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Total Synthesis of (−)-Aurantioclavine

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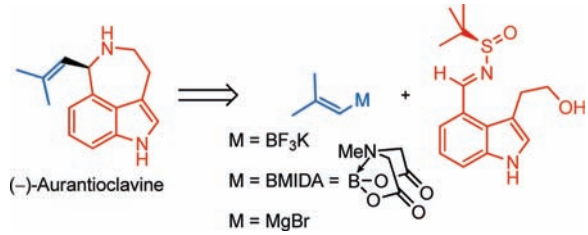
ABSTRACT



The concise total synthesis of (−)-aurantioclavine has been achieved by taking advantage of strategies for the asymmetric alkenylation of *N-tert*-butanesulfinyl imines. The enantiomerically pure natural product was prepared in 6 steps and 27% overall yield by using Rh-catalyzed addition of a *N*-methyliminodiacetic acid (MIDA) boronate and in 5 steps and 29% yield by employing a Grignard reagent addition sequence.

(−)-Aurantioclavine ((−)-**1**) was isolated from *Penicillium aurantiovirens* in 1981,[1] and soon after its discovery, concise syntheses of racemic aurantioclavine were reported in the literature.[2] This ergot alkaloid continues to attract considerable interest from the synthetic community due to its proposed role as an intermediate in the biosynthesis of the complex polycyclic alkaloids of the communesin family (Figure 1).[3,4] However, despite this attention, the asymmetric synthesis of aurantioclavine has only recently been accomplished in 13 steps and <1% overall yield from commercially available material.[5] Herein, we report a new, highly efficient synthesis of (−)-aurantioclavine that utilizes asymmetric alkenylation of a densely functionalized *N-tert*-butanesulfinyl imine.

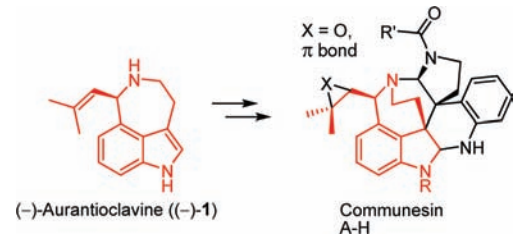


Figure 1. (−)-Aurantioclavine as an intermediate en route to the communesins.

Our approach to (−)-aurantioclavine is depicted in Scheme 1. We envisioned that the natural product could be accessed from sulfinamide **2** via cyclization to form the azepine ring followed by cleavage of the sulfinyl group. The asymmetric synthesis of sulfinamide **2** would be accomplished by the addition of the appropriate organometallic reagent to *N*-sulfinyl imine **3**.[6] This imine could in turn be generated by the condensation of *N-tert*-butanesulfinamide with the aldehyde resulting from formylation of 4-bromotryptophol.[7]

Installation of the formyl group was initially attempted via a traditional approach involving KH-mediated deproto-

(1) Kozlovskii, A. G.; Soloveva, T. F.; Sakharobskii, V. G.; Adanin, V. M. *Dokl. Akad. Nauk SSSR* **1981**, *260*, 230.

(2) (a) Yamada, F.; Makita, Y.; Suzuki, T.; Somei, M. *Chem. Pharm. Bull.* **1985**, *33*, 2162. (b) Hegedus, L. S.; Toro, J. L.; Miles, W. H.; Harrington, P. J. *J. Org. Chem.* **1987**, *52*, 3319. (c) Yamada, K.; Namerikawa, Y.; Haruyama, T.; Miwa, Y.; Yanada, R.; Ishikura, M. *Eur. J. Org. Chem.* **2009**, 5752.

(3) (a) May, J. A.; Stoltz, B. M. *Tetrahedron* **2006**, *62*, 5262. (b) May, J. A.; Zeidan, R. K.; Stoltz, B. M. *Tetrahedron Lett.* **2003**, *44*, 1203.

(4) The only syntheses to date of a communesin ((±)-communesin F): (a) Yang, J.; Wu, H.; Shen, L.; Qin, Y. *J. Am. Chem. Soc.* **2007**, *129*, 13794. (b) Liu, P.; Seo, J. H.; Weinreb, S. M. *Angew. Chem., Int. Ed.* **2010**, *49*, 2000. For a review on synthetic efforts toward the communesins, see: (c) Siengalewicz, P.; Gaich, T.; Mulzer, J. *Angew. Chem., Int. Ed.* **2008**, *47*, 8170.

(5) Krishnan, S.; Bagdanoff, J. T.; Ebner, D. C.; Ramtohul, Y. K.; Tambar, U. K.; Stoltz, B. M. *J. Am. Chem. Soc.* **2008**, *130*, 13745. In accomplishing the total synthesis of (−)-aurantioclavine the authors assigned the (*R*) absolute configuration.

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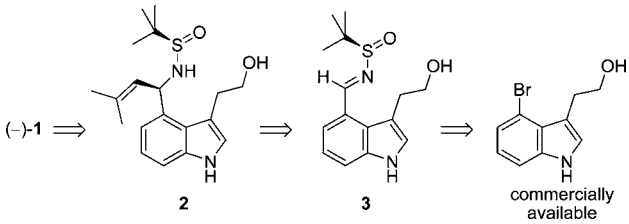
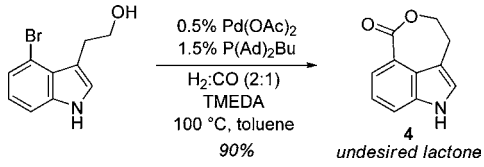
Scheme 1. Retrosynthetic Analysis of (−)-Aurantioclavine



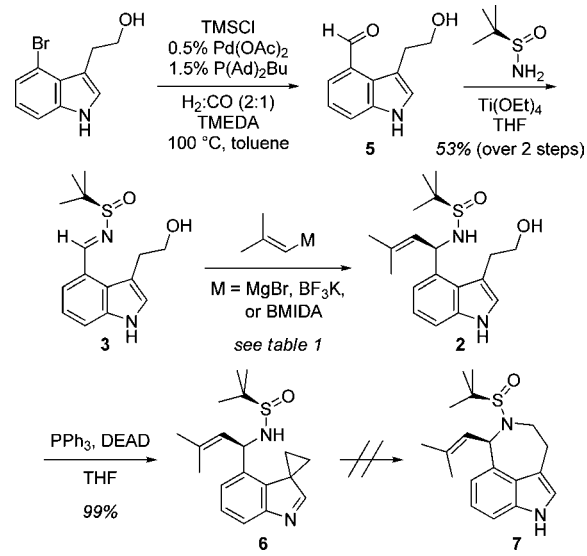
nation of the acidic sites, followed by a lithiation−formylation sequence with *t*BuLi and DMF.[8] While the desired aldehyde could be obtained by using this method, the reaction yield was highly variable due to the poor solubility of the initially formed dianion. We next turned to the highly efficient Pd-catalyzed formylation of aryl and heteroaryl bromides reported by Beller and co-workers.[9] While application of their general procedure resulted in complete conversion to undesired lactone **4** (Scheme 2), in situ protection of the alcohol with TMSCl prevented this cyclization and afforded the desired aldehyde **5** (Scheme 3). Isolation of aldehyde **5** was complicated by polymerization via intermolecular hemiacetal formation, and therefore the unpurified material was directly converted to *N*-*tert*-butanesulfinyl imine **3** in 53% yield over the two steps.

Scheme 2



With the substrate for the key reaction in hand, we explored the alkenylation of *N*-sulfinyl imine **3** (Table 1). Addition of Grignard reagent **8** as a solution in ether resulted in precipitation of the dianion and no desired product (entry 1). When a solution of the Grignard reagent in THF was employed, the reaction proceeded in good yield but with poor diastereoselectivity (entry 2). We recently developed a method for the rhodium-catalyzed addition of alkenyltrifluoroborates[10] and *N*-methyliminodiacetic acid (MIDA)

Scheme 3. Initial Route Toward the Synthesis of (−)-**1**



boronates[11] to *N*-*tert*-butanesulfinyl imines. Consistent with the higher diastereoselectivity previously observed in the addition of alkenylboron reagents, the additions of both MIDA boronate **9** (entry 3) and trifluoroborate **10** (entry 4) proceeded in moderate yields and with high diastereoselectivities. Taking advantage of the hydrolytic stability of the *N*-sulfinyl imine, higher yields could be attained by adding the trifluoroborate in three portions (entry 5). Significantly, the synthesis of sulfinamide **2** was achieved in high yield and selectivity without requiring protection of the alcohol or indole moieties.

The next step en route to the synthesis of (−)-aurantioclavine was cyclization to provide the azepine ring. We decided to use the Mitsunobu reaction for this cyclization because this approach has been used successfully for the formation of 5-membered rings with *N*-*tert*-butanesulfinamides and primary alcohols.[12] To our surprise, the Mitsunobu reaction of alcohol **2** resulted in formation of spiro[cyclopropyl]indolenine **6**[13] (Scheme 3). A variety of acidic conditions were explored for ring expansion of indolenine **6** to azepine **7**. Unfortunately, decomposition was observed with both Brønsted acids (HCl, TFA) and Lewis acids (BF_3OEt_2, $Yb(OTf)_2$, $AuCl_3$), and upon treatment with Schreiner's thiourea catalyst,[14] the indole−thiourea adduct was instead isolated. Furthermore, indolenine **6** was unreactive under basic conditions. When the sulfinamide moiety was deprotonated with KH, no reaction was observed.

(6) For reviews on the asymmetric synthesis of amines via *N*-*tert*-butanesulfinyl imines, see: (a) Ellman, J. A.; Owens, T. D.; Tang, T. P. *Acc. Chem. Res.* **2002**, *35*, 984. (b) Morton, D.; Stockman, R. A. *Tetrahedron* **2006**, *62*, 8869. (c) Ferreira, F.; Botuha, C.; Chemla, F.; Pérez-Luna, A. *Chem. Soc. Rev.* **2009**, *38*, 1162.

(7) 4-Bromotryptophol is commercially available or can be synthesized from 4-bromoindole according to the following: Yang, J.; Wu, H.; Shen, L.; Qin, Y. *J. Am. Chem. Soc.* **2007**, *129*, 13794.

(8) For the successful formylation of indoles containing one acidic site via this methodology, see: Moyer, M. P.; Shiurba, J. F.; Rapoport, H. *J. Org. Chem.* **1986**, *51*, 5106.

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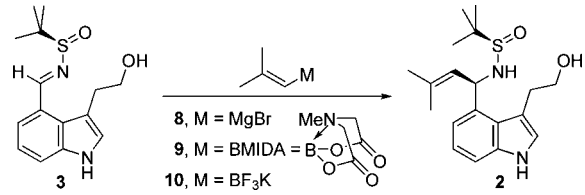
(12) (a) Tang, T. P.; Ellman, J. A. *J. Org. Chem.* **2002**, *67*, 7819. (b) Jakobsche, C. E.; Peris, G.; Miller, S. J. *Angew. Chem., Int. Ed.* **2008**, *47*, 6707.

(13) For previous characterization of spiro[cyclopropane-1,3′-indolenine] compounds, see: (a) Johansen, J. E.; Christie, B. D.; Rapoport, H. *J. Org. Chem.* **1981**, *46*, 4914. (b) Clossen, W. D.; Roman, S. A.; Kwiatkowski, G. T.; Corwin, D. A. *Tetrahedron Lett.* **1966**, *21*, 2271.

(14) *N*,*N*′-Bis[3,5-bis(trifluoromethyl)phenyl]thiourea, see: (a) Schreiner, P. R.; Wittkopp, A. *Org. Lett.* **2002**, *4*, 217. (b) Schreiner, P. R.; Wittkopp, A. *Chem.—Eur. J.* **2003**, *9*, 407.

(15) Cogan, D. A.; Liu, G.; Ellman, J. A. *Tetrahedron* **1999**, *55*, 8883.

Table 1. Alkenylation of *N*-Sulfinyl Imine **3** with Various Organometallic Reagents



entry	*M* (equiv)	yield (%)[a]	conversion (%)[a]	dr[b]
1[c]	MgBr in Et_2O (3.5 equiv)	0	38	
2[c]	MgBr in THF (3.5 equiv)	69	89	33:67
3[d]	BMIDA (2 equiv)	23	50	97:3
4[e]	BF_3K (2 equiv)	42	64	97:3
5[e]	BF_3K (3 × 1.5 equiv)	84 (81)[f]	94	97:3

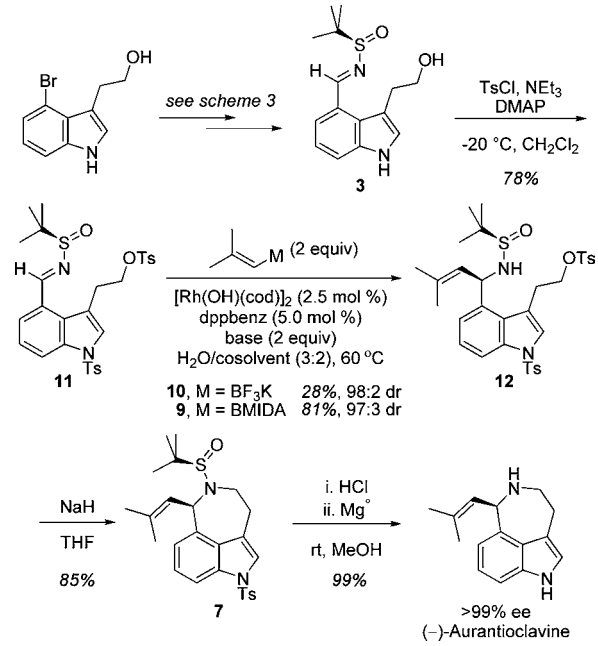
[a] Yield and conversion were determined by ^1H NMR relative to an external standard. [b] Diastereoselectivity was determined by HPLC comparison to authentic diastereomers. [c] Reaction was run in CH_2Cl_2.[15] [d] Reaction was performed with $[Rh(OH)(cod)]_2$, dppbenz, and K_3PO_4 in H_2O/dioxane.[11] [e] Reaction was performed with $[Rh(OH)(cod)]_2$, dppbenz, and NEt_3 in H_2O/DMF.[10] [f] Isolated yield of diastereomerically pure material.

The inability to carry forward spiro-indolenine **6** required us to revise our strategy. We hypothesized that cyclization without formation of the undesired indolenine would require deactivation of the indole. Selective protection of the indole moiety of **2** would be inefficient because it would require protecting group manipulations of the more nucleophilic alcohol. A much more appealing approach was tosylation of both the indole and alcohol, which would deactivate the indole while simultaneously activating the alcohol for a subsequent S_N2-mediated cyclization. Bis-tosylation of *N*-sulfinyl allylic amine **2** was met with limited success. Careful evaluation of the reaction products suggested that the sulfinamide moiety was unstable under these conditions. Fortunately, tosylation of the *N*-sulfinyl imine precursor (**3**) proceeded in good yield as long as the reaction solution was maintained at low temperature (Scheme 4).

While the Rh(I)-catalyzed addition of trifluoroborate **10** to bis-tosylated *N*-sulfinyl imine **11** was not very efficient, the newly developed MIDA boronate slow release conditions[11] provided sulfinamide **12** in high yield and diastereoselectivity (Scheme 4). After chromatography, diastereomerically pure **12** was isolated in 78% yield. Furthermore, cyclization of sulfinamide **12** proceeded smoothly upon deprotonation with NaH.

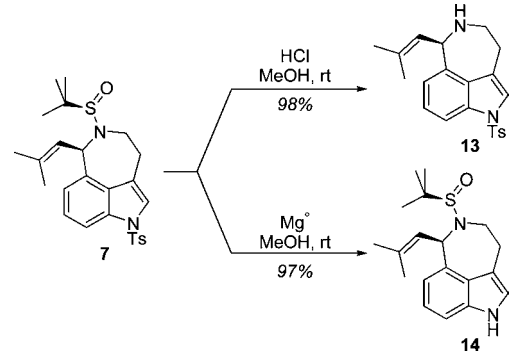
To complete the synthesis, only the removal of the sulfinamide and tosyl groups remained. Initial attempts to remove both of the protecting groups with a single reagent were unsuccessful. Treatment with MeLi or TBAF resulted in deprotection of the tosyl group as well as multiple other side products. Magnesium in methanol proved to be a mild and highly effective method for deprotection of the tosyl group (Scheme 5). Additionally, acidic alcoholysis with HCl in methanol, the general conditions for removing *tert*-butanesulfinyl groups,[15] resulted in quantitative deprotection

Scheme 4. Total Synthesis of (−)-Aurantioclavine via the Rh-Catalyzed Addition of MIDA Boronate **9**



of the sulfinyl group (Scheme 5). These straightforward deprotections could be carried out separately, in either order, or in one-pot. The ability to selectively deprotect either functional group provides great flexibility for subsequent synthetic approaches to the communesins, and the one-pot double-deprotection resulted in the formation of (−)-aurantioclavine in quantitative yield (Scheme 4).

Scheme 5. Selective Deprotection of Tosyl and Sulfinyl Groups



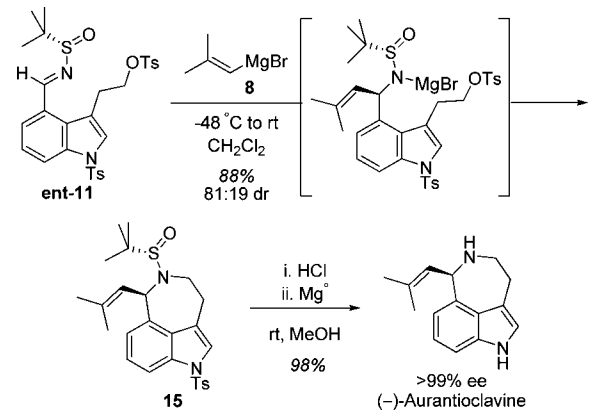
Despite the precedence for lower selectivity, we realized that Grignard reagent addition could prove more efficient than the addition of boron reagents if spontaneous cyclization occurred upon formation of the nucleophilic sulfinamide anion (Scheme 6).[16] The solvent of the Grignard solution was again found to be critical to reaction success, with no cyclization observed in ether. However, addition of Grignard **8** as a solution in the more highly

coordinating solvent THF cleanly afforded cyclized product **15** with moderate diastereoselectivity. After chromatography, diastereomerically pure product was isolated in 72% yield. It is noteworthy that because Grignard addition provides the opposite diastereoselectivity to that for the Rh-catalyzed addition of the MIDA boronate, both *N-tert*-butanesulfinyl azepine diastereomers **7** and **15** are accessible. The one-pot double-deprotection conditions were equally successful for azepine diastereomer **15**, providing (−)-aurantioclavine in high yield.

In summary, the asymmetric total synthesis of (−)-aurantioclavine has been accomplished in 6 steps and 27% overall yield by using a MIDA boronate and in 5 steps and 29% overall yield by using a Grignard reagent. The syntheses are considerably shorter and higher yielding than the previously reported synthesis[5] and provide rapid access to significant quantities of (−)-aurantioclavine. This work also highlights the synthetic utility of the various methodologies for the alkenylation of *N-tert*-butanesulfinyl imines.

(16) For the one-pot preparation of aziridines and pyrrolidines by Grignard reagent additions to halo-substituted *N-tert*-butanesulfinyl imines, see: (a) Denolf, B.; Mangelinckx, S.; Törnroos, K. W.; De Kimpe, N. *Org. Lett.* **2006**, *8*, 3129. (b) Reddy, L. R.; Prashad, M. *Chem. Commun.* **2010**, *46*, 222.

Scheme 6. Total Synthesis of (−)-Aurantioclavine via the Addition of Grignard Reagent **8**



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Supporting Information Available: Experimental procedures, characterization data, copies of ^{1}H and ^{13}C NMR spectra, and copies of HPLC traces. This material is available free of charge via the Internet at http://pubs.acs.org.

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