Natural Products Synthesis

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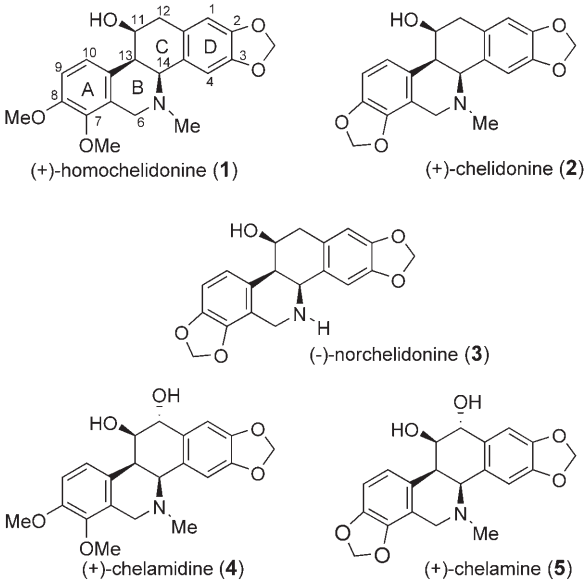
Enantioselective Total Synthesis of (+)-Homochelidonine by a Pd^{II}-Catalyzed Asymmetric Ring-Opening Reaction of a *meso*-Azabicyclic Alkene with an Aryl Boronic Acid**

*Helen A. McManus, Matthew J. Fleming, and Mark Lautens**

(+)-homochelidonine[1] (**1**) is a representative member of the hexahydrobenzo[*c*]phenanthridine alkaloids with *cis*-fused B/C rings, which occur in a number of plant species of the Papaveraceae family. Other structurally similar naturally occurring hexahydrobenzo[*c*]phenanthridine alkaloids include (+)-chelidonine[2] (**2**), (−)-norchelidonine (**3**), (+)-chelamidine (**4**), and (+)-chelamine (**5**, Scheme 1). Both **1** and **2** have been isolated from the roots of *Chelidonium majus* L., and chelidonine (**2**) was isolated as early as 1839.[3] Chelidonine has a wide range of pharmacological activities and has been used successfully in experimental oncology.[4]



Scheme 1. Structures of some hexahydrobenzo[*c*]phenanthridine alkaloids.

[*] Dr. H. A. McManus, Dr. M. J. Fleming, Prof. M. Lautens
Department of Chemistry
Davenport Chemical Laboratories
University of Toronto
80 St. George St., Toronto, ON M5S3H6 (Canada)
Fax: (+1) 416-946-8185
E-mail: mlautens@chem.utoronto.ca

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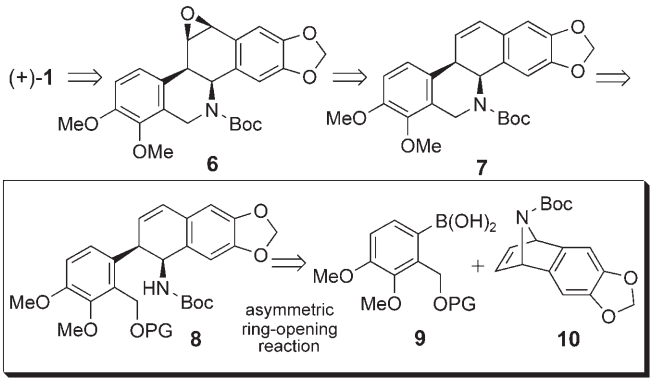
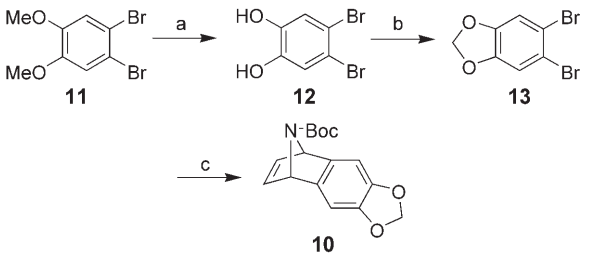
The alkaloid is also cytotoxic, has been shown to inhibit tubulin polymerization,[5] and is a major component of the drug Ukrain, a semisynthetic antitumor preparation derived from *C. majus* alkaloids.[6]

The syntheses of racemic homochelidonine[7] and the closely related chelidonine[8] have been reported in the literature, but to the best of our knowledge, no enantioselective total syntheses of these compounds exist to date. Herein we disclose the first enantioselective synthesis of (+)-homochelidonine which could be readily adapted to prepare a variety of hexahydrobenzo[*c*]phenanthridine alkaloids.

(+)-Homochelidonine has partially hydrogenated B and C rings, fully aromatic A and D rings, a hydroxy group at the C11 position, and three contiguous *syn* stereogenic centers. Our proposed retrosynthetic plan for an enantioselective total synthesis of (+)-homochelidonine is shown in Scheme 2. This route exploits the racemic ring-opening chemistry of azabicyclic alkenes with aryl boronic acids developed within our research group, in which two adjacent *syn* stereocenters are installed to form 1,2-dihydronaphthalenes.[9] It would therefore be necessary to develop an enantioselective metal-catalyzed variant of this reaction, in which the key step would be the addition of the trisubstituted aryl boronic acid **9** to azabenzonorbornadiene **10** to yield *cis*-1-amino-2-aryl-dihydronaphthalene intermediate **8**. A suitably functionalized *ortho* substituent on the boronic acid would allow for cyclization onto the B ring. It was initially considered that the *syn*-hydroxy group at the C11 position could be introduced by functionalizing the double bond of dihydronaphthalene **7** to give the corresponding *syn*-epoxide **6**, followed by selective opening of the ring with hydride.



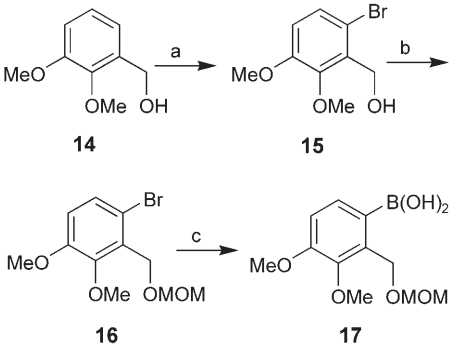
Scheme 2. Retrosynthetic analysis of (+)-**1**. Boc = *tert*-butylcarbonyl, PG = protecting group.



Scheme 3. Synthesis of *N*-Boc-azabicycle **10**: a) BBr_3, CH_2Cl_2, RT, 2 h, quant.; b) CH_2BrCl, Cs_2CO_3, DMF, 110 °C, 3 h, 75 %; c) *N*-Boc-pyrrole, *n*BuLi, PhMe, −78 °C to RT, 17 h, 71 %.

The first task was to prepare azabicycle **10** and suitably functionalized aryl boronic acid **9**. Azabicycle **10** was prepared in three steps from 4,5-dibromovertrole (**11**, Scheme 3). Treatment of **11** with boron tribromide gave **12** in quantitative yield, which was subsequently dialkylated with bromochloromethane to give **13** in 75 % yield. Slow addition of *n*BuLi to dibromide **13** generated a benzyne intermediate, which underwent an in situ Diels–Alder reaction with *N*-Boc-pyrrole to furnish *N*-Boc-azabicycle **10** in 71 % yield.

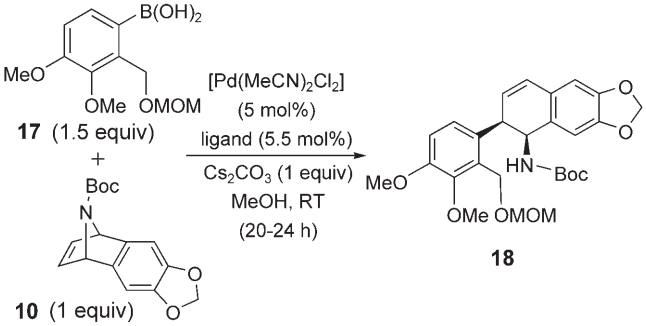
With azabicycle **10** in hand, we next set about preparing a suitable boronic acid **9**. A search of the literature revealed that the synthesis of a 3,4-dimethoxyphenylboronic acid **17** with an *ortho* MOM-protected hydroxymethyl moiety had been previously prepared by Nichols and co-workers.[10] The use of this boronic acid in the ring-opening reaction with azabicycle **10** would facilitate the formation of the B ring. Boronic acid **17** was prepared in three steps following a modified version of the reported procedure (Scheme 4). 2,3-Dimethoxybenzyl alcohol (**14**) was first regioselectively brominated with NBS to give aryl bromide **15** in 89 % yield. The hydroxy group was then protected as the MOM ether in 71 % yield by stirring **15** in dimethoxymethane at RT in the presence of a catalytic amount of LiBr and *p*-toluenesulfonic acid.[11] Aryl bromide **16** was converted into the corresponding boronic acid **17** in 63 % yield by lithium–halogen exchange with *n*BuLi and subsequent quenching with triisopropyl borate.



Scheme 4. Synthesis of boronic acid **17**: a) NBS, THF, RT, 30 min, 89 %; b) $CH_2(OMe)_2$, LiBr, TsOH, RT, 15 h, 72 %; c) *n*BuLi, THF, −78 °C 45 min; then $B(OiPr)_3$, −78 °C to RT, 18 h; then aqueous NH_4Cl, 63 %. NBS = *N*-bromosuccinimide, Ts = toluene-4-sulfonyl, MOM = methoxymethyl.

The next task was to evaluate the palladium(II)-catalyzed ring-opening reaction. Using our previously developed conditions for the racemic system ([Pd(dppp)Cl_2], Cs_2CO_3, MeOH, 60 °C, 24 h),[9a] the reaction gave **18** as a single diastereoisomer in 82 % yield (Table 1, entry 1). The *syn* relationship between the aryl and NHBoc groups was confirmed by a 2D ^{1}H NMR ROESY experiment. An enantioselective version of this reaction was next investigated. These reactions were carried out by first generating the chiral palladium(II) catalyst in situ by stirring the catalyst precursor bis(acetonitrile)dichloropalladium(II) with the appropriate chiral ligand in MeOH at room temperature prior to the addition of the reactants. A series of chiral ligands were examined (Table 1, entries 2–7). These reactions were carried out using 5 mol % catalyst, 5.5 mol % chiral ligand, and at room temperature to maximize enantiodiscrimination. The optimal ligand for the enantioselective ring opening of **10** with **17** was found to be (*S*)-tol-binap, which provided dihydronaphthalene **18** in 90 % yield and with 91 % *ee* (Table 1, entry 7).[12]

Table 1: Evaluation of ligands in the asymmetric ring-opening reaction.

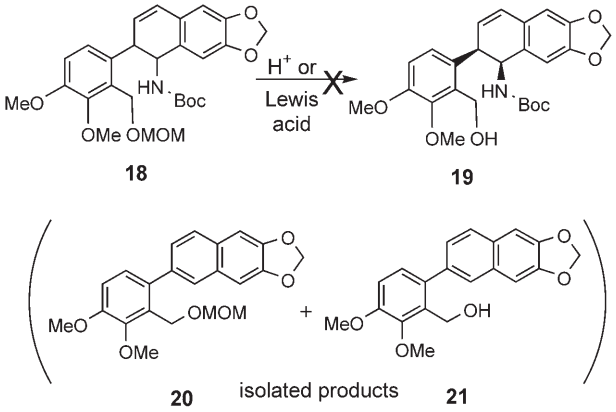


Entry	Ligand[a]	Yield [%][b]	*ee* [%][c]
1[d]	dppp	82	–
2	(*S*)-binap	48	87
3	(S,S)-chiraphos	66	40
4	(*R*)-monophos	25	14
5	(*R*)-segphos	61	77
6	(*R*,*R*)-Me-duphos	92	37
7	(S)-tol-binap	90	91

[a] dppp = propane-l,3-diylbis(diphenylphosphane), binap = 2,2′-bis(diphenylphosphanyl)-1,1′-binaphthyl, chiraphos = 2,3-bis(diphenylphosphino)butane, monophos = (3,5-dioxa-4-phosphacyclohepta[2,1-a;3,4-a′]dinaphthalen-4-yl)dimethylamine, segphos = 5,5′-bisdiphenylphosphino[4,4′]bi[benzo[1,3]dioxolyl], duphos = 2,5-diethylphospholano]benzene, tol = tolyl. [b] Yields of isolated products. [c] *ee* values determined by HPLC analysis (Chiralpak AD, hexane/2-propanol 90:10, flow rate 1.0 mL min^{-1}): t_r: 15.24 and 27.47 min, 20 °C. [d] Reaction carried out at 60 °C using 1 mol % catalyst.

Once we had established high enantioselectivity and reactivity for the palladium-catalyzed ring-opening reaction between **10** and **17**, we turned our attention to the cyclization of the dihydronaphthalene product **18** and the formation of the B ring of homochelidonine. Selective removal of the MOM group proved to be problematic. A variety of conditions were attempted: TMSCl,[13] $LiBF_4$,[14] *B*-chlorocatecholborane,[15] HCl/THF,[16] CBr_4/*i*PrOH,[17] PPTS/

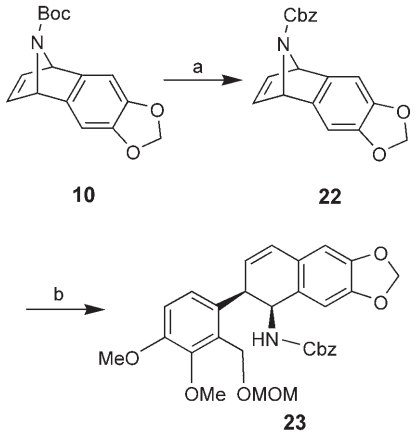
*t*BuOH,[18] 50% aqueous AcOH,[13] and *p*-TsOH/MeOH[19]. However, we only isolated the expected product **19** in low yield (< 25%), contaminated with the aromatic compounds **20** and **21**, presumably formed by concomitant removal of the Boc group and then elimination of ammonia under the acidic conditions (Scheme 5).



Scheme 5. Attempted cleavage of the MOM group of **18**.

An alternative approach used *N*-Cbz-protected azabicycle **22**, since we surmised that the resulting product, dihydronaphthalene **23**, would be stable to the acidic conditions required to remove the MOM group. *N*-Boc-azabicycle **10** was converted into *N*-Cbz-azabicycle **22** in 80% yield in a one-pot reaction by using TMSI for removal of the Boc group,[20] then addition of CbzCl to protect the resulting secondary amine. The asymmetric ring-opening reaction with boronic acid **17** gave dihydronaphthalene **23** in 89% yield and 90% *ee* (Scheme 6). One recrystallization from Et_2O gave dihydronaphthalene **23** in 80% yield and 99% *ee*. This reaction has been carried out on a multigram scale without any loss of enantiodiscrimination.[21]

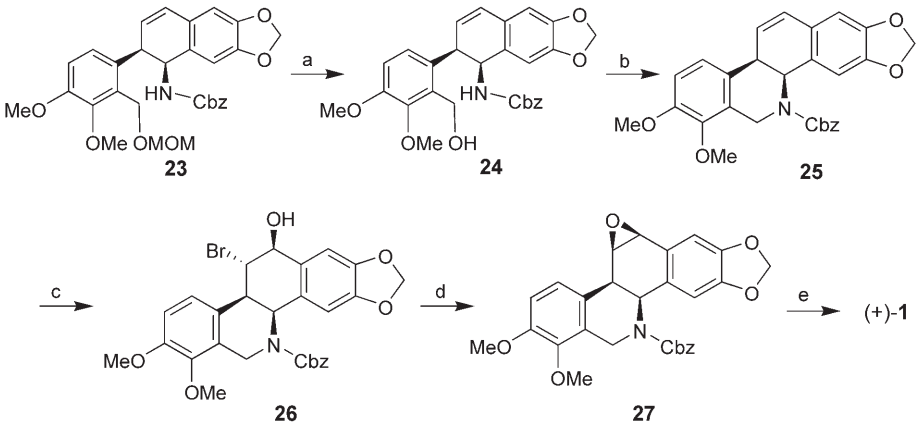
It was now possible to selectively remove the MOM group by stirring dihydronaphthalene **23** in concentrated HCl and THF/*i*PrOH to give the benzyl alcohol **24** in 75% yield (Scheme 7). Bromination of the benzyl alcohol group with carbon tetrabromide and triphenylphosphine, followed by a cyclization reaction with sodium hydride on the crude reaction mixture, resulted in the formation of the B ring, thus providing dihydronaphthalene **25** in 90% yield. Our attention now turned to the introduction of the *syn*-hydroxy group at C11. A single bromohydrin isomer was obtained in 75% by reaction of **25** with NBS in wet THF. The regio- and stereochemistry can be rationalized by the intermediate bromonium ion being formed on the least hindered face of the alkene, followed by attack of water at the benzylic position. Reaction of bromohydrin **26** with sodium *tert*-butoxide in THF yielded the *syn*-epoxide **27** in quantitative yield. With the oxygen functionality now installed on the correct side of the C ring, it was now necessary to carry out a regioselective hydride-mediated reduction of the epoxide, followed by removal of the Cbz group and methylation of the amine. This was carried out in a one-pot reaction in which epoxide **27** was heated with $LiAlH_4$ in 1,4-dioxane to give (+)-homochelidonine in 87% yield.



Scheme 6. Synthesis of dihydronaphthalene **23**: a) TMSI, NEt_3, CH_2Cl_2, reflux, 15 min; then CbzCl, RT, 3 h, 80%; b) $[Pd(MeCN_2)Cl_2]$ (5 mol%), (*S*)-binap (5.5 mol%), **17**, Cs_2CO_3, MeOH, RT, 6 h, 89%, 90% *ee* (80%, 99% *ee* after one recrystallization). Cbz = benzyloxycarbonyl, TMS = trimethylsilyl.

The spectroscopic properties of the synthetic material were in agreement with those of the natural product.[7c,21] The optical rotation ($[\alpha]_D^{25} = +120$ ($c = 1.0$ in EtOH)) confirmed the absolute stereochemistry.[1g] HPLC analysis of this compound on a chiral stationary phase gave an *ee* value of 99%, thus indicating that the enantiopurity of dihydronaphthalene **23** was maintained throughout the final sequence.

In summary, we have developed a new and general strategy for the synthesis of the hexahydrobenzo[*c*]phenanthridine alkaloids with a novel and highly enantioselective palladium(II)-catalyzed ring-opening reaction of a *meso*-azabicycle with an aryl boronic acid as the key step. We have demonstrated the power of this methodology for the first



Scheme 7. Completion of the synthesis of (+)-**1**: a) HCl, *i*PrOH/THF, RT, 8 h, 75%; b) CBr_4, PPh_3, CH_2Cl_2, 0°C, 1 h; then NaH, DMF, 0°C, 3 h, 90%; c) NBS, THF/H_2O, RT, 90 min, 75%; d) KO*t*Bu, THF, −78°C, 30 min, quant.; e) $LiAlH_4$, 1,4-dioxane, reflux, 12 h, 87%.

time in natural product synthesis and thus have completed the first enantioselective total synthesis of (+)-homochelidonine in 14 steps. The longest linear sequence is 11 steps and the overall yield is 15% from 4,5-dibromovertrole. Studies to find general conditions for the desymmetrization of *meso*-azabicycles with boronic acids and the application of this methodology to the synthesis of other hexahydrobenzo[*c*]phenanthridine alkaloids is currently under investigation.

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