Synthesis of the Antitumor Alkaloid (+)-Pancratistatin Using the β-Azidonation Reaction via a Prochiral 4-Arylcyclohexanone Derivative

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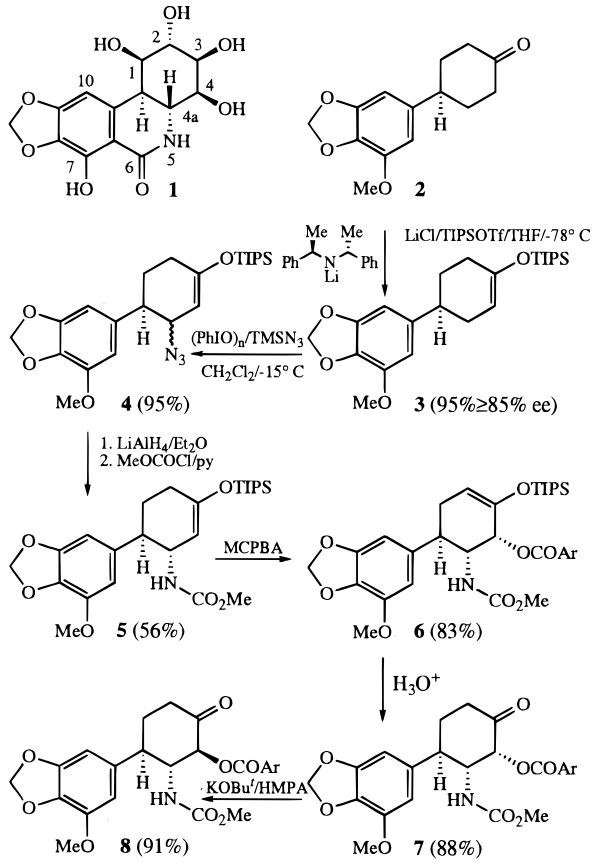
In 1984 Pettit and co-workers reported the structure of pancratistatin **1**, which was isolated from the roots of the Hawaiian Pancratium littorale Jacq.[1] Subsequently, pancratistatin **1** has become an important target for total synthesis because of its increasing potential as a clinically useful antitumor agent.[2] The supply of **1** is limited, and attempts to synthesize **1** from more abundant alkaloids such as narciclasine have not been successful.[3] There are four reported total syntheses of **1**. The synthesis of the racemate was first reported by Danishefsky,[4] and three enantioselective syntheses described by Hudlicky,[5] Trost,[6] and Haseltine[7] rely on enzymatic and catalytic chiral palladium methodology to introduce the correct absolute stereochemistry. While there is substantial literature describing the synthesis of *Amaryllidaceae* alkaloids in general,[8] the more highly functionalized compounds have proven tenaciously difficult to synthesize in an efficient and practical manner.[9]

The β-azido triisopropylsilyl (TIPS) enol ether functionalization reaction provides a unique strategy for the synthesis of pancratistatin **1** and *Amaryllidaceae* alkaloids in general.[10] The 4-prochiral arylcyclohexanone **2**[11] was treated with lithium (+)-bis(α-methylbenzyl)amide in THF containing lithium chloride, followed by TIPSOTf to give **3** in 95% yield with an ee of ≥85%.[12] Treatment of **3** with $(PhIO)_n/TMSN_3$ in CH_2Cl_2 at −15 °C rapidly produced **4** (95%) as a mixture of *trans*- and *cis*-diastereomers in a 3.5:1 ratio, Scheme 1. Exposure of the mixture to $LiBPh_4$ did not improve the ratio by equilibration via a putative enonium ion but led to decomposition and elimination to dienes.[10] Consequently, while the *trans*-/*cis*-ratio of **4** could not be improved, the yield of the required *trans*-**4** is approximately 75%. At this stage the stereoisomers could not be separated. Reduction of **4** using $LiAlH_4/Et_2O$, followed by treatment with $ClCO_2Me$/pyridine gave **5**, as a mixture of *trans*-/*cis*-diastereomers. On a large scale (>6 g) two crystallizations were sufficient to provide pure **5** (56% from **4**).

Scheme 1[a]



[a] Ar = 3-ClC_6H_4.

It was anticipated that epoxidation of **5** would proceed by axial addition, and eventually, after a series of intermediate steps, form **6**.[13] Indeed, treatment of **5** with *m*-chloroperoxybenzoic acid/CH_2Cl_2/imidazole gave **6** in excellent yield. Mild acid hydrolysis of **6** gave **7**, which on treatment with KOBu^t/HMPA at 90 °C resulted in complete conversion into **8** (91%).

At this stage it was necessary to convert **8** into the derived α,β-unsaturated ketone **11**. This proved to be extremely difficult

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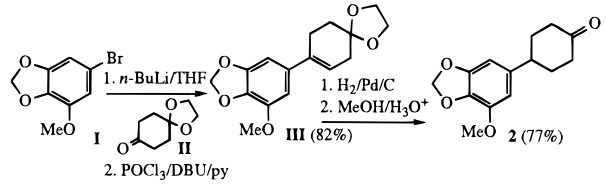
(9) The synthesis of 7-deoxypancratistatin has been achieved by several groups. Tian, X.; Maurya, R.; Königsberger, K.; Hudlicky, T. *Synlett* **1995**, 1125. Keck, G. E.; McHardy, S. F.; Murry, J. A. *J. Am. Chem. Soc.* **1995**, *117*, 7289. Chida, N.; Iitsuoka, M.; Yamamoto, Y.; Ohtsuka, M.; Ogawa, S. *Heterocycles* **1996**, *43*, 1385. Paulsen, H.; Stubbe, M. *Liebigs Ann. Chem.* **1983**, 535. Ohta, S.; Kimoto, S. *Chem. Pharm. Bull.* **1976**, *24*, 2977.
(10) Magnus, P.; Lacour, J.; Evans, P. A.; Roe, M. B.; Hulme, C. *J. Am. Chem. Soc.* **1996**, *118*, 3406.
(11) Bromine−lithium exchange of the known bromide **I** (Shirasaka, T.; Takuma, Y.; Imaki, N. *Synth. Comm.* **1990**, *20*, 1223), followed by addition of **II**, and dehydration of the initial adduct gave **III**. Hydrogenation of **III** and acid hydrolysis provided **2**.



(12) At the present time there is no predictive model that suggests a particular base and ketone will result in a specific chiral enolate. Therefore, predictions are based upon comparisons with experimental data for 4-substituted cyclohexanones and must be taken with caution. Simpkins, N. S. *Pure Appl. Chem.* **1996**, *68*, 691−694. Cox, P. J.; Simpkins, N. S. *Tetrahedron Asymm.* **1991**, *2*, 1−26. Bunn, B. J.; Simpkins, N. S. *J. Org. Chem.* **1993**, *58*, 533−534. Yamashita, T.; Sato, D.; Kiyoto, T.; Kumar, A.; Koga, K. *Tetrahedron Lett.* **1996**, *37*, 9195−9198.
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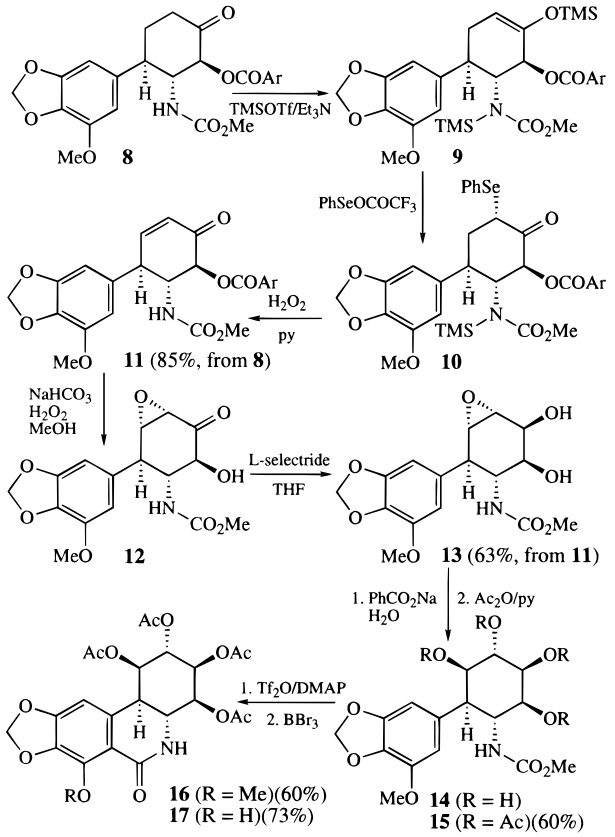
Scheme 2[a]



[a] Ar = 3-ClC_6H_4.

to do in an efficient manner, but eventually it was found that treatment of **8** with TMSOTf/Et_3N gave the bis-TMS adduct **9**. Exposure of **9** to $PhSeOCOCF_3$ gave the selenide derivative **10**, which was oxidized (H_2O_2/py) and eliminated to give **11** (85% overall). Treatment of **11** under the standard α,β-enone epoxidation conditions of H_2O_2/NaOH/MeOH gave **12** in low yield (25%). It was found that **12** was competitively destroyed by the strongly alkaline reaction conditions. Changing the reaction conditions to H_2O_2/$NaHCO_3$/MeOH/THF gave **12** (75%). Reduction of **12** with L-selectride/THF gave **13** (63% from **11**) as a single diastereomer. The diacetate derivative of **13** was characterized by X-ray crystallography. Interestingly, solvolysis of this diacetate in AcOH/Ac_2O/AcONa proceeded with inversion at C2, presumably through acetoxonium ion participation.[14] Treatment of **13** with $PhCO_2Na$/H_2O under the solvolytic conditions described by Hudlicky[5] gave **14**, which on acetylation produced **15** (60% from **13**).

Treatment of **15** under modified Bischler−Napieralski reaction conditions (Tf_2O/DMAP)[15] followed by acid hydrolysis gave **16** (60%) along with a small amount of the product of electrophilic substitution *ortho*- to the methylenedioxy group **16a** (7:1).[16] While **16** and **16a** could not be separated at this stage, it was found that exposure of the mixture to BBr_3/CH_2Cl_2/−78 to 0 °C gave **17** (73%, **16a** did not react), which was readily separated from **16a**.

Finally, removal of the acetate protecting groups from **17** with NaOMe/MeOH proceeded cleanly to give pancratistatin **1** (87%), which was identical with an authentic sample kindly supplied by Professor Tomas Hudlicky. The optical rotation (+38) closely matched the literature values (lit. values of +40.9, +48, and +44 see refs 5, 1, and 6, respectively), thus corroborating the emperical observations of Simpkins and Koga[12] that the choice of lithium (+)-bis(α-methylbenzyl)amide would result in the correct absolute configuration of **3** necessary to synthesize (+)-**1**.

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Supporting Information Available: Complete spectral information for compounds **1**−**17** (33 pages, PDF/print). See any current masthead page for ordering information and Web access instructions.

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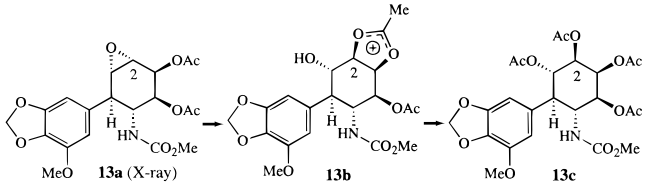
(14) The formation of **13c** is readily explained by acetoxonium ion **13b**, and since the acetic acid was wet, an ortho ester intermediate leads to **13c**.



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(16) The Bischler−Napieralski reaction was not regiospecific and produced about 10% of **16a**. The presence of the C1 acetoxy group appears to improve this ratio, since in related experiments lacking this functionality the ratio of the corresponding two lactams was 3:1.