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

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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.

(–)-Incarvillateine (–)-(**1**) is a monoterpene 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.³ 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.^{4–6}

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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>.

(-)-Incarvilleine 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 obtained from **4** through reduction of the imine, lactamization, and reduction of both the lactam and alkene. Cyclopentane **4** should be accessible in a key step by the intramolecular alkylation of **5** via Rh-catalyzed C–H activation⁷ followed by synalkene insertion and reductive elimination to 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.

Asymmetric allylation of commercially available **6** with allyltributyltin under Keck conditions proceeded in quantitative yield and with excellent enantioselectivity (Scheme 2).⁸ The resulting alcohol was subsequently protected as a TBS ether (**7**). Cross metathesis of **7** with methacrolein using Grubbs' 2nd generation catalyst provided **8** in good yield as a single isomer.⁹ Imine **5** was then formed through condensation of **8** with methylamine in the presence of molecular sieves.

The diastereoselective intramolecular alkylation of **5** was explored using conditions recently reported for the intermolecular β -alkenylation of α,β -unsaturated imines with alkynes (Table 1).¹⁰ 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)-PEt₂ was the most selective ligand, providing diastereomers **4** and **9** in a ~5:1 ratio (entry 7).¹¹ The high catalyst activity also allowed the catalyst loading to be reduced to 2.5 mol% (entry 8).

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 LiAlH_4 , followed by cleavage of the TBS protecting group under acidic conditions gave **3**.

Completion of the synthesis of (–)-incarvillateine was carried out in accordance with the previously reported sequence: Mitsunobu coupling between **3** and **2** followed by removal of the tosyl protecting groups.² 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/ PPh_3 (entries 1–5), ADDP (1,1'-(azodicarbonyl)dipiperidine)/ PBU_3 ¹² was evaluated 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 CH_2Cl_2 were found to be poor solvents for the reaction due to limited solubility of **2** at low temperatures (entries 4–5). Use of DEAD/ PPh_3 at low temperatures in THF provided the highest yield (entry 3).

Employing the optimal Mitsunobu coupling conditions from the model study, **14** was obtained from **2** and **3** in 55% yield (Scheme 4).¹³ 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%).² Sodium/anthracene¹⁴ proved to be optimal and provided (–)-incarvillateine (**1**) in high yield (Scheme 4).

In summary, a concise asymmetric synthesis of (–)-incarvillateine was accomplished in 11 steps and 15.4% overall yield representing a substantial improvement over the previously reported synthesis.^{2,15} The Rh-catalyzed alkylation of **5** simultaneously installed two of the five necessary stereocenters in the bicyclic piperidine while also stereospecifically introducing the tetrasubstituted, exocyclic alkene that enabled the rapid assembly of (–)-**1**.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Scheme 1.
Retrosynthesis of (-)-Incarvillateine

Scheme 2.
Synthesis of α,β -Unsaturated Imine **5**

Scheme 3.
Synthesis of bicyclic piperidine **3**

Scheme 4.
Synthesis of (-)-Incarvilleine

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

(P = TBS)

DMAPh =

entry	ligand	% Rh	% L	T (°C)	t (h)	4 + 9 (%) ^a	4:9 dr ^b
1	FePCy ₂	5	11	45	25	100	53:47
2	FePEt ₂	5	11	25	21	100	69:31
3	(DMAPh) ₂ PMe	10	22	25	8	100	75:25
4	(DMAPh)PMe ₂	10	22	45	19	100	75:24
5	(DMAPh)PCy ₂	5	11	45	21	34	62:38
6	(DMAPh)PEt ₂	5	11	22	54	100	86:14
7	(DMAPh)PEt ₂	5	11	45	6	100	83:17
8	(DMAPh)PEt ₂	2.5	5.5	45	6	100	83:17

^aYields based on H NMR integration relative to residual protio toluene as an internal standard.

^bDiastereomeric ratio determined by ¹H NMR. Fc: ferrocenyl. DMAPh: 4-(dimethylamino)phenyl.

Table 2

Mitsunobu Coupling of Model Substrate.

entry	reagents	<i>T</i> (°C)	solvent	% 11 ^a
1	DEAD, PPh ₃	65	THF	36
2	DEAD, PPh ₃	0	THF	61
3	DEAD, PPh₃	-20	THF	72
4	DEAD, PPh ₃	25	Dioxane	29
5	DEAD, PPh ₃	0	CH ₂ Cl ₂	33
6	ADDP, PBu ₃	65	Toluene	28
7	ADDP, PBu ₃	25	THF	0

^a Isolated yield based on 2-methylcyclopentanol. DEAD: (Diethyl diazocarbonylate), ADDP: (1,1'-(azodicarbonyl)dipiperidine)