



Title	Catalytic asymmetric synthesis of descurainin via 1,3-dipolar cycloaddition of a carbonyl ylide using Rh <sub>2</sub> (R-TCPTTL) <sub>4</sub>
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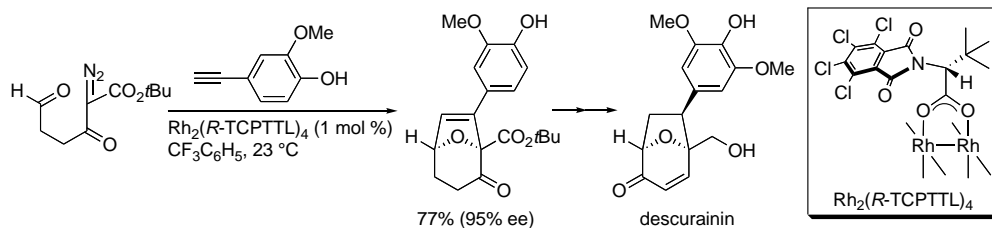
## Graphical Abstract

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### Catalytic asymmetric synthesis of descurainin via 1,3-dipolar cycloaddition of a carbonyl ylide using $\text{Rh}_2(\text{R-TCPTTL})_4$

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# Catalytic asymmetric synthesis of descurainin via 1,3-dipolar cycloaddition of a carbonyl ylide using $\text{Rh}_2(R\text{-TCPTTL})_4$

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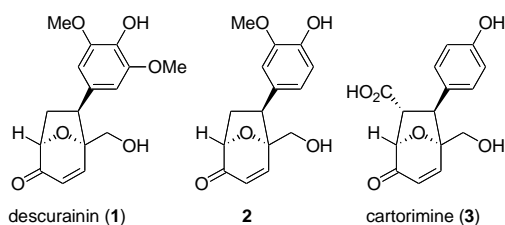
Chiral dirhodium(II) catalyst

Descurainin

## ABSTRACT

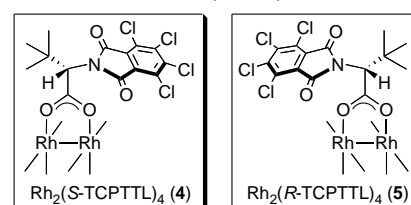
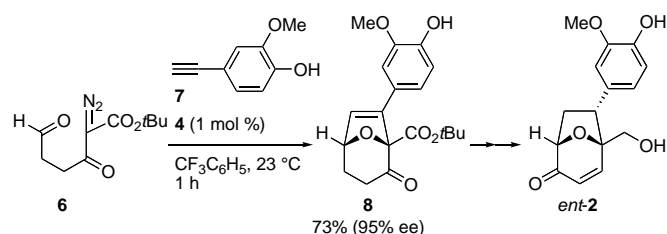
A catalytic asymmetric synthesis of descurainin has been achieved by incorporating an enantioselective 1,3-dipolar cycloaddition, a stereoselective alkene hydrogenation, an oxidation with Fremy's salt and a regioselective demethylation with  $\text{NbCl}_5$  as the key steps. The 1,3-dipolar cycloaddition of a carbonyl ylide derived from *tert*-butyl 2-diazo-5-formyl-3-oxopentanoate with 4-hydroxy-3-methoxyphenylacetylene in the presence of dirhodium(II) tetrakis[*N*-tetrachlorophthaloyl-(*R*)-*tert*-leucinate],  $\text{Rh}_2(R\text{-TCPTTL})_4$ , provided an 8-oxabicyclo[3.2.1]octane skeleton in 95% ee.

In 2004, Li and co-workers isolated descurainin (**1**) from the seeds of *Descurainia sophia* (L.) Webb ex Prantl, which are widely used as Chinese traditional medicine to relieve coughing, prevent asthma, reduce edema and promote urination.<sup>1</sup> Compound **2**<sup>2</sup> and cartorimine (**3**),<sup>3</sup> possessing an 8-oxabicyclo[3.2.1]oct-3-en-2-one ring system, were isolated from *Ligusticum chuanxing* Hort. and *Carthamus tinctorius* L. by the Wen and He groups, respectively. Snider and Grabowski reported a concise total synthesis of ( $\pm$ )-**1–3**, in which the fully functionalized 8-oxabicyclo[3.2.1]octenone skeleton was efficiently constructed by a possible biomimetic [5+2] cycloaddition of oxidopyrylium ion.<sup>4</sup>



The dirhodium(II) complex-catalyzed tandem cyclic carbonyl ylide formation–1,3-dipolar cycloaddition reaction sequence represents one of the most powerful methods for the rapid assembly of complex oxapolycyclic systems.<sup>5–8</sup> An

enantioselective version of this sequence catalyzed by chiral dirhodium(II) complexes has also been developed.<sup>9–12</sup> Recently, we reported an enantioselective 1,3-dipolar cycloaddition of a six-membered cyclic formyl-carbonyl ylide with phenylacetylene derivatives using dirhodium(II) tetrakis[*N*-tetrachlorophthaloyl-(*S*)-*tert*-leucinate],  $\text{Rh}_2(S\text{-TCPTTL})_4$  (**4**),<sup>13–15</sup> as a catalyst.<sup>16</sup> The reaction between *tert*-butyl 2-diazo-5-formyl-3-oxopentanoate (**6**) and 4-hydroxy-3-methoxyphenylacetylene (**7**) provided 8-oxabicyclo[3.2.1]octane derivative **8** in 73% yield with 95% ee (Eq. 1). Using this catalytic methodology, we achieved the first asymmetric synthesis of *ent*-**2**.<sup>16</sup> The absolute maximal molar circular dichroism of synthetic material *ent*-**2** ( $\Delta\epsilon$  –3.81 at 348 nm) displayed a startling difference in magnitude to that of natural product **2** ( $\Delta\epsilon$  +0.01 at 355 nm).<sup>2</sup> This observation



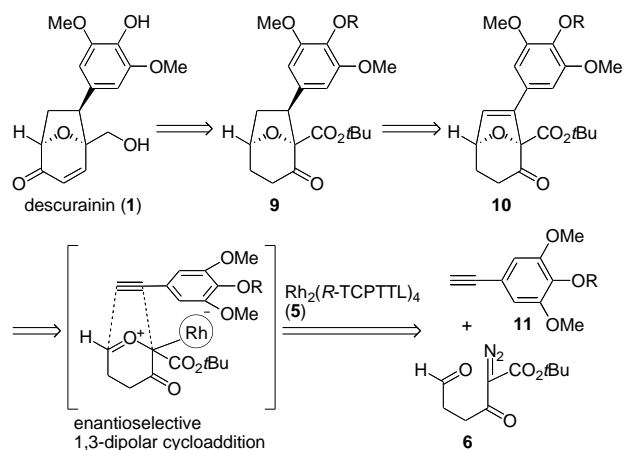
(1)

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suggested that natural product **2** might be biosynthesized in near-racemic form like polygalolides A and B.<sup>17,18</sup> Our results provided experimental support for the biogenetic hypothesis by Snider's group.<sup>4b</sup> As an extension of our study in this field, we herein report an asymmetric synthesis of descourainin (**1**) using the carbonyl ylide cycloaddition methodology.

Our synthetic strategy is outlined retrosynthetically in Scheme 1. We envisaged that **1** would be accessible from  $\beta$ -ketoester **9**, which would be derived from bicyclic compound **10** in a stereocontrolled manner. On the basis of our previous work,<sup>16</sup> we envisioned that the cycloaddition of a carbonyl ylide derived from  $\alpha$ -diazo- $\beta$ -ketoester **6** with phenylacetylene derivative **11** using  $\text{Rh}_2(\text{R-TCPTTL})_4$  (**5**)<sup>19</sup> would provide cycloadduct **10**.

Toward this end, we initially examined the reaction of  $\alpha$ -diazo- $\beta$ -ketoester **6**<sup>16</sup> with a variety of 3,5-dimethoxy-4-hydroxyphenylacetylene derivatives **11a–d** in the presence of 1 mol % of  $\text{Rh}_2(\text{R-TCPTTL})_4$  (**5**) in  $\alpha, \alpha, \alpha$ -trifluorotoluene at room temperature (Table 1, entries 1–4). The reaction of **6** with phenylacetylene **11a** bearing a free phenolic hydroxy group gave cycloadduct **12a** in 55% yield (entry 1). The enantiomeric excess of **12a** was determined to be 50% by HPLC using a Chiralcel OD-H column. Switching the dipolarophile to *tert*-butyldimethylsilyl (TBS)- or methyl-protected phenylacetylenes



**Scheme 1.** Retrosynthetic analysis of descourainin (**1**).

**Table 1**

Enantioselective 1,3-dipolar cycloaddition of a carbonyl ylide derived from **6** with **11a–d** and **7** using  $\text{Rh}_2(\text{R-TCPTTL})_4$  (**5**)<sup>a</sup>

entry	dipolarophile		product		
	R <sup>1</sup>	R <sup>2</sup>	Yield <sup>b</sup> (%)	ee <sup>c</sup> (%)	
1	<b>11a</b>	OH, OMe	<b>12a</b>	55	50
2	<b>11b</b>	OTBS, OMe	<b>12b</b>	39	26
3	<b>11c</b>	OMe, OMe	<b>12c</b>	44	20
4	<b>11d</b>	OAc, OMe	<b>12d</b>	62	1
5 <sup>d</sup>	<b>7</b>	OH, H	<i>ent</i> - <b>8</b>	77	95

<sup>a</sup> Unless otherwise noted, reactions were carried out as follows: a solution of **6** (45.3 mg, 0.2 mmol) and dipolarophile (3 equiv) in  $\text{CF}_3\text{C}_6\text{H}_5$  (1 mL) was added over 1 h to a stirred solution of  $\text{Rh}_2(\text{R-TCPTTL})_4$  (**5**) (3.95 mg, 1 mol %) in  $\text{CF}_3\text{C}_6\text{H}_5$  (1 mL) at 23 °C.

<sup>b</sup> Isolated yield.

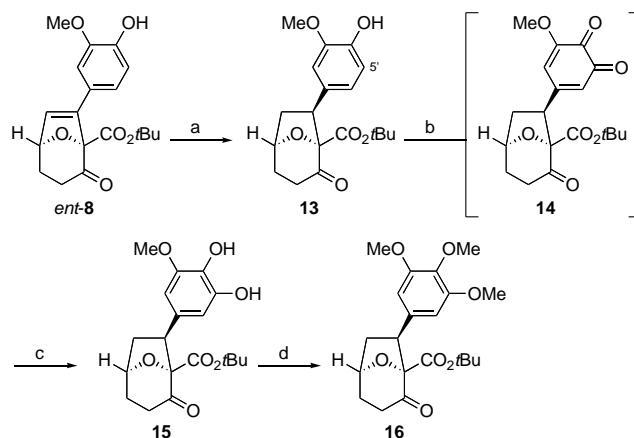
<sup>c</sup> Determined by HPLC. See the Supplementary data for details.

<sup>d</sup> The reaction was performed on a 7.0 mmol scale, in which the addition time was 3 h.

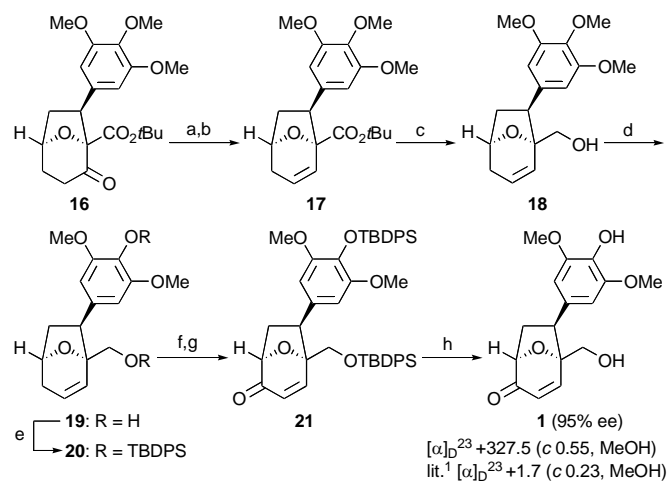
**11b** and **11c** resulted in a noticeable drop in both product yields (39% and 44%, respectively) and enantioselectivities (26% ee and 20% ee, respectively) compared to those with **11a** (entries 2 and 3). The use of acetyl-protected phenylacetylene **11d** caused a sharp drop in enantioselectivity, though cycloadduct **12d** was obtained in good yield (62% yield, 1% ee, entry 4). It is noteworthy that the steric and electronic nature of dipolarophiles markedly influenced both product yield and enantioselectivity.<sup>10b,c</sup> These unsatisfactory results led us to change our strategy. We envisioned that the enantiomer of bicyclic compound **8** possessing a 4'-hydroxy-3'-methoxybenzene ring would be an intermediate for the synthesis of **1** via installation of a methoxy group at the C5' position on the aromatic ring. Thus, the reaction of **6** with 4-hydroxy-3-methoxyphenylacetylene (**7**) as a dipolarophile in the presence of  $\text{Rh}_2(\text{R-TCPTTL})_4$  (**5**) was performed to provide the desired cycloadduct *ent*-**8**,  $[\alpha]_D^{22} -148.5$  (*c* 1.09,  $\text{CHCl}_3$ ), in 77% yield with virtually the same enantioselectivity (95% ee) as those found in our previous study (entry 5).<sup>16,20</sup>

Catalytic hydrogenation of *ent*-**8** provided exclusively the desired *endo*-bicyclic compound **13** as a single diastereomer in 99% yield (Scheme 2).<sup>21</sup> We then investigated installation of a hydroxy group at the C5' position on the aromatic ring via formation of *o*-quinone. Treatment of phenol **13** with  $(\text{KSO}_3)_2\text{NO}$  (Fremy's salt)<sup>22</sup> in the presence of  $\text{KH}_2\text{PO}_4$  gave *o*-quinone **14**. Keeping the reaction time short prevented significant loss of product yield. The resultant *o*-quinone **14** was immediately converted into catechol **15** by treatment with  $\text{Na}_2\text{S}_2\text{O}_4$  in 73% yield in two steps from **13**.<sup>23</sup> Since attempts at regioselective methylation of **15** were unsuccessful,<sup>24</sup> we turned our attention to the viability of a regioselective demethylation of trimethoxybenzene derivative. Treatment of **15** with MeI (4 equiv.) and  $\text{K}_2\text{CO}_3$  afforded per-methylated product **16** in quantitative yield.

With an efficient installation of a methoxy group at the C5' position realized, the stage was now set for completion of the asymmetric synthesis of **1** as illustrated in Scheme 3. Treatment of ketone **16** with NaHMDS at  $-78$  °C followed by addition of  $\text{PhNtF}_2$  and subsequent palladium-catalyzed reduction of the resulting enol triflate<sup>25</sup> furnished alkene **17** in 81% yield. Reduction of **17** with  $\text{LiAlH}_4$  provided alcohol **18** in quantitative yield. Next, regioselective demethylation of **18** was investigated under a variety of conditions. This transformation turned out to be even more difficult than we anticipated, as the bicyclic component was prone to decomposition under acidic conditions ( $\text{HBr}$ , TMSI,  $\text{MeSO}_3\text{H}/\text{NaI}$  or  $\text{BF}_3\cdot\text{OEt}_2/\text{NaI}$ ) frequently used in



**Scheme 2.** Reagents and conditions: (a)  $\text{H}_2$ , 10% Pd/C, MeOH, 1 h, 99%; (b)  $(\text{KSO}_3)_2\text{NO}$ ,  $\text{KH}_2\text{PO}_4$ , acetone/ $\text{H}_2\text{O}$  (3:1), 10 min; (c)  $\text{Na}_2\text{S}_2\text{O}_4$ ,  $\text{KH}_2\text{PO}_4$ , EtOAc/ $\text{H}_2\text{O}$  (5:1), 0.5 h, 73% (two steps); (d) MeI,  $\text{K}_2\text{CO}_3$ , acetone, reflux, 1 h, 99%.



**Scheme 3.** Reagents and conditions: (a) NaHMDS, THF,  $-78\text{ }^\circ\text{C}$ , 1 h, then,  $\text{PhNTf}_2$ ,  $-78$  to  $-10\text{ }^\circ\text{C}$ , 3 h, 96%; (b)  $\text{Pd}(\text{OAc})_2$ ,  $\text{PPh}_3$ ,  $n\text{Bu}_3\text{N}$ ,  $\text{HCO}_2\text{H}$ , DMF,  $60\text{ }^\circ\text{C}$ , 40 min, 84%; (c)  $\text{LiAlH}_4$ , THF,  $0\text{ }^\circ\text{C}$ , 1.5 h, 99%; (d)  $\text{NbCl}_5$ ,  $\text{ClCH}_2\text{CH}_2\text{Cl}$ ,  $70\text{ }^\circ\text{C}$ , 1 h, 79%; (e) TBDPSCI, imidazole, DMAP, DMF, 24 h, 84%; (f)  $\text{SeO}_2$ , dioxane, reflux, 24 h, 81%; (g)  $\text{MnO}_2$ ,  $\text{CH}_2\text{Cl}_2$ , 15 h, 90%; (h) TBAF, THF, 2 h, 74%.

this type of regioselective demethylation.<sup>26</sup> After considerable experimentation, the Arai–Nishida protocol with  $\text{NbCl}_5$  proved to be the method of choice.<sup>27</sup> Eventually, treatment of **18** with  $\text{NbCl}_5$  in 1,2-dichloroethane at  $70\text{ }^\circ\text{C}$  facilitated regioselective demethylation, affording phenol **19** as a sole product in 79% yield. Protection of the two hydroxy groups with TBDPSCI and imidazole provided bis-TBDPS ether **20** in 84% yield. Allylic oxidation of **20** with  $\text{SeO}_2$  followed by oxidation of the resulting allylic alcohol with  $\text{MnO}_2$  afforded enone **21** in 73% yield. Finally, removal of the two TBDPS protecting groups with TBAF completed the asymmetric synthesis of descurainin (**1**). The optical rotation of the synthetic material **1** (95% ee),<sup>28</sup>  $[\alpha]_D^{23} +327.5$  (c 0.55, MeOH), was greatly different from the literature value [lit.<sup>1</sup>  $[\alpha]_D^{23} +1.7$  (c 0.23, MeOH)], albeit with the same sign. This observation suggests that **1** could be biosynthesized in near-racemic form like natural product **2**.

In summary, we have achieved the first catalytic asymmetric synthesis of descurainin. The key features of this synthesis include an efficient construction of the 8-oxabicyclo[3.2.1]octane skeleton employing  $\text{Rh}_2(\text{R-TCPTTL})_4$ -catalyzed tandem formyl-derived carbonyl ylide formation–1,3-dipolar cycloaddition, a stereoselective alkene hydrogenation, an oxidation with Fremy's salt and a regioselective demethylation with  $\text{NbCl}_5$  developed by the group of Arai and Nishida. Further application of the catalytic enantioselective carbonyl ylide cycloaddition methodology to asymmetric synthesis of biologically active natural products is currently in progress.

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## Supplementary data

Supplementary data associated with this article can be found in the online version, at doi: xxx.

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  - Assuming that descurainin (**1**) might also possess the same absolute configuration as that of natural product **2**, we used Rh<sub>2</sub>(R-TCPTTL)<sub>4</sub> (**5**) instead of Rh<sub>2</sub>(S-TCPTTL)<sub>4</sub> (**4**).
  - The absolute configuration of *ent*-**8** was determined to be (1*S*,5*S*) by comparison of the sign of the optical rotation with the data reported in ref. 16.
  - Hodgson and co-workers reported *exo*-selective alkene hydrogenation of 8-oxabicyclo[3.2.1]oct-6-en-2-one derivatives. (a) Hodgson, D. M.; Avery, T. D.; Donohue, A. C. *Org. Lett.* **2002**, *4*, 1809–1811; (b) Hodgson, D. M.; Le Strat, F.; Avery, T. D.; Donohue, A. C.; Brückl, T. *J. Org. Chem.* **2004**, *69*, 8796–8803.
  - (KSO<sub>3</sub>)<sub>2</sub>NO, often referred to as Fremy's salt, has been used in the preparation of *o*- and *p*-benzoquinones, naphthoquinones, and some polycondensed quinones and in the oxidation of indolines. For a review, see: (a) Zimmer, H.; Lankin, D. C.; Horgan, S. W. *Chem. Rev.* **1971**, *71*, 229–246. For recent examples of oxidation with Fremy's salt used in the total syntheses of natural products, see: (b) Alvarez-Manzaneda, E.; Chahboun, R.; Cabrera, E.; Alvarez, E.; Haidour, A.; Ramos, J. M.; Alvarez-Manzaneda, R.; Hmamouchi, M.; Es-Samti, H. *Chem. Commun.* **2009**, 592–594; (c) Nielsen, L. B.; Slamet, R.; Wege, D. *Tetrahedron* **2009**, *65*, 4569–4577; (d) Ishii, S.; Fujii, M.; Akita, H. *Chem. Pharm. Bull.* **2009**, *57*, 1103–1106; (e) Inoue, K.; Ishikawa, Y.; Nishiyama, S. *Org. Lett.* **2010**, *12*, 436–439.
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