chem. Soc.* **1971**, *93*, 5465.
14. Zhang, H.; Padwa, A. *Org. Lett.* **2006**, *8*, 247.
15. Barton, D. H. R.; Crich, D.; Motherwell, W. B. *Tetrahedron* **1985**, *41*, 3901.
16. (a) Ziegler, F. E.; Belema, M. *J. Org. Chem.* **1997**, *62*, 1083; (b) Kato, T.; Hoshikawa, M.; Yaguchi, Y.; Izumi, K.; Uotsu, Y.; Sakai, K. *Tetrahedron* **2002**, *58*, 9213; (c) Harmata, M.; Wacharasindhu, S. *Org. Lett.* **2005**, *7*, 2563; (d) Malerich, J. P.; Maimone, T. J.; Elliott, G. I.; Trauner, D. *J. Am. Chem. Soc.* **2005**, *127*, 6276.
17. A related finding had been made by the Hudlicky group in their elegant total synthesis of (+)-pancratistatin. In an attempted deprotection of a *N*-tosyl amide using Na(Hg), it was observed that reduction of the lactam carbonyl group preferentially occurred and this finding was attributed to relief of ring strain.[3b]
18. Ley, S. V.; Norman, J.; Griffith, W. P.; Marsden, S. P. *Synthesis* **1994**, 639.
19. (a) Nace, H. R. *Org. React.* **1962**, *12*, 57; (b) Nakagawa, H.; Sugahara, T.; Ogasawara, K. *Org. Lett.* **2000**, *2*, 3181.
20. (a) Gao, Y.; Sharpless, K. B. *J. Am. Chem. Soc.* **1988**, *110*, 7538; (b) Lohray, B. B. *Synthesis* **1992**, 1035.