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Unified Approach to the Spiro(pyrrolidinyl-oxindole) and Hexahydropyrrolo[2,3-*b*]indole Alkaloids: Total Syntheses of Pseudophrynamines 270 and 272A

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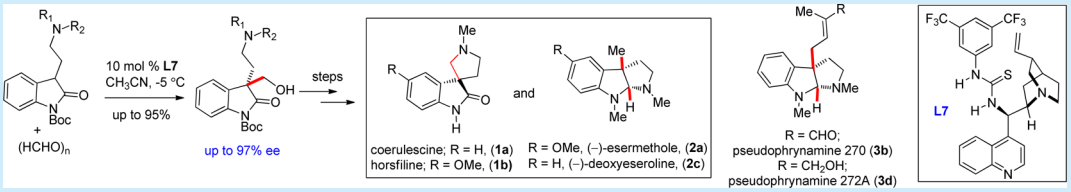
Supporting Information



ABSTRACT: The first enantioselective total syntheses of architecturally interesting prenylated pyrroloindole alkaloids, (−)-pseudophrynamines 272A (**3d**) and 270 (**3b**), have been achieved starting from enantioenriched 2-oxindoles having all-carbon quaternary stereocenters. A common strategy involving a thio-urea catalyzed aldol reaction is employed for the total synthesis of both spiro(pyrrolidinyl-oxindole) and hexahydropyrrolo[2,3-*b*]indole alkaloids.

Architecturally intriguing spiro(pyrrolidinyl-oxindole) alkaloids such as coerulescine (**1a**, Figure 1) and horsfiline (**1b**),

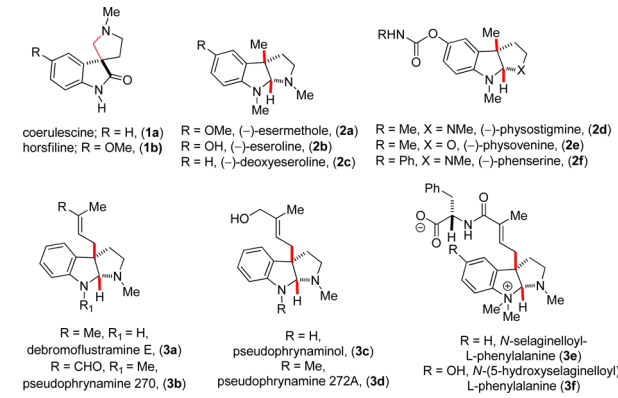


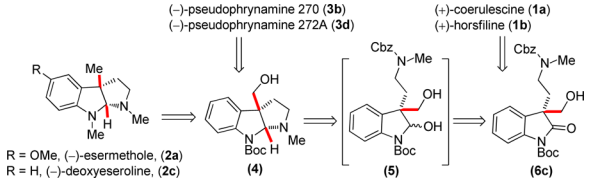
Figure 1. Selected pyrroloindoline and spiro-pyrroloindole alkaloids.

owing to the presence of the all-carbon quaternary stereocenters,[1] pose a great synthetic challenge. They were isolated from *Pharalis coerulescens*[2] in 1998 and *Horsfieldia superba*[3] in 1991, respectively, and since then, a number of efficient strategies for the construction of such quaternary stereogeniccenters were developed.[4] The hexahydropyrrolo[2,3-*b*]indole alkaloids (**2**−**3**, Figure 1), on the other hand, are frequently found in a range of natural alkaloids,[5] numerous marketed drugs, and drug candidates.[6] One of the congeners of this family, physostigmine (**2d**), isolated from the African Calabar bean seeds,[7] *Physostigma venenosum*,[8] displays huge biological activities. In fact, its therapeutic properties for the treatment of Alzheimer's disease, glaucoma, and myasthenia gravis[7,9] account for numerous synthetic reports for the synthesis of esermethole (**2a**) and physostigmine (**2d**).[10]

Hexahydropyrrolo[2,3-*b*]indole alkaloids (**3a**−**3f**, Figure 1) having a prenyl moiety adjacent to the pseudobenzylic **3a**-site, viz. flustramines,[11] pseudophrynamines,[12] and sellaginellic acid,[13] have gained considerable attention owing to their potential biological activities. Biosynthetically, these alkaloids are believed to be originated from L-tryptophan.[12] Although there are a few reports on diastereoselective approaches to access these moieties,[14] efficient enantioselective approaches to these targets still need to be addressed.[15]

Intrigued by their challenging structural arrays and impressive biological activities, we envisioned a unified approach to these targets in an asymmetric fashion. Retrosynthetically, we imagined that enantioenriched compound **6c** could serve as an advanced intermediate for the total syntheses of spiro(pyrrolidinyl-oxindole) alkaloids, coerulescine (**1a**) and horsfiline (**1b**), and hexahydropyrrolo[2,3-*b*]indole alkaloids, (−)-esermethole (**2a**) and (−)-deoxyeseroline (**2c**) (Scheme 1). Additionally, total syntheses of C-**3a** prenylated alkaloids,

Scheme 1. Our Retrosynthetic Analysis



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(−)-pseudophrynamines 270 (**3b**) and 272A (**3d**), could easily be achieved from a pyrroloindoline intermediate **4** (Scheme 1). We thought to access enantioenriched **6c** from 3-substituted 2-oxindole **8c** following a Dynamic Kinetic Asymmetric Transformation (DYKAT)[16] involving a hydroxymethylation reaction using paraformaldehyde as the C1 unit,[17] in the presence of a suitable bifunctional thio-urea ligand.

At the outset, enantioselective organocatalytic hydroxymethylations of 2-oxindoles **7a** and **7b** were carried out using paraformaldehyde in the presence of ligand **L1** (Figure 2).

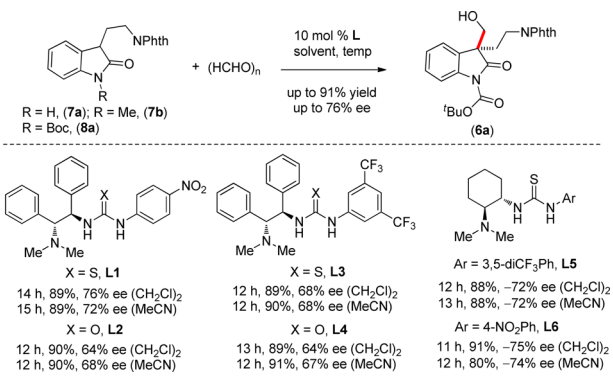


Figure 2. Optimization of aldol reaction of (±)-**8a** in the presence of TU-catalysts.

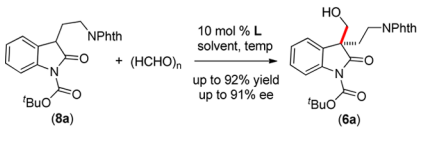
However, the reaction was not successful, and we imagined that the pH of the methine proton in **7a**−**b** might be responsible for this failure. To circumvent this, we changed the protecting group to an electron-withdrawing Boc-group which may enhance the acidity of the methine proton[10i,18] sufficiently by allowing a facile enolization of compound **8a**. We then carried out the reaction with **8a** using paraformaldehyde and in the presence of ligands **L1**−**L6** (Figure 2). The reactions were performed in dichloroethane and acetonitrile as solvent at room temperature. The product was formed in a maximum 76% enantioselectivity when 10 mol % of thio-urea **L1** was used as catalyst (Figure 2). Among other ligands used, **L5**[19] and **L6** were also found to be promising in affording product **6a** in the range 72−75% ee.

We then attempted the hydroxymethylation of **8a** in the presence of other ligands **L7**[20] and **L8** at 25 °C in the presence of dichloroethane and acetonitrile (Table 1). The reaction afforded 78% ee (entry 1) in dichloroethane using **L7**, whereas using **L8** afforded product in just 46% ee (entry 3). Solvent screening showed acetonitrile to be the best solvent, furnishing the product in up to 81% ee at 25 °C (entry 2). However, other solvents such as dichloromethane, chloroform, acetone, ethyl acetate, and tetrahydrofuran were not good for this reaction, affording products in the 35−71% ee range (entries 5−9). Ligand loading of 5 mol % yielded the product in 77% ee (entry 10).

Hydroxymethylation of **8a** was further studied in the presence of **L7** at different temperatures, and it was found that lower temperatures led to higher enantioselection with a maximum of 91% ee at −5 °C (Table 1, entry 15). Bifunctional thio-urea ligands **L9**−**L11** in acetonitrile at −5 °C afforded enantioenriched product **6a** in 85% ee, −87% ee, and −83% ee, respectively (Figure 3). Exhaustive optimization studies eventually led us to choose 10 mol % of **L7** in acetonitrile for asymmetric hydroxymethylation of **8a** with paraformaldehyde in acetonitrile at −5 °C.

We then looked for a substrate scope with a wide range of 2-oxindoles **8a**−**h**. All these substrates underwent a smooth

Table 1. Optimization of Aldol Reaction of (±)-8a



entry	catalyst	solvent	temp	time	yield (%) (**6a**)	% ee
1	10 mol % **L7**	$ClCH_2CH_2Cl$	25 °C	10 h	89%	78%
2	10 mol % **L7**	CH_3CN	25 °C	10 h	92%	81%
3	10 mol % **L8**	$ClCH_2CH_2Cl$	25 °C	11 h	90%	46%
4	10 mol % **L8**	CH_3CN	25 °C	12 h	92%	76%
5	10 mol % **L7**	CH_2Cl_2	25 °C	10 h	91%	68%
6	10 mol % **L7**	$CHCl_3$	25 °C	10 h	90%	35%
7	10 mol % **L7**	acetone	25 °C	20 h	86%	70%
8	10 mol % **L7**	EtOAc	25 °C	22 h	81%	66%
9	10 mol % **L7**	THF	25 °C	20 h	82%	71%
10	5 mol % **L7**	CH_3CN	25 °C	18 h	65%	77%
11	10 mol % **L7**	CH_3CN	0 °C	20 h	90%	85%
12	10 mol % **L7**	acetone	0 °C	22 h	81%	54%
13	10 mol % **L7**	CH_2Cl_2	0 °C	20 h	90%	73%
14	10 mol % **L7**	$(CH_2)_2Cl_2$	0 °C	20 h	89%	71%
15	10 mol % **L7**	CH_3CN	-5 °C	30 h	88%	**91%**

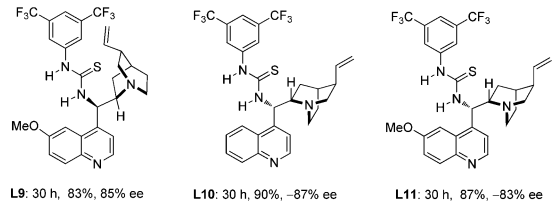


Figure 3. Optimization of aldol reaction of (±)-**8a** in the presence of TU-catalysts.

reaction to afford a variety of products **6a**−**h** in excellent yields with up to 97% ee (in the case of **6h**) (Figure 4). Interestingly, the TBS-protected hydroxyethyl group at the 3-position of 2-oxindoles (**8i** and **8l**) was also found to be a good aldol donor, furnishing products having an all-carbon quaternary stereocenters **6i** and **6l** in excellent yields and up to 95% ee. Also, an

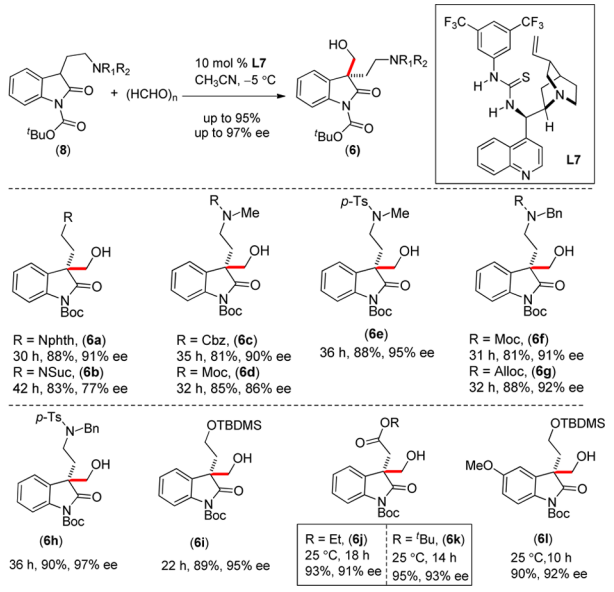


Figure 4. Substrates scope of TU-catalyzed hydroxymethylation.

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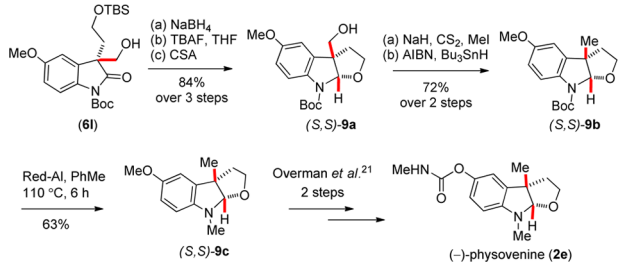
alkyl acetate group at the 3-position of 2-oxindoles (**8j** and **8k**) also proved to be good aldol donors, to afford products **6j** and **6k** in excellent yields in up to 93% ee (Figure 4).

Starting from the enantioenriched compound **6l**, we carried out the formal total synthesis of (−)-physovenine **2e** in a few steps (Scheme 2). First, we converted compound **6l** to advanced

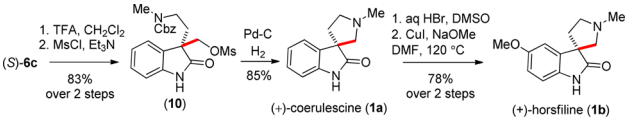
Scheme 2. Formal Synthesis of (−)-Physovenine (2e)



intermediate [6,5,5]-tricyclic core **9a** in 3 steps, which on subsequent deoxygenation afforded furoindoline intermediate **9b** (Scheme 2). The latter was then reduced in refluxing toluene to afford **9c** from where the synthesis of physovenine (**2e**) was already reported;[21] thus, our efforts led to the formal total synthesis of this alkaloid (Scheme 2).

Further, starting from compound **6c** as potential intermediate, we then turned our attention toward the total syntheses of alkaloids, (+)-coerulescine (**1a**) and (+)-horsfiline (**1b**). Compound **6c** was treated with trifluoroacetic acid to get oxindole which was further reacted with methanesulfonyl chloride to afford mesylate (+)-**10** in 83% yield over 2 steps (Scheme 3). The latter was then converted to naturally occurring

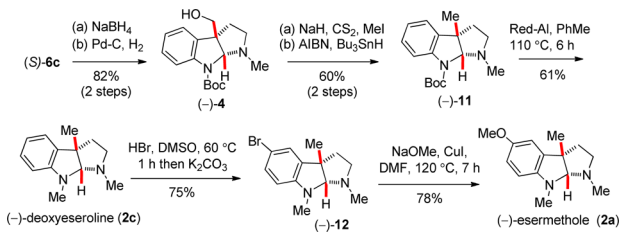
Scheme 3. Total Syntheses of (+)-Coerulescine (1a) and (+)-Horsfiline (1b)



(+)-coerulescine (**1a**) in 85% yield when subjected to catalytic Pd−C in ethanol (1 atm of H_2). Further, (+)-**1a** was treated with aqueous HBr in DMSO to furnish 5-bromo coerulescine in 93% yield (see Supporting Information for details), which was further treated with NaOMe in the presence of catalytic CuI to complete the total synthesis of (+)-horsfiline (**1b**) in 84% yield (78% over 2 steps from **1a**) (Scheme 3).

We further elaborated **6c** for the total synthesis of hexahydropyrrolo[2,3-*b*]indole alkaloids, deoxyeseroline (**2c**) as well (Scheme 4). 2-Oxindole **6c** was treated with $NaBH_4$ followed

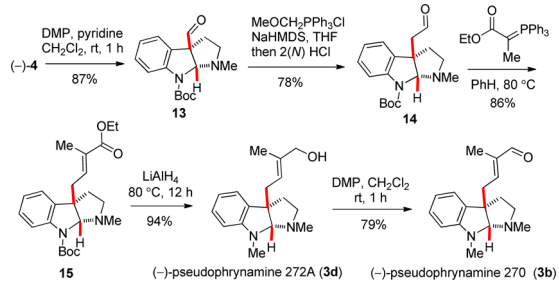
Scheme 4. Total Syntheses of (−)-Deoxyeseroline (2c) and (−)-Esermethole (2a)



by hydrogenolysis in the presence of catalytic Pd−C in ethanol (1 atm of H_2) to furnish [6,5,5]-tricyclic core (−)-**4** (Scheme 4). The latter on deoxygenation afforded pyrroloindoline intermediate (−)-**11** in 60% overall yield in 2 steps. (−)-**11** was further reduced with Red-Al in refluxing toluene to complete the total synthesis of (−)-deoxyeseroline (**2c**) in 61% yield (Scheme 4). Further, (−)-**2c** was treated with aqueous HBr (in DMSO) in ethyl acetate to afford 5-bromo compound (−)-**12** in 75% yield, which on subsequent treatment with NaOMe in the presence of catalytic CuI completed the total synthesis of (−)-esermethole (**2a**) in 78% yield (Scheme 4). This completed the formal total syntheses of pyrroloindoline alkaloids, physostigmine (**2d**)[10f,i] and phenserine (**2f**),[10k] from **2a** (Scheme 4).

Further, we were interested for the total syntheses of C-3a prenylated hexahydropyrrolo[2,3-*b*]indole alkaloids, (−)-pseudophrynamines 270 (**3b**) and 272A (**3d**). For this, a Dess-Martin periodinane (DMP) oxidation of compound (−)-**4** (Scheme 5)

Scheme 5. Total Syntheses of (−)-Pseudophrynamines 272A (3d) and 270 (3b)



afforded aldehyde **13**, which on subsequent homologation furnished advanced key intermediate **14** in 68% overall yield in 2 steps (Scheme 5). Next, the aldehyde **14** was treated with stabilized Wittig reagent to afford *α,β*-unsaturated ester **15** in 86% yield, which on subsequent treatment with $LiAlH_4$ simply completed the first total synthesis of (−)-pseudophrynamine 272A (**3d**) without event. Alkaloid (−)-**3d** was further oxidized with DMP to complete the first total synthesis of (−)-pseudophrynamine 270 (**3b**) as well (Scheme 5).

The stereochemical rationale for our hypothesized catalytic aldol process following a DYKAT phenomenon in the presence of thio-urea ligand **L7** is shown in Figure 5. It has been proposed

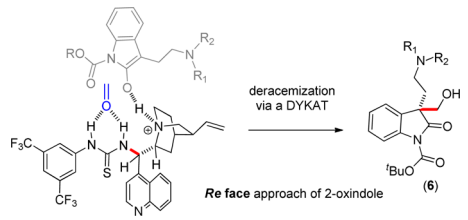


Figure 5. Stereochemical rationale.

that if the enolate of **8** can establish H-bonding with ligand **L7** and activate the nucleophile, **8**, and electrophile (formaldehyde), favorable stereoselectivity could be obtained *via* the *Re*-face approach of 2-oxindole leading to the formation of enantioenriched hydroxyl methylated product **6** (Figure 5).

In conclusion, we achieved the total syntheses of spiro(pyrrolidinyl-oxindole) alkaloids, (+)-coerulescine (**1a**) and (+)-horsfiline (**1b**), and hexahydropyrrolo[2,3-*b*]indole alkaloids, (−)-deoxyeseroline (**2c**) and (−)-esermethole (**2a**),

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sharing an all-carbon quaternary stereocenter in a highly efficient manner applying a unified enantioselective approach. In addition, the aforementioned strategy was also utilized for the first total syntheses of (−)-pseudophrynamines 272A (**3d**) and 270 (**3b**).

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b03082.

General experimental procedures and analytical data (PDF)

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Notes

The authors declare no competing financial interest.

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