ORGANIC LETTERS

2009
Vol. 11, No. 12
2579−2581

Organocatalytic Enantioselective Total Synthesis of (−)-Arboricine

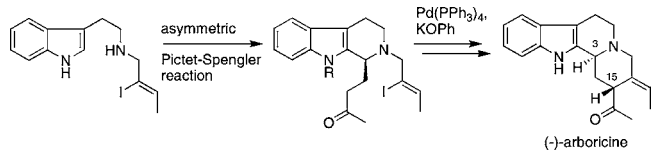
Martin J. Wanner,[†] Rowan N. A. Boots,[†] Bram Eradus,[†] René de Gelder,[‡] Jan H. van Maarseveen,*[,†] and Henk Hiemstra*[,†]

Van't Hoff Institute for Molecular Sciences, University of Amsterdam, Nieuwe Achtergracht 129, 1018 WS, Amsterdam, The Netherlands, and Institute for Molecules and Materials, Radboud University, Toernooiveld 1, 6525 ED Nijmegen, The Netherlands

j.h.vanmaarseveen@uva.nl; h.hiemstra@uva.nl

Received April 23, 2009

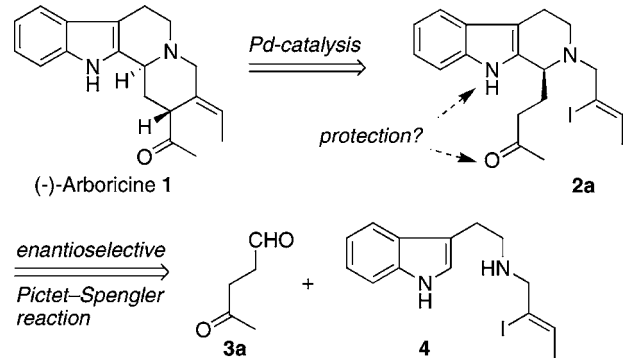
ABSTRACT



The tetracyclic indole alkaloid (−)-arboricine has been prepared using an asymmetric organocatalytic Pictet−Spengler reaction as the key step followed by a diastereoselective Pd-catalyzed iodoalkene/enolate cyclization. The absolute stereochemistry was unequivocally proven by X-ray crystallographic analysis and appeared to be opposite to the published structure in the original paper.

The deplancheine-type tetracyclic indole alkaloid arboricine **1** was isolated from the leafs of *Kopsia arborea* by Kam and co-workers and showed a moderate ability to reverse multidrug resistance in vincristine-resistant KB (VJ300) cells.[1] We have recently published studies on the asymmetric binolphosphoric acid-catalyzed Pictet−Spengler (PS) reaction of benzyltryptamines arriving at a variety of β-carbolines.[2] As an extension of this work, we report herein a concise and scalable synthesis of arboricine based on an asymmetric PS reaction of 4-oxo-pentanal and N_b-iodoolefin-functionalized tryptamine followed by a Pd(0)-catalyzed enolate cyclization (Scheme 1).

Scheme 1. Arboricine Retrosynthesis



The synthesis started with the known tryptamine **4**,[3] made in one step by alkylation of tryptamine with *Z*-2-iodo-2-butene-1-ol mesylate in 84% yield (not shown).[4] PS con-

[†] University of Amsterdam.
[‡] Radboud University.

(1) Lim, K. H.; Komiyama, K.; Kam, T. S. *Tetrahedron Lett.* **2007**, *48*, 1143–1145.

(2) (a) Sewgobind, N. V.; Wanner, M. J.; Ingemann, S.; de Gelder, R.; van Maarseveen, J. H.; Hiemstra, H. *J. Org. Chem.* **2008**, *73*, 6405–6408. For other recent enantioselective catalytic Pictet−Spengler reactions, see: (b) Taylor, M. S.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2004**, *126*, 10558–10559. (c) Seayad, J.; Seayad, A. M.; List, B. *J. Am. Chem. Soc.* **2006**, *128*, 1086–1087. (d) Wanner, M. J.; van der Haas, R. N. S.; de Cuba, K.; van Maarseveen, J. H.; Hiemstra, H. *Angew. Chem., Int. Ed.* **2007**, *46*, 7485–7487. (e) Klausen, R. S.; Jacobsen, E. N. *Org. Lett.* **2009**, *11*, 887–890. (f) Bou-Hamdan, F. R.; Leighton, J. L. *Angew. Chem., Int. Ed.* **2009**, *48*, 2403–2406.

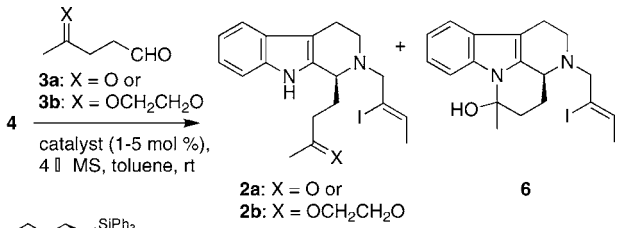
(3) Takayama, H.; Watanabe, F.; Kitajima, M.; Aimi, N. *Tetrahedron Lett.* **1997**, *38*, 5307–5310.

(4) Prepared via iodination of crotonaldehyde (see Supporting Information): Krafft, M. E.; Cran, J. W. *Synlett* **2005**, 1263–1266.

10.1021/ol900888e CCC: $40.75
Published on Web 05/19/2009

densation of **4** with aldehyde **3a** mediated by (*R*)-3,3′-triphenylsilyl-binol phosphoric acid **5a** ((*R*)-binol-PA, 5 mol %) in toluene in the presence of 4 Å molecular sieves at room temperature for 18 h gave β-carboline (*S*)-**2a**[5] together with aminal **6** in 55% yield and a 75/25 ratio, respectively, and an unacceptable 38% ee for both (*S*)-**2a** and **6**, as determined by chiral HPLC (Scheme 2). Gratifyingly,

Scheme 2. Asymmetric Pictet−Spengler Reaction



catalysts:
5a: (*R*)-Binol PA
5b: (*S*)-Binol PA
5c: (*R*)-H8-Binol-PA

ald.	catalyst	product	yield % (scale)	ee %
3a	**5a** (5 mol %)	(*S*)-**2a/6**	55[a] (0.1 mmol)	38
3b	**5a** (2 mol %)	(*S*)-**2b**	81 (0.1 mmol)	78
3b	**5b** (2 mol %)	(*R*)-**2b**	80 (0.1 mmol)	77
3b	**5c** (2 mol %)	(*S*)-**2b**	86 (1.0 mmol)	89
3b	**5a** (1 mol %)	(*S*)-**2b**	92 (5.0 mmol)	78

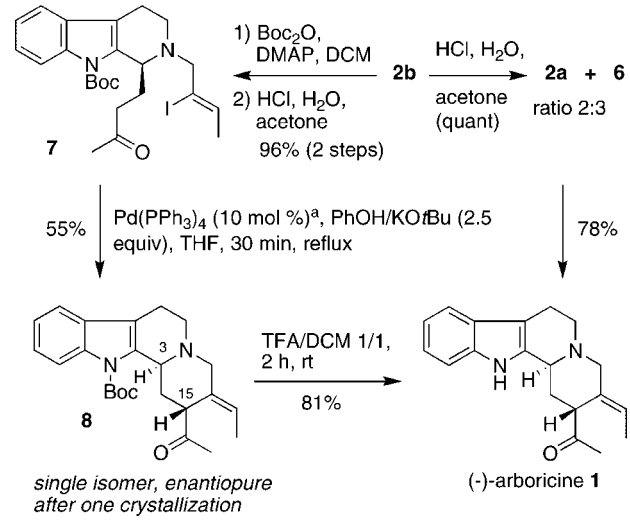
[a] ratio **2a**/**6** = 67/33

protection of ketone **3a** as the dioxolane **3b**[6] not only avoided aminal formation thus exclusively providing (*S*)-**2b** in 81% yield but also raised the ee to 78%. It is remarkable that installing the acetal protecting group, which is quite remote from the iminium intermediate, improves not only the ee but also the rate of the PS reaction allowing lower catalyst loadings down to 1%. The mildness of the process is underscored by the fact that the dioxolane-protected ketone remained unaffected. Obviously, (*R*)-**2b** was obtained starting from (*S*)-binol-PA. The best ee was obtained using the sterically slightly more demanding catalyst (*R*)-H_8-binol-PA **5c** that gave (*S*)-**2b** in 86% yield and 89% ee. Scaling up the reaction to 5 mmol only required 1 mol % of catalyst **5a** furnishing (*S*)-**2b** in an isolated yield of 92% and 78% ee.

To avoid possible racemization via acid-catalyzed scission of the bond between the asymmetric carbon atom and N_b or a retro PS process[7] during the hydrolysis of the acetal moiety, a Boc-protecting group was installed on the indole-nitrogen (Scheme 3). Treatment of **2b** with Boc_2O and DMAP followed by diluted HCl in acetone gave ketone **7** in 96% overall yield.

Now the stage was set for closure of the piperidine ring by a Pd(0)-catalyzed vinyl iodide−enolate coupling for which

Scheme 3. Palladium-Catalyzed Iodoalkene/Enolate Cyclization[a]



[a] With 5 mol % of $Pd(PPh_3)_4$ and 3 h reflux, the yield dropped to 33%, and also substantial amounts of an analogue of **8** were formed in which the double bond shifted into conjugation.

we selected the procedure published by Sole and Bonjoch relying on potassium phenoxide as a mild base to avoid migration of the isolated exocyclic double bond to a conjugated system with an endocyclic double bond.[8] After refluxing of **7** in THF for 30 min in the presence of $Pd(PPh_3)_4$ (10 mol %) and KOPh (2.5 equiv), all starting material was converted followed by workup to give **8** in 55% isolated yield as a single diastereoisomer.

A single recrystallization from the EtOAc/PE mixture gave enantiomerically pure **8** for which the X-ray structure confirmed the 3*S*,15*R* absolute stereochemistry as depicted in Figure 1. [9]

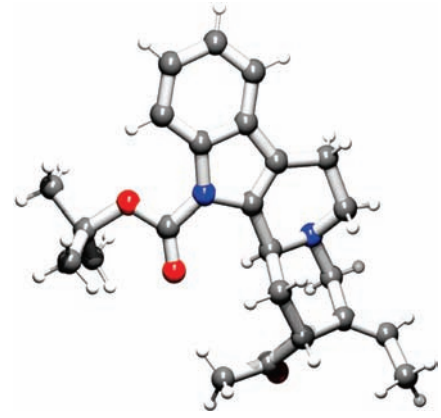


Figure 1. X-ray crystal structure of **8**.

(−)-Arboricine **1** was obtained after TFA-mediated removal of the Boc-protecting group of **8** in an isolated yield of 81%.[10] Synthetic arboricine was enantiopure as determined

(5) In preliminary catalyst screening experiments, we always used (*R*)-binol phosphoric acid. Our previous work (ref 2a and 2d) shows that this will lead to β-carbolines with the *S* configuration at C3.

(6) Prepared from ethyl levulineate via acetalization and DIBAL-H reduction (see Supporting Information). This aldehyde is very sensitive for air-oxidation and is always chromatographed before use. The corresponding carboxylic acid is an efficient Pictet−Spengler catalyst, and the ee immediately drops when this acid is present.

(7) Kumpaty, H. J.; Van Linn, M. L.; Kabir, M. S.; Försterling, F. H.; Deschamps, J. R.; Cook, J. M. *J. Org. Chem.* **2009**, *74*, 2771–2779.

with chiral HPLC. The sign of the optical rotation of our synthetic product (i.e., $[\alpha]_D$ −281 (*c* 0.23, $CHCl_3$)) and that of the natural material ($[\alpha]_D$ −110 (*c* 0.14, $CHCl_3$)) was the same showing that we had obtained the natural enantiomer. This means that the stereochemistry as suggested previously by Kam must be revised.

At this stage, we wondered if we could also synthesize arboricine without sacrificing the ee by omitting the indole-N-Boc-protecting group. Dissolving **2b** in diluted HCl in acetone gave quantitatively a mixture of **2a** together with aminal **6** in a 2/3 ratio, respectively. Gratifyingly, under the slightly basic conditions of the final Pd(0)-catalyzed cyclization, an equilibrium between **2a** and **6** existed enabling an efficient and diastereoselective conversion to arboricine **1** in a yield of 78%, albeit with an ee that dropped from 86% to 65%.

In conclusion, an efficient six-step synthesis starting from tryptamine gave the tetracyclic β-carboline arboricine in 33% overall yield using an enantioselective organocatalytic Pictet−Spengler reaction and a stereoselective intramolecular Pd(0)-catalyzed vinyl iodide−enolate coupling as the key steps. An alternative three-step route starting from tryptamine without the use of protecting groups gave arboricine in an overall yield of 35% but with a significantly lower ee.

Supporting Information Available: Detailed experimental procedures and spectroscopic data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OL900888E

(8) (a) Sole, D.; Urbaneja, X.; Bonjoch, J. *Adv. Synth. Catal.* **2004**, *346*, 1646–1650. For a similar reaction, see also: (b) Yu, J. M.; Wang, T.; Liu, X. X.; Deschamps, J.; Flippen-Anderson, J.; Liao, X. B.; Cook, J. M *J. Org. Chem.* **2003**, *68*, 7565–7581.

(9) CCDC 727699 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www. ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB21EZ, U.K.; fax (+44)1223-336-033; or deposit@ccdc.cam.ac.uk). The crystallographic data are also available in the CIF file in the Supporting Information.

(10) The ^1H and ^{13}C NMR spectra of synthetic arboricine were identical to the natural compound (see ref 1).