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Enantioselective Synthesis of Isocarbostyril Alkaloids and Analogs Using Catalytic Dearomative Functionalization of Benzene

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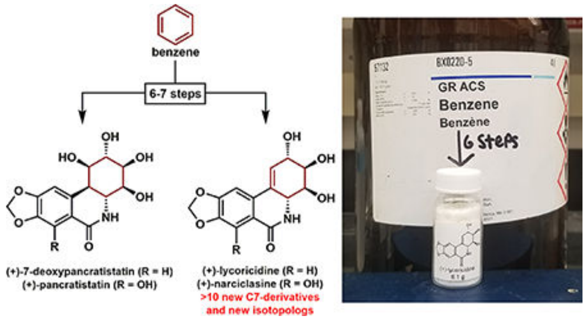
Abstract

Enantioselective total syntheses of the anticancer isocarbostyril alkaloids (+)-7-deoxypancratistatin, (+)-pancratistatin, (+)-lycoricidine, and (+)-narciclasine are described. Our strategy for accessing this unique class of natural products is based on the development of a Nicatalyzed dearomative *trans*-1,2-carboamination of benzene. The effectiveness of this dearomatization approach is notable, as only two additional olefin functionalizations are needed to construct the fully decorated aminocyclitol cores of these alkaloids. Installation of the lactam ring has been achieved through several pathways and a direct interconversion between natural products was established via a late-stage C-7 cupration. Using this synthetic blueprint, we were able to produce natural products on a gram scale and provide tailored analogs with improved activity, solubility, and metabolic stability.

Graphical Abstract



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

ASSOCIATED CONTENT
Supporting Information
The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.8b12123.
Experimental procedures, as well as spectroscopic and analytical data for all new compounds (PDF)
Crystallographic data for $C_{14}H_{13}NO_6$, H_2O (CIF)
Crystallographic data for $C_{17}H_{19}N_3O_6$ (CIF)
Crystallographic data for $C_{20}H_{22}BrN_3O_7$ (CIF)
Crystallographic data for $C_{17}H_{17}Br_2N_3O_5$ (CIF)

INTRODUCTION

Plants belonging to the Amaryllidaceae family have long been known for their medicinal properties; their importance was recognized by the Ancient Greeks, as crude plant extracts were prescribed by Hippocrates and his School of Medicine as remedies against various illnesses, including tumors.[1] Isolation studies revealed numerous compounds associated with the significant anticancer effects of these plants, including the isocarbostyril-type alkaloids (+)-7-deoxypancratistatin (**1**),[2] (+)-pancratistatin (**2**),[3] (+)-lycoricidine (**3**),[4] and (+)-narciclasine (**4**)[5] (Figure 1). These compounds exhibited significant growth-inhibitory potencies against several human cancer cell lines and showed unique cytotoxicity patterns that do not correlate with any known anticancer agents.[6] For example, experiments examining the cytotoxic profile of these compounds revealed noticeably reduced death in noncancerous cells relative to cancer cells, suggesting that their development as chemotherapeutics could result in fewer adverse side-effects.[7] Moreover, narciclasine (**4**) exhibited considerable activity in *in vivo* tumor models, including highly invasive human glioblastomas and apoptosis-resistant brain metastases,[8] albeit with toxicity also being reported in certain cases.[9] In addition to their potent anticancer activity, pancratistatin (**2**) and 7-deoxypancratistatin (**1**) also showed significant antiviral activity, such as in *in vivo* models for Japanese encephalitis,[10] and narciclasine (**4**) has been found to attenuate diet-induced obesity[11] and to possess anti-inflammatory properties.[12]

Despite these encouraging biological properties, the precise biomolecular mechanisms of action have not been fully elucidated. Pancratistatin is postulated to induce apoptosis through the intrinsic pathway, as evidenced by an increase in caspase-9 and caspase-3 activity, exposure of phosphatidyl serine, and destabilization of mitochondrial membrane potential.[13] Interestingly, the cytotoxic activity of narciclasine has been attributed to the extrinsic caspase-8 apoptotic pathway via the activation of the Fas and death receptor 4 (DR4) death inducing signaling complex (DISC).[7d] Furthermore, narciclasine has exhibited activity in cytostatic pathways that complement its cytotoxic ones. It has been shown to block peptide synthesis through direct inhibition of the A-site of the 60S ribosome.[14] These findings were further corroborated by cocrystallization of narciclasine (**4**) in the A-site of the 60S ribosome.[15] Additionally, **4** binds the translation elongation factor eEF1A, thereby impeding this protein’s secondary function of actin bundle formation and disrupting polysome organization and impairing cytokinesis.[8b] Likewise, similar activities are observed through the activation of GTPase RhoA in glioblastoma cells, causing the formation of F-actin stress fibers that disrupt cytokinesis.[8a]

These promising biological attributes sparked significant interest for large-scale production of isocarbostyrils **1–4** to enable preclinical evaluations. To this end, the highest yielding isolation of (+)-pancratistatin (**2**), from 100 kg of *Hymenocallis litoralis* grown in the Hawaiian wilderness, yielded 15 g (150 mg/kg, 0.015% yield) of **2**.[16] To secure more sustainable access, a biotechnological approach was developed involving a plant tissue culture cloning of the same plant species. Unfortunately, cultivation of these plants in fields and greenhouses in Arizona delivered only 9–24 mg/kg (0.0009–0.0024%) of pure material.[17] On the other hand, various isolation protocols for narciclasine have been reported in the literature, yielding 30–140 mg/kg of natural product from wet *Narcissus* plant bulbs.[18]

Due to the challenging isolation from natural sources, the isocarbostyrils **1–4** have been exceptionally attractive targets for chemical synthesis, with nearly 50 distinct strategies reported to date.[19–22] Despite many elegant approaches, the discovery of a sustainable route with practical access to these natural products has remained elusive, as nearly all biological evaluations of **1–4** have been conducted using isolated natural material. Nevertheless, these impressive synthetic endeavors enabled basic SAR studies that identified the core pharmacophore and provided more potent and selective analogs that could not be accessed through direct modification of the natural products.[6,13a]

Considering the lack of scalable approaches, we initially became interested in the synthesis of (+)-pancratistatins (**1** and **2**).[23] However, it was apparent at the outset of this work that the newly developed methodology, which was needed to streamline this task, would also create opportunities to explore the synthesis of (+)-lycoricidine, (+)-narciclasine, and tailored analogs thereof. Herein, we describe our synthetic approaches to isocarbostyrils **1–4**, and several designed analogs with improved physiochemical properties and metabolic stability. This work ultimately resulted in an interesting methodological development and led to an efficient and scalable synthesis of these intriguing alkaloids.

RESULTS AND DISCUSSION

Olefin-like Functionalization of Benzene

The ultimate synthetic challenge posed by isocarbostyrils **1–4** is the construction of the densely decorated aminocyclitol cores containing six or four contiguous stereocenters. We postulated that these motifs could be traced back to benzene using distinct alkene difunctionalization reactions, which would ideally set all the required functionality of pancratistatins (**1** and **2**), as well as lycoricidine (**3**) and narciclasine (**4**) in a stereoselective manner (Figure 2). Based on their substitution pattern, the pancratistatins could be derived from aminotetraols **5** or **6.** These hexafunctionalized cyclohexanes could be traced back to the corresponding dienes **7** and **8** by applying two different dihydroxylations. Finally, we hypothesized that dienes of this type could be obtained from benzene (**9**) through dearomative *trans*-1,2-carboamination with *N*-methyl-1,2,4-triazoline-3,5-dione (MTAD, **12**) and aryl Grignard reagents **10** or **11**. Using similar yet distinct disconnections, lycoricidine (**3**) and narciclasine (**4**) could originate from the corresponding functionalized lactam precursors **13** and **14**, which in turn, could be obtained from dienes **7** and **8**.

Based on the above retrosynthetic analysis, benzene (**9**) could be considered as a surrogate for the hypothetical 1,3,5-cyclohexatriene; thus, three olefin-type difunctionalization reactions would enable the key retrosynthetic disconnections and provide natural products **1–4** in a rapid and controlled fashion. However, due to the inherent resonance stabilization of benzene, these and related olefin-like dearomative transformations are practically nonexistent in synthetic organic chemistry. Only certain stoichiometric reactions of transitionmetal complexes[24] and microbial arene oxidation[25] can affect olefin-like dearomative functionalizations; however, such processes are not suitable for the desymmetrization of benzene.

Dearomative trans-1,2-Carboamination

At the onset of our studies, it was clear that the invention of a novel dearomatization process was crucial to the success of our synthetic plan. Since our laboratory has been involved in the development of dearomative functionalizations based on visible-light-promoted *para*-cycloaddition with arenophiles,[26] we postulated that the application of this chemistry in the presence of a transition metal catalyst and an aryl nucleophile could result in the desired *trans*-1,2-carboamination (Figure 3a). Particularly, we were keen to explore if the intermediate arenophile MTAD-benzene cycloadduct **15** could serve as a viable substrate for oxidative addition with low-valent transition metals, as it possesses an electron-deficient *bis*-allylic bridgehead urazole. We envisioned that a diene of type **15** could serve as a π-ligand, coordinating to the metal center and facilitating oxidative addition in an *anti*-fashion to the urazole moiety (**15** → **I**). This step would lead to cyclohexadienyl intermediate **II**, which could undergo transmetalation with an organometallic reagent to form η^5-species **III**. Finally, reductive elimination (**III** → **IV**) and diene decomplexation would yield product 16 and regenerate the metal catalyst.

Though catalysis involving η^5-species had not been previously reported, our studies were inspired by the wealth of chemistry employing stoichiometric reactions of η^5-complexes. Early work from Birch, and later findings from Pearson, Davies, Green, and Mingos, showcased highly regioand stereoselective outcomes in cationic cyclohexadienylmetal complexes with nucleophiles (Figure 3b).[27] For example, the most widely studied iron η^5-intermediate **19**, prepared from the corresponding 1,3-diene via complexation (**17** → **18**) and subsequent C–H abstraction (**18** → **19**), reacts with nucleophiles with exclusive 1,2-site-selectivity (**19** → **20**), due to the greater positive charge localized on the termini of the η^5-system.[27d] Encouraged by these precedents, we expected that symmetrical intermediate **III** should follow a similar mechanistic course to diene **IV** through an inner-sphere pathway, resulting in *syn*-delivery of a nucleophile relative to the metal center. Moreover, since the η^5-intermediate **III** is symmetrical, a reductive elimination step could enable enantiodiscrimination through differentiation of the enantiotopic termini of the cyclohexadienyl system. Thus, the desired product **16** could be formed in an enantioselective fashion by using a suitable chiral ligand bound to the metal center.

To probe the above-described reactivity of the arenophilebenzene cycloadduct with transition metals, we performed a series of prospecting investigations with aryl nucleophiles in combination with transition metals complexes. Catalysts based on Co, Ir, Rh, Cu, and Ni were primarily investigated as these metals have exceptionally rich repertoires of nucleophilic additions to their complexes containing allyl and dienyl ligands. Gratifyingly, by using the combination of [Ni(cod)$_2$] and phosphine ligands with organomagnesium bromide **10**, we were able to observe the desired product (Figure 3c). While monodentate phosphines and NHC-based ligands proved to be ineffective, most bisphosphines we tested furnished product **21**, with dppf delivering the highest yield in this series. Specifically, we identified that conducting the MTAD-benzene cycloaddition reaction in dichloromethane, followed by the addition of a Ni-catalyst ([Ni(cod)$_2$]/dppf = 10/20 mol %) and aryl Grignard reagent **10** delivered the desired dearomatized product **21** in 74% yield as a single diastereoand constitutional isomer (for X-ray of **21**, see Figure 3c). Although these experiments established the viability of a diastereoselective process, they did not address the feasibility of rendering the process enantioselective. Accordingly, we performed a comprehensive evaluation of chiral *P,P*- and *P,N*-bidentate ligands, and discovered that the PHOX-type ligand (R,R_p)-*i*Pr-Phosferrox afforded the desired product **21** in 75% yield and with high enantioselectivity (98:2 er).

Initial Approaches to (+)-Pancratistatins

With the first vicinal stereocenters in place, the stage was set for the introduction of the remaining four hydroxy substituents in a stereoselective manner to complete the pancratistatin core (Figure 4a). The initial plan involved formation of the *trans*-diol through hydrolytic opening of an epoxide, followed by Upjohn *cis*-dihydroxylation. However, early experiments with diene **21** and *m*CPBA or NBS/H_2O gave mixtures of products, likely due to the undesired directing effects of the urazole hydrazyl group ($pK_a = 5.8$ in water). Therefore, methylation of the urazole's nitrogen proved crucial for stereo- and chemoselective diene functionalization. This effect is likely due to a more rigid conformation, where the methyl group shields the bottom face of the diene. Such a conformation was supported by NOESY experiments revealing through-space correlation between the methyl group and several diene protons (see inset at the bottom of Figure 4). The methyl group was conveniently introduced (**21** → **7**) by simply adding Me_2SO_4 at the end of dearomatization sequence. Importantly, using a decreased catalyst loading ([Ni]/ligand = 5/10 mol %), this one-pot process allowed us to routinely prepare decagram batches of diene **7**.

With a robust sequence that allowed for the preparation of sufficient amounts of key diene **7**, we turned our attention to the next two olefin difunctionalization steps. Due to the electron-withdrawing effect of the urazole nitrogen, it was expected that the alkene distal to this moiety should react preferentially with electrophilic reagents. Indeed, installation of the *trans*-diol by means of a two-step sequence involving epoxidation with *m*CPBA and subsequent epoxide hydrolysis (NaOBz, H_2O, 100 °C) proceeded smoothly, delivering product **22** as a single diastereo- and constitutional isomer (for X-ray of **22,** see bottom of Figure 4). The last alkene transformation needed for establishing the hexasubstituted aminocyclitol core was Upjohn dihydroxylation,[28] which provided tetraol 23 in 91% yield.

The final sequence required to complete the synthesis of (+)-7-deoxypancratistatin (**1**) was the deprotection of urazole **23** to free amine **5** and its conversion to the corresponding lactam. Exploring known conditions to effect hydrolysis and N–N bond cleavage, such as heating in highly acidic or basic solutions followed by hydrogenolysis, led to complete decomposition of the starting material. Gratifyingly, we observed promising reactivity with hydride-based reducing agents. For example, exposure of urazole **23** to $LiAlH_4$ gave cyclic hydrazine hemiaminal **24** (Figure 4, bottom); however, this compound readily underwent oxidation under an ambient atmosphere, complicating its isolation and reproducibility. Therefore, we developed a one-pot procedure that directly reduced this sensitive intermediate to amine **5** by carefully quenching the $LiAlH_4$ reduction with Rochelle's salt, followed by immediate addition of Raney-Co and exposure of the reaction mixture to a hydrogen atmosphere.[29] Using this protocol, we consistently obtained free amine **5** in 60% yield on a multigram scale.

Additionally, we were able to secure amine **5** from diene **7** by an alternative pathway. Thus, subjecting diene **7** to NBS and H_2O gave bromohydrin **25** in 79% yield (for X-ray of **25**, see bottom of Figure 4). This intermediate underwent Upjohn dihydroxylation, and the resulting dibromotriol was subsequently exposed to weakly basic aqueous NaOBz to provide bromotetraol **26** through concomitant epoxide formation and hydrolysis. Similar, highly chemoselective hydrolytic opening of the corresponding intermediate epoxide diol was demonstrated by Hudlický during his approach to pancratistatins.[20b] Finally, the above-described sequential reduction with $LiAlH_4$ and Raney-Co furnished amine **5** through urazole fragmentation and protodehalogenation.

The ultimate objective, the construction of the lactam ring and completion of (+)-7-deoxypancratistatin (**1**), was initially achieved through Duff formylation (**5** → **27**) followed by Pinnick oxidation (**27** → **1**).[30] While formylation efficiently delivered the desired aldimine **27,** separation of this product from HMTA and its byproducts proved challenging, and oxidation to **1** continuously gave inconsistent results. Therefore, an alternative pathway was sought that could still rely on the readily available hexafunctionalized precursor **5**. Accordingly, we explored the Bischler–Napieralski reaction, as this key lactam forming strategy was successfully used by Banwell and others in similar molecular settings.[31] The corresponding isocyanate precursor **28** was readily prepared by sequential protection of amine with Boc and alcohols with acetates. The key cyclization was successfully accomplished with Hendrickson's reagent (triphenylphosphonium anhydride trifluoromethanesulfonate), delivering acetylated (+)-7-deoxypancratistatin that was converted to natural product **1** upon treatment with K_2CO_3 in MeOH.[32]

With the synthesis of (+)-7-deoxypancratistatin (**1**) completed, we turned our attention to (+)-pancratistatin (**2**), expecting that the lessons learned from the synthesis of **1** could be translated toward preparation of its congener as well (Figure 5). Indeed, enantioselective dearomative *trans*-1,2-carboamination of benzene (**9**) with more elaborate aryl Grignard reagent **11** furnished the desired diene 8 in 66% yield and 97:3 er. The subsequent epoxidation of this compound with *m*CPBA, consistently provided low yields, likely due to an increased steric hindrance introduced by an additional methoxy group on the arene moiety. Gratifyingly, *in situ* generated dimethyldioxirane[33] provided the desired allylic epoxide that was hydrolyzed to *trans*-diol **29** using aqueous NaOBz. The remaining steps, Upjohn dihydroxylation (**29** → **30**), urazole fragmentation (**30** → **6**), carbamate preparation (**6** → **31**), and Bischler–Napieralski reaction (**31** → **32**) proceeded smoothly, furnishing protected pancratistatin (**32**) in 87% yield. It is important to note that application of Hendrickson's reagent for this cyclization proved to be more efficient and selective (10:1 r.r) compared to most of the previously reported cyclizations in similar systems.[31] Finally, global deprotection of **32** with BBr_3 followed by NaOMe provided (+)-pancratistatin (**2**) in 50% yield over two steps.

Streamlined Synthesis of (+)-Pancratistatins

The above-described synthetic campaigns resulted in concise preparation of both (+)-pancratistatins in seven and nine steps, respectively. Though this accomplishment represents the shortest enantioselective approach to the pancratistatins to date, we felt there was still room for improvement, mainly to increase atom, step, and redox economy, all of which are desired for the practical synthesis of such compounds.[34] Specifically, installation of the *trans*-diol and lactam formation required intermediary steps, such as protecting group manipulations and discrete oxidation level alterations. Moreover, as in all previous synthetic endeavors, **1** and **2** each required individual *de novo* total synthesis from the corresponding C-7 substituted aromatic building blocks, which provided an additional roadblock in synthetic development. Finally, the precursor for functionalized Grignard reagent **11** required three synthetic operations from *o*-vanillin, whereas the precursor for Grignard **10** was commercially available.

With these key challenges in mind, we set forth to further streamline our synthesis of the pancratistatins and to provide a direct synthetic connection between **1** and **2** (Figure 6). During initial studies of the epoxidation of diene **7,** we frequently observed small amounts of the desired *trans*-diol **22** during the epoxidation step; therefore, we explored the viability of a one-pot, *trans*-dihydroxylation protocol. Indeed, this approach proved to be successful when the epoxidation reaction was conducted in the presence of *p*TsOH and a large excess of water.[35] In addition, the use of hexafluoroisopropanol (HFIP) as a solvent was essential[36] to obtain diol product **22** in 74% yield. This represented a marked increase in yield (63 → 74%) as well as removed a chromatographic purification from the early sequence, improving the preparation of diol **22**. At this point, the remaining transformations toward aminotetraol 5 remained the same, as they were already scalable and reproducible.

We next wanted to improve the overall efficiency of the lactam formation as our previously described approach required five protecting groups for the installation of a single carbonyl group. However, we knew that the introduction of carbonyl functionality in the presence of four free alcohols would prove challenging with respect to achieving the desired chemoselectivity. To this end, we were able to install a bromine substituent at the desired position (8:1 r.r.) on the electron-rich arene ring by exposing aminotetraol **5** to bromine under acidic conditions. The installed halogen provided a handle for the exploration of carbonyl insertion through carbonylative coupling chemistry. Accordingly, we began investigating various benchmark Pd-catalyzed carbonylative coupling procedures;[37] however, we unfortunately observed only complex mixtures of oxidized intermediates and precipitation of Pd black. This was somewhat expected, as palladium is well-known to oxidize similar substrates[38] and, to the best of our knowledge, carbonylative couplings involving aryl bromides in the presence of free primary and secondary alcohols has yet to be developed.

We then turned our focus to explore catalytic carbonylation based on other metals that are known to tolerate free alcohols. Along these lines, we tested a set of conditions reported by Caubere and co-workers that employed dicobalt octacarbonyl under highly basic aqueous conditions (5 M NaOH) and UV irradiation.[39] According to the proposed mechanism,[40] such transformations proceed through photoinduced electron- or charge-transfer complexes between aryl halides and $[Co(CO)_4]^-$, resulting in the formation of aroylcobalt carbonyl complexes of type **I-1**, which should readily collapse to lactam product **1** with concurrent regeneration of catalyst $[Co(CO)_4]^-$. Indeed, using Caubere's protocol we were encouraged to find that (+)-7-deoxypancratistatin (**1**) could be observed in low yield, with rest of the mass balance being recovered starting material and an amino acid, likely resulting from subsequent base-induced hydrolysis. This suspicion was further validated by the fact that longer reaction times led to lower yields and larger amounts of the amino acid, which proved challenging to convert back to **1.** Therefore, it became apparent that the highly basic reaction environment was causing the lower yields, and development of more neutral reaction conditions was needed. The main role of NaOH in the original report was to convert $Co_2(CO)_8$ to active $NaCo(CO)_4$, and to serve as a base that sequestered HBr. Thus, we prepared pure $NaCo(CO)_4$, and utilized it in the reaction alongside $NaHCO_3$ as a mild HBr scavenger, resulting in formation of (+)-7-deoxypancratistatin (**1**) in 72% overall yield from aminotetraol **5**. For ease of operation, the bromination and carbonylative coupling were performed in a single reaction vessel, with only a solvent exchange as an intermediary step.

The final synthetic challenge left was to establish a direct connection between the pancratistatins (**1** → **2**), which would completely remove the need for the use of tailored Grignard reagent **11** as well as *de novo* synthesis of **2**. In addition to providing this link, such a C-7 functionalization could also enable facile synthesis of analogs at this position. Many methods for this formal oxidative transformation were investigated, including direct sp^2 C–H oxidation,[41] indirect sp^2 C–H borylation/oxidation,[42] and various directed *ortho* metalation/oxidation procedures.[43] Undeterred, we eventually found that treating **1** with hexamethyldisilazane (HMDS) in the presence of catalytic amounts of iodine allowed for *in situ* generation of tetrasilylated 7-deoxypancratistatin **33,**[44] which could immediately be subjected to a cupration/oxidation sequence. This formal sp^2 C–H oxidation was accomplished using directed cupration with $(TMP)_2Cu(CN)Li_2$ and subsequent arylcuprate **I-2** oxidation with *t*BuOOH,[45] conditions recently reported by Uchiyama and co-workers that proved to be robust enough for our complex system, affording (+)-pancratistatin (**2**) in 62% yield after acidic workup. Of note is the use of HMDS/I_2 for global silylation of (+)-7-deoxypancratistatin prior to the deprotonative cupration, as other common silyl transfer agents, such as TMSCl, TMSCN, $TMSN_3$, *N,O-bis*(trimethylsilyl)acetamide (BSA), N-methyl-*N*-trimethylsilylacetamide (MSA), *N*-methyl-*N*-trimethylsilyltrifluoroacetamide (MSTFA), and *N,O-bis*(trimethylsilyl)trifluoroacetamide (BSTFA) left stoichiometric impurities that could not be removed without chromatographic purification. Though purification of **33** was possible, the rapid hydrolysis of the silyl groups on silica led to issues in reproducibility. On the other hand, as the only byproduct from the silylation with HMDS is NH_3, all volatiles and excess of the reagent could be removed simply through azeotropic distillation with toluene, leaving **33** in sufficient purity for the next operation. Thus, the described synthesis delivers (+)-7-deoxypancratistatin (**1**) and (+)-pancratistatin (**2**) in six and seven operations and in 19% and 12% overall yield. It is important to note that using this streamlined synthetic sequence, we have prepared several grams of both pancratistatins to date, showcasing the scalability of the abovedescribed approach.

Synthesis of (+)-Narciclasine

With the practical synthesis of pancratistatins completed, we turned our attention toward (+)-lycoricidine (**3**) and (+)-narciclasine (**4**). As shown in our retrosynthetic analysis (Figure 2), we surmised that compounds **13** and **14** could be viable intermediates to reach the unsaturated aminocyclitol core of 3 and 4 through a base-promoted epoxide isomerization and concurrent arylmetal attack into the urazole ring, resulting in carbonyl transfer and assembly of the lactam. We were particularly interested in exploring such intermediates because they could be readily traced back to dienes **7** and **8,** using olefin functionalization chemistry. In addition to our previous success in handling these compounds, we also recently improved the dearomative *trans*-1,2-carboamination strategy,[46] which permitted the preparation of these intermediates on a multidecagram scale without the use of a glovebox. Although we initially used 5 mol % of [Ni(cod)$_2$] as a precatalyst for the synthesis of the pancratistatins (Figures 4–6), we further optimized this protocol to permit the application of air-stable [Ni(acac)$_2$] in much lower loadings ([Ni]/ligand = 1.5/2.0 mol %).

At the onset of our studies toward (+)-narciclasine (**4**), we commenced by targeting key intermediate **14** (Figure 7). Thus, diene **8,** which was prepared in 66% yield and 97:3 er using the new protocol, was exposed to an excess of NBS in THF/H_2O, affording dibromide **34** as a single diastereo- and constitutional isomer in 85% yield. Exposure of this compound to Upjohn dihydroxylation conditions with a basic work up (K_2CO_3), followed by acetonide protection of the intermediate epoxy diol, gave key bromoepoxide **14** in 77% yield over two steps. One pot dihydroxylation/bromohydrin closure was developed for practical reasons, as the dibromotriol proved challenging to extract and purify. This compound, which is prepared from benzene in four steps, contains all the necessary atoms that are present in narciclasine (**4**), as well as strategically placed functional handles for conversion to the natural product. Specifically, the stereochemical relationship between the epoxide and the benzylic hydrogen is appropriate for a formal syn-epoxide elimination,[47] which would provide the desired allylic alcohol. Moreover, the aryl bromide moiety serves as a precursor to an arylmetal species that could add into the nearby urazole carbonyl group and form the desired lactam. To our delight, we discovered that the slow addition of *t*BuLi to a cold solution of **14** could achieve both epoxide isomerization and benzamide formation, likely through the intermediate **I-3**, providing compound **35** in 65% yield. Furthermore, although **14** contains two neighboring hydrogens, both in *syn*-quasi axial position (for an X-ray of similar compound **13**, see Figure 8, bottom) only product **35** was observed, resulting from elimination of the more acidic benzylic proton.[48]

With the phenanthridone skeleton completed, the final task en route to narciclasine (**4**) was reductive N–N bond cleavage of acylsemicarbazide **35** and global deprotection. This was achieved by slow addition of freshly prepared SmI_2, followed by mild heating and subsequent acidic workup, to deliver (+)-narciclasine (**4**) in 89% yield. Heating this reaction to 40 °C proved crucial to achieve full Sm(III)-mediated deprotection of the aryl methoxy group,[21k] and the acidic workup was favored over other common procedures, which gave heterogeneous mixtures that were tedious to separate and extract. Thus, using this six step protocol with 25% overall yield, we were able to obtain more than 600 mg of (+)-narciclasine (**4**) in a single pass from benzene (**9**).

Scalable Route to (+)-Lycoricidine and (+)-Narciclasine

With the successful application of the late-stage hydroxylation at C-7 in the case of pancratistatins (**1** → **2**, see Figure 6), we wondered if the same chemical connection could also be feasible between lycoricidine (**3**) and narciclasine (**4**). The major benefits of such a direct conversion would be (1) application of readily available Grignard **10** instead of noncommercial reagent **11**; (2) avoidance of individual *de novo* total synthesis of **3** and **4**; and (3) rapid preparation of C-7 analogs to fully explore this position of the pharmacophore.

By employing a glovebox-free procedure and operationally simple photoreactor, we prepared dearomatized product 7 on more than 100 mmol scale (>25 g) in 65% yield and 97:3 er after methylation with Me_2SO_4. Following a similar sequence to the one described above, diene 7 was subjected to two equivalents of NBS in THF and H_2O to produce bromohydrin **25** in 79% yield. Subsequent Upjohn dihydroxylation, base-mediated epoxide formation, and diol protection, furnished epoxy acetonide **13** in 78% overall yield, setting the stage for the key epoxide isomerization/lactam formation cascade (see bottom of Figure 8 for an X-ray of 13). Thus, dropwise addition of *t*BuLi to a cold solution of **13** provided intermediate **36** in 70% yield on >20 g scale. Interestingly, only 2.35 equiv of *t*BuLi were needed to achieve full conversion on large scale, as addition of further equivalents only led to decomposition of the product. Treatment of lactam **36** with SmI_2, followed by acidic work up delivered (+)-lycoricidine (**3**) in 94% yield, producing slightly over 8 g of this natural product in a single pass. Moreover, we obtained single crystals suitable for X-ray crystallographic analysis (Figure 8, bottom).[49] To avoid stoichiometric use of SmI_2, we have also explored reductive N–N bond cleavage employing catalytic amounts of SmI_2 with an electrochemical method recently reported by the Ackermann group (Figure 8 inset).[50] While the scalability of this reaction has yet to be tested, preliminary results suggest that a more economical approach could be feasible, as product **37** was obtained in 45% yield (52% of **36** recovered).

Finally, with ample amounts of (+)-lycoricidine (**3**) in hand, we set out to examine C-7 functionalization using the deprotonative cupration/oxidation conditions previously developed to convert (+)-7-deoxypancratistatin (**1**) to (+)-pancratistatin (**2**).[51] Our initial attempts employed lycoricidine acetonide **37** and required catalytic amounts of TFA to mediate the silylation, as I_2 led to the formation of byproducts. After numerous conditions were screened with lycoricidine acetonide **37**, only minimal (<10%) conversion to the desired product was observed. However, we found that direct conversion of lycoricidine (3) to silylated lycoricidine, followed by addition of $(TMP)_2Cu(CN)Li_2$, subsequent *in situ* oxidation of arylcuprate species with *tert*-butyl hydroperoxide, and acidic workup delivered (+)-narciclasine (**4**). Importantly, we were able to run this oxidation on a 3 g scale, obtaining a 57% yield and isolating >1.8 g of (+)-narciclasine (**4**). Over the course of this study, we conveniently prepared >20 g of 3 and >5 g of 4 in total, demonstrating the scalability of the approach described herein.

Synthesis and Biological Evaluation of C-7 Analogs

With gram amounts of (+)-lycoricidine (**3**) now readily available, as well as an established late-stage cupration procedure, we turned our attention to the preparation of the corresponding C-7 analogs (Figure 9). Previous synthetic efforts have provided basic structure–activity correlations, revealing the importance of certain functionalities and their stereochemical orientation, mainly on the aminocyclitol core.[8b] However, the influence of C-7 substitution has not been significantly investigated.[8a] This comes as no surprise, as each C-7 derivative would previously require a multistep synthesis, making the preparation of a library of C-7 analogs very time-consuming. By using Uchiyama's cupration-based strategy, alkyl- and amine-based functionalities were selectively introduced at position 7 in a single operation from **3** (Figure 9a). For example, exposure of lycoricidine-derived cuprate intermediate ***I*4** to alkyl electrophiles or *O*-benzoyl hydroxylamines provided a range of C- (**38–42**, **44**, and **46**) and *N*-substituted analogs (**47–51**), respectively.[52] Simple saponification of esters **42** and **44** provided carboxylic acids **43** and **45**. This C-7 diversification could be also applied to the pancratistatin series, as demonstrated with the preparation of 7-aminopancratistatin (**52**, Figure 9b). However, amine analogs **47**, **48**, and **52** could not be made directly due to purification issues and consequently had to be synthesized from the corresponding allyl substituted *O*-benzoyl hydroxylamine, followed by allyl deprotection (for example, see Figure 9b).

With a small library of analogs in hand (**38–52**), their anticancer activities, as well as those of the natural products (**1–4**), were measured using human lung and colon cancer cell lines (A549 and HCT116). As expected, the C-7 substituent plays an important role in the activity of these compounds. Alkyl substituents drastically reduced the activity as C-analogs **38–45** displayed weaker potency than lycoricidine (**3**), with activities ranging from 29 to >100 μM. Even derivatives containing hydrogen-bond donor or acceptor groups, such as homologue **41**, differing from narciclasine by an additional CH_2 group, proved to be less potent. Interestingly, 7cyanolycoricidine (**46**) showed increased activity when compared to lycoricidine (**3**) in HCT116 cells. Furthermore, introduction of an amino group improved activity over lycoricidine, as exemplified with 7-aminolycoricidine (**47**) which possesses an IC_{50} of 0.39 μM in HCT116 cells. However, other *N*-analogs containing alkylated amines, such as methylamine (**48**), acetamide (**49**), pyrrolidine (**50**), and morpholine (**51**) did not show significant cytotoxicity, pointing at the importance of an –XH type of motif (X = O, NH) for enhanced activity.

Finally, we also evaluated the solubility of the most active amino analogs (Figure 9c). Natural isocarbostyril alkaloids **1–4** are known to be highly insoluble; however, 7-aminolycoricidine (**47**) and 7-aminopancratistatin (**52**) showed 11and 6-fold increased solubility when compared to their natural counterparts. The improved aqueous solubility and comparable activity make these new C-7 amino analogs attractive targets for further diversification and study.

Metabolic Stability

Though numerous *in vitro* and several *in vivo* evaluations of isocarbostyril alkaloids gave promising results, there are no reports describing metabolism of these compounds, despite the fact that the results obtained from such studies would help with the planning or interpretation of clinical and toxicological studies. Over the years, many procedures have emerged for studying metabolic stability and the identification of metabolites, including deuterium labeling.[53] By taking advantage of the kinetic isotope effect (KIE) one can increase the metabolic stability of a compound by incorporating deuterium at the potentially metabolically compromised site.[54]

One of the unique advantages of the arenophile-based approach is the ability to provide selective access to tailored stable isotopologs, as most of the starting aromatic compounds are readily available in their deuterated forms (Figure 9d). Using our previous synthetic strategy, substitution of benzene (**9**) for benzene-d_6 (**9-d_6**) led to narciclasine analog **4-d_5**, which has each proton on the cyclitol core replaced with a deuterium. Likewise, employing selectively labeled Grignard precursor **11-d_2**, which can be easily prepared using CD_2Cl_2, we have been able to synthesize narciclasine isotopolog **4-d_2**, which has deuterium incorporated into the methylene bridge. With these differentially deuterated compounds in hand, we tested their activity and metabolic stability using a microsome assay. While both labeled compounds **4-d_5** and **4-d_2** have equipotent activity, they showed noticeably (~30%) greater metabolic stability when compared to narciclasine (**4**), suggesting that both the methylene bridge and the cyclitol core are susceptible to metabolic degradation.

CONCLUSION

The Amaryllidaceae isocarbostyril alkaloids have been inspiring the synthetic community for many decades, serving as benchmark molecules to showcase many creative approaches toward their unique molecular architectures and stereochemical complexity. The syntheses of isocarbostyril alkaloids (+)-7-deoxypancratistatin (**1**), (+)-pancratistatin (**2**), lycoricidine (**3**), and narciclasine (**4**) described herein utilize a new methodology and strategy, developed specifically for their highly decorated aminocyclitol core. The key asymmetric dearomative *trans*-1,2-carboamination of benzene (**9**) provided facile access to these natural products through diene intermediate 7, which served as a divergence point for the synthesis of **1–4**. Moreover, late-stage C-7 cupration of (+)-7-deoxypancratistatin (**1**) and lycoricidine (**3**) provided direct synthetic connection to (+)-pancratistatin (**2**) and narciclasine (**4**) in a practical, single operation.

Our streamlined route to the pancratistatins featured three olefin-like difunctionalizations of benzene and a late stage carbonylative coupling reaction that gave (+)-7-deoxypancratistatin (**1**) in six steps and 19% overall yield. One pot amidedirected deprotonative cupration and subsequent arylcuprate oxidation allowed for the installation of the C-7 hydroxyl group present in (+)-pancratistatin (**2**). The route to lycoricidine (**3**) featured a base-promoted epoxide isomerization/lactam formation cascade reaction followed by SmI_2 mediated N–N reductive cleavage, delivering the natural product in six steps and 26% overall yield. Utilizing this strategy, we have synthesized several grams of each natural product to date, showcasing the scalability of our approach. Furthermore, large scale access to these natural products, coupled with an enabling directed cupration, resulted in the synthesis of a small library of C-7 analogs. Of these, 7-aminolycoricidine (**47**) showed enhanced activity over its natural counterpart, as well as significantly improved aqueous solubility. The brevity of the described approach and the availability of deuterated starting arenes also prompted the synthesis of differentially deuterated narciclasine isotopologs **4-d_5** and **4-d_2**, both of which had improved metabolic stability when compared to nonlabeled natural product **4.** We anticipate that the concise and scalable syntheses, as well as new avenues for derivatization reported in this article, will provide a new practical means of supplying these medicinally important compounds and further invigorate their biological investigations.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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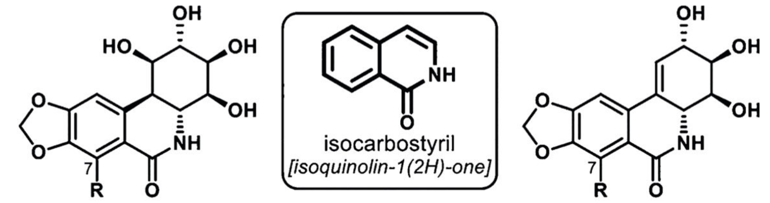


7-deoxypancratistatin (**1**, R = H)
pancratistatin (**2**, R = OH)

lycoricidine (**3**, R = H)
narciclasine (**4**, R = OH)

Figure 1.
Structures of isocarbostyril alkaloids (+)-7-deoxypancratistatin (**1**), (+)-pancratistatin (**2**), (+)-lycoricidine (**3**), and (+)-narciclasine (**4**).

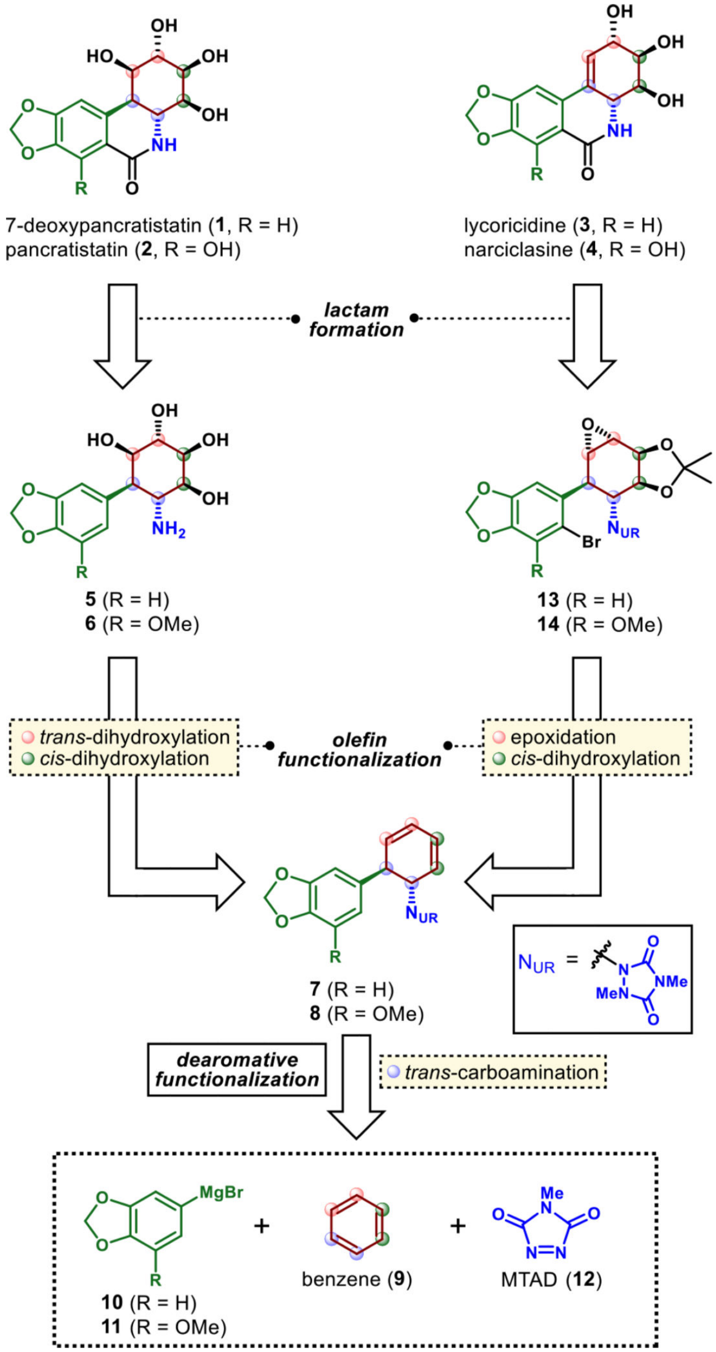


Figure 2.

Retrosynthetic analysis of isocarbostyril alkaloids **1–4** from benzene (**9**) using an olefin-functionalization approach.

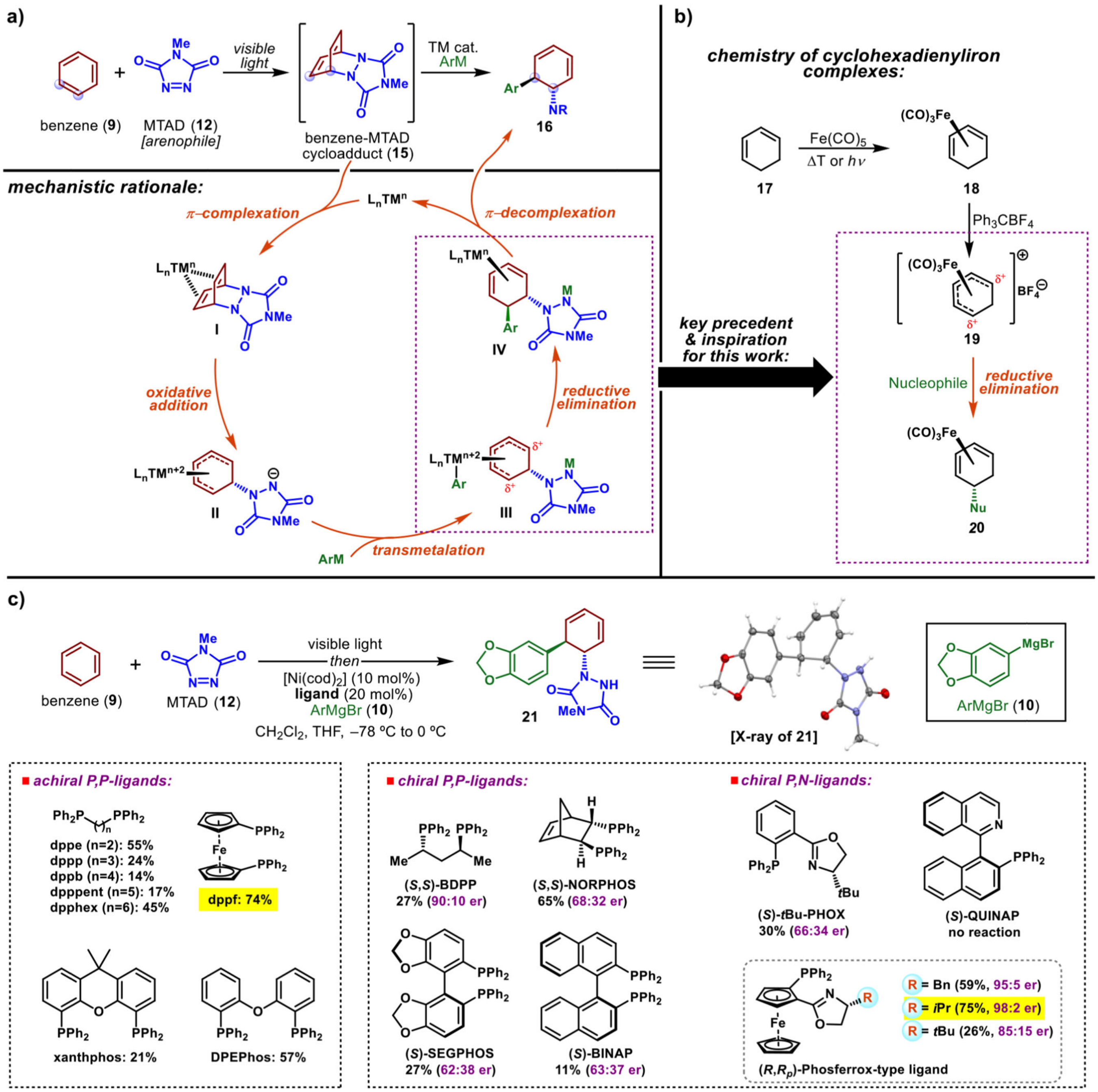


Figure 3.

(a) Concept and mechanistic rationale for dearomative *trans*-1,2-carboamination strategy. (b) General reactivity of cyclohexadienyliron complexes with nucleophiles. (c) Ligand scope for Ni-catalyzed dearomative *trans*-1,2-carboamination.

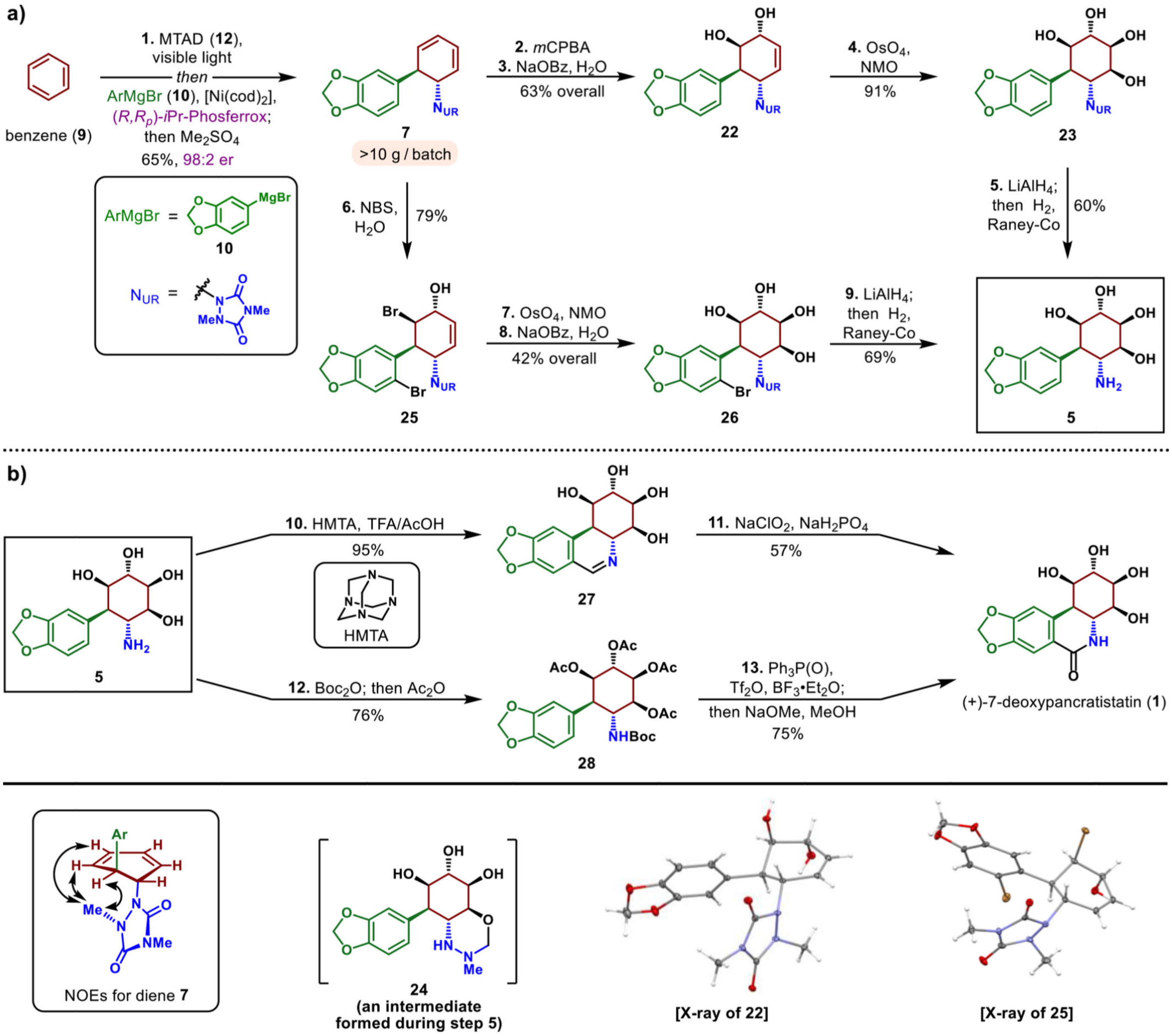


Figure 4.

First generation approaches to (+)-7-deoxypancratistatin (**1**). (a) Synthesis of aminotetraol **5**. (b) Conversion of aminotetraol **5** to (+)-7deoxypancratistatin (**1**). Reagents and conditions: 1. benzene (**9**), MTAD (**12**), CH_2Cl_2, visible light, −78 °C; then [Ni(cod)$_2$] (5 mol %), (*R*,*R$_p$*)-*i*Pr-Phosferrox (10 mol %), Grignard reagent 10, CH_2Cl_2, THF, −78 to +25 °C; then Me_2SO_4, K_2CO_3, 65% (98:2 er); 2. mCPBA, $NaHCO_3$, CH_2Cl_2, 25 °C; 3. NaOBz, H_2O, 100 °C, 63% over two steps; 4. NMO, OsO_4 (5 mol %), *t*BuOH, H_2O, 25 °C, 91%; 5. $LiAlH_4$, THF, reflux; then Rochelle salt; then Raney-Co, H_2 (1 atm), 60 °C, 60%; 6. NBS, THF, H_2O, 25 °C, 79%; 7. OsO_4 (5 mol %), NMO, citric acid, acetone, H_2O, *t*BuOH (1:1:2), 25 °C; 8. NaOBz, H_2O, 100 °C, 42% over two steps; 9. $LiAlH_4$, THF, reflux; then Rochelle salt; then Raney-Co, H_2 (1 atm), 60 °C, 69%; 10. HMTA, TFA, AcOH, 90 °C 95%; 11. $NaClO_2$, NaH_2PO_4, 2-methyl-2-butene, THF, H_2O, 25 °C, 57%; 12. Boc_2O, Et_3N, 1,4-

dioxane, H_2O, 25 °C; then Ac_2O, Et_3N, DMAP, CH_2Cl_2, 25 °C, 76%; 13. $Ph_3P(O)$, Tf_2O, $BF_3{\cdot}Et_2O$, CH_2Cl_2, 0 °C; then NaOMe, MeOH, 25 °C, 75%.

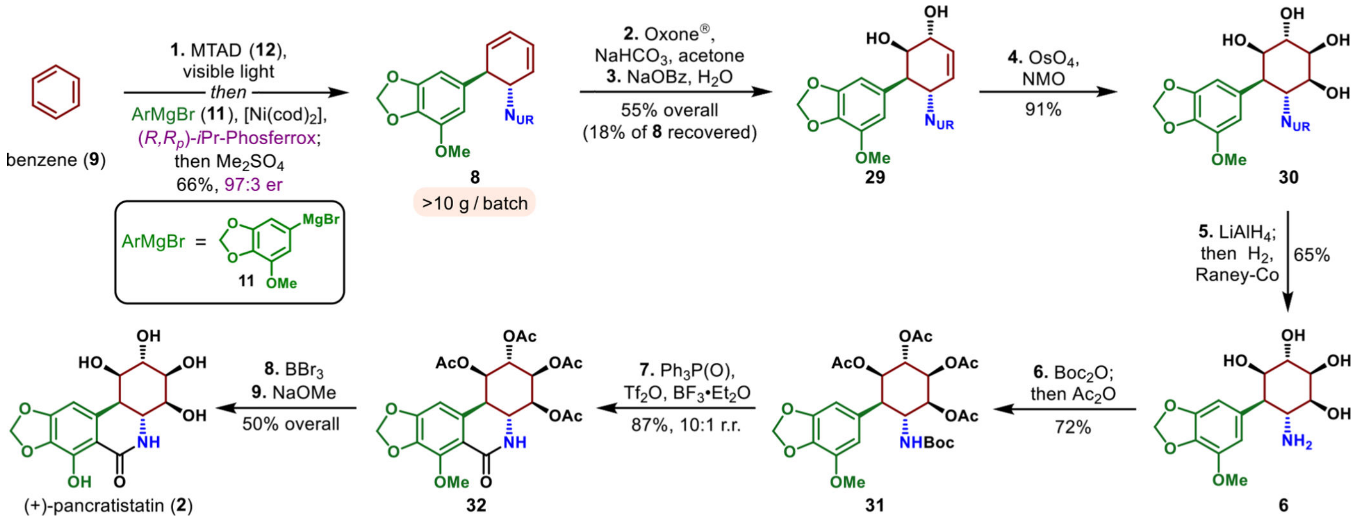


Figure 5.

First generation approach to (+)-pancratistatin (**2**). Reagents and conditions: 1. benzene (**9**), MTAD (**12**), CH_2Cl_2, visible light, −78 °C; then $[Ni(cod)_2]$ (5 mol %), (*R,R$_p$*)-*i*Pr-Phosferrox (10 mol %), Grignard reagent **11**, CH_2Cl_2, THF, −78 to +25 °C; then Me_2SO_4, K_2CO_3, 66% (97:3 er); 2. Oxone, $NaHCO_3$, acetone, H_2O, 25 °C; 3. NaOBz, H_2O, 100 °C, 55% over two steps (18% of 8 recovered); 4. NMO, OsO_4 (5 mol %), *t*BuOH, H_2O, 25 °C, 91%; 5. $LiAlH_4$, THF, reflux; then Rochelle salt; then Raney-Co, H_2 (1 atm), 60 °C, 65%; 6. Boc_2O, Et_3N, 1,4-dioxane, H_2O, 25 °C; then Ac_2O, Et_3N, DMAP, CH_2Cl_2, 25 °C, 72%; 7. $Ph_3P(O)$, Tf_2O, $BF_3{\cdot}Et_2O$, CH_2Cl_2, 25 °C, 87% (10:1 r.r.); 8. BBr_3, CH_2Cl_2, 25 °C; 9. NaOMe, MeOH, 25 °C, 50% over two steps.

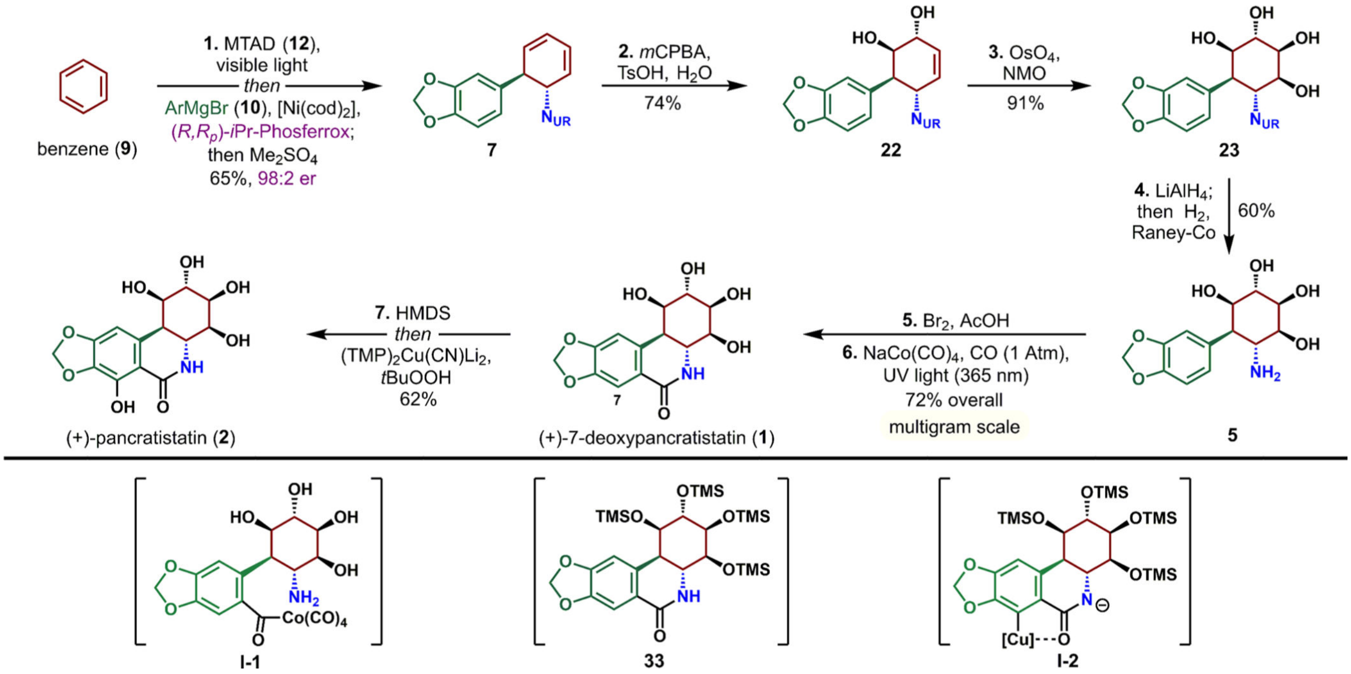


Figure 6.

Streamlined synthesis of pancratistatins **1** and **2**. Reagents and conditions: 1. benzene (9), MTAD (12), CH_2Cl_2, visible light, −78 °C; then $[Ni(cod)_2]$ (5 mol %), (*R,R$_p$*)-*i*Pr-Phosferrox (10 mol %), Grignard reagent **10,** CH_2Cl_2, THF, −78 to +25 °C; then Me_2SO_4, K_2CO_3, 65% (98:2 er); 2. *m*CPBA, *p*TsOH, CH_2Cl_2, HFIP, H_2O, 50 °C, 74%; 3. NMO, OsO_4 (5 mol %), *t*BuOH, H_2O, 25 °C, 91%; 4. $LiAlH_4$, THF, reflux; then Rochelle salt; then Raney-Co, H_2 (1 atm), 60 °C, 60%; 5. Br_2, AcOH, 25 °C; 6. $NaCo(CO)_4$ (30 mol %), *n*Bu_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; acidic workup, 62%.

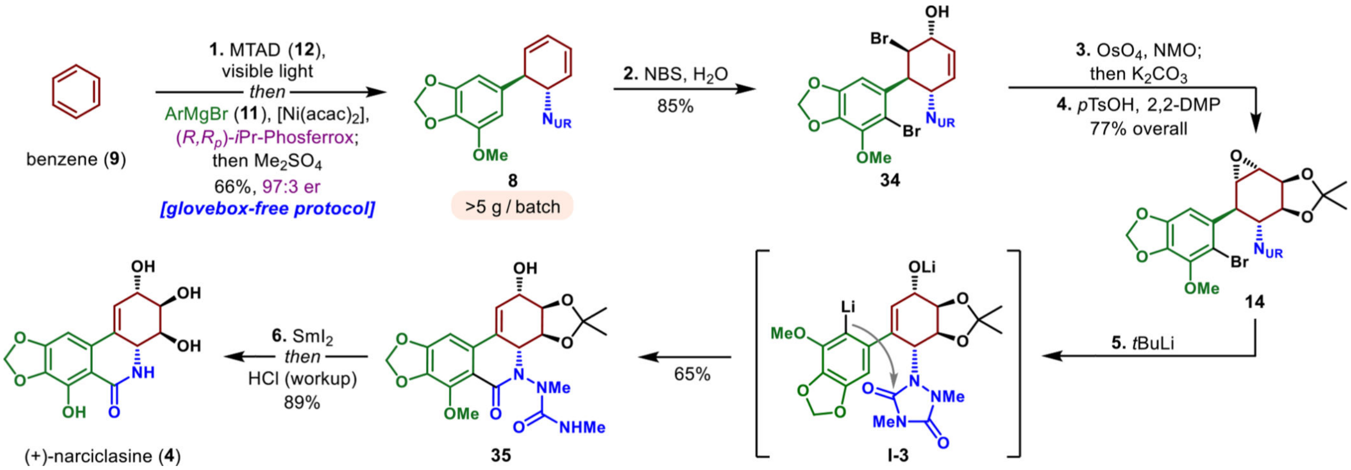


Figure 7.

Synthesis of (+)-narciclasine (**4**). Reagents and conditions: 1. benzene (**9**), MTAD (**12**), CH_2Cl_2, visible light, −78 °C; then [Ni(acac)$_2$] (1.5 mol %), (*R,R$_p$*)-*i*Pr-Phosferrox (2.0 mol %), Grignard reagent **11**, CH_2Cl_2, THF, −78 to +25 °C; then Me_2SO_4, K_2CO_3, 66% (97:3 er); 2. NBS, H_2O, THF, 25 °C, 85%; 3. OsO_4 (5 mol %), NMO, citric acid, acetone, H_2O, *t*BuOH, 25 °C; then K_2CO_3, 25 °C; 4. 2,2-dimethoxypropane, *p*TsOH (10 mol %), CH_2Cl_2, 25 °C, 77% over two steps; 5. *t*BuLi, THF, −78 °C, 65%; 6. SmI_2, MeOH, 0 °C; then 40 °C; then HCl, 0 °C, 89%.

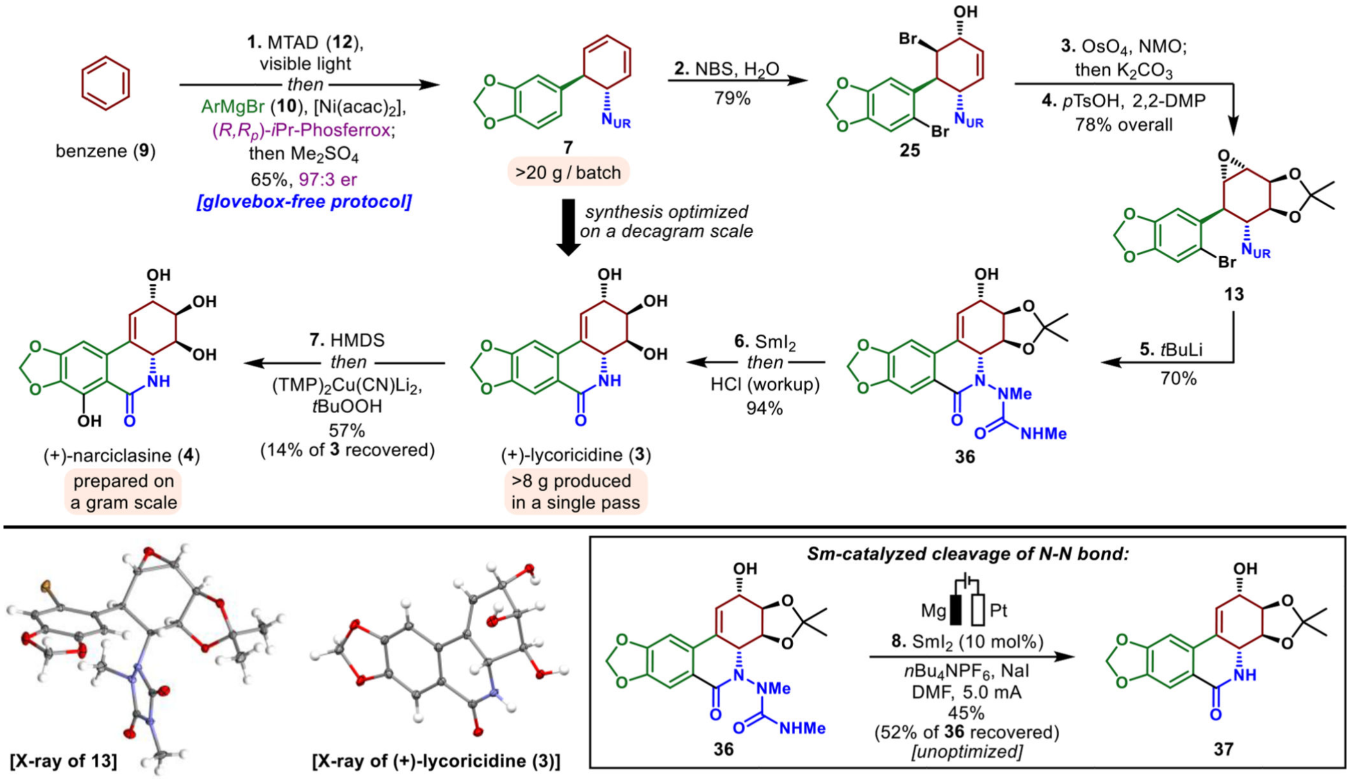
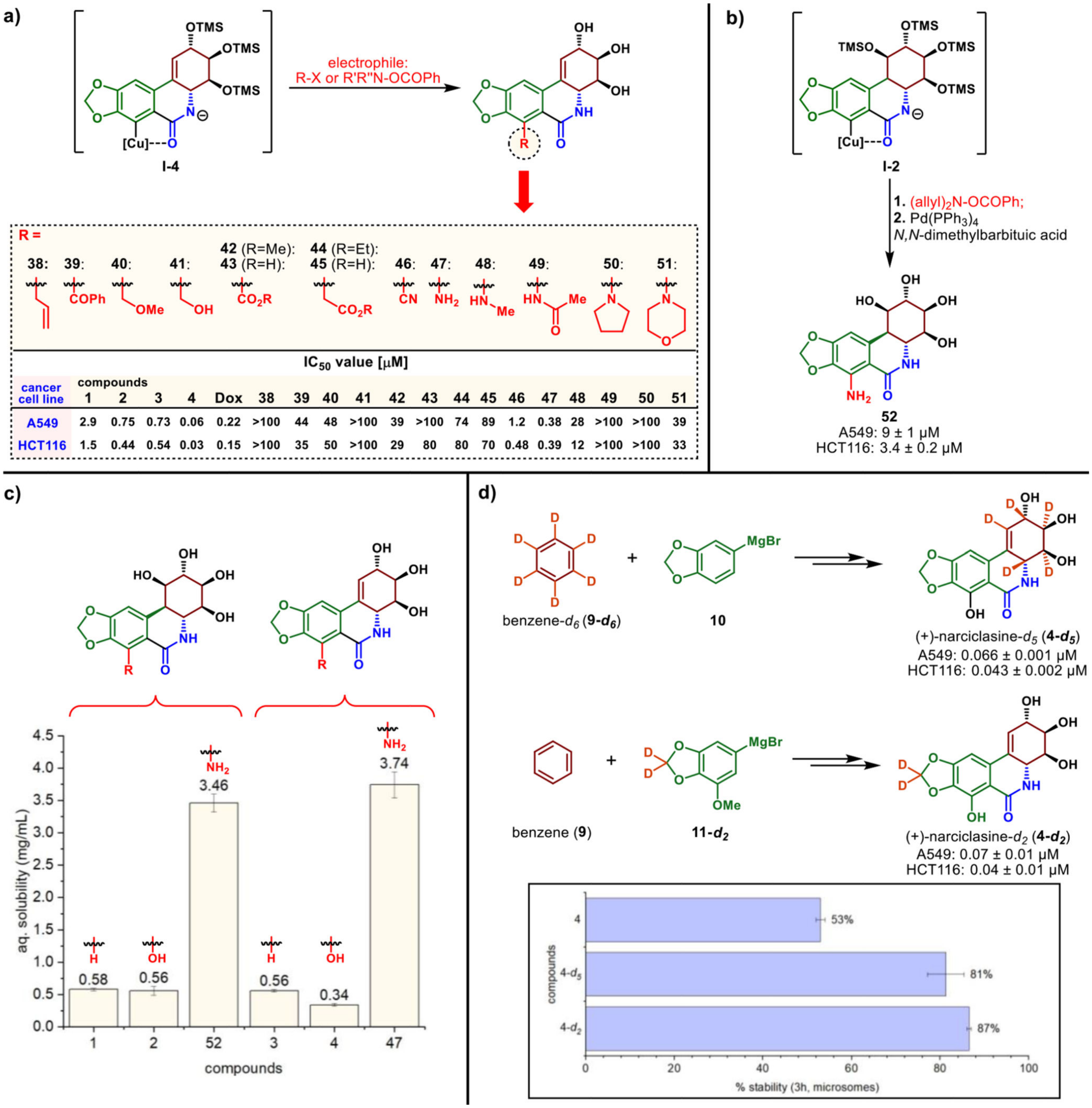


Figure 8.

Synthesis of (+)-lycoricidine (**3**) and (+)-narciclasine (**4**). Reagents and conditions: 1. benzene (**9**), MTAD (**12**), CH_2Cl_2, visible light, −78 °C; then [Ni(acac)$_2$] (1.5 mol %), (*R,R$_p$*)-*i*Pr-Phosferrox (2.0 mol %), Grignard reagent **10**, CH_2Cl_2, THF, −78 to +25 °C; then Me_2SO_4, K_2CO_3, 65% (97:3 er); 2. NBS, H_2O, THF, 25 °C, 79%; 3. OsO_4 (5 mol %), NMO, citric acid, acetone, H_2O, *t*BuOH, 25 °C; then K_2CO_3, 25 °C; 4. 2,2-dimethoxypropane, *p*TsOH (10 mol %), CH_2Cl_2, 25 °C, 78% over two steps; 5. *t*BuLi, THF, −78 °C, 70%; 6. SmI_2, MeOH, 0 °C, then HCl, 0 °C, 94%; 7. HMDS, TFA (1.0 mol %), MeCN, 25 °C; then solvent removal and $(TMP)_2Cu(CN)Li_2$, THF, −78 → 0 °C; then tBuOOH, THF, −78 °C; acidic workup, 57% (14% of **3** recovered); 8. NaI, *n*Bu_4NPF_6, SmI_2 (10 mol %), DMF, 25 °C, Mg anode, Pt cathode, 5.0 mA, 45% (52% of **36** recovered).



cancer cell line	1	2	3	4	Dox	38	39	40	41	42	43	44	45	46	47	48	49	50	51
A549	2.9	0.75	0.73	0.06	0.22	>100	44	48	>100	39	>100	74	89	1.2	0.38	28	>100	>100	39
HCT116	1.5	0.44	0.54	0.03	0.15	>100	35	50	>100	29	80	80	70	0.48	0.39	12	>100	>100	33

Figure 9.

(a) Late-stage preparation and anticancer activity of C-7 analogs of lycoricidine (**3**). Cell viability was assessed after 72 h using the Alamar Blue assay, *n* ≥ 3, SEM for each measurement is in the Supporting Information. Doxorubicin (Dox) was used as a reference. (b) Preparation and activity of 7-aminopancratistatin **52**. (c) Role of C-7 amine substituent on solubility. High throughput equilibrium solubility using miniaturized shake flask approach was used. Error is SEM, *n* ≥ 3. (d) Evaluation of metabolic stability of narciclasine (**3**) and its deuterated isotopologs (**4-d_5** and **4-d_2**). Stability was assessed in mouse liver microsomes. Compounds were incubated with microsomes for 3 h, and the percentage remaining was quantified relative to t_0 using an internal standard. Error is SEM, $n \geq 2$.