ChemPubSoc Europe

DOI: 10.1002/ejoc.201501435

EurJOC European Journal of Organic Chemistry

Full Paper

Asymmetric Synthesis

# A Modular Approach to the Asymmetric Synthesis of Cytisine

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*Dedicated to the memory of Dr. Uwe Kayser (1940–2013)*

**Abstract:** The asymmetric synthesis of (+)- and (–)-cytisine starts with Matteson homologations for the construction of a chiral C3-building block. Conversion of the C3-building block into a dihydropyridone is achieved by straightforward functional group interconversions and ring closing metathesis. After bromination, this central building block was diastereospecifically converted into cytisine in five steps.

## Introduction

Cytisine (**1**) is a member of the lupin alkaloid family, which can be isolated from parts (preferably the seeds) of the common laburnum tree.[1] Although it was first isolated in 1862,[2] the structure of this bispidine derivative eluded chemists for 70 years.[3] After the discovery of its remarkable pharmacological profile as a selective, but partial agonist at the $\alpha4\beta2$ subtype nicotinic acetylcholine receptor,[4] interest in direct chemical modification of the natural product[5] as well as its (diversity orientated) synthesis[6] has strongly increased. Furthermore, cytisine (**1**) has served as a lead structure in the development of Pfizer's smoking cessation agent varenicline (**2**) (Figure 1).[7]

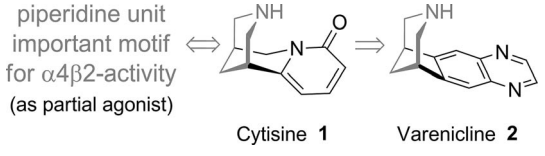
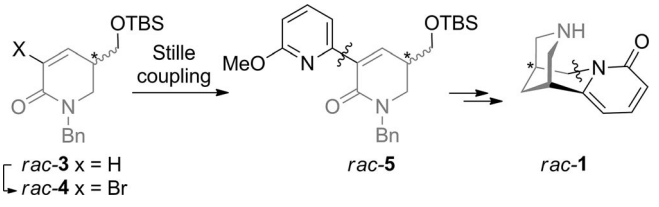



Figure 1. Structure of lupin alkaloid cytisine **1**, and smoking cessation agent Varenicline **2**.

Recent investigations into the mechanistic details of the activity profile for **1** have employed (i) the synthesis and subsequent testing of artificial ligands,[4a,5a–5j,6c–6f] (ii) *in silico* experiments,[8] as well as (iii) co-crystallization and X-ray analysis using suitable models for nicotinic acetylcholine receptors like the *Aplysia californica* acetylcholine-binding protein (AChBP).[9] These results indicate that the C-ring piperidine moiety of the partial agonist is a highly conserved region, whereas the pyridone moiety is amenable to some degree of structural variation.[10]

Stead and O'Brien concluded their 2007 review[6a] on syntheses of cytisine by highlighting two remaining challenges: (i) the need for a synthesis "*that delivers a late stage intermediate that is equipped with appropriate functionality for analogue preparation,*" and (ii) "*an efficient asymmetric synthesis of cytisine*".

Against this background, a modular synthesis has been published by Gallagher in 2011;[6b] this work specifically addresses the need for derivatives with a core-modified pyridone motif. The Gallagher approach (Scheme 1) relies on a common dihydropyridone precursor (*rac*-**3**) and its conversion to bromide *rac*-**4**. Subsequent bromide coupling with appropriate heteroaryl-stannanes provides access to compounds of type *rac*-**5**. Depending on the heteroaryl units used, these intermediates were easily converted into *rac*-cytisine or related derivatives in high yields.




Scheme 1. Key steps of the 2011 Gallagher cytisine synthesis.[6b]

Although the Gallagher synthesis provides access to core-modified derivatives in the variable pyridone region, their work does not address the 2nd challenge outlined by Stead and O'Brien.[6a] We now report a synthetic strategy to cytisine that succeeds in combining (and enhancing) the modular nature of Gallagher's approach and also provides asymmetric access to both enantiomers.[11]

## Results and Discussion

Although the endgame of Gallagher's synthesis is high yielding in its final steps, it relies on a moderately effective selenoxide elimination (50 % yield) to produce *rac*-**3** from the corresponding saturated lactam and subsequent bromine addition/elimi-

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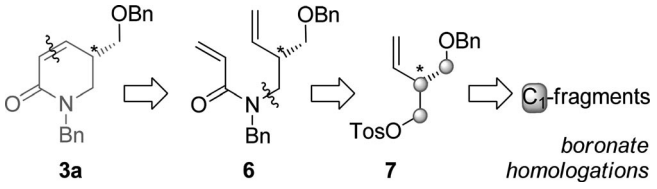
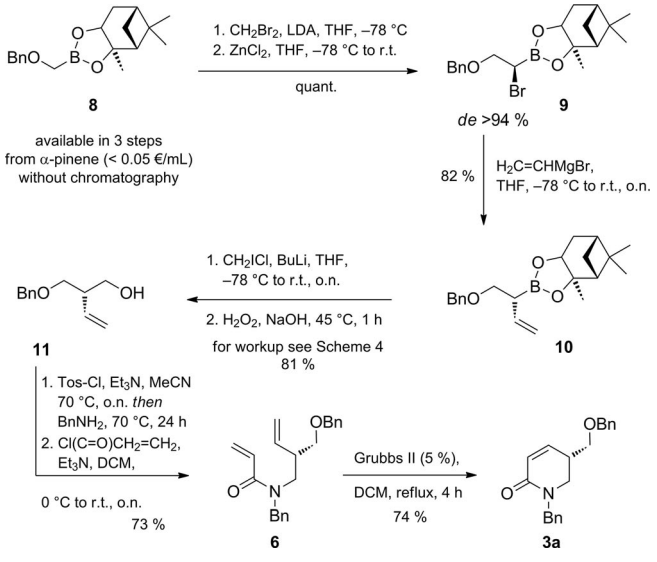
nation to produce *rac*-**4** (63 % yield). In addition, cleavage of the OTBS-ether was observed regularly in the latter reaction. Thus, channeling a precious, enantiomerically pure substrate through this bottleneck is unattractive.[12] We reasoned that avoiding the SeO-elimination altogether and using a more stable protecting group might improve yields. Consequently, our retrosynthetic analysis starts with benzyl ether **3a** as outlined in Scheme 2. First, clear cut disconnections are used to open the ring (RCM from **6**) and to then reduce the size of the molecule ($S_N2$ next to N), leading to precursor **7**. Although this asymmetrically protected diol is still relatively complex,[13] it is easily attained from $C_1$-fragments using Matteson homologations.[14]



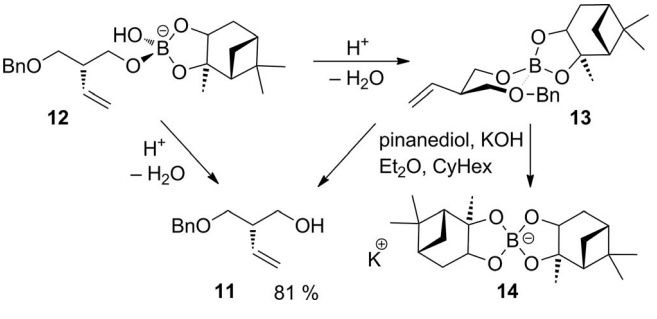

Scheme 2. Retrosynthetic analysis of dihydropyridone **3a**.

Thus, the synthesis of **3a**, as shown in Scheme 3, commenced with $C_1$-building block **8**,[15] which was easily prepared from the corresponding pinacol-boronate and (–)-pinanediol (see Supporting Information) with no need for chromatography. Pinanediol was made from α-pinene, both enantiomers of which are cheaply available in enantiomerically enriched form. The *ee* of **8** was determined by HPLC as 77 %, corresponding well to the optical purity of commercially available (–)-α-pinene (determined to be 79 %). If higher *ee* values are desired, enantiomerically pure or nearly pure pinanediol is commercially available or can be obtained by recrystallization from heptane.[16]




Scheme 3. Synthesis of pivotal precursor **3a**.

Addition of LDA to a solution of **8** and $CH_2Br_2$ at –78 °C generates the carbenoid $LiCHBr_2$ which forms an ate complex with **8**. Following the addition of $ZnCl_2$ and warming up to room temperature this ate complex undergoes a 1,2-rearrangement to deliver α-bromoboronate **9** in quantitative yield. Interestingly, the manner of $ZnCl_2$ addition was found to be crucial. When a commercially available solution of $ZnCl_2$ (1 M in $Et_2O$) was added 0.5–1 h after the addition of LDA, as described recently for similar systems,[17] the *de* did not exceed 80 %. Only by strictly following the procedure originally published by Matteson for this substrate,[15] was the reported diastereoselectivity (*de* > 94 %) achieved. This approach required removal of the volatile constituents at <0 °C following formation of the ate complex and before addition of $ZnCl_2$ solution at –78 °C.[18] This consideration needs to be especially highlighted since the diastereomers are not distinguishable in the $^1H$ NMR (300 MHz) of **9**, but can be identified by $^{13}C$ NMR when an appropriate signal to noise ratio is achievable.[19] The subsequent substitution with vinylmagnesium bromide yielded $C_2$-building block **10** in 82 % yield over both steps. Initially, yields for this reaction varied between 67 % and 88 %, and, in those cases where lower yields were obtained, pinanediol vinylboronate was identified as the major byproduct (up to 25 %). Two relevant factors for this variation became apparent: (i) the age/quality of the vinylmagnesium bromide solution, and (ii) the ability to maintain strict control over the reaction temperature. Temperature control was achieved by transferring the reaction mixture to a freezer (–20 °C) following addition of the Grignard reagent at –78 °C instead of simply allowing the cooling bath to warm up to room temperature overnight. In employing this method yields > 80 % can be achieved reproducibly. The *de* for this reaction was checked at a later stage (vide infra). For the preparation of **11**, reaction of allylboronate **10** with a suitable carbenoid ($LiCH_2X$) and subsequent oxidation was necessary. Initially, this was considered a rather critical step since allylboronates are known to rearrange at elevated temperatures,[20] and the only report of an attempt to react a moderately complex allylboronate derivative under similar conditions was unsuccessful.[21] Indeed, this reaction was initially quite capricious, often yielding < 50 % of **11** after chromatography, although it did appear to be relatively pure on the basis of TLC and $^1H$ NMR of the crude. A possible explanation for this observation is shown in Scheme 4. We considered that, upon hydrolysis, oxidation product **12** may very well form **11** as well as some stable borate esters[22] such as **13**, which would be stabilized by intramolecular interactions. To break down these side products we stirred the crude product in $Et_2O$/CyHex with pinanediol (same enantiomer) and aq. KOH (5 M) in order to form the more stable

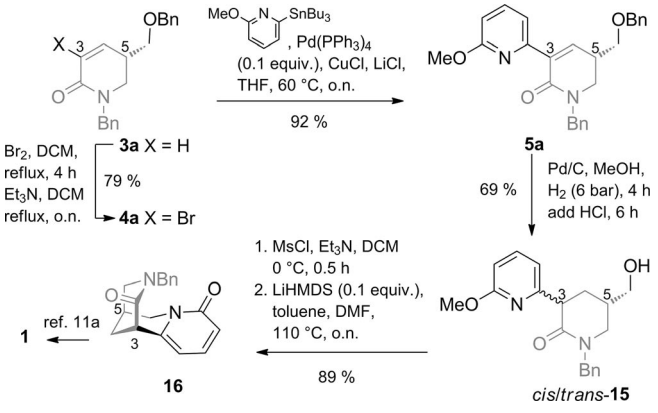



Scheme 4. Proposed mechanism for the hydrolysis of oxidation product **12**.

potassium bispinanediol borate **14**. As this white precipitate can be simply removed by filtration and used again for the preparation of pinanediol boronates[23] this method potentially allows for the recycling of the chiral director, but more importantly, the isolation of alcohol **11** in 81 % yield.

To obtain metathesis precursor **6**, the C3-building block **11** was first tosylated and then reacted with an excess of benzylamine. Isolation of the resulting amine required minimal workup, although the removal of excess benzylamine by distillation prior to the reaction with acryloyl chloride was necessary to suppress formation of undesired polymerization products. Building block **6** was obtained in 73 % yield using this approach. Ring closing metathesis furnished desired dihydropyridone **3a** in 74 % yield and with an overall yield of 36 % from $C_1$ building block **8**, requiring column chromatography only four times.

With the enantiomerically enriched precursor **3a** in hand, the synthesis of cytisine was completed as shown in Scheme 5.




Scheme 5. Completion of the enantioselective synthesis of cytisine (**1**).

Introduction of the $C^3$-bromide by addition of $Br_2$ in DCM followed by $Et_3N$ mediated elimination delivered the benzyl congener of pivotal precursor **4a** in 79 % yield, which was then subjected to a Stille-coupling, delivering alkene **5a**. Hydrogenation of this electron deficient alkene over palladium on charcoal in MeOH required an $H_2$ pressure of 6 bar. *O*-benzyl cleavage required the addition of 10 equiv. concentrated aqueous HCl.[24] In this way the cyclization-precursor **15**, was obtained as a 3:1 mixture of *cis*/*trans* epimers. As reported earlier,[6b] the diastereoselectivity of this hydrogenation is of little concern since the next step employs an in situ epimerization/cyclization that converts both epimers into desired bispidine **16**. Subsequent reduction and debenzylation yields cytisine.[11a]

To facilitate HPLC analysis of **16** for *ee* determinations, the reaction sequence was also applied to the enantiomeric series, starting from (+)-α-pinene to deliver the corresponding bispidine *ent*-**16**. The *ee* values obtained from both bispidine **16** (*ee* = 78 %) and its enantiomer *ent*-**16** (*ee* = 81 %) corresponded to those of their respective starting materials, (–)-α-pinene (79 % optical purity) and (+)-α-pinene (81 % optical purity), as well as to that of the $C_1$-building block **8** (vide supra).

As the *de* of $C_2$-building block **10** was not directly evident from NMR (vide supra), *ent*-**11** was prepared from recrystallized (+)-pinanediol (> 95 % *ee*, by HPLC and $^1$H NMR, see Supporting Information).[25] After derivatization with (*S*)-(+)-*O*-acetylmandelic acid, an *ee* of > 91 % was determined (see Supporting Information) for *ent*-**11**. Notably, even better results are probably possible using $C_2$-symmetric chiral directors such as DIPED or DICHED, which usually facilitate degradation of unwanted diastereomers.[14]

## Conclusions

In summary, we have developed an enantioselective synthesis for cytisine that proceeds in 13 linear steps, starting from pinanediol both enantiomers of which are commercially available. The overall yield is 9.7 %. Key to our approach is the synthesis of bromo dihydropyridone **4a** from chiral C3-building block **11**, which was prepared by iterative boronate homologations. Although **4a** contains only the atoms ultimately composing the *C*-ring piperidine moiety of cytisine (a biologically highly conserved region) it can be converted into target compound **1** in 5 steps with 34 % overall yield. This chiral precursor should therefore be a useful tool for the synthesis of highly enantiomerically enriched derivatives bearing modifications in the biologically important pyridine moiety.

## Experimental Section

**General:** All reactions were carried out in dried glassware under argon. Solvents for chromatography, unless purchased as *pro analysi* (p. a.) grade, were distilled from a rotary evaporator before use. THF was always freshly distilled from sodium/benzophenone. MeCN, DMF and DCM were distilled from $CaH_2$ and stored under argon over appropriate molecular sieves. Diisopropylamine was distilled from $CaH_2$ and stored in a Schlenk tube over 4 Å molecular sieves. BuLi, LiHMDS, vinylmagnesium bromide and $ZnCl_2$ were purchased as solutions and stored under argon at +7 °C. The precipitate formed by vinylmagnesium bromide under these conditions was carefully dissolved by gentle heating and shaking before use. CuCl was purchased in > 99 % purity and stored at +7 °C in a Schlenk tube under argon and shielded from light. LiCl was dried by vigorously heating (heatgun) under vacuum (<5 mbar) and was subsequently stored under argon. (+)- and (–)-(α)-Pinene were purchased from Acros: (+)-(α)-Pinene: $[\alpha]_D^{22}$ = +42.71 (neat) ≙81 % *ee* // (–)-(α)-Pinene: $[\alpha]_D^{22}$ = –41.26 (neat) ≙79 % *ee*.[26] All other reagents were used as supplied from commercial sources and stored appropriately. Analytical HPLC was carried out using a Jasco HPLC apparatus: PU-980 pump, UV-975 UV detector, LG-980-02 gradient unit and GT-103. Commercially available solvents were used as *pro analysi* (p. a.) grade eluents and degassed with a Labotec Gastorr GT-103. $^1$H and $^{13}$C NMR spectra were recorded in $CDCl_3$ with Bruker DMX 300 and Bruker DRX 500 spectrometers. IR spectra were measured with a Jasco FT/IR-430 spectrometer bearing an ATR attachment. Low and high resolution ESI mass spectra were recorded with Bruker amaZon SL and Bruker maXis 4G spectrometers, respectively.

**(3aS,4S,6S)-2-[(*S*)-1-(Benzyloxy)but-3-en-2-yl]-3a,5,5-trimethylhexahydro-4,6-methanobenzo[*d*][1,3,2]dioxaborole (*ent*-10):** LDA was freshly prepared by adding BuLi (1.9 M solution in hexane, 0.68 mL, 1.3 mmol) to diisopropylamine (1.6 mmol, 0.22 mL) in dry THF (1.5 mL) at –78 °C and stirring for 20 min at room temp. The resulting LDA solution was added dropwise to a mixture of benzyloxymethylboronate *ent*-**8** (300 mg, 1.0 mmol) and $CH_2Br_2$ (0.70 mL,

10 mmol) in THF (2 mL) at –78 °C. After stirring for 1 h at the same temperature the solvent was removed under reduced pressure (3 mbar) and cooling with an ice/NaCl bath (–10 to –5 °C) to yield the borate salt as a brown solid. The flask was returned to a –78 °C bath, before a solution of $ZnCl_2$ in $Et_2O$ (1 M, 2.8 mL, 2.5 mmol) was added and the reaction mixture was allowed to slowly warm up to room temp. overnight, after which time the solid had dissolved. The reaction mixture was diluted with an equal volume of CyHex and washed with saturated aq. $NH_4Cl$ (10 mL). The aqueous phase was re-extracted twice with CyHex/$Et_2O$ = 4:1. The combined organic phases were filtered through a column of $MgSO_4$ into a dried Schlenk tube and concentrated in vacuo to yield pinanediol (2-benzyloxy-1(*R*)-bromoethyl)boronate *ent*-**9** (396 mg) as a pale brown oil. An NMR sample (18 mg, 5 %) was removed and the rest of the crude product was used immediately for the next step. $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ = 7.41–7.28 (m, 5 H), 4.61 (s, 2 H), 4.38 (dd, *J* = 1.9, 8.8 Hz, 1 H), 3.93–3.74 (m, 2 H), 3.54 (dd, *J* = 6.4, 8.0 Hz, 1 H), 2.42–2.30 (m, 1 H), 2.23 (s, 1 H), 2.13–2.06 (m, 1 H), 1.96–1.85 (m, 2 H), 1.42 (s, 3 H), 1.30 (s, 3 H), 1.28 (d, *J* = 6.3 Hz, 1 H), 0.85 (s, 3 H) ppm. $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ = 138.0, 128.3, 127.7, 127.6, 86.8, 78.6, 73.1, 71.5, 51.2, 39.3, 38.3, 35.2, 28.3, 27.0, 26.2, 23.9 ppm. A solution of this crude product (< 0.95 mmol) in dry THF (10 mL) was cooled to –78 °C before a solution of vinylmagnesium bromide in THF (1 M, 1.4 mL, 1.4 mmol) was added dropwise. The reaction mixture was stored in the freezer at –20 °C overnight and heated to room temp. for 1 h, before it was diluted with an equal amount of CyHex, poured on saturated aq $NH_4Cl$ and extracted into $Et_2O$ (2 ×). The combined organic phases were dried with $Na_2SO_4$, filtered, and concentrated in vacuo. The residue was purified by flash chromatography (silica gel; CyHex/$Et_2O$, 19:1) yielding allylborane *ent*-**10** (266 mg, 0.78 mmol, 82 %) as a colourless oil. $R_f$ = 0.11 (silica gel; CyHex/EtOAc, 19:1). $[\alpha]_{546}^{24}$ = +14.5. $[\alpha]_{578}^{24}$ = +13.0. $[\alpha]_{589}^{24}$ = +12.0 ($CHCl_3$, *c* = 1.00). $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ = 7.46–7.12 (m, 5 H), 5.90 (ddd, *J* = 8.4, 10.3, 17.2 Hz, 1 H), 5.19–4.97 (m, 2 H), 4.54 (s, 2 H), 4.29 (dd, *J* = 1.9, 8.8 Hz, 1 H), 3.69–3.64 (m, 2 H), 2.43–2.26 (m, 2 H), 2.22–2.11 (m, 1 H), 2.06 (t, *J* = 5.3 Hz, 1 H), 1.93–1.81 (m, 2 H), 1.39 (s, 3 H), 1.29 (s, 3 H), 1.17 (d, *J* = 11.3 Hz, 1 H), 0.84 (s, 3 H) ppm. $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ = 138.6, 136.6, 128.2, 127.5, 127.3, 114.9, 85.8, 77.8, 72.8, 71.0, 51.2, 39.4, 38.1, 35.4, 28.5, 27.0, 26.4, 26.2, 23.9 ppm. IR (film): $\tilde{\nu}_{max}$ = 2919 (m), 2869 (w), 2360 (s), 2341 (m), 1454 (w), 1376 (s), 1339 (s), 1281 (m), 1239 (m), 1209 (w), 1098 (m), 1077 (s), 1030 (m), 991 (w), 938 (w), 904 (w), 735 (m), 697 (m) cm$^{-1}$. MS (ESI-ion trap): *m*/*z* = [M + Na]$^+$ calcd. for $C_{21}H_{29}BO_3Na$ 363.21, found 363.17. HRMS (ESI-Q-TOF) *m*/*z*: [M + Na]$^+$ calcd. for $C_{21}H_{29}BO_3Na$ 363.2106, found 363.2109.

**(*R*)-2-[(Benzyloxy)methyl]but-3-en-1-ol (*ent*-11):** BuLi (1.79 M solution in hexanes, 0.67 mL, 1.2 mmol) was added dropwise over 5 min to a solution of allylborane *ent*-**10** (340 mg, 1.00 mmol) and iodochloromethane (0.15 mL, 2.0 mmol) in absolute THF (10 mL) at –78 °C. The reaction mixture was warmed up to room temp. overnight, after which it was diluted with an equal volume of CyHex and extracted with saturated aq $NH_4Cl$. The aqueous layer was re-extracted with $Et_2O$. The combined organic phases were dried with $Na_2SO_4$ and concentrated in vacuo yielding the homologation product (354 mg, 1.00 mmol, quant.), which was used without further purification. $^1$H NMR of the crude material (300 MHz, $CDCl_3$): $\delta$ = 7.43–7.22 (m, 5 H), 5.81 (ddd, *J* = 7.7, 10.2, 17.5 Hz, 1 H), 5.18–4.94 (m, 2 H), 4.53 (d, *J* = 2.2 Hz, 2 H), 4.23 (dd, *J* = 2.2, 8.8 Hz, 1 H), 3.48–3.25 (m, 2 H), 2.70 (qd, *J* = 7.2, 14.1 Hz, 1 H), 2.39–2.25 (m, 1 H), 2.23–2.11 (m, 1 H), 2.03 (t, *J* = 5.6 Hz, 1 H), 1.94–1.74 (m, 2 H), 1.33 (s, 3 H), 1.28 (s, 3 H), 1.14 (d, *J* = 10.6 Hz, 1 H), 1.02 (dd, *J* = 6.6, 15.3 Hz, 1 H), 0.90 (dd, *J* = 7.8, 15.3 Hz, 1 H), 0.83 (s, 3 H). Part of the material (106 mg, <0.30 mmol) was dissolved in THF (3 mL) and cooled to 0 °C, before aq. NaOH (2 M, 3 mL) and $H_2O_2$ (30 %, 0.06 mL) were added simultaneously. A white precipitate formed, which was still visible after stirring for 1 h at room temp. The reaction mixture was heated to 45 °C for 1 h after which the precipitate had disappeared. The reaction was quenched by the addition of aq $Na_2S_2O_3$ (20 % by wt., 1 mL), poured onto saturated aq $NH_4Cl$ and extracted into $Et_2O$ (2 ×). The combined organic layers were dried with $Na_2SO_4$ and concentrated in vacuo. The residue was dissolved in $Et_2O$/CyHex, 1:1 (0.6 mL) and cooled to 0 °C. Recrystallized (+)-pinanediol (62 mg, 0.33 mmol) was dissolved in the mixture before aq. KOH* (5 M, 0.07 mL, 0.33 mmol) was added at the same temperature. To suspend the thick precipitate further $Et_2O$/CyHex (1:1, 2 mL) was added and the suspension was stirred overnight. The precipitate (**14**) was filtered and thoroughly washed with $Et_2O$/CyHex (1:1) until no more product was detectable by TLC in the washings. The combined filtrates were concentrated in vacuo and the residue was purified by flash chromatography (silica gel; CyHex/EtOAc, 4:1), yielding alcohol *ent*-**11** (46 mg, 0.24 mmol, 81 %) as a colorless oil. Data for *ent*-**11**: $R_f$ = 0.16 (silica gel; CyHex/EtOAc, 4:1). $[\alpha]_{546}^{24}$ = +32.0. $[\alpha]_{578}^{24}$ = +28.0. $[\alpha]_{589}^{24}$ = +26.0 ($CHCl_3$, *c* = 1.00). $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ = 7.40–7.07 (m, 5 H), 5.65 (ddd, *J* = 7.7, 10.2, 17.8 Hz, 1 H), 5.17–4.98 (m, 2 H), 4.46 (s, 2 H), 3.83–3.33 (m, 4 H), 2.70–2.45 (m, 1 H), 2.19 (t, *J* = 5.9 Hz, 1 H) ppm. $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ = 137.9, 135.8, 128.6, 128.5, 127.8, 127.6, 117.5, 73.4, 72.5, 65.1, 45.7 ppm. IR (film): $\tilde{\nu}_{max}$ = 3432 (m, br), 2862 (m), 2360 (s), 2341 (s), 1496 (w), 1455 (m), 1361 (m), 1206 (w), 1099 (s), 1029 (s), 918 (m), 736 (m), 698 (s) cm$^{-1}$. MS (ESI-ion trap): *m*/*z* = [M + Na]$^+$ calcd. for $C_{12}H_{16}O_2Na$ 215.10, found 215.11; [M + H]$^+$ calcd. for $C_{12}H_{16}O_2H$ 193.12, found 193.08. HRMS (ESI-Q-TOF) *m*/*z*: [M + Na]$^+$ calcd. for $C_{12}H_{16}O_2Na$ 215.1043, found 215.1026. Analysis of **14**: The precipitate was dried for several days under air after which 94 mg (≈ 0.24 mmol, ≈ 80 %) of a white solid remained. ESI-MS confirmed the formation of **14** and other pinanediol borate esters after redissolution in MeOH/EtOH: MS (ESI-ion trap) *m*/*z*: [Pinanediol$_2$B]$^-$ 347 (45), [PinanediolB(OEt)$_2$]$^-$ 283 (45), [PinanediolB(OEt)(OMe)]$^-$ 255 (100), [PinanediolBO]$^-$ 195 (35). **The rest of the crude homologation product was oxidized accordingly, but the order of addition of (+)-pinanediol and KOH was reversed upon which the yield dropped to 71 %.*

**(*S*)-*N*-Benzyl-*N*-{2-[(benzyloxy)methyl]but-3-en-1-yl}acrylamide (6):** A solution of alcohol **10** (125 mg, 0.65 mmol), $Et_3N$ (0.34 mL, 2.45 mmol) and TsCl (320 mg, 1.68 mmol) in MeCN (6.5 mL) was heated at 60 °C for 4 h. $R_f^{Tosylate\ 7}$ = 0.30 (silica gel; CyHex/EtOAc, 4:1). The reaction mixture was cooled to room temp., $BnNH_2$ (2.5 mL) was added and heating at 60 °C was continued for 14 h. Solvent and excess $BnNH_2$ were removed by kugelrohr distillation at 80 °C and 5 mbar pressure. After cooling to room temp. the residue was partitioned between aq NaOH (1 M) and EtOAc. The aqueous phase was re-extracted with EtOAc (2 ×), dried with $Na_2SO_4$, filtered, and concentrated in vacuo. Further $BnNH_2$ was removed by kugelrohr distillation at 70 °C and 5 mbar pressure. The residue was cooled to room temp. and dissolved in DCM (8 mL). The resulting solution was cooled to –5 °C before $Et_3N$ (1.7 mL, 12.3 mmol) was added. Acryloylchloride (0.64 mL, 7.85 mmol) was then added dropwise over 5 min. The reaction mixture was stirred for 10 min at –5 °C and then for 3 h at room temp. before saturated aq $NaHCO_3$ (10 mL) was added and the mixture extracted with EtOAc (3 ×). The combined organic phases were dried with $Na_2SO_4$, filtered, and concentrated in vacuo. The residue was purified by flash chromatography (silica gel; CyHex/EtOAc, 4:1) yielding metathesis precursor **6** (158 mg, 0.47 mmol, 73 %) as a pale yellow oil. $R_f$ = 0.16 (silica gel; CyHex/EtOAc, 4:1). *The NMR spectrum recorded at room temp. showed the presence of two discrete rotamers.* $^1$H NMR

(500 MHz, $CDCl_3$): $\delta$ = 7.38–7.21 (m, 9 H), 7.14 (d, *J* = 6.9 Hz, 1 H), 6.73 (dd, *J* = 10.4, 16.7 Hz, 0.5 H), 6.51 (dd, *J* = 10.1, 16.7 Hz, 0.5 H), 6.41 (ddd, *J* = 2.2, 17.0, 34.7 Hz, 1 H), 5.87–5.74 (m, 1 H), 5.68 (ddd, *J* = 2.2, 12.6, 28.1 Hz, 1 H), 5.19–5.09 (m, 2 H), 4.77 (d, *J* = 14.8 Hz, 0.5 H), 4.67–4.57 (m, 1.5 H), 4.54–4.44 (m, 2 H), 3.63 (dd, *J* = 6.6, 15.1 Hz, 0.5 H), 3.58–3.45 (m, 2 H), 3.40 (dd, *J* = 6.1, 9.3 Hz, 0.5 H), 3.26 (dd, *J* = 7.9, 15.1 Hz, 0.5 H), 2.95–2.83 (m, 0.5 H), 2.73–2.61 (m, 0.5 H) ppm. $^{13}C$ NMR (126 MHz, $CDCl_3$): $\delta$ = 167.2, 166.8, 138.2, 137.9, 137.6, 137.5, 137.0, 136.4, 128.8, 128.5, 128.5, 128.4, 128.3, 128.1, 127.8, 127.7, 127.6, 127.5, 127.3, 126.3, 118.0, 117.1, 73.2, 73.1, 71.6, 70.5, 51.9, 49.3, 48.3, 48.1, 44.4, 43.0, 26.9 ppm. IR (film): $\tilde{\nu}_{max}$ = 2856 (w), 1717 (w), 1649 (s), 1612 (s), 1495 (m), 1445 (s), 1359 (m), 1269 (w), 1214 (s), 1175 (w), 1148 (w), 1098 (m), 1078 (m), 1028 (m), 977 (m), 919 (m), 793 (m), 735 (s), 697 (s), 614 (w), 596 (w), 580 (w), 567 (w) $cm^{-1}$. MS (ESI-ion trap): *m*/*z* = $[M + Na]^+$ calcd. for $C_{22}H_{25}NO_2Na$ 358.18, found 358.17; $[M + H]^+$ calcd. for $C_{22}H_{25}NO_2H$ 336.20, found 336.17. HRMS (ESI-Q-TOF): *m*/*z* = $[M + Na]^+$ calcd. for $C_{22}H_{25}NO_2Na$ 358.1778, found 358.1798; $[M + H]^+$ calcd. for $C_{22}H_{25}NO_2H$ 336.1958, found 336.1960.

**(*S*)-1-Benzyl-5-[(benzyloxy)methyl]-5,6-dihydropyridin-2(1*H*)-one (3a):** A solution of metathesis precursor **6** (100 mg, 0.30 mmol) and Grubbs 2nd generation catalyst (11 mg, 14 µmol, 0.05 equiv.) in DCM (15 mL) was refluxed for 5 h. The reaction mixture was concentrated in vacuo and the residue was purified by flash chromatography (silica gel; CyHex/EtOAc, 4:1 → 7:3), yielding dihydropyridone **3a** (68 mg, 0.22 mmol, 74 %) as a pale yellow oil. $R_f$ = 0.10 (silica gel; CyHex/EtOAc, 7:3). $[\alpha]^{24}_{546}$ = +144.0. $[\alpha]^{24}_{578}$ = +126.0. $[\alpha]^{24}_{589}$ = +118.0 (*c* = 0.50, $CHCl_3$). $^1H$ NMR (300 MHz, $CDCl_3$): $\delta$ = 7.33–7.19 (m, 8 H), 7.19–7.12 (m, 2 H), 6.38 (dd, *J* = 4.2, 9.8 Hz, 1 H), 5.97 (dd, *J* = 1.7, 9.8 Hz, 1 H), 4.67 (d, *J* = 14.7 Hz, 1 H), 4.41 (d, *J* = 14.7 Hz, 1 H), 4.26 (s, 2 H), 3.39–3.12 (m, 4 H), 2.75–2.57 (m, 1 H) ppm. $^{13}C$ NMR (75 MHz, $CDCl_3$): $\delta$ = 163.8, 139.8, 137.6, 137.2, 128.5, 128.3, 128.2, 127.7, 127.6, 127.4, 126.0, 73.1, 69.3, 49.7, 46.6, 35.1 ppm. IR (film): $\tilde{\nu}_{max}$ = 3734 (w), 3060 (w), 3030 (w), 2922 (m), 2856 (m), 2360 (s), 2341 (m), 2159 (w), 1967 (w), 1733 (w), 1662 (s), 1609 (s), 1558 (w), 1541 (w), 1521 (w), 1482 (m), 1454 (m), 1435 (m), 1380 (w), 1361 (m), 1261 (m), 1204 (w), 1170 (w), 1090 (s), 1028 (w), 819 (s), 728 (s), 697 (s), 669 (w), 609 (m), 566 (w) $cm^{-1}$. MS (ESI-ion trap): *m*/*z* = $[M + Na]^+$ calcd. for $C_{20}H_{21}NO_2Na$ 330.15, found 330.09. HRMS (ESI-Q-TOF) *m*/*z*: $[M + Na]^+$ calcd. for $C_{20}H_{21}NO_2Na$ 330.1465, found 330.1464.

**(*S*)-1-Benzyl-5-[(benzyloxy)methyl]-3-bromo-5,6-dihydropyridin-2(1*H*)-one (4a):** Bromine (46 µL, 0.91 mmol) was added to a solution of dihydropyridone **3a** (140 mg, 0.46 mmol) in DCM (5 mL), which was then refluxed for 6 h. A solution of $Na_2S_2O_3$ (20 % by weight, 5 mL) was added and the mixture was extracted into DCM (3 ×). The combined organic phases were dried with $Na_2SO_4$, filtered, and concentrated in vacuo. The residue was dissolved in DCM (5 mL) and $Et_3N$ (0.64 mL, 4.6 mmol) was added. The reaction mixture was refluxed overnight, cooled to room temp. and stirred for a further 10 h at room temp., before it was poured into saturated aq $NH_4Cl$ and extracted into DCM (3 ×). The combined organic phases were dried with $Na_2SO_4$, filtered, and concentrated in vacuo. The residue was purified by flash chromatography (silica gel; CyHex/EtOAc, 4:1) yielding bromide **4a** (138 mg, 0.37 mmol, 79 %) as a pale yellow oil. $R_f$ = 0.17 (silica gel; CyHex/EtOAc, 4:1). $[\alpha]^{24}_{546}$ = +93.0. $[\alpha]^{24}_{578}$ = +80.0. $[\alpha]^{24}_{589}$ = +76.0 (*c* = 1.00, $CHCl_3$). $^1H$ NMR (300 MHz, $CDCl_3$): $\delta$ = 7.33–7.18 (m, 8 H), 7.18–7.07 (m, 2 H), 6.79 (d, *J* = 4.7 Hz, 1 H), 4.69 (d, *J* = 14.7 Hz, 1 H), 4.42 (d, *J* = 14.4 Hz, 1 H), 4.24 (s, 2 H), 3.46–3.24 (m, 3 H), 3.23–3.09 (m, 1 H), 2.77–2.55 (m, 1 H) ppm. $^{13}C$ NMR (75 MHz, $CDCl_3$): $\delta$ = 159.5, 140.4, 137.4, 136.7, 128.6, 128.4, 128.4, 127.9, 127.7, 120.2, 73.2, 68.4, 51.2, 46.7, 37.2 ppm. IR (film): $\tilde{\nu}_{max}$ = 3030 (w), 2923 (m), 2854 (m), 2359 (w), 2341 (w), 2089 (w), 1993 (w), 1657 (s), 1613 (m), 1495 (w), 1475 (m), 1453 (m), 1426 (w), 1360 (m), 1297 (w), 1260 (w), 1205 (m), 1173 (w), 1092 (m), 1073 (m), 1028 (w), 1002 (w), 957 (w), 909 (w), 882 (w), 863 (w), 838 (w), 735 (s), 697 (s), 613 (m), 585 (w), 553 (w) $cm^{-1}$. MS (ESI-ion trap): *m*/*z* = $[M + Na]^+$ calcd. for $C_{20}H_{20}BrNO_2Na$ 408.06, found 408.06. HRMS (ESI-Q-TOF) *m*/*z*: $[M + Na]^+$ calcd. for $C_{20}H_{20}BrNO_2Na$ 408.0570, found 408.0576.

**(*S*)-1′-Benzyl-5′-[(benzyloxy)methyl]-6-methoxy-5′,6′-dihydro-[2,3′-bipyridin]-2′(1′H)-one (5a):** 2-Methoxy-6-(tributylstannyl)pyridine (129 mg, 0.32 mmol) was added to a solution of bromide **4a** (90 mg, 0.23 mmol), CuCl (30 mg, 0.30 mmol), LiCl (12 mg, 0.30 mmol) and $Pd(PPh_3)_4$ (24 mg, 21 µmol) in absolute THF (3 mL). The reaction mixture was heated to 60 °C overnight, cooled to room temp. and concentrated in vacuo. The residue was purified by flash chromatography (silica gel; CyHex/EtOAc, 4:1) yielding coupling product **5a** (89 mg, 0.22 mmol, 92 %) as a pale yellow oil. $R_f$ = 0.26 (silica gel; CyHex/EtOAc, 4:1). $[\alpha]^{22}_{546}$ = +22.0. $[\alpha]^{22}_{578}$ = +18.0. $[\alpha]^{22}_{589}$ = +18.0 (*c* = 0.50, $CHCl_3$). $^1H$ NMR (300 MHz, $CDCl_3$): $\delta$ = 7.60 (d, *J* = 7.5 Hz, 1 H), 7.54–7.45 (m, 1 H), 7.32–7.11 (m, 11 H), 6.59 (d, *J* = 8.1 Hz, 1 H), 4.74 (d, *J* = 14.7 Hz, 1 H), 4.49 (d, *J* = 14.4 Hz, 1 H), 4.25 (s, 2 H), 3.53–3.30 (m, 3 H), 3.23 (t, *J* = 8.9 Hz, 1 H), 2.93–2.65 (m, 1 H) ppm. $^{13}C$ NMR (75 MHz, $CDCl_3$): $\delta$ = 163.5, 163.0, 150.1, 139.4, 138.8, 137.8, 137.5, 134.1, 128.6, 128.4, 127.8, 127.7, 127.5, 117.1, 109.8, 73.1, 69.2, 53.1, 50.3, 46.8, 35.3 ppm. IR (film): $\tilde{\nu}_{max}$ = 3901 (w), 3069 (w), 3853 (w), 3839 (w), 3819 (w), 3800 (w), 3750 (w), 3734 (w), 3710 (w), 3689 (w), 3675 (w), 3649 (w), 3628 (w), 3566 (w), 2952 (m), 2924 (m), 2855 (m), 2360 (s), 2341 (s), 2158 (w), 2024 (w), 1967 (w), 1868 (w), 1845 (w), 1827 (w), 1792 (w), 1771 (w), 1733 (w), 1716 (w), 1698 (w), 1684 (w), 1654 (m), 1577 (m), 1558 (w), 1541 (w), 1521 (w), 1507 (w), 1457 (m), 1437 (w), 1417 (w), 1362 (w), 1318 (w), 1259 (w), 1230 (w), 1173 (w), 1119 (w), 1092 (w), 1076 (w), 1029 (w), 873 (w), 808 (w), 736 (w), 696 (w), 668 (m), 650 (w), 614 (w), 566 (w) $cm^{-1}$. MS (ESI-ion trap): *m*/*z* = $[M + Na]^+$ calcd. for $C_{26}H_{26}N_2O_3Na$ 437.18, found 437.17; $[M + H]^+$ calcd. for $C_{26}H_{26}N_2O_3H$ 415.20, found 415.21. HRMS (ESI-Q-TOF) *m*/*z*: $[M + Na]^+$ calcd. for $C_{26}H_{26}N_2O_3Na$ 437.1836, found 437.1840; $[M + H]^+$ calcd. for $C_{26}H_{26}N_2O_3H$ 415.2016, found 415.2016.

**(3*S*,5*S*)-1-Benzyl-5-(hydroxymethyl)-3-(6-methoxypyridin-2-yl)-piperidin-2-one (*cis*-12) and (3*R*,5*S*)-1-Benzyl-5-(hydroxymethyl)-3-(6-methoxypyridin-2-yl)piperidin-2-one (*trans*-12):** A mixture of coupling product **5a** (28 mg, 67 µmol) and 10 wt.-% Pd/C (14 mg) in MeOH (0.7 mL) was stirred under an atmosphere of $H_2$ (6 bar) for 4 h. In order to achieve debenzylation as well, 2 drops of conc. aq HCl were added and stirring under an atmosphere of $H_2$ (6 bar) was continued overnight. The reaction mixture was filtered through celite and concentrated in vacuo. The residue was taken up in a mixture of saturated aq $NaHCO_3$ and EtOAc. The phases were separated and the aqueous layer was re-extracted into EtOAc (2 ×). The combined organic layers were dried with $Na_2SO_4$, filtered, and concentrated in vacuo. $^1H$ NMR confirmed reduction of the alkene but not debenzylation. The material thus obtained was dissolved in MeOH (0.7 mL), to which 10 wt.-% Pd/C (14 mg) and conc. aq HCl (0.05 mL, 10 equiv.) were added under Ar. The reaction mixture was stirred under an atmosphere of $H_2$ (6 bar) for 6 h. The reaction mixture was filtered through celite and concentrated in vacuo. The residue was taken up in a mixture of saturated aq $NaHCO_3$ and EtOAc. The phases were separated and the aqueous layer was re-extracted into EtOAc (2 ×). The combined organic layers were dried with $Na_2SO_4$, filtered, and concentrated in vacuo. The residue was purified by flash chromatography (silica gel; CyHex/EtOAc, 1:1) yielding a 3:1 mixture of isomers *cis*-**12** and *trans*-**12** (15 mg, 46 µmol, 69 %) as a pale yellow oil. $R_f$ = 0.29 (EtOAc). $^1H$ NMR (300 MHz, $CDCl_3$): $\delta$ = 7.56–7.46 (m, 2 H, C4′-*H*-*cis*, C4′-*H*-*trans*),

7.35–7.29 (m, 10 H, 5 × ArC-*H-cis*, 5 × ArC-*H-trans*), 6.88 (m, 2 H, C5′-*H-cis*, C5′-*H-trans*), 6.62 (d, *J* = 8.0 Hz, 2 H, C3′-*H-cis and trans*), 4.94 (d, *J* = 14.5 Hz, 1 H, C*H*$_2$Ph-*trans*), 4.93 (d, *J* = 14.5 Hz, 1 H, C*H*$_2$Ph-*cis*), 4.43 (d, *J* = 14.5 Hz, 1 H, C*H*$_2$Ph-*trans*), 4.40 (d, *J* = 14.5 Hz, 1 H, C*H*$_2$Ph-*cis*), 3.87–3.91 (m, 4 H, OC*H*$_3$-*cis*, C3-*H-trans*), 3.86 (s, 3 H, OC*H*$_3$-*trans*), 3.78 (dd, *J* = 10.5, 7.0 Hz, 1 H, C3-*H-cis*), 3.66–3.37 (m, 6 H, C5a-*H*$_2$-*cis*, C5a-*H*$_2$-*trans*, C6-*H*$_2$-*trans*, C5a-*H*$_2$-*cis*, C5a-*H*$_2$-*trans*, C6-*H*$_2$-*cis*), 3.25–3.14 (m, 2 H, C6-*H*$_2$-*cis*, C6-*H*$_2$-*trans*), 2.42 (m, 1 H, C5-*H-trans*), 2.27–2.05 (m, 5 H, C4-*H*$_2$-*trans*, C5-*H-cis*, C4-*H*$_2$-*cis*, C4-*H*$_2$-*trans*) ppm. $^{13}$C NMR only signals for *cis*-12 are reported: (75 MHz, $CDCl_3$): $\delta$ = 170.1, 163.8, 158.1, 138.9, 137.2, 128.5, 128.1, 127.4, 116.6, 108.7, 65.0, 53.2, 50.9, 50.4, 50.2, 36.3, 31.4 ppm. Spectroscopic data were consistent with those reported in the literature.[6b]

## Acknowledgments

The authors thank Prof. Dr. C. Schmuck for excellent laboratory conditions and fruitful discussions. Prof. Dr. G. Haberhauer and Mrs. H. Wöll are thanked for help with the HPLC experiments. Funding from the University of Duisburg, Germany and the Science Support Center, Essen, Germany

**Keywords:** Asymmetric synthesis · Natural products · Alkaloids · Metathesis · Rearrangement · Carbenoids · Boronate homologation

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[19] The *de* was estimated by integrating the $^{13}$C-NMR signals at 86.71 ppm (for **9**) and 86.79 ppm (for *epi*-**9**) as described by Matteson,[15] although we did not employ chromium(III) acetylacetonate.

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Received: November 13, 2015
Published Online: January 15, 2016

 