

Formal Syntheses of (–)- and (+)-Phalarine**

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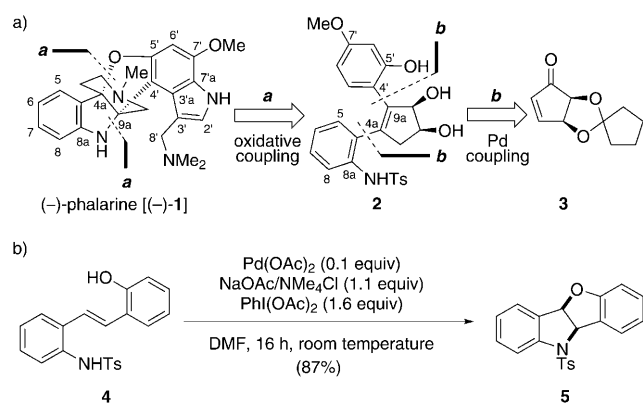
Careful assessment of the chemical constituents in vegetation is a critical process to ensure the safety of livestock. In a recent chemical investigation of the perennial grass *Phalaris coerulescens*, Colegate and co-workers reported the isolation and structural elucidation of a novel furanobisindole alkaloid that they subsequently named (–)-phalarine [(–)-1, Scheme 1 a].^[1] Although the toxicity effect of this new class

tion, which then evolved into an effective hypervalent iodine mediated oxidative cyclization process.

A cursory inspection of the molecular structure of (–)-phalarine [(–)-1] immediately revealed its central heterocyclic framework containing the C4a–O and C9a–N linkages and the C4a and C9a quaternary centers as the most daunting challenges in our foreseeable synthetic campaign (Scheme 1 a; bond formations *a*). With a cascade process in mind,^[3] we were inspired by a recent report from the Muniz group who had demonstrated a highly efficient palladium-catalyzed oxidative coupling reaction engaging phenolic tosylamide **4** to furnish the fused indoline dihydrobenzofuran tetracycle **5** in 87% yield (Scheme 1 b).^[4] The structural relationship between (–)-1 and tetracycle **5** was immediately apparent, therefore, retrosynthetically, the targeted molecule (–)-1 can be traced back to phenolic tosylamide **2** (accessed through bond formations *b*) that can undergo a late-stage expansion of its diol-containing cyclopentane ring to install the *N*-methyl piperidine moiety of (–)-1. Finally, the optically active and readily accessible cyclopentenone **3**^[5] was envisaged to provide traceless transfer of chirality to the C4a and C9a stereogenic centers.

As shown in Scheme 2, realization of the synthetic strategy commenced with an iodination of the optically pure cyclopentenone **3**^[5] to give the 2-iodo enone **6** in 64% yield. Stille^[6] cross-coupling between the iodide **6** and aryl stannane **7**^[6b] afforded 2-aryl enone **8**, which was then subjected to 1,4-reduction using K-selectride to furnish the α -aryl ketone **9** in 86% yield as an inconsequential mixture of diastereoisomers (ca. 11:1). The attachment of the second aryl unit onto **9** was carried out under the Suzuki–Miyaura^[7] conditions through the intermediacy of the triflate **10** and boronic acid **11** to deliver cyclopentene **12** in 83% yield. Conversion of the nitro functionality within **12** into the corresponding tosylamide took place uneventfully, through hydrogenation and subsequent tosyl protection of the aniline intermediate **13**; the tosylamide **14** was isolated in 94% yield over the two steps. In preparation for the crucial oxidative double cyclization to cast the indoline dihydrobenzofuran core of (–)-1, the BOM-protected phenolic hydroxy group within **14** was liberated under hydrogenolysis conditions to furnish the phenolic tosylamide **15** in 87% yield.

In accordance to the conditions reported by Muniz,^[4a] indeed, substrate **15** underwent palladium-catalyzed oxidative double cyclization to afford the targeted phalarine framework as a mixture of diastereoisomers (**16/16'** ca. 1.4:1), despite the disappointing 12% yield (Table 1, entry 1). With this initial result in hand, we set out to optimize this key reaction and our findings are summarized in Table 1. Changing the source of the oxidant from a hypervalent-iodine-based reagent (PIDA) to CuBr₂ (entry 2) or molecular oxygen (entry 3) had no beneficial effect on the



Scheme 1. a) Molecular structure of (–)-phalarine [(–)-1] and retrosynthetic analysis leading to **2** and **3**. b) Palladium-catalyzed tandem C–N and C–O bond formation reported by Muniz^[4a] leading to **5**. DMF = *N,N*-dimethylformamide, Ts = toluenesulfonyl.

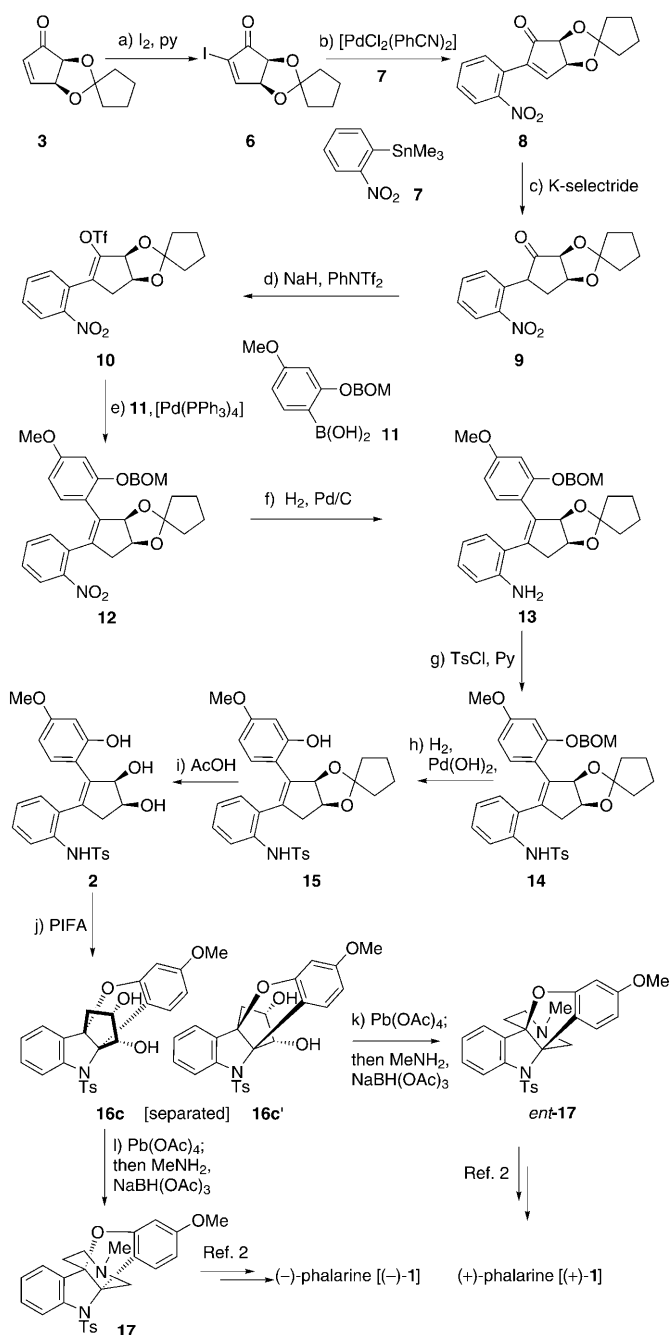
of indole alkaloid is yet to be established, the intricate molecular architecture of (–)-phalarine [(–)-1] presents an enticing challenge to the synthetic community and an opportunity to showcase the modern synthetic technologies and strategies. Indeed, the Danishefsky group was the first to accomplish this feat with an ingenious and highly instructive approach to access **1** in its racemic form.^[2b,c] The same group subsequently formulated a strategy based on a traceless transfer of chirality from *L*-tryptophan to achieve an asymmetric synthesis.^[2d] Herein we report the formal synthesis of both (–)-1 and (+)-1 by using an approach inspired by a palladium-catalyzed carbon–heteroatom bond-forming reac-

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reaction. However, we were pleasantly surprised to find that the oxidative double cyclization also took place in the absence of the palladium catalyst, giving a diastereomeric mixture of **16** and **16'** (ca. 1.4:1) in 30% yield (entry 4). This finding subsequently channeled our interest and investigation to the hypervalent iodine mediated oxidative cyclization process.^[8] The use of the more reactive PIFA reagent led to a notable increase in the reaction yield (entry 5), but variation in the solvent (entries 6–10) and reaction temperature (entries 11 and 12) had little influence on either the yield or diastereoselectivity of the reaction. Other oxidants such as I_2 , *N*-iodosuccinimide, ceric ammonium nitrate, Ag_2O , $Pb(OAc)_4$,

Scheme 2. Formal syntheses of (–)- and (+)-phalarine [(–)- and (+)-**1**]. Reagents and conditions: a) I_2 (1.5 equiv), py (2.0 equiv), 4-DMAP (0.2 equiv), CH_2Cl_2 , 25 °C, 3 h, 64%; b) **7** (1.2 equiv), $[PdCl_2(PhCN)_2]$ (0.05 equiv), $AsPh_3$ (0.1 equiv), CuI (0.1 equiv), NMP, 70 °C, 2.5 h, 63%; c) K-selectride (1.0 M in THF, 1.5 equiv), THF, 5 °C, 15 min, 86% (ca. 11:1 mixture of diastereoisomers by 1H NMR); d) NaH (60% wt/wt, 2.0 equiv), $PhNTf_2$ (1.5 equiv), DMF, 0 °C, 3 h, 90%; e) **11** (1.5 equiv), $[Pd(PPh_3)_4]$ (0.1 equiv), Na_2CO_3 (6.6 equiv), THF/ H_2O (5:1), 70 °C, 2.5 h, 83%; f) H_2 , Pd/C (10% wt/wt, 0.49 equiv), EtOH, 25 °C, 1.5 h; g) TsCl (2.0 equiv), py (10.0 equiv), CH_2Cl_2 , 25 °C, 12 h, 94% over two steps; h) H_2 , Pd(OH)₂ (20% wt/wt, 0.93 equiv), EtOAc, 25 °C, 1.5 h, 87%; i) AcOH/ H_2O (4:1), 25 °C, 20 h, 63% (75% brsm); j) PIFA (1.2 equiv), CH_2Cl_2 , –5 → 0 °C, 30 min, 68% (ca. 9:1 mixture of diastereoisomers by 1H NMR); k) $Pb(OAc)_4$ (1.5 equiv), NaHCO₃ (6.0 equiv), CH_2Cl_2 , 0 °C, 15 min, filtered and concentrated; then MeNH₂ (1.0 M in THF, 7.8 equiv), NaBH(OAc)₃ (5.0 equiv), AcOH (0.1 equiv), 1,2-dichloroethane, 25 °C, 48 h, 73%; l) $Pb(OAc)_4$ (1.5 equiv), NaHCO₃ (6.0 equiv), CH_2Cl_2 , 0 °C, 15 min, filtered and concentrated; then MeNH₂ (1.0 M in THF, 7.8 equiv), NaBH(OAc)₃ (5.0 equiv), AcOH (0.1 equiv), 1,2-dichloroethane, 25 °C, 48 h, 71%. 4-DMAP = 4-dimethylaminopyridine, BOM = benzyloxy methyl, K-selectride = potassium tri-*sec*-butylborohydride, NMP = *N*-methyl-2-pyrrolidone, PIFA = phenyliodine-bis-trifluoroacetate, py = pyridine, Tf = trifluorosulfonyl, Ts = toluenesulfonyl, brsm = based on recovered starting material.

and $K_3[Fe(CN)_6]$ proved ineffective for this process, but interestingly, the use of DDQ at elevated temperature gave **16'** as the sole product in 21% yield (entry 13). Since the variation in the reaction conditions had little effect on the productivity and diastereoselectivity of the oxidative double cyclization process, we turned our attention to alternative phenolic tosylamide substrates to seek additional improvements. We speculated that the steric environment around the secondary alcohols residing on the cyclopentene ring may have an influence on the diastereoselectivity of the cyclization reaction. Indeed, whereas the acetonide **15a**^[9] and TBS ether **15b**^[9] showed little affect on the diastereoselectivity of the reaction (entries 14 and 15), the diol **2** (prepared from deketalization of **15**, AcOH, 63% yield, 75% yield brsm) displayed a significantly improved diastereoselectivity in favor of the *syn* isomer (**16c**/**16c'** ca. 3:1). Changing the solvent from CH_3CN to CH_2Cl_2 and performing the reaction at –5 → 0 °C ultimately led to a 9:1 diastereoselectivity (entry 17). Stereoisomerically pure diols **16c** and **16c'** were independently elaborated into the piperidines **17** and *ent*-**17**, respectively, through a two-step procedure involving oxidative diol cleavage and double reductive amination (Scheme 2). All physical characteristics of the pentacycle **17** were identical to those reported by the Danishefsky group,^[2d] a key intermediate en-route to their asymmetric total synthesis of (–)-phalarine [(–)-**1**]. Thus, the successful preparation of **17** and *ent*-**17** constitute an asymmetric formal synthesis of (–)-phalarine [(–)-**1**] and (+)-phalarine [(+)-**1**], respectively.

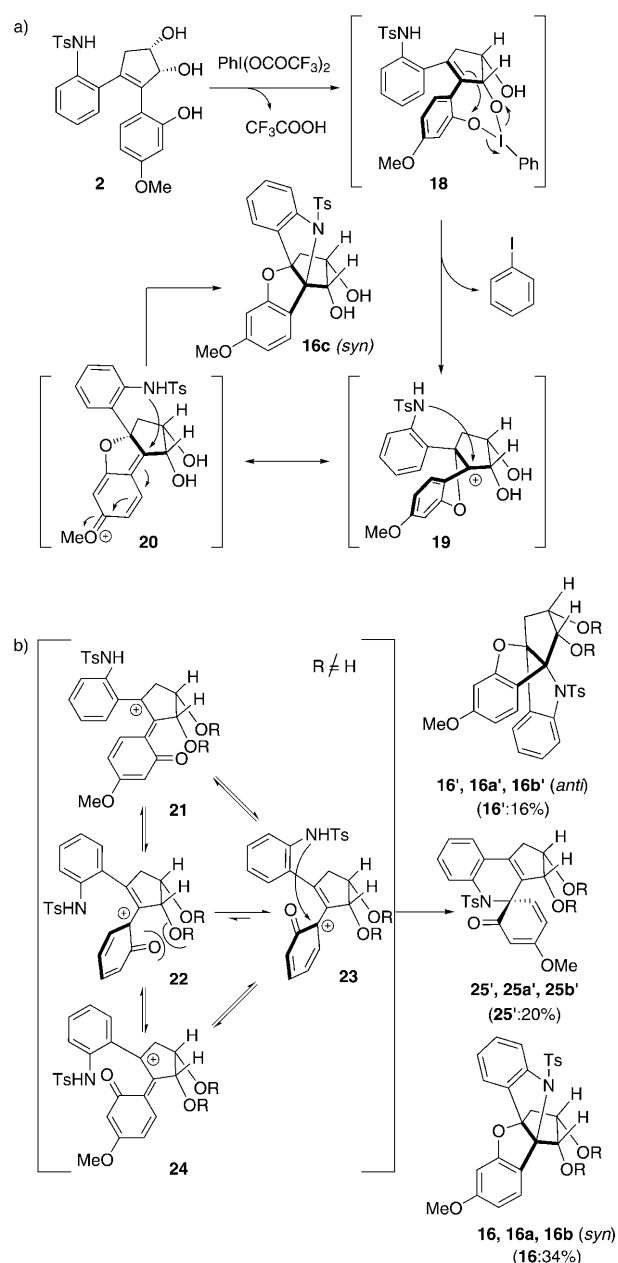
Next, a working model was put forward to rationalize the diastereoselectivities observed for the hypervalent iodine mediated, oxidative double cyclization of the phenolic tosylamides **15**, **15a**, **15b**, and **2** (Scheme 3). We hypothesized that in the presence of free secondary alcohols (e.g., **2**), $PhI(OCOCF_3)_2$ is likely to form a chelated species as depicted

Table 1: Oxidative double cyclizations of phenolic tosylamides **15–15b** and **2**.

Entry	Sub.	Conditions	Product	Yield [%] ^[a]	syn/anti ^[b]
1	15	Pd(OAc) ₂ (0.2 equiv), PIDA (1.5 equiv), CH ₂ Cl ₂ , 25 °C, 15 min	12	12	1.4:1
2	15	Pd(OAc) ₂ (0.2 equiv), CuBr ₂ (2.0 equiv), K ₂ CO ₃ (1.1 equiv), CH ₂ Cl ₂ , 25 °C, 48 h	10	10	1:1
3	15	Pd(OAc) ₂ (0.2 equiv), O ₂ (1 atm), NaOAc (1.1 equiv), DMF, 25 °C, 24 h	N.D.	N.D.	–
4	15	PIDA (1.5 equiv), CH ₂ Cl ₂ , 25 °C, 15 min	30	30	1.4:1
5	15	PIFA (1.5 equiv), CH ₂ Cl ₂ , 25 °C, 15 min	40	40	1.4:1
6	15	PIFA (1.5 equiv), CH ₃ CN, 25 °C, 10 min	45	45	1.4:1
7	15	PIFA (1.5 equiv), CH ₃ CN/H ₂ O (20:1), 25 °C, 10 min	42	42	1.4:1
8	15	PIFA (1.5 equiv), CF ₃ CH ₂ OH, 25 °C, 15 min	N.D.	N.D.	–
9	15	PIFA (1.5 equiv), THF, 25 °C, 15 min	21	21	1:1
10	15	PIFA (1.5 equiv), toluene, 25 °C, 15 min	40	40	1:2
11	15	PIFA (1.5 equiv), toluene, –5 → 0 °C, 35 min	51	51	1:1.3
12	15	PIFA (1.5 equiv), CH ₃ CN, –5 → 0 °C, 30 min	54	54	2:1
13	15	DDQ (10 equiv), THF, 25 → 70 °C, 48 h	21	21	anti only
14	15a	PIFA (1.5 equiv), CH ₃ CN, –5 → 0 °C, 30 min	42	42	1.1:1
15	15b	PIFA (1. equiv), CH ₃ CN, –5 → 0 °C, 30 min	60	60	1.4:1
16	2	PIFA (1.1 equiv), CH ₃ CN, –5 → 0 °C, 15 min	46	46	3:1
17	2	PIFA (1.2 equiv), CH ₂ Cl ₂ , –5 → 0 °C, 30 min	68	68	9:1

[a] Yields refer to chromatographically and spectroscopically homogeneous materials. [b] Determined by ¹H NMR spectroscopic analysis of the crude reaction mixture. The ratios are approximate. DDQ=2,4-dichloro-5,6-dicyanobenzoquinone, N.D.=not detected.

by the intermediate **18**. As a result of this coordination, the phenol-containing aromatic ring is rotated away from planarity with the cyclopentene olefin. This loss of planarity and subsequent C–O bond formation with concomitant liberation of PhI generates the intermediate **19** and its resonance stabilized form **20**. Finally, C–N bond formation preferentially delivered the *syn*-isomer **16c** as a consequence of the initially formed coordinated species **18**. The enhancement in diastereoselectivity upon changing solvent from CH₃CN (Table 1, entry 16) to CH₂Cl₂ (entry 17) is also supportive of the formation of the chelated substrate/PIFA complex **18** in a nonpolar solvent. In contrast, the substrates **15**, **15a**, and **15b**

**Scheme 3.** Working model for the diastereoselectivity observed in the hypervalent iodine mediated oxidative double cyclization.

are likely to generate stabilized and equilibrating species (**21–24**) upon activation with PhI(OCOCF₃)₂. Sequential C–N and C–O bond formations in **21** and **24** then give rise to the *anti*-**16'**, *anti*-**16a'**, and *anti*-**16b'**, and *syn*-**16**, *syn*-**16a**, and *syn*-**16b** oxidative double cyclization products. A competing pathway leading to the formation of the spirocyclic dienone **25'** was also observed; presumably through the conformationally preferred dienone **23** wherein the electrostatic interaction is minimized.

In summary the asymmetric formal total syntheses of (–)- and (+)-phalarine [(–)- and (+)-**1**] have been accomplished. The developed synthetic sequence featured a modular assembly of the phenolic tosylamide **2**, and a hypervalent

iodine mediated oxidative double cyclization inspired by palladium (IV) chemistry. The synthetic strategy disclosed herein should find application beyond the synthesis of phalarine, and enable the preparation of rationally designed molecules having this privileged scaffold, for chemical and biological investigations. Furthermore, mechanistic studies and application of the hypervalent iodine mediated oxidative double cyclization is currently in progress.

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- [9] The acetonide **15a** and TBS ether **15b** were prepared from ketal **14** by a three-step procedure, involving deketalization, either acetonide formation (for **15a**) or TBS protection (for **15b**), and removal of the BOM ether. For details, see the Supporting Information.
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