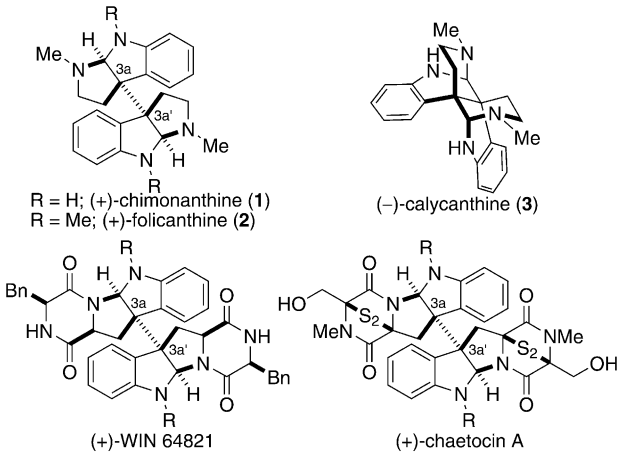
Synthetic Methods

DOI: 10.1002/anie.201201132

Catalytic Asymmetric Total Synthesis of Chimonanthine, Folicanthine, and Calycanthine through Double Michael Reaction of Bisoxindole**

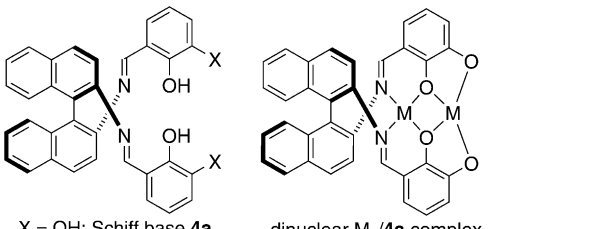
Harunobu Mitsunuma, Masakatsu Shibasaki, Motomu Kanai, and Shigeki Matsunaga**

Hexahydropyrroloindole alkaloids comprise a large family of natural products with attractive biological activities.[1] Among them, dimeric and oligomeric hexahydropyrroloindole alkaloids bearing vicinal quaternary stereogenic carbon centers at C_{3a} and $C_{3a'}$ have attracted significant interest as synthetic targets.[2] Syntheses of chimonanthine (**1**), folicanthine (**2**), and calycanthine (**3**; Scheme 1), which are in the simplest



Scheme 1. Representative dimeric hexahydropyrroloindole-derived family of alkaloids.

class of these alkaloids, have been intensively studied over decades.[2,3] Enantioselective construction of the dimeric core structure in chimonanthine and folicanthine, however, has been achieved by only a few groups.[4–7] The synthetic difficulty mainly arises from two structural features of the dimeric hexahydropyrroloindole core: a labile C_{3a}–$C_{3a'}$ σ bond[8] and sterically hindered vicinal quaternary stereogenic carbon centers. The first enantioselective total synthesis of chimonanthine and calycanthine was reported by Overman and co-workers; in this synthesis the contiguous quaternary carbon centers were elegantly constructed by either diastereoselective dialkylation or double Heck cyclization based on the selected chiral auxiliaries.[4] Movassaghi and co-workers established an efficient Co^{I}-promoted reductive homodimerization of 3-bromo-hexahydropyrrolo indoles derived from L-tryptophan, and achieved concise enantioselective total syntheses of various hexahydropyrroloindole alkaloids, including chimonanthine, calycanthine, and folicanthine.[5] Sodeoka and co-workers also achieved total synthesis of a related natural product, (+)-chaetocin, by using a related homodimerization strategy.[6] In striking contrast to these elegant precedents using stoichiometric amounts of chiral sources, catalytic asymmetric approaches for the construction of the dimeric hexahydropyrroloindole core still remain particularly challenging. Very recently, Gong and co-workers reported the first highly enantioselective catalytic asymmetric total synthesis of (+)-folicanthine through substitution of 3-hydroxyoxindole with an enecarbamate catalyzed by chiral phosphoric acids.[7] Because the product in the key enantioselective reaction, 3-indolyl-substituted oxindole, could not be directly converted into a dimeric hexahydropyrroloindole motif, several additional steps were required to achieve the total synthesis (12 steps in 3.7% overall yield). The results prompted us to communicate our studies on a straightforward catalytic asymmetric total synthesis of chimonanthine, calycanthine, and folicanthine. A chiral $Mn(4\text{-F-BzO})_2$/Schiff base **4a** catalyst (4-F-BzO = 4-fluorobenzoate, Scheme 2) and $Mg(OAc)_2$ promoted a sequential Michael reaction of a bisoxindole with nitroethylene, thereby directly affording a key intermediate with vicinal quaternary stereogenic carbon



Scheme 2. Structures of Schiff bases **4a**–**4d** and dinuclear Schiff base complexes. Cat. = catalyst.

[*] H. Mitsunuma, Prof. Dr. M. Kanai, Dr. S. Matsunaga
Graduate School of Pharmaceutical Sciences
The University of Tokyo
Hongo, Bunkyo-ku, Tokyo 113-0033 (Japan)
E-mail: kanai@mol.f.u-tokyo.ac.jp
smatsuna@mol.f.u-tokyo.ac.jp
Prof. Dr. M. Kanai, Dr. S. Matsunaga
Kanai Life Science Catalysis Project
ERATO (Japan) Science and Technology Agency
Hongo, Bunkyo-ku, Tokyo 113-0033 (Japan)
Prof. Dr. M. Shibasaki
Institute of Microbial Chemistry, Tokyo
Kamiosaki, Shinagawa-ku, Tokyo 141-0021 (Japan)

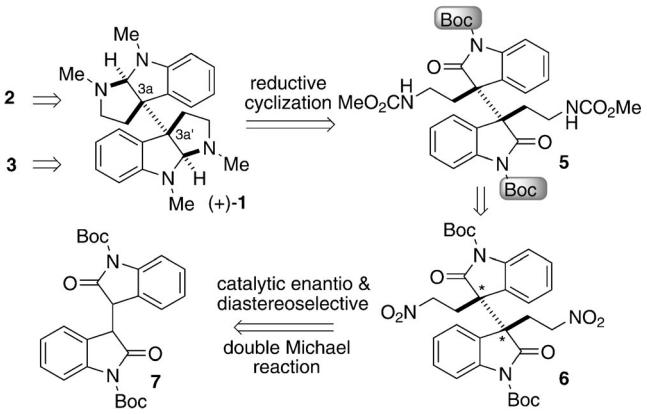
[**] We thank Prof. Kobayashi, Prof. Ohwada, Dr. Otani, and Dr. Ueno at the University of Tokyo for generous technical supports. This work was supported by Scientific Research on Innovative Areas from MEXT, ERATO from JST, Grant-in-Aid for Young Scientists (A) from JSPS, Inoue Science Foundation, and Takeda Science Foundation.

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201201132.

© 2012 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim

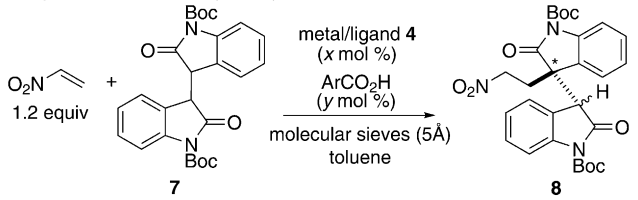
centers in high enantio- and diastereoselectivity. The double Michael adduct was successfully converted into chimonanthine (**1**) by reductive cyclization, while suppressing undesirable cleavage of the C_{3a}–$C_{3a'}$ σ bond.

Over the past decade, tremendous efforts have been devoted towards catalytic asymmetric syntheses of 3,3′-disubstituted oxindoles bearing quaternary carbon centers[9–12] as well as their applications in the enantioselective synthesis of monomeric hexahydropyrroloindole motifs in alkaloids.[1] Trials to apply the methodologies to the synthesis of dimeric hexahydropyrroloindole alkaloids bearing vicinal quaternary stereogenic carbon centers, however, had not been reported until Gong and co-workers recently reported the approach using 3-indolyl-substituted oxindole.[7] For a more straightforward approach to the target core structure, the use of bisoxindole as a substrate in the catalytic stereoselective double functionalization reaction is ideal. To our knowledge, however, there are no reports of a catalytic asymmetric reaction using bisoxindoles, possibly owing to the labile C_{3a}–$C_{3a'}$ σ bond and steric hindrance in formation of the vicinal quaternary carbon centers. Our synthetic strategy is summarized in Scheme 3. (−)-Calycanthine (**3**) and (+)-folicanthine (**2**) can be obtained from (+)-chimonanthine (**1**) in one step by following the reported procedure.[4,5a] In previous studies, the undesired cleavage of the C_{3a}–$C_{3a'}$ σ bond during reductive cyclization processes was often problematic and gave the desired dimeric hexahydropyrroloindole core in low yield.[13] Thus, we planned to use *tert*-butoxycarbonyl (Boc)-protected intermediate **5** to minimize undesired cleavage of the C_{3a}–$C_{3a'}$ σ bond during the reductive cyclization process. The intermediate **5** can be readily obtained from the key double Michael adduct **6**. To minimize the protection–deprotection process, we used Boc-protected bisoxindole **7** as a substrate in the key double Michael reaction with nitroethylene.



Scheme 3. Retrosynthetic Analysis.

Table 1: Optimization of catalytic asymmetric Michael reaction.



Entry	Metal source	Ligand (*x* mol%)	Benzoic acid Ar: (*y* mol%)	*T* [°C]	*t* [h]	Yield[d] [%]	*ee* [%]
1[a,b]	$Ni(OAc)_2$	**4a** (10)	none	RT	57	96	3
2[a,b]	$Co(OAc)_2$	**4a** (10)	none	RT	57	74	11
3[a,b]	$Mn(OAc)_2$	**4a** (10)	none	RT	57	65	55
4[a]	$Mn(OAc)_2$	**4a** (5)	Ph- (20)	50	5	87	85
5[a]	$Mn(OAc)_2$	**4a** (5)	4-MeO-C_6H_4- (20)	50	5	81	84
6[a]	$Mn(OAc)_2$	**4a** (5)	4-F-C_6H_4- (20)	50	5	83	86
7[a]	$Mn(OAc)_2$	**4a** (5)	4-F-C_6H_4- (10)	50	5	94	91
8[a]	$Mn(OAc)_2$	**4a** (5)	2,4,6-Me_3-C_6H_2- (20)	50	5	80	9
9[a]	$Mn(4\text{-F-BzO})_2$	**4a** (4.3)	none	50	5	90	95
10[c]	$Mn(4\text{-F-BzO})_2$	**4a** (4.3)	none	50	5	90	96
11[c]	$Mn(4\text{-F-BzO})_2$	**4a** (2.2)	none	50	9	87	96
12[c]	$Mn(4\text{-F-BzO})_2$	**4a** (0.88)	none	50	24	87	91
13[c]	$Mn(4\text{-F-BzO})_2$	**4b** (5)	none	50	5	19	2
14[c]	$Mn(4\text{-F-BzO})_2$	**4c** (5)	none	50	5	14	30[e]
15[c]	$Mn(4\text{-F-BzO})_2$	**4d** (5)	none	50	5	75	0

[a] Catalyst was prepared prior to use in metal source/ligand ratio of 2:1. [b] Reaction was run in the absence of molecular sieves (5 Å). [c] Catalyst was prepared prior to use in a metal source/ligand ratio of 1:1. [d] Determined by ^{1}H NMR analysis of the crude mixture. [e] *ent*-**8** was obtained as major enantiomer.

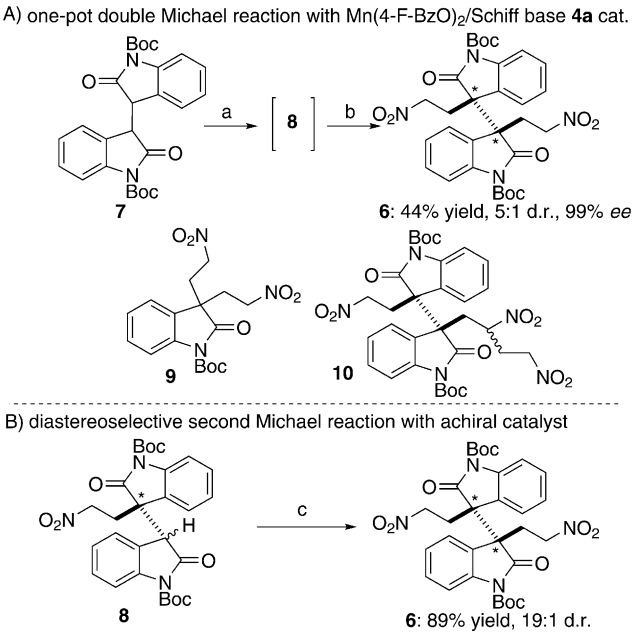
As a part of our ongoing research on catalysis by bimetallic Schiff base complexes, we recently reported homodinuclear Ni_2/**4a**, $Co_2(OAc)_2$/**4a**, and $Mn_2(OAc)_2$/**4a** complexes (Scheme 2) for Michael reactions of various nucleophiles with nitroalkenes.[14] Therefore, we first applied these complexes and related dinuclear Schiff base complexes[15] for the reaction of nitroethylene[16] and Boc-protected bisoxindole **7**, which was readily synthesized from commercially available oxindole and isatin in 87% yield (in two steps). Among the catalysts screened (Table 1, entries 1–3), $Mn_2(OAc)_2$/**4a** gave the best enantioselectivity, affording product **8** in 55% *ee* (entry 3). After optimization of the reaction conditions, such as additives and temperature, product **8** was obtained in 87% yield and 85% *ee* after five hours when using the $Mn_2(OAc)_2$/**4a** catalyst in the presence of molecular sieves (5 Å) and benzoic acid (20 mol%) at 50°C (Table 1, entry 4). 4-Methoxybenzoic acid and 4-fluorobenzoic acid gave comparable results (Table 1, entries 5–6), and product **8** was obtained in 91% *ee* with 10 mol% of 4-fluorobenzoic acid (Table 1, entry 7). Because sterically hindered 2,4,6-trimethylbenzoic acid resulted in poor enantioselectivity (9% *ee*, Table 1, entry 8), we speculated that the active catalyst species would be generated in situ by exchanging the counterion on Mn from acetate to benzoate derivatives in entries 4–7. We then utilized $Mn(4\text{-F-BzO})_2$ as a metal source, and a catalyst prepared from $Mn(4\text{-F-BzO})_2$, and ligand **4a** in a ratio of 2:1 gave the product in 90% yield and 95% *ee* (Table 1, entry 9). In striking contrast to our previous examples,[17] the catalyst from $Mn(4\text{-FBzO})_2$ and ligand **4a** mixed in 1:1 ratio also gave **8** in high enantioselectivity (Table 1, entry 10, 96% *ee*).[18] The catalyst loading was successfully reduced to 2.2 mol%, while the high enantioselectivity was maintained (Table 1, entry 11, 96% *ee*). With

 © 2012 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim

These are not the final page numbers!

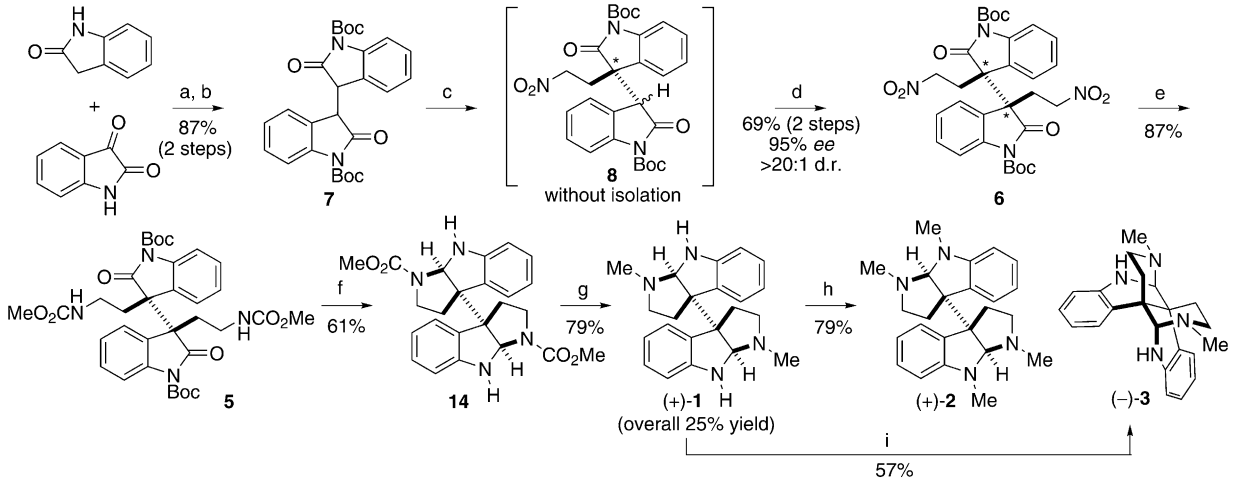
0.88 mol% catalyst, product **8** was obtained in good yield after 24 h, but the enantioselectivity slightly decreased (Table 1, entry 12, 91% *ee*). Other Schiff bases, **4b**, **4c**, and **4d**, resulted in poor enantioselectivity (Table 1, entries 13–15), thus suggesting that the hydroxy groups in Schiff base **4a** played an important role in constructing a highly enantioselective active catalyst.

We then tried to utilize the $Mn(4\text{-F-BzO})_2$/Schiff base **4a** (ratio 1:1) catalyst for one-pot double Michael reaction. The Schiff base catalyst, however, had only moderate reactivity toward the second Michael reaction, possibly owing to severe steric hindrance. Even after intensive optimization of the reaction conditions, desired product **6** from a double Michael reaction was obtained in up to only 44% yield (from **7**) and 5:1 d.r. when using 18 mol% catalyst (Scheme 4A, 99% *ee*). Analysis of the reaction mixture indicated that undesirable cleavage of the C_{3a}–$C_{3a'}$ σ bond occurred, giving byproduct **9**. The adduct **10**, likely produced because of the slow protonation of a nitronate intermediate after 1,4-addition, was also problematic.[19] We speculated that a sterically less hindered catalyst without bulky Schiff base ligand **4a** would be suitable to avoid these side reactions. Therefore, we screened various achiral metal acetates to achieve a diastereoselective second Michael reaction. Among the metal acetates screened,[20] 5 mol% of $Mg(OAc)_2{\cdot}4H_2O$ in the presence of 10 mol% of benzoic acid gave the best diastereoselectivity and yield and gave double Michael product **6** in 89% yield (determined by NMR spectroscopy with an internal standard) and 19:1 d.r. after 9.5 h (Scheme 4B).[21]



Scheme 4. A) One-pot double Michael reaction with Mn/ Schiff base **4a** catalyst. B) Diastereoselective second Michael reaction with achiral metal catalyst. Reagents and conditions: a) nitroethylene (1.2 equiv), $Mn(4\text{-F-BzO})_2$/Schiff base **4a** (ratio 1:1) catalyst (18 mol%), toluene, molecular sieves (5 Å), 50°C, 1.5 h; then additional nitroethylene (2 equiv), 2,6-di-*tert*-butylphenol (1 equiv), 50°C, 12 h, 44% yield (from **7**), 5:1 d.r., 99% *ee*; c) $Mg(OAc)_2{\cdot}4H_2O$ (5 mol%), benzoic acid (10 mol%), nitroethylene (1.2 equiv), molecular sieves (5 Å), 50°C, 9.5 h, 89% yield, 19:1 d.r.

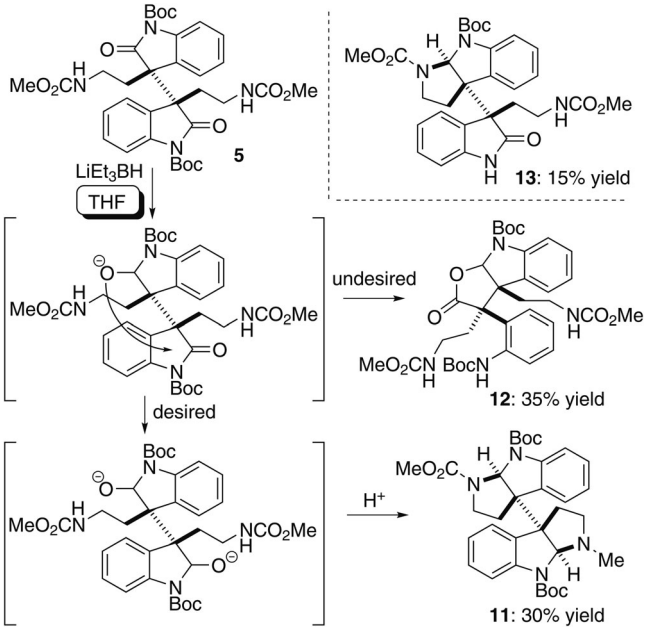
After the reaction conditions for the two key Michael reactions were optimized (Table 1 and Scheme 4), we investigated the sequential Michael reactions as shown in Scheme 5. After the first Mn-catalyzed asymmetric Michael reaction, the Mn catalyst was removed by passing the reaction mixture through a short pad of silica gel. The crude mixture of **8** was then subjected to a second Mg-catalyzed diastereoselective second Michael reaction with additional 1.2 equivalents of nitroethylene, resulting in isolation of double Michael adduct **6** in 69% yield and 95% *ee* with greater than 20:1 d.r. Conversion of the nitro groups into methyl carbamates proceeded to give **5** in 87% yield.



Scheme 5. Synthesis of (+)-**1**, (+)-**2**, and (−)-**3**: a) AcOH, conc. HCl (cat.), 110°C; b) Boc_2O, DMAP, CH_2Cl_2, RT, 6 h; PtO_2, AcOEt, H_2, RT, 12 h, 87% (2 steps); c) nitroethylene (1.2 equiv), $Mn(4\text{-F-BzO})_2$/**4a** (ratio 1:1) cat. (2.2 mol%), toluene, molecular sieves (5 Å), 50°C, 9 h; d) nitroethylene (1.2 equiv), $Mg(OAc)_2{\cdot}4H_2O$ (5 mol%), benzoic acid (10 mol%), THF, molecular sieves (5 Å), 50°C, 9.5 h, 69% yield (from **7** in 2 steps), 95% *ee*, >20:1 d.r.; e) $NiCl_2$, $NaBH_4$, dimethyl dicarbonate, MeOH, 87% yield; f) $LiEt_3BH$, toluene, −78°C to −40°C, 1 h; 4 M HCl in AcOEt, RT, 5 h; TFA, RT, 15 h, 61% yield; g) sodium bis(2-methoxyethoxy) aluminum hydride, toluene, reflux, 4.5 h, 79% yield; h) aq. HCHO, $NaBH(OAc)_3$, MeCN, RT, 0.5 h, 79% yield; i) AcOH, H_2O, 95°C, 48 h, 57% yield. DMAP = 4-dimethylaminopyridine, TFA = trifluoroacetic acid.

© 2012 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim

Then, the reductive cyclization from **5** was investigated in detail. We anticipated that the problematic cleavage of the C_{3a}–$C_{3a'}$ σ bond could be minimized by taking advantage of the Boc groups; 1) reduction of imide moieties would proceed at low temperature to avoid C–C bond cleavage, and 2) electron-withdrawing Boc groups would decrease the electron density of the nitrogen atom, thus suppressing undesired C–C bond cleavage, while the desired pathway to form hexahydropyrroloindole cores via an iminium cation would proceed chemoselectively.[22,23] As expected, the Boc-protected intermediate effectively suppressed the cleavage of the C_{3a}–$C_{3a'}$ σ bond. Treatment of **5** with commercially available $LiEt_3BH$ in THF, however, gave desired product **11** in only 30% yield after acidic work-up. Competitive intramolecular cyclization from a partially reduced adduct afforded **12** (35%) and **13** was also observed in 15% yield (Scheme 6). The use of $LiEt_3BH$ in toluene was effective to



Scheme 6. Problems in reductive cyclization process in THF.

suppress the undesired pathway, possibly because conformation of the substrate was changed through the coordination of the substrate to Li. The desired dimeric hexahydropyrroloindole core **11** was then successfully obtained after acidic treatment with HCl.[23a] Boc groups in **11** were also removed by further addition of TFA to the reaction mixture, giving **14** in 61% yield from **5** in one pot (Scheme 5, conditions f). The result of this step was superior to previous representative reductive cyclization procedures that started from a nonprotected or N-alkyl intermediate and used a strong reducing reagent, such as $LiAlH_4$, at a relatively high temperature.[13] Because **14** is a known intermediate, **14** was transformed into (+)-**1**, (+)-**2**, and (−)-**3** by following the reported procedures.[4,5a] Reduction of the methyl carbamate moieties with sodium bis(2-methoyethoxy)aluminum hydride gave (+)-chimonanthine (**1**) in 79% yield. (+)-Folicanthine (**2**) was obtained by methylation in 79% yield. Treatment of (+)-**1** in acetic acid and water at 95°C led to the equilibrium between (+)-**1** and the isomeric (−)-calycanthine (**3**), and (−)-**3** was isolated in 57% yield.

In summary, we achieved a catalytic asymmetric total synthesis of (+)-chimonanthine, (+)-folicanthine, and (−)-calycanthine. (+)-Chimonanthine was obatined in seven steps, 25% overall yield from commercially available oxindole and isatin. The vicinal quaternary stereogenic carbon centers were constructed by sequential Michael reactions of N-Boc-protected bisoxindole with nitroethylene catalyzed by a $Mn(4\text{-F-BzO})_2$/Schiff base **4a** catalyst and a $Mg(OAc)_2$/benzoic acid system. A dimeric hexahydropyrroloindole core was constructed in good yield without C–C bond cleavage.

Received: February 10, 2012
Published online: ■■ ■■, ■■■■

Keywords: asymmetric catalysis · asymmetric synthesis · salen · synthetic methods · total synthesis

[1] a) P. Ruiz-Sanchis, S. A. Savina, F. Albericio, M. Alvarez, *Chem. Eur. J.* **2011**, *17*, 1388; b) D. Crich, A. Banerjee, *Acc. Chem. Res.* **2007**, *40*, 151; c) U. Anthoni, C. Christophersen, P. H. Nielsen, *Alkaloids: Chemical and Biological Perspectives*, *Vol. 13*, New York, **1999**, pp. 163–236.

[2] Reviews: a) A. Steven, L. E. Overman, *Angew. Chem.* **2007**, *119*, 5584; *Angew. Chem. Int. Ed.* **2007**, *46*, 5488; b) M. A. Schmidt, M. Movassaghi, *Synlett* **2008**, 313.

[3] For representative early studies on racemic total synthesis of calycanthine and folicanthine, see: a) T. Hino, S.-i. Yamada, *Tetrahedron Lett.* **1963**, *4*, 1757; b) J. B. Hendrickson, R. Goschke, R. Ress, *Tetrahedron* **1964**, *20*, 565; c) A. L. Scott, L. Guo, F. McCapra, E. S. Hall, *J. Am. Chem. Soc.* **1964**, *86*, 302; d) C.-L. Fang, S. Horne, N. Taylor, R. Rodrigo, *J. Am. Chem. Soc.* **1994**, *116*, 9480; e) H. Ishikawa, H. Takayama, N. Aimi, *Tetrahedron Lett.* **2002**, *43*, 5637; f) Y.-X. Li, H.-X. Wang, S. Ali, X.-F. Xia, Y.-M. Liang, *Chem. Commun.* **2012**, *48*, 2343and references therein. For other examples, see reviews in Ref. [2].

[4] a) L. E. Overman, D. V. Paone, B. A. Stearns, *J. Am. Chem. Soc.* **1999**, *121*, 7702; b) L. E. Overman, J. F. Larrow, B. A. Stearns, J. M. Vance, *Angew. Chem.* **2000**, *112*, 219; *Angew. Chem. Int. Ed.* **2000**, *39*, 213.

[5] a) M. Movassaghi, M. A. Schmidt, *Angew. Chem.* **2007**, *119*, 3799; *Angew. Chem. Int. Ed.* **2007**, *46*, 3725; b) M. Movassaghi, M. A. Schmidt, J. A. Ashehurst, *Angew. Chem.* **2008**, *120*, 1507; *Angew. Chem. Int. Ed.* **2008**, *47*, 1485; c) J. Kim, J. A. Ashenhurst, M. Movassaghi, *Science* **2009**, *324*, 238; d) J. Kim, M. Movassaghi, *J. Am. Chem. Soc.* **2010**, *132*, 14376.

[6] E. Iwasa, Y. Hamashima, S. Fujishiro, E. Higuchi, A. Ito, M. Yoshida, M. Sodeoka, *J. Am. Chem. Soc.* **2010**, *132*, 4078.

[7] C. Guo, J. Song, J. Z. Huang, P. H. Chen, S. W. Luo, L. Z. Gong, *Angew. Chem.* **2012**, *124*, 1070; *Angew. Chem. Int. Ed.* **2012**, *51*, 1046.

[8] For discussion on the labile C_{3a}–$C_{3a'}$ σ bond and synthetic studies to avoid cleavage of the C_{3a}–$C_{3a'}$ σ bond, see: J. T. Link, L. E. Overman, *J. Am. Chem. Soc.* **1996**, *118*, 8166.

[9] General reviews on quaternary-carbon construction: a) C. J. Douglas, L. E. Overman, *Proc. Natl. Acad. Sci. USA* **2004**, *101*, 5363; b) B. M. Trost, C. H. Jiang, *Synthesis* **2006**, 369.

[10] General review on enantioselective synthesis of tetrasubstituted oxindoles: F. Zhou, Y.-L. Liu, J. Zhou, *Adv. Synth. Catal.* **2010**, *352*, 1381.

[11] For series of elegant catalyst-controlled enantioselective syntheses of complex cyclotryptamine alkaloids by Overman and

 © 2012 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim

These are not the final page numbers!

co-workers, see a review in Ref. [2a]. For the representative applications in higher-order polypyrrolidinoindoline alkaloids synthesis, see: A. D. Lebsack, J. T. Link, L. E. Overman, B. A. Stearns, *J. Am. Chem. Soc.* **2002**, *124*, 9008.

[12] Selected recent leading other examples, a) B. M. Trost, J. Xie, J. D. Sieber, *J. Am. Chem. Soc.* **2011**, *133*, 20611, and references therein; b) S. Ma, X. Han, S. Krishnan, S. C. Virgil, B. M. Stoltz, *Angew. Chem.* **2009**, *121*, 8181; *Angew. Chem. Int. Ed.* **2009**, *48*, 8037; c) R. He, S. Shirakawa, K. Maruoka, *J. Am. Chem. Soc.* **2009**, *131*, 16620; d) Y. Nakao, S. Ebata, A. Yada, T. Hiyama, M. Ikawa, S. Ogoshi, *J. Am. Chem. Soc.* **2008**, *130*, 12874; e) B. M. Trost, Y. Zhang, *J. Am. Chem. Soc.* **2006**, *128*, 4590.

[13] $LiAlH_4$ and sodium bis(2-methoxyethoxy)aluminum hydride (Red-Al) under harsh conditions were often utilized for reductive cyclization of either non-protected or N-alkyl precursors, resulting in low yield.[3] Overman et al. developed elegant alternative stepwise route to avoid undesirable C–C bond cleavage.[4,8]

[14] a) N. E. Shepherd, H. Tanabe, Y. Xu, S. Matsunaga, M. Shibasaki, *J. Am. Chem. Soc.* **2010**, *132*, 3666; b) Y. Xu, S. Matsunaga, M. Shibasaki, *Org. Lett.* **2010**, *12*, 3246; c) Z. Chen, M. Furutachi, Y. Kato, S. Matsunaga, M. Shibasaki, *Angew. Chem.* **2009**, *121*, 2252; *Angew. Chem. Int. Ed.* **2009**, *48*, 2218; d) Y. Kato, M. Furutachi, Z. Chen, H. Mitsunuma, S. Matsunaga, M. Shibasaki, *J. Am. Chem. Soc.* **2009**, *131*, 9168.

[15] For selected recent representative examples, see: a) H. Mihara, Y. Xu, N. E. Shepherd, S. Matsunaga, M. Shibasaki, *J. Am. Chem. Soc.* **2009**, *131*, 8384; b) S. Handa, V. Gnanadesikan, S. Matsunaga, M. Shibasaki, *J. Am. Chem. Soc.* **2010**, *132*, 4925; c) Y. Xu, L. Lin, M. Kanai, S. Matsunaga, M. Shibasaki, *J. Am. Chem. Soc.* **2011**, *133*, 5791.

[16] Because nitroethylene is too reactive and readily polymerizes, catalytic asymmetric reaction using nitroethylene is rather limited. See, a) Y. Chi, L. Guo, N. A. Kopf, S. H. Gellman, *J. Am. Chem. Soc.* **2008**, *130*, 5608; b) M. Wiesner, J. D. Revell, S. Tonazzi, H. Wennemers, *J. Am. Chem. Soc.* **2008**, *130*, 5610; c) T. Bui, S. Syed, C. F. Barbas III, *J. Am. Chem. Soc.* **2009**, *131*, 8758; d) H. Mitsunuma, S. Matsunaga, *Chem. Commun.* **2011**, *47*, 469.

[17] In previous reports on dinuclear Schiff base catalysts, mononuclear Schiff base catalysts had much lower reactivity and stereoselectivity than dinuclear Schiff base catalysts. Z. Chen, H. Morimoto, S. Matsunaga, M. Shibasaki, *J. Am. Chem. Soc.* **2008**, *130*, 2170; See also, Ref. [14a,c].

[18] Inductively coupled plasma (ICP) analysis suggested that the structure and Mn/**4a** ratio in catalysts from $Mn(4\text{-F-BzO})_2$ would be different from $Mn_2(OAc)_2$/**4a** catalysts derived from $Mn(OAc)_2$. Because the precise structures of $Mn(4\text{-F-BzO})_2$/**4a** catalysts have not yet been clarified, catalyst loading herein was presented based on the amount of chiral ligand **4a**. See the Supporting Information.

[19] When the pure desired product **6** was subjected to the reaction conditions in Scheme 4A, adduct **10** was not observed. Therefore, we speculate that **10** was obtained from a nitronate intermediate before protonation.

[20] Other metal acetates gave unsatisfactory diastereoselectivity and reactivity. Results in the presence of benzoic acid: $Mn(OAc)_2$ (40% yield, 5.2:1 d.r.), $Fe(OAc)_2$ (32% yield, 4.4:1 d.r.), $Co(OAc)_2$ (55% yield, 8.9:1 d.r.), $Cu(OAc)_2$ (44% yield, 5.8:1 d.r.), LiOAc (55% yield, 4.3:1 d.r.).

[21] For a plausible transition-state model of the diastereoselective second Michael reaction, see the Supporting Information.

[22] For detail explanation on the positive effects of Boc groups in reductive cyclization process, see the Supporting Information. Moreover, Boc groups would also play key roles in the double Michael reaction to increase the acidity of protons in bisoxindole as well as to improve the stereoselectivity by bidentate coordination to Mn and Mg metal centers, see: Y. Hamashima, T. Suzuki, H. Takano, Y. Shimura, M. Sodeoka, *J. Am. Chem. Soc.* **2005**, *127*, 10164.

[23] Reductive cyclization procedure using Boc-protected substrates for constructing a monomeric hexahydropyrroloindole core via iminium intermediates, see a) S. P. Govek, L. E. Overman, *J. Am. Chem. Soc.* **2001**, *123*, 9468; b) S. P. Govek, L. E. Overman, *Tetrahedron* **2007**, *63*, 8499; c) M. Movassaghi, M. A. Schmidt, J. A. Ashenhurst, *Org. Lett.* **2008**, *10*, 4009.

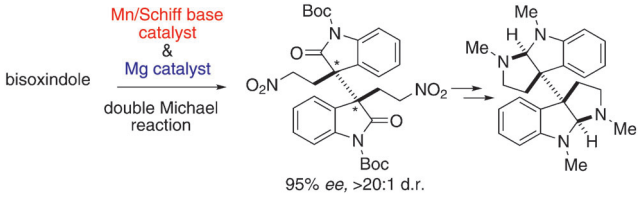
 © 2012 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim

Communications

Synthetic Methods

H. Mitsunuma, M. Shibasaki, M. Kanai,*
S. Matsunaga* ——— ■■■■–■■■■

Catalytic Asymmetric Total Synthesis of Chimonanthine, Folicanthine, and Calycanthine through Double Michael Reaction of Bisoxindole



Direct access: Sterically hindered vicinal quaternary carbon stereocenters were constructed by catalytic enantio- and diastereoselective double Michael reaction, providing straightforward access to dimeric hexahydropyrroloindole alkaloids. A $Mn(4\text{-fluorobenzoate})_2$/Schiff base complex and a $Mg(OAc)_2$/benzoic acid system were used as catalysts.

 © 2012 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim

These are not the final page numbers!