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# Concise Enantioselective Total Syntheses of (+)-Homochelidonine, (+)-Chelamidine, (+)-Chelidonine, (+)-Chelamine and (+)-Norchelidonine by a $Pd^{II}$-Catalyzed Ring-Opening Strategy

**Matthew J. Fleming, Helen A. McManus, Alena Rudolph, Walter H. Chan, Jérémy Ruiz, Chris Dockendorff, and Mark Lautens*[a]**

**Abstract:** New enantioselective syntheses of the B/C hexahydrobenzo[*c*]phenanthridine alkaloids (+)-homochelidonine, (+)-chelamidine, (+)-chelidonine, (+)-chelamine, and (+)-norchelidonine are described. Our rapid and convergent route to this class of natural products involved the development and application of a $Pd^{II}$-catalyzed asymmetric ring-opening reaction of a *meso*-azabicyclic alkene with an aryl boronic acid as the key step. By screening a variety of functionalized *ortho*-substituted aryl boronic acids, chiral ligands and reaction conditions we were able to prepare the requisite *cis*-1-amino-2-aryldihydronaphthalenes in high yield and in up to 90% *ee*. Early attempts to complete the synthesis of (+)-homochelidonine using an *N*-Boc azabicyclic alkene are described in full. The successful route required a protecting group alteration followed by B ring formation and then stereoselective installation of the C-11 *syn*-hydroxy group by regioselective epoxide ring-opening using a hydride source. Ring-opening of the same epoxide intermediate with water ultimately led to the synthesis of (+)-chelamidine. The same strategy was then used to synthesize the other structurally similar B/C hexahydrobenzo[*c*]phenanthridine alkaloids, (+)-chelidonine, (+)-chelamidine, and (+)-norchelidonine.

**Keywords:** alkaloids · asymmetric catalysis · polycycles · ring-opening · total synthesis

## Introduction

The B/C hexahydrobenzo[*c*]phenanthridine alkaloids[1] are a group of isoquinoline alkaloids that occur naturally in papaveraceous plants. They are characterized by the same basic skeleton **1**, which contains partially hydrogenated *cis*-fused B and C rings, fully aromatic A and D rings, a hydroxy group at C-11, and three contiguous *syn* stereogenic centers (Figure 1). Out of this family of alkaloids, chelidonine[2] (**4**) has received the most attention. Isolated from *Chelidonium majus* L. as early as 1839,[3] chelidonine has a range of proposed pharmacological activities including tubulin interaction within target cells causing mitotic arrest.[4] Chelidonine is also a major component of the drug Ukrain, a semisynthetic antitumor preparation derived from *C. majus* alkaloids.[5] *O*-Acyl and *O*-alkyl derivatives of chelidonine have also shown antinociceptive and antiserotoninergic effects, not reported for the parent alkaloid.[6] It has been isolated from different plant sources in both enantiomeric forms[7] and also as a racemic mixture[8] (for which a separate name-"Diphylline" was coined). The absolute stereochemistry has been unequivocally assigned by X-ray diffraction techniques.[9] Other structurally similar, naturally occurring B/C hexahydrobenzo[*c*]phenanthridine alkaloids include homochelidonine[8a,10] (**2**), chelamidine[8a,10c] (**3**), chelamine[8a,10c,d,11] (**5**) and norchelidonine[10d,12] (**6**) (Figure 1). These compounds contain the same basic skeleton **1** but differ in either the oxidation state at C-12, the functionality on the aromatic A ring and/or the degree of substitution on the nitrogen atom.

Limited efforts towards the syntheses of B/C hexahydrobenzo[*c*]phenanthridine alkaloids have been reported. These include racemic syntheses of homochelidonine,[13] chelamidine,[13c] chelidonine,[14] chelamine[14e] and norchelidonine.[14a,d]

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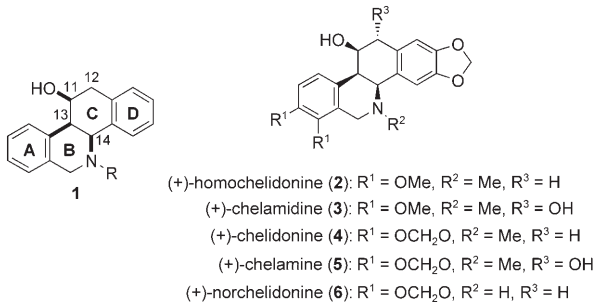
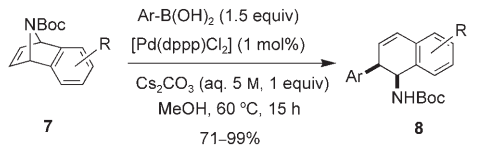



Figure 1. Structures of some B/C hexahydrobenzo[*c*]phenanthridine alkaloids.

An asymmetric synthesis of the B/C hexahydrobenzo[*c*]phenanthridine basic skeleton has also been described.[15]

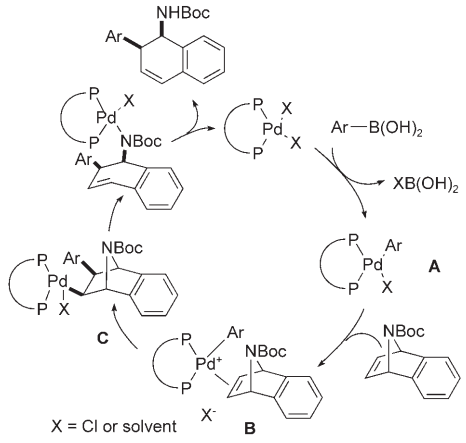
We were attracted to this class of natural products since it appeared the core structure could be prepared using our recently developed $Pd^{II}$-catalyzed ring-opening reaction of *meso*-azabicyclic-alkenes with aryl boronic acids.[16] In this paper, we report the evolution of the asymmetric version of this reaction into a strategy for the total synthesis of (+)-homochelidonine[17] and subsequently the 4 other hexahydrobenzo[*c*]phenanthridine alkaloids, (+)-chelamidine, (+)-chelidonine, (+)-chelamine, and (+)-norchelidonine.

**Racemic synthesis of *cis*-1-amino-2-aryldihydronaphthalenes**: We have previously reported the transition metal-catalyzed ring-opening of strained *N*-Boc azabicyclic alkenes **7** by the addition of aryl boronic acids.[16a] Using the optimized reaction conditions [[$Pd(dppp)Cl_2$] (1 mol%), aq. $Cs_2CO_3$ (1 equiv) in MeOH at 60°C], various azabicyclic alkenes, including both electron rich and electron deficient, were opened with a range of monosubstituted aryl and heteroaryl boronic acids giving *cis*-1-amino-2-aryldihydronaphthalenes **8** in good to excellent yields (71–99%, Scheme 1). The reaction was highly stereoselective with only the *cis*-isomer being observed. Catalyst loadings as low as 0.1 mol% were possible, giving complete conversion for the reaction of *N*-Boc-azabenzonorbornadiene with $PhB(OH)_2$ within 24 h. These reactions also proceeded in the absence of base but reaction times were longer.




Scheme 1. $Pd^{II}$-catalyzed ring-opening of azabicyclic alkenes with boronic acids. Boc = *tert*-butyl carbamate. dppp = propane-1,3-diylbis(diphenylphosphane).

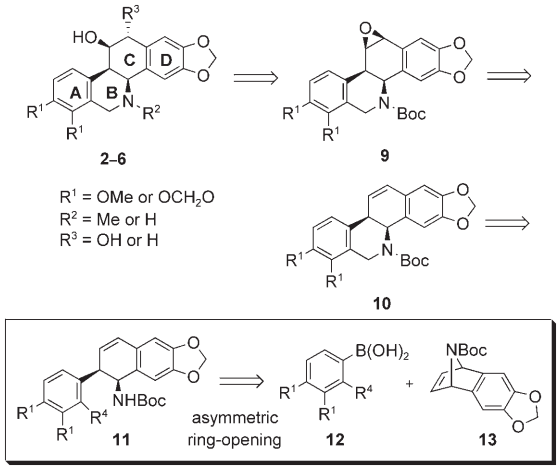
The proposed catalytic cycle begins with the transmetallation of the aryl group from the boronic acid to give aryl $Pd^{II}$ species **A** (Scheme 2). Association of **A** to the least hindered *exo*-face of the azabicyclic alkene gives cationic complex **B**, which undergoes *syn*-carbopalladation to give **C** followed by β-heteroatom elimination and dissociation to furnish the ring-opened product and regenerate the active $Pd^{II}$ catalyst. It is important to note that in this proposed catalytic cycle Pd remains in the +2 oxidation state throughout.




Scheme 2. Proposed catalytic cycle for $Pd^{II}$-catalyzed ring-opening of azabicyclic alkenes with aryl boronic acids.

**Retrosynthetic analysis**: Comparison between the basic B/C hexahydrobenzo[*c*]phenanthridine alkaloid skeleton **1** and generic compound **8** reveals that **8** contains the requisite tetralin core with *syn*-stereochemistry of the aryl and amino substituents at C-13 and C-14.

We envisaged that the key step in our retrosynthetic plan would be the enantioselective metal-catalyzed addition of a trisubstituted aryl boronic acid **12** to azabicyclic alkene **13** with concomitant ring opening to yield *cis*-1-amino-2-aryl dihydronaphthalene intermediate **11** (Scheme 3). A suitably functionalized *ortho*-substituent ($R^4$) on the boronic acid would allow for cyclization to the B ring to give **10**. Stereoselective epoxidization of the double bond in **10**, followed by regioselective ring-opening of the corresponding epoxide



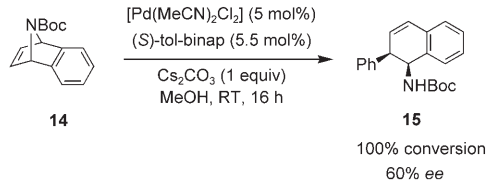

Scheme 3. Retrosynthetic analysis for B/C hexahydrobenzo[*c*]phenanthridine alkaloids.

**9** with a suitable nucleophile would add the desired functionality on the C ring with the correct orientation to ultimately lead to any of the B/C hexahydrobenzo[*c*]phenanthridine alkaloids **2–6**.

## Results and Discussion

**Assessing the feasibility of an enantioselective ring-opening reaction**: At the outset of this project, the main challenge was to develop a highly enantioselective $Pd^{II}$-catalyzed ring-opening of the *meso*-azabicyclic alkene **13** with aryl boronic acid **12**. The related oxabicyclic alkene substrate reacted in high yield and *ee*[16a] but the aza analogue proved to be a more challenging substrate perhaps due to the orientation of the Boc group or reduced activity in the ring-opening. Initial model-study reactions were carried out using readily available azabicyclic alkene[16e] **14** and $PhB(OH)_2$. Screening a variety of ligands and reaction conditions (solvent, temperature, base, boron source, $Pd^{II}$ precursor and additives) revealed that **15** could be obtained in quantitative yield and up to 60% *ee* when employing (*S*)-tol-binap as the chiral ligand (Scheme 4).[18] Maximum enantiodiscrimination was

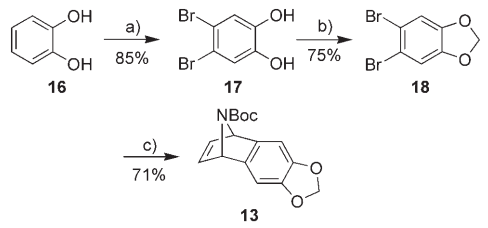



Scheme 4. Asymmetric ring-opening of azabicyclic alkene **14** with $PhB(OH)_2$. binap = 2,2′bis(diphenylphosphanyl)-1,1′-binaphthyl.

achieved by lowering the temperature to RT, while increasing the catalyst loading to 5 mol% to improve the rate of the reaction at this temperature.

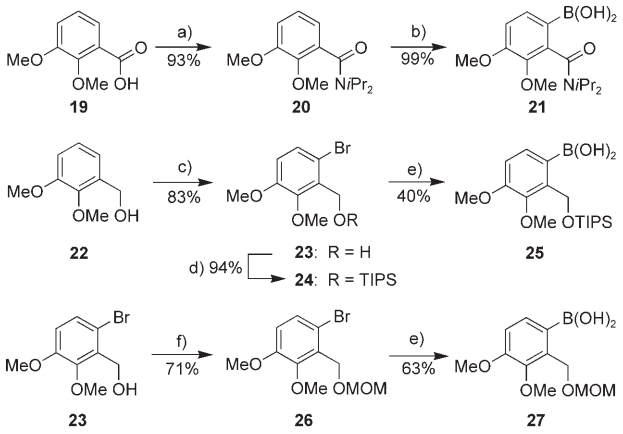
**Finding a suitable boronic acid**: Though we observed moderate stereoinduction using the unsubstituted azabicycle **14** and $PhB(OH)_2$, we decided to test the real system with a nucleophile bearing an *ortho* group, since subtle steric and electronic effects often influence *ee*. Our attention turned towards azabicycle **13**, which could be used to prepare the five B/C hexahydrobenzo[*c*]phenanthridine alkaloids **2–6**. Azabicycle **13** was readily prepared in three steps from catechol **16** (Scheme 5). Treatment of **16** with $Br_2$ gave dibromide **17** in 85% yield,[19] which was subsequently dialkylated with $ClCH_2Br$ to give **18** in 75% yield. Slow addition of *n*BuLi to dibromide **18** generated an aryne intermediate, which underwent an in situ Diels–Alder reaction with *N*-Boc pyrrole to furnish *N*-Boc azabicycle **13** in 71% yield.

We initially focused on the total synthesis of (+)-homochelidonine (**2**) and (+)-chelamidine (**3**), which would require the aryl boronic acid **12** to contain *meta* and *para*-OMe substituents and a viable *ortho*-substituent that could




Scheme 5. Synthesis of *N*-Boc azabicycle **13** a) $Br_2$, $CHCl_3$, RT, 20 h; b) $ClCH_2Br$, $Cs_2CO_3$, DMF, 110 °C, 3 h; c) *N*-Boc pyrrole, *n*BuLi, PhMe, −78 °C to RT, 20 h. DMF = *N*,*N*-dimethylformamide, RT = room temperature.

be manipulated into the B ring. A variety of boronic acids that fulfilled these criteria were synthesized (Scheme 6). Boronic acid **21** was prepared in three steps from 2,3-dimethoxybenzoic acid **19** by conversion to the corresponding acid chloride with oxalyl chloride. Directly treating the crude product with $iPr_2NH$ gave benzamide **20** in 93% yield over two steps. Subsequent directed *ortho*-metallation of **20** with *s*BuLi and TMEDA, trapping the resulting aryl lithium with $B(OMe)_3$ and acidic hydrolysis provided the diisopropylamide-substituted boronic acid **21** in 99% yield.[20] Boronic acid **25** was prepared by regioselectively brominating commercially available 2,3-dimethoxybenzyl alcohol **22** with NBS to give aryl bromide **23** in 83% yield. The benzyl alcohol was then protected with a TIPS group in 94% yield to give **24**, which was then converted to the corresponding boronic acid **25** in 40% yield by halogen-lithium exchange using *n*BuLi and subsequent quenching with $B(OiPr)_3$ followed by acidic hydrolysis. Boronic acid **27** was prepared by MOM-protection of the benzyl alcohol of aryl bromide **23** in 72% yield by stirring **23** in dimethoxymethane in the



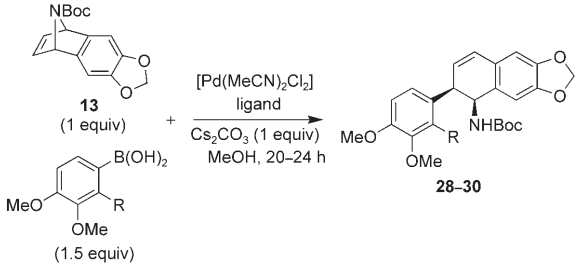

Scheme 6. Synthesis of boronic acids **21**, **25** and **27**: a) $(COCl)_2$, $CH_2Cl_2$, cat. DMF, RT, 2 h, then $iPr_2NH$, $Et_3N$, THF, 17 h; b) *s*BuLi, TMEDA, THF, −78 °C, 1 h then $B(OMe)_3$, −78 °C to RT, 18 h then $NH_4Cl$ (aq); c) NBS, THF, RT, 30 min; d) TIPSCl, imidazole, DMF, RT, 17 h; e) *n*BuLi, THF, −78 °C, 35 min, then $B(OiPr)_3$, −78 °C to RT, 18 h, then $NH_4Cl$ (aq); f) $CH_2(OMe)_2$, LiBr, *p*-TsOH, RT, 24 h. THF = tetrahydrofuran, TMEDA = tetramethylethylenediamine, NBS = *N*-bromosuccinimide, TIPS = triisopropylsilyl, Ts = toluenesulfonyl, MOM = methoxymethyl.

presence of a catalytic amount of LiBr and *p*-TsOH.[21] Aryl bromide **26** was converted to the corresponding boronic acid **27** by halogen-lithium exchange, followed by quenching with $B(OiPr)_3$ and acidic hydrolysis in 63% yield.[22]

With the required azabicycle **13** and a variety of *ortho*-substituted boronic acids in hand, we set about further evaluating the enantioselective ring-opening reaction. Each boronic acid was reacted with azabicycle **13** using the racemic conditions and then the previously optimized enantioselective conditions (Table 1). In each case an excess (1.5 equiv) of boronic acid was used as a significant amount of deboronated product was typically observed. Employing diisopropylamide-substituted boronic acid **21** and achiral ligand dppp gave the desired 1,2-dihydronaphthalene **28** in 81% yield (entry 1). This compound co-eluted with the deboronated product (**20**) thus NMR yields were reported. Using (*S*)-tol-binap as ligand gave **28** in 43% yield and 88% *ee* (entry 2). Boronic acid **25** and achiral ligand dppp gave dihydronaphthalene **29** in 55% yield (entry 3) while (*S*)-tol-binap gave **29** in only 29% yield and 42% *ee* (entry 4). Employing boronic acid **27** and dppp as ligand gave **30** in 82% yield (entry 5), while (*S*)-tol-binap gave **30** in 90% yield and 91% *ee* (entry 6). As boronic acid **27** provided the best reaction efficiency and enantioselectivities, it was used for the synthesis of (+)-homochelidonine (**2**) and (+)-chelamidine (**3**). Further screening of ligands and reaction conditions using boronic acid **27** were performed, however no improvement in *ee* was observed.[23] Additional studies were also performed on 1,2-dihydronaphthalene **28** but difficulties were noted with manipulating the diisopropyl amide unit so this route was abandoned.

Table 1. Evaluating boronic acids in the enantioselective ring-opening reaction.

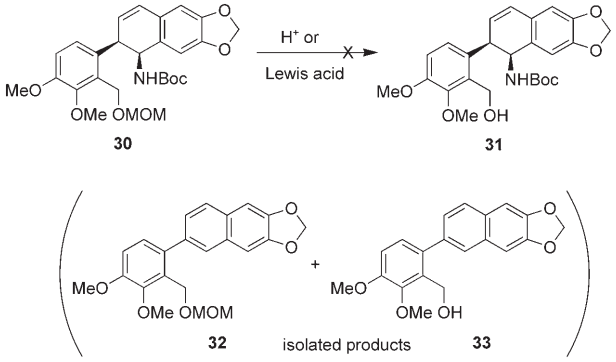



| Entry | Boronic acid | R | Ligand | Product | Yield [%][c] | *ee* [%][d] |
|---|---|---|---|---|---|---|
| 1[a] | **21** | C(O)N*i*Pr$_2$ | dppp | **28** | 81[e] | – |
| 2[b] | **21** | C(O)N*i*Pr$_2$ | (*S*)-tol-binap | **28** | 43[e] | 88 |
| 3[a] | **25** | $CH_2OTIPS$ | dppp | **29** | 55 | – |
| 4[b] | **25** | $CH_2OTIPS$ | (*S*)-tol-binap | **29** | 29 | 42 |
| 5[a] | **27** | $CH_2OMOM$ | dppp | **30** | 82 | – |
| 6[b] | **27** | $CH_2OMOM$ | (*S*)-tol-binap | **30** | 90 | 91 |

[a] 1 mol% $[Pd(MeCN)_2Cl_2]$, 1 mol% ligand, reaction carried out at 60°C. [b] 5 mol% $[Pd(MeCN)_2Cl_2]$, 5.5 mol% ligand, reaction carried out at RT. [c] Isolated yield unless otherwise stated. [d] Determined by chiral HPLC. [e] $^1H$ NMR yield using mesitylene as internal standard.

**Attempted selective deprotection of the MOM group**: With high enantioselectivity and reactivity for the $Pd^{II}$-catalyzed ring-opening reaction between azabicycle **13** and boronic acid **27**, our attention turned to cyclization of the dihydronaphthalene product **30** and the formation of the B ring of (+)-homochelidonine (**2**) and (+)-chelamidine (**3**).

Following literature precedent for selective MOM deprotection in the presence of an *N*-Boc group, dihydronaphthalene **30** was reacted with TMSCl and $Bu_4NBr$ in $CH_2Cl_2$[24] and HCl in *i*PrOH/THF.[25] However, in both instances the expected product was observed in low yield in addition to a mixture of products, including aromatic compounds **32** and **33** formed via concomitant Boc removal and elimination of ammonia (Scheme 7). Other methods commonly used for MOM deprotection were also unsuccessful ($LiBF_4$,[26] *B*-bromocatecholborane,[27] $CBr_4$/*i*PrOH,[28] PPTS/*t*BuOH,[29] 20% aq. AcOH[30] and *p*-TsOH/MeOH[31]).



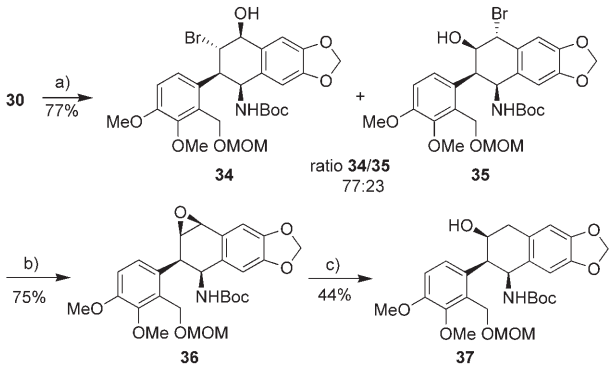

Scheme 7. Attempted selective removal of the MOM group.

**Elaboration of the alkene**: To overcome the problems encountered in the attempted selective MOM deprotection of dihydronaphthalene **30**, we proposed to first elaborate the alkene and introduce the required hydroxy group at the C-11 position. The resulting product alcohol **37** would not be as susceptible to aromatization.

We reasoned that the *syn*-hydroxy group could be introduced by means of a three-step synthetic route involving regio- and stereoselective bromohydrin formation, cyclization to the *syn*-epoxide **36** followed by regioselective ring-opening using a hydride nucleophile for (+)-homochelidonine and a water nucleophile for (+)-chelamidine.

Dihydronaphthalene **30** was therefore reacted with NBS in $THF/H_2O$ to give a mixture of bromohydrin regioisomers **34** and **35** (ratio **34**/**35** 77:23) in 77% yield (Scheme 8). Reaction of the mixture of regioisomers **34** and **35** with a hindered base yielded *syn*-epoxide **36** in 75% yield. Reacting epoxide **36** with $LiAlH_4$ in $Et_2O$ resulted in selective hydride attack at the benzylic position providing alcohol **37** in 44% yield. The *syn*-relationship between the three contiguous



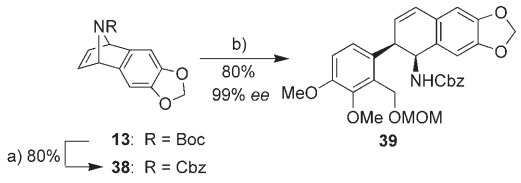

Scheme 8. Installation of the *syn*-hydroxy group: a) NBS, $H_2O$, THF, RT, 90 min; b) KO*t*Bu, THF, −78 °C, 30 min; c) $LiAlH_4$, $Et_2O$, RT, 6 h.

stereogenic centers was confirmed by a 2D $^1$H NMR-ROESY experiment.

Experiments were carried out in an effort to form the B ring of **37**. Unfortunately, attempts to selectively deprotect the MOM group of alcohol **37** using a variety of methods resulted in significant deprotection of the Boc group as well. As the resulting amino alcohol proved difficult to cyclize we subsequently abandoned this route.

**Completion of the synthesis of (+)-homochelidonine and (+)-chelamidine**: Boronic acid **27** was found to be necessary for high enantioselectivities and reaction efficiency for the ring-opening of **13**. However, selective removal of the MOM group in the presence of the Boc group proved to be problematic so it was decided to switch activating groups on the azabicyclic alkene and to attempt the asymmetric ring-opening reaction on *N*-Cbz azabicyclic alkene **38**. The resulting product, dihydronaphthalene **39**, should be less susceptible to carbamate deprotection under the acidic conditions required to remove the MOM group. An additional advantage of the Cbz group is that we envisaged it as a direct precursor to the *N*-Me targets as well as norchelidonine (**6**).

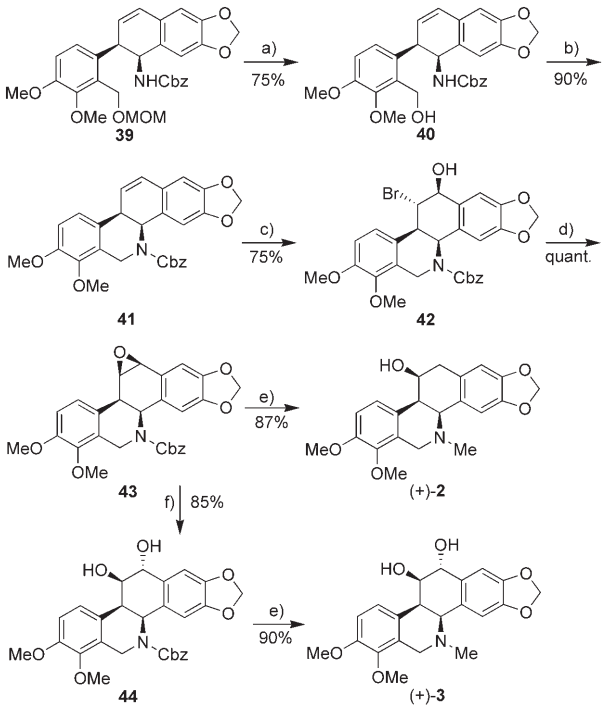
*N*-Boc azabicycle **13** was converted to *N*-Cbz azabicyclic alkene **38** in 80% yield, in a one pot reaction, using first TMSI for Boc removal[32] then carbamate protection of the resulting secondary amine by addition of CbzCl (Scheme 9). It was necessary to interconvert protecting groups as the aryne Diels–Alder reaction between *N*-Cbz pyrrole and dibromide **18** gave a poor yield of azabicyclic alkene **38**




Scheme 9. Synthesis of dihydronaphthalene **39**: a) TMSI, $NEt_3$, $CH_2Cl_2$, reflux, 15 min, then CbzCl, RT, 3 h; b) [Pd(MeCN$_2$)Cl$_2$] (5 mol%), (*S*)-tol-binap (5.5 mol%), **27**, $Cs_2CO_3$, MeOH, RT, 6 h. TMS = trimethylsilyl, Cbz = benzyloxycarbonyl.

(<25%). Pleasingly, the previously developed asymmetric ring-opening reaction conditions with boronic acid **27** gave dihydronaphthalene **39** in 89% yield and 90% *ee*. One recrystallization from $Et_2O$ gave dihydronaphthalene **39** in 80% yield with 99% *ee*. This reaction has been carried out on a multigram scale without any loss of enantiodiscrimination.

It was now possible to selectively remove the MOM group by stirring dihydronaphthalene **39** in conc. HCl and THF/*i*PrOH to give benzyl alcohol **40** in 75% yield (Scheme 10). We were unable to cyclize the B ring using




Scheme 10. Completion of the synthesis of (+)-homochelidonine (**2**) and (+)-chelamidine (**3**): a) HCl, *i*PrOH/THF, RT, 8 h; b) $CBr_4$, $PPh_3$, $CH_2Cl_2$, 0 °C, 1 h, then NaH, DMF, 0 °C, 3 h; c) NBS, $H_2O$, THF, RT, 90 min; d) KO*t*Bu, THF, −78 °C, 30 min; e) $LiAlH_4$, 1,4-dioxane, reflux, 18 h; f) $H_2O$, cat. $BiCl_3$, MeCN, 0 °C, 30 min.

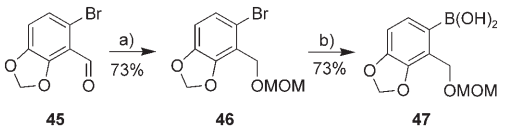
Mitsunobu conditions[33] but it was possible to convert the benzyl alcohol group to a benzyl bromide with $CBr_4$ and $PPh_3$ and carry out a 6-*exo-tet* cyclization by addition of NaH to the crude reaction mixture. Formation of the B ring was achieved, giving dihydronaphthalene **41** in 90% yield. Our attention now turned to introducing the *syn* C-11 hydroxy group. A single bromohydrin regio- and stereoisomer **42** was obtained in 75% by reaction of **41** with NBS in $H_2O$/THF. This reaction 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 **42** with KO*t*Bu in THF yielded *syn*-epoxide **43** in quantitative yield. Having installed the hydroxyl functionality on the correct side of the C ring it was now necessary to carry out a regioselective hydride re-

duction of the epoxide followed by Cbz reduction to the methylamine. This was achieved as a one pot reaction by heating epoxide **43** with $LiAlH_4$ in 1,4-dioxane to give (+)-homochelidonine in 87% yield. The spectroscopic properties of the synthetic material were in agreement with those of the natural product.[10c] The optical rotation ($[\alpha]_D^{25} = +120$ ($c$ = 1.0 in EtOH)) confirmed the absolute stereochemistry.[10c] Chiral HPLC analysis of this compound gave an enantiomeric excess of 99% indicating that the enantiopurity of dihydronaphthalene **39** was maintained throughout the final sequence.

Regioselectively ring-opening epoxide intermediate **43** with $H_2O$ in the presence of a catalytic amount of $BiCl_3$[34] gave diol **44** in 85% yield. Heating diol **44** with $LiAlH_4$ reduced the Cbz group to the methylamine to give (+)-chelamidine in 90% yield. The compound matched previously published spectroscopic data.[10c,13c]

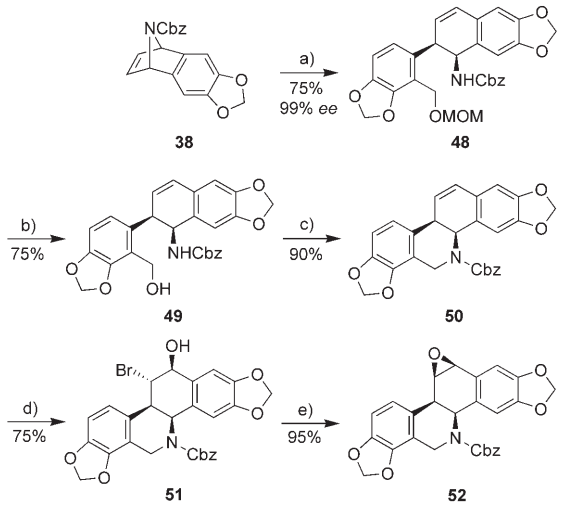
**Syntheses of (+)-chelidonine, (+)-chelamine and (+)-norchelidonine**: We now had a straightforward strategy to complete the synthesis of the other 3 *B*/*C* hexahydrobenzo[*c*]-phenanthridine alkaloids using boronic acid **47**. Three steps were required from commercially available aldehyde **45** (Scheme 11). Aldehyde **45** was reduced using $NaBH_4$ and the corresponding benzylic alcohol protected as the MOM ether in 73% over two steps. The aryl bromide **46** was then converted to boronic acid **47** by halogen–lithium exchange and trapping out the aryl lithium with $B(OiPr)_3$, followed by acidic hydrolysis.[35]



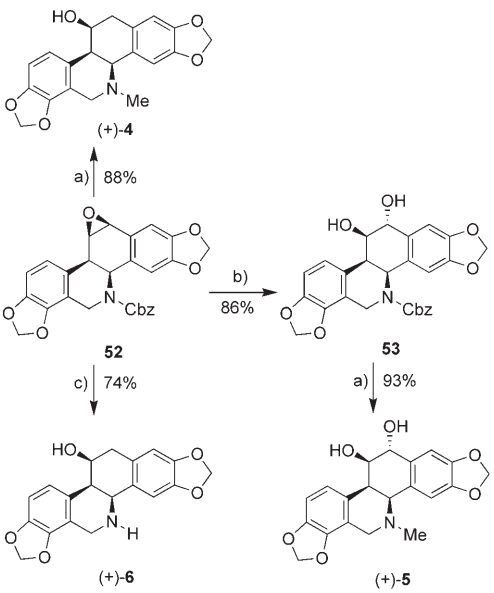

Scheme 11. Synthesis of boronic acid **47**: a) $NaBH_4$, MeOH, RT, 1 h then $CH_2(OMe)_2$, LiBr, *p*-TsOH, RT, 15 h; b) *n*BuLi, THF, −78°C 45 min, then $B(OiPr)_3$, −78°C to RT, 18 h, then $NH_4Cl$ (aq).

Carrying out the asymmetric ring-opening reaction using azabicyclic alkene **38** and boronic acid **47** under the developed conditions gave 1,2-dihydronaphthalene **48** in 89% yield and 90% *ee* (Scheme 12). One recrystallization gave **48** in 75% yield and 99% *ee*. Using the same four-step synthetic sequence on 1,2-dihydronaphthalene **48** (MOM removal, B ring cyclization, bromohydrin formation and intramolecular $S_N2$ substitution) gave the key epoxide intermediate **52**.

Heating epoxide **52** with $LiAlH_4$ in 1,4-dioxane gave (+)-chelidonine (**4**) in 88% yield (Scheme 13). The spectroscopic properties of the synthetic material were in agreement with those of the natural product.[2g,14d] Regioselectively ring-opening epoxide intermediate **52** with $H_2O$ in the presence of a catalytic amount of $BiCl_3$ gave diol **53** in 86% yield. Heating diol **53** with $LiAlH_4$ reduced the carbamate group to the methylamine to give (+)-chelamine (**5**) in 93% yield. The compound matched previously published spectroscopic data.[10c] Stirring epoxide **52** and catalytic Pd/C under an $H_2$ atmosphere regioselectively ring-opened the epoxide and removed the Cbz protecting group to give (+)-norchelidonine (**6**) in 74% yield. The compound matched previously published spectroscopic data.[10d,14d]




Scheme 12. Synthesis of key epoxide intermediate **52**: a) $Pd(MeCN_2)Cl_2$ (5 mol%), (*S*)-tol-BINAP (5.5 mol%), **47**, $Cs_2CO_3$, MeOH, RT, 6 h; b) HCl, *i*PrOH/THF, RT, 8 h; c) $CBr_4$, $PPh_3$, $CH_2Cl_2$, 0°C, 1 h, then NaH, DMF, 0°C, 3 h; d) NBS, THF/$H_2O$, RT, 90 min; e) KO*t*Bu, THF, −78°C, 30 min.




Scheme 13. Completion of the synthesis of (+)-chelidonine (**4**), (+)-chelamine (**5**) and (+)-norchelidonine (**6**): a) $LiAlH_4$, 1,4-dioxane, reflux 18 h; b) $H_2O$, cat. $BiCl_3$, MeCN, 0°C, 30 min; c) 1 atm $H_2$, cat. Pd/C, EtOH, RT, 2 h.

## Conclusion

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 $Pd^{II}$-catalyzed ring-opening reaction of a *meso*-azabicyclic alkene with an aryl boronic acid as the key step. In this way, we have demonstrated the power of this methodology for the first time in natural product synthesis and completed the first enantioselective total syntheses of (+)-homochelidonine, (+)-chelamidine, (+)-chelidonine, (+)-chelamine and (+)-norchelidonine. Due to the convergent nature of the synthesis it is now possible to prepare structural analogues of the hexahydrobenzo[*c*]phenanthridine alkaloids with potentially improved pharmacological properties.

## Experimental Section

**General**: All reactions were carried out under an argon atmosphere, in flame-dried round bottom flasks fitted with rubber septa, with magnetic stirring. Air- or water-sensitive liquids and solutions were transferred via syringe. Organic solutions were concentrated by rotary evaporation at 23–40 °C at 40 Torr unless otherwise stated. Solvents and reagents: Tetrahydrofuran, 1,4-dioxane and toluene were purified by distillation under $N_2$ from Na/benzophenone immediately prior to use. Triethylamine was purified by distillation under $N_2$ from NaOH immediately prior to use. Diethyl ether and dichloromethane were purified by the method of Pangborn et al.[36] All other solvents were used as received. *N*-Bromosuccinimide was recrystallized from $H_2O$ prior to use. Analytical thin-layer chromatography: Performed with Silicycle normal phase glass plates (0.25 mm, 60 A pore size, 230–400 mesh). Visualization was accomplished with 254 nm UV light and/or by immersion in potassium permanganate or phosphomolybdic acid solution, followed by brief heating using a heat gun. Chromatography: Flash and gradient column chromatography was carried out using Silicycle Ultra-Pure 230–400 mesh silica gel. Melting points were taken on a Fisher-Johns melting point apparatus and are uncorrected. Optical rotations were measured in a 5.0 or 10.0 cm cell with a Rudolph Autopol IV polarimeter digital polarimeter equipped with a sodium lamp source (589 nm), and are reported as follows: $[\alpha]_D^{T/^\circ C}$ = ($c$ = g 100 $mL^{-1}$, solvent). IR Spectroscopy: IR spectra were obtained using a Perkin-Elmer Spectrum 1000 FT-IR spectrometer as neat films or as solutions ($CHCl_3$ or $CH_2Cl_2$) on a NaCl plate. Data is presented as follows: frequency of absorption ($cm^{-1}$) and intensity of absorption (s = strong, m = medium, w = weak, br = broad). NMR spectroscopy: $^1H$ and $^{13}C$ NMR spectra were recorded at 23 °C in $CDCl_3$ with a Varian 400 (400 MHz/100 MHz) NMR spectrometer equipped with ATB8123-400 probe, or a Varian Mercury 400 (400 MHz/100 MHz) NMR spectrometer equipped with a Nalorac4N-400 probe. Recorded shifts for protons are reported in parts per million ($\delta$ scale) downfield from tetramethylsilane and are referenced to residual proton in the NMR solvent ($CHCl_3$: $\delta$ 7.26). Chemical shifts for carbon resonances are reported in parts per million ($\delta$ scale) downfield from tetramethylsilane and are referenced to the carbon resonances of the solvent ($CDCl_3$: $\delta$ 77.0). Data are represented as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, sept = septet, m = multiplet, br = broad), coupling constant ($J$, Hz) and integration. Mass spectrometry: High resolution mass spectra were obtained from a SI2 Micromass 70S-250 mass spectrometer (EI) or an ABI/Sciex Qstar mass spectrometer (ESI).

**Dibromocatechol 17**: A solution of $Br_2$ (13.9 mL, 272 mmol) in $CHCl_3$ (20 mL) was added dropwise over 1 h to a suspension of catechol **16** (15.0 g, 136 mmol) in $CHCl_3$ (150 mL) at 0 °C. After stirring at RT for 20 h dibromocatechol **17** (31.0 g, 85 %) was isolated by filtration as an off-white solid. M.p. 97–98 °C (lit.[19] m.p. 119 °C); $R_f$ = 0.46 (50 % EtOAc in hexane); $^1H$ NMR: $\delta$ = 7.14 (s, 2H), 5.29 ppm (s, 2H); $^{13}C$ NMR: $\delta$ = 143.5, 119.9, 114.9 ppm; IR ($CH_2Cl_2$): $\tilde{\nu}$ = 3582m, 3354s, 1589m, 1495s, 1415s, 1267m, 1173m, 860 $cm^{-1}$ m; MS (EI): $m/z$: 268 (100) [$M^+$], 159 (17), 77 (14); HRMS: $m/z$: calcd for $C_6H_4{}^{79}Br_2O_2$: 265.8578, found 265.8580 [$M^+$].

**Dibromide 18**: Bromochloromethane (4.36 mL, 65.3 mmol) was added to a stirred solution of dibromocatechol **17** (8.76 g, 32.7 mmol) and $Cs_2CO_3$ (16.0 g, 49.0 mmol) in anhydrous DMF (50 mL). The resulting purple/brown suspension was then heated to 110 °C for 3 h. After cooling to RT, the reaction mixture was filtered through a pad of celite which was then washed with EtOAc. Water (100 mL) was added to the filtrate, the organic layer was separated and the aqueous layer was extracted with EtOAc (2 × 100 mL). The combined organic layers were dried ($Na_2SO_4$) and the solvent removed under reduced pressure to give a brown solid. Purification by column chromatography (10 % EtOAc in hexane) gave dibromide **18** (6.86 g, 75 %) as a white solid. M.p. 82–83 °C; $R_f$ = 0.50 (10 % EtOAc in hexane); $^1H$ NMR: $\delta$ = 7.07 (s, 2H), 6.00 (s, 2H); $^{13}C$ NMR: $\delta$ = 147.9, 115.4, 113.2, 102.3; IR ($CH_2Cl_2$): $\tilde{\nu}$ = 3111s, 1700m, 1469m, 1378s, 1322m, 1138m, 930 $cm^{-1}$ m; MS (EI): $m/z$: 280 (100) [$M^+$], 143 (29), 62 (37); HRMS: $m/z$: calcd for $C_7H_4{}^{79}Br_2O_2$: 277.8578, found 277.8580 [$M^+$].

***N*-Boc azabicyclic alkene 13**: A mixture of dibromide **18** (5.99 g, 21.4 mmol) and freshly distilled *N*-Boc-pyrrole (5.35 mL, 32.0 mmol) in toluene (100 mL) was cooled to −78 °C. *n*BuLi (1.6 M in hexane; 29.4 mL, 47.0 mmol) was added dropwise over a period of 2.5 h. The resulting bright orange solution was allowed to warm up to RT over 3 h and then left for a further 17 h at RT. The reaction mixture was then quenched with water (70 mL) and the phases were separated. The aqueous layer was extracted with EtOAc (3 × 80 mL) and the organic layers were combined, dried ($MgSO_4$) and the solvent removed under reduced pressure to give a brown oil. Purification by column chromatography (10 % EtOAc in hexane) gave azabicycle **13** (4.37 g, 71 %) as an off-white solid. M.p. 91–93 °C; $R_f$ = 0.10 (10 % EtOAc in hexane); $^1H$ NMR: $\delta$ = 6.97 (br s, 2H), 6.84, (s, 2H), 5.91 (d, $J$ = 1.5 Hz, 1H), 5.87 (d, $J$ = 1.5 Hz, 1H), 5.40 (br s, 2H), 1.38 ppm (s, 9H); $^{13}C$ NMR: $\delta$ = 154.8, 144.3, 142.5, [104.7, 104.2], 101.4, 80.6, [66.9, 66.3], 28.1 ppm; IR ($CH_2Cl_2$): $\tilde{\nu}$ = 3441w, 2975m, 2930m, 1705m, 1461s, 1345m, 1367m, 1321s, 1293m, 1252m, 1166m, 1037 $cm^{-1}$ m; MS (EI): $m/z$: 287 (17) [$M^+$], 231 (24), 205 (52), 187 (21), 161 (41); HRMS: $m/z$: calcd for $C_{16}H_{17}NO_4$: 287.1157, found 287.1155 [$M^+$].

**Diisopropylarylamide 20**: DMF (0.40 mL, 5.17 mmol) was added dropwise to a solution of 2,3-dimethoxybenzoic acid (**19**) (5.00 g, 27.4 mmol) and oxalyl chloride (6.05 mL, 70.5 mmol) in $CH_2Cl_2$ (100 mL) at 0 °C. After stirring at RT for 2 h the reaction mixture was concentrated under reduced pressure to give a yellow solid. The solid was dissolved in THF (10 mL) and the resulting solution added to $NEt_3$ (3.82 mL, 27.4 mmol) and $iPr_2NH$ (3.87 mL, 27.4 mmol) in THF (70 mL) at 0 °C. After stirring at RT for 17 h the resulting suspension was filtered and washed with THF. Recrystallization ($Et_2O$/hexane) gave benzamide **20** (6.76 g, 93 %) as a yellow solid. M.p. 108–109 °C (lit.[37] m.p. 113–114 °C); $R_f$ = 0.30 (50 % EtOAc in hexane); $^1H$ NMR: $\delta$ = 7.05 (dd, $J$ = 8, 7.5 Hz, 1H), 6.88 (dd, $J$ = 8, 1.5 Hz, 1H), 6.75 (dd, $J$ = 7.5, 1.5 Hz, 1H), 3.87 (s, 3H), 3.85 (s, 3H), 3.69 (sept, $J$ = 7 Hz, 1H), 3.49 (sept, $J$ = 7 Hz, 1H), 1.54 (d, $J$ = 7 Hz, 3H), 1.53 (d, $J$ = 7 Hz, 3H), 1.16 (d, $J$ = 7 Hz, 3H), 1.04 ppm (d, $J$ = 7 Hz, 3H); $^{13}C$ NMR: $\delta$ = 167.9, 152.6, 144.6, 134.1, 124.6, 118.3, 111.9, 61.5, 55.7, 51.0, 45.5, 20.8, 20.7, 20.5, 20.2 ppm; IR ($CH_2Cl_2$): $\tilde{\nu}$ = 3651m, 2964m, 1626s, 1439m, 1341 $cm^{-1}$ s; MS (ESI): $m/z$: 266 (100) [$M$+$H^+$], 165 (50); HRMS: $m/z$: calcd for $C_{15}H_{24}NO_3$: 266.1750, found 266.1748 [$M$+$H^+$].

**Boronic acid 21**: A solution of benzamide **20** (2.00 g, 7.54 mmol) in THF (15 mL) was added dropwise to a solution of *s*BuLi (1.0 M; 8.29 mL, 8.29 mmol) and TMEDA (1.24 mL, 8.29 mmol) in THF (23 mL) at −78 °C. After 1 h of stirring, $B(OMe)_3$ (2.52 mL, 22.6 mmol) was added in one portion and the reaction was allowed to warm to RT and then left stirring for a further 18 h. The solution was acidified with aq. 1 M HCl (20 mL). The layers were separated and the aqueous layer was extracted with $CH_2Cl_2$ (3 × 40 mL). The combined organic layers were dried ($MgSO_4$) and solvent removed under reduced pressure to leave a yellow solid. Recrystallization (MeOH/$H_2O$) gave boronic acid **21** (2.31 g, 99 %) as a white solid. M.p. 93–95 °C; $R_f$ = 0.20 (100 % EtOAc); $^1H$ NMR: $\delta$ =

7.63 (d, $J=8$ Hz, 1H), 6.92 (d, $J=8$ Hz, 1H), 5.77 (brs, 2H), 3.91 (s, 3H), 3.83 (s, 3H), 3.64 (sept, $J=8$ Hz, 1H), 3.53 (sept, $J=8$ Hz, 1H), 1.58 (d, $J=8$ Hz, 6H), 1.09 ppm (d, $J=8$ Hz, 6H); $^{13}$C NMR: $\delta$ = 170.9, 154.4, 143.9, 137.6, 132.6, 111.7, 104.8, 61.5, 55.7, 51.8, 46.1, 20.4, 20.2 ppm; IR ($CH_2Cl_2$): $\tilde{\nu}$ = 3386s, 3162s, 2978s, 1610s, 1443m, 1357m, 1298m, 1266 cm$^{-1}$ m, MS (ESI): $m/z$: 310 (55) [$M$+H$^+$], 292 (100); HRMS: $m/z$: calcd for $C_{15}H_{25}BNO_5$: 310.1820, found 310.1829 [$M$+H$^+$].

**Aryl bromide 23**: NBS (12.7 g, 71.4 mmol) was added to a solution of 2,3-dimethoxybenzyl alcohol **22** (10.0 g, 59.5 mmol) in THF (45 mL) and stirred at RT until all the NBS had dissolved (approx. 30 min.). The THF was removed under reduced pressure and the residue was taken up in $Et_2O$ (110 mL). The resulting suspension was filtered to remove the insoluble succinimide and the filtrate was washed with aq. 2 M NaOH (2× 100 mL). The organic phase was dried ($MgSO_4$) and concentrated under reduced pressure to give a pale yellow oil. Purification by column chromatography (20% EtOAc in hexane) gave benzyl alcohol **23** (12.2 g, 83%) as a white solid. M.p. 66–68 °C (lit.[22] 76 °C); $R_f$=0.10 (20% EtOAc in hexane); $^1$H NMR: $\delta$ = 7.27 (d, $J=8.5$ Hz, 1H), 6.78 (d, $J=8.5$ Hz, 1H), 4.82 (d, $J=7$ Hz, 2H), 3.89 (s, 3H), 3.85 (s, 3H), 2.31 ppm (t, $J=7$ Hz, 1H); $^{13}$C NMR: $\delta$ = 152.3, 148.8, 133.9, 127.9, 114.8, 113.4, 61.7, 60.4, 56.0 ppm; IR ($CH_2Cl_2$): $\tilde{\nu}$ = 3426w, 2938m, 1576s, 1474m, 1413s, 1271s, 1229m, 1171m, 1079m, 1009 cm$^{-1}$ m; MS (ESI): $m/z$: 269 (100) [$M$+Na$^+$], 127 (35), 79 (40); HRMS: $m/z$: calcd for $C_9H_{11}BrNaO_3$: 268.9789, found 268.9780 [$M$+Na$^+$].

**Silyl ether 24**: A solution of benzyl alcohol **23** (1.00 g, 4.05 mmol), imidazole (551 mg, 8.09 mmol) and TIPSCl (1.04 mL, 4.86 mmol) in DMF (2 mL) were stirred at RT for 17 h. The reaction was diluted with EtOAc (10 mL) and aq. 1 M HCl (10 mL). The layers were separated and the aqueous layer was extracted with EtOAc (2×20 mL). The organic layers were combined, dried ($Na_2SO_4$) and concentrated under reduced pressure to give a yellow oil. Purification by column chromatography (10% EtOAc in hexane) gave silyl ether **24** (1.54 g, 94%) as a colorless oil. $R_f$=0.50 (20% EtOAc in hexane); $^1$H NMR: $\delta$ = 7.25 (d, $J=8.5$ Hz, 1H), 6.73 (d, $J=8.5$ Hz, 1H), 4.90 (s, 2H), 3.88 (s, 3H), 3.83 (s, 3H), 1.20–1.06 ppm (m, 21H); $^{13}$C NMR: $\delta$ = 152.6, 149.3, 134.4, 128.1, 116.2, 113.3, 62.0, 60.7, 56.1, 18.3, 12.4 ppm; IR (neat): $\tilde{\nu}$ = 2941s, 2864s, 1577w, 1474s, 1414m, 1278s, 1232s, 1060 cm$^{-1}$ s; MS (ESI): $m/z$: 425 (50) [$M$+Na$^+$], 231 (30), 216 (95), 214 (100); HRMS: $m/z$: calcd for $C_{18}H_{31}{}^{79}BrNaO_3Si$: 425.1118, found 425.1117 [$M$+Na$^+$].

**Boronic acid 25**: Aryl bromide **24** (750 mg, 1.86 mmol) was dissolved in THF (5 mL) and cooled to −78 °C. *n*BuLi (1.6 M in hexanes; 1.28 mL, 2.05 mmol) was added dropwise over a 20 min period and the reaction mixture was stirred at this temperature for a further 15 min. B(O*i*Pr)$_3$ (1.28 mL, 5.58 mmol) was added in a single portion and the reaction mixture was allowed to warm up to RT over 6 h and then stirred at this temperature for 12 h. The resulting orange suspension was cooled to 0 °C and acidified to pH 5–6 with saturated aq. $NH_4Cl$. The solvent was removed under reduced pressure to leave an aqueous residue which was extracted with $CH_2Cl_2$ (3×40 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure to give a yellow oil. Purification by column chromatography (20% EtOAc in hexane) gave an off-white solid which was recrystallized ($H_2O$) to give boronic acid **25** (274 mg, 40%) as a white solid. $R_f$=0.25 (25% EtOAc in hexane); $^1$H NMR: $\delta$ = 7.66 (d, $J=8$ Hz, 1H), 6.89 (d, $J=8$ Hz, 1H), 6.69 (s, 2H), 5.00 (s, 2H), 3.89 (s, 3H), 3.77 (s, 3H), 1.26–1.14 (m, 3H), 1.06 (s, 9H), 1.04 ppm (s, 9H); $^{13}$C NMR: $\delta$ = 154.4, 146.4, 137.3, 132.7, 132.7, 111.2, 61.4, 59.2, 55.6, 17.8, 11.9 ppm; IR ($CH_2Cl_2$): $\tilde{\nu}$ = 3375w, 2948s, 1580m, 1458m, 1261s, 1144m, 1095 cm$^{-1}$ m, MS (ESI): $m/z$: 391 (22) [$M$+Na$^+$], 195 (50), 180 (100), 165 (48); HRMS: $m/z$: calcd for $C_{18}H_{33}BNaO_5Si$: 391.2082, found 391.2084 [$M$+Na$^+$].

**MOM-protected benzyl alcohol 26**: LiBr (695 mg, 8.09 mmol) and *p*-TsOH·H$_2$O (770 mg, 4.05 mmol) was added to a solution of the benzyl alcohol **23** (10.0 g, 40.5 mmol) in dimethoxymethane (80 mL). The resulting mixture was then stirred at RT for 24 h. Brine (100 mL) was added to the resulting white suspension and the mixture was extracted with $Et_2O$ (2× 100 mL). The organic layers were combined, dried ($Na_2SO_4$) and concentrated under reduced pressure to give a yellow oil. Purification by column chromatography (20% EtOAc in hexane) gave bromide **26** (8.49 g, 72%) as a colorless oil. $R_f$=0.35 (20% EtOAc in hexane); $^1$H NMR: $\delta$ = 7.29 (d, $J=9$ Hz, 1H), 6.78 (d, $J=9$ Hz, 1H), 4.76 (s, 2H), 4.74 (s, 2H), 3.88 (s, 3H), 3.85 (s, 3H), 3.46 ppm (s, 3H); $^{13}$C NMR: $\delta$ = 152.3, 149.4, 131.2, 127.9, 116.2, 113.6, 96.4, 64.0, 61.7, 55.9, 55.4 ppm; IR ($CH_2Cl_2$): $\tilde{\nu}$ = 2940w, 1577w, 1475m, 1418m, 1378m, 1276s, 1232m, 1150m, 1101m, 1041 cm$^{-1}$ m; MS (ESI): $m/z$: 313 (100) [$M$+Na$^+$], 244 (25), 64 (20); HRMS: $m/z$: calcd for $C_{11}H_{15}BrNaO_4$: 313.0051, found 313.0048 [$M$+Na$^+$].

**Boronic acid 27**: Following the procedure to prepare boronic acid **25**, the addition of *n*BuLi (1.6 M in hexanes; 9.0 mL, 14.4 mmol) to aryl bromide **26** (3.81 g, 13.1 mmol) in THF (14 mL) followed by the addition of B(O*i*Pr)$_3$ (9.05 mL, 39.2 mmol), then aq. $NH_4Cl$ work-up, column chromatography (50% EtOAc in hexane) and recrystallization ($H_2O$) gave boronic acid **27** (2.11 g, 63%) as a white solid. M.p. 63–65 °C; $R_f$=0.20 (50% EtOAc in hexane); $^1$H NMR: $\delta$ = 7.62 (d, $J=8$ Hz, 1H), 6.92 (d, $J=8$ Hz, 1H), 6.40 (brs, 2H), 4.87 (s, 2H), 4.72 (s, 2H), 3.89 (s, 3H), 3.83 (s, 3H), 3.41 ppm (s, 3H); $^{13}$C NMR: $\delta$ = 154.4, 147.6, 134.1, 132.2, 126.8, 111.7, 95.3, 62.8, 61.3, 55.9, 55.6 ppm; IR ($CH_2Cl_2$): $\tilde{\nu}$ = 3380w, 2949s, 1589m, 1452m, 1419m, 1355m, 1279s, 1154m, 1098m, 1072 cm$^{-1}$ m; MS (ESI): $m/z$: 279 (100) [$M$+Na$^+$]; HRMS: $m/z$: calcd for $C_{11}H_{17}BNaO_6$: 279.1010, found 279.1007 [$M$+Na$^+$].

**1,2-Dihydronaphthalene 29** (Table 1, entry 4 conditions): [Pd(MeCN)$_2$Cl$_2$] (1.6 mg, 6.1 μmol) and (*S*)-tol-binap (4.5 mg, 6.7 μmol) were added to MeOH (0.5 mL) and the resulting catalyst mixture was stirred at RT for 1 h giving an orange solution. To this was added a solution of azabicycle **13** (35 mg, 0.12 mmol) and boronic acid **25** (67 mg, 0.18 mmol) in MeOH (0.5 mL) followed by $Cs_2CO_3$ (39 mg, 0.12 mmol) in one portion. The reaction mixture was allowed to stir for 22 h at RT and then dry loaded onto silica. Purification by column chromatography (15→25% EtOAc in hexane) gave dihydronaphthalene **29** (22 mg, 29%) as a white solid with an *ee* of 42% as determined by chiral HPLC analysis (Chiralpak AD, hexane/2-propanol 90:10, flow rate 1 mL min$^{-1}$; $t_R$ = 5.4 (minor), 6.2 min (major)); m.p. 107–110 °C; $R_f$=0.20 (15% EtOAc in hexane); $^1$H NMR: $\delta$ = 6.81 (d, $J=8.5$ Hz, 1H), 6.73 (s, 1H), 6.68 (d, $J=8.5$ Hz, 1H), 6.63 (s, 1H), 6.47 (d, $J=9.5$ Hz, 1H), 6.00–5.91 (m, 3H), 5.21 (t, $J=8.5$ Hz, 1H), 5.09 (d, $J=11$ Hz, 1H), 4.78 (d, $J=11$ Hz, 1H), 4.51–4.42 (m, 2H), 3.81 (s, 3H), 3.80 (s, 3H), 1.35 (s, 9H), 1.19–0.97 ppm (m, 21H); $^{13}$C NMR: $\delta$ = 155.1, 151.5, 147.1, 146.7, 133.6, 131.0, 130.0, 129.3, 127.2, 127.1, 124.5, 111.5, 107.2, 106.9, 100.9, 79.2, 61.5, 56.6, 55.6, 51.7, 39.2, 28.3, 18.0, 12.1 ppm; IR ($CH_2Cl_2$): $\tilde{\nu}$ = 3432w, 2941s, 2892s, 2866s, 1714s, 1485s, 1366m, 1276m, 1166m, 1044 cm$^{-1}$ m; MS (ESI): $m/z$: 634 (45) [$M$+Na$^+$], 321 (100); HRMS: $m/z$: calcd for $C_{34}H_{49}NO_7NaSi$: 634.3170, found 634.3162 [$M$+Na$^+$].

**1,2-Dihydronaphthalene 30** (Table 1, entry 6 conditions): Following the procedure to prepare 1,2-dihydronaphthalene **29**, the addition of the azabicycle **13** (1.00 g, 3.48 mmol) and boronic acid **27** (1.34 g, 5.22 mmol) in MeOH (10 mL) followed by $Cs_2CO_3$ (1.13 g, 3.48 mmol) to [Pd(MeCN)$_2$Cl$_2$] (45 mg, 0.17 mmol) and (*S*)-tol-binap (129 mg, 0.19 mmol) in MeOH (10 mL) gave after column chromatography (10% EtOAc in hexane) dihydronaphthalene **30** (1.56 g, 90%) as a white solid with an *ee* of 91% as determined by chiral HPLC analysis (Chiralpak AD, hexane/2-propanol 90:10, flow rate 1.0 mL min$^{-1}$): $t_R$ = 15.2 (minor), 27.5 min (major); m.p. 53–55 °C; $[\alpha]_D^{25}$ = +90 ($c$ = 1.0 in $CHCl_3$); $R_f$ = 0.23 (20% EtOAc in hexane); $^1$H NMR: $\delta$ = 6.83 (d, $J=8.5$ Hz, 1H), 6.74 (s, 1H), 6.64 (s, 1H), 6.50 (d, $J=9.5$ Hz, 1H), 5.99–5.91 (m, 4H), 5.17 (t, $J=8.5$ Hz, 1H), 4.81 (d, $J=11$ Hz, 1H), 4.74–4.62 (m, 4H), 4.20 (ddd, $J=7$, 4.5 Hz, 2, 1H), 3.84 (s, 3H), 3.82 (s, 3H), 3.40 (s, 3H), 1.35 ppm (s, 9H); $^{13}$C NMR: $\delta$ = 155.1, 151.6, 148.0, 147.1, 146.8, 130.9, 130.4, 129.7, 129.2, 127.4, 127.2, 124.7, 112.3, 107.3, 106.9, 101.0, 96.1, 79.3, 61.4, 60.4, 55.7, 55.5, 52.0, 39.6, 28.3 ppm; IR ($CH_2Cl_2$): $\tilde{\nu}$ = 3407w, 2923s, 1700s, 1507s, 1482s, 1364m, 1279s, 1244m, 1165m, 1037 cm$^{-1}$ m; MS (ESI): $m/z$: 522 (100) [$M$+Na$^+$]; HRMS (ESI): $m/z$: calcd for $C_{27}H_{33}NNaO_8$: 522.2098, found 522.2116 [$M$+Na$^+$].

**Bromohydrin regioisomers 34 and 35**: NBS (623 mg, 3.50 mmol) was added to a solution of dihydronaphthalene **30** (1.44 g, 2.89 mmol) in THF (27 mL) and $H_2O$ (3 mL) and the resulting orange solution was allowed to stir at RT for 90 min. The reaction mixture was diluted with $H_2O$ (50 mL) and EtOAc (50 mL) and the layers separated. The aqueous layer

was extracted with EtOAc (2×50 mL), the combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure to give a yellow oil. Purification by column chromatography (10→50% EtOAc in hexane) gave pure regioisomer **34** (420 mg, 23%) and a mixture of bromohydrins **34** and **35** (925 mg, 54%, **34**/**35** 66:34) as pale brown solids. $R_f$=0.44 (**34**), 0.42 (**35**) (50% EtOAc in hexane); regioisomer **34**: m.p. 98–102 °C; $^1$H NMR: $\delta$ = 7.11 (s, 1H), 6.83 (brd, 1H), 6.65 (brs, 2H), 5.97 (s, 2H), 5.06 (brs, 1H), 4.99 (dd, $J$=8.5, 3.5 Hz, 1H), 4.81–4.73 (m, 2H), 4.68 (d, $J$=6.5 Hz, 1H), 4.66 (d, $J$=6.5 Hz, 1H), 4.42 (brs, 2H), 4.08 (brs, 1H), 3.86 (s, 3H), 3.84 (s, 3H), 3.35 (s, 3H), 3.02 (brs, 1H), 1.26 ppm (brs, 9H); $^{13}$C NMR: $\delta$ 154.6, 151.5, 147.9, 147.7, 132.0, 130.4, 129.4 (x3), 124.4, 111.8, 107.7, 106.4, 101.3, 95.6, 79.5, 75.2, 61.5, 60.9, 55.7, 55.6, 54.8, 52.1, 46.1, 28.2 ppm; IR ($CH_2Cl_2$): $\tilde{\nu}$ = 3343m, 2936m, 1682w, 1582w, 1504w, 1366s, 1278s, 1237s, 1168 cm$^{-1}$ s; MS (ESI): $m/z$: 620 (100) [$M$+Na$^+$], 618 (100) [$M$+Na$^+$], 401 (25), 399 (25), 320 (55); HRMS: $m/z$: calcd for $C_{27}H_{34}{}^{79}BrNNaO_9$: 618.1309, found 618.1314 [$M$+Na$^+$]; $^1$H NMR (regioisomer mixture **34**/**35** 2:1): $\delta$ = 7.11 (s, 1H (major)), 7.00 (brs, 1H, (minor)), 6.83 (brd, 1H (major), 1H (minor)), 6.74–6.72 (brm, 2H (minor)), 6.65 (brs, 2H (major)), 5.99 (d, $J$=1.5 Hz, 1H (minor)), 5.97 (s, 2H (major), 1H (minor)), 5.63–5.60 (brm, 1H (minor)), 5.07 (brs, 1H (major)), 5.02 (d, $J$=3.5 Hz, 1H (minor)), 4.99 (dd, $J$=9, 4 Hz, 1H (major)), 4.86–4.41 (m, 6H (minor)), 4.80–4.72 (m, 2H (major)), 4.68 (d, $J$=7 Hz, 1H (major)), 4.65 (d, $J$=6.5 Hz, 1H (major)), 4.41 (brs, 2H (major)), 4.33 (t, $J$=6 Hz, 1H (minor)), 4.08–4.00 (brm, 1H (major)), 3.86 (s, 3H (major), 3H (minor)), 3.84 (s, 3H (major)), 3.83 (s, 3H (minor)), 3.44 (s, 3H (minor)), 3.35 (s, 3H (major)), 3.07 (brs, 1H (major)), 2.4 (d, $J$=8 Hz, 1H (minor)), 1.36 (s, 9H (minor)), 1.26 ppm (s, 9H (major)).

**Epoxide 36**: A solution of bromohydrins **34** and **35** (870 mg, 1.46 mmol) in THF (250 mL) was cooled to −78 °C. A solution of KO*t*Bu (1 M in THF; 1.46 mL, 1.46 mmol) was added dropwise via a syringe and the resulting solution was stirred at this temperature for 30 min. The reaction mixture was warmed to 0 °C and washed with cold water (100 mL). The layers were separated and the organic layer was dried ($Na_2SO_4$) and concentrated under reduced pressure to give epoxide **36** (565 mg, 75%) as a pale yellow solid. M.p. 77–78 °C; $R_f$=0.38 (50% EtOAc in hexane); $^1$H NMR (4:1 mixture of rotamers): $\delta$ = 7.38 (d, $J$=8.5 Hz, 1H (minor)), 7.32 (d, $J$=8.5 Hz, 1H (major)), 6.99 (d, $J$=8.5 Hz, 1H (minor)), 6.94 (d, $J$=8.5 Hz, 1H (major)), 6.94 (s, 1H (minor)), 6.93 (s, 1H (major)), 6.88 (s, 1H (major)), 6.73 (s, 1H (minor)), 6.01 (d, $J$=1.5 Hz, 1H (minor)), 5.99 (d, $J$=1.5 Hz, 1H (major)), 5.98 (d, $J$=1.5 Hz (minor)), 5.96 (d, $J$=1.5 Hz, 1H (major)), 5.14 (d, $J$=10.5 Hz, 1H (major)), 5.00 (ddd, $J$=10.5, 5, 1.5 Hz, 1H (major)), 4.95 (d, $J$=10.5 Hz, 1H (minor)), 4.88 (d, $J$=11 Hz, 1H (major)), 4.88–4.84 (m, 1H (minor)), 4.79 (d, $J$=10.5 Hz, 1H (minor)), 4.73 (d, $J$=11 Hz, 1H (major), 1H (minor)), 4.69 (d, $J$=6.5 Hz, 1H (major)), 4.68 (d, $J$=6.5 Hz, 1H (minor)), 4.64 (d, $J$=6.5 Hz, 1H (major), 1H (minor)), 3.94 (d, $J$=4.5 Hz, 1H (major)), 3.91 (d, $J$=4 Hz, 1H (minor)), 3.89 (s, 3H (minor)), 3.87 (s, 3H (major)), 3.85 (s, 3H (major), 3.83 (m, 2H (major), 3H (minor)), 3.79 (dd, $J$=4, 1.5 Hz, 1H (minor)), 3.69 (d, $J$=4.5 Hz, 1H (minor)), 3.33 (s, 3H (minor)), 3.32 (s, 3H (major)), 1.17 (s, 9H (major)), 1.14 ppm (s, 9H (minor)); $^{13}$C NMR (mixture of conformers): $\delta$ = [154.8 (major), 154.1 (minor)], [151.8 (minor), 151.7 (major)], 148.3 (minor + major), [148.2 (major), 147.9 (minor)], 147.2 (major + minor), [132.5 (major), 132.2 (minor)], [131.1 (minor), 130.0 (major)], [130.2 (major), 129.6 (minor)], [125.8 (minor), 125.3 (major)], 125.2 (major + minor), [112.5 (minor), 112.1 (major)], [110.3 (major), 109.9 (minor)], [109.8 (minor), 109.6 (major)], [101.43 (minor), 101.40 (major)], [96.4 (minor), 95.9 (major)], [79.01 (minor), 78.6 (major)], [61.5 (minor), 61.4 (major)], [60.8 (minor), 60.5 (major)], [59.6 (major), 59.3 (minor)], [55.8 (major), 55.6 (minor)], 55.5 (major + minor), [53.85 (minor), 53.76 (major)], [53.5 (minor), 51.7 (major)], [39.3 (minor), 39.2 (major)], [28.3 (major), 28.0 ppm (minor)]; IR ($CH_2Cl_2$): $\tilde{\nu}$ = 3434m, 2936m, 2250m, 1703s, 1488m, 1423m, 1366m, 1282m, 1246s, 1168 cm$^{-1}$ s; MS (ESI): $m/z$: 538 (100) [$M$+Na$^+$]; HRMS: $m/z$: calcd for $C_{27}H_{33}NNaO_9$: 538.2047, found 538.2053 [$M$+Na$^+$].

**Alcohol 37**: A solution of epoxide **36** (515 mg, 1.00 mmol) in $Et_2O$ (5 mL) was added dropwise to a suspension of $LiAlH_4$ (57 mg, 1.50 mmol) in $Et_2O$ (5 mL) at 0 °C. The reaction mixture was allowed to stir at this temperature for 1 h and then at RT for 5 h. The reaction was quenched by the sequential addition of acetone (6 mL), $Et_2O$ (6 mL) and water (6 mL) at 0 °C. The organic layer was separated and the aqueous layer extracted with $Et_2O$. The combined organic layers were dried ($Na_2SO_4$) and concentrated under reduced pressure to give a pink solid. Purification by column chromatography (50% EtOAc in hexane) gave alcohol **37** (228 mg, 44%) as an off-white solid. M.p. 74–76 °C; $R_f$=0.33 (50% EtOAc in hexane); $^1$H NMR: $\delta$ = 6.92 (d, $J$=8 Hz, 1H), 6.85 (s, 1H). 6.78 (d, $J$=8.5 Hz, 1H), 6.61 (s, 1H), 5.94 (d, $J$=1.5 Hz, 1H), 5.93 (d, $J$=1.5 Hz, 1H), 5.22 (t, $J$=8.5 Hz, 1H), 5.05 (d, $J$=11 Hz, 1H), 4.89 (d, $J$=9.5 Hz, 1H), 4.75 (s, 2H), 4.54 (d, $J$=11 Hz, 1H), 4.45–4.40 (m, 1H), 4.03–3.98 (m, 1H), 3.84 (s, 3H), 3.82 (s, 3H), 3.57 (brs, 1H), 3.42 (s, 3H), 2.99 (dd, $J$=16.5, 5 Hz, 1H), 2.75 (dd, $J$=16.5, 9 Hz, 1H), 1.34 ppm (s, 9H); $^{13}$C NMR: $\delta$ = 155.8, 151.6, 148.2, 147.0, 146.8, 131.7, 120.3, 130.2, 127.3, 124.1, 112.4, 108.8, 107.1, 101.0, 96.2, 79.4, 68.1, 61.5, 60.3, 55.9, 55.7, 51.7, 43.5, 35.5, 28.3 ppm; IR ($CH_2Cl_2$): $\tilde{\nu}$ = 3421w, 2932m, 1684w, 1484m, 1366m, 1279s, 1228s, 1166s, 1088 cm$^{-1}$ s; MS (ESI): $m/z$: 540 (100) [$M$+Na$^+$]; HRMS: $m/z$: calcd for $C_{27}H_{35}NNaO_9$: 540.2204, found 540.2208 [$M$+Na$^+$].

***N*-Cbz azabicyclic alkene 38**: $Me_3SiI$ (0.93 mL, 6.51 mmol) was added dropwise to a refluxing mixture of azabicycle **13** (1.70 g, 5.92 mmol) and $NEt_3$ (0.99 mL, 7.10 mmol) in $CH_2Cl_2$ (25 mL). After 15 min, the reaction was cooled to 0 °C and anhydrous MeOH (0.31 mL, 7.70 mmol) added. After 10 min freshly distilled benzyl chloroformate (1.10 mL, 7.70 mmol) was added and the reaction was left to stir for 3 h at RT. The reaction mixture was diluted with water (50 mL) and $CH_2Cl_2$ (25 mL) and the layers separated. The aqueous layer was extracted with EtOAc (2× 50 mL), the combined organic layers were dried ($MgSO_4$) and solvent evaporated under reduced pressure to give a brown oil. Purification by column chromatography (10% EtOAc in hexane) gave azabicycle **38** (1.52 g, 80%) as a pale brown solid. M.p. 101 °C; $R_f$=0.33 (30% EtOAc in hexane); $^1$H NMR: $\delta$ = 7.35–7.24 (m, 5H), 6.98 (brs, 2H), 6.84 (brs, 2H), 5.89 (dd, $J$=16, 1.5 Hz, 2H), 5.50 (s, 2H), 5.06 ppm (s, 2H); $^{13}$C NMR: $\delta$ = 155.0, 144.4, [143.7, 142.8], 142.3, 136.2, 128.4, 128.0, 127.8, [104.7, 104.6], 101.1, 67.2, 66.4 ppm; IR ($CH_2Cl_2$): $\tilde{\nu}$ = 3053w, 2986w, 1711m, 1462m, 1265s, 1092 cm$^{-1}$ w; MS (EI) $m/z$ 321 (25) [$M^+$], 251 (12), 91 (100); HRMS: $m/z$: calcd for $C_{19}H_{15}NO_4$: 321.1001, found 321.1000 [$M^+$].

**1,2-Dihydronaphthalene 39**: Following the procedure to prepare 1,2-dihydronaphthalene **29** (except the reaction was stirred for 6 h), the addition of the azabicycle **38** (1.88 g, 5.86 mmol) and boronic acid **27** (2.25 g, 8.79 mmol) in MeOH (16 mL) followed by $Cs_2CO_3$ (1.91 g, 5.86 mmol) to [Pd(MeCN)$_2$Cl$_2$] (75 mg, 0.29 mmol) and (*S*)-tol-binap (217 mg, 0.32 mmol) in MeOH (16 mL) gave after column chromatography (10% EtOAc in hexane) dihydronaphthalene **39** (2.78 g, 89%) as a pale brown foam with an *ee* of 90% as determined by chiral HPLC analysis (Chiralpak AD, hexane/2-propanol 85:15, flow rate 1.0 mL min$^{-1}$); $t_R$ = 18.0 (minor), 59.4 min (major); recrystallization (2% $CH_2Cl_2$ in $Et_2O$) gave dihydronaphthalene **39** (2.50 g, 80%) as a white solid with an *ee* of 99% as determined by chiral HPLC analysis. M.p. 106 °C; $[\alpha]_D^{25}$ =+97 ($c$ = 1.0 in $CHCl_3$); $R_f$=0.10 (20% EtOAc in hexane); $^1$H NMR: $\delta$ = 7.33–7.24 (m, 5H), 6.84 (d, $J$=8.5 Hz, 1H), 6.76 (s, 1H), 6.69 (d, $J$=8.5 Hz, 1H), 6.62 (s, 1H), 6.48 (d, $J$=9.5 Hz, 1H), 5.96 (dd, $J$=9.5, 4.5 Hz, 1H), 5.91 (d, $J$=1.5 Hz, 1H), 5.89 (s, 1H), 5.23 (t, $J$=9 Hz, 1H), 5.03 (d, $J$= 12.5 Hz, 1H), 5.04–5.02 (m, 2H), 4.73–4.61 (m, 4H), 4.23–4.20 (m, 1H), 3.82 (s, 3H), 3.78 (s, 3H), 3.40 ppm (s, 3H); $^{13}$C NMR: $\delta$ = 155.7, 151.5, 148.0, 147.1, 146.8, 136.4, 130.8, 130.2, 129.4, 128.9, 128.9, 128.3, 127.9, 127.4, 126.9, 124.5, 112.2, 107.3, 106.9, 100.9, 95.9, 66.5, 61.3, 60.2, 55.5, 55.3, 52.6, 39.6 ppm; IR ($CH_2Cl_2$): $\tilde{\nu}$ = 3430w, 2919w, 2253m, 1711m, 1651w, 1484m, 1379w, 1277m, 1040 cm$^{-1}$ m; MS (ESI): $m/z$: 556 (52) [$M$+Na$^+$], 322 (20), 321 (100), 290 (19); HRMS: $m/z$: calcd for $C_{30}H_{31}NNaO_8$: 556.1942, found 556.1941 [$M$+Na$^+$].

**Benzyl alcohol 40**: HCl (conc., 17 mL) was added to a solution of dihydronaphthalene **39** (1.50 g, 2.81 mmol) in *i*PrOH (70 mL) and THF (70 mL) and the resulting mixture stirred at RT for 8 h. After careful quenching with sat. aq. $NaHCO_3$ (100 mL) the layers were separated. The aqueous layer was extracted with EtOAc (2×100 mL), the combined organic layers were dried ($MgSO_4$) and solvent evaporated under reduced pressure. Purification by column chromatography (20→40%

EtOAc in hexane) gave benzyl alcohol **40** (1.03 g, 75%) as a white solid. M.p. 85°C; $[\alpha]_D^{22} = +29$ ($c = 1.0$ in $CHCl_3$); $R_f = 0.30$ (50% EtOAc in hexane); $^1$H NMR: $\delta$ = 7.35–7.28 (m, 3H), 7.19–7.16 (m, 2H), 6.91 (d, $J = 8.5$ Hz, 1H), 6.79 (s, 1H), 6.73 (d, $J = 8.5$ Hz, 1H), 6.64 (s, 1H), 6.53 (dd, $J = 9.5$, 2.5 Hz, 1H), 5.95–5.91 (m, 3H), 5.20 (dd, $J = 10$, 7 Hz, 1H), 4.95–4.69 (m, 5H), 4.30–4.28 (m, 1H), 3.90 (s, 3H), 3.82 (s, 3H), 3.07 ppm (brs, 1H); $^{13}$C NMR: $\delta$ = 155.7, 151.6, 147.9, 147.3, 147.1, 136.3, 133.5, 130.4, 128.7, 128.3, 128.1, 128.0, 127.9, 127.8, 126.7, 125.1, 111.9, 108.4, 106.9, 101.1, 66.6, 61.5, 56.5, 55.7, 52.5, 40.6 ppm; IR ($CH_2Cl_2$): $\tilde{\nu}$ = 3404br, 2938w, 1700s, 1484s, 1378m, 1276s, 1243s, 1082m, 1039 cm$^{-1}$ s; MS (ESI): $m/z$: 512 (15) [$M$+Na$^+$], 321 (100), 291 (20); HRMS: $m/z$: calcd for $C_{28}H_{27}NNaO_7$: 512.1679, found 512.1677 [$M$+Na$^+$].

**Dihydronaphthalene 41**: A solution of benzyl alcohol **40** (670 mg, 1.37 mmol) and $PPh_3$ (525 mg, 2.00 mmol) in $CH_2Cl_2$ (13 mL) was cooled to 0°C. $CBr_4$ (663 mg, 2.00 mmol) was added in one portion and the resulting solution was stirred at this temperature for 1 h. The reaction mixture was then diluted with $CH_2Cl_2$ (10 mL) and washed with water (2× 20 mL). The solvent was evaporated under reduced pressure to give the crude benzyl bromide. This was dissolved in anhydrous DMF (23 mL) and cooled to 0°C. NaH (60% in mineral oil; 80 mg, 2.00 mmol) was added in one portion and the suspension stirred at 0°C for 3 h. The reaction mixture was quenched by the addition of cold water (15 mL) and the layers separated. The aqueous layer was extracted with EtOAc (2× 20 mL), the combined organic layers were dried ($MgSO_4$) and solvent evaporated under reduced pressure. Purification by column chromatography (20% EtOAc in hexane) gave dihydronaphthalene **41** (581 mg, 90%) as a white solid. M.p. 169°C; $[\alpha]_D^{25} = +119$ ($c = 1.0$ in $CHCl_3$); $R_f = 0.46$ (50% EtOAc in hexane); $^1$H NMR: $\delta$ = 7.50–7.35 (m, 5H), 6.93 (d, $J =$ 8.5 Hz, 1H), 6.72 (d, $J = 8.5$ Hz, 1H), 6.61 (s, 1H), 6.50 (s, 1H), 6.44–6.38 (m, 2H), 5.87 (s, 1H), 5.85 (s, 1H), 5.81 (brs, 1H), 5.28 (brs, 2H), 5.11 (d, $J = 18$ Hz, 1H), 4.41 (d, $J = 18$ Hz, 1H), 3.80 (s, 3H), 3.78 (s, 3H), 3.60 ppm (brs, 1H); $^{13}$C NMR: $\delta$ = 156.2, 150.4, 147.2, 146.4, 144.3, 136.5, 128.4, 128.0, 127.9, 127.9, 127.6, 127.6, 127.5, 127.3, 126.2, 121.8, 110.9, 107.5, 105.7, 100.8, 67.5, 60.0, 55.6, 52.6, 39.1, 34.3 ppm; IR ($CH_2Cl_2$): $\tilde{\nu}$ = 2985w, 1699s, 1558m, 1482m, 1418m, 1278m, 1110m, 1037 cm$^{-1}$ m; MS (EI): $m/z$: 494 (90) [$M$+Na$^+$], 363 (20), 354 (21), 322 (22), 321 (100), 290 (21); HRMS: $m/z$: calcd for $C_{28}H_{25}NNaO_6$: 494.1574, found 494.1579 [$M$+Na$^+$].

**Bromohydrin 42**: Following the procedure to prepare bromohydrins **34** and **35**, the addition of NBS (226 mg, 1.27 mmol) to a solution of dihydronaphthalene **41** (547 mg, 1.16 mmol) in THF (10.4 mL) and $H_2O$ (1.20 mL) gave after work-up and column chromatography (20% EtOAc in hexane) bromohydrin **42** (495 mg, 75%) as a pale brown solid. Mp 75°C; $[\alpha]_D^{25} = +103$ ($c = 1.0$ in $CHCl_3$); $R_f = 0.33$ (50% EtOAc in hexane); $^1$H NMR: $\delta$ = 7.41–7.30 (m, 5H), 7.24 (d, $J = 8.5$ Hz, 1H), 6.82 (d, $J = 8.5$ Hz, 1H), 6.77 (s, 1H), 6.70 (s, 1H), 6.05 (d, $J = 6.5$ Hz, 1H), 5.92 (s, 2H), 5.30–5.27 (m, 3H), 5.14 (d, $J = 18$ Hz, 1H), 4.79 (d, $J =$ 8.5 Hz, 1H), 3.92 (d, $J = 18$ Hz, 1H), 3.88–3.85 (m, 1H), 3.80 (s, 3H), 3.77 (s, 3H), 1.37 ppm (d, $J = 10.5$ Hz, 1H); $^{13}$C NMR: $\delta$ = 155.9, 150.8, 148.9, 147.6, 144.9, 136.4, 128.9, 128.5, 128.1, 128.1, 127.7, 127.6, 125.6, 124.0, 111.1, 109.5, 105.8, 101.3, 72.5, 67.7, 60.1, 55.7, 53.4, 49.8, 39.7, 38.6 ppm; IR ($CH_2Cl_2$): $\tilde{\nu}$ = 3443br, 291s, 1682s, 1606m, 1504s, 1242s, 1039 cm$^{-1}$ s; MS (ESI) $m/z$ 590 (100) [$M$+Na$^+$], 550 (45), 470 (26), 343 (20), 320 (25), 241 (35); HRMS: $m/z$: calcd for $C_{28}H_{26}{}^{79}BrNNaO_7$: 590.0784, found 590.0783 [$M$+Na$^+$].

**Epoxide 43**: Following the procedure to prepare epoxide **36**, the addition of a solution of KO*t*Bu (1M in THF; 0.87 mL, 0.87 mmol) to bromohydrin **42** (495 mg, 0.87 mmol) in THF (175 mL) gave after work-up epoxide **43** (424 mg, quant.) as a pale yellow solid. M.p. 60°C; $[\alpha]_D^{25} = +112$ ($c = 1.0$ in $CHCl_3$); $R_f = 0.38$ (50% EtOAc in hexane); $^1$H NMR: $\delta$ = 7.37–7.30 (m, 5H), 7.05 (d, $J = 8.5$ Hz, 1H), 6.89 (s, 2H), 6.84 (d, $J =$ 8.5 Hz, 1H), 5.95 (d, $J = 1.5$ Hz, 1H), 5.91 (d, $J = 1.5$ Hz, 1H), 5.77 (d, $J =$ 8 Hz, 1H), 5.20–5.16 (m, 2H), 5.15 (brs, 1H), 4.24 (d, $J = 16$ Hz, 1H), 3.84–3.68 ppm (m, 9H); $^{13}$C NMR: $\delta$ = 156.6, 150.8, 148.6, 146.9, 144.6, 136.3, 128.7, 128.7, 128.7, 128.4, 128.0, 127.9, 125.2, 124.2, 111.1, 110.0, 101.2, 67.6, 60.5, 55.7, 52.4, 51.1, 38.1, 36.8 ppm; IR ($CH_2Cl_2$): $\tilde{\nu}$ = 3441s, 1694s, 1488s, 1417m, 1236m, 1096m, 1036 cm$^{-1}$ m; MS (ESI): $m/z$: 510 (100) [$M$+Na$^+$], 488 (25); HRMS: $m/z$: calcd for $C_{28}H_{25}NNaO_7$: 510.1523, found 510.1522 [$M$+Na$^+$].

**(+)-Homochelidonine (2)**:[10c] $LiAlH_4$ (36 mg, 0.96 mmol) was added in one portion to a solution of epoxide **43** (117 mg, 0.24 mmol) in 1,4-dioxane (5 mL) at RT and stirred at this temperature for 1 h. The reaction mixture was then heated to reflux for 18 h. After cooling to 0°C the excess $LiAlH_4$ was destroyed by successive addition of acetone (1 mL), $Et_2O$ (1 mL) and $H_2O$ (10 mL). The layers were separated and the aqueous layer was extracted with EtOAc (2×20 mL); the combined organic layers were dried ($MgSO_4$) and solvent evaporated under reduced pressure. Purification by column chromatography (30% EtOAc in hexane) gave (+)-homochelidonine (**2**) (77 mg, 87%) as a white solid with an *ee* of 99% as determined by chiral HPLC analysis (Chiralcel OD, hexane/2-propanol 85:15, flow rate 1.0 mL min$^{-1}$; $t_R$ = 18.4 (minor), 26.6 min (major)); m.p. 190–193°C (lit.[10c] m.p. 187–188°C); $[\alpha] = +120$ ($c = 1.0$ in EtOH) (lit.[10c] $[\alpha]_D^{25} = +128$ ($c = 1.1$ in EtOH)); $R_f = 0.26$ (50% EtOAc in hexane); $^1$H NMR: $\delta$ = 7.75 (brs, 1H), 6.98 (d, $J = 8.5$ Hz, 1H), 6.88 (d, $J = 8.5$ Hz, 1H), 6.67 (s, 1H), 6.65 (s, 1H), 5.95 (d, $J =$ 1.5 Hz, 1H), 5.94 (d, $J = 1.5$ Hz, 1H), 4.27–4.25 (m, 1H), 4.20 (d, $J =$ 16 Hz, 1H), 3.88 (s, 3H), 3.86 (s, 3H), 3.54 (brd, $J = 2$ Hz, 1H), 3.44 (d, $J = 16$ Hz, 1H), 3.23 (dd, $J = 17.5$, 1 Hz, 1H), 3.09 (dd, $J = 17.5$, 4.5 Hz, 1H), 2.96 (t, $J = 2.5$ Hz, 1H), 2.30 ppm (s, 3H); $^{13}$C NMR: $\delta$ = 150.6, 147.9, 145.1, 144.6, 130.3, 128.7, 128.7, 125.7, 123.1, 111.9, 111.7, 109.4, 100.9, 71.9, 62.6, 60.1, 55.9, 55.1, 42.5, 41.8, 39.6 ppm; IR ($CH_2Cl_2$): $\tilde{\nu}$ = 2914s, 1486m, 1278s, 1230m, 1081m, 1041m, 937 cm$^{-1}$ m; MS (EI): $m/z$: 369 (56) [$M^+$], 351 (100), 320 (35), 336 (20), 204 (22), 192 (19); HRMS (EI): $m/z$: calcd for $C_{21}H_{23}NO_5$: 369.1576, found 369.1575 [$M^+$].

**Diol 44**: $BiCl_3$ (3 mg, 0.01 mmol) was added to a solution of epoxide **43** (60 mg, 0.12 mmol) in $H_2O$ (0.6 mL) and MeCN (0.6 mL) at 0°C. After 30 min the reaction was diluted with $H_2O$ (5 mL) and $CHCl_3$ (5 mL). The layers were separated and the aqueous layer was extracted with $CHCl_3$ (2×5 mL). The combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure to give a yellow oil. Purification by column chromatography (50% EtOAc in hexane) gave diol **44** (53 mg, 85%) as a white solid. M.p. 103–104°C; $[\alpha]_D^{26} = +125$ ($c = 1.0$ in $CHCl_3$); $R_f = 0.21$ (70% EtOAc in hexane); $^1$H NMR: $\delta$ = 7.91 (d, $J =$ 8.5 Hz, 1H), 7.40–7.30 (m, 5H), 6.86 (s, 1H), 6.72 (d, $J = 8.5$ Hz, 1H), 6.52 (s, 1H), 5.85 (d, $J = 4$ Hz, 2H), 5.64 (d, $J = 5$ Hz, 1H), 5.25 (s, 2H), 5.04 (d, $J = 18$ Hz, 1H), 4.44 (dd, $J = 7.5$, 7 Hz, 1H), 4.04 (d, $J = 9$ Hz, 1H), 3.86 (d, $J = 18$ Hz, 1H), 3.80–3.67 (m, 7H), 2.90 ppm (brs, 2H); $^{13}$C NMR: $\delta$ = 156.3, 150.7, 148.0, 147.7, 144.4, 136.6, 131.3, 128.8, 128.4, 128.1, 127.7, 126.7, 126.0, 125.3, 111.2, 107.1, 105.9, 101.4, 76.4, 70.8, 68.0, 60.2, 55.8, 53.2, 40.6, 38.7 ppm; IR ($CHCl_3$): $\tilde{\nu}$ = 3436br, 3016m, 1700m, 1683m, 1496m, 1482m, 1215m, 1040 cm$^{-1}$ m; MS (ESI): $m/z$: 528 (100) [$M$+Na$^+$], 506 (33) [M+H$^+$], 355 (38), 337 (30); HRMS: $m/z$: calcd for $C_{28}H_{28}NO_8$: 506.1809, found 506.1820 [$M$+H$^+$].

**(+)-Chelamidine (3)**:[10c] $LiAlH_4$ (17 mg, 0.44 mmol) was added in one portion to a solution of diol **44** (55 mg, 0.11 mmol) in 1,4-dioxane (1 mL) at RT. The reaction mixture was then heated to reflux for 18 h. After cooling to 0°C the excess $LiAlH_4$ was destroyed by successive addition of acetone (1 mL), $Et_2O$ (1 mL) and $H_2O$ (10 mL). The layers were separated and the aqueous layer was extracted with EtOAc (2×20 mL); the combined organic layers were dried ($MgSO_4$) and solvent evaporated under reduced pressure. Purification by column chromatography (70% EtOAc in hexane) gave (+)-chelamidine (**3**) (38 mg, 90%) as a white solid. M.p. 230–232°C (lit.[10c] m.p. 231–232°C); $[\alpha]_D^{24} = +112$ ($c = 0.65$ in EtOH) (lit.[10c] $[\alpha]_D^{24} = +120$ ($c = 0.3$ in EtOH)); $R_f = 0.15$ (70% EtOAc in hexane); $^1$H NMR: $\delta$ = 7.65 (brs, 1H), 7.03 (d, $J = 8.5$ Hz, 1H), 6.95 (s, 1H), 6.88 (d, $J = 8.5$ Hz, 1H), 6.69 (s, 1H), 5.97 (d, $J = 1.5$ Hz, 1H), 5.95 (d, $J = 1.5$ Hz, 1H), 4.81 (d, $J = 2$ Hz, 1H), 4.20 (d, $J = 16$ Hz, 1H), 4.12–4.06 (m, 1H), 3.88 (s, 3H), 3.87 (s, 3H), 3.50 (d, $J = 2$ Hz, 1H), 3.46 (d, $J = 16$ Hz, 1H), 3.26 (brs, 1H), 2.28 (s, 3H), 2.05 ppm (brs, 1H); $^{13}$C NMR: $\delta$ = 150.6, 148.4, 146.9, 144.5, 130.9, 129.5, 128.8, 127.0, 123.2, 111.8, 110.5, 110.5, 101.3, 73.0, 62.2, 60.2, 56.0, 55.0, 42.5, 42.4, 36.9 ppm; IR ($CHCl_3$): $\tilde{\nu}$ = 3421br, 3017m, 1652w, 1496w, 1487 cm$^{-1}$ m; MS (ESI): $m/z$: 386 (100) [$M$+H$^+$]; HRMS: $m/z$: calcd for $C_{21}H_{24}NO_6$: 386.1598, found 386.1598 [$M$+H$^+$].

**MOM-benzyl ether 46**: $NaBH_4$ (662 mg, 17.5 mmol) was added in one portion to aryl aldehyde **45** (4.00 g, 17.5 mmol) in MeOH (80 mL) at RT. After stirring for 1 h, the reaction was carefully diluted with $H_2O$ (100 mL) and EtOAc (200 mL). The layers were separated and the aqueous layer was extracted with EtOAc (2×200 mL); the combined organic layers were dried ($MgSO_4$) and solvent evaporated under reduced pressure to give the crude benzyl alcohol. Following the procedure to prepare benzyl ether **26**, the addition of LiBr (304 mg, 3.5 mmol) and *p*-TsOH.$H_2O$ (333 mg, 1.75 mmol) to the crude benzyl alcohol in dimethoxymethane (40 mL) gave after work-up and column chromatography (20% EtOAc in hexane) aryl bromide **46** (3.51 g, 73%) as a colorless oil which solidified on standing. M.p. 42–44 °C (lit.[34] 43–45 °C); $R_f$=0.33 (25% EtOAc in hexane); $^1$H NMR: $\delta$ = 7.05 (d, $J$=8.5 Hz, 1H), 6.65 (d, $J$=8.5 Hz, 1H), 6.01 (s, 2H), 4.72 (s, 2H), 4.67 (s, 2H), 3.43 ppm (s, 3H); $^{13}$C NMR: $\delta$ = 148.0, 146.9, 125.3, 119.0, 116.2, 109.4, 101.8, 96.1, 63.0, 55.5 ppm; IR (neat): $\tilde{\nu}$ = 2884m, 2822w, 1499m, 1458s, 1378m, 1259s, 1238s, 1149s, 1046 cm$^{-1}$ s; MS (EI): $m/z$: 276 (65) [$M^+$], 274 (66) [$M^+$], 213 (54), 215 (55), 135 (100); HRMS: $m/z$: calcd for $C_{10}H_{11}{}^{79}BrO_4$: 273.9841, found 273.9843 [$M^+$].

**Boronic acid 47**: Following the procedure to prepare boronic acid **25**, the addition of *n*BuLi (1.6 M in hexanes; 7.50 mL, 12.0 mmol) to aryl bromide **46** (3.00 g, 10.9 mmol) in THF (50 mL) followed by B(O*i*Pr)$_3$ (7.55 mL, 32.7 mmol), acidic work-up, column chromatography (50% EtOAc in hexane) and recrystallization ($H_2O$) gave boronic acid **47** (1.91 g, 73%) as a white solid. M.p. 148–150 °C; $R_f$=0.20 (50% EtOAc in hexane); $^1$H NMR: $\delta$ = 7.44 (d, $J$=8.5 Hz, 1H), 6.82 (d, $J$=8.5 Hz, 1H), 6.27 (s, 2H), 5.99 (s, 2H), 4.77 (s, 2H), 4.71 (s, 2H), 3.41 ppm (s, 3H); $^{13}$C NMR: $\delta$ = 149.0, 146.7, 130.6, 127.1, 121.1, 108.2, 100.9, 95.1, 62.1, 55.9 ppm; IR ($CH_2Cl_2$): $\tilde{\nu}$ = 3380br, 2949s, 1588m, 1451m, 1420m, 1355s, 1279 cm$^{-1}$ s; MS (EI) $m/z$ 240 (10) [$M^+$], 239 (98), 179 (86), 178 (100), 148 (36), 135 (75), 76 (48); HRMS: $m/z$: calcd for $C_{10}H_{13}BO_6$: 240.0800, found 240.0808 [$M^+$].

**1,2-Dihydronaphthalene 48**: Following the procedure to prepare 1,2-dihydronaphthalene **29** (except the reaction was stirred for 6 h), the addition of the azabicycle **38** (1.39 g, 4.33 mmol) and boronic acid **47** (1.56 g, 6.50 mmol) in MeOH (12 mL) followed by $Cs_2CO_3$ (1.41 g, 4.33 mmol) to [Pd(MeCN)$_2$Cl$_2$] (57 mg, 0.22 mmol) and (*S*)-tol-binap (161 mg, 0.24 mmol) in MeOH (12 mL) gave after column chromatography (15% EtOAc in hexane) dihydronaphthalene **48** (1.90 g, 85%) as a colorless oil (which solidified on drying under high vacuum), with an *ee* of 90% as determined by chiral HPLC analysis (Chiralpak AD, hexane/2-propanol 85:15, flow rate 1 mL min$^{-1}$; $t_R$ = 22.6 (minor), 40.2 min (major)); recrystallization (hexane) gave dihydronaphthalene **39** (1.68 g, 75%) as a white solid with an *ee* of 99% as determined by chiral HPLC analysis. M.p. 55–57 °C; $[\alpha]_D^{26}$ =+6.1 ($c$ = 1.2 in $CHCl_3$); $R_f$ = 0.35 (50% EtOAc in hexane); $^1$H NMR: $\delta$ = 7.24–7.37 (m, 5H), 6.78 (s, 1H), 6.64–6.58 (m, 3H), 6.50 (dd, $J$=9.5, 2 Hz, 1H), 5.96–5.91 (m, 5H), 5.18–5.14 (m, 1H), 5.02–4.92 (m, 3H), 4.67–4.56 (m, 4H), 4.21 (brs, 1H), 3.36 ppm (s, 3H); $^{13}$C NMR: $\delta$ = 155.6, 147.2, 147.1, 146.1, 136.4, 131.9, 129.6, 128.8, 128.5, 128.1, 127.8, 127.8, 127.8, 126.8, 122.2, 117.9, 108.2, 107.7, 107.0, 101.1, 101.1, 95.7, 66.6, 59.8, 55.5, 52.7, 40.0 ppm; IR ($CHCl_3$): $\tilde{\nu}$ = 3393m, 2891s, 1714s, 1603w, 1505s, 1380s, 1233 cm$^{-1}$ s; MS (ESI): $m/z$: 540 (100) [$M$+Na$^+$], 413 (15), 395 (15), 305 (80), 275 (20); HRMS (ESI): $m/z$: calcd for $C_{29}H_{27}NNaO_8$: 540.1628, found 540.1615 [$M$+Na$^+$].

**Benzyl alcohol 49**: Following the procedure to prepare benzyl alcohol **40**, the addition of conc. HCl (14 mL) to dihydronaphthalene **48** (1.00 g, 1.93 mmol) in *i*PrOH (50 mL) and THF (50 mL) gave after work-up and column chromatography (20% EtOAc in hexane) benzyl alcohol **49** (667 mg, 75%) as a oil which solidified as a white foam on drying under high vacuum. M.p. 80–83 °C; $[\alpha]_D^{26}$ =−69 ($c$ = 2.7 in $CHCl_3$); $R_f$=0.40 (50% EtOAc in hexane); $^1$H NMR: $\delta$ = 7.34–7.29 (m, 3H), 7.17–7.15 (m, 2H), 6.80 (s, 1H), 6.69 (d, $J$=8 Hz, 1H), 6.64–6.62 (m, 2H), 6.52 (dd, $J$=10, 3 Hz, 1H), 6.03 (d, $J$=1 Hz, 1H), 5.97 (d, $J$=1 Hz, 1H), 5.95 (s, 2H), 5.90 (dd, $J$=10, 3 Hz, 1H), 5.18 (dd, $J$=10, 6.5 Hz, 1H), 4.94–4.91 (m, 2H), 4.83–4.78 (m, 2H), 4.72 (dd, $J$=12, 4 Hz, 1H), 4.30–4.27 (m, 1H), 3.02 ppm (dd, $J$=6, 4.5 Hz, 1H); $^{13}$C NMR: $\delta$ = 155.7, 147.5, 147.2, 146.6, 146.3, 136.2, 131.6, 128.6, 128.4, 128.1, 128.0, 127.9, 127.8, 127.7, 126.6, 122.5, 121.2, 108.8, 107.8, 106.9, 101.1, 66.7, 56.2, 52.4, 40.8 ppm; IR ($CHCl_3$): $\tilde{\nu}$ = 3429br, 3018m, 1703s, 1505s, 1484s, 1455s, 1215s, 1040 cm$^{-1}$ s; MS (EI): $m/z$: 473 (3) [$M^+$], 323 (22), 322 (100), 91 (55); HRMS: $m/z$: calcd for $C_{27}H_{23}NO_7$: 473.1475, found 473.1483 [$M^+$].

**1,2-Dihydronaphthalene 50**: Following the procedure to prepare dihydronaphthalene **41**, the addition of $CBr_4$ (501 mg, 1.51 mmol) to a solution of benzyl alcohol **49** (478 mg, 1.01 mmol) and $PPh_3$ (396 mg, 1.51 mmol) in $CH_2Cl_2$ (10 mL) gave after work-up the crude benzyl bromide. The addition of NaH (60% in mineral oil; 60 mg, 1.51 mmol) to the crude benzyl bromide in DMF (17 mL) gave after work-up and column chromatography (20% EtOAc in hexane) dihydronaphthalene **50** (414 mg, 90%) as a white foam. M.p. 87–90 °C; $[\alpha]_D^{25}$ =+31 ($c$ = 1.5 in $CHCl_3$); $R_f$=0.20 (20% EtOAc in hexane); $^1$H NMR: $\delta$ = 7.52–7.28 (m, 5H), 6.70 (d, $J$=8 Hz, 1H), 6.63–6.61 (m, 2H), 6.52 (s, 1H), 6.42 (d, $J$=3.5 Hz, 1H), 6.41 (s, 1H), 5.90 (d, $J$=1.5 Hz, 1H), 5.86 (s, 1H), 5.85 (d, $J$=1.5 Hz, 2H), 5.76 (brs, 1H), 5.30 (s, 2H), 5.04 (brs, 1H), 4.43 (d, $J$=13 Hz, 1H), 3.58 ppm (brs, 1H); $^{13}$C NMR: $\delta$ = 156.1, 147.3, 146.5, 145.3, 142.8, 136.4, 128.5, 128.1, 128.0, 128.0, 127.9, 127.7, 127.5, 127.4, 119.2, 114.4, 107.6, 106.7, 105.6, 101.2, 100.9, 67.6, 53.1, 38.4, 34.7 ppm; IR ($CHCl_3$): $\tilde{\nu}$ = 2896s, 1698s, 1600m, 1455m, 1312s, 1257s, 1105s, 1050 cm$^{-1}$ m; MS (ESI): $m/z$: 478 (90) [$M$+Na$^+$], 395 (100), 305 (100), 304 (100); HRMS: $m/z$: calcd for $C_{27}H_{21}NNaO_6$: 478.1261, found 478.1271 [$M$+Na$^+$].

**Bromohydrin 51**: Following the procedure to prepare bromohydrins **34** and **35**, the addition of NBS (98 mg, 0.55 mmol) to a solution of dihydronaphthalene **50** (228 mg, 0.50 mmol) in THF (4.5 mL) and $H_2O$ (0.5 mL) gave after work-up and column chromatography (20% EtOAc in hexane) bromohydrin **51** (207 mg, 75%) as a pale brown solid. M.p. 146 °C; $[\alpha]_D^{25}$ =+73 ($c$ = 2.8 in $CHCl_3$); $R_f$=0.20 (40% EtOAc in hexane); $^1$H NMR: $\delta$ = 7.42–7.33 (m, 5H), 7.01 (d, $J$=8 Hz, 1H), 6.79 (s, 1H), 6.71 (d, $J$=8 Hz, 1H), 6.70 (s, 1H), 6.09 (d, $J$=6 Hz, 1H), 5.93 (s, 3H), 5.87 (s, 1H), 5.30 (d, $J$=12 Hz, 1H), 5.26 (d, $J$=12 Hz, 1H), 5.05 (d, $J$=17 Hz, 1H), 4.81 (d, $J$=8.5 Hz, 1H), 3.96 (d, $J$=17 Hz, 1H), 3.84 (brs, 1H), 1.73 (brs, 1H), 1.62 ppm (d, $J$=9.5 Hz, 1H); $^{13}$C NMR: $\delta$ = 155.8, 148.9, 147.6, 145.8, 143.8, 136.3, 129.0, 128.5, 128.1, 127.8, 126.2, 125.4, 121.5, 115.5, 109.6, 107.1, 105.7, 101.6, 101.3, 72.5, 67.8, 53.4, 49.9, 39.9, 37.8 ppm; IR ($CHCl_3$): $\tilde{\nu}$ = 3445br, 3013w, 2893w, 1699s, 1484m, 1261 cm$^{-1}$ m; MS (ESI): $m/z$: 574 (50) [$M$+Na$^+$], 552 (5), 536 (60), 454 (65), 304 (30), 244 (100); HRMS: $m/z$: calcd for $C_{27}H_{23}{}^{79}BrNO_7$: 552.0655, found 552.0658 [$M$+H$^+$].

**Epoxide 52**: Following the procedure to prepare epoxide **36**, the addition of a solution of KO*t*Bu (1 M in THF; 0.36 mL, 0.36 mmol) to bromohydrin **51** (200 mg, 0.36 mmol) in THF (70 mL) gave after work-up epoxide **52** (162 mg, 95%) as a pale yellow solid. M.p. 85 °C; $[\alpha]_D^{25}$ =+101 ($c$ = 1.03 in $CHCl_3$); $R_f$=0.30 (50% EtOAc in hexane); $^1$H NMR: $\delta$ = 7.33–7.29 (m, 5H), 7.08 (brs, 1H), 6.89 (s, 1H), 6.82 (d, $J$=8 Hz, 1H), 6.73 (d, $J$=8 Hz, 1H), 5.96 (d, $J$=1.5 Hz, 1H), 5.93–5.91 (m, 3H), 5.76 (d, $J$=8 Hz, 1H), 5.19 (app q, $J$=12 Hz, 2H), 4.99 (d, $J$=16 Hz, 1H), 4.32 (d, $J$=16 Hz, 1H), 3.85–3.77 ppm (m, 3H); $^{13}$C NMR: $\delta$ = 152.0, 148.7, 147.0, 145.8, 143.1, 136.4, 128.6, 128.6, 128.4, 128.3, 128.1, 128.0, 127.6, 125.2, 121.5, 117.4, 110.0, 107.1, 101.2, 67.5, 58.2, 52.5, 51.4, 37.8, 37.0 ppm; IR ($CHCl_3$): $\tilde{\nu}$ = 2897w, 1699s, 1557w, 1504m, 1464s, 1317m, 1250s, 1111m, 1040 cm$^{-1}$ s; MS (ESI): $m/z$: 472 (20) [$M$+H$^+$], 428 (50), 411 (100), 321 (95), 320 (90), 293 (40); HRMS: $m/z$: calcd for $C_{27}H_{22}NO_7$: 472.1390, found 472.1378 [$M$+H$^+$].

**Diol 53**: Following the procedure to prepare diol **44**, the addition of $BiCl_3$ (3 mg, 8 μmol) to a solution of epoxide **52** (40 mg, 0.08 mmol) in $H_2O$ (0.4 mL) and MeCN (0.4 mL) gave after work-up and column chromatography (50% EtOAc in hexane) diol **53** (36 mg, 86%) as a white solid. M.p. 120–122 °C; $[\alpha]_D^{25}$ =+93 ($c$ = 1.0 in $CHCl_3$); $R_f$=0.21 (70% EtOAc in hexane); $^1$H NMR: $\delta$ = 7.74 (d, $J$=8.5 Hz, 1H), 7.40–7.32 (m, 5H), 6.89 (s, 1H), 6.65 (d, $J$=8.5 Hz, 1H), 6.55 (s, 1H), 5.89–5.88 (m, 2H), 5.86 (d, $J$=16 Hz, 1H), 5.85 (d, $J$=16 Hz, 1H), 5.69 (brs, 1H), 5.26 (s, 2H), 4.95–4.93 (m, 1H), 4.52 (t, $J$=7.5 Hz, 1H), 4.06 (d, $J$=8 Hz, 1H), 3.87 (d, $J$=16 Hz, 1H), 3.74 (s, 1H), 3.15 (brs, 1H), 2.43 ppm (brs, 1H); $^{13}$C NMR: $\delta$ = 155.5, 147.9, 147.6, 145.3, 142.9, 136.2, 130.9, 128.6, 128.6, 128.2, 128.0, 128.0, 126.5, 122.3, 115.5, 106.9, 105.7, 101.2, 101.1, 76.4, 70.6, 67.9, 53.3, 40.7, 37.7 pppm; IR ($CHCl_3$): $\tilde{\nu}$ = 3419br, 2897w, 1684s, 1499m, 1481s, 1458m, 1321m, 1240m, 1042 cm$^{-1}$ s; MS (ESI): $m/z$:

512 (40) [$M$+Na$^+$], 509 (50) [$M^+$], 490 (38), 428 (35), 411 (90), 321 (100), 320 (95); HRMS: $m/z$: calcd for $C_{27}H_{23}NNaO_8$: 512.1321, found 512.1320 [$M$+Na$^+$].

**(+)-Chelidonine (4)**:[14d] Following the procedure to prepare (+)-homochelidonine (**2**), the addition of $LiAlH_4$ (9 mg, 0.24 mmol) to epoxide **52** (30 mg, 0.06 mmol) in 1,4-dioxane (1.5 mL) gave after work-up and column chromatography (50% EtOAc in hexane) (+)-chelidonine (**4**) (18 mg, 88%) as a white solid. M.p. 212–213 °C (lit.[14a] m.p. 217–218 °C); $[\alpha]_D^{25}$ = +109 ($c$ = 0.9 in EtOH); $R_f$ = 0.20 (70% EtOAc in hexane); $^1$H NMR: $\delta$ = 7.62 (brs, 1H), 6.77 (d, $J$ = 8 Hz, 1H), 6.75 (d, $J$ = 8 Hz, 1H), 6.67 (s, 1H), 6.65 (s, 1H), 5.98 (d, $J$ = 1.5 Hz, 1H), 5.97 (d, $J$ = 1.5 Hz, 1H), 5.94 (d, $J$ = 2.5 Hz, 1H), 5.93 (d, $J$ = 2.5 Hz, 1H), 4.25–4.23 (m, 1H), 4.09 (d, $J$ = 15 Hz, 1H), 3.59–3.57 (m, 1H), 3.43 (d, $J$ = 15 Hz, 1H), 3.23 (dd, $J$ = 17.5, 1.5 Hz, 1H), 3.10 (dd, J = 17.5, 4.5 Hz, 1H), 2.99 (t, $J$ = 2.5 Hz, 1H), 2.28 ppm (s, 3H); $^{13}$C NMR: $\delta$ = 148.0, 145.5, 145.2, 142.9, 131.2, 128.7, 125.5, 120.4, 117.0, 111.9, 109.5, 107.4, 101.2, 101.0, 72.3, 62.8, 53.9, 42.4, 42.0, 39.6 ppm; IR ($CHCl_3$): $\tilde{\nu}$ = 3430br, 2878m, 2770m, 1494m, 1460s, 1372s, 1305 cm$^{-1}$ s, 1245; MS (ESI): $m/z$: 354 (100) [$M$+H$^+$]; HRMS: $m/z$: calcd for $C_{20}H_{20}NO_5$: 354.1335, found 354.1348 [$M$+H$^+$].

**(+)-Chelamine (5)**:[10c] Following the procedure to prepare (+)-chelamidine (**3**), the addition of $LiAlH_4$ (9 mg, 0.24 mmol) to diol **53** (30 mg, 0.06 mmol) in 1,4-dioxane (0.6 mL) gave after work-up and column chromatography (60% EtOAc in hexane) (+)-chelamine (**5**) (21 mg, 93%) as a white solid. M.p. 195 °C (lit.[10c] m.p. 201–202 °C); $[\alpha]_D^{25}$ = +102 ($c$ = 0.8 in EtOH) (lit.[10c] $[\alpha]_D^{21}$ = +111 ($c$ = 0.3 in EtOH)); $R_f$ = 0.20 (70% EtOAc in hexane); $^1$H NMR: $\delta$ = 7.59 (brs, 1H), 6.96 (s, 1H), 6.81 (d, $J$ = 8 Hz, 1H), 6.77 (d, $J$ = 8 Hz, 1H), 6.70 (s, 1H), 6.00 (d, $J$ = 1.5 Hz, 1H), 5.99 (d, $J$ = 1.5 Hz, 1H), 5.98 (d, $J$ = 1.5 Hz, 1H), 5.94 (d, $J$ = 1.5 Hz, 1H), 4.83 (s, 1H), 4.09 (d, $J$ = 15.5 Hz, 1H), 4.07 (s, 1H), 3.55 (d, $J$ = 3 Hz, 1H), 3.48 (d, $J$ = 15.5 Hz, 1H), 3.30 (t, $J$ = 2.5 Hz, 1H), 2.27 (s, 3H), 1.88 ppm (brs, 1H); $^{13}$C NMR: $\delta$ = 148.5, 147.0, 145.5, 142.9, 130.9, 130.5, 126.9, 120.5, 117.0, 111.7, 110.5, 107.6, 101.4, 101.3, 77.8, 73.0, 62.4, 53.8, 42.4, 37.1 ppm; IR ($CHCl_3$): $\tilde{\nu}$ = 3387br, 3017m, 2915w, 1502m, 1487m, 1465m, 1263m, 1215 cm$^{-1}$ s; MS (ESI): $m/z$: 370 (100) [$M$+H$^+$]; HRMS: $m/z$: calcd for $C_{20}H_{20}NO_6$: 370.1285, found 370.1298 [$M$+H$^+$].

**(+)-Norchelidonine (6)**:[14d] Epoxide **52** (30 mg, 0.06 mmol) and 10% Pd/C (6 mg, 6 μmol) were stirred in EtOH (0.6 mL) under an $H_2$ atmosphere (balloon) for 2 h. The reaction mixture was filtered through a pad of celite and the solvent evaporated under reduced pressure to give a yellow solid. Purification by column chromatography (25% hexane in EtOAc) gave (+)-norchelidonine (**6**) (16 mg, 75%) as a white solid. M.p. 197 °C (lit.[10d] m.p. 198–199 °C); $[\alpha]_D^{24}$ = +103 ($c$ = 0.8 in EtOH) (lit.[10d] $[\alpha]_D^{22}$ = +112 ($c$ = 0.4 in EtOH)); $R_f$ = 0.20 (100% EtOAc); $^1$H NMR: $\delta$ = 6.81 (d, $J$ = 8 Hz, 1H), 6.78 (d, $J$ = 8 Hz, 1H), 6.72 (s, 1H), 6.68 (s, 1H), 6.00 (d, $J$ = 1.5 Hz, 1H), 5.95–5.94 (m, 3H), 4.34–4.31 (m, 1H), 4.20 (d, $J$ = 15 Hz, 1H), 4.10 (d, $J$ = 15 Hz, 1H), 4.00 (d, $J$ = 3.5 Hz, 1H), 3.16 (dd, $J$ = 17, 2.5 Hz, 1H), 3.07 (dd, $J$ = 17, 3.5 Hz, 1H), 2.94 ppm (t, $J$ = 2.5 Hz, 1H) (OH and NH signals not visible); $^{13}$C NMR: $\delta$ = 147.7, 146.5, 145.4, 143.4, 130.7, 128.9, 127.4, 121.3, 117.3, 109.8, 108.4, 107.5, 101.2, 101.0, 72.3, 55.9, 43.8, 40.2, 39.1 ppm; IR ($CHCl_3$): $\tilde{\nu}$ = 3321br, 2891m, 1501m, 1483s, 1457m, 1354m, 1262s, 1231s, 1075 cm$^{-1}$ m; MS (ESI): $m/z$: 340 (100) [$M$+H$^+$]; HRMS: $m/z$: calcd for $C_{19}H_{18}NO_5$: 340.1179, found 340.1179 [$M$+H$^+$].

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