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# Total Synthesis of (+)-Hyacinthacine $A_1$ Using a Chemoselective Cross-Benzoin Reaction and a Furan Photooxygenation–Amine Cyclization Strategy

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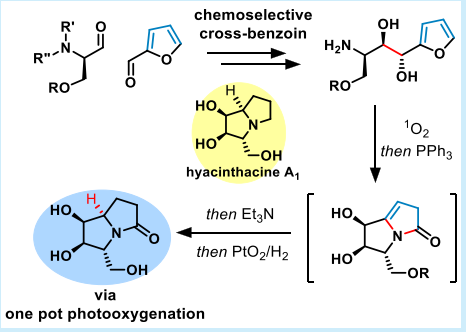
**ABSTRACT:** We report the shortest synthesis of glycosidase inhibitor (+)-hyacinthacine $A_1$ using a highly chemoselective N-heterocyclic carbene-catalyzed cross-benzoin reaction as well as a furan photooxygenation–amine cyclization strategy. This is the first such cyclization on a furylic alcohol, an unprecedented reaction due to the notorious instability of the formed intermediates. The photooxygenation strategy was eventually incorporated into a three-step one-pot process that formed the requisite pyrrolizidine framework of (+)-hyacinthacine $A_1$.




(+)-Hyacinthacine $A_1$ [**7** (Figure 1)] is a member of a large class of polyhydroxylated pyrrolizidine and indolizidine structures that act as glycosidase inhibitors.[1] These belong to the broader class of amino sugars, a group of compounds that have found significant use in glycobiology as tools and as frameworks for potential pharmaceuticals.[1,2] Important amino sugars include the various deoxynojirimycin derivatives,[3] Celgosivir,[4] and other neuraminidase inhibitors such as zanamivir.[5] (+)-Hyacinthacine $A_1$ (**7**) is especially interesting due to its low micromolar range inhibition, making it an important target for further study.[6] It is also one of the more challenging hyacinthacine derivatives to access, highlighting the need to develop more efficient methods for its preparation.[6,7]

Previously, in attempting to solve the chemoselectivity issues that plagued cross-benzoin reactions,[8] our group discovered that two aldehydes could be coupled catalytically with N-heterocyclic carbenes (NHCs) when one of the reactants was a protected amino aldehyde.[9,10] The reaction generates an $\alpha$-hydroxy-$\beta$-aminoketone [**3** (Figure 1)] with good yields and diastereoselectivities. We believed that incorporating a furan ring into this structure would make it more amenable to useful transformations,[11] thereby allowing us to target a variety of natural products.[12−15] The high availability and versatility of furans from biomass emphasize the importance of furthering our understanding of these transformations.[16]

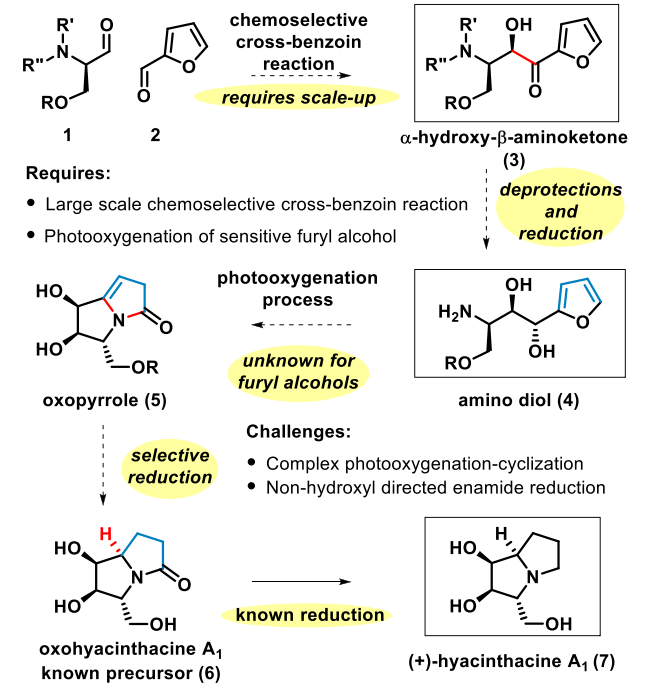



**Figure 1.** Strategy toward (+)-hyacinthacine $A_1$ (**7**).

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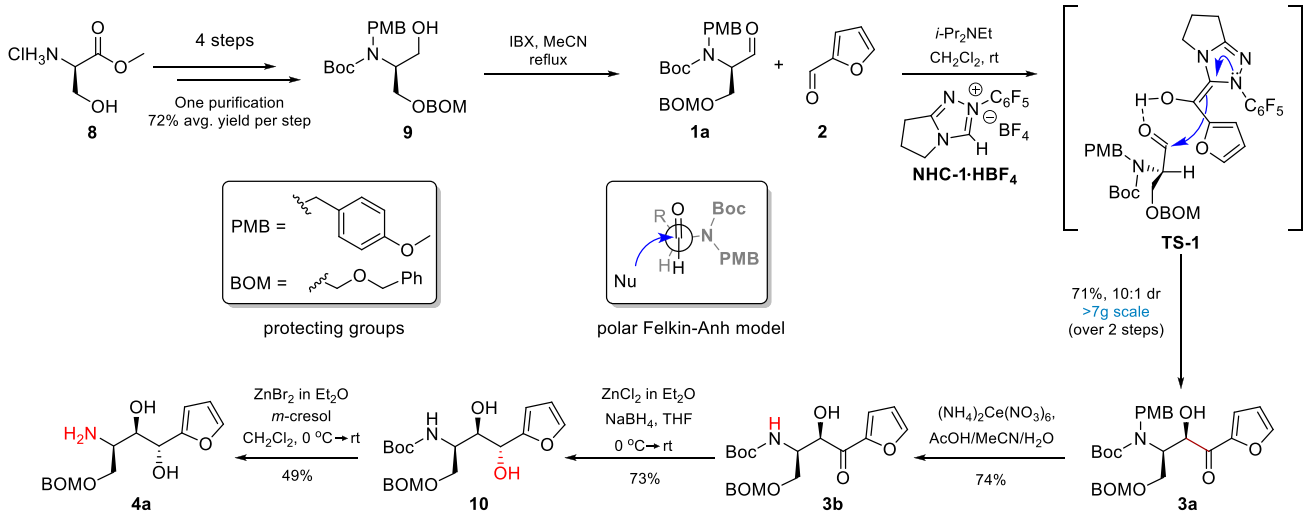
**Scheme 1. Synthesis of Aminodiol (4a)**




In our search of potential reactions, we were pleased to discover a recent elegant methodology developed by Vassilikogiannakis and co-workers that transformed furanylalkylamines into pyrrolizidine and indolizidine frameworks with singlet oxygen.[17] The oxidation was highly selective for the furan ring despite using unprotected amines. Unfortunately, these oxidations were exclusively performed on nonhydroxylated furanylalkylamines, likely due to the known degradation pathways during photooxygenations of furyl alcohols.[18] Despite these reported failures using furyl alcohols, we were hoping the problem could be overcome.

A photooxygenation−amine cyclization strategy was then envisioned to be used in conjunction with the chemoselective cross-benzoin reaction to produce oxopyrrole **5** (Figure 1), which we believed could be transformed into (+)-hyacinthacine $A_1$ [(+)-7]. Indeed, the route was successful, and we are delighted to report the shortest total synthesis of (+)-7, demonstrating the immense potential of both the cross-benzoin reaction and photooxygenation methodologies.

The synthesis began from the commercially available D-serine methyl ester [**8** (Scheme 1)] that could be converted to amino alcohol **9** in four steps with only one purification. Iodoxybenzoic acid (IBX) oxidation followed to generate the corresponding amino aldehyde **1a**, setting the stage for the first key step. The doubly protected amine was required for the polar Felkin−Anh selectivity in the cross-benzoin reaction (**TS-1**).[9b] The reaction proceeded smoothly to generate *α*-hydroxy-*β*-aminoketone **3a**, which could be isolated from the furfural dimer side product (**S4**) in 71% yield and with a 10:1 dr. Notably, the reaction could be performed on a multigram (>7 g) scale with no loss of yield or selectivity.

To reach the second checkpoint, the furyl ketone (**3a**) needed to be reduced and both nitrogen protecting groups (Boc and PMB) had to be removed. While furan rings can be quite robust, their reactivity is highly dependent on adjacent functionalities. As such, it is useful to comment on the difficulties we encountered during this stage of the synthesis. Removal of the PMB group could not be achieved by heterogeneous hydrogenation without affecting the furan ring. Additionally, oxidative PMB deprotection methods (DDQ and CAN) necessitated the presence of a furylic ketone as the lower ionization energies of furyl alcohols increase the ring's susceptibility to oxidation.[19]

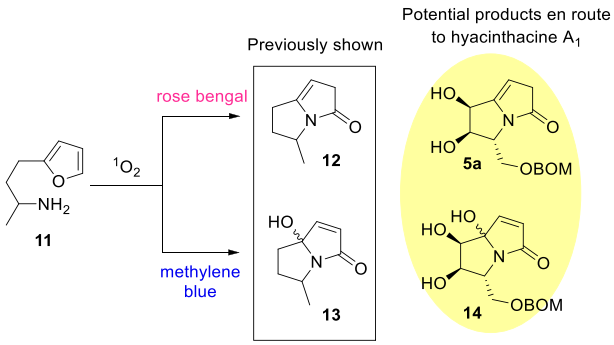
Conversely, Boc deprotection could not be performed on the more stable furyl ketone due to retro-Mannich reactions of the formed product. Furylic alcohols would also not be tolerant to excessively acidic (Brønsted or Lewis) conditions due to probable Piancatelli rearrangements. These restrictions proved to be challenging, but ultimately not intractable as a route could be mapped.

The deprotection sequence began with a CAN-mediated PMB group removal (**3a** to **3b**). The product (**3b**) could then be converted to the furylic alcohol (**10**) via a Zn(II) borohydride reduction, to afford the product predicted by the Cram-chelate model with >19:1 diastereoselectivity.[20]

The final Boc deprotection proved to be the most challenging step as strong Brønsted and Lewis acids caused the degradation of the furylic alcohol (**10**). After significant optimization, a mild protocol using $ZnBr_2$ in an $Et_2O/CH_2Cl_2$ solvent with *m*-cresol as an additive was found to be most effective in producing aminodiol **4a**.[21] Our arrival at the second checkpoint allowed us to finally survey the chemical space of the photooxygenation.

There were some tactical choices to be made as the methodologies explicated by Vassilikogiannakis allowed for the formation of two products (Scheme 2, **12** and **13**). Typical photosensitizers such as rose bengal (RB) and tetraphenylporphyrin (TPP) produce enamides such as **12**, while methylene

**Scheme 2. Possible Products after Photooxygenation**



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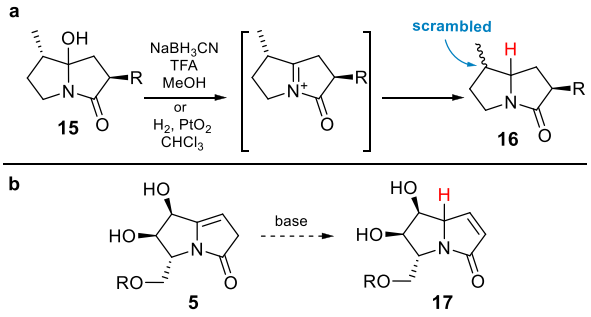
blue (MB) catalyzes a subsequent reaction with oxygen to form hemiaminals such as **13**.[17a] It was presumed that **13** would be difficult to reduce due to the necessity for iminium ion formation in the presence of multiple hydroxyl functionalities. Similar iminiums have been shown to tautomerize rapidly, resulting in a loss of stereochemical information about the adjacent stereocenter (Scheme 3a).[22]

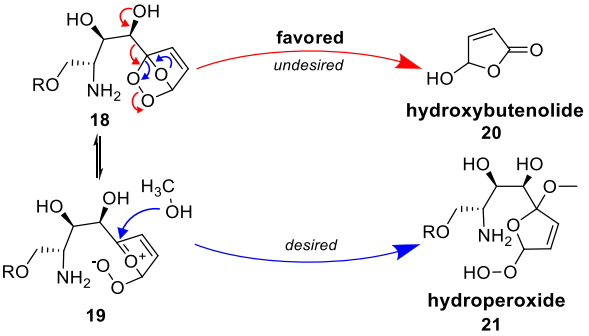
**Scheme 3. (a) Scrambling of the Adjacent Stereocenter during Reduction and (b) Proposed Base-Catalyzed Isomerization**




Thus, enamides of type **5** were targeted as it was expected that isomerization to the presumed thermodynamically favored amide **17** (Scheme 3b) could be achieved if traditional hydrogenations failed.

Initial photooxygenation experiments used conditions slightly modified from those reported by Vassilikogiannakis and co-workers.[17a] Methanol was chosen for the photooxygenation as it was postulated that the highly unstable endoperoxide intermediate [**18** (Scheme 4)] could be rapidly

**Scheme 4. Reactivity of Endoperoxide 18 in MeOH**




transformed into the more kinetically stable hydroperoxide (**21**), which would lead to the desired lactam **5a** (Scheme 2). Unfortunately, initial experiments (Table 1, entry 1) led to very poor yields (<5%). Various solvents, light sources, and photosensitizers were tested to no avail. It was believed that **18** was problematic in the photooxygenation as endoperoxides of furylic alcohols are well-known to degrade via fragmentation to hydroxybutenolides [**20** (Scheme 4)].[18a] We thought this degradation may be further accelerated by an intramolecular N−H−O hydrogen bond between the basic amine and the furylic alcohol.

To test this hypothesis, the photooxygenation of **4a** was completed at −78 °C in deuterated methanol. When the reaction mixture was heated to −10 °C, a considerable amount

**Table 1. Optimization of the Photooxygenation**

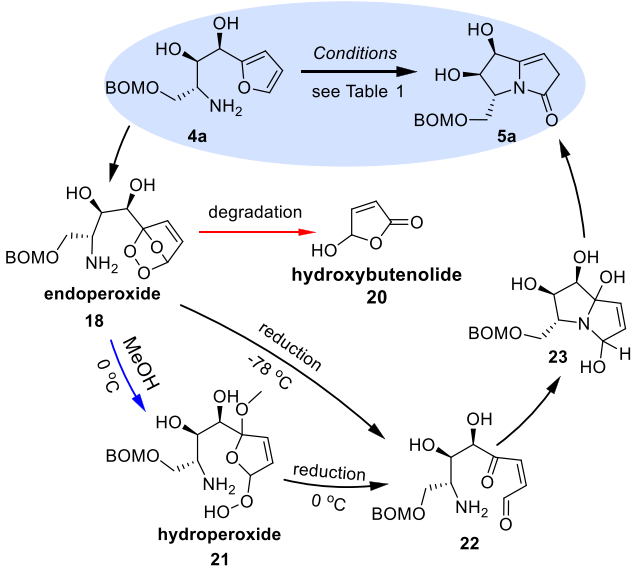
| entry | photooxygenation conditions[a] (photosensitizer/solvent/temp/additive) | quench | yield[b] (%) |
|---|---|---|---|
| 1 | MB or RB[c]/MeOH/0 °C/none | DMS | <5 |
| 2 | MB/MeOH/−78 °C/none | DMS | 16 |
| 3 | MB/MeOH/−78 °C/none | $PPh_3$ | 25 |
| 4 | MB/MeOH/−78 °C/*p*-TSA (1 equiv) | $PPh_3$ | 39 |
| 5 | TPP/THF:MeOH/−78 °C/none | $PPh_3$ | 15 |
| 6 | TPP/$CH_2Cl_2$/−78 °C/none | $PPh_3$ | 44 |
| 7 | TPP/$CH_2Cl_2$ (10% MeOH)/−78 °C/TFA (1 equiv) | $PPh_3$ | 45 |
| 8 | TPP/trichloroethylene/−78 °C/none | $PPh_3$ | 53 |

[a]Entry 1 was done with a 1000 W arc lamp. Entries 2−6 were done with a 300 W halogen lamp. Entries 7 and 8 were done with 6000 K LED strip lights. [b]Yields were determined by $^1$H NMR analysis of crude mixtures with trichloroethylene as an internal standard. [c]See ref 24.

of hydroxybutenolide (**20**) was observed by $^1$H NMR spectroscopy,[18a] indicating that its formation is more favorable than that of the desired hydroperoxide (**21**). Notably, quenching this crude material with dimethyl sulfide and triethylamine failed to afford any desired product and resulted in the disappearance of the hydroxybutenolide (Figure S2). These results suggested that no productive intermediates were present after the reaction mixture had been heated to −10 °C.[23]

To circumvent the fragmentation (**18** to **20**), we decided to reduce the endoperoxide directly at low temperatures (Scheme 5, **18** to **22**). Accordingly, performing the photooxygenation at −78 °C and directly adding a reductant resulted in an immediate improvement in yield (Table 1, entries 1−3).

**Scheme 5. Mechanism of the Photooxygenation**




Interestingly, yields improved further with the addition of 1 equiv of *p*-toluenesulfonic acid (*p*-TSA) (entry 4), which was thought to either neutralize the basic amine or accelerate the final step (**23** to **5a**). Various solvents were then explored (entries 5−8). Replacing methanol with chlorinated solvents produced the highest yields, with trichloroethylene (entry 8) as the best solvent. Acid additives in chlorinated solvents (entry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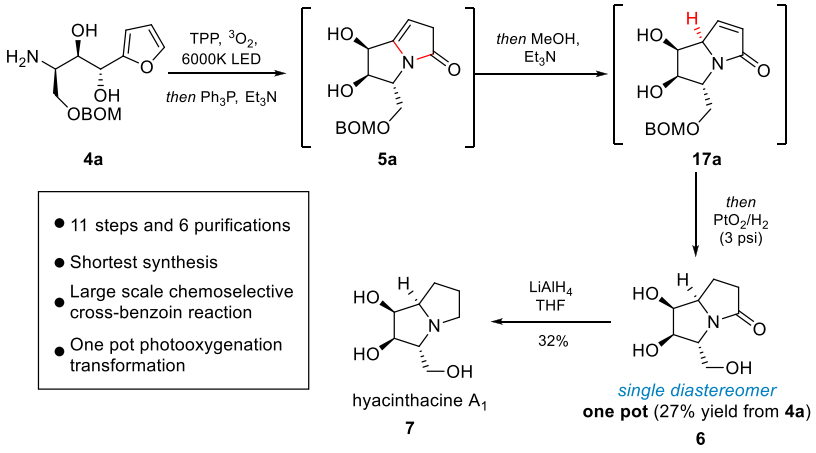
**Scheme 6. Preparation of (+)-Hyacinthacine $A_1$ (7)**




7) resulted in no further improvements. Nevertheless, an overall yield of 53% for such a complex sequence was considered excellent and allowed us to move forward with the synthesis.

With a reliable method for producing enamide **5a** (Scheme 5), we proceeded to the final stages of the synthesis. Attempts to effect reduction of the enamide using standard methods[22,25] ($Et_3SiH$/TFA, $NaBH_4$/AcOH, and Pd/$H_2$) were met with failure. This outcome was not unexpected as it was presumed that the iminium generated by protonating the enamine in **5a** would be highly unstable. Additionally, the instability of **5a** to silica or aqueous conditions prevented purification, rendering other transition metal-mediated reductions troublesome. Eventually, an isomerization of the double bond was sought.[26]

Unfortunately, all attempts to induce isomerization to **17a** in $CH_2Cl_2$ or other chlorinated solvents resulted in poor yields despite the use of stronger bases such as DBU. The best results were eventually obtained when the solvent was removed *in vacuo* and methanol was added directly to the reaction mixture with additional $Et_3N$ (Scheme 6).

We were delighted to find that this treatment resulted in the formation of $\alpha,\beta$-unsaturated lactam **17a** as a single diastereomer. The hydrogenation and hydrogenolysis of this compound were utlimately completed by adding $PtO_2$ and a hydrogen atmosphere (3 psi) directly to the crude methanol solution. Thus, the formal total synthesis of (+)-hyacinthacine $A_1$ [(+)-7] could be completed with an overall one-pot process yield of 27%. A final $LiAlH_4$ reduction[7b,27] produced (+)-hyacinthacine $A_1$ to complete the total synthesis in 11 steps.

In conclusion, we have developed a novel route toward (+)-hyacinthacine $A_1$. Key features of the synthesis include the use of a diastereoselective intermolecular aldehyde−aldehyde cross-benzoin reaction and a highly complex photooxygenation−amine cyclization cascade. Although protecting groups are required to obtain the desired selectivity in the benzoin reaction, deprotection was shown to be possible without perturbing the sensitive furan ring. Furthermore, the nature of the photooxygenation substrate (**4a**) suggests the method may be adaptable to other diastereomers or similarly complex substrates, potentially opening up the scope of the photooxygenation cascade considerably.

## ■ ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.1c00090.

Experimental procedures and characterization data (PDF)

FAIR data, including the primary NMR FID files, for compounds **1a**, **3a**, **3b**, **4a**, **5a**, **6**, **7**, **9**, **10**, **17a**, **S2**, and **S3** (ZIP)

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### Author Contributions

†K.P. and P.H. contributed equally to this work.


### Notes

The authors declare no competing financial interest.

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