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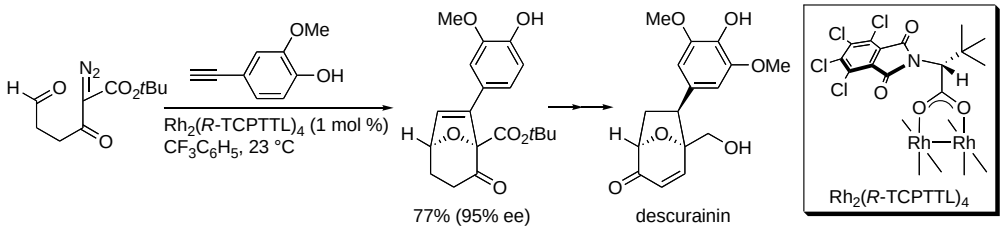

Catalytic asymmetric synthesis of descurainin via 1,3-dipolar cycloaddition of a carbonyl ylide using Rh_2(*R*-TCPTTL)$_4$

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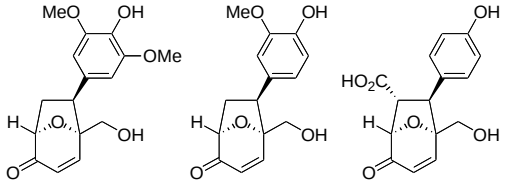
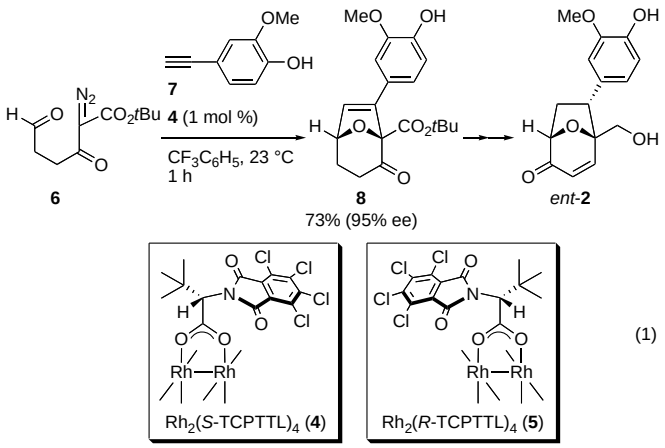
ABSTRACT

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 $NbCl_5$ as the key steps. The 1,3-dipolar cycloaddition of a carbonyl ylide derived from *tert*-butyl 2-diazo-5-formyl-3-oxopetanoate with 4-hydroxy-3-methoxyphenylacetylene in the presence of dirhodium(II) tetrakis[*N*-tetrachlorophthaloyl-(*R*)-*tert*-leucinate], Rh_2(*R*-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.[1] Compound **2**[2] and cartorimine (**3**),[3] possessing an 8-oxabicylo[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 (±)-**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.[4]



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.[5–8] An enantioselective version of this sequence catalyzed by chiral dirhodium(II) complexes has also been developed.[9–12] 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], Rh_2(*S*-TCPTTL)$_4$ (**4**),[13–15] as a catalyst.[16] The reaction between *tert*-butyl 2-diazo-5-formyl-3-oxopetanoate (**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**.[16] The absolute maximal molar circular dichroism of synthetic material *ent*-**2** (Δε −3.81 at 348 nm) displayed a startling difference in magnitude to that of natural product **2** (Δε +0.01 at 355 nm).[2] This observation



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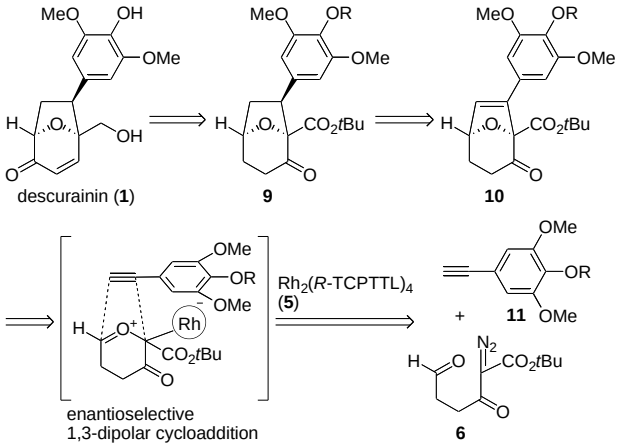
suggested that natural product **2** might be biosynthesized in near-racemic form like polygalolides A and B.[17,18] Our results provided experimental support for the biogenetic hypothesis by Snider's group.[4b] As an extension of our study in this field, we herein report an asymmetric synthesis of descurainin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

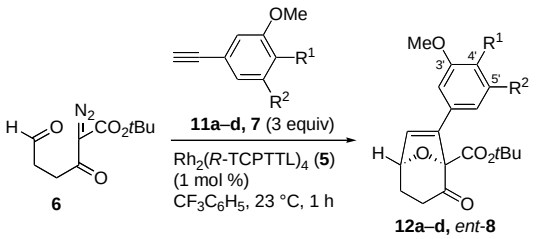
Our synthetic strategy is outlined retrosynthetically in Scheme 1. We envisaged that **1** would be accessible from β-ketoester **9**, which would be derived from bicyclic compound **10** in a stereocontrolled manner. On the basis of our previous work,[16] we envisioned that the cycloaddition of a carbonyl ylide derived from α-diazo-β-ketoester **6** with phenylacetylene derivative **11** using Rh_2(*R*-TCPTTL)$_4$ (**5**)[19] would provide cycloadduct **10**.

Toward this end, we initially examined the reaction of α-diazo-β-ketoester **6**[16] with a variety of 3,5-dimethoxy-4-hydroxyphenylacetylene derivatives **11a**–**d** in the presence of 1 mol % of Rh_2(*R*-TCPTTL)$_4$ (**5**) in α,α,α-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 descurainin (**1**).

Table 1
Enantioselective 1,3-dipolar cycloaddition of a carbonyl ylide derived from **6** with **11a**–**d** and **7** using Rh_2(*R*-TCPTTL)$_4$ (**5**)[a]



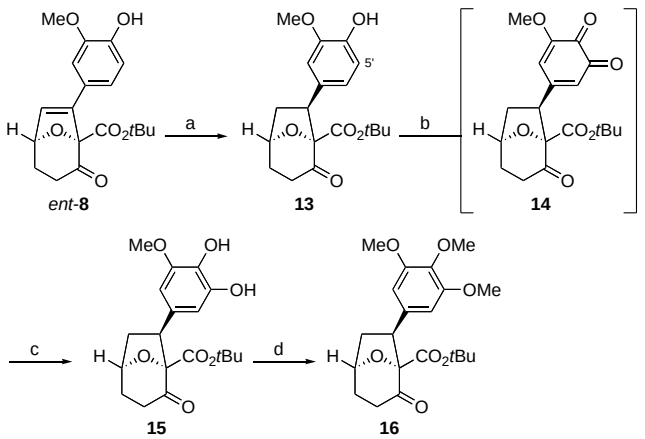
entry	dipolarophile	R^1	R^2	product	Yield[b] (%)	ee[c] (%)
1	**11a**	OH	OMe	**12a**	55	50
2	**11b**	OTBS	OMe	**12b**	39	26
3	**11c**	OMe	OMe	**12c**	44	20
4	**11d**	OAc	OMe	**12d**	62	1
5[d]	**7**	OH	H	*ent*-**8**	77	95

[a] Unless otherwise noted, reactions were carried out as follows: a solution of **6** (45.3 mg, 0.2 mmol) and dipolarophile (3 equiv) in $CF_3C_6H_5$ (1 mL) was added over 1 h to a stirred solution of Rh_2(*R*-TCPTTL)$_4$ (**5**) (3.95 mg, 1 mol %) in $CF_3C_6H_5$ (1 mL) at 23 °C.
[b] Isolated yield.
[c] Determined by HPLC. See the Supplementary data for details.
[d] The reaction was performed on a 7.0 mmol scale, in which the addition time was 3 h.

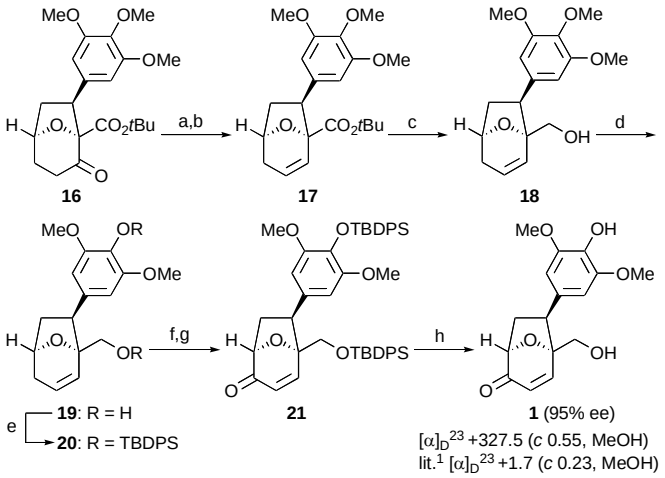
11b and **11c** resulted in a noticeable drop in both product yields (39% and 44%, respectively) and enantioselectivities (26% ee and 20% ee, respectively) compared to those with **11a** (entries 2 and 3). The use of acetyl-protected phenylacetylene **11d** caused a sharp drop in enantioselectivity, 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.[10b,c] 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 Rh_2(*R*-TCPTTL)$_4$ (**5**) was performed to provide the desired cycloadduct *ent*-**8**, $[\alpha]_D^{22}$ −148.5 (*c* 1.09, $CHCl_3$), in 77% yield with virtually the same enantioselectivity (95% ee) as those found in our previous study (entry 5).[16,20]

Catalytic hydrogenation of *ent*-**8** provided exclusively the desired *endo*-bicyclic compound **13** as a single diastereomer in 99% yield (Scheme 2).[21] 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 $(KSO_3)_2NO$ (Fremy's salt)[22] in the presence of KH_2PO_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 $Na_2S_2O_4$ in 73% yield in two steps from **13**.[23] Since attempts at regioselective methylation of **15** were unsuccessful,[24] we turned our attention to the viability of a regioselective demethylation of trimethoxybenzene derivative. Treatment of **15** with MeI (4 equiv.) and K_2CO_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 $PhNTf_2$ and subsequent palladium-catalyzed reduction of the resulting enol triflate[25] furnished alkene **17** in 81% yield. Reduction of **17** with $LiAlH_4$ 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 (HBr, TMSI, $MeSO_3H$/NaI or $BF_3{\cdot}OEt_2$/NaI) frequently used in



Scheme 2. Reagents and conditions: (a) H_2, 10% Pd/C, MeOH, 1 h, 99%; (b) $(KSO_3)_2NO$, KH_2PO_4, acetone/H_2O (3:1), 10 min; (c) $Na_2S_2O_4$, KH_2PO_4, EtOAc/H_2O (5:1), 0.5 h, 73% (two steps); (d) MeI, K_2CO_3, acetone, reflux, 1 h, 99%.



Scheme 3. Reagents and conditions: (a) NaHMDS, THF, −78 °C, 1 h, then, $PhNTf_2$, −78 to −10 °C, 3 h, 96%; (b) $Pd(OAc)_2$, PPh_3, nBu_3N, HCO_2H, DMF, 60 °C, 40 min, 84%; (c) $LiAlH_4$, THF, 0 °C, 1.5 h, 99%; (d) $NbCl_5$, $ClCH_2CH_2Cl$, 70 °C, 1 h, 79%; (e) TBDPSCl, imidazole, DMAP, DMF, 24 h, 84%; (f) SeO_2, dioxane, reflux, 24 h, 81%; (g) MnO_2, CH_2Cl_2, 15 h, 90%; (h) TBAF, THF, 2 h, 74%.

this type of regioselective demethylation.[26] After considerable experimentation, the Arai–Nishida protocol with $NbCl_5$ proved to be the method of choice.[27] Eventually, treatment of **18** with $NbCl_5$ in 1,2-dichloroethane at 70 °C facilitated regioselective demethylation, affording phenol **19** as a sole product in 79% yield. Protection of the two hydroxy groups with TBDPSCl and imidazole provided bis-TBDPS ether **20** in 84% yield. Allylic oxidation of **20** with SeO_2 followed by oxidation of the resulting allylic alcohol with 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),[28] $[\alpha]_D^{23}$ +327.5 (*c* 0.55, MeOH), was greatly different from the literature value [lit.[1] $[\alpha]_D^{23}$ +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 Rh_2(*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 $NbCl_5$ 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.

Acknowledgments

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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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28. The enantiomeric purity of the synthetic material **1** was determined to be 95% ee by comparison of the HPLC retention time with a racemic sample of **1**, which was prepared according to the literature. See ref. 4b.