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Efficient total synthesis of (+)-*exo*-, (−)-*endo*-brevicomin and their derivatives via asymmetric organocatalysis and olefin cross-metathesis

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Abstract—The catalytic enantioselective synthesis of (+)-*exo*-, (−)-*endo*-brevicomin and their derivatives is described herein. This approach involves the use of the organocatalyzed asymmetric α-aminoxylation of aldehyde, in situ indium mediate allyation and olefin cross-metathesis. This versatile strategy allows for the rapid synthesis of other members of this class of natural products.

Derivatives of the 6,8-dioxabicyclo[3.2.1]octanes are pheromones of a variety of bark beetle species and play an important role in the system of chemical communication amongst them. (+)-*exo*- and (−)-*endo*-Brevicomin (**1a** and **2a**, respectively, Fig. 1) are typical components of the attracting pheromone system of several bark beetle species of the *Dendroctonus* and *Dryocoetes* family.[1] In several species, while *exo*-brevicomin is an aggregation pheromone of the western pine beetle (*Dendroctonus brevicomis*), *endo*-brevicomin is a minor component accompanying *exo*-brevicomin and has been reported to be an antiaggregation pheromone for the southern pine beetle (*Dendroctonus frontalis*).[2] Since *exo*-brevicomin was first synthesized in racemic form,[3] derivatives of the 6,8-dioxabicyclo[3.2.1]octanes have been the arget of numerous synthesis in both racemic and enatiomerically pure forms.[4,5] The design of an efficient synthetic strategy still remains a challenge due to the preparation of more active analogues. Herein we report a short and efficient asymmetric synthesis of (+)-*exo*-, (−)-*endo*-brevicomin and their derivatives, based on asymmetric organocatalysis and olefin cross-metathesis.

Our synthetic approach towards the target molecule was based on the organocatalytic asymmetric α-aminoxylation of aldehyde and nitrosobenzene as the oxygen source.[6] Recently, Zhong has developed tandem aminoxylation–allylation reaction, which produced mono-substituted 1,2-diols.[7] We employed their organocatalytic α-aminoxylation–allylation reaction in the synthesis of brevicomin and their derivatives.[8]

Figure 1.

The synthesis of (+)-*exo*- and (−)-*endo*-brevicomin (**1a** and **2a**, respectively) begins with commercially available nitrosobenzene and butyraldehyde as illustrated in Scheme 1. The reaction was conducted by stirring butyraldehyde (1.2 equiv), nitrosobenzene (1.0 equiv) and L-proline (20 mol %) in DMSO at room temperature. When the colour of the reaction mixture turned to red from green, allyl bromide (1.5 equiv), sodium iodide (1.5 equiv) and indium (1.5 equiv) were added. After 10 min, the product **5** was isolated in 71% yield with the diastereoselectivity 3:2 (*syn*/*anti*).[9] The enantioselectivities of *syn*-**5** and *anti*-**5** were obtained with 98% ee over *syn*-**5** and 99% ee over *anti*-**5**. Though these *syn*-**5** and *anti*-**5** were able to separate by column chromatography, we carried out the next reactions without separation and separated diastereomers in the final stage.[10]

Keywords: Brevicomin; Isobrevicomin; Total synthesis; Organocatalysis; Olefin cross-metathesis.
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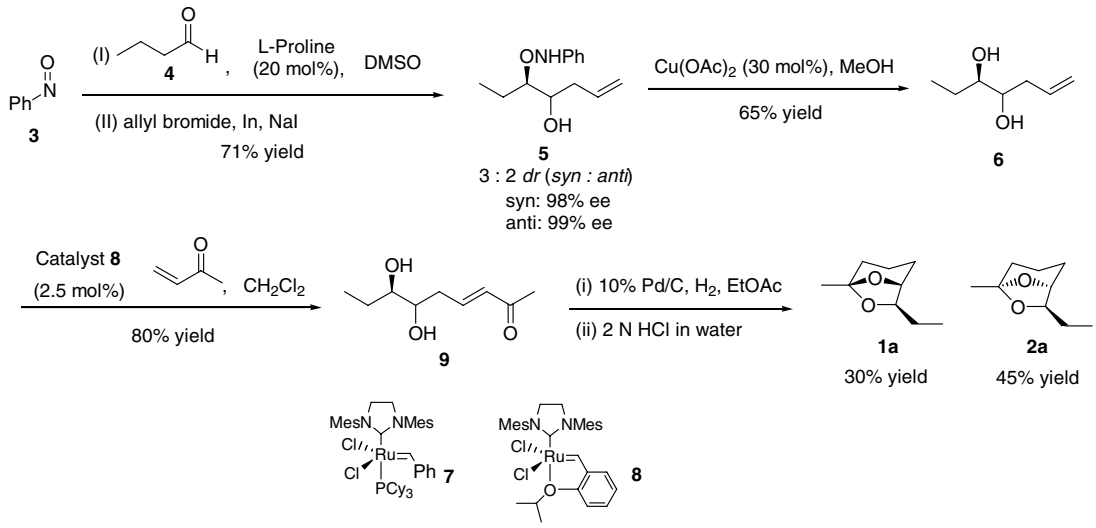


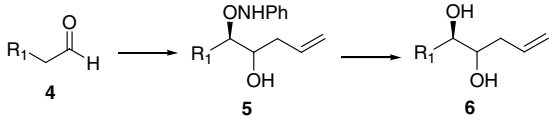
Scheme 1. Synthesis of (+)-*exo*-brevicomin **1a** and (−)-*endo*-brevicomin **2a**.

The *N*-phenylamino group from **5** was removed by the copper (II) catalyzed N–O cleavage reaction to give diol **6** in 65% yield.

The conversion of diol **6** to ketone **9** was achieved by olefin cross-metathesis with methyl vinyl ketone.[11] We initially examined the olefin cross-metathesis reaction of diol **6** with methyl vinyl ketone in the presence of catalytic amount (5 mol %) of Grubbs second generation catalyst (**7**). However, the desired product **9** was isolated in low yield (42%) after 24 h under reflux in CH_2Cl_2. To address this, we turned our attention to another olefin-metathesis catalyst (**8**). In the presence of catalyst (**8**) at room temperature, the reaction was fast proceeded to give ketone **9** in 80% yield after 6 h.[12] Finally, palladium catalyzed hydrogenation of **9** followed by dilution with excess 2 N HCl solution gave 30% of (+)-*exo*-brevicomin (**1a**) and 45% of (−)-*endo*-brevicomin (**2a**) after column chromatography (**1a**: $[\alpha]_D^{24}$ +69.5 (*c* 1.00, Et_2O), **2a**: $[\alpha]_D^{24}$ −78.8 (*c* 1.00, Et_2O)).[13] The physical and spectroscopic data of **1a** and **1b** are in full agreement with the literature data. We have also found that *syn*-diastereomer was less reactive than *anti*-diastereomer at the olefin cross-metathesis and final stage.

This strategy could be applied to synthesis of various brevicomin derivatives, including isobrevicomin.[14] First, the scope of organocatalytic α-aminoxylation–allylation reaction of various aldehydes and the copper-(II) catalyzed N–O bond cleavage reaction was investigated under same reaction condition (Table 1). In every case, the reaction gave the products **5** and **6** in good yields with excellent enantioselectivities (98–99% ee's). The aliphatic aldehydes afforded the desired product in the organocatalytic α-aminoxylation with nitrosobenzene in DMSO, whereas phenylacetaldehyde did not give the desired product **5** in the same reaction condition. However, when this reaction was carried out in $CHCl_3$ as solvent, followed by allylation in DMSO, desired product **5** was obtained in good yield (entry 3).

Table 1. Asymmetric synthesis of diol derivatives



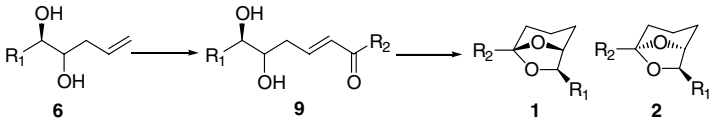
Entry	R_1	% Yield[a]		dr[b] (*syn*:*anti*)	% ee[c] (*syn*/*anti*)	
		5	**6**			
1	Et	71	65	3:2	98	99
2	Me	74	67	3:2	98	98
3[d]	Ph	67	61	3:2	99	99
4	Bn	72	80	3:2	99	99

[a] Yield was determined on the weight of isolated product.
[b] The *syn*:*anti* ratio was determined by ^{13}C NMR spectra.
[c] The ee was determined by chiral phase HPLC columns.
[d] α-Aminoxylation reaction was carried out in $CHCl_3$ at 4 °C.

Next, having the requisite diols in hand, we subjected to the olefin cross-metathesis, catalytic hydrogenation and acid-mediated cyclization. Our results are summarized in Table 2. The olefin cross-metathesis reaction of diol **6** with other cross-metathesis partners (ethyl vinyl ketone and benzyl vinyl ketone) allowed to obtain the desired product **9** in good yield. (+)-*exo*- and (−)-*endo*-Isobrevicomin were also obtained in this synthetic strategy.[15] In most cases, *syn*-diastereomer was less reactive than *anti*-diastereomer at the olefin cross-metathesis and final stage as mentioned above.

In conclusion, we have completed the total synthesis of (+)-*exo*-, (−)-*endo*-brevicomin and their derivatives in five step, based on the asymmetric organocatalysis and olefin cross-metathesis, as key steps. This versatile synthetic sequence could be employed for structure activity studies on brevicomin to determine the biologically relevant components of the architecture. The present asymmetric route represents potential route to other members of the 6,8-dioxabicyclo[3.2.1]octane family, which is now in progress and will be presented in due course.

Table 2. Synthesis of (+)-*exo*-and (−)-*endo*-brevicomin derivatives



Entry	R_1	R_2	% Yield[a]			$[\alpha]_D^{24}$ ($CHCl_3$) (**1** (*exo*)/**2** (*endo*))	
			9	**1** (*exo*)	**2** (*endo*)		
1	Et	Me	80	30	45	+69.5 (*c* 1.00)[b]	−78.8 (*c* 1.00)[b]
2	Et	Et	76	26	50	+55.0 (*c* 1.00)	−56.3 (*c* 1.00)
3	Et	Bn	95	60	(**1**/**2** = 2/3)[c]	—	—
4	Me	Et	60	24	38	+56.4 (*c* 0.45)	−74.1 (*c* 0.90)
5	Ph	Me	62	4	89	—[d]	−102.3 (*c* 1.00)
6	Bn	Me	75	28	62	+62.9 (*c* 1.00)	−21.4 (*c* 1.00)

[a] Yield was determined on the weight of isolated product.
[b] Et_2O was used as solvent.
[c] Product could not be separated by column chromatography. The **1** (*exo*)/**2** (*endo*) ratio was determined by ^1H NMR spectra.
[d] Not determined.

Acknowledgements

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10. 5-(*N*-Phenyl-aminooxy)-hept-1-en-4-ol (**5**). To a solution of nitrosobenzene **3** (1.07 g, 10 mmol) and butyraldehyde **4** (1.10 ml, 12 mmol) in DMSO (20 ml), L-proline (230 mg, 2.0 mmol) were added. After stirring for 15 min at room temperature, allyl bromide (1.30 ml, 15 mmol), sodium iodide (2.25 g, 15 mmol) and indium (1.72 g, 15 mmol) was added and stirred for 10 min. The reaction mixture was quenched with 0.5 M aqueous HCl solution and the aqueous layer was extracted with EtOAc. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$ and concentrated in vacuo. The crude residue was purified by flash column chromatography (15% EtOAc/hexane) to afford **5** (1.57 g, 71%). The diastereomeric ratio of the product was determined by ^{13}C NMR spectra. The enantiomeric excess of *syn*- and *anti*-diastereomer was measured by HPLC analysis after the separation of the isomer using column chromatography. *syn*-(*R*,*R*)-**5**: ^1H NMR (200 MHz, $CDCl_3$) 7.29 (t,

$J = 7.4$ Hz, 2H), 7.21 (s, 1H), 6.95–7.04 (m, 3H), 5.82–6.02 (m, 1H), 5.11–5.25 (m, 2H), 4.01–4.09 (m, 1H), 3.78–3.86 (m, 1H), 2.81 (br s, 1H), 2.29–2.38 (m, 2H), 1.53–1.83 (m, 2H), 1.11 (t, $J = 7.8$ Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) 148.6, 135.3, 129.1, 122.4, 117.7, 114.9, 87.4, 72.0, 37.0, 21.4, 11.0; HRMS calcd for $C_{13}H_{19}NO_2^+$ 221.1416, found 221.1414; HPLC (Chiralcel AD-H, 3.0% isopropanol/hexanes, 1 mL/min); $t_{minor} = 30.5$ min, $t_{major} = 35.6$ min, 98% ee; *anti*-(*R*,*S*)-**5**: ^{1}H NMR (200 MHz, $CDCl_3$) 7.29 (t, $J = 7.4$ Hz, 2H), 6.95–7.03 (m, 3H), 5.84–6.04 (m, 1H), 5.12–5.24 (m, 2H), 3.84–3.93 (m, 1H), 3.72 (dd, $J = 6.2$, 11.8 Hz, 1H), 2.23–2.51 (m, 2H), 1.59–1.88 (m, 2H), 1.05 (t, $J = 7.8$ Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) 148.6, 134.9, 129.1, 122.4, 117.8, 115.9, 86.8, 72.3, 38.2, 22.4, 10.1; HRMS calcd for $C_{13}H_{19}NO_2^+$ 221.1416, found 221.1417; HPLC (Chiralcel AD-H, 3.0% isopropanol/hexanes, 1 mL/min); $t_{minor} = 21.6$ min, $t_{major} = 25.1$ min, 99% ee.

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12. Compound **9**: ^{1}H NMR (200 MHz, $CDCl_3$) 6.69–6.94 (m, 1H), 6.07 (d, $J = 15.8$ Hz, 1H), 3.23–3.64 (m, 4H), 2.29–2.41 (m, 2H), 2.17 (s, 3H), 1.27–1.52 (m, 2H), 0.90 (t, $J = 7.4$ Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) 199.4, 199.3, 146.3, 145.6, 133.0, 132.9, 76.0, 75.4, 73.2, 72.7, 37.0, 34.7, 26.9, 26.3, 25.0, 10.4, 10.8; MS (EI) $m/z = 172$ (M^+).
13. Reported rotation values for (+)-*exo*-brevicomin: $[\alpha]_D^{25}$ +66.7 (*c* 1.40, Et_2O); Ref. 5c: $[\alpha]_D^{23}$ +71.5 (*c* 1.03, Et_2O); Ref. 5e: $[\alpha]_D^{23}$ +67.9 (*c* 1.41, Et_2O); Ref. 5f: $[\alpha]_D$ +66.6 (*c* 0.3, Et_2O); Ref. 5h: $[\alpha]_D^{20}$ +65.9 (*c* 1.90, Et_2O); Ref. 5i; reported rotation values for (−)-*endo*-brevicomin: $[\alpha]_D^{22}$ −78.9 (*c* 0.99, Et_2O); Ref. 5a: $[\alpha]_D^{25}$ −78.8 (*c* 0.8, Et_2O); Ref. 5d: $[\alpha]_D^{27}$ −77.4 (*c* 0.2, Et_2O); Ref. 5g.
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