A Second-Generation Radical-Based Synthesis of (+)-7-Deoxypancratistatin†

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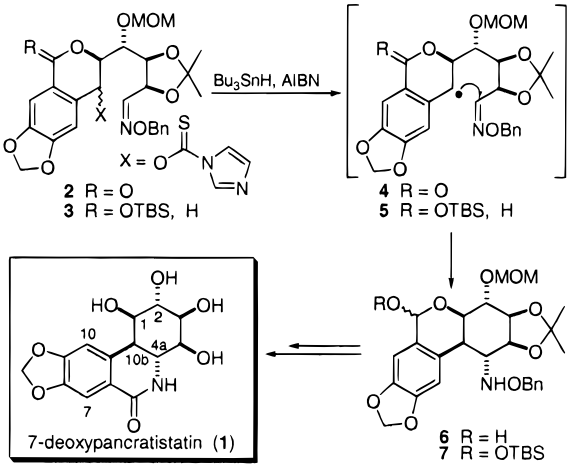
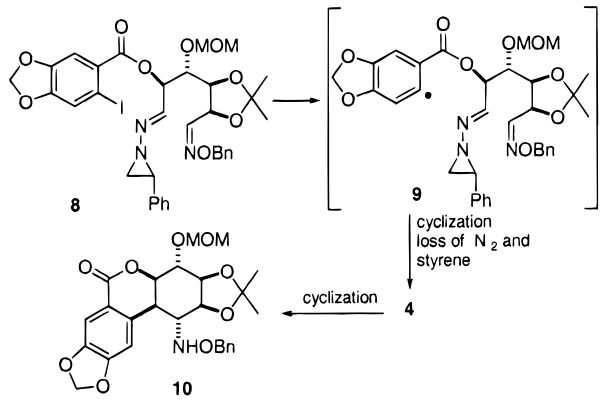
The Amaryllidaceae alkaloids continue to attract considerable interest as targets for total synthesis, due to their interesting biological activity and structural features.[1] Some time ago, we reported[2] a total synthesis of the naturally occurring alkaloid 7-deoxypancratistatin (**1**)[3] via an approach based upon the radical cyclization process indicated below. Our original intent, namely to utilize a lactone containing substrate **2**, was thwarted by the ease with which the lactone carbonyl suffered reduction by Bu_3SnH under the radical cyclization conditions. We thus completed the synthesis by conducting the radical cyclization on the TBS protected lactol **3**. Although this synthesis served to define the viability of the critical radical cyclization event, difficulties encountered in the construction of the requisite substrate and the aforementioned lactone reduction problem resulted in a sequence that was longer than we had envisioned.

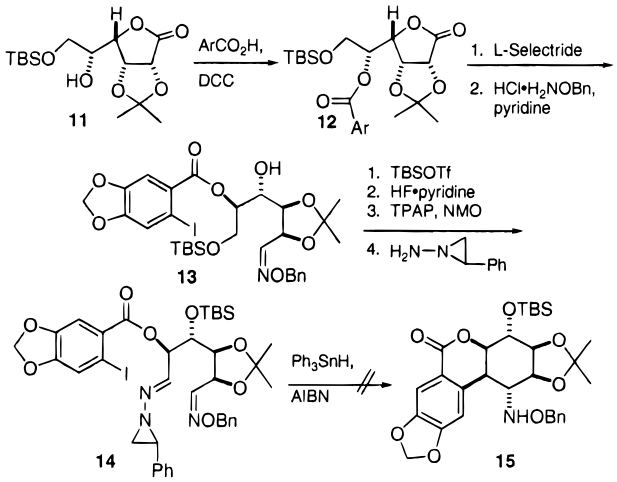


In considering more direct approaches to a key radical intermediate such as **4**, we became intrigued by the prospect of generating such a radical intermediate directly via a prior radical cyclization event. Thus, ignoring for a moment the lactone reduction problem, it seemed possible that radical intermediate **4** could itself be generated via cyclization of an aryl radical onto an *N*-aziridinylimine, employing the elegant process developed by Kim.[4] This 6-exo cyclization, with concomitant loss of nitrogen and styrene, would generate the same radical intermediate **4** previously shown to cyclize efficiently to give a single diastereomer of product.



We thus were led to reinvestigate the radical cyclization process using the lactone **2**. Despite extensive experimentation, no conditions for effecting this process in high yield could be identified using Bu_3SnH; however, the use of Ph_3SnH gave the desired lactone product **10** in 70% isolated yield, with very little lactone reduction observed. This finding thus set the stage for investigation of the double-radical cyclization approach indicated above.

The route began by esterification of **11**[5] with iodo piperonylic acid.[6] Selective reduction of the lactone carbonyl group was accomplished using L-Selectride (Aldrich), and the resulting lactol was converted to the *O*-benzyloxime **13**. Protection of the free hydroxyl group followed by desilylation of the primary TBS group gave the corresponding alcohol, which was oxidized and converted to the *N*-aziridinylimine by stirring in ethanol with 1-amino-2-phenylaziridine.[7]



Attempts at radical cyclization of **14** under the newly discovered Ph_3SnH protocol were unsuccessful, and no

† Dedicated to Professor E. J. Corey on the occasion of his 70th birthday.

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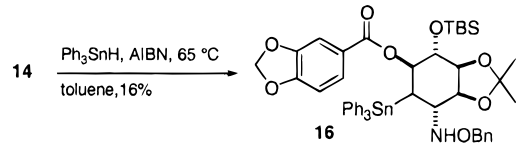
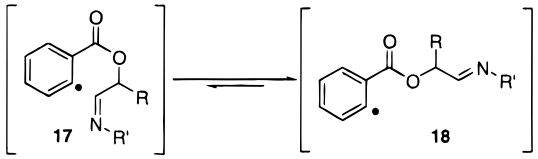
product corresponding to the desired tandem cyclization event could be isolated. Instead, products that appeared to derive from two independent events (Ar−I reduction and $Ph_3Sn^•$ addition to the *N*-aziridinylimine) were obtained. Thus, for example, in one reaction product **16** was isolated in 16% yield.



One possible reason for the failure to obtain the desired cyclization product in this reaction, which we had, in fact, considered as a potential complication, was the presence of the ester linkage in the tether connecting the two reactive moieties. Thus, the preferred conformation of esters is well-known to be s-trans, whereas a s-cis conformation is required for cyclization. This type of problem has been previously noted in other intramolecular reactions.[8]

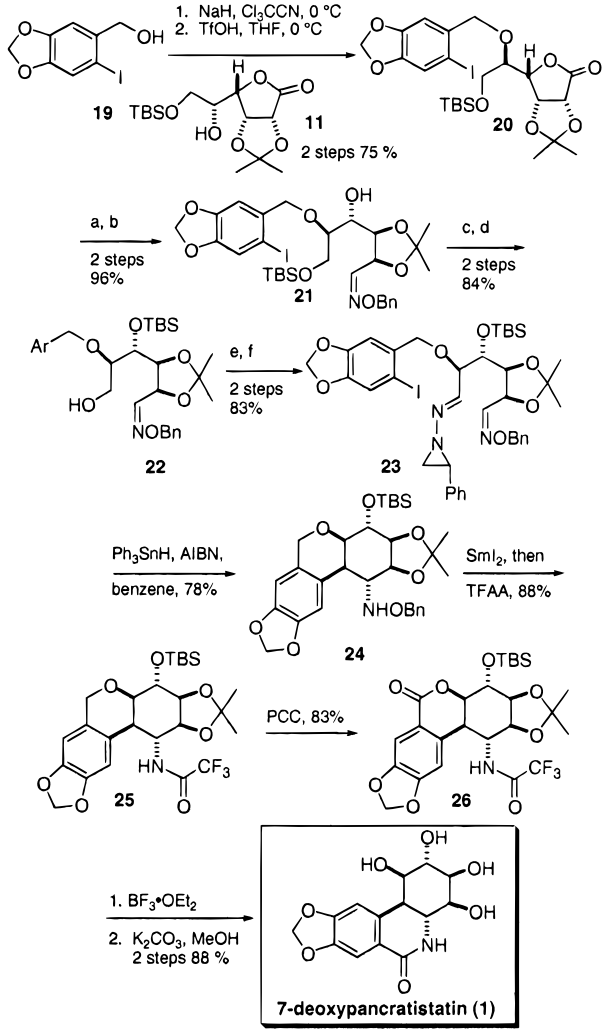


We therefore chose to investigate a parallel sequence using an ether linkage in place of the ester, with the idea of installing the requisite carbonyl group after conducting the cyclization event. To this end, iodopiperonol[6] was converted to the corresponding trichloroacetimidate in the normal way (NaH, Cl_3CCN) and used to alkylate alcohol **11**. Reduction of the lactone to the lactol with L-Selectride and *O*-benzyloxime formation gave **21** (96% yield over two steps), which was successively silylated (TBSOTf) and desilylated (HF·pyridine) to give the alcohol **22**. Oxidation (TPAP, NMO) and formation of the aziridinylimine then gave **23** in 83% yield (Scheme 1).

The key radical cyclization event required some optimization but ultimately proceeded very cleanly to afford **24** as a single diastereomer in 78% isolated yield. The optimal conditions again involved the use of Ph_3SnH and AIBN in benzene at 80 °C; somewhat lower yields were obtained using Bu_3SnH. Cleavage of the N−O bond using SmI_2 in THF[9] and direct quenching with TFAA gave the trifluoroacetamide **25** in 88% isolated yield. Installation of the carbonyl group was accomplished quite easily using PCC in CH_2Cl_2 at 55 °C,[10] to give lactone **26** in 83% isolated yield.

This intermediate differs from the one used in our previous synthesis only by the nature of the protecting group at the C_2 hydroxyl, TBS in the present case and MOM in the former. In the previous synthesis, both the MOM and acetonide protecting groups were easily removed using DOWEX-H^+ resin in methanol at 70 °C. We were most surprised to find that these conditions were ineffective in the present case, as were more forcing conditions utilizing higher temperatures and longer reaction times. Although the acetonide was hydrolyzed readily, the silyl ether linkage proved to be unusually robust. Eventually we found that both groups could be removed using BF_3·OEt_2[11] in CH_2Cl_2 to give the same triol lactone as previously prepared; lactone to lactam rearrangement was then effected using K_2CO_3 in dry methanol as before to give 7-deoxypancratistatin.

Scheme 1[a]



[a] Key: (a) L-Selectride, CH_2Cl_2, −78 °C; (b) HCl·H_2NOBn, pyridine; (c) TBSOTf, 2,6-ludidine, CH_2Cl_2, 0 °C; (d) HF·pyridine, THF; (e) TPAP, NMO, 4 Å MS; (f) 1-amino-2-phenylaziridine, EtOH, 0 °C.

The route described herein thus marks a considerable improvement over our earlier synthesis, which required 21 steps and afforded a 7% overall yield. The present synthesis is 13 linear steps from 6-iodopiperonol and proceeds in 21% overall yield. Moreover, the present synthesis quite nicely demonstrates the power of the Kim methodology in a rather highly functionalized and demanding case, given that the bimolecular rate constant for reaction of phenyl radicals with Bu_3SnH has been reported to be 5.9×10^8 M^{-1} s^{-1} at 30 °C[12] and that reasonable intramolecular hydrogen abstraction pathways are also present. Finally, the dramatic differences between reactions using Bu_3SnH versus those using Ph_3SnH with lactone **2** may prove useful in other circumstances.

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Supporting Information Available: Experimental procedures and full characterization data for compounds used in the main synthesis and copies of NMR spectra (33 pages).

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