Notes

Catalytic Asymmetric Construction of the \textit{exo}-7-Aryl-6,8-dioxabicyclo[3.2.1]octane Framework of Psoracorylifols B and C Using a Carbonyl Ylide Cycloaddition Strategy

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Psoracorylifols A-E were isolated from the seeds of \textit{Psoralea corylifolia} L., which is a well-known traditional Chinese medicine, by Yue and co-workers in 2006.1 These compounds have been shown to exhibit significant inhibitory activity against two strains of Helicobacter pylori (SS1 and ATCC 43504) at the level of MICs of 12.5 ~ 25 µg/mL, especially against \textit{H. pylori}-ATCC 43504, a drug-resistant strain with MIC of 128 µg/mL to resist metroniazole. In 2007, Yoshikawa and co-workers independently isolated psoracorylifols B (1) and C (2), possessing a 6,8-dioxabicyclo[3.2.1]octane ring system, from the same seeds.2

The 6,8-dioxabicyclo[3.2.1]octane skeleton is a common structural subunit in many biologically active natural products.3 Among a variety of synthetic routes to such bicyclic ketals,4 the dirhodium(II)-catalyzed tandem six-membered cyclic carbonyl ylide formation/1,3-dipolar cycloaddition reaction of \textit{α}-diazo-carbonyl compounds with aldehydes as dipolarophiles5,6 is one of the most direct and powerful methods for the construction of this ring system. As a seminal work, Padwa and co-workers reported a concise synthesis of \textit{exo}- and \textit{endo}-brevicomins employing the cycloaddition of a six-membered carbonyl ylide derived from 1-diazo-2,5-hexanediol with propionaldehyde in the presence of a catalytic amount of Rh$_2$(OAc)$_4$.6d,e Consequently, the development of an enantioselective version of this sequence catalyzed by chiral dirhodium(II) complexes has become a challenging objective. In this process, the chiral dirhodium(II) catalyst must be capable of associating with carbonyl ylide intermediates in the cycloaddition step,7-9 because catalyst-free carbonyl ylides are achiral.10 Recently, we reported catalytic enantioselective 1,3-dipolar cycloadditions of a six-membered carbonyl ylide derived from 1-diazo-5-phenyl-2,5-pentanediol (4a) with aromatic aldehydes 5a-d using dirhodium(II) tetrakis[N-benzene-fused-phthaloyl-](S)-valinate, Rh$_2$(S-BPTV)$_4$ (3), in which electron-deficient dipolarophiles such as 5b and 5c provided exclusively \textit{exo} cycloadducts 6ab and 6ac in good yields and with up to 92% ee (Scheme 1).11 As a logical extension of our studies, we addressed a catalytic asymmetric construction of the \textit{exo}-7-aryl-6,8-dioxabicyclo[3.2.1]octane framework of psoracorylifols B (1) and C (2). Herein, we report \textit{exo}- and enantioselective cycloadditions of a six-membered carbonyl ylide derived from 1-diazo-6-methyl-2,5-heptanediol (4b) with aromatic aldehydes under the catalysis of Rh$_2$(S-BPTV)$_4$.

\begin{scheme}[t]
\centering
\includegraphics[width=\textwidth]{Scheme1.png}
\caption{Enantioselective tandem carbonyl ylide formation/1,3-dipolar cycloaddition of 4a with 5a-d catalyzed by Rh$_2$(S-BPTV)$_4$ (3)\textsuperscript{1}}
\end{scheme}

\textsuperscript{1}This paper is dedicated to Professor Sunggak Kim on the occasion of his honorable retirement.
The ratio of endo cycloadducts was determined to be 79% by HPLC using Daicel Chiralpak IA. 

**Experimental Section**

**Representative procedure for the tandem carbonyl ylide formation/1,3-dipolar cycloaddition (entry 7 in Table 1).** Rh₄(S-BPTV)₄ (3.1 mg, 0.002 mmol, 1 mol%) was added in one portion to a solution of 4b (33.6 mg, 0.20 mmol) and 5h (84.9 mg, 0.40 mmol) in benzo trifluoride (2.0 mL) at 23 °C. After stirring for 5 min, the mixture was concentrated in vacuo. The ratio of 6bh and 7bh was determined to be 95:5 by ¹H NMR of the crude product. The residue was purified by column chromatography (silica gel, 1:2 hexane/benzene → 10:1 hexane/Et₂O) to give exo-7-(4-benzyloxyphenyl)-5-isopropyl-6,8-dioxabicyclo[3.2.1]octan-2-one (6bh) (43.3 mg, 0.123 mmol, 62%) as a white solid, along with endo isomer 7bh (1.6 mg, 0.04 mmol, 2%) as a white solid.

6bh: TLC Rf 0.21 (41.64 hexane/EtOAc, 1:1); mp 51.5 ~ 53.0 °C for 86% ee; [α]D²⁰ ~ 37.5 (c 1.01, CHCl₃) for 86% ee; IR (KBr) ν 2968, 1733, 1611, 1585, 1243 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 1.09 (d, J = 6.9 Hz, 3H, CH(C₃H₇)), 1.10 (d, J = 6.9 Hz, 3H, CH(CH₃)), 2.09 (ddd, J = 4.6, 8.0, 13.8 Hz, 1H, CH₂), 2.24 (heptet, J = 6.9 Hz, 1H, CH(CH₃)) 2.26 (m, 1H, CH₂) 2.54 (ddd, J = 1.2, 4.6, 8.0, 16.0 Hz, 1H, COCH₃), 2.61 (ddd, J = 8.0, 8.0, 16.0 Hz, 1H, CH₂) 4.41 (s, 1H, COCH₃), 4.98 (s, 1H, ArCH), 5.06 (s, 2H, PhCH₃O), 6.95 (d, J = 8.6 Hz, 2H, Ar), 7.29 (d, J = 8.6 Hz, 2H, Ar), 7.32-7.43 (m, 5H, Ar), 13C NMR (100 MHz, CDCl₃) δ 17.6 (CH₃), 17.9 (CH₃), 28.7 (CH₃), 32.5 (CH₂), 35.6 (CH₃), 70.0 (CH₂), 79.4 (CH), 86.4 (CH), 112.6 (C), 114.8 (CH), 127.4 (CH), 127.6 (CH), 128.0 (CH), 128.6 (CH), 132.5 (C), 136.8 (CH).

Table 1. Enantioselective cycloaddition of 4b with aldehydes 5a, b, d-h catalyzed by Rh₄(S-BPTV)₄ (3)

<table>
<thead>
<tr>
<th>entry</th>
<th>R</th>
<th>aldehyde</th>
<th>cycloadduct</th>
<th>yield (%)</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>5a H</td>
<td>6ba+7ba</td>
<td></td>
<td>62</td>
<td>91:9</td>
</tr>
<tr>
<td>2</td>
<td>5b NO₂</td>
<td>6bh+7bb</td>
<td></td>
<td>63</td>
<td>93:7</td>
</tr>
<tr>
<td>3</td>
<td>5e OMe</td>
<td>6he+7be</td>
<td></td>
<td>72</td>
<td>95:5</td>
</tr>
<tr>
<td>4</td>
<td>5f OAc</td>
<td>6hf+7bf</td>
<td></td>
<td>63</td>
<td>94:6</td>
</tr>
<tr>
<td>5</td>
<td>5d OMe</td>
<td>6lid+7ld</td>
<td></td>
<td>57</td>
<td>94:6</td>
</tr>
<tr>
<td>6</td>
<td>5g OOM</td>
<td>6lid+7lg</td>
<td></td>
<td>60</td>
<td>94:6</td>
</tr>
<tr>
<td>7</td>
<td>5h OBN</td>
<td>6lid+7lh</td>
<td></td>
<td>64</td>
<td>95:5</td>
</tr>
</tbody>
</table>

Notes

(C), 158.7 (C), 206.7 (C); EI-HRMS caleed for C₂₇H₄₀O₂ (M⁺) 352.1675, found 352.1673. 7th: TLC Rᵣ 0.30 (4:1 hexane/EtOAc); ¹H NMR (400 MHz, CDCl₃) δ 1.11 (d, J = 7.3 Hz, 3H, CH₂(C₆H₅)), 1.12 (d, J = 7.3 Hz, 3H, CH₂(C₆H₅)), 2.11-2.22 (m, 4H, CH₂), 3.27 (m, 1H, CH₂), 4.66 (dd, J = 1.4, 5.4 Hz, 1H, COCH₂), 5.03 (s, 2H, PhCH₂O), 5.21 (d, J = 5.4 Hz, 1H, ArCH), 6.93 (d, J = 8.6 Hz, 2H, Ar), 7.23 (d, J = 8.6 Hz, 2H, Ar), 7.33-7.43 (m, 5H, Ar).

The enantiomeric excess of 6hh was determined to be 86% by HPLC using a Daicel Chiralpak AD-H column (19:1 hexane/2-propanol, flow rate: 1.0 mL/min; detection: 230 nm): retention time: 14.4 min (major enantiomer), 17.3 min (minor enantiomer).

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References

6. For tandem carbonyl ylide formation/cycladdition of ethyl diazoacetate with p-nitrobenzaldehyde in the presence of the chiral dirhodium(II) carboxamidate catalyst Rh₄[(S-MEOX)₄] afforded the all-cis trisubstituted 1,3-dioxolane as the major product with 28% ee. Doyle, M. P.; Forbes, D. C. Chem. Rev. 1998, 98, 911.
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