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Total Synthesis of (+)-Pancratistatin by the Rh(III)-Catalyzed Addition of a Densely Functionalized Benzamide to a Sugar-Derived Nitroalkene

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Abstract

Herein, we report the concise total synthesis of (+)-pancratistatin, accessed in a 10 step linear sequence from commercially available inputs. The convergent synthesis features a highly diastereoselective Rh(III)-catalyzed C-H bond addition to a D-glucose derived nitroalkene and a late stage intramolecular transamidation to furnish the B ring lactam.

Graphical Abstract

The isocarbostryls, shown in Figure 1, are major constituents of the *Amaryllidaceae* alkaloids, of which there are over 500 identified compounds to date.¹ These heavily hydroxylated phenanthridone natural products have garnered significant attention due to their potent anticancer activity.^{2,3} In particular, (+)-pancratistatin (**1**), first isolated by Pettit and co-workers in 1984,⁴ has been shown to have significant cytotoxic activity in numerous cancer cell types,⁵ as well as antiviral⁶ and antiparasitic activity.⁷ (+)-Pancratistatin (**1**) is also classified as a mitocan because it selectively induces apoptosis in cancer cells by targeting the mitochondria.⁵

Due to its impactful biological activity, low natural abundance, and interesting structural features, pancratistatin has served as an important and intensively pursued synthetic target

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ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Full experimental details and characterization data (PDF)

Notes

The authors declare no competing financial interests.

that has culminated in a number of total syntheses ranging from 13 to 26 linear steps.⁸ Herein, we report the total synthesis of (+)-pancratistatin with a longest linear sequence of only 10 steps. The key reactions in the sequence are a highly diastereoselective, convergent coupling of fully elaborated fragments by C-H bond functionalization⁹ and a final intramolecular transamidation of fully deprotected material to provide the natural product.

In 2013, Sato *et al.* reported a concise strategy for the incorporation of the heavy oxygenated C ring of pancratistatin through the use of a D-glucose derived nitroalkene **2** (Scheme 1).⁸ⁿ The aryl cuprate generated from aryl bromide **A** was added to nitroalkene **2** to provide the conjugate addition product **B** in high yield and as a single diastereomer. Deprotection of the acetonide followed by a highly stereoselective cyclization of the resulting furanose with aqueous sodium bicarbonate in methanol gave carbocyclic intermediate **C** containing the fully elaborated C ring of (+)-pancratistatin with the appropriate stereochemistry at all 6 of the stereocenters. This material was then taken on in 9 additional steps to furnish (+)-pancratistatin (**1**) with the major challenge being introduction of the B-ring lactam.

While Sato *et al.* introduced a very elegant and efficient approach for the convergent assembly of the carbon framework of (+)-pancratistatin, their synthesis also underscores a considerable challenge encountered in many of the routes to the natural product. Namely, significant functional group manipulations have often been required to install the lactam functionality.³

We envisioned that using our recently reported method for the Rh(III)-catalyzed C-H bond addition to nitroalkenes,¹⁰ we could couple nitroalkene **2** and benzamide **3** to yield **4**, which contains the preinstalled amide functionality (Scheme 2). As inspired by Sato, we postulated that compound **4** would undergo acetonide and silyl deprotection and a subsequent intramolecular Henry reaction to afford **6**. For the formation of the lactam, we envisioned a nitro group reduction and intramolecular transamidation. In early (+)-pancratistatin synthetic studies a related transamidation using *sec*BuLi and a densely functionalized C ring resulted in elimination and side product formation.^{8b,d} With this in mind, we hoped that our recently reported conditions for dihydroisoquinolone formation via nitro group reduction and intramolecular transamidation under acidic conditions would be applicable for converting **6** to (+)-pancratistatin (**1**).¹⁰

We began by synthesizing the substrates for the key Rh(III) coupling step. Nitroalkene **2** was synthesized from the commercially available 1,2:5,6-di-*O*-isopropylidene- α -D-glucofuranose according to a previously reported procedure in 5 steps (Scheme 3).⁸ⁿ Phenol **3a** was prepared in 2 steps from piperonyl chloride through amide formation and subsequent hydroxylation via directed orthometalation, boration, and oxidation. Due to concerns about the potential incompatibility of the phenol in the key C-H bond functionalization step (*vide infra*), the phenol in **3a** was protected as the TBS and benzyl ethers to provide **3b** and **3c**, respectively, in high yields.

With substrates **2** and **3** in hand, we investigated the key Rh(III)-catalyzed C-H bond addition step (Table 1). Using [Cp*RhCl₂]₂ as the precatalyst, AgSbF₆ as the chloride abstractor, dichloroethane as the solvent, and a 60 °C reaction temperature, no conversion

was observed when phenol **3a** was used, presumably because chelation of the cationic Rh(III) complex by the phenol and amide moieties hindered catalysis (entry 1). We next evaluated the TBS protected phenol **3b** and observed only formation of free phenol **3a** via cleavage of the TBS group from the C-H bond substrate (entry 2). By using the more robust benzyl protected phenol **3c**, the desired product **4** was isolated in 63% yield and with >20:1 dr (entry 3). The very high diastereoselectivity is consistent with the addition of the cuprate of **A** to nitroalkene **2** as reported by Sato (*vide supra*), and can be attributed to the bulkiness of the silyl group on the furanose.⁸ⁿ After optimization of the reaction parameters, the stoichiometry of the less expensive coupling partner **3c** could be reduced to only 1.1 equiv providing the desired product **4** with >20:1 dr and a 73% isolated yield (entry 4).

Upon successfully identifying conditions for the Rh(III)-catalyzed C-H bond addition step, we next set out to form the fully elaborated C ring through a deprotection/intramolecular Henry reaction sequence analogous to that performed by Sato (Scheme 4).⁸ⁿ Removal of the acetonide and silyl group was accomplished by treating **4** with aqueous TFA at 50 °C, yielding **5**. Subjecting the crude furanose **5** to aqueous sodium bicarbonate in methanol at 50 °C afforded compound **6** as a 10:1 mixture of diastereomers. After purification, **6** was isolated as a single diastereomer in 66% overall yield for the two steps.

We next sought to form the final B ring lactam through a nitro group reduction and intramolecular transamidation. In our initial development of Rh(III)-catalyzed C-H bond additions to nitroalkenes we had found that treatment of addition products with Fe in a 1:1 mixture of EtOH/AcOH provided dihydroisoquinolones in high yield.¹⁰ Unfortunately, upon subjecting the densely functionalized intermediate **6** to these conditions, we observed only partial nitro group reduction and no cyclized product (not shown). After significant optimization of the reaction parameters, including temperature, solvent and reductant, we found that treatment of **6** with Zn in aqueous acetic acid at 140 °C in a sealed tube resulted in reduction of the nitro group, transamidation, and cleavage of the benzyl group,¹¹ to afford (+)-pancratistatin (**1**) (Scheme 5). Nitro group reduction could be performed at much lower temperatures, but the forcing conditions required for transamidation and benzyl cleavage resulted in competitive decomposition.

Interestingly, during the course of the reaction, neither of the two possible reaction intermediates **7** and **8** were detected (Scheme 5). There are two potential explanations for this observation. Slow formation of lactam **7** could have been followed by rapid acid-catalyzed debenzylation to give **1**. Alternatively, debenzylation could have occurred first to give **8** followed by rapid transamidation. Intramolecular hydrogen bonding between the phenol and amide could potentially have accelerated transamidation by enhancing the electrophilicity of the amide while also providing a desirable orientation for cyclization.

To test whether or not intramolecular hydrogen bonding would facilitate transamidation, the benzyl group of **6** was cleaved under Pd/C-catalyzed hydrogenolysis conditions (Scheme 6). Phenol **9** was then directly subjected to Zn in aqueous acetic acid with efficient cyclization at 100 °C affording (+)-pancratistatin (**1**) in 68% overall yield for the two steps.

In summary, the asymmetric total synthesis of (+)-pancratistatin (**1**) has been accomplished in a 10 step linear sequence beginning from commercially available inputs. This convergent route features a Rh(III)-catalyzed diastereoselective C-H bond addition to a D-glucose-derived nitroalkene and a late stage intramolecular transamidation to provide (+)-pancratistatin (**1**) in the shortest synthetic sequence reported to date.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Figure 1.
Isocarbostryl natural products, part of the Amaryllidaceae alkaloids.

Scheme 1.
Sato's Synthesis of (+)-Pancratistatin (1)

Scheme 2.
Synthetic Approach Towards (+)-Pancratistatin (1)

Scheme 3.
Synthesis of Starting Inputs

Scheme 4.
Formation of the C Ring

Scheme 5.

Possible Pathways for Nitro Group Reduction, Debenzylation and Transamidation

Table 1

Optimization of C-H Bond Addition Step

entry ^a	C-H bond substrate	yield (%) ^b
1	3a (R = H)	0
2	3b (R = TBS)	0
3	3c (R = Bn)	63 (>20:1 dr)
4 ^c	3c (R = Bn)	73 (>20:1 dr)

^aConditions: 1.0 equiv of **2**, 1.5 equiv of **3** with [Cp*RhCl₂]₂, AgSbF₆ in dichloroethane (0.2 M) at 60 °C for 18 h.

^bIsolated yield after silica gel chromatography.

^cOptimized conditions: 1.0 equiv of **2**, 1.1 equiv of **3** with [Cp*RhCl₂]₂, AgSbF₆ in dichloroethane (0.5 M) at 40 °C for 18 h.