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Article

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Enantioselective Divergent Syntheses of (+)-Bulleyanaline and Related Isoquinoline Alkaloids from the Genus *Corydalis*.

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ABSTRACT: The isoquinoline alkaloids isolated from the genus *Corydalis* possess potent and diverse biological activities. Herein, a concise, divergent, and enantioselective route to access these natural products is disclosed. Key transformations of our approach include a challenging Zn-ProPhenol catalyzed asymmetric Mannich reaction to build a quaternary stereogenic center and a rapid cationic Au-catalyzed cycloisomerization to the common structural skeleton of these natural products. Subsequent late-stage oxidations and modifications allow efficient access to the targeted alkaloids. Overall, 7 natural products have been successfully synthesized in 6 to 10 steps from readily available starting materials, including (+)-corynoline, (+)-anhydrocorynoline, (+)-12-hydroxycorynoline, (+)-12-hydroxycorynoloxine, (+)-corynoloxine, (+)-6-acetonylcorynoline, and (+)-bulleyanaline.

INTRODUCTION

Isoquinoline alkaloids constitute one of the largest and structurally diverse groups of natural products and are widely distributed among plants from the families Papaveraceae, Berberidaceae, Fumariaceae, Menispermaceae, Ranunculaceae, Rutaceae, and Annonaceae.[1] Among these natural products, the hexahydrobenzo[c]phenanthridine-type alkaloids isolated from the genus *Corydalis* possess potent and diverse pharmacological properties (Figure 1A).[2,3] For example, (+)-corynoline **1** exhibits reversible and non-competitive inhibition of acetylcholinesterase (AChE), which can be beneficial for treating memory impairments and Alzheimer's disease.[3a] Both (+)-**1** and (+)-12-hydroxycorynoline **3** have been shown to decrease the level of inflammatory mediators – including IL-6, IL-10, TNF-α and NO – in LPS-induced mice.[3b] Additionally, (+)-**1** and (+)-corynoloxine **4'** exhibits comparable inhibition for the adhesion of human polymorphonuclear leukocytes (PMNCs) to human umbilical vein cultured endothelial cells (HUVEC),[3c,d] and cytotoxicity against human A549, SK-OC-3, SK-MEL-2, and HCT15 tumor cells.[3e] Lastly, while being less potent than propiconazole, **1**, **1'**, and **4'** show noticeable anti-fungal activity against *C. herbarum*.[3f]

Despite the great therapeutic potentials of this family of natural products, synthetic efforts have focused almost exclusively on corynoline **1**, which is the major component of most *Corydalis* extracts, and only a few asymmetric syntheses have been reported.[4,5] Cushman and co-workers completed the first asymmetric synthesis of (+)-corynoline **1** using a ferrocene-derived chiral auxiliary in the key Mannich transformation.[5a] In 2014, Lautens and co-workers reported a formal synthesis of (+)-**1** utilizing the Ellman auxiliary as the source of chirality.[5b] The first synthesis of (+)-corynoline **1** employing asymmetric catalysis was reported in 2018 and features an elegant Pd-catalyzed asymmetric α-arylation to construct the quaternary stereocenter.[5c] The lack of synthetic efforts towards other less naturally abundant alkaloids compared to corynoline **1** as well as their pharmacological potential prompted us to develop a concise and atom-economical route to access these valuable natural products. Furthermore, due to their structural similarities, developing a divergent synthetic approach from a common intermediate is attractive. Herein, we present the enantioselective total synthesis of 7 different isoquinoline alkaloids: (+)-corynoline **1**, (+)-anhydrocorynoline **2**, (+)-12-hydroxycorynoline **3**, (+)-12-hydroxycorynoloxine **4**, (+)-corynoloxine **4'**, (+)-6-acetonylcorynoline **5'**, and (+)-bulleyanaline **5**, all diverging from the same key intermediate. This 10-step longest linear route from known material[6] accomplishes the first total synthesis of (+)-**4**, (+)-**4'**, (+)-**5**, and (+)-**5'** and the first asymmetric synthesis of (+)-**2** and (+)-**3**.

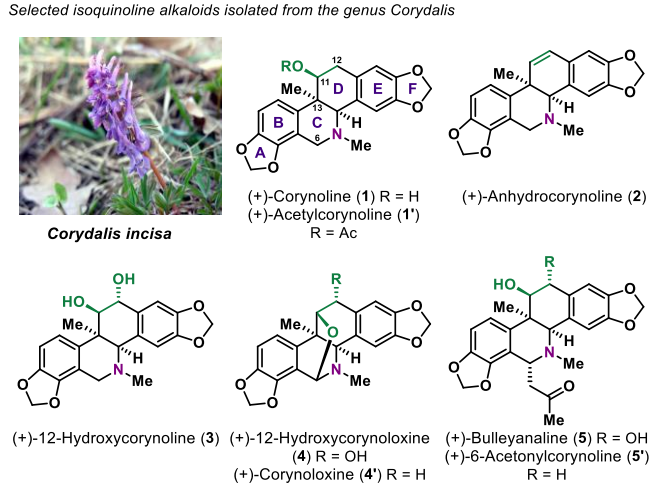
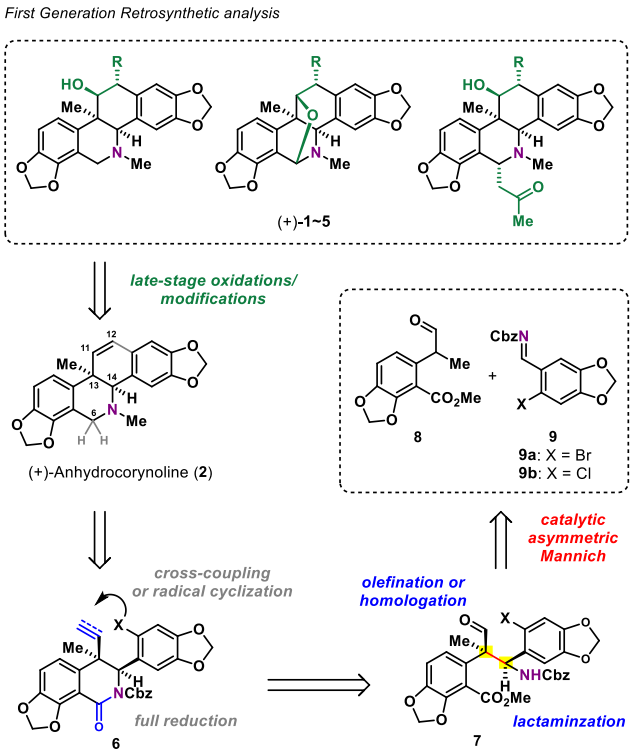


Figure 1. Selected isoquinoline alkaloids isolated from the genus *Corydalis* and their structural similarities.

From a structural perspective, the highlighted *Corydalis* alkaloids share a similar hexacyclic skeleton featuring a *cis* C/D ring system and a quaternary methyl group at C-13 position (Figure 1). The main structural differences arise from the degree of oxidation and substitution pattern at C-6, C-11, and C-12. As a result, we

decided to first synthesize (+)-anhydrocorynoline **2**, which is structurally the simplest (Scheme 1). More importantly, we anticipated that the olefin between C-11 and C-12 would enable late-stage chemo- and diastereoselective oxidations and modifications to access other members in the family.[7] In the original retrosynthetic analysis, the D ring of (+)-anhydrocorynoline **2** was envisioned to be constructed via an intramolecular cross-coupling or radical cyclization of the aryl halide to the unsaturated moiety. The tertiary amine could be obtained through the full reduction of the *N*-acyl carbamate motif of **6**. Piperidinone **6** could be synthesized from β-amino aldehyde **7** via either an olefination or homologation of the carbonyl group and subsequent lactamization to construct ring C. Finally, we aimed to employ a catalytic asymmetric Mannich reaction between aldehyde **8** and imine **9** of similar molecular weights to set the absolute configuration of the targeted alkaloids.

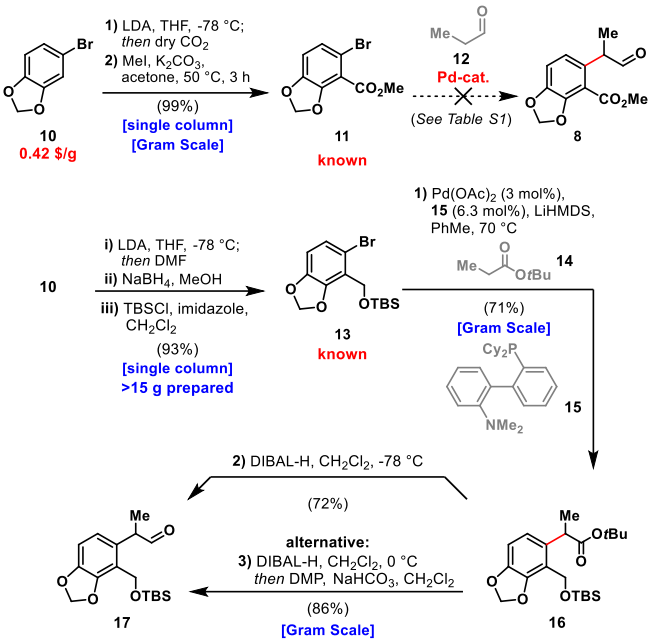
Scheme 1. First Generation Retrosynthetic Analysis of (+)-Anhydrocorynoline **2** and related alkaloids.



RESULTS AND DISCUSSION

Our synthesis commenced with the preparation of aldehyde **8** or structurally similar intermediates (Scheme 2). Originally, a direct Pd-catalyzed α-arylation of propionaldehyde **12** with aryl bromide **11** was envisioned. Compound **11** was readily prepared in quantitative yield from commercially available **10** in a two-step, single-chromatography sequence, including a selective *ortho*-lithiation using LDA, quenching with CO_2, and methylation of the corresponding acid. Despite having ample supply of aryl bromide **11**, the proposed α-arylation of propionaldehyde **12** using previously reported conditions[8] did not afford **8** (See Table S1). Partial dehalogenation with some unidentified byproducts were typically observed presumably due to the instability of the Pd-enolate.[9] As a result, another synthetic approach was investigated.

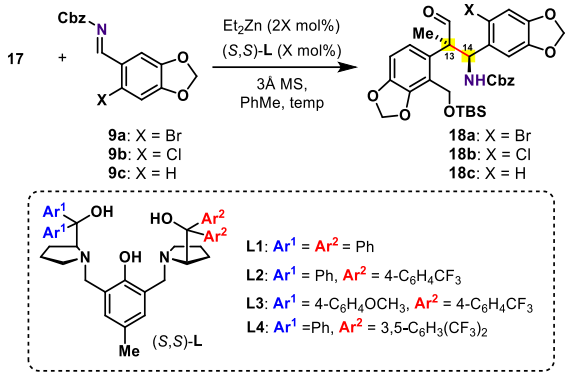
Scheme 2. Synthesis of Aldehyde **17** for the Catalytic Asymmetric Mannich Reaction



Starting from the same aryl bromide **10**, known compound **13** was prepared in decagram scale utilizing simple operations (Scheme 2). Intermediate **13** was then subjected to a direct α-arylation with *tert*-butyl propanoate **14** using $Pd(OAc)_2$ as the pre-catalyst and DavePhos **15** as optimal ligand, conditions developed by Buchwald and coworkers.[10] An initial attempt on small scale was successful, yielding the desired α-arylated adduct **16** in 66% yield. This process was later completed on multi-gram scale in 71% yield, providing sufficient material for subsequent transformations. DIBAL-H reduction at -78 °C then afforded aldehyde **17** in 72% yield. Alternatively, **17** could be obtained in 88% yield via full reduction of the ester of **16** to the corresponding alcohol followed by DMP oxidation.

With **17** in hand, the key asymmetric Mannich reaction with imine **9** was investigated (Table 1). We anticipated that this reaction would be challenging due to the generation of the quaternary stereocenter next to an amine moiety.[10] Reported catalytic asymmetric processes are mostly restricted to highly activated pronucleophiles,[12] such as 1,3-dicarbonyls, α-cyanocarbonyls, and oxindoles, and the use of nonactivated enolate precursors is rare.[13] However, in light of our recent work on Zn-ProPhenol-catalyzed asymmetric Mannich processes,[14] we believe this particular system could overcome the underlined challenge to generate the key intermediate for this synthesis. We initiated our studies using **17** and *N*-Cbz imine **9a** featuring an *o*-bromo motif in the presence of Zn-ProPhenol catalyst derived from commercially available **L1** (Table 1, entry 1-3). Unfortunately, no reaction was observed despite the reaction being performed at elevated temperature with 10 mol% catalyst loading. Analogous observations were also made using *o*-chloro imine **9b** (entry 4-5). The lack of reactivity is possibly due to steric effects from the bulky substituent (*ortho*-halogen) next to the reactive site.

Table 1. Study of Zn-ProPhenol-Catalyzed Asymmetric Mannich Reaction.[a]



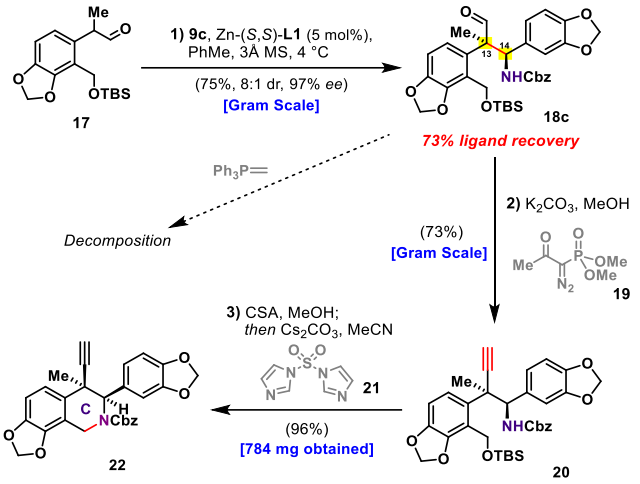
entry	9	L	x	T (°C)	h	18 (%)	dr, *ee* %
1	**9a**	**L1**	5	4	16	ND[b]	-
2	**9a**	**L1**	10	rt	16	ND	-
3	**9a**	**L1**	10	40	16	ND	-
4	**9b**	**L1**	10	rt	16	ND	-
5	**9b**	**L1**	10	60	16	ND	-
6	**9c**	**L1**	10	rt	16	78	2:1, 90%
7[c]	**9c**	**L1**	10	rt	48	<30	3:1, 84%
8	**9c**	**L1**	5	4	48	82	12:1, 97%
9	**9c**	**L2**	5	4	48	72	2:1, 94%
10	**9c**	**L3**	5	4	48	68	4:1, 89%
11	**9c**	***L4***	5	4	48	77	1:2, ND[d]
12[e]	**9c**	**L1**	5	4	48	75	8:1, 97%

[a] Reaction performed with **17** (0.2 mmol) and **9** (0.24 mmol). [b] Not detected. [c] THF was used as solvent. [d] Not determined. [e] Reaction performed with **17** (1.61 g, 5.00 mmol) and **9c** (1.55 g, 5.50 mmol).

To alleviate the steric interactions, imine **9c** was employed in the asymmetric Mannich process. Pleasingly, the desired product **18c** was obtained in 78% yield and 90% *ee*, albeit with modest diastereoselectivity (3:1 dr) (Table 1, entry 6). Switching the solvent from toluene to THF gave very low reaction conversion (<30% yield, 3:1 dr, 84% *ee*) (Table 1, entry 7). To improve the diastereoselectivity, different ligands and reaction temperatures were evaluated. Interestingly, lowering the temperature from room temperature to 4 °C drastically increased the dr to 12:1 without impacting the product conversion (Table 1, entry 8). Moreover, the catalyst loading can be reduced to 5 mol%. On the other hand, using other ligands, including **L2**, **L3**, and ***L4***, resulted in lower diastereomeric ratios (Table 1, entry 9-11). Finally, using **L1** as the optimal ligand, the reaction can be conducted on multi-gram scale to yield Mannich adduct **18c** in 75% yield, 8:1 dr, and 97% ee (Table 1, entry 12). Additionally, the ProPhenol ligand was recovered (73% recovery) and reused after simple chromatography on silica gel, lowering the effective catalyst loading of this process.

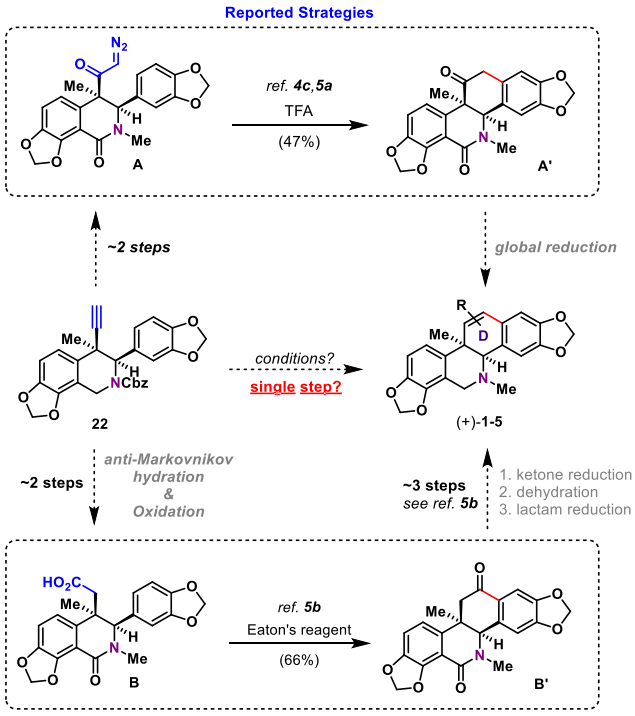
Homologation of aldehyde **18c** using Ohira-Bestmann reagent **19** afforded **20** in 73% yield, which has all the carbons for the hexacyclic skeleton of the natural products (Scheme 3). Interestingly, an attempt to undergo olefination using a standard Wittig reagent resulted in total decomposition, presumably due to retro-Mannich processes. Subsequently, deprotection of the benzylic alcohol followed by an *in situ* intramolecular S_N2 cyclization (after evaporation of MeOH) utilizing sulfonyldiimidazole **21** as the promoter allowed the formation of ring C **22** in 96% yield.

Scheme 3. Construction of Ring C



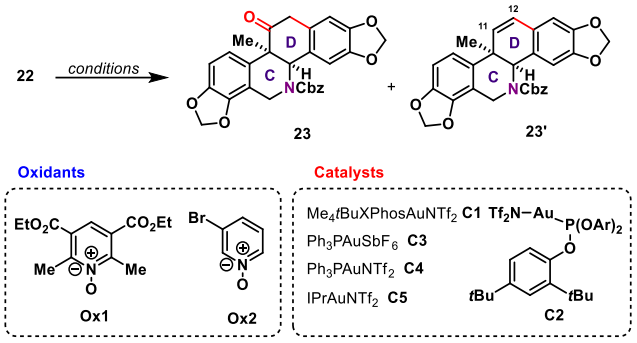
Due to the absence of the halogen required for the proposed cyclization shown in Scheme 1, an alternative approach needed be devised. Two strategies have been previously developed utilizing structurally similar substrates (Scheme 4). The first one involves an acid-mediated intramolecular carbene insertion of α-diazo ketone **A**[4c, 5a], whereas the second strategy relies upon a Friedel-Craft cyclization of carboxylic acid **B**[5b]. Despite having good to moderate yields, both sequences can be lengthy to convert the alkyne to the targeted functional groups for the cyclization. Moreover, at least three additional steps are required to convert **B'** to the alkaloids. In addition to high step counts, the generation of diazo intermediate **A** typically requires the use of explosive diazomethane.

Scheme 4. Strategies for the Formation of Ring D



These disadvantages prompted us to investigate a more atom- and step-economical alternative. As a result, we attempted to perform a cationic Au-catalyzed oxidative cyclization to directly convert **22** to ketone **23** in one-step, and the corresponding carbonyl group at the C-11 position would then be converted to the hydroxyl group present in most alkaloids shown in Figure 1. This elegant process has been previously reported by the Zhang and Gagosz group using pyridine oxides (**Ox1** and **Ox2**) as the oxidants.[15] Unfortunately, reactions using reported conditions did not generate the product **23** (Table 2, entry 1-5), presumably due to steric hindrance from the vicinal quaternary motif, precluding oxidants from approaching the internal carbon of the acetylene moiety. Interestingly, partial conversion to the cycloisomerized product **23'** was observed with higher catalyst loadings (Table 2, entry 2, 3, and 5). Since the olefin between C-11 and C-12 should enable chemo- and diastereoselective oxidations and modifications to the targeted alkaloids, we decided to optimize the formation of intermediate **23'**.

Table 2. Study of Au-Catalyzed Intramolecular Hydroarylation.

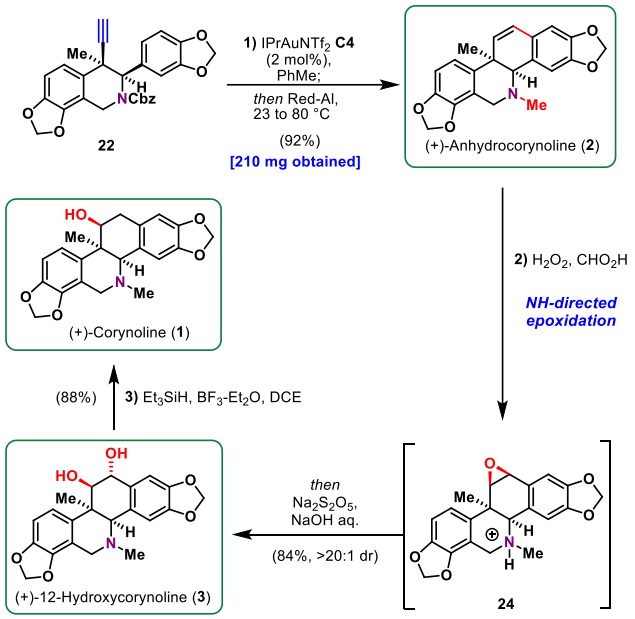


entry	[o]	[M]	x	solvent	T (°C)	23 %	23' %
1[a]	**Ox1**	**C1**	5	DCE	rt	ND[b]	-
2[a]	**Ox1**	**C1**	10	DCE	4	ND[b]	55
3[c]	**Ox1**	**C1**	10	DCE	4	ND[b]	50
4[d]	**Ox2**	**C2**	5	$CHCl_3$	60	ND[b]	-
5[d]	**Ox2**	**C2**	25	$CHCl_3$	60	ND[b]	60
6	-	**C1**	5	DCE	rt	-	70
7	-	**C3**	5	DCE	rt	-	80
8	-	**C4**	5	DCE	rt	-	85
9[e]	-	**C5**	5	DCE	rt	-	99
10[e]	-	**C5**	2	DCE	rt	-	99
11[e]	-	**C5**	2	PhMe	rt	-	99

[a]Reaction performed with **Ox1** (1.2 equiv.). [b]Not detected. [c]Reaction performed with **Ox1** (3 equiv.). [d]Reaction performed with **Ox2** (2 equiv.) and MsOH (1.2 equiv.). [e]Reaction completed in <2 min.

Pleasingly, removing the oxidant from the reaction afforded **23'** in 70% (Table 2, entry 6). Subsequent reaction optimizations identified $IPrAuNTf_2$ **C5** as the optimal catalyst for this reaction; only 2 mol% of **C5** was required, and the reaction was completed quantitatively within 2 minutes (Table 2, entry 10-11). More importantly, of the three possible cyclization modes, only *6-endo-dig* was observed. Both toluene and 1,2-dichloroethane (DCE) were compatible solvents for this process; however, toluene was selected since the subsequent one-pot Red-Al reduction was more effective in toluene than DCE (Scheme 5). The observed rapid cyclization can be attributed to the high electron density of the aryl group as well as its *syn* relationship with the acetylene moiety. Although similar hydroarylation processes have been developed using metal catalysts, such as Au, Cu, Ru, Hg, and Pt,[16] their applications to total synthesis, especially alkaloids, remain underexplored.[17] In general, transition metal-catalyzed cycloisomerizations are attractive strategies in modern synthesis due to their ability to rapidly build molecular complexity from simpler starting materials while maintaining perfect atom economy.[18]

Scheme 5. Asymmetric Synthesis of (+)-Corynoline (**1**), (+)-Anhydrocorynoline (**2**), and (+)-12-Hydroxycorynoline (**3**)

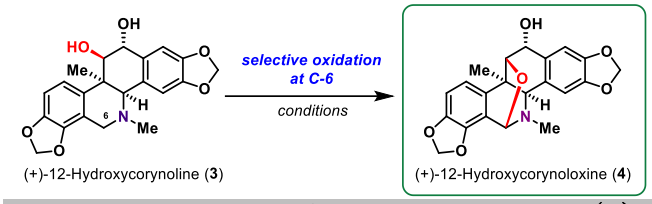


Since the transformation to **23'** was nearly quantitative, direct addition of Red-Al to the reaction mixture at elevated temperature then furnished (+)-anhydrocorynoline **2** in 92% yield (Scheme 5). Overall, 210 mg (25% overall yield) of (+)-**2** was obtained in 6 steps from known compound **13**. With (+)-**2** in hand, the next stage of the project was to perform oxidations and elaborations to other members in the family. Using a modified version of conditions reported by Ninomiya and co-workers,[4b] hydroxy groups were introduced at C-11 and 12 to deliver (+)-12-hydroxycorynoline **3** in 84% yield via epoxidation using *in situ*-generated performic acid followed by hydrolysis with NaOH. As described in the previous report, the excellent *endo* selectivity of the epoxidation is attributed to the interaction between the peracid and the ammonium cation. Although (±)-**3** has been previously converted to (±)-corynoline **1** via Pd-catalyzed hydrogenolysis,[4b] the required high pressure and low yield (35%) due to byproduct formation prompted us to investigate an alternative method. Pleasingly, treatment of (+)-**3** with Et_3SiH and BF_3-Et_2O afforded (+)-corynoline **1** in 88% yield.

With a reliable supply of (+)-**1** and (+)-**3**, the stage was set for the late-stage chemoselective oxidation at the C-6 position (Table 3). Although such transformations have been reported in the isolation papers and semi-syntheses, the use of toxic $Hg(OAc)_2$ as oxidant is not ideal, especially since stoichiometric elemental mercury is generated as a byproduct (Table 3, entry 1).[2c, 2d] As a result, we sought a more environmentally friendly and less toxic alternative. The use of DDQ resulted in a complex mixture, whereas tropylium

cation[19] gave around 60% conversion to the desired product, (+)-12-hydroxycorynoloxine **4** (Table 3, entry 2-3). Increasing the amount of oxidant or reaction temperature did not result in further improvements (Table 3, entry 5); however, the use of iodine with KOAc in refluxing ethanol[20] generated (+)-**4** cleanly and quantitatively in 5 h (Table 3, entry 5). The reaction time could be reduced to 1 h in the presence of K_2CO_3 (Table 3, entry 6).

Table 3. Study of the Late-Stage Oxidation at C-6 Position.



entry	conditions	4 (%)[a]
1	**Hg(OAc)$_2$** (5 equiv.), HOAc, reflux, 5 h	72
2	**DDQ** (2 equiv.), CH_2Cl_2, pH=7 buffer, rt, 1h	Decomp.
3	**Tropylium BF$_4$** (2 equiv.), MeCN, 60 °C, 3 h	60[b]
4	**Tropylium BF$_4$** (4 equiv.), MeCN, 60 °C, 5 h	64[b]
5	I_2 (1.1 equiv.), KOAc (3 equiv.), EtOH, reflux, 5 h	99
6	I_2 (1.1 equiv.), KOAc (3 equiv.), K_2CO_3 (3.0 equiv.), EtOH, reflux, 1 h	99

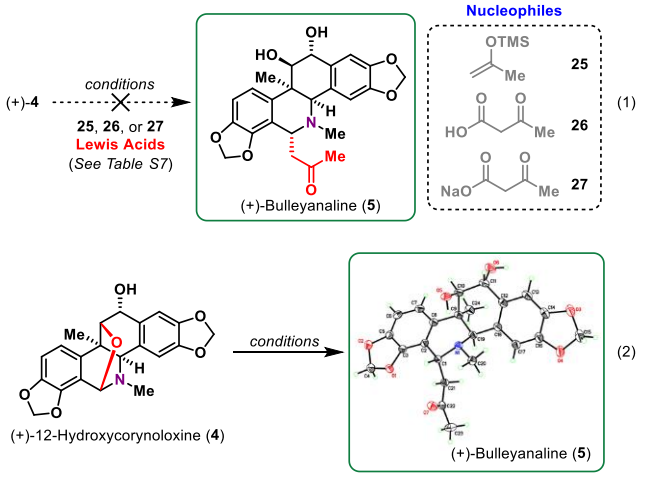
[a]isolated yield. [b]Conversion based on crude ^{1}H NMR analysis.

With (+)-4 in hand, our next goal was to synthesize (+)-bulleyanaline **5**, which has an extra acetonyl group at the C-6 position. Our initial plan was to open the hemiaminal of (+)-**4** using silyl enol ether **25** as the nucleophile in the presence of a Lewis acid as the promoter (Table 4, eq. 1). However, multiple attempts using a variety of metal and non-metal Lewis acids resulted in either no reaction or decomposition of (+)-**4** (See Table S7). Other pronucleophiles, including acetoacetic acid or its sodium salt,[2d] gave similarly poor results. Conditions using metal carbonates with acetone as the nucleophile also gave no reactivity.

Interestingly, some conversion of (+)-**4** to other side products was observed after prolonged treatment in CD_3OD with a trace amount of water. This then prompted us to investigate hydroxides as alternative promoters (Table 4, eq. 2). Pleasingly, treating (+)-**4** with NaOH in a mixture of H_2O and acetone at elevated temperature afforded (+)-bulleyanaline **5** in 20% yield (Table 4, entry 1). Switching the base to KOH improved the isolated yield to 35% (Table 4, entry 2). A further enhancement to 65% isolated yield was observed by replacing H_2O with methanol (Table 4, entry 3). Ultimately, carefully adjusting the reaction temperature and time allowed (+)-**5** to be obtained in 75% yield as a single diastereomer (Table 4, entry 4). Besides matching with the spectral data provided by the isolation work,[2d] the structure of (+)-**5** was unambiguously confirmed by single crystal X-ray diffraction upon recrystallization.[21]

Using the developed conditions for the selective oxidation at C-6, (+)-corynoline **1** was successfully converted to (+)-corynoloxine **4'** in 95% yield (Scheme 6). Treatment of (+)-4' with KOH in a mixture of acetone and methanol at elevated temperature afforded our final target, (+)-6-acetonylcorynoline **5'**, in 70% yield as a single diastereomer. A mechanism is proposed for the opening of the hemiaminal. We believe that under protic conditions, the hemiaminal of (+)-**4** and **4'** is in equilibrium with the corresponding aldehyde **28**, which can undergo aldol condensation with acetone to generate intermediate **29**. A diastereoselective intramolecular aza-Michael reaction then occurs to afford the desired products.

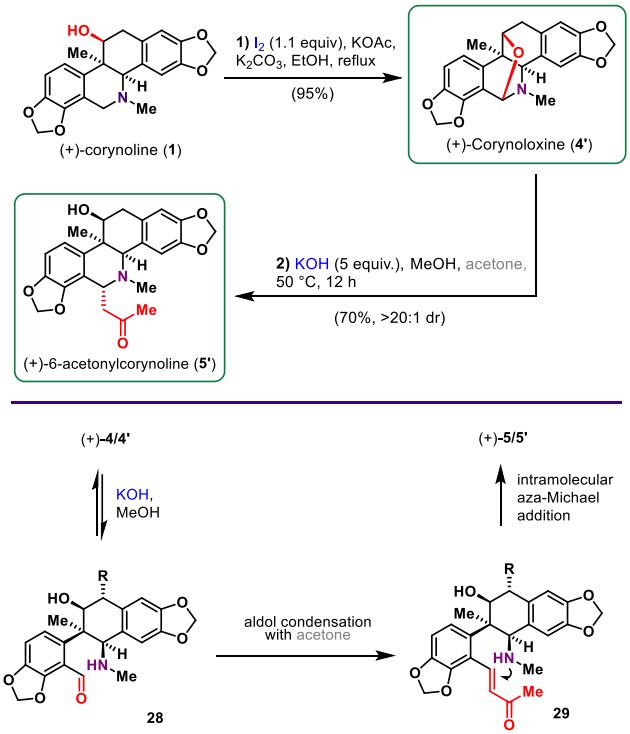
Table 4. Synthesis of (+)-Bulleyanaline **5** and Its Crystallographic Structure.



entry	conditions[a]	5 (%)[b,c]
1	**NaOH** (5 equiv.), H_2O, acetone, 60 °C, 24 h	20
2	**KOH** (5 equiv.), H_2O, acetone, 40 °C, 12 h	35
3	**KOH** (5 equiv.), MeOH, acetone, reflux, 20 h	65, >20:1 dr
4	**KOH** (5 equiv.), MeOH, acetone, 50 °C, 12 h	75, >20:1 dr

[a]Reaction performed with freshly-ground hydroxides. [b]isolated yield. [c]Diastereomeric ratio was determined by crude ^{1}H NMR analysis

Scheme 6. Synthesis of (+)-**4'** and **5'** and Proposed Mechanism



CONCLUSIONS

In summary, we report divergent and asymmetric syntheses of 7 isoquinoline alkaloids isolated from the genus *Corydalis*: (+)-corynoline **1**, (+)-anhydrocorynoline **2**, (+)-12-hydroxycorynoline **3**, (+)-12-hydroxycorynoloxine **4**, (+)-corynoloxine **4'**, (+)-6-acetonylcorynoline **5'**, and (+)-bulleyanaline **5**. The overall route proceeds in **10** longest linear sequence from known material **13** and accomplishes the first total synthesis of (+)-**4**, (+)-**4'**, (+)-**5**, and (+)-**5'** and the first asymmetric synthesis of (+)-**2** and (+)-**3** (See Scheme S1 for the final route). Although some of the alkaloids, especially corynoline **1**, have been previously synthesized, our route represents the most efficient and divergent approach, allowing synthesis of multiple natural products all diverging from a common intermediate. Moreover, a total of three catalytic transformations are involved within the 10-step sequence, highlighting the atom- and step-economy of this route. Highlights of our strategy include: (a) an enantio- and diastereoselective catalytic Mannich reaction to establish the absolute configuration of the natural products featuring a quaternary stereocenter; (b) a rapid catalytic cycloisomerization of **6** to construct the *cis* C/D ring system; and (c) selective late-stage oxidations and modifications of (+)-**2** into 6 other alkaloids in the family. The high overall yields and atom-economy should provide rapid and scalable access to these natural products and related analogs for further biological investigations and the development of novel therapeutic agents.

ASSOCIATED CONTENT

Supporting Information

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

Experimental procedures, analytical data (^{1}H-NMR, ^{13}C-NMR, MS, IR, and $[\alpha]_D$) for all new compounds, additional reaction optimization tables (PDF)

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Author Contributions

All authors have given approval to the final version of the manuscript.

Notes

The authors declare no competing financial interests.

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21. Crystallographic data for (+)-bulleyanaline **5** (CDCC 1943965) has been deposited at the Cambridge Crystallographic Data Centre.

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