Title
Asymmetric Synthesis of (-)-Incarvillateine Employing an Intramolecular Alkylation via Rh-Catalyzed Olefinic C-H Bond Activation

Permalink
https://escholarship.org/uc/item/55b8f2v8

Author
Tsai, Andy

Publication Date
2009-02-27
Asymmetric Synthesis of \((-\))-Incarvillateine Employing an Intramolecular Alkylation via Rh-Catalyzed Olefinic C–H Bond Activation

Andy S. Tsai, Robert G. Bergman,* Jonathan A. Ellman*

Department of Chemistry, University of California, Berkeley, California 94720

RECEIVED DATE (automatically inserted by publisher); E-mail: bergman@ccchem.berkeley.edu; jeliman@uclink.berkeley.edu

\((-\))-Incarvillateine \((-\))-\(\text{I}\) is a monoterpenoid alkaloid that has attracted attention due to its potent analgesic properties.\(^1\) The first enantioselective synthesis of this natural product was recently achieved,\(^2\) but required a number of steps to correctly set the stereochemistry of the five contiguous stereocenters on the bicyclic piperidine moiety. Herein, we report a concise asymmetric synthesis of \((-\))-incarvillateine employing an intramolecular alkylation of an olefinic C–H bond to set two of the stereocenters with simultaneous stereospecific introduction of an exocyclic, tetrasubstituted alkene framework upon which the bicyclic piperidine could rapidly be assembled.\(^3\)

\((-\))-Incarvillateine may be retrosynthetically disconnected to cyclobutane 2 and piperidine 3 (Scheme 1). The synthesis of 2 can be accomplished in two steps from commercially available ferulic acid.\(^2\) Piperidine 3 can be accessed from cyclopentane 4 through reduction of the imine, lactamization, and reduction of both the lactam and alkene. The formation of 4 can be achieved in a key step by the intramolecular alkylation of 5 via Rh-catalyzed C–H activation, which based upon the reaction mechanism,\(^4\) should exclusively provide the desired exocyclic double bond geometry and the anti relationship of the methyl and ester functionalities. Furthermore, the secondary TBS ether should result in diastereoselective alkylation to install the correct absolute stereochemistry at the methyl and ester stereocenters.

**Scheme 1.** Retrosynthesis of \((-\))-incarvillateine

Cross metathesis of 7 with methacrolein using Grubbs' 2nd generation catalyst provided 8 in good yield as a single isomer.\(^5\) Imine 5 was then formed through condensation of 8 with methyamine in the presence of molecular sieves.

**Scheme 2.** Synthesis of \(\alpha,\beta\)-Unsaturated Imine, 5

The diastereoselective intramolecular alkylation of 5 was explored using conditions recently reported for the intermolecular \(\beta\)-alkenylation of \(\alpha,\beta\)-unsaturated imines with alkynes (Table 1).\(^7\) Ferrocenyl (Fc) dialkyl phosphines (entries 1-2) as well as 4-(dimethylamino)phenyl (DMAPh) based phosphines (entries 3-8) were evaluated. Though many of the ligands explored were active, resulting in quantitative cyclization of 5, (DMAPh)-PEt\(_3\) was the most selective ligand, providing diastereomers 1 and 9 in a \(\sim\)5:1 ratio (entry 7).\(^8\) The high catalyst activity also allowed the catalyst loading to be reduced to 2.5 mol\% (entry 8).

**Table 1.** Ligand screen for the diastereoselective alkylation of 5

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ligand</th>
<th>% Rh</th>
<th>% L</th>
<th>(7) (°C)</th>
<th>(7) (%)</th>
<th>(4 + 9) (%)</th>
<th>(49)</th>
<th>(49)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>FeCOCy(_2)</td>
<td>5</td>
<td>11</td>
<td>45</td>
<td>25</td>
<td>100</td>
<td>53:47</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>FePEt(_3)</td>
<td>5</td>
<td>11</td>
<td>25</td>
<td>21</td>
<td>100</td>
<td>69:31</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>(DMAPh)(_2)PMe</td>
<td>10</td>
<td>22</td>
<td>25</td>
<td>8</td>
<td>100</td>
<td>75:25</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>(DMAPh)PMe(_2)</td>
<td>10</td>
<td>22</td>
<td>45</td>
<td>19</td>
<td>100</td>
<td>75:24</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>(DMAPh)Cy(_2)</td>
<td>5</td>
<td>11</td>
<td>45</td>
<td>21</td>
<td>34</td>
<td>62:38</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>(DMAPh)PEt(_3)</td>
<td>5</td>
<td>11</td>
<td>22</td>
<td>24</td>
<td>100</td>
<td>86:14</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>(DMAPh)PEt(_3)</td>
<td>5</td>
<td>11</td>
<td>45</td>
<td>6</td>
<td>100</td>
<td>83:17</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>(DMAPh)PEt(_3)</td>
<td>2.5</td>
<td>5.5</td>
<td>45</td>
<td>6</td>
<td>100</td>
<td>83:17</td>
<td></td>
</tr>
</tbody>
</table>

\(^a\) Yields based on \(^1\)H NMR integration relative to residual protio toluene as an internal standard. \(^b\) Diastereomeric ratio determined by \(^1\)H NMR. Fc: ferrocenyl. DMAPh: 4-(dimethylamino)phenyl.
Scheme 3. Synthesis of 3

Due to facile tautomerization of 4 to the ester conjugated dienamine, it was necessary to directly convert the crude compound to a more stable intermediate. This was accomplished through imine reduction with NaBH₄ followed by lactamization upon heating to provide 10, which after chromatography was isolated as a single diastereomer in 49% overall yield from 5 (Scheme 3). Hydrogenation of the tetrasubstituted olefin required high pressure and elevated temperature, but occurred exclusively on the less hindered face to yield 11. Reduction of 11 with LiAlH₄ followed by cleavage of the TBS protecting group under acidic conditions gave 3.

Completion of the synthesis of (-)-incarvillatine was carried out in accordance with the previously reported sequence: Mitsunobu coupling between 3 and 2 followed by removal of the tosyl protecting groups. The low reported yield in the Mitsunobu coupling reaction (30% based on the more valuable fragment 3), encouraged us to optimize this step. Commercially available trans-2-methylcyclopentanol (12) was used as the model substrate for 3 (Table 2). In addition to DEAD/PPh₃ (entries 1-5), ADDP/PBu₃ (1,1'-azodicarbonyl)diisopiperidine was explored as coupling reagents but showed diminished reactivity (entries 6-7). A range of temperatures and solvents was also investigated. Refluxing conditions reported in the prior synthesis were found to be unnecessary and in fact resulted in reduced yield for the model system (entry 1). Dioxane and CH₂Cl₂ were found to be poor solvents for the reaction due to limited solubility of 2 at low temperatures (entries 4-5). Use of DEAD/PPh₃ at low temperatures in THF provided the highest yield (entry 3). Employing these optimal conditions from the model study, 14 was obtained in 55% yield from 3 (Scheme 4).

Table 2. Mitsunobu Coupling of Model Substrate.

<table>
<thead>
<tr>
<th>entry</th>
<th>reagents</th>
<th>T (°C)</th>
<th>solvent</th>
<th>% 11³</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>DEAD, PPh₃</td>
<td>65</td>
<td>THF</td>
<td>36</td>
</tr>
<tr>
<td>2</td>
<td>DEAD, PPh₃</td>
<td>60</td>
<td>THF</td>
<td>18</td>
</tr>
<tr>
<td>3</td>
<td>DEAD, PPh₃</td>
<td>-20</td>
<td>THF</td>
<td>72</td>
</tr>
<tr>
<td>4</td>
<td>DEAD, PPh₃</td>
<td>25</td>
<td>Dioxane</td>
<td>29</td>
</tr>
<tr>
<td>5</td>
<td>DEAD, PPh₃</td>
<td>0</td>
<td>CH₂Cl₂</td>
<td>33</td>
</tr>
<tr>
<td>6</td>
<td>ADDP, PBu₃</td>
<td>65</td>
<td>Toluene</td>
<td>28</td>
</tr>
<tr>
<td>7</td>
<td>ADDP, PBu₃</td>
<td>25</td>
<td>THF</td>
<td>0</td>
</tr>
</tbody>
</table>

³ Isolated yield based on 2-methylcyclopentanol. DEAD: (Diethyl diazocarboxylate), ADDP: (1,1′-azodicarbonyl)diisopiperidine.


Alternatives to sodium amalgam for removal of the tosyl protecting groups in 14 were also explored because the yield reported in the literature was not satisfactory (58%). Sodium anthranilate proved to be optimal and provided (-)-incarvillatine in high yield (Scheme 4).

In summary, a concise asymmetric synthesis of (-)-incarvillatine was accomplished in 11 steps and 15.4% overall yield representing a substantial improvement over the previously reported synthesis. The Rh-catalyzed alkylation of 5 simultaneously installed two out of the five necessary stereocenters in the bicyclic piperidine while also stereospecifically introducing the tetrasubstituted, exocyclic alkene that enabled the rapid assembly of (-)-1.

Acknowledgment. This work was supported by NIH Grant GM069559 to J.A.E. and the Director and Office of Energy Research, Office of Basic Energy Sciences, Chemical Sciences Division, U.S. Department of Energy, under Contract DE-AC03-76SF00098 to R.G.B. We thank Denise A. Colby for providing ligands and helpful discussions. Work done under DOE Contract No. DE-AC02-05CH11231.

Supporting Information Available: Complete experimental details and spectral data for all compounds described. This material is available free of charge via the Internet at http://pubs.acs.org.

References

(8) Alternative hydroxyl protecting groups such as the benzyl ether were also examined, but resulted in decreases in both the rate and diastereoselectivity of the Rh-catalyzed alkylation.
(10) The major side product (22%) resulted from competitive amidation of one of the carboxylic acids in 2 with the hydrazine of reduced DEAD.
(12) The synthesis of racemic 3 has also been reported: Honda, Toshio, H.; Kanaeda K. J. Org. Chem. 2007, 72, 6541-6547.
ABSTRACT

An asymmetric total synthesis of (-)-incarvillateine, a natural product having potent analgesic properties, has been achieved in 11 steps and 15.4% overall yield. The key step is a rhodium-catalyzed intramolecular alkylation of an olefinic C-H bond to set two stereocenters. Additionally, this transformation produces an exocyclic, tetrasubstituted alkene through which the bicyclic piperidine moiety can readily be accessed.