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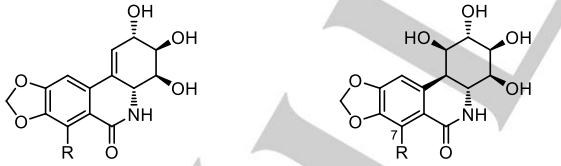
Total Synthesis of Lycoricidine and Narciclasine via Chemical Dearomatization of Bromobenzene

Emma H. Southgate, Daniel R. Holycross, and David Sarlah*

Abstract: The total synthesis of lycoricidine and narciclasine is enabled by the use of arenophile-mediated dearomative dihydroxylation of bromobenzene. Subsequent transpositive Suzuki coupling and cycloreversion deliver a key biaryl dihydrodiol intermediate, which is rapidly converted to lycoricidine through site-selective *syn*-1,4-hydroxyamination and deprotection. The total synthesis of narciclasine is accomplished via a late stage, amide-directed C–H hydroxylation of a lycoricidine intermediate. Moreover, the general applicability of this strategy to access dihydroxylated biphenyls has been demonstrated with several examples.

The isocarbostyril alkaloids from the Amaryllidaceae family of plants are an important class of natural products with impressive biological activities. Specifically, lycoricidine, narciclasine, 7-deoxypancratistatin, and pancratistatin (**1**–**4**, Scheme 1) are well-known anticancer agents,[1] exhibiting sub-micromolar inhibitory activity against multiple cancer cell lines.[2] Structurally, these alkaloids possess a highly functionalized aminocyclitol core, with four contiguous stereocenters in the case of lycoricidine (**1**) and narciclasine (**2**), and six in the case of 7-deoxypancratistatin (**3**) and pancratistatin (**4**). Due to their potential oncological relevance, as well as their low natural abundance, these metabolites have attracted significant interest in the synthetic community, resulting in numerous synthetic studies and several dozen total syntheses reported to date.[3-5] Nevertheless, the strategic applications of dearomative processes[6] to access the polyfunctionalized cyclohexenyl or cyclohexyl motifs of these natural products have been very limited, with only microbial arene oxidation used successfully by the Hudlicky[4g,5c] and Banwell groups.[4n,5f] Herein, we report the total synthesis of lycoricidine (**1**) and narciclasine (**2**) using a chemical-based dearomatization of bromobenzene, as well as a general method for the preparation of 4-aryl substituted *cis*-dihydrodiols.



1: lycoricidine (R = H)
2: narciclasine (R = OH)
3: 7-deoxypancratistatin (R = H)
4: pancratistatin (R = OH)

Scheme 1. Structures of lycoricidine (**1**), narciclasine (**2**), 7-deoxypancratistatin (**3**), and pancratistatin (**4**).

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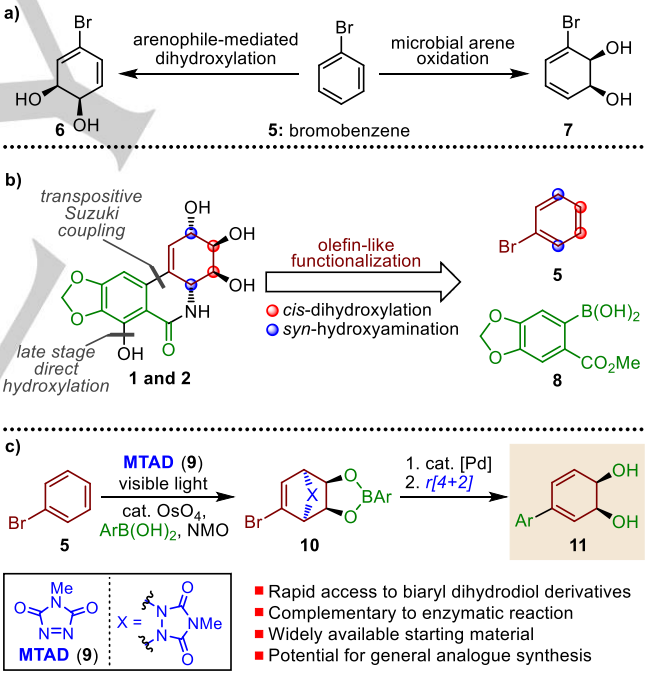
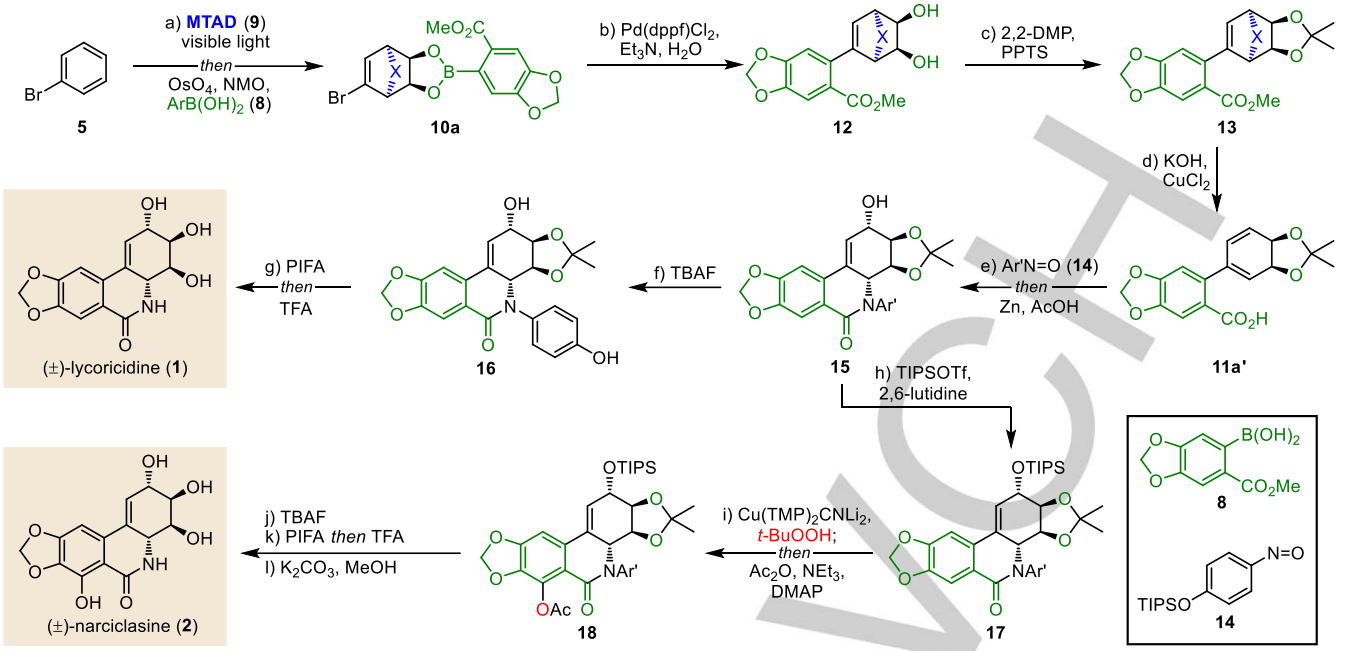
We have recently reported an arenophile-mediated dearomative dihydroxylation that provides access to dihydrodiol derivatives that are complementary to those obtained through biotechnological processes (i.e. **6** vs. **7**, Scheme 2a).[7] Specifically, the chemical dihydroxylation of bromobenzene (**5**) delivers bromo-3,4-dihydrodiol (**6**), a constitutional isomer that is well-suited for the synthesis of lycoricidine (**1**) and narciclasine (**2**), as the location of the vinyl bromide in **6** is properly situated for appending on the aryl portion of these molecules. Therefore, we envisioned that these natural products could be traced back to bromobenzene (**5**) and aryl boronic acid **8** by using Suzuki coupling and two olefin transformations to install the required *cis*-1,2-diol and 1,4-*syn*-aminodiol, as shown retrosynthetically in Scheme 2b. Additionally, we anticipated that the phenol moiety that distinguishes **2** from **1** could be introduced at a late stage in the synthesis, allowing for common intermediates to be used in the construction of both molecules.



Scheme 2. a) Chemical and biological dearomative dihydroxylation of bromobenzene (**5**). b) Key retrosynthetic disconnections for lycoricidine (**1**) and narciclasine (**2**). c) Preparation of 4-aryl substituted *cis*-dihydrodiols **11**.

Moreover, in order to increase the atom economy and overall yield of this dearomative approach, we reasoned that application of arenophile MTAD (**9**) with bromobenzene (**5**) under Narasaka-Sharpless dihydroxylation conditions[8] would permit expedited preparation of the required dihydroxylated biphenyl intermediate **11** (Scheme 2c). Under this protocol, the arylboronic acid serves as a turnover reagent for osmium and becomes embedded within the dearomatized product as a cyclic



Scheme 3. Total synthesis of (±)-lycoricidine (**1**) and (±)-narciclasine (**2**). Reagents and condition: a) PhBr (**5**), MTAD (**9**), white LEDs, CH_2Cl_2, −78 °C; then **8**, OsO_4 (10 mol%), NMO, CH_2Cl_2, −78 to 0 °C, 63%. b) $Pd(dppf)Cl_2$ (5 mol%), NEt_3, THF:H_2O = 9:1, 70 °C, 54%. c) PPTS (cat.), CH_2Cl_2:2,2-DMP = 1:1, 50 °C, 86%. d) KOH, *i*PrOH, 100 °C; then $CuCl_2$, pH = 7, RT, 93%. e) **14**, THF, 0 °C to RT; then Zn, AcOH, RT, 60%. f) TBAF, THF, 0 °C, 98%. g) PIFA, MeCN: H_2O = 9:1, 0 °C, then TFA, 0 °C, 95%. h) TIPSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C to RT, 77%. i) $(TMP)_2Cu(CN)Li_2$, THF, 0 °C; then *t*BuOOH, THF, −78 °C; then Ac_2O, NEt_3, DMAP, 0 °C to RT, 50% + 10% of free phenol derivative. j) TBAF, THF, 0 °C, 82%. k) PIFA, MeCN: H_2O = 9:1, 0 °C; then TFA, 0 °C, 92%. l) K_2CO_3, MeOH, 0 °C to RT, 68%. NMO = *N*-methylmorpholine-*N*-oxide, THF = tetrahydrofuran, dppf = 1,1′ -bis(diphenylphosphino)ferrocene, PPTS = pyridinium *p*-toluenesulfonate, 2,2-DMP = 2,2-dimethoxypropane, TBAF = tetrabutylammonium fluoride, TIPSOTf = triisopropylsilyl trifluoromethanesulfonate, TMP = 2,2,6,6,-tetramethylpiperidine, PIFA = bis(trifluoroacetoxy)iodobenzene, TFA = trifluoroacetic acid.

boronate ester (**5**→**10**). A subsequent transpositive Suzuki coupling and cycloreversion of the arenophile moiety would incorporate the aryl ring into the carbon framework of the molecule and deliver 4-aryl substituted *cis*-dihydrodiol **11**. Importantly, the preparation of biaryl dihydrodiols of type **11** has not been widely explored,[9] and the application of microbial oxidation to biphenyl substrates generally gives alternative constitutional isomers to the desired oxidation product **11**.[10] Only engineered enzymes can produce such compounds; however, their synthetic application has not been explored.[11]

We commenced our studies by arenophile-assisted dihydroxylation of bromobenzene (Scheme 3). Based on our previous work, we chose to employ Narasaka-Sharpless dihydroxylation, as this modification gave superior results with halogenated aromatic substrates. Accordingly, visible-light irradiation of bromobenzene (**5**) and arenophile MTAD (**9**) with subsequent addition of osmium tetroxide, boronic acid **8**, and NMO, delivered bicycle **10a** in 63% yield. Importantly, this reaction was routinely run on a multigram scale and more than 100 g of **10a** have been prepared to date in our laboratories. With intermediate **10a** in hand, which possesses both a vinyl bromide and an arylboronic ester, we turned our attention to the development of a transpositive Suzuki coupling to install the benzodioxole ring into the carbon framework of these alkaloids. Initial screening of reaction conditions using standard conditions with $Pd(PPh_3)_4$ as catalyst gave sub-optimal results, with protodeborylation as a major process. Extensive screening identified $Pd(dppf)Cl_2$ as an optimal catalyst in combination with triethylamine as a base in THF and furnished coupling product **12** in 54% yield. Small amounts of water proved crucial for high yields, likely for pre-hydrolysis of boronate ester to facilitate the pre-transmetalation event.[12] Next, acid-catalyzed acetonide protection of free diol with 2,2-dimethoxypropane and subsequent cycloreversion (KOH, heat then $CuCl_2$) cleanly afforded intermediate dihydrodiol **11a'**.

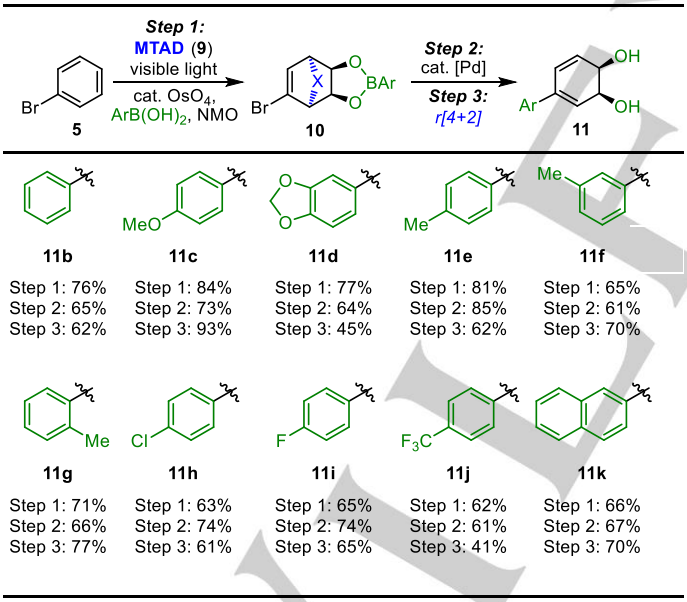
With the carbon skeleton completed and *cis*-1,2-diol installed, we turned towards the introduction of the required 1,4-*syn*-aminoalcohol moiety. To this end, we anticipated that nitroso-Diels–Alder with subsequent reduction of the N–O bond could deliver the desired motif, though we anticipated that electronic tuning of the nitroso cycloaddend might be required to obtain the desired constitutional isomer.[13] Indeed, we observed that cycloaddition with electron-rich arylnitroso species **14** proceded exclusively with desired selectivity, while acyl- and alkylnitroso species gave the opposite isomer. In order to facilitate deprotection of the amide nitrogen, a TIPS protected phenol nitroso was employed during the cycloaddition step; after zinc-mediated N–O cleavage, lactam **15** was produced as a single diastereo- and constitutional isomer. Deprotection of the phenol with TBAF (**15**→**16**), followed by one-pot oxidative cleavage and acetonide deprotection, afforded lycoricidine (**1**), whose physical properties (^1H and ^{13}C NMR, MS data) matched with those reported for the natural material.

Though more than a dozen chemical syntheses of lycoricidine (**1**) exist, its conversion to narciclasine (**2**) through late-stage arene C–H hydroxylation has never been established. We undertook this task and found that the amide **15** could serve also as a viable intermediate to narciclasine (**2**). Inspired by the

recent work from Uchiyama group,[14] we reasoned that a benzamide group could serve as a viable directing group for deprotonative cupration and subsequent oxidation of the resulting arylcuprate with *tert*-butyl hydroperoxide. Gratifyingly, silylation of alcohol **15** and hydroxylation of **17** under Uchiyama's conditions, with in situ acetylation, afforded intermediate **18**. Protection of the phenol moiety after hydroxylation stage proved crucial for subsequent oxidative deprotection of the tertiary amide. Thus, global deprotection (TBAF, PIFA then TFA, and K_2CO_3) afforded narciclasine (**2**).

Considering that dearomative dihydroxylation with arenophiles provides a new entry into the synthesis of biaryl *cis*-dihydrodiol derivatives from readily available bromobenzene and arylboronic acids, we evaluated the generality of this synthetic strategy (Table 1). Thus, a three step protocol involving: (1) dearomative Narasaka-Sharpless dihydroxylation of bromobenzene in the presence of a variety of aryl boronic acids, (2) transpositive Suzuki coupling, and (3) cycloreversion, furnished the desired biaryl dihydrodiol derivatives **11**. Different electronic and steric properties were tolerated during the course of this reaction; electron-rich (e.g. **11c**, **11d**) and electron-deficient (**11h**, **11i**, and **11j**) boronic acids could be employed, as well as arenes with substituents in the *ortho, meta,* and *para* positions relative to the boron atom. Finally, 2-naphthylboronic acid was used to afford polynuclear dihydrodiol **11k**.

Table 1. Synthesis of biaryl 3,4-dihydodiols derivatives.[a,b]



[a] Reaction conditions: **Step 1:** MTAD (**9**, 2.0 equiv), PhBr (**5**, 20 equiv), visible light, CH_2Cl_2, –78 °C; then $ArB(OH)_2$ (1.0 equiv), OsO_4 (10 mol%), NMO (2.4 equiv), -78 °C to r.t,. **Step 2:** $Pd(dppf)Cl_2$ (5.0 mol%), Et_3N (5.0 equiv.), THF/H_2O (9:1), 70 °C. **Step 3:** N_2H_4 (30 equiv) 100 °C, 12 h; then $CuCl_2$ (1.0 equiv.) pH = 7, r.t., 5 min. [b] Yield of isolated product.

In conclusion, (±)-lycoricidine (**1**) and (±)-narciclasine (**2**) have been synthesized using chemical dearomatization of bromobenzene in 7 and 10 steps, respectively. Employment of Narasaka–Sharpless dihydroxylation and subsequent transpositive Suzuki coupling incorporated the aryl ring of a boronic ester into the carbon skeleton, enabling rapid access to these molecules. Moreover, a unique deprotonative cupration/oxidation hydroxylation sequence allowed for the conversion of a late-stage lycoricidine intermediate into a precursor for narciclasine. Finally, this approach provided a concise entry into the synthesis of a variety of biaryl 3,4-dihydrodiols, which could greatly advance the synthesis of analogues of these important alkaloids.

Acknowledgements

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Keywords: lycoricidine • narciclasine • alkaloids • synthesis • dearomatization

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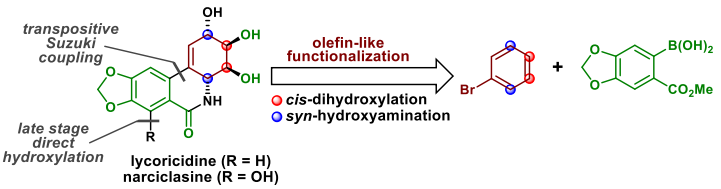

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Page No. – Page No.

Total Synthesis of Narciclasine and Lycoricidine via Chemical Dearomatization of Bromobenzene

Dearomative dihydroxylation of bromobenzene enables rapid and controlled access to the potent anticancer natural products narciclasine and lycoricidine. The approach is based on arenophile- and aryl boronic acid-assisted dearomative dihydroxylation and subsequent transpositive Suzuki coupling. The generality of this sequence is demonstrated with preparation of several *cis*-dihydroxylated biphenyls.