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Synthesis of (+)-Pancratistatins via Catalytic Desymmetrization of Benzene

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Supporting Information

ABSTRACT: A concise synthesis of (+)-pancratistatin and (+)-7-deoxypancratistatin from benzene using an enantioselective, dearomative carboamination strategy has been achieved. This approach, in combination with the judicious choice of subsequent olefin-type difunctionalization reactions, permits rapid and controlled access to a hexasubstituted core. Finally, minimal use of intermediary steps as well as direct, late stage C-7 hydroxylation provides both natural products in six and seven operations.

The plant-derived metabolites (+)-pancratistatin (**1**)[1] and (+)-7-deoxypancratistatin (**2**)[2] belong to a family of densely functionalized and stereochemically complex Amaryllidaceae alkaloids that are well-known for their potent anticancer activity (Figure 1).[3] For example, pancratistatin

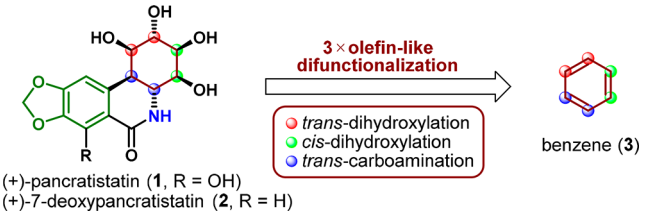

Figure 1. Structures of pancratistatin (**1**) and 7-deoxypancratistatin (**2**) and their retrosynthetic analysis.

(**1**) showed substantial *in vivo* activity against murine P-388 lymphocytic leukemia and murine M-5076 ovary sarcoma, and reduced growth of subcutaneous colon HT-29 tumors.[4] Moreover, experiments examining pancratistatin-induced apoptosis revealed noticeably reduced death in noncancerous cells relative to cancer cell lines, making these compounds appealing clinical lead candidates.[5] Finally, pancratistatins also showed significant antiviral activities, including *in vivo* models for Japanese encephalitis,[6] a disease for which no other known small-molecule anti-infective agent exists.

These promising biological properties made pancratistatins exceptionally attractive targets for chemical synthesis.[7,8] Nevertheless, despite numerous impressive efforts, only milligram quantities of pancratistatins have been prepared to date. Herein, we report a scalable and concise synthesis of (+)-pancratistatin (**1**) and (+)-7-deoxypancratistatin (**2**) from benzene (**3**) using a dearomative functionalization approach. Using this strategy, benzene can be seen as a surrogate for the hypothetical 1,3,5-cyclohexatriene that could readily undergo three olefin-type functionalizations and enable key retrosynthetic simplifications (Figure 1).

With the foregoing analysis in mind, we recognized that the development of a dearomatization process[9] that would also result in desymmetrization of benzene[10] was critical to our synthetic plan. We hypothesized that the application of visible-light-promoted *para*-cycloaddition of the N−N arenophile MTAD (**4**),[11] in combination with an aryl nucleophile (ArM) and transition metal catalysis (TM cat.), could provide *trans*-carboaminated product **6** (Figure 2). Specifically, the

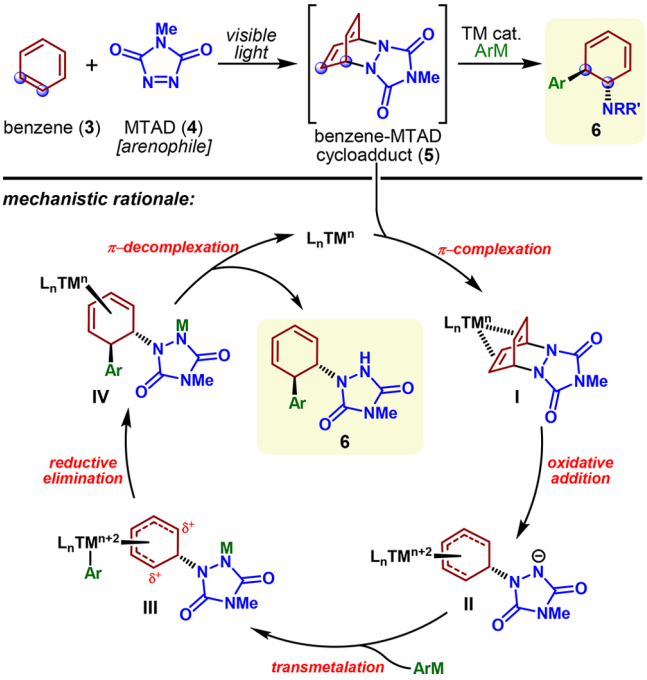

Figure 2. Design of dearomative *trans*-carboamination sequence.

intermediate MTAD-benzene cycloadduct **5** could serve as a viable substrate for oxidative addition due to its *bis*-allylic bridgehead positions bearing an electron-deficient urazole.[12] Mechanistically, we envisioned this catalytic process as commencing with π-coordination of the diene to the metal complex *anti* to the arenophile moiety (**5** → **I**). Subsequent oxidative addition should give cyclohexadienyl intermediate **II**, which should undergo transmetalation with an aryl metal

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J. Am. Chem. Soc. XXXX, XXX, XXX−XXX

reagent to form species **III**. This symmetric η^5-complex can then undergo reductive elimination to deliver diene complex **IV**. Finally, diene decomplexation yields the product and regenerates the metal catalyst. The central feature of this design is the generation and capture of η^5-cyclohexadienyl reactive intermediate; the desired 1,2-site-selectivity of the carboamination process would be favored because of the greater positive charge localized on the termini of the η^5-system.[13] Though no catalytic processes involving cyclohexadienyl complexes exist to date, such outcomes are well precedented in cases wherein cationic cyclohexadienylmetal complexes react with nucleophiles in a stoichiometric fashion.[14] Importantly, because of the symmetrical nature of the η^5-intermediate **III**, a suitable chiral ligand bound to the metal center could enable enantiodiscrimination that involves the differentiation of the enantiotopic termini of the cyclohexadienyl system, forming the desired product in an enantioselective fashion.

On the basis of this design, we began our investigations into the dearomative carboamination. Accordingly, we found that nickel-based catalysts with bidentate ligands, in combination with aryl Grignard reagents, gave the best results (Figure 3).

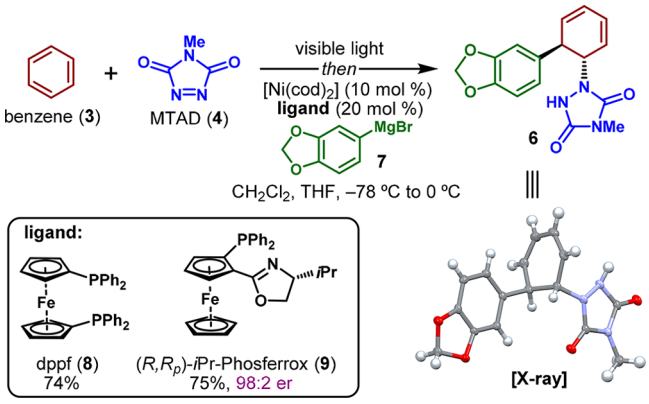

Figure 3. MTAD-mediated, Ni-catalyzed dearomative *trans*-1,2-carboamination of benzene.

Specifically, we identified that conducting the MTAD-benzene cycloaddition reaction in dichloromethane, followed by the addition of a Ni-catalyst ([Ni(cod)$_2$]/dppf (**8**) = 10/20 mol %) and aryl Grignard reagent **7** delivered the desired dearomatized product **6** in 74% yield as a single constitutional and diastereoisomer. In addition, we performed a comprehensive evaluation of chiral bidentate ligands,[15] and discovered that the PHOX-type ligand (R,R_p)-*i*Pr-Phosferrox (**9**) afforded desired product **6** in 75% yield and with high enantioselectivity (98:2 er).

The enantioselective, dearomative *trans*-carboamination of benzene serves as the key strategic maneuver as it installs the first two vicinal stereocenters and drastically simplifies synthetic entry to the pancratistatin core (Figure 4). Early on, we found that masking the acidic urazole hydrazyl group (pK_a = 5.8 in water) is crucial for the precise orchestration of subsequent stereoselective manipulations. Therefore, we selected the methyl group as it could be introduced simply by quenching the dearomatization reaction with dimethyl sulfate (**3** → **10**). Moreover, on a preparative scale, we were able to lower the catalyst and ligand loadings to 5 and 10 mol % without significant erosion in yield or selectivity (65% yield, 98:2 er, after methylation quench). Thus, by simply executing this reaction in a one-liter media bottle with commercial-grade visible-light diodes we were able to conveniently prepare dearomatized compound **10** on a decagram scale. It is worth noting that using this protocol, we have prepared >300 g of this carboaminated product in total.

With the key diene intermediate **10** in hand, the focus then shifted to the next two olefin difunctionalization operations, which would introduce the remaining four hydroxy substituents in a stereoselective manner and complete the pancratistatin core. Because of the electron-withdrawing effect of the urazole nitrogen, the alkene distal to this moiety reacted preferentially with electrophilic reagents. Thus, a chemo- and diastereoselective preparation of *trans*-diol **11** was accomplished using a one-pot protocol involving epoxidation with *m*CPBA and subsequent epoxide hydrolysis in the presence of *p*TsOH and a large excess of water.[16] In addition, the use of hexafluoroisopropanol (HFIP) as the solvent was essential to obtain diol product **11** in 74% yield.[17] Exposure of the remaining alkene in **11** to Upjohn dihydroxylation conditions[18] provided tetraol **12** in 91% yield and as a single stereoisomer. Importantly, this step completes the trifold olefin difunctionalization sequence that transforms benzene into the fully decorated pancratistatin core, establishes all six contiguous stereocenters, and sets the stage for lactam construction. To this end, deprotection of urazole **12** to free amine **14** using conditions to affect hydrolysis and N–N bond cleavage proved challenging, as aggressively acidic or basic conditions led to complete decomposition of starting material. Therefore, we explored hydride-based reducing agents and found that treatment of **12** with $LiAlH_4$ could reduce the urazole; however, the resulting cyclic hydrazine hemiaminal **13** proved unstable, complicating its isolation and the overall reproducibility of this step. To overcome this hurdle, we decided to developed a one-pot protocol that directly reduced urazole **12** to amine **14** without handling the sensitive intermediate **13**. Thus, $LiAlH_4$ reduction, followed by aqueous quench and subsequent addition of Raney-cobalt[19] under a hydrogen atmosphere, gave the best results and provided free amine **14** in 60% yield. Noteworthy, using this sequence, we were able to prepare several grams of aminotetraol precursor **14** in a single pass.

The final step, needed to complete isocarbostyril framework of the pancratistatins, namely the installation of the carbonyl group, was achieved in two steps comprising halogenation and intramolecular aminocarbonylation. To increase step economy and the overall efficiency of the synthesis,[20] we probed reactions that could function on the unprotected aminotetraol **14**. After extensive investigation, this task was effectively accomplished using bromination (Br_2 in AcOH),[21] followed by $NaCo(CO)_4$-catalyzed carbonylation under a CO atmosphere and UV light irradiation[22] to give the corresponding (+)-7-deoxypancratistatin (**2**) in 72% yield over the two steps. Moreover, we were able to conduct both transformations in a single reaction vessel, without the need of isolation and purification of the bromide intermediate, making this formal carbonyl insertion operation more practical on a gram scale.

Though more than a dozen chemical syntheses of (+)-7-deoxypancratistatin (**2**) exist, its conversion to (+)-pancratistatin (**1**) through late-stage C-7 arene hydroxylation has never been established. We undertook this task by exploring directed ortho metalations and found that hydroxylation of position C-7 could be affected using a cupration/oxidation sequence;[23] however, only when (+)-7-deoxypancratistatin (**2**) was persilylated with hexamethyldisilazane (HMDS).[24] According to control experiments (see Supporting Information), this

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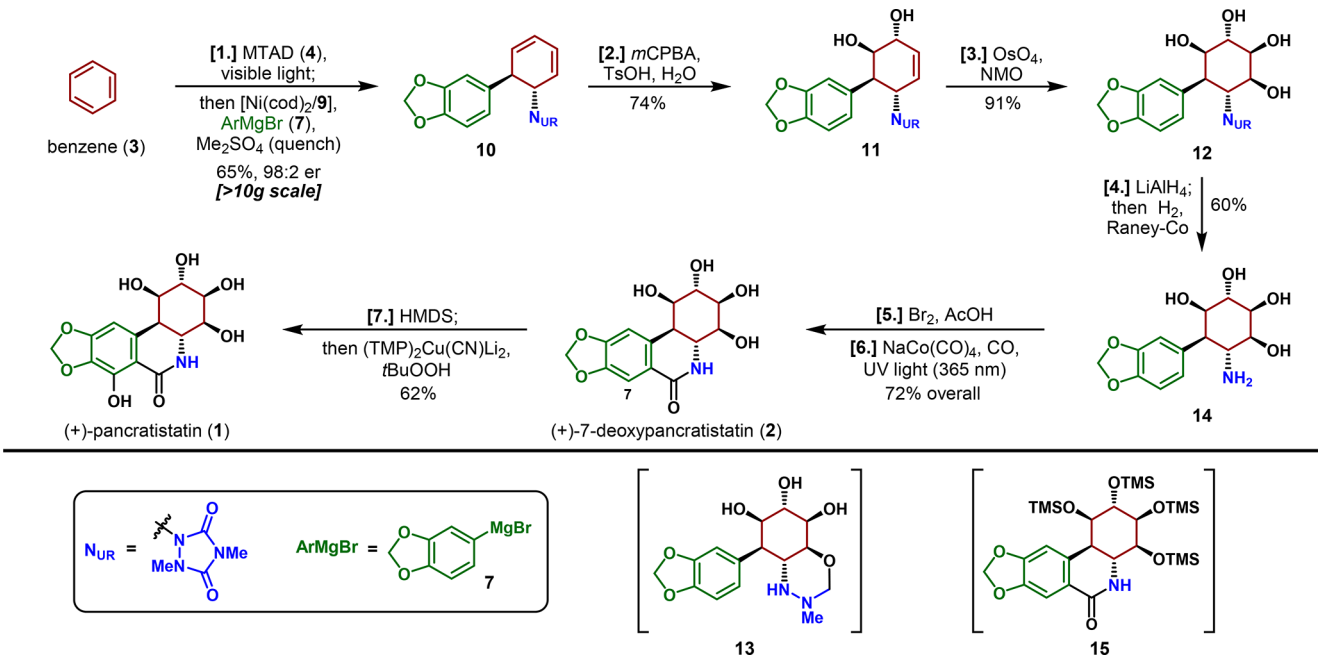

Figure 4. Synthesis of (+)-pancratistatins (**1** and **2**) from benzene (**3**). Reagents and conditions: [1.] benzene (**3**), MTAD (**4**), CH_2Cl_2, visible light, −78 °C; then $[Ni(cod)_2]$ (5 mol %), (R,R_p)-*i*Pr-Phosferrox (**9**, 10 mol %), arylmagnesium bromide **7**, CH_2Cl_2, THF, −78 °C to rt; quench with Me_2SO_4, K_2CO_3, 65% (98:2 *er*). [2.] *m*CPBA, TsOH, CH_2Cl_2, HFIP, H_2O, 50 °C, 74%. [3.] NMO, OsO_4 (5 mol %), *t*BuOH:H_2O, rt, 91%. [4.] $LiAlH_4$, THF, reflux; quench with Rochelle salt; then Raney-Co, H_2 (1 atm), 60 °C, 60%. [5.] Br_2, AcOH, rt. [6.] $NaCo(CO)_4$ (30 mol %), nBu_4NBr, CO (1 atm), $NaHCO_3$, H_2O, 1,4-dioxane, 365 nm light, 60 °C, 72% over two steps. [7.] HMDS, I_2 (1 mol %), MeCN, 80 °C; then solvent removal and $(TMP)_2Cu(CN)Li_2$, THF, −78 °C → 0 °C; then *t*BuOOH, THF, −78 °C, 62%.

direct arene hydroxylation is likely to proceed through the intermediacy of tetra-*O*-silylated-(+)-7-deoxypancratistatin (**15**), which undergoes C-7 cupration with $(TMP)_2Cu(CN)Li_2$. Subsequent *in situ* oxidation with *t*BuOOH and acidic workup furnished (+)-pancratistatin (**1**) in 62% yield.

In summary, we have completed the syntheses of (+)-7-deoxypancratistatin (**2**) and (+)-pancratistatin (**1**) in six and seven operations in 19% and 12% overall yield. Importantly, using this synthetic blueprint, we have prepared several grams of natural products **1** and **2** to date. The synthetic efficiency of our approach originates from the development of an enantioselective, catalytic, dearomative *trans*-carboamination of benzene for which no chemical or biological equivalent exists. This transformation permits access to the key diene **10** and greatly simplifies the synthetic approach to the amino-cyclitol core. Finally, by providing a chemical connection between (+)-7-deoxypancratistatin (**2**) and (+)-pancratistatin (**1**), this work also presents a notable departure from previous syntheses of the pancratistatins, in which each member required *de novo* synthesis using the properly C-7 functionalized aromatic starting material. We postulate that the myriad opportunities in alkene functionalization should render the dearomative carboamination strategy amenable to the preparation of other natural products, as well as a diverse set of congeners.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.7b10351.

Experimental procedures, as well as spectroscopic and analytical data for all new compounds (PDF)

Crystallographic data (CIF)

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Notes

The authors declare the following competing financial interest(s): The University of Illinois has filed a provisional patent on this work.

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