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Synthesis of 3-hydroxy 2-oxindoles via deacylative oxygenation (DaO) : Total synthesis of CPC-1†

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Abstract : We report an efficient deacylative oxygenation strategy for the synthesis of a variety of 3-hydroxy 2-oxindoles that takes advantage of deacylative oxidation using oxygen gas as green source of oxidants via a *retro*-Claisen condensation. A wide variety of products could be synthesized under mild reaction conditions. The aforementioned methodology has been utilized for total synthesis of CPC-1.

Keywords : Deacylative oxygenation, *retro*-Claisen activation, oxygen gas, allylalkoxide, 3-hydroxy 2-oxindoles.

Introduction

Since they have coevolved with their putative biological targets, natural products intersect biological space effectively and perturb its function in a highly controlled manner[1]. It is not surprising that natural products have endured as promising leads for drug discovery. A rapid access to small molecules that are guided by natural products appears to be quintessential for the success of a chemical genetics/genomics-based program[2]. In this regard, synthesis of 2-oxindole frameworks have been experiencing a dramatic expansion and becoming a hot research area in contemporary organic chemistry due to their unique reactivity and capacity to construct complex chiral frameworks[3]. They are widely distributed in natural products[3,4] and have broad applications in the discovery of pharmaceutically important molecules[5]. Among various 2-oxindole natural products, donaxaridine (**1a**) and donaxarine (**1b**) were isolated from the giant reed *Arundodonax* in 1976 (Fig. 1)[6a-b]. Convolutamydine A-B (**2a-b**) and convolutamydine E (**2c**) were isolated from the Floridian marine bryozoan *Amathiaconvoluta* by Kamano and co-workers[6c]. A new dimeric alkaloid arundaphine (**3a**), was isolated from roots and rhizomes of *Arundodonax* (Poaceae family)[6d]. In the culture broth of the marine Streptomyces strain B 9173 two closely related, maremycin A (**3b**) and B (**3c**), were isolated in 1995[6e]. 2-Oxindole alkaloids, paratunamides A (**3d**) and D (**3e**), containing a secologanin unit, were isolated from *Cinnamodendronaxillare* (Nees at Mart.), belonging to Canellaceae family (local name paratude). In Brazil "paratude" is used as a stomachic and a treatment for tonsillitis[6f].

Further, pyrrolidinoindoline-type alkaloids such as alline (**4a**) and CPC-1 (**4b**) were also isolated from various sources[6g]. Madindolines A (**5a**) and B (**5b**) were isolated from the fermentation broth of *Streptomyces nitrosporeus* K93-0711, which are selective inhibitors of interleukin-6[6h] consisting of two portions such as a 3*a*-hydroxy furoindoline fragment and a substituted cyclopentenedione moiety. In this regard, 2-oxindoles intermediates have been utilized in the synthesis of many bioactive natural pro-ducts sharing pyrroloindoline scaffolds, such asalline (**4a**), CPC-1 (**4b**), flustraminol B (**6**)[7], and furoindoline scaffolds, such as madindolines A (**5a**) and B (**5b**) (Fig. 2)[8].

†**The work is dedicated to Late Professor Asima Chatterjee.**
Invited Lecture.

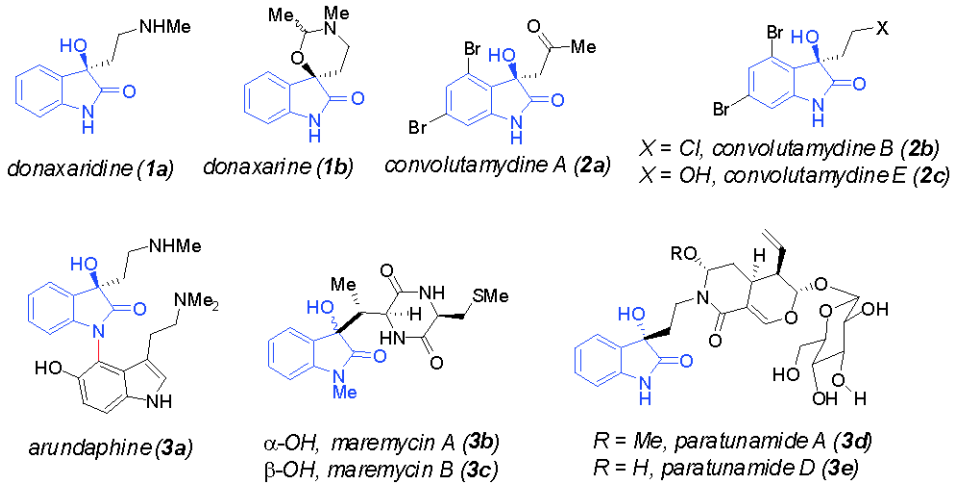


Fig. 1. Selected biologically active 3-hydroxy 2-oxindoles (**1-3**).

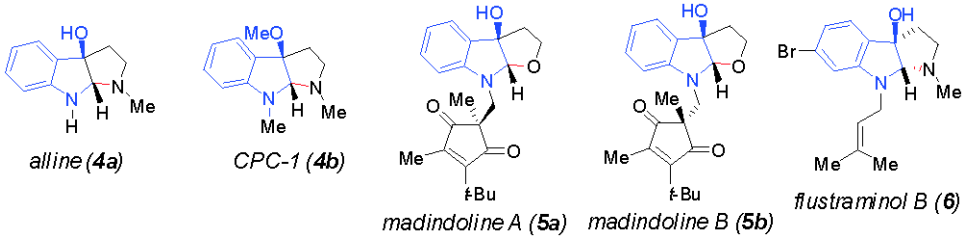


Fig. 2. Pyrroloindoline (**4a-b** and **6**) and furoindoline alkaloid **5**.

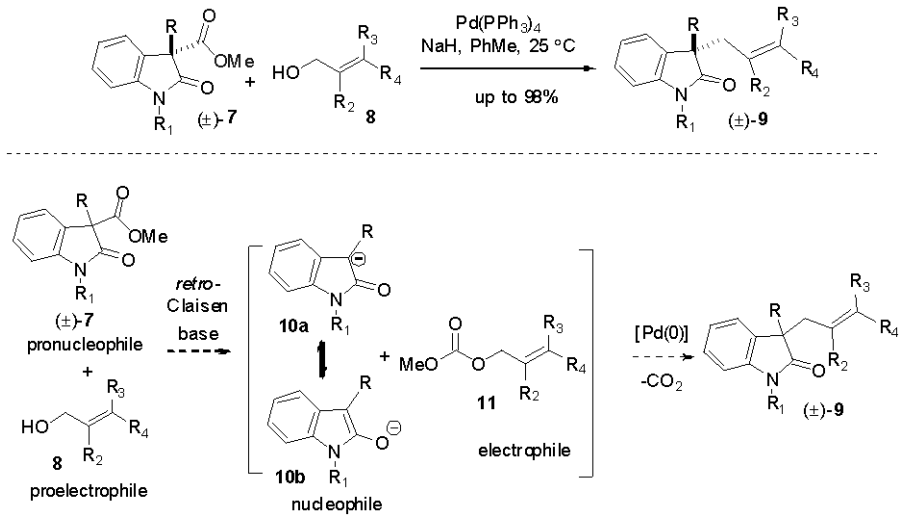
Further, 2-oxindoles have also served as potential intermediates for the synthesis of various 2-oxindole derivatives with C-3 quaternary center. Towards this, our group have explored Lewis acid catalyzed C-C bond forming reactions via Friedel-Crafts alkylations of 3-substituted 3-hydroxy 2-oxindole with various electron-rich aromatics[9], terminal alkynes[10], allylsilanes[11], acetophenones[12]. These reactions presumably go through *in situ* generation of reactive intermediate 2*H*-indol-2-one[13]. Owing to their therapeutic value, considerable efforts have been devoted to develop efficient methodology for the synthesis of 2-oxindoles[14] and indeed some elegant methologies have been reported to directly construct the 3-functionalized-3-hydroxy-2-oxindole framework[15].

Literature reports on the synthesis of 3-hydroxy 2-oxindoles include aldol reactions of ketones and aldehydes with isatins[16], metal-mediated 1,2-additions of carbon nucleophiles/equivalents[17]. Henry reaction of isatins with alkanes[18], the oxidation of 3-substituted indoles[19a-c] and 2-oxindoles[20], amino-oxygenation of 2-oxindoles[21]. There have been very few methods that can construct a 3-hydroxy 2-oxindole scaffold and bear a wide spectrum of functional groups at the C-3 position, *to the best of our knowledge*.

Results and discussion

Recently, we envisioned that an allylic alkoxide may induce a *retro*-Claisen condensation of an appropriately substituted 2-oxindole **7** to form allylmethyl carbonate **11** and an enolate **10b** as active intermediate via carbanion **10a** (Scheme 1)[22]. This enolate **10b** would then react with a Pd^{II}-π-allyl complex generated *in situ* by the reaction of allyl acetate **11** and Pd^0 to furnish various 2-oxindoles **9** with a quaternary center. A number of 2-oxindole scaffolds with a C-3 quaternary center have been synthesized utilizing aforementioned methodology (Scheme 1).

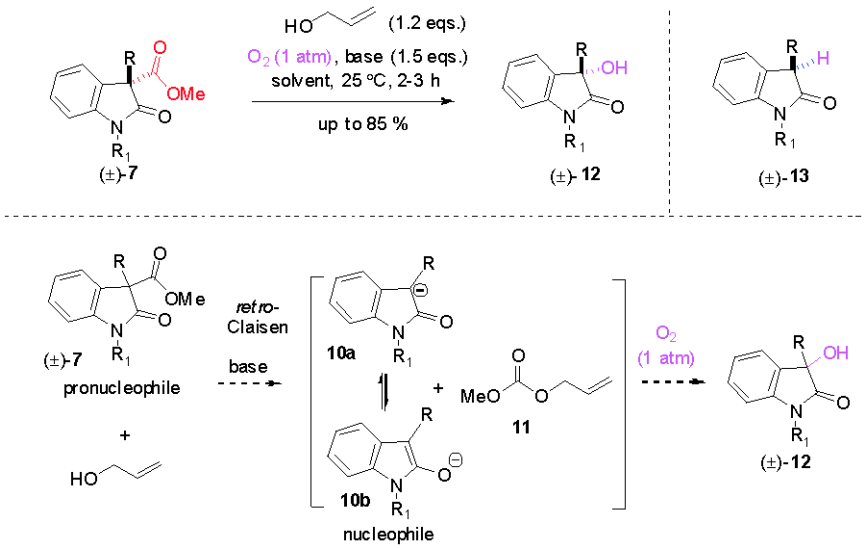
While working on this area, we have found that an efficient deacylative oxidation of 3-acyl-2-oxindoles



Scheme 1. Our report on Pd^0-catalyzed deacylative allylations for the synthesis of 2-oxindoles sharing C-3 quaternary center.

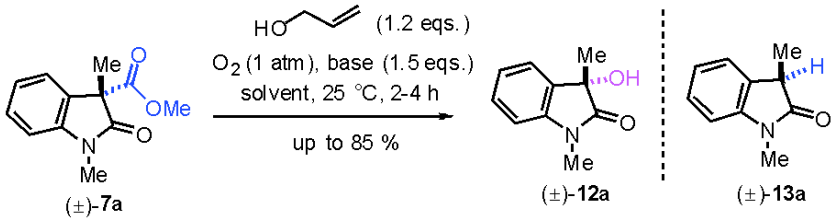
can be performed under O_2 atmosphere. We argued that, an allylalkoxide may induce a *retro*-Claisen condensation of an appropriately substituted 2-oxindole **7** to form enolate **10b** as active intermediate via carbanion **10a** (Scheme 2). This enolate **10b** would then react with oxygen gas as green source of oxidants to afford a number of 3-hydroxy 2-oxindoles. Herein, we report mild synthesis of 3-substituted 3-hydroxy 2-oxindole framework that takes advantage of deacylative oxidation using oxygen gas as green source of oxidants via a *retro*-Claisen condensation (Scheme 2).

Initially, optimization of deacylative oxygenation (DaO) was carried out with 1 equivalent of methyl 3-methyl *N*-methyl 2-oxindole 3-carboxylate **7a** (0.25 mmol) with 1.2 equivalent of allylalcohol (0.30 mmol) in the presence of 1.2 equivalent of different bases (0.30 mmol) under oxygen atmosphere (1 atm.) to afford 3-hydroxy *N*-methyl 2-oxindole **12a** (Table 1). It was found that we could isolate product **12a**, however, in combination with protonated 3-methyl *N*-methyl 2-oxindole **13a**. Clearly, compound **13a** was



Scheme 2. Deacylative oxygenation via *retro*-Claisen activation.

Table 1. Optimization of deacylative oxygenation (DaO) using oxygen gas as green source of oxidant



Sr. No.	Base (1.2 equiv.)	Solvent	Temp. (°C)	Time (h)	% Yield (**1a**)	% Yield (**13a**)
1.	Na_2CO_3	THF	25	2	23	63
2.	K_2CO_3	THF	25	3	15	62
3.	Cs_2CO_3	THF	25	3	18	71
4.	DBU	THF	25	4	27	52
5.	NaH	THF	25	3	38	44
6.	KO^{t}Bu	THF	25	3	29	41[c]
7.	NaH	THF	60	2	35	38
8.	KO^{t}Bu	THF	60	2	30	40
9.	NaH	PhMe	25	2	85	—
10.	KO^{t}Bu	PhMe	25	2	79	15
11.	NaH	DMSO	25	3	21	51
12.	NaH	DMF	25	4	32	49
13.	NaH	MeCN	25	3	70	17
14.	NaH	Et_2O	25	4	48	21
15.	NaH	CH_2Cl_2	25	3	42	18[c]
16.	NaH	$CHCl_3$	25	3	34	23[c]

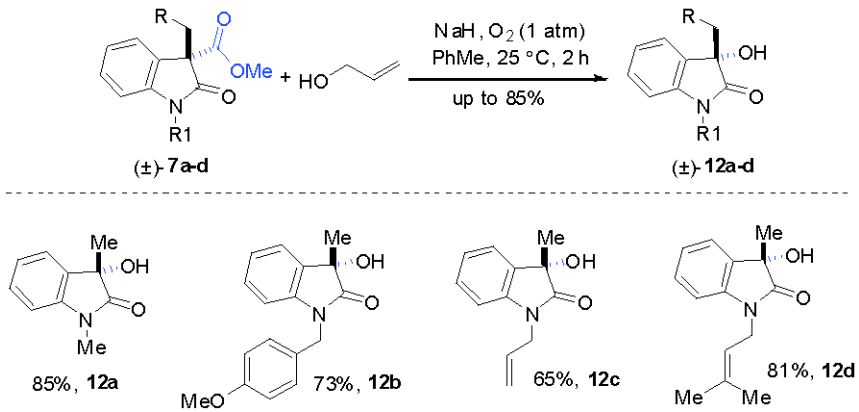
[a]Reactions were carried out using 0.5 mmol of **1a** (1 equiv.) with 0.6 mmol of base (1.2 equiv.) in 2 mL solvent under 1 atm. pressure of oxygen gas. [b]Isolated yields after column chromatography. [c]Decomposition of the rest of the mass balance.

observed because of incomplete oxidation, whereas protonation also encountered as byproduct. Therefore, various bases such as sodium carbonate, potassium carbonate, cesium carbonate, DBU, sodium hydride, and potassium *tert*-butoxide were employed for the oxidation via *retro*-Claisen condensation (entries 1–6).

Following exhaustive optimization, we observed that deacylative oxygenation (DaO) can be carried out with **7a** (0.25 mmol, 1 equiv.) in the presence of NaH or KO^{t}Bu[22] (1.2 equiv.) under oxygen atmosphere (1 atm.) to produce the desired 2-oxindole **12a** in 85% and 79% yields, respectively, at room temperature (entries 9–10). Further optimization using different solvents revealed that, toluene is superior over other solvents such as tetrahydrofuran, dimethyl sulfoxide, *N,N*-dimethyl formamide, acetonitrile, diethyl ether, dichloromethane, and chloroform (entries 11–16). Therefore, based on our optimization, 1.2 equivalent of NaH in toluene at room temperature was chosen as standard condition. This standard condition of deacylative alkylation (DaA) was applied to a variety of substrates.

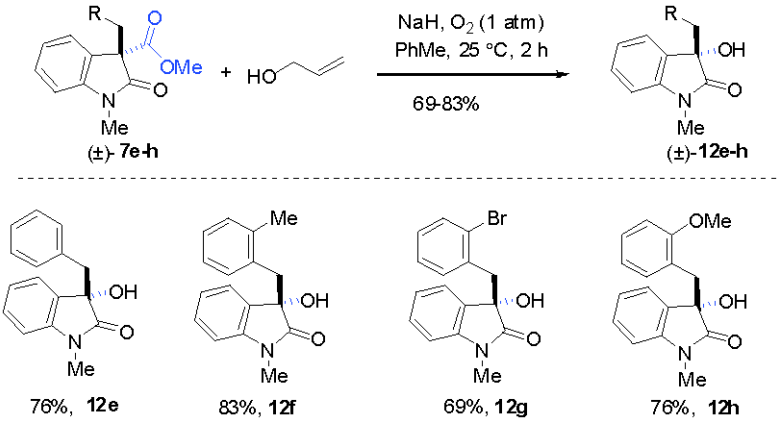
Under the optimized condition a variety of 3-methyl *N*-alkyl 2-oxindole 3-carboxylates such as *N*-methyl (**7a**), *N*-*p*-methoxybenzyl (**7b**), *N*-allyl (**7c**), and *N*-prenyl (**7d**) were utilized to afford a range of 3-hydroxy 2-oxindoles bearing hydroxyl group at the pseudobenzylic position (**12a-d**) in good yields (Scheme 3).

Further, a variety of methyl 3-benzyl *N*-methyl 2-oxindole 3-carboxylates such as 3-benzyl (**7e**), 3-(*o*-



[a]Reactions were carried out using 0.5 mmol of **7a-d** (1 equiv.) with 0.6 mmol of NaH (1.2 equiv.) in 2 mL of toluene under 1 atm. pressure of oxygen gas. [b]Isolated yields after column chromatography.

Scheme 3. Substrate scope of deacylative oxygenation of **7a-d**.



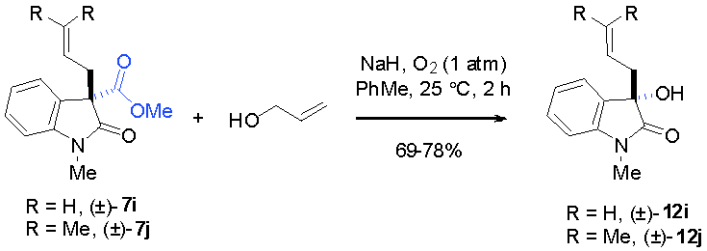
[a]Reactions were carried out using 0.5 mmol of **7e-h** (1 equiv.) with 0.6 mmol of NaH (1.2 equiv.) in 2 mL of toluene under 1 atm. pressure of oxygen gas. [b]Isolated yields after column chromatography.

Scheme 4. Further scope of deacylative oxygenation using **7e-h**.

methyl)benzyl (**7f**), 3-(*o*-bromo)benzyl (**7g**), and 3-(*o*-methoxy)benzyl (**7h**), were utilized to afford products **12e-h** in good yields (Scheme 4). Gratifyingly, challenging substrates like methyl 3-allyl/prenyl *N*-methyl 2-oxindole 3-carboxylates such as **7i-j** furnished products **12i-j** in 69–78% isolated yields (Scheme 5). Compounds **7i-j** are challenging in a sense that these are prone to undergo oxidation at the allylic position.

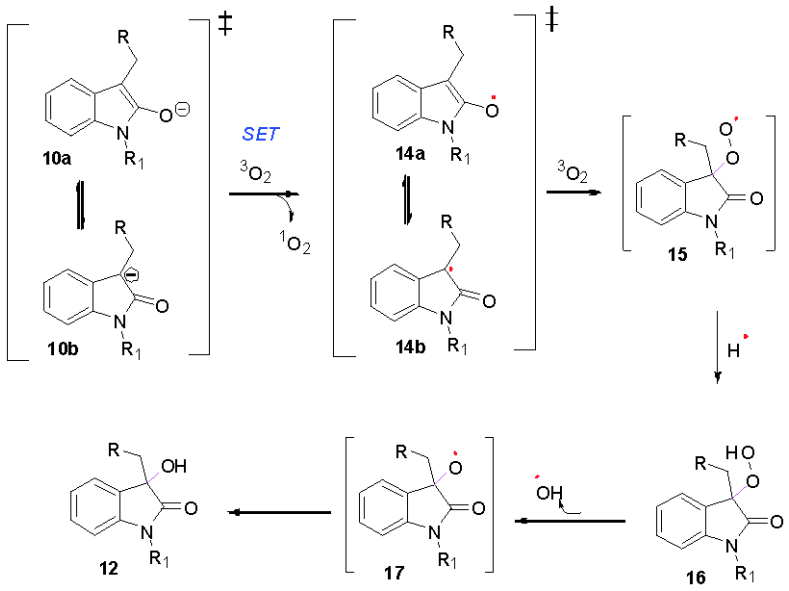
Mechanistically[23], an alkoxide may induce a *retro*-Claisen condensation of an appropriately substituted 2-oxindole **7** to form enolate **10b** as active intermediate via carbanion **10a** (see, Scheme 1). This enolate **10b** would then react with oxygen gas via a single electron transfer (SET) mechanism to afford a number of 3-hydroxy 2-oxindoles. Initially, a single electron transfer (SET) from carbanion **10b** could generate a 3° radical **14b**, which then stabilized as vinyloxy radical **14a**. This 3° radical would then react with singlet oxygen to generate a peroxy radical **15**, which could form peroxide **16** (Scheme 6). The later could release hydroxyl radical to generate *N*-alkyl 3-substituted 3-alkoxy radical **17**, which then afford product **12** by combination of hydrogen radical.

To illustrate the broad synthetic utility of this methodology, we undertook total synthesis of medicinally important compound CPC-1 (Fig. 2). Compound **12i** was methylated with methyl iodide in the presence of



[a]Reactions were carried out using 0.5 mmol of **7i-j** (1 equiv.) with 0.6 mmol of NaH (1.2 equiv.) in 2 mL of toluene under 1 atm. pressure of oxygen gas. [b]Isolated yields after column chromatography. [c]Decomposition of the rest of the mass balance.

Scheme 5. Deacylative oxygenation for the synthesis of **7i-j**.



Scheme 6. Proposed mechanism of deacylative oxygenation via a Single Electron Transfer (SET).

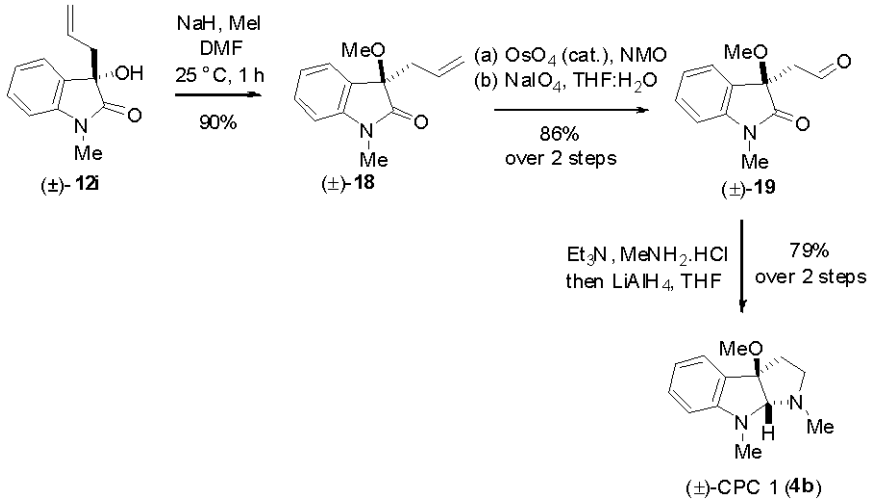
sodium hydride to afford **18** in 90% yield. Compound **18** was reacted with NMO in the presence of catalytic OsO_4 to afford diol, which was directly reacted with sodium meta periodate ($NaIO_4$) to affect oxidative degradation to furnish aldehyde **19** in 84% yields over 2 steps (Scheme 7). This aldehyde **19** was then reacted with methylamine hydrochloride salt in tetrahydrofuran to generate imine, which was reduced with lithium aluminum hydride to afford CPC-1 **4b** in 76% yields over 2 steps (Scheme 7).

In summary, we have developed efficient deacylative oxidation (DaO) for the synthesis of a variety of 3-substituted 3-hydroxy 2-oxyindoles **12** inspired by the "medicinal" scaffold of 3-substituted 3-hydroxy 2-oxindoles. This method relies on a deacylative oxidation (DaO) via a *retro*-Claisen condensation using oxygen gas as green source of oxidants. We have demonstrated the broad synthetic utility of our catalytic protocol in the efficient assembly of pharmaceutical important 3-hydroxy 2-oxindoles. As an application of this methodology, we have shown total synthesis of medicinally important compound CPC-1 (**4b**). Further applications of this catalytic strategy are underway and will be reported in due course.

Experimental

General procedure for 2-oxindole synthesis :

In a flame-dried seal tube allyl alcohol (0.55 mmol) was taken in toluene (2 mL) at room temperature. To this solution, NaH (60%, 0.60 mmol) was added at once, followed by 2-oxindole (0.5 mmol) under O_2



[a]All reactions were carried out using 0.2 mmol of starting material under nitrogen atmosphere. [b]Isolated yields after column chromatography.

Scheme 7. Total synthesis of naturally occurring pyrroloindoline alkaloid, CPC-1 (**4b**).

(balloon) 1 atm. The reaction mixture was stirred for 10 min. Upon completion the reaction (as judged by TLC analysis), it was quenched by adding few drops of water and extracted with EtOAc twice (6 mL×2). All organic extracts were collected and dried over $MgSO_4$ and concentrated under vacuo. The crude product was purified by flash chromatography on silica gel (30–40% EtOAc in n-hexane as eluent) to afford the desired product (±)-**12a-j**.

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Supporting Information

General experimental procedures, characterization data including ^1H NMR, ^{13}C NMR spectra of selected compounds. This material is available free of charge.

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