

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 for-

mation 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, (+)-chelamine, 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 interac-

tion 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 antiserotonergic 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]

[a] Dr. M. J. Fleming, Dr. H. A. McManus, A. Rudolph, W. H. Chan, J. Ruiz, Dr. C. Dockendorff, Prof. M. Lautens
Department of Chemistry
Davenport Chemical Laboratories, University of Toronto
80 St. George St., Toronto, ON M5S 3H6 (Canada)
Fax: (+1) 416-946-8185
E-mail: mlautens@chem.utoronto.ca

Supporting information for this article is available on the WWW under <http://www.chemeurj.org/> or from the author.

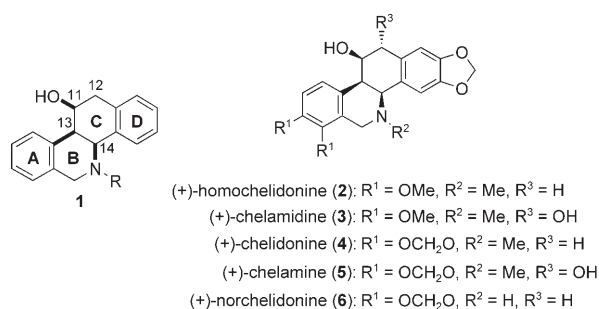
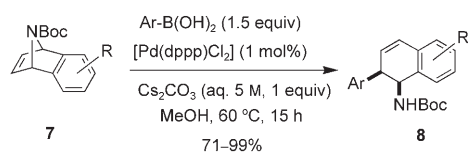


Figure 1. Structures of some B/C hexahydrobenzo[*c*]phenanthridine alkaloids.

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.

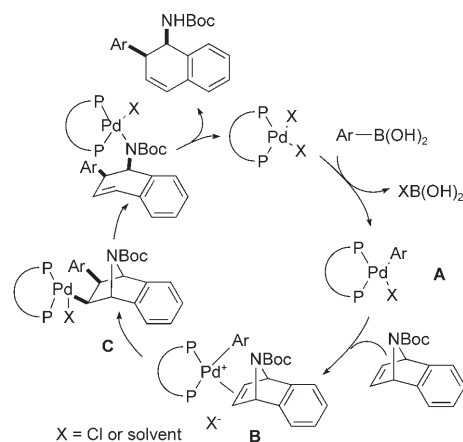
Racemic synthesis of *cis*-1-amino-2-aryldihydronaphthalenes: We have previously reported the transition metal-catalyzed ring-opening of strained *N*-Boc azabicyclic alkenes **7** by the addition of aryl boronic acids.^[16a] Using the optimized reaction conditions [[Pd(dppp)Cl₂] (1 mol %), aq. Cs₂CO₃ (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 reac-



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

tion 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-azabenzonorbomadiene with PhB(OH)₂ within 24 h. These reactions also proceeded in the absence of base but reaction times were longer.

The proposed catalytic cycle begins with the transmetalation 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 com-

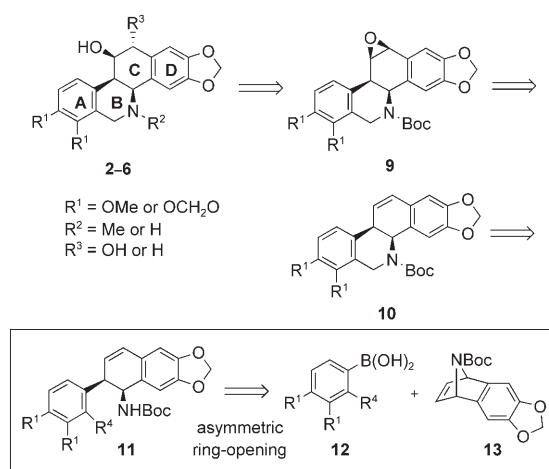


Scheme 2. Proposed catalytic cycle for Pd^{II}-catalyzed ring-opening of azabicyclic alkenes with aryl boronic acids.

plex **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.

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 (R⁴) 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

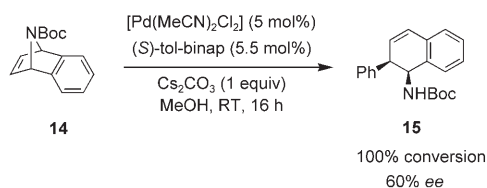


Scheme 3. Retrosynthetic analysis for B/C hexahydrobenzo[*c*]phenanthridine alkaloids.

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^[16c] **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

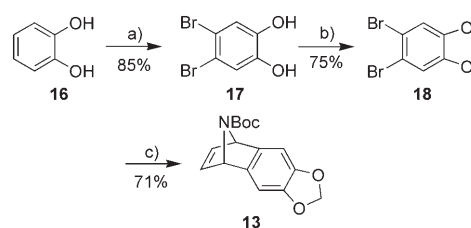


Scheme 4. Asymmetric ring-opening of azabicyclic alkene **14** with PhB(OH)₂. binap = 2,2'-bis(diphenylphosphanyl)-1,1'-binaphthyl.

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.

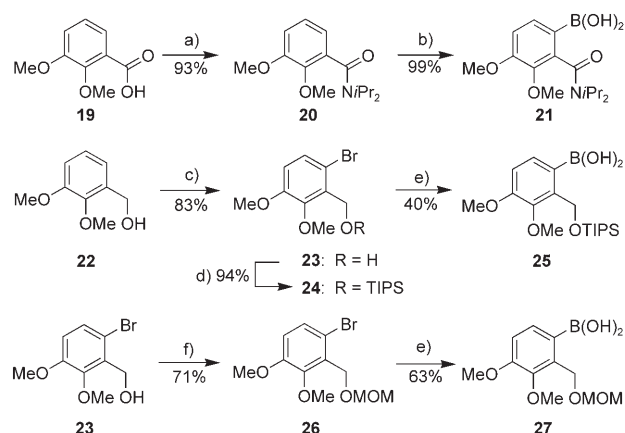
Finding a suitable boronic acid: Though we observed moderate stereoinduction using the unsubstituted azabicyclic **14** and PhB(OH)₂, we decided to test the real system with a nucleophile bearing an *ortho* group, since subtle steric and electronic effects often influence *ee*. Our attention turned towards azabicyclic **13**, which could be used to prepare the five B/C hexahydrobenzo[*c*]phenanthridine alkaloids **2–6**. Azabicyclic **13** was readily prepared in three steps from catechol **16** (Scheme 5). Treatment of **16** with Br₂ gave dibromide **17** in 85% yield,^[19] which was subsequently dialkylated with ClCH₂Br 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 azabicyclic **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 azabicyclic **13** a) Br₂, CHCl₃, RT, 20 h; b) ClCH₂Br, Cs₂CO₃, 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-dime-



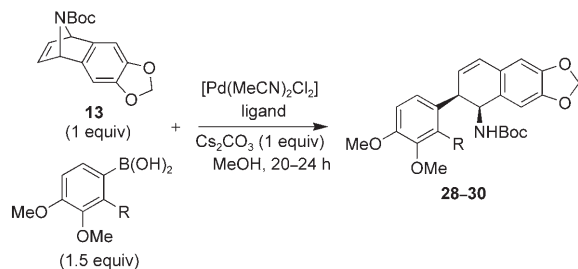
Scheme 6. Synthesis of boronic acids **21**, **25** and **27**: a) (COCl)₂, CH₂Cl₂, cat. DMF, RT, 2 h, then *i*Pr₂NH, Et₃N, THF, 17 h; b) *s*BuLi, TMEDA, THF, –78°C, 1 h then B(OMe)₃, –78°C to RT, 18 h then NH₄Cl (aq); c) NBS, THF, RT, 30 min; d) TIPSCl, imidazole, DMF, RT, 17 h; e) *n*BuLi, THF, –78°C, 35 min, then B(O*i*Pr)₃, –78°C to RT, 18 h, then NH₄Cl (aq); f) CH₂(OMe)₂, LiBr, *p*-TsOH, RT, 24 h. THF = tetrahydrofuran, TMEDA = tetramethylethylenediamine, NBS = *N*-bromosuccinimide, TIPS = triisopropylsilyl, Ts = toluenesulfonyl, MOM = methoxymethyl.

thoxybenzoic acid **19** by conversion to the corresponding acid chloride with oxalyl chloride. Directly treating the crude product with *i*Pr₂NH 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(O*i*Pr)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

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(O*i*Pr)₃ and acidic hydrolysis in 63% yield.^[22]

With the required azabicyclic **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 azabicyclic **13** using the racemic conditions and then the previously optimized enantioselective conditions (Table 1). In each case an excess (1.5 equiv)

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



Entry	Boronic acid	R	Ligand	Product	Yield [%] ^[c]	<i>ee</i> [%] ^[d]
1 ^[a]	21	C(O)NiPr ₂	dppp	28	81 ^[e]	–
2 ^[b]	21	C(O)NiPr ₂	(<i>S</i>)-tol-binap	28	43 ^[e]	88
3 ^[a]	25	CH ₂ OTIPS	dppp	29	55	–
4 ^[b]	25	CH ₂ OTIPS	(<i>S</i>)-tol-binap	29	29	42
5 ^[a]	27	CH ₂ OMOM	dppp	30	82	–
6 ^[b]	27	CH ₂ OMOM	(<i>S</i>)-tol-binap	30	90	91

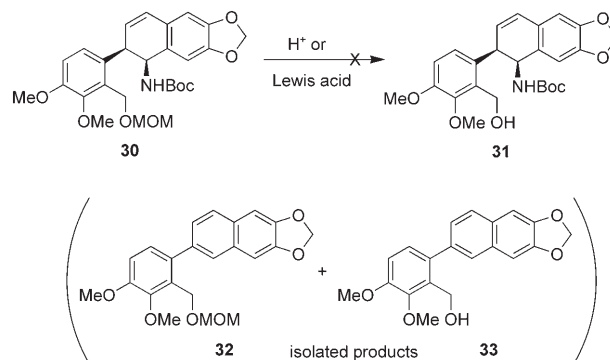
[a] 1 mol% [Pd(MeCN)₂Cl₂], 1 mol% ligand, reaction carried out at 60°C. [b] 5 mol% [Pd(MeCN)₂Cl₂], 5.5 mol% ligand, reaction carried out at RT. [c] Isolated yield unless otherwise stated. [d] Determined by chiral HPLC. [e] ¹H NMR yield using mesitylene as internal standard.

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.

Attempted selective deprotection of the MOM group: With high enantioselectivity and reactivity for the Pd^{II}-catalyzed ring-opening reaction between azabicyclic **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 Bu₄NBr in CH₂Cl₂^[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 (LiBF₄,^[26] *B*-bromocatecholborane,^[27] CBr₄/*i*PrOH,^[28] PPTS/*t*BuOH,^[29] 20% aq. AcOH^[30] and *p*-TsOH/MeOH^[31]).

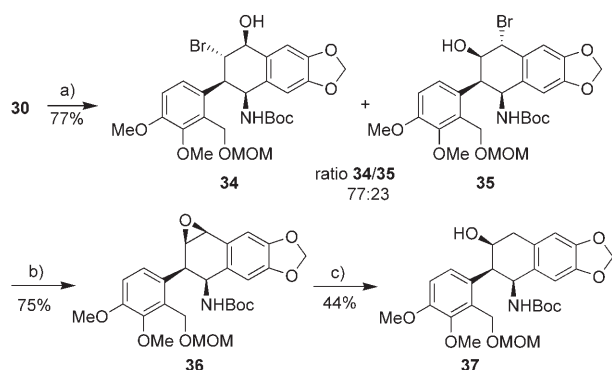


Scheme 7. Attempted selective removal of the MOM group.

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/H₂O 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 LiAlH₄ in Et₂O resulted in selective hydride attack at the benzylic position providing alcohol **37** in 44% yield. The *syn*-relationship between the three contiguous



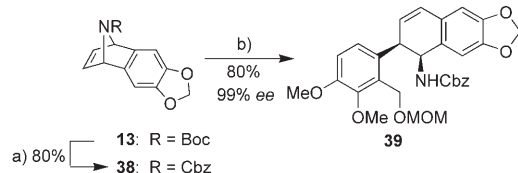
Scheme 8. Installation of the *syn*-hydroxy group: a) NBS, H₂O, THF, RT, 90 min; b) KO^tBu, THF, -78 °C, 30 min; c) LiAlH₄, Et₂O, RT, 6 h.

stereogenic centers was confirmed by a 2D ¹H 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**).

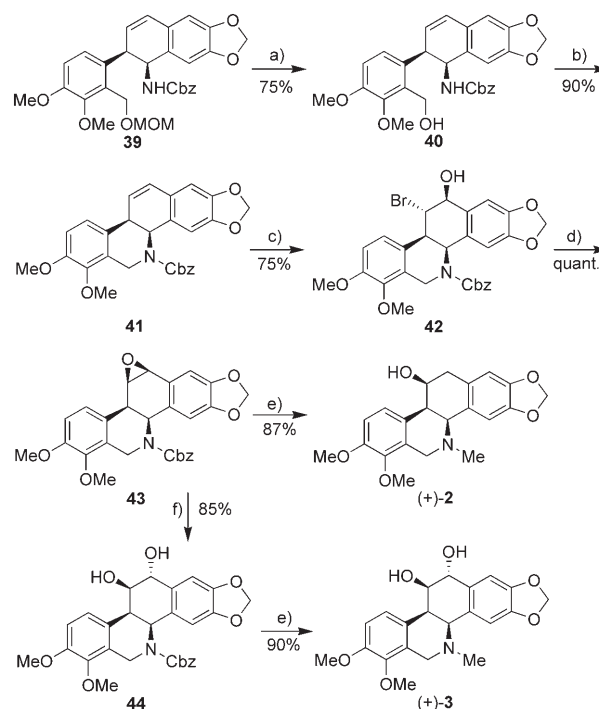
N-Boc azabicyclic **13** was converted to *N*-Cbz azabicyclic alkene **38** in 80% yield, in a one pot reaction, using first TMSI for Boc removal^[32] then carbamate protection of the resulting secondary amine by addition of CbzCl (Scheme 9). It was necessary to interconvert protecting groups as the 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, NEt₃, CH₂Cl₂, reflux, 15 min, then CbzCl, RT, 3 h; b) [Pd(MeCN)₂Cl₂] (5 mol %), (*S*)-tol-binap (5.5 mol %), **27**, Cs₂CO₃, 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 Et₂O 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



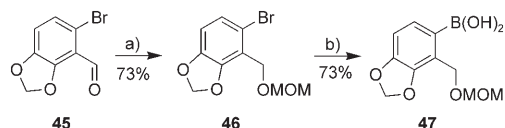
Scheme 10. Completion of the synthesis of (+)-homochelidonine (**2**) and (+)-chelamidine (**3**): a) HCl, *i*PrOH/THF, RT, 8 h; b) CBr₄, PPh₃, CH₂Cl₂, 0 °C, 1 h, then NaH, DMF, 0 °C, 3 h; c) NBS, H₂O, THF, RT, 90 min; d) KO^tBu, THF, -78 °C, 30 min; e) LiAlH₄, 1,4-dioxane, reflux, 18 h; f) H₂O, cat. BiCl₃, MeCN, 0 °C, 30 min.

Mitsunobu conditions^[33] but it was possible to convert the benzyl alcohol group to a benzyl bromide with CBr₄ and PPh₃ 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 H₂O/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^tBu 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 ($[\alpha]_{\text{D}}^{25} = +120$ ($c = 1.0$ 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]

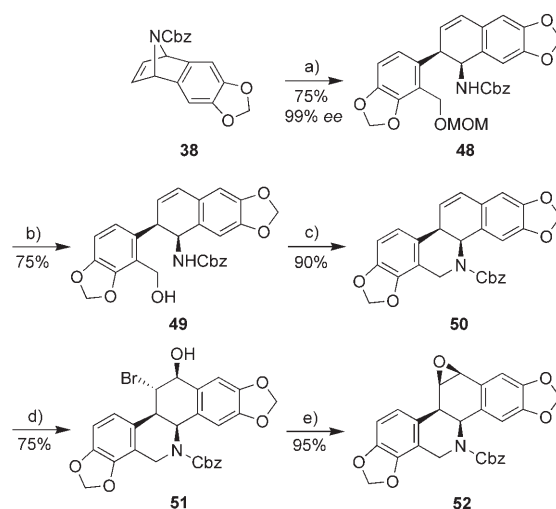
Syntheses of (+)-chelidonine, (+)-chelamine and (+)-norchelidonine: We now had a straightforward strategy to complete the synthesis of the other 3 *B/C* hexahydrobenzo[*c*]-phenanthridine alkaloids using boronic acid **47**. Three steps were required from commercially available aldehyde **45** (Scheme 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 $\text{B}(\text{O}i\text{Pr})_3$, followed by acidic hydrolysis.^[35]



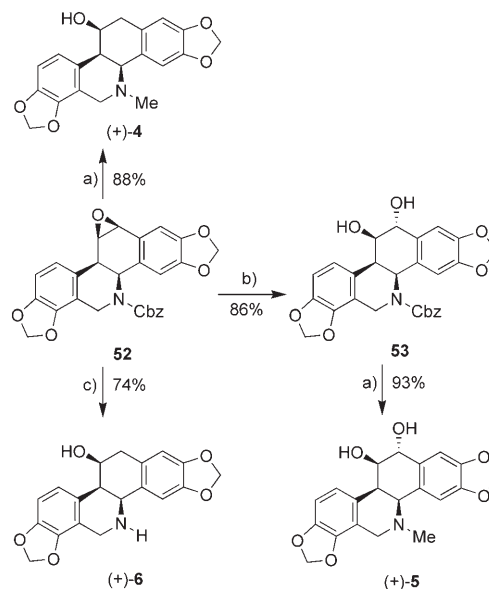
Scheme 11. Synthesis of boronic acid **47**: a) NaBH_4 , MeOH, RT, 1 h then $\text{CH}_2(\text{OMe})_2$, LiBr , *p*-TsOH, RT, 15 h; b) *n*BuLi, THF, -78°C 45 min, then $\text{B}(\text{O}i\text{Pr})_3$, -78°C to RT, 18 h, then NH_4Cl (aq).

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 $\text{S}_{\text{N}}2$ 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%



Scheme 12. Synthesis of key epoxide intermediate **52**: a) $\text{Pd}(\text{MeCN})_2\text{Cl}_2$ (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) $\text{KO}t\text{Bu}$, 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.

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]

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 N₂ from Na/benzophenone immediately prior to use. Triethylamine was purified by distillation under N₂ from NaOH immediately prior to use. Diethyl ether and dichloromethane were purified by the method of Pangborn et al.^[56] All other solvents were used as received. *N*-Bromosuccinimide was recrystallized from H₂O prior to use. Analytical thin-layer chromatography: Performed with Silicycle normal phase glass plates (0.25 mm, 60 Å 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: $[\alpha]_D^{25}$ ($c = \text{g } 100 \text{ mL}^{-1}$, solvent). IR Spectroscopy: IR spectra were obtained using a Perkin-Elmer Spectrum 1000 FT-IR spectrometer as neat films or as solutions (CHCl₃ or CH₂Cl₂) 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 ¹³C NMR spectra were recorded at 23 °C in CDCl₃ 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 (δ scale) downfield from tetramethylsilane and are referenced to residual proton in the NMR solvent (CHCl₃; δ 7.26). Chemical shifts for carbon resonances are reported in parts per million (δ scale) downfield from tetramethylsilane and are referenced to the carbon resonances of the solvent (CDCl₃; δ 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 Br₂ (13.9 mL, 272 mmol) in CHCl₃ (20 mL) was added dropwise over 1 h to a suspension of catechol **16** (15.0 g, 136 mmol) in CHCl₃ (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: δ = 7.14 (s, 2H), 5.29 ppm (s, 2H); ¹³C NMR: δ =

143.5, 119.9, 114.9 ppm; IR (CH₂Cl₂): $\tilde{\nu}$ = 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 C₆H₄⁷⁹Br₂O₂: 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 Cs₂CO₃ (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 (Na₂SO₄) 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: δ = 7.07 (s, 2H), 6.00 (s, 2H); ¹³C NMR: δ = 147.9, 115.4, 113.2, 102.3; IR (CH₂Cl₂): $\tilde{\nu}$ = 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 C₇H₄⁷⁹Br₂O₂: 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 (MgSO₄) and the solvent removed under reduced pressure to give a brown oil. Purification by column chromatography (10% EtOAc in hexane) gave azabicyclic **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: δ = 6.97 (brs, 2H), 6.84 (s, 2H), 5.91 (d, *J* = 1.5 Hz, 1H), 5.87 (d, *J* = 1.5 Hz, 1H), 5.40 (brs, 2H), 1.38 ppm (s, 9H); ¹³C NMR: δ = 154.8, 144.3, 142.5, [104.7, 104.2], 101.4, 80.6, [66.9, 66.3], 28.1 ppm; IR (CH₂Cl₂): $\tilde{\nu}$ = 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 C₁₆H₁₇NO₄: 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 CH₂Cl₂ (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 NEt₃ (3.82 mL, 27.4 mmol) and *i*Pr₂NH (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 (Et₂O/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: δ = 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); ¹³C NMR: δ = 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 (CH₂Cl₂): $\tilde{\nu}$ = 3651m, 2964m, 1626s, 1439m, 1341 cm⁻¹ s; MS (ESI): *m/z*: 266 (100) [*M*+H⁺], 165 (50); HRMS: *m/z*: calcd for C₁₅H₂₄NO₃: 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 CH₂Cl₂ (3 × 40 mL). The combined organic layers were dried (MgSO₄) and solvent removed under reduced pressure to leave a yellow solid. Recrystallization (MeOH/H₂O) 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: δ =

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): $\tilde{\nu} = 3386\text{s}, 3162\text{s}, 2978\text{s}, 1610\text{s}, 1443\text{m}, 1357\text{m}, 1298\text{m}, 1266\text{cm}^{-1}$ m, MS (ESI): m/z : 310 (55) [$M+\text{H}^+$], 292 (100); HRMS: m/z : calcd for $\text{C}_{15}\text{H}_{25}\text{BNO}_5$: 310.1820, found 310.1829 [$M+\text{H}^+$].

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. 2M 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); ^1H 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): $\tilde{\nu} = 3426\text{w}, 2938\text{m}, 1576\text{s}, 1474\text{m}, 1413\text{s}, 1271\text{s}, 1229\text{m}, 1171\text{m}, 1079\text{m}, 1009\text{cm}^{-1}$ m; MS (ESI): m/z : 269 (100) [$M+\text{Na}^+$], 127 (35), 79 (40); HRMS: m/z : calcd for $\text{C}_9\text{H}_{11}\text{BrNaO}_3$: 268.9789, found 268.9780 [$M+\text{Na}^+$].

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. 1M 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); ^1H 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): $\tilde{\nu} = 2941\text{s}, 2864\text{s}, 1577\text{w}, 1474\text{s}, 1414\text{m}, 1278\text{s}, 1232\text{s}, 1060\text{cm}^{-1}$ s; MS (ESI): m/z : 425 (50) [$M+\text{Na}^+$], 231 (30), 216 (95), 214 (100); HRMS: m/z : calcd for $\text{C}_{18}\text{H}_{31}^{79}\text{BrNaO}_3\text{Si}$: 425.1118, found 425.1117 [$M+\text{Na}^+$].

Boronic acid 25: Aryl bromide **24** (750 mg, 1.86 mmol) was dissolved in THF (5 mL) and cooled to -78°C . $n\text{BuLi}$ (1.6M 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. $\text{B}(\text{O}i\text{Pr})_3$ (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); ^1H 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): $\tilde{\nu} = 3375\text{w}, 2948\text{s}, 1580\text{m}, 1458\text{m}, 1261\text{s}, 1144\text{m}, 1095\text{cm}^{-1}$ m, MS (ESI): m/z : 391 (22) [$M+\text{Na}^+$], 195 (50), 180 (100), 165 (48); HRMS: m/z : calcd for $\text{C}_{18}\text{H}_{33}\text{BNaO}_5\text{Si}$: 391.2082, found 391.2084 [$M+\text{Na}^+$].

MOM-protected benzyl alcohol 26: LiBr (695 mg, 8.09 mmol) and $p\text{-TsOH}\cdot\text{H}_2\text{O}$ (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); ^1H 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): $\tilde{\nu} = 2940\text{w}, 1577\text{w}, 1475\text{m}, 1418\text{m}, 1378\text{m}, 1276\text{s}, 1232\text{m}, 1150\text{m}, 1101\text{m}, 1041\text{cm}^{-1}$ m; MS (ESI): m/z : 313 (100) [$M+\text{Na}^+$], 244 (25), 64 (20); HRMS: m/z : calcd for $\text{C}_{11}\text{H}_{15}\text{BrNaO}_4$: 313.0051, found 313.0048 [$M+\text{Na}^+$].

Boronic acid 27: Following the procedure to prepare boronic acid **25**, the addition of $n\text{BuLi}$ (1.6M 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 $\text{B}(\text{O}i\text{Pr})_3$ (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); ^1H 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): $\tilde{\nu} = 3380\text{w}, 2949\text{s}, 1589\text{m}, 1452\text{m}, 1419\text{m}, 1355\text{m}, 1279\text{s}, 1154\text{m}, 1098\text{m}, 1072\text{cm}^{-1}$ m; MS (ESI): m/z : 279 (100) [$M+\text{Na}^+$]; HRMS: m/z : calcd for $\text{C}_{11}\text{H}_{17}\text{BNaO}_6$: 279.1010, found 279.1007 [$M+\text{Na}^+$].

1,2-Dihydronaphthalene 29 (Table 1, entry 4 conditions): [$\text{Pd}(\text{MeCN})_2\text{Cl}_2$] (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 azabicyclo **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); ^1H 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): $\tilde{\nu} = 3432\text{w}, 2941\text{s}, 2892\text{s}, 2866\text{s}, 1714\text{s}, 1485\text{s}, 1366\text{m}, 1276\text{m}, 1166\text{m}, 1044\text{cm}^{-1}$ m; MS (ESI): m/z : 634 (45) [$M+\text{Na}^+$], 321 (100); HRMS: m/z : calcd for $\text{C}_{34}\text{H}_{49}\text{NO}_7\text{NaSi}$: 634.3170, found 634.3162 [$M+\text{Na}^+$].

1,2-Dihydronaphthalene 30 (Table 1, entry 6 conditions): Following the procedure to prepare 1,2-dihydronaphthalene **29**, the addition of the azabicyclo **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 [$\text{Pd}(\text{MeCN})_2\text{Cl}_2$] (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); ^1H 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): $\tilde{\nu} = 3407\text{w}, 2923\text{s}, 1700\text{s}, 1507\text{s}, 1482\text{s}, 1364\text{m}, 1279\text{s}, 1244\text{m}, 1165\text{m}, 1037\text{cm}^{-1}$ m; MS (ESI): m/z : 522 (100) [$M+\text{Na}^+$]; HRMS (ESI): m/z : calcd for $\text{C}_{27}\text{H}_{33}\text{NNaO}_8$: 522.2098, found 522.2116 [$M+\text{Na}^+$].

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 (MgSO₄) 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; ¹H NMR: δ = 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); ¹³C NMR: δ 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 (CH₂Cl₂): ν̄ = 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 C₂₇H₃₄BrNNaO₉: 618.1309, found 618.1314 [M+Na⁺]; ¹H NMR (regioisomer mixture **34/35** 2:1): δ = 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^tBu (1M 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 (Na₂SO₄) 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); ¹H NMR (4:1 mixture of rotamers): δ = 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)); ¹³C NMR (mixture of conformers): δ = [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 (CH₂Cl₂): ν̄ = 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 C₂₇H₃₃NNaO₉: 538.2047, found 538.2053 [M+Na⁺].

Alcohol 37: A solution of epoxide **36** (515 mg, 1.00 mmol) in Et₂O (5 mL) was added dropwise to a suspension of LiAlH₄ (57 mg, 1.50 mmol) in Et₂O (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), Et₂O (6 mL) and water (6 mL) at 0°C. The organic layer was separated and the aqueous layer extracted with Et₂O. The combined organic layers were dried (Na₂SO₄) 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); ¹H NMR: δ = 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); ¹³C NMR: δ = 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 (CH₂Cl₂): ν̄ = 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 C₂₇H₃₅NNaO₉: 540.2204, found 540.2208 [M+Na⁺].

N-Cbz azabicyclic alkene 38: Me₃SiI (0.93 mL, 6.51 mmol) was added dropwise to a refluxing mixture of azabicyclic **13** (1.70 g, 5.92 mmol) and NEt₃ (0.99 mL, 7.10 mmol) in CH₂Cl₂ (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 CH₂Cl₂ (25 mL) and the layers separated. The aqueous layer was extracted with EtOAc (2×50 mL), the combined organic layers were dried (MgSO₄) and solvent evaporated under reduced pressure to give a brown oil. Purification by column chromatography (10% EtOAc in hexane) gave azabicyclic **38** (1.52 g, 80%) as a pale brown solid. M.p. 101°C; *R*_f=0.33 (30% EtOAc in hexane); ¹H NMR: δ = 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); ¹³C NMR: δ = 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 (CH₂Cl₂): ν̄ = 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 C₁₉H₁₅NO₄: 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 azabicyclic **38** (1.88 g, 5.86 mmol) and boronic acid **27** (2.25 g, 8.79 mmol) in MeOH (16 mL) followed by Cs₂CO₃ (1.91 g, 5.86 mmol) to [Pd(MeCN)₂Cl₂] (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% CH₂Cl₂ in Et₂O) 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; [α]_D²⁵ = +97 (c = 1.0 in CHCl₃); *R*_f=0.10 (20% EtOAc in hexane); ¹H NMR: δ = 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); ¹³C NMR: δ = 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 (CH₂Cl₂): ν̄ = 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 C₃₀H₃₁NNaO₈: 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. NaHCO₃ (100 mL) the layers were separated. The aqueous layer was extracted with EtOAc (2×100 mL), the combined organic layers were dried (MgSO₄) 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; $[\alpha]_D^{25} = +29$ ($c = 1.0$ in CHCl_3); $R_f = 0.30$ (50% EtOAc in hexane); $^1\text{H NMR}$: $\delta = 7.35\text{--}7.28$ (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); $^{13}\text{C NMR}$: $\delta = 155.7, 151.6, 147.9, 147.3, 147.1, 136.3, 133.5, 130.4, 128.7, 128.3, 128.1, 128.0, 127.9, 127.8, 126.7, 125.1, 111.9, 108.4, 106.9, 101.1, 66.6, 61.5, 56.5, 55.7, 52.5, 40.6$ ppm; IR (CH_2Cl_2): $\tilde{\nu} = 3404\text{br}, 2938\text{w}, 1700\text{s}, 1484\text{s}, 1378\text{m}, 1276\text{s}, 1243\text{s}, 1082\text{m}, 1039\text{cm}^{-1}$ s; MS (ESI): m/z : 512 (15) $[\text{M}+\text{Na}^+]$, 321 (100), 291 (20); HRMS: m/z : calcd for $\text{C}_{28}\text{H}_{27}\text{NNaO}_7$: 512.1679, found 512.1677 $[\text{M}+\text{Na}^+]$.

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); $^1\text{H NMR}$: $\delta = 7.50\text{--}7.35$ (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); $^{13}\text{C NMR}$: $\delta = 156.2, 150.4, 147.2, 146.4, 144.3, 136.5, 128.4, 128.0, 127.9, 127.9, 127.6, 127.6, 127.5, 127.3, 126.2, 121.8, 110.9, 107.5, 105.7, 100.8, 67.5, 60.0, 55.6, 52.6, 39.1, 34.3$ ppm; IR (CH_2Cl_2): $\tilde{\nu} = 2985\text{w}, 1699\text{s}, 1558\text{m}, 1482\text{m}, 1418\text{m}, 1278\text{m}, 1110\text{m}, 1037\text{cm}^{-1}$ m; MS (EI): m/z : 494 (90) $[\text{M}+\text{Na}^+]$, 363 (20), 354 (21), 322 (22), 321 (100), 290 (21); HRMS: m/z : calcd for $\text{C}_{28}\text{H}_{25}\text{NNaO}_6$: 494.1574, found 494.1579 $[\text{M}+\text{Na}^+]$.

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. M.p. 75 °C; $[\alpha]_D^{25} = +103$ ($c = 1.0$ in CHCl_3); $R_f = 0.33$ (50% EtOAc in hexane); $^1\text{H NMR}$: $\delta = 7.41\text{--}7.30$ (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); $^{13}\text{C NMR}$: $\delta = 155.9, 150.8, 148.9, 147.6, 144.9, 136.4, 128.9, 128.5, 128.1, 128.1, 127.7, 127.6, 125.6, 124.0, 111.1, 109.5, 105.8, 101.3, 72.5, 67.7, 60.1, 55.7, 53.4, 49.8, 39.7, 38.6$ ppm; IR (CH_2Cl_2): $\tilde{\nu} = 3443\text{br}, 291\text{s}, 1682\text{s}, 1606\text{m}, 1504\text{s}, 1242\text{s}, 1039\text{cm}^{-1}$ s; MS (ESI) m/z : 590 (100) $[\text{M}+\text{Na}^+]$, 550 (45), 470 (26), 343 (20), 320 (25), 241 (35); HRMS: m/z : calcd for $\text{C}_{28}\text{H}_{26}\text{BrNNaO}_7$: 590.0784, found 590.0783 $[\text{M}+\text{Na}^+]$.

Epoxide 43: Following the procedure to prepare epoxide **36**, the addition of a solution of KOtBu (1 M 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); $^1\text{H NMR}$: $\delta = 7.37\text{--}7.30$ (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); $^{13}\text{C NMR}$: $\delta = 156.6, 150.8, 148.6, 146.9, 144.6, 136.3, 128.7, 128.7, 128.7, 128.4, 128.0, 127.9, 125.2, 124.2, 111.1, 110.0, 101.2, 67.6, 60.5, 55.7, 52.4, 51.1, 38.1, 36.8$ ppm; IR (CH_2Cl_2): $\tilde{\nu} = 3441\text{s}, 1694\text{s}, 1488\text{s}, 1417\text{m}, 1236\text{m}, 1096\text{m}, 1036\text{cm}^{-1}$ m; MS (ESI): m/z : 510

(100) $[\text{M}+\text{Na}^+]$, 488 (25); HRMS: m/z : calcd for $\text{C}_{28}\text{H}_{25}\text{NNaO}_7$: 510.1523, found 510.1522 $[\text{M}+\text{Na}^+]$.

(+)-Homochelidonine (2): $[\text{LiAlH}_4$ (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); $[\alpha]_D^{25} = +120$ ($c = 1.0$ in EtOH) (lit. $^{[10c]}$ $[\alpha]_D^{25} = +128$ ($c = 1.1$ in EtOH)); $R_f = 0.26$ (50% EtOAc in hexane); $^1\text{H NMR}$: $\delta = 7.75$ (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); $^{13}\text{C NMR}$: $\delta = 150.6, 147.9, 145.1, 144.6, 130.3, 128.7, 128.7, 125.7, 123.1, 111.9, 111.7, 109.4, 100.9, 71.9, 62.6, 60.1, 55.9, 55.1, 42.5, 41.8, 39.6$ ppm; IR (CH_2Cl_2): $\tilde{\nu} = 2914\text{s}, 1486\text{m}, 1278\text{s}, 1230\text{m}, 1081\text{m}, 1041\text{m}, 937\text{cm}^{-1}$ m; MS (EI): m/z : 369 (56) $[\text{M}^+]$, 351 (100), 320 (35), 336 (20), 204 (22), 192 (19); HRMS (EI): m/z : calcd for $\text{C}_{21}\text{H}_{23}\text{NO}_5$: 369.1576, found 369.1575 $[\text{M}^+]$.

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; $[\alpha]_D^{25} = +125$ ($c = 1.0$ in CHCl_3); $R_f = 0.21$ (70% EtOAc in hexane); $^1\text{H NMR}$: $\delta = 7.91$ (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); $^{13}\text{C NMR}$: $\delta = 156.3, 150.7, 148.0, 147.7, 144.4, 136.6, 131.3, 128.8, 128.4, 128.1, 127.7, 126.7, 126.0, 125.3, 111.2, 107.1, 105.9, 101.4, 76.4, 70.8, 68.0, 60.2, 55.8, 53.2, 40.6, 38.7$ ppm; IR (CHCl_3): $\tilde{\nu} = 3436\text{br}, 3016\text{m}, 1700\text{m}, 1683\text{m}, 1496\text{m}, 1482\text{m}, 1215\text{m}, 1040\text{cm}^{-1}$ m; MS (ESI): m/z : 528 (100) $[\text{M}+\text{Na}^+]$, 506 (33) $[\text{M}+\text{H}^+]$, 355 (38), 337 (30); HRMS: m/z : calcd for $\text{C}_{28}\text{H}_{28}\text{NO}_5$: 506.1809, found 506.1820 $[\text{M}+\text{H}^+]$.

(+)-Chelamidine (3): $[\text{LiAlH}_4$ (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); $[\alpha]_D^{25} = +112$ ($c = 0.65$ in EtOH) (lit. $^{[10c]}$ $[\alpha]_D^{25} = +120$ ($c = 0.3$ in EtOH)); $R_f = 0.15$ (70% EtOAc in hexane); $^1\text{H NMR}$: $\delta = 7.65$ (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); $^{13}\text{C NMR}$: $\delta = 150.6, 148.4, 146.9, 144.5, 130.9, 129.5, 128.8, 127.0, 123.2, 111.8, 110.5, 110.5, 101.3, 73.0, 62.2, 60.2, 56.0, 55.0, 42.5, 42.4, 36.9$ ppm; IR (CHCl_3): $\tilde{\nu} = 3421\text{br}, 3017\text{m}, 1652\text{w}, 1496\text{w}, 1487\text{cm}^{-1}$ m; MS (ESI): m/z : 386 (100) $[\text{M}+\text{H}^+]$; HRMS: m/z : calcd for $\text{C}_{21}\text{H}_{24}\text{NO}_6$: 386.1598, found 386.1598 $[\text{M}+\text{H}^+]$.

MOM-benzyl ether 46: NaBH₄ (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 H₂O (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 (MgSO₄) 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·H₂O (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); ¹H NMR: δ = 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); ¹³C NMR: δ = 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 C₁₀H₁₁⁷⁹BrO₄: 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 (H₂O) 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); ¹H NMR: δ = 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); ¹³C NMR: δ = 149.0, 146.7, 130.6, 127.1, 121.1, 108.2, 100.9, 95.1, 62.1, 55.9 ppm; IR (CH₂Cl₂): $\tilde{\nu}$ = 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 C₁₀H₁₃BO₆: 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 azabicyclic **38** (1.39 g, 4.33 mmol) and boronic acid **47** (1.56 g, 6.50 mmol) in MeOH (12 mL) followed by Cs₂CO₃ (1.41 g, 4.33 mmol) to [Pd(MeCN)₂Cl₂] (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; [α]_D²⁵ = +6.1 (*c* = 1.2 in CHCl₃); *R*_f = 0.35 (50% EtOAc in hexane); ¹H NMR: δ = 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); ¹³C NMR: δ = 155.6, 147.2, 147.1, 146.1, 136.4, 131.9, 129.6, 128.8, 128.5, 128.1, 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 (CHCl₃): $\tilde{\nu}$ = 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 C₂₀H₂₇NNaO₆: 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; [α]_D²⁵ = -69 (*c* = 2.7 in CHCl₃); *R*_f = 0.40 (50% EtOAc in hexane); ¹H NMR: δ = 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); ¹³C NMR: δ = 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 (CHCl₃): $\tilde{\nu}$ = 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 C₂₇H₂₃NO₇: 473.1475, found 473.1483 [M⁺].

1,2-Dihydronaphthalene 50: Following the procedure to prepare dihydronaphthalene **41**, the addition of CBr₄ (501 mg, 1.51 mmol) to a solution of benzyl alcohol **49** (478 mg, 1.01 mmol) and PPh₃ (396 mg, 1.51 mmol) in CH₂Cl₂ (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; [α]_D²⁵ = +31 (*c* = 1.5 in CHCl₃); *R*_f = 0.20 (20% EtOAc in hexane); ¹H NMR: δ = 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); ¹³C NMR: δ = 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 (CHCl₃): $\tilde{\nu}$ = 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 C₂₇H₂₁NNaO₆: 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 H₂O (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; [α]_D²⁵ = +73 (*c* = 2.8 in CHCl₃); *R*_f = 0.20 (40% EtOAc in hexane); ¹H NMR: δ = 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); ¹³C NMR: δ = 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 (CHCl₃): $\tilde{\nu}$ = 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 C₂₇H₂₃⁷⁹BrNO₇: 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; [α]_D²⁵ = +101 (*c* = 1.03 in CHCl₃); *R*_f = 0.30 (50% EtOAc in hexane); ¹H NMR: δ = 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); ¹³C NMR: δ = 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 (CHCl₃): $\tilde{\nu}$ = 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 C₂₇H₂₂NO₇: 472.1390, found 472.1378 [M+H⁺].

Diol 53: Following the procedure to prepare diol **44**, the addition of BiCl₃ (3 mg, 8 μmol) to a solution of epoxide **52** (40 mg, 0.08 mmol) in H₂O (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; [α]_D²⁵ = +93 (*c* = 1.0 in CHCl₃); *R*_f = 0.21 (70% EtOAc in hexane); ¹H NMR: δ = 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); ¹³C NMR: δ = 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 ppm; IR (CHCl₃): $\tilde{\nu}$ = 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); 1H 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 (CHCl₃): $\tilde{\nu} = 3430$ br, 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 (+)-chelamine (**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] $[\alpha]_D^{25} = +111$ ($c = 0.3$ in EtOH)); $R_f = 0.20$ (70% EtOAc in hexane); 1H 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 (CHCl₃): $\tilde{\nu} = 3387$ br, 3017m, 2915w, 1502m, 1487m, 1465m, 1263m, 1215 cm⁻¹ s; MS (ESI): m/z : 370 (100) $[M+H^+]$; HRMS: m/z : calcd for $C_{20}H_{20}NO_5$: 370.1285, found 370.1298 $[M+H^+]$.

(+)-Norchelidonine (6):^[14d] Epoxide **52** (30 mg, 0.06 mmol) and 10% Pd/C (6 mg, 6 μ mol) were stirred in EtOH (0.6 mL) under an H₂ 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); 1H 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: $\delta = 147.7, 145.5, 145.4, 143.4, 130.7, 128.9, 127.4, 121.3, 117.3, 109.8, 108.4, 107.5, 101.2, 101.0, 72.3, 55.9, 43.8, 40.2, 39.1$ ppm; IR (CHCl₃): $\tilde{\nu} = 3321$ br, 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 $[M+H^+]$.

Acknowledgement

We thank the NSERC, Merck Frosst Canada, and the University of Toronto for support of our programs.

- [1] a) M. Shamma, *The Isoquinoline Alkaloids*, Academic Press, New York, **1972**, p. 315; b) M. Shamma, J. L. Moniot, *The Isoquinoline Alkaloids Research, 1972–1977*, Plenum Press, New York, **1978**, p. 271; c) V. Simanek in *The Alkaloids, Vol. 26* (Ed.: A. Brossi), Aca-

demic Press, New York, **1983**, p. 185; d) T. Ishikawa, H. Ishii, *Heterocycles* **1999**, *50*, 627.

- [2] a) F. von Bruchhausen, H. W. Bersch, *Chem. Ber.* **1930**, *63*, 2520; b) E. Späth, F. Kuffner, *Chem. Ber.* **1931**, *64*, 370; c) H. W. Bersch, *Arch. Pharm.* **1958**, *291*, 491; d) E. Seoane, *An. R. Soc. Esp. Fis. Quim. Ser. B* **1965**, *61*, 755; e) C.-Y. Chen, D. B. MacLean, *Can. J. Chem.* **1967**, *45*, 3001; f) S. Naruto, S. Arakawa, H. Kaneko, *Tetrahedron Lett.* **1968**, *9*, 1705; g) P. Krajewski, L. Kozerski, G. Grykiewicz, E. Bednarek, J. Sitowski, *Magn. Reson. Chem.* **2000**, *38*, 757.
- [3] J. M. Probst, *Ann. Pharm.* **1839**, *29*, 113.
- [4] a) J. Wolff, L. Knipling, *Biochemistry* **1993**, *32*, 13334; b) A. Panzer, A. M. Joubert, P. C. Bianchi, E. Hamel, J. C. Seegers, *Eur. J. Cell Biol.* **2001**, *80*, 111.
- [5] J. W. Nowicky, G. Manolakis, D. Meijer, V. Vatanasapt, W. J. Brzosko, *Drugs Exp. Clin. Res.* **1992**, *1*.
- [6] G. Gryniewicz, E. Chojecka-Koryn, M. Gadzikowska, A. Chodkowska, E. Jagiello-Wójtowicz, *Eur. J. Med. Chem.* **2001**, *36*, 951.
- [7] a) J. Slavik, L. Slaviková, *Collect. Czech. Chem. Commun.* **1957**, *22*, 279; b) J. Slavik, L. Slaviková, *Collect. Czech. Chem. Commun.* **1959**, *24*, 3141.
- [8] a) J. Slavik, L. Slaviková, J. Brabenek, *Collect. Czech. Chem. Commun.* **1965**, *30*, 3697; b) L. Slaviková, *Collect. Czech. Chem. Commun.* **1968**, *33*, 635.
- [9] N. Takao, N. Bessho, M. Kamigauchi, K. Iwasa, K. Tomita, T. Fujiwara, S. Fujii, *Tetrahedron Lett.* **1979**, *20*, 495.
- [10] a) R. H. F. Manske, *Can. J. Res.* **1943**, *21b*, 140; b) N. Takao, M. Kamiguchi, K. Iwasa, N. Morita, *Arch. Pharm.* **1984**, *317*, 223; c) J. Slavik, E. Taborska, H. Bochorakova, *Collect. Czech. Chem. Commun.* **1994**, *59*, 429; d) M. Neèas, J. Dostál, I. Kejnovská, M. Vorlířková, J. Slavík, *J. Mol. Struct.* **2005**, *734*, 1.
- [11] J. Slavik, L. Slaviková, *Collect. Czech. Chem. Commun.* **1977**, *42*, 2686.
- [12] J. Slavik, *Collect. Czech. Chem. Commun.* **1959**, *24*, 3601.
- [13] a) I. Ninomiya, O. Yamamoto, T. Naito, *Heterocycles* **1977**, *7*, 137; b) I. Ninomiya, O. Yamamoto, T. Naito, *J. Chem. Soc. Perkin Trans. I* **1983**, 2171; c) M. Hanaoka, S. Yoshida, C. Mukai, *Tetrahedron Lett.* **1985**, *26*, 5163; d) M. Yoshida, T. Watanabe, T. Ishikawa, *Tetrahedron Lett.* **2002**, *43*, 6751.
- [14] a) W. Oppolzer, K. Keller, *J. Am. Chem. Soc.* **1971**, *93*, 3836; b) M. Cushman, T.-C. Choong, J. T. Valko, M. P. Kolek, *Tetrahedron Lett.* **1980**, *21*, 3845; c) M. Cushman, T.-C. Choong, J. T. Valko, M. P. Kolek, *J. Org. Chem.* **1980**, *45*, 5067; d) W. Oppolzer, C. Robbiani, *Helv. Chim. Acta* **1983**, *66*, 1119; e) M. Hanaoka, S. Yoshida, M. Annen, C. Mukai, *Chem. Lett.* **1986**, 739.
- [15] a) J. L. Vicario, D. Badia, E. Dominguez, A. Crespo, L. Carrillo, *Tetrahedron: Asymmetry* **1999**, *10*, 1947; b) J. L. Vicario, D. Badia, E. Dominguez, L. Carrillo, *Tetrahedron: Asymmetry* **2000**, *11*, 1227.
- [16] a) M. Lautens, C. Dockendorff, *Org. Lett.* **2003**, *5*, 3695; for examples of ring-opening reactions from our group prior to 2003, see: b) M. Lautens, K. Fagnou, S. Hiebert, *Acc. Chem. Res.* **2003**, *36*, 48; for ring-opening reactions after 2003, see: c) M. Lautens, S. Hiebert, *J. Am. Chem. Soc.* **2004**, *126*, 1437; d) P. Leong, M. Lautens, *J. Org. Chem.* **2004**, *69*, 2194; e) Y.-h. Cho, V. Zunic, H. Senboku, M. Olsen, M. Lautens, *J. Am. Chem. Soc.* **2006**, *128*, 6837; f) Y.-h. Cho, A. Fayol, M. Lautens, *Tetrahedron: Asymmetry* **2006**, *17*, 416; for arylative ring-openings of azabicyclic alkenes reported by others, see: g) D. K. Rayabarapu, C.-H. Cheng, *Acc. Chem. Res.* **2007**, *40*, 971; h) R. G. Arrayás, S. Cabrera, J. C. Carretero, *Synthesis* **2006**, 1205.
- [17] H. A. McManus, M. J. Fleming, M. Lautens, *Angew. Chem.* **2007**, *119*, 437; *Angew. Chem. Int. Ed.* **2007**, *46*, 433.
- [18] A. Rudolph, M. Lautens, unpublished results.
- [19] C. F. van Nostrum, S. J. Picken, A.-J. Schouten, R. J. M. Nolte, *J. Am. Chem. Soc.* **1995**, *117*, 9957.
- [20] B. I. Alo, A. Kandil, P. A. Patil, M. J. Sharp, M. A. Siddiqui, V. Snieckus, P. D. Josephy, *J. Org. Chem.* **1991**, *56*, 3763.
- [21] J.-L. Gras, Y.-Y. K. W. Chang, A. Guerin, *Synthesis* **1985**, 74.
- [22] A. M. Qandil, D. Ghosh, D. E. Nichols, *J. Org. Chem.* **1999**, *64*, 1407.
- [23] See Supporting Information.

- [24] C. Hermann, G. C. G. Pais, A. Geyer, S. M. Kühnert, M. E. Maier, *Tetrahedron* **2000**, *56*, 8461.
- [25] D. L. Boger, S. R. Brunette, R. M. Garbaccio, *J. Org. Chem.* **2001**, *66*, 5163.
- [26] R. E. Ireland, M. D. Varney, *J. Org. Chem.* **1986**, *51*, 635.
- [27] B. Cao, H. Park, M. M. Joullié, *J. Am. Chem. Soc.* **2002**, *124*, 520.
- [28] A. S.-Y. Lee, Y.-J. Hu, S.-F. Chu, *Tetrahedron* **2001**, *57*, 2121.
- [29] H. Monti, G. Léandri, M. Klos-Ringuet, C. Corriol, *Synth. Commun.* **1983**, *13*, 1021.
- [30] K.-F. Chan, Y. Zhao, L. M. C. Chow, T. H. Chan, *Tetrahedron* **2005**, *61*, 4149.
- [31] N. Kumagai, S. Matsunaga, T. Kinoshita, S. Harada, S. Okeda, S. Sakamoto, K. Yamaguchi, M. Shibasaki, *J. Am. Chem. Soc.* **2003**, *123*, 2169.
- [32] R. S. Lott, V. S. Chauhan, C. H. Stammer, *J. Chem. Soc. Chem. Commun.* **1979**, 495.
- [33] D. L. Hughes, *Org. React.* **1992**, *42*, 335.
- [34] I. Mohammadpoor-Baltork, S. Tangestaninejad, H. Aliyan, V. Mirkhani, *Synth. Commun.* **2000**, *30*, 2365.
- [35] A. Morin Deveau, T. L. Macdonald, *Tetrahedron Lett.* **2004**, *45*, 803.
- [36] A. B. Pangborn, M. A. Giardello, R. H. Grubbs, R. K. Rosen, F. J. Timmers, *Organometallics* **1996**, *15*, 1518.
- [37] T. J. Brenstrum, M. A. Brimble, R. J. Stevenson, *Tetrahedron* **1994**, *50*, 4897.

Received: November 11, 2007
Published online: January 17, 2008