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# An iodine catalyzed metal free domino process for the stereoselective synthesis of oxygen bridged bicyclic ethers†

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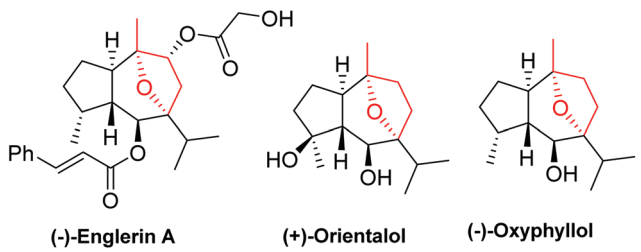
A domino reaction has been developed for the synthesis of oxygen bridged bicyclic ethers through the coupling of 4-(2-hydroxyethyl)cyclohex-3-enols with aldehydes in the presence of 10 mol% of molecular iodine in dichloromethane at 25 °C. This method is highly diastereoselective affording the corresponding bicyclic ethers, *i.e.* octahydro-4a,7-epoxyisochromenes in good yields with high selectivity. It is the first report on the synthesis of oxygen bridged bicyclic ethers using a domino Prins strategy.

## Introduction

An oxygen bridged bicyclic core (englerin) is frequently found in various natural products such as englerin, orientalol, oxyphyllol, saniculamoid A *etc*. (Fig. 1).[1]




(-)-Englerin A (+)-Orientalol (-)-Oxyphyllol

**Fig. 1** Representative examples for oxygen bridged oxabicycles.

They are known to exhibit promising cytotoxicity against renal cancer cell lines.[2] Of various oxygenated heterocycles, the tetrahydropyran ring is often present as a core structure of many biologically active natural products.[3] Therefore, several efforts have been made to develop efficient synthetic approaches for the synthesis of these heterocycles.[4]

Among them, Prins cyclization is one of the most reliable strategies for the construction of the tetrahydropyran ring system.[5,6] In particular, the Prins cascade is a highly convergent approach for the stereoselective synthesis of fused/bridged tetrahydropyran derivatives.[7,8] Besides its potential use in natural product synthesis,[9,10] the scope of this cascade process has not yet been explored for the synthesis of oxygen bridged oxabicycles from readily accessible aldehydes and 4-(2-hydroxyethyl)-1-methylcyclohex-3-enols. However, the development of a simple and metal-free approach for the construction of oxygen bridged oxabicycles using inexpensive and readily available reagents is well appreciated. Recently, molecular iodine has received considerable attention in organic synthesis because of its low cost and ready availability.[11] The mild Lewis acidity associated with iodine has enhanced its use in organic synthesis to perform several organic transformations using stoichiometric levels to catalytic amounts.[12]

Following our interest in the catalytic application of molecular iodine,[13] we herein report a metal-free approach for the synthesis of oxygen bridged oxabicycles from 4-(2-hydroxyethyl)-1-methylcyclohex-3-en-1-ol and aldehydes through a cascade of Prins cyclization. In a preliminary experiment, 4-(2-hydroxyethyl)-1-methylcyclohex-3-en-1-ol (**1**) was treated with 2,4,5-trifluorobenzaldehyde (**2**) in the presence of 10 mol% iodine in dichloromethane. To our delight, the reaction pro-

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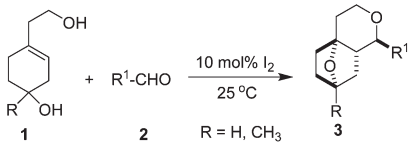
† Electronic supplementary information (ESI) available: Detailed procedures and spectroscopic data for novel compounds, and copies of $^{1}$H NMR and $^{13}$C NMR spectra of novel compounds prepared. CCDC 1048635. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c5ob00518c

**Table 1** Synthesis of oxygen bridged oxabicycles



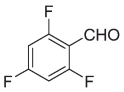
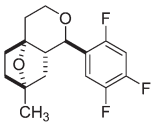
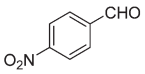
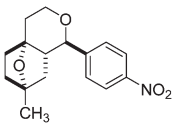
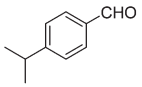
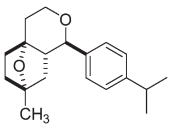
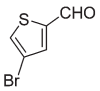
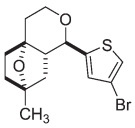
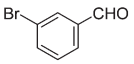
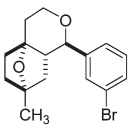
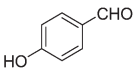
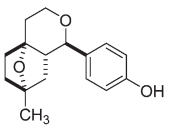
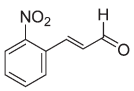
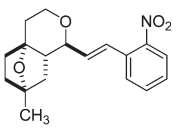
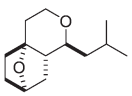
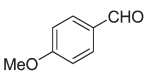
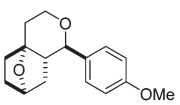
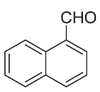
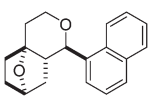
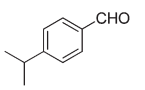
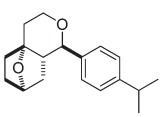
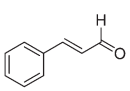
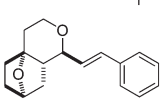
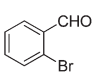
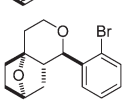
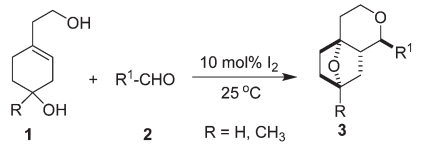
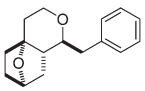
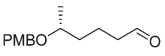
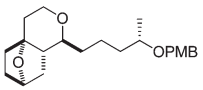
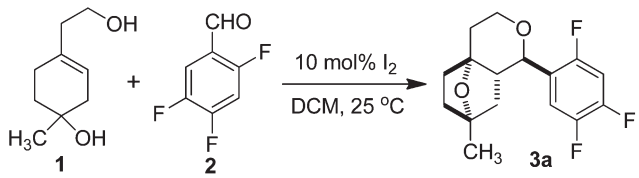

| Entry | Aldehyde (2) | Product[a] (3) | Time (h) | Yield[b] (%) |
|---|---|---|---|---|
| a |  |  | 4 | 82 |
| b |  |  | 4 | 80 |
| c |  |  | 4 | 79 |
| d |  |  | 4 | 82 |
| e |  |  | 3 | 80 |
| f |  |  | 3 | 69 |
| g |  |  | 4 | 80 |
| h |  |  | 2 | 78 |
| i |  |  | 4 | 70 |
| j |  |  | 3 | 80 |
| k |  |  | 4 | 78 |
| l |  |  | 5 | 76 |
| m |  |  | 3 | 73 |

**Table 1** *(Contd.)*




| Entry | Aldehyde (2) | Product[a] (3) | Time (h) | Yield[b] (%) |
|---|---|---|---|---|
| n |  |  | 4 | 72 |
| o |  |  | 5 | 80[c] |

[a] All products were characterized by NMR, IR and mass spectroscopy. [b] Yield refers to pure products after chromatography. [c] 9 : 1 ratio of diastereomers.




**Scheme 1** Cascade cyclization of endiol (**1**) with 2,4,5-trifluorobenzaldehyde (**2**).

ceeded smoothly at room temperature to afford the corresponding oxygen bridged bicyclic ether **3a** in 82% yield (entry a, Table 1) (Scheme 1).

The relative stereochemistry of compound **3a** has been derived by using 1D and 2D NMR experiments. The major nOe cross peaks are depicted in Fig. 2. The large scalar coupling constant between H1 and H2 ($^3J_{H1-H2}$ = 10.5 Hz) and the presence of the nOe cross peak between H1 and H5′ indicate that H1, H2 and H5′ protons are in the axial positions in the chair conformation as indicated in Fig. 2. The stereochemistry at C2, C3 and C7 was derived by the observation of nOe cross peaks between H1/H6′, H4′/H9, and H6′/H8 implying that the fused

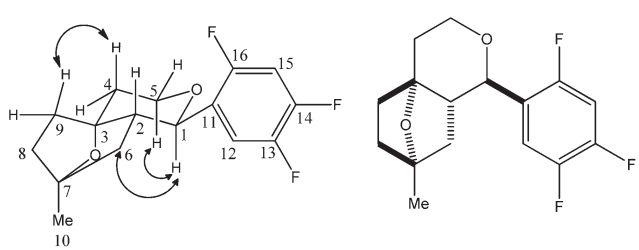



**Fig. 2** Characteristic nOe cross peaks of **3a**.

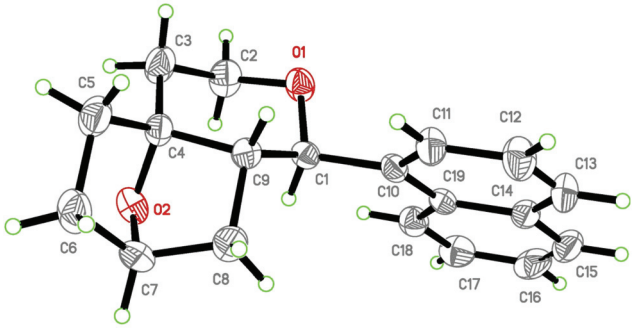



Fig. 3 ORTEP diagram of **3j**.

"O" is in the axial position whereas C6 in the equatorial position as indicated in Fig. 2.

The relative stereochemistry of **3j** was established by X-ray crystallography (Fig. 3).[14]

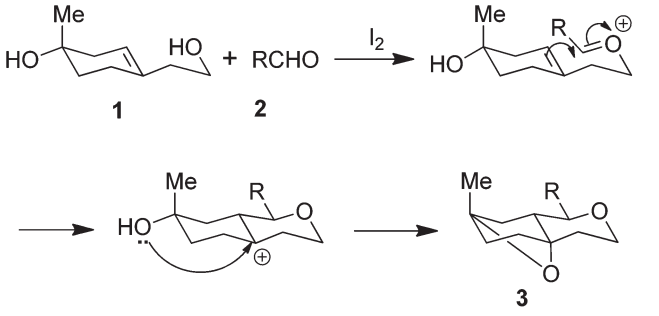
Inspired by the above results, we extended this method to various aldehydes like aromatic, heterocyclic and aliphatic aldehydes. Interestingly, several aromatic aldehydes such as *p*-nitro-, *p*-isopropyl-, *m*-bromo-, and *p*-hydroxy-derivatives participated well in this reaction (entries b, c, e and f, Table 1). Notably, electron-deficient substrates such as *p*-nitrobenzaldehyde also gave the desired product in good yield (entry b, Table 1). Furthermore, the reaction proceeded quite effectively with *p*-hydroxybenzaldehyde without the protection of the hydroxyl group (entry f, Table 1). In the case of aromatic aldehydes, the corresponding aryl substituted oxabicycles were obtained in good yields. In addition, a heteroaromatic substrate, *i.e.* 4-bromothiophene-2-carboxaldehyde, was also effective for this conversion (entry d, Table 1). In addition, the reaction was quite successful even with α,β-unsaturated aldehydes such as 2-nitrocinnamaldehyde and cinnamaldehyde (entries g and l, Table 1). The scope of this cascade reaction was further exemplified by the coupling of 4-(2-hydroxyethyl)-cyclohex-3-en-1-ol with different aldehydes (entries h–n, Table 1). In all cases, the corresponding products were obtained in good yields. This method works well with both aromatic and aliphatic aldehydes. In the case of aliphatic aldehydes, the corresponding alkyl substituted bicyclic ethers were obtained in relatively lower yield (entry h, Table 1). Remarkably, sterically hindered substrates such as 2,4,5-trifluorobenzaldehyde, 1-naphthaldehyde and 2-bromobenzaldehyde also gave the products in good yields (entries a, j, and m, Table 1). As expected, electron rich substrates such as *p*-hydroxy- and *p*-methoxybenzaldehydes gave the products comparatively in lower yields (entries f and i, Table 1). Finally, we attempted the coupling of 4-(2-hydroxyethyl)cyclohex-3-en-1-ol with styrene oxide under the influence of a catalytic amount of molecular iodine in dichloromethane at 25 °C. Interestingly, the desired product was obtained in 72% yield (entry n, Table 1). Therefore, this method was successful not only with aldehydes but also with epoxides. The reaction was further performed with chiral aldehydes to study the diastereoselectivity (entry o, Table 1). For instance, treatment of the chiral aldehyde **2o** afforded the desired product as a mixture of two diastereomers **3o** and **3o′** in 9 : 1 ratio. These diastereomers were purified by column chromatography and characterized by NMR, IR and mass spectroscopy. To know the efficiency, the reaction was carried out using different catalysts such as trifluoroacetic acid (TFA), *p*-toluenesulfonic acid (*p*-TSA), $BF_3{\cdot}OEt_2$ and TMSOTf.

Among them, molecular iodine was found to be the best catalyst in terms of conversion. Next, we examined the effect of solvents such as dichloromethane, acetonitrile, toluene and dimethoxyethane. Among them, dichloromethane gave the best results. No improvement in the conversion was observed either by increasing the reaction time or catalyst loading. In the absence of iodine, no cyclization was observed even after a long reaction time (24 h). The reactions proceeded smoothly at room temperature under mild and neutral conditions. No side products were detected under these conditions. No additives or stringent reaction conditions are required to facilitate the reaction. The scope and generality of this process is illustrated with respect to aldehydes and the results are presented in Table 1.

Mechanistically, the reaction was assumed to proceed *via* the formation of oxo-carbenium ions from 4-(2-hydroxyethyl)-cyclohex-3-en-1-ol and aldehydes after activation with molecular iodine. A subsequent attack of the olefin on the oxo-carbenium ion led to the formation of the carbocation, which is simultaneously trapped by a tertiary hydroxyl group to furnish the desired bicyclic ether (Scheme 2). Alternatively, iodine may react initially with the alcohol to generate HI, which may be responsible for the activation of the aldehyde to facilitate the reaction.

In this cascade process, the tertiary alcohol attacks preferentially from the less hindered side to produce the oxygen bridged oxabicycle **3** with high stereoselectivity. Recently, Barbero *et al.* showed the preferential equatorial attack of the internal nucleophile when termination of Prins cyclization occurs intramolecularly.[15]

In conclusion, we have demonstrated a novel metal-free approach for the synthesis of octahydro-4a,7-epoxyisochromene derivatives through a domino Prins cyclization between 4-(2-hydroxyethyl)cyclohex-3-en-1-ols and aldehydes. The use




Scheme 2 A plausible reaction pathway.

of readily accessible precursors and inexpensive molecular iodine makes it quite simple and more attractive. This method offers notable advantages such as mild/neutral conditions, good conversions and excellent selectivity.

## Experimental

IR spectra were recorded on a FT-IR spectrometer (KBr) and reported in reciprocal centimetres ($cm^{-1}$). $^1H$ NMR spectra were recorded at 600 MHz, 500 MHz, and 300 MHz and $^{13}C$ NMR spectra were recorded at 150, 125 MHz, and 75 MHz. For $^1H$ NMR, tetramethylsilane (TMS) was used as the internal standard ($\delta = 0$) and the values are reported as follows: chemical shift, integration, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad), and the coupling constants in Hz. For $^{13}C$ NMR, $CDCl_3$ ($\delta = 77.27$) was used as the internal standard and spectra were obtained with complete proton decoupling. Low-resolution MS and HRMS data were obtained using EI ionization. Reaction progress was monitored by thin layer chromatography (TLC) on precoated silica gel $GF_{254}$ plates and the spots were detected under UV light (254 nm).

### General procedure

To a stirred solution of aldehyde (1.1 mmol) and **1a** or **1b** (1.0 mmol) in dichloromethane (5.0 mL) was added 10 mol% of molecular iodine at 0 °C. The resulting mixture was stirred at 25 °C for the specified time. The progress of the reaction was monitored by TLC using ethyl acetate and hexane as the eluent. After completion, the mixture was quenched with water and the product was extracted with ethyl acetate. The organic layers were washed with aqueous sodium thiosulfate followed by a brine solution and dried over anhydrous sodium sulfate. Removal of the solvent followed by purification on silica gel (Merck 100–200 mesh) using ethyl acetate/hexane (2 : 8) as the eluent gave the pure tetrahydropyran.

## Acknowledgements

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## Notes and references

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