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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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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-(S)-tert-leucinate], Rh$_2$(S-TCPTTL)$_4$ (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. Compound 2 and cartorimine (3), possessing an 8-oxabicyclo[3.2.1]octenone skeleton, 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. An enantioselective version of this sequence catalyzed by chiral dirhodium(II) complexes has also been developed. 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) as a catalyst. 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. The absolute maximal molar circular dichroism of synthetic material ent-2 (Δ ε = 3.81 at 348 nm) displayed a startling difference in magnitude to that of natural product 2 (Δ ε = 0.01 at 355 nm). This observation

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suggested that natural product 2 might be biosynthesized in nearracemic form like polygalalides A and B.\textsuperscript{17,18} Our results provided experimental support for the biogenetic hypothesis by Snider’s group.\textsuperscript{26} As an extension of our study in this field, we herein report an asymmetric synthesis of descurainin (1) using the carbonyl ylide cycloadition 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,\textsuperscript{16} we envisioned that the cycloadition of a carbonyl ylide derived from α-diazo-β-ketoester 6 with phenylacetylene derivative 11 using Rh₂(R-TCPTTL)₄ (5)\textsuperscript{19} would provide cycloaduct 10.

Toward this end, we initially examined the reaction of α-diazo-β-ketoester 6\textsuperscript{16} with a variety of 3,3-dimethoxy-4-hydroxyphenylacetylene derivatives 11a–d in the presence of 1 mol % of Rh₂(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 cycloaduct 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-butylidemethylsilyl (TBS)- or methyl-protected phenylacetylene

\[
\text{Rh}_2(\text{R-TCPTTL})_4 (5) \quad \text{CF}_3\text{C}_6\text{H}_5, 23 \, ^\circ\text{C}, 1 \, \text{h}
\]

\[\text{Scheme 1. Retrosynthetic analysis of descurainin (1).}\]

Table 1

<table>
<thead>
<tr>
<th>Entry</th>
<th>Dipolarophile</th>
<th>Product</th>
<th>Yield (%)</th>
<th>ee (%)</th>
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<tbody>
<tr>
<td>1</td>
<td>11a OH OMe</td>
<td>12a</td>
<td>55</td>
<td>50</td>
</tr>
<tr>
<td>2</td>
<td>11b OTBS OMe</td>
<td>12b</td>
<td>39</td>
<td>26</td>
</tr>
<tr>
<td>3</td>
<td>11c OMe OMe</td>
<td>12c</td>
<td>44</td>
<td>20</td>
</tr>
<tr>
<td>4</td>
<td>11d OAc OMe</td>
<td>12d</td>
<td>62</td>
<td>1</td>
</tr>
<tr>
<td>5\textsuperscript{a}</td>
<td>7 OH H</td>
<td>ent-8</td>
<td>77</td>
<td>95</td>
</tr>
</tbody>
</table>

\textsuperscript{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 CF₃C₆H₅ (1 mL) was added over 1 h to a stirred solution of Rh₂(R-TCPTTL)₄ (5) (3.95 mg, 1 mol %) in CF₃C₆H₅ (1 mL) at 23 °C.

\textsuperscript{b} Isolated yield.

\textsuperscript{c} Determined by HPLC. See the Supplementary data for details.

\textsuperscript{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 cycloaduct 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.\textsuperscript{10c,d} 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 Rh₂(R-TCPTTL)₄ (5) was performed to provide the desired cycloaduct ent-8, [α]D\textsuperscript{23} = -148.5 (c 1.09, CHCl₃), in 77% yield with virtually the same enantioselectivity (95% ee) as those found in our previous study (entry 5).\textsuperscript{10c,20}

Catalytic hydrogenation of ent-8 provided exclusively the desired enta-bicyclic compound 13 as a single diastereomer in 99% yield (Scheme 2).\textsuperscript{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 (KSO₃)₂NO (Fremy’s salt)\textsuperscript{22} in the presence of KHPO₄ 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 Na₂S₂O₄ in 73% yield in two steps from 13.\textsuperscript{23,24} Since attempts at regioselective methylation of 15 were unsuccessful,\textsuperscript{24} we turned our attention to the viability of a regioselective demethylation of trimethoxybenzene derivative. Treatment of 15 with MeI (4 equiv.) and K₂CO₃ 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 PhN⁳⁺ and subsequent palladium-catalyzed reduction of the resulting enol triflate\textsuperscript{25} furnished alkene 17 in 81% yield. Reduction of 17 with LiAlH₄ 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, MeSO₂H/Nal or BF₃/ΟEt₂/Nal) frequently used in

\[\text{Scheme 2. Reagents and conditions: (a) H}_2, 10\% \text{ Pd/C, MeOH, 1 h, 99%}; (b) (KSO₃)₂NO, KHPO₄, acetone/H₂O (3:1), 10 min; (c) Na₂S₂O₄, KHPO₄, EtOAc/H₂O (5:1), 0.5 h, 73% (two steps); (d) MeI, K₂CO₃, acetone, reflux, 1 h, 99%.\]

\[\text{Scheme 3. Retrosynthetic analysis of 1.}\]
References and notes

8. In classification of reaction integration, tandem reaction is categorized as a time and space integration by the Yoshida group.
12. Very recently, Iwasawa and co-workers reported a catalytic asymmetric [3+2] cycloaddition of platinum-containing carbonyl

Acknowledgments

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Supplementary data

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

14. Charette and co-workers recently reported highly efficient asymmetric cyclopropanation with \(\alpha\)-nitro diazocacetophenones using Rh\(_2\)(S-TCPTTL)\(_4\) (4), where the X-ray crystal structure of 4 was determined: Lindsay, V. N. G.; Lin, W.; Charette, A. B. J. Am. Chem. Soc. 2009, 131, 16383–16385.


18. Recently, Peterson and co-workers reported that compound 2 could be produced from glucose, glycine, and ferulic acid in 3% yield in a simulated backing model system (10% moisture at 200 °C for 15 min). They also reported that 2 suppressed the bacterial lipopolysaccharide-mediated expression of two prototypical pro-inflammatory genes, inducible nitric oxide synthase and cyclooxygenase (COX)-2, Jiang, D.; Chiaro, C.; Maddali, P.; Prabhul, K. S.; Peterson, D. G. J. Agric. Food Chem. 2009, 57, 9932–9943.

19. Assuming that descurainin (1) might also possess the same absolute configuration as that of natural product 2, we used Rh\(_2\)(R-TCPTTL)\(_4\) (5) instead of Rh\(_2\)(S-TCPTTL)\(_4\) (4).

20. The absolute configuration of en-8 was determined to be (1S,5S) by comparison of the sign of the optical rotation with the data reported in ref. 16.


24. 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.