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One-pot total syntheses of natural products containing a THP-ring backbone: (±)-centrolobine and (±)-civet cat secretion

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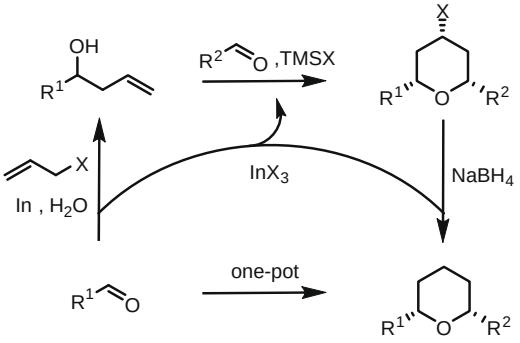
ABSTRACT

A one-pot strategy is devised and applied to the total syntheses of natural products with a THP-ring backbone. A special feature of this one-pot synthesis is the recyclability of the indium complex byproduct generated from the indium-mediated allylation reaction for concurrent catalysis in subsequent steps. Centrolobine and civet cat secretion are synthesized via this new method in overall yields of 58% and 23%, respectively.

The growth of organic synthesis, especially of useful compounds, has been facilitated by the many methodologies developed over decades. Among these, one-pot methods are attractive since they generate less waste, minimize isolation of intermediates in multi-step syntheses of complex molecular targets and save time and cost.[1] One-pot reactions can be classified roughly as tandem,[2a] domino[2b] or cascade[2c] reactions. For the successful implementation of one-pot strategies in natural product synthesis, it is important to maximize the overlap or compatibility factors (such as reagent, catalyst, solvent, and mechanism) of the sequential reactions. There are only a few reports on one-pot total syntheses of natural products from commercially available starting materials, and these still pose a challenge for synthetic chemists.

The *cis*-2,6-disubstituted-tetrahydropyran (THP) ring features in a large variety of biologically active natural products such as centrolobine and civet cat secretion. Our group, and others, have independently reported the InX_3-catalyzed Prins cyclization of homoallylic alcohols with aldehydes to produce *cis*-2,6-disubstituted-4-halo-THP products.[3] Subsequent dehalogenation using Bu_3SnH[3a,c,4] afforded the THP compounds. Herein, we report the one-pot syntheses of two natural products with a THP ring as the backbone, namely, centrolobine and civet cat secretion, in overall yields of 58% and 23%, respectively. One special feature of this one-pot synthesis is the recyclability of the indium complex byproduct generated from the indium-mediated allylation reaction, for use as the catalyst in subsequent steps. We envisaged that the indium complex byproduct[5] produced from the indium-mediated allylation of aldehydes with allyl bromide would also catalyze the subsequent Prins cyclization and dehalogenation ($NaBH_4$/InX_3)[6] (Scheme 1).

To develop a one-pot, three-step synthesis of THP-containing compounds, we needed to screen for the best solvent for each individual step. Our experience with the indium-mediated allylation reaction revealed that water is an excellent solvent for this step.[5a,b] As water is detrimental for subsequent steps, it is important that the indium-mediated allylation reaction is carried out either under solvent-free conditions or in a minimum amount of water. A de-



Scheme 1. Proposed hypothesis for constructing a THP ring.

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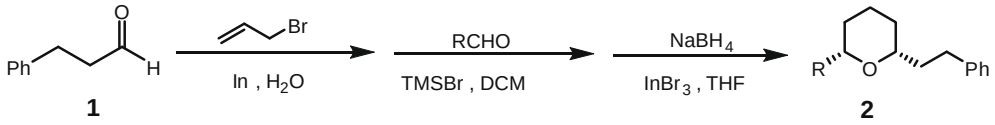
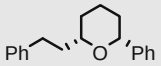
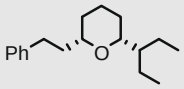
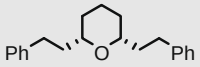
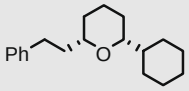
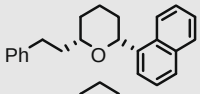
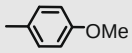
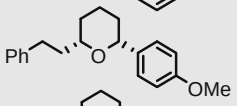
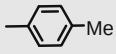
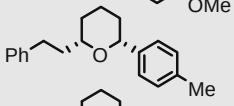
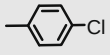
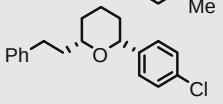
Table 1
The one-pot, three-step syntheses of tetrahydropyrans[a]

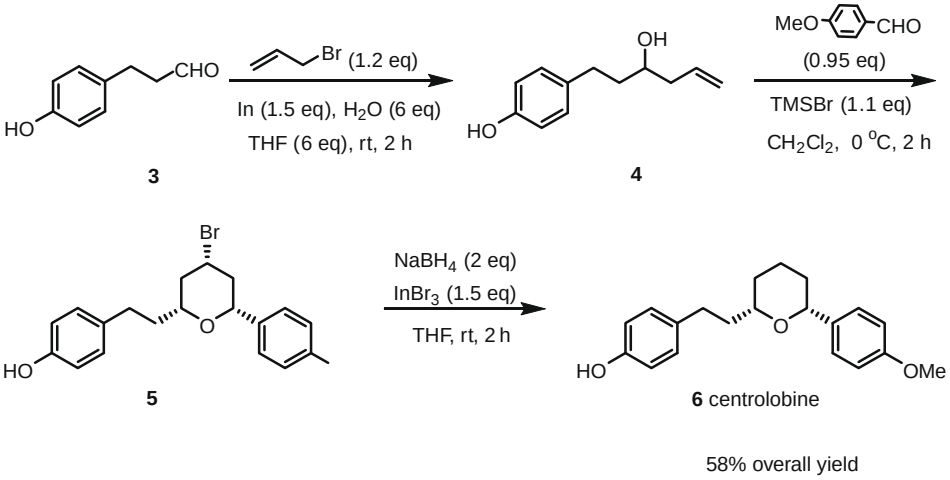


Entry	R	Product		Overall yield[b] (%)
1	–Ph		**2a**	59
2	$-CH(CH_2CH_3)_2$		**2b**	57
3	$-CH_2CH_2Ph$		**2c**	55
4	–Cy		**2d**	55
5			**2e**	54
6			**2f**	51
7			**2g**	60
8			**2h**	60

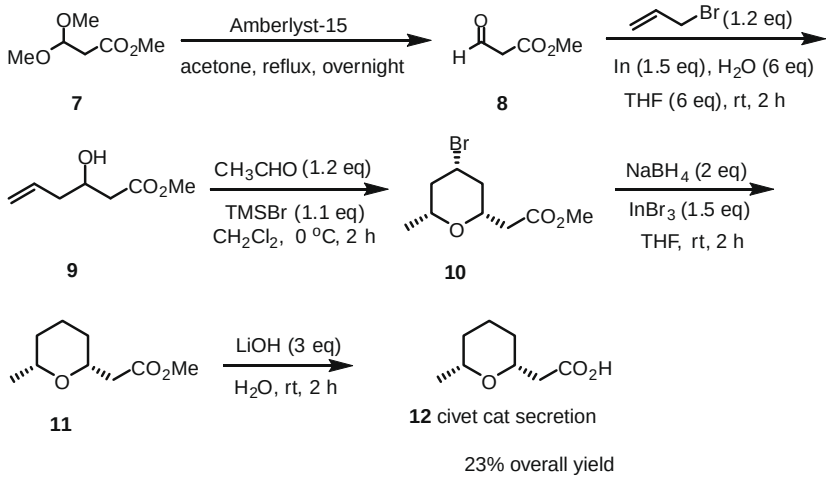
[a] Addition method: 1st step: Indium powder (1.5 mmol), allyl bromide (1.2 mmol), **1** (1 mmol) and water (6 mmol); 2nd step: TMSBr (1.1 mmol), aldehyde (0.95 mmol) and CH_2Cl_2 (2 mL); 3rd step: $InBr_3$ (1.5 mmol), $NaBH_4$ (2 mmol) and THF (2 mL).
[b] Yields based on aldehydes.

tailed solvent screen showed that dichloromethane was the best solvent for the Prins cyclization. On the other hand, THF was found to be the best solvent for the dehalogenation process.

It is important to note that the $NaBH_4/InX_3$ system (generated in advance or in situ)[7] reduces the 4-iodo and 4-bromo THP compounds efficiently but not the corresponding 4-chloro THP analogue. It was found that 1.5 equiv of InX_3 was essential for the reduction in the third step. Therefore, hydrocinnamaldehyde **1** was subjected to indium-mediated allylation followed by treatment with various aldehydes in a one-pot, three-step process



Scheme 2. Total synthesis of (±)-centrolobine via the one-pot method.



Scheme 3. Total synthesis of (±)-civet cat secretion via the one-pot method.

(Table 1).[8] The one-pot method worked with a wide variety of aldehydes, including alkyl and aromatic aldehydes, to form THP products **2** in moderate yields. The substituents on the aromatic aldehydes did not influence the overall yields (entries 1–8).

With the reaction conditions established, we applied this method to the one-pot total synthesis of centrolobine, an antibiotic natural product.[9] The synthesis commenced with allylation of aldehyde **3**[10] to give the homoallylic alcohol **4**, followed by Prins cyclization and debromination to produce centrolobine **6** in 58% overall yield (Scheme 2).

This one-pot, multiple-step method was also applied to the total synthesis of (6-methyl-2-tetrahydropyranyl) acetic acid **12**, which is a natural product isolated from glandular secretions of the civet cat (*Veverra civetta*),[11] as outlined in Scheme 3.

Commercially available acetal **7** was converted into aldehyde **8** by hydrolysis with Amberlyst-15. Subsequent allylation of **8** afforded homoallylic alcohol **9**, which was followed by Prins cyclization and debromination to produce methyl ester **11**. The natural product **12** was obtained by hydrolysis of the ester with lithium hydroxide. This one-pot, five-step method afforded **12** in 23% overall yield.

In conclusion, a one-pot strategy has been successfully designed and applied to the total synthesis of two natural products, (±)-centrolobine and (±)-civet cat secretion. This one-pot process provides a practical entry to diverse THP-based natural products and analogues. A special feature of this method is the recyclability of the metal complex byproduct generated from the initial step for catalysis of subsequent steps. Another feature is that no protection/deprotection of the hydroxy group is necessary. Extension to solid-supported synthesis and the application of this one-pot method to the total synthesis of more complex molecules are in progress.

Acknowledgements

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Supplementary data

Supplementary data (detailed experimental procedures, ^{1}H and ^{13}C NMR spectra, and analytical data for all compounds) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.05.053.

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7. The preparation of $InBr_2H$ is provided in the Supplementary data. Its in situ preparation is very simple. $InBr_3$ is added to the reaction mixture, followed by the addition of $NaBH_4$ in portions at rt.
8. Representative procedure for the one-pot, three-step synthesis of 2-phenethyl-3,4,5,6-tetrahydro-6-phenyl-2*H*-pyran (**2a**). To a mixture of **1** (0.1 g, 0.75 mmol), water (80 μL, 4.5 mmol) and indium powder (0.13 g, 1.13 mmol), was added allyl bromide (0.11 g, 0.89 mmol) dropwise at 0 °C. The mixture was subsequently stirred for 2 h at rt. After removal of excess allyl bromide on a rotary evaporator, the residue was dissolved in CH_2Cl_2 (2 mL). To the solution was added benzaldehyde (75 mg, 0.71 mmol) in one portion at rt, followed by dropwise addition of TMSBr (110 μL, 0.83 mmol) at 0 °C. After stirring for 2 h at rt, CH_2Cl_2 was removed on a rotary evaporator to give a residue which was dissolved in anhydrous THF (3 mL). $InBr_3$ (0.4 g, 1.13 mmol) was added in one portion to the solution followed by $NaBH_4$ (57 mg, 1.5 mmol) in small portions under nitrogen. The mixture was stirred for 2 h at rt, and quenched by addition of 1 N aqueous HCl. The mixture was extracted with ethyl acetate (3 × 10 mL). The combined organic layer was washed with saturated $NaHCO_3$ solution followed by brine. The organic phase was dried over anhydrous Na_2SO_4, filtered and concentrated to give a residue which was purified by flash chromatography eluting with 1:50 diethyl ether:hexane, to afford pure product **2a** (0.14 g, 59% over three steps) as a colourless liquid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.41–7.16 (m, 10H), 4.35 (dd, J = 11.3 Hz, 2.1 Hz, 1H), 3.49–3.43 (m, 1H), 2.83–2.72 (m, 1H), 1.98–1.76 (m, 4H), 1.68–1.60 (m, 2H), 1.59–

1.31 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 162.3, 143.6, 142.5, 128.5, 128.3, 128.2, 127.0, 125.8, 125.6, 79.3, 77.1, 38.1, 33.5, 31.7, 31.3, 24.1; FTIR (neat): 3061, 3026, 2934, 2857, 1602, 1495, 1452, 1387, 1306, 1209, 1088, 1045, 908, 750, 698, 552 cm^{-1}; HRMS (EI) m/z calcd for $C_{19}H_{22}O_1$ [M]$^+$: 266.1665. Found: 266.1663.

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