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Stereocontrolled Total Synthesis of Pancratistatin

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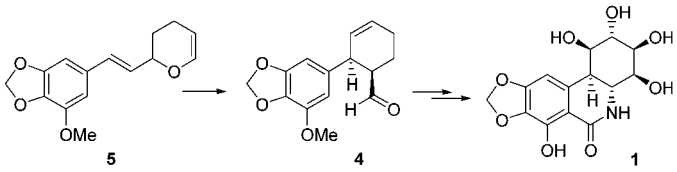
ABSTRACT



A new total synthesis of the antitumor alkaloids, pancratistatin (1), has been accomplished from readily available staring materials. The Claisen rearrangement of dihydropyranethylene 5 was employed to construct the A and C rings. Stereo- and regiocontrolled functional group interchange, such as iodolactonization, dihydroxylations, and a cyclic sulfate elimination reaction, allows for the production of the target natural product.

Pancratistatin (**1**, Figure 1) is a highly oxygenated phenanthridone alkaloid, which was isolated from the roots of *Pancratium littorale* by Pettit and co-workers in 1984.[1] This alkaloid exhibits a high level of in vitro and in vivo cancer cell growth inhibitory activity and antiviral activity.[2] The significant synthetic interest in pancratistatin stems from its promising pharmacological profile, low natural abundance, and unique structural features, as it contains six contiguous stereogenic centers in the C ring of a phenanthridone skeleton. The first total synthesis of the racemate was reported by Danishefsky in 1989,[3] and the first enantioselective synthesis of the natural enantiomer was recorded by Hudlicky in 1995.[4] In the same year, Trost presented an enantioselective synthesis with a high overall yield.[5] Since then, Haseltine,[6] Magnus,[7] and Rigby[8] have also presented

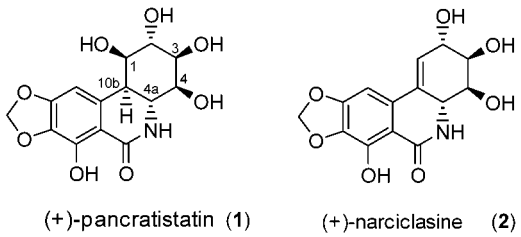


Figure 1. Structures of pancratistatin (**1**) and narciclasine (**2**).

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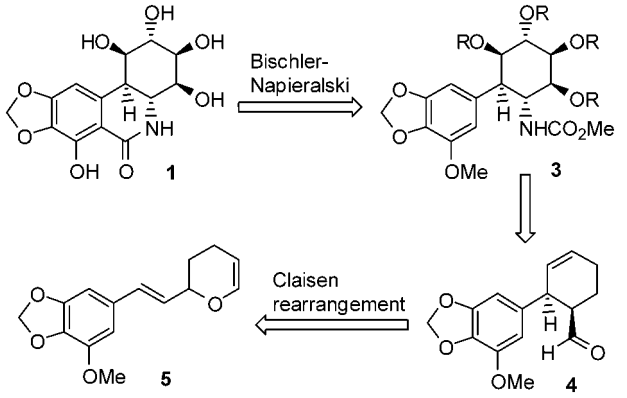
Scheme 1

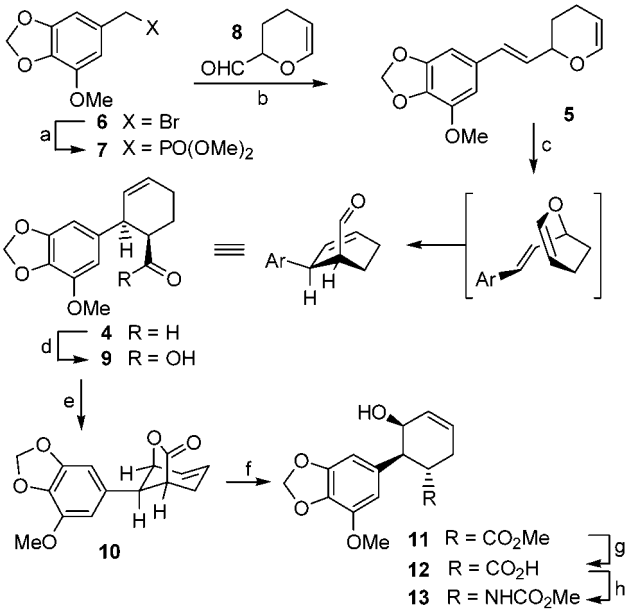


a new synthesis of (+)-pancratistatin. Recently, Pettit achieved the synthesis of (+)-**1** from the more abundant alkaloid (+)-narciclasine (**2**, Figure 1).[9] In this Letter, we wish to report our successful approach to the synthesis of (±)-pancratistatin.

The strategy of our synthesis is presented in Scheme 1. The B ring of the phenanthridone skeleton would be constructed at a relatively late stage of the synthesis by employing the Bischler−Napieralski reaction.[7,10] The requisite cyclization precursor **3**, which contains the six stereocenters in the C ring, could be stereoselectively synthesized from the *cis*-disubstituted cyclohexene **4**. The presence of a γ,δ-unsaturated carbonyl unit in compound **4** suggested the use of a Claisen rearrangement of 3,4-dihydro-2*H*-pyranylethylene **5**.[11]

The synthesis began by preparing the known bromide **6**[12] from the commercially available methyl gallate via a conventional four-step sequence. Treatment of **6** with excess trimethyl phosphite provided phosphonate **7** in 97% yield (Scheme 2).[13] Employing the Honer−Wadsworth−Emmons reaction between **7** and commercially available acrolein dimer **8** (1.1 equiv) in the presence of LHMDS in THF afforded the desired (*E*)-olefin **5** with very high stereoselectivity in 60% yield (92% yield based on the recovered starting material).[14] Only trace amounts (<1%) of the corresponding (*Z*)-olefin were detected in the crude NMR spectra. The Claisen rearrangement of dihydropyranethylene **5** (250 °C in a sealed tube) provided the *cis*-disubstituted cyclohexene **4** as a single isomer in 78% yield. As discussed by Büchi,[11] this rearrangement must proceed through a boatlike transition state.

Scheme 2[a]



[a] (a) $P(OMe)_3$, toluene, sealed tube, 180 °C, 2 h, 97%; (b) **8**, LHMDS, THF, 0 °C to rt, 22 h, 60% (92% based on the recovered starting material); (c) toluene, sealed tube, 250 °C, 20 h, 78%; (d) $NaClO_2$, $NaH_2PO_4 \cdot 2H_2O$, 2-methyl-2-butene, THF, *t*BuOH, H_2O, rt, 18 h, 90%; (e) (i) KI_3, aqueous $NaHCO_3$, CH_2Cl_2, rt, 20 h, (ii) DBU, benzene, reflux, 8 h, 78%; (f) NaOMe, MeOH, reflux, 20 h, 93%; (g) 1N LiOH, THF, rt, 18 h, 99%; (h) (i) DPPA, Et_3N, toluene, reflux, 15 h, (ii) NaOMe, MeOH, reflux, 0.5 h, 82%.

With the appropriately functionalized cyclohexene **4** in hand, our study focused on the selective introduction of the stereocenters in the C ring. First, the aldehyde group of **4** was oxidized with $NaClO_2$ to the corresponding carboxylic acid **9** in 90% yield. Iodolactonization of **9** under two-phase conditions followed by treatment of the resulting iodolactone with DBU in refluxing benzene led to the formation of the bicyclic lactone **10** with an overall yield of 78%.[15] Methanolysis of the lactone **10** with NaOMe at room temperature for 18 h afforded an inseparable equilibrium mixture (ca. 1:1 ratio) of hydroxy ester **11** and its C-4a epimer (pancratistatin numbering). However, when the methanolysis was carried out in refluxing methanol for 20 h, epimerization of the methoxycarbonyl group was accomplished very cleanly to give **11** as the only identifiable product in 93% yield. Saponification of the methyl ester **11** with LiOH was followed by a modified Curtius rearrangement[16] of the resulting acid **12** with diphenylphosphoryl azide in refluxing toluene to give a rather stable isocyanate intermediate that required further treatment with NaOMe/MeOH to generate the corresponding carbamate **13** in 82% overall yield.

The final C-ring functional group processing of **13** proceeded as follows (Scheme 3). At this stage, it was necessary to protect the free hydroxyl group of **13** to

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(14) Wittig reaction between the corresponding phosphonium bromide and acrolein dimer **8** in the presence of KOH and 18-crown-6 ether in CH_2Cl_2 provided a mixture of olefins with a *Z*/*E* ratio of 5:1 in 85% yield.
(15) Kobayashi, S.; Kamiyama, K. Ohno, M. *J. Org. Chem.* **1990**, *55*, 1169.
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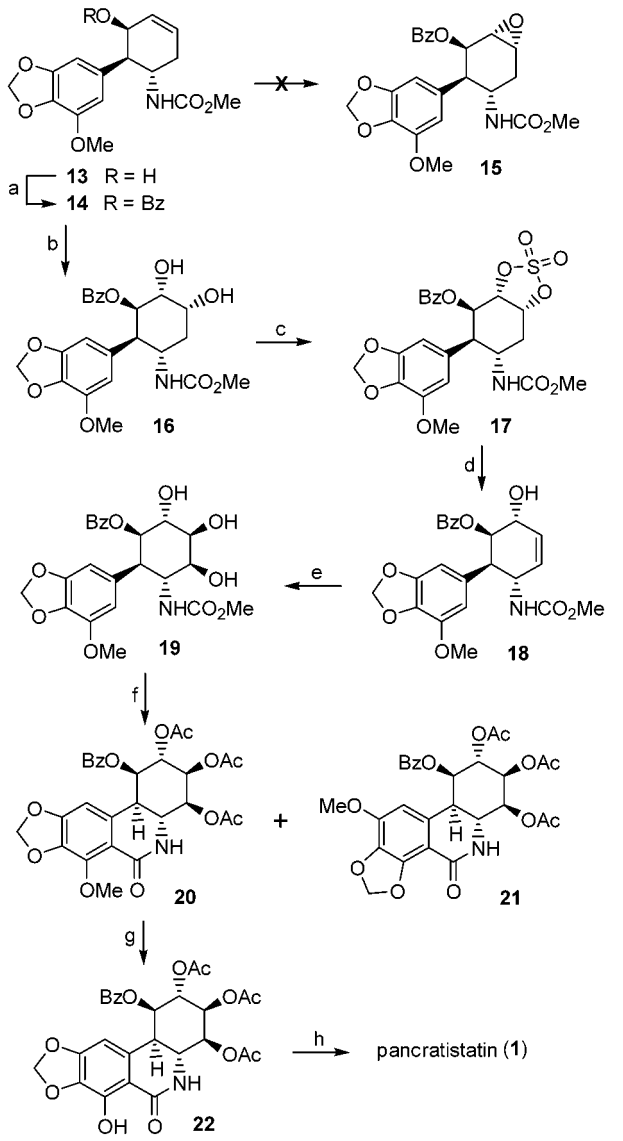
Scheme 3[a]



[a] (a) BzCl, Et_3N, DMAP, CH_2Cl_2, rt, 15 h, 99%; (b) OsO_4, NMO, THF/H_2O, rt, 20 h, 96%; (c) (i) $SOCl_2$, Et_3N, CH_2Cl_2, 0 °C, 0.5 h, (ii) Oxone, $RuCl_3 \cdot 3H_2O$, EtOAc/CH_3CN/H_2O, rt, 2 h, 83%; (d) DBU, toluene, reflux, 2 h, then H_2SO_4, H_2O/THF, rt, 4 h, 67%; (e) OsO_4, NMO, THF/H_2O, rt, 27 h, 88%; (f) (i) Ac_2O, DMAP, pyridine, CH_2Cl_2, rt, 1 h, 77%,(ii) Tf_2O, DMAP, CH_2Cl_2, 0 to 5 °C, 22 h, 78%; (g) BBr_3, CH_2Cl_2, −78 to 0 °C, 1 h, 65%; (h) NaOMe, MeOH, THF, rt, 4 h, 83%.

selectively install the C-2 hydroxyl group on the α-face. This was accomplished by reacting compound **13** with benzoyl chloride to furnish **14** in 99% yield. Attempted epoxidation of **14** to **15** with various regents such as mCPBA and dioxiranes was not successful, providing only decomposed materials. However, dihydroxylation of the $\Delta^{2,3}$-olefin with OsO_4 did occur on the α-face of the molecule to produce diol **16** in 96% yield. The stereochemistry of **16** was tentatively assigned as α, on the basis of steric considerations.

The regioselective elimination of the C-3 hydroxyl group to generate the requisite $\Delta^{3,4}$ unsaturation was achieved by employing the cyclic sulfate elimination reaction.[17] Treatment of diol **16** with thionyl chloride followed by oxidation with $RuCl_3 \cdot 3H_2O$/Oxone[18] provided the corresponding cyclic sulfate **17** in 83% yield. The reaction of cyclic sulfate **17** with DBU in refluxing toluene[17a] led, after acidic workup, to the formation of the desired allylic alcohol **18** (67% yield). Routine *cis*-dihydroxylation of **18** with OsO_4 afforded the single isomer **19** in 88% yield, thereby completing the functionalization of the C ring of pancratistatin. The structural assignment made for this compound was strongly supported by its relevant ^{1}H NMR coupling patterns and by comparing the ^{1}H NMR spectral data of the derived tetraacetate with those reported by Magnus.[7]

The remaining steps to pancratistatin required protection of the hydroxyl groups, formation of the final lactam B ring, and protecting group removal and were accomplished by employing reaction conditions analogous to those of Magnus et al.[7] Peracetylation of **19** (77%) was followed by a Banwell's modified Bischler−Napieralski cyclization,[7,10] which provided predominantly the desired product **20**, along with a minor amount of the regioisomer **21** in 78% combined yield and 7:1 regioselectivity. Treatment of an inseparable mixture of **20** and **21** with BBr_3 to remove the C-7 methyl group protection yielded **22** (65%) and unreacted **21**, which were now separable.[19] Finally, simple removal of protecting groups with NaOMe/MeOH afforded (±)-**1** in 83% yield, of which ^{1}H and ^{13}C NMR spectral data were in good agreement with those reported.[1,3−10]

In conclusion, we have accomplished the stereoselective synthesis of (±)-pancratistatin from readily available starting materials. We utilized the Claisen rearrangement of dihydropyranethylene **5** to construct the A and C rings, and subsequent iodolactonization, dihydroxylations, and cyclic sulfate elimination reactions to install six contiguous stereogenic centers in the C ring.

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Supporting Information Available: Full experimental procedures and spectral data of new compounds and ^{1}H NMR and ^{13}C NMR spectra of compounds **1**, **4**, **5**, **12**, **14**, **19**, and **22**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(19) This reaction patterned after a similar step in the Magnus synthesis.[7]